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# UNDERSTANDING HEREDITARY CANCER IN THE ERA OF MULTI- GENE PANEL TESTING

## *Collaborative Best Practices Review and Recommendations*

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## INTRODUCTION

The science underlying cancer is progressing quickly on many fronts. More and more genes with links to hereditary cancer are being identified. New treatments targeting genetic mutations linked to hereditary cancers are being developed. Advances in sequencing technology are making it possible to consecutively test many genes to identify risk for multiple types of cancers and as a result redefining our understanding of the hereditary basis of cancer.

These advances, however, offer only limited benefits if patients don't understand how they affect their risk and overall health. With an increasingly complex environment, there is an opportunity for patient advocacy organizations to assume a leadership role in helping patients understand the complex educational requirements and also the psychosocial considerations of this new world.

### Collaborative approach to hereditary cancer

In May 2015, Myriad Genetic Laboratories, a long-standing leader in hereditary cancer genetic testing, convened a group of representatives from 14 patient advocacy organizations that support those with risk for cancer and rare cancers. Participants discussed the changing needs of patients and families with regard to hereditary multi-gene panel testing. The discussion also encompassed opportunities to ensure adequate resourcing and partnerships for educating and advocating for their constituents. The dialog was unbranded in nature with the goal of identifying best practices that could span a range of advocacy organization constituents as the world of genetic testing quickly evolves. This paper summarizes the discussion for the benefit of these and other patient advocacy organizations as well as their patient-constituents.

### ANDREA

I spent my early childhood watching my father battle Hodgkin's lymphoma, only to lose his battle. His siblings had pre-cancerous colon and stomach polyps, his father had renal cancer and melanoma and his mother brain cancer. Other family members had pancreatic, breast and renal cancer.

I've lived my entire life wondering not if, but when, I'd be diagnosed. I decided to pursue a hereditary cancer panel test. In my mind, it was the perfect option, as there were a variety of cancers in my family, and this test would screen for multiple cancer genes in which harmful changes were known to increase cancer risks.

I was found to have a harmful change in the *CHEK2* gene, which carries up to a 48 percent risk of breast cancer. I now qualify for breast MRI in addition to mammogram on a regular basis.

## THE EVOLUTION AND PROMISE OF CANCER GENETIC TESTING

Cancer occurs when there are changes to genes that control the way our cells normally function, especially how they grow and divide. In many cases, these cell changes occur spontaneously during a person's lifetime. However, in 5 to 10 percent of all cancers, there are inherited genetic changes, or mutations. An individual with an inherited mutation is not always guaranteed a diagnosis of cancer,<sup>1</sup> but their risk for cancer can be much higher compared to the general population and in some cases (such as in the case of familial adenomatous polyposis), the cancer risk can be as high as 100 percent.<sup>2</sup> Research is providing extensive information on both common and rare genetic mutations and their links to hereditary cancers. The discovery of *BRCA1* and *BRCA2*, the first genes with mutations known to be associated with breast cancer,<sup>3</sup> led to the commercialization of genetic tests for use in identifying individual mutations in clinical practice.<sup>4</sup> Until recently, most testing for genetic mutations focused on single cancer syndromes or a small number of genes<sup>1</sup> and used a method of identifying changes in DNA called Sanger sequencing. This technology, currently viewed as the gold standard for sequencing, is expensive and yields an increase in costs proportionate to the quantity of DNA or genes being sequenced.

Recent technological advances in sequencing methodologies (known as "next generation sequencing" or "NGS") now enable simultaneous testing of multiple genes. NGS has given rise to multi-gene panel testing, by which laboratories analyze a panel, or set of multiple genes, quickly at little additional cost compared to single gene testing. As a result, many more hereditary cancer genes can be assessed and analyzed at the same time with just a single sample of DNA, usually obtained by drawing blood.

Researchers are finding that individuals with specific genetic mutations are at increased risk for specific cancer types. A single mutation may increase risk for several different cancer types while several different gene mutations may increase risk for a single type of cancer. This complexity makes it difficult to accurately identify the best genetic test for a given individual based upon their personal or family cancer history. In other words, it is challenging to accurately predict the genes that underlie a familial cancer syndrome by the pattern of inheritance within a family. Panel testing is an attractive, effective and efficient option for uncovering inherited cancer mutations.

## ADVANCEMENT OF PANEL TESTS

### Benefits

Because multiple gene mutations can be associated with increased risk for one cancer and one genetic mutation can be linked to increased risk for multiple cancers, panel testing can provide patients with a broader picture of their cancer risks. Panel tests also can lead to more precise treatment decisions offering convenience, time and cost savings compared to multiple single-syndrome tests. It is important, however, to keep in mind that even with negative results, or test results that don't identify any genetic mutations associated with hereditary cancer, many individuals and their families remain at increased risk for cancer due to family history, environmental and other genetic risk factors.

1. National Cancer Institute. The Genetics of Cancer. <http://www.cancer.gov/about-cancer/causes-prevention/genetics>. Accessed June 16, 2015.
2. Cancer.net. Genetic Testing for Cancer Risk. <http://www.cancer.net/navigating-cancer-care/cancer-basics/genetics/genetic-testing-cancer-risk>. Accessed June 16, 2015.
3. National Human Genome Research Institute. Learning About Breast Cancer. <https://www.genome.gov/10000507>. Accessed June 16, 2015.
4. Narod SA, Salmena L, *BRCA1* and *BRCA2* Mutations and Breast Cancer. *Discovery Medicine*; ISSN: 1539-6509; *Discov Med* 12(66):445-453, November 2011. <http://www.discoverymedicine.com/Steven-A-Narod/2011/11/25/brca1-and-brca2-mutations-and-breast-cancer/> Accessed June 16, 2015.

Evaluating the risk associated with a positive, a negative or uncertain genetic test result is best done by a genetic counselor or a healthcare provider specializing in genetics.

Panel tests can provide critical information when there are imperfect family histories due to knowledge gaps, limited or small family structures, and distant relationships or incorrectly communicated medical history information. Panel tests also can alert individuals to their genetic risk for a cancer not historically obvious within their family. While sometimes unexpected, this information can empower patients and their health care providers to be more alert to potential signs and symptoms of cancer. It also can potentially reduce the need for future genetic tests, which can be costly and time-consuming for patients, physicians, caregivers, genetic counselors and other cancer genetics experts.

## CHALLENGES AND OPPORTUNITIES

### Variants of Unknown Significance

One challenge of panel testing is that the more genes that are tested, the more likely variants of unknown significance (VUS) are to be identified as compared to single-gene testing. VUS are those mutations in which the sequence of a gene or part of a gene is identified as being different compared to a known sequence of the gene, but for which scientists have not yet determined whether that difference is associated with an increased risk of cancer. Thousands of variants<sup>5</sup> have been classified to date, some of which are more common than others. Many more variants remain in flux as VUS and require ongoing commitment of research to correctly classify.

Given their uncertainty, VUS should not be used to guide medical management according to guidelines issued by the National Comprehensive Cancer Network (NCCN). While VUS may not be recommended as determinants for medical management, they still have relevant value. In fact, the American Society of Clinical Oncology (ASCO) recently confirmed in a letter to the US Food and Drug Administration<sup>6</sup> (FDA) its position that information about variants is of value even when the strength of association with disease is unclear or contradictory.

### RUTH

After being diagnosed with breast cancer at age 44 and because of her extensive family history of breast cancer, Ruth underwent genetic testing for *BRCA1* and *BRCA2*. Her test results came back negative.

Three years later Ruth's sister was recommended for a multi-gene panel test after learning about other cancers in the family including gastric and colon cancer. She tested positive for *CDH1*, a mutation carrying higher risk of gastric, breast and colon cancers.

Ruth then tested for *CDH1* and also was found to be positive. Because of her result, Ruth underwent a specialized EGD stomach scan, which showed two cancer tumors. Because gastric cancer grows so quickly, Ruth opted to have her stomach removed.

Because of the knowledge of her genetic mutation and her preventive surgery, Ruth has lived to see her daughters to adulthood and to spend time with her beloved grandson. Although living without her stomach is not easy, she can say, **“I don't have fear because I have knowledge.”**

It can take years and thousands of individuals and their families undergoing testing to gain enough information to definitively determine the risk associated with a specific VUS. As an example, in the 1990s, there was a 30 to 40 percent VUS rate in *BRCA1* and *BRCA2* test results. At this time, the *BRCA1* and *BRCA2* VUS rate ranges between 1 to 3 percent and varies by laboratory.

Many years and resources have been spent developing new technologies and scientific approaches to identify whether specific mutations are cancer-causing or not. As more data are collected regarding the nature of a VUS, individuals who have had a VUS test result should have access to revised information about their specific test result during their lifetime. Further, most VUS will be classified as not clinically significant so timely access to a change in classification is extremely important. In some cases the uncertainty of a VUS can lead to unsupported screening and preventive surgery. High-quality laboratories should continually research variants and update health care providers, patients and researchers on VUS classification when a final determination is made.

### New Gene Mutation Discoveries

Another challenge of panel testing comes with the discovery of new genetic mutations. Guidelines and research surrounding the medical management of patients with these mutations may not be available at the time the mutation is identified.

Many patients are comfortable receiving genetic test results that include mutations about which little is currently known, as can be the case with panel tests. The benefit to having this information is in gaining a more accurate picture of risk as more information becomes available. For example, the publication of a *New England*

*Journal of Medicine* article showed that *PALB2* mutations increased risk for breast cancer and impacted screening guidelines. Similarly, *RAD51C* was a newly discovered gene whose mutation was associated with increased risk for ovarian cancer shortly after its discovery.

The possibility for identifying mutations associated with cancer risk that are not historically present in a person's family should also be mentioned. This finding can cause uncertainty in fully understanding risk and in developing a management strategy as well as leading to concern and confusion in the individuals being tested.

It is critical that patients be made aware of the limited research on some genes and the possibility of a variant result prior to testing. Access to genetic counselors and other health care providers with genetics expertise is also important to ensure the most appropriate test is ordered and properly interpreted.

While scientists may have little knowledge today about certain genes and their mutations' influence on cancer, ongoing testing and research can assist with refining the exact nature of mutations' relevance. One way knowledge about genes and genetic mutations is advancing is through registries and clinical results. Two such registries currently underway are the Prospective Registry of Multiplex Testing (**PROMPT**) and the **ABOUT** Patient Powered Research Network.

PROMPT is a collaboration among laboratories and clinical groups led by researchers from the University of Pennsylvania, the Dana Farber Cancer Institute, the Mayo Clinical Cancer

5. Egginton JM, Bowles KR, Moyes K, et al. A Comprehensive Laboratory-Based Program For Classification Of Variants Of Uncertain Significance In Hereditary Cancer Genes. *Clin Genet* 2014; 86: 229–237. doi: 10.1111/cge.12315
6. American Society of Clinical Oncology. Letter to United States Food and Drug Administration regarding Optimizing Regulatory Oversight of Next Generation Sequencing Diagnostic Tests Public Workshop; Request for Comments, Docket No. FDA-2014-N-2214, dated March 20, 2015.

Center and the Memorial Sloan Kettering Cancer Center. PROMPT focuses on understanding risks associated with newly identified cancer genes. PROMPT researchers follow individuals who have registered their mutations or variants of uncertain significance with the goal to help promote scientific discoveries about how these mutations affect health and cancer risk.<sup>7</sup>

The ABOUT Patient Powered Research Network is a registry supported by the Patient Centered Outcomes Research Institute, which is following long-term outcomes of people with a personal or family history consistent of HBOC, regardless of test results or whether or not they have had testing. The goal of this registry is simply to improve information and services, and ultimately the health and quality of life of individuals and families affected by hereditary HBOC cancers.

### Lab choice and quality

Lab accuracy is an important factor in choosing a test. While NGS offers many benefits, until the NGS technology advances further, results may be less reliable compared to Sanger sequencing. Therefore, guidelines established by the American College of Medical Genetics (ACMG) recommend that new mutations found

using NGS are to be re-confirmed using the Sanger sequencing method.<sup>8</sup> Because it can be challenging to stay abreast of constantly changing information, providers should take time to confirm if the lab(s) they select for testing are following these guidelines. Patients can also engage with their health care providers about laboratory choice and quality.

There are a variety of laboratory types, including labs whose sole focus has been genetic testing for hereditary cancer risk. Currently, several large reference labs, which historically have performed many different types of tests, are beginning to also offer genetic tests for hereditary cancer. As with genetic testing labs, patients whose tests are performed by reference labs generally are referred by physicians, and their tests are often paid through insurance or an assistance program. A number of labs now offer genetic tests directly to consumers and are available without physician referral. It is important to have guidance from a genetic counselor or other health care provider with cancer genetics expertise to direct testing, interpretation and management options.

7. <https://promptinfo.squarespace.com/about-us/>

8. [https://www.acmg.net/docs/ACMG\\_Lab\\_Standards\\_Next\\_Generation-Sequencing\\_Sept2013.pdf](https://www.acmg.net/docs/ACMG_Lab_Standards_Next_Generation-Sequencing_Sept2013.pdf)

## MARINA

In August 2012, I went to my doctor because of fibroids. After learning of my family history of breast and ovarian cancer and my Ashkenazi Jewish heritage, he suggested I test for BRCA mutations. I was reluctant, but he educated me about BRCA, what it does to carriers, their children and future generations and told me that I could likely have the cost of the test covered.

I was found positive for a *BRCA1* mutation and immediately scheduled hysterectomy and oophorectomy preventive surgeries. At my one-week, post-operation appointment, my doctor informed me that although the surgeries had saved my life, I was found to have a 1mm tumor in one fallopian tube and 6mm in the other. After further consultations, the decision was to give me six rounds of chemotherapy and staging surgery. Thanks to my doctor and his persistence in recommending testing to me, I am expected to be okay.

## GETTING TESTED

### Ensuring that appropriate patients are selected for testing

For health care providers, online tools can be valuable in triaging those interested in genetic testing, whether it be education to help them determine whether they are a good candidate for testing or information to guide them in creating profiles or pedigrees that visualize risk information. The tools also can prepare them with background information and potential questions for their discussions with health care providers, including genetic counselors. It is important to note again that 5 to 10 percent of cancers are hereditary; therefore, 90 percent are not. This reinforces the importance of hereditary cancer risk assessment to find the appropriate candidates for testing.

“Healthcare providers need a level of understanding to stratify patients and to understand what comprises a ‘5-alarm fire’ family history.”

- Sarah Storey, Bright Pink

Physicians on the front lines of care, such as primary care physicians (including family practitioners, internal medicine specialists or OB/GYNs), should have a basic understanding of how to stratify patients, when to order tests that are required for standard of care and when to refer patients. There is a need for education and improvement in this area. For example, historically only about 27 percent of women with ovarian cancer received genetic testing even though guidelines recommend testing for all patients with ovarian cancer.<sup>9</sup> In a study done by Stephanie Cohen, GC and her colleagues, health care providers acknowledged they need to play a role in the identification,

testing and/or referral of patients but that “they feel unprepared to address genetic testing issues,” potentially due to lack of training.<sup>10,11</sup>

Taking family histories regularly is vital for risk-stratifying patients and identifying genetic risk prior to diagnosis when cancer may be prevented. It is critical that health care providers regularly collect from their patients as detailed a family history as possible and that they understand when genetic counseling or testing referral may be appropriate as panel tests may offer great potential in this regard.<sup>12</sup>

On the other hand, it is also important for health care providers to understand that family history has some limitations since patients may not have accurate knowledge due to limited family structures, poor communication of history, misinformation or even adoptions in the family.

Demonstrating that risk can be present without a strong, known family history, a 2014 study revealed that 19.3 percent of identified Lynch syndrome patients in the study did not meet NCCN guidelines recommended for hereditary breast and ovarian cancer (HBOC) or Lynch syndrome testing.<sup>13</sup>

Furthermore, many cancer-causing genes may have lower penetrance meaning that although they increase cancer risk for a mutation carrier, the risk may not be as high as in some other

9. [http://www.nccn.org/professionals/physician\\_gls/PDF/genetics\\_screening.pdf](http://www.nccn.org/professionals/physician_gls/PDF/genetics_screening.pdf)
10. Cohen S, McIlvried D. Improving Access with a Collaborative Approach to Cancer Genetic Counseling Services. *Community Oncol.* 2013;10:227-234. doi: 10.12788/j.cmonc.0031
11. Herzog T, Saam J, Arnell C, et al. A State by State Analysis of BRCA1 and BRCA2 Testing in Patients with Ovarian Cancer
12. Diab S, Rodriguez P, Leininger A, et al. Experience in the Community Oncology Practice with a 25-Gene Hereditary Cancer Panel. Poster presented at: San Antonio Breast Cancer Symposium; December 10, 2014; San Antonio, Texas.
13. Kaushik P, Evans B, Moyes K, et al. Clinical Presentations of MMR Mutation Positive Patients With No Personal or Family History of Colon or Endometrial Cancer. Poster presented at Collaborative Group of the Americas on Inherited Colorectal Cancer Annual Meeting; September 15, 2014; New Orleans, Louisiana.

genes, and the effect on families may not be as dramatic in terms of cancers observed.

Advocacy organizations have long encouraged health care providers to involve patients in the risk stratification process. Today, advancements in cancer genetics are generating patient demand for more information on a topic that is more technical than ever before.

Patients can be educated through a variety of venues and materials, including:

- Printed materials
- Websites
- Webinars and live conference symposia
- eBooks, which allow for cultural and language adjustments on a case-by-case basis
- Videos, which can be customized using iPhone video pop-ins
- Online apps

Patient advocacy groups can take a leading role in creating resources for broad use with patients, ensuring these resources address key concerns and are patient-friendly.

Because health care providers are a key source of information for patients about the complex field of cancer genetics, health care provider education is critical. Patient advocacy groups should engage with professional societies to advocate and support continuing education. In addition, patient advocacy groups can encourage professional societies to include genetics courses as an educational priority at scientific conferences and in various programs.

### Access to genetics expertise

Another factor in the complexity surrounding testing for patients is the limited number of certified genetic counselors specializing in cancer. Of the 4,000 American Board of Genetic

Counselors-certified genetic counselors, only 29 percent of those in clinical practice specialize in oncology.<sup>14</sup> In a study by S. Gustafson, GC, a retrospective review of medical records from 117 patients, showed that one in two patients who were not offered genetic testing at the point of service may be lost to follow up.<sup>15</sup> Improved access to genetic counselors has shown an increased uptake for genetic testing and genetic counseling.<sup>10</sup>

**“We need to tap into professional societies for more training and continuing education.”**

- Lisa Schlager, FORCE

In addition, many health care practices do not or cannot employ a genetic counselor on staff. A best practices strategy would be to work with a genetic counselor to train the health care provider team to adequately stratify and refer or manage patients who are candidates for genetic testing.<sup>10</sup> Patients at low and average risk may also benefit from discussions of genetic risk. Additionally, average-risk patients who may not require genetic testing should be counseled on modifiable risk factors, such as changes in life style and preventative screenings.

Several professional societies are providing an increasing body of educational content and training regarding genetic testing and hereditary cancers. Societies including but not limited to the American Society of Clinical Oncology (ASCO), the American Society of Breast Surgeons (ASBS), the Society of Gynecologic Oncology (SGO) and the American College of Gynecology (ACOG), are enhancing resources

14. National Society of Genetic Counselors. Genetic Counseling Industry Statistics. 2014 Professional Status Survey: Executive Summary, 2014 PSS Full Infographic. <http://nsgc.org/p/cm/ld/fid=68>. Accessed June 16, 2015.

15. Gustafson S, Raymond V, Marvin M, et al. Outcomes of genetic evaluation for hereditary cancer syndromes in unaffected individuals. *Familial Cancer*, 14(1), 167-174. (2015). doi:10.1007/s10689-014-9756-x.



for their physician members who are seeking additional knowledge regarding the impact of genetics in the care of their patients.

Tertiary care centers can support rural area practices by employing a hybrid education model that incorporates online education, patient engagement and a coaching model. Remotely based genetic counselors can work together with local staff to stratify and counsel patients both virtually (via telemedicine) and through scheduled in-person visits.<sup>10</sup>

In her study, Stephanie Cohen also shows that genetic counseling via telephone or telemedicine are effective delivery systems of genetic information. While not yet widely adopted, these systems allow access to genetics expertise even for people in rural areas and those for whom in-person genetic counseling is not convenient or available. Some patients, however, prefer engaging with their existing and trusted health care provider face-to-face when discussing personal genetic information.

### Incorporating into practice

In clinical practice, it is important to create a workflow that makes risk stratification and testing manageable for health care professionals who are facing ever-increasing demands on their time. Nurses, nurse navigators and physician assistants trained in the identification of those at high risk for cancer can educate patients when physician time is limited.

Panel testing also requires that health care providers acknowledge and manage certain sensitivities, as not all patients may want to know their mutation status for all genes on the panel. Genetic counselors and other health care providers trained in genetics can help a patient decide if testing for a mutation in a single gene, multiple genes or an entire panel is right for them.

Incorporating genetic counseling and testing into clinical routine is valuable to patients and health care providers. Stephanie Cohen suggests in her study that continued exposure to genetic counseling tools and use of skills is important to maintain knowledge.<sup>10</sup> It also helps to standardize the process to ensure that patients who are determined to be high-risk and potentially tested are readily identified and managed according to NCCN guidelines and other standards of care.

Advocacy groups can support these efforts by partnering with health care facilities and practices to create educational materials and outreach groups for patients and health care providers. An example would be to pair advocacy group volunteers with trained social workers. Advocacy groups also can partner with physicians on how to proceed once patients are identified as high-risk or as candidates for counseling and testing.

**“Patients look to health care providers for answers, so it’s important to frame the conversation appropriately.”**

Jennifer Klemp, Cancer Survivorship Training

### Communicating results

It is important to assess each patient’s individual situation when a health care provider decides how to communicate the genetic test results. Ideally patients would receive their results in person with their health care provider and a genetic counselor available to help them process the implications of the results and guide them into the next steps and implications to the family.

In many cases, however, this ideal situation may not come to fruition due to distance, timeliness concerns, treatment decision-making concerns

or patient preference. In those cases, all options must be considered, including a telemedicine strategy with in-person follow up visits.

When health care providers communicate results to patients, it is critical to frame the conversation with a realistic but measured approach, including the possibility of test results revealing a VUS. One option is to delineate results through a black, white and gray framework. This analogy indicates that gray areas may not require drastic action now but are worthy of continued follow up based on the personal and family history of cancer. Visual decision trees that guide patients based upon positive, negative or uncertain results can be effective and provide a more realistic interpretation of results.

Test results must include education about increased risks associated with certain gene mutations. Next steps may include increased cancer screenings, preventive medication, preventive procedures or treatment.

Some surgeons, oncologists or other health care providers who are able to identify patients for testing may want additional support when reviewing the implications of the test results with the patient. If a genetic counselor is not available, a properly trained certified nurse, navigator or advanced practice provider might offer valuable service in this area.<sup>10</sup>

It also is important that patients are offered resources for additional counseling. Ideally health care practice teams would include an in-house genetic counselor or remote genetic counseling services. Specialized support resources may be available from patient advocacy organizations. Additionally, many genetic testing laboratories offer support services with genetic counselors to help answer general hereditary testing questions.

## BETH

Despite my family history of breast cancer and my mother and aunt testing *BRCA2*-positive, I didn't want to be tested. I agreed to talk with a counselor only because it was important to my mother. I was shocked when the counselor explained mastectomy as a preventative option. I grew agitated and wanted to RUN! Two weeks later, I learned I also carried the *BRCA2* mutation.

I first questioned the accuracy of the testing. Once I processed the information, part of me believed I would be in the smaller 13% of *BRCA* gene mutation carriers that do not get cancer, but in the end I decided on a prophylactic bilateral mastectomy.

Following surgery, to my surprise, my pathology report revealed a .9 cm ductal carcinoma in situ (DCIS) in my right breast that had been undetected in my mammogram three months prior, and undetected in my breast MRI nine months prior! It turns out I really dodged a bullet and am very, very lucky!!

My older sister tested one year later and her sense of relief at being negative revealed that she had unconsciously been carrying a heavy burden.

I am blessed to make proactive choices that spare me and my loved ones from larger pain and heartache down the road.

## COPING WITH RESULTS

### The emotional impact

Receiving genetic test results can provoke strong emotions in patients and family members, regardless of whether the results are positive or negative for increased hereditary cancer risk.

Sometimes, when patients learn that they have a hereditary risk for cancer, they experience guilt, thinking they may have passed the mutation to their children. They can experience spousal difficulties related to suddenly changed perspectives on having children and different viewpoints around preventive surgeries. On the other hand, when patients learn they are not at increased risk for hereditary cancer, they may feel guilt that they have a lower risk than other family members and may be uncertain about how to proceed.

Woven into this emotional maze is the fact that patients who undergo genetic testing do so for different reasons and at different points in their lives. Some who are tested may never have had a cancer diagnosis but are aware of a family history. Others have already been diagnosed with cancer and want to understand their risk for a second cancer, inform family members about potential risk or evaluate treatment options available.

While many patients appear to have positive feelings about their decision to test, the journey to that point may require some support. Psychosocial training is included in board-certified genetic counselor training programs, but patients might not realize they can access that aspect of genetic counselor services, or it may not be available to them due to constraints on access to genetic counselors.

Mental health professionals can help in coping with many of the concerns patients and families express around genetic testing. Additionally the Cancer Support Community, in partnership with the [American Psychosocial Oncology Society](#), offers a toll-free [Helpline](#) staffed by licensed mental health professionals who can provide over-the-phone counseling.

Finally, hearing other patient experiences through patient support groups, closed Facebook groups or message boards can be invaluable as individuals adjust to their new situation.

Health care providers should ensure that patients are aware of the various services and provide referrals to psychologists and mental health professionals as appropriate. Because advocacy organizations understand that cancer care extends beyond diagnosis and treatment, they are effective partners in ensuring that psychosocial issues, such as patient anxiety, family planning, sexual health and financial barriers, are included in the continuum of care.

### Educating patients

Educational materials can help patients understand more about cancer genetics and put their results into context. Information offered to patients should include the basics about genetics: what a gene is, what it does, why it matters and what happens if there is something wrong with the gene. It should also explain clearly how there may be familial risk apart from genetic risk.

Because of the complexity of the topic, it is important that patient education is written at a level accessible to those without higher levels of education. At the same time, care must be taken to not over-simplify such that patients become unduly alarmed on one hand or miss the need to explore preventive care options on the other hand. Information also needs

to incorporate the language differences and cultural contexts presented by the variety of constituents an organization represents.

**“We need educational resources that are accessible by all patients.”**

Travis Bray,  
Hereditary Colon Cancer Foundation

Educational materials should extend beyond the genetic mutations historically associated with one type of cancer. Educating broadly about hereditary cancer as a multi-cancer approach instead of specific syndromes like hereditary breast and ovarian cancer syndrome and Lynch syndrome is important when discussing multi-gene panel testing.

Materials should include basic information around the possibility of testing for a whole array of cancers and why knowing about other genetic mutations is important because of the increased risk for the development of cancer. A level of understanding related to the potential for other mutations and the overlap of certain syndromes, as well as the fact that family history alone may not be the most accurate predictor of which genes may be involved in causing cancer in a specific family, should be required of individuals or organizations educating patients and families.

If patients have already been diagnosed with cancer, materials should explain how testing can help guide their treatment decisions, how to inform family members or offer information on assessing risk for a subsequent cancer. Educational efforts can emphasize family history and encourage more complete documentation. They also can help patients distinguish between what is evidence-based and what isn't and delineate what is actionable now versus what could be actionable in the future.

Many families with a strong history of cancer may still test negative for known mutations on a hereditary cancer panel test. These families with “uninformative negative” results still need support and access to more frequent screening and other cancer risk management options indicated by their family history.

### A culture of support

Certain constituents may face stigmas in hereditary cancer testing and in taking preventive measures when results show a high risk for developing cancer. For example, in some cultures, family dynamics may prevent women from undergoing preventive surgery. Patients may worry about disappointing their families, or they may be discouraged from questioning the doctor or seeking a second opinion.

**“Information spreads through communities, gets passed to friends, relatives and neighbors, who are then more likely to suggest testing. It is a village effort.”**

Lori Flowers, Triple Step Toward the Cure

Many of these stigmas and roadblocks may be improved by a culture of support. For some communities, there is a “village” of support for identification, counseling, testing and appropriate treatment options. This effort can be initiated by providing patients and people who are close to them with information, which would then spread through communities and get passed to friends, relatives and neighbors. As the “village” effort creates a groundswell of educational support, advocates gain further support for their constituents' right to access testing. This support can include unaffected individuals, newly diagnosed patients and other patients at any time post-diagnosis.

Patient education should reflect a multi-disciplinary approach, including psychosocial oncology, fertility, integrative and primary care medicine, and focus on specific issues rather than body parts. Spousal support is an important element as couples work through difficult decisions related to having children and preventive surgeries. Psychosocial support can be useful in helping those who experience guilt believing they passed a genetic mutation to a family member.

Education can be provided in print, in person or over the phone or internet. Evening hours for in-person sessions may draw more participants, but it is important to offer multiple schedules and open sessions to all age groups and cancer types.

## ACCESS AND AFFORDABILITY OF MULTI-GENE PANEL TESTING

Because panel testing is relatively new, the access landscape is still evolving. For this reason, it is important that there be a focus on educating, advocating and ensuring broad insurance coverage and financial assistance are available.

“Taking a complete family history and simultaneously utilizing the data from cancer risk models can also help support coverage...”

Jennifer Klemp

In October 2014, the Cancer Support Community conducted a cross-sectional survey of adults affected by cancer as part of its Patient Access to Care Project. Twenty percent of respondents felt they did not have access to the care they needed, and the topmost concerns related to accessing genetic/biomarker

testing and counseling, accessing clinical trials and getting emotional support.<sup>16</sup>

Because panel testing is a critical health care tool and can be expensive, most patients depend on access through their health insurance. In some areas, insurance contracts and coverage policies will dictate the type of testing and laboratory available to patients. Some insurers have deemed panel testing as experimental; therefore, in order to keep up with the ever-changing landscape, data as well as patient demand and education are needed. In addition, providers need to be engaged and help ensure the right test is available to their patient.

Many insurers rely upon guidelines issued by organizations like the National Comprehensive Cancer Network (NCCN) to determine coverage policies. The NCCN has issued guidelines for assessing genetic or familial risk for breast and ovarian cancers, including Li Fraumeni and Cowden syndromes, and for colorectal cancers such as Lynch syndrome and polyposis syndrome (*FAP/APC/MYH*).<sup>17</sup> If patients meet the criteria established by a payer’s coverage policy, testing should be covered by their insurance. Guidelines, however, have been slow to assess multi-cancer panels, most likely due to the disease-specific structure of the organizations involved in developing guidelines.

In addition to NCCN, insurers may also look to U.S. Preventive Services Task Force (USPSTF) recommendations, especially for mandated Affordable Care Act (ACA) preventive benefits. The USPSTF is an independent, panel of experts charged with issuing preventive care recommendations based on existing evidence. The passage of the ACA put into place

16. Cancer Support Community. *Insight into Patient Access to Care in Cancer*. March 2015. <http://www.cancersupportcommunity.org/General-Documents-Category/Policy/Insight-into-Patient-Access-to-Care-in-Cancer.pdf>. Accessed June 16, 2015.

17. National Comprehensive Cancer Network. *NCCN Guidelines*. [http://www.nccn.org/professionals/physician\\_gls/f\\_guidelines.asp](http://www.nccn.org/professionals/physician_gls/f_guidelines.asp). Accessed June 16, 2015.

comprehensive health insurance reforms aimed to improve the quality of health care while making it more affordable and accessible.

To date, the only genetic testing with a USPSTF rating that is high enough to be a required preventive benefit under the ACA is BRCA testing. This recommendation does not include unaffected men who can also get breast cancer, and it does not consider the application of multi-gene panels for the same purposes. As multi-gene hereditary multi-cancer panels continue to rise in use, USPSTF will need to consider their benefits to preventing cancers beyond just those triggered by a BRCA mutation.

“We are making progress under the EARLY Act...”

Lisa Schlager, FORCE

Sometimes there is a need to genetically test patients whose cancer family history may not be definitive for a specific syndrome but rather may overlap more than one syndrome. In this case, a multi-gene panel test will prove most informative but may not fall within NCCN guidelines. Securing insurance coverage in these cases can present challenges. Health care providers and genetic counselors can increase the chances of testing coverage through detailed documentation and quality risk assessments.

Even when patients meet guidelines, sometimes their physician-recommended testing is still denied by their insurer. One advocacy group, Facing Our Risk of Cancer Empowered (FORCE), is developing a post-ACA insurance survey, which will help quantify how frequently genetic testing coverage is denied. This will be shared with partner organizations including the Young Survival Coalition, Ovarian Cancer National Alliance, National Ovarian Cancer Coalition and other groups supporting the cancer community.

Patients who need testing but are without insurance coverage may be able to explore other options for financial assistance, such as laboratory-sponsored patient assistance programs. There also are patient advocacy organizations that sponsor programs, which provide financial assistance directly to patients.

### Bolstering access through direct education of patients, providers and payers

There is a need for patient education on how to approach industry, insurers and providers for help with access. Patient advocacy groups are acutely aware of this need based upon their experience and conversations with their constituents. They can offer valuable resources to health care providers and patients through resources, such as letters of medical necessity, that provide a structured path in assessing and documenting need.

Information for insurers on the need for and benefits of genetic testing, together with compelling documentation can be a valuable tool in building a case for insurance coverage of multi-gene cancer panels. Additionally, resource guides for patients that identify industry-supported patient assistance programs (such as the Patient Advocate Foundation) that work with insurance providers or offer financial assistance can help those patients whose insurers do not provide access or who cannot otherwise afford testing.

### Addressing public policy challenges

It is important that patient advocacy organizations take an active role in ensuring that accurate information is being communicated to policymakers and stakeholders responsible for developing guidelines and coverage policies as they may not have expertise at a specialized level. For example, there have been cases where proposed guidelines recommended testing at too late an age based

on the average age of diagnosis for hereditary cancer patients. Advocacy organizations have reported a favorable response when clarifying information is provided.<sup>18</sup>

“We just wrote a letter to the US Preventive Services Task Force. The response was positive and immediate.”

Calaneet Balas, OCNA

Advocacy organizations must continue to raise their voices with data and support for positions on issues that impact patients and their families, such as the recently debated modifications to the Genetic Information Nondiscrimination Act (GINA) or the Education and Awareness Requires Learning Young (EARLY) Act aimed toward identifying BRCA-positive women at younger ages.

Another valuable tool that advocacy organizations can offer is a scorecard, which can be instrumental in driving change in the public policy realm. The advocacy group Ovarian Cancer National Alliance recently published a state report card that analyzes patient access to care on ten points and includes recommendations for each state.

As of this writing, there are numerous public policy issues at the forefront. Several advocacy organizations are actively working to ensure fair, unbiased and appropriate access to genetic testing.

- **USPSTF Guidelines on Breast Cancer Screening.** USPSTF recently released new draft guidelines on Breast Cancer Screening designed to replace 2009 guidelines. Several aspects of the proposed guidelines may worsen existing disparities, lead to confusion and endanger women in high-risk populations.
- **Bill to Exempt Employee Wellness Plans from Certain Americans with Disabilities Act and GINA Protections.** A bill recently introduced in Congress proposes changes to the Americans with Disabilities Act and GINA to permit employer-sponsored wellness programs to financially penalize or reward employees to answer personal and family health history questions in a health risk assessment questionnaire or physical exam. The changes would allow for penalties of up to 30 percent of one’s insurance premium for non-participation.
- **USPSTF Guidelines for BRCA Risk Assessment, Genetic Counseling, and Genetic Testing.** There are significant gaps in the guidelines, which are resulting in the inability of a portion of the population to access genetic counseling, testing and preventive services, including women with active disease.
- **Lack of USPSTF Guidelines for Screening and Cancer Risk Management:** Risk-management options such as breast MRI or prophylactic surgeries are not rated by USPSTF, which is significant since insurers are not obligated to pay for these unless they receive a rating of a certain grade.
- **Medicare and Medicaid Coverage of Genetic Counseling, Genetic Testing and Preventive Services.** In contrast to the USPSTF guidelines, Medicare will only cover genetic counseling and testing for women who have or have previously had breast or ovarian cancer and meet specific family history criteria consistent with NCCN guidelines for hereditary cancer. This leaves out “unaffected carriers” with a known mutation in the family or simply with significant family history unless Congress adds the benefit or Medicare issues a national coverage determination.

18. Ovarian Cancer National Alliance. Letter to United States Preventive Services Task Force regarding Draft Research Plan – Ovarian Cancer: Screening, dated April 20, 2015.

## CALL TO ACTION: MULTI-CANCER HEREDITARY CANCER CONSORTIUM

The groups convened for this discussion readily recognized the changing landscape of and the move toward multi-gene panel testing for patients versus single-syndrome testing for hereditary cancer risk. They voiced a strong desire to collaborate to ensure understanding of this expanding area and access to genetic counseling and testing.

**“We need to collaborate with each other. We have overlap with constituents and related diseases...”**

David Barley, NOCC

Recognizing the overlap of patients in this multi-cancer world, the organizations expressed the wish to align their approach in addressing challenges facing patients regardless of cancer type, including psychosocial aspects, preventive surgeries, difficult family conversations and more. Such a collaboration would allow the expansion in the number of patients reached and should be open to membership for all national organizations, professional societies and agencies that share an interest in hereditary cancer. This endeavor could also be open to companies across the industry for sponsorship.

A collaboration would look to examples of existing, successful multi-cancer collaborations, including the Cancer Insurance Checklist whose standalone website was created following the Institute of Medicine report on Cancer Care for the Whole Patient. The [Cancer Insurance Checklist](#) was comprised of 35 partners and supporting organizations and sponsored by a pharmaceutical company. The [Alliance for Quality Psychosocial Cancer Care](#), an informal coalition of professional and advocacy

organizations engaged in providing a range of services to cancer patients and survivors, also was created following the IOM report and has 33 members to date. Similarly the [Metastatic Breast Cancer Alliance](#), includes 34 Advocate Members and support from many pharmaceutical companies with treatments for breast cancer.

### Vision

The groups envisioned coming together at a very high level on a neutral website to offer educational materials applicable to hereditary cancers, including but not limited to colon cancer, breast and ovarian cancer syndromes. Each organization would provide resources so that the information would be available when patients are ready to access it. Resources could include existing information available via webinars, books and publications. For information about a specific hereditary cancer, patients would be directed to the appropriate cancer specialty group(s).

**“We can take a patient-centered point of view that cuts through industry siloes.”**

Sarah Storey, Bright Pink

The information would be patient-centric and consumer-friendly. It would account for a wide range of diversity in geography, ethnicity, education, gender, age, culture and cancer status. The collaboration potentially would include access to telephone-based, in-person or other type of real-world support in addition to social media and mobile-based components. Additionally, the collaboration would offer support to families and communities.



The resources would incorporate a feature through which site visitors could tag certain pieces of information from the consortium website and other websites for storage in personal profiles. The consortium would score external Web materials for reliability.

Topics, packaged into toolkits, would include where to access financial support, peer-support and patient journey information.

The idea of including genetic counseling specialists, oncologists and other resources for patients was suggested in addition to the possibility of adding resources for health care providers in the future.

The group also discussed potentially working together on policy issues, registries and other mutually beneficial initiatives as part of collaboration.

## Considerations

In discussing a potential consortium, the group identified the following requirements:

- Neutral, organizing body and staff to manage day-to-day; funding sources
  - It was recognized that the patient advocacy organizations have limited staffing and financial resources so the idea of resources and funding via genetic testing labs or other private industry such as pharmaceutical companies was proposed.
- Assessment of needs to organize and focus the effort
- Continual flow of updated information
- Content decision; editorial voice or clearinghouse
- Sustainability; nothing static or one-time

This was the first time representatives of various cancer groups were brought together to address the pros and cons of the growing availability of multi-gene, hereditary multi-cancer panel testing and the impact on patient outcomes. Participants agreed on the need for a united approach to act as a resource and educate, helping all cancer patients and those at risk. More assessment on the viability of this collaboration is needed and will be a future direction for this group.

## GLOSSARY

### Clinically significant<sup>19</sup>

Clinical significance refers to the practical or applied value or importance of the effect of an intervention—that is, whether the intervention makes a real (e.g., genuine, palpable, practical, noticeable) difference in everyday life to the clients or to others with whom the clients interact.

### Colorectal cancer<sup>20</sup>

Colorectal cancer is a term for cancer that starts in either the colon or the rectum. Colon cancer and rectal cancer have many features in common.

### Cowden syndrome<sup>21</sup>

Cowden syndrome is a disorder characterized by multiple noncancerous, tumor-like growths called hamartomas most commonly found on the skin and mucous membranes and an increased risk of developing certain cancers, often beginning at a young age, when patients are in their thirties or forties.

### DNA

Stands for deoxyribonucleic acid, a chemical used by living things to pass characteristics (called traits) from one generation to the next. DNA is often compared to a set of blueprints, a recipe or a code that contains genetic instructions used in the development and functioning of living organisms.

### DNA Sequencing

Determining the exact order of the base pairs in a segment of DNA. Sequencing can be used to detect disease-causing mutations.

19. <http://htomepage.psy.utexas.edu/homepage/class/Psy394Q/Research%20Design%20Class/Assigned%20Readings/Clinical%20Trials/Kazdin99.pdf>

20. <http://www.cancer.org/cancer/colonandrectumcancer/overviewguide/colorectal-cancer-overview-what-is-colorectal-cancer>

21. <http://ghr.nlm.nih.gov/condition/li-fraumeni-syndrome>

### Gene

A segment of DNA that contains the instructions to make a specific protein (or part of a protein). Genes are contained on chromosomes. Chromosomes, and the genes on those chromosomes, are passed on from parent to child. Errors in the DNA that make up a gene, also called mutations, can lead to diseases.

### Genetic mutation<sup>22</sup>

A gene mutation is a permanent alteration in the DNA sequence that makes up a gene, such that the sequence differs from what is found in most people.

### Genetic Counseling

A short-term educational counseling process for people and families who have or are at risk for a genetic disease. Genetic counseling provides patients with information about their condition and helps them make informed decisions.

### Genetic Testing

A test that analyzes DNA for changes or alterations.

### Hereditary

Something is typically called hereditary if it is something you are born with. Traits you inherit from your parents such as eye color, height or a risk for certain diseases, are passed from parent to child by information contained in genes. Sometimes diseases caused by a hereditary increased risk are also called “hereditary” (e.g., one is not born with breast cancer, but breast cancer caused by hereditary increased risk is called “hereditary breast cancer”).

22. <https://www.mskcc.org/blog/should-i-consider-multigene-panel-testing>

23. <http://ghr.nlm.nih.gov/handbook/testing/interpretingresults>

24. <http://ghr.nlm.nih.gov/handbook/genomicresearch/sequencing>

25. <http://ghr.nlm.nih.gov/handbook/testing/interpretingresults>

26. <http://ghr.nlm.nih.gov/handbook/genomicresearch/sequencing>

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## Hereditary Mutation

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A gene change in reproductive cells (egg or sperm) that becomes incorporated into the DNA of every cell in the body of offspring; hereditary mutations are passed on from parents to offspring. Also called germline mutation.

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## Inherit

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Acquiring a trait from one's parents. Traits such as eye color or hair color are inherited from a parent through genes.

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## Li Fraumeni syndrome<sup>23</sup>

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Li-Fraumeni syndrome is a rare disorder that greatly increases the risk of developing several types of cancer, particularly in children and young adults. Cancers most often associated with Li-Fraumeni syndrome include breast cancer, osteosarcoma and soft tissue sarcomas. Other cancers commonly seen in this syndrome include brain tumors, leukemias and adrenocortical carcinoma. Several other types of cancer also occur more frequently in people with Li-Fraumeni syndrome.

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## Lynch syndrome

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Lynch syndrome, also known as Hereditary Nonpolyposis Colorectal Cancer (HNPCC), is the most common of the hereditary colon cancer syndromes and is believed to account for 3% to 5% of all colorectal cancers.

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## Multi-gene panel testing<sup>24</sup>

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The multigene — also called multiplex — technology introduced in the United States in 2013 enabled researchers to simultaneously examine dozens of cancer genes at a cost that is comparable to that of tests for individual genes. Previously doctors and researchers looked at the inheritance of one potentially cancer-causing mutation at a time.

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## Mutation

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A harmful change (or alteration) in a gene that can be responsible for causing cancer or other disorders.

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## Negative genetic test result<sup>25</sup>

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A negative test result means that the laboratory did not find a change in the gene, chromosome, or protein under consideration. This result can indicate that a person is not affected by a particular disorder, is not a carrier of a specific genetic mutation or does not have an increased risk of developing a certain disease.

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## Positive genetic test result<sup>25</sup>

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A positive test result means that the laboratory found a change in a particular gene, chromosome, or protein of interest. Depending on the purpose of the test, this result may confirm a diagnosis, indicate that a person is a carrier of a particular genetic mutation, identify an increased risk of developing a disease (such as cancer) in the future, or suggest a need for further testing.

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## Sanger sequencing<sup>26</sup>

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Determining the order of DNA building blocks (nucleotides) in an individual's genetic code, called DNA sequencing, has advanced the study of genetics and is one method used to test for genetic disorders. The original sequencing technology, called Sanger sequencing (named after the scientist who developed it, Frederick Sanger), was a breakthrough that helped scientists determine the human genetic code, but it is time-consuming and expensive.

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## Single syndrome testing<sup>24</sup>

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Genetic tests that evaluate one potentially cancer-causing mutation at a time.

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## Unaffected individual

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Someone who has not been diagnosed with cancer

## RESOURCES

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### Bright Pink

<https://www.brightpink.org>

### Cancer Support Community

<http://www.cancersupportcommunity.org>

### Cancer Survivorship Training

<https://www.cancersurvivorshiptraining.com>

### Colon Cancer Alliance

<http://www.ccalliance.org>

### Fight Colorectal Cancer

<http://fightcolorectalcancer.org>

### Facing Our Risk of Cancer Empowered

FORCE, <http://www.facingourrisk.org/index.php>

### Hereditary Colon Cancer Foundation

<http://www.hcctakesguts.org>

### Li-Fraumeni Syndrome Association

<http://www.lfsassociation.org/what-is-lfs/>

### Living Beyond Breast Cancer

<http://www.lbbc.org>

### National Ovarian Cancer Coalition

<http://www.ovarian.org>

### Ovarian Cancer National Alliance

<http://www.ovariancancer.org>

### Stupid Cancer

<http://stupidcancer.org>

### Triple Step Toward the Cure

<http://triplesteptowardthecure.org>

### Young Survival Coalition

<https://www.youngsurvival.org>