A centuries-old math equation used to solve a modern-day genetics challenge

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Sean Tavtigian, PhD, a cancer researcher at Huntsman Cancer Institute (HCI) and professor of oncological sciences at the University of Utah. Credit: Huntsman Cancer Institute

Researchers developed a new mathematical tool to validate and improve methods used by medical professionals to interpret results from clinical genetic tests. The work was published this month in *Genetics in Medicine*.

The research was led by Sean Tavtigian, PhD, a cancer researcher at Huntsman Cancer Institute (HCI) and professor of oncological sciences at the University of Utah, in collaboration with genetics experts from around the United States.

Tavtigian utilized Bayes' Theorem, a math equation first published in 1763, as the basis of a computational tool he and the team developed to assess the rigor of the current, widely-used approach to evaluate the results of a clinical genetic test.

Clinical genetic testing is used in a variety of medical fields, including cancer care, obstetrics, and neurosciences, among others. Results of a genetic test may help to provide a definitive medical diagnosis, or assess the likelihood of a person to develop a particular disease before symptoms appear. The range of approaches employed to provide health care based on the results of the test can vary significantly. Patients may be at negligible risk for disease with no medical management required, or they may pursue costly, invasive medical treatment in an effort to stave off disease or manage and minimize symptoms.

With millions and millions of changes possible in genes that control health in any given person, the challenge of discerning which gene changes are likely to cause disease is vast. In the past few years, human genetic researchers have identified thousands of Variants of Uncertain Significance (VUS), that is, genetic changes without a known understanding of how they may impact a person's health. "A large fraction of VUS are believed to be generally harmless," describes Tavtigian. "One only wants to change the medical management of patients when the genetic testing identifies a variant that is likely to be disease-causing. Against a huge population of harmless VUS, how do you identify the small subset that are likely to require medical management?"

The research team set out to reduce subjectivity or interpretation bias in the review of genetic test results to determine whether a patient is susceptible to disease. Using the computational tool they designed, they tested 18 subjective rules recommended by the American College of Genetics and Genomics (ACMG) in the current framework for assessing results of clinical genetic tests. They found that the ACMG's system of 18 rules is statistically sound and that the rules are objectively strong. Also, the rules generally maintained their relative strength when tested against one another. Further, the team explored ways to allow the framework to continue to be employed as new findings about genetics are added to this body of knowledge.

"The scale of genetic testing used by specialists is growing exponentially, with genetic testing laboratories working to keep up with the demands of processing and interpreting the results of genetic tests," says Tavtigian. "The points of internal consistency that we found did not have to be true—yet they are, and it is important that the genetic testing community knows this. We hope this work will help accelerate application of results from these tests to make decisions about patient care, adding years to patient's lives."

More information: Sean V Tavtigian et al, Modeling the ACMG/AMP variant classification guidelines as a Bayesian classification framework, *Genetics In Medicine* (2018). DOI: 10.1038/gim.2017.210

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