RACGP
Royal Australian College of General Practitioners

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[7]
- false reassurance in instances when screening or other preventive action may be useful
- unnecessary financial cost to the patient[8] (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 illness[14] 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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