

A NEW CLINICAL DILEMMA

“The approach of testing for a small subset of genes for individual hereditary cancer syndromes is known to miss many individuals within this **same** highest risk population who would benefit from these interventions.

“SABrS states: [Multi-gene testing] is not only more efficient in evaluating patients at risk compared to sequential gene sequencing (ie, evaluating *BRCA* mutations first, then selecting additional genes if *BRCA* tests are negative), but also it is more cost-effective.¹⁰

Hereditary cancer testing has been utilized for decades to ensure highest risk patients were identified and offered medical management options to prevent cancer or reduce the likelihood of subsequent cancer diagnosis. Yet, the approach of testing for a small subset of genes for individual hereditary cancer syndromes is known to omit many individuals within this same highest risk population who would benefit from these interventions.

Data have emerged demonstrating that there are many genes in addition to *BRCA1* and *BRCA2* that are associated with an increased risk for breast cancer and ovarian cancer.¹⁻³ Known as genetic heterogeneity [different genes leading to the same cancers], it is now recognized through an increasing amount of published literature that the same type of cancer or family history of cancer can be caused by mutations in different genes. As well, the characteristics of one hereditary cancer syndrome can overlap with those of another syndrome.⁴⁻⁷ **With the technological advances in molecular diagnostics, testing for these additional genes can be performed simultaneously with *BRCA1* and *BRCA2*.**

Over the past 20 years, over 2 million patients have undergone hereditary cancer testing.⁸ Approximately 10% of breast cancer is known to be hereditary.⁹ Patients who tested positive indicating a diagnosis of hereditary cancer risk received individualized guideline-based medical management.¹⁰⁻¹² The remaining 90% of patients tested negative for a single syndrome. Despite having concerning histories that met the NCCN criteria, this large patient population may be over- or under-managed creating immediate and long-term waste in healthcare spend. Without the complete

information of patients' hereditary cancer risk, clinicians are not able to assess a patient for proper medical management. An incomplete diagnosis will lead to delays, which the Institute of Medicine's [IOM] Improving Diagnosis and Healthcare states is a medical error. According to the IOM, a delayed diagnosis should be defined by recognizing "...the number of times each year that an opportunity to make a diagnosis occurred [the denominator], how often the diagnosis was not made in a timely and accurate manner [numerator a], and how often the explanation was not communicated to the patient [numerator b]."¹³ Based on the IOM's example, testing in a step-wise fashion increases the chances of a delayed diagnosis and medical error. The impact upon the patient which the IOM emphasizes, is that there would be lost opportunities for results to impact medical management. **Additionally, testing in this step-wise fashion creates a number of unintended consequences for the payer and the patient**, including but not limited to increased cost, multiple prior-authorization requests, and potential appeals.^{10, 14}

Given that many additional genes can contribute to hereditary cancer risk, it is important to consider new testing policies in order to most effectively and cost-efficiently manage the 90% of patients still in need of a more comprehensive result.¹⁰ NCCN initiated this change when in 2014 it added to its HBOC guidelines that these patients should be considered for multi-gene testing.¹⁰ Then in 2016, their high risk colorectal hereditary cancer guidelines incorporated multi-gene testing to reflect the genetic heterogeneity discoveries.¹²

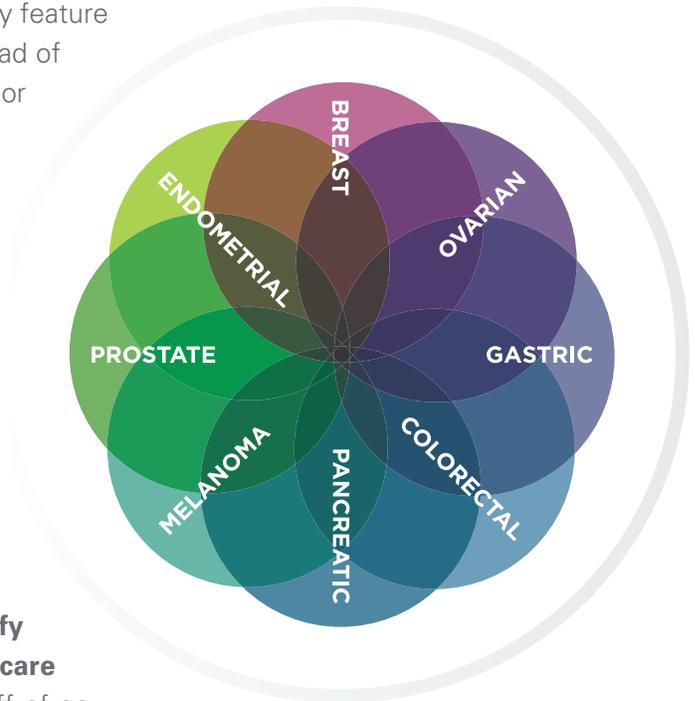
THE SOLUTION: CLINICALLY TARGETED HEREDITARY CANCER MULTI-GENE PANEL TEST

Myriad myRisk Hereditary Cancer analyzes 28 genes that have been shown to increase the risk for hereditary cancer. Most importantly, myRisk does not expand the intended use population. The same patient population who meet NCCN testing criteria for *BRCA* or Lynch syndrome testing is targeted, while providing more comprehensive genetic risk assessment.

The power of the myRisk solution is multi-faceted. One key feature is the test result that providers and patients receive. Instead of a test result only indicating whether the patient is positive or negative for a gene mutation, the **myRisk test provides a clinical decision support tool**. This tool outlines patients' cancer risks and the medical management recommendations endorsed by societal guidelines. Uniquely, all reports are based upon the individuals' genetic test result and family history, when provided. Patients and providers utilize this tool to tailor management plans targeted to patients' specific cancer risks.

Variants of uncertain significance (VUS) are inevitable outcomes of genetic testing. An implicit benefit of myRisk is the strength and integrity of its myVision[®] Variant Classification Program. **myVision is Myriad Genetic Laboratories' commitment to accurately identify and interpret variants to promote responsible healthcare spending and medical management.**¹⁵ A dedicated staff of genetic experts analyzes and reclassifies genetic variants to confidently catalogue variants as deleterious disease-causing mutations or benign. For this group of experts to be successful Myriad developed proprietary tools that augment accuracy and speed to classify variants. These tools are validated in peer-reviewed publications that demonstrate a greater than 99% confidence in the statistical methods that are utilized to classify variants.^{16,17}

With myRisk also comes Myriad's lifetime commitment to inform providers and patients of all reclassification changes. This new information is essential to patients' medical management and their overall care. Myriad is committed to provide the right information to the right patient at the right time—all with the intention to mitigate overall healthcare spend while improving personalized medical outcomes. Myriad's lifetime commitment extends to payers through its promise not to charge for update testing ordered by a physician for patients who received a negative myRisk test result previously, upon new genes added to the myRisk panel. Myriad recognizes that as science continues to progress its understanding of hereditary cancer, the myRisk panel will also evolve in order to provide the most clinically actionable results for patients. Myriad believes patients who have already had coverage for myRisk testing but received a negative result should benefit from scientific advances in hereditary cancer through update testing.



PUBLICATIONS

Myriad myRisk is supported by a number of peer-reviewed publications addressing analytical validity, clinical validity, and clinical utility, with numerous studies demonstrating the increased sensitivity of using panel testing to assess hereditary cancer risk across various tumor types.¹⁸⁻²⁷

TYPE OF STUDY	AUTHOR	TITLE	REFERENCE	TAKEAWAY
Analytical Validation	Judkins T, et al.	Development and Analytical Validation of a 25-Gene Next Generation Sequencing Panel that Includes the <i>BRCA1</i> and <i>BRCA2</i> Genes to Assess Hereditary Cancer Risk	<i>BMC Cancer</i> 2015 Apr 2;15:215. doi:10.1186/s12885-015-1224-y	Validation of 25-gene NGS panel demonstrating analytical sensitivity of greater than 99.9% with 100% concordance between next generation sequencing (NGS) and Sanger sequencing.
Clinical Validation	Langer LR, et al.	Hereditary cancer testing in patients with ovarian cancer using a 25-gene panel	<i>The Journal of Community and Supportive Oncology</i> , July 2016; 14:314-319. doi: 10.12788/jcso.0181	Demonstrates benefits of multi-gene panels for patients with personal history of ovarian cancer, particularly for the identification of moderate-penetrance mutations not otherwise identified by single-syndrome testing.
Clinical Validation	Saam J, et al.	Patients Tested at a Laboratory for Hereditary Cancer Syndromes Show an Overlap for Multiple Syndromes in Their Personal and Familial Cancer Histories	<i>Oncology</i> 2015;89(5):288-93	These data indicate the substantial clinical overlap between high risk family histories meeting HBOC and Lynch syndrome testing criteria and support the importance of a multi-gene panel test, so that patients can be simultaneously tested for multiple syndromes with overlapping phenotypes.
Clinical Validation	Tung N, et al.	Frequency of Mutations in Individuals with Breast Cancer Referred for <i>BRCA1</i> and <i>BRCA2</i> Testing Using Next-Generation Sequencing With a 25-Gene Panel	<i>Cancer</i> 2015; 121:25-33	Using Myriad myRisk for patients appropriate for HBOC testing, this study demonstrated 40-50% increase in clinical sensitivity compared to single syndrome testing.
Clinical Validation	Yorczyk A, et al.	Use of panel tests in place of single gene tests in the cancer genetics clinic	<i>Clin Genet</i> 2015 Sep; 88(3):278-82	The authors conclude that offering a first-tier panel test, which includes genes tertiary on the differential, could prevent inaccurate, or even limited, family histories from restricting testing options.
Clinical Validation	Yurgelun MB, et al.	Identification of a Variety of Mutations in Cancer Predisposition Genes in Patients With Suspected Lynch Syndrome	<i>Gastroenterology</i> 2015 Sep; 149(3):604-13	Using Myriad myRisk for patients appropriate for Lynch syndrome testing, this study demonstrated approximately 40% increase in clinical sensitivity compared to single syndrome testing.
Clinical Utility	Desmond A, et al.	Clinical Actionability of Multigene Panel Testing for Hereditary Breast and Ovarian Cancer Risk Assessment	<i>JAMA</i> 2015;1(7):943-951	Panel testing for HBOC patients identifies substantially more patients than syndrome-specific testing, and identifying all mutations is likely to change management for the majority of patients and their families.
Clinical Utility	Howarth DR, et al.	Initial Results of Multigene Panel Testing for Hereditary Breast and Ovarian Cancer and Lynch Syndrome	<i>Am Surg</i> 2015 Oct; 81(10):941-4	The use of panel testing more than doubled the identification rate of clinically significant pathogenic mutations that would have been missed with <i>BRCA</i> testing alone. Multi-gene panel testing provides additional information that may improve patient outcomes.
Clinical Utility	Ricker C, et al.	Increased yield of actionable mutations using multi-gene panels to assess hereditary cancer susceptibility in an ethnically diverse clinical cohort	<i>Cancer Genetics</i> 2016	Multi-gene panel testing increases the yield of mutations detected and adds to the capability of providing individualized cancer risk assessment. Of the mutations identified in this ethnically diverse population, nearly half (47.3%) would not have been identified if a targeted gene by gene testing approach had been utilized, based on personal/family history.

CONCLUSION

Mutations in the genes included in Myriad myRisk are documented to result in hereditary cancer risks that are great enough to warrant changes in management supported by medical societal recommendations. myRisk is proven to increase the identification of mutation carriers within the same NCCN recommended testing population.^{1,2} myRisk is a unique, multi-faceted solution to meet NCCN and other medical societal recommendations for hereditary cancer genetic testing. Make Myriad your valued partner in hereditary cancer risk assessment.

REFERENCES

1. Tung N, et al. Frequency of Mutations in Individuals with Breast Cancer Referred for *BRCA1* and *BRCA2* Testing Using Next-Generation Sequencing with a 25-Gene Panel, *Cancer* 2015;121(1):25-33.
2. Yurgelun MB, et al. Identification of a Variety of Mutations in Cancer Predisposition Genes in Patients with Suspected Lynch Syndrome, *Gastroenterology* 2015 Sep; 149(3):604-13.
3. Langer LR, et al. Hereditary cancer testing in patients with ovarian cancer using a 25-gene panel, *Journal of Community and Supportive Oncology* 2016;14(7):313-19.
4. Saam J, et al. Patients Tested at a Laboratory for Hereditary Cancer Syndromes Show an Overlap for Multiple Syndromes in Their Personal and Familial Cancer Histories, *Oncology* 2015;89(5):288-93.
5. Antoniou AC, et al. Breast-Cancer Risk in Families with Mutations in *PALB2*, *The New England Journal of Medicine* 2014;371(6):497-506. doi:10.1056/NEJMoa1400382.
6. Lerner-Ellis J, et al. Genetic Risk Assessment and Prevention: The Role of Genetic Testing Panels in Breast Cancer, *Expert Rev Anticancer Ther* 2015; 15(11):1315-26.
7. Minion LE, et al. Hereditary Predisposition to Ovarian Cancer, Looking Beyond *BRCA1/2*, *Gynecologic Oncology* 2015 Apr; 137(1):86-92.
8. Myriad internal data.
9. Hughes K, et al. Prevalence of Family History of Breast and Ovarian Cancer in a Single Primary Care Practice Using a Self-Administered Questionnaire, *The Breast Journal* 2003 9(1):19-25.
10. The American Society of Breast Surgeons' Research Committee, Consensus Guideline on Hereditary Genetic Testing for Patients With and Without Breast Cancer, American Society of Breast Surgeons Statement, www.breastsurgeons.org. Accessed 15 Sept 2016.
11. NCCN Guidelines: Genetic/Familial High-Risk Assessment: Breast and Ovarian. Version 1.2017.
12. NCCN Guidelines: Genetic/Familial High-Risk Assessment: Colorectal. Version 1.2016.
13. Cassel CK, et al. Measurement is Essential for Improving Diagnosis and Reducing Diagnostic Error: A Report from the Institute of Medicine, *JAMA* 2015; 314(23):2501-2.
14. Gallego CJ, et al. Next-Generation Sequencing Panels for the Diagnosis of Colorectal Cancer and Polyposis Syndromes: A Cost-Effectiveness Analysis, *J Clin Oncol* 2015 Jun 20; 33(18):2084-91.
15. Egginton J, et al. A Comprehensive Laboratory-Based Program for Classification of Variants of Uncertain Significance in Hereditary Cancer Genes, *Clin Genet* 2014 Sep;86(3):229-237. doi: 10.1111/cge.12315.
16. Morris B, et al. Classification of Genetic Variants in Genes Associated with Lynch Syndrome Using a Clinical History Weighting Algorithm, *BMC Genetics* 2016;17:99. doi 10.1186/s 12863-016-0407-0.
17. Pruss D, et al. Development and Validation of a New Algorithm for the Reclassification of Genetic Variants Identified in the *BRCA1* and *BRCA2* Genes, *Breast Cancer Research Treatment* 2014 Aug;147(1):19-32. doi:10.1007/s10549-014-3065-9.
18. Judkins T, et al. Development and Analytical Validation of a 25-Gene Next Generation Sequencing Panel that Includes the *BRCA1* and *BRCA2* Genes to Assess Hereditary Cancer Risk, *BMC Cancer* 2015 Apr 2;15:215. doi:10.1186/s12885-015-1224-y.
19. Tung N, et al. Frequency of Germline Mutations in 25 Cancer Susceptibility Genes in a Sequential Series of Patients With Breast Cancer, *J Clin Oncol* 2016 May 1; 34(13):1460-8.
20. Yorczyk A, et al. Use of panel tests in place of single gene tests in the cancer genetics clinic, *Clin Genet* 2015 Sep; 88(3):278-82.
21. Cragun D, et al. Panel-based testing for inherited colorectal cancer: a descriptive study of clinical testing performed by a US laboratory, *Clin Genet* 2014 Dec; 86(6):510-20.
22. Desmond A, et al. Clinical Actionability of Multigene Panel Testing for Hereditary Breast and Ovarian Cancer Risk Assessment, *JAMA* 2015;1(7):943-951.
23. Easton DF, et al. Gene-panel sequencing and the prediction of breast cancer risk, *N Engl J Med* 2015;372(23):2243-57.
24. Howarth DR, et al. Initial Results of Multigene Panel Testing for Hereditary Breast and Ovarian Cancer and Lynch Syndrome, *Am Surg* 2015 Oct; 81(10):941-4.
25. Ricker C, et al. Increased yield of actionable mutations using multi-gene panels to assess hereditary cancer susceptibility in an ethnically diverse clinical cohort, *Cancer Genetics* 2016.
26. Tung N, et al. Counselling framework for moderate-penetrance cancer-susceptibility mutations, *Nat Rev Clin Oncol* 2016 Sep;13(9):581-8. doi:10.1038/nrclinonc.2016.90.
27. Walsh T, et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing, *Proc Natl Acad Sci USA* 2011 Nov 1; 108(44):18032-7.