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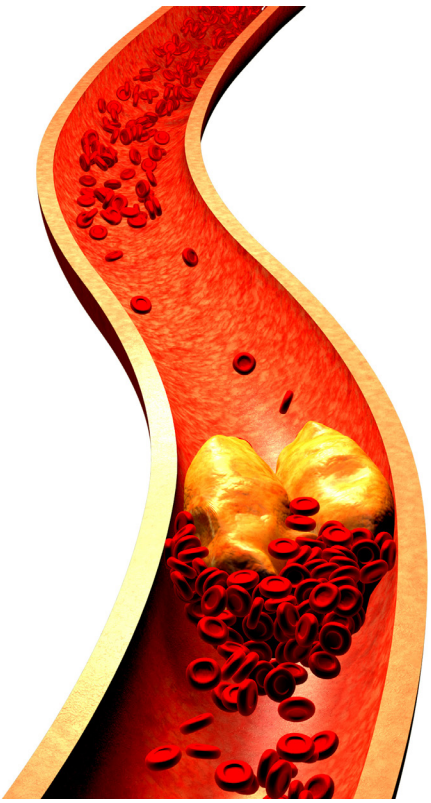
A Gene Expression Test to Assess the Likelihood of Obstructive Coronary Artery Disease



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Summary

- Coronary artery disease is the most common form of cardiovascular disease in Canada.
- A new blood test, Corus CAD, combines age, sex, and gene expression in an algorithm to determine the likelihood a person has obstructive coronary artery disease.
- Corus CAD is intended for use in patients with suspected undiagnosed obstructive coronary artery disease.
- There is interest in assessing Corus CAD in patient groups such as women with obstructive coronary artery disease who often have atypical symptoms and may not always be appropriately referred for follow-up testing.
- Studies have evaluated whether Corus CAD may help clinicians rule out coronary artery disease in some patients when used as a complement to patient history, risk factors, symptoms, physical examination, and other diagnostic tests.

Background

Coronary Artery Disease

Coronary artery disease (also called ischemic heart disease) is the most common type of cardiovascular disease in Canada.[1,2] It occurs when a build-up of plaque (atherosclerosis) narrows the arteries that bring blood to the heart, limiting the amount of oxygen the heart receives (ischemia).[1-3] Untreated coronary artery disease can lead to heart attack, stroke, or death.[2]

People with coronary artery disease often experience chest pain (angina) or shortness of breath.[1,2] Other symptoms of coronary artery disease include fatigue, pain, dizziness, and sensations of suffocating or burning starting from the centre of the chest and sometimes moving to other parts of the upper body, such as the arm, neck, or back.[2] Women with coronary artery disease often experience more subtle symptoms, such as vague chest discomfort.[2,3]

People presenting with stable symptoms of coronary artery disease are diagnosed using a combination of methods, including history, physical examination, symptom characteristics, risk factors (such as age, sex, excess body weight, and smoking), and diagnostic tests (such as non-invasive stress testing and invasive angiography). (see Box 1).[2-5]

Gene Expression

A person's DNA contains all the genetic information needed to build an estimated 20,000 different proteins.[12] Gene expression is the process by which genetic information encoded in DNA is used to generate gene products (e.g., proteins). The quantity and timing at which gene products are generated depends on many factors, including the type of cell (for example, heart or lung) and the presence of disease.[12]

Advances in science have allowed for the discovery and study of many biological markers (biomarkers) of gene expression.[12] When used alone or, more commonly, in combination with known risk factors, biomarkers can help predict the possibility of developing a disease, help diagnose the presence of disease, or determine how a disease will progress in an individual patient.[12]

A new test that measures the level of expression of genes associated with coronary artery disease, and incorporates age and sex, is intended to help clinicians assess the likelihood of obstructive coronary artery disease in patients presenting with stable symptoms.

The Technology

Corus CAD[13] (CardioDx, Redwood City, CA), is a blood test intended for use in people with symptoms suggestive of stable coronary artery disease to help clinicians rule out the possibility of obstructive coronary artery disease or help them plan for further testing and management.[14]

A Corus CAD sample kit contains all the materials necessary for the physician to take a patient's blood sample and send it to CardioDx for processing and analysis.[14,15] Testing involves the following steps:[14-17]

- Taking a standard venous blood draw from the patient during a clinician office visit
- Completing a patient profile and sending the sample to CardioDx in a temperature controlled package

Box 1: Common Tests for Coronary Artery Disease

Clinical Prediction Rules

- **Diamond-Forrester score** — A model for assessing patients with symptoms of coronary artery disease that incorporates age, sex, and type of chest pain to determine their likelihood of having coronary artery disease before testing.[6]

Non-Invasive Testing

- **Exercise Stress Testing** — Monitoring the electrical activity in the heart, while patients walk on a treadmill as the speed and incline gradually increase.[7]
- **Stress Echocardiography** — Using ultrasound to create images of the heart, before and after walking on a treadmill, to evaluate the presence of heart-wall motion abnormalities that indicate inadequate coronary blood flow.[8]
- **Myocardial perfusion imaging** — Using a combination of exercise stress testing and imaging to see the blood supply to the heart. Patients are injected with radioactive tracers that circulate through the blood. A gamma camera takes pictures of the heart while exercising and at rest. This technique can be performed using single photon emission computed tomography or positron emission tomography.[9]
- **Coronary computed tomography (CT) angiography** — Creating a cross-sectional or 3-D picture of the heart using X-ray images to determine if there are plaque or calcium deposits inside the arteries. CT angiography requires use of a contrast agent to show the blood vessels.[10]

Invasive Testing

- **Coronary angiography** — Inserting a catheter (a long flexible tube) into an artery in the wrist or groin and moving it to the heart, where a contrast agent is released and X-ray images are taken to detect blockages in the coronary arteries.[11]

- Processing the sample at CardioDx's laboratory
- Reviewing test results, presented as an Age/Sex/Gene Expression Score (ASGES), through CardioDx's online portal or by fax.

Once the blood sample is received by CardioDx, RNA is purified from the sample, complementary DNA is synthesized, and quantitative real-time polymerase chain reaction (qRT-PCR) is used.[16] Test results are calculated using the age, sex, and six gene expression terms, composed of 23 genes associated with coronary artery disease.[16,18] Some of the gene expression terms are unique to men, some are unique to women, and others occur in both sexes.[18] Following analysis, an ASGES is reported on a 40-point scale with a score of 1 representing a low likelihood of disease and 40 representing a high likelihood of disease.[16] The calculations used to determine the ASGES differ between men and women based on age, specific genes, and weighting of genes included in the test.[16] Test results are typically available to clinicians in a few days.[14]

Corus CAD is not intended for use in people who have previously had a heart attack or undergone cardiac revascularization procedures, who have a history of obstructive coronary artery disease, high-risk unstable angina, systemic infectious or inflammatory conditions, or diabetes, who are taking steroids or drugs that suppress the immune system, or who are receiving chemotherapy.[19]

Availability

The Corus CAD test is not currently available in Canada. The manufacturer intends to explore marketing the test in Canada in the future (David Levison, Chief Strategy Officer, CardioDx, Inc., Redwood City, CA: personal communication, 2017 Nov 6).

In the US, the test is available as a laboratory-developed test certified under the Clinical Laboratory Improvement Amendments.[20]

Cost

Canadian pricing for the Corus CAD test is not available. According to the manufacturer's documentation, the US cost of the test for uninsured patients is US$1,245.[21]

Who Might Benefit?

An estimated 2.4 million Canadians live with coronary artery disease.[22] In 2005-2006, 6.5% of all hospitalizations (excluding those for pregnancy) in Canada were related to coronary artery disease.[23] In 2004, 17.3% of all deaths were attributed to coronary artery disease.23 Thousands of Canadians are hospitalized or die because of a heart attack each year.[23] A 2016 report from the Chief Public Health Officer found that Canadians with lower household income, men, people over the age of 50, and Indigenous people were more likely to have cardiovascular disease.[24]

It is more difficult to diagnose coronary artery disease in women because of differences in presentation of symptoms and differences in the biology of the heart. Women are more likely to be incorrectly diagnosed with coronary artery disease using non-invasive methods, leading to increased use of more invasive diagnostic procedures.[2,25]

The Corus CAD test is only intended for use in a specific population of patients presenting with symptoms suggestive of coronary artery disease (see the Technology section). Many Canadians, such as people with diabetes, of whom 2% to 19% develop coronary artery disease,[26] would not benefit from receiving this test.

Methods

These bulletins are not systematic reviews and do not involve a detailed critical appraisal or a detailed summary of study findings. Rather they present an overview of the technology and available evidence. They are not intended to provide recommendations for or against a particular technology.

Literature Search Strategy

A peer-reviewed literature search was conducted using the following bibliographic databases: MEDLINE, PubMed, Embase, and the Cochrane Library (2017, Issue 05). Grey literature was identified by searching relevant sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters). No methodological filters were applied. The search was limited to English-language documents published between January 1, 2012, and May 8, 2017. Regular alerts updated the search until project completion; only citations retrieved before February 8, 2018, were incorporated into the analysis. Conference abstracts were excluded from the search results.

Study Selection

One author screened the literature search results and reviewed the full text of all potentially relevant studies. Studies were considered for inclusion if the intervention used included gene expression testing for obstructive coronary artery disease. Conference abstracts and grey literature were included when they provided additional information to that available in the published studies.

Peer Review

A draft bulletin was reviewed by two clinical experts and the manufacturer.

Current Practice

In Canada, obstructive coronary artery disease is commonly defined as greater than 50% stenosis in the left main coronary artery or greater than 70% stenosis in an epicardial artery (on the outer surface of the heart).[27,28]

The 2014 Canadian Cardiovascular Society Guidelines for the Management of Stable Ischemic Heart Disease outline the current evidence-based approach for diagnosing coronary artery disease in Canada.[4] Diagnosing coronary artery disease is complex and may involve both invasive and non-invasive testing (see Box 1), depending on a patient's history, physical examination, and initial test results.[4] All patients with suspected coronary artery disease should undergo a thorough history and physical examination to evaluate symptoms and risk factors for coronary artery disease (such as age, sex, history of smoking, and physical inactivity).[4] The results of this initial examination will inform a pretest probability (how likely it is a patient has coronary artery disease before diagnostic testing) that can be used to determine a testing plan.[4]

Depending on the patient and the pretest probability of coronary artery disease, the guidelines recommend clinicians refer patients for non-invasive or invasive testing.[4] The guidelines note that selecting the appropriate non-invasive test for a patient is complicated by the fact that no single test can provide all the information a clinician may need to make a diagnosis.[4]

In addition to the common tests listed in Box 1, if available, more specialized testing methods, such as positron emission tomography, CT perfusion scanning, or MRI, can also be considered to complement, or serve as an alternative to, other tests.[4] Clinicians are encouraged to consider minimizing patient exposure to radiation associated with some types of testing.[4]

The Evidence

We identified 19 studies of the Corus CAD test.[18,29-46] All but one of the studies[43] were funded or co-authored by the manufacturer, or by authors who have received funding from CardioDx.

Six studies form the central body of evidence of the validity and clinical utility of the test:

- PREDICT — Personalized Risk Evaluation and Diagnosis in the Coronary Tree[29]
- COMPASS — Coronary Obstruction Detection by Molecular Personalized Gene Expression[30]
- IMPACT-CARD — Investigation of a Molecular Personalized Coronary Gene Expression Test on Cardiology Practice Pattern[31]

- IMPACT-PCP — Primary Care Providers Use of a Gene Expression Test in Coronary Artery Disease[32]
- REGISTRY I — Investigation of a Novel Gene Expression Test for the Diagnosis of Obstructive CAD on Physician's Practice Pattern[33]
- PRESET registry — A Registry to Evaluate Patterns of Care Associated with the use of Corus CAD in Real World Clinical Settings.[34]

Of the remaining 13 studies:

- Seven were secondary analyses[18,35-40]
- Three were smaller studies of clinical utility that may be of interest to readers[41-43]
- Three examined the costs of using the test.[44-46]

Information about the six central studies and secondary analyses is presented by outcome in **Table 1**. Additional information on the validity and clinical utility of the test that may be of interest to readers is highlighted later in this section. Studies of other uses of the Corus CAD test or ASGES are presented in the **Concurrent Developments** section.

Central Studies

The six central studies of the Corus CAD test[29-34] generally included patients with no history of diabetes who presented with typical or atypical symptoms suggestive of coronary artery disease. Obstructive coronary artery disease was defined as one or more lesions (plaque) causing at least 50% loss in the diameter (stenosis) of a major artery. Although the studies all use the Corus CAD test, the outcome measured is ASGES; that is, the score produced by CardioDx after samples are received.

The studies used a threshold of 15 (14.75 in PREDICT[29]) out of 40 when interpreting the Corus CAD test results. A score of 15 or lower is considered low (at low risk of currently having obstructive coronary artery disease) and a score greater than 15 is considered elevated (at higher risk of currently having obstructive coronary artery disease). Corus CAD was also analyzed as a continuous variable (score 1-40) in the PREDICT and COMPASS studies.[29,30] These studies investigated test performance and change in clinician practice.

Test Performance

The clinical performance of the Corus CAD test was validated in two key studies (PREDICT and COMPASS: Table 1), both conducted at multiple sites across the US.[29,30] Researchers also conducted secondary analyses of the PREDICT study to explore the performance of the test in women[18,36] and reported on major adverse cardiovascular events (MACE) and coronary procedures after ASGES testing.[18,35,36]

Clinical Utility

Four central studies (IMPACT-CARD, IMPACT-PCP, REGISTRY I, and PRESET registry; **Table 1**) investigated the impact that using the Corus CAD test in clinical practice may have on patient management in the US.[31,33,34,47] Two smaller studies, reported as conference abstracts, also examined similar outcomes.[42,43] Two US cost studies also evaluated the impact of Corus CAD use on the number of patients referred for coronary angiography and other diagnostic tests.[44,45]

The impact of Corus CAD on the care of women was studied in a secondary analysis of data from the IMPACT-PCP and REGISTRY I studies,[38] in two secondary analyses of data from the PRESET registry (reported as conference abstracts),[39,40] and one additional study (reported as a conference abstract).[41] In addition, a secondary analysis of the PRESET registry evaluated the impact of Corus CAD on care in patients over the age of 65.[37]

None of the studies reported whether changes in clinician behaviour resulted in changes in direct health-related outcomes in patients.

Nine of the clinical utility studies also included secondary outcomes of MACE and coronary procedures.[31-34,37-41]

Cost Studies

The costs of using the Corus CAD test in US health care settings were modelled in one budget impact analysis[45] and one cost-utility analysis,[44] both published in 2014. Costs considered in both studies included those for different tests and procedures and those for subsequent treatments.[44,45] One study also considered the costs of lost patient time and heart attacks,[44] while the other study also considered the costs of office visits.[45] An economic analysis of the IMPACT-CARD study was also reported as a conference abstract.[46]

Concurrent Developments

Other uses for ASGES results are being explored, as are other applications and uses of the Corus CAD test.

Detection of Atherosclerosis and Stenosis

A study of a subset of 610 patients from the PREDICT and COMPASS studies sought to determine whether ASGES was associated with plaque burden and luminal stenosis.[48]

Researchers have also investigated whether ASGES is associated with plaque volume and plaque type as measured by intravascular ultrasound (the use of soundwaves to see the inside of blood vessels) in a subset of 18 patients without diabetes from the ATLANTA study (originally designed to compare the measurement of plaque characteristics using CT angiography and intravascular ultrasound).[49]

Change in ASGES Over Time

Using data from the COMPASS studies, researchers have assessed the stability of ASGES after one year in patients who did not have a cardiac event or procedure since the completion of the COMPASS study.[50]

Effect of Exercise on ASGES

To understand if the Corus CAD test can be used after exercise, researchers evaluated the effect of exercise stress on ASGES in a pilot study of 20 patients (10 women and 10 men), who underwent exercise stress testing.[51] The trial was funded by the manufacturer.[51]

Prediction of Future Cardiovascular Events

One study evaluated the correlation between Corus CAD scores and future cardiovascular events. A total of 1,116 patients from the PREDICT trial were followed for one year after angiography to monitor rates of major adverse cardiac events and cardiac interventions.[35] A conference abstract also reported on this outcome.[36]

A subgroup analysis of 2,370 patients in the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE study) without diabetes who received a Corus CAD test evaluated whether patients with an elevated ASGES were at greater risk of death, heart attack, hospitalization for unstable angina, or revascularization, than were patients with a low ASGES.[52]

Other Indications

The relationship of ASGES to obstructive coronary artery disease in people with rheumatoid arthritis has also been studied.[53]

Other Gene Expression Testing Applications

A recent statement from the American Heart Association describes several other advances in gene expression testing and the impact they may have on our understanding and diagnosis of cardiovascular disease.[12] Although there are many applications under investigation, Corus CAD is one of the few tests currently commercially available.

Implementation Issues

Training

Both the IMPACT-PCP and REGISTRY I studies reported training times of five hours to implement the test in primary care practices in the US.[32,33] The main purpose of training is to educate clinicians and other clinic personnel about the appropriate patient population for the test and how to interpret test results.

Validity in Different Ethnic Groups

A limitation of both the PREDICT and COMPASS studies is that they included primarily white patients.[29,30]

To evaluate performance in other ethnic and racial groups, researchers have reanalyzed data from the PREDICT study.[50] Further research may help improve the understanding of the performance of Corus CAD in different ethnic groups.

Exposure to Radiation and Contrast Agents

Three reports of using Corus CAD in clinical practice mention that test results finding a low ASGES could affect exposure to, and adverse events associated with, radiation and contrast agents used in non-invasive and invasive tests for coronary artery disease by reducing or eliminating the need for additional tests.[31,32,34] However, none of the studies evaluated these outcomes.

Diagnostic Yield

Several reports have noted the potential of ASGES to affect the number of patients referred for additional testing who actually have coronary artery disease.[29-32,44,45] None of the studies evaluated this outcome.

Final Remarks

The Corus CAD test has been studied in and is intended for use in a specific population of patients with suspected obstructive coronary artery disease. Studies of gene expression tests in small, carefully selected groups may not be generalizable to real-world clinical practice.[54]

No studies were identified that compare gene expression tests to more advanced methods of diagnostic testing for coronary artery disease. Studies are also needed to understand if changes in patient management result in better patient health outcomes through reducing unnecessary testing and associated adverse events.[20,38,54]

Table 1: Summary of Clinical and Cost Evidence

Study Name, Author, Publication Year, Location	Patient Characteristics; Sample Size (Incl. in Analysis)	Study Design	Intervention	Comparator or Reference Standard	Outcomes	Key Findings
Test Performance						
PREDICT, Rosenberg et al., 2010, US[29]	Pts referred for diagnostic CA angiography with a history of chest pain or atypical symptoms suggestive of CAD disease, or a high-risk of CAD; n = 1,569 (649 in validation arm) Prevalence of obstructive CAD = 37%	• Prospective • Multi-centre (39 sites)	• ASGES • D-F • MPI	CA	• Sensitivity[a] • Specificity[a] • NPV[a] • PPV[a] • ROC analysis[b]	" … the sensitivity was 85% with a specificity of 43%, corresponding to [NPV and PPV] of 83% and 46% respectively." (p. 7)[29] "The primary end point AUC was 0.70 …" (p. 6)[29]
	Secondary analysis using data from 1,160 pts (492 women and 668 men)[18] Prevalence of obstructive CAD in women = 22%				• Clinical correlates of obstructive CAD • Predictive value of site interpreted MPI • Predictive value of the ASGES	• "The probability of obstructive CAD increased with increasing [ASGES] for both men and women." (p. 323)[18] • " … [ASGES] was an independent predictor of obstructive CAD in the overall population ([OR] 2.53 …), as well as in the male (OR 1.99 …) and female (OR 3.45 …) subgroups separately, whereas MPI was not." (p. 323)[18]
	Secondary analysis of 1,160 pts (850)[35]	• Prospective • Multi-centre • (39 sites) • 1-year follow-up[c]			• Rate of MACE (defined as stroke, TIA, MI, or death) and interventional procedures after ASGES	"There were 17 [pts] with MACE, of which 15 occurred more than 30 days after index angiogram; 4 of these [pts] had earlier angiogram" (p. 370)[35]
	Secondary analysis of 1,328 pts (1,266)[36d]					"A total of 330 [pts] (26%) had procedures or MACE within 30 days and 21 (2.4%) had subsequent events (10, 16, 5 for MI, stoke, and death, respectively)."[36]

Study Name, Author, Publication Year, Location	Patient Characteristics; Sample Size (Incl. in Analysis)	Study Design	Intervention	Comparator or Reference Standard	Outcomes	Key Findings
Clinical Utility						
IMPACT-CARD, McPherson et al., 2013, US[31]	Pts with symptoms suggestive of CAD who did not have a history of CAD or diabetes referred to a cardiologist; n = 88 (83)	• Historically controlled before and after • Single centre (6 cardiologists receiving referrals from 30 primary care physicians) • 30-day and 6-month follow-up	Pt care plan with ASGES	Pt care plan without ASGES	• Change in diagnostic testing plan • Upgrade or downgrade in Pt management[g] • Rate of MACE (undefined) after introduction of ASGES	• " … changes in the recommended diagnostic testing plan … occurred in 58% of patients …" (p. 39)[31] • " … more patients had a decreased (39%, n = 32) versus increased (19%, n = 16) intensity of testing …" (p. 39)[31] • "No [MACE]s were observed for any of the 161 patients at 30-day and 6-months follow-up …" (p. 39)[31h]
IMPACT-PCP, Herman et al, 2013, US[32]	Pts without diabetes presenting to their primary care clinician[i] with suspected CAD; n = 261 patients (251)	• Uncontrolled before and after • Multi-centre • (4 primary care clinics) • 30-day follow-up	Pt care plan with ASGES	Pt care plan without ASGES	• Change in diagnostic plan • Upgrade or downgrade in Pt management[j] • Rate of MACE (undefined) after introduction of ASGES	• "The primary outcome demonstrated a change in diagnostic plan … following [ASGES] testing in 58% of patients …" (p. 261)[32] • " … more patients showed a reduction (n = 93) than increase (n = 52) in intensity of testing …" (p. 261)[32] • " … 1 (0.4%) had a [MACE] (hemorrhagic stroke in a patient with low [ASGES] 5 days after [ASGES] testing, judged by the clinical investigator to be not related to the study protocol)." (p. 262)[32]

Study Name, Author, Publication Year, Location	Patient Characteristics; Sample Size (Incl. in Analysis)	Study Design	Intervention	Comparator or Reference Standard	Outcomes	Key Findings
Clinical Utility						
REGISTRY I, Ladapo et al., 2015, US[33]	Primary care pts who have received the Corus CAD test; n = 342	• Prospective registry • Multi-centre • (7 community-based primary care practices) • 6-month follow-up	ASGES	NA	• Referral to cardiologists or for cardiac testing • Rate of MACE (such as coronary artery revascularization, hospitalization, or death)	• "There was a strong association between cardiac referral rates by low and elevate [ASGES] groups, was only 6% (10/167) of the low [ASGES] patients versus 70% (122/175) of the elevated [ASGES] patents were referred for further evaluation …" (p. 347)[33] • "The overall MACE rate was [approximately] 1.5% (5/339)" (p. 348)[33] • "All of the 167 low [ASGES] patients were available for follow-up, and there was 1 hospitalization (… [PCI]) and 1 death (acute respiratory failure judged not to be related to the intended use of the [ASGES] test." (p. 348)[33] • "Among the 172/175 elevated GES patients available for follow-up, there were 2 hospitalizations (emergent PCI/stent placement and syncope) and 1 death (MI)." (p. 349)[33] • " … there were 21 elective [invasive CA] procedures ([approximately] 6% of all study patients) performed during the follow-up period, including 2 in low GES patients and 19 … in elevated GES patients." (p. 349)[33]
Ladapo et al., 2015, US[38]	320 women enrolled in the IMPACT-PCP[47] and REGISTRY I[33] studies	Secondary analysis • Median follow-up 37 days (IMPACT-PCP) • Median follow-up 278 days (REGISTRY I)	See IMPACT-PCPC and REGISTRY I above	See IMPACT-PCPC and REGISTRY I above	• Rate of invasive CA • MACE rate • MACE/ revascularization	• "Four [invasive CAs] were performed in the combined analysis" (p. 1226)[38] • "The MACE rate … was approximately 0.9% (3 of 320)." (p. 1227)[38] • "The MACE/ revascularization (defined as percutaneous coronary intervention or stent placement) rate was approximately 1.2% (4 of 320)." (p. 1227)[38]

Study Name, Author, Publication Year, Location	Patient Characteristics; Sample Size (Incl. in Analysis)	Study Design	Intervention	Comparator or Reference Standard	Outcomes	Key Findings
Clinical Utility						
PRESET registry, Ladapo et al., 2017, US[34]	Primary care pts who have received the Corus CAD test; n = 934 (566)	• Prospective registry • Multi-centre (21 primary care practices) • 1 year follow-up	ASGES	NA	• Referral to cardiologists or for cardiac testing • Rate of MACE (defined as stroke [including TIA], MI, and cardiac-related death) or coronary artery revascularization procedure	• " … the difference in rates of cardiac referral between low and elevated ASGES patients was … 10% (26/252 of low ASGES patients referred, [versus] 44% (137/314) of elevated ASGES patients referred …" (p. 484)[34] • "There were 12 patients with [MACE] and 5 with revascularization." (p. 482)[34] • " … [MACE] were noted in 3/252 (1%) low ASGES patients … and 9/314 (3%) elevated ASGES patients …" (p. 482)[34]
	Secondary analysis of 176 pts over the age of 65.[37]					• " … 72 (41%) had a cardiac referral … in the 45-day period after [ASGES] testing." (p. 3)[34] • " … a referral rate of 12.5% (5/40) in those with low ASGES and 49.3% (67/136) in those with high ASGES …" (p. 3)[34] • "Thirteen of 136 (10%) participants with high ASGES had a [MACE] or revascularization (3 strokes or [TIAs], 3 [MIs], 3 deaths, 4 revascularizations) and 0 of 40 with low ASGES …" (p. 4)[34]
	Secondary analysis of 369 women[39d]					• "0.5% (2/369), both events were judged to be unrelated to the investigational agent or procedure." (p. 1400)[39]
	Secondary analysis of 288 women[40d]					• "Six patients experienced major adverse cardiovascular outcomes during follow-up: all were considered unrelated to obstructive CAD" (p. A-19)[40]

ASGES = Age/Sex/Gene Expression Score; AUC = area under the curve; CA = coronary angiography; CAD = coronary artery disease; COMPASS = Coronary Obstruction Detection by Molecular Personalized Gene Expression; CT = computed tomography; D-F = Diamond and Forrester Chest Pain Prediction Rule; IMPACT-CARD = Investigation of a Molecular Personalized Coronary Gene Expression Test on Cardiology Practice Pattern; IMPACT-PCP = Primary Care Providers Use of a Gene Expression Test in Coronary Artery Disease; MACE = major adverse cardiac event; MI = myocardial infarction; MPI = myocardial perfusion imaging; NA = not applicable; NPV = negative predictive value; OR = odds ratio; PPV = positive predictive value; PREDICT = Personalized Risk Evaluation and Diagnosis in the Coronary Tree; PRESET registry = A Registry to Evaluate Patterns of Care Associated with the use of Corus CAD in Real World Clinical Settings; pt = patient; REGISTRY I = Investigation of a Novel Gene Expression Test for the Diagnosis of Obstructive CAD on Physician's Practice Pattern; ROC = receiver operating characteristic; TIA = transient ischemic attack.

[a] Using ASGES cut off of 14.75.

[b] Calculated for a continuous ASGES (0-40), D-F, and MPI.

[c] Procedures and events occurring within 30 days of reference coronary angiography were considered baseline events.

[d] Only abstract format available.

[e] Using ASGES cut off of 15.

[f] Calculated for a continuous ASGES (0-40) and MPI.

[g] Upgrade in patient management = non-invasive cardiac testing (stress testing with or without imaging or CT angiography) or invasive coronary angiography; downgrade in patient management = medical therapy or no further testing.

[h] Includes historical controls

[i] Including doctors, nurse practitioners, and physician assistants.

[j] Upgrade in patient management = non-invasive cardiac testing (stress testing with or without imaging, CT angiography or coronary angiography) or invasive coronary angiography; downgrade in patient management = no additional testing or treatment, lifestyle changes, or medical therapy.

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