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 RNA Quantification for HIV-1 Infection

Scientific Background

The HIV virus replicates rapidly, with a replication cycle rate of approximately 1 day in which more than $10^9$ cells may be infected (Coffin & Swanstrom, 2013). Furthermore, reverse transcriptase 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). This leads 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, the duration of infection, and the 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 in the virus are common. Some drugs may be resisted with just one 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. Drug-resistant HIV variants can be assessed using phenotypic testing and genotypic testing (Kozal, 2018a).

Genotypic assays detect the presence of specific drug resistance mutations in the protease, reverse transcriptase, and integrase genes. For example, assays testing the resistance for nucleoside reverse transcriptase inhibitor (NRTI), non-nucleoside reverse transcriptase inhibitor (NNRTI), or protease inhibitor (PI) resistances may be performed. 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 virus in the presence of drug.
- The mutation is selected for during clinical therapy with that drug.
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- The presence of the mutation in clinical isolates is associated with phenotypic resistance and virologic failure (Kozal, 2018b).

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, 2018b).

Phenotypic resistance assays measure the extent to which an antiretroviral drug inhibits virus replication. Phenotypic testing typically assesses the fold-change in susceptibility of a patient’s virus and the treatment response as well as 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, 2018b).

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, 2018b). 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, 2018b).

Advantages of the phenotype assays include its ability to measure resistance more directly and examining the relative effect of multiple mutations on drug resistance. Limitations of the phenotype assays include a longer turnaround time, 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, 2018b). Both assays are limited by their decreased sensitivity for low-level minority variants that comprise less than 5 to 20 percent of the virus population (Kozal, 2018b).

Validity and Utility

Rosemary et al performed a comparison of two genotyping assays, ViroSeq and ATCC kit. 183 samples of viral load ≥1000 copies/mL that were sequenced by ViroSeq were randomly selected (85 successfully genotyped, 98 unsuccessfully genotyped). The ATCC kit was found to genotype 115 of the 183 samples, and out of the 98 unsuccessfully genotyped samples, the ATCC kit was able to genotype 42 of them. Overall, 127 of the 183 samples were genotyped. The authors noted that the sequences of the genotyped samples were 98% identical and had “similar HIVDR profiles at individual patient level” (Rosemary et al., 2018).

Zhang et al 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, Rhee, Taylor, & Shafer, 2005).

Shen et al 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, Yu, Harrison, & Weber, 2016).
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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-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 and show evidence of treatment failure.

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 is considered investigational.

Drug susceptibility phenotype prediction using genotypic comparison to known genotypic/phenotypic database is considered investigational.

Policy Guidelines

Guidelines and Recommendations

Department of Health and Human Services
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The Department of Health and Human Services (DHHS, 2018) updated their guidelines for using drug resistance assays in HIV infections in 2018. The guidelines recommend HIV genotyping or phenotyping in the following situations:

- **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.
- **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 (CIII).”

**European AIDS Clinical Society (EACS, 2018)**

The EACS recommends a genotypic resistance test at HIV diagnosis and virological failure. Genotyping is also recommended before ART 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 one as genotype tests are more available and more sensitive (EACS, 2018)

**International AIDS Society – USA Panel**

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”
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- 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”

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*

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

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)


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)


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.