

Secondary findings on diagnostic exome sequencing: Patient preferences and detection rates based on 1500 DES samples tested at a single clinical laboratory in the United States

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Introduction: Diagnostic exome sequencing (DES) involves the simultaneous analysis of virtually all exonic and flanking intronic sequences. Consequently, DES may result in the identification of secondary findings (SF), which are incidental deleterious variants unrelated to the testing indication. In 2013, the American College of Medical Genetics and Genomics (ACMG) issued recommendations pertaining to the reporting of disease-causing mutations within 56 genes identified incidentally during exome or genome analysis.

Methods: We examined the evolution of SF test offerings within a single clinical laboratory in the United States from 2011 to 2015. We also performed a retrospective analysis of the patient preferences and positive rates of SF from the ACMG recommended 56 and/or expanded gene lists among the first 1500 patients who underwent DES through our clinical laboratory.

Results: Of 1500 DES cases, 437 (29.1%) were ordered before ACMG published recommendations, and 1063 (70.9%) were issued after. Overall, 1361 of 1500 (90.7%) patients requested at least some SF results, and 451 (30.1%) of these cases requested results from more than the ACMG recommended gene list. The majority of cases (1214/1361; 89.2%) had no reported SF, and 47 (3.45%) of patients had at least one reported SF from among the ACMG recommended list of 56 genes.

Conclusions: Based on our experience, most patients proceeding with DES elected to receive at least some SF results. Almost 90% of these cases were negative. A continued evolution in the reporting of SF is anticipated as DES becomes increasingly utilized, and as disease-gene relationships are better elucidated.