Overview

Multi-gene panels for hereditary cancer are now entering clinical use. To help develop the most appropriate genetic counseling practices for these panels it is important to have careful measurements of their yield and performance by comparison with traditional genetic tests. Recently we described clinical results from panel testing of 198 patients (Kuriyan et al., J Clin Oncol 2014) which we expand on here in a larger patient population.

We collected over 1000 patients from two clinical centers, all of whom had been referred for hereditary breast/ovarian cancer risk counseling or assessment. 735 of these patients were prospectively recruited following NCCN criteria (family history and/or personal history) in order to best represent clinical experience. A separate 327 particularly high-risk cases were also collected either from a clinical biobank or from patients referred because of a known pathogenic variant in their family. We also supplemented this study with non-clinical reference samples. Previous test results on these individuals were available that we used in comparison to the 29-gene panel test results.

Analytic Performance: We see 100% concordance between the 29-gene next-generation sequencing (NGS) panel and the previous test results whenever corresponding tests were performed. Overall the panel had 100% sensitivity and 100% specificity compared to traditional methods. While certain classes of variation are known to be challenging for NGS (e.g. large sequence indels and small copy-number deletions) all such variants in this study were correctly reported by the NGS methods and bioinformatics pipelines we used.

Variant Classification: We see 99.8% concordance for BRCA1/2 pathogenicity assessments between the panel test and the previous test results.

Technical Aside: Del/Dup Calling by NGS

NGS was used to detect not only sequence alterations but also copy-number changes by two methods in this study: Read-depth: In NGS data, read depth varies across genomic regions although the pattern of relative depths is reproducible. Deviations from this pattern indicate copy-number changes. Using a coordinated set of laboratory protocols and data analysis methods (much as has been successfully done with microarrays) we demonstrated clinical levels of performance for events as small as an exon in most genes.

Discussion

Counseling breast/ovarian cancer patients and their families for panel test results can include a level of uncertainty and complexity. Some genes reported by panels confer only a modest increased risk; the spectrum of cancers in a family may or may not fit the spectrum commonly associated with a reported gene; VUS rates increase with panel testing; and finally counselors must address the reproductive and family implications of multiple mutations in panels which have both dominant and recessive modes of inheritance. Despite these challenges, the use of panels is increasing. As shown here, panels can generate reliable data and panels can uncover findings relevant to patient management that are otherwise missed. Data such as those reported here may help guide the ongoing discussion of ways to meet these genetic counseling challenges.