

Cancer genetic testing: applying scientific discovery to clinical practice

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Twenty years ago, incorporating genetic test results in clinical oncology practice would have seemed revolutionary. However, discoveries in cancer genetics today have, in some cases, become fully integrated into clinical care. The National Comprehensive Cancer Network has developed practice guidelines for detection, prevention, and risk reduction for patients with multiple hereditary cancer syndromes. The American Society of Clinical Oncology has published a policy statement on genetic testing for cancer susceptibility. Many cancer genetic tests are widely available clinically, and some are even marketed directly to consumers and are available for order over the Internet. Even with the improved accessibility and visibility of cancer genetic testing, there is much to learn through cancer genetics research, and there are many tests still not available outside research protocols.

The National Human Genome Research Institute defines a genetic test as “the analysis of human DNA, RNA, chromosomes, proteins, and certain metabolites in order to detect heritable disease-related genotypes, mutations, phenotypes, or karyotypes for clinical purposes.”¹ With regard to cancer genetics specifically, genetic testing is often employed for the purposes of clarifying the risk of a hereditary cancer syndrome in a patient and his/her family. A young woman with breast cancer and a family history of ovarian cancer might undergo testing for mutations in the *BRCA1* and *BRCA2* genes, for instance, to determine whether she has hereditary breast and ovarian cancer syndrome. A positive test result (indicating the presence of a germline *BRCA* gene mutation) could affect her surgical decisions and choice of surveillance options, as well as the level of risk for her relatives.

Clinical genetic testing

Regulation

Tests used in clinical practice (like *BRCA* gene testing [Table 1]) are generally performed in laboratories certified by the Clinical Laboratory Improvement Amendments (CLIA), which are regulated by the Centers for Medicare and Medicaid Services. CLIA aimed to improve Federal oversight of clinical laboratory processes and set quality standards that the laboratories must meet based on the laboratory’s specialty. However, many have criti-

cized CLIA’s gaps in governance when it comes to genetic testing. One criticism of the CLIA certification system is that there are no guidelines specific to a general “genetics” specialty. Therefore, the current system does not cover all of the special considerations that should be taken into account to ensure appropriate procedures, techniques, and interpretation of genetic tests. Laboratory directors often voluntarily perform proficiency testing, for instance, but it is not based on Federal regulatory standards.

The College of American Pathologists (CAP) has inspection guidelines for molecular labs and has additional performance requirements that exceed the scope of CLIA to increase quality control and assurances. Most commercial laboratories that offer cancer genetic testing are CLIA/CAP-certified. (In order for a laboratory to receive payment for billed services from Medicare and Medicaid, it must be certified by CLIA.) Not all laboratories offering direct-to-consumer genetic testing—that is, genetic testing that can be ordered directly by a patient without physician referral—are subject to this regulation. The risk related to these unregulated labs marketing unvalidated genetic tests is a concern being addressed by some state public health departments and will soon be investigated by the US Food and Drug Administration.^{2,3}

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Ordering

The American Society of Clinical Oncology (ASCO) recommends that genetic testing be conducted only in the setting of pre- and post-test counseling.⁴ It is generally required that individuals undergoing genetic testing for hereditary cancer syndromes provide written informed consent. Pretest counseling should include a description of the test to be ordered including its accuracy and possible outcomes, as well as the risks, benefits, limitations, and implications of testing.

Clinical genetic testing can be billed to a patient's insurance provider. In many cases, insurance companies have predetermined criteria for the coverage of genetic testing; appropriately tested individuals often face little out-of-pocket expense. The cost of genetic testing varies greatly and often depends on the nature of the test. Complete gene analysis in a family in which a hereditary cancer syndrome has yet to be identified can often cost more than \$1,000. In some cases, it is necessary to test multiple genes. In this scenario, the total cost of testing can be several thousand dollars. However, the cost of genetic testing decreases dramatically when a patient's family has been identified as carrying a specific gene mutation. In this case, the cost of testing for the family's specific mutation is usually less than \$500.

Reporting results

Simplistically, a clinical genetic test is classified as one in which the test was performed in a CLIA-certified laboratory and results are provided via written report given directly to the ordering clinician for the purposes of medical management. Clinical tests must have a reasonable turnaround time. Typically, test results are available in 2–8 weeks. A genetic test result report should contain basic information about the test performed as well as the predictive value of the re-

sult and interpretation. The result interpretation should be reviewed by a clinician who has expertise in cancer genetics and who is capable of incorporating the test result as well as other clinically relevant details into tailored recommendations for the patient. The

clinician will present options for cancer risk reduction and disease management based on the patient's medical and family histories and will work with other members of the oncology care team to arrange for appropriate cancer screening and surveillance.

TABLE 1

Cancer genetic tests available in the clinic

Disease/syndrome	Gene(s)
Ataxia telangiectasia	ATM (ATM1–ATM3)
Autoimmune lymphoproliferative syndrome	CASP8, CASP10
Beckwith-Wiedemann syndrome	11p15.5 del, KCNQ1OT1, CDKN1C, H19
Birt-Hogg-Dubé syndrome	FLCN (alias BHD)
Blackfan-Diamond syndrome	LRP2 (alias DBS), RPS19, RPS24
Bloom's syndrome	BLM
Carney complex	PRKAR1A
Costello syndrome	HRAS
Familial adenomatous polyposis	APC
Fanconi anemia	FA (FANCA–FANCL)
Hereditary breast/ovarian cancer	BRCA1, BRCA2
Hereditary diffuse gastric cancer	CDH1
Hereditary leiomyomatosis and renal cell carcinoma	FH
Hereditary melanoma	CDKN2A/p16, CDK4
Hermansky-Pudlak syndrome	HPS1, HPS3, HPS4
Juvenile polyposis syndrome	BMPR1A, SMAD4 (MADH4)
Li-Fraumeni syndrome	TP53
Lynch syndrome (HNPCC)	MLH1, MSH2, MSH6, PMS2
Multiple endocrine neoplasia 1/2	MEN1, MEN2, RET
MYH-associated polyposis	MYH
Neurofibromatosis 1/neurofibromatosis 2	NF1, NF2
Nevoid basal cell carcinoma syndrome	PTCH
Nijmegen breakage syndrome	NBS1
Papillary renal carcinoma	MET
Paraganglioma-pheochromocytoma syndrome	SDHB, SDHC, SDHD
Peutz-Jeghers syndrome	STK11 (LKB1)
PTEN hamartoma tumor syndrome (Cowden/Bannayan-Riley-Ruvalcaba syndrome)	PTEN
Retinoblastoma	RB
Rothmund-Thomson syndrome	RTS, RECQL5
Shwachman-Bodian-Diamond syndrome	SBDS
Tuberous sclerosis complex	TSC1, TSC2
Von Hippel-Lindau syndrome	VHL
Wilms' tumor	WT1, WT2
Xeroderma pigmentosa	XPA, XPC, DDB2, ERCC2, ERCC3, ERCC4, ERCC5

HNPCC = hereditary nonpolyposis colorectal cancer

Research-based genetic testing

Although clinical genetic testing for mutations in some genes like *BRCA1* and *BRCA2*, which are associated with hereditary breast and ovarian cancer syndrome, has been available for many years, genetic testing for some familial cancers still only remains possible through research protocols. Additionally, studies suggest that there are likely hereditary contributions to almost every tumor type including cancers of the prostate, thyroid, and lungs, for instance, for which clinical testing is not available because causative gene mutations have yet to be discovered.

Many research groups actively recruit families with a strong history of

a specific cancer type hoping to discover new associations of disease with germline (inherited) gene mutations. In the early stages of research, when a disease-causing gene remains unidentified, testing is often anonymous, and participants understand that there may be no promise of personal benefit. Once a researcher finds a gene suspected to harbor disease-associated mutations, further analysis must be performed to identify the mutation in additional families with the disease of interest. As these findings are reported in the literature, clinicians often seek access to testing for this newly identified gene. This desire for access sometimes begins before testing can be established in a CLIA-approved lab. In these instances, research testing protocols then become the only avenue

for obtaining clinically significant genetic testing results prior to availability of CLIA-approved testing.

Even after genetic testing is available clinically, research genetic testing may exist to further define the spectrum of mutation-associated risks and clinical features. Research-funded genetic testing can be mutually beneficial for investigators and patients because involvement of eligible families helps satisfy research aims and the family may receive free genetic testing.

Regulation

Research-based genetic testing is subject to regulation by the researcher's institutional review board (IRB). In order for a genetic testing research protocol to be approved, the IRB must determine that all reasonable protections are in place for participants entering the study. The IRB has requirements for the informed consent process, which include a discussion of the risks, benefits, and alternatives to enrollment in the study. A patient enrolled in a protocol that involves genetic testing should know up front whether or not to expect to be notified of the study-related results and the possible implications of those results should he or she enroll. Research laboratories are not required to be certified by CLIA unless they plan to report patient-specific results directly to participants for use in clinical care.

Research test results

Because most research laboratories are not required to uphold the same regulatory standards as clinical testing laboratories, there is often no expectation with regard to turnaround time for the receipt of test results. Some research studies do not report test results at all, whereas others may only provide overall study results when the findings have clinical significance. Research genetic test results should

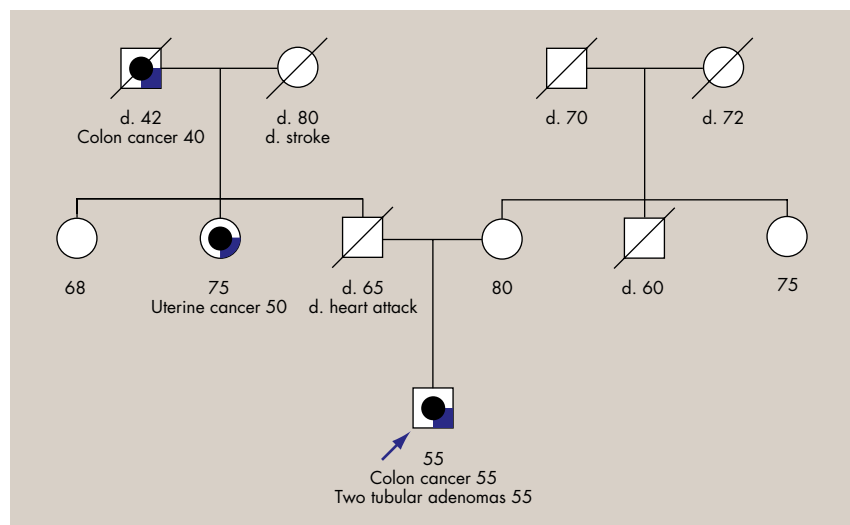


FIGURE 1 A 55-year-old male presented with a 6-month history of rectal bleeding and underwent colonoscopy. He was found to have two tubular adenomas and a mucinous colorectal carcinoma in the transverse colon. The patient had no other significant personal medical history. His family history was significant for a report of colorectal cancer in his paternal grandfather at age 40 and endometrial cancer in his paternal aunt at age 50. The patient qualified for a research study offered to all individuals with colorectal cancer to determine the frequency of Lynch syndrome in the general colorectal cancer patient population. (Lynch syndrome is the most common hereditary colorectal cancer syndrome and is associated with a lifetime risk of colorectal cancer of approximately 70%. Women with Lynch syndrome have up to a 40%–60% chance of developing endometrial cancer.⁵) The research protocol allowed for testing for mutations in four mismatch repair genes known to be associated with Lynch syndrome: *MLH1*, *MSH2*, *MSH6*, and *PMS2*. A point mutation was identified in *MSH6*. The patient was offered site-specific confirmation of his research result in a Clinical Laboratory Improvement Amendments-certified laboratory for approximately \$300. Without the research study, his genetic testing could have cost over \$2,000. The patient's research result was confirmed, and a standard result report was provided to his referring physician. His family members were offered genetic testing and can now screen for Lynch syndrome-associated cancers accordingly.⁶

be confirmed in a CLIA-approved clinical laboratory whenever possible in order to be reportable and useful for clinical decision-making.

Some research protocols incorporate CLIA confirmation of test results, which can eliminate the need for additional testing and associated costs for the participants. In other cases, participants are financially responsible for CLIA confirmation of their research results. Testing for a specific identified mutation is generally a small fraction of the cost of full gene analysis and can thus provide a significant financial savings to research participants while enhancing the body of knowledge about their hereditary syndrome (Figure 1^{5,6}).

The case example in Figure 1 illustrates the opportunity provided by some research studies. The studies direct clinical testing options so that the tests ordered are targeted to the gene of interest based on the research result. In such circumstances, the testing is less expensive and more specific.

In some cases, genetic tests for a particular hereditary cancer syndrome yield uninformative or negative results. Enrolling in a research study at this point can also be beneficial by hunting for the undiscovered causes of the hereditary cancer (Figure 2).

As in the case example described in Figure 2, many cancer genetics research protocols allow for a broad spectrum of experimental assays, which are neither feasible nor practical in the clinical setting. It is often possible to offer testing for multiple known and suspected causes of hereditary cancer syndromes through a single research protocol. Some research protocols aim to identify genes associated with cancers for which clinical genetic testing is not available. This step may involve investigating several candidate genes identified through genome-wide association studies or the enrollment of several relatives within families for linkage analysis.

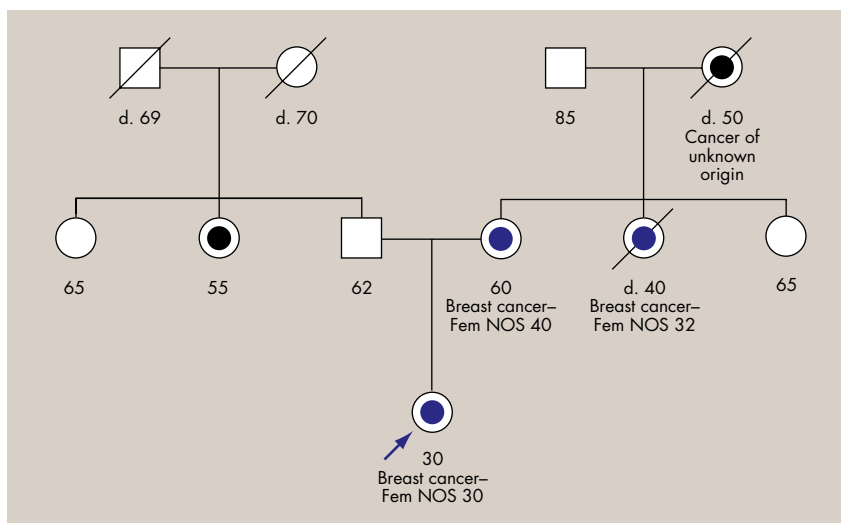


FIGURE 2 A 30-year-old woman was diagnosed with breast cancer, and her oncologist referred her for cancer genetics risk assessment and counseling. The genetic counselor involved in the case constructed a three-generation pedigree in preparation for the risk assessment and learned that the patient's mother had breast cancer at age 40, her maternal aunt had breast cancer at age 32, and her maternal grandmother had a cancer of unknown origin that spread to her bones, and she died at age 50. The clinical geneticist ordered genetic testing for mutations in *BRCA1* and *BRCA2*, and the patient did not have a detectable mutation in the *BRCA* genes. Given the striking family history of early-onset breast cancer, there is still a significant risk of a hereditary predisposition to breast cancer in this family. The patient, her mother, and her maternal aunt qualified for a research study that aims to identify additional causes of hereditary breast cancer through linkage analysis and genome-wide association studies. The family provided written informed consent and submitted blood samples to the research laboratory. The family may not receive results from the research study, but their participation may lead to discoveries beneficial to people with strong family histories of breast cancer.

All of the clinical genetic tests available today were developed in research laboratories; participation of patients in these protocols is essential for discovering new cancer-associated genes and for developing clinical assays useful in practice.

From the lab to the clinic

For researchers to transition a new discovery into a widely available clinical test, the test should be validated and should meet standards for quality control and assurances. However, there is little guidance regarding how much information is necessary for a test to enter the commercial arena. There are also few regulations for ongoing proficiency and validation updates once a test is available clinically and new discoveries are made.

The field of cancer genetics is constantly changing; it's not uncommon

for researchers to encounter conflicting results as discoveries are made. Thus, once a test is available clinically, clinicians must still exercise caution until the utility of the test has been proven. Some genes, such as *CHEK2* and the I1307K mutation in *APC*, for instance, are thought to be associated with a modest elevation of cancer risk. In these cases, other currently undiscovered modifying factors may ultimately affect the cancer risk and recommendations, as medical management may not be altered by the genetic testing results. In fact, ASCO recommends that testing for these "low-moderate" risk-associated genes be performed within the constructs of a research protocol only.⁴

Some inherited syndromes are so rare that the start-up costs for implementing CLIA-approved testing may be prohibitive. In other words, a

clinical laboratory may need to spend more money than it can hope to gain to refine the technology developed in the research laboratory and offer the test clinically. When this happens, testing for a given gene may remain solely under research protocols for long periods of time.

Summary

Genetic testing for predicting cancer risk remains a complex undertaking, even as some tests such as screening for mutations in *BRCA1* and *BRCA2* and the Lynch syndrome-associated mismatch repair genes have moved into mainstream oncology care. The ordering clinician should understand the limits and predictive value of testing as well as the residual cancer risk once genetic testing results are available. Since the general public is not typically informed about the ubiquitous “gray zones” that can be observed in genetic test results, the clinician should educate patients prior to testing and following disclosure and interpretation of results.

Genetic testing for some newly identified cancer-associated genes may only be available as part of a research protocol and may require veri-

fication of a specific research finding in a CLIA-approved laboratory for documentation and use in clinical care. Research studies remain important for people with rare syndromes for which clinical genetic testing development is impossible or impractical. Research also helps broaden our understanding of established hereditary cancer syndromes.

The field of cancer genetics is changing rapidly, and patient involvement in research protocols is essential for continued growth. Discoveries made in the research laboratories can translate into clinical testing options that can be used to plan personalized patient management and cancer screening after a transitional period of validation and technical implementation. As this process continues to evolve, additional regulation of genetic testing laboratories will be necessary to limit the risk of technology outpacing the clinical utility of genetic testing. In the meantime, oncologists and genetics specialists must work together to ensure that their patients receive the highest quality evidence-based care.

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Jumping the gun

In this continuing series of vignettes, we hear the perspective of patients, genetic counselors, and patient advocates on screening for and coping with hereditary cancer. The stories are instructive and open the door to discussion on genetic testing and counseling within community practices. This month's vignette concerns a physician who prematurely recommends prophylactic surgery to prevent ovarian cancer.

A patient's story

I made an appointment with a gynecologist who specializes in cancer-related cases. I needed a checkup, but I also wanted to discuss genetic screening and learn about advances in ovarian cancer detection. I have a strong family history of cancer, and recently my sister tested positive for a *BRCA1* mutation. I personally have never had cancer. At the appointment, I was met by a nurse who asked why I had requested the appointment and other basic questions. I told her about my sister's genetic screening results. I was examined by the fellow, and he asked about my family history, my sister's results, and my own plans. I indicated a scheduled mammogram (my first) and a desire for genetic screening, a CA-125 blood test, an ultrasound, and anything else they recommended.

He asked about my age (40), marital status (single), and number of children (0). Then he discussed the fact that with my family and personal histories, removing the ovaries was the recommended preventive measure.

Finally, the doctor came in. He introduced himself and said that he ran the ovarian family registry at that facility. He explained that normally he saw patients who were worried about being high risk without cause. But I, on the other hand, had legitimate reasons for concern. He and the fellow spoke to me about whether I had made the decision to have surgery yet. I repeated my interest in having genetic testing first and then appropriate screening based on the genetic test results. The doctor said that I could have the genetic testing done, but he believed it was unnecessary because

of my family history, the fact that screening was not an exact science, and the fact that other, as yet undiscovered, genes may be linked to ovarian cancer.

At that point, my head was spinning. The gynecologist's focus was on surgery, whereas I wanted to gather information about screening tests, genetic testing, and genetic counseling. Although my doctor believed that genetic testing was unnecessary, I persisted. I left the office with a referral to a genetic counselor and a prescription for a transvaginal ultrasound. I was overwhelmed and just wanted to get home to review the information I'd heard, speak to my sister, and do some research. Rather than scheduling prophylactic surgery right away, I wanted to get a better sense of my ovarian cancer risk.

Commentary by Debbie Pencarinha, CGC, Kingsport Hematology and Oncology Associates, Kingsport, TN

Despite many efforts to incorporate genetic education into medical training, it is common for healthcare providers to be less familiar with the implications of genetic testing. Information related to hereditary cancer risk assessment is constantly evolving, and when hereditary factors are suspected or known to be present in a family, it is important to refer patients to specialists in the field.

The patient in this vignette be-

comes overwhelmed by misinformation and her physician's desire to act immediately rather than confirming her true cancer risk. Since her sister tested positive for a *BRCA1* mutation, a dominant gene, the patient has a 50% chance of also having the mutation. It's important to note that the presence of a *BRCA1* gene mutation in the patient's sister identifies the cause of cancer in this family. Thus, if the patient also carries the *BRCA1* gene mutation, she is at a significantly in-

creased risk for both breast and ovarian cancers, necessitating increased surveillance and management. If, on the

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other hand, she tests negative for the known *BRCA1* gene mutation in her family (true negative), her risk returns to at least the background population risk. In this case, a prophylactic bilateral salpingo oophorectomy (PBSO), which her doctor is recommending regardless, would not be necessary.

The possibility of additional, “yet undiscovered genes” is primarily an issue when a *BRCA1/2* gene mutation has not been identified to explain the family history of cancer. Referral for genetic counseling and testing should be made prior to medical management recommendations for this patient. If she tests positive for the *BRCA1* gene mutation identified in her sister, the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology recommend that aggressive medical management options be offered, including increased surveillance, chemoprevention and prophylactic surgery such as prophylactic bilateral mastectomy and/or PBSO.

This procedure reduces the risk for ovarian cancer by approximately 96%; when performed premenopausally, it

reduces the risk of breast cancer by 50%–68%. These are interventions the patient may seriously consider despite her age, marital status, and lack of children given that her cancer risk would be significantly increased if the results of genetic testing were positive.

Even so, in this case, it would be important to explore the patient’s desire for preserving fertility. Surgical intervention prior to genetic counseling and testing could prematurely end the patient’s fertility; place her at

unnecessary surgical risk; potentially create unwarranted long-term menopausal side effects; and generally create undue emotional, physical, and financial costs.

Balanced discussions of surgical benefits, risks, limitations, and emotional implications are important. If genetic testing reveals a true negative result, management options would be drastically different.

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Commentary by Sue Friedman, Executive Director, FORCE, Tampa, FL

FORCE (Facing Our Risk of Cancer Empowered) receives many inquiries and Web posts from women whose doctors recommended they undergo prophylactic oophorectomy without a thorough assessment of their risk for ovarian cancer, information on the availability of genetic

testing, or a discussion of a negative genetic test result. Although prophylactic surgery is an effective risk-reducing option, it is not without risk and physical and emotional costs to women, particularly premenopausal women.

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