Clinical Utility of a Novel Coronary Heart Disease Risk-Assessment Test to Further Classify Intermediate-Risk Patients

Matthew D. Solomon, MD, PhD; Ahalya Tirupsur, MS; Evangelos Hytopoulos, PhD; Michael Beggs, PhD; Douglas S. Harrington, MD; Cynthia French, PhD; Thomas Quertermous, MD

Cardiovascular Medicine (Solomon, Quertermous), Stanford University School of Medicine, Stanford, California; Department of Biostatistics (Tirupsur, Hytopoulos), Department of Product Development (Beggs, French), and Clinical Laboratory (Harrington), Aviir Diagnostic Laboratories, Irvine, California; Department of Pathology (Harrington), Keck School of Medicine, University of Southern California, Los Angeles, California

Background: Current coronary heart disease (CHD) risk assessments inadequately assess intermediate-risk patients, leaving many undertreated and vulnerable to heart attacks. A novel CHD risk-assessment (CHDRA) tool was developed for intermediate-risk stratification using biomarkers and established risk factors to significantly improve CHD risk discrimination.

Hypothesis: Physicians will change their treatment plan in response to more information about a patient’s CHD risk level provided by the CHDRA test.

Methods: A Web-based survey of cardiology, internal medicine, family practice, and obstetrics/gynecology physicians (n = 206) was conducted to assess the CHDRA clinical impact. Each physician was shown 3 clinical vignettes representing community-based cohort participants randomly selected from 8 total vignettes. For each, the physicians assessed the individual’s CHD risk and selected preferred therapies based on the individual’s comorbidities, physical examination, and laboratory results. The individual’s CHDRA score was then provided and the physicians were queried for changes to their initial treatment plans.

Results: After obtaining the CHDRA result, 70% of the physician responses indicated a change to the patient’s treatment plan. The revised lipid-management plans agreed more often (74.6% of the time) with the current Adult Treatment Panel III guidelines than did the original plans (57.6% of the time). Most physicians (71.3%) agreed with the statement that the CHDRA result provided information that would impact their current treatment decisions.

Conclusions: The CHDRA test provided additional information to which physicians responded by more often applying appropriate therapy and actions aligned with guidelines, thus demonstrating the clinical utility of the test.

Introduction
Coronary heart disease (CHD) remains the leading cause of death and morbidity in the United States. Accurately identifying individuals with subclinical disease who may benefit from early interventions is a key to CHD prevention. The American College of Cardiology Foundation and American Heart Association (ACCF/AHA) guidelines recommend formal risk stratification based on clinical characteristics such as the Framingham Risk Score to calculate 10-year risk for individuals.1,2 Yet such risk-factor models are known to be inaccurate, especially in the intermediate-risk group.3,4 This may explain why fewer than 20% of surveyed physicians report using a risk calculator, with many physicians believing that the current risk-assessment tools are inadequate and time consuming, and that they exclude important risk factors.5,6 As a result, most physicians misclassify a patient’s CHD risk, with nearly two-thirds underestimating risk.7

Common risk-assessment tools place many individuals into an intermediate-risk category where many cardiac events occur, treatment guidelines are unclear, and patients require further risk stratification.8 To better define the
intermediate-risk group, a 5-year CHD risk-assessment (CHDRA) algorithm (MIRISK VP; Aviir, Inc., Irvine, CA) was developed to combine serum levels of 7 biomarkers associated with the biology underlying vulnerable plaque formation and rupture, along with age, sex, family history of myocardial infarction (MI), and diabetic status. The performance and clinical validation of the CHDRA algorithm to assess 5-year CHD risk in the intermediate-risk population has been reported. The current study was undertaken to determine the clinical utility of the CHDRA test by measuring its impact on physicians' treatment choices when provided the CHDRA results for intermediate-risk individuals. A secondary aim was to measure physician adherence to clinical guidelines for cholesterol management.

Methods

Study Design

A Web-based, cross-sectional survey was administered to 206 physicians from 40 states in the United States, distributed equally across cardiology, internal medicine, family practice, and obstetrics/gynecology (OB/GYN) specialties. Of 1113 physicians invited to participate, 639 started and 206 completed the survey. An honorarium of $65 was provided per completed survey; the survey was estimated to take 30 to 40 minutes to complete. The physicians provided practice information and were queried about their CHD risk-assessment tool use and opinions (see Supporting Information, Appendix, in the online version of this article). They were asked to report their usual follow-up appointment frequency, laboratory testing, and other primary-prevention measures for patients based on age, sex, clinical characteristics, and formal CHD risk category. The study was conducted in accordance with the applicable US laws and regulations.

Following an explanation of the CHDRA test and its performance characteristics, each physician was presented with 3 clinical vignettes. The vignettes were randomly selected from 8 total vignettes and reflected participants with 3 clinical vignettes. The vignettes were randomly distributed equally across cardiology, internal medicine, family practice, and obstetrics/gynecology (OB/GYN) specialties. Of 1113 physicians invited to participate, 639 started and 206 completed the survey. An honorarium of $65 was provided per completed survey; the survey was estimated to take 30 to 40 minutes to complete. The physicians provided practice information and were queried about their CHD risk-assessment tool use and opinions (see Supporting Information, Appendix, in the online version of this article). They were asked to report their usual follow-up appointment frequency, laboratory testing, and other primary-prevention measures for patients based on age, sex, clinical characteristics, and formal CHD risk category. The study was conducted in accordance with the applicable US laws and regulations.

Selection of the Clinical Vignettes

The 8 clinical vignettes were deemed to be intermediate risk (5-year risk of a CHD event, 3.50%–7.49%) based on a recalibrated Framingham 10-year CHD risk range of 10% to 20%. The CHDRA test reclassified 5 cases to high risk and 2 cases to low risk, and 1 case remained at intermediate risk.

Statistical Analysis

The physicians' vignette responses, before and after seeing the CHDRA result, were assessed for agreement with the ATP III guidelines for LDL targets and lipid-lowering therapies. A permutation approach was used to test for differences in physician decision percentages (see Supporting Information, Appendix, in the online version of this article). The significance of changes in cholesterol targets, lipid-testing frequency, and antihypertensive medication prescribing, in cases 1, 2, 3, 4, and 7, which were recategorized to high risk after seeing the CHDRA results, were assessed using the Bhapkar test (SAS version 9.3; SAS Institute Inc., Cary, NC). Values in cross-table cells with zero counts were imputed with a very small number (0.00001). All other analyses were completed using R (version 2.14.2). Statistical significance was set at 0.05.

Results

Out of 639 attempted surveys, 206 were completed (Table 1). These were divided nearly equally among the 4 medical specialties. Respondents were more likely to be male, yet well distributed across age and region. An overview of the 8 clinical vignettes is shown in Table 2. The mean age among vignette patients (balanced by sex) was 63 years. Each vignette was reviewed by 64 to 82 different physicians, giving a total 615 responses.

After obtaining the CHDRA result, 69.9% of the physician responses indicated a treatment- and management-plan change (63.3% changed appropriately with the direction of the physician's CHD risk profile). After completing all 3 clinical vignettes, an overview chart was shown including the physician's original risk classification, the CHDRA classification, and whether or not the individual had a coronary event (MI or unstable angina) within the 5-year study period. Questions about the CHDRA results were based on a 4- or 5-point Likert scale.
of risk-score change). Any change to the frequency of lipid testing, glucose testing, medical examination, referrals, lipid-lowering therapy, LDL-C target level, antihypertension therapy, or further testing was counted as a change.

For lipid-lowering therapy, physicians could choose a LDL-C target and prescribe medical therapy alone (ie, statins or other drugs), lifestyle change, or a combination of therapy, or further testing was counted as a change. In 35% of the physician responses, changes were to therapy and a shift to more aggressive LDL-C targets in CHDRA, there was a shift from lifestyle-only to medical and lifestyle change. For cases reclassified to high risk by the CHDRA score, the physicians recommended adding ≥1 antihypertensive agent (Table 5). No significant change in aspirin therapy occurred after providing the CHDRA score.

When asked to identify the utility of the CHDRA to risk-stratify intermediate-risk patients, 19% responded “extremely valuable,” 52% said “valuable,” 26% responded “slightly valuable,” and 3% said “not valuable at all” (see Supporting Information, Appendix Table 2, in the online version of this article). There were no significant differences between specialties. Of the family practice and OB/GYN physicians, 57.4% and 60.7%, respectively, stated they were at least “likely” to recommend CHDRA to their colleagues, whereas cardiologists (46.0%) and internists (54.9%) responded as “likely” or “extremely likely” to recommend (see Supporting Information, Appendix Table 3, in the online version of this article). Overall, 81% indicated some likelihood of recommending the test to a colleague. In addition, 71.3% agreed or strongly agreed that CHDRA would significantly impact their management choices. Similarly, OB/GYN (94.1%), family practice (87.0%), internist (76.4%), and cardiologist (62%) physicians agreed or strongly agreed that the CHDRA test “provides valuable information that they did not know before,” whereas 73.3% agreed or strongly agreed that the CHDRA and its results are “likely to have a significant impact on patient behavior by presenting the information to patients” (see Supporting Information, Appendix Table 4, in the online version of this article).

**Discussion**

Using clinical vignettes drawn from real patient cases in the Marshfield Clinic Personalized Medicine Research Project, adding the CHDRA test to traditional CHD risk assessments resulted in significant changes in physicians’ clinical management of cardiovascular (CV) risk factors. More aggressive and targeted risk-factor management for patients reclassified from intermediate risk to high risk of experiencing a cardiac event was consistent across physician specialties, including internists, family practitioners, OB/GYNs, and cardiologists. The changes included appropriate cholesterol management, with a significant proportion of respondents lowering LDL targets, adding medical therapy to reach those targets, and increasing the frequency of follow-up. Physicians across all 4 specialties were more likely to prescribe additional antihypertensive therapies among patients reclassified upward. In general, most physicians found the tool valuable to assist in the clinical management of intermediate-risk patients, and most would recommend the test to their colleagues.

Improving risk stratification of intermediate-risk individuals is a primary goal of the major CV societies. Fewer than 20% of physicians report using a risk calculator, and most physicians misclassify patient risk for CHD events.7,13 In addition, traditional risk-factor algorithms, such as the ATP III guidelines, 57.6% were concordant with the ATP III guidelines, 57.6% were concordant  

![Image of Table 1: Survey-Respondent Demographics](https://example.com/table1.png)

**Table 1. Survey-Respondent Demographics**

| Physician Specialty | Internal Medicine, %, n = 51 | Family Practice, %, n = 54 | OB/GYN, %, n = 51 |
|---------------------|-------------------------------|---------------------------|------------------|
| **Age, y**          |                               |                           |                  |
| 25–34               | 4.0                           | 7.8                       | 5.6              |
| 35–44               | 28.0                          | 33.3                      | 31.5             |
| 45–54               | 36.0                          | 35.3                      | 20.4             |
| ≥55                 | 32.0                          | 23.5                      | 42.6             |
| **Male physicians** | 84.0                          | 74.5                      | 68.5             |
| Practice region     |                               |                           |                  |
| Northeast           | 54.0                          | 45.1                      | 24.1             |
| Midwest             | 6.0                           | 9.8                       | 24.1             |
| South               | 28.0                          | 29.4                      | 25.9             |
| West                | 12.0                          | 15.7                      | 25.9             |
| Practice type, solo | 8.0                           | 25.5                      | 16.7             |
| Practice duration, >10 years | 68.0 | 72.5 | 77.8 | 84.3 |

**Abbreviations:** OB/GYN, obstetrics and gynecology.  
6. P = 0.4 permutation χ² test of age and across the physician specialties.  
7. P = 0.1 χ² test of sex and across the physician specialties.
Table 2. Clinical Characteristics of the Patient Case Profiles

| Patient Case Profile | 1   | 2   | 3   | 4   | 5   | 6   | 7   | 8   |
|----------------------|-----|-----|-----|-----|-----|-----|-----|-----|
| Age, y               | 62  | 75  | 59  | 66  | 77  | 43  | 67  | 56  |
| Sex                  | M   | M   | F   | F   | F   | M   | M   | F   |
| Weight, kg           | 78.6| 105 | 93.2| 69.1| 66.4| 95.9| 77.3| 68.6|
| BMI, kg/m²           | 25.6| 36.2| 43  | 26.1| 22.9| 26.4| 28.3| 26.8|
| SBP/DBP, mm Hg       | 136/80| 136/88| 120/80| 164/80| 194/102| 140/82| 122/80| 152/82|
| TC, mg/dL            | 123 | 186 | 244 | 268 | 227 | 258 | 214 | 215 |
| LDL-C, mg/dL         | 77  | 104 | 159 | 178 | 129 | 178 | 136 | 160 |
| HDL-C, mg/dL         | 34  | 51  | 37  | 49  | 76  | 42  | 39  | 38  |
| TG, mg/dL            | 73  | 90  | 260 | 115 | 89  | 153 | 189 | 104 |
| CRP, mg/dL           | 8.3 | 6.3 | 7.2 | 6.7 | 5.8 | 4.7 | 3.5 | 4.5 |
| Fasting glucose, mg/dL| 89 | 84  | 79  | 72  | 126 | 90  | 115 | —   |
| Cr, mg/dL            | 0.8 | 1.4 | 0.8 | 1.2 | 0.8 | 1.1 | 1.2 | 0.7 |
| Medical history      | HTN | HTN, HLD | HTN, HLD | HTN, HLD | DM, HTN, HLD | HTN | HTN | None |
| Current medications  | CCB, diuretic, ASA | α-Blocker, β-blocker, ASA | β-Blocker | ACEI | ACEI, ASA | ARB, CCB | β-Blocker, diuretic | — |
| Family history of CAD| No  | No  | Yes | Yes | Yes | No  | No  | Yes |
| Initial risk category | Int | Int | Int | Int | Int | Int | Int | Int |
| CHDRA risk category  | High | High | High | High | Int | Low | High | Low |

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ASA, acetylsalicylic acid (aspirin); BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CCB, calcium channel blocker; CHDRA, coronary heart disease risk assessment; Cr, creatinine; CRP, C-reactive protein; DM, diabetes mellitus; F, female; HDL-C, high-density lipoprotein cholesterol; HLD, hyperlipidemia; HTN, hypertension; Int, intermediate; LDL-C, low-density lipoprotein cholesterol; M, male; SBP/DBP, systolic blood pressure/diastolic blood pressure; TC, total cholesterol; TG, triglycerides.

Framingham Risk Score, are known to be inadequate. It is likely that a biomarker-based approach improving risk stratification, particularly for intermediate-risk patients, would have value in clinical practice. Indeed, the American College of Preventive Medicine specifically indicated that newer biomarker-based risk stratification might be helpful for intermediate-risk individuals by stimulating more favorable risk-factor modification and greater preventive effort to substantially reduce the number of CV deaths.

Real-world clinical utility from identifying individuals at high risk for a CHD event and implementing primary prevention with aggressive risk-factor reduction is well established. Yet intermediate-risk individuals are often given less aggressive primary-prevention goals because escalating treatment intensity also increases the risk of side effects from medications, and balancing benefits and risks is the hallmark of sound primary prevention. Interestingly, no significant “relaxation” in risk-factor management occurred among those cases down-classified from intermediate to low risk. Such decisions are consistent with recent calls for prudent interpretation of novel risk-reclassification methods.

Physicians from various specialties saw value in using the CHDRA test results, with family practitioners and OB/GYN physicians seeing the most value. That is not surprising, considering that these physicians typically are the primary physicians for many intermediate-risk patients, but they may have less formal training and experience with CHD risk-assessment tools than cardiologists and internists. A 2005 statin-usage study showed that cardiologists manage only 4% of the intermediate-risk patients and 11% of the high-risk patients. Internists manage 40% of intermediate-risk and 31% of high-risk patients, and family practice/general medicine and other physicians manage 56% of the intermediate-risk patients and 58% of the high-risk patients. Providing user-friendly and appropriate risk tools to aid family practice and OB/GYN physicians is valuable. Internists and cardiologists also benefit from easy-to-use tools to further stratify intermediate-risk patients.

The ACCF/AHA Guidelines for Screening of Asymptomatic Adults recommend further risk stratification of intermediate-risk individuals, who are generally defined as having a calculated 10-year risk of CHD in the 10% to 20% range. The tests recommended for consideration, such as C-reactive protein and computed tomography,
have shown only modest improvement in clinical utility as assessed by clinical net reclassification of intermediate-risk individuals. The need for greater risk discrimination remains.

The guidelines are clear for treating high-risk individuals, or those with preexisting CHD, by considering lipid therapy, aspirin, antihypertensives, diabetes control, nutrition, physical activity, and influenza vaccine. Yet there are numerous individuals within the intermediate-risk category who may actually be at high risk and would benefit from appropriate therapy. Using statins, aspirin, angiotensin-converting enzyme inhibitors, and β-blockers has been estimated to reduce recurrent cardiac events by as much as 80%. If everyone received recommended prevention activities, MIs would be reduced by 63% in the next 30 years. The call for improved risk assessment in asymptomatic individuals is a

Table 3. Change in Cholesterol Targets and Prescribing in Cases 1, 2, 3, 4, and 7 That Were Reclassified From Intermediate to High Risk

| Frequency of Lipid Testing, After Seeing CHDRA Results | Drugs to Achieve | Lifestyle to Achieve |
|-------------------------------------------------------|------------------|---------------------|
|                                                       | LDL-C <70 mg/dL  | LDL-C <100 mg/dL   |
|                                                       | LDL-C <130 mg/dL | LDL-C <160 mg/dL   |
|                                                       | Any LDL-C Level  | None               |
| Therapy Choice, Initial                                |                  |                     |
| Drugs to achieve                                      |                  |                     |
| LDL-C <70 mg/dL                                       | 42               | 1\(^a\)             |
| LDL-C <100 mg/dL                                      | 36\(^b\)         | 91                  |
| LDL-C <130 mg/dL                                      | 6\(^b\)          | 19\(^b\)            |
| LDL-C <160 mg/dL                                      | 0\(^b\)          | 1\(^b\)             |
| Any LDL-C level                                       | 1\(^b\)          | 0\(^b\)             |
| Lifestyle to achieve                                   |                  |                     |
| LDL-C <70 mg/dL                                       |                  |                     |
| LDL-C <100 mg/dL                                      | 15\(^b\)         | 12\(^b\)            |
| LDL-C <130 mg/dL                                      | 2\(^b\)          | 9\(^b\)             |
| LDL-C <160 mg/dL                                      | 1\(^b\)          | 0\(^b\)             |
| None                                                   | 14\(^b\)         | 3\(^b\)             |

Abbreviations: CHDRA, coronary heart disease risk assessment; LDL-C, low-density lipoprotein cholesterol. \(^a\)Total count = 22; indicates less appropriate (less aggressive) lipid targets and/or therapy. \(^b\)Total count = 144; indicates more appropriate (aggressive) lipid targets and/or therapy.

Table 4. Change in Frequency of Lipid Testing in Cases 1, 2, 3, 4, and 7 That Were Reclassified From Intermediate to High Risk

| Frequency of Lipid Testing, After Seeing CHDRA Results | Each Month | Every 3 Months | Every 6 Months | Each Year | Every 2 Years | Every 5 Years | Never |
|-------------------------------------------------------|------------|----------------|----------------|-----------|---------------|---------------|-------|
| Frequency of Lipid Testing, Initial                    |            |                |                |           |               |               |       |
| 1/month                                               | 7          | 0\(^a\)        | 0\(^a\)        | 0\(^a\)   | 0\(^a\)       | 0\(^a\)       | 0\(^a\) |
| 1/3 months                                            | 6\(^a\)    | 73             | 2\(^a\)        | 0\(^a\)   | 0\(^a\)       | 0\(^a\)       | 1\(^a\) |
| 1/6 months                                            | 3\(^b\)    | 35\(^b\)       | 125            | 5\(^a\)   | 0\(^a\)       | 0\(^a\)       | 0\(^a\) |
| 1/year                                                | 1\(^b\)    | 9\(^b\)        | 45\(^b\)       | 76        | 0\(^a\)       | 0\(^a\)       | 0\(^a\) |
| 1/2 years                                             | 0\(^b\)    | 0\(^b\)        | 1\(^b\)        | 5\(^b\)   | 4             | 0\(^a\)       | 0\(^a\) |
| 1/5 years                                             | 0\(^b\)    | 0\(^b\)        | 0\(^b\)        | 1\(^b\)   | 0\(^a\)       | 1           | 0\(^a\) |
| Never                                                 | 0\(^b\)    | 0\(^b\)        | 0\(^b\)        | 0\(^b\)   | 0\(^b\)       | 0\(^b\)       | 0\(^b\) |

Abbreviations: CHDRA, coronary heart disease risk assessment. \(^a\)Total count = 9; indicates less appropriate (less aggressive) lipid testing frequency. \(^b\)Total count = 106; indicates more appropriate (aggressive) lipid testing frequency.

Clin. Cardiol. 36, 10, 621–627 (2013) MD Solomon et al. Further intermediate-risk stratification in CHD Published online in Wiley Online Library (wileyonlinelibrary.com) DOI:10.1002/clc.22185 © 2013 The Authors. Clinical Cardiology published by Wiley Periodicals, Inc.
persistent theme in clinical practice guidelines as a means to improve healthcare effectiveness and outcomes. ¹

Achieving optimal levels of serum cholesterol as set forth by the ATP III guidelines has a well-documented impact and is a key feature of the American Heart Association 2020 strategic goals (a 20% improvement in CV health and a 20% reduction in disease). ²¹ By demonstrating an impact on the actions physicians take in response to improvements in patients’ CHD risk assessment, the CHDRA tool may help to achieve the American Heart Association goals.

This study has limitations. Because the risk-stratification tool is an assessment of CV risk-factor management based on clinical vignettes, some physicians may respond differently than they would to a physical examination. Although the 206 physicians who completed the survey represent a diverse sample of US physicians, nonparticipating physicians may have different perceptions, knowledge, and practice patterns. This focused survey contained some questions that forced the respondent to choose a best answer within a finite set of possibilities. A physician’s clinical experience is seldom as unambiguous. Physicians were also focused on CHD in this survey and therefore may have done better than with typical asymptomatic patients. Although this demonstrates that using the CHDRA test prompted shifts in therapy that increased compliance with guidelines, changes in patient behavior and adherence to therapy recommendations were not assessed. Although it is believed that early detection of CHD risk will aid in preventing cardiac events, changing physician behavior supports, yet does not ensure, changes in patient behaviors.

Conclusion

The CHDRA test, a biomarker-based risk-stratification tool, has a positive clinical utility leading physicians to substantially change their management of CV risk factors for patients reclassified from intermediate to high risk. Given these findings, this tool could be a valuable addition to the risk-stratification arsenal for patients at intermediate risk of a CHD event. Although we did not evaluate patient-level findings in this study, there is evidence that additional information about risk stratification may positively affect patient behavior. ²² Future research should prospectively measure the CHDRA test impact on clinical management and patient behavior.

Acknowledgments

The authors acknowledge the expertise and involvement of David Cristofaro and Taylor Reyes of Actionable Research in helping to design and administer the survey.

References

1. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2010;56:2182–2199.
2. Wilson PW, D’Agostino RB, Levy D, et al. Prediction of coronary heart disease using risk factor categories. Circulation. 1998;97:1837–1847.
3. Lim LS, Haq N, Mahmood S, et al. Atherosclerotic cardiovascular disease screening in adults: American College of Preventive Medicine position statement on preventive practice. Am J Prev Med. 2011;40:381.e1–381.e10.
4. Khot UN, Khot MB, Bajzer CT, et al. Prevalence of conventional risk factors in patients with coronary heart disease. JAMA. 2003;290:888–904.
5. Mosca L, Linfante AH, Benjamin EJ, et al. National study of physician awareness and adherence to cardiovascular disease prevention guidelines. Circulation. 2005;111:499–510.
6. Schmieder RE, Goebel M, Bramlage P. Barriers to cardiovascular risk prevention and management in Germany—an analysis of the EUROMA study. Vase Health Risk Manag. 2012;8:177–186.
7. Montgomery AA, Fahey T, MacKintosh C, et al. Estimation of cardiovascular risk in hypertensive patients in primary care. Br J Gen Pract. 2000;50:127–128.
8. Ford ES, Giles WH, Mokdad AH. The distribution of 10-year risk for coronary heart disease among US adults: findings from the National Health and Nutrition Examination Survey III. J Am Coll Cardiol. 2004;43:1791–1796.
9. Cross DS, McCarty CA, Hytopoulos E, et al. Coronary risk assessment among intermediate risk patients using a clinical and biomarker based algorithm developed and validated in two population cohorts. Curr Med Res Opin. 2012;28:1819–1830.
10. McCarty CA, Wilke RA, Giampietro PF, et al. Marshfield Clinic Personalized Medicine Research Project (PMRP) design, methods and recruitment for a large population-based biobank. Personalized Med. 2005;2:49–79.
11. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation. 2004;110:227–259.
12. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002;106:3143–3421.
13. Eaton CB, Galliher JM, McBride PE, et al. Family physicians’ knowledge, beliefs, and self-reported practice patterns regarding hyperlipidemia: a National Research Network (NRR) survey. J Am Board Fam Med. 2006;19:46–53.
14. Yeboah J, McClelland RL, Polonsky TS, et al. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. JAMA. 2012;308:788–795.
15. Farley TA, Dalal MA, Mostashari F, et al. Deaths preventable in the U.S. by improvements in use of clinical preventive services. Am J Prev Med. 2010;38:600–609.
16. Ma J, Sehgal NL, Ayman JZ, et al. National trends in statin use by coronary heart disease risk category. PLoS Med. 2005;2:e123.
17. Greenland P. Should the resting electrocardiogram be ordered as a routine risk assessment test in healthy asymptomatic adults? *JAMA.* 2012;307:1530–1531.
18. Smith SC Jr, Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. *Circulation.* 2011;124:2458–2473.
19. Muntner P, Mann D, Wildman RP, et al. Projected impact of polypill use among US adults: medication use, cardiovascular risk reduction, and side effects. *Am Heart J.* 2011;161:719–725.
20. Heidenreich PA, Trogdon JG, Khavjou OA, et al. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation.* 2011;123:933–944.
21. Lloyd-Jones DM, Hong Y, Labarthe D, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction. *Circulation.* 2010;121:586–613.
22. Wyman RA, Gimelli G, McBride PE, et al. Does detection of carotid plaque affect physician behavior or motivate patients? *Am Heart J.* 2007;154:1072–1077.