Guidelines for MTHFR polymorphism testing

Concerning: detection of the c.665C>T (p.A222V) variant in the MTHFR gene for multifactorial disorders including recurrent miscarriages, cardiovascular diseases and cancer

The College of Genetics and Rare Diseases recommends not to test this variant anymore for the above mentioned indications. From 01/02/19 on, this test will be deleted from the list of reimbursed genetic tests (Art 33) in Belgium.
The MTHFR gene codes for the enzyme methylenetetrahydrofolate reductase. This enzyme catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, the primary circulatory form of folate and a co-substrate for homocysteine remethylation to methionine. The c.665C>T (historically more commonly referred to as C677T) polymorphic variant in MTHFR is frequently observed in the Western population and has a carrier frequency that ranges between 20 à 40 %. This variant is known to decrease enzyme activity which can result in mild hyperhomocysteinemia.
In the past, studies have suggested an association between the presence of this variant and several multifactorial disorders such as recurrent pregnancy loss, cardiovascular diseases (thrombophilia) and cancer. However recent data have shown that these associations are often not reproducible and only found in specific populations (1).
Furthermore, the American College of Obstetricians and Gynecologists does not recommend testing for this MTHFR polymorphism in the evaluation for recurrent pregnancy loss or other negative pregnancy outcomes (2). The American College of Medical Genetics states that MTHFR polymorphism genotyping should not be ordered as part of the clinical evaluation for thrombophilia or recurrent pregnancy loss (3). In addition, the American Heart Association does not recommend testing for MTHFR polymorphisms as risk factor for coronary artery disease or venous thrombosis (4).
Based on these recent studies and advices, we conclude that testing for the c.665C>T (C677T); p.A222V polymorphic variant in the MTHFR gene has no value in situations of recurrent pregnancy loss, cardiovascular disease and cancer. We therefore ask to not order this test anymore for these indications.
Nevertheless, genetic analysis of the MTHFR gene is still recommended in case of rare forms of homocystinuria, caused by bi-allelic mutations in the MTHFR gene.

References:

1. Levin BL and Varga E. MTHFR: addressing genetic counseling dilemmas using evidence-based literature. Journal of Genetic Counseling 2016; 25(5): 901-911
2. American Congress of Obstetricians and Gynecologists (2013). Inherited thrombophilias in pregnancy. Washington (DC): American College of Obstetricians and Gynecologists.
3. Hickey SE et al. American College of Medical Genetics Practice guideline: lack of evidence for MTHFR polymorphism testing. Genetics in Medicine 2013; 15(2): 153-156

4. Greenland et al. ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association. Journal of the American College of Cardiology 2010; 56(25): 50-103

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