

EDITORIAL

PEDIATRIC GENETIC TESTING IN THE GENOMICS ERA

TESTES GENÉTICOS EM IDADE PEDIÁTRICA NA ERA GENÓMICA

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The revolutionary advances in genetic testing technologies of the past decade have allowed detailed analysis of a patient's whole genome with increased precision, speed and cost-effectiveness, substantially improving diagnostic rates. High-throughput genome-scale tests commonly used in pediatric care include chromosome microarray analysis (CMA) and whole exome sequencing (WES). CMA assesses genome-wide copy number variations (CNVs) and has been well established in clinical practice as the first-tier test in children with developmental delay/intellectual disability, autism spectrum disorder or multiple congenital anomalies, with diagnostic yields ranging from 12 to 28%.¹ WES is more recent and takes advantage of next-generation-sequencing (NGS) technology to analyze the protein coding regions of known genes (approximately 20.000) for sequence variants and can additionally screen for CNVs. WES is particularly useful in the etiological investigation of unspecific genetic conditions with multiple differential diagnoses and in disorders with genetic heterogeneity such as epilepsy, developmental delay/intellectual disability, sensorineural hearing loss or retinitis pigmentosa. The diagnostic yields of WES range from 15% to 50% and can be enhanced with trio analyses (proband and both parents).²

Regardless of the methodology, genome-scale clinical analyses generate large amounts of data and a set of candidate variants for each patient, presenting additional challenges in clinical interpretation. However, an essential contribution to accurate variant classification relies on specialized clinical skills rather than on technology alone, as underlined by the recent focus on detailed and standardized phenotype assessment for gene prioritization analysis in NGS.³

As the diagnostic paradigm shifts from conventional genetic testing, physicians are more often faced with ethical challenges that need consideration and thoughtful action to warrant clinical practice without harm, especially when patients are minors.⁴ These matters have been the subject of constant debate and several joint statements on the ethical, legal, policy, and psychosocial issues in genetic testing in children and adolescents have been published in the last decade.⁵ Some of the hot topics include informed consent, management of incidental/secondary findings, and confidentiality.

The process of informed consent regarding genome-scale genetic tests is more complex and time-consuming compared to previous diagnostic tools, and health care professionals can experience difficulties conveying information to parents unfamiliar with genetics concepts.⁶ As in other medical diagnostic evaluations in children, parents or guardians should be informed about the potential benefits and the potential harms, and their permission should be obtained, as well as, if possible, the minor's assent. However, a particular characteristic of genetic tests is their ability to provide presumptive information of relatives' health status. Family members share a proportion of their genetic makeup and diagnosing certain conditions in children can automatically disclose risk to parents and siblings. Contrary to conventional genetic tests, high-throughput analyses can also retrieve incidental/secondary findings, defined as clinically relevant information unrelated to the condition for which the genetic analysis was originally ordered, with a rate of up to 3.4% for patients of European descent and 1.2% of African descent.⁷ The discussion on incidental/secondary findings' reporting and disclosure has not yet reached consensus, with the perspectives of laboratory

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geneticists, clinicians and patients/parents not always in tune. Currently, most laboratories follow the American College of Genetics and Genomics recommendations of reporting pathogenic and likely pathogenic variants in 59 actionable disorders with no restraint in pediatric settings.⁹ For these reasons, a targeted analysis of WES data according to phenotype should first be considered in pediatric care.⁵

The storage and clinical access to the genetic information produced by large-scale diagnostic tests are also under discussion. Where should the data be stored and for how long? Should it be part of the patient's clinical file in a separate physical archive as for genetic information obtained from conventional genetic tests? Can the assisting physician access the data in the future if the child presents a second condition later in life? Once entering adulthood should the patient be made aware that high-throughput sequencing of his/her DNA took place and if other incidental findings were detected? Clear regulatory guidelines on how to address these relevant questions are yet to be defined.

In conclusion, measures should be put in place to improve safe navigation through genome-scale genetic testing. On the clinical side, pediatric care clinicians need to be aware of current technologies and be prepared to counsel parents about the range of results anticipated with the use of high-throughput platforms and potential impact in family planning. Additionally, written consent should be taken with the aid of illustrated pamphlets in accessible language and be part of the pre-genetic test counseling process. On the legal side, clear regulation should be defined regarding clinical genome-scale data access and storage. In the meantime, clinicians and laboratory geneticists should base their practice on current consensus statements and guidelines to guarantee equity and the best quality in clinical care.

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