UNMASKED
Heart Disease

Spokane Tribal Enterprise
Tshimakain Creek Research & Diagnostic, LLC

Douglas S. Harrington, M.D.
Medical Director
Tshamikain Creek Research & Diagnostic Laboratory

GUARDaHEART FOUNDATION First Nation

Health

the condition of being sound in body, mind, or spirit

a condition in which someone or something is thriving or doing well

Webster's Dictionary

Wellness

"is a state of optimal well-being that is oriented toward maximizing an individual's potential. This is a life-long process of moving towards enhancing your physical, intellectual, emotional, social, spiritual, and environmental well-being."

Mickinley Health Center University of Illinois

Heart Disease Facts: Native Americans

Heart disease occurs earlier and with more severe results

#1
Cause of death in Native populations

Lower age of onset
Most die before 65

Diabetes
Highest risk of any ethnic group (16% vs 8.7%)

Opioids and Heart Disease Research Project

- "People who took opioids were more than twice as likely to have a heart attack than their counterparts who took over the-counter painkillers."
  - Taking the drug as prescribed and for underlying medical concerns
- Using opiates incorrectly or taking them recreationally puts your heart at further risk
  - Injecting crushed or dissolved pills damages vital tissues
  - Street drugs often contain contaminates that cause even more harm to your heart and blood vessels

Vanderbilt University Study-Heart Disease Biggest Risk from Opioids

- Many opioid related deaths have been misclassified as overdoses
- Over twice as many patients died from cardiovascular and respiratory problems than from overdoses
- "More than two-thirds of the excess deaths for patients in the opioid group were due to cardiac disease rather than unintentional overdose"
- **"If there is this degree of misclassification, then previous research on opioid mortality, most of which has focused on overdose deaths identified from death certificates, has substantially underestimated the true risks of opioids."**

We Must Understand the Cause of Addiction to Be Able to Cure It

- The Partnership for a Drug-free America Experiment (1980s TV Campaign)
  - The original theory of addiction resulted from rat experiments that put single animals in a cage with two water sources (1970s)
    - Only water
    - Water laced with a drug (heroin or cocaine)
  - The rat would become obsessed with the drug water and consume it until it killed itself
  - The TV add explained that this occurred 9 times out of 10 and the same could happen to you

It is not as Simple as That-The Rest of the Story

- Bruce Alexander (Vancouver Professor of Psychology) experiments (1970s)
  - He noticed something odd in the original experiments
  - The animals were always alone in the cage with nothing else to do but take drugs
- What would happen if the animals were treated differently
  - He built Rat Park
  - It contained lush surroundings with Rat Tunnels, the best rat food, colored balls to play with, and many other rats to interact with

The Rat Park Result

- The same two bottles were in each set of cages
  - In the Rat Park cages, the rats did not like the drugged water
  - They mostly shunned it using only a quarter of the drugs that the isolated rats consumed
  - None of the Rat Park animals died
- Almost all of the isolated rats became addicted and died
- Was this something that only happens in rats or does it apply to humans

The Human "Rat" Experiment

- The Vietnam War was that experiment
  - 20% of the soldiers in the terrifying "cage" of the Vietnam War became addicts while there
  - There was tremendous fear that we were going to have an epidemic of returning addicted vets
  - In fact, 95% of the addicted soldiers simply stopped on their own (only a few had rehab)
- They had shifted from the terrifying cage to the pleasant one

The Meaning of the Rat Park

- Challenges the view that addiction is due to a moral failing
- Challenges the view that it is a disease in a chemically hijacked brain
- Addiction is an adaptation-it is not so much you, but rather your "cage"
- Is part of the the cure human connection and condition????

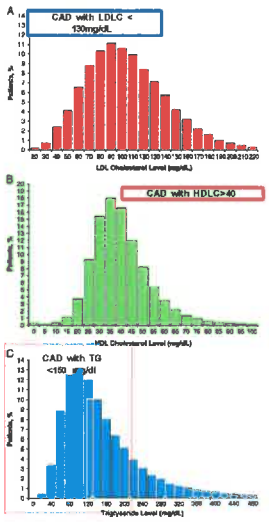
Get with the Guidelines Study

Lipid levels in patients hospitalized with coronary artery disease: An analysis of 136,905 hospitalizations in Get with the Guidelines

Despite being at **NCEP ATP III Goal** for
- LDLC >83% <130
- HDLC 45% >40
- Triglycerides 70% <150

Still required admission for symptomatic CAD

Highlights that simply focusing on lipids should be avoided when diagnosing Heart Disease



Sachdeva, et al. Lipid levels in patients hospitalized with coronary artery disease: An analysis of 136,905 hospitalizations in Get With The Guidelines. DOI: http://dx.doi.org/10.1016/j.ahj.2008.08.010

Nearly Half of all Heart Attacks May Be 'Silent'

- Nearly half of all heart attacks may be silent and like those that cause chest pain of other warning signs, silent heart attacks increase the risk of dying from heart disease and other causes.
- A heart attack does not always have classic symptoms, such as pain in your chest, shortness of breath and cold sweats
- In fact, a heart attack can occur without symptoms and it is called a silent heart attack (blood flow to the heart muscle is severely reduced or cut off completely).

"The outcome of a silent heart attack is as bad as a heart attack that is recognized while it is happening...And because patients don't know they have had a silent heart attack, they may not receive the treatment they need to prevent another one."

- - Elsayed Z. Soliman, M.D., MSc., M.S.

Study senior author and Director of the Epidemiological Cardiology Research Center at Wake Forest Baptist Medical Center, Winston-Salem, North Carolina

PUBLIC RELEASE: 16-MAY-2016 American Heart Association rapid access journal report

Challenges in Risk Assessment Tools

Survey of physicians reported fewer than 20% of physicians use a risk calculator.

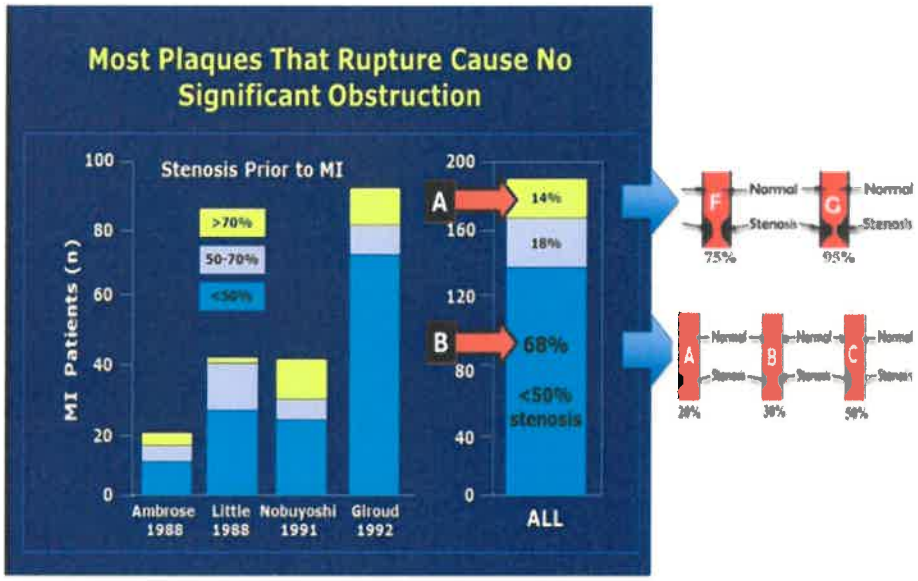
- Most physicians misclassify patient risk.
- Nearly two-thirds underestimate risk.[16,17]
- Physicians are further challenged to figure out broad utility of new risk assessment tools that have not been shown to work in populations independent from the one they were developed in.

LOW RISK | BORDERLINE RISK | HIGH RISK

Challenges

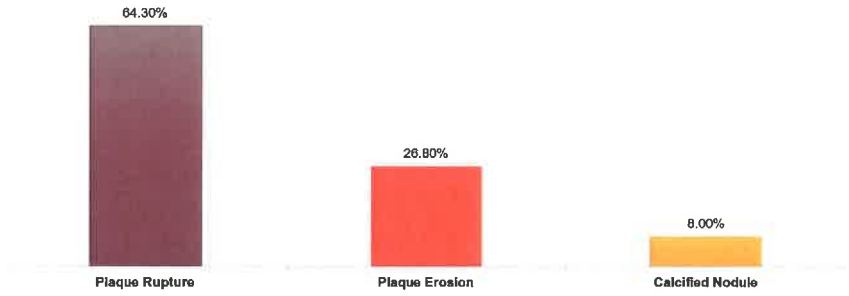
- Angiographic studies show:
  - Progression of coronary artery disease in humans is **neither linear nor predictable**
  - Apparent that arteriographically mild coronary lesions may undergo **significant progression to severe stenosis or total occlusion over a period of a few months**

Coronary Artery Calcification, Epidemiology, Imaging Methods, and Clinical Implications" the American Heart Association Science Advisory and Coordinating Committee on June 20, 1996



STEMI Studies with IVUS & OCT

(Optical Coherence Tomography)



Plaque Rupture (64.3%)
- These had less fibrous plaque
- Thin cap
- Greater plaque burden
- Dominant in men and women >50 years.

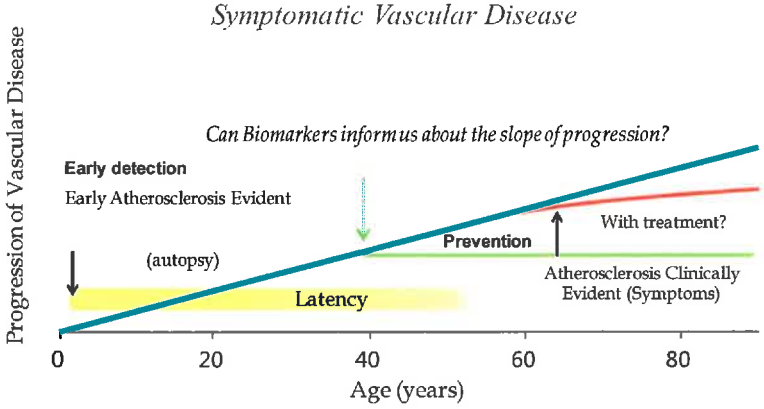
Plaque Erosion (26.8%)
- Greater plaque eccentricity
- Large lumen
- 54% more likely to have calcification, deeper calcium, a break of calcium sheet into lumen
- More constructive lumen with mild inflammation (younger women).

Calcified Nodule (8.0%)
- Greater than ½ have negative remodeling
- Calcium sheet: superficially located large calcification
- Older individuals

Higuma, et al. JACC vol. 8, No. 9 1166. 2015.

The Natural History of Vascular Disease

Long Latency Period for Incubation of Symptomatic Vascular Disease



Atherosclerosis Biology

Process of chronic endothelial injury increases permeability of the arterial wall

- Allows free radicals (i.e. oxidized lipid particles) to aggregate on the arterial surface
- Initiates the formation of lesions (atheroma)[1].

Endothelial injury stimulates production of signaling molecules

- Recruits leukocytes (monocytes, granulocytes, and T-cells) to the injury site
- Stimulates the proliferation of smooth muscle cells [2,3].

Recruited leukocytes transform into lipid-laden foam cells and expand the lesion[4].

- Growth factors are released
  - Stimulate the generation of new capillaries through angiogenesis
  - Provides the growing lesion with an adequate blood supply.

Expression of adhesion molecules/chemokines (MCP-1 and others) induce platelet, lymphocyte and monocyte adhesion, further activating the lesion injury.

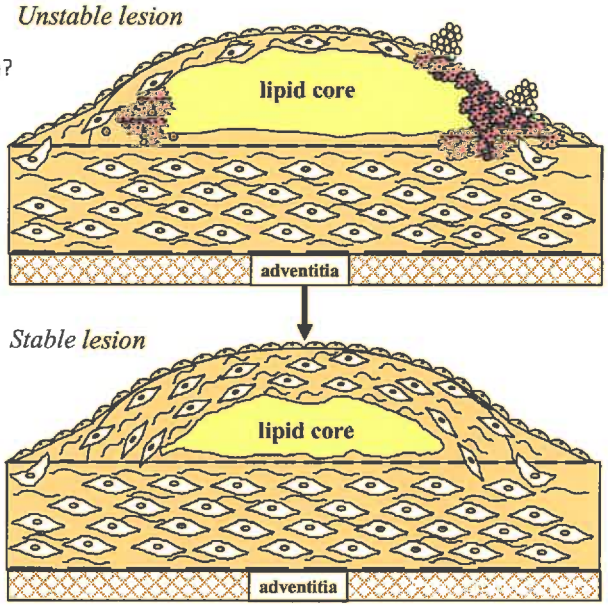
Smooth muscle cells alter and hypertrophy

- Apoptosis produces excessive amounts of collagen, elastin and proteoglycans
- Transforms the lesion into a fibrous plaque
  - Comprised of a lipid core and thin fibrous cap (unstable lesion or vulnerable plaque)[5].

Goal of Therapy

What facilitates this conversion?

- Statin pleiotropic effect
- Jardiance (Empagliflozin)
- Olive oil
- Avocado oil
- Grapeseed oil
- Mediteranean diet
- Aged garlic extract
- Omega 3 fish oil
- Riboceine
- Glutathioceine
- Resistance training
- Etc.



MODULE 2:

The PULS Cardiac Test

✓ Quantify Endothelial Damage

✓ Predict ACS

✓ Improve Patient Care

PULS CARDIAC TEST

9 Protein Unstable Lesion Signature (PULS) Validation

Gene expression work identified over 250 proteins expressed in mice and humans in vulnerable coronary plaque tissues

Narrowed proteins to those detectable in serum by immunoassay, including all clinically used biomarkers like MPO, hsCRP, and LP-PLA2 along with all global risk factors

Validation: NHLBI applied the 9 biomarker assessment to a second population **MESA** and confirmed the findings

The 9 biomarker algorithm predicts who is at risk for ACS in a 5 year period

All three systems identified **the same 9 biomarkers and the same 4 global risk factors**

1. Method of Akaike
2. Bayesian Method
3. Drop-in Deviance

Three different statistical software systems tested **all combinations of biomarkers** and **global risk factors** to identify sub-clinical disease and predict ACS

Path to Verification

Study	Population Summary	
Cohort A ADVANCE Kaiser	3179 adult individuals living in the San Francisco Bay area recruited between 2001 and 2003 Cases: 398 (post MI or UA) Control subjects: age 60 to 72 at the time of their study clinic visit with no history of CAD, ischemic stroke (CVA), or peripheral arterial disease (PAD) (n =928)	**Proof of concept**
Cohort B Orentriech Kaiser	1390 adult individuals recruited in the San Francisco/Bay Area between 1984-1992 Cases: 695 (MI or UA) Matched case-control design for age, sex, ethnicity and date from blood draw (average age: 62 years; 10 years of follow-up for AMI)	**Power of individual biomarkers**
Cohort C PMRP Marshfield Clinic	20,000 members of a Midwest Health Care system recruited between 2002 and 2004 (age range: 40-80 years old) Cases:362 (MI or UA) Controls: 722 (disease free at baseline and during the entire study)	**Prognostic algorithm discovery**
Cohort D MESA	7000 individuals from multiple centers around US recruited since 2000 (age range: 45-85) Controls: 495 (CHD free during study) Case individuals: 179 (Coronary Heart Disease)	**Verification and transportability**
Totals	31,569	

PULS Cardiac Test Performance in MESA

5,731 Patients	5 Year FRS-lipids	PULS Cardiac Test	Both
222 Events	18% DETECTED	46% DETECTED	61% DETECTED

Normal Values have a 97% Negative Predictive Value

Health Economic Benefits

3 fold decrease for Incremental Cost-effectiveness Ratio (ICER) with PULS Cardiac Test

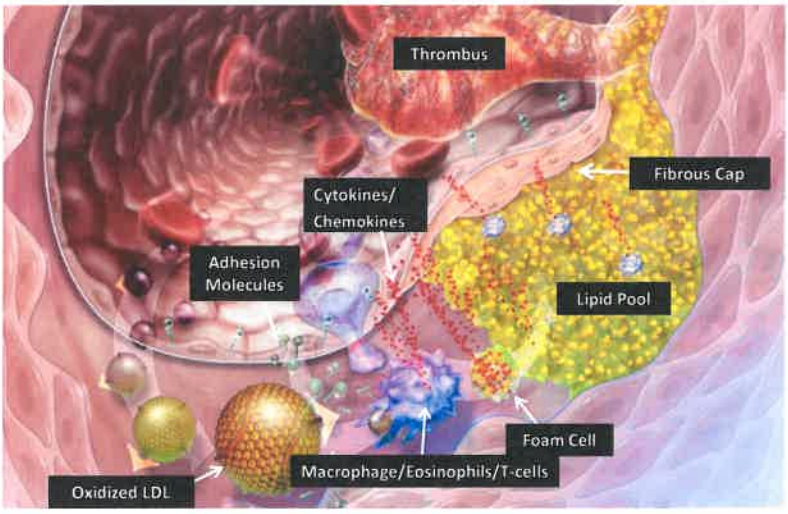
$71,456 QALY
Standard of Care

vs.

$22,895 QALY
PULS CARDIAC TEST

Quality-Adjusted Life Year (QALY) is a generic measure of disease burden, including both the quality and quantity of life lived.

Vulnerable Plaque

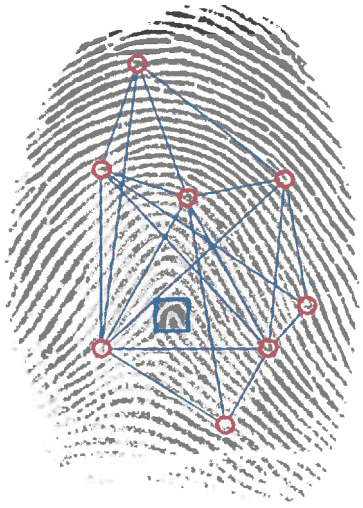


Optimal Identification of Early Disease Requires Multiple Biomarker Algorithm

Accuracy of Identification

- **1 point match = 2%**
- **2 point match =4%**
- **3 point match = 8%**
- **4 point match = 20%**
- **5 point match = 35%**
- **6 point match = 70%**
- **7 point match = 84%**
- **8 point match = 92%**
- **9 point match = 98%**

Unique signature of Proteins or Points



The Fingerprint Model

28

9 Proteins Are Signficant

9 clinically-significant protein biomarkers to measure the body's immune response to arterial or endothelial damage leading to unstable lesion formation and potential rupture.

Relation to Endothelial Damage & Unstable Cardiac Lesions	
MEASURES FORMATION & FREE RADICAL DAMAGE	
IL-16	"Signaling Molecule" triggers repair process. Immune response begins.
MEASURES IMMUNE RESPONSE	
MCP-3	Recruits monocyte/macrophages that form foam cells which clean up damaged cells, lipids, and cellular debris.
Eotaxin	Recruits eosinophils that consume fibrin and prevent blood clots.
CTACK	Recruits T-cells that regulate the local inflammatory response at the site of the lesion.
MEASURES PROGRESSION	
sFas	Cell repair "prevents cell death".
Fas Ligand	Initiates cell death and recycling.
HGF	Forms collagen. Stimulates tissue and repair.
MEASURES CLINICAL RISK FACTORS	
HDL	Helps remove bad cholesterol and neutralizes free radicals.
HbA1c	Diabetes marker.

MODULE 3:

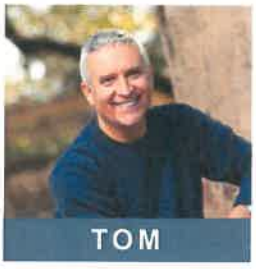
Clinical Application in Identifying the Vulnerable Patient

PULS CARDIAC TEST

CASE STUDY 1

The Young Patient with Vague Symptoms

Case 1: Background & Work-Up



Age: 56

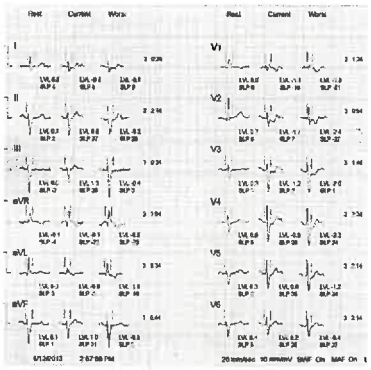
Patient Medical History	
Age/Sex	56 y/o Male
Smoke / Substance	No
Family History	No
Medication	No
BMI	Normal
Blood Pressure	Normal

Clinical Work-Up	Results
ASCVD Calculation (10 year)	5.4% - Normal
FRS Calculation (10 year)	7.1% - Normal
PULS Cardiac Test	11.41% - Elevated

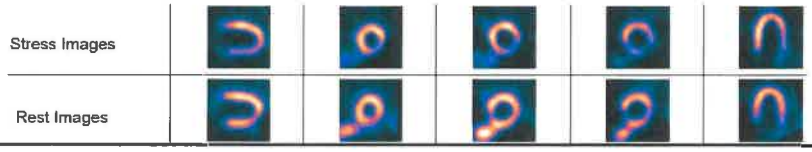
- 56 year old Caucasian male
- No family history
- Vague symptoms
- Lipids normal
- Framingham Risk normal
- American College of Cardiology Risk Calculator normal
- PULS Cardiac Test Elevated at 11.41% (over 5x expected for age)

Case 1: Diagnostic Studies

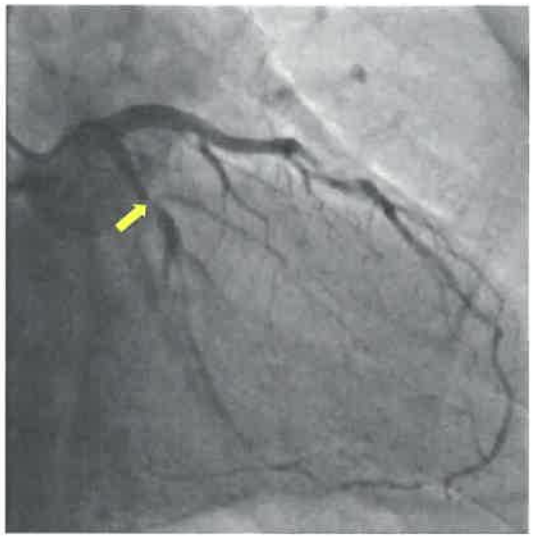
Echo stress



Perfusion Study-nuclear Medicine (lateral and inferior ischemia)



Case 1: Angiography & Treatment



- >90% lesion in LCX (Left Circumflex) Artery
- Successfully stented
- Patient is doing well

CASE STUDY 2

Asymptomatic CAD-Chronic Total Obstruction

Case 2: Background

Age: 78
Retired IT Professional

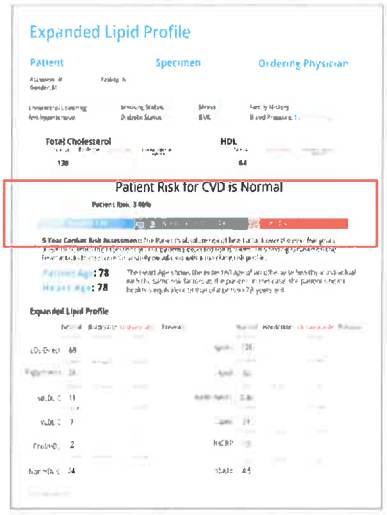
Patient Medical History	
Stress	Yes
Smoke / Substance	No
Family History	Mother had MI at 56 y/o
Medication	Previous Blood Pressure medication
BMI	Normal (20.0)
Blood Pressure	Normal (147/61)
EKG	NSR
Prev. Risk Assessment	1 year prior Results Borderline (3.6%)

- 78 y/o Middle Eastern male retired IT professional who had "no specific complaints" but was seen at his primary care doctor due to his daughter's concern that he seemed unmotivated and tired.
- The patient did indicate that he had been under excessive stress in the last year due to his family.

Case 2: Preliminary Work-Up

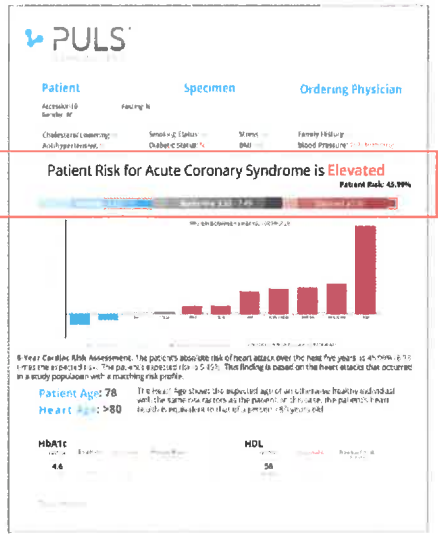
Clinical Testing	Results
Labs All Normal Total non-HDL Cholesterol sdLDL LDL ApoB	NSR
CIMT	Mild intimal thickening

- Lab testing was performed but was normal
- CIMT results showed mild intimal thickening.
- HMO Primary Care doctor felt patient was stable.
- Patient was discharged without further work-up
- Daughter took patient to out-of-network cardiologist



Case 2: Preliminary Work-Up

- Out of network Cardiologist performed the PULS Cardiac Test
- Results showed patient at 8.34x expected risk for an Acute Coronary Syndrome (ACS) for his age and an absolute 5-year score of 45.99% (expected 5.49%)



Case 2: Additional Work-Up

Clinical Testing	Results
CAC	600
Stress Test	Unable to perform due to knee problem
Angiography	Roughly 100% Blockage

- Further studies were performed:
  - CAC test 600
  - Unable to perform a stress test due to knee problem
- The patient was referred back to the original primary care physician who referred him to the in-network cardiologist
  - The patient underwent angiography that identified near 100% Blockage aka "widow-maker"
  - An interventional procedure (stent) was performed

Case 2: Before & After Stent

Pre-Stent
Almost 100% blockage of main artery

Post-Stent
Healthy blood flow

Case 2: Treatment & Follow-Up

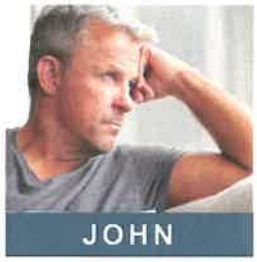
Follow-Up Medications	
Clopidogrel 75 mg	75 mg
Aspirin (baby)	81 mg
Atorvostatin	10 mg
Atenolol	25 mg

- Patient placed on medication regimen.
- Patient is currently doing well.
- Exercise tolerance and energy level back to "normal".

CASE STUDY 3

Asymptomatic "Macho Man" Confounding Symptoms

Case 3: Background



Age: 47

Special Forces

Patient Medical History	
Hypertension	No
Smoke	No
Family History	Father had MI at 44 y/o
Medication	No
Diabetic	No
Hyperlipidemia	No
BMI	Overweight 29.4
Blood Pressure	Normal
Weight	188 lbs
Pulse	70
Total Cholesterol	202
LDL	140
HDL	41
Lp(a)	7.1
Hs-CRP	0.7
EKG	NSR

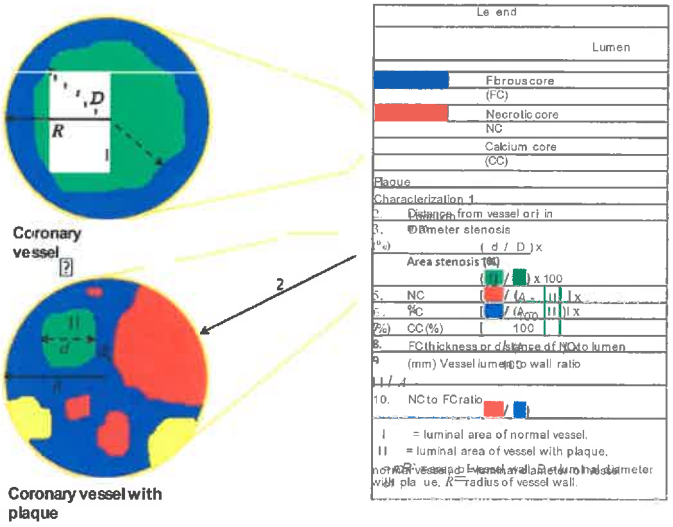
- 47 y/o Caucasian male Special Forces soldier with sporadic precordial left chest and shoulder pain since 2005
- Patient had history of multiple combat-related injuries including a left clavicular fracture with mal-aligned healing in 1992

Case 3: Preliminary Work-Up

- Negative treadmill stress test
- ACC/AHA Score 5.5% (normal)
- Framingham Score 7% (normal)
- C-IMT non-obstructive non-calcified and calcified plaque
- Echocardiogram performed
  - Trace PI, NSR, normal
- PULS Cardiac Test performed due to patient family history Results:
  - PULS Score elevated 8.07% (High Risk of ACS)
  - 5.34x expected risk (1.51%)

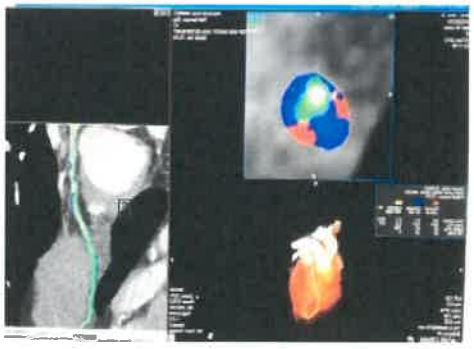
Clinical Work-Up	Results
EKG	NSR
Echocardiogram	Trace PI NSR Normal left ventricular contractility – EF 83% Left ventricular hypertrophy at 15.3 (athletic heart)
C-IMT	Non-obstructive non-calcified and calcified plaque
Stress Test	Negative
ASCVD Calculation (ATP IV)	5.5%
FRS Calculation	7%
PULS Cardiac Test	Score 8.07% 5.34x expected score (expected score 1.51%)

Case 3: CTA Performed

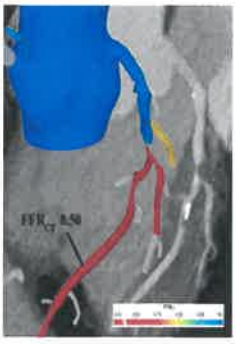


Case 3: CTA & FFR Results

LAD Coronary CTA Images



Patient FFR by CT



Case 3: Treatment & Follow-Up

Follow-Up Medications	
Clopidogrel 75 mg	Loading dose 600 mgs 75 mgs daily
Aspirin (baby)	325 mgs
Atorvostatin	40 mgs daily
Metoprolol succinate	50 mgs daily

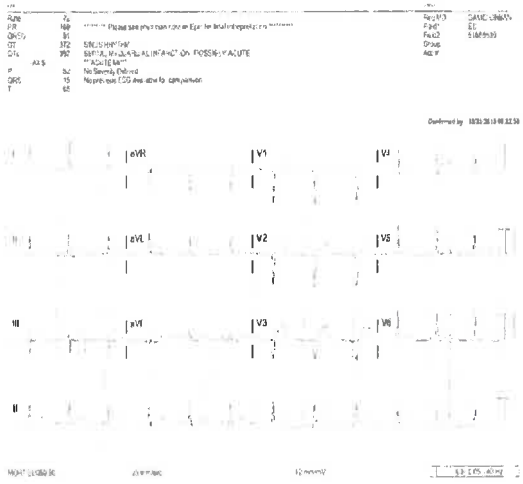
- Patient initiated aggressive medical therapy
- Patient scheduled for left heart cardiac catheterization with PCI on Monday following his Friday clinic visit to review findings because he was asymptomatic

Case 3: Disease Course

- Patient delayed initiation of his recommended medical therapy over the weekend because he "felt fine"
- Approximately 48 hours after follow-up of Coronary CTA, patient began having burning sternal pain and diaphoresis while playing video games which continued for over 30 minutes
- Patient's wife called EMS against patient's wishes for further evaluation

Case 3: EKG at Tampa General Hospital

EKG by EMS revealed a STEMI (Heart Attack) in the anterior lateral leads



Case 3: Work-Up

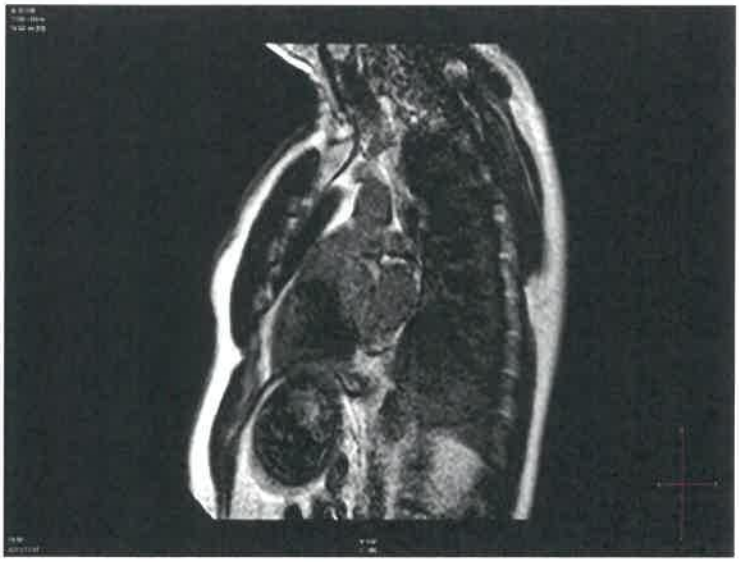
Echocardiogram:

- During STEMI – markedly depressed EF with akinesis of the anterior lateral walls extending down to the apex
- 48 hours past PCI-complete resolution of the abnormal territories with normalization of LV function

Before

After

Case 3: Cardiac MRI



CASE STUDY 4

The Physician Who
"Took it to Heart"

Case 4: Background

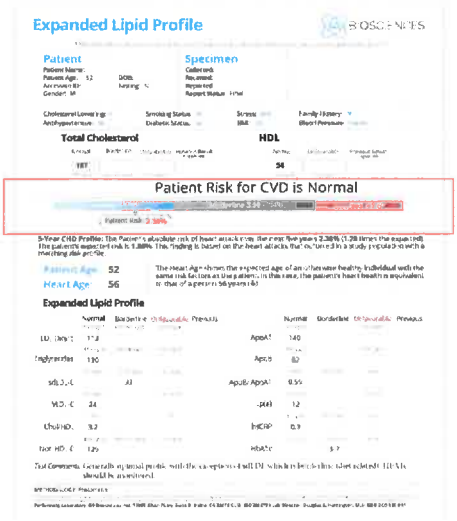
Age: 52

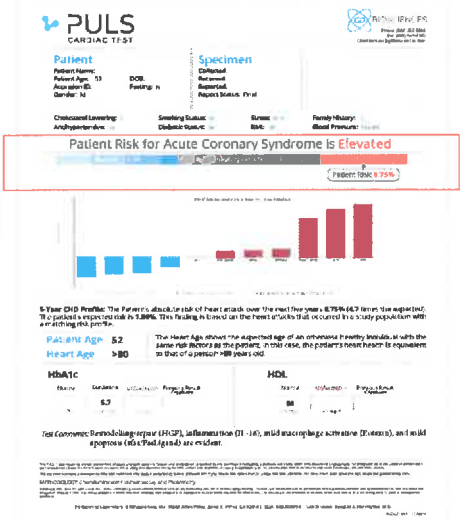
Physician

Patient Medical History	
Hypertension	No
Smoke / Substance	No
Family History	Yes
Medication	Cholesterol-lowering
Diabetic	Pre-diabetic
Hyperlipidemia	No
BMI	26
Blood Pressure	Pre-hypertension - 134/85

- 52 y/o physician
- Aware of "pre-diabetic" status
- Has focused on his cholesterol levels
  - Lipids Normal
  - HbA1c Borderline at 5.7%
- 5-year CVD risk: Normal (2.38%)
- 10-year ASCVD: Normal (3.6%)

Case 4: Lipid vs. PULS



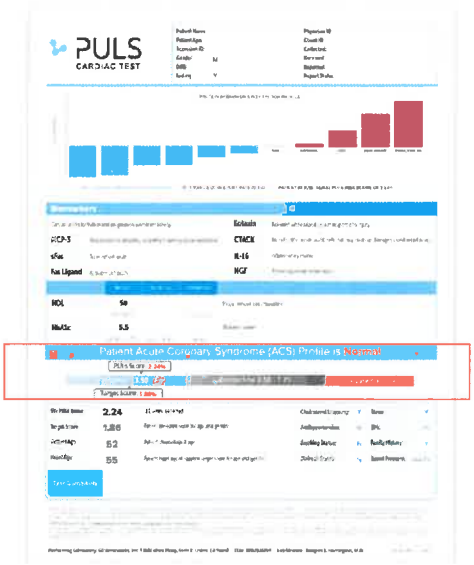


Case 4: PULS Follow-Up Results

Follow-up PULS results showed the physician had reduced his risk from 8.75% to Normal at 2.24% in 4 months with a lifestyle-only prescription:

1. Brisk walking 30" 3X/week
2. Resistance training with 12# kettle ball and 10 pound dumbbells 30" 3X/week
3. Cut out sugar and refined white carbs

Results:
1. 16 pound weight loss
2. HbA1c normal for first time in 10 years
3. PULS normal



CASE STUDY 5

The CEO Who
Toned it Down

Case 5 : Background

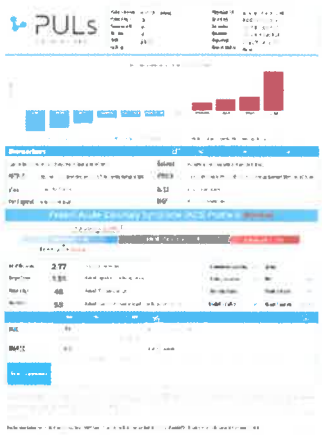
Mr. CEO

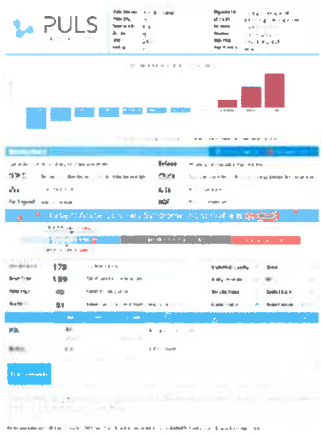
Age: 48
CEO

Patient Medical History	
Hypertension	No
Smoke / Substance	No
Family History	Yes
Medication	None
Diabetic	No
Hyperlipidemia	No
BMI	26
Blood Pressure	Normal

- 5-year CVD risk: Normal (2.38%)
- 10-year ASCVD: Normal (3.6%)

Case 5 : PULS vs. PULS





Questions

PULS
CARDIAC TEST