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."

Mckinley 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 contaminate.s 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
- LDL >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

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. Soloman, 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: 18 MAY 2010 American Heart Association press release 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.
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**
Most Plaques That Rupture Cause No Significant Obstruction

MI Patients (n)

- MI Patients
- Stenosis Prior to MI
- Stenosis

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
- 64% 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

Higama, et al. JACC vol. 8, No. 9:1130. 2015
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$^\text{2,3}$

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

Unstable lesion

What facilitates this conversion?

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

Stable lesion

MODULE 2:

The PULS Cardiac Test

✓ Quantify Endothelial Damage
✓ Predict ACS
✓ Improve Patient Care
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 immunocassay, 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.

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

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

Path to Verification

<table>
<thead>
<tr>
<th>Study</th>
<th>Population Summary</th>
<th>Proof of concept</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort A ADVANCE Kaiser</td>
<td>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 73 at the time of their study clinic visit with no history of CAD, ischemic stroke (CVA), or peripheral arterial disease (PAD) (n = 928)</td>
<td>Proof of concept</td>
</tr>
<tr>
<td>Cohort B Orentreich Kaiser</td>
<td>1390 adult individuals recruited in the San Francisco/Bay Area between 1984-1992 Cases: 895 (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)</td>
<td>Power of individual biomarkers</td>
</tr>
<tr>
<td>Cohort C PMRP Marshfield Clinic</td>
<td>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)</td>
<td>Prognostic algorithm discovery</td>
</tr>
<tr>
<td>Cohort D MESA</td>
<td>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)</td>
<td>Verification and transportability</td>
</tr>
<tr>
<td>Totals</td>
<td>31,569</td>
<td></td>
</tr>
</tbody>
</table>
PULS Cardiac Test Performance in MESA

<table>
<thead>
<tr>
<th></th>
<th>5 Year FRS-lipids</th>
<th>PULS Cardiac Test</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>5,731 Patients</td>
<td>18% DETECTED</td>
<td>46% DETECTED</td>
<td>61% DETECTED</td>
</tr>
<tr>
<td>222 Events</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 vs. $22,895 QALY

Standard of Care

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
9 Proteins Are Significant

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.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1β</td>
<td>MCP-1</td>
<td>sFlt</td>
<td>HDL</td>
</tr>
<tr>
<td>Immunoreactive leukocytes</td>
<td>Enzyme</td>
<td>Fas ligand</td>
<td>HbA1c</td>
</tr>
<tr>
<td></td>
<td>CRP</td>
<td>TGF</td>
<td>Diabetes marker</td>
</tr>
<tr>
<td></td>
<td>CRP</td>
<td>TGF</td>
<td></td>
</tr>
</tbody>
</table>

**Relation to Endothelial Damage & Unstable Cardiac Lesions**

**MODULE 3:**

Clinical Application in Identifying the Vulnerable Patient
CASE STUDY 1

The Young Patient with Vague Symptoms

Case 1: Background & Work-Up

<table>
<thead>
<tr>
<th>Patient Medical History</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age/Sex</td>
<td>56 y/o Male</td>
</tr>
<tr>
<td>Smoke / Substance</td>
<td>No</td>
</tr>
<tr>
<td>Family History</td>
<td>No</td>
</tr>
<tr>
<td>Medication</td>
<td>No</td>
</tr>
<tr>
<td>BMI</td>
<td>Normal</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Clinical Work-Up

<table>
<thead>
<tr>
<th>ASCVD Calculation (10 year)</th>
<th>5.4% - Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRS Calculation (10 year)</td>
<td>7.1% - Normal</td>
</tr>
<tr>
<td>PULS Cardiac Test</td>
<td>11.41% - Elevated</td>
</tr>
</tbody>
</table>

- 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)

<table>
<thead>
<tr>
<th>Stress Images</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest Images</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

- 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

- 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 5.48%)
Case 2: Additional Work-Up

<table>
<thead>
<tr>
<th>Clinical Testing</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAC</td>
<td>600</td>
</tr>
<tr>
<td>Stress Test</td>
<td>Unable to perform due to knee problem</td>
</tr>
<tr>
<td>Angiography</td>
<td>Roughly 100% Blockage</td>
</tr>
</tbody>
</table>

• Further studies were performed:
  o CAC test 600
  o 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
  o The patient underwent angiography that identified near 100% Blockage aka "widow-maker"
  o 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

<table>
<thead>
<tr>
<th>Follow-Up Medication</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel 75 mg</td>
<td>75 mg</td>
</tr>
<tr>
<td>Aspirin (baby) 81 mg</td>
<td></td>
</tr>
<tr>
<td>Atorvastatin 10 mg</td>
<td></td>
</tr>
<tr>
<td>Atenolol 25 mg</td>
<td></td>
</tr>
</tbody>
</table>

- 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

- 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

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

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%)

<table>
<thead>
<tr>
<th>Clinical Work-Up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>EKG: NSR</td>
<td></td>
</tr>
<tr>
<td>Echocardiogram: Trace PI</td>
<td>NSR</td>
</tr>
<tr>
<td></td>
<td>Normal left ventricular contractility – EF 83%</td>
</tr>
<tr>
<td></td>
<td>Left ventricular hypertrophy at 16.3 (athletic heart)</td>
</tr>
<tr>
<td>C-IMT: Non-obstructive non-calcified and calcified plaque</td>
<td></td>
</tr>
<tr>
<td>Stress Test: Negative</td>
<td></td>
</tr>
<tr>
<td>ASCVD Calculation (ATP IV): 5.5%</td>
<td></td>
</tr>
<tr>
<td>FRS Calculation: 7%</td>
<td></td>
</tr>
<tr>
<td>PULS Cardiac Test:</td>
<td>Score 8.07%</td>
</tr>
<tr>
<td></td>
<td>5.34x expected score (expected score 1.51%)</td>
</tr>
</tbody>
</table>
Case 3: CTA Performed

![Diagram showing coronary vessel with plaque]

Case 3: CTA & FFR Results

![LAD Coronary CTA Images and Patient FFR by CT]
Case 3: Treatment & Follow-Up

- 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

<table>
<thead>
<tr>
<th>Follow-Up Medications</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel 75 mg</td>
<td>Loading dose 600 mgs</td>
</tr>
<tr>
<td></td>
<td>70 mgs daily</td>
</tr>
<tr>
<td>Aspirin (baby)</td>
<td>325 mgs</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>40 mgs daily</td>
</tr>
<tr>
<td>Metoprolol succinate</td>
<td>50 mgs daily</td>
</tr>
</tbody>
</table>

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
Case 3: Cardiac MRI

CASE STUDY 4

The Physician Who "Took it to Heart"
Case 4: Background

- 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

Expanded Lipid Profile

<table>
<thead>
<tr>
<th>Patient</th>
<th>Specimen</th>
<th>Males</th>
<th>Females</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td>Males</td>
<td>150-200</td>
<td>150-200</td>
<td>Yes</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>Males</td>
<td>150-200</td>
<td>150-200</td>
<td>No</td>
</tr>
<tr>
<td>HDL</td>
<td>Males</td>
<td>40-100</td>
<td>40-100</td>
<td>Yes</td>
</tr>
<tr>
<td>LDL</td>
<td>Males</td>
<td>60-100</td>
<td>60-100</td>
<td>No</td>
</tr>
</tbody>
</table>

Patient Risk for CVD is Normal

PULS

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Males</th>
<th>Females</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC</td>
<td>4.5-5.5</td>
<td>4.5-5.5</td>
<td>Yes</td>
</tr>
<tr>
<td>WBC</td>
<td>4.5-10</td>
<td>4.5-10</td>
<td>Yes</td>
</tr>
<tr>
<td>HCT</td>
<td>40-50</td>
<td>40-50</td>
<td>Yes</td>
</tr>
<tr>
<td>Platelets</td>
<td>150-400</td>
<td>150-400</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Pleasant Risk for Acute Coronary Syndrome is Elevated
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

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

Mr. CEO

Age: 68
CEO

Past Medical History
- Hypertension: No
- Renal failure: No
- Family history: Yes
- Medication: None
- Diabetes: No
- Hypertension: No
- 5'H: No
- Blood Pressure: Normal

Case 5: PULS vs. PULS
Questions