

MEDICAL POLICY

POLICY TITLE	VIRAL TROPISM TESTING
POLICY NUMBER	MP 2.208

CLINICAL BENEFIT	<input type="checkbox"/> MINIMIZE SAFETY RISK OR CONCERN. <input type="checkbox"/> MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. <input type="checkbox"/> ASSURE APPROPRIATE LEVEL OF CARE. <input type="checkbox"/> ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. <input checked="" type="checkbox"/> ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. <input type="checkbox"/> ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	2/1/2025

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I. POLICY

HIV tropism testing (see Policy Guidelines section for testing methods) may be considered **medically necessary** for either of the following indications:

- Selecting patients for treatment with HIV coreceptor antagonists such as maraviroc when there is an immediate plan to prescribe a coreceptor antagonist; or
- An individual who has experienced virologic failure while receiving therapy that contains a CCR5 antagonist.

HIV tropism testing without immediate plans to prescribe HIV coreceptor antagonists such as maraviroc is **not medically necessary**. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with these procedures.

The following procedures are considered **investigational**, as there is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with these procedures.

- Repeat HIV tropism testing during coreceptor antagonist treatment
- HIV tropism testing to predict disease progression (irrespective of co-receptor antagonist treatment).

Policy Guidelines

HIV tropism testing does not have its own specific code but may use a variety of procedure codes, including, but not limited to, genotype/phenotype drug resistance testing codes. This policy will only apply if requests are actually for co-receptor tropism analysis.

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

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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 stepwise testing, with an initial standard sequencing with reflex to V3 deep sequencing if standard sequencing detects only CCR5-tropic virus.

A proviral DNA tropism assay can be utilized for patients with HIV RNA <1,000 copies/mL.

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO- Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: <https://www.fepblue.org/benefit-plans/benefit-plans-brochures-and-forms>

III. DESCRIPTION/BACKGROUND

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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) is 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.

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

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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.” Testing is needed 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.

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.

In patients with an undetectable viral load or detectable plasma HIV RNA <1,000 copies/mL, phenotypic co-receptor usage can be determined using proviral DNA obtained from peripheral blood mononuclear cells.

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. HIV tropism tests are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments 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.”

IV. RATIONALE

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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 RCTs. The 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-

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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. The 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.

The HHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A working group of the NIH Office of AIDS Research Advisory Council states that “co-receptor tropism testing is recommended for patients who exhibit virologic failure on a CCR5 antagonist”. Based on this societal guidance, for those who have failed coreceptor antagonist therapy who receive 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 who are undergoing tests to predict disease progression who receive HIV tropism testing, the evidence includes observational studies. The 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.

V. DEFINITIONS

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ANTIRETROVIRAL DRUGS are substances used to kill or inhibit the multiplication of retroviruses such as HIV.

GENOTYPE ASSAY is a test that determines if HIV has become resistant to the antiviral drug(s) the patient is currently taking. The test analyzes a sample of the virus from the patient’s blood to identify any mutations in the virus that are associated with resistance to specific drugs, also known as GART (Genotypic Antiretroviral Resistance Assay).

HIV TROPISM refers to the type of cytokine coreceptor used by HIV-1 when infecting the host cell. The viruses in most treatment-naïve patients use the CCR5 (R5) coreceptor. Conversely, the viruses in up to 50% of treatment-experienced patients use either the CXCR4 (X4) coreceptor or both coreceptors (R5 and X4). Viruses that use both coreceptors are called dual-mixed (D/M) viruses.

HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 (HIV-1) is the retrovirus isolated and recognized as the etiologic (i.e., causing or contributing to the cause of a disease) agent of AIDS.

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MUTATION is a sudden change in a gene or unit of hereditary material that results in a new inheritable characteristic. As related to HIV, during the course of HIV disease, mutated HIV strains may emerge in an infected individual. These mutated strains may differ widely in their ability to infect and kill different cell types, as well as in their rate of replication.

PHENOTYPIC ASSAY is a procedure whereby sample DNA of a patient's HIV is tested against various antiretroviral drugs to see if the virus is susceptible or resistant to these drugs.

RNA (RIBONUCLEIC ACID) is a nucleic acid, found mostly in the cytoplasm of cells (rather than the nucleus) that is important in the synthesis of proteins. The amount of RNA varies from cell to cell. RNA, like the structurally similar DNA, is a chain made up of subunits called nucleotides. Some viruses, such as HIV, carry RNA instead of the more usual genetic material DNA.

VIRAL LOAD refers to the amount of HIV- RNA present in the blood, expressed in the number of copies per milliliter of blood plasma.

VIROLOGIC FAILURE is defined as a confirmed viral load of more than 200 copies/mL.

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits, and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

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Capital Blue Cross' medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

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Covered when medically necessary for HIV tropism testing:

Procedure Codes							
87900*	87901*	87903*	87904*	87906*	87999*		

* HIV tropism testing does not have its own specific code but may use a variety of procedure codes, including, but not limited to, standard of care genotype/phenotype drug resistance testing codes. This policy will only apply if requests are for co-receptor tropism analysis.

ICD-10-CM Diagnosis Code	Description
B20	Human immunodeficiency virus [HIV] disease
Z21	Asymptomatic human immunodeficiency virus [HIV] infection status

IX. REFERENCES

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X. POLICY HISTORY

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MP 2.208	01/22/2020 Consensus Review. No change to the policy statements. References reviewed. Coding reviewed.
	05/04/2021 Minor Review. Under Policy Statement, added that testing for HIV tropism is MN for an individual who has experienced virologic failure while receiving therapy that contains a CCR5 antagonist. Under Policy Guidelines, added Proviral DNA tropism testing is available for patients with HIV RNA <1,000 copies/mL. In Description/Background, under HIV Coreceptor Antagonists, changed name of company that owns Cenicriviroc to Allergan. Added HIV Tropism and Virologic Failure to Definitions. References updated. Coding unchanged.
	02/25/2022 Consensus Review. No change to policy statement. References updated
	08/23/2023 Consensus Review. Policy guidelines, background, rationale, coding table and references updated.
	01/19/2024 Administrative Update. Clinical benefit added.
	07/29/2024 Consensus Review. References updated. Added asterisk with note to coding table.

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