Genotypic and Phenotypic Assays for HIV Drug Resistance

Policy Number: HS-165

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APPLICATION STATEMENT

The application of the Clinical Coverage Guideline is subject to the benefit determinations set forth by the Centers for Medicare and Medicaid Services (CMS) National and Local Coverage Determinations and state-specific Medicaid mandates, if any.
GENOTYPIC AND PHENOTYPIC ASSAYS FOR HIV DRUG RESISTANCE
HS-165

DISCLAIMER
The Clinical Coverage Guideline is intended to supplement certain standard WellCare benefit plans. The terms of a member’s particular Benefit Plan, Evidence of Coverage, Certificate of Coverage, etc., may differ significantly from this Coverage Position. For example, a member’s benefit plan may contain specific exclusions related to the topic addressed in this Clinical Coverage Guideline. When a conflict exists between the two documents, the Member’s Benefit Plan always supersedes the information contained in the Clinical Coverage Guideline. Additionally, Clinical Coverage Guidelines relate exclusively to the administration of health benefit plans and are NOT recommendations for treatment, nor should they be used as treatment guidelines. The application of the Clinical Coverage Guideline is subject to the benefit determinations set forth by the Centers for Medicare and Medicaid Services (CMS) National and Local Coverage Determinations and state-specific Medicaid mandates, if any. Note: The lines of business (LOB) are subject to change without notice; consult www.wellcare.com/Providers/CCGs for list of current LOBs.

BACKGROUND
The human immunodeficiency virus (HIV-1) replicates rapidly and demonstrates a high mutation rate with each replication cycle. Every mutation increases the potential for the development of drug-resistant virus strains. Additionally, human immunodeficiency virus persists within tissues throughout the body and likely sets off chain reactions of acute and chronic immune disturbances. Antiretroviral testing (ART) is utilized to determine the optimal initial antiretroviral regimen that can be used, or to determine if a patient may have a viral strain that is resistant to the current therapy regimen.

Pharmacotherapy selection and compliance are extremely important in the treatment of HIV-1. The optimal goal of antiretroviral therapy is to reduce plasma HIV-ribonucleic acid (RNA) to below detection by the most sensitive assay available (i.e., < 50 copies/ml). Sequential measurements of CD4 cell count and viral load at 4, 8–12, and 16–24 weeks, and regularly thereafter have been used to assess early response to antiretroviral therapy.

Resistance to antiretroviral drugs remains an important limitation to successful HIV-1 therapy. Factors associated with the development of drug resistance include the use of serial monotherapy, suboptimal treatment regimens, lack of patient compliance, and initiation of therapy late in the course of HIV infection. Resistance testing can improve treatment outcomes for infected individuals. Testing may include either a genotype or a phenotype measurement of the HIV-1 genome. These measurements are instrumental in establishing individually specific and effective drug treatment regimens based on the patient’s specific viral load response. Both types of assays have been shown to provide reliable and reproducible measures of resistance, with certain caveats: accuracy depends on the experience of the interpreter and laboratory; results from the available tests are not interchangeable, and clinically relevant thresholds of resistance have not been fully defined. Technical issues can sometimes prevent successful resistance testing when plasma HIV RNA levels are less than 500 to 1000 copies/mL. Despite these limitations, ART has become a standard of care in HIV medicine and its use for selected individuals with HIV-1 positivity is supported by several national and international professional societies/organizations.

Genotype assays detect drug-resistant mutations that are present in the relevant viral genes. Advantages include a rapid turn-around time and wide availability. Additionally, the appearance of resistant mutations may precede change in phenotype. Disadvantages: genotype may not correlate with phenotype, they require “expert interpretation”, possible failure to detect minor species, and genotypes are unable to access mutational interactions. These assays are generally preferred for antiretroviral-naïve patients.

Phenotype assays measure the ability of a virus to grow in different concentrations of antiretroviral drugs. These assays rely on cultured patient HIV isolates and report fold-changes in sensitivities in the presence or absence of drugs. Phenotypic tests can be useful in the interpretation of more complex resistance patterns. Virtual phenotypic resistance assays make use of a library of known matched genotypes and empirically tested phenotypes to predict a patient’s phenotype based on known genotype results. Advantages include the direct measure of viral drug susceptibility, and the ability to assess net effect of mutational interactions and cross-resistance patterns. Disadvantages: cost, longer turn-around time, the possible failure to detect minor species, and the appropriate cut-offs are not defined for all drugs.

Phenotypic assays include recombinant virus assays (RVAs) that predict which coreceptor the HIV virus uses to enter a cell (also known as tropism). The virus can enter through the CCR5 coreceptor, the CXCR4 coreceptor, or both. Predicting the tropism of the virus is important in the determination of an individual’s response to the class of HIV
drugs known as CCR5 antagonists (e.g., Maraviroc). Trofile™ (Monogram Biosciences, South San Francisco, CA) is currently the only commercially available diagnostic assay that can determine whether an individual patient’s human immunodeficiency virus (HIV-1) infection is CCR5, CXCR4, or both.

**POSITION STATEMENT**

Genotypic or phenotypic assays for HIV drug resistance testing is considered medically necessary to assess viral strains and select treatment strategies in the following circumstances:

- Members with Acute HIV infection when they enter into care prior to initiation of antiretroviral (ART). *(NOTE: A genotypic assay is generally the preferred test for antiretroviral-naïve members): OR,

- HIV-treated members to assist in the selection of active drugs when changing antiretroviral regimens in cases of virologic failure and HIV RNA levels ≥ 1,000 copies/mL or in members with HIV RNA levels ≥ 500 but < 1,000 copies/mL. *(NOTE: In the setting of virologic failure, drug resistance testing should be performed while the member is taking the failing antiretroviral regimen, or within four weeks of treatment discontinuation): OR,

- HIV-treated members who have suboptimal viral suppression to initial ART treatment, defined as <0.5 log decrease in HIV RNA level after four weeks of treatment, a confirmed HIV RNA level > 400 copies after 24 weeks, > 50 copies/mL after 48 weeks, or a repeated detectable HIV RNA level after prior suppression of viremia; OR,

- Members with established (chronic) HIV infection, at the time of entry into HIV care, regardless of whether therapy will be initiated. *(NOTE: a genotypic assay is generally the preferred test): OR,

- Pregnant women prior to initiation of therapy and for those entering pregnancy with detectable HIV RNA levels while on therapy. *(NOTE: A genotypic assay is the preferred test for this indication).

In addition, genotypic testing is recommended as the preferred resistance testing to guide therapy in patients with suboptimal virologic responses or virologic failure while on first or second regimens (AIII). Addition of phenotypic testing to genotypic testing is generally preferred for persons with known or suspected complex drug resistance mutation patterns, particularly to protease inhibitors (BIII). *(USPSTF, 2009)*.

In most situations genotypic testing is preferred because of the faster turnaround time, lower cost, and enhanced sensitivity for detecting mixtures of wild-type and resistant virus *(USPSTF, 2009)*.

HIV drug resistance testing is considered NOT medically necessary for ANY of the following:

- In members greater than four weeks after discontinuation of ART since the assays may not detect certain quasi-species in the absence of selective drug pressure: OR,

- Members who have plasma HIV RNA levels < 500 copies.mL, since HIV RNA at this level is too low for reliable detection with current assays: OR,

- Serial testing in members without virologic failure or suboptimal viral response: OR,

- Combined genotyping and phenotyping.

HIV tropism testing with co-receptor tropism assays *(Trofile™)* is considered medically necessary in EITHER of the following circumstances:

- Selecting members for treatment with a co-receptor antagonist (CCR5 inhibitor; maraviroc): OR,
• A member has experienced virologic failure on a CCR5 inhibitor.

HIV tropism testing with co-receptor tropism assay, in the absence of antiretroviral treatment failure (i.e. in the absence of plans to prescribe HIV co-receptor antagonists such as maraviroc) is considered NOT medically necessary.

HIV tropism testing with co-receptor tropism assay is considered NOT medically necessary for all other indications, included but not limited to the following:

• When using other co-receptor (genotypic) assay techniques; OR,
• Repeat HIV tropism testing during co-receptor antagonist treatment or after failure of co-receptor antagonists; OR,
• To predict disease progression, irrespective or co-receptor antagonist treatment.

CODING

CPT® Codes
87900 Infectious agent drug susceptibility phenotype prediction using regularly updated genotypic bioinformatics
87901 Infectious agent genotype analysis by nucleic acid (DNA or RNA); HIV-1, reverse transcriptase and protease
87903 Infectious agent phenotype analysis by nucleic acid (DNA or RNA) with drug resistance tissue culture analysis, HIV-1; first through 10 drugs tested
87904+ Infectious agent phenotype analysis by nucleic acid (DNA or RNA) with drug resistance tissue culture analysis, HIV-1; each additional drug tested *(List separately in addition to code for primary procedure)*
87999 Trofile Co-Receptor Tropism Assay

ICD-9-CM Procedure Codes - No applicable codes

HCPCS Level II Codes - No applicable codes

ICD-9-CM Diagnosis Codes
042 Human immunodeficiency virus [HIV] disease
647.60 – 647.64 HIV (042) in the mother, complicating pregnancy, childbirth, or the puerperium

ICD-10-CM Diagnosis Codes
B20 Human immunodeficiency virus [HIV] disease
O98.511 – O98.53 Other viral diseases complicating pregnancy
O98.711 – O98.72 Human immunodeficiency virus (HIV) complicating pregnancy
O98.73 Human immunodeficiency virus (HIV) complicating the puerperium


REFERENCES

MEDICAL POLICY COMMITTEE HISTORY AND REVISIONS

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<tr>
<td>5/7/2015</td>
<td>Approved by MPC. No changes.</td>
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<tr>
<td>6/5/2014</td>
<td>Approved by MPC. Added updated references to original 2008 USPSTF guideline.</td>
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<tr>
<td>4/5/2012</td>
<td>New template design approved by MPC.</td>
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<td>12/1/2011</td>
<td>Approved by MPC.</td>
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Clinical Coverage Guideline