J Community Genet (2011) 2:53–69
DOI 10.1007/s12687-011-0042-4

REVIEW

Genetic testing for familial/hereditary breast cancer—comparison of guidelines and recommendations from the UK, France, the Netherlands and Germany

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Received: 4 November 2010 / Accepted: 9 February 2011 / Published online: 2 March 2011

Abstract In this review, the national guidelines and recommendations for genetic testing for familial/hereditary breast cancer from the UK, France, the Netherlands and Germany were evaluated as to the inclusion criteria for genetic testing. In all four countries, access to genetic testing relies basically on the family history of breast and ovarian cancer. Similarities are obvious for most selection criteria. All four guidelines recommend embedding genetic testing within a framework of genetic counselling, and all agree to perform genetic testing first in an affected person. However, there are differences regarding the thresholds based on certain familial constellations, detailed description of selection criteria, the degree of relatedness between affected individuals and the counsellee, the age of diagnosis, the individual history of early onset breast cancer, bilateral breast cancer, the tumour morphology or the access to intensified surveillance. These differences and open questions not covered by the guidelines, e.g. on how to deal with phenocopies, unclassified variants, genetic variants in newly identified breast cancer susceptibility genes or with family constellations not fitting the criteria, are discussed. New evidence is usually slowly integrated into the guidelines. An

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exchange process towards the harmonization of the guidelines will ensure high quality health care across Europe.

Keywords Hereditary breast cancer · BRCA1 and BRCA2 · Genetic testing · Inclusion criteria · European comparison

Introduction

Genetic testing for breast cancer susceptibility has become an integral part of medical management. At-risk individuals can be provided with regular surveillance to identify breast cancer at an early stage. Prophylactic surgery aims to prevent the development of cancer, and in the near future, moving in the direction of individualized medicine, targeted therapies for affected mutation carriers will be available. The essential step towards a rational approach is how to identify individuals who will benefit from testing, without straining the financial budget of the national health system, although recently established techniques like next generation sequencing may significantly reduce the costs.

It is well known that genetic factors play an important role in the development of breast cancer (Foulkes 2008; Ripperger et al. 2009). Five to ten percent of breast cancers are believed to be caused by a genetic predisposition due to a mutation in a highly penetrant breast cancer gene (Chen et al. 2006). The two most important breast cancer genes are *BRCA1* and *BRCA2*, identified in 1994 and 1995, respectively (Miki et al. 1994; Wooster et al. 1995). Mutations in the breast cancer genes *BRCA1* and *BRCA2* account at most for 20–40% of inherited breast cancers (Wooster and Weber 2003). Women carrying a *BRCA1/2* mutation have a substantially elevated risk of developing breast and/or ovarian cancer (OMIM 113705 and OMIM 600185), i.e. a lifetime risk for breast cancer of up to 85%, and for ovarian cancer between 40% and 60% for *BRCA1* carriers and between 20% and 30% for *BRCA2* carriers (King et al. 2003). Furthermore, the individual risk to develop breast or ovarian cancer is influenced not only by the presence of a *BRCA1* or *BRCA2* mutation but also by the family history of cancer (Metcalfe et al. 2010). A woman already affected with breast cancer carrying a *BRCA1/2* mutation has a significantly higher risk of developing a second independent breast cancer or an ovarian cancer (Metcalfe et al. 2005; Pierce et al. 2006; Graeser et al. 2009). Thus, identification of a *BRCA1/2* mutation has important implications for the mutation carrier herself and also for the family.

According to the autosomal-dominant manner of inheritance, there is a 50% probability for each offspring to inherit the mutation and therefore to carry the elevated risk for breast and ovarian cancer. Once a pathogenic mutation has been identified in a family, predictive testing for healthy relatives becomes possible. Because of the substantially lower age of onset of hereditary tumours compared to sporadic breast cancer, women at risk need access to surveillance at a younger age. Intensified surveillance options should include annual breast magnetic resonance imaging (MRI; Leach et al. 2005). Furthermore, risk-reducing surgeries like mastectomy or bilateral salpingo-oophorectomy are options to decrease the risks of developing cancer and to lower mortality (Domchek et al. 2010). For affected mutation carriers, hope was raised that targeted chemotherapy will be available in the near future. Preclinical studies with PARP (poly(ADP-ribose)polymerase1) inhibitors showed that BRCA1/2-deficient tumour cells are selectively targeted (Bryant et al. 2005; Farmer et al. 2005). Clinical trials are ongoing to prove the clinical applicability and effect. First studies confirm the promising results (Tutt et al. 2010; Audeh et al. 2010).

Meanwhile, guidelines have been established on how to identify individuals at risk for familial breast cancer. Regulation of the field was initiated by the respective national leading stakeholders to ensure and control the quality of the process. Although a similar frequency of *BRCA1* and *BRCA2* mutation is assumed within developed countries, each country has established its own approaches on how to proceed in the case of familial breast cancer. The individual guidelines and recommendations are roughly similar. Nevertheless, they are a result of a growing superordinate process of how to deal with genetic information in accordance with the public attitude and the organization of the respective national health system: in this case, regarding the gatekeepers for the genetic service, differences are obvious. Since the European Union (EU) is built on the concept of free movement of goods, services, people and capital, the EU aims to safeguard the quality of health care for consumer protection reasons (Legido-Quigley et al. 2008). Delivery of health care is still the responsibility of the individual countries within the EU. Because of the growing mobility of professionals and patients, the EU's mission is to encourage and support progress to ensure high quality and comparable care across Europe. Recently, in January 2011, the European Parliament voted in favour of the EU Directive on patients' rights in cross-border healthcare (Commission of the European Communities 2008). Consequently, patients have the right to seek healthcare abroad and be reimbursed up to the amount they would have received at home.

This review aims to present and compare the existing national guidelines and recommendations related to the identification of at-risk individuals for familial breast cancer in the following four European countries: the UK, France, the Netherlands and Germany and to highlight the similarities and differences of the national approaches.

Methods

Data sources

Guideline publications, position papers and recommendations were eligible for inclusion.

The following national guidelines and recommendations were screened and compared:

- UK
- "Familial breast cancer: the classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care". NICE guideline CG041 (2006; http://www.nice.org.uk)
- France
- Documents published on the homepage http://www.e-cancer.fr/soins/prises-en-charge-specifiques/oncogenetique/ (Andrieu et al. 2009), mainly the "Synthèse du rapport sur l'estimation des besoins de la population pour les 10 années à venir en termes d'accès aux consultations et aux tests d'oncogénétique"
- "Cancer genetics: estimation of the needs of the population in France for the next 10 years" (Bonaïti-Pellié et al. 2009)
- The Netherlands
- "Erfelijke Tumoren: Richtlijnen voor Diagnostiek en Preventie" 2010 by the Netherlands Foundation for the Detection of Hereditary Tumours (STOET) and the Dutch Society of Clinical Geneticists (VKGN), available at http://www.stoet.nl/uploads/richtlijnenboekje.pdf
- Vereniging Klinische Genetica Nederland (VKGN)/ Werkgroep Klinische Oncogenetica (WKO). Beleid in mamma- en/of ovariumcarcinoomfamilies. Richtlijn 2005/2006 (Van Asperen et al. 2005)
- Germany
- "Interdisciplinary S3 guidelines for the Diagnosis, Treatment and Follow-up Care of Breast Cancer" (Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms, Kreienberg et al. 2008)
- "Stufe-3-Leitlinie Brustkrebs-Früherkennung in Deutschland" (Albert et al. 2008), http://www.senologie.org/download/pdf/s3_brustkrebsfrueherkennung_2008.pdf
- Beratung, Genetische Testung und Prävention von Frauen mit einer familiären Belastung für das Mamma- und Ovarialkarzinom—Interdisziplinäre Empfehlungen des Verbundprojektes "Familiärer Brust- und Eierstockkrebs" der Deutschen Krebshilfe (Schmutzler et al. 2003a, b)
- Guidelines for genetic diagnostics for hereditary cancer from the Federal Medical Council (Bundesärztekammer 1998), http://www.bundesaerztekammer.de/downloads/Krebs_pdf.pdf

The content of the documents was screened and compared regarding the following topics:

- Inclusion criteria to identify individuals at high risk for hereditary breast cancer
- Inclusion criteria for genetic testing
- Selection of genes investigated
- Setting of genetic testing, role of genetic counselling

Recommendations regarding the clinical management of at-risk women, like the surveillance programme or the attitude to prophylactic surgery, as well as superordinate acts, i.e. for prenatal genetic diagnostics, were not the objectives of this review.

Results

UK

The National Health System (NHS) in the UK is a tax-funded system and has a hierarchical structure consisting of primary, secondary and tertiary care. Within the NHS, the National Institute for Health and Clinical Excellence (NICE), as an independent organization, is responsible for providing guidance like setting quality standards to improve the quality of the NHS. NICE has commissioned specialists to develop guidelines for different issues. The NICE clinical guideline (CG) 41 was created in 2004 and focuses on "Familial breast cancer: the classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care". In 2006, a new version was released including an update solely of the clinical screening management. A further update is planned for 2011. The guideline covers the care of adult women who may be at an increased risk of developing breast cancer because of a family history of breast or other cancers. It concentrates mainly on the clinical management, regarding the different surveillance strategies according to the assessed breast cancer risk. Women without at least moderately increased risk remain in primary care. Women with a raised risk (that is, a 10-year risk of 3–8% for women aged 40–49 or a lifetime risk of 17% or greater but less than 30%) would be eligible for secondary care. High-risk women should be referred to tertiary care. The guideline was primarily developed for use by primary care physicians to facilitate identification and referral of women with an above population risk of developing breast cancer due to a family history of breast and/or ovarian cancer. It is recommended that, when a woman presents with breast cancer symptoms or has concerns about relatives with breast cancer, a first-

and second-degree family history should be taken in primary care to assess risk because this allows appropriate classification and care. Furthermore, healthcare professionals should respond to women who present with concerns, but should not, in most instances, actively seek to identify women with a family history of breast cancer. Women who are estimated to be at high risk (that is, a 10-year risk at age 40–49 years of greater than 8% or a lifetime risk of 30% or greater, or a 20% or greater chance of a faulty *BRCA1*, *BRCA2* or *TP53* gene in the family) should be referred to a specialist genetics clinic in tertiary care. In accordance with the tables of Claus et al. (1994) and the Collaborative Group on Hormonal Factors in Breast Cancer (2001), familial constellations have been defined in which the above-mentioned high risks are expected. Selected examples of family histories are given in the guideline as referral criteria. They are listed in Table 1. The NHS covers all genetic counselling and testing costs while the threshold for testing a family is quite high at 20% likelihood of carrying a mutation. Families selected according to the familial criteria are evaluated in the next step in the genetic service of tertiary care to assess the probability of a *BRCA1* or *BRCA2* mutation. For risk-assessment computer models, for example, Tyrer-Cuzick or BOADICEA can be used as prediction tool (Tyrer et al. 2004; Antoniou et al. 2008) but should not totally replace careful manual assessment of family trees by a genetic specialist. The Manchester scoring system was developed in 2003 to facilitate a simpler and more accurate selection of families for *BRCA1/2* testing (Evans et al. 2004). The current version of the Manchester scoring system, updated in 2009, is given in Table 2 (Evans et al. 2009). Scores are added for each cancer in a direct blood lineage, and the combined score is determined by adding the *BRCA1* and *BRCA2* scores. A combined score of 20 points can be used as a 20% threshold. Only families who reach a 20% threshold for mutation probability are eligible for genetic testing.

Annual MRI screening is offered for women in the 30–49-year age group who are estimated to be at high risk and meet certain criteria. This group includes mainly mutation carriers, but also women from 30 to 39 years with a 10-year risk greater than 8%, women from 40 to 49 years with a 10-year risk greater than 20% or women with a 10-year risk greater than 12% where mammography has shown a dense breast pattern.

Since the guideline covers not only the *BRCA1/2*-associated breast cancer risk but is also related to the *TP53*-related breast cancer risk, it is recommended that women from families containing the following criteria in addition to breast cancer be referred to a genetic specialist:

- Sarcoma in a relative younger than age 45 years
- Glioma or childhood adrenal cortical carcinomas
- Complicated patterns of multiple cancers at a young age.

The NICE guidelines propose that women who meet the criteria for referral to tertiary care should be offered a referral for genetic counselling regarding their risks and options. It is recommended that genetic testing begins with an affected relative. After identification of a mutation in an affected person, predictive genetic testing is then available for healthy relatives.

Furthermore, predictive genetic testing should not be offered without adequate genetic counselling, preferably as two sessions of pre-test counselling.

France

In France, access to cancer genetic services and testing is covered by the National Health Care System and in particular since 2003 through the initiative of the Cancer Plan. “The Cancer Plan 2009–2013” has been developed by the French Ministry of Health in coordination with the French National Cancer Institute (Institut National du Cancer (INCa)). It incorporates the knowledge on hereditary predisposition to cancer within the rubric “Oncogénétique”.

Presently, 106 genetic counselling units and 25 genetic laboratories are distributed throughout the whole country. They are funded through the National Cancer Institute and have to deliver an annual report about their activities to the institute. Therefore, exemplary statistics are available and presented on the website, e.g. with respect to hereditary breast and ovarian cancer and *BRCA1* and *BRCA2* genetic testing. According to the recommendations for good clinical practice for health care professionals regarding breast cancer, familial criteria that have to be fulfilled to refer an individual to genetic counselling are noticeably inclusive and presented in Table 1.

As reported in Bonaïti-Pellié et al. (2009) and the “Synthèse du rapport sur l'estimation des besoins de la population pour les 10 années à venir en termes d'accès aux consultations et aux tests d'oncogénétique” in 2008, the criterion regarding ovarian cancer has been extensively discussed within the responsible working group. To increase the percentage of detected *BRCA1/2* mutation carriers, recommendations have been extended to also include occurrence of an isolated ovarian cancer diagnosed before the age of 70 within the family as a criterion for genetic counselling. Furthermore, occurrence of ovarian cancer even at an older age together with breast cancer in first-degree relatives is accepted as an inclusion criterion. The role of the histopathologic features of the breast tumour for prediction of a mutation has also been discussed. Finally, it was decided that there is not sufficient evidence to consider the morphology. Regarding the approach towards genetic testing, it is recommended first to test an affected person, the so-called index patient. After identifi-

Table 1 Indication criteria for genetic testing for hereditary breast and ovarian cancer in the UK, France, the Netherlands, and Germany

UK	France	Netherlands	Germany
Referral to tertiary care for women with at least:	Referral to genetic counselling for women with at least:	Referral to clinical geneticist for women from following families with at least:	Counselling and genetic testing for women from families with at least:
		1. Family history of cancer	
		(a) Multiple affected females with breast cancer	
Two first-degree or second-degree relatives diagnosed with breast cancer at younger than an average age of 50 years (at least one must be a first-degree relative of the woman), *or*	Several women with breast ancer on the same side of the family	Two or more first-degree relatives with breast cancer diagnosed before the age of 50 years, *or*	Two women with breast cancer, with one of them ≤50 years, *or*
Three first-degree or second-degree relatives diagnosed with breast cancer at younger than an average age of 60 years (at least one must be a first-degree relative), *or*		Three or more first- or second-degree relatives with breast cancer, of which at least one tumour was diagnosed before the age of 50 years	Three women with breast cancer, independent of age
Four relatives diagnosed with breast cancer at any age (at least one must be a first-degree relative)			
		(b) Females affected with ovarian cancer	
Families containing one relative with ovarian cancer at any age *and* on the same side of the family	Ovarian cancer even at an older age together with breast cancer in first-degree relatives, *or*	Breast cancer diagnosed before the age of 50 years *and* one ovarian cancer on the same side of the family, *or*	One woman with breast *and* one woman with ovarian cancer, independent of age, *or*
One first-degree relative (including the relative with ovarian cancer) or second-degree relative diagnosed with breast cancer at younger than age 50 years, *or*	One woman with breast and ovarian cancer, *or*	Ovarian or fallopian tube cancer and breast cancer in the same person or in two women on the same side of the family, of which one was diagnosed before the age of 50 years, *or*	One woman with breast and ovarian cancer, independent of age, *or*
Two first-degree or second-degree relatives diagnosed with breast cancer at younger than an average age of 60 years, *or*	Several women with ovarian cancer on the same side of the family, *or*	Two first-degree or one first- and one second-degree relative with ovarian or fallopian tube cancer, *or*	Two women with ovarian cancers, independent of age
Another ovarian cancer at any age	Ovarian cancer diagnosed before the age of 70 years within the family	One ovarian or fallopian tube cancer of epithelial tumour histology diagnosed before the age of 50 years	
		(c) Affected males	
Families containing male breast cancer at any age *and* on the same side of the family, at least	One male breast cancer	Brother or father with breast cancer and on the same side of the family one breast or ovarian cancer in a woman	One male breast cancer and one woman with breast or ovarian cancer
One first-degree or second-degree relative diagnosed with breast cancer at younger than age 50 years, *or*			
Two first-degree or second-degree relatives diagnosed with breast cancer at younger than an average age of 60 years, *or*			
Very strong paternal history (four relatives diagnosed at younger than 60 years of age on the father's side of the family)			
		(d) Age at onset of single cases	
	One woman with breast cancer diagnosed under the age of 40 years	One woman with breast cancer diagnosed before the age of 35 years	One woman with breast cancer ≤35 years
		(e) Associated tumours	
		Breast or ovarian cancer before the age of 50 years and prostate cancer before the age of 60 years on the same side of the family	

Table 1 (continued)

UK	France	Netherlands	Germany
		2. Bilaterality	
Families containing bilateral cancer (each breast cancer has the same count value as one relative) One first-degree relative with cancer diagnosed in both breasts at younger than an average age of 50 years, *or* One first-degree or second-degree relative diagnosed with bilateral breast cancer *and* one first-degree or second-degree relative diagnosed with breast cancer at younger than an average age of 60 years	One woman with bilateral breast cancer	Bilateral breast cancer, with first tumour diagnosed before the age of 50 years	One woman with bilateral breast cancer or two primary breast cancers, with first tumour diagnosed before ≤50 years
		3. Receptor triple negativity	
		Triple-negative breast cancer diagnosed before the age of 40 years	
		4. Ethnicity	
Jewish ancestry		Jewish ancestry	

cation of a mutation, predictive testing can then be offered to healthy relatives.

Recommendations for the clinical management have also been developed and are specified separately. Intensified surveillance strategies including MRI screening are offered primarily for women carrying a *BRCA1* or *BRCA2* mutation. Regarding prophylactic surgical options, high-risk women from families in which no mutation was identified are mentioned separately. According to the recommendations for the "Chirurgie prophylactique dans les cancers avec prédisposition génétique", it is strongly advised to assess the woman's individual risk through an available mutation prediction model.

In a separate treatise of the French guidelines, it is assumed that hereditary cancer syndromes will only rarely be a matter for demand for prenatal or preimplantation diagnostics. Both types of diagnostics could be permitted under current French law after a favourable assessment by a specific advisory board. The precondition for applying prenatal or preimplantation diagnostics is the existence of a genetic disease within the family and knowledge of the disease-causing mutation. A request for diagnostics and a supporting decision from one of the multidisciplinary prenatal diagnostic centres are obligatory for each individual case. The opinions of French cancer geneticists and prenatal centre professionals differ according to the type of hereditary cancer involved (Julian-Reynier et al. 2009).

Netherlands

In the Netherlands, every citizen is required to purchase a basic health insurance package from a Dutch insurance company. Health insurance companies are legally obliged to offer at least this basic package and cannot reject anyone applying for it. Children below the age of 18 years have free access to the health care system, if their parents have a basic package. The cost is about 95 Euros per month, and basic medical care is covered. The Dutch government compensates those with low incomes by offering a care grant (*zorgtoeslag*). One can choose to purchase additional insurance for circumstances not included in the basic package. However, in this case, insurance companies can reject an application, and they have the right to determine the price. Coverage for genetic counselling and genetic testing is included within the basic care system. Therefore, access to genetic counselling and genetic testing is strictly regulated. Recommendations for the diagnostics and prevention of hereditary tumours are summarized in the "Erfelijke Tumoren: Richtlijnen voor Diagnostiek en Preventie" by the Netherlands Foundation for the Detection of Hereditary Tumours (STOET) and in the guideline for clinical geneticists "Beleid in mamma- en/of ovariumcarcinoomfamilies, Richtlijn 2005/2006" (Werkgroep Klinische

Oncogenetica (WKO)) by the Dutch Society of Clinical Geneticists (VKGN, Van Asperen et al. 2005). The latest issue of the STOET's so-called "blue booklet" was released in 2010. Management recommendations are given for every single hereditary tumour syndrome. It distinguishes between familial breast and ovarian cancer and hereditary breast and ovarian cancer. Familial breast cancer is defined according to given familial criteria, assuming a more than twofold increased risk for breast cancer. A specific surveillance programme is offered to these women, without including MRI screening. Details on specific points related to *BRCA1/2* testing are given in the latter document intended for clinical geneticists.

Indication criteria for referral to a clinical geneticist are given depending on the family characteristics or features of the individual tumour. At least one of the criteria given in Table 1 has to be fulfilled.

In the case of hereditary breast and ovarian cancer, genetic diagnostics is available to search for mutations in the breast cancer genes *BRCA1* and *BRCA2*. Mutation analysis has to be performed first in an index patient, an already affected woman. After a mutation is identified, predictive testing can be offered to healthy relatives from the beginning of a young adult age. Currently, genetic analysis can only be initiated by a clinical geneticist. Only to resolve diagnostic ambiguities is a medical specialist also allowed to initiate genetic testing. Regarding the counselling process, the Dutch recommendations place emphasis on the psychosocial care for counsellees.

Intensified surveillance including MRI screening is offered to *BRCA1* or *BRCA2* mutation carriers and to women who opt against testing, if they have a risk of 50% of being a mutation carrier, from families in which a mutation was previously identified.

Furthermore, the Dutch guidelines for clinical geneticists take into consideration the occurrence of phenocopies among breast tumours and deal with unclassified variants (UV) as genetic test results. It is suggested to perform segregation analysis within the family to clarify the effect of the UV.

Germany

The current health care system in Germany has a tradition of more than 120 years. Healthcare is delivered by private ambulatory care, mixed (public or private) hospital care and a mixed rehabilitation sector. Health care costs are covered by sickness funds for approximately 85% of the population, by private health insurance (10%) and communal and governmental sources (5%). Every gainfully employed individual has to have health care cost coverage by either a sickness fund or private health insurance. Sickness funds are based on the principle of solidarity, whereas private health insurance plans are based on individual risk. Sickness fund premiums, therefore, are differentiated solely by income. Sickness fund membership is compulsory if the yearly gross income does not exceed 50,000 Euros (expected to increase). Those earning in excess may opt for a private health plan. Sickness fund premiums are shared between employers and employees (subject to change in the future). The premium is based on a percentage of income and deducted from the monthly earnings of the employee: it amounts to ~15%. Sickness fund membership coverage is universal (ambulatory, hospital care, dental, ophthalmologic and rehabilitation) for the individual member, if gainfully employed, and his/her dependent family members (wife/husband and children). There is no direct payment of health care costs by the sickness fund member to the care provider. In contrast, private insurance requires direct payment to the care provider and reimbursement according to the plan.

In Germany, the German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC) was established in 1996 as a cooperative research project supported by the German Cancer Aid (Deutsche Krebshilfe). Twelve university-based interdisciplinary centres developed a standardized approach for the management of families with hereditary breast and ovarian cancer. This concept, including the genetic counselling, the molecular genetic diagnostics and the clinical surveillance, became part of the regular health care system in 2005.

The 12 GC-HBOC centres have direct contracts with most of the health insurance companies. Besides the genetic counselling, genetic testing and clinical surveillance are also offered at the centres. Because Germany is a Federal Republic, composed of 16 federal states, the cooperating health insurance companies can vary from state to state. Related to the decentralized health system and accepted market competition rules, private human genetic practices exist in parallel to the university-based centres also performing genetic counselling and testing. Although they do not have the above-mentioned direct contracts, the costs are mostly covered by the public health insurance independent of applying the strict inclusion criteria.

Recommendations for an interdisciplinary standardized management of women at risk for familial breast and ovarian cancer were first published by the GC-HBOC in 2003 in the German-speaking journal "Medizinische Genetik", the official journal of the German Society of Human Genetics, and the German-speaking "Zentralblatt für Gynäkologie", available in PubMed (Schmutzler et al. 2003a, b). The current criteria regarding those to whom interdisciplinary counselling and genetic testing should be offered in the special centres of the German Consortium yon Hereditary Breast and Ovarian Cancer (HBOC) are published in both German stage three guidelines "Interdisziplinäre

S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms" (Kreienberg et al. 2008) and "Stufe-3-Leitlinie Brustkrebs-Früherkennung in Deutschland" (Albert et al. 2008) and are given in Table 1. Both guidelines are approved by the highest German guidelines authority, the Association of the Scientific Medical Societies in Germany (AWMF). The familial criteria have been defined as an at least 10% a priori probability to carry a *BRCA1* or *BRCA2* mutation based on the mutation frequencies in 2900 German families (Meindl 2002).

Genetic testing is offered for both genes, *BRCA1* and *BRCA2*, and should first be performed in a woman affected with breast and ovarian cancer, the so-called index patient. After a mutation has been identified within the family, predictive testing is then available for healthy relatives. The rules for management of families with hereditary breast and ovarian cancer are based on the recommendations published in 2003 and summarized in detail in the not publicly available contracts between the university-based centres and the health insurance companies.

While the decision on mutation analysis is based on family constellation, clinical surveillance is based on thresholds determined by risk calculation programs: the individual's risk of heterozygosity and the lifetime risk for breast cancer. Both risks have to be assessed by the computer-based pedigree drawing and calculation model Cyrillic 2.1, which incorporates the modified Claus model (Claus et al. 1994). This risk calculation program includes the information on the family history, like the age of diagnosis of breast cancer and the degree of relatedness between the affected women and the counsellee. Although it is known that all available risk calculation models show considerable weaknesses (Antoniou and Easton 2006; Amir et al. 2010), Cyrillic 2.1 is a helpful tool and allows uniform decision-making across Germany. Thresholds of a risk of heterozygosity of ≥20% or a residual lifetime risk for breast cancer of ≥30% qualify a woman for management in the high risk group (Albert et al. 2008, 2009). These thresholds were set, since the lifetime risk for breast cancer decreases with age, while the risk of carrying a mutation stays the same. On the other hand, using the risk calculation program Cyrillic, these thresholds allow the possibility to offer intensified surveillance to young healthy women from at-risk families. Women from the high-risk group have access to the intensified surveillance programme, including annual MRI, independent of whether they undergo genetic testing or not. If no index patient is available for genetic testing because all affected women are deceased, a healthy woman can undergo genetic testing, if at least one of her risks is determined to be above the threshold. Only if a familial mutation has been ruled out is intensified surveillance not amenable. Women with a lifetime risk for breast cancer between 15% and 30% are classified in the moderate risk group and recommended a special surveillance programme without MRI.

According to the recommendations of the German Consortium for HBOC and the German Federal Medical Council (Bundesärztekammer), genetic testing can only be offered after informed consent has been obtained as a result of a comprehensive interdisciplinary genetic counselling, including enough time to think about possible consequences (Bundesärztekammer 1998; Schmutzler et al. 2003a).

Recently, the German Act on Genetic Diagnostics (Gendiagnostikgesetz 2009) came into practice. Informed consent is defined as the main purpose of the law, which regulates the conditions for genetic analysis and utilization of genetic data to avoid disadvantages and discrimination. The right "not-to-know" is deeply anchored in the law and has the same value as the right "to-know". Before a genetic test can be initiated, the test person has to be informed about the prospects and limitations of the test at-issue as well as about the consequences of the possible results and has to agree to the test in written form. In the case of predictive genetic testing, pre- and post-test genetic counselling is obligatory, and refusal has to be documented.

Discussion

Comparing the national guidelines and recommendations for genetic testing for hereditary breast and ovarian cancer in the UK, France, the Netherlands and Germany, the following remarks related to the point of public access of the documents and the simplicity in dealing with them have to be made. The Dutch "Erfelijke Tumoren: Richtlijnen voor Diagnostiek en Preventie" so-called "blue booklet" has to be highlighted as an ideal piece of work to guide one with the maximum transparency through the management of the different hereditary cancer syndromes. The chapter "Hereditary breast and ovarian cancer" is kept short and is easy to understand. Unfortunately, the document is up to now only available in Dutch, but a translation is planned for 2011. The guidelines of the other three countries are more detailed, in part repeating information, and they are therefore to some extent difficult to comprehend. The French website from the National Cancer Institute contains a lot of interesting background information and statistics. This website and also the related review article (Bonaïti-Pellié et al. 2009) are both available only in French. Being aware that the UK NICE guidelines have been created primarily to instruct primary care physicians, their elaborate structure becomes reasonable. Regarding the German situation, there is a lack of publicly accessible guidelines referring exclusively to hereditary breast and ovarian cancer. The German "Interdisciplinary S3 guidelines for the diagnosis, treatment and follow-up care of breast

cancer" (Kreienberg et al. 2008) is translated into English and publicly accessible but refer primarily to the management of breast cancer in general; hereditary breast cancer only represents a subchapter of this guideline. Under the assumption that this guideline was primarily developed for gynaecologists, detailed familial constellations are given, which are concomitantly the inclusion criteria for genetic testing. The concept for the management developed by the German Consortium for Hereditary Breast and Ovarian Cancer was published in German in 2003 (Schmutzler et al. 2003a). Members of the consortium regularly update the recommendations, but the results are not publicly available. One explanation is the federal structure of Germany. In contrast to the centrally regulated health care questions as in the UK, France and the Netherlands, in Germany, health insurance issues are regulated de-centrally by the federal states or even in smaller districts.

The issue of predictive genetic diagnostics for *BRCA1/2* mutations in the prenatal and preimplantation situation has not been systematically reviewed because of dynamic changes in social and legal standpoints related to this issue observed in all countries.

Indication criteria for genetic testing: similarities and differences

The prerequisite for genetic testing is the attendance of a genetic counselling session. The access to genetic counselling differs within the countries. While in the UK and the Netherlands for referral from primary care, a general practitioner or secondary care, a specialist is required, in France and Germany referral is usual, but not obligatory. An individual also has direct access to genetic counselling. In this case, difficulties can arise for reimbursement.

The indication criteria for genetic testing for hereditary breast and ovarian cancer rely in all four countries on the family history of breast cancer. Tables 1 and 2 give an overview of the distinct family constellations required for genetic testing. Several women with breast cancer are required (at least two), whereas at least one woman has to be diagnosed before the age of 50 years. Only in France is there no precise number of affected women or age at diagnosis required for access to genetic testing. The mandatory degree of relatedness is strictest in the UK NICE guidelines and less constrained in the French guidelines. Furthermore, an isolated individual history of early onset breast cancer is considered as an inclusion criterion in the Netherlands and Germany before the age of 35 years, in France before the age of 40 years, but not at all in the UK. Bilateral breast cancer in one woman is also accepted as an inclusion criterion in France without age limit and in the Netherlands and Germany with the first tumour diagnosed before the age of 50 years. In the UK, a woman with a first-degree relative with bilateral breast cancer at an average age of diagnosis younger than 50 years is recommended to be referred to a genetic service, but for inclusion for genetic testing, another affected person is required to reach the 20% probability threshold. Occurrence of ovarian cancer and male breast cancer within the family and partly also the morphology of the breast tumour are differentially considered in the four guidelines and discussed in further detail below.

All four guidelines recommend embedding genetic testing within the framework of genetic counselling.

Table 2 Manchester scoring system for *BRCA1/2* testing (Evans et al. 2004, 2009)

Cancer and patient age	*BRCA1*	*BRCA2*
FBC <30	6	5
FBC 30–39	4	4
FBC 40–49	3	3
FBC 50–59	2	2
FBC >59	1	1
MBC <60	5 (if *BRCA2* tested) for combined score=5 without prior testing	8
MBC >59	5 (if *BRCA2* tested) for combined score=5 without prior testing	5
Ovarian cancer <60	8	5 (if *BRCA1* tested) for combined score=5 without prior testing
Ovarian cancer >59	5	5 (if *BRCA1* tested) for combined score=5 without prior testing
Pancreatic cancer	0	1
Prostate cancer <60	0	2
Prostate cancer >59	0	1

Families referred to tertiary care are classified according to the Manchester scoring system for *BRCA1/2* testing. Scores are added for each cancer in a direct blood lineage (cancers on the same side of the family). The combined score is determined by adding both the *BRCA1* and *BRCA2* scores without consideration for prior testing; thus, MBC scores 5 points for *BRCA1* and ovarian cancer 5 for *BRCA2*. A combined score of 16 points can be used as a 10% threshold and 20 points as a 20% threshold in non-founder Western populations. In families with no unaffected females, a lower threshold could be used

FBC female breast cancer, *MBC* male breast cancer

According to a non-directive approach in genetic counselling, the UK NICE guidelines emphasize that "Healthcare professionals should respond to women who present with concerns, but should not, in most instances, actively seek to identify women with a family history of breast cancer". This section is from the original NICE guideline created in 2004, at a time when no definitive evidence of the possible interventions on life quality and expectancy was available. Taking newer data into account, a review of this section within an update of the NICE guidelines towards a more proactive approach could be expected.

Furthermore, it is emphasized in all four reviewed guidelines that genetic testing should first be performed in an index patient, a person with cancer. After a disease-causing mutation is identified within the family, predictive testing can then be offered.

Further differences were seen between the guidelines regarding the clinical management. Women who are eligible for genetic testing were not necessarily offered intensified surveillance including breast MRI, and those offered intensified surveillance were not automatically eligible for genetic testing. Access to intensified surveillance including breast MRI is in France and the Netherlands based mainly on the detection of a deleterious *BRCA1/2* mutation, while in the UK and Germany, it relies basically on the family history, whereby most women in the UK are eligible by the detection of a mutation. Since the clinical management was not the objective of this review, this is not discussed here in detail.

Handling of risk prediction models

Although it is well known that all risk prediction models are only suboptimal, each individual country endeavours to make the risk estimation process uniform and reproducible. Standardised approaches are the essential step towards evidence-based medicine, in order that clinical decisions do not depend solely on the experience of the health care provider. Risk prediction models are known and used in each country; however, the purpose or reason for their use differs in the four countries. There are no recommendations to use strictly one model. In the UK, risk prediction is applied to assess the likelihood of carrying a *BRCA1/2* mutation, since the test is offered only in case of an at least 20% probability of carrying a mutation. The Manchester scoring system is mainly applied for this purpose. As also developed by experts from the UK, BOADICEA is mainly applied to predict development of breast and ovarian cancer (Antoniou et al. 2004). In the French documents, risk prediction models, namely Claus, BRCAPRO, BOADICEA, Manchester and Tyrer-Cuzick, are mentioned as helpful tools in the clinical part "Chirurgie prophylactique dans les cancers avec prédisposition génétique" of the guideline regarding surveillance and prophylactic surgery. In the Netherlands, risk calculation models are recommended in clinical genetics. To predict the *BRCA1/2* mutation probability, Myriad, Manchester scoring system and BRCAPRO are applied. For the calculation of the lifetime risk, the Claus or the Claus-Extended model is in use (Jacobi et al. 2009). In Germany, the Cyrillic program, which incorporates the modified Claus model, is mainly in use, but application of other models is also accepted. Risk prediction in Germany is mainly performed to classify a woman according to her risk in the appropriate clinical surveillance program.

Ovarian cancer/prostate cancer

Compared to the breast cancer risk of *BRCA1* or *BRCA2* mutation carriers, the risk of developing ovarian cancer is many times higher for mutation carriers than for women from the general population. In the general population, around two out of 100 women will develop ovarian cancer during their lifetime. In contrast, up to 60 women out of 100 *BRCA1* mutation carriers and up to 30 out of 100 *BRCA2* mutation carriers will develop ovarian cancer (King et al. 2003). Newer data assume that 10% of all ovarian cancer cases are caused by mutations in the genes *BRCA1* and *BRCA2*, and approximately 30% of ovarian cancers due to mutations in these genes may be missed if one relies on a family history alone (Gulden and Olopade 2010). Therefore, it was suggested to offer genetic testing to every woman with ovarian cancer irrespective of her family history. Regarding the new targeted therapeutic opportunities with PARP inhibitors, identification of women with a BRCA-related cancer is reasonable and will play a role in individualized medicine once the drugs are licensed for treatment. Occurrence of ovarian cancer within the family is considered in all four national guidelines as a criterion to access for genetic testing, but only the French and the Dutch guidelines permit an isolated ovarian cancer as an inclusion criterion, in France with the age of diagnosis before 70 years and in the Netherlands before the age of 50 years.

In the UK and in Germany, the occurrence of another disease, either breast or ovarian cancer in the same women or within the family, is required.

In this context, it should be mentioned that the Dutch guidelines specifically consider occurrence of prostate cancer within the family. One prostate cancer before the age of 60 years together with a breast or ovarian cancer before the age of 50 years counts in the Netherlands as an inclusion criterion. Since an increased risk for prostate cancer at a younger age, in particular for *BRCA2* mutation carriers, is known (Liede et al. 2004), it seems reasonable for all guidelines to consider prostate cancer and possibly

further *BRCA1/2*-associated tumours, like pancreatic cancer, when occurring together with breast and/or ovarian cancer within a family, as an inclusion criterion. The UK guidelines are different in that they simply specify a 20% threshold rather than give an algorithm of examples. This means that models and scoring systems are required, and some of these do use prostate and pancreatic cancer within them (Amir et al. 2010; Evans et al. 2009). The Manchester scoring system, applied for selection for genetic testing, includes occurrence of prostate and pancreatic cancer within a family (see Table 2). Although the scores for this are low, they could be crucial in a borderline situation. Since the first selection step is on the level of the primary care physicians, it would be reasonable for them to work already with the Manchester scoring system, in order not to miss borderline families, instead of relying exclusively on the elaborate family constellations given in the NICE guidelines.

Consideration of the tumour morphology

Besides classifying women into a high-risk collective based exclusively on the family history, other criteria for classification would be helpful.

It has been repeatedly suggested that pathological data of the tumours should be incorporated in addition to the family history for prediction of a mutation in the breast cancer genes (Lakhani et al. 2002; Evans et al. 2009). Applying morphological features allowed Lidereau et al. already in 2000 to identify a *BRCA1* mutation in 28.6% of the group of both oestrogen receptor negative and high-grade tumours diagnosed before the age of 35 years, regardless of the family history. Particularly, *BRCA1*-related tumours, compared to sporadic breast cancers, are predominantly invasive-ductal high-grade (G3) carcinoma and show an over-representation of the so-called "triple-negative" phenotype, being negative for oestrogen-receptor, progesterone-receptor and HER2 expression (Gadzicki et al. 2009; Ahrens and Kreipe 2009). Furthermore, they exhibit typical features of basal-like carcinomas, expressing specific cytokeratins of the basal layer like CK5 and CK14. Additional characteristics are a lymphocytic infiltration of the tumour and fast growth with pushing margins. Because of the typical morphological features, in particular regarding the triple negativity, Young et al. (2009) identified a mutation in 11% of their collective of women affected with a triple-negative breast cancer before the age of 40 and concluded that women with early onset triple-negative breast cancer are candidates for genetic testing for *BRCA1*, even in the absence of a family history of breast cancer. The consolidation of the knowledge considering the morphology into the national guidelines is only realized in part. The Dutch indications include the criterion "breast cancer under age 40 and a hormone-receptor triple negative tumour". The French guidelines take note of the knowledge, but reason not to incorporate this criterion at the moment because of lack of evidence. The UK NICE guideline up to now do not take into consideration the pathologic subtype of the tumour, although this part of the guidelines has not been updated since 2004. However, even an isolated triple-negative breast cancer diagnosed <30 years of age still has less than the 20% probability of a mutation required by NICE in the UK. The new update of the Manchester scoring system suggests incorporating the breast pathology to assess a more exact adjustment of the probability of a mutation (Evans et al. 2009). The recent publication of Kwon et al. (2010) shows that testing of women younger than 50 years with triple-negative breast cancer, regardless of family history and ethnicity, is a cost-effective strategy and could reduce subsequent breast and ovarian cancer risks. Within the German Consortium, there is an internal discussion about this point of testing women with triple-negative breast cancer. The indication criteria for hereditary breast and ovarian cancer according to the German Society of Human Genetics take this into account (Deutsche Gesellschaft für Humangenetik 2008). Testing of isolated cases with a triple-negative phenotype is welcome under research conditions, but it is not part of the contract with the health insurance companies, that guarantee refunding.

Intervening healthy male relative

The problem of an intervening healthy male relative in assessing the family history is partly solved in the national recommendations. It may be assumed that this is the reason why no degree of relatedness between the counsellee and the affected women is given in France, the Netherlands and Germany. In France and Germany, even the degree of relatedness among the affected women themselves is not stated. The sole requirement is that the affected women are from one and the same side of the family. The UK Manchester scoring system requires that the cancers occurring are in a direct blood lineage on the same side of the family and thus allows a certain amount of scope, while the familial constellations given in the NICE guidelines for the first selection step refer mainly to first- and second-degree relatives and are therefore more limiting.

Access to clinical surveillance

In addition to regulating the access to genetic testing, all guidelines give recommendations for clinical surveillance, mostly differentiating between women at raised or moderate risk, also classified as familial breast and ovarian cancer, and high risk or hereditary breast and ovarian cancer. Differences are also noticeable between the impact of the

genetic test result on the recommendations for surveillance. While inclusion criteria for genetic testing are less constrained in France, they are much stricter in the UK. On the other hand, intensified screening options, including MRI, are recommended in France mainly to *BRCA1/2* mutation carriers. However, in France when such a medical prescription is offered for women with family history, the fees for screening examinations will be covered. Regarding the situation in the UK, although most women are eligible for intensified surveillance by detection of a mutation, according to the NICE guidelines, the clinical surveillance approach also includes women because of their family history. In the Netherlands, intensified surveillance including MRI is offered for mutation carriers and women from families with a mutation who have a 50% probability of being mutation carriers. In Germany, intensified surveillance is justified for high-risk women who present a risk of heterozygosity of ≥20% or a residual lifetime risk for breast cancer of ≥30%, independent of genetic testing. Informed consent and the right "not-to-know" are highly regarded; therefore, surveillance is guaranteed also without testing.

Relevance of the guidelines for clinical routine and open questions

Without doubt, the existence of guidelines and recommendations is most helpful for the daily routine. Presence of different family constellations can be aligned with the given examples to decide whether this is a case of a high-risk situation or not. The further management of an individual woman can therefore be easily assessed. The aim of nationwide criteria is to ensure cross-site consistency so that equal treatment of the family can be ensured independent of the location of the cancer genetics clinic in which the counsellees present. This point is of particular importance in the context of genetic services, since hereditary diseases affect the whole family and the individual family members often do not live in the same place. Following the criteria guarantees that subsequent decisions will not be guided by the opinion of the counsellor. However, there are problematic situations within genetic counselling and testing for hereditary breast and ovarian cancer that are not solved in the guidelines.

Families not fulfilling the criteria

A mentionable portion of families do not strictly fit the given criteria. This situation is additionally complicated by the fact that only about 50% of all women with a *BRCA1/2*-related tumour have a conspicuous family history due to small family size or transmission through the paternal line (King et al. 2003; de Sanjosé et al. 2003). This matter is hard to integrate into criteria defined by family constellations, in particular when they are very strictly defined. The final responsibility lies with the genetic counsellor. Related to her/his experience, the counsellor has to decide whether a genetic predisposition for breast cancer may exist in the presented family.

No index patient available

To ensure the highest informative value, there is agreement in all four national guidelines to perform mutation screening first in an affected individual, the so-called index patient. Only after identification of a disease-causing mutation can predictive testing for the identified mutation be offered to healthy relatives in a second step. However, genetic counsellors are also confronted with families that show a significant probability of carrying a mutation, but in which all affected individuals are already deceased. A rational approach has to be found in these situations. One possibility could be to discover, according to the pedigree, the individual with the highest risk and to offer this person genetic testing, even if this is not necessarily the counsellee herself. Furthermore, counsellors are faced with a related problem when the counsellee has been adopted and only has sparse information about her biological family or in families in which relatives are at odds with each other and the counsellee refuses to contact the index patient.

Phenocopies

Because of the relatively high prevalence of breast cancer in the general population, it is probable that a sporadic breast cancer will occur in a family with a *BRCA1/2* mutation. Therefore, from time to time, the genetic analysis reveals no mutation despite a high prior probability. The European Molecular Genetics Quality Network (EMQN) best practice guidelines for molecular genetics analysis in hereditary breast/ovarian cancer (Larsson et al. 2007) concentrated on this phenomenon of phenocopies and suggest testing a second person in the family to exclude the possibility that a woman with a sporadic case has been tested in the first instance. Indeed, phenocopies reduce the likelihood of identifying the mutation in a bone fide *BRCA1/2* family by 5–6% (Smith et al. 2007). Only the Dutch guideline for the clinical geneticists deals with this problem and indicates the possibility of phenocopies. A rational approach could be, for example, to remove this first tested woman, in whom the test result reveals no mutation, from the pedigree and to perform a new evaluation of the family. Only if the criteria are still fulfilled should a second woman be tested.

Unclassified variants

Dealing with variants of unclassified clinical significance (UVs) presents a real challenge within the counselling

practice. Approximately one third of all detected sequence changes within the *BRCA1* gene that are not deleterious mutations and are excluded as being polymorphisms are UVs. The number is even higher within the *BRCA2* gene with more than half of the detected sequence changes. The effect of these changes, which are mostly missense substitutions or very rare small in-frame deletions, both leading to amino acid sequence changes or intronic sequence changes, has been tried to be predicted with different prediction programs. The clarification of their significance by determining their frequencies and co-segregation, co-occurrence and LOH analysis is ongoing (Goldgar et al. 2004). Communicating a UV as a genetic test result harbours an unsatisfying situation. In some families, segregation analysis is possible to get an idea of the impact of the UV. Carriers of a UV are, in general, managed as individuals in whom mutation screening reveals no deleterious *BRCA1/2* mutation. A conclusion of clinical consequences, as for the recommendation of prophylactic oophorectomy, is much more difficult than for mutation carriers and depends on the family history. Despite the relatively high frequency of the UVs, again only the Dutch guideline for clinical geneticists deals with this point. It is recommended in the Netherlands to perform segregation analysis within the family.

Further breast cancer susceptibility genes and *BRCA1/2* modifiers

Mutations in the breast cancer genes *BRCA1* and *BRCA2* are only present in at the most one half of all families with hereditary breast cancer. Another small portion is due to mutations in further high-penetrance genes like *TP53*, *PTEN* or *CDH1*. The UK NICE guidelines do not only apply to *BRCA1* and *BRCA2* but also mention the *TP53* gene and the familial criteria, which have to be fulfilled to offer *TP53* testing. The French, the Dutch and the German recommendations concentrate in the case of hereditary breast and ovarian cancer only on the genes *BRCA1* and *BRCA2*. Since genetic counselling is in all countries the precondition prior to genetic testing, it could be assumed that while recording the family history, the genetic counsellor would notice whether another cancer-associated syndrome could be present in this family and offer testing for the corresponding gene. The resulting consequences associated with the detection of a mutation, e.g. avoiding radiation and therefore mammography in the case of a Li-Fraumeni syndrome, are a matter for the post-testing genetic counselling.

The risk for a *BRCA1/2* mutation carrier to indeed develop breast and/or ovarian cancer depends not only on the presence of the mutation in *BRCA1* or *BRCA2* but also on the individual genetic background. It could be shown that single-nucleotide polymorphisms (SNP) and rare alleles, previously associated with breast cancer susceptibility, may influence the disease risk (Antoniou et al. 2010a, b; Ramus et al. 2011). The individual constellation of these so-called modifiers seems to be the crucial point for the penetrance of the *BRCA1/2* mutation. Further modifiers of *BRCA1/2* are being constantly identified. Thus, it would be helpful to determine the spectrum of modifiers that need to be tested in case of detection of a *BRCA1/2* mutation and to define how to adopt the clinical management.

Furthermore, it is believed that additional very rare highly penetrant alleles exist, mostly of genes involved in DNA repair. Recently, *RAD51C*, a newly identified Fanconi anaemia-like gene, was described within a German collective as a very rarely altered third highly penetrant breast and ovarian cancer susceptibility gene (Meindl et al. 2010). These findings were adopted in Germany, and the GC-HBOC decided to implement *RAD51C* mutation screening (personal communication from Meindl A. and Schmutzler R.). The analysis is restricted to *BRCA1/2*-negative breast cancer families in which ovarian cancer also occurred. Further studies are needed to determine the frequency of *RAD51C* mutations in other populations.

Besides the very rare high-penetrance alleles, rare moderate-penetrance alleles and common low-penetrance alleles seem to be associated with an increased breast cancer risk (Turnbull and Rahman 2008; Foulkes 2008). The current explanation for the remaining non-*BRCA1/2*-families is considering the conception of a polygenic trait as a result of an interaction of multiple common genetic factors (Ripperger et al. 2009). There has been discussion about the role of the moderately penetrant variants, like *PALB2* or *CHEK2* and the reason to test for them. Since they are present in different frequencies within different populations, it is hard to find consensus about their relevance. There is evidence that *CHEK2* mutations led to a fourfold increased risk when they occurred in a familial context (Fletcher et al. 2009; Narod 2010). Assuming that the *CHEK2* effect is part of a combined effect of a set of modifying genes and inherited together with them, screening for at least the 1100delC mutation in *CHEK2* seems adequate. Because there is increasing knowledge and demand for *CHEK2* mutation screening within the general population, it would be helpful if the national guidelines would incorporate these insights and transparently discuss the clinical utility of the identification of a *CHEK2* mutation.

Individual breast cancer susceptibility is also influenced by the interaction of several common low-penetrance variants. Since the cumulative risk of the different patterns cannot be adequately interpreted at the moment and therefore not translated into clinical utility, genetic testing for low-penetrance variants is technically possible, but not recommended (Ripperger et al. 2009). It can be expected that, with the next generation sequencing technologies,

testing costs will be significantly reduced, and new insights will be gained in the near future. Screening for a composition of genes will become available to determine individual breast cancer risk (Morgan et al. 2010). Accompanied by the cost reduction, genetic testing could be applied to a wider range of individuals, bringing new insights into the risks associated with different patterns of alterations in cancer susceptibility alleles and characteristics on pheneotypes (Walsh et al. 2010). To control the complexity of information, tailored guidelines will then be needed for the clinical management of the different risk groups.

Conclusion

The reassuring result of comparing the national guidelines regarding genetic testing for familial/hereditary breast and ovarian cancer is that most of the families would be treated equally, regardless of whether they present in the UK, France, the Netherlands or Germany. However, despite the same state of knowledge, a small portion of families, in particular small families, families with transmission through the paternal line or families in which all index patients are already deceased, would experience different management and according to the guidelines would fulfil the criteria for genetic testing in one country but not in another. This situation is not in accordance with the European Union laws, so-called directives, which are enacted to implement and protect the idea of free movement of goods, services, people and capital. In the long term, the EU laws are steering towards establishing a general framework for the provision of safe, high quality and efficient cross-border health care in Europe (Nys 2010). Without any intention to interfere with Member States' competence regarding genetic testing, the European Commissions' Directorate General Research aims to ensure exchange of information and to identify actions which should be addressed at EU level in order to assure the highest quality of genetic testing (European Commission 2005). The highest priority was confirmed for the collaboration and exchange of information regarding quality assurance of genetic testing (Commission of the European Communities 2004). Furthermore, recently, the European Parliament has approved the uptake of cross-border healthcare.

Since competition usually enhances quality, it could be assumed that the harmonization process for the national guidelines regarding genetic testing for familial/hereditary breast and ovarian cancer will be a tool towards improvement that will guarantee safe and high quality health care across Europe for counsellees moving from one country to another and will also facilitate free movement for health care professionals.

A reasonable approach to harmonize the thresholds for inclusion could be a compromise between the strict family history-orientated NICE guidelines from the UK and the less constrained French criteria. The Dutch and German guidelines represent something in between, but there is still room for improvement. Everywhere, new scientific evidence is integrated with great delay. Only the Dutch guidelines, mainly in the part intended for clinical geneticists, consider associated *BRCA1/2*-related tumours, take into consideration the phenomenon of phenocopies, the consequences of detection of a UV and the knowledge of the relatively high portion of triple-negative tumours within *BRCA1*-associated breast cancer. These questions as well as the problem of an intervening male relative, or the situation that no index patient is available for testing, need to be reviewed. Regarding new targeted therapeutic strategies, the significance of the histology of the breast tumour, as mentioned above, as well as the value of an isolated ovarian cancer needs to be verified. A simple scoring method to classify the family, like the Manchester scoring system, seems to be a reasonable and an easy to use tool and suitable to assert throughout different European countries. In order to assess at least the probability of a *BRCA1/2* mutation, this selection approach would be helpful already at the first level. Furthermore, the question of how to deal with the newly identified breast cancer susceptibility genes as well as with the new upcoming high throughput sequencing technologies remains to be clarified. Furthermore, inclusion criteria for intensified surveillance including breast MRI vary significantly across the four countries.

Guidelines orientated on different levels and disciplines should be discussed, since the process for every player involved could possibly be thereby facilitated. General practitioners, clinical specialists, geneticists and researchers need different information and different support for decisions. An open communication process including all these topics seems most promising to react adequately to the current level of knowledge and to improve the quality of genetic counselling and testing for familial/hereditary breast and ovarian cancer across Europe.

Acknowledgements The authors gratefully acknowledge Gillian Teicke for her support in preparing the manuscript. This work was supported by the German Bundesministerium für Bildung und Forschung (BMBF, Federal Ministry of Education and Research), contract number 01GP0617. Prof. Evans is supported by the NIHR Biomedical Research Centre in Manchester.

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