INESSS
LE SAVOIR PREND FORME

SEPTEMBER 2024

Gene panel for the identification of inborn errors of immunity - Evaluation report on the repatriation of an analysis carried out outside of the province of Québec

English summary

Une production de l'Institut national d'excellence en santé et en services sociaux (INESSS)

Québec

SUMMARY

Gene panel for the identification of inborn errors of immunity - Evaluation report on the repatriation of an analysis carried out outside of the province of Québec

Context and Mandate

The mandate of the Réseau québécois de diagnostic moléculaire (RQDM), which includes the Centre québécois de génomique clinique (CQGC), is to address the current and future needs of the health and social services network in the fields of molecular diagnostics and personalized medicine, particularly regarding the diagnosis of rare diseases and oncology. To this end, the RQDM, supported by the Ministry of Health and Social Services (MSSS), has undertaken a comprehensive project to enhance technology, develop, and repatriate analyses performed by next-generation sequencing (NGS). The deployment of this project undoubtedly brings opportunities and risks to the overall NGS service offering and requires thoughtful consideration.

At the request of the MSSS, the Institut national d'excellence en santé et en services sociaux (INESSS) is conducting a rapid assessment of the relevance, issues, and, where appropriate, optimal implementation modalities associated with the repatriation of these analyses, from the overall perspective of the Quebec health care system. This report specifically addresses gene panels analyzed by NGS for the molecular diagnosis of inborn errors of immunity (IEI).

Method

The process involves a rapid review of scientific and gray literature, a budgetary impact analysis, and consultations with Quebec clinicians. Only documents presenting synthesized data or recommendations related to the use of NGS for IEI diagnosis were considered. INESSS established an advisory committee where members expressed their views on the various issues associated with the proposed analysis repatriation. The final conclusions are based on the triangulation of scientific data, positions taken by major consulted scientific societies, contextual information, and experiential knowledge.

Population Dimension

IEI are a group of diseases in which certain components of the human immune system are dysfunctional. These diseases are caused by pathogenic genetic variants that compromise both innate and adaptive immunity. The International Union of Immunological Societies (IUIS) has classified the phenotypes and genotypes associated with EII and identified 485 phenotypes linked to 448 genes so far. IEI affect both children and adults and they sometimes manifest themselves due to delayed expression or diagnosis. Genetic mechanisms, environmental factors, and triggering pathogens influence the phenotypic variability of the disease, which can result in increased susceptibility to infections, autoinflammatory manifestations, allergies, bone marrow failure syndrome, and malignancies.

In Canada, 3,047 patients with EII were registered in 2018, resulting in the prevalence of 8.2 per 100,000. However, the prevalence of EII in Quebec remains uncertain. According to a preliminary analysis by the INESSS, using data from outside Quebec, 566 requests for NGS analyses for EII diagnosis were recorded during the 2022-2023 year. Clinicians consulted believe that the volume of requests could double within 10 years, resulting in approximately 1,232 tests by 2032. From the clinicians' perspective, the diagnostic odyssey and waiting times for genetic diagnosis are significant challenges.

The proposed genetic analysis for IEI is based on a total of 12 virtual panels analyzed from whole exome sequencing (WES) data: 11 targeted virtual panels (comprising 9 to 228 genes) and 1 core panel for IEI (consisting of 497 genes). This virtual panel approach aims to limit issues related to the discovery of variants of uncertain significance (VUS) and accelerate the analysis of sequencing results. While the targeted virtual panel approach is acceptable, clinicians emphasize the importance of easy access to the core panel (either directly or sequentially) due to the variability of clinical manifestations.

Clinical Dimension

Clinical Utility

The literature suggests the genetic diagnosis of EII has a major impact on patients' quality of life. It allows for targeted management, tailored therapy, anticipation of complications, and guidance for genetic counselling.

Clinical Validity

The gene lists included in the proposed virtual panels were determined by the RQDM IEI workgroup based on the literature and recommendations from the IUIS.

Clinicians consulted stress the need for regular updates to the virtual panel composition to keep up with the rapid evolution of new mutations associated with IEI. In the context of atypical or complex phenotypes, some clinicians would like more flexible access to exome data. Furthermore, recommendations have been issued to ensure consistency in prescribing indications and panel gene composition.

Organizational Dimension

According to the consulted clinicians, expanding the prescribers to include immunologists, allergists, rheumatologists, and pediatric hematologists could reduce delays in IEI diagnoses. They also emphasize the importance of consent and genetic analysis forms in the sample trajectory. In addition, the analysis report should include comments on variant and gene implications and specify the sources and scores used to evaluate variants.

In terms of turnaround time for obtaining analysis results, a maximum of 3 months for most virtual panels and 3 weeks for SCID and HLH panels appears acceptable. However, some committee members highlight the lack of genetic counselling resources. Furthermore, access to medical expertise is a major challenge for remote regions.

Resource availability and the impact on subsequent interventions also remain uncertain due to challenges related to accurately assessing the number of planned analyses and the requirements for bioinformatics tools (licenses, data archiving).

Sociocultural Dimension

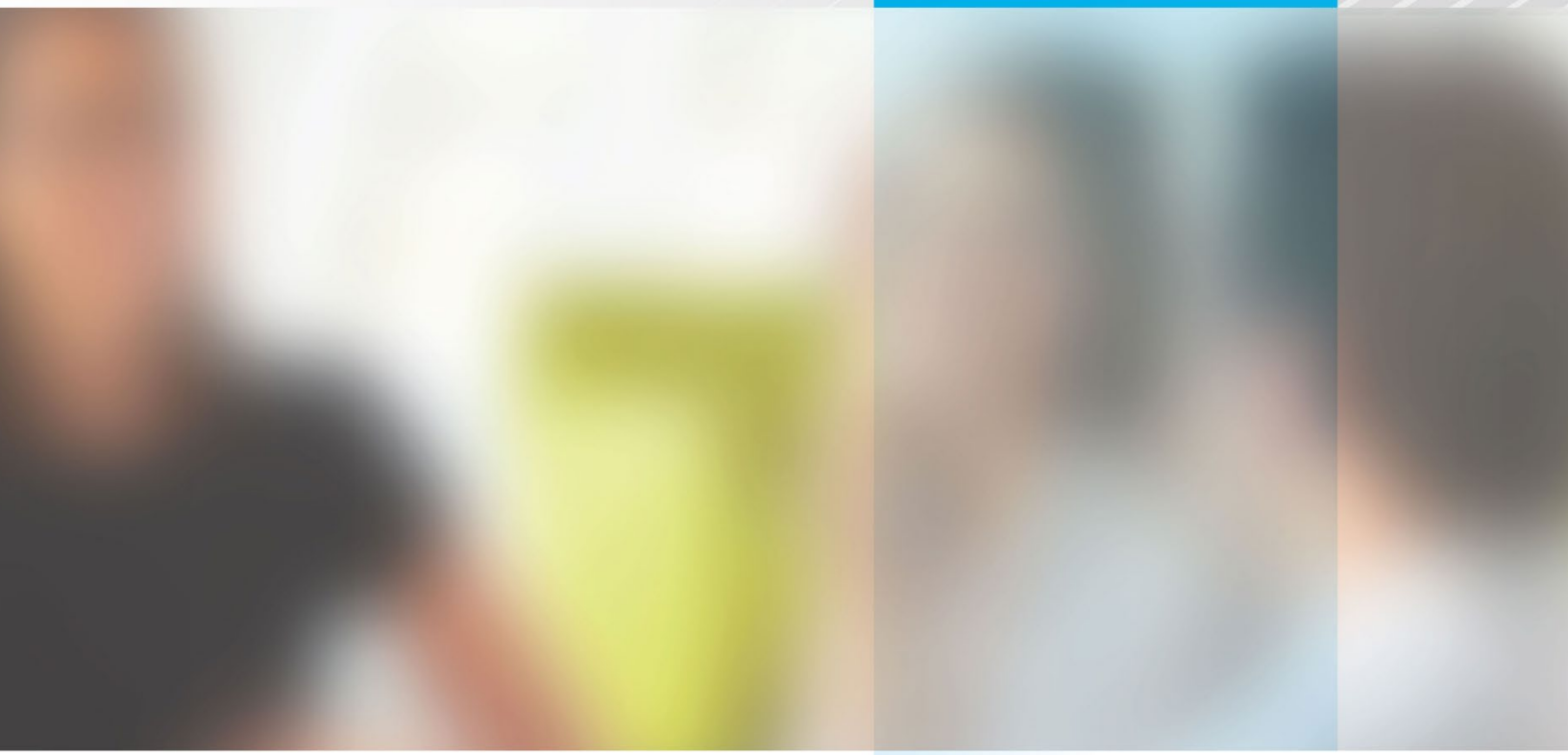
Ethical issues related to the discovery of genetic variants have been raised, for those concerning patient confidentiality and information protection. Some consulted clinicians for this report suggest that these issues should be evaluated within the RQDM and data specific to Quebec populations should be published, especially in cases of founder effects in certain regions. Mechanisms to ensure equitable access to genetic testing, as well as confidentiality and patient information protection must also be established.

Economic Dimension

The efficiency of whole-genome sequencing for the molecular diagnosis of IEI is unknown. Over the first three years, repatriating analyses performed outside of Quebec could generate savings of $ 0.972 million ($ 0.875 million to $1.07 million) or $0.353 million ($0.318 million to $0.388 million) if analyses were performed using WES or whole genome sequencing (WGS) data, respectively. Hence, the analysis through virtual panels using WES data would be the most affordable option. The costs of bioinformatics tools (licenses, data storage) as well as requests for other IEI panels in case of negative results could reduce these savings.

Conclusions

This state of knowledge is based on a rapid review of scientific and gray literature, as well as contextual information and experiential knowledge. It aims to provide guidance to the MSSS in its decision to repatriate genetic analyses for the diagnosis of IEI. While no major concerns were identified during this exercise, uncertainties related to available resources and service organization in Quebec were highlighted and should be explored to ensure optimal implementation.



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