The future of cardiovascular research

Amir Lerman, MD
Barbara Woodward Lips Endowed Professor.
Director Cardiovascular Research Center
Mayo Clinic, Rochester, MN

The future of cardiovascular research

- Past
- Present and immediate future: “wake up call”
- The Future

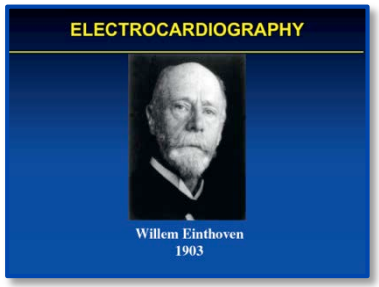
MAYO CLINIC

The ten advances that have defined modern cardiology

*Eugene Braunwald**

TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital, Boston, MA, USA
Department of Medicine, Harvard Medical School, Boston, MA, USA

Electrocardiography



Cholesterol and atherosclerosis

This truly seminal paper led ultimately to the cholesterol theory of atherogenesis, which in turn resulted in successful attempts to lower serum cholesterol in order to reverse, prevent, or at least retard the development of atherosclerosis and its complications.

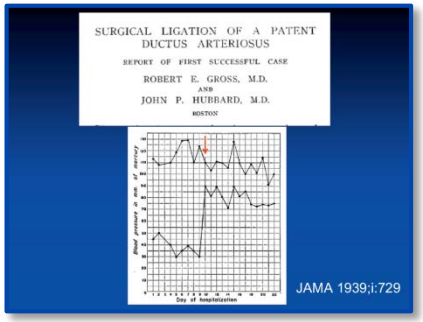
Anitschkow: Zentralblful Allgemeine Pathol Und Pathol Anat 1913;24:1

Cardiac catheterization

First carried out by Forssmann in 1929, a urologist, won the Nobel Prize

Cardiovascular surgery

The first cardiovascular operation in 1939, ligation of a patent ductus arteriosus in a seven and a half-year old girl



Coronary angiography and percutaneous coronary angioplasty

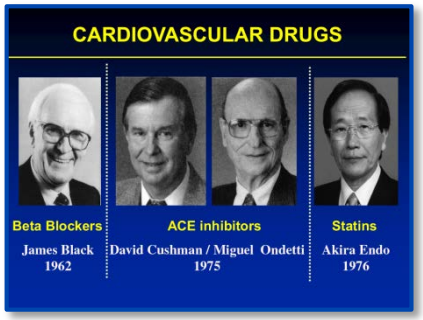
In 1958, while performing an angiogram of the aortic root, the tip of the catheter accidentally slipped into the ostium of the right coronary artery.

Sones et al: Circulation 20:773, 1959

The coronary care unit

In 1961, Desmond Julian, a registrar (fellow/resident) in cardiology at the Royal Infirmary in Edinburgh, wrote a brief paper describing the coronary care unit that was published in Lancet, in which he stated:

Cardiovascular drugs



Preventive cardiology

Kannel et al: The Framingham study Ann Intern Med 55:33, 1961

Cardiac imaging: Echocardiography

During World War II, ultrasound was widely used to detect submarines and to track torpedoes. The collaboration between two brilliant Norwegians, an emeritus Professor of Cardiology, Inge Edler, and an engineer, Helmut Hertz, led to the development of echocardiography.

Edler and Hertz: Kungl Fysiogr Sallsk Lund Forth24, 1954

Cardiac pacemakers and defibrillation

Mirowski et al:N Engl J Med 303:322, 2098

MAYO CLINIC

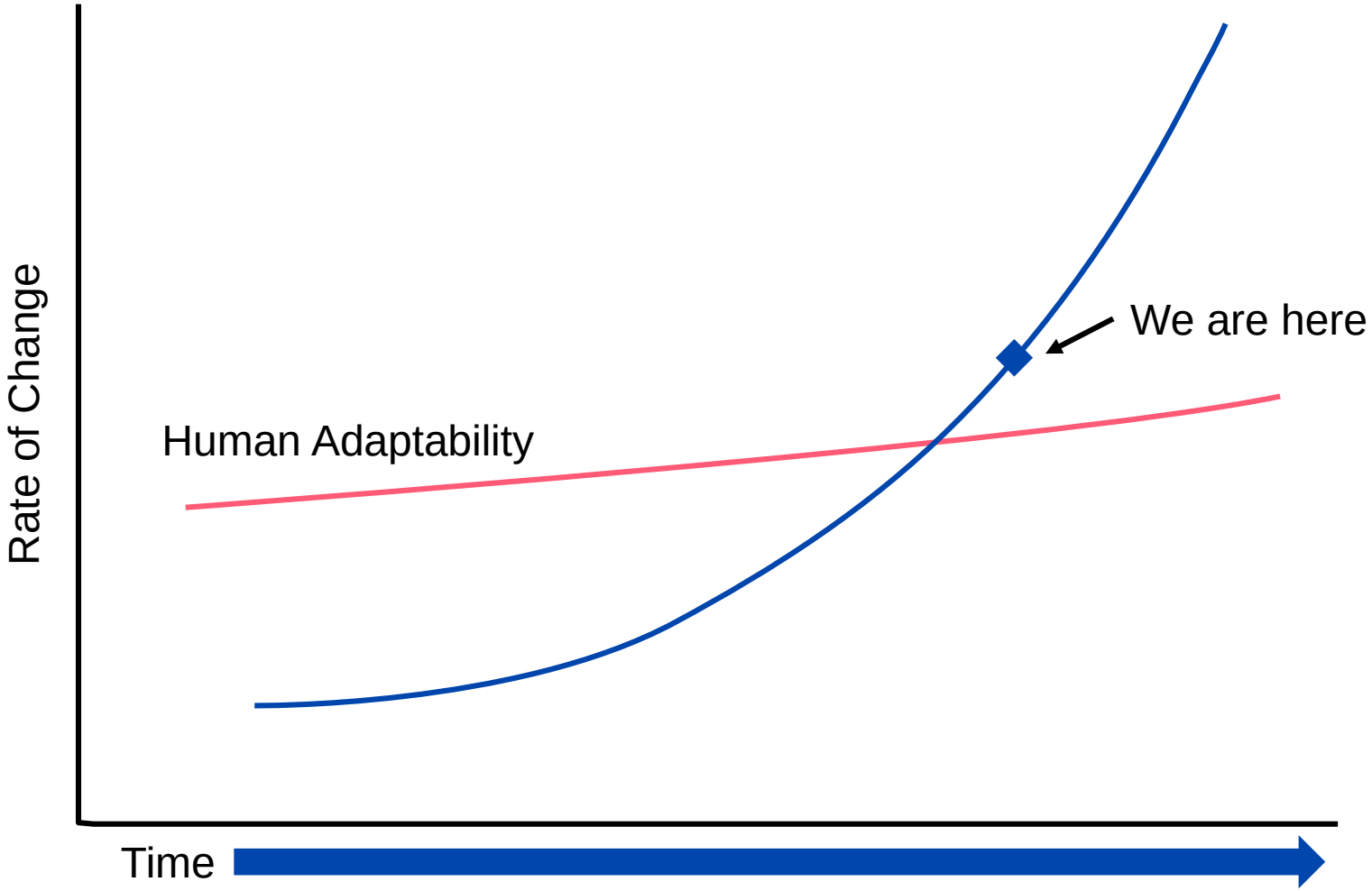
Braunwald et al: Trends in Cardiovascular Medicine 24:179, 2014

What Happened Before 2007?

- Facebook didn’t exist yet
- Twitter was still a sound
- Cloud was still in the sky
- 4G was a parking space
- “applications” were what you sent to college
- LinkedIn most people thought it was a prison
- Big Data was a good name for a rap star

Excerpt From: Thomas L. Friedman. “Thank You for Being Late.” iBooks. https://itunes.apple.com/us/book/thank-you-for-being-late/id1110015147?mt=11

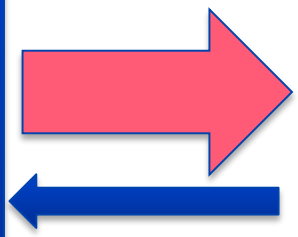
The Race Between Human and Technology



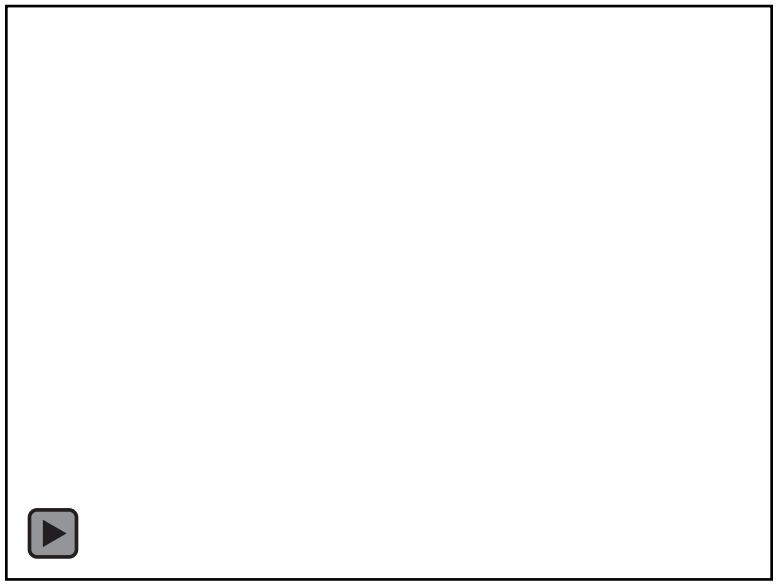
MAYO CLINIC

Where are the Future Opportunities in the Cardiovascular Field?

Unmet Patients' need

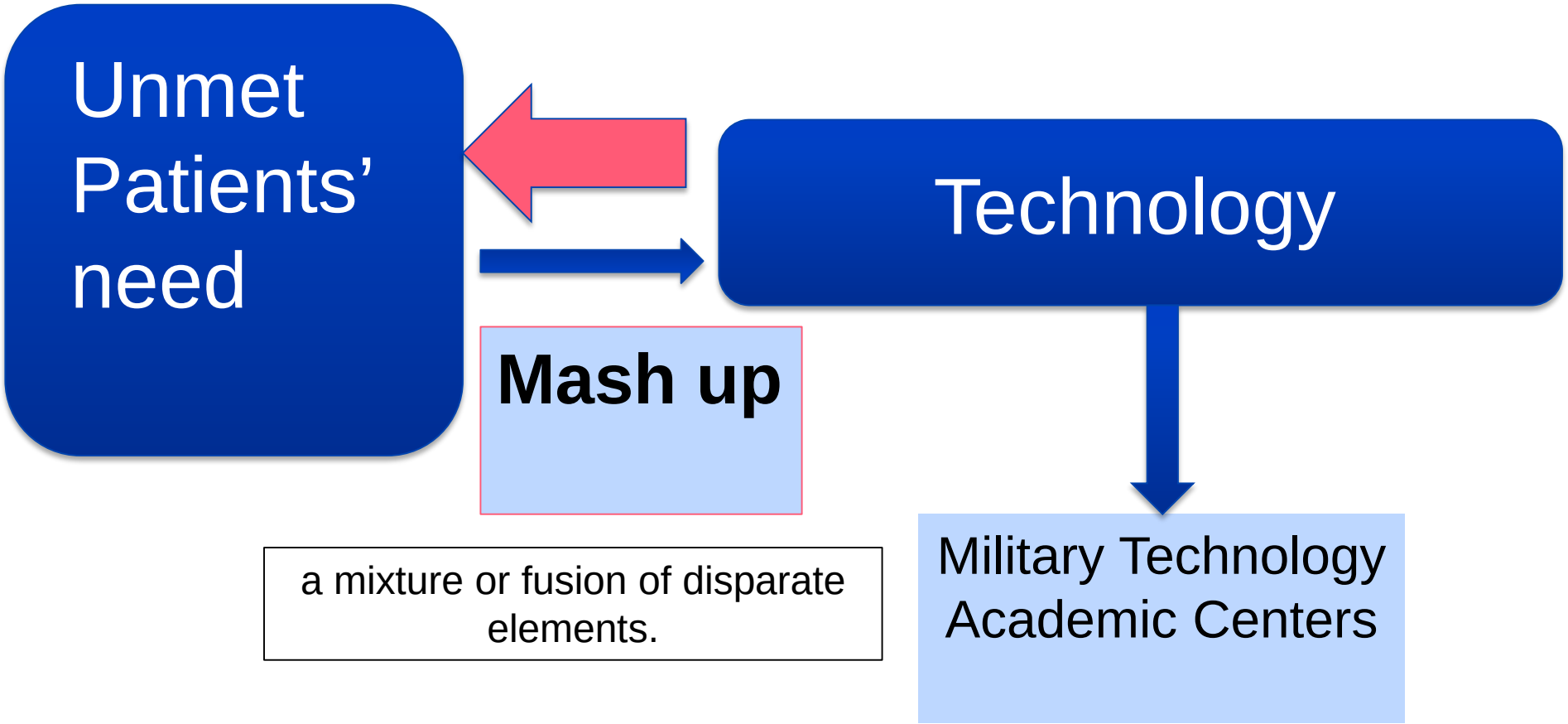


Technology



MAYO CLINIC

Where are the Future Opportunities in the Cardiovascular Field?



MAYO CLINIC

Where are the Future Opportunities in the Cardiovascular Field?

- Precision (Individualized) medicine
- big data analysis
- Remote medicine
- Robotic

MAYO CLINIC

Personalized Medicine: Precision medicine

Will provide the link between an individual's molecular and genetic and clinical profiles

Will effect

Therapy directed to the root cause of the disease will replace treating the symptoms

Pharmaceutical industry

MAYO CLINIC

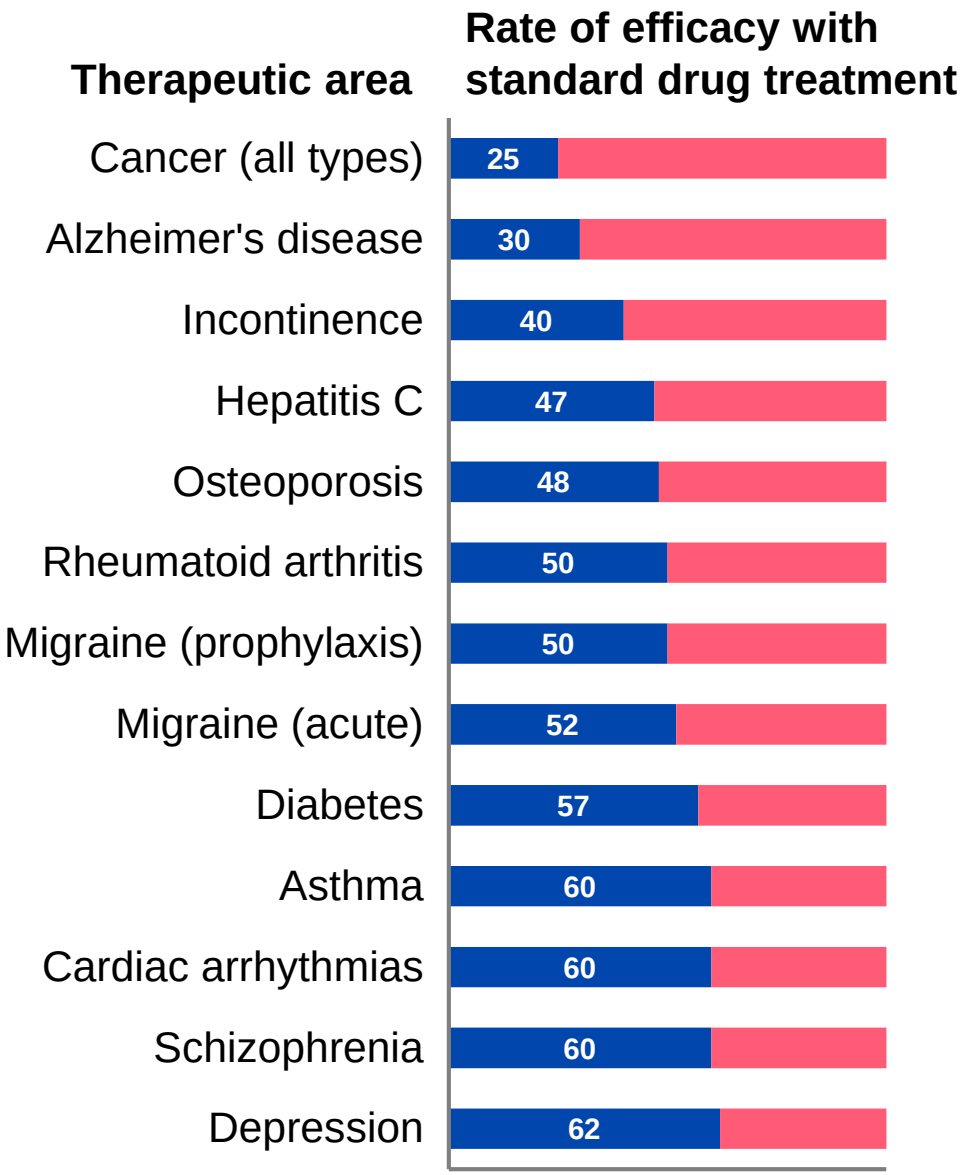
Symptoms

Medical History& Physical examination

Presumptive Diagnosis

Treatment based on large clinical trials

- **Wrong diagnosis**
- **Net effect of beneficial and toxic effects**

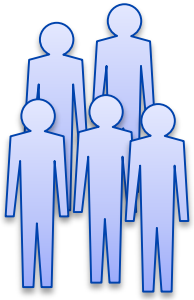


MAYO CLINIC

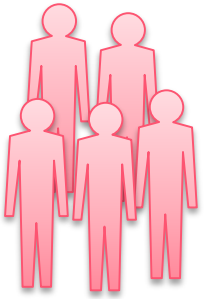
There are several aspects to personalized medicine

Diagnosis

Personalized treatment

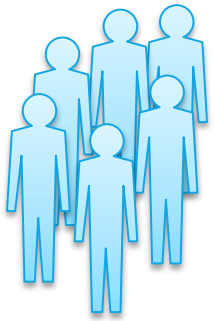


Drug toxic but beneficial



Drug toxic but **not** beneficial

Patient group



Drug **not** toxic and **not** beneficial

Same diagnosis, same prescription

Drug **not** toxic and beneficial

MAYO CLINIC

Diagnosis

- Affymetrix
- GeneLogic
- Curagen

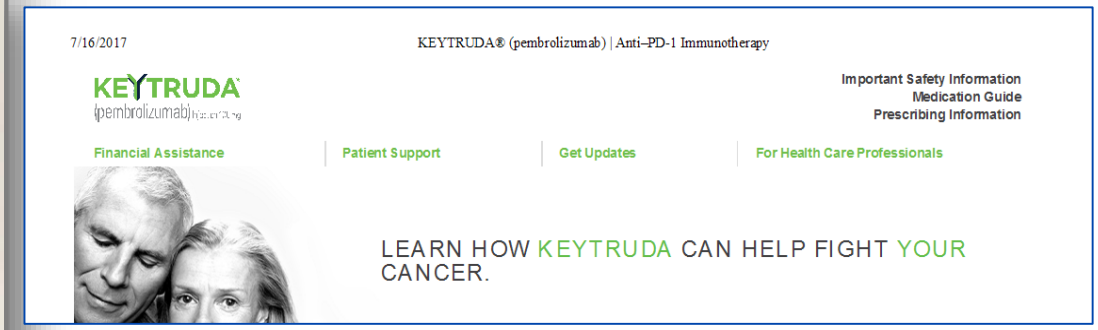
The use of of genetic markers to select patients for clinical trials may reduce adverse drug reaction by 10-20%

Caution: not covered by insurance

No firm data on link to therapy

No firm data from a randomized study on benefit

Treatment



FDA News Release

FDA approves first cancer treatment for any solid tumor with a specific genetic feature

For Immediate Release

May 23, 2017

Release

The U.S. Food and Drug Administration today granted accelerated approval to a treatment for patients whose cancers have a specific genetic feature (biomarker). This is the first time the agency has approved a cancer treatment based on a common biomarker rather than the location in the body where the tumor originated.

Keytruda (pembrolizumab) is indicated for the treatment of adult and pediatric patients with unresectable or metastatic solid tumors that have been identified as having a biomarker referred to as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR). This indication covers patients with solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options and patients with colorectal cancer that has progressed following treatment with certain chemotherapy drugs.

The number of patients in clinical trials

PATHOPHYSIOLOGY AND NATURAL HISTORY
CORONARY ARTERY DISEASE

1983

Coronary Artery Surgery Study (CASS): a randomized trial of coronary ... surgery

Survival data

CASS Principal Investigators and their Associate...

780 patients

ABSTRACT CASS includes a multicenter patient registry and a randomized controlled clinical trial. It is designed to assess the effect of coronary artery bypass surgery on mortality and selected nonfatal

---

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 12, 2007 VOL. 356 NO. 15

2007

Optimal Medical Therapy with or wi... for Stable Coronary Dise...

780 patients

William E. Boden, M.D., Robert A. O'Rourke, M.D., Koon K. Teo, M.B., B.Ch., Ph..., Ph.D., David J. Maron, M.D., William J. Kostuk, M.D., Merril Knudtson, M.D., Marcin Dada, ..., Paul Casperson, Ph.D., Crystal L. Harris, Pharm.D., Bernard R. Chaitman, M.D., Leslee Shaw, Ph.D., Gilbert Gosselin, M.D., Shah Nawaz, M.D., Lawrence M. Title, M.D., Gerald Gau, M.D., Alvin S. Blaustein, M.D., David C. Booth, M.D.,

---

Circulation
circ.ahajournals.org

Circulation. 1997;96:2162–2170
doi: 10.1161/01.CIR.96.7.2162

CrossMark click for updates

1829 patients

1997

Articles

Myocardial Infarction and Cardiac Mortality in the Bypass Angioplasty Revascularization Investigation (BARI) Randomized Trial

---

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 20, 2008 VOL. 359 NO. 21

2008

Rosuvastatin to Prevent Vascular Events in ... with Elevated C-Reactive Pro...

17,802 patients

Paul M Ridker, M.D., Eleanor Danielson, M.I.A., Francisco A.H. Fonseca, M.D., Jac... Genest, M.D., Antonio M. Gotto, Jr., M.D., John J.P. Kastelein, M.D., Wolfgang Koenig, M.D., Peter Libby, M.D.,

---

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 8, 2004 VOL. 350 NO. 15

2004

Intensive versus Moderate Lipid Lowering with Statins after Acute Coronary Syndromes

4126 patients

Christopher P. Cannon, M.D., Eugene Braunwald, M.D., Carolyn H. McC... D., Jean L. Rouleau, M.D., Rene Belder, M.D., Steven V. Joyal, M.D., Karen A. Hill... Ph.D., and Marian M. Skene, Ph.D., for the Pravastatin or Atorvastatin Evaluation and I... mbolysis in Myocardial Infarction 22 Investigators*

MAYO CLINIC

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 13, 2012 VOL. 367 NO. 11

2012

Fractional Flow Reserve–Guided PCI versus ... Therapy in Stable Coronary Di...

1220 patients

Bernard De Bruyne, M.D., Ph.D., Nico H.J. Pijls, M.D., Ph.D., Bindu Kalesa... M.D., Ph.D., Pim A.L. Tonino, M.D., Ph.D., Zsolt Piroth, M.D., Nikola Jagic, M.D., Sven Möbius... oufol, M.D., Ph.D., Nils Witt, M.D., Ph.D., Petr Kala, M.D., Philip MacCarthy, M.D., Thomas Engstro... M.D., Keith G. Oldroyd, M.D., Kreton Mavromatis, M.D., Ganesh Manoharan, M.D., Peter Ver...

Machine Learning

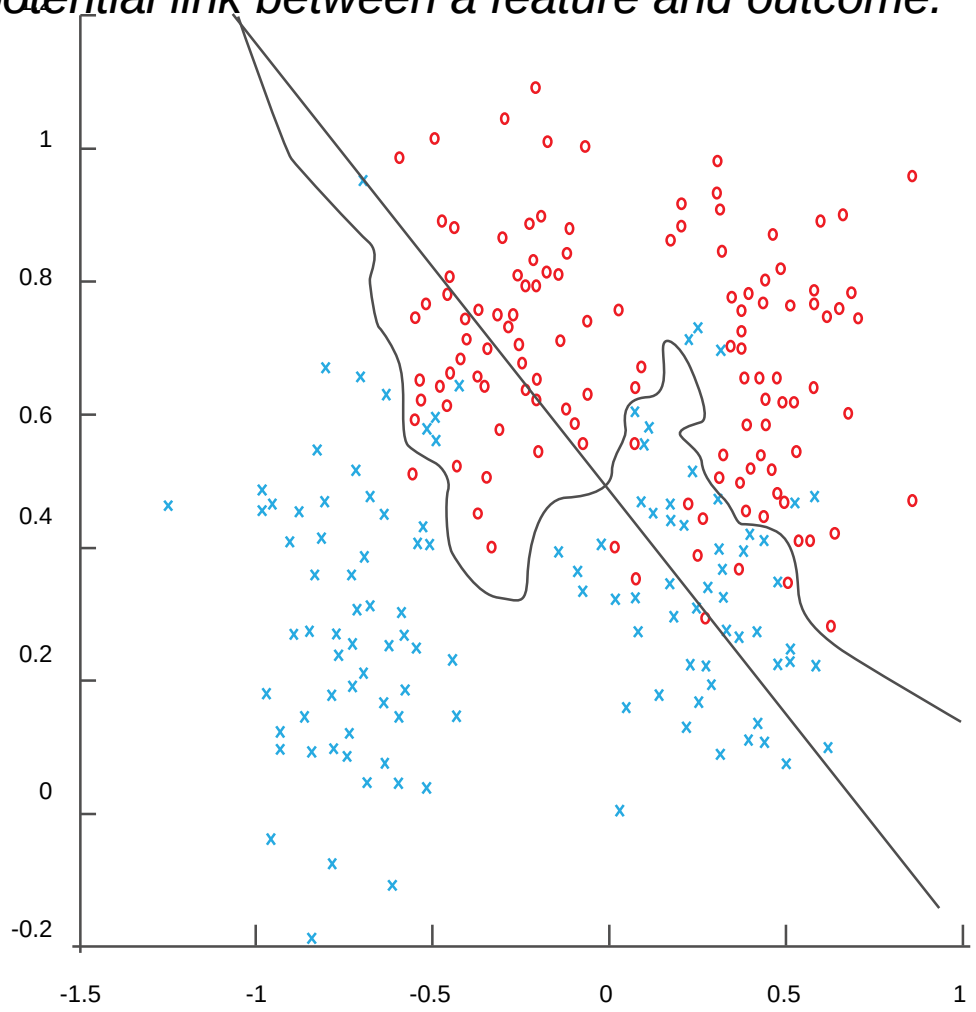
- Used by Amazon, Netflix, Google, Uber to predict consumer behavior
- Capable of analyzing large volumes of data
  - Can identify previously unknown associations
  - Established based on a machine-learning based financial trading company.
- Bring to light “hidden” information within existing medical data. Building decision support tools for personalized risk assessment of life threatening conditions.

Oermann et al: Scientific Reports 6:2116, 2016; Ghavidel et al: J Thorac Cardiovasc Surg 148:1291, 2014; Goldstein et al: Eur Heart J, 2016

MAYO CLINIC

Machine Learning vs Regression Modeling

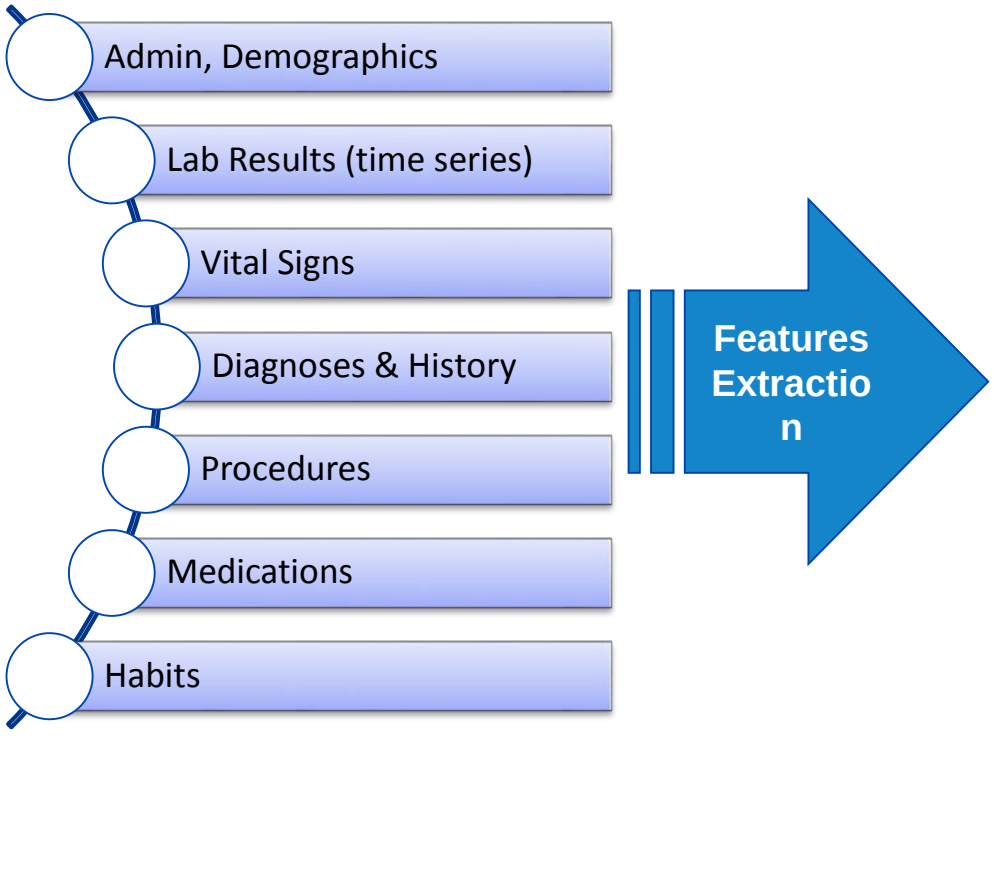
Machine learning is data driven rather than hypothesis driven(used by statisticians) potential link between a feature and outcome.



This graph represent relationship of 2 parameters but in reality multiple relationships are tested

MAYO CLINIC

Patient Featurization



Patient

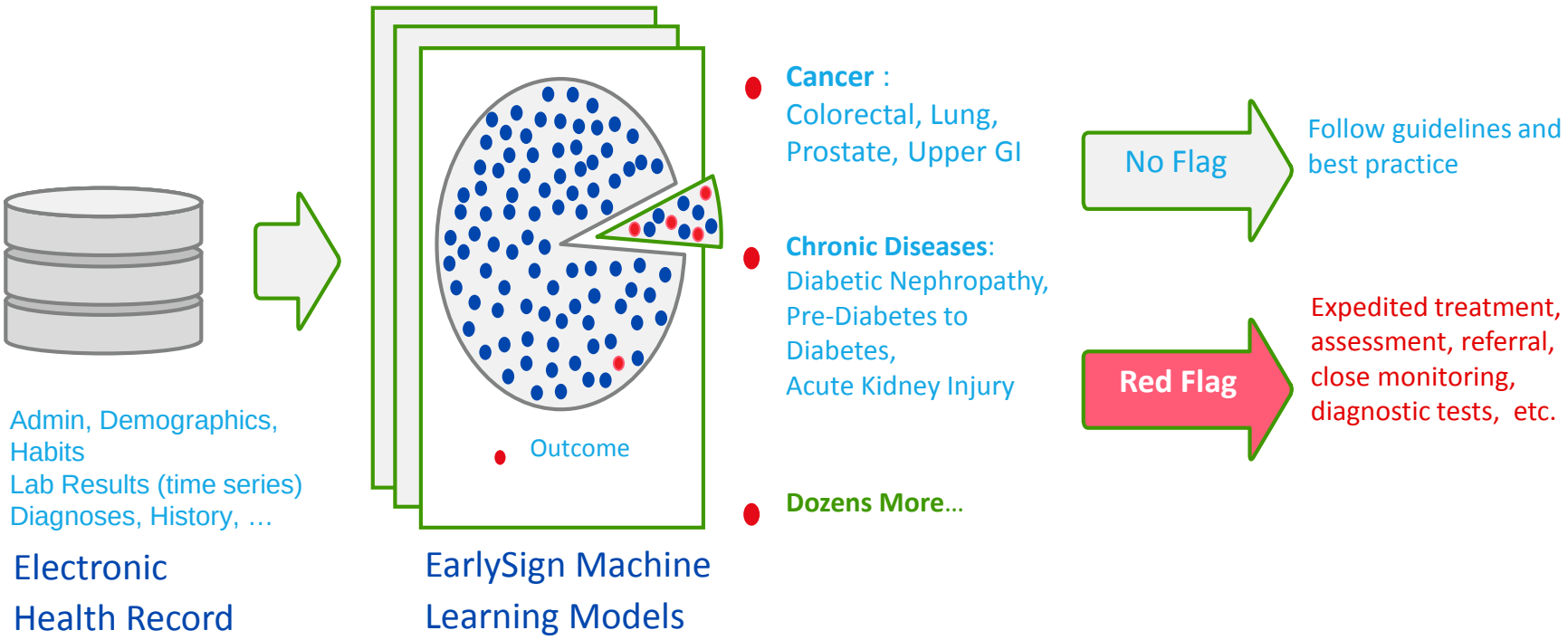
EHR Data

Patient Feature Vector

MAYO CLINIC

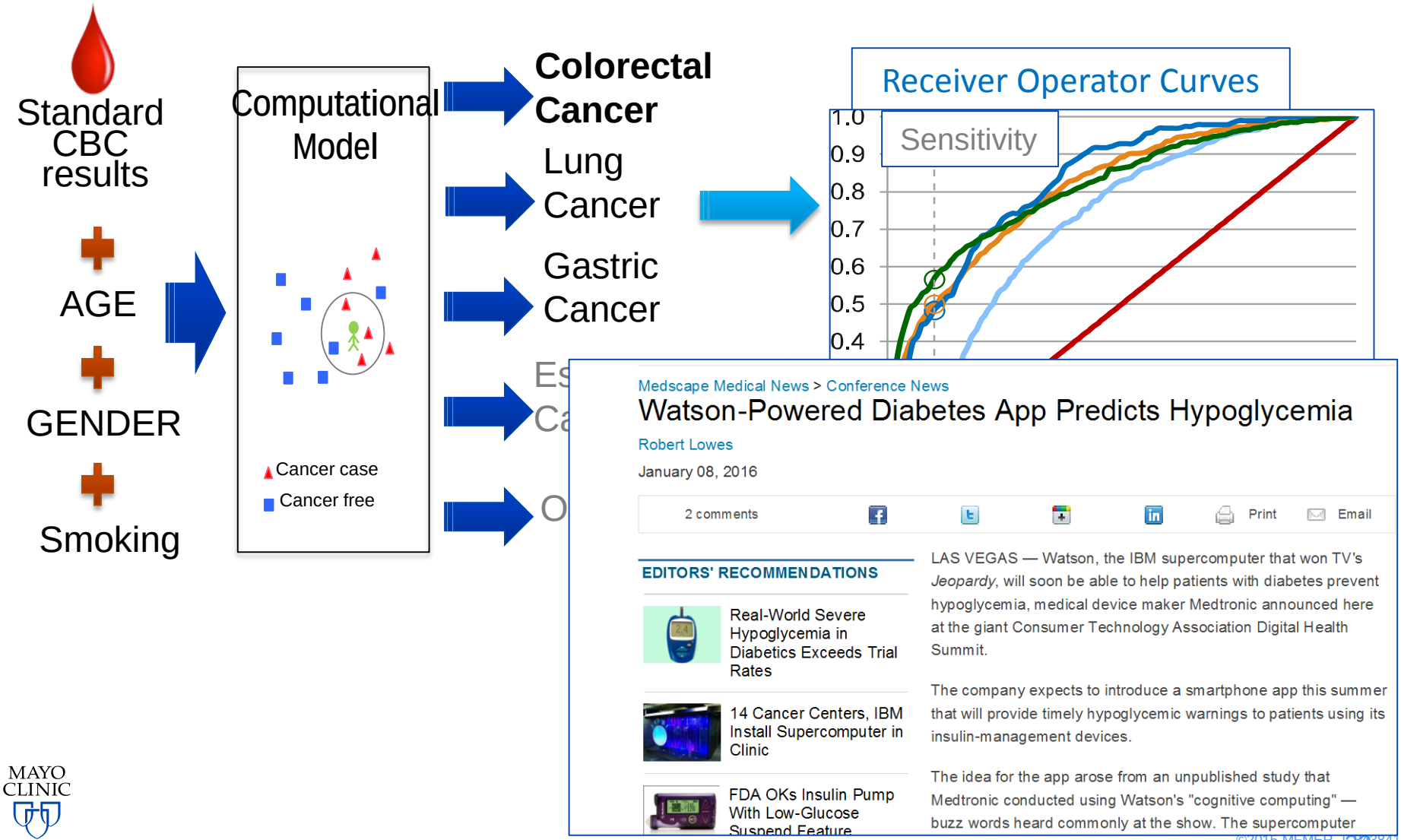
Predictive Models for Multiple Outcomes

- Address multiple types of outcomes and select those that are actionable

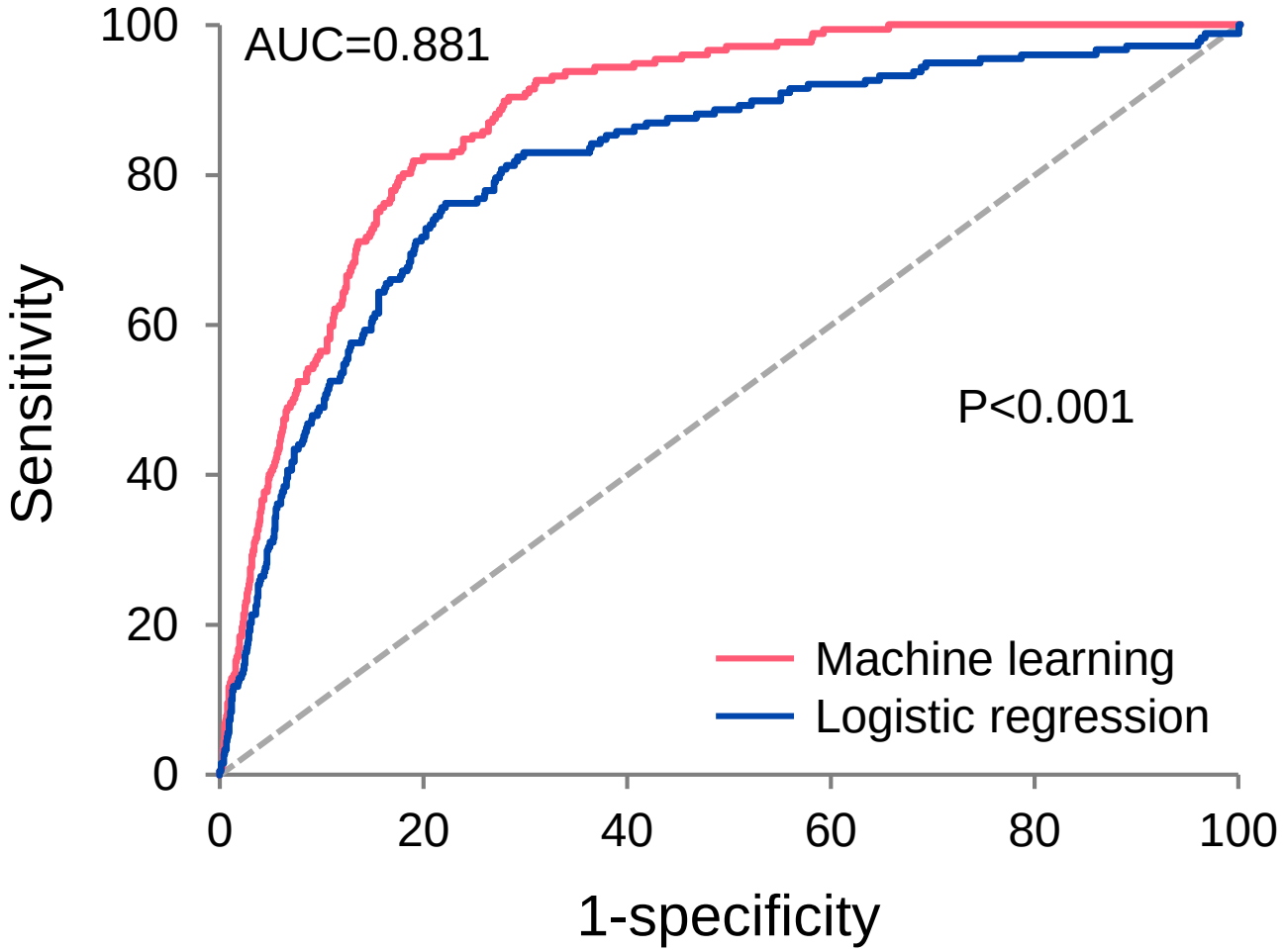


MeScore – a tool for eScreening

Use the results of a **low-cost** and **readily available** blood test to simultaneously calculate risk scores **for multiple types of cancers**

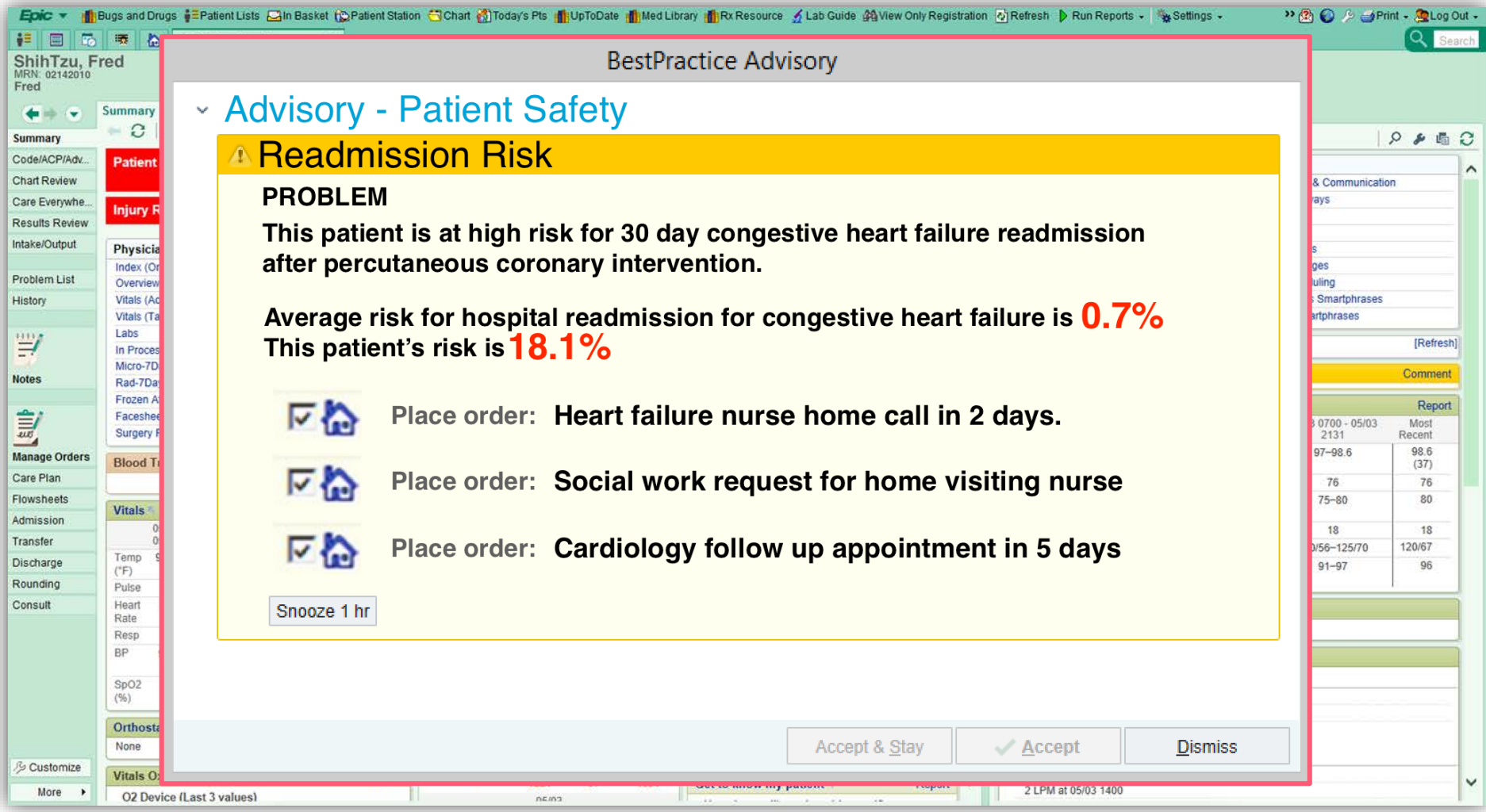


Death from Cardiovascular Cause ≤180 Days following PCI



MAYO CLINIC

Electronic Records Implementation



Perspectives

Bone Marrow Mononuclear Cell Therapy for Acute Myocardial Infarction

A Perspective From the Cardiovascular Cell Therapy Research Network

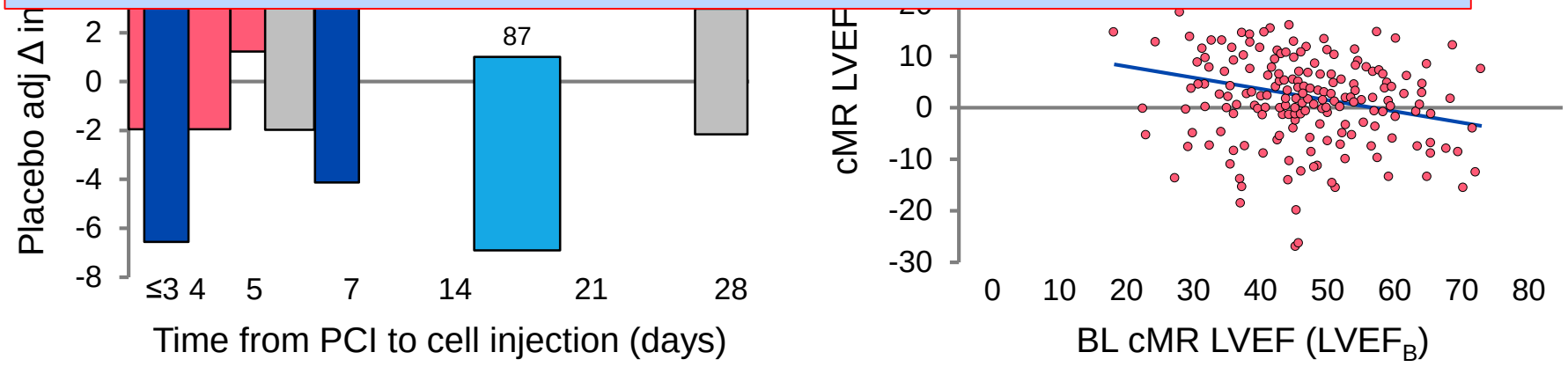
Robert D. Simari, Carl J. Pepine, Jay H. Traverse, Timothy D. Henry, Roberto Bolli, Daniel B. Spoon, Ed Yeh, Joshua M. Hare, Ivonne Hernandez Schulman, R. David Anderson, Charles Lambert, Shelly L. Sayre, Doris A. Taylor, Ray F. Ebert, Lemuel A. Moyé

***Abstract*—To understand the role of bone marrow mononuclear cells in the treatment of acute myocardial infarction, this overview offers a retrospective examination of strengths and limitations of 3 contemporaneous trials with attention to critical design features and provides an analysis of the combined data set and implications for future directions in cell therapy for acute myocardial infarction.** (*Circ Res*. 2014;114:1564-1568.)

Placebo-adjusted Effect Size for Δ in LVEF Over Time as a Function

Relationship Between Change in LVEF Over Time and BL EF in TIME

Mash-up: Between different technologies and cells

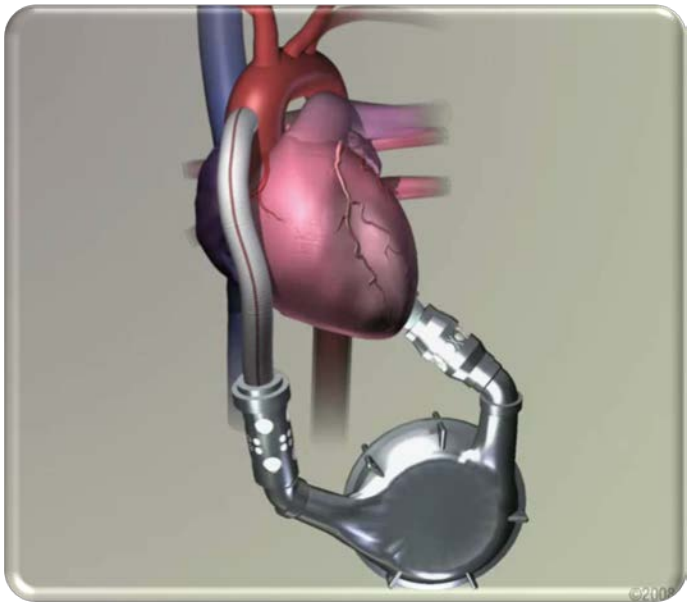


Simari et al: Circ Res 114:1564, 2014

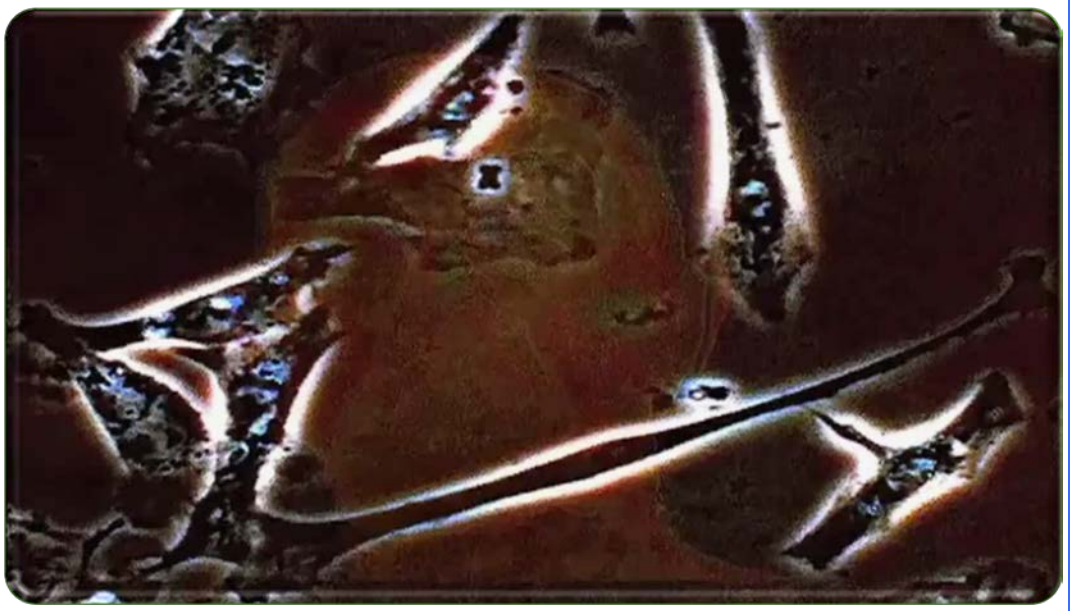
MAYO CLINIC

Synergy of Device and BioTech

Left Ventricular Assist Device



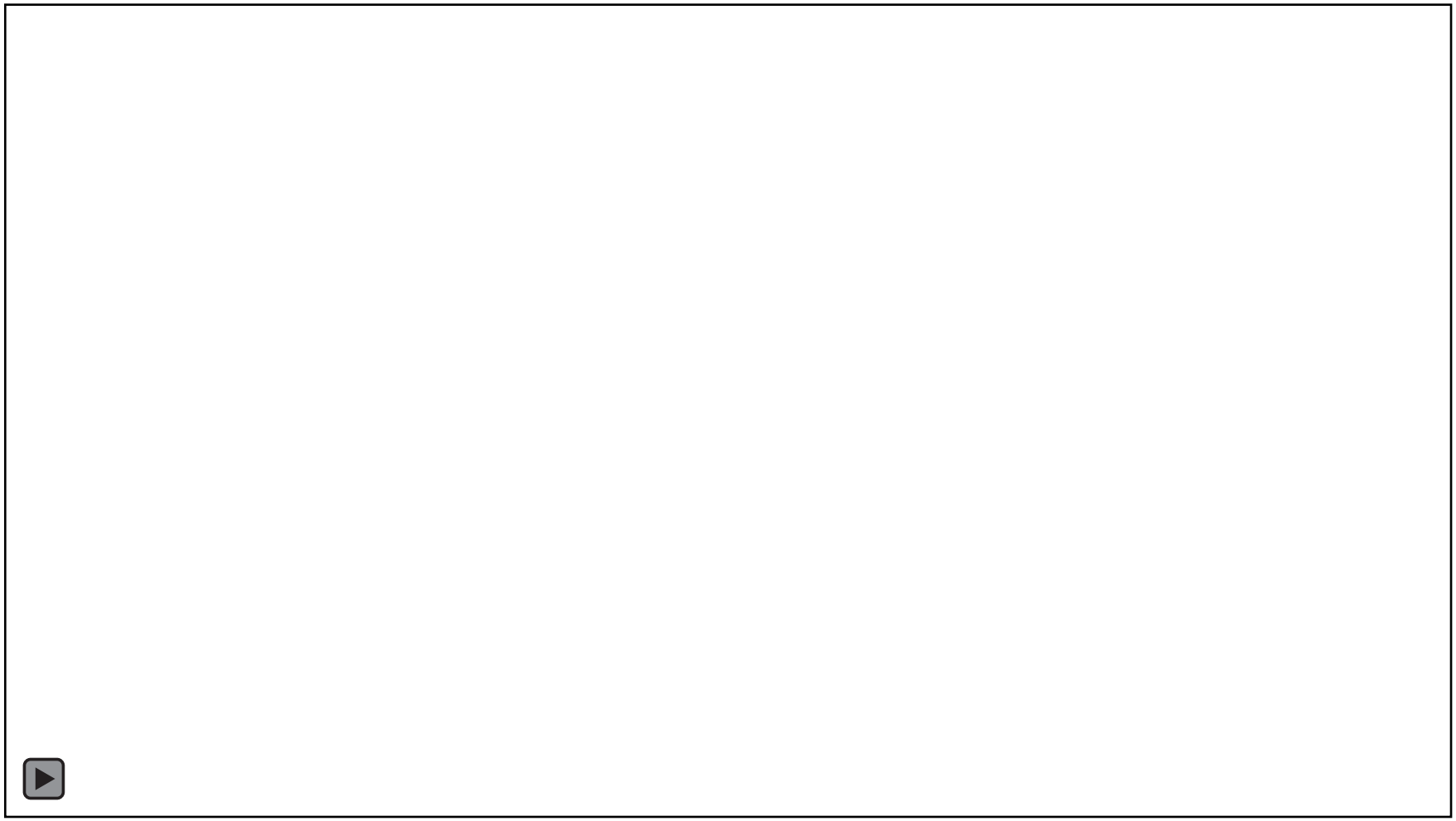
Beating Heart Cells Created from Stem Cells



Macrostructure stabilization → Microstructure integration

MAYO CLINIC

Building your own aortic valve



MAYO CLINIC

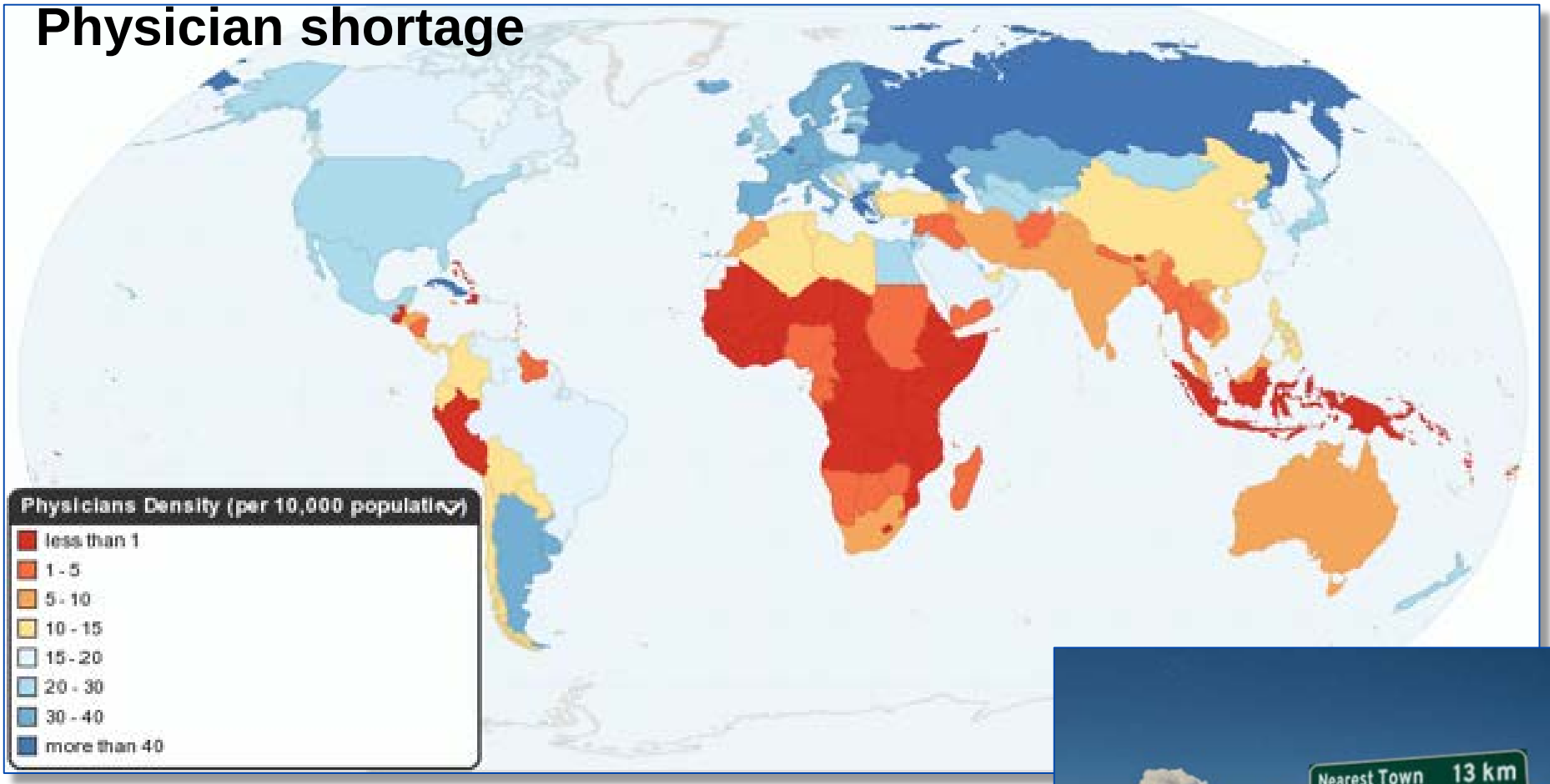
Where are the Opportunities in the Medical Field?

- Big data (machine learning)
- Precision (Individualized) medicine
- Remote diagnosis and treatment

MAYO CLINIC

Standardization and equalizing Access to care

Physician shortage



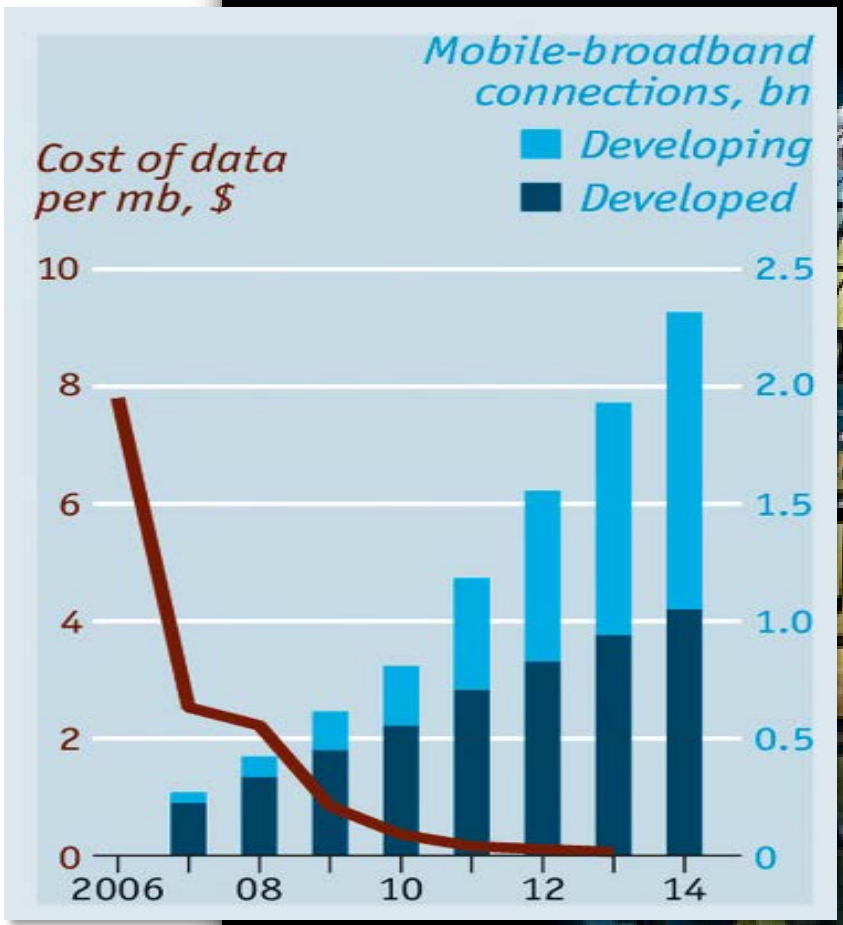
MAYO CLINIC

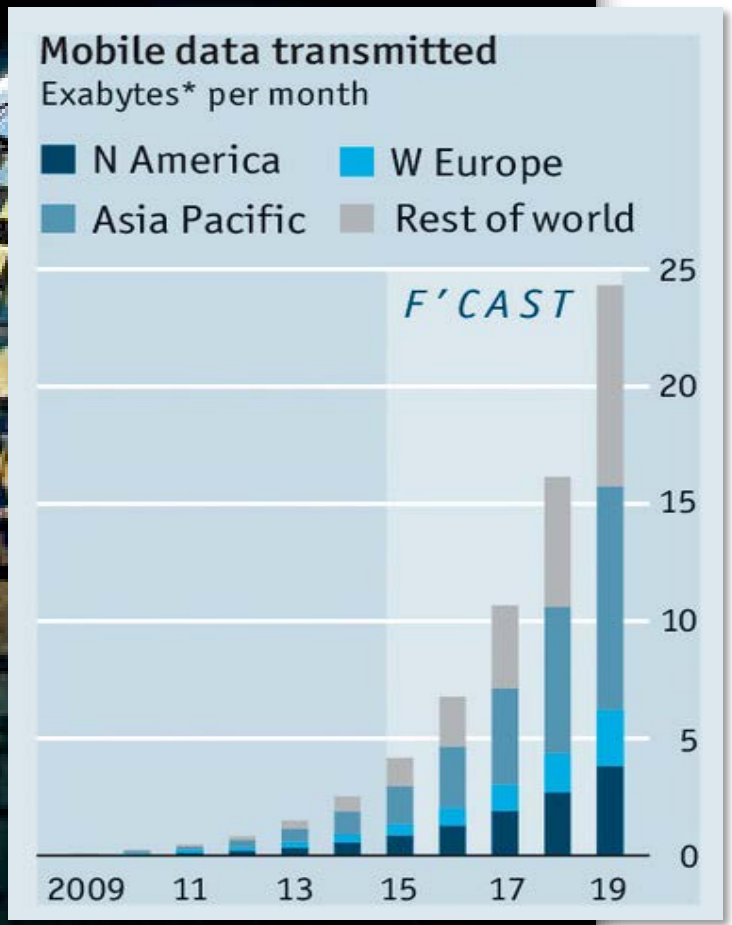
The Economist

FEBRUARY 28TH–MARCH 6TH 2015 Economist.com

Mosquito sex and malaria

Planet of the phones



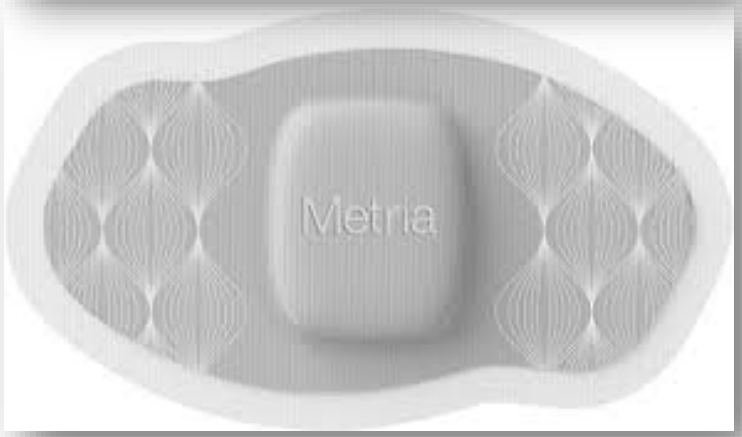


The Economist, Feb 2015

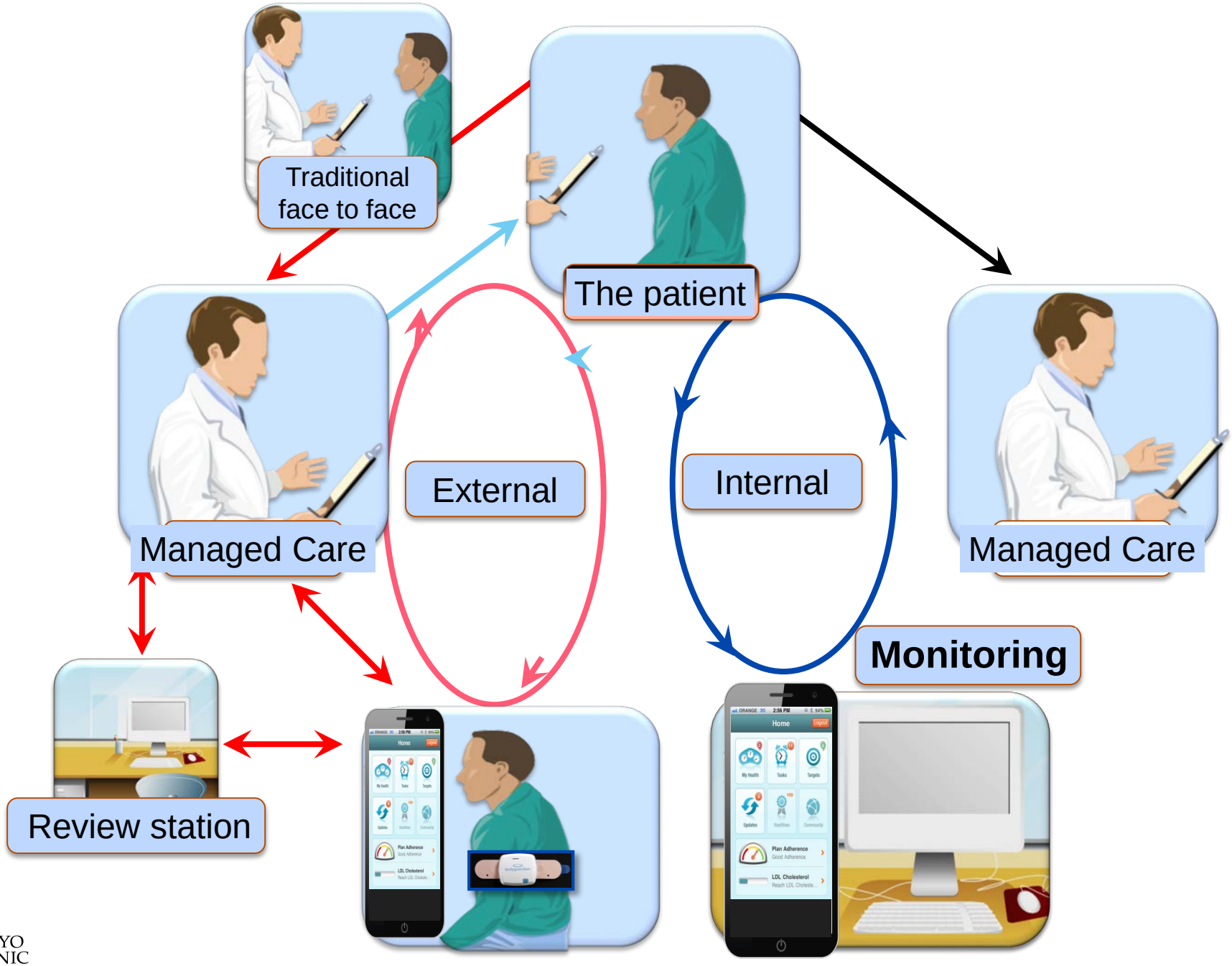
MAYO CLINIC

The Wearable Decade

…from watches, patches and tattoo's



MAYO CLINIC



MAYO CLINIC

Privacy in Healthcare: data security

63%

of customers are comfortable with storing their medical records on a cloud

39%

don't trust internet sites to keep my health information private and secure

Information customers are willing to share online

25%
Exercise/ physical activity

28%
Weight

26%
Sleep patterns

20%
Nutritional information (eg, calories consumed, etc)

25%
Symptoms/ general health complaints

15%
Vital signs (eg, blood pressure, heart rate, etc)

MAYO CLINIC

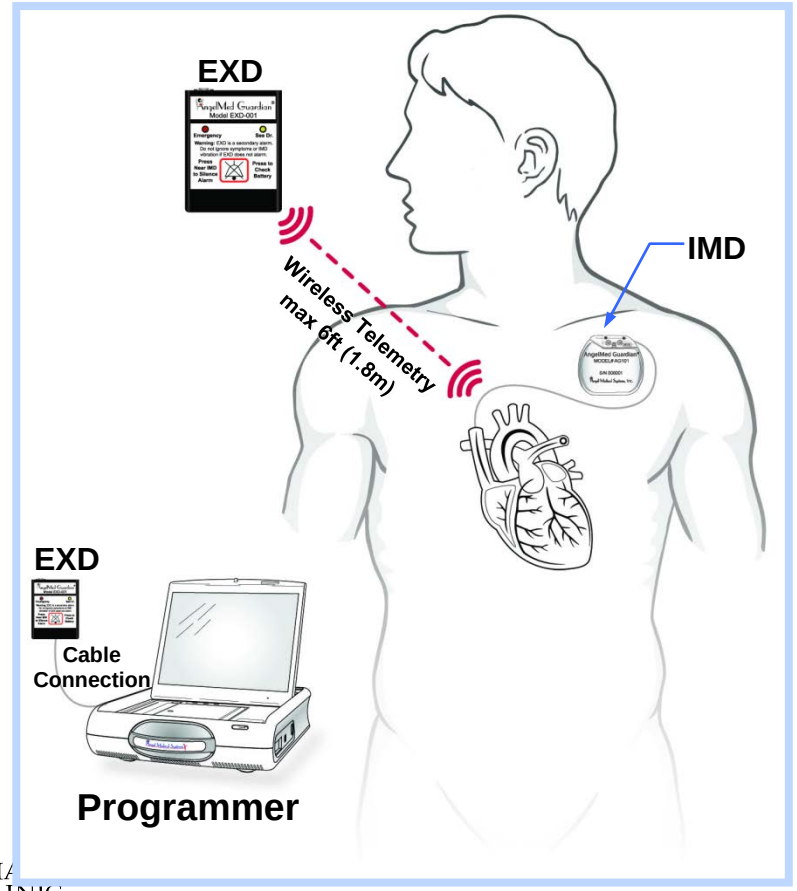
Journal of the American College of Cardiology
© 2010 by the American College of Cardiology Foundation
Published by Elsevier Inc.
Vol. 56, No. 14, 20
ISSN 0735-1097/$36.
doi:10.1016/j.jacc.2010.04.0

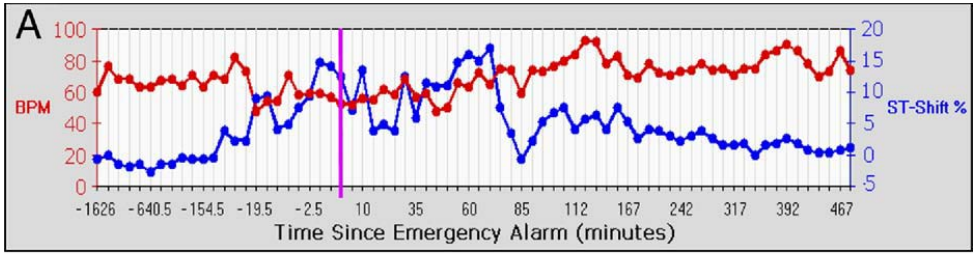
QUARTERLY FOCUS ISSUE: PREVENTION/OUTCOMES

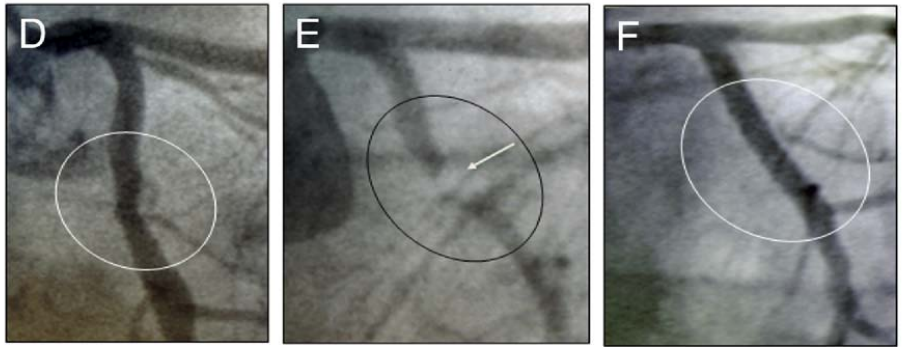
Initial Clinical Results Using Intracardiac Electrogram Monitoring to Detect and Alert Patients During Coronary Plaque Rupture and Ischemia

Tim A. Fischell, MD,* David R. Fischell, PHD,|| Alvaro Avezum, MD,‡ M. Sasha John, PHD,§|| David Holmes, MD,† Malcolm Foster III, MD,¶ Richard Kovach, MD,# Paulo Medeiros, MD,‡

Intracardiac monitoring was performed in 37 patients at high risk for acute coronary syndromes. The implanted monitor continuously evaluated the patients' ST segments sensed from a conventional pacemaker right ventricle apical lead, and alerted patients to detected ischemic events.



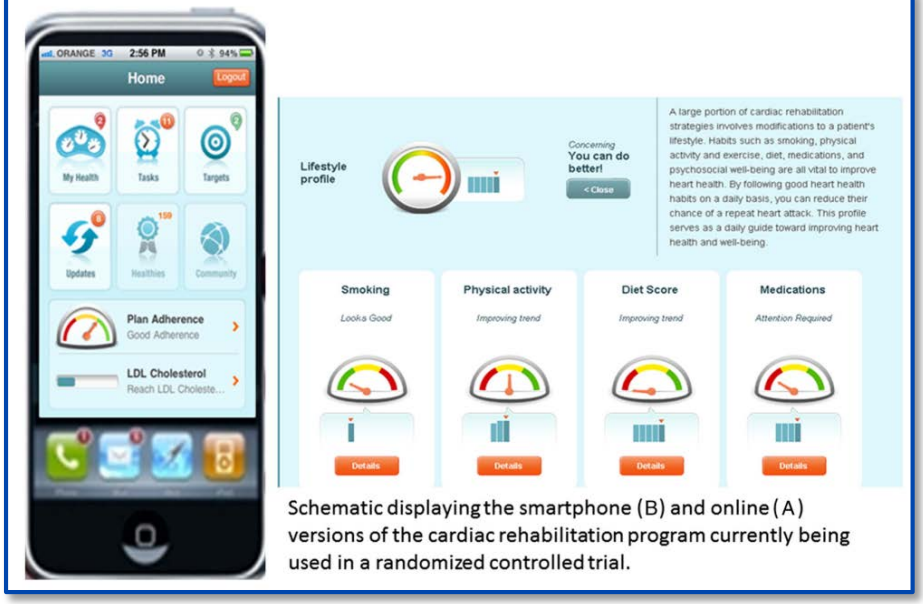




Using an online, personalized program reduces cardiovascular risk factor profiles in a motivated, adherent population of participants

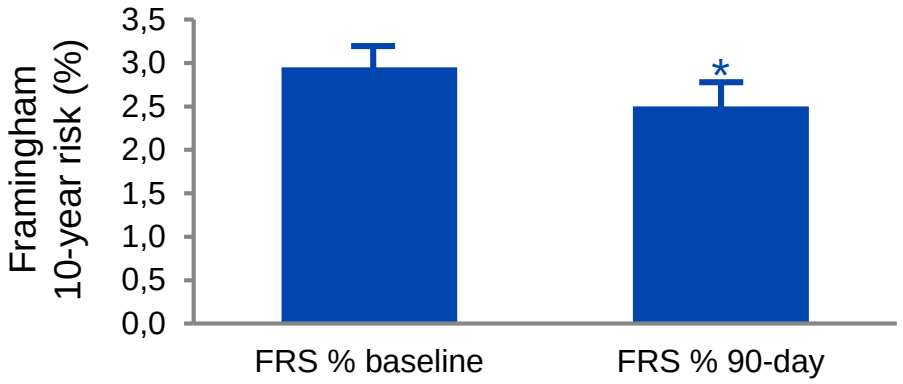
R. J. Widmer, MD, PhD,[a] Thomas G. Allison, PhD,[a] Brendie Keane, RN,[c] Anthony Dallas, MD,[c] Lilach O. Lerman, MD, PhD,[b] and Amir Lerman, MD[a] *Rochester, MN and Nashville, TN*

Methods: A cohort of employees in Tennessee was subjected to a health risk assessment at baseline. Those who did not meet all 5 healthy benchmarks – body mass index, blood pressure, glucose, total cholesterol and smoking status – were prospectively assigned to a web-based personal health assistant and had repeat measurements taken at 90 days

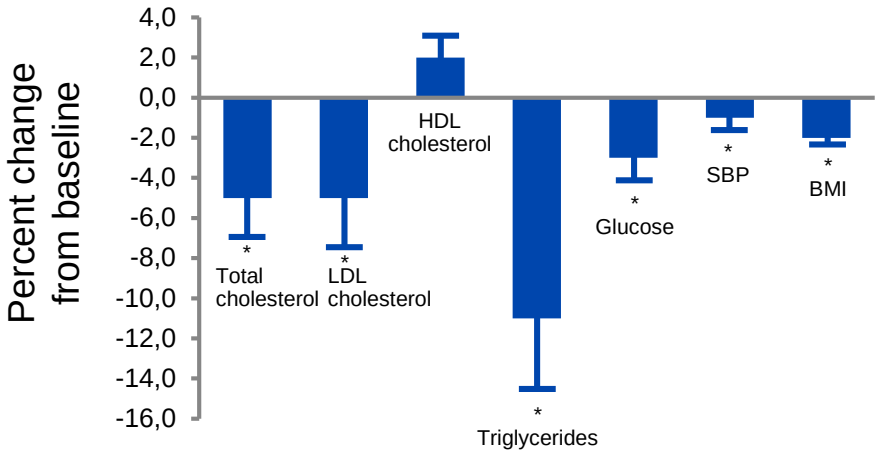


Schematic displaying the smartphone (B) and online (A) versions of the cardiac rehabilitation program currently being used in a randomized controlled trial.

Reductions in Raw FRS (left) and Converted FRS 10-year cardiovascular risk percentage (right)



Percent Change from Baseline in Risk Factors After Completing the Online PHA



MAYO CLINIC

Widmer & Lerman AHJ 2015

Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial

William T Abraham, Philip B Adamson, Robert C Bourge, Mark F Aaron, Maria Rosa Costanzo, Lynne W Stevenson, Warren Strickland, Suresh Neelagaru, Nirav Raval, Steven Krueger, Stanislav Weiner, David Shavelle, Bradley Jeffries, Jay S Yadav, for the CHAMPION Trial Study Group*

Patients with New York Heart Association (NYHA) class III heart failure, a previous hospital admission for heart failure were enrolled in 64 centers in the USA. They were randomly assigned by use of a centralized electronic system to management with a wireless implantable hemodynamic monitoring (W-IHM) system (treatment group) or to a control group for at least 6 months. Only

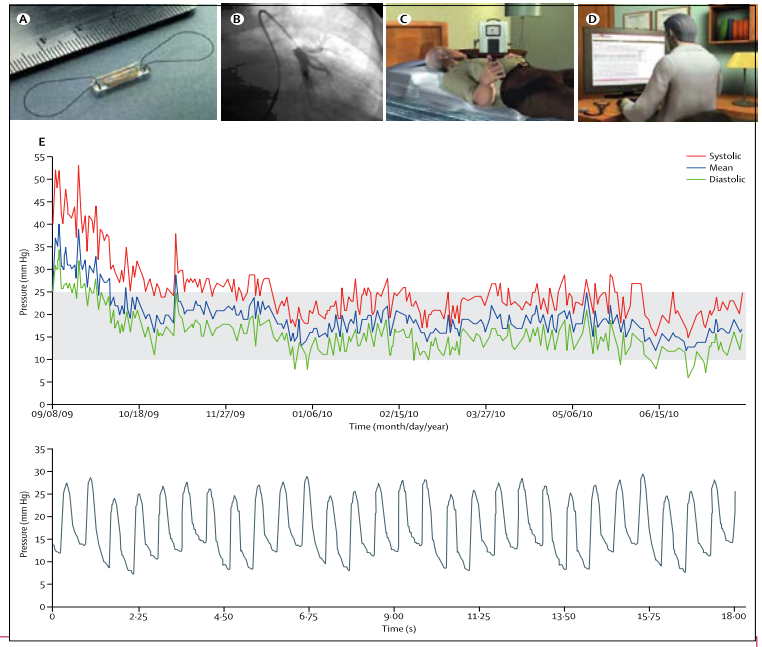
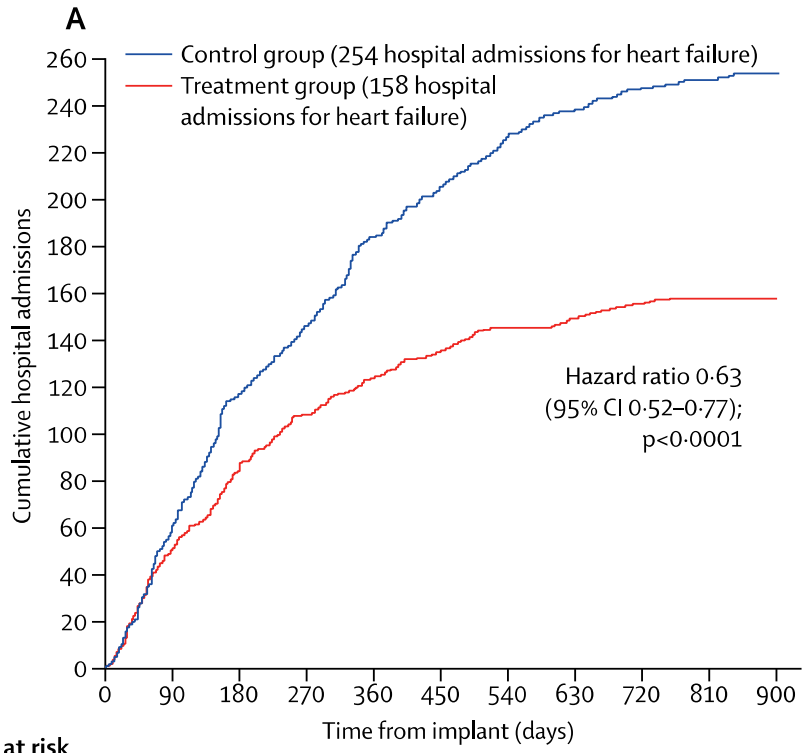
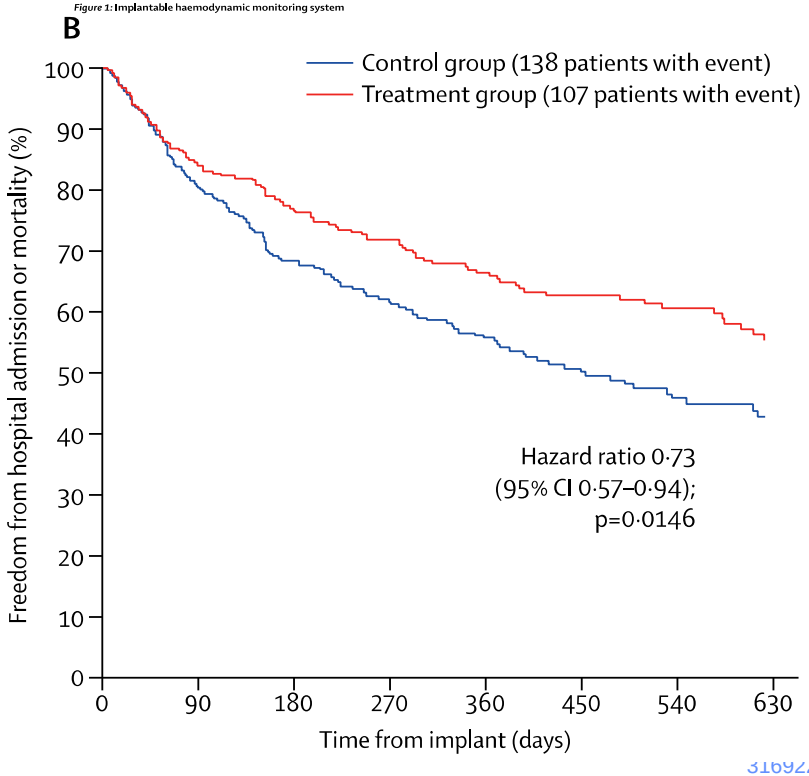


Figure 1: Implantable haemodynamic monitoring system

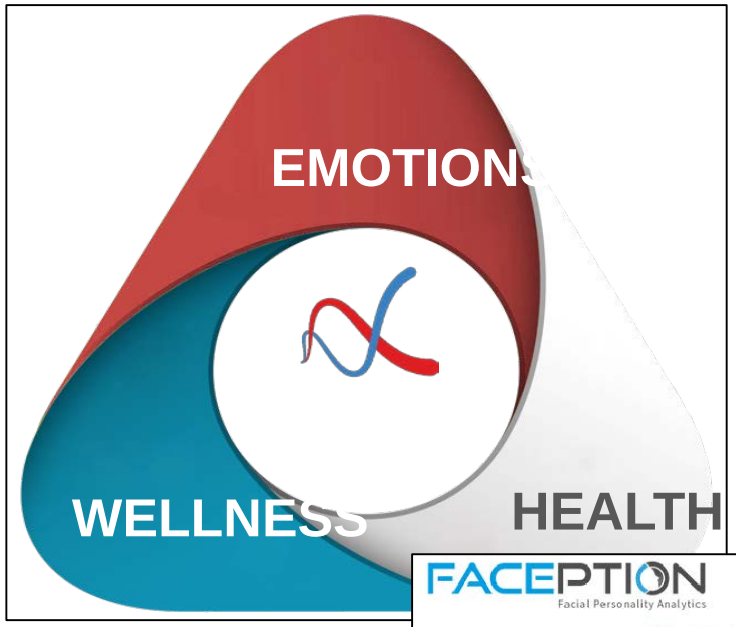




Number at risk

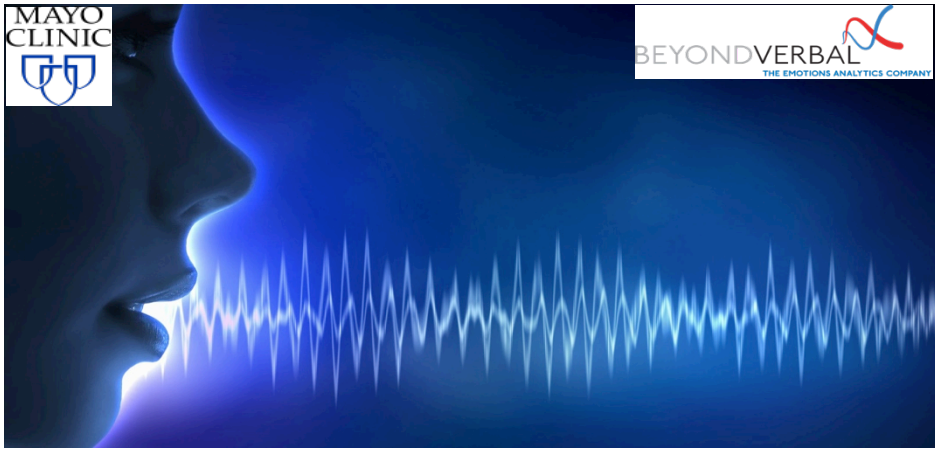
“Listening” to our body

It’s not what we say, It’s HOW we say it



Just Blink: New Device Detects Disease Through Eye Movement

Genetics and epigenetic play a large role in determining face shape,



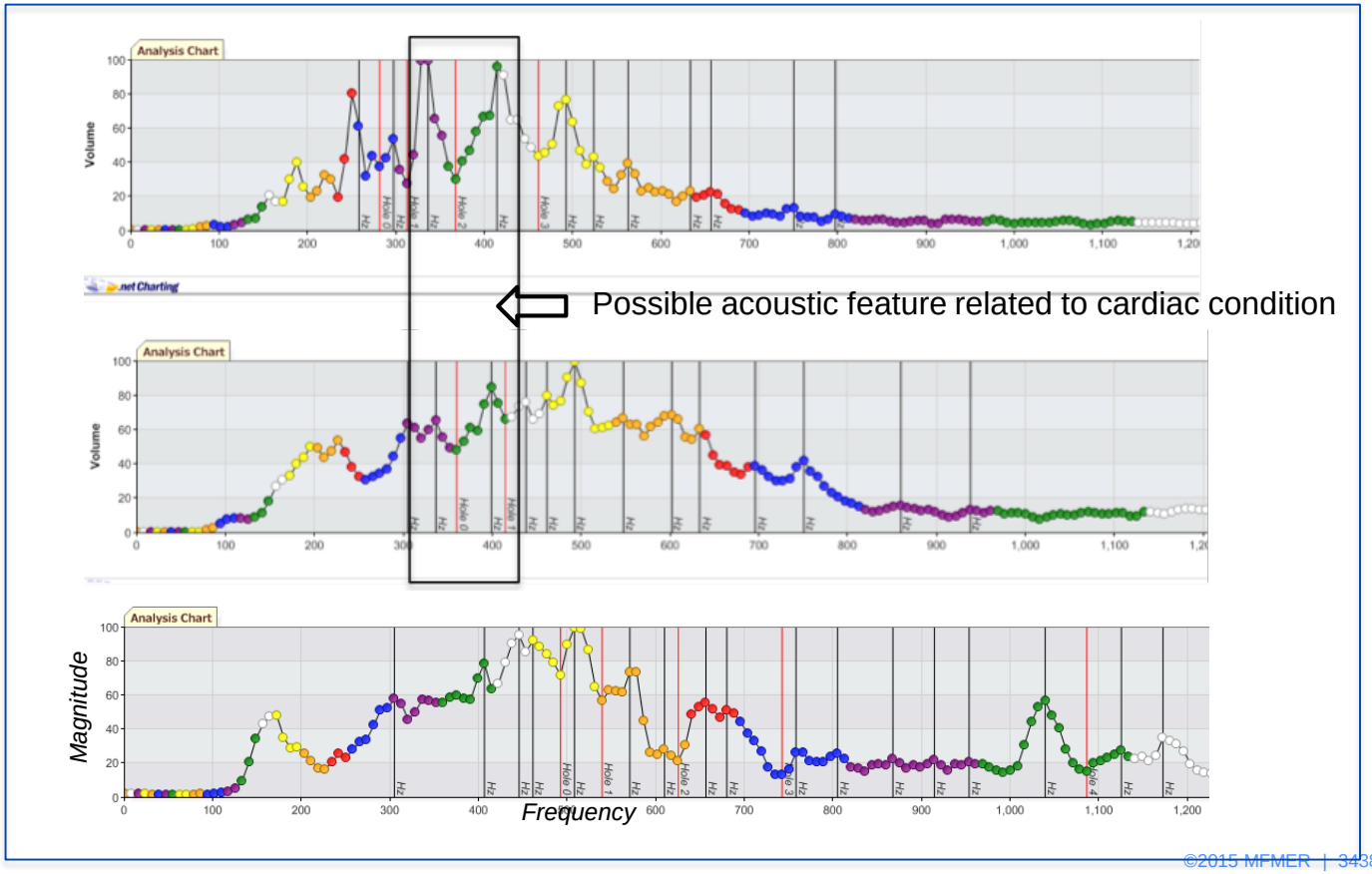
These figures illustrate representative voice signal characteristics signals from a patient prior and following coronary angiography and intervention as compared to a normal control.

Average FFT transform of selected voice recording segments

CAD patient prior to angiography

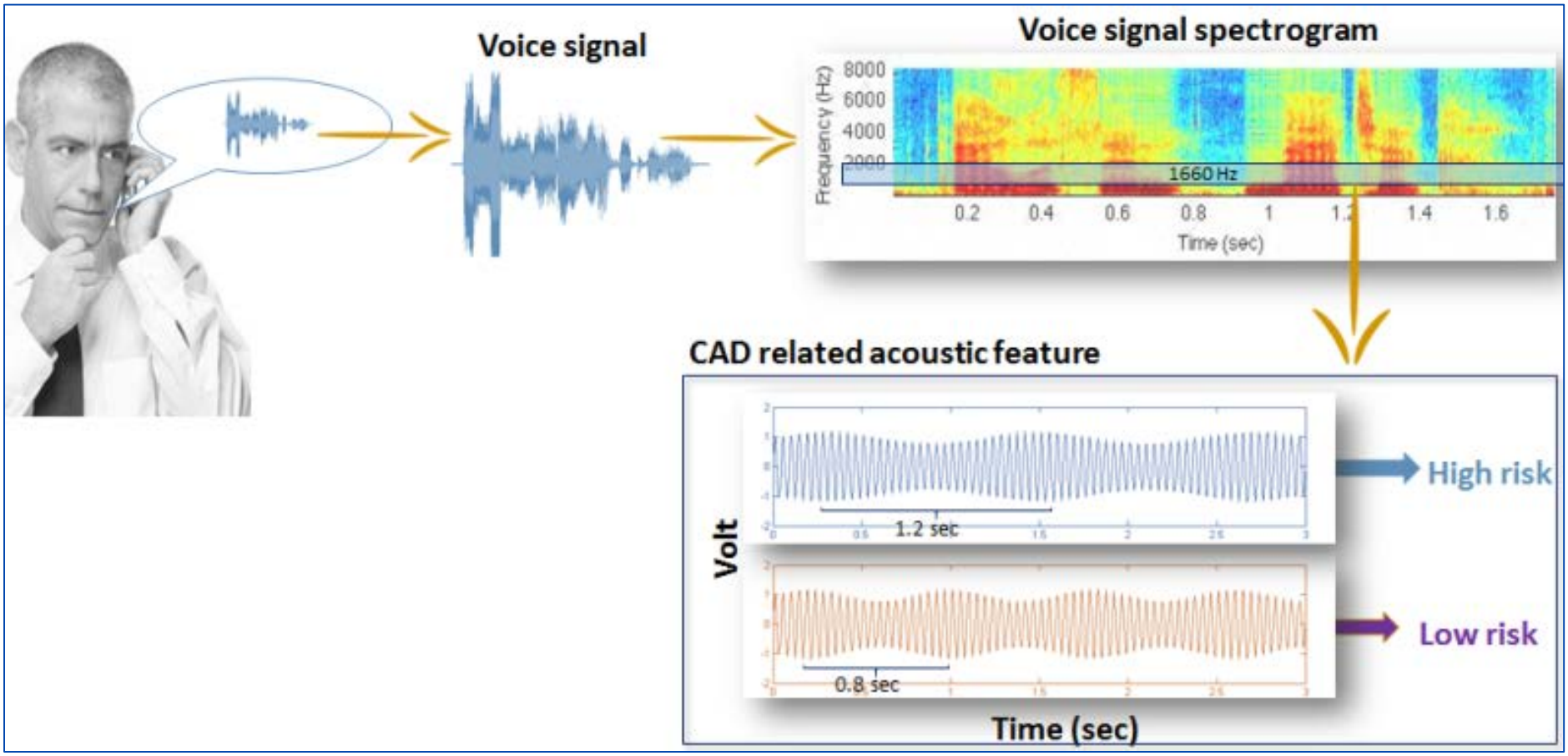
CAD patient after angiography and intervention

Example of voice signal of a healthy individual



MAYO CLINIC

Remote voice recognition of CAD



MAYO CLINIC

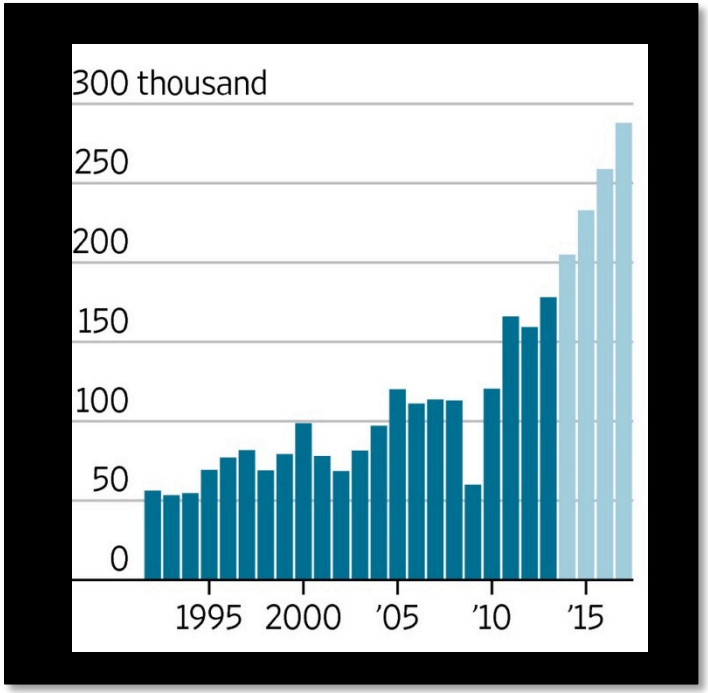
Where are the Opportunities in the Medical Field?

- Big data (machine learning)
- Precision (Individualized) medicine
- Remote diagnosis and treatment

MAYO CLINIC

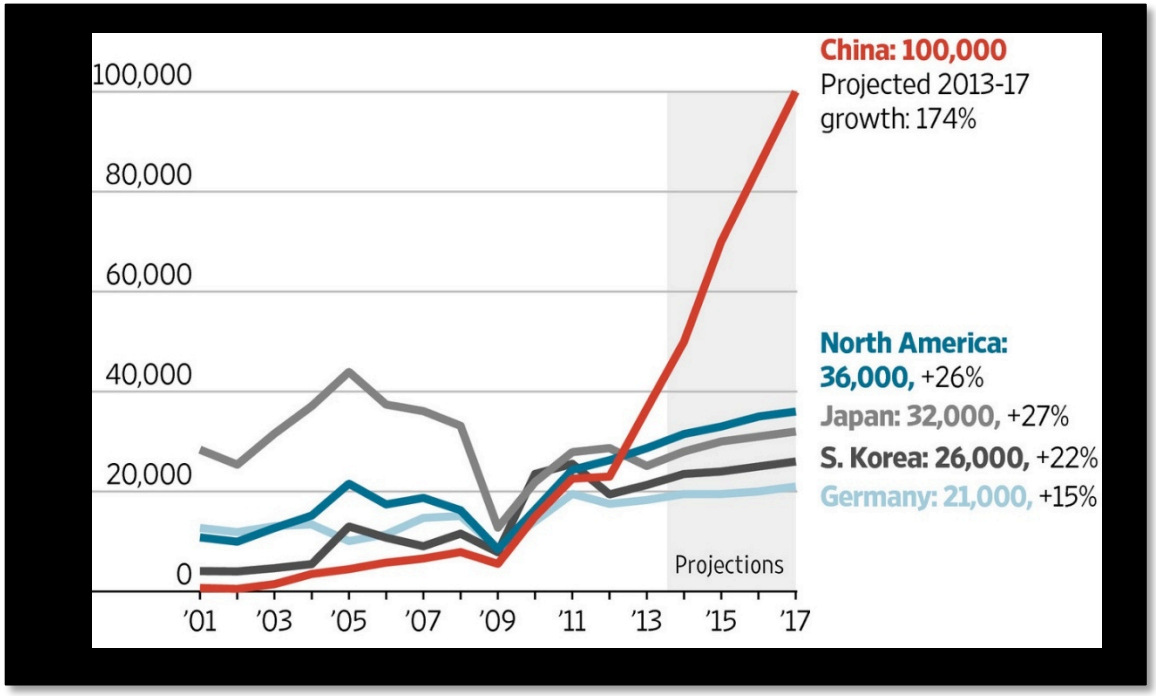
Robotic Revolution; across all industries

World-wide industrial robot installations



Automatic Nations

Top 5 markets for industrial robot sales

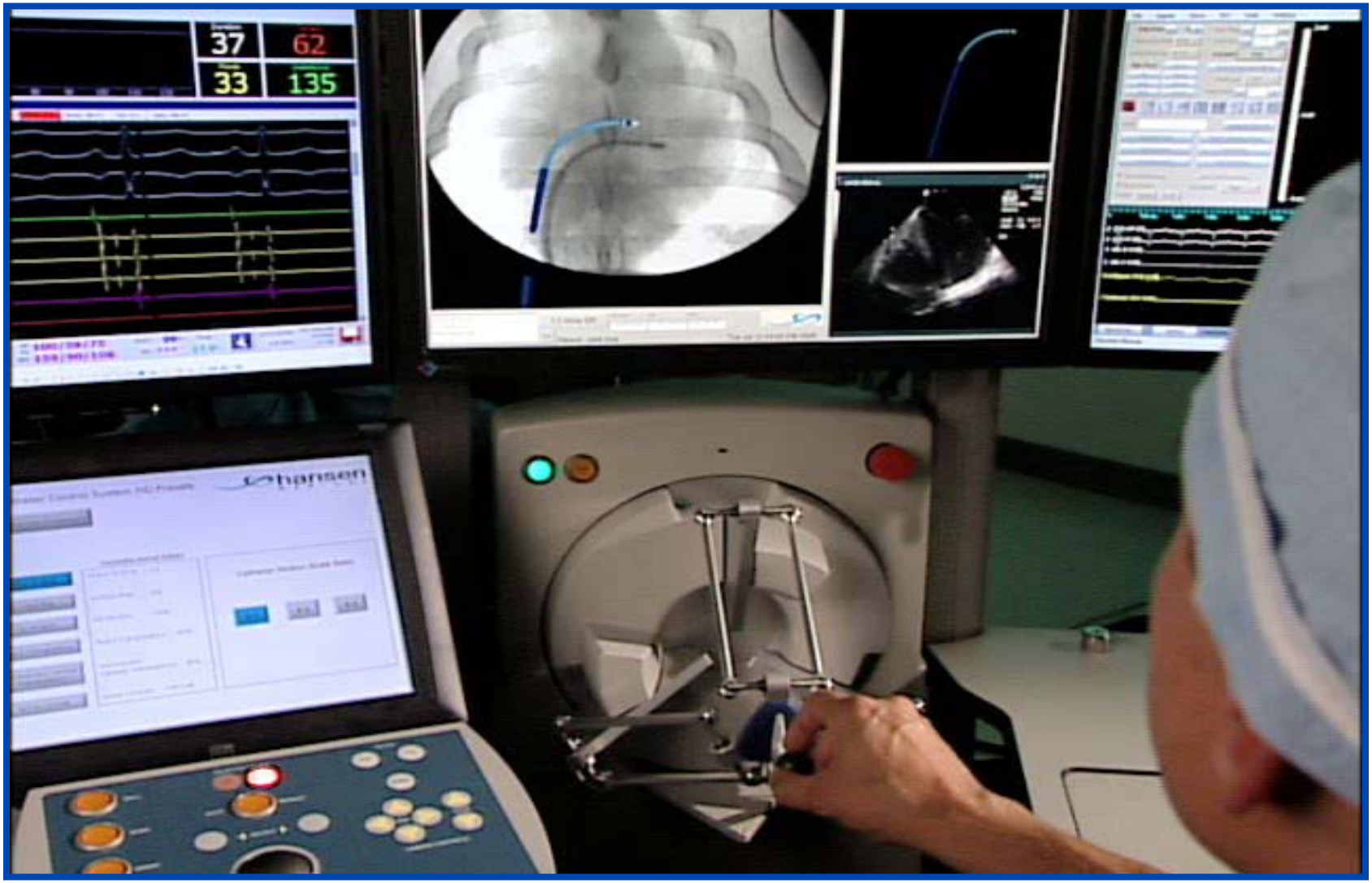


Source: International Federation of Robots

The Wall Street Journal. Feb 2015

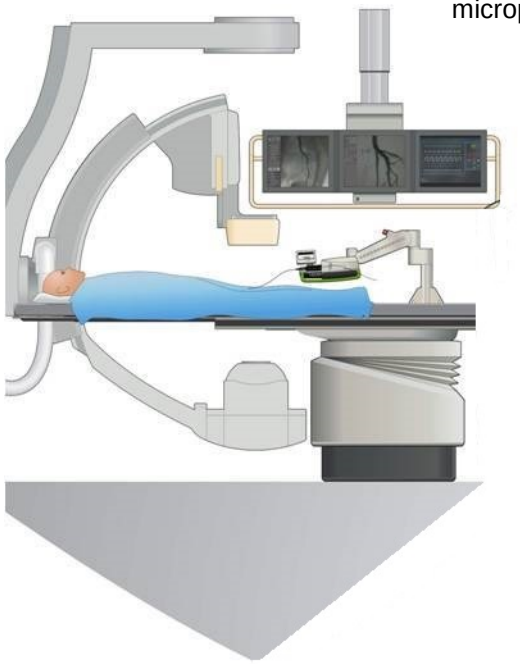
We now drive cars, have vision & vacuum robotically…we will not be manually controlling catheters in the future...

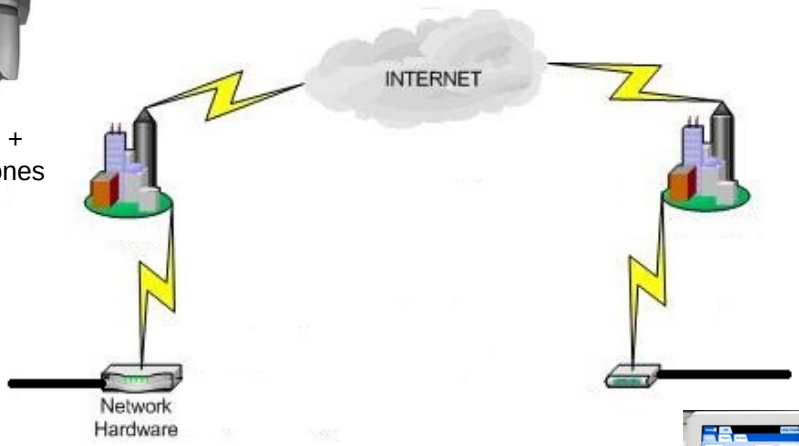
The synchrony of imaging and catheter movement …practice, plan and perfect…



Technology Requirements

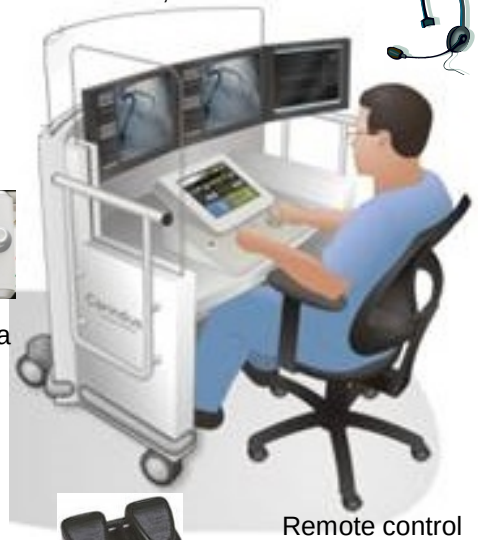
Cameras +
microphones





Fluoro, hemo, pt data,
FFR, IVUS

Remote camera
Controls



footswitch

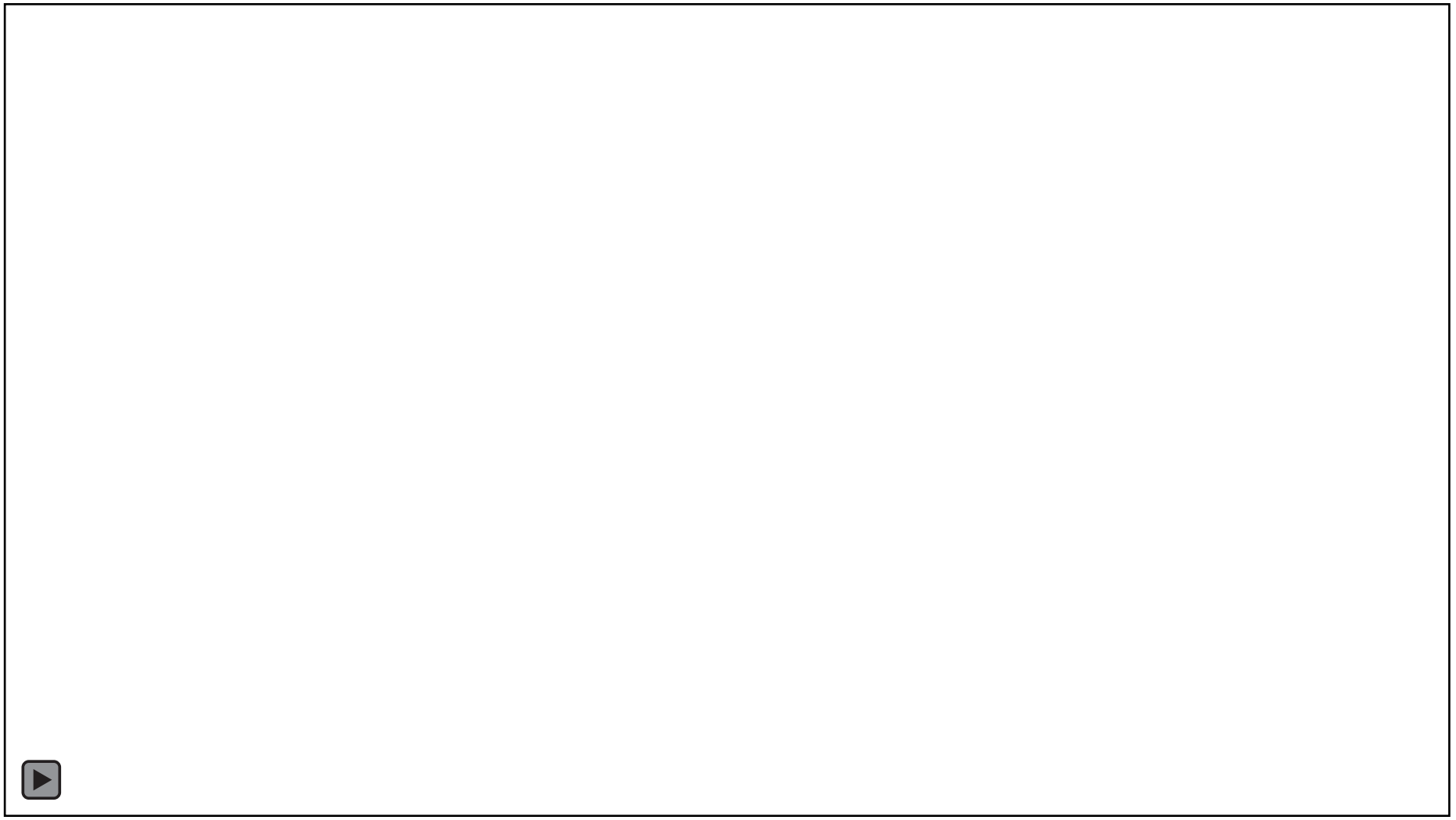
Remote control
of guide wires
balloons/stents
guide catheter

Cath lab – at the patient

Immerse IC virtually
into the cath lab
Education

MAYO CLINIC

Planning the procedure for the future



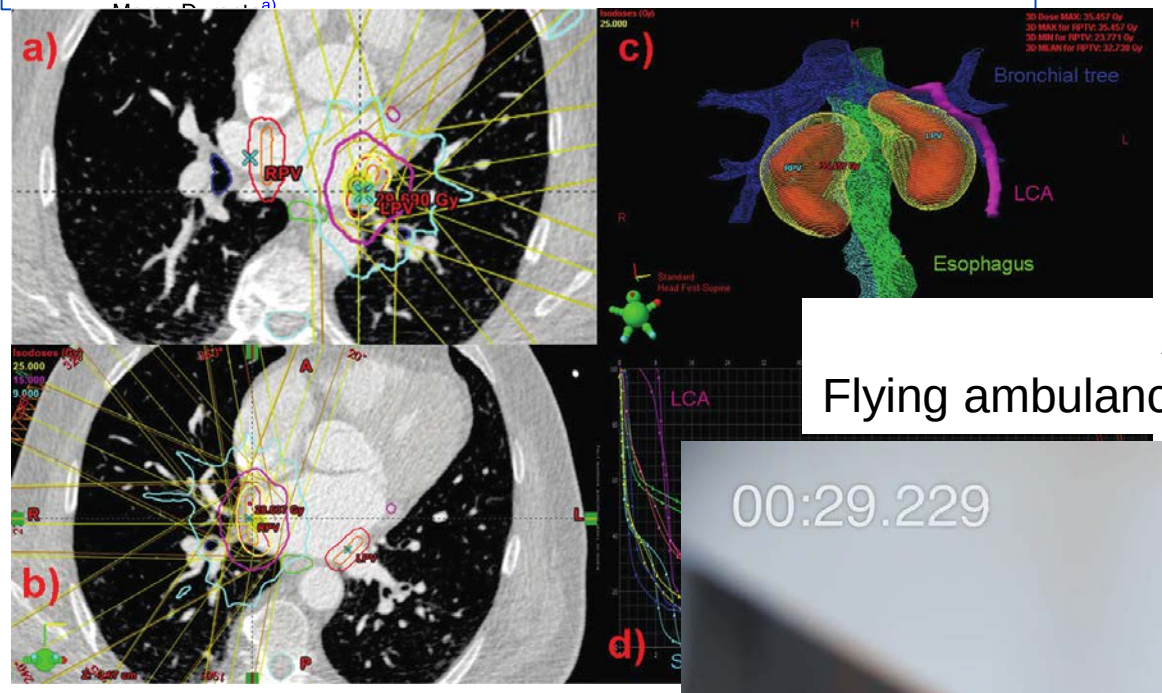
MAYO CLINIC

Particle therapy for noncancer diseases

Christoph Bert
GSI Helmholtzzentrum für Schwerionenforschung, Biophysics Department, Planckstraße 1, 64291 Darmstadt, Germany

Rita Engenhart-Cabillic
Philipps-University Marburg, Center for Radiology, Department of Radiation Therapy, Baldinger Strasse, 35043 Marburg, Germany

Future treatment by photon bean therapy for atrial fibrillation



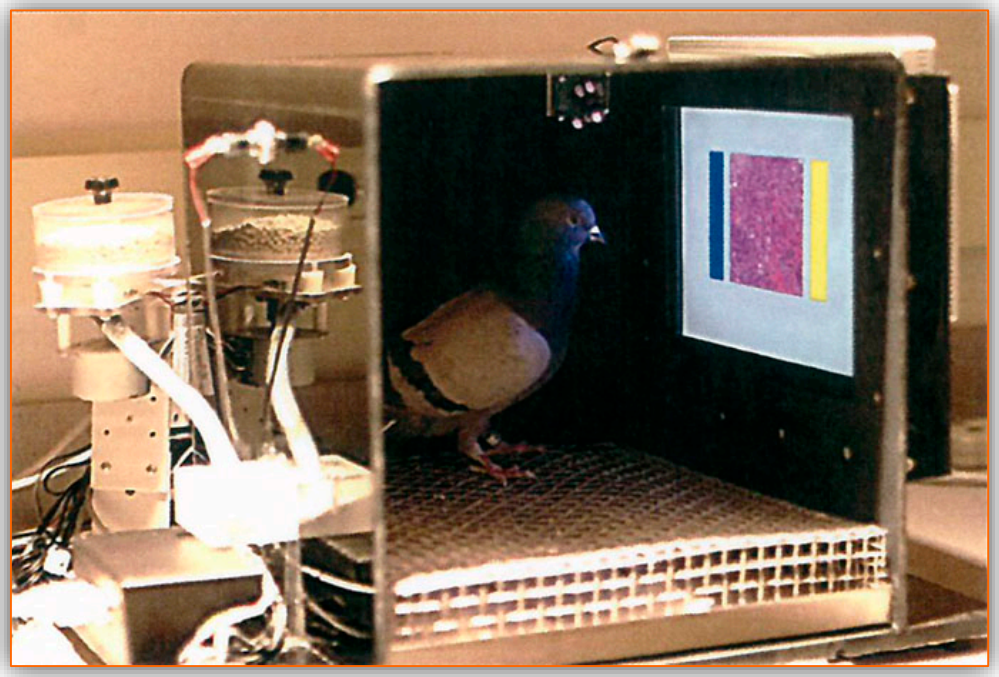
A good use of a drone
Flying ambulance drone to deliver emergency shock

MAYO CLINIC

RESEARCH ARTICLE

Pigeons (*Columba livia*) as Trainable Observers of Pathology and Radiology Breast Cancer Images

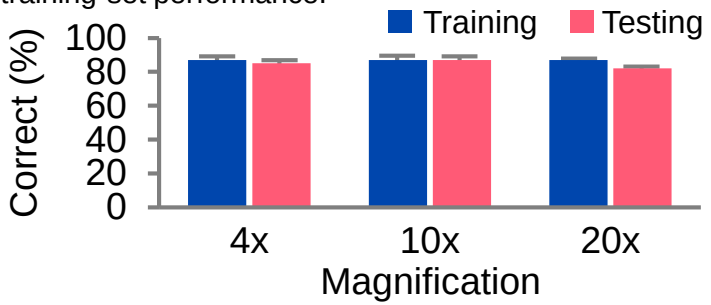
Pigeons (*Columba liva*) – share many visual system properties with humans – can serve as promising surrogate observers of medical images



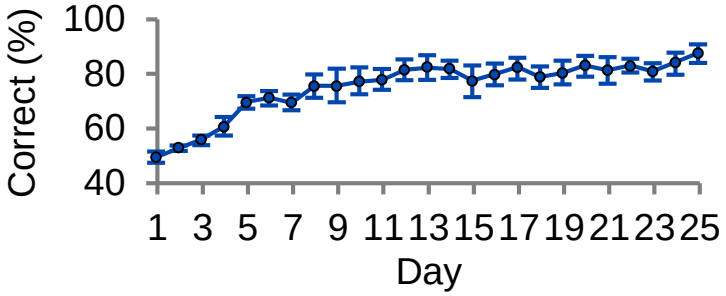
The pigeons' training environment

Generalization from training to test image sets.

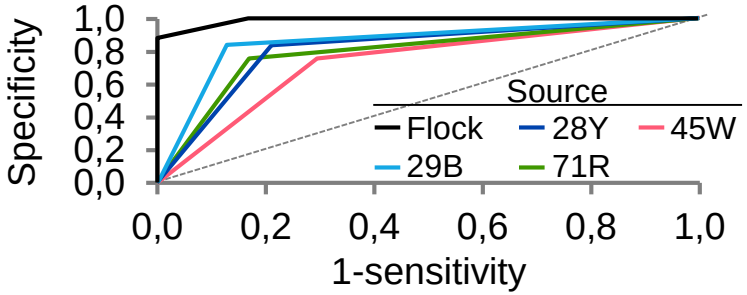
After training with differential reinforcement, the birds successfully classified previously unseen breast tissue images in the testing sets, at all magnifications, with no statistically significant decrease in accuracy compared to training-set performance.



Results of training and testing with mammograms with or without calcifications



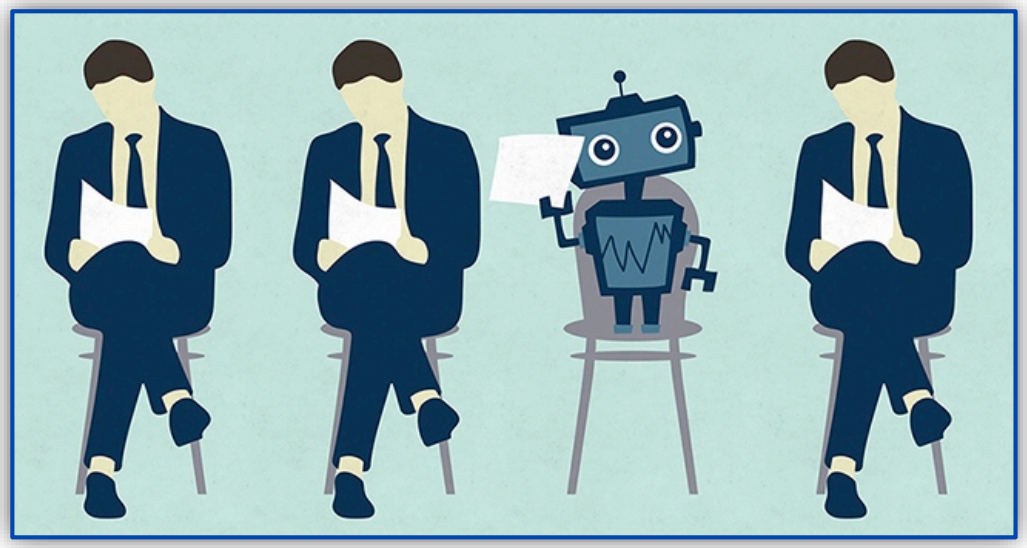
Flock sourcing. Pooling the birds' decisions led to significantly better discrimination



Levenson et al: PLoS ONE 10(11):e0141357, 2015

MAYO CLINIC

Robots Threaten These Jobs



Soon you could be competing with a robot for a job.

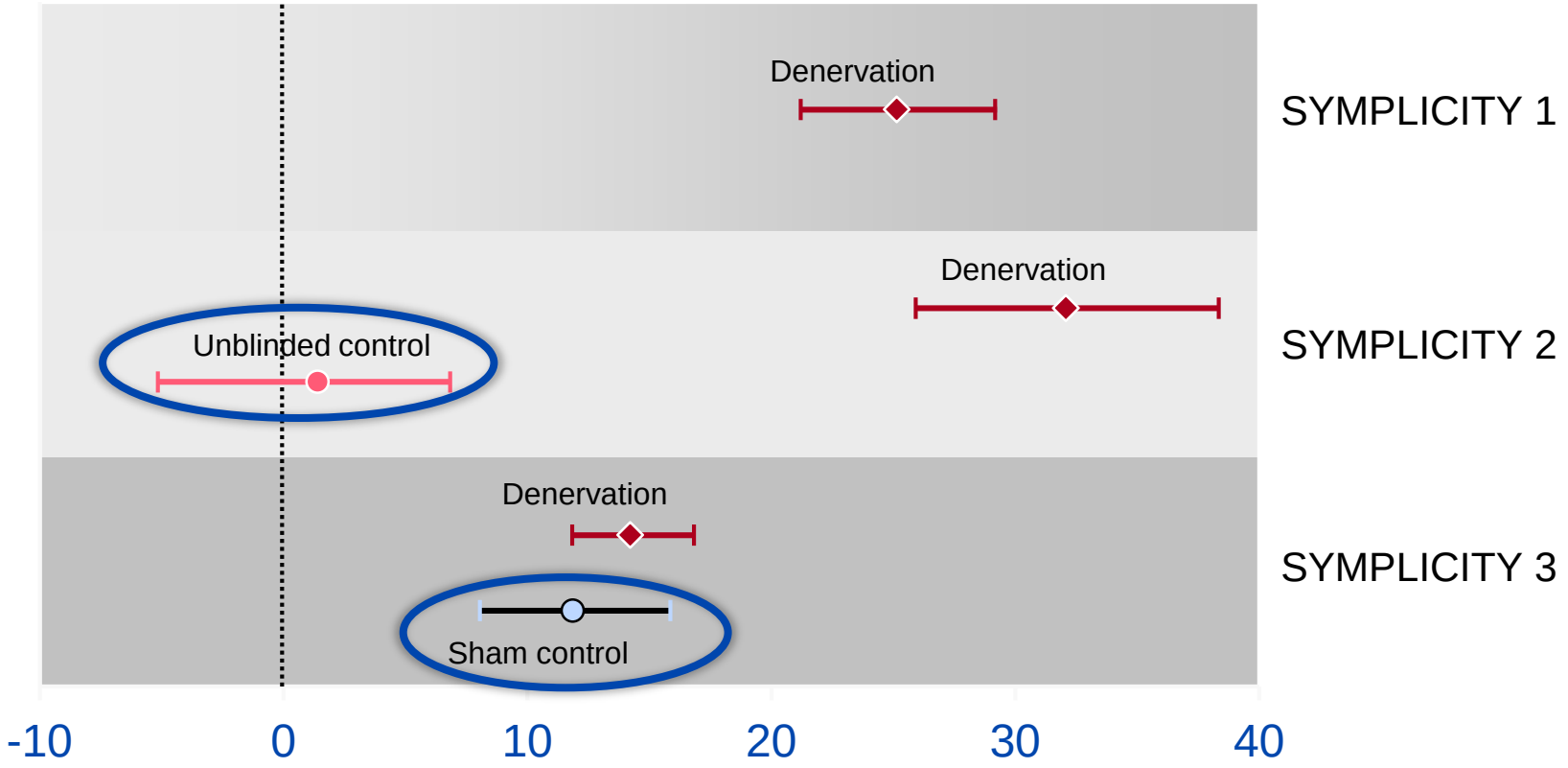
Economists are sharply divided over the exact timing of the threat from robots and other forms of futuristic technology. Some see an imminent threat, others believe it won't happen until later this century – If at all.

1. **Toll booth operators and cashiers:** People who work in the transactional space shouldn't be big fans of the Apple Watch or Apple Pay.
2. **Marketers:** Powerful advertising tools of the future may allow brands to fashion their messages to customers with precision accuracy.
3. **Interventional cardiologists and radiologists??**

Matt Egan CNN Money 2015

MAYO CLINIC

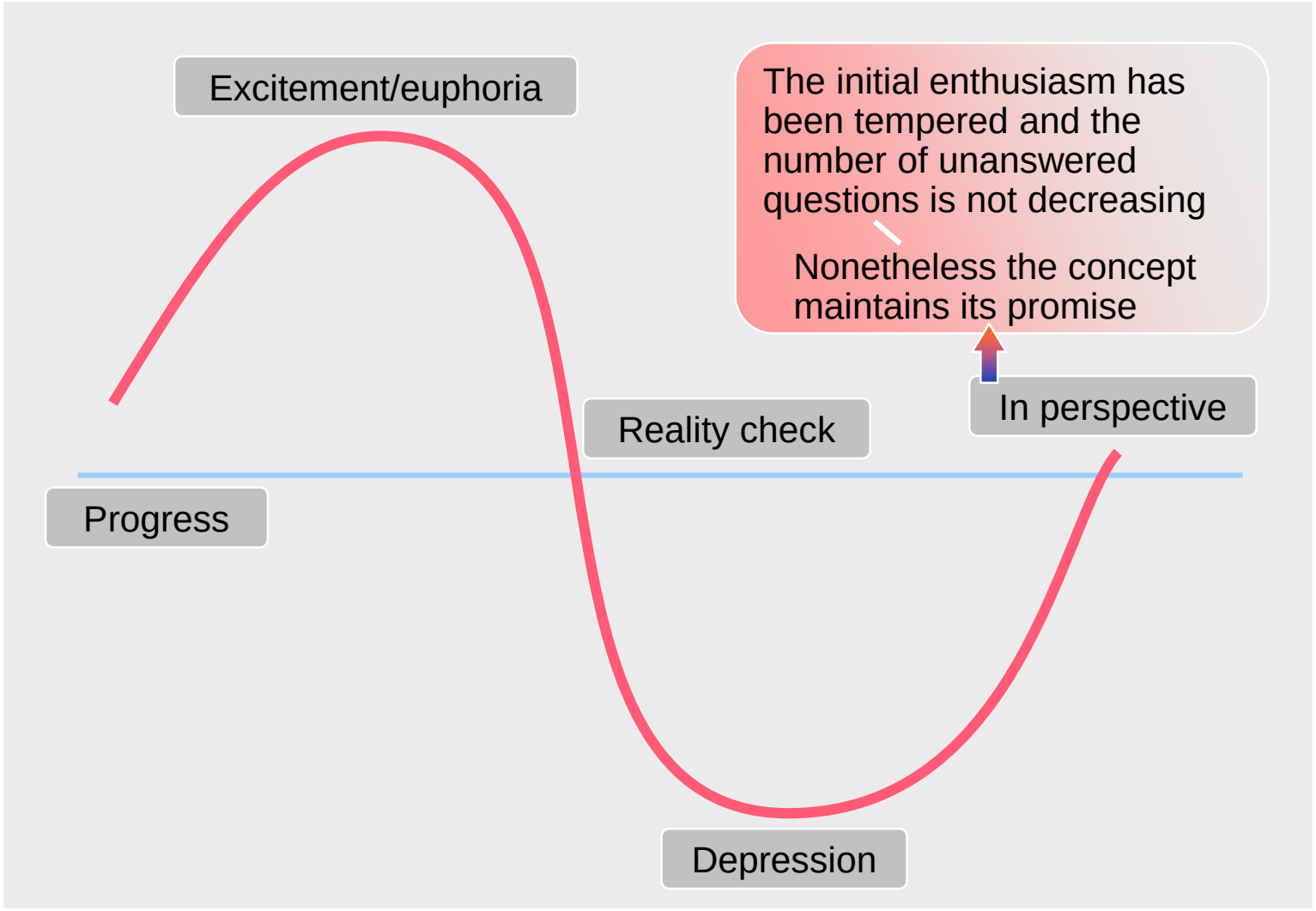
Comparison of Changes in SBP at 6 Months in 3 Trials of Renal Denervation



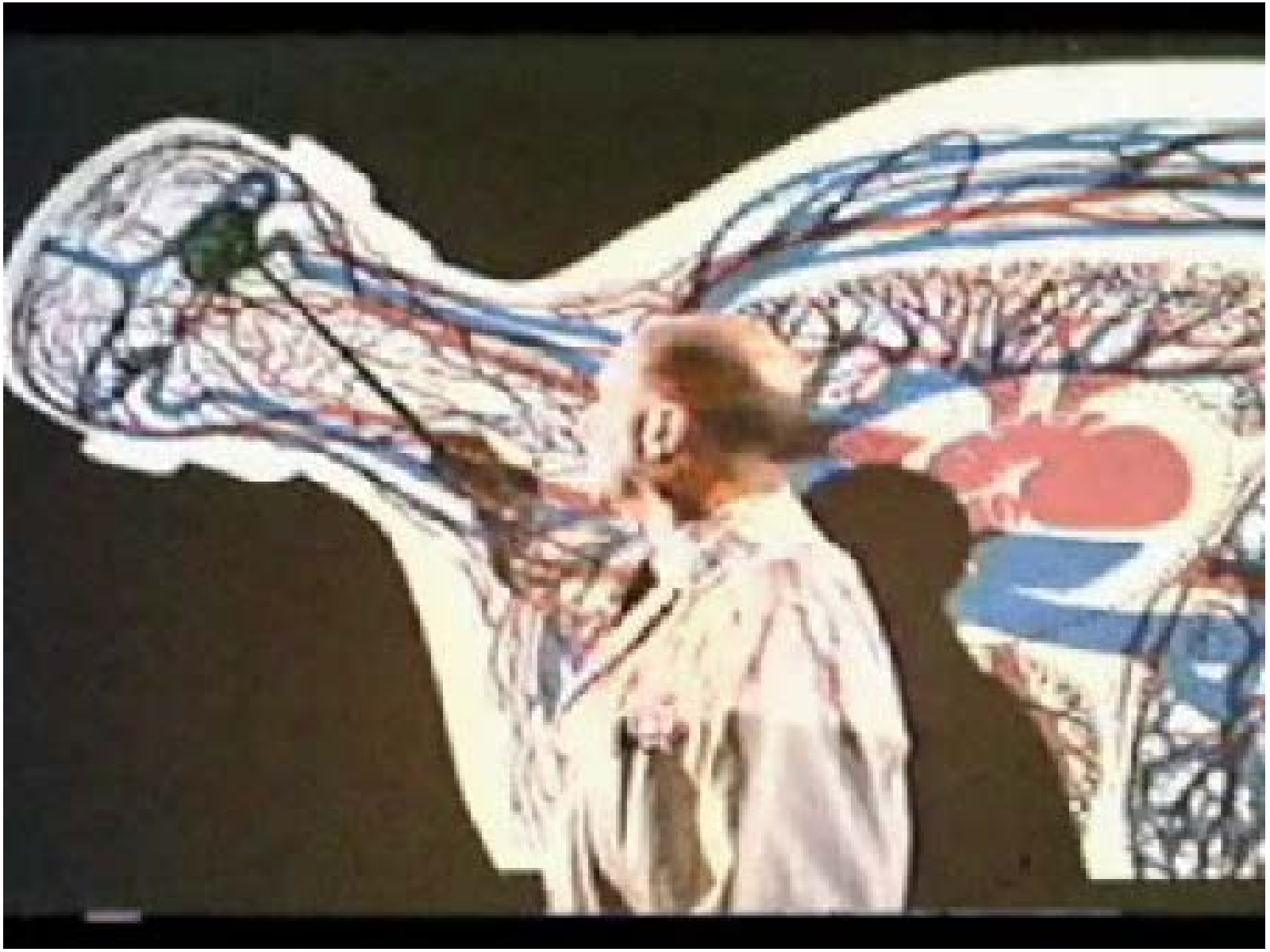
Pocock and Gersh: JACC, 2014

MAYO CLINIC

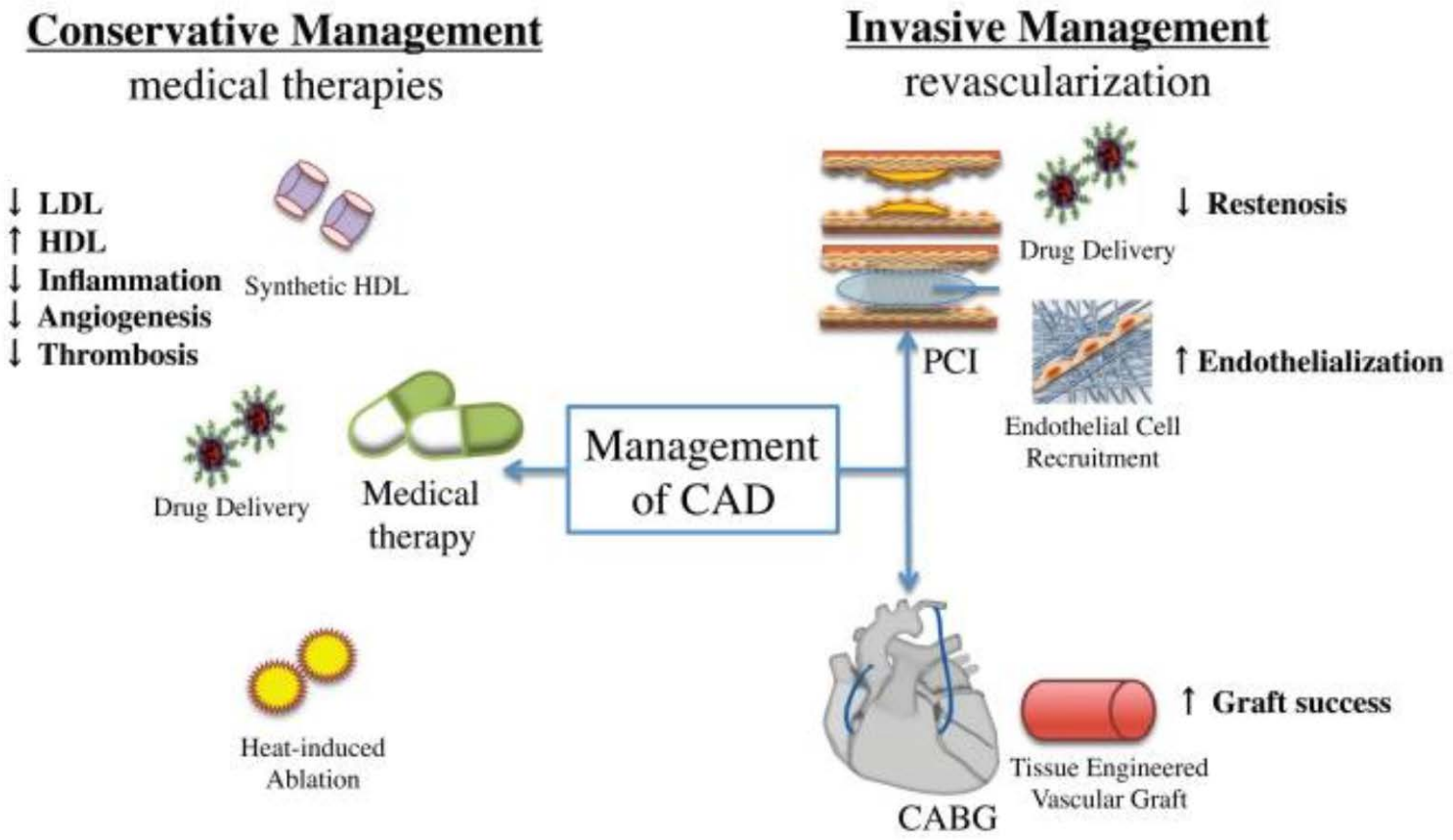
The Natural History of Evolving Therapies



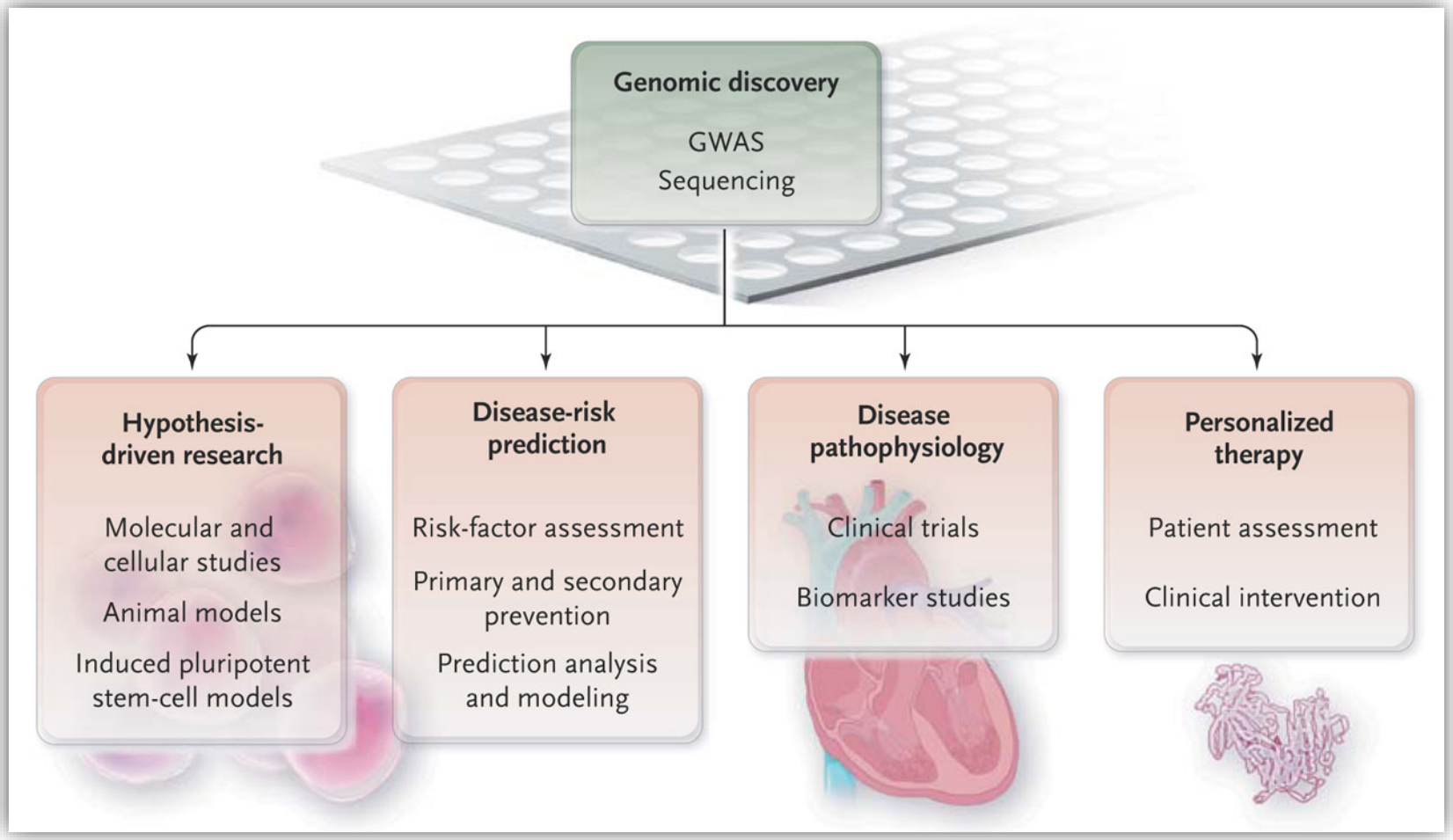
The future is here: *Fantastic Voyage 1966*



MAYO CLINIC



Investigative Pathways Leading from Gene Discovery to Clinical Application



O'Donnell and Nabel: N Engl J Med 365:2098, 2011

MAYO CLINIC

- Facebook didn’t exist yet
- Twitter was still a sound
- Cloud was still in the sky
- 4G was a parking space
- “applications” were what you sent to college
- LinkedIn most people thought it was a prison
- Big Data was a good name for a rap star
- Skype, for most people, was a typographical error.

- *Excerpt From: Thomas L. Friedman. “Thank You for Being Late.” iBooks. https://itunes.apple.com/us/book/thank-you-for-being-late/id1110015147?mt=11*

MAYO CLINIC

MAYO CLINIC

MAYO CLINIC