Human immunodeficiency virus (HIV) is a ribonucleic acid virus characterized by a high replication and mutation rate throughout all stages of infection. Due to this high replication and mutation rate, resistance to antiretroviral drug therapy may develop. Drug resistance remains a major limitation to successful HIV therapy. Resistance testing can improve treatment outcomes in an infected individual. Genotypic testing detects drug resistance mutations, while phenotypic testing measures the amount of drug necessary to inhibit or suppress viral replication. In addition, genotype results have been proposed to predict the phenotype by identifying similar genotypes from a large database of other HIV genotypes for which the phenotypes are known.

**Related Policies**

- Laboratory Testing for HIV Tropism

**Policy**

HIV genotyping or phenotyping may be considered medically necessary for any of the following indications:

- Failed course of antiviral therapy
- Suboptimal viral load reduction after antiviral therapy
- Acute or recent infection treatment decision guidance
- Antiretroviral naïve patients entering treatment

The following are considered investigational:

- Routine use of combined genotyping and phenotyping
- Drug susceptibility phenotype prediction using genotypic comparison to a known genotypic/phenotypic database

**Policy Guidelines**

HIV genotyping and phenotyping are commonly performed in reference laboratories.

**Benefit Application**

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the
contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program (FEP)) prohibit Plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

**Rationale**

The human immunodeficiency virus (HIV) is characterized by a high replication rate. The reverse transcription enzyme required for replication is error prone, resulting in a high rate of mutations, further leading to a swarm of related viruses (termed quasi-species) within the host. It is estimated that every possible single-point mutation occurs more than 10,000 times per day in infected individuals. While some of the mutations may be innocuous or render the virus unviable, others may confer resistance to antiviral drugs. It is likely that clones of drug-resistant viruses exist even before any antiviral therapy, but due to an associated replication or competitive disadvantage compared to the wild-type virus, the resistant clone only represents a small proportion of the total viral load. However, in the presence of antiviral drugs that selectively eliminate the wild-type virus, a resistant clone may rapidly emerge as the dominant quasi-species. Over time, this resistant clone may accumulate additional secondary mutations which overcome the original replication or competitive disadvantage. Virologic treatment failure (i.e., increasing viral loads) may result. Alternatively, due to the widespread use of antiviral therapy, patients may become infected with a resistant strain.

Current recommendations for initial drug therapy suggest the use of combination therapy with antivirals with different mechanisms of action designed to reduce the viral load to as low a level as possible. The four classes of agents available include:

- Nucleoside reverse transcriptase inhibitors (NRTI)
- Non-nucleoside reverse transcriptase inhibitors (NNRTI)
- Protease inhibitors (PI)
- Fusion inhibitors

This therapeutic principle is based on the concept that cessation of detectable HIV replication decreases the opportunity for accumulation of mutations that may give rise to drug-resistant viral variants. These regimens are referred to as highly active antiretroviral therapy (HAART). If initial drug therapy fails, as evidenced by rising HIV viral loads, it is likely that the emergent virus is drug resistant, unless failure is related to drug non-compliance. At this point, physicians must devise a salvage therapy, using drugs to which the virus likely remains sensitive. While drug resistance is most common in the setting of prior failed therapy, there have been reports of initial infection of drug-resistant strains, particularly to zidovudine, a drug that has been widely used since the 1980s.

Human immunodeficiency virus genotyping (i.e., gene sequencing) has revealed specific point mutations or combinations of mutations in the enzymes targeted by these drugs, i.e., viral protease and reverse transcriptase. These mutations may be associated with drug resistance. For example, a single-point mutation in HIV can confer high-level resistance to the antiviral lamivudine (an NRTI) and certain NNRTIs. In contrast, high-level resistance to
zidovudine (an NRTI) and certain protease inhibitors requires accumulation of three or more mutations. When only a single mutation is required for resistance, resistance may emerge within one month of treatment initiation. For this reason, these drugs are never used as monotherapy. In contrast, when multiple mutations are required, resistance may emerge only after months to years of therapy. Mutations that are common to several different drugs within a group will confer cross resistance. For example, cross resistance among the protease inhibitor drugs is common.

HIV phenotyping directly measures drug resistance by identifying the drug concentration necessary to inhibit virus replications, usually by 50. While phenotyping is a more direct measure of drug resistance compared to genotyping, the technique is labor intensive and technically challenging. Results of genotypes have also been used to predict the phenotype by identifying similar genotypes from a large database of other HIV genotypes for which the phenotypes are known. This data analysis is known as the VirtualPhenotype™.

The evolving understanding of the clinical significance of drug resistance has created interest in both HIV genotyping and phenotyping to identify active drug regimens in the following clinical settings:

- To determine the most effective salvage therapy in patients with drug resistance. For example, the virus seen during treatment failure may not be resistant to all drugs in a regimen
- To confirm that antiviral drug failure is due to drug resistance and not patient noncompliance
- To determine viral resistance at initial diagnosis of HIV infection

**Genotype and Phenotype in Patients Failing Drug Therapy**

A variety of randomized trials have compared phenotype- or genotype-directed antiviral therapies to standard care with empirically selected antiviral therapies. The primary endpoints of these studies consisted of virologic suppression at three to six months following randomization. The genotypic antiretroviral resistance testing (GART), Havana, and ARGENTA trials reported that salvage antiviral therapy directed by genotyping had improved virologic outcomes compared with standard therapy (Baxter et al., 2000; Tural et al., 2002; Cingolani et al., 2002). Only about 30% of patients achieved undetectable viral loads, and in most cases, the sustained response was short lived. Randomized studies of phenotype-directed therapy have shown less impressive results. While results of the VIRA3001 study reported a decrease in viral load in the phenotype- directed arm compared to the standard care arm, this reduction was not clinically significant by intent-to-treat analysis (Cohen et al., 2002). The California Collaborative Treatment Group (CCTG 575) trial showed no difference between the two arms either in terms of reduction in viral load or undetectable virus (Haubrich et al., 2005). Three randomized studies compared the results of genotype-directed and phenotype-directed therapy. (Meynard et al., 2002; Blanco et al., 2002; Wegner et al., 2002). These studies did not clearly establish the superiority of either genotyping or phenotyping. While non-randomized studies have suggested that combined genotyping and phenotyping may provide complementary information (Parkin et al., 2002), no randomized studies have compared the combination of genotyping and phenotyping to direct therapy compared to either genotyping or phenotyping alone. As noted previously, the results of genotyping can be compared to a database to predict the phenotype. Two randomized studies have suggested that therapy directed by the predicted phenotype is comparable to phenotype- directed therapy (Mazzotta et al., 2002; Perez-Elias et al., 2002). However, since the predicted
phenotype requires a preceding genotype, the more relevant comparison would be the outcomes of combined genotype/predicted phenotype-directed therapy compared to genotype-directed therapy alone. No such study has been reported.

DeLuca and colleagues (2006) reported that the benefit of genotype-guided treatment decisions continued over time in patients who failed antiviral therapy. Hirsch and colleagues (2005) noted no differences between genotyping and phenotyping in a series of 102 patients, but cautioned that the numbers of tests may not have been sufficient to detect differences. Dunn et al., (2005) reported on a randomized trial that did not demonstrate added value of phenotypic resistance in conjunction with genotypic testing in patients with virologic failure. A review article by Zolopa (2006) mentions potential problems caused by discordant results between genotyping and phenotyping and also mentions replication capacity as having potential prognostic value.

A 2007 report estimated the persistence of transmitted drug resistant variants in a cohort of 14 untreated men with recent seroconversion was 4.1 years (median). In contrast, in the absence of selective drug pressure, patients with treatment-acquired drug resistance experience little persistence and drug-sensitive virus rebounds over the course of 12 to 16 weeks (Little et al., 2008).

Areas with a relatively high prevalence of drug-resistant disease at diagnosis and at the time of initial treatment may find resistance testing helpful, given transmitted drug resistance is associated with a higher likelihood of virologic failure. Borroto-Esoda et al., (2007) reported the presence of resistance to the K103N mutation at baseline was statistically associated with virologic failure in both arms of a randomized controlled trial comparing two initial treatment regimens (n = 546, of whom n = 90 had some baseline resistance). Furthermore, the presence of any mutation (using genotypic resistance testing) was statistically associated with virologic failure in one treatment arm. In a second report, a subcohort (n = 208) of clinical trial patients receiving the same therapy, stated the time to virologic failure was significantly longer in patients who had no baseline resistance to NNRTIs compared to those with baseline resistance (HR 2.27, 95% CI 1.15 - 4.49) (Kuritzkes et al., 2008). Therefore, the prevalence of transmitted drug resistance may be important in guiding treatment decisions.

Finally, in a cohort study, Palella et al., (2009) evaluated the association between genotypic and phenotypic susceptibility testing (GPT) and its effect on survival. Results showed patients who had GPT had lower mortality rates than those who did not (2.0 versus 2.7 deaths per 100-person-years). In standard Cox models, GPT was also associated with improved survival after controlling for demographic characteristics, CD4+ cell count, HIV RNA levels and intensity of clinical follow-up. However, this study was not randomized and residual confounding may exist.

**Genotype and Phenotype in Treatment-Naïve Patients**

The prevalence in transmission of drug-resistant strains of HIV in this country ranges geographically from 5% to 26%. While there have been no controlled studies of resistance testing in treatment-naïve patients, some authors recommend either genotypic or phenotypic resistance testing in patients with acute HIV infection in geographic areas where drug-resistant strains of HIV are prevalent. In contrast, such testing is not generally recommended in patients with chronic, treatment-naïve HIV. This is based on the fact that genotypic or phenotypic testing may not detect drug-resistant species which were transmitted at the time of primary infection but have become a minor species in the absence of selective drug pressure. An alternative approach would be to reserve genotypic or phenotypic testing to those patients with chronic HIV infection who have a
suboptimal response to initial therapy.

While some modeling studies suggest that resistance testing could have value in treatment-naïve patients, trials are needed to demonstrate the clinical impact. Updated guidelines recommend drug resistance testing (generally genotyping) in treatment-naïve patients; however, this recommendation is based on expert opinion (Department of Health and Human Services (DHHS), 2006). This guideline notes that resistance testing in those who have failed antiviral therapy is supported by data from clinical trials.

Several studies estimated the prevalence of infection with virus resistant to at least one class of antiretroviral therapy among treatment naive patients (enrolled in U.S.-based studies from 2000 to 2004) at 10 to 16% (Kuritzkes et al., 2008; Eshleman et al., 2007; Parker et al., 2007). One of these (15.9%) was among recent (six months or less) seroconverters (Eshleman et al., 2007). In addition, prevalences as high as 24% in U.S. populations were reported in a review (Booth and Geretti, 2007).

**Clinical Guideline Recommendations**

Both the DHHS and the International AIDS Society (IAS) published clinical guidelines regarding resistance testing (Dybul et al., 2002; U.S. Public Health Service Task Force, 2002; Yeni et al., 2002).

The updated U.S. Treatment Guidelines (2008) currently recommend resistance testing with acute onset of infection, regardless of whether therapy will be initiated, in order to ascertain whether or not drug-resistant virus was transmitted. The information on which this recommendation is based was considered to be in part because transmitted drug resistance is thought to be fundamentally different from acquired (from treatment) drug resistance, both in its fitness (capacity to infect and replicate) and its persistence (does not revert to a minority species) (Booth and Geretti, 2007).

Randomized trials have suggested genotype-directed and, to a lesser extent, phenotype-directed therapy may result in improved short-term virologic outcomes in patients failing or having a suboptimal response to antiretroviral therapy. While guidelines suggest either type of assay may be recommended in treatment-naive patients with acute infection, particularly in geographic areas in which there is a high prevalence of resistant virus, this strategy has not been tested in controlled studies and therefore is considered investigational. No randomized studies have used combined genotype- and phenotype-directed therapy; therefore, this indication is considered investigational. However, the DHHS notes that there may be individual cases of such complexity that combined resistance testing may be helpful. Finally, no randomized studies have compared genotype alone with predicted phenotype (i.e., “virtual phenotype”).

**References**

4. Booth CL & Geretti AM. Prevalence and determinants of transmitted antiretroviral
Infections. Seattle, 2002; Abstract 589-T.


**Documentation Required for Clinical Review**

- No records required

**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

**MN/IE**

The following service/procedure may be considered medically necessary in certain instances and investigational in others. Services may be medically necessary when policy criteria are met. Services are considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.
<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>87900</td>
<td>Infectious agent drug susceptibility phenotype prediction using regularly updated genotypic bioinformatics</td>
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<tr>
<td></td>
<td>87901</td>
<td>Infectious agent genotype analysis by nucleic acid (DNA or RNA); HIV-1, reverse transcriptase and protease</td>
</tr>
<tr>
<td></td>
<td>87903</td>
<td>Infectious agent phenotype analysis by nucleic acid (DNA or RNA) with drug resistance tissue culture analysis, HIV 1; first through 10 drugs tested</td>
</tr>
<tr>
<td></td>
<td>87904</td>
<td>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)</td>
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</tbody>
</table>

| HCPCS   | None   |                                                                                                                                           |
| ICD-9 Procedure | None       |                                                                                                                                           |

| ICD-10 Procedure | For dates of service on or after 10/01/2015 |
| ICD-9 Diagnosis  | All Diagnoses                                    |
| ICD-10 Diagnosis  | All Diagnoses                                    |

**Policy History**

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
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</thead>
<tbody>
<tr>
<td>2/23/2000</td>
<td>Adopted BCBSA policy</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>6/28/2007</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td></td>
<td>Updated CPT codes added</td>
<td></td>
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<tr>
<td>7/2/2010</td>
<td>Policy revision with position change with title change from HIV Genotyping and Phenotyping</td>
<td>Medical Policy Committee</td>
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<tr>
<td>7/22/2010</td>
<td>Administrative update</td>
<td>Administrative Review</td>
</tr>
<tr>
<td>8/10/2010</td>
<td>Administrative update</td>
<td>Administrative Review</td>
</tr>
<tr>
<td>9/13/2010</td>
<td>Policy criteria revised</td>
<td>Policy statement clarification</td>
</tr>
<tr>
<td>12/31/2014</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
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</table>
Definitions of Decision Determinations

Medically Necessary: A treatment, procedure or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

Investigational/Experimental: A treatment, procedure or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California / Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a Split Evaluation, where a treatment, procedure or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements

This service (or procedure) is considered medically necessary in certain instances and investigational in others (refer to policy for details).

For instances when the indication is medically necessary, clinical evidence is required to determine medical necessity.

For instances when the indication is investigational, you may submit additional information to the Prior Authorization Department.

Within five days before the actual date of service, the Provider MUST confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should also be directed to the Prior Authorization Department. Please call 1-800-541-6652 or visit the Provider Portal www.blueshieldca.com/provider.

The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illness or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. These Policies are subject to change as new information becomes available.