

1 Feasibility of couple-based Expanded Carrier Screening offered by general 2 practitioners

3 **Running title:** Feasibility of GP-provided ECS

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9 **keywords**

10 expanded carrier screening, feasibility, general practice, informed choice

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29 **Conflict of interest**

30 The authors declare no conflict of interest.

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34 Abstract

35 Expanded carrier screening (ECS) aims to inform couples' reproductive choice, preferably
36 before conception. As part of an implementation study in which trained general
37 practitioners (GPs) offered a population-based ECS couple-test, we evaluated the feasibility
38 of the test-offer and degree of participant informed choice (IC). Trained GPs from nine
39 practices in the northern Netherlands invited 4,295 female patients aged 18-40 to take part
40 in couple-based ECS. Inclusion criteria were having a male partner, planning for children and
41 not being pregnant. We evaluated the feasibility of the organizational aspects, GP
42 competence and the content of the pre-test counselling. Participant satisfaction, evaluation
43 of pre-test counselling and degree of IC were measured using a longitudinal survey. We
44 explored GP experiences and their views on future implementation through semi-structured
45 interviews. 130 consultations took place. All participating GPs were assessed by genetic
46 professionals to be competent to conduct pre-test counselling. Most (63/108 (58%))
47 consultations took place within the planned 20 minutes (median 20, IQR 18-28). GPs
48 considered couples' prior knowledge level an important determinant of consultation length.
49 91% of patients were (very) satisfied with the GP counselling. After pre-test counselling,
50 231/237(97%) participants had sufficient knowledge and 206/231(88%) had a positive
51 attitude and proceeded with testing. Our pilot demonstrates that offering couple-based ECS
52 through trained and motivated GPs is feasible. Future large-scale implementation requires a
53 well-informed general public and a discussion about appropriate reimbursement for GPs
54 and health care coverage for couples. Providing (more) test information pre-appointment
55 may help reduce average consultation time.

56 Introduction

57 Next generation sequencing enables simultaneous screening for carrier status of many
58 genes associated with autosomal recessive (AR) conditions and some X-linked conditions,
59 called expanded carrier screening (ECS)¹. Where ECS is done prior to pregnancy, couples
60 found to be at increased risk of having a child affected by such a condition can consider
61 alternative reproductive options such as in vitro fertilization with pre-implantation genetic
62 diagnosis (PGT-M) or prenatal testing (PND) (with possible termination of an affected
63 pregnancy). However, a population-based ECS is not yet part of regular pre-conception care
64 in public health care systems, but several private companies and some academic centers
65 have started to develop and offer ECS tests for individuals or couples planning to conceive².
66 ECS aims to inform a couple about their risk of conceiving children with these genetic
67 conditions. In this paper, describing the first population-based implementation pilot of an
68 ECS test-offer by GPs, we decided to focus on severe AR conditions.

69 The Genetics Department of the University Medical Centre Groningen (UMCG) in the
70 Netherlands has developed and validated a couple-based ECS test for 50 AR conditions
71 associated with approximately 70 genes³. These conditions were selected because they are
72 early onset, serious diseases that result in severe physical or intellectual disabilities, severe
73 pain, or premature death. These criteria were recommended by an international expert
74 meeting at the UMCG in 2013, are supported by literature⁴⁻⁶ and current guidelines which
75 include criteria related to severity of illness¹. In the Dutch population approximately 1 in 150
76 couples are carriers for the same condition in this test⁷. For severe AR conditions, the risk of
77 being a carrier couple for an AR condition is about 1%⁸. The percentage of at risk couples
78 that can be identified through ECS in the general population depends on the composition of
79 the test-panel. For example, when 500 conditions (which are not all serious) are included,

80 detection rate is higher⁹ than in our (conservative) panel. Given that being a carrier of *any*
81 AR condition is common but the chance of carrying a particular condition is very low, it is
82 the positive combined 'couple-result' which conveys clinical utility for reproduction. We
83 therefore argue that a responsible approach to implementing ECS in a public health care
84 system is to offer it as a couple test and provide couple results only. This approach is
85 supported by the recently published Belgian guidelines¹⁰. In the test results, we report only
86 causal recessive variants, including known deleterious variants listed in databases (e.g.
87 Human Gene Mutation Database (HGMD), Biobase, Qiagen), and variants predicted to
88 truncate or affect gene expression.

89 We have previously reported that both health care professionals (HCPs) and the target
90 population support couple-based ECS in the general population with the GP as preferred
91 provider^{3,11}, and other studies have demonstrated that carrier testing for single-gene
92 disorders such as cystic fibrosis (CF) and hemoglobinopathies in primary care is feasible and
93 acceptable^{12,13}. More than 99% of the Dutch population are registered with a GP¹⁴, and
94 most GP care is included in the mandatory health insurance package all Dutch citizens carry.
95 In the Dutch healthcare system, GPs play a central role as gatekeeper for secondary or
96 tertiary care¹⁵, which makes extending their current preconception care responsibilities to
97 include a population-based ECS offer a logical approach. We therefore investigated whether
98 test-provision by GPs could be a feasible approach for ECS and result in informed choice of
99 couples who attended pre-test counselling. As most general HCPs lack the skills, confidence
100 and knowledge to communicate clinical genetics issues^{1,16-18}, we designed and provided
101 training to GPs and subsequently performed an implementation study where these trained
102 GPs offered the UMCG ECS-test to couples from the general population. This current study
103 is part of a larger study on the feasibility, uptake, and psychological impact of the test-offer.

104 **Methods**

105 **Provision of ECS test-offer and care:** Figure 1 displays the ECS test-offer and provision of
106 care. By sending out an invitation letter, participating GPs offered all potentially eligible
107 women registered in their practices the opportunity to take part in the ECS testing program.
108 Couples who were interested in the ECS test could make an appointment for pre-test
109 counselling with the inviting GP. Afterwards they would decide whether or not to proceed
110 with testing. The ECS-test was only accessible to couples who received pre-test counselling
111 and couples were required to attend pre-test counselling together.

112 Trained GPs were asked to provide pre-test counselling about ECS in combination with
113 general preconception care (GPC) advice (e.g. advice about folic acid supplementation,
114 cessation of alcohol use or smoking). For this counselling, a double-consultation time was
115 available (20 minutes). Referral to the Clinical Genetics department of the UMCG was
116 available for couples identified to have prior increased risk, e.g. due to suspected family
117 history of a genetic condition. Couples who proceeded with the ECS test could give a blood
118 sample using request forms provided by the GP. The UMCG Genomics Laboratory
119 performed the test. With a turn-around time of 8 weeks, GPs received a result for couples
120 who provided blood samples and then communicated the results to them. A couple was
121 considered a carrier couple if *both* couple members have a class IV or V variant in one of the
122 recessive disease genes included in the test.

123 Carrier couples, but also non-carrier couples with remaining questions, could be then
124 referred to Clinical Genetics for post-test counselling. We also launched a publicly accessible
125 website with general information about the 50 AR conditions, the ECS test, and related
126 procedures (www.dragerschapstest.umcg.nl). The research team, including the genetic

127 counsellor involved, could be contacted through the website. There were no patient
128 expenditures associated with the study and test-participation. PGT-M and PND for serious
129 conditions such as those included in this ECS-test are available to high risk couples. In the
130 Netherlands, costs of PGT-M and prenatal testing are covered by statutory health insurance.

131 **Study Design:** Figure 1 also depicts the study design. We used a mixed methods longitudinal
132 design with four study time points (T0-T3), with couples and GPs as study participants. GPs
133 were asked to evaluate each individual pre-test counselling at T1. At T3 they were invited to
134 take part in semi-structured one-to-one interviews to explore their overall experience with
135 test-provision. A genetics professional involved in the training supervised the first two pre-
136 test counselling sessions of each GP. Couples were asked to fill out an online survey. Couples
137 who attended pre-test counselling received three (T0, T1, T3) to four (T0, T1, T2, T3)
138 questionnaires, depending on whether they accepted the test-offer. The study protocol was
139 approved by the UMCG Medical Research Ethics Committee (METc 2015/384).

140 **Recruitment of GPs:** Study participation was open to GPs in the catchment area of the
141 UMCG. Staff from the Genetics Department and the Department of General Practice first
142 approached potentially interested GPs personally and a recruitment message was added to
143 a newsletter for GPs. GPs from 34 practices received the study information. Nineteen GPs
144 from nine practices agreed to participate. One practice (no. 9) withdrew during the study
145 because they were too busy to facilitate study participation. No further invitations were
146 sent, but participants already included could still attend pre-test counselling, and proceed
147 with testing.

148 Prior to the start of the study, all GPs were required to participate in a 2.5 hour training
149 session about pre-test counselling developed by the research team. This training session

150 included background information about ECS and other general aspects of preconception
151 care and an interactive session about reproductive genetic pre-test counselling. An
152 information booklet was provided to complement the training that provided background
153 information and a counselling guideline with important items to discuss. Two weeks after
154 the training, all GPs filled out an online questionnaire testing their knowledge. GPs received
155 individualized feedback on their incorrect answers prior to start of the counselling. Support
156 from the clinical genetics professionals was available as needed throughout the study.

157 **Recruitment of Couples:** Between January and December 2016., participating GPs selected
158 and invited all potential eligible women aged 18-40 registered in their practices to
159 participate. Eligibility criteria were not being pregnant, having a (male) partner and planning
160 to have children with this partner. Pregnant women were excluded, because the turnaround
161 time of the test-result was a maximum of eight weeks at that time. Additionally, the extra
162 skills probably needed for 'urgency counselling regarding ECS in pregnancy' requires
163 different counselling skills of GPs were not yet part of our preparatory training. The women
164 were asked to invite their partners in the study. Couples who were interested in the ECS test
165 could make an appointment for pre-test counselling with the GP after both partners had
166 given written consent to participation. They could decide whether to proceed with testing
167 after attending this appointment. Invitations were sent by mail and included a letter signed
168 by the GP, a response card and an information leaflet. This test information leaflet consisted
169 of the type of conditions included in the test, the chances of being a carrier couple and of
170 having an affected child, reproductive options available for carrier couples, and test
171 procedures. It also included a link to the website for further information. Women who were
172 eligible and interested in participating received more detailed study information.

173 **Measures:** Feasibility was evaluated in terms of the organizational aspects of this GP-
174 provided ECS test offer and the provision of care, with a focus on the pre-test counselling.
175 We explored GP experiences and views on the ECS test to evaluate feasibility and improve
176 future implementation. We adopted Marteau et al., (2001)'s definition of IC, who developed
177 the Multidimensional Measure of Informed Choice (MMIC) to measure IC in relation to
178 prenatal screening for Down's syndrome¹⁹. A choice was considered "informed" if
179 participants had sufficient knowledge and accepted the test offer (in case of a positive
180 attitude) or declined the test-offer (in case of a negative attitude)¹⁹. Table 1 displays the
181 topics and items investigated, which are based on relevant literature^{1,16,17,20-22}. The
182 organizational aspects of the ECS test-offer were evaluated quantitatively as the time used
183 for pre-test counselling and qualitatively through analysis focused on barriers and
184 facilitators. Pre-test counselling was evaluated in terms of competence, content and
185 patient-satisfaction. Competence was judged by the genetics professionals after supervision
186 and evaluated by GPs during the interviews. Both couples and GPs evaluated the content.
187 Couples also rated their satisfaction with pre-test counselling. Specific measures,
188 instruments and details are described in Suppl. 1.

189 **Quantitative data and analysis:** Data on the duration of the consultation and items
190 discussed during pre-test counselling were collected by a checklist for GPs that was filled out
191 after each pre-test counselling (T1). The checklist included eleven items that GPs were
192 required to discuss during pre-test counselling (see supplemental information for list). They
193 were asked to indicate if they discussed the item (yes, somewhat, no), and if not, why not.
194 Data on items discussed during pre-test counselling (i.e. their perceived importance and
195 time spent on them), satisfaction with pre-test counselling and informed choice were
196 collected by couples' questionnaires using the Roqua online tool for confidential clinical

197 data collection²³. The IC measure consisted of five knowledge items capturing essential
198 information about ECS testing and two attitude items. We also asked couples to fill out
199 these knowledge items after pre-test counselling as part of our provision of care to verify
200 that couples who proceeded with testing were aware of the correct information. We would
201 call them for additional discussion if they answered any of the five questions incorrectly.
202 Couples could refrain from having the test after this additional information, which
203 happened in one occasion. Data on consultation duration, items discussed during
204 counselling, patient satisfaction, and informed choice were described using percentages,
205 mean (SD) or median (IQR) where appropriate, using SPSS IBM version 23.

206 **Qualitative data and analysis:** Ten semi-structured one-to-one interviews were held with
207 GPs. Two GPs who conducted counselling did not participate due to lack of time and the GP
208 who withdrew from the study did also not participate. A topic guide was developed
209 containing open-ended questions related to the feasibility aspects of this GP-provided test.
210 Interviews were conducted by a trained researcher (JS), audio-recorded and transcribed
211 verbatim. The average duration of the interviews was 41 minutes (range 20-60 min). Data
212 analysis was conducted according to the framework approach of Ritchie and Spencer²⁴.
213 Framework analysis follows a process of familiarization, summarising and coding, which
214 results in matrices presenting the data per theme and case to allow more in depth analysis
215 and comparison across interviewees. Atlas –ti (version.5.2.18 copyright 1993-2018 by
216 ATLAS.ti Scientific Software Development GmbH Berlin) was used to facilitate analysis. Two
217 researchers (JS, LvdH) independently coded the first three interviews, and differences in
218 coding were discussed until consensus was reached. LvdH subsequently coded all
219 interviews, including the first three, while JS coded parts of all interviews randomly and
220 where LvdH had doubts. Final thematic framework matrices were subsequently discussed

221 within the research group until consensus was reached. The preliminary conclusions were
222 returned to the interviewees for member checking²⁵. We received six forms, all confirming
223 our conclusions.

224 Results

225 Inclusion and response

226 Table 2 shows that 19 GPs attended the training and 130 couples attended pre-test
227 consultation of whom 117 proceeded with testing. Six trained GPs did not conduct pre-test
228 counselling for reasons unrelated to the study. A genetic counsellor conducted one of the
229 pre-test counselling sessions because one couple found out they were already pregnant
230 after they had made their GP appointment. This couple was excluded from the analysis. Ten
231 GPs participated in the interviews. 240/260 (92%) of the individual participants responded
232 to the evaluation of the pre-test counselling. GPs returned 116/129 (90%) checklists.

233 **Evaluation of organizational aspects:** 58% of the pre-test counselling sessions lasted 20
234 minutes or less, with a median (IQR) of 20 minutes (18-28), indicating that the allocated
235 time of 20 minutes was sufficient for the majority of sessions. Qualitative findings from GP
236 interviews are illustrated with quotes presented in Table 3. Several GPs noted that couples
237 were well informed beforehand, and that this helped them provide counselling within this
238 time. GPs expected pre-test counselling sessions to last longer, if couples were less well-
239 informed, or for couples with little educational background. Some GPs mentioned that over
240 time they developed a routine for conducting the counselling, which reduced the time
241 required for preparation and counselling itself. GPs were positive about attendance of both
242 partners at counselling because the couple-test affects both partners equally and because
243 they considered discussing GPC with both partners important. No carrier couples were

244 identified. GPs did not experience any barriers in communicating the normal results or to
245 referring any couples at normal risk to Clinical Genetics for additional pre- or post-test
246 counselling. GPs or their healthcare assistants communicated the test results by phone,
247 email, or a combination, and some provided the couples with the lab results letter as well.

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

261 GPs and couples evaluated the content of the pre-test counselling as follows. GPs indicated
262 that most aspects included on the checklist, apart from GPC and 'communication and turn-
263 around time of the test-result', were at least discussed 'somewhat' in more than 90% of
264 consultations. Some participants indicated that they thought too little time was spent on
265 discussing the conditions included in the test (55 respondents (23%)) and the follow-up
266 options for high-risk couples (38 respondents (16%)). Some GPs explained they did not

267 discuss each condition in detail, instead discussing the conditions as categories as explained
268 during the training. While GPs indicated that in 36 consultations (31%) they either “did
269 somewhat” or “did not” discuss couples’ reproductive values, more than 85% of participants
270 indicated that the time spent on their and their partners’ values was exactly right.
271 Most GPs were positive about combining ECS pre-test counselling with GPC. GPs
272 indicated that, for example, due to lack of time, they “did not” discuss GPC in 31% or
273 discussed it “only somewhat” in 14% of consultations. Some GPs explained during the
274 interviews that the counselling might become too complex preventing couples from
275 remembering both. GPC was considered important or very important to discuss by 159
276 participants (67%), of whom 19/159 (12%) thought too little time was spent on this. In
277 contrast, 167 participants (70%) thought the right amount of time was spent discussing
278 GPC.

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

286 **GP views on future implementation:** In line with our previous research, after having
287 offered ECS testing, GPs considered themselves as the most suitable providers for a
288 population-based ECS couple-test. Advantages they mentioned were the low-threshold
289 of GP care, their familiarity with their patients and their background. One GP mentioned
290 that ECS-provision as standard care by all GPs might not be feasible because not all may

291 be able to keep up with technological advances in genetics. Some GPs suggested that
292 only motivated GPs willing to do so should be trained to provide ECS. These GPs could
293 become specialized in (reproductive) genetics, just as some GPs are currently specialized
294 in areas such as palliative or elderly care. Potential barriers that GPs mentioned were
295 resistance to additional workload in already too busy practices or negative attitudes
296 towards ECS. The eight-week turnaround time in our study, was considered acceptable
297 by the GPs for non-pregnant couples. For future implementation, several GPs suggested
298 the laboratory could also send the test result directly to couples. Negotiations with
299 health insurance companies and policy makers were considered necessary to decide on a
300 proper reimbursement fee for test-provision and whether to include ECS in the statutory
301 health insurance package (Table 3).

302 **Discussion**

303 In this paper we have presented the design of our implementation study of a GP-provided
304 ECS couple-test and our results on its feasibility and the degree of informed choice in
305 couples attending pre-test counselling. Implementing ECS responsibly requires a novel
306 approach¹, and our previous research suggested an important role for GPs^{3,11}. Our study
307 demonstrates that implementing an ECS couple-test consisting of a limited set of severe
308 conditions in the GP setting is a feasible approach that results in an informed decision in
309 most cases.

310 Importantly, all participating GPs felt and were judged competent to conduct pre-test
311 counselling after being given training, supported by genetic professionals on demand, and
312 assisted by a counselling-checklist. Participating couples were very satisfied with GP pre-test
313 counselling and the Dutch Society of General Practitioners recently stated their support for

314 (more) studies investigating the implementation of ECS in primary care²⁶. This approach
315 therefore has the potential to address the concerns about the current lack of genetic
316 literacy and counselling skills among non-genetics HCPs providing genetic tests^{1,18-20}, and
317 our results can inform options for responsible mainstreaming in genetics.

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

323 A study of CF carrier testing in primary care showed that GPs could conduct the (less
324 complex) counselling in an average of 12 minutes¹². According to participating GPs, pre-
325 test counselling within the allocated time was facilitated because couples were already
326 well-informed, perhaps due to the extensive study information, website and the
327 questionnaires participants filled out.

328 Our results suggest that GPs could have extended their pre-test discussion of the
329 reproductive options available for couples who are found to be both carriers of the same
330 condition, which would also include an assessment of the value system held by that couple.
331 Such discussions are standard practice for GPs, but our future training could be adjusted to
332 focus more on these aspects in the preconception setting. Couples do not often request
333 preconception consultations from GPs or other HCPs in the Netherlands²⁷, thus an added
334 benefit of the ECS test-offer meant that GPs could discuss or follow-up on GPC advice with
335 more couples –and both partners- than was routine. Future research could also explore
336 whether prenatal carrier screening is feasible in this setting and what necessary adjustments
337 should first be made in training and test-delivery. In the study we required both partners to

338 attend pre-test counselling together and GPs agreed that it was preferable to include both
339 partners jointly in the discussion of ECS as this affects both prospective parents. To lower
340 practical barriers to attend counselling, in the future GPs could use web-consultations or
341 face-to-face consultations at times desired (evenings/weekends), although this requires
342 additional training and adjusted infrastructure.

343 **Considerations regarding large-scale implementation of ECS in primary care**

344 Our research concentrated on the offer of ECS within primary care. Eligible women were
345 actively and individually approached by their GP by letter. Large scale implementation could
346 also be a more passive and collective approach, e.g. via posters, leaflets and information
347 about the test on GPs' websites. However, this requires the public to become more
348 knowledgeable on this topic, which means more educational efforts would need to be
349 aimed at this group. Moreover, couples could fill out an online decision-aid in advance to
350 inform and prepare them and facilitate efficient and effective pre-test counseling. No major
351 barriers to large-scale implementation were mentioned by GPs in our study provided they
352 can use 20 minutes for the counselling and that there are no financial barriers for them and
353 their patients. Our results should inform discussions with relevant stakeholders to negotiate
354 reimbursement for the consultation as well as the test.

355 GPs in our study suggested that ECS could be provided by 'specialized' GPs who focus on a
356 specific aspect of GP care. Not all GPs may be interested in investing the time and effort
357 necessary to obtain and maintain the required counselling skills, considering that the total
358 number of counselling sessions per GP might be relatively low. The specialization approach
359 would guarantee the necessary minimum number of pre-test counselling sessions per GP
360 per year to maintain competence. GP specialization already exists in the Netherlands in
361 areas such as elderly and palliative care. Other primary HCPs involved in preconception

362 care—such as midwives, community pediatricians or nurse practitioners—might also be
363 willing to offer ECS. In all scenarios, the role of Clinical Genetics in a population-based ECS
364 couple-test could focus on education, support/auditing and post-test counselling for carrier
365 couples.

366 **A couple-based test for severe recessive conditions only:** Salient features of our approach
367 to ECS were the well-considered composition of the test-panel and the provision of couple-
368 only results for this population-based offer through participating GPs. The composition of
369 the panel facilitated a generic type of consent and the couple-based strategy resulted in a
370 minimal need for post-test counselling by the GP or Clinical Genetics professionals. As time
371 to discuss all conditions in detail is limited and some couples desire more information,
372 extensive information about the conditions should be easily accessible for couples, as was
373 the case on our website. Not disclosing individual results remains a matter of debate given
374 the perceived utility for cascade screening²², as well as the participants' personal
375 preferences of the participants²⁸.

376 We argue that previous cascade screening approaches disclosing individual results, e.g. for
377 relatively frequent conditions, are no longer helpful when switching to population-based
378 ECS, especially given that everyone is likely to be a carrier of one or more recessive
379 conditions. If ECS was well known to the public and to HCPs and there were no (financial)
380 barriers to participating, the new approach would be to offer ECS testing to all couples
381 wishing to reproduce. Whilst some have expressed concern that individual results are
382 important if couples split up, our response to this is that a new couple test, i.e. a re-analysis
383 of the couple's or one of the couple's stored data, could be done in those cases. In the
384 Dutch health care systems these data (and the DNA) are stored for these and other

385 purposes. A referral to Clinical Genetics would only be necessary for couples with
386 prior/suspected increased risk due to family and/or personal health history and/or ethnic
387 background. The approach suggested in this study applies for ECS aimed at AR diseases only.
388 Our couple-based approach for severe AR conditions could (and perhaps should) be
389 complemented with individual screening for more prevalent X-linked conditions like Fragile-
390 X and Duchenne Muscular Dystrophy. It is important to evaluate in future studies what
391 would be necessary additionally to facilitate counselling and test-provision and which
392 adjustment would be needed for responsible implementation in the Dutch public health
393 system. In this paper we focused on free couple-based ECS in the Dutch public health system.
394 We anticipate that for non-reimbursed ECS and ECS in a private setting, arguments for
395 couple-based or reporting of individual carrier results could well be different. A discussion of
396 these arguments is beyond the scope of this paper.

397 **Conclusions and recommendations:** This GP-provided couple-based ECS test for a limited
398 number of severe AR conditions in the setting of preconception care, presents a timely and
399 responsible option to inform couples planning a pregnancy about their chances of having a
400 child affected by a severe genetic condition. This approach was not only feasible in
401 our setting, but also led to an informed choice for most participants. Future national
402 implementation could involve other dedicated GPs, or other primary HCPs willing to be
403 trained to provide the test, given that support as well as practical tools from a clinical
404 genetics service are available. Furthermore, some factors identified in our study should be
405 considered such as raising public awareness to facilitate a well-informed population and
406 resolution of reimbursement issues. Our approach, that was feasible in the (northern)
407 Netherlands, might be transferable to other (European) public health systems with easily

408 accessible primary health providers who are willing to be trained and have the necessary
409 resources to offer ECS.

410 **Acknowledgments** We thank Kate McIntyre for editing the manuscript, the UMCG for
411 financial support (Healthy Ageing Pilot) and the University of Groningen/UMCG and the
412 University of Southampton for funding the joint-PhD position. We would also like to thank
413 the participating couples and GPs without whom this study would not have been possible.
414 Supplementary materials are available at the EJHG's website.

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496 **Title and legends of figures:**

497 **Figure 1. Study design.** This is a mixed-methods longitudinal study in which assessments
498 were made at four time points (T0-T3) through either questionnaires and/or semi-
499 structured interviews, with couples and participating GPs as study participants.

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