BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:
HIV Genotyping and Phenotyping

Policy #: 264
Category: Laboratory

Latest Review Date: October 2020
Policy Grade: B

BACKGROUND:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

POLICY:

Effective for dates of service on or after March 2, 2018:

Blue Advantage will treat **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 as a **covered** benefit.

Blue Advantage will treat **HIV drug resistance testing, either phenotypic or genotypic**, used in other applications including, but not limited to its use in patients with previously untreated HIV as a **non-covered** benefit and as **investigational**.

Blue Advantage will treat **drug susceptibility phenotype prediction** using genotypic comparison to known genotypic/phenotypic database, also known as virtual phenotype testing, as a **non-covered** benefit and as **investigational**.

Refer also to Blue Advantage medical policy *#322 Laboratory Testing for HIV Tropism* for additional information.

Effective for dates of service on or after February 26, 2018, and prior to March 2, 2018:

For CPT codes 87901, 87903, 87904 and 87906, refer to LCD L33433

For CPT code 87900 refer to criteria below:

Blue Advantage will treat **drug susceptibility phenotype prediction** using genotypic comparison to known genotypic/phenotypic database, also known as virtual phenotype testing, as a **non-covered** benefit and as **investigational**.

Effective for dates of service on or after May 12, 2006 and prior to February 26, 2018:

Blue Advantage will treat **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 as a **covered** benefit.

Blue Advantage will treat **HIV drug resistance testing, either phenotypic or genotypic**, used in other applications including, but not limited to its use in patients with previously untreated HIV as a **non-covered** benefit and as **investigational**.

Blue Advantage will treat **drug susceptibility phenotype prediction** using genotypic comparison to known genotypic/phenotypic database, also known as virtual phenotype testing, as a **non-covered** benefit and as **investigational**.

Refer also to Blue Advantage medical policy *#322 Laboratory Testing for HIV Tropism* for additional information.

Blue Advantage 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 Advantage administers benefits based on the members' contract and 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.

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 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 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:

1. 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.
2. To confirm that antiviral drug failure is due to drug resistance and not patient non-compliance.
3. To determine viral resistance at initial diagnosis of HIV infection.

KEY POINTS:

This policy is based on evidence review of literature most recently performed on October 1, 2019.

Summary of Evidence

Three studies (Cingolani, Tural, Baxter) have been identified in which it is concluded that genotypic-resistance testing had a significant benefit on the virological response when choosing a therapeutic alternative. 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. The evidence is accepted as sufficient to consider the technology medically necessary.

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.

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. There have been no randomized studies that have compared genotype alone with predicted phenotype, i.e., "virtual phenotype". The evidence is insufficient to support this technology at this time.

U.S. Preventive Services Task Force
Not applicable.

KEY WORDS:
HIV drug resistance testing, phenotypic, genotypic, virtual phenotype, ART, antiretroviral therapy, HIV, drug susceptibility phenotype prediction, genotyping, phenotyping, viral load, virtual phenotype testing, Sentosa SQ HIV-1 Genotyping Assay, Vela Diagnostics

APPROVED BY GOVERNING BODIES:
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:

Clinical Characteristic	IS-USA Recommendation	U.S. Treatment Guidelines Recommendation*	Rationale from U.S. Treatment Guidelines
Primary HIV Infection	Recommend testing	Recommend testing	"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."
Chronic HIV Infection	Recommend testing	Consider testing	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.

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.

BENEFIT APPLICATION:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

CURRENT 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 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)
0219U	Infectious agent (human immunodeficiency virus), targeted viral next-generation sequence analysis (i.e., protease [PR], reverse transcriptase [RT], integrase [INT]), algorithm reported as prediction of antiviral drug susceptibility **(Effective 10/1/2020)**

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POLICY HISTORY:

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Updated Key Points, added references, February 2008
Medical Policy Group, February 2010
Medical Policy Group, December 2010
Medical Policy Group, February 2013
Medical Policy Group, May 2015
Medical Policy Group, February 2018
Medical Policy Group, October 2020: Reinstated policy effective February 26, 2018.
