Protocol

Laboratory Testing for HIV Tropism

(20449)

Medical Benefit		**Effective Date**: 07/01/15	**Next Review Date**: 05/19
Preauthorization	No	**Review Dates**: 05/09, 03/10, 03/11, 03/12, 03/13, 03/14, 03/15, 05/15, 05/16, 05/17, 05/18	

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.

Populations	Interventions	Comparators	Outcomes
Individuals: • With HIV infection who are being considered for HIV coreceptor antagonist therapy	Interventions of interest are: • HIV tropism testing	Comparators of interest are: • No HIV tropism testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Morbid events • Quality of life • Hospitalizations • Medication use • Treatment-related morbidity
Individuals: • With HIV infection receiving HIV coreceptor antagonist therapy or who have failed coreceptor antagonist therapy	Interventions of interest are: • HIV tropism testing	Comparators of interest are: • No HIV tropism testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Morbid events • Quality of life • Hospitalizations • Medication use • Treatment-related mortality • Treatment-related morbidity
Individuals: • With HIV infection who are undergoing tests to predict disease progression	Interventions of interest are: • HIV tropism testing	Comparators of interest are: • Plasma HIV RNA • CD4 count	Relevant outcomes include: • Overall survival • Disease-specific survival • Morbid events • Quality of life • Hospitalizations • Medication use

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 (e.g., maraviroc), which block specific coreceptor proteins.

SUMMARY OF EVIDENCE

For individuals who have HIV infection who are being considered for HIV coreceptor antagonist therapy who receive HIV tropism testing, the evidence includes randomized controlled trials (RCTs). Relevant outcomes are overall survival, disease-specific survival, morbid events, quality of life, hospitalizations, medication use, and treatment-related morbidity. RCTs on treatment-naive and treatment-experienced HIV-infected patients have provided evidence that selection of candidates for HIV coreceptor antagonist therapy using HIV tropism testing results in higher rates of treatment success compared with HIV coreceptor antagonist therapy without HIV tropism testing. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with HIV infection receiving HIV coreceptor antagonist therapy or who have failed coreceptor antagonist therapy who receive HIV tropism testing, the evidence includes post hoc analysis of RCTs and observational studies. Relevant outcomes are overall survival, disease-specific survival, morbid events, quality of life, hospitalizations, medication use, and treatment-related mortality and morbidity. Current evidence does not indicate improved outcomes with additional tropism monitoring during treatment. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with HIV infection who are undergoing tests to predict disease progression who receive HIV tropism testing, the evidence includes observational studies. Relevant outcomes are overall survival, disease-specific survival, morbid events, quality of life, hospitalizations, and medication use. Current evidence is inconsistent in as relates to whether HIV tropism testing independently predicts disease progression among HIV-infected patients. The evidence is insufficient to determine the effects of the technology on health outcomes.

POLICY

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

HIV tropism testing without immediate plans to prescribe HIV coreceptor antagonists such as maraviroc is **not medically necessary**.

Repeat HIV tropism testing during coreceptor antagonist treatment or after failure with coreceptor 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.

GENETIC COUNSELING

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

BACKGROUND

HIV

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) was the first coreceptor antagonist to be approved by the U.S. Food and Drug Administration (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 adults 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 events (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 the 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 (ESTA; Monogram Biosciences, South San Francisco, CA). 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; this is because the V3 loop interacts with the HIV co-receptor, and variants 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. In the United States, Quest Diagnostics (Madison, NJ) offers the only commercially available genotypic HIV coreceptor tropism assay, which uses triplicate population sequencing with reflex to ultra-deep 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 ultra-deep sequencing.

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). HIV tropism tests are is available under the auspices of the CLIA. Laboratories that offer LDTs must be licensed by the CLIA for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of this test.

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."[4]

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.

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