MASSACHUSETTS

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Medical Policy

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

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Policy Number: 742

BCBSA Reference Number: 2.04.134A
NCD/LCD: N/A

Related Policies

None

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO Blue[SM] and Medicare PPO Blue[SM] Members

Measurement of direct-acting antiviral drug metabolite levels for the purpose of monitoring adherence to treatment for hepatitis C infection is considered **INVESTIGATIONAL**.

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	This is **not** a covered service.
Commercial PPO and Indemnity	This is **not** a covered service.
Medicare HMO Blue[SM]	This is **not** a covered service.
Medicare PPO Blue[SM]	This is **not** a covered service.

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

CPT Codes

There are no specific CPT codes.

Description

DIRECT-ACTING ANTIVIRAL MEDICATIONS

Metabolites of some direct-acting antiviral (DAA) medications (eg, 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.[1] For the first-generation DAA boceprevir, Gordon et al (2012) analyzed adherence in the SPRINT-2 and RESPOND-2 trials.[2] 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.

The newer DAA medications (eg, 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.[3] 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. 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.[4] 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.[4] 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 (ie, 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 drug levels. It is intended for use with patients who are being treated with sofosbuvir (Sovaldi, Harvoni) as an aid for determining adherence.

Summary
Metabolites of some direct-acting antiviral (DAA) medications can be measured in the urine. Measurement of urine drug levels reflects serum drug levels and thus has the potential for use as a test of adherence.

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 published studies that evaluate the impact on adherence to DAA agents. Relevant outcomes are medication use. To demonstrate that such testing improves outcomes, randomized controlled trials 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 sustained virologic response. The evidence is insufficient to determine the effects of the technology on health outcomes.

Policy History
Date	Action
12/2019	Policy updated with literature review through December 1, 2019, no references added. Policy statements unchanged.
12/2015	New medical policy describing investigational indications. Effective 12/1/2015.

Information Pertaining to All Blue Cross Blue Shield Medical Policies
Click on any of the following terms to access the relevant information:
Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

References

1. LaFleur J, Hoop R, Morgan T, et al. High rates of early treatment discontinuation in hepatitis C-infected US veterans. BMC Res Notes. 2014;7:266. PMID 24758162
2. Gordon SC, Yoshida EM, Lawitz EJ, et al. Adherence to assigned dosing regimen and sustained virological response among chronic hepatitis C genotype 1 patients treated with boceprevir plus peginterferon alfa-2b/ribavirin. Aliment Pharmacol Ther. Jul 2013;38(1):16-27. PMID 23710734
3. Mathes T, Jaschinski T, Pieper D. Adherence influencing factors - a systematic review of systematic reviews. Arch Public Health. 2014;72(1):37. PMID 25671110
4. Lieveld FI, van Vlerken LG, Siersema PD, et al. Patient adherence to antiviral treatment for chronic hepatitis B and C: a systematic review. Ann Hepatol. May-Jun 2013;12(3):380-391. PMID 23619254
5. American Association for Study of Liver Diseases. Recommendation for Testing, Managing, and Treating Hepatitis C. http://www.hcvguidelines.org. Accessed November 28, 2016.

6. Department of Veterans Affairs. Chronic hepatitis C virus (HCV) infection: Treatment considerations from the Department of Veterans Affairs National Hepatitis C Resource Center Program and the HIV, Hepatitis, and Public Health Pathogens Programs in the Office of Patient Care Services. 2016; file:///C:/Users/MA06695/Downloads/treatment-considerations-2016-09-22.pdf. Accessed November 28, 2016.
7. World Heatlh Organization (WHO). Guidelines for the Screening, Care and Treatment of Persons with Chronic Hepatitis C Infection. 2016; http://apps.who.int/iris/bitstream/10665/205035/1/9789241549615_eng.pdf?ua=1. Accessed November 28, 2016.