Name of Policy: HIV Genotyping and Phenotyping

Policy #: 264
Category: Laboratory

Latest Review Date: February 2010
Policy Grade: Effective 02/06/2013:

Active Policy but no longer scheduled for regular literature reviews and updates.

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. 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.
**Description of Procedure or Service:**

HIV is an 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 three classes of antivirals available include nucleoside reverse transcription inhibitors (NRTI), non-nucleoside reverse transcription inhibitors (NNRTI), and protease inhibitors (PI). 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 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.

HIV 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 (a NRTI) and certain protease inhibitors requires accumulation of 3 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 Virtual Phenotype™.

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 non-compliance.
- To determine viral resistance at initial diagnosis of HIV infection.

**Policy:**

**HIV drug resistance testing, either phenotypic or genotypic** testing or combined phenotypic and genotypic testing in patients who have failed a course of antiviral therapy or who have suboptimal viral load reduction meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage.

**HIV drug resistance testing, either phenotypic or genotypic**, used in other applications including, but not limited to its use in patient with previously untreated HIV does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational.

**Drug susceptibility phenotype prediction** using genotypic comparison to known genotypic/phenotypic database, also known as virtual phenotype testing, does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational.

*Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the members' contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.*

**Key Points:**

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

There are several randomized trials that have looked at genotype-directed antiviral therapies compared to standard of care with empirically selected antiviral therapies. The primary endpoints of these studies consisted of virologic suppression at 3-6 months following randomization. These trials included the VIRADPT, GART, Havana, and ARGENTA trials. These trials are briefly summarized below.
 Durant, et al (1999), published the results of the VIRADAPT trial, which looked at virological and immunological impact of genotypic-resistance testing. 108 HIV-infected patients, whose therapy was failing, were randomly assigned to either genotypic-resistance testing (n = 65) or no resistance testing (control group, n = 43). The major endpoint was the change in HIV-1 RNA viral load. At 6 months, patients in the genotype arm had a significantly greater drop in mean viral load than did the control group (1.15 log_{10} copies/ml vs. 0.67 log_{10} copies/ml). At 6 months, 32% of patients in the genotyping arm and 14% of patients in the control group had a viral load of <200 copies/ml. They concluded that genotypic-resistance testing had a significant benefit on the virological response when choosing a therapeutic alternative and further study is warranted.

 Baxter, et al (2000), reported on the use of genotypic antiretroviral resistance testing (GART) to manage patients failing on a protease inhibitor and two nucleoside reverse transcriptase inhibitors. 153 HIV-infected patients were randomized to either a GART group (n = 78) or a no-GART group (n = 75). The results showed the GART group had better virologic responses (decrease by 1.19 log 10) than the no-GART group (decrease by –0.61 log 10). They concluded that GART with expert advice was superior to no-GART in patients failing triple drug therapy.

 Tural, et al (2002), reported on the HAVANA trial, which looked at whether HIV-1 genotyping and expert advice add additional virologic benefit to guide antiretroviral changes. 326 HIV-1 infected patients on stable antiretroviral therapy with virological failure had either genotyping or no genotyping. Patients who had HIV-1 genotyping had a higher probability of plasma HIV-1 RNA < 400 copies/ml (48.5% vs. 36.2%). They concluded that HIV-1 genotyping interpreted by a software package improved virological outcome when added to clinical information.

 Cingolani, et al (2002), reported on the ARGENTA trial. 174 patients with virological failure were randomly assigned to receive either standard of care or genotypic drug resistance testing. The study looked at both HIV viral loads and CD4 cell counts. At 3 months, 27% of the genotyping group and 12% of the control group had viral loads <500 copies/ml. At 6 months, the results were 21% and 17%, respectively. The authors concluded that the virological benefit of genotypic-guided treatment decisions was short-term.

 In summary, these 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.

 There have also been several randomized studies of phenotype-directed therapy, which have shown less impressive results.

 Cohen, et al (2002), reported on the VIRA 3001 trial that compared the effect of treatment decisions guided by phenotypic resistance testing (PRT) or standard of care (SOC) on short-term virological response. 272 patients on a failing regimen were randomized to receive either phenotypic resistance testing or standard of care. At 16 weeks, the PRT group had a greater portion of its patients with HIV-1 RNA levels <400 copies/ml than SOC group (46% vs. 34%).
Also, the PRT group had a significantly greater median reduction in HIV-1 RNA levels from baseline as compared to the SOC group. The authors concluded that PRT-guided treatment lead to increased use of “active” antiretroviral agents and a significantly better virological response.

Haubrich, et al (2005), reported on the CCTG 575 trial, which assessed pheonotype susceptibility testing (PHENO) with standard of care (SOC) to improve antiretroviral therapy. 238 patients were randomized to receive or not receive PHENO results for selecting antiretroviral regimens. The results showed the virological outcome was similar in both groups at 6 and 12 months.

There were 3 randomized studies (Maynard, Blanco, and Wegner) that compared the results of genotype-directed and phenotype-directed therapy.

Meynard, et al (2002), looked at phenotyping vs. genotyping vs. standard of care to choose antiretroviral therapy in patients failing protease inhibitor-containing regimens. 541 patients were randomized to either phenotyping (n = 190), genotyping (n = 192), or standard of care (n = 159). The results showed plasma HIV-1 RNA was <200 copies/ml at week 12 in 35% in phenotyping arm, 44% in genotyping arm, and 36% in standard of care arm. They concluded that overall, resistance essays did not show benefit over standard of care.

Blanco, et al (2002), looked at the usefulness of Genotypic Resistance Tests (G-tests) and real Phenotypic Resistance Tests (rP-tests) to guide treatment decisions in patients with therapeutic failures. 137 patients were randomized to G tests (n = 78) or P-tests (n = 59). The results showed no statistically significant differences between the two groups.

Wegner, et al (2002), reported on the long-term outcome of either genotype or phenotype resistance testing to guide therapy changes. 450 patients were randomized to genotype (G), phenotype (P), or viral burden (VB) arms. The study endpoint was persistent virologic failure (VF) despite a change in therapy and patients were followed a median of 525 days. The results showed resistance testing delayed the time to VF, but there was no difference in the G and P arms.

These 3 studies did not clearly establish the superiority of genotype or phenotype resistance testing.

Parkin, et al (2002), reported on a non-randomized study to evaluate whether genotype or phenotype methods give drug resistance information that is overlapping or complementary. The results showed the information from PT and GT tests is complementary. There have been no randomized studies comparing the combination of genotype and phenotype tests versus genotype and phenotypes tests individually to direct therapy.

There have been 2 randomized studies that have suggested that therapy directed by the predicted phenotype is comparable to phenotype-directed therapy.

Mazzotta, et al (2003), compared viroimmunologic response after real phenotype (r-PHT) vs. virtual phenotype (v-PHT) in patients failing highly antiretroviral therapy. 201 patients were randomized to the r-PHT or v-PHT arm and followed for a mean of 48 weeks with the primary
endpoint being the proportion of HIV plasma viral load (pVL) <400 copies/ml. The results showed virologic and immunologic outcomes did not differ in both groups.

Perez-Elias, et al (2003), reported on a prospective, randomized trial looking at drug resistance testing using recombinant viral phenotype method or virtual phenotype. 276 patients were randomized to either a phenotype group (n = 139) or a virtual phenotype group (n = 137) and followed for 24 weeks. The results at 24 and 48 weeks showed the virtual phenotype had a greater mean decrease in plasma HIV RNA. They concluded that virtual phenotype is at least as effective as phenotype to select an optimal treatment for patients who have failed previous regimens.

However, these 2 studies bring up another point. 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**
The prevalence of drug-resistant strains of HIV ranges geographically from 5% to 26% in this country and transmission of these strains has been documented. There have been no controlled studies of resistance testing in treatment-naïve patients. Some have recommended 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 to those patients with chronic HIV infection who have suboptimal response to initial therapy.

**Clinical Guideline Recommendations**
The Department of Health and Human Services and the International AIDS Society have published clinical guidelines regarding resistance testing. These were updated in 2003 and are summarized below:

<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>Recommend testing</td>
<td>Recommend testing</td>
<td>“If the decision is made to initiate therapy in a person with acute HIV 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>Recommend testing</td>
<td>Consider testing</td>
<td>Uncertain prevalence of resistant virus. Current assay may not detect minor drug-resistant</td>
</tr>
</tbody>
</table>

*Proprietary Information of Blue Cross and Blue Shield of Alabama
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| Species. Drug-resistant mutations may become minor species in the absence of selective drug pressure. |
|---|---|---|---|
| First or Multiple Regimen Failure | Recommend testing | Recommend testing | 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. |
| Pregnancy | Recommend testing if mother had detectable virus | With acute infection With virologic failure Suboptimal viral suppression High likelihood of resistant virus** | Essentially the same indications as in non-pregnant patients. |

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.”

**High likelihood of resistant virus is based on community prevalence of resistant virus, known drug resistance in women’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.

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 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. There are no randomized studies that 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. There have been no randomized studies that have compared genotype alone with predicted phenotype, i.e., “virtual phenotype”.

A literature search was performed for the period of October 2005 through February 2007. 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-naive patients, trials are needed to demonstrate the clinical impact. Updated guidelines recommend drug resistance testing (generally genotyping) in treatment-naive 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 policy statements are unchanged.

February 2010 Update
A literature search was conducted with an emphasis on U.S. based populations.

The updated U.S. 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.

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 have been 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 2 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% CI 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 U.S. based studies from 2000-2004) at 10-16%. One of these (15.9%) was among recent (6 months or less) seroconverters. In addition, prevalences as high as 24% in U.S. populations were reported in a recent review.

Consideration that infection with drug-resistant virus may be fundamentally different it its course, and that knowledge of the initial resistance pattern may decrease the incidence of virologic failure, the policy 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 medically necessary.

Key Words:  
HIV drug resistance testing, phenotypic, genotypic, virtual phenotype

Approved by Governing Bodies:  
Not applicable

Benefit Application:  
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply  
FEP contracts: No special consideration  
Pre-certification requirements: Not applicable

Current Coding:  
CPT codes:

87900 Infectious agent drug susceptibility phenotype prediction using regularly updated genotypic bioinformatics  
(Effective 01/01/2006)

87901 Infectious agent genotype, analysis by nucleic acid (DNA or RNA); HIV 1, reverse transcriptase and protease regions

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 ;each additional drug tested

87906 Infectious agent genotype analysis by nucleic acid (DNA or RNA); HIV-1, other region (e.g., integrase, fusion)  
(Effective 01/01/2011)
Infectious agent drug susceptibility phenotype using genotypic comparison to known genotypic/phenotypic database (Code deleted effective January 1, 2006)

References:


34. Zolopa AR. Incorporating drug-resistance measurements into the clinical management of HIV-1 infection. Journal of Infectious Diseases 2006; 194: S59-S64.

Policy History:
Medical Policy Group, February 2006 (3)
Medical Policy Administration Committee, March 2006
Available for comment March 14-April 27, 2006
Updated Key Points, added references, February 2008 (1)
Medical Policy Group, February 2010 (1) Updated Key Points, added references
Medical Policy Group, December 2010 (1) Coding Update-Added new CPT code and updated verbiage
Medical Policy Group, February 2013: Effective 02/06/2013: Active Policy but no longer scheduled for regular literature reviews and updates.

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.