



**GENOTYPIC AND PHENOTYPIC ASSAYS
FOR HIV DRUG RESISTANCE
HS-165**



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**Genotypic and Phenotypic
Assays for HIV Drug
Resistance**

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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.

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.

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 (Henry, 2006). 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 $\geq 1,000$ 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).

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 coreceptor tropism assays (Trofile™) **is considered medically necessary** in EITHER of the following circumstances:

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

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

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

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

*Current Procedural Terminology (CPT) 2010 American Medical Association: Chicago, IL.®©

REFERENCES

Peer Reviewed

1. Hammer SM, Eron JJ Jr, Reiss P, et al. Antiretroviral treatment of adult HIV infection: 2008 Recommendations of the International AIDS Society-USA Panel. JAMA. 2008; 300(5):555-570.
2. Hammer SM, Saag MS, Schlechter M, et al. Treatment for adult HIV infection. 2006 Recommendations of the International AIDS Society–USA Panel. JAMA. 2006; 296:827-843.
3. Hirsch MS, Brun-Vezinet F, Clotet B, et al. Antiretroviral drug resistance testing in adults infected with human immunodeficiency virus type I: 2003 recommendations of an International AIDS Society-USA Panel. Clin Infect Dis. 2003; 37:113-128.
4. Hirsch MS, Günthard HF, Schapiro JM, et al. Antiretroviral drug resistance testing in adult HIV-1 infection: 2008 recommendations of an International AIDS Society-USA Panel. Clin Infect Dis. 2008; 47(2):266-285.

Government Agencies, Professional and Medical Organizations

1. Centers for Medicare and Medicaid Services (CMS). National Coverage Determination: Serologic testing for acquired immunodeficiency syndrome (AIDS). NCD #190.9.
2. U.S. Department of Health and Human Services (DHHS). Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC). Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. November 3, 2008.

HISTORY AND REVISIONS

Date	Action
12/1/2011	<ul style="list-style-type: none">• New template design approved by MPC.
7/18/2011	<ul style="list-style-type: none">• Approved by MPC.