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Patia Marketing Diabetes Risk Test Including Polygenic Risk Score, Personalizable Prevention App

Apr 05, 2019 | Madeleine Johnson

NEW YORK (GenomeWeb) – Although using genetic markers to detect type 2 diabetes (T2D) risk is somewhat controversial, San Sebastián, Spain-based Patia is currently offering an assessment that includes a 16-SNP polygenic risk score. The company says its test differs from one recently launched by 23andMe in that its algorithms can better account for ethnicity and its tailored app provides more support to help patients stay free of diabetes.

The Centers for Disease Control and Prevention estimated in 2018 that nearly 9 percent of the US population, or 21 million people, have been diagnosed with T2D. The CDC has also reported that more than 84 million people in the US could be considered to be prediabetic and without intervention could develop T2D within five years. In Mexico, diabetes in general is the leading cause of death, with a prevalence of nearly 15 percent and more than 12 million people affected, according to the International Diabetes Foundation.

When Patia began working on its risk assessment in 2013, one of the goals was to address populations of Hispanic descent, which tend to be underrepresented in genome-wide association studies and subsequent risk scores and algorithms.

Its assessment, called DIABETESpredict, includes genotyping at 16 polymorphisms, according to the firm's medical director, Mirella Zulueta.

The assessment was developed in part from the results of the Carlos Slim Initiative in Genomic Medicine for the Americas (SIGMA) T2D Consortium at the Broad Institute and with collaborators at the University of Mexico, Zulueta said. The firm also relied on GWAS studies of almost 9,000 individuals, including people with T2D and controls, as well as on databases and other studies. It picked 16 SNPs with the highest predictive power, and then validated them in cohorts from Mexico and Europe.

Although one criticism of other genetic risk testing has been that the GWAS analyses on which the biomarker selection is based tend to be done on populations of European descent, the Patia test claims to allow for use in populations of many different ethnicities and ancestries.

For example, the 16 SNPs include two — *SLC16A11* and *HNF1A* – that were discovered in Latino populations. The assessment also incorporates patient-reported ethnicity and other information into population-specific algorithms in order to interpret the results. And, because it uses Thermo Fisher Scientific's TaqMan OpenArray for genotyping, it has a high throughput and low cost.

The DIABETESpredict assessment is available globally, Zulueta said, and currently the firm has customers in Europe, Mexico, the US, and the Middle East.

In a recent *Scientific Reports* study, Zulueta and her colleagues collaborated with researchers in Mexico to evaluate 1,234 non-diabetic controls and 1,219 diabetic patients, and then replicated the data in a case-control and a cross-sectional study with 2,904 and 1,901 patients, respectively.

"Our goal was not to show that polygenic risk scores were better or worse than clinical risk scores. That was not our interest," Zulueta explained. Rather, the team took an open-minded approach, and

ultimately observed that SNPs, obesity, and family history contributed about 8 percent, 7 percent, and 12 percent to type 2 diabetes, respectively. The contribution of the genetic risk score was also higher than the other factors if the disease began before a patient was 46 years old.

Last month 23andMe also debuted a T2D risk report that incorporates more than 1,000 SNPs into a polygenic risk score using an algorithm. The company has noted in a white paper that the assessment was developed using GWAS studies of people with European ancestry and that the score works best in those of European ancestry and doesn't work as well in African American populations. The 23andMe report provides customers with a risk score as well as information about lifestyle choices previously shown to lower the likelihood of T2D, according to the white paper.

However, besides its utility on many ethnicities, Zulueta noted that Patia's test is distinct from the 23andMe assessment in that Patia offers a comprehensive approach to intervention.

"Genotyping is OK, but it is not enough in terms of how we can help an individual with prevention," Zulueta said. "We try to understand, and put in context, the genetic testing with what might be going on for that person, so that the person receives information that could be helpful and supportive," she said.

Zulueta said Patia includes thorough lifestyle evaluations, and then personalizes its evaluation, tailoring suggested interventions to consider things like what is even possible given a person's existing health conditions, for example. Patients also download an app that can be used to track lifestyle changes — including by synching with wearable technologies to track physical activity — and that can provide patients with more information, and even a personalized diet with healthful recipes.

Patia plans to continue to expand in the US market, and is working with two private US reference labs, Zulueta said. The company will announce these collaborations in the near future.

Reaching out to more physicians is now the goal. "I believe the conventional medical community, for the most part, is still very conservative and very careful, as they have to be, to take up a new test, and prevention is not something a typical clinician thinks of," Zulueta said. Patia has been presenting its work at the American Diabetes Association conferences and that has helped create some traction, she said.

The skinny on PRS for T2D

There has been intense debate recently about using polygenic risk scores, or PRS, for chronic conditions in general. In contrast, the controversy over the usefulness of genetic risk scores for T2D in particular seems to have boiled up about five years ago, but there has been much less literature published on the subject recently.

And yet, the debate over PRS for T2D is not necessarily resolved, and the availability of new commercial tests may indeed reopen it.

The published literature demonstrates T2D risk is a very complex phenomenon, and the increase in risk due to a particular SNP is very small and seems to be greatly outweighed by other factors, like weight or diet.

Valeriya Lyssenko, a scientist at Lund University in Sweden, authored an evaluation in 2013 called "Genetic Screening for the Risk of Type 2 Diabetes: Worthless or Valuable?" that concluded genetic risk testing had small added value compared to other clinical risk factors. The evaluation also concluded that it has questionable clinical relevance, and that "genetic testing for the prediction of type 2 diabetes in high risk individuals is currently of little value in clinical practice."

In an email, Lyssenko noted that not much has changed in the ensuing six years. "The consensus in the field is that these tests cannot be used for diagnostic or prognostic purposes," she said.

Also in 2013, a working group called the Evaluation of Genomic Applications in Practice and Prevention, or EGAPP, published in *Genetics in Medicine* that there was insufficient evidence to recommend testing for the 28 specific predictive variants it evaluated, some of which are included in Patia's test.

And testing for more SNPs doesn't necessarily improve the predictions, either, said Cecile Janssens, an epidemiology researcher at Emory University.

Janssens co-authored a commentary about a recent study that attempted to make polygenic scores for five diseases using millions of SNPs. She suggested that such tests performed worse than scores built from GWAS SNPs only. Furthermore, in her opinion, "16 SNPs for diabetes are unlikely able to predict high and low risk" because each SNP contributes very little to overall disease risk, she said in an email.

"The 16 SNPs with the strongest effects may be as good as a score that adds 1,000s of SNPs with very weak effects, but both may not be predictive enough to identify people at high or low diabetes risk," she said.

Even supporters of PRS are "generally aware that the science doesn't convincingly support their optimistic views," she added. In her opinion, DNA testing can be very useful for monogenic disorders, and for common diseases such as age-related macular degeneration, Crohn's disease, or even type 1 diabetes, "but not for the diseases that we hear most about: type 2 diabetes and heart disease."

Still, there does not seem to be any official position on genetic risk assessment for T2D established by any professional societies or patient advocacy groups, either supporting or advising against genetic testing.

And, while acknowledging that the clinical validity of a genetic test for T2D might be low, a handful of researchers do seem to be somewhat more open to the possibility that these scores could have some usefulness, if not now then perhaps in the future.

This is particularly, and hypothetically, in the form of clinical utility, or basically whether getting a genetic risk score leads to the desired outcome of a patient making behavioral changes that prevent diabetes.

Indeed, "Although trials involving disclosure of results of genetic testing for type 2 diabetes have not shown positive effects on behaviors and clinical outcomes to date, this does not mean that such testing can't have value," said Corrine Voils, a researcher at the University of Wisconsin. "It just means that the interventions we have tried have not shown improvements," she added.

In a randomized control trial of a US Veteran population published in 2015, Voils and her colleagues showed that providing genetic results was no more effective than conventional risk counseling. A similar study — sometimes referred to as the Genetic Counseling/Lifestyle Change or GC/LC Study — followed up on patients six years after receiving genetic risk results for T2D, and found no evidence that genetic risk counseling improved outcomes.

However, while one 2016 meta-analysis also showed that communicating DNA based risk estimates in general does not seem to change patient behavior, a 2018 review found that it is possible to facilitate behavior change using genetic testing as a catalyst.

Some of the interventions that have been reported only involved one-time risk counseling, Voils said, "Which is likely insufficient to help people develop and practice behavioral skills needed to make lifestyle changes." However, at least one study paired risk information with a more comprehensive lifestyle intervention and found no effect, although it is "unclear if that trial was sufficiently powered to detect improvements in clinically relevant outcomes" such as reduced weight, Voils said.

"There may be some yet-untested method of providing genetic testing results combined with behavioral intervention that would show a benefit," she added.

Other groups have also hypothesized that genetic risk may motivate prevention measures among some at risk, "but that is yet to be demonstrated and refers more to personal utility," according to Allison Vorderstrasse, a researcher at New York University. She suggested that one main issue is, "If you provide a full picture of the risk of most preventable diseases, the genetic contribution is relatively small, and you would have to explain multiple risk factors to patients, including genetic risk. Therefore, the attribution of behavior change to genetic testing is difficult to examine, and to date has not been found in the studies conducted."

However, Sridharan Raghavan, a researcher at Rocky Mountain Regional VA Medical Center and the University of Colorado School of Medicine who worked with Voils on the trial measuring clinical utility of T2D PRS, noted that the SNPs found in Mexico, that seem to be absent in other populations, may have a larger effect. "It is possible that if [the Patia assessment] is tailored to that specific ancestry population they actually have better prediction," he said.

Jason Vassy, lead author on the GC/LC study and a researcher at the VA Boston Healthcare System, Brigham and Women's Hospital, and Harvard Medical School, said that while PRS have gotten better recently by incorporating hundreds to millions of SNPs, "there is still uncertainty on whether patients and their healthcare providers can use that predictive information to improve clinical outcomes, such as preventing the onset of type 2 diabetes." So far, risk information alone seems to be insufficient to "translate prediction into patient health behavior change," he said.

Yet, for some patients in a very high-risk genetic category, there may be more clinical utility, or even clinical validity, than has been previously appreciated, according to Robert Green, the director of the Genomes2People Research Program and a researcher and physician at Harvard Medical School and Brigham and Women's Hospital.

The markers have, after all, been discovered through various GWAS studies, and "they're true, they are statistically valid, and these markers individually are associated with disease," he said in an interview.

And, at the very least, there appears to be no overall harm done to patients by receiving their genetic risk scores. Raghavan noted that in the Voils study and GC/LC there was no evidence that getting a high-risk categorization led to any decline in a patient's health behavior.

Green also added that, besides doing no harm, there may be benefits to PRS for some populations at very high risk.

Recent PRS studies have re-excited people, he said, although now the clinical validity of such scores "merits serious attention."

In terms of clinical utility, "It is really hard to change people's behavior," Green noted, but it is possible that PRS can essentially produce, "a teachable moment" generated by the excitement of DNA, he said.

"I think that is completely valid. In medicine, we take advantage of teachable moments all the time … You have an opportunity to take something that has engaged the person's interest and turn it into a moment where you can teach them something important about their health," he said, adding that consumer-facing DNA testing is a perfectly valid teachable moment, "As long as it does not exaggerate its salience in the arena of the various risks," he said.

At Patia, Zulueta said she and her colleagues are "well aware of the ample debate about the clinical utility of genetic risk scores, not only in diabetes but in other chronic conditions."

Its assessment is "the entry point" to start to tease out factors and begin the conversation with the patient and the doctor about recommendations for prevention that are personal and unique to the individual, "and that consider the totality of the patient, not only their genetics, or family history, or weight," Zulueta said.

Raghavan said that if Patia is indeed packaging results with an app that alerts and reminds patients to make lifestyle changes, such as tracking their weight, for example, then that might have some impact. The field of mobile health is in its infancy, but there are small studies that suggest apps can help people with high cardio-metabolic risk adopt beneficial health behaviors, he said.

"If this tool actually does motivate people to modify their risk factors for diabetes then I think you could make an argument that it is clinically useful, even though the way they are measuring risk is potentially more expensive than lots of other ways we can measure risk of diabetes just as well," Raghavan said.

In the end, the overall clinical validity and utility of the Patia risk assessment would need to be determined in a controlled clinical trial.

Janssens said that while it is her impression that T2D risk prediction is an active area of research, she doesn't expect that future scores will be much more predictive than what we have right now. "The cause of T2D is not genetic enough to make a genetic test a strong predictor of disease," she said.

Zulueta meanwhile said that, like everything in nature and health, this particular area of medicine is not black or white, but rather is actively evolving. And, millions of people's lives are at risk.

"I personally try to not get attached to binary perspectives. Only time and experience will inform us," Zulueta said.

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