Economic Outcomes of a Precision Medicine Blood Test To Assess Obstructive Coronary Artery Disease: Results from the PRESET Registry

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INTRODUCTION

Assessment of symptomatic patients suspected of having coronary artery disease (CAD) has been a growing challenge for primary care providers over the past few decades (Chou 2015, Rio 2015). Clinicians have raised concerns that defensive medicine has increased testing. In combination with the modest positive predictive value of cardiac stress testing, these factors may have contributed to a rising trend in cardiology referrals and increases in the use of costly and invasive tests and procedures (Chou 2015, Huffman 2011, Ko 2013, Ladapo 2014, Studdert 2005). Of particular concern has been the low yield of invasive coronary angiographies (ICA) performed in the United States (Patel 2010, Douglas 2015). From a managed care perspective, this trend translates into $5.9 billion spent in the United States on advanced cardiac tests and procedures, along with additional spending for associated complications (Rio 2015, Levin 2016). In response to this and other economic pressures, policy-makers have introduced accountable care organizations (ACOs) (Nyweide 2015, Schwartz 2015), implemented disease management programs (Scott 2000), and integrated diagnostic and procedural cost data into point-of-care decision support systems (Feldman 2013). Economic pressures have also stimulated scientific research into more effective and efficient diagnostic technologies.

Precision medicine holds significant promise for improving care and managing costs in cardiovascular care (Ashley 2015, Klemes 2012). A previously validated and commercially available blood test with an age/sex/gene expression score (ASGES) in this diagnostic workup has shown a 96% negative predictive value, as well as an 85% decreased likelihood of cardiac referral among low-score outpatients at 45 days. The objective was to explore the one-year cost implications of ASGES use among symptomatic outpatients.

Purpose: The evaluation of obstructive coronary artery disease (CAD) is inefficient and costly. Previous studies of an age/sex/gene expression score (ASGES) in this diagnostic workup have shown a 96% negative predictive value, as well as an 85% decreased likelihood of cardiac referral among low-score outpatients at 45 days. The objective was to explore the one-year cost implications of ASGES use among symptomatic outpatients.

Design: A prospective PRESET Registry (NCT01677156) enrolled stable, nonacute adult patients presenting with symptoms suggestive of obstructive CAD at 21 U.S. primary care practices.

Methodology: Demographics, clinical factors, and ASGES (defined as low ≤15 or elevated >15), as well as management plans post-ASGES, were collected. The economic endpoint analysis was based on the cost of cardiovascular-related tests, procedures, office visits, emergency room visits, and hospitalizations during one year after testing.

Results: The analysis included 566 patients, 51% of whom were women and the median age was 56. Forty-five percent had a low ASGES. The mean cost of cardiovascular care for patients in the year following ASGES was $1,647 for patients with a low ASGES versus $2,709 for those with an elevated score (39% reduction, P=.03 by Wilcoxon rank test). This relationship remained after multivariate analysis that adjusted for patient demographics and clinical covariates (P<.001).

Conclusion: The ASGES helped identify patients with low current likelihood of obstructive CAD. These patients had lower costs of cardiovascular care during one year of follow-up. Early reductions in cardiac referrals at 45 days among these patients persisted at one year.
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of referral to a cardiologist or for advanced cardiac testing in the first 45 days after testing (Ladapo 2017). However, the economic endpoints of this precision medicine test at one year have not been described. Assessing one-year economic outcomes is relevant because cost savings associated with reductions in early referrals may be offset by increases in down-stream referrals (Girod 2000). Therefore, the objective of this study was to examine the economic outcomes of a clinical decision strategy incorporating ASGES in the evaluation of outpatients with symptoms suggestive of obstructive CAD in a primary care setting. An additional area of interest was to determine whether early reductions in cardiac referrals seen among low ASGES patients translated into longer-term cost differences.

METHODS

Study tool

The ASGES blood test (Corus CAD, CardioDx Inc., Redwood City, Calif.) is a quantitative in vitro diagnostic test yielding an algorithmic score incorporating a gene expression profile of peripheral white blood cells together with the patient’s age and sex. The test assesses the current likelihood of obstructive CAD, defined as ≥1 atherosclerotic plaque causing ≥50% luminal diameter stenosis in a major coronary artery (≥1.5 mm lumen diameter), and it has been correlated with both invasive quantitative coronary angiography (QCA) and core-lab computed tomography angiography (CTA) (≥2.0 mm) (Thomas 2013, Rosenberg 2010).

Study population

The PRESET Registry (A Registry to Evaluate Patterns of Care Associated with the Use of Corus CAD in Real World Clinical Care Settings, NCT01677156) initially enrolled out-patients from 21 U.S. primary care practices between August 2012 and August 2014. The patients were evaluated by primary care providers with typical and atypical symptoms suggestive of obstructive CAD. Institutional review board approval was granted by Quorum Review Inc. All enrolled patients signed an approved informed consent form. Additional information about PRESET and ASGES validation studies has been previously published (Thomas 2013, Ladapo 2017, Lansky 2012).

The ASGES blood test was conducted for all patients participating in the study, and the report about the results was provided to the clinician within a median of three days from the blood draw. For all enrolled patients, venous blood samples were collected in a PAXgene RNA Blood Tube (PreAnalytix, Valencia, Calif.) during the outpatient clinic visit. Samples were shipped to a single CLIA-certified (Clinical Laboratory Improvement Amendments) and CAP-accredited (College of American Pathologists) laboratory (CardioDx Inc.) for analysis. Clinicians received information on score interpretation and the likelihood of current ob-structive CAD in tested patients and incorporated the ASGES into their practices at their discretion. Baseline demographic and clinical data as well as follow-up cardiac referrals were recorded at 45-day follow-up. Hospital and emergency department admissions as well as any further referrals to advanced cardiac testing or follow-up visits were monitored and recorded in the registry database during the one year after ASGES.

Study inclusion criteria included outpatients presenting with either a typical (e.g., chest pain and shortness of breath) or at least one atypical (jaw pain, palpitations, malaise, fatigue, burning in the chest) symptom plus a cardiovascular risk factor.

Study exclusion criteria included patients with a history of myocardial infarction (MI) or revascularization procedures, current diagnosis of type 1 or 2 diabetes or hemoglobin A1c > 6.5%, suspected acute MI, high-risk unstable angina, New York Heart Association class III or IV heart failure symptoms, cardiomyopathy with ejection fraction ≤35%, severe cardiac val-vular diseases, current systemic infectious or inflammatory conditions, or recent treatment with immuno-suppressive or chemotherapeutic agents. Detailed information on the study design, patient flow chart, and exclusion criteria of the PRESET Registry have been previously described (Ladapo 2017).

Study data and analytic approach for costs

To estimate the cost of outpatient cardiac tests, the 2016 Medicare Physician Fee Schedule (MPFS) was used, including the technical component (CMS 2017a). For inpatient procedures, we combined physician fees with MEDPAR Inpatient Hospital Data for fiscal year 2015 (CMS 2017b). These data were used to derive mean reimbursements for diagnosis-related groups by divid-ing total Medicare reimbursement by total number of discharges in 2015.

To estimate the cost of major adverse cardiac events (MACE), Healthcare Cost and Utilization Project (HCUP) data were used, with values adjusted to 2015 U.S. dollars (HCUP 2014). We estimated the cost of outpatient office visits to be $168 per visit, based on Medicare reimbursement rates, ir-
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Total cost of care included cardiovascular-related office visits, tests, hospital admissions, and emergency department visits. These data were evaluated for a period of one year after the index ASGES. Results for cardiovascular referrals within the first 45 days were reported in a prior PRESET Registry publication. Those results showed patients with a low versus an elevated ASGES were less likely to be referred to cardiology or advanced cardiac testing (10% vs. 44%, respectively; adjusted odds ratio 0.18, \( P<0.001 \)) (Ladapo 2017).

**Data analysis**

Descriptive statistics for univariate and multivariate analyses, including mean, median, interquartile range, standard deviation, counts and percentages, and counts of missing data records, were calculated for continuous and categorical variables. Tests for statistical association between cost of care and ASGES classification as a binary variable (low score ≤15 vs. elevated >15) and as a continuous variable were performed using Wilcoxon rank testing and trend testing. Logistic regression and log-linear regression were performed and adjusted for patient characteristics and clinical covariates associated with obstructive CAD, including hypertension, dyslipidemia, smoking, race/ethnicity, and body mass index (BMI). A \( P \) value less than .05 was considered statistically significant. All analyses were performed using R (R Development 2011).

**RESULTS**

The economic endpoint analysis included 566 patients from the PRESET registry with one-year follow-up data from 21 primary care sites across the U.S. The cohort was 51% female and had a median age of 56 years. The median BMI was 30, 17% were smokers (smoked at least one cigarette in the past 30 days), and dyslipidemia and hypertension were present in 53% and 46% of patients, respectively. Chest pain and other typical anginal symptoms were noted in 37% of patients. Other patients had atypical symptoms suggestive of obstructive CAD, such as heartburn, dizziness, palpitations, back pain, and malaise in combination with a common cardiovascular risk factor. Patients had a median ASGES of 18, with 252 (45%) patients with ASGES ≤15 (Table 1).

The mean cost of care for these symptomatic patients being evaluated for obstructive CAD, including the ASGES and the primary office visit, was $2,243 (interquartile range, $1,413–$1,748) over the one-year period. The cost of care varied significantly by ASGES (Table 2). Using the ASGES as a binary variable, the mean cost of care was 39% lower for the low-ASGES patients than for the elevated-ASGES patients: $1,647 (interquartile range, $1,413–$1,581) for low-ASGES patients versus $2,709 (interquartile

| TABLE 1: Clinical and demographic characteristics of patients in the PRESET registry (N=566) |
|----------------------------------|----------------------------------|----------------------------------|
| Characteristic                  | Overall population              | Low (≤15) ASGES patients (n=252) | Elevated (>15) ASGES patients (n=314) |
| Median age (range)              | 56 (22–96)                      | 50 (22–77)                        | 61 (27–96)                          |
| Female                          | 288 (51%)                       | 218 (77%)                        | 70 (22%)                           |
| Race                            |                                  |                                  |                                  |
| White                           | 484 (86%)                       | 196 (78%)                        | 288 (92%)                          |
| Black                           | 59 (10%)                        | 43 (17%)                         | 16 (5%)                            |
| Asian                           | 11 (2%)                         | 8 (3%)                           | 3 (1%)                             |
| American Indian or Alaska Native| 1 (<1%)                         | 1 (<1%)                          | 0 (<1%)                            |
| Other                           | 11 (2%)                         | 4 (2%)                           | 7 (2%)                             |
| Median BMIa (range)             | 29.6 (15.3–71.6)                | 29.7 (17.2–71.6)                 | 29.4 (15.3–67.2)                   |
| Mean systolic BPb (SD)          | 129.7 (+16.8)                   | 126.5 (+16.8)                    | 132.3 (+17.1)                      |
| Diastolic BPb (SD)              | 76.9 (+11.6)                    | 76.5 (+11.7)                     | 77.3 (+11.6)                       |
| Smoking status                  |                                  |                                  |                                  |
| Current                         | 98 (17%)                        | 48 (19%)                         | 50 (16%)                           |
| Quit within last month          | 3 (1%)                          | 1 (0%)                           | 2 (1%)                             |
| Quit > 1 month ago              | 117 (21%)                       | 38 (15%)                         | 79 (25%)                           |
| Never                           | 348 (61%)                       | 165 (65%)                        | 183 (61%)                          |
| Typical anginal symptoms/chest pain | 212 (37%)                    | 109 (37%)                        | 113 (36%)                          |
| Hypertension                    | 260 (46%)                       | 91 (36%)                         | 169 (54%)                          |
| Dyslipidemia                    | 298 (53%)                       | 102 (41%)                        | 196 (63%)                          |

ASGES=age/sex/gene expression score, BMI=Body mass index, BP=blood pressure, SD=standard deviation.

\( ^a_n=558, ^b_n=559. \)
**DISCUSSION**

The ASGES has been previously demonstrated to more accurately identify patients with obstructive CAD than Diamond–Forrester scores, Morise scores, and stress myocardial perfusion imaging (MPI) (Thomas 2013).

In this prospective, community-based registry of patients evaluated for suspected obstructive CAD, the ASGES demonstrated economic utility in its association with cardiovascular costs in the year after testing. During one year of follow-up, the cost of cardiovascular care was 39% lower for patients with a low ASGES than those with an elevated score. In addition, there was a strong correlation between increasing ASGES and increasing health care costs during the follow-up period. This finding remained robust in a multivariate model after adjusting for clinical factors associated with obstructive CAD.

Importantly, by differentiating patients who subsequently accrued relatively low or high health care costs at one year, the ASGES demonstrated...
that its association with reductions in cardiovascular referrals at 45 days among patients with a low ASGES is durable over a longer time period. This analysis extends our previous findings by demonstrating the significant relationship between ASGES and subsequent cardiac care, including noninvasive testing, cardiac catheterization, and health care utilization associated with costly MACE.

While an association between baseline test results and subsequent noninvasive and invasive testing and costs has been demonstrated for stress and coronary CTA (Shaw 1999, Min 2012, Hachamovitch 2012), our study is the first to report this finding for a precision medicine test for obstructive CAD. The fully quantitative format of the ASGES is also a particularly unique characteristic. Analogous metrics for stress MPI include the summed stress score (SSS) and summed rest score (SRS), but these scores have limitations and have been criticized for ambiguities related to their clinical interpretation. In the SPARC (Study of Myocardial Perfusion and Coronary Anatomy Imaging Roles in Coronary Artery Disease) registry, Hachamovitch (2012) reported that postimaging referrals for catheterization increased in proportion to the degree of abnormality seen in initial tests, but the intensity of this change was limited. In contrast, interpretation of the ASGES is unambiguous and has been validated to represent the current likelihood of obstructive CAD.

With regard to the cost of care, we previously evaluated the cost-effectiveness of the ASGES and reported a cost-effectiveness ratio of $72,000 per quality-adjusted life-year (QALY) compared with a no-testing strategy (Phelps 2014). Its economic value is therefore comparable to other diagnostic technologies for evaluating suspected CAD (Ladapo 2009, Garber 1999, Kuntz 1999). While our prior work in ASGES cost-effectiveness was based on the application of decision-analytic methods and modeling, the current study could inform real-world estimates of cost-effectiveness by incorporating community practice patterns (Hochheiser 2014).

Methodological differences complicate comparisons to other observational studies on cost of care. For example, in Shaw (1999) et al., three-year costs of care (with stress MPI priced at $2,387–$3,010 in 1995 U.S. dollars) included the costs of noninvasive tests, catheterization, and cardiac hospitalizations based on micro-cost accounting system estimates and Medicare hospital charge data. In a similar analysis of the SPARC registry, two-year costs of care (with stress MPI priced at $3,965 in 2008 U.S. dollars) included a similar combination of events as the analysis by Shaw et al (Hlatky 2014). These cost estimates were based on the Medicare fee schedule. Our results suggest that the cost of ASGES is likely to be comparable.

Limitations
There are several limitations to our analysis. First, our analysis does not include a control group. It is not possible, therefore, to attribute health care costs definitively to ASGES-directed care versus usual care. However, to address this limitation, we conducted logistic regression analysis with adjustments for confounders and identified a statistically independent association between the ASGES and cost of care in a one-year follow-up period.

Second, our data did not provide insights about the clinical discussions between patients and physicians af-
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Diagnostic testing for obstructive CAD is common, and test results along with sociodemographic factors may be influential in these decisions (Patel 2010, Douglas 2015). Further studies may address the economic value of ASGES-directed care versus usual care in a head-to-head comparison.

Another potential limitation is the focus on costs associated with cardiovascular care only. Costs from noncardiovascular office visits, tests, and hospital admissions were excluded from this analysis to minimize the influence of outlier non-CV-related utilization on our results. This methodology has been used in other related studies (Weisman 2015, Clark 2005). Because the follow-up period of one year was relatively short, we were also unable to report the association of low versus high ASGES on costs over a longer period of time. Finally, we did not enroll patients whose initial diagnostic test was stress nuclear or stress echocardiography, rather than ASGES; therefore, we cannot make cost comparisons between these diagnostic strategies and the ASGES.

CONCLUSION

The ASGES blood test helped identify patients who were unlikely to have obstructive CAD. These patients had lower costs of cardiovascular care during one year of follow-up. Early reductions in cardiac referrals among these patients at 45 days persisted at one year. Taken together, these findings support the economic utility of the ASGES as a precision medicine blood test for symptomatic outpatients with suspected obstructive CAD.

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REFERENCES


