Protocol

Genetic Testing for Human Leukocyte Genes (HLA)

Medical Benefit		**Effective Date**: 01/01/17	**Next Review Date**: 11/20
Preauthorization	Yes	**Review Dates**: 11/16, 11/17, 11/18, 11/19	

Preauthorization is required for ankylosing spondylosis and carbamazepine testing.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

DESCRIPTION

The human leukocyte antigen (HLA) system is a gene complex encoding the major histocompatibility complex (MHC) proteins in humans. The role of these cell-surface proteins involves regulating the immune system in humans. Different classes of these genes perform different functions and are associated with disease defense, organ transplant rejection, and the ability to defend against cancers while mutations in HLA are suspected in some autoimmune diseases.

POLICY

SOLID ORGAN TRANSPLANTATION

Human Leukocyte Genes (HLA) testing may be considered **medically necessary f**or High Resolution Class 1-DR HLA matching for solid organ transplant (recipient) for kidney, heart, lung and other elective solid organ transplants.

Screening for the presence of HLA antibodies using flow cytometry may be **medically necessary** for solid organ transplants.

HLA testing is **not medically necessary** for High Resolution Class 1-DR HLA matching for corneal transplants.

BONE MARROW TRANSPLANTATION/HEMATOPOIETIC CELL TRANSPLANTATION

HLA testing may be considered **medically necessary** for high resolution HLA allele-level typing for the HLA-A, B, C Class I and DRB1, DQB1, DPB1, and DQA1 Class II loci in allogeneic bone marrow transplantation and hematopoietic cell transplantation.

High resolution HLA allele-level typing for the HLA-A, B, C Class I and DRB1, DQB1, DPB1, and DQA1 Class II loci for autologous bone marrow transplantation is **not medically necessary**.

DISEASE ASSOCIATION

Testing for HLA-B*27 may be considered **medically necessary** to confirm the diagnosis of presumed ankylosing spondylitis or related inflammatory disease, in symptomatic individuals who have had comprehensive clinical and biochemical studies, seronegative spondylopathy, ulcerative colitis related spondylopathy, reactive arthritis (Reiter's Syndrome), iritis or uveitis.

Testing for iHLA-DQ2 by HLA-DQB1*02 and of DQ8 by HLA-DQB1*0302 may be considered **medically necessary** for suspected celiac disease and gluten hypersensitivity in individuals who have not responded to a gluten-free diet; AND, for individuals with borderline or ambiguous celiac-associated antibody results or small-bowel biopsy results or unclear diagnosis.

Testing for HLA-DQ6 may be considered **medically necessary** for suspected narcolepsy.

Human Leukocyte Genes (HLA) testing for disease association is **not medically necessary** in the following situations:

- HLA-B*27 for the diagnosis of symptomatic members with presumed ankylosing spondylitis or related inflammatory disease who are rheumatoid factor positive or ANA positive
- HLA-DQ2 by HLA-DQB1*02 and of DQ8 by HLA-DQB1*0302 testing for celiac disease and gluten hypersensitivity in members for ANY of the following
    - Symptomatic members with an unequivocal diagnosis by small bowel biopsy and serology; OR
    - The pre-symptomatic evaluation of family members of members with confirmed celiac disease; OR
    - The screening of healthy members with no family history of celiac disease.

Testing for HLA-B*27 testing for ankylosing spondylitis or related inflammatory disease is considered **investigational** in all other situations.

HLA-DQ2 and HLA-DQ8 testing for celiac disease is considered **investigational** in all other situations.

PHARMOCOGENETICS

Testing for HLA-B*5701 may be considered **medically necessary** when testing is performed prior to the initiation of an abacavir-containing regime in the treatment of HIV Infection.

Testing for HLA-B*1502 genotyping may be considered **medically necessary** for risk stratification when the testing is performed prior to the initiation of carbamazepine therapy for members with Asian ancestry.

PLATELET ADMINISTRATION

HLA testing for the identification of HLA compatible platelets for transfusion may be considered **medically necessary** when standard typing is not adequate.

BACKGROUND

SOLID ORGAN TRANSPLANTATION

Since the ability to type HLA was recognized, the matching of organ and tissue donors with intended recipients has had a significant positive impact on the outcome following organ transplants. The most notable impact is seen in transplantation of kidney or bone marrow. More variables influence the outcome for transplantation of hearts and lungs including ischemia, availability of donors and clinical needs of the recipient. HLA typing has little influence in corneal grafts except when being transplanted into a vascularized bed.

BONE MARROW TRANSPLANTATION/HEMATOPOIETIC CELL TRANSPLANTATION

Hematopoietic cell transplantation (HCT) refers to a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of cytotoxic drugs with or without whole body radiotherapy. HCT is an established treatment for certain hematologic malignancies.

ANKYLOSING SPONDYLOSIS

Ankylosing spondylitis (AS) is a chronic, systemic, inflammatory disease that affects primarily the sacroiliac joints

and spine. The earliest and most significant complaint is often low back pain, which may also be felt in the buttock and may eventually lead to limited spinal mobility. Diagnosis is accomplished through evaluation of symptoms, physical exam and imaging. Treatment centers around lifestyle changes, symptomatic relief through the use of physical therapy and exercise, patient education and NSAIDS. At times, joint replacement may be necessary to alleviate the damage with the most common procedure being a total hip replacement.

The cause of ankylosing spondylosis is unclear and there is no curative treatment. There is strong inference for a genetic component. The HLA B27 gene is common finding and significantly increases an individual's risk of developing this disease although this finding does not correlate inevitably with an eventual diagnosis. Strong familial associations have also been recognized.

CELIAC DISEASE

Celiac Disease (CD), also referred to as celiac sprue or gluten-sensitive enteropathy, is a relatively common disorder with variable clinical expression. It is characterized by inflammation of the small intestine resulting from an immunologic intolerance to gluten (i.e., proteins derived from wheat, barley, and rye). The symptoms of the disease are markedly variable and can be broadly subdivided into intestinal and extraintestinal manifestations; the latter is thought to be related to nutrient malabsorption. Many of the symptoms of CD (e.g., diarrhea, abdominal pain, weight loss) are nonspecific and are often overlooked. In addition, the disease may develop at any time in life, from infancy to very old age.

CD is associated with the human leukocyte antigen (HLA). Approximately 90% to 95% of patients with CD carry the HLA-DQ2 allele, and the remaining 5% to 10% carry the HLA-DQ8 allele. However, not all people with one of these two alleles will develop CD. A positive biopsy result is considered the criterion standard for diagnosis.

Population-based screening surveys suggest a prevalence of one in 250 to 500 in most countries, including the United States.

NARCOLEPSY

Narcolepsy is defined as a sleep disorder that is characterized by disruption of a normal sleep-wake cycle, resulting in excessive daytime sleepiness. Other recognized symptoms include cataplexy, hallucinations and sleep paralysis. The disorder is rare and the same symptoms may appear in other disorders sometimes delaying diagnosis or causing other conditions to be explored including learning problems or seizure disorders.

There is no curative treatment and intervention is based on presenting symptoms and their severity. Lifestyle changes including structured sleep schedules, adequate exercise and controlled caffeine intake for example along with medications to enhance wakefulness or sleep states may improve quality of life.

Changes in several genes have been identified as posing increased risk for narcolepsy. It is theorized that environmental factors play a role in development of this condition as well. A small percentage of cases of narcolepsy occur as part of family clusters which do not represent a clear pattern of inheritance.

HLA-DQ6 variations have been strongly associated with narcolepsy, although the exact mechanism by which the risk of developing the disorder is increased is unknown.

ABACAVIR

Abacavir is a Nucleoside Reverse Transcriptase Inhibitor which is approved by the U.S. Food and Drug Administration for treatment of HIV. Among the life threating side effects which can occur with this medication are lactic acidosis and liver disease. When a hypersensitivity reaction is recognized, abacavir is discontinued immediately as symptoms will worsen with continued use and will recede rapidly if discontinued. Symptoms may include fever, rash, constitutional symptoms, gastrointestinal tract symptoms, and respiratory symptoms.

There is a strong correlation between patients who develop a hypersensitivity reaction and patients who have the HLA-B*5701 allele.

CARBAMAZEPINE

Carbamazepine in an anticonvulsant used primarily to treat seizures and it is used to relieve certain types of pain such as trigeminal neuralgia and diabetic neuropathy. It may also be used in mental health conditions such as bipolar disorder.

Genotyping for the HLA-B*1502 allelic variant in patients of Asian ancestry, prior to considering drug treatment with carbamazepine due to risks of severe dermatologic reactions, is recommended by the U.S. Food and Drug Administration labeling for carbamazepine. Serious dermatologic reactions, including sometimes fatal dermatologic reactions (including toxic epidermal necrolysis [TEN] and Stevens-Johnson Syndrome[SJS]) may occur in individuals with the HLA-B*1502 allele. HLA-B*1502 is found almost exclusively in patients with ancestry across broad areas of Asia. FDA Labeling on carbamazepine products contains the warning "patients with ancestry in genetically at-risk populations should be screened for the presence of HLA-B*1502 prior to initiating treatment with carbamazepine. Patients testing positive for the allele should not be treated with carbamazepine unless the benefit clearly outweighs the risk."

PLATELET TRANSFUSION

Patients who rely on platelets transfusion to manage disease (i.e., acute myeloid leukemia, thrombocytopenia) sometimes develop platelet refractoriness so that response to transfusion therapy is inadequate. In these situations HLA typing has proven effective as an intervention to provide improved outcomes.

REGULATORY STATUS

HLA typing is offered by several laboratories.

RELATED PROTOCOLS

Allogeneic Hematopoietic Cell Transplantation for Genetic Diseases and Acquired Anemias

Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms

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Services that are the subject of a clinical trial do not meet our Technology Assessment and Medically Necessary Services Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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