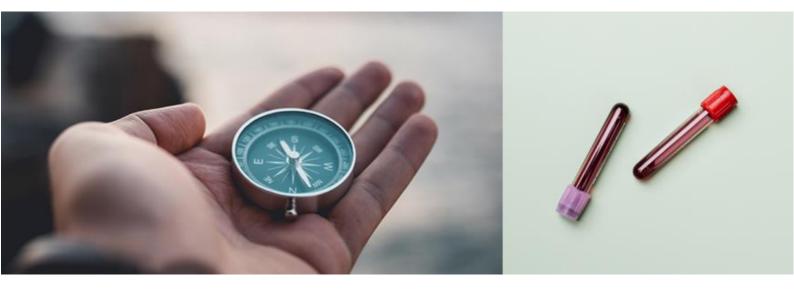


First do no harm: A guide to choosing wisely in general practice

For GPs – MTHFR gene testing



GPs' use of methylenetetrahydrofolate reductase (MTHFR) gene testing. RACGP position

- Avoid requesting a MTHFR gene test as there is no causal link between MTHFR gene variations and particular diseases,¹ and no substantial evidence to support the use of MTHFR gene testing in routine clinical practice.²
- There is no evidence-based treatment that will improve health outcomes for a patient who has one or both MTHFR gene variants,³ so knowledge of a patient's MTHFR gene status is unlikely to change how you manage and treat the patient.²

Traffic lights

RED

Do not take this action

- Do not routinely order MTHFR gene testing in general practice.⁴
- Do not order MTHFR gene testing as part of clinical evaluation for thrombophilia or early pregnancy loss.⁴

ORANGE

Under specified circumstances, take this action

 Appropriate paediatric referral or a repeat screening may be required if you suspect homocystinuria in a newborn.¹

GREEN

Take this action

- Women of childbearing age should take the standard dose of folic acid supplementation to prevent neural tube defects during pregnancy, regardless of their *MTHFR* status.⁴
- Explain to patients that the results of this test would not change their treatment.
- For patients who are carriers of the variants of the MTHFR gene, continue to provide normal care.²

Patient harms and risks

Ordering *MTHFR* gene testing in asymptomatic healthy patients could result in:

- unnecessary investigations for a range of conditions
- anxiety in pregnant women concerned about neural tube defects in the first trimester, recurrent pregnancy
 loss or congenital anomalies (even though the link between these and an MTHFR gene variant is weak^{5,6})
- increased parental distress and unnecessary blood testing of children thought to have autism spectrum disorder, even though the presence of an *MTHFR* gene variant will not change the diagnosis or outcome?
- false reassurance in instances when screening or other preventive action may be useful
- unnecessary financial cost to the patient⁸ (a variation in the *MTHFR* gene does not affect treatment of any condition a patient might have, therefore there is no Medicare Benefits Schedule rebate for this test and it cannot be bulk billed).

Overview

- Methylenetetrahydrofolate reductase (MTHFR) is the key enzyme in folate metabolism.⁹
- Overwhelmingly, the evidence suggests that general practitioners (GPs) should not routinely use MTHFR testing.²
- The *MTHFR* gene test identifies two gene variants that, while common in healthy populations, are associated with mildly elevated homocysteine levels in the blood.^{2,9}
- Some studies have indicated a weak correlation between higher homocysteine levels and myocardial infarction and venous thromboembolism.^{2,9,10}
- Folic acid supplementation before and during early pregnancy has been shown to protect against neural tube defects in a pregnancy, for women with and without *MTHFR*.¹
- In 2009, Australia introduced mandatory folate fortification of wheat flour used in bread and this has reduced the number of people with red blood cell folate levels below the reference range.¹¹
- Complementary and alternative practitioners often offer *MTHFR* testing to investigate recurrent pregnancy loss, ^{12,13} fertility, autism spectrum disorder,⁷ mental illness¹⁴ and cancer risk.²
- Although the *MTHFR* variants are associated with several medical conditions, clinical management is not changed by knowing which variant the patient has.
- When considering the usefulness of *MTHFR* testing for a patient, consider the following.¹¹
 - 1. **Analytical validity**: Does the test accurately reflect the biology of the patient (the two variants can be identified and appear to have caused a reduction in folate metabolism)?
 - 2. **Clinical validity**: Will the test increase your knowledge of the patient's disorder of concern? There is conflicting evidence about the relevance of *MTHFR* variants in many disorders confounded by the complexity of folate metabolism, folate supplementation/fortification, genetic and dietary factors.
 - 3. **Clinical utility**: Will the test result change treatment of the disorder? In studies reporting an association between *MTHFR* and a disorder, the association is usually weak (many people with a variant will not develop the disorder, and many people without a variant will develop the disorder).

Although tests for *MTHFR* gene variants have analytical validity, the clinical validity is uncertain, and the clinical utility is not demonstrated in the evidence.¹¹

Alternatives – what can I do for the patient?

- If a patient is seeking a cause for an illness, or seeking evidence that the illness is genetic, discuss and define the possibilities.^{2,15}
- Explain the potential harms of over-investigation, including the cost of the test and the lack of a meaningful outcome.¹⁵
- Encourage open discussion about *MTHFR* gene testing, thereby building and supporting therapeutic relationships and shared decision making that is based on evidence.
- Continue to encourage standard care, including preventive exercises, folate supplements for women of childbearing age, management of comorbidity and lifestyle changes.^{1,2,15}
- Offer psychological support if the patient is distressed by a potential diagnosis.¹⁵
- Treat physical symptoms and continue to manage the patient's expectations about current treatment of any condition they have, including relevant tests.¹⁵
- Refer to other specialist colleagues or a multidisciplinary team as appropriate.¹⁵

Resources

- The RACGP, First do no harm: a guide to choosing wisely in general practice MTHFR gene testing patient resource
- The RACGP, Genomics in general practice MTHFR gene testing
- The RACGP, Appropriate diagnostic testing Patient information
- Human Genetics Society of Australasia and Choosing Wisely Australia, Don't undertake genetic testing for methylenetetrahydrofolate reductase (MTHFR), apolipoprotein E (APOE), and other such tests where the clinical utility for diagnostic purposes is extremely low
- NSW Government and Centre for Genetics Education, MTHFR gene testing
- Dean L, Medical genetics summaries
- The Royal College of Pathologists of Australasia, Position statement, MTHFR genetic tests

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4 First do no harm: A guide to choosing wisely in general practice For GPs - MTHFR gene testing

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We acknowledge the Traditional Custodians of the lands and seas on which we work and live, and pay our respects to Elders, past, present and future.

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