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Editorial

Whole Exome Sequencing: A Necessary Tool for the Future of Clinical Cancer Care

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ABBREVIATIONS

WES: Whole Exome Sequencing

INTRODUCTION

Germline testing for clinical cancer care and risk assessment is commonly employed as approximately 10% of all cancers are thought to have a heritable component [1]. Due to the genetic heterogeneity of inherited cancer risk factors, current testing is performed by focusing on a panel of associated risk genes to increase the likelihood of finding a causal genetic variant. Despite the introduction of larger and more inclusive gene panels, issues of low diagnostic yield remain, and inconclusive results often generate additional burden on clinicians, patients and relatives. Our knowledge of inherited risk is still evolving, meaning that testing panels continue to be updated. Therefore, many question the utility of panels in favor of a whole genome or exome approach in which genes can be analyzed post hoc without the need for additional sampling. Genetic testing seems poised for this approach, but hesitation remains due to concerns of quality, cost and practicality. Below we weigh the advantages and disadvantages of panel testing versus whole exome sequencing (WES). In doing so, we assert that recent advances in technology indicate that the field should begin the shift to whole exome/genome sequencing, starting with the implementation of WES for those with a cancer diagnosis and suspicious family history.

ADVANTAGES OF WHOLE EXOME SEQUENCING (WES) OVER PANEL TESTING

One argument against employing exome sequencing in favor of panel testing is that it would sacrifice quality for quantity. High quality variant calls are necessary for reliable clinical genetic diagnosis and WES is not ideal for detection of variants in regions high in GC content, with many nucleotide repeats, or with homology to other regions of the genome [2]. Panel testing focuses on a small number of genes allowing for the luxury of more coverage, greater read depth and thus higher quality reads. Because panel testing allows for deeper sequencing than WES [3], panels are believed to have superior detection of known pathogenic variants and thus a better diagnostic yield. However, as technology advances and bio informatics pipelines for variant calling improve, the quality of WES data will inevitably reach comparable clinical sensitivity. A recent study assessing the coverage in 100 samples demonstrated that 99.7% of pathogenic variants were detectable by WES at clinical sensitivity and all pathogenic variants had at least some coverage on exome sequencing [4]. Another study compared the diagnostic performance of WES to two panels, TruSight Cancer and a custom panel of 122 genes, and among the shared genes, a similar number of variant calls were identified despite greater average read depth in panels [3].

Another important consideration aside from call quality is cost. The cost discrepancy between WES and panel testing is narrowing and the potential future benefits of exome sequencing may outweigh the difference. Although sequencing exomes is more expensive than panels, they provide additional patient data regarding genes that may soon be clinically relevant and therefore evaluable without the need for retesting. Panels can quickly become outdated with each novel gene discovery and insurance will often only cover genetic testing once. Another valid concern for molecular diagnostic labs is testing turn-around time. Many smaller labs may not be set up for performing WES quickly at a high volume, and sometimes immediate clinical decisions are made based on mutational status. Therefore, the value of choosing exome sequencing over panel testing should be made on a case by case basis.

The transition from panel to genome/exome approach should begin with cases that are highly suspect of inherited risk. For instance, the National Comprehensive Cancer Network guidelines stipulate that women diagnosed with ovarian cancer should undergo genetic testing regardless of family history [5]. Although offering panel testing is likely sufficient for most cases, those patients with a family history of breast or ovarian cancer would likely benefit more from WES. This is due to an issue of "missing heritability" in hereditary ovarian cancer, whereby our current knowledge only explains approximately half of the germline risk [6,7]. A recent study employed WES on women diagnosed with ovarian cancer with suspected inherited risk, and discovered several loss of function mutations in candidate genes not currently featured on testing panels including a truncating variant *FANCM* previously shown to associate with familial breast cancer [8,9]. Another study used high throughput sequencing on

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104 familial breast cancer cases and identified a novel loss of function truncation variant in the candidate gene *KIAA1919* [10]. By analyzing only the genes known to be associated with disease, clinical geneticists are limited in their ability to identify novel genetic risk loci and properly counsel patients. Adopting the approach of WES for patients diagnosed with cancer suspected to be hereditary will be an invaluable tool because the discovery of novel disease associated mutations will better equip clinical geneticists and patients in cancer risk assessment. A two-step process would be most practical, by which cancer associated genes are analyzed first, and if no deleterious germline mutation is found, the analyst can then evaluate candidate genes of interest.

CONCLUSION

The value of the additional findings that WES will yield is difficult to estimate, but will provide answers for many individuals and their families. While panel testing has provided insight into cancer risk, many more mutations and associated genes have yet to be implicated. Implementing WES in place of a panel where feasible should be considered when genetic testing is appropriate. Clinical testing facilities may still choose to analyze only genes with well-established risk associations. Over time, the vast amount of data generated from WES will prove invaluable to the field of genetic testing by minimizing the issue of missing heritability, increasing diagnostic yield and improving patient care.

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