# NAC Statement on RHD Genotyping in Prenatal Patients

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| Date of Original Release: | March 28, 2017 |
| Date of Last Revision: | March 15, 2022 |
| Publication Date: | May 24, 2022 |

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## LIST OF ABBREVIATIONS

**DNA** Deoxyribonucleic Acid
**HDFN** Hemolytic Disease of the Fetus and Newborn
**NIPT** Non-Invasive Prenatal Testing
**RBC** Red Blood Cells
**RhD** Rhesus Blood Group, D Antigen
**RHD** Rhesus Gene
**RhIg** RhD Immunoglobulin

## SUMMARY OF REVISIONS

| Revision Date | Detail |
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| **MAY 2022** | Document divided into sections to improve organization: introduction, current state, and recommendations |
| | Updated and expanded background information including the current state of RhD testing for patients with weak D in Canada |
| | Added a recommendation for perinatal RhIg administration and transfusion of RhD negative blood components for prenatal patients who type as RhD negative or have a variant D other than weak D Type 1, 2, and 3. |

## SECTION 1.0: INTRODUCTION

RhD negative individuals exposed to RhD antigen have a greater than 30% risk of developing an alloimmune antibody against the RhD antigen [1,2]. Development of anti-D may lead to complications, including acute or delayed hemolytic transfusion reaction and contribute to severe hemolytic disease of the fetus and newborn (HDFN).

Prevalence of RhD expresssion varies by ethnicity. RhD negative phenotype is seen in 18% of Caucasian, 7.3% of African and 2% of Asian individuals. Individuals who are RhD negative lack RhD antigen expression on the red cell surface and either lack the *RHD* gene altogether or have an altered *RHD* gene which does not result in antigen expression (absent D antigen).

A small subset of the population have a variant RhD antigen (referred to as partial D and weak D). An estimated 0.2% - 1.0% of Caucasians have variant D phenotypes [3]. Variant D phenotypes are more common in those with an African ethnic background. Patients with partial D or weak D antigens can have weaker reactions with standard serological testing or RhD typing reactions that vary with different testing reagents or methods.

Recognizing individuals with variant D is important as all subtypes of partial D and some subtypes of weak D are at risk for alloimmunization when exposed to a wild-type RhD antigen (present in the majority of RhD positive persons). Weak D types 1, 2, 3 or 4 are identified in 61% of individuals with a variant D upon *RHD* genotyping in Canada, with an overall prevalence of weak D in pre-natal patients of 0.4% [5]. Individuals with a weak D type 1, 2 or 3 are not at risk of forming anti-D and therefore can be managed safely as RhD-positive, i.e. can be transfused with RhD positive red blood cells (RBC) and do not require perinatal Rh immunoglobulin (RhIg). On the other hand, persons with most other weak D types, and those with partial D antigens are at risk for alloimmunization and should be treated as RhD negative, i.e. receive only RhD negative RBCs and receive perinatal RhIg. Expert opinion on the management of prenatal patients with weak D type 4.0 varies. Providing these individuals with RhIg prophylaxis during pregnancy and RhD negative RBCs for transfusion is the most cautious approach until additional data is available [4]. Unfortunately, routine serological testing is unable to differentiate patients with weak D Type 1, 2 and 3 from the other D variants and *RHD* genotyping must be performed in order to establish the risk for alloimmunization and the requirement for RhIg prophylaxis.

In 2015 the College of American Pathology and AABB issued a Joint Statement recommending *RHD* Genotyping for Pregnant Women and Other Females of Childbearing Potential with a Serologic Weak D Phenotype in the United States [3].

We propose a standardized approach for RhD blood group determination in pregnant patients with an aim to minimize risks of alloimmunization with anti-D and reduce inappropriate utilization of RhIg and RhD-negative blood components.

## SECTION 2.0: CURRENT STATE IN CANADA

Currently, in Canada there is no national standard on further investigation and management of patients who present with a weak D phenotype on pre-transfusion or prenatal testing. A few provinces have developed guidance documents (for e.g., British Columbia and Quebec) [8.9]. Depending on the individual institutional policy, such patients may be labeled RhD positive, RhD negative or RhD indeterminate. If a female patient with Partial D is erroneously labeled as RhD positive, she may be transfused with RhD positive RBCs and not be offered perinatal RhIg, possibly leading to alloimmunization and HDFN. On the other hand, a female patient with weak D Type 1, 2 or 3 may be erroneously labeled as RhD negative and receive unnecessary perinatal RhIG. Such practice also leads to unnecessary utilization of RhD negative RBCs when RhD positive RBCs could be transfused safely. In Canada if all pregnant women with a variant D phenotype were identified and their *RHD* genotype determined, an estimated 900 prenatal women who are currently managed as RhD-negative could be managed as RhD positive, avoiding 1800 injections of RhIg annually [5,6].

*RHD* genotyping is offered by the Canadian Blood Services for prenatal patients with discrepant, weak or inconclusive serological RhD test results when results may modify management. Moreover, RBC genotyping may be offered by other local qualified and accredited laboratories. Best practices dictate that the genotyping report should include interpretation of the results and recommendations on RhIg candidacy and assigned RhD group for RBC transfusion. Depending on location, the decision to perform genotyping is determined by local institutional policies. A recent Canadian Survey [7] indicates that most Canadian laboratories refer samples from prenatal women for *RHD* genotyping when variant D phenotype is suspected. However, about 20% of institutions report that they do not obtain genotyping results in this setting.

## SECTION 3.0: RECOMMENDATIONS

To provide safe and appropriate care for prenatal patients with variant D phenotype and to standardize care across Canada, we recommend that:

1) **Prenatal patients with discrepant, weak or inconclusive serological RhD test results should be further investigated with *RHD* genotyping to determine RhIg candidacy and optimal red blood cell RhD type for transfusion**.

This practice is unlikely to result in a significant cost increment in terms of *RHD* testing for the provinces since it is already an established practice in some provinces, and survey data indicates that 80% of institutions currently perform this testing [7]. Prenatal patients with a variant D phenotype are rare (0.4 %) [5]. Since the majority of patients with variant D phenotype have Weak D types 1, 2 or 3 and can be regarded as Rh positive, any increased cost of testing will likely be outweighed by the savings derived from avoiding unnecessary RhIG.

2) **Prenatal patients who type as RhD negative or who are determined to have variant D other than weak D Type 1, 2, and 3 should be considered candidates for perinatal RhIg administration and should be transfused with RhD negative blood components.**

Individuals with a weak D type 1, 2 or 3 are not at risk of forming anti-D and therefore can be managed safely as RhD-positive, i.e. can be transfused with RhD positive red blood cells (RBC) and do not require perinatal Rh immunoglobulin (RhIg).

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