

Corporate Medical Policy

HIV Genotyping and Phenotyping AHS – M2093

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Description of Procedure or Service

Description

Human immunodeficiency virus (HIV) is an RNA retrovirus that infects human immune cells (specifically CD4 cells) causing progressive deterioration of the immune system ultimately leading to acquired immune deficiency syndrome (AIDS) characterized by susceptibility to opportunistic infections and HIV-related cancers (CDC, 2014).

Related Policies

Plasma HIV-1 and HIV-2 RNA Quantification for HIV Infection

Scientific Background

Human immunodeficiency virus (HIV) targets the immune system, eventually hindering the body's ability to fight infections and diseases. If not treated, an HIV infection may lead to acquired immunodeficiency syndrome (AIDS) which is a condition caused by the virus. There are two main types of HIV: HIV-1 and HIV-2; both are genetically different. HIV-1 is more common and widespread than HIV-2.

HIV replicates rapidly; a replication cycle rate of approximately one to two days ensures that after a single year, the virus in an infected individual may be 200 to 300 generations removed from the initial infection-causing virus (Coffin & Swanstrom, 2013). This leads to great genetic diversity of each HIV infection in a single individual. As an RNA retrovirus, HIV requires the use of a reverse transcriptase for replication purposes. A reverse transcriptase is an enzyme which generates complimentary DNA from an RNA template. This enzyme is error-prone with the overall single-step point mutation rate reaching $\sim 3.4 \times 10^{-5}$ mutations per base per replication cycle (Mansky & Temin, 1995), leading to approximately one genome in three containing a mutation after each round of replication (some of which confer drug resistance). This rate is comparable to other RNA viruses. This pace of replication, duration of infection, and size of the replicating population allows the retrovirus to evolve rapidly in response to selective influences (Coffin & Swanstrom, 2013).

Due to the high rate of mutation in HIV viruses, drug resistance mutations are common. Some drugs may be resisted by a single mutation—these drugs have a “low genetic barrier” to resistance. Such mutations are common enough to be termed “signature mutations,” which are frequently associated with a specific drug resistance. For example, the K103N mutation commonly leads to resistance for efavirenz. Efavirenz is a standard retroviral medication used to treat and prevent HIV and AIDs. To combat this, medical professionals can now assess drug-resistant HIV variants using phenotypic testing and genotypic testing (Kozal, 2019a).

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Genotypic assays detect the presence of specific drug-resistance mutations in several different genes (protease, reverse transcriptase, and integrase genes). For example, assays may test for resistance in nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), or protease inhibitors (PIs). The definition of a resistance conferring mutation is blurred, but generally includes one or more of the following conditions:

- The mutation confers phenotypic resistance when introduced into a drug-sensitive laboratory strain of HIV.
- The mutation is selected for during serial in vitro passage of the virus in the presence of a drug.
- The mutation is selected for during clinical therapy with that drug.
- The presence of the mutation in clinical isolates is associated with phenotypic resistance and virologic failure (Kozal, 2019b).

Interpretation of genotypic data may be done either by clinical expertise or through a database (in which the genotype is correlated with the phenotype) (Kozal, 2019b).

Several HIV genotypic assays are available. The ViroSeq HIV-1 Genotyping system by Abbott helps to detect HIV-1 genomic mutations that may lead to resistance to certain types of antiretroviral drugs (Abbott, 2018). Further, the ATCC® HIV-1 Drug Resistance Genotyping Kit has been developed by the American Type Culture Collection (ATCC), the Centers for Disease Control and Prevention (CDC) and Thermo Fischer Scientific; this is a real time- polymerase chain reaction (rt-PCR) assay which may help to identify and monitor HIV-1 drug resistance (ATCC, 2014).

Phenotypic resistance assays measure the extent to which an antiretroviral drug inhibits viral replication. Phenotypic testing typically assesses the fold-change in susceptibility of a patient's virus and the treatment response, while also correlating the mutations present with the fold-change in susceptibility. Recombinant virus assays (RVAs) are used; protease, reverse transcriptase, or integrase gene sequences from circulating viruses are inserted into a reference strain of HIV, and this new HIV strain is measured by the phenotypic assay. The primary phenotypic assay is "PhenoSense" from LabCorp although "Antivirogram" was used in the past (Kozal, 2019b). The Human Immunodeficiency Virus 1 (HIV-1) PhenoSense GT® Plus Integrase (Monogram® Phenotype + Genotype) test by LabCorp measures HIV genotypic and phenotypic resistance from plasma samples (LabCorp, 2020).

Advantages of the genotype assays include lower cost and shorter turnaround time. However, interpretation of these assays is complicated by combinations of individual mutations that may have a differential effect on resistance that differs from the individual mutation alone (Kozal, 2019b). Mutation combinations are known to cause resistance to certain drugs, but increase susceptibility to others, impact viral fitness, and contribute to major pathways of resistance; additionally, the interactions of mutations affecting various mechanisms can be difficult to predict. Over 20 rules-based genotypic interpretation systems (GIS) have been proposed (Fox et al., 2007; Kozal, 2019b).

Advantages of phenotypic assays include an ability to measure resistance more directly and examine the relative effect of multiple mutations on drug resistance. Limitations of the phenotypic assays include a longer turnaround time, greater expense, and biologic cut-offs above achievable drug levels. Phenotypic resistance assays may be helpful when evaluating HIV strains with known or suspected complex drug resistance mutation patterns as their actual resistance may not be accurately predicted by simply detecting the presence of multiple mutations (Kozal, 2019b). Both assays are limited by decreased sensitivity for low-level minority variants that comprise less than 5 to 20 percent of the virus population (Kozal, 2019b).

Analytical and Clinical Validity and Utility

Rosemary et al. (2018) performed a comparison of two genotyping assays, ViroSeq and ATCC kit. A total of 183 samples with a viral load ≥ 1000 copies/mL were sequenced by ViroSeq and randomly selected (85 successfully genotyped, 98 unsuccessfully genotyped). The ATCC kit also genotyped 115 of the 183 samples, and out of the 98 unsuccessfully genotyped samples, the ATCC kit was able to genotype 42. Overall, 127 of the 183 samples were genotyped. The authors noted that the sequences of the

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genotyped samples were 98% identical and had “similar HIVDR profiles at individual patient level” (Rosemary et al., 2018).

Zhang, Rhee, Taylor, and Shafer (2005) compared two phenotyping assays, Antivirogram and PhenoSense. Reverse transcriptase inhibitor susceptibility results were evaluated for 202 isolates from Antivirogram and 126 from PhenoSense. The authors found the median deviance for wild-type and mutant isolates to be lower for PhenoSense compared to Antivirogram, and PhenoSense was more likely to detect resistance to abacavir, didanosine, and stavudine when common drug resistance mutations were present (Zhang et al., 2005).

Shen, Yu, Harrison, and Weber (2016) assessed the ability to predict phenotypic drug resistance from genotypic data. The authors used two machine learning algorithms to predict drug resistance to HIV protease inhibitors and reverse transcriptase inhibitors as well as the severity of that resistance from a query sequence. The accuracy of these classifications was found to be >0.973 for eight PR inhibitors and 0.986 for ten RT inhibitors and the r^2 was 0.772–0.953 for the PR cohort and 0.773–0.995 for the RT cohort. The algorithms’ results were verified by “five-fold cross validation” on the genotype-phenotype datasets (Shen et al., 2016).

Taylor et al. (2019) have developed a MiSeq-HyDRA platform for enhanced HIV drug resistance genotyping and surveillance; this platform uses next generation sequencing (NGS) as opposed to Sanger sequencing (SS) methods which are limited due to low data throughput and limited detection of low abundant drug resistant variants (LADRVs). NGS and SS are both DNA sequencing techniques. The authors tested this novel platform with HIV-1 samples amplified at viral loads of $\geq 1,000$ copies/ml. “The gross error rate of this platform was determined at 0.21%, and minor variations were reliably detected down to 0.50% in plasmid mixtures (Taylor et al., 2019).” The authors conclude by stating that this genotypic platform using NGS has many advantages including an increased sensitivity for LADRV detection, reduced costs and labor, and the potential to routinely monitor for HIV drug resistance.

Raymond et al. (2020) evaluated the performance of the Vela Dx Sentosa next-generation sequencing (NGS) system for HIV-1 DNA genotypic resistance. 40 DNA samples were analyzed with Vela Dx Sentosa assay and the results were compared with Sanger sequencing. The Vela Dx Sentosa assay was 100% successful in amplifying and sequencing the protease and reverse transcriptase, and 86% successful in amplifying integrase sequences when the HIV DNA load was greater than 2.5 log copies/million cells. The Sentosa and Sanger sequencing were concordant for predicting protease-reverse transcriptase resistance in 20% of the 14/18 samples which were successfully sequenced. Sentosa was able to predict a higher level of resistance in three of the samples. The Vela Dx Sentosa predicted the prevalence of drug resistance to protease inhibitors (7%), nucleoside reverse transcriptase inhibitor (59%), nonnucleoside reverse transcriptase inhibitor (31%), and integrase inhibitors (20%). Overall, the authors conclude that the Vela Dx Sentosa assay can accurately predict HIV DNA drug resistance (Raymond et al., 2020).

Fogel et al. (2020) also analyzed the ability of next-generation sequencing methods to analyze HIV drug resistance. In this case, 145 plasma samples were analyzed using the ViroSeq HIV-1 Genotyping System and the veSEQ-HIV assay. Results were compared with the Abbott RealTime Viral Load assay. 142 HIV protease and reverse transcriptase sequences and 138 integrase sequences were obtained with ViroSeq. On the other hand, veSEQ-HIV detected 70.4% of the samples with protease, reverse transcriptase, and integrase sequences. Drug resistance mutations were detected in 33 ViroSeq samples and 42 veSEQ-HIV samples. Overall, veSEQ-HIV predicted more drug resistance mutations and worked better for larger viral loads. Results from veSEQ-HIV strongly correlated with the results from Abbott RealTime Viral Load assay. The authors conclude that the veSEQ-HIV assay provided results for most samples with higher viral loads, was accurate for predicting drug resistance mutations, but detected mutations at lower levels compared with the ViroSeq assay (Fogel et al., 2020).

Applicable Federal Regulations

Multiple genotypic and phenotypic assays exist for the assessment of HIV mutations. Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-

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developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for HIV Genotyping and Phenotyping when it is determined the medical criteria or reimbursement guidelines below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When HIV Genotyping and Phenotyping is covered

Reimbursement for HIV genotyping or phenotyping is allowed in patients who have failed a course of antiviral therapy OR have suboptimal viral load reduction OR have been noncompliant with therapy.

Reimbursement for HIV genotyping or phenotyping is allowed for guiding treatment decisions in patients with acute or recent infection (within the last 6 months).

Reimbursement for HIV genotyping or phenotyping in antiretroviral naive patients entering treatment is allowed.

Reimbursement for HIV genotyping or phenotyping is allowed for all HIV-infected pregnant women before initiation of antiretroviral therapy and for those entering pregnancy with detectable HIV RNA levels while on therapy.

When HIV Genotyping and Phenotyping is not covered

Reimbursement is not allowed for routine use of combined genotyping and phenotyping.

Reimbursement is not allowed for drug susceptibility phenotype prediction using genotypic comparison to known genotypic/phenotypic database.

Policy Guidelines

Guidelines and Recommendations

Department of Health and Human Services(DHHS) (DHHS, 2019, 2020a, 2020b)

The Department of Health and Human Services (DHHS, 2019, 2020a, 2020b) updated their guidelines for using drug resistance assays in HIV infections. The guidelines recommend HIV genotyping or phenotyping in the following situations:

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- “In acute (early) HIV infection: Drug-resistance testing is recommended. A genotypic assay is generally preferred. Treatment should not be delayed while awaiting results of resistance testing.”
- “HIV drug-resistance genotype testing should be performed in women living with HIV whose HIV RNA levels are above the threshold for resistance testing (i.e., >500 to 1,000 copies/mL) before initiating antiretroviral therapy (ART) in antiretroviral (ARV)-naive pregnant women who have not been previously tested for ARV resistance, initiating ART in ARV-experienced pregnant women (including those who have received pre-exposure prophylaxis), or modifying ART regimens for women who are newly pregnant and receiving ART drugs or who have suboptimal virologic response to the ARV drugs started during pregnancy (DHHS, 2020b).”
- “If the use of an integrase strand transfer inhibitor (INSTI) is being considered and INSTI resistance is a concern, providers should supplement standard resistance testing with a specific INSTI genotypic resistance assay. INSTI resistance may be a concern if a patient received prior treatment that included an INSTI, or a patient has a history with a sexual partner on INSTI therapy (DHHS, 2020b).”
- “In ART-naive patients with chronic HIV infection: Drug-resistance testing is recommended at entry into HIV care to guide selection of initial ART. A genotypic assay is generally preferred.”
- “In patients with virologic failure: Drug-resistance testing is recommended in patients on combination ART with HIV RNA levels >1,000 copies/mL. In patients with HIV RNA levels >500 copies/mL <1000 copies/ml, testing may not be successful but should still be considered. A standard genotypic resistance assay is generally preferred for patients experiencing virologic failure on their first or second regimens and for those with noncomplex resistance patterns.”
- “Adding phenotypic testing to genotypic testing is generally preferred in patients with known or suspected complex drug-resistance patterns.”
- “In patients with suboptimal suppression of viral load: Drug resistance testing is recommended in patients with suboptimal viral load suppression after initiation of ART.”
- “In HIV-infected pregnant women: Genotypic resistance testing is recommended for all pregnant women before initiation of ART (AIII) and for those entering pregnancy with detectable HIV RNA levels while on therapy.”

DHHS does not recommend drug-resistance assays in the following situations:

- “After therapy is discontinued: Drug-resistance testing is not usually recommended more than 4 weeks after ARV drugs are discontinued.”
- “In patients with low HIV RNA levels: Drug-resistance testing is not usually recommended in patients with a plasma viral load <500 copies/ml.”
- In Patients with Undetectable Viral Load or Low-Level Viremia: “HIV-1 proviral DNA resistance assays may be useful in patients with HIV RNA below the limit of detection or with low-level viremia, where a HIV RNA genotypic assay is unlikely to be successful.”

The DHHS also added guidelines on genotypic and phenotypic testing for pediatric HIV infection:

- “Antiretroviral (ARV) drug- resistance testing is recommended at the time of HIV diagnosis, before initiation of therapy, in all ARTnaive patients (AII). Genotypic resistance testing is preferred for this purpose.”
- “Phenotypic resistance testing should be considered (usually in addition to genotypic resistance testing) for patients with known or suspected complex drug resistance mutation patterns, which generally arise after a patient has experienced virologic failure on multiple ARV regimens (DHHS, 2020a).”

The Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM) Sub-Committee for Guidance on HIV Management in Australia (ASHM, 2018)

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The Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM) Sub-Committee for Guidance on HIV Management in Australia has released commentary to the US DHHS Guidelines for the use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents. The Panel's recommendations are below:

“For Antiretroviral Therapy-Naive Persons:

- HIV drug-resistance testing is recommended at entry into care for persons with HIV to guide selection of the initial antiretroviral therapy (ART) regimen (AII). If therapy 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 antiretroviral (ARV)-naive patients (AIII).
- In persons with acute or recent (early) 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 (RT) and protease (PR) genes. If transmitted integrase strand transfer inhibitor (INSTI) resistance is a concern, providers should ensure that genotypic resistance testing also includes the integrase gene (AIII).

For Antiretroviral Therapy-Experienced Persons:

- HIV drug-resistance testing should be performed to assist the selection of active drugs when changing ART regimens in the following patients:
 - Persons with virologic failure and HIV RNA levels >1,000 copies/mL (AI)
 - Persons with HIV RNA levels >500 copies/mL but <1,000 copies/mL, drug-resistance testing may be unsuccessful but should still be considered (BII)
 - Persons with suboptimal viral load reduction (AII)
- When a person with HIV experiences virologic failure while receiving an INSTI-based regimen, genotypic testing for INSTI resistance (which may need to be ordered separately) should be performed to determine whether to include a drug from this class in subsequent regimens (AII).
- Drug-resistance testing in the setting of virologic failure should be performed while the person is taking prescribed ARV drugs or, if that is not possible, within 4 weeks after discontinuing therapy (AII). If more than 4 weeks have elapsed since the ARVs 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).
- Genotypic testing is preferred over phenotypic resistance testing to guide therapy in persons with suboptimal virologic response or virologic failure while on first- or second-line regimens and in individuals 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 persons with known or suspected complex drug-resistance mutation patterns (BIII).
- All prior and current drug-resistance test results, if available, should be considered when constructing a new regimen for a patient (AIII).

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

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 (ASHM, 2018).”

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European AIDS Clinical Society (EACS) (EACS, 2018, 2019, 2020)

The EACS recommends a genotypic resistance test at HIV diagnosis and virological failure. Genotyping is also recommended before ART (antiretroviral therapy), or ideally at the time of HIV diagnosis (EACS, 2019). Additional genotypic recommendations include if the patient was not previously tested or if the patient is at risk of a super-infection. The EACS recommends a genotypic test over a phenotypic test as genotype tests are more available and more sensitive (EACS, 2018, 2020).

International AIDS Society – USA Panel (Hirsch et al., 2008)

The International AIDS Society recommends antiretroviral drug resistance testing in adult HIV-1 infection in the following situations (Hirsch et al., 2008):

- Untreated established HIV-1 infection: The guidelines recommend resistance testing for all patients at the time of diagnosis of HIV-1 infection as part of the initial, comprehensive assessment
- Treatment failure: The society states that “because of the high prevalence of infection due to drug-resistant virus among antiretroviral-treated patients with confirmed, detectable plasma virus, drug resistance testing should be performed in all cases of treatment failure”
- Acute and early phase HIV-1 infection: The guidelines state “genotypic resistance testing is recommended for any patient who presents within several months after HIV-1 infection because of the high reported rates of transmitted drug resistance”
- Pregnancy: The society recommends genotypic resistance testing “for all HIV-1-infected pregnant women with detectable plasma virus, both for their own health and for the health of their infants”

International Antiviral Society – USA Panel (Gunthard et al., 2019)

The International Antiviral (formerly AIDS) Society-USA expert panel has provided the following recommendations:

“Recommendations for Methods for HIV-1 Resistance Testing

- As a first choice, genotypic resistance testing is recommended (evidence rating AIIa).
- Phenotypic resistance testing is recommended, in certain situations:
 - to evaluate HIV susceptibility to new and investigational drugs when drug-resistant mutation patterns have not been fully established (evidence rating AIIa);
 - when genotypic test results are too complex to interpret (evidence rating CIII); or
 - when ART options are highly limited and, as a result, salvage ART must rely on residual susceptibilities to different drugs that are difficult to predict from genotypic data (evidence rating CIII).
- The recommended compartment for drug resistance testing is plasma (evidence rating AII).
- Inclusion of the protease and first half of the reverse transcriptase (up to at least nucleotide 215) is recommended for all genotypic testing (evidence rating BIII).
- Routine InSTI resistance testing in drug-naïve individuals is currently not recommended (BIII).
- Baseline InSTI resistance testing is recommended in select patients with evidence of TDR, such as those with nRTI- or multi-class resistance (evidence rating AIII).
- Monitoring of TDR/pretreatment drug resistance to InSTI in selected sites in resource-rich settings and low- and middle-income countries is recommended (evidence rating AIII).
- Sequencing of other regions (C-terminus of reverse transcriptase, gag) or even a near full-length of HIV-1 is not recommended for routine clinical management (evidence rating AIIa).
- Genotypic tropism testing is recommended if a CCR5 antagonist is considered for treatment (evidence rating BIIa).

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- Peripheral blood mononuclear cell genotypic resistance testing is recommended in patients with low-level viremia or in patients who are virologically suppressed (evidence rating AIII) (Gunthard et al., 2019)”

New York State Department of Health AIDS Institute (NYSDOF, 2020)

Determining HIV Drug Resistance

- When determining the optimal regimen for achieving viral suppression, clinicians should perform genotypic resistance testing that includes the protease (A2), reverse transcriptase (A2), and integrase genes (B2) at baseline, whether or not ART is being initiated.
 - In patients experiencing treatment failure [a] or incomplete viral suppression; such testing should be performed while patients are still on therapy, but no later than 4 weeks after stopping ART, given the rapid return of wildtype virus. (A2)
 - Perform co-receptor tropism testing prior to initiation of a CCR5 antagonist. (A1)
 - If fusion inhibitor resistance is suspected, that test should be obtained as a supplement to the other genotypic resistance tests. (A2) (NYSDOF, 2020).”

European HIV Drug Resistance Guidelines Panel (Vandamme et al., 2011)

Guidelines from the European HIV Drug Resistance Guidelines Panel include the following:

“Postexposure prophylaxis

- Use genotypic information from the index case to guide PEP. If this genotype is not known, do not delay PEP, but if a sample from the index case is available, genotype index case to change or simplify PEP if needed.

Which assay to use

- The panel recommends the use of genotyping in most routine clinical situations. Current genotyping can be performed below a viral load of 1,000 copies/ml.
- Consider additional phenotyping for new drugs, in heavily pretreated patients and for HIV-2 where genotyping is not easily interpretable (Vandamme et al., 2011).”

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: 87900, 87901, 87903, 87904, 87906, 0219U

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

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Policy Implementation/Update Information

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- 1/1/19 New policy developed. BCBSNC will provide coverage for HIV genotyping and phenotyping when it is determined to be medically necessary because the medical criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (sk)
- 9/10/19 Reviewed by Avalon 2nd Quarter 2019 CAB. Added “Related Policies” section. Policy Guidelines updated. References updated. Coding table removed from the Billing/Coding section of the policy. Medical Director review 8/2019. (sk)
- 10/29/19 Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. (gm)
- 3/10/20 Specialty Matched Consultant Advisory Panel review 2/19/2020. (sk)
- 7/28/20 Reviewed by Avalon 2nd Quarter 2020 CAB. Literature review updated. Not Covered section changed from Medical Necessity to Reimbursement language, where needed. Policy Guidelines updated. References updated. Medical Director review 7/2020. (bb)
- 3/9/21 Specialty Matched Consultant Advisory Panel review 2/17/2021. (sk)
- 8/24/21 Reviewed by Avalon 2nd Quarter 2021 CAB. Scientific Background updated. Policy Guidelines updated. New code 0219U added to Billing/Coding Section. References updated. Medical Director review 8/2021. (sk)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.