



PERSPECTIVES

Perspectives on molecular screening in pediatrics

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Abstract

Today, as the field of molecular genetics continues to evolve rapidly, there is a growing gap of new technological tools available for the molecular study of genetic diseases, allowing precision diagnosis in a large number of critically ill patients, as well as in patients who are still asymptomatic [1-3]. These diseases are silent, disabling and difficult to manage; they become a daily challenge that requires multidisciplinary intervention by specialists, who are often scarce in areas of difficult access, as they are found in third and fourth level hospitals. This is especially true in our Latin American countries where we observe centralization of specialized services in the capital cities [4,5]. At present we do not have precise statistics in our region for these diseases, but it is clear that the impact is increasing. Nowadays we do not give enough in the consultation, before we were only left with an impression diagnosis. With the important take-off of genomics, the world has changed and accurate diagnosis at the right time is what modifies the management and improves the prognosis of patients.

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The number of genetic diseases is estimated to encompass more than 10,000 different conditions [6,7], among which copy number variations (CNVs), chromosomal alterations and monogenic disorders happen to be the majority. However, in more than half of the pathologies their genetic basis is unknown, which means that in 50% of the diseases the genotype-phenotype relationship has not been demonstrated, but overall they affect about 6-8% of the general population, with an estimated greater than 400 million people worldwide [8,9].

Some children with complex clinical pictures of rare diseases undergo an endless list of tests, which has been termed a "diagnostic odyssey" [10]. This diagnosis can take up to 10 years to be determined, with the group of monogenic diseases being the main ones due to their great genetic heterogeneity.

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Most of the identified genetic variants are considered pathogenic and located in the adjacent coding and intronic regions of genes, producing changes in their function, protein alterations and generating the pathological phenotype with a Mendelian inheritance pattern (autosomal dominant, autosomal recessive, X-linked dominant and recessive, Y-linked, uniparental disomy and imprinting disorders).

Both the reduced costs of molecular analysis techniques and the association of genomic variants with the clinic have allowed the creation of databases have boosted the application of genomics in pediatric clinical practice [11]. Moreover, most of these diseases debut in childhood, and in up to two-thirds of patients, symptoms begin before the age of two years, although they can appear at any stage of life, making early diagnosis a priority.

There are about 6,000 rare genetic diseases and 300 million individuals affected by these diseases [12]. It is estimated that more than 30% are severe and that children die before the age of five. More than half of the patients affected by a rare disease present with motor, intellectual or sensory deficits and even easily recognizable chronic pain during their lifetime.

Implementing screening

Today, we are closer to achieving exome or whole genome sequencing in all critically ill newborns suspected of having an underlying genetic condition in the neonatal intensive care unit, presenting with clinical symptoms similar or coincident with early detection metabolic disorders and even in apparently healthy and asymptomatic preterm newborns, which would become the advantage of early diagnosis [13].

The genomic study of a patient may include the sequencing of family members, it must be directed by the diagnostic suspicion. This is performed on the set of genes that could be related to the suspected disease, either by clinical data or by the patient's family history, as well as on the most frequent diseases in that country. This careful selection of patients to be studied guarantees excellent screening, good resource management, and a better understanding of the disease.

Over the years, after having been unattainable, there has been a significant decrease in the cost of base sequencing, ensuring

cost-effectiveness. Its most important impact is observed in pediatric patients with the reduction of morbimortality in acute clinical pictures, thus benefiting families and reducing the economic burden on health services.

Despite advances, we will always have a diagnostic gap with rare diseases. Although these diseases are relatively frequent in pediatrics, due to their complexity and variability of clinical presentation, they are often underdiagnosed or overlooked, something that could be avoided if all our patients had access to molecular screening. However, it is here that the dilemma of the high cost of drugs to treat these diseases begins, where about 10 percent of diagnosed patients have pharmacological treatment [14].

Recall that congenital malformations and genetic diseases are among the leading causes of death in pediatrics. The availability of molecular screening would be a great tool for the analysis and early diagnosis of these diseases, allowing timely interdisciplinary and protocolized treatment and support that could substantially improve the quality of life of our patients and their families. This reality is observed in both developed and developing countries in our region [15].

In conclusion, genomic medicine and translational research are a reality in our region. It is necessary that we continue to educate in the correct implementation of this technology, both for the benefit of our patients and for the most effective use of health services with coherent molecular screening policies.

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