

Principles and criteria guiding the use
of parent-child trio genome-wide
sequencing in constitutional genetics -
A report to support the work of the
RQDM

English summary

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SUMMARY

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Introduction

The mandate of the Réseau québécois de diagnostic moléculaire (RQDM), of which the Centre québécois de génomique clinique (CQGC) is a part, is to meet the current and future needs of the health and social services network in the field of molecular diagnostics and personalized medicine. To this end, RQDM, with the support of the Ministère de la Santé et des Services sociaux (MSSS), has undertaken a vast provincial project to upgrade technology, develop, and repatriate analyses performed by next-generation sequencing (NGS).

In order to standardize, supervise, and ensure the quality of the NGS services currently being developed in Quebec, representatives of the MSSS, the RQDM and the CQGC jointly asked the Institut national d'excellence en santé et en services sociaux (INESSS) to review the state of knowledge on the principles and criteria for the use of genome-wide sequencing in a parent-child trio, in comparison with analysis of the index case alone (solo or singleton analysis), in the context of molecular diagnosis of a disease in constitutional genetics.

Methodology

The present state of knowledge is a synthesis of the results of a rapid literature review conducted by the INESSS on the principles and criteria for the use of parent-child trio sequencing in constitutional genetics. Publications were selected according to previously established PIPOH criteria. These documents include, among others, technology and health intervention assessment reports, systematic reviews, guidelines, clinical practice guides, and recommendations or positions of learned societies dealing with the subject. A preliminary version of the report was read by two expert members of the RQDM to validate the direction of the work and to ensure that the needs of the MSSS and the RQDM were met.

Results

Based on a rapid literature review and the main learned societies consulted, parent-child trio genome-wide sequencing analysis is generally recommended in the context of a rare, non-specific, and sporadic genetic disease, with no family history for the observed phenotype or frequently caused by *de novo* variants, and for which numerous genes are potentially responsible.

In this context, trio analysis is considered superior to solo analysis because it reduces the number of uncertain results and variants that need to be examined, notably by excluding probably benign familial variants. It also increases the reliability of variant calling, enables the identification of *de novo* mutations, and the immediate phasing of variants of interest. When parental samples are obtained at the same time as the child's, trio analysis promotes the return of results within a clinically useful timeframe, which is particularly important for urgent medical conditions, especially in prenatal and neonatal settings. Based on some studies, parent-child trio analysis could also increase diagnostic yield, particularly in enriched populations of individuals with neurological or neurodevelopmental disorders, non-specific, or non-isolated (complex) dysmorphic syndromes, multisystem disorders, and in the context of urgent neonatal conditions of suspected genetic origin. The increased diagnostic yield of trio analysis is mainly due to its ability to detect *de novo* and compound heterozygous variants.

Trio analysis may, however, increase the burden associated with consent, genetic counseling, sequencing data storage, and may cause delays associated with obtaining parental samples. There is also an increased risk associated with secondary or incidental parental discoveries, and of revealing non-paternity or undisclosed consanguinity. Some variants inherited from parents may not be identified if they have a mild phenotype that is not obvious, or if they are asymptomatic carriers – e.g., variable or incomplete penetrance and expressivity.

Trio analysis is currently more expensive than solo analysis. However, although the generalizability and transferability of the results to the Quebec context are uncertain, analysis of the economic studies reviewed suggests that trio genome-wide sequencing is likely to be more efficient for some of the contexts evaluated, including intellectual disability and unexplained developmental delay, mitochondrial diseases, prenatal diagnosis in the presence of multiple congenital anomalies, suspected genetic neurological disorders, and undiagnosed rare childhood diseases, whether performed as a first or second-line procedure, i.e., following standard genetic tests that are sometimes recommended in certain contexts.

Given the variety of clinical conditions for which trio sequencing would be performed, estimating the annual number of analyses for Quebec is difficult and, consequently, its budgetary impact remains uncertain. However, using intellectual disability and developmental delay as the context of use, trio exome sequencing could represent an expenditure of \$1.9 million over the first three years. Depending on the proportion of trio sequencing and the target population, the budgetary impact could vary between \$1.4 million and \$3.3 million. It should be remembered, however, that this is an underestimate of the actual budgetary impact, since not all conditions for which trio sequencing could potentially be performed are included in the analysis.

Conclusion

This report has gathered the available and relevant literature concerning the principles and criteria making it possible to guide the choice of proceeding with a parent-child trio analytical approach compared to a solo approach in the context of genome-wide sequencing to establish the molecular diagnosis of constitutional genetic diseases.

The findings presented in this report should help to support working groups wishing to develop genome-wide analyses to establish the molecular diagnosis of rare constitutional genetic diseases, and to determine in which circumstances parent-child trio analyses should be offered.

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