

The Need for Creative New Methods in Clinical Research

Michael S Lauer, MD, FACC, FAHA

Director, Division of Cardiovascular Sciences
National Heart, Lung, and Blood Institute

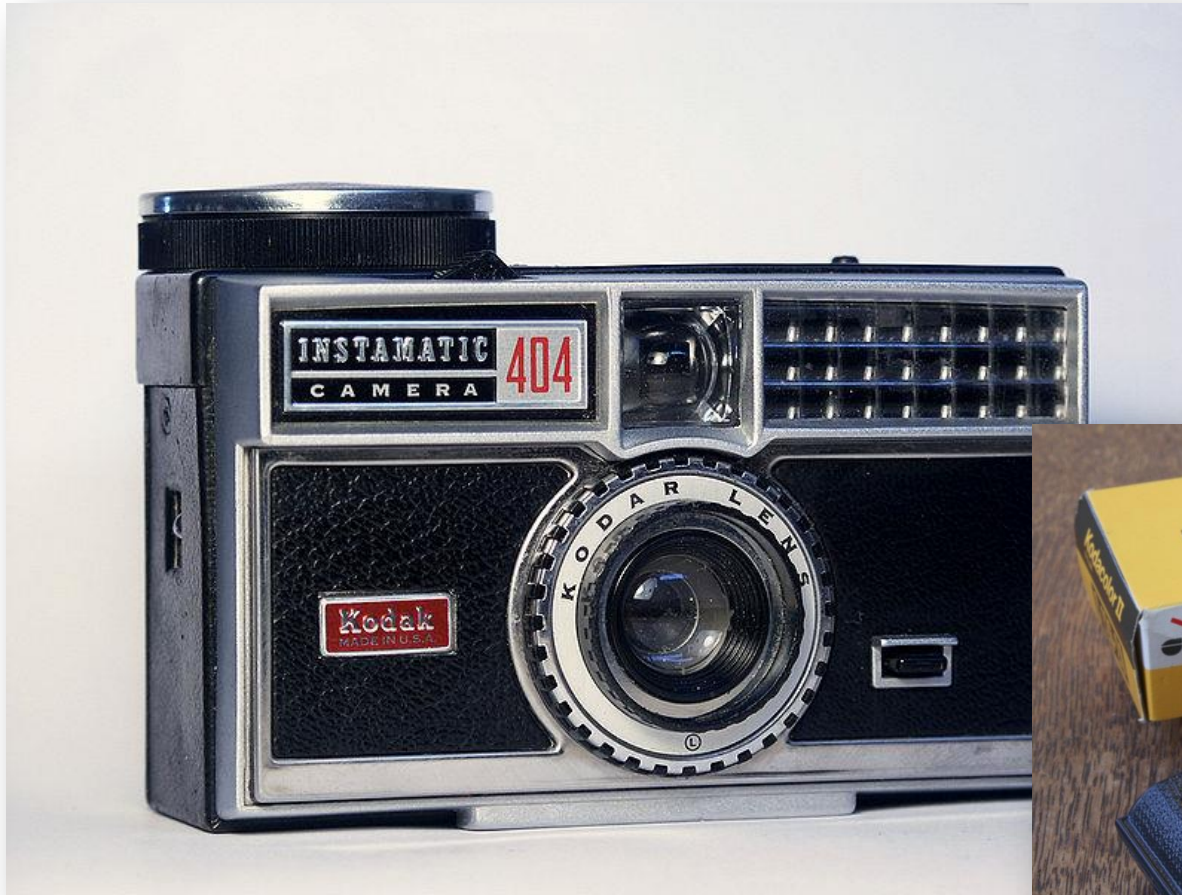
Financial disclosures: None

Workshop on Innovative Study Designs and Methods for Developing,
Testing and Implementing Behavioral Interventions to Improve Health

April 2, 2014



When I was a Teenager ...



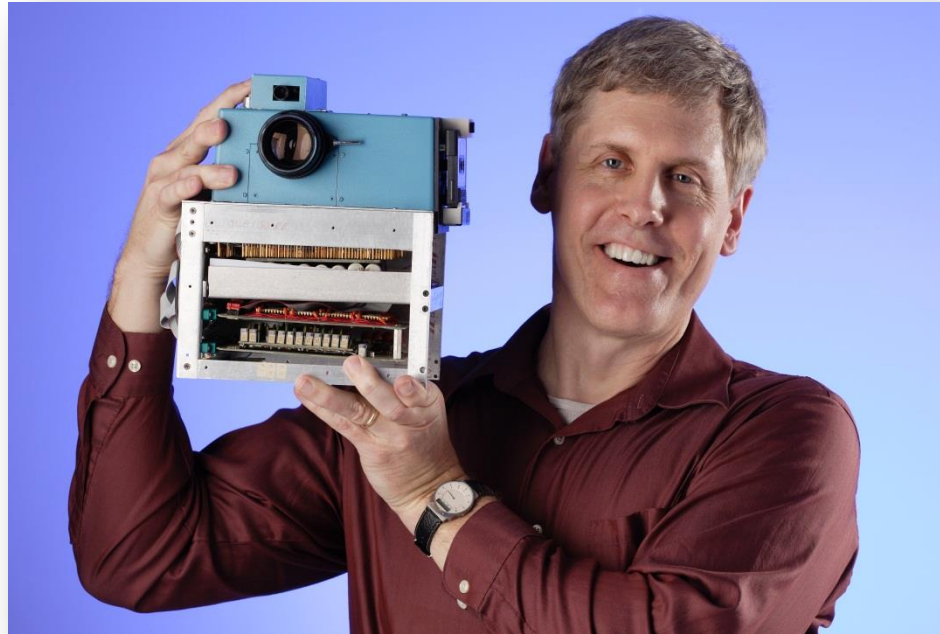
In 1976 Kodak claimed

90% film

85% cameras



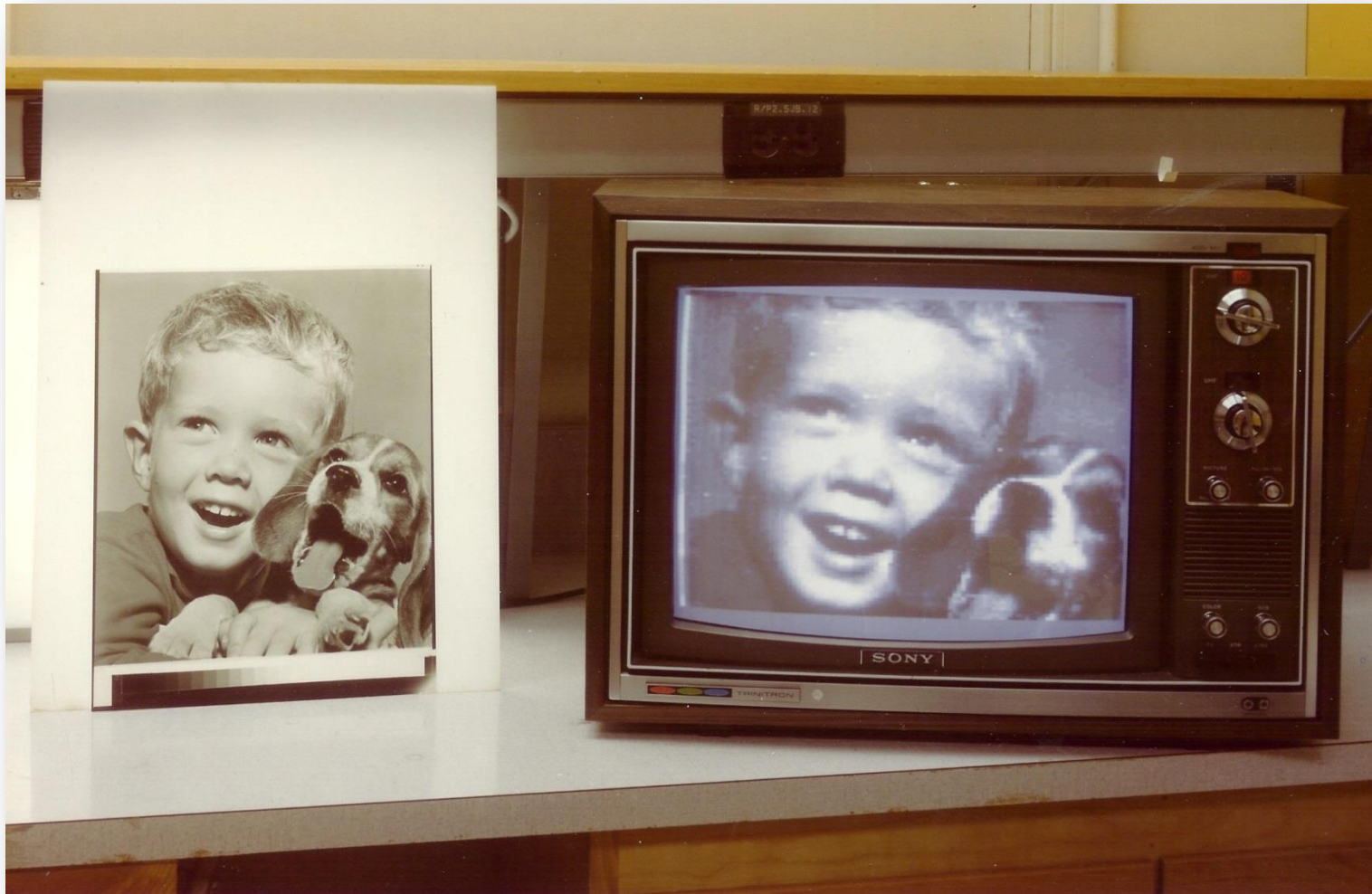
An Invention



“But it was filmless photography, so management’s reaction was, ‘That’s cute, but don’t tell anyone about it.’”

Steve Sasson, quoted in the *NY Times*, May 20, 2008

Obviously Inferior Technology



And The Rest is ...

How Kodak Failed - Forbes

Forbes New Posts +3 posts this hour Most Popular Billionaire Behind Red

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37  Share

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13  +1

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How Kodak Failed

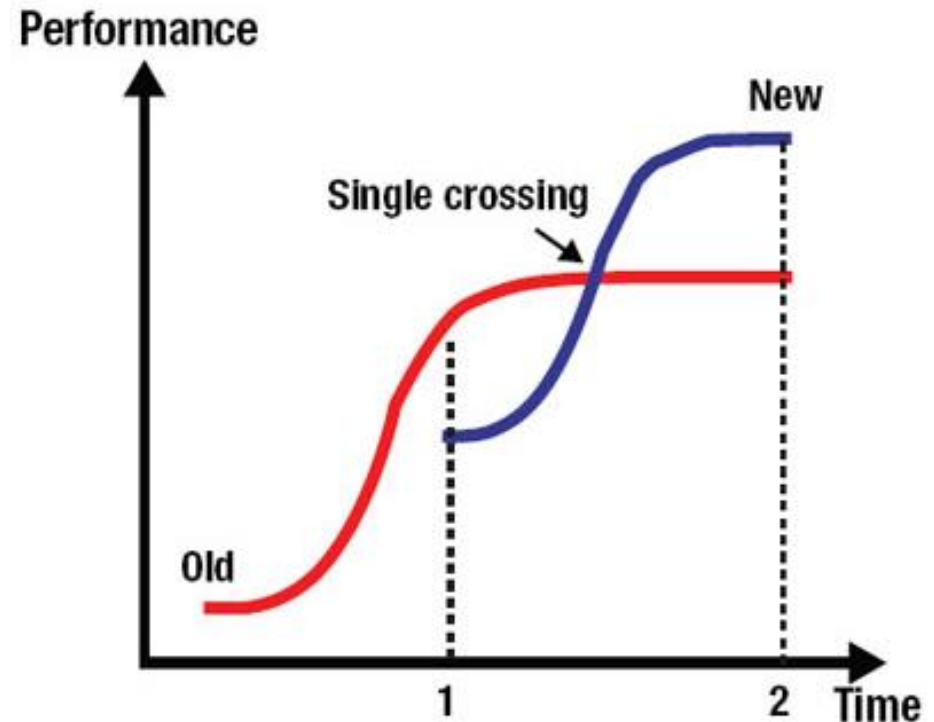
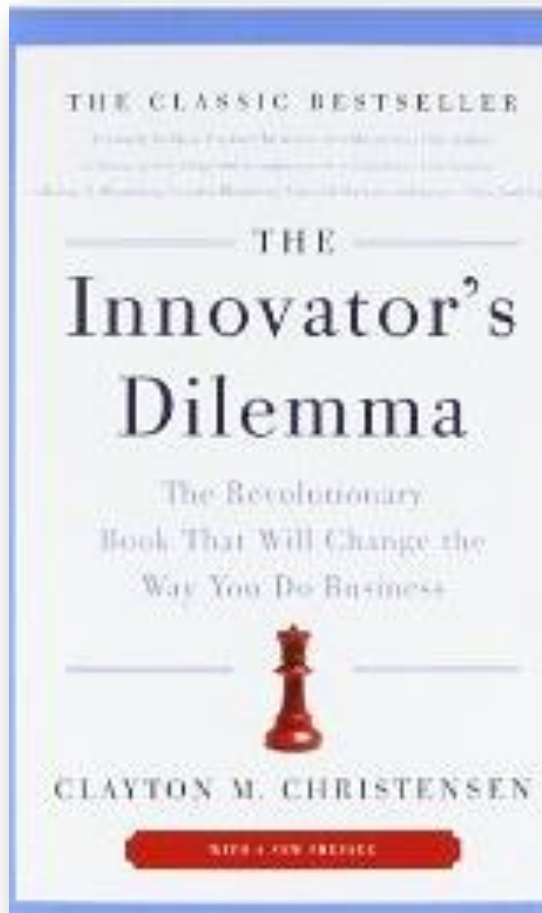
 6 comments, 5 called-out [+ Comment now](#)

(Update 1-19-2012 — Kodak has filed for bankruptcy protection.)

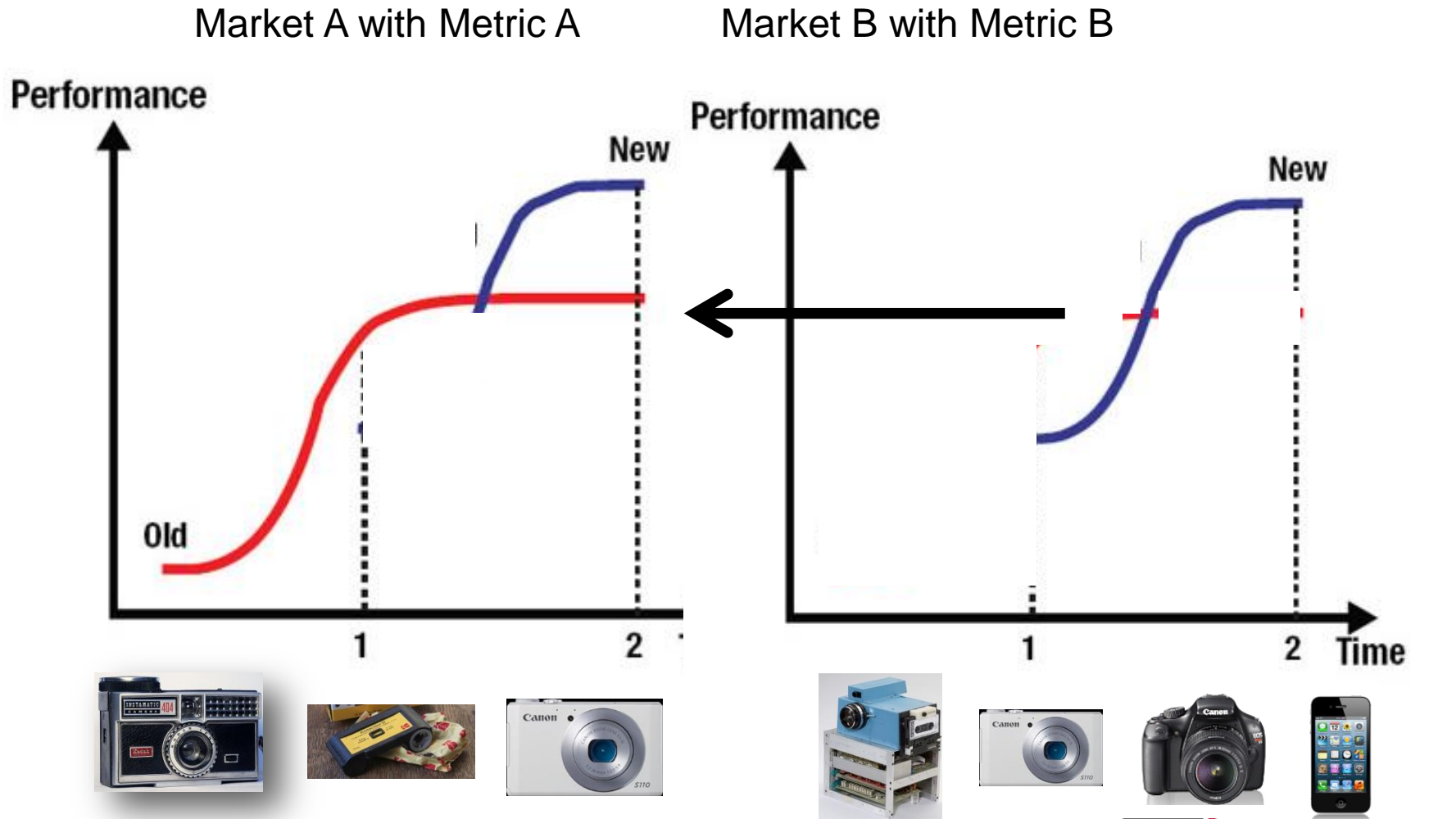
There are few corporate blunders as staggering as Kodak's missed opportunities in digital photography, a technology that it invented. This strategic failure was the direct cause of Kodak's decades-long decline as digital photography destroyed its film-based business model.



A Recurring Pattern



Enter the Disruptive Technology



Explicit Challenges



EDITORIAL

Enabling Scientific Innovation

The U.S. system for funding research was designed to function well in times of growth. It is failing now because the system as a whole is contracting. Scientists have little time or incentive to be innovative. What is to be done? The funding agencies must admit that it is not humanly possible to predict, with high accuracy, which research projects ultimately will have the most impact. When there are too many of these, as at present, the agencies must find other ways to decide which to support. That will be hard.

Why We Must Pay Attention



EDITORIAL

A Threat to Medical Innovation

With 10 to 15% paylines at some institutes (or even less), the current situation makes grant evaluation nearly impossible and is putting truly excellent laboratories out of business. In the spirit of “never waste a good crisis,” a serious evaluation of many NIH extramural policies and programs is warranted. They include centers and other large collective funding efforts as well as ***expensive clinical and epidemiological research.***

“Classic” Clinical Trial Business Model

Size

- Mostly small N
- Huge budgets

Endpoints

- Mostly surrogate
- Clinical trials employ adjudication

Setting

- Research enterprise – “parallel universe”
- “High-grade” data – audited, monitored

Characteristics of Clinical Trials Registered in ClinicalTrials.gov, 2007-2010

Robert M. Califf, MD

Deborah A. Zarin, MD

Judith M. Kramer, MD, MS

Rachel E. Sherman, MD, MPH

Laura H. Aberle, BSPH

Asba Tasneem, PhD

Context Recent reports highlight gaps between guidelines-based treatment recommendations and evidence from clinical trials that supports those recommendations. Strengthened reporting requirements for studies registered with ClinicalTrials.gov enable a comprehensive evaluation of the national trials portfolio.

Objective To examine fundamental characteristics of interventional clinical trials registered in the ClinicalTrials.gov database.

Methods A data set comprising 96 346 clinical studies from ClinicalTrials.gov was downloaded on September 27, 2010, and entered into a relational database to analyze

We've Been Disruptive Before

EFFECTIVENESS OF INTRAVENOUS THROMBOLYTIC TREATMENT IN ACUTE MYOCARDIAL INFARCTION

GRUPPO ITALIANO PER LO STUDIO DELLA STREPTOCHINASI
NELL'INFARTO MIOCARDICO (GISSI)*

Summary In an unblinded trial of intravenous streptokinase (SK) in early acute myocardial infarction, 11 806 patients in one hundred and seventy-six coronary care units were enrolled over 17 months. Patients admitted within 12 h after the onset of symptoms and with no contraindications to SK were randomised to receive SK in addition to usual treatment and complete data were obtained in 11 712. At 21 days overall hospital mortality was 10·7% in SK recipients versus 13% in controls, an 18% reduction ($p=0\cdot0002$, relative risk 0·81). The extent of the beneficial effect appears to be a function of time from onset of pain to SK infusion (relative risks 0·74, 0·80, 0·87, and 1·19 for the 0–3, 3–6, 6–9, and 9–12 h subgroups). SK seems to be a safe drug for routine administration in acute myocardial infarction.

The Lancet · Saturday 22 February 1986



“It started with no funding and skepticism in some quarters but today GISSI is recognized as an Italian achievement that has changed cardiology treatment worldwide.”

Forgetting ... and Remembering ...

VIEWPOINT

Transforming Clinical Trials in Cardiovascular Disease

Mission Critical for Health and Economic Well-being

Elliott M. Antman, MD

Robert A. Harrington, MD

Perhaps the most exciting opportunity for CVD researchers is to capitalize on the advances in systems and computational biology that can inform first-in-human, proof-of-

“As large trials became popular...the original simplicity was lost...leading to increasingly complex trials. The unintended consequence has been to threaten the very existence of RCTs, given the operational complexities and ensuring costs. An ideal opportunity would be to embed randomization in the EMR... introducing randomization into registries sponsored by societies.”

Disruptive Approach: Leverage Big Data...

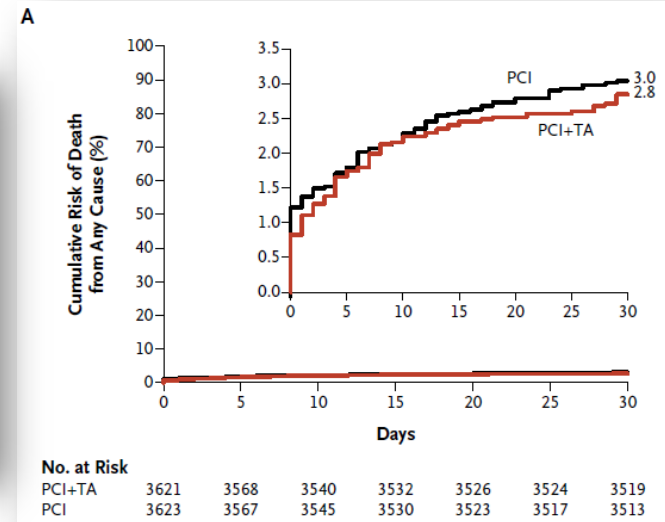
The NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

OCTOBER 24, 2013

VOL. 369 NO. 17

Thrombus Aspiration during ST-Segment Elevation Myocardial Infarction



The Randomized Registry Trial — The Next Disruptive Technology in Clinical Research?

Michael S. Lauer, M.D., and Ralph B. D'Agostino, Sr., Ph.D.

Cost (incremental) = US \$300,000
(\$50 per patient)

EMR: Not New

The NEW ENGLAND JOURNAL of MEDICINE

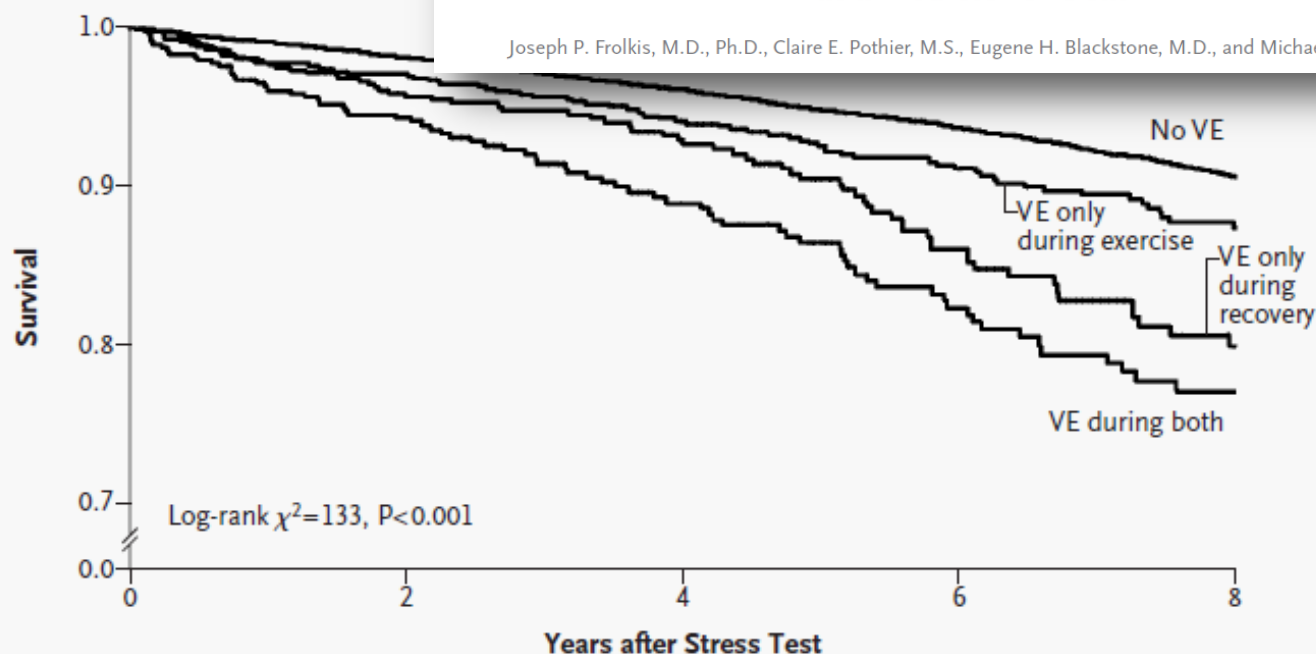
ESTABLISHED IN 1812

FEBRUARY 27, 2003

VOL. 348 NO. 9

Frequent Ventricular Ectopy after Exercise as a Predictor of Death

Joseph P. Frolkis, M.D., Ph.D., Claire E. Pothier, M.S., Eugene H. Blackstone, M.D., and Michael S. Lauer, M.D.



No. at Risk

	27,219	26,295	22,900	19,576	16,708	13,971	11,283	9,292	6,480
No VE									
VE only during exercise	945	900	840	687	598	504	418	352	255
VE only during recovery	589	564	474	425	331	276	226	162	121
VE during both	491	459	403	329	265	231	190	148	122

Behavioral Trial ...

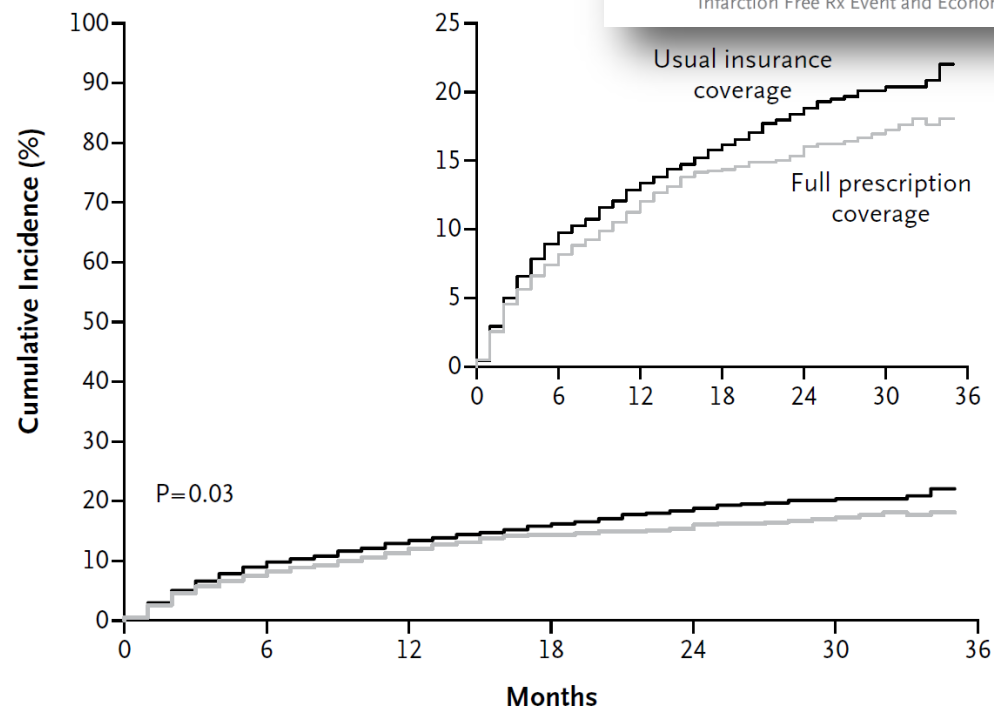
The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Full Coverage for Preventive Medications after Myocardial Infarction

Niteesh K. Choudhry, M.D., Ph.D., Jerry Avorn, M.D.,
Robert J. Glynn, Sc.D., Ph.D., Elliott M. Antman, M.D.,
Sebastian Schneeweiss, M.D., Sc.D., Michele Toscano, M.S.,
Lonny Reisman, M.D., Joaquim Fernandes, M.S., Claire Spettell, Ph.D.,
Joy L. Lee, M.S., Raisa Levin, M.S., Troyen Brennan, M.D., J.D., M.P.H.,
and William H. Shrank, M.D., M.S.H.S., for the Post-Myocardial
Infarction Free Rx Event and Economic Evaluation (MI FREEE) Trial

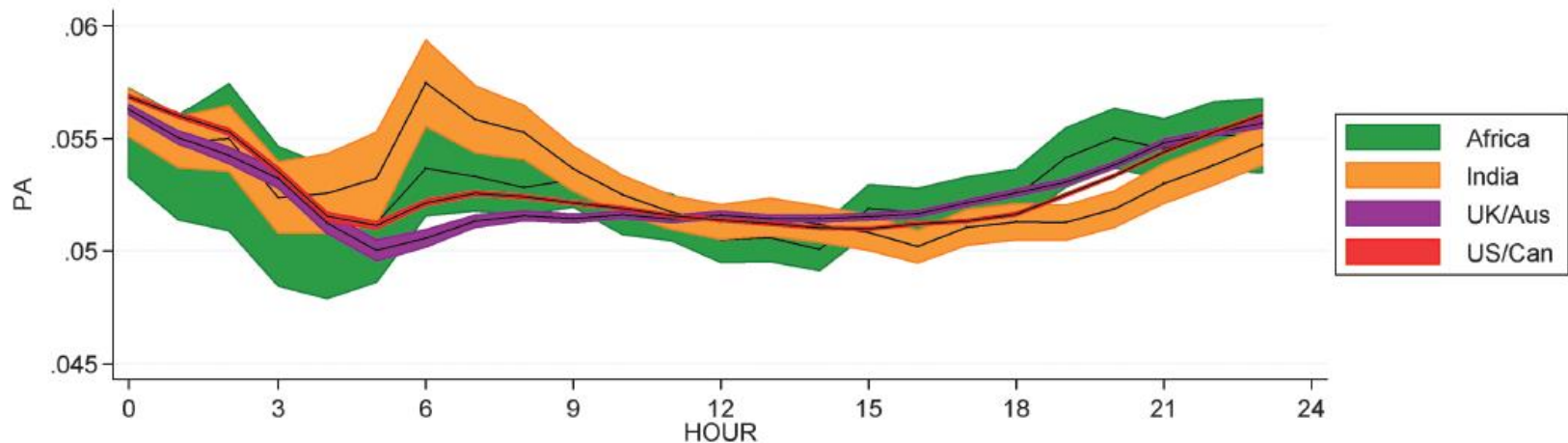
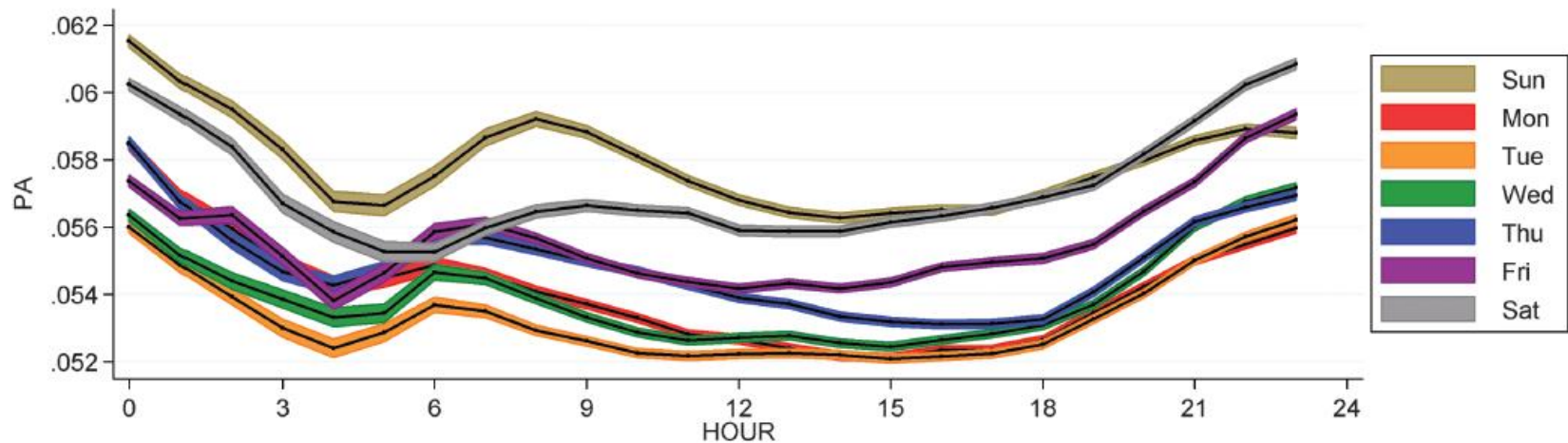
First Fatal or Nonfatal Vascular Event



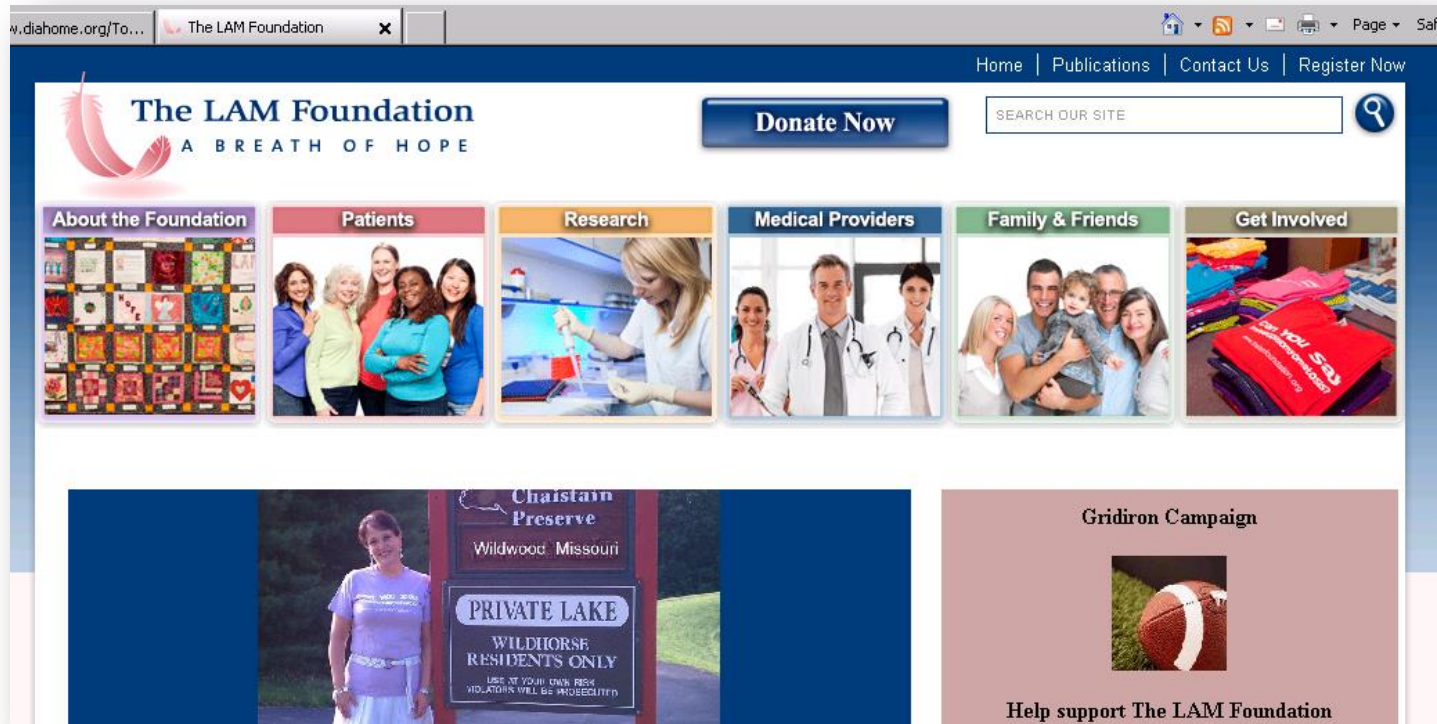
No. at Risk

Usual insurance coverage	3010	2361	1652	1099	662	379	131
Full prescription coverage	2845	2295	1572	1013	625	340	135

Useful Data from Twitter?!



Another Disruptive Technology: Patients



“The LAM Foundation urgently seeks safe and effective treatments, and ultimately a cure, for LAM through **advocacy and the funding of promising research**. We are dedicated to serving the scientific, medical and patient communities by offering information, resources and a worldwide network of hope and support.”

What it Took...

EDITORIALS



Patient Organizations and Research on Rare Diseases

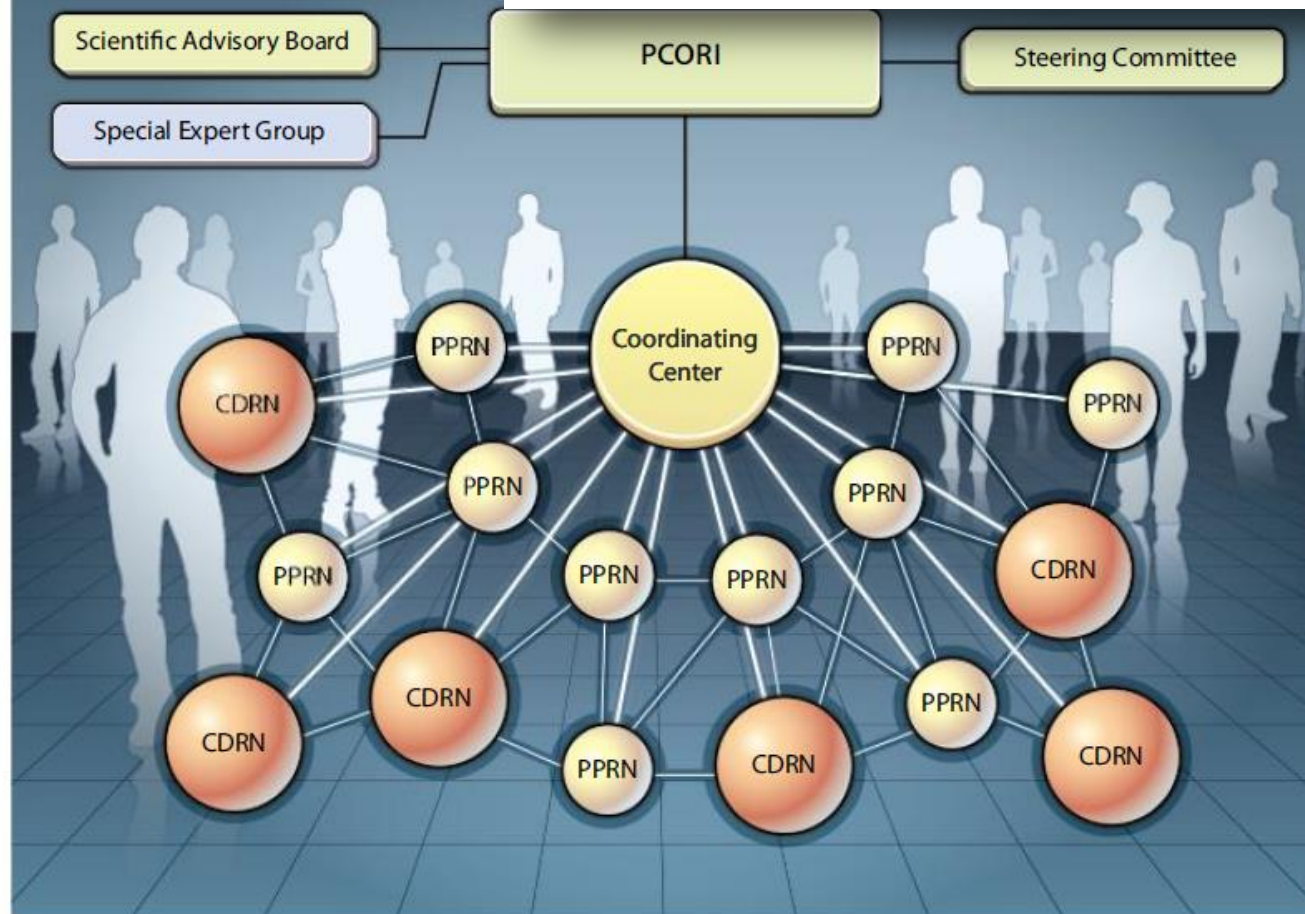
Julie R. Ingelfinger, M.D., and Jeffrey M. Drazen, M.D.

“This research study shows that when patients and researchers work together toward a common goal, advances can be made. The research community contributes ideas and investigative know-how, and patients who have the illness contribute their personal insights, biologic samples, and their time to prove principles. Most important, patients with such a rare disease are willing to put themselves at risk in order to find a treatment or a cure.”

Network News: Powering Clinical Research

Joseph V. Selby,¹ Harlan M. Krumholz,^{2,3} Richard E. Kuntz,^{3,4}
Francis S. Collins^{3,5*}

The Patient-Centered Outcomes Research Institute announces bold plans to build a National Patient-Centered Clinical Research Network that will unite millions of patients through a coordinated collaboration with researchers and health care delivery organizations.



Possible “New” Disruptive Models

Size – both bigger and smaller

- Huge N – robust estimates, heterogeneity
- Streamlined budgets – grows a bigger pie

Endpoints – what really matters

- Patient-oriented with minimal adjudication

Setting – increasingly integrated world

- Within patient-care units and communities
- Leverage digital data sources
- Mobile technologies to recruit, intervene, record
- Patients as partners, not subjects

How to Win with Disruptive Technologies

Embed into existing projects

Create “small sub-organizations”

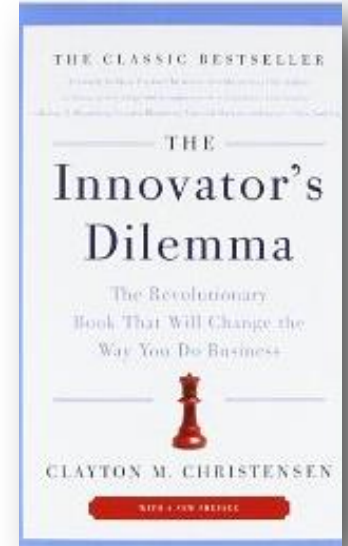
- Generate excitement
- Thrilled with “small wins”

Fail early, often, and inexpensively

- Test & refine behavioral interventions
in smaller pilots *before* large *inexpensive* RCTs
- NIH HCS Collaboratory

Look for new markets, compete elsewhere

- Existing markets can mislead us





National Heart, Lung,
and Blood Institute