Diagnostic exome sequencing beneficial among patients with a prior diagnosis

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Abstract:

Clinical diagnostic exome sequencing (DES) provides data on all the coding exons of the genome and is currently indicated when prior tests have been negative, when the phenotype fits with the clinical spectrum of multiple genes, and/or when the phenotype is not consistent with any known clinical picture. DES has not only identified pathogenic alterations in genes not previously associated with the disease, but it has also revealed broader phenotypes not previously considered as part of the clinical spectrum within genes with well-established disease-associations. Even in cases where the patient has been provided with a clinical diagnosis or appropriate differential diagnosis, DES may still be pursued to identify the underlying molecular etiology when a single gene test was not available or when DES is more cost- and time-effective than the sequential gene-by-gene approach. A retrospective analysis of the first 200 reported patients undergoing DES at one laboratory revealed that prior to testing, 10% had a clinical diagnosis. Among the 20 clinical diagnoses made prior to DES testing, 3 (15%) were associated with 1-3 genes, while multiple genes could be implicated in the rest (85%). DES provided a definitive molecular diagnosis (including characterized and novel genes) in 53% of patients with a prior clinical diagnosis. The detection rate was lower (33%) in cases those with only 1-3 genes associated with the diagnosis, than those with multiple suspected genes (75%), thought to be attributed to the low overall clinical detection rate of the suspected gene(s). Gene coverage was greater than 95% for all of the cases associated with 1-3 genes. These results highlight the clinical utility of DES, even among patients with a prior diagnosis, as it may reveal the underlying molecular etiology of the disease of interest when multiple genes may be involved.