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Hereditary Cancer Testing in a Value-Based World: The Evolving Standard of Care

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"It is more important to understand what kind of patient has a disease, than what disease a patient has acquired."
—Sir William Osler, 1849-1919

CASE EXAMPLE*

In 2012, a 38-year-old woman died of breast cancer at 24 weeks postpartum. Her Ashkenazi Jewish mother died of ovarian cancer at age 40. From age 29, this patient had requested breast cancer gene (BRCA) testing from her 3 different ObGyns, but all refused to test her, stating that testing takes too much time, would not be covered by insurance, and that she did not meet required criteria. During her 2 subsequent pregnancies, she was seen by 2 different genetic counselors working with maternal-fetal medicine physicians (MFMs) (referenced below as GC1 and GC2, respectively); she requested BRCA testing from both, yet neither recommended it. During the first pregnancy (2009) GC1 did not elicit a cancer family history until it was offered by the patient. Using 1999 American College of Medical Genetics and Genomics (ACMG) criteria, GC1 informed the patient that she did not meet criteria for BRCA testing. During her second pregnancy, GC2 made note of the family history of cancer, yet advised her to wait until after her delivery to have testing. At 36 weeks gestation, she reported a painless breast mass to her ObGyn, who diagnosed a swollen milk gland and said "not to worry." At her 2-week postpartum visit, she reported an enlarging painless breast mass, which was diagnosed as mastitis and treated with antibiotics. At 4 weeks postpartum, the unresolved mass caused her ObGyn to consult with a breast surgeon. Breast and node biopsies revealed stage 3 poorly differentiated invasive ductal breast cancer, and genetic testing by the surgeon confirmed suspicion of a BRCA1 mutation, presumably inherited from her mother. She underwent radiation and chemotherapy, but treatment was unsuccessful and she died of metastatic disease, leaving behind a husband, toddler, and 6-month-old newborn. Claims for negligence arising from failure to diagnose the hereditary cancer syndrome, failure to offer the option of prophylactic mastectomy (which likely would have prevented the malignancy altogether), and ultimately delayed diagnosis of breast cancer were brought against all 3 ObGyns along with both genetic counselors and their supervising MFMs. These claims resulted in a multi-million dollar settlement that included all practitioners.

INTRODUCTION

Commemorating the 20th anniversary of BRCA genetic testing, we are increasingly conscious of the social, economic, and medico-legal impacts of genetic cancer risk on both personal and public health. An ever-growing number of medical societies and expert panels have now charged clinicians with the duty to evaluate and manage their patients' cancer risk profiles, with particular attention to those individuals carrying genetic mutations that confer elevated cancer susceptibility, a process commonly known as hereditary cancer risk assessment, or HCRA.[1-4]

*This case example is based on real events.

DISCLOSURES
Dr. Frieder reports that he is a consultant and speaker for Myriad Genetic Laboratories. Susan Kendig reports that she is a consultant for Myriad Genetic Laboratories.

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This article is written for women's health care clinicians, and will address the current status of hereditary cancer genetic testing, focusing on the evolution of pan-cancer, multigene panel testing in the context of value-based medicine.

In the mid-1990s, single syndrome testing for hereditary breast and ovarian cancer (HBOC) and Lynch syndrome became clinically available. Today, genetic testing provides a pathway for recognition of predisposition to hereditary cancers, facilitating the opportunity to consider risk-reduction and early-detection strategies.[5] Increasing evidence of reduced morbidity and mortality with such interventions has contributed to the development of consensus recommendations for cancer screening and prevention guidelines in specified high-risk populations.

Most recently, technologic advancements have allowed for the increased detection of mutations as well as the discovery of additional genes associated with cancer predisposition. "Next generation sequencing (NGS)" now provides cost-effective, multi-gene panels, evaluating the inherited risk for 8 major cancer sites: breast, ovary, uterus, colon, skin (melanoma), stomach, pancreas, and prostate, as well as many other inherited malignancies. Importantly, a pan-cancer panel approach to HCRA has the potential to identify actionable mutations that would be missed by a traditional single gene/single syndrome approach to testing.[6] In a 2015 study, utilizing a 25-gene panel approach for patients with breast cancer deemed appropriate for HBOC testing nearly doubled the detection of inherited cancer risks compared with single-syndrome testing.[7] Many of these mutations were found in recently described genes, for which there now exist medical society guidelines and evidence-based literature to direct management.[8-10] The former approach, limiting testing to BRCA or Lynch-associated genes, would erroneously classify many patients with a familial risk profile rather than identify their true hereditary predisposition. Based on the value of multi-gene panel testing, medical society guidelines now recognize this approach as appropriate.[1,9,11]

Due to this emerging standard of care, multi-gene panel testing has become more widely available through various clinical laboratories. It is important to recognize that these panels are highly variable in the component genes as well as the value and accuracy of the results. Furthermore, although clinical testing laboratories are Clinical Laboratory Improvement Amendments (CLIA)-certified, this does not evaluate accuracy, nor is there currently any US Food and Drug Administration (FDA) regulation over these tests. There is only 1 FDA-approved test for BRCA1 and BRCA2 testing, which is required in order to prescribe olaparib, a poly (ADP-ribose) polymerase inhibitor (PARPi) used for treatment of patients with refractory ovarian cancer.[12]

As clinicians, we rely on lab accuracy in guiding critical decisions in patient care, and making an informed decision as to which laboratory to use is essential to patient safety and clinician liability. **TABLE 1** lists factors one should consider when deciding between laboratories offering genetic testing. Of particular importance is the degree to which a laboratory relies on public research databases to classify genetic variants, as there are well-established limitations in relying on these uncurated resources.[13] It is due to these limitations that the National Institutes of Health is dedicating over $25 million toward the reorganization of such databases.[14]

ACOG Position Statement
Ordering of Genetic Tests 12/17/15

- "Recent proposals, including several by health care insurers and one by the Centers for Medicare and Medicaid Services (CMS), suggest that genetic counseling must be provided by an individual "certified" in genetic counseling before genetic testing could be ordered. The American College of Obstetricians and Gynecologists and the American Congress of Obstetricians and Gynecologists (ACOG) firmly opposes these restrictions because they impose unnecessary barriers to timely care. Moreover, ACOG opposes such attempts to restrict the scope of practice of obstetrician-gynecologists, who are fully qualified to provide pre-test counseling to their patients."[24]
- "This position is aligned with the American Medical Association Policy H-460.902, "Opposition to Genetic Testing Restrictions Based on Specialty," which specifically opposes limiting the ordering of genetic testing based solely on physician specialty or other non-medical criteria, and also opposes requirements for utilization of non-affiliated medical specialists or non-physicians prior to ordering genetic testing." [24]
- "In conclusion, ACOG reaffirms its position that obstetrician-gynecologists are fully trained and qualified to counsel patients regarding genetic issues specific to pregnancy and women's health-associated cancers, and that the ordering of genetic testing should not be restricted by a requirement for pre-testing genetic counseling by a separate provider. This requirement would jeopardize our patients' access to timely care." [24]

TABLE 1 Factors to Consider When Selecting Genetic Testing Laboratories

Does the genetic testing laboratory:

- Provide data supporting their technical and interpretive accuracy, including validation studies?
- Demonstrate a tailored approach to test design, based on characteristics of gene(s) tested?
- Detail algorithm/techniques for classifying genetic variants?
- Provide support and communication to clinicians as variants are re-classified?
- Curate internal or external databases used to interpret technical lab findings?

MODELS OF CARE

Three established, yet disparate, models are used to translate predictive cancer genomics into primary care medical practice for patients at risk for hereditary or familial cancer syndromes. These commonly accepted strategies for identification, risk assessment, genetic testing, interpretation, and management include:

(1) Referral model: Referral to academic, community-based, or telephone-based genetic counselors.

(2) Point of care model: Primary/specialty-physician directed care, with selective referral of complicated cases or cases with non-straightforward results.
(3) Hybrid/integrated model: Clinicians with focused specialty training in genetics providing clinical consultations, with genetics professionals reserved for patients with complicated risk profiles.

Based on the current US population of 320 million, at least 32 million (10%) have a cancer family history that could influence medical management, with the objective to reduce the burden of cancer. In addition, there are over 1 million carriers of cancer susceptibility mutations, of which 95% are yet to be found.[15] Based on a 5% to 10% pretest probability of finding a mutation, it would follow that 10 million to 20 million Americans would meet current guidelines for genetic testing. There are approximately 2900 genetic counselors in the United States, with only 29% working specifically in cancer genetics.[16] Due to the overwhelming need, limited number of cancer genetic counselors in the United States, frequent geographic barriers, and long wait-times, the traditional referral model, sending patients from primary care clinicians to genetic counselors, will not suffice. There are several studies that have documented the marked lack of compliance amongst patients referred for a genetics consultation, due to a variety of personal and economic barriers.[17-23] The point of care and hybrid models have the potential to surpass the referral model through improved teamwork that optimizes patient access, compliance, and ultimate identification of patients carrying pathogenic mutations. Clinicians will preserve their primary care role, while elevating genetic counselors to their appropriate functions as leaders, teachers, and resources for specialty consultation.

Progress in the development of clinician-friendly, commercially available genetic tests for cancer susceptibility is one example of the role of precision medicine in informing clinical decision making in preventing, diagnosing, and treating specific, genetically linked cancers. The assimilation of this technology into the everyday clinical setting provides an extraordinary opportunity to improve health care outcomes. As technologies have advanced, women's health care clinicians have begun offering risk assessment, genetic testing, and cancer prevention services directly through their practices. A recent Position Statement from ACOG reaffirms ObGyns are fully trained and qualified to provide pre-test counseling in addition to ordering genetic testing for their patients.[24] Nationwide, more than 75,000 clinicians are now ordering genetic testing for their patients—meeting National Comprehensive Cancer Network (NCCN) guidelines for appropriateness of testing in over 93% of test requests[25]—and subsequently managing their patient's care based on risk stratification and, as per multiple society guidelines, directing and supporting this point of service practice.

Notably, insurance coverage is generally available, as illustrated by the average patient's out-of-pocket cost of under $100. In 2015, over 80% of patients experienced a zero co-pay for this testing.[25] BRCA risk assessment, counseling, and testing for women who have family members with breast, ovarian, tubal, or peritoneal cancer is given a "B" rating by the US Preventive Services Task Force. As such, assessment, counseling, and testing for BRCA is included in the preventive services available to women without cost sharing under the Affordable Care Act preventive services provisions.[26]

High-risk patients are easily identified in a primary care setting through the use of a focused, family history questionnaire, which should be updated at least annually and at the time of routine physical examination or problem-oriented encounter. Experience has shown that primary care clinicians will commonly identify 1 to 2 patients per day who meet current NCCN guidelines for genetic testing. Medical society guidelines discuss the importance of obtaining, assessing, and actively using family history in health care decisions.[27,28]

"A hereditary cancer risk assessment is the key to identifying patients and families who may be at increased risk of developing certain types of cancer. This assessment should be performed by obstetrician-gynecologists...and should be updated regularly."[2]

—ACOG Committee Opinion 634 (2015)

INFORMED CONSENT

Informed consent is a communication process, whereby a patient is enabled to make an informed and voluntary decision about accepting or declining medical care.[29] Expert panels and professional guidelines consistently recommend basic elements of informed consent for genetic testing, with the goal for the patient to come away with an understanding of the purpose of the test, possible results, and associated uncertainties.[1,4,30-32] This requires that the clinician involved in providing informed consent is knowledgeable about heritable cancers. **TABLE 2** reflects elements of informed consent for hereditary cancer genetic testing.

TABLE 2 Elements of Pretest Informed Consent for Hereditary Cancer Genetic Testing[1]

1. Purpose of the test
2. Information about the gene(s) being tested, including associated range of risk
3. Possible test results (positive, negative, uncertain variant)
4. Implications of result on medical management of patient
5. Implication of genetic test result for family members
6. Economic considerations
7. Protections and possible risks of genetic discrimination
8. Psychosocial aspects
9. Confidentiality
10. Future use of DNA sample
11. Importance of disclosure of test results
12. Alternatives to genetic testing

THE VALUE PROPOSITION

Germline testing for heritable cancers is a well-established element of medical care for identified at-risk patients due to the tremendous value it provides to both the patient and the clinician in preventing or mitigating adverse health outcomes related to cancer.[1]

Public Health/Patient Perspective

Innovations in medicine can provide health benefits that mitigate risks, and in some cases result in ultimate cost savings. From a policy perspective, the goal is to identify and reduce cases in which costs have increased without a concomitant increase in value. Value to the patient, when considered within the context of cost of new technologies, can be measured in calculation of change of health care cost compared with the monetized gains in quality-adjusted life years. Comparative analysis of cancer spending in 16 industrialized countries indicates that countries with the highest per patient cancer spending experienced more rapid progress in reducing cancer mortality.[33]

Current clinical integration models, such as medical homes and accountable care organizations, provide a framework for comprehensive, integrated care delivery systems in which providers across the spectrum of health care services agree to be accountable for the cost, quality, and overall health of a designated population, and share in savings generated through meeting quality and efficiency targets. Precision medicine concepts are well aligned with risk-based payment mechanisms designed to incentivize improved patient and population health outcomes based on improvements in the quality and efficiency of health care service delivery. Precision medicine approaches to care seek to optimize patient outcomes through genetic screening programs that allow for more precise diagnoses of diseases and subtypes, selection of medication, treatment or prevention modalities best tailored for a specific patient group, or likelihood of disease recurrence.[34] In this way, preventive or therapeutic interventions can be targeted to those patients who would benefit from the intervention, while sparing expense and adverse effects for those who would not benefit.[5]

TABLE 3 ICD-10 Dx Codes

	Personal hx	Family hx	Current dx
Breast	Z85.3	Z80.3	C50.XXX
Ovary	Z85.43	Z80.41	C56.9
Endometrium	Z85.42	Z80.49	C54.1
Colon	Z85.038	Z80.0 (all GI)	C18.X
Screening for Suspected Genetic Disease Carrier State			Z13.71
Family History of Carrier of Genetic Disease			Z84.81
Confirmed Known Mutation Carrier State; Genetic Susceptibility to Malignant Neoplasm of ___:			
Breast		Z15.01	
Ovary		Z15.02	
Endometrium		Z15.04	
Colon (or other)		Z15.09	
Risk-reduction Encounter		Z71.9	

Abbreviations: dx, diagnosis; hx, medical history.
Note: .X and .XXX need more specific diagnosis code.
Source: http://www.cms.gov/Medicare/Coding/ICD10. Search: "ICD-10 Code Lookup"

TABLE 4 CPT Billing Codes

Problem, New Patient	99201-99205
Problem, Established Patient	99211-99215
Problem, Consultation	99241-99245
Preventive Care, New Patient	99385-99387 (age)
Preventive Care, Established Patient	99401-99443
Telephone Management	99441-99443 (not always measureable)

In addition to early recognition through appropriate risk assessment and application of genetic testing technologies, precision medicine lends itself to more accurate and efficient use of treatment modalities. For example, a tumor's molecular profile can be matched to a targeted companion therapy, thus reducing the cost of one-size-fits-all treatment or trials of less effective therapies. One recent example includes the approval of the PARPi olaparib by the FDA on December 19, 2014. Olaparib represents one of the first new therapies in over a decade for patients with refractory ovarian cancer.[12] There are additional ongoing trials examining the use of PARPis for patients with breast cancer or prostate cancer, representing true advances in precision medicine. Further, use of gene expression profiling to inform breast cancer treatment management decisions can help to predict disease recurrence risk, thus providing valuable information for patients and their physicians in deciding whether or not use of adjuvant therapies would provide benefit and value to the patient.[35] Incorporation of standardized genetic risk assessment strategies, appropriate testing, and follow up for persons at risk for certain hereditary cancers can further improve the practice's ability to meet quality metrics and improve patient safety.

Coding and Billing

Appropriate billing and coding for HCRA encounters are critical to sustain the clinical focus and momentum within our practices, **as compensation is provided by most insurance carriers**. Generally, 10% to 20% of a primary care physician's patients will be identified as having an elevated, familial risk profile, thereby qualifying patients for additional medical care, and often results in an **additional 1 to 2 problem-focused/risk-reduction/imaging office visits per year.** Patients diagnosed with genetic syndromes will constitute an additional 1% to 2% of the practice, and they too will need additional office-based and/or surgical care, which are typically compensated services.

Standard *International Classification of Diseases, Tenth Revision* (ICD-10) diagnoses (Dx) and Current Procedural Terminology (CPT) billing coding applies to patients with cancer family or personal histories, or known germline mutations for cancer susceptibility. **TABLES 3** and **4** illustrate current coding that may be used for various types of encounters. (Note:

ICD-10 Z-codes have replaced the previous ICD-9 V-codes for personal and family histories of cancer. ICD-10 C-codes have replaced the previous ICD-9 140-209 codes for current personal cancer. CPT coding has remained the same.)

MEDICO-LEGAL LIABILITY

Documentation

Failure to provide appropriate genetic counseling, recommend genetic testing, or discuss recommended surveillance and possible preventive measures for patients assessed to be predisposed to familial or hereditary cancers, as is evident in our exemplar case, increases risk of litigation.[36,37]

Accordingly, procedures must be in place that assure timely assessment and cancer surveillance consistent with current evidence-based guidelines, with opportunities for prophylactic and risk-reduction interventions. Failures in assessment, monitoring for cancer, and providing care coordination are implicated in malpractice litigation related to cancer risk.[36,38]

Our initial case example illustrates core medical errors across the continuum of the patient's health care that may have contributed to the devastating outcome. Diagnosis-related errors are identified as a leading cause of malpractice claims within the outpatient setting, more often resulting in death and major disability than any other allegation group. In primary care, diagnosis-related allegations accounted for 72.1% of claims, surpassing medication and treatment-related complaints.[39] Cancer diagnoses, specifically colorectal and breast cancer, are consistently cited within the top 4 most common diagnosis-related complaints.[39-41] Although missed diagnosis is the allegation associated with most paid claims overall,[41] other studies have identified delayed diagnosis as a key contributor to malpractice complaints.[39]

The case at hand illustrates 2 core failures noted as top contributors to malpractice risk:

1. Although the family history of ovarian cancer in a first-degree relative was documented, the ObGyn did not evaluate the patient's symptoms within the context of her cancer family history.
2. Despite the suspicious family history, the physicians and genetic counselors consistently failed to order appropriate diagnostic tests that would have confirmed her BRCA syndrome, likely enabling an early-stage diagnosis or actual prevention of the advanced breast cancer which took her life.

As this case illustrates, when there are multiple breakdowns in patient care leading to a missed cancer diagnosis, the risk of a malpractice suit is greatly increased. It is incumbent that ObGyns and primary care clinicians engage in active cancer risk assessment with all patients, and become knowledgeable about cancer genetics and current evidence-guiding practice, regardless of professional discipline. Health care providers who are not trained to provide cancer-related genetic assessments should have a system in place for referral when "red flags" are identified in the family and/or personal history, or upon physical examination.

Additionally, clinicians are responsible for coordinating post-assessment cancer prevention and early diagnosis plans, which may include regular, risk-specific screenings, prophylactic interventions, further monitoring for development of cancer, and referrals to specialist care. Patients transitioning between primary and specialty care encounter difficulty in scheduling, lapses of information, duplicative testing, and confusion about the respective health care providers' responsibilities in their care.[42] Failure to coordinate an appropriate management plan, which includes managing ambiguous results or conflicting specialist recommendations, can lead to increased liability exposure.[36]

"…Recommend that primary care providers screen women who have family members with breast, ovarian, tubal, or peritoneal cancer…to identify a family history that may be associated with an increased risk for potentially harmful mutations in breast cancer susceptibility genes...Women with positive screening results should receive genetic counseling and, if indicated…testing."[4]

—B Recommendation. US Preventive Services Task Force Recommendation Statement 2/18/2014

For more malpractice case examples, please see **Appendix A** in the digital version of this supplement that can be found in the "Supplements" section at obgmanagement.com.

SUMMARY

Women's health care clinicians are uniquely positioned to identify individuals at increased risk for hereditary or familial cancers. When implemented using consistent policies guiding appropriate risk assessment, informed consent, testing, management, and possible referral, the process is highly suitable for integration into a busy clinical practice, as per recent society recommendations. The early identification of a suspected hereditary cancer syndrome can lead to additional evaluation and cost-effective interventions that can substantially reduce cancer risk, with proven reductions in morbidity and mortality. The high human and economic cost of cancer care can be significantly impacted by cancer prevention in easily identified patients, through use of a pan-cancer hereditary cancer panel for appropriate patients.

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APPENDIX A Malpractice Case Examples

Case	Summary	Liability Triggers	Liability-Reduction Strategies
Downey v Dunnington (2008)[a]	Physician incorrectly recorded patient's family history as bilateral breast and ovarian cancer in first-degree relatives. Although this history qualified the patient for genetic testing, the physician informed her that the Department of Public Aid would not cover such testing, and failed to inform her of available grants to pay for the tests. Based on the physician's recommendation, patient chose to have a bilateral mastectomy and breast reconstruction. Postoperative tissue pathology revealed no malignancy. The trial court verdict was in favor of the defendant; physician was upheld on appeal.	Failure to verify family history and genetic risk prior to performing invasive or irreversible procedures	• Develop a standardized process for initial review and annual update of comprehensive cancer-related family history in first-, second-, and third-degree relatives • Utilize evidence-based criteria, risk assessment tools, and decision support tools to identify patients who may benefit from further genetic assessments/testing • Verify the patient's medical history and presence of a relevant germline mutation before implementing interventions
Morse v Davis (2012)[b]	35-year-old man sought medical care reporting gastrointestinal symptoms including rectal bleeding. Physician had treated patient's mother for colon cancer but did not note this in chart. No follow-up regarding rectal bleeding on subsequent visit. Subsequently diagnosed with stage 4 cancer of the bowel. The trial court's verdict in favor of the plaintiff was upheld on appeal.	Failure to obtain or update a comprehensive family cancer history	• Develop a standardized process for initial review and annual update of comprehensive cancer-related family history in first-, second-, and third-degree relatives • If the patient presents with symptoms indicative of cancer or receives a diagnosis of cancer, review and update family history for cancer diagnoses in first-, second-, and third-degree relatives
Downes v Trias (2012)[c]	A Connecticut woman sued her physician for failing to warn that her extensive family history of breast cancer suggested a genetic risk of ovarian cancer. The Connecticut Supreme Court upheld a $4 million jury verdict in favor of the plaintiff after she went on to develop ovarian cancer.	Failure to consider family history in further testing and management recommendations	• Verify the patient's medical history and presence of a relevant germline mutation before implementing interventions

[a]Downey v Dunnington, 384 Ill. App. 3d 350, 895 N.E.2d 271, 2008.
[b]Morse v Davis. 675 N.E. 2nd 148 : Ind. App., 2012.
[c]Downes v Trias. 49 A.3d 180 : Conn. Sup, 2012.