An Age- and Sex-Specific Peripheral Blood Gene Expression Score Correlates With Future Cardiovascular Events: Insights From the PROMISE Trial

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INTRODUCTION

- In patients presenting with symptoms suggesting obstructive coronary artery disease (oCAD), improved diagnostic and prognostic biomarkers are needed.
- Improved diagnosis and risk stratification can inform:
  - Decisions about invasive diagnostic testing
  - Intensity of risk factor modification
  - Search for alternative causes of symptoms
- An Age- and Sex-specific Gene Expression Score (ASGES) is a novel, blood-based biomarker validated for diagnosing oCAD in nondiabetic patients.
  - The ASGES is reported as a score from 1–40
  - An ASGES >15 is associated with higher likelihood of oCAD
- The Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) was a randomized controlled trial in outpatients presenting with symptoms suggestive of oCAD comparing two diagnostic testing strategies:
  - Coronary computed tomographic angiography (CTA)
  - Functional stress testing
- The PROMISE trial biorepository banked baseline biologic samples including whole blood for RNA analyses

OBJECTIVES

- Confirm the association between the ASGES and oCAD in nondiabetic patients in a lower risk population
- Assess whether the ASGES is predictive of CAD-related events in nondiabetic patients
- Compare risk of events in patients with a low ASGES vs. negative/low-risk noninvasive test result

METHODS

- The ASGES was determined using an algorithm that incorporates age, sex, and the peripheral blood expression of 23 genes measured by real-time PCR in an automated fashion in the CardioDx CLIA laboratory.
- Of the 3742 patients who participated in the PROMISE biorepository, 809 with diabetes, 439 who failed sample quality analysis, and 141 on anti-inflammatory medications were excluded.
- Definitions:
  - Obstructive CAD:
    - ≥70% stenosis in a main coronary artery or ≥50% left main stenosis using CTA data
  - Extent of CAD was defined based on maximum percent stenosis using CTA data.
  - Primary composite clinical endpoint:
    - Death from any cause
    - Myocardial infarction (MI)
    - Unstable angina hospitalization (UA)
    - Revascularization
- Statistical analysis
  - ASGES as continuous and binary (> or ≤15)
  - Logistic regression for oCAD and extent of CAD models
  - Cox-proportional hazard regression, c-index, and net reclassification index (NRI) for clinical endpoint models
  - Multivariate models adjusting for Framingham Risk Score (FRS)

RESULTS

1) 2370 patients (95% of PROMISE nondiabetic patients) met inclusion/exclusion criteria

Table 1. Baseline Demographic and Disease Related Characteristics by Age- and Sex-specific Gene Expression Score (ASGES)

Characteristic	ASGES Category		Total	P-value
	ASGES ≤15 (N=1058)	ASGES >15 (N=1312)	(N=2370)	
Age, y Mean (SD)	59.2 (6.02)	61.3 (9.55)	60.3 (8.23)	<.001
Sex				<.001
Female	1020/1058 (96.4%)	224/1312 (17.1%)	1244/2370 (52.5%)	
Race				<.001
Multiracial	12/1056 (1.1%)	8/1308 (0.6%)	20/2364 (0.8%)	
White	929/1056 (88.0%)	1221/1308 (93.3%)	2150/2364 (90.9%)	
Black	97/1056 (9.2%)	63/1308 (4.8%)	160/2364 (6.8%)	
Other	18/1056 (1.7%)	16/1308 (1.2%)	34/2364 (1.4%)	
Cardiac risk factors				
Hypertension	651/1058 (61.5%)	782/1312 (59.6%)	1433/2370 (60.5%)	.340
Dyslipidemia	715/1058 (67.6%)	838/1312 (63.9%)	1553/2370 (65.5%)	.059
Peripheral arterial disease or cerebrovascular disease	61/1058 (5.8%)	68/1312 (5.2%)	129/2370 (5.4%)	.534
Metabolic syndrome	253/1058 (23.9%)	365/1312 (27.8%)	618/2370 (26.1%)	.031
Smoker				<.001
Never	551/1058 (52.1%)	612/1312 (46.6%)	1163/2370 (49.1%)	
Current smoker (within past 2 weeks)	200/1058 (18.9%)	217/1312 (16.5%)	417/2370 (17.6%)	
Former smoker	307/1058 (29.0%)	483/1312 (36.8%)	790/2370 (33.3%)	
Family history of premature CAD	380/1053 (36.1%)	372/1306 (28.5%)	752/2359 (31.9%)	<.001
Depression	337/1058 (31.9%)	227/1312 (17.3%)	564/2370 (23.8%)	<.001
Sedentary lifestyle	512/1055 (48.5%)	510/1308 (39.0%)	1022/2363 (43.3%)	<.001
Framingham risk score (2008) Mean (SD)	11.2 (6.41)	23.7 (12.47)	18.1 (11.9)	<.001
Body mass index, kg/m² Mean (SD)	30.0 (6.26)	30.0 (5.33)	30.0 (5.76)	.512

2) In CTA arm, oCAD associated with ASGES >15

- 115 of 1137 (10.1%) had oCAD
- Odds ratio = 2.5 [95% CI, 1.6–3.8], *P* <0.001
- Higher extent of CAD associated with continuous ASGES (Figure 1)

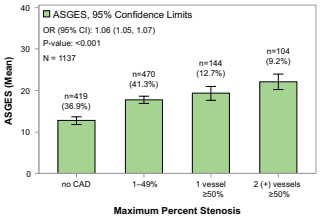

Figure 1. Association of ASGES and Extent of CAD Odds ratio reflects association between a 1 unit increase in continuous ASGES (range 1–40) and risk of higher extent of CAD category

3) ASGES > 15 associated with higher risk of primary clinical endpoint (Table 2, Figure 2)

- Primary endpoint occurred in 143 of 2370 (6%) over 25 months median follow-up
- Primary endpoint — driven by revascularization — remained associated after adjustment for FRS (Table 2)

Table 2. Association Between ASGES (>15 versus ≤15) and Clinical Outcomes.

Characteristic	Unadjusted		Adjusted	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Death/MI/UA/revasc.	2.64 (1.80–3.89)	<.001	1.70 (1.10–2.64)	.017
Death/MI/UA	1.76 (1.02–3.02)	.042	0.98 (0.52–1.87)	.960
Death	1.28 (0.60–2.71)	.520	0.74 (0.30–1.83)	.508
MI	2.66 (0.73–9.65)	.138	1.51 (0.35–6.59)	.583
UA	2.39 (0.87–6.58)	.091	1.34 (0.41–4.35)	.625
Revasc.	3.94 (2.34–6.65)	<.001	2.69 (1.52–4.79)	<.001

4) Event rates in patients with ASGES ≤15 (n = 1058, 3.2%) were similar to those with negative/low-risk noninvasive test results (n = 1963, 2.6%)

5) The ASGES provided independent and incremental information beyond noninvasive test results for the primary endpoint (Table 3)

- An ASGES >15 associated with primary endpoint independent of noninvasive test result: OR = 2.27 [95% CI 1.51–3.42], *P*<.001

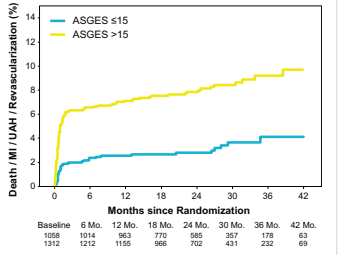

Figure 2. Association of ASGES and Risk of CAD Related Events Unadjusted Kaplan-Meier curves for patients with ASGES >15 vs. ≤15.

Table 3. Adding ASGES to Noninvasive Testing for Predicting Primary Composite Endpoint (n = 2255[a]).

	C-Statistic (95% CI)			NRI		
	Model 1[b]	Model 2[c]	Difference (95% Bootstrap CI)[d]	Continuous NRI (95% Bootstrap CI)	Event NRI	Nonevent NRI
ASGES (≤15, >15)	0.758 (0.716–0.800)	0.794 (0.751–0.836)	0.036 (0.011–0.061)	43.2% (23.5%–59.9%)	50.4%	-7.3%
Continuous ASGES	0.758 (0.716–0.800)	0.811 (0.767–0.855)	0.053 (0.024–0.081)	41.1% (20.5%–59.4%)	32.7%	8.4%

NRI, net reclassification index.
[a]Patients with ASGES and interpretable initial noninvasive test results.
[b]Model 1 relates noninvasive test results to primary composite endpoint.
[c]Model 2 relates noninvasive test results and age- and sex-specific gene expression score (ASGES) to primary composite endpoint.
[d]Based on 100 bootstrap samples.

SUMMARY AND CONCLUSIONS

- An ASGES measured at baseline in the PROMISE study was associated with obstructive CAD in nondiabetic patients.
- A higher ASGES was associated with a higher rate of revascularization procedures independent of Framingham risk score.
- Patients with an ASGES <15 had an event rate that was similar to those with negative/low-risk noninvasive test results.

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DISCLOSURES

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