

Homocysteine

MDL Test Number: 662

Methodology: Immunoassay

CPT Codes: 83090



Specimen Collection Platform:

Serum in Serum Separator Tube (SST)

Turnaround Time:

24 - 72 hours

Stability:

Room temperature

Test Additions*:

30 days to add tests

Specimen Collection:



1. Immediately after blood collection, invert the tube(s) gently 5 times to ensure mixing of clot activator.



2. Allow the tube to rest upright for at least 30 minutes after collection to ensure proper clotting.



3. Centrifuge for at least 15 minutes at 2200-2500 RPM within one hour of collection.



4. Do not remove the stopper or pour off serum.



What is Homocysteine?

Homocysteine is an amino acid formed inside cells as the body works through methionine, an amino acid that comes from protein in the diet. It does not stay in that form for long. The body either converts it back to methionine, a step that needs folate and vitamin B12, or converts it onward toward cysteine, a step

that needs vitamin B6. Most of the homocysteine in blood is attached to protein, and this test measures the total of all of its forms.

Because both disposal routes depend on B vitamins, the blood level rises when folate, vitamin B12, or vitamin B6 runs short — often before other signs of a shortage appear. Kidney function, thyroid status, several medications, and inherited differences in the enzymes involved also move it. A raised homocysteine is therefore a signal that one of these processes has been disturbed, rather than a diagnosis on its own.

Why test for Homocysteine?

Homocysteine is measured to find what is raising it and to judge what a raised level means:

- **To follow up on a borderline vitamin B12 or folate result.** Homocysteine rises when either vitamin is functionally short, so it can settle the question when the vitamin level itself sits in the grey zone.
- **Before and during pregnancy, when folate demand rises sharply,** and a shortage affects both mother and pregnancy.
- **In polycystic ovary syndrome, also called polyendocrine metabolic ovarian syndrome (PMOS/PCOS),** where pooled data show homocysteine running higher than in women without it, and higher again where there is insulin resistance.
- **In an underactive thyroid.** Homocysteine rises when the thyroid is clearly underactive, most often from Hashimoto thyroiditis, an autoimmune condition far more common in women. It comes back down once thyroid hormone replacement restores normal thyroid function.
- **In people whose diet or digestion limits how much B vitamin they absorb:** vegetarian and vegan diets, celiac disease, weight-loss surgery, and long-term use of metformin or acid-reducing medication.
- **As an additional marker in someone with a personal or family history of heart attack, stroke, or clots** that the usual risk factors do not explain. What that association does and does not support is set out under Limitations.



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Special Instructions:

- **SAME supplements:** S-adenosylmethionine, sold over the counter as SAME for mood and joint symptoms, can make homocysteine read falsely high. Tell the ordering provider about any SAME being taken before the sample is drawn.
- **Medications that change the result:** The manufacturer directs that results be interpreted with caution in patients taking methotrexate, nitrous oxide, 6-azauridine triacetate, or anticonvulsants, including carbamazepine and phenytoin. Several of these work against folate or vitamin B12 in the body, so they raise homocysteine, as well as complicating the measurement.
- **Biotin supplements:** Biotin, sometimes sold as vitamin B7 and found in hair, skin, and nail products, can interfere with tests of this kind. This test showed no meaningful change up to 1500 nanograms per milliliter, which is well above the level an ordinary supplement produces. Tell the ordering provider about any biotin being taken.
- **Comparing results over time:** Results from different methods and different laboratories are not interchangeable. Serial results should be run by the same laboratory on the same method wherever possible.

Limitations:

Every laboratory test has limits. For homocysteine, the main ones are:

- A raised homocysteine has been linked consistently to heart attack and stroke. But large randomized trials of folic acid and B vitamins lowered homocysteine without reducing those events, and current cardiovascular guidelines do not recommend screening for it routinely. The result describes an association, not something that treating the number alone is known to fix.
- The kidney clears homocysteine, so the level rises as kidney function falls. A raised result in someone with reduced kidney function may be reporting the kidney rather than a vitamin shortage.
- The test reports results between 2 and 50 micromoles per liter. Results below the lower figure are reported as less than 2 micromoles per liter.
- Two compounds closely related to homocysteine are picked up to a small degree by this method: cystathionine, which is formed in the same pathway, and S-adenosylmethionine. The amounts are small, but they are part of why a single value is read alongside the vitamin levels rather than alone.
- Heterophilic antibodies, antibodies against animal proteins that some people carry, are more common in people routinely exposed to animals or animal products, and can produce an odd result. Asfotase alfa, a manufactured form of alkaline phosphatase used to treat hypophosphatasia, interferes with tests that detect using alkaline phosphatase, and the manufacturer directs that samples from patients taking it be run by a different method.
- A homocysteine result is one piece of a larger picture. It is meant to be read together with the patient's symptoms, medical history, and other test results, never on its own.

Reference Range(s):

Results are reported in micromoles per liter ($\mu\text{mol/L}$). Homocysteine varies with age and sex — men run higher than women, and women's levels rise after menopause — but the manufacturer publishes one adult interval rather than separate ones. The interval below comes from the manufacturer's own study of 120 apparently healthy adults aged 22 to 66 tested on this method.

- **Adults:** central 95% of that reference group, **5.0 to 12 $\mu\text{mol/L}$**
- **Median of that group:** **7.7 $\mu\text{mol/L}$**

A result outside these ranges is not automatically a problem, and a result inside them does not rule one out. Only the ordering provider can interpret what a given number means for a given patient. Patients should always go by the reference range printed on their own laboratory report.

Analyte	Disorder	Expected Value*
Homocysteine	PCOS/PMOS	↑
Homocysteine	Elevated cardiovascular risk	↑
Homocysteine	Vitamin B12 deficiency	↑
Homocysteine	Folate deficiency	↑
Homocysteine	Underactive thyroid (Hashimoto)	↑

*↑ – Increased.

What are some references that discuss the medical necessity of testing Homocysteine?

1. Devalia V, et al. Guidelines for the diagnosis and treatment of cobalamin and folate disorders. *Br J Haematol*, **166**, 496–513 (2014).
2. National Institute for Health and Care Excellence. *Vitamin B12 Deficiency in Over 16s: Diagnosis and Management* NICE Guideline NG239 (NICE, London, 2024).
3. Jacques PF, et al. The effect of folic acid fortification on plasma folate and total homocysteine concentrations. *N Engl J Med*, **340**, 1449–1454 (1999).
4. Ulloque-Badaracco JR, et al. Homocysteine, vitamin B12, and folate circulating levels in women with and without polycystic ovary syndrome: a systematic review and meta-analysis. *Womens Health (Lond)*, **20**, 17455057241279039 (2024).
5. Nedrebø BG, et al. Plasma total homocysteine levels in hyperthyroid and hypothyroid patients. *Metabolism*, **47**, 89–93 (1998).
6. Martí-Carvajal AJ, et al. Homocysteine-lowering interventions for preventing cardiovascular events. *Cochrane Database Syst Rev*, **8**, CD006612 (2017).



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