Rare Single-Gene Variants Confer High Risk for Mental Health Conditions, Geisinger Study Shows

Researchers suggest physicians should more routinely order genetic testing for patients with mental health disorders, a group that has historically been undertested.

By Jessica Kim Cohen

RESEARCHERS AT Geisinger Health System have produced data that provide a fuller picture of the prevalence of genetic variants linked to mental health disorders, and they believe their findings provide support for integrating genetic testing more routinely in patient care.

Researchers analyzed genomic test results and electronic health record (EHR) data from patients enrolled in Geisinger's MyCode Community Health Initiative, a precision medicine project, and found a subset had genetic variants associated with neurodevelopmental psychiatric disorders (NPD) like intellectual disability, schizophrenia, and bipolar disorder, according to results published in the *American Journal of Psychiatry* in December.

Testing for such genetic variants among patients with these types of mental health disorders could improve clinical outcomes, the study's authors concluded. "Diagnostic testing to identify rare pathogenic variants should be offered to symptomatic individuals with NPDs, given the significant personal utility of a genetic diagnosis and the potential to improve outcomes through anticipatory medical monitoring," they wrote.

For the study, researchers analyzed sequenced exomes of more than 90,000 patients for pathogenic single-gene variants in 94 genes known to increase the risk of NPDs. The study comprised patients in the DiscovEHR cohort, a subset of MyCode that has genetic test results linked to anonymized EHR data. Geisinger is collaborating on the DiscovEHR effort with Regeneron Genetics Center, an R&D subsidiary of pharmaceutical company Regeneron.

In total, 0.34 percent of the 90,595 patients had at least one genetic variant associated with an NPD. When factoring in results from previous research at Geisinger that identified patients with 31 multigenic copy number variants (CNV) associated with NPDs, collectively about 1.1 percent of patients – roughly one in 89 – carried either a relevant single-gene variant or CNV, according to the study authors.

"This study confirms the important contributory role of rare genomic variants in NPDs," the study authors wrote.

Furthermore, an analysis of ICD-9 and -10 diagnosis codes revealed that one-third of patients who carried a genetic variant had been diagnosed with an NPD. When researchers homed in on patients with variants in eight NPD-linked genes – TRIO, NAA15, ASH1L, ZNF292, IRF2BPL, CLTC, GIGYF1, and POGZ – they found that

between 40 percent and 53 percent of the cohort had been diagnosed with a mental health disorder, such as intellectual disability, schizophrenia, and bipolar disorder.

"That's pretty substantial," said Christa Martin, CSO at Danville, Pennsylvania-based Geisinger and founding director of the health system's Autism & Developmental Medicine Institute (ADMI), and senior author on the paper. The proportion of pathogenic variant carriers with a mental health disorder is likely much higher than one-third, Martin suspects, but researchers may not be able to identify these patients due to the limitations of EHR data.

For example, the present analysis would have missed patients whose diagnoses about NPDs were documented in unstructured clinical notes. Patients could also be seeking mental healthcare outside of Geisinger, or they could have mild presentations of NPDs that their doctors haven't diagnosed.

An estimated 14.6 percent of patients without a relevant genetic variant also had been diagnosed with NPDs, according to the study. NPDs are "highly complex," study authors wrote, with a range of clinical presentations and contributing factors. The effects of genetic variants are modulated by genomic, environmental, and experiential factors across an individual's lifetime.

The paper represents one of the first studies to look at the prevalence of NPD-related single-gene variants across a broad adult population, according to Martin. Much of the research to date has used cohorts of patients who have had genetic testing after experiencing symptoms of an NPD.

The study by Martin and colleagues elucidates to what extent people who haven't been diagnosed with an NPD have such genetic variants – an ongoing question in neurodevelopmental genetics, said Aaron Besterman, an assistant professor in the psychiatry department at the University of California, San Diego and a psychiatrist in the child and adolescent psychiatry service at Rady Children's Hospital-San Diego.

"If we're not looking in the population in general, then we won't know for sure" the actual prevalence of NPD-associated variants, said Besterman, who wasn't involved in the Geisinger study. In his view, this study confirms that while most people don't have genetic variants associated with NPDs, more do than may have been previously appreciated.

For patients with NPDs, genetic results can inform their medical management by identifying if they're at increased risk for other diseases or providing more insight into their prognosis. And if parents are receiving genetic results of a child, the results could have implications for future pregnancies.

For example, a deletion on chromosome 17 is associated with autism spectrum disorder and schizophrenia, as well as an increased risk for diabetes in young adulthood. "Knowing that information allows you to try to manage the risk for diabetes and get ahead of that," Martin said.

Even though the identification of pathogenic variants may not "drastically" change the management of an NPD patient, Besterman hopes advances in pharmacogenomics and even gene therapy could eventually change that. He is interested to see if future research suggests changes to care management for patients who have a genetic variant but no symptoms of an NPD.

Martin, a geneticist by training, said one of her goals as Geisinger CSO is to "get genetics out of the genetics clinic and into broader healthcare."

> "We can't send everyone to a geneticist just to order the test," Christa Martin, CSO at Geisinger Health System, said. "It creates a huge bottleneck with waiting lists."

Diagnostic genetic tests for NPDs are available today, but aren't frequently used outside of medical genetics settings, researchers from Geisinger and the Hospital for Sick Children in Toronto wrote in an article in *Current Opinion in Genetics and Development* last year, calling for the industry to set cross-disciplinary consensus recommendations on genetic testing for children and adults with NPDs.

Recommendations for genetic testing can vary by society. The American College of Medical Genetics and Genomics recommends offering genetic testing for those with autism, as well as exome or genome sequencing for pediatric patients with developmental delay or intellectual disability. The American Psychiatric Association lists genetic testing as a suggested assessment for schizophrenia patients in practice guidelines. The International Society of Psychiatric Genetics, by contrast, considers fragile X molecular testing and chromosomal microarray analysis as part of the standard work-up for those with autism, intellectual disability, and developmental delay, and exome sequencing is increasingly being used as a first-tier test; the society doesn't have any molecular testing recommendations for schizophrenia.

Yet even in areas like autism, where there's widespread agreement on the utility of genetic testing, uptake has been low. A 2021 study in *Frontiers in Pediatrics* noted between 16.5 percent and 45 percent of pediatric patients with autism and 43 percent of patients with intellectual disability have undergone genetic testing, despite recommendations from several medical societies.

Limited test adoption is often attributed to the fact that psychiatrists and psychologists aren't trained in medical genetics, and as such, they might not be confident in selecting tests or interpreting results, researchers wrote in the *Current Opinion in Genetics and Development* article. In cases where NPD specialists do want genetic assessments for their patients, they tend to refer patients to medical geneticists to determine which tests to order. That can create a bottleneck, given a shortage of medical geneticists, and patients may not keep referral appointments.

At Geisinger, the health system has implemented a model in which clinicians at ADMI order exome sequencing for pediatric patients diagnosed with autism, intellectual disability, and developmental delay, Martin said. In fact, it's one of the first steps clinicians take after providing a diagnosis. Genetic counselors then work with clinical team members to review genetic results and relay that information to patients.

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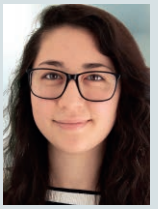
Genetic testing for bipolar disorder and schizophrenia are "on our radar" at Geisinger, Martin added, but the health system is continuing to research diagnostic yield and how such results would be used in clinical care.

"We need to collect more evidence [on medical utility]," Martin said. She added that previous research has already indicated NPD patients find genetic results beneficial, suggesting at least personal utility – with many patients expressing appreciation at having a medical explanation for symptoms they've been struggling with. It's "providing an individual with an answer to why they might have this condition," she said. PMQ



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