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Next Generation Sequencing Hereditary Cancer Gene Panels

English summary

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Québec

SUMMARY

Next Generation Sequencing Hereditary Cancer Gene Panels

Background and mandate

Requests for authorization for medical laboratory services that are not available in Québec are mainly for high-throughput simultaneous sequencing of multiple genes using the so-called next-generation approach. The province's laboratories have the technology and expertise to perform these tests. With a view to achieving economies of scale and promoting more judicious use of this technology, the Ministère de la Santé et des Services sociaux (MSSS) has undertaken to quickly repatriate several tests performed by next-generation sequencing (NGS), under the governance of the Réseau québécois de diagnostic moléculaire (RQDM). The rollout of this vast project undoubtedly entails opportunities and risks with respect to the overall offer of services and requires reflection along these lines.

At MSSS's request, the Institut national d'excellence en santé et en services sociaux (INESSS) is conducting a rapid assessment of the relevance of, the issues surrounding and, when appropriate, the optimal implementation mechanisms for the repatriation of these tests, from the overall perspective of Québec's healthcare system. The present report deals specifically with the analysis of NGS hereditary cancer gene panels.

Method

The process included a rapid review of the scientific and grey literature for the clinical and economic aspects, a budget impact analysis, and consultations with Québec experts. Only documents containing synthesis data or recommendations concerning the use of an NGS test for the molecular diagnosis of hereditary cancers were selected. INESSS set up an advisory committee, whose members were invited to express their views on the various issues and considerations regarding the repatriation of the proposed tests. The final findings are based on the triangulation of the scientific data, the positions of the main learned societies consulted, and the contextual data and experiential knowledge gathered.

Clinical contexts and proposed tests

Cancer is the leading cause of death in Canada. It is estimated that approximately 40% of Canadians will develop cancer in their lifetime and that 25% will die from it. Up to 10% of the most common cancers are hereditary. In other words, they are caused by pathogenic mutations in one or more oncogenes.

The purpose of hereditary cancer gene panels analyzed by NGS is to identify or confirm the genetic etiology of a clinical presentation suggestive of a hereditary cancer syndrome. The cancers covered by these panels concern the following anatomical sites: breast, ovary,

endometrium, colon/rectum, prostate, pancreas, stomach, and conditions associated with a predisposition to intestinal polyposis.

Clinical validity

In hereditary genetics, the clinical validity of a multigene panel analyzed by sequencing is determined, among other things, by the association of the genes in the panel with the targeted disease. Panels should therefore include all the genes for which variants have been clearly identified as being responsible for at least one of the targeted cancers (pathogenic variants). The requester intends to use eight virtual panels of genes associated with hereditary cancers, which will be analyzed using the sequencing data from the 105 genes in the Canadian Inherited Cancer Panel. Of these, a total of 31 genes (overall virtual panel) will be reported based on the clinical presentation and current oncogenetic knowledge.

Clinical utility

Data from the literature and the expert consultations are in accord that the proposed molecular investigations help improve the health of individuals by identifying those who are genetically predisposed to developing one or more cancers. In fact, targeted and individualized interventions aimed at detecting cancer earlier and preventing its occurrence or recurrence can be carried out in these individuals.

The learned societies and experts consulted also agree that priority should be given to using a multigene panel approach instead of a single-gene approach, taking into account a combination of information regarding the clinical presentation, examination and family history. The genes included in the proposed panels and the criteria for accessing the panels are consistent with information found in the literature.

Implementation considerations

In light of the consultations held, standardizing the criteria for accessing genetic tests across the province and creating clinical algorithms to guide the care and services offered to patients are key elements for implementing these panels in the healthcare system. As well, updating mechanisms should be put in place to ensure that patient management is supported by relevant scientific evidence.

Having non-medical genetics specialists order the test, manage the results, and do the patient follow-ups could ease the burden on geneticists, but they would have to be supported by specialized training and detailed, up-to-date clinical algorithms. Obtaining patients' informed consent is paramount, regardless of who orders the test.

The implementation of hereditary cancer gene panels should be accompanied by consistency in the quality of molecular diagnostic service and in the turnaround time across the province that is comparable to that currently offered by outside laboratories. In addition, some experts expressed concern about the lack of clear policies on the management and disclosure of variants of uncertain significance (VUS).

Economic analysis

INESSS is not able to rule on the efficiency of the NGS for hereditary cancer panels. In fact, no economic evaluation in the Québec context has been carried out, and the results in the literature are either not available for some cancers, or uncertain or not transposable to the Québec context for others.

With regard to the budget impact, based on the assumptions made, including hereditary cancer gene panels in the *Répertoire québécois et système de mesure des procédures de biologie médicale* could generate savings of close to $600,000 over the first three years in serving patients throughout Québec. According to the sensitivity analyses performed, these savings could range from close to $9.5M to costs of approximately $1.2M for the same period. It should be noted that the extent of these savings depends largely on the cost of implementing this technology, the sequencing throughput of each instrument, and the number of tests performed. In fact, if there were to be a significant increase in the number of tests, as proposed by the experts consulted, the repatriation costs would be greater than those currently generated by sending the tests outside Québec. Lastly, an increase in genetic counselling resources, which was not taken into consideration in the analyses, could generate additional costs and reduce the potential savings.

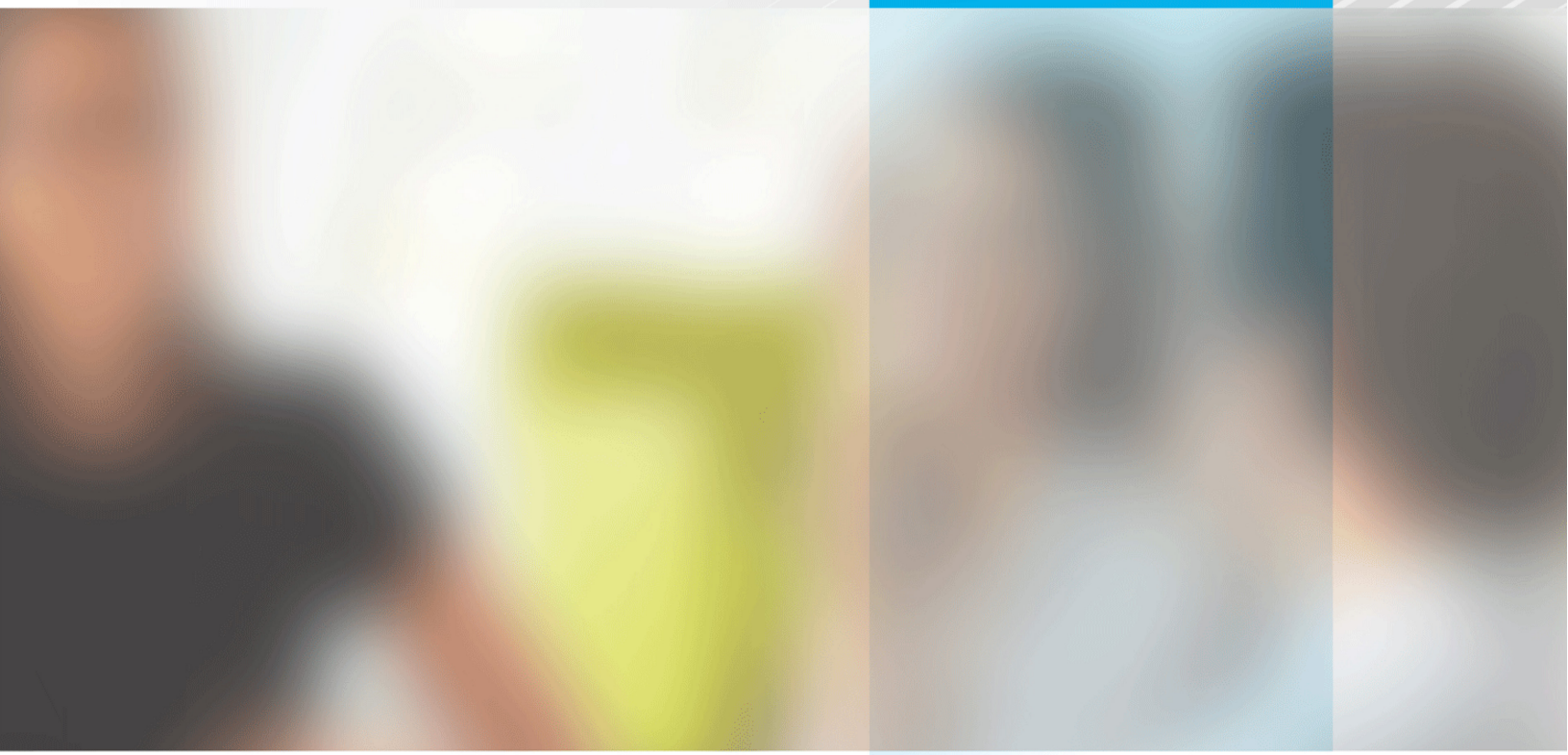
Conclusion

The findings and conclusions in this report are based on a rapid review of the scientific and grey literature and on contextual data and experiential knowledge. The approach consists of a rapid risk analysis for guiding the ministerial decision regarding the repatriation of tests for the molecular diagnosis of hereditary cancer in adults. During this exercise, certain issues were raised regarding the rollout of this test.

Standardizing access to germline genetic testing for cancer predisposition syndromes across the province is a desire shared by most of the experts consulted. Using algorithms and clinical indications supported by current scientific evidence would contribute to this standardization. The ordering of this test by non-medical genetics specialists should be supervised or reserved for those who are adequately trained and able to manage post-test follow-ups.

According to the experts consulted, the service offered for these tests must be comparable to that provided by the outside laboratories, particularly in terms of quality, reliability, speed, and result traceability. A number of experts also stressed the importance of properly planning, or planning for, the genetic counselling and clinical patient follow-up needs and resources at the provincial level.

Lastly, a rapid review of the economic literature and a budget impact analysis revealed several uncertainties. They call for caution with respect to these panels' efficiency and the projected potential savings.



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