BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:
HIV Genotyping and Phenotyping

Policy #: 264
Latest Review Date: November 2024
Category: Laboratory

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:

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 (including, but not limited to Sentosa SQ HIV-1 Genotyping Assay), as a **non-covered** benefit and as **investigational**.

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 drug resistance testing is used to determine whether a patient with HIV has a mutated form of the virus present in their body that is resistant to antiretroviral therapy (ART).

HIV is an RNA virus characterized by a high replication rate. The reverse transcription enzyme required for replication is error prone and can lead to mutations. These mutations cause different HIV strains (clones), particularly if the patient is currently or has previously been treated with ART. If an antiretroviral resistance clone develops, the patient's viral load will rise, and over time, this resistant clone may accumulate additional secondary mutations and become the dominant strain.

Initial drug therapy recommendations 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.

HIV genotyping identifies the presence of mutations that are known to confer reduced drug susceptibility. Several studies have suggested that resistance testing may be useful in assessing the success of salvage anti-retroviral therapy, and improving short-term virological response. 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. Phenotypic and genotypic tests appear to provide similar results. Currently, there is insufficient information as to which approach is preferable in any particular clinical setting.

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 review of medical literature most recently performed through November 4, 2024.

Summary of Evidence

In a 2018 Cochrane review, the effectiveness of anti-retroviral resistance testing in reducing mortality and morbidity in HIV positive people was investigated. Primary outcomes of interest were mortality and virological failure. Data was analyzed on an intention-to-treat (ITT) basis using a random-effects model. 11 RCTs were included in the review. All of these trials enrolled patient who had previous exposure to ART. Seven studies used genotypic testing, two studies used phenotypic testing, and two studies used both genotypic and phenotypic testing. The authors of the review concluded that resistance testing probably improved virological outcomes in people who have had virological failure in trials conducted years ago. These researchers found no evidence in treatment-naive people; resistance testing did not demonstrate important patient benefits in terms of risk of death or progression to AIDS. The evidence is sufficient to prove that use of the technology results in an increase in net health outcomes for patients who have failed a course of antiviral therapy or who have a suboptimal viral load reduction. The evidence is insufficient to prove that the use of the technology results in an increase in net health outcomes for all other indications, including patients who have never been treated with anti-retrovirals.

Automated DNA extraction and sequencing (Virtual phenotype testing) has been investigated. Identified studies show varying levels accuracy within different subtypes of the disease. There currently exists of a paucity of evidence to prove that this technology is clinically superior to the current standard of care. Well-designed studies are need to further examine the accuracy and clinical utility of HIV DNA genotyping. The evidence is insufficient to prove that the use of the technology results in an increase in net health outcomes.

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.

Practice Guidelines and Position Statements
The Department of Health and Human Services' (DHHS') Panel on Antiretroviral Guidelines for Adults and Adolescents
Updated in 2023, The Panel's Recommendations Regarding Drug-Resistance Testing:
For Initial Treatment of HIV:

- HIV drug-resistance testing is recommended at entry into care for people with HIV to guide the selection of the initial antiretroviral (ARV) regimen (AII). If antiretroviral therapy (ART) is deferred, repeat testing may be considered at the time of ART initiation (CIII).
- Genotypic, rather than phenotypic, testing is the preferred resistance testing to guide therapy in ARV-naive patients (AIII).
- In people with early (acute and recent) HIV infection, in pregnant people with HIV, or in people who will initiate ART on the day of or soon after HIV diagnosis, ART initiation should not be delayed while awaiting resistance testing results; the regimen can be modified once results are reported (AIII).
- Standard genotypic drug-resistance testing in ARV-naive persons involves testing for mutations in the reverse transcriptase and protease genes. If transmitted integrase strand transfer inhibitor (INSTI) resistance is suspected or if the person has used long-acting cabotegravir (CAB-LA) as pre-exposure prophylaxis (PrEP) in the past, providers should ensure that genotypic resistance testing also includes the integrase gene (AIII).

For Antiretroviral Therapy-Experienced People:

- HIV drug-resistance testing should be performed to assist the selection of active drugs when changing ARV regimens in—
    - People with virologic failure and HIV-RNA levels >200 copies/mL (AI for >1,000 copies/mL, AIII for 501–1,000 copies/mL, CIII for confirmed HIV RNA 201–500 copies/mL). For people with confirmed HIV-RNA levels >200 copies/mL but <500 copies/mL, drug-resistance testing may be unsuccessful but should still be considered.
    - People with suboptimal viral load reduction (AII).
- Reverse transcriptase and protease genotypic resistance testing should be performed on everyone with virologic failure; integrase resistance testing (which may need to be ordered separately) should be performed on individuals experiencing virologic failure while receiving an INSTI-based regimen (AII).

- For persons taking a non–long-acting ARV regimen, drug-resistance testing in the setting of virologic failure should be performed while the person is still taking their ARV regimen or, if that is not possible, within 4 weeks after discontinuing their ARV regimen (AII). If more than 4 weeks have elapsed since the non–long-acting agents were discontinued, resistance testing may still provide useful information to guide therapy; however, it is important to recognize that previously-selected resistance mutations can be missed due to lack of drug-selective pressure (CIII).
- Given the long half-lives of the long-acting injectable ARV drugs, resistance testing (including testing for resistance to INSTIs) should be performed in all persons who have experienced virologic failure on a regimen of long-acting CAB and rilpivirine or acquired HIV after receiving CAB-LA as PrEP, regardless of the amount of time since drug discontinuation (AIII).
- Genotypic testing is preferred over phenotypic-resistance testing to guide therapy in people with suboptimal virologic response or virologic failure while on first- or second-line regimens and in people in whom resistance mutation patterns are known or not expected to be complex (AII).
- The addition of phenotypic- to genotypic resistance testing is recommended for people with known or suspected complex drug-resistance mutation patterns (BIII).
- All prior and current drug-resistance test results, when available, should be reviewed and considered when constructing a new regimen for a patient (AIII).

Rating of Recommendations: A = Strong; B = Moderate; C = Weak

Rating of Evidence: I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

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:
On March 19, 2019, Vela Diagnostics USA Inc. submitted a request for De Novo classification of the SENTOSA SQ HIV Genotyping Assay. FDA reviewed the request in order to classify the device under the criteria for classification set forth in section 513(a) (1) of the FD&C Act.

On November 5, 2019, FDA issued an order to the requester classifying the device into class II. FDA is codifying the classification of the device by adding 21 CFR 866.3955. We have named the generic type of device “Human immunodeficiency virus drug resistance genotyping assay using next generation sequencing technology,” and it is identified as a prescription in vitro

diagnostic device intended for use in detecting HIV genomic mutations that confer resistance to specific antiretroviral drugs. The device is intended to be used as an aid in monitoring and treating HIV 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:

Adopted for Blue Advantage, February 2006
Available for comment March 28-May 11, 2006
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.

Medical Policy Group, October 2021: Reviewed by consensus. No new published peer-reviewed literature available that would alter the coverage statement in this policy.
Medical Policy Group, October 2022: Reviewed by consensus. No new published peer-reviewed literature available that would alter the coverage statement in this policy.
Medical Policy Group, October 2023: Reviewed by consensus. No new published peer-reviewed literature available that would alter the coverage statement in this policy.
UM Committee, December 2023: Policy approved by UM Committee for use for Blue Advantage business.
Medical Policy Group, November 2024: Reviewed by consensus. No new published peer-reviewed literature available that would alter the coverage statement in this policy.
UM Committee, November 2024: Annual review of policy approved by UM Committee for use for Blue Advantage business.
