Development Of Biomarkers For Precision Medicine In An Era Of Evolving Technology: Specimens, Standards, And Signatures

ISEV CONFERENCE

December 13, 2017

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Precision Medicine is Biomarker-Dependent

Healthcare Realities	21st Centu…ne
▪ Healthcare spending ~ $3.0T* in U.S.	▪ Ea… based …ens)
▪ Expected to rise >4%* per … 2021 (~20% of econo…	…se …res from biospecimens)
▪ Canc… in ne…	…ecular- and genomically-based treatment using targeted agents (with biomarker-driven diagnostics used to interrogate biospecimens)
▪ Siloed he… enterprise…	…ical research …st inefficiencies
	▪ Connection of research ➡ clinic in seamless *feedback loop* (patient specmens tie research to clinical care)

Precision (Personalized) Medicine - Depends on Availability of HIGH-QUALITY BIOSPECIMENS AND BIOMARKERS

* Data from Centers for Medicare and Medicaid Services

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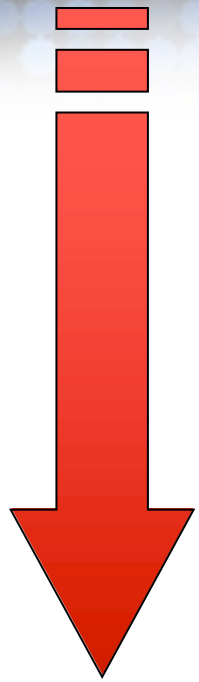
Technology-Driven "Omics" Revolution = Increased Problems in Biomarker Discovery and Development



Increasing layers of complexity

(The "Omes")

Genome (NGS)

Transcriptome (Microarray, RNAseq)

Proteome (Mass Spec)

Epigenome (ChIPseq, Bisulfite seq)

Metabolome (CE-Mass Spec)

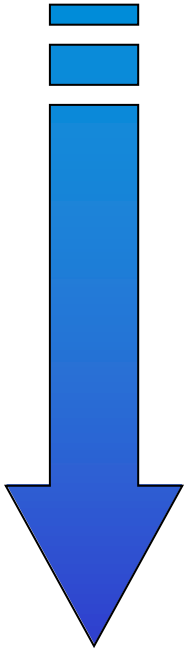
Microbiome (NGS)

****

Context of Spatial Relationships

And Microenvironments

Complex Systems that Continually Evolve



Increasing limitations: Data quality, size, and rate of production, analytics, clinical trials, regulatory pathways

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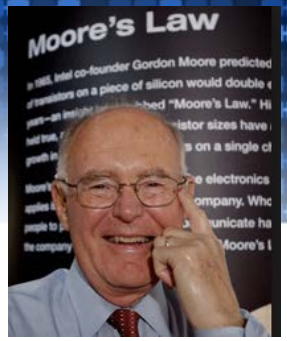
Technology Development
Unleashing the Potential for Progress



- **Technological change has been EXPONENTIAL, not linear**
  - **Moore's Law (1965) -** Intel's Gordon Moore predicts that the power of computing technology* would double every 18 months (exponential progress)

    *Number of transistors in a dense integrated circuit (computer microprocessor)
  - **Became the mantra of technology development in general**
  - **Faster, better AND cheaper**
- **Explosive technology development has created a tsunami of new data**

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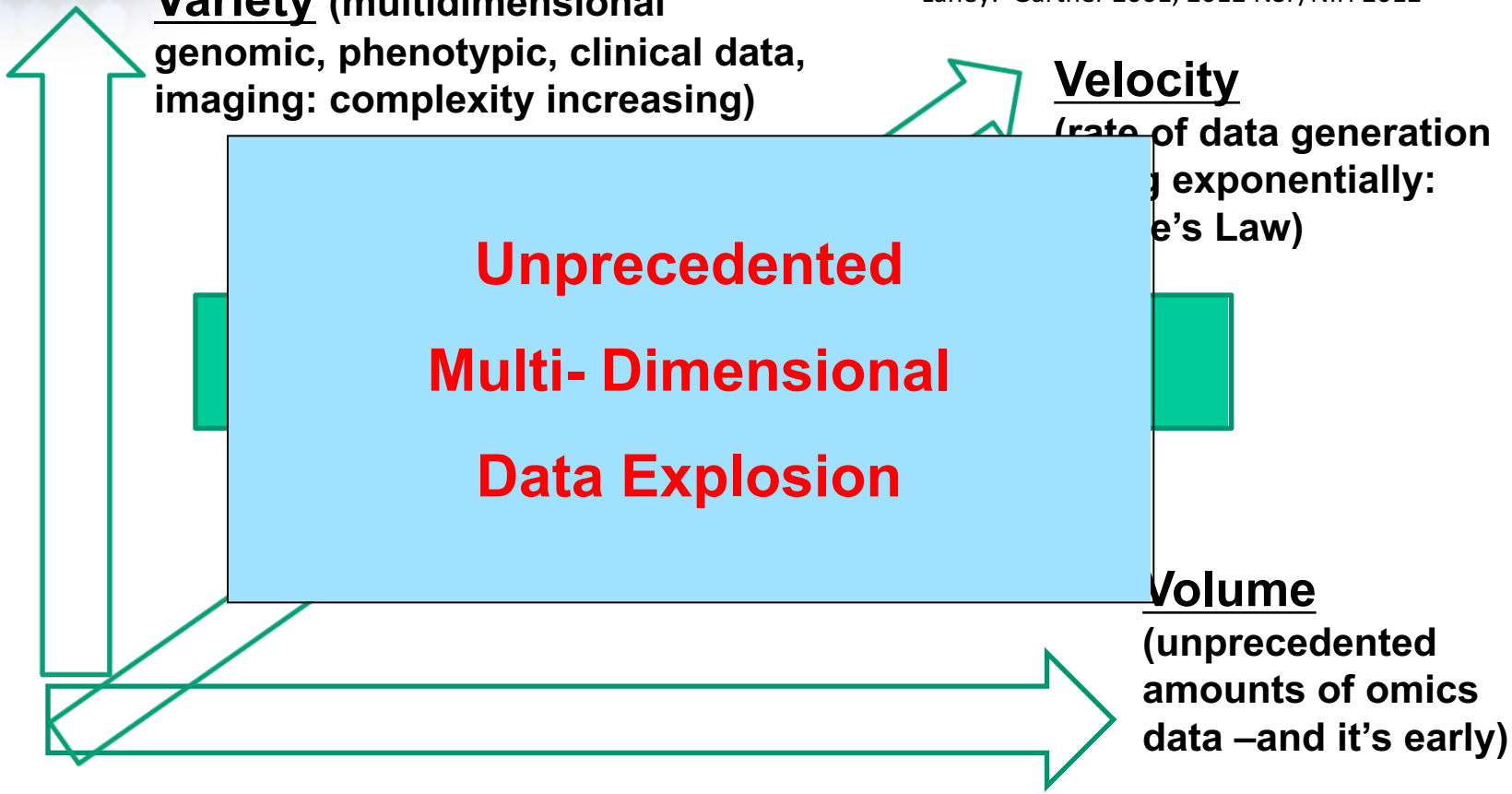
Challenge: The "Big Data" Explosion in Biomedicine

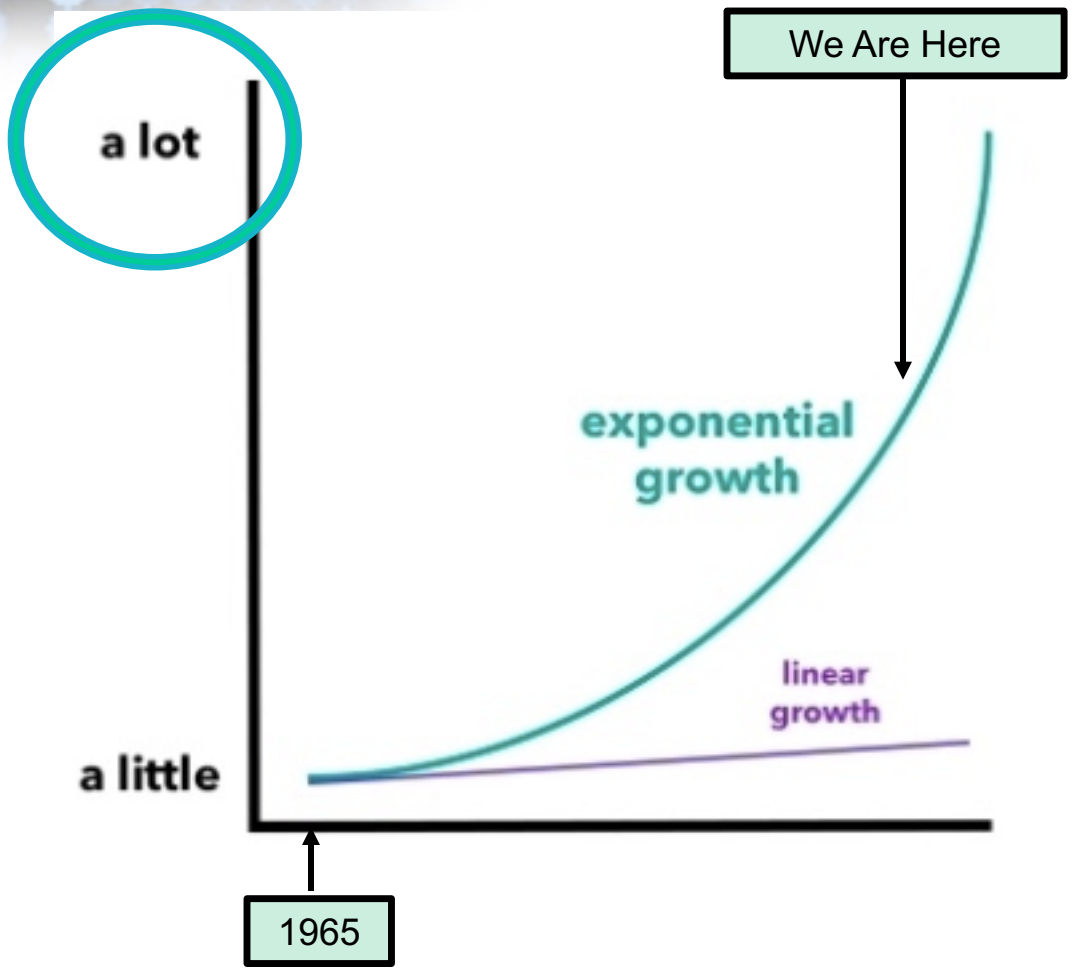
Adapted from
Laney: Gartner 2001, 2012 NSF/NIH 2012



" BIG DATA"

The "Age of Acceleration"* : Exponential Growth of Technology

*Thomas Friedman



How much is "a lot"?

The Power of an Exponential:

- Doubling "one" just 63 times equals about 18 quintillion (an 18 with 18 zeros)
- We've been doubling the power of technology every 18 months since 1965

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Exponential Growth of Technology

According to a calculation by Intel engineers, if the 1971 Volkswagen had followed the same trajectory as the Intel microprocessor, today it would:

- **Go 300,000 miles per hour**
- **Get 2,000,000 miles per gallon of gas**
- **Cost 4 cents**

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Exponential Growth of Technology in Biomedicine: Whole Genome Sequencing

Portable PCR! Testing the miniPCR for DNA sequencing in the field

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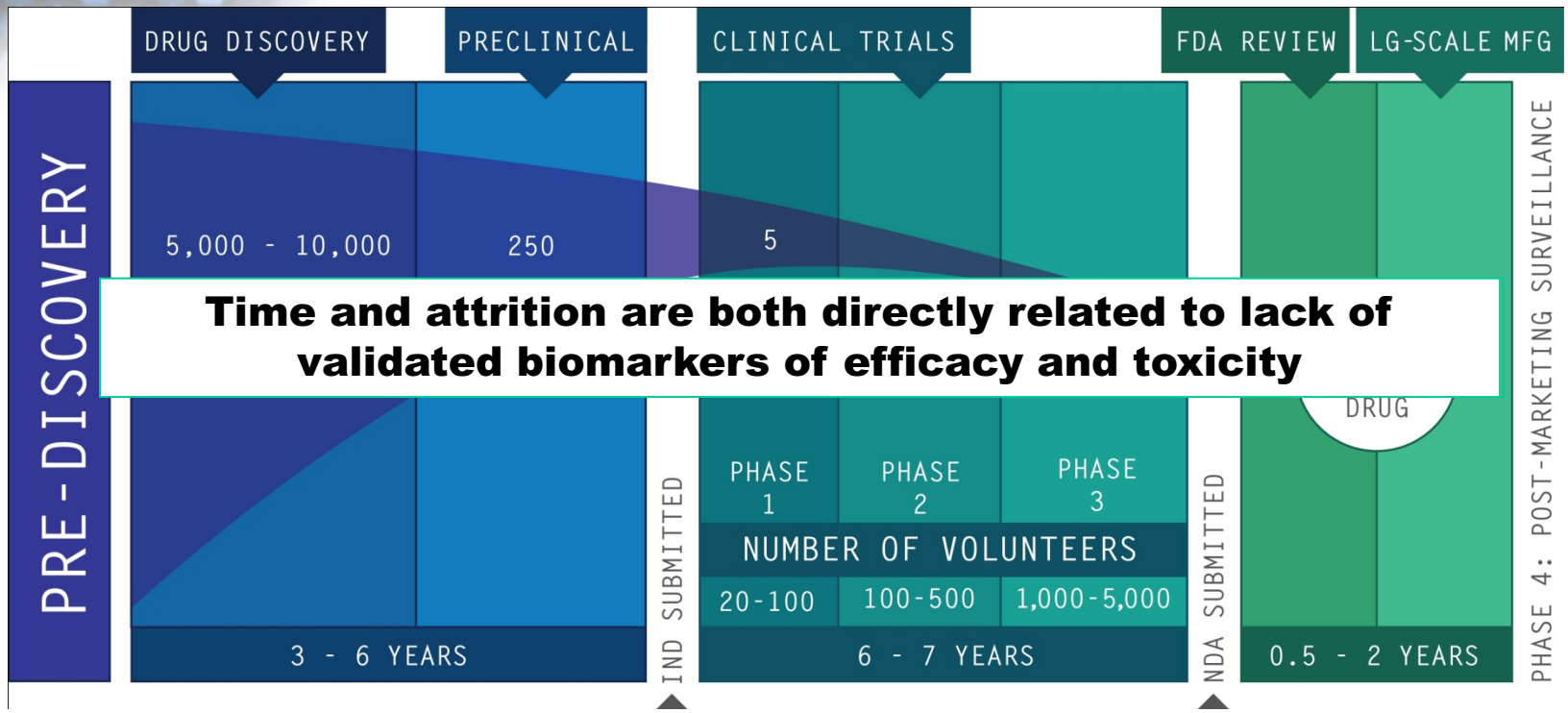
Yet Biomarker and Clinical Trials Experience Massive Attrition, Long Duration, High Cost



5-10,000:1 chance of success **12 Years** **~ US$ 2-5 B**

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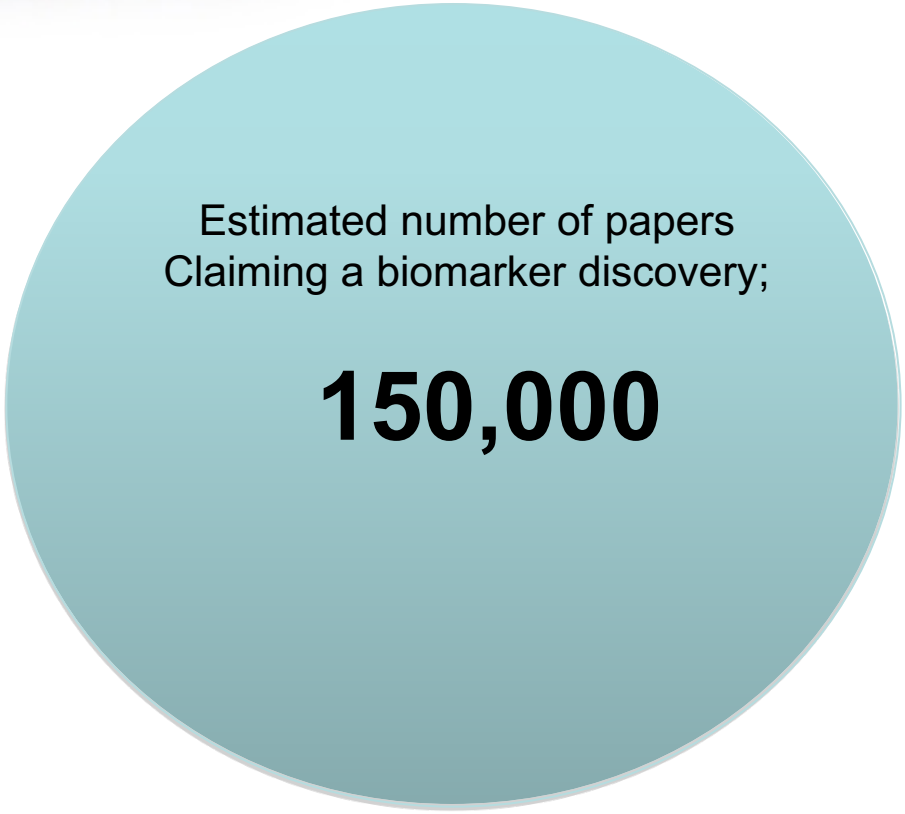
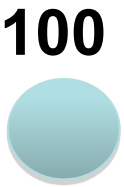
Biomarker “Discovery” Failure





Estimated number of biomarkers routinely used in the clinic

Source: Poste G. Nature 469, 156-157 13 Jan 2011

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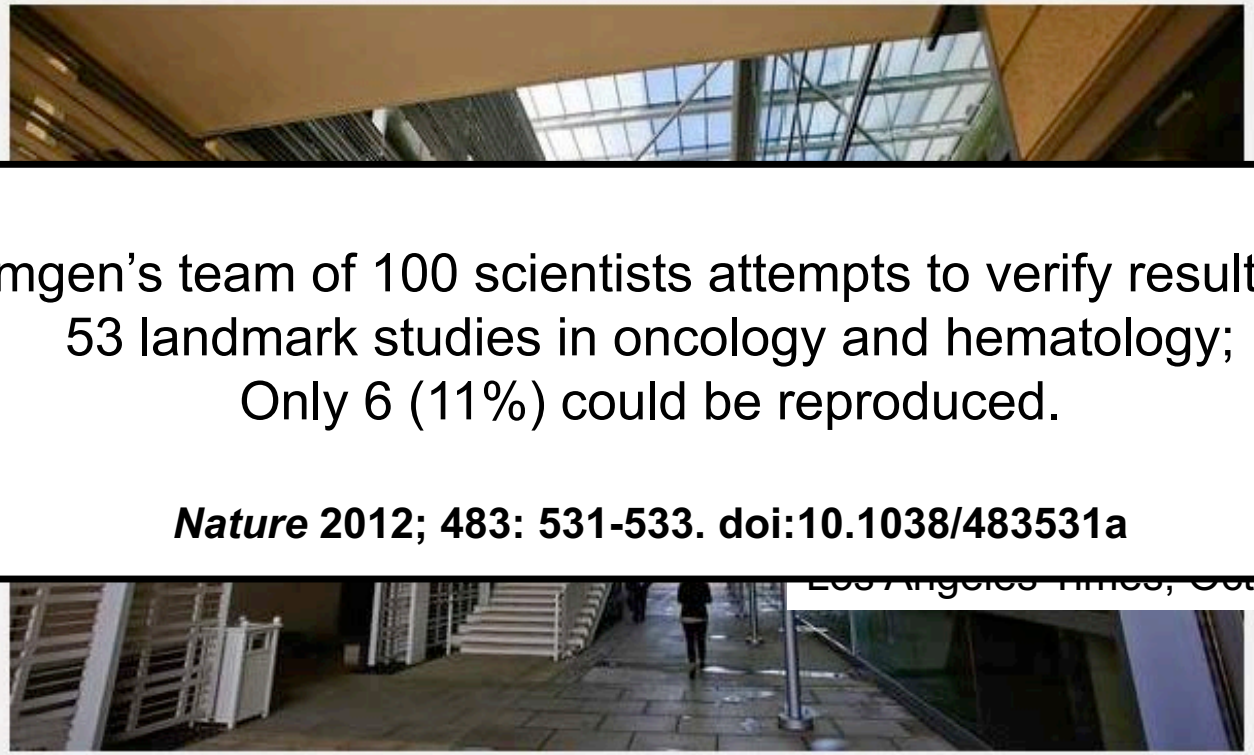
Biomedical Scientific Discovery in General Has a Reproducibility Problem

Science has lost its way, at a big cost to humanity

Researchers are rewarded for splashy findings, not for double-checking accuracy. So many scientists looking for cures to diseases have been building on ideas that aren't even true.



A few years ago, scientists at Amgen set out to double-check the results of 53 landmark papers in cancer research and blood biology. Only six could be proved valid. Above is an Amgen building in Thousand Oaks. (Anne Cusack, Los Angeles Times / April 25, 2013)

Amgen's team of 100 scientists attempts to verify results of 53 landmark studies in oncology and hematology; Only 6 (11%) could be reproduced.

***Nature* 2012; 483: 531-533. doi:10.1038/483531a**

Los Angeles Times, October 27, 2013

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How Widespread Are Failures to Reproduce Published Biomedical Science? Some High-Profile Examples

- Mass spec diagnostic for ovarian cancer – results due to experimental artifact and bias – control and experimental groups run separately (Lancet, 2002)
- 5 of 7 largest molecular epidemiology cancer studies did not classify patients better than chance (JNCI, 96:2004)
- Microarray drug sensitivity signatures from cell lines – to predict patient response (named one of top100 breakthroughs in 2006) could not be reproduced in large clinical trial in 2009 (Nature Medicine, 2006)
- Of 18 published microarray studies, only 2 were reproducible (Science, 2011)
- Bayer scientists can reproduce only 20-25% of 67 key published experiments and halts 2/3 of its target validation projects as a result (*Nature Reviews Drug Discovery* 10, 712 doi:10.1038/nrd3439-c1, 2011)

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Academic Biomedical Science: Reproducibility Rate of 10-30%

- Flipping a coin would be superior to reading *Science* or *Nature* in making pharma business decisions based on academic research.
- US government spends nearly $31 billion in research grants to academic scientists every year through the NIH
  - 10% reproducibility rate ➔ 90% of this money ($28 billion) is wasted
- Pollution of the biomedical literature by bad studies and bad data:
  - What do we really know? What can we really trust?
- Wasted money, wasted time, lost opportunities
- Why should patients and the public believe in what we do?

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Irreproducibility in Biomedical Research: A Crisis in Confidence (Public View)

The Economist | World politics | Business & finance | Economics

Unreliable research

Trouble at the lab

Scientists like to think of science as self-correcting. To an ala

Oct 19th 2013 | From the print edition

the Atlantic November 2010

Lies, Damned Lies, and Medical Science

MUCH OF WHAT MEDICAL RESEARCHERS CONCLUDE IN THEIR STUDIES IS MISLEADING, EXAGGERATED, OR FLAT-OUT WRONG. SO WHY ARE DOCTORS—TO A STRIKING EXTENT—STILL DRAWING UPON MISINFORMATION IN THEIR EVERYDAY PRACTICE? DR. JOHN IOANNIDIS HAS SPENT HIS CAREER CHALLENGING HIS PEERS BY EXPOSING THEIR BAD SCIENCE.

By David H. Freedman

PLOS | MEDICINE

Why Most Published Research Findings Are False

John P. A. Ioannidis

Published: August 30, 2005 • DOI: 10.1371/journal.pmed.0020124

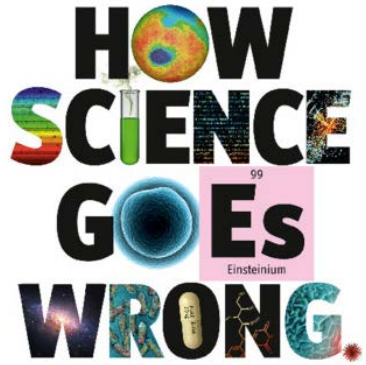
Abstract

Summary

There is increasing concern that most current published research findings are false. The probabili the number of other studies on the same question, and, importantly, the ratio of true to no relation framework, a research finding is less likely to be true when the studies conducted in a field are sm and lesser preselection of tested relationships; where there is greater flexibility in designs, definiti and other interest and prejudice; and when more teams are involved in a scientific field in chase o designs and settings, it is more likely for a research claim to be false than true. Moreover, for man simply accurate measures of the prevailing bias. In this essay, I discuss the implications of these

The Economist

Washington's lawyer surplus
How to do a nuclear deal with Iran
Investment tips from Nobel economists
Junk bonds are back
The meaning of Sachin Tendulkar



THE NEW YORKER

ANNALS OF SCIENCE

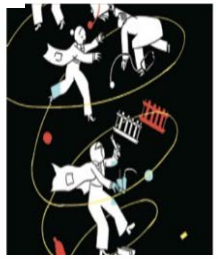
THE TRUTH WEARS OFF

Is there something wrong with the scientific method?

BY JONAH LEHRER

DECEMBER 13, 2010

On September 18, 2007, a few dozen neuroscientists, psychiatrists, and drug-company executives gathered in a hotel conference room in Brussels to hear some startling news. It had to do with a class of drugs known as atypical or second-generation antipsychotics, which came on the market in the early nineties. The drugs, sold under brand names such as Abilify, Seroquel, and Zyprexa, had



December 2011

THE WALL STREET JOURNAL.

WSJ.com

HEALTH INDUSTRY | DECEMBER 2, 2011

Scientists' Elusive Goal: Reproducing Study Results

By GAUTAM NAIK

Two years ago, a group of Boston researchers published a study describing how they had destroy targeting a protein called STK33. Scientists at biotechnology firm Amgen Inc. quickly pounced dozen researchers to try to repeat the experiment with a goal of turning the findings into a drug.

"This is one of medicine's dirty secrets: Most results, including those that appear in top-flight peer-reviewed journals, can't be reproduced"

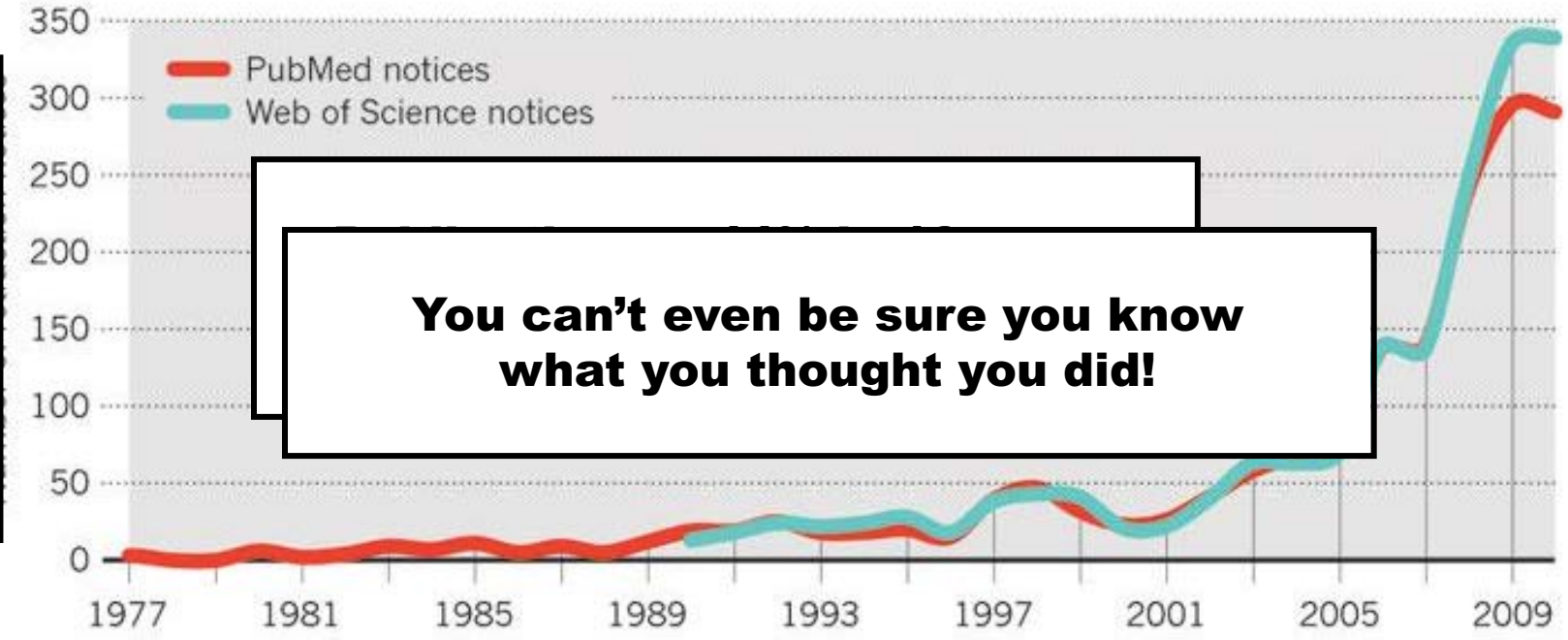
Irreproducibility in Biomedical Research: Wasteful but a Cultural Norm (Researcher View)

nature

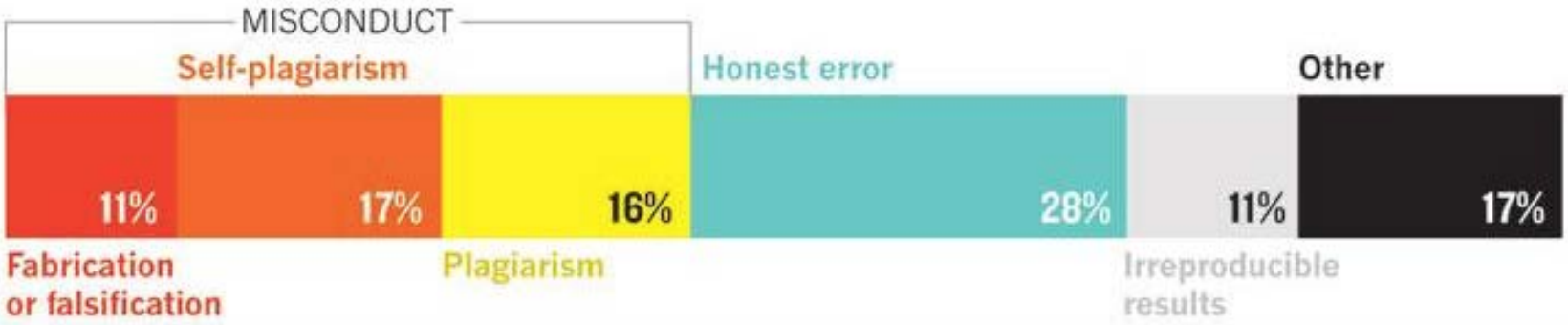
- Few scientists attempt to repeat their own studies
- Publications often based on the one time out of multiple attempts that an experiment actually worked
- External validation (by another lab) is extremely rare
- Few, if any analyses, focus on the quality and consistency of the biological materials that are the test subjects for biomarkers

Here Today, Gone Tomorrow

Retractions



You can't even be sure you know what you thought you did!



White House Takes Notice of Irreproducibility in Science and Seeks Public Input

August 21, 2014

- **Federal Register:**
- **The Office of Science and Technology Policy and the National Economic Council request public comments …….**
- **“Given recent evidence of the irreproducibility of a surprising number of published scientific findings, how can the Federal Government leverage its role as a significant funder of scientific research to most effectively address the problem?”**

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Taking Action

- **Public sector: NIH Rigor and Reproducibility Workshop, 2014**
  - Joint meeting with Science and Nature publishing groups
  - Refers to rigor in use/description of biological reagents (antibodies), cell lines and animals, but omits reference to human biological materials
- **Private Sector: The Reproducibility Project**
  - Joint venture between Science Exchange and Center for Open Science
  - Independently replicating research results from 50 high-impact cancer biology studies published from 2010-2012 using the Science Exchange network of expert scientific labs also omits reference to human biological materials

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Why Most Published Research Findings Are False

John P. A. Ioannidis

Published: August 30, 2005 • https://doi.org/10.1371/journal.pmed.0020124

Contributing Factors

- **Inadequate study power and flawed design**
- **Lack of external validation (independent testing by other teams)**
- **Bias**

Corollaries

- **The smaller the study**
- **The smaller the effect size**
- **The greater the number of tested relationships**
- **The greater the flexibility in designs, definitions, outcomes & analytical modes**
- **The greater the financial interests and prejudices**
- **The hotter the scientific field (Proteus phenomenon)**

…… the less likely the findings are to be true

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A Word About Bias and Biospecimens

JOURNAL OF CLINICAL ONCOLOGY

Official Journal of the American Society of Clinical Oncology

Sources of Bias in Molecular Marker Research in Cancer
- David F. Ransohoff and Margaret L. Gourlay, 2010

Table 1. Sources and "Locations" of

Source of Bias	Location of Bias: Before or After Specimens Are Received in the Laboratory: Before	After	Example
Features of subjects, determined in selection: Age Sex Comorbid conditions Medications	X		Cancer subjects are male, whereas control subjects are mainly female. Bias: Assay results may depend on sex.
Specimen collection	X		Cancer specimens come from one clinic, whereas controls come from a different clinic. Bias: Assay results may depend on conditions that differ between clinics.
Specimen storage and handling	X	X	Cancer specimens are stored for 10 years because it takes longer to collect them, whereas control specimens are collected and stored over 1 year. Bias: Assay results may vary with duration of storage, or with different numbers of thaw-freeze cycles.
Specimen analysis		X	Cancer specimens are run on one day, whereas control specimens are run on a different day. Bias: Assay results may depend on day of analysis in a machine that "wanders" over time.

NOTE. The table shows examples of different sources of bias and the location of the bias before or after specimens are received in the laboratory. The list is not exhaustive; other biases may be important, and the biases listed may or may not be important in any given research study, depending on details of biology and technology (ie, what is being measured and how it might be influenced).

Quality Biomarker Data Begins with Quality Analytes

Garbage in…

Purgamentum init,
exit purgamentum.

…Garbage out

Diamonds in……

Modified from Jerry Thomas

Sources of Irreproducibility of Biomarker Measurement: Preanalytical Variables

Collection Tubes and Order of draw

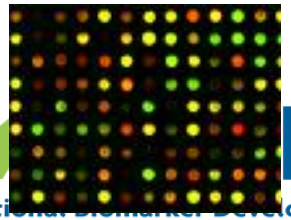
Processing Procedure, Temperature and Time

Blood Draw Procedure

Distribution & Storage

Patient Consent and Preparation

Molecular Analysis



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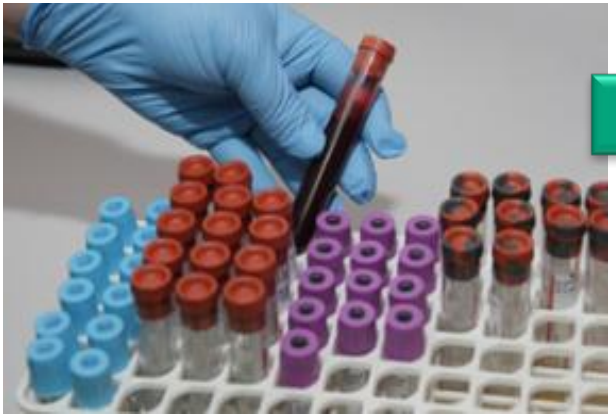
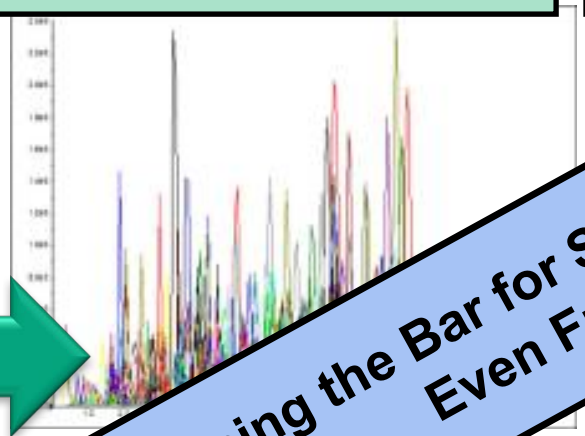
Evolution Of Biomarker Testing In The “Omics Era”

Unianalyte Tests



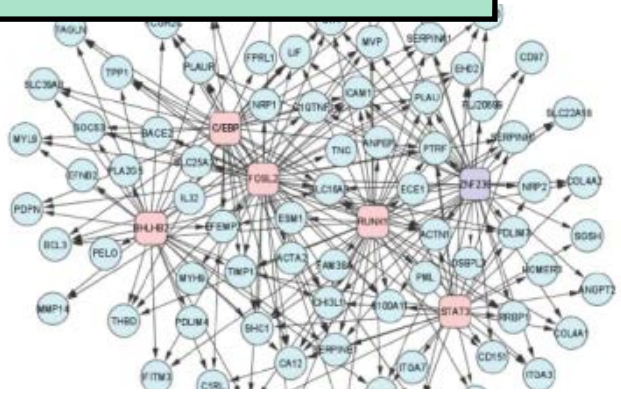
Multianalyte Tests



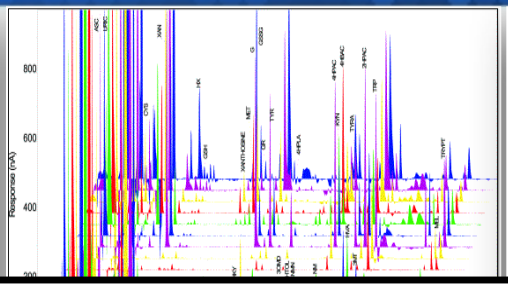
Omics Analyses

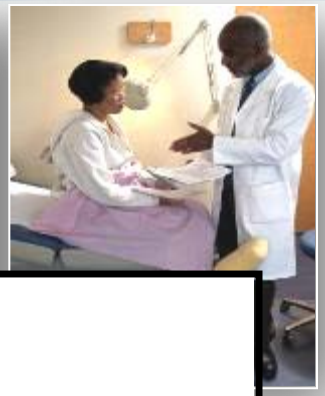
Raising the Bar for Specimen Quality Even Further!

…etworks and Systems

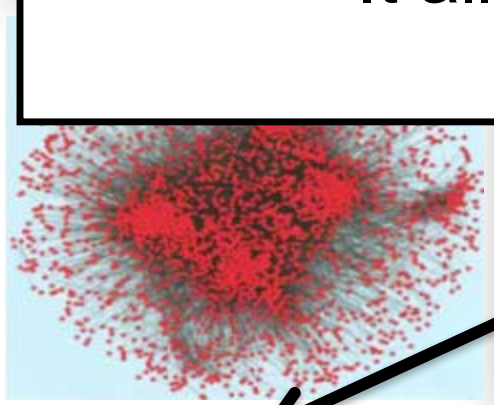


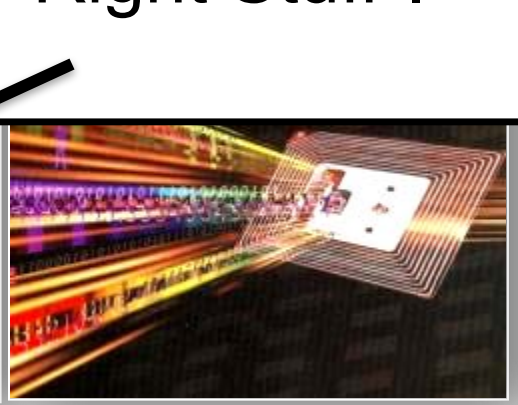
And It's Getting Far More Challenging



It all starts with the "Right Stuff".






Biospecimens and Analysis of Molecular Pathway/ Network Perturbations

Multiplex Assays and Complex Signal Deconvolution Algorithms

Novel Instrumentation, Automation and Large Scale Informatics

Patient Profiling, Rational Rx and Health Monitoring

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Courtesy of G. Poste

Evidence-Based Preanalytics and the Need for Biospecimen Science

- Preanalytics: all factors and steps that precede the analysis
- Ability to artefactually alter the biospecimen integrity (molecular content and molecular quality)
- Biospecimen science: the study of the impact of preanalytical variables of different types on different classes of molecules and markers as measured on different analytical platforms
- The sine qua non of evidence-based SOPs
- The data everyone wants and no one wants to pay for
- Reproducibility requires rigorous real-time, up-front management and documentation of preanalytics
  - You can't go back
  - Technology won't fix it

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Preanalytical Variables and Exosome Analysis

- **A Recognized Challenge**
  - Lee et al., Ann Pediatr Endocrinol Metab 2016: 21: 119-25
  - Baek et al., J Immunological Methods 2016; 438: 11-20
  - Mullier et al., J Thromb Haemost 2013: 11: 693-96.
  - Lacroix at al., J Thromb Haemost 2012: 10:437-46.
  - McDonald et al., Clin Chem 2011; 57: 833-40.
  - Set et al., Vasc Health Risk Mangag 2008; 4: 769-74.

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Preanalytical Variables and Exosomes

Draw Variables

- Tourniquet vs. none
- Tourniquet time
- Central line or artery vs. peripheral vein
- Draw order
- Tube type

NOTE: some of these variables have been shown to create artefactual exosome formation

e*

- Type of port (if used for access)
- Tube agitation during transport*
- Time to centrifugation*
- Centrifuge speed*
- Number of centrifugations*
- Use or not of discard tube
- Temperature and duration of storage

Patient Variables

- Smoking
- Exercise
- Pregnancy
- Blood pressure
- Trauma and wound healing
- Age (age-associated mutations)
- Body mass
- Systemic disorders: inflammatory, immunological, hormonal, inflammatory, cardiovascular
- Other

*Studied: shown to have impact on exosome count

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Exosome Preanalytics: Proceed with Caution

- Can results of studies be confidently compared when many preanalytics are unknown and uncontrolled and compliance with protocols is not rigorous?
- Current state of the science: Focus on analysis and clinical context; ignore preanalytical issues
- Reproducibility may be challenging
- Urgent need for biospecimen research is needed for evidence-based SOPs

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Preanalytics and Exosomes

Garbage in…

Rigor, Reproducibility, and Reliable Science…..
Patients Are Relying on Us

…Garbage out

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Development Of Biomarkers For Precision Medicine In An Era Of Evolving Technology: Specimens, Standards, And Signatures

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