Medical Policy

Laboratory Testing for HIV Tropism

Policy Number: 008
BCBSA Reference Number: 2.04.49
NCD/LCD: N/A

Related Policies
None

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity
Medicare HMO BlueSM and Medicare PPO BlueSM Members

HIV tropism testing with either the phenotypic assay or V3 population genotyping may be **MEDICALLY NECESSARY** for selecting patients for treatment with HIV co-receptor antagonists such as maraviroc when there is an immediate plan to prescribe a coreceptor antagonist.

HIV tropism testing without immediate plans to prescribe HIV co-receptor antagonists such as maraviroc is **NOT MEDICALLY NECESSARY**.

Repeat HIV tropism testing during co-receptor antagonist treatment or after failure with co-receptor antagonists is **INVESTIGATIONAL**.

HIV tropism testing to predict disease progression (irrespective of co-receptor antagonist treatment) is **INVESTIGATIONAL**.

Prior Authorization Information
Pre-service approval is required for all inpatient services for all products. See below for situations where prior authorization may be required or may not be required for outpatient services.

Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.
N/A indicates that this service is primarily performed in an inpatient setting.

<table>
<thead>
<tr>
<th>Outpatient</th>
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<tbody>
<tr>
<td>Commercial Managed Care (HMO and POS)</td>
<td>No</td>
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<tr>
<td>Commercial PPO and Indemnity</td>
<td>No</td>
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</tbody>
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CPT Codes / HCPCS Codes / ICD Codes
The following codes are included below for informational purposes. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

CPT Codes
There is no specific CPT code for this service.

Description
HIV-1, which causes AIDS, uses coreceptor proteins (either CCR5 or CXCR4) on the surface of target cells to enter and infect the cells. The most commonly transmitted strains of HIV-1 bind to CCR5 and are said to have “tropism” for CCR5-expressing cells. Dual or mixed (D/M) tropic viruses can bind to either receptor type. It is estimated that around 85% of treatment-naive patients harbor CCR5-tropic virus only, around 15% harbor D/M virus, and less than 1% are infected with CXCR4-tropic virus alone. CXCR4-tropic virus is associated with immunosuppression and later stages of disease. Coreceptor antagonists have been designed to interfere with the interaction between HIV-1 and its coreceptors.

HIV Coreceptor Antagonists
Maraviroc (Selzentry™, Pfizer) is the first coreceptor antagonist to be approved by FDA. Maraviroc is a selective, slowly reversible, small-molecule antagonist of the interaction between human cell surface CCR5 and HIV-1 gp120, also necessary for HIV-1 cell infection. Blocking this interaction prevents CCR5-tropic HIV-1 entry into cells. However, CXCR4-tropic HIV-1 entry is not prevented. According to the drug’s original label, maraviroc, in combination with other antiretroviral agents, is indicated for adult patients who are infected with only CCR5-tropic detectable HIV-1, who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents.1

The currently approved maraviroc label indicates that maraviroc is indicated for combination antiretroviral treatment for adults infected with only CCR5-tropic HIV-1, without discussion of the presence of viral replication.2 The FDA-approved full prescribing information for the drug states: “Tropism testing must be conducted on a current sample with a highly sensitive tropism assay that has demonstrated the ability to identify patients appropriate for use of SELZENTRY.” This is because efficacy was not demonstrated in a phase 2 study of maraviroc in patients with D/M or CXCR4-tropic HIV-1. Due to potential adverse effects (hepatic and cardiac toxicity), maraviroc should only be used in indicated patients.

Other HIV coreceptor antagonists are in the drug development pipeline. Cenicriviroc (Tobira Therapeutics) is a small-molecule antagonist of both CCR5 and CCR2, a receptor involved in a number of inflammatory diseases, that is currently being investigated for treatment of CCR5-tropic HIV.3 In January 2015, cenicriviroc was granted fast track designation by FDA for the treatment of nonalcoholic steatohepatitis in patients with liver fibrosis, but the drug does not yet have FDA approval.

HIV Tropism Testing
HIV tropism testing is available by either phenotypic or genotypic methods. Tropism testing with a phenotypic assay, a cellular-based assay that functionally determines tropism, is available with the enhanced sensitivity TrofileTM assay (Monogram Biosciences, South San Francisco, CA) assay (ESTA).

This phenotypic assay uses virus stocks pseudotyped with envelope sequences derived from patient plasma to infect cell lines engineered to express CCR5 or CXCR4 HIV-2 coreceptors. Genotypic tropism testing is based on sequencing the third variable (V3) loop of the HIV glycoprotein 120 gene, because the
V3 loop interacts with the HIV coreceptor, and mutations in V3 are associated with measurable changes in HIV tropism. Tropism assignment is derived from the sequence data using a bioinformatic algorithm such as geno2pheno (G2P). In the United States, the only commercially available genotypic HIV coreceptor tropism assay is available from Quest Diagnostics, which uses triplicate population sequencing with reflex to ultradeep sequencing if only CCR5-tropic virus is detected. Quest Diagnostics also offers a proviral DNA tropism test (Trofile DNA) which sequences the tropism of HIV-1 DNA that has integrated into the host genome of infected T-lymphocytes via triplicate population sequencing, without the use of ultradeep sequencing.

**Summary**

HIV tropism testing can determine the predominant coreceptor protein used by HIV to infect target cells. Tropism testing can help select patients for treatment with HIV coreceptor antagonists, such as maraviroc, which block specific coreceptor proteins.

Based on the evidence from the clinical studies used for U.S. Food and Drug Administration (FDA) approval, and the labeled requirement for tropism testing immediately before initiating a course of maraviroc, HIV tropism testing using the enhanced sensitivity version of the phenotypic Trofile assay is considered medically necessary for both treatment-experienced and treatment-naive patients who are being considered for immediate treatment with maraviroc.

The evidence comparing HIV V3 population genotyping to original Trofile and enhanced sensitivity Trofile assay (ESTA), using maraviroc response as the reference for all assays, strongly suggests that genotyping is equivalent to Trofile assays in selecting patients likely to respond to maraviroc, the outcomes of interest. Studies evaluating genotyping and using paired ESTA results for reference suggest that genotyping may be somewhat less sensitive for detecting CXCR4-tropic samples, but these studies were smaller, and most did not test in triplicate. V3 ultra-deep sequencing methods appear to have greater sensitivity in identifying CXCR4-tropic viruses, and therefore are likely to identify additional patients with HIV tropism who are negative on standard sequencing. Based largely on the maraviroc response results, HIV V3 population genotyping is considered medically necessary for patients considering immediate maraviroc treatment.

Either phenotyping or genotyping may be used to determine tropism when considering maraviroc treatment; both are not required.

Currently, patient management decisions are based on monitoring of CD4 cell counts and HIV plasma viral load. Studies would be needed to support improved outcomes with additional tropism monitoring during treatment. Pending such studies, tropism testing during treatment with coreceptor antagonists is investigational. In addition, data are not available to support the use of phenotypic tropism testing to predict prognosis, or to determine tropism in advance of a possible need for a regimen change to a coreceptor antagonist at a later date; accordingly, these indications are also investigational.

**Policy History**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>8/2015</td>
<td>BCBSA National medical policy review. Policy statement changed to be consistent with FDA prescribing information for maraviroc. Effective 8/1/2015.</td>
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<tr>
<td>1/2015</td>
<td>BCBSA National medical policy review. Policy statement amended with “either” before second two conditions to clarify that patients do not have to meet both criteria to undergo tropism testing. Effective 1/1/2015.</td>
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<tr>
<td>5/2013</td>
<td>New references from BCBSA National medical policy.</td>
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<tr>
<td>2/2013</td>
<td>BCBSA National medical policy review.</td>
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<td>Date</td>
<td>Details</td>
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<tr>
<td>8/2010</td>
<td>Medical policy ICD 10 remediation: Formatting, editing and coding updates. No changes to policy statements.</td>
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Information Pertaining to All Blue Cross Blue Shield Medical Policies
Click on any of the following terms to access the relevant information:
- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

References
3. Efficacy, Safety, and Tolerability of Cenicriviroc (CVC) in Combination With Truvada or Sustiva Plus Truvada in HIV 1-infected, Antiretroviral Treatment-naïve, Adult Patients Infected With Only CCR5-tropic Virus. 2013;


