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RCPA
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Position Statement

Subject:	**MTHFR Genetic Tests**
Approval Date:	May 2016, April 2021
Review Date:	April 2025
Review By:	Genetic Advisory Committee
Number:	4/2016

The Royal College of Pathologists of Australasia (RCPA, the "College") is the peak body representing pathologists and clinical scientists nationally. We are committed to the responsible use of pathology to guide to medical decision-making by healthcare professionals and patients.

Pathology laboratories nationally have noted increasing requests for "MTHFR tests" as well as frequent commentary about such tests in the media. The College is concerned that the requests for MTHFR testing do not necessarily reflect the current state of knowledge regarding the use of this test in the delivery of healthcare.

The enzyme, *5,10-methylenetetrahydrofolate reductase* (MTHFR), plays a key role in the metabolism of the vitamin, folate. Folate, in its turn, plays a critical role in many biochemical reactions. Two common variations of the MTHFR gene, described technically as c.665C>T (p.Ala222Val) and c.1286A>C (p.Glu429Ala), reduce the activity of the MTHFR enzyme[1]. Given the critical role of folate in a myriad of biochemical reactions, it is reasonable to postulate that these MTHFR variants play a role in the pathogenesis of many different disorders.

There have been thousands of studies of the association of MTHFR variants with disorders such as thromboembolism, stroke, peripheral artery disease, migraine, hypertension, miscarriage, infertility, neural tube defects, cancer, psychiatric disorders, and chemotherapy toxicity. In considering the potential role of MTHFR gene tests in the management of such conditions, there are three issues that need to be addressed[2]:

1. **Analytical validity** *i.e. does the test result accurately reflect the biology in the patient?* There is no doubt that the two MTHFR variants can be correctly identified and that they do reduce the enzymatic synthesis of 5-methyltetrahydrofolate, the primary form of folate in plasma.
2. **Clinical validity** *i.e. is the test result relevant in understanding the disorder of concern?* There is frequently conflicting evidence about the relevance of MTHFR variants in the development of a specific disorder. Many common disorder are caused by multiple factors, folate metabolism is complex, and genetic and dietary factors can mimic or mask the association between MTHFR and disorder. Hence it is not surprising that some studies report an association between MTHFR variants and a specific disorder, while others do not. Critical analysis of these research studies is further confounded by the widespread use of folate fortification of basic foods in some communities. This raises the possibility that there may be an association between MTHFR variants and disorder in communities without folate fortification, but the association is lost in communities with folate fortification.
3. **Clinical utility** *i.e. will the treatment of the patient be altered by the test result?* In studies which report an association between MTHFR variants and a disorder, the association is usually weak. This means that many people with the variant do not develop the disorder, and many people who lack the variant do develop the disorder. As a result, the presence or absence of an MTHFR variant does not provide a reliable indicator of a predisposition to develop a specific disorder in an individual. Furthermore, in 2009, Australia introduced mandatory folate fortification of wheat flour used for bread making. This intervention reduced the prevalence of people with RBC folate levels below the reference range[3]. Folate fortification could potentially mask any limitation in folate metabolism due to MTHFR variants, and would minimise any benefit from taking further supplements of folate. As a result, the utility of testing for MTHFR variants for medical

decision-making may be limited.

Recommendation

The Royal College of Pathologists of Australasia considers that there is insufficient evidence of benefit to recommend MTHFR testing at present. Although tests for MTHFR gene variants have analytical validity, the clinical validity is uncertain and the clinical utility is unproven. Accordingly, **the College does not recommend MTHFR testing as a basis for medical decision-making in patients who receive a normal, folate-fortified diet.**

This stance is in keeping with guidelines by various professional bodies representing obstetricians and gynaecologists(4), medical geneticists(1), haematologists(5) and general practitioners(6), which do not support the use of MTHFR testing in the management of patients with a variety of disorders.

There is a fourth consideration in the assessment of a genetic test[2] i.e. is there any ethical, legal, or social consequence from testing that should be considered? It is one thing to say that there is insufficient evidence of benefit to recommend MTHFR testing, but is there sufficient evidence of harm to recommend against such testing? The test itself carries little risk, and the use of oral folate or related compounds also carries little risk for a patient. There is a financial cost as MTHFR testing is not covered by the Medical Benefits Scheme, and folate supplements are not covered by the Pharmaceutical Benefits Scheme. Of greater concern is the less tangible cost of a person being labelled as having a genetic disorder despite the lack of robust evidence to support such a [6]conclusion[7]. The only result of testing and treating could be the patient being stigmatised.

For these reasons, **the College recommends against MTHFR testing in the management of common disorders in patients who receive a normal, folate-fortified diet.**

This position will be reviewed periodically by the College in the light of new scientific evidence that is published.

References

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