



July 25, 2013 (Revised)

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RE: Draft Local Coverage Determination:
Molecular Pathology Procedures for Human Leukocyte Antigen (HLA) Typing (#DL33732)

To Whom It May Concern:

Thank you for the opportunity to comment on this Draft Local Coverage Determination. We appreciate the work required to review this topic and develop a Local Coverage Determination. We do have concerns and questions which we will address in the order they appear in DL33732. We have identified the draft language being addressed in italics.

NARRATIVE:

PCR-SSP

PCR-SSP is also used to determine HLA-A, -B, -C, -DR and DQ locus types at a resolution similar to serological testing. PCR-SSP is a very rapid test that can be performed in 3-4 hours from the time a sample is received. PCR-SSP is used for typing deceased organ donors when speed is an important consideration. PCR-SSP can also be used to provide higher resolution testing and may be employed to resolve alleles.

PCR-SSP can also be used to determine DP locus types. It is defined by cellular responses and there are no serological equivalents. Serology is no longer used therefore it is not anticipated that a serologic equivalent will be developed. HLA-DP is used in transplant evaluations based on the increasing evidence of rejection based on HLA-DP.

REQUEST: Add language to include use of PCR-SSP DP locus types without reference to serologic testing.

1. Transplantation:

• Standard of care identification of determination of HLA matching for hematopoietic stem cell/bone marrow transplantation -allele-level typing will provide clinical guidance for the HLA-A,B,C Class I and DRB1 and DQB1 Class II loci in the average transplant program because it is well established that mismatches at certain HLA loci between donor-recipients are closely linked to the risk of graft versus host disease.

HLA-DPB1 and DQA1 should be included. Testing for HLA-DPB1 and DQA1 is not indicated in all donor-host testing. It can be indicated in certain cases in particular for unrelated transplantation pairs. It is necessary to go to the sequence level (graft vs host) to evaluate donors to reduce the risk of graft versus host disease. (Blood. 2013 May 30;121(22):4603-10; Transplantation. 2010 Nov 27;90(10):1117-24).

REQUEST: Add HLA-DPB1 and DQA1 to the list.

Potential marrow donors may enroll with a national registry such as the United States National Marrow Donor Program or the Canadian Blood Services registry. A national registry is maintained by the United Network for Organ Sharing, (UNOS).

UNOS does not maintain a national registry for marrow donors.

REQUEST: Delete statement on UNOS.

2. Disease Association:

• *“Standard of care testing to diagnose certain HLA related diseases/conditions when the testing is supported by the clinical literature and is informative for the direct management of a patient bearing a certain allele(s).”*

“It is not expected that more than one test would be required in a given beneficiary’s lifetime.”

While we understand the intent of this statement with respect to frequency based on medical need, the relationship of genes to linked conditions and the structure and intent of the CPT codes for testing do not make this something that can be managed easily with respect to adjudicating claims.

The CPT codes for HLA testing are not specific for one gene or even to a specific method. Each code describes a specific result, e.g. low, intermediate or high resolution, as a result of testing performed on either a ‘locus’ (AKA gene) or allele. For simple conditions with defined genetic associations, a single CPT code may be sufficient. However, some conditions and their associated genes can have hundreds of alleles and require a combination of CPT codes in multiple units to appropriately diagnose the condition.

Diagnosis	Gene/allele	CPT code to bill/#units
Ankylosing Spondylitis	HLA-B27	81374
Acute anterior uveitis	HLA-B27	81374
Birdshot retinopathy	HLA-A29	81374
Behcet’s disease	HLA-B51	81374
Psoriasis	HLA-Cw6	81374

Diagnosis	Gene/allele	CPT code to bill/#units
Celiac disease	HLA-DQ2, (DQA1*05/DQB1*0201 or 0202)	81377 (DQA1*05) 81383x2 (DQB1*0201 or 0202)
	HLA-DQ8 (DQA1*03/DQB1*0302)	81377(DQA1*03) 81383 (DQB1*0302)
Rheumatoid Arthritis	HLA-DR4	81377

Thus, with respect to this statement, the limitation on testing to once per beneficiary’s lifetime would be an inappropriate limitation.

REQUEST: Please remove this statement from the DLCD or clarify the limitations to which it should apply, i.e. to what the one/lifetime limitation will be applied: the diagnosis, the gene, the allele, or the CPT code(s) used to report the testing. Please provide instruction on how to bill for services where testing for other conditions is done under the same CPT code so that test for other conditions or other medical reasons will not be inappropriately or inadvertently denied as exceeding the lifetime limit.

“Possible covered indications when standard laboratory testing (tissue typing) not adequate...”

It is unclear what is being referred to as “other types of tissue typing”. The standard for tissue typing in the past was serology, e.g. antibody typing, ABO blood typing. However, serology has been replaced by DNA typing as the standard, the HLA typing addressed in this draft LCD. Serology is no longer performed for these purposes. We suggest that the medical necessity of the test be guided by the clinical guidelines, NIH and CDC Consensus statements or recommendations or the evidence that supports best practices. In the case where neither of these is available, we would recommend use of guidance from experts as expressed in peer reviewed articles

REQUEST: If there are other types of tissue typing to which this state is referring, we would ask that they be specified so that we can respond to the appropriateness of the testing for diagnosis/management.

If the language refers to serology, then we would request that this statement be removed or modified as noted above.

• “HLA-B*27 for the diagnosis of symptomatic patients with presumed ankylosing spondylitis or related inflammatory disease in cases where other methods of diagnosis would not be appropriate or have yielded inconclusive results (NCD 190.1)

- 1) Attributing NCD requirement to conditions not cited in the NCD.

We have reviewed NCD 190.1, created in 2003. It states that ankylosing spondylitis is covered “in cases where the methods of diagnosis would not be appropriate or have yielded inconclusive results”. It goes further and has contractors request documentation supporting the medical

necessity of the test “in all cases where ankylosing spondylitis is indicated s the reason for the test.”

The NCD does not address HLA testing for the other conditions, “or related inflammatory disease”, included in this statement in the DLCD.

REQUEST: Modify the statement to remove “or related inflammatory disease” so that it accurately reflects the statement of coverage as cited in NCD 190.1 for ankylosing spondylitis.

2) Coverage of testing for HLA-B*27

The NCD cited does not include language which would prohibit the contractor from covering other conditions for histocompatibility testing, e.g. language such as ‘only covered’, or ‘limited to the following’, When there is not a restriction or specific direction about coverage from CMS on a condition/service, the contractor has the discretion to develop a LCD on the matter.

If it is the intention of First Coast to take the position that simple conditions with defined genetic associations, testing for HLA-B*27 for any inflammatory condition has not been proven to be safe and effective and that all determinations of the medical need will be individual, then that should be a separate statement with medical evidence provided that supports that position.

In a review of the Sources of information and Basis for Decision, we do not see anything that references inflammatory conditions and/or HLA-B*27. Therefore, we do not believe First Coast has provided evidence to support a limitation or additional requirements for HLA-B*27 for inflammatory disease.

REQUEST: We would ask that First Coast develop a Draft Local Coverage Determination that addresses HLA-B*27 for inflammatory conditions, with appropriate medical evidence cited to support its position. We believe the evidence is there to support coverage of HLA-B*27 to include other disorders associated with it, such as uveitis, reactive arthritis (previously referred to as Reiter syndrome), inflammatory bowel disease, and psoriatic arthritis and welcome the opportunity to work with First Coast to develop the evidence. The safety and effectiveness of HLA testing for these conditions is well-established in the medical literature and medical practice.

In the meantime, delete the reference to inflammatory conditions. No medical evidence has been provided to support the need for such a limitation and burden on the contractor and providers to implement.

• In the work-up of certain patients with an unclear diagnosis of celiac disease and gluten hypersensitivity usually related to ambiguous standard laboratory results and/or inconsistent biopsy results (e.g., HLA-DQ2 and DQB1*02)

The question is how First Coast plans to implement this requirement. The documentation does not require documentation must be submitted.

- Should documentation be submitted at the time of claims submission?
- Will this be a post-payment action, request for document in individual cases?

REQUEST: Clarify how this will be implemented.

• *Tests considered screening in the absence of clinical signs and symptoms of disease(HLA-DQB1*06:02P as a positive/negative predictor for narcolepsy* (From the limitations section)

This is cited as an example of when a test would not be covered. Because it is not addressed anywhere else in this DLCD nor in any other First Coast LCD, we consider this to meet the criteria to be coverage determination by the contractor, which should be included in this section of the LCD and open for public comment.

The fact that there is one citation related to the topic suggests this is First Coast's intent as well.

Reference cited: Nakayama J, Miura M, Honda M, et al. Linkage of human narcolepsy with HLA association to chromosome 4p13-q21. *Genomics* 2000 Apr 1; 65(1):84-6

The classification of narcolepsy does include the HLA type, with different clinical prognosis and course associated with the different types of narcolepsy and its causes.

Nearly 98% of patients with narcolepsy test positive on sleep cataplexy for specific human leukocyte antigen (HLA) subtypes, particularly HLA-DQB1*0602. This antigen is found in just 20% of the general population. ([Narcolepsy | University of Maryland Medical Center](http://umm.edu/health/medical/reports/articles/narcolepsy#ixzz2ZoH58Sza) <http://umm.edu/health/medical/reports/articles/narcolepsy#ixzz2ZoH58Sza>)

In the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) currently being finalized, there will be 3 groups for hypersomnolence:

- 1) narcolepsy caused by hypocretin (orexin) deficiency, a disorder associated with Human Leukocyte Antigen (HLA) marker DQB1*06:02. This group is thought to be autoimmune. Almost all cases involve cataplexy.
- 2) Kleine-Levin Syndrome (KLS), and
- 3) syndromes with hypersomnolence unexplained by hypocretin abnormalities. Generally, cataplexy is not associated with this group. This is the most frequently diagnosed.

Treatment differs depending on the diagnosis. Treatment for the narcolepsy/hypocretin deficiency is well-defined and includes using sodium oxybate, stimulants and/or antidepressants as well as behavioral modifications

- Mignot, EJ. A practical guide to the therapy of narcolepsy and hypersomnia syndromes. [Neurotherapeutics](#). 2012 Oct;9(4):739-52. doi: 10.1007/s13311-012-0150-
- [Woo HI](#), [Joo EY](#), [Hong SB](#), [Lee KW](#), [Kang ES](#). Use of PCR with sequence-specific primers for high-resolution human leukocyte antigen typing of patients with narcolepsy. [Ann Lab Med](#). 2012 Jan;32(1):57-65. doi: 10.3343/alm.2012.32.1.57. Epub 2011 Dec 20.

REQUEST: We request that the First Coast's assessment of whether HLA testing in narcolepsy meets the 'reasonable and necessary' criteria be placed in this section on Diagnosis. We ask that First Coast reconsider its position and create a specific DLCD that describes the medical evidence that supports its recommendation.

3. Pharmacogenetics:

- *Standard of care testing to diagnose certain HLA related drug hypersensitivity reactions when the testing is supported by the clinical literature and is informative for the direct management of a patient bearing a certain allele(s) associated to fatal skin drug reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis).*
-

“It is not expected that more than one test would be required in a given beneficiary’s lifetime.”

See previous comments on operational issues with this requirement.

“Possible covered indications”

This does not provide significant guidance for the physician or the patient as to whether claims submitted to First Coast on half of beneficiaries will be covered for testing for the indications cited.

It is our understanding that the purpose of the DLCD is to indicate what testing for clinical conditions that would be considered to meet the ‘medical necessity’ requirement as well as those that would not.

Indications identified:

- *HLA –B*5701 when testing performed prior to the initiation of an abacavir-containing regimen in the treatment of HIV Infection.*
- *HLA-B*1502 when genotyping may be useful for risk stratification when the testing is performed prior to the initiation of carbamazepine therapy in the treatment of patients at high risk of having this allele. HLA-B*1502 occurs almost exclusively in patients with ancestry across broad areas of Asia, including South Asian Indians.*

We are in agreement with the indications cited for HLA-B*5701 and HLA-B*1502 testing.

Tests assessing the risk of allopurinol hypersensitivity reactions (HLA-B*58:01P)

We disagree with the position taken on this subject. In considering our response to this position, we looked for Medicare’s guidance on what type of information is needed to support our position. We used the section on “Evidence Supporting LCDs” (PIM 100.8 §13.7.1) as guidance.

References cited:

- Chao J and Terkeltaub R. A Critical Reappraisal of Allopurinol Dosing, Safety, and Efficacy for Hyperuricemia in Gout. *Current Rheumatology Reports* 2009, 11:135–140.
- Profaizer G. HLA Alleles and Drug Hypersensitivity Reaction. *ASHI Quarterly*. Fourth Quarter 2010, p 8-13.

Limitations and concerns identified in the 2010 newsletter article from AH have been addressed in subsequent clinical studies and analysis of the data. In Japan, a warning has been added to the allopurinol label to required testing in high risk populations. The coverage statement for carbamazepine should also be applied to allopurinol, based on the medical evidence.

We have identified more recent peer-reviewed published literature including consensus guidelines from the American College of Rheumatology which we believe reflect the current standard of practice relative to testing for allopurinol hypersensitivity reactions.

In general, if a drug has a known high risk of developing an adverse event or complication, AND the adverse events require hospitalization and pose a threat to life AND there are other treatment alternatives AND it is possible to identify who is at highest risk of developing the adverse event, then it becomes expected medical practice that such testing be performed to prevent patients at risk for an adverse event that could have been avoided.

In this case, testing for HLA-B*58:01P in those at high risk for adverse reaction (ASH) is appropriate in order to avoid putting the patient at unnecessary, known risk of developing life-threatening adverse event from the drug (the spectrum of allopurinol associated hypersensitivity reactions).

1. The relationship between allopurinol and allopurinol associated hypersensitivity reactions (ASH) such as Stevens Johnson Syndrome and TEN is established in the medical literature.
2. ASH includes Stevens-Johnson syndrome, toxic epidermal necrolysis, as well as systemic disease with a clinical constellation of features such as eosinophilia, vasculitis, rash, and major end-organ disease.
 - The estimated incidence of AHS is ~1:1,000 in the US.
 - The potential for hospitalization and severe morbidity and the reported mortality rate is estimated at 5% for SJS and 30-50% for TEN. (Somkura), the American College of Rheumatology guideline estimates the mortality at about 20–25%.
3. The link between allopurinol ASH and HLA-B*5801 has been established (Chung 2007, Chung 2012)
 - Somkura et al performed a systematic review and concluded that there is a “strong and significant association between HLA-B*5801 and allopurinol-induced SJS/TEN.
 - The risk of developing SJS/TEN among those allopurinol users with HLA-B*5801 is significantly increased by 80-97 times compared to those without the gene. (Somkura 2011)
 - While it is a multifactorial condition, Hun et al concluded that it places a significant role in SIS/TEN occurrence. (Hung)
 - Tassaneehakul reported a positive predictive value of 1.52% and a negative value of 100% for screening Thai individuals for risk of allopurinol ASH. All those with ASH carried the allele; whereas only 13% of controls had the alleles. Sensitivity was 100% and specificity 87% for predicting allopurinol-induced SJS/TEN.
4. The relationship between allopurinol and SJS/TEN compared to the relationship between carbamazepine and SJS/TEN (From Somkura):
 - “It has a more pronounced effect on allopurinol-induced SJS/TEN compared to those found in the case of HLA-B*1502 and CBZ induced SJS/TEN. In the latter case, the incidence may be associated with other contributing factors (i.e. other genes) to trigger the adverse drug reaction,”
 - “The relationship between HLA-B*5801 and allopurinol-induced SJS/TEN has been validated in different populations and may be a universal phenomenon since it has been identified in all Chinese, Japanese, Thai, Korean and European patients.”
 - The risk for SCARS was higher for those treated with allopurinol than for those treated with carbamazepine as reported by Mockenhaupt.

5. Those at higher risk of developing a reaction can be identified: (Jung 2011)
- “There is a stronger association between the HLA-B*5801 and allopurinol induced SCARS in races with a higher frequency of HLA-B*5801: the frequency in the Korean population is 12.2%, relative high and 92.3% of patients with allopurinol induces SCARS were positive for HLA-B*5801.”
 - Renal insufficiency is a risk factor but the incidence of SCARS increases to 18% in those positive for HLA-B*5801, which was 45 times higher than the general population.(Therefore, HLA-B*5801 allele screening may be considered in patients who will be treated with allopurinol.

Specialty Recommendations: 2012 American College of Rheumatology Guidelines for Management of Gout

In the core recommendations in the use of allopurilon, (Table 3) it states:

“Prior to initiation, consider HLA–B*5801 in selected patients, specifically in subpopulations at higher risk for severe allopurinol hypersensitivity reaction (e.g., Koreans with stage 3 or worse CKD, and Han Chinese and Thai irrespective of renal function; evidence A) “

In their discussion, they state

“prior to initiation of allopurinol, HLA–B*5801 testing should be considered in select patient subpopulations at an elevated risk for AHS (evidence A). Those with HLA–B*5801 and of Korean descent with stage 3 or worse CKD (HLA–B*5801 allele frequency !12%), or of Han Chinese or Thai extraction irrespective of renal function (HLA–B*5801 allele frequency !6–8%), have been highlighted in the literature as prime examples of subjects at high risk for AHS, marked by HLA–B*5801 hazard ratios of several hundred (59–61). Such high-risk individuals were recommended to be prescribed an alternative to allopurinol if HLA–B*5801 positive (evidence A). The TFP recommended that the HLA–B*5801 screening be done by the rapid, widely available polymerase chain reaction (PCR)–based approach (evidence A) that, in only ~10% of tests, requires more cumbersome follow-up HLA–B*5801 sequencing for inconclusive results. Significantly, the TFP did not recommend universal HLA–B*5801 allopurinol screening.”

Phillips provides valuable comparison of numbers needed to test (NNT) to prevent 1 case of specific drug reactions for abacavir, allopurinol and carbamazepine. Phillips 2011. Figure 2, page S63.

Drug	HLA Allele	HLA Carriage Rate	Prevalence of diagnosis	Negative Predictive Value	Positive Predictive Value	NNT to prevent one case
Abacavir	B*5701	6-8% Caucasian, <1% African/Asian, 2.5% African American	8% (includes 3% true HSR and 2-7% false positive diagnosis)	100% for patch test confirmed	55%	13
Allopurinol	B*5801	9-11% Han Chinese 1-6% Caucasian	1/250-1/1000	100% in Han Chinese*	3%	250
Carbamazepine	B*1502	10-15% Han Chinese, 0.1% Caucasian	<1-6/1000	100% in Han Chinese	3%	1000

*100% in Thai, Tassaneehakul 2009.

REQUEST: We believe the medical evidence supports the acceptance and importance of HLA-B*5801 prior to the initiation of allopurinol therapy in treatment of patients at high risk for severe hypersensitivity reaction, e.g. Koreans with stage 3 or worse CKD and all those of Han Chinese and Thai descent a under tests/conditions covered for pharmacogenomics. We believe it should be covered.

4. Identification of HLA compatible platelets for transfusion when standard typing is not adequate.

In the past, the standard for evaluating compatible platelets was serology. However, molecular testing has replaced serology as the standard typing. It is used in “preparing blood platelet transfusions, (particularly where multiple infusions are involved)”. (NCD §190.1)

REQUEST: If there are other types of tissue typing that is histocompatibility compatibility testing to which this state is referring, we would ask that they be specified so that we can respond to the appropriateness of the testing for diagnosis/management.

If the language refers to serology, then we would request that this statement be removed or modified as noted above. Otherwise, we would request that HLA testing for platelet transfusion be covered when medically indicated. We have included our recommendations for CPT codes and ICD-9 diagnosis codes in subsequent section.

LIMITATIONS

“the following will be considered noncovered due to statutory exclusion, lack of Medicare benefit category, or not reasonable, or necessary as applicable:

We would disagree with this statement because it is not consistent with the language of the law and Medicare instructions for contractors as provided in the manuals. It is true that some applications would not be covered by Medicare but we disagree on the suggested reasons.

There is a benefit category for molecular pathology testing: ‘medical and other health services’ in section 1832(a)(1); it specifies physicians services [1832(a)(B)(I)]. “Medical and other health services” are defined in 1861(s); they include physician services [1861 (q)] and diagnostic services (1861(s)(2)(C)).

For a statutory exclusion, per PIM, applies if “the service/item is statutorily excluded by other than §1862(a)(1) of the Act;” (PIM 100-8, §3.6.2.5) The critical language is “other than §1862(a)(1) of the Act”. Molecular pathology is NOT one of the items specifically cited as excluded by the statute in [1862(a)(2) through (25)]. Therefore, a denial would not be for reasons of statutory exclusion.

That leaves the last main reasons for denial. As per PIM 100.8, §3.6.2.5, a service/item can be denied because it is “not reasonable and necessary as defined under §1862(a)(1) of the Act”. The limitations cited would be examples that fit this statement. And we agree that some applications of molecular pathology procedures would not meet the criteria for coverage based on these requirements and denied as ‘not medically necessary’.

We are addressing this in some detail because the reason for not covering a service is relevant to liability issues with the patient/beneficiary and to the obligation of the contractor with respect to development of Local Coverage Determinations. It also clarifies for the beneficiary and the physician where their disagreement with a noncoverage decision resides and with who it needs to be addressed, e.g. the contractor or Congress.

REQUEST: We request that you remove the reference to ‘statutory exclusion’ and ‘lack of Medicare benefit category ‘in reference to the subject of this DLCD (HLA testing) and the reasons cited for denying coverage.

Tests assessing the risk of allopurinol hypersensitivity reactions (HLA-B*58:01P)

This section describes, in basic terms, the kind of things that cannot be covered based on the Medicare law and regulations. A statement about testing one specific gene/allele for one type of hypersensitivity does not seem to belong in the section under general limitations of the Medicare program.

It appears to be a conclusion about testing for a specific condition, which should be based on a review of the evidence (medical literature) and would be presented as local coverage determination. It would fit in the section on Pharmacogenomics with the statements about testing for other potential drug reactions, carbamazepine and abacavir. We have addressed it there.

Tests to measure the quality of a process or those used for Quality Control/Quality Assurance (QC/QA), i.e., tests performed to ensure a tissue specimen matches the patient

There are 2 ways that tests are performed to ensure a tissue specimen matches the patient. The most common one is part of the laboratory Quality Control/Quality Assurance program as part of CLIA. These tests are performed to ensure quality of lab procedures to protect the safety of the patient for all tests provided. These tests are part of a real time check of test quality which monitors the performer, the test & lab’s environment focusing on test method validation, calibration, instruments, reagents & suppliers. (Yost June 2008). Its purpose is to monitor test systems and quality, identify and correct problems effectively. They are not associated with testing and care associated with a specific patient, nor are the results applied to the specific patient. They would not meet the requirement that they are being done to diagnose or treatment a specific patient’s illness or injury. It is understood that these tests are not covered by Medicare.

There are circumstances in which clinical protocol requires verification testing prior to the release of results for use in the patient. The tests are being performed for the individual patient and will be used in treating their illness. Because of the high risk of life-threatening consequence associated with the use of false results, it is a standard of care for tests being performed to determine if the donor is a match to perform the test on 2 different samples, e.g. for bone marrow transplant. This is required to verify that the donor is a correct match so that the wrong donor is not chosen. The National Marrow Donor Program (NMDP) standard 9.1370 requires that this procedure be followed in transplants (“Transplant Center shall verify the HLA typing of the donor, in accordance with NMDP policy, using a new sample.”) The same is required of autologous and allogeneic cord blood products, American Association of Blood Banks (AAABB reference standard 5.16B.5.A) Foundation U Accreditation for Cellular Therapy (FACT) has a similar standard. These tests are considered to be an integral, essential part of the process of testing tissue and verifying their safe and appropriate use for medical purposes.

REQUEST: Clarify that testing in accordance with NMDP, AABB and FACT are recognized as integral to the process of correctly matching donor-host for medical use for an individual patient and are considered to meet the ‘reasonable and necessary’ criteria for coverage.

.....
Tests considered screening in the absence of clinical signs and symptoms of disease, Tests to determine risk for developing a disease or condition

While we understand this is limited by the Medicare law, in the field of genetics, testing family members for genetic conditions is an important aspect of population health and prevention. We would be remiss if we did not restate the clinical value of this testing in that it provides information that can alert the patient and physician be alert to the need to evaluate new symptoms considered to be phenotypic presentation of the condition.

Tests considered screening in the absence of clinical signs and symptoms of disease (e.g., HLA-DQB1*06:02P as a positive/negative predictor for narcolepsy), and

This statement appears to combine 2 points. The first relates the limitations on Medicare coverage in general. The second is an example of a condition/gene/allele that meets this limitation is a local coverage determination.

- 1) A better example within this field of medicine would be HLA-DQ testing in an asymptomatic beneficiary who has a family member with who has tested HLA-DQ2 or DQ8 positive for celiac disease.
- 2) Inclusion of HLA-DQB1*06:02P as a positive/negative predictor for narcolepsy in the list as an example of a limitation

The coverage HLA-DQB1*06:02P for narcolepsy is not addressed as a LCD in this draft or in any other First Coast LCD that we have identified. Therefore, if it is the intent of First Coast to state that it has determined that HLA-DQB1*06:02P for narcolepsy does not meet the reasonable and necessary criteria for coverage because the only use supported in the medical literature is when it is done in asymptomatic patients, that should be addressed separate from this list. That is an LCD decision. It should be included in the section on “Diagnoses” so that it is clear First Coast is presenting this as part of the LCD process and it is open for public comment.

We have addressed it in the section on Diagnosis for this reason.

REQUEST: Delete “HLA-DQB1*06:02P as a positive/negative predictor for narcolepsy” as an example of the use of tests that demonstrate this limitation. Replace it with a more appropriate, topic related example.

Tests that confirm a diagnosis or known information

We would qualify this. If it is part of the criteria for diagnosing a condition, as defined by national guidelines or published peer-reviewed articles, the testing should also be covered.

Diagnostic testing is used for a number of recognized purposes in the practice of medicine:

- To confirm a suspected diagnosis
- To provide additional information about the physiologic/structural conditions associated with the signs/symptoms and provide additional guidance on the cause.

We understand that these must be medically necessary and appropriate for the patient and condition. However, we would like to emphasize that molecular pathology testing should be held to the same standard, and not more rigorous or limited, as other diagnostic tests covered when used to confirm suspected medical diagnoses– like chest x-rays, CT, MRIs, PET scans, EKG, and other blood tests.

Standards of practice have been developed for diagnosing many conditions and include genetic testing requirements and recommendations.

- i. Cases in which the diagnosis is made on the basis of phenotype, presentation, and other lab tests (genetic testing is not needed).
- ii. In most cases, even if the clinical presentation is consistent with a diagnosis of a genetically-based condition, the definitive diagnosis cannot be made until the genetic testing confirms it. This is similar to the use of diagnostics to confirm a presumptive diagnosis made on the basis of history, symptoms, and examination, such as glucose testing to confirm the suspected diagnosis of diabetes or an x-ray to confirm the suspected diagnosis of fracture of a bone.

It would be medically inappropriate to give the diagnosis of a genetically-based condition without performing the testing that would confirm the genetic evidence, especially if they are part of the clinical guidelines for that condition. This is especially true when it is a hereditary mutation that would have implications for reproduction and family member risk.

Proposed/Draft Process Information

the J9-MAC will; Request documentation supporting the medical necessity of the test from the physician in all cases where ankylosing spondylitis is indicated as the reason for the test.”

Our question is how this will be implemented. The question is how First Coast plans to implement this requirement. The documentation does not require documentation must be submitted.

- Should documentation be submitted at the time of claims submission?
- Will this be a post-payment action, request for document in individual cases?

REQUEST: Clarify how this will be implemented.

When the documentation does not meet the criteria for the service rendered or the documentation does not establish the medical necessity for the services, such services will be denied as not reasonable and necessary under Section 1862(a)(1)(A) of the Social Security Act.

As per PIM 100.8, §3.6.2.5, a service/item can be denied because it is “not reasonable and necessary as defined under §1862(a)(1) of the Act”.

Section 1862(a)(1)(**A**) only addresses the nonpayment – “that no Medicare payment shall be made for items and services which are not reasonable and necessary for the diagnosis or treatment of illness or injury...”

There are other reasons recognized in the law and described by Medicare for why a service could be denied as not medically necessary, e.g. frequency in excess of medical need or exceeding a once in a lifetime limit on coverage. These are listed under Section 1862(a)(1)(A) through (P).

REQUEST: Delete the “(A)” in the justification for denial to be consistent with the PIM instructions: §1862(a)(1) and to include all the reasons for a denial as not reasonable and necessary.

CPT/HCPCS Codes and ICD-0 Codes that support medical necessity

Group 2 Paragraph. Medicare is establishing the following limited coverage for CPT code 81381 for services meeting coverage criteria for HLA-B*1502 testing.

Group 2 Codes:

[780.31 - 780.39 opens in new window](#) FEBRILE CONVULSIONS (SIMPLE), UNSPECIFIED - OTHER CONVULSIONS

V58.69* LONG-TERM (CURRENT) USE OF OTHER MEDICATIONS

Group 2 Medical Necessity ICD-9 Codes Asterisk Explanation: ** V58.69 must also be reported with each primary diagnosis code. This is a dual diagnosis requirement.

The statement is that this policy would establish “limited coverage” for CPT code 81381 for HLA-B*1502 testing, however, this code HLA-B*1502 is not the only gene/allele combination for which this code is appropriately billed. In Group 4, it is the same code used to report HLA-B*5701. It is also used for transplant evaluation and is included Group 1 codes for Group 1 ICD-9 codes for transplantation.

REQUEST: Will the coverage of this CPT code be limited to the ICD9 codes cited in Group 1, Group 2 and Group 4 and all other diagnoses will be denied as ‘not medically necessary’? Please clarify.

Group 3 Codes: limited coverage for 81383. Associated with ICD-9 579.0 Celiac Disease.

We have a number of concerns.

1) One CPT code identified with Celiac disease. There are potentially 6 gene/allele associated with 97% of celiac patients: HLA-DQ2 (DQA1*05/DQB1*02) or HLA-DQ8 ((DQA1*03/DQB1*0302) or both”. The diagnosis requires testing of a minimum of 3 gene/alleles. Which CPT codes billed would depend on the level of resolution performed by the individual lab.

The following tables provides an example of how 3 different labs test for celiac disease and would code their services.

CPT Code	Dx covered	Code Descriptor	Testing/Reporting Options for Celiac Disease		
81376	Group 1	HLA Class II typing, low resolution (eg, antigen equivalents); one locus (eg, HLA-DRB1 /3/4/5, -DQB1, -DQA1, -DPB1, or -DPA1), each	DQA1		
81377	Group 1	one antigen equivalent, each		X3 DQA1*05 DQB1*02 DQA1*03	
81382	Group 1	HLA Class II typing, high resolution (ie, alleles or allele groups); one locus (eg, HLA-DRB1, -DRB3, -DRB4, -DRB5, -DQB1, -DQA1, -DPB1, or -DPA1), each	DQB1		testing of 2 Class II loci: all HLA-DQA1* all DQB1*
81383	Group 1; limited coverage for 579. celiac	one allele or allele group (eg, HLA-DQB1*06:02P), each		DQB1*03:02	

REQUEST: Recognize the following CPT codes for testing for celiac disease: 81376, 81377, 81382 and 81383.

2) The ICD-9 used to report testing for the condition.

If the test is being performed to confirm a diagnosis, then it is more likely the diagnosis will be related to the patient’s symptoms that suggest celiac disease as the problem. Other diagnoses that could be used would be diarrhea, constipation, IBS.

REQUEST: expand the ICD-9 list to include symptoms associated with celiac disease: bloating, diarrhea, constipation, malabsorption

3) Limitation on covering CPT code 81383 to testing for celiac disease and transplantation testing Group 1 and Group 3 (see table in 1).

There are 2 sets of diagnoses codes for which the CPT code would be covered. If the CPT code is only approved for the diagnoses codes cited in this draft LCD, testing for other conditions that would be reported under this code will be inappropriately denied. Our question is whether that is the intent?

If it is not the intent, how should claims for testing for other conditions which would be appropriately coded under CPT code 81383 be submitted?

REQUEST: Provide additional guidance on status of use of this CPT Code for testing when used for other conditions.

We respectfully ask that you consider our comments which were prepared by a consortium of members of the Association for Molecular Pathology, the ASHI (American Society for Histocompatibility and Immunogenetics) the American College of Medical Genetics, and Laboratory directors, staff and consultants who provide service to Medicare beneficiaries covered by First Coast. We are happy to be of assistance in providing additional clinical information, references, contacts, or whatever is needed to assist you with this DLCD. Please direct your correspondence to Phillip Ruiz, MD, PhD, University of Miami, Miller School of Medicine, Miami, FL (pruiz@med.miami.edu).

Sincerely,

A handwritten signature in black ink, appearing to read "Jennifer L. Hunt". The signature is fluid and cursive, with the first name being the most prominent.

Jennifer L. Hunt, MD, MEd
President

Medicare references

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