Adverse Events in Cancer Genetic Testing: The Third Case Series

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Abstract: After repeated media attention in 2013 due to the Angelina Jolie disclosure and the Supreme Court decision to ban gene patents, the demand for cancer genetic counseling and testing services has never been greater. Debate has arisen regarding who should provide such services and the quality of genetics services being offered. In this ongoing case series, we document 35 new cases from 7 states (California, Connecticut, Florida, Georgia, Missouri, Pennsylvania, and Utah) and the District of Columbia of adverse outcomes in cancer genetic testing when performed without the involvement of a certified genetic counselor. We identified 3 major themes of errors: wrong genetic tests ordered, genetic test results misinterpreted, and inadequate genetic counseling. Patient morbidity and mortality were an issue in several of these cases. The complexity of cancer genetic testing and counseling has grown exponentially with the advent of multigene panels that include rare genes and the potential for more variants of uncertain significance. We conclude that genetic counseling and testing should be offered by certified genetics providers to minimize the risks, maximize the benefits, and utilize health care dollars most efficiently.

Key Words: Cancer genetics, genetic testing, genetic counseling, adverse events, BRCA, Lynch syndrome

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The demand for cancer genetic testing services has never been greater. This is especially true following the May 2013 Angelina Jolie disclosure that she pursued a prophylactic bilateral mastectomy after learning she carries a *BRCA1* gene mutation[1] and the unanimous Supreme Court decision to ban gene patents 1 month later.[2] The SCOTUS decision opened the floodgates for other laboratories to compete in the *BRCA* marketplace, driving down cost and opening access to *BRCA1* and *BRCA2* (*BRCA1/2*). In turn, reporting of *BRCA* mutations can now be included on multigene panel tests that are offered through some laboratories. These panels use next-generation sequencing to detect mutations in multiple genes associated with overlapping phenotypes. The facilitation of proper genetic testing and interpretation of results continues to grow in complexity.

Multiple studies indicate that between 30% and 50% of health care dollars spent on genetic testing are wasted on inappropriate genetic tests and that the majority of physicians order either too much or incorrect testing in even straightforward cases.[3–6] In September 2013, Cigna became the first national insurance company to require that patients receive genetic counseling by a certified provider before they will consider coverage for hereditary breast or colon cancer testing. In a surprising response, the American Society of Clinical Oncology opposed Cigna's decision, despite more than a decade's worth of data demonstrating that the majority of physicians do not have the time or expertise to offer genetic counseling and testing.[5–19] The American Society of Clinical Oncology published a statement that the Cigna policy creates "a barrier to the appropriate use of genetic testing services" and "prohibits patients from seeking this service from their own providers."[7] Fueling the debate about who is best to perform these services, a large laboratory continues to market genetic testing as a "simple blood test" and encourages clinicians, nurses, and now mammogram technicians, with little or no training in genetics, to offer this testing to patients.[21]

In 2010 and 2012, we published the first 2 case series documenting errors in the delivery of cancer genetics services and the implications for patients and clinicians.[22,23] In these articles, we identified 3 major themes of errors: wrong genetic tests ordered, genetic test results misinterpreted, and inadequate genetic counseling. Since then, 20 additional reports of negative outcomes in cancer genetic counseling have been documented by researchers in Minnesota.[24]

In this article, we present 34 new cases of adverse outcomes in cancer genetic counseling and testing obtained from genetic counselors participating in the National Society of Genetic Counselors Cancer Special Interest Group.

METHODS

The National Society of Genetic Counselors Cancer Special Interest Group participants were invited to submit cases illustrating errors that occurred when cancer genetic testing was performed without the involvement of a certified genetic counselor. Cases were collected in October 2013, and those selected represent incidents in 7 states (California, Connecticut, Florida, Georgia, Missouri, Pennsylvania, and Utah) and the District of Columbia and were chosen for inclusion because they represent unique themes or major patterns.

The pedigrees presented have been altered to protect patient and family confidentiality. The alterations were made in such as was as not to detract from the clinical discussion.

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RESULTS: THEMES IN CLINICAL CASE REPORTS

Wrong Test Ordered or Recommended

In 13 reported cases, the wrong genetic test was ordered. In 2 cases, a potentially avoidable cancer resulted; in others, it represented a waste of health care funds.

Wrong Test Ordered, Resulting in Cancer Diagnoses

The clinicians of a 33-year-old male diagnosed with diffuse gastric cancer ordered Lynch syndrome testing, which was negative. The patient's sister was diagnosed with diffuse gastric cancer at age 23 years (Fig. 1). A half-sibling was later diagnosed with stage IV diffuse gastric cancer at age 31 years. Genetic testing ordered by a genetic counselor in the Southeast on this patient revealed that she carried a germline CDH1 mutation. This patient died within a year of her advanced cancer diagnosis. If the appropriate genetic syndrome had been recognized and germline testing ordered properly, this young woman's diagnosis and death may have been circumvented. In addition, the siblings' diagnoses of diffuse gastric cancer in their 20s to 30s warranted a clinical diagnosis of hereditary diffuse gastric cancer syndrome. Although the age at diagnosis is variable within hereditary diffuse gastric cancer syndrome families, the average age at gastric cancer diagnosis is 38 years.[9–11] Therefore, prophylactic gastrectomy is often recommended before age 28 years, 10 years younger than the average age at diagnosis.[25–27] In this family, clinical recommendations should have included close surveillance with endoscopy beginning in the teenage years and consideration of prophylactic gastrectomy given the family history of a diagnosis at age 23 years.

In a second case, a woman diagnosed with breast cancer in her mid-20s was offered *BRCA1/2* testing by her oncologist. When testing revealed no mutation, she was treated with breast-conserving therapy that included a lumpectomy, chemotherapy, and radiation. She was diagnosed with a second primary breast cancer in the ipsilateral breast 2 years later and again treated with breast-conserving therapy and radiation. At age 30 years, she was seen by a genetic counselor, who ordered p53 testing, and a mutation was detected. A diagnosis of breast cancer before the age of 30 years is suggestive of a p53 mutation,[28–31] and the National Comprehensive Cancer Network (NCCN) testing guidelines now include a recommendation for p53 testing in women diagnosed with breast cancer at younger than 36 years whose *BRCA1/2* testing is negative.[32] The absence of p53 testing in this patient denied her the ability to tailor her treatment during both of her breast cancer diagnoses, including consideration of bilateral mastectomy, avoidance of radiation, and surveillance for other Li-Fraumeni–associated cancers. Radiation exposure in p53 carriers is known to increase the risk of subsequent cancers, such as second primary breast cancers, sarcomas, and thyroid cancers, particularly within the radiation field of radiation, and likely contributed to the development of this patient's second breast cancer diagnosis within the same breast.[33,34] The patient is now pursuing a bilateral mastectomy with reconstruction, which will likely be complicated by her 2 previous surgeries and radiation. Her risks for other cancers seen in this syndrome (soft tissue sarcomas, osteosarcomas, brain tumors, adrenocortical carcinoma, leukemias, and various others) are elevated based on her mutation status and warrant surveillance.[35,36] The implications for her family members are significant, and there are implications even for the youngest of family members if they are confirmed to carry the familial p53 mutation.[36]

Wrong Test Ordered, Misuse of Health Care Dollars, or Inappropriate Testing

In 2 cases, the hospital send-out laboratories, which do not include genetics professionals, changed incoming test orders. In the first case, *BRCA1* and *BRCA2* testing was ordered for a 55-year-old African American woman with an advanced triple-negative breast cancer. The send-out laboratory changed the order to a more expensive, multigene panel to include detection of mutations in genes associated with hereditary breast, colon, and ovarian cancers that, at the time, did not include *BRCA1/2* testing. After the turnaround time had passed, the error was revealed, and the laboratory director was questioned about the change to the test order. The laboratory director confidently replied that the panel included testing for the *BRCA1/2* genes when it, in fact, did not. This testing was not covered by the patient's insurance, and she was billed ~$4000 out of pocket. The patient was

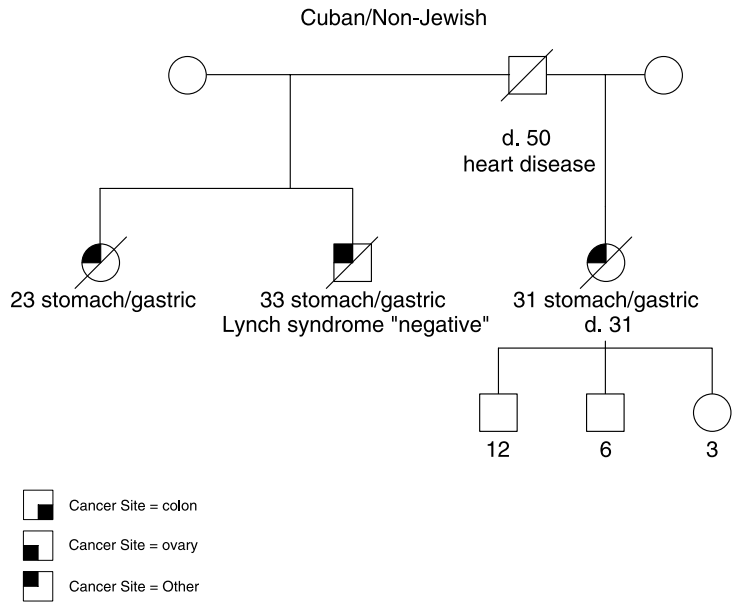

FIGURE 1. The wrong genetic test was ordered in this family resulting in a cancer diagnosis.

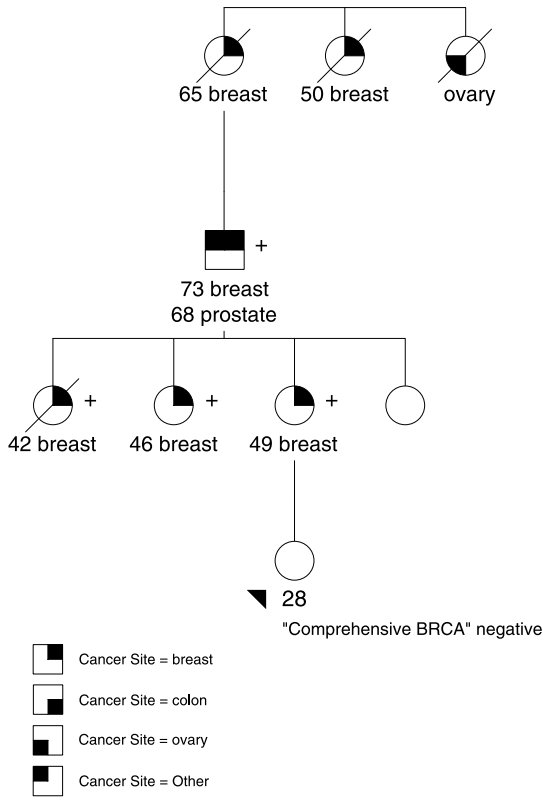

FIGURE 2. The wrong genetic test was ordered in the family resulting in a misuse of healthcare resources.

ultimately referred for genetic counseling; *BRCA1/2* was ordered, and a *BRCA2* mutation was revealed. In a second case, the send-out laboratory added Lynch syndrome testing and deleted APC rearrangement and MYH testing for a 66-year-old man with polyposis. The patient was lost to follow-up and never had the recommended testing.

In 5 reported cases from the Northeast, Southeast, and Southwest, clinicians ordered "comprehensive *BRCA1/2*" testing in families with a reported familial *BRCA* or Lynch syndrome mutation. Comprehensive *BRCA1/2* testing costs up to ~$3340, and single-site testing costs up to $475, with the average cost of testing now dropping. This overordering of testing represents unnecessary spending of health care dollars, at the expense of insurance companies and/or the patient. It can also result in the patient receiving inaccurate results. In the most striking of cases, a 28-year-old unaffected woman tested "negative" through *BRCA1/2* full sequencing and was told by her gynecologist that she was no longer at risk (Fig. 2). However, this family's mutation was detectable only by rearrangement testing, which had not been ordered. Rearrangement testing includes the detection of large genomic deletions and duplications. The patient learned of the mistake 2 years later when another family member's genetic counselor reviewed her results. The patient experienced significant anxiety learning that she was still at 50% risk for the familial mutation, required additional testing, and had not been followed as high risk for 2 years.

In another reported case from the Mid-Atlantic, a general internist ordered what he thought was *BRCA1/2* testing on an unaffected 24-year-old. When she tested "positive," he told her she was at high risk for breast and ovarian cancer and referred her for cancer genetic counseling. Upon review of her test result, BCR-ABL was ordered, not *BRCA1/2*. BCR-ABL is a test to diagnosis, monitor the response to treatment, and detect disease recurrence in individuals with leukemia. This patient needed subsequent referral to hematology for clarification of her result.

In another case, a genetic counseling office in the Northeast received a call from a mother after receiving a laboratory order for *BRCA1/2* testing on her 3 minor children (aged 17, 14, and 12 years) from their pediatrician. The children's paternal aunt was known to carry a *BRCA2* mutation. Testing minors for adult-onset conditions is generally not recommended as the risks for *BRCA*-related cancers in young adults are extremely low, and medical management options usually do not change until age 25 years for young *BRCA*-positive females.[37] Instead of testing 3 minor children, the genetic counselor recommended testing the children's father for the known mutation, to which he was amenable. His results revealed that he did not carry the familial mutation and was interpreted as a "true negative." The genetic counselor's approach was in line with numerous organizations' recommendations against testing minors and saved 3 minor children from the potentially anxiety-provoking and inappropriate process of childhood testing for an adult-onset condition.[37] This approach was also vastly more cost-effective.

Other erroneous test examples include *BRCA1/2* testing ordered on a blood sample in a female patient who was a previous bone marrow transplant recipient and was cytogenetically 46, XY. The DNA test result represented her donor's genetics, instead of her own, and although she was a good candidate to have *BRCA1/2* testing based on an early-onset breast cancer diagnosis, her insurance company would likely deny testing as it had already been performed, but erroneously. In patients with previous bone marrow transplants, the high quantity of donor cells in blood and saliva requires the collection of cultured cells or fresh/fresh frozen tissue for accurate germline DNA testing. In another case, a 33-year-old with a sigmoid colon cancer had normal microsatellite instability (MSI) screening on his tumor. The patient had no family history of cancer; however, his oncologist went on to order Lynch syndrome testing (~$4500 at the time), an expensive germline test in a patient whose risk for Lynch syndrome had been previously reduced by normal MSI screening in combination with a negative family history.

Results Misinterpreted

Genetic test result misinterpretation was another common theme among the cases reported. We received 9 cases of errors resulting in cancer diagnoses, unnecessary surgery, or inaccurate medical management recommendations.

Result Misinterpreted, Resulting in Cancer Diagnoses

A 52-year-old unaffected woman accompanied her niece for genetic counseling in a Mid-Atlantic state (Fig. 3) and reported that she tested *BRCA1/2* negative through her gynecologist years ago. She commented that her past experience was "nothing like this, my gynecologist just made me spit in a tube, and they called and told me it was negative." The genetic counselor obtained these records, which revealed a *BRCA1* mutation had been detected 4 years earlier. The gynecologist wrote "neg " with his signature on the result. The genetic counselor notified the gynecologist of the mistake, and he contacted the patient stating that her first result revealed a variant that had recently been updated as a mutation. This was not accurate—her mutation was clearly delineated on her original report. The patient went on to have an uneventful prophylactic bilateral salpingo-oophorectomy (BSO). However, she was diagnosed with a stage 1B triple-negative breast cancer upon workup for prophylactic bilateral mastectomy, which required surgery and chemotherapy. She stated several times that she would have had prophylactic surgery years ago if she had

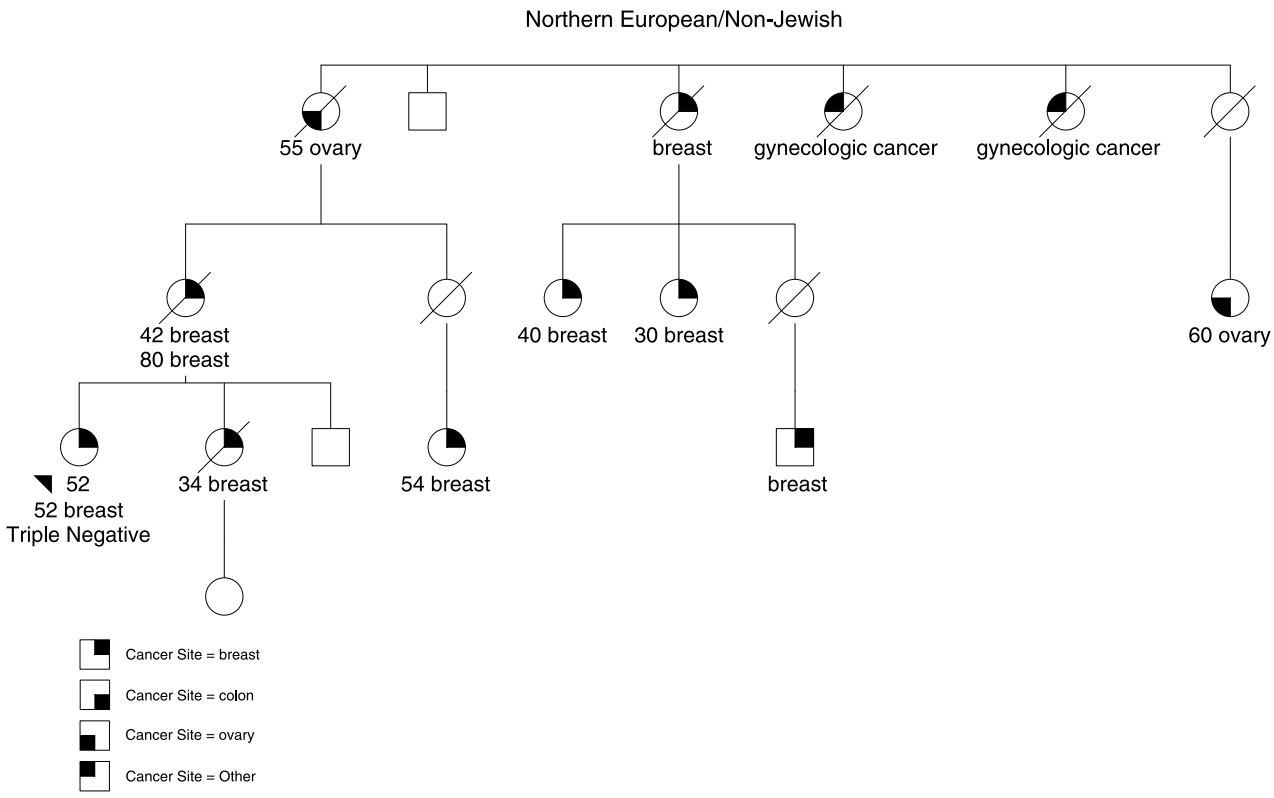

FIGURE 3. This woman's genetic testing was misinterpreted resulting in her cancer diagnosis.

known her *BRCA* status because she watched her mother and sister die of breast cancer. Subsequently, her 35-year-old niece tested positive for the familial mutation and was diagnosed with a stage IV triple-negative breast cancer with bone metastases upon "prophylactic" bilateral mastectomy. Another relative developed an advanced ovarian cancer. Both of these relatives have aggressive cancers with poor prognoses. These relatives' diagnoses and probable death may have been prevented if the original patient had had genetic counseling, and her straightforward results had been interpreted correctly. This would have given her the opportunity to notify at-risk family members sooner.

Result Misinterpreted, Leading to Unnecessary Surgery

We received 4 cases of inappropriate surgeries from the Northeast, Mid-Atlantic, and Western states. These included 3 reported cases of prophylactic oophorectomies and 1 prophylactic bilateral mastectomy based on the misinterpretation of *BRCA* "variant of uncertain significance" or "variant, favor polymorphism" as true deleterious mutations. In 1 case, the gynecologist performed BSO in multiple family members and reported to the genetic counselor that she feels that the variant classification (favor polymorphism) must be wrong because there has to be something in this family and this must be it. In the fifth case, a surgeon ordered *BRCA1/2* testing for a 61-year-old with triple-negative breast cancer who did not meet NCCN guidelines for testing. The patient's surgeon referred her for genetic counseling when she tested *BRCA* "positive." However, the genetic counselor's review of the result revealed that the patient in fact carried a "genetic variant, favor polymorphism" and not a mutation. Her scheduled oophorectomy was canceled.

Result Misinterpretation, Resulting in Inaccurate Medical Management Recommendations

A 62-year-old man from the Northeast was given a clinical diagnosis of Muir-Torre syndrome by his dermatologist after immunohistochemical staining on a sebaceous adenoma detected at age 58 years was abnormal. Immunohistochemistry (IHC) looks at the presence or absence of Lynch syndrome proteins (MLH1, MSH2, MSH6, and PMS2) in tumors. There are limited data on the percentage of sporadic sebaceous adenomas that exhibit an abnormal IHC or the sensitivity and specificity of this approach.[38] However, it has been suggested that routine IHC not be performed on sebaceous lesions in the absence of a significant personal or family history of colorectal cancer.[38] The referring physician recommended that the patient have a colonoscopy every 2 years because of the increased risk of colon cancer. Multiple colonoscopies over 6 years revealed a total of 2 polyps. This patient's history included more than 1000 skin lesions, the majority of which were squamous cell carcinomas. He also had a melanoma diagnosed at age 55 years. His family history included several cases of melanoma and a basal cell carcinoma. There were no reported cases of colon, uterine, ovarian, or gastrointestinal cancers in the family. When the referring provider was questioned about the diagnosis of Muir-Torre that was documented in this patient's medical record, the provider was uncertain of the reason for this diagnosis. Panel testing, including genes related to Lynch syndrome and other skin-related syndromes, was negative for detectable mutations. Although this gentleman appears to have a predisposition to skin cancer, neither his personal nor family history warrants a Muir-Torre diagnosis or frequent colonoscopies, screenings that are not without cost or possible complications.

In a somewhat similar case, also from the Northeast, a 51-year-old man was told he had Lynch syndrome by his oncologist based on abnormal tumor testing. Screening studies on his tumor revealed a high MSI, and IHC demonstrated that MLH1/PMS2 were absent. BRAF testing and MLH1 methylation were negative. The patient was referred to genetic counseling to discuss the meaning of Lynch syndrome for his own medical management and implications for his family members, including 3 teenage children. Although his tumor studies were abnormal, no germline genetic testing could be found in his records. A conversation with his oncologist revealed that germline testing had never been ordered, and that this oncologist thought his screening tests meant that the patient had Lynch syndrome. The genetic counselor ordered MLH1 sequencing and deletion/duplication testing, which revealed no mutations, and the patient was counseled that these results were reassuring in context of his family history (Fig. 4).[39] The patient was relieved, but still very skeptical and confused after believing he had Lynch syndrome for several months.

In a pediatric case, an oncologist ordered p53 sequencing only in a 12-year-old girl diagnosed with an astrocytoma. Her results revealed homozygous p53 variants that were interpreted as a common polymorphism on the test report. The family was told that the findings were significant, which led them to demand emergency genetic counseling for the "mutation" in their family and testing for unaffected family members. The genetic counselor's research and interpretation concluded that these variants were common in the family's ethnic background and not likely to be significant. Affected family members were offered additional testing (p53 rearrangement testing) but were lost to follow-up. The family continues to be confused by the initial result and frustrated that unaffected family members have not been offered testing.

No Genetic Counseling

Twelve cases were received that illustrated little or no genetic counseling. In the most striking of these cases, a young man died of an advanced cancer diagnosis, and in another family, children were needlessly screened repeatedly with colonoscopies.

No Genetic Counseling, Resulting in an Advanced Cancer Diagnosis and Death

A 21-year-old man was referred for genetic counseling after presenting to the emergency room with severe abdominal pain that was determined to be widely metastatic colon cancer. At the time of surgery, he was found to have multiple juvenile polyps and later tested positive for a *BMPR1A* mutation (associated with juvenile polyposis syndrome) via his genetic counselor. The genetic counselor's review of the case revealed that the patient's father had been diagnosed with multiple juvenile polyps at age 14 years, treated with a colon resection, and presented with advanced colon cancer at age 51 years (Fig. 5). Although the father's medical records documented juvenile polyposis, and he was treated at a major medical institution in the Northeast with a well-known cancer genetics program, he was never referred for genetic counseling or testing. The father died within a year of his diagnosis at age 51 years. The father's presentation was consistent with juvenile polyposis, yet he was never offered genetic counseling or testing. His detailed medical records lacked genetic

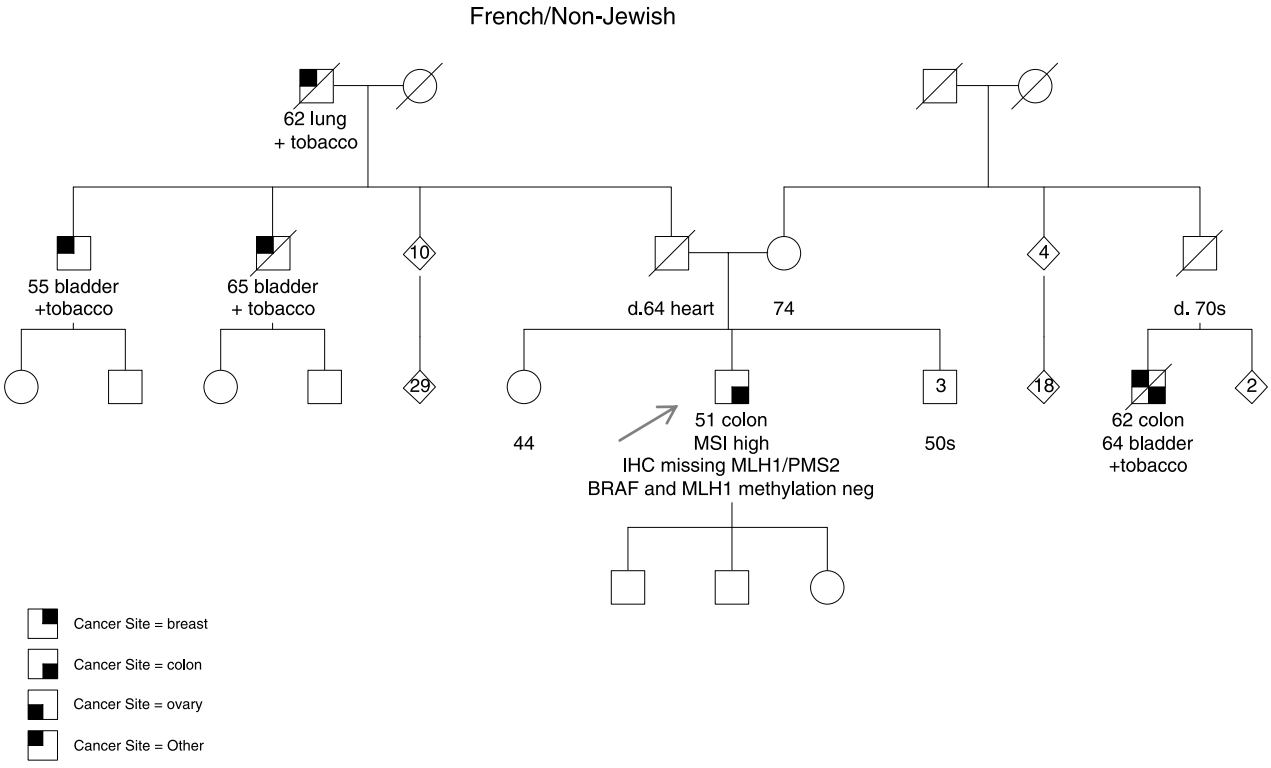

FIGURE 4. This patient's results were misinterpreted and he was given inaccurate medical management recommendations in the context of his large, mostly unaffected maternal and paternal families.

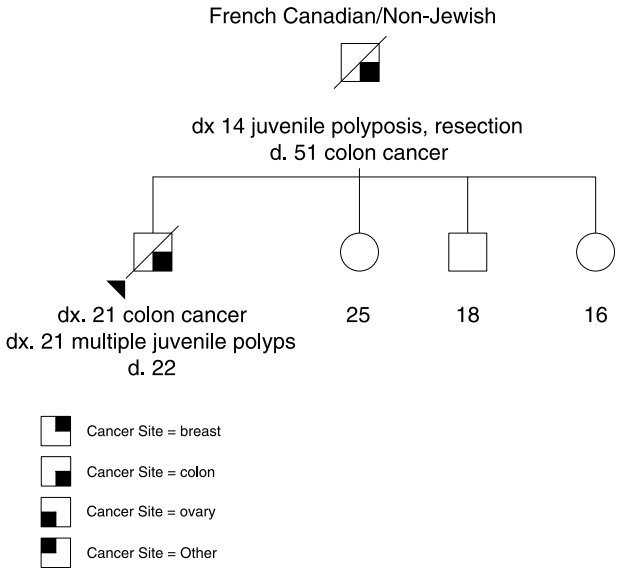

FIGURE 5. This family received no genetic counseling resulting in an advance dearly-onset cancer diagnosis and death.

counseling, testing, and surveillance recommendations for his family members. The young consultant in this case died shortly after his 22nd birthday.

No Genetic Counseling Resulting in Inaccurate Medical Management Recommendations

A gastroenterologist from the Northeast recommended following all unaffected family members from a family with a clinical diagnosis of familial adenomatous polyposis with colonoscopies beginning at age 9 years instead of referring them to genetic counseling. No family member had been offered genetic testing. A 12-year-old unaffected boy was finally referred to genetic counseling after having several normal colonoscopies. His mother attended the appointment with him, which revealed that she was diagnosed with polyposis at age 13 years, had a colectomy due to polyps at age 21 years, and also has congenital hypertrophy of the retinal pigment epithelium. The young patient's maternal uncle and first cousin were diagnosed with polyposis at age 12 years and had colectomies. This patient's mother was offered testing and found to carry a frank APC mutation. The 12-year-old patient was tested and is "true negative" for his mother's mutation. The gastroenterologist's recommendation to offer colonoscopies to all unaffected family members represented inappropriate use of invasive, expensive screening when genetic testing was available to provide informative carrier status.

No Genetic Counseling

We received reports of 10 additional cases where little to no genetic counseling was provided to the patient. This included a 27-year-old *BRCA2*-positive woman who was tested by her oncologist based on her recent breast cancer diagnosis and planned to have a BSO in her late 20s, although this recommendation was not consistent with her test results or her personal or family history. These patients' genetic counseling appointments were often their first exposure to accurate information regarding their testing and, for some, the first time they were learning of their results that had never been disclosed by their ordering providers. In 1 case, a 36-year-old woman diagnosed with a triple-negative breast cancer had repeatedly requested genetic counseling and was told she was not a candidate because she was not Jewish. The patient was offered testing 5 years later, tested *BRCA1* positive, and was not offered genetic counseling or resources. The patient finally self-referred to genetic counseling several years later and was overwhelmed with gratitude at the amount of support references given to her. In another case, a 56-year-old woman diagnosed with triple-negative breast cancer repeatedly asked her surgeon and oncologist for a referral to genetic counseling before deciding on her treatment plan. She was told that she was not a candidate and went on to have breast-conserving therapy that included radiation. She was eventually referred to genetic counseling to appease her. Her personal history of a triple-negative breast cancer diagnosed under age 60 years met NCCN testing guidelines, and her family history of breast and ovarian cancer added to her risks. She learned that she carried a *BRCA1* mutation and went on to pursue prophylactic BSO. She is now planning to have a bilateral mastectomy, which will likely be complicated by her previous radiation treatment.

DISCUSSION

The cases presented here add to previously published literature demonstrating that inaccurate ordering and interpretation of genetic testing result in inefficient use of limited health care dollars, inappropriate medical management recommendations, unnecessary prophylactic surgeries, psychosocial distress, false reassurance for patients, and increased morbidity and mortality.[22–24]

Numerous studies have evaluated factors contributing to errors in cancer genetics, including deficiencies in time, education, training, experience, and knowledge, as well as limitations in appropriate risk assessment and case interpretation by non-genetics professionals.[7–19] Data demonstrate that many medical providers have difficulty interpreting even basic pedigrees and genetic test results.[40–42] In a recent study, ~80% of primary care physicians rated themselves on their personal knowledge of breast and colon cancer genetics as "not at all" or "somewhat" confident.[43] This is alarming, given that one third to one half of these same providers would not refer to a genetics specialist, even when they suspected a serious hereditary cancer syndrome.

As genetic technology continues to grow and becomes more commonplace, accurate test ordering and interpretation will be paramount in maximizing the benefits, and minimizing the risks, of this technology. Unfortunately, errors in these areas are very common.[42]

In parallel with the theme "wrong test ordered" presented here, evidence continues to mount that the majority of physicians order either too much or incorrect testing in even straightforward cases.[4–6] In 1 publication, genetic counselors at a diagnostic testing laboratory modified or canceled an average of 107 genetic test orders per month after reviewing the appropriateness of the case.[4] This represented a modification or cancelation of ~30% of tests because of inaccurate ordering and a savings ~$36,451 per month. With the cost of cancer genetic tests averaging $3000 to $5000, this represents a tremendous system-wide waste of health care dollars and inaccuracy. These financial burdens are likely transferred to larger patient populations and society as many medical institutions and insurance companies absorb the initial costs of these mistakes.

The complexity of testing reached new heights with the unanimous June 2013 Supreme Court decision to ban gene patents. This decision opened the floodgates for other laboratories to compete in the *BRCA1/2* marketplace, and the majority have done so by including *BRCA1* and *BRCA2* in multigene panels. There are now more than 5 laboratories offering *BRCA* "panels" whose genes, costs, turnaround times, and insurance coverage vary significantly. Depending on the patient's personal or family history, there are other panels specifically geared toward breast, ovarian, uterine, kidney, colon, and pancreas cancer. Genetic testing for heritable breast and ovarian cancer syndrome and Lynch

syndrome are 2 of the more recognizable cancer syndrome; thus, nongenetics providers often order *BRCA1/2* or Lynch alone, and a negative result is typically the stopping point. Providers may tell families that the cancers are not hereditary, period, and just "bad luck." Although this may be the appropriate stopping point for many individuals/families, additional single-gene or panel testing should be considered in appropriate families whose history are suggestive of several different genetic syndromes, or those with overlapping phenotypes.[44] This testing may need to be considered upfront as many insurance companies are unlikely to pay for subsequent testing that could have been covered if an appropriate panel was ordered initially. For example, many genetic counselors consider a 6-gene panel related to a hereditary predisposition to breast cancer for women diagnosed with breast cancer at younger than 36 years to obtain information on *BRCA1/2* as well as p53.[32] Based on the personal and family history features presented, clinicians' development of differential diagnosis is critical to guide their testing strategies. Our cases series illustrates that nongenetics providers have difficulty choosing an appropriate genetic test even in "straightforward" scenarios and existing literature supporting this.[4–6] The advent of multigene panels is likely to add to the complexity of choosing which test is most appropriate for which patient in varying clinical settings.

The expanded test offerings have also compounded the intricacies of result interpretation and recommendations made for medical management. While some panels include only genes with established clinical management guidelines (e.g., *p53*, *BRCA1*, *CDH1*), others include a laundry list of upward of 50 genes, many of them lesser-known genes (e.g., *BRIP1*, *NBN*, *MRE11A*) for which cancer risks are ill-defined and medical management options unknown. It is expected to take several years to compile accurate cancer risk estimates and appropriate recommendations for surveillance and risk reduction for many of the lesser-known genes. The counseling of patients who test "true negative" for moderate to low penetrance genes is also complicated by the absence of strong causative data to link these genes to the phenotype within the family. Risk estimation in such families and the recommendations for medical management will likely result from a blend of test results and family history information. Furthermore, the rate of "variants of uncertain significance" will likely be higher in the lesser-known genes, and the reporting style of these variants is likely to vary from one laboratory to another. As the cost of testing technology continues to decrease (with some multigene panels costing just a few hundred dollars less than traditional *BRCA1/2* testing [~$4000]), the cost-effectiveness of ordering multigene panels is appealing. However, clinicians ordering these panels should be fully aware and ready to tackle the challenges posed by the results of these tests.

This is particularly concerning in an era in which testing companies are canvassing physicians, and now mammography technicians, and encouraging them to perform their own testing.[21] Clinicians are also being approached by large commercial laboratories offering to provide medical management recommendations for patients on whom they order expensive, multigene panels. They propose doing this based on the personal and family history that the clinician has included with the sample. However, test request forms used to document this information are often incomplete. Sifri et al[45] reported that ages of cancer diagnoses were elicited only 8% of the time by primary care physicians. In addition, patient reports of their family history are often inaccurate and need to be confirmed with records, when possible.[46] Results need to be interpreted in combination with the affected/unaffected status of the individual tested, family structure, ratio of affected/unaffected relatives, data on family members who altered their cancer risks artificially (e.g., total hysterectomies at young ages, which reduces the risk of ovarian, uterine, and breast cancers), and confirmation of pathology and family history with medical records. Interpretation by a third-party laboratory, without direct patient contact and detailed family history information, is fraught with inaccuracies. The potential impact of result misinterpretation on the patient and his/her family is great, and therefore, accurate, methodical interpretation is paramount.

The free market for *BRCA1/2* testing has also created competition among laboratories vying for a piece of these sales. Laboratories have begun to pressure their affiliates and use manipulative tactics to secure their profits in this volatile field. Genetic counseling centers have reported pressure from clinicians to use specific laboratories for testing, while these same clinicians are listed as receiving financial incentives or hefty speaker's fees from these laboratories. The conflict of interest is clear. Other laboratories have approached genetic counseling centers threatening to aggressively market/siphon off their referring clinician base if the center did not use their product.

Many professional groups have recognized the need for proper informed consent, accurate test ordering, and complex result interpretation, and these organizations have adopted standards encouraging clinicians to refer patients to genetics experts. The US Preventive Services Task Force recommends that women whose family history is suggestive of a *BRCA1/2* mutation be referred for genetic counseling before being offered genetic testing.[47] The American College of Surgeons Commission on Cancer standards include "cancer risk assessment, genetic counseling, and testing services provided to patients either on-site or by referral, by a qualified genetics professional."[48] Access to genetic counseling is improving with Internet, phone, and satellite-based telemedicine services available.[49] Insurers are recognizing the need for accurate ordering/interpreting, and several are requiring genetic counseling by a certified genetic counselor before genetic testing is covered.[50]

This series of case reports adds to the existing literature of errors in the delivery of cancer genetic services when performed without genetic counseling by a certified provider. The method of case collection from cancer genetic professionals is an important potential bias, and the study was qualitative, not systematic. Nongenetics professionals' perspectives on these cases were not solicited, and thus their input not included. The cases illustrated here shine a light on errors that are occurring at alarming frequencies nationwide. While some nongenetics providers have taken it upon themselves to become well versed in genetics, as the use of genetic technology becomes less expensive and inversely complex, it is unrealistic to expect clinicians without specialized graduate training in genetics to provide these services. It will only be with the maintenance of high standards for thorough genetic counseling by certified providers that potential risks of genetic testing will be reduced and the maximum benefits of genetic technology realized.

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