INBRIEF | Summarizing the Evidence

Genome-Wide Sequencing for Unexplained Developmental Delays and Multiple Congenital Anomalies: A Rapid Qualitative Review

Key Messages

- Families and clinicians see genome-wide sequencing (a form of genetic testing) as a valuable tool for potentially determining the cause of a child's unexplained condition (e.g., developmental delays or congenital anomalies). Knowing the cause, or causes, of their child's condition can provide families with an initial sense of relief and help provide feelings of closure to a lengthy series of diagnostic tests (sometimes referred to as "diagnostic odysseys").
- A family's desire to know the cause of their child's condition is often coupled with hopes that test results will lead toward new treatment strategies. For some, these hopes are frustrated when results show a genetic cause, or likely genetic cause, without any known clinical action. For some, this frustration may be alleviated through conversations with clinicians that clearly explain, prior to testing, the possible outcomes of testing and the potential clinical action of the results.
- It is common for parents to question whether they are the cause of their child's condition. This can lead to feelings of guilt and fear. Clinicians can help alleviate parents' fears by carefully and thoroughly presenting and discussing test results (e.g., talking about genetic causes without using language that assigns blame, highlighting the role chance plays in the transmission of genetic diagnoses).
- Families express a desire for incidental (additional and unintentional) findings when the condition is severe and there is predefined clinical action to be taken. Knowing about incidental findings is not desired when there is limited clinical action to be taken and when parents feel it might hinder their child's ability to make their own decisions in the future.

Context

About one-half of those living with congenital anomalies (birth defects) do not have a specific cause or diagnosis identified. These individuals are given a label of "unexplained developmental delay." It is common for these individuals to be subjected to multiple diagnostic tests, which may occur over many months or years. Genome-wide sequencing (GWS) involves technologies with the potential to provide definitive diagnoses to conditions otherwise undetected by clinical presentation and the examination of environmental causes alone.

Technology

GWS technologies (including both whole exome and whole genome sequencing) are used to evaluate and detect gene variants (mutations) that may be the cause of a certain condition. This is accomplished through a blood draw that is sent to a laboratory for analysis. After the sequencing, analysis, and interpretation of the test results, pathogenicity is labelled along a scale from pathogenic to benign. Pathogenicity refers to the potential capacity of a gene variant to cause unexplained developmental delays and multiple congenital anomalies. The American College of Medical Genetics has developed and standardized five descriptive reporting categories: pathogenic (disease-causing), likely pathogenic, variant of uncertain significance, likely benign, and benign.

GWS involves newer sequencing technologies (also referred to as next-generation sequencing) that can read large amounts of genetic information simultaneously. This makes the process substantially faster than more traditional sequencing methods but requires the efforts of multiple, highly specialized professionals working across various disciplines. These newer technologies also increase the number of genetic variants (mutations) identified that may be casually relevant to a person's condition (i.e., variation of uncertain significance) but cannot be known with certainty.

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Issue

Once test results and interpretations of pathogenicity are confirmed, they are returned to clinics and shared with patients and their families. Patients and families take this information and find ways of incorporating it into their lives. Understanding families' and clinicians' experiences with, and perspectives of, genetic testing can provide valuable insight into common issues families face along their journey. This knowledge can also provide clinicians with insight about how to approach conversations about genetic testing with patients and families.

Methods

A limited literature search was conducted of key resources, and titles and abstracts of the retrieved publications were reviewed. Full-text publications were evaluated for final article selection according to predetermined selection criteria (population, intervention, context or setting, outcomes, and study designs).

Results

The literature search identified 436 citations. After screening the abstracts, 25 were deemed potentially relevant, and 13 studies met the criteria for inclusion in this review — seven semi-structured interviews, three interviews, two video-recorded consultations between geneticists and families, and one self-reported questionnaire and interview.

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