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Navigating New Developments in Cancer Genetic Testing: Science and Informed Consent in the Era of Multi-Gene Panels

BY JULIE S. MAK, MS, MSC, LCGC

"The times they are a-changing'"

—Bob Dylan

The majority of cancers are caused not by inherited genetics, but rather by a combination of aging, environment, and chance. Inherited risk factors are relatively rare, affecting about one percent of people in general and about five to ten percent of cancer patients. However, identifying people who have inherited risk factors can be a powerful tool for targeted cancer treatments, and ideally, for early detection and prevention of cancer in your patients and their relatives.

WHO SHOULD UNDERGO GENETIC TESTING?

Traditionally, the strategy for genetic testing began with identifying people at high risk based on their personal and family histories. Classic signs of inherited cancer risk include

- early-onset cancers, e.g. breast or colon cancer under age 50
- multiple primary cancers, including bilateral breast cancer
- rare cancers, e.g. ovarian and fallopian tube cancers, male breast cancer
- family history of the same or related cancer types, e.g. breast and ovarian cancer, colon and endometrial cancer

These signs are still important to recognize, as they will aid in identifying high-risk families where genetic testing is most likely to make a difference. These factors also affect insurance coverage of genetic testing.

Yet family history has limitations that may include small family size or limited communication between family members. So although a strong personal or family history of cancer is still the most important indicator of possible hereditary risk and is still required for insurance coverage, advances in genetic testing technology ("next generation" or "massively parallel" sequencing) has made the self-pay cost of genetic testing as low as $250. This makes it financially feasible to offer sophisticated genetic testing for any individual who has a desire to learn more about their genetic risk for developing cancer.

At this time, it still makes sense to focus clinician time and insurance coverage on counseling and testing patients who meet the high-risk criteria defined by the National Comprehensive Cancer Network (NCCN) and other organizations, as well as those who have tested positive for increased genetic risk. For people without traditional indications for testing, there are unanswered questions about how to use testing resources as well as how to apply some of the data derived from high-risk families. However, it is important to be aware of the expanded opportunities for testing for individuals who are motivated to pursue it. A related point to be aware of is that patients may now come into the health care system with testing they have done through less conventional channels. Depending on the source of information, some of these tests should be repeated in traditional testing laboratories.

FINDING THE RIGHT TEST

Many physicians refer to genetic counselors for genetic testing. This helps ensure that their patients are provided with the latest information and test options and that the patients are given the time to consider detailed information about the implications of genetic testing.

Whether you are referring to specialists or managing testing in your own practice, it is important to understand the testing options that have emerged in the last five years. The

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same DNA sequencing technology that has driven down the cost of testing has also fueled an enormous expansion in test offerings. The standard in genetic testing is shifting from single-gene testing (such as BRCA1 and BRCA2) to multi-gene panels. These panels examine 20 to more than 50 genes at a time. Multi-gene panels became commercially available in 2012 and took off in 2013 after the Supreme Court of the United States ruled that human genes could not be patented.

Multi-gene panels have several advantages. They provide the most complete genetic risk assessment for your patient, with the highest chance of either identifying an inherited mutation or, conversely, the greatest reassurance in ruling out major inherited risk factors. Multi-gene panels are also cost-efficient, as most insurance plans will pay for genetic testing only once for a specific indication.

The range of test offerings is a moving target that changes frequently. Two broad considerations are: (1) a cancer-specific panel vs. one that includes genes for multiple types of hereditary cancers, and (2) a panel focused on more well-known and high-risk mutations (generally 20-40 genes) vs. an expanded panel (50 or more genes).

There are a couple of key lessons in the data from the first few years of panel testing. The first is that most common indications for cancer genetic testing include a differential of multiple genes as in breast cancer (BRCA1, BRCA2, ATM, CDH1, CHEK2, PALB2, PTEN, STK11, TP53) or colon cancer (APC, EPCAM, MLH1, MSH2, MSH6, PMS2, GREM1, POLE, POLD1). This means that to fully assess for potential inherited risk for a particular cancer, testing should include multiple genes.

The other lesson is that the clinical indication does not always match the genetic diagnosis, indicating that the spectrum of cancer in most syndromes is wider than previously thought. For example, in a 2016 study of over 10,000 cases referred for evaluation of germline cancer genes among patients who had a breast cancer history and a germline mutation, 39 percent of the mutations were in BRCA1 and BRCA2 and 11 percent were in Lynch Syndrome genes or other high risk genes, but 50 percent were in moderate or unknown risk genes. Although these and other findings support the use of multi-gene panels and the selection of cross-cancer panels over cancer-specific panels, the benefit of expanding the panels beyond 20 to 40 genes for most patients is still under study.

INFORMED CONSENT IN THE MULTI-GENE PANELS ERA

While multi-gene and cross-cancer panels are arguably the preferred test in most cases, they create their own additional challenges. One of them is informed consent. The topic of informed consent for cancer genetic testing is addressed by practice guidelines from multiple professional societies, including the American Society of Clinical Oncology, the American Society of Human Genetics, and the American College of Obstetricians and Gynecologists. Some questions to consider when giving informed consent for genetic testing include:

- When is the testing being done relative to the expected time of onset of the disease process? For example, there are

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Some Broad Categories of Genes Found on Typical Multi-gene Panels

Risk/Prevalence	Gene	Cancers Associated with a mutation
High-risk, more common	BRCA1, BRCA2	Female breast, ovarian, male breast, prostate, pancreatic, melanoma
	Lynch Syndrome (MLH1, MLH2, MSH6, PMS2, EPCAM)	Colon endometrial, ovarian, small bowel, sebaceous carcinoma, other
	APC, MUTYH (recessive)	Colon polyposis and cancer
High-risk, rare	TP53 (Li-Fraumeni Syndrome)	Breast, sarcoma, leukemia, brain, adrenocortical, other
	PTEN (Cowden Syndrome)	Breast, thyroid, endometrial, other
	CDH1	Diffuse gastric, lobular breast
	STK11 (Peutz-Jeghers Syndrome)	Gastrointestinal, breast, pancreas
	BMPR1A, SMAD4	Colon juvenile polyps and cancer
	CDKN2A, CDK4	Melanoma (for CDKN2A, pancreatic)
Moderate or undetermined risk	PALB2	Breast, pancreatic
	ATM	Breast, possibly others
	CHEK2	Breast, colon, prostate, possibly others
	BRIP1, RAD51C, RAD51D	Ovary, possibly breast
	BARD1, NBN	Breast, possibly ovary
	GREM1, POLD1, POLE	Colon polyps and cancer

California and Physician Assisted Dying: What Should Physicians Know?

BY RUCHIKA MISHRA, PHD

In 2016 California became the fifth state in the country to implement a law on physician assisted dying. The End of Life Option Act (ELOA)[1] allows terminally ill patients to request a medication from their physician that would aid them in their death. The year the law was passed, a survey of 1,097 Californians showed that 76 percent of the respondents across the political and demographic spectrum supported the practice. The law enables a specific and detailed process with required forms, reporting mechanisms, and explicit eligibility requirements for patients.

Physician Participation

Participation is voluntary for providers. This means that any physician, health care facility, health system, health care plan, or pharmacy can opt out. Participation not only includes being a part of the process but also extends to providing information. Physicians may decline to participate for reasons of conscience, morality, or ethics. For non-participating physicians, there is no duty to transfer care to an ELOA participating physician; however it is crucial that the patient does not feel abandoned during the process and that the physician-patient relationship remains intact.

Patient Qualifications

Patients need to meet specific eligibility criteria to qualify under the law. The patient must be an adult California resident with medical decision-making capacity who has a terminal illness (an incurable and irreversible illness that has been medically confirmed and will, within reasonable medical judgment, result in death within six months). The patient also needs to have the physical and mental ability to self-administer the aid-in-dying drug. The patient has to make the request voluntarily and cannot use friends, family, caregivers, legally-appointed medical decision makers, an Advance Directive, or POLST form to make the request.

ELOA Process

The patient's Attending Physician (a physician with primary responsibility for the health care of the patient and treatment of their terminal illness) confirms the diagnosis, prognosis of terminal illness, and patient's capacity to make medical decisions and ensures the patient qualifies under the law. The patient is required to make two oral requests to their Attending Physician 15 days apart followed by a witnessed written request in a statutory form. All three voluntary requests must be received directly by the Attending Physician. The requests also must be made without the presence of others except if an interpreter is needed. The physician needs to ensure that the patient is making an informed decision, including an understanding and acknowledgment of the relevant facts, medical diagnosis and prognosis, potential risks associated with taking the drug to be prescribed, probable result of taking the drug to be prescribed, and feasible alternatives or additional treatment opportunities, including comfort care, hospice care, palliative care, and pain control.

The patient is then referred to an independent, qualified Consulting Physician who confirms the diagnosis, prognosis, and capacity. If there are any concerns about the patient's ability to make medical decisions, the patient must be referred to a mental health specialist (psychiatrist or a licensed psychologist) for evaluation.

If the patient wishes to proceed, the Attending Physician may provide the aid-in-dying drug by either dispensing it directly to the patient or by delivering the prescription to a participating pharmacist. The patient also must be provided with the Final Attestation Form and the Attending Physician is to instruct the patient about completing the form 48 hours prior to ingesting the drug.

Documentation and Reporting

The Attending Physician must comply with all documentation requirements and submit all necessary forms. This includes the Attending Physician Checklist and Compliance Form as well as the Consulting Physician Compliance Form. The Attending Physician must submit copies of both the Attending and Consulting Compliance forms and the patient's written request to the California Department of Public Health within 30 days of writing the prescription. The Attending Physician Follow-Up Form must be completed within 30 calendar days of the patient's death.

Administration of Drugs

The law allows for another individual to assist the patient with the preparation of the medication to be administered. However, the patient must self-administer the drug. Individuals who assisted the patient with the preparation of the medication are legally protected as long as they do not assist the patient with administering the lethal medication.

Legal Protection

Physicians are protected from civil and criminal liability if they choose to participate in the law. They shall not be subject to censure, discipline, suspension, loss of license, loss of privileges, loss of membership, or other penalty for participating in good faith compliance with the law or for refusing to participate. Additionally, a health care provider shall not be subject to civil, criminal, administrative, disciplinary, employment, credentialing, professional discipline, contractual liability, or medical staff action, sanction, or penalty or other liability for participating in the law. No actions taken in compliance with the provisions of the law shall constitute a claim of neglect or elder abuse.

Legal Challenges

In May, a Superior Court judge in Riverside County ruled that the law was unconstitutional. The California Attorney General immediately appealed the decision, and the Fourth District Court of Appeals in Riverside re-instated the law—at least as *PRF News* went to press. Like other politically and emotionally-charged health care issues, this may take some time to reach a final resolution. ■

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cautions about testing minors for risk of adult-onset cancers.

- What are the cancer risks associated with a positive result and what are the options for cancer surveillance and prevention?
- What are the implications for cancer risk in family members? Court cases have set the precedent of a "duty to warn" in situations where family members other than the patient may be found to have an increased cancer risk.

With the introduction of panel testing, additional topics that need to be addressed in pre-test informed consent and/or post-test counseling include:

- Acknowledgement that panels include a wide range of genes and that mutations in these genes vary widely with regard to the associated cancers and the level of risk. For example, mutations in some genes are linked to breast cancer risk without ovarian cancer risk or vice versa, or the level of risk may be lower, and thus recommendations for risk-reducing surgery vary.
- As shown in the table on page 2, there is limited and evolving information about mutations in some genes.
- A patient's personal and family history may not be consistent with mutations identified through testing.
- Panels have a higher rate of mutations of uncertain clinical significance.

In all circumstances, but particularly when there is a mutation in a moderate-risk gene and/or a gene that is not consistent with your patient's history, it is important to consider both family history and genetic test results in forming a management plan. Genetic counselors are experienced at integrating this information, including factoring in statistical risk models and partnering with specialists in breast, gastrointestinal, and gynecologic oncology, as well as other specialties, to develop an individualized plan for each family. Additionally, most genetics clinics have a mechanism for long-term followup, so patients can benefit from the latest data on genes, cancer risk, and management.

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Variants (mutations) of Uncertain Significance (VUS) are common with large multi-gene panels and are found in 20 to 50 percent of test results. While it is tempting to try to attribute meaning to these findings, it is important to know that 90 to 95 percent of these mutations that are reclassified turn out to be benign; they simply represent normal variation between humans that had not been fully described at the time of testing. In most cases, the recommended course of action is to treat your patient based on his or her medical history, and not the VUS. Genetic counselors or other specialists, including those based at the genetic testing laboratory, are good resources for evaluating genetic test results, including those with a VUS.

KNOW YOUR RESOURCES

Because cancer genetics is changing quickly, it is important to know where to look for assistance with complex cases and to keep up with the latest updates in genetic science.

All major cancer centers now provide dedicated cancer genetics clinics, where genetic counselors, physicians, nurse practitioners, and researchers work together to interpret and evaluate the complex data generated by multi-gene genetic panel testing. These clinics are an excellent resource for patient referrals, peer consultations, and continuing education.

Genetic testing laboratories are highly specialized, and their staffs include genetic counselors, MDs, and PhD scientists who often provide individual consultations and continuing education opportunities.

Multiple professional societies review new genetic information and make recommendations about genetic testing and medical management of patients with inherited risk. The most detailed guidelines can be found by clicking the NCCN Guidelines tab at www.nccn.org and further clicking on "Detection, Prevention, & Risk Reduction" for "Genetic/Familial High-Risk Assessment: Breast and Ovarian" and "Genetic/Familial High-Risk Assessment: Colorectal."

Finally, none of this progress would have been made without research. Many major cancer centers offer patient registries that include mechanisms for research as well as long-term followup and clinical trials opportunities for patients. PROMPT (Prospective Research on Multiplex Testing) is a national registry studying the outcomes of multi-gene panel testing. I encourage you to connect your patients to these resources for the benefit of their long-term medical care and that of their families. ■

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