HIV Genotyping and Phenotyping

Policy #  00067
Original Effective Date:  01/28/2002
Current Effective Date:  07/16/2014

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider Human Immunodeficiency Virus (HIV) genotyping and phenotyping to be eligible for coverage in patients who have failed a course of antiviral therapy or have suboptimal viral load reduction.

Based on review of available data, the Company may consider Human Immunodeficiency Virus (HIV) genotyping or phenotyping to be eligible for coverage in patients with acute or recent infection for guiding treatment decisions.

Based on review of available data, the Company may consider Human Immunodeficiency Virus (HIV) genotyping or phenotyping to be eligible for coverage in antiretroviral naïve patients entering treatment.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers combined genotyping and phenotyping to be investigational. *

Based on review of available data, the Company considers drug susceptibility phenotype prediction using genotypic comparison to known genotypic/phenotypic database to be investigational. *

Background/Overview
Human Immunodeficiency Virus is a ribonucleic acid (RNA) virus characterized by a high replication rate throughout all stages of infection. 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. In fact, 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 anti-viral drugs. It is likely that clones of drug-resistant viruses exist even before any anti-viral 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 anti-viral 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 that overcome the original replication or competitive disadvantage.
Virological treatment failure (i.e., increasing viral loads) may result. Alternatively, due to the widespread use of anti-viral 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 transcription inhibitors [NRTI], non-nucleoside reverse transcription inhibitors [NNRTI], protease inhibitors [PI] and 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 HAART (highly active antiretroviral therapy). 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 noncompliance. 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 (a 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.

Human Immunodeficiency Virus phenotyping directly measures drug resistance by identifying the drug concentration necessary to inhibit virus replication, 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.
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Rationale/Source
Genotype and Phenotype in Patients Failing Drug Therapy
A variety of randomized trials have compared phenotype or genotype directed antiviral therapies compared 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. For example, the VIRADPT, GART, Havana and ARGENTA trials reported that salvage antiviral therapy directed by genotyping had improved virologic outcomes compared with standard therapy. Even so, 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. The CCTG575 trial showed no difference between the two arms either in terms of reduction in viral load or undetectable virus. Three randomized studies compared the results of genotype-directed and phenotype-directed therapy. 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, no randomized studies have compared the combination of genotyping and phenotyping to direct therapy compared to either genotyping or phenotyping alone. As noted in the Background/Overview section, 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. 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.

Genotype and Phenotype in Treatment-Naïve Patients
Transmission of drug-resistant strains of HIV has been documented; their prevalence ranges geographically from 5%–26% in this country. While there have been no controlled studies of resistance testing in treatment-naïve patients, some 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, based on the fact that genotypic or phenotypic testing may not detect drug-resistant species that 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 for those patients with chronic HIV infection who have a suboptimal response to initial therapy.

Clinical Guideline Recommendations
Both the Department of Health and Human Services and the International AIDS Society have published clinical guidelines regarding resistance testing, which are summarized in the following Table.

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>IS-USA Recommendation</th>
<th>U.S. Treatment Guidelines Recommendation*</th>
<th>Rationale from U.S. Treatment Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary HIV Infection</td>
<td>Consider testing</td>
<td>Consider testing</td>
<td>If the decision is made to initiate therapy in a person with acute HIV</td>
</tr>
</tbody>
</table>

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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>infection, using resistance testing to optimize the initial antiretroviral regimen is a reasonable, albeit untested strategy.</td>
</tr>
<tr>
<td>Chronic HIV Infection</td>
<td>Consider testing</td>
<td>Testing not generally recommended</td>
<td>Uncertain prevalence of resistant virus. Current assay may not detect minor drug resistant species. Drug-resistant mutations may become minor species in the absence of selective drug pressure.</td>
</tr>
<tr>
<td>First or Multiple Regimen Failure</td>
<td>Recommend Testing</td>
<td>Recommend Testing</td>
<td>Determine the role of resistance in drug failure and maximize the number of active drugs in the new regimen, if indicated. Determine the role of resistance and maximize the number of active drugs in the new regimen, if indicated.</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Recommend testing if mother had detectable virus</td>
<td>With acute infection With virologic failure Suboptimal viral Suppression High likelihood of resistant virus(\Delta\Delta)</td>
<td>Essentially the same indications as in non-pregnant patients.</td>
</tr>
</tbody>
</table>

\(\Delta\) Note that these guidelines do not make a distinction between genotype or phenotype resistance assays. As noted in the text of the U.S. recommendations, “There are currently no prospective data to support the use of one type of resistance assay over the other (i.e., genotyping vs. phenotyping) in different clinical situations. Therefore, one type of assay is generally recommended per sample; however, in the setting of a complex prior treatment history, both assays may provide important and complementary information.” The text of the IAS-USA Panel states, “The clinical value of drug resistance testing is recognized and it is now considered standard-of-care in the management of treatment failure. Data are not yet available on which methods or type of resistance testing is superior in any given clinical setting.”

\(\Delta\Delta\) High likelihood of resistant virus is based on community prevalence of resistant virus, known drug resistance in woman’s sex partner or other source of infection.

The guidelines of the International AIDS Society were updated in 2004; however, this update did not address the role of HIV genotyping or phenotyping.
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Summary
Randomized trials have suggested that 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 that either type of assay may be recommended in treatment-naïve 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 remains investigational. No randomized studies have used combined genotype- and phenotype-directed therapy; therefore, this indication remains investigational. However, the Department of Health and Human Services 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”).

A literature search was performed for the 2005 review, with a particular focus on genotype predicted phenotype (virtual phenotype) and the role of genotyping or phenotyping in treatment naïve patients. No additional studies were identified that would prompt reconsideration of the coverage statement; therefore, the policy is unchanged.

A literature search was performed for the 2006 and 2007 reviews. None of the articles identified would alter the policy conclusions. DeLuca and colleagues reported that the benefit of genotype-guided treatment decisions continued over time in patients who failed antiviral therapy. Hirsch and colleagues 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 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 mentions potential problems caused by discordant results between genotyping and phenotyping and also mentions replication capacity as having potential prognostic value. 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. This guideline notes that resistance testing in those who have failed antiviral therapy is supported by data from clinical trials. Thus, the coverage statements are unchanged.

A literature search was conducted for the July 2008 with an emphasis on US-based populations.

The updated US treatment guidelines 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). Contributing to these observations, a 2007 report estimated that 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 12-16 weeks.
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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 that transmitted drug resistance is associated with a higher likelihood of virologic failure. Two recent reports were identified. Borroto-Esoda et al report that 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 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. A second report, in a sub-cohort (n = 208) of clinical trial patients receiving the same therapy, reported that 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% Conf. Int 1.15 – 4.49). In this light, the prevalence of transmitted drug resistance may be important in guiding treatment decisions. Several studies estimated the prevalence of infection with virus resistant to at least one class of antiretroviral therapy among treatment naïve patients (enrolled in US-based studies from 2000–2004) at 10-16%. One of these (15.9%) was among recent (six months or less) seroconverters. Additionally, prevalences as high as 24% in US populations were reported in a recent review.

Considering that infection with drug-resistant virus may be fundamentally different in its course, and that knowledge of the initial resistance pattern may decrease the incidence of virologic failure, the coverage statement is changed for the use of genotype or phenotype testing in recent onset infection or, if a patient is entering care years after infection occurred, at the start of treatment. Thus, testing in these situations may also be considered eligible for coverage.

References

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

<table>
<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
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<tbody>
<tr>
<td>CPT</td>
<td>87900, 87901, 87903, 87904, 87906</td>
</tr>
<tr>
<td>HCPCS</td>
<td>No codes</td>
</tr>
<tr>
<td>ICD-9 Diagnosis</td>
<td>042, V08</td>
</tr>
<tr>
<td>ICD-9 Procedure</td>
<td>No codes</td>
</tr>
</tbody>
</table>

Policy History

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12/06/2001  Medical Policy Committee review
01/28/2002  Managed Care Advisory Council approval
06/24/2002  Format revision. No substance change
03/31/2004  Medical Director review
04/20/2004  Medical Policy Committee review
04/26/2004  Managed Care Advisory Council approval
04/05/2005  Medical Director review
05/17/2005  Medical Policy Committee review. Policy statement coverage eligibility amended to include patients who have suboptimal viral load in addition to patients who have failed a course of antiviral therapy.
05/23/2005  Managed Care Advisory Council approval
05/03/2006  Medical Director review
05/17/2006  Medical Policy Committee approval. Format revision including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
05/02/2007  Medical Director review
07/02/2008  Medical Director review
07/16/2008  Medical Policy Committee approval. Background and rationale/source updated. HIV genotyping and phenotyping is eligible for coverage in patients with acute or recent infection for guiding treatment decisions, and for antiretroviral naïve patients entering treatment.
07/02/2009  Medical Director review
07/22/2009  Medical Policy Committee approval. No change to coverage eligibility.
07/01/2010  Medical Policy Committee approval
12/31/2010  Coding updated
07/07/2011  Medical Policy Committee review

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06/28/2012 Medical Policy Committee review
07/27/2012 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/27/2013 Medical Policy Committee review
07/10/2014 Medical Policy Committee review
07/16/2014 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 07/2015

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
   1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
   2. credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
   3. reference to federal regulations.

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A. in accordance with nationally accepted standards of medical practice;
B. clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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