NorthShore, Invitae Partnering to Advance NGS Cancer Risk Test for Proactive Screening

May 23, 2017
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NEW YORK (GenomeWeb) – NorthShore University HealthSystem is working with molecular diagnostics firm Invitae to advance a next-generation sequencing test for cancer risk that will combine analysis of around 100 inherited high-risk genes, such as BRCA1, BRCA2, and ATM, with several hundred SNPs comprising a "genetic risk score."

The prognostic ability of the SNP-based genetic risk score, developed by Jianfeng Xu, vice president of translational research at NorthShore, has been evaluated across a number of cancer indications, such as prostate cancer, and other diseases. But based on the latest research on inherited high-risk cancer genes, Xu and colleagues have decided that incorporating those genes with the genetic risk score and patients' family history of cancer will yield a more robust prognostic test.

The NGS test developed within the NorthShore/Invitae collaboration will be performed in Invitae's CLIA- and CAP-certified lab, CEO Sean George said by email. For Xu, the goal behind advancing this test is to eventually use it as a proactive screen for cancer risk that is applicable broadly, especially for individuals who lack family or medical history to warrant screening according to existing guidelines. He plans to expand the test's use in the future for inherited risk assessment of other conditions.

Currently at NorthShore, patients who consent to partake in several ongoing studies can receive testing on a similar panel performed at Counsyl's CLIA-certified lab. In these studies, researchers are taking participants' family history, testing them for high-penetrance cancer risk genes, and evaluating their genetic risk score.

One study has enrolled 250 men with high prostate-specific antigen levels, or those who are concerned about their prostate health, and is evaluating how participants react to their genetic risk score and if their score modifies screening strategies. Another study looks at how genetic risk score impacts breast, colon, and prostate cancer screening for 500 patients in the primary care setting, who have donated blood samples for genomic research. NorthShore will conduct a third study looking at the utility of the genetic risk score across a number of different cancers.

Some of the first data on the utility of NorthShore's strategy to combine genetic risk score with high-risk inherited genes and family history is emerging in prostate cancer. For example, early results from the study involving 250 men with high PSA levels suggest that "patients are really understanding when they are at risk and need to be screened," said Brian Helfand, a urologist at

NorthShore. Conversely, when patients get a low genetic risk score, "they relax a little bit about the frequency of their prostate cancer screening," he added.

At the American Urologic Association's annual meeting earlier this month, Helfand presented data from a study involving participants from more than 800 families with a history of prostate cancer and showed that the genetic risk score was able to differentiate high-risk individuals even when family members had similar prostate cancer risk based on family history

Currently, family history mainly influences prostate cancer screening strategies. The American Cancer Society recommends men begin discussing the risks and benefits of prostate cancer screening starting at age 40 if they have more than one first-degree relative with prostate cancer at an early age; at age 45 if they are African American and have a first-degree relative with the disease; and at age 50 if they are at average risk and expected to live at least 10 more years.

Studies suggest that men with a relative with prostate cancer have between 1.5 and 2.5-fold higher risk for the disease. However, less than 10 percent of men have a family history of the disease, and many men do not have complete knowledge of family members with the illness.

For patients who don't have family history, genetic testing can fill in the gaps. "We know from past studies that genetic risk score identifies many more men who are at high risk than ever would be suggested by family history," Helfand said. "The genetic risk score is independent of family history and if you look at genetic risk score and family history, you'll identify 20 percent more patients by family history alone."

By current guidelines, men who are high risk based on family history and other factors are screened using PSA testing or digital rectal exams, and their PSA levels then determine the frequency of future screenings. However, there has been much debate about PSA-based prostate cancer screening since the US Preventive Services Task Force recommended against it in 2012, reasoning that PSA testing results in overdiagnosis of slow-growing cancers unlikely to impact a man's health in his life time.

Recently, though, the USPSTF softened its stand against PSA screening, saying that men between the ages of 55 and 69 should consult with their physicians to determine the appropriateness of getting screened.

Combining genetic risk score, high penetrance risk genes, and family history is "a more comprehensive testing strategy that can identify those at highest risk [for aggressive disease] but avoid the overscreening and overdiagnosis associated with prostate cancer in the past," Helfand said.

Part of Xu's research focus has been on identifying genetic factors for cancer that can account risks not captured by the SNPs in the genetic risk score. Last year, Xu was part of a research team that reported in *European Urology* that men with inherited mutations in BRCA1/2 and ATM are at heightened risk for aggressive prostate cancer and are more likely to die from the disease than men without these germline mutations.

At the AUA meeting, NorthShore presented research that adds to this knowledge. One study, presented by Xu showed that CHEK2 mutations increased risk for the disease, but couldn't

differentiate between lethal and indolent forms. In another study of 300 patients who died of prostate cancer, germline mutations in DNA repair genes were associated with shorter survival and death at an earlier age.

Based on these and other studies, Helfand and Xu support early and proactive screening for men who are at the highest risk defined by family history, genetic risk score, and high penetrance genes. The studies ongoing at NorthShore are testing the waters and gauging how comfortable physicians are in offering genetic risk testing and the feasibility of offering it as part of routine visits.

NorthShore is collaborating with Invitae to advance the NGS test in the hopes that it may be more broadly implemented in the future. Invitae is a like-minded partner and has already dipped its toes into the "proactive" genetic testing space.

For more than a year, the company has been piloting a service, called Genetic Health Screen, for patients who don't meet guidelines for genetic testing but who nonetheless wish to know their risk for diseases. Recently, Invitae expanded its test panel (which must be ordered by a doctor) to include 139 medically actionable genes, and began offering panels focused on cardiovascular conditions and cancer to help patients make more informed screening or treatment decisions.

Although a number of companies have begun offering similar testing services, experts at the American College of Medical Genetics and Genomics annual meeting discussed challenges, such as the ability of primary care docs to manage the information from genomic tests appropriately and if such testing will increase healthcare costs unnecessarily. This kind of broad genetic screening program, Xu admitted, is difficult to implement since it isn't standard practice in healthcare. At a minimum, he would like to see the NGS test developed with Invitae to be initially available for early adopter primary care physicians who want to use it to target prevention strategies for asymptomatic cancer patients.