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

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ABSTRACT

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.

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, policymakers 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) can be used in the diagnostic workup of symptomatic patients suspicious for obstructive CAD. In the COMPASS study in a cohort of symptomatic men and women referred for myocardial perfusion imaging, the ASGES has been shown to have a 96% negative predictive value and 89% sensitivity (Thomas 2013). These results suggest that the ASGES may help address a growing national concern with reducing unnecessary testing and increasing the precision of testing, which the Choosing Wisely (ABIM 2017), Image Gently (Image Gently Alliance 2017), and All of Us (NIH 2017) initiatives also seek to address.

The recent PRESET Registry showed that patients with a low ASGES had an 85% decreased odds 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 downstream 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).

Some abbreviations used in this article

ASGES – age/sex/gene expression score
CAD – coronary artery disease
CTA – computed tomography angiography
MI – myocardial infarction
MPI – myocardial perfusion imaging

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 outpatients 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 obstructive 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 valvular diseases, current systemic infectious or inflammatory conditions, or recent treatment with immunosuppressive 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 dividing 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, irrespective of whether the visit was to a primary care physician or specialist.

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*<.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).

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 BMI[a] (range)	29.6 (15.3–71.6)	29.7 (17.2–71.6)	29.4 (15.3–67.2)
Mean systolic BP[b] (SD)	129.7 (±16.8)	126.5 (±16.8)	132.3 (±17.1)
Diastolic BP[b] (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.

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 2
Costs and utilization in low ASGES vs. elevated ASGES groups

Test or visit	Low ASGES	Elevated ASGES	Cost per unit	Data source for cost
CABG	0	1	$27,745	HCUP
Stroke or TIA (hospital admission)	1	2	$13,565	HCUP
PCI (revascularization with stent)	0	10	$12,604	CMS Physician Fee Schedule (92933)
ICA (inpatient without MCC)	0	4	$4,060	CMS Physician Fee Schedule (93454) plus MS-DRG (303)
Stroke or TIA (ED visit)	1	1	$3,255	CMS Physician Fee Schedule (99218) plus MS-DRG (066)
ICA (outpatient)	0	2	$2,814	CMS Physician Fee Schedule (93454)
ED visit (high/urgent severity)	2	1	$1,542	MEPS
ED visit (moderate severity)	0	1	$1,486	MEPS
Myocardial perfusion imaging	10	53	$1,189	CMS Physician Fee Schedule (78452)
Clinic visit	136	134	$168	2013 CMS Physician Fee Schedule (99204) adjusted for 2015

CABG=coronary artery bypass graft, ED=emergency department, HCUP=Healthcare Cost and Utilization Project, ICA=invasive coronary angiography, MCC=major complications or comorbidities, MEPS=Medical Expenditure Panel Survey, PCI=percutaneous coronary intervention, TIA=transient ischemic attack.

range, $1,413–$1,913) for elevated–ASGES patients (*P*=.03 by Wilcoxon rank test). After multivariate adjustment for patient demographics and clinical covariates, the mean cost of care was 17% lower in low-ASGES patients than those with an elevated score (*P*<.001 by log linear regression) (Table 3). The demographic factors of nonwhite race and current smoker were also independently associated with higher costs.

There was also a statistically significant trend in increased costs associated with every 5-unit increase in ASGES (*P*<.001). The mean cost was $1,561 for patients with ASGES 1–5, $2,140 for patients with ASGES 16–20, and $3,987 for patients with ASGES 36–40 (Figure).

During one year of follow-up, there was no evidence that reductions in referrals for additional cardiovascular testing among patients with a low ASGES at 45 days were offset later on by compensatory testing.

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

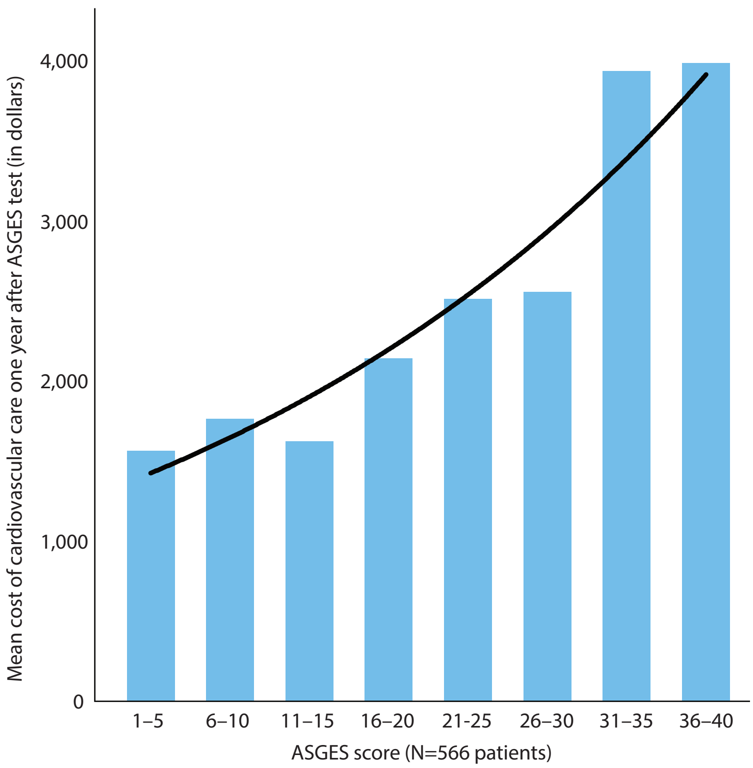
TABLE 3
Log-linear regression model of costs in the year after testing for ASGES

Predictor (or variable)	Estimate	95% CI		*P* value
Low (≤15) ASGES	0.83	0.76	0.90	<0.0001
White race	0.88	0.78	0.99	0.04
BMI ≥30	1.00	0.92	1.09	0.95
Current smoker	1.12	1.01	1.24	0.03
Hypertension	0.96	0.88	1.05	0.35
Dyslipidemia	1.03	0.95	1.12	0.52

ASGES=age/sex/gene expression score, BMI=body mass index, CI=confidence interval.

FIGURE

As ASGES goes up, so do cardiovascular costs



ASGES=age/sex/gene expression score.

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 after testing for ASGES, so the reduced follow-up costs might be the result of patients refusing follow-up care after testing for ASGES or the resolution of their symptoms. Nonetheless, our analysis reports actual rather than prescribed utilization of health care resources after testing. Furthermore, a recent meta-analysis demonstrated analogous variability in referral to invasive coronary angiography after cardiac stress test results, and similar variability was demonstrated in a large registry of patients referred for MPI, positron emission tomography, or coronary CTA (Ladapo 2013). A third limitation was that we did not collect detailed information about patient or physician preferences. While we know that higher ASGES was associated with a higher likelihood of cardiac referral, we were limited in our insights about reasons for variation in referral rates among both low-score and high-score patients. However, our previous studies show that the variation in referral rates after initial 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 non-cardiovascular 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 that 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

ABIM (American Board of Internal Medicine). Choosing Wisely. www.choosingwisely.org. Accessed April 18, 2018.

Ashley EA. The precision medicine initiative: a new national effort. *JAMA*. 2015;313(21):2119–2120.

CMS (Centers for Medicare & Medicaid Services). Physician fee schedule. Nov. 2, 2017a. www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/PhysicianFeeSched. Accessed April 18, 2018.

CMS. MEDPAR limited data set (LDS) — hospital (national). July 27, 2017b. www.cms.gov/Research-Statistics-Data-and-Systems/Files-for-Order/LimitedDataSets/MEDPARLDSHospitalNational.html. Accessed April 18, 2018.

Chou R; High Value Care Task Force of the American College of Physicians. Cardiac screening with electrocardiography, stress echocardiography, or myocardial perfusion imaging: advice for high-value care from the American College of Physicians. *Ann Intern Med.* 2015;162(6):438–447.

Clark MA, Bakhai A, Pelletier EM, Cohen DJ. Clinical and economic effects of coronary restenosis after percutaneous coronary intervention in a managed care population. *Manag Care.* 2005;14(4):42–44,46–51.

Douglas PS, Hoffmann U, Patel MR, et al. Outcomes of anatomical versus functional testing for coronary artery disease. *N Engl J Med.* 2015;372(14):1291–1300.

Feldman LS, Shihab HM, Thiemann D, et al. Impact of providing fee data on laboratory test ordering: a controlled clinical trial. *JAMA Intern Med.* 2013;173(10):903–908.

Garber AM, Solomon NA. Cost-effectiveness of alternative test strategies for the diagnosis of coronary artery disease. *Ann Intern Med.* 1999;130(9):719–728.

Girod CS, Axene DV. Prospective value-based assessment of new health care technologies and practices. *Manag Care.* 2000;9(8):38–40,43–47.

Hachamovitch R, Nutter B, Hlatky MA, et al. Patient management after noninvasive cardiac imaging results from SPARC (Study of Myocardial Perfusion and Coronary Anatomy Imaging Roles in Coronary Artery Disease). *J Am Coll Cardiol.* 2012;59(5):462–474.

HCUP (Healthcare Cost and Utilization Project). HCUP projections. Acute myocardial infarction (AMI) and acute stroke 2003 to 2014. Report #2014-02. Aug. 18, 2014. www.hcup-us.ahrq.gov/reports/projections/2014-02.pdf. Accessed April 18, 2018.

Hlatky MA, Shilane D, Hachamovitch R, et al. Economic outcomes in the Study of Myocardial Perfusion and Coronary Anatomy Imaging Roles in Coronary Artery Disease registry: the SPARC study. *J Am Coll Cardiol.* 2014;63(10):1002–1008.

Hochheiser LI, Juusola JL, Monane M, Ladapo JA. Economic utility of a blood-based genomic test for the assessment of patients with symptoms suggestive of obstructive coronary artery disease. *Popul Health Manag.* 2014:17(5):287–296.

Huffman MD, van Geertruyden PH. Does low pre-test probability of coronary artery disease reflect overuse of stress testing? *JACC Cardiovasc Imaging.* 2011;4(10):1143–1144.

Image Gently Alliance. Have-a-heart and Image Gently. www.imagegently.org/Procedures/Cardiac-Imaging. Accessed April 18, 2018.

Klemes A, Seligmann RE, Allen L, et al. Personalized preventive care leads to significant reductions in hospital utilization. *Am J Manag Care.* 2012;18(12):453–460.

Ko DT, Tu JV, Austin PC, et al. Prevalence and extent of obstructive coronary artery disease among patients undergoing elective coronary catheterization in New York State and Ontario. *JAMA.* 2013;310(2):163–169.

Kuntz KM, Fleischmann KE, Hunink MG, Douglas PS. Cost-effectiveness of diagnostic strategies for patients with chest pain. *Ann Intern Med.* 1999;130(9):709–718.

Ladapo JA, Blecker S, Douglas PS. Physician decision making and trends in the use of cardiac stress testing in the United States: an analysis of repeated cross-sectional data. *Ann Intern Med.* 2014;161(7):482–490.

Ladapo JA, Blecker S, Elashoff MR, et al. Clinical implications of referral bias in the diagnostic performance of exercise testing for coronary artery disease. *J Am Heart Assoc.* 2013;2(6):e000505.

Ladapo JA, Budoff M, Sharp D, et al. Clinical utility of a precision medicine test evaluating outpatients with suspected obstructive coronary artery disease. *Am J Med.* 2017;130(4):482.e11–482.e17.

Ladapo JA, Jaffer FA, Hoffmann U, et al. Clinical outcomes and cost-effectiveness of coronary computed tomography angiography in the evaluation of patients with chest pain. *J Am Coll Cardiol.* 2009;54(25):2409–2422.

Lansky A, Elashoff MR, Ng V, et al. A gender-specific blood-based gene expression score for assessing obstructive coronary artery disease in nondiabetic patients: results of the Personalized Risk Evaluation and Diagnosis in the Coronary Tree (PREDICT) trial. *Am Heart J.* 2012; 164(3):320–326.

Levin DC, Parker L, Halpern EJ, Rao VM. Recent trends in imaging for suspected coronary artery disease: what is the best approach? *J Am Coll Radiol.* 2016;13(4):381–386.

Min JK, Koduru S, Dunning AM, et al. Coronary CT angiography versus myocardial perfusion imaging for near-term quality of life, cost and radiation exposure: a prospective multicenter randomized pilot trial. *J Cardiovasc Comput Tomogr.* 2012;6(4):274–283.

NIH (National Institutes of Health). All of Us research program. https://allofus.nih.gov. Accessed April 18, 2018.

Nyweide DJ, Lee W, Cuerdon TT, et al. Association of Pioneer Accountable Care Organizations vs traditional Medicare fee for service with spending, utilization, and patient experience. *JAMA.* 2015;313(21):2152–2161.

Patel MR, Peterson ED, Dai D, et al. Low diagnostic yield of elective coronary angiography. *N Engl J Med.* 2010;362:886–895.

Phelps CE, O'Sullivan AK, Ladapo JA, et al. Cost effectiveness of a gene expression score and myocardial perfusion imaging for diagnosis of coronary artery disease. *Am Heart J.* 2014;167(5):697.e2–706.e2.

R Development Core Team. *R: a language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing. 2011. www.R-project.org. Accessed April 19, 2018.

Rio P, Ramos R, Pereira-da-Silva T, et al. Yield of contemporary clinical strategies to detect patients with obstructive coronary artery disease. *Heart Int.* 2015;10(1):12–19.

Rosenberg S, Elashoff MR, Beineke P, et al. Multicenter validation of the diagnostic accuracy of a blood-based gene expression test for assessing obstructive coronary artery disease in nondiabetic patients. *Ann Intern Med.* 2010;153(7):425–434.

Schwartz AL, Chernew ME, Landon BE, McWilliams JM. Changes in low-value services in year 1 of the Medicare Pioneer Accountable Care Organization program. *JAMA Intern Med.* 2015;175(11):1815–1825.

Scott I, Harper C, Clough A, West M. WESTCOP: a disease management approach to coronary artery disease. *Aust Health Rev.* 2000;23(2):96–112.

Shaw LJ, Hachamovitch R, Berman DS, et al. The economic consequences of available diagnostic and prognostic strategies for the evaluation of stable angina patients: an observational assessment of the value of precatheterization ischemia. Economics of Noninvasive Diagnosis (END) Multicenter Study Group. *J Am Coll Cardiol.* 1999;33(3):661–669.

Studdert DM, Mello MM, Sage WM, et al. Defensive medicine among high-risk specialist physicians in a volatile malpractice environment. *JAMA.* 2005;293:2609–2617.

Thomas GS, Voros S, McPherson JA, et al. A blood-based gene expression test for obstructive coronary artery disease tested in symptomatic nondiabetic patients referred for myocardial perfusion imaging the COMPASS study. *Circ Cardiovasc Genet.* 2013;6(2):154–162.

Weisman SM, Brooks EA. Costs and benefits of bundled community-based screening for carotid artery stenosis, peripheral artery disease, and abdominal aortic aneurysm. *Manag Care.* 2015;24(1):45–53.