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Multi-gene panel testing for hereditary cancer susceptibility: A new paradigm

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EXECUTIVE SUMMARY

This article addresses the importance of hereditary cancer panel testing. No longer are single syndrome tests the best diagnostic for hereditary cancer risk. Panel testing addresses multiple genes that are associated with a single cancer, as well as single genes that implicate multiple cancers.

To optimize patient care, it is important to determine who is the best candidate within a family to test, and identify laboratories with the greatest accuracy in results.

WHAT IS HEREDITARY CANCER MULTI-GENE PANEL TESTING?

Hereditary cancer multi-gene panel testing represents a new paradigm in clinical genetic testing for inherited cancer susceptibility.[1] The previous model was based on the analysis of one or a small number of genes for individual, classically defined syndromes, that considered the patient's personal and family cancer history. The new model encompasses simultaneous analysis of a larger number of genes targeting specific cancer sites including breast, colorectal, ovarian, endometrial, gastric, pancreatic, melanoma, and prostate (**FIGURE 1**).

Panels address the emerging clinical dilemma that multiple genes may be associated with risk of one hereditary cancer and that multiple cancer risks can be influenced by a single mutation. Panels address this overlap by evaluating several well-known, and other yet to be identified associations and syndromes of diverse cancer susceptibility. When panel testing is compared with current hereditary breast and ovarian cancer (HBOC) and Lynch syndrome (LS) testing, up to 50% more mutations are found in HBOC patients and 60% more mutations are found in LS patients that would have been missed in single-gene testing.[2] Many of these mutations would be implicated in the patient's personal or family history, yet some may not have been predicted based on clinical presentation, representing previously undetected cancer risks and medical management opportunities (**FIGURE 2**).

The Society of Gynecologic Oncology (SGO) has issued a statement concluding that panel testing simplifies the initial diagnostic journey, as it will cover multiple genes that may be involved in the assessment of cancer susceptibility. Additionally, evaluating family history based on single syndromes can be too narrow and lead to a false sense of security about a patient's true cancer risks and possible mismanagement. The interpretation of results, however, can be complicated by the multiple potential outcomes of testing.[3] Many physicians and genetic counselors are unfamiliar with the less common genes that may have reduced penetrance, poorly understood expression, higher rates of variants of uncertain significance (VUS), and less clearly defined management options. In contrast to highly penetrant HBOC *(BRCA1/2)* and LS associated mutations, positive test results for a less penetrant gene may not actually raise the likelihood of cancer significantly over the patient's calculated familial risk, but the potential for increased surveillance and intervention for multiple related syndromic cancers may be of significant value to both the patient and her family.

The solution to this apparent complexity is to know where to find more information about genes and related syndromes. There are panel tests that specifically address this issue by

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Dr. Freider reports that he is a consultant and speaker for Myriad Genetics Laboratories.

FIGURE 1 The new model of simultaneous analysis

Genes	Breast	Ovarian	Colorectal	Endometrial	Melanoma	Pancreatic	Gastric	Prostate	Other
BRCA1, BRCA2	●	●			●	●		●	
MLH1, MSH2, MSH6 PMS2, EPCAM		●	●	●		●	●		●
STK11	●	●	●	●		●	●		●
APC, BMPR1A, SMAD4			●			●	●		●
MUTYH			●						●
CDKN2A, CDK4					●	●			
TP53	●	●	●	●	●	●	●	●	●
PTEN	●		●	●					●
CDH1	●		●				●		
PALB2, ATM	●					●			
CHEK2	●		●					●	
NBN	●							●	
BARD1	●								
BRIP1, RAD51C	●	●							
RAD51D		●							

offering multiple clinical resources and the integration of societal management guidelines within the genetic test results. Many of the panel genes also have National Comprehensive Cancer Network (NCCN) reviews and current guidelines. The remaining genes are clinically significant based on extensive literature documentation of associated cancers and their recommended management.

WHY SINGLE-GENE/SYNDROME TESTING IS NO LONGER OPTIMAL CARE

March 2014 marked the 20th anniversary of the identification and cloning of *BRCA1* and the recognition of its role in HBOC syndrome.[4] Reduction in morbidity and mortality through early diagnosis, along with primary and secondary prevention of breast and ovarian cancer, have become a reality using proven surveillance, along with medical and surgical risk-reducing options.

Current research now identifies numerous other genes as causative in an additional 15% of suspected HBOC families.[5] Highly penetrant genetic mutations in *TP53* (Li-Fraumeni syndrome), *PTEN* (Cowden syndrome), *CDH1* (Hereditary Diffuse Gastric Cancer syndrome), and *STK11* (Peutz Jeghers syndrome) have long been recognized as possible causes of hereditary breast cancer, and now panel testing includes these along with moderately penetrant genes such as checkpoint kinase 2 *(CHEK2)*, ATM serine/thereonine kinase *(ATM),* and partner and localizer of *BRCA2 (PALB2)*. These examples show that single-gene, or disease-specific, testing is no longer the best method to care for patients.

WHY PANELS MAY BE THE NEW STANDARD OF CARE

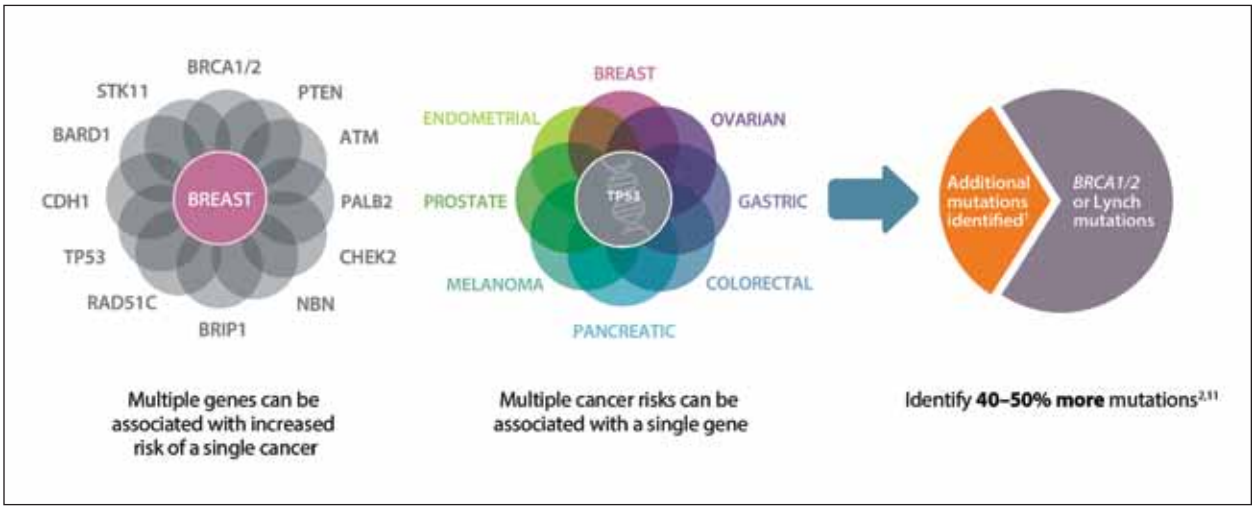
Significant syndromic overlap between numerous genes associated with a given cancer can make test selection a difficult and sometimes misdirected process. There are now 13 different genes that may be causative of hereditary breast cancer; 13 genes for hereditary colon cancer; and 9 genes for hereditary ovarian cancer.[2] Among these, each gene has its own group of associated cancers and spectrum of penetrance and expression, all with considerable overlap.

This significant diagnostic overlap exists even within the commonly ordered HBOC and LS tests. Up to 6.9% of HBOC tested patients also qualify for LS testing criteria, and up to 30% of LS tested patients are also appropriate for HBOC testing.[7] Therefore, a hereditary cancer panel should evaluate a broad number of genes that assess risk for clinically actionable cancers, and provide a summary of medical society guidelines for patient results that aid in appropriate management considerations.

IDENTIFYING PATIENTS

Current American Society of Clinical Oncology (ASCO) guidelines advise that genetic testing should be:[8]

FIGURE 2 The clinical dilemma



- offered to clinically appropriate, at-risk populations with a personal or family history suggesting hereditary cancer
- conducted by a trained clinician
- conducted with pretest and posttest counseling
- conducted through a process of informed consent
- performed by a licensed and accredited clinical laboratory
- interpreted by a knowledgeable provider

According to NCCN guidelines, patient's personal and/or family cancer history should be evaluated for genetic testing.[9] Maternal and paternal heredity are equally important, and a three-generation family history should be taken.

Appropriate candidates for multi-gene panel testing include patients who are already affected by cancer, as well as those who are unaffected with significant family histories suggestive of a hereditary cancer syndrome. Additional candidates are patients who have had previous genetic, single syndrome testing, with negative results. As with the older model of patient identification, testing of the index patient in the family is preferred; however, this is often difficult to accomplish. Therefore, as advised by NCCN as acceptable clinical practice, we should test our unaffected patients because we have access and responsibility to them.

With respect to hereditary cancer syndromes, appropriate test candidates have the following: personal or family histories of cancer that occured at an age earlier than the usual presentation; multiple cancers; or rare cancers. Family histories involving HBOC syndrome typically are noted to have breast cancer younger than age 50, bilateral breast cancer, ovarian cancer, and male breast cancer and/or may have histories of melanoma, pancreatic cancers, or high-grade prostatic cancers. Families of Ashkenazi Jewish descent are at particularly increased risk for having HBOC syndrome. Families with LS are notable for colorectal or endometrial cancer prior to age 50, along with gastric or ovarian cancer at any age. Other less common LS cancers include brain, pancreatic, biliary, uroepithelial, small bowel and sebaceous neoplasms (**FIGURE 3**).

FIGURE 3 Red flags for hereditary cancer

An individual with a personal or family history of any ONE of the following:

	Multiple 2 or more	**Young** age 50 or younger	**Rare** any age
Breast	●	●	‡
Prostate	●		
Melanoma	●		
Ovarian	● ●		●
Pancreatic	● ●		
Colorectal	●	●	†
Endometrial	●		†
Gastric	●		
Other**	●		

● Hereditary Breast and Ovarian Cancer (HBOC)-associated cancers§
● Lynch-associated cancers^

†Abnormal MSI/IHC or histology. ‡Male breast cancer, triple negative breast cancer. **Other Lynch Syndrome-associated cancers, 10 or more gastrointestinal adenomatous polyps. §HBOC syndrome-associated cancers include breast (including ductal carcinoma in situ [DCIS]), ovarian, pancreatic, and aggressive prostate cancers. ^Lynch syndrome-associated cancers include colon/rectal, uterine/endometrial, ovarian, stomach/gastric, kidney/urinary tract, biliary tract, small bowel, pancreas, brain and sebaceous adenoma cancers.

HOW TO TEST: POINT OF CARE RATHER THAN REFERRAL

The time-honored concept of patient identification with early referral to a genetic counselor has demonstrated notable deficiencies over the last 20 years. The referral model is outdated, and a new paradigm has emerged considering there are fewer than 400 cancer genetics professionals in the entire country, as listed in the National Cancer Institute (NCI) Cancer Genetics Registry. With the goals of preventing cancer and saving lives and families, approximately 60,000 physicians in primary and specialty care, as well as mid-level practitioners, have obtained the modest, remedial training needed to enable high quality care for their patients, while reserving referrals to genetic specialists for the most complex patient cases.

The core principles of this new paradigm include:

1. **Screen** all patients with an annual family cancer history questionnaire.
2. **Evaluate** the questionaire with the patient at the time of the encounter. Every abnormal questionnaire represents a family with elevated and actionable cancer risk.
3. **Diagnose** all patients using their genetic test results and risk calculations in one of the three risk profiles: Sporadic, Familial/Personal, or Hereditary risk.
4. **Manage** each patient's care for personalized cancer prevention. A cancer prevention plan includes coordination and integration of an appropriate medical team with a designated navigator providing outreach to family members and education about lifestyle change, family planning, surveillance, and medical and surgical risk reduction.

HOW TO CHOOSE A LABORATORY

Multiple genetic testing laboratories now offer both single-gene/syndrome and multi-gene panel testing, with significant differences in both technical and interpretive accuracy. Classification of genetic variants involves highly complex processes, reliable databases, and frequent review of the literature by top level scientists. Unfortunately, there is no current laboratory regulation for accuracy and equivalence of genetic testing, and the majority of labs do not have peer reviewed and published studies validating the accuracy of their genetic testing. Clinical Laboratory Improvements Amendments (CLIA) regulation ensures quality of routine laboratory procedure but does not address issues of technical and interpretive accuracy in genetic testing. A flurry of both local and national labs recently joined the marketplace without the experience or knowledge to produce reliable, accurate diagnoses.

As the patient's advocate, healthcare providers are obligated to provide the highest level of care in all matters, including the choice of laboratories to which a specimen may be sent. These genetic test results have life-changing and life-saving consequences to both the patient and her family, thus a technical or interpretative error can affect multiple generations within a family.

Factors to consider in choosing a genetic laboratory include:

- Published results of validation studies with numbers of patients and technical accuracy
- Published results of VUS rates
- Database disclosure and methods used to assign variant classification
- Periodic review schedule and notification for VUS reassignment
- Clinical review confirming optimal test was ordered
- Efficient turnaround time
- Genetic education and interpretive resources to physicians
- Assistance to physicians for process integration and office procedures
- Actual out-of-pocket cost to the patient; Affordable Care Act regulations now provide 100% coverage to most patients, regardless of laboratory's retail fee

INTERPRETATION OF RESULTS

Patients undergoing panel testing will receive one of three possible results, similar to single-syndrome testing:

1. **Positive**: A gene mutation was found in one of the tested genes, indicating increased risk for cancer specific to that gene mutation. Cancer screening and prevention recommendations will target the syndromic cancers.
2. **Negative**: No clinically significant genetic variants were identified within the tested genes. Cancer risk assessment and management is based on empiric analysis of personal and family history. Risk assessment models for breast cancer should be considered.
3. **Inconclusive**: A genetic variant was identified; however, current knowledge cannot predict if the variant is benign or pathogenic. Cancer risk assessment and management is based on empiric analysis of personal and family history. VUS is common and can be found in up to 30% of panel testing results.

IMPACT ON PROVIDERS

Advancement in panel testing provides clinicians with a unique tool to support the diagnostic process when applied to an appropriate at-risk population. This reflects and supports the American College of Obstetricians and Gynecologists (ACOG) and ASCO guidelines referencing responsible patient centered hereditary cancer screening. Genetic risk evaluation and testing has been delivered inconsistently to patients in the past, as was reported by ASCO's 2011 Quality Oncology Practice Initiative (QOPI), which noted that only 60% of oncologists were performing adequate family history intake, and less than half of the identified at-risk patient population was being appropriately tested for hereditary cancer.[9] Recognizing the relative inaction within the ObGyn community, ACOG issued a similar practice bulletin in 2009, stating that hereditary cancer risk assessment and testing "should be a routine part of obstetric and gynecologic practice."[10]

The ability to identify these genetic causes of hereditary cancer in combination with modern medical interventions for surveillance and primary prevention creates a unique and powerful opportunity to benefit our patients. Additional physician benefits include improved practice revenue from the provision of high-risk services to both familial and hereditary risk patients, as well as the decreased liability from prevention and early recognition of cancers.

CONCLUSION: A NEW PARADIGM

Experience in genetic testing and management of *BRCA1/2* mutation cancer susceptibility has served as a model for the integration of clinical genomics into the everyday practice of personalized medicine over the past 20 years. Hereditary cancer multi-gene panel testing now represents a new paradigm and powerful advancement in the diagnosis and clinical management of cancer susceptibility, with improved power to identify more patients who are carrying undiagnosed pathogenic mutations. Multi-gene panel testing and update panel testing are currently available to all physicians, midlevel practitioners and genetic counselors. ACOG advises that hereditary cancer risk assessment should be a routine part of ObGyn care; we must continue to expand our horizons in both knowledge and practice as we move further into the age of personalized medicine and preventive care.

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