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Clinical Impact of Somatic Genomic Testing on Breast Cancer Care

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Abstract

Developments in our understanding of the molecular biology of breast cancer have had a direct impact on the investigations needed to provide optimal breast cancer care. Somatic genomic tests are now used routinely to inform decisions regarding adjuvant chemotherapy use in selected early breast cancer patients, and to identify patients with advanced disease who can potentially benefit from novel targeted agents.

In this overview, we describe the somatic genomic tests currently available within the National Health Service (NHS) for early and advanced breast cancer patients. We review the underlying biology and the evidence base for clinical utility of these tests in routine clinical practice. In addition, we identify the somatic genomic biomarkers currently in use in breast cancer clinical trials that are most likely to influence future breast cancer management. We also consider the challenges associated with tissue-based genomic testing in advanced breast cancer and the role of circulating tumour deoxyribonucleic acid (ctDNA) testing.

Key words: Breast cancer; Genomic test; Somatic test

Introduction

Tumour molecular features have been used to inform management decisions and provide prognostic information in breast cancer for over 30 years, in the form of oestrogen receptor (ER) and subsequently human epidermal growth factor receptor 2 (HER2) status. However, the last decade has seen a rapid increase in use of genomic data in breast cancer. Somatic genomic tests, investigating tumour-derived DNA or RNA, are now used routinely to inform decisions regarding adjuvant chemotherapy in selected early breast cancer patients and to identify patients with advanced disease who can potentially benefit from novel targeted agents. This review describes the somatic genomic tests currently available within the National Health Service (NHS) for early and advanced breast cancer, as well as the somatic genomic biomarkers currently under investigation in clinical trials. We also consider the challenges associated with tissue-based genomic testing in advanced breast cancer and the role of circulating tumour deoxyribonucleic acid (ctDNA) testing. Constitutional (germline) genomic data are also becoming increasingly important in breast cancer management and this issue is addressed separately in the companion article (Cheah *et al.*, 2024).

Gene Expression Profiles (Molecular Profile Tests)

The landmark studies of Perou and Sorlie introduced the concept of categorising breast tumours according to ribonucleic acid (RNA) expression patterns with prognostic associations [1,2]. Several commercial gene expression profile tests have subsequently been developed for ER-positive HER2 negative breast tumours to provide individualised estimates of breast cancer recurrence risk. Each of these tests uses quantitative methodology to compare transcriptome expression of genes associated with breast cancer proliferation and metastatic spread with that of control genes. Complex algorithms are used to produce an overall score that estimates recurrence risk for the individual patient. The relative risk benefit from chemotherapy is then applied with the aim of identifying patients who will not

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receive significant absolute benefit to justify the addition of adjuvant chemotherapy and can therefore be spared cytotoxic drug-associated toxicities. Conversely, such testing may also identify patients at higher risk of recurrence than would have been estimated from traditional clinicopathological risk factors.

The National Institute for Health and Care Excellence (NICE) has approved three molecular profiling tests in early ER-positive HER 2 negative breast cancer: Oncotype DX®, Prosigna®, and EndoPredict®. NICE recommendations specify that patients are eligible for these tests if they have an intermediate risk of distant recurrence using a validated score such as PREDICT [3] or the Nottingham Prognostic Index [4] and test results will assist decision-making regarding adjuvant systemic therapies. NICE approval although NICE approval originally applied only to node-negative early breast cancer, this has recently been extended to include postmenopausal patients with 1–3 positive lymph nodes [5]. [Table 1].

Oncotype DX®

This test quantifies a 10-year distant recurrence risk in ER-positive, HER2-negative breast cancer patients and is the only molecular profile test that predicts relative treatment benefits from chemotherapy. The test is based on a reverse transcription-quantitative polymerase chain reaction (RT-PCR) 21 gene assay (16 genes associated with malignant behaviour and 5 control housekeeping genes) [6]. Key determinants in interpreting Oncotype DX results are the nodal and menopausal status of the patient. Oncotype DX was initially validated in the TAILORx trial, which included >10,000 women with ER positive node negative early breast cancer and demonstrated that endocrine therapy was noninferior to chemoendocrine therapy in patients with a mid-range recurrence score (11–25). There was some benefit of chemotherapy in patients aged ≤50 [7]. The RxPonder trial assessed chemotherapy benefit in 5083 patients with 1–3 positive nodes [8]. The trial reported that there was insufficient benefit from adjuvant chemotherapy in postmenopausal women with an Oncotype DX recurrence risk score of <25, whilst all premenopausal women benefitted from chemotherapy. Questions remain about the validity of RxPonder results in premenopausal women as there is lack of data on ovarian suppression.

Prosigna®

This test estimates distant recurrence-free survival at 10 years in postmenopausal ER positive HER2-negative early breast cancer. It measures the expression of 50 genes based on direct messenger ribonucleic acid (mRNA) counting using fluorescent probes and an nCounter Digital Analyser (PAM50 test). A combined analysis using data from the ABCSG-8 and TransATAC trials demonstrated that the Prosigna test could identify patients with 1–3 nodes positive early breast cancer in whom adjuvant chemotherapy could be safely omitted [9]. Currently Prosigna® is being further investigated in patients with larger and/or node-positive tumours in the prospective UK study OPTIMA [10].

EndoPredict®

This test predicts the likelihood of developing metastatic disease within 10 years of a diagnosis of early breast cancer. It assesses the expression of 12 genes through reverse

Table 1
Commercial molecular profiling tests available in the NHS for selected ER positive HER2 negative early breast cancers

Number of genes	21 gene assay	50 gene assay	12 gene assay
Method	Reverse transcription-quantitative PCR	Direct mRNA counting	Reverse transcription-quantitative PCR
Utility	Prognostic	Prognostic	Prognostic
Key clinical trials	TAILORx [6], RxPonder [7]	ABCSG-8 and ATC [8]	GEICAM 9906 [10]
Test location	Genomic Heath Laboratory U.S.A	Selected NHS laboratories	Myriad laboratory, Munich
Licence	Pre- and post-menopausal node negative ER+ HER 2 negative early breast cancer 1-3 nodes positive	Postmenopausal Node negative ER+ HER2 negative early breast cancer 1-3 nodes positive	Pre- and post-menopausal node negative ER+ HER2 negative early breast cancer 1-3 nodes positive
NICE recommendations	ER+ HER2-node negative disease with intermediate risk of recurrence. Post-menopausal ER+ HER 2 early breast cancer 1-3 nodes positive	ER+ Her2-node negative disease with intermediate risk of recurrence. Postmenopausal ER+ HER 2 early breast cancer 1-3 nodes positive	ER+ HER2-node negative disease with intermediate risk of recurrence. Postmenopausal ER+ HER2 early breast cancer 1-3 nodes positive
NICE guidance	https://www.nice.org.uk/guidance/dg58/chapter/1-Recommendations	https://www.nice.org.uk/guidance/dg58/chapter/1-Recommendations	https://www.nice.org.uk/guidance/dg58/chapter/1-Recommendations

transcription polymerase chain reaction (RT-PCR). EndoPredict® was clinically validated using RNA from patients in the GEICAM 9906 trial [11].

The Genomic Landscape of Breast Cancer

A diverse range of somatic genomic variants have been described in breast tumours, with the genomic landscape of primary breast cancers showing differences compared to metastatic breast cancer (MBC) [12]. The landmark Cancer Genome Atlas Program (TCGA described over 30,000 somatic mutations in 510 early breast tumours with 20 different genes being implicated [13]. *TP53* was the most commonly mutated gene (in 37% of tumours) followed by *PIK3CA* (36%). Only three genes were mutated in >10% of cases (*TP53, PIK3CA, and GATA3*). In the TGCA breast cancer cohort, 47 out of 507 patients had deleterious somatic and germline mutations in 9 different breast cancer predisposition genes, supporting the hypothesis that up to 10% of breast cancers may have a heritable component.

Breast cancer evolves with time, and treatment can cause the acquisition of new mutations, which may confer treatment resistance. Pearson *et al.* reported enrichment of *HER 2* (6.19%), *AKT1* (7.14%), and *NF1* (8.1%) mutations in a cohort of 210 MBC patients compared to the primary disease [12]. Of these, *NF1* mutations were most frequently acquired and not present in the primary disease. Loss of *NF1* also resulted in endocrine resistance through both ER-dependent and independent mechanisms [12]. Targeting these acquired somatic mutations could open new lines of treatment.

Genomic Biomarkers Currently Included in the NHS Genomic Test Directory

The following somatic genomic tests are currently available for breast cancer via the regional NHS genomic laboratory hubs [Table 2].

PIK3CA Mutations

The *PIK3CA* gene transcribes the p110α protein, a subunit of phosphatidylinositol 3-kinase (PI3K). Activating mutations in *PIK3CA* can cause rapid proliferation of cancer cells [14]. *PIK3CA* mutations are found in up to 40% of primary breast cancers and up to 53% of MBC and are a negative prognostic factor in ER positive HER 2 negative MBC. Alpelisib is an oral α-specific PI3K inhibitor that selectively inhibits p110α. The SOLAR-1 trial investigated the addition of Alpelisib to fulvestrant in ER-positive HER 2-negative breast cancer patients who had progressed on first-line endocrine therapy [15]. This trial showed a progression-free survival (PFS) advantage in patients with *PIK3CA*-mutated MBC receiving alpelisib and fulvestrant compared to those treated with placebo plus fulvestrant (11 months vs 5.7 months), but only 6% of patients had received prior cyclin-dependant Kinase 4/6 inhibitor (CDKi) therapy. The subsequent phase II BYLieve trial confirmed alpelisib activity in 121 *PIK3CA* mutated ER positive HER 2 negative MBC patients previously treated with CDKi, with a 12-month PFS of 50% [16]. In 2022, NICE approved alpelisib as a treatment option for *PIK3CA* mutated ER positive HER2 negative MBC patients who had progressed on aromatase inhibitor plus CDKi therapy [17]. INAVO 121, a phase III trial comparing alpelisib to inavolisib, a novel selective PI3Kα inhibitor, is currently recruiting [18].

Neurotrophic Tyrosine Receptor Kinase (NTRK) Gene Fusions

The NTRK gene family comprises *NTRK1, NTRK2,* and *NTRK3,* which encode tropomyosin receptor kinase (TRK) proteins (TRKA, TRKB, and TRKC) [19]. The TRK proteins regulate cell signalling, and NTRK sequence rearrangement can lead to uncontrolled cell growth. *NTRK* fusion gene rearrangements are found across a wide variety of tumours, but frequency varies significantly between different tumour types [20]. NICE approved the NTRK inhibitors entrectinib and larotrectinib for patients harbouring *NTRK* gene fusion rearrangements in solid tumours who had exhausted all current lines of treatment, based on data from multiple basket studies [21,22]. Testing for *NTRK* fusion genes is available for any metastatic solid tumour who would meet the NICE criteria for NTRK inhibitor therapy. However, the prevalence of *NTRK* fusion genes in breast cancers is less than 1% except in the rare secretory breast carcinoma where the *NTRK3* fusion gene prevalence is over 90% [23].

Genomic Biomarkers Under Investigation in Breast Cancer Clinical Trials

Oestrogen Receptor Alpha Gene Mutation (ESR1)

A common mechanism of acquired resistance to endocrine therapy in ER-positive breast cancers is the development of mutations in *ESR1*. *ESR1* mutations result in oestrogen-independent ER activation and resistance to aromatase inhibitors but not ER inhibitors [24]. The frequency of *ESR1* mutations is relatively low in primary breast cancer (0–3%), but between 6%-55% in ER-positive MBCs, which have progressed on endocrine treatment [25]. The Emerald phase III trial enrolled ER+ HER2-patients who had progressed on 1–2 lines of endocrine treatment and previously been treated with a CDKi. Patients were randomised to receive elacestrant (an oral selective ER degrader) or standard of care endocrine monotherapy (fulvestrant or an aromatase inhibitor) [24]. 47.8% of the patients recruited had a tumour with an *ESR1* mutation. The progression-free survival (PFS) in the elacestrant arm was superior to the aromatase inhibitor arm in all patients (hazard ratio (HR) 0.70), but greater benefit was seen in patients harbouring an *ESR1* mutation (HR 0.55; 12-month PFS 26.8% vs 8.2%). The European Medicine Agency has approved elascestrant for use in postmenopausal women, with ER-positive, HER2-negative, locally advanced, or MBC with an activating *ESR1*

Table 2
Other somatic genomic tests for breast cancer currently included in the national genomics test directory version 8 published 8 January 2024 [61]

Test	Target genes	Test scope	Technology/Tissue requirements	Breast cancer stage and subtype	Other eligibility criteria	Utility
Multitarget NGS panel	*PIK3CA*	Small variant detection	Panel Formalin fixed tissue	Stage IV ER positive, HER 2 negative	Molecular assessment will aid diagnosis or management	Predictive-metastatic. Licensed therapy available via Cancer Drug Fund (CDF) (Alpelisib)
Multitarget NGS panel	*NTRK1* *NTRK2* *NTRK3*	Structural variant detection	Panel Formalin fixed tissue	Stage IV Any subtype	Patient's clinical status means they are eligible for an NTRK inhibitor in the event an NTRK rearrangement is detected	Predictive-metastatic. Licensed therapy available via CDF (Entrectinib/ Larotrectinib)
FISH/RT-PCR	*ETV6* *NTRK3*	Structural variant detection	Targeted mutation testing Formalin fixed tissue		To support testing for suspected secretory carcinoma of the breast. Specialist pathology review indicates that molecular assessment will aid diagnosis or management	Diagnostic
*DPYD Hotspot	*DPYD*	Small variant detection	Targeted mutation testing Blood sample	Any stage Any subtype	Patient planned to receive fluoropyrimidine treatment	Predictive-pharmacogenomics
Whole genome sequencing (WGS)	WGS tumour and germline	All variant types	WGS Fresh frozen tissue	Any stage Any subtype	Patient has exhausted all standard of care diagnostic and management	Predictive- clinical trial access
Triple negative breast cancer WGS (Pilot)	WGS tumour and germline	All variant types	WGS Fresh frozen tissue + blood	Any stage Any subtype ER negative, HER2 negative	•Histologically proven TNBC •At any point in treatment •Routine standard of care testing should proceed in parallel.	Predictive- clinical trial access

*DPYD is included in the cancer NGTD but is a constitutional (germline) genomic test.

mutation who have disease progression following ≥1 line of endocrine therapy, including a CDKi [26]. It is anticipated that *ESR1* testing will be included within the NHS National Genomic Test Directory if elacestrant receives approval from NICE.

AKT

The phosphatidylinositol 3-kinase *(PI3K)/AKT* signalling pathway is frequently activated in triple-negative breast cancer (TNBC) (25%), as well as advanced ER-positive breast cancers (>50%) [27,28]. The mechanism is either through activating mutation in the *PIK3CA* or *AKT* genes and/or inactivating mutations in the *PTEN* gene [27]. AKT acts as a central hub in multiple signalling pathways, resulting in unregulated cell growth. Capivasertib is a highly selective small-molecule kinase inhibitor with activity against AKT1, AKT2, and AKT3 [27]. In the PAKT phase II trial, addition of capivasertib to first-line paclitaxel chemotherapy in metastatic TNBC resulted in a significantly improved overall survival (19.1 months vs 12.6 months HR 0.61) [27]. The median PFS was 5.5 months for the capivasertib group compared to 3.6 months for the placebo group (HR 0.64). Subgroup analysis indicated increased benefit with capivasertib in patients with *PIK3CA/AKT1/PTEN* altered tumours with a median PFS of 9.3 months compared to 3.6 months for the placebo group (HR 0.14) [27].

The phase II FAKTION trial investigated fulvestrant plus capivasertib or placebo after progression on an aromatase inhibitor in metastatic ER positive breast cancer [28]. A significant improvement in PFS was seen with capivasertib (10.3 months vs 4.8 months, HR 0.58, p = 0.0044) in the overall population. An initial prespecified analysis did not show significantly greater benefit with capivasertib in patients with an altered *PI3K/AKT/PTEN* pathway compared to wildtype patients [28]. However, a recent reanalysis using a more extensive set of genomic biomarkers to define an altered *PI3K/AKT/PTEN* in pathway reported improved PFS and overall survival (OS) in the expanded pathway-altered subgroup receiving capivasertib compared to the placebo group (median PFS: 12.8 vs 4.6 months; adjusted HR 0·44), but no statistically significant differences in PFS or OS in the subgroup with no identified pathway alterations [29]. The phase III CAPItello-291 trial (n= 708) has now reported a median PFS of 7.2 months with fulvestrant–capivasertib vs 3.6 months with fulvestrant-placebo in the entire trial population (n = 708) and a median PFS of 7.3 months (fulvestrant–capivasertib) vs 3.1 months fulvestrant-placebo, HR 0.5) in the 289 (40%) patients who had an *AKT* pathway alteration; this may similarly reflect differences in the sequences used to define pathway alterations and also potentially the testing of archived tissue, which did not include mutations acquired during subsequent treatment exposures [30]. In June 2024, the European Medicines Agency approved the use of capivasertib in combination with fulvestrant for the treatment of adult patients with ER positive, HER2-negative locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following recurrence or progression on or after an endocrine-based regimen [31].

HER2 Mutations

Amplification of the *HER2* gene is seen in around 20% of breast cancers and is usually associated with a poorer prognosis [32]. Overexpression of *HER2* results in activation of growth factor signalling pathways, including the *PI3K-AKT-mTOR* pathway, leading to uncontrolled cell growth. Since the introduction of systemic therapies targeting *HER2,* the overall survival of patients with HER2 positive breast cancer has dramatically improved [33]. Genomic profiling of cancers has now identified somatic mutations in *HER2* and *HER3,* which can occur without gene amplification [34]. A global phase II multi-histology basket study (SUMMIT) enrolled 141 patients, including 25 with breast cancer. The patients were found to have 31 unique *HER 2* and 11 unique *HER 3* mutations; however, only *HER2* mutations were seen in breast cancer [34].

Neratinib is a pan-HER tyrosine kinase inhibitor approved by NICE for extended adjuvant therapy of HER2-positive early breast cancer after adjuvant trastuzumab [35,36]. The phase II PlasmaMATCH clinical trial reported clinical responses in 5 out of 20 MBC patients with HER mutations treated with neratinib [37]. Another phase II trial (MutHER) looked at neratinib alone and in combination with fulvestrant in 40 patients with HER2 mutated, nonamplified MBC. Although this did not show superiority of adding fulvestrant to neratinib, responses were seen in patients receiving both neratinib single agent and the neratinib-fulvestrant combination [38].

Somatic BRCA Mutations

Germline *BRCA1* or *BRCA2* mutations are found in 5%–10% of breast cancer patients, but around 3% may have only somatic mutations with no underlying germline mutations [39]. Some *BRCA* pathogenic variants are not easily detected with standard somatic testing technologies. Therefore, a negative somatic test for *BRCA* mutation does not negate the need for germline testing where clinically indicated [40].

Poly-adenosine diphosphate ribose polymerase (PARP) is an enzyme that assists in repairing single-strand DNA breaks. PARP inhibitors (PARPi) block this enzyme, which leads to an accumulation of unrepaired single-strand breaks, which results in the collapse of the replication fork during DNA replication [41]. This leads to double-stranded breaks. Homologous recombination (HR) is a mechanism where cells repair double-stranded breaks. However, patients with germline ± somatic BRCA mutations are deficient in homologous recombination (HRD). Hence PARPi causes synthetic lethality in these patients with HRD where the cancer cells are unable to repair single strand as well as double strand repairs leading to cell death.

The PARPi olaparib and talazoparib have been licensed for second-line treatment of metastatic HER2-negative breast cancers with a germline mutation in *BRCA1*/*BRCA 2* based on data from the OlympiAD and EMBRCA trials, respectively [42,43] and talaozoparib has recently been recommended by NICE for this indication [45]. Adjuvant olaparib therapy for high-risk HER2-negative early breast cancer with germline *BRCA1/BRCA2* mutations is recommended by NICE [44]. Although PARPi are licensed for use in patients with somatic *BRCA* mutations in other tumour types (prostate cancer); in breast cancer, their use is currently limited to patients with germline *BRCA* mutations. Clinical trials are in progress to investigate if breast cancer patients with somatic *BRCA 1/BRCA2* mutations benefit from PARPi in the absence of germline mutations.

Homologous Repair Deficiency (HRD) Signatures

Up to 40% of familial and sporadic breast cancers can exhibit HRD [46]. Testing for HRD can involve detection of underlying driver mutations and/or nonspecific changes to the genome resulting from HRD. Genomic features associated with HRD include **i)** somatic mutations in key HR-related genes, **ii)** epigenetic silencing through promoter methylation, **iii)** frequent copy number variations, and **iv)** large-scale structural variants. Different HRD tests assess for variable combinations of these features [46]. Patients with *BRCA* mutations and/or HRD have DNA repair defects, which can confer sensitivity to agents that cause inter-strand cross-links, like platinum-based chemotherapy [47–49].

Studies in ovarian cancer have resulted in the licensing of PARPi for patients with HRD tumours, as well as those with

germline and somatic *BRCA* mutations. However, PARPi also shows activity in ovarian cancer regardless of *BRCA* or HRD status. Previous studies indicated that PARPi efficacy was minimal in breast cancer patients who are germline *BRCA* wildtype [42,43]. Clinical studies are now underway to investigate whether HRD is a predictive factor for PARPi responses in breast cancer patients without a germline or somatic *BRCA* mutation [50].

Tumour Mutational Burden (TMB)

TMB is defined as the number of somatic mutations per megabase of a sequenced genome as calculated from either whole genome sequencing or very large gene panels. It corelates with the tumour neoantigen burden, T-cell infiltration, and response to immune checkpoint inhibitors (ICIs) in many solid tumour types [51]. TNBC generally has a higher mutation rate than other breast cancer subtypes.

NICE have recommended atezolizumab and pembrolizumab with chemotherapy (paclitaxel or nab-paclitaxel) for treating metastatic programmed cells death 1 ligand 1 (PD-L1)-positive triple negative breast cancer on the basis of the Impassion 130 and KEYNOTE-355 trials [52,53]. PD-L1 has limitations as a biomarker due to heterogeneous expression, variable assay interpretation, and lack of standardisation [54]. TMB is already being used to predict benefit in melanoma, lung, urothelial, and colon cancers [54] but its predictive value in breast cancer is yet to be determined.

Whole Genomic Sequencing (WGS) in Breast Cancer

WGS is included in the NHS National Genomic Test Directory (NGTD) for any patient with advanced breast cancer who has exhausted all routine treatment options. Pilot studies offering WGS for patients with early TNBC are in progress at some sites.

Whole genome sequencing (WGS) refers to DNA sequencing of approximately 20,000 genes, including protein coding and nonprotein coding (including regulatory) regions. It is the most comprehensive genomic testing currently available in the clinical setting and can detect copy number variants (CNVs) and structural rearrangements more effectively than gene panel tests. NHS WGS additionally mandates sequencing of germline DNA in parallel to the tumour sample, and hence information regarding underlying cancer predisposition gene (CPG) mutations is also provided. WGS is available within the NHS for advanced cancers with the aim of identifying genomic features not otherwise listed in the NHS NGTD that may permit entry to genomically stratified early phase clinical trials whilst also collecting extensive genomic data for research purposes. Use of WGS in early TNBC is specifically being offered in order to explore the clinical utility of access to germline and somatic *BRCA1/2* and other breast CPG sequence data, as well as HRD and TMB, which are potential predictors of response to PARPi and immune checkpoint inhibitors (ICI), respectively. The NHS WGS pathway only accepts fresh frozen tumour samples in view of the higher DNA requirements for WGS compared to gene panel tests.

Sampling Techniques in Somatic Testing

Evolution of tumour phenotype with cancer progression has been well documented in breast cancer for many years, with multiple studies reporting variations in ER and/or HER2 status between primary and metastatic tumour samples, and between tissue samples from different metastatic sites or at different time points [55,56]. Next-generation sequencing (NGS) of ctDNA has rapidly garnered interest as a means of demonstrating the overall genomic landscape in metastatic disease through a simple blood test whilst sparing patients the risk and pain of tissue biopsy.

Studies of *PIK3CA* mutations have demonstrated high concordance between tissue and ctDNA testing [57]. The UK phase II platform study (plasmaMATCH) proved the feasibility of using ctDNA testing to select metastatic breast cancer patients for mutation-directed therapy [35] and concluded that ctDNA testing offered “rapid and accurate genotyping with sufficient clinical validity to be used in routine clinical practice”.

ctDNA is more likely to give false negative results than tissue testing, as not all tumours shed cells into the circulation; patients receiving a negative *PIK3CA* ctDNA test result should have a confirmatory tissue-based test. ctDNA tests are particularly attractive for genomic variants associated with treatment resistance as repeated blood tests are more acceptable to patients and require less hospital resources than repeated biopsies. The PADA-1 clinical trial has raised the intriguing possibility that longitudinal ctDNA-based assessments of emerging *ESR1* mutations could be used to direct changes in endocrine therapy in patients on first line CDK 4/6/aromatase inhibitor therapy prior to evidence of clinical progression with a beneficial impact on patient outcomes [58].

Tissue-based biopsies will still be needed for immunohistochemistry and for some copy number-based assessments [35]. However, ctDNA is likely to become an important companion diagnostic in the MBC setting, providing improved understanding of tumour biology and tracking the emergence of acquired resistance mutations.

The use of ctDNA liquid biopsies to detect and diagnose metastatic disease before it is radiologically visible has been well described in breast cancer and is also an exciting prospect for the future [59]. However, the clinical utility of this approach is not yet fully understood, and the European Society of Medical Oncology (ESMO) guidelines for ctDNA recommend that this remains a research tool at present [60].

Conclusion

Somatic genomic data are increasingly becoming part of the routine assessment of selected early and advanced breast cancer patients. Access to novel targeted agents will be reliant on access to appropriate companion genomic tests. Understanding the genomic landscape of primary and metastatic breast cancer is key to identifying the appropriate sources of tissue-based genomic testing. ctDNA

testing is less invasive for patients than repeated tissue biopsies; it offers an attractive opportunity to sample a more representative genomic landscape in metastatic cases and to track the emergency of resistance-associated mutations in real time.

Author contributions

This article was conceived and designed by EC. TH performed literature searches and wrote the first draft. RC, MR and EC reviewed and edited the article. All authors agreed on the final version of this article.

Conflict of Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: E.R.Copson reports a relationship with Astra-Zeneca that includes: consulting or advisory, funding grants, and speaking and lecture fees. E.R. Copson reports a relationship with Novartis that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. E.R. Copson reports a relationship with Daaichi-Sankyo that includes: funding grants. E.R. Copson reports a relationship with Roche that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. E.R. Copson reports a relationship with Menarini Stemline Oncology that includes: consulting or advisory. E.R. Copson reports a relationship with Pfizer that includes consulting or advisory and speaking, and lecture fees. E.R. Copson reports a relationship with SECA that includes: non-financial support. R. I. Cutress reports a relationship with SECA that includes nonfinancial support. M.Remer reports a relationship with Roche that includes: consulting or advisory. M.Remer reports a relationship with Daiichi Sankyo that includes: consulting or advisory. M.Remer reports a relationship with Eli-Lilly that includes consulting or advisory. M. Remer reports a relationship with Merck that includes travel reimbursement. M.Remer reports a relationship with MSD that includes consulting or advisory. M. Remer reports a relationship with Novartis that includes consulting or advisory. M.Remer reports a relationship with Bristol Myers Squibb that includes: consulting or advisory. M.Remer reports a relationship with AstraZeneca that includes consulting or advisory. M.Remer reports a relationship with Pfizer that includes consulting or advisory. M.Remer reports a relationship with Chugai that includes consulting or advisory. R.I Cutress reports a relationship with Astra-Zeneca that includes funding grants. E.R.Copson reports a relationship with Eli-Lilly that includes consulting or advisory and speaking and lecture fees. E.R.Copson is cancer lead for the NHS England Central and South Genomics Laboratory Hub.

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