

Consensus Recommendations of the German Consortium for Hereditary Breast and Ovarian Cancer

Kerstin Rhiem^a Bernd Auber^b Susanne Briest^c Nicola Dikow^d
Nina Ditsch^e Neda Dragicevic^f Sabine Grill^g Eric Hahnen^a Judit Horvath^h
Bernadette Jaegerⁱ Karin Kast^a Marion Kiechle^g Elena Leinert^j
Susanne Morlot^b Michael Püsken^k Dieter Schäfer^l Sarah Schott^m
Christopher Schroederⁿ Ulrike Siebers-Renelt^h Christine Solbach^o
Nana Weber-Lassalle^a Isabell Witzel^p Christine Zeder-Göß^e
Rita K. Schmutzler^a

^aCenter for Familial Breast and Ovarian Cancer, Center for Integrated Oncology, Cologne, Faculty of Medicine, University Hospital Cologne, Cologne, Germany; ^bDepartment of Human Genetics, Hannover Medical School, Hannover, Germany; ^cDepartment of Obstetrics and Gynaecology, University Hospital of Leipzig, Leipzig, Germany; ^dInstitute of Human Genetics, University of Heidelberg, Heidelberg, Germany; ^eDepartment of Gynecology and Obstetrics, University Hospital of Augsburg, Augsburg, Germany; ^fInstitute of Human Genetics, Julius-Maximilians-Universität Würzburg, Würzburg, Germany; ^gDepartment of Gynecology and Obstetrics, University Hospital Klinikum Rechts der Isar, Technical University Munich (TUM), Munich, Germany; ^hInstitute for Human Genetics, University Hospital Münster, Münster, Germany; ⁱDepartment of Gynaecology and Obstetrics, University Hospital Düsseldorf, Heinrich-Heine University Düsseldorf, Düsseldorf, Germany; ^jDepartment of Gynaecology and Obstetrics, University Hospital Ulm, Ulm, Germany; ^kDepartment of Radiology, Faculty of Medicine, University Hospital Cologne, Cologne, Germany; ^lInstitute for Human Genetics, University of Frankfurt, Frankfurt, Germany; ^mDepartment of Obstetrics and Gynaecology, University of Heidelberg, Heidelberg, Germany; ⁿInstitute of Medical Genetics and Applied Genomics, University Hospital Tübingen, Tübingen, Germany; ^oDepartment of Gynecology and Obstetrics, University Hospital Frankfurt, Frankfurt, Germany; ^pDepartment of Obstetrics and Gynaecology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Keywords

Consensus · Panel testing · Hereditary breast cancer · Hereditary ovarian cancer · *BRCA1* · *BRCA2*

Abstract

Background: The German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC) has established a multigene panel (TruRisk[®]) for the analysis of risk genes for familial breast and ovarian cancer. **Summary:** An interdisciplinary team of experts from the GC-HBOC has evaluated the avail-

able data on risk modification in the presence of pathogenic mutations in these genes based on a structured literature search and through a formal consensus process. **Key Messages:** The goal of this work is to better assess individual disease risk and, on this basis, to derive clinical recommendations for patient counseling and care at the centers of the GC-HBOC from the initial consultation prior to genetic testing to the use of individual risk-adapted preventive/therapeutic measures.

© 2021 The Author(s)
Published by S. Karger AG, Basel

Introduction

With the TruRisk[®] gene panel, the German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC) offers genetic diagnostics according to the latest state of science. The multigene analysis includes “core genes” for which sufficient evidence for the association with an increased risk of breast and/or ovarian cancer exists. This means that these genes have been tested for their clinical validity. Only for these genes an expert consensus was established in 2017/2018 (*ATM*, *BRCA1*, *BRCA2*, *CDH1*, *CHEK2*, *NBN*, *PALB2*, *RAD51C*, *RAD51D*, *TP53*) [1]. The consensus has now been updated and expanded to include the “new” core genes of the TruRisk[®] gene panel (*BARD1*, *BRIP1*) [2, 3]. As part of the consensus process, an interdisciplinary panel of experts of the GC-HBOC has updated the recommendations using data from the GC-HBOC and international literature. However, exclusive knowledge on increased cancer risks is not sufficient to derive evidence-based preventive clinical measures (e.g., intensified breast cancer surveillance, risk-reducing bilateral/contralateral mastectomy, bilateral risk-reducing salpingo-oophorectomy [RRSO]). For this purpose it is necessary to prove the clinical benefit. This is given if the preventive measures lead to an advantage for the endpoints such as mortality, morbidity, and quality of life. With regard to hereditary breast and ovarian cancer, such evidence exists so far only for the two high-risk genes *BRCA1* and *BRCA2*, although final data on mortality reduction through intensified breast cancer surveillance and risk-reducing bilateral mastectomy are still pending for these two genes as well. For all other genes, the efficiency of risk-reducing measures has not yet been sufficiently demonstrated. This is particularly important with regard to proven or suspected genotype/phenotype correlations. This means that a genetically defined cancer subtype may have a specific histopathological feature and a specific course of disease, which may influence the effectiveness of preventive measures.

The primary task of the GC-HBOC is to close this knowledge gap and at the same time offer those affected the best possible prevention. The GC-HBOC has therefore established and tested a concept of knowledge-generating care in the field of risk-adapted prevention. This concept provides that the best and most conclusive prevention concept is offered on the basis of the available evidence and that this concept is regularly evaluated and continuously improved through documentation and evaluation of results. For this purpose, the GC-HBOC, with the support of the Federal Ministry of Education and Research, is establishing a national registry HerediCaRe (Hereditary Cancer Registry) (funding code: 01GY1901), which will be linked to the clinical cancer registries in the future in order to obtain long-term data. The HerediCaRe

registry provides the long-term documentation of genetic and clinical data from the routine care of families with a hereditary predisposition to breast and ovarian cancer who are cared for in one of the centers of the GC-HBOC or in the cooperating certified cancer centers. This includes information on the constellation of cancers within the family and information on the presence of risk factors for cancer. In addition, data on general health and health status as well as on early detection and follow-up examinations are recorded and scientifically evaluated. Furthermore, DNA from a patient’s blood sample, is also obtained and stored as part of the registry study. The DNA is used for a molecular genetic analysis and the result of the genetic analysis is also documented and used for scientific questions. Current results from the scientific data analysis of the registry are to be communicated to physicians, consulting agencies, and patients as part of a continuous and constantly improving educational program. This ensures a high-quality standard in patient care and risk counseling within the GC-HBOC. If new findings from the registry should have consequences for the care of the families, the family members participating in the study will be informed immediately within a “recall system.” After the funding phase by the Federal Ministry of Education and Research, the registry will continue to exist and serve as a basis for national care structures.

The following consensus recommendations should be considered and classified within the framework of this overall concept. An interdisciplinary team of experts of the GC-HBOC has evaluated the available data on risk modification in the presence of a pathogenic (disease-causing) mutation in these genes based on a structured literature review and within the framework of a formal consensus process. The consensus recommendations are explicitly not recommendations for standard care. Rather, they serve as information about current options and are bound to the contracts for special care according to §140a (SGB V). These also include the offer of cooperation between the centers of the GC-HBOC and certified breast and gynecological cancer centers. This gives the certified centers the opportunity to participate in the knowledge-generating care of persons at risk. For diseased persons at risk, this concept offers the possibility of non-directive counseling near home according to the current state of knowledge, which can be supported by further offers such as decision aids and decision coaching.

The “Well-Known” Genes BRCA1 and BRCA2: New Information

The high-risk genes *BRCA1* and *BRCA2* are associated with significantly increased lifetime risks of breast and ovarian cancer in women [4, 5]. Since their identification, they have been the subject of intensive research providing data on age-related disease risks, tumor phenotypes, risk-

adjusted prevention options, and targeted therapy strategies. These are incorporated into the recommendations of the GC-HBOC and form the basis for corresponding guideline recommendations (AWMF guideline program, breast/ovarian cancer; <https://www.awmf.org/leitlinien/aktuelle-leitlinien.html>).

New data that have been included in the recommendations for prevention in the presence of a *BRCA1* and *BRCA2* mutation take into account, among other things, the evaluation of the 10-year data from the GC-HBOC's intensified breast cancer surveillance program. Here, an early diagnosis (stage 0 and IA/N0) could be shown in 76%/90% (*BRCA1*) and 75%/88% (*BRCA2*) of cases [6]. Data on the hard endpoint mortality are still pending. The age for discussion of RRSO as an option has been reduced to 35 years for women with *BRCA1* mutations due to individual cases of disease before the age of 40 (cumulative risk 2%, 95% CI 1–3%) and is recommended at 40 years of age [4]. There is increasing evidence that RRSO has a marginal (for female *BRCA2* mutation carriers >5 years after surgery) or no effect (for female *BRCA1* mutation carriers) on breast cancer risk [7, 8]. For the first time, there is evidence that bilateral risk-reducing mastectomy shows a survival advantage in healthy women with *BRCA1* mutations, whereas this could not be shown for *BRCA2* mutation carriers [9].

Other Risk Genes of the TruRisk® Gene Panel and Their Clinical Evaluation

As a result of technical progress in molecular genetics (next-generation sequencing), a number of other risk genes for breast and ovarian cancer have been identified and their significance analyzed [2, 3, 10]. For the majority of these genes, population-specific mutation prevalence, age-related disease risks, tumor subtypes, and data on the effectiveness of preventive measures are not yet sufficiently known. Data on cancer risks are mostly available from case-control studies and less frequently from prospective cohort studies. If an association (odds ratio or relative risk) between the presence of a mutation and the occurrence of cancer is described in these studies, this is not sufficient as a basis for decisions on the offer of preventive measures. Both collectives may also be subject to various biases. Therefore, studies on genotype-phenotype correlations and clinical disease progression in prospective cohort studies are necessary, since their data are more reliable and thus more suitable for the interpretation of genetic findings.

Extension of the TruRisk® Gene Panel: BARD1 and BRIP1

In 2015, the first version of the TruRisk® gene panel was developed at GC-HBOC and adapted to the current state of research every year. These recommendations have been published since 2017.

Within the framework of international collaborative projects, the consortium plays a major role in the identification of new risk genes. These genes (research genes) are validated via the TruRisk® gene panel and, if an association with breast and/or ovarian cancer is detected, are included in the group of core genes.

BARD1 interacts with *BRCA1* and supports tumor suppressor function by acting on DNA double-strand repair and initiating apoptosis. Data on *BARD1* and its association with breast and ovarian cancer were initially not consistent. While some case-control studies showed the association of *BARD1* with an increased risk of breast cancer [11, 12], other studies could not prove this [13, 14].

The same applies to the role of *BARD1* in the development of ovarian cancer [15–17]. Within the GC-HBOC, 4,469 breast and 451 ovarian cancer cases with negative *BRCA1/2* mutation status were examined in 2019 compared to 2,767 healthy women as controls. *BARD1* mutations were diagnosed in 0.5% of the breast cancer patients examined and a moderate risk increase for breast cancer (OR 5.35, 95% CI 3.17–9.04, $p < 0.00001$) with a significant association with breast cancer before the age of 40 was shown (OR 12.04, 95% CI 5.78–25.08, $p < 0.00001$) [3]. An association with an increased risk of ovarian cancer was not seen in this study. Due to the moderately increased risk of breast cancer, female mutation carriers are offered participation in the intensified breast cancer surveillance in the specialized centers of the GC-HBOC.

In a further case-control study of the GC-HBOC with 6,341 breast and 706 ovarian cancer patients, a significant association of *BRIP1* with the occurrence of ovarian cancer was demonstrated (OR 20.97, 95% CI 12.02–36.57, $p < 0.0001$), especially with a diagnosis at >61 years of age (OR 29.9, 95% CI 14.99–59.66, $p < 0.0001$) [2]. A significant association of *BRIP1* mutations with breast cancer could not be shown in this study. Since further studies have shown a contradictory association with the development of breast cancer [14, 18], *BRIP1* mutation carriers are currently offered participation in the intensified breast cancer surveillance in addition to RRSO.

Role of NBN Clarified by Evaluation of Study Data from GC-HBOC

The inclusion of the *NBN* gene in routine clinical diagnostics was controversially discussed. This is mainly due to the low mutation detection rate outside the Slavic population. Therefore, it was urgently necessary to generate further data through the TruRisk® gene panel analyses in order to optimize the risk assessment for *NBN*. Studies by Couch et al. [12] (OR 1.13, 95% CI 0.73–1.75, $p = 0.59$) and Thompson et al. [19] indicate that there is no increased risk for breast cancer (OR 1.13, 95% CI 0.73–1.75, $p = 0.59$; OR 0.67, 95% CI 0.11–4.0, $p = 1.00$). The current evaluation of the TruRisk® gene panel of 5,589

BRCA1/2-negative index patients of the GC-HBOC could also not confirm *NBN* as a breast cancer risk gene (OR 1.39, 95% CI 0.73–2.64, $p = 0.363$) [10]. Based on this data, *NBN* has been removed from the group of core genes of the TruRisk® gene panel. To evaluate the significance as a risk gene for ovarian cancer, *NBN* is still maintained on the panel as a “research gene.” Such adjustments mean that the TruRisk® gene panel is now at the most up-to-date scientific level for genetic testing of risk genes for familial breast and ovarian cancer.

Mutations in RAD51C and RAD51D Increase Breast Cancer Risk

In the GC-HBOC in 2010, the gene *RAD51C* was identified as a risk gene in *BRCA1/2*-negative families with breast and ovarian cancer burden [20]. Initially, a significant association with mutations in the genes *RAD51C* and *RAD51D* was shown for the occurrence of ovarian cancer with a cumulative risk of about 10% until the age of 70 years [21, 22]. The recent work of Yang et al. [23] confirms the cumulative ovarian cancer risk up to the age of 80 years (*RAD51C* 11%, 95% CI 6–21% and *RAD51D* 13%, 95% CI 7–23%) and also shows that the risk of disease increases up to the age of 60 years and decreases thereafter. So far, a significant association between *RAD51C/D* mutations and breast cancer has not been clearly demonstrated [21, 22]. The current analysis by Yang et al. [23] on 125 families with a pathogenic mutation in *RAD51C* and 60 with a pathogenic mutation in *RAD51D* indicates an increased breast cancer risk for *RAD51C/D* mutation carriers. Until the age of 80 years, the cumulative risk is 21% (95% CI 15–29%) for *RAD51C* mutation carriers and 20% (95% CI 14–28%) for *RAD51D* mutation carriers. In addition, for both breast and ovarian cancer risks, a modification due to familial predisposition could be demonstrated in the study. The ovarian cancer risk is about 35% for *RAD51C/D* mutation carriers with two first-degree relatives who also have ovarian cancer. The risk of breast cancer increases to about 45% with two first-degree relatives [23]. Clinical recommendations for women with *RAD51C/D* mutations include the offer of participation in the intensified breast cancer surveillance and RRSO.

Germline Mutations in the Genes CDH1, CHEK2, PALB2, PTEN, TP53 – Individual Decision for Risk-Reducing (Contralateral) Mastectomy

For the syndrome-associated genes *TP53*, *PTEN*, and *CDH1*, tumor penetrances have been derived from families that meet the clinical criteria for Li-Fraumeni syndrome (*TP53*), Cowden syndrome (*PTEN*), or hereditary diffuse gastric cancer (*CDH1*). Families with breast and ovarian cancer phenotypically often differ significantly from these families. This suggests other co-segregating

gene variants or modifying factors and other penetrances in families selected according to hereditary breast and ovarian cancer criteria. Therefore, mutation penetrances from syndrome-associated families cannot simply be adopted. Again, data on prospective tumor incidence rates in cohort studies are urgently needed.

The following data refer mainly to the classic syndrome-associated families: in families with Li-Fraumeni syndrome, germline mutations in the highly penetrant *TP53* gene are responsible for a variety of tumor diseases, including sarcomas, adrenocortical carcinomas, and brain tumors. The lifetime risk for tumor disease is >80% for female mutation carriers [24]. For women, the lifetime risk of breast cancer is approximately 55% [25]. In families that do not meet the classical criteria for Li-Fraumeni syndrome, early breast cancer patients (<30 years) show an empirical mutation frequency of up to 8% [24, 26, 27].

The high rates of about 20% de novo mutations, which are not detectable in the parent generation, must be taken into account [28]. An inconspicuous family history therefore does not exclude a *TP53*-associated tumor disposition at all. A particular challenge in the analysis of *TP53* is the differentiation of germline variants from somatic variants. The latter may be detectable as postzygotic mosaic or as a result of clonal hematopoiesis in the blood. The differentiation is relevant for the patients themselves and their families [29–31]. A misinterpretation can be of great importance for tested persons. For example, the detection of clonal hematopoiesis should lead to a control with regard to the development of acute lymphocytic leukemias or myelodysplastic syndromes. If it is wrongly assumed that the detected mutation is a germline mutation, this will result in unnecessary screening examinations with the risk of invasive procedures to confirm false positive findings.

Furthermore, a recent study of the influence of adjuvant irradiation in breast cancer patients with a *TP53* germline mutation suggests that the incidence of carcinomas and sarcomas is increased in the irradiation field [32]. International recommendations therefore consider therapeutic mastectomy instead of breast-conserving surgery with subsequent radiation as indicated and put post-mastectomy radiation under discussion if there is an increased risk of recurrence [33].

Germline mutations in the tumor suppressor gene *PTEN* are responsible for Cowden’s syndrome, a rare disease characterized by multiple hamartomas and breast, endometrial, and thyroid carcinomas, among others. Female patients have a lifetime risk of developing cancer of approximately 85% and a cumulative breast cancer risk of 67–85% up to the age of 60 years [34, 35]. An increased risk for ovarian cancer is not known to date. *PTEN* is currently being further evaluated for its role in breast and ovarian cancer.

Germline mutations in the E-cadherin gene (*CDH1*) are causative for hereditary diffuse gastric cancer. Patients also show an increased risk of breast cancer, especially of the lobular subtype [36]. Initial data on age-related disease risk in families with gastric cancer indicate that the lifetime risk of breast cancer is approximately 50% [37, 38]. The cumulative risk for gastric cancer is reported to be 40–70% for men carrying *CDH1* germline mutations and 30–80% for women with *CDH1* germline mutations [37, 39].

Due to the risk of multiple tumor diseases caused by mutations in genes such as *PTEN*, *TP53*, and *CDH1*, mutation carriers are offered integration into an interdisciplinary oncological care concept at oncological centers for proof of benefit [40, 41].

Mutations in the risk gene *PALB2* increase the risk of breast cancer and are associated with a lifetime risk of about 50% up to 80 years (53%, 95% CI 44–63%) [42]. A relative risk of about 7 is reported (95% CI 5.82–8.85, $p = 6.5 \times 10^{-76}$). There is currently insufficient evidence that women carrying *PALB2* germline mutations have a significantly increased risk of ovarian cancer. The lifetime risk up to the age of 80 is 5% (95% CI 2–10%), but shows a broad confidence interval, which is why it is recommended to take into account the patient's own and family anamnesis when deciding on RRSO in individual cases. The lifetime risk for breast cancer in male mutation carriers is slightly below 1% (95% CI 0.2–5%) and is calculated with a relative risk of 7.34 (95% CI 1.28–42.18, $p = 2.6 \times 10^{-2}$). *PALB2* mutations have also been detected in families with an increased incidence of pancreatic cancer. Here the lifetime risks are about 2–3% (95% CI women 1–4%, 95% CI men 2–5%).

The lifetime risk of breast cancer in women with *CHEK2* mutations is about 20% [43]. An age-dependent risk could be determined for the founder mutation c.1100delC, which was identified mainly in the Northern European population (OR 2.59, 95% CI 1.23–5.47 for <35 years, OR 1.4, 95% CI 0.93–2.12 for >65 years) [44]. For the subgroup of estrogen receptor-positive breast tumors, OR was 3.26 (95% CI 1.05–10.18) in patients with disease age <35 years and 1.58 (95% CI 1.01–2.49) in patients >65 years [44]. The occurrence of variant c.1100delC is also associated with a slightly increased risk of developing contralateral breast cancer (RR 2.7, 95% CI 2.0–3.7). *CHEK2* variant c.1100delC was also associated with a slightly increased risk of papillary thyroid carcinoma (OR 6) [45], gastric carcinoma (HR 5) [46], prostate carcinoma (OR 2 unselected, OR 3 familial) [47], and colorectal carcinoma (OR 2) [48].

For female mutation carriers of the genes *CDH1*, *CHEK2*, *PALB2*, and *PTEN*, risk-reducing bilateral mastectomy is an individual decision taking into account the patient's own and family history and competing risks. For

women with *PALB2* and *PTEN* mutations, this also applies to the weighing of pros and cons with regard to a risk-reducing contralateral mastectomy. For female *CHEK2* mutation carriers of variant c.1100delC, risk-reducing contralateral mastectomy should be discussed as an option, taking into account the competing risks, whereas for female *CDH1* mutation carriers it is usually not an option at present. All mutation carriers are offered intensified breast cancer surveillance. As there is no evidence of an increased risk of ovarian cancer for mutation carriers of the genes (*CDH1*, *CHEK2*, *PTEN*, *TP53*) so far, there is no recommendation for RRSO. Table 1 summarizes the preventive options for carriers of mutations in one of the core genes of the TruRisk® gene panel.

10-Year Experience from the GC-HBOC's High-Risk Breast Cancer Surveillance

The GC-HBOC was able to evaluate the 10-year data (2006–2015) of 4,573 healthy women with a high risk of breast cancer (954 *BRCA1* mutation carriers, 598 *BRCA2* mutation carriers, 3,021 *BRCA1/2*-negative women with increased risk) who participated in the intensified screening program at the consortium centers [6]. A total of 221 primary breast cancers (185 invasive, 36 in situ) were diagnosed. Of these, 84.5% were diagnosed at an early stage (0 or I). The sensitivity of the program was 89.6% (95% CI 84.9–93.0) with no significant differences between risk groups or by age. Specificity was significantly lower in the first screening round (84.6%, 95% CI 83.6–85.7) than in subsequent screening rounds (91.1%, 95% CI 90.6–91.7, $p < 0.001$). The evaluation of the screening data also revealed that the cancer detection rates of *BRCA1/2*-negative women with increased risk of disease (age group 30–39 years: 2.9%, 95% CI 5.8–20.7) are significantly lower than those of *BRCA1/2* mutation carriers (>20%). The positive predictive value (PPV) of *BRCA1/2*-negative women with increased risk of disease (age group 30–39 years 2.8%, 95% CI 1.3–6.1) is also significantly lower than that of *BRCA1/2* mutation carriers (*BRCA1*: 27.4%, 95% CI 21.5–34.2; *BRCA2*: 22%, 95% CI 15.9–31.1%). This has led to a change in the criteria for inclusion in the GC-HBOC's intensified breast cancer surveillance program for *BRCA1/2*-negative women with increased risk of disease [49].

Management of Variants of Unclear Significance

The German Consortium has reacted to the increased number of genetic variants of unclear significance (VUS) in connection with the analysis of new risk genes with three measures: 1. with the establishment of an interdisciplinary expert panel (Task Force) for the classification of VUS in pathogenicity classes and the introduction of a registry (“HereditVAR,” funded by the German Cancer Aid) [50–52], 2. with the establishment of a recall system

Table 1. Offer on preventive measures for female mutation carriers depending on the mutated gene of the TruRisk® gene panel

Gene	IBCS	RRBM	RRCM	RRSO
<i>ATM</i>	Yes	Usually no	Usually no	Usually no
<i>BRCA1</i>	Yes	Option	Option depending on age at first diagnosis, family history of breast cancer, competing risks such as prognosis of MaCa/OvCa/other of MaCa/OvCa/other carcinomas, comorbidities, life expectancy	Option (from 35 years), recommendation (from 40 years)
<i>BRCA2</i>	Yes	Option	Option depending on age at first diagnosis, family history of breast cancer, competing risks such as prognosis of MaCa/OvCa/other of MaCa/OvCa/other carcinomas, comorbidities, life expectancy	Recommendation from 40 years
<i>BARD1</i>	Yes	Usually no	Usually no	Usually no
<i>BRIP1</i>	Yes	Usually no	Usually no	Option (at the onset of menopause)
<i>CDH1</i>	Yes	Individual decision taking into account personal and family history	Usually no	Usually no
<i>CHEK2</i>	Yes	Individual decision taking into account personal and family history	Individual decision taking into account personal and family history and depending on competing risks	Usually no
<i>PALB2</i>	Yes	Individual decision taking into account personal and family history	Individual decision taking into account personal and family history and depending on competing risks	Individual decision taking into account personal and family history
<i>PTEN</i>	Yes	Individual decision taking into account personal and family history and depending on competing risks	Individual decision taking into account personal and family history and depending on competing risks	Usually no
<i>RAD51C/RAD51D</i>	Yes	Usually no	Usually no	Option (at the onset of menopause)
<i>TP53</i>	Yes	Individual decision taking into account personal and family history and depending on competing risks	Individual decision taking into account personal and family history and depending on competing risks	Usually no

Overview of the offers on preventive measures within the framework of the consensus conference of the GC-HBOC (<https://www.konsortium-familiaerer-brustkrebs.de/konsensusempfehlung/>). IBCS, intensified breast cancer surveillance within the centers of the GC-HBOC; RRBM, risk-reducing bilateral mastectomy; RRCM, risk-reducing contralateral mastectomy; RRSO, risk-reducing salpingo-oophorectomy; usually not = for example, depending on factors in the patient's own and/or family cancer history.

by which carriers of sequence variants are immediately informed about their classification by the task force, and 3. with the introduction of multi-professional genetic diagnostic boards for the evaluation of mutations in risk genes with regard to clinical options.

The Importance of Predictive Testing

If a disease-causing mutation is diagnosed in one of the core genes, predictive genetic testing can be offered for additional family members. If a mutation in the genes *BRCA1*, *BRCA2*, *CDH1*, *PALB2*, *PTEN*, and *TP53* is not detected in healthy counselors, they can be relieved of increased cancer risks.

In the case of a *TP53* mutation, it should be clarified in advance whether it is a germline mutation. If an *RAD51C*, *RAD51D*, or *BRIP1* mutation is excluded, the relief applies only to the ovarian cancer risk. With regard to breast cancer risk, complete relief is currently not possible with inconspicuous predictive testing for mutations in the

moderately penetrant genes *ATM*, *CHEK2*, *BARD1*, *BRIP1*, *RAD51C*, and *RAD51D*. Since the disease risks are strongly dependent on the familial burden, additional modifying factors or co-segregating mutations in other risk genes are suspected. Accordingly, in these cases a risk calculation should be performed taking into account family history and genetic test results. With correspondingly increased computational risks (currently 10-year risk for breast cancer of >5%; Boadicea v5), non-mutation carriers also receive the offer to participate in the intensified breast cancer surveillance before the age of 50 years under the assumption that genes not yet known in the sense of an oligogenic or polygenic inheritance are jointly responsible for the development of breast cancer.

Additional Risks for the Offspring

Some risk genes can lead to early childhood syndrome-associated diseases in the offspring if they are present in bi-allelic form, that is, one mutated gene each from the

Table 2. Heterozygote frequencies of genes from TruRisk® panel

	Heterozygote frequency	Risk for a diseased child if the carrier status of one parent is confirmed	Risk for a diseased child in the general population	Phenotype
<i>ATM</i>	1:285~0.0035 ^A	1:1,140	~1:330,000	Ataxia teleangiectatica (AT)
<i>BRCA1</i> (FANCS)	1:476~0.0021 ^{B*}	1:1,905*	~1:900,000	Letal/Fanconi anemia (FA ^D)
<i>BRCA2</i> (FANCD1)	1:322~0.0031 ^{B*}	1:1,290*	~1:410,000	Fanconi anemia (FA ^D)
<i>BRIPI</i> (FANCI)	1:714~0.0014 ^C	1:2,856	~1:2,000,000	Fanconi anemia (FA ^D)
<i>NBN</i>	1:666~0.0015 ^A	1:2,667	~1:1,800,000	Nijmegen-Breakage-syndrome (NBS)
<i>PALB2</i> (FANCN)	1:833~0.0012 ^A	1:3,333	~1:2,800,000	Fanconi anemia (FA ^D)
<i>RAD51C</i> (FANCO)	1:769~0.0013 ^A	1:3,077	~1:2,400,000	Fanconi anemia (FA ^D)

Heterozygote frequency based on ExAC, non-TCGA NFE, data (^A[10]; ^B[53]; ^C[2]). The heterozygote frequencies refer exclusively to protein truncating mutations. ^A Complete penetrance is assumed for the disease probabilities. ^D The prevalence of Fanconi anemia is estimated at 1:350,000 to 1:100,000 births, with most cases being caused by *FANCA* (66%), *FANCC* (10%), or *FANCG* (9%) (no breast cancer risk genes). * Heterozygote frequencies are population specific. Higher *BRCA1/2* heterozygote frequencies have been described for the Jewish population (0.5% for *BRCA1* and 0.6% for *BRCA2* [54]).

father and mother. The probability for the occurrence of such a syndrome is low in the general population, but significantly higher for offspring of mutation carriers (Table 2). Therefore, it is recommended to inform about the risk of an existing mutation in the paternal line and, if necessary, to indicate a gene analysis.

Conclusion

The primary task of the GC-HBOC is to close existing gaps in knowledge and at the same time offer the best possible prevention to those seeking advice. The consortium has therefore established and tested a concept of knowledge-generating care in the field of risk-adapted prevention. This concept provides for the best currently available prevention concept to be offered on the basis of the available evidence, which is regularly evaluated and continuously improved through documentation and evaluation of results. For this purpose, the GC-HBOC is currently setting up a national registry „HereditCaRe“ with the support of the Federal Ministry of Education and Research, which will allow a long-term evaluation of the course of hereditary tumor subtypes through networking with the clinical cancer registries. This is a first satellite

registry, which will allow the linking of genetic data and clinical data with the help of a trustee, taking into account data protection.

Conflict of Interest Statement

Christopher Schroeder reports research support from Illumina and Bristol Myers Squibb and institutional research support from Novartis.

Funding Sources

There are no funding sources.

Author Contributions

K.R. and R.K.S. were responsible for the conception and implementation of the consensus conference and for the drafting of this paper. All authors made significant contributions to data collection and interpretation as part of the consensus process. All authors reviewed the manuscript and contributed to the final version.

References

- Waha A, et al. Konsensusempfehlung des Deutschen Konsortiums Familiärer Brust- und Eierstockkrebs zum Umgang mit Ergebnissen der Multigenanalyse. *Geburtsh Frauenheilk*. 2017;77:733–9.
- Weber-Lassalle N, Hauke J, Ramser J, et al. BRIP1 loss-of-function mutations confer high risk for familial ovarian cancer, but not familial breast cancer. *Breast Cancer Res*. 2018 Jan 24;20(1):7.
- Weber-Lassalle N, Borde J, Weber-Lassalle K, et al. Germline loss-of-function variants in the BARD1 gene are associated with early-onset familial breast cancer but not ovarian cancer. *Breast Cancer Res*. 2019 Apr 29;21(1):55. Published.
- Kuchenbaecker KB, Hopper JL, Barnes DR, et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. *JAMA*. 2017;317(23):2402–16.
- Engel C, Fischer C, Zachariae S, et al. Breast cancer risk in BRCA1/2 mutation carriers and noncarriers under prospective intensified surveillance. *Int J Cancer*. 2020;146(4):999–1009.
- Bick U, Engel C, Krug B, et al. High-risk breast cancer surveillance with MRI: 10-year experience from the German consortium for hereditary breast and ovarian cancer. *Breast Cancer Res Treat*. 2019;175(1):217–28.
- Heemskerk-Gerritsen BA, Seynaeve C, van Asperen CJ, Ausems MG, Collée JM, van Doorn HC, et al. Breast Cancer Risk After Salpingo-Oophorectomy in Healthy BRCA1/2 Mutation Carriers: Revisiting the Evidence for Risk Reduction. *J Natl Cancer Inst*. 2015;107(5):djv033.
- Mavaddat N, Antoniou AC, Mooij TM, et al. Risk-reducing salpingo-oophorectomy, natural menopause, and breast cancer risk: an international prospective cohort of BRCA1 and BRCA2 mutation carriers. *Breast Cancer Res*. 2020;22(1):8.
- Heemskerk-Gerritsen BAM, Jager A, Koppert LB, et al. Survival after bilateral risk-reducing mastectomy in healthy BRCA1 and BRCA2 mutation carriers. *Breast Cancer Res Treat*. 2019;177(3):723–33.
- Hauke J, Horvath J, Groß E, et al. Gene panel testing of 5589 BRCA1/2-negative index patients with breast cancer in a routine diagnostic setting: results of the German Consortium for Hereditary Breast and Ovarian Cancer. *Cancer Med*. 2018;7(4):1349–58.
- Slavin TP, Maxwell KN, Lilyquist J, Vijai J, Neuhausen SL, Hart SN, et al. The contribution of pathogenic variants in breast cancer susceptibility genes to familial breast cancer risk. *NPJ Breast Cancer*. 2017;3:22.
- Couch FJ, Shimelis H, Hu C, Hart SN, Polley EC, Na J, et al. Associations between cancer predisposition testing panel genes and breast cancer. *JAMA Oncol*. 2017;3(9):1190–6.
- Lu HM, Li S, Black MH, Lee S, Hoiness R, Wu S, et al. Association of breast and ovarian cancers with predisposition genes identified by large-scale sequencing. *JAMA Oncol*. 2019;5(1):51–7.
- Castera L, Harter V, Muller E, Krieger S, Goardon N, Ricou A, et al. Landscape of pathogenic variations in a panel of 34 genes and cancer risk estimation from 5131 HBOC families. *Genet Med*. 2018;20(12):1677–86.
- Norquist BM, Harrell MI, Brady MF, Walsh T, Lee MK, Gulsuner S, et al. Inherited mutations in women with ovarian carcinoma. *JAMA Oncol*. 2016;2(4):482–90.
- 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).
- Lilyquist J, LaDuca H, Polley E, et al. Frequency of mutations in a large series of clinically ascertained ovarian cancer cases tested on multi-gene panels compared to reference controls. *Gynecol Oncol*. 2017;147(2):375–80.
- Easton DF, Lesueur F, Decker B, Michailidou K, Li J, Allen J, et al. No evidence that protein truncating variants in BRIP1 are associated with breast cancer risk: implications for gene panel testing. *J Med Genet*. 2016;53(5):298–309.
- Thompson ER, Rowley SM, Li N, McInerney S, Devereux L, Wong-Brown MW, et al. Panel testing for familial breast cancer: calibrating the tension between research and clinical care. *J Clin Oncol*. 2016;34(13):1455–9.
- Meindl A, Hellebrand H, Wiek C, et al. Germline mutations in breast and ovarian cancer pedigrees establish RAD51C as a human cancer susceptibility gene. *Nat Genet*. 2010;42:410–4.
- Song H, Dicks E, Ramus SJ, et al. Contribution of germline mutations in the RAD51B, RAD51C, and RAD51D genes to ovarian cancer in the population. *J Clin Oncol*. 2015;33:2901–7.
- Loveday C, Turnbull C, Ramsay E, et al. Germline mutations in RAD51D confer susceptibility to ovarian cancer. *Nat Genet*. 2011;43:879–82.
- Yang X, Song H, Leslie G, Engel C, Hahnen E, Auber B, et al. Ovarian and breast cancer risks associated with pathogenic variants in RAD51C and RAD51D. *J Natl Cancer Inst*. 2020 Dec 14;112(12):1242–50.
- Bougeard G, Renaux-Petel M, Flaman JM, et al. Revisiting Li-Fraumeni Syndrome From TP53 Mutation Carriers. *J Clin Oncol*. 2015;33(21):2345–52.
- Mai PL, Best AF, Peters JA, DeCastro RM, Khincha PP, Loud JT, et al. Risks of first and subsequent cancers among TP53 mutation carriers in the National Cancer Institute Li-Fraumeni syndrome cohort. *Cancer*. 2016 Dec 1;122(23):3673–81.
- Ruijs MW, Verhoef S, Rookus MA, et al. TP53 germline mutation testing in 180 families suspected of Li-Fraumeni syndrome: mutation detection rate and relative frequency of cancers in different familial phenotypes. *J Med Genet*. 2010;47:421–8.
- McCuaig JM, Armel SR, Novokmet A, et al. Routine TP53 testing for breast cancer under age 30: ready for prime time? *Fam Cancer*. 2012;11:607–13.
- Gonzalez KD, Buzin CH, Noltner KA, et al. High frequency of de novo mutations in Li-Fraumeni syndrome. *J Med Genet*. 2009;46:689–93.
- Batalini F, Peacock EG, Stobie L, et al. Li-Fraumeni syndrome: not a straightforward diagnosis anymore—the interpretation of pathogenic variants of low allele frequency and the differences between germline PVs, mosaicism, and clonal hematopoiesis. *Breast Cancer Res*. 2019 Sep 18;21(1):107. Published.
- Renaux-Petel M, Charbonnier F, Théry JC, et al. Contribution of de novo and mosaic TP53 mutations to Li-Fraumeni syndrome. *J Med Genet*. 2018;55(3):173–80.
- Weber-Lassalle K, Harter P, Hauke J, et al. Diagnosis of Li-Fraumeni Syndrome: Differentiating TP53 germline mutations from clonal hematopoiesis: Results of the observational AGO-TR1 trial. *Hum Mutat*. 2018;39(12):2040–6.
- Le AN, Harton J, Desai H, Powers J, Zelley K, Bradbury AR, et al. Frequency of radiation-induced malignancies post-adjuvant radiotherapy for breast cancer in patients with Li-Fraumeni syndrome. *Breast Cancer Res Treat*. 2020 May;181(1):181–8s.
- Tung NM, Boughhey JC, Pierce LJ, Robson ME, Bedrosian I, Dietz JR, et al. Management of Hereditary Breast Cancer: American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Guideline. *J Clin Oncol*. 2020 Jun 20;38(18):2080–2106.
- Tan MH, Mester JL, Ngeow J, Rybicki LA, Orloff MS, Eng C. Lifetime cancer risks in individuals with germline PTEN mutations. *Clin Cancer Res*. 2012;18(2):400–7.
- Bubien V, Bonnet F, Brouste V, et al. High cumulative risks of cancer in patients with PTEN hamartoma tumour syndrome. *J Med Genet*. 2013;50(4):255–63.
- Petridis C, Arora I, Shah V, et al. Frequency of Pathogenic Germline Variants in CDH1, BRCA2, CHEK2, PALB2, BRCA1, and TP53 in Sporadic Lobular Breast Cancer. *Cancer Epidemiol Biomarkers Prev*. 2019;28(7):1162–8.
- Roberts ME, Ranola JMO, Marshall ML, et al. Comparison of CDH1 Penetrance Estimates in Clinically Ascertained Families vs Families Ascertained for Multiple Gastric Cancers. *JAMA Oncol*. 2019;5(9):1325–31.
- Xicola RM, Li S, Rodriguez N, et al. Clinical features and cancer risk in families with pathogenic CDH1 variants irrespective of clinical criteria. *J Med Genet*. 2019;56(12):838–43.
- van der Post RS, Vogelaar IP, Carneiro F, Guilford P, Huntsman D, Hoogerbrugge N, et al. Hereditary diffuse gastric cancer: updated clinical guidelines with an emphasis on germline CDH1 mutation carriers. *J Med Genet*. 2015;52(6):361–74.
- Tischkowitz M, Colas C, Pouwels S, Hoogerbrugge N; PHTS Guideline Development Group; European Reference Network GEN-TURIS. Cancer Surveillance Guideline for individuals with PTEN hamartoma tumour syndrome. *Eur J Hum Genet*. 2020 Oct;28(10):1387–93.

- 41 Frebourg T, Bajalica Lagercrantz S, Oliveira C, Magenheim R, Evans DG; European Reference Network GENTURIS. Guidelines for the Li-Fraumeni and heritable TP53-related cancer syndromes. *Eur J Hum Genet*. 2020 Oct; 28(10):1379–86.
- 42 Yang X, Leslie G, Doroszuk A, Schneider S, Allen J, Decker B, et al. Cancer Risks Associated With Germline PALB2 Pathogenic Variants: An International Study of 524 Families. *J Clin Oncol*. 2020 Mar 1;38(7):674–85.
- 43 Hu C, Polley EC, Yadav S, et al. The contribution of germline predisposition gene mutations to clinical subtypes of invasive breast cancer from a clinical genetic testing cohort. *J Natl Cancer Inst*. 2020 Dec 14;112(12):1231–41.
- 44 Schmidt MK, Hogervorst F, van Hien R, et al. Age- and Tumor Subtype-Specific Breast Cancer Risk Estimates for CHEK2*1100delC Carriers. *J Clin Oncol*. 2016;34(23):2750–60.
- 45 Siołek M, Cybulski C, Gąsior-Perczak D, Kowalik A, Kozak-Klonowska B, Kowalska A, et al. CHEK2 mutations and the risk of papillary thyroid cancer. *Int J Cancer*. 2015;137(3): 548–52.
- 46 Näslund-Koch C, Nordestgaard BG, Bojesen SE. Increased Risk for Other Cancers in Addition to Breast Cancer for CHEK2*1100delC Heterozygotes Estimated From the Copenhagen General Population Study. *J Clin Oncol*. 2016;34(11):1208–16.
- 47 Hale V, Weischer M, Park JY. CHEK2 (*) 1100delC Mutation and Risk of Prostate Cancer. *Prostate Cancer*. 2014;2014:294575.
- 48 Xiang HP, Geng XP, Ge WW, Li H. Meta-analysis of CHEK2 1100delC variant and colorectal cancer susceptibility. *Eur J Cancer*. 2011;47(17):2546–51.
- 49 Quante AS, Engel C, Kiechle M, Schmutzler RK, Fischer C. Umstrukturierung der Risikoberechnung für die intensiviertere Früherkennung im Deutschen Konsortium für Brust- und Eierstockkrebs. *Der Gynäkologe*. 2020; 53:259–64.
- 50 Plon SE, Eccles DM, Easton D, 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.
- 51 Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17:405–24.
- 52 Wappenschmidt B, Hauke J, Faust U, Niederacher D, Wiesmüller L, Schmidt G, et al. Criteria of the German Consortium for Hereditary Breast and Ovarian Cancer for the Classification of Germline Sequence Variants in Risk Genes for Hereditary Breast and Ovarian Cancer. *Geburtshilfe Frauenheilkd*. 2020 Apr; 80(4):410–29.
- 53 Maxwell KN, Domchek SM, Nathanson KL, Robson ME. Population Frequency of Germline BRCA1/2 Mutations. *J Clin Oncol*. 2016 Dec;34(34):4183–5.
- 54 Metcalfe KA, Poll A, Royer R, Llacuachqui M, Tulman A, Sun P, et al. Screening for founder mutations in BRCA1 and BRCA2 in unselected Jewish women. *J Clin Oncol*. 2010 Jan 20;28(3):387–91.