



FEP Medical Policy Manual

FEP 2.04.82 Genetic Testing for Inherited Thrombophilia

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Related Policies:

2.04.23 - Homocysteine Testing in the Screening, Diagnosis, and Management of Cardiovascular Disease and Venous Thromboembolic Disorders

Genetic Testing for Inherited Thrombophilia

Description

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Inherited thrombophilias are a group of disorders that predispose individuals to thrombosis. Genetic testing is available for some of these disorders and could assist in the diagnosis and/or management of patients with thrombosis. For example, testing is available for types of inherited thrombophilia, including variants in the 5,10-methylenetetrahydrofolate reductase (*MTHFR*) gene, the *factor V* gene (factor V Leiden [FVL] variant), and the prothrombin (*factor II*) gene.

OBJECTIVE

The objective of this evidence review is to determine whether genetic testing for 5,10-methylenetetrahydrofolate reductase, *factor V* gene, and prothrombin gene variants improves the net health outcome in individuals with inherited thrombophilias.

POLICY STATEMENT

Genetic testing for inherited thrombophilia, including testing for the *factor V Leiden* variant, prothrombin gene variants, and variants in the 5,10-methylenetetrahydrofolate reductase (*MTHFR*) gene, is considered **investigational**.

POLICY GUIDELINES

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology - "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign" - to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Genetic counseling is primarily aimed at individuals who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Commercial thrombophilia genetic tests are available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

The FDA has cleared several genetic tests for thrombophilia for marketing through the 510(k) process for use as an aid in the diagnosis of patients with suspected thrombophilia. Some of these tests are listed in Table 1.

Table 1. Genetic Tests for Thrombophilia Cleared by FDA

Test	Manufacturer	Cleared	510(k) No.
Ancestrydna Factor V Leiden Genetic Health Risk Test	Ancestry Genomics, Inc.	08/13/2020	K192944
cobas Factor II and Factor V Test	Roche Molecular Systems, Inc.	01/12/18	K172913
IMPACT Dx™ Factor V Leiden and Factor II Genotyping Test	Agena Bioscience ^a	06/14	K132978
Invader Factor II, V, and MTHFR (677, 1298) tests	Hologic	04/06/11	K100943, K100980, K100987, K100496
VeraCode Genotyping Test for Factor V and Factor II	Illumina	04/28/10	K093129
eSensor Thrombophilia Risk Test, FII-FV, FII, FV and MTHFR (677, 1298) Genotyping Tests	GenMark Dx ^b	04/22/10	K093974
INFINITI™ System Assay for Factor II & Factor V	AutoGenomics	02/07/07	K060564
Xpert Factor II and Factor V Genotyping Assay	Cepheid	09/18/09	K082118
Verigene Factor F2, F5, and MTHFR Nucleic Acid Test	Nanosphere	10/11/07	K070597
Factor V Leiden Kit	Roche Diagnostics	12/17/03	K033607
Factor II (Prothrombin) G20210A Kit	Roche Diagnostics	12/20/03	K033612

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.

FDA: Food and Drug Administration.

^a FDA marketing clearance was granted to Sequenom Bioscience before it was acquired by Agena Bioscience.

^b FDA marketing clearance was granted to Osmetech Molecular Diagnostics.

Other commercial laboratories may offer a variety of functional assays and genotyping tests for *F2* (prothrombin, coagulation factor II) and *F5* (coagulation factor V), and single or combined genotyping tests for *MTHFR*.

In November 2017, the 23andMe Personal Genome Service (PGS) Genetic Health Risk was granted a de novo classification by the FDA (class II with general and special controls, FDA product code: PTA). This is a direct-to-consumer test that has been evaluated by the FDA for accuracy, reliability, and consumer comprehension. This test reports whether an individual has variants associated with a higher risk of developing harmful blood clots. This report is based on a qualitative genetic test for single nucleotide polymorphism detection of Factor V Leiden variant in the *F5* gene (rs6025) and Prothrombin G20210A variant in the *F2* gene (rs1799963/i3002432). Similarly, in August 2020, Ancestry Genomics, Inc was granted the same de novo classification by the FDA (class II with general and special controls, FDA product code: PTA). This AncestryDNA Factor V Leiden Genetic Health Risk Test reports whether an individual has variants associated with a higher risk of developing harmful blood clots. This report is based on a qualitative genetic test for single nucleotide polymorphism detection of Factor V Leiden variant in the *F5* gene (rs6025).

RATIONALE

Summary of Evidence

For individuals who are asymptomatic with or without a personal or family history of venous thromboembolism (VTE) or who are asymptomatic with increased VTE risk (eg, due to pregnancy) who receive genetic testing for variants in 5,10-methylenetetrahydrofolate reductase (*MTHFR*), or genetic testing for coagulation *factor V* and coagulation factor II, the evidence includes a large randomized controlled trial (RCT), prospective cohort analyses, retrospective family studies, case-control studies, and meta-analyses. Relevant outcomes are morbid events and treatment-related morbidity. The clinical validity of genetic testing has been demonstrated by the presence of a factor V Leiden (FVL) variant or a prothrombin gene variant, and an association with an increased risk for subsequent VTE across various populations studied. However, the magnitude of the association is relatively modest, with odds ratios most commonly between 1 and 2, except for family members of individuals with inherited thrombophilia, for whom odds ratios are somewhat higher. The clinical utility of testing for FVL or prothrombin variants has not been demonstrated. Although the presence of inherited thrombophilia increases the risk for subsequent VTE events, the increase is modest, and the absolute risk of thrombosis remains low. Available prophylactic treatments (eg, anticoagulation) have defined risks of major bleeding and other adverse events that may outweigh the reduction in VTE and therefore result in net harm. Currently, available evidence has not defined a role for thrombophilia testing for decisions on initiation of prophylactic anticoagulation or the length of anticoagulation treatment. For *MTHFR* testing, clinical validity and clinical utility of genetic testing are uncertain. Because clinical utility of testing for elevated serum homocysteine itself has not been established, the utility of genetic testing also has not been established. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

Many guidelines and position statements on testing for thrombophilia have been published over the last 2 decades. These guidelines have evolved over time, are often inconsistent, and do not typically give specific parameters on when to perform genetic testing. The following are examples of U.S. guidelines developed by major specialty societies and published more recently.

American Board of Internal Medicine Foundation- Choosing Wisely Campaign

Choosing Wisely, an initiative of the American Board of Internal Medicine Foundation, seeks to promote discussions between clinicians and patients to choose care that is: supported by evidence, not duplicative of other tests or procedures already received, free from harm, and truly necessary. Medical specialty societies and their national organizations have identified tests or procedures commonly used in their field whose necessity should be

questioned and discussed. The following medical specialist groups have contributed recommendations to *Choosing Wisely* lists specifically related to testing for inherited thrombophilias (Table 2).

Table 2. Medical Society Recommendations on Testing for Inherited Thrombophilias

Society	Year	Recommendation
American Society of Hematology (ASH) ^{38,}	NA	"Don't test for thrombophilia in adult patients with venous thromboembolism (VTE) occurring in the setting of major transient risk factors (surgery, trauma or prolonged immobility)."
		"Thrombophilia testing is costly and can result in harm to patients if the duration of anticoagulation is inappropriately prolonged or if patients are incorrectly labeled as thrombophilic. Thrombophilia testing does not change the management of VTEs occurring in the setting of major transient VTE risk factors. When VTE occurs in the setting of pregnancy or hormonal therapy, or when there is a strong family history plus a major transient risk factor, the role of thrombophilia testing is complex and patients and clinicians are advised to seek guidance from an expert in VTE." Additional recommendations from ASH for specific populations are summarized in a later section.
Society for Maternal-Fetal Medicine ^{39,}	2022	"Don't do an inherited thrombophilia evaluation for women with histories of pregnancy loss, fetal growth restriction (FGR), preeclampsia and abruption."
		"Scientific data supporting a causal association between either methylenetetrahydrofolate reductase (MTHFR) polymorphisms or other common inherited thrombophilias and adverse pregnancy outcomes, such as recurrent pregnancy loss, severe preeclampsia and IUGR, are lacking. Specific testing for antiphospholipid antibodies, when clinically indicated, should be limited to lupus anticoagulant, anticardiolipin antibodies and beta 2 glycoprotein antibodies."
	NA	"Don't test women for MTHFR mutations."
		"MTHFR is responsible for the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate. Genetic variants C677T and A1286C have been associated with a mild decrease in enzymatic activity, which in the setting of reduced folate levels has been found to be a risk factor for hyperhomocysteinemia. Although hyperhomocysteinemia is a risk factor for cardiovascular disease and venous thrombosis, its cause is multifactorial and independent of the MTHFR genotype, even in homozygotic individuals. Despite earlier (mostly case control) studies that found an association between the MTHFR genotype and adverse outcomes, recent studies of more robust design have not replicated these findings. Due to the lack of evidence associating genotype independently with thrombosis, recurrent pregnancy loss, or other adverse pregnancy outcomes, MTHFR genotyping should not be ordered as part of a workup for thrombophilia."
American Society for Reproductive Medicine (posted on the the ASH website) ^{38,}	NA	"Don't routinely order thrombophilia testing on patients undergoing a routine infertility evaluation."
		"There is no indication to order these tests, and there is no benefit to be derived in obtaining them in someone that does not have any history of bleeding or abnormal clotting and in the absence of any family history. This testing is not a part of the infertility workup. Furthermore, the testing is

		costly, and there are risks associated with the proposed treatments, which would also not be indicated in this routine population."
American College of Medical Genetics and Genomics ^{40,}	2017	"Don't order MTHFR genetic testing for the risk assessment of hereditary thrombophilia."
American Society of Hematology and American Society of Pediatric Hematology/Oncology ^{38,}	NA	"Don't order thrombophilia testing on children with venous access (i.e., peripheral or central) associated thrombosis in the absence of a positive family history."
		"Testing for inherited forms of thrombophilia does not influence the initial management of a first episode of provoked venous thrombosis and should not be performed routinely. The results of such testing have not been shown to either predict recurrence of venous thrombosis or inform the intensity or duration of anticoagulant therapy. Thrombophilia testing has substantial financial cost, and a positive result has the potential for misinterpretation of risk assessment leading to undue psychological distress or impact on childbearing plans, as well as possible life insurance discrimination for affected patients."

Abbreviations: NA: not available.

American College of Chest Physicians

Since 2016, the American College of Chest Physicians (2021) guidelines and expert panel report on antithrombotic therapy for venous thromboembolism (VTE) disease no longer include recommendations for pregnant women with known *factor V Leiden* or prothrombin *G20210A* variants, which had been included in the 2012 edition.^{41,42,43} Also, there are no guidelines on genetic testing for thrombophilia. The 2008 edition had indicated that the presence of a hereditary thrombophilia was not a major factor to guide duration of anticoagulation for VTE.^{44,}

American College of Medical Genetics and Genomics

In 2025 , the American College of Medical Genetics and Genomics (ACMG) published updated technical standards for genetic testing for variants associated with VTE, with a focus on factor V Leiden and factor II. Regarding testing indications, the ACMG states the following:

Genetic Factor	Recommendation
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FVL and factor II	General Recommendations - Recommended in patients with VTE when the results will influence treatment and clinical management decisions. - Recommended in patients and certain asymptomatic relatives to reduce the risk of provoked VTE through counseling about preventive measures in circumstances of elevated risk. - Not recommended indiscriminately for all patients with VTE or for the general population. Testing indications from different professional organizations vary. Specific Circumstance Recommendations - Recommended for VTE at unusual sites (such as cerebral and splanchnic venous thrombosis). - Recommended for individuals with VTE provoked by pregnancy or postpartum. - Recommended for individuals with VTE associated with the use of OCs. - Recommended for personal history of VTE with a positive family history of thrombophilia diagnosed in a first- or second-degree relative or first-degree relative with VTE at a young age. - Recommended for individuals with low APC resistance activity. - Not recommended for screening for FVL variant and factor II variants in individuals with a history of fetal loss or adverse pregnancy outcomes without a personal history of VTE or a family history of thrombosis due to insufficient clinical evidence.
MTHFR	Not recommended for routine MTHFR variant testing for thrombophilia, recurrent pregnancy loss, or other adverse perinatal events.

Abbreviations: APC: activated protein C; OC: oral contraception; VTE: venous thromboembolism.

American College of Obstetricians and Gynecologists

The American College of Obstetricians and Gynecologists (ACOG; 2018; reaffirmed in 2025) published management guidelines for inherited thrombophilias in pregnancy.⁴⁵ These guidelines stated that a definitive causal link between inherited thrombophilias and adverse pregnancy outcomes could not be made. Screening for inherited thrombophilias is controversial, but may be considered for pregnant women in the following situations if testing will influence management:

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

Table 3. Guidelines for Managing Inherited Thrombophilias During Pregnancy

Recommendation	GOE	LOE
In women with personal histories of VTE, testing for inherited thrombophilias should include FVL, prothrombin G20210A mutation, and tests for deficiencies in antithrombin, protein S and protein C	C	Consensus and expert opinion
Testing for inherited thrombophilias in women who have experienced fetal loss or adverse pregnancy outcomes, including placental abruption, preeclampsia, or fetal growth restriction, is not recommended because there is insufficient evidence that anticoagulation therapy reduces recurrence	B	Limited or inconsistent scientific evidence
Because an association between either heterozygosity or homozygosity for the <i>MTHFR</i> C677T polymorphism and any negative pregnancy outcomes, including any increased risk for VTE, has not been shown, screening with either <i>MTHFR</i> mutation analyses or fasting homocysteine levels is not recommended	B	Limited or inconsistent scientific evidence

FVL: *factor V Leiden*; GOE: grade of evidence; LOE: level of evidence; VTE: venous thromboembolism.

The ACOG practice bulletin for early pregnancy loss (2018; reaffirmed in 2025) states that "Maternal or fetal chromosomal analyses or testing for

inherited thrombophilias are not recommended routinely after one early pregnancy loss. Although thrombophilias commonly are thought of as causes of early pregnancy loss, only antiphospholipid syndrome consistently has been shown to be significantly associated with early pregnancy loss." ⁴⁶,

American Society of Hematology

In addition to the general recommendation provided in Table 5, which states to avoid testing for hereditary thrombophilia in adult patients with VTE occurring in the setting of major transient risk factors (surgery, trauma or prolonged immobility), a 2023 American Society of Hematology (ASH) guideline made conditional recommendations for hereditary thrombophilia testing in the following scenarios:⁴⁷,

- patients with VTE associated with nonsurgical major transient or hormonal risk factors;
- patients with cerebral or splanchnic venous thrombosis, in settings where anticoagulation would otherwise be discontinued;
- individuals with a family history of antithrombin, protein C, or protein S deficiency when considering thromboprophylaxis for minor provoking risk factors and for guidance to avoid COCs [combined oral contraceptives]/hormone replacement therapy;
- pregnant women with a family history of high-risk thrombophilia types; and
- patients with cancer at low or intermediate risk of thrombosis and with a family history of VTE.

Anticoagulation Forum

In 2016, Stevens et al published a guidance document initiated by the Anticoagulation Forum.⁴⁸, The guidance was intended to inform clinical decisions regarding duration of anticoagulation following VTE and primary prevention of VTE in relatives of affected patients. Statements were based on existing guidelines and consensus expert opinion when guidelines were lacking. The authors concluded that, "Thrombophilia testing is performed far more frequently than can be justified based on available evidence; the majority of such testing is not of benefit to the patient and may be harmful." Table 4 summarizes the guidance statements for each question considered in the document.

Table 4. Guidance for the evaluation and treatment of hereditary and acquired thrombophilia (adapted from Stevens et al [2016])⁴⁸,

Question	Guidance Statement	Limits/Exceptions
Should thrombophilia testing be performed to help determine duration of anticoagulation following provoked VTE?	Do not perform thrombophilia testing following an episode of provoked VTE.	
Should thrombophilia testing be performed to help determine duration of anticoagulation following unprovoked VTE?	Do not perform thrombophilia testing in patients following an episode of unprovoked VTE.	If a patient with unprovoked VTE and low bleeding risk is planning to stop anticoagulation, test for thrombophilia if test results would change this decision.
Should family members of patients with VTE or hereditary thrombophilia undergo thrombophilia testing?	Do not test for thrombophilia in asymptomatic family members of patients with VTE or hereditary thrombophilia.	
Should female relatives of patients with VTE or hereditary thrombophilia who are considering using estrogen-containing medications be tested for thrombophilia?	Do not test for thrombophilia in asymptomatic family members of patients with VTE or hereditary thrombophilia who are contemplating use of estrogen.	If a woman contemplating estrogen use has a first degree relative with VTE and a known hereditary thrombophilia, test for that thrombophilia if the result would change the decision to use estrogen.
Should female relatives of patients with VTE or hereditary thrombophilia who are contemplating pregnancy be tested for thrombophilia?	Do not test for thrombophilia in asymptomatic family members of patients with VTE or hereditary thrombophilia who are contemplating pregnancy.	If a woman contemplating pregnancy has a first degree relative with VTE and a known hereditary thrombophilia, test for that thrombophilia if the result would change VTE prophylaxis decisions.
When thrombophilia testing is performed, at what point in the patient's care should this be done?	Do not perform thrombophilia testing at the time of VTE diagnosis or during the initial 3-month course of anticoagulant therapy. When testing for thrombophilias following VTE,	

use either a 2-stage testing approach or perform testing after a minimum of 3 months of anticoagulant therapy has been completed, and anticoagulants have been held.

VTE: Venous thromboembolism.

Evaluation of Genomic Applications in Practice and Prevention

The Evaluation of Genomic Applications in Practice and Prevention (2011) recommendations did not support the clinical utility of genetic testing for *factor V Leiden* and prothrombin variants for prevention of initial episodes of VTE or for recurrence.⁴⁹ The recommendations have been archived.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
September 2013	New policy	
September 2014	Replace policy	Policy updated with literature review adding references 5-8, 10-11, 24 and 29, references 4 and 12 were updated. There are no changes to the policy statement.
September 2018	Replace policy	Policy updated with literature review through March 5, 2018; references 16 and 23 added; references 29-32, 34, and 37 updated. The policy is revised with updated genetics nomenclature; "mutations" changed to "variants" throughout policy. Policy statement otherwise unchanged except "not medically necessary" corrected to "investigational" due to 510k FDA clearance.
September 2019	Replace policy	Policy updated with literature review through March 4, 2019; references added. Policy statement unchanged.
September 2020	Replace policy	Policy updated with literature review through March 26, 2020; references added. Policy statement unchanged.
September 2021	Replace policy	Policy updated with literature review through April 7, 2021; references added. Policy statement unchanged.
September 2022	Replace policy	Policy updated with literature review through April 1, 2022; reference added. Policy statement unchanged.
September 2023	Replace policy	Policy updated with literature review through March 29, 2023; no references added. Policy statement unchanged.
September 2024	Replace policy	Policy updated with literature review through March 26, 2024. Policy statement unchanged.
December 2024	Replace policy	Policy updated with literature review through March 26, 2024. Policy statement unchanged.
May 2025	Replace policy	Policy updated with literature review through March 11, 2025; references added. Policy statement unchanged.
June 2026	Replace policy	Policy updated with literature review through February 24, 2026; references added. Policy statement unchanged.

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.