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COUNSELING AND TESTING (C REISER AND C WALTON, SECTION EDITORS)

Multigene Cancer Panels: Implications for Pre- and Post-test Genetic Counseling

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Abstract

Purpose of Review The availability of multigene cancer panel testing (MCPT) has revolutionized the care of individuals and families at risk for hereditary cancer. This review discusses fundamental components of genetic counseling, test selection, result interpretation, and follow-up related to MCPT.

Recent Findings Routine use of MCPT increases the diagnostic yield for major hereditary cancers such as breast, ovarian, and colon, with the identification of pathogenic variants in high- and moderate-penetrance genes. In addition, the larger the panel, the more likely one or more variants of uncertain significance will be identified. Furthermore, although index cases who test negative after multigene panel testing may derive some reassurance about hereditary risk, assessment and management based on personal and family history are the keys.

Summary Given the complexity of MCPT, pre- and post-test genetic counseling approaches have been adapted to optimize the delivery of information and support to patients and their families.

Keywords Cancer genetics · Genetic counseling · Multigene cancer panels · Cancer genetic testing

Introduction

Genetic counseling and testing for hereditary cancer risk is a standard part of clinical care for high-risk individuals. In the USA, cancer susceptibility testing is the most commonly performed genetic test in adults [1]. From the mid-1990s to 2013, most cancer genetic testing for predisposition to breast, ovarian, and colorectal cancer was limited to *BRCA1* and *BRCA2* (*BRCA*) and Lynch syndrome genes [2, 3]. Then, a notable transformation occurred in 2013 when patents on the *BRCA* genes were lifted [4••]. Immediately thereafter, laboratories leveraged next-generation sequencing technologies to simultaneously test for pathogenic variants (PVs) in several cancer susceptibility genes, also known as multigene cancer panel testing (MCPT). Now, the use of such panels has mostly supplanted single gene or sequential gene testing in the USA, particularly given that the cost of testing has significantly declined [5].

Thus, in the current era of MCPT, the approach to pre- and post-test genetic counseling has evolved to address the multifaceted informational and support needs of patients and their families [4••, 6•, 7–9]. In this review, we discuss the components of pre- and post-test genetic counseling, including test/panel selection, test result outcomes, and complexities in result interpretation. We also discuss familial and medical management implications.

This article is part of the Topical Collection on *Counseling and Testing*

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Pre-Test Genetic Counseling

Risk Assessment

A central component of cancer genetic counseling is the collection of detailed personal and family history data to provide an individualized risk assessment and to formulate a

differential diagnosis [10]. During this process, it is also important to assess the patient's goals related to genetic counseling and testing (e.g., to obtain information for treatment planning, screening, and risk reduction decisions, or to learn about relatives' cancer risks).

For patients with a history of cancer, information is collected about the type of cancer, age at diagnosis, pathology, treatment, and if applicable, tumor genetic test results, as well as personal risk factors [11]. A minimum three generation pedigree including both the maternal and paternal sides is also constructed (see Fig. 1) [12]. This process is used to determine if the patient meets qualitative criteria for a recognized cancer predisposition syndrome and genetic testing, and whether there is a family member who might be a better candidate in whom to initiate testing [12, 13••, 14••, 15]. For example, in Fig. 1, if the 36-year-old presents for genetic testing, her sister who had breast cancer at 42 is the more informative person in whom to initiate testing.

Tiered-Binned Model

When counseling about MCPT, there is a broad range of information to convey so that patients can make an informed decision [6•, 16, 17]. Prior to MCPT, pre-test genetic counseling sessions generally reviewed the cancer risks and management guidelines for each gene being tested [17]. Now, many genetic counselors utilize a "tiered-binned model" [6•, 17, 18]. In this approach, genes on various panels are categorized based on the extent to which PVs increase the risk of developing cancer and thus, how likely it is that the identification of such PVs would change recommendations for medical management [6•].

High-Risk vs. Moderate-Risk vs. Newer Preliminary Evidence Genes

Genes on a multigene cancer panel are divided into three risk categories: high-risk genes, moderate-risk genes, and newer preliminary evidence genes [19–21, 22••]. There are currently no established criteria on what risk level defines high risk versus moderate risk [20, 22••]. In general, PVs in high-risk genes confer a relative risk of 4 or higher for the major associated cancers (e.g., breast and ovarian in *BRCA*; colon cancer in Lynch syndrome genes; see Table 1) [13••, 14••, 20, 22••, 23]. Genes in this category also include those associated with well-recognized, but rare, cancer syndromes (e.g., Peutz-Jeghers, Li-Fraumeni). PVs in moderate risk genes generally confer a relative risk of 2 to 4 for at least one cancer [13••, 14••, 19, 20, 22••]. PVs in newer genes are associated with elevated risks of one or more cancers, but more research is

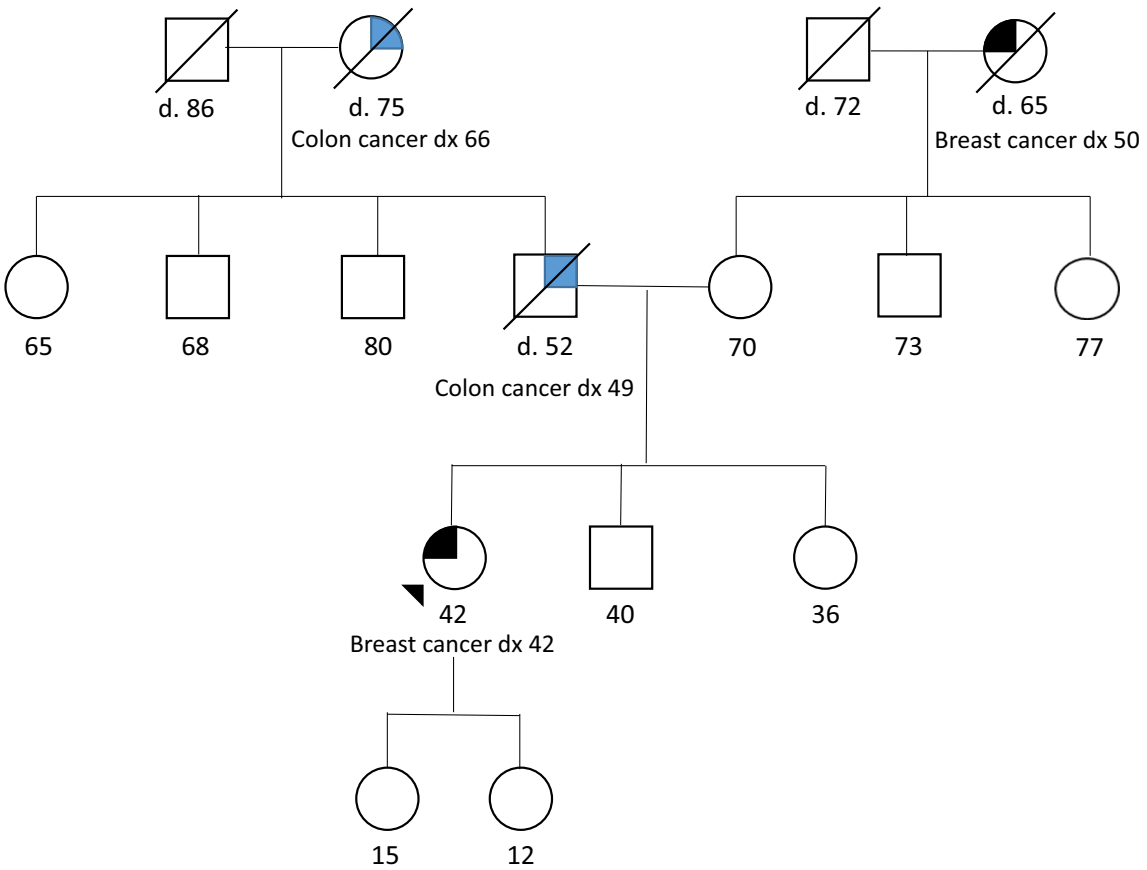

Fig. 1 Pedigree

Table 1 Lifetime risks of cancer associated with PVs in high- and moderate-penetrance genes [11, 13••]

	Cancer		
	Breast	Colorectal	Ovarian
High-risk genes			
BRCA1/2	69–72%	Insufficient evidence	17–44%
PALB2	33–58%	Not increased	Insufficient evidence
MLH1	12–25%	46–49%	11–20%
Moderate-risk genes			
ATM	33–38%[1]	Not increased	Increased risk—not quantified
BRIP1	Insufficient evidence	Not increased	6%
CHEK2	28–37%[1,2]	Increased risk—not quantified	Not increased

[1] Risks depend on the PV identified

[2] Risk is dependent on family history of breast cancer

needed to determine the magnitude of risk and what the associated cancer spectrum entails [21, 24, 25]. Importantly, some high- and moderate-risk genes have preliminary evidence for risks of other cancers (e.g., *ATM* PVs are associated with an increased risk of breast cancer and may also be associated with ovarian and prostate cancer) [26, 27, 28••].

Types of Possible Results

The three types of possible results (positive, negative, and variant of uncertain significance or VUS), as well as general implications of each, are discussed during pre-test genetic counseling. Additional details about test result interpretation are discussed later in this paper.

VUSs are alterations within the DNA for which there are insufficient data supporting a link with disease. With MCPT, the chance of having a VUS test result is not insubstantial. For example, about 29% of tested individuals had at least 1 VUS when a 25-gene broad multicancer susceptibility panel was used [29••]. Thus, particularly for patients who choose to pursue large panels, it is important to counsel them to anticipate the strong possibility that one or more VUS results will be obtained and that about 90% of VUSs are eventually reclassified as benign [30••, 31]. The VUS rate and how a patient would feel about receiving this type of result are discussed during pre-test counseling [11, 32]. Therefore, attitudes about uncertainty may be a factor in test selection (described below).

General Discussion of Management

During the pre-test session, examples of potential recommendations for medical management are discussed based on possible outcomes of testing, and in consideration of the patient's personal and family history. For example, for newly diagnosed breast cancer patients who may use genetic testing results to guide surgery decisions (i.e., breast conservation versus bilateral mastectomy), or for healthy women who are considering risk-reducing mastectomy based on a strong family history, it is important to emphasize that PVs in high-risk genes such as *BRCA* and *PALB2* may prompt stronger consideration of risk-reducing mastectomy versus PVs in moderate risk genes (e.g., *ATM*) or genes in which the breast cancer risks are unclear (Lynch) [13••, 14••, 33]. Furthermore, discussion includes which PVs may result in recommendations to undergo (*BRCA*) or strongly consider (*BRIP1*) risk-reducing oophorectomy [13••], or how the identification of some PVs (e.g., *MUTYH*, Lynch) may result in a recommendation for earlier and more frequent colonoscopies [14••]. Finally, we emphasize that while there are some evidence-based recommendations for management of high-risk PVs [34, 35], most recommendations are based on expert opinion [13••, 14••, 22••].

Unexpected Findings

With MCPT, it is possible that a PV will be identified that does not explain the patient's personal or family history of cancer, such as a PV in a colon cancer susceptibility gene in a family suggestive of hereditary breast cancer [36, 37••, 38, 39••]. In a study on outcomes of individuals undergoing panel testing, approximately 5% of individuals with breast cancer had a PV or likely PV identified in Lynch syndrome genes, while 9.7–10.9% of individuals with colon, stomach, or endometrial cancer had PVs in *BRCA* [39••]. Moreover, because of the reduced penetrance of PVs in moderate-risk genes, family history may be even less predictive of test result outcome. Thus, we discuss the importance of including high- and moderate-risk genes on all panels to cover this possibility [13••, 14••, 22••, 33].

Lab and Test Selection

MCPT offered by clinical labs may encompass 80 genes or more, though many panels include fewer than half this number, and are highly variable in their composition [25, 40]. For instance, panels may be limited to genes in which PVs predispose predominantly to one or more specific cancer types (e.g., breast, gastrointestinal, gynecologic) or they may include only high- to moderate-risk genes for which there are national guidelines about how to manage carriers of a PV [24]. Stat panels to test high-risk breast cancer genes may be selected for patients making time-sensitive breast cancer treatment decisions, as they generally have a faster turnaround time of 1–2 weeks (compared to approximately 2–4 weeks for a general MCPT) [40].

Although guidelines from the American Society of Clinical Oncology and the National Comprehensive Cancer Network mention MCPT, guidelines do not currently exist on how to select a MCPT [13••, 14••, 41]. Multiple factors go in to the decision on which MCPT to order from which lab: differentials based on personal and family history, diagnostic yield, clinical utility for the patient and family, robustness of VUS classification, patient preference, insurance requirements, turnaround time, and ease of test ordering [25, 32, 42–46]. Other factors that contribute to lab selection include the ability to customize panels, the option to reflex to test additional genes after the original panel, whether the lab is in- or out-of-network with patient's insurance, and whether the lab offers a patient self-pay option.

Data about the frequency of PVs demonstrate the clinical utility of MCPT and may guide panel selection based on provider and patient preferences [25, 44–46]. Research on MCPT indicates that the diagnostic yield of this approach to genetic testing is higher than stepwise testing. Indeed, most of the incremental yield of panel testing is from the identification of PVs in moderate-risk genes [29••, 47, 48]. Studies focused on MCPT for hereditary breast and ovarian cancer have found that of the individuals who test positive for a PV, half test positive for *BRCA1* or *BRCA2* and most of the other half test positive for another breast cancer gene [19, 29••]. After *BRCA*, the other most commonly identified PVs are consistently in three high (*PALB2*)- to moderate-risk (*ATM*, *CHEK2*) genes [19, 26, 29••, 47, 48].

Patient preference also plays an important role [32, 49–51]. Thus, a shared decision-making approach can help optimize panel selection and patient satisfaction with testing decisions [43, 52]. As mentioned, because an inconclusive VUS result may increase distress, it is important to discuss the VUS rate and uncertainty surrounding this type of result during pre-test counseling [53]. While adding more genes to a panel increases the chance of a VUS result, it increases the degree to which a negative result is informative. For example, a breast cancer patient who tests negative for a 36-gene breast and gynecologic cancer panel is less likely to harbor an undetected PV than if she had tested negative with a 12-gene breast cancer guidelines-based panel. Some patients who are uncomfortable with uncertainty may choose to limit testing to high- or high- and moderate-risk genes only, whereas others may opt for a larger cancer panel so that they have as much information as possible, even with the potential for more VUS results. When offered the option of a limited panel with only high-risk genes, or a larger panel with high and moderate-risk genes, patients often select the larger panel to obtain more information for themselves and their family [32, 50, 51]. However, it is important to convey to patients that including established or preliminary genes on a broad panel for cancers that do not appear to be syndromic within the family will not likely offer reassurance about the etiology of those cancers. Providing patients with information about their testing options allows them to make an informed decision about which panel best suits their reasons for pursuing genetic testing [50, 51].

Other Reasons for Referral

Updated Testing

Patients who previously had negative *BRCA* or Lynch syndrome testing are now being referred to genetic counseling for updated genetic testing with MCPT. For example, some patients tested only for *BRCA* did not undergo complete analysis of these genes to include analysis of large genomic rearrangements [54]. Thus, MCPT would include comprehensive testing of these genes as well as other high- and moderate-risk genes [19, 26, 29••, 47, 48].

Cascade Testing

Some patients are referred to genetic counseling for cascade testing (i.e., they are relatives of individuals who have tested positive for a PV) [55]. The main focus of the genetic counseling session is to discuss the patient's chance of testing positive for the familial PV and the cancer risks and management based on a positive or negative result [55, 56].

Until recently, most patients who presented for cascade testing were offered testing only for the familial PV, and additional genetic testing was recommended only if there was a significant family history of cancer on the side without the known familial mutation, or 3-site *BRCA* testing was offered if there was Ashkenazi Jewish ancestry [13••]. However, increasingly, these patients are offered MCPT, particularly when no other family members have had panel testing [57]. A recent study on panel testing in 1084 first-degree relatives who were referred due to a known familial mutation found that 5% had a PV in a gene other than what was previously identified in the family [58••]. Thus, in our practice, we offer these patients the option of MCPT and have a detailed discussion of the benefits,

risks, and limitations of this type of testing. For example, if the 42-year-old in Fig. 1 tests positive for a PV in a breast cancer gene from MCPT, her sister should still consider a panel in addition to familial mutation testing because of the family history of colon cancer, especially since their father was diagnosed at a young age.

Positive Somatic Genetic Testing

The primary intent of tumor genetic testing is to identify somatic PVs to guide treatment decisions, but it may incidentally identify PVs that are germline [59]. Patients should undergo genetic counseling if they have a somatic PV that is suspicious of being a germline PV. The focus of the genetic counseling session is discussing the chance that the somatic PV is germline, and the cancer risks and management recommendations (particularly for relatives) if it is found to be germline. In our practice, we recommend MCPT for these patients, especially if their personal and/or family history is suggestive of a hereditary cancer susceptibility. Tumor genetic testing may miss identifying PVs in the tumor due to allele dropout or due to differences in the technology and classification of PVs between somatic and germline genetic testing [60, 61].

Cost of Testing

A portion of the pre-test counseling session focuses on "genesurance" (i.e., whether insurance will cover genetic testing and expected out of pocket costs) [45, 62••]. Insurance providers often use national guidelines, such as National Comprehensive Cancer Network criteria for *BRCA* testing, to determine coverage of testing [63]. In addition, based on recommendations from the United States Preventive Services Task Force (USPSTF), the Affordable Care Act (ACA) mandates that private insurance companies cover *BRCA* genetic counseling and genetic testing for unaffected women at high risk, including those at risk for inheriting a familial PV [64]. Some insurance companies explicitly state what criteria must be met to cover *BRCA* or Lynch syndrome testing [65]. Coverage of MCPT is more complex. Insurance companies are either not explicit in stating coverage of panel testing or some may not cover panel testing because it may be considered experimental [63, 65, 66]. Most genetic testing labs offer the option of notifying patients if their out of pocket cost is expected to be over a certain amount, such as $100 or $250, before the lab moves forward with testing [63]. In addition, some clinical labs offer a patient self-pay price, which can be offered to patients whose insurance will not cover testing.

Informed Consent and Discussion of Discrimination and Privacy

An important component of the informed consent process is discussing the laws that are in place to protect patients' genetic information and to protect against discrimination [67]. The Genetic Information Nondiscrimination Act (GINA) protects most patients from being discriminated against in the areas of health insurance and employment [68]. However, GINA has no provisions about underwriting in the life, long-term, or disability insurance markets, although some state laws may provide additional protections [69]. HIPAA and GINA also have provisions that prohibit outside entities from accessing genetic test results [67].

Post-Test Genetic Counseling

During the pre-test counseling session, a plan should be made about whether the patient would like to receive the results in person or by telephone. As discussed above, test results fall into one of 3 categories: positive, variant of uncertain significance, or negative.

Pathogenic or Likely Pathogenic Results

Management of an individual with a PV is determined by the gene involved as well as the patient's medical and family history. Management guidelines exist for high-risk genes [13••, 14••, 70] and primarily include increased surveillance, chemoprevention, or risk-reducing surgery. PVs in some genes, such as *BRCA* and Lynch genes, may influence cancer treatment with use of targeted immunotherapy [71, 72]. While management guidelines exist for many high-risk genes, less information is available for moderate-risk or newer genes, and clear guidelines for managements may not be available [13••, 14••, 22••].

Unexpected Pathogenic Results

One challenge that has arisen with MCPT is how to manage patients with PVs in rare high-risk genes when neither the patient's personal nor family history meets clinical diagnostic criteria. For example, PVs in *CDH1*, which is associated with hereditary diffuse gastric cancer and lobular breast cancer, have been identified in 43–67% of families that do not meet criteria for this syndrome [73]. Although guidelines recommend prophylactic total gastrectomy between ages 18 and 40 for *CDH1* PV carriers [74], in light of the lower lifetime risk of gastric cancer in unselected families (33–42%), it is unclear whether this guideline should be followed in such families, especially given the morbidity and major lifestyle changes that may occur after a prophylactic gastrectomy [73, 75, 76••].

Variants of Uncertain Significance (VUS)

As previously stated, VUSs are genetic alterations that do not have an established link with disease. If a VUS is identified, it is not used for predictive testing in unaffected family members nor should it be used as the basis for medical management decisions. While the majority of variant classifications are consistent among laboratories, among those submitting to ClinVar, a publicly available database, 3.5% of all uploaded variant classifications contained medically significant differences [77••]. In our practice, when differences in laboratory interpretation which could affect medical management are identified, we review the available information from these sources with the individual/family. We may advise additional screening based on family history, but we do not typically recommend risk-reducing surgeries until the discrepancy is resolved. Patients are advised that reclassification may often take months to years. In one study, of the variants that were reclassified, the median time to reclassification was 39 months [78].

Once a variant is reclassified, laboratories may have different policies on re-contacting ordering providers. If an updated laboratory report is issued, the provider should make an effort to recontact the patient regarding the classification [79]. We encourage patients to maintain current contact information with our clinics, and to check in with us periodically to see if there are any updates to variant classification.

Negative Results

Despite the fact that MCPT has yielded an increased number of positive results, the majority of patients who present for genetic testing receive negative results. In a study by Rosenthal et al., over 250,000 individuals were tested with a 25-gene broad cancer panel and 64.5% had no PVs or VUSs [29••]. The interpretation of these results is often more complex than interpreting positive or VUS results, and overall, these patients' cancer risks are quite heterogeneous. Although negative results may be reassuring, they must be interpreted in the context of personal and family history. There are two types of negative results: true negative and uninformative negative. A true negative result is when an individual did not inherit the familial PV. An uninformative negative result occurs when no PV is identified in a person with a personal and/or family history of cancer, but hereditary cancer risk cannot be definitively ruled out.

In *uninformative negative* families, no PV may have been identified because the causative gene was not analyzed, the cancer in the family may be sporadic (due to a combination of genetic, environmental, lifestyle, or hormonal factors), or a PV is located in a gene that was tested but may have been missed due to technical limitations of the analysis. As an example of the latter, individuals with absent MSH2 staining on colon or uterine tumor tissue and family histories suggestive of Lynch syndrome may have an inversion in the *MSH2* gene that is not detectable by some commercial labs [80]. In families with negative genetic testing and breast cancer but with no family history of ovarian cancer, the risk for ovarian cancer does not appear to be increased [81••, 82]. For example, if the 42-year-old affected woman in Fig. 1 tests negative after a comprehensive MCPT, this provides reassurance about her ovarian cancer risk. However, she has an increased risk for a contralateral breast cancer based on her age of diagnosis and the age of diagnosis of her grandmother [83••].

For the unaffected 36-year-old in Fig. 1, although a negative result from MCPT rules out most hereditary colon cancer risk, her risk is still elevated based on her family history. As such, colonoscopy would be recommended at age 39 (10 years younger than her father's age at diagnosis) [84]. She would also be at increased risk for breast cancer based on family history. For unaffected women, the Tyrer-Cuzick model incorporates family history, negative *BRCA* test results, biopsy history, reproductive factors, and breast density to estimate risk [85]. For women with a lifetime risk of breast cancer of ≥ 20%, annual breast MRI is recommended [13••]. Chemoprevention with tamoxifen can also be considered if the 5-year Gail model risk is ≥ 1.7% [86].

A *true negative* result indicates that the individual did not inherit a familial mutation; thus, cancer risks are generally similar to those of the general population [81••]. However, these individuals may still be at increased risk for cancer due to shared risk factors with their affected relatives, cancer risks from the other side of their family, or rarely, a second PV that was not detected. Women who test negative for a moderate-risk gene PV (e.g., in *ATM* or *CHEK2*) may still have an increased chance of breast cancer based on their family history of cancer [22••, 87]. For example, in Fig. 1, if the 36-year-old tests negative for the PV in *CHEK2* that her 42-year-old affected sister carries, her breast cancer risk may still be elevated based on the family history of breast cancer. In these cases, screening and risk reduction recommendations may still be based on the family history instead of the "true negative" genetic test result [22••, 87]. Breast cancer risk calculation models, such as Tyrer-Cuzick, and other data on breast cancer risk in women negative for a moderate risk familial PV can be used to approximate breast cancer risk and determine whether additional screening (e.g., breast MRI) is indicated [22••, 87].

For unaffected women with an uninformative negative genetic test for high- and moderate-risk genes, some laboratories provide a polygenic risk score (PRS) based on genome-wide association studies (GWAS) of single-nucleotide polymorphism (SNPs). However, the relevance of PRS to nonEuropean Caucasians is limited, and there are currently no data about how to reconcile discrepant risk assessments or whether to alter medical management recommendations based solely on PRS [88, 89]. For these reasons, in our

practice, we do not currently incorporate PRS into risk management.

Reproductive Considerations

Identification of a PV in some genes increases the risk for an autosomal recessive condition. For example, variants in the DNA repair genes *BRCA2*, *PALB2*, *RAD51C*, and *BRIP1* are associated with the autosomal recessive condition Fanconi anemia. Testing of the partner of a carrier of a PV or likely PV in one of these genes should be considered for reproductive decision-making [90].

Psychological Impact of Testing

One study of individuals undergoing panel testing found that patients undergoing MCPT were not likely to experience increased anxiety, depression, or uncertainty [91]. General anxiety decreased with pre-test counseling and total knowledge increased across all time points. There were no significant differences based on testing results, whether positive, negative, or uncertain. However, another study found mutation carriers show higher levels of distress than individuals with negative or VUS results [92]. For individuals with no personal history of cancer, VUSs were associated with higher levels of distress than negative results [53]. One possible explanation is that patients may interpret the VUSs as contributing to their cancer or may mistakenly believe that they had a pathogenic variant [93, 94••, 95]. It remains to be seen whether patients who do not undergo comprehensive pre- and/or post-test genetic counseling continue to have favorable psychological outcomes.

Conclusions

MCPT has gradually supplanted the use of single gene or sequential gene testing. Although this testing has several potential benefits with respect to increasing diagnostic yield and revealing actionable findings, there are also potential limitations and risks associated with this testing. Pre- and post-test genetic counseling has evolved to address these complex issues in risk assessment and management. Because of the potential uncertainty around testing and management, shared decision-making and an assessment of patients' goals and preferences are critical to maximizing the likelihood of positive outcomes from testing.

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Compliance with Ethical Standards

Conflict of Interest Ms. Kolla declares no conflicts of interest.
Ms. Grady reports consulting fees from ActX (Seattle, WA).
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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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