MEDICAL POLICY

POLICY TITLE	**NON-INVASIVE TECHNIQUES FOR THE EVALUATION AND MONITORING OF PATIENTS WITH CHRONIC LIVER DISEASE**
POLICY NUMBER	**MP 2.252**

CLINICAL BENEFIT	☒ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☐ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**11/1/2024**

I. POLICY

FibroSURE multianalyte assay may be considered **medically necessary** for the evaluation of patients with chronic liver disease.

FibroSURE multianalyte assay more than once per year is considered **not medically necessary**.

Other multianalyte assays with algorithmic analyses are considered **investigational** for the evaluation or monitoring of patients with chronic liver disease.

Transient elastography (FibroScan) imaging may be considered **medically necessary** for the evaluation of patients with chronic liver disease.

- Appropriate to be used prior to treating hepatitis C in order to determine the duration of treatment.
- Appropriate to be used to monitor patients with chronic liver disease to determine any fibrosis progression over time.

Transient elastography (FibroScan) imaging more than once per year is considered **not medically necessary**.

The use of other noninvasive imaging, including but not limited to magnetic resonance elastography, acoustic radiation force impulse imaging (ARFI; e.g., Acuson S2000), or real-time tissue elastography, is considered **investigational** for the evaluation or monitoring of patients with chronic liver disease. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Use of this technology for purposes not contained in this policy is considered **not medically necessary.**

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at:
https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies

III. DESCRIPTION/BACKGROUND

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Biopsy for Chronic Liver Disease

The diagnosis of non-neoplastic liver disease is often made from needle biopsy samples. In addition to establishing a disease etiology, liver biopsy can determine the degree of inflammation present and can stage the degree of fibrosis. The degree of inflammation and fibrosis may be assessed by different scoring schemes. Most of these scoring schemes grade inflammation from 0 to 4 (0 = no or minimal inflammation, 4 = severe) and fibrosis from 0 to 4 (0 = no fibrosis, 4 = cirrhosis). There are several limitations to liver biopsy, including its invasive nature, small tissue sample size, and subjective grading system. Regarding small tissue sample size, liver fibrosis can be patchy and thus missed on a biopsy sample, which includes only 0.002% of the liver tissue. A noninvasive alternative to liver biopsy would be particularly helpful, both to initially assess patients and then as a monitoring tool to assess response to therapy. The implications of using liver biopsy as a reference standard are discussed in the Rationale.

Hepatitis C Virus

Infection with hepatitis C virus (HCV) can lead to permanent liver damage. Liver biopsy is typically recommended before the initiation of antiviral therapy. Repeat biopsies may be performed to monitor fibrosis progression. Liver biopsies are analyzed according to a histologic scoring system; the most commonly used one for hepatitis C is the Metavir scoring system, which scores the presence and degree of inflammatory activity and fibrosis. The fibrosis is graded from F0 to F4, with a Metavir score of F0 signifying no fibrosis and F4 signifying cirrhosis (which is defined as the presence throughout the liver of fibrous septa that subdivide the liver parenchyma into nodules and represents the final and irreversible form of disease). The stage of fibrosis is the most important single predictor of morbidity and mortality in patients with hepatitis C.

Biopsies for hepatitis C are also evaluated according to the degree of inflammation present, referred to as the grade or activity level. For example, the Metavir system includes scores for necroinflammatory activity ranging from A0 to A3 (A0 = no activity, A1 = minimal activity, A2 = moderate activity, A3 = severe activity).

Hepatitis B Virus

Most people who become infected with hepatitis B virus (HBV) recover fully but a small portion will develop chronic HBV, which cause lead to permanent liver damage. As with HCV,

identification of liver fibrosis is needed to determine timing and management of treatment, and liver biopsy is the criterion standard for staging fibrosis. The grading of fibrosis in HBV also uses the Metavir system.

Alcoholic Liver Disease
Alcoholic liver disease (ALD) is the leading cause of liver disease in most Western countries. Histologic features of ALD usually include steatosis, alcoholic steatohepatitis (ASH), hepatocyte necrosis, Mallory bodies (tangled proteins seen in degenerating hepatocytes), a large polymorphonuclear inflammatory infiltrate, and, with continued alcohol abuse, fibrosis and possibly cirrhosis. The grading of fibrosis is similar to the scoring system used in hepatitis C. The commonly used Laënnec scoring system uses grades 0 to 4, with 4 being cirrhosis.

Nonalcoholic Fatty Liver Disease
Nonalcoholic fatty liver disease (NAFLD) is defined as a condition that pathologically resembles ALD but occurs in patients who are not heavy users of alcohol. It may be associated with a variety of conditions, including obesity, diabetes, and dyslipidemia. The characteristic feature of NAFLD is steatosis. At the benign end of the spectrum of the disease, there is usually no appreciable inflammation, hepatocyte death, or fibrosis. In contrast, nonalcoholic steatohepatitis (NASH), which shows overlapping histologic features with ALD, is an intermediate form of liver damage, and liver biopsy may show steatosis, Mallory bodies, focal inflammation, and degenerating hepatocytes. NASH can progress to fibrosis and cirrhosis. A variety of histologic scoring systems have been used to evaluate NAFLD. The NAFLD activity score

(NAS) system for NASH includes scores for steatosis (0-3), lobular inflammation (0-3), and ballooning (0-2). Cases with scores of 5 or greater are considered NASH, while cases with scores of 3 and 4 are considered borderline (probable or possible) NASH. The grading of fibrosis is similar to the scoring system used in hepatitis C. The commonly used Laënnec scoring system uses grades 0 to 4, with 4 being cirrhosis.

NONINVASIVE ALTERNATIVES TO LIVER BIOPSY
Multianalyte Assays

A variety of noninvasive laboratory tests are being evaluated as an alternative to liver biopsy. Biochemical tests can be broadly categorized into indirect and direct markers of liver fibrosis. Indirect markers include liver function tests such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), the ALT/AST ratio (also referred to as the AAR), platelet count, and prothrombin index. In recent years, there has been growing understanding of the underlying pathophysiology of fibrosis, leading to direct measurement of the factors involved. For example, the central event in the pathophysiology of fibrosis is activation of the hepatic stellate cell. Normally, stellate cells are quiescent but are activated in the setting of liver injury, producing a variety of extracellular matrix (ECM) proteins. In normal livers, the rate of ECM production equals its degradation, but in the setting of fibrosis, production exceeds degradation.

Metalloproteinases are involved in intracellular degradation of ECM, and a profibrogenic state exists when there is either a down regulation of metalloproteinases or an increase in tissue inhibitors of metalloproteinases (TIMP). Both metalloproteinases and TIMP can be measured in

the serum, which directly reflects fibrotic activity. Other direct measures of ECM deposition include hyaluronic acid or α2-macroglobulin.

While many studies have been done on these individual markers, or on groups of markers in different populations of patients with liver disease, there has been interest in analyzing multiple markers using mathematical algorithms to generate a score that categorizes patients according to the biopsy score. It is proposed that these algorithms can be used as an alternative to liver biopsy in patients with liver disease. The following proprietary, algorithm-based tests are commercially available in the United States.

FibroSURE (Also Known as FibroTest)

HCV FibroSURE
The HCV FibroSURE uses a combination of 6 serum biochemical indirect markers of liver function plus age and sex in a patented algorithm to generate a measure of fibrosis and necroinflammatory activity in the liver that correspond to the Metavir scoring system for stage (i.e., fibrosis) and grade (i.e., necroinflammatory activity). The measures are combined using a linear regression equation to produce a score between 0 and 1, with higher values corresponding to more severe disease. The biochemical markers include the readily available measurements of α_2-macroglobulin, haptoglobin, bilirubin, γ-glutamyl transpeptidase (GGT), ALT, and apolipoprotein AI. Developed in France, the test has been clinically available in Europe under the name FibroTest since 2003; it is exclusively offered by LabCorp in the United States as HCV FibroSURE.

ASH FibroSURE
ASH FibroSURE (ASH Test) uses a combination of 10 serum biochemical markers of liver function together with age, sex, height, and weight in a proprietary algorithm; the test is proposed to provide surrogate markers for liver fibrosis, hepatic steatosis, and ASH. The biochemical markers include α_2-macroglobulin, haptoglobin, apolipoprotein AI, bilirubin, GGT, ALT, AST, total cholesterol, triglycerides, and fasting glucose. The test has been available in Europe under the name AshTest™ (BioPredictive); however, and the test is exclusively offered by LabCorp in the United States as ASH FibroSURE.

NASH FibroSURE
NASH FibroSURE (NASH Test) uses a proprietary algorithm of the same 10 biochemical markers of liver function in combination with age, sex, height, and weight and is proposed to provide surrogate markers for liver fibrosis, hepatic steatosis, and NASH. The biochemical markers include α_2-macroglobulin, haptoglobin, apolipoprotein A1, bilirubin, GGT, ALT, AST, total cholesterol, triglycerides, and fasting glucose. The test has been available in Europe under the name NashTest™ (BioPredictive); however, the test is exclusively offered by LabCorp in the United States as NASH FibroSURE.

FIBROSpect II
FIBROSpect II uses a combination of 3 markers that directly measure fibrogenesis of the liver, analyzed with a patented algorithm. The markers include hyaluronic acid, TIMP-1, and α_2-

macroglobulin. FIBROSpect II is offered exclusively by Prometheus Laboratories. The measures are combined using a logistic regression algorithm to generate a FIBROSpect II index score, ranging from 1 to 100 (or sometimes reported between 0 and 1), with higher scores indicating more severe disease.

NONINVASIVE IMAGING TECHNOLOGIES

Noninvasive imaging technologies to detect liver fibrosis or cirrhosis among patients with chronic liver disease are also being evaluated as alternatives to liver biopsy. The noninvasive imaging technologies include transient elastography (e.g., FibroScan), magnetic resonance elastography, acoustic radiation force impulse imaging (ARFI; e.g., Acuson S2000), and real-time tissue elastography (e.g., HI VISION Preirus). Noninvasive imaging tests have been used in combination with multianalyte serum tests such as FibroTest or FibroSURE with FibroScan.

Transient Elastography

Vibration-controlled transient elastography (Fibroscan®) is the most commonly used imaging-based fibrosis assessment method in the United States. It can be performed at bedside in an ambulatory office setting, is rapid to perform, has a wide range of scores (2.5−75 kPa), is associated with acceptable intra-observer and inter-observer reproducibility, and has been validated in large cohorts worldwide in a spectrum of liver diseases, including hepatitis B, hepatitis C, fatty liver disease, and autoimmune liver disorders, among others. FibroScan uses a mechanical vibrator to produce mild amplitude and low-frequency (50 Hz) waves, inducing an elastic shear wave that propagates throughout the liver. Ultrasound (US) tracks the wave, measuring its speed in kilopascals, which correlates with liver stiffness. Increases in liver fibrosis also increase liver stiffness and resistance of liver blood flow. Transient elastography does not perform as well in patients with ascites, higher body mass index, or narrow intercostal margins. Although FibroScan may be used to measure fibrosis (unlike liver biopsy), it does not provide information on necroinflammatory activity and steatosis, nor is it accurate during acute hepatitis or hepatitis exacerbations.

Acoustic Radiation Force Impulse Imaging

ARFI uses an US probe to produce an acoustic “push” pulse, which generates shear waves that propagate in tissue to assess liver stiffness. ARFI elastography evaluates the wave propagation speed (measured in meters per second) to assess liver stiffness. The faster the shear wave speed, the harder the object. ARFI technologies include Virtual Touch Quantification and Siemens Acuson S2000 system. ARFI elastography can be performed at the same time as a liver sonographic evaluation, even in patients with a significant amount of ascites.

Magnetic Resonance Elastography

Magnetic resonance elastography uses a driver to generate 60-Hz mechanical waves on the patient’s chest well. The magnetic resonance equipment creates elastograms by processing the acquired images of propagating shear waves in the liver using an inversion algorithm. These elastograms represent the shear stiffness as a pixel value in kilopascals. Magnetic resonance elastography has several advantages over US elastography, including: (1) the ability to analyze larger liver volumes; (2) the ability to analyze liver volumes of obese patients or patients with

ascites; and (3) the ability to precisely analyze viscoelasticity using a 3-dimensional displacement vector.

Real-Time Tissue Elastography
Real-time tissue elastography is a type of strain elastography that uses a combined autocorrelation method to measure tissue strain caused by manual compression or a person's heartbeat. The relative tissue strain is displayed on conventional color B mode US images in real time. Hitachi manufacturers the real-time tissue elastography devices, including one called HI VISION Preirus. The challenge is to identify a region of interest while avoiding areas likely to introduce artifacts, such as large blood vessels, the area near the ribs, and the surface of the liver. Areas of low strain increase as fibrosis progresses and strain distribution becomes more complex. Various subjective and quantitative methods have been developed to evaluate the results. Real-time tissue elastography can be performed in patients with ascites or inflammation. This technology does not perform as well in severely obese individuals.

REGULATORY STATUS

In November 2008, Acuson S2000™ Virtual Touch (Siemens AG, Erlanger, Germany), which provides acoustic radiation force impulse imaging, was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process (K072786).

In August 2009, AIXPLORER® Ultrasound System (SuperSonic Imagine, Aix en Provence, France), which provides shear wave elastography, was cleared for marketing by FDA through the 510(k) process (K091970).

In June 2010, Hitachi HI VISION™ Preirus™ Diagnostic Ultrasound Scantier (Hitachi Medical Systems America, Twinsburg, OH), which provides real-time tissue elastography, was cleared for marketing by FDA through the 510(k) process (K093466).

In April 2013, FibroScan® (EchoSens, Paris, France), which uses transient elastography, was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process (K123806).

In February 2017, ElastQ Imaging shear wave elastography (Royal Phillips, Amsterdam, the Netherlands) was cleared for marketing by FDA through the 510(k) process (K163120).

FDA product code: IYO.

American Association for the Study of Liver Diseases and Infectious Diseases Society of America

In 2020, the American Association for the Study of Liver Diseases and Infectious Diseases Society of America guidelines for testing, managing, and treating hepatitis C virus (HCV) recommended that, for counseling and pretreatment assessment purposes, the following should be completed:

"Evaluation for advanced fibrosis using noninvasive markers and/or elastography, and rarely liver biopsy, is recommended for all persons with HCV infection to facilitate decision making

regarding HCV treatment strategy and determine the need for initiating additional measures for the management of cirrhosis (eg, hepatocellular carcinoma screening) Rating: Class I, Level A [evidence and/or general agreement; data derived from multiple randomized trials, or meta-analyses]"

The guidelines noted that there are several noninvasive tests to stage the degree of fibrosis in patients with HCV. Tests included indirect serum biomarkers, direct serum biomarkers, and VCTE. The guidelines asserted that no single method is recognized to have high accuracy alone and careful interpretation of these tests is required.

American Gastroenterological Association Institute
In 2017, guidelines published by the American College of Gastroenterology Institute on the role of elastography in chronic liver disease indicated that, in adults with chronic hepatitis C, they recommended VCTE, if available, rather than nonproprietary, noninvasive serum tests (APRI, FIB-4) to detect cirrhosis. This was a a strong recommendation with moderate quality of evidence. They also noted, that in adults with chronic hepatitis B virus and chronic HCV, VCTE has superior diagnostic performance for diagnosing cirrhosis when compared to the APRI and FIB-4 tests (moderate quality of evidence for HCV, low quality of evidence for hepatitis B virus). In addition, the guidelines state that, in adults with HCV, magnetic resonance-guided elastography has little or no increased diagnostic accuracy for identifying cirrhosis compared with VCTE in patients who have cirrhosis, and has lower diagnostic accuracy than VCTE in patients who do not have cirrhosis (very low quality of evidence).

IV. RATIONALE

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SUMMARY OF EVIDENCE

Multianalyte Serum Assays
For individuals who have chronic liver disease who receive FibroSURE serum panels, the evidence includes systematic reviews of more than 30 observational studies (>5000 patients). Relevant outcomes are test accuracy and validity, morbid events, and treatment-related morbidity. FibroSURE has been studied in populations with viral hepatitis, nonalcoholic fatty liver disease, and alcoholic liver disease. There are established cutoffs, although they were not consistently used in validation studies. Given these limitations and the imperfect reference standard, it is difficult to interpret performance characteristics. However, for the purposes of deciding whether a patient has severe fibrosis or cirrhosis, FibroSURE results provide data sufficiently useful to determine therapy. Specifically, FibroSURE has been used as an alternative to biopsy to establish eligibility regarding the presence of fibrosis or cirrhosis in several RCTs that showed the efficacy of hepatitis C virus treatments, which in turn demonstrated that the test can identify patients who would benefit from therapy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have chronic liver disease who receive multianalyte serum assays for liver function assessment other than FibroSURE, the evidence includes systematic reviews of

observational studies. Relevant outcomes are test accuracy and validity, morbid events, and treatment-related morbidity. Studies have frequently included varying cutoffs, some of which were standardized and others not validated. Given these limitations and the imperfect reference standard, it is difficult to interpret performance characteristics. There is no direct evidence that other multianalyte serum assays improve health outcomes; further, it is not possible to construct a chain of evidence for clinical utility due to the lack of sufficient evidence on clinical validity. The evidence is insufficient to determine the effects of the technology on health outcomes.

Noninvasive Imaging

For individuals who have chronic liver disease who receive transient elastography, the evidence includes many systematic reviews of more than 50 observational studies (>10,000 patients). Relevant outcomes are test accuracy and validity, morbid events, and treatment-related morbidity. Transient elastography (FibroScan) has been studied in populations with viral hepatitis, nonalcoholic fatty liver disease, and alcoholic liver disease. There are varying cutoffs for positivity. Failures of the test are not uncommon, particularly for those with high body mass index, but these failures often went undetected in analyses of the validation studies. Given these limitations and the imperfect reference standard, it can be difficult to interpret performance characteristics. However, for the purposes of deciding whether a patient has severe fibrosis or cirrhosis, the FibroScan results provide data sufficiently useful to determine therapy. In fact, FibroScan has been used as an alternative to biopsy to establish eligibility regarding the presence of fibrosis or cirrhosis in the participants of several RCTs. These RCTs showed the efficacy of hepatitis C virus treatments, which in turn demonstrated that the test can identify patients who would benefit from therapy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have chronic liver disease who receive noninvasive radiologic methods other than transient elastography for liver fibrosis measurement, the evidence includes systematic reviews of observational studies. Relevant outcomes are test accuracy and validity, morbid events, and treatment-related morbidity. Other radiologic methods (e.g., magnetic resonance elastography, real-time transient elastography, acoustic radiation force impulse imaging) may have similar performance for detecting significant fibrosis or cirrhosis. Studies have frequently included varying cutoffs not prespecified or validated. Given these limitations and the imperfect reference standard, it is difficult to interpret performance characteristics. There is no direct evidence that other noninvasive radiologic methods improve health outcomes; further, it is not possible to construct a chain of evidence for clinical utility due to the lack of sufficient evidence on clinical validity. The evidence is insufficient to determine the effects of the technology on health outcomes.

V. DEFINITIONS

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N/A

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of

benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

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Capital Blue Cross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when **Medically Necessary** for FibroSURE testing and transient elastography (FibroScan):

Procedure Codes						
0002M	0003M	0166U	76981	76982	76983	81517
81596	91200					

Investigational and therefore not covered when used to report multianalyte assays with algorithmic analyses other than FibroSURE**:**

Procedure Codes							
83520	83883	0468U					

Noninvasive imaging (other than FibroScan) including magnetic resonance elastography is considered **investigational:**

Procedure Codes							
0344U	76391						

ICD-10-CM Diagnosis Codes	Description
B18.0	Chronic viral hepatitis B with delta-agent
B18.1	Chronic viral hepatitis B without delta-agent
B18.2	Chronic viral hepatitis C
B18.8	Other chronic viral hepatitis
K70.0	Alcoholic fatty liver
K70.2	Alcoholic fibrosis and sclerosis of liver
K73.0	Chronic persistent hepatitis, not elsewhere classified
K73.1	Chronic lobular hepatitis, not elsewhere classified
K73.2	Chronic active hepatitis, not elsewhere classified
K74.0	Hepatic fibrosis
K74.00	Hepatic fibrosis, unspecified
K74.01	Hepatic fibrosis, early fibrosis
K74.02	Hepatic fibrosis, advanced fibrosis
K74.1	Hepatic sclerosis
K74.2	Hepatic fibrosis with hepatic sclerosis
K74.3	Primary biliary cirrhosis
K74.4	Secondary biliary cirrhosis
K74.69	Other cirrhosis of liver
K75.4	Autoimmune hepatitis
K75.81	Nonalcoholic steatohepatitis (NASH)
K76.0	Fatty (change of) liver, not elsewhere classified
K76.82	Hepatic encephalopathy

IX. REFERENCES

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X. POLICY HISTORY

TOP

MP-2.252	**1/25/19** Consensus review **MP-2.252**. No change to policy statements. Background and references updated. Rationale condensed.
	02/13/2020 Consensus review. No change to policy statements. References updated, coding and literature reviewed. New April 2020 Codes 0014M and 0166U added to policy. Effective 4/1/2020
	9/1/20 Administrative update. Added ICD 10 K74.00, K 74.01, K74.02

MEDICAL POLICY

POLICY TITLE	**NON-INVASIVE TECHNIQUES FOR THE EVALUATION AND MONITORING OF PATIENTS WITH CHRONIC LIVER DISEASE**
POLICY NUMBER	**MP 2.252**

	01/21/2021 Consensus Review. No change to policy statements. Background and rationale reviewed. References reviewed and updated.
	9/12/2022 Administrative update. Added 0344U Effective 10/1/2022
	12/09/2022 Consensus Review. No change to policy stance, updated background and references.
	12/12/2023 Admin Update. Code 0014M deleted, added new code 81517. Effective 1/1/2024.
	12/13/2023 Consensus review. No change to policy stance, updated references.
	06/11/2024 Admin update. New code 0468U, effective 7/1/2024