

Joint Statement on Phasing-In *RHD* Genotyping for Pregnant Women and Other Females of Childbearing Potential with a Serologic Weak D Phenotype

Background

AABB and the College of American Pathologists sponsored an Interorganizational Work Group on *RHD* Genotyping that was charged with developing recommendations to clarify clinical issues related to Rh blood typing in persons with a serologic weak D phenotype. Red blood cells that express a weak D phenotype, formerly D^u, agglutinate weakly or not at all using anti-D typing reagents, but agglutinate moderately or strongly after the addition of an antihuman globulin reagent, i.e., a positive weak D test.¹ An estimated 0.2% - 1.0% of Caucasians inherit a weak D phenotype. In a racially and ethnically diverse urban population in the United States, approximately 80% of persons with a weak D phenotype were identified to have a weak D type 1, 2 or 3 when additional testing included *RHD* genotyping.^{1,2} Persons with a weak D type 1, 2 or 3 can be managed safely as Rh-positive and such women, if pregnant, do not require Rh immune globulin. For more than 50 years, the recommended practice in the United States has been to Rh type patients using laboratory methods that interpret weak D phenotypes as Rh-negative. The intent of this practice has been to protect Rh-negative persons, particularly Rh-negative women of childbearing potential, from inadvertent exposure and alloimmunization to Rh-positive red blood cells. *RHD* genotyping methods are now available that can identify those persons with a weak D phenotype who can be managed as Rh-positive (weak D types 1, 2 or 3).

The Work Group was organized in response to a CAP survey that revealed a lack of standard practice in the United States for laboratory testing and interpreting the Rh blood type of patients, including pregnant women, with a weak D phenotype.³ The survey revealed that in most laboratories, blood samples from blood donors are tested for their Rh type by methods intended to detect and interpret a weak D phenotype as Rh-positive. In the same or another laboratory, blood samples from patients, including pregnant women, are tested by methods intended to avoid detection of a weak D phenotype and, thereby, interpret the result as Rh-negative. The Work Group's report, published in the March 2015 issue of journal **Transfusion**, contains the data and information supporting this Joint Statement.¹ A copy of the [report](#) is attached to this Joint Statement.

Consequences of current practice

Current practice for testing and interpreting Rh typing results appears to be highly successful in preventing alloimmunization to the D blood group antigen and Rh hemolytic disease of the fetus/newborn.⁴ However, there are unwarranted consequences associated with the practice of

avoiding detection of weak D phenotypes, including unnecessary injections of Rh immune globulin and transfusion of Rh-negative red blood cells – always in short supply – when Rh-positive red blood cells could be transfused safely. If all pregnant women in the United States with a weak D phenotype were identified and their *RHD* genotype determined, an estimated 13,360 pregnant women who are currently managed as Rh-negative could be managed as Rh-positive, avoiding 24,700 injections of Rh immune globulin annually.¹

Recommendation of the Work Group

RHD genotyping is recommended whenever a weak D phenotype is detected by routine Rh blood typing of pregnant women and other females of childbearing potential. The Work Group rates this as strong recommendation, based on high-quality evidence from observational studies (1A).⁵ The Work Group also considered a recommendation to standardize routine laboratory methods for Rh typing that would increase detection of all patients with D variant phenotypes, including partial D, as well as weak D phenotypes. While desirable, such a recommendation is technically complex, likely controversial, and would divert the focus from our advocacy for phasing-in *RHD* genotyping when a pregnant woman's routine Rh typing detects a serologic weak D phenotype. The immediate benefit of determining the *RHD* genotype of pregnant women with a weak D phenotype will be fewer unnecessary injections of Rh immune globulin.

Efforts to foster the application of genomic medicine to promote more personalized and accurate medical care have been enhanced by recent coding and reimbursement changes for *RHD* genotyping. The American Medical Association has recently approved the addition of a new analyte(s) for CPT code 81403 for *RHD* genotyping (Tier 2 Molecular pathology procedure, Level 4) and reimbursement rates for the Tier 2 code are being established by some payers. A study of the financial implications of *RHD* genotyping concluded that for many pregnant women with a serologic weak D using *RHD* genotyping to guide the use of Rh immune globulin may be clinically beneficial without increasing overall costs.⁶ Phasing in *RHD* genotyping is a feasible and appropriate first step for delivering specific benefits of molecular science to a well-defined and relatively limited number of patients. *RHD* genotyping will support more precise decision-making in obstetrical practice and transfusion medicine.

References

1. Sandler SG, Flegel WA, Westhoff CM, Denomme GA, Delaney M, Keller MA, Johnson ST, Katz L, Queenan JT, Vassallo RR, Simon, CD. It's time to phase in *RHD* genotyping for patients with a serologic weak D phenotype. *Transfusion*. 2015;55:680-9.

2. Haspel RL, Westhoff CM. How do I manage Rh typing in obstetric patients? *Transfusion*. 2015;55:470-4.
3. Sandler SG, Roseff S, Dormen RE, Shaz BH, Gottschall J, for the CAP Transfusion Medicine Resource Committee. Policies and procedures related to testing for weak D phenotypes and administration of Rh immune globulin/Results and recommendations related to supplemental questions in the comprehensive transfusion medicine survey of the College of American Pathologists. *Arch Pathol Lab Med* 2014;138:620-5.]
4. Bowman J. Thirty-five years of Rh prophylaxis. *Transfusion* 2003;43:1661-6.
5. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schunemann HJ. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ Clin Res Ed* 2008;336:924–6.
6. Kacker S, Vassallo R, Keller MA, Westhoff CM, Frick KD, Sandler SG, Tobian AR. Financial implications of *RHD* genotyping of pregnant women with a serologic weak D phenotype. *Transfusion* 2015 Mar 21. doi: 10.1111/trf.13074. [Epub ahead of print]

Members of the Work Group

Organizational representatives: Susan T. Johnson (AABB), Louis Katz, MD (America’s Blood Centers), John T. Queenan, MD (American College of Obstetricians and Gynecologists), Richard Benjamin, MD, PhD, FRCPath (American Red Cross), COL Clayton D. Simon, MD (Armed Services Blood Program), S. Gerald Sandler, MD (Chair, College of American Pathologists).

Scientific consultants: Willy A. Flegel, MD; Connie M. Westhoff, PhD; Gregory A. Denomme, PhD; Meghan Delaney, DO, MPH; Margaret A. Keller, PhD.