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Comparing family history and genetic tests for predicting complex disease risk

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In a new theoretical study, 23andMe, the personal genetics company, developed a mathematical model which shows that family history and genetic tests offer different strengths. The study results suggest that both family history and genetics are best used in combination to improve disease risk prediction. The full results of the study have now been published online in the journal *PLOS Genetics*.

Family history is most useful in assessing risks for highly common, heritable conditions such as coronary artery disease. However, for diseases with moderate or low frequency, such as Crohn's disease, family history accounts for less than four percent of disease heritability and is substantially less predictive than genetic factors in the overall population. The study results indicate single nucleotide polymorphism (SNP)-based genetic tests can reveal extreme likelihood ratios for a relatively large percentage of individuals, thus providing potentially valuable evidence in differential diagnoses.

"Both family history and genetics are important tools for assessing an individual's risk for disease," 23andMe CEO and co-founder Anne Wojcicki said. "We believe it will become increasingly important for individuals and physicians to know both family history and genetic profile to provide optimal healthcare."

Lead author and 23andMe scientist Chuong Do, Ph.D, worked with 23andMe senior medical director Uta Francke, M.D., and principal scientists David Hinds, Ph.D., and Nicholas Eriksson Ph.D. to make a

comprehensive comparison of family health histories and genetic testing to assess risk for 23 different conditions. These conditions included coronary artery and heart diseases, type 1 and 2 diabetes, prostate cancer, Alzheimer's disease, breast cancer, lung cancer, Crohn's and celiac disease, ovarian cancer, melanoma, bipolar disease and schizophrenia among others.

The analysis confirms that family history is most useful for highly common, heritable conditions and for single-gene (Mendelian) disorders with high penetrance, where the specific genetic cause is not yet known. For relatively common diseases that may have many contributing genetic and environmental factors, such as coronary artery disease, knowing that your father had the disease is helpful at predicting whether or not you might be at risk for the same condition.

For less common diseases involving many weak genetic factors, such as Crohn's disease, knowing family history seldom helps in making a risk prediction, in part, because these diseases are uncommon enough that they would rarely show up in the immediate family health history. When family histories are uninformative, genetic testing may still reveal the genetic variants that would put an individual at a higher or lower risk for the condition. For example, Crohn's disease might not show up in a family history, but the risk prediction from a genetic test can be relatively more informative.

"These results indicate that for a broad range of diseases, already identified SNP associations may be better predictors of risk than their family history-based counterparts, despite the large fraction of missing heritability that remains to be explained," stated lead researcher Chuong Do, Ph.D. "They also suggest that in some cases, individuals may benefit from supplementing their family medical history with genetic data, in particular, as genetic tests are improving and more risk factors are discovered."

"This study addresses the false division between these two diagnostic tools, genetic testing versus family health histories, where the approaches have traditionally been portrayed as competing alternatives," explained Uta Francke, M.D., senior medical director. "Physicians rely on a variety of tools such as a stethoscope or a thermometer – both are useful in their own way. Similarly, family health histories and genetics both offer different but equally valuable information to inform patient care."

"Using genetic testing or SNP-association based methods to estimate risk for some rare complex diseases is as good as family histories can be at estimating risk for common heritable conditions," Dr. Francke continued, "and for individuals who don't have access to their family health history, genetic testing can alert them to risks they wouldn't be aware of otherwise."

The authors use their theoretical model to demonstrate the limits of predictive testing while also outlining specific areas where genetic tests have the potential to be medically useful. These results, which provide a cautiously optimistic outlook on the future of genetic testing, contrast with the conclusions reached in an independent study published earlier this year in *Science Translational Medicine*.

This investigation follows a number of previously published studies that utilized the company's customer database in identifying new genetic associations for a variety of health conditions, including the discovery of two novel genetic associations for Parkinson's disease, published in *PLOS Genetics*; five novel significant genetic associations for hypothyroidism in the largest known genome-wide association study of hypothyroidism conducted to date published online in the journal *PLOS ONE*; six novel associations for male pattern baldness and their unexpected association with common diseases including prostate cancer and Parkinson's disease also published in PLOS Genetics; and seven

novel associations for breast size, published in BMC Medical Genetics, three of which are also associated with breast cancer.

More information: www.plosgenetics.org/article/info%3Adoi%2F10.1371%2Fjournal.pgen.1002973

Provided by 23andMe Inc.