Hereditary Cancer Risk Assessment:
The Case For Next-Generation Sequencing Gene Panel Testing
# TABLE OF CONTENTS

I. Overview ......................................................................................... 1

II. Genetic Testing and the Path to Optimal Clinical Decisions .......... 2
    CMTP Model Coverage Guidelines for Clinical Next Generation Sequencing in Oncology .......... 3

III. Medical Management of Hereditary Cancer Risk ...................... 4
     Figure 1 – Population Risk ................................................................. 4
     NCCN-recommended surveillance and prevention approaches for individuals with known cancer risk-associated gene mutations .......................................................... 5

IV. Rethinking Hereditary Cancer Based on Current Genetic Evidence .............................................. 7
    Figure 2 – Genes Related to HBOC ..................................................... 7
    Associated Risk for Other Cancer Types .............................................. 8
    Penetrance and Clinical Actionability .................................................. 8
    Figure 3 – Pleiotropy ........................................................................... 8
    Figure 4 – Penetration ........................................................................ 8
    Summary ............................................................................................... 9
    Interpretive Accuracy ............................................................................ 10

V. Managing Variants of Uncertain Significance (VUS) ................. 10
    Figure 5 – myVision® Variant Classification Process .......................... 11
    Summary .............................................................................................. 12

VI. Toward Best Practice in Hereditary Cancer Testing: Hereditary Cancer Panel Tests ........................................... 13
    NCCN Guidelines Involving Multi-gene Testing in HBOC and CRC ............................................. 13
    Summary .............................................................................................. 13

VII. A Chain of Evidence Tool for Payer Decision Making .............. 14

VIII. Conclusion .................................................................................. 15

IX. References ..................................................................................... 16
Hereditary Cancer Risk Assessment: The Case For Next-Generation Sequencing Gene Panel Testing

I. OVERVIEW

The rapidly expanding knowledge base in genomic medicine has opened promising avenues for Next-Generation Sequencing (NGS) gene panel testing in high-risk hereditary cancers, including breast and ovarian cancer (HBOC) and colorectal cancer (CRC). If validated thoroughly and sagely applied, these hereditary cancer panel tests can supply more timely and precise risk information to clinicians and patients than can the current practice standard of stepwise single-gene or single-syndrome testing (NCCN-HBOC Version 1.2017; NSGC 2017; ASBrS 2017; SGO 2014.1; SGO 2014.2; Lancaster et al., 2015). Guideline-based use of panel tests can lead to precision medical management, improving health outcomes and patient quality of life at reduced cost both to the patient and across the healthcare system (NCCN-HBOC Version 1.2017; NSGC 2017; ASBrS 2017; SGO 2014.1; SGO 2014.2; Lancaster et al., 2015).

Guideline-based use of hereditary cancer panels can lead to tailored medical management, improving health outcomes and patient quality of life, at a reduced cost both to the patient and across the healthcare system.

Insurance payers face uncertainty, however, in evaluating panel tests for clinical use, coverage and reimbursement (Trosman et al., 2017). To help patients receive correct medical management, payers seek validated tests that provide clear results and link to decision pathways specified in established clinical practice guidelines. The payers’ conundrum is that while panels meeting these criteria are available, the test offerings themselves differ significantly. Available panel tests vary with respect to the genes included, sequencing methods and mutation classification approaches. In the absence of established clinical utility standards for hereditary cancer panel tests, payers and laboratories alike deal with ambiguity. For this reason, best practice should rely on selecting a panel testing resource that:

- Aligns with established clinical practice guidelines such as those provided by the National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO), or others meeting Institute of Medicine criteria;
- Covers a comprehensive range of genes known to influence hereditary cancer risk in ways that impact medical management;
- Leverages technical expertise through optimized test design;
- Uses validated, published and up-to-date variant classification tools;
- Offers a lifetime commitment to update patients and providers at no charge when a variant is reclassified;
- Shortens the time from test to medical management decisions and reduces the cost burden as compared with stepwise single-gene or single-syndrome testing.
II. GENETIC TESTING AND THE PATH TO OPTIMAL CLINICAL DECISIONS

Diagnostic laboratories have borne the burden of evidence for clinical utility and cost effectiveness of hereditary cancer panel tests in the absence of broadly accepted genetic testing standards. In the early 2000s, the U.S. Centers for Disease Control’s ACCE framework guided the early adoption of genetic tests by defining the concepts of analytic validity, clinical validity and clinical utility (Haddow and Palomaki, 2003):

- **Analytic validity**: Ability of a test to measure, accurately and reliably, the genetic information it is designed to analyze;
- **Clinical validity**: How well the genetic information measured by the test correlates with the defined health status or outcome of interest; and
- **Clinical utility**: The usefulness of a test in clinical practice to improve health outcomes through test-informed decisions about treatment. Can also include quality of life and cost effectiveness outcomes.

Building on this framework, the Center for Medical Technology Policy (CMTP) in 2013 established best practices for molecular test developers to generate evidence of clinical utility. Through its logical “chain of evidence” guidance, CMTP combined analytic and clinical validity with an expanded definition of clinical utility, which includes showing that test-informed medical management decisions improve not only patient health outcomes, but also quality of life and cost effectiveness (CMTP 2013).

Even with updated terms, it remains a challenge to fit panels into the traditional payer approach to evaluating genetic tests for coverage. Whereas approval of many diagnostics and procedures relies appropriately on long-term, randomized clinical studies to support positive coverage decisions, this requirement is less realistic for panels, where:

1. Prospective, long-term studies can put patient health and quality of life at risk;
2. The increased number of genes and statistical challenges require unfeasibly large cohort sizes and long study periods;
3. Surrogate data and modeling can supply ample and sufficient evidence to support a positive coverage decision without risking patient health; and
4. Testing in the intended use population of high-risk individuals can prove more cost- and time-efficient than can alternative medical management routes.

A June 2017 *Journal of the American Medical Association* report highlights these challenges. This report describes a 20-year prospective study of women with *BRCA1* and *BRCA2* mutations, assessing their risk of developing cancer over time (Kuchenbaecker et al., 2017). The study provided new insight into the risk level for women with mutations over time, the influence on risk of family history and mutation position within the genes, and differences in breast versus ovarian cancer risk. At the same time, study leaders noted that the two-decade timeline, the cost and the
effort required to power the study – from study participants as well as across the research network – evidenced the lack of similar efforts in the field. Might alternate approaches using on-hand resources, such as powerful and collaborative real-time analysis of existing data, provide sufficient alternative evidence to support test use for patient benefit?

In 2015, CMTP addressed these challenges specifically with proposed Initial Medical Policy and Model Coverage Guidelines for Clinical Next Generation Sequencing in Oncology (CMTP 2015). Though this framework was created for evaluating NGS tumor analysis panels designed to guide cancer treatment rather than hereditary cancer panels, it tackles challenges shared by both test functions and thus serves as a useful model. Acknowledging the limited feasibility of long-term prospective studies, this framework put forth more achievable criteria.

**CMTP Model Coverage Guidelines for Clinical Next Generation Sequencing in Oncology**

1. Evidence for panel gene-therapeutic interaction, as demonstrated by available FDA-approved companion diagnostics;

2. Panel genes recommended for decision-making for the underlying diagnosis in nationally recognized clinical guidelines such as NCCN, ASCO or others;

3. Panel genes designated as standard of care for the underlying condition by several NCCN member institutions;

4. Publication of peer-reviewed journal articles by the test provider supporting the conclusion that use of the genomic information provided is safe, effective and reasonably likely to provide a health benefit for the patient;

5. Total cost of the NGS gene panel analysis does not exceed the cumulative cost for analysis of each included gene; and

6. Laboratory conducting the analysis is CLIA-certified and CAP-accredited for NGS testing.

(CMTP 2015)

These criteria are equally suited to NGS panel testing in hereditary cancer, to inform medical management for cancer prevention. The framework considers carefully the reimbursement barriers and opportunities frequently articulated by payers (Trosman et al., 2017).
III. MEDICAL MANAGEMENT OF HEREDITARY CANCER RISK

The goal of multi-gene panel testing in hereditary cancer assessment is to identify or rule out an elevated risk that warrants a change in medical management. Early detection and medical management can prevent or delay cancer onset, positively impact patient outcomes, improve quality of life, and reduce cost burden (Domchek S et al., 2010; Vogel VG et al., 2010; Lowry KP et al., 2012; Finch AP et al., 2014; Metcalfe K et al., 2014; Metcalfe K et al., 2015).

Research advances have increased the precision of estimating risk (Figure 1):

- **Low Risk:** General population, lacking clear patterns of cancer in the family health history;
- **Moderate Risk:** Inherited pattern of cancer is evident in the family health history; and
- **Highest Risk:** Hereditary predisposition to cancer, confirmed by hereditary cancer testing.

Hereditary cancer testing is appropriate for those who meet NCCN clinical criteria for hereditary/highest risk, and it is essential to distinguish these patients from moderate risk populations. For patients whose test results point to a well-defined hereditary cancer syndrome, changes in medical management and tailoring of treatment to optimize outcomes are clear.
For patients who are clinically assessed at high risk but who are not tested, or for those with high risk that cannot be defined by a single gene or syndrome, management routes are less obvious. These patients face the possibility of clinical under- or over-management. Expanded panel testing, combined with an ever-growing validated and published reference base, addresses these cases by identifying gene variants that lie outside the small set of highest-penetrance genes; yet impart increased risk. In addition, panel tests can reveal increased risk beyond the primary cancer type indicated (NCCN-CRC Version 1.2017; NCCN-HBOC Version 1.2017). Notably, employing panels does not expand the intended use population; rather, multi-gene panel tests provide more information, beyond single-gene or single-syndrome testing, for the same high-risk population.

NCCN offers detailed guidelines for genetic and familial high-risk assessment in HBOC and CRC prior to hereditary cancer testing (NCCN-HBOC Version 1.2017; NCCN-CRC Version 1.2017). As an example, the current NCCN-recommended formal risk assessment for HBOC is a multi-step process to be conducted with patient counseling and includes:

1. Evaluating patient needs and concerns;
2. Collecting a detailed family health history;
3. Analyzing patient and family history with validated risk assessment models;
4. Medical and surgical history;
5. Physical examination;
6. Estimation of absolute risk for breast and/or ovarian cancer; and
7. Establishing evidence for a heritable genetic mutation(s) predisposing to cancer.

Only after patients meet specified criteria for elevated risk does NCCN recommend consideration of genetic testing, along with pre-and post-test counseling. The choice of single-gene, single-syndrome or multi-gene panel testing should be informed by patient data, family history and other risk assessment details. NCCN recommends panel testing as a potentially more efficient and cost effective approach in cases where “more than one gene can explain an inherited cancer syndrome” (NCCN-HBOC Version 1.2017).

If testing reveals pathogenic mutations in one or more genes known to impact hereditary cancer, NCCN recommends surveillance and prevention approaches to reduce the likelihood of getting cancer, improve patient quality of life, and reduce the cost burden.

Alternately, hereditary cancer testing can reveal variants of uncertain significance (VUS), which are gene alterations with no validated correlation to a known outcome. For such cases, NCCN recommends participating in research programs aimed at determining the biological

NCCN-recommended surveillance and prevention approaches for individuals with known cancer risk-associated gene mutations

- Increased frequency of and/or more tailored screening for the primary cancer type indicated by the identified gene(s) and mutation(s);
- Careful screening for other cancer types known to be associated with the identified gene(s) and mutation(s); and
- Prophylactic surgical approaches (such as mastectomy and salpingo-oophorectomy in HBOC).
and disease significance of such variants. Myriad Genetic Laboratories (Myriad) is a participating laboratory in the Prospective Registry of Multiplex Testing (PROMPT). This research registry follows people who carry mutations or variants identified through panels, to ascertain more fully their clinical significance over time (PROMPT).

Most importantly, clinical best practices guarantee patient access to ongoing evaluation of the VUS relative to constantly evolving information, along with notification if the disease significance changes (Trosman et al., 2017).

Myriad aligns its hereditary cancer testing, result interpretation, and clinical decision support tools closely with NCCN guidelines. Myriad’s robust variant classification program with a lifetime commitment is an integral component of testing processes to update providers on changes in variant significance at no charge, for application to patient care.
IV. RETHINKING HEREDITARY CANCER BASED ON CURRENT GENETIC EVIDENCE

NCCN provides clear guidance for assessing whether a patient is at elevated risk for established hereditary cancer syndromes. This is an essential first step prior to genetic testing.

Once high risk of hereditary cancer is established, genetic testing is warranted. Current scientific evidence has prompted changes in clinical practice guidelines including consideration beyond the primary disease risk and the most obvious implicated gene(s) including:

- Additional genes that influence disease risk to a level that warrants a change in medical management; and
- Associated risk for other types of cancer.

Traditionally, HBOC genetic testing has focused on BRCA1 and BRCA2, as these were the first genes found to confer a clear increase in cancer risk. However, current guidelines recognize that within HBOC, numerous additional genes associate with increased risk (Tung N et al., 2015; Langer et al., 2016; NCCN-HBOC Version 1.2017) (Figure 2).

Accordingly, these genes are included in commercially available hereditary cancer panel tests. Similar data have emerged for familial high-risk CRC — for example, in Lynch Syndrome, for which the number of risk-associated genes has expanded to five (Yurgelun et al., 2015; Yurgelun et al., 2017; NCCN-CRC Version 1.2017).

Sometimes, a hereditary cancer panel test will detect mutations in addition to or wholly separate from the results a clinician might anticipate based on the patient’s clinical risk information. Panels are designed to detect such mutations, empowering the clinician to assess patient disease risk more completely and to act upon it with clinical management when indicated by medical society guidelines. The American College of Medical Genetic and Genomics (ACMG) has provided clinician guidance for reporting unanticipated findings to patients (Kalia et al., 2017).
**Associated Risk for Other Cancer Types**

Conversely, a single gene can be associated with multiple cancer risks. While Lynch Syndrome predisposes most frequently to CRC, it also carries increased risk of ovarian and endometrial cancer in women, along with cancers of the stomach, small intestine, liver, gallbladder ducts, upper urinary tract, brain, and skin in both men and women (Järvinen et al., 2000; Lindor et al., 2006; Saam J et al., 2015). Therefore, panel testing for Lynch Syndrome has medical management implications that range far wider than for CRC alone (Figure 3).

**Penetrance and Clinical Actionability**

Penetrance, expressed as a percentage, refers to the proportion of people with a genetic variant who also develop the associated health condition. If a variant does not produce the disorder in all people who have it, the condition has reduced (or incomplete) penetrance (Figure 4).
Hereditary cancer syndromes have been historically associated with genes that are considered highly penetrant and result in significant cancer risk. Other genes were found to be moderately penetrant, meaning that they do not increase a patient’s risk to the same extent – but they do raise risk to a level that warrants a change in medical management, according to clinical practice guidelines (Tung et al., 2016). The distinction between highly and moderately penetrant has grown arbitrary (Easton et al., 2015) as the overlap among cancer types has become more apparent (Kalia et al., 2017). Instead of categorizing genes based on penetrance, a better-informed and more pragmatic approach poses questions such as:

1. Is the level of risk high enough to warrant a change in medical management?
2. What is clinically actionable?
3. Which genes carry a cancer risk that would warrant medical management change based upon guidelines? (Southey et al., 2016; Tung et al., 2016)

**Summary**

In hereditary cancer, an assumed ratio of a single gene to a single cancer risk has grown scientifically outdated and clinically incomplete (Yurgelun et al., 2015). As a result, clinicians face increasing difficulty in identifying one specific gene or syndrome to address a patient’s particular family history, or for predicting a patient’s risk of a specific type of cancer. In reality, a range of known genes overlaps meaningfully with numerous cancer types. This prompts a change in best practices for hereditary cancer testing. Overly narrow single-gene or single-syndrome assessment can miss clinically important information, leading to suboptimal clinical management, delayed treatment, poor patient outcomes, and unnecessary costs. The broader assessment provided by panel tests provides clear advantages when it includes genes specified by established clinical practice guidelines and based upon peer-reviewed, published relevance to cancer risk.

In reality, a range of known genes overlaps meaningfully with numerous cancer types. This prompts a change in best practices for hereditary cancer testing. Overly narrow single-gene or single-syndrome assessment can miss clinically important information, leading to suboptimal clinical management, delayed treatment, poor patient outcomes, and unnecessary costs.
V. MANAGING VARIANTS OF UNCERTAIN SIGNIFICANCE (VUS)

The greatest challenge in demonstrating panel test clinical validity is classifying measured gene variants into one of three categories:

1. **Benign**: The variant has no influence on disease risk;
2. **Pathogenic mutation**: The variant associates with increased disease risk; and
3. **VUS**: Conclusive evidence about the variant’s effect on disease risk is not available at the time of testing.

**Interpretive Accuracy**

Classification depends on high interpretive accuracy, which requires:

- Using up-to-date, clinically validated, peer-reviewed and published tools;
- Associating each variant with known risk for multiple relevant cancer types;
- Expressing accurately the impact of multiple variants on the overall risk for a single inherited cancer type; and
- Establishing ongoing, automated reclassification processes with amended reporting.

No standardized criteria exist for classifying gene variants, so laboratories must develop and validate their own methods. The American College of Medical Genetics and Genomics, with the Association of Molecular Pathology, has developed variant analysis guidelines (Richards et al., 2015). However, these guidelines are subject to individual interpretation and have resulted in inconsistent variant classification across diagnostic laboratories. Therefore, they have proven insufficient for reliable standardization.

A recent study across commercial laboratories highlights the critical need for interpretive accuracy in clinical hereditary cancer tests (Balmaña et al., 2016). In this study, multiple laboratories evaluated inherited cancer susceptibility test results for 518 patients, using data from the Prospective Registry of Multiplex Testing (PROMPT). Variant interpretation across four laboratories differed for 155 (26%) patients. Of these, 56 (11%) had variants with conflicting interpretations – ranging from VUS to pathogenic – that could affect medical management choices. Among 603 total variants identified in these patients, 221 (37%) were classified as VUS, 191 (32%) as pathogenic, and 34 (6%) as benign. Therefore, when selecting a genetic test that can impact medical management with life-altering outcomes, validating the testing laboratory’s variant classification methods is crucial.

A 2017 study comparing classifications for 4,250 variants in BRCA1 and BRCA2 between a single reference laboratory (Myriad) and a commonly used public database (ClinVar) revealed discordant classifications for up to 26.7% of variants (Gradishar et al., 2017). Results of this study highlight the discordance among laboratories and indicate that clinicians who check classifications in ClinVar will experience limited value.
In best practice, classification tools are published in peer-reviewed studies that clearly demonstrate their accuracy. Myriad has published its proprietary tools and uses them as part of a multi-pronged approach to variant classification (Eggington, et al., 2014; Pruss et al., 2014; Judkins et al., 2015). When possible, Myriad sets a 99.5% confidence threshold for variant classification techniques (Figure 5).

Multiple lines of evidence are required for variant classification, including:

- Review of published literature, including known health impact and biochemical function of the variant;
- Population frequency analysis, which evaluates the frequency of the variant in a population relative to the overall health and cancer incidence in a population;
- Myriad’s proprietary health history weighting analysis (Pheno).
- Myriad’s proprietary statistical modeling (M-CO);
- RNA splicing analysis, including data from Myriad’s internal RNA lab (inSite); and
- Structural and functional analysis of proteins encoded by risk-associated genes.
Automated reclassification processes continue to drive down the VUS rate. Over time, Myriad’s reclassification process has resulted in a VUS rate of <1% for BRCA1 (Mundt and Chen, 2016).

**Summary**

Despite careful and thorough analysis, VUSs are inevitable in multi-gene panel testing, and new information about genetic variants in cancer emerges every day. Reclassification of a variant can impact the medical management recommendations and choices made by the provider and patient. Therefore, a testing laboratory should provide a lifetime commitment to reviewing and reclassifying variants, and updating providers in a timely manner at no charge. Payers concur, calling for a “standardized process, infrastructure and accountability for recontacting” (Trosman et al., 2017). Variant information management and reclassification should be an iterative process, taking place on a dynamic rather than scheduled basis. Automated systems can best assist with these efforts. (Myriad’s Pheno and M-Co are examples of automated and validated processes for reclassification.)
VI. TOWARD BEST PRACTICE IN HEREDITARY CANCER TESTING: HEREDITARY CANCER PANEL TESTS

In the decades since high-penetrance genes involved in HBOC and CRC first surfaced, hereditary cancer testing policies have advocated a syndrome-based approach to diagnosing hereditary risk. As more genes were found to contribute to risk, payers incorporated gene-by-gene testing into their policies. The substantial list of genes now known to influence hereditary cancer risk has made stepwise testing ineffective. For example, a single-syndrome test for high-penetrance genes might return a negative result for a patient assessed with a familial risk of cancer. Other genes known to increase risk for a cancer would also merit evaluation. For this patient, arriving at an accurate diagnosis proves time-consuming and costly, with associated risk of medical mismanagement. Recognizing the length of time it would take to obtain all results with a gene-by-gene approach and the impact of having to wait to pursue medical management based upon those results, providers have overwhelmingly switched to panel testing. Also recognizing the impact, such delayed diagnosis in stepwise testing is considered to be a medical error according to the IOM report, Improving Diagnosis and Healthcare (National Academies of Sciences, Engineering, and Medicine, 2015).

NCCN Guidelines Involving Multi-gene Testing in HBOC and CRC

In 2014, NCCN introduced recommendations for multi-gene panel testing into clinical practice guidelines for HBOC. As of June 2016, NCCN clinical practice guidelines for HBOC and CRC both incorporated gene panels into its testing algorithms for patients meeting the criteria for high-risk familial cancer.

Summary

Hereditary cancer panel tests have been developed as a tool to address the expanding number of genes found to contribute to a range of hereditary cancer risk. By evaluating the status of multiple genes, results from panel testing bring patients to appropriate medical management more quickly and cost effectively than can stepwise single-gene or single-syndrome approaches. Providers recognize this value for their patients as indicated by their preference for panels. The next section describes a contemporary and robust tool for payers in evaluating evidence to support panel coverage decisions.
VII. A CHAIN OF EVIDENCE TOOL FOR PAYER DECISION MAKING

To justify panel coverage and reimbursement, payers need evidence of clinical utility in the form of medical management decisions that improve outcomes and reduce cost. The CMTP Chain of Evidence paper (CMTP 2013) and Initial Medical Policy and Model Coverage Guidelines for Clinical Next Generation Sequencing in Oncology (CMTP 2015) provide useful frameworks for test providers to organize and present supporting data. Evidentiary details for each offering are provided in product-specific publications.

By combining the CMTP frameworks with NCCN and other established guidelines, we present a straightforward, multi-step tool for payers in evaluating panels. This tool accommodates contemporary understanding of the overlap among cancer types and the genes involved, supports optimal use of feasibly gathered clinical data, and promotes close adherence to established clinical practice guidelines.

1. Does the gene mutation warrant medical management?
2. Are cancer risks well-defined in individuals with gene mutations?
3. Do clinical practice guidelines recommend changes in medical management based on gene mutations?
4. Are the associated risks sufficient enough to cause a change in medical management?

Diagnostic laboratories best support adoption and use of their products by ensuring positive answers for Steps 1, 2, and 4 through collection and peer-reviewed publication of evidence. They have limited control over Step 3, the responsibility for which lies primarily with clinicians and patients and is best achieved through clinician education and appropriate patient counseling. That said, diagnostic laboratories retain the responsibility for delivering current and accurate interpretation and clinical guideline references with test results, along with educating and updating providers and patients as appropriate.
VIII. CONCLUSION

When applied properly within the NCCN-designated intended use population, multi-gene panel tests address healthcare providers’ imperative to broaden the hereditary cancer testing range, keeping pace with the overlap among cancer types and the genes involved. That said, provider adherence to established clinical practice guidelines is essential for ensuring the utility of panel tests in the intended patient population. Diagnostic laboratories support optimal clinical and patient-reported outcomes by employing best practices in technology, variant interpretation and information management, combined with a commitment to updating results as information changes and standardizing practices across the field.

Panel tests can reduce associated financial costs and delays for patients and payers by replacing stepwise testing with comprehensive single-step assessment and by informing medical management decisions earlier in the clinical process. With the advent of precision medicine, hereditary cancer panel tests serve as an invaluable tool for assessing hereditary risk with a depth not previously possible, helping patients make the right management decisions at the right time.
IX. REFERENCES


Mundt E and Chen D., Medical Services, Myriad Genetic Laboratories, Inc. Lowering the Rate of Variants of Uncertain Significance on Myriad’s myRisk Hereditary Cancer Panel. White paper presented June 2016.


