Original Article

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

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

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

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. 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 payer 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 laboratories 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. Other populations, particularly in Mediterranean regions, have an asymptomatic population prevalence of the TT variant over 30%. The MTHFR C677T variant is the main genetic determinant of serum homocysteine levels. 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. 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) and the American College of Medical Genetics (ACMG), among others, 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.

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. 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

| 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 Statement¹³ | No                                                | No                                                                 |
| ACOG                      | 2001 | Practice Bulletin Guideline¹⁵ | No                                                | No                                                                 |
| CAP                       | 2002 | Expert Consensus Recommendation¹² | No                                                | No                                                                 |
| AHA                       | 2005 | Expert Recommendation¹⁷ | No                                                | Yes-optional                                                        |
| ACCP                      | 2008 | Clinical Guideline¹⁴ | No                                                | No                                                                 |
| BHSC                      | 2010 | Clinical Guideline¹⁴ | 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 inpatient 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
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. 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.

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.

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