

The Collaboratory at Age 2: Back to the Future

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NIH Common Fund HCS Collaboratory
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Our Favorite Philosopher



“The future ain’t what it used to be.”

“If you don't know where you're going, you might not get there.”

-- Yogi Berra

What the Future Used to Be (déjà vu again)

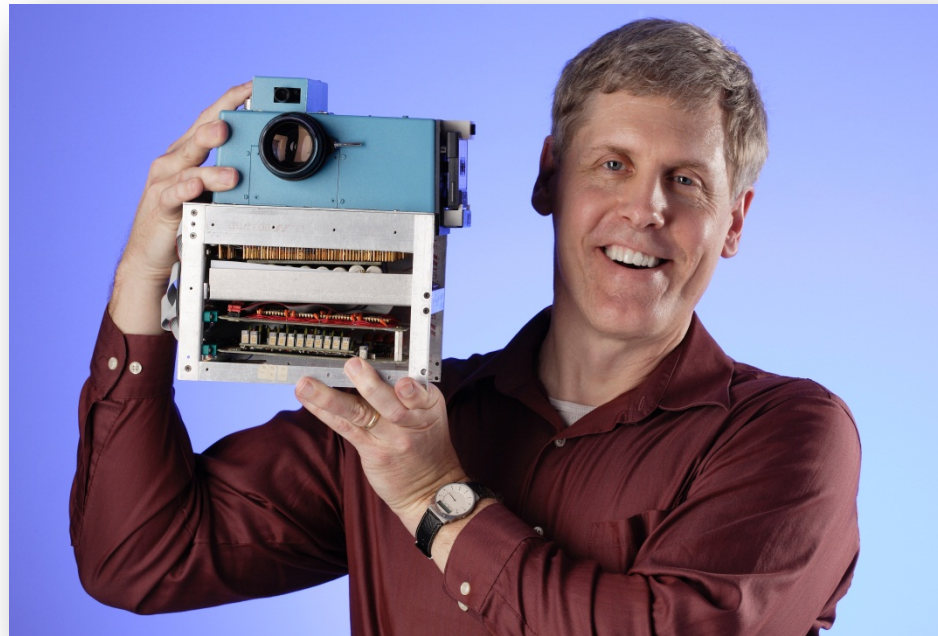
In 1976 Kodak claimed

90% film

85% cameras



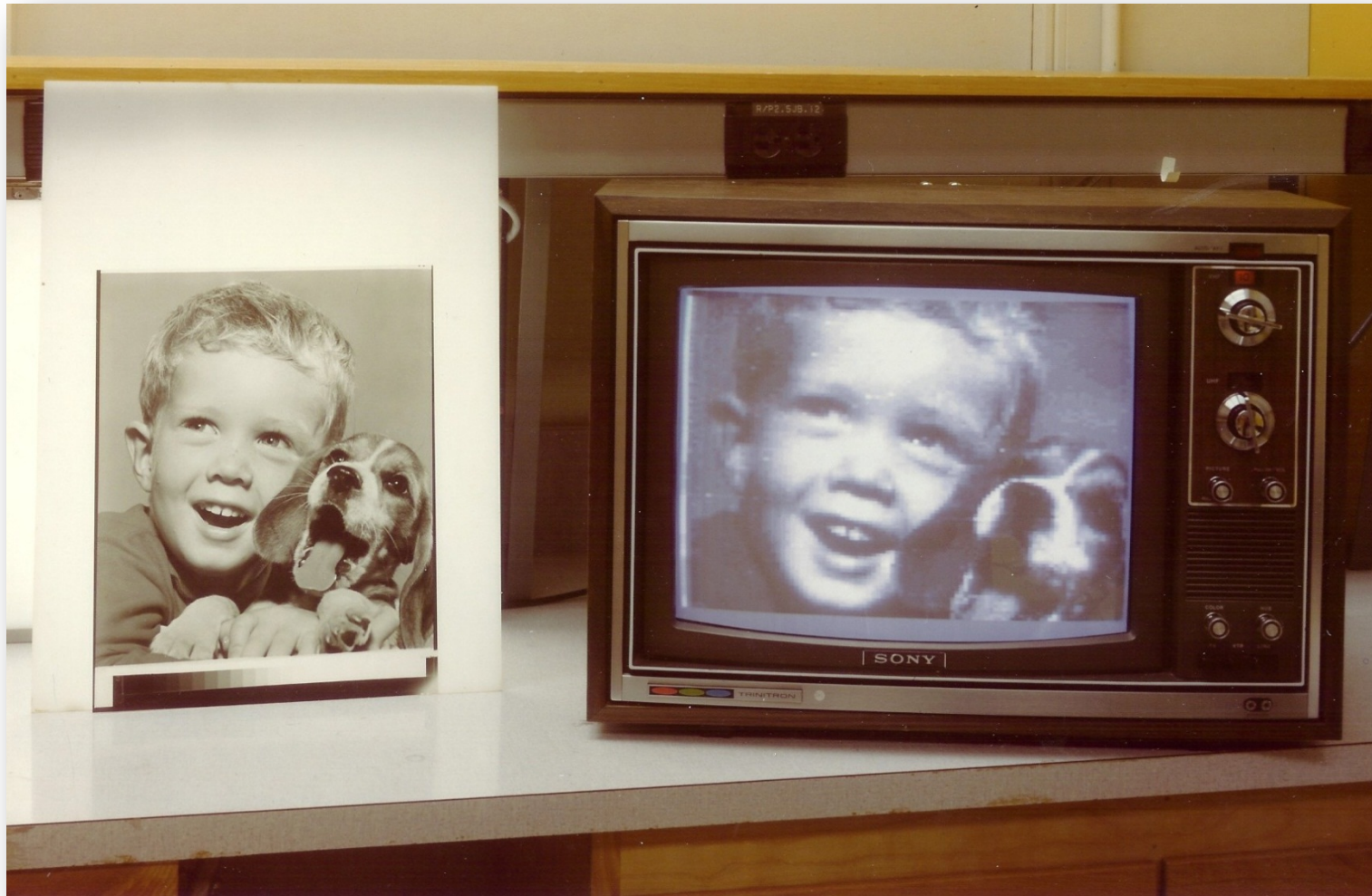
They Didn't Want to Go There



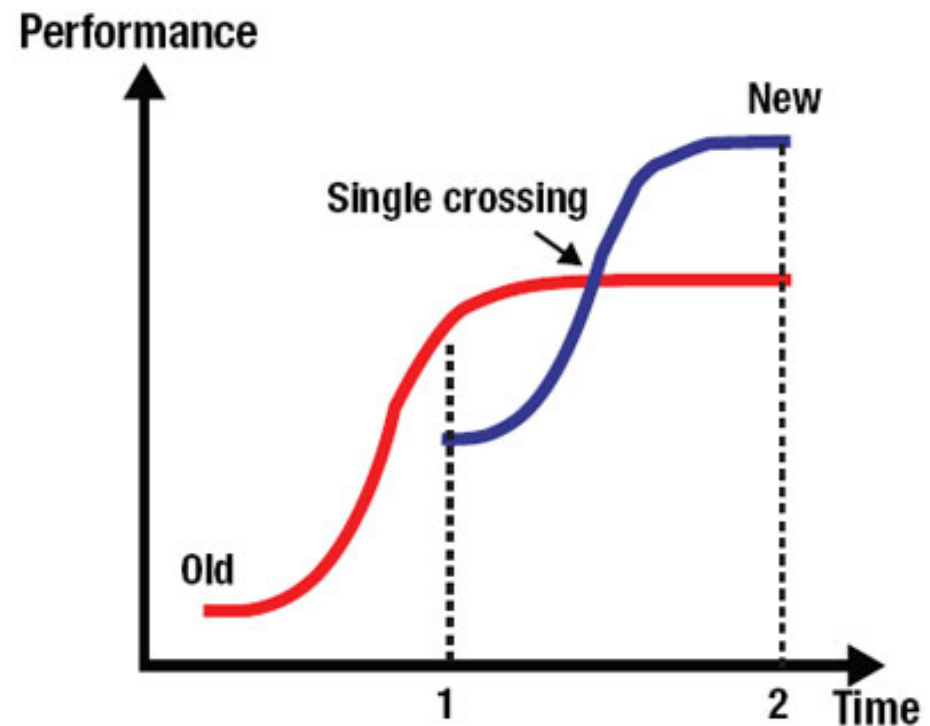
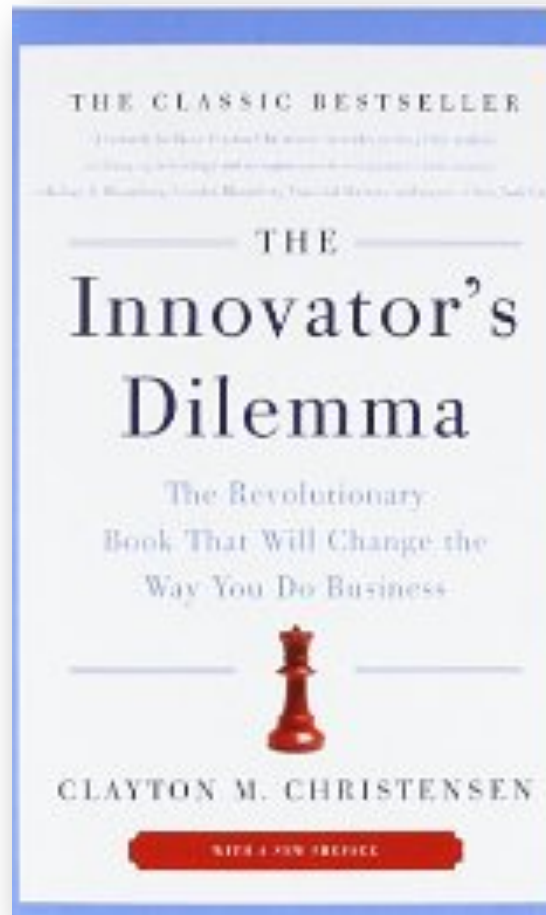
“But it was filmless photography, so management’s reaction was, ‘That’s cute, but don’t tell anyone about it.’”

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

Because it was Obviously Inferior



Recurring Pattern: Don't Want to Go There



Not Knowing Where You're Going

“In 1980, Mario Capecchi applied for a grant from the NIH. Capecchi described three separate projects. Two of them were solid stuff with a clear track record and a step-by-step account of the project deliverables.

The third project was wildly speculative ... The NIH strongly advised him to drop it.”

Tim Harford



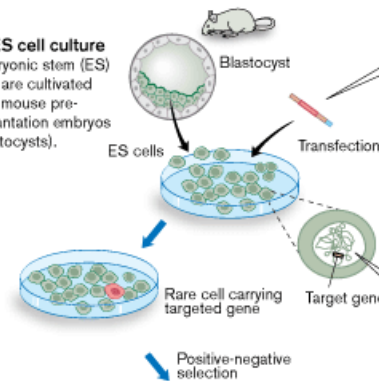
By Accident? ...

“What did Capecchi do? He took the NIH’s money and, ignoring their admonitions, poured almost all of it into his risky gene-targeting project. It was, he recalls, a big gamble. In 2007, he was awarded the Nobel Prize ...” Tim Harford

General strategy for gene targeting in mice

Step 1 Gene targeting in ES cells

1. ES cell culture
Embryonic stem (ES) cells are cultivated from mouse pre-implantation embryos (blastocysts).



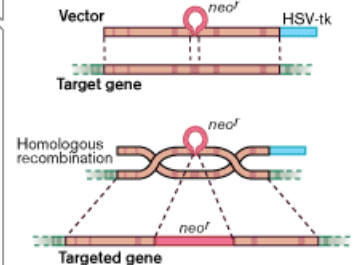
4. Proliferation of targeted ES cell
Selection for presence of *neof* and absence of HSV-tk enriches targeted ES cells.

Pure population of ES cells carrying targeted gene

2. Construction of targeting vector
The vector contains pieces of DNA that are homologous to the target gene, as well as inserted DNA which changes the target gene and allows for positive-negative selection

3. ES cell transfection

The cellular machinery for homologous recombination allows the targeting vector to find and recombine with the target gene.



Step 2 From gene targeted ES cells to gene targeted mice

5. Injection of ES cells into blastocysts

The targeted ES cells are injected into blastocysts...

...where they mix and form a mosaic with the cells of the inner cell mass from which the embryo develops.

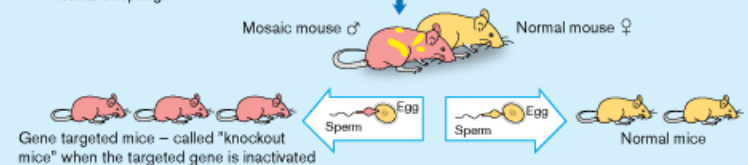
The injected blastocysts are implanted into a surrogate mother where they develop into mosaic embryos.



6. Birth and breeding of mosaic mice

The mosaic mice mate with normal mice to produce both gene targeted and normal offspring.

Born mosaic mice



© The Nobel Committee for Physiology or Medicine Illustration: Annika Röhl

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“Classic” Model – Where We Were?

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. As one

Where We Want to Go With Clinical Trials

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
- Patients as partners, not subjects

We Are Disrupting the Conversation ...

VIEWPOINT

The Imperative of Overcoming Barriers
to the Conduct of Large, Simple Trials

Rethinking Clinical Trials™

A Living Textbook of Pragmatic Clinical Trials

Welcome to the Living Textbook

Welcome to the NIH Collaboratory's *Rethinking Clinical Trials: A Living Textbook*. The *Living Textbook* is designed to provide a complete suite of information to conduct, analyze & disseminate pragmatic clinical trials (PCTs). Although still in development, the web-based formatting allows us to deliver a flexible, continuously updatable reference with high-quality, expertly curated content.

“Our goal in creating *Rethinking Clinical Trials* is to provide a living document to guide the many different people with an interest in practical (or ‘pragmatic’) clinical trials and health systems research.”

—Robert M. Califf, MD

NIH Collaboratory Principal Investigator



VIEWPOINT

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

Ethics and Regulatory Complexities for Pragmatic
Clinical Trials

Clinical Research
FORUM
Analysis. Advocacy. Action.

ANNUAL MEETING AND AWARDS DINNER
APRIL 9-10, 2014
Omni Shoreham Hotel
Washington, D.C.

Top 10 Clinical Research Achievement Awardees



Recipient of the 2014 Distinguished Clinical Research Award

Susan S. Huang, MD, MPH

Associate Professor, Infectious Disease
University of California- Irvine School of Medicine
Medical Director, Epidemiology and Infection Prevention
“Targeted vs. Universal Decolonization to Prevent ICU Infection”

VIEWPOINT

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Embedding Cardiovascular Research Into Practice

And The Landscape ...

FOCUS

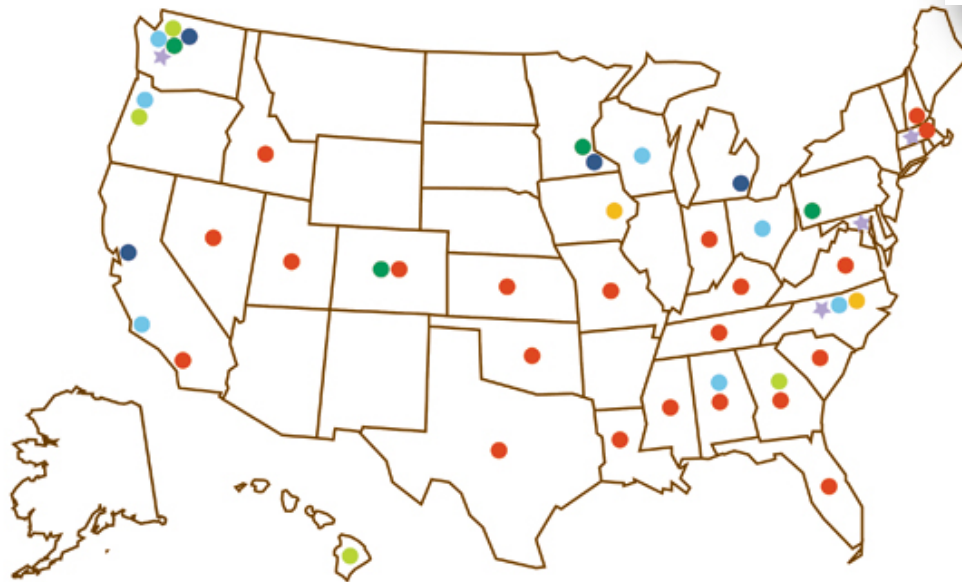
POLICY

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.

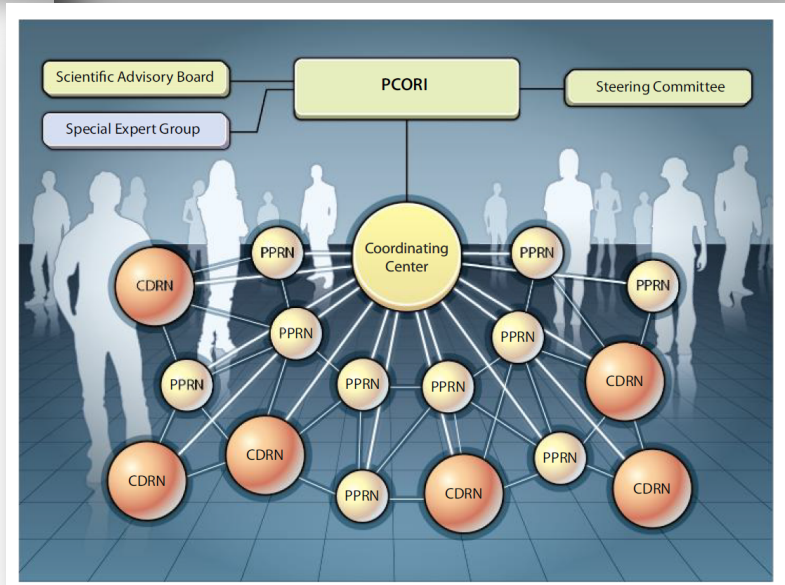
NIH Health Care System Research Collaboratory



- ★ Collaboratory Coordinating Center
- Nighttime Dose of Anti-Hypertensive Medications
- Prevent Suicide Attempt
- Reduce Mortality in End Stage Renal Disease (sites to be selected from units across all 50 states)

- Stop Colon Cancer in Priority Populations
- Chronic Pain in Primary Care
- Reduce Infections and Readmissions
- Lumbar Image Reporting and Epidemiology

Additional sites to be determined



Editorial

PCORnet: turning a dream into reality

Francis S Collins,¹ Kathy L Hudson,¹ Josephine P Briggs,²
Michael S Lauer³

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and Blood Institute

Making Disruption Happen

Embed into existing projects

Create “small sub-organizations”

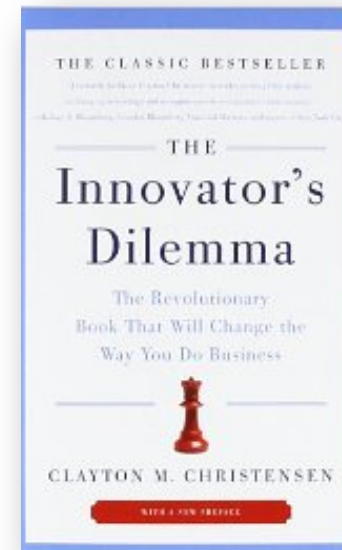
- Generate excitement
- Thrilled with “small wins”

Fail early, often, and inexpensively

Utilize resources, but not processes/values

Look for new markets, compete elsewhere

- Existing markets can mislead us



That Other Great Philosopher



“Prediction is very difficult, especially about the future”

-- Niels Bohr

(or maybe Piet Hein or maybe Robert Storm Peterson)



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