Schizophrenia study suggests advanced genetic scorecard cannot predict a patient's fate

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With the help of cutting-edge computer programs, researchers at the Icahn School of Medicine at Mount Sinai went through the genetic and medical records of more than 8,000 schizophrenia patients. They found that a tool commonly used in research for evaluating a person's genetic risk for a disease, called a polygenic risk score, was no better at predicting the outcome of a patient's disease over time than written reports. The results raise important questions about the use of polygenic risk scores in real-world, clinical situations, and also suggest that a doctor's written report may be an untapped source of predictive information.

"Treating schizophrenia patients is a heart-wrenching experience. One of the hardest parts about taking care of patients is trying to determine whether each patient's condition will worsen or improve. If we could do that, then we might help relieve the suffering that the patients and their loved ones experience," said Alexander W. Charney, MD, Ph.D., Assistant Professor in the Departments of Psychiatry and Genetics and Genomic Sciences at Icahn Mount Sinai and the senior author of the study published in *Nature Medicine*. "Our results show that for the mental illnesses most deeply characterized at the genetic level, the current state of genetics research cannot solve this problem just yet."

Affecting about 20 million people worldwide, schizophrenia is a life-shortening mental disorder that alters the way a person thinks, acts, and perceives reality. Typically, symptoms appear in the late teens to early thirties and can last a lifetime. While some patients may respond well to treatment, others do not at all.

Although it is a highly inherited disease, the majority of cases cannot be linked to a single gene. Instead, scientists have found that the risk of suffering from schizophrenia is influenced by a complex combination of normal genetic variants, none of which on their own contribute a great amount to risk but together account for many cases. Currently, nearly 300 such variants have been associated with schizophrenia.

The polygenic risk score is a commonly used method for summarizing the genetic component of a person's risk for a disease. Over the past decade, many large studies have shown that the risk scores of schizophrenia patients are significantly higher than that of healthy controls. Similar results have been seen in studies on other disorders such as hypertension and diabetes.

"The polygenic risk score basically adds up all of the traits that are associated with a complex disorder. Initially it was designed to be descriptive tool. More recently, scientists have proposed that it could be an effective tool for precision medicine wherein a person's genetics is used to diagnose disease and predict outcomes," said Isotta Landi, Ph.D., a post-doctoral fellow in Dr. Charney's lab and the lead author of the study. "In this study we wanted to rigorously test out whether the polygenic risk score could also be a predictive tool."

At first, the researchers compared the genetic and medical records of 762 schizophrenia patients stored in the Mount Sinai Health System's BioMe BioBank program. Specifically, they tested whether a patient's polygenic risk score for schizophrenia could predict six poor outcomes of each patient any better than the information derived from the medical reports written by doctors.

To do this, Dr. Landi worked with others to develop advanced computer programs that calculate polygenic risk scores from a patient's genetic data and use natural language processing tools to extract information

from written reports.

They found that two of the outcomes—aggressive behavior and the need for hospitalization—were significantly associated with higher polygenic risk scores. However, the scores were no more effective at predicting these outcomes than was the information derived from the written reports, and combining the two did not change predictability.

Follow-up experiments supported these results. For instance, the researchers saw no change in the results when they tried to predict outcomes only in people with the highest polygenic risk scores.

Finally, they saw the same trend when they analyzed genetic and medical records of 7,779 patients stored in the Genomic Psychiatry Cohort, a large National Institutes of Health-funded project. Once again, the polygenic risk scores did not improve upon the ability of clinical data to predict poor outcomes.

"Our results suggest that more work needs to be done to harness the potential that genetics has to improve the treatment of schizophrenia patients," Dr. Charney said. "The results also suggest that the detailed medical reports that doctors write may contain much more valuable and predictive information than we originally anticipated."