Homocysteine enzymatic assay

A strong, independent risk factor for cardiovascular disease

References

Flexible configurations for tailor made solutions

With the cobas modular platform, the cobas 4000, 6000 analyzer series and cobas 8000 modular analyzer series, Roche has developed a platform concept based on a common architecture that delivers tailor-made solutions for diverse workload and testing requirements. The cobas modular platform is designed to reduce the complexity of laboratory operation and provide efficient and compatible solutions for network cooperation.

Flexible and intelligent solutions

• Multiple configurations with tailor-made solutions for higher efficiency and productivity
• Consolidation of clinical chemistry and immunochemistry with more than 200 parameters for cost and workflow improvements
• Future sustainability through easy adaptation to changing throughput and parameter needs

• Consistency of interaction with hardware, software and reagents for less training and more staff flexibility
• Consistency of patient results due to a universal reagent concept

Cardiovascular disease (CVD) is a major health concern that continues to grow. CVD is already responsible for more deaths globally than any other disease and the huge burden it places upon healthcare systems and society is predicted to become even greater:

- CVD was estimated to be responsible for 173 million deaths in 2008, which represents 30% of the global total. Of these deaths, an estimated 72 million were due to ischaemic heart disease (IHD) and 5.7 million were due to cerebrovascular disease (stroke).5
  - More than 80% of CVD deaths occur in low- and middle-income countries, with men and women affected almost equally.
  - Annual deaths from CVD are predicted to reach almost 25 million by 2030, with heart disease and stroke remaining the leading causes.1
  - The projected economic cost to the USA in 2010 was $444.2 billion, which takes into account the cost of health services, medication, and lost productivity.

Mitigating the impact of increasing CVD can be achieved by combining the early detection of at-risk individuals with the adoption of risk-lowering behaviors. The importance of reliable diagnostic markers for identifying at-risk individuals is highlighted by the fact that the first sign of heart disease in 25% of adults with CVD is fatal heart attack.1 Furthermore, conventional risk factors, such as high serum cholesterol levels and high blood pressure, fail to account for all cases of CVD. For example, more than 75% of heart attacks occur in patients with normal serum cholesterol.1 Therefore, there is a clinical need to expand the number of diagnostic tools available for evaluating an individual’s risk of CVD. Numerous extensive studies have demonstrated that the concentration of blood homocysteine, a thiol-containing amino acid, can serve as an excellent ‘new’, clinically useful risk factor for CVD.9–10

Homocysteine as a causal factor in CVD

An association between elevated blood homocysteine (hyperhomocysteinemia) and atherothrombotic disease was first proposed in the late 1960s following observations in children with homocystinuria (a rare autosomal recessive disorder caused by enzyme deficiencies in homocysteine metabolism) who displayed extensive atherosclerotic plaques similar to those observed in adults with CVD.11 Subsequent observations from approximately 80 clinical and epidemiologic studies have demonstrated that hyperhomocysteinemia is an independent, dose-dependent risk factor for atherosclerotic vascular disease and for arterial and venous thromboembolism.6 For example, moderate-to-intermediate hyperhomocysteinemia is present in 12–47% of patients with coronary, cerebral, or peripheral arterial occlusive diseases.12

Homocysteine is highly cytotoxic and elevated levels within the bloodstream are believed to damage the endothelial lining of arterial vessels, which subsequently leads to inflammation and the formation of atherosclerotic plaques that eventually restrict the flow of blood to the heart and other organs (Figure 1). Several other, potentially synergistic, mechanisms have been proposed to explain how excess homocysteine promotes atherosclerosis:

- Alteration of endothelial phenotype and reduced production of the endogenous vasodilator nitric oxide13–19
- Deposition of cholesterol and other fats following degradation of dense aggregates formed from homocysteine thiolactone and low-density lipoprotein20
- Connective tissue changes induced by exposure and proliferation of the underlying smooth muscle and extracellular matrix20

Figure 1: Excess circulating homocysteine increases the risk of cardiovascular disease

“Numerous clinical and epidemiologic studies have established elevated blood homocysteine as a potent independent risk factor for vascular disease in the general population.”10
Measurement of homocysteine

Homocysteine is produced within cells by the metabolism of methionine from dietary protein. Intracellular concentrations are kept low by export into the plasma, where it becomes oxidized rapidly and circulates as one of three forms (Figure 2). The parameter measured most frequently in clinical laboratories is the combined sum of all three forms, which is referred to as “total homocysteine”.

Table 1: Upper reference limits for blood total homocysteine

<table>
<thead>
<tr>
<th>Demographic group</th>
<th>Upper reference limit for total homocysteine (μmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant women</td>
<td>Folate supplemented 6 10</td>
</tr>
<tr>
<td>Children (&lt;15 years)</td>
<td>8 10</td>
</tr>
<tr>
<td>Adults (15–65 years)</td>
<td>12 15</td>
</tr>
<tr>
<td>Elderly (&gt;65 years)</td>
<td>18 20</td>
</tr>
<tr>
<td>Post-methionine load (4–6 hours)*</td>
<td>5-fold fasting level, or 40 μmol/L increase</td>
</tr>
</tbody>
</table>

* Results from a European population (n = 800) not supplemented with folate.

Total homocysteine 2 hours after methionine load is approximately 75% of the value measured after 4 hours.

Although homocysteine screening of the general population is currently not recommended, recommendations for screening regimens in the three clinical settings described above have been published (Table 3).

Hyperhomocysteinemia detected through testing can be classified as either moderate, intermediate or severe (Table 2). 4

Table 2: Classification of hyperhomocysteinemia

<table>
<thead>
<tr>
<th>Category</th>
<th>Homocysteine level</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>15–30 μmol/L</td>
<td>within the general population: &lt;10%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>30–100 μmol/L</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Severe</td>
<td>&gt;100 μmol/L</td>
<td>&lt;0.02%</td>
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</tbody>
</table>

Homocysteine in risk assessment and diagnosis

The American Association for Clinical Chemistry recommends measurement of blood total homocysteine in three clinical settings: 9

- Assessment as a risk factor for CVD
- Diagnosis of homocystinuria
- Identification of individuals with (or at risk of developing) folate (vitamin B9) or cobalamin (vitamin B12) deficiency

Although homocysteine screening of the general population is currently not recommended, recommendations for screening regimens in the three clinical settings described above have been published (Table 3).

Target group

CVD patients or patients at high risk of CVD
Patients with symptoms of homocystinuria or a sibling with homocystinuria
Patients with folate or cobalamin deficiency
Patients treated for folate or cobalamin deficiency

Rationale for testing

Exclude homocystinuria and identify patients at high risk of CVD events and mortality
Monitor treatment response and compliance
Exclude or confirm homocystinuria
Monitor treatment response or detect relapse

Frequency of testing

At entry into medical system, possibly every 3–5 years thereafter
Every 2–4 weeks until values are stable, then annually or following change in treatment regimen
At entry into medical system; every 3–5 years in high-risk groups
2–4 weeks after initiation of therapy, then annually or when symptoms arise

Terminology

Protein-bound Non-protein-bound (free)

Table 3: American Association of Clinical Chemistry recommendations for homocysteine testing

Abbreviations: CVD, cardiovascular disease; CVD patients or patients at high risk of CVD.

Hyperthyroidism

Hypothyroidism

Renal failure

C677T MTHFR

CBS-deficiency

MTHFR-deficiency

Figure 3: Range of values for blood total homocysteine observed in individuals affected by different physiologic and pathologic factors

* Combined with folate deficiency

** Effect of alcohol depends on whether consumption is high and chronic (increased total homocysteine) or moderate (decreased total homocysteine)

Abbreviations: CBS, cystathionine-β-synthase; MTHFR, N5,N10-methylenetetrahydrofolate reductase.
Further evidence for the effect of homocysteine reduction on CVD risk comes from a large epidemiologic study of the impact of the folate fortification program in the USA and Canada. The fortification program began in 1996 as an attempt to prevent birth defects, but the study found the program also reduced the mortality rate from stroke and heart attacks. For example, stroke mortality declined almost 5% per year following fortification compared with a decline of only 1% prior to 1997. Overall, the researchers estimate the folate fortification program prevented 31,000 deaths from stroke and 17,000 deaths from heart disease every year from 1998 to 2001.

Clinical approach to lowering homocysteine

Patients with manifest CVD or at high risk of developing CVD should have their total homocysteine measured and be encouraged to adhere to their physician’s advice for treatment if the level is >15 μmol/L. Total homocysteine levels can be lowered by various homocysteine-lowering agents, such as vitamin supplements, betaine, and N-acetylcysteine. Lifestyle changes can also help reduce levels and the adoption of healthy behaviors, such as a balanced diet, cessation of smoking, regular exercise, and consumption of only moderate amounts of caffeine and alcohol, all have considerable positive health benefits beyond the prevention of CVD (Figure 5).

Meta-analysis of 72 studies has demonstrated significant associations between blood total homocysteine and the risk of ischemic heart disease, deep vein thrombosis & pulmonary embolism, and stroke. According to the authors, the results of the meta-analysis provide further strong evidence for a causal relationship between elevated blood homocysteine and CVD. The authors estimate that lowering blood total homocysteine by 3 μmol/L would reduce an individual’s risk of ischemic heart disease by 16%, deep vein thrombosis by 25%, and stroke by 24% (Figure 4).

Homocysteine in CVD risk reduction

Table 4: Patient factors influencing the level of blood total homocysteine

<table>
<thead>
<tr>
<th>Patient factors</th>
<th>Effect upon blood total homocysteine levels</th>
<th>Decrease within reference range</th>
<th>Moderate hyperhomocysteinemia</th>
<th>Intermediate hyperhomocysteinemia</th>
<th>Severe hyperhomocysteinemia</th>
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<tbody>
<tr>
<td>Genetic</td>
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<tr>
<td>CBS defects – homozygous</td>
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<td>CBS defects – heterozygous</td>
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<td>MTHFR defects – homozygous</td>
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<td>MTHFR defects – heterozygous</td>
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<td>MTHFR – thermolabile mutation</td>
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<td>Cobalamin mutations</td>
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<td>Down syndrome</td>
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<td>Physiologic</td>
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<td>Increasing age</td>
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<td>Male sex</td>
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<td>Impaired renal function</td>
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<td>Increasing muscle mass</td>
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<td>Pregnancy</td>
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<td>Lifestyle</td>
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<td>Deficient vitamin intake</td>
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<td>Smoking</td>
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<td>High caffeine consumption</td>
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<td>Alcohol consumption**</td>
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<td>Physical exercise</td>
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<td>Clinical</td>
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<td>Vitamin B6 deficiency*</td>
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<td>Vitamin B6 deficiency</td>
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<td>Vitamin B9 deficiency</td>
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<td>Renal failure</td>
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<td>Hepatocellular disorders</td>
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<td>Hyperthyroidism</td>
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<td>Hypothyroidism</td>
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<td>Early diabetes</td>
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<td>Drugs</td>
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<td>Folate antagonists (methotrexate)</td>
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<td>Vitamin B9 antagonists*</td>
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<td>Vitamin B6 antagonists</td>
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<td>Adenosinephosphate hydrolase inhibitors</td>
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<td>Antiepileptics (phenytoin)</td>
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<td>Thiamine, vitamin therapy</td>
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<td>Antioxidants</td>
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<td>Others (L-dopa, cholestyramine, niacin)</td>
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</table>

| Moderate, intermediate, and severe hyperhomocysteinemia defined by the ranges 15 – 30 μmol/L, 30 – 100 μmol/L, and >100 μmol/L, respectively. |
| * Individuals heterozygous for CBS defects or with vitamin B6 deficiencies usually display normal fasting total homocysteine levels, but display an increased level following methionine load test. |
| ** Effect of alcohol depends on whether consumption is high and chronic (increased total homocysteine) or moderate (decreased total homocysteine). |

Abbreviations: CBS, cystathionine-β-synthase; MTHFR, N5,N10-methylenetetrahydrofolate reductase.

“Modest reduction of homocysteine is predicted to reduce the risk up to 25% for cardiovascular disease.”

Clinical approach to lowering homocysteine

Patients with manifest CVD or at high risk of developing CVD should have their total homocysteine measured and be encouraged to adhere to their physician’s advice for treatment if the level is >15 μmol/L. Total homocysteine levels can be lowered by various homocysteine-lowering agents, such as vitamin supplements, betaine, and N-acetylcysteine. Lifestyle changes can also help reduce levels and the adoption of healthy behaviors, such as a balanced diet, cessation of smoking, regular exercise, and consumption of only moderate amounts of caffeine and alcohol, all have considerable positive health benefits beyond the prevention of CVD (Figure 5).

Figure 4: Predicted decrease in CVD risk following reduction in blood total homocysteine concentration.

Whiskers represent the upper and lower 95% confidence intervals for the calculated decrease in risk.

Figure 5: Lowering blood total homocysteine requires concerted efforts between clinicians and patients.
Homocysteine in non-CVD settings

Diagnostic testing of blood total homocysteine can be useful in many non-CVD clinical settings:

Homocystinuria

Rare genetic deficiencies in the enzymes responsible for homocysteine metabolism lead to severe hyperhomocysteinemia (usually >100 μmol/L) and urinary excretion of large amounts of homocysteine. Independent of the specific enzyme defect, these patients have a high risk of premature, and frequently fatal, thromboembolic events. Children and young adults should be tested if they exhibit symptoms of thromboembolism, lens dislocation, progressive myopia, osteoporosis, Marfan-like appearance, unexplained mental retardation, psychiatric disorders, and megaloblastic anemia. Siblings or children of patients with homocystinuria should also be tested.

Folate and cobalamin deficiencies

Folate deficiency occurs in individuals of all ages and usually results from poor diet, malabsorption, alcoholism, or the use of certain drugs; it is also common during pregnancy. The prevalence of folate deficiency has decreased significantly in regions where a food fortification program has been introduced. For example, the prevalence in adults in the USA is currently <2%, whereas it was approximately 20% before fortification.

Cobalamin deficiency is most often observed in the elderly (prevalence: 10 - 15%), where it is nearly always attributable to malabsorption caused by gastric atrophy, ileal disease, or lack of intrinsic factor (pernicious anemia). Newborns also frequently exhibit low cobalamin. Age-independent causes of cobalamin deficiency include inadequate intake (e.g. vegetarians) or the use of certain drugs.

Renal failure

There is an inverse relationship between renal function and blood total homocysteine: most dialysis patients (>85%) display hyperhomocysteinemia. Elevated blood total homocysteine is associated with an increased risk of hemodialysis access thrombosis, which is a common complication in dialysis patients.

Psychiatric disorders

Elevated blood total homocysteine is associated with depression, especially in the elderly, as well as with schizophrenia. There is an inverse relationship in the elderly between cognitive scores and blood total homocysteine concentrations, as well as a dose-dependent association with Alzheimer’s disease. Patients with vascular dementia or white matter disease also frequently exhibit high total homocysteine concentrations.

Pregnancy complications and birth defects

Pregnant women have lower blood total homocysteine than women who are not pregnant, with concentrations >10 μmol/L rarely observed. Elevated blood total homocysteine during pregnancy is associated with an increased risk of placental vasculopathy, which can lead to preeclampsia, recurrent early pregnancy loss, premature delivery, low birth weight, and placental abruption or infarction. Women who have experienced previous pregnancy complications or had a child with a birth defect should be tested, as should those with (or at risk of developing) folate/cobalamin deficiencies.

Diabetes mellitus

The elevated levels of blood total homocysteine observed in patients with diabetes are believed to relate to the degree of diabetic nephropathy. Homocysteine concentrations are a greater risk factor for death in patients with type 2 diabetes compared with patients without diabetes.25 Furthermore, the estimated survival time of patients with type 2 diabetes and a blood total homocysteine concentration >14 μmol/L is significantly shorter than patients with diabetes and concentrations <14 μmol/L.26

Roche Homocysteine enzymatic assay

The Roche Homocysteine enzymatic assay incorporates a range of features to ensure ease of use and reliability of results. The fully automated assay is based on the enzyme cycling method and requires only 10 minutes to generate results from samples as small as 14 μL. The assay is as user-friendly as conventional clinical chemistry assays and is compatible with all automated clinical chemistry analyzers, including cobas c, COBAS INTEGRA®, and MODULAR® ANALYTICS® systems.

In being cost-effective, fast, robust, easy to perform, stable over time with excellent accuracy and precision, and with an analytical range covering the 5 - 99.5 percentiles of the general population, the Roche Homocysteine enzymatic assay fulfills all the performance criteria recommended by the American Association for Clinical Chemistry.4

Comparison with other methods

There are currently three main analytical methods for evaluating blood total homocysteine levels in patient samples:
- Chromatographic methods
- Immunoassays
- Enzyme cycling methods

There are significant differences between the three methods with regard to assay precision, speed, and cost (Figure 6). Enzyme cycling uses fewer reagents and is faster on a ‘per test’ basis, which means the method is also the least expensive. Additional savings are possible due to the absence of a need for sample pretreatment, specialized instruments, or dedicated operators.

Cystathionine interference

The Roche Homocysteine enzymatic assay displays greater specificity than other methods due to a lack of interference from cystathionine (an intermediate product in homocysteine metabolism). Cystathionine levels are significantly elevated in millions of renal failure patients and which are affected by this interference can overestimate total homocysteine by as much as 20 - 300%.

Chemical principle of the enzyme cycling method

The Enzyme cycling method represents the latest cutting-edge technology and has rapidly become the preferred method used in clinical laboratories, especially those routinely testing large numbers of samples.

The first step in the reaction is that all three forms of homocysteine present within a sample are reduced to homocysteine by the cleavage of disulphide bonds. The "free" homocysteine is then converted to methionine under the action of the enzyme homocysteine methyltransferase and a methyl donor (S-adenosylmethionine, SAM). This transmethylation reaction converts SAM to S-adenosylhomocysteine (SAH), which is immediately hydrolyzed to adenosine and homocysteine by the enzyme SAH hydrolase. The homocysteine generated from SAM subsequently enters the methionine conversion reaction catalyzed by homocysteine methyltransferase, thus forming a cyclic reaction leading to an accumulation of adenosine that can be measured through an NAD+/NADH-coupled reaction detectable at 340 nm.

Chemical principle of the enzyme cycling method

1. Reduction of oxidized homocysteine (Hcy-S-Protein) using a reductant (e.g. DTT or GSSG) to free homocysteine (Hcy)
2. Cleavage of disulfide bonds
3. Enzymatic methylation of homocysteine to methionine
4. Photometric measurement at 340 nm

Figure 6: Relative performance of the three analytical methods for measuring blood total homocysteine.

Abbreviations: HPLC, high performance liquid chromatography.
CVD is the biggest killer in terms of global disease and its impact is predicted to grow due to the ageing populations of many countries.

- Commonly evaluated risk factors do not account for all cases of CVD.

Blood total homocysteine is a strong, independent risk factor for CVD.

- The relationship between elevated homocysteine and CVD is causal and probably due to multiple, potentially synergistic, pathogenetic mechanisms.
- Modest reduction in blood total homocysteine is predicted to confer large reductions in risk from CVD.

- <15 μmol/L is considered a normal fasting level of blood total homocysteine, although European laboratories tend to use a value of 12 μmol/L as the upper reference limit in adults.
- Upper reference limits depend on age and whether an individual has access to food fortified with folate or dietary supplements.

- Measurement of blood total homocysteine is recommended for risk assessment in CVD patients, diagnosis of the rare genetic disease homocystinuria, and identification of individuals with (or at risk from) folate or cobalamin deficiency.

Homocysteine measurements may be useful to assist prevention and/or monitoring in many other clinical settings including: psychiatric illness, cognitive impairment in the elderly and Alzheimer’s disease, pregnancy complications, and diabetes mellitus.

- The Roche Homocysteine enzymatic assay is a cutting-edge diagnostic tool for measuring blood total homocysteine concentrations in serum or plasma samples which offers:
  - Excellent performance
  - Precision over the entire measuring range
  - Roche Homocysteine is more specific than other methods because it does not interfere by cystathionine
  - Reliable results with optimized reproducibility enabling clinical decision in follow-up
  - High efficiency
  - All requested tests can be done out of one tube on a consolidated platform
  - Consolidation of more than 130 clinical chemistry markers improves turnaround time
  - Maximum convenience
  - Cost, labour and time savings through optimized workflow
  - Long on-board stability for cost-effective reagent usage.

Summary

- CVD is the biggest killer in terms of global disease and its impact is predicted to grow due to the ageing populations of many countries.
- Commonly evaluated risk factors do not account for all cases of CVD.
- Blood total homocysteine is a strong, independent risk factor for CVD.
- The relationship between elevated homocysteine and CVD is causal and probably due to multiple, potentially synergistic, pathogenetic mechanisms.
- Modest reduction in blood total homocysteine is predicted to confer large reductions in risk from CVD.
- <15 μmol/L is considered a normal fasting level of blood total homocysteine, although European laboratories tend to use a value of 12 μmol/L as the upper reference limit in adults.
- Upper reference limits depend on age and whether an individual has access to food fortified with folate or dietary supplements.
- Measurement of blood total homocysteine is recommended for risk assessment in CVD patients, diagnosis of the rare genetic disease homocystinuria, and identification of individuals with (or at risk from) folate or cobalamin deficiency.
- Homocysteine measurements may be useful to assist prevention and/or monitoring in many other clinical settings including: psychiatric illness, cognitive impairment in the elderly and Alzheimer’s disease, pregnancy complications, and diabetes mellitus.
- The Roche Homocysteine enzymatic assay is a cutting-edge diagnostic tool for measuring blood total homocysteine concentrations in serum or plasma samples which offers:
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  - Precision over the entire measuring range
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  - High efficiency
  - All requested tests can be done out of one tube on a consolidated platform
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