Gamut of Genetic Testing for Neonatal Care

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KEYWORDS

• Genetic testing • Perinatal diagnostics • Clinical genetics • Neonatal diagnostics
• Exome sequencing

KEY POINTS

- The choice of genetic testing will depend upon history, physical examination, and differential diagnosis.
- A molecular diagnosis is important for management, natural history, and future studies.
- Consultation with a medical geneticist can facilitate the selection of the appropriate genetic tests.
- This article discusses the clinical utility and indications for each of a host of genetic testing options available for a referring neonatologist.

INTRODUCTION

There are over 3500 known monogenic genetic diseases, most of which present during the first 28 days of life.[1] Despite the fact that these are monogenic Mendelian disorders, clinical diagnosis of most of these conditions is complicated in several ways, including pleiotropy (1 gene presenting multiple phenotypes), clinical heterogeneity (symptoms overlapping with other disorders), and genetic heterogeneity (multiple genes associated with the same phenotype or disease). Moreover, with the rapid advances in sequencing technologies, the identification of new genetic diseases and novel genes associated with known diseases makes it difficult for clinicians to maintain an up-to-date knowledge of clinical genetics. Although a treatment or management protocol may not be available for many genetic diseases, timely diagnosis is nonetheless important for natural history, management decisions, and recurrence risks. The appropriate choice of genetic testing can provide an accurate and usually rapid diagnosis.

Rapid and cost-effective genetic testing is currently available in multiple forms. Genetic technologies have evolved dramatically to offer a wide variety of tests,

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each with increasing clinical utility and yields (Fig. 1).[2–4] Although conventional G-banded karyotyping and fluorescence in situ hybridization (FISH) are still used extensively, chromosomal microarray (CMA) testing is the most widely used cytogenetic diagnostic tool. CMA is also considered the first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies.[4] Biochemical genetic testing includes enzymatic assays, chromatography methods, and mass spectrometry assays. Biochemical testing is the mainstay of newborn screening programs leading to the definitive diagnosis of inborn errors of metabolism. Current molecular genetic testing encompasses targeted mutation testing, single-gene sequencing, next-generation sequencing (NGS)-based multigene panel testing, whole-exome sequencing, and whole-genome sequencing. With the availability of so many different testing options, clinicians need guidance when trying to select the best diagnostic test for their patients with potential genetic conditions. Therefore, general recommendations and consensus statements are needed to help clinicians make the best choice for their patients.[3,4] This article discusses the full gamut of genetic testing, along with the clinical utilities and indications for each test type, in the context of neonatal care. Although a brief introduction to the different cytogenetic tests available is provided, the major focus of the article is a discussion of the strengths and limitations of the available clinical molecular genetic tests.

CYTOGENETIC TESTING

The peripheral blood karyotype (also called a G-banded karyotype for the Giemsa stain used to visualize the chromosome bands) and fluorescent in situ hybridization

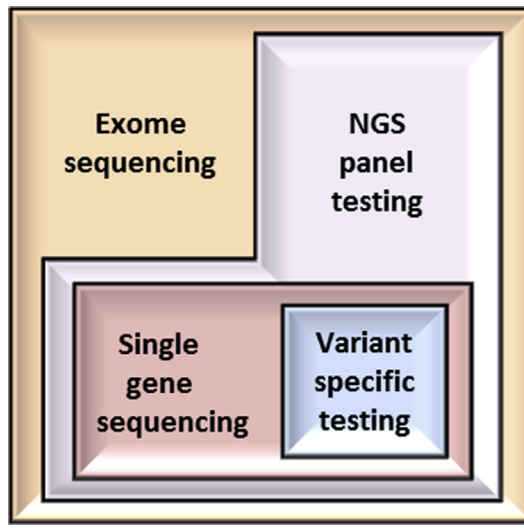

Fig. 1. Pictorial representation of the clinical utilities of the various molecular genetic tests currently available. While variant specific testing interrogates known and highly frequent variant associated with a disease for rapid diagnosis, single-gene sequencing by Sanger method interrogates the entire gene implicated with a disease, more specifically when the disease has high allelic heterogeneity. NGS panel testing involves sequencing of multiple genes, all of which are known to be associated with a specific disorder or phenotype. ES interrogates all genes (more specifically exons) in the human genome regardless of the phenotype and is often the preferred diagnostic test when the clinical presentation is atypical, complex or nonspecific, or when a disease specific panel is not clinically available.