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Position Paper

## European Breast Cancer Council manifesto 2018: Genetic risk prediction testing in breast cancer



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## Manifesto—call to action

Information about a person's genetic make-up is providing crucial clinical information about risk, prevention and treatment in breast cancer and other diseases and is a rapidly evolving field. Genetic tests that predict someone's risk of getting breast cancer are now widely available not only in national health systems but also commercially, including on the Internet, for low cost and frequently unregulated for quality and guidance. The results of such tests can be complex and misinterpreted if people do not have access to high-quality explanation and counselling and can lead to pressure on health systems if testing increases (such as with the 'Angelina Jolie' effect in the US and elsewhere).

It is important that genetic risk prediction in breast cancer is available to people and their doctors, and the European Breast Cancer Council (EBCC) recognises that people have freedom to obtain the latest genetic tests if they are unavailable through national health systems. But tests must be of high quality, and information must be interpreted by appropriate healthcare professionals to give people an accurate understanding; to inform evidence-based interventions; and to avoid possible harm, both physical and psychological, through unnecessary interventions and anxiety. Indeed, the European Parliament considered introducing a ban on all direct-to-consumer advertising of genetic tests in the forthcoming regulation on *in vitro* diagnostic medical devices, although this was not included in the final version.

We call on policymakers, health professionals and advocates in all European countries to:

- Ensure genetic risk testing in national health services is carried out according to the latest evidence-based guidelines, with informed consent and access to clinical geneticists/genetic counsellors, and is available in breast cancer services
- Act now to regulate commercial genetic testing products according to their safety and performance ahead of the impending EU In Vitro Diagnostic (IVD) Regulation 2017/746 and to protect against misleading advertising, including a requirement to provide links to official patient information sites of European and national bodies
- Ensure that informed consent, counselling and medical supervision are provided for all genetic tests that have high-risk implications as these will not be mandated by the EU IVD Regulation
- Inform health professionals such as primary care doctors about genetic testing and breast cancer risk and provide pathways to refer people to breast cancer services with specialists in clinical cancer genetics and genetic counsellors
- Ensure patients diagnosed with breast cancer receive the current standard of care for genetic and genomic testing by a multidisciplinary team in a breast centre or unit, including access to clinical cancer genetic specialists
- Encourage healthcare providers and health professionals to participate in European networks and research programmes about all aspects of genetic and genomic testing, including clinical and psychosocial impacts.

## 1. What is genetic testing?

In cancer, genetic tests are used for two main purposes:

- To identify faults in genes that have high risk for cancer and are inherited and also to assess the risk from lower risk genetic variations, with tests carried out usually on blood or saliva samples from healthy people or those with cancer
- To determine the genetic 'signature' of a cancer from a tumour sample so that it can be characterised for treatment where appropriate.

For inherited risk, apart from several high risk gene mutations, some known since the 1990s, genome sequencing – the approach pioneered in the Human Genome Project – is revealing more gene associations with risk. With this technique, researchers are homing in on 'panels' of genes and mutations that may confer small additional risk, including the most common type of genetic variation, single nucleotide polymorphisms (SNPs; known as 'snips').

Hereditary mutations are known as 'germline' or 'constitutional'; other mutations that occur in cells to cause cancer are called 'somatic' and are not inherited

and passed on, but researchers are finding that germline genes including those implicated in breast cancer can also be subject to somatic mutation.

It is a complex and rapidly moving area of human biology—and one that can profoundly affect people's outlook on their health and that of their family, and the way that society reacts in terms of healthcare provision and regulation of welfare and financial services such as life insurance. Left unregulated and unsupervised, genetic testing in relation to breast cancer can lead to psychological harm and irreversible decisions, such as having risk-reducing mastectomies, that people may come to regret. But genetic risk testing may also confer life-saving benefit and must be offered appropriately.

High-profile cases—such as that of film actor Angelina Jolie, who underwent a risk-reducing double mastectomy after finding that she is a carrier of a breast cancer causing gene and highlighted first in just one newspaper article [1]—have raised the profile of genetic testing and resulted in a massive increase in the rates of gene testing. In turn, the 'Angelina Jolie effect' has raised questions about whether there has been a net beneficial gain in terms of appropriate referrals and healthcare costs and about the communication of

information to the public and primary care professionals [2,3,4].

This manifesto focuses on genetic tests on healthy people to establish their inherited cancer risk as they are not currently subject to adequate regulation at present in most European countries. But we also mention genomic testing for people with breast cancer, to ensure that readers are clear about the spectrum of such tests and where they apply, in line with our previous manifesto on the imperative to establish universal multidisciplinary breast cancer units in Europe that include specialists in cancer genetics and genetic counsellors [5].

## 2. Genetic testing and breast cancer

### 2.1. Tests on healthy people

Most people know that a family history of breast cancer can increase a person's risk of developing the disease (we include both women and men when we refer to a person/patient). Breast cancer is one of the several cancers where certain germline mutations can increase the risk and where predictive tests can be carried out. These can be divided into two groups:

- High/moderate-risk mutations. Mutations in two genes, known as *BRCA1* and *BRCA2* (BReast CAncer 1 and 2), account for most high-risk hereditary breast cancers. However, *BRCA1/2* mutations are uncommon (but above the European Union definition of 'rare', 1 in 2000)—about 0.25%–0.5% of women are carriers of harmful mutations in either gene, although some groups have a higher prevalence [6]. These genes are also causes of ovarian and prostate cancers and increase the risk of some other cancers. *BRCA1/2* mutations are responsible for nearly half of families with multiple cases of breast cancer and up to 90% of families with both breast and ovarian cancer [7]. However, only about 3% of breast cancers overall are caused by *BRCA1/2* mutations (and 10–15% of ovarian cancers) [8]. Calculating the individual risk for carrying *BRCA1/2* pathogenic variants has been difficult; recent research on a large prospective cohort of women in Europe has helped to clarify the numbers—it found that the cumulative breast cancer risk to the age of 80 years was 72% for *BRCA1* and 69% for *BRCA2* carriers [9]. There are other high penetrance mutations, for example in *TP53*, which is rare but has a high risk for a range of cancers, including young onset breast cancer, and *TP53* is included in familial breast cancer management [11]. There are also moderate penetrance mutations identified through genomic technology which mostly confer lower risk and which are now widely tested for in multi-gene panels, but clinical utility is the subject of ongoing research [10].
- Lower risk germline mutations. Recent work has uncovered many more genetic variants—more than 200—that are associated with altered breast cancer risk. Although each conveys a very much smaller risk than *BRCA1/2*, in certain combinations, they could be responsible for additional aggregations of hereditary breast cancers.

This is a rapidly growing field that has major implications for how health systems, health professionals and patients assess the risk of breast cancer and which could eventually alter the approach to breast cancer screening, one of the world's major cancer detection programmes.

The EBCC is particularly concerned about the quality and availability of appropriate genetic testing for germline mutations, given that in many countries, such testing is available outside of the regulated healthcare systems in the form of direct-to-consumer testing. Concerns include the following:

- People may have inaccurate perceptions about the magnitudes and implications of risk and may be subject to misleading claims by advertising of genetic tests
- Tests can be interpreted inaccurately or be of poor quality, resulting in false positives and negatives (see the following section 'Direct-to-consumer concerns'). This may lead to unnecessary worries and inappropriate interventions that can be life changing, such as a risk-reducing mastectomy
- There is a need for high-quality predictive risk testing, and there are well-established protocols for family testing and counselling for *BRCA1/2* mutations, but they may not be universally applied or easily accessible even in national healthcare systems
- The growth of tests for panels of genes of both moderate and low risk raises more complexity about information and counselling. In many cases, the implications of such tests are not fully understood or inadequately validated. Misinterpretation of these tests, especially outside of regulated healthcare settings, may cause serious harms.

### 2.2. Tests for patients with breast cancer

There are two main areas for intervention:

- Tests for germline mutations, as stated previously. Some patients with breast cancer are offered genetic testing for *BRCA1/2* and other cancer genes as they can affect treatment decisions and prognosis as well as future risks (i.e. for ovarian cancer) and also could have implications for families.
- Tests on breast cancer tissue for somatic mutations to determine prognosis and treatment options. This is a major area of research and clinical implementation, such as with 'gene arrays'—panels of breast cancer mutations that can help decision-making in, for example, whether to use adjuvant chemotherapy (medical therapy after surgery) to reduce the chances of recurrence—and with tumour sequencing to determine treatment with targeted biological drugs and combinations of therapies.

The EBCC is less concerned about these aspects of genetic/genomic tests as they mostly take place in regulated healthcare settings. However, such testing can also take place in unregulated facilities that do not practise evidence-based guidelines for treating, and counselling on, breast cancer, and there are also wide inequalities in access to such care around Europe.

### 3. Status of testing for breast cancer

Within healthcare systems, there is a clear pathway for genetic risk testing for the main breast cancer genes. There is currently no generally accepted rationale for testing healthy people with no family history of breast cancer – testing for *BRCA1/2* (and also *TP53* and certain other mutations) is indicated only when there is evidence that there is likely to be an inherited faulty gene owing to a close relative with breast cancer having been tested positive or a broader family history of breast cancer. Certain groups, such as women of Ashkenazi Jewish descent, are known to be much more likely to be carriers of certain *BRCA1/2* gene faults and may be tested without a family history of breast cancer. *BRCA1/2* gene testing can also be offered to people with breast cancer, especially if they are young (aged 50 years or less) and have certain types of cancer (in particular, triple-negative breast cancer is linked to *BRCA1* mutation carriers). Genetic testing for *BRCA*-related cancers has been ranked as a ‘tier 1’ level of evidence by the US Centres for Disease Control and Prevention [12].

Policies for carrying out the current evidence-based practice for *BRCA1/2* testing have been set out in several countries, but as a publication from NHS England notes, there is a need to address ‘the current unacceptable variation in access to genetic testing for *BRCA1* and *BRCA2*’ [13]. Inequalities in access to testing are likely to exist across Europe.

*BRCA* tests are usually carried out on blood samples but can also be performed on buccal scrape and saliva samples. The traditional test method is direct DNA sequencing (known as Sanger sequencing), which is costly and time consuming and has limitations (which can be supplemented by other techniques), but the sensitivity of Sanger sequencing for *BRCA1/2* is about 99% for typical intragenic point mutations (although it does not cover ‘large rearrangements’ and ‘deep intronic’ mutations), and it remains in widespread use and is particularly suitable for single gene analysis.

Next-generation sequencing (NGS) methods, however, are now a rapid growth technology and are faster and less costly, while also enabling more mutation types to be tested for, the testing of many genes simultaneously or even the assessment of the whole genome.

*BRCA1/2* are large genes, and there are thousands of variants in each, and new methods must demonstrate how they are validated to uncover variants that are harmful, benign or of unknown clinical impact (called variants of unknown significance [VUS]). It is beyond the scope of this manifesto to discuss the complexities of gene sequencing, but while results can be clear for certain founder mutations (such as those in Ashkenazi Jewish descent), there is ongoing research on the clinical relevance of certain classes of mutations, on VUS, and on various populations. For example, the prevalence of

*BRCA1/2* pathogenic (harmful) mutations varies considerably among ethnic groups and geographical areas, and methodology should account for these differences [14,15,16]. Tests can also look for a specific mutation that has been found in a relative with breast cancer, as well as looking at the entire gene.

Some guidelines have been issued about the use of NGS for the diagnosis of genetic disorders [17]. But NGS is enabling a rapid expansion of genetic testing and new challenges, including in *BRCA* [18]. A recent study of 20 European laboratories showed that a majority are now using NGS for *BRCA*, with a low error rate, although the laboratories in this study have a significant *BRCA* caseload (>300 germline cases a year), participate in external quality assurance schemes, do not outsource their work and some are accredited to the ISO medical laboratory standard [19].

Regardless of the method, providing the correct information, support, counselling and pathways to possible testing is essential for the *BRCA1/2* genes, not just for breast cancer but for the other cancers associated with these genes. There are implications for a range of interventions—from lifestyle changes to taking chemoprevention drugs such as tamoxifen and to surgery such as mastectomy that must be taken only in high-quality healthcare settings. In the EBCC’s view, this medical activity should only be taken in a breast cancer centre or unit that includes a cancer genetics multidisciplinary team.

Research is moving fast; for example, researchers have recently reported that population testing for *BRCA1/2* and moderate-risk gene mutations may be cost-effective, which could change clinical practice as the current clinical criteria/family history misses 50% of mutation carriers even within cancer cases [20]; and that there is no survival difference in young breast cancer patients who are *BRCA1/2* carriers [21]. Such research underpins the need for the integration of genetics in the breast cancer centre.

The expansion into gene panel/genome testing also raises more questions about clinical validity, actionability and clinical utility.

#### *Direct-to-consumer concerns*

With that in mind, people in many countries can now opt privately for *BRCA1/2* tests and for other genetic tests associated with breast and other cancers. The size of the direct-to-consumer (DTC) market is growing rapidly, but there is a clear difference between companies that offer relatively superficial reports of ancestry and health with only low-risk attributes and those offering a service for high-risk conditions. There are concerns about the accuracy and marketing of tests that have high-risk and actionable consequences, with *BRCA1/2* in particular.

The best-known company in DTC is 23andMe, which currently operates in the US, UK and some other

countries with ancestry and health tests and which has recently been authorised by the US Federal Drug Administration (FDA) to carry out certain genetic tests, including *BRCA1/2*. Earlier, in 2013, the company had been warned by the FDA about marketing a service that included *BRCA1/2* testing in the US ‘because of the potential health consequences that could result from false-positive or false-negative assessments for high-risk indications. For instance, if the *BRCA*-related risk assessment for breast or ovarian cancer reports a false positive, it could lead a patient to undergo prophylactic surgery, chemoprevention, intensive screening or other morbidity-inducing actions, while a false negative could result in a failure to recognise an actual risk that may exist.’ [22].

*BRCA1/2* tests are now widely available in the UK and other European countries. Some private testing companies only accept requests for genetic testing from a person’s doctor, which is clearly good practice. But others will act outside of clinical guidelines and provide the test to consumers, and now for very low cost. For example, a UK company, BRCATESTUK, offers a *BRCA1/2* test for £295 and a ‘pan-cancer’ panel of up to 30 genes for £395. This price includes a pretest consultation and post-test genetic counselling, but it is not entirely clear what is provided for this low cost, and there is little information about the test, which comes from a US firm called Color Genomics—which itself offers the *BRCA1/2* two gene test for just \$99 and will send a saliva collection kit worldwide.

In the absence of counselling, there is a possibility of distress and lack of knowledge [23], and information from multigene panels ‘needs to be interpreted with caution to avoid the potential to provide clinical misinformation and cause harm’ [24].

Apart from kits for high- and moderate-risk genes, there are already DTC polygenic risk products on the market (and are likely to be more soon) that examine a multitude of low-risk mutations. Such polygenic risk is currently being researched to add to risk prediction models for breast cancer and could be informative where there are no high-risk mutations in people with a family history of breast cancer [25]. In these cases, breast cancer risk assessment might require a correct combination of family history, personal risk factors and the polygenic risk score. This assessment is complex and requires an adequate analysis of interactions and validation.

These tests add greatly to complexity. Myriad Genetics, the company that originally held patents on *BRCA1/2*, has launched just such a test called riskScore; it looks at 86 SNP variations that are associated with breast cancer risk. In the US, prescription drugs and medical devices can be marketed to consumers even if they must be ordered by a doctor.

The issue is that consumers do not have access to information that allows them to choose high-quality services that will accurately report breast cancer risk from genetic findings. Not all laboratories have

certification, and people buying tests may not even know which country the laboratories are in. Results, especially uncertain and secondary findings, will vary, and there is no standard for reporting how they relate to breast cancer risk, no requirement to participate in research programmes and share data, and a current lack of regulation in how tests are marketed.

Researchers at one of the major testing companies, Ambry Genetics, recently analysed samples from which other DTC companies had reported genetic variants in raw data supplied to consumers, finding that 40% of variants in a variety of genes were false positives [26]. ‘In addition, some variants designated with an ‘increased risk’ classification in DTC raw data or by a third-party interpretation service were classified as benign at Ambry Genetics and several other clinical laboratories and are noted to be common variants in publicly available population frequency databases.’ The majority of false-positive variants were found in the *BRCA1/2* genes.

The authors say that many DTC genetic testing laboratories use a form of SNP genotyping array for their assay, which is not ‘comprehensive full-gene sequencing nor does it include gross deletion or duplication analyses, which are both routinely part of clinical diagnostic testing with the use of NGS and microarray/multiplex ligation-dependent probe amplification methodologies.’

They conclude that their study ‘demonstrates the importance of confirming DTC raw data results in a diagnostic laboratory that is well versed in clinical-grade variant detection and classification’.

There is also concern that a primary business model of some DTC companies is data collection from potentially millions of people that can be used for lucrative private research, similar to the way that the major social media platforms work with vast amounts of valuable anonymised data. In the US, the Federal Trade Commission has issued advice to consumers about the privacy implications of DNA test kits [27].

The EBCC emphasises that it is very important that a genetic test with a high-risk possibility is not just a blood or saliva test and a positive or negative result. A test must also comprise counselling about the result, which may be uncertain, what it means in the individual’s personal and family context, and a pathway to other health services that may be needed, including confirmation by an accredited diagnostic laboratory.

The consequences of a lack of a ‘joined-up approach’ with appropriate quality control are illustrated in a news item from the US where a woman who received testing for *BRCA1/2* was told, wrongly, she had *BRCA1* and *MLH1* gene mutations and Lynch syndrome, which led to unnecessary referrals for mastectomy and hysterectomy [28].

While this is an extreme case, it is by no means isolated, and other research shows that people who are identified as carriers of VUS *BRCA1/2* mutations may opt for mastectomy, given other risk factors such as

family history, while not appreciating that ‘...over time, a significant proportion of *BRCA1/2* VUS were reclassified, illustrating the importance of appropriate counselling regarding VUS’ [29].

#### 4. Information, counselling and breast centres/units

The EBCC is concerned that there is a lack of information for people about genetic testing, and also that as recommendations for more testing are made by clinical guidelines, the capacity of clinics and laboratories to offer timely results and high-quality interpretation will be put under increasing pressure, especially for sufficient numbers of geneticists and counsellors, and as the take-up of DTC testing increases.

There are online guides about genetic testing in breast cancer, mainly on *BRCA1/2* [30], but little is provided by health services on DTC products and on the testing of panels of genes for a range of risk for certain cancers. The EBCC would like to see consistent European-wide information available in printed form in places such as primary and secondary care clinics, as well as online, and ideally prominently situated on advertising of tests, referring potential customers to receive adequate medical advice before ordering them.

An article that examined the provision of genetic counselling in the European DTC market suggests an ‘urgent need for private companies selling genetic testing DTC to consider their delivery of care’. The authors found a lack of pretest genetic counselling in particular and said it should be ‘mandatory to clearly explain on the companies’ websites what the role of genetic counselling is and make it easily available, before and after the test, by appropriately trained and regulated genetic health professionals’ [31]. It is also potentially negligent, they add, to suggest that customers can ‘contact their local genetic counsellor’ when there are no mechanisms to do so. It is ‘negligent for companies to offer testing that raises anxiety among their customers and then expect other healthcare services to pick up the pieces’.

Regarding healthcare systems, the European Society of Breast Cancer Specialists (EUSOMA) has requirements for specialist breast centres [32] that must include the services of a clinical geneticist, who is described as a medical specialist concerned with the assessment of genetic risk and counselling for individuals or families with increased risk of breast cancer (counsellors work as part the team). A breast centre (or unit) must at least have an agreement for people to see a clinical geneticist if the role cannot be provided at the site. The requirements also note the following:

- Genetic testing for *BRCA1/2* must be available, and a molecular geneticist should be accessible for consultation by the specialists in the genetics clinic
- Risk assessment counselling and DNA testing for *BRCA1/2* mutations in a selected high-risk group should be offered

- Psychological support should be available to people when necessary to support them to assimilate their genetic risk
- Patient data from genetic clinics should be formally recorded in a database, and the team should be involved in research.

The European Commission Initiative on Breast Cancer includes a quality assurance scheme for breast cancer services in Europe that will be available for implementation by 2020 [33]. It has a certification and accreditation framework for breast cancer services and includes genetic evaluation and testing at screening (for women at increased risk), diagnosis and treatment in the patient pathway.

The EBCC highlights the following recent research as particularly relevant to the professional practice of helping people manage genetic risk information:

- A study that evaluated the ability of women at risk of hereditary breast and ovarian cancer to select the extent of genetic testing concluded that women were sufficiently able to self-identify the level of testing they were comfortable with after receiving genetic counselling, which the authors describe as ‘a highly specialised service’ and an ‘important component of comprehensive care for women with a personal or family history of cancer suggestive of hereditary risk’ [34].
- An article titled ‘Faulty *BRCA1*, *BRCA2* genes: how poor is the prognosis?’ examines the case of ‘Sophie’, who has been told that as a *BRCA1/2* carrier, she has an 87% chance of getting breast cancer [35]. It explains that the risk is not an imminent threat and that much more needs to be considered other than the 87% figure alone.
- Supporting disclosure to family members—how the proband (the person who is the starting point in a genetic intervention) can be supported in talking to relatives [36]. The CASCADE study in Switzerland is developing factors that enhance cascade genetic testing of relatives [37].
- A before-and-after study of establishing a hereditary cancer unit in a university hospital in Madrid showed a clear improvement in family history records, referrals and preventive surgeries in breast cancer patients at increased genetic risk after the implementation of the unit [38].
- A US study looked at the experience of men with *BRCA* mutations [39].

#### 5. Regulation and policy

In 2017, the European Union adopted what some see as long overdue new regulation on *in vitro* diagnostic medical devices (the IVD Regulation) [40], which includes predictive genetic tests (and also companion tests on diseases such as cancer that, for example, predict treatment response). According to GeneWatch UK, the main requirement for a company or institution which places the software or test on the market is to produce a technical dossier which includes clinical information such as the positive predictive value of the test and which demonstrates laboratory quality assurance and quality management [41]. This dossier will be assessed by ‘notified

bodies', which must award the test a CE mark before it can be placed on the market (including if the test is sold via the Internet or by overseas companies).

Article 4 of the regulation covers genetic information, counselling and informed consent and will require countries 'to ensure that where a genetic test is used on individuals ... the individual being tested or, where applicable, his or her legally designated representative, is provided with relevant information on the nature, the significance and the implications of the genetic test, as appropriate.' It also calls for access to counselling for genetic tests that provide information on the genetic predisposition for medical conditions and/or diseases that are generally considered to be untreatable.

However, the IVD Regulation has set out grounds for divergence around Europe, considering that 'divergent national rules regarding the provision of information and counselling in relation to genetic testing' might not have much impact on the operation of the single market. The IVD Regulation does though prohibit misleading advertising of IVD medical devices. The European Parliament wanted an advertising ban on genetic testing, but this was not adopted in the final text.

Furthermore, the IVD Regulation does not come into force until May 2022.

There is already divergent regulation on genetic testing around Europe that looks set to continue in some respects even after the IVD Regulation. There is limited data on the national law for DTC tests, but a 2017 article found a fragmented regulatory landscape and a wide spectrum of rules [42]. It noted that the EU approach covers genetic test as products and not as services, which tend to be regulated at the national level in any case. Questions addressed for European countries were the following:

- Is medical supervision mandatory in the context of genetic testing?
- Is genetic counselling mandatory in the context of genetic testing?
- Are there specific requirements for informed consent that may apply in the context of genetic testing?

At one end of the spectrum is France, which essentially bans DTC genetic testing, 'by limiting the use of genetic testing to specific health-related tests, mandating the involvement of healthcare professionals and penalising users of tests that do not fulfil these conditions'. Similarly, Germany has legislation that has been considered by some as targeting DTC genetic testing and limiting the access German consumers may have to it. 'On the other end are many countries that do not provide any specific legislation on genetic testing (such as Luxembourg, Poland and Romania), and, as a result, the only restrictions in place are those based on more general laws, usually regarding healthcare services and patients' rights.'

GeneWatch UK notes that the EU's IVD Regulation will not overturn the bans in place for DTC genetic tests or prevent such bans in the future.

The authors of the regulation article note that the aims of the EU's IVD Regulation are 'pragmatic' in focusing on safety and performance and giving leeway for member states to adapt requirements for medical supervision, genetic counselling and informed consent in their clinical practice. While some have criticised this as a missed opportunity to have more effective oversight of DTC genetic testing services, '...imposing strict uniform standards ... by means of an EU regulation seems impractical and restrictive and beyond the legislative competence of the EU'.

Other protocols and guidelines are available for establishing standards. They include the Council of Europe's Additional Protocol on genetic testing for health purposes [43] and guidelines from the European Society of Human Genetics [44] and the Organisation for Economic Co-operation and Development (OECD) [45]. Countries that have requirements for genetic counselling for some types of tests have been guided by the Oviedo Convention's Article 12 on predictive genetic tests.

Another article from 2012, considered genetic testing legislation in Western Europe and also provides valuable background on the regulatory picture and emphasised the growing challenge of DTC testing [46].

Concerning advertising of genetic tests, a 2017 article provides an overview of the European and national picture, and considered a tiered approach—a ban on tests that could have a serious impact on consumers' health, while leaving those with no real possibility of health-related harm to the strict accuracy criteria in any advertising [47].

While there was little evidence for either benefit or harm of DTC genetic testing according to a systematic review from 2015 [48], the authors say '...it is unacceptable that online companies offer genetic testing lacking scientific evidence, no proven clinical utility and misleading marketing claims' and note that the 'expected benefits of whole-genome scanning may be larger when tests are targeted only to specific at-risk populations and not to populations at large because of the moderate predictive ability of these current tests'.

The EBCC also highlights these organisations and projects for resources and direction:

- EuroGentest is a project funded by the European Commission to harmonise the process of genetic testing, from sampling to counselling, across Europe. The goal is to ensure that all aspects of genetic testing are of high quality. The project website has details on laboratory certification, counselling guidelines, ethics and patient rights (<http://www.eurogentest.org>). An allied body is the European Molecular Genetics Quality Network (<https://www.emqn.org>)
- The PHG Foundation, a biomedical think tank, has published 'whole-genome sequencing in screening for breast

cancer', which investigates the impact of routine testing for heritable conditions using whole-genome sequencing where these conditions are not part of the primary purpose of testing, using the example of inherited breast cancer [49]. It says it is 'imperative to ensure that robust processes are in place for managing and understanding these complex data and appreciating the levels of uncertainty about clinical validity and utility of testing positive for a pathogenic variant'

- The UK government's concordat with the Association of British Insurers, which has placed a moratorium on the use of predictive genetic test results by insurers until 1 November 2019 [50]
- A clinical guideline from the UK's National Institute for Health and Care Excellence on familial breast cancer, which was updated in 2017 and has protocols on genetic testing [11]; an update of the US Preventive Services Task Force recommendation on genetic risk assessment and *BRCA* mutation testing for breast and ovarian cancer susceptibility [51].

## 6. Conclusion

Predictive genetic testing for breast cancer and other diseases is a crucial area of research and ongoing clinical implementation. The complexity of the biology and algorithms needed to interpret data is increasing and is placing pressure on health services already hard pressed to provide services such as high-quality genetic counselling. The market for DTC tests is also growing rapidly amid a fragmented regulatory picture in Europe under which there are fundamental questions about whether such tests even fall within legal definitions of health services. The nature of the Internet means that people can easily circumvent any European and national restrictions on DTC testing in any case.

To maximise benefits and minimise possible harms, the EBCC considers that the breast cancer community in Europe must lead in implementing the call to action in this manifesto.

## Conflict of interest statement

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