Whole genome sequencing not informative for all, study shows

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With sharp declines in the cost of whole genome sequencing, the day of accurately deciphering disease risk based on an individual's genome may seem at hand. But a study involving data of thousands of identical twins by Johns Hopkins investigators finds that genomic fortune-telling fails to provide informative guidance to most people about their risk for most common diseases, and warns against complacency born of negative genome test results.

Findings from the Johns Hopkins researchers' evaluation of the predictive value of whole genome sequencing are published online April 2 in Science Translational Medicine.

Whole genomic sequencing catalogs all of the genes that a person inherits from each parent. On average, any two individuals' genomes differ in 4.5 million positions scattered throughout their genomes. Whole genome sequencing identifies those differences and links them to known or suspected contributions to an individual's risk of certain diseases.

The Johns Hopkins research casts doubt on whether whole genome sequencing can reliably predict the majority of future medical problems that will be encountered by most people who take such tests.

"We believe that genomic tests will not be substitutes for current disease prevention strategies," says Bert Vogelstein, M.D., Clayton Professor of Oncology at the Johns Hopkins Kimmel Cancer Center, co-director of

the Ludwig Center for Cancer Genetics, and investigator of the Howard Hughes Medical Institute. "Prudent screening, early diagnosis and prevention strategies, such as not smoking and removing early cancers, will be the keys to cutting disease death rates."

To investigate the predictive potential of whole genome sequencing, the Johns Hopkins team used data recorded on thousands of identical twins entered into registries in Sweden, Denmark, Finland, Norway and the National Academy of Science's National Research World War II Veterans Twins Registry. "Identical twins share the same genome, and if the genome were the determining factor for common diseases, then the prevalence of a specific disease in an individual whose twin has that disease can be used to determine how well whole genome sequencing could predict an individual's disease risk," says Vogelstein.

The Johns Hopkins team collected information on the incidence of 24 diseases among the twin-pair groups, including cancer, as well as autoimmune, cardiovascular, genitourinary, neurological and obesity-associated diseases. To predict disease risk, they used mathematical models designed by Johns Hopkins graduate student Nicholas Roberts, D.V.M., and Joshua Vogelstein, Ph.D., assistant research scientist at the Johns Hopkins University Whiting School of Engineering and Bert Vogelstein's son, in collaboration with Giovanni Parmigiani, Ph.D., professor of biostatistics and computational biology at the Dana-Farber Cancer Institute. The models were used to calculate the capacity of whole genome sequencing to predict the risk of each disease based on typical thresholds used by doctors to initiate preventive or therapeutic measures.

Their analysis shows that whole genome sequencing could alert most individuals to an increased risk of at least one disease, signaled by a positive test result, but most people would get negative test results for the majority of diseases studied, failing to forewarn them of the diseases

they may ultimately develop.

Kenneth Kinzler, Ph.D., co-director of the Ludwig Center at Johns Hopkins and professor of oncology, provides an example of what their analysis showed: "As many as two percent of women undergoing whole genome sequencing could receive a positive test result for ovarian cancer, alerting them that they have at least a one-in-ten chance of developing that cancer over their lifetime. The other 98 percent of women who receive a negative test for ovarian cancer will not be guaranteed a lifetime free of ovarian cancer because their risk of developing it is very similar to that of the general population. So, a negative test is not a 'free pass' to discount the chance of acquiring any particular disease."

The investigators say their analysis specifically shows that whole-genome-based tests are not highly informative for predicting cancer in most individuals without a strong family history of the disease. On the other hand, genetic tests could identify, theoretically, more than three-quarters of patients who may develop four of the diseases studied – coronary heart disease in men, thyroid autoimmunity, type 1 diabetes and Alzheimer's disease.

"In families with strong histories of cancer, whole genome sequencing can still be very informative for identifying inherited genes that increase cancer risk," says Victor Velculescu, M.D., Ph.D., professor of oncology, who with Vogelstein and Kinzler provided some of the first evidence that inherited pancreatic cancer genes can be identified in families through whole genome sequencing. "But hereditary cancers are rare. Most cancers arise from mutations acquired through environmental exposures, lifestyle choices and random mistakes in genes that occur when cells divide."

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