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# Homocysteine Testing

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**Number: 0763**

## Policy

*\*Please see amendment for Pennsylvania Medicaid at the end of this CPB.*

Aetna considers homocysteine testing (measurements of plasma homocysteine) medically necessary for the following indications:

- Assessment of borderline vitamin B12 deficiency, where the results will impact the member's management (see [CPB 0536 - Vitamin B-12 Therapy \(../500\\_599/0536.html\)](#));  
or
- Assessment of homocystinuria caused by cystathionine beta synthase deficiency (Note: For newborn screening, measurements of plasma homocysteine/total homocysteine are performed only when hyper-methioninemia has been confirmed); or
- Assessment of idiopathic venous thrombo-embolism, recurrent venous thrombo-embolism, thrombosis occurring at a young age (i.e., less than 45 years of age), or thrombosis at an unusual site.

Aetna considers homocysteine testing experimental and investigational for all other indications, including the following (not an all inclusive list) because its effectiveness for these indications has not been established:

- As a biomarker for the development and/or progression of erectile dysfunction
- As a diagnostic marker for age-related macular degeneration
- As a diagnostic marker for Alzheimer's disease
- Assessment of acquired thrombophilia

## Policy History

### Last Review

10/25/2019

Effective: 08/08/2008

Next

Review: 08/27/2020

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### Review

History

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### Definitions

## Additional Information

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- Assessment of autism (see [CPB 0648 - Autism Spectrum Disorders \(../600\\_699/0648.html\)](#))
- Assessment of cardiovascular disease or stroke risk (see [CPB 0381 - Cardiovascular Disease Risk Tests \(../300\\_399/0381.html\)](#))
- Assessment of cognitive impairment and dementia (e.g., Alzheimer's disease, Binswanger's disease)
- Assessment of depression
- Assessment of Down's syndrome
- Assessment of fracture risk (see [CPB 0562 - Biochemical Markers of Bone Remodeling \(../500\\_599/0562.html\)](#))
- Assessment of Gaucher's disease
- Assessment of HELLP syndrome
- Assessment of lung transplant candidates
- Assessment of Meniere's disease
- Assessment of migraine headaches
- Assessment of movement disorders (e.g., Huntington's disease, Parkinson's disease, and primary dystonia)
- Assessment of multiple sclerosis
- Assessment of polycystic ovary syndrome
- Assessment of premature ovarian failure
- Assessment of primary carnitine deficiency
- Assessment of recurrent pregnancy loss (see [CPB 0348 - Recurrent Pregnancy Loss \(../300\\_399/0348.html\)](#))
- Assessment of retinal artery occlusion
- Assessment of retinal branch vein occlusion
- Assessment of stroke risk
- In-vitro fertilization planning (assessment and treatment of implantation failure)
- Management of 5,10-methylenetetrahydrofolate reductase (MTHFR) abnormalities
- Management of celiac disease
- Management of inflammatory bowel disease
- Management of pulmonary hypertension
- Monitoring of methotrexate therapy
- Monitoring of s-adenosylmethionine therapy
- Monitoring response to vitamin B-12 therapy.

## Background

Homocysteine is an amino acid used to make protein and to build and maintain tissue. Excess levels in the blood are purported to increase the risk of stroke, certain types of heart disease or peripheral artery disease (PAD).

Homocysteine (Hcy), a sulphur-containing amino acid, is formed from the conversion of methionine into cysteine. It is usually rapidly metabolized via 1 of 2 pathways: (i) a vitamin B12- and folate-dependent re-methylation pathway that regenerates methionine, or (ii) a vitamin B6-dependent trans-sulphuration pathway that converts 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 micromol/L), intermediate (31 to 100 micromol/L), or severe (greater than 100 micromol/L). Measurements of Hcy levels are usually performed after fasting; levels of 12 micromol/L are considered normal, and levels below 10 micromol/L are considered desirable.

Increases in plasma Hcy concentration (pHcy) can arise from various causes: (i) genetic defects in the enzymes involved in Hcy metabolism, (ii) nutritional deficiencies in vitamin co-factors, and (iii) 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 nicotinic acid) (Rosenson and Kang, 2007).

The most common form of genetic hyper-homocysteinemia results from production of a thermo-labile variant of methylene tetrahydrofolate reductase (MTHFR) with reduced enzymatic activity. The gene encoding for this variant contains an alanine-to-valine substitution at amino acid 677 (C677T). The responsible gene is common, with a population frequency estimated between 5 % to 14 %. Homozygosity for the thermo-labile variant of MTHFR (TT genotype) is a relatively common cause of mildly elevated pHcy in the general population, often occurring in association with low serum folate levels (Rosenson and Kang, 2007). Harmon and colleagues (1996) quantified the contribution of the thermo-labile mutation to the hyper-homocysteinemic phenotype in a working male population (n = 625). Serum folate and vitamin B12 concentrations were measured and their relationship with Hcy status and MTHFR genotype were assessed. They found that 11.5 % of the subjects were homozygous for the TT genotype. However, for those in the top 5 to 10 % of pHcy, the frequency rose to 48 % and 36 %, respectively. Homozygotes also had the lowest serum folate concentrations.

However, the role of screening for MTHFR variants during pregnancy to ascertain risks of neural tube defects (NTDs) and/or recurrent pregnancy loss is unclear.

### Role of Hcy in 5,10-MTHFR Abnormalities

Finnell and associates (2002) stated that despite the fact that NTDs are the most common congenital malformations of the central nervous system, investigators have yet to identify responsible gene(s). Research efforts have been productive in the identification of environmental factors, such as peri-conceptional folic acid supplementation that modulate risk for the development of NTDs. Studies of the folic acid biosynthetic pathway led to the discovery of an association between elevated levels of Hcy and NTD risk. Researchers subsequently identified single nucleotide polymorphisms in the gene coding for the enzyme 5,10-MTHFR. Association studies suggested it was a potential risk factor for NTDs, because the thermo-labile form of the enzyme led to elevated pHcy when folic acid intake is low. Numerous studies analyzing MTHFR variants have resulted in positive associations with increased NTD risk only in certain populations, suggesting that these variants are not large contributors to the etiology of NTDs. With limited understanding of the genes involved in regulating NTD susceptibility, the paucity of data on how folic acid protects the developing embryo as well as the observed decrease in birth prevalence of NTDs following folic acid supplementation and food fortification, it makes little sense for prospective parents to be tested for MTHFR variants, or for variants of other known folate pathway genes.

Makino and co-workers (2004) studied whether polymorphisms of MTHFR and the endothelial nitric oxide synthase (eNOS) are associated with recurrent pregnancy loss (RPL). They concluded that the nitric oxide concentration but not the polymorphism of MTHFR and eNOS gene and hyper-homocysteinemia are associated with RPL.

O'Leary and colleagues (2005) stated that methionine synthase reductase (MTRR) regenerates methylated cobalamin levels from the oxidized cob(II)alamin form and in so doing plays a crucial role in maintaining the active state of methionine synthase (MTR), which is an essential enzyme catalyzing the conversion of Hcy to methionine. Single nucleotide polymorphisms (SNPs) within the MTRR gene may potentially compromise MTR activity leading to elevated pHcy, a known risk factor for NTDs. These researchers studied the MTRR polymorphisms I22M (66A-->G), S175L (524C-->T), and K350R (1049A-->G) as potential NTD risk factors in a large homogeneous Irish NTD population. Degree of risk was assessed via case/control comparison, log-linear analysis, and transmission disequilibrium testing. No association was found between NTDs and I22M in mothers ( $p = 0.16$ , odds ratio [OR] 1.14 [0.95 to 1.38],  $n = 447$ ) or cases ( $p = 0.13$ , OR 1.15 [0.96 to 1.38],  $n = 470$ ) compared to controls ( $n = 476$ ). A dominant I22M paternal effect was found through case/control comparison and log-linear modeling ( $p = 0.019$ ) (goodness-of-fit,  $p = 0.91$ , OR 1.46 [1.10 to 1.93],  $n = 423$ ). No significant NTD association was found with S175L or K350R in cases or their parents and no interactions were observed between these polymorphisms and the D919G variant of MTR or the A222V variant of 5,10-MTHFR. These investigators also compared the frequencies of I22M, S175L, and K350R in African-Americans

versus American-Caucasians. The frequencies of I22M and K350R differed significantly between the two groups ( $p = 0.0005$  and  $p = 0.0001$ , respectively). These findings do not support an important role for these MTRR variants in NTDs.

### Role of Hcy in Coronary Heart Disease or Stroke Risk

While Hcy has been reported to exhibit atherogenic and prothrombotic properties, and histopathological hallmarks of Hcy-induced vascular injury include intimal thickening, elastic lamina disruption, smooth muscle hypertrophy, marked platelet accumulation, and the formation of platelet-enriched occlusive thrombi, its role in coronary heart disease and stroke is unclear. In randomized trials, reduction in Hcy levels has failed to lower overall risk for cardiovascular disease (CVD).

Genest and colleagues (2000) noted that the epidemiological evidence linking total plasma Hcy to atherosclerosis is mainly derived from case-control studies, however the strength of this association is weak in prospective studies. Thus, the causal relationship between total plasma Hcy and heart disease is not as strong as one would like to make recommendations regarding screening and treatment for the prevention of CVD.

In a double-blind, randomized controlled trial, Toole and associates (2004) examined if high doses of folic acid, vitamin B6, and vitamin B12, given to lower total Hcy levels would reduce the risk of recurrent stroke over a 2-year period compared with low doses of these vitamins. A total of 3,680 adults with non-disabling cerebral infarction were included in this study. Subjects received best medical and surgical care plus a daily multi-vitamin containing the United States Food and Drug Administration's reference daily intakes of other vitamins; patients were randomly assigned to receive once-daily doses of the high-dose formulation ( $n = 1,827$ ), containing 25 mg of vitamin B6, 0.4 mg of vitamin B12, and 2.5 mg of folic acid; or the low-dose formulation ( $n = 1,853$ ), containing 200 microg of vitamin B6, 6 microg of vitamin B12 and 20 microg of folic acid. Main outcome measures were recurrent cerebral infarction (primary outcome); coronary heart disease (CHD) events and death (secondary outcomes). Mean reduction of total Hcy was 2 micromol/L greater in the high-dose group than in the low-dose group, but there was no treatment effect on any end point. The unadjusted risk ratio for any stroke, CHD event, or death was 1.0 (95 % confidence interval [CI]: 0.8 to 1.1), with chances of an event within 2 years of 18.0 % in the high-dose group and 18.6 % in the low-dose group. The risk of ischemic stroke within 2 years was 9.2 % for the high-dose and 8.8 % for the low-dose groups (risk ratio, 1.0; 95 % CI: 0.8 to 1.3) ( $p = 0.80$  by log-rank test of the primary hypothesis of difference in ischemic stroke between treatment groups). There was a persistent and graded association between baseline total Hcy level and outcomes. A 3-micromol/L lower total Hcy level was associated with a 10 % lower risk of stroke ( $p = 0.05$ ), a 26 % lower risk of CHD events ( $p < 0.001$ ), and a 16 %

lower risk of death ( $p = 0.001$ ) in the low-dose group and a non-significantly lower risk in the high-dose group by 2 % for stroke, 7 % for CHD events, and 7 % for death. The authors concluded that in this trial, moderate reduction of total Hcy after non-disabling cerebral infarction had no effect on vascular outcomes during the 2 years of follow-up. However, the consistent findings of an association of total Hcy with vascular risk suggested that further exploration of the hypothesis is warranted and longer trials in different populations with elevated total Hcy may be necessary.

Lewis et al (2005) stated that despite the statistical association of Hcy with vascular events, a causal association is unproven, and there is no convincing biological mechanism by which small increases in pHcy would promote CVD. Hankey (2006) noted that there is insufficient evidence to confirm that Hcy is a modifiable causal risk factor for stroke, or to recommend routine screening for, or treatment of, raised plasma total Hcy levels with folic acid and other vitamins, to prevent ischemic stroke. Moreover, the Thrombosis Interest Group of Canada (Houston et al, 2006) stated that there is no evidence to support routine measurement of Hcy in patients with arterial or venous disease. The Group also noted that fasting plasma or serum Hcy concentrations may be measured as a part of the investigation of selected patients with venous thrombo-embolism, especially those with idiopathic thrombosis, recurrent thrombosis, and thrombosis at a young age or at an unusual site. The finding of elevated Hcy by itself would not influence management, as it is a relatively weak risk factor for thrombosis and has not been shown to increase the risk of recurrence. The rationale for its measurement is that the risk associated with elevated Hcy augments the risk associated with other thrombophilic disorders such as Factor V Leiden, and a longer duration of anti-coagulation may be warranted in patients with multiple thrombophilias.

The B-Vitamin Treatment Trialists' Collaboration (2006) reviewed the design and statistical power of 12 randomized trials assessing the effects of lowering Hcy with vitamin B supplements on risk of CVD. The authors concluded that the strength of association of Hcy with risk of CVD may be weaker than had previously been believed. Extending the duration of treatment in these trials would allow any effects associated with prolonged differences in Hcy concentrations to emerge. Establishing a prospective meta-analysis of the ongoing trials of Hcy lowering should ensure that reliable information emerges about the effects of such interventions on CVD outcomes.

Lonn (2007) summarized observational studies linking Hcy to ischemic heart disease, stroke, and venous thrombo-embolism. These studies support weak associations between Hcy and vascular risk. A number of recent large randomized controlled studies failed to demonstrate benefit for Hcy lowering with B vitamin supplements in the prevention of cardiovascular events and venous thrombosis. However, these trials may have been insufficiently powered to detect modest but clinically important treatment benefits. Thus, completion of ongoing large

randomized studies is essential. The author concluded that the status of Hcy as a target for intervention in the prevention of athero-thrombotic arterial and venous disease is uncertain. Current evidence does not support the use of B vitamin supplements to reduce vascular risk. Ongoing large randomized studies will provide further clarity on this subject.

Lazzerini et al (2007) examined the relationship between Hcy and CVD in patients affected with autoimmune diseases (ADs), reviewing the most recent literature data and also providing their experience. Although the large amount of available studies showed that mild hyperhomocysteinemia represents a common finding in patients affected with several autoimmune diseases, the actual role of Hcy in the development of CVD in the course of AD is still unclear, perhaps, with the only exception of the systemic lupus erythematosus. In the other conditions, the role of Hcy in the pathogenesis of vascular complications is still a matter of debate, as the result of conflicting reports and/or lack of an adequate body of investigation.

In a double-blind, randomized controlled trial, Jamison et al (2007) examined if high doses of folic acid and B vitamins administered daily would reduce mortality in patients with chronic kidney disease (CKD). Median follow-up was 3.2 years for 2,056 participants aged 21 years or older with advanced CKD (estimated creatinine clearance less than or equal to 30 mL/min) (n = 1,305) or end-stage renal disease (n = 751) and high Hcy levels (greater than or equal to 15 micromol/L). Subjects received a daily capsule containing 40 mg of folic acid, 100 mg of vitamin B6, and 2 mg of vitamin B12 or a placebo. The primary outcome was all-cause mortality. Secondary outcomes included myocardial infarction (MI), stroke, amputation of all or part of a lower extremity, a composite of these 3 plus all-cause mortality, time to initiation of dialysis, and time to thrombosis of arterio-venous access in hemodialysis patients. Mean baseline Hcy level was 24.0 micromol/L in the vitamin group and 24.2 micromol/L in the placebo group. It was lowered 6.3 micromol/L (25.8 %;  $p < 0.001$ ) in the vitamin group and 0.4 micromol/L (1.7 %;  $p = 0.14$ ) in the placebo group at 3 months, but there was no significant effect on mortality (448 vitamin group deaths versus 436 placebo group deaths) (hazard ratio [HR], 1.04; 95 % CI: 0.91 to 1.18). No significant effects were demonstrated for secondary outcomes or adverse events: there were 129 MIs in the vitamin group versus 150 for placebo (HR, 0.86; 95 % CI: 0.67 to 1.08), 37 strokes in the vitamin group versus 41 for placebo (HR, 0.90; 95 % CI: 0.58 to 1.40), and 60 amputations in the vitamin group versus 53 for placebo (HR, 1.14; 95 % CI: 0.79 to 1.64). In addition, the composite of MI, stroke, and amputations plus mortality ( $p = 0.85$ ), time to dialysis ( $p = 0.38$ ), and time to thrombosis in hemodialysis patients ( $p = 0.97$ ) did not differ between the vitamin and placebo groups. The authors concluded that treatment with high doses of folic acid and B vitamins did not improve survival or reduce the incidence of vascular disease in patients with advanced CKD or end-stage renal disease.

In a randomized, double-blind, placebo-controlled study, Albert and colleagues (2008) examined if a combination of folic acid, vitamin B6, and vitamin B12 would lower risk of CVD among high-risk women with and without CVD. A total of 5,442 women who were United States health professionals aged 42 years or older, with either a history of CVD or 3 or more coronary risk factors, received a combination pill containing folic acid (2.5 mg), vitamin B6 (50 mg), and vitamin B12 (1 mg) or a matching placebo, and were treated for 7.3 years. Main outcome measures were a composite outcome of myocardial infarction, stroke, coronary revascularization, or CVD mortality. Compared with placebo, a total of 796 women experienced a confirmed CVD event (406 in the active group and 390 in the placebo group). Patients receiving active vitamin treatment had similar risk for the composite CVD primary end point (226.9/10,000 person-years versus 219.2/10,000 person-years for the active versus placebo group; relative risk [RR], 1.03; 95 % CI: 0.90 to 1.19;  $p = 0.65$ ), as well as for the secondary outcomes including myocardial infarction (34.5/10,000 person-years versus 39.5/10,000 person-years; RR, 0.87; 95 % CI: 0.63 to 1.22;  $p = 0.42$ ), stroke (41.9/10,000 person-years versus 36.8/10,000 person-years; RR, 1.14; 95 % CI: 0.82 to 1.57;  $p = 0.44$ ), and CVD mortality (50.3/10,000 person-years versus 49.6/10,000 person-years; RR, 1.01; 95 % CI: 0.76 to 1.35;  $p = 0.93$ ). In a blood substudy, geometric mean pHcy was decreased by 18.5 % (95 % CI: 12.5 % to 24.1 %;  $p < 0.001$ ) in the active group ( $n = 150$ ) over that observed in the placebo group ( $n = 150$ ), for a difference of 2.27 micromol/L (95 % CI: 1.54 to 2.96 micromol/L). The authors concluded that after 7.3 years of treatment and follow-up, a combination pill of folic acid, vitamin B6, and vitamin B12 did not reduce a combined end point of total cardiovascular events among high-risk women, despite significant Hcy lowering.

In an editorial that accompanied the afore-mentioned article, Lonn (2008) stated that currently vitamin B supplements can not be recommended for the prevention of CVD events with the exception of rare genetic disorders, and there is no role for routine screening for elevated Hcy levels.

A Cochrane systematic evidence review (Martí-Carvajal et al, 2009) concluded that "[r]esults from available published trials suggest that there is no evidence to support the use of HLI [homocysteine lowering interventions] to prevent cardiovascular events."

The U.S. Preventive Services Task Force (USPSTF, 2009) concluded that the evidence is insufficient to assess the balance of benefits and harms of using Hcy levels to screen asymptomatic men and women with no history of CHD to prevent CHD events.

The American Academy of Family Physicians' "Summary of recommendations for clinical preventive services" (AAFP, 2012) concludes that for coronary heart disease (CHD), the current evidence is insufficient to evaluate the balance of benefits and harms of using the non-traditional

risk factors discussed in this statement to screen asymptomatic men and women with no history of CHD to prevent CHD events. The non-traditional risk factors included in this recommendation are high-sensitivity C-reactive protein, ankle-brachial index, leukocyte count, fasting blood glucose level, periodontal disease, carotid intima-media thickness, coronary artery calcification score on electron-beam computed tomography, Hcy level, and lipoprotein(a) level.

In a post-hoc analysis of the China Stroke Primary Prevention Trial (CSPPT), Huang and colleagues (2017) examined if a change in serum tHcy levels is associated with first stroke risk. These researchers analyzed 16,867 participants of the CSPPT with tHcy measurements at both baseline and exit visits. The primary outcome was first stroke; the secondary outcome was a composite of CV events consisting of CV death, MI, and stroke. The percent decline in tHcy was calculated as  $[(\text{baseline tHcy} - \text{exit tHcy})/\text{baseline tHcy} \times 100]$ . Over the median treatment duration of 4.5 years, participants who developed a 1st stroke had a significantly lower percent decline in tHcy ( $\beta = -5.7$ ; 95 % CI: -8.8 to -2.6) compared to their counterparts. A 20 % tHcy decline was associated with a reduction in stroke risk of 7 % (HR 0.93; 95 % CI: 0.90 to 0.97). When percent decline in tHcy was assessed as tertiles, a significantly lower stroke risk was found in those in tertiles 2-3 (HR 0.79; 95 % CI: 0.64 to 0.97) compared with participants in tertile 1. Similar results were observed for the composite of CV events. The beneficial effect associated with greater tHcy reduction was observed across strata for age, sex, treatment group (with versus without folic acid), MTHFR C677T genotypes, baseline tHcy and serum folate levels, and blood pressure (BP) control. The authors concluded that percent lowering in tHcy was significantly associated with a reduction in 1st stroke risk in Chinese adults with hypertension, and if further confirmed, may serve as a useful indicator for folic acid treatment efficacy on stroke prevention.

The authors stated that this study had several drawbacks. First, post-hoc analyses of randomized trials have inherent limitations, such as the possibility of residual imbalance in some unmeasured predictive factors at baseline. Second, these investigators used a fixed dose of folic acid (0.8 mg daily) alone without including other B vitamins. However, a previous study reported that vitamin B12 (median 0.4 mg/day) only produced a 7 % (95 % CI: 4 % to 9 %) further reduction in tHcy, and vitamin B6 had no significant effect. Moreover, it has been suggested that the beneficial effect of folic acid therapy could possibly be offset by the toxicity associated with a high-dose of cyanocobalamin, especially among patients with impaired renal function. Third, tHcy was assessed only at the baseline and the exit visits. More frequent measurements of tHcy would allow for a more accurate assessment of the association between the change in tHcy and stroke risk. Thus these researchers stated that confirmation of these findings in more studies is essential.

### Role of Hcy in Multiple Sclerosis

Vrethem and colleagues (2003) examined if multiple sclerosis (MS) is associated with vitamin B12 deficiency. These researchers measured serum vitamin B12, plasma folate, serum methylmalonic acid (MMA), pHcy as well as cerebrospinal fluid (CSF) MMA and Hcy in 72 patients with MS and 23 controls. The mean pHcy level was significantly increased in MS patients (11.6 micromol/L) compared with controls (7.4 micromol/L) ( $p = 0.002$ ). Seven patients showed low serum vitamin B12 levels but only 1 of them had concomitant high pHcy. None of them showed high serum MMA. Plasma or blood folate levels did not differ between MS patients and controls. These researchers found no significant differences in mean values or frequency of pathological tests of serum B12, serum MMA, mean corpuscular volume (MCV), hemoglobin concentration, CSF Hcy or CSF MMA between patients and healthy subjects. There were no correlations between CSF and serum/plasma levels of MMA or Hcy. Serum vitamin B12, serum MMA, pHcy, CSF Hcy or CSF MMA were not correlated to disability status, activity of disease, duration of disease or age. The authors concluded that the relevance of the increased mean value of pHcy thus seems uncertain and does not indicate functional vitamin B12 deficiency. However, they can not exclude the possibility of a genetically induced dysfunction of the Hcy metabolism relevant for the development of neuro-inflammation/degeneration. These findings indicated that, regardless of a significant increase in pHcy in MS patients, the disease is not generally associated with vitamin B12 deficiency since they did not find any other factors indicating vitamin B12 deficiency. Analysis of CSF MMA and CSF Hcy, which probably reflects the brain vitamin B12 status better than serum, are not warranted in MS. The authors concluded that B12 deficiency, in general, is not associated with MS.

Ramsaransing and associates (2006) stated that there is evidence that Hcy contributes to various neurodegenerative disorders, and elevated pHcy levels have been observed in patients with MS. These investigators examined if and why pHcy levels are increased in MS, and whether they play a role in the disease course. They compared pHcy in 88 patients with MS and 57 healthy controls. In the MS group, 28 had a benign course, 37 were secondary progressive, and 23 primary progressive. To explore the underlying mechanisms, these investigators measured serum levels of vitamins B6 and B12, folate, interleukin (IL)-12, tumor necrosis factor (TNF)-alpha, leukocyte nitric oxide production, and plasma diene conjugate levels (measure of oxidative stress). Mean pHcy was higher in patients (13.8 micromol/L) than in controls (10.1 micromol/L;  $p < 0.0001$ ). However, there were no significant differences in Hcy levels between the three clinical subgroups of MS. Serum concentrations of vitamin B6, vitamin B12, and folate were not different between patients with MS and controls. In the MS group, there were no correlations between pHcy and the serum levels of IL-12 or TNF-alpha, leukocyte nitric oxide production, or plasma diene conjugate levels. The authors concluded that elevated pHcy occurs in both benign and progressive disease courses of MS, and seems unrelated to immune activation, oxidative stress, or a deficiency in vitamin B6, vitamin B12, or folate.

## Role of Hcy in Polycystic Ovary Syndrome

Badawy and colleagues (2007) examined the relationship between insulin resistance and increased serum Hcy in women with polycystic ovarian syndrome (PCOS). A total of 90 PCOS women as a study group and 35 women with infertility due to other causes as a control group were enrolled in this study. Outcome measures included serum Hcy levels in the presence and absence of insulin resistance in PCOS patients. Homocysteine levels were significantly higher in PCOS patients than in the controls. Considering 11 micromol/l as the cut-off level for a normal Hcy level, 41.1 % of PCOS patients (37 out of 90) and 2.9 % of control group (1 out of 35) had high Hcy levels. With regard to insulin resistance, 23 % of PCOS patients without insulin resistance (9 out of 39) had a high Hcy level, while 47 % of PCOS patients with insulin resistance (24 out of 51) had high Hcy level, thus demonstrating the effect of insulin resistance on the Hcy level. The authors concluded that there is a strong association between serum Hcy and insulin resistance in women with PCOS that contributes to the long-term complications of PCOS.

On the other hand, Schachter et al (2007) reported that in women with insulin-resistant PCOS, pHcy were significantly reduced by both B vitamins and metformin, but to a greater degree by B vitamins, and higher pregnancy rates were associated with vitamin B treatment. Also, Carlsen et al (2007) reported that metformin treatment in women with PCOS does not increase serum Hcy levels in the non-pregnant or the pregnant state. There is currently a lack of evidence regarding the association of monitoring of Hcy levels in women with PCOS and "fertility". Furthermore, Battaglia et al (2008) noted that PCOS is a condition associated with an increased vascular risk, however, the use of Hcy testing for assessing the risk of CHD has not been established.

## Role of Hcy in Osteoporosis / Fractures

High Hcy levels in adults have been associated with osteoporotic fractures in some, but not all, studies. However, it is unclear if high levels of Hcy have a direct effect on bone or if the effect is mediated through another factor, such as poor nutrition (Rosenson and Kang, 2007).

In a double-blind, randomized controlled trial, Sato et al (2005) examined if treatment with folate and vitamin B12 would reduce the incidence of hip fractures in patients with hemiplegia following stroke. A total of 628 consecutive patients aged 65 years or older with residual hemiplegia at least 1 year following first ischemic stroke were included in this study. Patients were assigned to daily oral treatment with 5 mg of folate and 1,500 microg of vitamin B12, or double placebo; 559 completed the 2-year follow-up. Main outcome measure was incidence of hip fractures in the 2 patient groups during the 2-year follow-up. At baseline, patients in both groups had high levels

of plasma Hcy and low levels of serum cobalamin and serum folate. After 2 years, pHcy decreased by 38 % in the treatment group and increased by 31 % in the placebo group ( $p < 0.001$ ). The number of hip fractures per 1000 patient-years was 10 and 43 for the treatment and placebo groups, respectively ( $p < 0.001$ ). The adjusted relative risk, absolute risk reduction, and the number needed to treat for hip fractures in the treatment versus placebo groups were 0.20 (95 % CI: 0.08 to 0.50), 7.1 % (95 % CI: 3.6 % to 10.8 %), and 14 (95 % CI: 9 to 28), respectively. No significant adverse effects were reported. The authors concluded that in this Japanese population with a high baseline fracture risk, combined treatment with folate and vitamin B12 is safe and effective in reducing the risk of a hip fracture in elderly patients following stroke. An editorial that accompanied this article (van Meurs and Uitterlinden, 2005) noted that the final proof of causality between circulating Hcy levels and fracture risk will have to come from elucidation of the biological mechanism underlying this relationship.

Selhub (2006) noted that elevated pHcy is associated with increased total and CVD mortality, increased incidence of stroke, increased incidence of dementia and Alzheimer's disease, increased incidence of bone fracture, and higher prevalence of chronic heart failure. This multitude of relationships between elevated plasma total Hcy (tHcy) and diseases that afflict the elderly point to the existence of a common denominator that may be responsible for these diseases. The author stated that whether this denominator is Hcy itself or whether Hcy is merely a marker remains to be determined.

In a population-based prospective study, Gjesdal et al (2007) examined if plasma levels of tHcy, folate, and vitamin B12 and the MTHFR 677C-->T and 1298C-->T polymorphisms predicted hip fracture. A total of 2,639 women and 2,127 men who were 65 to 67 years of age were included in this study. Cox proportional hazard regression was used to estimate fracture risk according to levels of plasma tHcy, folate, and vitamin B12 and for different genotypes. Over a median follow-up period of 12.6 years, hip fracture was recorded in 184 (7.0 %) women and 90 (4.2 %) men. The adjusted hazard ratio (95 % CI) for fracture in subjects with high (greater than or equal to 15 micromol) compared with low levels (less than 9.0 micromol) of tHcy was 2.42 (1.43 to 4.09) among women and 1.37 (0.63 to 2.98) among men. Dose-response analyses indicated a positive association between plasma tHcy and risk of fracture in both sexes and a negative association between plasma folate and risk of fracture among women only. Plasma vitamin B12 level or MTHFR genotype was not significantly related to risk of fracture after adjustments for confounding factors. The association between tHcy and risk of hip fracture was only slightly weakened by adjustments for plasma levels of vitamin B12 and folate. The authors concluded that tHcy seems to be a predictor for hip fracture among elderly men and women. Folate was a predictor among women only, whereas vitamin B12 and MTHFR genotype did not predict hip fracture. These findings corroborated the hypothesis that Hcy may play a role in the pathogenesis of osteoporotic fractures.

## Role of Hcy in Recurrent Pregnancy Loss

Hague (2003) stated hyper-homocysteinemia has been associated with vascular disease, although whether it is cause or effect is still a matter of debate. In normal pregnancy, Hcy concentrations fall. Disturbance of maternal and fetal Hcy metabolism has been associated with fetal NTDs, 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 NTDs, no other strategies have been identified in relation to Hcy metabolism that will reliably reduce the frequency of these other common obstetric pathologies.

Krabbendam et al (2005) noted that thrombophilias are suggested to play a role in recurrent miscarriage. These researchers evaluated the literature of the past 10 years regarding the association between thrombophilias and recurrent miscarriage. They concluded that there is a large variety in applied study methodology. Thus, they defined criteria for an adequate study on the relationship of thrombophilias on recurrent pregnancy loss: (i) no exclusion criteria for patients or at least the same criteria for patients and controls; (ii) a clear definition of the gestational age at previous losses; (iii) a well-described control group; (iv) clear description of the test methods and moment of testing; and (v) a clear description of the (non) significant differences or odds ratio between cases and controls. Eleven out of 69 studies fulfilled these criteria. Their results show significant higher serum Hcy levels among women with a history of recurrent miscarriage. No relation was found between recurrent miscarriage and the MTHFR-C667T mutation. No relation was observed for the levels of antithrombin, protein C and protein S. Seven studies on the association of factor V Leiden (FVL) and/or pathologic activated protein C ratio (pAPCR) showed that FVL may play a role in second trimester losses, as do antiphospholipid antibodies. Studies on the prothrombin gene mutation yielded conflicting results. Consequently, large prospective studies according to the afore-mentioned criteria are needed to establish if there is a relationship between thrombophilias and recurrent miscarriage at all. At present, there is only justification for testing for Hcy levels, antiphospholipid antibodies and FVL in women with a history of recurrent miscarriage.

ACOG guidelines on inherited thrombophilias in pregnancy (2014) state that, because of the lack of association between heterozygosity or homozygosity for 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.

## Role of Hcy in Homocystinuria Caused by Cystathionine Beta-Synthase Deficiency

Homocystinuria is an inherited disorder in which patients are unable to properly process certain amino acids. The principal biochemical features of this condition are markedly elevated pHcy, tHcy, plasma concentrations of methionine as well as increased urinary concentration of 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 affects at least 1 in 200,000 to 335,000 people worldwide. Other forms of homocystinuria are much rarer. Moreover, the hallmarks of homocystinuria caused by CBS deficiency are developmental delay/mental retardation, ectopia lentis (dislocation of the ocular lens) and/or severe myopia, skeletal abnormalities as well as thrombo-embolism. There are two phenotypic variants of homocystinuria: (i) B6-responsive, and (ii) 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. Patients are often tall and slender with an asthenic habitus and are prone to osteoporosis. Thrombo-embolism is the major cause of early death and morbidity. Intelligence quotient (IQ) in individuals with homocystinuria usually ranges from 10 to 138; with the mean IQ of affected 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, hypo-pigmentation, pancreatitis, malar flush, and livedo reticularis (Picker and Levy, 2006).

Complications of homocystinuria should be treated appropriately (e.g., surgical intervention for ectopia lentis). Treatments should aim to correct the biochemical abnormalities, especially to control pHcy and prevent thrombosis. Individuals identified by newborn screening are treated shortly after birth to maintain pHcy below 11 micromol/L. For newborn screening, measurements of Hcy (plasma and/or urine) are performed only when hyper-methioninemia has been confirmed. Measurement of plasma concentrations of amino acids and Hcy in at-risk siblings immediately after birth ensures reduction of morbidity and mortality by early diagnosis and treatment. Prophylactic anti-coagulation during the third trimester of pregnancy and post-partum in women with homocystinuria is recommended to reduce risk of thrombo-embolism (Picker and Levy, 2006).

### Role of Hcy in In-Vitro Fertilization Planning

The role of Hcy testing in in-vitro fertilization (IVF) or intra-cytoplasmic sperm injection (ICSI) has not been established. Jerzak and colleagues (2003) determined fasting tHcy in follicular fluid or serum of women experiencing reproductive failure after spontaneous or IVF. A total of 8 non-pregnant recurrent spontaneous abortion (RSA) women, 8 normal healthy women with previous successful pregnancy outcome and 15 women undergoing IVF (6 with unexplained infertility [UI], 6 with male factor [MF], 3 with tubal obstruction [TO]) were enrolled in this study. Total fasting Hcy concentrations were established by ELISA method in serum of RSA and normal

healthy women or ovarian follicular fluid of women undergoing IVF. Mean fasting tHcy concentration in study group were as follows: RSA: 18.63  $\mu\text{mol/L}$   $\pm$  6.67, normal: 13.98  $\mu\text{mol/L}$   $\pm$  6.62, UI: 20.62  $\mu\text{mol/L}$   $\pm$  8.19, MF: 22.60  $\mu\text{mol/L}$   $\pm$  7.87, TO: 36.75  $\mu\text{mol/L}$   $\pm$  13.26. These researchers found that RSA women have had significantly higher serum Hcy concentration when compared to normal healthy women ( $p < 0.05$ ). Among women undergoing IVF, those with following IVF success had not significantly lower Hcy level when compared to those with IVF failure (22.81  $\mu\text{mol/L}$   $\pm$  11.27 versus 24.54  $\mu\text{mol/L}$   $\pm$  9.50,  $p > 0.05$ ). The authors concluded that these preliminary data suggested that high hcy level may negatively influence pregnancy outcome following natural or IVF. It can not be excluded that elevated Hcy concentrations contribute to defective chorionic villous vascularization during early stages of gestation.

Pacchiarotti and associates (2007) evaluated the effect of the hyper-homocysteinemia on pregnancy rate, implantation rate and abortion rate after IVF. Data from a total of 48 infertile couples with hyper-homocysteinemia were prospectively collected for this study. All patients underwent a standard down regulation protocol for ovarian stimulation. Oocytes recovery was performed at 36 hrs after hCG administration. Embryo transfer took place at 48 hrs after insemination. The patients were matched in 2 groups that received or did not receive therapy (group A and group B, respectively) to normalize Hcy plasma level. Pregnancy rate, implantation rate and abortion rate varied significantly ( $p < \text{or} = 0.05$ ) between the 2 groups. The number and quality of embryos transferred did not differ between the groups. The authors concluded that the results suggested that hyper-homocysteinemia could affect IVF outcome.

Boxmeer et al (2009) examined if biomarkers of the Hcy pathway are associated with IVF outcome. These researchers investigated biomarkers of the Hcy pathway for associations with embryo quality and biochemical pregnancy in women undergoing IVF or ICSI treatment ( $n = 181$ ). In the treatment cycle, blood and monofollicular fluid samples were collected for determination of folate, cobalamin and tHcy concentrations. Of all the women in the study, 67 % used folic acid supplements. In blood, a significant correlation was established between high cobalamin and better embryo quality [standardized adjusted regression coefficient: -0.17, 95 % CI: -0.30 to -0.01]. In monofollicular fluid of non-supplemented women, high cobalamin correlated with better embryo quality (estimate: -0.87; 95 % CI: -1.68 to -0.06), whereas high tHcy resulted in poor embryo quality (estimate: 1.01; 95 % CI: 0.08 to 1.95). However, in monofollicular fluid of supplemented women, high tHcy correlated with better embryo quality (estimate: -0.58; 95 % CI: -1.12 to -0.04). In the total group, a 2-fold increase of monofollicular fluid folate corresponded with a 3.3 times higher chance (95 % CI: 1.09 to 9.71) of achieving pregnancy. The authors concluded that an optimal Hcy pathway in follicular fluid is associated with a better embryo quality and chance of pregnancy.

Nafiye and colleagues (2010) examined the serum and follicular fluid concentrations of insulin resistance parameters and Hcy and their effect on IVF outcome in non-obese, non-hyperandrogenemic polycystic ovary syndrome (PCOS) patients. A total of 97 women underwent IVF; subjects were categorized according to IVF indications: group 1 with PCOS, group 2 with subfertile male partners, group 3 with UI. Serum and follicular fluid parameters from the first follicle on the day of oocyte retrieval were analyzed. Serum and follicular fluid insulin resistance parameters, Hcy, sex hormone levels, and laboratory and clinical IVF outcome were studied. Serum insulin, homeostasis model assessment estimate of insulin resistance (HOMA-IR), and Hcy levels were significantly higher in subjects having PCOS. However, these significant differences in serum insulin resistance and Hcy levels were not seen in the follicular microenvironment. There were no differences in clinical pregnancy rates between study groups. The authors concluded that despite elevated serum insulin, HOMA-IR, and Hcy levels, and their effects on oocyte numbers and maturation in PCOS patients, there were no differences in follicular parameters and clinical pregnancy rates between hyper-insulinemic and hyper-homocysteinemic PCOS patients and the other 2 groups.

#### Role of Hcy in Retinal Artery Occlusion

Weger et al (2002) stated that hyper-homocysteinemia has been established as an important risk factor for cardiovascular diseases. These researchers examined if hyper-homocysteinemia and/or homozygosity for the MTHFR C677T mutation are associated with an increased risk for retinal artery occlusion (RAO). In a retrospective case-control study, these investigators studied 105 consecutive patients with RAO and 105 age- and sex-matched control subjects. Fasting plasma Hcy levels were determined by high-performance liquid chromatography, while genotypes of the MTHFR C677T mutation were determined by polymerase chain reaction. Mean plasma Hcy levels were significantly higher in patients with RAO compared with control subjects (12.2 +/- 4.8 micromol/L versus 10.3 +/- 3.4 micromol/L;  $p = 0.003$ ). Hyper-homocysteinemia was defined by the 95th percentile of control plasma Hcy levels as 15.8 micromol/L; 20 (19.1 %) patients with RAO exceeded this level and were therefore classified as hyper-homocysteinemic compared with 5 (4.8 %) control subjects ( $p = 0.003$ ). The OR for these patients was calculated at 4.7 (95 % CI: 1.5 to 15.1). Mean plasma folate levels were significantly lower in patients than in the control group (5.6 +/- 2.3 ng/ml versus 6.3 +/- 2.5 ng/ml;  $p = 0.04$ ). The prevalence of the homozygous genotype of MTHFR C677T mutation did not significantly differ between patients and controls. The authors concluded that these findings suggested that hyper-homocysteinemia, but not homozygosity, for the MTHFR C677T mutation is associated with RAO.

Hong et al (2011) evaluated the diagnostic efficacy of plasma tHcy and C-reactive protein (CRP) levels for ocular ischemic syndrome (OIS). In all, 87 patients with retinal vein occlusion (RVO), 955 patients with a stenosis of internal carotid artery (ICA) less than 90 % and 159 patients with a stenosis of ICA greater than 90 % were included between 2003 and 2009. A total of 43 patients with a stenosis ICA greater than 90 % were diagnosed as OIS. Fasting tHcy, CRP, lipid profiles, creatinine were measured, and diagnostic values of hyper-homocysteinemia or elevated CRP for OIS were evaluated. The mean plasma levels of tHcy (18.8  $\mu\text{mol/L}$ ) and CRP (1.1 $\text{mmol/L}$ ) were the highest in patients with OIS among the groups. The prevalence of hyper-homocysteinemia (72 %) and elevated CRP (77 %) were the highest in OIS among the groups. In patients with stenosis of ICA, the diagnostic sensitivity/specificity for OIS was 70/79 % in hyper-homocysteinemia and 73/73 % in elevated CRP. The diagnostic sensitivity and specificity for OIS were 53 and 86 % in both hyper-homocysteinemia and elevated CRP. The lipid profiles and creatinine levels were similar among the groups. The authors concluded that these findings suggested that hyper-homocysteinemia and elevated CRP may be associated with the development of OIS. The measurements of tHcy and CRP in blood may help to assist the diagnosis of OIS in a stenosis of ICA.

Parchand et al (2012) reported primary branch RAO in a case with idiopathic retinal vasculitis, aneurysms, and neuro-retinitis syndrome. These researchers performed a review of medical case records, color fundus photographs, and fundus fluorescein angiography of a 23-year old man diagnosed with idiopathic retinal vasculitis, aneurysms, and neuro-retinitis. The patient presented with sudden painless decreased vision in right eye since 1 day. Ocular examination revealed a best-corrected visual acuity (BCVA) of counting fingers 1 feet in the right eye and 20/20 in the left eye, relative afferent pupillary defect in the right eye, 1+ vitreous cells in both eyes, optic disk neovascularization with massive peri-papillary and perivascular lipid exudation, and occluded smaller vessels in both eyes. In addition, there was an area of retinal opacification in the posterior pole along the infero-temporal arcade in the right eye. The patient underwent color fundus photography, fluorescein angiography, and a detailed systemic work-up. Fundus fluorescein angiographic features were suggestive of idiopathic retinal vasculitis, aneurysms, and neuro-retinitis in both eyes with branch RAO in the right eye. Detailed systemic work-up revealed raised serum Hcy levels. The patient underwent scatter retinal photocoagulation in both eyes and also was started on folic acid and pyridoxine supplementation. At 1 year of follow-up, the BCVA in the right eye improved to 20/60. Posterior segment examination showed reduced exudation, resolution of optic disk neovascularization in both eyes, and clearing of retinal opacification in the right eye. Also, the levels of serum Hcy decreased over 1 year. The authors concluded that primary branch RAO can be an atypical presentation of idiopathic retinal vasculitis, aneurysms, and neuro-retinitis syndrome. Such a case should be thoroughly investigated for underlying hyper-coagulable state. Also, a careful long-term follow-up is needed for these patients to prevent any neovascularization sequelae.

Coban-Karatas et al (2013) described the case of a child with central RAO and hyper-homocysteinemia. A 13-year old girl developed sudden vision loss and was hospitalized for diagnosis and treatment. Her physical examination was normal except for her ophthalmologic examination. Her serum Hcy level and lipoprotein(a) were elevated to 45.27  $\mu\text{mol/L}$  and 61 mg/dL, respectively. A homozygous mutation was identified for MTHFR at position C677T. The authors concluded that this report documented central RAO was associated with the risk factors of hyper-homocysteinemia caused by MTHFR C677 T mutation and high lipoprotein(a) level in a child. Retinal artery occlusion is rare in children. This case emphasized the need for a systemic evaluation for hyper-homocysteinemia and lipoprotein(a) levels in children with retinal vascular occlusion of uncertain etiology.

Furthermore, an eMedicine review on "Branch retinal artery occlusion" (Nathan, 2014) as well as an UpToDate review on "Central and branch retinal artery occlusion" (Hedges, 2015) do not mention homocysteine testing as a diagnostic tool.

### Role of Hcy in Other Conditions

There is conflicting evidence regarding whether Hcy is an independent risk factor for dementia (e.g., Alzheimer's disease, Binswanger's disease) (Rosenson and Kang, 2007). Silbert et al (2008) examined the association of plasma Hcy and C-reactive protein (CRP) with cognition in patients scheduled for coronary artery bypass graft (CABG) surgery. Cognition was assessed in 264 patients using a standard battery of neuropsychological tests. Patients were classified as having pre-existing cognitive impairment (PreCI) by reference to a healthy control group or post-operative cognitive dysfunction (POCD) by reference to baseline test scores. PreCI was present in 37.3 % of patients, and POCD was present in 18.3, 12.1 and 13.6 % of patients at 1 week, 3 months and 12 months post-operatively. On multi-variate analysis, neither Hcy nor CRP was independently associated with cognition at any testing time but both were strongly associated with age and left ventricular function. The authors concluded that PreCI and POCD are present in a substantial proportion of patients undergoing CABG surgery but there is no independent association with either baseline Hcy or CRP levels. It is possible that cognitive impairment may result from the vascular disease rather than a direct association with either Hcy or CRP.

Teper and O'Brien (2008) stated that the relationship between vascular disease and depression can not be solely explained by current established risk factors or the effects of treatment for depression. Other mechanisms must apply, and there is some evidence for common genetic factors. Promising future lines of investigation include Hcy, cytokines and endothelial dysfunction. They noted that more longitudinal studies combined with measurements of these biomarkers are needed.

Ho and colleagues (2011) stated that high Hcy has been causatively linked to Alzheimer disease (AD) and vascular dementia (VaD) in old age, but research methodologies and outcome measures are heterogeneous. It remains unclear whether the findings can be generalized across studies. In a systematic review/meta-analysis examined if high Hcy level is a risk factor for cognitive decline in elderly. Random-effects meta-analyses were conducted on studies examining the relationship between Hcy level and risk of developing dementia/cognitive decline between comparison groups. Meta-regression identified patient- and trial-related factors, which may contribute to heterogeneity. A total of 17 relevant studies (6,122 participants; 13 cross-sectional and 4 prospective studies) were included. Compared with controls, Hcy was significantly elevated in AD (pooled standardized mean difference [SMD]: 0.59; 95 % CI: 0.38 to 0.80; significant heterogeneity:  $\tau = 0.105$ ) and VaD (pooled SMD: 1.30; 95 % CI: 0.75 to 1.84; significant heterogeneity:  $\tau = 0.378$ ). Meta-regression identified mean age as significant moderator for AD versus controls and mean age and mean folate levels as significant moderators for VaD versus controls. Homocysteine was significantly higher in VaD relative to AD (pooled SMD: 0.48; 95 % CI: 0.23 to 0.73; moderately significant heterogeneity:  $\tau = 0.076$ ); proportion of men and mean folate levels were significant moderators. High-Hcy level was not associated with risk of developing dementia in prospective studies (pooled odds ratio: 1.34; 95 % CI: 0.94 to 1.91, non-significant heterogeneity:  $\tau = 0.048$ ). The authors concluded that individuals with AD and VaD have higher Hcy levels than controls; however, a causal relationship between high-Hcy level and risk of developing dementia is not supported. They stated that more prospective studies and randomized controlled trials are required to test the therapeutic benefits of lowering Hcy levels.

Almeida et al (2008) stated that the prevalence of depression in later life increases with plasma tHcy. High tHcy accounts for about 15 % of prevalent cases, but observational studies are prone to confounding and bias. Genetic association studies are not prone to the same sources of error and offer an opportunity to explore the consistency and external validity of this association. These researchers examined if tHcy is causally related to depression in later life. A total of 3,752 men aged 70 years or older (Health in Men Study) were included in this study. Main outcome measure were 15-item Geriatric Depression Scale and self-reported past or current treatment for depression. In the Health in Men Study, the OR of prevalent depression increased 4 % (OR, 1.04; 95 % CI: 1.02 to 1.05) with every unit increase of tHcy (micromoles per liter). The tHcy was 0.19 mg/L higher among participants with the MTHFR C677T TT genotype compared with the CC genotype. The meta-analysis showed that older adults with high tHcy had increased risk of depression (OR, 1.70; 95 % CI: 1.38 to 2.08) and TT carriers were 22 % more likely than CC carriers to have current depression or a history of depression (OR, 1.22; 95 % CI: 1.01 to 1.47). The authors concluded that the triangular association between the MTHFR genotype, tHcy, and depression implies that higher concentrations of tHcy increase the risk of depression and that lowering tHcy by 0.19 mg/L could reduce the odds of depression by about

20 %. They noted that confirmatory data from sufficiently powered randomized trials of Hcy-lowering therapy are now needed to test if the relationship between tHcy and depression is truly causal.

In a meta-analysis, McGimpsey and colleagues (2009) evaluated the role of plasma tHcy concentrations and homozygosity for the thermolabile variant of the MTHFR C677T gene as risk factors for retinal vein occlusion (RVO). Data sources included MEDLINE, Web of Science, and PubMed searches and searching reference lists of relevant articles and reviews. Reviewers searched the databases, selected the studies, and then extracted data. Results were pooled quantitatively using meta-analytic methods. Main outcome measures were tHcy concentrations and MTHFR genotype. There were 25 case-control studies for tHcy (1,533 cases and 1,708 controls) and 18 case-control studies for MTHFR (1,082 cases and 4,706 controls). The mean tHcy was on average 2.8 micromol/L (95 % CI: 1.8 to 3.7) greater in the RVO cases compared with controls, but there was evidence of between-study heterogeneity ( $p < 0.001$ ,  $I(2) = 93\%$ ). There was funnel plot asymmetry suggesting publication bias. There was no evidence of association between homozygosity for the MTHFR C677T genotype and RVO (odds ratio [OR] 1.20; 95 % CI: 0.84 to 1.71), but again marked heterogeneity ( $p = 0.004$ ,  $I(2) = 53\%$ ) was observed. The authors concluded that there was some evidence that elevated tHcy was associated with RVO, but not homozygosity for the MTHFR C677T genotype. Both analyses should be interpreted cautiously because of marked heterogeneity between the study estimates and possible effect of publication bias on the tHcy findings. They stated that because of the presence of heterogeneity and publication bias, no recommendation can be made with regard to routine investigation and treatment of elevated tHcy in the setting of RVO.

Oterino et al (2010) stated that it has been suggested that Hcy and the 5'-10'-MTHFR C677T variant are implicated in the pathogenesis of migraine. Homocysteine has the potential to damage endothelium and accelerate atherosclerosis. Genetic factors such as the MTHFR C677T polymorphism, and other polymorphisms in folate-related genes associated with high Hcy levels, may contribute to increasing this vascular risk. These investigators recruited 427 migraine patients (199 without aura [MO]; 228 with aura [MA]), and 310 controls in a neurologic clinic. Plasma Hcy levels and 6 polymorphisms corresponding to 6 folate-related genes, including the MTHFR C677T variant, were determined in all migraine subjects and in a subset of 155 controls. These researchers found higher sex-adjusted Hcy levels in MA (mean of 11.02 micromM) than MO patients (9.86 micromM;  $p = 0.005$  for the difference). Plasma Hcy levels higher than 12.0 micromM doubled the risk for MA (OR = 2.145; 95 % CI: 1.3 to 3.4;  $p = 0.001$ ), and those higher than 15.0 micromM incurred a 6-fold increase (OR = 5.95; 95 % CI: 2.1 to 20.0,  $p < 0.001$ ). The number of MTHFR 677T alleles was the best genetic predictor of Hcy levels ( $r(2) = 0.06$ ;  $p = 6.2e-6$ ; corrected for genetic variants analyzed) and this effect remained significant after correction for other confounding factors. Using multi-dimensionality reduction

approaches, these researchers observed significant epigenetic interaction among some of the folate-related genetic variants to predict higher Hcy levels, and also among higher Hcy levels and folate-related genetic variants to predict the end-diagnosis of MA only among migraineurs. In controls, Hcy levels and the number of MTHFR 677T alleles were found to be intermediate between those observed in MA and MO patients. The authors concluded that these findings suggest that MA patients have higher Hcy levels. They also observed complex epigenetic interaction among folate-related enzymes, sex, and Hcy levels predicting MA phenotype. Nevertheless, genetic factors explained only a minor proportion of the variance for both Hcy plasma levels and for predicting MA phenotype. Determination of MTHFR C677T polymorphisms and Hcy levels may be useful to identify patients with a high risk of suffering from MA.

Spijkerman et al (2005) explored to what extent Hcy, S-adenosylmethionine (SAM), S-adenosylhomocysteine, total folate, 5-methyltetrahydrofolate (5-MTHF), vitamin B12, and vitamin B6 are associated with endothelium-dependent, flow-mediated vasodilation (FMD), and whether these associations are stronger in individuals with diabetes or other cardiovascular risk factors. In this population-based study of 608 elderly people, FMD and endothelium-independent nitroglycerin-mediated dilation (NMD) were ultrasonically estimated from the brachial artery (absolute change in diameter [ $\mu\text{m}$ ]). High SAM and low 5-MTHF were significantly associated with high and low FMD, respectively (linear regression coefficient, 95 % CI: 48.57 microm (21.16 to 75.98) and -32.15 microm (-59.09 to -5.20), but high Hcy was not (-15.11 microm (-42.99 to 12.78)). High SAM and low 5-MTHF were also significantly associated with high and low NMD, respectively. Nitroglycerin-mediated dilation explained the association of 5-MTHF with FMD but not of SAM. No interactions were observed for diabetes or cardiovascular risk factors. The authors concluded that in this elderly population, both SAM and 5-MTHF are associated with endothelial and smooth muscle cell function. The effect of Hcy on endothelial function is relatively small compared with SAM and 5-MTHF. The relative impact of SAM, 5-MTHF, and Hcy, and the mechanisms through which these moieties may affect endothelial and smooth muscle cell function need clarification.

In a double-blind, placebo-controlled, randomized clinical trial, Thompson et al (2009) examined if exogenous SAM (AdoMet) increases the level of plasma Hcy, a potential cardiovascular risk factor, in healthy human subjects. A total of 52 healthy human volunteers were included in this study. Subjects received placebo or AdoMet (800 mg per day) for 4 weeks; Hcy levels were measured before and after administration of AdoMet or placebo. The primary outcome measure was change in Hcy level. Secondary outcome measures included an interim Hcy determination (at 2 weeks) and changes in levels of high-sensitivity CRP (hsCRP), lipids, and alanine aminotransferase. There was no statistically significant change in Hcy between groups. Similarly, no statistically significant differences in change in Hcy or hsCRP levels were observed

at 2 or 4 weeks. There was a small but statistically significant increase ( $p < 0.04$ ) in alanine aminotransferase at week 2 and a statistically significant decrease ( $p < 0.04$ ) in total cholesterol in the AdoMet group compared with the placebo group. The authors concluded that AdoMet at a daily dose of 800 mg for 4 weeks does not appear to significantly affect Hcy levels in the blood.

Hooshmand and colleagues (2010) examined the relation between serum levels of homocysteine (tHcy) and holotranscobalamin (holoTC), the active fraction of vitamin B12, and risk of incident AD in a sample of Finnish community-dwelling elderly. A dementia-free sample of 271 subjects aged 65 to 79 years derived from the Cardiovascular Risk Factors, Aging, and Dementia (CAIDE) study was followed up for 7 years to detect incident AD. The association between serum tHcy and holoTC with AD was analyzed with multiple logistic regression after adjusting for several potential confounders, including common vascular risk factors. The ORs (95 % CI) for AD were 1.16 (1.04 to 1.31) per increase of 1  $\mu\text{mol/L}$  of tHcy at baseline and 0.980 (0.965 to 0.995) for each increase of 1  $\text{pmol/L}$  baseline holoTC. Adjustment for several potential confounders including age, sex, education, APOE-4 allele, body mass index, Mini-Mental State Examination, smoking, stroke, and blood pressure did not alter the associations: ORs (95 % CI) for AD became 1.19 (1.01 to 1.39) for tHcy and 0.977 (0.958 to 0.997) for holoTC. Adjusting for holoTC attenuated the tHcy–AD link (OR changed from 1.16 to 1.10, 95 % CI: 0.96 to 1.25). The holoTC–AD relationship was less influenced by controlling for tHcy (OR changed from 0.980 to 0.984, 95 % CI: 0.968 to 1.000). Addition of folate did not change any of the results. The authors concluded that these findings suggested that both tHcy and holoTC may be involved in the development of AD. The tHcy–AD link may be partly explained by serum holoTC. The role of holoTC in AD should be further investigated. It is as yet unclear whether holoTC or Hcy is the key player in the association. Careful examination of the evidence is needed to ascertain who is the perpetrator in the complex pathology of AD and other dementias.

Veeranna et al (2011) examined if adding Hcy to a model based on traditional CVD risk factors improves risk classification. These researchers performed a post-hoc analysis of the MESA (Multi-Ethnic Study of Atherosclerosis) and NHANES III (National Health and Nutrition Examination Survey III) datasets. Homocysteine was used to predict composite CVD and hard CHD events in the MESA study and CVD and CHD mortality in the NHANES III survey using adjusted Cox-proportional hazard analysis. Re-classification of CHD events was performed using a net re-classification improvement (NRI) index with a Framingham risk score (FRS) model with and without Hcy. Homocysteine level (greater than 15  $\mu\text{mol/l}$ ) significantly predicted CVD (adjusted hazard ratio [aHR]: 1.79, 95 % CI: 1.19 to 1.95;  $p = 0.006$ ) and CHD events (aHR: 2.22, 95 % CI: 1.20 to 4.09;  $p = 0.01$ ) in the MESA trial and CVD (aHR: 2.72, 95 % CI: 2.01 to 3.68 ;  $p < 0.001$ ) and CHD mortality (aHR: 2.61, 95 % CI: 1.83 to 3.73;  $p < 0.001$ ) in the NHANES III, after adjustments for traditional risk factors and C-reactive protein. The level of Hcy, when added to FRS, significantly re-classified 12.9 % and 18.3 % of the overall and 21.2 % and 19.2

% of the intermediate-risk population from the MESA and NHANES cohorts, respectively. The categoryless NRI also showed significant reclassification in both MESA (NRI: 0.35, 95 % CI: 0.17 to 0.53;  $p < 0.001$ ) and NHANES III (NRI: 0.57, 95 % CI: 0.43 to 0.71;  $p < 0.001$ ) datasets. The authors concluded that from these 2 disparate population cohorts, they found that addition of Hcy level to FRS significantly improved risk prediction, especially in individuals at intermediate risk for CHD events. Moreover, the authors noted that there were several drawbacks with this study: (i) a single sample of Hcy was measured at baseline in both the MESA and NHANES III cohorts. Homocysteine levels are subject to variation based on food intake, diurnal changes, and position during blood draw; these variations might have led to non-differential misclassification and attenuation in effect sizes, (ii) low cobalamin or folate levels, which were not accounted for, could result in elevated Hcy, and (iii) the possibility of unmeasured confounders and residual confounding affecting study results can not be ruled out -- such issues are inherent limitations of observational cohort studies.

In an editorial that accompanied the afore-mentioned study, Mangoni and Woodman (2011) stated that "[a]lthough informative, the data from Veeranna et al need to be interpreted with caution for a number of reasons ... Further studies are required to ascertain the role of Hcy concentration in risk reclassification in cerebrovascular disease, peripheral arterial disease, and heart failure ..... If Hcy is to be used as a screening tool in primary prevention, it is imperative that further trials are conducted in low- and intermediate-risk patients without previous CVD. Only then can the real value of measuring Hcy as a nontraditional risk factor or risk marker be quantified".

In a prospective controlled study, Gulhan and associates (2011) investigated serum Hcy and asymmetric dimethyl-arginine (ADMA) levels in patients with premature ovarian failure (POF). A total of 69 women (32 with POF and 37 apparently healthy women) were included in the study. Fasting blood samples were drawn to measure serum Hcy and ADMA levels using ELISA method. The study and control group had a mean age of 37.3 +/- 2.6, 37.5 +/- 2.5 years; a mean Hcy level of 13.54 +/- 5.19, 12.71 +/- 3.99 mmol/L and a mean ADMA level of 1.32 +/- 0.27, 1.26 +/- 0.36 mmol/L, respectively. There were no statistically significant differences between the 2 groups in terms of Hcy and ADMA levels ( $p$  values of 0.465 and 0.423, respectively). A negative significant correlation was found between estradiol and ADMA ( $p < 0.05$ ). The authors concluded that Hcy and ADMA levels did not change in comparison with the control group, which suggested that estrogen deficiency in patients with POF does not have any effect on Hcy and ADMA levels.

Pinna et al (2012) determined the plasma levels of the sulfur-containing amino acids Hcy, cysteine, cysteinylglycine, glutamylcysteine, glutathione and taurine in patients with BRVO and in healthy subjects and examined if there are statistically significant differences between patients and controls. Homocysteine, cysteine, cysteinylglycine, glutamylcysteine, glutathione and taurine plasma levels were measured in 40 patients with BRVO and 80 age- and gender-matched control subjects by using laser-induced fluorescence capillary electrophoresis methods. Wilcoxon's or Student's t test was used, when appropriate, to determine differences between the groups. Conditional logistic regression analysis was performed to determine the risk factors for BRVO. Branch retinal vein occlusion patients showed significantly lower plasma concentrations of cysteinylglycine ( $p = 0.02$ ) and taurine ( $p < 0.0001$ ) than controls. Conversely, there were no significant differences in plasma Hcy, cysteine, glutamylcysteine and glutathione between patients with BRVO and controls. Conditional logistic regression analysis revealed an odds ratio of 0.95 (95 % CI: 0.92 to 0.98,  $p = 0.001$ ) for taurine and 0.86 (95 % CI: 0.78 to 0.96,  $p = 0.006$ ) for cysteinylglycine. The authors concluded that the findings of this study failed to demonstrate an association between BRVO and the plasma levels of Hcy, cysteine, glutamylcysteine and glutathione. Cysteinylglycine and taurine were significantly lower in BRVO patients, thus suggesting that reduced plasma levels of these sulfur-containing amino acids may contribute to the pathogenesis of BRVO.

Furthermore, there is insufficient evidence on the role of Hcy in any of the following conditions (not an all-inclusive list):

- Acquired thrombophilia
- Autism
- Down's syndrome
- Gaucher's disease
- HELLP syndrome
- Meniere's disease
- Methotrexate therapy
- Monitoring response to vitamin B-12 therapy
- Movement disorders (e.g., Huntington's disease, Parkinson's disease, and primary dystonia)
- Primary carnitine deficiency
- Pulmonary hypertension

#### Role of Hcy in the Management of Celiac Disease/Inflammatory Bowel Disease

Ruisi and colleagues (2015) noted that Crohn's disease and ulcerative colitis are both systemic chronic diseases that alter bowel physiology. The central process in inflammatory bowel disease (IBD) and the associated manifestations are the result of B-cell production of IgG autoantibodies directed against self-antigens in various organ systems including coronary endothelium.

Previous studies have demonstrated significant micro-vascular endothelial dysfunction in patients with IBD compared to patients not affected by the disease. These investigators analyzed the relation, if any, between IBD and the development of premature coronary artery disease (CAD). They queried their hospital database to find IBD patients admitted to the hospital from January 1, 2007 to December 31, 2008. Patients with traditional cardio-vascular (CV) disease risk factors including hypertension, congestive heart failure (CHF), diabetes, aged greater than or equal to 65 years, hyperlipidemia, family history, end-stage renal disease (ESRD), and greater than 5 pack-year smoking history were excluded from the study cohort. The charts of the remaining 300 patients with diagnosed IBD were then analyzed for the incidence of CV disease events including acute myocardial infarction (MI), unstable angina, positive stress testing, and any cardiac intervention including coronary angioplasty and/or intra-coronary stent implantation. Of the 300 patients included, only 1 patient had a CV disease event. This patient had a positive exercise stress thallium test. Otherwise, the remaining 299 patients (99.7 %) did not have any reported CV disease events over the 2-year follow-up period. The authors concluded that most of the clinical sequelae of CV disease events are the result of inflammatory changes at the vascular level. While IBD is associated with a chronic inflammatory state as reflected by high sedimentation rates, CRP, Hcy levels, etc., the data appeared to indicate that chronic inflammation in the absence of traditional risk factors is not associated with an increased risk of premature CV disease events. They stated that more wide-scale prospective studies should be performed to elucidate the relationship, if any, between chronic inflammation and CV disease risk.

Peterson and Grossman (2016) stated that although many people have symptoms of celiac disease (CD), it can take a while to diagnose. Villous atrophy may be present long before any gastro-intestinal (GI) symptoms. An important point to acknowledge is that CD could be identified earlier in some women with a positive family history; CD also could be the cause of some women's reproductive problems. Primary care providers, using comprehensive history taking, are in the unique position to identify individuals who may have CD, assist women in gaining knowledge about a gluten-free diet, order diagnostic testing, and refer to a gastroenterologist. The positive change in fertility with a simultaneous improvement of nutrient deficiencies shortly after adopting a gluten-free diet indicates a possible link between such nutrients and sex hormone function. High levels of Hcy, which can negatively impact fertility, have also been linked to individuals with problems, such as CD, that decrease vitamin B12 absorption.

Furthermore, UpToDate reviews on “Management of celiac disease in adults” (Ciclitira, 2016), “Overview of the medical management of mild to moderate Crohn disease in adults” (Farrell and Peppercorn, 2016 ), and “Management of mild to moderate ulcerative colitis in adults” (MacDermott, 2016) do not mention homocysteine testing as a management tool.

### Role of Hcy in Age-Related Macular Degeneration

Pinna and colleagues (2018) noted that there is still no agreement on tHcy role in age-related macular degeneration (ARMD). These researchers performed a systematic review and meta-analysis of the published data on the correlation between tHcy and ARMD. Medline/PubMed and ISI Web of Sciences searches were performed according to MOOSE guidelines. Case-control studies were eligible for inclusion. Participants and controls were ARMD patients and subjects without ARMD. The main outcome measure was wet ARMD; Hcy level was the main exposure variable. Data were pooled using a random-effects model. A total of 12 case-control studies were identified: 10 assessed wet ARMD, 4 dry ARMD, 1 early ARMD, 1 late ARMD, and 1 any ARMD. As for wet AMD, there was a total of 453 cases and 514 controls. Mean tHcy was on average 1.1  $\mu\text{mol/L}$  (95 % CI: 0.96 to 1.25) greater in wet ARMD cases, but there was evidence of extreme between-study heterogeneity ( $p < 0.001$ ,  $I^2 = 91.8\%$ ). In a model homogenous for age, including 6 wet ARMD studies (214 cases, 274 controls), mean tHcy was on average 0.58  $\mu\text{mol/L}$  (95 % CI: 0.35 to 0.73) greater in the case group, a not statistically significant result ( $p = 0.144$ ) associated with moderate heterogeneity ( $I^2 = 39.2\%$ ). The authors concluded that the findings of this meta-analysis indicated that there was some weak evidence that increased tHcy might be associated with wet ARMD; however, this result should be interpreted cautiously, because of a marked between-study heterogeneity and the possible effect of publication bias. They stated that future studies, preferably of cohort design, are needed before any firm conclusions on the putative role of increased tHcy on ARMD can be drawn.

### Role of Hcy in Alzheimer's Disease

Janel and colleagues (2017) stated that early identification of Alzheimer's disease (AD) risk factors would aid development of interventions to delay the onset of dementia, but current biomarkers are invasive and/or costly to assess. Validated plasma biomarkers would circumvent these challenges. These researchers previously identified the kinase DYRK1A in plasma. To validate DYRK1A as a biomarker for AD diagnosis, these investigators measured the levels of DYRK1A and the related markers brain-derived neurotrophic factor (BDNF) and Hcy in 2 unrelated AD patient cohorts with age-matched controls. Receiver-operating characteristic curves and logistic regression analyses showed that combined assessment of DYRK1A, BDNF and Hcy had a sensitivity of 0.952, a specificity of 0.889 and an accuracy of 0.933 in testing for AD. The blood levels of these markers provided a diagnosis assessment profile. Combined

assessment of these 3 markers out-performed most of the previous markers and could become a useful substitute to the current panel of AD biomarkers. The authors concluded that these results associated a decreased level of DYRK1A with AD and challenged the use of DYRK1A inhibitors in peripheral tissues as treatment. The role of Hcy as a diagnostic marker for AD needs to be further investigated.

### Role of Hcy for Assessment of Lung Transplant Candidates

UpToDate reviews on “Lung transplantation: An overview” (Hachem, 2018a) and “Lung transplantation: General guidelines for recipient selection” (Hachem, 2018b) do not mention measurement of homocysteine as an approach for management of lung transplant candidates.

### Role of Hcy as a Biomarker for the Development and/or Progression of Erectile Dysfunction

Sansone and colleagues (2018) noted that elevated levels of serum homocysteine (Hcy) have been associated with cardiovascular diseases and endothelial dysfunction, conditions closely associated with ED. In a meta-analysis, these investigators examined serum Hcy levels in subjects with ED compared to controls in order to clarify the role of Hcy in the pathogenesis of ED. Medline, Embase, and the Cochrane Library were searched for publications investigating the possible association between ED and Hcy. Results were restricted by language, but no time restriction was applied. Standardized mean difference (SMD) was obtained by random effect models. A total of 9 studies were included in the analysis with a total of 1,320 subjects (489 subjects with ED; 831 subjects without ED). Pooled estimate was in favor of increased Hcy in subjects with ED with a SMD of 1.00, 95 % CI: 0.65 to 1.35,  $p < 0.0001$ . Subgroup analysis based on prevalence of diabetes showed significantly higher SMD in subjects without diabetes (1.34 (95 % CI: 1.08 to 1.60)) compared to subjects with diabetes (0.68 (95 % CI: 0.39 to 0.97),  $p < 0.0025$  versus subgroup without diabetes). The authors concluded that findings from this meta-analysis suggested that increased levels of serum Hcy were more often observed in subjects with ED. They stated that based on existing literature on this topic, a causative role for hyperhomocysteinemia as an independent risk factor for ED could be postulated, although confirmation would require interventional studies aimed to decrease serum Hcy levels considering erectile function as primary outcome. These researchers stated that actually, only in rat model of hyperhomocysteinemia has been observed an improvement in erectile function after being treated with a demethylation agent. These investigators also reported significantly higher levels of Hcy in subjects without diabetes, compared to diabetic men. They noted that while one could assume that this is further proof of a multi-factorial pathogenesis for ED, it is also a clear

indication that future research in this field should examine the possible association with other known risk factors such as smoking habit and obesity in order to adequately address the possible effects of different variates.

The authors stated that this study has several drawbacks, most notably the small number of studies (n = 9) involved and the lack of a clear definition of ED. A single study assessed presence of ED by means of a single question (“How would you describe your ability to get and keep an erection that is adequate for satisfactory intercourse?”). The remaining studies used validated questionnaires: in detail, 4 studies used the IIEF and 4 studies used the IIEF-5. However, most studies did not report separate measurements of serum Hcy based on the degree of severity of ED.

CPT Codes / HCPCS Codes / ICD-10 Codes

*Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":*

Code	Code Description
CPT codes covered if selection criteria are met:	
83090	Homocysteine
ICD-10 codes covered if selection criteria are met [for medically necessary tests]:	
D51.0 - D51.9	Vitamin B12 deficiency anemia
D81.818	Other biotin-dependent carboxylase deficiency
D81.819	Biotin-dependent carboxylase deficiency, unspecified
E53.8	Deficiency of other specified B group vitamins
E72.10 - E72.11 E72.19	Disturbances of sulphur-bearing amino-acid metabolism [not covered for management of 5,10-methylenetetrahydrofolate reductase (MTHFR) abnormalities]
I26.01 - I26.99	Pulmonary embolism
I81	Portal vein thrombosis
I82.0 - I82.91	Other venous embolism and thrombosis
ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):	
D68.51 - D68.69	Primary or other thrombophilia
E10.10 - E13.9	Diabetes mellitus
E28.2	Polycystic ovarian syndrome

<b>Code</b>	<b>Code Description</b>
E28.310 - E28.319	Primary ovarian failure
E71.41	Primary carnitine deficiency
E75.00 - E75.19	GM2 gangliosidosis, other and unspecified gangliosidosis
E75.22	Gaucher disease
E75.23	Krabbe disease
E75.25	Metachromatic leukodystrophy
E75.29	Other sphingolipidosis
E75.4	Neuronal ceroid lipofuscinosis
E75.6	Lipid storage disorder, unspecified
E78.00 - E78.01	Hypercholesterolemia
E78.6	Lipoprotein deficiency
F01.50 - F99	Mental disorders
G10	Huntington's disease
G11.0 - G11.9	Hereditary ataxia
G12.0 - G12.9	Spinal muscular atrophy and related syndromes
G13.2 - G13.8	Systemic atrophy primarily affecting the central nervous system in myxedema and other diseases classified elsewhere
G20 - G21.9	Parkinson's disease and secondary parkinsonism
G23.0 - G23.9	Other degenerative diseases of basal ganglia
G24.01 - G24.9	Dystonia
G25.0 - G26	Other extrapyramidal and movement disorders
G30.0 - G30.9	Alzheimer's disease
G31.01 - G31.09	Frontotemporal dementia
G31.1	Senile degeneration of brain, not elsewhere classified
G31.2	Degeneration of nervous system due to alcohol
G31.81 - G31.9	Other specified degenerative diseases of nervous system
G32.0	Subacute combined degeneration of spinal cord in diseases classified elsewhere
G32.81	Cerebellar ataxia in diseases classified elsewhere
G35	Multiple sclerosis
G43.001 - G43.919	Migraine

<b>Code</b>	<b>Code Description</b>
G80.3 - G80.9	Cerebral palsy
G89.0 - G89.4	Pain, not elsewhere classified
G90.01 - G90.09	Idiopathic peripheral autonomic neuropathy
G90.2	Horner's syndrome
G90.3	Multi-system degeneration of the autonomic nervous system
G90.4	Autonomic dysreflexia
G90.50 - G90.59	Complex regional pain syndrome I (CRPS I)
G90.8 - G90.9	Other and unspecified disorders of the autonomic nervous system
G91.0 - G91.9	Hydrocephalus
G93.7	Reye's syndrome
G93.89 - G93.9	Other and unspecified disorders of the brain
G94	Other disorders of brain in diseases classified elsewhere
G95.0 - G95.9	Other and unspecified diseases of spinal cord
G99.0 - G99.2	Autonomic neuropathy and myelopathy in diseases classified elsewhere
H34.00 - H34.9	Retinal vascular occlusions
H35.30 - H35.3293	Degeneration of macula
H81.01 - H81.09	Meniere's disease
I10 - I16.2	Hypertensive diseases
I20.0 - I22.9, I24.0 - I25.9	Ischemic heart diseases
I25.10	Atherosclerotic heart disease of native coronary artery without angina pectoris
I27.0, I27.20 - I27.29	Pulmonary hypertension
I50.1 - I50.9	Heart failure
K50.00 - K50.919	Crohn's disease
K51.90 - K51.919	Ulcerative colitis
K52.0 - K52.9	Other and unspecified noninfective gastroenteritis and colitis
K90.0	Celiac disease
N46.01 - N46.9	Male infertility [in-vitro fertilization planning(assessment and treatment of implantation failure)]

Code	Code Description
N52.01 - N52.9	Male erectile dysfunction
N96	Habitual aborter
N97.0 - N97.9	Female infertility [in-vitro fertilization planning(assessment and treatment of implantation failure)]
O03.0 - O03.9	Spontaneous abortion [recurrent pregnancy loss]
O09.291 - O09.299	Supervision of pregnancy with other poor reproductive or obstetric history
O14.20 - O14.25	HELLP syndrome
O26.20 - O26.23	Pregnancy care of habitual aborter
Q90.0 - Q90.9	Down syndrome
R52	Pain, unspecified
Z13.6	Encounter for screening for cardiovascular disorders [CVD or stroke risk]
Z31.441	Encounter for testing of male partner of patient with recurrent pregnancy loss
Z51.81	Encounter for therapeutic drug level monitoring [methotrexate, vitamin B-12, s-adenosylmethionine therapy]
Z76.82	Awaiting organ transplant status [assessment of lung transplant candidates]
Z79.899	Other long term (current) drug therapy [methotrexate, vitamin B-12, s-adenosylmethionine]
Z82.49	Family history of ischemic heart disease and other diseases of the circulatory system

The above policy is based on the following references:

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**Amendment to  
Aetna Clinical Policy Bulletin Number: 0763  
Homocysteine Testing**

There are no amendments for Medicaid.