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# Large-Scale Multigene Panel Study of Hereditary Cancer Risk Refines Gene Associations

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NEW YORK – Investigators at Ambry Genetics, the Mayo Clinic in Rochester, the University of Utah, and the University of California at Irvine have tapped into Ambry's large collection of multigene panel test results to clarify hereditary cancer associations in high-risk patients — identifying gene-specific cancer associations they hope will inform future hereditary cancer test guidance.

"In a clinical diagnostic laboratory setting, we feel like we really have an opportunity, because we see [samples from] so many patients," explained Holly LaDuca, senior manager of clinical affairs research at Ambry Genetics. "There's just so much benefit to aggregating the data and giving that back so clinicians can see, on a large scale, what we are finding from hereditary cancer panel testing."

In an effort to tease out relationships between susceptibility to six cancer types and germline mutations in a wide range of cancer-related genes, she and her colleagues retrospectively analyzed data for some 165,000 individuals who were tested with multigene panels at the Ambry Genetics diagnostic lab in California between March of 2012 and December of 2016, focusing on pathogenic and likely pathogenic variants in 32 cancer-related genes.

"It's a way of benchmarking where these genes fall in terms of the magnitude of risk," LaDuca said, though she cautioned that the gene-specific findings were more robust in some cancer types than others, simply because more individuals with those cancer types are referred for testing.

Their findings, published in the journal *Genetics in Medicine* in mid-August, pointed to gene-specific cancer risks that were broader than expected based on current testing guidelines — with some genes contributing to susceptibility for multiple cancer types and others potentially conferring higher cancer risk than previously reported.

The available data "support even broader use of larger panels that contain a variety of hereditary cancer genes," the authors concluded, "even when patients lack classic clinical features associated with some of the genes, as evidenced by the mismatch in testing criteria met with what genes were actually mutated in some patients."

"This study came to a lot of the same conclusions that many of us have suspected based on clinical experience, as more people with personal and family histories of cancer undergo multigene panel testing — especially people who aren't textbook for certain cancer syndromes," said Meagan Farmer, a certified genetic counselor and genetic counseling business manager for My Gene Counsel, who was not involved in the study.

"We continue to see pathogenic associations between genes and cancers that surprise us, and we continue to see overlap between cancer risk for many genes, which is a good argument for the use of multigene testing," Farmer noted.

As patient management strategies continue to evolve, she said, even more studies like this will be needed to continue to clarify gene-cancer associations and refining estimates around the magnitude of risk associated with specific variants.

"It's important to remember that just because we find a pathogenic variant in someone with cancer does not mean that that variant is causative of their cancer," Farmer said. "When we use these bigger panels, we could also incidentally be detecting some variants. That could still be important for their care, and for their family, but it's trickier from an interpretation standpoint."

"As we're adding genes to panels that are more frequently mutated and that … have lower penetrance, we're going to see more and more of this," added Ellen Matloff, a certified genetic counselor and president and CEO of digital health company My Gene Counsel, who was not involved in the study.

Consequently, it is important to educate clinicians about follow-up steps for patients who do have apparent risk variants on panel tests, she said — from asking the right questions about an individual's broader family history to ordering appropriate follow-up tests.

She also sees a continuing need for clinician and patient education when it comes to issues such as testing eligibility, since so many individuals who meet current hereditary test guidelines still do not receive testing — particularly male patients, the elderly, and individuals from non-white populations.

In the *Genetics in Medicine* study, for example, most of the patients tested were white women, she noted, hinting that many eligible patients are not getting the type of hereditary cancer testing that might impact their own treatment as well as their family members.

"We may not be offering enough genetic testing and counseling to men who are at risk, and also to people of color and non-white ethnicities," Matloff said. "And if we are offering it to them, there are other barriers — whether they be cultural barriers or insurance barriers — that we're not clearing."

Almost 73 percent of individuals included in the study had a personal history of melanoma, breast, ovarian, colorectal, pancreatic, or uterine/endometrial cancers, while the remaining patients were tested because of a family history of related cancers. More than 94 percent of the patients profiled were female.

Over the time frame of the new analysis, more and more clinicians did seem to opt for multigene panel testing for their patients, LaDuca noted, while the number of genes included on those panels has continued to grow. While some individuals included in the analysis had just five genes tested, for example, others received panel tests that spanned 49 genes.

Still, it remains difficult for many providers to know which multigene test they should select for patients who meet hereditary cancer test criteria based on their personal or family history, both in terms of the number and of the types of genes tested.

"There's a disconnect between what clinicians are ordering and what the guidelines are addressing, so this [study] really helps put the data out there that guideline committees can use to help expand upon current testing guidelines and identify more patients in a responsible way," LaDuca suggested.

The researchers found that 13.8 percent of ovarian cancer patients carried germline pathogenic variants in at least one of the 32 genes tested. In contrast, germline risk variants turned up in just over 8 percent of individuals with melanoma.

On the gene side, the analyses highlighted several instances of hereditary cancer risk involving genes not typically associated with an individual's actual cancer — from pathogenic RAD51D variants in breast cancer patients to BRCA1/2 mutations in individuals with uterine or endometrial cancers.

When the investigators looked at the risk variants that would be missed by analyzing only the BRCA1 and BRCA2 genes in individuals who met BRCA1/2 test criteria, for example, they estimated that three of five individuals with risk variants in other breast- and ovarian cancer-related genes would be missed using the more targeted approach compared to multigene panel testing.

Just over 46 percent of patients who met criteria for Lynch syndrome gene testing had mutations in established genes for that syndrome, while more than half had pathogenic variants in other genes that are potential hereditary cancer contributors.

Conversely, almost 6 percent of individuals found to be carrying pathogenic BRCA1 or BRCA2 variants did not meet National Comprehensive Cancer Network (NCCN) testing guidelines at the time. When it came to Lynch syndrome genes, clinicians following testing criteria would have missed nearly 27 percent of pathogenic variant carriers, the researchers reported.

'"We're hoping for [this study] to serve as a clinical resource, of sorts, so people can have an idea of what they can expect to find for their patients with testing," LaDuca said.

In particular, the results highlighted breast cancer risk associated with pathogenic variants in a gene called BARD1, which is not among the genes recommended for testing under NCCN guidelines related to breast cancer. Based on the available multigene panel test data, the team estimated that some pathogenic variants in BARD1 can roughly double an individual's risk of developing breast cancer.

BARD1 "falls in line with several other genes that do have recommendations for increased breast cancer screening — where patients are getting MRIs in addition to their mammograms," LaDuca said. Even so, for individuals with risk variants in that gene "there aren't any recommendations for increased breast cancer surveillance like there are for other genes that are in a similar risk category," since past evidence was insufficient to convince the NCCN committee.

"BARD1 has been suggested as a breast cancer predisposition gene before," Farmer noted. "At this point, it's still in the category of having limited data. We need to collect more, because we would hate to over-screen people and potentially put them through unnecessary breast biopsies and anxiety until we really know what that means."

"I think it's wonderful that this is contributing to the data" available, she added, noting that NCCN guidelines on screening continue to change as more and more information like this becomes available.

Although the investigators started digging into the diagnostic yields, gene associations, and mutation frequencies associated with specific clinical indications or cancer subtypes, they plan to continue such analyses as Ambry's patient collection and panels expand in the future. They also expect to explore inherited cancer risk for patients with other cancer types or subtypes.

With mounting evidence to suggest that some cancer treatments are more effective in individuals with certain hereditary cancer mutations, such as in BRCA1/2, LaDuca said, she expects to see more individuals receive testing as well, including the subset of individuals who already meet testing criteria but are consistently missed.

"It's a disservice to patients if guidelines aren't consistent with clinical practice," she explained, calling for a "data-driven approach to help with the evolution of testing guidelines."

"What this study shows us is that even if educated professionals are cherry-picking genes, they're going to get it wrong," Matloff said. "It would be in the best interest of payers, clinicians, and the general public to cover some of these panels and to make people aware that they're candidates for genetic counseling and testing."

Given the findings popping out of the new analysis, she said, it is clear that panel test interpretation may be nuanced. Moreover, the results found in the high-risk population of individuals with a personal or family history of cancer cannot be expected to neatly carry over to the general population, where hereditary cancer screening is expected to be even more complex.

"We don't have enough data at this point to say that their risks are the same or that their options should be the same," Matloff said.

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