


The Future of Pathology: Complexity, Convergence, and Change

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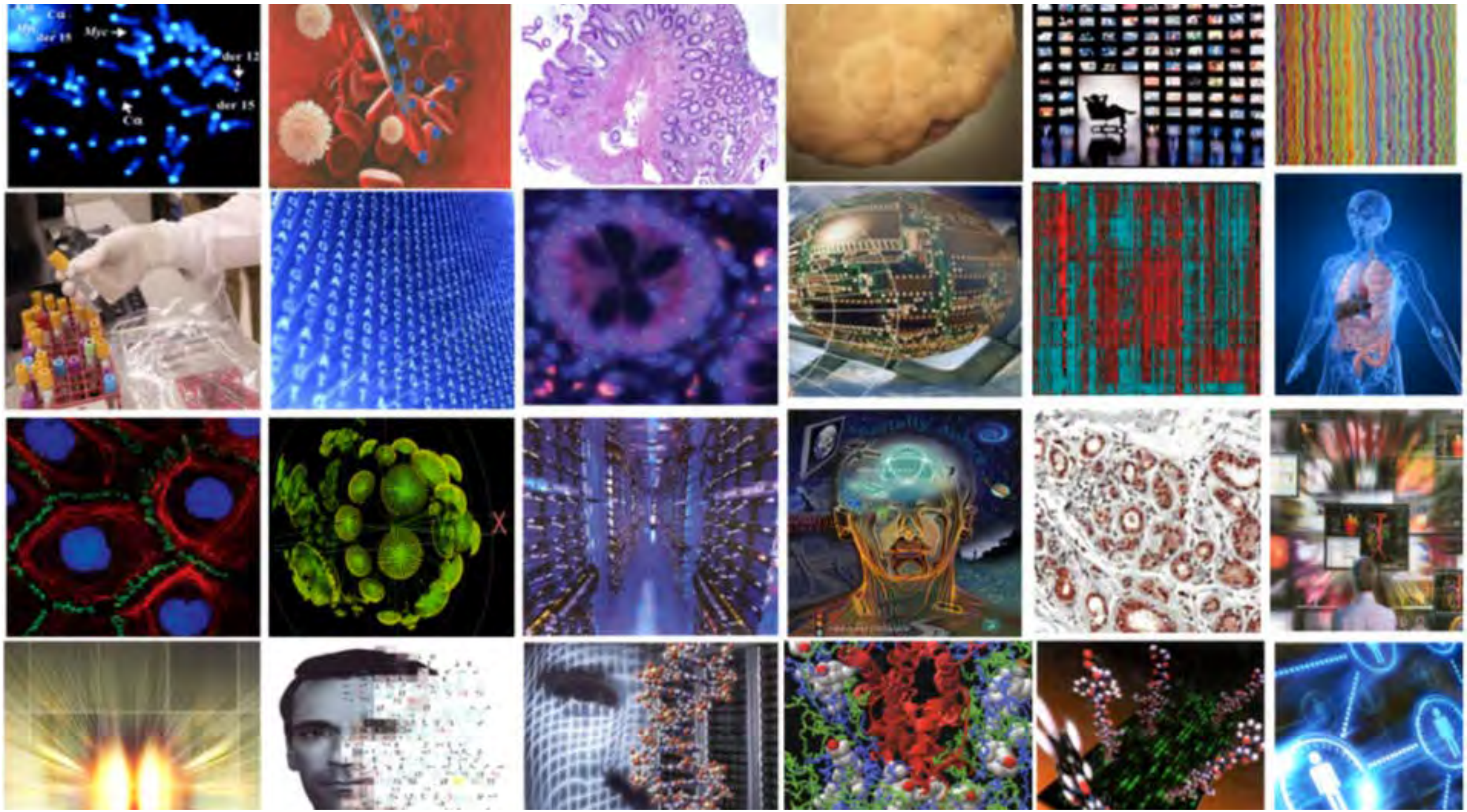
CMO, Complex Adaptive Systems Institute

NBDA
National Biomarker Development Alliance

ASU Complex Adaptive Systems
Arizona State University

Brindley Lecture
UTMB Department of Pathology
Galveston, TX
May 15, 2017

The Changing Landscape of Medicine; New Tools, New Knowledge, New Era



The Convergence of Advanced Technologies, Molecular Biology, and Data Science

Cover of *Nature* 2001
First draft of human genome published

BioIT World 2011 - by **Sorena Nadaf, M.S. M.MI**
Director - Translational Informatics, CIO

Technology Development
Unleashing the Potential for Progress

- **Technological change is 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)

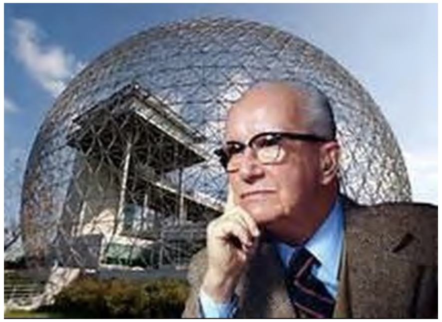
    *Number of transistors in a dense integrated circuit (computer microprocessor)

  - **Became the mantra of technology development in general**
  - **Faster, better AND cheaper**

- **Explosive technology development has created a tsunami of new data**

Technology Development
Unleashing the Potential for Progress

- **Exponential ↑ in data has resulted in exponential ↑ in human knowledge**
  - **90% of world's data produced in last 2 years (held true for 30+ years)**
  - **In 2025, the amount of data produced in a week will equal all of the data produced by mankind during its entire existence up until 2013**
- **Buckminster Fuller's Human "Knowledge Doubling Curve"**
  - **Until 1900, doubled every century**
  - **By end of WWII – doubling every 25 years**
  - **Current average – doubling 12 months**
  - **With build-out of the Internet of Things – doubling every 12 hours**



The Internet of Things (IoT), the Growth of Human Knowledge, and the Connection of the Medical Universe

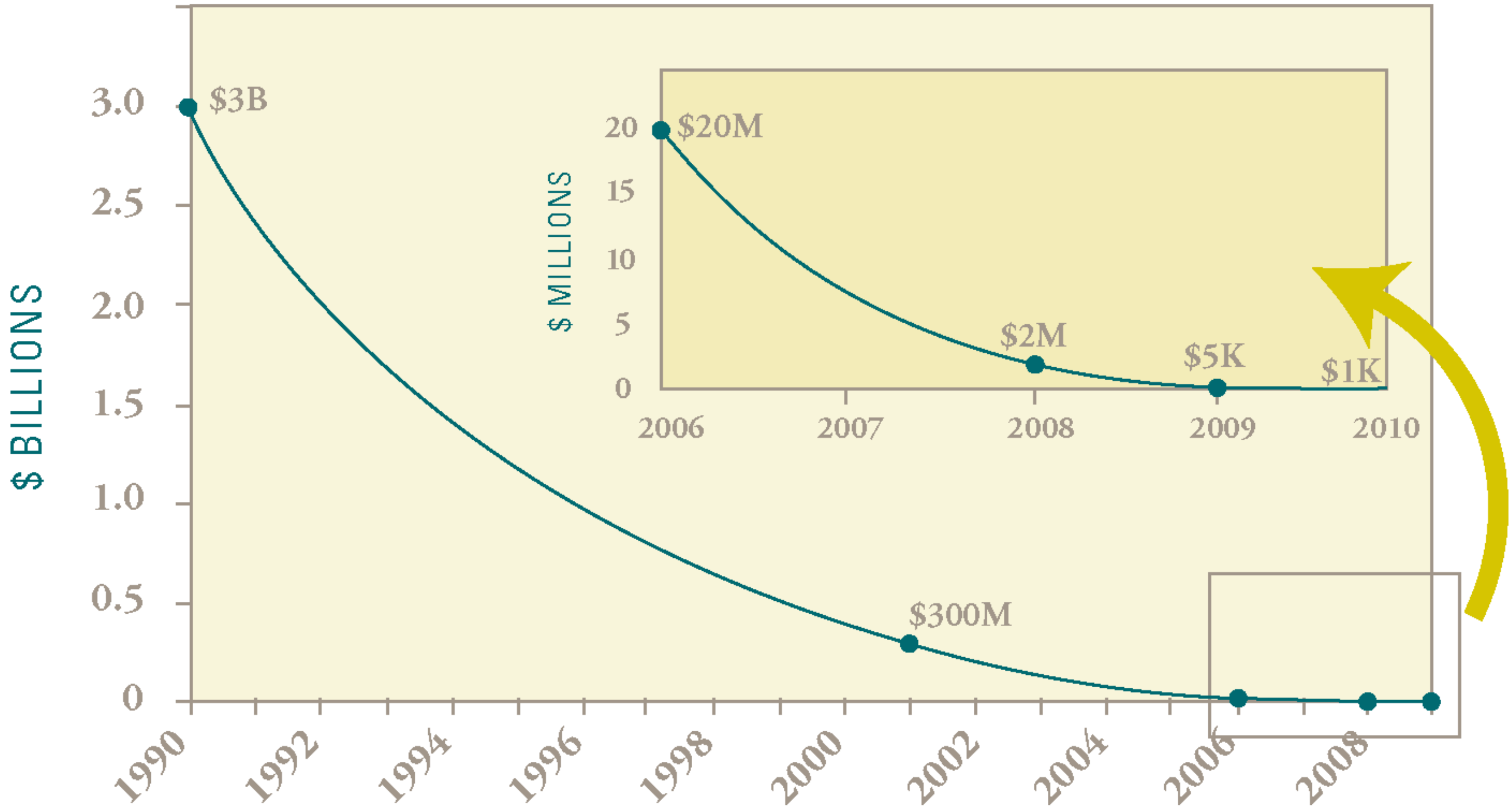
- **The IoT interconnects embedded sensors and computing devices within the internet structure**
  - **Smart objects, automation, wearables, machine-2-machine**

- **IoT uses:**
  - **Energy management**
  - **Environmental sensing systems**
  - **Urban planning**
  - **Transportation systems**
  - **Management of cities / urban systems**
  - **Law enforcement**
  - **Warfare**
  - ***Medicine and healthcare systems***

Disruptive Technological Advances: Changes in the Science and Practice of Medicine

- **High-throughput, inexpensive molecular analysis: the $1000 genome**
- **Large-scale GWAS linking genetic variation to disease and treatment response**
- **Data science that analyzes, integrates and models huge amounts of data representing complex layers of biology**
- **Information technology removing the limitations of human cognitive capacity**

Disruptive Technological Advances: The $1K Genome



Sources: Wheeler DA et al., Nature 2008; 452:872-6; Mardis E. Genome Biology 2006; 7:112; Keim B. Wired Science October 06, 2008; The 2009 and 2010 values are projected. Current cost of complete genome sequencing (as of April 2009) is $60,000 (Applied Biosystems).

Personalized Medicine Coalition. The Case for Personalized Medicine. Available at: http://www.personalizedmedicinecoalition.org/communications/pmc_pub_5_09.php. Accessed August 26, 2009.

The $1000 Genome;
Are We There Yet? Yes, Finally!

Matthew Herper
Forbes Staff

PHARMA & HEALTHCARE 1/14/2014 @ 9:14PM | 33,669 views

The $1,000 Genome Arrives -- For Real, This Time

- FORBES 2014

Illumina HiSeqX:

- **16 genomes per day for $16,000**
- **Cost of machine: $16M**

Disruptive Technological Advances: Whole Genome Sequencing Becomes the New CBC

Yesteryear*	Y2K	Today	Tomorrow
1990	2000	2017	2017+
• 8 years	• 6-12 months	• <24 hours	• 8 hours
• $3 billion	• $100 million	• $1000	• $100+

*Mike and I are at MGH

Disruptive Technological Advances: Changing the Science and Practice of Medicine

- High-throughput, inexpensive molecular analysis: the $1000 genome

- **Large-scale genome-wide association studies (GWAS) linking genetic variation to disease risk**

- Data science that analyzes, integrates and models huge amounts of data representing complex layers of biology

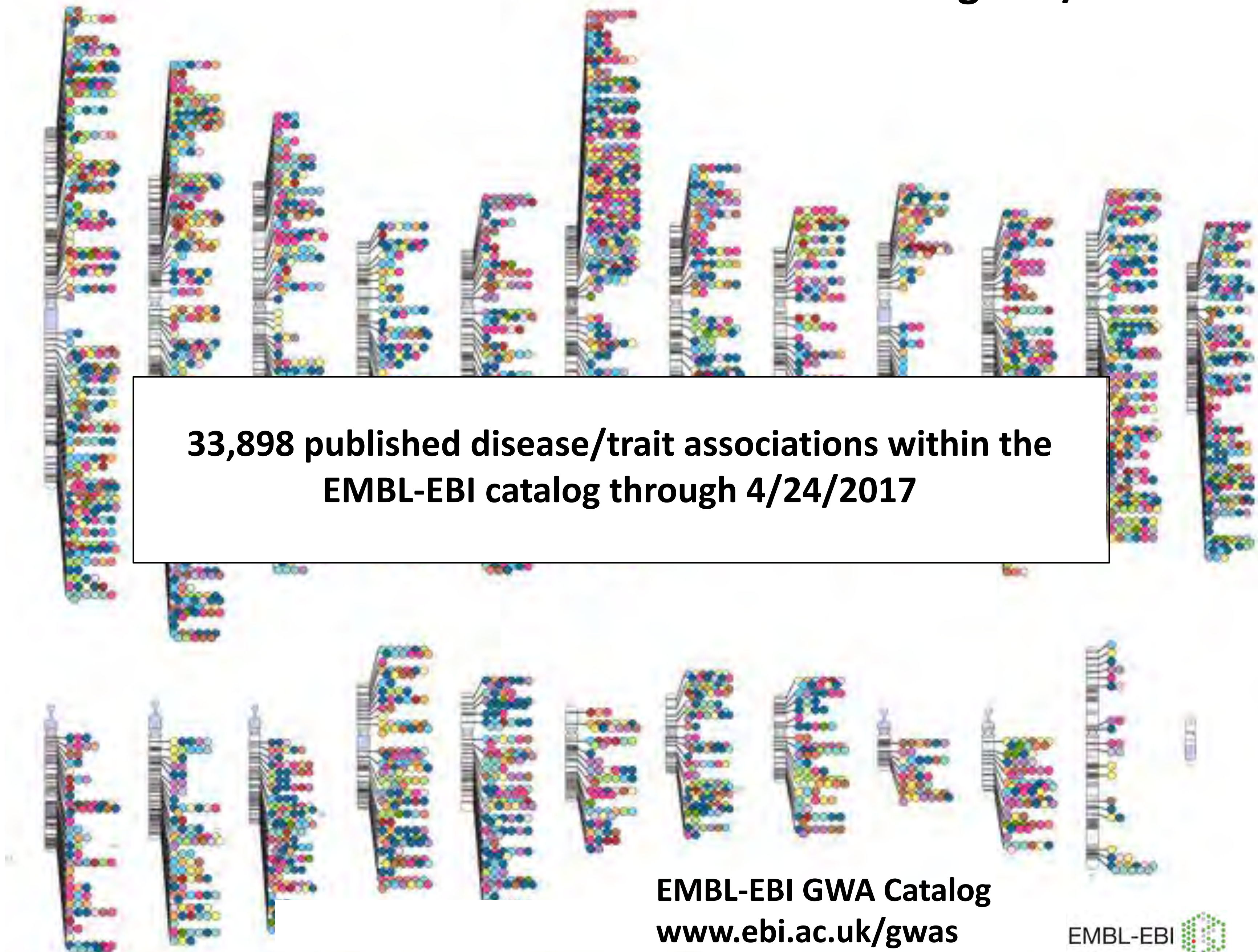
- Information technology removing the limitations of human cognitive capacity

Accelerating Pace of Discovery of Genomic Basis of Disease Risk

Second quarter 2008

Manolio, Brooks, Collins, J Clin Invest 2008; 118: 1590-625. **Graphic courtesy of NCI, Not for Distribution**.

Published Genome-Wide Associations through 12/2014



33,898 published disease/trait associations within the EMBL-EBI catalog through 4/24/2017

EMBL-EBI GWA Catalog
www.ebi.ac.uk/gwas

EMBL-EBI

Coming Next: The Internet of DNA

MIT Technology Review

Internet of DNA

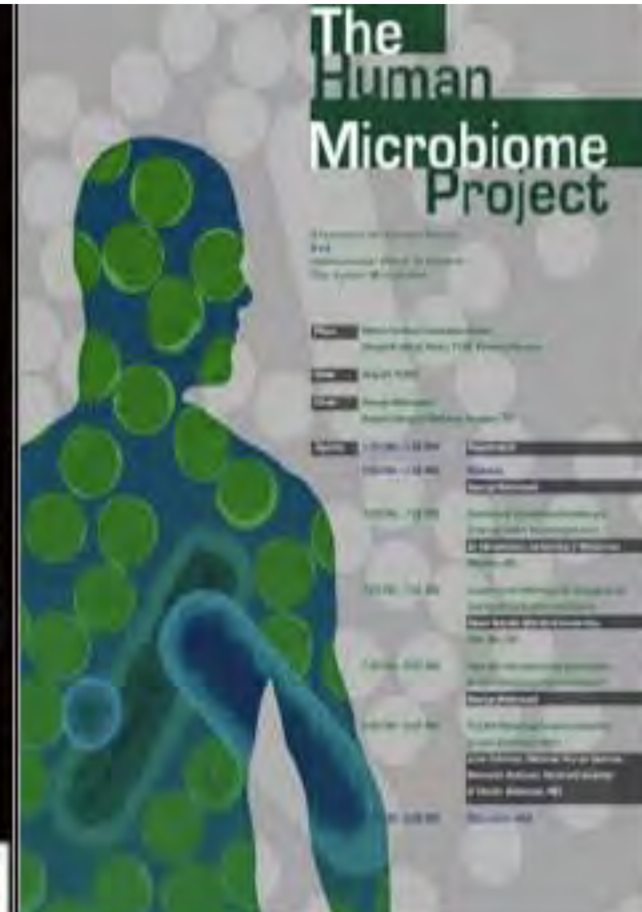
A global network of millions of genomes could be medicine's next great advance.

Availability: 1-2 years

by Antonio Regalado

MIT Tech Review 2015

And After That, Those Other Genomes We Carry Around



Disruptive Technological Advances: Changing the Science and Practice of Medicine

- Rapidly approaching the $1000 genome
- Large-scale GWAS linking genetic variation to disease and treatment response
- **Data science that analyzes, integrates and models huge amounts of data representing complex layers of biology and clinical medicine**
- Information technology removing the limitations of human cognitive capacity

Democratization of Technology and Data Access

Empowerment of researchers and clinicians to access increasing amounts and types of complex data at high speed

…… from molecules to pathways to systems to clinical phenotypes

Genes ⟷ Genomes ⟷ Transcriptomes Proteomes ⟷ Pathways ⟷ Clinical Data

All from their computer… tablet…. smart phone…

Disruptive Technological Advances:
Changing the Science and Practice of Medicine

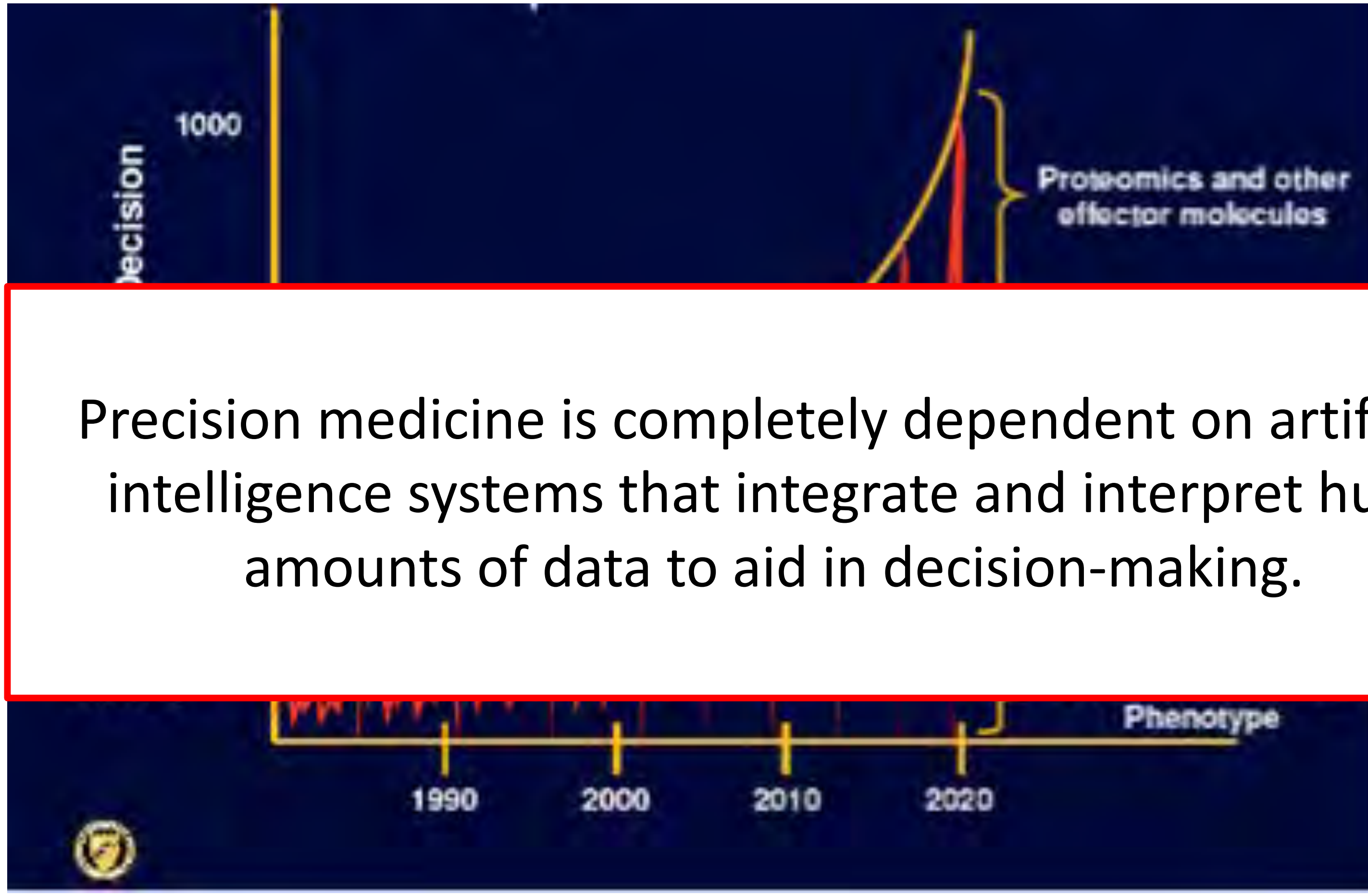
- High-throughput, inexpensive molecular analysis: the $1000 genome

- Large-scale GWAS linking genetic variation to disease and treatment response

- Data science that analyzes, integrates and models huge amounts of data representing complex layers of biology

- **Information technology removing the limitations of human cognitive capacity**

Biomedical Data Have Far Outstripped the Cognitive Capacity of Human Beings



>2,000,000 proteins*

SNPs in
Map

00 genes

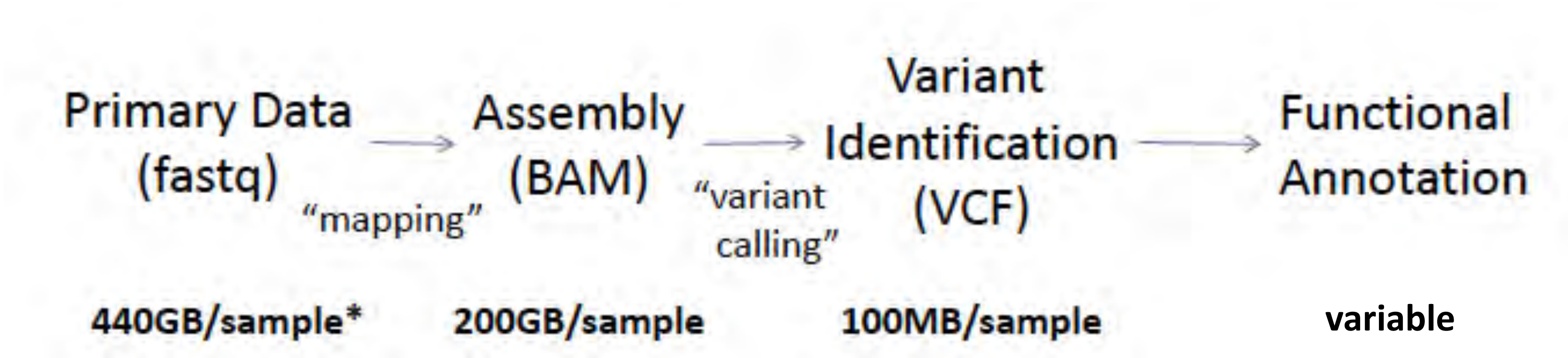
Precision medicine is completely dependent on artificial intelligence systems that integrate and interpret huge amounts of data to aid in decision-making.

*AMA Science 2014

Stead W. Beyond Expert Based Practice. Presented at: Institute Of Medicine; October 8, 2007.

Precision Medicine Is a Big Data Dilemma
Exhibit #1: Sequencing a Genome

Human genome = 3.2 billion base pairs



Whole Genome Analysis (60x coverage) → **≈1,000 GB/sample***

***Each biopsy sample of a cancer may have a different genome.**

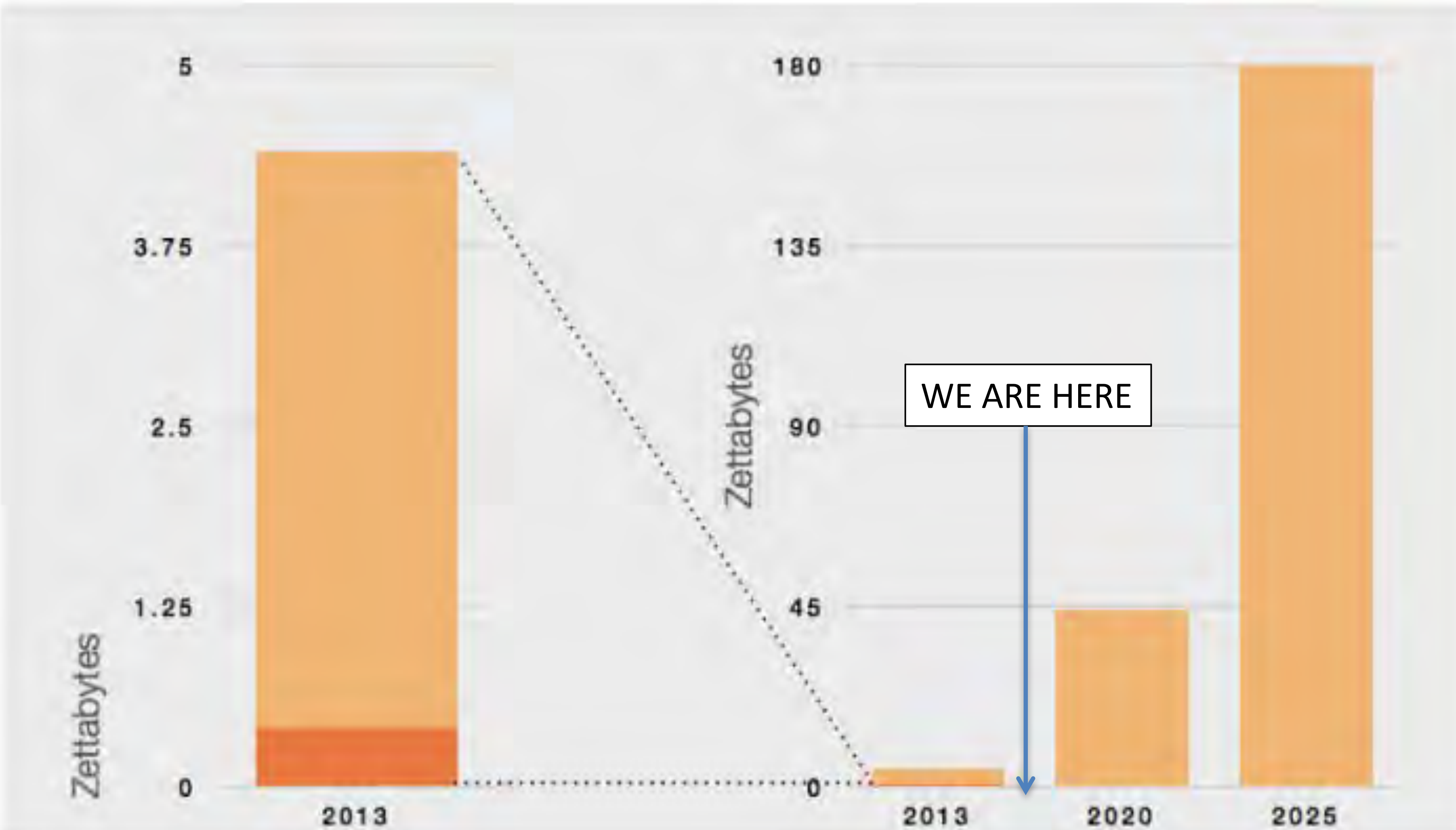
Data: How Big Is Big?

- **1,000 gigabytes = 1 terabyte**
  - **1 TB = 333,333 MP3 songs (sound compression files)**
  - **235 TB = entire contents of the Library of Congress**

- **1,000,000 gigabytes = 1,000 terabytes (1,000 genomes) = 1 petabyte**
  - **1 PB = entire storage capacity (hard drive) of the human brain**
  - **1 PB = 63,000 "dumb" smart phones (16 GB)**
  - **1 PB of MP3 songs would take 2,000 years to play**
  - **2 PB = content of all US research libraries**
  - **50 PB = entire written works of humankind from the beginning of time**
  - **Large Hadron collider produces 100 PB per day!**

- **The zettabyte era (1,000,000,000,000,000,000,000 bytes) is upon us**

The Zettabyte Era

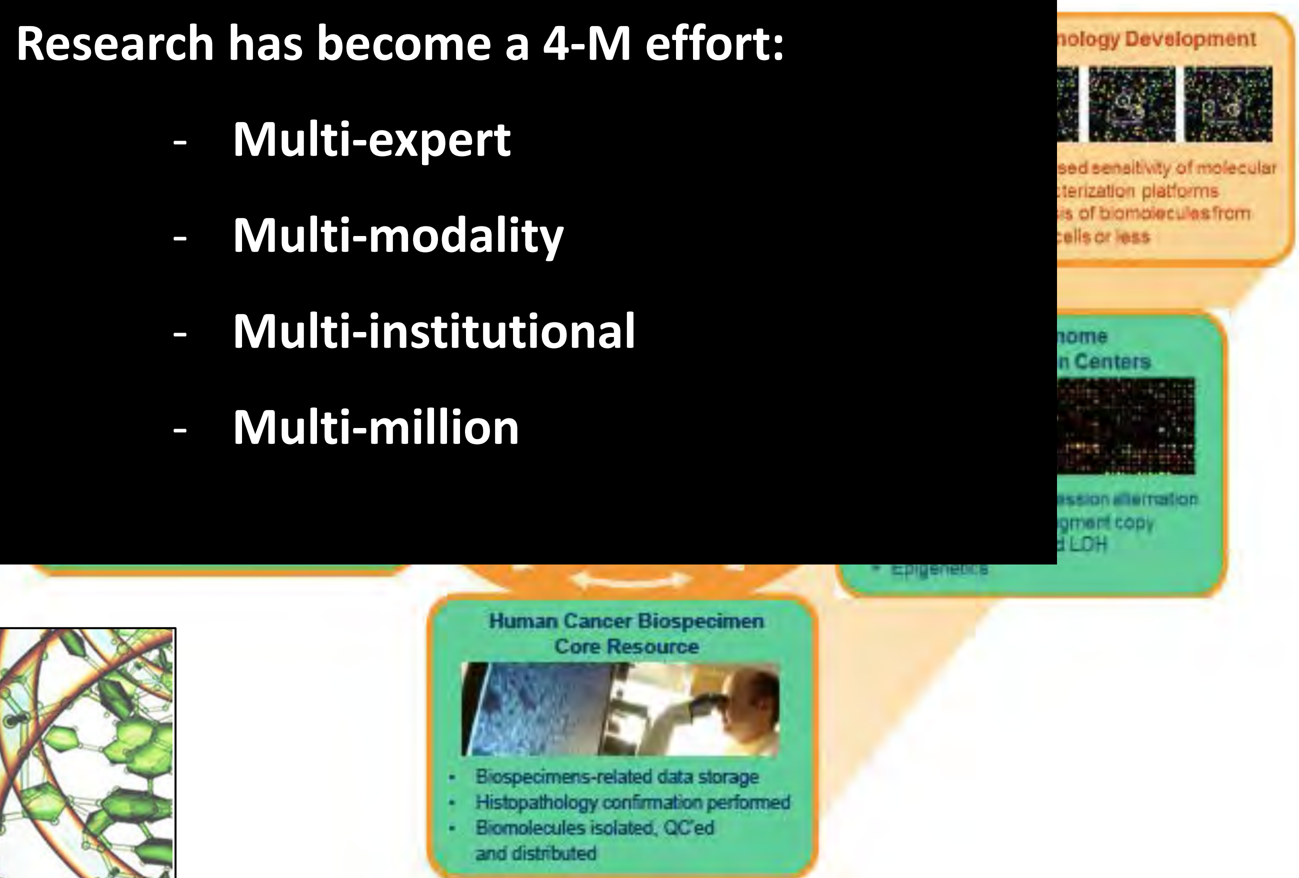


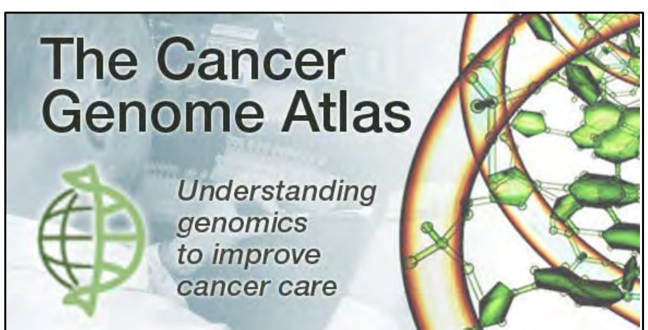
Research: Cancer, Team Science, Whole Genome Sequencing and Large-Scale Data Production

- **Cancer is the best example of enterprise-wide genomic, transcriptomic, methylomic and (now) proteomic analysis and to enable precision medicine**

Research has become a 4-M effort:

- **Multi-expert**
- **Multi-modality**
- **Multi-institutional**
- **Multi-million**

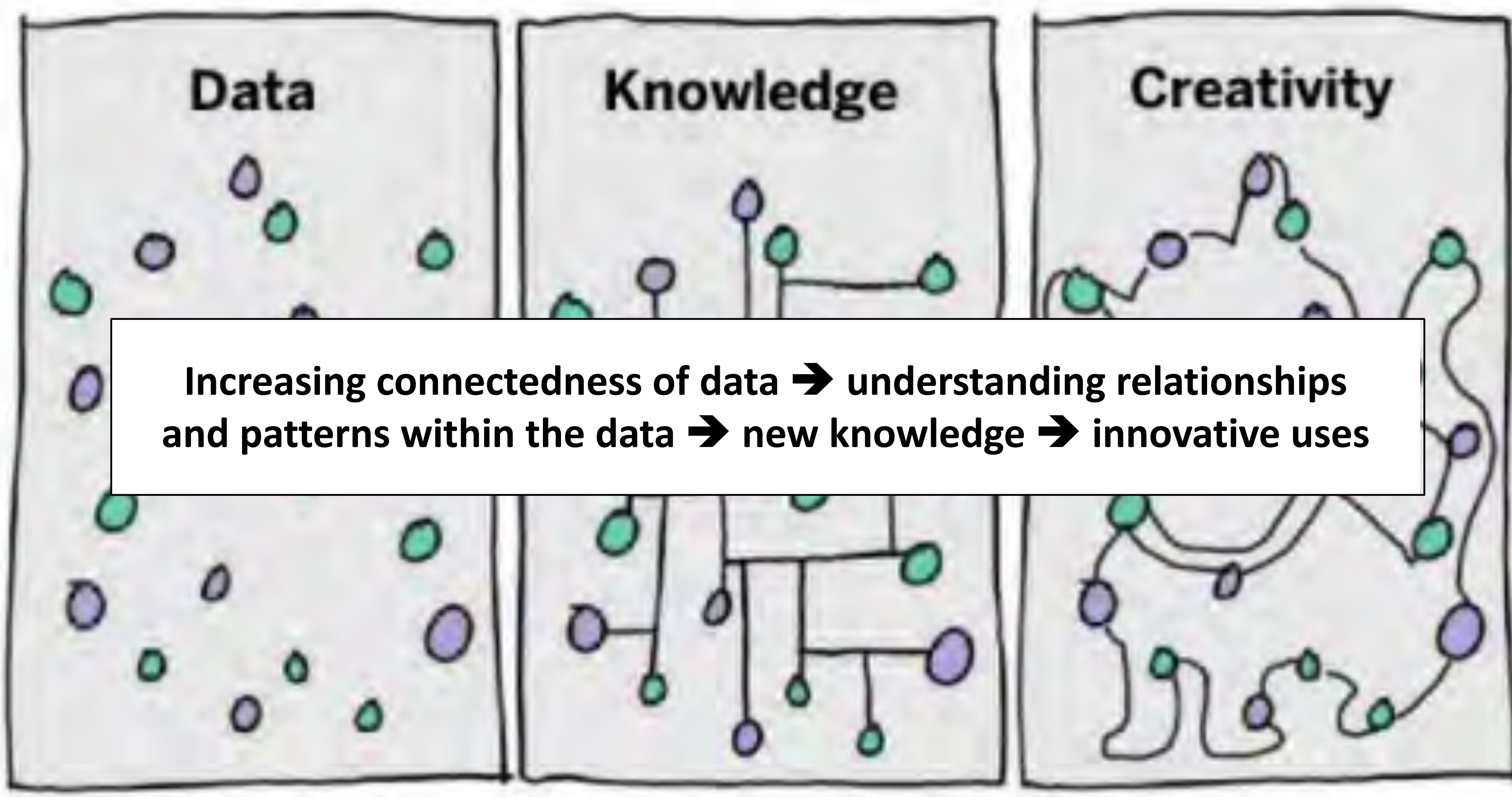




As Has Medical Practice:
Healthcare Has Progressively Evolved Into a Big-Business, Data-Intensive Enterprise

Clinical data, laboratory data, imaging data, outcomes data, billing data, operational data, quality management data, personnel data, compliance data, revenue data, costs data, logistics data, malpractice data, insurance data, etc, etc. etc.

Payoffs for Patients Are Dependent on the Evolution of Data into Progress



Increasing connectedness of data ➔ understanding relationships and patterns within the data ➔ new knowledge ➔ innovative uses

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

But Its Complicated: Data Quality and Data Sharing Challenges must Be Overcome

- **The standards needed to assure data quality and reproducibility within and across these activities are lacking.**
- **The incentives to change this have been lacking**
  - **Require time, effort and resources for standards development and enforcement**
- **We have been misled into thinking that data volume can compensate for poor or unknown data quality**
- **The incentives to share data have been weak and the incentives to hoard data have been strong (e.g., IP and privacy).**

FREE THE DATA
www.free-the-data.

Promoting ethical and efficient sharing of genomic data for research

The unfolding calamity in genomics is that a great deal of life-saving information, though already collected, is inaccessible.

MIT Technical Review

And We Don't Know What We Don't Know: We Need To Be Prepared for Disruptiion

Hon. D. Rumsfeld
US Secretary
of Defense

Response to query about evidence on weapons of mass destruction and the Iraq government

"known knowns"

- Validated knowledge
- Decisions with high predictability of success

"known unknowns"

- Known knowledge gaps (complete or incomplete) about relevant factors
- Limitations of predictability and accuracy of decisions

"unknown unknowns"

- Conceptual and cognitive blank spaces
- Rude shocks/disruption by unanticipated interactions between known factors or completely new interactions between unknown/unrecognized factors

Other Big Challenges for Integration of Big Data into Clinical Care

Google’s Mastery of Big Data Provides Big Opportunities

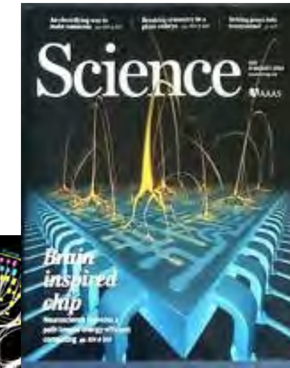
Google is Deve
Nanoparticle S
Biomarker Det

Andrew Conrad, Head of Life Sciences
announced last week at the Wall Stree
Digital conference that Google is devel
wearable sensor that can receive signa
circulating nanoparticles.

Much of the World's Data Is Unstructured: Technology Is Meeting this Challenge

- IBM's Watson: Processes natural language and uses cognitive computing to make decisions
- Instantly "reads" all medical literature and medical records, makes associations to answer questions
- Machine learning: constantly adapting to shifts in knowledge
- Utility for medical purposes is currently under study at major cancer centers

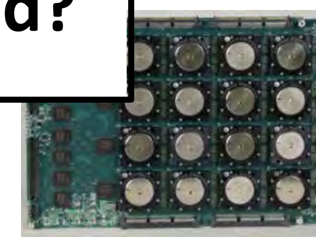
Human Brain vs. Neuromorphic Computing
Current Scorecard: Wetware vs. Hardware



- Human brain: Excels at complex tasks with low energy usage
  - No programming needed
  - 100 billion neurons; 100 trillion synapses
- Super computer brain (in evolution):
  - IB
    co

Can the virtual house officer be far behind?

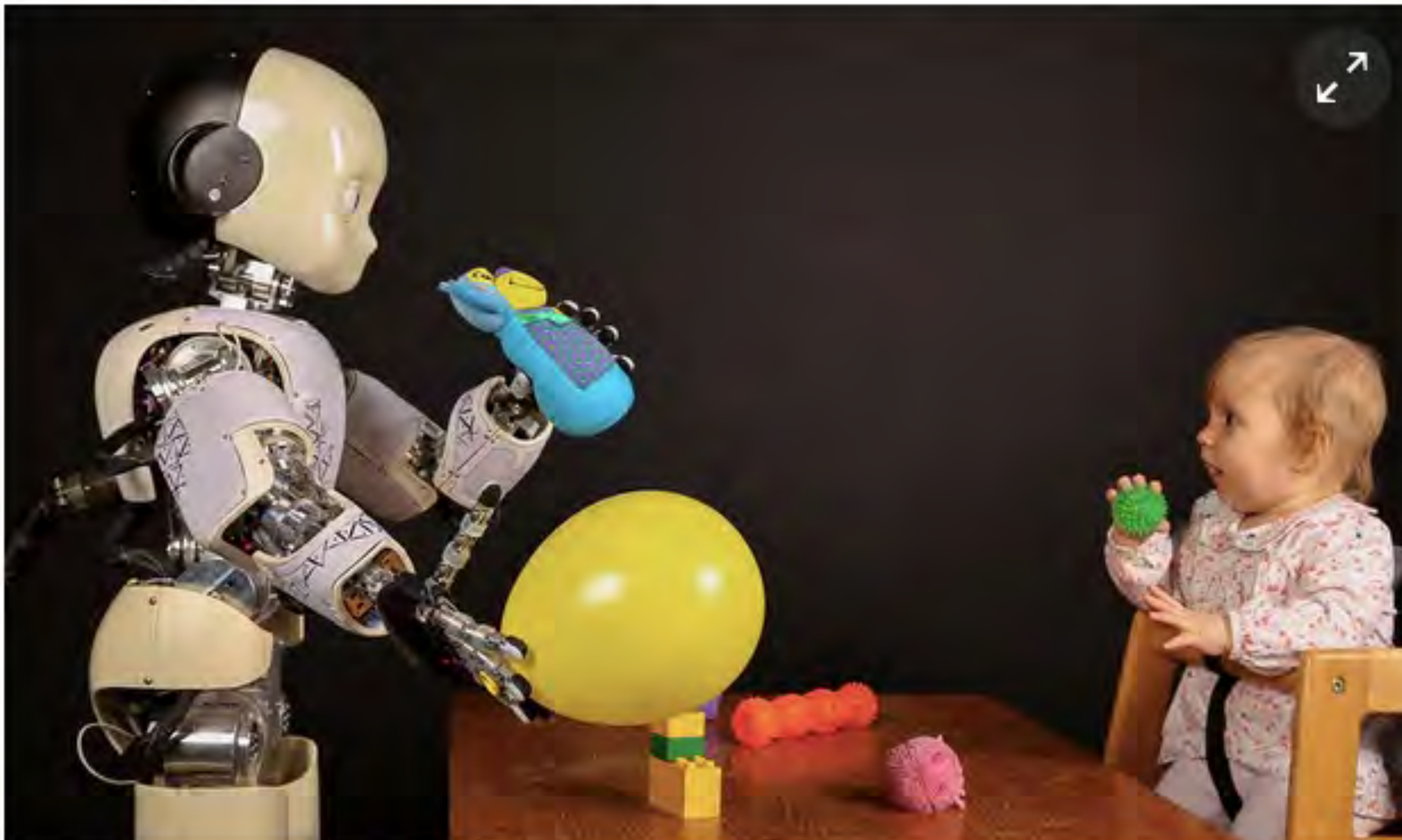
    - Would require 12 gigawatts to perform at brain speed
    - 12 gigawatts = combined power consumption of LA and NYC



  - IBM's TrueNorth neuromorphic computer, (transistors wired to form 1M digital "neurons" with 256M "synapses") accomplishes complex tasks like pattern recognition at high speed and low energy: "brain on a chip"
  - Google's Deep Mind technology: goal – create "intelligence" by combining machine learning and neuroscience to build algorithms for decision-making

AI will create 'useless class' of human, predicts bestselling historian

Smarter artificial intelligence is one of 21st century's most dire threats, writes Yuval Noah Harari in follow-up to Sapiens



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Technology Is Changing the World of Clinical Data Collection and Analysis

Ultrasound anywhere

HEALTH

Facial-recognition software finds a new use: diagnosing genetic disorders

By KATE SHERIDAN @sheridan_kate / APRIL 10, 2017

Doctor Android

In the same way that Luther challenged the Catholic Church, smartphones are poised to upend the medical profession.

THE WALL STREET JOURNAL.

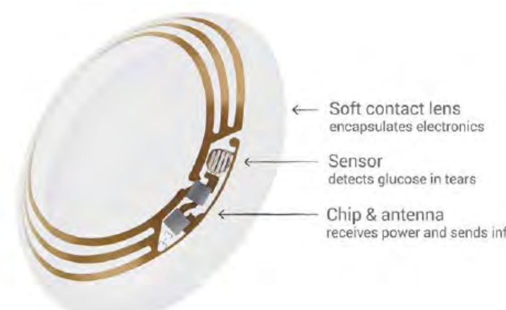
Biosensor Technology Is Expanding the World of REAL TIME Data Collection and Health Assessment

cardiovascular diabetes fitness

Telehealth “wearables” monitoring devices

shipments **of telehealth devices grow to about 7 million by 2018**

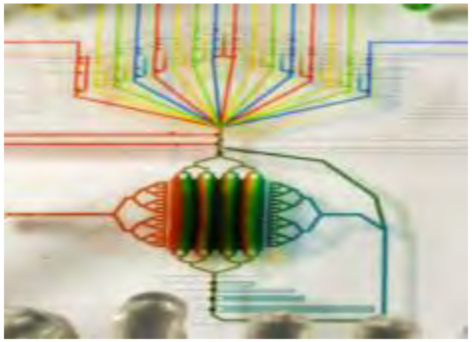
Source: www.ihs.com World Market for Telehealth – 2014 Edition

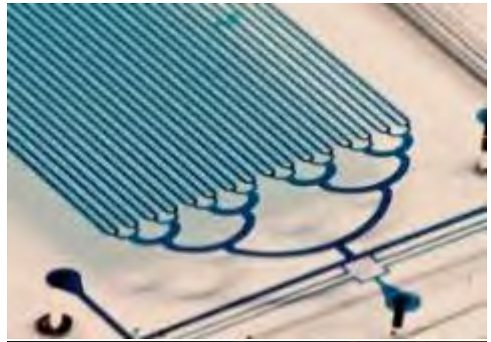


Google’s “smart” contact lens measures glucose levels

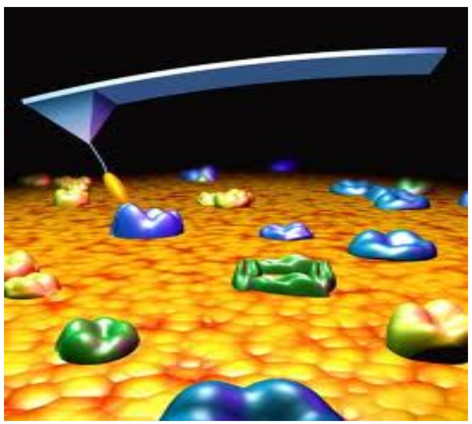
Take two wearables, and call me in the morning.

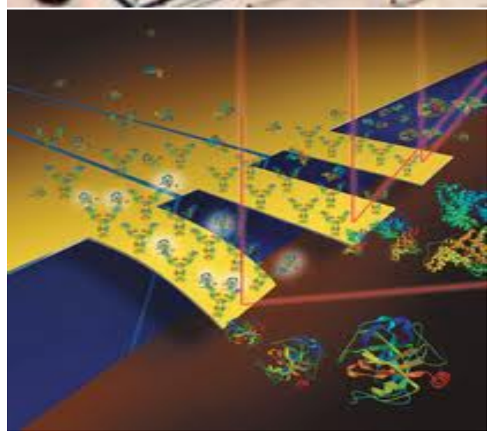
Technology Is Changing the World of Real Time, Point-of-Care Molecular Analysis



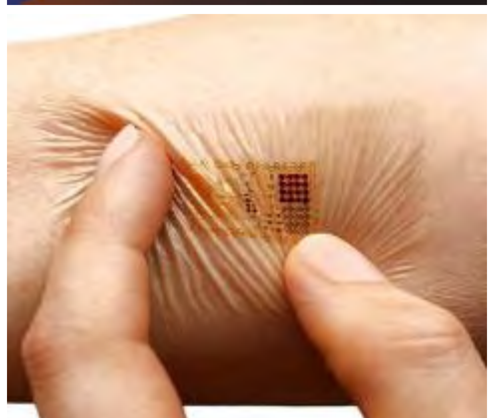


“Lab-on-a-Chip”





“Lab-on-a-Tip”



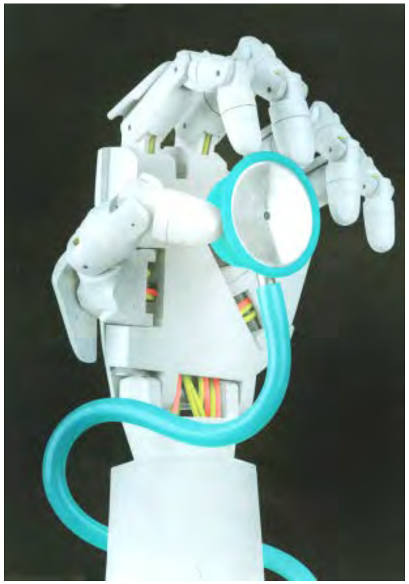
“Lab-Always On”
and
“Lab-On-Me”

Beyond Real Time, Point-of-Care Molecular Analysis to Real Time Point-of-Care Therapy

Continuous … nsmission to

Technology Is Changing the World of Physician-Patient Interactions, Follow-Up, Consultations: Medical Skype, Mobile Devices, and Telemedicine

Technology Is Changing the World of Home Healthcare: Robotics and Telemedicine

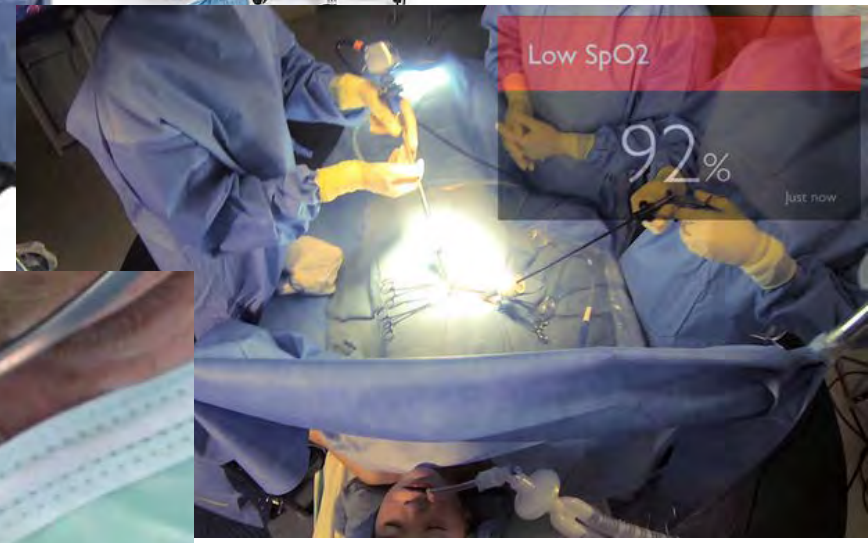


RP-VITA Remote Presence Robot:
(iRobot Corp) FDA 501(k) clearance 1/24/13

DocBot Physician Assistant

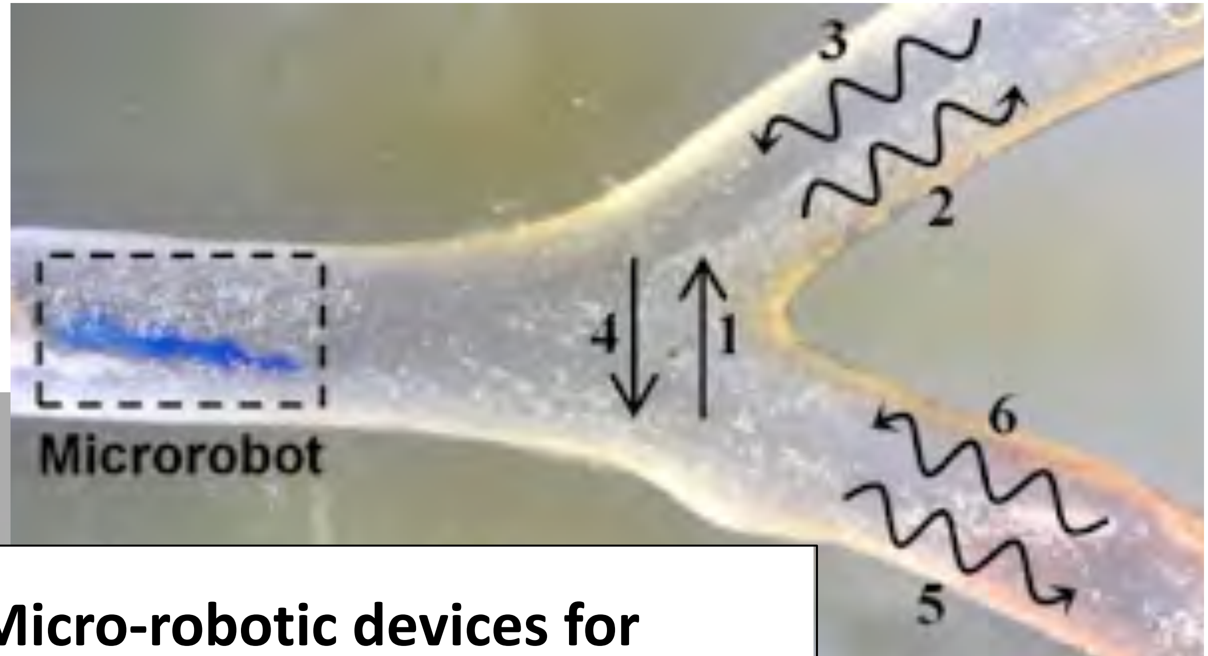
Technology Is Changing the World of Hospital Healthcare and Expanding the Abilities of Physicians

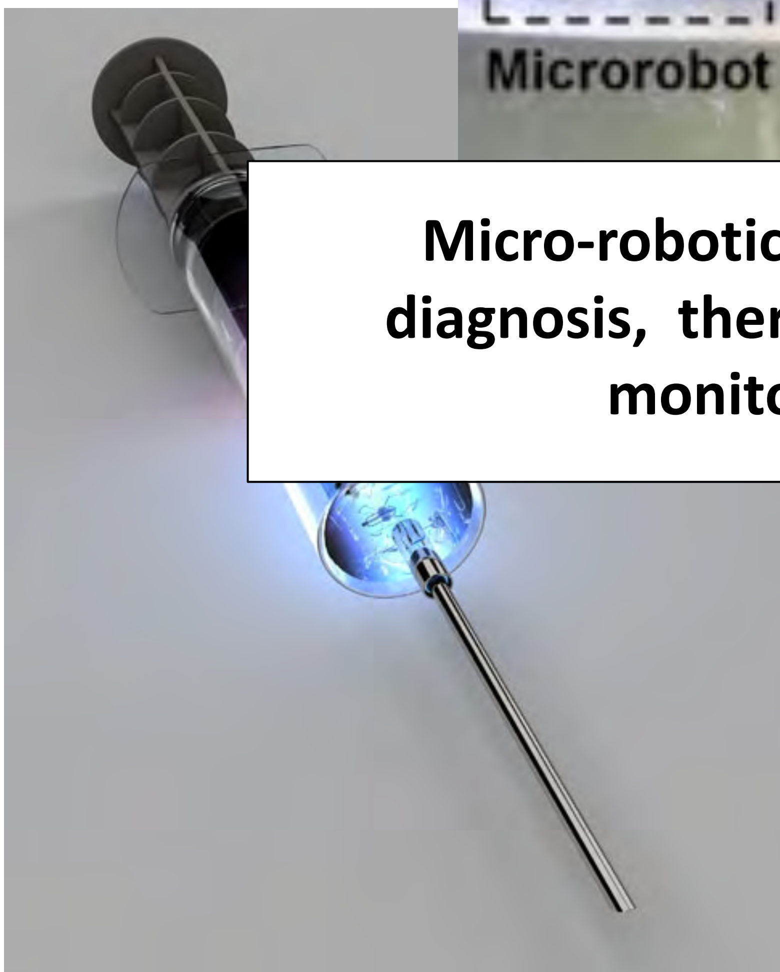
Robotic Surgery: Augmented Control, Visualization, Dexterity

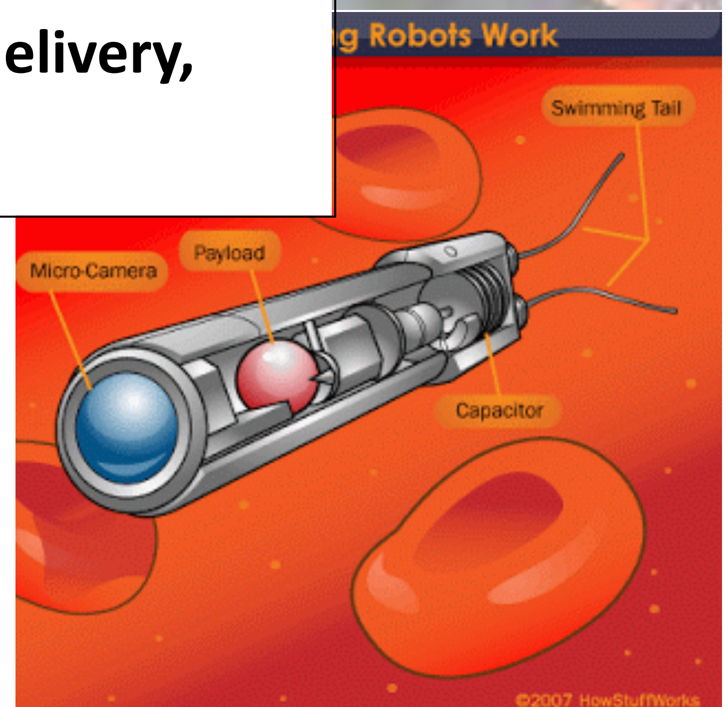


Google Glass: Augmented Reality

Robotic Tools of All Sizes Are Changing Medicine

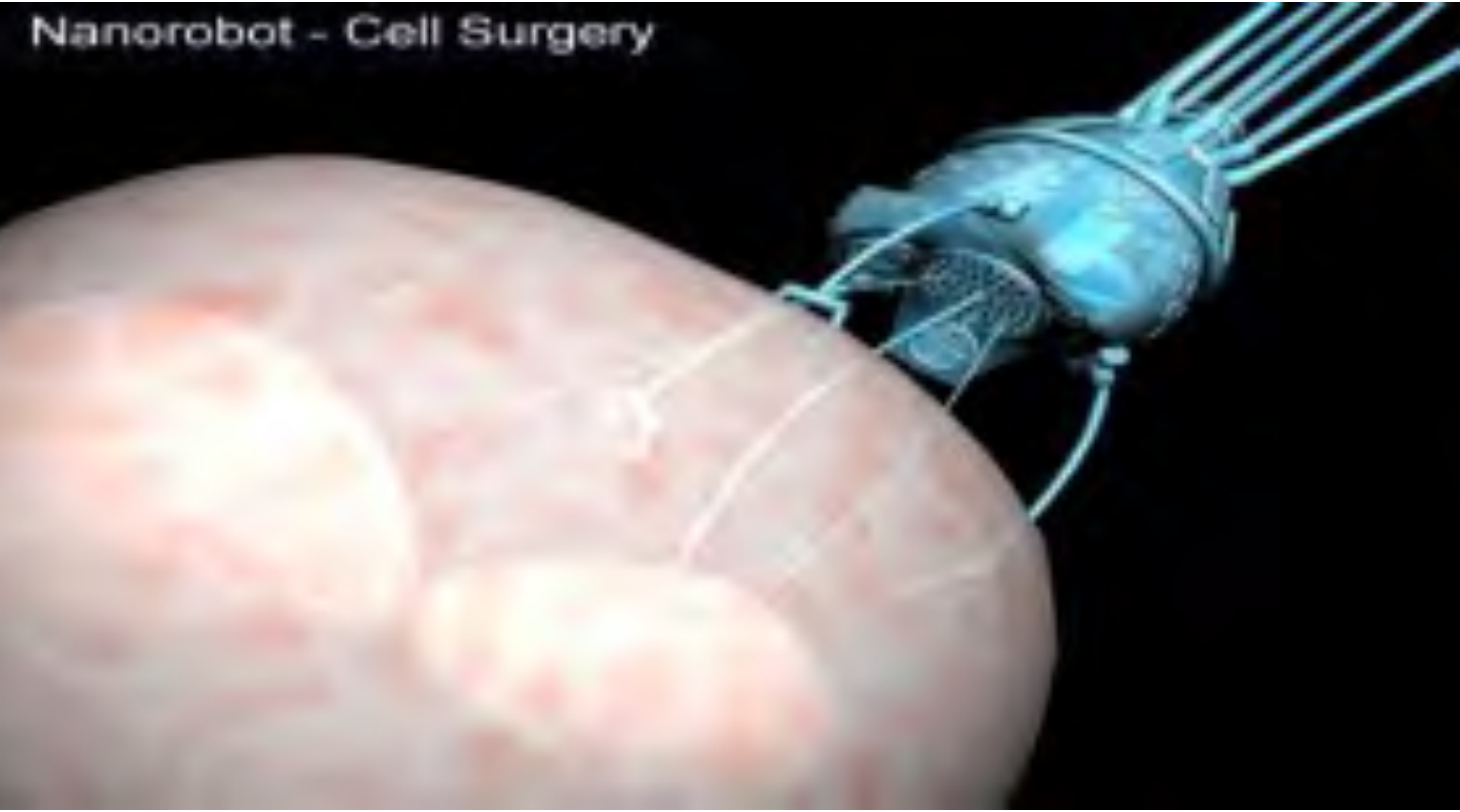




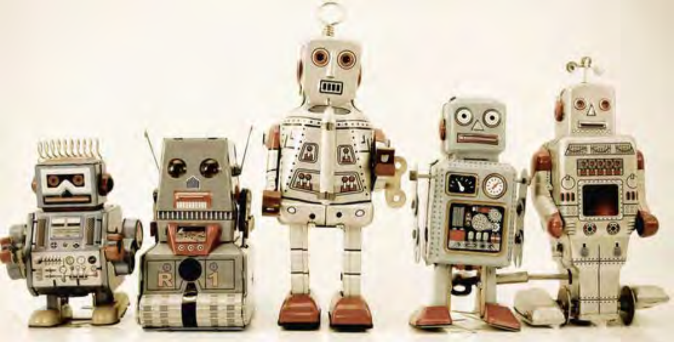


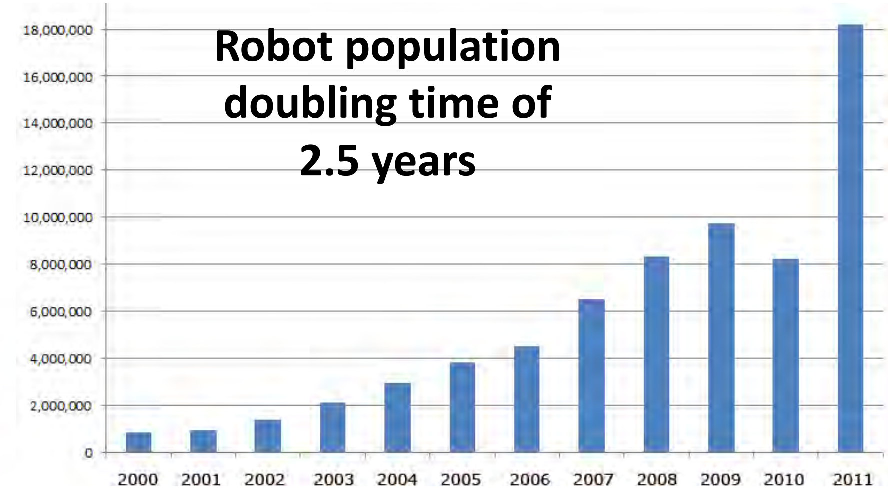
Micro-robotic devices for diagnosis, therapy delivery, monitoring

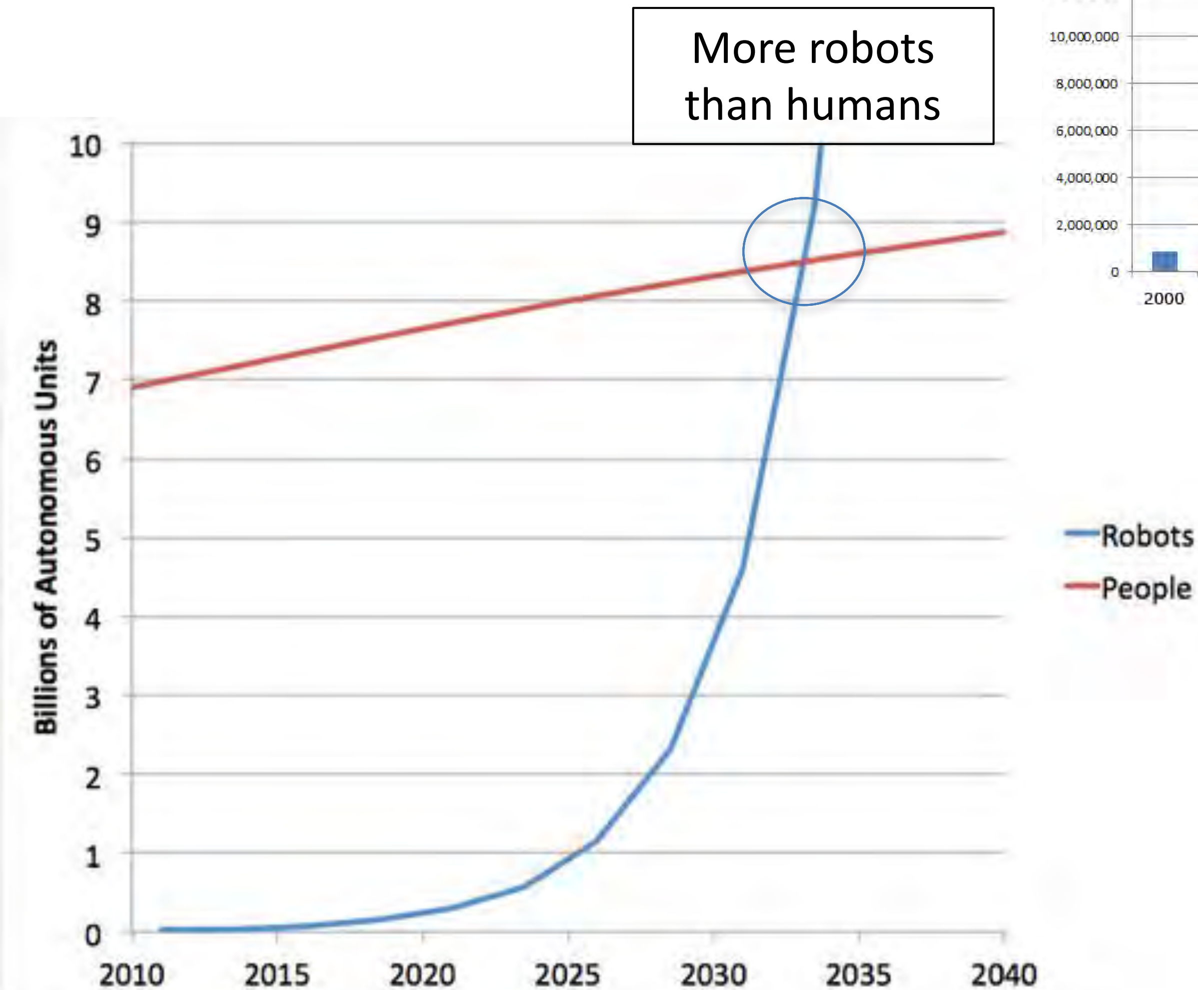
Next Up: Nanorobotic Surgery?

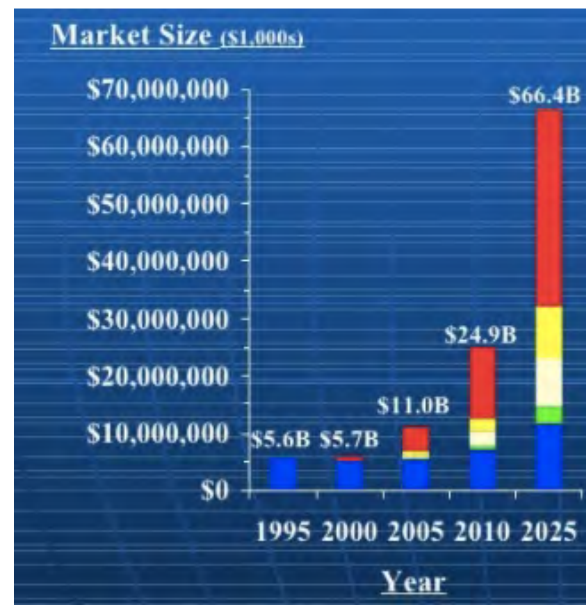


World Robot Population
(Not Counting Micro- or Nano-Robotics)





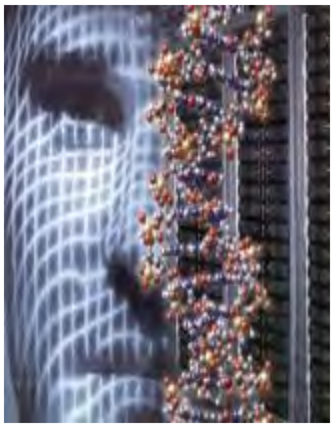




Yellow = Medical Market

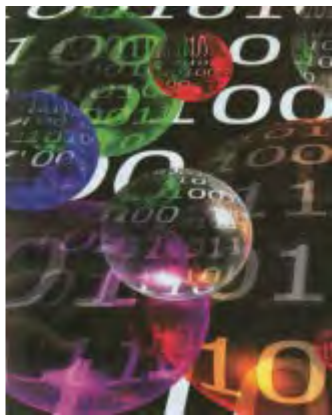
There's Much More Technology Coming

Biotechnology, Synthetic Biology



"Bio-Space"

Ubiquitous Sensing Devices & Social Networks (IoT)



"Connected Space"

Advanced Computing and Modeling

"Cyberspace" and "Simulation Space"

Human-Machine Interactions

"Cognitive Space"

Disruptive Technologies To Come

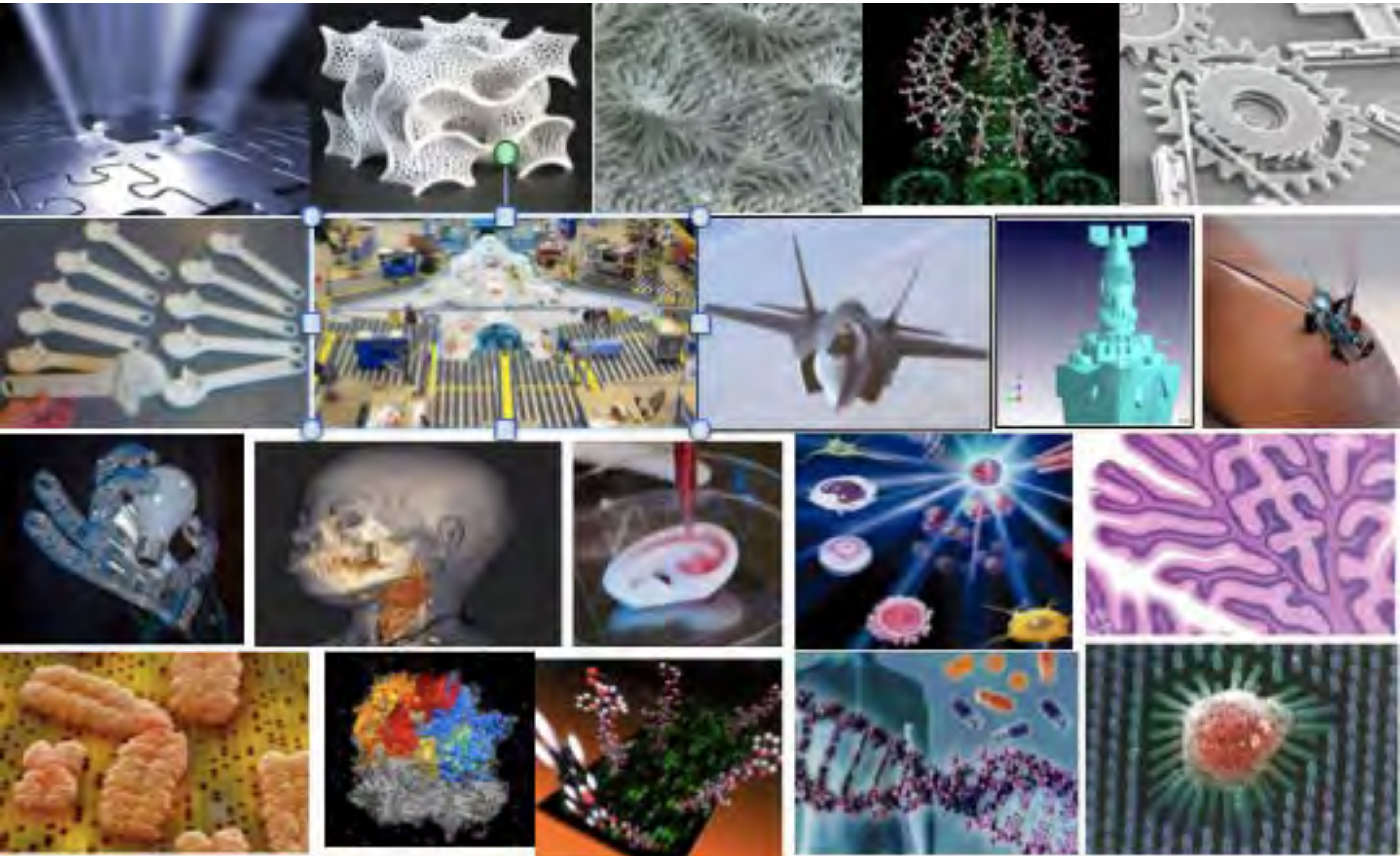
?

"Competition and Opportunity Space"

New Patterns of Technology Fusion, Evolution, and Adoption

Slide courtesy of George Poste

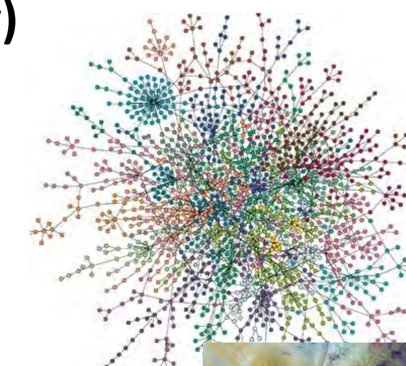
Supported by Advanced Manufacturing, 3-D Fabrication, Nanofabrication and New Assembly Technologies

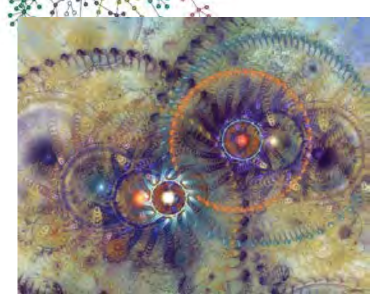


Astonishing Biomedical Insights Enabled by Technology: Quintessential Example Is Cancer Complexity

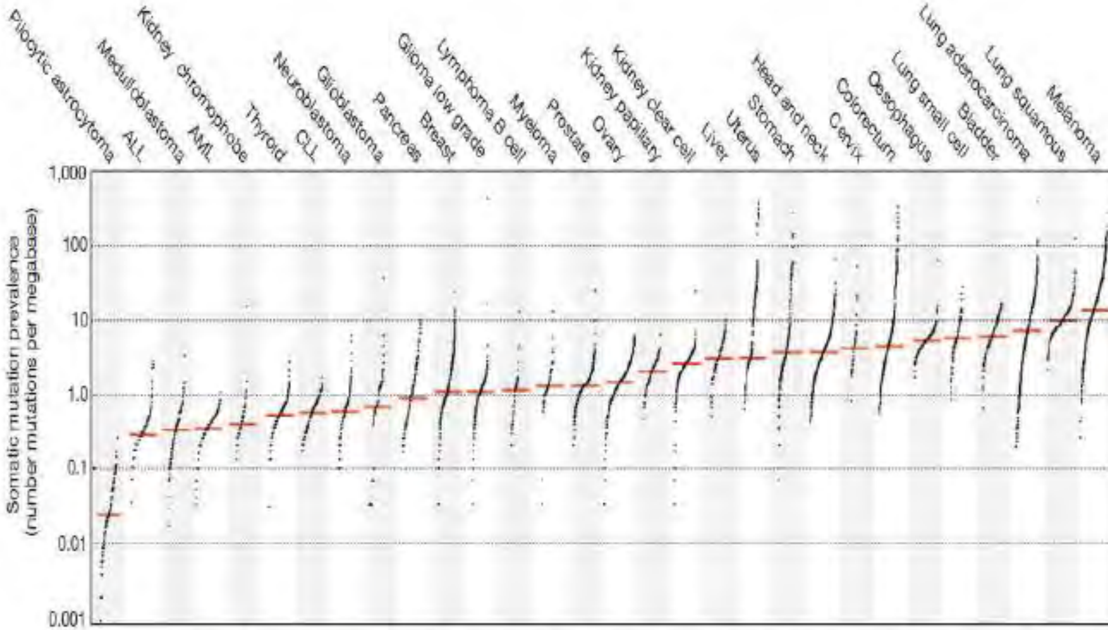
- **Cancer genome complexity revealed: Formidably complex catalog of genomic changes and molecular network disruptions**
  - **Networks are highly interactive and redundant**

- **Cancer evolution exposed: Continued accumulation of genomic alterations generating numerous clones and sub-clones with different genomic alterations and phenotypes (heterogeneity)**
  - **In a patient**
    - **Within a lesion**
    - **Between lesions**
  - **Between patients**
  - **Treatment-driven evolution (selection and fitness)**





Panorama of Extravagant Genomic Alterations in Cancer

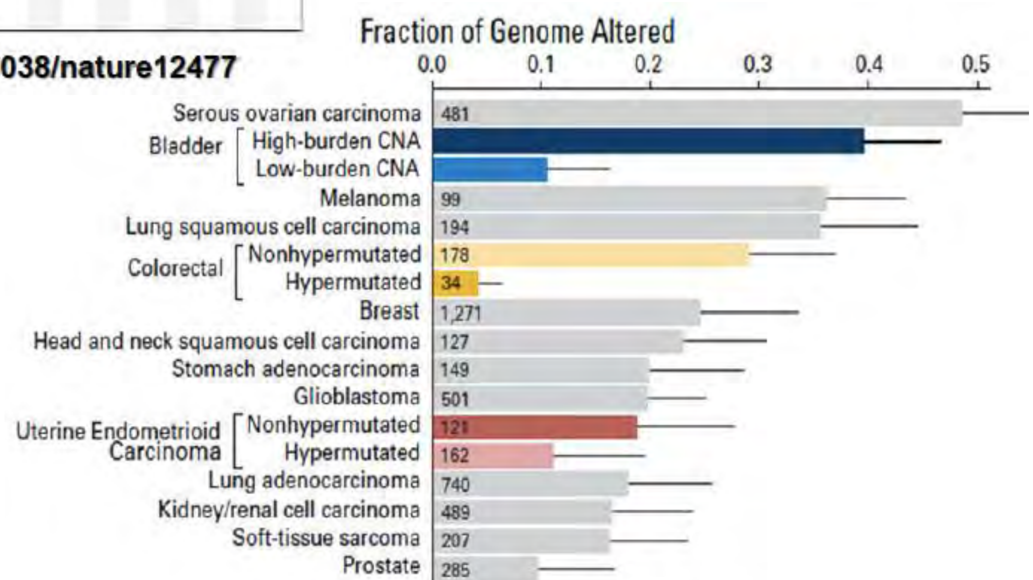


Mutations per megabase tumor DNA (3K megabases in human genome)

Average 10 per megabase for lung cancer and melanoma

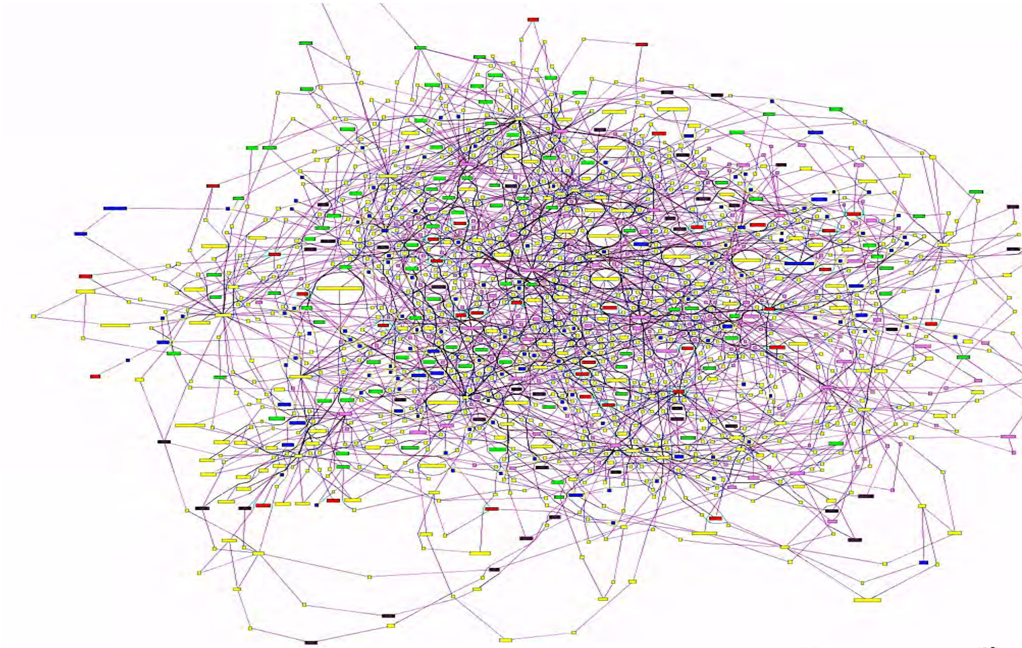
From: L. B. Alexandrove et al. (2013) Nature doi:10.1038/nature12477

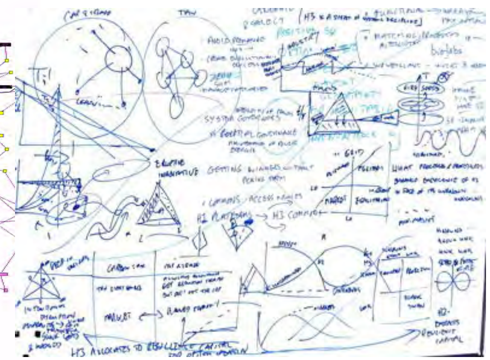
Copy number alterations in solid tumors

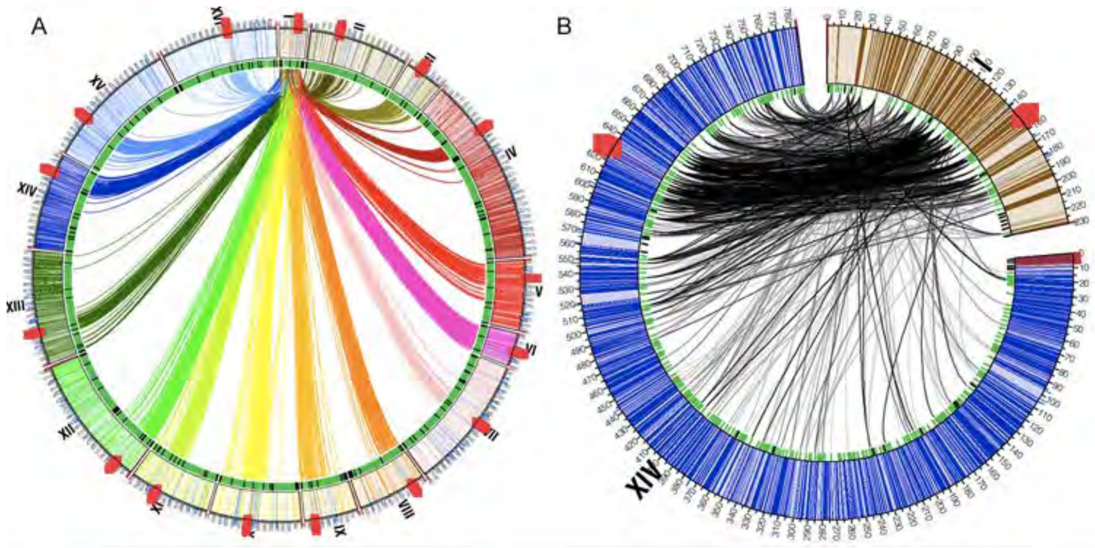


From: G. Iyer et al. (2013) JCO 31, 3133

The Complexity of Gene, Chromosome, and Network Interactions

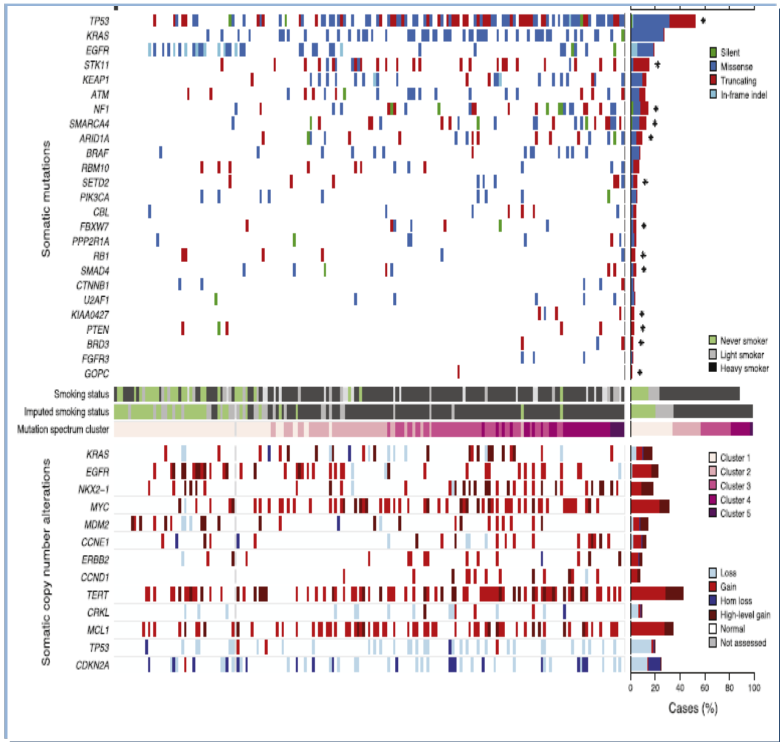






Landscape of Extreme Heterogeneity of Genomic Alteration in Lung Cancer

Each column is a separate cancer



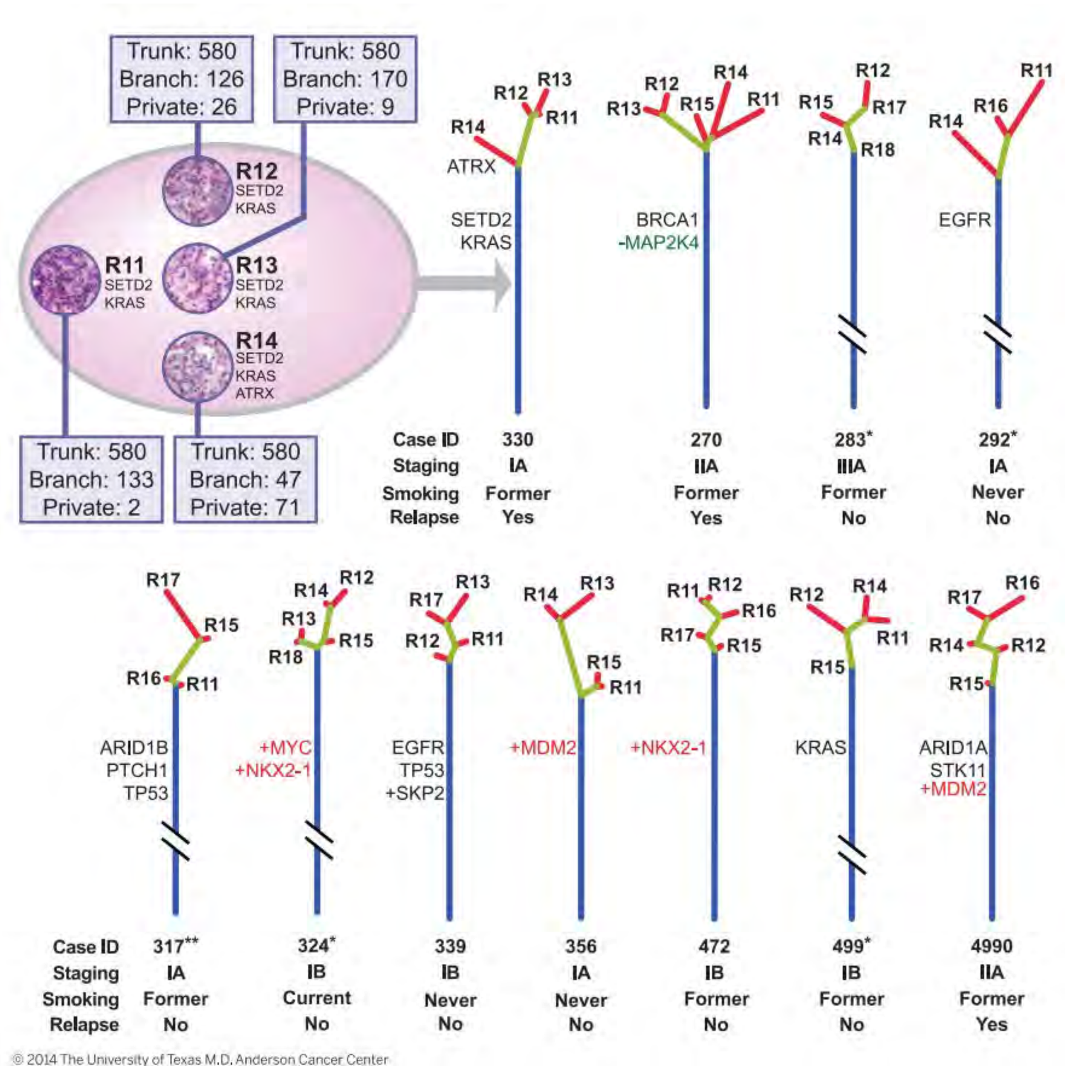
Mutations in Individual Non-small Cell Lung Cancer

Drug Targets in Individual Non-Small Cell Lung Cancers

- “Malignant snowflakes”: each cancer carries multiple unique mutations and other genome perturbations (such as epigenomic changes)
- Disturbing implications for therapeutic ‘cure’ and development of new Rx

(Cell 2012. Vol. 150: pp. 1107 and 1121)

Phylogenetic Profiles
of Intratumoral Clonal Heterogeneity in 11 Lung Cancers:

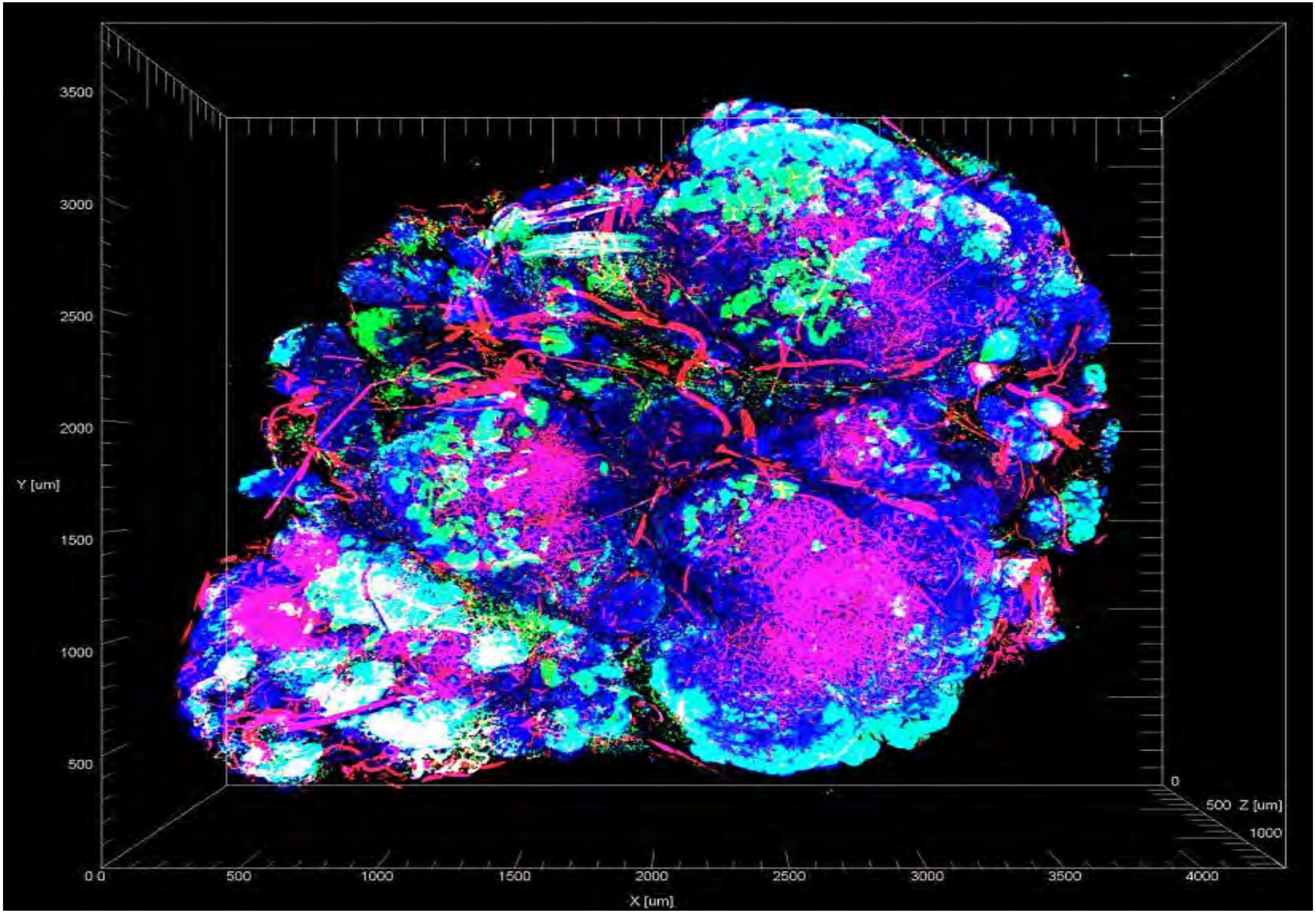


DIFFERENT CLONES IN SAME CANCER

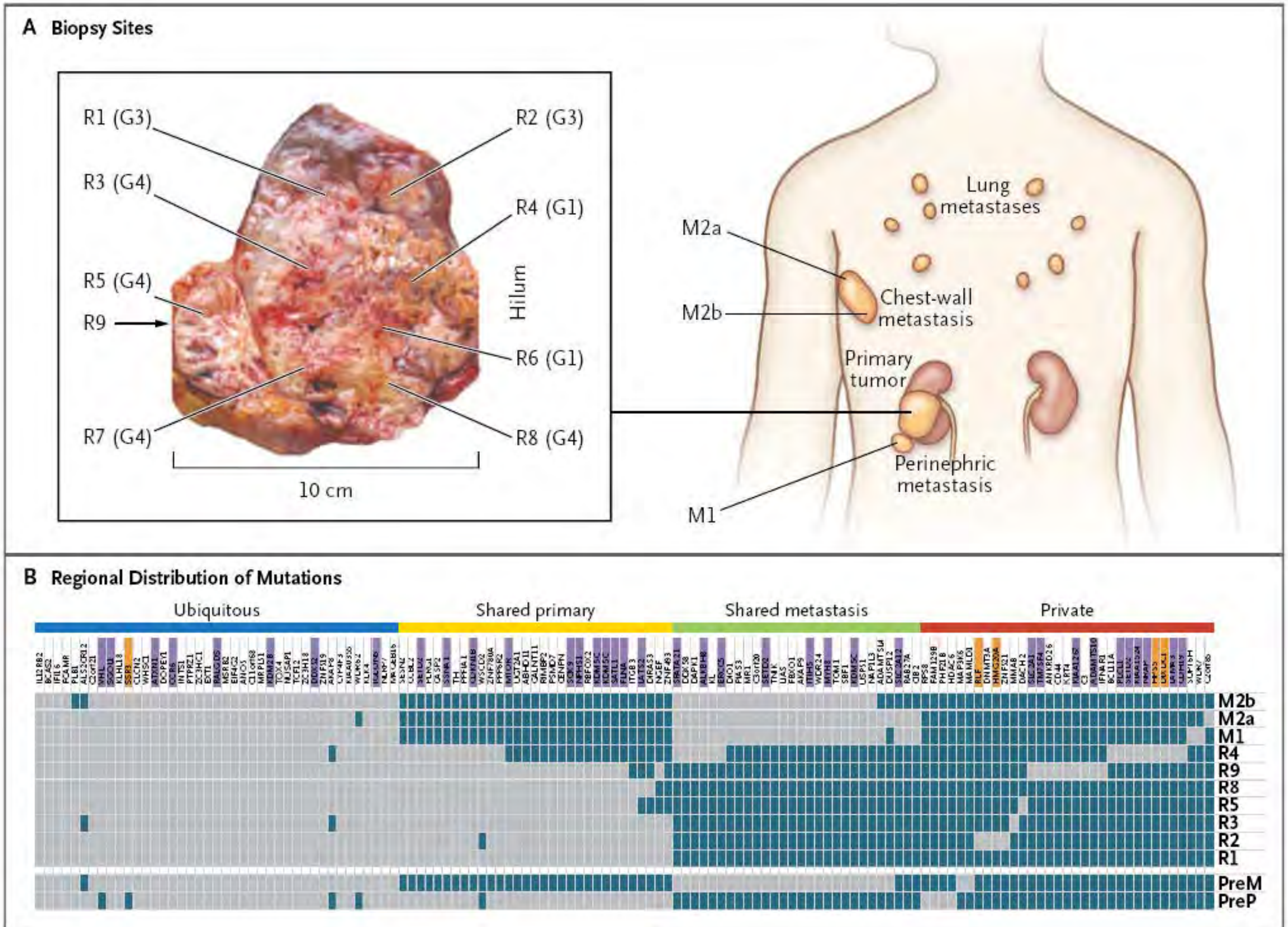
- **Trunk (Blue): Mutations present in all regions**
- **Branch (Green): Mutations present in some regions**
- **Private (Red): Mutations present in only one region**

Zhang et al. Science 2014; Oct 10

Mapping Tumor Heterogeneity



Intra-Tumoral Genetic Heterogeneity: Multiple Regions of Primary Kidney Cancer and 3 Different Metastases



Gerlinger et al. NEJM 2012;366:883-92

Malignant Snowflakes

Review

How many molecular subtypes? Implications of the unique tumor principle in personalized medicine

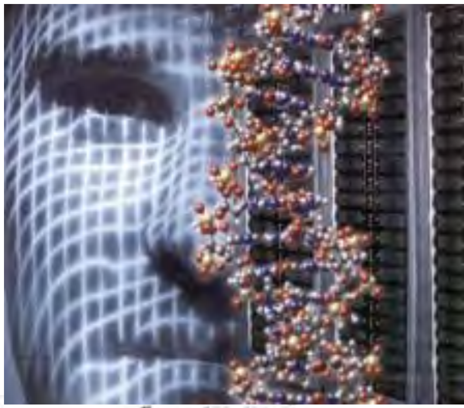
Shuji Ogino, Charles S Fuchs & Edward Giovannucci

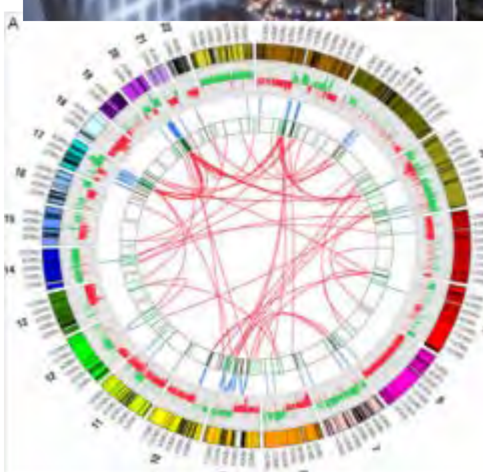
Pages 621-628 | Published online: 09 Jan 2014

Essentially, each tumor possesses its own unique characteristics in terms of molecular make-up, tumor microenvironment and interactomes within and between neoplastic and host cells. Starting from the

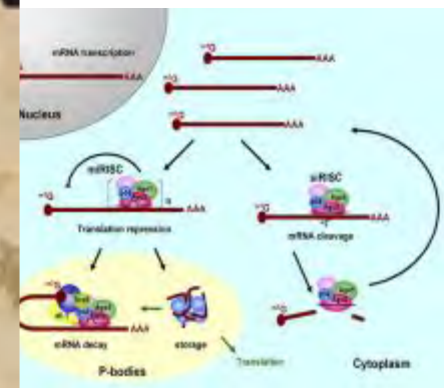
Integrating the … e Normal and

Genomics





Network Regulatory Mechanisms

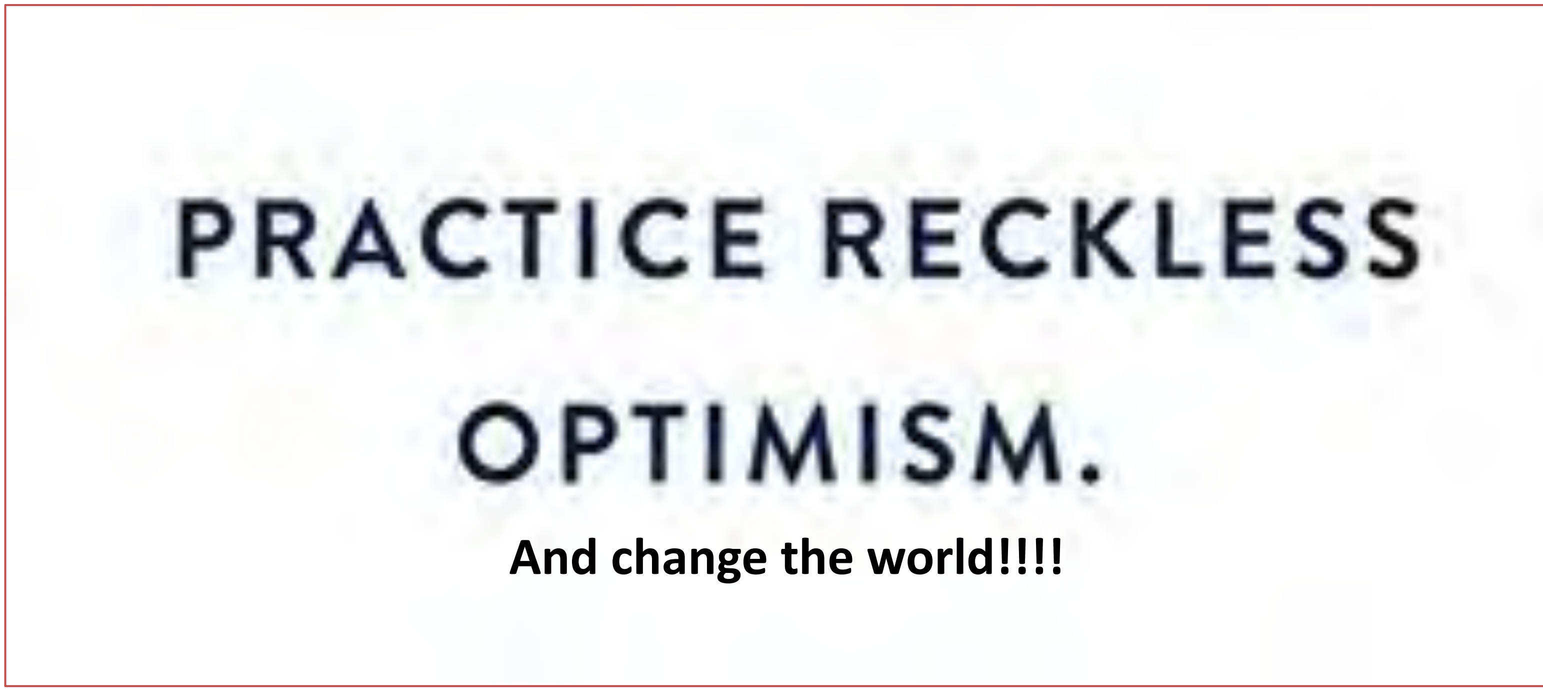


ID of Causal Relat… Network Perturbat…

…d Signatures of Disease …n to Disease

Closing Thoughts…….

- Everything I have talked about there today was non-existent when I became a pathologist.



And change the world!!!!

The Future of Pathology: Complexity, Convergence, and Change

Carolyn Compton, MD, PhD
Professor of Life Sciences, Arizona State University
Professor of Laboratory Medicine and Pathology, Mayo Clinic School of Medicine
Adjunct Professor of Pathology, The Johns Hopkins School of Medicine
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CMO, Complex Adaptive Systems Institute

NBDA
National Biomarker Development Alliance

ASU Complex Adaptive Systems
Arizona State University

Brindley Lecture
UTMB Department of Pathology
Galveston, TX
May 15, 2017