Errors in Genetic Testing: The Fourth Case Series

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Purpose: In this ongoing national case series, we document 25 new genetic testing cases in which tests were recommended, ordered, interpreted, or used incorrectly.

Methods: An invitation to submit cases of adverse events in genetic testing was issued to the general National Society of Genetic Counselors Listserv, the National Society of Genetic Counselors Cancer Special Interest Group members, private genetic counselor laboratory groups, and via social media platforms (i.e., Facebook, Twitter, LinkedIn). Examples highlighted in the invitation included errors in ordering, counseling, and/or interpretation of genetic testing and did not limit submissions to cases involving genetic testing for hereditary cancer predisposition. Clinical documentation, including pedigree, was requested. Twenty-five cases were accepted, and a thematic analysis was performed. Submitters were asked to approve the representation of their cases before manuscript submission.

Results: All submitted cases took place in the United States and were from cancer, pediatric, preconception, and general adult settings and involved both medical-grade and direct-to-consumer genetic testing with raw data analysis. In 8 cases, providers ordered the wrong genetic test. In 2 cases, multiple errors were made when genetic testing was ordered. In 3 cases, patients received incorrect information from providers because genetic test results were misinterpreted or because of limitations in the provider's knowledge of genetics. In 3 cases, pathogenic genetic variants identified were incorrectly assumed to completely explain the suspicious family histories of cancer. In 2 cases, patients received inadequate or no information with respect to genetic test results. In 2 cases, result interpretation/documentation by the testing laboratories was erroneous. In 2 cases, genetic counselors reinterpreted the results of people who had undergone direct-to-consumer genetic testing and/or clarifying medical-grade testing was ordered.

Discussion: As genetic testing continues to become more common and complex, it is clear that we must ensure that appropriate testing is ordered and that results are interpreted and used correctly. Access to certified genetic counselors continues to be an issue for some because of workforce limitations. Potential solutions involve action on multiple fronts: new genetic counseling delivery models, expanding the genetic counseling workforce, improving genetics and genomics education of nongenetics health care professionals, addressing health care policy barriers, and more. Genetic counselors have also positioned themselves in new roles to help patients and consumers as well as health care providers, systems, and payers adapt to new genetic testing technologies and models. The work to be done is significant, but so are the consequences of errors in genetic testing.

Key Words: Cancer genetic testing, direct-to-consumer screening and testing, genetic counseling, genetic counseling delivery models, genetic services, genetic testing, genetic testing adverse events,
genetic test misinterpretation, genomics, multigene panel testing

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The availability of genetic testing is growing at an exponential rate. In a 2018 study providing an overview of the current genetic testing landscape, authors estimated that there were approximately 75,000 genetic tests on the market, with 10 new tests being introduced daily.[1] Fourteen percent of these tests, and 2 to 3 of the new tests introduced per day, were panel tests, a category that includes (but is not limited to) multigene panels (e.g., disease-specific panels), whole-exome sequencing tests, and whole-genome analysis tests.

Although multigene tests are widely available, especially in the oncology setting, many experts, including the National Comprehensive Cancer Network (NCCN), note that they are best used in the context of expert genetic counseling given their complexity.[2] Challenges of multigene panels include the 20% to 30% of variants identified by such tests are variants of uncertain significance; pathogenic variants in moderate risk genes may not be actionable; data with respect to newer genes may be limited; unexpected pathogenic variants may be detected that do not align with a patient's medical/family history; and differences in testing techniques, technologies, interpretation, and reporting by the various laboratories.

In addition to increasing availability of medical-grade genetic testing, there has been rapid growth in direct-to-consumer (DTC) genetic testing. Direct-to-consumer testing refers to tests that consumers can purchase online themselves, with either no or very limited involvement of a physician or health care provider. Direct-to-consumer kits are sent directly to consumers where they can provide a sample at home (often a saliva sample) and send it back to the company. Most consumers receive their results online. More than 14 million people have undergone such DTC testing, and that number is expected to reach 100 million by 2021.[3] In the genetics space, such testing may include ancestry, lifestyle/fitness, entertainment, and/or some health information (including reporting of the common Jewish pathogenic *BRCA1/2* variants).[4] Some companies also allow users to download their raw data files. There are third-party tools that allow raw data downloads from DTC to be analyzed,

although medical-grade confirmation of any finding is necessary, a point that is often missed by consumers and some providers.

We previously published 3 case series on adverse outcomes due to errors in genetic testing in 2010, 2012, and 2014. Increasing access to, and complexity of, available genetic information without genetics expertise continues to contribute to such errors. In this article, we present 25 new cases of errors in genetic testing obtained from genetic counselors (GCs) after sending invitations for case submissions through the general National Society of Genetic Counselors (NSGC) Listserv, the NSGC Cancer Special Interest Group, private GC laboratory groups, and social media.

METHODS

An invitation to submit cases of adverse events in genetic testing was issued to the general NSGC Listserv, the NSGC Cancer Special Interest Group members, private GC laboratory groups, and via social media platforms (i.e., Facebook, Twitter, LinkedIn). Examples highlighted in the invitation included errors in ordering, counseling, and/or interpretation of genetic testing and did not limit submissions to cases involving genetic testing for hereditary cancer predisposition. Clinical documentation, including pedigrees, and approval of case representation were requested of those submitting cases. Twenty-five cases were accepted, and a thematic analysis was performed.

Results: Case Reports and Themes

Wrong Genetic Test Ordered or Recommended

In 4 reported cases, the wrong genetic test was ordered because the ordering clinician did not recognize the features of a rare genetic condition, did not perform a comprehensive review of patient/family history, and/or had a lack of familiarity with the genetic etiology of the suspected disease.

- In the first case, multiple members of a family had been seen by different providers due to early-onset breast cancer, gastrointestinal polyposis, and/or intellectual disability. Two physicians ordered genetic testing: one ordered BRCA testing for a female family member with early-onset breast cancer, and the second ordered APC testing (for familial adenomatous polyposis) for a young male family member with polyposis. Both tests were negative. A certified GC then saw another family member with polyposis, took a comprehensive family history, and asked targeted medical history questions. She realized her patient met the diagnostic criteria for Cowden syndrome and ordered *PTEN* testing, and a pathogenic *PTEN* variant was detected.[2]
- In the second case, a colorectal surgeon paged a GC to ask how to order protein truncation testing for a patient he suspected had familial adenomatous polyposis. The GC advised the provider that this was an outdated testing method and offered to see the patient. Similarly to the first case, the patient met the clinical diagnostic criteria for Cowden syndrome and was found to have a pathogenic *PTEN* variant.
- In the third case, *FMR1* deletion/duplication analysis was ordered by a provider who suspected his/her patient had fragile X syndrome, although *FMR1* repeat expansions are the most common cause of this condition. A GC working in the testing laboratory caught this error and communicated the methodology mistake, and the correct test was ordered. The patient was found to have an *FMR1* expansion, which would have been missed by the initial test.
- In a fourth case, a woman was referred for consultation with a genetics professional after her gynecologist attempted to order BRCA testing before learning that her insurance company required consultation with a genetics professional. The genetics professional reviewed the patient's medical and family history and learned that the patient had a significant maternal family history of breast cancer, which could be due to a pathogenic variant(s) in any one of several breast cancer–associated genes. She also had a paternal family history of paraganglioma, pheochromocytoma, and kidney cancer. The genetics nurse therefore ordered an extensive multigene panel, and the patient was found to have a pathogenic *SDHB* variant, which is causative of paraganglioma-pheochromocytoma syndrome. Guideline-based follow-up screening detected a paraganglioma.[5,6] This genetic syndrome and subsequent diagnosis would have been missed had the gynecologist ordered BRCA testing alone.

In 4 cases, providers ordered the wrong genetic test even after patients reported relatives with confirmed genetic diagnoses. In 3 of the 4 cases, genetic diagnoses were therefore initially missed. In the fourth, a GC caught the error prior to testing.

- A patient was seen by a GC in a pediatric brain tumor survivorship clinic because of his history of astrocytoma at age 14 years and family history of Lynch syndrome. He had reportedly tested negative for the familial pathogenic *MLH1* variant. The GC requested the genetic test results of the patient and his affected family members and learned that the familial pathogenic variant was a large rearrangement in *MLH1*, which would be missed by the *MLH1* sequencing that was originally ordered by his oncologist. The correct testing was ordered and was positive. As recommended by the NCCN, the patient was immediately referred for colonoscopy given that an affected relative was diagnosed with colorectal cancer in his 20s.[7]
- In a second case, a woman told her primary care physician (PCP) that her sister was diagnosed with breast cancer and was found to be *PALB2+*. The PCP was uncertain of what to order, and before testing was ordered, the patient established care with a new PCP. That PCP ordered *BRCA* testing alone (≥$2000), which was negative, and referred the patient to a gynecologist, who realized that *PALB2* testing had not been ordered. The gynecologist referred the patient to a breast surgeon who then referred the patient to a GC. Appropriate genetic testing was ordered by the GC. The patient was counseled that she may be responsible for covering a self-pay price of $475 for genetic testing because she had already undergone *BRCA* testing that year, but the testing laboratory ultimately did not balance bill the patient. The patient was ultimately found to have a pathogenic *PALB2* variant after 7 months, at least $2000 in wasted genetic testing fees, and consultations with 5 different providers.
- In the third case, a 20-year-old woman was seen by an endocrinologist because of her family history of multiple endocrine neoplasia type 1 (MEN1), where testing was ordered and reportedly negative for the condition ($1200). She sought a second opinion with a new endocrinologist given that she was experiencing MEN1 symptoms, and he referred the patient to a GC. The GC reviewed the patient's genetic test result and learned that genetic testing for MEN2 (*RET* analysis) rather than *MEN1* gene testing was previously ordered. The GC ordered appropriate genetic testing, and it confirmed a molecular diagnosis of MEN1 for the patient.
- In the fourth case, a provider ordered *PMS2* analysis for a patient due to her family history of Lynch syndrome. A GC employed by the laboratory requested a copy of an affected

family member's genetic test result to arrange targeted testing, and she learned that the familial pathogenic variant was in the *MSH2* gene, not the *PMS2* gene. She informed the ordering provider, and the correct targeted test was performed, leading to a Lynch syndrome diagnosis for the patient.

In 3 cases, more genetic testing than was necessary was ordered. Health care dollars were wasted in the first 2 cases, whereas a GC caught the error in the last case.

- In the first case, a woman was referred for counseling after testing BRCA2+ through her gynecologist. The patient's mother was BRCA2+ (breast cancer diagnosed [breast ca dx] at 33 years), her maternal aunt was BRCA2+ (breast ca dx at 43 years), a maternal uncle was BRCA2+ (pancreatic ca dx at 60 years), her maternal grandmother (MGM) had a history of breast and colon cancers, and her MGM's mother had a history of breast cancer. The paternal family history was not suspicious. Although the familial pathogenic BRCA2 variant was known, tracked with cancers in the family, was consistent with the reported family history, and there was no suspicious paternal family history of cancer, the gynecologist ordered a multigene panel including analysis of more than 20 genes. The reported price of this multigene panel was approximately $3730, compared with the price of targeted testing, which would have been approximately $180. This resulted in $3550 of wasted genetic testing dollars.
- In a second case, a hematologist ordered testing for the common disease-causing *HFE* variants ($100) for a woman suspected to have hemochromatosis, and the results were negative. The provider did not order additional testing, and the patient relocated. The next year, she was referred to a hematologist at a tertiary center who ordered testing for the same common pathogenic variants ($100), which was again negative. More extensive panel testing was recommended; however, the local provider ordered testing for the common pathogenic *HFE* variants a third time instead ($100), which was again negative. The provider then finally ordered the more extensive panel, which identified a pathogenic *SLC40A1* variant, confirming a diagnosis of hemochromatosis type 4. A year passed between her initial test and panel test, delaying diagnosis and potentially leading to worsening iron depositions in her liver during that timeframe. Unnecessarily repeating previously ordered testing twice also wasted $200 in testing cost alone, not to mention the cost and time of multiple appointments with hematologists.
- In the last case, a provider ordered full sequencing of the *XIAP* gene for a patient whose brother was diagnosed with X-linked lymphoproliferative disorder due to a pathogenic *XIAP* variant. A laboratory GC recognized that targeted *XIAP* testing was more appropriate and advised the ordering provider, and the order was corrected. This saved approximately $1090.

In 2 cases, multiple errors were made when genetic testing was ordered.

- In the first, a man told his physician the he had a family history of fragile X syndrome and was concerned he may be a premutation carrier, which is associated with fragile X–associated tremor/ataxia syndrome. His physician ordered chromosome analysis ($800) rather than *FMR1* expansion testing, the appropriate test. Laboratory personnel recognized the error and advised the physician of the appropriate test, which he ordered. Testing identified a premutation in the patient. The provider then ordered a chromosome microarray ($2000) for the patient unnecessarily and referred him to a GC. This resulted in a delayed diagnosis for the patient and approximately $2000 in wasted genetic testing dollars. Without the intervention of the GC and laboratory personnel, $2800 would have been wasted.
- In the second case, a hematology provider attempting to order carrier testing for the mother of a male with severe hemophilia A ordered *F8* gene inversion testing. This genetics workup for the mother was important for both family planning reasons (80% chance of being carrier because son was first affected in the family) and because some female carriers have clotting activity less than 40% and are at risk of bleeding.[8] A laboratory GC reviewed the order in conjunction with the son's positive *F8* test result and recognized that the son had a missense variant that would not be picked up by the *F8* gene inversion testing that was ordered. The laboratory GC advised the ordering provider of this, and the correct order for targeted testing ($530) was placed. However, once preauthorization was completed, the provider unnecessarily placed a new order for full *F8* gene sequencing ($1000). The laboratory GC again intervened, and the correct test was ultimately performed and was negative. This saved $470 in genetic testing dollars and assisted in getting the mother the appropriate test and accurate interpretation.

Result Misinterpretation/Incorrect Genetic Counseling

In 3 cases, patients received incorrect information from providers because genetic test results were misinterpreted or because of limitations in the provider's knowledge of genetics.

- A woman was referred to a GC for targeted BRCA2 testing based on the report that relatives were BRCA2+. The GC reviewed the family history and relatives' genetic test results. The patient's MGM was diagnosed with breast cancer at age 33 years, and 2 of the MGM's nieces (the patient's maternal first cousins once-removed) were diagnosed with breast cancer in their 50s. The GC learned that one of the distant cousins was found to have a BRCA2 variant of uncertain significance (VUS), rather than a pathogenic variant. This VUS was incorrectly assumed to be the cause of the breast cancer in the family, and the MGM and other relatives subsequently underwent testing for this VUS alone. This approach in relatives was incorrect because (1) testing for a VUS outside a variant classification program is not ideal, especially for medical management purposes, and (2) the patient's MGM had a more suspicious personal history of cancer, and comprehensive genetic testing in her case would be more likely to be informative.[9] The MGM and the patient's mother both declined genetic testing, so the patient underwent comprehensive multigene testing, which was negative. This was considered an uninformative result.
- In the second case, a patient received a frenzied voicemail from a nurse at the in vitro fertilization (IVF) clinic through which she was about to undergo her first IVF cycle. The nurse reported that carrier testing results were back and that both the patient and her husband were spinal muscular atrophy carriers and that the patient was also a fragile X carrier. The IVF clinic closed early because of an impending hurricane and was not expected to reopen for several days. The patient sought genetic counseling, and after calling multiple genetic testing laboratories, the GC located the patient's carrier test results. The GC reviewed the results and realized the nurse was mistaken. Neither the patient nor her husband was a carrier of SMA, fragile X, or any other disorders. The nurse misunderstood the report, resulting in significant psychosocial distress for the couple with respect to the upcoming IVF plans and their 2 small children.
- In a third case, a provider ordered unspecified cystic fibrosis (CF) carrier testing for the partner of a woman who is a known CF carrier. The physician incorrectly documented that the risk to have a child with CF if 2 people are carriers is 1 in 3 (rather than

1 in 4) and then told the couple that, based on the husband's negative unspecified *CFTR* gene testing, the risk to have a child with CF was 0% (inaccurate). The exact residual risk in this case is unknown given that the physician did not document what CFTR analysis he ordered for the husband.

In 3 cases, pathogenic genetic variants identified were incorrectly assumed to completely explain the suspicious family histories of cancer. In order to fully evaluate these families, GCs recommended additional genetic testing or testing of more informative relatives.

- In the first case, a man was referred for targeted *BRCA2* testing due to the identification of a pathogenic *BRCA2* variant in his mother after *BRCA1/2* analysis. This result was confirmed by the GC, but upon review of the family history, it was clear that this pathogenic variant was unlikely to fully explain the family history. The patient's MGM had a history of ovarian cancer, and his MGM's sister had a history of breast cancer. However, the patient's maternal grandfather had a history of prostate cancer, and 3 of his sisters had histories of early-onset breast cancer. In short, his mother could have inherited the pathogenic *BRCA2* variant from either of her parents, with the potential for a second disease-causing variant on the other side of the family. The GC offered and the patient elected to proceed with multigene panel testing. The patient was found to have only the pathogenic *BRCA2* variant identified in his mother but was counseled that other maternal relatives should still consider more comprehensive testing.
- In the second case, a breast surgeon ordered BRCA testing for a patient based on her personal history of breast cancer at age 61 years as well as her family cancer of breast cancer (sister diagnosed at 40 years, maternal first cousin dx at 26 years). The patient was found to have a pathogenic *BRCA2* variant and a *BRCA1* VUS and was referred for genetic counseling. The GC performed a comprehensive review of the family history and determined the patient also met the NCCN criteria for genetic testing for Lynch syndrome because of her paternal family history of colorectal cancer and maternal family history of early-onset uterine cancer.[7] The GC offered, and the patient elected to proceed, with Lynch syndrome testing, for which the insurance company was additionally charged more than $4000, a cost that could have been avoided if the correct panel was originally ordered. The patient was subsequently found to have a pathogenic *MSH6* variant and therefore a diagnosis of Lynch syndrome, in addition to BRCA-related breast and/or ovarian cancer syndrome. This information was critical for the medical management of this patient and her family members.
- In a third case, a woman was seen for genetic counseling after her gynecologist recommended risk-reducing mastectomies and oophorectomy based on the identification of a single pathogenic *MUTYH* variant in the patient and because of the patient's mother's history of breast cancer (dx at 52 years) and ovarian cancer (dx at 48 years, disease course and treatment atypical for ovarian cancer). The patient's mother had not undergone genetic testing. The patient was counseled by the GC that 1% to 2% of North Europeans have a pathogenic *MUTYH* variant and that this is associated with a possible modest increased risk of colon cancer and a questionable modest increased risk of breast cancer; it is unlikely that the *MUTYH* finding would fully explain her mother's history.[10] The GC recommended that the patient's mother undergo comprehensive genetic testing, and her mother's multigene breast/gynecologic cancer panel was negative, including for the pathogenic *MUTYH* variant identified in the daughter. The GC referred the patient to a high-risk breast clinic for coordination of increased breast cancer screening based on family history.

Inadequate Genetic Counseling/Informed Consent

In 2 cases, patients received inadequate or no information with respect to genetic test results.

- In the first case, a developmental pediatrician ordered *MECP2* analysis for a 13-year-old girl with several medical issues including autism, global developmental delays, and seizures. The *MECP2* testing was positive, confirming a diagnosis of Rett syndrome, but this result was not disclosed to the family by the pediatrician. The patient was already established with medical genetics at another institution and had previous negative microarray and chromosome analysis. Whole-exome sequencing was recommended but declined by the family. Genetics was not involved in the *MECP2* testing ordered by the pediatrician. Genetics learned of this result 4 years later through review of medical records when the patient returned for follow-up and contacted the pediatrician so that he/she could discuss the result. This 4-year delay could have resulted in improper medical care, such as prescription of a QT-prolonging drug though individuals with Rett syndrome are at increased risk of arrhythmia. The delay likely caused the family unnecessary uncertainty and psychosocial distress.
- In the second case, a female patient came to medical attention at 3 to 4 months of age with possible seizures. Medical genetics was consulted, and a single-nucleotide polymorphism microarray was recommended as well as multiple metabolic tests. These tests were normal. Neurology independently ordered a comprehensive epilepsy panel, which returned a *TSC2* VUS. Neurology disclosed this result to the family, but the family did not receive adequate counseling, did not understand the meaning of a genetic VUS and thought the child had had tuberous sclerosis complex (TSC). Once neurology realized the family was confused, they sent them for consultation with a GC. The family had several questions about whether additional testing might uncover something "worse than TSC" and recurrence risk. After being informed that the *TSC2* variant was not classified as pathogenic and that her clinical presentation was not typical of TSC, whole-exome sequencing with proper pretest counseling was performed. The patient was found to have biallelic likely pathogenic *NARS2* variants, associated with combined oxidative phosphorylation deficiency 24. Her health declined quickly, and she died at approximately 6 months of age. Although the outcome was unfortunate, the family expressed that pretest and posttest counseling was very valuable to them during a very stressful and emotional period.

Laboratory Error

In 2 cases, result interpretation/documentation by the testing laboratories was erroneous, but careful review of test results by GCs avoided errors in patient management.

- In the first case, a woman was referred for genetic counseling and medical management recommendations after being told she was *BRCA2*+. The genetics professional reviewed the test result, noted that the specific *BRCA2* variant was classified by the laboratory as a low penetrance variant, and noticed that the references in the result report were from 1998. The genetics specialist also noted that the variant is listed as likely benign by sources in ClinVar and ClinVitae. Staff from 2 reputable genetic testing laboratories additionally confirmed that their respective laboratories considered the variant benign. The genetics professional recommended testing for the patient's mother who was more likely to be an informative testing candidate given her personal history of early-onset breast cancer. The patient's mother elected to proceed and did not have the previously identified *BRCA2* variant but did have 2 other VUSs: one in *RAD51C* and

one in *AXIN2*. The family was appropriately counseled that management should be based on family history alone.

- In the second case, a patient underwent testing for a familial pathogenic *BRCA1* variant, and the GC who saw her ordered targeted testing via the same laboratory through which the patient's sister had previously tested positive. When the results were available, the GC reviewed the test report, which read "negative," although the report clinical summary details indicated that the same pathogenic variant was detected in her patient. The GC confirmed with the testing laboratory that the testing was in fact positive. The laboratory had reportedly opted not to activate the computer program used to screen for such errors in the case of single site testing, and both the person who wrote the report and the clinical geneticist who signed off on it missed the error. Had the GC not carefully reviewed her patient's result, the patient could have been counseled that she was not at higher risk and been followed with general population cancer screening guidelines rather than offered appropriate, and potentially lifesaving, cancer screening and risk-reducing measures.

Direct-to-Consumer Genetic Testing

The introduction and significant growth of DTC genetic testing and raw data analysis present challenges to consumers and health care providers who are often unaware of the limitations of such testing and the appropriate follow-up medical-grade testing. In 2 cases, GCs interpreted this information for people who had undergone such testing and analysis and ordered appropriate follow-up medical-grade testing.

- In the first case, a physician ordered DTC testing for himself and submitted his raw data file to a third-party interpretation company. Results of that analysis indicated that a pathogenic *TP53* variant was detected, a result that, if confirmed, is consistent with Li-Fraumeni syndrome, a hereditary cancer syndrome with upward of a 90% lifetime risk of cancer and potential childhood onset in affected relatives. The physician was rightfully worried and sought a genetic counseling consultation. The GC ordered *TP53* testing for him through a medical-grade laboratory, and this testing was negative. The GC then learned of several other cases of patients being reported to have the same variant after testing through the same DTC laboratory and pursuing raw data analysis. She asked the DTC company about it and was informed that the laboratory would stop including this specific finding in raw data files even if detected—a solution that could itself be considered problematic. For instance, some consumers could undergo testing and raw data analysis knowing that they have a family history of a specific genetic variant but not be aware that the DTC laboratory is no longer reporting it. They may be falsely reassured when that variant is not in their raw data. It is important to note that DTC testing companies often specify that raw data files should not be used to inform medical care.
- In the second case, a man self-referred to genetic counseling to discuss multiple suspicious findings after processing his raw data from a DTC company through a third-party interpretation tool. In his case, raw data analysis reported a pathogenic *BRCA1* variant that is a founder mutation in people of Jewish ancestry. The patient was of Jewish ancestry and provided his GC with a copy of his mother's *BRCA1*+ medical-grade test report. She has a history of ovarian cancer. The patient's raw data analysis additionally included identification of a pathogenic *RYR1* variant listed in the third-party tool's summary as causative of malignant hyperthermia. Testing for both variants was repeated through a medical-grade laboratory and confirmed both findings. With respect to the pathogenic *BRCA1* variant, the patient learned that, contrary to his previous notions, he is at increased risk of BRCA-associated cancers, and there are NCCN guidelines outlining medical management for at-risk men.[7] With respect to the pathogenic *RYR1* variant, the medical-grade laboratory report indicated that the specific *RYR1* variant is associated with autosomal recessive disease (meaning both gene copies must contain a pathogenic variant to cause disease) and not autosomal dominant disease. This highlighted that even after confirmation care must be taken to ensure that counseling is accurate and not solely based on the report of a third-party tool.

DISCUSSION

Genetic testing is complicated, and it is becoming more complicated, accessible, and widely used by the day. Making an accurate genetic diagnosis requires extensive review of a patient's medical history and family history, knowledge of major and minor features of often rare diseases, and the etiology of the diseases, as well as careful test selection.[11] Even after genetic testing, appropriate counseling and medical management require nuanced test interpretation that accounts for innate complexities of genetics (e.g., penetrance, residual risk) and a patient's medical and family histories. It is unreasonable to expect nongenetics clinicians to provide this high level of care when the average physician visit is 20 minutes, and the majority of these clinicians do not have adequate and/or ongoing training in genetics and genomics.[12,13] It is crucial that patients and consumers receive accurate genetic counseling, given that errors in genetic testing can lead to dire consequences, including missed and/or delayed diagnoses, incorrect medical management recommendations, inefficient use of health care and patient dollars, patient psychosocial distress/false reassurance, and increased morbidity and mortality for the patient and his/her extended family.[14–17]

Several stakeholders in the field have voiced concerns with respect to access to certified genetic counseling services given that the field was estimated to be understaffed by almost 50% in 2017.[18] Some centers have significant patient backlogs, and many nonurban areas of the United States and most other countries have very limited access to GCs. In an effort to make accurate genetic counseling services more readily available, innovative approaches to providing access to these providers are being utilized, including phone and web-based counseling.[19] These services make it possible for patients and consumers to reach a certified GC from any location, in multiple languages (including ASL), any day of the week, and at a variety of times throughout the day and night. Some centers are offering group counseling to accommodate more patients.[19] In addition, several alternative delivery models and tools using new technology to provide digital health solutions have been introduced in this space.[20] In short, access is not a viable reason to refuse patients accurate genetic counseling by a certified provider. These services, delivery models, and tools each play roles in helping patients, consumers, and providers ensure the right test is ordered and that results are interpreted accurately, while saving the health care system precious health care dollars.

In order to connect more patients and consumers with genetics expertise, there must be a focus on creating more providers with genetics expertise. A crucial rate-limiting step in increasing access is the relative paucity of genetic counseling training programs. As of March 2018, there were 42 training programs in the United States and Canada (5 more under review) and 20 additional programs globally, most of which have small class sizes.[21,22] More training programs are needed, as are innovative training models that can allow for increased class sizes if GC workforce issues are to be addressed. Incentive programs, such as federal tuition support in exchange for agreeing to work in underserved areas, may also be helpful. Additional genetics expertise should be created by strengthening genetics and genomics education for nongenetics professionals and creating

educational campaigns that target nongenetics professionals who order genetic testing. Genetic counselors should be a resource for other colleagues not only as a referral option, but also for such education efforts.

However, access should not only be considered in terms of being able to identify a source of genetics expertise for a given patient/consumer. Access must also be considered in terms of equality in referral patterns as well as insurance coverage/payment of multiple genetic counseling delivery models and appropriate genetic testing. Additional economic modeling may be necessary to demonstrate the value of improved reimbursement of genetic counseling services. Forward-thinking insurers have already begun to cover confirmatory genetic testing for consumers who have some significant medical findings uncovered in their DTC testing. Many more insurers should cover genetic counseling, traditional medical-grade genetic testing, and confirmatory testing after suspicious DTC findings.[23]

Policy changes are also necessary. State and federal legislation should support the ordering of genetic testing by certified GCs, as 9 states already do. Genetic counselors should also be covered Medicare/Medicaid providers, and HR 7083, the "Access to Genetic Counselor Services Act of 2018," which was introduced in the US House of Representatives in October of 2018, aims to accomplish this.[24] These efforts would additionally be supported by achieving licensure for GCs in every state, or alternatively and perhaps more effectively, via federal licensure. At this time, GCs can become licensed in 22 states, with 3 additional states with bills passed.[25]

This case series adds to the existing literature of errors in the delivery of genetic services without the involvement of a health care provider trained and certified in genetics. The method of case collection from GCs and certified genetics nurses is a potential source of bias, and the study was qualitative, not systematic. The perspectives of nongenetics professionals were not solicited and therefore not included. Additionally, appropriate test selection is a subjective and evolving subject. For instance, as the cost of genetic testing comes down, ordering multigene panels becomes the norm, and providers become more comfortable with the potential for identification of variants of uncertain significance or incidental findings; one could argue that selecting a multigene panel over a more targeted test is not an error but a judgment call. Many, but not all, of the cases submitted included clinical documentation such as pedigrees. All submitters approved the representation of their cases before submission of the manuscript. However, reliance on submitter self-report and confirmation is a limitation of this study.

Genetic counselors continue to play critical roles in helping patients and their providers navigate medical-grade genetic testing, will now bridge the gap from DTC genetic testing to the health care arena, and must be ready to partner with other health care professionals to improve genetics literacy and access as well as quality of genetics and genomics care. As we quickly move into an era where more than one-third of Americans will have had either medical-grade or DTC genetic testing, we must think of ways to maximize the benefits of these tests, while minimizing the potential risks. Potential solutions involve action on multiple fronts—new GC delivery models, expanding the GC workforce, improving genetics and genomics education of nongenetics health care professionals, addressing health care policy barriers, and more. The work to be done is significant, but so are the consequences of errors in genetic testing.

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