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ACMG PRACTICE RESOURCE

Management of individuals with germline variants in *PALB2*: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG)

Marc Tischkowitz[1], Judith Balmaña[2], William D. Foulkes[3], Paul James[4,5], Joanne Ngeow[6,7], Rita Schmutzler[8,9], Nicoleta Voian[10], Myra J. Wick[11], Douglas R. Stewart[12], Tuya Pal[13] and ACMG Professional Practice and Guidelines Committee[14]*

PURPOSE: *PALB2* germline pathogenic variants are associated with increased breast cancer risk and smaller increased risk of pancreatic and likely ovarian cancer. Resources for health-care professionals managing *PALB2* heterozygotes are currently limited.

METHODS: A workgroup of experts sought to outline management of *PALB2* heterozygotes based on current evidence. Peer-reviewed publications from PubMed were identified to guide recommendations, which arose by consensus and the collective expertise of the authors.

RESULTS: *PALB2* heterozygotes should be offered *BRCA1/2*-equivalent breast surveillance. Risk-reducing mastectomy can be considered guided by personalized risk estimates. Pancreatic cancer surveillance should be considered, but ideally as part of a clinical trial. Typically, ovarian cancer surveillance is not recommended, and risk-reducing salpingo-oophorectomy should only rarely be considered before the age of 50. Given the mechanistic similarities, *PALB2* heterozygotes should be considered for therapeutic regimens and trials as those for *BRCA1/2*.

CONCLUSION: This guidance is similar to those for *BRCA1/2*. While the range of the cancer risk estimates overlap with *BRCA1/2*, point estimates are lower in *PALB2* so individualized estimates are important for management decisions. Systematic prospective data collection is needed to determine as yet unanswered questions such as the risk of contralateral breast cancer and survival after cancer diagnosis.

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INTRODUCTION

Germline pathogenic/likely pathogenic (P/LP) variants in *PALB2* (Partner and Localizer of *BRCA2*) were first associated with increased cancer risk in 2007[1–3] and clinical testing has been available since then. Testing for *PALB2* increased with its inclusion on multigene cancer panels starting around 2012–2013. It has come to be considered as the third most important breast cancer gene after *BRCA1* and *BRCA2* following the 2014 publication of robust breast cancer risk estimates that overlap with *BRCA2*.[4] Despite the emerging importance of this gene, there is a dearth of guidelines regarding the clinical management of women and men with *PALB2* germline P/LP variants (henceforth called "heterozygotes"). Given the recently published updates on *PALB2*-associated cancer risks,[5,6] there remains a gap in implementing

[1]Department of Medical Genetics, National Institute for Health Research Cambridge Biomedical Research Centre, University of Cambridge, Cambridge, UK. [2]Hereditary Cancer Genetics Group, Vall d'Hebron Institute of Oncology (VHIO) and Medical Oncology Department, Hospital Universitari Vall d'Hebron, Vall d'Hebron Hospital Campus, Barcelona, Spain. [3]Departments of Human Genetics, Oncology and Medicine, McGill University, Montréal, QC, Canada. [4]Sir Peter MacCallum Department of Oncology, The University of Melbourne, Melbourne, VIC, Australia. [5]Parkville Familial Cancer Centre, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia. [6]Genomic Medicine, Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore. [7]Cancer Genetics Service, Division of Medical Oncology, National Cancer Centre, Singapore, Singapore. [8]Center for Molecular Medicine Cologne (CMMC), University of Cologne, Cologne, Germany. [9]University Hospital of Cologne, Center of Integrated Oncology, CIO and Center of Familial Breast and Ovarian Cancer, Cologne, Germany. [10]Genetic Risk Clinic, Providence Cancer Institute, Portland, OR, USA. [11]Departments of Obstetrics and Gynecology and Clinical Genomics, Mayo Clinic, Rochester, MN, USA. [12]Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD, USA. [13]Department of Medicine, Vanderbilt University Medical Center/Vanderbilt-Ingram Cancer Center, Nashville, TN, USA. [14]American College of Medical Genetics and Genomics, Bethesda, MD, USA. *The Board of Directors of the American College of Medical Genetics and Genomics approved this practice resource on 25 January 2021. email: documents@acmg.net

this information to optimize patient care. Consequently, it is a timely opportunity to translate these and other findings into clinical practice for *PALB2* heterozygotes.

The recent international effort to estimate cancer risk for *PALB2* heterozygotes was based on 524 families,[5] and highlighted the need to develop a practice resource through the lens of an international workgroup, through synthesis and practical application of existing data to guide clinical practice. *BRCA1* and *BRCA2* have long been considered "high risk" breast cancer genes, while *ATM* and *CHEK2* have been considered "moderate risk" breast cancer genes. However, *PALB2* clearly blurs these distinctions given that the range of breast cancer risks associated with *PALB2* overlaps with risks associated with "high" and "moderate" risk genes.[7] Through this Clinical Practice Resource, we provide guidance on personalized risk estimation, especially through the use of CanRisk-BOADICEA,[8,9] the only risk estimation tool that currently incorporates *PALB2*.

MATERIALS AND METHODS

After proposal approval and review of potential or actual conflicts as per the relevant American College of Medical Genetics and Genomics (ACMG) policies, the workgroup developed a list of clinical areas in the management of *PALB2* heterozygotes. Workgroup members were identified with expertise in clinical cancer genetics, breast and gynecologic surgery, and medical oncology from Australia, Asia, the United States, Canada, the United Kingdom, and Europe. After approval of a proposal by the ACMG Board, workgroup members assembled relevant peer-reviewed publications based on knowledge of the existing literature and performed additional PubMed searches (as of January 2021). Publications that investigated populations, large clinic cohorts (more than 100 heterozygotes, preferably from multiple institutions), and large case series were prioritized; however, we acknowledge that not using a systematic evidence review approach, while pragmatic, may have led to some pertinent literature being missed. Clinical management recommendations were derived by consensus from this literature (through monthly teleconference calls and email review) and the collective expertise of the authors. Working and final drafts were reviewed and approved by members of the Professional Practice and Guidelines Committee and the ACMG Board of Directors.

RISK ESTIMATION

The initial studies in 2007 that identified an increased risk of breast cancer in *PALB2* heterozygotes were subsequently confirmed by multiple small studies, culminating in an international collaboration of 154 families by the *PALB2* Interest Group,[4] which has recently been expanded to 524 families.[5] The estimated risk of female breast cancer to age 80 years was 53% (95% confidence interval [CI]: 44–63%). The relative risk for a female *PALB2* heterozygote born between 1950 and 1959 was 7.18 (95% CI: 5.82–8.85); this relative risk increases in women from more recent birth cohorts. The same study reported a modest increased risk of ovarian cancer of 0.6% (95% CI: 0.3–1.3%) to age 50 and 4.8% (95% CI: 2.4–9.7%) to age 80, with findings confirmed in a case–control study ($n = 14,135$ cases) that estimated the risk to age 80 to be 3.2% (95% CI: 1.8–5.7%).[6] Two recent, very large breast case–control studies estimated the odds ratio (OR) for *PALB2*-related breast cancer risk to be 3.83 (95% CI: 2.68 to 5.63[10] and 5.02 (95% CI: 3.73–6.76),[11] with no increased risk for missense variants.[11] The absolute risks of developing breast or ovarian cancer are predicted to be influenced by cancer family history.[5] For example, the estimated absolute risk of developing breast cancer by age 80 years varies from 52% (95% CI: 42–62%) for a female with an unaffected mother at age 50 years and unaffected maternal grandmother at age 70 years to 76% (95% CI: 69–83%) for a female with two affected first-degree relatives.[5] Similarly, the estimated risk of developing ovarian cancer by age 80 years varies from 5% (95% CI: 2–10%) for a female with no family history of ovarian in first and second-degree relatives to 16% (95% CI: 8–28%) for a female whose mother and sister developed ovarian cancer at age 50 years. These risk estimates are also modified by polygenic modifiers (see below) that can be combined with lifestyle factors to give a personalized risk estimate such as CanRisk.[8] There are currently no prospective risk estimates for contralateral breast cancer; one study estimated the 5-year cumulative incidence of contralateral breast cancer to be 10%, but this was retrospective and based on small numbers.[12] The risks for pancreatic cancer in *PALB2* heterozygotes are estimated to be 2–3% (95% CI: females: 1–4%; males: 2–5%) to age 80 years compared with 1.5% in the general population. For male breast cancer the risk is 1% (95% CI: 0.2–5%)[5] compared with a general population risk of less than 0.1%. Germline *PALB2* P/LP variants have been detected in a few gastric cancer cases,[13,14] but it is not known if this is a true association. There is no consistent evidence for increased risks in prostate or colorectal cancer. Although germline *PALB2* P/LP variants have been reported in children with certain cancers (see below), no large-scale studies providing estimates of risk are available.

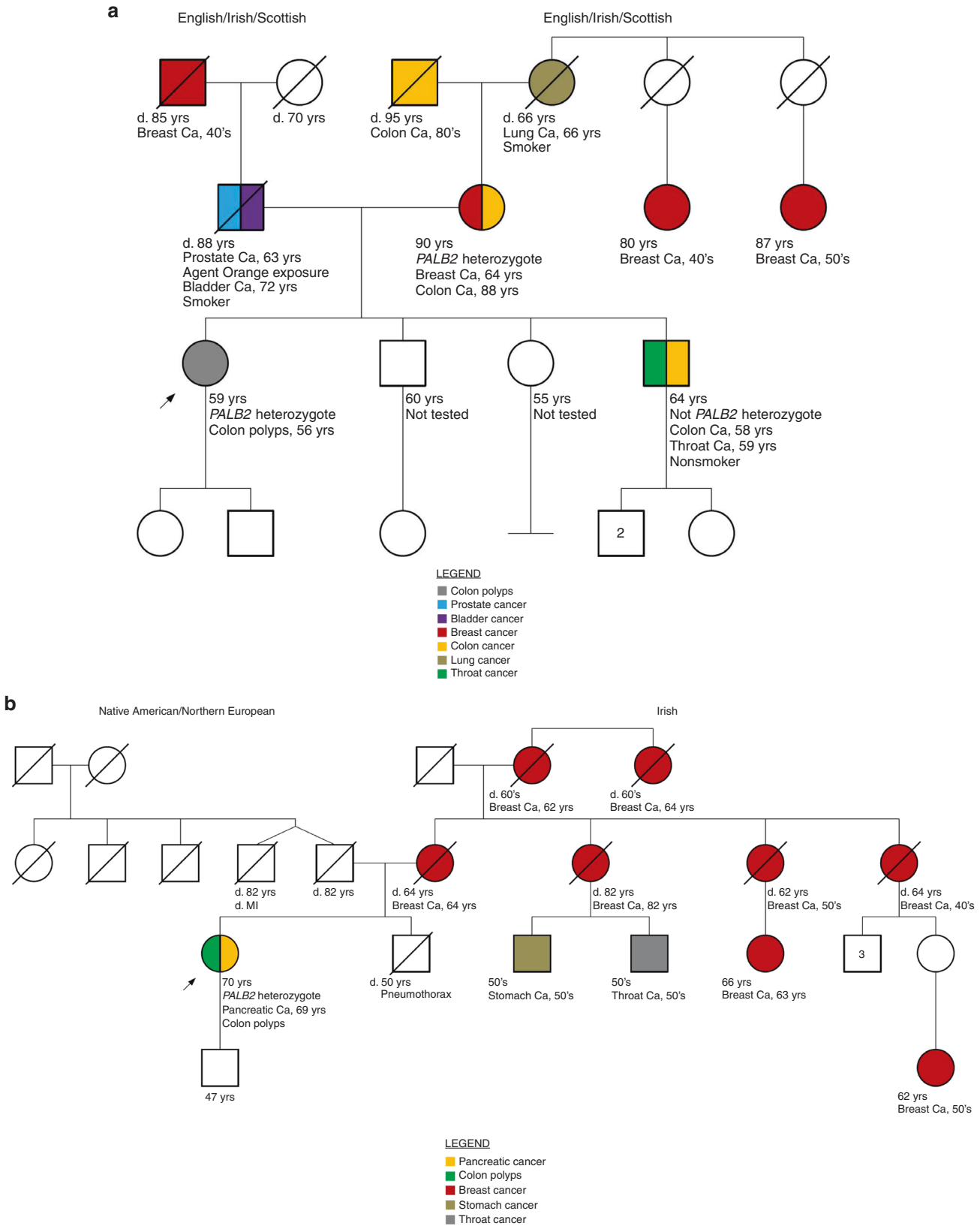
POLYGENIC RISK SCORE AND OTHER MODIFIERS

Variation elsewhere in the genome may modify cancer risks associated with *PALB2* P/LP variants. Genome-wide association studies have identified large numbers of common genomic variants that contribute to an individual's risk of breast cancer. The cumulative effect of these individually minor risks is summarized in a polygenic risk score (PRS) and numerous studies have shown that this measure provides effective stratification of breast cancer risk in the general population.[15] For some breast cancer predisposition genes, studies have demonstrated that the risk associated with a P/LP variant combines with the risk from the PRS in a multiplicative fashion,[16,17] and this may be a general principle, although evidence to support this assertion is needed. For single genes with more moderate effect, modification by the PRS is sufficient to change an individual's final risk classification and their corresponding clinical management. Information on polygenic risk has come predominantly from studies restricted to populations of European ancestry and the extent to which this can be applied for women with other ethnic backgrounds is unclear,[18] although recent studies have found that the established PRS has some value at least in Asian populations.[19] Few studies have directly examined PRS modification in women with P/LP variants in *PALB2*, and the most significant study to date examined the effect of a PRS incorporating 86 common variants in a large cohort undergoing testing for multiple cancer associated genes that included 906 heterozygotes of *PALB2* pathogenic variants.[7] In this group, the strength of the association of the PRS with breast cancer risk was the same (or only slightly reduced) in women who harbored *PALB2* P/LP variants as measured in nonheterozygotes. When factoring in PRS, mammographic density, and lifestyle/hormonal risk factors, 8% of heterozygotes would have a lifetime risk less than 30%, 63% of heterozygotes would fall in the 30–60% range, and 29% of heterozygotes would have *BRCA1/BRCA2* equivalent lifetime risks of greater than 60%.[8] The modifying effect of the PRS is essentially independent of the risk associated with family history and these and other conventional risk factors can be combined into a single personalized risk assessment. When and if PRS becomes available in the clinical setting this integrated approach can be implemented in some online assessment tools such as CanRisk,[8,20] although there are no data yet that directly demonstrate improved clinical outcomes from the greater individualization of risk.

- *ACMG recommends the use of personalized risk estimates (e.g., CanRisk) in guiding clinical management.*

INDICATIONS FOR GENETIC TESTING

Testing for germline P/LP *PALB2* variants is usually done as part of a wider gene panel, e.g., for breast, ovarian, and/or pancreatic



cancer. Case studies illustrating *PALB2* testing in practice are shown in Fig. 1. Overall indications for genetic testing for inherited breast cancer per these guidelines are based on personal and/or family cancer history, taking into account age at diagnosis (at or below age 45), triple-negative breast cancer (at or below age 60), or presence of another primary cancer or family history of cancers. A diagnosis of ovarian or pancreatic cancer in an individual is sufficient to meet current National Comprehensive Cancer Network (NCCN) guidelines for germline testing.[21] In addition, germline testing should be offered when a *PALB2* variant is

Fig. 1 Case studies illustrating *PALB2* testing in practice. (**a**) A 59-year-old female without a prior history of cancer had cascade testing through her gynecologist, which identified a pathogenic variant in *PALB2*, c.695del (p.Gly232fs), originally identified in her 90-year-old mother who was diagnosed with colon cancer at age 88 and had a prior diagnosis of breast cancer at age 64. The patient was advised by her gynecologist to have a risk-reducing oophorectomy and presented for a second opinion to a hereditary cancer clinic for guidance. She was having annual mammograms and breast magnetic resonance images (MRIs) with normal results, as well as colonoscopy every five years, due to the family history of colon cancer, with two benign colon polyps detected during the last one. Discussion points: (1) In the absence of a family history of ovarian cancer, a risk-reducing salpingo-oophorectomy is not typically recommended in women with a *PALB2* P/LP variant who would have a lifetime risk of ovarian cancer of 3–5%. (2) Management of raised colorectal cancer risk is based on the family history, not *PALB2* carrier status. (3) The patient does not meet guidelines for pancreatic cancer surveillance, given lack of family history for this malignancy. (**b**) A 70-year-old female referred to clinic for genetic evaluation and testing, following diagnosis of metastatic pancreatic cancer treated with chemotherapy, with a strong family history of breast cancer. Tumor testing identified one *PALB2* pathogenic variant c.3113G>A (p.Trp1038Ter), which was confirmed following genetic evaluation and subsequent germline testing. Discussion points: (1) If the son has inherited the pathogenic variant, pancreatic cancer surveillance could be considered, as he would meet both International Cancer of the Pancreas Screening (CAPS) and National Comprehensive Cancer Network (NCCN) guidelines for individuals in whom surveillance is considered reasonable. Ideally, such surveillance is done in the context of a research study. (1) If any of the maternal cousins have inherited the pathogenic variant, current NCCN guidelines do not recommend pancreatic cancer surveillance for *PALB2* heterozygotes and 3rd degree relatives with pancreatic cancer. (2) The family history of breast cancer puts this family at the higher range of risk estimates, based on modifying risks. (3) The identification of *PALB2* may guide treatment options including use of platinum-based treatment or poly (ADP-ribose) polymerase (PARP) inhibitors, some of which may be through clinical trials.

identified through tumor testing. Genetic and oncology professional societies have endorsed consenting for the return of P/LP germline variants detected as part of tumor sequencing (American Society of Clinical Oncology [ASCO];[22] ACMG[23]). For *PALB2*, this is especially relevant given the increasing availability of promising targeted therapies contingent on a P/LP germline variant, such as poly(ADP)-ribose polymerase (PARP) inhibitors.

- *ACMG recommends that PALB2 should be included in breast, ovarian, and pancreas germline cancer gene panels.*

VARIANTS OF UNCERTAIN SIGNIFICANCE

The identification of variants of uncertain significance (VUS) in *PALB2* represents a considerable clinical challenge. Published studies on *PALB2* penetrance and risk have focused on predicted protein truncating variants (frameshift, nonsense, splice, exonic deletions/duplications), and the first P*ALB2* missense variant to be determined as pathogenic was c.104 T>C (p.Leu35Pro), which abrogates the *PALB2–BRCA1* interaction and disables its abilities to promote homologous recombination.[24] Three groups have recently published their experiences with the use of a range of functional assays to characterize *PALB2* missense variants[25–27] (summarized by Southey and colleagues[28]). The combined functional and epidemiological evidence published to date suggest that only a small minority of known missense variants are potentially pathogenic. The ClinGen Hereditary Breast, Ovarian and Pancreatic Cancer Variant Curation Expert Panel (https://clinicalgenome.org/affiliation/50039/) is working to define specifications of the ACMG and the Association for Molecular Pathology (AMP) rules for missense variants including integration of functional data. A VUS should not be used to guide clinical management but must be periodically re-reviewed to determine changes in interpretation based on emerging data.

- *ACMG recommends that PALB2 VUS are not used to guide clinical management.*

PATHOLOGY AND OUTCOMES

The initial reports of the pathological features of *PALB2*-related breast cancers were based on the Finnish founder variant that accounts for ~0.7% of all breast cancer in Finland. This variant, c.1592delT p.(Leu531fs), was strongly associated with high-grade triple-negative breast cancer (TNBC) (55% vs. 9.4% for nonfamilial breast cancer).[29] Subsequent studies, while reporting that *PALB2*-related breast cancers were usually high grade, did not find as high a frequency of TNBC,[12,30–33] but recent and very large commercial sequencing studies have shown that TNBC cases are substantially enriched (1.4%) for germline pathogenic variants in *PALB2*.[34,35] This relationship also holds true in Asian breast cancer patients[31,36] and in African American breast cancer patients, where there is a particularly strong association with TNBC (OR 23.5, $P < 0.001$) (by comparison, the OR for the TNBC association with *BRCA1* pathogenic variants in this population was 180).[37]

Recent molecular studies have shown that as for *BRCA1* and *BRCA2*, biallelic inactivating pathogenic variants in *PALB2* (seen in two-thirds of breast cancer tumors with germline pathogenic variants in *PALB2*) are nearly always associated with mutational signatures associated with defects in homologous recombination repair deficiency (HRD).[32,33,38–40] Li et al. identified patterns and frequencies of somatic alteration in *PALB2*-related breast cancer that distinguished them from The Cancer Genome Atlas (TCGA) breast cancer cases of the same immunohistochemical phenotype.[32] Overall, *PALB2*-related breast cancers appear to be more biologically similar to *BRCA2*- than to *BRCA1*-related breast cancer,[3,32,33] and all three forms of hereditary breast cancer are much more alike to each other than any of them are to non-HRD-related familial breast cancer, or to breast cancer in general.

How do these pathology features influence outcome following a breast cancer diagnosis? In the first study of outcome, the survival following breast cancer appeared to be significantly worse for familial *PALB2* cases than for either sporadic or familial (non-*BRCA1*, *BRCA2*, or *PALB2*) breast cancer.[29] In support of this, a study of metastatic compared with early breast cancer noted that *PALB2* was one of eight genes more frequently mutated in metastatic than early breast cancer.[41] A recent study of nearly 3,000 unselected breast cancers in China showed that nearly 1% carry a *PALB2* pathogenic variant; overall survival of these women was significantly worse compared to those with no *PALB2* pathogenic variant.[31] The most comprehensive analysis of survival was based on two founder pathogenic variants in Poland, where 12,529 women with breast cancer were genotyped. Nearly 1% were found to have one of these two variants, compared with 0.2% in controls. The 10-year survival for *PALB2* heterozygotes was only 48%, compared with 75% for those without these variants (hazard ratio [HR] for death = 2.27, $P < 0.0001$).[12] Despite these troubling findings, HRD-high tumors may respond better to chemotherapy,[33] so it will be important to include variant status of *PALB2* to interpret results of some targeted therapies in breast cancer clinical trials.

- *ACMG recommends prospective collection of clinical data from PALB2 heterozygotes to establish clear metrics on treatment outcome and survival.*

SURVEILLANCE AND RISK-REDUCING SURGERY

Breast cancer risks have now been well documented in female *PALB2* heterozygotes, thus establishing *PALB2* as a major cancer susceptibility gene. Therefore, recent guidelines such as the NCCN guidelines for genetic familial high-risk assessment,[21] Australian national oncology guidelines (eviQ)[42] the European Society of Medical Oncology,[43] and the German S3 guideline for breast cancer[44] consider *PALB2* a moderate-to-high-risk gene for breast cancer. Although the clinical utility of preventive measures as outlined in the analytical validity, clinical validity, clinical utility, and ethical, legal and social implications (ELSI) (ACCE) model is not sufficiently proven yet,[45] there is a demand for clinical intervention that needs to be addressed. Accordingly, the NCCN guidelines include recommendations for breast cancer surveillance for female *PALB2* heterozygotes. Also, ASCO, the American Society for Radiation Oncology, and the Society for Surgical Oncology Guideline have recently published breast management guidelines for patients who carry P/LP variants in hereditary breast cancer genes.[46] Based on published risks, intensified breast cancer surveillance for women carrying P/LP *PALB2* variants is recommended. This includes early onset of surveillance including mammograms, tomosynthesis, and magnetic resonance images (MRIs) with contrast starting at the age of 30 years. The optimal surveillance strategy remains to be determined with regard to the addition and frequency of mammograms and age of termination of surveillance. Importantly, clinical utility of intensified surveillance with regard to key surrogate markers, e.g., positive and negative predictive values of the surveillance strategy and hard endpoints, i.e., mortality and morbidity reduction, is largely missing and may depend on the specific phenotype of *PALB2*-associated breast cancer.

Among *PALB2* heterozygotes, NCCN recommends discussion of risk-reducing bilateral mastectomy, with nipple-sparing mastectomy as an option (www.asco.org/breast-cancer-guidelines).[21] Comprehensive counseling including a three-generation pedigree, tailored cancer risk assessment, the personal life situation and preferences of the counselee; all need to be considered when counseling for prophylactic surgery. Nongenetic risk factors such as dense breast tissue and hormonal/lifestyle modifiers may be included.[8,15] Importantly, age-specific risks (e.g., within the next ten years) should be communicated to allow counselees to make a decision over a manageable period of time. Competing risks due to other health risks and pre-existing conditions need to be considered. Given the lack of data on contralateral breast cancer risk, with regard to contralateral mastectomy, the person's current circumstances and competing risk factors should be considered, and a shared decision-making approach should be employed. Breast cancer surveillance in those with a previous breast cancer who have remaining breast tissue should be performed according to the guidelines for healthy heterozygotes.

Establishing recommendations for *PALB2*-associated ovarian cancer risks has been more challenging. Two recent studies have estimated risk to 80 years to be 3.2% (95% CI: 1.8–5.7%)[6] and 5% (95% CI: 2–10%)[5] compared with a population-based lifetime risk of 1.5–2%. Both studies estimated the risk to age 50 years to be well under 1%. Currently, the NCCN guidelines acknowledge that *PALB2* heterozygotes have an increased risk for ovarian cancer and cite insufficient evidence, based on variant status alone, to recommend risk-reducing salpingo-oophorectomy (RRSO).[21] Based on this information, risk-reducing bilateral salpingo-oophorectomy should be considered in a nondirective counseling process taking additional risk and protective factors into consideration as outlined above. In case of a decision in favor of RRSO, performing the procedure at or after menopause may be appropriate, considering that the risk before this is very small. For patients undergoing tubal ligation for contraception, opportunistic salpingectomy could be considered.[47] The benefit of ovarian cancer surveillance through the use of pelvic ultrasound and CA-125 levels is considered insufficiently sensitive for early detection of ovarian cancer and therefore not recommended. Women should be counseled regarding the limitations of this surveillance.

The NCCN and the International Cancer of the Pancreas Surveillance (CAPS) Consortium[48] recently updated pancreatic cancer surveillance recommendations, through annual MRI or magnetic resonance cholangiopancreatography (MRCP) and/or endoscopic ultrasound (EUS). Specifically, per NCCN guidelines, if a first- or second-degree relative is affected with pancreatic cancer, surveillance may be considered beginning at age 50.[21] Per CAPS recommendations, if a first-degree relative is affected with pancreatic cancer, surveillance may be considered beginning at age 45–50.[48] It is important to recognize that pancreatic cancer surveillance recommendations are mainly based on consensus rather than more rigorous evidence assessments, as additional data continue to be collected to determine benefits from surveillance. Although in the United States, surveillance for pancreatic cancer is encouraged in the context of a surveillance study, the position in the United Kingdom is based upon a lack of current data to support efficacy, thus pancreatic cancer surveillance is not recommended outside of a research study.

ACMG recommends

- *Surveillance for breast cancer should be equivalent to that for BRCA1/2 heterozygotes.*
- *Risk-reducing mastectomy can be considered as an option. The decision should be guided by personalized risk assessment.*
- *Ovarian cancer surveillance should not be offered, and risk-reducing salpingo-oophorectomy should include shared decision making and should rarely be considered before the age of 50.*
- *Pancreatic cancer surveillance should be considered, but ideally as part of a clinical trial.*

THERAPEUTIC IMPLICATIONS OF *PALB2* GENE VARIATION

Inactivating variants in *PALB2*, when associated with biallelic inactivation in the tumor (i.e., loss of heterozygosity or biallelic variants) confer a deficiency in the homologous recombination pathway.[32,49] This molecular phenotype makes these tumors more vulnerable to DNA-damaging agents, including platinum-based chemotherapy. In this regard, several case reports have described remarkable clinical activity of platinum-based chemotherapy in patients with *PALB2*-associated advanced breast or pancreatic cancer.[50–53] Some of the prior studies have retrospectively demonstrated an extended progression-free survival and even overall survival when incorporating platinum-based chemotherapy in patients with pancreatic ductal carcinomas harboring *BRCA1/2* or *PALB2* variants.

Similarly, cells with HRD are exquisitely sensitive to poly(ADP)-ribose polymerases (PARP), which prompted the clinical development of PARP inhibitors (PARPi) in patients with *BRCA1* and *BRCA2* variants and later to a wider group of patients harboring dysfunctional homologous recombination repair. A preclinical in vivo study performed in patient-derived xenografts (PDX) from patients with breast cancer showed that PDXs from *PALB2* germline variant heterozygotes were homologous recombination repair pathway deficient as assessed by nuclear RAD51 foci. Additionally, all 11 breast cancer samples from patients carrying a germline *PALB2* variant scored RAD51 foci negative, confirming this deficiency and providing evidence to clinically develop PARPi in this group.[49]

To date there are no randomized controlled trials specifically targeting patients with pathogenic germline *PALB2* variants. Given the mechanistic similarities and presentation with *BRCA1/BRCA2*-

associated cancers, it is not surprising that oncologists have in recent years used similar regimens as those that have been successful in patients with germline *BRCA1/2* P/LP variants (see Supplementary Table 1). Notably, some pancreatic adenocarcinoma trials have included patients with pathogenic germline *PALB2* variants alongside *BRCA1/2* patients, and some trials in patients with metastatic breast cancer and an associated germline variant or somatic variant in homologous recombination repair pathway genes beyond germline *BRCA1/2* have also provided very promising data among *PALB2* heterozygotes.[54,55] Within the talazoparib trial, 13 patients had breast cancer and five had a germline *PALB2* variant.[54] Among them, four had high HRD scores by Myriad MyChoice genomic score and three had a partial response after treatment with talazoparib. In the olaparib trial, of 11 patients with advanced breast cancer and a *PALB2* variant, 9 achieved a partial response (82%) and 2 had stable disease.[55] Overall, the median duration of response was nine months. Interestingly, the majority were ER+/HER2- and one was HER2+. These preliminary findings provide strong rationale to warrant further clinical development of PARPi in this population. Finally, among patients with advanced prostate cancer and homologous recombination repair pathway deficiency, clinical evidence is accumulating to show that PARPi are effective in this population where *PALB2* variants achieved the second highest response rate to olaparib behind *BRCA1/2* variants.[56,57]

- *ACMG recommends PALB2 heterozygotes should be considered for the same therapeutic regimens and trials as those for BRCA1/2.*

GENETIC COUNSELING

Despite the increasing recognition of the importance of *PALB2* predisposing to inherited breast cancer, the evidence to support cancer risks and management remains understandably less developed compared with that for *BRCA1* and *BRCA2*. As a result, there remain challenges in genetic counseling, risk assessment, and sharing management recommendations, as clinicians outline both what is known and what is not yet known to these patients, to guide them to make the best decision for themselves. Additional complexities include the range of risks that cross the threshold between moderate and high-penetrance genes. Consequently, *PALB2* may be considered a prototypic gene to highlight the significant limitations in categorizing genes according to high versus moderate penetrance, and it provides an ideal lens through which to develop consensus and a framework for how to think about risks as a continuous rather than categorical (or discrete) variable. It follows that these factors also impact the use of established risk reduction strategies (e.g., risk-reducing mastectomy), originally implemented for genes categorized as high penetrance (e.g., *BRCA1/2*), compared with surveillance, which is generally the risk management strategy recommended for genes categorized as moderate penetrance (e.g., *ATM*, *CHEK2*). *PALB2* heterozygotes or those with a family history of such are advised to follow up with a genetics provider periodically for updates. There is no established genotype–phenotype correlation. *PALB2* has recently been added to the ACMG Secondary Findings v3.0 list.[58,59]

FANCONI ANEMIA

Biallelic germline L/LP variants in the homozygous or compound heterozygous state in *PALB2* is a very rare cause of Fanconi anemia, FA-N (incidence less than 1 in 3 million), a childhood-onset condition associated with bone marrow failure, physical abnormalities, organ defects, and an increased risk of certain cancers.[60,61] The high risk for certain childhood cancers in FA-N was soon recognized including medulloblastoma[60,62] and Wilms tumor.[60,63] Large-scale studies have uncovered P/LP *PALB2* heterozygous variants in osteosarcoma, leukemia, brain tumors and soft-tissue sarcoma,[64] and pediatric high-grade glioma.[65] The detection of germline *PALB2* P/LP variant(s) in a child with Fanconi anemia and/or childhood cancer offers an opportunity for cascade testing to determine whether other adult family members are at risk. Conversely, while genetic counseling of individuals with a P/LP *PALB2* variant may include discussion of biallelic inheritance (and implications to family planning with consideration of partner testing prior to achieving pregnancy), in reality, outside of countries with a founder variant, this risk is very small (assuming a *PALB2* carrier frequency of 1 in 700, the probability of a liveborn offspring with Fanconi anemia will be less than 1 in 2,800 as some P/LP variant combinations are likely to be embryonic lethal). Additional family planning considerations include discussion of preimplantation genetic diagnosis to identify P/LP *PALB2* variants at the embryo stage. Generally, prenatal diagnosis through amniocentesis or chorionic villus sampling is not typically offered for detection of a P/LP *PALB2* variant in the fetus, given that this is an adult onset cancer predisposition syndrome.

- *ACMG does not recommend testing partners of PALB2 heterozygotes in the reproductive setting, unless they are from a country with founder variants or it can be justified by the partner's family history of cancer.*

RESEARCH GAPS IN CLINICAL AREAS OF NEED

There remains a paucity of data on *PALB2* heterozygotes compared with *BRCA1/BRCA2*, both in terms of cancer incidence, spectrum, and clinical outcomes. This extends to establishing the full spectrum of childhood cancer risk in *PALB2*-related Fanconi anemia. Genome-first and/or population-scale sequencing approaches could be used to improve risk estimates and the clinical application of polygenic scores will further refine risk estimates. Prospective data collection is needed to determine the efficacy of surveillance and risk-reducing surgery as well as establishing the contralateral breast cancer risk. Efforts should be addressed at better histopathological and molecular characterization of *PALB2*-related cancers, and how this influences clinical outcome. The role of chemoprevention needs to be established, and *PALB2* heterozygotes should be eligible for the same or equivalent therapeutic studies as *BRCA1/BRCA2*. *PALB2* heterozygotes are much less common than *BRCA1/2* outside of countries with founder populations, but large international collaborations make it feasible to collect enough data to facilitate evidence-based management approaches.

CONCLUSION

The recommendations made here have been based on expert opinion using comprehensive literature ascertainment approach, but not systematic review. There is strong evidence that P/LP *PALB2* variants confer a range of breast cancer risks across what is considered moderate to high; consequently, enhanced surveillance and the option of risk-reducing interventions are warranted. The risk range for this gene underlies the need to move away from compartmentalizing *PALB2* and consider risk to be a continuous variable from high to moderate, influenced by family history, polygenic risk score, and other factors.[7] The same applies to other breast cancer genes. Changing this paradigm will allow us to move to personalized risk estimates by placing the risk from the P/LP variant in the context of other risk factors and develop strategies to translate this information to enhance medical management. There is reasonable evidence that *PALB2* P/LP variants confer a small to moderately increased risk for ovarian cancer that may warrant risk-reducing interventions, albeit their clinical benefit is not sufficiently proven yet with respect to the

efficacy of preventive measures to reduce morbidity and mortality. Likewise, there is reasonable evidence that such variants confer a small to moderately increased risk of pancreatic cancer, but the role of surveillance remains controversial. Given the many uncertainties, those at risk for *PALB2*-related cancers, and the health professionals who care for them are encouraged to contribute follow-up data to long term studies, thereby facilitating the generation of prospective cancer risk estimates and the evaluation of prevention measures. Current evidence supports the consideration of platinum-based regimens and clinical trials of PARPi in patients with germline P/LP *PALB2* variants and breast, ovarian, prostate, or pancreatic cancer, especially when biallelic inactivation and HRD are present.

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ADDITIONAL INFORMATION

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Correspondence and requests for materials should be addressed to ACMG.

Supplementary Table 1. Summary of key published treatment studies that included *PALB2*-related cancers

Cancer type	*PALB2* status of study population	Treatment	Response	Reference
Breast	Case series of two patients with metastatic breast cancer a) 1st patient 51-year old female heterozygous for *PALB2* c.3323delA b) 2nd patient 47-year old female – tumor testing identified a c.3323del variant. Germline testing subsequently showed a pathogenic germline *PALB2* c. 509_510delGA variant.	a) Received carboplatin and gemcitabine as her 2nd line after germline testing b) was treated with multiple lines of endocrine therapy (fulvestrant, letrozole, and palbociclib) and chemotherapy (single agents nab-paclitaxel, eribulin, and navelbine and a combination cyclo-phosphamide, methotrexate, and fluorouracil regimen) before receiving single agent carboplatin	a) Complete remission within 3 months, with sustained no evidence of disease after follow up. b) near-complete remission which was sustained for 2 months, but patient had to stop treatment due to thrombocytopenia.	1
Breast	Two cohorts of patients with measurable disease enrolled between March 2018 and January 2020: one contained those with germline variants in non-*BRCA1/2* homologous recombination–related genes (cohort 1, n = 27) and one contained those with somatic mutations in these genes or *BRCA1/2* (cohort 2, n = 27). 13/54 had *PALB2* P/LP variants	Patients received olaparib at 300 mg twice daily until disease progression. The primary endpoint was objective response rate, with the endpoint being met if there were four or more responses (≥ 15% rate) in each 27-patient cohort.	Median follow-up was 4.2 months. In cohort 1 (germline variant other than *BRCA1/2*), objective response was observed in nine patients (all partial responses; 33%) and the clinical benefit rate at 18 weeks was 50%. In cohort 2 (somatic mutations in homologous recombination–related genes), objective response was observed in eight patients (all partial responses; 31%) and the clinical benefit rate at week 18 was 48%.	2
Pancreas	15.4% of the patients included in the study had *PALB2* P/LP germline variants. The rest were *BRCA1/2* heterozygotes. There was no analysis by gene.	Platinum based therapy – FOLFIRINOX, FOLFOX or gemcitabine/cisplatin.	No breakdown for *PALB2* P/LP was available. For P/LP patients (including *BRCA1/2*), partial response and stable disease were seen in 58% and 21% respectively. None achieved complete remission.	3
Pancreas	Patients with homologous recombination gene P/LP variants were included in the study, of which 31 were *BRCA1/2/PALB2* heterozygotes (further breakdown not available).	No breakdown available, but 61% of the study population received a platinum-based regime as 1st line. Regimes included FOLFIRINOX, FOLFOX, gemcitabine/cisplatin regimes.	Response not evaluated. Instead, patients with homologous recombination repair pathway deficiency were found to have improved progression-free survival (compared with no homologous recombination repair deficiency) when treated with 1L platinum (HR, 0.44), but not with 1L-non-platinum. They also had	4

			improved overall survival, regardless of their first-line treatment; although most had a platinum-based therapy along their treatment course.	
Pancreas	Study population of 29 *BRCA1/2/ PALB2* heterozygotes. Two of the 29 cases were *PALB2* P/LP heterozygotes, rest were *BRCA1/2.*	72% received platinum-based therapy during their treatment course: 12 (48.0%) received oxaliplatin, three (12.0%) received cisplatin, two (8.0%) received both oxaliplatin and cisplatin.	Heterozygotes had median overall survival of 20.1 months, with 94% 1-year overall survival. No objective response rate reported. Subgroup analysis comparing oxaliplatin to cisplatin did not demonstrate a difference between regimens.	5
Pancreas	*BRCA1/2/PALB2* heterozygotes with stage III/IV cancer. Three of 50 (6%) were *PALB2* P/LP heterozygotes.	Combination of cisplatin, gemcitabine, and veliparib (arm A) and for cisplatin and gemcitabine (arm B). Of the *PALB2* heterozygotes, one was in arm A, two were in arm B.	No breakdown for PALB2 P/LP heterozygotes available. For the entire study, the response rate to cisplatin/gemcitabine was 65.2%. With the addition of veliparib, the response rate was 74.1%, 74% of patients in arm A and 65.2% in arm B had partial response. Disease control rate at any time point (which includes complete remission, partial response and stable disease) was 100% in arm A and 78% in arm B.	6
Ovarian	367 individuals were recruited with ovarian carcinoma, fallopian tube, endometrial or peritoneal carcinomas, 87 had a germline HR mutation, of which 2 were *PALB2* heterozygotes.	No breakdown available regarding which platinum agent was used	71 of 85 (84%) primary carcinomas with a homologous recombination repair variant (germline or somatic) demonstrated platinum sensitivity – defined as complete remission and maintenance of complete remission for 6 months after therapy. No further breakdown available. Of 16 recurrent carcinomas with a homologous recombination repair variant, 5 (31%) remained platinum sensitive.	7
Prostate	49 patients evaluated, all of which underwent both somatic and germline testing.	Olaparib 400 mg twice daily was given to all patients.	14 of 16 biomarker-positive patients (88%) had a response to olaparib. Of the 2 *PALB2* P/LP heterozygotes, one whose tumor had biallelic *PALB2* P/LP variants, had a durable partial response that lasted for 39 weeks.	8

			The other with monoallelic deletions of both *BRCA2* and *PALB2* also had a clear partial response.	
Prostate	98 patients had DNA damage response gene P/LP variants and were included in the study, of which 7 *PALB2* P/LP variants were detected (6 germline, 1 somatic).	Olaparib 300 mg twice daily given to three patients, 400 mg twice daily given to the other four.	Of the *PALB2* P/LP heterozygotes, four of seven patients responded to treatment (composite overall response and radiological RECIST response). Level of response (complete remission vs partial response) was not detailed.	9
Prostate	Case study on a 43-year old heterozygote with castration resistant cancer with loss of heterozygosity was identified in the tumor.	Single-agent treatment with the PARP inhibitor olaparib, with addition of cisplatin after PSA increased.	Progressive disease after 6 weeks of olaparib, then stable disease for 3 months after cisplatin was added. This was considered significant as disease was previously refractory to all other lines.	10

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