Urinary Metabolite Tests for Adherence to Direct-Acting Antiviral Medications for Hepatitis C

Archived Medical Policy

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Policy # 00483
Original Effective Date: 11/16/2015
Archived Date: 11/15/2017

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers measurement of direct-acting antiviral drug metabolite levels for the purpose of monitoring adherence to treatment for hepatitis C infection to be investigational.*

Background/Overview

DIRECT-ACTING ANTIVIRAL MEDICATIONS
Metabolites of some direct-acting antiviral (DAA) medications (e.g., sofosbuvir) can be measured in the urine. Measurement of urine drug levels reflects serum levels and thus has the potential for use as a test of adherence.

While DAA medications have been a breakthrough treatment for chronic hepatitis C infection, they are also very costly. This produces a greater incentive to manage and monitor use to avoid prescribing in situations where they will be of no benefit. Maximizing adherence will ensure that the greatest amount of treatment benefit is achieved, and that the medications are being used in the most cost-effective manner.

Adherence to Treatment for Hepatitis C infection
Adherence to a full course of medication treatment is largely unknown for many of the newest DAA medications. However, data from adherence to other medications for hepatitis C infection suggest that it may be suboptimal on average. A prior Veteran’s Administration study on rates of discontinuation for interferon and ribavirin in patients with hepatitis C infection reported that 54.9% of all patients discontinued treatment early. For the first-generation DAA boceprevir, Gordon et al (2012) analyzed adherence in the SPRINT-2 and RESPOND-2 trials. Adherence above 80% was reported for 63% of the treated patients in 1 trial and 71% in the other. For patients with adherence above 80%, the sustained virologic response (SVR) was 86% and 90% in the respective trials. By contrast, for patients with adherence below 80%, rates of SVR were 8% and 32%, respectively.

*This statement does not pertain to all patients and should not be used as a standard for clinical practice.
The newer DAA medications (e.g., sofosbuvir, simeprevir, ledipasvir) have greater efficacy, fewer adverse effects, and greater convenience than earlier agents. This would be expected to improved adherence; however, empirical data for this is lacking, particularly data on treatment in real-world settings.

Some literature on factors influencing adherence to hepatitis C treatment has been published, but most is prior to availability of DAAs. A 2014 systematic review analyzed 9 studies on factors influencing adherence. Two factors had a significant negative association with adherence, psychiatric disorders, and higher doses of medications. In addition, female gender showed a trend toward a negative association. Human immunodeficiency virus (HIV) coinfection and hemoglobin level were positively associated with adherence. Another systematic review in 2013 evaluated adherence to treatment for hepatitis B and C infections, prior to availability of DAAs. This review included 13 studies on hepatitis C. Mean adherence rates in these studies ranged from 27% to 97%, and the percentage of patients who had adherence rates above 80% ranged from 27% to 96%.

In addition to maximizing treatment success and cost-effectiveness, knowledge about treatment adherence can assist clinicians in managing treatment failures. Some patients will not achieve a SVR, even with the newer agents with the greatest efficacy. In these patients, retreatment is an important consideration, and can be difficult. In deciding on retreatment, information that would indicate whether the failure is due to nonadherence or nonresponse to the medication is helpful in determining whether retreatment is indicated, and in determining which medication(s) should be used during retreatment.

Methods of Measuring Adherence
Various methods can be used to monitor adherence. Patient report is the most common and efficient method, but this is the most subjective and has been shown to overestimate adherence. Pill count is another method, but is more cumbersome, and can be easily manipulated by patients. More sophisticated monitoring methods, such as sensors built into pill bottles, are expensive and usually reserved for research studies.

Measuring concentrations of medication in the serum or urine may be the most objective measure for evaluating adherence. This requires a blood or urine sample, and good benchmarks for levels that indicate optimal adherence. There is some ability to manipulate these results (i.e., if correct doses are taken near the time of measurement but not at other times), but this is more difficult than with other methods.

SOF-Adhere
SOF-Adhere is a commercially available assay for the presence of metabolites to sofosbuvir. The test is performed on a patient’s urine sample, and uses liquid chromatography mass spectrometry to measure
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drug levels. It is intended for use with patients who are being treated with sofosbuvir (Sovaldi, Harvoni) as an aid for determining adherence.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Urine metabolite tests for adherence to antiviral medications for hepatitis C infection (e.g., SOF-Adhere®‡; Precision Toxicology) are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of this test.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

Measurement of serum DAA metabolites is best considered a potential component of a therapeutic intervention for hepatitis C infection, with the intent of improving treatment response by increasing adherence. The optimal study design for a therapeutic intervention is a randomized controlled trial (RCT) that includes clinically relevant measures of health outcomes. RCTs are particularly important when evaluating adherence because the multiple potential variables influencing adherence will be difficult to control for in nonrandomized studies.

A review of the MEDLINE database did not identify any published studies addressing the efficacy of measuring serum DAA metabolites to assess compliance. Several abstracts and meeting presentations, representing unpublished studies, were cited on the test developer’s website (Precision Toxicology).

RCTs are needed to evaluate the efficacy of measurement of serum DAA metabolites in monitoring adherence. These RCTs should compare treatment using urine monitoring for adherence with treatment not using urine monitoring (i.e., either a comparison with no adherence monitoring or a comparison with alternative methods of monitoring adherence). Outcomes of treatment should be, at minimum, adherence measured as rigorously as possible and/or treatment response.

SUMMARY OF EVIDENCE

For individuals who have hepatitis C infection and are receiving treatment with DAA medications who receive monitoring adherence to DAAs by measuring urinary metabolites, the evidence includes no
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published studies that evaluate the impact on adherence to DAA agents. Relevant outcomes are medication use. To demonstrate that such testing improves outcomes, RCTs are needed to assess treatment with and without measurement of DAA metabolites. Ideally, the outcome measures in these trials would be adherence to DAAs and SVR. The evidence is insufficient to determine the effects of the technology on health outcomes.

References

Policy History

Original Effective Date: 11/16/2015
10/29/2015 Medical Policy Committee review
11/16/2015 Medical Policy Implementation Committee approval. New Policy.
10/01/2016 Coding update
11/03/2016 Medical Policy Committee review
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
11/02/2017 Medical Policy Committee review. Recommend archiving policy.

Next Scheduled Review Date: Archived medical policy.

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®), copyright 2016 by the American Medical Association (AMA).

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*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

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2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
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