Adverse Events in Cancer Genetic Testing

Medical, Ethical, Legal, and Financial Implications

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Abstract: Cancer genetic counseling and testing are now integral services in progressive cancer care. There has been much debate over whether these services should be delivered by providers with specialized training in genetics or by all clinicians. Adverse outcomes resulting from cancer genetic counseling and testing performed by clinicians without specialization in genetics have been reported, but formal documentation is sparse. In this review, we present a series of national cases illustrating major patterns of errors in cancer genetic counseling and testing and the resulting impact on medical liability, health care costs, and the patients and their families.

Key Words: genetic counseling, genetic testing, BRCA1, BRCA2, Lynch syndrome, cancer genetics

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Over the past decade, cancer genetic counseling and testing have become essential services in progressive cancer care. With this evolution, there has been much debate over who is best suited to provide genetic services. Traditionally, genetic counseling and testing have been provided by individuals with graduate education, specialized training, and board certification in genetics. However, the push in recent years by some professional organizations and genetic testing companies has been to suggest that all health care providers should provide genetic counseling and testing services themselves. The impetus for this push on the part of the genetic testing companies is controversial, in that the aggressive sales representatives from these companies receive financial incentives for every test ordered and every new ordering provider.

Some potential benefits for provision of genetic counseling and testing by all health care providers, and not just specialists, have been proposed.[1,2] These benefits include that established providers have long-term relationships with their patients and thus deeper knowledge of the patient's overall health and that this may allow greater access to genetic services particularly in underserved populations where there are geographical, cultural, or language barriers.[1,2] Conversely, much of the literature over the past decade cites potential barriers, areas of concern, and negative outcomes from genetic counseling and testing being performed by providers without specialized training in this area.[2,3] Besides a handful of well-known lawsuits, little has been published demonstrating actual clinical examples of adverse outcomes resulting from cancer genetic counseling and testing performed by clinicians without specialization in this area.

In 2010, we published the first known national series of cases of this kind.[3] In this article, we will discuss additional cases and controversies. Both the cases in this article and those published in our previous series were obtained from genetic counselors who participate in the National Society of Genetic Counselors Cancer Special Interest Group listserv. For the current article, genetic counselors from the National Society of Genetic Counselors Cancer Special Interest Group were invited in January 2012 to submit cases of adverse outcomes of cancer genetic counseling and testing performed by providers without specialization in this area for inclusion in a case series publication. Cases were chosen for inclusion that illustrated unique themes/major patterns of errors in cancer genetic counseling and testing. Cases included originated from 5 of the United States (California, Connecticut, Georgia, Massachusetts, and Tennessee). Multiple colleagues informally reported additional cases but were unwilling to formally report them for inclusion, citing fear of pushback from the clinicians involved and/or potential conflicts with the commercial company that performs much of the cancer genetic testing in the United States and is also the largest employer of genetic counselors in the United States.

We will also review the literature on the factors that may contribute to these errors and the potential barriers and areas of concern related to clinicians without extensive knowledge, training, or certification in genetics providing cancer genetic counseling and testing.

THEMES IN CLINICAL CASE REPORTS

Wrong Testing Ordered

In many of the reported cases, the wrong genetic test was ordered. In some cases, this led to inaccurate medical management recommendations, and in others, unnecessary testing and expenditure of health care dollars.

Wrong Testing Ordered, Resulting in Inaccurate Medical Management Recommendations

In one case, a 19-year-old unaffected female patient of Italian ancestry presented to a gastroenterologist for reflux and gastrointestinal symptoms. The doctor elicited a family history of polyposis in the patient's father and documented that he had "screened the patient for an APC gene mutation" (associated with familial adenomatous polyposis [FAP]). The patient's blood work from that visit indicated a normal complete blood count and F5L screen (ie, a normal assay for activated protein C, also

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abbreviated "APC"). A colonoscopy was not ordered, nor was the patient referred to genetics. Notes from the patient's follow-up care with this physician make no further mention of genetics or FAP. A year later, the patient was seen by a new physician and referred for a colonoscopy and cancer genetic counseling. Testing ordered by the genetic counselor revealed that the patient carried a detectable APC gene mutation, and the patient was found to have polyposis upon colonoscopy. The original gastroenterologist in this case ordered the wrong test and apparently closed the case based on a false-negative result. Ninety-three percent of patients with classic FAP go on to develop colorectal cancer by the age of 50 years without colectomy.[4] The average age at diagnosis of colon cancer in untreated individuals with FAP is 39 years.[4]

In another case, a 63-year-old unaffected woman of English, not Jewish, ancestry was seen by her primary care physician because of her concerns about her family history, which included a sister diagnosed with ovarian cancer and a mother who died of early-onset breast cancer. The primary care physician ordered testing for the 3 BRCA mutations that are common among individuals of Jewish ancestry, which was negative. The patient received a copy of the test results with a note from her physician, "BRCA [smiley face]." The sister with ovarian cancer later had full sequencing of the BRCA1 and BRCA2 genes and was found to carry a BRCA2 mutation (not the one common among Ashkenazi Jews, as expected based on their ancestry). Five years later, the original patient was referred to a cancer genetic counselor by her radiologist to make sure she had had the correct testing. The genetic counselor ordered testing for the familial BRCA2 mutation identified in the sister, and the patient, fortunately, tested true negative. However, if she had carried the mutation, many serious adverse consequences (including cancer diagnoses) could have resulted for her and her at-risk adult children from her not knowing her correct BRCA status for many years.

In a third case, an oncologist referred a 23-year-old woman of Mexican, not Jewish, ancestry who was recently diagnosed with bilateral breast cancer for genetic counseling. The referral read "genetic counseling and BRCA testing for surgical decision making." Upon taking the patient's family history, the counselor learned that the patient had a sibling who was diagnosed with a glioblastoma at age 14 years and died at age 16 years. Based on the patient's personal history of very early-onset bilateral breast cancer and family history of a childhood brain tumor, the genetic counselor instead ordered testing for mutations in the p53 gene associated with Li-Fraumeni syndrome. The patient was found to carry a p53 mutation and therefore learned she was not a good candidate for chest wall irradiation. The patient had previously been counseled by her physician that she would need a prophylactic bilateral salpingo-oophorectomy at age 23 years because of the association of BRCA mutations and ovarian cancer, and this suggestion (which would have been controversial, even in a BRCA carrier) was difficult to counter with the patient even after a p53 mutation had been identified.

Unnecessary Testing/Misuse of Health Care Dollars

Ordering the wrong genetic testing can also lead to the unnecessary expenditure of thousands of dollars, which is then charged to the insurance company and/or the patient. In one such example, a patient was seen by his surgeon based on the fact that his sister carried a known MSH2 mutation associated with Lynch syndrome. The surgeon ordered full sequencing of the MSH2 gene though his office's laboratory, and the charge for this testing with the laboratory send-out fees was $4700. The patient's insurance, justly, denied payment for this test. The patient was then seen by a cancer genetic counselor when his daughter decided to pursue testing. He was very upset when he learned that the appropriate testing (for the single familial mutation) would have cost ~$475. The patient was also angry that, despite all of this extra expense, his doctor had given him little pertinent Lynch syndrome information except that he carried the same mutation that his sister carried; he had not been given detailed information about his cancer risks, screening recommendations, and risks and recommendations for other family members.

Results Misinterpreted

Misinterpretation of genetic test results was another common error observed in our series of cases. Many of the cases of result misinterpretation involved variants of uncertain significance, which are among the more difficult results to interpret. However, other cases demonstrated that result misinterpretation occurred in simple, straightforward cases.

Result Misinterpretation, Resulting in an Advanced Cancer Diagnosis

A 46-year-old woman of Polish, not Jewish, ancestry was referred to cancer genetic counseling because of her recent diagnosis of stage III ovarian cancer and strong family history of breast cancer (Fig. 1). She initially reported that one of her relatives who had breast cancer had BRCA testing in a different country and tested negative. At the end of her appointment, she recalled that she had BRCA testing through her gynecologist's office 16 months earlier at age 45 years and was told it was "normal." However, after discussing that she would now meet the testing company's criteria for large rearrangement testing (BART) in BRCA1/2 at no additional cost, the patient chose to proceed with testing. Upon receiving the request for this additional testing, the laboratory sent the genetic counselor a fax indicating that the patient would not qualify for free BART rearrangement testing because her initial testing was positive for a deleterious mutation in BRCA1. The counselor contacted the ordering gynecologist to determine what had occurred and what the patient had been told about her results. The gynecologist was shocked, and very upset, to learn that the patient carried a mutation and to realize that she had misinterpreted the result, which was clearly printed in capital letters in a box at the top of the page. The gynecologist had noticed only the wording listed next to the BRCA2 gene and a targeted rearrangement panel that indicated that no mutation was detected in that gene. The gynecologist contacted the patient about this error, and the patient was then seen for follow-up genetic counseling. The patient and her husband were painfully aware that if her results had been read correctly 16 months earlier, she could have had a prophylactic BSO and probably avoided a likely fatal advanced ovarian cancer diagnosis. The patient and her husband indicated that they planned to sue her gynecologist.

Another case in which the significance of test results was misinterpreted demonstrates how inaccurate information given to one patient can impact multiple other family members. A 60-year-old man of Irish ancestry diagnosed with breast cancer was seen for cancer genetic counseling based on his personal history and his family history that included 5 cases of ovarian cancer (Fig. 2). One of his maternal cousins with ovarian cancer carried a known BRCA1 mutation. The patient reported that his sister was tested for this familial BRCA1 by her gynecologist and learned that she did not carry this mutation. She was told that since she did not have this mutation, none of her siblings (including this gentleman) would carry this mutation, and none of them needed testing. After his cancer diagnosis, this gentleman had testing and learned that he carried the familial BRCA1

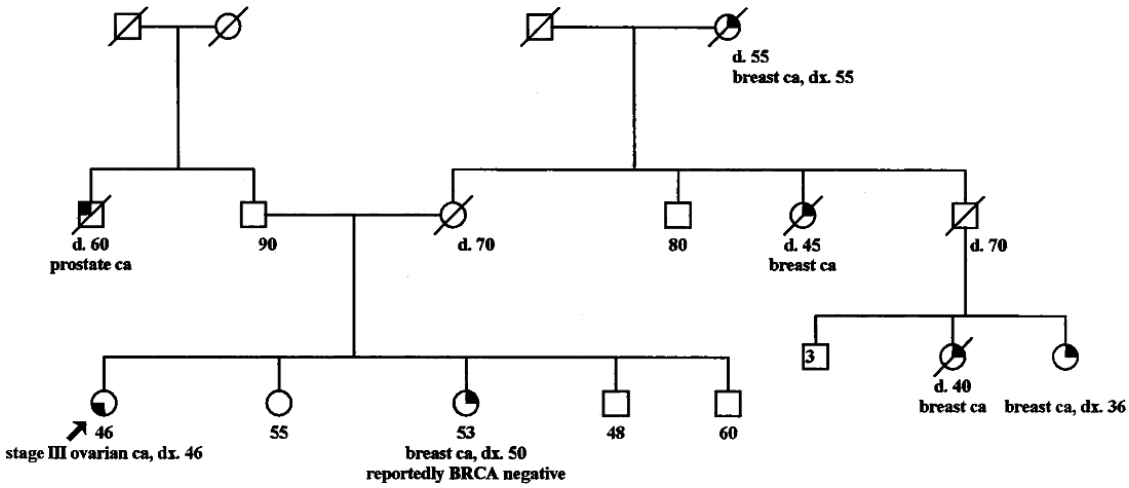

FIGURE 1. Pedigree for a female patient whose BRCA1-positive test result was misinterpreted as negative, resulting in an advanced ovarian cancer diagnosis.

mutation. He was angry that his sister and their family had been given misinformation about their risks. He indicated that he would have sought care for the lump he had found behind his nipple much sooner if he had known he was at increased risk, and this may have allowed him to be diagnosed at an earlier stage, avoid chemotherapy, and to have a better prognosis.

Result Misinterpretation, Leading to Unnecessary Prophylactic Surgery

A 42-year-old patient with a confirmed diagnosis of FAP and an APC gene mutation was referred for genetic counseling by her gastroenterologist because she had had genetic testing several years earlier through her colorectal surgeon, but had never had formal genetic counseling. When the genetic counselor took the patient's personal history, she learned that the patient had had a total hysterectomy and bilateral salpingo-oophorectomy at age 41 years based on her surgeon's assessment that she "was at an increased risk for cancer there" because of her genetic test results. The surgeon had apparently confused the cancer risks associated with FAP with the ovarian and uterine cancer risks seen with Lynch syndrome. This patient had undergone unnecessary surgery and premature menopause because of this misinformation.

One of the more common result misinterpretations in this, and previous, case series was a variant of uncertain significance being falsely interpreted as a known disease-causing mutation. In one case, a 30-year-old woman was referred to a cancer genetic counselor after being tested by her gastroenterologist and told that she carried an MSH6 mutation (Fig. 3). The patient sobbed through her appointment with the genetic counselor indicating that her doctor had told her that she would need to have a hysterectomy and therefore would not be able to have children. She had never had a diagnosis of cancer but had a strong family history of colon cancer including her father, sister, paternal aunt, and paternal grandfather diagnosed at ages 45, 26, 47, and 60 years, respectively (Fig. 3). Upon reviewing her test results, the genetic counselor discovered that the patient actually carried a

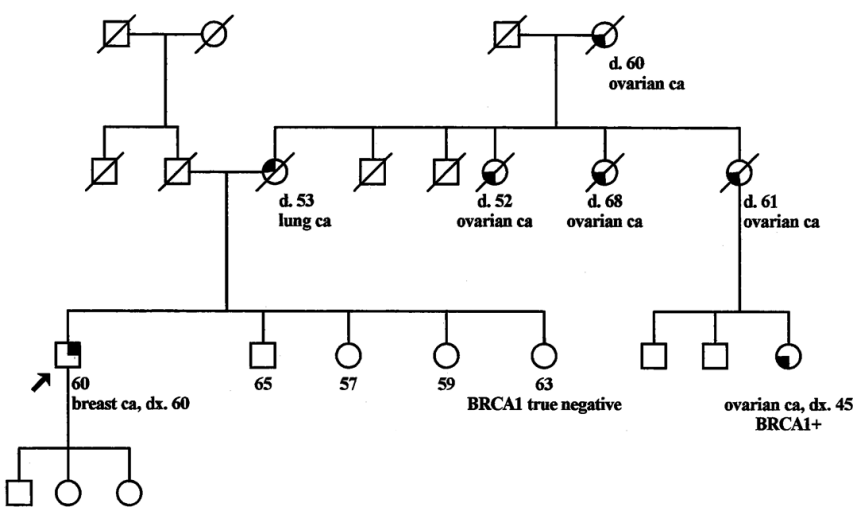

FIGURE 2. Pedigree for a male patient whose sister's BRCA negative test result was misinterpreted leading to a delay in testing and an advanced male breast cancer diagnosis.

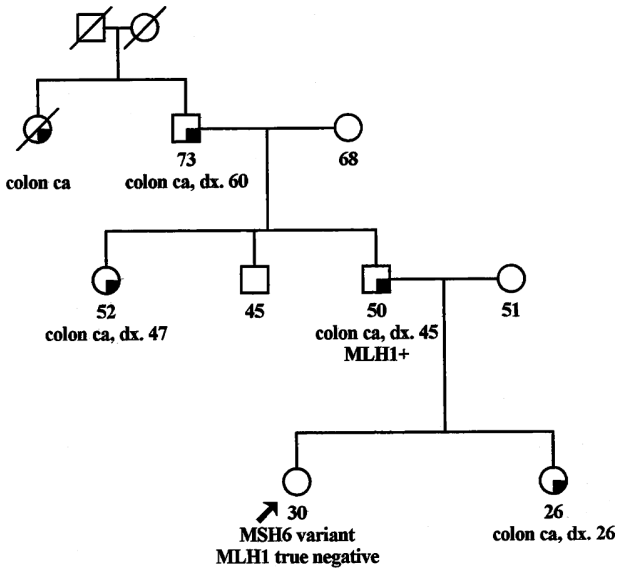

FIGURE 3. Pedigree for a female patient whose MSH6 variant of uncertain significance test result was misinterpreted as a deleterious mutation leading to recommendations for unnecessary prophylactic surgery.

variant of uncertain significance. Many of the affected relatives were living, so genetic testing was recommended in an affected relative. Her father had genetic counseling and testing and learned that he carried a deleterious MLH1 mutation. The patient subsequently had testing and learned that she did *not* carry the MLH1 mutation identified in her father that was responsible for the cancers in her family. She was thus not at increased risk for colon, uterine, and ovarian cancer and did not need to have a prophylactic hysterectomy.

Inadequate Genetic Counseling

In some cases, inadequate genetic counseling was the main error that occurred and included incomplete information about implications and options for the patient and/or their family members and practices that go against widely accepted ethical principles in cancer genetic counseling and testing.

Ethical Issues

The parents of a 7-year-old healthy girl of Ashkenazi Jewish ancestry, at the urging of a relative who is a physician, obtained a test kit from a genetic testing company and requested that their daughter's pediatrician order BRCA testing based on their Jewish ancestry and the father's family history of ovarian cancer. The pediatrician complied with their request, and the child was found to carry a BRCA1 mutation. When the parents were seen for genetic counseling, they were upset to learn that this information would also directly impact whichever parent carried the mutation in terms of increased cancer risk and that either of them could carry this mutation and should have testing since they were both of Jewish ancestry. Upon learning the future impact of this mutation for their daughter and the fact that her medical management in childhood would not change based on this information, they left indicating that they wished they had not had her tested at this time. When there is no immediate medical benefit (ie, interventions that can be offered in childhood), it is almost universally recommended that testing for adult-onset conditions be deferred until adulthood when the individual can make an informed decision about testing because there are potential risks or concerns about testing in childhood including adverse psychosocial reactions, discrimination, and stigmatization.[5–9] This recommendation is also based on the ethical principles of respecting the autonomy of the child and their right not to know.[5–9]

POTENTIAL FACTORS CONTRIBUTING TO ERRORS IN CANCER GENETIC COUNSELING AND TESTING

The literature regarding medical errors across all specialties suggests that certain factors increase the likelihood that errors will occur, including case complexity, time pressures, inadequate experience, insufficient knowledge or training, and poor communication.[10–12] Several of these factors may make these errors more likely among providers without extensive knowledge, training, or certification in genetics than among cancer genetics professionals, including lack of familiarity and inadequate knowledge and training.[10–12] Numerous national and international studies have shown that many providers have inadequate knowledge of genetics to prepare them for providing genetic counseling and testing.[2,13–18] These studies have consistently shown significant deficiencies among nonspecialists in knowledge essential for providing cancer genetic counseling and testing, including inheritance patterns, risk factors for hereditary cancer syndromes, and gene penetrance.[13–18] Even in a recent study of medical residents (who presumably would have the most current education and training in genetics), significant deficits in knowledge of key concepts, including associated cancer risks and inheritance patterns, were identified.[17]

These deficiencies in knowledge are likely related to the fact that the majority of medical professionals have little formal training in genetics.[2,18] A survey of gynecologists found that 65% had no formal classroom or clinical training in genetic testing in gynecologic practice.[18] Even among the youngest physicians (aged ≤40 years), who were likely to have the most modern training, the majority (62.4%) reported not having received formal training in genetics.[18] In 2004, a survey of US and Canadian medical schools found that 62% provided 20 to 40 hours of medical genetics course work, and 18% provided less than 20 hours.[19] Most of this instruction took place during the first year of medical school and focused on general concepts, not practical application.[19]

Time pressures probably also contribute to errors in cancer genetic counseling and testing performed by clinicians without extensive training and knowledge in this area. Genetic counseling and testing are complex and time-consuming processes that minimally involve obtaining a detailed personal and 3-generation family medical history and providing thorough pretest informed consent and posttest result disclosure and interpretation.[20,21] Professional guidelines suggest that the informed consent process should include a discussion of what testing to consider, whom to test in the family, possible test results and their implications for the individual and family members, options for cancer screening and risk reduction, economic considerations, and psychosocial considerations.[20,21] Thus, in busy clinic settings where primary care physicians and gynecologists have an average of 20 minutes or less per patient encounter,[22] it is unrealistic and unfair to ask these providers to add a service as complex as cancer genetic counseling and testing to an already busy appointment. In fact, many physicians self-report lack of time as a barrier to providing genetic counseling and testing services.[2,16,23]

In addition to having inadequate knowledge and time to provide genetic counseling and testing services, experts cite concerns that many physicians have insufficient familiarity with

the unique, complex ethical and psychosocial issues that are often part of the genetic counseling process (e.g., the impact of results on the entire family, policies regarding testing minors for adult-onset conditions, and concerns about genetic discrimination).[2,24–27] Numerous professional guidelines uniformly discourage testing minors for adult-onset disorders (including hereditary cancer syndromes) unless there are immediate medical interventions available in childhood that will reduce morbidity or mortality.[5–9] Yet, a 2010 survey of primary care physicians showed that 31% would "unconditionally" recommend testing a healthy 13-year-old girl for her mother's BRCA mutation.[26] One of the case examples presented above where a pediatrician ordered BRCA testing on a 7-year-old girl provides a parallel clinical illustration of this study.

Clinicians without extensive training and knowledge in genetics may also not be sufficiently aware of current policy guidelines and laws in order to accurately inform patients about insurance coverage for testing, existing protections against genetic discrimination, and whether they are an appropriate candidate for testing.[24,25,27] A 2009 survey of family physicians showed that more than half (54.5%) had no awareness of the Genetic Information Nondiscrimination Act of 2008 (GINA), a national law that provides protection against genetic discrimination by health insurers and employers.[27] Even among those physicians who reported having some basic knowledge of GINA, many were not aware of the particular areas protected (i.e., group health insurance, private individual health insurance, employment) by GINA and the limitations of GINA (i.e., no protections regarding life or long-term care insurance).[27]

A secondary concern raised by these cases is the waste of health care dollars on unnecessary testing and procedures. Particularly in the current economy, rising health care costs are a significant subject of attention from the government, physician groups, employers, and the general public.[28] US health care costs have been consistently increasing at a rapid pace, twice that of inflation. In 2010, US health care expenditures reached $2.6 trillion dollars or 17.6% of the gross domestic product.[29] Many experts agree that health care costs are significantly higher than necessary and that waste, overuse, and inappropriate or unnecessary care are some of the major contributors to this excess.[28,29] In addition to the cases in this series, 2 recent studies demonstrate how unnecessary genetic testing may be contributing to excess health care spending. One survey of 1500 physicians asked them to distinguish between clinical scenarios representing cases where the risk was sufficiently increased to warrant BRCA testing and cases where the risk was low and testing was not warranted based on published guidelines.[30] Although 25% of the physicians had ordered BRCA testing in the past year, 45% chose at least 1 low-risk scenario as warranting testing, and only 19% were able to correctly identify which scenarios warranted tested and which did not.[30] In another recent study, physicians were asked whether to recommend testing and which testing they would order for at-risk relatives of a patient based on the patient carrying a deleterious mutation or a variant of uncertain significance.[31] The majority (82%) would inappropriately order testing when the result was a variant of uncertain significance, and in both situations, most would inappropriately choose to order comprehensive sequencing, which would result in at least a 9-fold increase in unnecessary testing costs.[31] These findings were independent of physicians' experience or specialty.[31] In response to this expensive problem, several insurance companies are now tracking the number of inappropriate requests for genetic testing, requiring prior notification or authorization for genetic testing, encouraging or requiring genetic counseling by providers with expertise and/or board certification in genetics before testing, and covering care by telemedicine genetic counseling services for their members.[32–35]

Numerous lawsuits have found health care providers negligent with regard to genetic testing, including several involving hereditary cancer syndromes.[36,37] Physicians appear to be the most common target of these lawsuits in which they were found negligent for failing to collect a sufficient family history, refer to a genetic counselor or geneticist, recognize the possibility of a hereditary cancer syndrome, recommend appropriate testing, recommend suitable risk reduction options, and/or warn at-risk relatives.[36] In 2 similar lawsuits from the past decade, women who were diagnosed with ovarian cancer and ultimately died of their disease and their families successfully sued their physicians for failing to refer them for genetic counseling and testing and/or advise them about their options for risk reduction based on their strong family histories of breast and ovarian cancer.[37] A number of other cases have found physicians negligent in recognizing and appropriately advising patients regarding hereditary colon cancer in their families.[38]

Over the past decade, direct-to-consumer marketing for genetic tests has become more widespread targeting both physicians and consumers. Although there is no direct evidence to suggest that these campaigns have contributed to an increase in adverse events in cancer genetic counseling and testing, experts have voiced potential concerns. One concern is that genetic testing practice patterns of primary care providers may be more strongly influenced by direct marketing, lay press, and threats of malpractice than by expert protocols and journal articles.[2] Direct-to-consumer marketing campaigns by the testing company that holds the exclusive patents on testing for the BRCA1 and BRCA2 genes have been a particular focus of controversy. This company has openly stated that in order to grow their revenue they expanded their sales force and focused on urging gynecologists and oncologists to provide cancer genetic counseling and testing in their offices rather than referring patients to a genetic counselor.[35] The testing company insists that community physicians are prepared to perform genetic counseling, and their sales force provides "genetic counseling education" for office physicians and their staff.[35] However, this is contrary to the bulk of the available data that suggest that most providers lack the time, knowledge, and awareness to provide adequate genetic counseling. It also conflicts with the Commission on Cancer Program Standards, which directly state that "educational seminars offered by commercial laboratories about how to perform genetic testing are not considered adequate training for cancer risk assessment and genetic counseling."[21] There is clearly a conflict of interest here because the individuals providing the "education" work for a commercial company that profits from the testing.

Another disturbing possibility is that physicians may be delegating the genetic counseling and testing process to office staff. A survey of New York obstetrician-gynecologists showed that, in many cases, office staff, including secretaries, were accountable for completing genetic test requisitions, reviewing test results, and giving test results to patients.[39] Forty-four percent of physicians in the study reported that secretaries filled out genetic test requisitions, 59% reported that secretaries review the results, and 86% report that secretaries communicated results to patients over the phone.[39] These findings raise questions about what steps are taken to ensure that office personnel are properly equipped and capable of performing these tasks, particularly if sales representatives from testing companies are providing the "genetic counseling education" to physicians' office staff.

Recent advances in technology have led to the development of more complicated genetic and genomic testing options,

including multiple gene panels, as well as whole exome and whole genome sequencing. Although these new testing options offer the promise of many benefits in terms of "personalized medicine" and advances in the diagnosis and treatment of both rare and common diseases, they have generated new concerns and heightened existing concerns about the potential medical, legal, social, and ethical challenges of genetic testing.[40–43] Whole exome and whole genome tests generate massive amounts of data, including potentially hundreds or thousands of variants per individual.[40,41] The significance of these variants and the function and clinical impact of many of the genes containing these variants are unknown.[40,43] The interpretation of how these genetic changes impact health is likely to be far more complex, involving weaker associations, lower-penetrance mutations, and interactions between multiple genes and the environment.[42,43] Unfortunately, our ability to generate massive amounts of genetic data has far outpaced our ability to analyze and interpret the clinical significance of these data.[40] Thus, using this information clinically to care for patients poses significant challenges even for providers with extensive knowledge and experience in medical genetics. The amount and complexity of these data also poses significant ethical and legal challenges, including what constitutes informed consent, the potential for incidental findings, what information to disclose to patients, how the data should be stored and shared, who owns the data, and implications for the patient and family members.[40–42]

The cases illustrated here demonstrate that errors with major medical, legal, financial, and ethical implications are occurring today in relatively straightforward genetic testing scenarios. As the field becomes more, and not less, complex, it is unrealistic and unfair to expect the average clinician to provide genetic counseling and testing services alone.

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