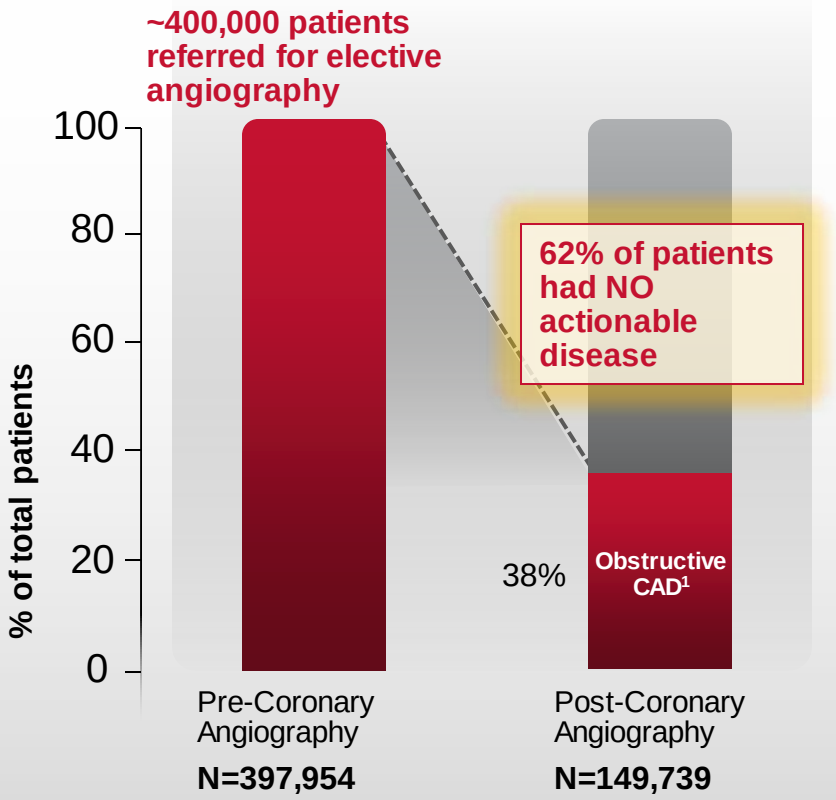
Vast Majority of Patients Have No Obstructive CAD at Elective Cath in U.S.

The NEW ENGLAND JOURNAL of MEDICINE



Usual Care Results in Unnecessary Testing:

- Majority of patients (84%) received noninvasive diagnostic tests[2] prior to referral to catheterization

Low yield at invasive angiography is a challenge for patients and payers

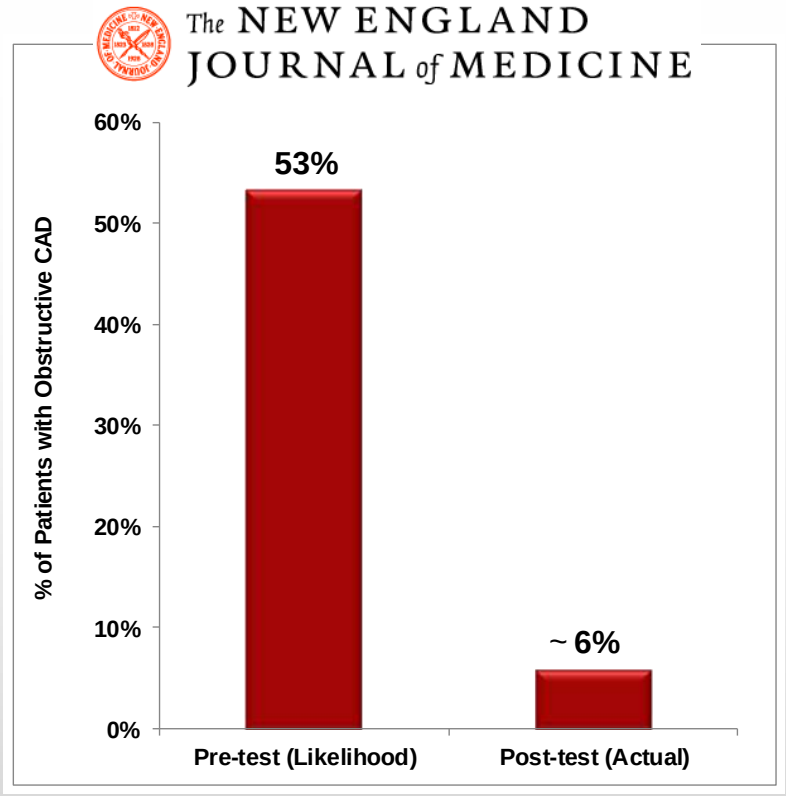
[1] In the study by Patel et al., obstructive CAD was defined as stenosis of 50% or more of the diameter of the left main coronary artery or stenosis of 70% or more of the diameter of a major epicardial or branch vessel that was more than 2.0 mm in diameter

[2] Resting ECG, exercise or pharmacological stress, echocardiography, radionucleotide, CT scans, or other heart scans

Patel MR et al. *N Engl J Med* 2010;362:886-95.

CARDIODX

NHLBI-PROMISE Study Confirm the Low Prevalence of Obstructive CAD and Need for Better Stratification Tools



US Randomized, Controlled Study in Non-acute Symptomatic Patients (N=10,003):[1]

- Enrolled patients in the outpatient, community setting* (87.7% chest pain or dyspnea on exertion)
- Coronary CT-angiography (CTA) vs. functional testing (67% stress nuclear, 23% stress echo, 10% exercise ECG)
- No difference in clinical outcomes[ł] between CTA and functional testing (3.3% vs 3.0%, p-value=0.75)
- Challenges in diagnosing obstructive CAD in Patel *NEJM* 2010 are still prevalent today

Low rate of obstructive CAD (~6%) in patients referred for anatomical or functional testing reinforces "the opportunity to improve the selection of patients for noninvasive testing beyond currently accepted approaches." - *Study authors*

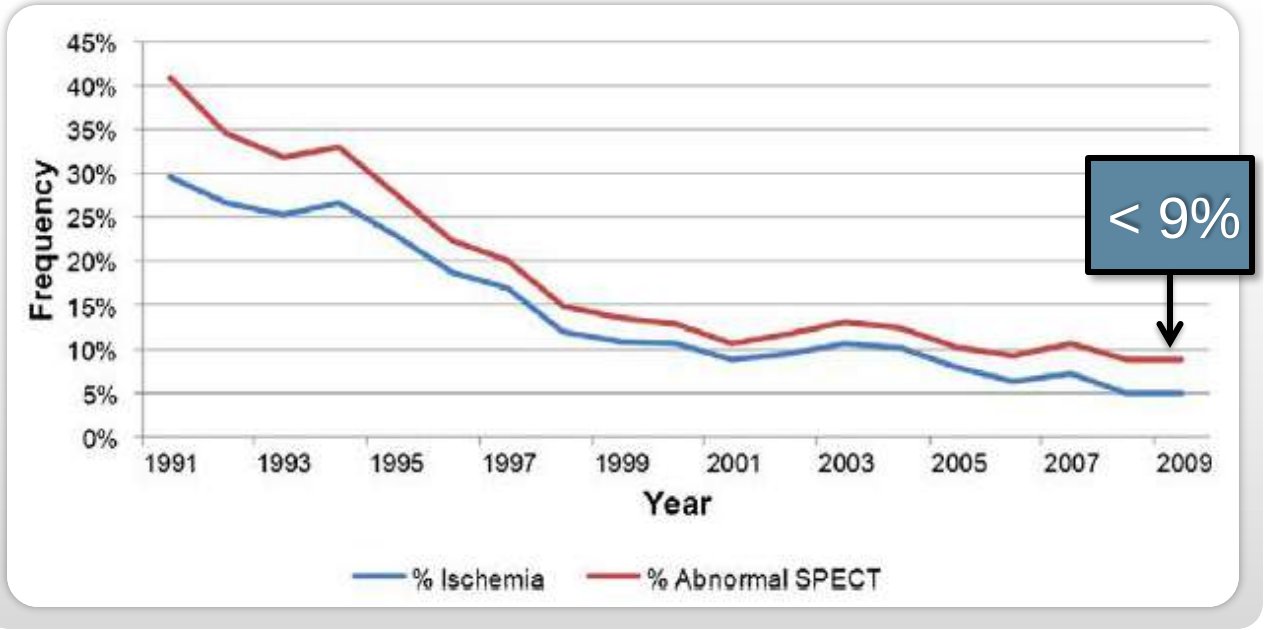
*193 sites participated

[ł]defined as all-cause death, nonfatal MI, unstable angina hospitalization, or major procedural complications

[1]Douglas P, et al. *N Engl J Med.* 2015;372(14):1291-1300

Abnormal/Positive MPI Findings have Declined to < 9%: Suggesting Patients Referred Today are at Low Risk

Yearly Frequency of Abnormal and Ischemic SPECT-MPI



JACC
Journal of the American College of Cardiology

- Frequency of abnormal SPECT-MPIs has decreased over time
- In 2009 the prevalence of abnormal stress SPECT-MPI was 8.7%
- The low rate of positive MPI might be due to over-usage of nuclear stress tests

"The declining frequency of inducible myocardial ischemia, particularly among exercising patients without typical angina, suggest a need to refine the future diagnostic workup of patients with suspected CAD."

Rozanski, et al. *J Am Coll Cardiol.* 2013;61:50:1054-1065.

CARDIODX®

Corus® CAD is a Precision Medicine Blood Test for the Assessment of Obstructive CAD

Corus CAD

- Blood test that incorporates age, sex and gene expression to calculate a score (1-40) corresponding to likelihood of obstructive CAD
- Quickly and safely helps clinicians assess the likelihood of obstructive CAD in the outpatient setting
- Helps clinicians rule patients out for further cardiac workup

Clinically used to help clinicians identify symptomatic patients unlikely to have obstructive CAD

Strong Performance

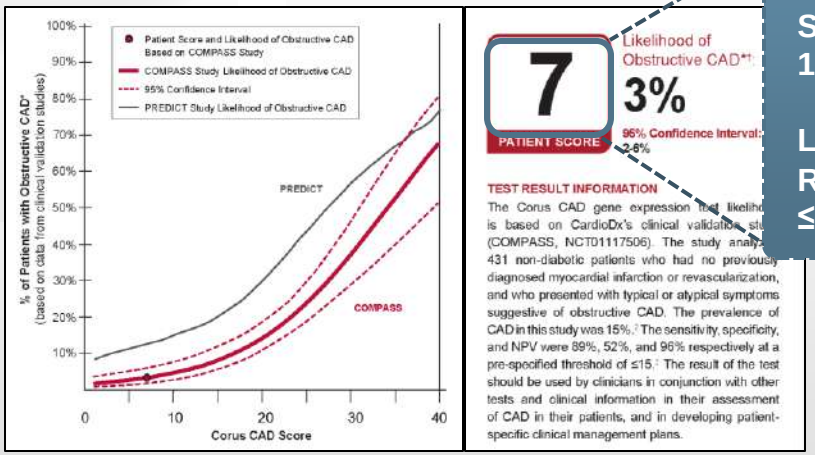
Test Performance:

High Negative Predictive Value: 96%[1]

Clinically Relevant:

46% of Patient Have Lower Scores (≤15[1])

Patient Report



Patient Scores 1-40

Low Range ≤15

[1]The COMPASS study found that the Corus CAD algorithm has a sensitivity of 89% and an NPV of 96% at the pre-specified threshold of 15 in the overall population of men and women referred to MPI.

Thomas GS et al. Circ Cardiovasc Genet 2013;6:154-162.

CARDIODX®

Corus® CAD Test Measures Known Biology

CASP5/IL 18RAP/TNFAIP6

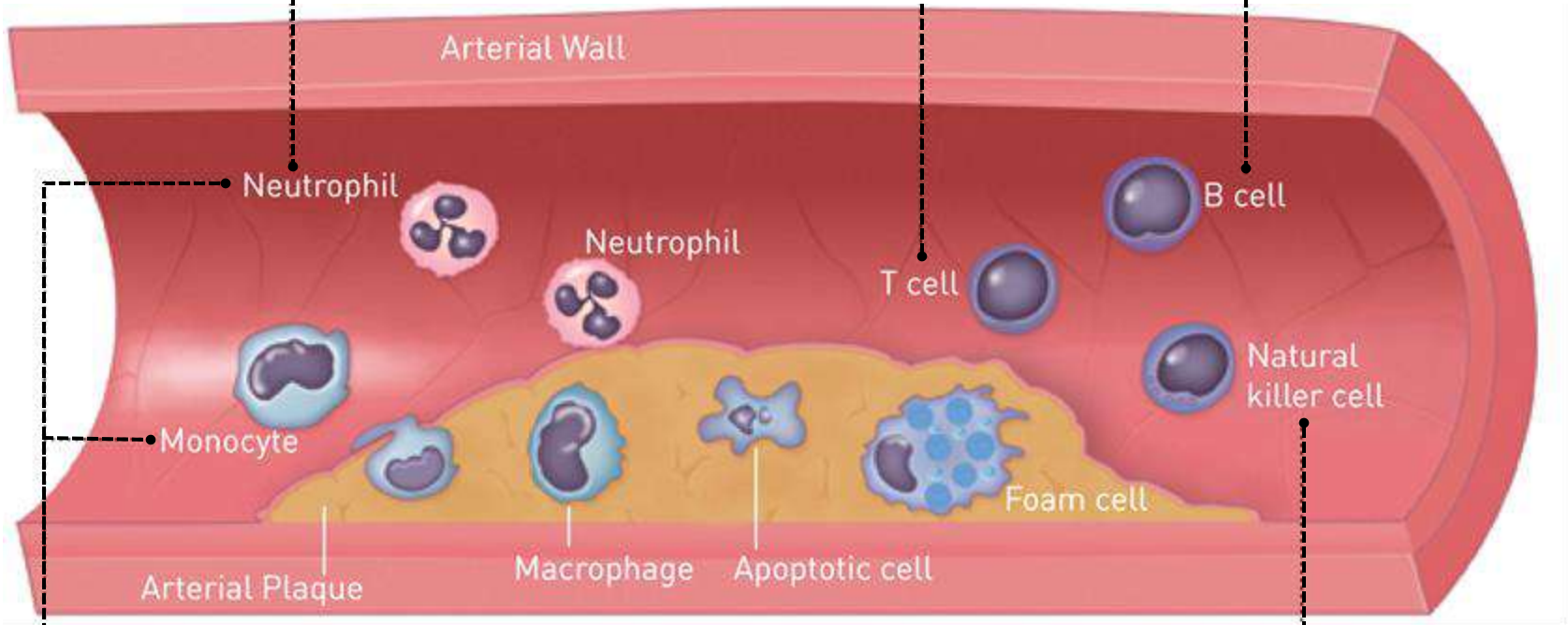
Apoptosis and inflammatory signaling response

CD3/TMC8

Adaptive immune response to atherosclerosis

CD79B/SPIB

Adaptive immune response to atherosclerosis



S100A12/S100A8/CLEC4E

Oxidative damage and cellular necrosis

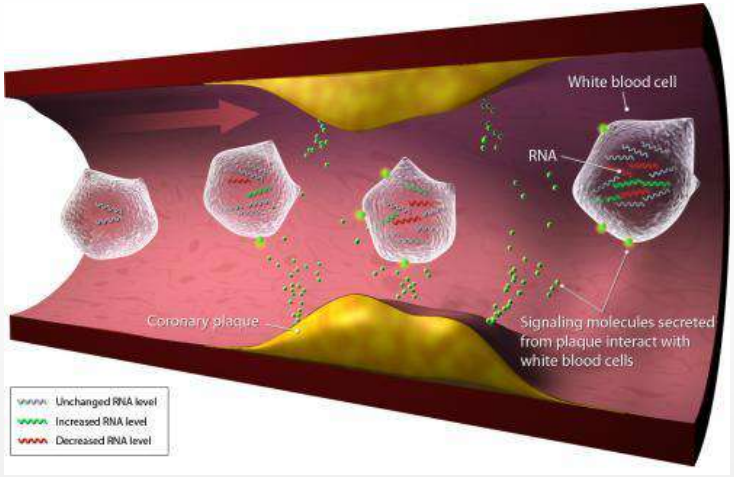
SLAMF7/KLRC4

Innate immune response to atherosclerosis

CARDIODX

Gene Expression Testing (Corus CAD) vs. Genetic Testing

Current State – RNA, Gene Expression



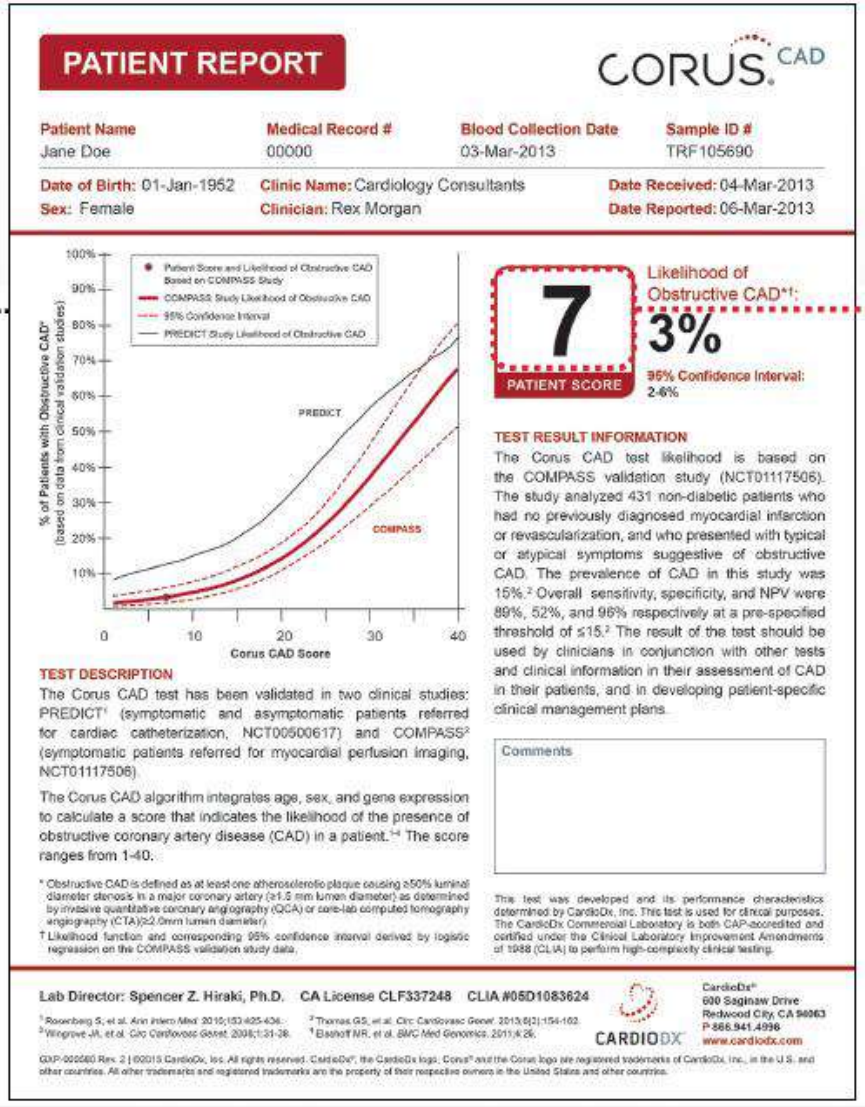
- Gene Expression Testing measures the activity of specific RNA known to be involved in disease processes.
- RNA levels change depending on a person's disease status.
- Provides a current-state assessment of disease.

Future State – DNA, Genetic Testing

- Genetic Tests determine DNA sequences, or detect polymorphisms.
- These sequences remain constant throughout a person's lifetime and can help estimate a person's future risk of developing disease.

Corus® CAD Patient Report

Graph:
Depicts the relationship between test score and the likelihood of obstructive CAD in the clinical validation study.



PATIENT REPORT

CORUS CAD

Patient Name	Medical Record #	Blood Collection Date	Sample ID #
Jane Doe	00000	03-Mar-2013	TRF105690

Date of Birth: 01-Jan-1952 **Clinic Name:** Cardiology Consultants **Date Received:** 04-Mar-2013
Sex: Female **Clinician:** Rex Morgan **Date Reported:** 06-Mar-2013

TEST DESCRIPTION

The Corus CAD test has been validated in two clinical studies: PREDICT[1] (symptomatic and asymptomatic patients referred for cardiac catheterization, NCT00500617) and COMPASS[2] (symptomatic patients referred for myocardial perfusion imaging, NCT01117506).

The Corus CAD algorithm integrates age, sex, and gene expression to calculate a score that indicates the likelihood of the presence of obstructive coronary artery disease (CAD) in a patient.[3,4] The score ranges from 1-40.

* Obstructive CAD is defined as at least one atherosclerotic plaque causing ≥50% luminal diameter stenosis in a major coronary artery (≥1.5 mm lumen diameter) as determined by invasive quantitative coronary angiography (QCA) or core-lab computed tomography angiography (CTA)(≥2.0mm lumen diameter).

† Likelihood function and corresponding 95% confidence interval derived by logistic regression on the COMPASS validation study data.

7
PATIENT SCORE

Likelihood of Obstructive CAD*†:
3%
95% Confidence Interval: 2-6%

TEST RESULT INFORMATION

The Corus CAD test likelihood is based on the COMPASS validation study (NCT01117506). The study analyzed 431 non-diabetic patients who had no previously diagnosed myocardial infarction or revascularization, and who presented with typical or atypical symptoms suggestive of obstructive CAD. The prevalence of CAD in this study was 15%.[2] Overall sensitivity, specificity, and NPV were 89%, 52%, and 96% respectively at a pre-specified threshold of ≤15.[2] The result of the test should be used by clinicians in conjunction with other tests and clinical information in their assessment of CAD in their patients, and in developing patient-specific clinical management plans.

Comments

This test was developed and its performance characteristics determined by CardioDx, Inc. This test is used for clinical purposes. The CardioDx Commercial Laboratory is both CAP-accredited and certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) to perform high-complexity clinical testing.

Lab Director: Spencer Z. Hiraki, Ph.D. CA License CLF337248 CLIA #05D1083624

[1] Rosenberg S, et al. Ann Intern Med. 2010;153:425-434.
[2] Wingrove JA, et al. Circ Cardiovasc Genet. 2009;1:31-38.
[3] Thomas GS, et al. Circ Cardiovasc Genet. 2013;6(2):154-162.
[4] Elashoff MR, et al. BMC Med Genomics. 2011;4:26.

CARDIODX
CardioDx®
600 Saginaw Drive
Redwood City, CA 94063
P 866.941.4996
www.cardiodx.com

One easy-to-interpret score with a value that ranges between 1 and 40. Higher values associated with higher likelihood of obstructive CAD.

CARDIODX

Strong Evidence Package

22+ **Papers** Published in Peer-Reviewed Journals, 60+ **Abstracts Presented at Scientific Meetings**

Analytical Validity

How accurate and reproducible is the test?

- PREDICT Algorithm Development (N=640)
- CLIA Lab Analytical Validity Study
- CAP Accreditation
- Licensed in all 50 states, including NY

Clinical Validity

How does the test perform in a population?

- PREDICT Validation Study (N=526)
- PREDICT Gender-Specific Analysis (N=1,160)
- COMPASS Validation Study (N=431)

Clinical Utility

Does the test influence clinical decisions?

- PREDICT (N=1,116) and COMPASS Follow-Up (N=420)
- IMPACT-CARD Study (N=166)
- IMPACT-PCP Study (N=251)
- REGISTRY I Study (N=342)

Economic Utility

Does the test provide economic value?

- Budget Impact Model
- Cost-Effectiveness Analysis

Corus® CAD Performance in Independent Validation Studies

Corus CAD was designed to be a rule-out test

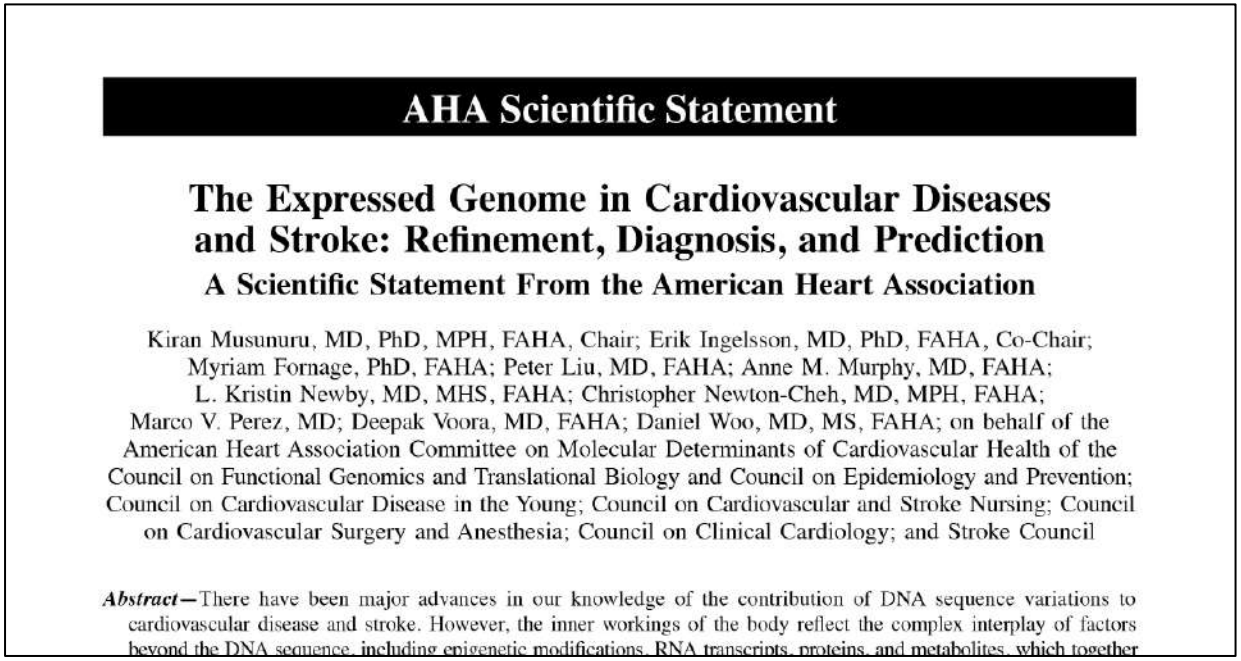
Corus CAD Performance*	COMPASS (N= 431)	PREDICT (N= 526)
Sensitivity	89%	85%
NPV	96%	83%
Specificity	52%	43%
Prevalence of Obstructive CAD	15%	37%

*Performance associated with a score threshold of 15 in a population of men and women combined

Thomas GS et al. *Circ Cardiovasc Genet* 2013;6:154-162.
Rosenberg S et al. *Ann Intern Med* 2010;153:425-434.

CARDIODX®

AHA 2017 Scientific Statement Highlights the Value of Corus® CAD



AHA Scientific Statement

The Expressed Genome in Cardiovascular Diseases and Stroke: Refinement, Diagnosis, and Prediction

A Scientific Statement From the American Heart Association

Kiran Musunuru, MD, PhD, MPH, FAHA, Chair; Erik Ingelsson, MD, PhD, FAHA, Co-Chair; Myriam Fornage, PhD, FAHA; Peter Liu, MD, FAHA; Anne M. Murphy, MD, FAHA; L. Kristin Newby, MD, MHS, FAHA; Christopher Newton-Cheh, MD, MPH, FAHA; Marco V. Perez, MD; Deepak Voora, MD, FAHA; Daniel Woo, MD, MS, FAHA; on behalf of the American Heart Association Committee on Molecular Determinants of Cardiovascular Health of the Council on Functional Genomics and Translational Biology and Council on Epidemiology and Prevention; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; Council on Clinical Cardiology; and Stroke Council

***Abstract*—**There have been major advances in our knowledge of the contribution of DNA sequence variations to cardiovascular disease and stroke. However, the inner workings of the body reflect the complex interplay of factors beyond the DNA sequence, including epigenetic modifications, RNA transcripts, proteins, and metabolites, which together

AHA Position on Corus CAD:

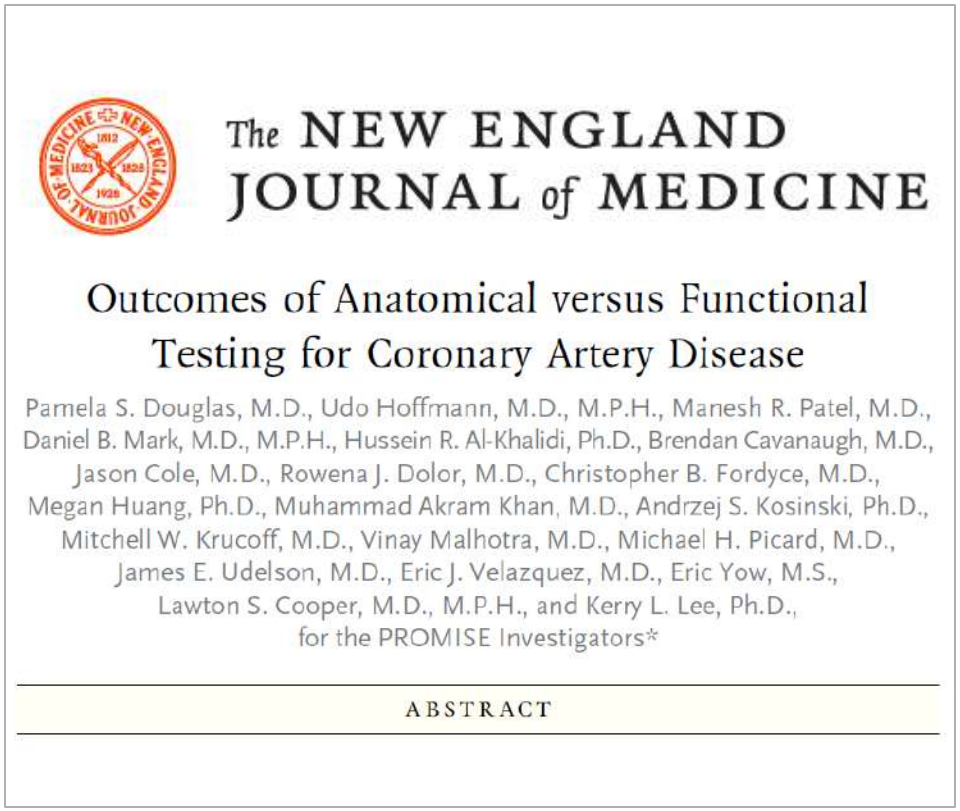
"The Corus CAD test is a clinically available diagnostic test that has been evaluated, has been deemed to be valid and useful…"[1]

[1]Musunuru K et al. *Circ Cardiovasc Genet.* 2017;10(4):e1-e25.

CARDIODX®

PROMISE Study: **PRO**spective **M**ulticenter **I**maging **S**tudy for **E**valuation of Chest Pain

NHLBI-sponsored, Multicenter, Randomized Trial Comparing Functional (Stress Testing) vs. Anatomical testing (CCTA) with Regards to Clinical Outcomes, 10,003 Patients Enrolled



The NEW ENGLAND JOURNAL of MEDICINE

Outcomes of Anatomical versus Functional Testing for Coronary Artery Disease

Pamela S. Douglas, M.D., Udo Hoffmann, M.D., M.P.H., Manesh R. Patel, M.D., Daniel B. Mark, M.D., M.P.H., Hussein R. Al-Khalidi, Ph.D., Brendan Cavanaugh, M.D., Jason Cole, M.D., Rowena J. Dolor, M.D., Christopher B. Fordyce, M.D., Megan Huang, Ph.D., Muhammad Akram Khan, M.D., Andrzej S. Kosinski, Ph.D., Mitchell W. Krucoff, M.D., Vinay Malhotra, M.D., Michael H. Picard, M.D., James E. Udelson, M.D., Eric J. Velazquez, M.D., Eric Yow, M.S., Lawton S. Cooper, M.D., M.P.H., and Kerry L. Lee, Ph.D., for the PROMISE Investigators*

ABSTRACT

Corus CAD Substudy

- ~4,000 subjects enrolled in genomics substudy; Corus CAD test performed on ~2,300 non-diabetic patients
- Primary endpoint: Association of Corus CAD scores with cardiovascular events (death, myocardial infarction (MI), unstable angina (UA), revascularization)
  - Median FU of 25 months
- Exploratory endpoint: Association of Corus CAD with obstructive[ǂ] CAD in patients in CCTA arm (n = ~1,100)

*193 sites participated

[1]Douglas PS, et al. *N Engl J Med*. 2015;372(14):1291-1300

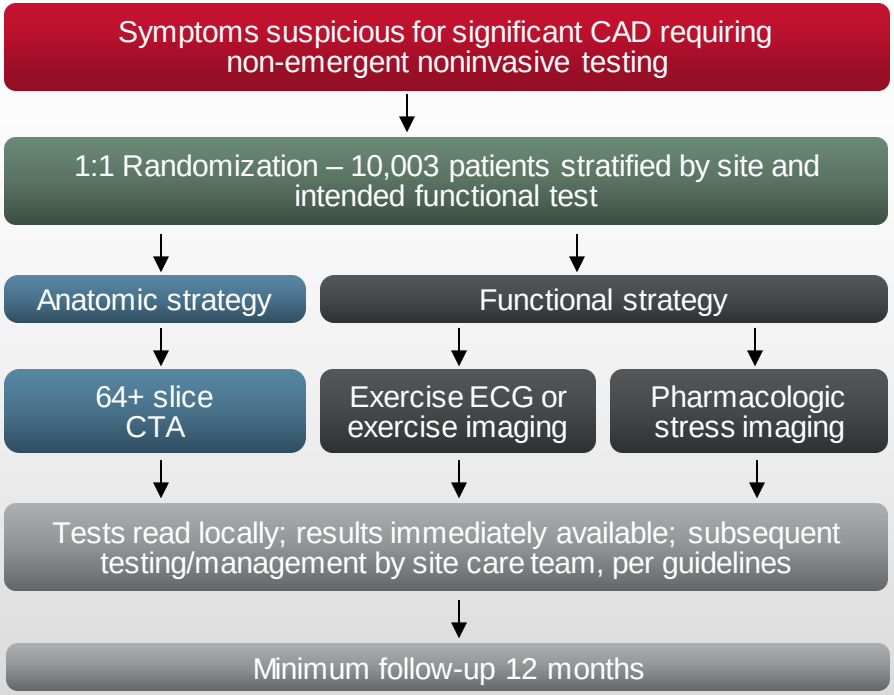
[ǂ] Obstructive CAD is defined as at least one atherosclerotic plaque causing > 70% in a major coronary artery as determined by coronary computed tomography angiography

CARDIODX

PROMISE Study: Prospective Multicenter Imaging Study for Evaluation of Chest Pain

NHLBI-sponsored, Multicenter, Randomized Trial Comparing Functional (Stress Testing) vs. Anatomical testing (CCTA) with Regards to Clinical Outcomes
10,003 Patients Enrolled

PROMISE Trial Design



Corus CAD Substudy

- ~4000 subjects enrolled in genomics substudy; Corus CAD test performed on ~2300 non-diabetic patients
- Primary endpoint: Association of Corus CAD scores with cardiovascular events (death, myocardial infarction (MI), unstable angina (UA), revascularization)
  - Median FU of 25 months
- Exploratory endpoint: Association of Corus CAD with obstructive[†] CAD in patients in CCTA arm (n = ~1100)

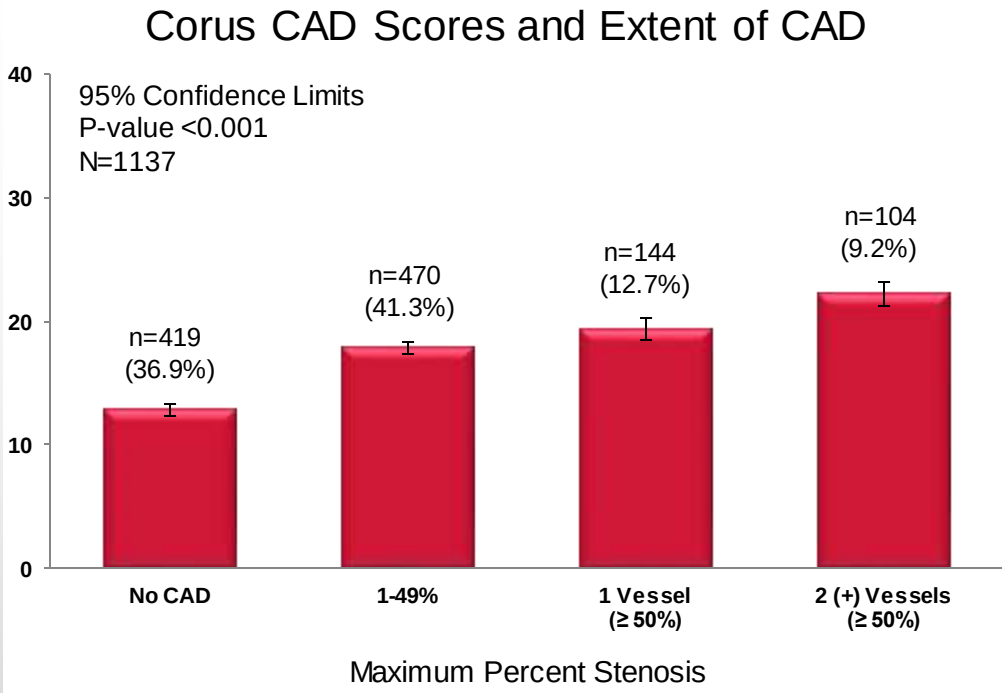
*193 sites participated

[1]Douglas PS, et al. *N Engl J Med*. 2015;372(14):1291-1300

[†]Obstructive CAD is defined as at least one atherosclerotic plaque causing > 70% in a major coronary artery as determined by coronary computed tomography angiography

CARDIODX®

PROMISE Study Independently Confirmed that Corus CAD Scores Correlated with the Presence and Extent of CAD



PROMISE CT-Angiography Arm

- Prevalence of Obstructive CAD: 10% (115/1137)
- Corus CAD scores >15 was associated with increased likelihood of obstructive CAD (OR 2.5, p<0.001)
- Consistent with PREDICT and COMPASS trial results, Corus CAD scores are associated with the presence and extent of coronary artery disease, including obstructive disease

Voora D, et al. *Am Heart J* 2016;184:133-140.

CARDIODX®

PROMISE Trial Substudy: Patients with Low Corus CAD Scores Had Similar Clinical Outcomes to CTA or Stress Testing at 25-Months

25-Month Follow-Up

	Corus CAD Low Scores ≤15 (n=1058)	Noninvasive Testing (n=1963)
Testing Modalities	**Corus CAD Blood Test**	**Coronary CT-Angiography (CTA); Stress Nuclear, Stress Echo, or Exercise ECG**
Primary Composite Endpoint*	**3.2%**** 34/1058	**2.6%**** 52/1963

"Findings from the PROMISE substudy demonstrate the potential utility of a simple blood test in the initial evaluation of symptomatic patients with suspected CAD to help clinicians determine next steps and make clinical decisions."

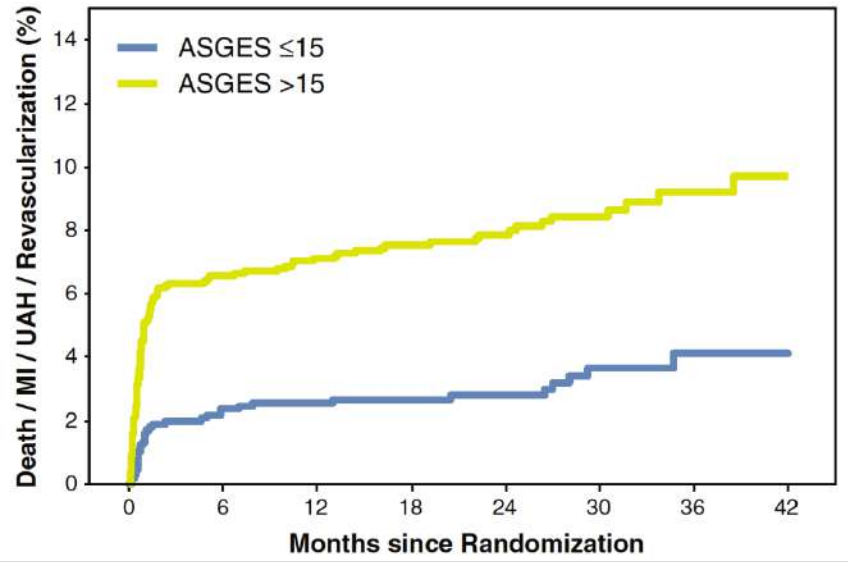
- *Deepak Voora, M.D., PI of PROMISE Trial Substudy*
Duke Center for Applied Genomics & Precision Medicine

*Defined as all-cause death, nonfatal MI, unstable angina hospitalization, or revascularization
**p-value = 0.29

CARDIODX®

PROMISE Substudy (25-Month Follow-Up): There is a Significant Association Between Corus® CAD Score and Clinical Outcomes

Value as a binary variable (≤15 vs. >15)*



Value as a continuous variable (1 - 40)

The higher the Corus CAD score (as a continuous variable), the higher the likelihood of MACE/revascularization at 25 month follow up [HR=1.06 (95%CI 1.04-1.08), p < 0.001 for each 1-point increase in Corus CAD score].

* Unadjusted Kaplan-Meier curves for patients with high (N15) or low (≤15) Corus CAD. The primary composite endpoint was death, myocardial infarction (MI), unstable angina hospitalization (UAH), and revascularization.

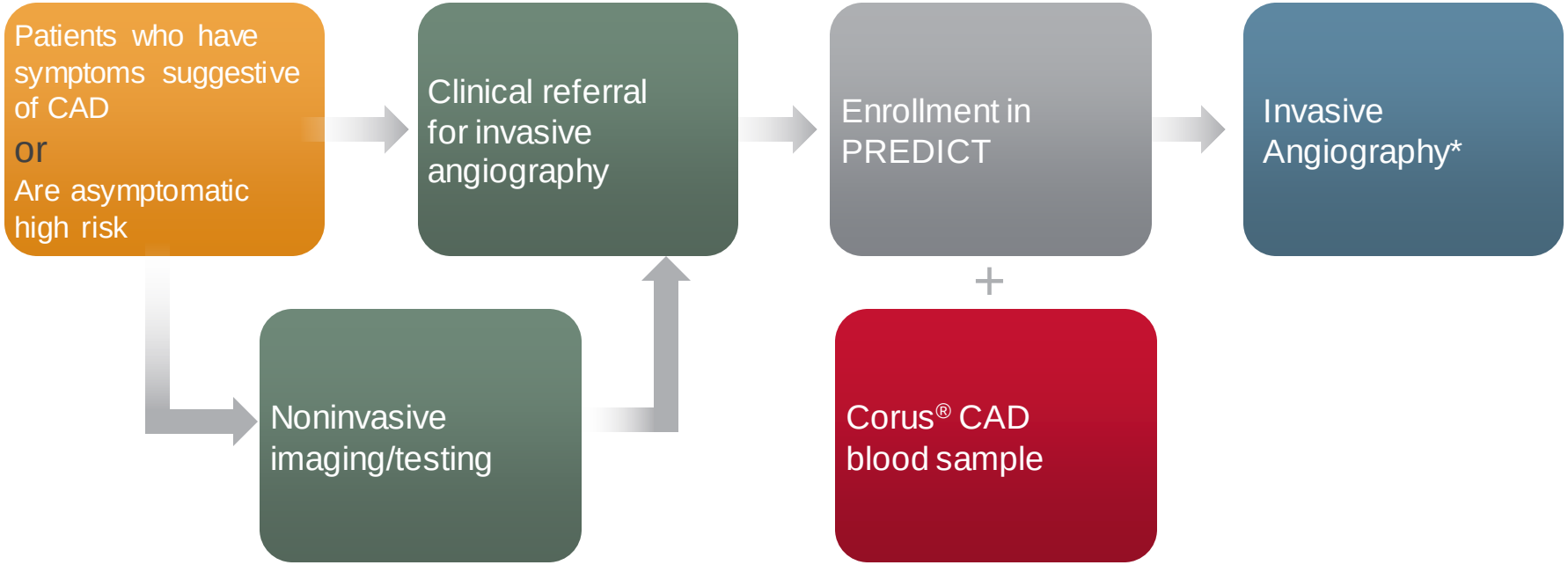
Voora D, et al. *Am Heart J* 2016;184:133-140.

CARDIODX®

PREDICT Study - Cath Lab Population

Annals of Internal Medicine®

PREDICT (Personalized Risk Evaluation and Diagnosis In the Coronary Tree)

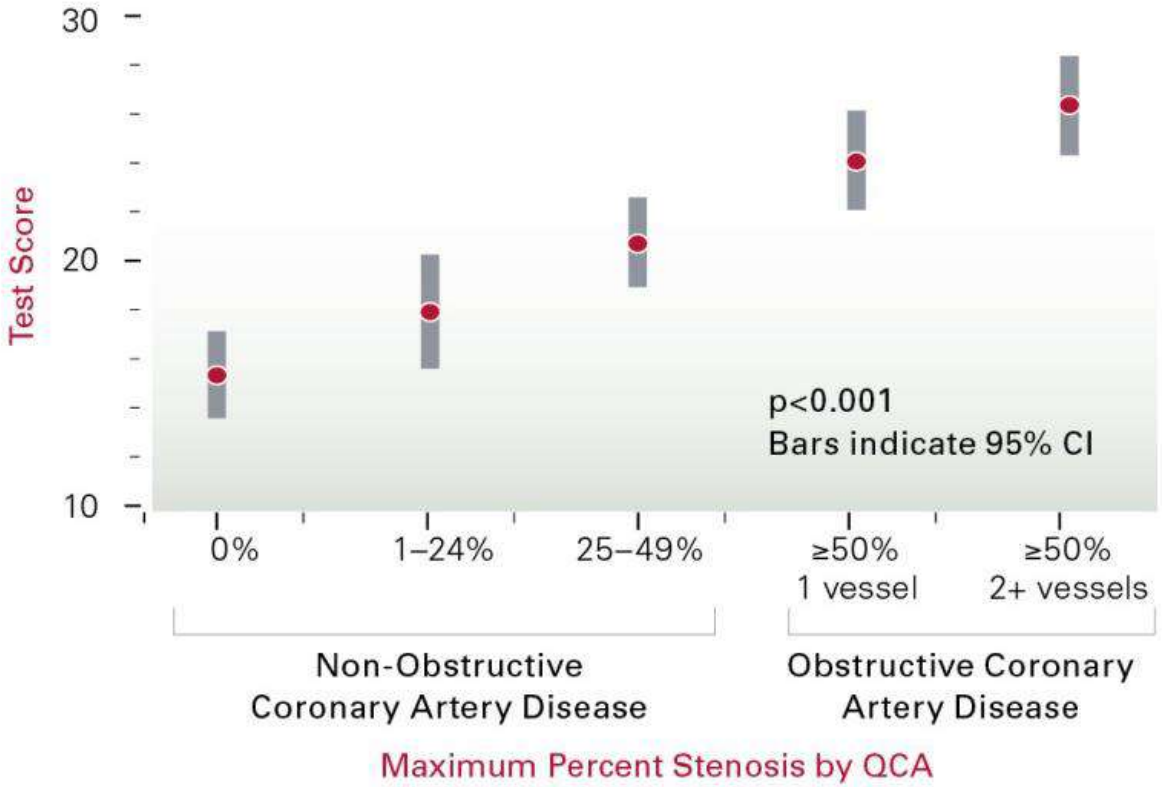


- Primary Endpoint: Corus CAD performance by ROC analysis
- Study PI: Eric Topol, MD, Scripps Research Institute
- 39 U.S. sites, 1,343 patients

*Data analyzed by quantitative coronary angiography (QCA) core lab.
Rosenberg S et al. *Ann Intern Med* 2010;153:425-434.

CARDIODX®

PREDICT Study: Corus® CAD Score is Proportional to the Presence and Extent of Obstructive CAD



The Corus CAD score correlates with maximum percent stenosis:
A higher test score corresponds to a higher likelihood of obstructive CAD.

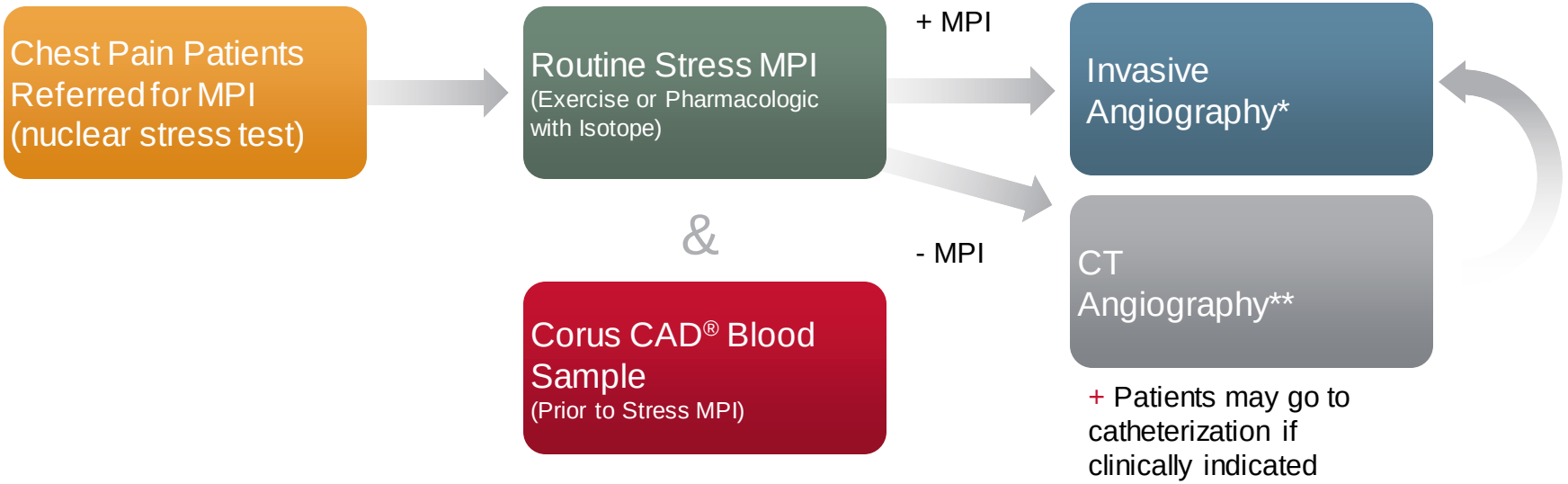
Rosenberg S, et al. *Ann Intern Med.* 2010;153:425-434.

CARDIODX®

COMPASS Study – MPI Referred Population

Published in Circulation: Cardiovascular Genetics

COMPASS (Coronary Obstruction Detection by Molecular Personalized Gene Expression)



- Primary Endpoint: Corus CAD performance by ROC analysis
- Steering Committee: Greg Thomas, MD, MPH, John McPherson, MD, Alexandra Lansky, MD, Szilard Voros, MD
- 19 U.S. sites, 431 patients

* Data analyzed by Quantitative Coronary Angiography (QCA) core lab.
** Data analyzed by CT Angiography core lab.
Thomas GS et al. *Circ Cardiovasc Genet* 2013;6:154-162.

MPI = Myocardial Perfusion Imaging

CARDIODX®

Comparative Effectiveness: Corus® CAD vs. MPI (Nuclear Stress Test) Performance in COMPASS Study

	Corus CAD*	MPI**
Sensitivity	**89%**	**27%**
Specificity	**52%**	**92%**
NPV	**96%**	**88%**
PPV	**24%**	**35%**

In the COMPASS trial, Corus CAD outperformed MPI in sensitivity (89% vs. 27%, p<0.001) and negative predictive value (96% vs. 88%, p<0.001) for ruling out obstructive CAD.

* Performance associated with a score threshold of 15 in men and women combined
** Site-read MPI. Core-lab MPI sensitivity = 36%, NPV = 88%
Thomas GS et al. *Circ Cardiovasc Genet* 2013;6:154-162.

CARDIODX®

Why is the Sensitivity for MPI Low in the COMPASS Study?
Historically Reported Nuclear Stress Test (MPI) Performance Is Distorted Due to Low Referral Rate

- Majority of historical studies distort MPI performance because they only capture data from patients with a **positive MPI,** as very few negative MPI patients are referred for further testing (e.g., invasive coronary angiography)

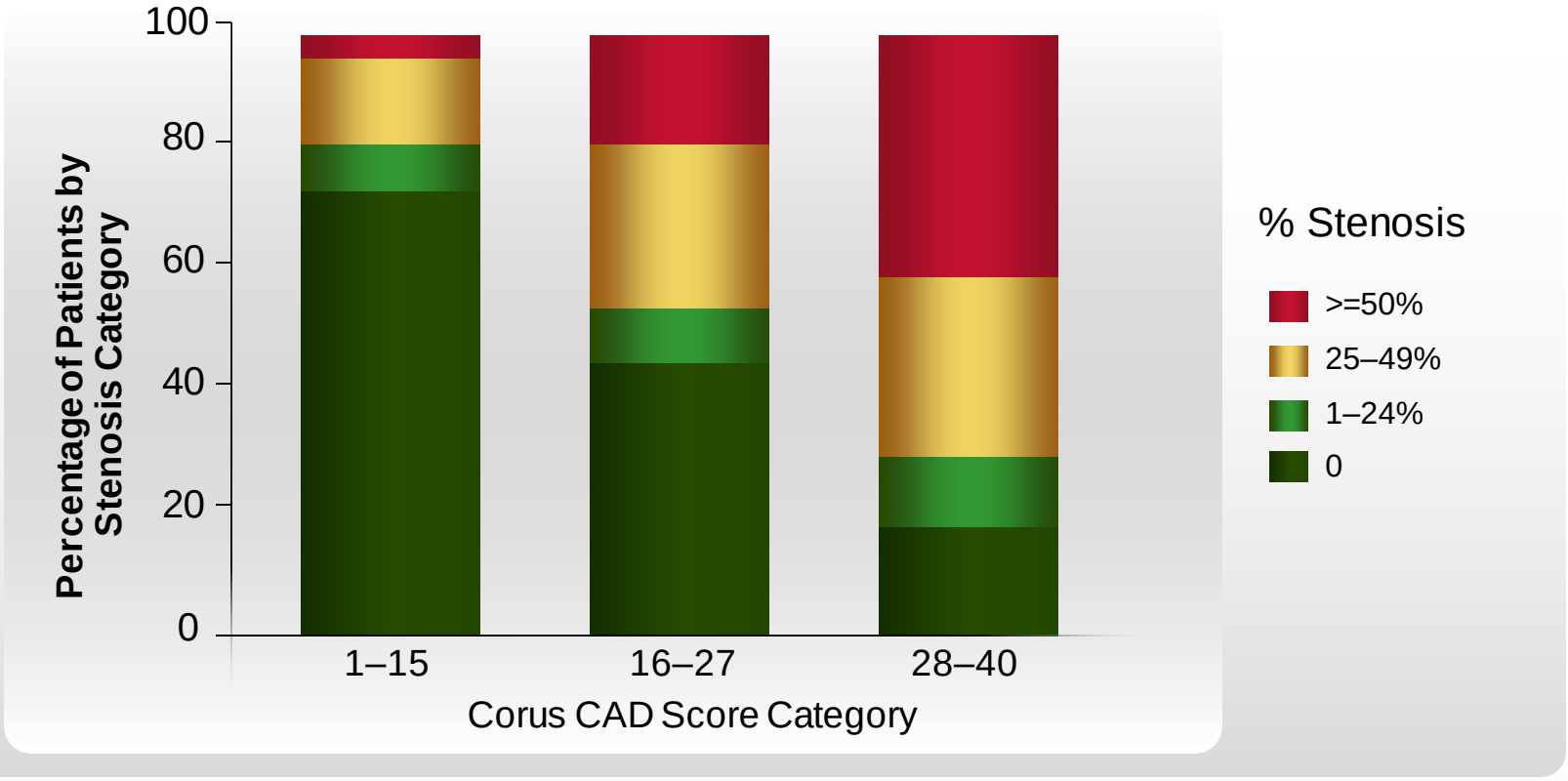
MPI Performance	Unadjusted*	Adjusted**	COMPASS***
Sensitivity	85%	38%	27%
Specificity	69%	99%	92%

Diagnostic performance of MPI when adjusted for referral rate differences is similar to that reported in the COMPASS trial

* Diagnostic effectiveness based on random-effects meta-analysis of sensitivity and specificity reported in 30 studies of exercise MPI
** Adjusted for referral rates to cardiac catheterization after positive or negative exercise test; referral rate for MPI positive = 42.5%, MPI negative = 4%
Unadjusted and Adjusted MPI performance and referral rates from: Ladapo J et al. *J Am Heart Assoc*. 2013;2(6):e000505
***COMPASS Site-read MPI. Core-lab MPI sensitivity = 36%, specificity = 90%. Performance from: Thomas GS et al. *Circ Cardiovasc Genet* 2013;6:154-162.

CARDIODX®

COMPASS Study: Higher the Corus® Score, the Higher the Likelihood of Obstructive CAD and Presence of CAD



- In patients with low Corus CAD scores (≤15), 96% of patients did not have obstructive CAD
- The higher the Corus CAD score, the higher the likelihood of obstructive CAD (≥50% stenosis) and moderate CAD (25-49%), and the lower the likelihood of no disease

Thomas GS, et al. *Circ Cardiovasc Genet.* 2013;6:154-162. (COMPASS)

CARDIODX®

COMPASS Study: Low Corus® CAD Scores Associated With Decreased Revascularization, MACE Rates

	COMPASS 6 mo	
	Revascularization Events Within 1 mo	MACE* and Revascularization Events Within 2-6 mos
Corus CAD ≤15	**0.5 %** 1/192	**0%** 0/192
Corus CAD >15	**10.5%** 24/228	**1.3%** 3/228
Population	Prevalence = 15% All patients referred for MPI Reflects intermediate risk population	

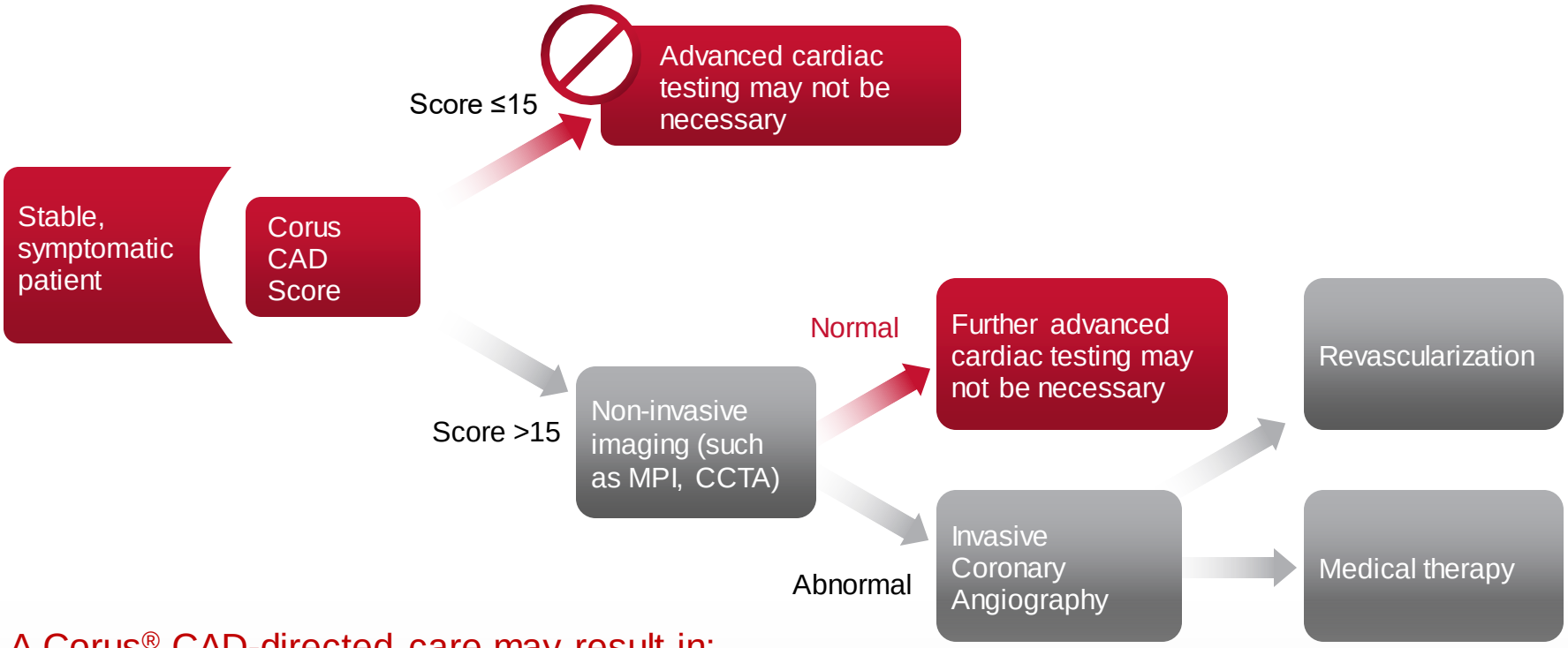
Increased Corus CAD score was associated with increased event likelihood in COMPASS (*P*=0.001)

* MACE: Major adverse events = MI, Stroke/TIA, all cause mortality; Subsequent revascularization procedures = PCI and CABG

Thomas GS, et al. *Circ Cardiovasc Genet* . 2013;6(2):154-162.

CARDIODX®

COMPASS Study: Corus® CAD can Help Healthcare Systems Rule-Out Low Risk Patients from Unnecessary Cardiac Imaging and Caths



A Corus® CAD-directed care may result in:

- 46% fewer MPIs*
- 29% fewer diagnostic ICA procedures
- Diagnostic yield of ICA at 47%, improved from 35%

Thomas G, et al. *Circulation: Cardiovascular Genetics*. 2013;6(2):154-162. (COMPASS)
*46% of the population in the COMPASS Study received low Corus CAD scores ≤15

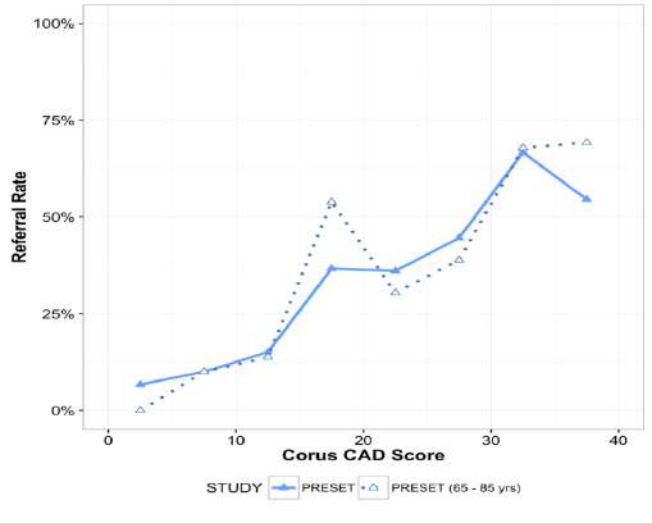
CARDIODX®

PRESET Registry: There is a Significant Association Between Corus® CAD Scores and Cardiac Referrals/Testing

Value as a binary variable (≤15 vs. >15)

	Referred to Cardiology or Advanced Cardiac Testing	Not referred	p-value
Corus ≤15 (n = 252)	26 (10%)	226 (90%)	**<0.0001**
Corus >15 (n = 314)	137 (44%)	177 (56%)	

Value as a continuous variable (1 - 40)



Ladapo JA, Budoff M, Sharp D, et al. Clinical Utility of a Precision Medicine Test Evaluating Outpatients with Suspected Obstructive Coronary Artery Disease, *The American Journal of Medicine* (2017), doi: 10.1016/j.amjmed.2016.11.021 and Internal Reports

CARDIODX®

PRESET Registry: Corus® CAD Score is Correlated with Safety Endpoints (1-year)

- Low Corus CAD Scores were associated with low clinical event rates at 12 months
- Clinical findings were consistent with the COMPASS and PROMISE Substudy

12-Month Follow-Up	Score ≤ 15	Score > 15
MACE and Revascularization	**3 / 252 (1.2%)** Of the 252 Patients with Low Corus CAD Scores, 3 had a clinical event at 12-months	**14 / 314 (4.5%)*** Of the 314 patients with High Corus CAD Scores (defined as >15), 14 had clinical events at 12-months

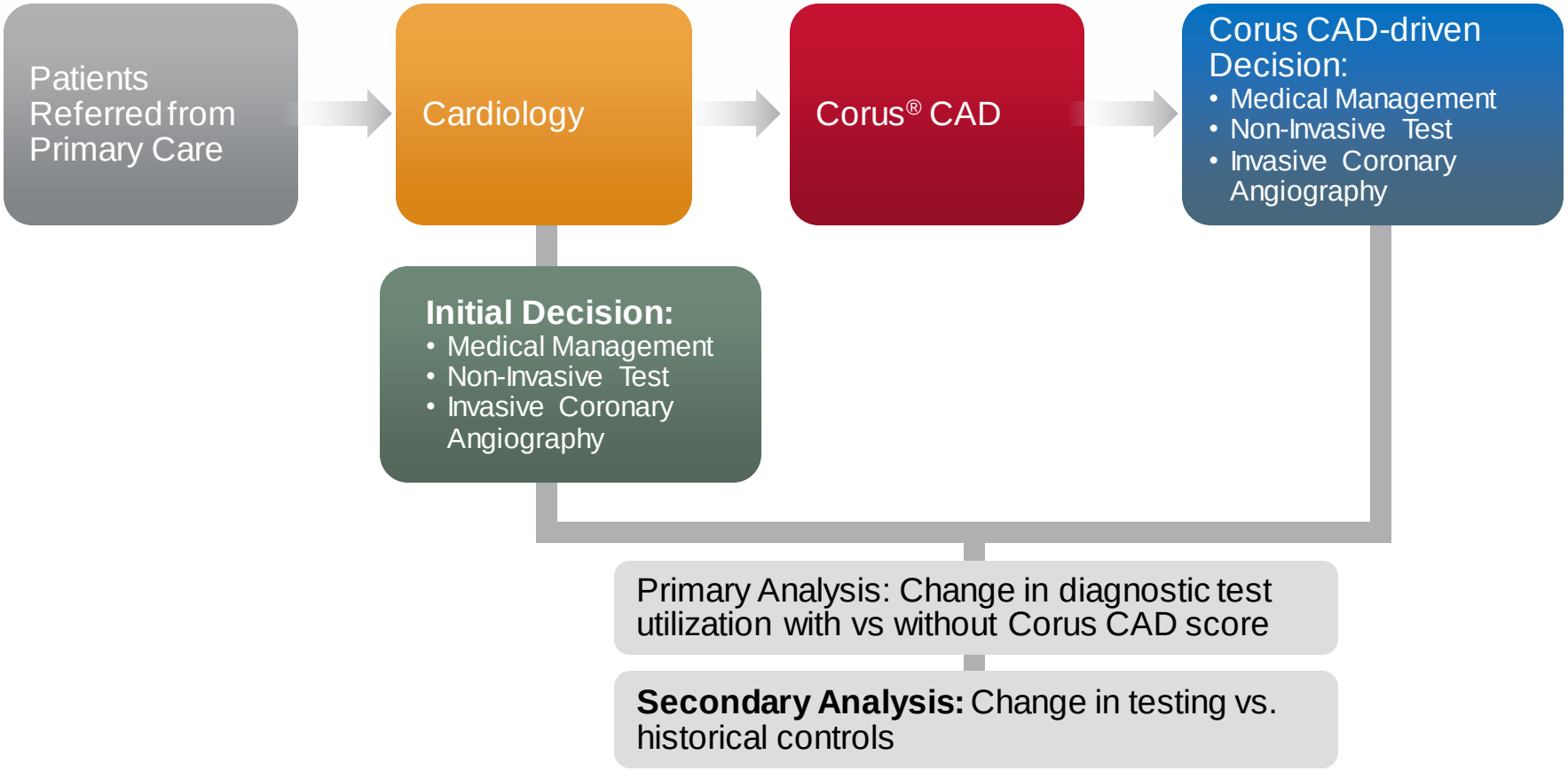
* p = 0.03

Ladapo JA, Budoff M, Sharp D, et al. Clinical Utility of a Precision Medicine Test Evaluating Outpatients with Suspected Obstructive Coronary Artery Disease, *The American Journal of Medicine* (2017), doi: 10.1016/j.amjmed.2016.11.021.

CARDIODX®

IMPACT-CARD Trial Design
Published in *Critical Pathways in Cardiology*

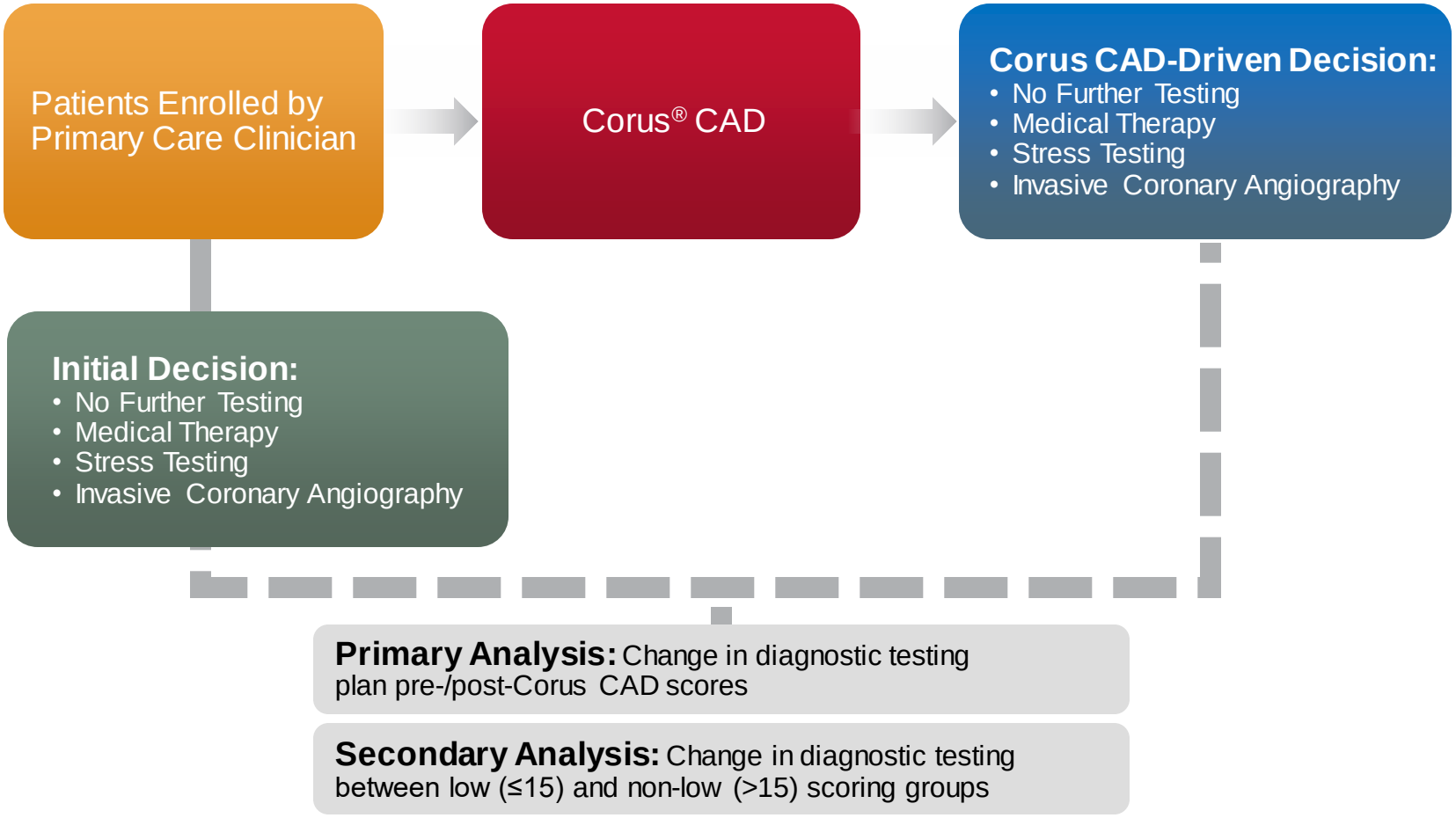
IMPACT (Investigation of a Molecular Personalized Coronary Gene Expression Test on Cardiology Practice Pattern)



McPherson JA et al. *Crit Pathw Cardiol* 2013;12(2):37-42.

CARDIODX®

IMPACT-PCP Trial Design
Published in *Journal of the American Board of Family Medicine*



Herman L et al. *J Am Board Fam Med.* 2014; 27:258-267.

CARDIODX®

Physicians Change Their Behavior Based on Corus® CAD: Decreased Testing in Low Score Patients

	Percentage of Total Corus CAD Patients	Decreased Testing	Increased Testing
IMPACT-CARD[1] Corus CAD ≤15	**63%** 52/83	**56%** 29/52	**0%** 0/52
IMPACT-PCP[2] Corus CAD ≤15	**51%** 127/251	**60%** 76/127	**2%** 3/127

In the both the cardiology and primary care setting, Corus CAD reduced downstream cardiac testing* among patients with low (≤ 15) Corus CAD scores

* e.g. MPI, CT angiography (CTA) and/or invasive angiography

[1] McPherson JA et al. *Crit Pathw Cardiol.* 2013;12(2):37-42.

[2] Herman L et al. *J Am Board Fam Med.* 2014; 27:258-267.

CARDIODX®

Consistent Clinical Utility Results (n=676 patients)

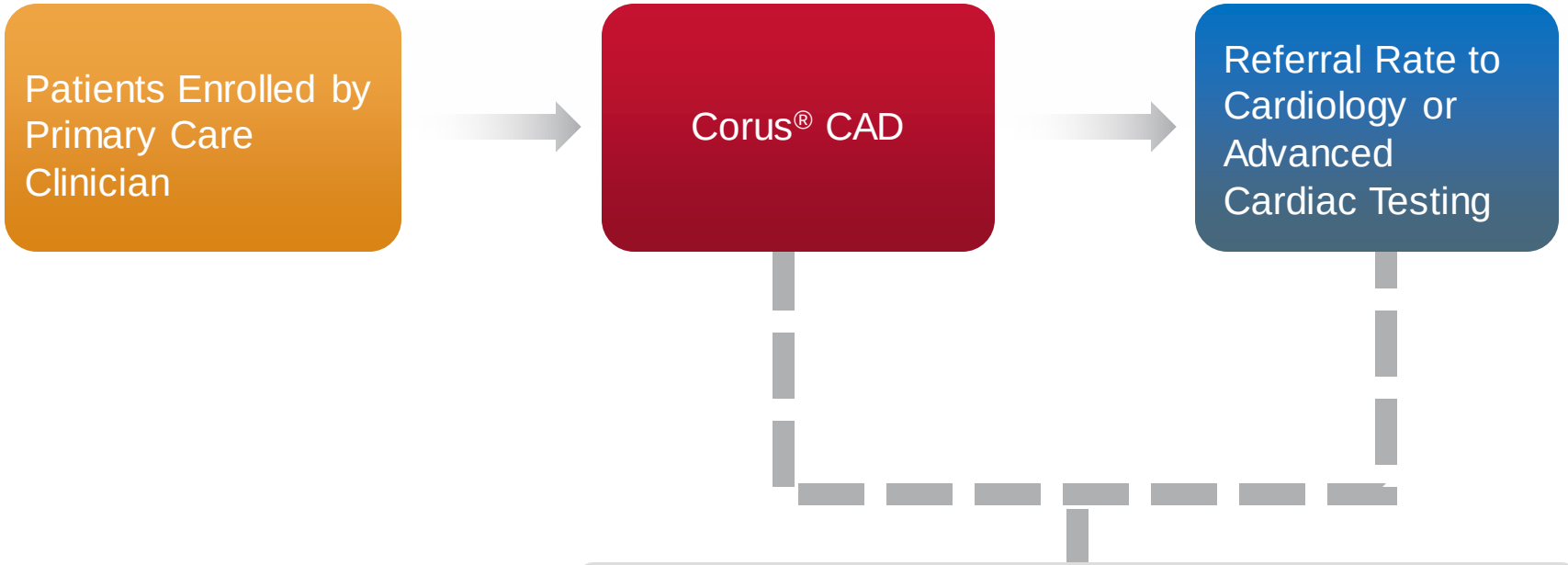
Trial	Size (N)	Outcome Measure	Efficacy (Referral Rates)		Safety
			Corus® CAD ≤ 15	Corus® CAD >15	# Events
IMPACT–CARD[1]	83	Referral to testing	8%	71%	0 (180 days)
IMPACT-PCP[2]	251	Referral to testing	5%	82%	1 (30 days, event not related)
REGISTRY I[3]	342	Referral to testing or cardiology	6%	70%	2 (avg. 264 days, 1 event not related)

Patients with low Corus CAD scores have less downstream cardiac testing and fewer referrals to cardiologists

[1] McPherson JA et al. *Crit Pathw Cardiol*. 2013;12(2):37-42.
[2] Herman L et al. *J Am Board Fam Med*. 2014; 27:258-267.
[3] Ladapo JA et al. *Am J Med Qual*. 2014 May 5. [Epub ahead of print].

CARDIODX®

REGISTRY I Study Design
In Collaboration with CHI, a Unit of Humana



Ladapo JA et al. *Am J Med Qual*. 2015;30(4):345-352.

CARDIODX®

REGISTRY I Trial Results: Corus® CAD Low Score Patients Had Fewer Cardiac Referrals

	Percentage of Total Corus CAD Patients	Referral Rate to Cardiology or Advanced Cardiac Testing
Corus CAD ≤15	**49%** 167/342	**6%** 10/167

The usage of Corus CAD was associated with a low referral rate to cardiology or advanced cardiac testing in low score patients

Safety of Corus CAD score in clinical decision making supported by low MACE* rate of ~0.6% during 264 day average follow-up period

Ladapo JA et al. *Am J Med Qual*. 2015;30(4):345-352.
*MACE: Major adverse events = MI, Stroke/TIA, all cause mortality

Corus® CAD and Elderly Patients

- In elderly patients, the prevalence of *obstructive* CAD is less than 10% in woman and less than 30% in men
- **Convenience**
- Prevent unnecessary imaging tests and radiation
  - They are often subjected to radiation from other non-cardiac testing
  - 1 Nuclear imaging test = 39 mammograms in radiation
- Elderly patients present with vague, atypical symptoms and especially in women
  - Patient history is just not adequate
  - They are more likely to ignore mild symptoms, thinking its part of getting old
- More likely to get false positives and false negatives with stress testing
  - In woman due to breast attenuation
  - More difficult to achieve 85% of maximum heart rate
- Increased risk of complications during Cath, especially in women

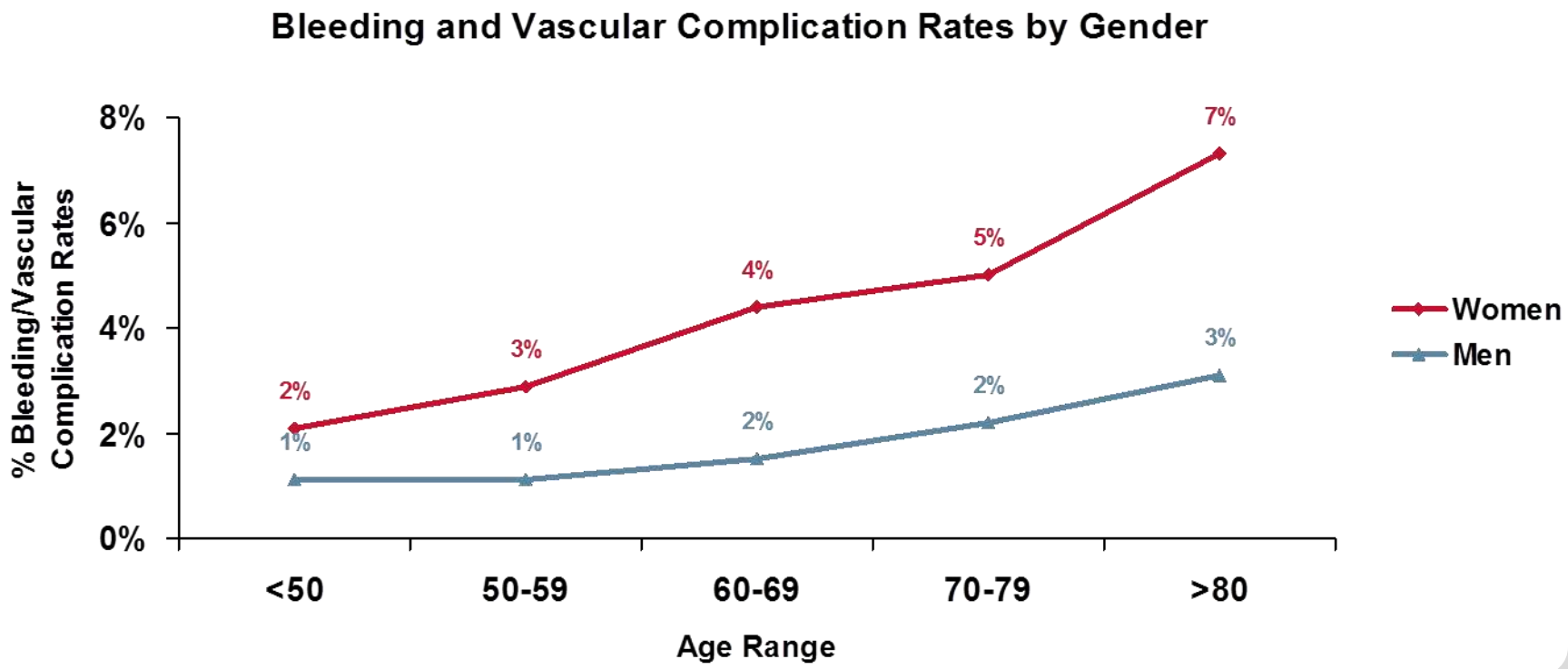
Women Present More Challenges in the Diagnosis of CAD and Have Higher Risks/Complications with Current Tests

Challenges in Women

- Women present with atypical, non-specific and milder symptoms of CAD[1]
- High rates of false-negative and false-positive noninvasive test results[2]
- Low rates of obstructive disease at invasive coronary angiography[3,4]
- Increased side effects, such as radiation exposure[5,6] and contrast agent-induced nephropathy[7]
- Increased risk of thyroid dysfunction due to contrast agents[8]
- Increased risk of bleeding and vascular complications[9]

1. Miller CL, et al. *J Adv Nursing.* 2002;39:17-23.
2. Kwok Y, et al. *Am J Cardiol.* 1999;83:660-666.
3. Patel MR, et al. *N Engl J Med.* 2010;362:886-895.
4. Lansky A, et al. *Am Heart J.* 2012;164(3):320-6.
5. Fazel R, et al. *N Engl J Med.* 2009;361(9):849-857.
6. Chen J, et al. *J Am Coll Cardiol.* 2010;56(9):702-711.
7. Sidhu, et al. *Am J Cardiol.* 2008;102:1482-1486.
8. Rhee CM, et al. *Arch Intern Med.* 2012;172:153-159.
9. Ahmed, et al. *Circ Cardiovasc Interv.* 2009;2:423-429.

Invasive Coronary Angiography: Women and Older Patients Have Higher Complication Rates



10 Center North New England Registry of PCI (N=46,830):*

- Higher bleeding & vascular complication rates associated with female gender and older age
- Overall rate of bleeding and vascular complications was statistically significantly higher in women than men ($P<0.004$)

* 58% of PCIs indicated for emergent conditions (unstable angina, STEMI, NSTEMI, cardiogenic shock) and 42% were indicated for stable conditions
Ahmed, et al. *Circ Cardiovasc Interv.* 2009;2:423-429.

Majority of Chest Pain (90%) Presenting to Primary Care is Not Attributable to CAD

Epidemiology of Chest Pain in Primary Care Setting

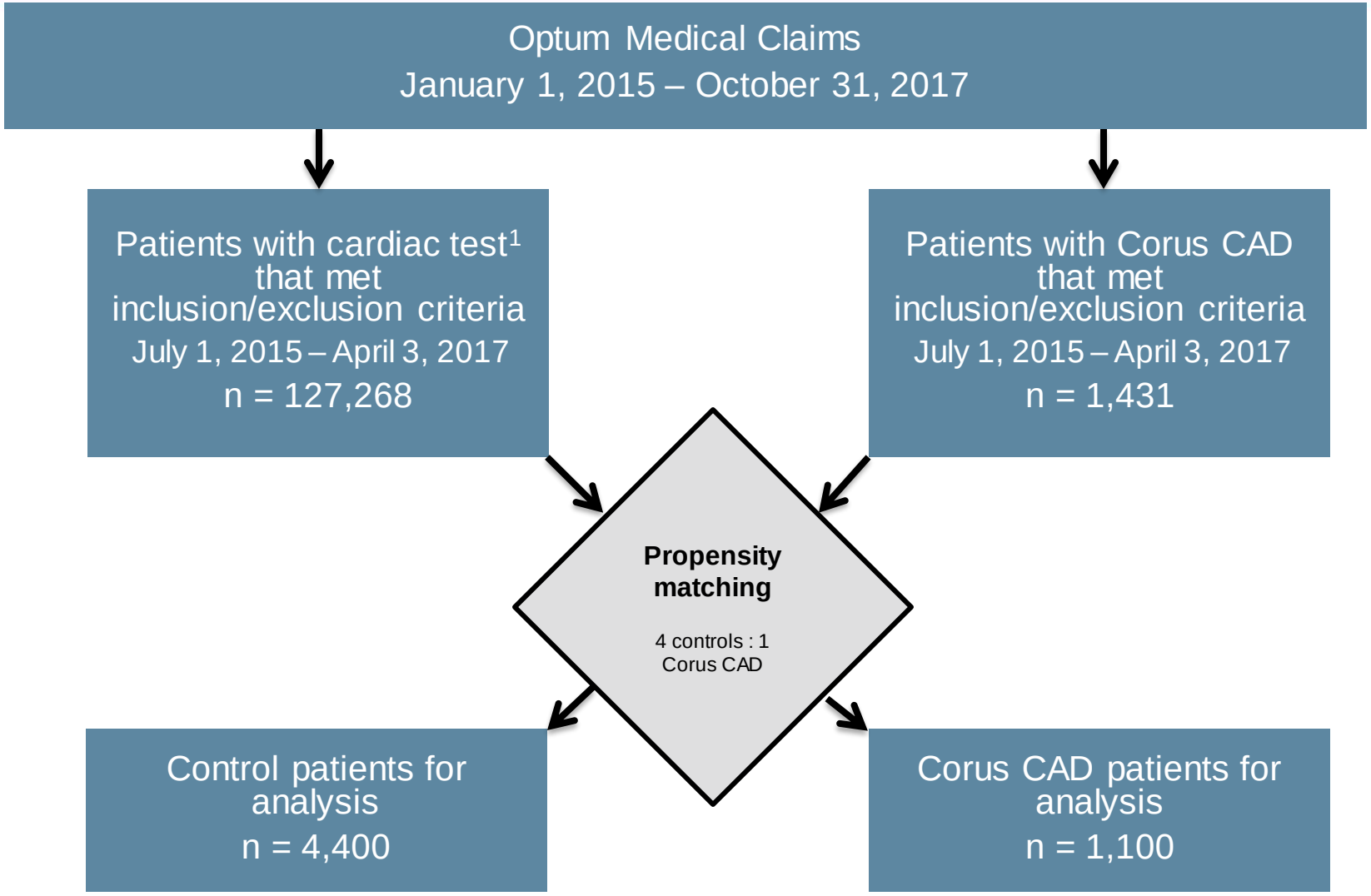
Diagnosis*	Percentage of patients presenting with chest pain in United States
Musculoskeletal condition	**36**
Gastrointestinal disease	**19**
Serious cardiovascular disease**	**16**
Stable coronary artery disease	**10**
Unstable coronary artery disease	**1.5**
Psychosocial or psychiatric disease	**8**
Pulmonary disease***	**5**
Non-specific chest pain	**16**

Majority of symptomatic patients evaluated for suspected CAD are ultimately diagnosed with non-cardiac causes:

- Over half are GI or musculoskeletal conditions
- Nearly a third are psychological, pulmonary, or nonspecific
- But only 10% are stable CAD

* Diagnoses are listed in order of prevalence in United States
** Including infarction, unstable angina, pulmonary embolism, and heart failure
*** Including pneumonia, pneumothorax, and lung cancer
Cayley WE, et al. *Am Fam Physician.* 2005;72:2012-2021.

Data Extraction Schema



[1]Tests include myocardial perfusion imaging (MPI), stress EKG, stress echo, or coronary CTA

CARDIODX®

Data Analysis Summary

The Corus CAD patients had fewer tests and procedures as compared to usual care control patients, specifically:

1. Corus CAD care patients had fewer functional and anatomical tests
2. Corus CAD care patients had fewer invasive cardiac angiographies
3. Corus CAD care patients had fewer coronary revascularizations
4. Corus CAD care patients had fewer office, emergency, and hospital visits

The reduction in downstream testing and procedures had no negative impact on patient outcomes as Corus CAD care patients had lower or similar MACE rates

Endpoints at 60 Days - All Patients (n=5,500)

Test	Cohort	Patients	%	P Value
Functional and Anatomical Tests[1]	Corus	180	16.4%	<0.0001
	Control	1,229	27.9%	
Invasive Angiography (ICA)	Corus	14	1.3%	<0.0001
	Control	246	5.6%	
Revascularization and CABG	Corus	6	0.5%	0.0005
	Control	80	1.8%	

	Cohort	Patients	%	P Value
CAD Related Utilization (Office Visits, ER Visits, and Inpatient Admissions)	Corus	19	1.7%	<0.0001
	Control	176	4.0%	

[1]Tests include myocardial perfusion imaging (MPI), stress EKG, stress echo, or coronary CTA

Endpoints at 180 Days - All Patients (n=5,500)

Test	Cohort	Patients	%	P Value
Functional and Anatomical Tests[1]	Corus	238	21.6%	<0.0001
	Control	1,359	30.9%	
Invasive Angiography (ICA)	Corus	29	2.6%	<0.0001
	Control	286	6.5%	
Revascularization and CABG	Corus	9	0.8%	0.0020
	Control	92	2.1%	

	Cohort	Patients	%	P Value
CAD Related Utilization (Office Visits, ER Visits, and Inpatient Admissions)	Corus	29	2.6%	0.0002
	Control	221	5.0%	

***Conclusions**: In the overall population, patients that received the Corus CAD test received fewer advanced cardiac tests, were sent to the cardiac cath lab less frequently, had fewer revascularization procedures, and fewer CAD related utilizations than patients that did not receive the Corus CAD test.*

[1]Tests include myocardial perfusion imaging (MPI), stress EKG, stress echo, or coronary CTA

MACE Rates at 180 Days - All Patients (n=5,500)

	Cohort	Patients	Rate %	Odds Ratio (95% CI)	P Value
MACE Events[1]	Corus	3	0.3%	0.53 (0.16, 1.76)	0.46
	Control	23	0.5%		

Conclusion: **In the overall population, patients that received the Corus CAD test were at no greater risk of MACE events than those who did not receive the Corus CAD test**. Therefore, the reduction of testing and procedures seen in patients that receive the Corus CAD test does not put patients at greater risk of MACE.

[1]MACE events in myocardial infarction, hospitalization due to unstable angina, and TIA/stroke

Endpoints at 60 Days - Commercial (n=4,079)

Test	Cohort	Patients	%	P Value
Functional and Anatomical Tests[1]	Corus	132	16.6%	<0.0001
	Control	1,071	32.6%	
Invasive Coronary Angiography (ICA)	Corus	12	1.5%	<0.0001
	Control	167	5.1%	
Revascularization and CABG	Corus	5	0.6%	0.0994
	Control	52	1.6%	

	Cohort	Patients	%	P Value
CAD Related Utilization (Office Visits, ER Visits, and Inpatient Admissions)	Corus	13	1.6%	0.0189
	Control	113	3.4%	

[1]Tests include myocardial perfusion imaging (MPI), stress EKG, stress echo, or coronary CTA

Endpoints at 180 Days - Commercial (n=4,079)

Test	Cohort	Patients	%	P Value
Functional and Anatomical Tests[1]	Corus	172	21.7%	<0.0001
	Control	1,145	34.9%	
Invasive Coronary Angiography (ICA)	Corus	21	2.6%	0.0007
	Control	190	5.8%	
Revascularization and CABG	Corus	8	1.0%	0.3041
	Control	61	1.9%	

	Cohort	Patients	%	P Value
CAD Related Utilization (Office Visits, ER Visits, and Inpatient Admissions)	Corus	18	2.3%	0.0349
	Control	139	4.2%	

Conclusion: In the commercial population, **patients that received the Corus CAD test received fewer advanced cardiac tests, were sent to the cardiac cath lab less frequently, and had a lower level of CAD related utilization** than patients that did not receive the Corus CAD test.

[1]Tests include myocardial perfusion imaging (MPI), stress EKG, stress echo, or coronary CTA

CARDIODX

MACE Rates at 180 Days - Commercial (n=4,079)

	Cohort	Patients	Rate %	Odds Ratio (95% CI)	P Value
MACE Events[1]	Corus	3	0.4%	0.77 (0.23, 2.67)	1.0000
	Control	16	0.5%		

Conclusion: In the commercial population, **patients that received the Corus CAD test were at NO greater risk of MACE events than those who did not receive the Corus CAD test.** Therefore, the reduction of testing and procedures seen in patients that receive the Corus CAD test does not put patients at greater risk of MACE.

[1]MACE events in myocardial infarction, hospitalization due to unstable angina, and TIA/stroke

Significance of Claims Analysis

- Large study, allowing for sub-group analysis by insurance type and sex
- No bias or Hawthorne effect given retrospective analysis
- Represents actual clinical decisions made
  - Incorporating physicians true understanding of Corus CAD
  - Incorporating the constraints and complexities of medical practice today
- Confirms our key value messages to payors
  - Corus CAD is used to help rule out downstream testing and procedures
  - Clinician use Corus CAD to identify symptomatic patients that are at low risk of obstructive coronary artery disease
  - Clinicians choose NOT to order addition testing and procedures for those low risk patients
  - Reduction in testing and procedures can improve patient outcome and reduces costs

Conclusions for the Commercial Insurance Population

1. Patients that receive the Corus CAD test had fewer functional and anatomical tests ordered
2. Patients that receive the Corus CAD test had fewer invasive coronary angiography procedures
3. Patients that receive the Corus CAD test had fewer cardiac related office visits, ED visits, and hospital admissions
4. The reduction in testing and procedures in the Corus CAD arm did not impact patient outcomes as seen in MACE rates

Corus CAD provides clinical utility and patient benefit by reducing the downstream testing and procedures in the commercial insurance population

Inclusion / Exclusion Criteria

Inclusion Criteria	
Corus CAD Arm	**Control Arm**
Typical or atypical symptom with risk factor consistent with potential coronary artery disease (intended use criteria for Corus CAD)	
Received Corus CAD (index event) July 2015 – April 2017	Received an MPI, stress echo, stress EKG, or coronary CT Angiography (index event) July 2015 – April 2017
Continuously enrolled in the health plan for 6 months prior and 6 months post the index event	
Age 21+	

Exclusion Criteria
History of Myocardial Infarction (MI)
Current MI or acute coronary syndrome
Any previous coronary revascularization
Diabetes
Suspected unstable angina
Systemic Infections
Systemic inflammatory or auto-immune conditions
Oncological Conditions
Any major surgery within two months

Propensity Matching

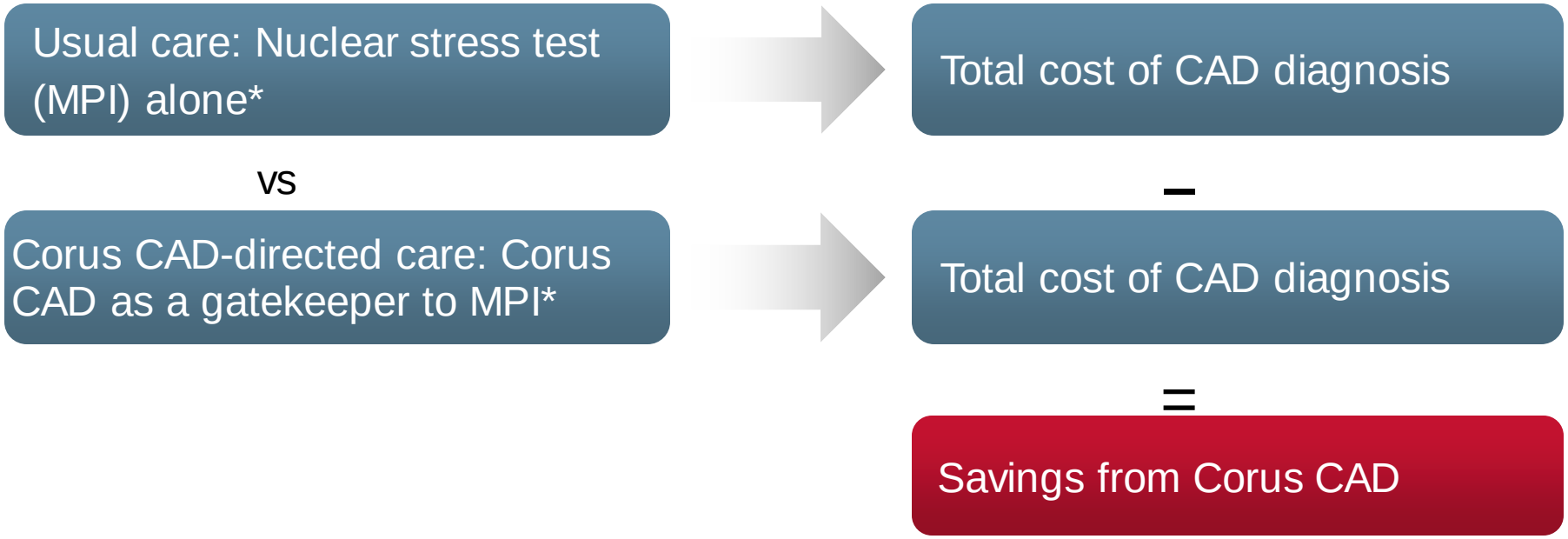
- To ensure comparability between the two arms, the following criteria were used for propensity matching:
  - Age
  - Sex
  - Geography
  - Typical vs atypical symptoms
  - Comorbidities (COPD, hypertension smoking, dyslipidemia)
  - Minority population of zip code
  - Commercial insurance vs. Medicare Advantage
- After propensity matching, study included 1,100 Corus CAD patients and 4,400 control patients
- An outlier analysis was also completed, removing 0.06% (n=71) of the patients

Breakdown by Sex and Insurance Type

	Commercial			Medicare Advantage		
Sex	**Control**	**Corus CAD**	**Total**	**Control**	**Corus CAD**	**Total**
Female	1,713 *(52%)*	412 *(52%)*	2,125 *(52%)*	698 *(63%)*	194 *(63%)*	892 *(63%)*
Male	1,572 *(48%)*	382 *(48%)*	1,954 *(48%)*	417 *(37%)*	112 *(37%)*	529 *(37%)*
Total	3,285	794	4,079	1,115	306	1,421

Corus® CAD Budget Impact Model
Published in *Population Health Management*

- Estimates the economic value of Corus CAD within a health plan's member population over a 1-year time horizon
  - Conservative analysis that excludes patient impact from radiation dosing (and attributable cancer risk) and test layering beyond MPI



* MPI performance based on peer-reviewed literature; Corus CAD performance based on multicenter COMPASS study
Hochheiser LI et al. *Popul Health Manag.* 2014;17:287-296.

CARDIODX®

Corus® CAD as a Gatekeeper Results in PMPM Savings of $0.77 for a Commercial Health Plan

For a 500,000 member health plan,* Corus CAD over 1 year at 50% capture rate results in:

1,192 fewer nuclear stress tests (MPIs)

437 fewer invasive coronary angiographies

Total annual health plan savings: $4.6M

PMPM savings: $0.77

Commercial Cost Assumptions:

- Nuclear Stress Test (MPI) = $1,276**
- Cardiologist Office Visit = $177
- Invasive Angiography = $11,459**
- Revascularization = $21,985**
- Optimal Medical Therapy = $1,000
- Corus CAD List Price = $1,245

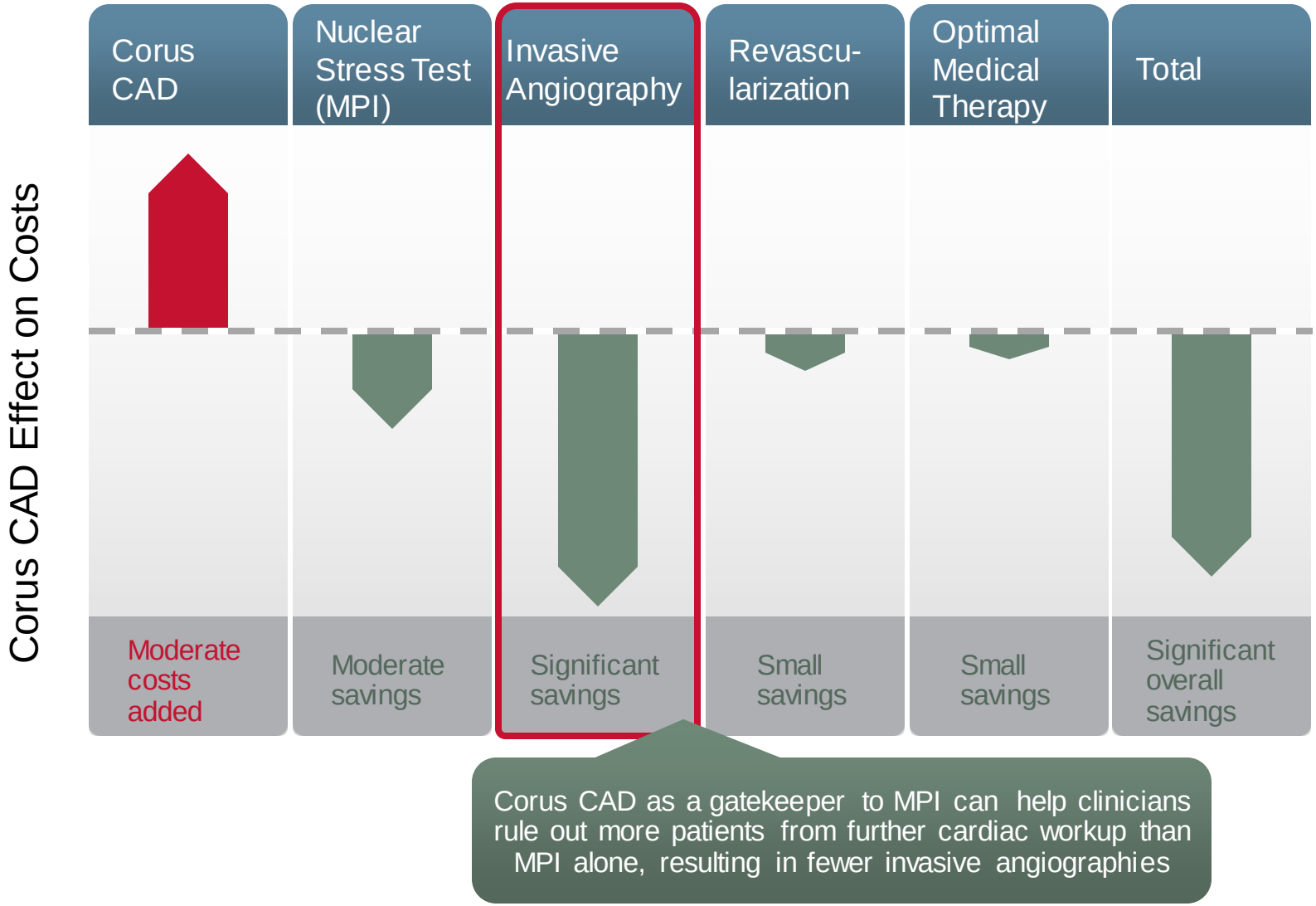
• Incidence of office visits for Corus CAD eligible patients is 1.04%, or 5,200 eligible lives. Corus CAD performance based on a pre-specified threshold of 15 in the overall population of men and women referred to MPI.

** Costs are based on administrative claims data from a large U.S. health plan associated with OptumInsight.

Hochheiser LI et al. *Popul Health Manag.* 2014;17:287-296.

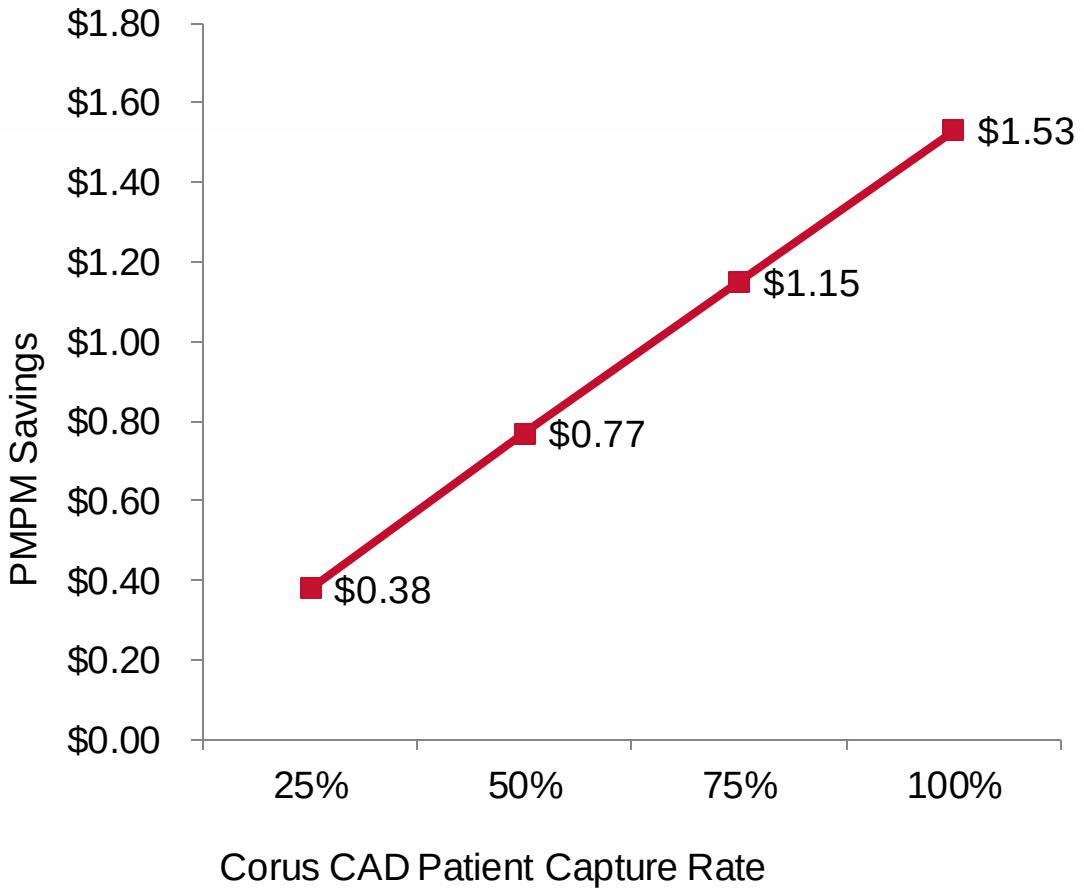
CARDIODX®

Reduction in Invasive Coronary Angiography with Corus® CAD Drives PMPM Savings



CARDIODX®

Corus® CAD as a Gatekeeper Results in PMPM Savings for a Commercial Health Plan at Lower Capture Rates



Commercial Cost Assumptions:

- Nuclear Stress Test (MPI) = $1,276*
- Cardiologist Office Visit = $177
- Invasive Angiography = $11,459*
- Revascularization = $21,985*
- Optimal Medical Therapy = $1,000
- Corus CAD List Price = $1,245

Model run for a plan with 500,000 covered lives to illustrate impact at 1 year. Incidence of office visits for Corus CAD eligible patients is 1.04% or 5,200 eligible lives.

* Costs are based on administrative claims data from a large U.S. health plan associated with OptumInsight.
Hochheiser LI et al. *Popul Health Manag.* 2014;17:287-296.

CARDIODX®

Usual Care is Inefficient and Results in Low Rates of Obstructive CAD at Invasive Coronary Angiography

Symptomatic patient in clinic office with no known prior CAD

Usual Care

Exercise Treadmill

Patient referred for MPI +/- ECHO

Up to 9 days**

Myocardial Perfusion Imaging

and/ or

Stress Echo

Patient referred for Cath

Up to 7 days**

Invasive Coronary Angiography

75% of women will not have obstructive CAD[1]

Potential referral

Corus CAD Care

Patient has blood drawn

Same Day

CORUS CAD

Patient receives test score

<72 Hours

Clinician uses Corus CAD and other information to determine if the patients probability warrants further cardiac testing

No further cardiac testing

**Average times based on CardioDx market research conducted at AHA, ACC. Times likely to be longer if patient presents to primary care

CARDIODX®

Corus® CAD Intended Use

- **Corus® CAD** is intended for women and men (ages 21 to 85) with **stable** symptoms suggestive of obstructive coronary artery disease
  - Typical symptoms (i.e. chest pain, shortness of breath) or
  - Atypical symptoms (i.e. dizziness, nausea, jaw and/or left arm pain) **plus** at least one cardiovascular risk factor

- **Corus® CAD** is ***not*** intended* for patients
  - Diagnosed with diabetes (or on diabetic medications)**
  - With a history of heart attack or revascularization
  - With active infection or inflammatory disease
  - Receiving chemotherapy within the past 12 months or steroids/other immunosuppressants within the past 2 months

*Since these conditions/agents are inflammatory in nature and may independently alter test results

**Non-diabetic patients taking metformin and pre-diabetic patients are not excluded from receiving the test

CARDIODX®