Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 11/1/24**
(See policy history boxes for previous effective dates)

Title: Laboratory Testing for HIV Tropism

Description/Background

HIV

HIV-1, which causes AIDS, uses coreceptor proteins (either CCR5 or CXCR4) on the surface of target cells to enter and infect the cells. The most commonly transmitted strains of HIV-1 bind to CCR5 and are said to have "tropism" for CCR5-expressing cells. Dual or mixed (D/M) tropic viruses can bind to either receptor type. It is estimated that around 85% of treatment-naïve patients harbor CCR5-tropic virus only, around 15% harbor D/M virus, and less than 1% are infected with CXCR4-tropic virus alone. CXCR4-tropic virus is associated with immunosuppression and later stages of disease. Coreceptor antagonists have been designed to interfere with the interaction between HIV-1 and its coreceptors.

HIV Coreceptor Antagonists

Maraviroc (Selzentry™, Pfizer) is the first co-receptor antagonist to be approved by the U.S. Food and Drug Administration (FDA). Maraviroc is a selective, slowly reversible, small-molecule antagonist of the interaction between human cell surface CCR5 and HIV-1 gp120, also necessary for HIV-1 cell infection. Blocking this interaction prevents CCR5-tropic HIV-1 entry into cells. However, CXCR4-tropic HIV-1 entry is not prevented. According to the label, maraviroc, in combination with other antiretroviral agents, is indicated for adult patients who are infected with only CCR5-tropic detectable HIV-1, who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents.[1]

The currently approved maraviroc label indicates that maraviroc is indicated for combination antiretroviral treatment for adults infected with only CCR5-tropic HIV-1, without discussion of the presence of viral replication.[2] The FDA-approved full prescribing information for the drug states: "Tropism testing must be conducted on a current sample with a highly sensitive tropism assay that has demonstrated the ability to identify patients appropriate for use of SELZENTRY." This is because efficacy was not demonstrated in a phase 2 study of maraviroc in patients with

D/M or CXCR4-tropic HIV-1. Due to potential adverse effects (hepatic and cardiac toxicity), maraviroc should only be used in indicated patients.

Other HIV coreceptor antagonists are in the drug development pipeline. Cenicriviroc (Tobira Therapeutics) is a small-molecule antagonist of both CCR5 and CCR2, a receptor involved in a number of inflammatory diseases, that is currently being investigated for treatment of CCR5-tropic HIV.[3] In January 2015, cenicriviroc was granted fast track designation by FDA for the treatment of nonalcoholic steatohepatitis in patients with liver fibrosis, but the drug does not yet have FDA approval.

HIV Tropism Testing

HIV tropism testing is available by either phenotypic or genotypic methods. Tropism testing with a phenotypic assay, a cellular-based assay that functionally determines tropism, is available with the enhanced sensitivity Trofile™ (Monogram Biosciences, South San Francisco, CA) assay (ESTA). This phenotypic assay uses virus stocks pseudotyped with envelope sequences derived from patient plasma to infect cell lines engineered to express CCR5 or CXCR4 HIV-2 co-receptors. Genotypic tropism testing is based on sequencing the third variable (V3) loop of the HIV glycoprotein 120 gene, because the V3 loop interacts with the HIV co-receptor, and mutations in V3 are associated with measurable changes in HIV tropism. Tropism assignment is derived from the sequence data using a bioinformatic algorithm such as geno2pheno (G2P). In the United States, the only commercially available genotypic HIV coreceptor tropism assay is available from Quest Diagnostics, which uses triplicate population sequencing with reflex to ultradeep sequencing if only CCR5-tropic virus is detected. Quest Diagnostics also offers a proviral DNA tropism test (Trofile DNA) which sequences the tropism of HIV-1 DNA that has integrated into the host genome of infected T-lymphocytes via triplicate population sequencing, without the use of ultradeep sequencing.

Regulatory Status:

The FDA-approved full prescribing information for maraviroc (Selzentry™, Pfizer) states that "Tropism testing must be conducted with a highly sensitive and specific tropism assay that has demonstrated the ability to identify patients appropriate for [maraviroc] use."[4]

Currently-available HIV tropism tests are performed as LDTs. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; LDTs must meet the general regulatory standards of CLIA. Testing for HIV tropism is available under the auspices of CLIA Laboratories that offer LTDs and must be licensed by CLIA for high-complexity testing.

Medical Policy Statement

The safety and effectiveness of HIV tropism testing have been established. It is a useful diagnostic option for patients meeting patient selection guidelines.

Inclusionary and Exclusionary Guidelines

Inclusions

- HIV tropism testing with either the phenotypic assay or V3 population genotyping for selecting patients for treatment with HIV co-receptor antagonists such as maraviroc when there is an immediate plan to prescribe a coreceptor antagonist.

Exclusions:

- Either phenotypic or V3 population genotypic testing may be used to determine HIV tropism; ***both*** are not necessary.
- HIV tropism testing *without* immediate plans to prescribe HIV co-receptor antagonists such as maraviroc.
- *Repeat* HIV tropism testing during co-receptor antagonist treatment or after failure with co-receptor antagonists.
- HIV tropism testing to predict disease progression (irrespective of co-receptor antagonist treatment).

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

87906 87999

Other codes (investigational, not medically necessary, etc.):

N/A

Rationale

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. The following is a summary of the key literature.

HIV TROPISM TESTING TO IDENTIFY CANDIDATES FOR HIV CORECEPTOR ANTAGONIST THERAPY

Clinical Context and Test Purpose

The purpose of HIV tropism testing in patients who have HIV infection is to inform a decision whether the patient might be a candidate for treatment with HIV coreceptor antagonist therapy.

The question addressed in this evidence review is: Does assessment of HIV tropism, to identify HIV-infected patients who are candidates for HIV coreceptor therapy, result in an improved health outcome compared with HIV coreceptor therapy without HIV tropism testing?

The following **PICOs** were used to select literature to inform this review.

Populations
The relevant populations of interest are treatment-naive and treatment-experienced HIV-infected patients.

Interventions
The interventions of interest are HIV tropism testing using the Trofile assay, the enhanced sensitivity Trofile assay (ESTA), V3 sequencing, or V3 deep sequencing.

Comparators
The comparator of interest is no HIV tropism testing.

Outcomes
The potential beneficial outcomes of primary interest would be identification of HIV-infected patients who might benefit from treatment with HIV coreceptor antagonist therapy.
The potential harmful outcomes are those resulting from a false test result. False-positive or false-negative test results can lead to the initiation of unnecessary treatment and adverse events from that treatment or under-treatment.

Setting
Ordering and interpreting HIV tropism testing should be done by physicians specializing in infectious diseases. Most patients are likely to be tested in an outpatient setting. Referral for genetic counseling is important for the explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Technically Reliable
The technical reliability of different HIV tropism testing and comparison in performance of these testing techniques are discussed in this section.

Tropism Testing Using the Trofile Assay or Enhanced Sensitivity Trofile Assay
For the clinical studies of patients with treatment failure, Whitcomb et al (2007) determined tropism at enrollment and again at baseline was determined using the original phenotypic Trofile assay for 2560 potential enrollees; 56% were CCR5-tropic only and were eligible for the clinical trials. Most other patients had D/M HIV infection; CXCR4-infection alone is rare. Of the patients enrolled, 90% had CCR5-tropic virus at baseline, 4% had D/M tropic virus, and 5% had non-typable virus infection. The original phenotypic Trofile assay had a turnaround time of 14 to 18 days, failed to work in 3% to 7% of patients, and required at least 1000 copies/mL of HIV RNA.[5] The assay was 100% effective in detecting model CXCR4-tropic or D/M HIV present in a 10% mixture, and 83% effective at a 5% mixture. Validation studies also indicated 100% accuracy of results for 38 samples with known tropism, and 100% reproducibility including repeat assays using multiple operators, instrumentation, reagent lots, and conducted over a 14-day period. No false-positive results were obtained on samples that were HIV-negative but positive for either hepatitis B or C virus.

An enhanced sensitivity Trofile assay (ESTA) has replaced the original Trofile. The ESTA can detect CXCR4-tropic virus present at levels less than 0.3% of the total virus population, and at that level of virus or higher, the assay is stated to be 100% sensitive.[26] Total viral concentration of at least 1000 copies/ml is required. However, ESTA remains limited by long turnaround time and the relatively high minimum level of viremia required, making it not useful in patients in virologic failure with low viremia. Additionally, a small proportion of samples cannot be successfully phenotyped with either generation of the Trofile assay.[7]

The MERIT study of treatment-naive patients was retrospectively reanalyzed using ESTA; approximately 15% of the subjects originally identified as CCR5-tropic had D/M- or CXCR4-tropic virus by ESTA.[8]

Wilkin et al (2011) used ESTA to reanalyze samples from four large cohort studies that had originally been evaluated for HIV tropism with the original Trofile assay.[9] Nine percent to 26% of patients with CCR5-tropic virus by the original Trofile assay had CXCR4-using virus by ESTA.

V3 Population Genotyping to Determine Tropism

The Trofile assay is a cell-based, functional (phenotypic) assay. Genotypic assays are based on the sequencing of the patient-derived HIV-1 gp 120 V3 domain, which determines the protein amino acid sequence for the major determinant of co-receptor binding. This sequencing method results in a V3 sequence that represents the average or dominant viral population sequence for each patient. The HIV V3 sequence is used to infer HIV-1 tropism using web-based bioinformatic interpretation tools developed from prior data. These are most often geno2pheno co-receptor[10,11] and position-specific scoring matrices.[12,13] Newer genotypic assays have incorporated additional components of the HIV envelope genotype (e.g., gp41) and/or components of the gp 120 gene other than the V3 domain.[14]

Genotyping can be conducted on either viral RNA samples (plasma) or on proviral DNA (peripheral blood mononuclear cells), the latter allowing tropism determination in the context of undetectable viremia.[15] Other potential advantages of genotypic assays are reduced cost, shorter turnaround time, fewer sample failures.[16]

Early genotyping studies with comparisons with original Trofile assay results reached contradictory conclusions regarding the adequacy of genotyping for predicting CXCR4 co-receptor usage. Some of the variability in genotype-phenotype assay correlation may have been due to the lower sensitivity of the original Trofile assay, and some variability may have accrued from inclusion of samples containing HIV subtypes other than B (the dominant form in Europe, the Americas, Japan, Thailand and Australia). Ultimately, the best indication against which tropism assay results should be compared is the virological outcome of patients who receive CCR5-antagonist medication.[17] Comparison of different tropism assay techniques with reference to virologic outcome of patients is discussed in the Clinical Validity section.

Newer bioinformatics algorithms continue to be developed, some of which incorporate clinical variables such as HIV-1 viral load and nadir CD4-positive count, into their prediction modeling.[18] Some studies, such as that reported by Ceresola et al (2015) in a cohort of 67 subjects with HIV, have suggested that the G2P algorithm may be more likely to overestimate the frequency of CCX4-tropic viruses compared with other methods.[19]

Table 1 summarizes studies that have evaluated the results of V3 sequencing using ESTA as the reference standard; treatment outcomes were not considered in these analyses. All studies sequenced HIV V3 RNA from plasma (standard assay); two additionally sequenced HIV V3 DNA from whole blood, which targets proviral DNA (useful for patients with low plasma levels of virus). In general, the sensitivity results indicate that V3 genotyping detects somewhat fewer CXCR4-tropic viral samples than does ESTA; the specificity results indicated that the false-positive rate is not high (i.e., few CCR5-tropic samples were identified as CXCR4-tropic). Assay concordance was relatively high. Where reported, genotyping results for proviral DNA appeared very similar to those for RNA in paired samples from the same patient population (see also Tropism Testing in Patients With Undetectable Viral Load section).

Overall and based largely on the studies of tropism assays with reference to maraviroc treatment outcome (see Clinical Validity section), the evidence has suggested that HIV V3 genotyping classifies patients as well as Trofile assays. Genotyping has additional advantages of shorter turnaround time, ability to generate results for patients who cannot be assayed by Trofile, and more access to assay providers.

Table 1. Performance of HIV V3 Genotyping with Reference to ESTA

Study	N	Patients	RT-PCR Replicates	V3 Genotyping Algorithm	V3 Genotyping vs. ESTA, %		
					Sensitivity	**Specificity**	**Concordance**
Prosperi et al (2010)[16]	55	Patients failing antiretroviral treatment	1x	G2P clonal, FPR=5.75% G2P clonal, FPR=10% G2P clonal, FPR=5.75% G2P clonal, FPR=10%	RNA=55 55 DNA=68 67	RNA=96 79 DNA=86 71	RNA=83 71 DNA=82 71
Svicher et al (2010)[15]	365	63% treatment-experienced patients	1x	G2P clonal, FPR=5% G2P clonal, FPR=10%	49 55	96 89	81 78
Sanchez et al (2010)[20]	119	Naïve and treatment-experienced patients	1x (?)	G2P clonal, FPR=5% G2P clonal, FPR=10%	37 57	93 84	79 77
Strang et al (2009)[21,a]	79	Patients evaluated for maraviroc therapy	?	G2P, FPR range, 1%-20%	NR	NR	Range, 70-94
Pou et al (2009)[22,a]	79	Banked samples, pre-ART	3x	G2P	RNA=40 DNA=36	RNA=100 DNA=100	RNA=78 DNA=77

ART: antiretroviral therapy; ESTA: enhanced sensitivity Trofile assay; FPR: false-positive rate (used as cutoff value); G2P: geno2pheno coreceptor system; NR: not reported; RT-PCR: reverse-transcriptase polymerase chain reaction.
[a] Abstract

Tropism Testing by Deep Sequencing

Because of concern that standard V3 sequencing methods used for tropism testing might miss clinically significant minor HIV variants, so-called “deep sequencing” (i.e., V3 sequencing using

next-generation sequencing methods) has been investigated for tropism testing. While standard sequencing essentially determines a population average V3 loop sequence, deep sequencing allows simultaneous sequencing and quantifying of thousands of individual V3 variants within a viral population. From this, the proportion of non-R5 variants in a given sample can be calculated using bioinformatic interpretation tools similar to those for standard V3 genotyping. Similar to the standard V3 sequencing methods, the false-positive rate for tropism prediction must be prespecified. Retrospective analyses have used G2P and a false-positive rate of 3.5% or less. The proportion of the viral population that can be detected as non-CCR5 for maraviroc treatment to remain effective has been established as 2% or less.[23] Other studies have also reported high concordance between deep sequencing and current tropism assays[17,24] and between different sequencing platforms.[25] Gibson et al (2014) reported high concordance (84%, κ=0.37) between tropism prediction for samples sequenced with deep sequencing and those sequenced with population-based sequencing.[26]

Tropism Testing in Patients With Undetectable Viral Load

The original studies of genotypic tropism tests, such as those shown in Table 1, were conducted on RNA samples from viremic patients. However, there has been interest in the use of maraviroc as part of a simplification strategy in patients already on antiretroviral therapy with undetectable plasma HIV RNA levels. Another potential indication is as intensification strategy in patients with prolonged suppression of HIV levels but with impaired CD4 gains. A 2012 study by Svicher et al demonstrated the feasibility of determining viral tropism using sequencing of proviral DNA with prediction of tropism with the geno2pheno algorithm in peripheral blood mononuclear cells from 53 subjects with HIV, most of whom had undetectable (94.3%) or low (3.7%) viral loads.[27] Additional studies, outlined in Table 2, have demonstrated high rates of concordance between tropism predicted by proviral DNA or RNA sequencing.

Table 2. Performance of HIV Proviral DNA Genotyping

Study	Study Population	DNA Sequence Success Rate	V3 Genotyping Algorithm	Comparison	Concordance	Sens	Spec
Prosperi et al (2010)[16]	55 patients failing antiretroviral treatment	NR		Proviral DNA vs RNA (ref) (n=29)	87.5% (κ=0.74; 95% CI 0.53 to 0.95; p<0.001)	NR	NR
Svicher et al (2014)[28]	253 patients with plasma HIV-1 RNA <50 copies/mL	• 93.5% for VL >100 copies HIV DNA/10^6 PBMCs • 60% for VL<100 copies HIV DNA/10^6 PBMCs	G2P clonal, FPR=5.75%	Proviral DNA (whole blood or PBMCs) vs RNA (ref) (n=143)	96.5%	NR	NR
Brown et al (2014)[29]	42 patients with plasma HIV-1 RNA ≥1000 copies/mL	97.6%	G2P clonal, FPR=10%	Proviral DNA (whole blood) vs RNA (ref)	93% (κ=0.85)	100%	89%
				Proviral DNA (PBMCs) vs RNA (ref)	95% (κ=0.90)	100%	93%
				Proviral DNA (whole blood or PBMCs) vs RNA (ref)	98% (κ=0.95)	100%	96%

CI: confidence interval; ESTA: enhanced sensitivity Trofile assay; FPR: false-positive rate; G2P; geno2pheno; NR: not reported; PBMC: peripheral blood mononuclear cell; ref: reference group; Sens: sensitivity (defined as concordant x4 results between test and reference methods/reference method CCX4); Spec: specificity (defined as concordant CCR5 results between test and reference methods/reference method CCR5); VL: viral load.

Section Summary: Technically Reliable

The evidence comparing HIV V3 population genotyping with original Trofile and ESTA using maraviroc response as the reference for all assays, strongly suggests that genotyping is equivalent to the Trofile assays in selecting patients likely to respond to maraviroc, the outcomes of interest. Studies evaluating genotyping and using paired ESTA results for reference suggest that genotyping might be somewhat less sensitive for detecting CXCR4-tropic samples; however, these studies were smaller, and most did not test in triplicate. V3 ultra-deep sequencing methods appear to have greater sensitivity in identifying CXCR4-tropic viruses, and therefore are likely to identify additional patients with HIV tropism who are negative on standard sequencing. Based largely on the maraviroc response results, HIV V3

population genotyping is considered medically necessary for patients considering immediate maraviroc treatment.

Clinically Valid

HIV Coreceptor Antagonist Therapy in Treatment-Experienced Patients

The Maraviroc versus Optimized Therapy in Viremic Antiretroviral Treatment-Experienced Patients (MOTIVATE) 1 and 2 trials assessed the efficacy of maraviroc in patients previously treated or resistant to 3 antiretroviral drug classes and with HIV-1 RNA levels exceeding 5,000 copies/mL.[30] MOTIVATE-1 was conducted in Canada and the United States, and MOTIVATE-2 in Australia, Europe and the United States, using identical study designs. A total of 1,075 patients were randomized to 3 trial arms, and 1,049 received at least one dose of study drug: placebo (n=209), maraviroc once daily (n=414), or maraviroc twice daily (n=426). Selected subjects had only CCR5-tropic HIV-1 infections, as determined by the original Trofile assay for HIV tropism (see 'Tropism Testing,' following). At 48-weeks follow-up in an intention-to-treat analysis, 16% in the placebo group and 45% in both maraviroc-treated groups had HIV-1 RNA levels less than 50 copies/mL. The mean increase in CD-4 count from baseline was 60 in the placebo group compared to 120 in the maraviroc groups. Based on the early trial results and review by the FDA Antiviral Drugs Advisory Committee, the FDA concluded that, compared to placebo, maraviroc significantly reduced HIV RNA copy number, and significantly increased CD4 cells, both validated markers of improved health outcomes.[31] At nearly 2 years of follow-up (96 weeks), 81% to 87% of maraviroc-treated patients maintained these responses with no new or unexpected events impacting safety.[32] At 5-year follow-up, 46 deaths were reported, with ongoing low rates of hepatic failure, malignancy, and myocardial infarction.[33]

In contrast, in a trial of 167 patients infected with dual- or mixed-tropic HIV-1, randomized to receive optimal therapy plus maraviroc or placebo, there was no difference in outcomes between treatment groups, indicating maraviroc treatment failure in patients harboring assay-detectable CXCR4-tropic HIV-1 populations.[34]

HIV Coreceptor Antagonist Therapy in Treatment-Naive Patients

The MERIT (Maraviroc versus Efavirenz in Treatment-Naive Patients) study is a randomized, double-blind, multicenter study in subjects infected with CCR5-tropic HIV-1 according to the original Trofile assay.[8] Patients had plasma HIV-1 RNA levels of at least 2,000 copies/mL and did not have: 1) prior antiretroviral therapy for longer than 14 days, 2) an active or recent opportunistic infection or primary HIV-1 infection, or 3) resistance to zidovudine, lamivudine or efavirenz. Subjects were randomized to 2 doses of either maraviroc or efavirenz, each in combination with zidovudine/lamivudine. In a pre-planned interim analysis, the lower dose of maraviroc failed to meet prespecified efficacy criteria and was discontinued. Patients were stratified by screening HIV-1 RNA levels and by geographic region. The median CD4 cell counts and mean HIV-1 RNA at baseline were similar for both treatment groups.

At 96 weeks, after re-analysis using results from an enhanced sensitivity Trofile assay (ESTA; see 'Tropism Testing,' section next), virologic response rates in both treatment arms were approximately equal, and there were fewer discontinuations due to adverse events in the maraviroc arm.

Although most newly infected patients harbor CCR5-tropic HIV virus alone, a study of 150 individuals from 2 recent seroconverter cohorts documented 4% infection with detectable CXCR4-tropic virus (either mixed or, rarely, CXCR4-only), indicating that tropism analysis is necessary, even for the recently infected.[35]

Comparison of HIV Tropism Testing Methods to Identify Candidates for HIV Coreceptor Antagonist Therapy

Table 3 summarizes the results of studies comparing V3 genotyping results with virologic outcomes after maraviroc treatment. Because most studies use G2P for interpretation, only these results are presented. Where reported, results of original Trofile and ESTA results are also shown. Only the study reported by Gonzalez-Serna et al (2012) was prospective; for the others, V3 genotyping was conducted retrospectively on banked samples.[36] McGovern et al (2010)[37] likely included data reported by Harrigan et al (2009).[38] Results varied by the false-positive rate cutoff chosen for the G2P algorithm. If the result provided by G2P for a specific V3 sequence was higher than the chosen cutoff, the prediction of HIV-1 coreceptor tropism was CXCR4. Because the G2P distributions for CCR5- and CXCR4-tropic viruses overlapped, no cutoff value permitted perfect classification. Using a higher cutoff value was considered a conservative choice because predictions of CXCR4-tropism were more likely to be true predictions; the trade-off was that some true CXCR4-tropic HIV infections would be falsely identified as CCR5-tropic. For example, a cutoff value of 5.75% was optimized retrospectively for the MOTIVATE trial data (2009),[39] but, for routine clinical practice, the 2011 European guidelines on HIV-1 tropism testing recommended a cutoff of 10% for sequencing of samples in triplicate, or a cutoff of 20% when only a single sequence is generated.[40]

The results in Table 3 indicate that, depending on the G2P cutoff value chosen, V3 sequencing results can be generated that are very similar in their ability to predict response to maraviroc to both the original Trofile assay and the ESTA test. The Gonzalez-Serna study reported somewhat different results, with lower sensitivity and higher specificity for maraviroc response using similar G2P cutoff values.[36] This study prospectively enrolled patients attending the infectious disease service of a university hospital, as opposed to the other retrospective studies of carefully selected clinical trial participants, but was also much smaller. Sequencing in this study was not done in triplicate (as it was in the other studies)

Table 3. Performance of HIV V3 Genotyping, Trofile, and ESTA Assays With Reference to Maraviroc Treatment Outcomes

Characteristics	McGovern et al (2012)[41]	Harrigan et al (2009)[38,a]	Gonzalez-Serna et al (2012)[36]	McGovern et al (2010)[37]
Sample size	705	623	73	1164
Patients	Drug-naive patients from MERIT trial	Treatment-experienced patients from MOTIVATE and 1029 studies	Patients with persistent viral load and on treatment hiatus	Treatment-experienced patients from MOTIVATE and 1029 studies
RT-PCR replicates	3×	3×	1×	3×
VR definition	<50 copies/mL at week 48	• <50 copies/mL or reduction • ≥2 log at week 8	• <50 copies/mL or reduction • ≥1 log on day 8	• <50 copies/mL or reduction • ≥2 log at week 8
V3 genotyping algorithm	G2P, FPR=5.75%	G2P, FPR=5%	• G2P clonal • FPR=5% • FPR=10%	G2P, FPR=5%
V3 genotyping vs VR to MVC	Sens=94% Spec=13%	Sens=85% Spec=36%	Using FPR=5%: • Sens=58% • Spec=89% Using FPR=10% • Sens=68% • Spec=83%	Sens=89% Spec=24%
Original Trofile vs VR to MVC	NR	Sens=90% Spec=31%	NR	Sens=92% Spec=20%
ESTA vs VR to MVC	Sens=91% Spec=22%	NR	NR	NR

ESTA: enhanced sensitivity Trofile assay; FPR: false-positive rate (used as cutoff value); G2P: geno2pheno coreceptor system; MERIT: Maraviroc versus Efavirenz Regimens as Initial Therapy trial; MOTIVATE: Maraviroc Plus Optimized Therapy in Viremic Antiretroviral Treatment-Experienced Patients trials; MVC: maraviroc; NR: not reported; RT-PCR: reverse-transcriptase polymerase chain reaction; Sens: sensitivity; Spec: specificity; VR: virologic response.
[a] Abstract.

The studies in Table 4 suggest that deep sequencing has similar performance characteristics as ESTA and the original Trofile assay in predicting response to maraviroc treatment. Moreover, as noted by Swenson et al (2011), the group of patients with 2% to 20% non-CCR5 virus, according to deep sequencing, had minority non-CCR5 variants that were not reliably detected by the original Trofile assay; however, this particular group of patients had poor response to maraviroc, with 27% of the patients achieving virologic suppression at week 48—this is similar to the non-CCR5 group as a whole (26%) and to patients with greater than 20% non-R5 virus (25%).[42] Kagan et al (2012) reanalyzed samples from the MOTIVATE and A4001029 studies to compare ultra-deep sequencing either alone or as a reflex test following standard triplicate V3 sequencing with the ESTA test.[43] Both ultra-deep sequencing methods demonstrated improved sensitivity in identifying maraviroc responders compared with standard sequencing. These results would suggest that detection of minority non-CCR5 variants by deep sequencing may be important for predicting response.

A 2014 prospective, phase 3 trial by Heera et al, which randomized treatment-naive patients with HIV to genotypic or phenotypic (Trofile) testing, showed no significant differences in treatment response.[45] Previously presented results of European cohort studies have shown maraviroc virologic extended response rates of 69% to 82% in those patients in which HIV variants were genotypically classified CCR5-tropic.[46]

Nozza et al (2016) conducted a multicenter, randomized, open-label, noninferiority trial among treatment-experienced subjects with HIV-1 RNA of 500 or more copies per milliliter.[47] One hundred fifty-five participating patients were randomized (1:1) to undergo coreceptor tropism testing by the G2P algorithm (false-positive rate >10%) or the Trofile assay before starting a new antiretroviral regimen. Only patients with an R5 tropic virus were enrolled and received

treatment with maraviroc plus optimized background therapy. The primary end point was the 48-week proportion of patients with treatment success (defined as HIV RNA <50 copies/mL). In the Trofile arm, 87% of patients achieved treatment success at 48 weeks, and in the G2P arm, 89% achieved treatment success at 48 weeks; these results suggest noninferiority.

Garcia et al (2014) reported in abstract form the results of the PROTEST study, which evaluated the initiation of maraviroc plus 2 nucleoside reverse-transcriptase inhibitors in aviremic subjects based on genotypic tropism testing of proviral DNA, rather than viral RNA.[48] The study included 74 maraviroc-naive HIV-1 patients with viral load less than 50 c/mL on stable antiretroviral therapy, requiring medication change due to toxicity, and CCR5-tropic HIV by proviral DNA genotypic tropism testing. Of the included subjects, 62 (84%) maintained a viral load less than 50 c/mL through 48 weeks of therapy. The remaining 12 (16%) discontinued treatment: 2 (3%) withdrew informed consent; 2 (3%) died of non-study-related causes; 5 (7%) developed protocol-defined virologic failure; and 1 each (1% each) had a shift to CCX4 between the screening and baseline visits or was lost to follow-up, or developed an antiretroviral therapy-related adverse event.

Clinically Useful

Among patients who are undergoing HIV tropism testing to determine if they are suitable for maraviroc treatment, there is no direct evidence that HIV tropism testing results in improved health outcome in terms of overall or disease-specific survival. However, there is evidence that selection of candidates for HIV coreceptor antagonist therapy using HIV tropism tests results in a high rate of treatment success, demonstrated as increased virologic suppression. Plasma viral load is the single best predictor of progression to AIDS and death. Successful virologic suppression leads to longer overall survival and disease-specific survival among HIV-infected patients.[49,50]

Table 4. Performance of HIV V3 Deep Sequencing, Trofile, and ESTA Assays With Reference to Maraviroc Treatment Outcomes

Characteristics	Gonzalez-Serna et al (2011)[36]	Swenson et al (2011)[44]	Swenson et al (2011)[42]	Kagan et al (2012)[43]
Sample size	27	859	851	327
Patients	Patients with persistent viral load and on treatment hiatus	Drug-naive patients from MERIT trial	Treatment-experienced patients from MOTIVATE and A4001029 studies	Treatment-experienced patients from MOTIVATE and A4001029 studies who received MVC
RT-PCR replicates	3×	3×	3×	3×
VR definition	• <50 copies/mL or reduction • ≥1 log on day 8	<50 copies/mL at week 48	<50 copies/mL at week 48	<50 copies/mL or >2 log decline at week 8
V3 genotyping algorithm	G2P clonal, FPR ≤3.5%	G2P clonal, FPR ≤3.5%	• $PSSM_{X4/R5}$, FPR ≥ -4.75 • ≈90% conc with G2P	• G2P, FPR ≤5.75% • $PSSM_{X4R5}$, FPR ≥ -4.75
V3 genotyping vs VR to MVC	Sens=83% Spec=22%	Sens=93% Spec=15%	Sens=83% Spec=36%	PPV[a]=65% NPV[a]=61%
Original Trofile vs VR to MVC	NR	NR	Sens=93% Spec=17%	NR
ESTA vs VR to MVC	NR	Sens=90% Spec=21%	NR	PPV=66% NPV=59%

conc: concordance; ESTA: enhanced sensitivity Trofile assay; FPR: false-positive rate (used as cutoff value); G2P: geno2pheno coreceptor system; MERIT: Maraviroc versus Efavirenz Regimens as Initial Therapy trial; MOTIVATE: Maraviroc Plus Optimized Therapy in Viremic Antiretroviral Treatment-Experienced Patients trials; MVC: maraviroc; NPV: negative predictive value; NR: not reported; PPV: positive predictive value; PSSM: position-specific scoring matrix; RT-PCR: reverse-transcriptase polymerase chain reaction; Sens: sensitivity; Spec: specificity; VR: virologic response.

[a] PPV refers to the proportion of CCR5 subjects who achieved virologic response at 8 wk. NPV refers to the proportion of non-CCR5 subjects who failed to have a virologic response at 8 wk.

Section Summary: HIV Tropism Testing to Identify Candidates for HIV Coreceptor Antagonist Therapy

Evidence from randomized controlled trials (RCTs) and observational studies has suggested high sensitivity of the Trofile assay, the ESTA test, V3 sequencing, and V3 deep sequencing in identifying treatment-naive and treatment-experienced HIV-infected candidates for HIV coreceptor antagonist therapy, with treatment outcome as the reference. Studies have also suggested a moderate (>70%) level of concordance between different HIV tropism testing techniques.

HIV TROPISM TESTING FOR TREATMENT MONITORING AND THERAPY FAILURE

Clinical Context and Test Purpose

The purpose of HIV tropism testing in patients with HIV infection receiving treatment with HIV coreceptor antagonist or who have failed coreceptor antagonist therapy is to monitor or detect possible tropism switching.

The question addressed in this evidence review is: Does assessment of HIV tropism among HIV-infected patients undergoing maraviroc therapy, or patients who have experienced virologic failure while on maraviroc therapy, result in an improved health outcome compared with no testing to identify HIV tropism switching?

The following **PICOs** were used to select literature to inform this review.

Populations
The relevant populations of interest are 1 of 2 patient populations: (1) HIV-infected patients undergoing treatment with HIV coreceptor antagonists; or (2) patients who have failed coreceptor antagonist therapy.

Interventions
The interventions of interest are HIV tropism testing using the Trofile assay, ESTA, V3 sequencing, or V3 deep sequencing.

Comparators
The comparator of interest is no HIV tropism testing.

Outcomes
The potential beneficial outcomes of primary interest would be identification of HIV-infected patients who might benefit from changes in antiretroviral therapy regimen.

The potential harmful outcomes are those resulting from a false test result. False-positive or false-negative test results can lead to the initiation of unnecessary treatment and adverse events from that treatment.

Setting
Ordering and interpreting of HIV tropism testing should be done by physicians specializing in infectious diseases. Most patients are likely to be tested in an outpatient setting. Referral for genetic counseling is important for the explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Technically Reliable
Evidence on the technical reliability of different HIV tropism testing techniques has been discussed in the section on identifying candidates for HIV coreceptor antagonist therapy.

Clinically Valid
Viral strains transmitted in vivo are usually CCR5-tropic.[51] Over time, and more often after antiretroviral treatment, detectable CXCR4-tropic virus emerges in about half of patients, and this virus is associated with rapid CD4 cell depletion and clinical disease progression.[52,53] However, patients whose infection remains predominately CCR5-tropic can also experience disease progression. HIV-1 viral load is a strong prognostic indicator of HIV disease progression, and suppression of viral load is a critical goal of antiretroviral therapy.[7] Viral rebound (virologic failure) is typically followed by a reduction in CD4 cell count (immunologic failure), and if not adequately addressed by changes in treatment, by HIV-related events (clinical progression). Thus, the success of any antiretroviral treatment regimen is monitored by measuring HIV-1 RNA level and CD4 cell count; significant changes direct patient management.

The prominent reason for individual treatment failure in the clinical studies was an outgrowth of a minor CXCR4-tropic virus population not detected at screening. However, treatment failure with CCR5-tropic virus alone also occurred, indicating that resistance to CCR5 antagonists occurs independently of tropism. In vitro studies have provided extensive information on resistance; mechanisms may involve the ability of HIV to bind the CCR5 inhibitor-receptor

complex. Resistance to CCR5 antagonists has been associated with an increased affinity for CCR5, changes in the gp120 V3 loop, and with other gp120 (or other envelope) changes.

A concern about treatment with CCR5 coreceptor antagonists is that small, undetectable populations of CXCR4-tropic virus would be enriched and would accelerate disease progression. However, in a randomized, placebo-controlled phase 2 study of maraviroc treatment of patients with D/M-tropic infections, there was no evidence that this was the case.[4] The association between CXCR4 tropism (defined with the original Trofile assay) and clinical progression has been shown to be independent of CD4 cell count and HIV-1 RNA level (adjusted hazard ratio, 3.82; 95% confidence interval, 1.69 to 8.60; p=0.001, vs. patients with CCR5-tropic infection only).[54]

Fatkenheuer et al (2008) performed a post hoc analysis of the virologic response according to HIV tropism at baseline and at treatment failure[55] using pooled data from the MOTIVATE 1 and 2 trials. Virologic failure occurred in 53% of placebo-treated patients and in 22% to 23% in the maraviroc treatment arms. However, of the 133 treatment failures in the maraviroc groups, 76 (57%) had CXCR4 or D/M tropism, as compared with only 6 (6%) of 95 in the placebo group; this finding raises concerns that maraviroc treatment could lead to the emergence of CXCR4-tropic subpopulations and, ultimately, more rapid development of clinical progression. However, this was not the case because the CXCR4 maraviroc treatment failures were not associated with declines in CD4 cell counts or with disease progression.

Raymond et al (2015) conducted a multicenter study to characterize virologic failure in patients treated with maraviroc (n=27).[56] Patients had been screened for HIV tropism using population-based V3 genotyping before maraviroc initiation. Authors determined HIV tropism and resistance of R5 viruses to maraviroc at baseline and at virologic failure retrospectively using an ultra-sensitive recombinant virus assay. Among the 27 patients experiencing virologic failure, 12 harbored CXCR4-using viruses, and 15 had R5 viruses at failure. Four of the 12 harboring CXCR4 viruses were infected with D/M-tropic viruses, according to the recombinant virus assay before maraviroc initiation.

The most common mechanism of maraviroc treatment failure is the emergence of a CXCR4-tropic viral population. However, this does not necessarily correlate with rapid clinical progression.[57]

Clinically Useful

For HIV-infected patients who are receiving maraviroc treatment, there is no direct evidence that HIV tropism testing—both during treatment monitoring and at virologic failure—results in improved health outcomes. The lack of evidence that HIV tropism testing might predict treatment failure among patients who are on maraviroc therapy, therefore, suggests that HIV tropism testing in this population might not result in improved health outcomes. Treatment failure is detected by increased viral load and decreased CD4 cell count,[7] indicating that maraviroc treatment can be discontinued.

Section Summary: HIV Tropism Testing for Treatment Monitoring and Therapy Failure

The evidence for the use of HIV tropism testing for treatment monitoring and virologic failure in patients receiving maraviroc treatment includes post hoc analysis of data from RCTs and observational studies. While the emergence of the CXCR4-tropic viral population is the most common mechanism of maraviroc treatment failure, treatment failure is also common among

patients with CCR5-tropic viruses. There is no evidence that tropism testing for treatment monitoring might predict treatment failure.

HIV TROPISM TESTING FOR HIV PROGNOSIS

Clinical Context and Test Purpose

The purpose of HIV tropism testing in patients who have HIV infection is to identify patients who might experience rapid disease progression, such as the short-term risk of AIDS and death.

The following **PICOs** were used to select literature to inform this review.

Populations

The relevant population of interest is HIV-infected patients.

Interventions

The interventions of interest are HIV tropism testing using the Trofile assay, ESTA, V3 sequencing, or V3 deep sequencing.

Comparators

The comparator of interest is no HIV tropism testing.

Outcomes

The potential beneficial outcomes of primary interest would be identification of HIV-infected patients who might benefit from changes in antiretroviral therapy regimen.

The potential harmful outcomes are those resulting from a false test result. False-positive or false-negative test results can lead to the initiation of unnecessary treatment and adverse events from that treatment or under-treatment.

Setting

Ordering and interpreting of HIV tropism testing should be done by physicians specializing in infectious diseases. Most patients are likely to be tested in an outpatient setting. Referral for genetic counseling is important for the explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Technically Reliable

Evidence on the technical reliability of different HIV tropism testing techniques has been discussed in the section on identifying candidates for HIV coreceptor antagonist therapy.

Clinically Valid

Aside from the specific situation of maraviroc treatment failure, CXCR4-tropic virus infection has been associated with more rapid disease progression, compared with CCR5 infection, in several studies (e.g., Wilkin et al [2011],[9] Almeida et al [2014],[58] Visseaux et al [2014][59]). However, other studies have demonstrated no independent association between the HIV tropism and HIV-related outcomes, including short-term risk of AIDS and death[60] and hepatic fibrosis in HIV/hepatitis C virus–coinfected patients.[61]

Casadella et al (2017) conducted a nested case-control study within the EuroSIDA cohort to investigate whether plasma HIV-1 tropism testing could identify subjects at higher risk for clinical progression and death in routine clinical management.[62] Cases (N=100) were subjects with AIDS or who had died from any cause, with a plasma sample of HIV-1 RNA greater than 1000 copies/mL available for tropism testing 3 to 12 months prior to the event. At least 1 matched (for age, HIV-1 RNA, and HCV status) control per case was selected (N=166). Baseline tropism was not associated with the risk of clinical progression or death (OR=0.66; 95% CI, 0.33 to 1.33). Female gender (OR=2.13; 95% CI, 1.04 to 4.36), being on antiretroviral therapy (OR=2.12; 95% CI, 1.15 to 4.41), baseline CD4 count (OR=0.90; 95% CI, 0.80 to 1.00), per 100 cells/mm^3 higher and calendar year of sample (OR=0.84; 95% CI, 0.77 to 0.91) per more recent year were independently associated with disease progression.

Castagna et al (2016) conducted a longitudinal cohort study of HIV-1-treated adults to determine the rate of HIV tropism switch among subjects using antiretroviral therapy both in presence of persistently detectable (PD) or undetectable (PU) viral load and to evaluate the association between tropism switch and disease progression.[63] Over a median follow-up period of 22.6 months (range, 19.8-28.1 months), 124 PD and 71 PU patients showed similar rates of switch to a non-R5 virus (PD=6.9/100 person-years; 95% CI, 3.7 to 11.2/100 person-years; PU=8.0/100 person-years; 95% CI, 3.4 to 14.5/100 person-years). Switch to non-R5 virus was predicted by nadir CD4-positive count before the start of the follow-up period. Twenty-two (18%) PD and 4 (6%) PU subjects experienced disease progression (p=0.02). The risk of disease progression was independently associated with disease progression (adjusted hazard ratio, 4.06; 95% CI, 1.20 to 13.80).

Clinically Useful
Currently, there is no direct evidence that HIV tropism testing for assessment of disease progression among HIV-infected patients results in improvement of health outcomes. More studies are required comparing HIV tropism testing with other tests (CD4, viral load) for predicting disease progression.

Section Summary: HIV Tropism Testing for HIV Prognosis
The evidence for the use of tropism testing for HIV prognosis includes nested case-control and cohort studies. While some studies demonstrated an association between the HIV tropism and HIV-related outcomes, the findings have been inconsistent. Viral load and CD4 count remain independently associated with disease progression among HIV-infected patients across studies.

SUMMARY OF EVIDENCE
For individuals who have HIV infection who are being considered for HIV coreceptor antagonist therapy who receive HIV tropism testing, the evidence includes RCTs. Relevant outcomes are overall survival, disease-specific survival, morbid events, quality of life, hospitalizations, medication use, and treatment-related morbidity. RCTs on treatment-naive and treatment-experienced HIV-infected patients have provided evidence that selection of candidates for HIV coreceptor antagonist therapy using HIV tropism testing results in higher rates of treatment success compared with HIV coreceptor antagonist therapy without HIV tropism testing. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with HIV infection receiving HIV coreceptor antagonist therapy or who have failed coreceptor antagonist therapy who receive HIV tropism testing, the evidence includes post hoc analysis of RCTs and observational studies. Relevant outcomes are overall survival, disease-specific survival, morbid events, quality of life, hospitalizations, medication use, and treatment-related mortality and morbidity. Current evidence does not indicate improved outcomes with additional tropism monitoring during treatment. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with HIV infection who are undergoing tests to predict disease progression who receive HIV tropism testing, the evidence includes observational studies. Relevant outcomes are overall survival, disease-specific survival, morbid events, quality of life, hospitalizations, and medication use. Current evidence is inconsistent in as relates to whether HIV tropism testing independently predicts disease progression among HIV-infected patients. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

HIV Medicine Association-Infectious Disease Society of North America

The HIV Medicine Association of the Infectious Disease Society of North America released updated guidelines on the on the management of persons infected with HIV in 2013.[64] These guidelines state that tropism testing should be performed if the use of a CCR5 antagonist is being considered (strong recommendation, high quality evidence). The guidelines also state that “routine tropism testing is not recommended prior to initiation of other regimens because of cost and lack of demonstrated benefit.” The guidelines do not specify the preferred method of tropism testing.

European Consensus Group

The European Consensus Group on clinical management of tropism testing states that tropism testing is indicated for patients who fail treatment or have unacceptable toxicity and a CCR5 inhibitor is being considered.[40] In the absence of evidence, the group provides no guidance regarding tropism testing for newly diagnosed patients whose immediate treatment plan does not include a CCR5 inhibitor. In the absence of adequate data, the group could provide no guidance regarding the question of testing treatment-naïve patients prior to the start of a regimen not including a CCR5 inhibitor, in anticipation of need for a fast change to a CCR5 inhibitor due to the toxicity of the initial treatment regimen. For patients with a plasma HIV RNA load >1,000 copies/ml, tropism testing can be done by Trofile ESTA or by population genotypic analysis of the V3 loop, indicating for both a moderate level of evidence based on well designed, nonrandomized trials or cohort studies with long-term clinical outcomes. For patients with a plasma HIV RNA load <1,000 copies/mL, genotyping is the preferred method.

Health and Human Services Panel
The Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents published federally approved HIV/AIDS medical practice guidelines in 2014 (updated 2018), which make the following recommendations on coreceptor tropism assays[65]:

- Recommendations with "A" (strong) rating:
  - A coreceptor tropism assay should be performed whenever the use of a CCR5 coreceptor antagonist is being considered (level of evidence: I [data from randomized controlled trials]).A phenotypic tropism assay is preferred to determine HIV-1 coreceptor usage (level of evidence: I).
- Recommendations with "B" (moderate) rating:
  - Coreceptor tropism testing is also recommended for patients who exhibit virologic failure on a CCR5 antagonist (level of evidence: III [expert opinion]).
  - A genotypic tropism assay should be considered as an alternative to predict HIV-1 coreceptor usage (level of evidence: II [data from well-designed nonrandomized trials or observational studies with long-term clinical outcomes]).

Government Regulations
National /Local:

There are no national or local Medicare coverage determinations on this topic. Requests would be reviewed on an individual consideration basis.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

Genetic Testing – HIV Genotyping and Phenotyping (retired)

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through July 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
5/1/07	3/26/07	5/1/07	Joint policy, "Infectious Agent Drug Susceptibility Phenotype Prediction Using Regularly Updated Genotypic Bioinformatics" established
7/1/08	5/17/08	5/1/08	Routine maintenance
5/1/11	3/17/11	3/3/11	Added tropism to the policy. Policy title changed to "Genetic Testing - Genotyping and Phenotyping for HIV Treatment, Including Tropism (e.g., Trofile®) and Virtual Phenotyping"
3/1/13	12/11/12	12/31/12	Policy title changed from "Genetic Testing - Genotyping and Phenotyping for HIV Treatment, Including Tropism (e.g., Trofile®) and Virtual Phenotyping." Policy split into two parts to mirror BCBSA policies; this section entitled "Laboratory Testing for HIV Tropism." The other policy is entitled, "Genetic Testing-Genotyping and Phenotyping for HIV Treatment." No change in policy status.
5/1/14	2/24/14	3/3/14	Minor updates to rationale and references; no change in policy status.
11/1/15	8/18/15	9/16/15	Routine maintenance. Removed criteria from the bullet under the inclusions to be consistent with FDA prescribing information for maraviroc. References and rationale updated.
9/1/16	6/21/16	6/21/16	Routine policy maintenance. No changes to policy status.
9/1/17	6/20/17	6/20/17	Routine policy maintenance. No changes in policy status.
9/1/18	6/19/18	6/19/18	Rationale updated, added references 11, 13, 47, 49, 50, 55, 60 and 61. No changes in policy status.

11/1/19	8/20/19		Routine policy maintenance. No change in status.
11/1/20	8/18/20		Routine policy maintenance. No change in policy status.
11/1/21	8/17/21		Routine maintenance
11/1/22	8/16/22		Routine policy maintenance, no change in policy status.
11/1/23	8/15/23		Routine policy maintenance, no change in status. Vendor managed: Avalon. (ds)
11/1/24	8/20/24		Routine policy maintenance, no change in status. Vendor managed: Avalon. (ds)

Next Review Date: 3rd Qtr. 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: LABORATORY TESTING FOR HIV TROPISM

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply.
BCNA (Medicare Advantage)	See government section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.