INSTRUCTIONS FOR USE

This protocol provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee's document (e.g., Certificate of Coverage (COC) or Evidence of Coverage (EOC)) may differ greatly. In the event of a conflict, the enrollee's specific benefit document supersedes this protocol. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the plan benefit coverage prior to use of this Protocol. Other Protocols, Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Protocols, Policies and Guidelines as necessary. This protocol is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

COMMERCIAL & MEDICAID COVERAGE RATIONALE

**Tropism testing in human immunodeficiency virus (HIV) patients prior to initiating treatment with CCR5 inhibitors (e.g. maraviroc) is medically necessary.**

NOTE: This guidance relates to Tropism Testing only. Other forms of HIV panels and portfolios are **not medically necessary**. Examples include the phenotypic assays including PhenoSense® and related tests and phenotype/genotype assays including “PhenoSense GT® and related tests.
The human immunodeficiency virus (HIV) is the virus that causes acquired immunodeficiency syndrome (AIDS). HIV can be further classified as HIV-1 or HIV-2. HIV-1 is the primary cause of AIDS. HIV-2, while similar to HIV-1, is primarily found outside of the United States. For purposes of this medical policy, HIV refers to HIV-1.

HIV attacks the immune system by infecting and destroying its host cell, the CD4+ lymphocyte, a type of white blood cell that is vital to fighting off infection. HIV requires a co-receptor for entry into target cells (known as tropism). The virus can enter through a CCR5 co-receptor, a CXCR4 co-receptor or both (dual/mixed). Knowing which co-receptor the virus uses is an important predictor of a patient's response to a class of anti-HIV drugs called CCR5 inhibitors. Maraviroc is the first in this class of drugs to receive FDA approval. Rather than fighting HIV inside white blood cells, maraviroc prevents the virus from entering uninfected cells by blocking the predominant route of entry, the CCR5 co-receptor (FDA, 2007).

Trofile is a complex diagnostic test that identifies the tropism of a patient's HIV. Earlier versions of the assay failed to routinely detect low levels of CXCR4-utilizing variants; however, it has since been revised with enhanced sensitivity. Although this more sensitive assay has had limited use in prospective clinical trials, it is now the only one that is commercially available. Tropism testing generally requires a plasma sample with an HIV-1 level of greater than or equal to 1000 copies/mL (DHHS, 2011; updated 2013).

**CLINICAL EVIDENCE**

Whitcomb, et al. (2007) conducted a validation study of an assay for determining HIV-1 coreceptor tropism (Trofile). Accuracy, reproducibility, linearity, sensitivity and specificity were established by evaluating the tropisms of well-characterized viruses and the variability among replicate results from samples tested repeatedly. The viral subtype, hepatitis B virus or hepatitis C virus coinfection, and the plasma viral load did not affect assay performance. Minority subpopulations with alternate tropisms were reliably detected when present at 5 to 10%. The plasma viral load above which samples can be amplified efficiently in the Trofile assay is 1,000 copies per ml of plasma. The minor variant was 100% detectable when present at a frequency of 10% and was 85% detectable when present at a frequency of 5%. No false-positive or false-negative amplification results were observed in three replicate evaluations. The authors concluded that the Trofile assay can be used to identify patients most likely to benefit from treatment regimens that include a coreceptor inhibitor and to monitor patients on treatment for the emergence of resistant virus populations that switch coreceptor tropism.

Braun and Weismann (2007) reviewed the characteristics of four phenotypic recombinant virus assays (RVA) available to predict coreceptor usage: Trofile (Monogram Biosciences), Phenoscript (VIRalliance), XtrackC/ PhenX-R (inPheno) and a platform developed by Virco. Trofile and Phenoscript represent single-cycle assays and are able to determine coreceptor tropism without cocultivation of HIV particles in cell culture. Trofile offers the most clinically validated data with currently about 25,000 analyzed samples. The detection of minority variants is a limitation of all population-based assays and varies between 1 and 10%, depending on the assay used. Although all assays are validated for the assessment of coreceptor tropism in different HIV-1 subtypes, there is still a need for further evaluations. The authors conclude that overall, RVAs confirm efficiency and accuracy, making them suitable for the clinical management of HIV infected individuals treated with coreceptor antagonists.
Skrabal et al. (2007) conducted an evaluation study to measure concordance between two recombinant phenotypic assays for HIV coreceptor usage (Trofile and TRT) and an HIV envelope genotypic predictor. HIV coreceptor usage was obtained from both phenotypic assays for 74 samples, with an overall 85.1% concordance. There was no evidence of a difference in sensitivity between the two phenotypic assays. A bioinformatic algorithm based on a support vector machine using HIV V3 genotype data was able to achieve 86.5% and 79.7% concordance with the Trofile and TRT assays, respectively, approaching the degree of agreement between the two phenotype assays. In most cases, the phenotype assays and the bioinformatic approach gave similar results. However, in cases where there were differences in the tropism results, it was not clear which of the assays was "correct."

U.S. Department of Health and Human Services (DHHS) guidelines (DHHS, 2011; updated 2013) recommend that a co-receptor tropism assay be performed whenever the use of a CCR5 inhibitor is being considered (AI). Co-receptor tropism testing is also recommended for patients who exhibit virologic failure on a CCR5 inhibitor (BIII). A phenotypic tropism assay (e.g., Trofile) is preferred to determine HIV-1 co-receptor usage (AI). A genotypic tropism assay should be considered as an alternative test to predict HIV-1 co-receptor usage (BII).

Strength of recommendation:
AI - strong recommendation based on data from randomized controlled trials.
BII - moderate recommendation based on data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes.
BIII - moderate recommendation based on expert opinion

Professional Societies
Infectious Diseases Society of America (IDSA)
The IDSA guidelines for the management of persons infected with HIV state that tropism testing should be performed if the use of a CCR5 antagonist is being considered (strong recommendation, high quality evidence) (Aberg et al., 2013).

International AIDS Society - USA Panel
Tropism assay to confirm R5 virus should be done before prescribing maraviroc. Maraviroc is not effective in persons who have X4 or dual/mixed X4/R5 virus infection. Drugs that block CCR5 have durable antiretroviral activity only if the individual is infected with HIV that uses CCR5 exclusively and not CXCR4. The use of these drugs thus requires receptor tropism screening. Phenotypic or genotypic assays may be used. Strength of recommendation: A1a - Strong evidence from 1 or more randomized controlled clinical trials published in the peer-reviewed literature (Thompson et al., 2012; Thompson et al., 2010).

European Consensus Group on Clinical Management of Tropism Testing
Testing for HIV tropism is recommended before prescribing a chemokine receptor blocker. The European Consensus Group panel recommends HIV-tropism testing for the following groups: drug-naive patients in whom toxic effects are anticipated or for whom few treatment options are available; patients who have poor tolerability to or toxic effects from current treatment or who have central nervous system pathology; and patients for whom therapy has failed and a change in treatment is considered. In general, an enhanced sensitivity Trofile assay and V3 population genotyping are the recommended test methods. (Vandekerckhove et al, 2011).
The Trofile™ co-receptor tropism test is regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA); therefore, premarket approval from the FDA is not required.

Pfizer, Inc. received FDA approval for maraviroc/Selzentry® on August 6, 2007. NDA 022128. Maraviroc is a CCR5 co-receptor antagonist indicated for combination antiretroviral treatment of adults infected with only CCR5-tropic HIV-1 detectable, who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents. Maraviroc is not approved for use in patients 16 years of age or younger. Safety and efficacy are not established in treatment-naive HIV infected people or in those with dual- or mixed-tropic or with CXCR4-tropic virus. Tropism and treatment history should guide the use of maraviroc. Additional information available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022128s012lbl.pdf, Accessed February 2019.

APPLICABLE CODES

The codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered health service. Coverage is determined by the benefit document. This list of codes may not be all inclusive.

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<th>Description</th>
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<tr>
<td>87906</td>
<td>Infectious agent genotype analysis by nucleic acid (DNA or RNA); HIV-1, other region (e.g., integrase, fusion)</td>
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<tr>
<td>87999</td>
<td>Unlisted microbiology procedure</td>
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CPT® is a registered trademark of the American Medical Association.

REFERENCES


### PROTOCOL HISTORY/REVISION INFORMATION

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The foregoing Health Plan of Nevada/Sierra Health & Life Healthcare Operations protocol has been adopted from an existing UnitedHealthcare coverage determination guideline that was researched, developed and approved by the UnitedHealthcare Coverage Determination Committee.