Laboratory Testing for HIV Tropism

Preauthorization is not required.

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

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.

Summary of Evidence

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

HIV tropism testing (see Policy Guidelines for testing methods) may be considered **medically necessary** for selecting patients for treatment with HIV co-receptor antagonists such as maraviroc when there is an immediate plan to prescribe a co-receptor 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**.

Policy Guidelines

Testing should be conducted immediately before intended prescribed use of maraviroc to obtain the most accurate prediction of tropism at the start of treatment.

Either phenotypic or V3 population genotypic testing may be used to determine HIV tropism; both are not necessary.

V3 population genotypic testing may be conducted by either standard V3 sequencing via Sanger methods (amplification and population sequence analysis of patient-derived V3 region) OR V3 deep sequencing methods (synonyms: ultra-deep sequencing; pyrosequencing; next-generation sequencing). In the U.S., the only currently commercially available plasma HIV DNA coreceptor genotypic test (requires HIV viral load of 1000 copies/mL or more) includes step-wise testing, with an initial standard sequencing with reflex to V3 deep sequencing if standard sequencing detects only CCR5-tropic virus.

Background

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.

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. 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. 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 Trofile™ 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.

Regulatory Status

The FDA-approved full prescribing information for maraviroc (Selzentry™, Pfizer) states that: “Tropism testing must be conducted with a highly sensitive and specific tropism assay that has demonstrated the ability to identify patients appropriate for [maraviroc] use.”

Currently-available HIV tropism tests are performed as LDTs. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; LDTs must meet the general regulatory standards of CLIA. Testing for HIV tropism is available under the auspices of CLIA Laboratories that offer LTDs and must be licensed by CLIA for high-complexity testing.

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


