Homocysteine Testing

Medical Policy #: 02.04.22
Original Effective Date: December 2009
Reviewed: July 2022
Revised: July 2022

DESCRIPTION

Homocysteine is an amino acid used to make protein and to build and maintain tissue. Homocysteine levels are helpful in clarifying the diagnosis when serum vitamin B12 or folate concentrations are equivocal and also in the work-up of homocystinuria. Excess levels of homocysteine in the blood are purported to increase the risk of certain conditions such as venous thromboembolism, recurrent pregnancy loss, osteoporosis, dementia/cognitive impairment, autism, multiple sclerosis, and aortic dissection.

Homocysteine (Hcy), a sulphur-containing amino acid, is formed by the conversion of methionine into cysteine. It is usually rapidly metabolized by one of two pathways: 1) a vitamin B12 and folate dependent remethylation pathway that regenerates methionine, or 2) a vitamin B6 and folate dependent trans-sulphuration pathway that converts homocysteine (Hcy) to cysteine. Thus, low levels of these vitamins/co-factors are associated with hyper-homocysteinemia which can be classified as moderate (15 to 30 mciromol/L).

Measurements of homocysteine (Hcy) levels are usually performed fasting. Normal homocysteine concentrations range between 5 and 15 micromol/L, and levels below 10 micromol/L are considered desirable. Hyperhomocysteinemia has been classified as follows:

- Moderate 15 to 30 micromol/L
- Intermediate 31 to 100 micromol/L
- Severe >100 micromol/L

Elevations in the plasma homocysteine concentration (pHcy) can arise from various causes: genetic defects in the enzymes involved in homocysteine (Hcy) metabolism nutritional deficiencies in vitamin co-factors, and other factors such as chronic conditions/diseases (e.g., obesity, smoking, physical inactivity, hypertension, hypercholesterolemia, diabetes mellitus and chronic kidney failure) and medications (e.g. fenofibrate, methotrexate, and nicotine acid).

Vitamin supplementation with folate lowers homocysteine levels. In individuals who are treated to lower homocysteine levels treatment may consist of folic acid (1mg/day), vitamin B6 (10mg/day) and vitamin B12 (0.4mg/day). Normalization of the homocysteine concentration has been reported within two weeks, but further lowering of homocysteine levels occur by six weeks. The dose of folic acid should be increased up to 5 mg/day as needed to lower the homocysteine concentration below 15 micromol/L. In patients with homocysteine concentration >30 micromol/L or chronic renal failure the initial dose of folic acid is 5mg/day. A diet rich in fruits, vegetables, and low-fat dairy products and low in saturated and total fat also can lower fasting serum homocysteine.

Homocystinuria

Homocystinuria also known as cystathionine beta synthase deficiency or CBS deficiency, is an autosomal recessively inherited disorder in which individuals are unable to properly process certain amino acids. The principal biochemical features of this condition are markedly elevated plasma homocysteine concentration (pHcy), total homocysteine (tHcy), plasma concentrations of methionine as well as increased urinary concentration of homocysteine (Hcy). The most common form of homocystinuria is caused by the lack of cystathionine beta synthase (CBS), a vitamin B6 dependent enzyme. Homocystinuria caused by CBS deficiency effects at least 1 in 200,000 or 335,000 people worldwide. Other forms of homocystinuria are much rarer.

Early diagnosis and interventions have helped prevent some of the complications of homocystinuria, including ectopia lentis (dislocation of the ocular lens) and/or severe myopia, developmental delay/mental retardation, and skeletal abnormalities.

There are two phenotypic variants of homocystinuria: 1) B6-responsive, 2) B6-non-responsive. The former is typically milder than the latter. In the majority of untreated affected individuals, ectopia lentis occurs by 8 years of age. Individuals are often tall and slender build with asthenic habitus (long limbs, an angular profile, and prominent muscles or bones) and are prone to osteoporosis. Intelligence quotient (IQ) in individuals

with homocystinuria usually ranges from 10 to 138; with the mean IQ in individuals with B6-responsiveness being 79 versus 57 for those who are B6-non-responsive. Other features that may occur include seizures, psychiatric problems, extra-pyramidal signs such as dystonia, hypopigmentation, pancreatitis, malar flush (redness of cheeks), and livedo reticularis (mottled discoloration of the skin).

Laboratory studies for homocystinuria include serum homocysteine level. Treatments should aim to correct the biochemical abnormalities and to normalize homocysteine levels. Individuals identified by newborn screening are treated shortly after birth to maintain plasma homocysteine (pHcy) below 11 micromol/L. For newborn screening, measurements of homocysteine (Hcy) are performed only when hyper-methioninemia has been confirmed. Complications of homocystinuria should be treated appropriately (e.g., surgical intervention for ectopia lentis). The evidence is sufficient to determine the testing results in a meaningful improvement in net health outcomes.

Venous Thromboembolism

The most common presentation of venous thrombosis are deep vein thrombosis (DVT) of the lower extremities and pulmonary embolism. The causes of venous thrombosis can be divided into two groups; hereditary and acquired and are often multiple in a given individual.

Inherited thrombophilia is a genetic tendency to venous thromboembolism. Acquired risk factors or predisposing conditions for thrombosis include a prior thrombotic event, recent major surgery, presence of central venous catheter, trauma, immobilization, malignancy, pregnancy, the use of oral contraceptives, antiphospholipid syndrome (APS) and myeloproliferative disorders.

A major theory delineating the pathogenesis of venous thromboembolism (VTE), often called Virchow's triad, which proposes that VTE occurs as a result of:

- Alterations in blood flow (i.e., stasis)
- Vascular endothelial injury
- Alternations in the constituents of the blood (i.e., inherited or acquired hypercoaguable state)

Hyper-homocysteinemia (elevation of homocysteine level in blood) has been associated with an increased risk for venous thromboembolic disease (pulmonary embolism and deep vein thrombosis) but is currently considered a relatively weak prothrombotic factor.

Determination of homocysteine concentration may also be offered as part of the risk assessment for individuals at high-risk of VTE events or who have experienced idiopathic VTE, recurrent VTE, thrombosis occurring at a young age, or thrombosis at an unusual site.

Clinical Context and Test Purpose
The purpose of testing homocysteine levels in asymptomatic individuals at risk of VTE or of individuals who have VTE events is to inform management decisions such as whether to lower homocysteine levels.

Populations
The relevant populations of interest are individuals who are asymptomatic with the risk of VTE and those who have had VTE events.

Interventions
The relevant intervention of interest is homocysteine testing. Individuals with or at risk of VTE may be assessed in the outpatient setting by a primary care medical provider or a specialist managing VTE.

Comparators
The following practice is currently being used to manage those at risk of VTE and those who have had VTEs: routine care without homocysteine testing, and therefore no folic acid or vitamin B supplementation for homocysteine lowering. The comparator would ideally be in populations where the food supply is not fortified.

Outcomes
The general outcomes of interest are change in disease status and morbid events associated with VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE).

The time frame from outcomes varies but it is expected to be 3 or more years for assessment of DVT or PE.

Summary of Evidence: Venous Thromboembolism
For individuals who are asymptomatic with the risk of venous thromboembolism (VTE) or individuals who have experienced VTE events who receive homocysteine testing, the evidence includes observational studies and RCTs of homocysteine-lowering interventions. Evidence from RCTs evaluating homocysteine-lowering interventions does not support the hypothesis that lowering homocysteine levels with folate and/or B vitamins reduces the risk of VTE. Only a single RCT was designed to test for VTE as a primary outcome. Further randomized clinical trials are needed to help clarify the use of supplementation for prevention of VTE. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

Vitamin B12 Deficiency
Vitamin B12 deficiency and folate deficiency often co-exist and are not easily differentiated on a clinical basis. Accordingly, such individuals should be evaluated for both deficiencies. The first step should entail determination of vitamin B12 and folate concentrations. Serum vitamin B12 levels can be interpreted as follows:

- Normal result: >300 pg/mL (>221 pmo/L) vitamin B12 deficiency unlikely
- Borderline result: 200 to 300 pg/mL (148 to 221 pmo/L) vitamin B12 deficiency possible
- Low result: <200 pg/mL (<148 pmo/L) – consistent with vitamin b12 deficiency

Individuals with serum vitamin B12 values at the lower end of the normal range or in the borderline range (described above) may be vitamin B12 deficient and respond to replacement therapy. Measurement of serum homocysteine appears to be more sensitive for the diagnosis of these deficiencies than serum vitamin levels alone and is helpful in clarifying the diagnosis when serum vitamin B12 or folate concentrations are equivocal. Serum concentrations of homocysteine are elevated in vitamin B12 deficiency due to a decreased rate of metabolism. The evidence is sufficient to determine the testing results in a meaningful improvement in net health outcomes.

Role of Homocysteine in Other Conditions

Clinical Context and Test Purpose
The purpose of testing homocysteine levels is to inform management decisions such as whether to lower or raise homocysteine levels.

Populations
The relevant population of interest is individuals with conditions in which homocysteine concentrations may affect their risk or management.

Interventions
The relevant intervention of interest is homocysteine testing.

Comparators
In the routine care in the treatment and management without homocysteine testing

Outcomes
The general outcome of interest is change in disease status and morbid events attributable to high homocysteine levels.

Aortic Dissection
Aortic dissection is relatively uncommon, but it often presents acutely as a catastrophic illness with severe chest or back pain and acute hemodynamic compromise. Early and accurate diagnosis and treatment are crucial for survival. Serum markers for acute aortic dissection are emerging as a diagnostic option, particularly in screening individuals in the setting of differentiating chest pain to include homocysteine testing.

Some studies have shown individuals with acute aortic dissection present with a higher homocysteine and low folate compared to chronic aneurysms. However, routine blood tests are generally nondiagnostic in aortic dissection. A diagnosis of acute aortic dissection depends upon demonstration of the dissection on imaging studies, which

defines the extent of aortic involvement and identifies sites of entry and reentry, branch vessel involvement, aortic insufficiency, and pericardial effusion. No one study is capable of obtaining all the information that is needed to fully evaluate aortic dissection, and therefore, a combination of studies is often obtained and is also dependent on if the individual is hemodynamically stable or not.

Based on the review of the peer reviewed medical literature, while studies may have shown a high circulating homocysteine with acute aortic dissection, tissue homocysteine expression from these individuals have never been investigated. Further studies are needed on the pathogenic mechanism of the disruption of homocysteine metabolism to provide a therapeutic strategy regarding acute aortic dissection. Also, routine serum marker testing is generally nondiagnostic in aortic dissection diagnosis and management and the utility of serum markers needs further evaluation. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Autism

Substantial characteristics of autism are cognitive and psychophysical disorders. Etiopathogenetic factors (cause and subsequent development of an abnormal condition or of a disease) are thought to be responsible for development of autism in children with genetic predisposition as well as have their effect on the severity of the disorders. The main problem of early identification of individuals affected by autism spectrum disorder is that there are no clear diagnostic criteria. Based on review of the peer reviewed medical literature the evidence is insufficient to determine the effects of homocysteine testing for the assessment of autism on net health outcomes.

There are many reports about the significant roles of some amino acids in neurobiology and the treatment of autism. A review by Ghanizadeh (2013) reviewed the role of amino acids levels in autism. No published review article about the level of amino acids in autism was found. The levels of glutamate and homocysteine are increased in autism while the levels of glutamine and tryptophan are decreased. Findings regarding the plasma levels of taurine and lysine are controversial. The urinary levels of homocysteine and essential amino acids in both the untreated and treated autistic children are significantly less than those in the controls. Current findings support that many children with autism suffer from amino acids metabolism impairment, however, the current literature suffers from many methodological shortcomings which needed to be considered in future studies. Some of them are age, gender, developmental level, autism symptoms severity, type of autism spectrum disorders, medical comorbidities, intelligent quotient, diet, concomitant medications, body mass index, and technical method of assessment of amino acids. Children with autism more likely have essential amino acids deficiency, and this may make them prone to a higher deficiency if they are under a specific diet.

There are many shortcomings in the current literature regarding the level of amino acids in autism and further studies should investigate the following:

- Whether the levels of different amino acids are associated with age and gender in autism.

- Examine whether the profile of amino acids in autism is associated with the developmental level and autism symptom severity.
- Autism is one of the disorders in the spectrum of pervasive developmental disorders. Whether the pattern of amino acids is different between the different types of autism spectrum disorders needs to be clarified. Whether current findings can be generalized to all the types of autism needs to be investigated.
- Future studies should examine the possible role of any diet regimen or food habits as covariate factors. It should be clarified whether the possible profile of amino acids in autism is secondary to the food and diet pattern.
- Gastrointestinal problems are not uncommon in children with autism (constipation, abdominal pain, bloating, diarrhea, and/or nausea), is there any role for these problems to impact amino acids levels in autism.

Based on review of the peer reviewed medical literature the evidence is insufficient to determine the effects of homocysteine testing in the treatment and management of autism on net health outcomes.

Dementia and Cognitive Impairment

There is conflicting evidence about whether homocysteine is an independent risk factor for dementia or cognitive impairment. The potential mechanisms whereby homocysteine might mediate cognitive decline and dementia include neurotoxicity induced by activation of N-methl-D-aspartate (NMDA receptors; promotion of apoptosis; vascular injury from promotion of atherogenesis and proliferation of smooth muscle cells; platelet activation; increased burden of ischemic strokes and white matter lesions. However, some studies suggest that the association between abnormal homocysteine levels as well as other changes in serum vitamin concentrations reflects early weight loss as a manifestation of early dementia rather than its cause. Homocysteine lowering therapy using supplementation with vitamins B12 and B6 has not been shown to improve cognitive function or prevent cognitive decline. Also, homocysteine testing is generally not recommended or included in the standard evaluation of dementia.

In 2014, the American Academy of Neurology (AAN) reported on the results of a 2-year study on vitamin B treatment on cognitive performance. This study was one of the largest to date to test long-term use of supplements and thinking and memory skills. The study involved people with high blood levels of homocysteine, an amino acid. High levels of homocysteine have been linked to memory loss and Alzheimer's disease. Since homocysteine levels can be lowered with folic acid and vitamin B12 supplements, the hope has been that taking these vitamins could also reduce the risk of memory loss and Alzheimer's disease. Early observational studies showed there may be some benefit to thinking and memory skills in taking folic acid and vitamin B12, but the results of later randomized controlled trials were less convincing. For the current study, 2,919 people with an average age of 74 took either a tablet with 400 mg of folic acid and 500 mg of vitamin B12 or a placebo every day for two years. Tests of memory and thinking skills were performed at the beginning and end of the study. All of the participants had high

blood levels of homocysteine. The authors concluded, homocysteine levels decreased more in the group taking the B vitamins than in the group taking the placebo, unfortunately there was no difference between the two groups in the scores on the thinking and memory tests.

The evidence is insufficient to determine the effects of the technology on net health outcomes.

Multiple Sclerosis (MS)
Elevated homocysteine levels have been observed in individuals with MS. Studies have examined why plasma homocysteine levels are increased in MS, and whether they play a role in the disease course. Findings indicated that regardless of significant increase in plasma homocysteine levels in MS individuals, the disease is not generally associated with vitamin B12 deficiency. Therefore, homocysteine testing is considered investigational because the effectiveness of this testing for this indication has not been established. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Osteoporosis
High homocysteine levels in adults have been associated with osteoporotic fractures in some, but not all studies. It is not clear, however, whether high levels of homocysteine have a direct effect on bone or whether the effect is mediated through another factor, such as poor nutrition, and it is uncertain whether folic acid supplementation is beneficial for osteoporosis. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Recurrent Pregnancy Loss
In normal pregnancy, homocysteine concentrations fall. Disturbance of maternal and fetal homocysteine metabolism has been associated with fetal neural tube defects, with various conditions characterized by placental vasculopathy, such as pre-eclampsia and abruption, and with recurrent pregnancy loss. Apart from folate supplementation, which has been clearly shown to halve the risk of fetal neural tube defects, no other strategies have been identified in relation to homocysteine metabolism that will reliably reduce the frequency of these other common obstetric pathologies. Routine testing of women with recurrent pregnancy loss for inherited thrombophilias to include fasting homocysteine levels is not currently recommended because there is lack of association between this testing and negative pregnancy outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

Practice Guidelines and Position Statements

American College of Obstetricians and Gynecologist (ACOG)
(2018) ACOG updated their practice bulletin; no. 138 to no. 197, inherited thrombophilias in pregnancy and the recommendations include the following:

- Screening for inherited thrombophilias is not recommended with a history of fetal loss or adverse pregnancy outcomes including abruption, preeclampsia, or fetal growth restriction because there is insufficient clinical evidence that antepartum prophylaxis with unfractionated heparin or low-molecular weight heparin prevents recurrence in these patients.
- Because of the lack of association between either heterozygosity or homozygosity for the methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism and any negative pregnancy outcomes, including any increased risk for venous thromboembolism, screening with either MTHFR mutation analyses or fasting homocysteine levels is not recommended.

(*Accessed June 2022*)

American Society for Reproductive Medicine (ASRM)

(2012) The American Society for Reproductive Medicine (ASRM) issued a committee opinion regarding evaluation and treatment of recurrent pregnancy loss, which included the following statement: "Inherited Thrombophilias**:** Screening for inherited thrombophilias (specifically, Factor V Leiden and the prothrombin gene mutations, protein C, protein S and antithrombin deficiencies) may be clinically justified when a patient has a personal history of venous thromboembolism in the setting of a non-recurrent risk factor (such as surgery) or a first degree relative with a known or suspected high risk thrombophilia. Although an association between hereditary thrombophilias and fetal loss has been suggested, prospective cohort studies have failed to confirm this. Routine testing of women with recurrent pregnancy loss for inherited thrombophilias is not currently recommended."

This committee opinion does not address the measurement of homocysteine levels. (*Accessed June 2022)*

Regulatory Status

Several of the homocysteine test systems have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process.

Homocysteine Test Systems

Assay	Laboratory	Approval Date
A/C Automatic Enzymatic Hcy [Homocysteine] Assay	AntiCancer Inc.	2008
Diazyme Enzymatic Homocysteine Assay	Diazyme Laboratories	2012
Homocysteine Enzymatic Assay	Roche Diagnostics	2012
Teco Enzymatic Homocysteine Assay	Teco Diagnostics	2007

This table is not intended to be all inclusive.

PRIOR APPROVAL

Not applicable.

POLICY

See Related Medical Policy

- 02.04.04 Cardiovascular Disease Risk Tests

Medically Necessary

The measurement of plasma homocysteine levels may be considered **medically necessary** for the following indications:

- Assessment of individuals with borderline vitamin B12 deficiency (200 to 300 pg/mL), where the results will impact the individual's management; **or**
- Assessment of individuals with homocystinuria (also known as cystathionine beta synthase deficiency or CBS deficiency).

Investigational

Homocysteine testing is considered **investigational** for all other indications including but not limited to the following:

- Assessment and management of aortic dissection
- Assessment and management of Autism
- Assessment and management of cognitive impairment and dementia
- Assessment and management of multiple sclerosis
- Assessment and management of osteoporosis (fracture risk)
- Assessment of recurrent pregnancy loss
- Assessment of venous thromboembolism inherited or acquired
- When the above criteria are not met

Based on peer reviewed medical literature there is insufficient evidence to support conclusions concerning the net health outcomes or benefits associated with homocysteine testing for the above indications (*not an all-inclusive list*).

Note: For homocysteine testing related to cardiovascular disease risk see the related medical policy 02.04.04 Cardiovascular Disease Risk Tests.

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 83090 Homocysteine

SELECTED REFERENCES

- Lonn E, Yusuf S, Arnold MJ et al. Homocysteine lowering with folic acid and B vitamins in vascular disease. N Engl J Med. 2006 Apr 13; 354(15):1567-77.
- Jamison RL, Hartigan P, Kaufman JS et al. Effect of homocysteine lowering on mortality and vascular disease in advanced chronic kidney disease and end-stage renal disease: a randomized controlled trial. JAMA. 2008 Sep 12; 298(10):1163-70.
- Song Y, Cook NR, Albert CM et al. Effects of homocysteine-lowering treatment with folic acid and B vitamins on risk of type-2 diabetes mellitus in women: a randomized controlled trial. Diabetes. 2009 Jun 2. [Epub ahead of print]
- Grundy SM, Cleeman JI, Merz CN et al. Implications of recent trials for the National Cholesterol Education program Adult Treatment Panel III guidelines. Circulation. 2004 Jul 13; 110(2):227-39.
- Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group, Armitage JM, Bowman L, Clarke RJ et al. Effects of homocysteine-lowering with folic acid plus vitamin B12 vs placebo on mortality and major morbidity in myocardial infarction survivors: a randomized trial. JAMA. 2010;303(24):2486-94.
- Clark R, Halsey J, Bennett D, et al. Homocysteine and vascular disease: review of published results of the homocysteine-lowering trials. J Inherit Metab Dis 2011; 34(1):83-91.
- Refsum H, Smith AD, Ueland PM, et al. Facts and Recommendations about Total Homocysteine Determinations: An Expert Opinion. Clinical Chemistry 2004;50(1):3-32.
- Stanislawska-Sachadyn A, Woodside JV, Sayers CM, Yarnell JW, et al. The transcobalamin (TCH2) 776C>G polymorphism affects homocysteine concentrations among subjects with low vitamin b12 status. Eur J Clin Nutr. 2010;64:1138-1343.
- Varga EA, Sturm AC, Misita CP and Moll S. Homocysteine and MTHFR Mutations: Relation to Thrombosis and Coronary Artery Disease. Circulation 2005;11:e289-e293.
- Deshmukh US, Joglekar CV, Lubree HG, et al. Effect of physiological doses of oral vitamin B12 on plasma homocysteine: a randomized, placebo-controlled, double-blind trial in India. Eur J Clin Nutr. 2010 May;64(5):495-502.

- Kokturk N, Kanbay A, Aydogdu M, et al. Hyperhomocysteinemia prevalence among patients with venous thromboembolism. Clin Appl Thromb Hemost. 2011 Oct;17(5):487-93.
- Ray JG, Kearon C, Yi Q, et al. Homocysteine-lowering therapy and risk for venous thromboembolism: a randomized trial. Ann Intern Med. 2007 Jun 5;146(11):761-7.
- Van der Molen EF, Verbruggen B, Novakova I, et al. Hyperhomocysteinemia and other thrombotic risk factors in women with placental vasculopathy. BJOG. 2000 Jun;107(6):785-91.
- Bergen NE, Jaddoe VW, Timmermans S, et al. Homocysteine and folate concentrations in early pregnancy and the risk of adverse pregnancy outcomes: the Generation R Study. BJOG. 2012 May;119(6):739-51.
- U.S. Preventative Services Task Force. October 2009. Using Nontraditional Risk Factors in Coronary Heart Disease Risk Assessment, Recommendation Statement.
- https://www.uspreventativeservicestaskforce.org
- American Heart Association. January 20, 2012. Homocysteine, Folic Acid and Cardiovascular Disease. http://www.heart.org
- American Journal of Obstetrics and Gynecology vol.197, issue 5, November 2007. Antithrombotic Therapy and Pregnancy: Consensus Report and Recommendations for Preventative and Treatment of Venous Embolism and Adverse Pregnancy Outcomes.
- American College of Obstetricians and Gynecologists (ACOG). Inherited thrombophilias in pregnancy. Washington (DC): American College of Obstetricians and Gynecologists (ACOG); 2013 Sep. 12 p. (ACOG practice bulletin; no. 138).
- American Society for Reproductive Medicine, Evaluation and Treatment of Recurrent Pregnancy Loss: Committee Opinion 2012. Also available at www.asrm.org/Guidelines Fertil Steril 2012;98:1103-11
- MedScape. Homocystinuria/Homocysteinemia. Updated November 4, 2014. Also available at http://emedicine.medscape.com/article/1952251-overview
- UpToDate. Overview of Homocysteine, Robert S. Rosenson, M.D., David S. Kang, M.D., PhD. Topic last updated October 26, 2020. Also available at https://www.uptodate.com
- UpToDate. Diagnosis and Treatment of Vitamin B12 and Folate Deficiency, Stanley L. Schrier, M.D., Topic last updated June 13, 2017. Also available at https://www.uptodate.com
- UpToDate. Risk Factors for Cognitive Decline and Dementia, Eric B. Larson, M.D., MPH, Topic last updated June 19, 2017. Also available at https://www.uptodate.com
- UpToDate. Overview of the Causes of Venous Thrombosis, Kenneth A Bauer M.D., Gregroy YH Lip, M.D., FRCPE, FESC, FACC. Topic last updated February 5, 2019. Also available at https://www.uptodate.com
- Picker J, Levy H. Homocystinuria Caused by Cystathionine Beta-Synthase Deficiency, Gene Reviews last updated November 13, 2014. NCBI Bookshelf. A

service of the National Library of Medicine, National Institutes of Health. http://www.ncbi.nlm.nih.gov
- U.S. National Institute of Health (NIH), National Library of Medicine. Homocystinuria. Genetics Home Reference. Bethesda, MD: Also available at http://ghr.nlm.nih.gov/condition=homocystinuria
- Wang C, Han L, Wu Q, et al. Association between homocysteine and incidence of ischemic stroke in subjects with essential hypertension: A matched case-control study. Clin Exp Hypertens. Nov 2015;37(7):557-562. PMID 25992490
- Yi X, Zhou Y, Jiang D, et al. Efficacy of folic acid supplementation on endothelial function and plasma homocysteine concentration in coronary artery disease: A meta-analysis of randomized controlled trials. Exp Ther Med. May 2014;7(5):1100-1110. PMID 24940394
- Liu Y, Tian T, Zhang H, et al. The effect of homocysteine-lowering therapy with folic acid on flow-mediated vasodilation in patients with coronary artery disease: a meta-analysis of randomized controlled trials. Atherosclerosis. Jul 2014;235(1):31-35. PMID 24814647
- van Dijk SC, Enneman AW, Swart KM, et al. Effects of 2-year vitamin B12 and folic acid supplementation in hyperhomocysteinemic elderly on arterial stiffness and cardiovascular outcomes within the B-PROOF trial. J Hypertens. Sep 2015;33(9):1897-1906; discussion 1906. PMID 26147383
- UpToDate. Clinical Manifestations and Diagnosis of Vitamin B12 and Folate Deficiency. Stanley L. Schrier M.D., Topic last updated March 22, 2019. Also available at https://www.uptodate.com
- Peng HY, Man CF, Xu J, et al. Elevated homocysteine levels and risk of cardiovascular and all-cause mortality: a meta-analysis of prospective studies. J Zhejiang Univ Sci B. Jan 2015;16(1):78-86. PMID 25559959
- UpToDate. Osteoporotic Fracture Risk Assessment. E. Michael Lewiecki M.D., Topic last updated September 5, 2018. Also available at https://www.uptodate.com
- van Meurs JB, Dhonukshe-Rutten RA, van der Klift M, et. al. Homocysteine levels and the risk of osteoporotic fracture. N Engl J Med 2004;350(20):2033. PMID 15141041
- McLean RR, Jacques PF, Selhub J, et. al. Homocysteine as a predictive factor for hip fracture in older persons. N Engl J Med 2004;350(20):2042. PMID 15141042
- Dhonukshe-Rutten RA, Pluijm SM, de Groot LC, et. al. Homocysteine and vitamin B12 status relate to bone turnover markers, broad band ultrasound attenuation, and fractures in healthy elderly people. J Bone Miner Res 2005;2096):921. PMID 15883631
- Gerdhem P, Ivaska KK, Isaksson A, et. al. Associations between homocysteine, bone turnover, BMD, mortality, and fracture risk in elderly woman. J Bone Miner Res 2007;22(1):127. PMID 17032146
- Perier MA, Gineyts E, Munoz F, et. al. Homocysteine and fracture risk in postmenopausal women the OFELY study. Osteoporos Int 2007;18(10);1329. PMID 17549579

- McLean RR, Jacques PF, Selhub J. et. al. Plasma B vitamins and their relation with bone loss and hip fracture in elderly men and women. J Clin Endocrinol Metab 2008;93(6):2206. PMID 18364381
- Leboff MS, Narweker R, LaCroix A, et. al. Homocysteine levels and risk of hip fracture in postmenopausal women. J Clin Endocrinol Metab 2009;94(4):1207. PMID 1914498
- Farina N, Jerneren F, Turner C, et. al. Homocysteine concentrations in the cognitive progression of Alzheimer's. Exp Gerontol 2017 Dec 1;99:146-150. PMID 29024723
- Jozefczuk J, Kasprzycka W, Czarnecki R, et. al. Homocysteine as a diagnostic and etiopathogenic factor in children with autism spectrum disorder. J Med Food 2017 Aug;20(8):744-749. PMID 28598237
- Ghanizadeh A. Increased glutamate and homocysteine and decreased glutamine levels in autism. A review and strategies for future studies of amino acids in autism. Dis Markers 2013;35(5):281-286. PMID 24167375
- Fahmy EM, Elfayoumy NM, Abdelalim AM, et. al. Relation of serum levels of homocysteine, vitamin B12 and folate to cognitive functions in multiple sclerosis patients. Int J Neurosci 2018 Sept;128(9):835-841. PMID 29384421
- Dardiotis E, Arseniou S, Sokratous M, et. al. Vitamin B 12, folate, and homocysteine levels and multiple sclerosis: a meta-analysis. Mult Scler Relat Disord 2017 Oct 17:190-197. PMID 29055456
- Nikita L, Rasalie AM, Janneka P, et. al. Results of 2-year vitamin B treatment on cognitive performance. Neurology Dec 2014 83 (23) 2158-2166
- ACOG Practice Bulletin No. 197 Inherited Thrombophilia in Pregnancy. Obstet Gynecol 2018 Jul;132(1):e18-E34. PMID 29939939
- UpToDate. Clinical Features and Diagnosis of Acute Aortic Dissection. James H. Black III M.D., Warren J. Manning M.D. Topic last updated March 11, 2021. Also available at https://www.uptodate.com
- Sbarouni E, Georgeiadou P, Analitis A, et. al. High homocysteine and low folate concentrations in acute aortic dissection. Int J Cardiol 2013 Sept 20:168(1):463-6. PMID 23073272
- Aday A.W., Duran E.K., Van Denburgh M. et al. Homocysteine Is Associated With Future Venous Thromboembolism in 2 Prospective Cohorts of Women. Originally published May 27, 2021.;41:2215–2224 https://doi.org/10.1161/ATVBAHA.121.316397Arteriosclerosis, Thrombosis, and Vascular Biology. Available at: https://www.ahajournals.org/doi/10.1161/ATVBAHA.121.316397#d1e2717
- Pinard A., Jones G.T., Milewicz D.M., Genetics of Thoracic and Abdominal Aortic Diseases. Aneurysms, Dissections and Ruptures. Circulation ResearchVolume 124, Issue 4, 15 February 2019; Pages 588-606. https://doi.org/10.1161/CIRCRESAHA.118.312436. Available at: https://www.ahajournals.org/doi/epub/10.1161/CIRCRESAHA.118.312436
- Mititelu RR, Albu CV, Bacanoiu MV, et al. Homocysteine as a Predictor Tool in Multiple Sclerosis. Discoveries (Craiova). 2021;9(3):e135. Published 2021 Sep 28. doi:10.15190/d.2021.14

- De Martinis, M., Sirufo M.M., Nocelli C., et al. Hyperhomocysteinemia is Associated with Inflammation, Bone Resorption, Vitamin B12 and Folate Deficiency and MTHFR C677T Polymorphism in Postmenopausal Women with Decreased Bone Mineral Density. International Journal of Environmental Research and Public Health. 15 June 2020. 17, 4260. doi:10.3390/ijerph17124260
- Annefleur D.O., Hensen W.M., Lifering S.C. et al., Hyperhomocysteinaemia and the risk of recurrent venous thrombosis: results from the MEGA follow-up study. First published: 01 July 2019. Volume 187, Issue 2. https://doi.org/10.1111/bjh.16075. Available at: https://onlinelibrary.wiley.com/doi/full/10.1111/bjh.16075

POLICY HISTORY		
Date	**Reason**	**Action**
July 2022	Annual Review	Policy Revised
July 2021	Annual Review	Policy Revised
July 2020	Annual Review	Policy Renewed
July 2019	Annual Review	Policy Revised
July 2018	Annual Review	Policy Revised
July 2017	Annual Review	Policy Renewed
July 2016	Annual Review	Policy Revised
August 2015	Annual Review	Policy Revised
September 2014	Annual Review	Policy Revised
October 2013	Annual Review	Policy Renewed
December 2012	Annual Review	Policy Revised
July 2012	Annual Review	Policy Renewed
August 2011	Annual Review	Policy Renewed

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

*CPT® is a registered trademark of the American Medical Association.