HPA and RBC Antigen Genotyping

Human Platelet and Red Blood Cell Antigen Genotyping

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Molecular testing of red blood cell or human platelet antigens in individuals to determine alloimmunization status or risk is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedure addressed by this guideline	Procedure code
BLOODchip® ID CORE XT	0084U
Gene analysis (Human Platelet Antigen 1) for common variant	81105
Gene analysis (Human Platelet Antigen 2) for common variant	81106
Gene analysis (Human Platelet Antigen 3) for common variant	81107
Gene analysis (Human Platelet Antigen 4) for common variant	81108
Gene analysis (Human Platelet Antigen 5) for common variant	81109
Gene analysis (Human Platelet Antigen 6) for common variant	81110
Gene analysis (Human Platelet Antigen 9) for common variant	81111
Gene analysis (Human Platelet Antigen 15) for common variant	81112
Fetal RHD genotyping using maternal plasma (e.g. SensiGene)	81403

Procedure addressed by this guideline	Procedure code
Navigator ABO Blood Group NGS	0221U
Navigator ABO Sequencing	0180U
Navigator CO Sequencing	0181U
Navigator CROM Sequencing	0182U
Navigator DI Sequencing	0183U
Navigator DO Sequencing	0184U
Navigator FUT1 Sequencing	0185U
Navigator FUT2 Sequencing	0186U
Navigator FY Sequencing	0187U
Navigator GE Sequencing	0188U
Navigator GYPA Sequencing	0189U
Navigator GYPB Sequencing	0190U
Navigator IN Sequencing	0191U
Navigator JK Sequencing	0192U
Navigator JR Sequencing	0193U
Navigator KEL Sequencing	0194U
Navigator KLF Sequencing	0195U
Navigator LU Sequencing	0196U
Navigator LW Sequencing	0197U
Navigator Rh Blood Group NGS	0222U
Navigator RHD/C/E Sequencing	0198U
Navigator SC Sequencing	0199U
Navigator XK Sequencing	0200U
Navigator YT Sequencing	0201U
PreciseType HEA Test	0001U
PrecisionBlood Red Cell Antigen Genotyping	0246U
Prenatal Detect RhD	0536U

Procedure addressed by this guideline	Procedure code
RBC antigen analysis	81479
RHD Deletion analysis	81403
Rh Test (Natera)	0494U
UNITY Fetal Antigen NIPT	0488U
Versiti Red Cell Genotyping Panel	0282U

Criteria

Requests for molecular testing for tissue antigen typing are reviewed using the following criteria.

Human Platelet Antigen (HPA) Genotyping

Testing for human platelet antigens through molecular genotyping is medically necessary for individuals with clinical indications as outlined here.

- Member has at least one of the following:
 - Post-transfusion purpura 5-10 days after a blood transfusion, or
 - Suspected Neonatal Alloimmune Thrombocytopenia (NAIT)/ Fetal and Neonatal Alloimmune Thrombocytopenia (FNAIT) based on clinical presentation during pregnancy or neonatal period, or
 - Pregnancy or newborn with suspected or diagnosed NAIT/FNAIT, or
 - Female partner had a previous child with NAIT/FNAIT and is known to be alloimmunized, or
 - Fetus with suspected NAIT/FNAIT based on clinical presentation (ie: intracranial bleeding on ultrasound), and fetal diagnostic testing is medically necessary, or
 - Previous child with NAIT/FNAIT and there is a risk for this disorder in a current pregnancy based on parental HPA genotypes, and prenatal risk assessment is desired. or
 - Platelet refractoriness despite receiving HLA matched platelets, or
 - Platelet refractoriness in the context of being unable to find compatible platelets for transfusion, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Other considerations

Targeted HPA genotyping is not medically necessary when assessed as part of a pharmacogenomics or coagulopathy workup.

The procedure codes billed for HPA genotyping (including, but not limited to ITGB3 and ITGA2B) are not medically necessary outside of those indications outlined above, including for use in pharmacogenomics panels or to assess other cardiovascular disease states.

For information on pharmacogenomics panels, please refer to the guideline *Pharmacogenomic Testing for Drug Toxicity and Response*.

Red Blood Cell (RBC) Antigen Genotyping

Testing for red blood cell antigens through molecular genotyping is considered medically necessary when the member has a documented risk for red blood cell alloimmunization as outlined here.

- · One of the following criteria must be met:
 - Member has weak D antigen on serology, or
 - Member is pregnant and has erythrocyte antibodies identified, or
 - Member is the parent of a pregnancy or newborn suspected of having or at risk for Hemolytic Disease of the Fetus and Newborn (HDFN), or
 - Pregnancy or newborn is suspected of having or at risk for Hemolytic Disease of the Fetus and Newborn (HDFN), or
 - Member has warm autoantibodies. or
 - Member is receiving certain monoclonal antibody therapies (such as anti CD38 therapy), or
 - Member has a blood disorder requiring frequent transfusions (such as sickle cell disease, some forms of thalassemia, autoimmune hemolytic anemia, or myelodysplasia), or
 - Member has a result from a traditional serology (hemagglutination) assay that is not consistent with the antibody that they are expressing, or
 - Member has evidence of an antigen that cannot be detected, or is not easily detected, by traditional hemagglutination (including the Dombrock antigen, complex Rh phenotypes, Fy silencing mutations, and MNS system mutations), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Other considerations

Although most genotyping tests should only be performed once per lifetime, it may be medically necessary to repeat RBC antigen genotyping in some individuals. These requests will be reviewed on a case by case basis.

Fetal RHD Genotyping Using Maternal Plasma

Fetal RHD genotyping using cell free fetal DNA in maternal plasma is medically necessary when the following criteria are met:

- Member is currently pregnant and has antibodies to Rh (D) (is alloimmunized), AND
- Genotyping on the father of the current pregnancy, if performed, shows heterozygosity for RHD, AND
- Member has declined amniocentesis for the purpose of genotyping fetal amniocytes for RHD, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

For all other indications, fetal HPA or RBC genotyping using maternal plasma is considered Experimental, Investigational, or Unproven.

- Experimental, Investigational, or Unproven (E/I/U) refers to tests, or uses of tests, that have insufficient data to demonstrate an overall health benefit. This typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity) and significantly improves patient health outcomes (clinical utility). Such tests are also not generally accepted as the standard of care in the evaluation or management of a particular condition.
- In the case of laboratory testing, FDA approval or clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight. In addition, FDA approval or clearance often does not include an assessment of clinical utility.

Billing and Reimbursement

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

Genotyping is reimbursable once per lifetime.

Targeted HPA genotyping (CPT codes 81105-81112) is not reimbursable as part of a pharmacogenomics workup. The following criteria are used to determine if targeted HPA genotyping is being performed as part of a pharmacogenomics workup:

 When billed on the same date of service with any pharmacogenomic testing procedure code (for more details, please refer to the guideline *Pharmacogenomic Testing for Drug Toxicity and Response*).

What are tissue antigens?

An antigen is a substance (protein, sugar, or lipid) that is on the surface of a cell. Red blood cell antigens are on the surface of red blood cells (RBC), while human platelet antigens (HPA) are on the surface of platelets.

Individuals can be exposed to red blood cell or human platelet antigens that they do not have on their cells through blood transfusion or pregnancy. Once exposed, they may become alloimmunized to these antigens and mount an immune response to them if they are presented again (e.g., during future transfusions).^{1,2}

If subsequent antigen exposure occurs during pregnancy, the fetus/newborn is at risk for serious disease.

- Red Blood Cell Antigens: Fetuses and newborns of alloimmunized mothers are at risk for developing Hemolytic Disease of the Fetus and Newborn (HDFN). Symptoms include high output cardiac failure and kernicterus.^{3,4}
- Human Platelet Antigens: Fetuses and newborns of alloimmunized mothers are at risk for developing Fetal and Neonatal Alloimmune Thrombocytopenia.
 (FNAIT). Symptoms include thrombocytopenia and intracranial, gastrointestinal, or genitourinary hemorrhage.^{5,6} Unlike HDFN, FNAIT can occur in a first pregnancy.^{5,6}

Test information

Laboratory work-up of alloimmunization may include serology (antibody and/or antigen analysis) and molecular analysis.

Human Platelet Antigen (HPA) Genotyping

Molecular testing for human platelet antigens is typically performed in specialized reference laboratories via laboratory developed tests. Testing typically consists of targeted genotyping for specific, well-described gene variants.

Red Blood Cell (RBC) Antigen Genotyping

Molecular testing for red blood cell antigens is typically performed in specialized reference laboratories via laboratory developed tests, but RBC antigen panels may also be performed on FDA-approved instrument platforms. Testing may consist of targeted genotyping for specific gene variants, gene sequencing, or deletion analysis.

Table: Selected Red Blood Cell Antigens and Corresponding Genes

RBC antigen names, abbreviations, and genes

Red Blood Cell Blood Group Name	Antigen Abbreviation	Gene
RH	RHD/C/E	RHCE / RHD
ABO	ABO	ABO
Colton	СО	AQP1
Cromer	СКОМ	CD55
Diego	DI	SLC4A1
Dombrock	DO	ART4
Н	FUT1	FUT1
Se	FUT2	FUT2
Duffy	FY	ACKR1
Gerbich	GE	GYPC
MN	GYPA	GYPA
Ss	GYPB	GYPB
Indian	I	CD44
Kidd	JK	SLC14A1
Junior	JR	ABCG2
Kell	KEL	KEL
Lutheran inhibitor	KLF	KLF1
Lutheran	LU	BCAM
Landsteiner-Wiener	LW	ICAM4

Red Blood Cell Blood Group Name	Antigen Abbreviation	Gene
Scianna	SC	ERMAP
Kell (X-linked)	хк	хк
YT	YT	ACHE
Knops	KN	CR1
Vel	Vel	SMIM1

Guidelines and evidence

American College of Obstetricians and Gynecologists

The American College of Obstetricians and Gynecologists (ACOG, 2018) Practice Bulletin 192 Management of Alloimmunization During Pregnancy made the following recommendations after maternal antibodies are identified:³

- "The initial management of a pregnancy involving an alloimmunized patient is determination of the paternal erythrocyte antigen status."
- "The fetal genotype should be assessed when the paternal genotype is thought to be heterozygous or is unknown."

A clinical practice update to this bulletin (ACOG, 2024) stated the following regarding recommendations after maternal antibodies are identified:⁷

- "Paternal RHD zygosity testing using genotypic analysis is recommended for Rh-D alloimmunization risk assessment. It may be reasonable to defer or discontinue fetal surveillance for anemia in the setting of paternal genotyping that is RHD homozygous negative."
- "Because cfDNA testing possesses performance characteristics that appear comparable with those of molecular testing, while avoiding the rare complications and costs associated with diagnostic genetic testing, it is reasonable to use it as an alternative tool for fetal RHD testing among alloimmunized patients with potentially atrisk pregnancies who decline amniocentesis."
- "Cell-free DNA for the assessment of selected non—Rh-D red blood cell antigens may be considered for pregnant patients declining amniocentesis, after weighing cost, access, and the encouraging-yet-limited data supporting its use."

ACOG Practice Bulletin 181 Prevention of Rh D Alloimmunization (2017) stated:4

- "All pregnant women should be tested at the time of the first prenatal visit for ABO blood group and the Rh D type and screened for the presence of erythrocyte antibodies."
- "If Rh D antibodies are present because of sensitization, anti-D immune globulin is not beneficial, and management should proceed in accordance with protocols for Rh D-alloimmunized pregnancies."
- "If paternity is certain and the father is known to be Rh D negative, antenatal prophylaxis is unnecessary."
- "Despite the improved accuracies noted with noninvasive fetal RHD genotyping, cost comparisons with current routine prophylaxis of anti-D Immunoglobulin at 28 weeks of gestation have not shown a consistent benefit and, thus, this test is not routinely recommended."

Regarding maternal weak D phenotype on serology, ACOG Bulletin 181 (2017) stated:⁴

- "An attractive solution to this problem [maternal weak D phenotype] is to perform molecular genetic RHD typing in weak D phenotype individuals as suggested by the Work Group on RHD Genotyping."
- "Clinicians are advised to administer Rh D immune globulin to patients with weak D blood type in appropriate clinical situations, by the same rationale as that for Rh D typing blood donors, until further scientific and economic studies are available."

American Society of Hematology

The American Society of Hematology (ASH, 2020) stated the following in their guidelines for transfusion support for sickle cell disease:¹

- "The ASH guideline panel recommends prophylactic red cell antigen matching for Rh (C, E or C/c, E/e) and K antigens over only ABO/RhD matching for patients with SCD (all genotypes) receiving transfusions (strong recommendation based on moderate certainty in the evidence about effects)."
- "The ASH guideline panel suggests an extended red cell antigen profile by genotype or serology over only ABO/RhD typing for all patients with SCD (all genotypes) at the earliest opportunity (optimally before the first transfusion) (conditional recommendation based on very low certainty in the evidence about effects)."
- "Extended red cell antigen matching (Jk^a, Jk^b, Fy^a, Fy^b, S/s) may provide further protection from alloimmunization."

In a 2014 Mini Review, the ASH stated:²

- "One to two percent of all patients who receive transfusions develop antibodies to RBC antigens."
- Between 10 and 30% of patients receiving chronic transfusions are alloimmunized, typically before the 15th transfusion.
- "Once alloimmunization occurs, the likelihood of additional antibody responses is also relatively high. In surgical, pregnant, and non-hematologic malignancy patients,

once RBC antibodies have been induced, 20 percent to 25 percent of patients form additional antibodies after subsequent transfusions and thus become multiply alloimmunized."

- In this review, ASH lists the following scenarios in which red blood cell antigen genotyping may be helpful:
 - Hemoglobinopathy patients at baseline,
 - Alloimmunized patients who are expected to need additional transfusions,
 - Alloimmunized patients with a co-existing autoantibody,
 - Patients who have been recently transfused,
 - Prenatal diagnosis in pregnancies at risk for hemolytic disease of the newborn.

Regarding platelet refractoriness, ASH (2020) recommended ordering HLA/HPA antibody screening tests and either platelet crossmatching or HLA/HPA matched platelets in individuals with thrombocytopenia, repeated poor response to platelet transfusion, and HLA/HPA antibodies.⁸

British Committee for Standards in Haematology

In a 2017 guideline on red cell transfusion in sickle cell disease, the British Committee for Standards in Haematology stated:⁹

- "An extended phenotype (or genotype) including C, c, E, e, K, k, Jka, Jkb, Fya, Fyb, S, s should be performed on all patients at baseline. If the patient is S- s-, then U typing should be performed (Milkins et al, 2013). If the patient has not been transfused within 3 months then this can be undertaken serologically, otherwise the genotype needs determination by molecular techniques (Chou & Westhoff, 2011; Milkins et al, 2013) through an appropriate reference laboratory."
- "Select ABO extended Rh and K matched units negative for the relevant antigen(s) to which there are current or historical antibodies."
- "If the identity of the new alloantibody is in doubt despite further specialist testing, consider providing extended antigen matched blood (if serological phenotyping cannot be used because of the presence of transfused donor red blood cells, the sample should be sent to an appropriate reference laboratory for molecular red cell genotyping)."

In a 2017 guideline on the use of platelet transfusions the British Committee for Standards in Haematology stated: 10

- Post-transfusion purpura (PTP) is "a rare condition associated with severe thrombocytopenia following blood transfusion and caused by antibodies against platelet-specific antigens. Bleeding can be serious and fatal". The condition usually occurs 5-10 days after transfusion.
- "Management is based on individual case reports and case series."

 "Current practice is to transfuse high dose intravenous immunoglobulin without waiting for the results of laboratory investigations, with random donor platelets reserved to control severe bleeding."

In a 2021 guideline on the management of sickle cell disease in pregnancy, the British Committee for Standards in Haematology stated:¹¹

"If transfusion is needed, pregnant women with SCD should be given ABO-compatible, extended Rh- and Kell-matched, CMV-negative units. If there are clinically significant red cell antibodies (current or historical) then the red cells selected should be negative for the corresponding antigens (1C)."

College of American Pathologists and AABB

A College of American Pathologists (CAP) and AABB Work Group on RHD Genotyping (2015) made the following recommendation regarding genotyping individuals with a weak D phenotype on serology:¹²

"The Work Group recommends that RHD genotyping be performed whenever a
discordant RhD typing result and/or a serological weak D phenotype is detected in
patients, including pregnant women, newborns and potential transfusion recipients. It
is anticipated that the immediate benefit will be fewer unnecessary injections of RhIG
and increased availability of RhD-negative RBCs for transfusion."

The AABB reiterated on their website: 13

 "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 highquality evidence from observational studies (1A)."

International Collaboration for Transfusion Medicine

The International Collaboration for Transfusion Medicine Guidelines (ICTMG, 2019) guideline on fetal and neonatal alloimmune thrombocytopenia stated: 14

- "If there is clinical suspicion of fetal and neonatal alloimmune thrombocytopenia (FNAIT), manage as FNAIT without waiting for laboratory confirmation (moderate evidence, strong recommendation)."
- "Fetal HPA typing, preferably using non-invasive methods, if adequately quality assured, should be performed during pregnancy when the father is unknown, unavailable for testing or heterozygous for the implicated antigen (moderate evidence, strong recommendation)."
- "Antenatal IVIG administration to the mother, commencing at 12–16 weeks gestation, should be offered to all women in a subsequent pregnancy with maternal fetal incompatibility who have had a previous fetus or neonate with FNAIT-related ICH (very low evidence, strong recommendation)."

Newborn Services Clinical Guideline: Auckland District Health Board

The Auckland, New Zealand District Health Board points to the Starship Child Health (2019) clinical management guideline on neonatal alloimmune thrombocytopenia, which stated the following regarding FNAIT:⁵

- "Neonatal Alloimmune Thrombocytopenia (NAIT) results from maternal human
 platelet antibodies (HPA) against fetal platelet antigens inherited from the father. In
 contrast to rhesus haemolytic disease, platelet allo-immunization can occur during the
 first pregnancy."
- "Definitive diagnosis of NAIT depends on parental testing."
- Maternal and paternal genotyping is recommended in this clinical guideline.
 If paternity is uncertain or no paternal sample is available, fetal genotyping is recommended.

Royal College of Obstetricians and Gynaecologists

In a 2019 guideline addressing pregnancies at risk for alloimmune thrombocytopenia, the Royal College of Obstetricians and Gynaecologists stated: 15

- There is no evidence to support routine screening for pregnancies at risk of FNAIT (Fetal and Neonatal Alloimmune Thrombocytopenia).
- "IVIg in pregnancy is safe and likely to be effective. It seems reasonable to start therapy at 16–18 weeks of gestation in an at-risk pregnancy."

Selected Relevant Publications

Multiple review articles have addressed human platelet antigen genotyping, specifically with regard to Fetal and Neonatal Alloimmune Thrombocytopenia (FNAIT).

A review by Winklehorst and colleagues (2017) stated: 16

- "When FNAIT is suspected, or in case of a family member with FNAIT, diagnostic
 work-up should ideally include HPA genotyping of mother, father, and child to
 establish possible HPA incompatibilities, as well as serological testing (maternal
 paternal serum crossmatch, and a maternal platelet antibody screening)."
- "If, in case of suspicion due to an affected family member, after the HPA-typing, the pregnant woman turns out to be HPA-1a negative, the HPA-1a type of father and, in case of paternal heterozygosity, consequently fetus can be determined."
- "Adequate diagnosis does not only contribute to adequate management in the index cases, but is just as important for taking adequate measures in subsequent pregnancies to prevent bleeding complications."
- "When the father is homozygous, every consecutive pregnancy is incompatible and therefore the fetus is at risk. When the father is heterozygous, fetal genotyping has to be performed."

A review by Mella and colleagues (2015) stated: 17

- "Approximately 80% of pregnancies affected by NAIT have maternal antibodies that
 are directed against platelet antigen HPA-1a with the remaining 20% being affected
 by the other HPA types. Studies have shown that approximately 98% of Caucasian
 women express HPA-1a (genotype HPA-1a/HPA-1a or HPA1a/HPA1b) and about 2%
 of Caucasian women are HPA-1a negative (genotype HPA-1b/HPA-1b). The second
 most common platelet antigen causing NAIT in Caucasians is HPA-5b antigen,
 followed by HPA-1b and HPA-15."
- "In at-risk pregnancies, mothers are antigen negative (most commonly HPA-1b) and fathers are either antigen-positive homozygous (genotype HPA-1a/1a) or heterozygous (genotype HPA-1a/1b)."
- "If the parental genotypes are different and the mother has specific antibodies to the putative antigen, then the pregnancy is at risk for NAIT and fetal/neonatal antigen typing would then be indicated."

A review by Peterson and colleagues (2013) stated: 18

- "Some have argued that it may be cost-effective to perform such screening routinely and offer special case management to the 10% of HPA-1a-negative women who produce antibody (Husebekk et al, 2009) but at the present time this is not practiced in the absence of a family history of NAIT, e.g., in a sister."
- "A first affected neonate with NAIT in a family is normally identified when clinical signs
 of bleeding are evident at or shortly after birth and a platelet count confirms isolated
 thrombocytopenia."

Platelet Refractoriness

A review by Stanworth et al. (2015) stated the following regarding platelet refractoriness: 19

- "If there are poor responses to HLA-selected platelet transfusions, the reasons should be sought including poor HLA compatibility of the selected product, nonimmune platelet consumption and HPA and ABO incompatibility."
- "Depending on the results of these investigations, the appropriate management could be the use of ABO-identical or HPA-selected platelet concentrates if the specificity of the HPA anti-bodies can be identified."

Fetal RhD Genotyping Using Maternal Plasma

Overall, there is moderate quality evidence that the diagnostic accuracy of fetal RhD genotyping is high after 11 weeks gestation in nonalloimmunized women with singleton pregnancies. There is a paucity of evidence evaluating alloimmunized women and women with multiple pregnancies. Moderate quality evidence suggests fetal RhD genotyping may lead to reductions in unnecessary anti-D therapy in nonalloimmunized women. Very low quality evidence suggests fetal RhD genotyping for guiding targeted anti-D therapy may reduce the number of alloimmunization events in nonalloimmunized women. Very low quality evidence suggests fetal RhD genotyping may lead to reductions in unnecessary monitoring

and invasive procedures in alloimmunized women. There is a paucity of evidence evaluating the effects of fetal RhD genotyping on patient health outcomes, such as fetal morbidity/mortality or maternal quality of life.

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for human platelet and red blood cell antigen genotyping will ensure that testing will be available to those members most likely to benefit from the information provided by the assays. For those not meeting criteria, it ensures alternate diagnostic/management strategies are considered. However, it is possible that some members who would benefit from the testing, but do not meet clinical criteria, will not receive an immediate approval for testing.

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