Should all patients undergoing genetic testing for hereditary breast cancer syndromes be offered a multigene panel?

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Purpose of review
We aim to demonstrate why multigene panel testing (MGPT) is the superior testing option for individuals undergoing hereditary cancer genetic testing. We will outline the clinical benefits and possible limitations of MGPT for individuals at risk for a hereditary cancer syndrome.

Recent findings
The use of MGPT increases the identification of individuals with hereditary cancer syndromes. Recent studies continue to prove that MGPT is a superior option to single gene/or syndrome testing. MGPT is a cost-effective testing approach for those meeting criteria for genetic testing. Individuals interested in MGPT should understand the benefits and limitations of this approach, including an increase in variant identification and possible incidental findings. MGPT also increases the number of individuals who would benefit from cascade testing.

Summary
MGPT should be considered as the standard approach to hereditary cancer genetic testing as opposed to single gene or single syndrome testing. MGPT identifies a larger proportion of individuals with a hereditary cancer syndrome and leads to better management and improved uptake of cascade testing.

Keywords
hereditary cancer syndromes, multigene panel testing, pathogenic variants, risk assessment

INTRODUCTION

Multigene panel testing (MGPT) has changed the landscape of genetic counselors' approach to hereditary cancer genetic testing. An individual's personal and/or family history of cancer may be suspicious for more than one hereditary cancer syndrome. MGPT allows analysis of multiple genes and syndromes at one time, providing more data in a quicker timeframe. In addition to the benefits of turnaround time, MGPT is a more efficient and cost-effective way to evaluate an individual for a spectrum of hereditary cancer syndromes. MGPT is also useful in individuals who have previously tested negative using single gene/syndrome testing. Recent studies have shown that the use of MGPT increases the identification of individuals at risk for hereditary cancer syndromes. This, in turn, improves clinical management of these individuals and subsequent cascade testing of at-risk family members. The studies also highlight the need for more inclusive testing criteria and the importance of understanding the limitations of testing. Known limitations of MGPT include variants of uncertain significance (VUS), incidental findings and uninformative results.

IDENTIFICATION OF APPROPRIATE INDIVIDUALS TO TEST

The most recent iteration of The National Comprehensive Cancer Network (NCCN) Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic guidelines (NCCN BOP V1.2022) outline criteria that are used to identify individuals who are appropriate for genetic evaluation [1]. In recent years, these guidelines have included information about

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KEY POINTS

- Multigene panel should be the gold standard when offering germline genetic testing.
- Although an understanding the NCCN and other national guidelines is imperative, they can also be restrictive and pathogenic variants may be missed. This also highlights the importance of using a multigene panel.
- There are significant limitations and nuances to using a multigene panel and interpreting results. We encourage those ordering multigene panel tests to be familiar with these.
- Multigene panel testing, hereditary cancer syndromes, pathogenic variants, risk assessment.

when to consider using MGPT. This includes individuals undergoing genetic evaluation for the first time and those who have been offered single gene testing previously. NCCN recommends phenotype-directed testing based on personal and family history.

CHOOSING THE RIGHT TEST

Previous studies have shown that MGPT is more efficient and cost-effective than single gene or single syndrome testing. Prior to the implementation of MGPT, the standard approach to hereditary cancer genetic testing centered on the syndrome at the top of the differential list with the highest yield of a possible pathogenic variant. If the individual had features suggestive of multiple hereditary cancer syndromes, testing for these genes was performed in a stepwise fashion, which was neither cost-effective nor efficient, particularly for those individuals using the information for surgical or treatment decision-making. In many cases, multiple testing attempts would not be covered by an individual's health insurance and the cost of testing was a barrier. Therefore, many individuals would not undergo the most complete testing that was clinically appropriate.

Recent studies have shown that without the use of MGPT, clinically relevant mutations would be missed. Bono *et al.* [2▪▪] observed that without the use of this testing approach, 15.1% of pathogenic and likely pathogenic variants would have been missed. Specifically looking at their breast cancer cohort, 24 out of 165 individuals (14.5%) harbored pathogenic/likely pathogenic variants in non-BRCA cancer susceptibility genes. Fanale *et al.* [3] studied the impact of MGPT on individuals with a personal history of bilateral breast cancer and observed that 14.4% of pathogenic variants would have been missed with single syndrome, BRCA testing. These two studies emphasize the importance of using MGPT as a standard of care approach to hereditary cancer genetic testing. Interestingly, LaDuca *et al.* [4▪▪] noted that less than half (33.1%) of pathogenic variants identified in individuals meeting criteria for BRCA testing were identified in those two genes. This echoes the previous studies showing a large proportion of pathogenic variants would be missed without implementing MGPT as the standard of care.

Missing pathogenic variants will also lead to inappropriate management of affected individuals. For example, of the 15.1% of missed pathogenic variants in the Bono *et al.* study [2▪▪], 17% of them were in CHEK2. CHEK2 is defined as a moderate penetrance hereditary cancer gene known to increase the risk of breast cancer and colon cancer. In addition to the missed information for possible risk of contralateral breast cancer, NCCN guidelines specifically recommend colonoscopy every 5 years for these individuals. The most common missed pathogenic variant in Fanale *et al.* [3] was also in CHEK2.

Individuals who previously underwent hereditary cancer genetic testing using the single gene or single syndrome approach strongly benefit from MGPT. Beyond the data previously described regarding the identification of non-BRCA pathogenic variants, many individuals who underwent BRCA testing in its early years of clinical use were not eligible for comprehensive testing. Gene analysis is considered comprehensive when it includes both sequencing and deletion/duplication (del/dup) testing. LaDuca *et al.* [4▪▪] found that greater than 10% of all pathogenic variants detected using MGPT were del/dups. This includes del/dup analysis for BRCA, which previous testing did not include for many individuals.

UTILIZATION OF RESULTS

MGPT is considered more cost-effective and efficient as compared to single gene or syndrome testing. This is primarily true for those individuals with a newly diagnosed cancer where results of genetic testing have treatment implications. MGPT results can aid in surgical planning for those with a newly diagnosed breast cancer. Individuals with certain pathogenic variants may be at increased risk for contralateral breast cancer. Depending on which non-BRCA gene the pathogenic variant is identified in, NCCN recommends either consideration of risk-reducing mastectomy or recommendation for this based on clinical and family history factors. Without the benefit of MGPT results, these individuals are not able to make a fully informed surgical decision. This could result in a future cancer diagnosis which

becomes a larger burden on the healthcare system compared to a prophylactic surgery.

It should be emphasized that result interpretation of MGPT, regardless of a pathogenic variant or not, should be integrated with the traditional risk assessment approach. Shin *et al.* [notes that medicine is shifting to a more personalized and precision medicine approach. Personal and family histories in conjunction with the results of MGPT should be used to establish cancer and noncancer related management plans. When interpreting a negative MGPT result in an individual whose personal or family history remain concerning for a hereditary cancer syndrome or familial cancer risk, one should apply known empiric risks and manage accordingly.

OTHER CONSIDERATIONS

After the disclosure of a pathogenic variant and a review of the management recommendations, cascade testing is an important topic to address. Griffin *et al.* [5] state that the United States healthcare system has relied on patients to disclose their genetic testing results to family members and encourage cascade testing. In their cohort of individuals with hereditary gynecologic cancers, 97% of individuals had notified at least one relative of their genetic results but this did not always correlate with an uptake of testing. They reported that first-degree female relatives were more likely to undergo genetic testing than male relatives (59% vs 21%). This study highlighted four features associated with a higher uptake of cascade testing: mutation-specific genetic testing uptake (higher uptake in BRCA families vs Lynch syndrome families), gender of family member (low male uptake), relationship status (single individuals had a higher testing uptake vs married individuals), and family dynamics. They also noted barriers not specifically addressed including patient recollection of information, concerns about privacy and discrimination, and financial cost of testing. Genetic counselors have used family letters as a way to help individuals communicate their test results to at-risk relatives. Griffin *et al.* [5] note that cascade testing increased by 50% with the use of family letters. As nongenetic counselors continue to order and interpret MGPT results, it is crucial that results disclosure include discussion and encouragement of cascade testing. Provision of genetic test results should be accompanied by documentation to aid in the discussion with family members.

As the NCCN guidelines become more inclusive over time and the cost of testing becomes less of a barrier, genetic testing is becoming more accessible to individuals meeting criteria for testing. But data continues to show that pathogenic variants can be identified in individuals who do not meet criteria for genetic testing. LaDuca *et al.* observed that 5.8% of patients with pathogenic variants did not meet criteria for testing. This study ushered in a call to action to revise testing guidelines. This same study also highlights that disease-specific panels will also miss clinically relevant pathogenic variants. For their cohort of patients meeting criteria for breast cancer genes, 67% of pathogenic variants were identified in non-BRCA genes and 5.2% of these variants were in the Lynch syndrome genes (MLH1, MSH2, MSH6, PMS2, EPCAM). Conversely, of the 53.8% of pathogenic variants identified in individuals who met criteria for Lynch syndrome, 8.8% of these pathogenic variants were in BRCA. Continued revision of testing criteria is critical to ensure that individuals with a hereditary cancer syndrome are not missed and that appropriate surveillance and management recommendations are initiated appropriately. Previous studies have even questioned whether testing criteria is a barrier, rather than a tool. This shows the importance of expert clinical assessment being used to recommend genetic testing and the continued affordability of testing and laboratory assistance programs for those that may not meet the current criteria.

A third consideration for those offering MGPT is the increased identification of VUS and the importance of how to interpret them. Shin *et al.* [6] emphasizes that the rate of VUS identification varies across races and ethnicities. Their study included a Korean cohort of individuals with breast cancer. They detected VUSs in 13.5% of individuals, but emphasize that is a low detection rate compared to previous studies. They elected to exclude missense mutations with conflicting interpretations of benign and likely benign reported by other laboratories. LaDuca *et al.* noted that VUS rates depend on the size of the MGPT ordered. Using a 17-gene panel, at least one VUS was identified in 5.4% of individuals. This is compared to 39.5% of individuals carrying at least one VUS using a 34-gene panel. These studies highlight the frequency of VUSs and the importance of knowing how to manage them. The interpretation of a VUS is key. In the majority of cases, VUSs are considered nondiagnostic genetic variants and should not be used as a factor in making management recommendations. Many laboratories offer VUS reclassification programs for those variants that are suspicious for pathogenicity. Providers ordering MGPT are encouraged to utilize these programs when appropriate to aid in the reclassification process. Inaccurate diagnosis and management of VUSs can burden the healthcare system due to inappropriate recommendations being made to individuals that do not have a hereditary cancer syndrome, including increased surveillance or preventive surgeries. Providers should feel confident in how to utilize the laboratory's internal data, online

databases to compare classifications between laboratories like ClinVar, and referrals to genetic counselors as needed (including the growing population of telehealth genetic counseling companies). It is important for those providers ordering MGPT to not only know how to interpret a VUS but to utilize a laboratory with a robust VUS interpretation and reclassification program. Providers should value a VUS interpretation program and variant reclassification program when selecting a laboratory.

Lastly, incidental findings are an aspect to MGPT that should be considered. As broader multigene panel tests are ordered, pathogenic variants are being identified that may not be clinically relevant to the individual being tested, but may have important implications for other family members. This includes monoallelic pathogenic variants associated with recessive conditions. Bono *et al.* noted that the most frequent pathogenic variant identified in their breast cancer cohort was an MUTYH missense variant in 5 individuals (20.6% of pathogenic variants detected). Although there is some data suggesting a possible association with breast cancer, NCCN does not currently recommend increased breast cancer surveillance for monoallelic MUTYH pathogenic variants. However, in addition to adjusting the frequency of colonoscopies for monoallelic MUTYH carriers, this result is clinically relevant for other family members as those with biallelic pathogenic variants in MUTYH have a diagnosis of MUTYH-associated polyposis. This highlights the importance of cascade testing for these recessive conditions. Additionally, one individual in this same cohort carried a RAD50 pathogenic variant. NCCN classifies RAD50 as having insufficient evidence for an association with breast cancer in the monoallelic setting but is associated with autosomal recessive Nijmegen breakage syndrome-like disorder. This would be clinically relevant to family members of childbearing age.

It has been documented that despite early increased uptake of MGPT for cancer risk assessment, there is a lack of confidence in result interpretation among providers (attached is the article). This demonstrates the belief in utility of these tests but also highlights the challenge of results interpretation. It is imperative that ordering providers feel confident in handling VUS as well as incidental findings when ordering MGPT. Provider comfort level with ambiguous results no doubt impacts patient understanding and perception of results and may influence uptake of appropriate follow-up care or cascade testing. Sherr *et al.* [7▪] highlighted themes used to make decisions based on results of genetic testing, including VUSs. Individuals stated that they relied heavily on their healthcare provider to make what information was imperative for individuals when understanding the results of genetic testing, including VUSs. One common theme was the confidence in the interpretation provided by their healthcare provider and the ability to relay that information to other providers. In cases where individuals felt uncertain about their results, they relied on their own research to inform their decisions. When interpretation proves complicated, referral to a genetic counselor can help solidify the interpretation of these results and how they are communicated to the individual.

CONCLUSION

MGPT continues to become more routinely used as the optimal genetic testing option for individuals at risk for a hereditary cancer syndrome. Multiple studies, including those highlighted above, emphasize the vast improvement in detecting pathogenic variants. This leads to better surveillance and management of these individuals and downstream cascade testing of their family members. In addition to the benefits of MGPT, these studies also highlight important limitations that ordering providers should be aware of. Individuals who are considering MGPT should be advised of these limitations to make an informed decision about proceeding with testing. The interpretation of results from MGPT should include a traditional risk assessment to ensure that appropriate surveillance recommendations are made. Providers ordering MGPT should feel confident in being able to not only interpret results with pathogenic variants, but also those more ambiguous results, including VUSs and incidental findings.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

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