PRECISION ONCOLOGY NEWS

Complex Genetic Testing Errors Emerge Amid Increasing Panel Use, Consumer Access, Case Series Finds

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NEW YORK – Errors in the ordering and interpretation of genetic tests for cancer, as well as in communicating results, are continuing to occur, and a newly published report highlighting some of these errors suggests that the nature of the mistakes are reflective of the rapid growth in the market — particularly with next-generation sequencing panels — and increasing consumer access through direct-to-consumer offerings.

In a case series published in the July/August edition of *The Cancer Journal*, long time genetic counselor Ellen Matloff and experts from various institutions reported on 25 new cases where the inappropriate tests were recommended and ordered by healthcare providers, genetic variants were interpreted incorrectly, and the wrong results were relayed to patients. Many of these cases involved cancer patients where large NGS panels are increasingly used to garner insights into disease risk and inform prevention strategies.

Greater access to NGS panel and growth in the low-cost consumer genetic testing market has undoubtedly increased genetic testing options for patients, providing information that benefits them and their family's care. On the other hand, increasing options in the hands of providers and patients with limited genetics expertise also has the potential to cause confusion about what test is appropriate to order and how the results should be interpreted in the context of a particular patient's medical scenario.

This is the fourth case series about genetic testing adverse events that Matloff and colleagues have published to date. "A decade after the first [adverse events case series] paper, the glaring errors we are still seeing are only getting worse," said Matloff, the last author of the paper and CEO of digital health company My Gene Counsel. "With larger panels and more companies providing direct-to-consumer testing and raw data analysis, it's even more complicated."

In the cases highlighted in the paper by Matloff *et al.*, the involvement of a genetic counselor, often at the last minute, thwarted the error from impacting patient care. The authors emphasize the importance of involving genetic counselors to avoid genetic testing errors, but also acknowledged that a limited workforce makes it difficult to access traditional, face to face counseling for every case. They suggested a multipronged approach, including improving genetics education of healthcare professionals, lifting policy barriers, such as the lack of Medicare reimbursement for counselors, and investing in non-traditional genetic counseling delivery models.

Among the laboratory errors highlighted in the series, there was one instance where a lab did not interpret a genetic variant's clinical significance correctly and another case where a lab indicated the wrong variant classification at the top of the report. In the first example, a

woman was told that she was positive for a BRCA2 mutation, and was referred for genetic counseling.

Luckily, the genetics professional carefully checked the test report and noted that the lab classified the variant as low penetrance and that the references were from 1998. The counselor then checked how other labs classified it in the public variant database ClinVar and spoke to staff from other labs and determined that this variant was now considered likely benign or benign. Because this patient's mother had early onset breast cancer and testing revealed she didn't have the same BRCA2 variant, this family was counseled based on family history.

Another lab mistake occurred when a patient underwent targeted testing for a known familial pathogenic BRCA1 mutation. The test report came back and read "negative" though in the clinical summary portion it was indicated that the patient did, in fact, have this mutation. "The laboratory had reportedly opted not to activate the computer program used to screen for such errors in the case of single site testing," Matloff and colleagues wrote. "Both the person who wrote the report and the clinical geneticist who signed off on it missed the error."

Matloff and colleagues also highlighted instances in which clinicians ordered the wrong test because they didn't recognize a rare genetic condition, or didn't conduct a thorough review to catalogue relevant family history of cancer or a specific pathogenic genetic mutation. For example, a patient with a history of a type of brain cancer, called astrocytoma, and a family history of Lynch syndrome, was initially thought to be negative for the familial pathogenic variant in MLH1, a well-known gene associated with the hereditary colorectal cancer condition.

However, when a genetic counselor did a more thorough family history workup and requested genetic test results of affected family members, it was noted that a large rearrangement in MLH1 was inherited among family members, and this variant would have been missed by the MLH1 sequencing test that was originally ordered. The right test revealed this patient was, in actuality, positive for the familial variant, and was referred for colonoscopy since one of his relatives had colorectal cancer in his 20s.

The case series featured cases where more genetic testing was ordered than was necessary. There were errors where test results were misinterpreted due to healthcare providers' lack of genetics knowledge, and where detected pathogenic variants were incorrectly assumed to completely explain inherited cancer risk. All these mistakes invariably resulted in unnecessary costs to the patient and the healthcare system.

For example, a doctor ordered BRCA testing for a woman based on her personal and family history of cancer, which identified a BRCA2 pathogenic mutation and a variant of unknown significance in BRCA1. However, a thorough family history taken by a genetic counselor determined that she was actually eligible for Lynch syndrome testing, resulting in an additional charge of $4,000 to the insurer. The patient was eventually found to have a genetic variant linked to Lynch syndrome, in addition to having hereditary breast and ovarian cancer syndrome, and she should have received more comprehensive panel testing from the start.

Perhaps the most egregious mistake in the paper is a case where a woman was recommended for risk-reducing mastectomies and oophorectomy because she harbored a single pathogenic MUTYH variant. Her mother had a history of breast and ovarian cancer, but had not undergone genetic testing.

When this patient saw a genetic counselor, she learned that between 1 percent and 2 percent of Europeans have a pathogenic MUTYH variant and that this particular variant was linked to only a modest increased risk of colon cancer and "a questionable modest

increased risk of breast cancer," unlikely to fully explain her mother's cancers. Ultimately, the mother did get tested specifically on a panel of breast and ovarian cancer genes and received a negative report, and the family was referred to a high-risk breast cancer clinic for screening based on their family history.

This patient in this story was counseled by Meagan Farmer, genetic counseling business manager at My Gene Counsel, and the first author of the published case series. She noted that while several of the cases in the paper highlight how increased access to NGS panel testing benefited patients, identifying clinically significant variants that otherwise may have been missed, increased access to broader panels is also picking up variants in genes that healthcare providers are unfamiliar with.

As a result, when healthcare providers who lack expertise in genetics encounter markers, such as the MUTYH variant associated with modest breast cancer risk, they're treating it like it is a pathogenic mutation in a high penetrance cancer risk gene, like BRCA1 or BRCA2. While a pathogenic variant in a moderate breast cancer risk gene might mean the patient should undergo more frequent screening, it doesn't mean they need a mastectomy or oophorectomy.

"Since people are so aware of BRCA1 and BRCA2 they are treating everything like that," said Farmer, who formerly headed up the Cancer Genetic Counseling Program at the University of Alabama at Birmingham. "We're seeing often that in the case of breast cancer people are overreacting."

Other studies have also documented instances where testing has identified pathogenic variants in moderate risk genes or variants of unknown significance (which shouldn't be used to make medical decisions), but patients have nonetheless decided to get risk-reducing surgeries. Some of these decisions may possibly have been based on other factors such as patients' own history of cancer or their family's history with cancer.

Certainly, Farmer has seen cases where she felt that risk-reducing surgeries weren't warranted based on genetic testing results alone. "In my own practice, historically, I saw some women that underwent prophylactic surgery because a VUS was found, or [an alteration] in a gene that might not have been causative," she said. "At that point you're just trying to do the best you can for family members."

Matloff shared a recent case that she learned about within a major healthcare system that's not in the paper. The patient had a PALB2 mutation associated with increased risk for breast cancer that segregated in the family. However, it was in the medical records that she had a pathogenic BRCA mutation. The genetics team traced the chain of records back to a provider who had initially noted that the patient had a "BRCA-ish syndrome," and subsequently others involved in her care just assumed that meant she had a BRCA mutation, and even recommended she have her ovaries removed.

"I do think that since panel testing has started that if people find either a VUS or a completely different mutation in a completely different gene, they're jamming it in there with BRCA," Matloff said, making the point that not all cancer-linked mutations, even in the same genes, have the same clinical management implications. "What our paper really illustrated well is [the need for] … really nuanced genetic counseling, for example for Lynch syndrome, based not only on the gene that is involved but on the latest data on how that gene in Lynch syndrome is different from another gene in Lynch syndrome. That is such a far cry from where we are right now."

The latest case series also highlights the negative impact of a relatively new phenomenon: increased consumer access to genetic information from DTC testing firms and third-party data analysis shops.

A number of studies have shown that these third-party data analysis providers have a high rate of false-positive results. However, patients are receiving this information online and in their homes without the important context that a genetics expert can provide.

One example in the paper involved a man who had used a third-party interpretation tool to analyze his raw DTC testing data, which flagged a cancer linked BRCA1 variant that is a founder mutation in those of Jewish ancestry, and a RYR variant suggested to be causative of malignant hypothermia.

The man was of Jewish ancestry, and his mother was positive for a BRCA1 mutation and had a history of ovarian cancer. He sought genetic counseling, and through this process had medical-grade testing, which confirmed he had a BRCA1 mutation and was at increased risk for BRCA-associated cancers — a finding with management implications.

The RYR1 variant was more complicated and highlighted the importance of genetic counseling and confirmatory medical grade testing. Although most cases of malignant hyperthermia susceptibility are autosomal dominant, requiring one pathogenic variant, confirmatory testing showed this particular RYR1 variant to be associated with autosomal recessive disease, and the patient did not have two copies necessary to cause the disease.

Farmer noted that consumers are often confused about the type of information they're getting from a DTC company like 23andMe, and how that service differs qualitatively from third-party raw data analysis providers. Consumers also may not know to seek out confirmatory testing after an online service identifies a potentially disease associated finding, even though the US Food and Drug Administration has approved 23andMe's cancer risk tests with the caveat that results should be confirmed by medical grade testing before they are used to make care decisions.

"It was really helpful for genetic counselors to be able to step in and say not so much that there was an error in raw data analysis but that additional medical grade testing is necessary," Farmer said, suggesting that these types of raw data analysis errors are likely occurring a lot but not being recognized or reported, since there aren't a lot of pathways for consumers to receive confirmatory testing.

The errors highlighted in this series are those submitted by genetic counselors and nurses after the authors put out a request for case submissions through professional society listservs, social media and other forums. In most cases, genetic counselors caught the mistakes at the last minute, for example, just before the wrong test was ordered, or they found out about an error after the wrong test was already performed and took steps to mitigate the impact on the patient.

"A lot of times there's just never a genetic counselor involved," Farmer noted. "For plenty of cases, we just don't even hear about them."

Given the pace of growth in the genetic testing market, however, it's unlikely that a genetic counselor will be able to have a face-to-face discussion with every patient who is receiving testing. An oft-cited statistic is that there are 14 new genetic tests entering the market daily. At the same time, expert bodies have recently expanded genetic testing guidelines in a variety of cancer and prenatal settings, enabling more people to be eligible for testing who previously weren't.

"When you look in the prenatal area, every single pregnant woman is a candidate for some sort of genetic testing," Matloff said. "Every single patient with ovarian, pancreas, metastatic prostate cancer, and many patients with breast cancer are candidates for genetic testing."

At the same time, it's not possible to educate physicians so they can order the right test for every patient and clinical scenario they encounter. "Thinking that we're going to train all

physicians to be genetic counselors, that's not going to happen," Matloff added. "We really think that some sort of scalable system for patients, but also providers, to make sure that they're getting the advantage of rich, genetic counseling information that matches the test results, may be the way to go."

For example, the company Matloff started, My Gene Counsel, uses digital solutions, such as detailed online reports and telegenetics to help consumers receive up-to-date information on their genetic test results. The company has also launched a pilot program to provide counselling and confirmatory testing to those who have a family history of cancer and have learned of their cancer risk through a DTC genetic testing company or third-party data analysis service.

Such services would proliferate if more insurers began requiring and covering them, and some are covering confirmatory testing, for example, and require genetic counseling. And "many more insurers should cover genetic counseling, traditional medical-grade genetic testing, and confirmatory testing after suspicious DTC findings," the authors of the paper wrote.

The latest genetic testing case series also aligns with a concerted push in the counseling community to pass a new law that would allow certified genetic counselors to be recognized as healthcare providers by the US Centers for Medicare & Medicaid Services and receive reimbursement for their services. Currently, CMS doesn't recognize genetic counselors as healthcare providers, andthe Access to Genetic Counselor Services Act of 2019, which was reintroduced in the US Congress in June, would require that genetic counselors be reimbursed for counseling Medicare beneficiaries in the same way these services are covered when provided by a physician.

"The fact that CMS is not recognizing genetic counselors and reimbursing them is such an expensive and dangerous practice," Matloff said.

The National Society of Genetic Counselors, which worked with legislators on the Medicare payment bill, has made the case that expanding access to genetic counselors makes good economic sense for CMS. The group commissioned a healthcare consulting firm to conduct a study, which projected $4 billion in potential Medicare savings over a decade if certified genetic counselors were to help patients and physicians order the right genetic tests. Moreover, when genetic counselors provide such services and are reimbursed at 85 percent of the fee that physicians get for the same services, it could lead to potential Medicare savings of $50.7 million over a decade.

Although the present case series makes a strong case for increasing access to genetic counselors to avoid costly errors and patient harm, Farmer noted that the aim is to highlight the gaps in care so the field recognizes them and works together to address them on many fronts.

"We don't want people to read this and think everyone has to see a genetic counselor, [because] it's not feasible at this point with workforce limitations," she said. "We want genetic counselors to read it and think of how they can be part of a solution, whether that be thinking about alternative service delivery models like telemedicine … or even just education of non-genetics providers."

And while every doctor can't become a genetics expert, a more realistic goal may be to give doctors enough knowhow to recognize when they need help in ordering the right test or deciphering reports. "We can make them better at understanding when to refer patients, and when something may be outside of their wheelhouse," Farmer said.