Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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Joint Medical Policies are a source for BCBSM and BCN medical policy information only. These documents are not to be used to determine benefits or reimbursement. When Centers for Medicare and Medicaid (CMS) coverage rules are not fully developed, this medical policy may be used by BCBSM or BCN Medicare Advantage plans 42 CFR § 422.101 (b)(6). Please reference the appropriate certificate or contract for benefit information. This policy may be updated and is therefore subject to change.

***Current Policy Effective Date: 7/1/25**
(See policy history boxes for previous effective dates)

Title: Genetic Testing-Human Platelet Antigen Genotyping

Description/Background

Neonatal alloimmune thrombocytopenia (NAIT) is a disorder in which fetal platelets contain an antigen inherited from the father that the mother lacks, most commonly human platelet antigen (HPA)-1a incompatibility. The mother then develops antibodies against this paternal antigen and these antibodies cross the placenta and bind to the fetal platelets. Clearance of the antibody-coated platelets results in fetal/neonatal thrombocytopenia; platelet function remains relatively normal. In contrast to Rh(D) alloimmunization, NAIT often affects a first pregnancy.[6]

The mother of a fetus with NAIT is usually asymptomatic. The spectrum of fetal disease ranges from mild asymptomatic thrombocytopenia to severe thrombocytopenia leading to spontaneous intracranial hemorrhage, which is often fatal. Intracranial hemorrhage is associated with platelet counts primarily less than 20,000/microL, particularly less than 10,000/microL. Extracranial fetal hemorrhage is extremely rare. NAIT often affects the first pregnancy of an at-risk couple but is not suspected until after delivery unless the mother's sister has a history of an affected child, fetal intracranial hemorrhage is noted on an ultrasound examination, or prenatal screening has been performed. Intracranial hemorrhage occurs in 7 to 26 percent of NAIT, and up to 75 percent of these hemorrhages occur prenatally between 20 weeks of gestation and term.[6]

Human platelet antigen (HPA) variants can be detected by direct PCR. This is a molecular test using a DNA-based capture binding assay to genotype and identify the HPA polymorphism.

Platelet antigen genotyping (HPA-1 to HPA-6 and HPA-15) is currently under investigation for the following circumstances:

- In fetal or neonatal testing when parents have had a prior affected pregnancy; or

- An unexplained intracranial hemorrhage is detected; or
- Maternal and paternal testing when a fetus or neonate is suspected of having neonatal alloimmune thrombocytopenia (also referred to as perinatal alloimmune thrombocytopenia; or
- In women planning a pregnancy who have a sister with a previously affected pregnancy or a pregnancy with posttransfusion purpura

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Regulatory Status

There are no assay kits approved by the U.S. Food and Drug Administration (FDA) genotyping for human platelet antigen. Clinical laboratories may develop and validate tests in-house ("home-brew") and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing.

Medical Policy Statement

Human platelet antigen genotyping for neonatal alloimmune thrombocytopenia (NAIT) is established. It may be considered a useful diagnostic option for carefully selected individuals who meet the selection criteria.

Inclusionary and Exclusionary Guidelines

Inclusions:
Testing for human platelet antigen genotyping is considered established for the following indications:

1) Fetal and neonatal testing (when **one** of the criteria is met):
    a. Suspected diagnosis of Neonatal Alloimmune Thrombocytopenia (NAIT) based on clinical presentation;
    b. Intracranial hemorrhage in the neonatal period of unknown cause;
    c. Neonatal thrombocytopenia;
    d. Either parent has had a prior affected pregnancy with NAIT;
2) Maternal and paternal testing (when **one** of the criteria is met):
    a. Fetus or newborn suspected or diagnosed with NAIT;
    b. Female partner had a previous child with NAIT and is known to be allo-immunized;
    c. A female planning a pregnancy whose sister had a previous pregnancy affected by NAIT.

All providers requesting this test should be able to provide pre and posttest genetic counseling to the family.

Exclusions:

- All other indications for Human Platelet Antigen genotyping not mentioned above are considered experimental/investigational.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

81105	81106	81107	81108	81109	81110
81111	81112				

Other codes (investigational, not medically necessary, etc.):

N/A

Note: Code(s) may not be covered by all contracts or certificates. Please consult customer or provider inquiry resources at BCBSM or BCN to verify coverage.

Rationale

Fetal/neonatal alloimmune thrombocytopenia is the most common cause of severe thrombocytopenia in the fetus and in an otherwise healthy newborn. Bertrand et al (2010) reported data concerning 239 pregnancies in 75 HPA-1bb women.[1] Analysis of the index cases (diagnosis of fetal/neonatal alloimmune thrombocytopenia) did not show any significant correlation between the severity of the disease and the maternal genetic background (ABO blood group and HLA-DRB3 allele). Subsequent pregnancies were managed, and therapy effectiveness was evaluated. The highest mean newborn platelet count was observed for a combination of intravenous immunoglobulin and steroids (135 x 109/L; 54 newborns) compared with intravenous immunoglobulin alone (89 x 109/L; 27 newborns). The maternal anti-HPA-1a antibody concentration measured before any treatment and before 28 weeks of gestation was predictive of the fetal status. The weighted areas under curves of the maternal alloantibody concentrations may be predictive of therapy response. The authors concluded that this large retrospective survey gives new insights on maternal predictive parameters for fetal status and therapy effectiveness which may allow for noninvasive strategies.

Peterson et al (2014) performed studies to define more fully how often HPAs trigger maternal immunization leading to NAIT.[2] In a Phase 1 study, fathers of selected NAIT cases not resolved by serologic testing but thought to have a high likelihood of NAIT on clinical and serologic grounds were typed for low frequency human platelet antigens (LFHPAs) by DNA sequencing. In a Phase 2 study, high-throughput methods were used to type fathers of 1067 consecutive unresolved NAIT cases for LFHPAs. Mothers of 1338 unresolved cases were also typed to assess the prevalence of LFHPAs in a population racially/ethnically similar to the fathers. In Phase 1, LFHPAs were identified in 16 of 244 fathers (6.55%). In Phase 2, LFPAs were found in only 28 of 1067 fathers (2.62%). LFHPAs were identified in 27 of 1338 maternal samples (2.01%). HPA-9bw was by far the most common LFHPA identified in the populations studied and was the only LFHPA that was significantly more common in fathers than in mothers of affected infants ($p = 0.02$). Maternal immunization against recognized LFHPAs accounts for only a small fraction of the cases of apparent NAIT not resolved by standard serologic testing. Typing of the fathers of such cases for LFHPAs is likely to be

rewarding only when a maternal antibody specific for a paternal platelet glycoprotein is demonstrated and/or there is compelling clinical evidence for NAIT.

Carmo et al (2017) investigated human platelet antigen frequencies in immune thrombocytopenia patients from the state of Amazonas, Brazil and investigated the potential association between specific antigens and risk for immune thrombocytopenia.[3] In this study, human platelet antigen typing was performed by BeadChip technology to determine allelic variants of 11 systems (HPA-1 to HPA-9, HPA-11 and HPA-15). Thirty-six patients (8 male and 28 female) with a median age of 34 years (range: 9-69 years) were evaluated and compared with data from Amazonas blood donors. Platelet counts varied from 3 to 98×10 /L. The allele frequencies were 0.944 for HPA-1a, 0.056 for HPA-1b, 0.847 for HPA-2a, 0.153 for HPA-2b, 0.555 for HPA-3a, 0.444 for HPA-3b, 0.805 for HPA-5a, 0.222 for HPA-5b, 0.9975 for HPA-9a, 0.025 for HPA-9b, 0.486 for HPA-15a and 0.513 for HPA-15b. Among immune thrombocytopenia individuals, no b allele of the HPA-4, -6, -7, -8 and -11 were found. This study suggests HPA-1a, HPA-3b and HPA-5b are immune thrombocytopenia-specific autoepitopes.

In a study determining the incidence of HPA1, HPA2 and HPA5 polymorphisms, Eyada et al (2017) looked at 120 Egyptian immune thrombocytopenic purpura (ITP) patients and 120 healthy Egyptian subjects.[4] Human platelet antigen (HPA) genotyping was done using the polymerase chain reaction-restriction fragment length polymorphism. The frequency of HPA1 allele a and b was 78.75 and 21.25% in controls, 80.8 and 19.2% in ITP, respectively. HPA2 allele a and b frequency was 86.25 and 13.75% in controls and of 74.6 and 25.4% in patients, respectively. HPA5 allele a and b frequency was 87.5 and 12.5% in controls, in patients it was 85 and 15%, respectively. With the exception of HPA2, no other significant difference was encountered in HPA allele frequency between controls and ITP patients. The current study noted that in all the studied HPA systems 1, 2 and 5, the 'a' allele is more prevalent than the b allele; the most frequent genotype was the homozygous a/a genotype. HPA2b frequency, homo- and hetero-zygous HPA2b genotype frequencies were significantly higher in ITP patients compared to controls. The authors concluded that HPA2b are 2.37 times more likely to develop ITP compared to those without this allele. The relatively high allele frequency of the HPA1b in the Egyptian population may suggest that this ethnic group has a higher risk of alloimmunization.

Refsum et al (2017) conducted a study to determine the frequency of associated maternal platelet alloimmunization in a population of neonates born from 32 weeks of gestation and diagnosed with an intracranial hemorrhage (ICH).[5] The Swedish Neonatal Quality (SNQ) register was used to identify neonates diagnosed with an ICH born between 2003 and 2012. Mothers were invited to donate peripheral blood, to investigate their HPA-1a antigen status, and test for anti-HPA and anti-HLA Class I alloantibodies. Clinical data for the neonates were retrieved from the SNQ register and available clinical records. Of 286 registered neonates, 278 mothers were contacted. Of 105 analyzed maternal samples, two (1.9%) were HPA-1a antigen negative. Antibody analyses revealed in total three (2.9%) mothers with anti-HPA: one mother (0.94%) with anti-HPA-1a and two mothers (1.9%) with anti-HPA-5b, of whom one had concurrent anti-HPA-15a. Twenty-four percent tested positive for anti-HLA Class I antibodies. A total of 8.5% of neonates (5/59) with PLT counts available in clinical records were severely thrombocytopenic, with PLT counts of less than 50 × 10 /L. This retrospective cohort reveals a wide range of factors associated with ICH in neonates born from 32 weeks of gestation and suggests PLT alloimmunization to be a less common contributor than anticipated.

In 2017, Kamphuis et al evaluated the management and outcome of a large international cohort of cases of pregnancies complicated by fetal and neonatal alloimmune thrombocytopenia (FNAIT).[6] This was an observational prospective and retrospective cohort study of all cases of FNAIT entered into the international multicenter No IntraCranial Haemorrhage (NOICH) registry during the period of 2001-2010. The authors evaluated human platelet antigen (HPA) specificity, the antenatal and postnatal interventions performed, and clinical outcome. A total of 615 pregnancies complicated by FNAIT from 10 countries were included. Anti-HPA-1a was the most commonly implicated antibody. Antenatal treatment was administered in 273 pregnancies (44%), varying from intrauterine platelet transfusion to maternal administration of immunoglobulins, steroids, or a combination of those. Intracranial haemorrhage was diagnosed in 23 fetuses or neonates (3.7%). Overall perinatal mortality was 1.14% (n = 7). The data show that antenatal treatment for FNAIT results in favorable perinatal outcome. Over time, in most centers, treatment for FNAIT changed from an invasive to a complete non-invasive procedure.

Chen et al (2017) explored the incidence of alloantibody against the HPA in pregnant women and its associations with NAIT in China.[7] A multicenter, prospective cohort study design was used, and 55,497 pregnant women were recruited for the first screening of the anti-HPA antibody at 12 to 28 weeks of gestational age. Subjects who were positive in the first screening for the anti-HPA antibody were included in the exposure group. Re-tests of the antibody titer, antigen-specificity and genotyping of HPA and HLA were conducted during admission. A ratio of 1:1 paired individuals with the same ethnicity and parity but testing negative for the anti-HPA antibody were randomly selected to be included in the non-exposure group. NAIT would be diagnosed in the newborns on day one of the birth. The HPA of the neonates in the exposure group would also be genotyped by sequencing. Associations of maternal HLA with the occurrence of the anti-HPA antibody and correlation of the severity of NAIT with the titer of the anti-HPA antibody would be further analyzed. The authors concluded that the titer of the anti-HPA antibody is a much better indicator of the severity of NAIT. The levels of the anti-HPA antibody have significant correlations with the risk and the severity of neonatal thrombocytopenia.

Khaspekova et al (2018) studied the mechanisms underlying the development of NAIT in Russia.[8] Genetic polymorphisms of human platelet alloantigens (HPA) -1, -2, -3, -4, -5, and -15 were evaluated in 27 families having the newborns with NAIT. NAIT was diagnosed according to the following criteria: (1) newborn with thrombocytopenia; (2) mother with no thrombocytopenia and no increase of platelet associated IgG, (3) presence of antibodies reacting with paternal platelets in maternal plasma / serum. HPA genotyping revealed incompatibilities in 23 out of 27 tested families. In these 23 families HPA-1 conflicts were detected in 16 ones (70%). In 8 cases mothers were homozygous carriers of rare HPA-1b allele and in another 8 cases – of HPA-1a allele which cased incompatibilities with fetal HPA-1a and HPA-1b respectively. In 5 out of 23 families (22%) there were incompatibilities with fetal HPA-15 (HPA-15a, n=2 and HPA-15b, n=3), in 1 family – with HPA-5b (4%), and in 1 family – with HPA-3b (4%) alloantigens. The authors concluded that the main causes of NAIT in Russia were HPA-1a and 1b conflicts and HPA 15 conflicts were the second frequent.

SUMMARY OF EVIDENCE

The evidence includes studies examining maternal platelet alloimmunization and the incidence of NAIT. The data suggests HPA-1a, HP/a-3b and HPA-5b are immune thrombocytopenia-specific autoepitopes. Individuals who express these alleles may be more likely to develop immune thrombocytopenic purpura compared to those without these alleles. Data also shows that the titer of the anti-HPA antibody is a much better indicator of the severity of NAIT. The levels of the anti-HPA antibody have significant correlations with the risk and the severity of neonatal thrombocytopenia. The data show antenatal treatment for FNAIT results in favorable perinatal outcomes as well as positive changes to the treatment for FNAIT from invasive to a complete non-invasive procedure. The evidence is sufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

No practice guidelines or position statements were found regarding human platelet antigen genotyping for neonatal alloimmune thrombocytopenia.

Ongoing and Unpublished Clinical Trials

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
Unpublished			
NCT02934906	Study on the anti-HPA antibodies caused neonatal alloimmune thrombocytopenia in Chinese pregnant women	55497	Dec 2019
NCT03408158	HPA antibodies and the distribution of antigen and antibodies	25000	Dec 2018
NCT04067375	Towards routine HPA-screening in pregnancy to prevent FNAIT (HIP)	4000	Apr 2021
NCT02899598	Genotyping of human platelet alloantigens: non-invasive prenatal diagnosis	48	Jul 2017

NCT: national clinical trial

Government Regulations

National:

There is no national Medicare coverage determination on this topic.

Local:

There is no national Medicare coverage determination on this topic.

Codes 81105-81112 are shown on the 2024 CMS fee schedule with a fee attached.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

Genetic Testing and Counseling

References

1. Bertrand G, Moustapha D, Martageix C, and Kaplan C. Prediction of the fetal status in noninvasive management of alloimmune thrombocytopenia. Blood. March 2011;117(11):3209-3213.
2. Peterson JA, Gitter M, Bougie DW, et al. Low-frequency human platelet antigens as triggers for neonatal alloimmune thrombocytopenia. Transfusion. May 2014;54(5):1286-1293.
3. Carmo JCD, Klippel PS, Cordeiro SDC, et al. Molecular typing of human platelet antigens in immune thrombocytopenia patients in northern Brazil. Rev Bras Hematol Hemoter. Apr 2017;39(2):122-126.
4. Eyada TK, Amin DG, Samih I, and Khedr SM. Human platelet antigen 1, 2 and 5 gene polymorphisms in Egyptians and their potential association with susceptibility to immune thrombocytopenic purpura in Egyptian patients. Hematology. Aug 2017;1-6. [Epub ahead of print]
5. Refsum E, Hakansson S, Mortberg A, et al. Intracranial hemorrhages in neonates born from 32 weeks of gestation-low frequency of associated fetal and neonatal alloimmune thrombocytopenia: a register-based study. Transfusion. Nov 2017; [Epub ahead of print]
6. Kamphuis MM, Tiller H, Akker ES, et al. Fetal and neonatal alloimmune thrombocytopenia: management and outcome of a large international retrospective cohort. Fetal Diagn Ther. May 2017; 41(4):251-257.
7. Chen L, Liu Z, Liu T, et al. Neonatal alloimmune thrombocytopenia caused by anti-HPA antibodies in pregnant Chinese women: a study protocol for a multicenter, prospective cohort trial. BMC Preg Childbirth. Aug 2017; 17(1): 281.
8. Khaspekova SG, Golovkina LL, Donush EK, et al. Maternal incompatibilities with fetal human platelet alloantigens -1a, -1b and -15 are the main causes of neonatal alloimmune thrombocytopenia in Russia. Ter Arkh. Aug 2018; 90(7):65-69.
9. Paida MJ. Neonatal alloimmune thrombocytopenia: parental evaluation and pregnancy management. Available at: https://www.uptodate.com. Accessed March 2025.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through March 2025, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
7/1/18	4/17/18	4/17/18	Joint policy established
7/1/19	4/16/19		Routine policy maintenance. No change in policy status.
7/1/20	4/14/20		Routine policy maintenance. No change in policy status.
7/1/21	4/20/21		Routine policy maintenance. No change in policy status.
7/1/22	4/19/22		Routine policy maintenance, no change in policy status.
7/1/23	4/18/23		Routine policy maintenance, no change in policy status. Vendor managed: N/A. (ds)
7/1/24	4/16/24		Policy status changed from E/I to established with criteria. Rationale updated, references added. Codes 81105-81112 moved to established. Vendor managed: N/A (ds)
7/1/25	4/15/25		Routine policy maintenance, no change in status. Vendor managed: N/A (ds)

Next Review Date: 2nd Qtr. 2026

Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN:	Revised:
BCBSM:	Revised:

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING-HUMAN PLATELET ANTIGEN GENOTYPING

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered per policy
BCNA (Medicare Advantage)	See government section
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.