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NEWS

Whole genome sequencing fails to predict risk of most common diseases

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Whole genome sequencing fails to provide useful guidance on the risk of the most common diseases, according to results published this week of a study comparing risk in thousands of pairs of identical twins.

Whole genome sequencing analyses all the genes coded for by a person's entire DNA. The cost of the procedure has fallen dramatically over the past few years, so there has been growing interest in its potential for predicting risk of disease.

Each person has millions of genetic variants, and the contribution of nearly all these variants to any disease is unknown, making it very difficult to assess the benefit of whole genome sequencing in determining the risk of a particular disease.

But this question can be answered by looking at identical twins. "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," said Bert Vogelstein, professor of oncology at the Johns Hopkins Kimmel Cancer Center, Baltimore, and the study's lead author. "We used twins as a natural experiment to estimate the capacity of genome sequencing to determine disease risk, even though we didn't know their genome sequence."

The group analysed data on disease incidence from more than 53 000 pairs of monozygotic twins on registries in Denmark, Finland, Norway, Sweden, and the US National Academy of Science's national research second world war veterans twins registry (*Science Translational Medicine* doi:10.1126/scitranslmed.3003380).

They looked at the incidence of 24 diseases, including autoimmune, cardiovascular, genitourinary, neurological, and obesity associated diseases and cancer. The group then used mathematical models to estimate the capacity of whole genome sequencing to predict the risk of each disease, on the basis of typical thresholds used to initiate preventive or therapeutic measures.

Their results showed that most people would get negative results from whole genome sequencing for 23 of the 24 diseases. But these negative results would generally not be very informative, because the risk of developing 19 of the 24 diseases in people testing negative would still be, at a minimum, 50-80% of that in the general population.

For example, the study findings predict that up to 2% of women undergoing whole genome sequencing would receive a positive test result for risk of ovarian cancer. This would indicate at least a one in 10 chance of developing this cancer during their lifetime. "But the other 98% 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 [1.4%]," said Kenneth Kinzler, professor of oncology at Johns Hopkins and a study coauthor.

However, in the best case scenario the study indicates that more than 90% of people tested might be alerted to a clinically significant predisposition to at least one disease.

Vogelstein said, "Our results suggest that genetic testing, at its best, will never be a crystal ball that predicts future risk of disease, other than in individuals with a strong family history of a condition. It will not be a substitute for preventive and public health strategies incorporating routine check-ups and risk management based on history, physical status, and lifestyle."

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