Testing for Inherited Susceptibility to Breast Cancer

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KEYWORDS

• Genetic susceptibility • Genetic testing • Genetic risk

KEY POINTS

- Early approaches to genetic testing for breast cancer risk were based on certain assumptions about the nature of that predisposition.
- With the passage of time, the therapeutic relevance of inherited risk has become clearer and centered the sensitivity of testing.
- The importance of sensitivity has led to calls for universal testing of all breast cancer patients.
- A combination of age-based and guideline-based testing offers extremely high sensitivity and a negative predictive value.
- Broad (universal) testing using large multigene panels introduces the risk of misinterpretation and mismanagement of genetic alterations that are less familiar to nongenetics clinicians.

INTRODUCTION

Although 1 in 8 (12.9%) US women will develop breast cancer in their lifetime,[1] not everyone is at the same risk for the disease. Individual women are at higher or lower degrees of risk based on well-known factors such as age at menarche and menopause, age at first live birth, parity, and mammographic density. Environmental factors such as obesity and alcohol may also play a role. Family history, of course, has long been known to be one of the major contributors to the variation in individual breast cancer risk.[2] Shared genetic factors largely mediate this influence of family history. Based on a Nordic twin study, 31% (95% confidence interval [CI] 11%–51%) of the variation in breast cancer risk can be attributed to heredity.[3]

Over the last 40 years, a huge scientific effort has identified the genetic underpinnings of much (but not all) of this hereditability. These genetic factors are conventionally

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divided into 3 broad categories: (1) rare high-penetrance genetic variants (present in <1% of the population with relative risks of 5 or higher), (2) rare moderate penetrance variants (<1% prevalence, relative risks of generally 2–5), and (3) common variants (also known as single-nucleotide polymorphisms [SNPs], present in >1% of the population, sometimes nearly 50%, and associated with relative risks of <1.5, more commonly <1.2). What follows is a brief discussion of these categories.

RARE, HIGH-PENETRANCE VARIANTS

Rare, high-penetrance variants are responsible for familial cancer syndromes that were first suspected because of pedigree analysis. Familial cancer syndromes, including those that involve breast cancer, nearly always manifest an autosomal dominant pattern of predisposition. Traditionally, these syndromes were recognized by (1) the apparent transmission of the predisposition by both males and females, with a 50% chance of a parent passing the predisposing genetic variant to each child; (2) onset of disease at a younger age than in the general population; (3) increased risk of bilateral cancers in paired organs, such as the breasts; and (4) often increased risks at more than one organ site. Before the era of routine genetic testing, the penetrance (risk of cancer) associated with these rare variants appeared to be very high, often over 90%.

The first familial cancer syndromes described were linked to rare cancers, such as retinoblastoma (Hereditary retinoblastoma, described in twins by Benedict in 1929) and childhood sarcoma (Li-Fraumeni syndrome, first described in 1969).[4,5] Interestingly, the first description of Li-Fraumeni syndrome, eventually shown to be due to pathogenic variants in *TP53*, noted the association of childhood sarcoma with very early-onset breast cancer. These syndromes were very rare, and it was not until Henry Lynch described autosomal dominant colon/endometrial and breast/ovary cancer families that consideration was given to the potential role of rare variants in the causation of common malignancies.[6,7] Newman and King compiled the statistical evidence for a rare "breast cancer gene" in 1988 and, using the techniques available at that time, localized the position of this gene, which came to be known as *BRCA1*, to 17q21.[8,9] The gene itself was cloned in 1994, with a second gene, *BRCA2*, identified shortly thereafter.[10,11]

Although pathogenic variants in *BRCA1* and *BRCA2* cause the hereditary breast and ovarian cancer syndrome (HBOC), breast cancer is seen in several other familial cancer syndromes. Li-Fraumeni (*TP53*) was mentioned earlier. Breast cancer is also a component tumor of Cowden syndrome (*PTEN*), hereditary diffuse gastric cancer (*CDH1*), and the Peutz-Jeghers syndrome (*STK11*).[12–14] Fortunately, these syndromes are quite rare, unlike HBOC.

RARE, MODERATE PENETRANCE VARIANTS

The high-penetrance genes associated with autosomal dominant cancer syndromes were mainly identified through positional cloning techniques. This approach was feasible due to the ability to easily "track" the gene through pedigrees and seek recombination events. Other risk genes were identified through candidate gene approaches, often in women who were not part of families with clear autosomal dominant transmission. For example, breast cancer risk was noted to be increased in women from families in which children had been diagnosed with ataxia-telangiectasia, a *recessive* disorder of childhood that was found to be associated with alterations in the *ATM* gene.[15] *CHEK2* was initially identified as a possible cause of Li-Fraumeni syndrome.[16] The presence of a common *CHEK2* founder variant in Northern Europe (c.1100delC) facilitated the

establishment of this gene as a less-penetrant susceptibility gene.[17] Other genes became candidates because of a growing understanding of the components of DNA damage repair pathways and the ability to conduct large case-control studies using next-generation sequencing technology, including studies comparing the entire exomes of women with or without cancer.

It has been challenging to come to a consensus on a list of breast cancer susceptibility genes. In general, moderate penetrance variants do not cause a recognizable autosomal dominant pedigree pattern, and the associated risks are similar to those associated with having an affected first-degree relative (relative risk of 1.8–1.9).[18,19] This presents 2 issues. First, large studies are needed to establish whether a particular gene has a statistically significant association with risk. This is further complicated by the observation that some genes may have subtype-specific predispositions (eg, for estrogen receptor-negative disease but not for the more common estrogen receptor-positive disease). Second, because pathogenic variants in individual genes are rare, defining the exact degree of associated risk has been complicated by statistical variation within relatively wide CIs. Two large recent population-based case-control studies have gone far toward consolidating a list of accepted susceptibility genes. The Breast Cancer Association Consortium (BCAC) published an analysis of 34 suspected susceptibility genes in 60,466 women with breast cancer and 53,461 controls.[20] Hu and colleagues reported an analysis of 28 genes in 32,247 women with breast cancer and 32,544 controls from the CARRIERS Consortium.[21] The results of these studies are summarized in **Table 1**.

Genes associated with significantly increased risks in both studies were *ATM*, *CHEK2*, *BRCA1*, *BRCA2*, and *PALB2*. Genes associated with risk in the larger BCAC analysis but not the CARRIERS analysis were *BARD1*, *MSH6*, *RAD51 C*, and *RAD51D*. Although the associations did not reach statistical significance in the CARRIERS study, this may have been a result of the difference in sample size, since the prevalence of alterations in these genes was similar between the 2 studies, with similar odds ratios. Certain known associations (eg, *CDH1, NF1, PTEN, STK11, TP53*) were not clearly identified in these population-based studies. This may be because many of these syndromes present at a young age with clinical features (*PTEN, NF1, STK11*) or with malignancy (*TP53*). These individuals would not be included in a population-based ascertainment of breast cancer cases (who would be excluded if a mutation were known) and controls (who would be excluded if they manifested clinical features of a predisposition syndrome). It is important to note that breast cancer associations were *not* confirmed for several genes that are often included on commercial multigene panels, including *BRIP1*, *NBN*, and *RAD50*.

In both reports, *ATM* and *CHEK2* variants were associated with greater risks of estrogen receptor (ER)-positive disease than of ER-negative. For *BARD1*, *BRCA1*, *BRCA2*, *PALB2*, *RAD51C*, and *RAD51D*, risks of an ER-negative disease were greater. In the BCAC analysis, there were also age effects, with odds ratios declining significantly with age for *BRCA1*, *BRCA2*, *CHEK2*, *PALB2*, *PTEN*, and *TP53*.

Taken together, these studies clearly establish *ATM*, *CHEK2*, and *PALB2* as breast cancer susceptibility genes. *ATM* and *CHEK2* would be considered of moderate penetrance, while the risk associated with *PALB2* variants is similar to that resulting from *BRCA2* variants, and *PALB2* could therefore be considered a high-penetrance gene. There are also indications that *BARD1*, *RAD51C*, and *RAD51D* variants are linked to an increased risk of ER-negative breast cancer although the risk of breast cancer overall is only marginally increased. Another important outcome of these studies is the estimate of pathogenic variant prevalence in the general population (**Table 2**). These results suggest that approximately 0.37% (1 in 270) of control women

Table 1
Statistically significant associations with all breast cancer genes in either population-based study[20,21]

	BCAC (48,826 Cases, 50,703 Controls)			CARRIERS (32,247 Cases, 32,544 Controls)		
Gene	N (%) Cases	N (%) Controls	OR (95% CI)	N (%) Cases	N (%) Controls	OR (95% CI)
ATM	294 (0.6%)	150 (0.3%)	2.10 (1.71–2.57)	253 (0.78%)	134 (0.41%)	1.82 (1.46–2.27)
BARD1	62 (0.12%)	32 (0.06%)	2.09 (1.35–3.23)	49 (0.15%)	35 (0.11%)	1.37 (0.87–2.16)
BRCA1	515 (1.05%)	58 (0.11%)	10.57 (8.02–13.93)	275 (0.87%)	37 (0.11%)	7.62 (5.33–11.27)
BRCA2	754 (1.54%)	135 (0.27%)	5.85 (4.85–7.06)	417 (1.29%)	78 (0.24%)	5.23 (4.07–6.77)
CHEK2	704 (1.44%)	315 (0.625)	2.54 (2.21–2.91)	349 (1.08%)	138 (0.42%)	2.47 (2.02–3.05)
MSH6	39 (0.08%)	23 (0.05%)	1.96 (1.15–3.33)	39 (0.12%)	32 (0.10%)	1.13 (0.70–1.83)
PALB2	274 (0.56%)	55 (0.11%)	5.02 (3.73–6.76)	148 (0.46%)	38 (0.12%)	3.83 (2.68–5.63)
RAD51C	54 (0.11%)	26 (0.05%)	1.93 (1.20–3.11)	41 (0.13%)	35 (0.11%)	1.20 (0.75–1.93)
RAD51D	51 (0.10%)	25 (0.05%)	1.80 (1.11–2.93)	26 (0.08%)	14 (0.04%)	1.72 (0.88–3.51)

Abbreviations: CI, confidence interval; OR, odds ratio.

Table 2
Prevalence of pathogenic variants in relevant genes in 83,247 combined controls[20,21]

Gene	N	%
ATM	284	0.34%
BARD1	67	0.08%
BRCA1	95	0.11%
BRCA2	213	0.26%
CHEK2	453	0.54%
PALB2	93	0.11%
RAD51 C	61	0.07%
RAD51D	39	0.05%

carry a pathogenic variant in *BRCA1* or *BRCA2*, and 0.99% (1 in 100) carry a variant in *ATM*, *CHEK2*, or *PALB2* (assuming that the number of women carrying variants in 2 or more genes is small).

COMMON VARIATION AND BREAST CANCER RISK

Although variants in high- or moderate-penetrance genes are more common than initially suspected, they are still quite rare and cannot account for a substantial portion of the hereditability of breast cancer. Therefore, more hereditability must result from common variation.

The invention of massively parallel, "next-generation" sequencing facilitated large-scale whole-genome sequencing that allowed an appreciation of the staggering amount of normal variation in the human population.[22] The 1000 Genomes project assessed the whole genomes of over 2500 individuals from around the world and cataloged 84.7 million SNPs, 3.6 million short insertion/deletions, and 60,000 structural variants. Early on, researchers realized that this variation could, in theory, be used to identify genomic regions associated with breast cancer susceptibility.[23] A series of genome-wide association studies (GWAS) were conducted, comparing the prevalence of individual SNPs in cases and controls to identify specific loci associated with case status (reviewed in the paper by Lilyquist and colleagues[24]). These studies identified over 180 individual SNPs associated with breast cancer with high degrees of statistical significance (called "genome-wide significance," generally requiring $P < 10^{-5}$ or greater, in order to adjust for extreme multiple testing).

Each SNP is associated with a very small increase in risk (odds ratios >1.4 and most with OR of 1.10 or less), limiting the value as individual predictors. However, knowledge of genotypes (and associated risks) at multiple SNPs allows the construction of polygenic risk scores (PRS), which can be more meaningful. As an example, Mavaddat and colleagues reported on the construction and validation of a breast cancer PRS using 313 SNPs from a prior GWAS.[25] Each standard deviation of the PRS was associated with an increase in hazard ratio of 1.61 (95% CI 1.57–1.65), and women with the highest PRS have an estimated lifetime risk of 32.6% (compared to 2% for those with the lowest). PRS also modify contralateral breast cancer risk as well as risks in women with pathogenic variants in *BRCA1* or *BRCA2* or moderate-penetrance genes.[26–30] PRS is largely independent of traditional risk factors although PRS obviously does make some contribution to familial risk.[31] After appropriate adjustment for this shared component of risk, PRS can be combined with existing risk-assessment models to

generate a comprehensive risk assessment for women without identified genetic susceptibility and for women with alterations in moderate-penetrance genes.[28,32–36] Clinical deployment of these comprehensive models is underway although there are still many aspects of the clinical use of PRS that remain to be standardized.[37]

INTRODUCTION OF GENETIC TESTING FOR BREAST CANCER SUSCEPTIBILITY

In the early 1990s, while researchers were seeking to identify *BRCA1* (and *BRCA2*), parallel conversations began about how to offer genetic testing to the families participating in the discovery studies, particularly the unaffected relatives. As moderate-penetrance genes were not yet identified, discussions were exclusively about testing for *BRCA1/2* variants. The conversations were shaped by several assumptions, many of which have since been shown to be incorrect.

The first assumption was that pathogenic variants in these genes would be rare, even though the segregation analysis of Newman and King predicted an allele frequency of 0.0006 (which corresponds to a heterozygote prevalence of 0.11%, exactly what was observed for *BRCA1* in the BCAC controls described above).[9] The second assumption was that women with pathogenic variants would be at extremely high risk of breast cancer (80% or greater by age 70), along with a substantially increased risk of ovarian cancer.[38,39] Along with this pessimistic understanding of risk, there was also uncertainty about the effectiveness of preventive interventions like mastectomy and salpingo-oophorectomy.[40,41] Breast MRI was not yet available. There were no immediately obvious therapeutic implications for women who had cancer. And, lastly, there was substantial concern about the possibility of adverse psychological response to the finding of a pathogenic variant as well as negative social consequences such as discrimination and stigmatization.[42] Despite these limitations, there was significant (but not universal) interest in testing among women who had participated in the research ascertainments.[43] And, in the United States, there was rapid commercialization and promotion of testing, particularly since the group that identified *BRCA1* was tightly linked to a commercial enterprise that established an exclusive patent position on the gene sequence and uses thereof.

Because of the complexities surrounding germline genetic testing and because testing was at first exclusively for personal utility (with no clearly effective clinical interventions), a rigorous paradigm was deployed for pretest counseling, documented informed consent, and posttest counseling to ensure understanding both before and after testing, as well as to provide support in the event of adverse psychological responses.[44–47] Germline genetic testing was to be handled differently than other tests used for asymptomatic individuals because of the perceived exceptional nature of this information. The closest paradigm was Huntington's disease rather than hypercholesterolemia. Not all agreed with this concept of "genetic exceptionalism,"[48] but the principle of pretest genetic counseling became established and, in many places, a prerequisite to testing.

CHALLENGES TO THE STANDARD MODEL

Since 1996, when *BRCA* testing began to become widely available (at least in the United States), the utility and necessity of the standard model for genetic testing in breast cancer have been questioned. Many of the assumptions that underlay the genetic counseling model have turned out to be incorrect. The breast and ovarian cancer risks associated with pathogenic variants in *BRCA1* and *BRCA2* are significantly higher than those of the general population but not as high as those calculated from the study of the early high-risk families.[49] Severe psychological distress in reaction

to test results has not been limiting although some individuals do experience adverse responses to genetic information.[50] Systemic discrimination and stigmatization have not materialized. And preventive interventions such as risk-reducing mastectomy, risk-reducing salpingo-oophorectomy, and enhanced surveillance with breast MRI are all clearly effective (although not completely so).[51–59] All these factors argued for the potential *clinical* utility of testing for unaffected women, which eventually led to the endorsement of testing for appropriate unaffected women by the U.S. Preventive Services Task Force.[60,61]

While various lines of evidence were establishing the potential benefit in unaffected women, the *therapeutic* importance of testing women with breast cancer also became clear. Among families who participated in the efforts to clone *BRCA1* and *BRCA2*, there was a clear increased incidence of bilateral cancer, as would be expected from a high-penetrance single-gene predisposition. Once the genes were identified, the absolute risks of metachronous contralateral disease were found to be high in women with breast cancer and pathogenic variants. In 1 large analysis, the risk of contralateral cancer in women with *BRCA1* pathogenic variants was 40% in the 20 years after the index diagnosis.[49] For women with *BRCA2* variants, the risk was 26%. In response to this risk, a significant number of women with pathogenic variants opt for bilateral mastectomy at the time of initial surgery, even if they are otherwise candidates for breast conservation. While this approach clearly reduces the risk of second breast cancer, the impact on survival is controversial. Some reports have suggested an overall survival benefit; however, these studies are not definitive, and the conclusions probably do not apply to all patients.[62,63] Age at diagnosis, risk of mortality from index cancer diagnosis, and whether the pathogenic variant is in *BRCA1* or *BRCA2* are all likely to impact any potential survival benefit. Hence, breast conservation is not contraindicated in *BRCA* carriers.[64] Nonetheless, knowledge of BRCA status at diagnosis can be extremely important in guiding women and their surgeons in choice of local therapy.

Knowledge of *BRCA* status is also important in guiding the selection of systemic therapy. In the metastatic setting, platinum-based chemotherapy treatment appears to be more effective than taxanes in patients with *BRCA*-associated triple-negative breast cancer.[65] In addition, treatment of *BRCA* carriers with metastatic disease using inhibitors of poly-ADP-ribose polymerase (PARP inhibitors, eg, olaparib, talazoparib) provides an advantage in progression-free (but not overall) survival compared to physician's choice of nonplatinum chemotherapies.[66–68] Recently, the OlympiA study demonstrated that the addition of a PARP inhibitor to a standard adjuvant therapy improved survival.[69]

Knowledge of *BRCA* status has been important to decisions about local treatment since the early 1990s and is now important to treatment selection in both late and early-stage disease. For this reason, some have recommended that genetic testing be offered to all women with breast cancer.[70] It would not be possible to deploy this model using the standard testing approach of pretest and posttest counseling by trained genetics professionals, as there simply are not enough genetic counselors and the workforce is not evenly geographically distributed. There is, however, significant literature on "mainstreaming" genetic testing, also known as clinician-directed testing, illustrating that it is safe and acceptable to both patients and providers.[71–76] One could therefore envision a "2-track" system whereby affected women who need genetic information rapidly for treatment decision-making could receive clinician-directed testing after pretest education while unaffected women seeking risk assessment (or women with a past diagnosis for who the information is not immediately therapeutically relevant) could receive standard pretest counseling. Apart from

efficiency, 1 additional advantage to a cascade approach (testing affected women and then extending testing to family members of those found to carry pathogenic variants) is that all *BRCA* carriers in the population could, in theory, be identified much more quickly than by unselected population screening.[77]

CONSIDERATIONS REGARDING UNIVERSAL TESTING

Genetic testing of all women with breast cancer at the time of diagnosis would have several potential benefits. If such testing became a part of standard care, it would substantially reduce the chance that a *BRCA* carrier would be "missed." It could also reduce existing racial and geographic disparities in genetic testing related to access to pretest counseling. As mentioned, it could accelerate the identification of most if not all carriers in the population if cascade testing were effective. And early modeling studies suggest that the approach could be cost-effective compared to family history-based testing although these were based on European cost assumptions which may not be appropriate for all health systems.[78,79]

The question then becomes, why not use universal testing? The first question is whether testing *all* women with breast cancer is necessary to achieve the stated goals, or whether strict adherence to guideline criteria-based testing would be sufficient.[80] Guidelines vary from country to country, and even among health systems within a country. In the United States, the National Comprehensive Cancer Network (NCCN) guidelines are the most widely accepted (**Table 3**). These guidelines are quite permissive and very nonspecific. In a large analysis of unselected women with breast cancer seen at the Mayo Clinic between 2000 and 2016, Yadav and colleagues reported that 1872 of 3907 women (47.9%) met the 2019 NCCN criteria.[81] These criteria limited testing of women with triple-negative breast cancer to those aged 60 years or younger, so the proportion of women meeting the 2022 criteria (with no age limit on triple-negative disease) is likely to be slightly higher. The sensitivity of the older NCCN criteria was 86.9% (93/107) for *BRCA1* or *BRCA2* alterations and 82.6% (100/122) for *BRCA1*, *BRCA2*, or *PALB2* alterations. It is likely that the more recent criteria (testing all women with triple-negative cancer) are more sensitive, as another recent analysis indicated that approximately 3% of such women carried a *BRCA1*,

Table 3
NCCN criteria for genetic testing (version 2.2022)

Age	Additional Criteria
≤45	No other criteria needed
46–50	Multiple synchronous or metachronous primaries ≥1 Close relative with breast, ovary, prostate, pancreas cancer Unknown or limited family history
≥51	≥1 Close relative with breast cancer ≤ 50, male breast, ovarian, pancreas, metastatic prostate ≥2 Close relatives with breast and/or prostate cancer (at any age) ≥3 Diagnoses of breast cancer (total, including bilateral/metachronous) in patient and relatives
Any	Triple-negative breast cancer Lobular breast cancer with family history of diffuse gastric cancer Male breast cancer ≥1 Relative with male breast cancer Ashkenazi Jewish ancestry

BRCA2, or *PALB2* pathogenic variant if they were older than 65 years.[82] The sensitivity of the NCCN criteria for moderate-penetrance genes such as *CHEK2* and *ATM* was lower (67/110, 60.9%),[81] which is not unexpected as the criteria are designed to identify strong predispositions.

While the sensitivity analyses suggest that the NCCN criteria are insufficient, it is important to remember that the prevalence of pathogenic variants is quite low overall. Therefore, the negative predictive value (NPV) of the NCCN criteria (even without expanding to all triple-negative disease) is very high. Of the 2035 women not meeting the NCCN criteria, 2021 did not have *BRCA1* or *BRCA2* alterations (NPV 99.3%), and 2013 did not have *BRCA1*, *BRCA2*, or *PALB2* alterations (NPV 98.9%). If onetests all women aged 60 years or younger and those older than 60 years who meet the NCCN criteria, the NPV of these combined criteria for *BRCA1* or *BRCA2* would be 99.6%.

Taken together, these data suggest that women who are older than 60 years and do not otherwise meet the NCCN criteria are very unlikely to carry a *BRCA1*, *BRCA2*, or *PALB2* alteration that would have immediate clinical relevance (either for surgical treatment or for treatment with a PARP inhibitor).[83] Testing all women 60 or younger would increase the number of women tested by about 20% (from the approximately 50% who meet the NCCN criteria to approximately 70% of all patients). This approach would still have a slightly lower NPV for non-BRCA predisposition genes (97.8%). However, alterations in genes other than *BRCA1*, *BRCA2*, and *PALB2* do not have immediate therapeutic relevance. Contralateral cancer risks are undefined, and thus, finding pathogenic variants does not support routine preventive mastectomy,[84] especially since a meaningful proportion of women carrying moderate-risk variants are not even at elevated cancer risk due to modification by polygenic risk and traditional risk factors.[28,33,36] Universal testing will therefore substantially increase the number of women who need to be tested (and thus societal cost) and, since nearly all testing is now done through multigene panels, will increase the chance that a woman will be found to carry either a variant of uncertain significance or a pathogenic alteration in a gene that is not therapeutically actionable and may be of uncertain relevance to her family members.[85]

SUMMARY

There has been enormous progress since the discovery of *BRCA1* and *BRCA2* in the mid-1990s. Germline variation has clear relevance with decisions for women with breast cancer and their families regarding surgical prevention, cancer surveillance, and treatment of established early- and late-stage disease. Because of this clear clinical utility (at least for *BRCA1* and *BRCA2*), the traditional referral/genetic counseling model presents a potential barrier to getting women the information they need in a timely manner. For time-sensitive treatment decision-making, newer clinician-directed testing approaches should be promoted. At the same time, the involvement of genetic counselors and other clinical cancer genetics professionals is critical for result interpretation, especially for variants of uncertain significance and pathogenic variants in genes other than *BRCA1* or *BRCA2*. This involvement is crucial to avoid misinterpretation and mismanagement while also ensuring appropriate family engagement for cascade testing when appropriate. Older women with breast cancer (older than 60 years) who do not meet the current NCCN criteria are extremely unlikely to carry a pathogenic variant in *BRCA1*, *BRCA2*, and probably *PALB2*. Multigene panel testing may identify non-*BRCA* variants in this setting although the NPV of the NCCN criteria is high even for these genes. If multigene panel testing is performed, whether in women meeting NCCN criteria or not, engagement of genetics professionals in the posttest setting is even more crucial as the interpretation of non-*BRCA* variants and

determination of associated risks is a dynamic field. This is particularly the case if a panel is chosen that includes several genes that are not typically associated with breast cancer.

CLINICS CARE POINTS

- NCCN criteria have a high, but less than 100%, sensitivity for the detection of pathogenic variants in *BRCA1* and *BRCA2* and an even lower sensitivity for the detection of pathogenic variants in "moderate-penetrance" genes.
- Including an age threshold (eg, testing women younger than 60 years without regard to criteria and using risk-based testing above that age) will improve sensitivity marginally.
- Broader testing will identify more pathogenic variants in genes other than *BRCA1* and *BRCA2*. These variants do not have treatment implications (apart from *PALB2*), and the risks to unaffected women are highly modified by polygenic risk and by traditional risk factors. This modification is such that a significant proportion of women with pathogenic variants in moderate-penetrance genes are not at significantly increased risk of breast cancer.
- If broad testing is to be undertaken without pretest counseling, it is essential that a cancer genetics professional be engaged to assist interpretation and management of variants that are unfamiliar to the ordering clinician.

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