Healthy Blue

Medical Policy

Subject:	Prothrombin G20210A (Factor II) Mutation Testing		
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Description/Scope

This document addresses prothrombin G20210A (factor II) mutation testing for the screening, diagnosis and management of prothrombin-related thrombophilia.

Position Statement

Investigational and Not Medically Necessary:

Prothrombin G20210A (factor II) mutation testing is considered **investigational and not medically necessary** for all indications.

Rationale

The prothrombin gene is positioned on chromosome 11 at band p11. A sequence variant in the 3' untranslated region of prothrombin, G20210A (c.*96G>A) is associated with an elevation in plasma prothrombin levels. The prevalence of prothrombin G20210A has been estimated to be present in 2% of healthy individuals and approximately 7% of individuals affected with venous thromboembolism (VTE). Prothrombin G20210A is inherited in autosomal dominant mode with variable penetrance. The clinical expression of prothrombin-related thrombophilia is highly variable. Many individuals who are homozygous or heterozygous for the 20210G>A (G20210A or c.*97G>A) allele in factor II never develop thrombosis. While most individuals with prothrombin-related thrombophilia do not experience a first thrombotic event until adulthood, some individuals have recurrent VTE before age 30 years (Kujovich, 2014).

Prothrombin G20210A (factor II) mutation testing is being explored as a means to screen for, diagnose and manage prothrombin-related thrombophilia. Genetic testing is required to make a definitive diagnosis of a prothrombin G20210A mutation. Plasma prothrombin concentration is not a reliable marker for prothrombin G20210A mutations because the range of plasma concentrations of prothrombin in heterozygotes may fall within the normal range. There are no specific clinical features that clearly identify prothrombin-related thrombophilia. The "gold standard" for prothrombin mutation detection involves the sequencing of the specific genetic region of the gene of interest but a variety of other reference methods may be employed due to the complexity and high costs associated with sequencing. Prothrombin gene mutation analysis may be offered as a specific DNA test or as part of a thrombophilia panel which may include mutations testing for the MTHFR variant and factor V Leiden (Kujovich, 2014).

Analytical Validity
The analytical validity of genetic testing for the prothrombin gene mutation is high. The published peer-reviewed literature reports that the analytic sensitivity and specificity for the prothrombin gene mutation is greater than 98% (Hertzberg, 2005). A 2009 comprehensive review of analytic validity studies examined a total of 23 studies on the concordance of prothrombin gene mutations with a reference standard and found that nearly all studies reported a 100% concordance. Twelve studies reviewed multiplex methods to test simultaneously for both the prothrombin G20210A mutation and factor V Leiden (FVL) and reported 100% concordance with reference standards (Segal, 2009a). According to Bradley and colleagues (2012), based on studies carried out in the United States, combined analytic sensitivity and specificity for prothrombin G20210A testing was 98.4% and analytic specificity was 99.7%. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group has also determined that there is convincing evidence that testing for the prothrombin G20210A mutation can be performed both accurately and reliably (EGAPP, 2011).

Clinical Validity
Researchers have investigated the clinical validity (the association of the prothrombin gene mutation with subsequent risk of VTE) in individuals with and without prior VTE. Coppens and colleagues (2008) investigated whether thrombophilia testing reduces the risk of recurrent venous thrombosis. Using data extrapolated from the Multiple Environmental and Genetic Assessment of Risk Factors for Venous Thrombosis (MEGA) study, a large, population-based, case-control study that investigated whether testing for thrombophilia in individuals with a first episode of venous thrombosis was associated with a decrease in recurrence rate, researchers identified 197 participants with a recurrence of venous thrombosis and matched them (based on age, sex, geographic region and year of venous thrombosis) with subjects who were free of recurrent venous thrombosis. Thrombophilia testing was performed in 35% of cases and in 30% of controls. After correction for sex, age, family history, geographic region, presence of clinical risk factors, and year of first venous thrombosis, the odds ratio (OR) remained unchanged. The authors reported the recurrence rate for venous thrombosis was similar in individuals who were tested for thrombophilia compared with individuals who were not tested (OR=1.2; 95% confidence interval [CI], 0.9 to 1.8). The results of this study suggest that the presence of FVL or the prothrombin G20210A mutation was not associated with an increased recurrence rate of venous thrombosis.

In a prospective follow-up study (the Leiden Thrombophilia Study [LETS]), Christiansen and colleagues (2005) followed 474 individuals who had completed a course of anticoagulation for a mean of 7.3 years. At baseline, all study participants were tested for thrombophilia; 29 participants (6%) were found to have a prothrombin mutation. However, participants with a prothrombin mutation did not demonstrate an increased risk of recurrence (hazard ratio [HR], 0.7; 95% CI, 0.3 to 2.0). Clinical factors associated with recurrence were variables such as provoked versus unprovoked VTE, patient sex, and oral contraceptive use.

Marchorii and colleagues (2007) conducted a meta-analysis of prospective studies to explore the risk of recurrent VTE among heterozygous carriers of factor V Leiden or prothrombin G20210A mutation. The authors identified 10 studies that were included in the meta-analysis. Among the 3208 participants with a first occurrence of VTE, there were 212 (17.9%) heterozygous carriers of prothrombin G20210A with follow-up ranging from 0.75 to 8.3 years. The relative risk (RR) of VTE recurrence conferred by the heterozygous carriage of prothrombin G20210A mutation was 1.20 (range 0.89 to 1.61) using the Mantel-Haenszel fixed-effects model and 1.36 (1.02 to 1.82) using

the Der Simonian and Laird random effects method. The authors concluded that in symptomatic individuals with VTE, heterozygous carriage of prothrombin G20210A mutation is difficult to interpret since it varies according to the assessment method used.

In 2008, Kearon and colleagues endeavored to determine whether thrombophilic defects increase recurrent VTE during warfarin therapy. A total of 661 participants with unprovoked VTE who were randomized to receive extended low-intensity (international normalized ratio [INR], 1.5-1.9) or conventional-intensity (INR, 2.0-3.0) anticoagulant therapy were tested for thrombophilia and followed for a mean of 2.3 years. One or more thrombophilic defects were present in 42% of the participants. The overall rate of recurrent VTE per patient-year was 0.9%. Recurrent VTE was not increased in the presence of factor V Leiden (HR, 0.7; 95% CI, 0.2-2.6); the 20210G>A prothrombin gene mutation (HR, 0); antithrombin deficiency (HR, 0); elevated factor VIII (HR, 0.7; 95% CI, 0.1-5.4); elevated factor XI (HR, 0.7; 95% CI, 0.1-5.0), or elevated homocysteine (HR, 0.7; 95% CI, 0.1-5.3), but demonstrated a trend to an increase with an antiphospholipid antibody (HR, 2.9; 95% CI, 0.8-10.5). Compared with individuals with no thrombophilic defects, the rate of recurrence was not increased in the presence of one (HR, 0.7; 95% CI, 0.2-2.3) or more than one (HR, 0.7; 95% CI, 0.2-3.4) defect. The authors concluded that single or multiple thrombophilic defects are not associated with a higher risk of recurrent VTE during warfarin therapy.

Mahajerin and colleagues (2014) reported the findings of a single center, retrospective cohort study of pediatric subjects (0-20 years of age) who presented with VTE to explore patterns of thrombophilia testing in pediatric VTE. All individuals with VTE confirmed by imaging were eligible and the presence of significant risk factors was evaluated. A total of 392 subjects (239 inpatient and 153 outpatient) met the inclusion criteria. Thrombophilia testing (prothrombin gene mutation, MTHFR; FVL; protein C, protein S, antithrombin activity; antiphospholipid antibodies and plasminogen activator inhibitor-1 levels) was ordered in 310 of the 392 subjects (79%). Positive results were found in 37 participants (12%). Thrombophilia rate differences between outpatient and inpatient cohorts did not reach statistical significance except for protein C deficiency, which was significantly higher in the outpatient group. In the inpatient group, the presence of a central venous line was significantly associated with not having tests done ($p<0.0022$). This study of pediatric VTE demonstrated a low thrombophilia rate in both the inpatient and outpatient settings. The authors concluded that the role of thrombophilia testing should be explored further in other pediatric subjects and noted that that the "presence or absence of thrombophilia rarely influences VTE management."

Because thrombophilias have been implicated as a possible cause of recurrent pregnancy loss (RPL), researchers have also investigated the relationship between prothrombin G20210A mutations and females with a history of obstetric complications. Kovalevsky and colleagues (2004) conducted a systematic review and meta-analysis to evaluate the association between hereditary thrombophilias and RPL. The analysis included only case-control studies with RPL (two or more pregnancy losses in the first or second trimester) and confirmed FVL and prothrombin gene (G20210A) mutations by DNA analysis. The authors selected a total of seven studies for the G20210A analysis. Stratified and multivariate logistic regression analyses were completed with the use of aggregate data. Results were confirmed using fixed- and random-effects meta-analyses models with a total of 530 cases compared with 837 controls, for which there was no evidence for heterogeneity of overall risks across studies for association with prothrombin G20210A ($p=0.51$). The combined overall risk for the association between RPL

and G20210A was 2.0 (95% CI, 1.0-4.0; p=0.03). Similar results were generated using the logistic regression and both fixed- and random-effects meta-analysis models. The authors concluded that carriers of the G20210A prothrombin gene mutation have double the risk of experiencing two or more miscarriages compared with women without thrombophilias.

Kist and colleagues (2008) conducted a meta-analysis to evaluate the relationship between markers of thrombophilia (for example, FVL, prothrombin G20210A, MTHFR C677T) and adverse pregnancy outcomes with respect to potential confounders across studies. The authors identified a total of 98 case-control studies with clear definitions of one or more of the candidate confounders including ethnicity (for example, Caucasian or non-Caucasian), severity of illness, and method of testing (functional testing and/or genetic testing). Adverse pregnancy outcomes measured included recurrent fetal loss, fetal growth restriction, preeclampsia and placental abruption. Severity of illness was described by: (a) trimester of recurrent fetal loss; (b) proteinuria level, blood pressure , and gestational age at delivery in preeclampsia; (c) gestational age at delivery, percentile of low birth weight, and any additional adverse outcomes in combination with fetal growth restriction; and (d) gestational age at delivery with placental abruption. For prothrombin G20210A and fetal growth restriction, the authors report finding confounding by severity of illness and ethnicity. In less severe cases without other adverse outcomes, there was no significant difference in prothrombin G20210A compared with controls, while more severe cases with other adverse outcomes in combination with fetal growth restriction were 5.9 times more likely to have the prothrombin G20210A mutation compared with controls (95% CI, 2.7-12.9).

Prenatal and Preimplantation Diagnosis
According to a review by Kujovich (2011), prenatal diagnosis is possible using amniocentesis (usually performed at ~15-18 weeks' gestation) or chorionic villus sampling (usually performed at ~10-12 weeks' gestation). Preimplantation genetic testing can also be performed. Although technically possible, preimplantation and prenatal diagnosis are rarely performed because the prothrombin gene mutation only increases the relative risk for thrombophilia and is not predictive of a thrombotic event.

Clinical Utility
Researchers have also investigated the clinical utility of prothrombin G20210A mutation testing. The EGAPP Working Group provides the following insight into determining the clinical utility of testing for the prothrombin G20210A mutation:

> Clinical utility depends on the extent to which identification of a FVL or PT mutation alters management in index cases with VTE and leads to health-related outcomes that are significantly improved over current practice. Among family members of index cases, clinical utility again depends on the extent to which management changes when a mutation is identified and most importantly how effectively such management leads to avoidance of VTE. A test may be found to have clinical validity (i.e., be a legitimate risk factor for the disorder) without having clinical utility if there is not sufficient evidence to show benefits resulting from use of the test (EGAPP, 2011).

Wu and colleagues (2006) reported the findings of a systematic review and cost-effectiveness analysis of screening for thrombophilia in high-risk situations (the Thrombosis: Risk and Economic Assessment of Thrombophilia Screening [TREATS] study). While the authors acknowledged that thrombophilia defects including FVL, high plasma factor VIIIc levels and prothrombin G20210A are associated with the occurrence of postoperative VTE in elective hip or knee replacement therapy, universal thrombophilia screening in women prior to prescribing oral estrogen preparations, in women during pregnancy and in individuals undergoing major orthopaedic surgery is not supported by current evidence. The authors reported that the "findings from this study show that selective screening based on prior VTE history is more cost-effective than universal screening." The authors concluded that "large prospective studies should be undertaken to refine the risks and establish the associations of thrombophilias with VTE among hormone users and in patients undergoing orthopaedic surgery."

In 2009, Segal and colleagues explored whether FVL testing alone, or in combination with prothrombin G20210A testing, leads to improved clinical outcomes in adults with a personal history of VTE or to improved clinical outcomes in adult family members of mutation-positive individuals. A total of 124 articles were included in the review. The authors found high-grade evidence that anticoagulation reduces recurrent events in probands with the prothrombin G20210A mutation. However, there was low-grade evidence that the relative reduction with treatment is comparable to that seen in individuals without mutations. The authors also reported that there was moderate evidence to support the conclusion that neither harms nor benefits of testing have been demonstrated conclusively. (Segal, 2009a).

Bradley and colleagues (2012) conducted an evidence-based review to determine if testing for heritable thrombophilias in women with recurrent pregnancy loss would lead to improved pregnancy outcomes. The authors found that there was moderate evidence that anticoagulation of women with recurrent pregnancy loss and factor II variants would currently lead to net harms.

Authoritative Recommendations and Practice Guidelines
Several organizations have published guidelines or recommendations which address prothrombin G20210A mutation testing.

The 2001 guidelines published by the American College of Medical Genetics (ACMG) recommends that individuals that are positive for factor V Leiden or APC resistance also be tested for the prothrombin G20210A gene mutation. In addition, the ACMG advises that when possible, testing for the prothrombin gene mutation and Factor V Leiden be performed simultaneously. This guideline provides guidance for when testing for any thrombophilia is appropriate. However, this criteria was modified in an ACMG guideline that was published in 2005 (Grody, 2001; Spector, 2005).

In 2002, the American College of Pathologists (CAP) published consensus recommendations which indicated that testing for the prothrombin G20210A mutation is "appropriate in patients with VTE (particularly for idiopathic VTE), for younger patients, and/or for patients with a family history of thrombosis." The authors also stated that:

> Routine testing for factor V Leiden and prothrombin G20210A is not recommended in adult patients with arterial stroke. However, these tests can be considered in certain unusual cases,

> such as pediatric patients with stroke. These assays may also be useful for patients with cerebral venous thrombosis."

Both of these recommendations were assigned an evidence grade Level 2 (based on a small number of well-designed prospective studies) (Van Cott, 2002).

The 2005 ACMG guidelines on technical standards and guidelines for VTE indicate that prothrombin G20210A mutation testing may have some utility in the following circumstances:

- Age < 50, any venous thrombosis;
- Venous thrombosis in unusual sites (such as portal hepatic, mesenteric, and cerebral veins);
- Recurrent venous thrombosis;
- Venous thrombosis and a strong family history of thrombotic disease;
- Venous thrombosis in pregnant women or women taking oral contraceptives;
- Myocardial infarction in female smokers under age 50.

Other situations in which testing may be appropriate include the following:

- Venous thrombosis, age > 50, except when active malignancy is present;
- Asymptomatic relatives of individuals known to have factor V Leiden. Knowledge that they have factor V Leiden may influence management of pregnancy and may be a factor in decision-making regarding oral contraceptive use;
- Women with recurrent pregnancy loss or unexplained severe preeclampsia, placental abruption, intrauterine fetal growth retardation or stillbirth. Knowledge of factor V Leiden carrier status may influence management of future pregnancies. Known carriers of these mutations can be treated with anticoagulants during pregnancy to support a normal outcome.

Routine testing is not recommended for patients with a personal or family history of arterial thrombotic disorders (e.g., acute coronary syndromes or stroke) except for the special situation of myocardial infarction in young female smokers. Testing may be worthwhile for young patients (< 50 years of age) who develop acute arterial thrombosis in the absence of other risk factors for atherosclerotic arterial occlusive disease (Spector, 2005).

In their Clinical Guidelines for Testing for Heritable Thrombophilia, the British Committee for Standards in Haematology and the British Society for Haematology (BSH) concluded the following:

> Testing for heritable thrombophilias is not indicated in unselected patients presenting with venous thrombosis. Testing selected patients may give an indication of risk of recurrence following completion of anticoagulant therapy, for example those presenting with venous thrombosis at an early age (<40 years) and who are from apparent thrombosis-prone families (more than two other symptomatic family members) …other selected patient groups in whom the results of testing may influence treatment are children with purpura fulminans and pregnant women at risk of venous thrombosis. The decision to test

these selected patients should be based on whether or not test results are likely to influence treatment decisions (Baglin, 2010).

In 2011, the EGAPP Working Group emphasized that the decision to test an individual for prothrombin mutation status should be based on the likelihood that test results would influence treatment. EGAPP reached the following conclusions regarding the utility of FVL and prothrombin G20210A mutation testing:

- There is no evidence that knowledge of FVL/PT mutation status in patients with VTE affects anticoagulation treatment to avoid recurrence.
- There is convincing evidence that anticoagulation beyond three months reduces recurrence of VTE, regardless of mutation status.
- There is no evidence that knowledge of FVL/PT mutation status among asymptomatic family members of patients with VTE leads to anticoagulation aimed at avoiding initial episodes of VTE (EGAPP, 2011).

In 2012, American College of Chest Physicians (ACCP) published two evidence-based guidelines on antithrombotic therapy and the prevention of thrombosis. The documents provide the following recommendations regarding prothrombin G20210A mutation testing:

- For pregnant women with no prior history of VTE who are known to be homozygous for factor V Leiden or the prothrombin 20210A mutation and have a positive family history for VTE, we suggest antepartum prophylaxis with prophylactic- or intermediate-dose LMWH and postpartum prophylaxis for 6 weeks with prophylactic-or intermediate-dose LMWH or VKAs targeted at INR 2.0 to 3.0 rather than no prophylaxis (Grade 2B).
- For pregnant women with no prior history of VTE who are known to be homozygous for factor V Leiden or the prothrombin 20210A mutation and who do not have a positive family history for VTE, we suggest antepartum clinical vigilance and postpartum prophylaxis for 6 weeks with prophylactic- or intermediate dose LMWH or VKAs targeted at INR 2.0 to 3.0 rather than routine care (Grade 2B) (Bates, 2012; Guyatt, 2012).

The 2018 American College of Obstetricians and Gynecologists (ACOG) Clinical Practice Bulletin on Inherited Thrombophilias in Pregnancy does not recommend routine thrombophilia testing. They state that "screening for inherited thrombophilias is useful only when results will affect management decisions, and it is not useful in situations in which treatment is indicated for other risk factors." They recommend targeted assessment for inherited thrombophilia in the following scenarios:

- A personal history of VTE, with or without a recurrent risk factor, and no prior thrombophilia testing.
- A first-degree relative (eg, parent or sibling) with a history of high-risk inherited thrombophilia.

Based primarily on consensus and expert opinion (Level C), ACOG also stipulates that "screening tests for inherited thrombophilias should include factor V Leiden mutation; prothrombin G20210A mutation; and antithrombin, protein S, and protein C deficiencies" (ACOG, 2018).

Summary

The peer-reviewed scientific literature strongly suggests that the pathogenesis of VTE is multifactorial and is affected by the interaction of inherited and acquired risk factors. Individuals who are heterozygous for the prothrombin G20210G mutation alone may have a low risk for VTE formation unless they also have another inherited or acquired risk factor. The degree of thrombotic risk in those homozygous for the G20210A prothrombin gene mutation is unclear, but it is believed to be substantially higher than that in heterozygotes. Although predictive testing in asymptomatic individuals and in relatives of known prothrombin G20210A mutation carriers is technically feasible, the clinical utility of such testing is hampered by the low penetrance of the mutations and the appreciable inherent risk of prophylactic anticoagulant therapy. At the current time, there is a lack of evidence in the peer-reviewed literature demonstrating a definitive causal relationship between inherited thrombophilias and adverse pregnancy outcomes. Because the thrombotic events associated with the prothrombin G20210A mutation are of later (typically adult) onset and of low penetrance, there is no indication for newborn screening. Both prophylactic treatment and the treatment of active VTE typically include the use of anticoagulants. The duration of anticoagulation therapy is based on the risk of recurrence balanced with the risk of major hemorrhage; however, the peer-reviewed scientific literature has not yet identified a definitive role of prothrombin G20210A mutation testing for decisions related to the duration of anticoagulation therapy. It is not clear that an individual who is positive for prothrombin G20210A gene mutation would be treated any longer or more intensively than an individual who does not have the mutation.

Background/Overview

Thrombophilia (also known as hypercoagulability) leads to the inappropriate formation of blood clots. In adults, this disorder most commonly manifests as VTE, such as deep vein thrombosis (DVT) in the legs and pulmonary embolism (PE). In women, VTE may result in adverse pregnancy outcomes. It has been estimated that in the United States, approximately 300,000 to 600,000 individuals are affected by VTE annually.

The predisposition to form clots may be caused by genetic factors, acquired changes in the clotting mechanism, or, more commonly, an interaction between genetic and acquired factors. Independent environmental factors contributing to VTE include, but are not limited to: male sex, confinement to a nursing home or hospital, older age, smoking; trauma sufficient to require hospitalization, malignant neoplasm, neurologic disease with chronic extremity paresis, superficial vein thrombosis, and prior central venous catheter or transvenous pacemaker. Additional risks for women include pregnancy and use of oral contraceptives, tamoxifen, raloxifene and estrogen replacement therapy (Spector, 2005).

Genetic risk factors for VTE include:

- Activated protein C resistance (factor V Leiden mutations;
- Hyper-homocysteinemia (MTHFR mutations);

- Protein C deficiency;
- Protein S deficiency;
- Prothrombin deficiency; and
- Prothrombin gene mutations.

Morbidity and mortality in individuals with thrombophilia are primarily the result of VTE and PE. The risk for thrombosis may be significantly increased in individuals with a combination of two or more risk factors for thrombosis. Any multiplicity of risk factors, whether acquired or hereditary, elevates the risk for thrombosis.

Prothrombin (factor II) is a protein in the blood that is essential for the formation of blood clots. A specific change in the genetic code causes the body to produce an excessive amount of the prothrombin protein which can result in excessive blood clotting. Individuals with this condition are said to have a prothrombin mutation, a factor II (FII or F2) mutation, a prothrombin variant or prothrombin G20210A. A common sequence variance of the prothrombin gene (G20210A) has been associated with elevations in plasma prothrombin levels and is a known risk factor for DVT and PE. The prothrombin G20210A mutation, found almost exclusively in Caucasians, is the second most common genetic risk factor for venous thrombosis.

Researchers are exploring the use of prothrombin G20210A mutation testing as a tool to screen for, diagnose and manage prothrombin-related thrombophilia. Prothrombin G20210A mutation testing is offered by a variety of laboratories that have current Clinical Laboratory Improvement Amendments certifications.

Definitions

Analytical validity: The ability of a genetic test to accurately and reliably measure the genotype of interest; the technical performance of the test, in terms of accurately identifying the genetic markers to be measured.

Clinical utility: The ability of the test to alter patient management and improve clinical outcomes.

Clinical validity: The ability of a genetic test to predict or detect the associated phenotype or disorder.

Deep vein thrombosis (DVT): A blood clot in one of the deep veins of the body.

Prothrombin: A blood clotting protein; also referred to as coagulation factor II, factor II or F2.

Pulmonary embolism (PE): A clot that travels via the bloodstream and lodges in the lungs.

Thrombophilia: A blood coagulation abnormality that increases the risk of thrombosis; also known as hypercoagulability.

Thrombosis: The presence of blood clots in the blood vessels.

Venous thromboembolism: The formation of a blood clot in the veins.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:
For the following procedure code; or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT

81240	*F2 (prothrombin, coagulation factor II)* (eg, hereditary hypercoagulability) gene analysis, 20210G>A variant

ICD-10 Diagnosis

All diagnoses

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Factor II (FII, F2)
Prothrombin
Thrombophilia

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Reviewed	01/24/2019	Medical Policy & Technology Assessment Committee (MPTAC) review. Rationale, References, and Websites sections updated.
Reviewed	02/27/2018	MPTAC review. The document header wording updated from "Current Effective Date" to "Publish Date." Updated References and History sections.
Reviewed	02/02/2017	MPTAC review. Updated review date, References and History sections.
New	08/04/2016	MPTAC review. Initial document development.