J Pathol Inform

Editor-in-Chief:
Anil V. Parwani , Pittsburgh, PA, USA
Liron Pantanowitz, Pittsburgh, PA, USA

OPEN ACCESS
HTML format

For entire Editorial Board visit : www.jpathinformatics.org/editorialboard.asp

Original Article

Laboratory informatics based evaluation of methylene tetrahydrofolate reductase C677T genetic test overutilization

David A. Cohen, Brian H. Shirts[1], Brian R. Jackson[2,3], Lisa S. Parker[4,5]

Department of Pathology and Genomic Medicine, Houston Methodist Hospital, Houston, TX, [1]Departments of Pathology, University of Washington School of Medicine, Seattle, WA, [2]University of Utah, School of Medicine, [3]ARUP Institute for Clinical and Experimental Pathology, Salt Lake City, UT, [4]Department of Human Genetics, [5]Center for Bioethics and Health Law and University of Pittsburgh, Pittsburgh, PA, USA

E-mail: *David A. Cohen - dacohen@houstonmethodist.org
*Corresponding author

Received: 04 August 13 Accepted: 11 September 13 Published: 29 November 13

This article may be cited as:
Cohen DA, Shirts BH, Jackson BR, Parker LS. Laboratory informatics based evaluation of methylene tetrahydrofolate reductase C677T genetic test overutilization. J Pathol Inform 2013;4:33.

Available FREE in open access from: http://www.jpathinformatics.org/text.asp?2013/4/1/33/122389

Abstract

Background: Laboratory data can provide a wide range of information to estimate adherence to guidelines and proper utilization of genetic testing. The methylene tetrahydrofolate reductase (MTHFR) C677T variant has been demonstrated to have negligible utility in patient management. However, the testing of this variant remains pervasive. The purpose of this study was to develop methods to analyze concordance of clinician ordering practices with national guidelines. **Methods:** We used laboratory data to extract specific data elements including patient demographics, timestamps, physician ordering logs and temporal relationship to chemistry requests to examine 245 consecutive MTHFR tests ordered in 2011 at an academic tertiary center. A comprehensive chart review was used to identify indications for testing. These results were correlated with a retrospective analysis of 4,226 tests drawn at a range of hospitals requesting testing from a national reference laboratory over a 2-year period. MTHFR ordering practices drawn from 17 institutions were examined longitudinally from 2002 to 2011. **Results:** Indications for testing included cerebrovascular events (40.0%) and venous thrombosis (39.1%). Family history prompted testing in eight cases. Based on acceptable hypercoagulability guidelines recommending MTHFR C677T testing only in the presence of elevated serum homocysteine, 10.6% (22/207) of adult patients met an indicated threshold at an academic tertiary center. Among 77 institutions, 14.5% (613/4226) of MTHFR testing met recommendations. **Conclusion:** We demonstrate an effective method to examine discreet elements of a molecular diagnostics laboratory information system at a tertiary care institution and to correlate these findings at a national level. Retrospective examination of clinicians' request of MTHFR C677T genetic testing strongly suggests that clinicians have failed to adjust their ordering practices in light of evolving scientific and professional organization recommendations.

Key words: Clinical laboratory informatics, genetic education, genetic testing utilization, methylene tetrahydrofolate reductase C677T, predictive genetic testing

Access this article online

Website: www.jpathinformatics.org

DOI: 10.4103/2153-3539.122389

Quick Response Code:

INTRODUCTION

With the continuing implementation of the 2010 Affordable Care Act, there is increasing emphasis on the role of the clinical laboratory in the adoption of evidence-based guidelines that address appropriate

ordering of laboratory tests. However, for a majority of the over 2,300 genetic tests available to clinicians from clinical laboratories, there exist limited evidence-based guidelines to sufficiently guide ordering physician of their proper usage in clinical practice.[1] Laboratory data including patient demographics, physician and department ordering logs, timesheets and temporal relationship with other laboratory chemistry requests provide a rich source of information for the interpretation of proper utilization. Clinical laboratories have an opportunity to use this information for targeted clinicians' feedback on the overuse of genetic testing.

When updated evidence-based guidelines are published demonstrating a laboratory test has low clinical utility, it is expected that clinicians should refrain from ordering. Proper utilization is especially important for genetic testing due to the financial, psychological and substantial ethical risks involved in extracting genetic information. There has been limited examination of how clinicians actually modify their ordering of genetic testing with low clinical utility and what indications may prompt testing that does not follow professional society recommendations. Better understanding by molecular diagnostic laboratories on adherence of clinicians to evolving evidence-based guidelines could improve efforts to provide clinician and payor specific feedback. We investigated genetic testing for the methylene tetrahydrofolate reductase (MTHFR) C677T polymorphism and its relationship to serum homocysteine requests as a test case to understand clinicians' incorporation of genetic tests into patient care. This example may shed light on larger issues that will arise as hospital clinical laborites offer an array of molecular diagnostics tests for an increasing number of disorders.

Background on Genetic Testing of MTHFR Polymorphisms

The MTHFR C677T genetic variant has an estimated homozygous prevalence of 5-14% in United States population based on ethnicity.[2] Other populations, particularly in Mediterranean regions, have an asymptomatic population prevalence of the TT variant over 30%.[3] The MTHFR C677T variant is the main genetic determinant of serum homocysteine levels.[4,5] Due to hypercoagulable risks associated with hyperhomocysteinemia, including future venous and arterial thrombosis, stroke and myocardial infarction, clinicians have historically tested this variant while also measuring serum homocysteine.

Although early meta-analyses in the early 1990s initially supported a consistently weak positive association between MTHFR C677T and thrombotic disease (Odds ratio 1.1-1.6), further well-designed studies with larger folate-replete populations have found no significant risk especially in developed countries.[6-11] Expert consensus statements from professional organizations recommend against clinical genotyping of MTHFR due to its negligible clinical utility in patients with thrombotic events. The College of American Pathologists (CAP)[12] and the American College of Medical Genetics (ACMG),[13] among others,[14-16] have published recommendations against testing this variant since 2001 [Table 1]. The American Heart Association has published expert consensus recommendations suggesting testing may be appropriate only in the setting of hyperhomocysteinemia.[17]

Despite this guidance from numerous professional organizations against testing for MTHFR C677T, the variant appears to be frequently ordered in the United States. Clinical MTHFR C677T testing is available from 64 North American laboratories and individuals may order the variant on their own from numerous direct-to-consumer laboratories including 23andMe and NevoDHA.[1] Individual genetic tests do not use current procedure terminology codes, so it is impossible to assess directly how often MTHFR testing is ordered in the United States. However, MTHFR has been included as one of the

Table 1: Published expert consensus recommendations available evaluating the utilization of MTHFR C677T testing for thrombosis and inherited thrombophilia

Professional organization	Year	Type of clinical consensus	Recommendation for stand-alone MTHFR C677T testing?	Reflex testing in presence of elevated serum homocysteine (>13 umol/L)?
ACMG	2001	Working Group Consensus Statement[13]	No	No
ACOG	2001	Practice Bulletin Guideline[15]	No	No
CAP	2002	Expert Consensus Recommendation[12]	No	No
AHA	2005	Expert Recommendation[17]	No	Yes-optional
ACCP	2008	Clinical Guideline[16]	No	No
BHSC	2010	Clinical Guideline[14]	No	No

ACMG: American college of medical genetics, ACOG: American college of obstetrics and gynecology, CAP: College of american pathologist, AHA: American heart association, ACCP: American college of chest surgeons, BHSC: British hematology standards committee, MTHFR: Methylene tetrahydrofolate reductase

20 "Tier 1" molecular tests comprising 80% of molecular pathology testing in the United States. As a comparison, in 2004 the Italian Society of Human Genetics recorded 13,677 MTHFR C677T tests performed that year, making it the fourth most commonly ordered genetic test in Italy with only cystic fibrosis, factor V Leiden and Prothrombin 20210A testing being more common.[18]

METHODS

Detailed, comprehensive chart review at a large academic tertiary care institution was combined with a retrospective review of ordering practices at a major national reference laboratory to evaluate utilization patterns in MTHFR C677T genetic testing in contrast to guideline recommendations.

The University of Pittsburgh Medical Center (UPMC) is an integrated hospital health system comprising of an academic tertiary care institution and a children's hospital. We sought to understand the indications for which MTHFR C677T testing is ordered from a tertiary care institution such as UPMC. After obtaining approval from the Institutional Review Board (IRB) at the University of Pittsburgh, we used the Helix laboratory information system (LIS) to identify all consecutive MTHFR C677T variant tests ordered between 1/01/2011 and 12/31/2011 by UPMC clinicians in the in-patient setting. All whole blood specimens were processed solely in the molecular diagnostic division of the UPMC pathology laboratory using the Hologic Invader assay platform as described previously.[19] In accordance with the IRB protocol, a retrospective electronic medical record chart review was performed for the 245 patients to extract specific data elements not available in the LIS, including documentation of serum homocysteine levels drawn during the same admission, indications for testing and follow-up management. For three patients the primary ordering clinician was not known. Homocysteine serum levels were not included for pediatric patients as the children's hospital uses an inaccessible LIS system.

Although any MTHFR testing would be considered unnecessary by most guidelines,[12,16] we chose to evaluate test utilization based on the most liberal guidelines.[17] We coded the presence of serum homocysteine testing reflexively followed by MTHFR C677T testing in the presence of hyperhomocysteinemia (>13.0 umol/L) to be the least stringent acceptable indication for MTHFR testing based on the American Heart Association's recommendations. Ordering MTHFR as a stand-alone test and ordering a homocysteine level after reporting a MTHFR variant were considered as "an unacceptable indication" for MTHFR testing based on expert consensus statements from CAP, ACMG, British Hematology Standards Committee and American College of Obstetrics and Gynecology.

We then sought to determine whether the practices witnessed at UPMC in the adult inpatient setting were also seen at ARUP Laboratories, a national reference laboratory affiliated with the University of Utah Department of Pathology that performs molecular testing for a large number of institutions across the United States. Analysis of ARUP ordering data for MTHFR C677T and serum homocysteine was performed on fully de-identified data under a protocol deemed exempt by the University of Utah IRB. Both at UPMC and at ARUP, MTHFR is not included as part of an inherited thrombophilia panel, so MTHFR testing must be specifically requested.

To examine whether clinicians adhered to guidelines regarding MTHFR testing in the presence of elevated serum homocysteine, we determined whether MTHFR orders between 01/01/2010 and 12/31/2012 from ARUP were associated with a serum homocysteine level ordered on the same patients within a one-year window. Using a one-year time period for serum homocysteine level allowed for the capture of patients with hyperhomocysteinemia who subsequently were evaluated for the MTHFR variant at a later time point in the out-patient setting. To gauge heterogeneity in reporting results, we stratified sample laboratory reports by type of institution. We defined a small community hospital as having fewer than 250 beds. We defined a large regional hospital as one with a tertiary care academic affiliation or greater than 250 beds.

In addition, we sought to evaluate the trend in MTHFR ordering practices since the publication of guidelines in 2001 by analyzing MTHFR ordering practices from only institutions that routinely requested MTHFR testing as a send-out test from ARUP between 2002 and 2011. Seventeen institutions met these criteria. To avoid increases due to consolidation of laboratory out-patient volume, MTHFR C677T requests were normalized to total monthly client volume requested from ARUP Laboratories and the ratio was indexed relative to 2002 testing levels.

RESULTS

At UPMC only 10.6% (22/207) of adult in-patient MTHFR C667T tests were ordered for individuals with hyperhomocysteinemia. In 2011, 245 inpatients, of which 38 were pediatric inpatients, received MTHFR testing with an average age of 41.1 (standard deviation 19.6, 62.2% of female). The most common indications for ordering the MTHFR test were a work-up for a cerebrovascular event (39.1%) and venous thrombosis (40.0%). Other minor indications for testing included transplantation evaluation, vasculitis and migraines with aura, intrauterine fetal demise and surgical clearance. Eight asymptomatic patients received testing due to concern about a family history of the variant. Internal medicine clinicians (91) including

hematology/oncology (46) and cardiology (10) most commonly requested testing followed by neurology (87) and surgery (22). Other ordering departments included family medicine, dermatology, ophthalmology and physical medicine and rehabilitation [Table 2].

Within the study period, 125 adult in-patients of 207 (60.1%) had a homocysteine serum measurement drawn. In these cases, 83.2% of patients were found to have normal levels (<13 umol/L). Of the 21 individuals with moderately elevated homocysteine, (13-60 umol/L), 6 (27.2%) had the 677TT phenotype, a modest increased prevalence associated with this variant. No patients had severely elevated homocysteine (>60 umol/L). The prevalence of 677TT individuals (9.79%) in this patient population was not significantly different from the general United States population ($P = 0.739$).

We sought to determine whether there was similar evidence of MTHFR overutilization at other institutions. We limited our evaluation to 77 institutions in 32 states that routinely ordered both serum homocysteine and MTHFR C677T testing from ARUP between 9/1/09 and 3/1/12 in order to limit potential bias from hospitals that perform serum homocysteine testing in-house or may refer to ARUP only for internal laboratory quality controls. Institutions requesting MTHFR C677T testing included small community hospitals, regional hospitals, women and children hospitals, cancer centers, academic institutions and commercial reference labs. Tests were performed at a range of institutions including small community hospitals (43.9%) as well as large regional and academic centers (49.6%) with a small proportion of tests requested from out-patient laboratories. During the study period we identified MTHFR genotyping for 4,226 individuals; 314 patients had MTHFR genotyping performed multiple times.

At ARUP, 1,990 individuals (52.9%) had stand-alone MTHFR testing. Of those in whom homocysteine was also measured, only 14.5% of MTHFR tests were ordered for individuals with hyperhomocysteinemia [Figure 1]. A total of 11 patients (0.2%) had severely elevated homocysteine (>60 umol/L). Homocysteine co-testing was ordered at statistically different frequency at community hospitals (58.3%) and regional academic centers (48.8%) ($P < 0.01$). The prevalence of 677TT individuals (11.1%) in these 4,226 patients also showed non-significance compared with the general population ($P = 0.494$).

Next we examined the chronological trend in MTHFR ordering to determine whether MTHFR test ordering practices have been affected by guidelines. Our hypothesis was that MTHFR testing should have declined over time after evidence-based guidelines published in 2001 and 2002 recommended against its use. In 2003, 344 tests were ordered cumulatively from these 17 institutions and 1402 tests were ordered from these same institutions in 2011. MTHFR ordering trends at several individual institutions remained stable. When normalized to total volume, cumulative MTHFR orders from 17 institutions showed overall levels of MTHFR testing increasing until 2008 then progressively declining [Figure 2].

DISCUSSION

We observed that clinical MTHFR C677T testing was performed at an academic tertiary care institution primarily in the context of hypercoagulable work-ups, despite longstanding recommendations against this practice from CAP and other professional societies. At UPMC in 2011, continued utilization of MTHFR C677T testing was performed for thrombotic events across a wide

Table 2: Indications for MTHFR C677T testing by specialty at university of pittsburgh medical center from 245 consecutive requests in 2011

	VTE	CVA	Other**	FHX	Unknown	IUFD	Total
Neurology	3	77	3	1	2	1	87
Hematology/oncology	30	3	5	3	4	1	46
Internal medicine*	30	9	1	0	4	1	45
Pediatrics	6	0	5	4	8	0	23
Surgery	13	5	3	0	1	0	22
Family medicine	8	1	3	0	0	0	12
Ophthalmology	1	0	0	0	0	0	1
Orthopedics	1	0	0	0	0	0	1
PMR	1	1	0	0	0	0	2
Radiology	1	0	0	0	0	0	1
Dermatology	0	1	1	0	0	0	2
Unspecified	2	1	0	0	0	0	3
Total	96	98	21	8	19	3	245

VTE: Venous thrombotic event, CVA: Cerebrovascular accident, FHx: Family history, IUFD: Intrauterine fetal demise, PMR: Physical medicine and rehabilitation, MTHFR: Methylene tetrahydrofolate reductase, *Including cardiology, general IM, critical care/pulmonary, endocrine, GI, infectious disease, rheumatology, **Lupus, vasculitis, transplant evaluation, surgical clearance, ITP, migraines, depression

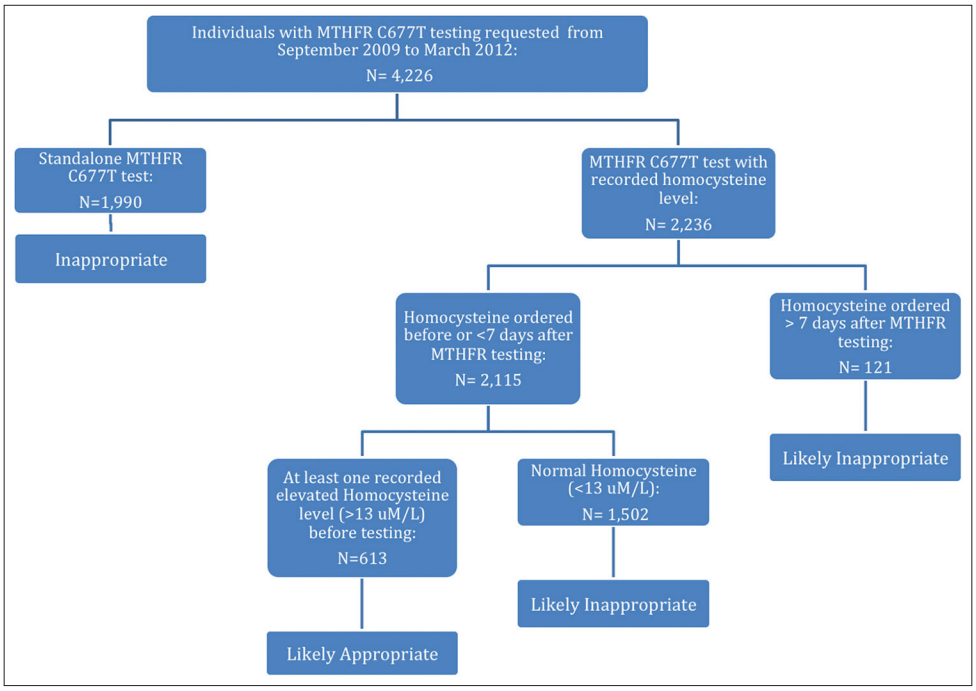

Figure 1: Workflow diagram illustrating data from ARUP laboratories used in the evaluation of proportion of inappropriate methylene tetrahydrofolate reductase C677T tests requested

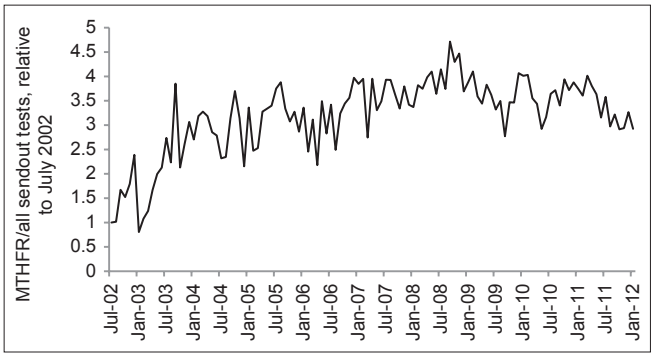

Figure 2: Monthly number of requests normalized to total client volume from 17 institutions which continuously ordered methylene tetrahydrofolate reductase C677T testing from ARUP laboratories

variety of specialties with only 10.6% of adult in-patient MTHFR tests ordered in the presence of concurrent hyperhomocysteinemia. We saw similar trends in ordering of MTHFR at a national sample for both in-patients and out-patients. In a limited sample size studied longitudinally from 2002 to 2011 progressive declines in MTHFR testing volume after 2008 was observed. These positive results suggest clinicians may be modifying their previous ordering practices based on increasing awareness of the test's low clinical utility. However, considering the 13,491 tests performed at just one of the 64 North American laboratories, which perform MTHFR C677T testing, it is likely that inappropriate ordering is not limited to a small number of clinicians or patients.

Continued ordering of MTHFR genetic reflects not only clinicians' limited implementation and knowledge of published guidelines, but also a number of the health system and patient-related related factors. In the event of dramatic thrombotic events, there exists a presumed professional responsibility, as well as a strong desire by patients, for clinicians to discover its cause, including possible underlying genetic predisposition for thrombophilia. Moreover, there is limited accountability for the cost or subsequent downstream effects after hospital discharge of testing as clinicians attempt to provide an explanation for why such events occur. A positive MTHFR result might lead to repeat diagnostic testing, additional office visits, genetic counseling and even anticoagulation therapy. As we have seen at our own institution, the knowledge of a homozygous MTHFR variant may also prompt asymptomatic family members to request genetic testing and specialist evaluation further extending downstream costs.

Like all retrospective evaluations, our study faces the limitations of potential incomplete ascertainment of subjects and the lack of full clinical information for all patients tested. Although retrospective review of consecutive patients at one academic center showed MTHFR tests are predominantly ordered following hypercoagulable events, this finding cannot necessarily be extrapolated to other institutions. Nevertheless, data from ARUP mirrored the more detailed findings from UPMC indicating that the MTHFR test overutilization similar to that identified at UPMC may be widespread.

In addition to the financial costs of ordering any unnecessary laboratory test, there exist special concerns

with unnecessary genetic testing. Unlike most routine clinical laboratory testing that has relevance only at one specific time point, genetic test results represent a finding that holds for the lifetime of patient, that may or may not acquire clinical significance in the future and that may have relevance for patients' relatives.[20] Although studies have examined the empiric benefit of genetic testing in cancer screening to reduce anxiety, these benefits have not been shown with genetic testing for common polymorphisms, such as MTHFR C677T, which contribute negligible disease risk.[21,22]

We suspect the dilemma of discordance between ordering practices in MTHFR testing and appropriate indications as reflected in clinical guidelines will be repeated as the interest in using personalized medicine in clinical practice increases. Clinical laboratories have the opportunity to educate clinicians ordering testing with low clinical utility. With an increasingly diverse and complex array of genetic tests, laboratories may be able to take a more proactive role to limit unnecessary testing. For example, clinical laboratories can remove the ability of clinicians to order outdated testing, put in place reflex protocols or require pathologist approval. In the case of MTHFR C677T genetic testing, other approaches include the use of informatics applications such as diagnostic decision support tools, interactive laboratory reports and user-friendly selection menus that clearly provide updated professional recommendations. Analytical software and cost calculators can provide visual comparisons of the frequency of testing among peers and hospitals both at a local and national level.

Predictive genetic testing for common diseases should only occur when a particular result will change clinical management or provide meaningful prognostic information to inform decisions of patients and their relatives. To best serve patients, only clinicians experienced in genetic testing should responsibly order genetic tests. However, in the face of rapidly evolving evidence many physicians are unprepared to evaluate indications for genetic testing and convey genetic results to patients. Our study suggests the need to further develop, test and implement better informatics methods to educate clinicians about genetic testing and to provide ongoing, updated information when guidelines change. Education should also seek to increase clinician awareness of the potential downstream effects of genetic testing, including psychological burden, financial costs and additional consultation.

ACKNOWLEDGMENT

The authors and especially DAC, would like to acknowledge the contribution to this project of Jeffrey A. Kant, MD, PhD, whose contributions to this project would have merited authorship and who passed away unexpectedly prior to the final drafting of this article. DAC was a post-sophomore pathology fellow at the University of Pittsburgh from 2011 to 2012.

REFERENCES

1. GeneTests, 2012. Available from: http://www.ncbi.nlm.nih.gov/sites/GeneTests/?db=GeneTests. [Last accessed on 2012 Aug 3].
2. Botto LD, Yang Q. 5,10-Methylenetetrahydrofolate reductase gene variants and congenital anomalies: A HuGE review. Am J Epidemiol 2000;151:862-77.
3. Wilcken B, Bamforth F, Li Z, Zhu H, Ritvanen A, Renlund M, *et al*. Geographical and ethnic variation of the 677C>T allele of 5,10 methylenetetrahydrofolate reductase (MTHFR): Findings from over 7000 newborns from 16 areas world wide. J Med Genet 2003;40:619-25.
4. Frosst P, Blom HJ, Milos R, Goyette P, Sheppard CA, Matthews RG, *et al*. A candidate genetic risk factor for vascular disease: A common mutation in methylenetetrahydrofolate reductase. Nat Genet 1995;10:111-3.
5. Harmon DL, Woodside JV, Yarnell JW, McMaster D, Young IS, McCrum EE, *et al*. The common 'thermolabile' variant of methylene tetrahydrofolate reductase is a major determinant of mild hyperhomocysteinaemia. QJM 1996;89:571-7.
6. Arruda VR, von Zuben PM, Chiaparini LC, Annichino-Bizzacchi JM, Costa FF. The mutation Ala677 –>Val in the methylene tetrahydrofolate reductase gene: A risk factor for arterial disease and venous thrombosis. Thromb Haemost 1997;77:818-21.
7. Margaglione M, D'Andrea G, d'Addedda M, Giuliani N, Cappucci G, Iannaccone L, *et al*. The methylenetetrahydrofolate reductase TT677 genotype is associated with venous thrombosis independently of the coexistence of the FV Leiden and the prothrombin A20210 mutation. Thromb Haemost 1998;79:907-11.
8. Den Heijer M, Lewington S, Clarke R. Homocysteine, MTHFR and risk of venous thrombosis: A meta-analysis of published epidemiological studies. J Thromb Haemost 2005;3:292-9.
9. Tsai AW, Cushman M, Tsai MY, Heckbert SR, Rosamond WD, Aleksic N, *et al*. Serum homocysteine, thermolabile variant of methylene tetrahydrofolate reductase (MTHFR), and venous thromboembolism: Longitudinal Investigation of Thromboembolism Etiology (LITE). Am J Hematol 2003;72:192-200.
10. Bezemer ID, Doggen CJ, Vos HL, Rosendaal FR. No association between the common MTHFR 677C->T polymorphism and venous thrombosis: Results from the MEGA study. Arch Intern Med 2007;167:497-501.
11. Naess IA, Christiansen SC, Romundstad PR, Cannegieter SC, Blom HJ, Rosendaal FR, *et al*. Prospective study of homocysteine and MTHFR 677TT genotype and risk for venous thrombosis in a general population – Results from the HUNT 2 study. Br J Haematol 2008;141:529-35.
12. Eldibany MM, Caprini JA. Hyperhomocysteinemia and thrombosis: An overview. Arch Pathol Lab Med 2007;131:872-84.
13. Grody WW, Griffin JH, Taylor AK, Korf BR, Heit JA, ACMG Factor V. Leiden Working Group. American College of Medical Genetics consensus statement on factor V Leiden mutation testing. Genet Med 2001;3:139-48.
14. Baglin T, Gray E, Greaves M, Hunt BJ, Keeling D, Machin S, *et al*. Clinical guidelines for testing for heritable thrombophilia. Br J Haematol 2010;149:209-20.
15. Barbour LA, ACOG Committee on Practice Bulletins – Obstetrics. ACOG practice bulletin. Thrombembolism in pregnancy. Int J Gynaecol Obstet 2001;75:203-12.
16. Bates SM, Greer IA, Pabinger I, Sofaer S, Hirsh J, American College of Chest Physicians. Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:844S-86.
17. Varga EA, Sturm AC, Misita CP, Moll S. Cardiology patient pages. Homocysteine and MTHFR mutations: Relation to thrombosis and coronary artery disease. Circulation 2005;111:e289-93.
18. Dallapiccola B, Torrente I, Morena A, Dagna-Bricarelli F, Mingarelli R. Genetic testing in Italy, year 2004. Eur J Hum Genet 2006;14:911-6.
19. Patnaik M, Dlott JS, Fontaine RN, Subbiah MT, Hessner MJ, Joyner KA, *et al*. Detection of genomic polymorphisms associated with venous thrombosis using the invader biplex assay. J Mol Diagn 2004;6:137-44.

20. Shirts BH, Parker LS. Changing interpretations, stable genes: Responsibilities of patients, professionals, and policy makers in the clinical interpretation of complex genetic information. Genet Med 2008;10:778-83.
21. Green RC, Roberts JS, Cupples LA, Relkin NR, Whitehouse PJ, Brown T, *et al*. Disclosure of APOE genotype for risk of Alzheimer's disease. N Engl J Med 2009;361:245-54.
22. Bosch N, Junyent N, Gadea N, Brunet J, Ramon y Cajal T, Torres A, *et al*. What factors may influence psychological well being at three months and one year post BRCA genetic result disclosure? Breast 2012;21:755-60.