



Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejancer.com



Position Paper

Genetic counselling and testing of susceptibility genes for therapeutic decision-making in breast cancer—an European consensus statement and expert recommendations



Christian F. Singer ^{a,*}, Judith Balmaña ^b, Nicole Bürki ^c,
Suzette Delaloge ^d, Maria Elisabetta Filieri ^e, Anna-Marie Gerdes ^f,
Eli Marie Grindedal ^g, Sileni Han ^h, Oskar Johansson ⁱ, Bella Kaufman ^j,
Mateja Krajc ^k, Niklas Loman ^l, Edith Olah ^m, Shani Paluch-Shimon ⁿ,
Natalija Dedic Plavetic ^o, Kamil Pohlodek ^p, Kerstin Rhiem ^q,
Manuel Teixeira ^r, D. Gareth Evans ^s

^a Medical University of Vienna, Department of Obstetrics and Gynecology, Vienna, Austria

^b Medical Oncology Department, Hospital Vall d'Hebron, Vall d'Hebron, Institute of Oncology, Universitat Autònoma de Barcelona, Barcelona, Spain

^c Department of Gynecology and Obstetrics, University Hospital Basel (UHB), Spitalstrasse 21, 4031, Basel, Switzerland

^d Department of Cancer Medicine, Gustave Roussy, 114 Rue Edouard Vaillant, 94800 Villejuif, France

^e Department of Medical Oncology, University Hospital of Modena, Via del Pozzo, Modena, Italy

^f Department of Clinical Genetics, Rigshospitalet, Copenhagen, Denmark

^g Department of Medical Genetics, Oslo University Hospital, Oslo, Norway

^h Department of Gynecology and Obstetrics, UZ Leuven, Leuven, Belgium

ⁱ Landspítali-the National University Hospital of Iceland, Reykjavik 101, Iceland

^j Breast Oncology Institute, Sheba Medical Center, Tel Hashomer, Israel

^k Institute of Oncology Ljubljana, Slovenia, Zaloska 2, 1000 Ljubljana, Slovenia

^l Department of Clinical Sciences, Division of Oncology and Pathology, Lund University Hospital, 221 85 Lund, Sweden

^m Department of Molecular Genetics, National Institute of Oncology, Budapest, Hungary

ⁿ Shaare Zedek Medical Centre, Jerusalem, Israel

^o Department of Oncology, Division of Medical Oncology, University Hospital Centre Zagreb, University of Zagreb, School of Medicine, Zagreb, Croatia

^p Second Department of Gynecology and Obstetrics, Comenius University of Bratislava, Faculty of Medicine, 82606 Bratislava, Slovakia

^q Center for Familial Breast and Ovarian Cancer, Center for Integrated Oncology, Medical Faculty, University Hospital of Cologne, D-50931 Cologne, Germany

^r Department of Genetics, Portuguese Oncology Institute, Porto, Portugal

* Corresponding author: Department of OB/GYN and Comprehensive Cancer Center, Medical University of Vienna Waehringer Guertel 18-20, 1090 Vienna, Austria. Fax: +43 (0)1 40400 23230.

E-mail address: christian.singer@meduniwien.ac.at (C.F. Singer).

¹ www.meduniwien.ac.at

^s Department of Genomic Medicine, Division of Evolution and Genomic Science, University of Manchester, MAHSC, St Mary's Hospital, Manchester M13 9WL, United Kingdom

Received 21 August 2018; received in revised form 9 October 2018; accepted 10 October 2018
Available online 22 November 2018

KEYWORDS

BRCA;
BRCA1;
BRCA2;
Metastatic breast cancer;
Genetic testing;
Genetic counselling;
Hereditary breast cancer

Abstract An international panel of experts representing 17 European countries and Israel convened to discuss current needs and future developments in *BRCA* testing and counselling and to issue consensus recommendations. The experts agreed that, with the increasing availability of high-throughput testing platforms and the registration of poly-ADP-ribose-polymerase inhibitors, the need for genetic counselling and testing will rapidly increase in the near future. Consequently, the already existing shortage of genetic counsellors is expected to worsen and to compromise the quality of care particularly in individuals and families with suspected or proven hereditary breast or ovarian cancer. Increasing educational efforts within the breast cancer caregiver community may alleviate this limitation by enabling all involved specialities to perform genetic counselling. In the therapeutic setting, for patients with a clinical suspicion of genetic susceptibility and if the results may have an immediate impact on the therapeutic strategy, the majority voted that *BRCA1/2* testing should be performed after histological diagnosis of breast cancer, regardless of oestrogen receptor and human epidermal growth factor receptor 2 (HER2) status. Experts also agreed that, in the predictive and therapeutic setting, genetic testing should be limited to individuals with a personal or family history suggestive of a *BRCA1/2* pathogenic variant and should also include high-risk actionable genes beyond *BRCA1/2*. Of high-risk actionable genes, all pathological variants (i.e. class IV and V) should be reported; class III variants of unknown significance, should be reported provided that the current lack of clinical utility of the variant is expressly stated. Genetic counselling should always address the possibility that already tested individuals might be re-contacted in case new information on a particular variant results in a re-classification.

© 2018 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Background

As per the most recent data from the International Agency for Research on Cancer (IARC), the lifetime risk for a woman in most parts of Europe and Israel varies between approximately 8% and 12% [1]. Women with one or more affected family members face a further increase in their lifetime risk, but the cumulative risk is highest in women who carry a *BRCA1* or *BRCA2* germline mutation: from a prospective study, *BRCA1* carriers will develop breast cancer by age 80 years with a probability of 72%, and *BRCA2* carriers, with a probability of 69% [2]. Mutation carriers who have been diagnosed with breast cancer have a 26% (*BRCA2*) to 40% (*BRCA1*) chance of developing contralateral breast cancer in the following 20 years. Women with a *BRCA* variant also carry a substantial risk for developing ovarian cancer, which ranges from 17% in *BRCA2* to 44% in *BRCA1* carriers, and which is considerably higher than the 2% lifetime risk of the general population [2,3].

Knowledge of the individual mutation status thus not only allows to assess individual cancer risks and to consider intensified early detection strategies or risk

reducing surgery but increasingly also has therapeutic implications for women who have already developed breast or ovarian cancer: *BRCA* mutation carriers with newly diagnosed early breast cancer often chose bilateral mastectomy over unilateral lumpectomy [4]. In addition, women with newly diagnosed breast cancer who undergo rapid early genetic testing have also been demonstrated to prefer mastectomy over lumpectomy [5]. Two recent clinical trials with advanced breast cancer have convincingly demonstrated that the poly-ADP-ribose-polymerase (PARP)-inhibitors olaparib and talazoparib prolong progression-free survival of *BRCA1* and *BRCA2* mutation carriers beyond what conventional chemotherapy regimens are able to achieve in this setting [6–13]. A large adjuvant trial investigating the efficacy of olaparib in *BRCA1/2* germline mutation carriers with early breast cancer (OLYMPIA) is ongoing [14].

With the availability of Next Generation Sequencing (NGS), it is now possible to offer mutational analysis for *BRCA1* and *BRCA2* and several other moderate- to high-risk penetrance genes that elevate the lifetime risk of developing breast cancer as part of a diagnostic routine with a short turnaround time and diminishing

costs. The increasing role of and demand for genetic testing for therapeutic purposes has infrastructural, legislative and financial consequences. In the light of these recent developments and the arising clinical and ethical questions, a panel of experts in *BRCA* testing representing 17 European countries and Israel convened to assemble information on the current status of *BRCA* and other gene testing across Europe and Israel and to formulate consensus recommendations for *BRCA* testing in the metastatic breast cancer context.

2. Methods

Nineteen experts from the following countries participated in the consensus process: Austria, Belgium, Germany, Croatia, Denmark, France, Hungary, Iceland, Israel, Italy, Norway, Portugal, Slovakia, Slovenia, Spain, Sweden, Switzerland and the UK. The medical specialities represented are as follows: clinical or medical geneticists (32%), oncologists (37%), gynaecologists (26%) and surgeons (5%). Forty-three percent worked in an academic setting (for instance non-university-based national research centres or university-associated public health hospitals or national cancer center with genetic research), 30% at a university, 13% in non-profit organisations, 4% in the private setting and 9% in other types of work settings.

A consensus method was applied [15]. Twenty-seven questions relevant to genetic counselling and testing in affected and non-affected women with a familial breast or ovarian cancer background were sent out to panel members before the meeting and were open for discussion and subsequent voting during the expert panel meeting. Conflict of interest statements were collected in writing at the meeting, and panelists with a conflict of interest in one or more questions were asked to abstain from voting at the respective question. Questions could be modified during the voting session if >50% of panelists agreed. Most questions were not modified; however, some questions were rendered more precisely following discussion. The meeting was recorded, and all modifications from the pre-defined questions were documented in writing. Voting results were translated into panel recommendations conveying the strength of panel support for each recommendation based on the following rules: An ‘agreement/consensus’ was defined as an agreement among >75% of panelists, and a ‘majority’ was defined as an agreement among 50%–75% of panelists. The proportion of panelists abstaining from vote was recorded for each question.

We present here the results of all panel discussions regarding the 27 questions submitted to the panel. In the Appendix, the questions asked and the votes obtained for each question are summarised; the individual question numbers are cross-referenced between this summary and the Appendix (e.g. [Q1] in the summary refers to question 1 in the appendix). The written report was

circulated in an iterative open email process until consensus was reached. The results reported below are explained based on the votes and discussions of the panel.

For the purpose of the consensus meeting, the term ‘predictive testing’ was defined as genetic testing of healthy individuals with a personal/familial (hereditary) breast and/or ovarian cancer (HBOC) background, irrespective of whether an identified pathogenic variant has been described in their family or not, and testing of individuals with a history of breast or ovarian cancer in whom the test result has no direct therapeutic consequence. The aim of predictive testing is to provide a genetic cancer risk estimation. ‘Therapeutic testing’ was defined as genetic testing in which the result has a direct or indirect implication on cancer treatment. The term ‘pathogenic variant’ was used for class IV and V genetic variations [16].

3. Recommendations

3.1. Genetic counselling

Given the fact that the identification of pathogenic variants in *BRCA1* or *BRCA2* and other additional genes has clinical implications, a growing demand for counselling and testing is expected in the near future. While the experts agreed that the availability of high-throughput sequencing technologies such as NGS across Europe is adequate to cover the increased demand for testing in the years to come, the majority of experts (60%) also stated that it will not be possible to address the need for predictive and therapeutic counselling within the next five years [Q18], if restricted to clinical geneticists exclusively (as currently organised in most countries).

3.1.1. Counselling in the predictive setting

Within the next 5 years, the workload for predictive counselling was expected to increase by 50% by 39% of experts, and to increase by 100% by another 33% of experts [Q19]. All experts agreed that waiting times for counselling in the predictive setting should not exceed 2 months, but given the limitations in infrastructure for appropriate counselling and aftercare, a range of 2–6 months would be acceptable [Q10]. To decrease waiting times in non-affected members from HBOC families, the majority of experts (71%) agreed that genetic counselling in the predictive setting should—if possible within national legislation—not be restricted to clinical geneticists or genetic counsellors [Q16]. It was also noted that predictive counselling of unaffected individuals from HBOC families usually involves a broader perspective than therapeutic counselling, and usually covers individual risks for other malignancies, descendant’s risk to inherit mutations, preventive options, lifestyle issues and

so on. And, therefore, professional training, particularly of non-geneticists, needs to account for these aspects. In addition, predictive counselling often necessitates professional psycho-oncological support which is best given by involving trained psycho-oncologists.

3.1.2. Counselling in the therapeutic setting

With regards to genetic counselling in a therapeutic setting, all experts agreed that the workload will increase in the years to come: the majority of experts expected the workload to double (44%) or increase by more than 100% (33%) within the next 5 years [Q20]. Because counselling of already affected individuals is often primarily focused on direct therapeutic implications and recurrence risks, all experts agreed that—within the respective national legal framework—all adequately trained professions, including clinical geneticists, genetic counsellors (physicians and non-physicians), oncologists, surgeons, gynaecologists and trained nurses, should be authorised to perform genetic counselling for affected women [Q15]. In patients with metastatic breast cancer, experts unanimously agreed that the waiting time between the indication for genetic counselling and the availability of the result of the genetic analysis should not exceed 3 weeks to avoid significant delays in treatment, because the test results often have immediate therapeutic implications for this group of patients [Q11]. In addition, in patients with newly diagnosed early breast cancer, in whom surgical decision-making depends on the result of genetic testing, preferential testing should be attempted to prevent delays in curative surgery.

3.1.3. Educational needs

The experts concluded that, to enable easily accessible and nationwide genetic counselling, and to guarantee short waiting times particularly in therapeutic counselling, educational efforts are urgently needed. Initiatives suggested by the experts included online tutorials, webinars or training courses in genetic counselling that could be offered to interested physicians or breast care nurses. Because gene panel testing now also allows detection of pathogenic variants in genes beyond *BRCA1* and *BRCA2* that may have substantial clinical implications for other malignancies, most major guidelines also recommend a multidisciplinary and multilevel counselling approach [6–9,17,18].

4. Genetic testing

4.1. Genetic testing in the predictive setting

During the panel discussion, questions arose around the true definition of ‘predictive’ in the light that very often testing starts with an affected family member and relatives are tested as a second step. The panel agreed on the definition set forth in the methods section of this publication.

The experts concurred with 94% agreement that predictive genetic testing in healthy individuals with a familial background of breast cancer should not be restricted to *BRCA1/2* [Q5]. A set of high-risk actionable genes with evidence of clinical impact was defined as a minimum required panel of high risk actionable genes [Q7]. This basic gene panel was set to include *BRCA1*, *BRCA2*, *TP53* (particularly if the patient has an early disease onset or family history suggestive of Li-Fraumeni syndrome) and *PALB2*. It was, however, also agreed that different populations may require different gene sets. Gene panels discussed at the meeting included *BRCA1*, *BRCA2*, *TP53*, *PTEN*, *PALB2*, *STK11*, *ATM*, *CHEK2*, *CDH1*, *MLH1*, *MSH2*, *MSH6*, *BRIP1* and *RAD51D/C*. Different panelists felt a justification for a selection of some of these genes, but there was an agreement between the experts that the previously mentioned four genes represented the absolute minimum of genes that should be tested.

Experts also agreed (83%) that, given the low cost and high-throughput that can now be achieved by NGS, analysing a number of the most common *BRCA1/2* variant loci (i.e. “hotspot testing”), rather than completely sequencing the whole genes is not acceptable [Q14]. A possible exception would only be founder mutations that represent more than 99% of pathogenic variants identified in the gene of interest in a specific geographical region or setting.

Overall, the panel expressed that, in the setting of limited resources, the goal of genetic counselling and testing strategies should rather focus on providing *BRCA1/2* testing to a larger number of potential carriers, than on investigating large gene panels in a smaller number of individuals.

4.2. Genetic testing in the therapeutic setting

The experts agreed (89%) that currently *BRCA1/2* testing is not indicated solely on the basis of a diagnosis of breast cancer, because the prevalence of *BRCA1/2* germline mutations is low in the absence of a suggestive family history, or young age at onset [Q1], although it was shown that, for example, in Norway more than 60% of identified mutation carriers did not have a suggestive family history [19]. The diagnosis of TNBC, the presence of a family history, young age at onset and the presence of a clinical setting in which the detection of a *BRCA1/2* germline mutation would qualify a patient for PARPi treatment are indications for *BRCA1/2* testing [Q21]. In these cases, the majority of experts (69%) recommend that testing should be offered after the histological proof of breast cancer and should not be restricted to the advanced cancer setting [Q22]. Already today, the presence of a suggestive family history and young age at onset are relative indications for expedited *BRCA1/2* testing in many countries, if an early breast cancer patient considers bilateral mastectomy in case a germline mutation is detected.

This implies that with the approval of PARPi in advanced disease, genetic testing may increasingly become an integral part of the routine workup in both early and advanced breast cancer.

When asked to whom genetic testing should be offered in the metastatic setting, the majority of experts (60%) voted that *BRCA1/2* testing should be offered to all patients, while 20% of experts voted that *BRCA1/2* testing should be limited to patient with a familial/personal history suggestive of a *BRCA1/2* mutation [Q27]. The majority of experts consequently also voted that *BRCA1/2* testing should be offered to patients with human epidermal growth factor receptor 2 (HER2) positive (59%) [Q26] and HR positive (57%) [Q28] disease, even if family history is not suggestive. This recommendation was given in light of the recently published Assessment of the Efficacy and Safety of Olaparib Monotherapy Versus Physicians Choice Chemotherapy in the Treatment of Metastatic Breast Cancer Patients With Germline *BRCA1/2* Mutations. (OlympiAD) [11] and A Study Evaluating Talazoparib (BMN 673), a PARP Inhibitor, in Advanced and/or Metastatic Breast Cancer Patients With *BRCA* Mutation (EMBRACA Study) (EMBRACA) [13] trial results, and explicitly acknowledged the fact that the likelihood for a pathogenic variant in *BRCA1/2* in a breast cancer patient, who has no family history, is around 2% [20]. It was, however, also discussed that clinical data addressing the efficacy of PARPi in HER2 positive metastatic breast cancer are not available. Therefore, the panelists argued that it is debatable whether countries with limited health-care resources should implement a more restrictive testing strategy. Seventy-four percent of experts were in favour of also testing additional breast cancer-associated genes [Q2], even if the efficacy of PARPi has not been clinically validated in the non-*BRCA1/2* setting, and although few genes are known, in particular *PALB2* [21] and *BRIPI* [22], in which a functional alteration might still have potential surgical consequences such as bilateral mastectomy or risk reducing bilateral salpingo-oophorectomy. However, the therapeutic benefit of risk-reducing surgery in mutation carriers with advanced breast cancer is questionable.

Despite the unanimous support for generalised testing, it was also cautioned that as long as the test results particularly in low or intermediate penetrance genes are not clinically actionable, the mere knowledge of ‘having a mutation’ might result in false treatment expectations in affected individuals. The experts felt that particularly pretest counselling of breast (and ovarian) cancer patients should convey the limited clinical consequences particularly in women with non-*BRCA1/2* mutations. Pretest counselling should also include implications of the genetic result for relatives, particularly in case high penetrance gene mutations are detected. All experts were in favour of a structured oncological

counselling pathway [Q36], which should also involve informed consent before gene testing.

4.3. Genetic testing in breast cancer tissue

The majority of experts (74%; two experts abstained) agreed that in routine clinical practice genetic testing of tumour tissue for the detection of somatic *BRCA1/2* and other breast cancer-associated genes should not be part of a diagnostic algorithm in metastatic breast cancer [spontaneous question arising from discussion]. The presence of somatic gene alterations does not currently have a therapeutic consequence and does not absolve from germline testing. It should, however, be noted that the prevalence of somatic mutations in *BRCA1/2* is likely to be higher than previously thought. In a recently published article including 273 Swedish breast cancer patients, the likelihood of a *BRCA1/2* mutation being somatic was $\sim 1/3$, and germline, $2/3$ [23]. It was therefore remarked that, while available evidence does not currently support routine *BRCA1/2* or panel testing in tumour tissue, it is nevertheless important for research purposes and may have clinical consequences in the future. It will therefore be particularly important to determine the prevalence of somatic genetic variants of *BRCA1/2* and other breast cancer related genes in metastatic tissue, and to further improve the quality of genetic testing in tissue biopsies.

5. Reporting

5.1. Reporting of mutations and VUS in *BRCA1* and *BRCA2*

The majority of experts (74%) agreed that variants of unknown significance (VUS) should be reported in *BRCA1/2* [Q6]. However, experts felt that, unless a variant is classified as pathogenic (i.e. class IV and V variants), it should not be used for medical decisions or for predictive testing in relatives at risk. In this context, it was cautioned that with increasing medical knowledge, the currently used five-tier classification of a particular variant may change over time, and genetic counselling should therefore always address the possibility that already tested individuals might be recontacted in case new information on a particular variant results in a re-classification.

The experts, unanimously believe that an international initiative is preferable over isolated local research, to study and to subsequently reclassify class III variants into either class IV/V or class I/II variants, and that laboratories should be mandated to routinely reevaluate individual *BRCA1/2* sequence variants prospectively to reclassify, if new evidence becomes available. This should already be addressed in a forward-looking statement in the initial laboratory report.

5.2. Reporting of germline mutations and VUS in gene panels

Experts agreed (79%) that in principle, VUS should not only be reported if in *BRCA1/2* but also in other gene panel genes [Q9]. It was, however, also pointed out by several experts that VUS in high risk genes would have higher clinical importance than VUS in lower risk genes. Consequently, in a setting where large gene panels are used, which also comprise genes which are associated with a small or ill-defined increase in cancer risks, 16% of experts would report VUS only in genes with a high relative risk. Forty-seven percent of panelists suggested VUS should only be reported in genes with moderate and high relative risk, whereas 37% opted for reporting all genetic findings, even if the VUS-associated risk is low [Q8]. For most experts, such a prioritisation was deemed to be important given the fact that VUS in low and moderate penetrance genes are probably very common in the general population as well, and their detection in individuals from HBOC families would therefore not have clinical consequences. This is a particularly important aspect in the predictive testing of young women in whom the knowledge of a genetic variation—which they might perceive as ‘potentially dangerous’—could result in a significant psychological burden and an ethical dilemma in their life planning.

6. Conclusion

The clinical efficacy of *BRCA1/2*-specific targeted therapies and the growing demand for predictive testing in women with a HBOC background have resulted in a profound increase in the demand for genetic counselling and testing. It is expected that the current restriction of counselling to clinical geneticists in several countries will lead to a shortage in counselling slots and to a prolongation of already long waiting times. Alternative options to provide genetic counselling are needed, and education of oncological caregivers (both medical and non-medical) is an appropriate strategy to overcome the current shortages. Genetic testing in both, the predictive and therapeutic setting, should not be limited to *BRCA1* and *BRCA2* but should also include genes beyond *BRCA1/2*. VUS in general pose a considerable challenge because of the limited actionability and potential psychological consequences in carriers and their families. Somatic testing in tumour tissue is not presently recommended in breast cancer patients, but ongoing research might challenge this recommendation in the future.

Role of the funding source

Travel expenses for (some) participants were sponsored by an unrestricted grant from AstraZeneca (AZ).

AZ had no role in the organization of the meeting, in the invitation of panel members, and in the selection of questions. Participants were solely selected because of scientific expertise in the *BRCA* field and regional distribution, thereby representing European countries and Israel.

Disclosures

Judith Balmaña, Nicole Bürki, Maria Elisabetta Filieri, Eli Marie Grindedal, Sileni Han, Oskar Johansson, Bella Kaufman, Mateja Krajc, Edith Olah, Kamil Pohlodek, Christian F. Singer, and Manuel Teixeira have nothing to declare. Suzette Delaloge received lecture fees from and is a member of the advisory board of AstraZeneca and Pfizer. D. Gareth Evans has received travel grants from AstraZeneca and Amgen. Anna-Marie Gerdes was a member of the advisory board of AstraZeneca in 2016. Niklas Loman received lecture fees from AstraZeneca and Novartis and has participated in an advisory board of Amgen. Shani Paluch-Shimon has participated an advisory board of AstraZeneca. Natalija Dedic Plavetic received lecture fees from AstraZeneca. Kerstin Rhiem received lecture fees from and, in 2012, was a member of the advisory board of AstraZeneca.

Conflict of interest statement

None declared.

Acknowledgements

Margit Hemetsberger, hemetsberger medical services, Vienna, Austria, helped with the writing of this manuscript. Philipp Pappenscheller, Vienna Medical University, helped with the evaluation of the questionnaires and voting results and the organisation of the meeting. D Gareth Evans is supported by the NIHR Manchester Biomedical Research Centre.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejca.2018.10.007>.

References

- [1] Bray F, Colombet M, Mery L, Piñeros M, Znaor A, Zanetti R, et al. Cancer incidence in five continents, vol. XI (electronic version). In: Cancer IAFRo; 2017. Lyon.
- [2] Kuchenbaecker KB, Hopper JL, Barnes DR, Phillips KA, Mooij TM, Roos-Blom MJ, et al. Risks of breast, ovarian, and contralateral breast cancer for *BRCA1* and *BRCA2* mutation carriers. *J Am Med Assoc* 2017;317(23):2402–16.
- [3] Chen S, Parmigiani G. Meta-analysis of *BRCA1* and *BRCA2* penetrance. *J Clin Oncol* 2007;25(11):1329–33.
- [4] Chiba A, Hoskin TL, Hallberg EJ, Cogswell JA, Heins CN, Couch FJ, et al. Impact that timing of genetic mutation diagnosis

- has on surgical decision making and outcome for BRCA1/BRCA2 mutation carriers with breast cancer. *Ann Surg Oncol* 2016;23(10):3232–8.
- [5] Cortesi L, Razzaboni E, Toss A, De Matteis E, Marchi I, Medici V, et al. A rapid genetic counselling and testing in newly diagnosed breast cancer is associated with high rate of risk-reducing mastectomy in BRCA1/2-positive Italian women. *Ann Oncol* 2014;25(1):57–63.
 - [6] Cardoso F, Costa A, Senkus E, Aapro M, Andre F, Barrios CH, et al. 3rd ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 3). *Ann Oncol* 2017;28(12):3111.
 - [7] Cardoso F, Costa A, Senkus E, Aapro M, Andre F, Barrios CH, et al. 3rd ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 3). *Ann Oncol* 2017;28(1):16–33.
 - [8] Cardoso F, Costa A, Senkus E, Aapro M, Andre F, Barrios CH, et al. Corrigendum to "3rd ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 3)" [*Breast* 31 (February 2017) 244–259]. *Breast* 2017;32:269–70.
 - [9] Cardoso F, Costa A, Senkus E, Aapro M, Andre F, Barrios CH, et al. 3rd ESO-ESMO international consensus guidelines for Advanced Breast Cancer (ABC 3). *Breast* 2017;31:244–59.
 - [10] Metcalfe K, Gershman S, Ghadirian P, Lynch HT, Snyder C, Tung N, et al. Contralateral mastectomy and survival after breast cancer in carriers of BRCA1 and BRCA2 mutations: retrospective analysis. *BMJ* 2014;348:g226.
 - [11] Robson M, Im SA, Senkus E, Xu B, Domchek SM, Masuda N, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. *N Engl J Med* 2017;377(6):523–33.
 - [12] Tutt A, Tovey H, Cheang MCU, Kernaghan S, Kilburn L, Gazinska P, et al. Carboplatin in BRCA1/2-mutated and triple-negative breast cancer BRCAness subgroups: the TNT Trial. *Nat Med* 2018;24(5):628–37.
 - [13] Litton JK, Rugo HS, Ettl J, Hurvitz SA, Goncalves A, Lee KH, et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. *N Engl J Med* 2018;379(8):753–63.
 - [14] Tutt A, Kaufman B, Garber J, Gelber R, McFadden E, Goessl C, et al. 216TiP - OlympiA: a randomized Phase III trial of olaparib as adjuvant therapy in patients with high-risk HER2-negative breast cancer (BC) and a germline BRCA1/2 mutation. *Ann Oncol* 2017;28(suppl 5):v43–67.
 - [15] Fink A, Kosecoff J, Chassin M, Brook RH. Consensus methods: characteristics and guidelines for use. *Am J Public Health* 1984;74(9):979–83.
 - [16] Plon SE, Eccles DM, Easton D, Foulkes WD, Genuardi M, Greenblatt MS, et al. Sequence variant classification and reporting: recommendations for improving the interpretation of cancer susceptibility genetic test results. *Hum Mutat* 2008;29(11):1282–91.
 - [17] National Institute for Health and Care Excellence. In: *Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer*; 2017.
 - [18] National Comprehensive Cancer Network. Version 1.2018. In: *NCCN clinical practice guidelines in oncology (NCCN Guidelines®): genetic/familial high-risk assessment: breast and ovarian*; 2017.
 - [19] Grindedal EM, Heramb C, Karsrud I, Ariansen SL, Maehle L, Undlien DE, et al. Current guidelines for BRCA testing of breast cancer patients are insufficient to detect all mutation carriers. *BMC Cancer* 2017;17(1):438.
 - [20] Nilsson MP, Torngren T, Henriksson K, Kristofferson U, Kvist A, Silfverberg B, et al. BRCAsearch: written pre-test information and BRCA1/2 germline mutation testing in unselected patients with newly diagnosed breast cancer. *Breast Cancer Res Treat* 2018;168(1):117–26.
 - [21] Antoniou AC, Casadei S, Heikkinen T, Barrowdale D, Pylkas K, Roberts J, et al. Breast-cancer risk in families with mutations in PALB2. *N Engl J Med* 2014;371(6):497–506.
 - [22] Ramus SJ, Song H, Dicks E, Tyrer JP, Rosenthal AN, Intermaggio MP, et al. Germline mutations in the BRIP1, BARD1, PALB2, and NBN genes in women with ovarian cancer. *J Natl Cancer Inst* 2015;107(11).
 - [23] Winter C, Nilsson MP, Olsson E, George AM, Chen Y, Kvist A, et al. Targeted sequencing of BRCA1 and BRCA2 across a large unselected breast cancer cohort suggests that one-third of mutations are somatic. *Ann Oncol* 2016;27(8):1532–8.