IN THIS ISSUE

NGS workflows vary in detecting challenging variants

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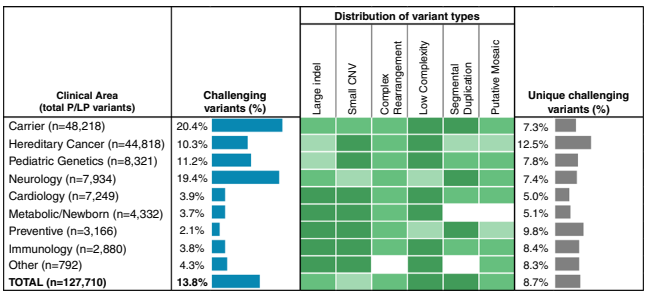

Clinical genetic tests use next-generation sequencing (NGS) to facilitate diagnosis of hereditary cancer, cardiovascular, and neurological disorders and reproductive carrier screening, among other indications, as well as to inform patient care. However, well-known shortcomings of short-read NGS methods allow some technically challenging variants such as large indels, small copy-number variants, complex alterations, and variants in low-complexity or segmentally duplicated regions to remain undetected. In this issue, Lincoln and colleagues assess the impact of technically challenging variants on the implementation, validation, and diagnostic yield of common clinical genetic tests. To determine how well 10 NGS-based workflows detected challenging variants, the researchers conducted an inter-laboratory pilot study using synthetic plasmids containing pathogenic variants known to be technically challenging for NGS. The researchers titrated the plasmids into genomic DNA from the Genome in a Bottle cell line at concentrations to appear heterozygous. Samples were provided to seven laboratories for blinded sequencing. All 10 workflows were able to sequence and analyze the synthetic plasmids; however, only three workflows detected all 13 challenging variants. Only two variants were detected by all 10 workflows. The researchers further validated one workflow with clinician-ordered testing of more than 470,000 patients. More than 21% of patients carried one or more pathogenic or likely pathogenic (P/LP) variant. Of the more than 127,000 P/LP variants, nearly 14% met criteria for being technically challenging and were present across a range of indications. The findings indicate that technically challenging variants are prevalent and that the analytic and clinical sensitivities of NGS workflows vary in response to the bioinformatics pipeline and the types of variants that the pipeline is designed and validated to detect. —*V. L. Dengler, News Editor*

Polygenic risk scores fine-tune risk estimates for *BRCA1/2* heterozygotes

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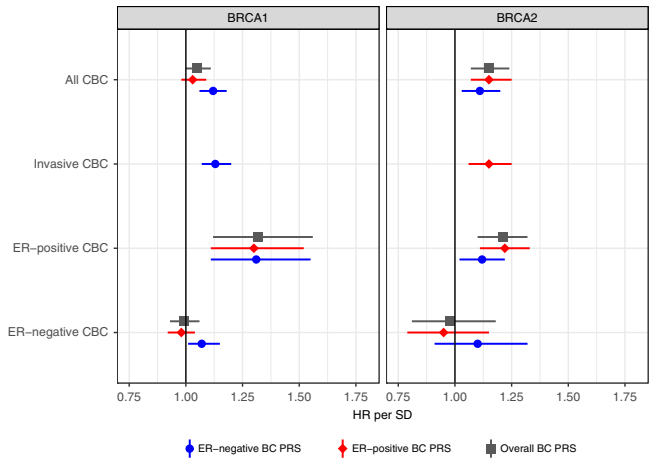

Germline pathogenic variants in *BRCA1* or *BRCA2* (*BRCA1/2*) confer risk for developing breast cancer and women with heterozygous *BRCA1/2* variants are at increased risk of developing contralateral breast cancer (CBC). Contralateral mastectomy reduces CBC risk but is an invasive intervention with burdensome psychosocial side effects such as postoperative complications and an inability to breastfeed in the future, complicating decision-making for these patients. Individualized risk estimates using polygenic risk scores could offer improved risk stratification and help with decision-making regarding treatment. Lakeman and a host of study collaborators and colleagues evaluated whether polygenic risk scores based on 313 breast cancer–associated variants (PRS_{313}) associated with CBC risk in *BRCA1/2* heterozygous women of European ancestry. The researchers identified more than 1,400 *BRCA1* and nearly 650 *BRCA2* heterozygotes diagnosed with CBC before enrollment in the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA), a large international retrospective series. They determined that the cumulative 10-year risk for developing CBC in the cohort was 25% for *BRCA1* heterozygotes and 19% for *BRCA2* heterozygotes. Association analyses revealed that for *BRCA1* heterozygous women, estrogen receptor (ER)-negative PRS_{313} showed the strongest association with CBC risk. In contrast, ER-positive PRS_{313} showed the strongest association for *BRCA2* heterozygotes. When the researchers assessed interaction with age at first breast cancer diagnosis, they found that for women younger than 40 years old, the cumulative 10-year CBC risks were between 22% and 32% for *BRCA1* heterozygotes and 13% and 23% for *BRCA2* heterozygotes. The findings indicate that PRS can be used to fine-tune CBC risk estimates in *BRCA1/2* heterozygous women of European ancestry. The authors conclude that incorporating additional risk factors will improve risk prediction. —*V. L. Dengler, News Editor*

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