IN THIS ISSUE

Revisiting exome data reduces costs and increases yield for inherited disorders

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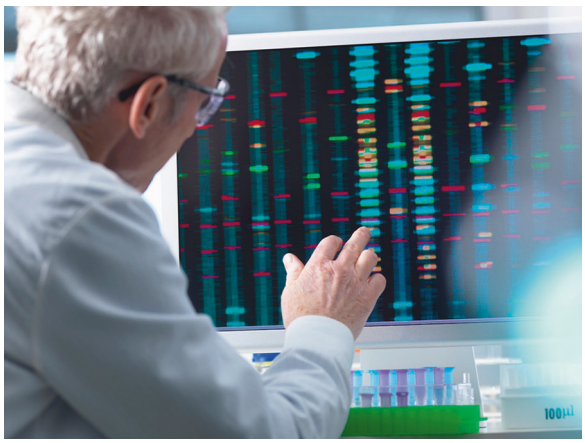

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Reanalyzing exome data after one year increases diagnostic yield and costs less than pursuing other testing pathways for patients with undiagnosed Mendelian disorders, according to a study presented in this issue. The Australia-based research team investigated whether reanalysis after one year makes economic and diagnostic sense in a cohort of 54 patients from 37 families, all recruited from genetics clinics in New South Wales. Initial exome sequencing yielded diagnoses in 11 of 37 cases. Families with more than one affected member had a lower rate of diagnosis (20% from three families). Reanalysis after one year resulted in new diagnoses in four families, increasing the diagnostic rate from 30% to 41%. Two of these diagnoses could be accounted for by the publication of new disease–gene associations since the original analysis was conducted. In one case, a new variant in a retinitis pigmentosa–related gene solved a genetic mystery for a large family with multiple affected members. While the variant had been known, it was not covered in the first analysis. The new diagnosis was due to implementation of an improved bioinformatics pipeline with higher variant detection sensitivity. The research findings, which consisted of a somewhat unusual combination of diagnostic data and economic analysis, demonstrated that for each additional diagnosis, $586 was saved due to avoiding unnecessary diagnostic testing. The economic analysis included a subset of 14 patients with intellectual disability for whom full medical records were available. For this group, the team compared the average cost per patient, average cost per diagnosis, and incremental cost per additional diagnosis for the initial analysis and one-year reanalysis. While the economic findings are limited to the Australian economic and medical system, the results apply to any clinical genetics lab. Given the speed of innovation in genomics bioinformatics, reexamination of exome data in undiagnosed patients makes sense for patients suspected of having Mendelian disorders. —*Karyn Hede, News Editor*

Women with true-negative *BRCA1/BRCA2* test results have no increased risk of breast cancer

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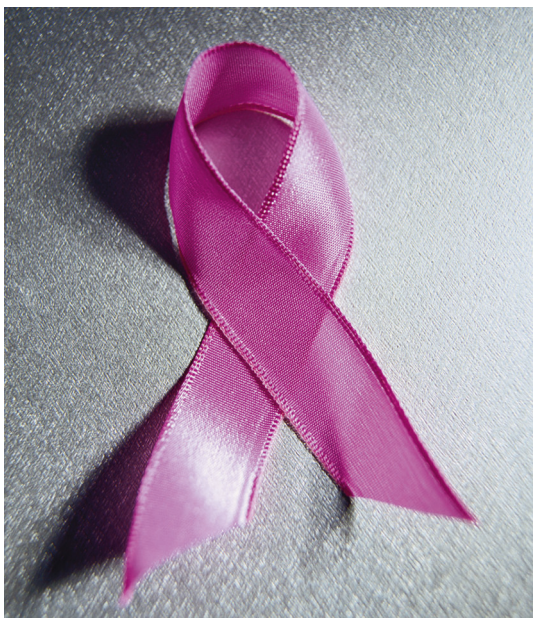

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Data from the largest prospective study done to date suggest that women who receive a true-negative test result for inherited breast cancer gene variants (that is, negative testing for a known familial pathogenic variant) are not at increased risk for subsequent development breast or ovarian cancers. The findings, reported in this issue, provide the most robust data available on the question of whether individuals in families of carriers, who are not carriers themselves, nonetheless have an elevated risk of developing breast or ovarian cancer. Several previous studies had produced conflicting results. Here, a large collaborative research group used data from the Epidemiological Study of Familial Breast Cancer (EMBRACE) to revisit the question with a larger data set. The EMBRACE study is an ongoing prospective study of cancer risks in *BRCA1/BRCA2* mutation carriers and their relatives in the United Kingdom and the Republic of Ireland. The study began recruitment in 1997 of families in which at least one member had tested positive for *BRCA1* or *BRCA2* gene variants. Isolating data for only noncarriers, the researchers obtained data on 1895 noncarriers. Among these predictive test negatives eligible for inclusion in the analysis, 23 developed invasive breast cancer. Cases were evenly spread among families with *BRCA1* mutations (12) and *BRCA2* families (11). Overall, the risk of invasive breast cancer in these women was 9.4% by age 85. Similarly, of 1736 noncarriers eligible for the ovarian cancer analysis, two cases occurred, both in women from *BRCA2* families. Overall, the relative risk was no higher in this group than in the general population. — *Karyn Hede, News Editor*

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