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Implementing Population-based Expanded Carrier Screening Reporting Couple Results Only: A Mixed Methods Approach

by

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Thesis for the degree of Doctor of Philosophy

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Abstract

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IMPLEMENTING POPULATION-BASED EXPANDED CARRIER SCREENING REPORTING COUPLE RESULTS ONLY: A MIXED METHODS APPROACH

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Genomic technologies now enable efficient and relatively inexpensive carrier screening for multiple (autosomal) recessive (AR) conditions simultaneously- called expanded carrier screening (ECS). ECS could be offered routinely to any couple who may want [further] children and inform their reproductive decision-making at a time where they could still change their reproductive plans. The aim of this PhD research was to investigate whether offering ECS to the general population adopting an approach where couple results only were reported would meet criteria for responsible implementation. I investigated the following elements: harms and benefits of offering ECS to the general population; clinical utility for reproductive decision-making; uptake and informed choice; and feasibility of test provision by non-genetics health professionals (HCPs). The unique aspect of this test offer is the approach to report couple results only, as opposed to reporting individual carrier states, and I explored this aspect in depth.

I used a mixed methods methodological approach and the empirical research was split in two phases. Phase 1 was a implementation pilot study where trained general practitioners (GPs) offered a couple-based ECS test consisting of 50 severe AR conditions to the general population. Uptake, feasibility, informed-choice and psychological outcomes were investigated using longitudinal quantitative surveys (couples) and semi-structured interviews (GPs). Phase 2 was a qualitative study using focus groups and interviews in the fertility clinic to explore couples' and health professionals' (HCPs) views regarding and experiences of offering a couple-based ECS test in more detail.

In Phase 1, I found that approximately 15% of the eligible population accepted the test offer within approximately one month. Most participants made an informed choice to undergo ECS testing and there were no indications that the test offer is associated with negative psychological outcomes in this population. Test provision by motivated and trained GPs was feasible. Participants were satisfied with receiving couple results. Phase 2 findings demonstrate that both HCPs and couples struggled with the concept of reporting couple results only, as individual carrier states were perceived as useful for reproductive decisions in some situations. HCPs appreciated the limited clinical utility of reporting individual results, although some were unsure about their responsibilities towards gamete donors, where there is a discrepancy between the social and genetic "couple".

This research demonstrates that introducing couple-based ECS to the general population by non-genetics health professionals could be such a responsible approach. My research did not suggest any significant harms of offering this type of testing in an implementation pilot setting. The next step to evaluate ECS to couples from the general population should be a large-scale nation-wide study to address the current gaps in knowledge, including longer term societal impact of an ECS routine test offer, and follow-up of carrier couples. If the purpose of an ECS test offer to couples from the general population is to inform couples' reproductive decisions and enable meaningful reproductive options, a test offer focused on a limited set of severe AR conditions and generated as couple results is justified.

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I confirm that:

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   1. Schuurmans J, Birnie E, Ranchor A V., Abbott KM, Fenwick A, Lucassen A, et al. GP-provided couple-based expanded preconception carrier screening in the Dutch general population: who accepts the test offer and why? Eur J Hum Genet. 2020 Sep 30;28(2):182–92.
   2. Schuurmans J, Birnie E, van den Heuvel LM, Plantinga M, Lucassen A, van der Kolk DM, et al. Feasibility of couple-based expanded carrier screening offered by general practitioners. Eur J Hum Genet. 2019;27(5):691–700.

Signature: ..... Date:.....

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Preface

As a medical student I was always interested in translational research, enabling new scientific discoveries related to human development and genetics to be brought into clinical practice. As part of my medical training, I participated in a study on imaging the microstructural brain development in extremely premature neonates in the neonatal intensive care unit and this made me acutely aware of the ethical issues both clinicians and parents face as part of the care for extremely ill babies. Advances in technology can be used to 'save' these sick babies, but does this mean that we always should? This sparked my interest in ethical issues raised by these advances in technology. When the opportunity came up to research the ethical issues raised by another example of rapid advances- the ability to routinely screen prospective parents for a range of diseases they may pass on to their future children- which was not previously possible, I thought this was perfect for an in depth PhD study. I have found that the skills and knowledge I have gained in the past five years regarding how to deal with ethical issues in clinical genetics are incredibly helpful in my current work as a junior doctor in clinical genetics at the UMC Utrecht.

Structure of the PhD: a joint-degree between two universities: This research was undertaken as a joint PhD degree between the University of Groningen in the Netherlands and the University of Southampton in the United Kingdom. The joint nature of this PhD is also reflected in the setting of the empirical research. The research was divided in two empirical research phases: Phase 1 was conducted in the Netherlands and Phase 2 took place in the United Kingdom. The thesis is divided into 5 chapters. Chapter 1 is a critical appraisal of the relevant literature which ends with the rationale, aims and objectives of this research. Chapter 2 is a discussion of the overarching, mixed-methods methodology for this PhD and I discuss the methods chosen to address the research questions. To fulfil the requirements of the University of Groningen, the empirical research conducted in Phase 1, and presented in Chapter 3, has been submitted for publication. Two papers have been accepted after peer-review in the European Journal of Human Genetics and one manuscript is being prepared for submission. In Chapter 4, I summarise and reflect on the methods I used for the Phase 2 research, and present and discuss the findings of this Phase. In Chapter 5, I bring together the findings from the two empirical research phases in relation to the overall research question and provide recommendations for clinical practice

and future research. I also discuss the strengths and limitations of the work and assess the quality of the research. Whilst this thesis is mainly written in the first person voice, Chapter 3, which presents the results from the first phase of this research is written mainly in third person voice given that this is conventional for the scientific journals where the papers were published.

Abbreviations

ACMG	American College for Medical Genetics and Genomics
AD	autosomal dominant
AR	autosomal recessive
ART	Artificial reproductive technology
DCS	Decisional Conflict Scale
DNA	desoxyribonucleic acid
CF	cystic fibrosis
ECS	expanded carrier screening
EOI	expression of interest
ESHG	European Society of Human Genetics
FA	framework analysis
GP	general practitioner
HCP	health care professional/provider
HFEA	Human Fertilisation and Embryology Authority
IVF	in vitro fertilisation
MMR	mixed methods research
NHS	National Health Service
NGS	Next Generation Sequencing
NIPT	non-invasive prenatal test
NBS	new-born screening
PIS	participant information sheet
PGT-M	Pre-implantation genetic testing for monogenic disorders (previously known as preimplantation genetic diagnosis or PGD)

Abbreviations

STAI	State-Trait Anxiety Inventory
UMCG	University Medical Centre Groningen
WHO	World Health Organisation
NL	The Netherlands
SMA	spinal muscular atrophy
TA	thematic analysis
UK	United Kingdom
X-L	X-linked

Chapter 1 Literature review

1.1 Chapter outline

In this chapter, I introduce and analyse the concept of couple-based expanded carrier screening (ECS), the novel approach proposed in this thesis. I discuss the literature regarding how to evaluate whether the introduction of ECS in a health care setting is responsible, focussing on the ethical, practical and psychosocial aspects of ECS implementation.

1.2 Introducing the topic of this PhD research

In this thesis, I investigated how couple-based preconception expanded carrier screening (ECS) could be introduced in a real world (pilot) setting to guide the implementation of this type of testing into a health care setting. By making use of new genomic technology, couple-based ECS enables informing of prospective parents about their chances of having a child with a severe genetic condition.

Fortunately, most children are born healthy. Nevertheless, in Western countries approximately 2-3% of children are born every year with a congenital abnormality (1,2) that requires hospital care in the first year of life (3). These congenital abnormalities may be of genetic, non-genetic (e.g. environmental or infectious) or multifactorial origin. Congenital abnormalities which are (partly) caused by genetic factors include chromosomal abnormalities such as Down's syndrome, single-gene defects (e.g. recessive conditions such as cystic fibrosis (CF) or sickle cell disease), congenital heart disease and neural tube defects.

The preconception time period is increasingly acknowledged as a window of opportunity for interventions to optimise the perinatal health of the future mother and maximise the chances of conceiving healthy children (4–6). Preconception care has been defined by the World Health Organisation (WHO) as 'the provision of biomedical, behavioural and social health interventions to women and couples before conception occurs' with the ultimate aim 'to improve maternal and child health, in both the short and long term (7). According to the Health Council of the Netherlands, provision of preconception care involves advising

couples regarding behaviour changes to optimise the health of mother and child and facilitating couples' reproductive decisions with non-directive information about (for example) genetic testing. A glossary of terms is included to explain the concepts of genetic testing and screening and how these relate to ECS. An example of general preconception care is advising women who would like to become pregnant to use folic acid supplementation. Folic acid supplementation has been associated with a reduced number of children born with severe congenital abnormalities such as spina bifida. Spina bifida is a condition where the neural tube fails to close properly resulting in high morbidity and mortality (8). Another example of preconception care is the identification of couples at increased risk of having children with a genetic condition based on their family history. These couples can then be referred for specialist counselling (9,10). A negative family history is not informative regarding reproductive risk of having children with autosomal recessive (AR) conditions. A different approach is required to identify couples at increased risk of conceiving children affected by those conditions, such as expanded carrier screening (ECS).

Identifying prospective parents at risk of having children with AR and X-linked (X-L) conditions is possible *before* conception as well as prenatally, but a routine test offer is not (yet) available for couples from the general population. In the glossary of terms I also define what I mean by general population and high risk populations. Currently, genetic screening for reproductive purposes offered to the general population most often takes place during pregnancy (10). An example of such a test offer to all *pregnant* women is the non-invasive prenatal test (NIPT) as screening for chromosomal abnormalities such as Down's syndrome (11–13). Reproductive genetic screening enables couples to be informed about their reproductive risk of having children with genetic conditions. Couples identified at increased risk of having children affected by a genetic condition may utilise several alternative reproductive options to conceive to avoid conception or prevent the birth of a child affected by this condition.

As of 2019, around 1900 recessive conditions have been identified (14). These AR conditions range in severity, but collectively these conditions are suggested to account for a significant percentage of childhood mortality and morbidity (15–17). For example, Kingsmore et al., (2012) reported that approximately 18% of childhood morbidity and 20% of childhood mortality was caused by Mendelian disease (18). Estimating the burden of

disease caused by AR conditions however is challenging, as the exact number of AR conditions is unknown, conditions range from mild to lethal prenatally or in early childhoodand the relative contribution of recessive conditions to the burden of disease of congenital abnormalities depends on the ethnic and geographic origin of the population (3).

Most carriers of AR conditions are asymptomatic and therefore not routinely identified or aware that they carry this mutation. If both (prospective) parents are carriers of the same AR condition, then in each pregnancy, these couples have a 1 in 4 chance of having children affected by this condition. Whilst most AR conditions are rare, it is thought that everyone is a carrier of an average of 2.8 severe AR conditions (15) and, when mild ones are included this number increases to over 20 conditions (14). The chances of being a carrier *couple* for an AR condition are approximately 1% depending on the ethnic composition of the population or whether any founding effects are present (19,20) and the chances of being a carrier couple for a severe condition in the UMCG test in the Dutch general population, are estimated to be 1 in 150 (19,21). This is comparable to the (average) risk of having a child with Down's syndrome for which prenatal screening is routinely offered (22). Depending on the population, these figures infer that approximately 1 in 400- 1 in 600 pregnancies would be affected by an AR or X-L condition (19,23). As some of these AR conditions may have such profound health implications, prospective parents may want to know about their chances of having children affected by these conditions. Identifying so-called carrier couples before they embark on a pregnancy could enhance their reproductive decisions and provide them with alternative reproductive options(24).

I focus on the offer of preconception genetic screening for conditions that have an AR pattern of inheritance, but some of the issues addressed in this thesis may also be relevant for other types of reproductive genetic screening as well as for prenatal ECS. In order to understand the proposed approach of providing couple-based results, it is important that the mechanisms of inheritance for genetic conditions are explored. These mechanisms are described in Box 1.1 and Box 1.2. The reproductive options available to couples having an increased risk to conceive children with AR conditions are summarised in Box 1.3.

Box 1.1 How genetic information is passed on from parents to offspring: mechanisms of inheritance

How genetic information is passed on from parents to offspring: mechanisms of inheritance

Genetics can be defined as the scientific study of inherited variation in living organisms and the cellular and molecular processes responsible for this variation (25). During the 1860s, the Austrian monk, Mendel, described how certain traits are passed on from parents to offspring. Mendel proposed a theory of inheritance from his breeding experiments with peas and realised that one copy of a gene – the allele - is inherited from each parent (26). Whether a trait is expressed in the phenotype depends on the mode of inheritance: dominant or recessive. Autosomal recessive (AR) inheritance means that the condition manifests only if the alleles inherited from both parents are non-functional or faulty. In contrast, only one faulty allele is required for a dominant condition to be expressed. During reproduction, the gametes - sperm and oocytes - contain half of the genetic code. This means that each child receives one half of their genetic information from the mother and the other half from their father. Certain inherited variations, sometimes called mutations, can predispose to disease. Our genotype -the composition of our genes - affects how traits or predispositions are expressed as a phenotype. Phenotype refers to our observable characteristics, such as eye colour, behaviour and manifestations of genetic disease. Human haploid DNA consists of approximately 3 billion letters per cell. Humans share most of this DNA (99.9%), but the remaining 0.1% equates to 3 million variants and determine our differences. Certain inherited variations, sometimes called mutations can predispose to disease, if they interfere with the function of the proteins produced by the genes. As part of their genotype, most people carry one or more AR mutations (11,27) but as a carrier, these usually do not lead to symptoms of the disease. This should not be confused with being a carrier of an autosomal dominant condition (AD). Carriers of an AD condition are predisposed to developing the disease and therefore this could have health implications for the individual. For example, in a family where breast cancer is common due to a disease-causing mutation in the BRCA1/2 gene, female carriers of this gene alteration have a substantially increased risk of developing breast or ovarian cancer (28).

Box 1.2 Autosomal recessive inheritance and offspring risk

Autosomal recessive inheritance and offspring risk

In order to establish a couple's reproductive risk, i.e. whether the offspring of a couple could potentially be affected by a recessive condition, it is necessary to examine the genetic information of both prospective parents together. Only if both parents are carriers of the same AR condtion –so-called carrier couples-, their chances of having children with AR conditions are increased. These couples can pass on three possible genotypes to their offspring:

1) Either a maternal or a paternal copy of the faulty gene: the child will be a carrier, referred to as heterozygous (the same genotype as the parents).
2) Two faulty copies of the gene: the child will be homozygous for the mutation and affected by the condition in question.
3) Two non-faulty copies of the gene: the child will be homozygous for the functional allele.

As explained in the figure below, carrier couples have a one in four (25%) risk of having an affected child, a one in two (50%) risk for a child who is a carrier and a one in four (25%) risk of having a child with the third genotype. Thus, carrier couples have a 75% chance that the child will be unaffected because the couple passes on one or both functional alleles, that is, genotypes one and three. This risk is the same for each pregnancy. This research focusses on carrier testing for AR conditions as opposed to, for example, AD conditions, where only one parents needs to carry the faulty gene that can affect their offspring. Nevertheless, some of the issues discussed will also apply to carrier testing for conditions following a different pattern of inheritance, such as those caused by genes present on the X-chromosome. An example of an X-linked condition for which carrier testing is available is Fragile X-syndrome (32).

Box 1.3 Alternative Reproductive Options for Carrier Couples of an Autosomal Recessive Condition

Alternative reproductive options for carrier couples of an autosomal recessive condition

If both people in a couple are carriers of the same AR condition and have become pregnant, in each pregnancy, the couple have a one in four (25%) chance of having an affected child. A carrier test can help provide the couple with information about their chances of having children affected by this condition, which they can use to make decisions regarding their reproductive plans. These couples may consider alternative reproductive options to conceive to avoid the conception or birth of a child affected by this condition, or may wish to prepare themselves for the care of a child who has a severe genetic condition.

The following options are available to carrier-couples before conception:

1) Conceive naturally and run the one in four risk of having an affected child.

2) Conceive naturally and test during pregnancy to see whether the fetus has inherited the genetic condition in question, or not. Couples might consider termination of pregnancy (TOP) if the fetus is affected.

3) Use donor gametes (egg or sperm) that do not carry the same mutation in question to conceive.

4) Use In Vitro Fertilisation (IVF) and Pre-implantation Genetic Diagnosis (PGT-M) to test whether an embryo is affected and transfer only those embryos that are unaffected.

5) Adopt children.

6) Refrain from having children.

7) To choose another reproductive partner who is not a carrier of the same condition.

1.2.1 From single gene to expanded screening

Reproductive risk for AR and X-L conditions can be determined by finding out whether one or both prospective biological parents (or gamete donors) are carriers of such a condition. In order to determine carrier status, a laboratory test is performed using deoxyribonucleic-acid (DNA) isolated from a blood or saliva sample. The order of the letters of the DNA-code is determined with sequencing techniques. This DNA sequence is then interpreted to find out whether a mutation is present in the gene(s) of interest.

Until recently, limitations due to costly and time consuming sequencing technology meant that carrier screening was possible only for single or a few conditions at any one time. This is why carrier screening was mainly available to certain groups/populations who were at known prior risk of having children with AR conditions based on ancestry or geographical origin or family history (25). In countries with a high prevalence of certain AR conditions, population screening programmes were introduced to reduce the burden of disease and lower the financial burden on the health care system (26). Often, cascade testing –the systematic testing of relatives and their spouses- was offered for those identified as carriers. Depending on policy in clinical genetics services cascade screening may be done irrespective of population carrier frequencies. Carrier screening for CF, an AR condition that is relatively common in most ethnic populations is recommended for all pregnant women by American, as well as some European and Australian professional societies (25,27).

Local initiatives were set up, facilitating carrier screening in smaller communities with a high prevalence of certain founder mutations, such as specific regions in the Netherlands and Canada (28,29). In the Dutch setting, carrier screening is organised as a clinic where midwives collaborate with clinical geneticists to enable couples from this founder population to be informed about their reproductive risk (30). Given that the burden of disease is relatively high in these populations, the demand for the test offer and the desire to be informed about reproductive risk often came from within the community –see also Dor Yeshorim in section 1.2.4.3. In other words, these are examples of a bottom up approach to developing carrier screening programmes, in contrast to the more top-down population-based approach discussed in this thesis.

As carriers for AR are asymptomatic and not routinely identified, in many cases, children with severe AR conditions are born to parents who were unaware of their carrier status.

Technological progress in the past decade, collectively called next generation sequencing (NGS), has resulted in a dramatic decrease in time and costs of genetic testing (31). Instead of carrier testing for conditions one by one, these new technologies enable routine carrier testing for multiple AR conditions simultaneously: expanded carrier screening (15,18). The development of ECS allows a change from previous practice: it means that all couples who would like to have children could be tested routinely, and be informed about their risk of having children affected by AR conditions at a time where they can still adapt their reproductive plans if they wish to do so. I use the following working definition of ECS:

A screening test for carrier status of multiple AR conditions simultaneously, to couples or individuals utilising donated gametes who are not previously known to be at increased risk compared to the general population of having children affected by the AR conditions included in the test.

Whilst ECS has not (yet) been implemented in routine care for any couple wishing to have children, ECS tests are available as direct-to-consumer or through some academic centres (32). A carrier screening offer to the population as a whole, irrespective of ancestry, has also been defined as pan-ethnic or universal screening.

1.2.2 Possible settings for a population-based ECS test offer: primary care (NL) and fertility clinic (UK)

Clinical genetics services in the Netherlands and through the NHS in the UK are very similar and are not set up to provide services for population-based reproductive genetic screening. In the Netherlands, provision of genetic and genomic testing is restricted by law. This means that only the seven Dutch academic medical centres are licenced to provide this care through their accredited genomic laboratories and provision of pre- and post test genetic counselling is (mainly) organised through the associated clinical genetics departments. In the NHS, genetic services used to be organised into 23 regional clinical genetic services and associated accredited genetic laboratories. Currently, the structure of the NHS-based clinical genetics services is being reorganised and genomic testing will be delivered by a network of seven Genomic Laboratory Hubs, building on the experience gained from the 100.000 Genomes Project (33).

ECS test-provision test offer by non-genetics professionals seems more likely, also indicated by the preferences of potential users and providers (21). Two settings where couples who are thinking about getting pregnant are likely to access health services are primary health care: 1) General practice (and obstetricians/midwives in case of pre- or postnatal ECS) and 2) Fertility clinics. As not all couples can conceive naturally, fertility clinics provide another setting where preconception care is provided. Couples or individuals referred for fertility treatment are not at an increased prior risk of having children with AR conditions compared to couples conceiving naturally (unless the reason for referral is a positive family history of an AR condition). Therefore, these couples fall within my definition of general population, i.e. individuals or both members of a couple who do not belong to high-risk populations based on family history, ancestry or geographical origin (1).

ECS is currently not (yet) part of general preconception care, but in the Netherlands, the GP was considered as the preferred provider for couple-based ECS in the general population. More than 99% of the Dutch population are registered with a GP (34), and most GP care is included in the mandatory health insurance package all Dutch citizens carry. In the Dutch healthcare system, GPs play a central role as gatekeeper for secondary or tertiary care (35), which makes extending their current preconception care responsibilities to include a population-based ECS offer a logical approach. Whilst the Dutch Society of General Practitioners stated their support for studies investigating ECS in primary care (36), no literature on a potential ECS-offer in the UK primary care setting is yet available. Several studies suggested that healthcare professionals (HCPs) welcome the possibility of carrier testing for couples undergoing fertility treatment (37,38) and some private fertility clinics in the UK have already implemented this type of testing for their patients (39–41).

Fertility clinics use assisted reproductive technology (ART) to help couples conceive. Couples or individuals use fertility treatment for various reasons and multiple fertility treatments exist. For example, to overcome unwanted sub- or infertility, treatment options include intra uterine insemination (IUI) or In vitro fertilisation (IVF) either with a couple's own gametes or donor gametes. Donor gametes can also be used when a partner cannot provide the second gamete. A donor can be anonymous, or recipients could bring a donor they know. Egg donation has two different approaches: egg sharing, where a woman donates some of her eggs after IVF if multiple oocytes can be collected and altruistic egg donation. Furthermore, those who had a previous child with a genetic condition might use

IVF and PGT-M (previously known as pre-implantation genetic diagnosis or PGD) in order to avoid having another child with the same condition. Couples or individuals receiving preconception care in a more specialised medical setting such as the fertility clinic may experience an ECS test offer differently compared to couples who are trying to conceive naturally.

Although the Dutch health care system and the NHS in the UK are organised slightly differently, both are based on the principle of social solidarity. The Dutch health care system is funded by social health insurance, which mainly includes a combination of private (obligatory) health insurance and taxation. In the Netherlands, all citizens are required to pay statutory health insurance. This covers most essential health care, such as GP care and services provided by hospitals or midwives. The Dutch can purchase additional health care for services that are not covered by statutory health care such as dental care >18years and need to pay a certain amount of money (currently around 400 euro/year) as 'own risk' for hospital care such as genetic counselling and testing. In the UK there is a two-tier system, with the tax-funded NHS, mostly free care at the point of delivery and universally accessible for all those 'ordinarily' citizen and a separate private health sector.

1.2.3 A clinically useful test offer for reproductive genetic screening such as expanded carrier screening

The premise is that a test is only of clinical utility when the result is also of analytic and clinical validity. That is to say, any test which produces inaccurate results, or positive results that do not truly predict whether individuals or couples are indeed at high reproductive risk have no clinical utility and have the potential to cause psychological distress. Whilst technology allows screening for as many as 1500 conditions simultaneously, more does not necessarily mean better, and the number of conditions included should be weighed against the clinical utility of a test offer which enables couples to make more informed reproductive decisions. The following criteria are commonly used to determine which conditions should be included for reproductive genetic testing to establish a test offer that is of clinical utility.

These criteria include disease severity (or 'seriousness', 2) age of onset, 3) treatability, 4) penetrance and expressivity and 5) carrier frequency (24,42,43). That is to say, the more severe a condition is likely to be, the earlier the onset and the clearer the phenotype, the

more likely it is that a condition is recommended for reproductive genetic screening (44). Or, as stated by the American College of Medical Genetics and Genomics (ACMG) (42) as those "[disorders] *that most at-risk patients and their partners identified in the screening program would consider having a prenatal diagnosis to facilitate making decisions surrounding reproduction".* A fifth criteria is the carrier frequency of a condition. The more common it is that someone is a carrier of a certain condition in the general population, the more likely it will be that this condition is included in carrier screening panels.

Including conditions that are very rare, may negatively affect the possibility that a positive test result actually means that a couple are both carriers of the same condition (45) and professional guidelines sometimes recommend a minimum carrier frequency for conditions to be included in ECS panels (46). Including conditions in ECS that are very common but not severe, such as hemochromatosis, may increase the number of carrier couples a test can identify, but at the same time reduces the clinical utility of the test result for reproductive decisions.

Whether the information about being a carrier couple is relevant to people's reproductive decisions in practice likely depends on various factors, such as the risks of being a carrier couple, how this knowledge would affect their reproductive plans, but also the severity of the conditions included in the test. Yet, exactly which conditions are severe enough is difficult to determine. Perceptions of severity are subjective: prospective parents might perceive the seriousness of a condition depending on previous experiences (47), or have a different perception than HCPs (48). Furthermore, both partners of a couple might not perceive the seriousness or severity of a condition in the same way.

Research suggests that professionals disagree to some extent as to whether one should classify certain conditions as serious or severe. A classification system based on disease characteristics, such as intellectual disability, created an approach to categorise conditions into mild, moderate, severe and profound (49,50). Advances in medical technology have changed the extent to which certain conditions are treatable, and views on how to define severity likely have changed over the past fifteen years. What makes the discussion about a clinically useful test offer even more difficult, is that the market for ECS has become a global market. For profit companies marketing ECS tests from the USA into Europe, do not necessarily change their panels to comply with the European recommendations. An

example of such an ECS test was offered by Gendia, a company operating from Belgium (51).

The third criterion to rank conditions in terms of severity is the availability of treatment (49,52). The more treatable a condition is, the less severe its ranking would be. Treatability in itself is also difficult to define, and the extent to which conditions are treatable is subjective and may change during the course of a patient's lifespan. Life expectancy of children born with CF in 1991-1995 was 34 years, whereas for infants born in 2015 this had increased to 45.2 years (53). Another example of a condition for which symptoms and life expectancy may change in the coming years is SMA. The drug nusinersen has been launched as a promising candidate for treatment of this severe neuromuscular disorder. Where previously, children with a severe type of SMA would die shortly after birth or in infancy due to the natural course of the disease, children newly diagnosed with this condition may have a better outcome, if treated promptly. However, a lot of uncertainty remains and concerns have been raised regarding limited evidence for sustained benefit and safety, high treatment costs, fair allocation of treatment and coverage of costs by health insurers or public health care systems such as the NHS (54). Thus, improvement in the management and treatment challenges views on the severity of genetic conditions such as CF and infant onset SMA, for which carrier screening in the general population is recommended by the ACMG in the USA (55,56). If a treatment is very burdensome to a family and the patient, a condition such as phenylketonuria for which treatment is available, might still be classified as severe. Newborn screening might also miss some treatable conditions or a newborn screening test-result may arrive too late. Adding these treatable conditions to ECS disease panels could be justified to prevent diagnostic delay and harm (45), especially if treatment immediately after birth is life-saving.

The fourth criterion for conditions to be included in ECS is related to the penetrance and variable expressivity of a condition. Even if a person inherits a mutation from both parents, the disease will not necessarily manifest, this is called reduced penetrance. Some conditions are characterised by a range of symptoms, which can be different in affected individuals: this is referred to as 'variable expressivity'. An example of a common recessive condition that is not fully penetrant is haemochromatosis (57) and Gaucher disease has variable expressivity (58). As more is understood about the etiology of diseases, the more apparent it has become that multiple genes may play a part in the manifestation of

conditions. Infrequently, being a carrier has health implications, for example, carriers of Gaucher disease are at risk of developing Parkinson's disease (59). Moreover, genes interact with environmental influences and yet unknown factors; our phenotype therefore is a composition of multiple factors, and genotype is one of those. An area of study looking into these other factors is known as epigenetics (60). In this research, the focus is on AR conditions for which the genotype-phenotype is relatively clear-cut and well-understood.

Perceptions and classifications of disease severity are important because these affect the composition of ECS test panels, and therefore the clinical utility of the test in terms of reproductive risk and prevention of harm in future offspring. In practice, ECS disease panels currently available vary in the number of diseases, the mode of inheritance, and the severity of the conditions (32). Consequently, some disease-panels are of more clinical utility regarding reproductive risk/the health of future offspring than others. For example, the commercial company based in the US which was previously known as Counsyl, offered a test including nonsyndromic hearing loss and deafness, phenylketonuria and hemochromatosis – conditions with a range of severity, age of onset, treatability and penetrance (61). In contrast, the UMCG panel includes only childhood onset conditions with severe physical or intellectual disabilities for which no treatment is available (21). Simply including as many conditions as possible is arguably unethical and has the potential to compromise reproductive decision-making, in particular if it has limited clinical utility. At the very least, the limitations of these panels should be communicated and offering tests of limited clinical utility is ethically contested.

1.2.3.1 How a test is offered and how results are reported: A couple-based approach to expanded carrier screening

Carrier testing can be offered at any time in one's reproductive life, but the two stages at which ECS is of most clinical utility are the preconception and (early) prenatal stage. In certain settings, carrier screening is offered premaritally or to adolescent individuals for cultural and religious reasons (62). If carrier testing is offered before a reproductive partner is known, individual carrier states are generated and/or reported. Once a reproductive partner or, in case of couples using a donor, a gamete donor is known, carrier testing can be offered to both gamete providers at the same time. In that case, results can be reported as individual carrier states, couple results, or as both. There has been some debate as to whether results of carrier testing are better reported as couple results or individual carrier

states (38,45,63,64). I focus on ECS offered to couples or individuals/couples and gamete donors, at the preconception stage and an approach where results can be reported as couple results only.

1.2.3.1.1 Definitions

There are various possibilities as to how carrier testing can be offered to couples (or individuals using a gamete donor) and how results are reported. These options are defined below:

1 (parallel): Both gamete providers provide a DNA sample: only a couple result is reported.

2 (parallel): Both gamete providers provide a DNA sample: both a couple result and individual carrier states are reported.

3 (sequential): One gamete provider provides a DNA sample (often this is the woman; or for gamete donation this could also be the donor). The second gamete provider is asked to provide a DNA sample only if the first partner has been identified as a carrier for an AR condition in the test.

Thus, if ECS is offered as a couple test, DNA samples are tested in parallel. If results are reported as individual carrier states, an ECS test offer could also be done sequentially.

There are various advantages and disadvantages of sequential versus parallel testing. Janssens et al., (2017) write that reporting individual carrier states and performing ECS sequentially, may be advantageous when one partner is (temporarily) unavailable for testing. In addition, if people have to pay for carrier screening, testing one partner first may be beneficial. However, the second partner will have to be tested eventually, particularly if testing is done for multiple recessive conditions simultaneously, as it is likely that the first partner is a carrier of at least one or more AR conditions. These advantages and disadvantages of sequential compared to parallel testing may be viewed differently when testing is adopted in high-risk populations rather than an ECS test offer for the general population. Reporting individual carrier states when testing sequentially has been associated with transient feelings of psychological distress if the first partner is tested positive until the result of the second partner is known (65,66) or until after genetic counselling (67). Parallel testing precludes the possibility of transient psychological distress in this scenario. If there is a time delay between testing of the first and second partner,

sequential testing may negatively affect how soon couples could conceive, or if a test is done prenatally, this may restrict the available reproductive options (68).

Several studies have looked at public views on couple-based testing and described seemingly contradictory preferences (64,69). For example, Henneman and Ten Kate (2002) found that for single gene carrier testing in the general population, couples indicated a preference for reporting individual carrier states as well as couple results, mainly because they felt that no information should be withheld from them (63). As confirmed by the findings of a recent survey of the UK public where participants were asked to select 3 words out of 12, reported that 'informative', 'personal' and 'helpful' were chosen most (70), the general public generally have a positive and deterministic association with genetic/genomic testing (71). This may affect their views and expectations around reporting individual carrier states for AR conditions as well, which could be problematic if unrealistic expectations arise about any health implications due to being a carrier of an AR condition. As knowledge of the individual carrier state of AR conditions holds no health implications for the unaffected person themselves, it is appropriate to question whether the individual carrier state should be considered a result. Arguably, if a couple result is considered the only 'result' from ECS, by not generating individual carrier states, no clinically useful information is being withheld from couples regarding their reproductive risk. Plantinga et al., (2019) found that when a couple result was framed as the only result that was relevant for reproductive risk, 76% of couples would not object to receiving a couple result only (64). Disclosing couple results only is not a completely new approach. In the 1990s, couple-based antenatal carrier testing for CF was proposed (65,72). CF carrier screening was not incorporated in the UK health care system, because, according to the UK Genetic Screening Committee, it did not abide by the Wilson and Jungner criteria. Currently (2020), this recommendation is under revision.

By reporting couple results, the burden of reproductive risk is shared amongst both members of a couple and it results in less individuals identified as a carrier of an AR condition. Some, but not all studies reported that being identified as a carrier of an AR condition was associated with (transient) lower perception of health (67,73), however, no conclusions can be drawn from the literature as to whether a couple-based approach or disclosing individual results leads to more negative psychological effects (65,74,75). Being identified as a carrier of a specific AR condition may have the potential for discrimination

or stigmatisation, although this is not reported in the literature (30,73). Several studies demonstrated other advantages of couple-based testing, such as a reduced burden on counselling and analysis (76,77). Some may argue that individual results should be reported for cascade screening of family members, because siblings of carriers for a severe recessive condition have an increased risk to be a carrier of the same condition. As not all couples stay in the same relationship, some argue that individual carrier states this information may be helpful when they have a new reproductive partner (38). Arguably, in those cases a new (updated) couple test could be offered to the new couple.

Genomic technology has confirmed that being a carrier of an AR condition is very common, but of a particular condition is low (61,77,78). As the knowledge about a person's carrier state holds clinical utility only when considered in the context of the partner's carrier status -unless it is in the context of a known a priori increased risk- adopting a couple-based approach for ECS would be more appropriate. When individual carriers are planning to conceive with carriers of the same condition, their chances to have a child with that condition are substantially increased (i.e. one in four or 25% in every pregnancy). It seems less useful to identify individuals as carriers of rare AR conditions, because this means that many would receive a 'positive' result, whilst this result is not relevant in determining reproductive risk on its own. Pooling many different individually rare conditions into one test, however, brings the chance of a positive result in both members of a couple in the general population to around 1% (19,20,79). Thus, the real clinical utility of ECS lies in the health of the future child, for which only the combined carrier status of the 'couple' - both gamete providers- is relevant (45).

1.2.3.1.2 Different couples fertility/primary care population

In reproductive medicine, the notion of a 'couple' is complex. Outside the world of clinic-based reproductive medicine, the social couple (i.e. the individual(s) intending to raise the future child) and the genetic couple (i.e. both gamete providers) often are the same. Clearly, for a donor-recipient couple consisting of the recipient and an egg or sperm donor, the genetic and social couple are different. In addition, these 'couples' may also consist of a single person who decided to conceive using a donor gamete. As discussed in section 1.2.2, the settings where ECS is likely to be offered in the Netherlands and the UK are general practice, i.e. primary health care, (NL) and the fertility clinic (UK). The implications of couple-based ECS in a fertility setting are likely to be different than in a primary care

setting. For example, a positive couple result may lead to a change in genetic couple (switching to another gamete donor), or an additional treatment is required to avoid placing an affected embryo in the uterus after IVF treatment (PGT-M). Couples using fertility treatment who are conceiving in a medical setting may experience this test offer differently compared to couples who do not require ART to conceive. I was interested in exploring the ethical issues and implications for practice that couple testing raises in this setting, because the implications of a genetic couple-based result are likely to be different based on this unique context.

1.2.3.1.3 An example of reporting couple results: Dor Yehsorim

A specific setting where match-making based on 'genetic couple-hood' was succesfully introduced and is now common practice is the premarital matching-stage in the Orthodox Jewish community called Dor Yeshorim (80). When Dor Yeshorim was initiated in 1983, by a rabbi who lost many of his children to Tay Sach's disease, its purpose was to bring down the number of children born with Tay Sachs disease and provide a means to reduce suffering for children and their families without having to consider the implications of marrying a carrier of the same condition (i.e not having children, or having to consider prenatal diagnosis and terminating affected pregnancies) (81). Since the introduction of carrier testing in 1971 (82), although not exclusively through Dor Yeshorim, the incidence of this disease has been successfully reduced by more than 90% (83). Interestingly, probably the major element in its success was the possibility to incorporate the genetic testing in this premarital matchmaking, and therefore the acceptance of and initiative by the religious leaders who have a conservative view on contraception, abortion and the use of ART (84). Currently, the programme is available in 11 countries and also includes other highly prevalent conditions in the Jewish Ashkenazi population, such as CF (81). Such testing is offered in adolescence, with results remaining in a database until a potential couple match is made. Potential couples are only informed whether they are 'genetically compatible or incompatible', without communicating individual carrier results (85). Several arguments are used as to why individual results are not returned. These include prevention of discrimination and stigmatisation of carriers and their families (38,84). Also, individual results are considered a 'burden of useless information'.

In other words, a couple-based approach to carrier screening has been proven to be acceptable in the Dor Yeshorim setting. For the general population, this may be different,

and currently, individual carrier states are reported for carrier testing for AR conditions. However, the possibility to offer ECS for multiple rare conditions to couples without prior risk questions this current practice and arguably, a couple-based approach which focuses on offspring risk and only provides couple results could well be preferable over reporting individual carrier states. Moreover, studying the ethical issues regarding couple-based ECS not only in a general practice, but also in a fertility setting enables an in depth exploration of the concept of couple results, due to the unique aspects of this setting where the social and genetic couple are sometimes different.

1.2.4 Development of the UMCG couple-based expanded carrier screening test

Given that the technology was available to offer ECS to the general population, the Genetics Department of the University Medical Centre Groningen (UMCG) took several steps leading up to the development of a pilot implementation study. The aim of this pilot study was to find out whether and how ECS might be introduced in the Dutch health care system in a responsible way. First, an international expert meeting at the UMCG in 2013 was held which led to two important recommendations regarding the design of an ECS test offer.

1) ECS should target severe, early childhood onset, recessive conditions

Based on this recommendation, the UMCG developed and validated a population-based test offer composed of 50 AR conditions with early-onset in childhood, which result in severe physical abnormalities and/or severe intellectual disabilities, or shortened lifespan, or severe pain and for which no curative treatment is available. The risk of being a carrier couple for this set of 50 conditions is approximately 1 in 150 (19,21).

The UMCG ECS test that was used in Phase 1 and 2 of my research was a targeted NGS Agilent SureSelect specified panel for 50/70 diseases and 70/90 genes, which aims to identify all (likely) pathogenic mutations and has high sensitivity and specificity (86). At the same time, the UMCG test is not diagnostic for reproductive risk of AR conditions. For example, not all causative genes for AR conditions are known (even if all known genes are screened, as is done in whole exome sequencing or WES). Most ECS tests include a limited number of genes. Furthermore, ECS tests also differ in how reproductive risk is determined at gene level. Some ECS tests only look for a limited set of known mutations/variants per gene, whereas others aim to identify all potentially pathogenic mutations in the genes included in the test (87). Variants of uncertain significance (VUS) –biomarker may be

present, but it is uncertain whether this has any clinical relevance when clinical symptoms are absent- complicate the interpretation of the variant in terms of clinical relevance. Missense mutations/variants -a change in the letters of the DNA that results in an altered amino acid in the protein encoded for by the gene in question- which are not described in the literature cannot be defined as pathogenic or likely pathogenic. Observed in a patient with a matching clinical phenotype however, the classification of a variant may shift towards (likely) pathogenic even though other evidence is less convincing. The interpretation of missense variants in couples undergoing ECS is complicated as for AR without a family history, there is no clinical phenotype. These classification issues are a burden for the laboratory staff and clinicians and classifying VUSes in light of a clinical phenotype may be easier than just based on biological hallmarks and literature cases. Especially when the latter are limited or not available. ECS is a screening test and given these complexities, it is never possible to state that a negative test result means that a couple is not a carrier couple for a recessive condition and even not for the conditions in that specific test. For the UMCG test it was decided not to report VUSes.

It was argued that this test should be offered adopting a couple-based approach, which meant that ECS would be offered to couples (not to individuals) and results were reported as couple results only, i.e. no individual carrier states were reported (21,64). A carrier couple was defined as both members of the couple carrying a class V (*pathogenic*) or IV (*likely pathogenic*) variant in the same gene included in the test. The test was developed in such a way that no individual carrier states could be reported. When the two gamete providers undergo a blood test, their DNA is analysed in a combined analysis pipe-line and the test result would either be positive -both gamete providers are carriers of the same AR condition- or negative -both gamete providers are not carrier of the same AR condition. If one partner is carrier of an AR condition in the test, but the other partner is not a carrier, the test result would be negative ‘not a carrier couple’, see Figure 1.1.

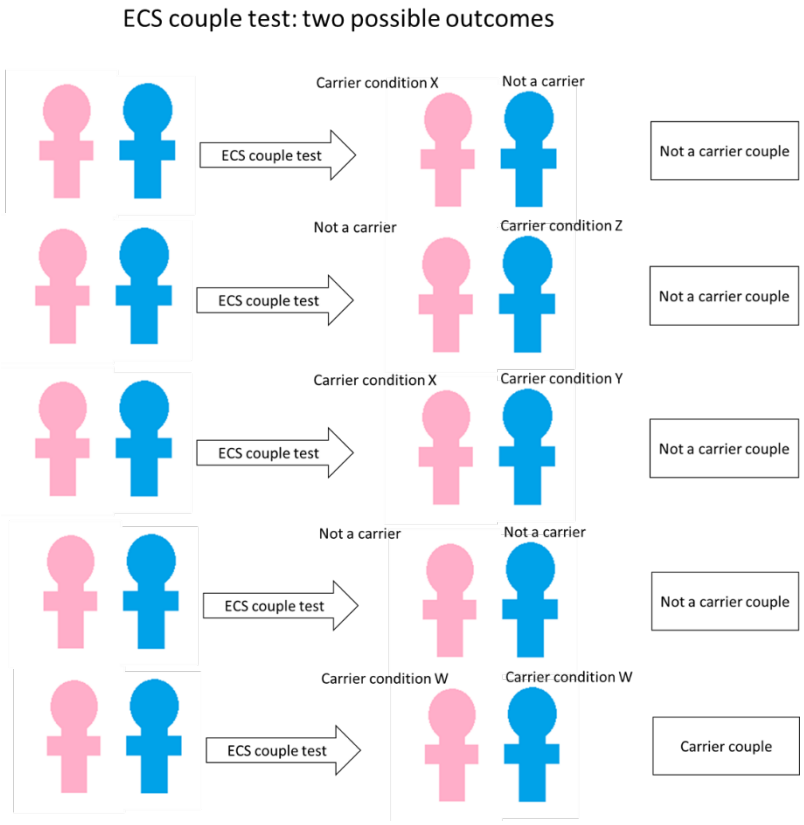

Figure 1.1 Possible results ECS couple testing

A second recommendation was the following:

2) Research amongst the target population and potential providers should be conducted before starting a pilot study to actually offer the test

The acceptability of the couple-based ECS test to health professionals and potential users was explored. Both health care provideres (HCPs) and the Dutch target population considered the general practitioner (GP) as the most suitable provider for this type of testing (21,88). This is in agreement with results from several international studies which showed that carrier testing for single-gene disorders such as CF provided by the GP or in a primary care setting was feasible and acceptable (89–91). An online survey among 504 prospective users was performed to investigate intentions towards hypothetically offering the UMCG test (21,92). Results showed that 34% of the participants would accept this ECS-offer, 51% were neutral and 15% did not have the intention to undergo this type of testing. Participants did not object to the couple-based approach (21,64). In the meantime, initiated by the Genetics Department of the UMCG, a wider discussion was held with the Dutch public about the possibility and desirability of an ECS test offer to the whole population. Focus groups with prospective users about communication of the UMCG ECS

test supported the development of a website (www.dragerschapstest.umcg.nl) and an information leaflet. In summary, the UMCG has developed an ECS test consisting of 50 severe, early onset, AR conditions, reporting couple-based results only, and with the GP as most suitable provider.

Based on the findings of this previous research, I set out to investigate whether the desired approach, namely an ECS test offer to couples from the general population provided by the GP would meet criteria for responsible implementation in a pilot setting. I also conducted an in depth exploration of the ethical issues around reporting couple results only. The findings of this PhD research can inform future large-scale population-based implementation of ECS in a health care setting.

1.3 Ethical framework of couple-based ECS for the general population

An ECS test offer design depends on for example the clinical setting in which it is offered, the population to which the test offer is provided, what is considered a clinically useful test, i.e. the aim of the test offer, whether tests are offered to couples or individuals, and how results are generated and communicated, i.e. as individual carrier states or as couple results. I am interested in an ECS test offer in a health care setting to couples who are not at increased prior risk compared to the general population of having children with AR conditions. A discussion of the issues regarding carrier screening in high risk populations or direct-to-consumer test offers is outside the scope of this thesis. Delatycki et al., (2019) provide a global overview of approaches to carrier screening, including approaches in countries with population screening for conditions with high prevalence such as Israel (25).

When carrier testing is offered to any couple who would like to have children, irrespective of ancestry or family history, the test offer could also be considered a form of population screening. The UK Human Genetics Commission issued a report in 2011 "*Increasing options, informing choice"*, which stated that there were no ethical, social or legal principles preventing preconception carrier screening from being acceptable as population screening (2). In 2019, the Health Council of the Netherlands' advised the Dutch Minister of Health to consider offering preconception carrier testing for Spinal Muscular Atrophy (SMA) as part of an ECS test offer to the general population (93).

One common aim for a population screening programme is to detect serious disease in individuals who do not (yet) experience any symptoms. If serious disease or an increased risk to develop disease is detected at an early stage, treatment or prevention can start as soon as possible. An example of such a population screening programme is new-born screening for severe metabolic conditions for which early treatment is available. Traditionally, population screening programmes were evaluated by weighing the benefits of early detection in people affected by serious disease against potential harms posed by screening on the population as a whole (94). As rapid technological advances in genetics and genomics challenged the suitability of the classic criteria, Andermann et al., (2008) adapted these to encompass genetic testing/screening programmes (95) The Health Council of the Netherlands issued criteria for genetic screening in 1994, taking into consideration the ethical, legal and psychosocial factors specific to genetic screening programmes (96). Such factors include the following: A genetic test result is not only relevant for the individual screened, but could also have implications for family members. In addition, availability of appropriate treatment is an irrelevant criterion for a carrier screening programme, given that carriers of AR conditions are not affected by this condition (97). Unlike other types of population screening, reproductive genetic screening sets out to identify individuals or couples –healthy individuals- who are not at increased risk of disease themselves to identify whether their chances of having children affected by genetic conditions are increased. Knowledge about their reproductive risks could give these couples or individuals the option to change their reproductive plans if they wished to do so. This type of genetic screening primarily aims to enhance people's reproductive decision-making, which refers to the concept of reproductive autonomy, and is discussed in more detail in section 1.4. Reducing the number of children born with severe genetic conditions could be considered a secondary benefit of this type of screening, and this has the potential to prevent suffering in future children and their families (97). As reducing the number of people born with a certain condition as the purpose of reproductive genetic screening is considered morally problematic (98), the outcome measure for reproductive genetic screening is different from other types of screening. Another commonly used and relevant framework to evaluate new genetic tests is the ACCE framework described by Burke et al., (2002) (99), which stands for analytic validity, clinical validity, clinical utility and ethical/psychosocial issues (99,100).

Evaluating the introduction of couple-based ECS for couples from the general population is not necessarily different from evaluating other reproductive genetic screening tests. As with any screening offer, benefits of offering the test should be weighed against potential harms and a continuous debate is required to define what is responsible (24). In contrast to communities where certain AR conditions are more prevalent, the demand for this test offer does not originate from within the community, and the design of the test offer is a more top-down, rather than bottom-up approach. Most people in the general population or health professionals providing these tests will not be familiar with many of the (rare) AR conditions included in an ECS test offer. Therefore, it is important to include all 'stakeholders', such as the intended target population, as part of the discussion as to what approach to ECS is responsible (24). What is unique about the ECS test offer I am studying is the approach to report couple results only. When investigating whether this ECS test offer would meet criteria for responsible implementation in a health care setting, assessment of the couple-based approach requires particular attention.

Recent advances in genomics allow carrier testing for multiple AR conditions simultaneously. This means that such testing is now possible for any couple thinking about having children. Whilst technology makes this possible, this does not mean that it should be offered or be available and reimbursed within public health care systems. Thus, these developments have raised questions and issues that are currently underexplored. In order to find out whether introducing couple-based ECS is indeed responsible and therefore ethically justified as a test offer to couples from the general population, evaluating the existing initiatives is an important step.

Several professional bodies have published recommendations regarding ECS (24,43), minimally pertaining to what conditions to include in disease-panels. These recommendations do not always align and defining such criteria is challenging given the complexity of the issues involved. In particular, criteria regarding the ethical, practical and psychosocial aspects are challenging to define. Existing frameworks, such as the Andermann criteria and the ACCE framework mentioned previously are useful starting points for determining what those criteria might be. Drawing on these frameworks, the ESHG published twelve recommendations to evaluate responsible implementation of ECS (24). These recommendations, summarised in Box 1.4 address ethical, practical, psychosocial and technical aspects for evaluating the introduction of ECS to couples from

the general population. They are thought to cover the key aspects for evaluating the introduction of ECS in the general population and they provide a useful background against which to develop discussion as to how to define what a responsible approach should be to offering ECS as a couple-based test. At the same time, the recommendations are rather broad, and lack the specificity to use them as a tool to establish whether a particular test offer is responsible or not.

Box 1.4 ESHG recommendations for responsible implementation

1. The primary purpose of carrier screening is inform individuals without a known family risk of recessive disorders about genetic disease risk in future offspring and the reproductive options available to autonomous choices
2. Priority should be given to ECS for early onset severe childhood disorders. Tests should have high clinical validity and established clinical utility and focus on sequence variants that clearly affect function
3. Before initiating ECS, an evidence-base should be established regarding: significance of screened variants, sensitivity and specificity of the tests, immediate and downstream costs of the test and screening offer, psychological and social impact, types of interventions that could improve informed decision making and public acceptability of carrier screening
4. ECS should, where possible, be offered before conception as this maximises reproductive options and has fewer time constraints, which is likely to be less stressful than during pregnancy
5. Effectiveness of ECS should be measured by assessing the extent to which it optimises informed choice and reproductive decision making
6. Attention should be given to psychological, social and counselling related aspects. Pre-and post-test counselling should be available. Post-test counselling by genetics professionals should be available. Public should be informed about the disorders and various aspects of carrier screening
7. Informed consent is challenging. New models for consent should be evaluated with regard to informed decision making for couples.
8. Participation should be voluntary, and informed, consent should be given freely with sufficient time to decide. There should be equity of access to testing
9. Genetic testing and counselling should be provided by accredited laboratories and appropriately trained professionals
10. Quality of care should be maximal and care should continue irrespective of couples choices to proceed with testing or their reproductive choices. Introducing ECS should not be used to reduce standards of care for children born with disease.
11. HCPs involved in providing the service should be adequately trained and the public should be educated to improve understanding of the complexity of genetic testing. There should be an open dialogue about benefits and harms with all stakeholders
12. Governments and public health authorities should adopt an active role in discussing the responsible introduction of ECS.

The following aspects of the recommendations were addressed in the research prior to this PhD. Validation and development of the UMCG ECS test took place prior to the start of this PhD by the accredited laboratory of the Genetics Department and the test only included early onset severe conditions (recommendation 1). Research was conducted amongst the target population and a public debate was organised to involve the general public in discussions around the acceptability and desirability of this type of screening. In addition, preferences regarding test provision (recommendation 3) were explored amongst potential providers as well as the target population. This resulted in a clinically relevant couple-based ECS test consisting of 50 severe, early onset, AR conditions. The GP was considered as the most suitable provider. To support GPs in providing pre-test counselling, a training and materials to use during pre-test counselling were developed prior to the start of this PhD research (recommendation 9+11). Based on the previous research and gaps in the current

scientific literature, I identified the next steps regarding couple-based ECS implementation to couples from the general population to address in Phase 1 and Phase 2 of this research and link these to the recommendations provided by the ESHG (24).

1.3.1 Gaps in the literature addressed in this PhD research

- Previous research on ECS focussed on a real-world test offer in high-risk groups, or on a hypothetical test offer in a population without increased prior risk. I set out to investigate whether the intention of the target population to take part in couple-based ECS reported in a hypothetical scenario could be confirmed when ECS couple-testing was actually offered to Dutch general population (recommendation 3+4) in an implementation pilot setting.
- Couple-based ECS could be considered a form of reproductive genetic screening. Unlike other types of population screening, reproductive genetic screening sets out to identify healthy individuals or couples who are not at increased risk of disease themselves. Rather, as a couple, their chances of having children affected by genetic conditions are increased. That is why I aimed to examine whether couples were able to make informed choices regarding taking part in this type of testing (recommendation 5).
- Potential harms of a couple-based ECS test offer include adverse psychological outcomes in couples who are offered this type of testing. I examined psychological outcomes in those receiving the test offer (recommendation 3).
- A test offer provided by the GP was preferred by the target population. As this would be the first time couple-based ECS would be offered in a primary care setting by GPs, I addressed whether this desired test-provision was feasible in practice and to the satisfaction of both couples and GPs (recommendation 6, 9, 11).
- One of the fundamental questions relates to whether adopting a couple-based approach reporting couple results only rather than (also) reporting individual carrier states for ECS is more appropriate. Previous research in a hypothetical scenario demonstrated that the target population did not object to this approach. Reporting couple results is not recommended which is why this concept needed to be explored in more depth.

I aimed to study these complex issues regarding a couple-based approach to ECS in a primary care and a fertility setting to build a comprehensive picture of how these changes are being perceived and how this type of testing could be introduced into a health care setting in a responsible way.

Here I attempt to define what a responsible approach to couple-based ECS as studied in this research might look like:

- Aim: A test offer is of clinical utility for informing reproductive decision-making and takes into account the wellbeing of future offspring and the alternative reproductive options after a positive test result are meaningful for couples and those using donor gametes (section 1.4)
- Taking part in couple-based ECS is based on an informed choice (section 1.5)
- The benefits in terms of reproductive decision making for couples undergoing the test outweigh the harms on the target population as a whole (section 1.6)
- The proposed approach is feasible in practice for non-genetics professionals (section 1.7)

This definition is in agreement with existing frameworks and published recommendations regarding responsible implementation of ECS for the general population. I return to the elements of this definition in Chapter 5, where I discuss to what extent couple-based ECS is responsible and ethically justified based on my empirical findings and provide recommendations for clinical practice and further research.

1.4 Reproductive choice and prevention of harm

In this section I focus on the notion of reproductive autonomy, as phrases such as 'enabling reproductive decision-making', 'enhancing reproductive choice', are often used to describe the purpose of ECS and as a justification for its introduction (24,43). At the same time, couple-based ECS also has the potential to prevent serious suffering for future offspring, if couples decide to avoid the conception of a child with an AR condition. However, of prevention is usually not explicitly mentioned as the purpose of carrier testing for reproductive risk (24,101) and may be considered problematic. I also compare preconception ECS to prenatal ECS and discuss the alternative reproductive options available to carrier couples.

The concept of autonomy and its use in medicine is complex; different authors define it in different ways; for example, O'Neill (2002) defines the concept of autonomy as "*someone's capacity for independent decisions and actions*"(102). Autonomy involves self-determination over one's life, one's body and the choices or decisions one makes. With respect to medical decisions, the British Medical Association (BMA) defines autonomy as follows: "*The right of competent adults to make informed decisions about their own medical care.*" (103). In this thesis, I have adopted the following working definition for reproductive autonomy regarding couple-based ECS:

'Couples and individual's capacity to make informed and meaningful reproductive decisions using couple-based ECS'

Reproductive autonomy is often linked to reproductive freedom or procreative liberty, which is characterised as the right to control one's own reproductive life without coercion (102). Procreative liberty is considered an important moral right which, according to Robertson, should be given presumptive priority. That is to say, whether to reproduce or not is of such personal importance that only the person concerned is best placed to make that decision (104). Reproductive freedom means that individuals are able to exercise control over whether to have children, how many children and when to conceive these children. The extent to which couples or individuals can exercise their right to reproductive freedom depends on whether this is considered a positive or a negative right. A positive right means that it should be facilitated by others (such as the state). A negative right means that there is no obligation on others, but individuals (or couples) should still be allowed to exercise this right. An example of exercising a negative right regarding reproductive autonomy could be the following. Couples or individuals who cannot conceive naturally, could still access private fertility services, if state-funded fertility services are not available. In addition, couples or individual can exercise their right to avoid conception to some extent, by using inexpensive or free contraception and safe abortion services in both the UK and Dutch health care systems. The use of reproductive genetic technology for selective reproduction, i.e. the choosing of characteristics for future children such as sex, is more restricted. Couple-based ECS in this context could be considered a negative reproductive right.

Technological advances such as couple-based ECS also give prospective parents a choice over certain characteristics of their future children before conception. Yet, whether these

reproductive 'choices' should be seen purely in light of a right to self-determination regarding reproductive decisions is questioned by O'Neill (102). I agree with O'Neill's argument that given that the aim of reproduction is to bring a child into the world, whose future depends on its prospective parents, it is important to consider how any decisions affect future offspring. Moreover, in order for a choice to enhance autonomy, it should have some meaning or to put it another way, people should be able to act upon their choice. O'Neill illustrated this succinctly with *"Whatever else people think about individual or personal autonomy, they do not equate it with mere choice"*(102). Therefore, it is important to evaluate whether the options that are available to carrier couples are indeed meaningful regarding their reproductive decisions, but also how these affect the health and wellbeing of their future child. In the context of couple-based ECS, it is also interesting to consider what/ how autonomy should be conceptualised when the couple often consists of two individuals, who need to make an informed decision together, regarding their future offspring.

Thus, couple-based ECS should not only be evaluated in light of reproductive decision-making for couples, it is also important to evaluate the impact of such a test offer on the health of the future child. Given that approximately 1% of couples are carriers of the same AR condition, would this mean that it is reasonable to expect all couples to consider undergoing couple-based ECS for severe AR conditions?

1.4.1 Do prospective parents have a responsibility to consider undergoing couple-based ECS?

Bonte et al., (2014) attempt to provide an answer to the question as to what extent couples have a moral duty to undergo genetic testing to avoid the conception of a child with a severe genetic condition (105). The authors suggest that preconception responsibilities depend on several principles: reasonable foreseeability, adequate control, adequately proximate causation, proportionality, and reasonable prudence (105). In summary, these principles mean that depending on how likely it is that a couple intends to conceive in the short term, and the higher the a priori risk of having children affected by a genetic condition, the more couples have a moral duty to undergo carrier testing. Whilst many people in the general population may be unaware of their chances of conceiving children with recessive conditions, this does not necessarily mean that they do not want to be

informed. However, if couples make it clear that they do not wish to receive any information about possible risks regarding their reproductive future, those wishes should be respected in light of their 'right not to know'.

Van der Hout et al., (2018) discuss a responsibility of prospective parents to consider undergoing ECS and avoiding the conception of a child with a severe condition and referred to this as procreative non-maleficence (106). These authors argue that when couples find out about their increased risk before conception, avoiding the conception of children with severe genetic conditions could be an acceptable justification for offering ECS, whereas it would be ethically problematic to say that couples who are pregnant with a child that is affected by a genetic condition should undergo a termination. Nevertheless, as van der Hout et al., (2019) state, parents may have conflicting moral considerations, e.g. whether they think using IVF and PGT-M is acceptable, that override this responsibility to avoid the conception of a child with a severe genetic condition. Taken together, if ECS is offered as a couple-based test for severe conditions to couples from the general population who think about conceiving in the near future, it could be argued that they have a responsibility to consider undergoing ECS prior to conception to prevent suffering in future offspring. Whether they decide to proceed with testing is up to them and may depend on their views of the alternative reproductive options available.

1.4.2 Prevention, the disability critique and eugenics.

Prevention is usually not explicitly mentioned as the purpose of carrier testing for reproductive risk (24,101). There are a number of reasons for this: 1) fear of eugenics and 2) the views of disability rights advocates or the expressivist argument.

As Buchanan et al., (2002) describe, in the late 1800s, beginning of the 20th century, Francis Galton, Charles Darwin's cousin, initiated a global eugenics movement. Eugenicists believed in the heritability of behavioral traits and intended to use the 'new genetics' to prevent degeneration of the population. When force or coercion are employed to restrict reproductive freedom for societal goals, eugenics is clearly morally problematic. For example, in the United States, forced sterilisations took place to prevent the 'unfit' from reproducing. In Nazi Germany, eugenics became a justification for the morally apprehensive policy of racial hygiene (107). In contrast, Caplan et al., (1999) defined eugenics as using genetics for 'the goals of obtaining perfection, avoiding disease, or

pursuing health with respect to individuals [without the] need [to] involve coercion or force'(108), which is more applicable to this discussion about eugenics and carrier testing. Wilkinson poses the question as to whether Caplan et al.,'s interpretation of eugenics might not be morally problematic and even desirable if it aims to prevent suffering from severe genetic conditions (109).

The expressivist argument states that genetic testing to prevent the birth of children with a disability sends a negative message about the value of the lives of those already living with a disability and their right to exist (107,109). In addition, parents of children with a disability might experience societal pressure and feel they are held 'responsible or accountable' because they could have prevented their child's birth. If most couples choose to avoid having a child with a genetic condition after a positive ECS couple result by terminating an affected pregnancy, this could be interpreted as if the lives of those living with a disability are worth less. Some have argued, against the expressivist argument, that if a woman or couple decides to terminate an affected pregnancy, it does not necessarily follow that they do not value individuals living with this disability. As explained by Buchanan et al., (2002): *"It is not the people with the disabilities that we devalue, it is the disabilities themselves"*(107). Apart from preventing the future child from having a disability, other reasons to avoid the birth/conception of a future child may include wanting to avoid strains on the relationship, protecting the welfare of other siblings in a family, or not being able to provide for the child with disabilities financially or emotionally. None of these necessarily send a negative message about the value of the lives of people with a disability.

If couple-based ECS becomes routine practice for all couples planning a pregnancy, we might suspect that most couples who decide to have a carrier test will act on a positive result by avoiding the birth of a child with that condition. The population screening programmes for Tay Sachs (83) and haemoglobinopathies (110), have meant that the incidence of these diseases has decreased dramatically. Avoiding the term prevention as an aim for genetic testing would be unnecessarily politically correct, when in certain circumstances, it can be justified or might even be ethically desirable to prevent the conception of children with severe genetic conditions. Defining what constitutes the suffering for which genetic testing could be justified is, however, complex. To prevent reoccurrence of immoral eugenics, safeguards i.e. voluntariness of a screening programme (111) and facilities for those with a disability, should be put into place.

An example as to how ECS could be offered to benefit the health of future offspring is carrier testing for metabolic conditions included in NBS which could be lethal before the NBS test results are known. If these conditions are included in ECS, measures can be put in place immediately after birth to ensure the right treatment is provided. On the other hand, if couples are aware of their couple carrier status prior to conception or during pregnancy, they may consider to avoid the birth/conception of a child affected by such a (treatable) condition.

1.4.3 Alternative reproductive options for preconception and prenatal ECS

Whilst carrier testing is possible at any time in one's reproductive life (112,113), the two stages at which an ECS couple-test is most likely to be of clinical utility is either during pregnancy or preconceptually. There are relevant differences between prenatal and preconception ECS and preconception testing has several advantages. The differences are related to for instance the reproductive options available after a positive test result, the health professionals involved in test provision (i.e. midwives/obstetricians/fertility staff; or GPs) and access to care.

Most importantly, a positive couple result before conception allows for more reproductive options than during pregnancy. At that stage, there are only two possibilities: 1) to find out whether the fetus is affected – and consider termination of the pregnancy (TOP) or prepare for the birth of their affected child- or 2) to run the risk of one in four of having an affected child. Another advantage of testing at the preconception stage is that the decision to have a test is made under less time pressure. Procedures for both prenatal diagnosis and abortion are more invasive later in pregnancy than at an early stage. Whether all the reproductive options are actually available to carrier couples depend on various factors. Access to additional services for ART, including PGT-M, or prenatal testing not only depend on what services are available in a particular clinic, but these procedures are bound by professional guidelines or legislation and available funding within a public health care system (114). Fertility treatment packages that are available through the NHS for example, depend on the commissioning of funds in a particular area. In a public health care system, funding to support fertility treatment including PGT-M might be unavailable to carrier couples, if commissioning groups decide not to allocate the available budget to these services. In Southampton, one IVF cycle is NHS funded (115), whereas other areas comply

with National Institute for Health and Care Excellence (NICE) clinical guideline, which recommend funding three IVF cycles (116):

"In women aged under 40 years who have not conceived after 2 years of regular unprotected intercourse or 12 cycles of artificial insemination (where 6 or more are by intrauterine insemination), offer 3 full cycles of IVF, with or without ICSI. If the woman reaches the age of 40 during treatment, complete the current full cycle but do not offer further full cycles." p24

How meaningful reproductive options such as prenatal testing or PGT-M are for couples undergoing couple-based ECS, depends on various factors including the laws allowing these procedures and a couple's view as to whether they think these are acceptable options for them. Embryo-selection is not available for all AR conditions. For example, in the UK, the criteria for PGT-M are defined in the Human Fertilisation and Embryology Act (2008), and conditions are licensed by the Human Fertilisation and Embryology Authority (HFEA) (117). In the Netherlands, PGT-M is available in one academic center (Maastricht). A national committee called the 'Landelijke Indicatiecommissie PGD' (established in 2009) decides whether it is ethically and socially acceptable for a condition to be included for PGT-M.

When receiving a positive couple result, switching partner does not seem to be a particularly desirable option for couples who are planning to have children together, apart from a match-making situation as Dor Yeshorim. An interesting 'type of couple' in this respect is the gamete-donor/recipient couple. For those using anonymous sperm or egg donors, it might be possible to switch gamete provider without any implications -provided enough suitable donors are still available. For any other couple using their own gametes to conceive, the stage of their relationship at the time of testing might affect how they view this possibility. Fertility treatment is an emotionally and psychologically challenging process (118,119). Couples who do not require fertility treatment to conceive might try and conceive naturally and opt for prenatal testing first, if they wish to avoid having a child affected by the AR condition, rather than choose IVF and PGT-M. When no meaningful options are available to couples who would want to avoid having an affected child in case they are a carrier couple, knowledge about the test result might *compromise* their reproductive autonomy. In this case, any couple or individual might be better off trying to conceive without knowledge of their couple-carrier status. A negative couple test does not guarantee healthy offspring and might convey a false sense of reassurance if couples do

not understand this residual risk. Given the complexity of this decision making, pre-and post test counselling should be offered to all couples who consider undergoing couple-based ECS to facilitate informed/autonomous decision making (24).

Lastly, not all pregnancies are planned (120) and currently couples are more likely to access prenatal health services than seeking advice from HCPs before conceiving (121). This means that not all couples are aware of the benefits of couple-based ECS prior to pregnancy. On the other hand, couples may also simply not be interested yet in thinking about health risks in future offspring before pregnancy, whereas they would be interested in this during pregnancy. Thus, whilst testing prior to pregnancy seems more optimal, in practice this type of testing may happen and be beneficial for couples both at the preconception and prenatal stage.

1.4.4 Rights of the pregnant woman and the moral status of the embryo and fetus

Whether couple-based ECS takes place prior to conception or during pregnancy affects the question as to the moral status of the pregnant woman, the couple and the fetus. For preconception ECS the moral status of the fetus is not a concern at the time of testing. How one perceives this moral status during pregnancy will affect the ethical acceptability of genetic testing for reproductive purposes and the available reproductive options. For instance, whether prenatal testing or IVF are indeed options for a couple. As such I will outline the most common arguments in this debate.

The fundamental issue of personhood relates to how the moral status of an embryo and fetus compares to that of the pregnant woman (122). I will adopt Singer's definition of human person: a rational and self-aware or self-conscious being and a member of the *Homo sapiens* species (122). If one accepts that a fetus has some moral status, a tension arises between their rights and those of the pregnant woman. In particular the woman's right to reproductive autonomy, self-determination and bodily integrity in so far as it impacts on the fetus or embryo. Arguments around at what moment life begins, and therefore what rights should be assigned to the fetus, affect the acceptability of using prenatal testing and IVF. The acceptability of using IVF does not only concern the couple or pregnant woman, but also affects the health professionals involved in creating babies, as they have a professional responsibility to protect the wellbing of the future child. If a couple, or individual, believe that life starts at conception, neither IVF nor abortion would

be viewed as acceptable: the fetus is seen as a human being from this point and therefore has equivalent rights to life (123). IVF is seen as problematic given that usually only one or two out of several embryos will be implanted in the uterus. The 'left-over' embryos are discarded or used for scientific purposes (124). From this perspective, both IVF involving 'left-over' embryos and abortion are considered acts of murder and therefore morally wrong (125–127).

Some individuals or couples who would like to conceive may believe termination of pregnancy or the use of ART is not necessarily morally wrong. They might argue that the fetus gradually gains moral status, therefore, an early term abortion might be morally acceptable, whereas a late-term termination is considered morally problematic. Defining the moral status of a fetus in this case is more complex, because it is difficult to pinpoint when personhood starts. Different milestones have been suggested: viability, or the capacity for independent survival outside the uterus; birth and the beginning of consciousness or sentience. Each of these are problematic (122). For example, if viability is the point up to which an abortion is permissible, this is determined by the current state of medical technology. In the West, technology now enables survival of neonates at 22 weeks gestational age, which would not be the case in lower and middle income countries, or in the West twenty years ago. Should having moral status be dependent on available technology?

Similarly, if the level of consciousness is what confers personhood, the stage of brain development would define the moral status of the fetus. Evidence from studies on fetal brain development show that the fetus mostly exists in a sleep-like state and is not conscious. Important neurons related to consciousness -thalamocortical connections- are established between 23-35 weeks of pregnancy and this is the stage at which a fetus might be able to process sensory input. Pain reflexes might already be present a few weeks earlier (128).

When ECS is offered to couples who would like to have children, it is important to discuss their views related to abortion, because these influence the available reproductive options after a positive result. Procedures for both prenatal diagnosis and abortion are more invasive later in pregnancy than at an early stage. Termination of pregnancy is decriminalised under certain circumstances covered in the Abortion Act (1967) for England, Scotland and Wales (129) and legally permitted as a medical procedure in the Netherlands

up to 24 weeks (130,131). A fetus does not have any legal rights until after birth in both jurisdictions. In both the UK and the Netherlands, abortion is available up to term if certain requirements are met. Box 1.3 depicts the criteria of the Abortion Act (1967) for England, Scotland and Wales. Dutch criteria are similar and are summarised in Box 1.4.

Box 1.5 Abortion Act 1967

Medical termination of pregnancy. Abortion Act 1967 E+W+S

(1)Subject to the provisions of this section, a person shall not be guilty of an offence under the law relating to abortion when a pregnancy is terminated by a registered medical practitioner if two registered medical practitioners are of the opinion, formed in good faith—

(a)that the pregnancy has not exceeded its twenty-fourth week and that the continuance of the pregnancy would involve risk, greater than if the pregnancy were terminated, of injury to the physical or mental health of the pregnant woman or any existing children of her family; or

(b)that the termination is necessary to prevent grave permanent injury to the physical or mental health of the pregnant woman; or

(c)that the continuance of the pregnancy would involve risk to the life of the pregnant woman, greater than if the pregnancy were terminated; or

(d)that there is a substantial risk that if the child were born it would suffer from such physical or mental abnormalities as to be seriously handicapped.

Source: http://www.legislation.gov.uk/ukpga/1967/87/contents [accessed 12-11-2019]

Box 1.6 Dutch Criteria for Late Term Abortion

Dutch Criteria for Late Term Abortion

- The unborn child must have a disorder so serious that medical experts believe that medical treatment following the birth will be futile. There must be no doubt about the diagnosis and prognosis;
- The unborn child must be suffering, or must be likely to suffer following its birth, with no prospect of improvement;
- The mother must make an explicit request for the pregnancy to be terminated on the grounds of the physical or mental suffering the situation is causing her;
- The physician must have given the parents a full explanation of the diagnosis and prognosis. This means that both the physician and the parents must be convinced that there is no reasonable alternative solution given the child's situation;
- At least one other, independent physician must have examined the child and given a written opinion on compliance with the due care criteria listed above;
- The pregnancy must be terminated with all due care.

Source:
https://www.government.nl/topics/euthanasia/euthanasia-and-newborn-infants [accessed 12-11-2019]

1.5 Facilitating informed choice and uptake

One of the main roles for genetics professionals is to facilitate decision-making when couples or individuals are faced with complex decisions regarding genetic testing/screening. Genetic counselling has been defined as: 'the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. This process integrates the following:

- Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence
- Education about inheritance, testing, management, prevention, resources and research

- Counselling to promote informed choices and adaptations to the risk or condition'(132)

Given the challenges of facilitating informed decision making for couples considering ECS, Henneman et al., (2016) recommend that all research which introduces ECS should include informed choice as an outcome measure to evaluate couples' informed decision-making (24). One commonly used definition of informed choice proposed by Marteau et al., (2001) is that the decision is consistent with people's values and based on sufficient knowledge (133) which can be operationalised quantitatively by combining a measure of knowledge, attitude and behaviour (test-uptake or test-decline). The Multi-Dimensional Measure of Informed Choice (MMIC) by Marteau et al., (2001) is a widely used validated measure in research on prenatal screening for Down's syndrome (133,134).

Couples need to weigh up a range of factors before deciding to participate. That is why counselling about ECS would for example include the meaning of being a carrier information about the test (conditions, test-accuracy, and purpose), the risks of having a positive result, the benefits and harms of testing and a discussion of the implications of a positive and negative result (135). Psychological reactions to the test offer, social and relational factors are also likely to be relevant aspects of genetic counselling prior to deciding about an ECS-offer. Due to the complexity of this decision-making, couples may experience feelings of (anticipated) regret or decisional conflict before and after making a decision about accepting a couple-based ECS test offer.

What makes pre-test counselling for couple-based ECS particularly challenging, is that it is clearly not feasible, time and resources wise, to discuss all conditions individually. In addition, if all conditions were discussed one by one, couples may feel overloaded with information. To overcome this limitation for genome wide approaches to genetic testing, various models of informed consent have been proposed. When using a generic consent approach, conditions in an expanded test could be described in general terms (136). Whereas generic consent overcomes the limitations of discussing every condition individually, there is a risk of oversimplifying, depending on what conditions constitute the test panel. Alternatively, a tiered approach -presenting information about conditions as part of separate categories- might be a more feasible alternative (49). This resembles the 'binning' approach for consent about disclosure of additional or incidental findings: these are placed into different 'bins' based on the actionability of the result (137). Several studies

have sought an appropriate method for a tiered-approach to consent for ECS using categories based on severity of the conditions (49,138,139). This is complicated, because HCPs might not have any experience with some of the rare conditions included in ECS. Leo et al., (2016) proposed a classification system validated by women who had undergone carrier testing previously (140). Others have asked professionals to rank severity criteria based on disease characteristics (49). However, using the average ranking by HCPs to classify conditions could be problematic, as it does not represent the disease spectrum, or worst case scenario, and lacks information as to whether professionals reached consensus. The HFEA have taken the approach where conditions are licensed for PGT-M based on the worst case scenario. Subsequently, the clinical team decides whether PGT-M is warranted for licensed conditions in individual scenarios.

Other concerns relate to the level of understanding that is required for making an informed decision and the extent to which health professionals have a duty to ensure this level is met. Corrigan (2003) suggests that the focus on the informational aspects of consent leads to 'empty ethics' if the social context and relational aspects of decision-making are overlooked (141). To shift the focus to a more collaborative process, Samuel and Dheensa et al., (2017) proposed taking a virtue-ethics approach for consent in clinical genetics. This collaboration is based on HCPs' characteristics such as trustworthiness, openness and honesty (142). However, this approach requires a good HCP-patient relationship. When non-genetics professionals such as GPs offer couple-based ECS, the relational aspect of the collaborative process is likely to be present more, than when tests are offered in a one-off conversation.

Consent is a means through which autonomous choice for health care decisions is embedded in the law and professional guidelines. Legally, consent is valid only if a person giving consent has capacity, if the person's decision is informed and if underoing a genetic test voluntary (143). Even though it is important, it does not mean that if consent is obtained, this will guarantee an ethically high standard of care (144). The notion of consent needs to be considered alongside other standards of ethical practice. These include HCPs' duties towards patients, such as to prevent patients from harm and provide safeguards against discrimination or unfair treatment (144). Consent for clinical genetic testing is a complex process and its scope is different from other clinical situations, as a genetic test result might have implications for family members, and due to the increase in technological

possibilities, findings might be unanticipated (142). In summary, facilitating informed decision-making for ECS is challenging, due to the complexity of the information, the debate around what consent is most appropriate and the question as to what constitutes an informed choice in this setting.

1.5.1 Uptake of couple-based ECS

Whilst for population screening with the purpose of early detection and prevention a high uptake is considered an indicator of success, for reproductive genetic screening aimed to enhance couples' reproductive decisions, this is different. In most Western societies, reproductive genetic screening is not offered for public health benefits, and therefore the purpose of this type of test offer is not to have a high uptake of screening. Rather, the number of couples who make an informed decision, i.e. a decision that is consistent with their values and based on sufficient information (133) is recommended as an outcome measure of this type of screening. Uptake itself could be conceptualised more as an indicator of interest from the target population. Uptake figures are informative because they demonstrate whether actual uptake reflects couples' intentions and could highlight potential barriers in test accessibility.

Uptake is also informative because it enables an exploration of who decides to take part in this type of testing. Studies on reproductive genetic counselling and testing demonstrate that often, this type of screening is accessed more by people with a higher socioeconomic status (145,146). Unequal representation of couples from the target population is problematic if couple-based ECS is not accessible to all couples who would like to make use of this type of testing and if information leading to informed choice is not equally available or sufficiently understood to make a decision.

In order to prevent the introduction of a genetic test based on 'supplier push', rather than consumer demand, it is important to investigate why couples would accept a genetic test such as ECS. De Wert et al., (2012) suggests that societal pressure to have a test is a more plausible risk threatening reproductive autonomy than the fear of a recurrence of eugenics through government coercion (111). Future studies could look into the what extent this also applies to couple-based ECS. If the aim of couple-based ECS is defined as enhancing couples' reproductive decisions, research could identify factors that might restrict autonomous decision making or decisions that are based on unrealistic expectations or the

wrong information. For example, studies have shown that difficulty in refusing a test offered directly by a health care provider, or willingness to contribute to research resulted in a higher uptake of carrier testing for CF (147). This is why in a study by Metcalfe et al., (2008) for Fragile X carrier testing, participants were not allowed to give a blood sample at the time of pre-test counselling, but only after having had some time to think about their decision (148). Factors affecting acceptance or decline of an ECS test offer might be different to single-gene carrier testing, because couples will not be familiar with most of the conditions included in couple-based ECS. Intention to accept a test might differ from actual uptake, for example if people perceive the time and effort it takes to participate in testing as a barrier (149).

1.6 Balancing harms and benefits

Benefits of undergoing ECS include being more informed regarding reproductive decisions. Furthermore, carrier couples may consider using alternative reproductive options; non-carrier couples may feel relieved that they are not at increased risk of having children affected by those recessive conditions included in the test. Potential harms of such an ECS test offer to the general population could include adverse psychological reactions, such as feelings of distress and decisional uncertainty, but also negative social implications like a feeling or fear for discrimination or stigmatisation of those identified as a carrier (couple). Potential harms of a couple-based ECS test offer to couples from the general population have been expressed regarding over-medicalisation of the preconception period and a social pressure to undergo reproductive genetic screening.

Potential negative effects of an ECS test offer could be feelings of psychological distress such as anxiety or worry for both those accepting as well as those declining this offer. First, receiving an ECS test could confront eligible couples with unsolicited information about the risks of having a child with rare severe genetic disorders, which may result in psychological distress and challenges couples' right not to know. Attending pre-testing counselling, and giving a blood sample may also cause psychological distress (24,67,73,150). Third, receiving a positive couple carrier result has the potential to cause stress and anxiety (73,150,151). The decision-making process regarding participating in ECS and other types of reproductive genetic screening is complex and could lead to feelings of decisional conflict or (anticipated) regret (12,152) emphasising the importance of pre-test counselling.

Several studies have reported that participants were worried or anxious about their results shortly after a positive result was disclosed, but that genetic counselling has the potential to decrease the stress or anxiety. Studies investigating the psychological outcomes associated with an actual population based ECS offer by non-genetics health professionals have not been published yet. A recent US study by Kauffman et al., (2018) reported that a normal ECS test-result is associated with favourable psychological outcomes (153). No studies (as far as I am aware) have been published to date which report on the psychological outcomes of couples who were offered ECS, but decided not to proceed with testing. Earlier studies demonstrated that carrier screening for (mainly) single, or a few conditions is not associated with major adverse psychological reactions and initial feelings of psychological distress mostly dissipate over time (67). A recently published review on reproductive decisions for those identified as carrier couples demonstrates that most couples decide to change their reproductive plans to avoid conceiving a child with a severe genetic condition (154).

1.6.1 Social implications

1.6.1.1 Over-medicalisation of the preconception period, normalisation of testing

Whether inviting the target population could be harmful, depends on how the test is presented to the target population and whether the information presented is considered a burden or helpful. Concerns have been raised about ECS's potential for medicalisation of pregnancy (155). For couple-based ECS, this would mainly refer to medicalisation of the preconception period. Technology increasingly determines our lives and our health care. The same holds true for the pathway from conception to antenatal care to childbirth. This medicalisation of pregnancy and childbirth was defined by Oakley as "*the process whereby a particular area of social behaviour (pregnancy) comes to be separated off from social behaviour in general and reconstituted as a specialist, technical subject under the external jurisdiction as some expert authority.*" (156). An example of technology in a reproductive setting is the use of ART to help couples conceive who cannot reproduce naturally. Medicalisation of pregnancy is different from other technologically controlled aspects of our lives, as it has been criticised as a way to control women's reproductive lives (156). Some aspects of antenatal care, such as prenatal screening, could be considered as defining all pregnancies, thus not only those at high risk of maternal or infant mortality, in terms of

potential pathology and away from women's lives and social context (156). Couple-based ECS aims to identify couples without a known prior increased risk of being a carrier couple. A positive test result will most likely result in a medical trajectory to conceive a child without the recessive condition, if for example carrier couples decide to use IVF and PGT-M or prenatal diagnosis to avoid having a child affected by a genetic condition. On the other hand, if a child is born and is affected by a recessive condition unexpectedly, the life of the child and its family are also likely to be highly medicalised. Concerns regarding an ECS test offer regarding over-medicalisation of the preconception period might be of lesser concern to couples who use ART, as for these couples, conception is already a medical and often costly process to overcome unwanted sub-or infertility.

The more tests are routinely incorporated within the health care system, the more likely it is people assume that these are 'the normal thing to do' (157). Public campaigns to raise awareness about a new technology enable patients to make better informed decisions, but could also enforce this view (38). In the discussion about NIPT, prior to its implementation, concerns were raised about this routinisation, which are also likely to apply to couple-based ECS (24,52,111). Others were concerned that directivity of counselling towards accepting the test would become more directive rather than non-directive and would 'erode' informed choice (158). Explanations as to why this might happen include lack of adequate training or available time for counselling (159). Several studies showed that these fears were not supported by evidence for prenatal reproductive screening (52,160).

1.6.1.2 Stigmatisation or discrimination

In contrast to previous approaches, an ECS can be offered to couples irrespective of ancestry or family history. Population or 'universal' screening of any couple has the potential to decrease stigmatisation or discrimination of people from certain ethnic backgrounds and improves equity in access to care (38,43), although several studies indicated that carrier status was not considered stigmatising (24,73).

1.6.1.3 A slippery slope towards designer babies

The increasing choice in reproductive genetic technology might imply that couples can 'choose' a wide range of features in their future offspring, such as athletic ability, musicality, or intelligence. Some may fear a slippery slope, where couples might want to select embryos or have a termination of pregnancy for a fetus' eye colour. It is interesting

to consider the implications of a (dystopian) future and how the decisions related to current technology affect the likelihood of such a 'Brave New World' scenario becoming reality. When genetic testing for reproductive purposes is freely available, Levitt suggests that choices and options need to be managed, especially if the choices are unfamiliar and the consequences could be serious (161). Clinical utility is arguably the decisive factor for tests offered in a public health care setting.

1.7 Feasibility of providing couple-based ECS to the general population

In order to offer couple-based ECS in practice, according to the preferences of the target population and HCPs, it seems likely that non-genetics professionals are most suitable to provide this type of testing. This raised the question as to whether non-genetics professionals have the skills and knowledge to provide this test type of testing. Appropriate support and training is required if non-genetics professionals take pre-test counselling, as many lack understanding of genetic mechanisms (37,162).

Another concern raised in the literature regarding a routine test offer referred to a potential strain on the existing (tertiary) genetic services for post-test counselling if many people choose to have these tests (37,44). Cultural and political barriers between other specialists and genetics professionals could influence the implementation of ECS (36,163). The body of literature around implementation science may provide some insight into how introducing couple-based ECS into primary care could investigated. Nilsen (2015) defined implementation science as 'the scientific study of methods to promote the systematic uptake of research findings and other evidence-based practices into routine practice to improve the quality and effectiveness of health services and care (164). For example, studying the facilitators (enablers) and barriers of new practices has been used to develop implemention frameworks to help introduce research into clinical practice (165). In addition, it is important to address implementation issues at different organisational levels.

1.8 Summary: Evaluating couple-based ECS in the general population

Recent advances in genomics allow carrier testing for multiple AR conditions simultaneously. This means that such testing is now possible for any couple thinking about having children. Whilst technology makes this possible, this does not mean that it should

be offered or be available within public health care systems. Thus, these developments have raised questions and issues that are currently underexplored and evaluating the existing initiatives is an important step. The overall research aim was to find out whether introducing couple-based ECS is indeed responsible, according to the definition proposed in section 1.3 and therefore ethically justified as a test offer to couples from the general population.

To address the overall research aim, a convergent mixed methods design was used, being a type of design in which quantitative and qualitative data are collected in parallel, analysed separately and then merged. The study was divided into two phases. Phase 1 was an implementation pilot of GP-provided couple-based ECS for couples from the general population in the Netherlands. Phase 2 was a qualitative study of HCPs' and couples' views and experiences of coupe-based ECS in a fertility setting in the UK. See Figure 1.2 for an overview of the two phases. The reason for collecting both quantiative and qualitative data is to provide a comprehensive picture of the different elements used to assess responsible implementation, including ethical, psychosocial and practical implications, of a couple-based ECS test offer for both HCPs and couples or reproductive age at no known prior increased risk. In Chapter 2, I discuss the methodological approach and choice of methods for Phase 1 and 2.

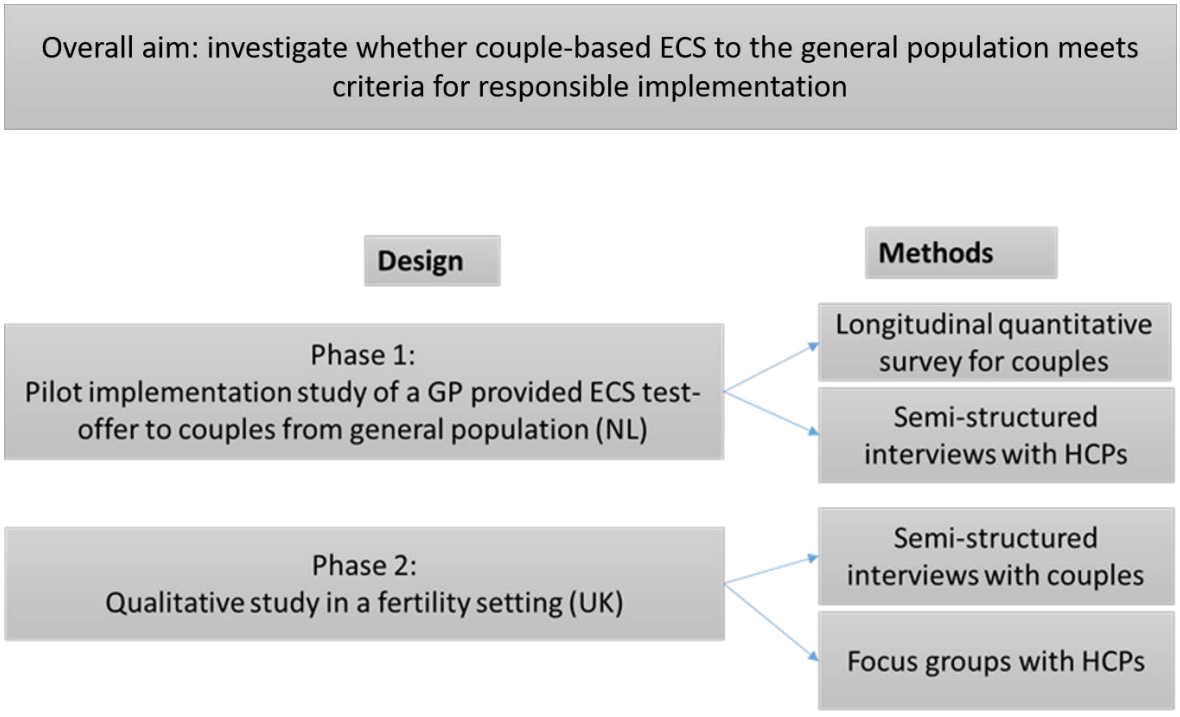

Figure 1.2 Overview of Phase 1 and Phase 2 of this PhD research

Chapter 2 Methodology and Methods

2.1 Chapter outline

The purpose of this chapter is to outline my methodological approach and choice of methods. My overall research objective was to explore the ethical, practical and psychosocial implications of couple-based expanded carrier screening (ECS) for couples without a known increased risk of having children affected by AR conditions based on family history or ancestry, to ensure whether it can be introduced in a responsible way in a health care setting. The research was conducted as a mixed methods interdisciplinary project and consisted of two phases. The first phase was an implementation pilot of couple-based ECS provided by general practitioners (GPs) to address uptake, feasibility and psychological outcomes in a primary care setting. Data was generated through a combination of quantitative and qualitative methods. In the second phase, I focused on the ethical issues and practical implications of couple-based ECS in a fertility setting and aimed to explore the views and experiences of patients and health professionals (HCPs) on the ethical issues and practical implications of couple-based ECS in this setting using a qualitative interviews and focus groups.

2.2 Methodological approach

Any research is shaped by the basic set of beliefs researchers hold about the world (166,167). This worldview is sometimes referred to as a research paradigm (167). These beliefs reflect how researchers perceive the nature of what is being studied (ontology); what can be known about what is being studied and the researchers' position in relation this knowledge (epistemology); and how researchers generate the knowledge to answer their research questions (methodology) (167,168). Researchers' views on the nature of what is being studied and what can be known about it determine how research is designed and conducted, what findings are produced and how these should be evaluated.

The positivist tradition, which used to dominate scientific inquiry (167), reflects the view that there is one reality, with an independent existence, waiting to be 'discovered' by the researcher through quantitative methodologies such as scientific experiments. Experiments

are designed in an attempt to exclude any bias that might influence the results. In the postwar era, positivist research was criticised for being too reductionistc, stripped of context, and therefore less relevant for application in the real world. In this research, the 'real world' is represented by, amongst others, HCPs and patients who are part of two health care settings where couple-based ECSis offered: primary care provided by GPs and fertility clinics. Post-positivisism developed as a response to criticism, reflectinga critical realist ontological position. A critical realist stance still maintains that there is one reality, independent of our observation but, in contrast to positivism, post-positivists would argue that that this reality can only be imperfectly and probabilistically known. Whilst quantitative methods are often prioritised and post-positivist research in health care settings may still aim to make generalisable claims, qualitative approaches are increasingly used to contextualise research and increase its applicability to practical, real life situations (167). Post-positivist research wa are considered the 'natural heir' of positivist research (167) and dominated, social scientific inquiry until the 1980s (166). Currently, research paradigms cover a much wider range of perspectives. For example, constructivism and interpretivism are associated with a relativist ontological stance. A relativist holds the view that multiple realities co-exist, which are constructed by individuals or social actors, where no reality is more truthful than another. Research paradigms now more often emphasise more qualitative approaches that promote inclusion of values and ethics as part of the research process (167). Patient involvement in research could be seen as an attempt to mark more ethical ways of conducting research; for example, patients' experiences of a particular condition make them experts in understanding their symptoms and identifying gaps in knowledge relating to the management of their condition (169). Including patient experiences in the design process of medical research has the potential to improve the relevance of the research questions that are addressed and therefore the quality of the research outomces. An overview of currently existing/prevalent research paradigms can be found in Table 2.1.

Epistemological stances can be characterised by the extent to which knowledge is objective or subjectve, and how researchers are positioned in relation to the knowledge that is generated. A positivist would consider knowledge to be objective and the researcher remain detached from the research process to eliminate bias. More subjective epistemological stances, for example those of constructivism, are associated with the meaning of certain

social phenomena as constructed through the participants' perspective. As a consequence, research conducted through a more subjective lense most often utilises qualitative methodologies. The role of the researcher in this approach is to facilitate construction of scientific knowledge by/with the research participant and to some extent, provide their own interpretations of the meaning participants attach to certain phenomena (168).

Some perspectives regarding the nature of what is being studied and what can be known about what is being studied may overlap, and research in the real world cannot always be captured from within a given research paradigm (168). For example, Maxwell et al., argue that some mixed methods research could be informed by a realist ontological perspective and a moderate constructivist/interpretivist epistemological stance (170). However, ontological and epistemological perspectives derived from different types of scientific traditions such as the natural sciences or the social sciences may also conflict with each other, precisely because of the differences in views of reality and how knowledge is preferably constructed. For example, approaches to studying the concept of ethnicity in relation to preconception screening are likely to be very different between a molecular geneticist who is interested in this concept as a predictor of reproductive risk and a sociologist who seeks to understand how this is used by couples planning a pregnancy.

A more recently proposed approach to research is that of pragmatism, which cannot be easily placed within the philosphical paradigms/traditions. Rather than to discover reality, or create meaning through people's perceptions or interpretations of a social phenomenon, for pragmatists, the purpose of the research is to have a positive impact on what is being studied: 'To gain knowledge in the pursuit of desired ends'(166). This means that pragmatists are not committed to a specific epistemological or ontological position, but the research problem as such shapes what methodology and method is considered most appropriate to address a given problem (171). Both qualitative and quantitative approaches can be suitable from a pragmatist standpoint, as long as they produce the knowledge relevant to answer the research question, which is why mixed methods methodology is often adopted for pragmatic research projects. It is important to consider how the mixing of methods/methodologies makes sense as part of the 'intellectual puzzle' the research project aims to unravel and still be of use in practice (168).

As someone who started out with a background in life sciences and clinical medicine, where it is uncommon to discuss these issues, reflecting on the philosophical underpinnings of this research was quite challenging for me. Most research that was familiar prior to starting this PhD was quantitative. In the (bio) medical sciences, discussion often focuses on the appropriateness of various quantitative methods rather than on the philosophical questions regarding the nature of what is being studied or a theory of knowledge. Interestingly, during my medical degree, I was asked to conduct an interview on patients' experiences of their journey as cancer patients. This interview made me realise that patients' lived experiences can actually provide invaluable insight into clinical care and research. Thus, I learnt that both 'words' and numbers or a combination of the two can constitute valid knowledge for research which aims to have a positive impact in health care. What I can know about couple-based ECS implementation and how I can know about this is constrained by what I consider to constitute the 'real world' of what I aim to study and what can be known about it.

I believe that there is a reality 'out there' and empirical methods such as qualitative and quantitative approaches can be used to uncover an imperfect view of this reality, consistent with a critical realist perspective. I believe that the researcher's interpretation of both qualitative and quantitative findings can lead to some (objective) understanding of reality. In other words, through the interpretation of empirical data, and combining this with conceptual analysis of the ethical issues, it is possible to arrive at a (more or less) objective view as to whether couple-based ECS is ethically justified and or responsible in these settings. To summarise, in this research, I align broadly with a post-positivist worldview. The overall methodological approach adopted is a pragmatic approach to mixed methods research (MMR) in order to arrive at an outcome that is useful in practice. The MMR approach will be explained in more detail in section 2.2.1.

To guide me through the methodological/'philosophical' thinking about my research project, I focused on the following three questions: 1) What is it that I aim to study? 2) What can I know about what I aim to study? 3) How can I know what I aim to study?

The answers to these questions are presented in Table 2.2. I also found it helpful to think about methodological issues keeping in mind Mason's (168) suggestion that all research revolves around solving an intellectual puzzle. I aim to build a comprehensive picture of how

ECS, an example of a technological development in reproductive genetic technology, is being perceived by both couples and HCPs, and how this technology might be responsibly implemented in a health care setting. My intellectual puzzle resulted in the following study objectives as presented in Figure 2.1:

Phase 1: Implementation pilot of GP-provided couple-based ECS to couples from the Dutch general population

1. Determine the uptake of a couple-based GP-provided couple-based ECS test to couples from the general population
2. Describe why couples from the general population accept or decline couple-based ECS
   - Determine couples' preferences regarding couple-based ECS or ECS where individual carrier states are disclosed
3. Determine whether a couple-based ECS test-offer provided by GPs is feasible
   - Identify the barriers and facilitators for GPs to offer couple-based ECS in a feasible manner
   - Explore GPs' views on future implementation of couple-based ECS in the general population
   - Determine whether couples proceeding with ECS couple-based testing made an informed decision
4. Examine psychological outcomes and reproductive intentions of GP-provided couple-based ECS in the general population

Phase 2. Couple-basd ECS: Exploring the Experience in the Fertility Clinic

1. Explore HCPs' views on the ethical issues raised by couple-based ECS in a fertility setting and identify the implications for clinical practice
2. Explore and analyse the views of couples on the ethical, practical and psychosocial issues raised by couple-based ECS in a fertility setting

General Discussion: Responsible Implementation of Couple-based ECS in the general population

In the discussion I bring together the findings of both phases to address to what extent couple-based ECS to the general population is a responsible approach and ethically justified.

Figure 2.1 Overview of study objectives

Table 2.2.1: An overview of the ontological, epistemological and methodological positions related to the four common research paradigms based on multiple sources (167,168,171).

	Positivism	**Post-positivism**	**Critical theory**	**Contructivism**
Ontology	Realism: Independent reality that can be discovered	(Critical) realism: Independent reality that can be imperfectly known	Historical realism. Reality is shaped by social, political and historical factors	Relativism Multiple realities co-exist
Epistemology	Objectivist, world is governed by laws that can be discovered	Objectivist, focus on reliability and validity, and eliminate bias. Context as meaningful knowledge	Researcher seeks to uncover social and historical processes and power imbalances	Subjectivist, Knowledge as socially constructed. Researcher intends to make sense of the meaning others have about the world
Methodology and methods	Quantitative methods, scientific experiments	Mainly Quantitative, May include qualitative methods	Qualitative and quantitative methods,	Qualitative methods
Methods	Scientific experiments	Scientific experiments, e.g. RCTs	Critical analysis, historical review	Ethnography Case studies

Table 2.2.2 Ontological, epistemological and methodological questions

Phase 1:	**What is the nature of what is being studied?**	**What can I know about what is being studied?**	**How can I know what is being studied?**
1: Uptake	Attitudes, behaviour, preferences	Participants' responses to the survey. Contact with the GPs' practice to find out whether couples made an appointment and contact with the genomics laboratory whether they received blood samples	Quantitative/ numerical approaches: longitudinal survey and descriptive and mainly univariate statistical analysis
2: Feasibility 3: Informed Choice	1: Time 2: Views and experiences 3: Participants' informed choices (attitude and knowledge)	1: What GPs write down on the checklist 2: What GPs tell me about their views and experiences 3: Participants responses to a knowledge test and responses to the survey	1: Quantitative approach and univariate statistical analysis 2: Qualitative approach, semi-structed interviews and framework analysis 3: Quantitative approach, using a measure of informed-choice Multidimensional Measure of Informed Choice (MMIC) Univariate statistical analysis
3: Psychological outcomes	Psychological reactions, conceptualised as anxiety, worry, decisional conflict and anticipated regret, Reproductive intentions	Participants' responses to standardised questionnaires as part of the survey at different points in time	Quantitative approach using STAI-6, adapted 6-item Cancer Worry Scale and Decisional Conflict Scale. Univariate statistical analysis

Phase 2 Aims	**What is the nature of what is being studied?**	**What can I know about what is being studied?**	**How can I know what is being studied?**
1: Explore HCPs' views on the ethical issues in a fertility setting and identify the implications for clinical practice 2: Explore and analyse couples' views and experiences on the ethical practical and psychosocial issues raised by couple-based ECS in a fertility setting	1: HCPs views and experiencese 1: Fertility patients' views and experiences	1: Account/exploration of HCPs views and experiences in discussion with colleagues: what HCPs talked about during the focus groups 2: Account/exploration of patients' views and experiences: what participants tell me during the interviews	1: Qualitative approach: focus groups 2: Qualitative approach: in depth interviews 1&2: Thematic analysis to identify and interpret patterns within the data that could represent patients' and HCPs' views and experiences in a more or less objective way

2.2.1 Mixed methods methodology

In health sciences, a mixed methods methodological approach is increasingly common (172,173). For example, participants views and experiences are explored through qualitative methods to inform the development of new technologies or as part of clinical trials (174,175). Even though mixed-method research (MMR) is increasingly considered legitimate as a third methodological approach, next to quantitative and qualitative approaches, (176,177), whether it is methodologically sound to combine qualitative and quantitative methods has been a topic of debate (166). There are important differences between qualitative and quantitative approaches. The strength of quantitative research lies in its potential to generalise findings to populations as a whole and in its attempts to eliminate bias. Strengths of qualitative research include its ability to give participants a voice, provide a detailed description of experiences and give meaning to the social world by capturing context and setting (178). MMR has been considered problematic, because some commentators have argued that qualitative and quantitative methodologies originate from different perspectives on what constitutes knowledge and the ability of this knowledge to explain reality (epistemology and ontology) (166,179). Precisely because of this, they suggest that qualitative and quantitative methodologies are incommensurable and therefore should not be used in combination (180). On the other hand, proponents of mixed methods argue that a combination of both qualitative and quantitative methods can offset any weakness of either method on its own (176). In other words, mixed-method research can provide a more comprehensive understanding of a complex research problem. Others view the research question as their starting point for decisions on which methodological approach to adopt: if the research questions warrant a combination of qualitative and quantitative methods, a mixed methods approach is considered appropriate (181). Moreover, Greene et al., (1989) outline several purposes of MMR; for instance, where different methods are used to study overlapping and different facets of a research problem, the purpose of using mixed methods is complementarity (182). Furthermore, expansion –exploring an interesting result from a quantitative study in depth using qualitative methods- is another reason to adopt a mixed methods approach (182). It is pertinent that when using such a design, analytical rigour is maintained by addressing the quality of the analysis for each research phase separately as well as whether it meets criteria for evaluating mixed methods research, further discussed in section 2.5

As a working definition of MMR, I used the following definition by Creswell (2015) (183):

"An approach to research in the social and behavioural sciences in which the investigator gathers both quantitative (close-ended) and qualitative (open-ended) data, integrates the two, and draws interpretations based on the combined strengths of both sets of data to understand research problems."

2.2.2 Mixed methods design

Multiple different MMR designs have been proposed in the literature (176,179,184). For example, Creswell (2018) distinguishes between three main types: convergent, explanatory sequential and exploratory sequential. A convergent design means that qualitative and quantitative findings come together at the end of the research process with the purpose of obtaining complementary data on the same topic (171). An explanatory sequential design means that qualitative data is used to explain aspects of previously conducted quantitative research. In an exploratory sequential design, quantitative research is conducted after initial qualitative research to see whether the qualitative findings are generalisable to a population as a whole. An example of this type of design is the research that led up to this PhD regarding a hypothetical scenario of the UMCG couple-based ECS test. This research initially utilised qualitative methods to explore the acceptability, desirability and preferences around ECS couple-based test-provision amongst potential providers and users (88). The target population was defined as couples of reproductive age, who would like to have (more) children. The findings from this qualitative work then informed the development of a quantitative survey conducted to confirm these attitudes and intentions in a generalisable sample of the target population (21,64,92), which is represented in Figure 2.1.

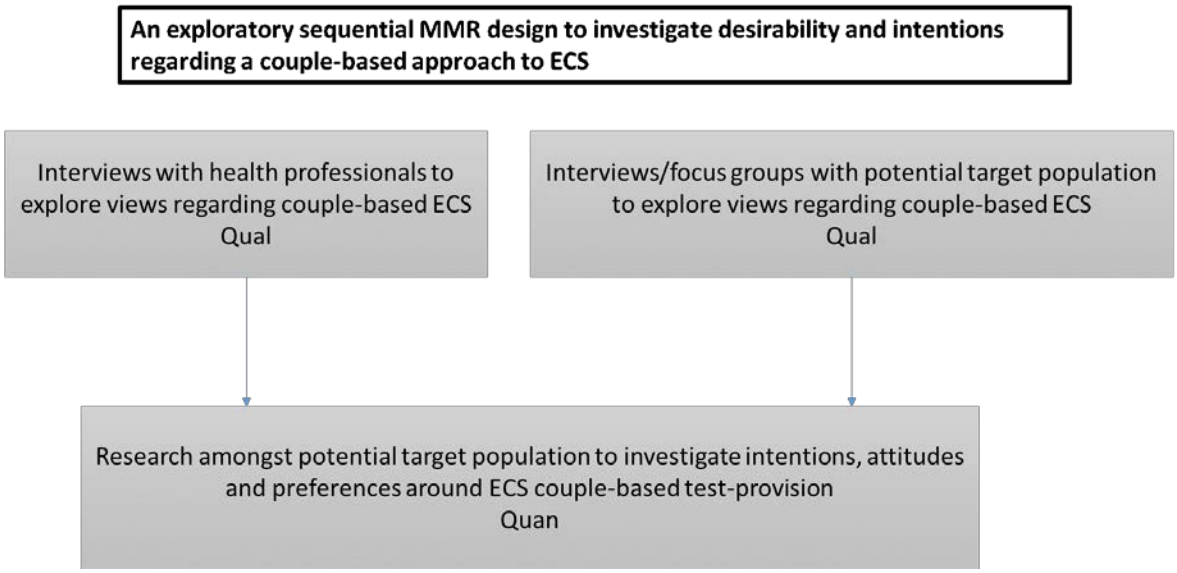

Figure 2.2 Schematic overview of research conducted prior to this PhD illustrating an exploratory sequential design

I set out to evaluate whether couple-based ECS could be a responsible approach to carrier screening in the general population by providing a comprehensive picture of the ethical, practical and psychosocial issues of this type of testing. Before introducing couple-based ECS in routine care, it was important to study whether the desired test offer reported in the previous research could be a responsible approach in practice. In addition, due to the debate around the acceptability/justification of this novel couple-based approach to ECS, the ethical and practical issues regarding the concept of a couple result required a more in depth exploration. The multidisciplinary expert meeting held in 2013 and the findings of the previous research on intention and preferences of the test-provision informed the composition of the UMCG couple-based test, the couple-based approach taken, the pilot implementation study (Phase 1) and therefore the design of this research. The previous research showed that approximately one third of the target population had the intention to undergo the UMCG couple-based ECS test if it were to be offered to them, that the GP was considered as most suitable provider and a couple-based approach was not considered problematic (21).

Phase 1 consisted of an implementation pilot to evaluate whether the desired approach to couple-based ECS, when offered by GPs to couples from the Dutch general population, would meet criteria for responsible implementation. The following aspects were investigated: First, I aimed to determine the uptake of the test offer to confirm whether this positive intention of the target population (i.e. couples of reproductive age) also meant

that they would make use of this testing in practice. As this would be the first time that non-genetics professionals, in this case GPs, provided an ECS test offer, the second objective was to investigate whether this desired test-provision was feasible. Thirdly, as the purpose of this type of testing is to enhance couples' reproductive decisions, it was considered important to measure the outcome of any ECS test offer by means of the number of people who made an informed choice to take part (24). As part of the harm/benefit analysis to determine whether the benefits of offering this type of testing outweigh potential harms, the fourth aim was to determine the psychological outcomes of couples who were offered the UMCG couple-based ECS test. Finally, participants' reproductive intentions were examined.

I aimed to generate data that could be generalisable to the target population as a whole regarding the uptake, psychological outcomes and feasibility of this test offer, and chose a primarily quantitative approach for these study objectives. To study feasibility, I also aimed to explore barriers and facilitators experienced by individual GPs who had provided the test offer in more depth, and their views on future implementation; for this purpose, a qualitative approach was more suitable. Moreover, a qualitative approach to explore GPs' experiences in depth enabled me to generate data to contextualise certain aspects of the quantitative data, such as participants' evaluation of the GPs' pre-test counselling. Thus the feasibility of this couple-based test offer was investigated using both quantitative and qualitative methods.

In Phase 2, I utilised qualitative methods to explore the ethical and practical issues raised by a couple-based approach to ECS for both couples and health professionals in more depth. A qualitative approach is particularly suitable to capture the nuances of ethical dilemmas in clinical practice that are difficult to obtain using quantitative methods (185–187). In Phase 2, I aimed to generate an in depth, contextualised account of both HCPs and couples' views and experiences of couple-based ECS in a fertility setting.

The nature of the study objectives warranted both generalisable data and in depth contextualised data, which is why I drew on the strengths of both qualitative and quantitative methods. The following three aspects regarding the qualitative and quantitative stages of the research are relevant to consider when deciding which MMR design to use: the order (sequential or parallel); the stage of integration; and priority given to each component (177). This research was divided into two phases and the data for each

sub-question were analysed separately. Most of the Phase 1 empirical research was carried out prior to the start of Phase 2. That is why it was possible to use some of the Phase 1 findings to inform parts of the Phase 2 research. For example, data from the GP interviews in Phase 1 helped inform the focus group schedule for Phase 2, regarding practical considerations of test-provision. Couples' reasons in favour of and against accepting this couple-based ECS test offer were examined using a quantitative survey in Phase 1 and also explored in the Phase 2 interviews. The findings from the empirical research phases are discussed in Chapter 5, where I evaluated whether couple-based ECS is a responsible and therefore also ethically justified approach to offering ECS for couples in the general population. Thus, whilst the overall design broadly follows a convergent MMR design as defined previously, there is some overlap with an explanatory sequential design for those aspects where the Phase 1 research informed the Phase 2 research.

In summary, a convergent MMR design was used since the combination of both quantitative and qualitative methods provided a better, complementary understanding of my overall research aim: to study this novel approach couple-based to ECS in the general population in order to assess whether this type of testing meets criteria for responsible implementation (see Figure 2.3 and Table 2.3). Adopting an MMR approach to studying the introduction of couple-based ECS in the general population aligns with previous literature investigating similar issues regarding reproductive genetic screening (73,160,188–191).

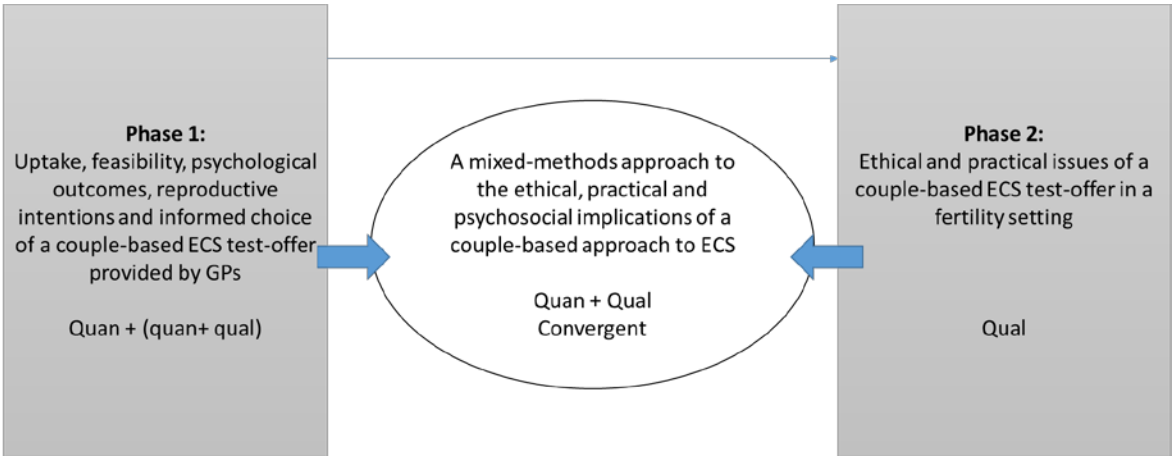

Figure 2.3 Schematic overview of convergent MMR design

Table 2.3 Overview of research design for phase 1 and 2: differences and similarities

	Phase 1	Phase 2
Setting	Primary care: test provision by non-genetics health professional	Fertility clinic: test-provision by non-genetics professional
Participants	Couples from the general population and GPs	Couples having fertility treatment and HCPs involved in clinical genetics services and/or fertility care
Site for the research	GP primary care setting supported by regional clinical genetics service (NL)	Secondary/tertiary care: fertility clinic supported by regional clinical genetics service (UK)
Number of participants	Target population: 1000 women and their partners; Study inclusion: approximately 200 couples/ 10-15 GP practices	20-25 couples, 25-50 HCPs
Type of data to be collected	Quantitative data: survey responses Qualitative data: interview transcripts	Qualitative data, interview and focus group transcripts
Methods of data generation	Online surveys and semi-structured interviews	Semi-structured interviews and focus groups
Method of analysis	Descriptive statistical analysis, univariate analysis, repeated measures analysis; framework analysis	Thematic analysis

2.2.3 Choice of primary care (NL) and fertility setting (UK)

As mentioned in the preface, this work forms the basis for a joint PhD between the University of Groningen/UMCG and the University of Southampton. This gave me the opportunity to carry out research activities based at the two different Universities. The rationale for conducting the first part of this research in the primary care setting in the Northern Netherlands (pilot implementation study), was a continuation of the previous preliminary research conducted in the Groningen research group. This research demonstrated that both the Dutch target population and potential providers, e.g. different

health professionals such as GPs and clinical geneticists, held positive views of this couple-based test offer and the GP was considered as the most suitable provider by most of them (21,88). As discussed in section 1.2.2 the GP plays a central role as gatekeeper for secondary or tertiary care (35), a GP consultation is free of charge for patients and readily accessible.

In the UK, it was unlikely that ECS would be offered by GPs in the near future, given that the evidence-base to support introducing such a test offer in the NHS is not (yet) available, but fertility clinics were interested in providing ECS to their patients. Introduction of ECS in a fertility setting is supported by several studies, mainly in the United States (US), which have suggested that healthcare professionals welcome the possibility of ECS for couples undergoing fertility treatment (37,38). Increasingly, in the UK and other countries with a more prominent private fertility sector such as Spain (39), fertility clinics have been introducing ECS to replace their current carrier screening for gamete donors. Given that fertility clinics in the UK often provide both private and NHS services, they have the opportunity to introduce new technology that is not yet available on the NHS. By conducting the second phase in a fertility setting, I could include a unique set of perspectives, i.e. where the social and genetic couple are different that would not have been possible in the first phase. Thus, as the fertility setting may raise different issues to couple-based ECS and couple results may be perceived differently when the social and genetic couple are different, this was thought to be an interesting and relevant setting to further explore the ethical issues regarding couple-based ECS.

Conducting research in two different settings meant that the study sample for the quantitative and qualitative stages of this research were different. Using different individuals as research participants in the two phases has advantages and disadvantages. The advantage of a different sample was that the two forms of data were independent. On the other hand, it places some limitations on the extent to which some of the findings from Phase 1 and Phase 2 can be integrated to address the overall research aim (171).

2.3 Qualitative methods

In this section, I outline the approaches to qualitative data generation and analysis that were considered for this thesis. In Phase 1 I used a qualitative approach to examine aspects of feasibility of the ECS couple-based test offer by exploring GPs experiences of providing

the test offer and their views on future implementation. In Phase 2 I aimed to gain in depth understanding of the views and experiences of both couples and health professionals around the ethical issues and practical aspects of couple-based ECS in a fertility setting.

2.3.1 Interviews and focus groups

I considered both focus groups and semi-structured interviews as methods to generate data because these are both suited to explore participants' experience and views on a particular topic. A focus group is a guided discussion among multiple participants, whereas the interview is usually a one-to-one conversation with a researcher and research participant (90,192). There are benefits and disadvantages of using both focus groups and interviews. An important difference between focus groups and interviews is the interaction between the participants (178). Focus group participants can challenge each other's views and express (dis)agreements which can generate interesting data about the issues and concerns participants might have in relation to the topic (193). As suggested by Kitzinger (1994), if for example a focus group consists of participants who already are an existing group (work colleagues), focus groups might come close to represent a natural situation and participants might interact and express their opinions as they would do in everyday life. In such circumstances, participants might also be able to provide or recall relevant examples of each other's experiences and challenge each other with any inconsistencies (193).

Phase 1: In order to generate data about the experiences of individual GPs of providing the test offer, I chose semi-structured interviews rather than focus groups, because it enabled an in depth discussion of the individual's GP's experience of offering this test in their practice. Furthermore, I could focus on their personal and professional views on how this type of testing should be offered in the future. Individual semi-structured interviews, guided by an interview framework, were suitable for the purpose of discussing a set number of topics with all participants, which also allowed for some flexibility and unanticipated discussions. In addition, conducting individual interviews enabled an iterative approach, where new topics mentioned by one interviewee could be explored in subsequent interviews. It would also have been interesting to conduct a focus group to contrast and compare the experiences of the different GPs, but this would have been

difficult to do logistically, as GPs were dispersed geographically and had busy time schedules.

Phase 2: I utilised focus groups to explore HCPs view on the issues of a couple-based ECS in a fertility setting. An interactive method of data collection, where participants could discuss their disagreements, and reflect on their current practice together, was thought to result in rich data and therefore be most appropriate. To most participants, this topic was new and focus groups are better suited than interviews to explore people's views on a topic that they are not yet very familiar with (178). A drawback of using this approach could be that when participants feel they have a personal stake in the issue, they could dominate the discussion and be less open to other participants' views. Logistically, it was easier to arrange focus groups in Phase 1 compared to Phase 1, given that participants worked in the same clinic.

To explore couples' views and experiences in Phase 2, I chose interviews and not focus groups to collect data. Fertility treatment and genetic screening might be considered a sensitive topic. In a one-to-one setting, participants might be more willing to reveal sensitive information due to the 'privacy' of the setting. On the other hand, as suggested by Kitzinger, a benefit of focus groups might be that a less inhibited participant might break the ice of discussing a sensitive or taboo topic for the other, shyer participants (193); and safety in numbers, or a collective experience of having to use fertility services to conceive might enable discussion of sensitive issues. Another reason for choosing interviews rather than focus groups was the individualised treatment process of each of the couples, bringing particular issues regarding couple-based ECS that could be explored in more detail in an interview setting rather than in focus groups. Since I intended to explore participants' experiences before and after they received the ECS test-results, logistically, interviews were easier to arrange than focus groups.

I decided to let participants decide whether they preferred to be interviewed jointly or individually; this was an ethical and practical issue in itself. A one-to-one interview as well as a two-to-one interview will have its own advantages and disadvantages in terms of the data it will generate (194–196). Two members of a couple might disagree or agree with each other about couple-based ECS, which could result in the identification of relevant ethical dilemmas and increase the richness of the data, in a similar way as would be possible in a focus group discussion. When interviewing the couples jointly, one partner may give

an answer that is acceptable to the other partner, even though it might not (completely) reflect their own views. In that scenario, individual interviews might give a more 'honest' representation of people's views. However, if both members of the couple are present, Bjornholt and Farstad (2014) suggest that they have more control over the story that is being told which avoids a situation where one partner discloses information in an interview that the other partner feels uncomfortable about (196). Couple-based ECS may have different implications for each member of a couple that could affect their views and experiences. For instance, when the social and the genetic couple are different, only the partner who is the gamete provider has to undergo the actual blood test and receive a test-result regarding their carrier status, whereas the outcome of the test-result is relevant for both partners, as this has implications for the health of their future child. Using interviews with a single partner as well as joint interviews were thought to provide a better picture of the issues inherent to couple-based ECS. Practically, giving couples the option to choose whether they preferred to be interviewed as a couple or individually, meant that it was easier to organise the interviews in such a way that was most convenient for the participants. I aimed to conduct interviews with couples and focus groups with HCPs in parallel in the Phase 2 research. This gave me the opportunity to explore interesting aspects that came out of the focus group analysis during the interviews and vice versa.

2.3.2 Qualitative data analysis

Various approaches to qualitative data analysis were reviewed to address the research questions I set out to explore. I aimed to identify patterns in the data to provide insight into the research aims, but not with the explicit purpose of developing new theory. In addition, as a researcher relatively new to qualitative research, I needed an approach that would enable me to finish this research within the timespan available for this PhD (i.e. 4 years). One such approach is grounded theory which aims to develop new theory from 'the ground' up, rather than deductively through pre-defined ideas (197). As Phase 1 provided me with prior understanding about the issues I aimed to explore in Phase 2, a grounded theory approach was a less suitable method to approach data analysis.

I decided to utilise framework analysis (FA) by Richie and Spencer for the analysis of the interviews with GPs in phase one and thematic analysis (TA) as described by Braun and Clarke for the interviews and focus groups in phase two (178,198).

FA and TA were developed to provide a structured and systematic approach to identifying patterns in qualitative data. Both follow similar initial stages of analysis, including transcription of the interviews/focus groups, familiarisation with the data, coding/indexing and identifying and analysing patterns in the data to create themes that shed light on the research questions. In addition, both approaches can be used flexibly as they are not bound by theoretical positions such as a particular epistemological or ontological stance (178,199) and therefore fitted with my pragmatic approach.

FA was a suitable method for data analysis in Phase 1 for multiple reasons. First, the questions I aimed to explore in Phase were more structured and did not require as much of an in depth approach as in Phase 2. In FA the data are structured and presented per theme and case, allowing for comparison across interviewees. This approach enabled me to use a set of pre-defined questions about feasibility, whilst still allowing GPs to bring up new topics and discuss their personal views on future implementation. Given that it was necessary to compare the experiences of the individual GPs, FA worked well in this phase, as it allowed for more in depth analysis and comparison across interviewees. The data analysis was undertaken as a collaboration with a health psychologist who assisted in coding the data. FA allows for a detailed analysis and a concurrent transparent audit trail, which is one of the reasons why it is considered particularly helpful for analysis in a multidisciplinary team (199). Potential pitfalls I took account when conducting FA was a temptation to quantify qualitative data due to its structured approach, and as with many qualitative approaches, an underestimation of the time required to conduct the analysis (199).

In Phase 2, the purpose of the qualitative analysis was to create a rich and detailed interpretation of participants' views on the ethical issues and practical implications of couple-based ECS in a fertility setting. These research objectives required a more inductive approach to identify participants' views and experiences on the topic. For this purpose, TA described by Braun and Clarke, was considered more appropriate (178). Additionally, TA enabled an analysis process that was feasible within the time span of this phase and it is accessible to novice researchers (178). A detailed description of how I applied TA in this research is presented in Chapter 4. Other methods for qualitative data analysis, such interpretative phenomenological analysis (IPA) also aim to identify patterns in data, however this method was considered less appropriate for this research. IPA aims to

generate meaning through detailed accounts of individual participants' lived experiences and understanding of a certain social phenomenon (200) which is inconsistent with the critical realist stance I have taken.

2.3.3 Sampling

Sampling in qualitative research differs sampling in quantitative research because of the distinct purposes of each approach. A quantitative study aims to select a large representative sample of a certain population to generalise findings and eliminate bias. In qualitative research, different sampling strategies are used, including purposeful, theoretical and convenience sampling. These strategies vary depending on the methods used or the stage of the research. Purposeful sampling is a very common strategy that involves selecting participants who are thought to provide information-rich data (184). A different type of qualitative sampling originally articulated in GT is theoretical sampling; which is a systematic and detailed process that follows from the data, rather than from criteria defined prior to the study. Theoretical sampling and how to approach it, is contested and defined/described in various ways in the literature (201). Theoretical sampling is useful to develop the concepts or potential themes that are identified during the analysis of the data in more depth. Convenience sampling approaches select participants simply based on being easily accessible to the researcher, e.g. undergraduate students (178). This method is criticised for being least rigorous and therefore less justifiable (178,202).

In qualitative research, it is often not possible to define a sample size prior to the study. The question as to how many interviews are enough to answer a research question is complicated in qualitative research. Methodological considerations, such as the purpose of the study, but also practical issues and potentially review board requirements could be taken into consideration (184,203,204). A concept that is often associated with this question is data saturation. Data saturation refers to the process of sampling until no new data is identified for theory building as derived from GT by Glaser and Strauss (1967)(197,202). However, its relevance and application across the range of qualitative research to determine when data collection is complete is debated (204–207). For example, whereas Morse (1995) argues that all qualitative research requires data saturation, others take the view that the application and use of saturation depends on the theoretical stance

of the researcher (205,206). In addition, criteria were proposed to define data saturation as the stage in the analysis when sufficient conceptual depth has been reached (206). In Phase 1, I interviewed all GPs who provided test-counselling, as this was the only approach I could take to get the full range of experiences. Had the number of GPs taking part in the study been larger, I would have taken a different approach to recruitment, adopting a purposeful sampling strategy and taking data saturation into account to determine when to finish recruitment. In Phase 2 data saturation was one of the factors, alongside restrictions in terms of word count, time and recruitment difficulties, which I took into consideration regarding sample size. Given that I did not take a GT approach to data analysis I did not define data saturation in relation to building theory, rather as the point at which my thematic framework could answer the research questions I aimed to address with sufficient depth.

2.4 Quantitative methods

2.4.1 Quantitative survey

To address the research objectives regarding uptake, feasibility, informed choice and psychological outcomes, I aimed to collect data that could be generalisable to the target population for ECS, i.e. couples of reproductive age. That is why a quantitative approach using a longitudinal survey to investigate couples' perspectives was considered the most appropriate method

Surveys and structured interviews were considered as potential methods for quantitative data collection; a quantitative survey was the most appropriate method for this research, given that structured interviews would be too time-consuming for both participants and researcher. A potential drawback of a quantitative survey compared to face-to-face structured interviews could be that as a researcher it is not possible to be certain that the participant filled out the questions themselves or independently from their partner. This was relevant in this research, for example because data from individual participants regarding psychological outcomes may be less valid if partners influence each other when filling out the survey.

Participants were asked to fill out the surveys online as with limits on budget and time, the benefits of an online survey outweighed those of paper surveys. Web-based surveys are

increasingly used as a replacement for paper surveys (208) and are considered psychometrically equivalent, which means that the reliability and validity of both methods were found to be comparable (209). There are several advantages and disadvantages to this approach. The advantages of using an online survey include a reduction in the costs of postage and reduced time to input the responses into the computer for statistical analysis. Given that the data could be imported in analysable format, this web-based approach reduced the potential for errors due to manual inputting of the data. Literature shows conflicting results as to whether web-based surveys result in lower response rates and selection bias in comparison to traditional paper surveys (208,210,211). Selection bias due to the use of an online survey was likely to be negligible in this population given that the target population could be expected to use email on a regular basis and have access to the internet.

The survey design was based on the research described in Plantinga et al., (2016) and Voorwinden et al., (2017) (21,92), which explored the attitudes and intention towards accepting a hypothetical ECS couple-based test offer. Most of the measures included in these surveys were based on two theories of health behaviour: Azjen's Theory of Planned Behaviour (TPB) ((1991))(212) and the Health Belief Model (213), which are two theoretical frameworks commonly used to explain health behaviour (214–216) including the uptake of genetic carrier testing (73,82,92,217). Results from Voorwinden et al., 2017, using TBP and HBM constructs, confirm that, in line with the literature about single-gene carrier testing, perceiving more benefits, having a more positive attitude, not being religious, having current plans to get pregnant, and experiencing the choice as easy could explain 45% of the variance in intention to accept couple-based ECS (92). TPB and HBM items were derived from existing literature on prenatal screening and preconception carrier testing respectively (218,219). The reasons for and against accepting ECS are based on key ethical arguments previously described in Plantinga et al., (2016). As this was the first study investigating an actual ECS offer in this setting, items for measures specific for ECS were not available. The existing items were adjusted to the setting of this research, i.e. an actual ECS test offer, using standard Likert scale. To measure patient satisfaction with counselling and psychological outcomes, existing validated scales were used.

Anxiety was measured using the short form of the State-Trait Anxiety Inventory (STAI-6) (220). The STAI-6 consists of six items rated on a 4-point scale (1 not at all, 4 very much)

ranging from 4-24. A higher score indicates a higher level of anxiety. Scores on the STAI-6 were transferred to scores for the 20-item STAI by dividing the scores by 6 and multiplying by 20. Scores on the full-item STAI range from 20-80. The convergent validity of the Dutch form of the short STAI with the 20-item full STAI showed a correlation of 0.95. (220,221). The STAI-6 has been used previously to measure anxiety in general practice preconception care, demonstrating an average of 36.4 for women aged 18-40 (222). This was used as a reference value. A cut-off of 40 was used to indicate clinically relevant elevated levels of anxiety (223). Given the lack of validated instruments to measure worry about carrier testing, I adapted the following 6-item Cancer Worry Scale to measure worry regarding being a carrier couple, see below (224). Items were measured on a four point Likert scale (almost never-almost always), i.e. the score could range from 6-24. A higher score indicated a higher level of worry about being a carrier couple.

6-item worry scale:

- How often have you thought about the chances of being a carrier couple?
- How often have your thoughts about the chances of being a carrier couple influenced your mood?
- How often have your thoughts about the chances of being a carrier couple restricted you in your daily activities?
- How worried are you about the possibility of being a carrier couple?
- How often have you been worried about the chances of being a carrier couple?
- To what extent is this worry a problem for you?

Decisional conflict regarding test participation was measured after counselling (T1), after testing (T2) and at 6 months after T0 or T1 (T3) using the 16-item Decisional Conflict Scale (DCS). DCS aims to measure decisional uncertainty, factors contributing to uncertainty and perceived effective decision-making (225,226). The response mode is a five-point scale (0= totally disagree, 4 totally agree). Cronbach's αs varied between 0.84 and 0.94 over time. Individual scores were summed, divided by 16 and multiplied by 25 to obtain the total DCS score (score range: 0-100). A higher score indicates more decisional uncertainty/conflict. Reference values are available: no decisional conflict (scores below 25), moderate decisional conflict (scores between 25-≤ 37.5), and high degree of decisional conflict (scores above 37.5)(227).

Anticipated decisional regret was evaluated at T0 and satisfaction with the decision to take part in this test was evaluated at T3. Anticipated decisional regret was measured with one item on a 5-point Likert scale: 'I think that I would regret not having taken part in this test

offer later on'. The response mode was totally disagree-totally agree on a scale from 1-5. A higher score indicates more anticipated regret. Scores were dichotomised into regret (scores≥4) and neutral/no regret (scores ≤3). Being satisfied with one's decision whether to undergo couple-based ECS was measured using the item "I am satisfied with my decision" from the DCS. Scores were dichotomised into dissatisfied (scores ≤2) and neutral/satisfied (scores ≥3).

Patient satisfaction with counselling was measured using the 7-item Clinical Genetics Satisfaction Indicator (CGSI) adopted by the Dutch Society of Clinical Genetics (228). Internal consistency was high (Cronbach's α=0.92) and comparable to that of the English version (Cronbach's α=0.90) (228). I also included a self-constructed item to rate overall patient satisfaction with pre-test counselling. A description of the quantitative survey items used to answer the research questions are presented in Chapter 3.

2.4.1.1 Pilot testing

Surveys for this study were not pilot-tested for validity purposes given that the survey items were very similar to previously used items in surveys investigating intention and attitudes for a hypothetical ECS test offer in the Groningen research group (21,92) and validated items used in the literature. I asked several colleagues of various educational backgrounds to fill out the surveys and feedback on readability and lay-out. The comments received after this mainly related to the length of the surveys. Therefore, the surveys were shorted by leaving out the PANAS scale (Positive And Negative Affect Scale) which aimed to address one aspect of psychological impact of the test offer that was considered least relevant to the research objectives. In order to evaluate the pre-test counselling conducted by the GPs, a checklist was developed where GPs could indicate the time they spent on counselling, what items they discussed (and if not, why they had not discussed these items) for each pre-test counselling.

2.5 How to evaluate the quality of my research

The quality of mixed-methods research can be assessed in multiple ways. The quality of quantitative research is evaluated according to different standards than qualitative research, as each methodology uses different sampling methods, methods for data analysis and ways to interpret findings, reflected in the mixed-methods appraisal tool by Hong et

al., (2018)(229). Moreover, a mixed methods study should not only be assessed for the qualitative of the quantitative and qualitative aspects in isolation. Mays and Pope propose two broad criteria by which to judge the quality of qualitative research: relevance and validity (230). Validity in qualitative research refers to how the researcher has interpreted the data and whether this in accordance with the experiences of the participants. At the same time, when using qualitative methods, the analysis *is* the interpretation of the researcher and therefore does not necessarily conform to the experiences of the participants individually. Relevance refers to whether the research adds knowledge, increases confidence in existing knowledge, and the extent to which findings are transferable to other settings. Validity and relevance can be obtained in multiple ways, such as through the sampling strategy, rigour of the analysis member validation and transferability and I reflect on each of these elements. Teddlie and Tashakkori (2009) developed a framework, 'the integrative framework for inference quality', which integrates an assessment of the quality for the qualitative and quantitative aspects of a mixed methods study and how these two are integrated or combined to address the mixed methods research aim (231). The framework assesses ten steps, from study design to analysis and data interpretation. To evaluate the quality of my research, I drew on these above-mentioned frameworks (see Chapter 5: strengths and limitations).

Box 2.1 Integrative framework for inference

Integrative framework for inference Teddlie and Tashakkori
Study design
1. Suitability
2. Design fidelity
3. Within design consistency
4. Analytic adequacy
Interpretative rigor
5. Interpretative consistency
6. Theoretical consistency
7. Interpretative agreement
8. Interpretative distinctiveness
9. Integrative efficacy
10. Interpretative correspondence

Chapter 3 Phase 1 Evaluating GP-provided couple-based ECS to couples from the general population in a pilot setting

3.1 Chapter outline

This chapter presents the empirical research for Phase 1, an implementation pilot of GP-provided couple-based ECS to couples from the Dutch general population. In section 3.1, I discuss the rationale for this research and I outline the study objectives in 3.3. Sections 3.4 and 3.5 cover the methods for this research, in section 3.7 present the findings followed by a discussion and conclusion in section 3.8. The findings regarding uptake, feasibility and informed choice have been published in the European Journal of Human Genetics, a peer-reviewed journal (232,233). The manuscript regarding the psychological outcomes is being prepared for submission. The accepted manuscripts are included in appendix A.

3.2 Introducing the implementation pilot

As discussed in the literature review in Chapter 1, next generation sequencing (NGS) enables fast and relatively inexpensive simultaneous testing for carrier status of multiple (rare) genetic conditions called expanded carrier screening (ECS) (15). ECS has the potential to enhance couples' reproductive decisions by informing them about their risk of having children affected by (severe) genetic conditions (24). Couples found to be at increased risk might wish to consider alternative reproductive options to avoid the conception or prepare themselves for the birth of a child with a severe genetic condition. Such alternative reproductive options include in vitro fertilisation (IVF) and pre-implantation genetic testing (PGT-M), utilising non-carrier donor gametes or prenatal diagnosis (PND) (and consider a termination of pregnancy if the fetus is affected).

ECS can inform reproductive decisions before and during pregnancy. Preconception ECS is considered preferable over a prenatal test offer (24,234). The main benefits of offering ECS prior to pregnancy are twofold. First, carrier couples can be identified at a time when they can still think through multiple options to avoid the birth of an affected child if that is something they would consider. Second, they have more time to weigh these options without experiencing the emotional and physical stress associated with pregnancy.

The Genetics Department of the University Medical Centre Groningen (UMCG) in the Netherlands developed and validated a population-based ECS-test for a limited set of 50 severe early-onset AR conditions for which no curative treatment is available. Based on the outcome of an international expert meeting, and supported by recent guidelines (24,235) this gene-panel was developed to evaluate its potential for ECS implementation within the Dutch public health system. The conditions included in the test carry no known health implications for the individuals in the couple; the only known health implications relate to their future offspring and a couple-based approach to ECS was adopted. If both members of a couple are carriers for the same AR condition - i.e. carrier couples - then for each pregnancy there is a risk of 1 in 4 or 25% of an affected child. A couple was considered a carrier couple if *both* couple members have a class IV (*likely pathogenic*) or V (*pathogenic*) variant in one of the recessive disease genes included in the test. PGT-M and PND for serious conditions such as

those included in this ECS-test are available to high-risk couples. In the Netherlands, costs of PGT-M and prenatal testing are covered by statutory health insurance.

Previous research among potential users demonstrated an interest in such a test and also identified the general practitioner (GP) as the preferred provider (21,92). More than 99% of the Dutch population are registered with a GP (34), and most GP care is included in the mandatory health insurance package all Dutch citizens carry. In the Dutch healthcare system, GPs play a central role as gatekeeper for secondary or tertiary care (35), which makes extending their current preconception care responsibilities to include a population-based ECS offer a logical approach. Most general health professionals (HCPs) lack the skills, confidence and knowledge to communicate clinical genetics issues (10,24,162,236). With these results in mind, a pilot implementation study was designed in which GPs offered this couple-based ECS to women and their partners from the general population at no financial cost. GPs who participated in the implementation study were given a training in preparation for the pre-test counselling.

As with any screening test, it is important to investigate and weigh potential harms as well as potential benefits, before deciding on implementation as a routine offer to the eligible population (24,95). The aim of the Phase 1 research was to evaluate whether GP-provided couple-based ECS would meet criteria for responsible implementation as a test offer to couples from the general population. The main aim of this test offer was not to encourage as many people as possible to undergo couple testing, but to enable couples to make an informed decision taking part in this type of testing. That is why I examined how many eligible couples were willing to be informed in more detail about ECS by their GP and how many of such couples decided to proceed with testing after receiving counselling. This aligns with recommendations from international professional societies which describe the main aim of ECS as to facilitate informed reproductive decision-making (24,235). Potential harms of an ECS test offer can include adverse psychological outcomes for both those accepting as well as those declining this offer. Being offered this kind of testing and undergoing the test procedures might result in feelings of psychological distress, such as worry and anxiety (24,67,73,150). For example, receiving an ECS test alone could confront eligible couples with unsolicited information about the risks of having a child with rare severe genetic disorders. For those accepting the test offer, test procedures may also cause short-term psychological

distress. Individuals and couples have to weigh up a range of factors before deciding to participate in ECS, such as risk information, harms and benefits of undergoing the test and whether the reproductive options for those being identified as a carrier couple are available and meaningful to them (135). That is why the decision-making process regarding participating in this and other types of reproductive genetic screening is complex and could lead to feelings of decisional conflict or (anticipated) regret (12,152). Earlier studies demonstrated that carrier screening for (mainly) single, or a few conditions is not associated with major adverse psychological reactions and initial feelings of psychological distress mostly dissipate over time (67). Studies investigating the psychological outcomes associated with an actual population based ECS-offer by non-genetics health professionals have not been published yet as far as I am aware. To evaluate whether this test offer was indeed a responsible approach to couples from the general population, I defined four main study objectives for this Phase 1 research: uptake, informed choice, feasibility and psychological outcomes. The METC of the UMCG, the Netherlands, approved the study protocol for this implementation pilot (METc 2015/384).

3.3 Study objectives:

The aim of the Phase 1 reserarch, an omplementation pilot of GP-provided ECS for couples from the general population was to evaluate whether this approach to couple-based ECS meets criteria for responsible implementation. I defined the following study objectives:

Objectives:

- Determine the uptake of a couple-based GP-provided ECS test to couples from the general population
    - Describe why couples from the general population accept or decline ECS
    - Examine couples preferences' regarding couple-based ECS or ECS reporting individual carrier states
- Measure informed-choice for couples undergoing couple-based ECS
- Determine whether a couple-based ECS test offer provided by GPs is feasible
    - Identify the barriers and facilitators for GPs to offer couple-based ECS in a feasible manner
    - Explore GPs' views on future implementation
- Examine the psychological outcomes in couples being offered GP-provided couple-based ECS.

3.4 Methods

3.4.1 Sampling and recruitment:

Inclusion criteria:

1): Women aged 18-40 registered with a participating GP.

2): Having a (male) partner.

3): Planning to have children with this partner.

Exclusion criteria:

1): Being pregnant.

Women aged 18-40 were included because this is the period in which they are most likely to plan a pregnancy. This 'one-off' approach is different from a potential future large-scale implementation of this type of test. If couple-based ECS becomes part of routine care, couples can make use of this type of testing when this is convenient for them. Pregnant women were excluded, because the turnaround time of the test result was a maximum of eight weeks. Limited reproductive options are available for carrier couples during pregnancy and a positive result might lead to increased anxiety and time pressure to make a decision. In addition, pre-test counselling during pregnancy would be more complex for GPs and this was not considered appropriate when offering this type of testing for the first time. Inclusion was open to women (or couples) who were not interested in the test offer **and** to those couples who considered accepting the test and attended pre-test counselling.

Sample size: A minimum of 50 couples participating in the study was required to address the study objectives. To realise this minimum number, 10-15 GP practices were needed to invite their female patients between 18-40 years old, which would be approximately 5000 women. It was estimated that approximately 20% of female patients registered with their GP would belong to the eligible population (89). From previous studies, it was estimated that out of all eligible couples, 10-25% would visit the GP for a pre-test counselling and of these couples, 50-90% are expected to actually take the ECS test (89,149). If 5000 women were invited, approximately 1,000 women would be eligible to participate. If 10-25% of these (100-250)

visited their GP and 50-90% (50-225) accepted the test offer, the minimum inclusion of 50 couples would be reached.

Recruitment: A three-phase recruitment strategy was adopted, see Figure 3.1. Firstly, recruitment of the GP practices took place. Secondly, these GP practices invited their female patients aged 18-40 years. The third step of the recruitment strategy was for women to invite their partners to take part in the research.

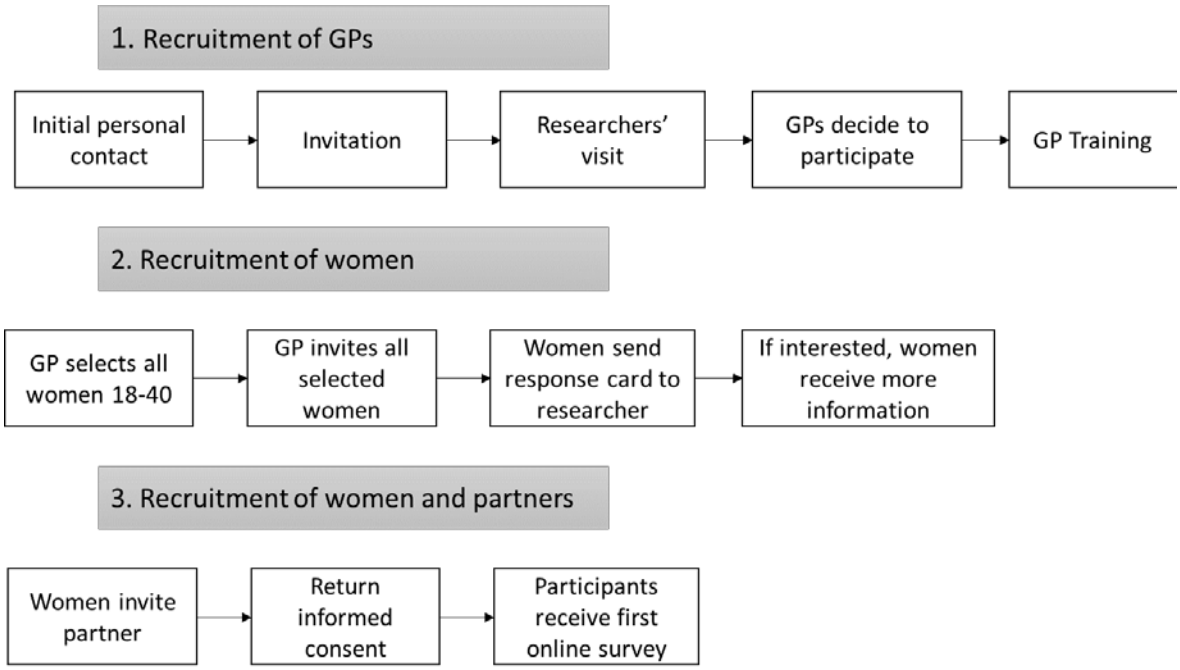

Figure 3.1 Overview of recruitment strategy

The three-step strategy was adopted for multiple reasons. The ethical and practical issues around recruitment of the research participants were discussed with GPs as their views were important in informing the approach adopted. GPs selected and invited their female participants between 18-40 years old themselves, as this was required due to data protection laws and confidentiality. In addition, this approach represented a more realistic scenario regarding potential future implementation than sending the invitation on behalf of the research team. Furthermore, by adopting a stepwise approach, the amount of information could be staggered with the initial information containing essential, but limited information to make a decision regarding participation in the research. Given that some women may prefer not to receive detailed information about a potential risk of having children with genetic conditions, this would, to some extent, respect women's right 'not to know'. The

recruitment strategy meant that the onus to decide about research participation was on the woman. Men from these practices who were of reproductive age were not invited, unless their partner received an invitation. Whilst the advantage of this approach was that couples did not receive a double invitation, we may have missed some men whose partners were not registered with the same practice. Inviting all men of reproductive age, i.e. all men above 18, was logistically not feasible and a large proportion of the invitations would have gone to those who were not eligible to participate.

The invitation included a letter, a response card and an information leaflet including a link to a website with general information about the test and the research, www.dragerschapstest.umcg.nl. The letter was finalised after incorporating feedback on a draft from participating GPs. All GPs approved and signed the letter. If required, costs for stamps and envelopes were reimbursed by the Department of Genetics. Recruitment materials are included in Appendix B.

All women who were invited by the GP were asked to return a response card on which they could express their interest in participation. Before providing consent to participate, women and their partners who were interested to do so, received detailed written information. They could get in contact with the research team for additional questions by email, telephone or through the contact form on the website.

Step 1: Recruitment of GPs: General practitioners in the catchment area of the UMCG were eligible to participate. To protect GPs from an overburden of research invitations, all GP-related research is monitored via a research network of GPs in the Northern Netherlands and the recruitment of GPs was a collaboration between the Department of Genetics and the Department of General Practice and Elderly Care Medicine. Multiple recruitment strategies were adopted, because a random invitation to all eligible GPs would have been costly. Staff of the Genetics Department and the Department of General Practice first approached potentially interested GPs personally. All potential participants received an invitation-letter, which explained the research and their role. This initial recruitment resulted in six interested practices. To increase participation, a recruitment message was included in a regular UMCG-newsletter for GPs. One practice responded to the email, another practice was recruited

through another practice that already participated and one GP contacted the research team after reading a publication about the research.

GPs from 34 practices received the information about the research, of which 17 practices declined and eight practices did not reply. The response rate was 9/34 (26%). Reasons for declining participation included personal circumstances of GPs or specific circumstances at the practice, an overflow of invitations to participate in research, and a negative attitude towards ECS. I gave a short presentation to answer additional questions about research participation at the nine interested practices. After they had had time some time to consider participation, all decided to proceed. The next step was to arrange the training session.

Support for GPs: All GPs were required to undertake training, developed by a multidisciplinary team from the Genetics Department of the UMCG. This implementation study was the first time that GPs were involved in delivering this type of genetic testing and the training and subsequent supervision of GPs when they conducted their first two pre-test counselling sessions were incorporated to ensure an adequate standard of care. For this reason, training was also a requirement by the METc. A genetic counsellor was also appointed so that GPs could consult her with counselling questions throughout the research.

The training took approximately 2.5 hours and counted towards professional accreditation. The training was divided into three sections: 1) background information, 2) a knowledge quiz and 3) counselling skills including a role-play with scripted scenarios for GPs to practice. I gave these training sessions together with a genetic counselor. My role was to provide the background information session, do the knowledge quiz and participate in the role-plays. The genetic counselor conducted the session on reproductive genetic counselling. A booklet with background information, a practical guideline to use during counselling and a checklist with important items to discuss were provided as support materials. Approximately two weeks after the training, all GPs were asked to evaluate the training online and fill out a knowledge test. I would contact GPs who failed a question to discuss their answers before proceeding with the pre-test counselling. Apart from the training, a supervision scheme was included as well, in a similar way as to how new genetic counsellors or registrars start their clinical work. We evaluated two pre-test counselling sessions with each GP individually, using a checklist with important aspects to discuss. After the genetic counselor or I had supervised and

evaluated the two pre-test counselling sessions, GPs were allowed to conduct the pre-counselling on their own.

Seven GP training sessions were held in total. The number of GPs who attended each session was between two and five. In total, nineteen GPs attended the training sessions of whom thirteen conducted pre-test counselling during the research. One GP went on prolonged sick leave, one GP was on a temporary contract, one GP went on maternity leave, and one GP decided to retire and two GPs did not conduct test counselling due to the low number of participating couples in their practice.

Step 2 &3: Recruitment of women and their partners: Recruitment started in January 2016 and lasted until December 2016. All GPs selected their female patients age 18-40. GPs did not make any other pre-selection, unless they deemed it too distressing to send the invitation to a patient. We anticipated that to some women the offer might not be relevant or very sensitive. That is why we included a statement that whilst the letter addressed all eligible women, it might not apply to their own personal situation. Whether GPs should make a more 'active' pre-selection, or whether the invitations could indeed be sent to all women between 18-40 years old constituted an ethical dilemma that was discussed extensively within the team. We therefore consulted GPs who were experienced in taking part in clinical research. When, as a GP, you invite all women of a certain age category in a small town or village, many will know each other. They might ask each other whether they have also received an invitation and whether they are going to take part. If a few women are excluded by the GP, for example due to mental health problems, or fertility issues, these women may be caught off guard and feel they need to justify why they have not received an invitation. These GPs felt that making an active pre-selection by not inviting these women could also be harmful. We discussed this at the start of the research with all GPs and they felt comfortable with this approach. They also prepared their administrative staff to deal with questions that might be raised by women who considered the invitation harmful. Some women, and parents of a woman with a disability felt uncomfortable about receiving the invitation and informed their GPs. As far as I have been informed, these situations were adequately and sensibly dealt with by the GPs and their administrative/nursing staff.

All women who received the invitation were asked to return the response card to the research team. On the response card, they could indicate whether they were eligible. If they were interested in participating, they could provide their personal details to receive further information. Women, who did not want to participate, could write down their reason for this. Women were asked to invite their partners and return the consent forms for both of them. One reminder to return the consent forms was sent per regular mail to women who expressed interest in research participation. This reminder was written in a non-directive way to avoid any pressure for women and their partners to take part in the research. If couples were interested in having the test and decided to make a GP appointment, participation of both partners was a requirement.

3.4.2 Procedures

Process of care: If couples were interested in having the test, they (both partners together) were required to make a regular preconception care appointment with their GP.

After this pre-test consultation, they could go ahead with the test with a request form provided by the GP. To make sure all those who were having the test based their decision on correct information, requirements of the METC included a knowledge test, which was sent to all couples who had attended pre-test counselling at the start of the second questionnaire. If participants who provided a blood sample did not answer all five items correctly, I or the genetic counsellor would call them to explain the concepts again. Once they were informed about the correct answers, couples could still refrain from having their result disclosed. Those who received a phone call to discuss their understanding of the test have had an additional interaction with a health professional and therefore might have a better recall of information. It was very time-consuming to reach all participants who answered an item incorrectly and in a few cases this delayed the analysis of the couple test.

Once samples from both partners were received, the couple test was performed and results were sent to the GP within 8 weeks. The GP then communicated the result to the couples. In case of a positive test, the couple would receive an urgent referral to the Clinical Genetics service for post-test counselling. A referral to Clinical Genetics could also be made at any point in the care process if required, for instance, when a couple was found to be at high a priori risk of a genetic condition based on family history. The allocated time for this

consultation is 20 minutes. The UMCG-test was offered free of charge by the Department of Genetics of the UMCG to couples participating in the research.

Research procedures: Prior to the research, all GPs were required to undertake training in preparation for pre-test counselling. At the end of the research period, the participating GPs were invited to take part in a semi-structured interview. GPs were asked to fill out a checklist after each consultation. Couples were asked to fill out a longitudinal quantitative online survey at four time points. Depending on whether couples attended pre-test counselling and accepted the test offer, they received a minimum of two, to a maximum of four questionnaires. For an overview of these procedures for couples, see Figure 3.2.

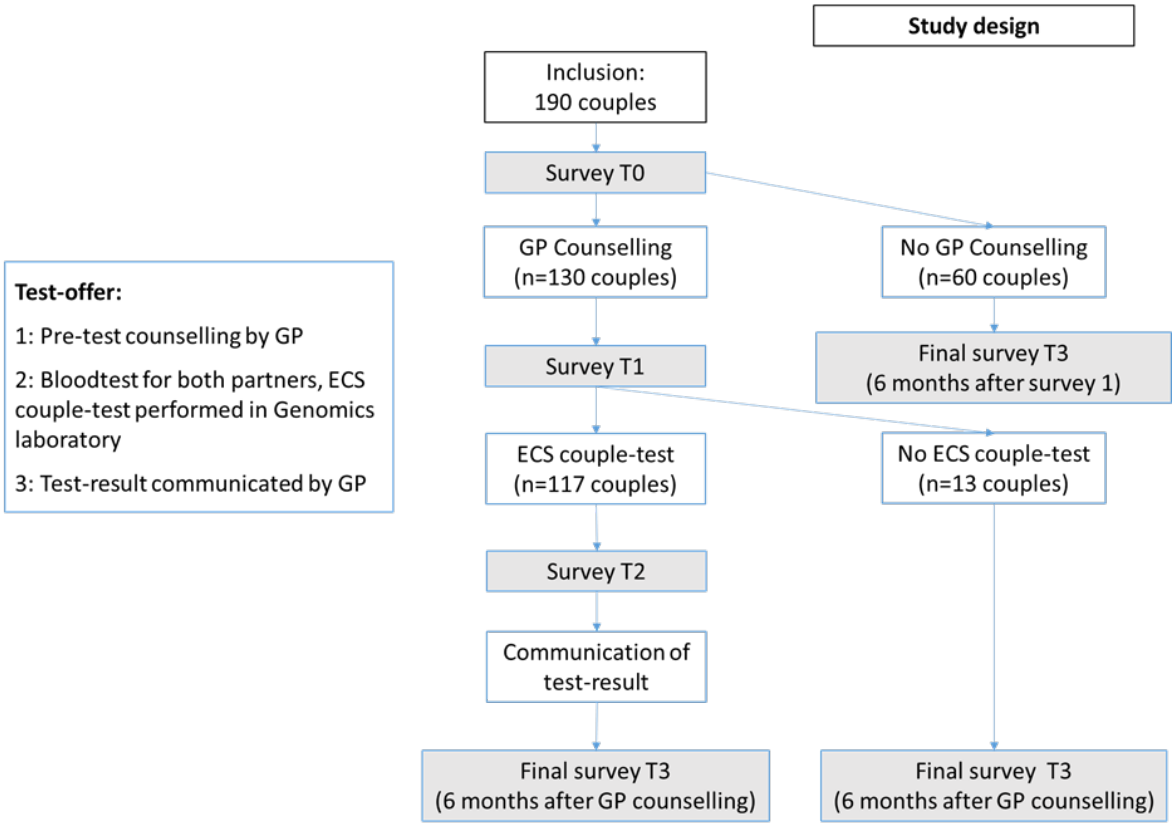

Figure 3.2 Flow diagram of study procedures

3.4.2.1 Survey administration

Surveys were administered at four different pre-defined time-points. These time-points included the initial test offer (baseline), pre-test counselling, the actual blood test, and long-term effects (six months after T0 or after T1 if couples attended GP counselling). All

participants in the survey, regardless of whether they made an appointment with their GP and/or accepted the test offer, received a baseline questionnaire (T0) and a follow-up questionnaire at the end of the research (T3). In sum, couples who attended the pre-test counselling and accepted the test offer were eligible for all four questionnaires (T0-T3). Couples who attended the pre-test counselling but declined the test offer were eligible for questionnaires T0, T1 and T3. Participants who rejected the test offer beforehand or did not attend the pre-test counselling were eligible for surveys T0 and T3.

To account for those who do not have access to an email address, it was possible for both members to receive their survey at the same email address and paper surveys could have been made available upon request. Various approaches to reach a sufficient response rate. For instance, completing the first survey was required prior to attending the GP appointment. If participants did not respond to surveys, they were sent an email reminder after three weeks. If the participant had not responded after two reminders, a phone call was attempted to discuss whether they still wanted to continue with the research. After they had received a phone call, no further reminders were sent.

3.5 Measures and Materials

3.5.1 Outcome measures uptake

I defined uptake and test offer acceptance as follows:

1) The proportion of women and their partners who accepted the test offer as part of the total number of women who were invited (denominator n=4,295),

2) The proportion of women and their partners who accepted the test offer as part of an estimated eligible population (denominator n=859). The estimated eligible population was 859 women (or 20% of the 4,295 invited women).

3) The proportion of women and their partners who accepted the test offer (n=130) as part of the total number of women who participated in the research (denominator n=190).

The ECS test-uptake rate was calculated as the proportion of couples who proceeded with testing after pre-test counselling.

Using three definitions of test offer acceptance may result in confusion because most publications only focus on the second definition. This was discussed extensively with my supervisors. I reached the conclusion that all three measures are relevant. The reason for not including only rate no.2 is that this is based on an estimate using external data and I also wanted to present both the absolute numbers as well as the estimated acceptance rates. Nevertheless, the second definition is likely the most relevant/realistic outcome measure in the context of this research.

3.5.2 Variables included in the survey

For an overview of the survey items used to investigate uptake see Table 3.1. At T0, participants' sociodemographic characteristics, factors related to their relationship and reproduction, their own health and their experiences with (presumed) hereditary conditions, genetic counselling and testing were recorded. In addition, data was collected on their intention to participate in testing and their perceived barriers to test participation. After six months, at T3, data was collected on how participants retrospectively viewed their decision about ECS-testing and their views on couple-based test-provision.

Table 3.1 Overview survey items uptake

Uptake survey items	T0	T3
Sociodemographic characteristics	✓	
Factors related to relationship and reproduction	✓	
Self-reported health and experiences with (presumed) hereditary conditions and genetic testing	✓	
Intention to participate in couple-based ECS	✓	
Perceived barriers to test-participation	✓	
Views on couple based ECS		✓
Retrospective view on decision to take part in couple-based ECS		✓

3.5.2.1 Characteristics of test offer acceptors and decliners

Sociodemographic characteristics. Age was divided into three categories in a similar way as reported by Plantinga et al. (2016): 18-23; 24-33; >33 years of age. Participants' educational level, marital status and religiosity were classified according to the Statistics Netherlands (CBS) definitions. Educational level was further summarised as: 'basic' (finished primary school, lower secondary school or vocational training), 'intermediate' (finished higher level secondary school or intermediate vocational training) or 'high' (finished higher vocational training or university). Relationship status was classified as 'marriage or civil partnership', 'living together' or 'not living together'. Religiosity was measured by asking whether respondents were religious (0 =no, 1=yes and practising, 2= yes, but not practising). This was dichotomised into no or yes (including both practising and non-practising).

Relationship and reproductive characteristics. Relationship satisfaction was measured on a 10-point scale (1=very unsatisfied, 10=very satisfied)(237,238). Participants were also asked within what timeframe they were planning to have children and whether they already had children. To be comparable to other relevant Dutch studies, timing to next pregnancy was adapted from Henneman et al., 2001, who dichotomised into <2 years (short term) and >2 years (long term)(219). These were further categorised into: (<0.5 years, 0.5 years-2 years, 2-5 years, >5 years, unsure)

Health status and experiences with hereditary conditions and genetic testing. Participants were asked to rate their own health on a five-point scale (poor, moderate, good, very good, excellent). They were also asked whether they suffered from a chronic condition and were presented with fourteen categories such as respiratory conditions (e.g. asthma), visual problems and mental health issues (yes/no). In addition to this, respondents were asked to indicate whether they, or any of their family members or friends, suffered from a (presumed) hereditary condition and/or whether they had ever had genetic counselling and testing themselves.

3.5.2.2 Intention, barriers and views on couple-based test-provision

Intention (T0): Intentions towards couple-based ECS before pre-test counselling were measured with the item 'I intend to accept the offer of this couple-based ECS-test' on a 7

point scale (unlikely-likely). Intentions were classified into 'positive' (6-7), 'neutral' (3-5) and 'negative' (1-2).

Barriers (T0): Data were collected about the extent to which participants perceived the time and effort of test-participation, having to make a GP appointment and giving a blood sample, as barriers for taking part in this test offer. These four items were measured on a Likert scale from 1-5 (totally disagree-totally agree).

Intention (T0): Test-decliners were asked whether it was a considered decision not to proceed with testing (yes/no). If it was not, they could indicate their reasons why (e.g. we could not come to a common decision as a couple, it just did not happen, I had not thought about it anymore, it was not possible to be at the GP appointment together).

Couple-based test offer (T0): Participants were also asked to indicate their main preference as to how test results were disclosed. They were asked to indicate *one* preference out of the following four options: 1: couple results; 2: individual carrier results; 3: no preference; 4: not sure).

3.5.2.3 Arguments for and against accepting the couple-based test offer

At T0, participants indicated their reasons why they would accept or decline ECS testing and they were presented with seven arguments in favour and ten arguments against taking a couple-based ECS test (21). All participants were asked which single argument they considered most important in accepting and which single argument they considered most important in declining the test offer.

3.5.3 Response cards

In addition, 70 eligible (members of) couples who returned the response card but decided not to take part in the research (and therefore the ECS-test) explained why they decided not to participate in the research.

3.5.4 Data analysis

Given that partners within a couple might have different views about this couple-based ECS test offer, individual participants were included in the analysis for all outcome measures apart

from acceptance and uptake rate. Descriptive data are presented using mean (SD), median (IQR) or numbers (percentages) where appropriate. To compare test acceptors and decliners, unpaired T-tests were used for continuous variables and Chi^2 tests for categorical variables.

3.5.5 Outcome measures feasibility and informed choice

Feasibility was evaluated in terms of the organisational aspects of this GP-provided ECS test offer and the provision of care, with a focus on the pre-test counselling. I explored GPs' experiences and views on the ECS test to evaluate feasibility and improve future implementation. I adopted Marteau et al., (2001)'s definition of informed choice, who developed the Multidimensional Measure of Informed Choice (MMIC) to measure informed choice in relation to prenatal screening for Down's syndrome (133). A choice was considered "informed" if participants had sufficient knowledge and accepted the test offer (in case of a positive attitude) or declined the test offer (in case of a negative attitude)(133). Table 3.2 displays the topics and items investigated, which informed by relevant literature (24,37,38,44,162,236).

Table 3.2 Overview of items used to measure Feasibility and Informed Choice

Topics	***Quantitative***		***Qualitative***
	Instrument, time point (subject)	*Items/measures*	
A. FEASIBILITY			
1. Organizational aspects of GP-provided ECS test offer	Checklist at T1 (GP)	Start and end time of pre-test counselling sessions	Barriers and facilitators of : • Duration of pre-test counselling • Both partners attending pre-test counselling • Communicating test result • Referrals
2. Evaluation of care: competence and satisfaction	Survey at T1 (couples)	Patient satisfaction (overall +CGSI(228), see supplementary materials	• Self-judgment GPs during interviews • Professional judgment genetics professional after supervision
3. Evaluation of pre-test counselling: content	Checklist at T1 (GP) Survey at T1 (couples)	Items discussed during counselling. Importance and length of items discussed during counselling.	Barriers and facilitators of: Discussing the aspects included on the checklist

4.Views about implementation	Interview at T3 (GP)	N.A.	
B.INFORMED CHOICE			
Informed choice	Survey at T0 and T1 (couples)	Informed choice measured using adapted MMIC (133), see supplementary materials	

The organisational aspects of the ECS test offer were evaluated quantitatively as the time used for pre-test counselling and qualitatively through analysis focused on barriers and facilitators. Pre-test counselling was evaluated in terms of competence, content and patient-satisfaction. Competence was judged by the genetics professionals after supervision and evaluated by GPs during the interviews. Both couples and GPs evaluated the content. Couples also rated their satisfaction with pre-test counselling.

Items discussed during counselling (see Table 3.3): Self-constructed items were used to measure how important participants considered the items discussed by the GP on a Likert-scale from 1-5 (anchors very unimportant- very important) and how they rated the time spent on each of these topics on a Likert scale from 1-5 (anchors too little-too much).

In the GPs' checklist, items 1-8 and 11 are the same as the items included in the survey for the participating couples. In addition to these, the following two items were included: The norms and values of the couple in relation to this ECS test and the turnaround time and communication of the test result. I asked GPs to indicate to what extent they discussed these during the counselling (yes, somewhat, no).

Table 3.3 Evaluation of Pre-test Counselling: items discussed

	Items discussed during counselling
1	The purpose of ECS for severe genetic conditions.
2	Information about the conditions included in the test
3	Chances of being a carrier of one of the conditions included in the test
4	Chances of having a child with one of the conditions in the test
5	Test-procedures (both partners providing a blood sample)
6	Certainty of the test result
7	Costs associated with the test
8	Reproductive options in case of a positive result
9 (not on GP checklist)	Your norms and values in relation to this ECS test
10 (not on GP checklist)	Your partner's norms and values in relation to this ECS test
11	Other aspects of a healthy pregnancy (folic acid, no smoking/alcohol)
Extra times included on GP Checklist	Couples' norms and values regarding ECS
	Turnaround time and communication of test result

Patient satisfaction with counselling: Patient satisfaction with counselling was measured using the 7-item Clinical Genetics Satisfaction Indicator (CGSI) adopted by the Dutch Society of Clinical Genetics (228). I also included a self-constructed item to rate overall patient satisfaction with pre-test counselling on a scale from 1 -5 (*very unsatisfied-very satisfied*).

Degree of informed choice: The degree of informed choice was evaluated using an adapted version of the Multi-Dimensional Measure of Informed Choice (MMIC) (133). A choice was considered informed if participants had sufficient knowledge and made a decision consistent with their attitude towards participating in the ECS-test (133). Based on discussions within the multidisciplinary research team, five knowledge items were constructed to cover the essentials of ECS see Box 3.1:

Box 3.1 Items knowledge test

1. A carrier of a severe genetic condition from this test has a change in the gene for this condition, but does not have the condition itself. (true)
2. If my partner and I will be told that we are not carriers of the same condition, then this means that we will have a healthy child. (False)
3. If my partner and I will be told that we are carriers of the same condition, we will have a 25% or 1 in 4 chance of having a child affected by the condition. (True)
4. If my partner and I will be told that we are carriers of the same condition, we can decide ourselves what we want to do with this information. (True)
5. A normal test result means that there is still a very small risk that we will have a child affected by one of the conditions in the test. (True)

Response mode was "true", "false" or "I do not know" for each item. Moreover, attitude towards participating in the ECS test was measured with two items on a seven-point scale (good/bad; acceptable/unacceptable). These scores were reclassified as negative (1,2), neutral (3-5) and positive (6,7). I defined sufficient knowledge as a score ≥3/5 items answered correctly, which is in accordance with a recent publication on informed choice in non-invasive prenatal testing for chromosomal abnormalities (160). Attitude was defined as positive if both items were scored positive. Attitude was defined as negative if both items were scored as negative. All other scores were classified as neutral. The attitude was considered in accordance with their decision if they either accepted testing and displayed a positive attitude, or did not accept testing and displayed a negative attitude.

3.5.5.1 Quantitative data and analysis

Data on the duration of the consultation and items discussed during pre-test counselling were collected by a checklist for GPs that was filled out after each pre-test counselling (T1). The checklist included eleven items that GPs were required to discuss during pre-test counselling (see Table 3.2). They were asked to indicate if they discussed the item (yes, somewhat, no), and if not, why not. The measure of informed choice consisted of five knowledge items capturing essential information about ECS testing and two attitude items. Data on consultation duration, items discussed during counselling, patient satisfaction, and informed choice were described using percentages, mean (SD) or median (IQR) where appropriate, using SPSS IBM version 23.

3.5.5.2 Qualitative data and analysis

Ten semi-structured one-to-one interviews were held with GPs. Two GPs who conducted counselling did not participate due to lack of time and the GP who withdrew from the research did not participate. An interview schedule was developed within the multidisciplinary research team with open ended items to address the feasibility aspects of the test offer and to explore GPs views on future implementation. The interview guide was designed in such a way that the first question around a topic was meant to explore the GP's experience of a certain aspect of the test offer. Subsequently, I probed about facilitating and limiting factors, and explored how these factors affected the test offer during the research and if the GP thought they would affect future implementation. Topics included:

1) Motivations to take part in the research
2) Preparation for test-provision (such as training, supervision, preparing other staff members in the surgery, sending the invitations etc.)
3) Expectations about test-uptake, ideas around offering ECS during pregnancy
4) Pre-test counselling (such as what items did you actually discuss, why, which were more or less important to discuss, did the checklist help, , did you explore whether couples were sufficiently informed, any unexpected questions from couples, how long did it take)
5) Post-test counselling (such as, did results arrive in time, how were results communicated, did you encounter any problems)
6) Feasibility of a future national test offer provided by GPs (such as: does it fit within general preconception care, what are limiting or facilitating factors, what else would you need to be able to do this on a larger scale?)
7) Evaluating own competence/ability to provide this test offer in the future
8) Other

Developing the interview guide was an iterative process. After several rounds of feedback by the supervisory team, the guide was piloted in a practice interview with the genetic counsellor who was also a member of the research team. This was helpful to structure the interview more logically and uncovered some aspects that were not included, such as the feasibility aspects of the post-test counselling. After this practice interview had been discussed with the supervisory team, the topic guide remained very similar throughout the interviews, given that

there was a set number of aspects that I aimed to explore. During each interview there was room for GPs to elaborate on aspects that they felt were not covered my questions and some of these aspects I added to the interview schedule for the next interview, such as GPs' view that due to conducting this pre-test counselling, they had an opportunity to talk to a group of patients –healthy young couples- they would not normally see together. The first interview transcripts were discussed within the supervisory team for completeness and to evaluate how the interviews were conducted, for example looking at whether the questions were phrased sufficiently open-ended.

The interviews were audio-recorded and transcribed verbatim. The average duration of the interviews was 41 minutes (range 20-60 min). Data analysis was conducted according to the framework approach of Ritchie and Spencer (198). Framework analysis follows a process of familiarization, summarising and coding, which results in matrices presenting the data per theme and case to allow more in depth analysis and comparison across interviewees. Atlas – ti (version.5.2.18 copyright 1993-2018 by ATLAS.ti Scientific Software Development GMbH Berlin) was used to facilitate analysis. A health psychologist (LvdH) assisted with data analysis. We each independently coded the first three interviews, and differences in coding were discussed until consensus was reached. LvdH subsequently coded all interviews -including the first three- while I coded parts of all interviews randomly and where LvdH had doubts. Final thematic framework matrices were subsequently discussed within the research group until consensus was reached. The preliminary conclusions were returned to the interviewees for member checking (239). Six GPs returned the forms, and their responses confirmed the conclusions of the analysis.

3.5.6 Outcome measures psychological outcomes

Psychological outcomes were conceptualised as anxiety, worry, decisional conflict, anticipated regret and satisfaction to receiving a couple-based ECS test offer in test-decliners as well as test-participants. I investigated the following aspects. Firstly, I studied whether levels of anxiety and worry upon receiving the test offer were within acceptable limits for acceptors and decliners of that offer. Secondly, I investigated whether long-term effects on anxiety and worry were seen in these groups. I also examined decisional conflict, and anticipated regret. Anticipated regret was related to participants' satisfaction with the

decision (not) to proceed with testing. Reproductive intentions were included to examine whether and how undergoing ECS affected couples' reproductive decisions. The measures used to examine anxiety (STAI-6), worry (adapted 6-item cancer worry scale (CWS)), anticipated regret, satisfaction with decision-making and decisional conflict (Decisional Conflict Scale (DCS)) were described in Chapter 2, section 2.4.

Table 3.4 Survey items used to investigate psychological outcomes

Concepts (instruments)	**T0 before GP counselling**	**T1 after GP counselling**	**T2 after testing**	**T3 Six months after T0 or T1**
Socio demographic variables	✓			
Self-rated health/experiences of genetic chronic conditions, genetic conditions and genetic testing	✓			
Mastery Pearlin Mastery Scale	✓			
Anxiety 6-item STAI	✓	✓	✓	✓
Worry Adapted 6-item Cancer Worry Scale	✓	✓	✓	✓
Decisional conflict Decisional Conflict Scale - **Satisfaction with decision**		✓	✓	✓
Anticipated regret	✓			

3.5.6.1 Sociodemographic variables and participant characteristics

I recorded sociodemographic variables, relationship variables, timing of next pregnancy, self-rated health, presence of chronic condition, experiences with hereditary conditions, genetic counselling and testing, and intention to take part in ECS test offer. In the first survey (T0), demographic characteristics regarding age, sex, relationship status, educational level were recorded. Participants' educational level and marital status were classified according to the Statistics Netherlands (CBS) definitions and further summarised as described in section 3.5.2 (232).

3.5.6.2 Reproductive intentions

To measure reproductive intentions, I used the survey item reported previously by Lakeman et al., (2008)(73) which asked whether the test result influenced participants' ideas about having children (Response mode: Yes/No/possibly/I do not know). If that was the case, participants were asked to indicate one reason out of the following six options:

- I am surer about having children,
- I now have doubts about having a child,
- I want more children than I did before the carrier testing,
- I want less children than I did before the carrier testing,
- I now definitely do not want any (more) children,
- My ideas have changed in other ways

3.5.6.3 Analysis

Participant were divided into three groups: 1) test offer decliners (=no GP counselling, no test); 2) test decliners after GP counselling (= GP counselling, no test), 3) test acceptors/participants (GP counselling and test). Variables were summarised using mean (SD) for variables with normal distributions; median (IQR) for variables with skewed distributions; and n (%) for nominal and ordinal variables.

1) Mean anxiety in response to the test offer (T0) between test offer acceptors and test offer decliners was compared with the independent Student's t-test. Comparison with the population reference score of 36.4 (35.4-37.3) (222) was made using the independent Student's t-test. Clinically relevant STAI scores were defined as the proportion of STAI scores ≥40 and Cohen's d. Worry scores between groups 2 and 3 and group 1 in response to the test offer (T0) were compared with the Mann-Whitney U test. Reference scores for worry are unavailable.

2) anxiety/worry scores at T3 were summarised using means/medians, proportion of scores >=40 and Cohen's d. To examine the long-term effect in anxiety and worry, the within-person change in anxiety and worry scores between T0 and T3 was estimated and compared these between groups with the paired Student's t-test and the Wilcoxon signed rank test, respectively, and Cohen's d.

3) DCS per time point was summarised as mean DCS score (SD) and interpreted using the abovementioned reference values. Anticipated regret (T0) and satisfaction with decision (T3) were summarised as proportions.

4) Whether the test result affected participants' reproductive intentions was summarised using percentages for the following categories (yes, no, possibly, unsure). In all analyses, the magnitude of the differences was interpreted using Cohen's effect size (d): 0.2 was considered as small, 0.5 as medium and 0.8 as large (240). A p-value <0.05 (two-sided) was considered a statistically significant difference.

3.6 Ethical issues

Consent: Written consent was asked prior to the research. If women had not returned the consent forms within three weeks after sending the information, they received one letter as reminder. General practitioners consented to participate in the research verbally.

Confidentiality: To protect participants' anonymity and confidentiality as much as possible, consent forms with personal data were stored in a locked cabinet. Password protected computers from the academic hospital were used and only those who needed to were given access to the folders containing the data. For the online data collection I used an online paid tool developed by researchers from the UMCG, which is used to collect confidential clinical data (Roqua). In this tool, personal data are not linked to survey data (188).

Since the timing of the questionnaires depends on the date and time of the appointments with the GP and the arrival of the blood samples, the administrative files could not be completely anonymous. The knowledge test was not anonymous, therefore the answers were separated from the actual questionnaire.

As several GPs had their practices in the city centre of Groningen, a number of colleagues or acquaintances received an invitation to participate. On a couple of occasions, I knew someone who actually participated in the research personally, or I knew a participant was a family member of one my colleagues who was probably unaware of their participation. I tried to take extra care not to have the computer screen visible to my colleagues when I had to look at personal data from participants.

3.7 Findings

3.7.1 Recruitment, inclusion and response to the survey

We received 848 response cards and in total, 509 women who returned the response card were not eligible (reasons listed in Figure 3.2). Seventy eligible women indicated that they did not want to participate. The eligible women who were interested in taking part (n=269) received detailed information about the research, were asked to invite their partner to participate with them and to return consent forms for both of them. After we received their written consent, 191 couples were eventually sent the first survey (T0). Subsequently, one couple was excluded because they became pregnant before filling out survey no. 1.

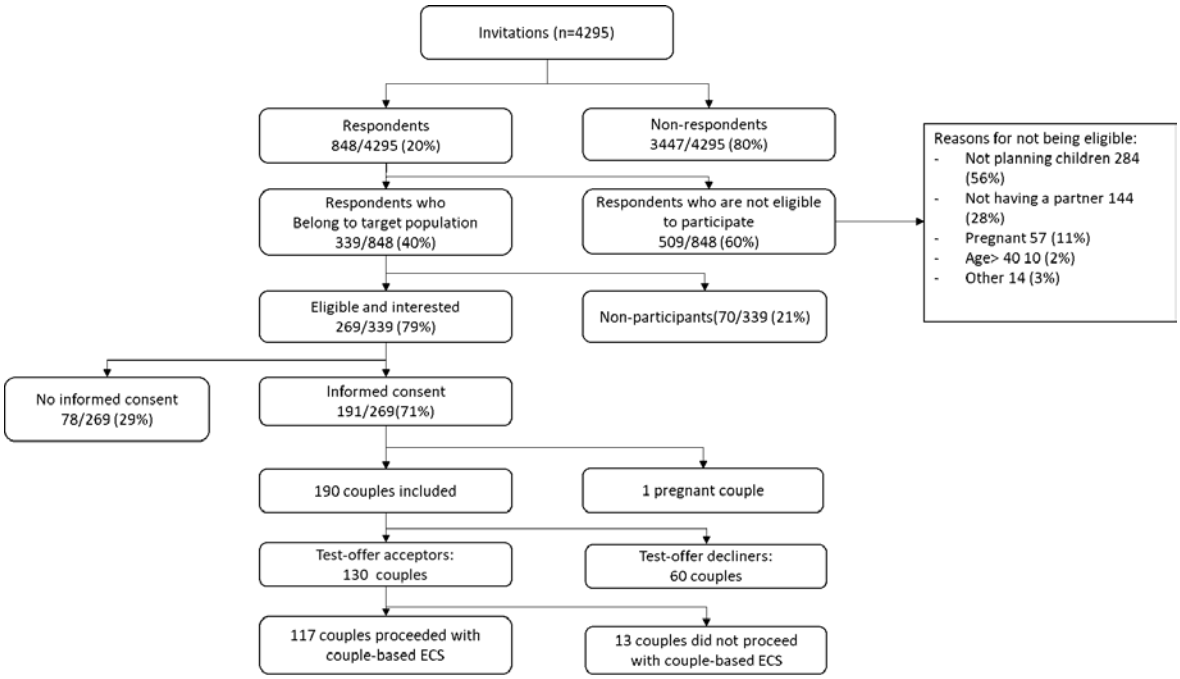

Figure 3.3 Flow diagram of inclusion and recruitment

Upon receiving written consent, 191 couples were sent survey T0. One couple was excluded due to unexpected pregnancy. Thus, in total, 190 couples were included in the research (380 participants). 358/380 (93%) participants returned T0, 238/260 (92%) T1, 193/234 (82%) T2 and 227/358 (64%) participants returned T3. In 168 cases, both members of a couple provided T0 data, 115 provided T1 data, 88 provided T2 data and 91 provided T3 data. 240/260 (92%) of the individual participants responded to the evaluation of the pre-test counselling. GPs returned 116/129 (90%) checklists. For an overview of the participating GPs, see Table 3.4.

Table 3.5 Overview of participating GPs, pre-test counselling and tests performed per practice

Participating practice ID (Interview no.)	Type of practice	GPs attended training	No. GPs conducted counselling	No. women invited	No. pre-test counselling sessions	No. couple tests performed
1 (6)	City	1	1	500	24	23
2 (4)	City	1	1	528	12	12
3 (3)	Village	2	1	276	4	3
4 (8&9)	Town	6	4	1045	23	20
5 (2&5)	Town	3	2	780	27	25
6 (1)	Town	1	1	407	18	14
7 (7)	Village	1	1	262	5	5
8 (10)	Town	2	1	330	5	4
9 (NA)	City	2	1	167	12	11
Total		19	13	4295	130	117

3.7.2 Uptake

3.7.2.1 Test offer acceptance and test uptake rate

In total, 130 couples attended pre-test counselling and 117 of these couples proceeded with testing. This resulted in the following test offer acceptance and test-uptake rates:

1) Test offer acceptance was 3% (130/4295) (95%CI 3%-4%) of the total invited population (i.e. women between 18 and 40 registered with the participating GPs)
2) Test offer acceptance was 15% (130/859) (95%CI 13%-18%) of the estimated eligible population and 68% (130/190) (95%CI 61%-75%) for the participants included in this survey.
3) The uptake rate of the ECS test in participants having attended the GP-consultation was 90% (117/130) (95%CI 84%-95%).

3.7.2.2 Characteristics of test offer acceptors and decliners

Sociodemographic, relationship and health characteristics: Table 3.6 displays the characteristics of test offer acceptors and decliners. The average age in this sample was 29 (SD 5.5) years and 50% of participants were between 24-33 years old. The majority of

participants had an intermediate or higher education (93%), and 43% had already finished higher education. Twenty-four percent were religious and 25% were not (yet) living together. The relationship satisfaction rate was a median of 9 out of 10 (IQR 8-9). Fifteen percent already had children (n=55) and 16% were planning a pregnancy within six months. Thirty-nine percent reported at least one chronic condition, mainly asthma, migraine or mental health problems, but 97% described their health as good to excellent. Thirty percent had experiences with (supposedly) hereditary conditions in their family or friends, and 13 participants (4%) had previously had genetic counselling and testing. Most of these participants (n=11), made an appointment with the GP to discuss couple-based ECS.

Test offer acceptors and decliners differed significantly in the highest level of education achieved: test offer acceptors more frequently had a higher educational level. They also less frequently had children, were more satisfied with their relationship and were less likely to plan a pregnancy within the next two years. Test offer acceptors and decliners were comparable in age, religiosity, experiences with genetic counselling and testing, and having chronic and presumed hereditary conditions.

Table 3.6 Sociodemographic characteristics of the sample

Sociodemographic characteristics	All N=358	Test offer acceptors N=259	Test offer decliners n=99
Age (y) mean (SD)	29.1 (5.5)	29.4 (5.5)	28.7 (5.4)
Gender			
female	185 (51.7)	130 (49.4)	55 (57.9)
male	173 (48.3)	129 (49.6)	44 (44.4)
Age category			
18-24	69 (19.3)	46 (17.8)	23 (23.2)
24-32	180 (50.3)	134 (51.7)	46 (46.5)
>33	109 (30.4)	79 (30.5)	30 (30.3)
Religiosity			
Yes	84 (23.5)	65 (25.1)	19 (19.2)
Educational level **			
basic	25 (7.0)	14 (5.4)	11 (11.1)
intermediate	178 (49.7)	117 (45.2)	61 (61.6)
high	155 (43.3)	128 (49.4)	27 (27.3)
Marital status			

Sociodemographic characteristics	All N=358	Test offer acceptors N=259	Test offer decliners n=99
married/civil partnership	77 (21.5)	59 (20.8)	18 (18.2)
living together	196 (54.7)	146 (56.4)	50 (50.5)
not living together	90 (25.1)	59 (22.8)	31 (31.3)
Children *			
yes	55 (15.4)	31 (12)	24 (24.2)
Relationship satisfaction *			
median (IQR)	9 (8-9)	9 (8-9)	8 (8-9)
Timing of next pregnancy *			
<0.5y	56 (15.6)	35 (13.5)	21 (21.2)
0.5-2y	103 (28.8)	74 (28.6)	39 (39.4)
2-5y	126 (35.2)	102 (39.4)	24 (24.2)
>= 5y	36 (10.1)	27 (10.4)	9 (9.1)
unsure	27 (7.5)	21 (8.1)	6 (6.1)
Self-rated health			
excellent	90 (25.1)	73 (28.2)	17 (17.2)
very good	129 (36.0)	95 (36.7)	34 (34.3)
good	127 (35.5)	83 (32.0)	44 (44.4)
moderate	12 (3.4)	8 (3.1)	4 (4.0)
poor	0 (0.0)	0 (0.0)	0 (0.0)
Do you suffer from a chronic condition?			
no	218 (60.9)	162 (62.5)	56 (56.6)
Any experiences with hereditary conditions in your family or friends?			
no experience	252 (70.4)	179 (69.1)	73 (73.7)
Did you have genetic testing and counselling in the past?			
yes	13 (3.6)	11 (4.2)	2 (2.0)

3.7.2.3 Intention, barriers and views on this couple-based test offer

Table 3.7 displays participants' intentions, barriers to participation and views on couple-based test offer.

Intention: The majority (87%) of participants had a positive intention towards test-participation, but test offer acceptors rated their intention more often as 'likely' compared to

test offer decliners (93% vs. 69%). Forty-four percent of test offer decliners indicated that the decision to decline the test offer had not been a considered one, and the reasons they most often indicated to explain why they did not attend pre-test counselling were 'it just had not happened' (n=7) or 'it was not possible to make a GP appointment together with my partner' (n=6).

Barriers: Test offer decliners indicated significantly more frequently that test participation took a lot of time and effort. In addition, 20% of test offer acceptors and 35% of test offer decliners agreed or totally agreed with the statement that having to make a GP appointment was a barrier to their participation.

Views on couple-based test-provision: Fifty-seven percent of test offer acceptors and 48% of test offer decliners indicated that, if they had to indicate a single preference between couple results or individual results they would prefer to receive couple results. Fifteen percent of test offer acceptors and 11% of decliners would prefer a test that would give them individual carrier states. Twenty-four percent of test offer acceptors and 27% of decliners had no preference and 5% of test offer acceptors and 14% of decliners were not sure what they preferred.

Table 3.7 Intention, barriers and views on couple-based ECS

Intention, barriers and views on couple-based test-provision	**All** **N (%)**	**Test offer acceptors** **N (%)**	**Test offer decliners** **N (%)**
Intention (survey 1)	N=352 (6 missing)	N=256 *(3 missing)*	N=96 *(3 missing)*
Intention ** **likely** **neutral** **unlikely**	 306 (86.9) 30 (10.6) 19 (5.4)	 240 (92.7) 15 (5.8) 4 (1.5)	 66 (68.8) 15 (15.6) 15 (15.6)
Intention (survey 2)	N=54	N=9	N=45

Intention, barriers and views on couple-based test-provision	**All** **N (%)**	**Test offer acceptors** **N (%)**	**Test offer decliners** **N (%)**
(only participants who did not have ECS-testing)			
Not having the test was a 'deliberate' decision **yes** **no**	33 (61.1) 21 (38.9)	8 (88.9) 1 (11.1)	25 (55.6) 20 (44.4)
If not, the reason for this was: **we could not come to a common decision as a couple** **it just did not happen** **I had not thought about it anymore** **it was not possible to be present at the GP appointment together** **other, such as pregnancy**	0 (0) 7 (33.3) 2 (9.5) 6 (28.6) 6 (28.6)	0 (0) 0 (0) 0 (0) 0 (0) 1 (100)	0 (0) 7 (35.0) 2 (10.0) 6 (30.0) 5 (25.0)
Barriers (survey 1)	*N=348* *(10 missing)*	N=256 *(3 missing)*	N=92 *(7 missing)*
I think that test-participation takes a lot of time ** **totally disagree** **disagree** **agree nor disagree** **agree** **totally agree**	69 (19.8) 149 (42.8) 99 (28.4) 28 (8.0) 3 (0.9%)	53 (20.7) 123 (48.0) 65 (25.4) 15 (5.9) 0 (0)	16 (17.4) 26 (28.3) 34 (37.0) 13 (14.1) 3 (3.3)
I think that test-participation takes a lot of effort ** **totally disagree** **disagree**	71 (20.4) 174 (50.0)	57 (22.3) 135 (52.7)	14 (15.2) 39 (42.4)

Intention, barriers and views on couple-based test-provision	**All** **N (%)**	**Test offer acceptors** **N (%)**	**Test offer decliners** **N (%)**
agree nor disagree	83 (23.9)	55 (21.5)	28 (30.4)
agree	17 (4.9)	8 (3.1)	9 (9.8)
totally agree	3 (0.9)	1 (0.4)	2 (2.2)
I think having to make a GP appointment before test-participation is a barrier**			
totally disagree	55 (15.8)	48 (34.4)	7 (7.6)
disagree	126 (36.2)	98 (38.3)	28 (30.4)
agree nor disagree	85 (24.4)	60 (23.4)	25 (27.2)
agree	65 (18.7)	40 (15.6)	25 (27.2)
totally agree	17 (4.9)	10 (3.9)	7 (7.6)
I think having to give a blood sample is a barrier			
totally disagree	113 (32.5)	88 (34.4)	25 (27.2)
disagree	129 (37.0)	93 (36.3)	36 (39.1)
agree nor disagree	62 (17.8)	45 (17.6)	17 (18.5)
agree	33 (9.5)	22 (8.6)	11 (12.0)
totally agree	11 (3.2)	8 (3.1)	3 (3.3)
Views on couple-based test provision (T2)	N=221 *6 missing*	N=177 *5 missing*	N=44 *1 missing*
Preferences for disclosure of ECS results			
couple results only	122 (53.7)	101 (57.1)	21 (47.7)
individual results	32 (14.1)	27 (15.3)	5 (11.4)
no preference	52 (22.9)	40 (22.6)	12 (27.3)
not sure	15 (6.6)	9 (5.1)	6 (13.6)

Arguments for and against accepting the couple-based test offer: Table 3.8 shows that sparing a child a life with a severe genetic condition was considered the single most important

argument to (potentially) accept this ECS test (29.6%). Other arguments that participants chose as most important were that they felt they had a responsibility as future parents to have this test (18%) and that a good result would be a great relief (13.0%). The distribution of these arguments was about the same for test offer acceptors and decliners. Examples of 'other' arguments participants provided in favour of accepting ECS were curiosity, for the benefit of science, and due to experiences with genetic conditions in the family. Table 3.9 shows that for the participating couples the most important argument against having this ECS-test was that the test result would not influence their decision to have children (26.5%). Again, the distribution between test offer acceptors and test offer decliners was similar (25% and 30%, respectively). Twenty-seven percent of test offer acceptors and 18% of test offer decliners provided additional explanations as to why they would not want to have the ECS-test, such as a worry that after a positive test result they would decide not to have children at all. Some stated they did not see any reason why not to undergo couple-based ECS.

Table 3.8 Arguments in favour of accepting the couple-based ECS test offer

Arguments in favour of couple-based ECS	**All N=355** ***3 missing***	**Test offer acceptors N=259**	**Test offer decliners N=96** ***3 missing***
I think that my partner and I as (future) parents have a responsibility to do this test	63 (17.7)	50 (19.3)	13 (13.5)
I want to spare our child a life with a severe hereditary disease	105 (29.6)	78 (30.1)	27 (28.1)
If the test shows that we together are not carriers, this would be a great relief	46 (13.0)	33 (12.7)	13 (13.5)
I want to prevent my partner and I having to take care of a child with a severe hereditary disease	38 (10.7)	33 (12.7)	5 (5.2)
I want to know in good time if our child is at risk so as not to be confronted by having to make a choice about a late abortion	38 (10.7)	28 (10.8)	10 (10.4)
I want to be able to prepare myself for having a child with a severe hereditary disease	36 (10.1)	23 (8.9)	13 (13.5)
I think that abortion should be prevented if possible	6 (1.7)	1 (0.4)	5 (5.2)
Other (e.g. to benefit science, previous experiences with genetic conditions in the family)	23 (6.5)	13 (5.0)	10 (10.4)

Table 3.9 Arguments against accepting the couple-based ECS test offer

Arguments against couple-based ECS	**All N=355** ***3 missing***	**Test offer acceptors N=259**	**Test offer decliners N=96** ***3 missing***
I do not want to know if my partner and I are carriers	27 (7.6)	14 (5.4)	13 (13.5)
I am against selecting children by screening (such as in this test)	13 (3.7)	7 (2.7)	6 (6.3)
I am afraid that if we turn out to be carriers this will have consequences for my relationship	33 (9.3)	22 (8.5)	11 (11.5)
I am afraid that if we turn out to be carriers this will have consequences for my insurance policies	12 (3.4)	12 (4.6)	0 (0)
I am afraid that if we turn out to be carriers we will be regarded as people with a disease	7 (2.0)	7 (2.7)	0 (0)
I am afraid that if we turn out to be carriers this will be registered with the authorities	11 (2.8)	10 (3.9)	1 (1.0)
I am afraid that if we turn out to be carriers we will end up in a medical treadmill	46 (13.0)	35 (13.5)	11 (11.5)
The test result will have no influence on my having children with my partner	94 (26.5)	65 (25.1)	29 (30.2)
A test would take away the romance of a pregnancy	19 (5.4)	12 (4.6)	7 (7.3)
By taking a test, becoming pregnant is no longer natural	6 (1.7)	5 (1.9)	1 (1.0)
Other contra arguments (e.g. I don't see any reason why not to accept the test offer)	87 (24.5)	70 (27.0)	17 (17.7)

3.7.2.4 Response cards

As figure 3.2 showed, 70 women who were eligible for participation in the research explained on the response card why they were not interested in taking part. The majority cited reasons against having couple-based ECS, rather than issues regarding declining research participation, such as a perception that ECS results in over-medicalization of pregnancy, health-related issues, no perceived need to be tested (yet) and anticipating anxiety about the impact of a positive test result.

3.7.3 Feasibility and Informed Choice

Evaluation of organizational aspects: 58% of the pre-test counselling sessions lasted 20 minutes or less, with a median (IQR) of 20 minutes (18-28), indicating that the allocated time of 20 minutes was sufficient for the majority of sessions. Qualitative findings from GP interviews are illustrated with quotes presented in Table 3.11. Several GPs noted that couples were well informed beforehand, and that this helped them provide counselling within this time. GPs expected pre-test counselling sessions to last longer, if couples were less well-informed, or for couples with little educational background. Some GPs mentioned that over time they developed a routine for conducting the counselling, which reduced the time required for preparation and counselling itself. GPs were positive about attendance of both partners at counselling because the couple test affects both partners equally and because they considered discussing GPC with both partners important. No carrier couples were identified. GPs did not experience any barriers in communicating the normal results or to referring any couples at normal risk to Clinical Genetics for additional pre- or post-test counselling. GPs or their healthcare assistants communicated the test results by phone, email, or a combination, and some provided the couples with the lab results letter as well.

Evaluation of pre-test counselling: Based on their experiences in this research, GPs and genetics professionals considered training test-providers essential to ensuring quality of the test provision. After GPs were supervised twice, the genetic professionals considered all thirteen GPs competent to conduct counselling on their own. Counselling support from the clinical genetics professionals was requested twice for couples who were pregnant during the research and once for a couple who had misunderstood the purpose of the test. All GPs interviewed said they felt able to provide the pre-test counselling mainly because of the training, supervision and additionally provided materials. Some GPs specifically said they used the checklist as a practical guidance, and all felt this covered the essential aspects of a pre-test counselling well. Participants evaluated the pre-test counselling with a mean satisfaction score of 4.7/5 (SD 0.5). The majority of participants (54.7%) gave the highest score of 5.0. 91% of participants were *satisfied* or *very satisfied* with GP pre-test counselling.

GPs and couples evaluated the content of the pre-test counselling as follows. GPs indicated that most aspects included on the checklist, apart from GPC and ‘communication and turn-

around time of the test result', were at least discussed 'somewhat' in more than 90% of consultations. Some participants indicated that they thought too little time was spent on discussing the conditions included in the test (55 respondents (23%)) and the follow-up options for high-risk couples (38 respondents (16%)). Some GPs explained they did not discuss each condition in detail, instead discussing the conditions as categories as explained during the training. While GPs indicated that in 36 consultations (31%) they either "did somewhat" or "did not" discuss couples' reproductive values, more than 85% of participants indicated that the time spent on their and their partners' values was exactly right.

Most GPs were positive about combining ECS pre-test counselling with general preconception counselling. GPs indicated that, for example, due to lack of time, they "did not" discuss GPC in 31% or discussed it "only somewhat" in 14% of consultations. Some GPs explained during the interviews that the counselling might become too complex preventing couples from remembering both. General preconception counselling was considered important or very important to discuss by 159 participants (67%), of whom 19/159 (12%) thought too little time was spent on this. In contrast, 167 participants (70%) thought the right amount of time was spent discussing GPC.

Informed choice: After pre-test counselling by the GP, the number of participants with a sufficient level of knowledge had improved from 195/237 (83%) to 231/237 (97%) (Table 3.10). Five of six who displayed insufficient knowledge –and a positive attitude- after pre-test counselling, proceeded with testing. Another seven participants did not proceed with testing, even though their attitude was positive and knowledge sufficient. The provision of care pathway –as described in the methods section- prevented participants to make a final decision based on insufficient knowledge.

Table 3.10 informed choice before and after pre-test counselling by the GP

Before pre-test counselling (T0) (n=237)	**Positive attitude n (%)**	**Negative attitude n (%)**	**Neutral attitude n (%)**	**Total n (%)**
Sufficient knowledge	173 (83)	0 (0)	22 (79)	195 (83.)
Insufficient knowledge	36 (17)	0 (0)	6 (21)	42 (18)
Total	209 (88)	0	28 (12)	237
After pre-test counselling (T1) (n=237)	**Positive attitude n (%)**	**Negative attitude n (%)**	**Neutral attitude n (%)**	**Total n (%)**
Sufficient knowledge	213 (90)	0 (0)	18 (8)	231 (97)
Insufficient knowledge	5 (2)	0 (0)	1 (0)	6 (2.5)
Total	218 (92)	0 (0)	19 (8)	237

GP views on future implementation: In line with the previous research, after having offered ECS testing, GPs considered themselves as the most suitable providers for a population-based ECS couple test. Advantages they mentioned were the low-threshold of GP care, their familiarity with their patients and their background. One GP mentioned that ECS provision as standard care by all GPs might not be feasible because not all may be able to keep up with technological advances in genetics. Some GPs suggested that only motivated GPs willing to do so should be trained to provide ECS. These GPs could become specialised in (reproductive) genetics, just as some GPs are currently specialised in areas such as palliative or elderly care. Potential barriers that GPs mentioned were resistance to

additional workload in already too busy practices or negative attitudes towards ECS. The eight-week turnaround time in this research context was considered acceptable by the GPs for non-pregnant couples. For future implementation, several GPs suggested the laboratory could also send the test result directly to couples. Negotiations with health insurance companies and policy makers were considered necessary to decide on a proper reimbursement fee for test-provision and whether to include ECS in the statutory health insurance package (Table 3.11).

Table 3.11 GP quotes from interviews

Feasibility aspect	Quote (Interviewee)
Evaluation of care: organizational aspects of the GP-provided test offer	*"I particularly liked the training course, which was essential. It would be difficult to provide the ECS test without doing the training course first." Interviewee 10*
	"At first, I thought 30 minutes should be planned for each consultation. ... But later I reduced it to 20 minutes, because it was feasible in 20 minutes. .. Also because at a certain moment you know what to discuss. Well, and people were often perfectly able to tell about the test. Most of them." Interviewee 5
Evaluation of care: content	*"I discussed the items on the checklist with everyone, because I thought those were the essential points. So [amongst others] about what types of diseases were included. What the chances were, that it [the ECS test] does not offer any guarantee [of a healthy baby], and that there were no costs involved [for the couple]. That's it, in brief." Interviewee 5*
	"What is really important is that they realize that it's the couple being tested and not the individuals, that the result says nothing about each individual only something about the couple together." Interviewee 3
Views on future implementation: Suitable provider	*[Reasons why the GP is suitable]…"well, of course it's close to the patient, most patients, even these healthy young people know their GP. And that means that, in a counselling like this, the threshold to ask questions is likely to be lower, or to return. They know where to find us when they need to." Interviewee 8*
Views on future implementation	*"Well.., I think that with the right provision of information, it could very well be part of this general preconception care advice." Interviewee 4*
Views on future implementation	*"The solidarity [healthcare insurance] system here [in the Netherlands] means that if you want to reach people, you should cover the costs." Interviewee 7*

3.7.4 Psychological outcomes

3.7.4.1 Psychological outcomes after receiving the test offer

3.7.4.1.1 Anxiety

Figure 3.4 shows the mean anxiety levels (with 95%CI of mean) for the total group as well as three subgroups at the different time points and Table 3.12 demonstrates the crude STAI-6 and worry scores.

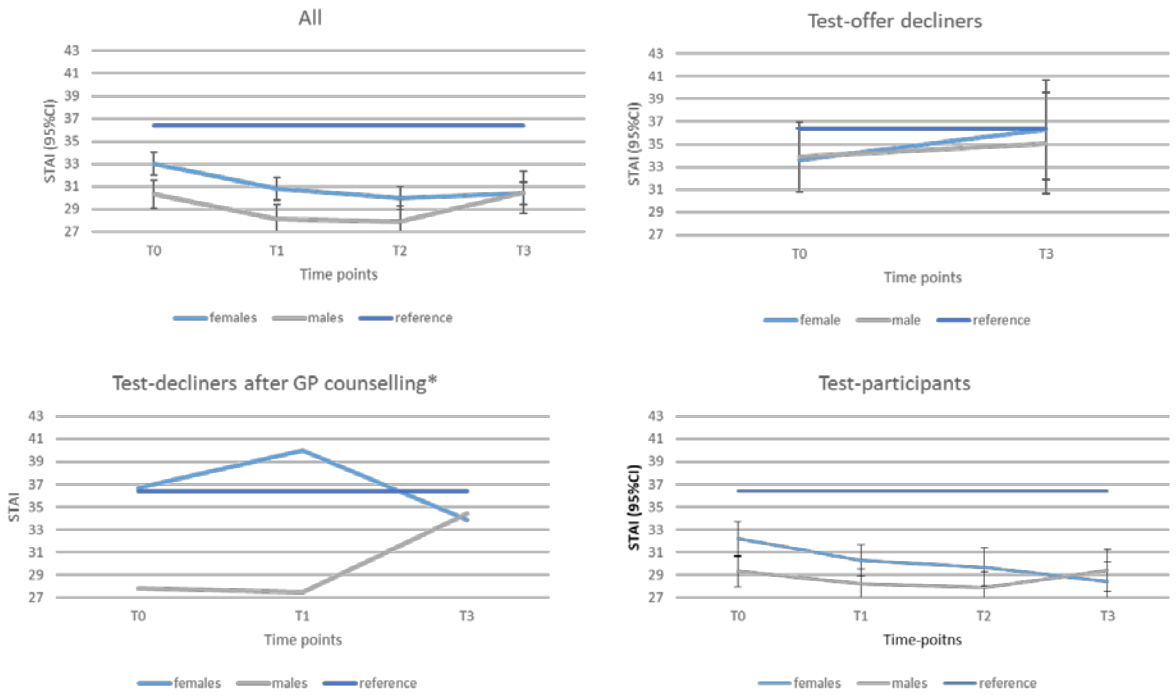

Figure 3.4 Mean STAI scores (with 95%CI of mean) by group over time.

Table 3.12 Anxiety and worry scores at T0

	Group 1 test offer decliners **n=120**	**Group 2 test decliners** **n=26**	**Group 3 test acceptors** **n=234**	**Group 1 vs Groups 2+3**	**Groups 1+2 vs Group 3**
STAI*					
Mean (SD)**	33.68 (10.12)	32.64 (11.42)	30.74 (8.17)	33.68 (10.12) vs.	33.47 (10.35) vs.

				30.92 (8.51)	30.74 (8.17)
Comparison of subgroups				2.76 (95%CI 0.65-4.87) P=0.010	2.73 (95%CI: 0.75-4.71) p=.007
Cohen's d				0.32	0.19
STAI ≥40	26 (27.1%)	6 (25.0%)	35 (15.0%)	27.1% vs. 15.9%, p=.017 (Chi2)	26.7% vs. 15.0% p=.008 (Chi2)
Worry* **					
Median (IQR)	6.0 (6.0-7.0)	6.0 (6.0-8.5)	6.0 (6.0-7.0)		
Comparison of subgroups				6 (6.0-7.0) vs. 6.0 (6.0-7.0), p>.99 (MWU)	6 (6.0-7.0) vs. 6.0 (6.0-7.0), p=.80 (MWU)
Cohen's d				0.03	0.35

*Missing data: 24 individuals (group 1) and 2 individuals (group 2)
**significantly lower than the reference value of mean 36.4 (95%CI of mean: 35.4-37.3) for group 1 (p=.02) and group 3 (p<.001); comparable to the reference value for group 2 (p=.09)
***Missing data: 25 individuals (group 1) and 2 individuals (group 2)

At T0, the mean STAI scores were significantly lower than the population reference of 36.4 (95%CI: 35.4-37.3) for test offer decliners (p=.02) and test acceptors (p<.001), and comparable to the reference for test-decliners after GP counselling (p=.09). Test offer decliners reported higher mean anxiety levels than all participants who attended GP counselling (irrespective or undergoing the test) (mean difference 2.76, p=0.010; effect size 0.32). All participants who did not undergo testing reported higher mean anxiety at T0 than test-acceptors (mean difference 2.73, p=.007; effect size 0.19).

3.7.4.1.2 Worry

Figure 3.5 shows the median (IQR) worry levels for the three groups and the total group at the different time-points.

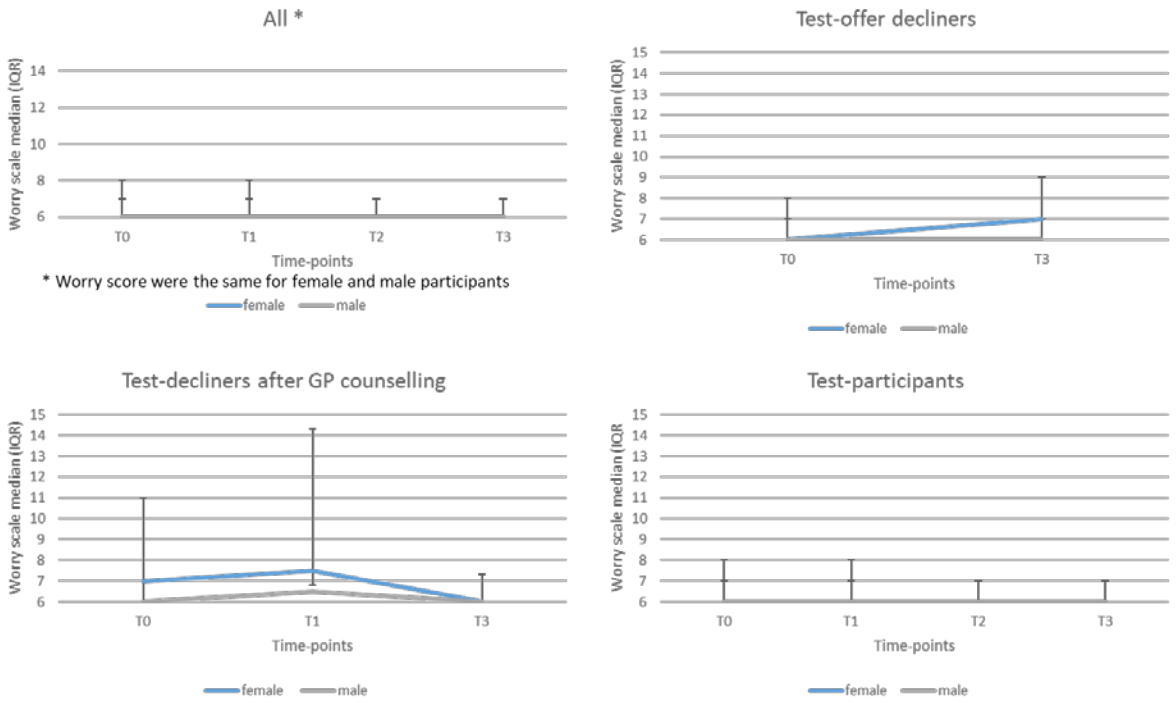

Figure 3.5 Median worry scores (adapated 6-item CWS scores) by group over time

At T0, the worry scores were not significantly different between test offer decliners and all participants who attended GP counselling (p>0.99; effect size 0.03), nor between all test decliners and test acceptors (p=0.80, effect size 0.35).

3.7.4.2 Psychological outcomes: long term differences (T3-T0)

3.7.4.2.1 Anxiety

Figure 3.3 also shows the mean anxiety scores by group at T3. See table 3.13 for the crude data. At T3, the mean STAI scores were comparable for the population reference of 36.4 for test offer decliners (p=.77) and test decliners (p=.51) but significantly lower for test acceptors (p<.001). Test offer decliners at T3 reported higher mean anxiety levels than test acceptors (mean difference 7.08, p<0.001; effect size 0.79). The joint group 1 and 2, i.e. the test-decliners, showed the same trend but did not differ significantly compared to test acceptors (mean difference 5.23, p=.34, effect size 0.59).

Table 3.13 STAI and worry scores at T3

	Group 1 test offer decliners n=120	**Group 2 test decliners n=26**	**Group 3 test acceptors n=234**	**Group 1 vs group 3**	**Group 2 vs group 3**	**Groups 1+2 vs group 3**	**Group 1 vs groups 2+3**
STAI*							
Mean (SD), Mean difference (95%CI of mean difference)	35.93** (10.70)	34.07** (15.26)	28.84 ** (8.43)	7.08 (4.13-10.03)	5.23 (-6.53 – 16.99)	6.77 (3.42-10.13)	6.82 (3.78-9.87)
p-value#				p<.001	P=.34	P<.001	P<.001
Cohen's d				0.79	0.59	0.74	0.74
STAI ≥40	17 (37.8%)	2 (22.2%)	22 (12.7%)	37.8% vs. 12.7%	22.2% vs 12.7%	35.2% vs. 12.7%	37.8% vs. 13.2%
P-value##				P<.001	P=.61	P<.001	P<.001
Worry***							
Median (IQR)	6 (6-7)	6 (6-7.5)	6 (6-7)			6 (6-7) vs 6 (6-7)	6 (6-7) vs 6 (6-7)
P-value$				P=.59	P=.61	P=.50	P=.63
Cohen's d				0.02	0.18	0.05	0.02

* Missing data: 75 individuals (group 1), 17 individuals (group 2) and 61 individuals (group3)

** Comparison to the reference value of mean 36.4 (95%CI of mean: 35.4-37.3(222)for group 1 (p=.77) and group 2 (p=.51); significantly lower than the reference value for group 3 (p<.001)

*** Missing data: 76 individuals (group 1), 17 individuals (group 2) and 61 individuals (group3).

Differences tested with independent Student's t-test

Differences tested with Fisher's Exact test (group 2 vs 3) or Pearson's chi-square test (other comparisons)

$ Differences between groups tested with the non-parametric Mann-Whitney U test

All test-decliners reported higher mean anxiety than test acceptors (mean difference 6.77, p<.001, effect size 0.74). Clinically relevant anxiety (i.e. STAI score ≥40) was reported more

frequently by test offer decliners compared to test acceptors (37.8% vs. 12.7%, p<.001) and by test decliners (group 1 + 2) compared to test acceptots (35.2% vs. 12.7%, p<.001).

Table 3.14 shows the within-group differences in STAI scores between T0 and T3. Differences and effect sizes were small, suggesting that for each group mean/median STAI at T3 was comparable with the mean/median STAI at T0.

Table 3.14 within group differences in STAI and worry scores over time

	Group 1 **test offer decliners** **n=120**	**Group 2** **test decliners** **n=26**	**Group 3** **test acceptors** **n=234**
STAI*			
Mean within group difference (95%CI)**#	1.04 (95%CI: -1.79 – 3.86)	-3.33 (IQR: -6.67 -15.00)	0.0 (IQR: -6.67 - 3.33)
p-value#	P=0.46	P=0.87	P=0.015
Cohen's d	0.1	0.3	0.2
Worry*			
Median within group difference (IQR)**	0 (-1, 0)	0 (-5, 0)	0 (0, 1)
P-value$	P=.33	P=.14	P=.90
Cohens' d	0.20	0.42	0.03

3.7.4.2.2 Worry

Figure 3.5 depicts the median worry scores at T3. (Table 3.13 shows the crude data.) At T3, the median worry scores of groups 1 and 2 (i.e. test decliners) were comparable to test acceptors (median 6; p=.59 and p=.61, respectively) and effect sizes were small. Table 3.14 shows the within-group differences in worry scores between T0 and T3. For all three groups, worry scores were not significantly different between T0 and T3 (test offer decliners: p=.33, test decliners after GP counselling: p=.14; test acceptors: p=.90) and differences can be

interpreted as small (effect sizes all <0.20). This suggests that long-term differences in worry within groups are negligible.

3.7.4.3 Decision-making

3.7.4.3.1 Decisional conflict

Figure 3.6 shows the mean DCS scores per group over time (for crude data, see Table 3.15). After counselling (T1), most individuals rated decisional conflict as low to moderate. None of the test decliners after GP counselling and 7.5% of test acceptors rated decisional conflict as high. After 6 months (T3), high decisional conflict was reported more frequently by test offer decliners than in test acceptors (38.6% vs. 8.8%, p<.001). Decisional conflict rates were not significantly different between all participants who attended GP counselling (p=.67). Most participants who attended GP counselling indicated low to moderate levels of decisional conflict (about 90%), whereas the majority of test offer decliners reported moderate to high levels of decisional conflict (about 80%).

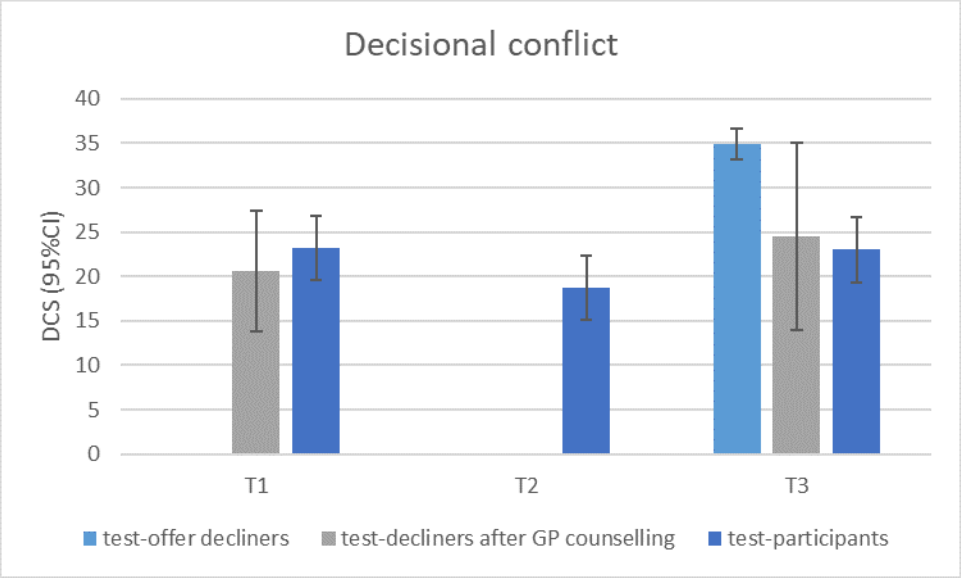

Figure 3.6 Decisional conflict scores by group over time

Table 3.15 Decisional conflict, anticipated regret and satisfaction with decision (not) to undergo testing

	Group 1 Test offer decliners n= 120	**Group 2 Test decliners n=26**	**Group 3 Test acceptors n=234**	**Total n=380**
Decisional conflict*,**				
T1: Low	NA	7 (70.0%)	116 (50.9%)	123
Moderate	NA	3 (30.0%)	95 (41.7%)	98
High	NA	0 (0.0%)	17 (7.5%)	17
T2: Low	NA	NA	139 (72.8%)	139
Moderate	NA	NA	49 (25.7%)	49
High	NA	NA	3 (1.6%)	3
T3: Low***	9 (20.5%)	4 (44.4%)	94 (55.0%)	107
Moderate	18 (40.9%)	4 (44.4%)	62 (36.3%)	84
High	17 (38.6%)	1 (11.1%)	15 (8.8%)	33
Satisfaction with decision making$				
T0: Anticipated regret#	N=93 33 (35.5x%)	N=24 14 (58.3%)	N=232 127 (55.0%)	N=347 174 (50.1%)
T3	N= 45 (%)	N=9 (%)	N=173 (%)	N=227
Dissatisfied with decision	4 (8.9%)	0 (0.0%)	1 (0.6%)	5 (2.2%)

3.7.4.3.2 Anticipated regret and satisfaction:

Table 3.15 also displays reported satisfaction with decision making at T0 and T3. At T0, test offer decliners reported anticipated regret regarding test participation less frequently than test decliners after GP counselling (35.5.% vs 58.3%, p=.04) and than test acceptors (35.5x% vs. 55.0%, p<.001). At T3, 222 (97.8%) individuals were satisfied with their decision irrespective of what that decision was. Four test offer decliners were dissatisfied with their

decision not to undergo testing of which two had anticipated regret at T0. One test acceptor with anticipated regret at T0 was dissatisfied with the decision to have ECS testing.

3.7.4.3.3 Reproductive intentions:

All couples who had the test received normal (i.e. non-carrier) couple results. For 150/168 (89.3%) of these test acceptors, the test-result had not influenced their reproductive plans, i.e. wanting to have children with this partner. Four individuals (4.2%) were not sure about whether the test result had changed their reproductive plans. The remaining 14 individuals indicated that the test-result had certainly (n=8, 4.8%) or possibly (n=6, 3.6%) changed their plans: they were more certain about having children with this partner.

3.8 Discussion

3.8.1 Summary

In this Chapter, I presented the findings of regarding the implementation pilot study of couple-based ECS by trained Dutch GPs to couples from the general population. First, the findings regarding uptake of the test offer were demonstrated. Participants' characteristics, views and barriers in terms of access and acceptance were identified. These findings demonstrate that approximately 3% of all women approached and 15% of the estimated target population attended pre-test counselling with their GP, that is, were test offer acceptors, of whom 90% proceeded with the test. Secondly, I presented the findings regarding feasibility and informed choice. These findings demonstrated that implementing an ECS couple test consisting of a limited set of severe conditions in the GP setting was a feasible approach that resulted in an informed decision in most cases. Thirdly, I presented the findings regarding psychological outcomes and reproductive intentions. After receiving the test offer, all study participants reported mean anxiety scores lower than or comparable to the population reference. Mean worry was low and remained stable over time. Individuals who attended GP counselling and proceeded with testing reported less anxiety and worry compared to those who did not undergo testing. Long term changes in anxiety and worry were absent. Short-term increased worry was only seen after GP counselling (T1), in the subgroup that attended GP counselling but declined testing (group 2). At the individual level,

a minority of participants reported clinically relevant increased anxiety, especially in the test offer decliners and test decliners after GP counselling. Decisional conflict was low to moderate for most test-acceptors and test-decliners, but most test offer decliners reported moderate to high levels of decisional conflict at follow-up. Finding out that they were not a carrier couple did not affect participants' reproductive intentions, or occasionally, they were more certain about having children with this partner.

3.8.2 Uptake

A few other studies have looked at uptake for single/few genes carrier testing in the Dutch general population. Henneman et al., (2003) reported a 25% rate of test offer acceptance of GP-provided cystic fibrosis (CF) carrier screening and an acceptance rate of 10% when couples attended educational sessions. Lakeman et al. (2009) reported a test offer acceptance rate of 3% in their study on ancestry-based hemoglobinopathies and CF carrier testing by GPs in the Netherlands(149). Although uptake rates in this research are similar to those from Henneman et al. (2003), differences in the design of the research prevent direct comparison of results. Furthermore, Gilmore et al., (2017) reported a 66% decline rate amongst eligible women in genomic carrier screening for reproductive purposes after being asked by telephone to participate(146). This suggests that more eligible women decided to participate than in this research. However, differences in research design, such as the mode of invitation, eligibility criteria of having had carrier testing previously, and the option to receive medically actionable secondary findings, preclude direct comparison. Uptake figures are informative because they demonstrate whether actual uptake reflects couples' intentions and could highlight potential barriers in test accessibility. Although, as stated earlier, the main purpose of offering ECS in this setting was to inform couples' reproductive decisions (24,235) and maximising uptake rates was not an aim in itself.

In line with the existing literature (149,241), test offer acceptance in this research was lower than stated intentions. The findings demonstrate that practical barriers likely played a role for some test offer decliners in this research, in particular having to make an appointment with the GP together, which was partly due to the design of this research. It is preferable that any future nation-wide large-scale test offer should still include pre-test counselling, because couples prefer to discuss this type of testing with a health professional, their GP in particular,

and because this was shown feasible and resulted in informed decisions (21). Gilmore et al., (2017) also found that logistical barriers such as lack of time were reasons mentioned frequently for women to decline participation in genomic carrier screening (146). In addition, Gilmore et al., (2017) suggest that healthy individuals might not feel as much need to overcome barriers to test-participation in comparison to affected populations (such as parents of children affected by a genetic condition), where test-participation is usually higher (146). Opportunities to alleviate the impact of these barriers are available and include web consultations with GPs, consultations outside office hours, and targeted information materials or decision aids to increase efficiency of the pre-test counselling, as well as the possibility to consult genetics professionals when necessary.

Apart from practical barriers, there are alternative reasons why the uptake rates in this research may deviate from those expected in future nationwide large-scale implementation. Firstly, the study was conducted in the northern part of the Netherlands, an area where participation in reproductive/prenatal genetic testing is typically lower than other areas of the Netherlands (145). In addition, design related issues other than attending GP counselling with both partners may have resulted in lower acceptance rates. Most notable examples are the study's consent procedure where 29% of women interested in participation did not return the consent forms and the test offer was conditional upon survey participation. Thirdly, this test offer was a new and one-time offer, as ECS is not (yet) part of routine preconception care. Given that not all pregnancies are planned and most couples access health services prenatally rather than prior to conception, offering ECS during pregnancy as well may improve access to care. Finally, given that the UMCG couple test was offered to couples free of charge, I could not examine to what extent co-payment might be a barrier to test-participation. Research indicates that whilst people are willing to pay for ECS (21,242), this is often lower than the actual cost of the test itself; thus financial barriers might also diminish access to care, particularly for couples with low income. GPs agreed that it was preferable to include both partners jointly in the discussion of ECS as this affects both prospective parents. To lower practical barriers to attend counselling, in the future GPs could use web-consultations or face-to-face consultations at times desired (evenings/weekends), although this requires additional training and adjusted infrastructure.

3.8.2.1 Acceptors and Decliners

The majority of study participants had a positive intention towards test-participation, and this was high even among test-decliners (69%). Test offer acceptors and decliners in this research were comparable in terms of socio-demographic characteristics, health status and experiences with chronic or hereditary conditions. In contrast to Gilmore et al. (2017), I did not find that participants having experiences with any kind of, self-defined (presumed) hereditary conditions more frequently accepted testing (146). In this research, couples who had experiences with (presumed) hereditary conditions, may have associated this less with their reproductive risk of having children with the specific severe AR conditions in this ECS test. The difference may also partly be due to the possibility to receive medically actionable secondary findings, as Kauffman et al. (2017), reporting on the same study, found that participants' main motivation was to obtain this general health information. Most experiences with (presumed) hereditary conditions are likely to be adult-onset disease (243).

Test offer acceptors more often had a higher educational level than test offer decliners, which was also higher than the Dutch general population (244). Other studies on reproductive genetic counselling and testing show similar findings (145,146,190). Acceptors also differed from decliners regarding their reproductive/relationship profile in this research: they less often already had children, had a higher relationship satisfaction, and were less likely to plan their pregnancy in the very near future. These differences may suggest selection bias, but unequal representation is only problematic when access to the ECS test and information leading to informed choice are not equally available to all couples planning a pregnancy. Further research on the determinants of test offer acceptance including these aspects, couples' decision-making and couple dynamics, may help to identify relevant subgroups of patients to tailor information strategies and remove barriers to test-participation. The intention rate for ECS-testing of participants in this research (87%) was more than double the intention rate in the previous research regarding a hypothetical scenario (34%) (21). Therefore, in this research subsection of couples of reproductive age were identified, who would like to make use of couple-based ECS when it was made available to them through the GP free of charge, but it is unlikely that the participants' characteristics are generalisable to all couples planning a pregnancy.

3.8.2.2 Reasons to accept and decline

All participants were asked to indicate their reasons for or against taking part in ECS, regardless of whether they chose to accept the test offer. The reasons test offer acceptors and test offer decliners considered most important for or against ECS did not differ much. This was unexpected, but an explanation for these similarities might be the relatively homogenous study sample of which most started with the intention to accept this couple-based ECS test offer. At the same time, I was also interested in understanding why not all eligible couples were interested in taking part. The explanations on the response cards reflected a variety of ethical, personal and practical arguments. Given that I only had access to a small group of those eligible women who decided not to take part in the research, more in depth exploration of motivations for undertaking and not undertaking ECS in the general population could be helpful to gain a better understanding of the desirability of offering ECS and potential barriers preventing all eligible couples from accessing ECS. The most important reason for participants to accept (to spare a child a life with a severe genetic condition) or decline testing (the test would not alter their reproductive plans) are in line with the literature (21,24,69) and align with the current aim of offering ECS testing (enhancing couples' reproductive choice); participants' reasons to decline the test offer were not based on misunderstanding about the purpose of the test, or fears of discrimination or stigmatization. As second most important reason to accept couple-based ECS, 18% of participants considered this their responsibility as a future parent. The perceived feeling of responsibility as a future parent to undergo ECS, is also brought forward in the paper of Van der Hout et al. (2019), who discuss this should be included as an aim for a (preconception) ECS test offer alongside reproductive choice (106).

If they have to indicate a single preference after being informed about the aims of ECS, the majority of research participants indicated a preference for a couple-based approach over disclosing individual results. These results underline the findings of the previous study amongst potential users about couples' views on couple-based ECS (64). It should be noted that the response rate of survey T3 was relatively low in comparison to that of survey T0. Most of the drop-outs were test offer decliners, who had a 45% response rate compared to 70% for test offer acceptors. This means that the findings from survey T3 should be viewed

with caution regarding the views of test offer decliners. Regarding potential differences, participants with a higher educational level were more likely to respond to T3.

Given that it is the combined 'couple result' which conveys information for reproductive decision-making, arguably, ECS couple testing would be the new approach to offer carrier screening for AR conditions to the general population. In this Phase 1 research, I focused on couple-based ECS as a free of charge test offer in the Dutch public health system. Currently, ECS is not yet equally available and/or affordable to all couples planning a pregnancy. That is to say, in certain contexts, arguments for couple-based testing or reporting individual carrier states may be different, such as for high frequency conditions in certain populations especially when cascade testing is reimbursed and population based ECS is not (yet), when using whole exome sequencing in consanguineous populations and for ECS in a private setting.

3.8.3 Feasibility and Informed Decision Making

Importantly, all participating GPs felt and were judged competent to conduct pre-test counselling after being given training, supported by genetic professionals on demand, and assisted by a counselling-checklist. Participating couples were very satisfied with GP pre-test counselling and the Dutch Society of General Practitioners recently stated their support for (more) studies investigating the implementation of ECS in primary care (36). This approach therefore has the potential to address the concerns about the current lack of genetic literacy and counselling skills among non-genetics HCPs providing genetic tests, and these findings can inform options for responsible mainstreaming in genetics.

Most pre-test counselling sessions were conducted within the allotted time span of 20 minutes, with additional counselling sometimes needed to discuss general preconception care. In some situations, it might be more effective to separate the two types of counselling: directive (e.g. advice not to smoke or drink alcohol) and non-directive (facilitate reproductive decision-making in line with couples' values).

A study of CF carrier testing in primary care showed that GPs could conduct the (less complex) counselling in an average of 12 minutes (89). According to participating GPs, pre-test counselling within the allocated time was facilitated because couples were already well-informed, perhaps due to the extensive study information, website and the

questionnaires participants filled out.

The findings of this research suggest that GPs could have extended their pre-test discussion of the reproductive options available for couples who are found to be both carriers of the same condition, which would also include an assessment of the value system held by that couple. Such discussions are standard practice for GPs, but future training could be adjusted to focus more on these aspects in the preconception setting. Couples do not often request preconception consultations from GPs or other HCPs in the Netherlands (245), thus an added benefit of the ECS test offer meant that GPs could discuss or follow-up on GPC advice with more couples –and both partners- than was routine

This research concentrated on the offer of ECS within primary care. Eligible women were actively and individually approached by their GP by letter. Large scale implementation could also be a more passive and collective approach, e.g. via posters, leaflets and information about the test on GPs' websites. However, this requires the public to become more knowledgeable on this topic, which means more educational efforts would need to be aimed at this group. Moreover, couples could fill out an online decision-aid in advance to inform and prepare them and facilitate efficient and effective pre-test counselling. No major barriers to large-scale implementation were mentioned by GPs in our study provided they can use 20 minutes for the counselling and that there are no financial barriers for them and their patients. These findings should inform discussions with relevant stakeholders to negotiate reimbursement for the consultation as well as the test, as was also mentioned by Henneman et al., (2016) as one of the recommendations for responsible implementation of ECS (24).

GPs in this research suggested that ECS could be provided by 'specialised' GPs who focus on a specific aspect of GP care. Not all GPs may be interested in investing the time and effort necessary to obtain and maintain the required counselling skills, considering that the total number of counselling sessions per GP might be relatively low. The specialisation approach would guarantee the necessary minimum number of pre-test counselling sessions per GP per year to maintain competence. GP specialisation already exists in the Netherlands in areas such as elderly and palliative care. Other primary HCPs involved in preconception care—such as midwives, community pediatricians or nurse practitioners—might also be willing to offer ECS.

In all scenarios, the role of Clinical Genetics in a population-based ECS couple test could focus on education, support/auditing and post-test counselling for carrier couples.

Salient features of the adopted approach to ECS were the well-considered composition of the test-panel and the provision of couple-only results for this population-based offer through participating GPs. The composition of the panel facilitated a generic type of consent and the couple-based strategy resulted in a minimal need for post-test counselling by the GP or Clinical Genetics professionals. As time to discuss all conditions in detail is limited and some couples desire more information, extensive information about the conditions should be easily accessible for couples, as was the case on the UMCG website.

3.8.4 Psychological outcomes:

3.8.4.1 Anxiety and worry

Despite differences in setting, research design and included couples, the results on anxiety are comparable with the study of Kraft et al., (2018) which showed that anxiety scores at T0 were low and remained stable and low in women who participated in preconception ECS and received negative (normal) results (153). Furthermore, the test offer decliners and test decliners after counselling reported on average higher anxiety scores than the test acceptors. This is also comparable to the study of Kraft et al., who found higher anxiety levels in the group that did not undergo ECS but just received regular care compared to those undergoing ECS (153). Metcalfe at al. (2017), in their study on preconception and prenatal Fragile X carrier screening, reported higher baseline (36.3-38.7) as well as 1 month follow-up anxiety scores (34.3-34.5) in non-pregnant women compared to my research and the study of Kraft et al (2018)(152,153).

The proportion of individuals reporting increased anxiety in my research (18-19%) was comparable to the 17.2% (test negative results) and 22.3% (untested individuals) at 3-6 months follow-up as reported by Honnor et al., (2000) in a study about CF carrier testing in the general population (246), despite some lack of clarity about their definition of ‘raised anxiety’. My results are comparable to or slightly higher than the percentages reported by Metcalfe et al.: 15-19% at baseline and 12-16% at 1 month follow-up in non-pregnant women using the Depression Anxiety Stress Scale (DASS)(152).

The proportion of participants who did not proceed with testing and reported clinically relevant anxiety was larger than that in test acceptors. Metcalfe et al. found the same trend: clinically relevant anxiety is more frequently reported in individuals who decide not to participate in testing (152). This finding could have multiple explanations. First, it is common that a certain proportion of people in the general population have increased anxiety levels at any one time as anxiety may be caused by other factors beyond this test offer. Furthermore, these relatively high percentages may have been caused by small numbers and selective response. The finding that test offer acceptors show lower levels of anxiety compared to test offer decliners might indicate that especially people with low(er) anxiety levels have accepted the test offer.

Worry was not reported in the Honnor et al. and Metcalfe at al studies. Kraft et al. studied worry about test accuracy, concern for family members and privacy concerns about the test result. Despite differences in concepts and instruments used, their mean worry and concerns scores are low and stable over time, a finding comparable to my research (153).

3.8.4.2 Decisional conflict, satisfaction and regret

After counselling and at follow-up, the vast majority of test-decliners after counselling and test-acceptors hardly felt conflicted about their decision to undergo testing. In contrast, almost 40% of test offer decliners reported high decisional conflict at follow-up. This is in line with Metcalfe at al.: high decisional conflict and decisional uncertainty occurs more frequently among those not tested (152). Possible explanations for the high decisional conflict rates among test offer decliners are the following. First, this subgroup possibly felt unsure about whether to undergo testing. O'Connor et al. demonstrated that higher DCS scores are found in people who are unsure about participation in screening or delay their decision (247). This could apply to test-decliners in my research, as most of them had a positive intention towards accepting this test offer at baseline but room for delay was minimal as couples had to make a GP appointment within approximately 1 month. Secondly, the test offer decliners, while being approached with the 6 month's survey, may have been confronted once more with a decision that was difficult for them to make the first time, or an issue they considered already dealt with in the past. Moreover, decisional satisfaction was high irrespective of the decision taken.

3.8.4.3 Reproductive intentions

My results regarding reproductive intentions are comparable to Lakeman et al., (2008) and Kraft et al., (2018) who report that over 90% of test-participants who were not identified as a carrier couple did not intend to change their reproductive plans and some felt more certain (73,153). This suggests an expected and reassuring minimal impact on reproductive decisions for those testing negative. However, one should be aware that this may lead to false reassurance if couples do not understand the residual risk or that ECS does not guarantee future children will not have genetic conditions (37). A recently published review on reproductive decisions for those identified as carrier couples demonstrates that most couples decide to change their reproductive plans to avoid conceiving a child with a severe genetic condition (154). Due to the (expected) absence of test-positive results, I could not investigate this nor was that my aim.

Strengths of this research regarding psychological outcomes are that I included couples who were not interested in accepting the test offer, and I distinguished between those who declined the test offer (and counselling) and those who declined the offer after counselling. There are also several limitations that merit discussion. Firstly, the scores on the first survey (T0) perhaps do not represent a 'true' baseline measurement, as participants had already been informed about the study and had the possibility to read the information leaflet before filling out the first survey. It is important to note that the mean T0 scores were comparable to levels reported in similar studies (e.g.(30,221,222)). Secondly, in this study, I analysed individuals, not couples, assuming that their responses were independent from each other. This choice is debatable. Previously, the Groningen research group have shown that views regarding ECS between couples are comparable (64) but this does not necessarily imply that their anxiety, worry, or DCS scores are also correlated. Finally, individuals who did not proceed with testing were less likely to fill out the last survey. Although these low numbers may affect generalisability, response did not seem to be selective. It is possible that the type of test offer, i.e. both couple members are tested simultaneously and only the couple result is disclosed, may have contributed to the favourable psychological outcomes, but I could not investigate this in my research. Future research should clarify if disclosure of individual carrier results in

those that opt for this, leads to in misunderstanding of individual health implications, negative feelings of being a carrier, stigmatisation and more anxiety and worry (62,248). Moreover, large-scale implementation of ECS should include a follow-up to determine the psychological impact and impact on reproductive decisions in those being identified as carrier couples (249).

3.8.5 Concluding remarks

This GP-provided couple-based ECS test for a limited number of severe AR conditions in the setting of preconception care, presents a timely and responsible option to inform couples planning a pregnancy about their chances of having a child affected by a severe AR condition. This approach was not only feasible in this setting, but also led to an informed choice for most participants and no meaningful adverse psychological outcomes were found. Future national implementation could involve other dedicated GPs, or other primary HCPs willing to be trained to provide the test, given that support as well as practical tools from a clinical genetics service are available. Furthermore, some factors identified in this research should be considered such as raising public awareness to facilitate a well-informed population and resolution of reimbursement issues. The approach taken in this research, that was feasible in the (northern) Netherlands, might be transferable to other (European) public health systems with easily accessible primary health providers who are willing to be trained and have the necessary resources to offer ECS. In conclusion, these results suggest that this approach to couple-based ECS could be provided by GPs is responsible in this setting.

Preferences regarding the ECS test offer indicated that the target population felt a couple-based approach to ECS was acceptable. Not disclosing individual results remains a matter of debate given the perceived utility for cascade screening (38), as well as the participants' personal preferences of the participants (63). During the course of this PhD (2016-2020), other ECS test offers have been developed in a number of public health care systems, such as that of Belgium and Australia. (250). How results are reported differs between these initiatives. For example, in Belgium, the Superior Health Council advised to report couple results only, but enable disclosure of individual carrier states if people request those (45). Therefore, whilst the couple-based test offer seems acceptable, how results are reported is still a matter of debate. In Phase 2, I aim to gain a more in depth, contextual understanding of both couples and HCPs' views and experiences when couple-based ECS is offered in a

fertility setting. In Chapter 4, I discuss the methods and findings for Phase 2: Couple-based Expanded Carrier Screening: Exploring the Experience in the Fertility Clinic.

Chapter 4 Phase 2 Couple-based Expanded Carrier Screening: Exploring the Experience in the Fertility Clinic

4.1 Chapter outline

Phase 2 consisted of qualitative research, focused on the ethical issues inherent in the provision of couple, rather than individual results as well as on the practical issues and implications for clinical practice this type of testing might raise in a fertility setting. The concept of providing couple results was the unique aspect of the ECS test offer I set out to investigate in my research. This is why the aim of this second Phase was to conduct an in depth exploration of this concept as part of the overall evaluation as to whether couple-based ECS would meet criteria for responsible implementation.

This chapter is divided into two main sections: Methods (4.3) and Findings (4.4). In Phase 2, I focussed on the ethical issues raised by reporting couple results only, rather than reporting individual carrier states when expanded carrier screening (ECS) is offered to couples with no prior risk of having children affected by autosomal recessive (AR) conditions. The fertility clinic enabled me to explore the ethical issues in a setting where the social and genetic couple are sometimes different.

ECS was not routinely available for couples referred for fertility treatment. In the NHS, carrier testing for cystic fibrosis (CF) is already part of the mandatory screening of potential gamete donors (251) and guidelines recommend that carrier testing for other conditions is offered based on the donor's ethnic background and family history of genetic conditions. International sperm banks increasingly perform ECS on their donors, however, reproductive risk of recessive conditions can only be determined if similar services are also offered to recipients (252–254). No carrier testing was yet available for couples using their own gametes to conceive unless they would meet the family history or ancestry-based NHS criteria for carrier testing.

Two fertility clinics in the Wessex region were interested in introducing ECS into their clinical service, and they were willing to explore whether these new genomic developments could be helpful in improving their current practice.

The clinics considered the couple-based ECS test developed by the Department of Genetics of the University Medical Centre Groningen (UMCG) as potentially clinically relevant for their patients, both recipients of donated gametes and for couples using their own gametes in an assisted reproductive technology (ART) setting. In contrast to the implementation pilot presented in Chapter 3, couples or individuals who wanted to make use of the test offer in the two fertility clinics had to pay for the test themselves. Both fertility clinics offered similar clinical services, including Intra Uterine Insemination (IUI), In Vitro Fertilisation (IVF) with or without Intra Cytoplasmic Sperm Injection (ICSI), and fertility preservation. Gamete donation (sperm as well as egg donation) was available in the two clinics and surrogacy was an option in one clinic (clinic no. 2). At the time when the research was conducted, both clinics accepted patients who were funded by the National Health Service (NHS) as well as privately funded patients. Clinic 2 decided to incorporate this test into their clinical services.

Couples and individuals referred for fertility treatment were invited to take part in semi-structured interviews. Couples who accepted the test offer were also asked to participate in a follow-up interview after they had received their test-result. Health care professionals (HCPs) working in fertility care and clinical genetics were asked to participate in focus groups. HCPs who had been actively involved in providing the test offer were asked to take part in a second focus group. Data analysis took place iteratively following the thematic analysis approach proposed by Braun and Clarke (178).

4.2 Research question and objectives

The main research question I aimed to address in Phase 2 was the following: What are couples' and HCPs' views and experiences regarding the ethical and practical issues of couple-based ECS in a fertility setting?

This research question resulted in the following objectives:

- Identify and analyse the ethical issues and practical considerations for couples when they are offered couple-based ECS in a fertility setting

- Explore whether a couple-based approach raises different issues for couples where the social and genetic couple are not the same
- Identify and analyse the key ethical issues for HCPs when couple-based ECS is implemented as part of standard fertility treatment
- Identify the implications for practice and/or practical barriers to implementation of couple-based ECS in a fertility setting for HCPs

4.3 Methods Phase 2. Couple-based Expanded Carrier Screening: Exploring the Experience in a fertility setting

In the following sections, I discuss and reflect on the methods I used to address the study objectives as defined previously. I start with a discussion of the methods for the research with couples and individuals referred for fertility treatment, followed by a discussion of those used with HCPs. For each of these, I outline the research design, including sampling and recruitment and provide an overview of the procedures and research participants. I first describe what I set out to do and subsequently reflect on how this approach changed throughout the course of the research. In addition, I discuss the development of the interview framework and focus group topic guide, and the analysis of the data. I end with a reflection on some of the ethical issues I encountered during the research. The research received NHS ethics approval (REC 16 LO1966). Relevant documents, such as the research protocol and participant information sheets (PIS) can be found in appendix B.

4.3.1 Interviews with couples

4.3.1.1 Research design

This research was originally intended as longitudinal, whereby the UMCG couple-based ECS test would be offered by fertility consultants to their patients (initially for couples or individuals using an egg donor) with interviews taking place prior to and after they had received the test-result. Thus, couples or individuals who were being offered the test could take part in two interviews. When I use the words interview participants, I refer to these study participants. Consultants were to receive training prior to the start of the test offer in order to be able to provide pre-test counselling. This initial approach changed because the first clinic

that I recruited decided not to offer the ECS test during the research period. This meant that in this clinic I could only do interviews with couples based on a hypothetical scenario. A second clinic was then recruited who were interested in introducing this test in their clinic and this allowed me to do a second series of interviews as intended (i.e. before couples received pre-test counselling and after receiving a test-result for those deciding to undergo couple-based ECS); pre-test counselling training of consultants also took place in this clinic.

4.3.1.1.1 Sampling and recruitment:

Sampling

To obtain information rich data and to cover a range of perspectives, I initially adopted a purposeful sampling strategy where I set out to recruit participants who varied in age, gender/sex, type of funding as well as 'type of genetic couple'. Access to fertility treatment and NHS funding depends on the age of the woman, because female fertility and success rate of the treatment decreases with age. This means that the experience of fertility treatment and how the offer of ECS is viewed might be different for a 'young' couple (e.g. below 35 years) compared to that of an 'older' couple (i.e. aged 35 or over). Secondly, it is likely that male and female participants will bring different perspectives for a number of reasons. For example, medical procedures necessary in fertility treatment are different for men and women: women sometimes require hormone treatment and IVF involves several invasive procedures such as oocyte retrieval. Apart from the distinct physical aspects of fertility treatment between men and women, the psychological, social and emotional implications of infertility and fertility treatment and coping strategies are likely to also be different (255). A third factor that I used for my purposeful sampling strategy, was the type of funding, i.e. whether couples received NHS funding or whether their treatment was funded privately. Fertility treatment can be very costly. Whilst the UK National Institute for Health and Care Excellence (NICE) recommends funding for three cycles of IVF treatment for women under 40 years and 1 cycle for women aged 40-42 (116), local Clinical Commissioning Groups (CCGs) make decisions about who is eligible for NHS-funding and what is covered by this. For example, the Southampton City CCG allows NHS funding for one cycle of IVF only (115). The type of funding and restrictions regarding NHS funding might therefore be important in whether couples decide to proceed with ECS or not. Lastly, couples undergoing fertility

treatment may use either their own gametes (egg and sperm), or use sperm or oocyte donors to conceive. In other words, the person who contributes the genetic material to the conception might not be the social parent who intends to raise the future child. This also means that the social parent does not undergo ECS testing him/herself. These factors might contribute to their views on couple-based ECS.

Sample size: I expected that 20-25 interviews would be sufficient to explore issues between/within couples. No agreement exists in the literature about the minimum number of interviews that would be enough for a qualitative research project and this depends on various factors, such as sample heterogeneity, purpose and scope of the research (204). As discussed in Chapter 2 (section 2.3) I arrived at this number taking into consideration advice from my supervisors, other qualitative studies with a similar aim, such as Dheensa et al., 2016 (256), considerations regarding data saturation and likely restraints in terms of recruitment, time and word-limit of this thesis.

Recruitment

Recruitment took place in three steps: 1) identification of potential participants by the clinical team, 2) consent, including expression of interest & initial discussion and completion of the consent form. First, the clinical care teams identified patients eligible for participation and provided them with a PIS. The PIS provided information about the background of the research, the procedures involved, the research team and contact details of the patient advise and liaison service (PALS). The PIS also included an expression of interest sheet (EOI). If couples/individuals were interested to take part, they provided their contact details on the EOI. I received the EOIs in the post or the clinical care team gave me/emailed me the EOIs from their patients. Subsequently, I contacted these potential participants over the phone to discuss participation in the research and answered any questions they still had as part of the consent process. If they agreed to participate, we arranged a time and date for the interview. At the beginning of each interview, all participants signed a consent form after having had the opportunity to ask additional questions.

Given the research aims, the eligibility criteria were as follows: couples or individuals who were referred for fertility treatment and (in the second clinic) who were offered ECS. Recruitment took place between February 2017 and January 2019. Recruitment in clinic

1continued until April 2018 and recruitment in clinic 2 took place between August 2018 and January 2019. I do not know the exact number of people who were informed about the research, as members of the clinical team who recruited for me did not collect this information.

I received an EOI form from 25 'couples', eighteen couples form clinic 1 and seven couples from clinic 2. Some participants filled out an EOI individually, some as a couple. I did not manage to discuss participation with all of these potential participants, as some did not answer their phone or respond to emails. Two potential participants cancelled their interview the day before and no further date was agreed as any attempt at rescheduling did not get a positive response. In total, the number of interviews that took place was 14. I interviewed 16 individuals, comprising ten 'couples'. One couple, who were interviewed about a hypothetical scenario, had limited time to finish the interview, which is why we continued the interview on a different day. One couple was interviewed both before testing and after the result had been disclosed.

4.3.1.1.2 Overview of participants

See Table 4.1 for an overview of participants' characteristics reflecting the purposeful sampling strategy: ten female and six male participants were included and the age range was between 32 and 50 years. Four women and one male participant were aged <35 years. A range of different type of couples were included such as single women using a sperm donor, same sex couples, couples using IVF with their own gametes and couples using an egg donor and surrogate. In addition, four couples received NHS funding for their fertility treatment or had received NHS funding in the past. All participants were given a pseudonym and this is how I refer to them when presenting the findings in section 4.4.

Table 4.1 Overview interview participants

Participant characteristics	Couple 1	Couple 2		Couple 3	
Pseudonym	Sally	Jasmine	Helena	Lucy	Dean
Age	32	36	32	41	46
Gender	Female	Female	Female	Female	Male
Highest level of education	A-level	Postgraduate	Undergraduate	Undergraduate	Undergraduate
Part of genetic couple and/or social couple	Genetic and social couple	Genetic and social couple	Social couple	Social couple	Genetic and social couple
Funding	Private	Private		Private	
Mode of conception	IVF with donor sperm	IUI With donor sperm		IVF/egg donation possibility	
Test offer: accept/decline; not offered	Not offered	Not offered		Not offered	

Participant characteristics	Couple 4		Couple 5	
Pseudonym	Matthew	Jane	Ginny	Andrew
Age	40	32	32	41
Gender	Male	Female	Female	Male
Highest level of education	Postgraduate	Undergraduate	GCSE	A-level

Participant characteristics	Couple 4		Couple 5	
Part of social and/or genetic couple	Social and genetic couple	Social and genetic couple	Social and genetic couple	Social and genetic couple
Funding	Combination of NHS and private		NHS	
Mode of conception	IVF		IVF	
Test offer: accepted/declined/not offered	Not offered		Not offered	

Participant characteristics	Couple 6		Couple 7		Couple 8
pseudonym	Emma	Charlie	Olivia	John	Emily
Age	Unknown	unknown	47	50	40
Gender	Female	Male	Female	Male	Female
Highest level of education	Unknown	unknown	Accountancy qualification	A level	Between A-level and degree
Part of social and/or genetic couple	Social and genetic	Social and genetic	Social	Social and genetic	Social and genetic
Funding	Private		Private		NHS
Mode of conception	IVF, possibility of egg donation		Egg donation and surrogacy (IVF)		IVF
Test offer: accepted/declined/not offered	Declined		Accepted, normal result		Declined

Participant characteristics	Couple 9	Couple 10
pseudonym	Sarah	Eduardo
Age	38	34
Gender	Female	male
Highest level of education	Postgraduate	A-level
Funding	Combination of NHS and private funding	Private
Mode of conception	IVF with donor sperm	IVF, egg donation and surrogacy
Part of social and/or genetic couple	Social and genetic couple	Social and genetic couple
Test offer: accepted/declined/not offered	Declined	Accepted

4.3.1.2 What changed and why regarding the design of the research

In Clinic 1, the interviews were conducted around a hypothetical scenario, because the clinic decided not to offer this test to their patients. At the same time, they were still supportive of the research and I continued otherwise as planned. I accepted any couple or individual referred for fertility treatment who were interested to participate, regardless of the type of treatment or type of couple. Clinic 2 decided to offer all patients ECS couple testing from August 2018 onwards and any couple/individual who was offered the ECS-test was eligible to take part in the research.

Each interview, irrespective whether they were from Clinic 1 or Clinic 2 started with a brief discussion of what participants knew about couple-based ECS. I provided a brief explanation of what ECS entails to participants from Clinic 1 and asked them to read an information leaflet about the test during the interview. In addition, all information packs from Clinic 2 to new patients included detailed written information about the test and test-procedures. However, this information was not yet routinely included for the participants in my research. Thus, interview participants from Clinic 2 mainly received information about the test from their consultants.

As it proved rather difficult to recruit couples into the research, I did not manage to include 20-25 participants/couples. Some practical barriers prevented recruitment of more couples. Firstly, I depended on the goodwill of the very busy consultants to identify eligible people. Not all patients who expressed interest in the research decided to take part and some cancelled their interviews at the last minute. In addition, based on regulations regarding research ethics, patients could not take part in more than one study at any one time, which limited the number of people I could approach. I was confident when I finished recruitment that I had sufficiently rich data to support the conceptual themes and address the research objectives I set out to study as discussed in section 2.3.

4.3.1.3 Development of the interview framework:

In this section, I discuss the interview framework that was used to guide the interviews and how it developed throughout the research. The interview framework was a dynamic document, which developed further during the course of the research. The initial framework,

as submitted for NHS ethics review was based on critical review of the literature, experiences during Phase 1 and discussion with my supervisors. The main topics discussed in each interview are presented in Table 4.2.

Table 4.2 Overview interview framework

Overview interview framework	
Introduction	Discussion of any outstanding issues, signing of the consent forms, explaining my role of researcher, start recording the interview
Topic 1	Background, reasons for fertility referral
Topic 2	Exploring first thoughts about test offer
Topic 3	Views and experiences with genetic testing as part of fertility treatment
Topic 4	Discussion of test with partner
Topic 5	Important reasons to accept test
Topic 6	Important reasons not to accept the test offer
Topic 7	Decision-making
Topic 8	Meaning of a positive test-result
Topic 9	Meaning of a couple result
Debrief	Room for any questions, evaluation

4.3.1.3.1 Reflections on how the interview framework was adapted throughout the research

I adapted the interview framework to test and explore the theoretical concepts in more detail at several stages of the analysis process as the interviewing progressed.

After the first few interviews, it became clear that most participants understood the concept of the couple result regarding reproductive risk, but struggled with expressing how it affects them, or why it would make sense to request individual results (or not). I aimed to explore this aspect in more depth as the interviews progressed and intended to check participants' understanding more explicitly. The second aspect that I thought was particularly interesting was how couples' perceived their investments in their fertility treatment (financially, emotionally, and psychologically) in relation to how useful ECS would be to them. Some

potentially interesting factors I identified were the increasing commercialisation of fertility care, NHS commissioning, and people's strong desire to conceive in this setting.

As I recruited a second clinic, which introduced the ECS test as part of their clinical service, I could also explore the ethical issues related to actual rather than the hypothetical scenario and the HCP's role in this decision-making process. After interviewing five couples about a hypothetical test offer, I started interviewing couples who were actually offered ECS couple testing. I was interested in whether an actual test offer would result in different views on the concept of couple testing, participants' views on an ECS test offer and their motivations to undergo testing. I aimed to explore in more detail what participants meant by 'the more information the better'; and whether participants confused the purpose of ECS with the purpose of fertility treatment. In the focus groups conducted with HCPs from the clinical genetics service and Clinic 1, HCPs expressed concerns that couples might misunderstand the purpose of this test as providing an explanation to couples' fertility problems or increase their chances of establishing a pregnancy. The interviews in the clinic 2 allowed me to explore these issues from the perspective of the couples.

4.3.1.4 Data analysis

Data analysis for both the interviews as well as the focus groups took a qualitative approach by using thematic analysis as described by Braun and Clarke (146). The process of conducting thematic analysis is presented in Table 4.3 and follows six steps. These steps are followed not necessarily in strict chronological order, but rather in an iterative way.

Table 4.3 Six steps of thematic analysis

1. Familiarisation with the data
2. Generating initial codes
3. Searching for themes
4. Reviewing themes
5. Defining and naming themes
6. Producing the report

Familiarisation with the data meant that I immersed myself in the data and started to get a feel of what the data contained in relation to the research question. I familiarised myself with the data by listening to the audio-recordings of the interviews, doing several transcriptions

myself and reading through the transcripts several times. At the same time, I made notes about aspects of the data that could be of interest to the research question, such as people's misunderstanding of genetics, and how their views of ECS were different when they talked about their personal circumstances compared how they thought this type of genetic testing would have societal implications. .

For the second step, I used the process of coding to identify and label parts of the data that were meaningful in relation to the research question. Initially, the codes comprised broader labels, such as: 'motivations of couples to participate in ECS', 'couple-testing' and 'societal implications'. These bigger chunks of data were subsequently used for more in depth, line by line coding. The third step involved refinement of themes. For example, in one of the first rounds of analysis, I considered 'responsibility as a future parent' as a potential theme. When I reread the extracts associated with this candidate theme, it became clear that responsibility was not the overarching concept. Rather, it seemed that the overarching concept was more related to the idea that the more information couples received, the more informed they felt about their reproductive decisions. Moreover, many participants expressed a desire to have a healthy child, given the difficulties of conceiving, and the possibilities fertility treatment provided them with a little bit more control over this. Therefore, I redefined the theme around responsibility into: 'The more information the better the chances of conceiving a healthy child'. Subsequently, I tried to map all potential themes into a thematic map, see Figure 4.1.

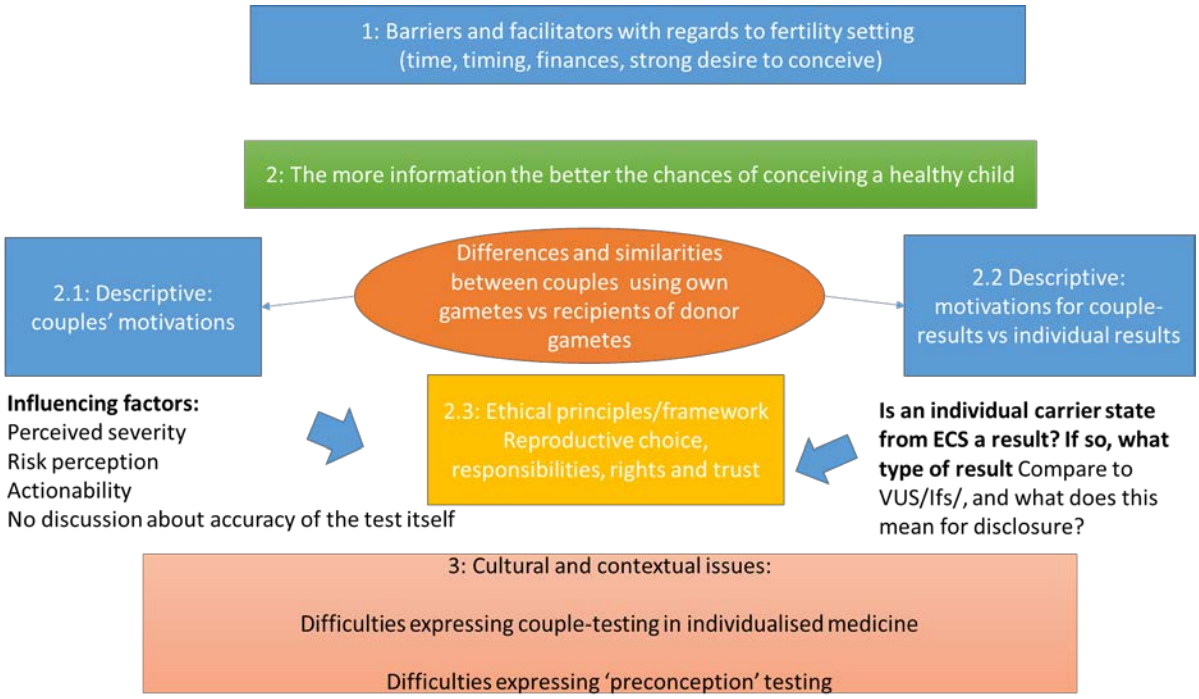

Figure 4.1 Initial thematic map

When I started writing up the analysis, it became clear that this thematic map was too elaborate and I therefore struggled to create a logical narrative for the data. After a lot of redrafting, I came up with another thematic map, which was simpler, but still conveyed the same overall idea: that couples' initial view is that ECS is beneficial because it would provide them with information regarding their reproductive risk but, in practice, their views regarding couple-based ECS in a fertility setting are very nuanced and cannot be captured by 'enhancing reproductive decisions' alone.

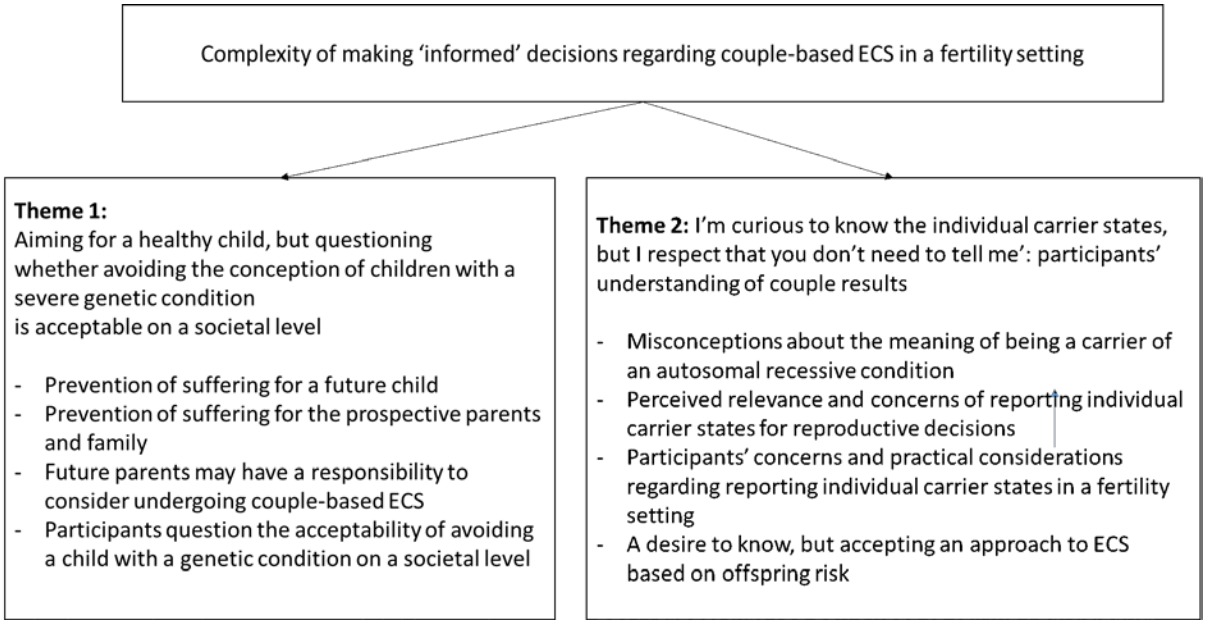

Figure 4.2 Final thematic map

Thus, the pre-final phase of data analysis consisted of writing a detailed analysis for each theme, defining the scope and content for each theme and how they fitted together in the narrative of the data. At this stage, it was also important to review the hierarchy of the themes and whether these were able to be divided into subthemes. The final writing up phase involved writing the complex story of the data in a way that was convincing and valid.

4.3.1.5 Ethical issues related to the research with patients referred for fertility treatment

Written consent was obtained before the start of each interview. Transcripts were anonymised, and anonymity was maintained by ensuring that all participants were allocated an ID number and that the match between ID number and participant names were stored in a secure and separate location from the rest of the research data. I also gave all interview participants a pseudonym. Conducting the research posed low risks to me as a researcher. I followed the University of Southampton lone-workers policy https://www.southampton.ac.uk/waar/HR/staying-safe.page to ensure my own safety when interviewing participants on my own. Some interviews were conducted in the fertility clinics where staff were aware of my presence. When I conducted an interview at the participants' house, I informed one of my colleagues of the address. I sent a message when I arrived and when I left the participants' house. We also agreed that my colleague would contact me by telephone if I had not left the participants' house within two hours after my arrival.

Asking couples to discuss their fertility treatment might raise anxiety or stress. Participants were informed that the interview could be stopped and continued at a later date or that they could withdraw from the research. If this had been necessary, I would have discussed with couples who were distressed that they should inform their clinical care team or I would have referred them to a patient support group such as the Infertility Network UK that offers those facilities. From experience in previous research and from the literature it is known that risks and uncertainties associated with genetic screening might be difficult for people to understand.

All couples from Clinic 1 mentioned that if couple-based ECS were offered to them, they would have liked to (consider to) have this test and all of these couples thought it should be made available to anyone planning a pregnancy. I knew this test was not going to be offered to them, but by interviewing them, or even providing them with information about the research, I made them aware of a risk they may not have considered previously. Thus, the ethical issue of conducting a study with a hypothetical scenario is that people are informed about a potential risk of having a severely disabled child, learn about options of how to potentially avoid this, but then are not actually being offered those options. On the other hand, I was very clear that the test was not available in the consent conversations and at the start of each interview. As the technology is not (yet) standard practice, this also makes this research timely, and exploring couples' views is important before a test like this is going to be offered routinely. I did not get the impression that the couples found this particularly troubling. Most told me they had enjoyed the discussion.

I considered several ethical issues regarding conducting interviews with the couples who were actually being offered this type of testing. They might have made their mind up about testing prior to the interview and the interview might change the way they thought or the discussion might lead to conflict between partners if their motivations did not align. I intended to be careful not to impose my own views or oppose their views, but, at the same time, I also aimed to probe and explore why they had certain views in enough depth. In addition, couples might have misunderstood the purpose of the test and even though I corrected them if they said something that was incorrect, I was not their health provider and I did not want to undermine the relationship with the HCP who counselled them. This meant that I took a tactful approach in what I said and how I went about saying this in relation to couples' understanding of the

test and test-proceedings. As my supervisor advised me, couples might say one thing to me, but say something different to the consultant/staff in the clinic, which I tried to remember whilst doing the interviews.

4.3.2 Focus groups with health professionals

4.3.2.1 Research design

The initial research design was such that HCPs could take part in a focus group before couple-based ECS became part of their clinical practice and a few months afterwards. This longitudinal design was utilised so that it was possible to explore whether HCPs' views on the ethical issues would change/develop and find out about any issues they encountered in practice. This was not possible for all participants: Some professionals were part of the clinical genetics service rather than the fertility clinic and therefore were not involved in the actual test offer; and secondly, as clinic 1 decided not to proceed with this test offer, only professionals who were actively involved with the test offer in clinic 2 were asked to take part in a follow-up focus group.

4.3.2.1.1 Sampling and recruitment

Sampling

I adopted a purposeful sampling strategy for HCPs and aimed to include HCPs ranging in seniority and from different professional backgrounds, for example laboratory scientists in genetics and embryology, nurses, consultants in clinical genetics and reproductive medicine and genetic counsellors. I anticipate that 4-6 focus groups with a group size between 2-6 participants were enough to explore the ethical issues among professionals. Participants were able to choose their group, whenever possible, so they could speak freely without the boundaries of hierarchy or dependency in future professional relationships. All participants were aged 18 or over.

Recruitment

I recruited my participants as follows. First, I sent an email with the PIS attached to those professionals who were identified as potentially interested in participation. After they had expressed interest, I contacted them about any questions they might still have and arranged

a time and place for the focus group to take place. In the clinical genetics service, this was done per email invitation to all clinical genetics staff involved in prenatal genetics. I subsequently arranged two dates and times for a focus group, which were convenient for most of them. In fertility Clinic 1, 15 HCPs expressed interest in participating in the research. In Clinic 2, recruitment was arranged per group-email invitation forwarded by the clinic's manager and subsequently a date and time was arranged on which most interested staff members were available. The follow-up focus group was arranged with those members of staff who were actively involved in providing the test offer.

4.3.2.1.2 Overview of participants

In total, six focus groups took place. Two focus groups were held with clinical genetics' staff, two focus groups took place in the first fertility clinic and two in the second fertility clinic. The last focus group was a follow-up focus group after the fertility clinic had been offering couple-based ECS for several months and participants were HCPs who had been actively involved in the test offer. The number of participants per focus group varied from 4-10. Not all HCPs who had expressed interest were present during the focus groups. In addition, some HCPs who had not initially expressed their interest took part when they heard about the focus group taking place.

Table 4.4 outlines the range of professionals included in each focus group. Some participants represented two different roles, for example fertility nurse and donor coordination, or embryologist and clinic manager.

4.3.2.1.3 Reflection on recruitment:

The purposeful sampling strategy that I adopted aimed to include participants with a variety of backgrounds and a range in seniority. Overall, I included clinical staff, such as doctors, nurses, midwives and genetic counsellors, laboratory staff including embryologists and andrologists, and administrative staff, including donor coordinators, quality managers and health care assistants. From Clinic 1, only a few clinical staff (only nurses) participated, as it turned out to be very difficult for doctors who expressed interested in participation to actually attend . Therefore, I aimed to include doctors in the focus groups in Clinic 2. In addition, whilst I managed to include laboratory staff from the fertility clinic, I was not able to include any

molecular genetics staff. I intended to conduct a separate focus group with laboratory specialists in clinical genetics, but this was unsuccessful. I presented my research at one of the research seminars of the genetics laboratory and tried to recruit participants at the same time, however, none of the staff expressed interested in participating in this research. I tried a different approach where I negotiated a date with one of the senior staff members with the idea of conducting a focus group with the laboratory staff present on the day, but only limited dates were available and unfortunately, on those days I had other research commitments. Apart from a variety in professional backgrounds, I also aimed to include a range in seniority. Overall, the purposeful sampling strategy was successful in this respect, as I included trainees from various professional backgrounds as well as consultants and nurses with more than twenty years of experience in the field.

4.3.2.1.4 Training of fertility professionals in Clinic 2

As clinic 2 decided to incorporate the UMCG couple-based test in their clinical service, the professionals involved in test-provision needed to receive training before the test could be offered. In addition, information materials were developed to include in the information packages the clinic sent out to all their future patients (for an example see appendix B). This training was set up in a similar way as the training for the general practitioners (GPs) in Phase 1. An experienced genetic counsellor from the clinical genetics service was invited to discuss the necessary background information about genetics, AR inheritance and important aspects regarding pre/post-test counselling. The fertility consultants could contact this genetic counsellor for questions when they started offering the test to their patients and they could refer their patients to the clinical genetics service if necessary for additional counselling. I provided extra information regarding the logistics of the blood samples and the research project and together we led the discussion around some of the (ethical) issues that were brought up by the consultants. In addition, I provided the consultants with a checklist of important information, similar to the checklist for the GPs in Phase 1, and the genetic counsellor provided some images to explain genetics and AR inheritance, which HCPs could use in practice. Most of the fertility consultants already provided pre/post-test counselling for prenatal genetic screening, such as the non-invasive prenatal test (NIPT), which meant that they were familiar with some of the complex issues they might encounter in practice.

Table 4.4 Overview focus group participants

Recruitment Focus groups	Clinic 1 Hypothetical test offer	Clinic 2 Test offer introduced in clinical service	Clinical Genetics Service
1	10 participants, all female • *Administrator (2x)* • *Patient pathway coordinator/NHS funding coordinator* • *Finance administrator* • *Lab manager and clinical embryologist* • *Fertility nurse and donor coordinator* • *Health care assistant (2x)* • *Fertility nurse*	10 participants 9 female 1 male • *Nurse and midwife* • *Midwife* • *Sonographer* • *Fertility nurse* • *Doctor (2x)* • *Embryologist* • *Nurse manager* • *Donor coordinator/administrator* • *Donor team leader*	4 participants 3 female, 1 male • *Genetic counsellor* • *Trainee genetic counsellor* • *Specialist registrar in clinical genetics (senior)* • *Specialist registrar in clinical genetics*
2	5 participants, all female • *Trainee embryologist* • *Senior embryologist/ head of fertility* • *Andrologist* • *Quality manager* • *Donor coordinator*	4 participants, all female, • *Consultant reproductive medicine* • *Nurse manager* • *Consultant gynaecologist* • *Consultant fertility*	4 participants, all female • *Genetic counsellor* • *Consultant prenatal genetics* • *Genetic counsellor* • *Genetic counsellor*

4.3.2.2 Development of the focus group topic guide

The focus group topic guide was developed based on the findings of Phase 1, literature review and discussions with the supervisory team. The focus group topic guide that received ethics approval is presented in Box 4.1:

Box 4.1 Focus group topic guide

1: Short introduction of the topic

2: Introduction of participants (professionals background), experiences with carrier screening

3: Ethical issues concerning the implementation of expanded carrier screening in the fertility population

Topics might include, but are not limited to

- Ethical issues associated with couple testing and gamete donors
- 'reproductive autonomy'
- Equal access to health care
- Who should be offered these tests?
- Which diseases to include on these gene panels and why
- Medicalization of pregnancy
- Consent/informed choice
- Rights and duties for patients and health care professionals

4: Practical issues for implementation.

Topics might include, but are not limited to:

- Who are stakeholders in this process
- How to inform patients and health care professionals about the possibility of carrier screening
- How to embed carrier screening in the fertility treatment procedures?
- Requirements of pre-test counselling

5: any other issues not mentioned or discussed before

For example, personal or professionals motivations whether or not to offer expanded preconception carrier screening

The topic guide was intended as a flexible, guiding document during the focus group discussions. That is to say, the topic guide was not restrictive and new topics that were brought up by participants were explored further if considered relevant to the research question. Additionally, analysis of the interviews and focus groups mutually informed the focus group topic guide and interview framework. Given that professionals from various medical specialties were included in the study, some topics were particular relevant to some, but less relevant to other participants.

4.3.2.3 Data analysis

The data analysis of the focus groups followed a similar approach as the analysis of the interviews. I started by transcribing some of the focus groups myself to familiarise myself with the data. Subsequently, I read through the transcripts several times and made initial notes. For example, I identified that the first part of each focus group was spent on trying to get HCPs to come to an understanding of what couple testing actually involves. Furthermore, in certain focus groups it was clear that some participants played a more dominant role in the discussion than others. Whether the clinic had decided to offer testing or not, seemed to affect the attitudes of health professionals towards the test offer, e.g. in Clinic 1 HCPs felt more negative about introducing ECS than in Clinic 2, where a more neutral/positive discussion took place. I then systematically went through the transcripts to develop an initial coding scheme and tried to code as much data as possible.

ECS was a completely new concept to many participants in the focus groups. During the focus groups and the analysis process it became apparent that discussing the concept of reporting couple results only could not be done independently from discussing an ECS test offer in a fertility setting (irrespective of whether this would be couple-based or reporting individual carrier states). In addition, it was interesting to note that some of the issues that I identified were related to introducing a new technology into a clinical setting more generally rather than ethical issues specific to couple-based ECS. I have tried to separate the issues related to introducing new technology from the issues specific to ECS, however, some of these are entangled, such as the importance of training HCPs to conduct pre-test counselling. To address the study objectives, I identified two main themes based on the focus group data (see Figure 4.3):

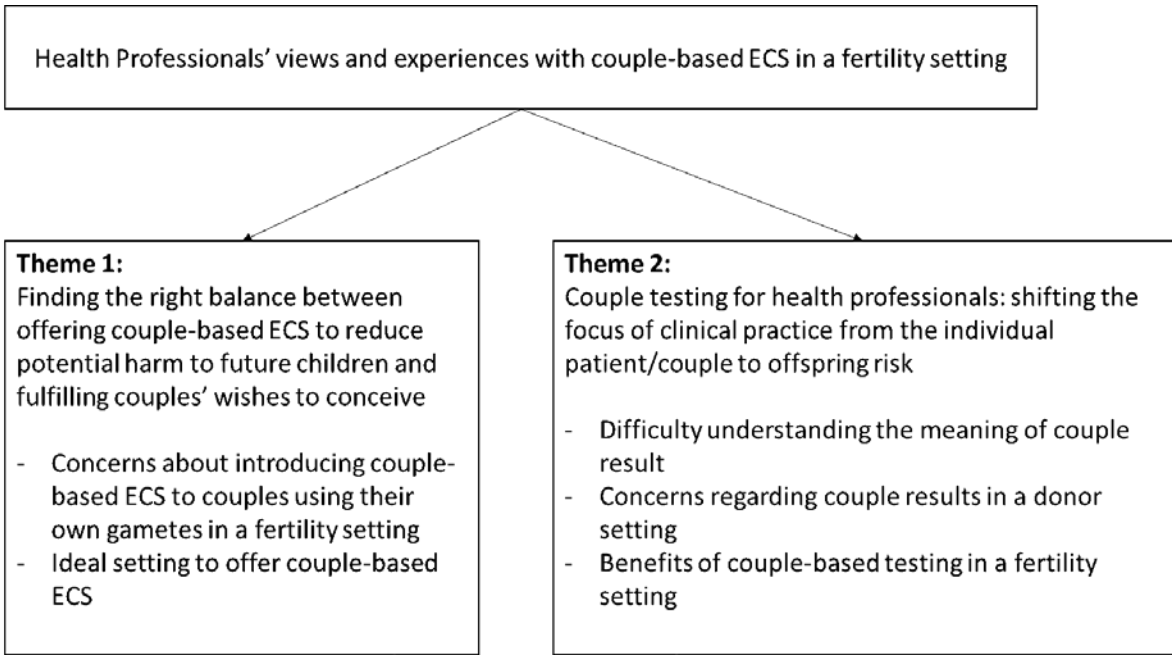

Figure 4.3 Thematic Map for focus group analysis

Analogous to the writing up of the interviews, the final stage of the analysis involved writing the complex story of the data in a way that is convincing and valid. Quotes or extracts from the transcripts were incorporated to support the claims made in the analysis/interpretation of the data. I edited quotes to make them more understandable. An example of how the analysis progressed from initial coding, to more analytic and conceptual coding is provided in Appendix C. A software package (NVIVO) was used to manage the data and assist data analysis.

4.3.2.4 Potential ethical issues related to the focus group research

4.3.2.4.1.1 Consent, confidentiality and anonymity

Written consent was obtained before the start of each focus group. Data was anonymised and anonymity was maintained by ensuring that all participants were allocated an ID number and that the match between ID number and participant names were stored in a secure and separate location from the rest of the research data. Focus group participants knew each other, which meant that complete confidentiality could not be guaranteed. This was discussed with all participants at the start of each focus group. If they wished to do so, they could withdraw from participation after this discussion, but this did not happen.

It is important to note that in November 2016, the fertility sector in the UK was featured in a BBC Panorama documentary called 'Inside Britain's Fertility Business'. This documentary raised concerns about the evidence-base for so-called 'add-ons' to fertility treatment. The sector was accused of pressuring their patients into paying for these expensive additions to their treatment for which only limited scientific evidence is available to prove that these add-ons improve pregnancy success rates in practice. Due to the rapid developments in reproductive treatments, for which government funding sometimes lacks behind, fertility clinics may introduce new treatments that could improve fertility rates. The boundaries between what should be considered experimental treatments, and those for which sufficient evidence is available may sometimes be blurry (257). However, offering costly add-ons outside of a research setting for which no scientific evidence is available is clearly problematic. A consensus statement by the Human Fertilisation and Embryology Authority in collaboration with ten professional and patient organisations in fertility care highlighted the importance of being transparent to patients about the level of scientific evidence for add-ons and the costs involved (258). The public debate around these add-ons was still very prevalent during the empirical research for Phase 2 and therefore may have affected some of the views expressed in focus groups and interviews.

4.3.2.5 Summary

In Phase 2, I focused on the ethical issues inherent in the provision of couple, rather than individual results as well as the particular issues that any fertility treatment might bring to such testing. Semi-structured interviews were held with couples and individuals having fertility treatment and focus groups were conducted with HCPs working in fertility care and associated specialities. Data was thematically analysed according to the approach developed by Braun and Clarke to identify themes relevant to the study objectives.

4.4 Findings Phase 2. Couple-based Expanded Carrier Screening: Exploring the Experience in a fertility setting

4.4.1 Outline

In the following sections, I present and discuss the findings of the second empirical research phase. The findings are divided into six sections. First, I introduce the participants who took part in the interviews, summarise their reasons for using fertility treatment and define the genetic (i.e. gamete providers) and social couple (intention to raise the child). I have numbered the couples. To avoid confusion between single participants and couples, I also use the word 'couple' when I refer to a single woman using a sperm donor as gamete provider, even though they are not a couple as in a romantic relationship. In the subsequent four sections (4.2.2-4.2.5), I present the thematic analysis of the interviews and focus groups. I end with a summary and discussion of key findings (section 4.2.6). Couple-based ECS in a fertility setting was a topic most participants had not encountered before and this is why it was not possible to explore the issues around the concept of couple testing and leave aside the issues around provision of couple-based ECS in a fertility setting. I organised the findings from the interviews and focus groups such that the issues regarding introducing ECS in a fertility more generally are discussed first. Subsequently, I present the findings regarding the ethical issues of a couple-based approach to ECS.

1: I defined the following two themes illustrating the issues around couple-based ECS in this setting more generally:

1) (HCPs) Finding the right balance between offering couple-based ECS to reduce potential harm to future children and fulfilling couples' wishes to conceive
2) (Interview participants) Aiming for a healthy child, but questioning whether this is acceptable on a societal level

2: Both HCPs and couples initially grappled with the concept of reporting couple results only. HCPs acknowledged the benefits of a couple-based approach, but questioned whether this was always appropriate when couples or individuals made use of donated gametes. Whilst a large number of participants expressed a desire to know their individual carrier states, these same participants explained that they were generally accepting of

receiving couple results, because they understood that it was the couple result that would be of relevance to the health of their future child. I defined the following two themes:

3) (HCPs) Couple testing for health professionals: shifting the focus of clinical practice from the individual patient/couple to offspring risk
4) (Interview participants) Participants' understanding of couple results: 'I am curious to know the individual carrier states, but I respect that you do not need to tell me'

4.4.2 Introducing the participants

Couple 1: Sally

Sally is a single woman in her early thirties. Due to her work as a health professional, Sally has some medical knowledge, but she does not have any detailed knowledge about genetics. She would like to start a family on her own. That is why, after several unsuccessful attempts to conceive on her own using sperm purchased through the internet, she decides to ask a fertility clinic for help. She is now planning to conceive using IVF and an anonymous sperm donor provided by the clinic. At the same time, to save costs, she shares some of her eggs with another couple.

- Genetic couple= Sally + sperm donor
- Social couple= Sally

Couple 2: Jasmine and Helena

Jasmine and Helena are university educated. Helena has a history of mental illness and has been told by her psychiatrist that the likelihood of passing on this condition is high. As Jasmine and Helena would like to avoid this risk, they decided to try and conceive through IUI with Jasmine as the biological mother of the baby utilizing a sperm donor provided by the clinic.

- Social couple: Jasmine and Helena
- Genetic couple: Jasmine and sperm donor

Couple 3: Lucy and Dean

Lucy is in her early, and Dean in his late forties. Dean has two children from a previous marriage. They have tried to conceive for a few years. They underwent several unsuccessful IVF cycles using their own gametes, which has taken quite a heavy emotional and financial toll. Their consultant has now suggested another IVF cycle, but rather than using their own gametes, he proposed to use an egg donor in combination with Dean's sperm. In that case,

Lucy will still be able to carry the baby and the likelihood of a successful pregnancy will be increased by using an egg donor who is younger than Lucy.

- Social couple: Lucy and Dean
- Genetic couple: Dean and egg donor

Couple 4: Jane and Matthew

Jane is in her early thirties and Matthew in his early forties. They both are university educated and both working. They would like a sibling for their daughter who was conceived through IVF and thus have returned to the clinic. Prior to any treatment, Jane and Matthew unexpectedly found out they conceived naturally. With some caution, as the pregnancy was in a very early stage, they were hopeful this time it was going to be successful unaided.

- Social couple: Jane and Matthew
- Genetic couple: Jane and Matthew

Couple 5: Ginny and Andrew

Ginny is in her early thirties and Andrew is in his early forties. They are about to start their first round of IVF. They previously had a stillbirth and due to surgical complications, Ginny's tubes are not functioning properly anymore. They are still a bit unsure what the IVF process is going to look like, but are also excited that they have finally started this journey. Ginny has a sister with a disability which means that she has some knowledge about what life is like for children who are disabled.

- Social couple: Ginny and Andrew
- Genetic couple: Ginny and Andrew

Couple 6: Emma and Charlie

Emma and Charlie have been trying to conceive for about eight years, but they have not yet been successful. The reason for their infertility is unknown. They are now at the point where they need to decide whether to change course and switch from using their own gametes to try and utilizing an egg donor. In this case, the social couple will be Lucy and Charlie. The genetic couple of the potential child is yet unclear and depends on how they decide to proceed. It might be the case that both Lucy and Charlie will provide the gametes, as they still have a frozen embryo. It might be that an anonymous egg donor and Charlie are the genetic couple, or another scenario that has not yet been discussed. Depending on the course of treatment, they will consider ECS couple-testing.

- Social couple: Emma and Charlie

- Genetic couple: Emma and Charlie or Charlie and egg donor

Couple 7: John and Olivia

Olivia and John are a couple, both in their late forties with a 5-year old healthy girl. They would like to start another round of fertility treatment. They previously used an egg donor and surrogate host and are looking for a similar arrangement to have a second child. When they came to the fertility clinic this time around, they were offered couple-based ECS for 70 severe recessive conditions and decided they would like to undergo testing. Fortunately, the test-result is normal and they have started their fertility treatment with the surrogate.

- Social couple: Olivia and John
- Genetic couple: John and egg donor

Couple 8: Emily

Emily is a 40 year-old woman who is married to Callum (age unknown). They tried to conceive naturally, but so far have not been successful. Their fertility consultant discussed the possible treatment options and suggested IVF using their own gametes. Emily is under time pressure in relation to her treatment because her funding will run out shortly. Given this, they decide ECS couple-testing is not appropriate at the moment.

- Social couple: Emily and Callum
- Genetic couple: Emily and Callum

Couple 9: Sarah

Sarah is a 38-year-old woman who recently split up with her partner. She has a daughter (age unknown) from this previous relationship who was conceived with assisted reproductive technology at the same clinic. She would like to have another child, this time as a single mother via sperm donation. Sarah has some insight into the lives of children with a disability and this affects her views on reproductive genetic testing. At the time of the interview, Sarah has already chosen the sperm donor she would like to use and is ready to start her next IVF cycle. ECS couple-testing raises financial barriers and she decides not to undergo testing.

- Social couple: Sarah
- Genetic couple: Sarah and sperm donor

Couple 5: Eduardo

Eduardo is a 34-year-old man, originally from South America. He and his partner Nathan (age unknown) have decided to start a family. As they are a same sex male couple, they need someone to provide the egg and they have asked a family friend to be the egg donor: and Eduardo will provide the sperm. They have also been linked to a surrogate, so everything seems in place to start their fertility treatment. Eduardo is very interested in genetics, and he and his partner (the social couple) agree that they would like to know of any risks in advance and agree to ECS couple-testing.

- Social couple: Eduardo and Nathan
- Genetic couple: Eduardo and egg donor

4.4.3 Theme 1. Finding the right balance between offering couple-based ECS to reduce potential harm to future children and fulfilling couples' wishes to conceive

All focus group (HCP) participants acknowledged the benefits of giving couples the option to use ECS, as this could spare a child a life with a severe genetic condition and prevent a negative impact on the parents and family.

> *Well it's taking away that risk of however many births a year of affected children there may be in the UK* Embryologist, clinic manager (clinic 1)

Whilst this abstract benefit was something all HCPs agreed on, some, but not all HCPs also felt that therefore couple-based ECS should become part of their clinical service for couples using their own gametes. In this theme, I discuss the concerns raised by some HCPs as to why this type of testing would not be appropriate for those using their own gametes to conceive and how mitigating these concerns through adequate counselling would be possible according to others. I have also included a discussion as to how HCPs' experiences in practice affected their initial views on a couple-based ECS test offer in their clinic. Most professionals agreed that in practice, this type of testing was more likely to benefit patients using a donor compared to those using their own gametes.

> *[Donor recipients] assume they're going to have a baby, [...] And I always have to say, whilst we screen for this, this and this, there are always go be an x amount of recessive genes that both of you could carry [...] Then some of them might ask if there's a test available [..] that now hopefully there will be.* Donor coordinator (clinic 2)

Whilst both couples/individuals using a donor without pre-existing fertility problems and couples using ART because they have problems conceiving naturally have a strong desire

to conceive, the focus for their treatment is different. Couples with fertility problems' first hurdle is establishing a pregnancy, whilst those using donor gametes without pre-existing fertility problems assume they will have a baby and are focused more on the 'end product', in terms of the baby's characteristics and health. When considering introducing couple-based ECS into their clinical services, fertility HCPs thought that balancing their professional responsibilities to help couples conceive and creating healthy babies was a difficult balance to strike. Some HCPs held the view that their clinics should make this type of test available, as this was something for the couples themselves to decide whether to take up or not.

> *I think that if people are using their own gametes and they wish to screen out, [..] embryos that carry a disorder, [which could cause] their child all sorts of problems, then that would be the benefit of the test for me.* Fertility nurse (clinic 2)

When discussing the benefits of introducing couple-based ECS, all HCPs reflected on the implications of *not* introducing this type of testing in their clinical practice. For example, it may result in withholding information from prospective parents that they would have liked to know before trying to conceive. As children with these severe AR conditions are often born unexpectedly to two parents who were unaware of their couple carrier status, HCPs thought that some couples would like to have this information before starting their treatment. Some felt that patients had the responsibility to consider having this type of testing, and many felt a responsibility as fertility professionals to provide this option if it were available: and:

> *I very much do think we have a responsibility because this test is there. Legally, if a patient has a baby with a problem and we hadn't offered this test and this test is available then we could be held responsible. But if we offer it and the couples say we've considered and we're not interested then that's different.* Consultant reproductive medicine (clinic 2)

As the consultant emphasises, some HCPs were afraid that not offering this testing, whilst it is available, could result in liability for the fertility clinic in case a child was born with a recessive condition that could have been included in such testing. This anticipation of a potential liability if a child is born with a serious condition, may also partly arise from other legal cases around genetic testing in a fertility clinic that were currently being investigated in court. On the other hand, some HCPs expected that a large proportion of couples using their own gametes might not be interested in couple-based ECS and some HCPs were

hesitant about offering ECS to these couples, as they were concerned this may pose an unnecessary burden to this, in their words, already vulnerable patient population.

Potential to pose a burden on an already vulnerable population

HCPs identified several aspects of the test offer, which they thought could compromise rather than enhance couples' reproductive autonomy. Some HCPs questioned whether a couple-based ECS test offer in a fertility setting might undermine patients' consent to testing. HCPs expressed their concerns that couples might feel pressured to undergo testing if the test was discussed by a fertility consultant or that patients might falsely believe couple-based ECS is a routine part of the clinical service. HCPs thought it was important for patients to realise that couple-based ECS would be a choice, but not something that they should take up.

> *I mean, it is hopefully not the way it is presented, they (couples) stop realise that it is an option and don't actually think about it.* Genetic counsellor (clinical genetics service)

In addition, HCPs were worried that their patients might base their decision to undergo couple-based ECS on a misunderstanding of the purpose of the test. That is to say, couples might falsely understand that ECS would help them establish a pregnancy, rather than reducing the chances of having a child with an AR condition. In practice, HCPs in fertility clinic 2 indicated that in their experience, this misconception did not arise in their discussions with their patients.

> *I didn't get that muddle at all* Consultant reproductive medicine (no.1) (clinic 2)

> *I think probably because you're introducing it not as a fertility test but as a different test.* Consultant reproductive medicine (no. 2) (clinic 2)

HCPs were aware of this potential confusion and separated the discussion regarding ECS from talking about the fertility treatment itself. This might not always have been clear to couples, as during the interviews, one of the couples (Emma and Charlie) who had experienced multiple miscarriages, mentioned several times that a reason why they were interested in genetic testing was to find out why they could not conceive. It was difficult to ascertain whether they had truly understood the purpose of ECS.

HCPs also held the view that it was important for couples to understand the implications

of a couple-based ECS test result. For instance, that a good test-result does not guarantee having a healthy child. Receiving a 'normal' test-result could lead to some sense of false reassurance, as couples might not understand that with this test only a limited set of conditions is included and does not take away other risks around pregnancy that could cause a child to have health issues, such as oxygen deprivation during birth:

> *And when they're going through IVF those are quite precious pregnancies [...] and it provides some reassurance, but I wonder whether it provides false reassurance [...] because you think oh I have a genetic test, and it has not shown anything, so my children are going to be fine.* Genetic counsellor (clinical genetics service)

Whilst a good test result could lead to false reassurance, HCPs were also concerned that couples might misinterpret a positive (bad) test result. That is to say, they were concerned that couples might falsely believe that if they received a positive couple result this meant that they could not have children together. Misunderstandings regarding the implications of both a 'good and a bad' test result might affect people's decisions to undergo ECS and thereby compromise their reproductive decisions.

Another reason why some HCPs felt that offering this type of testing may compromise couples' reproductive autonomy was that they questioned the impact of ECS in relation to people's overall chances of conceiving a child with health problems. In other words, the chances of being a carrier couple (i.e. 1 in 150) and the subsequent risk of having affected children (i.e. 1 in 4) were thought to only pose a relatively small risk to the future child. The implications of incorporating this type of testing into an already stressful fertility treatment to avoid having a child with a severe genetic condition included in this test would for some HCPs not weigh up against this, in their perception, small reproductive risk. HCPs raised concerns about the impact a couple-based ECS test offer might have on patients' wellbeing and some suggested that being offered this type of testing may cause an additional layer of stress on an already demanding fertility journey, or couples may regret their decision to undergo testing afterwards. HCPs talked about they have observed their patients going through fertility treatment and discussed how they have seen it result in couples breaking up their relationship due to the stress it could cause:

> *And then what happens if there is something, the effect that's going to then have maybe on their relationship [...] it's stressful enough when you're having IVF treatment without the added stress of finding maybe something like that as well.* Embryologist (clinic 1)

Adding couple-based ECS to the mixture of IVF treatment might be too much for these couple. In addition to a potential impact on couples' psychological wellbeing, HCPs also discussed how ECS may pose a financial burden on patients: the ECS test offer is not yet part of NHS care, and therefore couples had to pay for the test themselves. Some HCPs feared that these costs, on top of an already expensive fertility treatment package, might prevent interested couples from taking part, or unduly pressurise others into paying for treatment that they could not afford.

> *Yeah, but also people that don't have the funds but feel that they have to have it because it's something else extra that they put so much pressure on themselves that they think they have to find the money to have it done.* Donor coordinator (clinic 1)

Thus, the costs of an ECS test offer were considered a potential unnecessary burden for couples undergoing fertility treatment. Another factor that HCPs mentioned was that often NHS funding may only be available for a limited amount of time. A 6-8 week turn-around-time for a test result could then be problematic for couples as this could be another hurdle in the way of their journey to conceive.

Due to these issues, some HCPs thought it was outside their professional responsibilities to offer ECS. After taking into account both the benefits and potential harms of this type of testing in a fertility setting, these professionals thought that this setting might not be suited to provide ECS to couples with difficulties conceiving. They felt that this type of testing should be available at an earlier stage by for example primary care physicians and offering couple-based ECS to couples using their own gametes in a fertility setting was currently inappropriate and outside their realm of professionals responsibilities.

> *We make babies in the tubes, you know we have embryologists, we have nurses, we have doctors, and all the other supporting staff, but this is not, this is outside of their domain of responsibility…* Quality manager (clinic 1)

Although some HCPs reached the conclusion that offering couple-based ECS was outside their realm of responsibility as professionals working in a fertility clinic, they also felt conflicted about this, because they could withhold couples from information relevant to their reproductive decisions, as was how interview participants felt. Thus, not offering ECS to these couples because they might be vulnerable could be considered overly protective and paternalistic.

Concerns regarding downstream implications of a couple-based ECS test offer

Apart from the reasons given as to why the test offer may compromise couples' reproductive decisions, HCPs also reflected on how the current organisation of fertility services may affect specific aspects of couple-based ECS test-provision and downstream implications for patients and fertility clinics. Whilst in a primary care setting, social couples identified as carrier couples may take their chances, conceive naturally and then opt for prenatal testing, in a fertility setting HCPs thought that terminating such precious pregnancies would be a more difficult option for couples to consider:

> *Yes, because then they have to consider whether or not they would terminate a pregnancy if it has the condition. And I think that our patients who have had very long journeys to become pregnant [would not want to get into the situation where they have to make that decision]. C*onsultant reproductive medicine (no. 3) (clinic 2)

A large number of HCPs held the view that adding pre-implantation genetic diagnosis (PGT-M) to an in vitro fertilisation (IVF) treatment would be the most sensible alternative reproductive option for couples wishing to avoid having a child affected by an AR condition. Whilst PGT-M was considered the most logical option for carrier couples according to HCPs, none of the clinics where the focus groups were conducted currently holds a licence for PGT-M and this is why some HCPs felt that offering couple-based ECS to their patients could be problematic for couples using their own gametes (switching to another gamete provider may not be an option.) As illustrated by the following quote, lack of PGT-M provision at their clinic was considered problematic:

> *And then you've got the ethical problem of well they live in [city A] they don't really want to go up to [city B], it's you know now they've got information but we can't really help*. Embryologist, clinic manager (clinic 1)

HCPs discussed several alternatives to be able to facilitate this type of service for their patients. For example, they talked about whether to apply for a PGT-M licence themselves or refer patients to clinics where both ECS and PGT-M were available. Potential disadvantages for patients, which HCPs alluded to, were that travel distance might be longer, and patients are likely to be treated by two different teams of medical professionals and thus need to develop a new trusting relationship with professionals in the other clinic. On the other hand, some HCPs thought that they should be able to deal with the

downstream implications of those tests results appropriately, as the percentage of couples who were likely to be identified as carrier couples was thought to be very small.

Adequate counselling can mitigate concerns regarding couple-based ECS for those using their own gametes

As discussed previously, some HCPs held the view that offering couple-based ECS might overburden patients who are undergoing fertility treatment. However, other HCPs, who also thought that these patients might be less interested in this type of testing, were of the opinion that there was no valid reason to deny these couples the option to consider using couple-based ECS:

> *I don't think there's any ethical problem with saying these things are available, if you wanted to do it [...] it's just then everything that comes afterwards, how the results are presented, how will the clinics deal with the counselling side* Donor coordinator (clinic 2)

Rather than highlighting all the potential ways in which couple-based ECS could compromise their patients' reproductive decision-making, these HCPs stressed that the complexity of this type of genetic testing could be tackled with good counselling. They felt optimistic that counselling could mitigate the potential for misunderstanding or feelings of distress and couple-based ECS could be provided to couples without causing any harm.

Genetics and fertility professionals talked about potential issues regarding counselling about couple-based ECS in this setting, such as the complexity of discussing genetic testing and who would be the right professional to do the counselling. Genetics professionals in particular, but also some fertility professionals, pointed out the complexity of genomic testing and how the interpretation of these tests may lead to uncertain results. How to deal with such results was a point of concern, in particular as this information could be used to inform decisions regarding termination of pregnancy or transferring embryos in IVF. If a pregnancy is terminated based on an uncertain result, or a result that in the future may be interpreted differently, HCPs felt that this could be problematic.

> *Yeah and that would lead to more uncertainty during pregnancy, and that is not specifically needed, if one has got a definite mutation and the other one has a VUS what are you going to do with that?* SpR clinical genetics (clinical genetics service)

According to some genetics professionals, an important aspect of pre-test genetic counselling, was that 'doing nothing' with a test-result that identifies a couple as having an increased risk of having a child with a severe genetic condition, should always be discussed as an option. Fertility professionals discussed their experience with couples who have a family history of a genetic condition and still decided to proceed with fertility treatment. In those scenarios, which create difficult dilemmas regarding the welfare of the future child and prospective parents' reproductive autonomy, fertility clinics have procedures in place to resolve these issues in practice, such as specialist fertility counselling and consulting the local ethics committee for advice. HCPs from both clinics mentioned the clinical ethics committee as an appropriate medium to discuss these issues and as a means to receive advice on ethical dilemmas raised in clinical practice:

> *But I think the ethics is really hard. You need ethics committee help, you need the genetic counselling support. It's not something just as fertility consultants we can deal with on our own.* Consultant reproductive medicine (no.1) (clinic 2)

Both genetics and fertility professionals were unanimous in their views regarding a need for fertility professionals to be adequately trained to provide pre-test counselling and a need for genetics professionals to cover post-test counselling for couples being identified as carrier couples for an AR condition. HCPs talked about how providing a good counselling service would require a collaboration between fertility clinics and genetics departments to deliver care that is up to speed with these new developments in genetic technology:

> *I know that there are people like the sort of job coming into role, which is the Genetic Counsellor, who is basically a scientist who is also dealing with counselling people about the implications of the genetic test specifically*. Embryologist, clinic manager, (clinic 1)

A genetic counsellor who could work within a fertility setting was thought to be a good option to bridge the gap between the two specialties necessary to provide adequate care to their patients.

Counselling in practice:

HCPs said that in their experience, most couples, would require more than one consultation to enable their patients to make an informed decision regarding undergoing couple-based

ECS, and that they as fertility professionals, after training and some practice, were able to provide this pre-test counselling.

> *It's not fair to say they've got informed consent for it have they really [after one conversation], cause they just haven't taken it all in. [...]*
>
> *Just thinking, it's like anything when you're offering a test, you need to get this information across, what are the sentences I'm going to use to make that understandable and succinct as well* Consultant reproductive medicine (no.2) (clinic 2)

Having offered ECS, HCPs also reflected on whether offering this type of testing was indeed appropriate to all couples undergoing fertility treatment. Some couples were not interested in ECS, because they would not have considered this type of testing had they conceived naturally. This echoes the sentiment expressed by some of the women who took part in the interviews that they wished that their assisted conception journey could be 'as normal as possible'. On the other hand, these HCPs also reflected that couples could see this test offer as an opportunity to reduce risks of having an unhealthy child that in the current health system they would otherwise not get. HCPs' experiences after having offered ECS were that if this type of testing delayed couples' treatment, or was considered expensive, patients did not proceed with ECS testing:

> *The two things that put couples off are firstly, it's going to delay their treatment, which many of them don't want by the time they get to this point and secondly it's the additional cost when they're already paying a lot of money for treatment.* Consultant reproductive medicine (no. 3) (clinic 2)

Apart from these barriers for their patients which prevented them from taking part, in practice, HCPs also reflected that they had offered testing to some, but not all of their patients, and this may indicate that couple-based ECS was inappropriate to discuss with certain couples at a particular time in their fertility treatment. For example, HCPs said they more often discussed this type of testing with patients who had something 'genetic' in their family, or those with a long fertility trajectory:

> *Those that were using donor I talked to about it, with all of those. And those who are, perhaps, a bit further down the line we were struggling to get good embryos I was talking to all of those. But the others right at the beginning, it seemed to be somehow a little bit too much for them.* Consultant reproductive medicine (no. 1) (clinic 2)

These experiences raise questions around the right timing of this type of testing for those couples using their own gametes, but also the extent that HCPs might be overprotective of their patients in trying not to burden them with information overload. Reflecting on their professional role as doctors involved in making babies, HCPs who had been involved in test-provision thought that perhaps couple-based ECS or a focus on maximising the chances of having a healthy baby should be discussed before starting fertility treatment. For instance, one of the consultants illustrated how she responded to queries from patients who mentioned to her that they did not understand why this type of testing would be available to them, but not to couples conceiving outside of a fertility setting:

> *Because you are having treatment you have the opportunity to avoid having a baby with a very serious problem and that's really why we're offering it. Because otherwise the first time you will know you have an issue is when your baby is born with a serious problem.* Consultant reproductive medicine (no. 1), (clinic 2)

Although prioritising a 'healthy' baby over 'pregnancy' at the start of a fertility journey might be the right thing to do according to some HCPs, it would change the way fertility clinics have organised their services.

Ideal setting to offer couple-based ECS

Due to this tension of making babies vs healthy babies and the difficulties of incorporating couple-based ECS for couples with fertility problems identified during the focus groups, both genetics and fertility professionals reflected on what the ideal setting for ECS might be. Given that fertility couples are at the same a priori risk of having children affected by AR conditions as any other couple, some HCPs took the position that couple-based ECS should be available to any couple planning a pregnancy, at any relevant point in the health care system.

> *If it is an NHS publicly funded thing, yes it is strange it would just be offered through fertility, because it is something we might want to offer as genetics department, or our pre-natal units.* SpR (clinical genetics service)

Offering ECS testing in a fertility setting, when not incorporated within the NHS, may have the potential to create inequalities in health of future offspring between those who can afford paying for these tests and those who cannot.

> *You're able to offer these private tests because our technology has advanced hugely, but the funding is majorly lagging behind, [and] that's not very equal.* Genetic counsellor (clinical genetics service)

As highlighted in this quote, both fertility and genetics HCPs raised concerns about offering couple-based ECS in a fertility setting in terms of equality and concerns on a more societal level. Some genetics professionals also questioned whether it actually matters whether equal access to care is relevant in this scenario or not. They questioned whether ECS is something that should be considered as essential care, or whether it was simply something extra that people can pay for if they would like to know, in a similar way as some people pay for a whole body MRI-scan. On the other hand, some HCPs also said that couples could see this test offer in a fertility setting as an opportunity to reduce risks of having an unhealthy child that in the current health system they would otherwise not get. Once it has been incorporated in this setting, it might be easier to collect evidence for policy makers to introduce it in the health care system as a whole.

4.4.4 Theme 2. Aiming for a healthy child, but questioning whether avoiding the conception of children with a severe genetic condition is acceptable on a societal level

In this theme, I discuss the reasons as to why participants would consider using couple-based ECS to inform their reproductive decisions and consider avoiding the conception of a child with a severe recessive condition. As summarised by Helena (couple 2), all participants initially felt that the more information about genetic tests they received, the better the chances of having a healthy child:

> *I would say that I prefer to be informed and take the decision than not being informed, make a baby and then discover something that could have been spotted before* (Helena, hypothetical test offer; couple 2)

Helena expressed her motivation towards undergoing ECS couple testing in terms of the more information the better the chances of having a healthy child. During the course of the interviews, it became clear that participants' initial positive stance towards being offered this type of testing was more nuanced regarding the question as to whether couple-based ECS could enhance their reproductive decisions in practice. At the same time, participants questioned whether their reasons for considering couple-based ECS to avoid conceiving a child with a severe genetic condition were morally acceptable. The three main reasons

participants provided as to why they would consider using this type of testing were: Prevention of suffering for the future child/quality of life; prevention of suffering for the family; and a responsibility as a future parent to maximise the chances of having a healthy child.

Prevention of suffering for a future child

Participants' primary consideration to undergo couple-based ECS originated from a desire to prevent suffering for future children, confirming the findings from the Phase 1 research regarding the uptake of the UMCG couple-based ECS test in a primary care setting (see Chapter 3). For example, for Andrew and Ginny this was an important reason, as they wanted to maximise the chances that any future children would have a good quality of life:

> *We've always felt that any tests that are currently available, we would have them, because, we would want to know, if someone wasn't going to have the quality of life, then…*Andrew (hypothetical test offer, couple 5)

Participants used phrases such as 'quality of life', 'a decent life' to emphasise their desire to have children who would get a good start in life without being affected by a severe genetic condition. Quality of life used in this context, just like severity of illness (as discussed in Chapter 1), is a subjective term and means different things to different people. Most participants took the view that conditions included in couple-based ECS should have a serious impact on the health of the future child, rather than conditions that are less serious or traits which are not health-related. Some participants drew on expectations created by the media and science fictions films that genetic testing for reproductive purposes might lead to choosing non-health related traits or characteristics in future children, which some participants referred to as 'designer' babies. Couple-based ECS was seen not about creating 'perfect' or 'designer' children, but to protect their future children from harm that could be prevented. Moreover, participants felt this should not be about prevention of any suffering, but the conditions should have a serious impact. Participants also reflected on the implications for the National Health Service (NHS) if testing were to be offered for less serious conditions and thought that couple-based ECS for conditions that were not serious could place an unnecessary burden on the health system. Jane underlined the view that prospective parents should only be offered tests for serious conditions:

> *[testing should not be offered] for conditions that don't have an impact on either the carer's life or the child's life because you'd be endlessly testing, and I genuinely don't think that most people would actually want those tests.* Jane (hypothetical test offer, couple 4)

Participants alluded to how their views towards accepting a couple-based test offer changed depending on the stage of their fertility treatment and their reproductive history. A number of participants articulated a tension between considering undergoing this type of testing at the current stage of their fertility treatment, and not having considered it when they were trying to conceive naturally or at the start of their fertility treatment. It appeared that prevention of harm in future children became more important the longer couples using their own gametes were unsuccessful at establishing a pregnancy. The timing of the test offer within the course of couples' fertility treatment may mean different decisions are made about undergoing couple-based ECS. Couples 3 (Lucy and Dean, hypothetical test offer) and 6 (Emma and Charlie, actual test offer) both had experienced a long fertility journey, but had not been successful at establishing a pregnancy. These couples in particular talked about how their experience of being in the fertility treatment process changed how they felt about this type of testing and their thoughts about having a child with a severe genetic condition. Lucy explained how the huge investment in terms of time, energy and money in trying to get pregnant over the course of several years made it more likely that she would now consider couple-based ECS to prevent suffering in future children:

> *And I think, ultimately, I don't want to be going through all of this, and yes we want a baby, but I want a child that has got a decent life to it [...] I don't think I would have considered it before we'd been on the journey* Lucy (hypothetical test offer; couple 3)

Whilst at the beginning of their fertility treatment, participants were mainly focused on trying to conceive, the more time had passed without becoming pregnant, the more they started to consider quality of life for their future child as a deciding factor in how to proceed with their fertility treatment. HCPs in the focus groups made a similar observation that at different stages of their fertility treatment, patients' focus between trying to conceive or trying to maximise the chances of having a healthy child change.

In some cases, logistical or practical reasons caused a tension between participants' longing to conceive and a desire to prevent harm in future offspring. For participants such as Emily, it felt like the actual decision not to proceed with couple-based ECS was more or less made

for her, as she was concerned that the time delay on her treatment that would be caused by an ECS couple-test would reduce her chances to become pregnant:

> *Am I now putting myself in a position where I could be ploughing on with IVF treatment, to then have a child that has some sort of significant deficiency in the future, [..] but at the same time, I am conscious that I am already 40 years old, I have already been waiting four years, I've already fought to get to this point, I only have 12 months to undergo treatment…* Emily (actual test offer; couple 8)

Emily's description of her fertility treatment as a battle she has 'fought' for really hard demonstrates that there are many competing factors that play a role in participants' decision making. For Emily, pausing the treatment to allow for a couple-based ECS test result to come back in six weeks felt like too big a risk to take regarding her chances to conceive. On the other hand, she anticipated she might regret this decision if a child was born with a severe genetic condition which could have potentially been prevented. These conflicting considerations may indicate that participants could experience a feeling of anticipated regret or guilt towards their future child if they decided not to undergo ECS couple testing, for example by prioritising the actual fertility treatment over having couple-based ECS. Emma, who was at a different stage of her fertility treatment compared to Emily, illustrated how it would be beneficial to her to know in advance about their chances of conceiving a child that may die in early childhood, as she would not be able to cope with that at this stage of her fertility treatment:

> *Trying for 8 years, doing ten cycles of IVF and then finally give birth to a child that dies within the first couple of weeks. That would be our journey done.* Emma (actual test offer; couple 6)

This suggests that at this point in her reproductive journey, Emma would do anything she could to reduce the chances of having a child with a serious genetic condition. The quote illustrates that at this stage, she would not be able to go back to fertility treatment and try for another child, if they had a child that would die at a young age. In summary, the first reason for participants to consider using couple-based ECS was to prevent harm in future children by avoiding the conception of a child with a genetic condition. Participants' considerations and decisions regarding undergoing this type of testing in practice were influenced by their fertility journey and how having couple-based ECS could fit within their treatment.

Prevention of suffering for the prospective parents and family

Jane alluded to another reason why participants considered couple-based ECS: In families with a child affected by a genetic condition, it is likely that the lives of other people, such as parents or siblings would also be affected because of for example the child's need for medical care and support:

> *[testing should not be offered] for conditions that don't have an impact on either the carer's life or the child's life because you'd be endlessly testing, and I genuinely don't think that most people would actually want those tests.* Jane (hypothetical test offer; couple 4)

Participants held the view that the decisions around this type of genetic testing were very personal. Individual circumstances may mean that people are unable to look after and care for the needs of a child with a severe disability. Thus, the second reason why participants thought that ECS could be helpful to them was the possibility to avoid harm/suffering for themselves as the family of a child affected by a genetic condition. During the interviews, participants reflected quite extensively on what it would mean to have a child with a genetic condition and how this affected their views on whether they would choose to undergo couple-based ECS.

When participants discussed the potential impact of having a child with a genetic condition on them as future parents or on other siblings in the family, they drew on their experiences at work, or from observations of the lives of colleagues or friends. For instance, Sarah, who worked as a health professional, explained that this had taught her that a severely disabled child could negatively affect the lives of other siblings in the family, even though the child might enjoy some quality of life. For this reason, she would consider using reproductive genetic screening to avoid conceiving a child with a genetic condition, even if this would go against her values as a professional, supporting people living with a disability. At the same time, participants talked about the emotional impact of having a child with a severe genetic condition and articulated that they thought they would not be able to cope with this as a parent, as illustrated by John (couple 7):

> *All couples who have a child want a healthy child, even with my first born, it was always a bit of a fear, you know, what if, there is something wrong, what if, we end up with a child that is mentally handicapped or physically handicapped, and I'm not sure if I would cope with that, if I'm perfectly honest.* John (actual test offer; couple 7)

For some participants, being able to prevent the impact of having a child with a life limiting illness could be a key motivation to consider couple-based ECS. At the same time, they also questioned whether 'personal' considerations were 'good' enough reasons for avoiding the conception of a child affected by a genetic condition. Examples of these personal considerations included expectations of what their family should look like, or having to make certain sacrifices in terms of career and personal life. As Dean (couple 3) described this struggle/moral dilemma in terms of 'being selfish':

> *So, again it comes back to the selfishness…if I make a decision that I'm not going to let a child with a massive disability even start come into being because actually it means a huge impact on my life, that I'm going to have to give up my job, I'm gonna have to be a stay at home carer, am I ready to do all of that?* Dean (hypothetical test offer; couple 3)

Participants negotiated the tension between a desire to prevent having a child with a serious genetic condition because it could have a negative impact on their lives and whether this was morally acceptable as a justification to make use of couple-based ECS.

Future parents may have a responsibility to consider undergoing couple-based ECS

A third reason for participants to consider using this type of testing was a desire to minimise risks and feeling a responsibility to maximise the chances of having a healthy pregnancy and child. This perceived responsibility was affected by the type of couple (donor vs non-donor) and whether social couples were able to make a decision about undergoing couple-based ECS together. Most participants who discussed their views in terms of a responsibility to reduce/minimise risks of having a child affected by a genetic condition were planning to use donor gametes to conceive. Those using their own gametes were generally more focussed on their fertility problems and discussed using ECS in terms of prevention of suffering for the child or themselves. For example, Sally, who was still at the beginning of her treatment with donor sperm, felt that undergoing ECS could be another precautionary method, such as taking folic acid and not drinking/smoking during pregnancy to maximise the chances of having a healthy baby.

> *Everything that would help me prevent from having an unhealthy pregnancy [...] they're certain things you don't do to try and help you to get a healthy pregnancy, so it's along those same lines* Sally (hypothetical test offer; couple 1)

Those using donor gametes might place more weight on minimising risks for future offspring as a reason to undergo couple-based ECS compared to other people, as was also

mentioned by HCPs in the focus groups. As highlighted by Eduardo, one explanation for this difference between couples using a donor and couples using their own gametes could be the implications of a positive test result: being able to 'switch' to a different gamete donor might be an easier choice than the reproductive options available to couples using their own gametes.

> *So, that means then, we have to choose a different gamete provider. To make sure the risks are to a minimum or none.* Eduardo (actual test offer; couple 10)

Even though an ECS couple-based test would minimise a couple's chances of having a child with the 70 conditions it tests for, it would not guarantee a healthy child. Eduardo wanted to make sure the risks are 'a minimum or none', which may indicate a potential for false reassurance if the test result was normal, i.e. that he and the egg donor were not identified as a carrier couple. Some participants also discussed how the option to switch to another donor was perceived as easy in the abstract, but was not so simple in practice and depended on when couple matching was introduced in their fertility treatment. Some participants talked about how they felt strongly about their choice of a gamete donor, or that they prioritised physical resemblance over being informed about genetic risk factors. Some social couples who were thinking about the option of using a gamete donor felt that they did not want to give other people the impression that their future child was not biologically 'theirs':

> *I am more worried about having a child people thought was ours, than the medical side of things, actually. Sounds <u>really</u> shallow, doesn't it?* Lucy (hypothetical test offer; couple 3)

This also demonstrates how conflicted participants felt about their apparent desire to keep the details of how their future child was conceived to themselves and prioritise making that possible over being informed about potential health risks in the future child. This uncomfortable feeling expressed by Lucy may be associated with various factors related to the use of artificial reproductive technology, such as the use of donor gametes to conceive, people's desire to have children that are biologically theirs and an oversimplified view of how genetics affects our physical appearance. The feeling of having a responsibility as a future parent to consider this type of testing, and at the same time, considering other factors that may weigh stronger in the balance, could again suggest that participants had feelings of anticipated regret or guilt towards the future child when they considered not

making use of couple-based ECS. These feelings might be similar to what participants expressed when they talked about a desire to prevent suffering in their future children, but at the same time they decided not to use couple-based ECS because they were worried that their chances of conceiving would be reduced.

How couples make these decisions together seems relevant when evaluating how 'enhancing reproductive autonomy' as an aim for couple-based ECS works in practice. In contrast to most medical decisions, where individuals make decisions about their own healthcare, for ECS, it is mainly the social couple who needs to make an informed 'autonomous' decision together. Couple-based ECS means that both gamete providers need to undergo the actual blood test. For social couples using their own gametes to conceive, this means that both partners would need to consent to testing and a single person utilising donor gametes would consent on their own. For those not providing the gamete in a social couple, the test-result is still relevant for both partners, as the outcome of the test would inform both partners in the social couple of their chances of becoming parents to a child with a genetic condition. Thus, the decision to have couple-based ECS is relevant even if some future parents do not undergo the blood test themselves. Most social couples, irrespective of whether one or both of them would provide gametes, said that they would be able to reach a common decision, as illustrated by Lucy and Dean, who explained that they would try to reach a consensus based on their shared values:

> *I think we've got the same principles…* Lucy (hypothetical test offer; couple 3)

> *Yeah, we are of a like mind enough to be able to have that conversation, to be able to come to a consensus agreement that actually we can agree. I think, you know, we haven't been together for ever, we've been together six years, but we do have those conversations about things in life where we come to an agreement.* Dean (Lucy's partner; couple 3)

If, however, couples cannot agree on their decision to undergo this type of testing, or what they would do with a positive test result, the situation becomes a bit more complex. In that case, it may turn out that reproductive autonomy of one partner conflicts with the reproductive autonomy of the other partner. One partner may have strong feelings and decide that they would like to do as much as they can to try and avoid having a child with a genetic condition. The other partner may feel that any child, regardless of having a genetic condition would be welcome. It is not difficult to imagine how this could lead to a situation where one partner dominates the decision over the other partner and that this

could compromise their reproductive decision making as a couple. For instance, Sarah compared her current to her previous situation, when she was still married and had to decide about prenatal screening for Down's syndrome.

> *And he really wanted it [the prenatal screening]. Because for **him** [added emphasis] it absolutely made a difference, cause we wouldn't have had that baby if it was going to have Down's syndrome. And I guess it is the same principle [whether you would act on the decision or not] that would sway your decision making about whether [to undergo ECS]* Sarah (actual test offer, couple 9)

Thus, the third main reason why couples considered undergoing couple-based ECS was that participants felt they had a responsibility as a future parent to maximise the chances of having a healthy child. Whether they could act on this responsibility also depended on whether in practice, they would be able to reach a decision as a couple.

Participants question the moral acceptability of avoiding a child with a genetic condition on a societal level

Whilst participants discussed their reasons for considering or choosing to undergo couple-based ECS, they also questioned whether it was (always) acceptable to avoid the conception of a child affected by a genetic condition. Some participants thought it was a difficult issue as to whether preventing the conception of children with a severe genetic condition was acceptable on a societal level. Those participants illustrated their views regarding the potential societal implications of couple-based ECS with what they knew about prenatal screening for Down's syndrome. Often they had heard in the news that in countries such as Iceland or Denmark, prenatal screening for Down's syndrome has resulted in a significant reduction in the number of children born with this condition. The option to make decisions before conception, meant that for some participants, it was more acceptable to consider prevention of harm in future offspring as a purpose of offering couple-based ECS than for prenatal screening, as illustrated by Jasmine:

> *Denmark apparently would be the first country without Down's syndrome, because they offer those tests to detect, [...on the one hand this is good…] because less people suffering growing up, but then I would say, [this may be problematic, but in case of testing before conception] they don't exist, because they haven't been conceived, maybe I can say yes [this is acceptable].* Jasmine (hypothetical test offer; couple 2)

Offering prenatal screening with the purpose of reducing the number of births of children affected by a genetic condition is generally considered ethically problematic, as outlined in

Chapter 1 (98). However, as Jasmine highlights, if it is possible to make a decision to avoid conception of a child with a severe genetic condition, rather than to terminate a pregnancy, this would be more acceptable to her, because there is not 'something' yet which could be prevented from being born. In other words, using couple-based ECS is more acceptable than prenatal screening, because it does not necessarily involve termination of a pregnancy.

At the same time, it was also interesting to note that participants struggled with the idea of 'avoiding the conception of a potential child', which they often linked to terminating a pregnancy. Avoiding conception will not result in preventing 'a particular child' from being born. At this point, there is no child yet, but it seemed quite difficult for participants to conceptualise avoiding something that does not exist. The more familiar discourse around the implications of prenatal screening may lead to misunderstandings about screening prior to conception as participants sometimes conflated the two. The potential misconception where preconception testing is confused with testing during pregnancy could be important for health professionals to take into consideration when facilitating couples' decision-making regarding whether to undergo ECS testing.

Some participants drew on their experiences of working with children with a disability to illustrate why they felt conflicted about the possibility of avoiding the conception of children with genetic conditions from a societal point of view. Lucy (couple 3) gave an example of someone she knew with cystic fibrosis and reflected on the complexity of the issues involved. For instance, it is not always possible to know in advance how a particular condition is going to affect a future child, and children with a disability may still enjoy their lives or bring joy to the lives of others, as she had experienced. She questioned whether it was desirable to avoid the conception of children with these conditions, but she also acknowledged that it would be a personal decision to do so. Some participants also alluded to the impact testing may have on people living with a disability, as illustrated by Emma (couple 6):

> *So you're not just eradicating the condition, but you're then basically saying that people with those severe conditions, you're making the choice whether they should live or not* Emma (actual test offer; couple 6)

This could be interpreted as: 'whether they should live or not', resembled the discussion around the disability rights critique in relation to prenatal screening.

In summary, whilst most participants held positive views about this test offer regarding its potential to inform their reproductive decisions, and prevent harm for future children and their families, they also pointed to the complexity of making use of this test offer in practice. Participants discussed the issues this raised for them personally, for society and for them as a couple or individual using fertility treatment.

4.4.5 Theme 3. Couple testing for health professionals: shifting the focus of clinical practice from the individual patient/couple to offspring risk

This theme focuses on HCPs' views regarding the concept of reporting couple results only when offering ECS to couples and individuals in a fertility setting. The couple-based approach's focus on reproductive risk was considered a benefit. At the same time, HCPs also discussed how adopting a couple-based approach to ECS is different to how they currently use carrier testing for gamete donors and what issues this could raise for their patients, donors and their clinical practice.

Difficulties understanding the concept of couple result which focuses on reproductive risk

HCPs did not have any difficulties understanding couple testing in terms of reproductive risk. However, some initially struggled to understand the concept of reporting couple results only, which is why, during the first part of each focus group with fertility HCPs, the concept of a couple result was discussed to clarify its meaning. When I asked them about the issues they envisaged, some interpreted individual carrier status as having meaning in relation to the health of the individual, or that of family members and (future) children. Some HCPs worried that they would withhold information from their patients that could be useful for their own health.

> *But surely if you know someone is a carrier of a potentially life-threatening or life-limiting condition, it's only right that we tell them isn't it, because if you don't tell them how can they make any informed choices about anything or about their future or, siblings, children.* Midwife (clinic 2)

This illustrates that some HCPs interpreted being a carrier of an AR condition as having health implications for the individual. In the discussion with their colleagues, HCPs gained a better understanding of what it meant to be a carrier of an AR condition, and some participants drew on examples from their own family or clinical practice. This discussion around the meaning of being a carrier of an AR condition and the misconceptions that HCPs held is exactly what makes the debate around the ethical issues interesting, but also complicated. Whilst all HCPs and couples understood the purpose of ECS as informing couples about their reproductive risk, still, it seemed quite difficult to disentangle this from their perceptions of individual carrier states as being meaningful for the individual rather than in terms of offspring risk only. Interestingly, when I asked whether HCPs would feel more comfortable about providing a couple-based ECS test offer if this was phrased/framed in terms of reproductive risk, rather than asking two prospective parents to undergo carrier screening, they thought this framing would make a positive difference towards accepting the approach of reporting couple results:

> *Yes it would be [different], it essentially means, only twenty-five percent chance of one in four risk for their offspring, [...] But for them, as a couple, there is no risk at all to their health as long as they are carriers.* Consultant obstetrician and gynaecologist (clinic 2)

HCPs reflected on previous experiences where couples had received individual carrier states and what the implications might be of being identified as a carrier, whilst this is not important for the couple's reproductive risk. One HCP gave an example of a couple who had received their individual carrier states from a private test who were very distressed as they misinterpreted their individual carrier status as being affected by the condition in question.

> *We had a couple [who] both presented in a clinic sobbing their hearts out because he had three recessive abnormalities and she'd got one and they thought they were gonna get those conditions so they'd read it all up and they had decided they might as well book their funeral now really.'* Consultant reproductive medicine no.1 (clinic 2)

In addition, another reason for HCPs to be in favour of a couple-based approach was that reporting individual carrier states may have negative implications for couples' relationships. It may result in blame on one partner of a couple for being a carrier of an AR condition, whereas this has no health implications for themselves or their offspring.

> *If you're looking at an individual, is that then going to put a strain on their relationship if one's a carrier [...] that's my problem is it's a bit of a confused knowledge, could be one individuals fault.* Andrologist (clinic 1)

When one of the participants (embryologist clinic 2, focus group 5) argued that couple-based testing is acceptable as long as you discuss with your patients what the test-result means and what the limitations of the test are, most other health professionals in clinic 2, agreed with this view, as it focuses on reproductive risk. Some HCPs were aware that other clinics had already introduced ECS and often report individual carrier states, which was considered problematic by some, as this approach may distract from the purpose of the test.

> *They're doing the non-couple ones [...] So I think the way this test is done is more useful in that you know it's a couple compatibility thing and you don't know if you carry unnecessarily something which is perhaps more useful.* Consultant reproductive medicine no 1. (clinic 2)

Interestingly, this consultant uses the word 'compatibility' when referring to the couple aspect of the test. In this context, the consultant aimed to emphasise that it is the couple result that is important for the health of future children. However, if used in a different context, this word could be interpreted in a different way and may suggest that carrier couples are not supposed to have children together.

Generally, HCPs thought that a couple-based test offer to couples using their own gametes was not problematic unless these types of couples change partners in the future. As fertility treatment itself may cause a couple to break up their relationship, HCPs felt that this may be more relevant in these couples than those not using fertility treatment to conceive. In the following excerpt, HCPs discussed that, in their view, not reporting individual carrier states potentially withholds information from people that could be relevant for their future reproductive decisions. Some felt that not providing individuals with individual carrier states may convey a false sense of reassurance.

> *I think it's if they then, you know a lot of couples do split up over IVF because it's so stressful, if they think well I'm in the clear, it's fine, and actually they are a carrier, a single person is a carrier, that could then be an issue later down the line for them; that would be my worry.* Andrologist (clinic 1)

Some HCPs initially felt uncomfortable about not reporting individual carrier states, and this was partly due to misconceptions regarding the meaning of being a carrier of an AR

condition. At the same time, HCPs also argued that when couple-testing is discussed as conveying information about couples' chances to have an affected child, and couples are informed about the advantages and limitations of the test, a couple-based approach was acceptable and even preferable as it focuses on reproductive risk.

Implications for cascade screening of family members

Not reporting carrier states represented a change in clinical genetics' practice, in particular, the way genetics professionals deal with family members of couples identified as a carrier-couple. As the HCPs explained, clinical genetics' professionals currently report individual carrier results and decide whether they offer carrier testing to a partner of a carrier based on the carrier frequency in the population. Genetics professionals discussed how they should deal with family members of couples who were offered couple-based ECS in a fertility setting. Some professionals felt that family members of carrier couples may need counselling to be informed about their reproductive risk. Depending on that reproductive risk they may or may not be offered carrier testing themselves. When I suggested that both false reassurance, and informing family members could be avoided by offering a new test to a new couple, some HCPs argued that because ECS is not yet routinely available, siblings of carriers may miss out on a test offer that could be useful to them:

> *If you are not getting a result back because only one of you is a carrier, and you're only reporting back the couple result, not the individual result, [..] and if other family members are not going through IVF and are also carriers, then they still got an increased risk and not being offered anything..* Genetic counsellor (clinical genetics service)

For genetics professionals, concerns regarding a perceived relevance for individual carrier states were not only relevant in case a couple splits up, as was the case for fertility professionals, but could also be extended to cascade screening of family members.

Concerns regarding couple-based ECS in a donor programme

Irrespective of HCPs' views as to whether reporting couple results only was acceptable, the question as to how to incorporate couple-based donor screening in practice, raised ethical and practical issues in both fertility clinics regarding the consent procedures for donors. Fertility HCPs were particularly concerned about the implications to get consent from donors to undergo carrier testing, but not to receive the outcome of the testing. HCPs

talked about a sense of discomfort about discussing this new approach with the donors, because they felt they would be withholding information from donors. HCPs assumed that (at least some) donors would want to know the individual carrier states, as HCPs imagined they would like to know that information themselves.

> *I still don't see how you can run some screening tests without their consent...And I'm sure there are a lot of donors that would be fine with it and understand, but I'm sure there will then be those will think well it's a test you're running on me, I want to know the result.* Donor coordinator (clinic 1)

This suggests that some HCPs' interpretation of consent may be based on a misunderstanding. That is to say, valid consent can still be obtained, even if a donor is not informed about their individual carrier states. For example, if HCPs explain to a donor that they will not be informed about the outcome of this test, because the couple test result is only relevant for the recipient in their decision-making around their choice regarding a suitable donor, and if the donor is happy to proceed and has understood that they could have a similar couple-test with their (future) own reproductive partner if they wanted to be informed about their own reproductive risk, this could still constitute valid consent.

At the same time, if couples would be interested in knowing their individual carrier states, they could decide to purchase a different test that suits their interests:

> *Alternative tests are out there if patients want to have that profile, or information that this compatibility testing won't give them.* Embryologist (clinic 2)

As part of the consent conversation HCPs can discuss alternative options for couples or individuals who would like to know more about their genetic information than this type of testing can give them.

Interestingly, when HCPs discussed the couple-based aspect of ECS with donors in practice (in clinic 2), they were surprised by how accepting donors were of this approach. Whilst some HCPs felt that they personally would want to know their own carrier states, they realised that for donors this did not appear to be a concern. When I explored whether due to actually offering these tests in practice, their views on ECS couple-testing had changed, HCPs confirmed that their concerns about not reporting individual carrier states were taken away by the positive responses of the donors.

> *The only recent thing I changed was an anxiety about individuals not knowing their results. But from talking to patients, they were less anxious about that than I was* Consultant reproductive medicine (no.2) (clinic 2)

Whilst HCPs were concerned about not reporting individual carrier states to donors, as they feared they were withholding relevant information from them, this was not reflected in their conversations with donors in practice. An explanation for the initial discomfort felt by HCPs was that not reporting individual carrier states is different from how carrier testing was performed for other AR conditions. For example, all donors undergo carrier testing for cystic fibrosis (CF), and are given their individual carrier states. If a potential donor would be identified as a carrier, these donors are currently not allowed to proceed with gamete donation. Thus, by adopting a couple-based approach to ECS, some HCPs felt they might withhold information from donors about individual carrier status for AR conditions that they currently provide these donors with after CF carrier testing.

Some HCPs questioned whether sequential testing would be preferable in a donor setting compared to adopting a couple-based approach. HCPs provided two main reasons for this. They questioned whether it was acceptable to have multiple recipients pay for and undergo a couple-test with the same donor if the donor's results could be stored somewhere. Financial reasons were part of this line of argument: if the sperm/egg donor was not a carrier for any AR conditions in the test, HCPs felt that recipients would be paying for the test unnecessarily. In addition, if the donor were to be a carrier, some HCPs assumed it would be easier and cheaper to test the recipient for carrier status of only that specific condition, rather than perform a new couple test.

> *I think the only way it can and should be used, is to be having a profile on file, that could be run, you know and [..] if that person has no problems, then it shouldn't be run ad infinitum, [..] but if we know it's got this mutation, then we only run for that mutation [..] well because that would in theory be cheaper* Embryologist, clinic manager (clinic 1)

Secondly, HCPs often assumed that the lab would keep a list of the donor's carrier states. If 'someone somewhere' knows, participants felt donors should be informed about their own individual carrier states, as this was 'their' information. These HCPs attributed meaning to these individual carrier states for the donor's (future) reproductive decisions. As individual carrier states could, according to these HCPs be meaningful for donors, some

HCPs argued that sequential rather than couple-testing should be performed in a donor-recipient setting.

The implications of a sequential approach to ECS in a donor-recipient setting are that donors would have to be informed about their carrier status and are either excluded from further donation (which is likely to happen in many cases), or all recipients would have to be tested.

Genetics HCPs discussed their experience when working in the 100.000 Genomes Project where patients/parents mentioned that they had 'a right to know' regarding their genetic information and they anticipated that having this right might also be an argument used by patients/couples to ask for their individual carrier states. However, they felt that a right to know is not simply a right to be given all the data that is generated by sequencing someone's genome, rather, in a clinical context, patients had a right to know information and receive interpretation of data that was meaningful. When couples are informed that this test will provide them with information about their reproductive risk by generating a couple result, there can be no right to know individual carrier states or any genetic data as such if these are not meaningful:

> *You agree what you will and won't be told and you can't suddenly say, well oh this information is about me, therefore I am entitled to it [...]I am not sure that in terms of genomic information[..] there is a right for an individual to know something that isn't definite and isn't actually meaningful* SpR (clinical genetics service)

Benefits of a couple-based approach in a donor screening programme

HCPs talked about how sequential ECS in a donor-recipient situation is a similar approach to that currently used by commercial sperm banks who perform ECS on individual donors. Many recipients use donor (sperm) gametes from international sperm banks as only a few local sperm donors are available. If a couple-based approach is not adopted uniformly by all providers of donor sperm, fertility clinics will not be able to offer a couple result to all their recipients. HCPs reflected on how this currently poses dilemmas for them as HCPs and for recipients of donated gametes. If there is not matching result for both recipient and donor, but only the donor's individual carrier states, this complicates counselling of the recipient regarding reproductive risk.

> *They [commercial sperm bank] have been screening for everything, every possible question they've been asked, do you have this, is there any family history of it, and you can do all of that, but without having it on the other half, it's not going to make any difference Donor coordinator (clinic 2)*

HCPs anticipated that individual carrier states reported by commercial sperm banks could cause anxiety to recipients as most donors would be carriers of an AR condition and recipients cannot apply for carrier testing on the NHS. This reinforces the argument that a couple-based approach may be more appropriate, even in a donor-recipient scenario.

HCPs weighed up how introducing this type of testing may impact on the current shortage of donors. If donors had to give blood every time a new couple test was performed, some HCPs were worried that this would cause an unnecessary burden on their donors. Some HCPs thought that making ECS mandatory might lead to donor shortages as HCPs were worried that having to undergo this type of testing could scare off suitable people from donating. On the other hand, as was raised by both genetics and fertility HCPs, if donors who are carriers of a condition could still donate to a recipient who they were 'compatible' with, reporting couple results could be beneficial. That is to say, couple-based ECS could have the potential to reduce donor shortages and provide clinics with an option to avoid having to let go of suitable donors based on their carrier status for AR conditions. When a couple-based approach is adopted, donors and recipients will be matched on the basis of their couple carrier status. This also means that donors who are carriers of CF, or other recessive conditions, can then still donate their gametes to those recipients who are not carriers of the same condition.

> *In this process you wouldn't need to know because whether we knew or not, we wouldn't then need to exclude them, so, you wouldn't have a great donor that suddenly, oh no, he's CF positive, we have to not use him.* Embryologist, clinic manager (clinic 1)

Thus, a potential beneficial aspect of a couple-based approach to ECS would be hat suitable donors who are currently discarded on the basis of their individual carrier status could still be used if matched to a recipient who is not a carrier of the same condition. Another benefit of couple-based ECS in a donor setting according to HCPs was that the alternative reproductive options for patients using a donor gamete are relatively simple. In other words, by causing minimal or no harm, it was possible for couples to change the donor's gamete to a non-carrier match. Given that HCPs held the view that when couples are using

a donor switching to another one in case they are identified as a carrier-couple was easy, some HCPs felt it was unethical for couples not to switch donors given the increased chances of conceiving a child with a genetic condition.

> *[..]if it is just a [social] couple it will be very stressful for them finding out that, but if they are a carrier [with a donor] you can always look for another donor who doesn't have it, so you're not doing any harm in that situation.* Fertility doctor (clinic 2)

However, not all interview participants took the same stance. Whether changing to another donor was acceptable to them depended on the stage of their fertility treatment, how they balanced 'genetic compatibility' with other characteristics of the donor and when the matching would take place. The main reason for some HCPs not to offer this type of testing to recipients of donor-gametes was due to practical issues regarding how to implement this type of testing in the donor programme. If those practical issues were solved, reporting couple result was considered less problematic.

4.4.6 Theme 4. 'I'm curious to know the individual carrier states, but I respect that you don't need to tell me': participants' understanding of couple results

In this theme, I discuss participants' views on the concept of couple-based ECS and identify the ethical and practical issues couple results may bring for those undergoing fertility treatment. Examples of questions asked to explore participants' views were: What do you think about couple testing? What do you think it means to be a carrier for an autosomal recessive (AR) condition? Why do you think individual carrier states should be reported or not?

Misconceptions about the meaning of being a carrier of an autosomal recessive condition

During the interviews it became clear that participants could relate to the meaning of a positive couple result for their own reproductive plans and their future children relatively easily. At the same time, their views regarding couple results and not reporting individual carrier states were often based on misconceptions about the implications being a carrier of an AR condition would have for their own future health. The extent to which participants conveyed meaning to individual carrier states depended on their personal reproductive context, e.g. whether they used donor gametes to conceive or their own gametes. Participants' understanding of couple testing was not 'stable' throughout the interviews and sometimes they would go back and forth between understanding and

misunderstanding. For some participants, talking through the issues during the interview was helpful in developing their understanding of the topic and their views on not reporting individual carrier states. Participants sometimes changed their views as their understanding became more coherent. In the end, many arrived at the conclusion that reporting individual carrier states was irrelevant, as these would not be informative for their reproductive risk. Whilst a large number of participants expressed an initial desire to know their individual carrier states, the same participants were generally accepting of receiving couple results only, as they understood the couple result as what would be of relevance to the health of their future children. During the process of data analysis, I kept this potential for misunderstanding in mind as it appeared such an integral part of how participants reached their views. Reporting individual carrier results could compromise people's ability to make informed decisions, if health-related decisions are based on misconceptions regarding the meaning of being a carrier of an AR condition.

The meaning of being a carrier for an AR condition was something that participants struggled with, as it appeared difficult for them to grasp the irrelevance of individual carrier states regarding health-related decisions. Participants often based their reasons in favour of reporting individual carrier states on misconceptions that these would convey information about their own (future) health. For example, participants might misinterpret being a carrier of an AR condition as having a genetic predisposition for that condition themselves. Sarah expressed this misconception when discussing why she thought individual carrier states should not be 'withheld' from people, including gamete donors. She reflected on this by drawing on her experience when working in the NHS:

> *So the donor wouldn't be told if they were a carrier? With my NHS hat on that feels a bit unethical.*
>
> *I: Why is that?*
>
> *Sarah: For somebody to know that you'd have a condition? Or a potential condition and then not to know? For the donor and you not to know?* Sarah (actual test offer; couple 9)

If people, like Sarah, have the feeling that relevant information is being withheld from them, not reporting individual carrier states could lead to a breach of trust in the relationship with their HCPs. A feeling that relevant information is being kept away from them could be seen as especially difficult or unfair in a fertility setting, as fertility patients

have to place a lot of trust in their HCPs as they feel as if the control over their chances to establish a pregnancy lies in the hands of their HCPs.

Perceived relevance and concerns of reporting individual carrier states for reproductive decisions

Whilst participants understood that an abnormal couple result could be relevant in informing their current reproductive decisions, some were interested in their individual carrier states for their future reproductive plans. For example, they anticipated that not being identified as a carrier for any condition in this test would also be reassuring for their reproductive risk with a future partner or another donor. Some participants held the view that if they were aware of their individual carrier states, this would be helpful to breach the topic of reproductive risks with a future partner and they could then encourage those partners to undergo ECS. On the other hand, some explained that knowledge of individual carrier states could feel as an unwelcome responsibility to inform future partners. Sarah felt more positive about this possibility when she explained why she would be interested to know her individual carrier states:

> *Just to know if I could have potential problems in the future [..] if I went on to have a relationship and we wanted to have another child [..] cause if I know that I am a carrier for anything it would be at the back of my mind, [..] so at least I know, they definitely would have to get tested.* Sally (hypothetical test offer; couple 1)

Using a similar argument, participants also felt about these could be relevant for gamete donors for their future or current reproductive plans. For the reasons mentioned above, some participants felt that being informed about individual carrier states should be optional, and it is up to them whether or not they would request that information. Reporting couple results only, but allowing people to request their individual carrier states if they ask for it, is similar to the approach for population-based ECS recently recommended by the Superior Health Council in Belgium (45). If requesting individual carrier states were to be a possibility in practice, this also affects how the analysis of the test is performed in the laboratory and pre-and post-test counselling.

Participants' concerns and practical considerations regarding reporting individual carrier states in a fertility setting

Participants also discussed potential concerns of reporting individual carrier states in a fertility setting. For example, within a romantic relationship, they thought that knowledge

about individual carrier states could lead to feelings of blame or guilt, in a similar way that not being able to conceive might cause blame or guilt on one partner. For example, a participant illustrated that the other partner in her social and genetic couple felt guilty about not being able to conceive naturally, even though rationally, both knew that their fertility problems were not something one of them could be blamed for. Analogously, this participant thought that if individual results for ECS were reported and one partner was a carrier for a certain condition, that partner could feel guilty for potentially transmitting a genetic condition to their children, even though this would be irrational.

Some also felt that donors were providing a service and therefore any test result would be less relevant to them in comparison to the social couple who would be raising the future child. If donors were informed about individual carrier states, or the couple carrier status, they might refrain from donating and therefore the chances of finding a suitable donor would be jeopardised or become more limited.

> *So my concern about that is, [...] if you share that information, [...] and the donor goes, no I don't want to be responsible [...] and then they could withdraw from the process.* Lucy (hypothetical test offer; couple 3)

Lucy's quote indicates that people would sometimes consider continuing their fertility treatment with a donor who is a carrier match with the other gamete provider. This situation is likely to result in an ethical dilemma for the HCPs' involved, as the risks of conceiving a child that is affected by a genetic condition would be high.

Some of the reasons in favour of reporting individual carrier states in a fertility setting were quite rational reasons, regarding finances and logistics. If participants who were using donated gametes were found to be a carrier couple with one donor, they thought having to undergo and pay for a new ECS couple test was problematic. However, if ECS couple testing were cost-free, and testing would be routinely done as part of the donor-recipient matching procedure, some felt that there was no reason why individual carrier states should be reported.

> *I was just thinking it would be easier, for couples using a donor, to pick out a match would be easier for the clinic, and for a couple not to go through a sort of individual testing* Charlie (actual test offer couple 6)

> *it just seems a lot simpler than you know, in an ideal world it would be a standard for a donor just to have the preconception screening done and have their lists held by the clinic and then the clinic know when they're making a suggestion for a donor it is just an extra check that can be looked at.* Emma (actual test offer couple 6)

If given a choice of only 'compatible' donors, Charlie would be happy to receive a couple result. Some others reflected that individual carrier states could be used as part of the donor characteristics on which to base their choice of donor. How a couple-based approach would be incorporated in a donor screening programme affected participants' views on reporting carrier states and the ethical and practical issues they experienced.

A desire to know, but accepting an approach to ECS based on offspring risk

Several participants brought forward reasons as to why they would be interested in knowing their individual carrier states, which were not based on the misconceptions discussed previously. These reasons implied a curiosity about their genetic information more generally, rather than a specific interest in their carrier status for a particular condition(s). To some, like Matthew, knowledge for the sake of knowledge was considered something 'good' and reporting individual carrier states would provide this additional knowledge. Others also mentioned a human curiosity, expressed as wanting to know everything about themselves, as a reason to find out about their carrier states for AR conditions. These participants acknowledged that the information may not be useful, but that they would simply like to know.

> *I think it's really quite exciting, you know to know whether I'm a carrier of something I find really interesting not frightening. It's again important to me; knowledge is useful. It doesn't mean it will change anything in my life, but it's just another thing that's interesting for me* Matthew (hypothetical test offer; couple 4)

A distinct point to the mere curiosity about genetic knowledge in general, was that some participants had hoped that being informed about individual carrier states may indirectly reveal information about their genetic 'identity', their ancestry or biological family. For example, Eduardo, who identifies as mixed-race, had been tested for carrier status of CF previously and was found to be a carrier of this condition. He associated his positive carrier status for CF with having European ancestors, as he was aware that CF has a higher carrier frequency in Caucasians. In addition, John, who was adopted as a child, was hopeful that individual carrier states could be utilised as a source of information about his biological family's medical history. This was information that they wanted and if this test would not

give them that information, they might try and get it somewhere else. Despite participants' curiosity about their genetic information, a commonly held view was that being curious would not necessarily mean that individual carrier states should be reported, as it would not inform their current reproductive decisions.

> *If you've got the opportunity to know everything about everything, let's know everything. [..], but in terms of, if the exam question is, what is going to affect my pregnancy, and the only thing that can affect my pregnancy, [..] is when we are carriers of the same DNA information, then the rest of it, whilst being interesting, is not necessary.* Emily (actual test offer; couple 8)

Various phrases were used to indicate that participants were accepting of the couple-based approach, such as: 'I respect that', 'I get that', 'I understand that' 'I'm satisfied with that'. Participants respected the decision being made by the test-provider, or the clinic, not to report individual results demonstrating that they placed trust in the relationship with their health professionals:

> *Then it's back to genetics, because it is up to the clinic to reveal results, and it'll just say there is no match, and therefore it can go ahead, have a baby. [..] And then I'm satisfied with that. Pretty satisfied with that*. Eduardo (actual test offer; couple 10)

The relevance or meaning participants attached to knowledge about individual carrier states was contextual and may change depending on the composition of the genetic vs the social couple. Sarah reflected on the different meaning she attached to knowledge about individual carrier states now she was trying to conceive on her own utilising donated gametes, rather than with a partner who provided the other gamete.

> *At the time I thought I was always going to be married to him, so it didn't matter whether I was the carrier or not, what mattered was whether we were a match then. But now that I'm on my own, and there was a possibility that I could get pregnant with this donor, or another donor or a person, then that matters more maybe?* Sarah (actual test offer; couple 9*)*

Her view on reporting individual carrier states now she was planning to raise a child without a partner, may also indicate that she did not identify with the word 'couple', in couple test. Some participants explicitly expressed the view that the word 'couple-test' may not be the right phrasing for this type of testing. Some thought that the word 'couple' could be eliminated from the name, as gamete donors would not be part of their social couple. Others felt that the word couple implied that both partners would receive information from the test, or that an abnormal couple result would imply that their relationship was less valid:

> *[with the word couple-test] you instantly think about the two of you tested and therefore, you get back into that debate around that you should be informed of [..] whether you're a carrier or not, so I suppose it, does that name imply that you're going to get something different to what the result is actually aiming to be?* John (actual test offer; couple 7)

Eliminating the word couple and focussing on the future baby, may be more helpful to emphasise the purpose of this type testing for couples' reproductive decisions and the health of the future child.

Explaining couple-based ECS with a focus on the 'offspring' risk, rather than a focus on what is not reported may be more acceptable and facilitate pre- and post-test counselling. Jasmine compared having couple-based ECS to going to the general practitioner (GP) for a blood test; she suggested that patients should be informed if the test result were important for reproductive decisions: only if both gamete providers are identified as carriers of the same condition. This seems like an interesting and useful analogy as to how results of carrier testing could be conceptualised and discussed.

> *At the GP, you do the blood test and they don't call if everything is fine, they call you when something is wrong, […]*Jasmine (hypothetical test offer; couple 2)

Focussing on the 'offspring risk' or what is important for people's reproductive decisions, rather than on what is not reported, could be a helpful way to explain and discuss couple-based ECS.

4.4.7 Summary and discussion of main findings

4.4.7.1 Summary

In Phase 2, I set out to identify and analyse the ethical issues and practical implications that couple-based ECS would raise for HCPs and couples/individuals in a fertility setting. All interview participants held positive, but nuanced views about this type of testing, and their motivations to consider using couple-based ECS were based on a desire to prevent suffering for their future children, their family and a perceived responsibility as a future parent to undergo these types of tests. The findings also demonstrated that the timing of the test offer in a fertility setting, as well as the stage of treatment and any costs involved are factors influencing couples' decisions to undergo couple-based ECS. Health professionals acknowledged the benefits of giving their patients the option to avoid conceiving children

with a severe genetic condition, and at the same time discussed how they should balance their responsibilities to help couples conceive and create healthy babies.

4.4.7.2 Acceptability of a couple-based approach to ECS in a fertility setting

Whilst many participants felt that being informed about what AR conditions they carry as an individual would be interesting to know, reporting individual carrier states was not considered necessary as the couple result was the result that was relevant for their reproductive decisions. Views regarding reporting individual carriers states were often (at least initially) based on misconceptions regarding the meaning of being a carrier of an AR condition for the health of the individual.

Whereas reporting couple results was not considered problematic by most HCPs for couples undergoing fertility treatment using their own gametes, practical and ethical issues were raised regarding a couple-based approach when utilising donated gametes. For example, HCPs were afraid consent to carrier testing would be compromised if donors did not receive their individual carrier states. Arguably, a couple-based approach to ECS makes the recruitment process for donors more inclusive and may have the potential to reduce donor shortage. Interestingly, the current UK donor guidelines allow for such as match-based system of carrier testing for gamete donors and recipients (251).

Apart from a focus on reproductive risk (i.e. clinical utility), a couple-based approach, according to some HCPs and interview participants, may also be favourable in terms of psychosocial impact and to avoid potential misunderstanding of the meaning of being a carrier for an AR condition, especially for those using their own gametes. Interview participants reflected on how meaningful individual carrier states were to them in their personal contexts. For example, depending on their reproductive circumstances (i.e. conceiving using a donor or with their own partner), reporting individual carrier states was considered more or less relevant. That is to say, for those utilising donor gametes, the perceived relevance of reporting individual carrier states was higher than for couples using their own gametes.

Some participants conveyed meaning to individual carrier states regarding future reproductive decisions with a new reproductive partner, or a new donor. Some mentioned that a ‘good’ test result with one partner would feel reassuring for their reproductive risk with another partner. These reasons for reporting individual carrier states are

understandable but concerning at the same time. As discussed in Chapter 3, some participants in the Phase 1 research felt more certain about their reproductive decisions after receiving a 'normal' result. For a test that includes only a limited number of conditions, the reproductive risk with a new partner if no individual carrier states were found, is likely to be reduced substantially in comparison to reproductive risk for those AR conditions in the general population. At the same time, a 'normal' test result with one partner could give a false sense of reassurance as it does not necessarily mean that the outcome of a test with another partner would be the same. As technology and knowledge about the meaning of genetic variants for these type of conditions is evolving rapidly, the scope of these tests is likely to change in the near future. Test results may need to be updated accordingly. In addition, if individual carrier states were reported and someone was found to be a carrier, this knowledge could be distressing if a new reproductive partner decided not to have carrier testing.

This test offer was couple-based and couples did not have a choice between a couple result and individual carrier states. If patients take the view that relevant information is being withheld from them, this may have implications for the doctor-patient relationship and affect the trust they place in their HCPs. Whilst HCPs were afraid donors would not agree to a couple-based approach to ECS and request their individual carrier states, in practice, HCPs did not experience this as an issue, nor did interviewees ultimately reflect this fear.

4.4.7.3 Importance of pre-test counselling and facilitating informed decision making: potential for misunderstanding

The potential for misunderstanding regarding several important aspects of couple-based ECS in a fertility setting, such as the purpose of the test, the meaning of being a carrier, residual risk and a potential for false reassurance, all emphasise the importance of pre-test counselling to facilitate informed decisions. At the same time, this also raises questions around what level of detail is required to understand the mechanism of inheritance for AR conditions, or the ability of non-genetics HCPs to discuss these complex concepts. I do not know to what extent participants' understanding is a reflection of how HCPs discussed and explained couple-based ECS in clinic, as I did not observe the pre-test counselling as part of my research. Both genetics and fertility HCPs thought that adequate pre- and post-test

counselling to facilitate autonomous decision-making and protect a vulnerable patient population was required when offering ECS, in line with current recommendations regarding responsible implementation of ECS (24,42,46). As ECS in a fertility setting bridges the two medical specialities, a collaboration between the two was considered essential for follow-up counselling and support by fertility as well as genetics HCPs.

Interview participants' confusion about the meaning of being a carrier for an AR condition might be related to the different ways the word carrier is used in everyday language. For example, being a carrier of a dominant condition such as hereditary breast cancer (e.g. caused by a mutation in BRCA1) is different from being a carrier for an AR condition. Carriers of the BRCA predisposition are at substantially increased risk of developing cancer themselves. Awareness about this condition among the public is quite widespread, ('Angelina Jolie effect') which may also affect people's views about carrier status for an AR condition (259). Thus, some participants may have conflated the meaning of being a carrier for an AR condition with having a genetic predisposition to develop an autosomal dominant condition.

4.4.7.4 What is a result?

Previously, when carriers came forward due to family history of a recessive condition, or when individuals were offered carrier screening based on ancestry, arguably, an individual carrier state could be considered a result. Knowledge of the index case led to cascade screening practices to identify any family members who were also carriers of the same condition and therefore at potential reproductive risk if their partner was also a carrier. The introduction of NGS challenges the definition of a 'result' from genomic testing as genomic research has confirmed that we are all carriers of AR conditions.

The same technological developments that have made ECS possible also mean that it is more cost-effective to adopt a couple-based approach rather than a sequential testing approach. The interpretation of the data and the multidisciplinary meetings required to discuss the results is what makes this testing expensive, not the sequencing itself (personal communication, see appendix X). This means that a couple-based approach is likely to be more cost-effective than sequential testing, even in a donor setting, in contrast to what HCPs expected. I argue that offering a couple test to all new reproductive couples, or to a gamete donor and their reproductive partner, could resolve concerns regarding perceived

relevance of individual carrier states for future reproductive decisions.

4.4.7.5 ECS in a fertility setting

ECS is not a treatment to help people conceive per se; rather, it provides couples with the option to reduce the chances of having a child affected by a genetic condition. HCPs identified a tension between their traditional responsibility to 'make babies', and the responsibilities new reproductive technologies pose on them regarding protecting the welfare of the future child. They debated the question as to whether they should offer ECS to all their patients to reduce the chances of conceiving children affected by severe AR conditions. Some felt clinics should actively offer this type of testing, others felt this was outside their realm of responsibility. However, not offering ECS to couples using their own gametes may withhold information from them that they would have liked to know, and HCPs feared a potential for liability if a child is born affected by an AR condition and they had not offered couple-based ECS to their patients. Currently, no legal/professional framework regarding offering ECS in a fertility setting exists as professional guidelines in the UK do not yet include recommendations regarding this type of testing. Thus, it depends on how professionals weigh the reasonableness and proportionality of reducing the risk of conceiving children affected by genetic conditions by offering ECS. The European Society of Human Reproduction and Embryology (ESHRE) recommends these are the leading principles when considering additional genetic screening in a donor programme (260).

One of the reasons why couple-based ECS in a donor setting was considered more beneficial than for couples using their own gametes was related to the alternative reproductive options available. Whilst HCPs may perceive switching donor as the 'easy' option, this was not always perceived similarly by interview participants. Whether switching donor was considered easy was dependent on how couples balanced 'genetics' with other characteristics of a donor, the severity of a condition, potential donor shortages, and financial barriers. Decisions regarding the way couple-based ECS is incorporated into the donor-screening programme, such as a test offer where clinics let recipients choose between 'compatible' donors only, may therefore alleviate some of the ethical issues in this setting.

The chances of being a carrier couple are the same for couples using ART to conceive compared to other couples from the general population. This is why HCPs held the view

that if ECS ever became part of routine NHS care, the primary care setting may be better suited to offer these types of tests. However, given that currently ECS is not available to any couple planning a pregnancy, fertility clinics could take up this role. When fertility clinics offer ECS, it is likely that couples will need to pay on top of their fertility treatment, and that the turn-around-time for the result may delay their treatment. Currently (2020), several fertility clinics in the UK have decided to offer this type of testing; these tests differ in composition (e.g. some include up to 600 conditions), and conditions vary in severity, penetrance and how they might affect the child's health, strengthening the need for a discussion on a national level regarding the criteria for test panels that should be offered in a fertility setting.

4.4.8 Strengths and limitations of the Phase 2 research:

This research is the first to present an in depth analysis of couples' and HCPs' views on ECS in a fertility setting and their views and experiences with a couple-based ECS test offer in practice. I included a range of perspectives, including couples and individuals using different types of fertility treatment and a range of professionals involved in clinical genetics and fertility treatment. As this research took place in a setting where ECS was actually offered to couples, the findings of this research are being fed back and will be incorporated to improve clinical practice in the future. When I presented the findings to HCPs working in one of the clinics, the findings resonated with them, irrespective of whether they had taken part in the research or not.

Not all couples were actually offered ECS and some of the findings are based on a hypothetical scenario without having received pre-test counselling. The difference in how these couples were informed about ECS may have influenced their understanding of the topic and thus their views on the issues such testing may bring. Furthermore, participants from Clinic 1 did not actually have to make a decision. As was demonstrated in Phase 1, intention and actual behaviour to take part in couple-based ECS do not always correspond and that is why some of the views expressed by interview participants from Clinic 1 may change if they were actually offered the test. Furthermore, I intended to include laboratory specialists, however, this turned out not to be possible in practice. Future research could look into this group of professionals. Theoretical sampling by selecting a different group of participants or changing the setting of this research was not realistic for various reasons

such as difficulty in recruitment, the small pool of eligible participants, and restrictions of my REC permission with respect to the site. Coyne (1997) states that a similar approach (i.e. exploring theoretical concepts further based on the analysis rather than changing setting or including a new group of participants) is often used in qualitative research for reasons similar to those described above (201). If these restrictions had not been there, I could have for example extended the scope of the research to include the experiences of parents who have a child affected by a genetic condition, or to a clinic in another demographic setting. Lastly, the analysis demonstrated that the ethical issues around introducing ECS in a fertility setting more generally and the ethical issues raised by couple testing specifically were entangled. This is why I decided to present the findings in such a way as to include issues related to both aspects of the couple-based ECS test offer, rather than focus on the issues raised by couple testing alone.

Chapter 5 Discussion and concluding remarks

5.1 Summary of this PhD research

Advances in genomic technology over the past decades have facilitated relatively inexpensive and quick carrier screening for multiple autosomal recessive (AR) conditions simultaneously, called expanded carrier screening (ECS). ECS could be offered routinely to any couple who may want [further] children to inform them about their chances of having children with this type of conditions before conception. As such, couples could use ECS to inform their reproductive decision-making at a time where they can still change their reproductive plans if they wish to do so.

In this thesis, I studied whether introducing couple based ECS for couples with no increased prior risk would meet criteria for responsible implementation in a health care setting and whether reporting couple results only, as opposed to individual carrier states, would be justifiable. The elements of responsible implementation I investigated included harms and benefits of offering ECS to the general population; whether the test offer was of clinical utility for couples planning a pregnancy and whether the reproductive options were meaningful; uptake and informed choice; and feasibility of test provision by non-genetics HCPs. Moreover, what is unique about this test offer is the approach to report couple results only, as opposed to reporting individual carrier states. I argue that the combined carrier status of both prospective parents is the result that is of clinical utility for reproductive decisions, and this is the aspect I explored in depth.

I adopted a mixed methods methodological approach and the empirical research was split in two phases. In Phase 1, I conducted a pilot implementation study where a couple-based ECS test, developed by the Genetics department of the UMCG, was offered to couples from the Dutch general population. This test consisted of 50 severe AR conditions, and was provided by trained general practitioners (GPs), as previous research demonstrated that these professionals were considered as most suitable by potential providers and the target population (21). To confirm whether this approach was responsible in practice, I examined uptake, feasibility, informed choice and psychological outcomes using longitudinal surveys (couples) and semi-structured interviews (GPs). Eligible couples could decide whether or not they were interested in the test offer, attending pre-test counselling and proceeding

with testing after counselling. Attending pre-test counselling was required for both members of a couple before undergoing ECS testing. I found that approximately 15% of the eligible population accepted the test offer within about one month. All GPs who were interviewed felt competent to provide pre-test counselling with the training and support provided by a genetic counsellor. Most participants made an informed decision to undergo ECS testing and there were no indications that the test offer is associated with negative psychological outcomes in this population. Participants were satisfied with receiving couple results.

Phase 2 consisted of qualitative research using focus groups and interviews in the fertility clinic to explore couples' and health professionals' (HCPs) views regarding and experiences of offering a couple-based ECS test in more detail. I focussed on the ethical issues and practical implications of reporting couple results only. The fertility setting was a perfect setting to study this because the genetic and social couple are sometimes different. I found that different issues were raised in a fertility setting, especially where donor gametes were utilised. Most couples and professionals considered such a couple-based approach acceptable, but HCPs questioned their responsibilities regarding gamete donors, as currently individual carrier states are reported.

The joint findings of Phase 1 and Phase 2 suggest that, looking at the previously defined elements of responsible implementation, a couple-based ECS test offer is a responsible approach in this setting. My research led me to question whether individual carrier states for rare AR conditions should still be considered "a result". Based on these findings, I argue that adopting an ethical framework which focuses on reproductive choice, offspring risk and providing meaningful reproductive options for those couples who are identified as carriers, as was done in this research, is helpful in justifying a couple-based approach to ECS.

5.2 Evaluating the introduction of couple-based ECS

Based on the findings of my research, I reflect as to whether couple-based ECS to couples from the general population meets the elements of my definition for responsible implementation. My definition was based on existing frameworks for evaluating genetic tests (95,261) and is in agreement with more recent professional recommendations

regarding ECS implementation for the general population (24). The first element I investigated was whether the couple-based ECS was of clinical utility for reproductive decisions and whether it allowed for meaningful reproductive options for carrier couples. I found that prospective parents considered they would change their reproductive plans based on the outcome of the test to ensure their future child did not have a genetic condition that would make them suffer (262). Phase 1 findings revealed that couples attached value to test-negative results as it made them feel more reassured about having children. Findings from both phases indicated that some prospective parents perceived a sense of responsibility to undergo ECS testing in order to maximise the chances of having a healthy child (232). The most important reason for declining the test offer in Phase 1 was that a positive test result would not change couples' reproductive plans. These findings demonstrated that participants' motivations in both Phase 1 and 2 aligned with the purpose of offering ECS, namely to enable couples to make more informed reproductive decisions. ECS offered before conception allows prospective parents to consider alternative reproductive options to a termination of pregnancy. As expected, Phase 1 findings are not informative as to whether the available reproductive options are meaningful to couples, as no carrier couples could be followed. Phase 2 findings suggest that new pathways need to be developed such that the, according to HCPs, preferred route for carrier couples in a fertility setting, i.e. adding PGT-M to an IVF procedure, is feasible. In addition, ECS testing itself, or some reproductive options are not accessible to all couples, due to limits regarding age or finances.

In Phase 1 and 2, the UMCG test consisted of a relatively small set of severe, early onset childhood conditions. This approach resulted in a clinically useful test and informed choice was reached in the majority of participants in Phase 1. Phase 2 findings demonstrated that couples would mainly want to make use of these tests if conditions were included that would seriously impact the life of a future child or their own lives. In order to establish clinically useful tests, regular revisions regarding what conditions are severe enough to be included in these types of tests is important. Advances in treatment of genetic conditions mean that some currently untreatable conditions may become treatable in the future (54). Treatability of a condition is one of the factors influencing whether reproductive genetic screening for certain conditions is better offered preconception, prenatally or as newborn screening or at multiple time points. However, criteria regarding which conditions to

include in ECS test panels are not uniform and this is reflected in existing ECS test-panels (32)(42,43,46). For example, the ESHG recommendations focus on early, severe, childhood onset conditions, US guidance includes conditions with varying severity and age of onset (42,43). Clearly such differences will affect the proportion of couples that are identified as carrier couples and whether ECS test results are meaningful in informing couples' reproductive decisions.

As ECS test panels include increasingly more, rare or different types of conditions (i.e conditions that are mild, less penetrant, have variable expressivity or are inherited in an dominant or X—linked way, both clinical utility and informed choice may decline overall. Adding more, increasingly rare conditions to ECS will not significantly increase the number of carrier couples identified (263). Pre-test counselling is likely to be more complex. Given that the aim of offering ECS is to enable couples to make more informed reproductive decisions, one should be cautious to expand these tests with conditions couples may not change their reproductive plans for. More research is needed to evaluate how including more, or different types of conditions would affect reproductive decisions and levels of informed choice.

The second element I investigated related to informed choice and uptake of the couple-based ECS test offer. I evaluated informed choice, alongside uptake, using a self-adapted version of the MMIC in Phase 1. These findings demonstrated that participants were well informed, which was supported by the experiences of the GPs, who thought that most participants were already aware of the issues before attending counselling. In Phase 2, it became clear that some participants struggled to understand the meaning of being a carrier of an AR condition in relation to their own health. Examining the concept of informed choice using both quantitative and qualitative tools thus added depth to my understanding of their decision making.

It is important to note that although I have focussed on the offer of ECS for AR conditions, some ECS panels also include X-linked (X-L) conditions. Since the mode of inheritance of these conditions is different, and solely dependent on the status of the prospective mother, a couple result is not appropriate for this type of test. If a woman is a carrier of an X-L condition there is a 50% chance that her sons will inherit the condition, whilst there is a 50% chance that her daughter will inherit her carrier status. Some initiatives have investigated carrier screening for Fragile X syndrome in the general population (264) but

we considered we needed to evaluate the desirability and acceptability of this type of testing amongst the target population before adding it to our UMCG ECS panel. For example, X-L status is more likely than AR carrier status to have some (albeit usually milder) health implications for the female carrier. This may be a particularly relevant consideration when offering ECS to oocytes donors (97).

Whilst in Phase 1, the test was provided at no expense, in Phase 2 couples had to pay to access this type of testing. The findings of Phase 2 demonstrated that this was a barrier for some couples who would otherwise have been interested in taking part, which is in agreement with the literature. For example, Plantinga et al., 2016 demonstrate that whilst couples would be willing to pay for ECS, however, the amount they would like to spend is much less than what ECS would currently cost (21). Phase 1 findings demonstrated that having to attend pre-test counselling with both members of a couple present was a barrier. In the future, this aspect could be addressed by facilitating pre-test counselling in other ways, such as using e-consultations, or evening clinics, as some GPs already offer.

The third element I assessed regarding responsible implementation was whether this couple-based ECS test offer was associated with any harms that outweigh the reproductive benefits. Phase 1 findings demonstrated that there were no striking adverse psychological outcomes in the study population. A minority of study participants expressed clinically relevant anxiety and decisional regret, and this was more often the case for test-decliners than test-acceptors. Feeling a responsibility to undergo ECS to maximise the chances of having healthy children had not previously been mentioned in the empirical literature as a motivation to undergo carrier screening in the general population, although papers deliberating ethical issues around purpose and justification of offering this type of testing do (97,105,106). Van der Hout et al (106) argue that prospective parents may have a responsibility to consider the health (or not) of their future children and that this might be a justification for preconception ECS. At the same time, prospective parents may perceive pressure to undergo reproductive genetic screening (265) and this is a matter that deserves further research. Introducing ECS as population screening, for example through a government-funded public health programme might also raise concerns regarding eugenics and disability rights (97) and this was indeed raised as a potential worry by some participants in Phase 2. These are some of the potential harms to which careful attention needs to be given to ensure that decisions whether to undergo ECS couple-testing are made

without coercion or perceived pressure. Equity of access is not yet relevant since such testing is not yet routinely available in the Netherlands or the UK. I would have liked to explore the impact of receiving a test offer on couples who decided not to undergo testing. This is a difficult group to study as many chose not to take part in the research, although I could extract some reactions from the response cards and included survey results from test offer decliners in Phase 1. I expect that studying the impact on this group as a whole would be beneficial in informing how to balance harms for couples not interested in ECS with the reproductive benefits for couples who would make use of this testing.

The fourth element pertained to the feasibility of a couple-based ECS test offer to the general population. The Phase 1 research demonstrated that trained GPs supported by genetics professionals were willing and able to provide such an approach. Post-test counselling was available in both Phase 1 and Phase 2, but no carrier couples were identified and therefore post-test counselling was not necessary. As part of this thesis, I was involved in debate in the media and the Dutch Parliament as well as the HFEA, Genomics England in the UK and a wide range of HCPs in both countries to improve understanding amongst both the general public and HCPs. A working group including clinical geneticists, laboratory staff, researchers and ethicists was established at the outset to discuss, evaluate and adapt the existing initiatives within the Dutch health care system. The purpose of these discussions are to reach consensus as to how an ECS test offer should be designed and to generate professional guidelines when this type of testing is offered to the Dutch general population. This collaboration between all Dutch clinical genetics centres and genomics laboratories has for example resulted in draft guidelines for an ECS test offer for couples from high risk populations (1).

Thus, I managed to study these elements regarding responsible implementation most relevant at this stage of the introduction of ECS in a health care setting in some shape or form in my thesis. Before starting this PhD, several aspects regarding responsible implementation mentioned in the ESHG consensus statement were already known. For example, the acceptability amongst the target population and HCPs, certain technical aspects of the test, and what the most preferred mode of test-provision was (i.e. test provision by general practitioners). This thesis has contributed evidence regarding multiple aspects. First, a small but substantial percentage of the target population, comparable to previous single-gene carrier screening, accepted the test offer. Second, the reasons why

couples accept/decline ECS testing are in line with the aim of offering this type of testing and most participants made an informed choice to take part. The desired mode of test-provision was feasible with motivated and trained non-genetics professionals and no significant harms were identified. The Phase 1 and 2 research did not investigate whether ECS couple-based testing was cost-effective and, as no carrier couples were identified, I could not follow-up their reproductive decisions. Moreover, the limited time-period prevented me from exploring long term implications of a couple-based ECS test offer to the general population.

In summary, with regards to the elements studied in this research, a couple-based ECS test offer focusing on a limited set of severe conditions, provided by non-genetics professionals was responsible in this setting. The next step of conducting a large-scale study has become reality as during the course of my research (2015-2020), policy and research around introducing ECS in health care systems around the world has been changing. I was involved in debate in governmental and public health institutes, and the desirability of offering preconception ECS was a topic of debate in the Dutch Parliament and the Health Councils of Belgium and the Netherlands (2,10,45,93,266). In 2019, the Health Council of the Netherlands' advised the Dutch Minister of Health to consider offering preconception carrier testing for Spinal Muscular Atrophy (SMA) as part of an ECS test offer to the general population (93). This may open the door to investigating whether ECS can be implemented in the Dutch health care system in a large-scale research project. In Australia (McKenzie's Mission) and Belgium, large-scale initiatives to introduce ECS for the general population have started.

5.3 Couple or individual results?

The aspect I focused on in particular in this research was the concept of a couple result - i.e. one where the individual members of the couple will only be able to infer their own carrier status if they are a carrier couple. I argue that couple results are the results that have clinical utility for reproductive decisions whilst individual carrier states do not. One study of a hypothetical scenario, where members of the general public were asked whether they would prefer ECS couple results or individual carrier states, demonstrated a preference for the latter (69). That said, such hypothetical research may not reflect an actual offer and is very dependent on how the questions are pitched to participants as

suggested by Plantinga et al., 2019. Below I outline some of the pros and cons identified in my research of using couple results in a health care setting.

In Phase 2, I demonstrated that participants often held misconceptions about what being a carrier of an AR condition meant for their own health: i.e. they thought being a carrier would mean they would have some features of the condition. In turn this could mean they would make misinformed decisions about their reproductive future, worry about developing a genetic condition or pass on incorrect information to relatives regarding their reproductive risk. Kauffman et al., (2017) showed that when individual carrier states (and secondary findings) are reported, women decide to have ECS to influence decisions about their own healthcare, not for reproductive risk (243). Interestingly, the Phase 2 participants did not have problems interpreting the couple result as having implications for their reproductive decisions. Therefore limiting the offer of the test result to one that has clinical utility- rather than one that might be misunderstood- seems preferable. It is possible that couple results only may lead individuals to feel that information is being withheld from them, but if the pre-test counselling carefully explains that individual carrier states are not important to their own health, this potential loss of trust in the healthcare provider can be avoided.

Various arguments have been cited in the literature, and in my empirical research as to why individuals should be told their individual carrier states: (a) Some HCPs thought that if 'someone somewhere knows' about carrier state, then it would be unethical not to report them to individuals. However, it is feasible to set up a laboratory system that reports on couple results, without individual carrier results being "known"- it could be a computer algorithm for example and would not enter a person's data record. b) A common reason given for wanting individual carrier states is that they are perceived as relevant for future reproductive decisions (38): If I know I'm a carrier then I might ask my future partner/donor to undergo carrier testing for that condition. Historically, this argument was correct but with the advent of ECS, couple testing could simply be repeated each time a couple changed and this would be far more efficient. In the meantime, these couples are not burdened with information that lacks meaning for current reproductive decisions and could cause misunderstandings. Moreover, as technology develops, and information regarding the interpretation of genetic variants increases, a new, updated ECS test may be more accurate than using 'old' individual carrier states. For ECS tests containing tens or hundreds

of conditions, it is very likely that the first partner is a carrier for one or more conditions (14). This means that the second partner would need to be tested anyway so reporting individual carrier states would not be financially advantageous.

HCPs considered that the reduction in time and costs required for counselling and processes in the laboratory for couple versus individual carrier reporting should be taken into account. The reason why couple-based ECS is more efficient is mainly related to the reduced need for multidisciplinary meetings to decide about pathogenicity of variants, and the number of variants that need to be analysed and reported is far fewer. This consideration will be important as preconception ECS is scaled up within populations.

The more conditions included in ECS tests, the more likely it becomes that milder or treatable conditions will also be included in the panel. In my view this makes the arguments for couple testing even stronger. The focus then needs to be on counselling and querying whether the aim of the test offer is to inform reproductive decisions, as being a carrier couple of a mild condition might not influence reproductive decision making.

In Phase 2, I found that there were couples using a donor and those using their own gametes who identified different issues regarding couple results. In this situation, the term 'couple' takes on a different meaning since the genetic and social couple are not the same where a donor is used. This raises interesting questions about consent and feedback, and what a donor recipient might find out about their donor that is more than the standard description services usually offer. In addition, as the actual testing is done on the donor and the other gamete provider, but the test result is also relevant for the partner in a couple who is not the gamete provider, questions may arise around the extent to which this partner should be involved in providing consent to this type of testing.

In my research I came across an interesting scenario where recipients order sperm from a commercial sperm bank overseas. The information about the donor may include individual carrier status for AR conditions. This has little clinical utility unless the same carrier screening can be offered to the recipient. Recipients may make false inferences that a donor is not suitable, whereas it is not possible to draw any meaningful conclusions based on this information alone, and indeed most people are carriers for at least one AR condition without ever being aware of it.

Genetics professionals raised concerns that reporting couple results only would prevent cascade screening for family members of an individual identified as a carrier. However, this argument precedes the advent of ECS tests, which can pick up carrier couples far more effectively than any cascade screening programme for carrier status can. Indeed, research indicates that cascade screening as a means of population screening for any AR conditions in the general population is less effective (267); not all carriers inform their relatives and not all relatives subsequently access carrier testing themselves (268,269).

Although couple tests might replace individual carrier reporting in the future, we are some way off of this scenario being a reality for all, and currently couple tests are only available through such initiatives as the UMCG panel as studied here. Some people argue that in the interim, if a condition has a high carrier frequency in the general population, for example for cystic fibrosis (CF) in northern Europeans, then individual carrier states should be reported so that carrier couples can be identified via this route. Although cascade screening of carrier findings is given as justification for finding more couples for a condition where carrier frequency is common, my view is that with the advent of ECS this will soon be outdated. In any case it seems a rather inefficient route since for most carriers identified through cascade screening, the chance of being a carrier couple is still less than 5% (1 in 20).

Phase 2 explored couples' and HCPs' thoughts about reporting individual carrier states, and found that views in favour were often based on misconceptions about risks, many of which disappeared once their understanding of the meaning of being an individual or couple carrier of an AR condition improved. Whilst interview participants often mentioned that they were interested in knowing their carrier states, they did not consider this a reason as to why carrier states should be reported in a health care setting. I therefore consider that reporting couple results is justified when ECS is offered both to couples from the general population and for those using donated gametes. Taking all these arguments into consideration, I conclude that offering couple testing to any couple planning a pregnancy would be preferable over cascade screening of family members when someone is identified as a carrier for a (rare) AR condition.

In Chapter 1, I discussed the relevant factors when designing a carrier screening offer, including the population, the setting, limitations regarding technology and to whom the test should be offered. I then examined whether and how results should be reported, i.e.

as couple results or individual carrier states. I concluded that couple results were preferable to individual carrier states in Phase 1 and 2 of this research, but acknowledge that this depends on the setting in which the offer is made. Below I briefly consider some different settings.

For tests that are available direct-to-consumer, public health decisions about utility usually receive less attention and the exchange is more of a commercial one where the customer gets the information they pay for. One might say that as long as the information provided explains why individual carrier states are not informative of health risks, individuals should be able to request those results. On the other hand, reporting individual carrier states for direct-to-consumer tests could be harmful if people make health-related decisions based on this information, due to misconceptions about the result. As a result, the burden on the publicly funded health services may increase unnecessarily.

Ethical arguments in favour of reporting couple results are the same for consanguineous couples as those who have an increased risk compared to the general population for having children with AR conditions if no family history of AR conditions is present (270). Individuals and couples who have a family history of a specific condition or are otherwise identified as being high risk (1) are offered carrier testing through clinical genetics services. For people in high risk populations based on ancestry or geographical origin, reporting individual carrier states for conditions with a high carrier frequency may have perceived clinical utility, in a similar way as previously described for CF. In exceptional circumstances, if their partner is unavailable, not willing to be tested, or if testing is costly, reproductive decisions may be made based on carrier status of the individual alone, as the chances are high that the partner is also a carrier, as may be the case for sickle cell disease or thalassemia (1).

5.4 Strengths and limitations, evaluating the quality of this research

In this section, I evaluate the quality of my research and discuss the strengths and limitations. Quality of quantitative research is evaluated according to different standards than qualitative research. This is articulated for example by the different sampling methods, methods for data analysis and how findings are interpreted. An important aspect of quality assessment in mixed methods research is how the findings of the different strands of research are integrated with one another. In this discussion, I brought together

the findings from Phase 1 and 2 to evaluate whether couple-based ECS could be a responsible approach in the general population. The two phases produced findings supporting this couple-based approach for a limited set of severe conditions and underlined the importance of counselling and a collaboration between non-genetics and genetics professionals to provide good quality services. Qualitative and quantitative approaches were complementary and generated findings that were overall consistent with each other.

I believe my study design had the following strengths: (1) the study objectives incorporated previously identified criteria for responsible implementation. (2) I chose different methods of data collection and analysis to provide depth in answering the research questions. (3) The joint PhD provided me with the opportunity to study an actual couple-based ECS test offer in two different settings. (4) that several of my findings have already been published – demonstrating that this PhD research has value to the scientific community. Several Phase 2 publications are still to come but the Phase 2 roundtable discussion including fertility HCPs and patients (included in appendix A) will be submitted next. Theoretical consistency is demonstrated because the overall findings of this research are generally consistent with existing literature regarding implementation of carrier screening in the general population. I found the use of mixed methods quite challenging and at the start of the research felt particularly inexperienced with the qualitative component. I recognise that the robustness and richness of the data produced by the first interviews and focus groups may be more limited. However, experienced qualitative researchers closely supervised the analysis process of the qualitative data in both Phase 1 and Phase 2.

There are some limitations to this research. A first limitation concerns the internal validity of the Phase 1 findings. For some of the items included in the survey for the Phase 1 research, I had to self-construct measures, because validated instruments were (still) lacking or only partially validated. This concerned for example the worry scale and the knowledge items of the informed choice measure. Although these instruments were optimised and discussed with expert advisers in the supervisory team, these were not formally validated. It is unclear if, and to what degree, this may have affected the findings.

Another element is external validity/generalisability. For the Phase 1 research, the characteristic features of the study setting may have affected my findings. The most important ones are: (a) the setting in the North of the Netherlands where people are less

inclined to take part in (reproductive genetic) screening (b) participation of GPs and couples based on non-random voluntary participation (c) a one-time test offered without co-payment. Uptake of reproductive genetic screening in the North of the Netherlands is (slightly) lower than in other parts of the country, which may have also been the case regarding uptake of ECS. When ECS is offered nation-wide, intention and actual uptake of ECS may therefore be higher. Regarding (b) self-selection of participating GPs/GP practices may have led to the selection of GPs/practices with a relatively favourable attitude to or interest in preconception care or screening, and this may have resulted in a relatively positive execution of the research and evaluation of the feasibility of this test offer provided by GPs. Participating GPs/practices might not be not representative for the average Dutch GP/practice, however that is not necessarily problematic. Even if ECS is implemented nation-wide, it may be the case that only motivated GPs are going to specialize in provision of these services. Furthermore, the 190 participating couples in the Phase 1 research are likely to be a selective sample from the 4295 invited women, given that many participants had a positive intention and a large percentage has received higher education. At the same time, selective participation is only problematic if it means that people who would be interested in participation are excluded, for example because the information was too complex. The one-off free test offer might not be completely representative of a normal 'preconception' setting. This limits the prediction regarding uptake of the test offer for large-scale implementation, and I hypothesised in Chapter 3 how large-scale uptake may be higher or lower than what was found in this research and the extent to which ECS was actually offered as part of preconception care.

In contrast to quantitative data, qualitative data should aim to reflect the diversity of a sample rather than be a representation of the population as a whole. The purposeful sampling strategy I adopted was successful, as I recruited a variety of participants in line with the participant characteristics I defined at the start. At the same time, I was also limited in my sampling, because the clinical care team identified the sample for me and in clinic 1, I found it difficult to recruit doctors, as they were often too busy to take part. That is why in clinic 2, I specifically targeted my recruitment to consultants. I had also intended to include laboratory staff in my sample, but this turned out not to be possible in practice, as they did not reply to my invitation. I had sufficiently rich data to identify interesting themes in the data in order to answer my research questions.

The interview schedule and focus group topic guide were discussed with supervisors. I conducted a pilot focus group for the qualitative study in the fertility clinic. Suggestions from supervisors and pilot participants have been incorporated appropriately. I extensively discussed the coding and analysis within the supervisory team to ensure I addressed the right questions and focused on the relevant aspects of the data to answer the research questions. In addition, I wrote a detailed methods section (Chapter 4.2) to reflect on the choices I made during the research. Doing both interviews with patients and focus groups with HCPs allowed me to contrast and compare their views and experiences to some extent, in order to end up with a more comprehensive picture of the ethical and practical issues (triangulation). As a medical doctor, I found it difficult sometimes to stay in my role as researcher and I was aware that my own views on reproductive screening are not necessarily the same as those of the participants. These are all factors that affect how I interacted with my participants and therefore these could have influenced the data and my interpretation of the data. Fertility HCPs (including those who did not take part in my research when I gave a presentation at clinic 2) and the couple whose account I wrote for publication as a roundtable discussion (see appendix X) felt that my interpretation of the data resonated with their views. Therefore, I am quite confident that the conclusions I have drawn based on the findings of this research are valid.

It is possible that cultural differences with regards to reproductive genetic screening between the research settings (primary care in the Netherlands, fertility care in the UK) limit the generalisability and transferability of findings from one setting to the other. However, my experience is that most cultural differences were rather minor and that the 2 phases complemented each other well.

5.5 Implications for policy and care

Preconception or prenatal test provision: My findings, and those in the literature, suggest that the preconception stage is the optimal timing for a couple-based ECS offer (24,234). This improves the reproductive options available, allows more time to think through the options and decision making can occur without the additional physical and emotional stress of a pregnancy. At the same time, ECS might also benefit couples during a pregnancy. Currently more couples access prenatal rather than preconception care, therefore uptake

of carrier testing is often higher during pregnancy, and not all pregnancies are planned. Prenatal ECS gives carrier couples the possibility to consider termination of an affected pregnancy or use the knowledge to prepare themselves for the birth of a child that is affected by a severe genetic condition.

In the fertility setting, pregnancy was often viewed as more precious, and was emotionally and financially more costly for all parties involved. For this reason prenatal ECS may be more difficult in this setting than in a primary care setting. Furthermore, it is much easier to offer a preconception test to couples who are trying to conceive, those who do not need fertility services often do not come to medical attention in the preconception period. At the same time, offering ECS in a fertility setting could also lead to more pressure for couples to undergo testing, which was a worry expressed by some HCP participants in Phase 2.

Regarding large-scale implementation, a prenatal couple-based ECS test offer would mean that GPs need more training regarding the specific issues of ECS during pregnancy, urgent referral to clinical genetics and obstetrics for discussion of prenatal testing should be available and other non-genetics professionals such as midwives may be more suitable to perform pre-test counselling than GPs. However, not all HCPs providing prenatal care may consider this part of their role (234). It is also important to explore whether a likely higher prenatal uptake is due to informed decision-making, or pressure to undergo this type of testing as it is offered along with other types of screening such as the NIPT. Given that this a rather different approach than preconception ECS, future research should address these specific issues before introducing prenatal ECS more generally.

Raising awareness about preconception care: In Phase 1, GPs felt that offering couple-based ECS provided them with a new opportunity to discuss preconception care with young healthy couples they would otherwise not see. Given that couple-based ECS cannot by far remove all aspects of reproductive risk, it is important to raise awareness for general preconception care and, as was done in Phase 1, embed couple-based ECS within preconception care, or when offered prenatally, integrated in the prenatal screening offer. When couples access preconception or prenatal care, GPs, or other primary care providers such as midwives could then actively offer couple-based ECS at the same time. The one-off, more active approach taken in Phase 1 did not appear to have any harmful consequences, but the impact on people who were not interested in this type of information and who did not reply, remains unknown. As some couples do not access general preconception care, a

drawback of this more opportunistic approach, is that these couples are not informed about the possibility to undergo ECS at the preconception stage. Raising awareness about the existence of these tests and improving genetic literacy in the population might enable a more equally accessible test offer at the preconception stage.

Training of non-genetics professionals: My research confirms previous findings that knowledge and confidence to discuss couple-based ECS can be relatively easily acquired by non-genetic HCPs. I demonstrated a model as to how non-genetics professionals could be trained to provide adequate counselling, with high patient satisfaction, high levels of informed choice and self-reported and 'judged' competence by genetics professionals. Once genetics education is incorporated more generally into the medical curriculum and the registrar training programmes, genetic literacy and skills to discuss genetic testing are likely to increase.

5.6 Gaps in knowledge, recommendations for future research

My research did not identify any carrier couples because as per the design, the numbers studied were not sufficient to identify (many) carrier couples. Further research should focus on long-term follow up regarding reproductive decision-making and the impact of being identified as a carrier couple after undergoing ECS to complement (mostly American) publications on this topic (271). The next step in introducing couple-based ECS into the healthcare system should be a large-scale study to investigate this type of testing in the general population, as is currently the case in Australia.

Secondly, clearly, longer-term consequences are beyond the scope of a PhD study, but issues such as perceived social pressures to undergo this type of testing which could compromise couples' reproductive autonomy and any potential implications for people living with a disability need to be considered.

Findings from both Phase 1 and Phase 2 emphasised that primary care would be the ideal setting to offer this type of testing. Thus, it is important to investigate how appropriate reimbursement or commissioning for GPs (or other primary health providers) should be organised, how ECS could be included in health insurance packages/ NHS commissioning and what the best pathway would be to PGT-M services

A final aspect regarding responsible implementation that was not addressed in this research is cost-effectiveness. When couple-based ECS are to be incorporated into a government funded health care system, cost-effectiveness is an important factor to take into consideration (24,97). ECS was demonstrated to be cost-effective when a 176-condition disease panel in a private health care setting in the United States was compared to minimal screening (e.g. CF and SMA)(20). Similar analyses could be performed to evaluate cost-effectiveness regarding the UMCG test offer in the Dutch general population. Couples' reproductive autonomy could be compromised if a high uptake of screening is required to achieve a cost-effective screening programme (97).

5.7 Concluding remarks

The test offer as described in this thesis is now available at cost price through several GPs in the Northern Netherlands and in the fertility clinic participating in this research. In the near future, this test offer may be available for all couples and individuals/couples using a donor who would like to make use of it.

Defining a responsible approach to introducing ECS to couples from the general population is complex and requires evaluation of many technological, ethical, psychosocial and practical aspects of a test offer. Recommendations from professional societies such as the ESHG were useful tools to address the relevant aspects regarding the design and evaluation of a responsible test offer. I demonstrated that introducing couple-based ECS to the general population by non-genetics health professionals could be such a responsible approach. My research did not suggest any significant harms of offering this type of testing in an implementation pilot setting. Therefore, the next step to evaluate ECS to couples from the general population should be a large-scale nation-wide study to address the current gaps in knowledge, including longer-term societal impact of a routine test offer, and follow-up of carrier couples. Recently, such large-scale research projects have started in Belgium and Australia. Based on the elements of responsible implementation I studied in this research, a test offer focused on a limited set of severe AR conditions providing couple-results only is justified.

Appendix A Manuscripts

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ARTICLE

GP-provided couple-based expanded preconception carrier screening in the Dutch general population: who accepts the test-offer and why?

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Abstract

Next generation sequencing has enabled fast and relatively inexpensive expanded carrier screening (ECS) that can inform couples' reproductive decisions before conception and during pregnancy. We previously showed that a couple-based approach to ECS for autosomal recessive (AR) conditions was acceptable and feasible for both health care professionals and the non-pregnant target population in the Netherlands. This paper describes the acceptance of this free test-offer of preconception ECS for 50 severe conditions, the characteristics of test-offer acceptors and decliners, their views on couple-based ECS and reasons for accepting or declining the test-offer. We used a survey that included self-rated health, intention to accept the test-offer, barriers to test-participation and arguments for and against test-participation. Fifteen percent of the expected target population—couples potentially planning a pregnancy—attended pre-test counselling and 90% of these couples proceeded with testing. Test-offer acceptors and decliners differed in their reproductive characteristics (e.g. how soon they wanted to conceive), educational level and stated barriers to test-participation. Sparing a child a life with a severe genetic condition was the most important reason to accept ECS. The most important reason for declining was that the test-result would not affect participants' reproductive decisions. Our results demonstrate that previously uninformed couples of reproductive age, albeit a selective part, were interested in and chose to have couple-based ECS. Alleviating practical barriers, which prevented some interested couples from participating, is recommended before nationwide implementation.

Introduction

Next generation sequencing allows fast and relatively inexpensive simultaneous testing for carrier status of many (rare) genetic conditions called expanded carrier screening (ECS) [1]. Deciding what to include in ECS is a complex issue and may depend on for example the target population or the setting in which ECS is offered. As a study by Chokoshvili et al. demonstrates, currently available tests vary greatly in composition of the test-panel [2] and may consist of autosomal recessive (AR), X-linked or in some cases even autosomal dominant conditions. ECS can inform reproductive decisions before and during pregnancy. Couples found to be at increased risk might wish to consider alternative reproductive options to conceive, e.g. in vitro fertilisation and pre-implantation genetic testing (PGT), non-carrier donor gametes or prenatal testing.

The Genetics Department of the University Medical Centre Groningen (UMCG) in the Netherlands developed and validated a population-based ECS test for a limited set of 50 severe early-onset AR conditions for which no curative treatment is available. Based on the outcome of an international expert meeting, and supported by recent guidelines [3, 4], we developed this gene-panel to evaluate its potential for ECS implementation within the public

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health system. Whilst in the future, this test could also be complemented with individual carrier screening for X-linked conditions [5, 6], here we chose to focus on AR conditions only, and adopted a couple-based approach. If both members of a couple are carriers for the same AR condition—i.e. carrier-couples—then for each pregnancy there is a risk of one in four or 25% of an affected child. The conditions included in the test carry no known health implications for the individuals in the couple; the only known health implications relate to their future offspring. Previous research among potential users demonstrated an interest in such a test and also identified the general practitioner (GP) as the preferred provider [7, 8]. With these results in mind, we conducted a pilot implementation study in which GPs offered this couple-based ECS to women and their partners from the general population at no financial cost. The main aim of this test-offer was not to encourage as many people as possible to undergo couple-testing. We were primarily interested in how many eligible couples were willing to be informed in more detail about ECS by their GP and how many of such prepared couples made a decision to proceed with testing. This aligns with recommendations from international professional societies which describe the main aim of ECS as to facilitate informed reproductive decision-making [3, 4]. We previously reported that the test-offer is feasible and results in informed choice [5]. Here, we describe the initial interest in this GP-provided couple-based ECS from the target population, the characteristics of couple members who decide to accept and decline the test-offer and their reasons why.

Methods

Study design and test-offer

Figure 1 outlines the different elements of our study design and ECS test-offer. Nine GP practices in the catchment area of the UMCG sent out letters to all women aged 18–40 registered with their practices, inviting them to take part in the implementation study. Women were asked to invite their male partners to participate and written consent was requested from both partners. As Fig. 1 shows, all participating couples, regardless of whether they attended pre-test counselling or proceeded with testing, were asked to fill out two online surveys: Survey 1 at study onset and (if they had filled out Survey 1), Survey 2 6 months afterwards. Couples who were interested in the test-offer, could make an appointment for pre-test counselling with the woman's GP within ~1 month. We asked both partners to attend counselling together, after which they could decide whether they would like to have the screening test.

Prior to the start of the study, all GPs received training to prepare them for the ECS pre-test counselling and the first two counselling sessions for each GP were supervised by a clinical genetics professional. GPs could also refer couples at high a priori risk (e.g. consanguineous couples) and couples needing additional pre-test counselling directly to the Department of Clinical Genetics. Further details about the study design and GP involvement have been reported elsewhere [5]. We also launched a publicly accessible website, www.dragerschapstest.umcg.nl, with general information about the study and the test that also included details on how to ask questions to the research team. For GPs, support from a genetic counsellor from the research team was available throughout the study. The ECS test was offered free of charge to participating couples. If couples received a positive couple result, reproductive options such as PGT and prenatal testing would be covered by statutory health insurance to all the Dutch citizens. The Medical Research Ethics Committee (METc) of the UMC Groningen approved the study protocol (METc 2015/384).

Recruitment and study inclusion

Figure 2 displays the recruitment and inclusion of participants in the study. Between January and December 2016, the GPs invited 4295 women aged 18–40 to participate. Women over 40 were excluded from this study because ethical issues may arise due to limited access to PGT for women older than 40 in the Netherlands. All were asked to return the response card to indicate their eligibility and interest in taking part. Women were eligible for participation if they had a male partner, were planning to have children with this partner and were not pregnant. We excluded pregnant women for two main reasons. Firstly, this was the first time GPs were offering ECS and our initial training focused on the least complex pre-test counselling. Secondly, the turn-around-time of the test-result was a maximum of 8 weeks, which limits the time for couples to consider a potential termination of pregnancy in case of a positive test-result. Fourteen women were not eligible for 'other' reasons, for example they could not conceive biologically with their partner due to gender affirming treatment. A test-result was considered positive only if both partners have a class IV or V variant in the same recessive disease gene included in the test.

Materials and measures

Data were collected via questionnaires using the Roqua online tool for confidential clinical data collection [9]. We asked participants ($n = 190$ couples) to fill in the surveys independently from their partners. The survey design was based on research described in [7, 8] that explored attitudes,

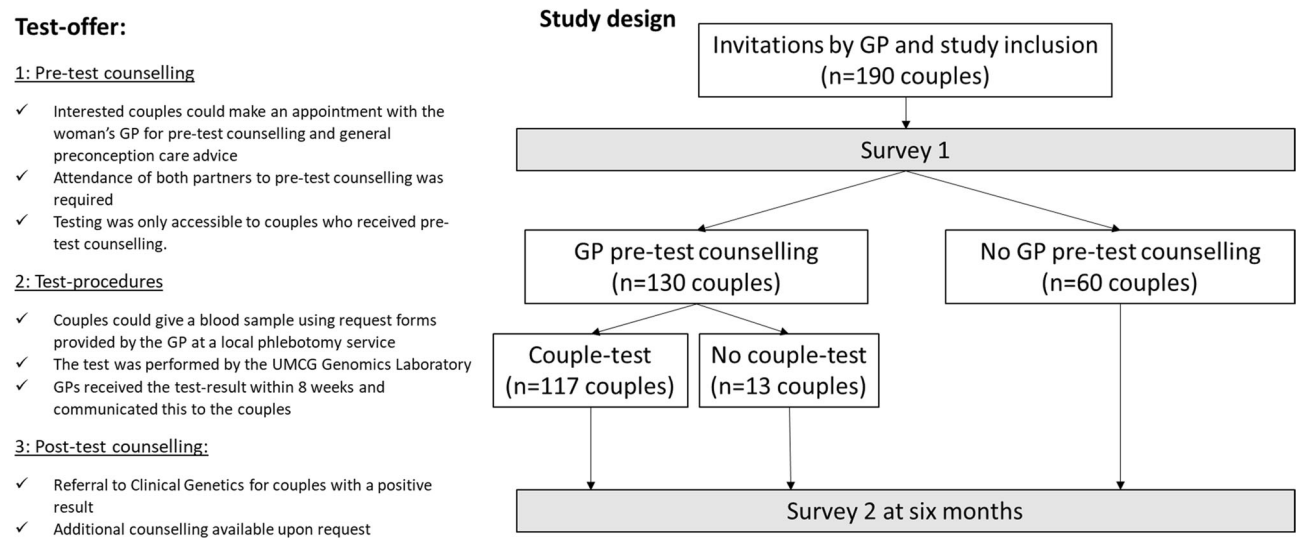

Fig. 1 Overview of test-offer and study design

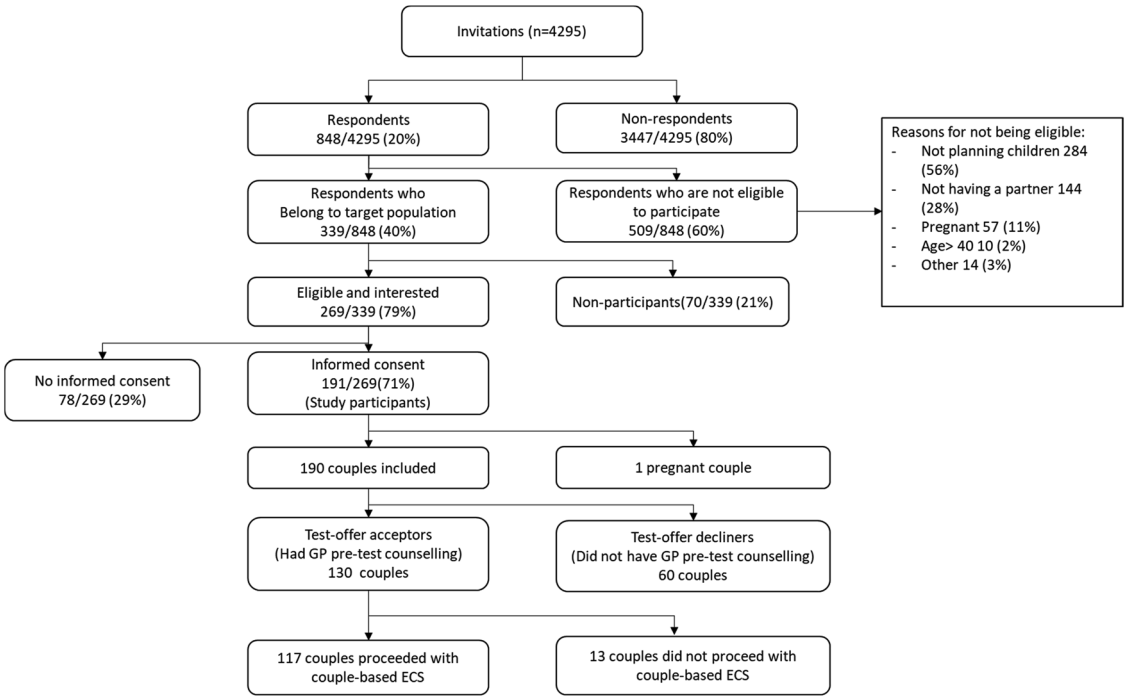

Fig. 2 Flow diagram of recruitment and inclusion

intentions and reasons for and against accepting couple-based ECS in a hypothetical scenario. The reasons for and against accepting ECS are based on key ethical arguments previously described in [7]. Survey 1 recorded participants' sociodemographic characteristics, factors related to their relationship and reproduction, their own health and their experiences with (presumed) hereditary conditions, genetic counselling and testing. In addition, we collected data on their intention to participate in testing and their perceived barriers to test-participation. After 6 months, in Survey 2, we collected data on how participants retrospectively viewed their decision about ECS testing and their views on couple-based test-provision.

Test-offer acceptance and uptake rate

We distinguished test-offer acceptance (defined as attending pre-test counselling by the woman's GP) from actual ECS test-uptake because the main aim of the test-offer was to inform couples and encourage them to discuss test-

participation with the GP if they were interested, an aim separate from the final uptake of the couple-based ECS test itself. We calculated an additional acceptance rate based on the estimated eligible population (couples planning a pregnancy). Previous research showed that ~20% of women between 18 and 40 years of age would be eligible for the test-offer [10, 11]. In our case, we estimated the eligible population as 859 women (or 20% of the 4295 invited women). Thus, in this paper, we use the following three definitions of test-offer acceptance:

(1) The proportion of women and their partners who accepted the test-offer as part of the total number of women who were invited (denominator $n = 4295$),
(2) the proportion of women and their partners who accepted the test-offer as part of an estimated eligible population (denominator $n = 859$),
(3) the proportion of women and their partners who accepted the test-offer ($n = 130$) as part of the total number of women who participated in the study (denominator $n = 190$).

Lastly, the ECS test-uptake rate was calculated as the proportion of couples who proceeded with testing after pre-test counselling.

Variables included in the survey

Characteristics of test-offer acceptors and decliners

Sociodemographic characteristics Age was divided into three categories in a similar way as reported by Plantinga et al. [7]: 18-23-24-33; >33 years of age. Participants' educational level, marital status and religiosity were classified according to the Statistics Netherlands (CBS) definitions. Educational level was further summarised as: 'basic' (finished primary school, lower secondary school or vocational training), 'intermediate' (finished higher level secondary school or intermediate vocational training) or 'high' (finished higher vocational training or university). Relationship status was classified as 'marriage or civil partnership', 'living together' or 'not living together'. Religiosity was measured by asking whether respondents were religious (0 = no, 1 = yes and practising, 2 = yes, but not practising). This was dichotomised into no or yes (including both practising and non-practising).

Relationship and reproductive characteristics Relationship satisfaction was measured on a 10-point scale (1 = very unsatisfied, 10 = very satisfied) [12, 13]. Participants were also asked within what timeframe they were planning to have children and whether they already had children. To be comparable with the other relevant Dutch studies, timing to next pregnancy was adapted from Henneman et al., who dichotomised into <2 years (short term) and >2 years (long term) [14]. We further categorised these into: (<0.5 years, 0.5 years-2 years, 2–5 years, >5 years, unsure)

Health status and experiences with hereditary conditions and genetic testing We asked participants to rate their own health on a 5-point scale (poor, moderate, good, very good and excellent). They were also asked whether they suffered from a chronic condition and were presented with fourteen categories, such as respiratory conditions (e.g. asthma), visual problems and mental health issues (yes/no). In addition to this, we asked respondents to indicate whether they, or any of their family members or friends, suffered from a (presumed) hereditary condition and/or whether they had ever had genetic counselling and testing themselves.

Intention, barriers and views on couple-based test-provision

Intention (Survey 1) Intentions towards couple-based ECS before pre-test counselling were measured with the item 'I intend to accept the offer of this couple-based ECS-test' on a 7-point scale (unlikely–likely). Intentions were classified into 'unlikely' (1-2), 'neutral' (3-5) and 'likely' (6-7).

Barriers (Survey 1) We collected data about the extent to which participants perceived the time and effort of test-participation, having to make a GP appointment and giving a blood sample, as barriers for taking part in this test-offer. These four items were measured on a Likert scale from 1 to 5 (totally disagree to totally agree).

Intention (Survey 2) We asked test-decliners whether it was a considered decision not to proceed with testing (yes/no). If it was not, they could indicate their reasons why (e.g. we could not come to a common decision as a couple, it just did not happen, I had not thought about it anymore, it was not possible to be at the GP appointment together).

Couple-based test-offer (Survey 2) Participants were also asked to indicate their main preference as to how test-results were disclosed. They were asked to indicate *one* preference out of the following four options: 1: couple results; 2: individual carrier results; 3: no preference; 4: not sure.

Arguments for and against accepting the couple-based test-offer

In Survey 1, we asked participants about the reasons why they would accept or decline ECS testing by presenting them with seven arguments in favour and ten arguments against (listed

in Tables 3 and 4) taking a couple-based ECS test. We asked all participants which single argument they considered most important in accepting and which single argument they considered most important in declining the test-offer.

Response cards

In addition, we received explanations of 70 eligible (members of) couples who returned the response card but decided not to take part in the study (and therefore the ECS test).

Data analysis

Given that partners within a couple might have different views about this couple-based ECS test-offer, individual participants were included in the analysis for all outcome measures apart from acceptance and uptake rate. Only respondents who filled out survey 1 were sent survey 2 and so response rates for survey 2 were calculated based on the number of participants who filled out survey 1. Descriptive data are presented using mean (SD), median (IQR) or numbers (percentages) where appropriate. To compare test acceptors and decliners, unpaired *T*-tests were used for continuous variables and χ^2 tests for categorical variables. Analyses were done using IBM SPSS version 23 (IBM Corp., Armonk, NY, USA).

Results

Response and study inclusion

Figure 2 is a flow diagram of the study. We received 848 response cards and in total, 509 women who returned the response card were not eligible (reasons listed in Fig. 2). Seventy eligible women indicated that they did not want to participate. The eligible women who were interested in taking part ($n = 269$) received detailed information about the study, were asked to invite their partner to participate with them and to return consent forms for both of them. After we received their written consent, 191 couples were eventually sent Survey 1. Subsequently, one couple was excluded because they became pregnant before filling out survey no. 1. Thus, in total, we included 190 couples (380 participants), 358/380 (94%) participants returned Survey 1 and 227/358 (63%) participants returned Survey 2.

Test-offer acceptance and test-uptake rate

In total, 130 couples attended pre-test counselling and 117 of these couples proceeded with testing. This resulted in the following test-offer acceptance and test-uptake rates:

(1) Test-offer acceptance was 3% (130/4295) (95% CI 3–4%) of the total invited population (i.e. women aged between 18 and 40 registered with the participating GPs)
(2) Test-offer acceptance was 15% (130/859) (95% CI 13-18%) of the estimated eligible population and 68% (130/190) (95% CI 61–75%) for the participants included in this survey study.
(3) The uptake rate of the ECS test in participants having attended the GP-consultation was 90% (117/130) (95% CI 84–95%).

Characteristics of test-offer acceptors and decliners

Sociodemographic, relationship and health characteristics

Table 1 displays the characteristics of test-offer acceptors and decliners. The average age in our study sample was 29 (SD 5.5) years and 50% of participants were between 24 and 33 years old. The majority of participants had an intermediate or higher education (93%), and 43% had already finished higher education. Twenty-four percent were religious and 25% were not (yet) living together. The relationship satisfaction rate was a median of 9 out of 10 (IQR 8–9). Fifteen percent already had children ($n = 55$) and sixteen percent were planning a pregnancy within 6 months. Thirty-nine percent reported at least one chronic condition, mainly asthma, migraine or mental health problems, but 97% described their health as good to excellent. Thirty percent had experiences with (supposedly) hereditary conditions in their family or friends, and 13 participants (4%) had previously had genetic counselling and testing. Most of these participants ($n = 11$), made an appointment with the GP to discuss couple-based ECS.

Test-offer acceptors and decliners differed significantly in the highest level of education achieved: test-offer acceptors more frequently had a higher educational level. They also less frequently had children, were more satisfied with their relationship and were less likely to plan a pregnancy within the next two years. Test-offer acceptors and decliners were comparable in age, religiosity, experiences with genetic counselling and testing, and having chronic and presumed hereditary conditions.

Intention, barriers and views on this couple-based test-offer

Table 2 displays participants' intentions, barriers to participation and views on couple-based test-offer.

Table 1 Sociodemographic characteristics

Sociodemographic characteristics	All $n = 358$	Test-offer acceptors $n = 259$	Test-offer decliners $n = 99$
Age (year) mean (SD)	29.1 (5.5)	29.4 (5.5)	28.7 (5.4)
Gender			
Female	185 (51.7)	130 (49.4)	55 (57.9)
Male	173 (48.3)	129 (49.6)	44 (44.4)
Age category			
18–24	69 (19.3)	46 (17.8)	23 (23.2)
24–32	180 (50.3)	134 (51.7)	46 (46.5)
>33	109 (30.4)	79 (30.5)	30 (30.3)
Religiosity			
Yes	84 (23.5)	65 (25.1)	19 (19.2)
Educational level**			
Basic	25 (7.0)	14 (5.4)	11 (11.1)
Intermediate	178 (49.7)	117 (45.2)	61 (61.6)
High	155 (43.3)	128 (49.4)	27 (27.3)
Marital status			
Married/civil partnership	77 (21.5)	59 (20.8)	18 (18.2)
Living together	196 (54.7)	146 (56.4)	50 (50.5)
Not living together	90 (25.1)	59 (22.8)	31 (31.3)
Children*			
Yes	55 (15.4)	31 (12)	24 (24.2)
Relationship satisfaction*			
Median (IQR)	9 (8–9)	9 (8–9)	8 (8–9)
Timing of next pregnancy*			
<0.5 year	56 (15.6)	35 (13.5)	21 (21.2)
0.5–2 year	103 (28.8)	74 (28.6)	39 (39.4)
2–5 year	126 (35.2)	102 (39.4)	24 (24.2)
≥5 year	36 (10.1)	27 (10.4)	9 (9.1)
Unsure	27 (7.5)	21 (8.1)	6 (6.1)
Self-rated health			
Excellent	90 (25.1)	73 (28.2)	17 (17.2)
Very good	129 (36.0)	95 (36.7)	34 (34.3)
Good	127 (35.5)	83 (32.0)	44 (44.4)
Moderate	12 (3.4)	8 (3.1)	4 (4.0)
Poor	0 (0.0)	0 (0.0)	0 (0.0)
Do you suffer from a chronic condition?			
No	218 (60.9)	162 (62.5)	56 (56.6)
Any experiences with hereditary conditions in your family or friends?			
No experience	252 (70.4)	179 (69.1)	73 (73.7)
Did you have genetic testing and counselling in the past?			
Yes	13 (3.6)	11 (4.2)	2 (2.0)

Test-offer acceptors and decliners were compared using *T*-tests for continuous variables and χ^2 tests for categorical variables. A *p* value of 0.05 was considered statistically significant. *p value <0.05. **p value <0.01

Intention

The majority (87%) of study participants had a positive intention towards test-participation, but test-offer acceptors rated their intention more often as 'likely' compared with test-offer decliners (93% vs. 69%). Forty-four percent of test-offer decliners indicated that the decision to decline the test-offer had not been a considered one, and the reasons they most often indicated to explain why they did not attend pre-test counselling were 'it just had not happened' ($n = 7$) or 'it was not possible to make a GP appointment together with my partner' ($n = 6$).

Barriers

Test-offer decliners indicated significantly more frequently that test-participation took a lot of time and effort. In addition, 20% of test-offer acceptors and 35% of test-offer decliners agreed or totally agreed with the statement that having to make a GP appointment was a barrier to their participation.

Views on couple-based test-provision

Fifty-seven percent of test-offer acceptors and forty-eight percent of test-offer decliners indicated that, if they had to indicate a single preference between couple results or individual results they would prefer to receive couple results. Fifteen percent of test-offer acceptors and eleven percent of decliners would prefer a test that would give them individual carrier states. Twenty-four percent of test-offer acceptors and twenty-seven percent of decliners had no preference and five percent of test-offer acceptors and fourteen percent of decliners were not sure what they preferred.

Arguments for and against accepting the couple-based test-offer

Table 3 shows that sparing a child a life with a severe genetic condition was considered the single most important argument to (potentially) accept this ECS test (29.6%). Other arguments that participants chose as most important were that they felt they had a responsibility as future parents to have this test (18%) and that a good result would be a great relief (13.0%). The distribution of these arguments was about the same for test-offer acceptors and decliners. Examples of 'other' arguments participants provided in favour of accepting ECS were curiosity, for the benefit of science, and due to experiences with genetic conditions in the family. Table 4 shows that for the participating couples the most important argument against having this ECS test was that the test-result would not influence their decision to have children (26.5%). Again, the distribution between test-offer acceptors and test-offer decliners was similar (25% and 30%, respectively). Twenty-seven percent of test-offer acceptors and eighteen percent of test-offer decliners provided additional explanations as to why they would not want to have the ECS test, such as a worry that after a positive test-result they would decide not to have children at all. Some stated they did not see any reason why not to undergo couple-based ECS.

Table 2 Intention, barriers and views on couple-based test-provision

Intention, barriers and views on couple-based test-provision	All *n* (%)	Test-offer acceptors *n* (%)	Test-offer decliners *n* (%)
Intention (survey 1)	*n* = 352 (6 missing)	*n* = 256 (3 missing)	*n* = 96 (3 missing)
Intention**			
Likely	306 (86.9)	240 (92.7)	66 (68.8)
Neutral	30 (10.6)	15 (5.8)	15 (15.6)
Unlikely	19 (5.4)	4 (1.5)	15 (15.6)
Intention (survey 2) (only participants who did not have ECS testing)	*n* = 54	*n* = 9	*n* = 45
Not having the test was a 'deliberate' decision			
Yes	33 (61.1)	8 (88.9)	25 (55.6)
No	21 (38.9)	1 (11.1)	20 (44.4)
If not, the reason for this was:			
We could not come to a common decision as a couple	0 (0)	0 (0)	0 (0)
It just did not happen	7 (33.3)	0 (0)	7 (35.0)
I had not thought about it anymore	2 (9.5)	0 (0)	2 (10.0)
It was not possible to be present at the GP appointment together	6 (28.6)	0 (0)	6 (30.0)
Other, such as pregnancy	6 (28.6)	1 (100)	5 (25.0)
Barriers (survey 1)	*n* = 348 (10 missing)	*n* = 256 (3 missing)	*n* = 92 (7 missing)
I think that test-participation takes a lot of time**			
Totally disagree	69 (19.8)	53 (20.7)	16 (17.4)
Disagree	149 (42.8)	123 (48.0)	26 (28.3)
Agree nor disagree	99 (28.4)	65 (25.4)	34 (37.0)
Agree	28 (8.0)	15 (5.9)	13 (14.1)
Totally agree	3 (0.9%)	0 (0)	3 (3.3)
I think that test-participation takes a lot of effort**			
Totally disagree	71 (20.4)	57 (22.3)	14 (15.2)
Disagree	174 (50.0)	135 (52.7)	39 (42.4)
Agree nor disagree	83 (23.9)	55 (21.5)	28 (30.4)
Agree	17 (4.9)	8 (3.1)	9 (9.8)
Totally agree	3 (0.9)	1 (0.4)	2 (2.2)
I think having to make a GP appointment before test-participation is a barrier**			
Totally disagree	55 (15.8)	48 (34.4)	7 (7.6)
Disagree	126 (36.2)	98 (38.3)	28 (30.4)
Agree nor disagree	85 (24.4)	60 (23.4)	25 (27.2)
Agree	65 (18.7)	40 (15.6)	25 (27.2)
Totally agree	17 (4.9)	10 (3.9)	7 (7.6)
I think having to give a blood sample is a barrier			
Totally disagree	113 (32.5)	88 (34.4)	25 (27.2)
Disagree	129 (37.0)	93 (36.3)	36 (39.1)
Agree nor disagree	62 (17.8)	45 (17.6)	17 (18.5)
Agree	33 (9.5)	22 (8.6)	11 (12.0)
Totally agree	11 (3.2)	8 (3.1)	3 (3.3)
Views on couple-based test-provision (T2)	*n* = 221 (6 missing)	*n* = 177 (5 missing)	*n* = 44 (1 missing)
Preferences for disclosure of ECS results			
Couple results only	122 (53.7)	101 (57.1)	21 (47.7)
Individual results	32 (14.1)	27 (15.3)	5 (11.4)
No preference	52 (22.9)	40 (22.6)	12 (27.3)
Not sure	15 (6.6)	9 (5.1)	6 (13.6)

Test-offer acceptors and decliners were, where relevant, compared using *T*-tests for continuous variables and χ^2 tests for categorical variables. A *p* value of 0.05 was considered statistically significant

**p value < 0.01

Response cards

As Fig. 2 shows, 70 women who were eligible for study participation explained on the response card why they were not interested in taking part. The majority cited reasons against having couple-based ECS, rather than issues regarding declining study participation, such as a perception that ECS results in over-medicalization of pregnancy, health-related issues, no perceived need to be tested (yet) and anticipating anxiety about the impact of a positive test-result.

Table 3 The most important arguments in favour or having a couple-based ECS test

Arguments in favour of couple-based ECS	All $n = 355$ (3 missing)	Test-offer acceptors $n = 259$	Test-offer decliners $n = 96$ (3 missing)
I think that my partner and I as (future) parents have a responsibility to do this test	63 (17.7)	50 (19.3)	13 (13.5)
I want to spare our child a life with a severe hereditary disease	105 (29.6)	78 (30.1)	27 (28.1)
If the test shows that we together are not carriers, this would be a great relief	46 (13.0)	33 (12.7)	13 (13.5)
I want to prevent my partner and I having to take care of a child with a severe hereditary disease	38 (10.7)	33 (12.7)	5 (5.2)
I want to know in good time if our child is at risk so as not to be confronted by having to make a choice about a late abortion	38 (10.7)	28 (10.8)	10 (10.4)
I want to be able to prepare myself for having a child with a severe hereditary disease	36 (10.1)	23 (8.9)	13 (13.5)
I think that abortion should be prevented if possible	6 (1.7)	1 (0.4)	5 (5.2)
Other (e.g. to benefit science, previous experiences with genetic conditions in the family)	23 (6.5)	13 (5.0)	10 (10.4)

Table 4 The most important arguments against having a couple-based ECS test

Arguments against couple-based ECS	All $n = 355$ (3 missing)	Test-offer acceptors $n = 259$	Test-offer decliners $n = 96$ (3 missing)
I do not want to know if my partner and I are carriers	27 (7.6)	14 (5.4)	13 (13.5)
I am against selecting children by screening (such as in this test)	13 (3.7)	7 (2.7)	6 (6.3)
I am afraid that if we turn out to be carriers this will have consequences for my relationship	33 (9.3)	22 (8.5)	11 (11.5)
I am afraid that if we turn out to be carriers this will have consequences for my insurance policies	12 (3.4)	12 (4.6)	0 (0)
I am afraid that if we turn out to be carriers we will be regarded as people with a disease	7 (2.0)	7 (2.7)	0 (0)
I am afraid that if we turn out to be carriers this will be registered with the authorities	11 (2.8)	10 (3.9)	1 (1.0)
I am afraid that if we turn out to be carriers we will end up in a medical treadmill	46 (13.0)	35 (13.5)	11 (11.5)
The test-result will have no influence on my having children with my partner	94 (26.5)	65 (25.1)	29 (30.2)
A test would take away the romance of a pregnancy	19 (5.4)	12 (4.6)	7 (7.3)
By taking a test, becoming pregnant is no longer natural	6 (1.7)	5 (1.9)	1 (1.0)
Other contra arguments (e.g. I do not see any reason why not to accept the test-offer)	87 (24.5)	70 (27.0)	17 (17.7)

Discussion

This paper presents the initial interest from women 18–40 years and their partners of the first offer of cost-free couple-based ECS by trained (Dutch) GPs to couples from the general population and identifies their characteristics, views and barriers in terms of access and acceptance. Our results demonstrate that ~3% of all women approached and 15% of the estimated target population attended pre-test counselling with their GP, that is, were test-offer acceptors, of whom 90% proceeded with the test.

A few other studies have looked at uptake for single/few genes carrier testing in the Dutch general population. Henneman et al. [10] reported a 25% rate of test-offer acceptance of GP-provided cystic fibrosis (CF) carrier screening and an acceptance rate of 10% when couples attended educational sessions. Lakeman et al. reported a test-offer acceptance rate of 3% in their study on ancestry-based hemoglobinopathies and CF carrier testing by GPs in the Netherlands [11]. Although uptake rates in our study are similar to those from Henneman et al. [10], differences in study design prevent direct comparison of results. Furthermore, Gilmore et al. reported a 66% decline rate amongst eligible women in genomic carrier screening for reproductive purposes after being asked by telephone to participate [15]. This suggests that more eligible women decided to participate than in our study. However, differences in study design, such as the mode of invitation, eligibility criteria of having had carrier testing previously, and the option to receive medically actionable secondary findings, preclude direct comparison. Uptake figures are informative because they demonstrate whether actual uptake reflects couples' intentions and could highlight potential barriers in test accessibility. Although, as we stated above, our main purpose of offering ECS in a reproductive setting is to inform couples' reproductive decisions [3, 4] and maximising uptake rates is not an aim in itself.

In line with the existing literature [11, 16], test-offer acceptance in our study was lower than stated intentions. Our results demonstrate that practical barriers likely played a role for some test-offer decliners in our study, in particular having to make an appointment with the GP together, which was partly due to the design of our study. It is preferable that any future nationwide large-scale test-offer should still include pre-test counselling, because couples prefer to discuss this type of testing with a health professional, their GP in particular, and because this has

shown to be feasible and resulted in informed decisions [7]. Gilmore et al. also found that logistical barriers such as lack of time were reasons mentioned frequently for women to decline participation in genomic carrier screening [15]. In addition, Gilmore et al. suggest that healthy individuals might not feel as much need to overcome barriers to test-participation in comparison to affected populations (such as parents of children affected by a genetic condition), where test-participation is usually higher [15]. Opportunities to alleviate the impact of these barriers are available and include web consultations with GPs, consultations outside office hours, and targeted information materials or decision aids to increase efficiency of the pre-test counselling, as well as the possibility to consult genetics professionals when necessary.

Apart from practical barriers, there are alternative reasons why the uptake rates in our study may deviate from those expected in future nationwide large-scale implementation. Firstly, the study was conducted in the northern part of the Netherlands, an area where participation in reproductive/prenatal genetic testing is typically lower than other areas of the Netherlands [17]. In addition, design related issues other than attending GP counselling with both partners may have resulted in lower acceptance rates. Most notable examples are the study's consent procedure where 29% of women interested in participation did not return the consent forms and the test-offer was conditional upon survey participation. Secondly, our test-offer was a new and one-time offer, as ECS is not (yet) part of routine preconception care. Given that not all pregnancies are planned and most couples access health services prenatally rather than prior to conception, offering ECS during pregnancy as well may improve access to care. Finally, given that our test was free of charge, we could not study to what extent copayment might be a barrier to test-participation. Research indicates that whilst people are willing to pay for ECS [7, 18], the price people are willing to pay is often lower than the actual cost of the test itself; thus, financial barriers might also diminish access to care, particularly for couples with low income.

Acceptors and decliners

The majority of study participants had a positive intention towards test-participation, and this was high even among test-decliners (69%). Test-offer acceptors and decliners in our study were comparable in terms of sociodemographic characteristics, health status and experiences with chronic or hereditary conditions. In contrast to Gilmore et al. and to our expectations, we did not find that participants having experiences with any kind of, self-defined (presumed) hereditary conditions more frequently accepted testing [15]. In our study, couples who had experiences with (presumed) hereditary conditions, may have associated this less with their reproductive risk of having children with the specific severe AR conditions in this ECS test. The difference may also partly be due to the possibility to receive medically actionable secondary findings, as Kauffman et al., reporting on the same study, found that participants' main motivation was to obtain this general health information. Most experiences with (presumed) hereditary conditions are likely to be adult-onset disease [19].

Test-offer acceptors more often had a higher educational level than test-offer decliners, which was also higher than the Dutch general population [20]. Other studies on reproductive genetic counselling and testing show similar findings [15, 17, 21]. Acceptors also differed from decliners regarding their reproductive/relationship profile in this study: they less often already had children, had a higher relationship satisfaction, and were less likely to plan their pregnancy in the very near future. These differences may suggest selection bias, but unequal representation is only problematic when access to the ECS test and information leading to informed choice are not equally available to all couples planning a pregnancy. Further research on the determinants of test-offer acceptance including these aspects, couples' decision-making and couple dynamics, may help to identify relevant subgroups of patients to tailor information strategies and remove barriers to test-participation. The intention rate for ECS testing of participants in this study (87%) was more than double the intention rate in our previous survey study investigating couple-based ECS testing in a representative sample from the general population (34%) [7]. We therefore identified a subsection of this population who would like to make use of couple-based ECS when it was made available to them through the GP free of charge, but it is unlikely that the participants' characteristics are generalisable to all couples of reproductive age.

Reasons to accept and decline

We asked all participants to indicate their reasons for or against taking part in ECS, regardless of whether they chose to accept the test-offer. The reasons test-offer acceptors and test-offer decliners considered most important for or against ECS did not differ much. This was unexpected, but an explanation for these similarities might be the relatively homogenous study sample of which most started with the intention to accept this couple-based ECS test-offer. At the same time, we were also interested in understanding why not all eligible couples were interested in taking part. The explanations on the response cards reflected a variety of ethical, personal and practical arguments. Given that we only had access to a small group of those eligible women who decided not to take part in the study, more in depth

exploration of motivations for undertaking and not undertaking ECS in the general population could be helpful to gain a better understanding of the desirability of offering ECS and potential barriers preventing all eligible couples from accessing ECS. The most important reason for participants to accept (to spare a child a life with a severe genetic condition) or decline testing (the test would not alter their reproductive plans) are in line with the literature [3, 7, 22] and align with the current aim of offering ECS testing (enhancing couples' reproductive choice); participants' reasons to decline the test-offer were not based on misunderstanding about the purpose of the test, or fears of discrimination or stigmatisation. As second most important reason to accept couple-based ECS, 18% of participants considered this their responsibility as a future parent. The perceived feeling of responsibility as a future parent to undergo ECS, is also brought forward in the paper of Van der Hout et al., who discuss this should be included as an aim for a (preconception) ECS test-offer alongside reproductive choice [23].

If they have to indicate a single preference after being informed about the aims of ECS, the majority of study participants indicated a preference for a couple-based approach over disclosing individual results. These results underline the findings of our previous study amongst potential users about couples' views on couple-based ECS [6]. It should be noted that the response rate of survey 2 was relatively low in comparison to that of survey 1. Most of the drop-outs were test-offer decliners, who had a 45% response rate compared with 70% for test-offer acceptors. This means that the findings from survey 2 should be viewed with caution regarding the views of test-offer decliners. Regarding potential differences, participants with a higher educational level were more likely to respond to survey 2.

Given that it is the combined 'couple-result' which conveys information for reproductive decision-making, arguably, ECS couple-testing would be the new approach to offer carrier screening for AR conditions to the general population. This couple-based ECS test-offer could be complemented with individual carrier screening for X-linked conditions in the future. In this study, we focused on couple-based ECS as a free of charge test-offer in the Dutch public health system. We acknowledge that currently, ECS is not yet equally available and/or affordable to all couples planning a pregnancy. That is why, in certain contexts, arguments for couple-based testing or reporting individual carrier states may be different, such as for high frequency conditions in certain populations especially when cascade testing is reimbursed and population-based ECS is not (yet), when using whole exome sequencing in consanguineous populations and for ECS in a private setting.

Conclusion

This study demonstrated that at least 15% of previously uninformed couples planning a pregnancy albeit a selective part, were interested and accepted the offer of a free, GP-provided couple-based ECS test. Lowering practical barriers, as identified in this study, leading to a test-offer that is easily and equally available to all couples planning a pregnancy could facilitate access for those with the intention to participate. Understanding the determinants for test-uptake and the barriers for non-participation of interested couples are necessary for the development of health policy and can inform future implementation of ECS in different settings.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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ARTICLE

Feasibility of couple-based expanded carrier screening offered by general practitioners

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Abstract

Expanded carrier screening (ECS) aims to inform couples' reproductive choice, preferably before conception. As part of an implementation study in which trained general practitioners (GPs) offered a population-based ECS couple-test, we evaluated the feasibility of the test-offer and degree of participant informed choice (IC). Trained GPs from nine practices in the northern Netherlands invited 4295 female patients aged 18–40 to take part in couple-based ECS. Inclusion criteria were having a male partner, planning for children and not being pregnant. We evaluated the feasibility of the organizational aspects, GP competence and the content of the pre-test counselling. Participant satisfaction, evaluation of pre-test counselling and degree of IC were measured using a longitudinal survey. We explored GP experiences and their views on future implementation through semi-structured interviews. 130 consultations took place. All participating GPs were assessed by genetic professionals to be competent to conduct pre-test counselling. Most (63/108 (58%)) consultations took place within the planned 20 min (median 20, IQR 18–28). GPs considered couples' prior knowledge level an important determinant of consultation length. 91% of patients were (very) satisfied with the GP counselling. After pre-test counselling, 231/237(97%) participants had sufficient knowledge and 206/231 (88%) had a positive attitude and proceeded with testing. Our pilot demonstrates that offering couple-based ECS through trained and motivated GPs is feasible. Future large-scale implementation requires a well-informed general public and a discussion about appropriate reimbursement for GPs and health care coverage for couples. Providing (more) test information pre-appointment may help reduce average consultation time.

Introduction

Next generation sequencing enables simultaneous screening for carrier status of many genes associated with autosomal recessive (AR) conditions and some X-linked conditions, called expanded carrier screening (ECS) [1]. Where ECS is done prior to pregnancy, couples found to be at increased risk of having a child affected by such a condition can consider alternative reproductive options such as in vitro fertilization with pre-implantation genetic diagnosis (PGT-M) or prenatal testing (PND) (with possible termination of an affected pregnancy). However, a population-based ECS is not yet part of regular pre-conception care in public health care systems, but several private companies and some academic centers have started to develop and offer ECS tests for individuals or couples planning to conceive [2]. ECS aims to inform a couple about their risk of conceiving children with these genetic conditions. In this paper, describing the first population-based implementation pilot of an ECS test-offer by GPs, we decided to focus on severe AR conditions.

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The Genetics Department of the University Medical Centre Groningen (UMCG) in the Netherlands has developed and validated a couple-based ECS test for 50 AR conditions associated with approximately 70 genes [3]. These conditions were selected because they are early onset, serious diseases that result in severe physical or intellectual disabilities, severe pain, or premature death. These criteria were recommended by an international expert meeting at the UMCG in 2013, are supported by literature [4–6] and current guidelines which include criteria related to severity of illness [1]. In the Dutch population approximately 1 in 150 couples are carriers for the same condition in this test [7]. For severe AR conditions, the risk of being a carrier couple for an AR condition is about 1% [8]. The percentage of at risk couples that can be identified through ECS in the general population depends on the composition of the test-panel. For example, when 500 conditions (which are not all serious) are included, detection rate is higher [9] than in our (conservative) panel. Given that being a carrier of *any* AR condition is common but the chance of carrying a particular condition is very low, it is the positive combined 'couple-result' which conveys clinical utility for reproduction. We therefore argue that a responsible approach to implementing ECS in a public health care system is to offer it as a couple test and provide couple results only. This approach is supported by the recently published Belgian guidelines [10]. In the test results, we report only causal recessive variants, including known deleterious variants listed in databases (e.g., Human Gene Mutation Database, Biobase, Qiagen), and variants predicted to truncate or affect gene expression.

We have previously reported that both health care professionals (HCPs) and the target population support couple-based ECS in the general population with the GP as preferred provider [3, 11], and other studies have demonstrated that carrier testing for single-gene disorders such as cystic fibrosis (CF) and hemoglobinopathies in primary care is feasible and acceptable [12, 13]. More than 99% of the Dutch population are registered with a GP [14], and most GP care is included in the mandatory health insurance package all Dutch citizens carry. In the Dutch healthcare system, GPs play a central role as gatekeeper for secondary or tertiary care [15], which makes extending their current preconception care responsibilities to include a population-based ECS offer a logical approach. We therefore investigated whether test-provision by GPs could be a feasible approach for ECS and result in informed choice of couples who attended pre-test counselling. As most general HCPs lack the skills, confidence and knowledge to communicate clinical genetics issues [1, 16–18], we designed and provided training to GPs and subsequently performed an implementation study where these trained GPs offered the UMCG ECS test to couples from the general population. This current study is part of a larger study on the feasibility, uptake, and psychological impact of the test-offer.

Methods

Provision of ECS test-offer and care

Fig. 1 displays the ECS test-offer and provision of care. By sending out an invitation letter, participating GPs offered all potentially eligible women registered in their practices the opportunity to take part in the ECS testing program. Couples who were interested in the ECS test could make an appointment for pre-test counselling with the inviting GP. Afterwards they would decide whether or not to proceed with testing. The ECS-test was only accessible to couples who received pre-test counselling and couples were required to attend pre-test counselling together.

Trained GPs were asked to provide pre-test counselling about ECS in combination with general preconception care (GPC) advice (e.g., advice about folic acid supplementation, cessation of alcohol use or smoking). For this counselling, a double-consultation time was available (20 min). Referral to the Clinical Genetics department of the UMCG was available for couples identified to have prior increased risk, e.g., due to suspected family history of a genetic condition. Couples who proceeded with the ECS test could give a blood sample using request forms provided by the GP. The UMCG Genomics Laboratory performed the test. With a turn-around time of 8 weeks, GPs received a result for couples who provided blood samples and then communicated the results to them. A couple was considered a carrier couple if *both* couple members have a class IV or V variant in one of the recessive disease genes included in the test.

Carrier couples, but also non-carrier couples with remaining questions, could be referred to Clinical Genetics for post-test counselling. We also launched a publicly accessible website with general information about the 50 AR conditions, the ECS test, and related procedures (www.dragerschapstest.umcg.nl). The research team, including the genetic counsellor involved, could be contacted through the website. There were no patient expenditures associated with the study and test-participation. PGT-M and PND for serious conditions such as those included in this ECS-test are available to high risk couples. In the Netherlands, costs of PGT-M and prenatal testing are covered by statutory health insurance.

Study design

Figure 1 also depicts the study design. We used a mixed methods longitudinal design with four study time points (T0–T3), with couples and GPs as study participants. GPs were asked to evaluate each individual pre-test counselling at T1. At T3 they were invited to take part in semi-structured one-to-one interviews to explore their overall experience with test-provision. A genetics professional

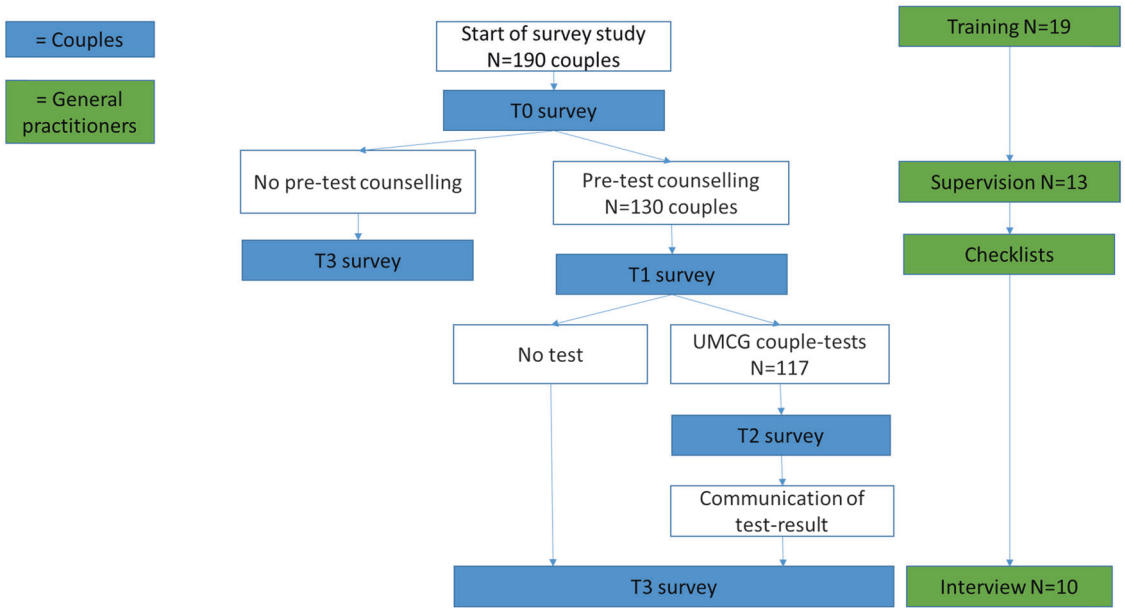

Fig. 1 Overview of ECS test-offer, provision of care and study design. GPs provided pre-test counselling to couples interested in ECS testing. Subsequently, couples could decide to proceed with testing. We used a mixed-methods longitudinal study in which assessments were made at four time points (T0-T3) through either questionnaires and/or semi-structured interviews, with couples and participating GPs as study participants

involved in the training supervised the first two pre-test counselling sessions of each GP. Couples were asked to fill out an online survey. Couples who attended pre-test counselling received three (T0, T1, T3) to four (T0, T1, T2, T3) questionnaires, depending on whether they proceeded with testing. The study protocol was approved by the UMCG Medical Research Ethics Committee (METc 2015/384).

Recruitment of GPs

Study participation was open to GPs in the catchment area of the UMCG. Staff from the Genetics Department and the Department of General Practice first approached potentially interested GPs personally and a recruitment message was added to a newsletter for GPs. GPs from 34 practices received the study information. Nineteen GPs from nine practices agreed to participate. One practice (no. 9) withdrew during the study because they were too busy to facilitate study participation. No further invitations were sent, but participants already included could still attend pre-test counselling, and proceed with testing.

Prior to the start of the study, all GPs were required to participate in a 2.5 h training session about pre-test counselling developed by the research team. This training session included background information about ECS and other general aspects of preconception care and an interactive session about reproductive genetic pre-test counselling. An information booklet was provided to complement the training that provided background information and a counselling guideline with important items to discuss. Two weeks after the training, all GPs filled out an online questionnaire testing their knowledge. GPs received individualized feedback on their incorrect answers prior to start of the counselling. Support from the clinical genetics professionals was available as needed throughout the study.

Recruitment of couples

Between January and December 2016, participating GPs selected and invited all potentially eligible women aged 18-40 registered in their practices to participate. Eligibility criteria were not being pregnant, having a (male) partner and planning to have children with this partner. Pregnant women were excluded, because the turnaround time of the test-result was a maximum of eight weeks at that time. Additionally, the extra skills probably needed for 'urgency counselling regarding ECS in pregnancy' requires different counselling skills of GPs which were not yet part of our preparatory training. The women were asked to invite their partners in the study. Couples who were interested in the ECS test could make an appointment for pre-test counselling with the GP after both partners had given written consent to participation. They could decide whether to proceed with testing after attending this appointment. Invitations were sent by mail and included a letter signed by the GP, a response card and an information leaflet. This test information leaflet consisted of the type of conditions included in the test, the chances of being a carrier couple and of having an affected child, reproductive options available for carrier couples, and test procedures. It also

included a link to the website for further information. Women who were eligible and interested in participating received more detailed study information.

Measures

Feasibility was evaluated in terms of the organizational aspects of this GP-provided ECS test-offer and the provision of care, with a focus on the pre-test counselling. We explored GP experiences and views on the ECS test to evaluate feasibility and improve future implementation. We adopted Marteau et al., (2001)'s definition of IC, who developed the Multidimensional Measure of Informed Choice (MMIC) to measure IC in relation to prenatal screening for Down's syndrome [19]. A choice was considered 'informed' if participants had sufficient knowledge and accepted the test offer (in case of a positive attitude) or declined the test-offer (in case of a negative attitude) [19]. Table 1 displays the topics and items investigated, which are based on relevant literature [1, 16, 17, 20–22]. The organizational aspects of the ECS test-offer were evaluated quantitatively as the time used for pre-test counselling and qualitatively through analysis focused on barriers and facilitators. Pre-test counselling was evaluated in terms of competence, content and patient-satisfaction. Competence was judged by the genetics professionals after supervision and evaluated by GPs during the interviews. Both couples and GPs evaluated the content. Couples also rated their satisfaction with pre-test counselling. Specific measures, instruments and details are described in Suppl. 1.

Quantitative data and analysis

Data on the duration of the consultation and items discussed during pre-test counselling were collected by a checklist for GPs that was filled out after each pre-test counselling (T1). The checklist included eleven items that GPs were required to discuss during pre-test counselling (see supplemental information for list). They were asked to indicate if they discussed the item (yes, somewhat, no), and if not, why not. Data on items discussed during pre-test counselling (i.e., their perceived importance and time spent on them), satisfaction with pre-test counselling and informed choice were collected by couples' questionnaires using the Roqua online tool for confidential clinical data collection [23]. The IC measure consisted of five knowledge items capturing essential information about ECS testing and two attitude items. We also asked couples to fill out these knowledge items after pre-test counselling as part of our provision of care to verify that couples who proceeded with testing were aware of the correct information. We would call them for additional discussion if they answered any of the five questions incorrectly. Couples could refrain from having the test after this additional information, which happened in one occasion. Data on consultation duration, items discussed during counselling, patient satisfaction, and informed choice were described using percentages, mean (SD) or median (IQR) where appropriate, using SPSS IBM version 23.

Qualitative data and analysis

Ten semi-structured one-to-one interviews were held with GPs. Two GPs who conducted counselling did not participate due to lack of time and the GP who withdrew from the study did also not participate. A topic guide was developed containing open-ended questions related to the feasibility aspects of this GP-provided test. Interviews were conducted by a trained researcher (JS), audio-recorded and transcribed verbatim. The average duration of the interviews was 41 minutes (range 20-60 min). Data analysis was conducted according to the framework approach of Ritchie and Spencer [24]. Framework analysis follows a process of familiarization, summarizing and coding, which results in matrices presenting the data per theme and case to allow more in depth analysis and comparison across interviewees. Atlas –ti (version.5.2.18 copyright 1993-2018 by ATLAS. ti Scientific Software Development GMbH Berlin) was used to facilitate analysis. Two researchers (JS, LvdH) independently coded the first three interviews, and differences in coding were discussed until consensus was reached. LvdH subsequently coded all interviews, including the first three, while JS coded parts of all interviews randomly and where LvdH had doubts. Final thematic framework matrices were subsequently discussed within the research group until consensus was reached. The preliminary conclusions were returned to the interviewees for member checking [25]. We received six forms, all confirming our conclusions.

Results

Inclusion and response

Table 2 shows that 19 GPs attended the training and 130 couples attended pre-test consultation of whom 117 proceeded with testing. Six trained GPs did not conduct pre-test counselling for reasons unrelated to the study. A genetic counsellor conducted one of the pre-test counselling sessions because one couple found out they were already pregnant after they had made their GP appointment. This couple was excluded from the analysis. Ten GPs participated in the interviews. 240/260 (92%) of the individual participants responded to the evaluation of the pre-test counselling. GPs returned 116/129 (90%) checklists.

Table 1 Overview of items used to measure feasibility and informed choice

Topics	Quantitative		Qualitative
	Instrument, time point (subject)	Items/measures	
A. Feasibility			
1. Organizational aspects of GP-provided ECS test offer	Checklist at T1 (GP)	Start and end time of pre-test counselling sessions	Barriers and facilitators of:
			• Duration of pre-test counseling
			• Both partners attending pre-test counselling
			• Communicating test-result
			• Referrals
2. Evaluation of care: competence and satisfaction	Survey at T1 (couples)	Patient satisfaction (overall + CGSI(1), see supplementary materials	• Self-judgment GPs during interviews
			• Professional judgment genetics professional after supervision
3. Evaluation of pre-test counselling: content	Checklist at T1 (GP)	Items discussed during counselling.	Barriers and facilitators of: Discussing the aspects included on the checklist
	Survey at T1 (couples)	Importance and length of items discussed during counselling.	
4.Views about implementation	Interview at T3 (GP)	N.A.	
B. Informed choice			
Informed choice	Survey at T0 and T1 (couples)	Informed choice measured using adapted MMIC(2), see supplementary materials	

Table 2 Overview of participating GPs, pre-test counselling and tests performed per practice

Participating practice ID (interview no.)	Type of practice	GPs attended training	No. GPs conducted counselling	No. women invited	No. pre-test counselling sessions	No. couple-tests performed
1 (6)	City	1	1	500	24	23
2 (4)	City	1	1	528	12	12
3 (3)	Village	2	1	276	4	3
4 (8&9)	Town	6	4	1045	23	20
5 (2&5)	Town	3	2	780	27	25
6 (1)	Town	1	1	407	18	14
7 (7)	Village	1	1	262	5	5
8 (10)	Town	2	1	330	5	4
9 (NA)	City	2	1	167	12	11
Total		19	13	4295	130	117

Evaluation of organizational aspects

58% of the pre-test counselling sessions lasted 20 minutes or less, with a median (IQR) of 20 minutes (18–28), indicating that the allocated time of 20 minutes was sufficient for the majority of sessions. Qualitative findings from GP interviews are illustrated with quotes presented in Table 3. Several GPs noted that couples were well informed beforehand, and that this helped them provide counselling within this time. GPs expected pre-test counselling sessions to last longer, if couples were less well-informed, or for couples with little educational background. Some GPs mentioned that over time they developed a routine for conducting the counselling, which reduced the time required for preparation and counselling itself. GPs were positive about attendance of both partners at counselling because the couple-test affects both partners equally and because they considered discussing GPC with both partners important. No carrier couples were identified. GPs did not experience any barriers in communicating the normal results or to referring any couples at normal risk to Clinical Genetics for additional pre- or post-test counselling. GPs or their healthcare assistants communicated the test

Table 3 GP quotes from interviews

Feasibility aspect	Quote (Interviewee)
Evaluation of care: organizational aspects of the GP-provided test-offer	"I particularly liked the training course, which was essential. It would be difficult to provide the ECS test without doing the training course first." Interviewee 10
	"At first, I thought 30 minutes should be planned for each consultation… But later I reduced it to 20 minutes, because it was feasible in 20 minutes… Also because at a certain moment you know what to discuss. Well, and people were often perfectly able to tell about the test. Most of them." Interviewee 5
Evaluation of care: content	"I discussed the items on the checklist with everyone, because I thought those were the essential points. So [amongst others] about what types of diseases were included. What the chances were, that it [the ECS test] does not offer any guarantee [of a healthy baby], and that there were no costs involved [for the couple]. That's it, in brief." Interviewee 5
	"What is really important is that they realize that it's the couple being tested and not the individuals, that the result says nothing about each individual only something about the couple together." Interviewee 3
Views on future implementation: Suitable provider	[reasons why the GP is suitable]…"well, of course it's close to the patient, most patients, even these healthy young people know their GP. And that means that, in a counselling like this, the threshold to ask questions is likely to be lower, or to return. They know where to find us when they need to." Interviewee 8
Views on future implementation	"Well.., I think that with the right provision of information, it could very well be part of this general preconception care advice." Interviewee 4
Views on future implementation	"The solidarity [healthcare insurance] system here [in the Netherlands] means that if you want to reach people, you should cover the costs." Interviewee 7

results by phone, email, or a combination, and some provided the couples with the lab results letter as well.

Evaluation of pre-test counseling

Based on their experiences in this study, GPs and genetics professionals considered training test-providers essential to ensuring quality of the test provision. After GPs were supervised twice, the genetic professionals considered all thirteen GPs competent to conduct counselling on their own. Counselling support from the clinical genetics professionals was requested twice for couples who were pregnant during the study and once for a couple who had misunderstood the purpose of the test. All GPs interviewed said they felt able to provide the pre-test counselling mainly because of the training, supervision and additionally provided materials. Some GPs specifically said they used the study checklist as a practical guidance, and all felt this covered the essential aspects of a pre-test counselling well. Participants evaluated the pre-test counselling with a mean satisfaction score of 4.7/5 (SD 0.5). The majority of participants (54.7%) gave the highest score of 5.0. 91% of participants were *satisfied* or *very satisfied* with GP pre-test counselling.

GPs and couples evaluated the content of the pre-test counselling as follows. GPs indicated that most aspects included on the checklist, apart from GPC and 'communication and turn-around time of the test-result', were at least discussed 'somewhat' in more than 90% of consultations. Some participants indicated that they thought too little time was spent on discussing the conditions included in the test (55 respondents (23%)) and the follow-up options for high-risk couples (38 respondents (16%)). Some GPs explained they did not discuss each condition in detail, instead discussing the conditions as categories as explained during the training. While GPs indicated that in 36 consultations (31%) they either "did somewhat" or "did not" discuss couples' reproductive values, more than 85% of participants indicated that the time spent on their and their partners' values was exactly right.

Most GPs were positive about combining ECS pre-test counselling with GPC. GPs indicated that, for example, due to lack of time, they "did not" discuss GPC in 31% or discussed it "only somewhat" in 14% of consultations. Some GPs explained during the interviews that the counselling might become too complex preventing couples from remembering both. GPC was considered important or very important to discuss by 159 participants (67%), of whom 19/159 (12%) thought too little time was spent on this. In contrast, 167 participants (70%) thought the right amount of time was spent discussing GPC.

Informed choice

After pre-test counselling by the GP, the number of participants with a sufficient level of knowledge had improved from 195/237 (83%) to 231/237 (97%) (Table 4). Five of six participants who displayed insufficient knowledge –and a positive attitude- after pre-test counselling, proceeded with testing. Another seven participants did not proceed

with testing, even though their attitude was positive and knowledge sufficient. Our provision of care pathway –as described in the methods section- prevented participants to make a final decision based on insufficient knowledge.

GP views on future implementation

In line with our previous research, after having offered ECS testing, GPs considered themselves as the most suitable providers for a population-based ECS couple-test. Advantages they mentioned were the low-threshold of GP care, their familiarity with their patients and their background. One GP mentioned that ECS-provision as standard care by all GPs might not be feasible because not all may be able to keep up with technological advances in genetics. Some GPs suggested that only motivated GPs willing to do so should be trained to provide ECS. These GPs could become specialized in (reproductive) genetics, just as some GPs are currently specialized in areas such as palliative or elderly care. Potential barriers that GPs mentioned were resistance to additional workload in already too busy practices or negative attitudes towards ECS. The eight-week turnaround time in our study, was considered acceptable by the GPs for non-pregnant couples. For future implementation, several GPs suggested the laboratory could also send the test result directly to couples. Negotiations with health insurance companies and policy makers were considered necessary to decide on a proper reimbursement fee for test-provision and whether to include ECS in the statutory health insurance package (Table 3).

Discussion

In this paper we have presented the design of our implementation study of a GP-provided ECS couple-test and our results on its feasibility and the degree of informed choice in couples attending pre-test counselling. Implementing ECS responsibly requires a novel approach [1], and our previous research suggested an important role for GPs [3, 11]. Our study demonstrates that implementing an ECS couple-test consisting of a limited set of severe conditions in the GP setting is a feasible approach that results in an informed decision in most cases.

Importantly, all participating GPs felt and were judged competent to conduct pre-test counselling after being given training, supported by genetic professionals on demand, and assisted by a counselling-checklist. Participating couples were very satisfied with GP pre-test counselling and the Dutch Society of General Practitioners recently stated their support for (more) studies investigating the implementation of ECS in primary care [26]. This approach therefore has the potential to address the concerns about the current lack of genetic literacy and counselling skills among non-genetics HCPs providing genetic tests [1, 18–20], and our results can inform options for responsible mainstreaming in genetics.

Most pre-test counselling sessions were conducted within the allotted time span of 20 minutes, with additional counselling sometimes needed to discuss GPC. In some situations, it might be more effective to separate the two types of counseling: directive (e.g., advice not to smoke or drink alcohol) and non-directive (facilitate reproductive decision-making in line with couples' values).

A study of CF carrier testing in primary care showed that GPs could conduct the (less complex) counselling in an average of 12 minutes [12]. According to participating GPs, pre-test counselling within the allocated time was facilitated because couples were already well-informed, perhaps due to the extensive study information, website and the questionnaires participants filled out.

Our results suggest that GPs could have extended their pre-test discussion of the reproductive options available for couples who are found to be both carriers of the same condition, which would also include an assessment of the value system held by that couple. Such discussions are standard practice for GPs, but our future training could be adjusted to focus more on these aspects in the preconception setting. Couples do not often request preconception consultations from GPs or other HCPs in the Netherlands [27], thus an added benefit of the ECS test-offer meant that GPs could discuss or follow-up on GPC advice with more couples –and both partners- than was routine. Future research could also explore whether prenatal carrier screening is feasible in this setting and what necessary adjustments should first be made in training and test-delivery. In the study we required both partners to attend pre-test counselling together and GPs agreed that it was preferable to include both partners jointly in the discussion of ECS as this affects both prospective parents. To lower practical barriers to attend counselling, in the future GPs could use web-consultations or face-to-face consultations at times desired (evenings/weekends), although this requires additional training and adjusted infrastructure.

Considerations regarding large-scale implementation of ECS in primary care

Our research concentrated on the offer of ECS within primary care. Eligible women were actively and individually approached by their GP by letter. Large scale implementation could also be a more passive and collective approach, e.g., via posters, leaflets and information about the test on GPs' websites. However, this requires the public to become more knowledgeable on this topic, which means more educational efforts would need to be aimed at this group. Moreover, couples could fill out an online decision-aid in advance to inform and prepare them and facilitate efficient

Table 4 informed choice before and after pre-test counselling by the GP

Before pre-test counselling (T0) ($n = 237$)	Positive attitude n (%)	Negative attitude n (%)	Neutral attitude n (%)	Total n (%)
Sufficient knowledge	173 (83)	0 (0)	22 (79)	195 (83.)
Insufficient knowledge	36 (17)	0 (0)	6 (21)	42 (18)
Total	209 (88)	0	28 (12)	237
After pre-test counselling (T1) ($n = 237$)	Positive attitude n (%)	Negative attitude n (%)	Neutral attitude n (%)	Total n (%)
Sufficient knowledge	213 (90)	0 (0)	18 (8)	231 (97)
Insufficient knowledge	5 (2)	0 (0)	1 (0)	6 (2.5)
Total	218 (92)	0 (0)	19 (8)	237

and effective pre-test counseling. No major barriers to large-scale implementation were mentioned by GPs in our study provided they can use 20 minutes for the counselling and that there are no financial barriers for them and their patients. Our results should inform discussions with relevant stakeholders to negotiate reimbursement for the consultation as well as the test.

GPs in our study suggested that ECS could be provided by 'specialized' GPs who focus on a specific aspect of GP care. Not all GPs may be interested in investing the time and effort necessary to obtain and maintain the required counselling skills, considering that the total number of counselling sessions per GP might be relatively low. The specialization approach would guarantee the necessary minimum number of pre-test counselling sessions per GP per year to maintain competence. GP specialization already exists in the Netherlands in areas such as elderly and palliative care. Other primary HCPs involved in preconception care—such as midwives, community pediatricians or nurse practitioners—might also be willing to offer ECS. In all scenarios, the role of Clinical Genetics in a population-based ECS couple-test could focus on education, support/auditing and post-test counselling for carrier couples.

A couple-based test for severe recessive conditions only

Salient features of our approach to ECS were the well-considered composition of the test-panel and the provision of couple-only results for this population-based offer through participating GPs. The composition of the panel facilitated a generic type of consent and the couple-based strategy resulted in a minimal need for post-test counselling by the GP or Clinical Genetics professionals. As time to discuss all conditions in detail is limited and some couples desire more information, extensive information about the conditions should be easily accessible for couples, as was the case on our website. Not disclosing individual results remains a matter of debate given the perceived utility for cascade screening [22], as well as the participants' personal preferences [28].

We argue that previous cascade screening approaches disclosing individual results, e.g., for relatively frequent conditions, are no longer helpful when switching to population-based ECS, especially given that everyone is likely to be a carrier of one or more recessive conditions. If ECS was well known to the public and to HCPs and there were no (financial) barriers to participating, the new approach would be to offer ECS testing to all couples wishing to reproduce. Whilst some have expressed concern that individual results are important if couples split up, our response to this is that a new couple test, i.e., a re-analysis of the couple's or one of the couple's stored data, could be done in those cases. In the Dutch health care system these data (and the DNA) are stored for these and other purposes. A referral to Clinical Genetics would only be necessary for couples with prior/suspected increased risk due to family and/or personal health history and/or ethnic background. The approach suggested in this study applies for ECS aimed at AR diseases only. Our couple-based approach for severe AR conditions could (and perhaps should) be complemented with individual screening for more prevalent X-linked conditions like Fragile-X and Duchenne muscular dystrophy. It is important to evaluate in future studies what would be necessary aditionally to facilitate counselling and test-provision and which adjustment would be needed for responsible implementation in the Dutch public health system. In this paper we focused on free couple-based ECS in the Dutch public health system. We anticipate that for non-reimbursed ECS and ECS in a private setting, arguments for couple-based ECS or reporting of individual carrier results could well be different. A discussion of these arguments is beyond the scope of this paper.

Conclusions and recommendations

This GP-provided couple-based ECS test for a limited number of severe AR conditions in the setting of pre-conception care, presents a timely and responsible option to inform couples planning a pregnancy about their chances of having a child affected by a severe genetic condition. This approach was not only feasible in our setting, but also led to an informed choice for most participants. Future national

implementation could involve other dedicated GPs, or other primary HCPs willing to be trained to provide the test, given that support as well as practical tools from a clinical genetics service are available. Furthermore, some factors identified in our study should be considered, such as raising public awareness to facilitate a well-informed population and resolution of reimbursement issues. Our approach, that was feasible in the (northern) Netherlands, might be transferable to other (European) public health systems with easily accessible primary health providers who are willing to be trained and have the necessary resources to offer ECS.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Ethics Roundtable for submission to the Journal of Medical Ethics

Background

Genomic technology now allows relatively inexpensive and efficient simultaneous screening for carrier status of multiple genes associated with autosomal recessive (AR) and some X-linked conditions; this is called expanded carrier screening (ECS) (1). ECS represents a big shift from previous practice; in the past such testing was limited to those with a family history of a particular condition, or populations where the condition was particularly prevalent, but now any couple planning a pregnancy can be informed about their risk of having children with AR/ X-linked conditions. Whilst most recessive conditions are rare, collectively they cause a significant proportion of childhood morbidity and mortality (2).

If both prospective parents are carriers of the same condition, each time they have a child there is a 1 in 4 chance that the child will be affected. If couples are informed about their 'couple-carrier' status prior to conception, those who are identified as carrier-couples can consider alternative reproductive options. These options include in vitro fertilization with pre-implantation genetic diagnosis, prenatal testing (with possible termination of an affected pregnancy), using non-carrier donor gametes, adoption or refraining from having children.

We are all carriers of some AR conditions, this (usually) has no impact on our health and the likelihood of carrying any particular condition is low. When many (rare) conditions are combined in one test, however, this brings the chance of the same carrier result in *both* members of a couple (in the general population) to around 1%. This is an equivalent risk level at which other population screening programmes are offered, such as the non-invasive prenatal screening test for chromosomal abnormalities (NIPT) (3). Currently, ECS is not yet routinely offered in public health care systems around the world, but ECS tests are available through some academic centers and private providers e.g. in fertility clinics(4).

What is the ethical issue(s)?

Whilst technology allows ECS to be offered to any couple planning a pregnancy, this does not mean that it *should* be available, or be funded by a public health care system. Furthermore,

several concerns have been raised. For example, whether a test-offer to all couples has the potential to cause psychological distress, whether couples might feel they should undergo ECS testing when it is offered to them, and how a routine test-offer might affect the lives of people with a disability (1,5,6).

There has also been debate about whether such tests should be offered using a couple-based approach or on an individual basis (1,7). Being a carrier of *any* AR condition is common but the chance of carrying a particular condition is very low, it is the positive combined 'couple-result' which is informative for reproductive decisions. Not reporting individual results remains a matter of debate and represents a shift from how carrier testing was done in the past. Some may argue that individual carrier states are useful when couples split up. In that case, however, the best solution arguably would be to offer the new couple another couple-test. The question posed by ECS is no longer 'is this partner or relative also a carrier of condition x?' but rather 'is this particular couple a carrier-couple for any of the AR disease screened for?'

A couple-based approach might raise different ethical and practical issues for couples conceiving unaided, compared to couples using assisted reproductive technology and in particular those conceiving with donor gametes. The notion of a couple is different in different settings, as when using donor gametes, there may be both a genetic couple and a social couple.

This round table discussion explores the views of professionals and patients, in different settings as to whether a couple-based approach to ECS is ethically justified.

The couple's perspective

Olivia and John are a couple in their late forties with a 5-year old healthy boy and they would like to start another round of fertility treatment. They previously used an egg donor and surrogate host, and are looking for a similar arrangement to have a second child. When they came to the fertility clinic this time around, they were offered couple-based expanded carrier screening for 70 severe recessive conditions. They have come a long way on their fertility journey and would like to maximise the chances of their child having the best possible start in life.

They carefully considered the challenges of caring for a severely disabled child, both for the parents and the child, and felt they wanted to maximise their chances of having a healthy child. When imagining what life would be like as a parent of a child with a serious health problem, John is anxious about not being able to cope with that. Olivia remembers the experience of her friends, who had a child with a genetic condition and were devastated by the unexpected diagnosis and their child's untimely death.

It is important to them that this test only includes serious conditions. That is to say, if they were identified as having an increased chance of having a child affected by a serious condition, this would definitely mean they would choose to change their donor. For conditions that are less serious, they would need more information about what life would be like for both parents and child, to know how this would affect their decisions. They decide to go ahead and have the ECS couple-test once the clinic has offered them a donor-match.

Although having this ECS-test may prolong the process of their fertility treatment, testing prior to conception means more options are available than finding out during or after pregnancy. As a couple using fertility treatment, the options available to them in case of an abnormal couple-test result are less disruptive compared to couples conceiving naturally. If the ECS test shows that the donor and John are a carrier "couple", a relatively easy fix is to switch their donor for one that is not a carrier-match with John. Fortunately, the donor agrees to undergo the test and when the test-result comes back normal, an embryo is placed in the surrogate host.

John will not find out whether he, as an individual, is a carrier of a condition included in the test, because it only reports whether or not the combination of his genetics and that of the

donor would result in an increased chance of having a child with a serious genetic disease. On the one hand, John finds this a bit disappointing, because one of his motivations for undergoing genetic testing is curiosity about his own genetic background. He hopes that a genetic test, such as ECS, might reveal something about any potential risks to his health or that of his children that he was not previously aware of. Olivia and John found it quite difficult to get their heads around the idea that even if the test-result shows that John is a carrier, this would not have any implications for his health, or the health of their children. John suspects that if he was told he was a carrier of a condition included in the test, this would nevertheless cause him to worry about it. After giving it some thought, John and Olivia are content with the approach of not reporting John's individual carrier states. After all, gaining knowledge about their own health is not the purpose of the test. What they aim to find out is whether they have an increased chance of conceiving a child that might not be healthy.

Both John and Olivia hope that in the future, when these tests are more common, the costs will come down. Given that the costs for ECS were added to the costs for their fertility treatment, they suspect that for some couples who would like to make use of these tests, this is currently not affordable. John and Olivia both think that ideally, ECS should be offered to any couple planning a pregnancy, as all might benefit from this information to make more informed decisions regarding the health of their future children.

Roundtable perspective: genetic counsellor

The first time I encountered the couple-based approach to expanded carrier screening (ECS), as genetic counsellor, I was a bit sceptical. The concept challenges our traditional practice of genetic counselling, which is focused on individuals/couples with a genetic diagnosis in their family context. Nevertheless, the changes in technological possibilities and recent experiences in clinic have made me reconsider my initial scepticism. I would now argue that couple-based ECS is the most appropriate approach for ECS for autosomal recessive (AR) conditions when offered to couples planning a pregnancy.

As a genetic counsellor I am trained to think about the patient in their family context. Most of our genetic information is shared with our family members. If one member of a family is diagnosed with a genetic predisposition, the chances for a relative to be equally affected by this genetic predisposition can be high. Thus, in clinical genetics practice, informing relatives about a genetic predisposition that occurs in their family is important as this information is relevant to that person's health.

Our (traditional) approach to carrier testing for AR conditions is different from other types of genetic testing/counselling. If someone is a carrier for an AR condition, the chances that their siblings are carriers for the same condition are 2/3. This, however, does not necessarily mean that we would offer genetic testing to all those family members. Whether we actually offer genetic testing to relatives also depends on the carrier frequency in the population. For example, for some AR conditions, such as cystic fibrosis, the carrier frequency in the general population in the UK is relatively high (1 in 25). If the carrier frequency in a population is low, we would not offer carrier testing to relatives or the partner of a carrier routinely.

Previously, in our genetic service, we would only see couples who have a family history of an AR condition or couples from specific ethnic backgrounds. Especially in those high-risk populations, it made sense to offer cascade screening for family members, as the chances of the partners being a carrier for the same condition are relatively high. A couple of years ago, there was not much demand from other (low risk) couples to be screened for AR conditions prior to starting a family. Moreover, even if they asked to be screened, there was nothing that we could realistically offer them on the National Health Service. That is why I felt that couple-

testing was unnecessary. Why would we not just give people their individual carrier states if that is what they prefer?

In recent years/months, however, more couples have asked for genetic tests prior to starting a family. A recent case in our department involved a same sex female couple who had purchased sperm from the United States. The donor sperm had been tested using an expanded carrier test looking for over 200 conditions. The testing showed that most of the donors were carriers of at least something, although some were mild conditions. The couple reported that they selected the donor sperm, based on the looks of the donor and then excluded donors on basis of carrier status. Eventually selecting a donor who was a carrier of Duarte Galactosemia, which most donors appeared to be. Testing for Galactosemia has now been offered to the couple, but has raised some anxiety about the condition. What has not been asked is whether the couple would have selected a different donor, had the ECS been applied to the donor and couple and only a couple result provided.

So why did I change my mind? In my experience, it is quite difficult for people to understand what it means to be a carrier and some people were devastated to hear that they or their gamete donor was a carrier of an AR condition. This psychological distress is unnecessary, as being a carrier does not have any implications for the individual's health. Moreover, if one partner were a carrier for such a rare condition, we would not offer carrier testing for the other partner, given that the chances of them also being a carrier are too low. Only the couple test-result is important for their reproductive decisions. As genetic counsellors, we can support couples in making choices regarding their reproductive plans that are appropriate for them. In my opinion, this couple-based approach would be justified and appropriate in all cases of ECS for AR conditions, irrespective of its carrier frequency in the population.

Laboratory geneticist's perspective

Technological advances in genetics also raise ethical and practical issues regarding technical aspects of analyzing and identifying couples at risk in the laboratory. In this commentary, I will discuss the most important issues ECS raises from the perspective of a laboratory/molecular geneticist. I will then argue why a couple-based approach to ECS may solve these issues.

The challenge of classifying novel variants

Next-generation sequencing (NGS) has provided the technical means to not only screen the full disease related gene but also analyze multiple genes simultaneously. As a consequence, a growing number of diseases is included in ECS tests. With this increase in genes analyzed, the chances of finding one or more potentially harmful variants increases accordingly. Not only established pathogenic variants are found in higher numbers. Novel variants that may be potentially harmful, but lack evidence to substantiate their risk, are also increasingly observed.

Classifying these novel variants is a challenge. Without being substantiated by literature or databases, the geneticist is dependent on *in silico* software tools to predict a possible biological effect, whereas the performance of *in silico* tools are considered moderate. The impact of a missense variant[1][DT1] is predicted considering criteria such as the evolutionary amino acid or nucleotide conservation, the location and context within the protein sequence, and the biological consequence of the amino acid substitution. Since most of these computer-based algorithms are only 65–80% accurate even when examining *known* disease variants, such an approach is not ideal (ACMG standards: Richards et al., Genetics in Medicine 2015; Tian et al., Sci Rep 2019). Functional testing -testing in a living organism, such as a specific cell line or an animal model- would give better proof of the biological effect. However, this is time consuming and currently only done in specific cases in specific laboratories.

[1] *a change in one of the letters of the DNA code which changes the amino-acid composition of the protein*

Harmful variants in genes that may have health implications for the individual carrier

A second issue relevant when introducing ECS is the possibility to detect variants in genes which may (also) have health implications for the individual carrier. The ACMG provided a list

of 59 actionable genes for which disclosure is recommended if a potentially pathogenic variant is found. There has been a lot of debate if one should opportunistically screen for potentially harmful variants in those genes when the result is unrelated to the aim of the performed test. Since most of the genes in this ACMG list behave dominantly, the chance of encountering them in an ECS test seems minimal. However, there are examples in which genes are associated with a dominant (late onset) actionable condition as well as a recessive (early onset) disease. Having a (likely) pathogenic variant in one allele of the *BRCA1* gene, for instance, increases the risk to develop breast and ovarian cancer in an individual carrier. Loss of function of both alleles causes Fanconi anemia [MIM 617883] with clinical features including congenital abnormalities, abnormal production of blood cells and malignancies, justifying its presence in an ECS test. More extended ECS tests do include genes like *BRCA1*.

Harmful variants in genes that are associated with mild and severe disease
A third issue is related to the variable expressivity of conditions. Some of the genes are associated with severe as well as mild phenotypes. Potentially pathogenic variants in those genes should be reported since the phenotype expression often cannot be predicted from the observed variant. However, the clinical consequences for future offspring are unclear.

To summarize the above, the major burden in NGS testing lies in the fact that a lot of issues surrounding (novel) variant classification are uncertain, unclear or based on little evidence. Most *in silico* tools are low in specificity and although literature and database information on individual variants is growing, a lot is currently unknown. For other pathogenic variants a relation with the aim of the test appears doubtful. To facilitate decision-making multidisciplinary meetings are held in most laboratories. Since being a carrier may have serious consequences in preconception and prenatal care, arguments used in assigning a class 4 or 5 label to any variant are carefully weighted. Classification procedures like that, however, are time consuming and increase the workload on technical and medical staff considerably. If we were able to lower the overall number of variants that have to be classified, without losing out on the aim of the test (i.e. assessing the risk of a couple on having a child with one of the recessive diseases tested for) a lot of the workload would be reduced.

A couple-based approach

Using a couple-based approach, only variants in corresponding genes are subject of further analysis. This means that if a harmful variant is found in one partner, only the corresponding gene in the partner needs to be scrutinized, all other variants will not be seen. The majority of secondary findings and variants of yet unknown significance do not require further analysis if a couple-based approach was adopted. As a consequence, a couple-based approach reduces the need for time consuming multidisciplinary team (MDT) meetings. And the final result the couple receives would be based on a lot less uncertainty.

In our laboratory practice no individual scores are analyzed. Individual carriers will not be detected and as a consequence cascade screening in family members will not be pursued. One can argue that by not giving individual results, family members who potentially are also carriers, are denied information that could have led to changes in their reproductive decisions (if their partners also turn out to be carriers). For instance, if SMA testing, for which the population frequency is rather high, is done outside an ECS setting, the geneticist will provide individuals with their carrier status. This means that there is a difference in handling within the laboratory, between couple-based ECS and traditional genetic testing, which may feel as unfair. If a couple-based ECS is available to all couples planning a pregnancy, such cascade screening is not required anymore.

Roundtable discussion: researcher's perspective

This roundtable perspective is based on the findings of my PhD research into the ethical, psychosocial and practical issues of a couple-based approach to Expanded Carrier Screening (ECS) over the past five years (2016-2020) (see supplementary material for a summary of the methods I used).

One study of a hypothetical scenario, where members of the general public were asked whether they would prefer couple results or individual carrier states, demonstrated a preference for the latter (8). That said, such hypothetical research may not reflect an actual offer and is very dependent on how the questions are pitched to participants. We demonstrated that couples of reproductive age did not object to an offer of receiving couple results only (9,10). I argue that couple results are the results that have clinical utility for reproductive decisions whilst individual carrier states do not. Below I outline some of the pros and cons of using couple results for ECS in the general population.

My research demonstrated that health professionals as well as patients referred for fertility treatment often held misconceptions about what being a carrier of an AR condition meant for their own health: i.e. they thought being a carrier would mean they would have some features of the condition. In turn this could mean they would make misinformed decisions about their reproductive future, worry about developing a genetic condition or pass on incorrect information to relatives regarding their reproductive risk. Kauffman et al., (2017) showed that when individual carrier states (and secondary findings) are reported, women decide to have ECS to influence decisions about their own healthcare, not for reproductive risk (11). Interestingly, participants in my study did not have problems interpreting the couple result as having implications for their reproductive decisions. Therefore limiting the offer of the test result to one that has clinical utility- rather than one that might be misunderstood- seems preferable. It is possible that couple results may lead individuals to feel that information is being withheld from them, but if the pre-test counselling carefully explains that individual carrier states are not important to their own health, this potential loss of trust in the healthcare provider can be avoided.

Various arguments have been cited in the literature, and in my empirical research as to why individuals should be told their individual carrier states: (a) Some HCPs thought that if

'someone somewhere knows' about carrier state, then it would be unethical not to report them to individuals. However, it is feasible to set up a laboratory system that reports on couple results, without individual carrier results being "known"- it could be a computer algorithm for example and would not enter a person's data record. b) A common reason given for wanting individual carrier states is that they are perceived as relevant for future reproductive decisions (7): If I know I'm a carrier then I might ask my future partner/donor to undergo carrier testing for that condition. Historically, this argument was correct but with the advent of ECS, couple testing could simply be repeated each time a couple changed and this would be far more efficient. In the meantime, these couples are not burdened with information that lacks meaning for current reproductive decisions and could cause misunderstandings. Interview participants often mentioned that they were interested in knowing their carrier states, they did not consider this a reason as to why carrier states should be reported in a health care setting.

Moreover, as technology develops, and information regarding the interpretation of genetic variants increases, a new, updated ECS test may be more accurate than using 'old' individual carrier states. For ECS tests containing tens or hundreds of conditions, it is very likely that the first partner is a carrier for one or more conditions (12). This means that the second partner would need to be tested anyway so reporting individual carrier states would not be financially advantageous. Considerations regarding the reduction in time and costs required for counselling and processes will be important as preconception ECS is scaled up within populations.

I found that, not surprisingly, there were couples using a donor and those using their own gametes who identified different issues regarding couple results. In this situation, the term 'couple' takes on a different meaning since the genetic and social couple are not the same where a donor is used. This raises interesting questions about consent and feedback, and what a donor recipient might find out about their donor that is more than the standard description services usually offer. In addition, as the actual testing is done on the donor and the other gamete provider, but the test result is also relevant for the partner in a couple who is not the gamete provider, questions may arise around the extent to which this partner should be involved in providing consent to this type of testing.

Genetics professionals raised concerns that reporting couple results only would prevent cascade screening for family members of an individual identified as a carrier. However, this argument precedes the advent of ECS tests, which can pick up carrier couples far more effectively than any cascade screening programme for carrier status can. Indeed, research indicates that cascade screening as a means of population screening for any AR conditions in the general population is less effective (13); not all carriers inform their relatives and not all relatives subsequently access carrier testing themselves (14,15).

Although couple tests might replace individual carrier reporting in the future, we are some way off this being a reality for all, and currently couple tests are only available through such initiatives as the UMCG panel as studied here. Some people argue that in the interim, if a condition has a high carrier frequency in the general population, for example for cystic fibrosis (CF) in northern Europeans, then individual carrier states should be reported so that carrier couples can be identified via this route. Although cascade screening of carrier findings is given as justification for finding more couples for a condition where carrier frequency is common, my view is that with the advent of ECS this will soon be outdated.

I therefore consider that reporting couple results is justified when ECS is offered both to couples from the general population and for those using donated gametes. Taking all these arguments into consideration, I conclude that offering couple testing to any couple planning a pregnancy would be preferable over cascade screening of family members when someone is identified as a carrier for a (rare) AR condition.

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Appendix B Recruitment materials

Klinische Genetica

Dragerschapstest - voor paren met een kinderwens

Al vóór de zwangerschap laten onderzoeken wat de kans is op het krijgen van een kind met een ernstige erfelijke ziekte

Een dragerschapstest voor paren met een kinderwens

Iedereen is drager van één of meerdere erfelijke ziekten. Vaak weten we niet dat we drager zijn omdat we de ziekte zelf niet hebben. De afdeling Genetica van het Universitair Medisch Centrum Groningen (UMCG) heeft een dragerschapstest ontwikkeld voor paren met een kinderwens. Het lezen van deze folder kan u helpen om wel of niet voor de dragerschapstest te kiezen. De dragerschapstest geeft aan of u en uw partner drager zijn van dezelfde ernstige erfelijke ziekte. Als dat het geval is, heeft u een sterk verhoogde kans op het krijgen van een kind met die ziekte.

De dragerschapstest is bedoeld voor alle paren met een kinderwens. Er hoeft niet al een erfelijke ziekte bij u of in uw familie(s) voor te komen. De test is alleen bestemd voor paren (niet individueel) en vindt plaats nog voordat u zwanger bent.

Waarop wordt getest?

De dragerschapstest onderzoekt of u en uw partner drager zijn van een van de ongeveer vijftig erfelijke ziekten uit deze test. Bij deze ziekten gelden één of meer van de volgende punten:

- De ziekte begint op jonge leeftijd.
- Het kind lijdt pijn.
- Het kind is lichamelijk zwaar gehandicapt.
- Het kind is verstandelijk zwaar gehandicapt.
- Het kind komt soms op jonge leeftijd te overlijden.

Voorbeelden van ziekten uit de dragerschapstest zijn:

- Epidermolysis Bullosa; een ernstige huidziekte.
- Ataxia telangiectasia; een ernstige aandoening van het zenuwstelsel en afweersysteem.

Geen van deze ziekten is te genezen. Een overzicht van de ziekten waarop getest wordt, kunt u vinden op: www.dragerschapstest.umcg.nl

Hoe groot is de kans op dragerschap?

De kans dat u en uw partner beide drager zijn van dezelfde erfelijke ziekte uit deze test is ongeveer 1 op 150. Als één van deze ziekten in de familie voorkomt of als u familie van elkaar bent, is deze kans groter. Wanneer u beide drager bent van dezelfde erfelijke ziekte, is er elke zwangerschap een kans van 1 op 4 dat u een kindje krijgt met deze ziekte. Mocht uit de test blijken dat u beide geen drager bent van dezelfde ziekte, dan is er nog steeds een kans dat u een kindje krijgt met een van deze ziekten. Deze kans is dan echter veel kleiner geworden.

Hoe wordt de test afgenomen?

Als u interesse in de test heeft, kunt u een gesprek aanvragen bij uw huisarts. De test wordt gedaan door een bloedafname bij zowel de man als de vrouw. Wanneer u na het gesprek met de huisarts besluit de test te doen, zal de huisarts op de praktijk bloed laten afnemen of u doorverwijzen naar het huisartsenlab voor bloedafname. De uitslag krijgt u te horen van uw huisarts. Deze ontvangt de uitslag na maximaal acht weken.

Drager, en dan?

Als blijkt dat u allebei drager bent van dezelfde ernstige erfelijke ziekte, dan zijn er verschillende vervolgkeuzes:

- U kunt ervoor kiezen de kans te accepteren, zwanger te worden en verder geen stappen te ondernemen.

- U kunt proberen om op natuurlijke wijze zwanger te worden. In de zwangerschap kunt u vervolgens een prenatale test doen, bijvoorbeeld een vlokkentest of vruchtwaterpunctie. Als uit deze test blijkt dat het kind de ernstige ziekte heeft geërfd, dan kunt u ervoor kiezen de zwangerschap af te breken of u kunt zich extra voorbereiden op een kindje met deze ziekte.
- U kunt er over nadenken om zwanger te worden via de IVF/ICSI-procedure en dan embryoselectie te laten doen. Hierbij worden embryo's onderzocht op de ziekte. Alleen bevruchte embryo's zonder ziekte worden in de baarmoeder teruggeplaatst.
- U kunt nadenken over mogelijkheden zoals draagmoederschap, bevruchting met donorzaad of donoreicel of adoptie.
- U kunt ook besluiten om helemaal af te zien van het samen krijgen van kinderen.

Kosten

De kosten voor de dragerschapstest voor paren worden in het kader van het wetenschappelijk onderzoek vergoed.

Deelnemen aan de test of heeft u vragen?

Wilt u de dragerschapstest laten doen? Of heeft u nog vragen? Maak dan een afspraak met uw huisarts. Ook kunt u kijken op: www.dragerschapstest.umcg.nl

Genetic testing before pregnancy: Do prospective parents have an increased chance of a child with a severe genetic condition

First page

Background

Some conditions arise as the result of a child inheriting a particular gene fault from both parents. The parents are known as **carriers** of that condition, because they also have a working copy of the gene which compensates for the faulty one and so they may never know they have this faulty copy. It turns out that we are **all** carriers of one or more genetic conditions. Being a carrier of a condition has no medical consequences for that person and they may not have any family history of the condition in question.

In the past, we did not routinely test for such conditions because each is individually rare and so the chances that both members of a couple are a carrier for the same condition is very low (for most such conditions the chance is less than 1 in 7,500).

Because genetic technology has moved on a lot in recent years it is now possible to test for many different conditions in one test. This means that although the chance for each individual condition remains low, when you group many together in one test, the chance of finding couples that both carry the same condition increases.

This information leaflet aims to help you decide whether or not to have a test that looks for 50 different severe genetic conditions in one go.

Who is this test for?

The test is for any couples or those couples or individuals using gamete donors who want to have a child. The test cannot be done on an individual basis. This is because it is only if you as a couple, or those using donor gametes, are both carriers of the same condition that you will have a chance of an affected baby. For those who are using a donor, the test will examine the donor and the genetic parent . The test is performed before pregnancy.

The test result will indicate whether or not *both prospective parents or the prospective parent and egg or sperm donor* carry the same severe genetic

condition. If this is the case, then the chance of having a child with that disease is increased substantially. We will then discuss with you what your options are.

What do we test for?

The test examines whether both *prospective parents or the prospective parent and egg or sperm donor* are a carrier of one or more conditions in the test. This test includes 50 severe inherited conditions.

For this test we have selected very severe conditions with an early onset that would result in one or more of the following features:

- Severe pain
- Severe physical disability
- Severe learning difficulties
- High chance of death in childhood.

We have deliberately not included any treatable conditions in this panel.

What is the chance of being a carrier couple and what does this mean?

The chance of being a carrier couple for one of the diseases is approximately 1 in 150. If a family member has already been diagnosed with one of these conditions, or if *both prospective biological parents* are related to each other (eg. cousins), the chance of being a carrier couple could be higher.

If *both prospective parents or the prospective parent and egg or sperm donor* are carriers for the same condition, there is a 1 in 4, 25%, chance of having a child with the condition in *each* pregnancy.

If *the prospective parents or the prospective parent and egg or sperm donor* are not a carrier couple for one of the diseases in the test, there is still a very remote chance you will have a child with one of these conditions, because the test cannot 100% guarantee to detect all carrier states. However, the chance is then very low indeed.

How do I take the test?

If you decide you would like to take this test, once you have had a chance to discuss it with a healthcare professional, you need to give a small sample of blood, and the result will be available within eight weeks.

We are a carrier couple, what next?

If you are a carrier couple for one of the severe inherited conditions, there are several options available:

- You could conceive as planned and accept the increased risk of having a child with a severe inherited condition.
- You could conceive as planned and perform a prenatal test to see whether or not the pregnancy is affected. If it is, then termination of pregnancy might be considered.
- You could consider preimplantation genetic diagnosis (PGD) which involves In-vitro fertilisation (IVF) and then embryo selection, where only those embryos who are not affected are transferred into the womb.
- You could decide to choose another donor

If you have further questions do not hesitate to contact us.

ONDERZOEK NAAR DRAGERSCHAPSTEST VOOR PAREN MET KINDERWENS

UITNODIGING VOOR DEELNAME

Geachte mevrouw,

Graag wil ik u de mogelijkheid geven om deel te nemen aan een medisch-wetenschappelijk onderzoek van het Universitair Medisch Centrum Groningen (UMCG).

Het onderzoek gaat over het aanbieden van een 'dragerschapstest' aan paren die over niet al te lange tijd een kind willen krijgen, dus *voorafgaand* aan een zwangerschap. De uitslag van deze (bloed-)test laat zien of er een verhoogde kans is op een kind met een zeer ernstige erfelijke ziekte. In de test zitten 50 ziekten. Als de uitslag aangeeft dat er een verhoogde kans is, zijn er manieren om de geboorte van een kind met die ziekte te voorkomen, als u dat wilt. De test is (juist ook) bedoeld voor paren bij wie geen erfelijke ziekten in de familie voorkomen.

De test wordt aangeboden via een geselecteerd aantal huisartsen in de Noordelijke regio. Onze huisartspraktijk doet mee aan dit onderzoek. *Alle vrouwen tussen de 18 en 40 jaar oud worden met deze brief ingelicht over het onderzoek en uitgenodigd mee te doen.* U behoort tot deze groep en daarom wordt u de mogelijkheid geboden om (gratis) de dragerschapstest te doen. Op voorhand is het niet goed mogelijk om te selecteren wie *precies* in aanmerking komt, daarom is deze brief naar de hele groep gestuurd.

Deze test is nieuw in Nederland en zeer betrouwbaar gebleken. Omdat de test nog niet eerder mocht worden aangeboden is nog niet goed bekend of de doelgroep blij is met het aanbod van deze test, of er juist problemen mee heeft. Dit willen de onderzoekers graag nagaan met een (online) vragenlijstonderzoek voordat de test (eventueel) in heel Nederland wordt aangeboden. Uw hulp is daarbij nodig.

Het is voor de onderzoekers belangrijk om een goed beeld te krijgen van hoe de hele groep vrouwen tussen 18 en 40 jaar die de test krijgt aangeboden over deze test denkt. Ook wanneer u geen interesse heeft in deelname aan de dragerschapstest is uw deelname aan het vragenlijstonderzoek van belang.

In de bijgevoegde folder vindt u meer informatie over de dragerschapstest en een verwijzing naar de website hierover.

Als u wilt deelnemen aan het vragenlijstonderzoek, vult u dan bijgevoegde antwoordkaart in. U krijgt dan van de onderzoekers uitgebreide informatie over het onderzoek en formulieren toegestuurd waarop u toestemming voor deelname aan het onderzoek moet geven.

U kunt alleen deelnemen aan de dragerschapstest samen met uw partner en als u nog niet zwanger bent. Vrouwen die al weten dat zij een verhoogde kans hebben op een kind met een erfelijke aandoening komen meestal wel in aanmerking voor deze test, dit kunt u met mij bespreken.

Mocht u interesse hebben in deelname aan de dragerschapstest en/of dit verder willen bespreken, dan kunt u nadat u de toestemmingsformulieren heeft opgestuurd, samen met uw partner een afspraak bij mij maken voor een consult.

Deelname is niet verplicht. Mocht u niet deel willen nemen aan het vragenlijstonderzoek en ook niet aan de dragerschapstest dan wordt het op prijs gesteld als u uw reden voor niet-deelname aan wilt geven op de bijgevoegde antwoordkaart.

Bij voorbaat dank voor uw medewerking.

Met vriendelijke groet,

Antwoordkaart Onderzoek Dragerschapstest UMCG 2015

Het UMCG doet onderzoek naar een dragerschapstest voor paren met kinderwens. U bent door uw huisarts uitgenodigd om deel te nemen aan dit onderzoek.

U behoort tot de doelgroep van het onderzoek naar de dragerschapstest als u:

- Tussen de 18 en 40 jaar bent
- Een partner heeft
- Samen met uw partner (ooit) een kinderwens heeft
- Nog niet zwanger bent

Vraag 1: Behoort u tot de doelgroep van het onderzoek?

Ja. Ga dan verder bij vraag 2.

Nee. We zouden het erg op prijs stellen als u hieronder de reden waarom u niet tot de doelgroep behoort in wilt vullen en de antwoordkaart in de bijgevoegde antwoordenvelop wilt opsturen.

Ik behoor niet tot de doelgroep, want

- o Ik ben niet tussen de 18-40 jaar
- o Ik heb geen partner
- o Ik en/of mijn partner heb(ben) geen kinderwens (meer)
- o Ik ben zwanger

Vraag 2: Bent u geïnteresseerd in deelname aan het vragenlijstonderzoek en/of wilt u graag samen met uw partner de dragerschapstest laten doen?

Ja. Vul dan hieronder uw gegevens in en stuur deze antwoordkaart op in bijgevoegde antwoordenvelop. U ontvangt dan op korte termijn uitgebreide informatie en toestemmingsformulieren voor deelname aan het onderzoek.

Naam:……

Adres……..Postcode……

Woonplaats……

Telefoonnummer……

Nee. We zouden het erg op prijs stellen als u hieronder de reden waarom u niet wilt deelnemen wilt invullen en de antwoordkaart in de bijgevoegde antwoordenvelop wilt opsturen.

Ik behoor wel tot de doelgroep, maar

- o De reden dat ik niet mee wil doen is…..……
- o Ik wil de reden hiervoor liever niet vertellen

NHS
Health Research Authority

London - City & East Research Ethics Committee
Bristol Research Ethics Committee Centre
Whitefriars
Level 3, Block B
Lewins Mead
Bristol
BS1 2NT

Telephone: 02071048033/53

Please note: This is an acknowledgement letter from the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

09 November 2016

Ms Juliette Schuurmans
University of Southampton/University Medical Center Groningen
Clinical Ethics and Law, Room AB 203 MP 801
University of Southampton, Southampton General Hospital
South Academic Block Tremona Road Southampton SO16 6YD

Dear Ms Schuurmans

Study title: **Implementation of Expanded Preconception Carrier Screening: Exploring the Ethical, Social and Practical Issues through Experiences of Couples referred for Fertility Treatment and Health Care Professionals Views'.**
REC reference: **16/LO/1966**
IRAS project ID: **203780**

Thank you for your response of 8th Nov 2016. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 24 October 2016

Documents received

The documents received were as follows:

Document	*Version*	*Date*
Participant consent form [Consent form interviews]	2.0	08 November 2016
Participant Information Sheet Focus Groups	version 2	08 November 2016
Participant information sheet interviews	2.0	08 November 2016
Response to Additional Conditions Met		08 November 2016

Approved documents

The final list of approved documentation for the study is therefore as follows:

Document	*Version*	*Date*
Covering letter on headed paper [Covering Letter]	1.0	12 October 2016
Interview schedules or topic guides for participants [focus group framework]	1.0	10 October 2016
Interview schedules or topic guides for participants [Interview schedule]	1.0	10 October 2016
IRAS Application Form [IRAS_Form_14102016]		14 October 2016
IRAS Application Form XML file [IRAS_Form_14102016]		14 October 2016
Letter from sponsor [letter from sponsor]	1.0	11 October 2016
Other [Summary CV member of research team Dr Dheensa]	1.0	29 July 2016
Participant consent form [Consent form focus groups]	1.0	10 October 2016
Participant consent form [Consent form interviews]	2.0	08 November 2016
Participant information sheet (PIS) [Participant Information Sheet Focus Groups]	version 2	08 November 2016
Participant information sheet (PIS) [participant information sheet interviews]	2.0	08 November 2016
Referee's report or other scientific critique report [Peer review form]	1.0	06 September 2016
Research protocol or project proposal [Study Protocol]	1.0	10 October 2016
Response to Additional Conditions Met		08 November 2016
Summary CV for Chief Investigator (CI) [Summary CV Chief Investigator J Schuurmans]	1.0	10 October 2016
Summary CV for student [Summary CV J Schuurmans PhD student]	1.0	10 October 2016
Summary CV for supervisor (student research) [CV academic supervisor]	1.0	31 March 2016
Summary CV for supervisor (student research) [Summary CV academic supervisor]	1.0	29 July 2016

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

16/LO/1966 **Please quote this number on all correspondence**

Yours sincerely

Rajat Khullar
REC Manager
E-mail: nrescommittee.london-cityandeast@nhs.net

Copy to: *Ms Juliette Schuurmans, University of Southampton/University Medical Center Groningen*
Ms Emily Stimpson, University Hospital Southampton NHS Foundation Trust

NHS
Health Research Authority

London - City & East Research Ethics Committee
Bristol Research Ethics Committee Centre
Whitefriars
Level 3, Block B
Lewins Mead
Bristol
BS1 2NT

Telephone: 02071048033/53

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

24 October 2016

Ms Juliette Schuurmans
PhD-student
University of Southampton/University Medical Center Groningen
Clinical Ethics and Law, Room AB 203 MP 801
University of Southampton, Southampton General Hospital
South Academic Block Tremona Road Southampton
SO16 6YD

Dear Ms Schuurmans

Study title:	**Implementation of Expanded Preconception Carrier Screening: Exploring the Ethical, Social and Practical Issues through Experiences of Couples referred for Fertility Treatment and Health Care Professionals Views'.**
REC reference:	**16/LO/1966**
IRAS project ID:	**203780**

The Proportionate Review Sub-committee of the London - City & East Research Ethics Committee reviewed the above application on 20 October 2016.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager Mr Rajat Khullar, nrescommittee.london-cityandeast@nhs.net. Under very limited circumstances

(e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Ethical opinion

On behalf of the Committee, the sub-committee gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

1. *The Consent form for the interviews mentions. "I give permission for some of my responses to be used in reports from the study provided there are no links to my name." This should be changed to "anonymised responses" i.e. not referring to any identifiable things like names, ages or other personal information.*

2. *The term 'links' could be misunderstood for hyper-links. Please rephrase suitably.*

3. *Participant Information Sheet (PIS) should clarify that the study has been ethically reviewed by London City & East Research Ethics Committee.*

You should notify the REC once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. Revised documents should be submitted to the REC electronically from IRAS. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which you can make available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA Approval (England)/ NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the

procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion").

Approved documents

The documents reviewed and approved were:

Document	*Version*	*Date*
Covering letter on headed paper [Covering Letter]	1.0	12 October 2016
Interview schedules or topic guides for participants [focus group framework]	1.0	10 October 2016
Interview schedules or topic guides for participants [Interview schedule]	1.0	10 October 2016
IRAS Application Form [IRAS_Form_14102016]		14 October 2016
IRAS Application Form XML file [IRAS_Form_14102016]		14 October 2016
IRAS Checklist XML [Checklist_14102016]		14 October 2016
Letter from sponsor [letter from sponsor]	1.0	11 October 2016
Other [Summary CV member of research team Dr Dheensa]	1.0	29 July 2016
Participant consent form [Consent form focus groups]	1.0	10 October 2016

Participant consent form [consent form interviews]	1.0	10 October 2016
Participant information sheet (PIS) [Participant information sheet focus groups]	1.0	10 October 2016
Participant information sheet (PIS) [Participant information sheet interviews]	1.0	10 October 2016
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Research protocol or project proposal [Study Protocol]	1.0	10 October 2016
Summary CV for Chief Investigator (CI) [Summary CV Chief Investigator J Schuurmans]	1.0	10 October 2016
Summary CV for student [Summary CV J Schuurmans PhD student]	1.0	10 October 2016
Summary CV for supervisor (student research) [CV academic supervisor]	1.0	31 March 2016
Summary CV for supervisor (student research) [Summary CV academic supervisor]	1.0	29 July 2016

Membership of the Proportionate Review Sub-Committee

The members of the Sub-Committee who took part in the review are listed on the attached sheet.

There were no declarations of interest

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document “After ethical review – guidance for researchers” gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form

available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project.

16/LO/1966	**Please quote this number on all correspondence**

Yours sincerely

pp Dr John Keen
Chair

Email: nrescommittee.london-cityandeast@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

"After ethical review – guidance for researchers"

Copy to: *Ms Emily Stimpson, University Hospital Southampton NHS Foundation Trust*

London - City & East Research Ethics Committee

Attendance at PRS Sub-Committee of the REC meeting on 20 October 2016

Committee Members:

Name	*Profession*	*Present*	*Notes*
Ms Alison Eden	Manager Patient Recruitment	Yes	
Mrs Lisa Johnson	Clinical Manager	Yes	
Dr John Keen	GP (REC Chairman)	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Mr Rajat Khullar	REC Manager

Health Research Authority

Ms Juliette Schuurmans
PhD-student
University of Southampton/University Medical Center Groningen
Clinical Ethics and Law, Room AB 203 MP 801
Southampton General Hospital
Tremona Road, Southampton
SO16 6YD

Email: hra.approval@nhs.net

29 November 2016

Dear Ms Schuurmans

Letter of HRA Approval

Study title:	**Implementation of Expanded Preconception Carrier Screening: Exploring the Ethical, Social and Practical Issues through Experiences of Couples referred for Fertility Treatment and Health Care Professionals Views'.**
IRAS project ID:	**203780**
REC reference:	**16/LO/1966**
Sponsor	**University Hospital Southampton NHS Foundation Trust**

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from www.hra.nhs.uk/hra-approval.

Appendices

The HRA Approval letter contains the following appendices:

- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

After HRA Approval

The document *"After Ethical Review – guidance for sponsors and investigators",* issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

In addition to the guidance in the above, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the HRA website, and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the HRA website.

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-hsc-rd-review/.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please email the HRA at hra.approval@nhs.net. Additionally, one of our staff would be happy to call and discuss your experience of HRA Approval.

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

Your IRAS project ID is **203780**. Please quote this on all correspondence.

Yours sincerely

Simon Connolly
Senior Assessor

Email: hra.approval@nhs.net

Copy to: *Ms Emily Stimpson, University Hospital Southampton NHS Foundation Trust*

Appendix A - List of Documents

The final document set assessed and approved by HRA Approval is listed below.

Document	*Version*	*Date*
Interview schedules or topic guides for participants [focus group framework]	1.0	10 October 2016
Interview schedules or topic guides for participants [Interview schedule]	1.0	10 October 2016
IRAS Application Form [IRAS_Form_14102016]		14 October 2016
Letter from sponsor [letter from sponsor]	1.0	11 October 2016
Other [Summary CV member of research team Dr Dheensa]	1.0	29 July 2016
Participant consent form [Consent form interviews]	2.0	08 November 2016
Participant consent form [Consent form focus groups]	1.0	10 October 2016
Participant information sheet (PIS) [Participant Information Sheet Focus Groups]	version 2	08 November 2016
Participant information sheet (PIS) [participant information sheet interviews]	2.0	08 November 2016
Research protocol or project proposal [Study Protocol]	1.0	10 October 2016
Summary CV for Chief Investigator (CI) [Summary CV Chief Investigator J Schuurmans]	1.0	10 October 2016

Appendix B - Summary of HRA Assessment

This appendix provides assurance to you, the sponsor and the NHS in England that the study, as reviewed for HRA Approval, is compliant with relevant standards. It also provides information and clarification, where appropriate, to participating NHS organisations in England to assist in assessing and arranging capacity and capability.

For information on how the sponsor should be working with participating NHS organisations in England, please refer to the, *participating NHS organisations*, *capacity and capability* and *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* sections in this appendix.

The following person is the sponsor contact for the purpose of addressing participating organisation questions relating to the study:

Name: Ms Juliette Schuurmans

Tel: 02381205082

Email: js1v15@soton.ac.uk

HRA assessment criteria

Section	HRA Assessment Criteria	Compliant with Standards	Comments
1.1	IRAS application completed correctly	Yes	No comments
2.1	Participant information/consent documents and consent process	Yes	Agreed applicant will add IRAS number to documents before use.
3.1	Protocol assessment	Yes	No comments
4.1	Allocation of responsibilities and rights are agreed and documented	Yes	The sponsor is the single participating NHS organisation. There is no requirement for a statement of activities.
4.2	Insurance/indemnity arrangements assessed	Yes	Where applicable, independent contractors (e.g. General Practitioners) should ensure that the professional indemnity provided by their medical defence organisation covers the activities expected of them for this research study

Section	HRA Assessment Criteria	Compliant with Standards	Comments
4.3	Financial arrangements assessed	Yes	Study forms part of a sponsored PhD. No external funding applied for.
5.1	Compliance with the Data Protection Act and data security issues assessed	Yes	No comments
5.2	CTIMPS – Arrangements for compliance with the Clinical Trials Regulations assessed	Not Applicable	
5.3	Compliance with any applicable laws or regulations	Yes	No comments
6.1	NHS Research Ethics Committee favourable opinion received for applicable studies	Yes	No comments
6.2	CTIMPS – Clinical Trials Authorisation (CTA) letter received	Not Applicable	
6.3	Devices – MHRA notice of no objection received	Not Applicable	
6.4	Other regulatory approvals and authorisations received	Not Applicable	

Participating NHS Organisations in England

This provides detail on the types of participating NHS organisations in the study and a statement as to whether the activities at all organisations are the same or different.
At the participating NHS organisation staff and service user participants will be recruited and the research activities will take place. If this study is subsequently extended to other NHS organisation(s) in England, an amendment should be submitted to the HRA, with a Statement of Activities and Schedule of Events for the newly participating NHS organisation(s) in England. The Chief Investigator or sponsor should share relevant study documents with participating NHS organisations in England in order to put arrangements in place to deliver the study. The documents should be sent to both the local study team, where applicable, and the office providing the research management function at the participating organisation. For NIHR CRN Portfolio studies, the Local LCRN contact should also be copied into this correspondence. For further guidance on working with

participating NHS organisations please see the HRA website.

If chief investigators, sponsors or principal investigators are asked to complete site level forms for participating NHS organisations in England which are not provided in IRAS or on the HRA website, the chief investigator, sponsor or principal investigator should notify the HRA immediately at hra.approval@nhs.net. The HRA will work with these organisations to achieve a consistent approach to information provision.

Confirmation of Capacity and Capability

This describes whether formal confirmation of capacity and capability is expected from participating NHS organisations in England.
This is a single site study sponsored by the site. The R&D office will confirm to the CI when the study can start.

Principal Investigator Suitability

This confirms whether the sponsor position on whether a PI, LC or neither should be in place is correct for each type of participating NHS organisation in England and the minimum expectations for education, training and experience that PIs should meet (where applicable).
The chief investigator will be the principal investigator at the participating NHS organisation. GCP training is not a generic training expectation, in line with the HRA statement on training expectations.

HR Good Practice Resource Pack Expectations

This confirms the HR Good Practice Resource Pack expectations for the study and the pre-engagement checks that should and should not be undertaken
The researcher has existing contractual arrangements with the participating NHS organisation. No access arrangements are required.

Other Information to Aid Study Set-up

This details any other information that may be helpful to sponsors and participating NHS organisations in England to aid study set-up.
• The applicant has indicated that they do not intend to apply for inclusion on the NIHR CRN Portfolio.

Preconception Carrier Screening: Exploring the Experience in the Fertility Clinic

Research Team:

PhD-student:
Juliette Schuurmans,
Address:
Clinical Ethics and Law, Room AB 203, MP 801, University of Southampton, Southampton General Hospital, South Academic Block, Tremona Road, Southampton, SO16 6YD. email: js1v15@soton.ac.uk

Supervisors:
Dr. Angela Fenwick, associate professor
Prof. Anneke Lucassen, consultant clinical genetics

Other members of the research team:
Dr. Sandi Dheensa, postdoctoral research fellow

Funder: University of Southampton and University of Groningen (joint PhD contract)
Sponsor: University of Southampton Hospital Trust

Study Protocol

Research questions:
1: What are the views and experiences of couples who are referred to Complete Fertility Centre on the ethical, practical and social implications of preconception carrier screening as optional part of their fertility treatment?

2A*: What are the key ethical issues for health care professionals when expanded preconception carrier screening is implemented as part of standard fertility treatment?*
2B: What are the implications for practice and/or practical barriers to implementation of expanded preconception carrier screening as part of fertility treatment?

Background to Study/Summary of Literature
Due to new technological developments in genome sequencing it is now possible to screen prospective parents, before pregnancy, for many severe inheritable diseases simultaneously (Grody et al., 2013; Bolhuis 2014; Inthorn, 2014), while costs are declining (Bolhuis, 2014; Hayden, 2014). These conditions with early onset account for approximately 20% of infant mortality and 10% of paediatric hospitalizations (Srinivasan et al. 2010; Bell et al, 2011).

Expanded preconception carrier screening (PCS), provides prospective parents with information about their risk of being a carrier couple for a severe hereditary disease. Carrier couples have a 25% chance of having an affected child in each pregnancy. They can use this information for reproductive decisions. Various options are available to prevent the birth of an affected child such as prenatal testing, using donor gametes and IVF using embryo-selection. Also, parents could prepare for the birth of an affected child. PCS could potentially reduce psychological stress for parents as previously an affected child would have been born unexpectedly.

Implementation of PCS raises several important ethical, social and practical issues. For example, who should provide these tests? What diseases should be included? Is it over medicalization of pregnancy, and do people make informed decisions? Whereas studies concerning the clinical significance of expanded carrier screening in the fertility clinic have been published recently (eg. Martin et al., 2015), no studies have been published on the ethical, social and practical issues in this population. Recently, a qualitative interview concerning-population based expanded preconception carrier screening study amongst health care professionals in Sweden was published (Matar et al., 2016). No equivalent study has been performed from the UK perspective, nor a qualitative study focusing on the infertile population in particular. Therefore, our study will be twofold. Firstly, we would like to conduct a longitudinal qualitative interview study with couples referred for fertility treatment who will be offered PCS. Secondly, we would like to explore the views of health care professionals involved in fertility treatment and genetic screening on the ethical and practical issues by means of focus groups. The focus group study and the interview study will be performed concurrently.

Study Design:
A qualitative exploratory study:
1: **Patients**: Longitudinal study with depth interviews with couples who are referred for treatment to the Complete Fertility Centre.
2: HCPs: A focus group study with health care professionals involved in fertility treatment and genetic screening. Health care professionals who might be involved when carrier screening is implemented in fertility care will be invited to participate. The sample will include (but is not limited to) clinical embryologists, fertility specialists, nurses, genetics professionals.

Sample size:
For qualitative research it is not always possible to define a sample size prior to the study.
1: **Patients:** We expect 20-25 interviews will be sufficient to explore issues between/ within couples. Couples will be able to choose whether they want to take the interview individually or as a couple.
2: **HCPs:** We anticipate focus groups no: (4-6) with a group size between 2-6 participants to be enough to explore the ethical issues among professionals. We will enable participants to choose their group so they can speak freely, without feeling the boundaries of hierarchy or dependency in future professional relationships.

Setting:
1: Participants are patients referred for fertility treatment at Complete Fertility Centre. Interviews will be conducted at a location that is convenient for the participant. This might be at the fertility clinic or at a participant's home. Complete Fertility Centre is the only site where participants will be included.
2: We will arrange a comfortable, quiet room to conduct the focus groups where participants feel comfortable to openly express their views and experiences. This might be at the hospital, the fertility clinic or the University.
Sample:
1: We will use a purposeful sample. Given the possibility of recruitment issues, we will take anyone who comes in, but if there is a possibility, we would like to have a spread between NHS/self-funded; age and gender.

Relationship between the sample and the researcher:
1: There is no direct relationship between Juliette Schuurmans (JS) and the participants.
2: The PI (Prof Anneke Lucassen) is a clinical geneticist and some of her colleagues might be recruited, but the focus groups will be conducted by JS.

Identification of the sample:
1: Initial identification of suitable couples will be undertaken by the clinical care team of Complete Fertility Clinic. The members of the research team will not be involved in clinical care for the participants.
2: Eligible participants will be identified by asking the staff of the fertility centre who we could best approach. Furthermore, Professor Anneke Lucassen will be able to identity which professionals in the genetics department are involved with genetic

screening for reproductive purposes. We will ask those who have been approached if they know others who might be interested in participation as well.

Recruitment:
1: Couples will be identified by the clinical care team of Complete Fertility Clinic when they are referred for treatment. The potential participant will be given a Participant Information Sheet (EOI) including information about the test and the study by a member of the clinical care team. They will also receive an expression of interest sheet where they can provide their contact details. This EOI will be returned to the research team by regular mail or left at the fertility clinic and collected by the researcher. A stamped envelope will be provided. A member of the research team will subsequently contact the participant to answer additional questions and to arrange a time and date for the interview. The initial identification of patients will therefore be done by members of the clinical care team and not by members of the research team. Follow-up of people who expressed their interest in the study will be carried out by the research team.

2: Recruitment will be done in several steps. First, we will send an email with the participant information sheet (including expression of interest sheet) to those professionals who've been identified as potentially interested in participation. They can return the expression of interest sheet to the research team or contact us by email or telephone to express their interest in participation. A member of the research team will then contact them to discuss the research and any questions they might still have and arrange a time and place for the focus group to take place.

Inclusion criteria and exclusion criteria and screening tools
1:Inclusion criteria are:
- Age>18 years

Exclusion criteria:
- Patients (or partners of patients) who are already pregnant
- Gamete donors

2: Health care professionals and other stakeholders who might be involved in genetic screening offered in the fertility clinic. The sample will most likely include (but is not limited to) clinical embryologists, fertility specialists, nurses, genetics professionals.

Participants who cannot speak and understand English proficiently, or who have sensory difficulties, will not be excluded. Such individuals will be asked what their needs are and provisions will be made to try and meet these needs. For example, if someone with limited English proficiency wants to take part, a hospital interpreter can be arranged for them and/or translations of information material could be provided on an individual basis. If someone with visual impairments wants to participate documents can be provided for them in large print.
For the focus group study, participants who are not proficient in English will not take part since all participants will work in NHS practice.

How will consent be obtained :
1: The participants will be given an information sheet and an expression of interest form by a member of their clinical care team. The participants will be given enough time to consider whether they wish to express an interest in participating. Interested

participants will return the expression of interest forms to the research team. They can return the EOI by regular mail or leave the EOI at the fertility clinic to be collected by the researcher. A member of the research team will then telephone or email the individual to see if they still want to participate, which will give them more time to deliberate and ask questions. If they are still interested, an interview time will be arranged. Written consent will be obtained before the start of the interview. After the first interview, the researcher will ask whether or not the participants are interested in participating in a second interview if they choose to have the test. Depending on the personal treatment plan a time period will be set after which the researcher can contact the participants again to arrange a time and location for the second post-test interview and discuss any questions they might still have.

2: When eligible participants have expressed their interest in participation, a member of the research team will contact them by email or telephone to ask whether they still have questions. If they are still willing to participate, a time and place for the focus goup will be arranged. A consent form will be signed before focus groups commence. JS will explain why consent is being taken and read through the consent form. JS understands the ethical principles underpinning informed consent. Individuals who lack capacity to consent will not be recruited.

- **All participants will be given a participant information sheet and all participants will be asked to sign a consent form.**

Anonymity and confidentiality:
Given the qualitative interviews and focus groups will be conducted face-to-face these will not be anonymous.
However, data will be anonymised and anonymity will be maintained by ensuring that all participants are allocated an ID number and that the match between ID number and participant names are stored in a secure and separate location from the rest of the research data. Furthermore, the participants' identity will be known to other focus group participants and the researchers cannot guarantee that others in these groups will respect the confidentiality of the group; however we will make this clear on the PIS and discuss the issue at the beginning of the focus group.

Data will be stored on University computers. All university computers are password protected. A specific folder is used for documents and audio data relating to this project that only members of the research team have access to. Recordings will be destroyed after the interviews and focus groups have been transcribed and verified.

Interventions and Measurements

What will happen to the participants/sample?
1: The participants will be in the study for 90 or 180 minutes, depending on whether there will be one or two interviews. 90 minutes is the maximum expected duration of one interview. All interviews will be audio-recorded.
2: Participants will take part in a focus group discussion. This discussion will be audio-recorded. The focus groups will take approximately 60-90 minutes. All focus groups will be audio-recorded.

Explain what will be measured/explored and how
1: This study aims to explore the views and experiences of couples referred to Complete Fertility Centre on the ethical, practical and social implications when expanded carrier couple screening is offered to them as an optional part of their fertility treatment. We will conduct in depth interviews with couples or individuals referred for fertility treatment who are offered preconception carrier screening. In cases where participants have the test, they will be asked to participate in a second interview after the test result has been disclosed.
The data generated from an individual interview might be different than from an interview with a couple. We expect both types of data to be relevant to answer our research question. The decision that needs to be made about taking the test affects both partners, however it might affect them in different ways, since one partner needs to give blood while the other partner does not. Furthermore, partners might feel hesitant to express their actual feelings. Therefore, we will have the participants decide whether they prefer to be interviewed as a couple or as individuals. Practically, for a couple interview both partners need to be present at the same time, this might be more difficult to organise than individual interviews.

2: We will explore the ethical issues for health care professionals when expanded preconception carrier screening is offered to patients referred for fertility treatment. Furthermore, we will also explore practical barriers for implementation. We will design a focus group framework with a list of the topics that are known from existing literature and from our own experiences. We will conduct a small pilot focus group to see whether the framework is correct or still needs adaptation.

Outline how the data will be analysed:
For both the interviews and the focus groups, we will take a qualitative approach by using elements of grounded theory and using thematic analysis drawing on constant comparison. Data will be coded and categorised and themes will be identified. The first three interviews will be coded by two researchers independent of each other and these will be compared to each other to discuss the similarities and discrepancies. A software package for qualitative data analysis will be used to assist data analysis and data management.

Management of the study and the risks involved:

Outline what pilot work has already been completed or outline the pilot work that will be carried out as part of the project, as applicable
1: We will conduct pilot interviews as part of the research project in order to find out whether the interview schedule is appropriate or needs to be adapted. Pilot interviews will be held with members of the research team..
2: An interview study has been performed in the Netherlands by JS where general practitioners are asked about their experiences with the offer of preconception carrier screening to the general population. Even though this is a different group of health care professionals and a different patient population similar themes might emerge.

Outline the potential risks/harm to participants in the study (including the researcher/s)
1: Issues regarding reproduction can be a sensitive topic for people who are referred to a fertility clinic.

Furthermore, if the interviews are conducted at the participant's home there could be a safety risk for the interviewer.
2: health care professionals taking part in a focus groups with colleagues they currently work with might fear that openly discussing their opinion will affect their working relationship.

How will you *attempt to prevent* the potential risks/harm from occurring?
1: Talking about their fertility treatment might be stressful for people. Participants will be told they can always stop the interview and continue at a later moment or withdraw from the study.

Regarding lone working: We will follow the University of Southampton lone-workers policy to ensure the safety of the interviewer.
http://www.southampton.ac.uk/hr/services/lone-worki ng/index.page

2: We will organise a number of different focus groups to allow some choice for the participants.

How will you *manage* any that do arise?
1: Distress: If they feel stressed, participants can ask to stop the interview. They can either withdraw from the study altogether or continue the interview at another time. We will refer couples who express distress to their clinical care team or to a patient support group such as the Infertility Network UK which offers facilities for patient support:
http://www.infertilitynetworkuk.com/

and Complete Fertility Centre also has an infertility support group:
http://www.completefertility.co.uk/infertility_support_group.php

the Patient Advice and Liaison Service:
Tel: 023 8120 6325
Email: patientsupportservices@uhs.nhs.uk

Lone working:
We will adopt strategies such as a sign-in system, where another member of the research team will be notified when the researcher has entered the house of the interviewee. After a set amount of time, the other member of the research team will check if everything is alright. The location of the interview will be known to the other member of the research team in order to be able to alert emergency services if needed.

2: Participants who feel they are not able to openly express their feelings or who feel distressed by the topic can stop participation at any time during the focus group.

How will data be stored securely during and after the study?
The Faculty of Medicine at Southampton has a policy that data should be stored for 15 years after the end of the project. Research data will be stored electronically on the designated folder for this project that only the research team will have access to.

Raise any ethical problems not covered elsewhere and how you will deal with them.
1: Understanding the topic: From experience in previous research and from the literature we know that risks and uncertainties associated with genetic screening might be difficult for people to understand. Therefore, it is important to provide them with clear information in the participant information sheet. Furthermore, we will make sure to explore their understanding of the important issues prior to and during the interview.

List of references:
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Martin J, Asan, Yi Y, Alberola T, Rodríguez-Iglesias B, Jiménez-Almazán J, Li Q, Du H, Alama P, Ruiz A, Bosch E, Garrido N, Simon C. (2015). Comprehensive carrier genetic test using next-generation deoxyribonucleic acid sequencing in infertile couples wishing to conceive through assisted reproductive technology.Fertil Steril. 2015 Nov;104(5):1286-93.

Matar, A. Kihlbom U., Höglund, A.T. Swedish healthcare providers' perceptions of preconception expanded carrier screening (ECS)—a qualitative study
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Plantinga M, Birnie E, Abbott KM, Sinke RJ, Lucassen AM, Schuurmans J, Kaplan S, Verkerk MA, Ranchor AV, van Langen IM. Population-based preconception carrier screening: how potential users from the general population view a test for 50 serious diseases.

Srinivasan, B.S., Evans, E.A., Flannick, J., Patterson, A.S., Chang, C.C., Pham, T., Young, S., Kaushal, A., Lee, J., Jacobson, J.L., Patrizio, P. (2010), A universal carrier test for the long tail of Mendelian disease. *Reproductive Biomedicine Online.* 4: 537-551.

Carrier Screening: Exploring the Experience in the Fertility Clinic

Focus Group Framework:

1: Short introduction of the topic

2: Introduction of participants (professionals background), experiences with carrier screening

3: Ethical issues concerning the implementation of expanded carrier screening in the fertility population

- Topics might include, but are not limited to
    - Ethical issues associated with couple testing and gamete donors
    - ‘reproductive autonomy’
    - Equal access to health care
    - Who should be offered these tests?
    - Which diseases to include on these gene panels and why
    - Medicalization of pregnancy
    - Consent/informed choice
    - Rights and duties for patients and health care professionals

4: Practical issues for implementation.

- Topics might include, but are not limited to:
    - Who are stakeholders in this process
    - How to inform patients and health care professionals about the possibility of carrier screening
    - How to embed carrier screening in the fertility treatment procedures?
    - Requirements of pre-test counselling

5: any other issues not mentioned or discussed before

- For example, personal or professionals motivations whether or not to offer expanded preconception carrier screening

Participant Information Sheet for healthcare professionals

Carrier Screening: Exploring the Experience in the Fertility Clinic

Purpose and background of the study

New developments in genetics have made it possible to test for many conditions at the same time and we can do this much faster and cheaper than before. We can also test people who are planning to have children before conception for diseases they might pass on to their child. Complete Fertility Centre would like to offer patients this so-called “preconception carrier screening test”. The result of this test will show if there is an increased risk of passing on a severe genetic disease to the child. For this study, we would like to understand the views of health care professionals on the ethical issues and practical implications of carrier screening for reproductive purposes as part of fertility treatment.

Why am I invited to take part in this study?

You are invited to take part in this study, because you are a health care professional working in a field related to genetic screening for reproductive purposes. Because of this, you might be, sooner or later, professionally involved with preconception carrier screening. We are therefore interested in your views on the ethical and practical issues related to implementation of preconception carrier screening in the fertility clinic.

Do I have to take part?

No, it is up to you whether or not you agree to take part in the study. If you agree to take part and then later change your mind you are free to withdraw at any time. We will destroy your data if you want us to.

What would taking part involve?

We invite you to participate in a focus group discussion together with other health care professionals. The group will consist of approximately 2-6 participants. The focus group discussion will last approximately 60-90 minutes. With your permission, we will audio-record the focus group discussion, and later write up the recording. The focus group discussion will help us to identify important issues about the view of health care professionals on preconception carrier screening.

What are the possible benefits of taking part?

There are no direct personal benefits to taking part but you might find it useful to discuss your views with other health care professionals. We hope that the data collected will contribute to a greater understanding of the issues raised in this

area and that we can use this to find out how carrier screening can be implemented in a responsible way in clinical practice.

What are the possible disadvantages and risks of taking part?

Although we ask all focus group participants to respect the confidentiality of the focus group discussion, we cannot guarantee that all participants will do so and there is a risk that participants may tell others outside of the group what has been discussed.

You might fear that freely expressing your opinion amongst colleagues could affect your future working relationships but we will do our best to organize a number of different focus groups to allow some choice.

Will my taking part in the study be kept private and confidential?
Confidentiality and anonymity
All the information collected in the focus groups will be kept strictly confidential by the research team. We ask each participant in these focus groups to respect the confidentiality of the discussion and not to report comments made by individual focus group participants to others outside of the focus group.

We will store all your data securely. We will keep your name and contact details separate to your focus group transcript. You will be assigned a unique ID number. We will remove identifying names or places from the focus group transcript so that your identity is not known to readers.

In our reports or publications, we will include things that people say in their interviews. We will always make this information anonymous—we will never use a person's own name. If there is any data that may identify an individual, we will not use it in reports or publications.

We may use the data for future research in this area. If you do not want us to, you can just let us know.

What will happen to the results of the research study?
We will publish the findings of the research in scientific journals and conferences. We have also set up a website (http://www.southampton.ac.uk/cels) where you can read about the research. You can contact us or refer to the website if you would like a summary of the main findings.

Who is organising and funding the research?
The research team organising the study is Juliette Schuurmans, PhD-student, Dr. Angela Fenwick, Dr. Sandi Dheensa and Prof. Anneke Lucassen. The study is part of a fully-funded PhD project by the University of Southampton and the University Medical Center Groningen, the Netherlands.

Who has reviewed the study?
An independent group of people, called a Research Ethics Committee, review all research in the NHS. London City and East Research Ethics Committee has reviewed and approved this study. The REC reference number is 16/LO/1966

What do I do now?
If you would like to take part in this study, please complete the 'expression of interest' form. You can return it by email, regular mail, or contact us by telephone. One of our team will subsequently contact you to discuss the study in more detail, and give you the chance to ask questions. If you still want to take part, they will arrange a suitable time and venue for the focus group. You will then be asked to complete a consent form before the interview, which will give you another opportunity to ask any questions.

Further information
If you have any queries, please contact Juliette Schuurmans (023 8079 5082) js1v15@soton.ac.uk.

Thank you for taking the time to read this information.

Carrier Screening: Exploring the Experience in the Fertility Clinic

HCP Expression of Interest Sheet.

I am happy to be contacted by a member of the research team

Name:……

Telephone nr:……

Email address:……

Date __/__/__

Please return by email, regular mail or contact us by telephone

To Juliette Schuurmans, PhD-student;

CELS, MP 801, University of Southampton, Southampton University Hospital Trust, , South Academic Block, Tremona Road, Southampton SO16 6YD

Email: js1v15@soton.ac.uk

Tel.no.: 02381 205082

Health care professional FOCUS GROUP CONSENT FORM

Title of Project: Carrier Screening: Exploring the Experience in the Fertility Clinic.

Name of Researcher: Juliette Schuurmans, PhD student

Please initial box

1. I confirm that I have read the information sheet dated..... (version.....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason ☐

3. I understand that audio recording will be used to assist with the accurate recall of participants' responses and that I can request that the equipment be switched off at any time during the focus group. Recordings will be destroyed once they are transcribed ☐

4. I give permission for some of my responses to be used in reports from the study provided there are no links to my name. ☐

5. **I agree to take part in the above study.** ☐

	Yes	No
OPTIONAL 6. *I give permission for my comments on the focus group transcript to be used anonymously in future ethically approved studies related to implementation of preconception carrier screening.*	☐	☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

Carrier Screening: Exploring the Experience in the Fertility Clinic: Interview guide

Introduction

- Discussion of any outstanding issues. Signing written consent form
- Introduction of myself as the researcher, PhD student
- Recording of the interview

1: couples and individuals who are referred for fertility treatment and who have been offered preconception carrier screening

1: Could you tell me briefly how you came to be referred to the fertility clinic?

2: What were your first thoughts when you heard about this test?

- Could you tell me in your own words what you think this test is about?
- What did your HCP tell you? Was this information clear?
- Did you read the information leaflet?
- Did you look up any information about this type of preconception screening test?
  - What type of information were you looking for? (eg. type of diseases/risk of being a carrier/how to take this test)
  - Where did you look for information? (internet/social media/medical info/information leaflets etc.)
  - What did you find? Is this important information for you and if so why? Did you look for something specific, but couldn't find it?
- What did you think about these tests after you had looked for information?

3: Are you pleased this test is offered to you?

- Why or why not?
- Do you think this type of testing should be offered to all couples who use fertility treatment to get pregnant? Or to all couples, also in the general population?

4: How do you feel about genetic testing as part of your fertility treatment?

- Could you explain to me why you feel like this?
- How does this test relate to other tests/to the entire fertility treatment procedure?
- Do you have any experiences with genetic testing before pregnancy (yourself/family members/friends)?

5: Did you discuss having the test with your partner?

- How important is your partner's opinion in taking this test?
- How does having to make this decision affect you as a couple/your relationship?
- If no, why did you not discuss this with your partner?
- Did you discuss this with other people?
- If yes, with whom? Why?
- If not, why not? Will you do this in the future?

6: What are important reasons for you to consider taking the test?

7: What are important reasons for you to consider not to take the test?

8: Have you decided whether or not you want to have the test performed?

- If no, why haven't you made a decision yet?
    - More information? Not clear?
    - Need more counseling/support?
    - Did you ask people who are close to you for advice? Why them? What did they say?
    - Does it affect you emotionally? Why/How?

- If yes: What do you think you will find out if you participate? What do you hope/expect to find out? Do you have any worries about receiving the result of the test?

9: Have you considered receiving a result that means that you have an increased risk to have a child with a severe genetic disease?

- How do you think you would feel if this happens to be the case?
- Have you thought about what you might do if you find out you have an increased risk to have a child with a severe genetic disease?
- Would this change your 'reproductive plans'?

10: How do you feel about receiving a result that is based on the combined results of the prospective father and the egg donor? This means that you will only be told that either both are carriers of the same severe disease, or both are not carriers of the same disease

- Would this be different if you were not using donor gamete (egg or sperm?)
- Would this affect your decision to have the test performed or not?
- What do you think it means to be a carrier?

11: Any/something you would like to add?

12: Closing off: do you have any advice for health care professionals who are offering this test, for example which health care provider you prefer to talk to about this?

13: Would it be ok if I contact you for a follow-up interview after you have received the test result? If yes, how would you prefer we contact you for this follow-up interview?

2: couples who have taken the test and received the test-result

1: Looking back, how did you feel during the different stages of the procedure?
    - What/who influenced you?

2: What was the test-result you received? What do you think it means?
- How did the result affect you? How does it affect your future reproductive plans?
- In case the result meant that both are carriers of the same genetic disease::
    - What options did you consider after receiving the test result? Did you talk about this together? What were the things you agreed/disagreed about? How did you reach your decision in the end?
    - What have you decided to do?

3: How was the result disclosed to you?
- What information did you receive?
- What kind of support did you receive?
- How have you experienced this?

4: Have you discussed this test result with others?
- Family/friends; Why? Or why not?
- How did they respond?

5: How do you feel about receiving a result that is based on the combined results of the prospective father and the egg donor? This means that either both are carriers of the same severe disease, or both are not carriers of the same disease?

6: After having taken this test, how do you feel about carrier screening before pregnancy? Why?
- To whom do you think carrier screening should be offered? Why?
- Would you have made the same decision if you were offered the test again?

7: Any/something you would like to add?

8: Closing off: do you have any advice for health care professionals who are implementing this test?

INTERVIEW CONSENT FORM

Title of Project: Carrier Screening: Exploring the Experience in the Fertility Clinic.

Name of Researcher: Juliette Schuurmans, PhD student

Please initial box

1. I confirm that I have read the information sheet dated..... (version.....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason ☐

3. I understand that audio recording will be used to assist with the accurate recall of participants' responses and that I can request that the equipment be switched off at any time during the interview. Recordings will be destroyed once they are transcribed ☐

4. I give permission for some of my responses to be used in reports from the study provided these responses are anonymised. ☐

5. I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers within our research group ☐

6. I agree to take part in the above study. ☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

Participant Information Sheet

Carrier Screening: Exploring the Experience in the Fertility Clinic

Purpose and background of the study

New developments in genetics have made it possible to test for many conditions at the same time and we can do this much faster and cheaper than before. We can also test people who are planning to have children before conception for diseases they might pass on to their child. If you make use of an egg donor, the test can be performed using blood from the prospective father and the egg donor. Complete Fertility Clinic would like to offer patients this so-called "preconception carrier screening test". The result of this test will show if there is an increased risk of passing on a severe genetic disease to the child. For this study, we would like to understand the views and experiences of couples who are offered the test.

Why am I invited to take part in this study?

You are invited to take part in this study, because you have been referred for fertility treatment and you are being offered the preconception carrier screening test.

Do I have to take part?

No, it is up to you whether or not you agree to take part in the study. If you agree to take part and then later change your mind you are free to withdraw at any time. We will destroy your data if you want us to.

What would taking part involve?

We invite you and your partner to participate in an interview with one of the members of our research team. You can be interviewed individually or as couple. We are interested in the views of couples who want to take the test, as well as couples who do not want to take the test. This interview will take a maximum of 90 minutes. With your permission, we will audio-record the interview, and later write up the recording. This written copy of your interview is called a transcript. Your interview will help us to identify important issues about the experience of people who are offered the test. If you decide to take the screening-test, we will also ask you to participate in a second interview after you have received the result of the test and started the fertility treatment.

What are the possible benefits of taking part?

You might find it useful to discuss your experiences of the test-offer and fertility treatment. We will use the information from this study to find out how we can implement the screening-test in a responsible way in clinical practice.

What are the possible disadvantages and risks of taking part?

Talking about genetic screening and fertility treatment can be difficult or upsetting. If you find the interview difficult, you can stop and carry on at another time. Alternatively, you can withdraw from the study completely. You can contact your clinical care team if you would like to talk to a healthcare professional about anything that comes up in the interview. If there is another problem, you can contact patient support groups such as:

The Infertility Network UK which offers various facilities for patient support: http://www.infertilitynetworkuk.com/

Complete Fertility Centre also has an infertility support group: http://www.completefertility.co.uk/infertility_support_group.php

Patient Advice and Liaison Service:
Tel: 023 8120 6325. Email: patientsupportservices@uhs.nhs.uk

Will my taking part in the study be kept private and confidential?
Your data will be kept confidential—only the research team will see it.
We will store all your data securely. We will keep your name and contact details separate to your interview transcript which will be assigned an unique ID number. We will remove identifying names or places from the interview transcript so that your identity is not known to readers of it.

In our reports or publications, we will include things that people say in their interviews. We will always make this information anonymous—we will never use a person's own name. If there is any data that may identify an individual, we will not use it in reports or publications.

We may use your interview transcript for future research about preconception carrier screening. If you do not want us to, you can just let us know.

What will happen to the results of the research study?
We will publish the findings of the research in journals for people working in universities and in healthcare. We have also set up a website (http://www.southampton.ac.uk/cels) where you can read about the research. You can contact us or refer to the website if you would like a summary of the main findings.

Who is organising and funding the research?
The research team organising the study is professor Anneke Lucassen, dr. Angela Fenwick, dr. Sandi Dheensa and dr. Juliette Schuurmans, PhD-student.

Who has reviewed the study?
An independent group of people, called a Research Ethics Committee, review all research in the NHS. London City and East Research Ethics Committee has reviewed and approved this study. The REC reference number is 16/LO/1966

What do I do now?
If you would like to take part in this study, please complete the 'expression of interest' form. You can return it in the enclosed stamped addressed envelope or give it to a member of staff at the Fertility Clinic. A member of the research team will then collect the expression of interest sheet from the clinic. One of our team will subsequently contact you to discuss the study in more detail, and give you the chance to ask questions. If you still want to take part, they will arrange a suitable time and venue for the interview. You will then be asked to complete a consent form before the interview, which will give you another opportunity to ask any questions.

Further information
If you have any queries, please contact Juliette Schuurmans (023 8079 5082) js1v15@soton.ac.uk.

Thank you for taking the time to read this information.

Carrier Screening: Exploring the Experience in the Fertility Clinic

Expression of Interest Sheet.

I am happy to be contacted by a member of the research team

Name:……

Telephone nr:……

Email address:……

Date __/__/__

Please return in the stamped addressed envelope.

If you have lost the envelope you can return the sheet to:

Juliette Schuurmans, PhD-student;

CELS, MP 801, University of Southampton, Southampton General Hospital, South Academic Block, Tremona Road, Southampton SO16 6YD

Wessex Fertility

Written by…. Date

WHO IS THIS LEAFLET FOR

This information leaflet contains information for our patients who will be offered the option of carrier screening. This information leaflet will explain what this means for you as a gamete recipient or as a couple pursuing fertility treatment with your own gametes.

WHAT IS CARRIER SCREENING?

All our genes come in pairs and it is quite common to be a carrier of a condition, i.e. have one faulty copy of a gene and never know anything about it. This is because the working copy of the gene compensates for the faulty copy and keeps us healthy. Thus, often we do not know if we are carriers, because this causes us no health problems and we may not have any family history of the condition(s) in question.

Some genetic conditions arise as the result of a child inheriting two faulty copies of a gene, one from each parent. The parents are carriers of the condition, because apart from the faulty copy they also have a working copy of the gene to compensate for the faulty one. If a child inherits two faulty copies, they have the condition. This is called autosomal recessive inheritance.

Previously, we did not perform routine carrier testing of such conditions in prospective parents because each condition is individually rare and the chances of both members of a couple being a carrier for the same condition are very low (less than 0.1% or 1 in 1000 for most conditions).

Recent advances in genetic technology make it possible to test for many different carrier states in just one test (for the test discussed here we have included 70 conditions). By combining 70 different conditions we find that the overall chance that both members of a couple -or gamete donor and recipient- are carriers for the same genetic condition is around 1 in 150.

WHO IS THIS TEST FOR?

The test is performed before start of the treatment and is suitable for any couple pursuing treatment. This can be either treatment using their own gametes, or couples and individuals pursuing treatment using donor gametes. A ‘couple’ in this instance being defined as both gamete providers (i.e. you and the gamete donor).

WHAT DO WE TEST FOR?

We have chosen to combine 70 inherited conditions because they start at a young age and meet one or more of the following criteria:

- The disease is not curable.
- The disease is usually difficult to treat.
- A child with the disease is likely to be severely physically disabled.
- A child with the disease is likely to be severely developmentally delayed.
- A child with the disease is likely to die at a young age.

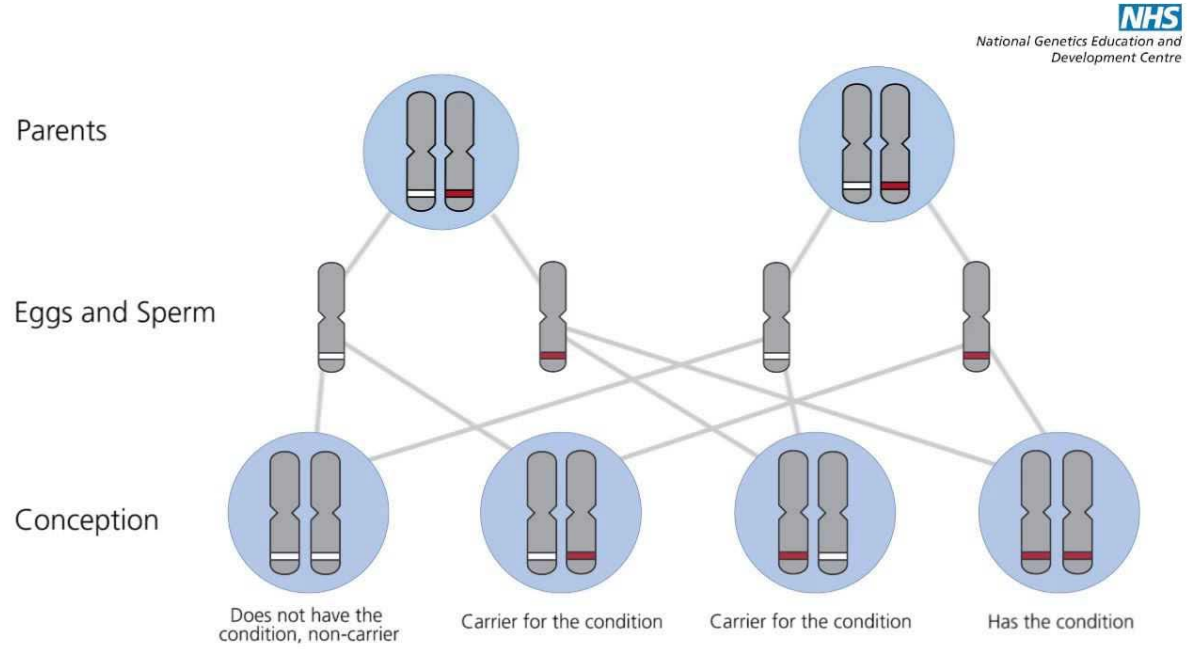
The test also includes some diseases that are treatable only if they are diagnosed early and treatment begins very soon after birth. A full list of conditions included can be found by visiting the following website: www.couplecarrierscreening.umcg.nl

WHAT IS THE CHANCE OF BEING A CARRIER COUPLE AND WHAT DOES THIS MEAN?

The chance of being a carrier couple for one of the tested conditions is approximately 1 in 150. If a family member has already been diagnosed with such a condition, or if **both gamete providers are related biologically** (i.e. cousins), the chances of being carriers could be higher.

The test is offered as a 'couple test', because the test result only has health implications for the future child, if we combine the result of both gamete providers. The test will result in one of two outcomes:

- both gamete providers are a carrier for the same genetic condition X.
- both gamete providers are not a carrier for the same genetic condition included in the test.



If both gamete providers are found to be a carrier couple for the same condition (red bar), there is a **1 in 4 chance (25%)** of having an affected child with each and every pregnancy**.**

If both gamete providers are not a carrier couple for any of the conditions in the test, there is still a very small chance of having a child with one of the conditions, as the test cannot 100% guarantee the detection of all carrier states. The residual risk is however extremely low

WHAT ARE THE COSTS INVOLVED?

It is £1500 for the Preconception Couples' Carrier Screening. Samples are processed at the Department of Genetics, Universitair Medisch Centrum Groningen in The Netherlands.

HOW DO I TAKE THE TEST?

You will have the opportunity to discuss preconception carrier screening with a consultant at your initial consultation. If you decide the test is for you, a blood sample is taken from both gamete providers, with results being available within 6 weeks. For patients using

donor sperm, we cannot offer the test for sperm purchased from external sperm banks. Only locally recruited Wessex donors would be available to be tested.

WHAT HAPPENS NEXT?

If both gamete providers are not a carrier for the same severe genetic condition, a treatment cycle will start as planned.

If both gamete providers are carriers of the same genetic condition, there are several options available:

For recipients of a donor:

- You will be matched with a different donor

For couples using their own gametes to conceive:

- Conceive as planned and perform a prenatal test to see whether or not the pregnancy is affected. If it is, termination of pregnancy might be considered.
- Consider preimplantation genetic diagnosis (PGD) and embryo selection, whereby only unaffected embryos are transferred in treatment. *Please note PGD is not available at Wessex Fertility, and a referral would be made to pursue this.*
- Conceive as planned and accept the increased risk of having a child with a severe inherited condition.
- Choose to use a donor
- No further treatment and exploring options of adoption.

Genetic support and implications counselling is available for patients if required.

RESEARCH STUDY AT THE UNIVERSITY OF SOUTHAMPTON

Along with the introduction of the Couples' Carrier Screening, we are working with the University of Southampton to take part in a study to explore the use of such carrier screening in a fertility clinic, and the experience of participants.

Patients are invited to take part in the study, which involves one or two discussions with the research lead – one after your consultation, then a second after your results. You will be provided with a further information sheet detailing the study and your involvement. Participation is voluntary, and patients can withdraw at any time – you may still proceed with the couples' test if you choose not to participate in the study.

Wessex Fertility

Written by…. Date…..

WHO IS THIS LEAFLET FOR?

This information leaflet contains information for our altruistic gamete donors about a genetic test that we are offering to our patients. We are now offering the option of carrier screening for gamete recipients and their donors. This information leaflet will explain what this means for you as a gamete donor.

WHAT IS CARRIER SCREENING?

All our genes come in pairs and it is quite common to be a carrier of a condition, i.e. have one faulty copy of a gene and never know anything about it. This is because the working copy of the gene compensates for the faulty copy and keeps us healthy. Thus, often we do not know if we are carriers, because this causes us no health problems and we may not have any family history of the condition(s) in question.

Some genetic conditions arise as the result of a child inheriting two faulty copies of a gene, one from each parent. The parents are as carriers of the condition, because apart from the faulty copy they also have a working copy of the gene to compensate for the faulty one. If a child inherits two faulty copies, they have the condition. This is called autosomal recessive inheritance.

Previously, we did not perform routine carrier testing of such conditions in prospective parents because each condition is individually rare and the chances of both members of a couple being a carrier for the same condition are very low (less than 0.1% or 1 in 1000 for most conditions).

Recent advances in genetic technology means it is now possible to test for many different carrier states in just one test (for the test discussed here we have included 70 conditions). By combining 70 different conditions we find that the overall chance that both members of a couple -or gamete donor and recipient- are carriers for the same genetic condition is around 1 in 150.

WHO IS THIS TEST FOR?

The test is performed before start of the treatment and is suitable for any couple pursuing treatment. This can be either treatment using their own gametes, or couples and individuals pursuing treatment using donor gametes. A ‘couple’ in this instance being defined as both gamete providers (i.e. you and the recipient).

WHAT DO WE TEST FOR?

We have chosen to combine 70 inherited conditions because they start at a young age and meet one or more of the following criteria:

- The disease is not curable.
- The disease is usually difficult to treat.
- A child with the disease is likely to be severely physically disabled.
- A child with the disease is likely to be severely developmentally delayed.
- A child with the disease is likely to die at a young age.

The test includes also some diseases that are treatable only if they are diagnosed early and treatment begins very soon after birth. A full list of conditions included can be found by visiting the following website: www.couplecarrierscreening.umcg.nl

Wessex Fertility

WHAT RESULTS ARE PROVIDED?

The test is offered as a 'couple test', because the test result only has health implications for the future child, if we combine the result of both gamete providers. This means that you **will not receive the results of the carrier screening**. The test will result in one of two outcomes:

- both gamete providers are a carrier of the same genetic condition X.
- both gamete providers are not a carrier of the same genetic condition included in the test.

WHAT DOES THE TEST-OFFER ENTAIL FOR ME?

STEP 1:

You will have the opportunity to discuss preconception carrier screening with a consultant at your initial consultation. If you agree to testing and you are matched with a recipient, they will then decide if this test is for them. We would ask you to attend for an additional blood sample to be processed. The results will available within 6 weeks, and you will need to await the results before proceeding with a treatment cycle.

STEP 2:

After the test has been done, there are two possible scenarios:

- If you and your recipient do not carry the same genetic condition, a treatment cycle will start as planned.

- If the test result indicates that both the donor and recipient carry the same genetic condition, the **recipient will be informed,** as the risks of having a child with that disease are greatly increased (1 in 4 or 25% for each and every pregnancy). The recipient will then be matched with a new donor who does not have the same carrier status.

Genetic support and implications counselling is available for patients if required.

Appendix C Examples of coding for thematic analysis

C.1 Focus group transcript

P4: Yeah, I think of little, it might potentially it increases stress, [ECS in fertility causes stress]

just for what everybody else says, [agreement amongst participants] it might increase the stress considerably, and the big question is whether there is any benefit to that.[balancing harms/benefits of test offer; questioning benefits]

If somebody is in a couple and they do want to have a child, and they do find out that potentially there might be something wrong with their child, [before conception there is not child yet, prenatal/preconception confusion?] what do they do then! [implications of positive test result]

[new topic] It's a completely unexplored territory; it's so brand new, science is obviously still investigating what our options are out there and what couples do with that information,[need for research amongst target population] in that case, would they rather not know; you might wonder. [HCPs try to imagine what couples would do]

P3: I think my issue is [HCP expressing concern], it's that you're looking at a carrier, so, are you screening the couple, so if there's an issue of a couple, then obviously that's going to affect treatment [couple result is relevant for further treatment options] but if you're looking at an individual, is that then going to put a strain on their relationship if one's a carrier [reporting individual carrier state may affect relationship; example of harm of individual carrier state] still might not have any future impact later,[individual carrier state is not relevant for current reproductive plans] but then if they split and he or she goes elsewhere, that's my problem [perceived relevance of individual carrier states for reproductive decisions in the future] is it's a bit of a confused knowledge [difficult concept; potential for misunderstandings], could be one individuals fault[impact of being a carrier for an AR condition: could cause blame/guilt].

P5: But they only get the results for the couple, [HCPs trying to understand the concept of couple testing through discussion]

P2: which again is another ethical, so you don't get your own individual results ['right to know?'; not reporting individual carrier states is an ethical issue for HCPs].

P3: But then that bothers me as well [HCPs agree amongst each other; worry about not reporting individual carrier states].

I: Why would that bother you specifically?

P3: I think it's if they then, you know a lot of couples do split up over IVF because it's so stressful,[IVF is stressful] if they think well I'm in the clear, it's fine, and actually they are a carrier[potential for misunderstand couple result as definitely not being a carrier as an individual], a single person is a carrier, that could then be an issue later down the line for them [perceived relevance of individual carrier states] that would be my worry [HCP expressing concern about not reporting individual carrier states].

P5: And that they wouldn't know.

P3: And they wouldn't know, yeah.

P4: Can they demand this information['right to know']? Like you know, does the carrier, is it under the Data Protection Act, something?[what does the law say about not reporting individual carrier states?]

P2 My understanding is, you can't, so, [HCP has correct understanding of concept of couple testing; explains what she believes a couple test means]

if you know I'm a man, you're a lady, and we have a couple screening, we don't get, the information held is purely as a couple, because you'll be a carrier, we'll all be carriers of something, we'll all be carriers for three or four something or other, so only if they matched, you'd get a positive result, and that's where it's sort of flagged-up, the issues around the donor, because we felt the ethical problems around that was having a donor test that only ever ran through [issue with gamete donation and couple testing]

C.2 Interview transcript

I: so if I understand correctly, you would be… Would you be interested in having a test like this,

Emily: yeah, I think it if timing was not as immediate, [timing of the test offer as a factor influencing couples decision making] I would have thought even more carefully about the implications [implications of test result important in decision making] , because you're making a decision that could change your whole life. That sounds very dramatic, but I'm already making the decision to have a baby. But there is a whole world of difference between having a healthy baby and having a genetically deformed baby and I think.. I have enough immediate friends and colleagues that have [experiences of friends and family] that, I have a boss who has a severely autistic daughter and I think that is a genetic, because I know that there is genetic and non-genetic autism, but she is never going to progress passed two or three years old [seriousness how a condition affects a child's development/life]. And he talks very candidly, you know very truthfully [impact of having a child with a genetic condition on parents] about he feels that his parenthood was robbed from him, cause all those things that he thought he was going to do with his child ,were taken from him when she was diagnosed very early on, at sort of within six months, because she is always going to be a toddler, as she is always going to need help and his whole life is now about funding the future for her when he is not there anymore. So you know, I see things like that, as much as you can be very excited about having a baby, and it can change your life and not necessarily for the better [reproductive decisions can be life changing]. And likewise I think I mentioned on the phone that my sister had a baby and ehm,[experience of friends and family] it was her first and they had a very difficult struggle on the second scan, because Niece was recognised as having deformities, and they could see that there was a problem I think with the hand, but they weren't entirely sure what else it affected, [uncertainty] End of excerpt 1

Start of excerpt 2:

I: and now we come with the genetic testing, cause could you tell me a little bit about what you've got from the conversation with Consultant, and what you've read from the information, what do you think this test is about?

Olivia: my understanding is that John is screened to see if there are any defective genes in his gene-pool and hopefully we will find a donor, and then the donor, if they are happy to and they consent, then they will be screened also, and it's not about whether they age have defective genes, because they may well do, because we all have them, because it's about whether they have the same defective gene in the same place, because when they both carry the same defect, that's potentially when there could be an issue, [exploring understanding of couple testing]

when they both have a defect in the same place, and I think that's the only incidence when the clinic would tell us when there is a defective gene, cause when there is something anywhere else, different places, they don't need to tell us

I: is that also what you understood?

John: that is what I was saying, yeah that is what I understood as that being the purpose, and then there is some sort of secondary question about sort of about my, sort of why I want to have that done I suppose, [motivations for undergoing ECS] ehm, which for me that is, I may have explained over the phone, there are two reasons really, one I don't think any couple wants a child, you know wants a , oh sorry, all couples who have a child want a healthy child [desire to have a healthy child], and even with W, even with my first born, it was always a bit of a fear, you know, what if, there is something wrong, what if, we end up with a child that is mentally handicapped or physically handicapped, and I'm not sure if I would cope with that, [fear of not being able to cope with a child with a serious conditions as a motivation to undergo ECS] f I'm perfectly honest, all I know is that it puts a massive strain on relationships, on the siblings,[impact of having a child with a serious illness on the family] so in my mind, I want to, like most thing you do in life, minimise that risk, but you can never sort of completely [desire to minimise risks/maximise chances of having a healthy child]

Olivia: there are never any guarantees [understanding of risks around pregnancy]

Glossary of Terms

The words testing and screening might cause confusion because they refer to different, but related concepts and depending on the context the same word may have multiple meanings. I discuss two meanings of the word screening as used in this thesis: screening as a test offer; and a 'screening' test.

Carrier test (for autosomal recessive disease): a test, which aims to identify the presence or absence of a genetic biomarker to determine an individual's carrier status, irrespective of the context in which the test is commissioned or performed (i.e population screening or clinical setting).

1: Screening as a test offer (of which carrier screening is an example):

The systematic application of a genetic or non-genetic test or enquiry to people who are asymptomatic but are being invited or encouraged to take part with the purpose of detecting risk factors for disease or abnormalities or disease or abnormalities in an early, actionable stage (10,272,273). Screening can be offered to detect individuals (at risk of) having a serious, but treatable illness *themselves*, but also to individuals or couples to detect those who are at increased risk of having *children* with a serious illness (=reproductive risk). Knowledge of reproductive risk enables individuals or couples to make more informed reproductive decisions.

Population screening (bevolkingsonderzoek in Dutch) as defined by the Dutch Health Council, is a specific form of screening which is offered and initiated by for example a health care professional, and not requested by the individual. Population screening defined in this way is not limited to screening offered to a subsection of the population (such as breast cancer screening), e.g. as a screening programme offered by the health authorities, but could also be an offer of screening to individuals (2). Thus, an ECS test offer to couples provided by GPs or midwives without those couples specifically requesting such screening would fall within this definition of population screening. This type of screening falls under the Dutch Population Screening Act (WBO). A license is required for population screening that aims to detect untreatable conditions. Carrier screening for reproductive risk is not a type of screening that requires a license, because the people who are screened are not at risk of developing the untreatable conditions in the test themselves. In the UK, the National

Screening Committee advises the UK government and the NHS about all aspects of population screening and supports implementation of population screening. Recommendations regarding population screening programmes are published on their website:

https://www.gov.uk/government/groups/uk-national-screening-committee-uk-nsc. (accessed 15-03-2020).

High-risk populations and couples: couples, individuals or groups from the population who are at increased prior risk of being a carrier (couple) of one or more AR conditions in comparison to the background population to be a carrier (couple) for those conditions. Once identified as being at prior risk of having children with specific AR conditions, these couples or individuals can be referred for genetic counselling and are offered carrier screening for these conditions (1).

Consanguineous couples are also at a priori increased risk of having children with AR conditions in comparison to the background population (270). As it is unknown for what AR conditions children of consanguineous couples are at increased risk, unless there is a family history, these couples could be offered ECS, rather than a targeted panel of specific conditions as is done in ancestry-based carrier screening (274).

General population: individuals or both members of a couple who do not belong to high-risk populations or couples (1). Whilst couples accessing fertility treatment may not be able to conceive naturally, this does not usually mean that they have an increased risk of having children with genetic conditions. Therefore, couples accessing fertility treatment fall within this definition of general population.

Ancestry-based carrier screening: carrier screening in high-risk populations based on ethnicity or geographical origin (1). The tests used for screening include genes for conditions that are relatively more frequent in certain populations. For example, carrier screening for Tay Sachs disease in Ashkenazi Jews, carrier screening for thalassemia in people from Cyprus or Sardinia.

Target population for ECS: The invited population who are offered screening usually has a higher *a priori* risk as a whole. The target population for screening as is used in this thesis is defined as couples (women and their partners) of reproductive age with a wish to have

children (Phase 1) or couples using artificial reproductive technology and those using donated gametes to conceive (Phase 2).

2: ECS as a screening test

Usually, the first step in distinguishing between screening and diagnostic testing is the aim of the test. The definition of a diagnostic test is a test aimed 'to establish presence/absence of disease', or, in case of presymptomatic genetic testing, presence or absence of disease risk (such as a BRCA1 mutation that runs in a family). The aim of a screening test is 'to detect (carriers of) potential disease indicators' An ECS test aims to identify individuals, or in this thesis, couples, who have an increased (i.e. 25% chance) reproductive risk to pass on genetic conditions included in the test and could be considered a screening test. The UMCG ECS test that was used in Phase 1 and 2 of my research was a targeted NGS Agilent SureSelect specified panel for 50/70diseases and 70/90 genes, which aims to identify all (likely) pathogenic mutations and has high sensitivity and specificity (86).

Clinical utility: in its narrowest sense, this concept means how useful a test result is in informing clinical decision-making. For example, when a test result is diagnostic for insulin-dependent diabetes, insulin therapy can be prescribed. With advances in genomics, a broader interpretation of clinical utility is more common. That is to say, clinical utility could also refer to how useful a genetic test result is to inform reproductive decisions or whether any psychosocial benefits exist (e.g. predictive genetic test for Huntington disease). In this thesis, when I refer to clinical utility, I mean that information regarding the chances of having children with AR conditions based on the results of an ECS test which couples can use to make reproductive decisions falls within this definition.

I have adopted the following working definition of **expanded carrier screening (ECS)** for this thesis: A screening test for carrier status of multiple AR conditions simultaneously, to couples or to individuals utilising donated gametes who are not previously known to be at increased risk compared to the general population of having children affected by the AR conditions included in the test. Others have also defined ECS irrespective of ancestry as Universal Expanded Carrier Screening (UCS)(275). Given that the UMCG test was developed with the Dutch general population in mind, I use the term ECS and not UCS.

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