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Developing a high-quality, sample-to-result Hereditary Breast and Ovarian Cancer Panel Assay Pipeline for using a novel sequencing platform.

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Abstract:
Background: Recent testing recommendations for *BRCA1/2* emphasize the changing landscape for hereditary breast and ovarian (HBOC) from medical history-based to genomic screening approach, and the public health benefit due to clear actionability and ascertainment of the latter approach. Currently, 20 genes are recommended for screening for HBOC based on payor reimbursement and evidence-based guidelines. However, prevention remains inadequate; plagued by a) high test cost, and b) challenges in NGS data quality in genes that are difficult to resolve by standard targeted sequence capture. Most sequencing platforms offer cost effective sequencing with substantial multiplexing. Therefore, high-throughput sequencers do not often fit well with smaller scale clinical testing platforms that require fast turn-around times and the ability to process a few samples at a time.`**Approach:** We developed a cost-effective comprehensive testing approach using a novel sequencing platform that enables flexibility in scale while matching the cost of the highest throughput platforms. The Element Aviti benchtop sequencer provides a testing solution with flexible scale that enables small batch sizes with low error rate and novel performance for mutation detection of both point mutations and indels. Nine genes (*BRCA1, BRCA2, EPCAM, MLH1, MSH2, MSH6, PMS2, PTEN, STK11)* often include challenging CNV events that are relevant to report in the screening test. We explore software and library preparation methods to enhance the detection of complex variants in these genes. Screening accuracy performance was assessed on all workflows on a blinded series of samples using custom CNV calling tools across the 9 genes. **Results:** In a pilot study of 51 patient samples we have compared current clinical short read sequencing with a new sequencing platform by Element Biosciences. The error profiles look similar and overall concordance for a total of 272 clinical relevant variants from ClinVar show concordance in 270 cases with 2 sites being inconclusive due to a neighboring homoploymer run for both platforms. All 10 pathogenic variants including CNV variants could be detected on both platforms. We will further present a summary and comparison of the utilized workflows for target capture and sequencing with a focus on CNV workflow to detect CNV events in challenging regions. **Conclusion:** A novel NGS algorithm was optimized for detecting SNVs, indels and CNVs including difficult CNV events that met the cost and quality aspects. Its routine use would therefore enable early surveillance. The approach can be extended to other application of screening of public health importance.

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