Noninvasive Fetal RhD Blood Group Genotyping: Recommendation

DRAFT RECOMMENDATION

- The Quality business unit at Ontario Health, based on guidance from the Ontario Health Technology Advisory Committee, recommends publicly funding noninvasive fetal RhD blood group genotyping for:
    - Alloimmunized RhD negative pregnancies
    - Nonalloimmunized RhD negative pregnancies conditional on attaining reasonable cost-effectiveness in the future

RATIONALE FOR THE RECOMMENDATION

The Ontario Health Technology Advisory Committee has reviewed the findings of the health technology assessment[1] and the recommendation of a subcommittee, the Ontario Genetics Advisory Committee.

Test accuracy was found to be high, and the evidence showed positive outcomes when pregnancy management moved from a universal to targeted anti-D prophylaxis approach for nonalloimmunized pregnancies and from a universal to targeted intensive monitoring for alloimmunized pregnancies with the use of noninvasive fetal RhD blood group genotyping (fetal RhD genotyping). Patients and providers supported the routine provision of fetal RhD genotyping as part of RhD negative pregnancy care, and the economic analysis demonstrated that using the test is cost saving in RhD alloimmunized pregnancies. Both the Ontario Genetics Advisory Committee and the Ontario Health Technology Advisory Committee reached consensus in favour of publicly funding fetal RhD genotyping for RhD alloimmunized pregnancies.

The price of fetal RhD genotyping was found to be a key factor in the cost-effectiveness analysis for nonalloimmunized pregnancies. Both committees acknowledged that the price of testing would need to be much lower for it to be cost-effective when used for RhD nonalloimmunized pregnancies. Both committees also noted that making the test available for both populations would be simpler for clinicians.

In addition, the committees considered that while the harms associated with a universal prophylaxis approach with RhIG for nonalloimmunized pregnancies are difficult to quantify, they acknowledged that using RhD genotyping would avoid unnecessary treatment in some individuals. The Ontario Genetics Advisory Committee members anticipated that there will be a need for public and provider education when implementing the test, including counselling of RhD negative pregnant people, and that the availability of fetal RhD genotyping should not take away the option for individuals to receive Rh-immunoglobulin prophylaxis instead of having the test.

Decision Determinants for Noninvasive Fetal RhD Blood Group Genotyping

Decision Criteria	Subcriteria	Decision Determinants Considerations
Overall clinical benefit How likely is the health technology/intervention to result in high, moderate, or low overall benefit?	**Effectiveness** How effective is the health technology/ intervention likely to be (taking into account any variability)?	Noninvasive fetal RhD blood group genotyping using cell-free fetal DNA from maternal blood in RhD negative pregnancies (fetal RhD genotyping) has high test accuracy, sensitivity, specificity, and positive and negative predictive values. The evidence suggests that using fetal RhD genotyping to guide care of RhD negative pregnancies largely avoids unnecessary RhIG prophylaxis in nonalloimmunized RhD negative pregnancies not at risk of alloimmunization (GRADE: Low); may lead to high compliance with targeted RhIG prophylaxis in nonalloimmunized RhD negative pregnancies at risk of alloimmunization, but the evidence is very uncertain (GRADE: Very low); leads to large uptake rates of fetal RhD genotyping of 84% or higher as part of care for nonalloimmunized RhD negative pregnancies (GRADE: Low).
	Safety How safe is the health technology/ intervention likely to be?	The evidence suggests that fetal RhD genotyping may reduce the risk of alloimmunization when used to target administration of prenatal RhIG prophylaxis, compared with RhIG prophylaxis administered only after birth or potentially sensitizing events, but the evidence is very uncertain (GRADE: Very low); and, may avoid unnecessary invasive procedures in alloimmunized RhD negative pregnancies not at risk of hemolytic disease of the fetus and newborn, but the evidence is very uncertain (GRADE: Very low). The test is noninvasive, and conducted using a simple maternal blood draw, from which cell-free fetal DNA is analyzed.
	Burden of illness What is the likely size of the burden of illness pertaining to this health technology/intervention?	RhD incompatibility during pregnancy can trigger the mother's immune system to create antibodies that can attack the red blood cells of an RhD-positive fetus in the next pregnancy. This leads to potentially serious, sometimes fatal, health problems for the baby before or after birth. Currently, all RhD-negative pregnant people receive an injection that prevents the development of anti-D antibodies. If antibodies have already developed, those pregnancies are closely monitored. All RhD negative pregnancies receive these interventions in Ontario even though an estimated 40% of RhD negative pregnancies are not incompatible.
	Need How large is the need for this health technology/intervention?	RhD negative blood type occurs in about 15% of Caucasian populations, 3% to 5% in black African populations, and ≤ 1% of East Asian and Indigenous populations.
Patient preferences and values How likely is adoption of the health technology/intervention to be congruent with patient preferences	**Patient preferences and values** Do patients have specific preferences, values, or needs related to the health condition, health technology/ intervention, or life impact that are relevant to this assessment? (Note: The preferences and values of family	Quantitative information from the literature found that RhD negative pregnant people support routine offering of RhD genotyping as part of pregnancy care, with a preference to be adequately informed about the test process, attributes, timing and risks in advance of the test, ideally in a dialogue with their healthcare provider.

Decision Criteria	Subcriteria	Decision Determinants Considerations
and values and with ethical or legal standards?	members and informal caregivers are to be considered as appropriate.)	Qualitative information from the literature and direct patient engagement found a positive response to the potential impact and use of RhD genotyping. Participants desired additional information and assurances of safety of the test for themselves and the fetus.
	Autonomy, privacy, confidentiality, and/or other relevant ethical principles as applicable Are there concerns regarding accepted ethical or legal standards related to patient autonomy, privacy, confidentiality, or other ethical principles that are relevant to this assessment? (Note: The preferences and values of the public are to be considered as appropriate.)	A pregnant person cannot make a fully informed decision about RhIG treatment without knowing fetal RhD status. Other ethical concerns include resource stewardship in reserving resources (RhIG and monitoring) only for those who need it, and potential opportunity cost of the test being equal to savings from reduced RhIG/system expenses.
Equity and patient care How could the health technology/ intervention affect equity of access and coordination of patient care?	**Equity of access or outcomes** Are there disadvantaged populations or populations in need whose access to care or health outcomes might be improved or worsened that are relevant to this assessment?	Currently, the genotyping test is only available to RhD negative pregnant people meeting certain criteria via the Ministry of Health Out-of-Country Prior Approval Program. Awareness and use of the test vary across the province.
	Patient care Are there challenges in the coordination of care for patients or other system-level aspects of patient care (e.g., timeliness of care, care setting) that might be improved or worsened that are relevant to this assessment?	In a review of the quantitative preferences literature, more than half of obstetric health care providers were supportive of offering the test. Alloimmunized pregnant people may need to travel or move for intensive monitoring that is available only at a tertiary care centre. Testing may be challenging in remote areas or even urban centres without adequate infrastructure to send blood samples within required time (e.g., 24–72 hours).
Cost-effectiveness How efficient is the health technology/ intervention likely to be?	**Economic evaluation** How efficient is the health technology/ intervention likely to be?	**Nonalloimmunized pregnancies:** fetal RhD genotyping compared with usual care would not be generally considered cost-effective, unless the price of testing is much lower than it is currently. **Alloimmunized pregnancies:** fetal RhD genotyping compared with usual care is associated with lower costs and greater benefits.
Feasibility of adoption into health system How feasible is it to adopt the health technology/intervention into the Ontario health care system?	**Economic feasibility** How economically feasible is the health technology/intervention?	**Nonalloimmunized pregnancies:** adopting fetal RhD genotyping will lead to an increased budget of $2.6 million in year 1 (80% uptake) to $3.4 million in year 5 (100% uptake), with a total of $14.8 million over 5 years. **Alloimmunized pregnancies:** adopting fetal RhD genotyping will lead to a possible cost savings of $9 million in year 1 and $12 million in year 5, with a total of $51 million over 5 years.
	Organizational feasibility How organizationally feasible is it to implement the health technology/ intervention?	Fetal RhD genotyping is best implemented in a centralized lab(s) to allow for sufficient volumes of samples for reliable testing and efficient workup. **Nonalloimmunized pregnancies:** The Canadian Blood Services has a reference lab with infrastructure to support fetal RhD genotyping in this population and

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		are looking into providing this service for Ontario and other Canadian provinces. **Alloimmunized pregnancies:** A hospital laboratory in Ontario has validated this test for alloimmunized pregnancies and has infrastructure to conduct fetal RhD genotyping in this population.

Abbreviations: RhD, rhesus D blood type; RhIG, Rh-immunoglobulin.

REFERENCE

(1) TBA

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