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By Monica Heger

NEW YORK (GenomeWeb) – As next-generation sequencing panels become increasingly common tools in the field of cancer, genetic counselors that can explain the complexity and nuances of such panels are critical.

In the August issue of the *Journal of Genetic Counseling*, several groups detailed their strategies for counseling on an individual's risk of developing cancer.

In one study, researchers from Albert Einstein College of Medicine and New York University described their approach to developing a 41-gene hereditary cancer panel, including how they decided which genes should be on the panel, which patients should be offered testing, and how to tackle genetic counseling.

In a second study, a working group of genetic counselors in Colorado discussed their efforts to methodically evaluate 11 moderately penetrant cancer risk genes so that they could better counsel on the different variants identified.

Being able to accurately report on the findings of such panels is increasingly important as patients are becoming more aware of panel testing and want to know their risk of developing cancer or whether sequencing can identify an effective treatment.

"Many women are now saying they want to know their breast cancer risk, even without a significant family history," Harry Ostrer, a professor at the Albert Einstein College of Medicine, told *Clinical Sequencing News*.

Ostrer said he is concerned that panels may be provided without an accurate risk assessment or the ability to communicate what those risks mean to the patient. For instance, patients with a 20

percent lifetime risk of developing breast cancer versus patients with an 80 percent risk may make very different decisions regarding preventative measures — including potentially opting for prophylactic mastectomy — so it is important that risk assessment is accurate and communicated well, Ostrer said.

As panel testing becomes more common in oncology, there is an "increasing need for genetic counseling as well as physician education across the board," Ostrer said.

While there is a wealth of information about germline variants in the genes BRCA1 and BRCA2, much less is known about other genes, many of which are frequently included in commercial panels, he said.

Ostrer and his group from Albert Einstein, in collaboration with researchers from New York University, analyzed Ambry Genetics' hereditary breast, ovarian, and colorectal cancer panels; GeneDx's breast/ovarian and colon cancer panels; and the University of Washington's hereditary cancer panel that includes genes associated with risk for breast, ovarian, colon, endometrial, pancreatic, endocrine, and skin cancers. The team also did a comprehensive literature review of the genes included in the panels in order to inform the development of its own panel for hereditary breast, ovarian, and colon cancer.

Ostrer said that accurate risk assessment is a major challenge for a number of reasons. First, when looking through the available literature on genes and their association with risk of developing cancer, the way risk is expressed is different depending on the gene. While the majority of studies use odds ratios when describing risk, others present risk as a cumulative lifetime risk or absolute risk, he said, making it more difficult to communicate to patients.

Second, while genes such as BRCA1 and BRCA2 have been well-studied and there is a significant amount of data on variants to these genes and how they impact risk, there is much less data on other genes. In addition, many genes have much lower, or are of unknown, penetrance.

Ostrer said that while there is broad agreement about many of the commonly mutated genes that impact hereditary cancer, there is less agreement about rarer genes. "That's the major source of difference among the panels," he said, "where you establish the threshold."

Third, patients will often have mutations to more than one gene, and it is not always clear how these multiple risk factors contribute to a patient's overall risk.

"People want to know what they're being tested for and what it means if they have a positive or a negative result," Ostrer said.

In order to resolve these challenges, it will be important to do functional studies of the lesser known genes, to determine their contribution to risk and their penetrance in the population. In addition, it will be important for professional organizations to weigh in with recommendations about best practices for incorporating panel testing into practice.

Ostrer said that while currently genetic testing for cancer susceptibility is mainly targeted to those with a family history, he foresees such tests eventually moving into the general population.

Already, evidence suggests that only about half of breast cancer patients with BRCA1 or BRCA2 mutations had evidence of family history, he said, and as such there is interest in doing population testing within the Ashkenazi Jewish population, where the BRCA1 and BRCA2 mutations are the most common. "That will represent doing this on a larger scale," he said.

In the second study published in the *Journal of Genetic Counseling*, a working group of genetic counselors in Colorado addressed the challenges of counseling for NGS-based cancer predisposition testing and attempted to establish a consensus of the best practices.

While genes such as BRCA1 and BRCA2 are highly penetrant and can cause as much as a 20-fold increase in cancer risk over the general population, many other genes that are tested for on NGS panels have only a moderate association with risk.

"How much an abnormality actually impacts cancer risk and how much that impactsmedical management is really unknown for most of those genes," Kami Schneider, a pediatric oncology genetic counselor at Children's Hospital Colorado and the University of Colorado, Denver, told *CSN*.

As such, the group tackled a list of 11 moderately penetrant genes that often yield results that are challenging to interpret. Each member was assigned a gene to research and present to the group for discussion. They created templates for each of the genes that included a summary of the gene, clinical utility, and case examples where available.

The goal was to better understand the genes that were on the panels, Schneider said. "There are not clinical guidelines for a lot of the genes that get added to the panels, and often little is known in terms of the clinical utility of them."

Schneider said the group decided to take on the study after discussing case reports and their individual challenges with interpreting rare variants. "We were all doing it independently, and it seemed like we could collaborate, so we didn't have to independently research each gene."

She added that the process, while helpful, often yielded frustrating results. "Depending on the gene, identification of many of the mutations in them don't currently change patient management," she said. "The actual application, we're just not there yet."

Going forward, the group plans to continue its monthly conference calls to discuss plans for clinical implementation of their findings and will also begin evaluating additional genes.

Genetic counselors "need to work together and not in isolation," Schneider said. "There is too much out there for us to figure out on our own."

Monica Heger tracks trends in next-generation sequencing for research and clinical applications for GenomeWeb's *In Sequence* and *Clinical Sequencing News*. E-mail Monica Heger or follow her GenomeWeb Twitter accounts at @InSequence and @ClinSeqNews.

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