Local Coverage Determination (LCD):
MolDX: Blood Product Molecular Antigen Typing (L38331)

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Noridian Healthcare Solutions, LLC	A and B MAC	01112 - MAC B	J - E	California - Northern
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Noridian Healthcare Solutions, LLC	A and B MAC	01212 - MAC B	J - E	American Samoa Guam Hawaii Northern Mariana Islands
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MolDX: Blood Product Molecular Antigen Typing

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CMS National Coverage Policy

Title XVIII of the Social Security Act (SSA), §1862(a)(1)(A), states that no Medicare payment shall be made for items or services that "are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member."

42 Code of Federal Regulations (CFR) §410.32 Diagnostic x-ray tests, diagnostic laboratory tests, and other diagnostic tests: Conditions.

CMS Internet Online Manual Pub. 100-02 (Medicare Benefit Policy Manual), Chapter 15, Section 80, "Requirements for Diagnostic X-Ray, Diagnostic Laboratory, and Other Diagnostic Tests"

Coverage Guidance

Coverage Indications, Limitations, and/or Medical Necessity

This policy provides limited coverage for molecular phenotyping of blood product antigens as part of the pre-transfusion evaluation for patients who may require or are expected to require a blood product transfusion(s) (Red Blood Cells, Platelets or Leukocytes) when at least one of the following criteria is met:

- Long term, frequent transfusions anticipated to prevent the development of alloantibodies (e.g. sickle cell anemia, thalassemia, chronic transfusion dependent hematologic disorders or other reasons); OR
- Autoantibodies or other serologic reactivity that impedes the exclusion of clinically significant alloantibodies (e.g. autoimmune hemolytic anemia, warm autoantibodies, patient recently transfused with a positive DAT, high-titer low avidity antibodies, patients about to receive or on daratumumab therapy, other reactivity of no apparent cause); OR
- Suspected antibody against an antigen for which typing sera is not available; OR
- Laboratory discrepancies on serologic typing (e.g. rare Rh D antigen variants)

Laboratory developed tests (LDTs) that perform molecular phenotyping of blood product antigens may be considered covered for the same indications if the test demonstrates validity and clinical utility equivalent to or better than covered tests as demonstrated in a technical assessment.

Medicare does not expect molecular testing to be performed on patients undergoing surgical procedures such as bypass or other cardiac procedures, hip or knee replacements or revisions, or patients with alloantibodies identifiable by serologic testing that are not expected to require long term, frequent transfusions. The medical necessity for molecular blood product phenotyping must be documented in the patient's medical record.

Blood product molecular antigen typing tests are considered germline tests and thus must comply with relevant Medicare or Contractor policies regarding germline testing.

As molecular genotyping includes a review of many genes that code for cellular antigens that must be evaluated for proper patient care, single gene tests are not reasonable and necessary.

If there is a rare instance that a single blood product antigen is reasonable and necessary, its utility must be appropriately documented in the patient's medical record for validation by medical review.

Summary of Evidence

For patients who require a blood product transfusion, an important step taken prior to the transfusion of any blood product is compatibility testing between the recipient's serum and the blood product being transfused. In addition to the ABO and Rh system there are 34 other recognized blood group antigen systems by the International Society of Blood Transfusion.[1] Identifying the blood product antigens to which the transfusion recipient will have an immune reaction is a critical component of this compatibility testing, though for most patients identification of ABO and Rh compatibility is sufficient.[2] However, for patients who have alloantibodies or patients who have a predisposition to develop alloimmunization (e.g. patients with sickle cell disease and others who are chronically transfused), compatibility testing of additional systems may be needed.[2,3] Hemagglutination has traditionally been the most common serologic method of determining a blood product phenotype. In this technique, the patient's RBCs are tested with antisera specific for the antigens of interest.[2,4] However, this method has limitations. It requires direct agglutination typing sera for the antigen, and hemagglutination testing results are not meaningful if a patient has a positive direct antiglobulin test (DAT).[3,4] In addition, serologic phenotyping is likely to be erroneous in the transfused patient who may have persistent donor blood products in circulation, such as patients getting chronic frequent transfusions, and it has been suggested that chronically transfused patients or patients who have had a massive transfusion should not receive phenotyping using serological methods, or that if serological methods are used, they should be confirmed with molecular techniques.[3,5]

Because molecular genotyping is not subject to the limitations of conventional serologic testing, the transfusion community has recognized molecular typing as a potential tool to aid in the determination of immune compatibility between donated blood products and the transfusion recipient in a number of circumstances where conventional methods may not be adequate, such as in patients who have a positive direct antigen test, in patients who have been recently transfused or those who are chronically transfused,[6] in patients where a distinction between autoantibodies and alloantibodies is needed, or in situations where the presence of a weakly reactive anti-body is suspected.[2,3,7,8]

Prior to broad clinical availability of molecular genotyping in the United States, a number of studies demonstrated both the feasibility of this technique and the incremental information it could provide over serologic typing in limited clinical contexts.

As early as 1999, a study from Germany in patients receiving chronic transfusions demonstrated disparate molecular Rh phenotyping in 7 of 27 patients compared to serologic typing.[9] Soon afterwards, Reid and others demonstrated that DNA from blood samples could be used to genotype patients who had recently been transfused.[6] Castilho et al confirmed the unreliability of serologic testing when they showed that 6 of 40 molecular genotypes differed from serologic phenotypes in multiple-transfused sickle cell anemia (SCA) patients[10], and in 9 of 10 alloimmunized thalassemic patients.[11] A number of investigators have replicated these findings, most notably Bakanay et al when they demonstrated genotypic and phenotypic discrepancies in 19 or 37 multi-transfused patients in multiple alleles.[12] The discrepancies aided in the selection of antigen-matched blood products and improved RBC survival, ultimately improving patient care. A recent case report by Wagner[13] highlighted the practical utility of molecular testing over serologic testing for chronically transfused patients.

In a prospective observational study, Klapper et al. used the HEA BeadChip™ to provide extended human erythrocyte antigen (xHEA) phenotyped donor units and recipient patient samples.[14] XHEA-typed units were assigned to pending

transfusion requests using a web-based inventory management system to simulate blood order processing at four hospital transfusion services. The fraction of requests filled (FF) in 3 of 4 sites was > 95% when matching for ABO, D and known alloantibodies, with an FF of > 90% when additional matching for C, c, E, e, and K antigens. The most challenging requests came from the fourth site where the FF was 62 and 51% respectively, even with a limited donor pool. A small prospective observational study by Da Costa et al, found that 21 of 35 sickle cell anemia (SCA) patients had discrepancies or mismatches, mainly in the Rh, Duffy, Jk and MNS blood groups, between the genotype profile and the serologically-matched blood unit for multiple antigens.[15] These authors report that their genotype-matching program resulted in elevated hemoglobin levels, increased time between transfusions and prevented the development of new alloantibodies.

Two papers showed the feasibility of routinely applying molecular blood banking techniques in a hospital transfusion service. Routine RBC testing has been implemented in a large tertiary care hospital in Los Angeles, CA to maximize efficient use of blood units.[16] Patients with warm or cold reacting autoantibodies, patients with SCA and patients with antibodies that could not be identified were molecularly genotyped and received molecularly matched blood from the hospital's genotyped donor inventory. The practical implementation of molecular erythrocyte antigen typing was described for a large hospital in Cleveland, OH;[17] pre-transfusion molecular typing is performed on chronically transfused patients, patients with autoantibodies, multiple antibodies, when no antigen specific antibody is available for testing and to solve laboratory discrepancies. The authors note that the major benefit of molecular typing is its application for patients who cannot be typed by serology due to an unsuitable sample. Valid results can be obtained even when they have been transfused within a few days of testing or have been massively transfused. Samples selected for molecular testing were based on an algorithm.

The emergence of novel medications, particularly monoclonal antibodies, has also created challenges for serologic phenotyping methods. Two recent research studies have demonstrated that treatment with daratumumab, a CD38 monoclonal antibody, can bind to CD38 expressed on the surface of red blood cells (RBCs) and interferes with serologic testing, thereby preventing cross match.[18] More recent evidence suggests that treatment with Hu5F9-G4, an IgG4 monoclonal antibody targeting CD47 also interferes with pretransfusion testing. [19]

Analysis of Evidence
(Rationale for Determination)

Numerous prior Medicare coverage decisions have considered the evidence in the hierarchical framework of Fryback and Thornbury[23] where Level 2 addresses diagnostic accuracy, sensitivity, and specificity of the test; Level 3 focuses on whether the information produces change in the physician's diagnostic thinking; Level 4 concerns the effect on the patient management plan and Level 5 measures the effect of the diagnostic information on patient outcomes. To apply this same hierarchical framework to analyze an in vitro diagnostic test, we utilized the ACCE Model Process for Evaluating Genetic Tests.[24] The practical value of a diagnostic test can only be assessed by taking into account subsequent health outcomes. When a proven, well established association or pathway is available, intermediate health outcomes may also be considered. For example, if a particular diagnostic test result can be shown to change patient management and other evidence has demonstrated that those patient management changes improve health outcomes, then those separate sources of evidence may be sufficient to demonstrate positive health outcomes from the diagnostic test.

It has long been recognized that immunohematologic compatibility is critical to a successful blood product

transfusion. It has also long been recognized that serologic methods of determining compatibility, while useful in many cases have limitations for particular groups of patients. Molecular methods for blood product antigen determination are not subject to the same limitations, and FDA-approved tests using molecular methods have been developed and validated to detect particular alleles within particular blood group systems. As such, FDA-approved tests are reasonable and necessary for blood product antigen typing in patients for whom a transfusion is needed when conventional serologic testing methods are inadequate or at a high risk of producing unreliable or misleading results.

The evidence review here did not seek to identify laboratory-developed tests intended to be used for the same purpose. However, since FDA-approved tests to detect all clinically significant alleles are not available at this time as the position statement from AABB, America's Blood Centers, and American Red Cross[25] notes, laboratory developed tests (LDTs) remain important to allow for the identification of unusual alleles unlikely to be readily available on FDA-approved platforms. LDTs may be considered reasonable and necessary if peer-reviewed evidence demonstrates that a rigorous validation has been done to show that they accurately predict/identify the blood product antigens.

General Information

Associated Information

The patient's medical record must contain documentation that fully supports the medical necessity for services included within this LCD. (See "Coverage Indications, Limitations, and/or Medical Necessity") This documentation includes, but is not limited to, relevant medical history, physical examination, and results of pertinent diagnostic tests or procedures.

Documentation supporting the medical necessity should be legible, maintained in the patient's medical record, and must be made available to the MAC upon request.

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Revision History Information

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASON(S) FOR CHANGE
12/06/2020	R1	**Under Coverage Indications, Limitations and/or Medical Necessity** verbiage in the first paragraph was revised from "This policy provides limited-coverage for molecular phenotyping of blood product antigens performed on Food and Drug Administration (FDA) approved tests in line with their FDA-approved use for patients who are required or expected to require a blood product transfusion (Red Blood cell, Platelets or White Blood cells) meeting at least one of the following criteria:" to now read "This policy provides limited coverage for molecular phenotyping of blood product antigens as part of the pre-transfusion evaluation for patients who may require or are expected to require a blood product transfusion(s) (Red Blood Cells, Platelets or Leukocytes) when at least one of the following criteria is met:". Verbiage in the fourth sentence was revised from "Blood antigen typing tests are considered germline tests and thus must comply with relevant Contractor policies regarding germline testing." to now read "Blood product molecular antigen typing tests are considered germline tests and thus must comply with relevant Medicare or Contractor policies regarding germline testing." **Under Bibliography** corrected the links in references #1 and #20.	• Provider Education/Guidance

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASON(S) FOR CHANGE
		At this time 21st Century Cures Act will apply to new and revised LCDs that restrict coverage which requires comment and notice. This revision is not a restriction to the coverage determination; and, therefore not all the fields included on the LCD are applicable as noted in this policy.	

Associated Documents

Attachments

N/A

Related Local Coverage Documents

Article(s)
A57124 - Billing and Coding: MolDX: Blood Product Molecular Antigen Typing
A58505 - Response to Comments: MolDX: Blood Product Molecular Antigen Typing
LCD(s)
DL38331 - MolDX: Erythrocyte Molecular Antigen Typing

Related National Coverage Documents

N/A

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