Special Report: exome sequencing for clinical diagnosis of patients with suspected genetic disorders
BlueCross BlueShield Association

Record Status
This is a bibliographic record of a published health technology assessment. No evaluation of the quality of this assessment has been made for the HTA database.

Citation

Authors' objectives
The objective of this Special Report is to compare Sanger sequencing and next-generation sequencing clinical molecular methods for diagnosing disorders that are caused by mutations in a single gene, and the potential uses of exome sequencing for molecular diagnosis. We first describe exome sequencing using next-generation sequencing and compare it with Sanger sequencing. Second, three clinical scenarios caused by single-gene disorders where exome sequencing might be applied are described. Finally, we review evidence related to its clinical use in evaluating patients with undiagnosed suspected genetic disorders accompanied by multiple anomalies—focusing on diagnostic yield and potential impact on patient outcomes.

Authors' conclusions
Exome sequencing using next-generation technology has recently become available as a laboratory-developed diagnostic clinical laboratory test. A major indication for use is molecular diagnosis of patients with suspected genetic disorders. These patients may be left without a satisfactory clinical diagnosis of their disorder despite a lengthy diagnostic odyssey involving a variety of traditional molecular and other conventional diagnostic tests. For some patients, exome sequencing obtained after initial diagnostic evaluation (that may include other genetic testing) has failed may avoid the diagnostic odyssey and return a likely causal variant. Currently, the diagnostic yield appears to be no greater than 50% and possibly less for patients with suspected genetic disorder accompanied by multiple anomalies. Medical management decisions, including initiation of new treatment or discontinuing inappropriate treatment, may result for only a subset of those diagnosed. Reproductive decisions for parents considering an additional pregnancy may be informed by determining the mode of inheritance. Appropriate use of exome sequencing requires considerable genetic, clinical, and genetic counseling expert.

Final publication URL

Additional data URL

Indexing Status
Subject indexing assigned by CRD

MeSH
Humans; Genetic Testing; Genetic Diseases, Inborn; Exome

Language Published
English

Country of organisation
United States
English summary
An English language summary is available.

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AccessionNumber
32013000682

Date abstract record published
23/09/2013