ASU COMPLEX ADAPTIVE SYSTEMS
ARIZONA STATE UNIVERSITY

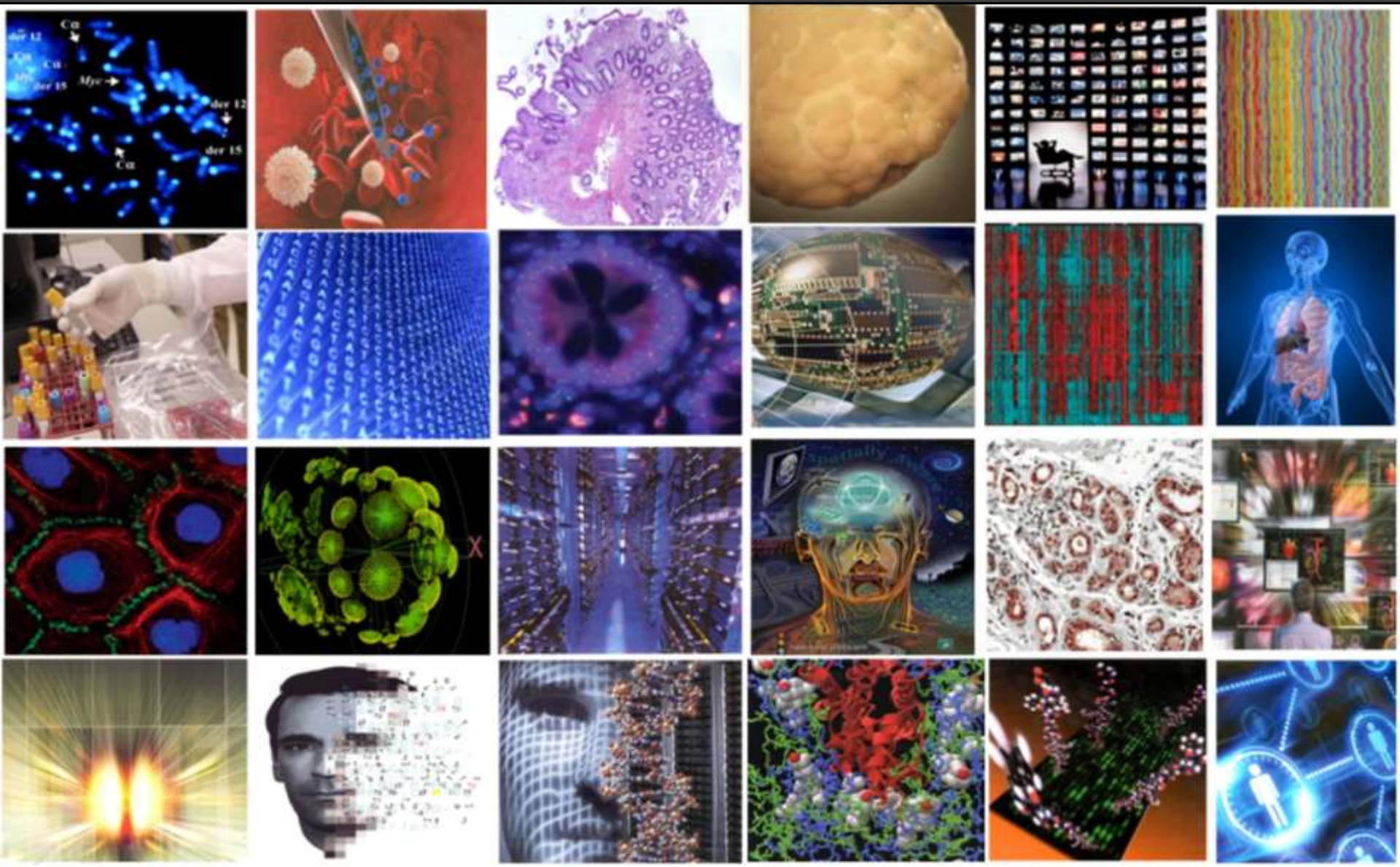
Transformational Technologies in Biomedical R&D and Healthcare Delivery

Dr. George Poste
Chief Scientist, Complex Adaptive Systems
and Del E. Webb Chair in Health Innovation
Arizona State University
480-727-8662 george.poste@asu.edu
www.casi.asu.edu

Hever 18, Lansdowne, VA

4 May 2013

Slides available @ http://casi.asu.edu/



The Imperative to Achieve Sustainability in Healthcare: Societal (Economic) and Individual (Wellness)

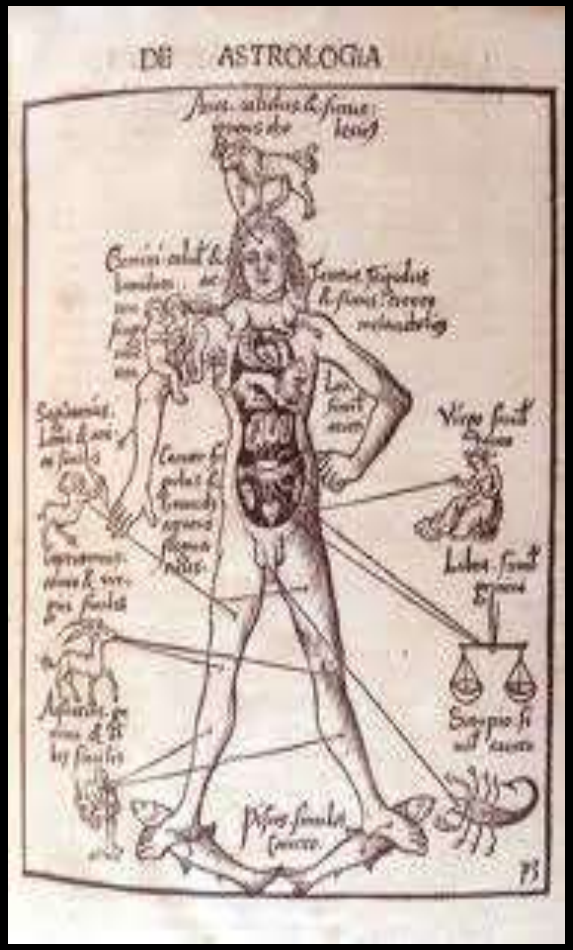
Balancing Infinite Demand Versus Finite Resources in an Era of Economic Constraint

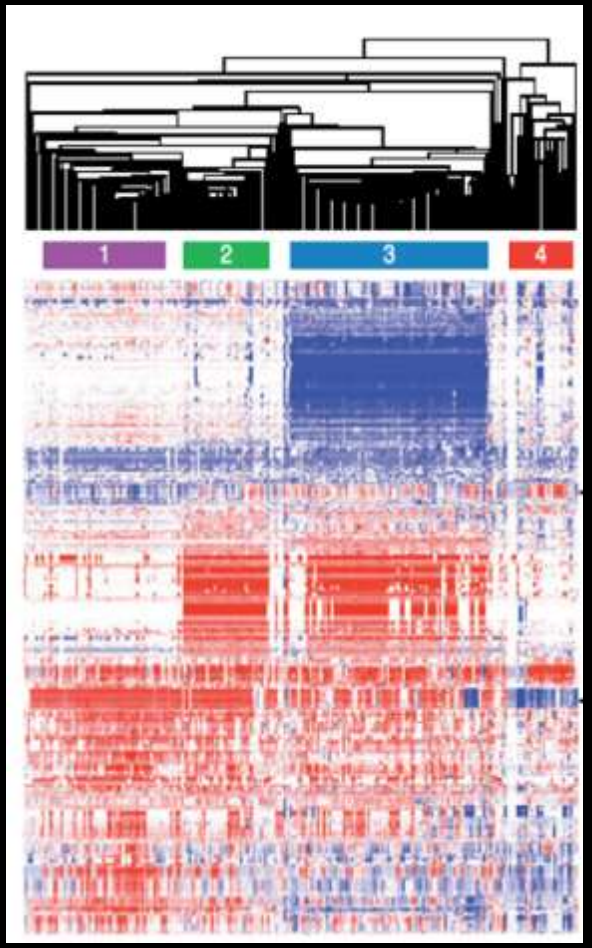
More Effective Management of Chronic Disease in Aging Populations

Shift From a "Do More, Bill More"(FFS) Delivery System To Integrated Care and Managing Individual Risk to Improve Outcomes and Control Cost

Technology, Innovation and New Value Propositions

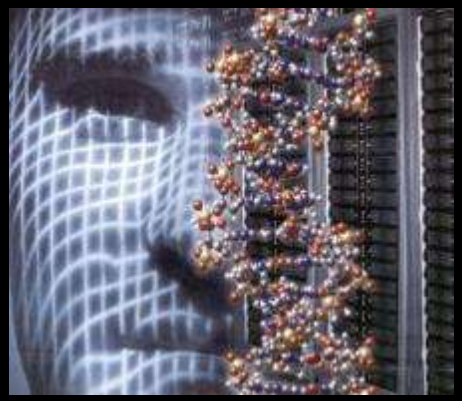
Medical Progress:
From Superstitions to Symptoms to Signatures



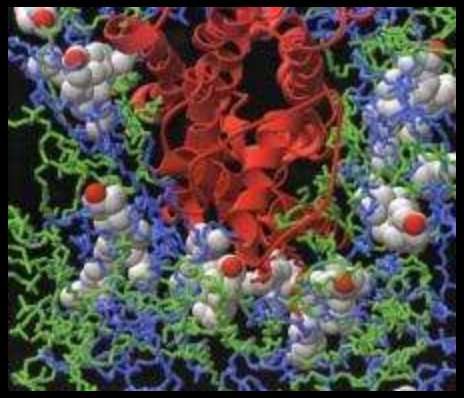


Mapping The Molecular Signatures of Disease: The Intellectual Foundation of Rational Diagnosis and Treatment Selection

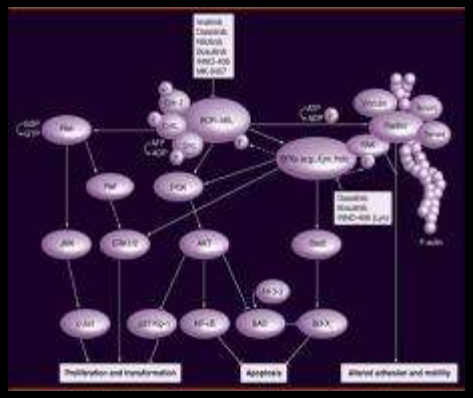
Genomics



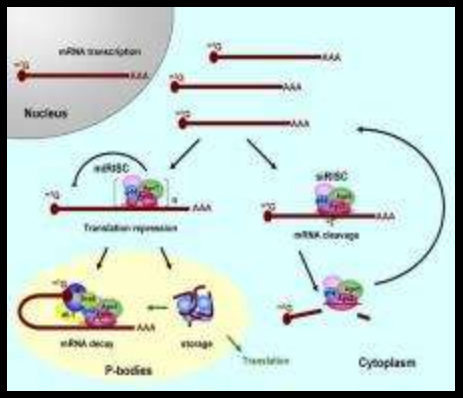
Proteomics

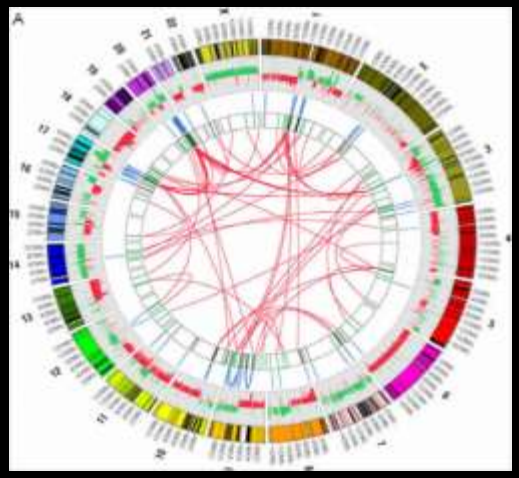


Molecular Pathways and Networks



Network Regulatory Mechanisms

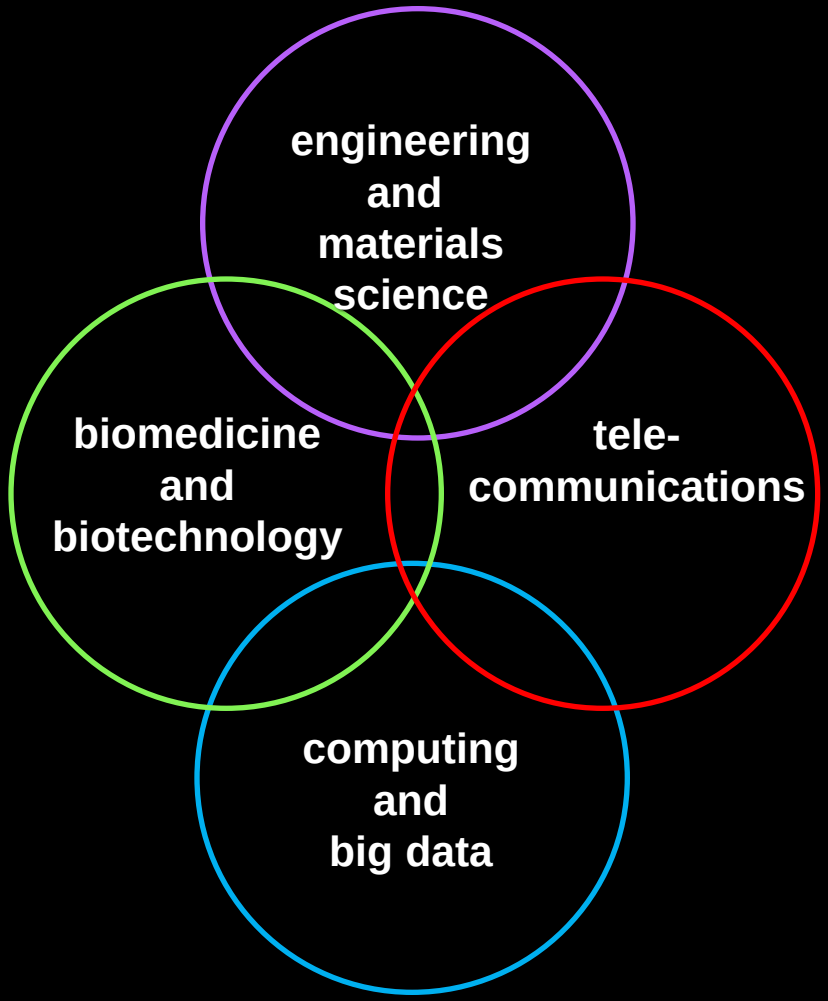




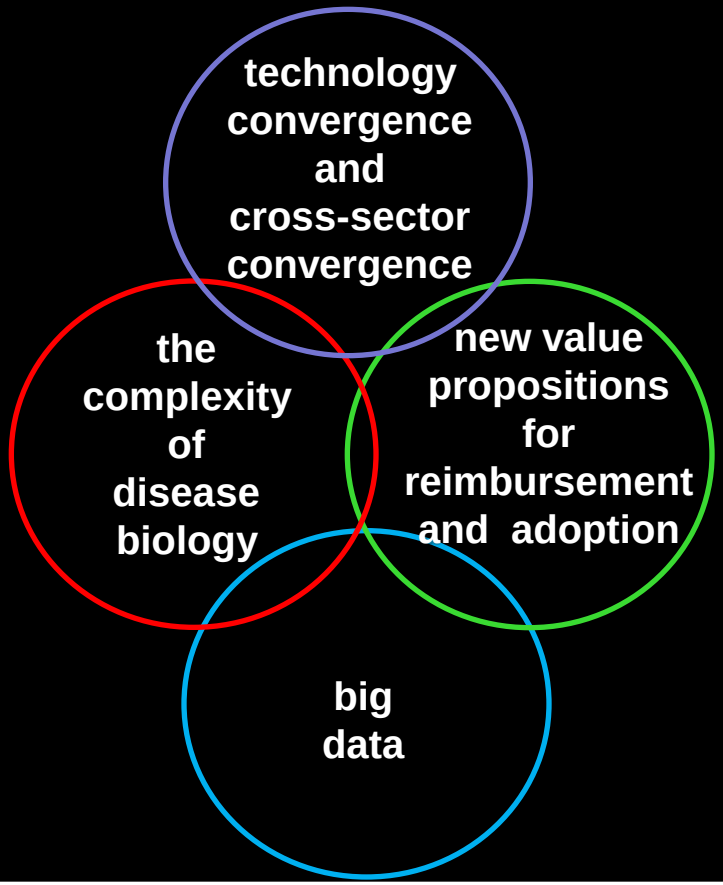
ID of Causal Relationships Between Network Perturbations and Disease

Patient-Specific Signals and Signatures of Disease or Predisposition to Disease

Technology Convergence and Disruption in Healthcare



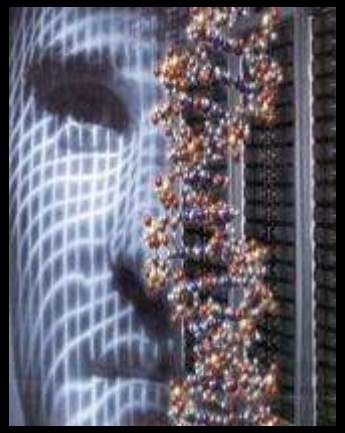
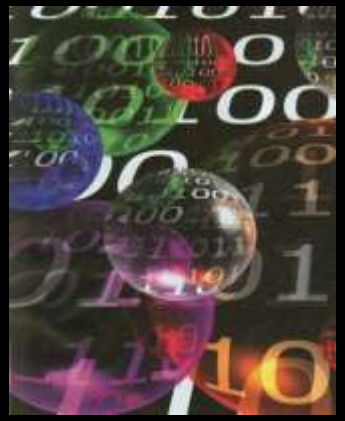
“Thinking Beyond the Pill”
Leveraging Rx Value In Broadened Healthcare Domains



Integrated Solutions

Integrated Solutions
Rx, Dx, Devices, HIT and ACKM

Accelerating Convergence: Conceptual, Technological, Informational and Commercial

Biomedicine, Biotechnology, Synthetic Biology	Ubiquitous Sensing/ Devices & Social Networks	Advanced Computing and Modeling	Neurosciences and Human-Machine Interactions	Disruptive Technologies
				?
"Bio-Space"	"Connected Space"	"Cyberspace" and "Simulation Space"	"Cognitive Space"	"Competition and Opportunity Space"

New Patterns of Technology Fusion, Evolution and Adoption

New Knowledge Networks

New Participants

New Markets and Business Models

Transformational Technologies and Major Challenges in Biomedical R&D and Healthcare: Understanding the Design and Control of Complex Networks

- (epi)genotype
- molecular networks and cellular specificity
- genome engineering networks

→ phenotype (phenomes)

→ network perturbation/ dysregulation in disease

→ cellular reprogramming and synthetic biology

- brain networks

→ cognition and behavior

→ brain machine interface technology

- digital networks

→ data-intensive R&D and new knowledge networks

→ new products and services

→ social media and healthcare

→ implications for education, scientific methods

Will Low Cost Whole Genome Sequencing Change Everything?

The $1000 (or less) Whole Genome Sequence (WGS)

The $? Interpreted WGS

The $? Reimbursed WGS for Clinical Use

Techno-optimism and the Seduction of New Technologies: Omnipresent Hype and Herd Mentalities

Genome Sequencing: The Competitive Landscape is Crowded

WGS:
The Protracted Journey to Routine Clinical Utility in Major Multigenic Diseases?

- closing current ‘holes’ to get to ‘wholes’ (Heidi Rehm)
- still major technical challenges in capturing ***complete*** and ***accurate*** WGS
- actionable data
- unraveling complex epistatic and epigenetic events in late-onset multigenic diseases
- size of clinical cohorts needed to validate actionable correlations for regulatory approval
- reimbursement
- ‘the incidentalome’

The Utility Matrix for Genome Sequencing (2013)

<table>
<tr><th>Decision</th><th>Single Genes</th><th>Gene Panels</th><th>WES</th><th>WGS</th></tr>
<tr><td rowspan="3">actionable variants</td><td>inherited and rare disorders</td><td>Rx targets: response/ resistance</td><td rowspan="3">late onset multi-genic diseases</td><td>microbes</td></tr>
<tr><td>carrier screening</td><td>PGx & Rx adverse events</td><td>rare diseases</td></tr>
<tr><td>NIPT</td><td>NIPT aneuploidy</td><td></td></tr>
<tr><td rowspan="3">informative but not yet actionable</td><td rowspan="3"></td><td>potential Rx targets but no Rx</td><td colspan="2">multi-genic neurodev. disorders</td></tr>
<tr><td rowspan="2"></td><td colspan="2">GWAS</td></tr>
<tr><td></td><td></td></tr>
<tr><td>unknown significance</td><td></td><td></td><td></td><td></td></tr>
</table>

WGS and Claims Outstripping Current Analytical Capabilities for Disease Predisposition Risk Profiling (PDx)

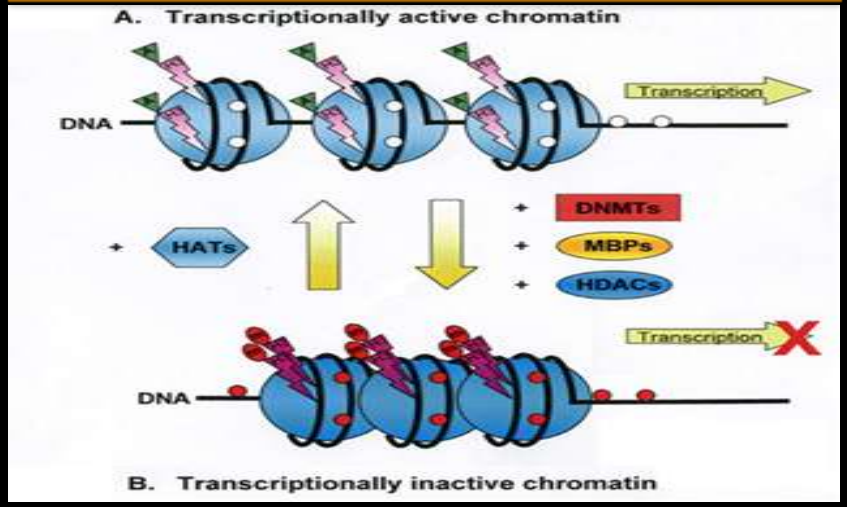
Understanding Genome Organization and Regulation

- topology
- role of non-coding regions and the RNA universe
- TF-binding and chromatin states in cell differentiation and disease

The Epigenome

Effect of Maternal Diet/Stress/Rx exposure on Germ Line Genome (+ trans-three-generational?)

Modulation of Gene Expression/Regulation by Environmental Factors, Xenobiotics and Rx (The Exposome)



IHEC
International Human Epigenome Consortium

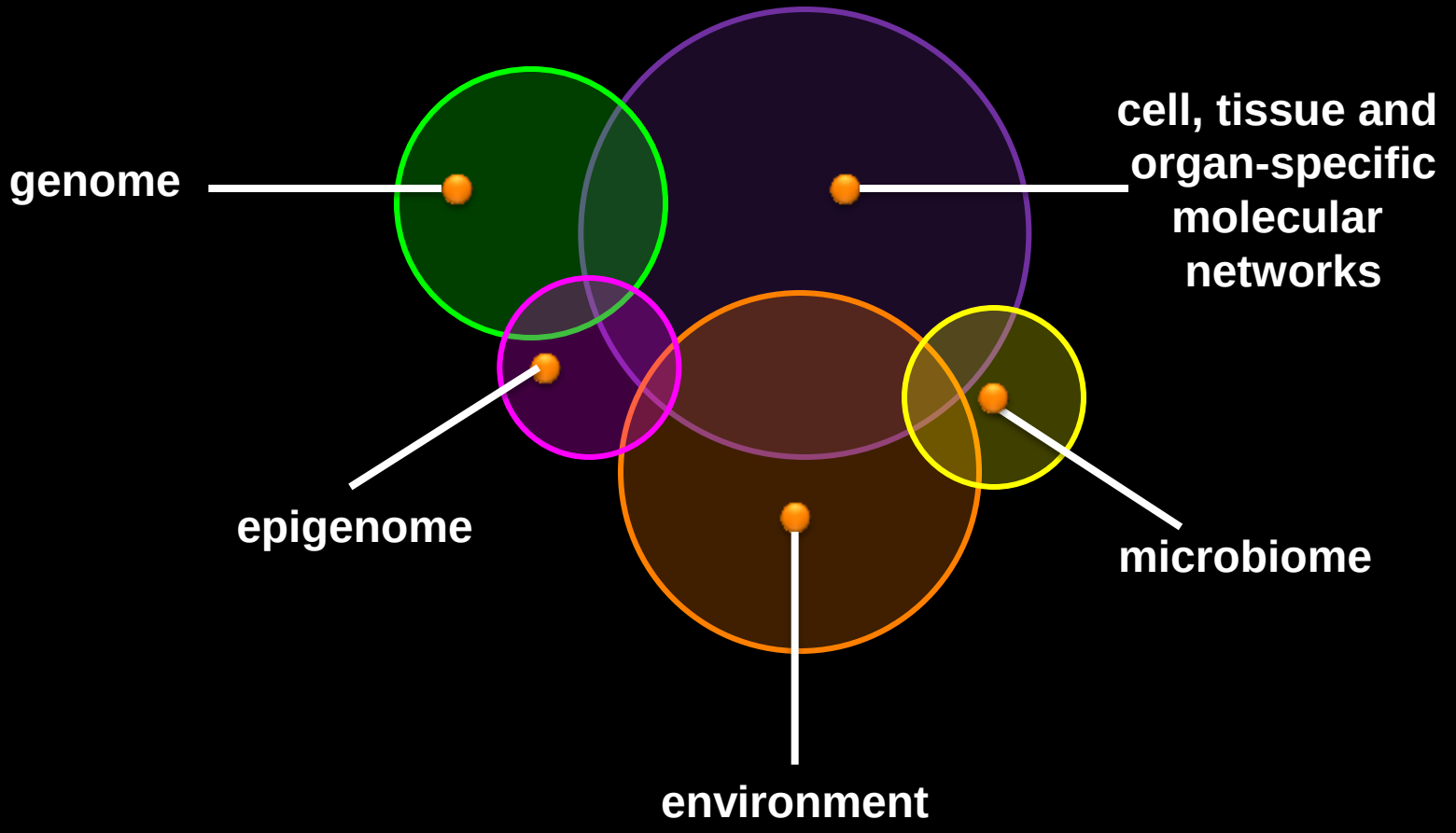
International Human Epigenome Consortium

- **1000 reference genomes by 2020**

project blueprint

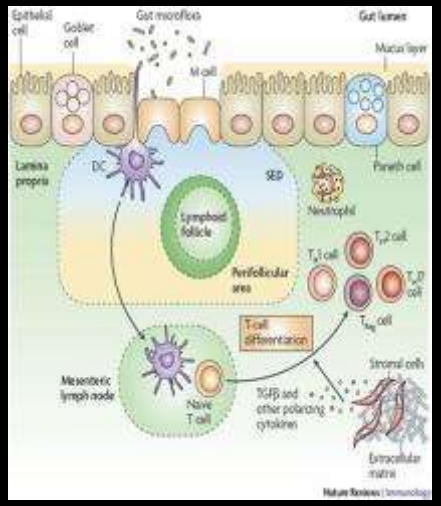
- **launch September 2011 with €30-million**
- **map epigenome in 60 human blood cell classes and neoplastic counterparts**

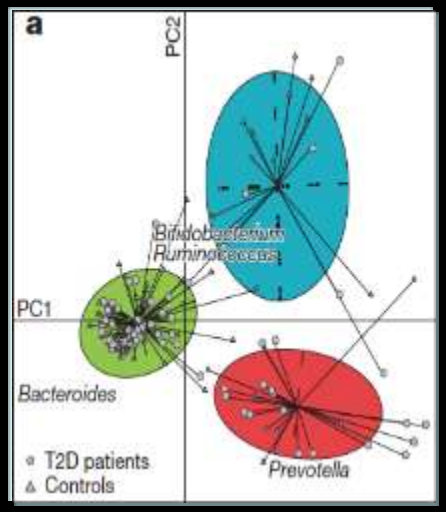
The Complex Interplay Between the Genome, Molecular Networks and Environmental Factors

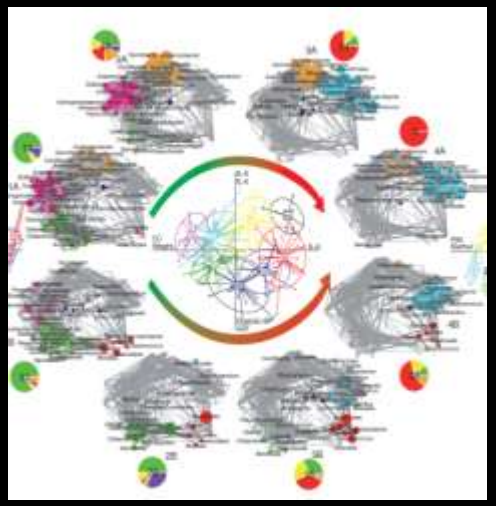


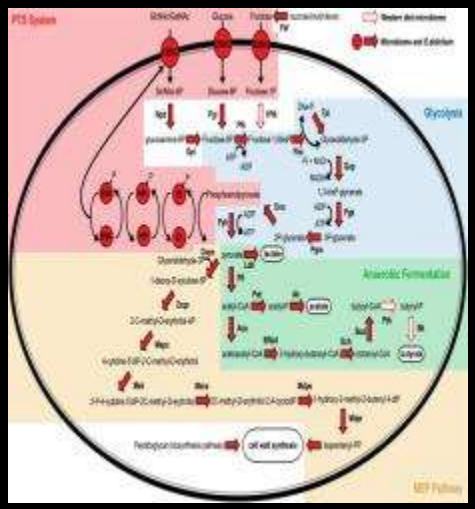
Commensal Microbiomes: The “Frenemy Within”

Metagenome-wide Association Studies (MGWAS)









Immune-Mediated GI Diseases

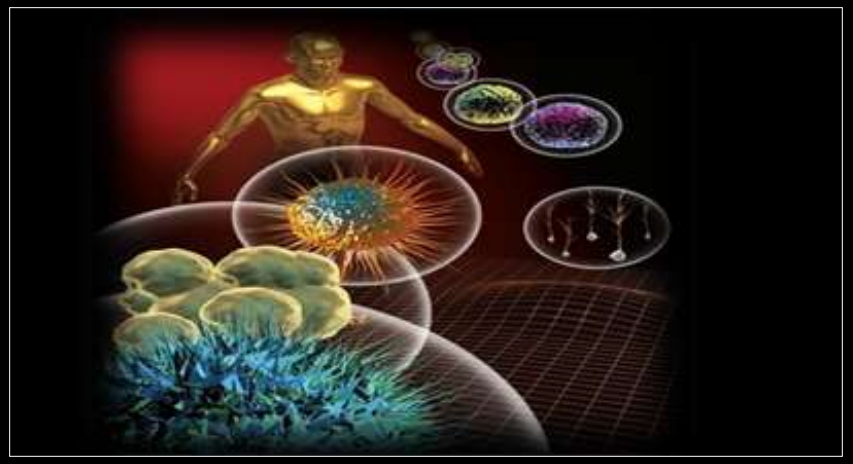
Type 2 Diabetes Profile

Aging Metabolism and Fragility

Metabolic Activation of Carcinogens/ Pollutants

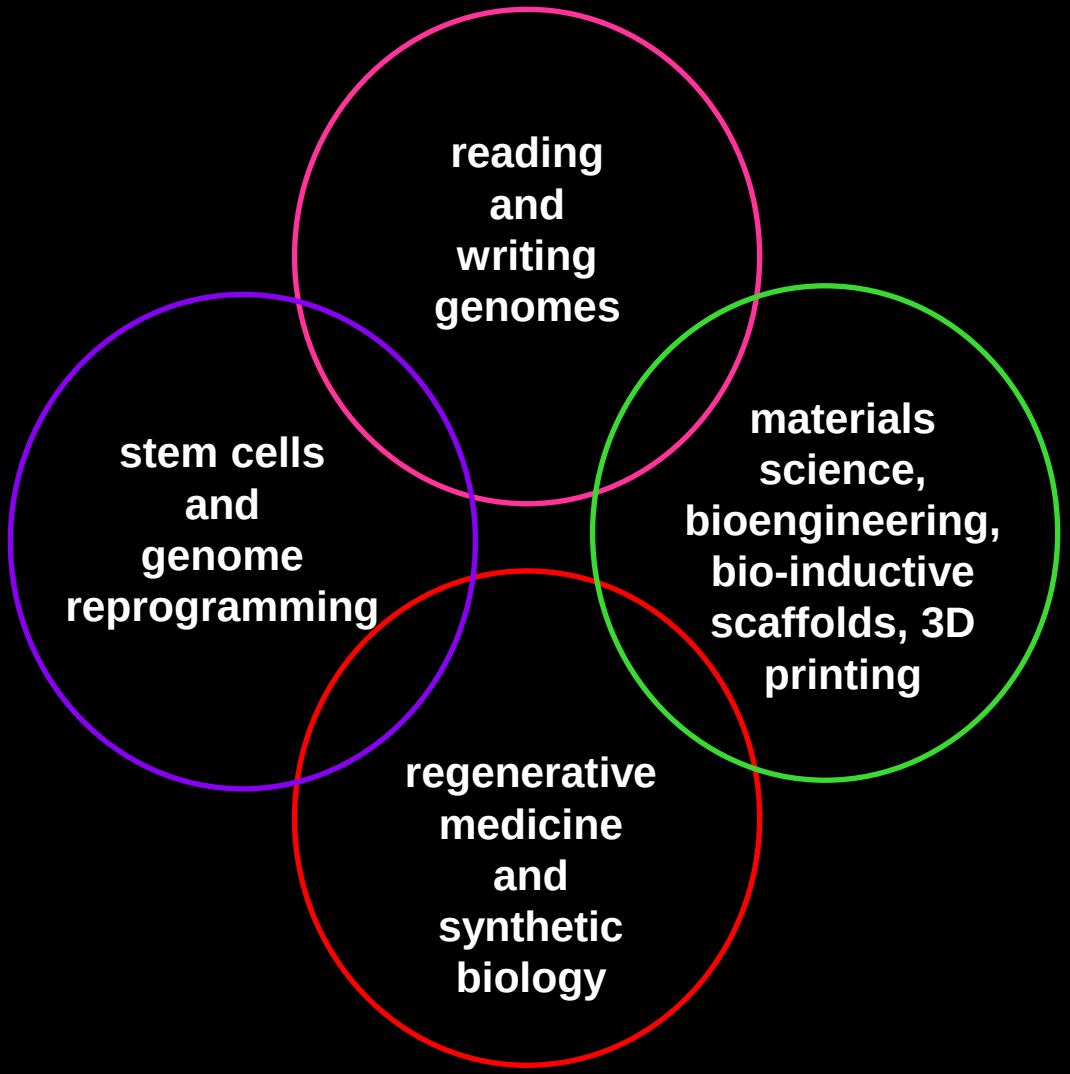
Make Me……

Reprogramming ESCs/iPSCs to Generate Specific Cell Lineages as Committed Precursors or End-Stage Differentiated Cells

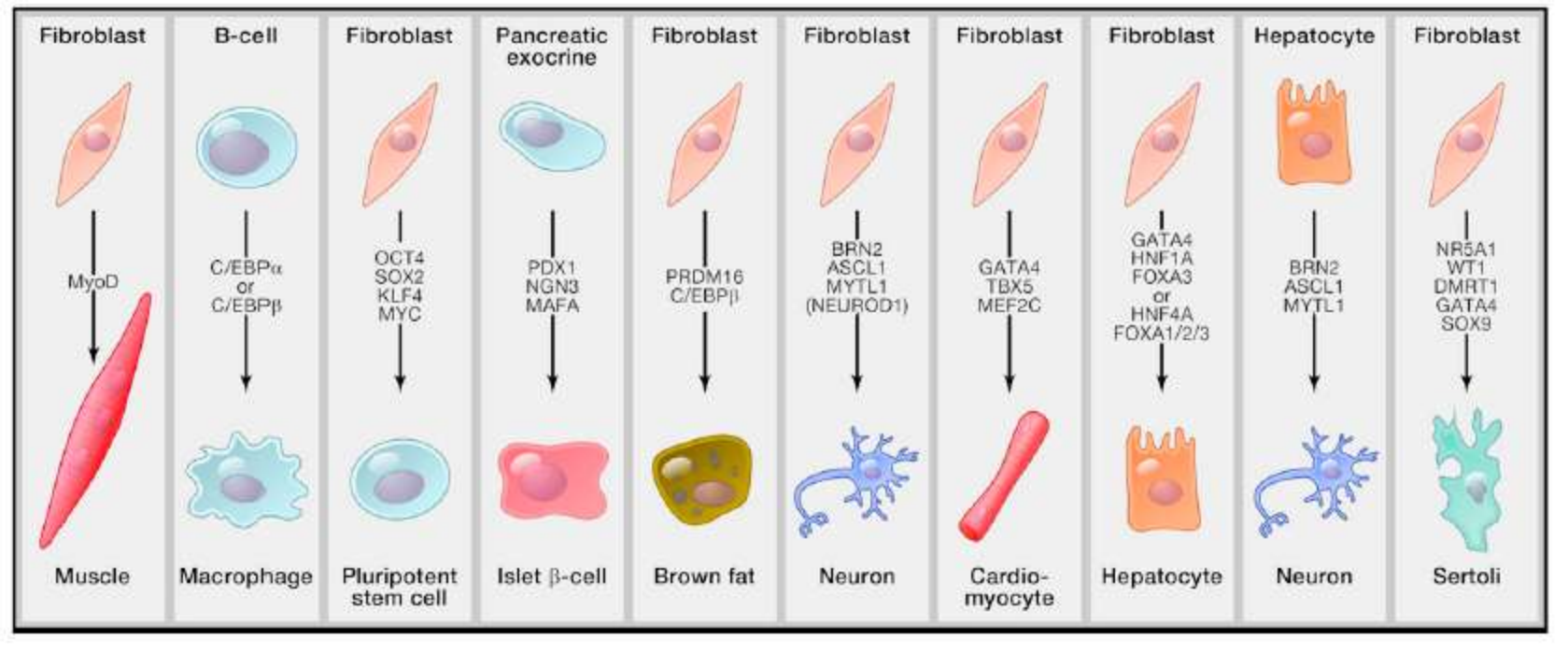


(Re)Building Complex Histiotypic Structures with Full Homeostatic Controls

Make Me……


reading and writing genomes
stem cells and genome reprogramming
materials science, bioengineering, bio-inductive scaffolds, 3D printing
regenerative medicine and synthetic biology

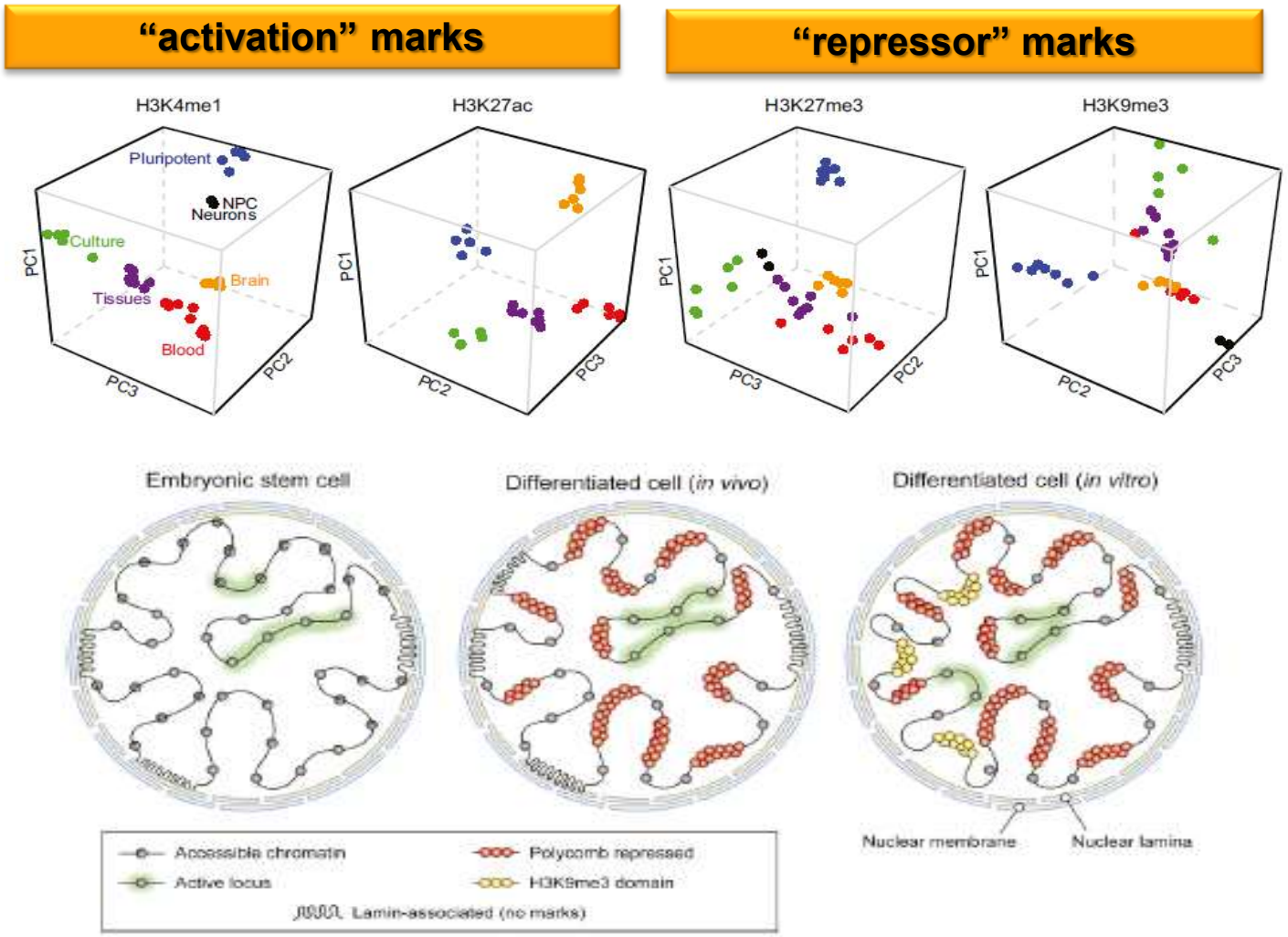
Master Transcriptional Regulators and Reprogramming Factors in Mammalian Cell Lineages



From: T. I. Lee and R. A. Young (2013) Cell 152, 1237

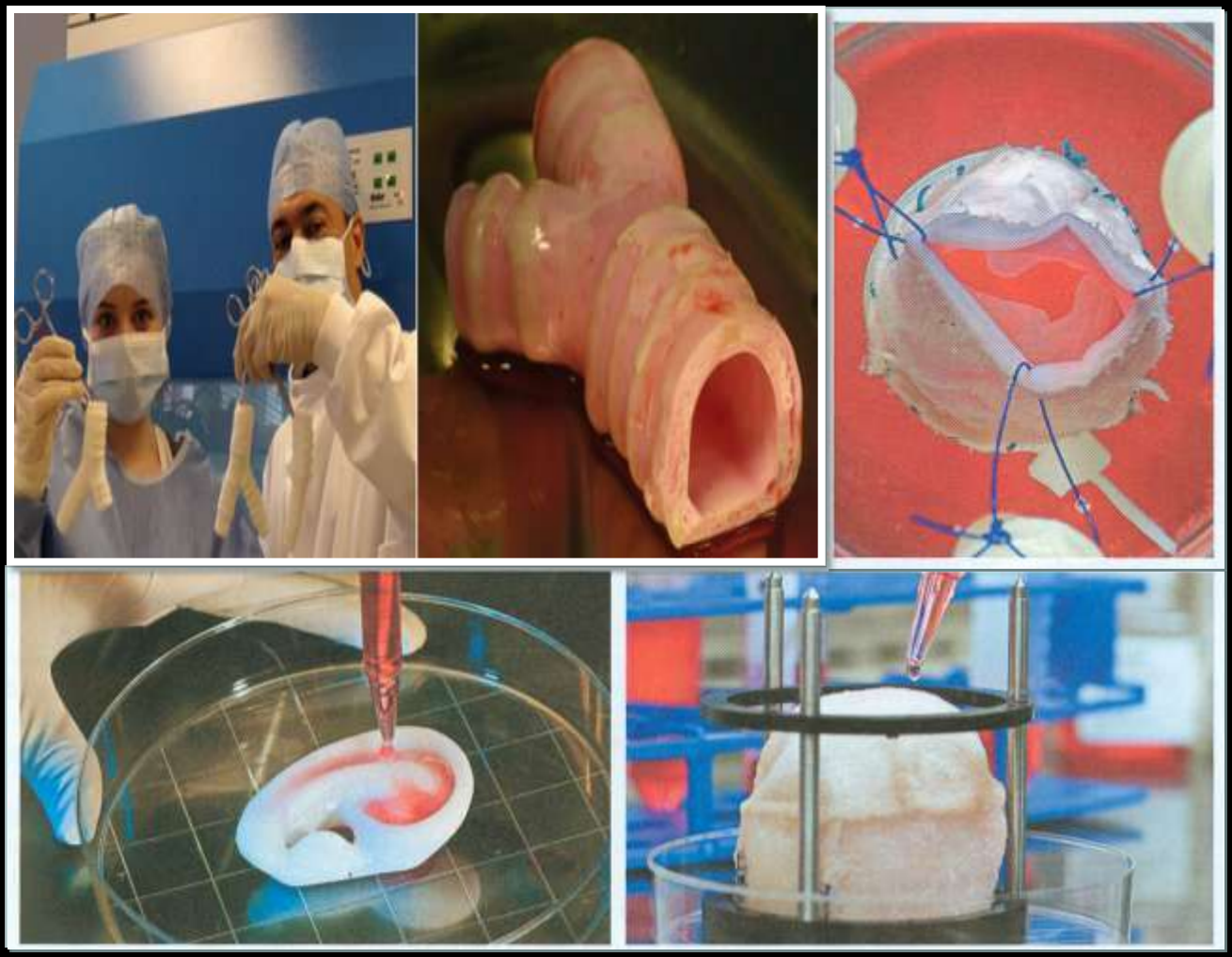
Validation of (Epi)Genomic Fidelity for Therapeutic Uses

Analysis of Chromatin-State Landscapes for ESCs/iPSCs, Tissues In Vivo, and Primary Cell Cultures



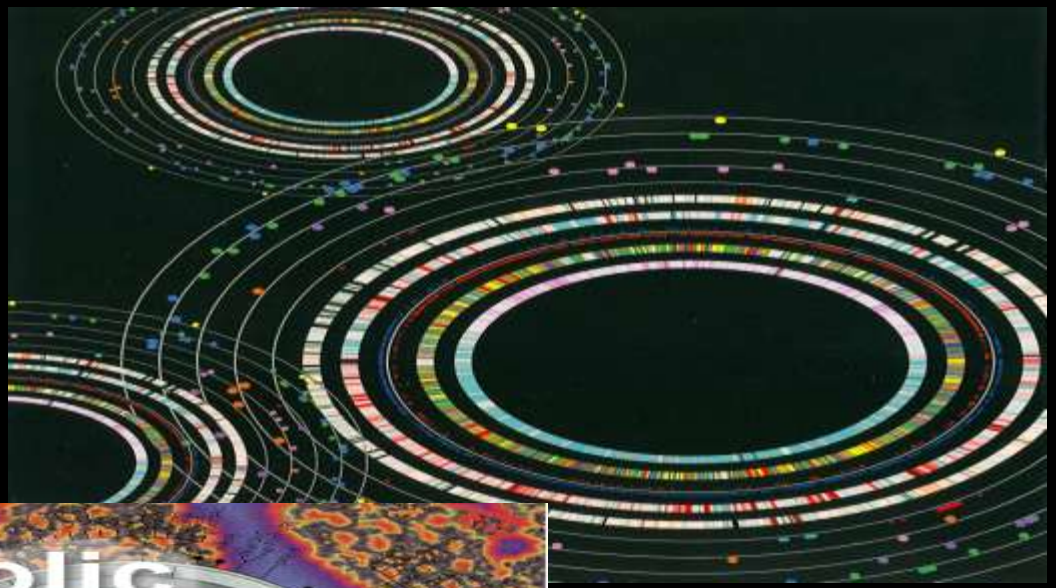
From: J. Zhu et al. (2013) Cell 152, 642

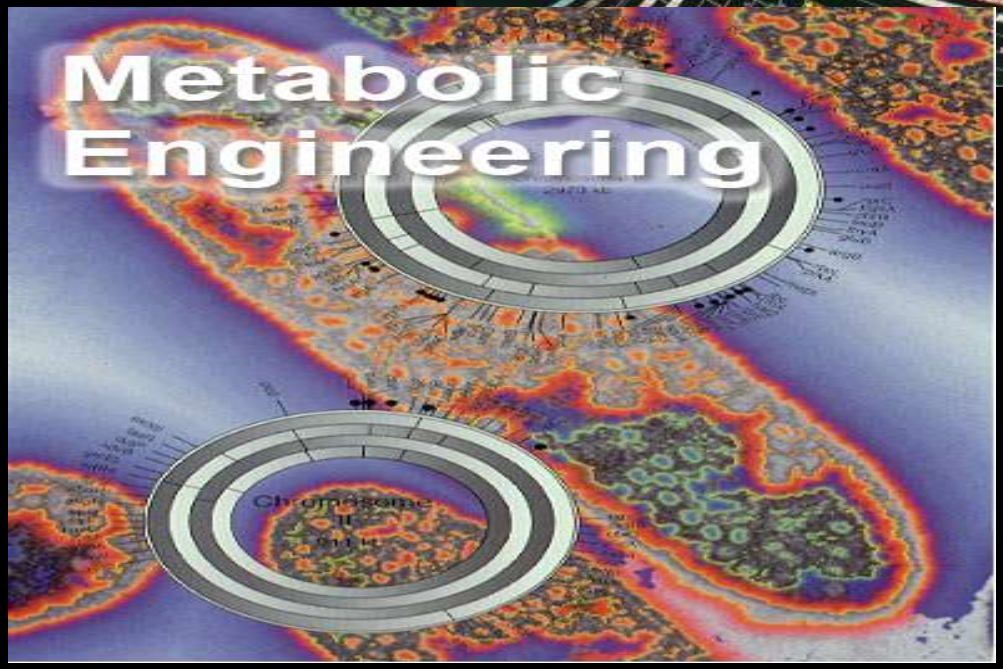
Seeding of Autologous Cells Onto Biocompatible Scaffolds to Generate Implantable Organ-Mimetic Structures



Synthetic Biology: Engineering Microbial Genomes

Programmable Genomes





A New Industrial Ecology and Novel Biosyntheses


华大基因
BGI


AGRAQUEST
better food. better world.


RaNA
Therapeutics


MONSANTO


atlasventure


THE UNIVERSITY OF CALIFORNIA
LET THERE BE LIGHT
DAVIS


PACIFIC
BIOSCIENCES


BAYER


Sapphire
Energy


Bayer CropScience


syngenta

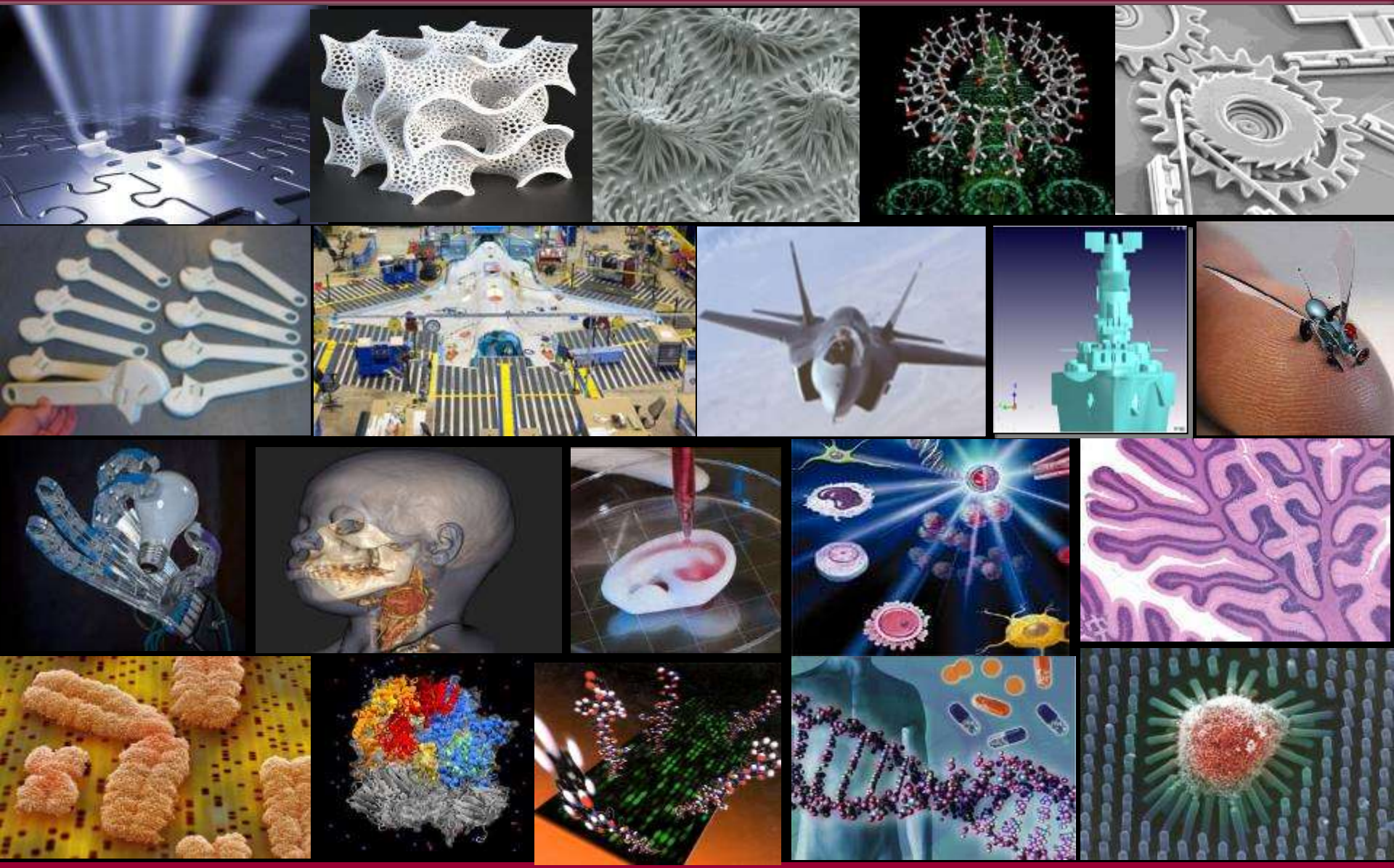

deVGen


PASTEURIA
bioscience


BECKER
UNDERWOOD


BASF
The Chemical Company

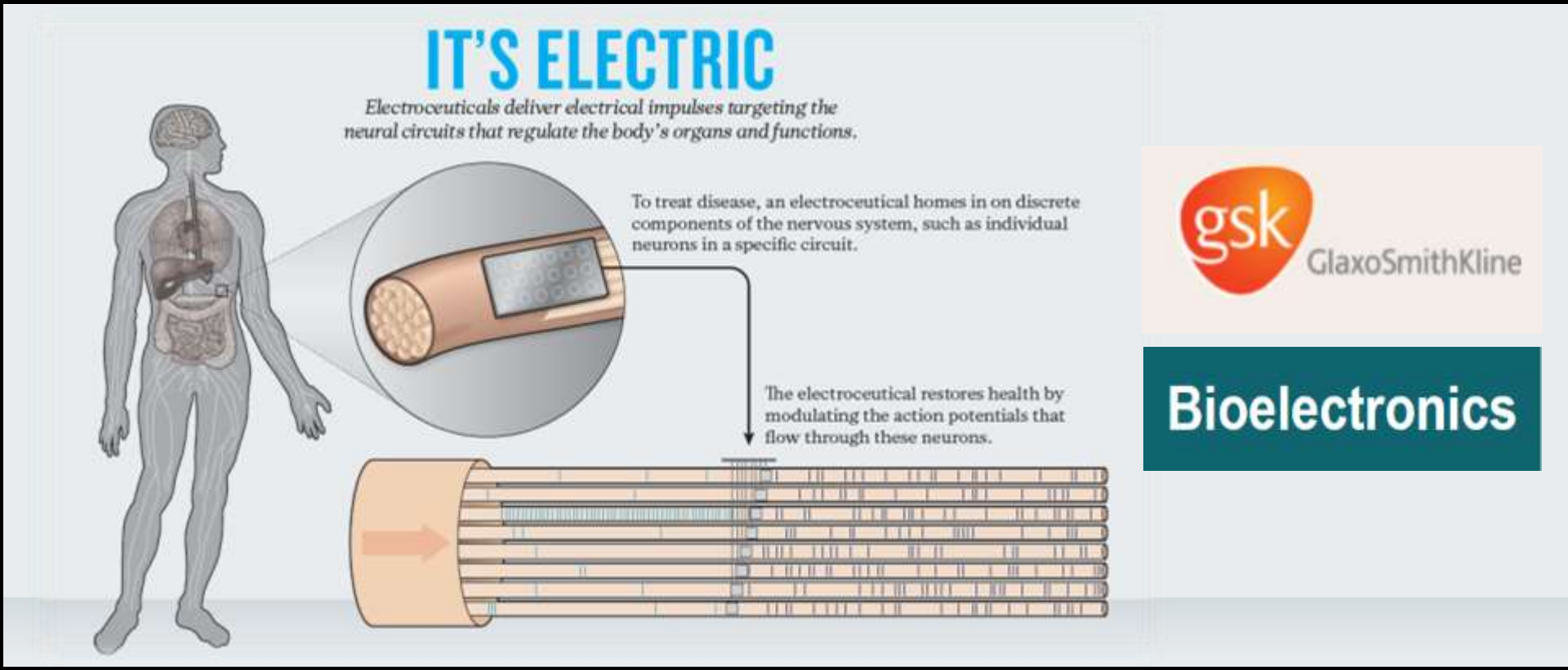
Advanced Manufacturing
Digital Programming of 3-D Fabrication and New Assembly Technologies



Programmable Matter:
Computer-Controlled 3D Assembly of Structures of Increasing Complexity

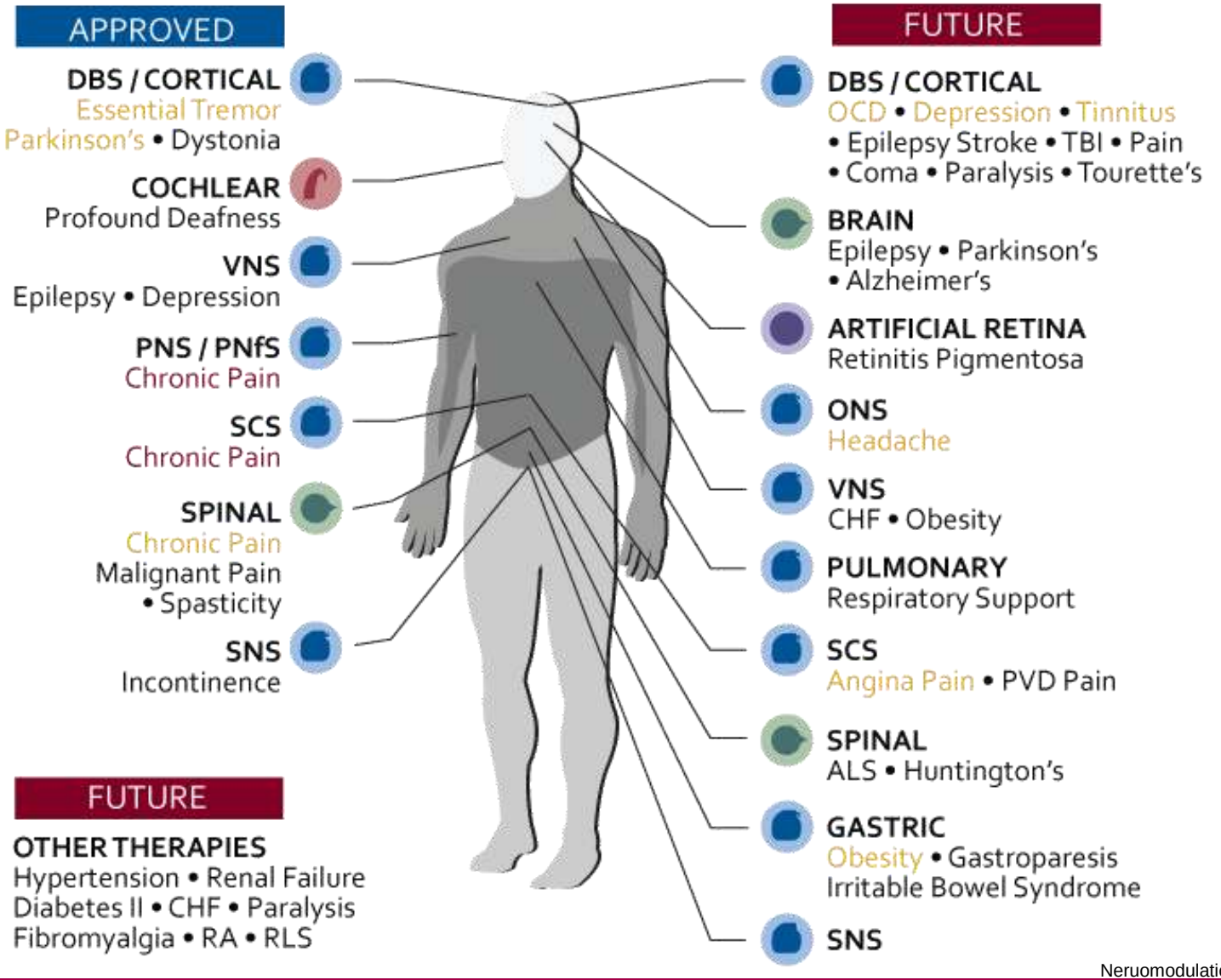
- digital code for automated assembly of complex multi-scale structures
- uncoupling of design from fabrication and rise of point-of-need (PON) production capabilities
- 3D printing
  - spatio-temporal assembly at nano-/ Ångstrom-level scale
  - abiotic materials
  - biotic materials
  - abiotic:biotic hybrids
- 4D systems
  - dynamic behavior of constructed systems

Electroceuticals:
The Use of Electrical Impulses to Modulate Neural Circuits



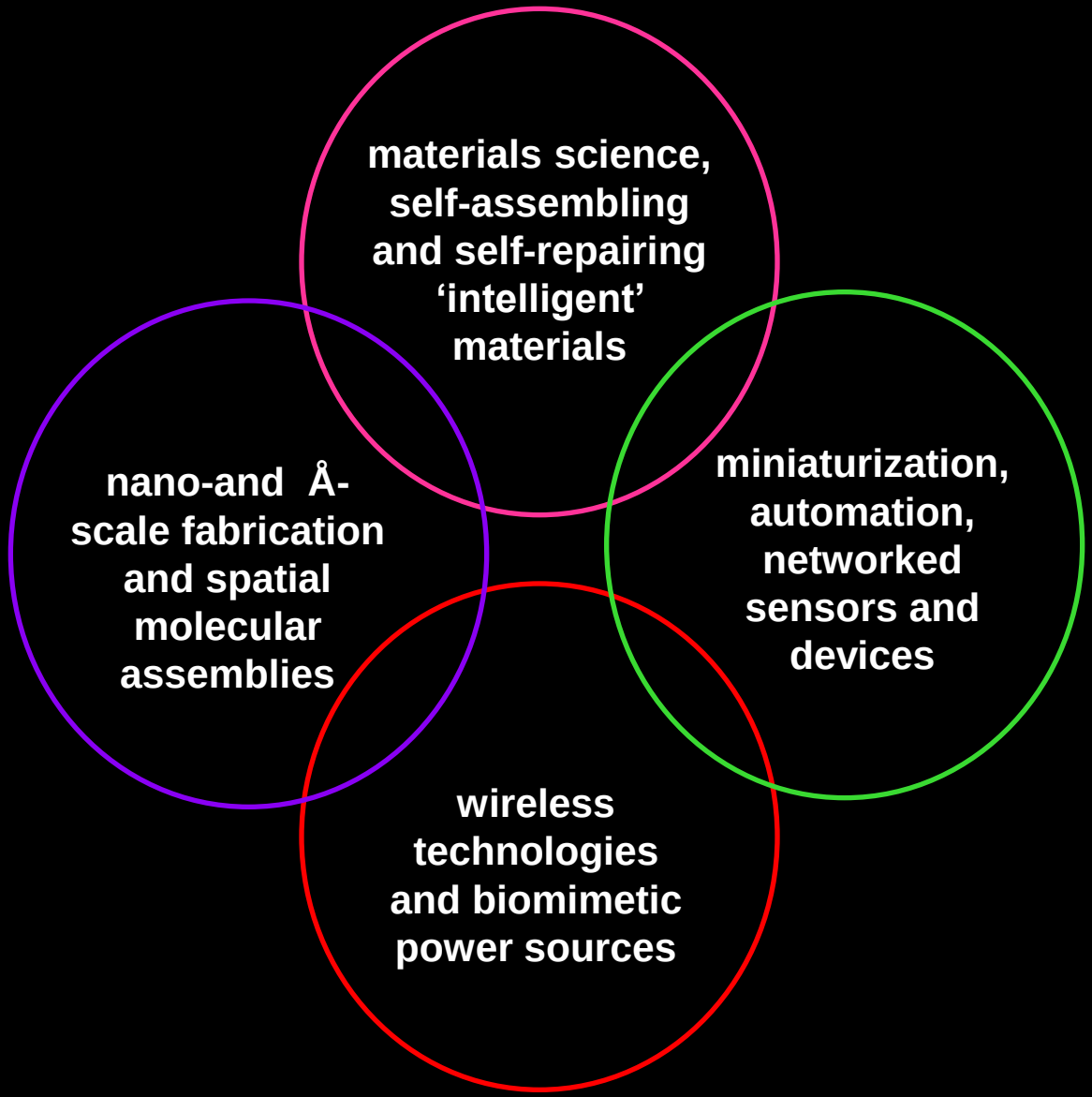
From: K. Framm et al. (2013) 496, 161

Neuro-modulation Devices

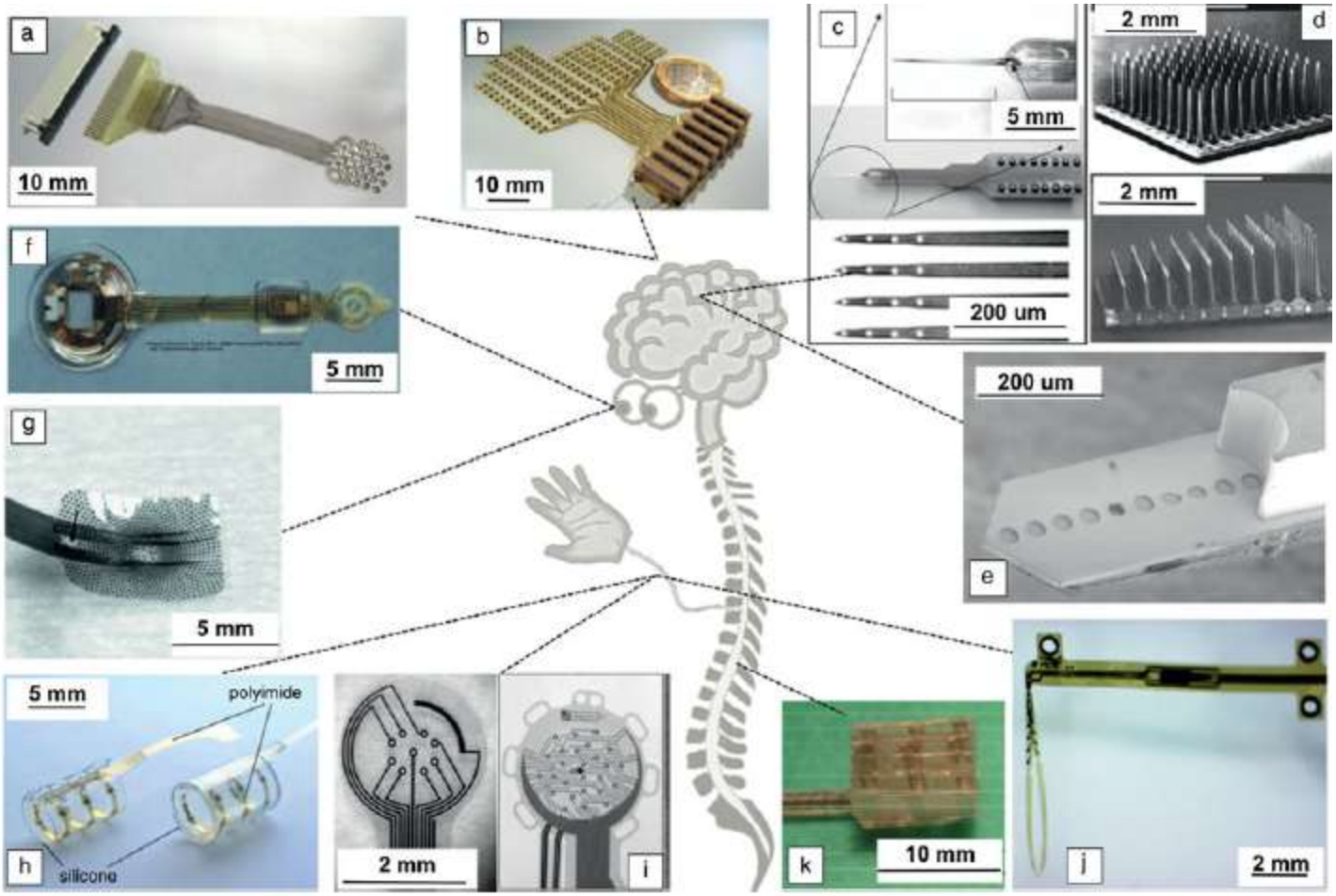


Medtech insight
Neruomodulation devices March 2013

Sensor World: Biomedicine Meets Materials Science, Engineering and Telecommunications



Implantable Microelectrode Arrays for Different Sections of the Nervous System

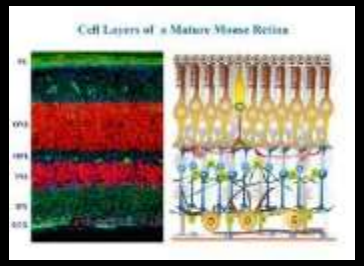


From: J. Ordonez et al. (2013) MRS Bulletin 37, 590

The BRAIN Initiative (2 April 2013)
Brain Research Through Advancing Innovative Neurotechnologies

The Brain Initiative: Mapping Neuronal Network Connectivities In Escalating Brain Complexity

150,000 neurons



1 million neurons

10 million neurons

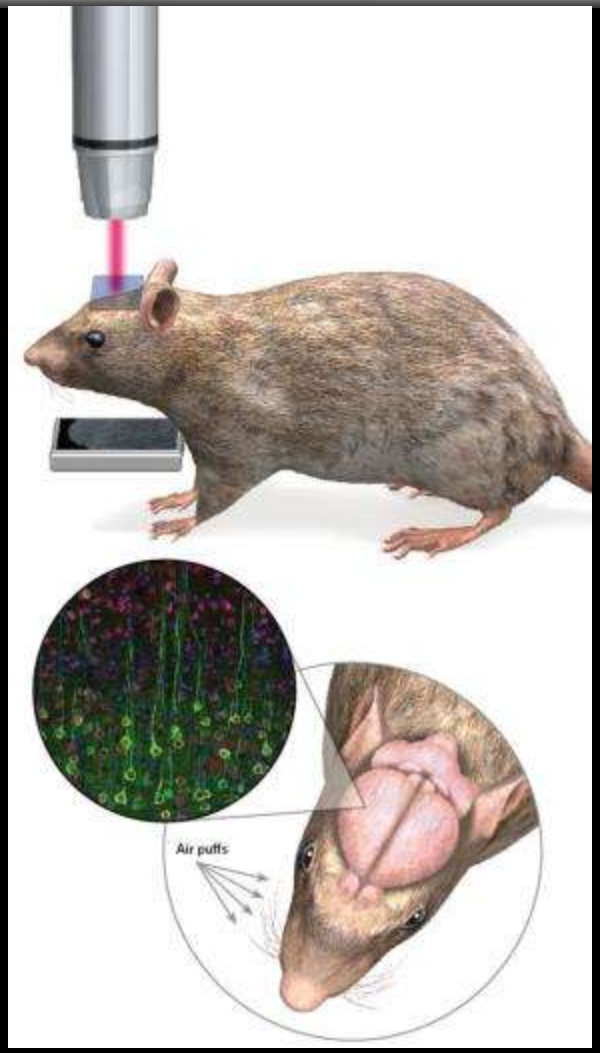
950 neurons: reconstruction in 5 years

A Comparison of High Performance Network Computing: Cortical Simulations at Cat Scale*

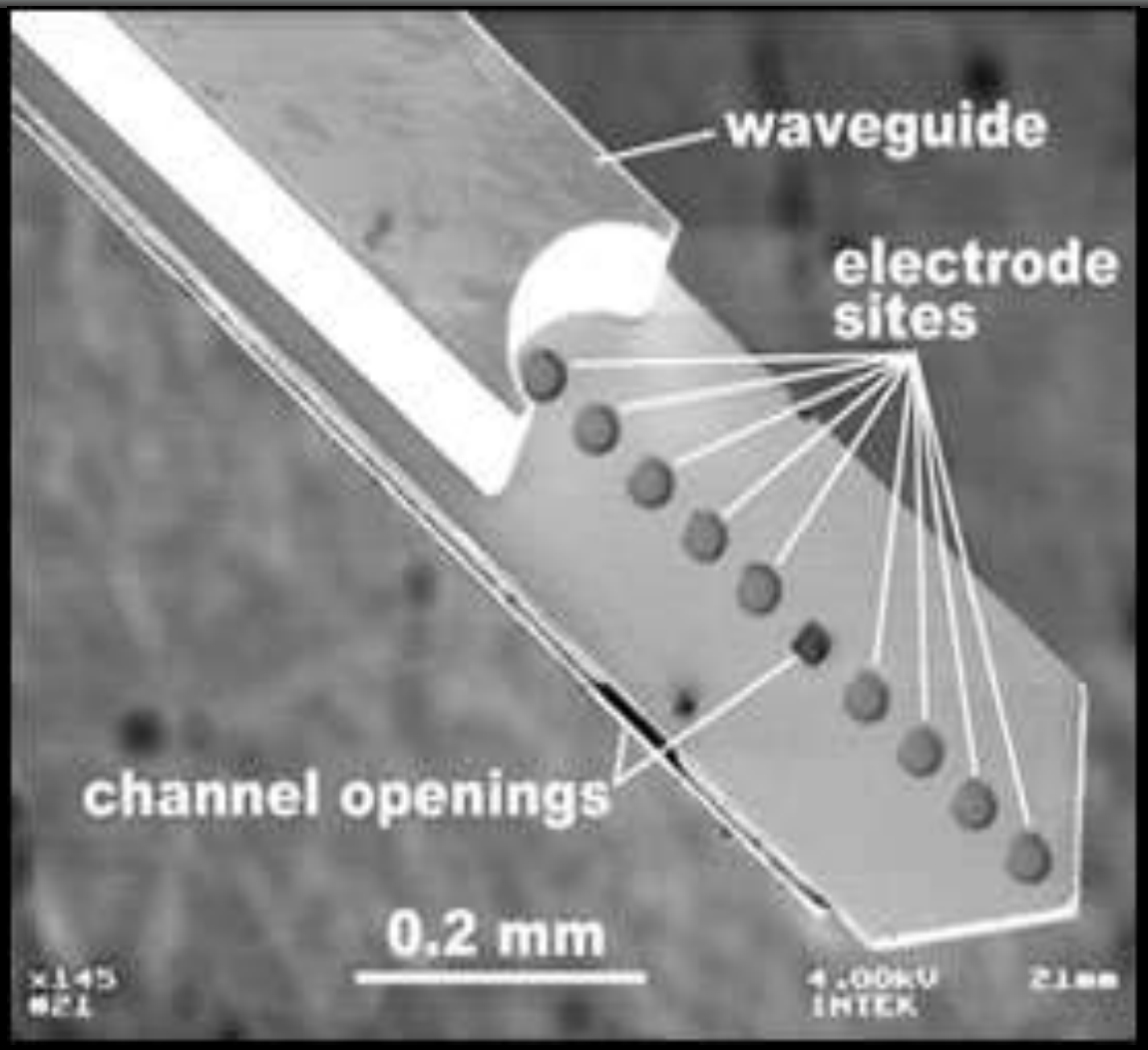
147,456 CPUs 144 TB Main Memory but still 83x slower firing rate

*Data in R. Ananthanaryanin et al. (2009)
Proc. IEEE/ACM High Perf. Network Computing

Optogenetics
In Vivo Activation or Inhibition of Neurons Labeled with Microbial Opsin Genes



Transgenic
Label Insertion



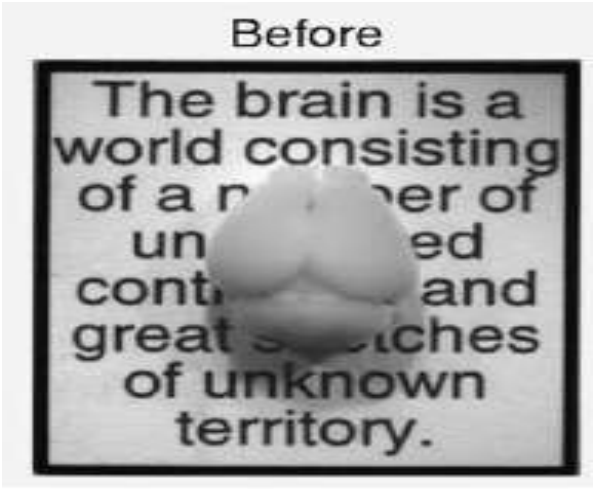
Microelectrode
Label Insertion

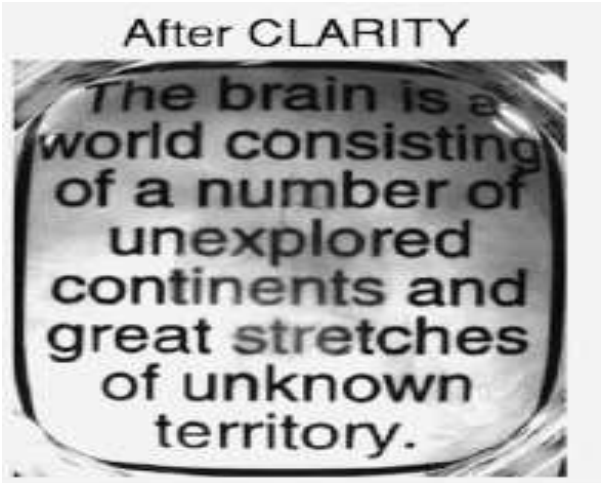
3D Mapping of Brain Structure and CNS Network Functions

- mapping the complex topologies and excitation patterns in neuronal networks
- integration of long-distance regional connectivities and local columnar architectures

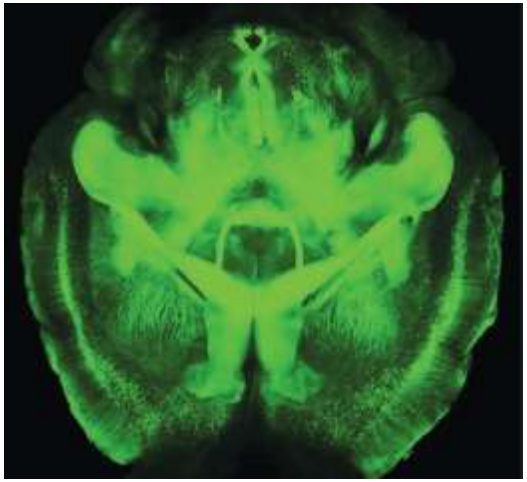
CLARITY: Lipid Clearing in Acrylamide Infused Whole Brains by SDS and 3D Mapping of Neural Networks

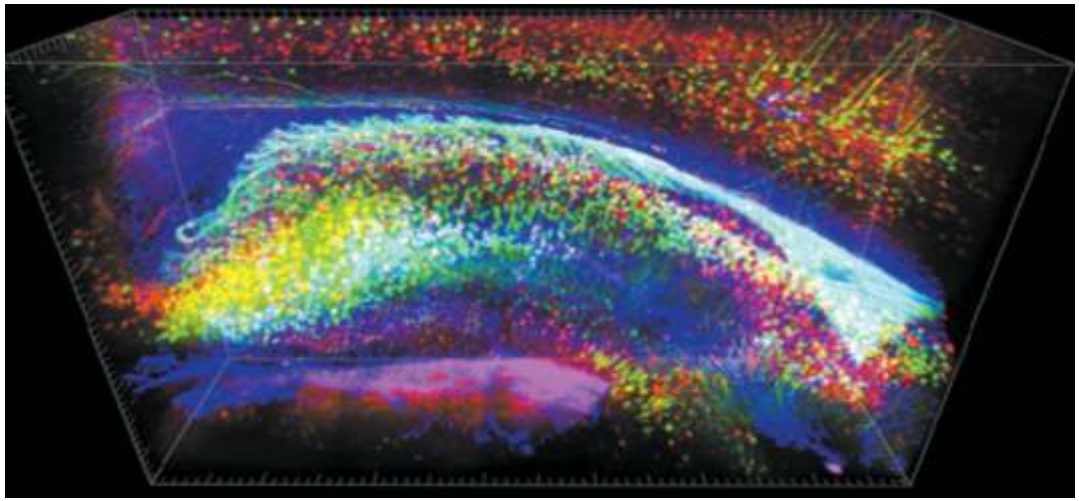
Karl Deisseroth





(Quote from S. R. Y. Cajal)



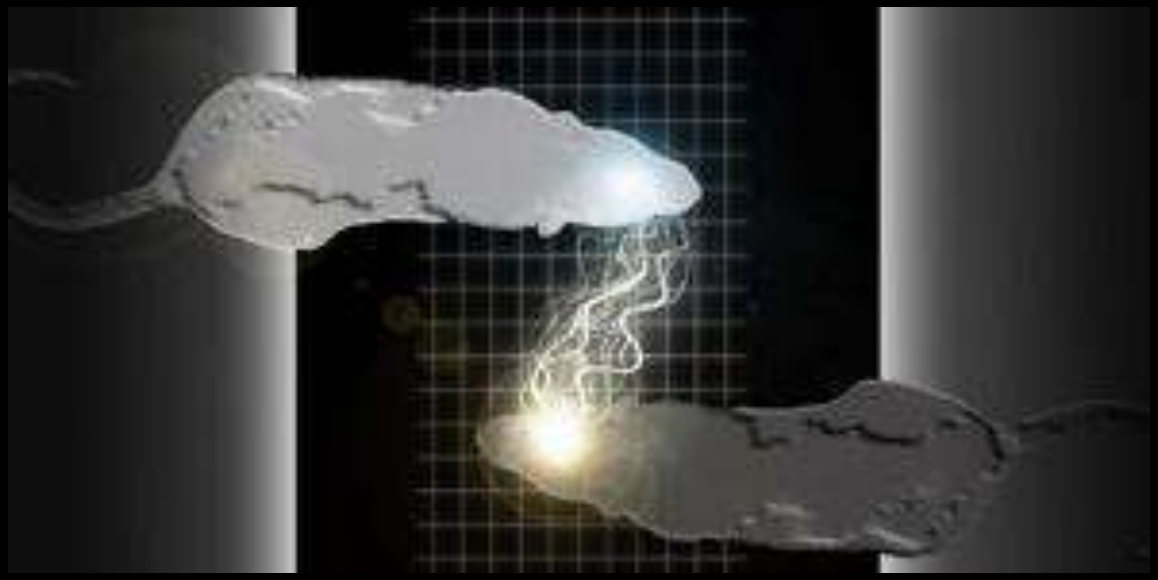


Optical Retinal Prostheses

- artificial stimulation of surviving nerve cells in outer-retinal degeneration of bionic vision restoration
- holographic optogenetic stimulation of patterned neuronal activity with millisecond temporal resolution at individual cell scale

Reutsky-Gefen et.al. (2013) Nature Comm. 4, doi.10.1038/ncomms2500

“Brain Net”



- first brain-to-brain link via remote transfer of encoded brain pattern to decoder animal and triggering of behavioral mimicry
- build inventory of codes to elicit specific behavior in target (decoder)
  - control of animals
  - design of new control systems for robots
- legal and ethical implications of extension to elicited behavior (control, modulation) of humans

Brain: Machine Interface Technologies
Direct Cognitive Control of External Devices

Data: The Fastest Growing Resource on Earth
Building an Integrated Healthcare Infocosm

Biomedical R&D and Healthcare Delivery as Increasingly Data-Intensive Disciplines

Managing the Data Deluge

The V5 Challenge of Big Data:
Volume, Variety, Velocity, Verification, Value

“The Fourth Site of Care is going to be the Internet.”

George Halvorson
CEO, Kaiser Permanente
Statement at ONC 2012 Annual Meeting


134 digital health companies
each raised $2M+ in 2012
ROCK HEALTH

m.Health

Real Time Remote Health Monitoring and Chronic Disease Management

Lifestyle and Fitness

Information for Proactive Health Awareness (Wellness)

The Proliferation of Mobile Devices in Healthcare

Mobile Devices and Telemedicine

The Quest for Minimally Invasive Monitoring of Multiple Health Status Markers

QUALCOMM TRICORDER XPRIZE

“The Walk and Die Syndrome:” On Site Monitoring of TBI and Cerebral Hematoma

- undetected TBI problem in Iraq/Afghanistan theaters
- 30% wounded combatants suffered head injury, 40% of which have brain hematomas

Infrascanner
200 ADS Medical

- OD of hematoma on IR scan differs from normal brain
- handheld unit
- disposable AA batteries

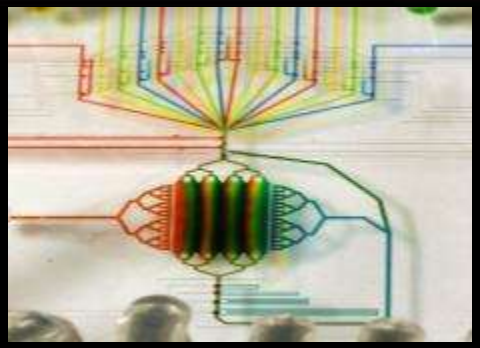
Geodemographic Information Systems (GIS): Real-Time, Front Line, Ground Zero Data from Field Sampling and Sentinels

Maintaining Global Preparedness for a High Virulence Pandemic

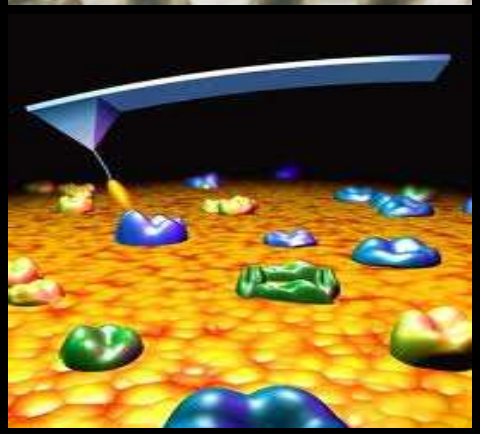
World Health Organization

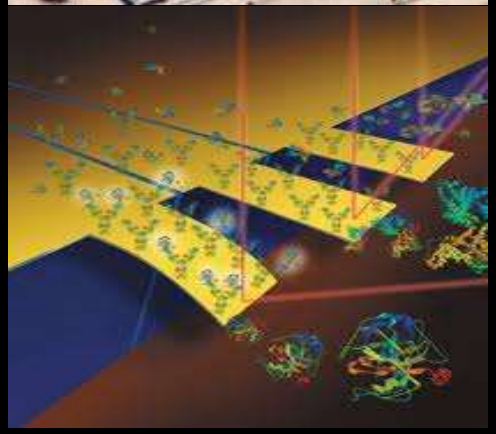
- April 2013 announcement will now first release new epidemiological data (eg. H7N9) via Twitter

Miniaturization of Analytical Technologies

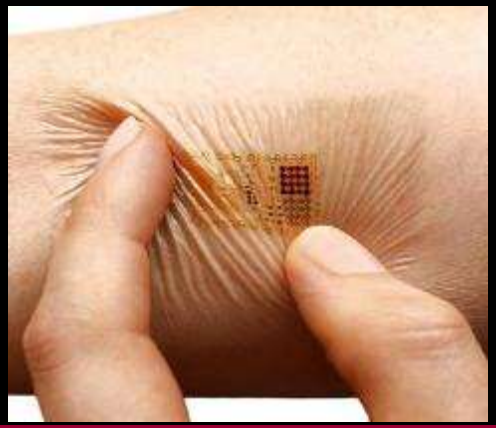


“Lab-on-a-Chip”

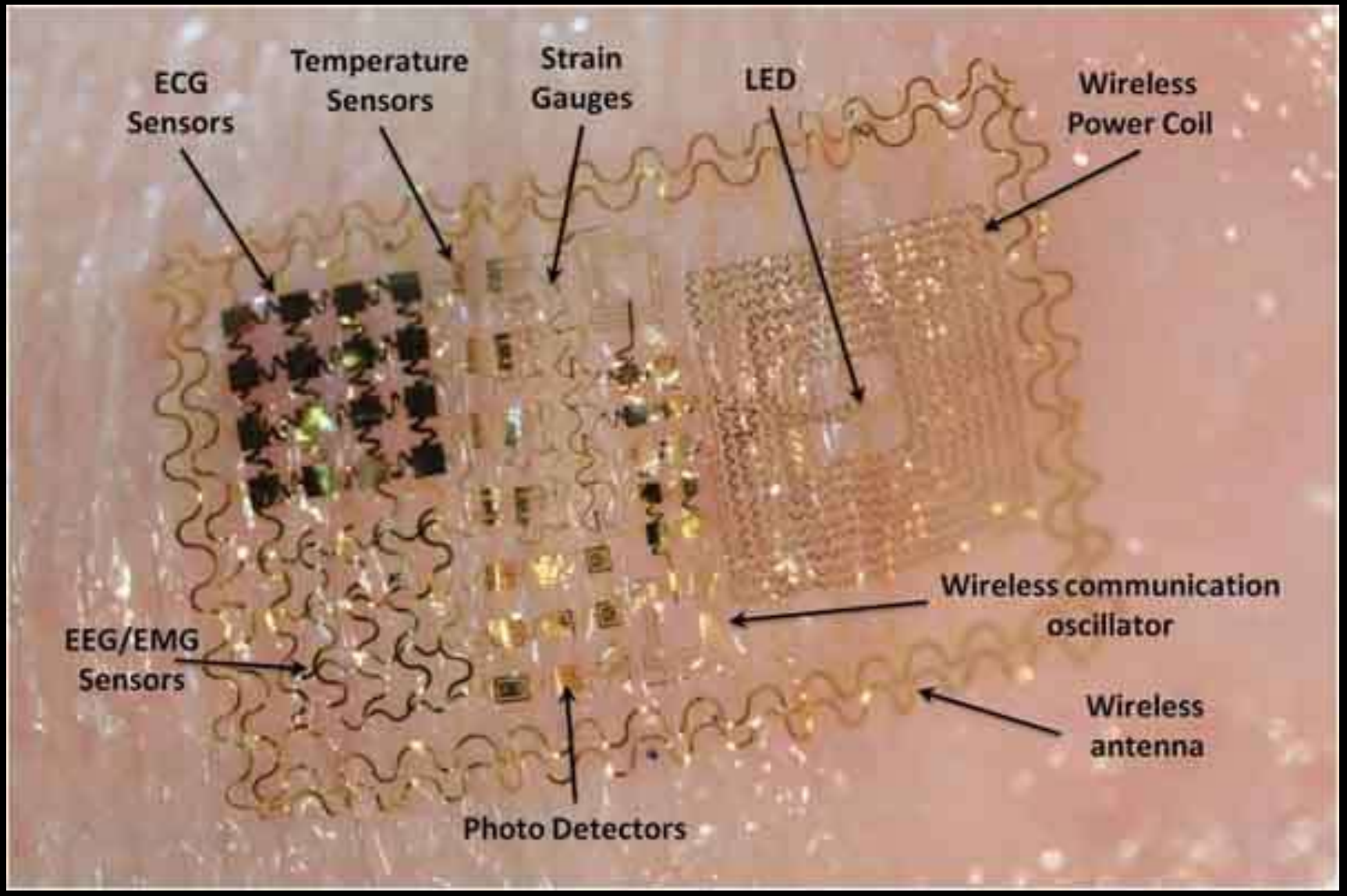




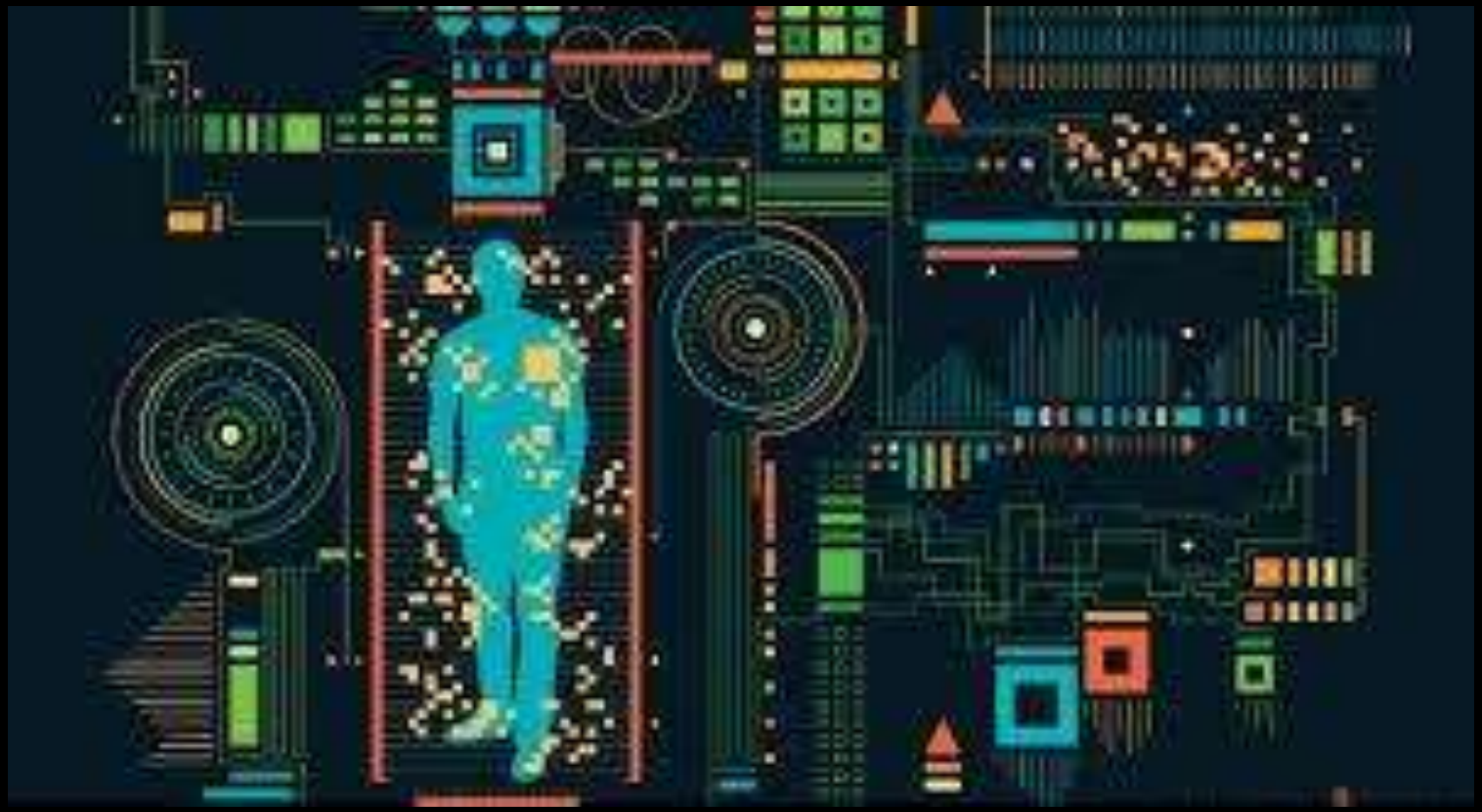
“Lab-on-a-Tip”



“Lab-Always On”
and
“Lab-On-Me”


ECG Sensors
Temperature Sensors
Strain Gauges
LED
Wireless Power Coil
Wireless communication oscillator
EEG/EMG Sensors
Wireless antenna
Photo Detectors

The Measured (Quantified) Self: Real Time Biometrics of Health Status



Every Individual Becomes Their Own Control

Health eHeart: Framingham Meets e.World

- recruitment of 1 million participants
- from profiling every two years (Framingham) to daily monitoring
- longitudinal observational monitoring with every individual acting as own control
- large sample size and avoidance of selection bias
- 1.5% cohort = entire Framingham study (15,000 participants)

Gray Technologies:
Independent But Monitored Living for Aging Populations

compliance

cognitive stimulation

Fujitsu's 'smart walking stick'

early alert of deterioration

use of home appliances and lifestyle

Robotics: Telemedicine and Home Healthcare

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

For Trevor Jones: Your Next Acquisition? The Robotic Coach to Improve Your Golf Swing

Mobile Devices, Sensors and Remote Health Status Monitoring: The Changing 'Care Space' and Improved Continuity in Care Provision

- from fixed, tethered, compartmentalized, provider-centric facilities

to

- distributed- and virtual-architectures linking multiple providers, home, work and the internet

expanded 'points-of-touch' with the health systems

improved continuity of care and data integration

- from reactive, incident-centric, poorly coordinated and sequential referrals and inefficient post-incident follow-up(s)

to

- pervasive, persistent monitoring of health status for pre-emptive risk mitigation, improved compliance and personal stewardship of health

Retail Healthcare:
New Services and Value-Based Shopping for Healthcare

Forging a New Relationship With Patients

- diabetes self-management program using digital coaching and wireless glucose meter to transmit data to clinical monitors

- improve patient outcomes through interactive web application for patients and doctors
- initial focus on patients at risk for diabetes and cardiovascular disease

- pharmacy-based service in the UK to provide health screenings to prevent heart attack and stroke

U.S. Department of Health & Human Services

www.hhs.gov

Patient Network

Bringing Your Voice to Drug and Device Approval and Safety

Search

Home | About Us | Get Involved | Learn How Drugs & Devices Get Approved | Find Out About Clinical Trials | Find Other Treatment Options | Get Disease Information

Learn About the new Web Site

Become a Patient Rep

Make Your Voice Heard

Drug & Device Development

Share your unique perspective and serve on an advisory committee.

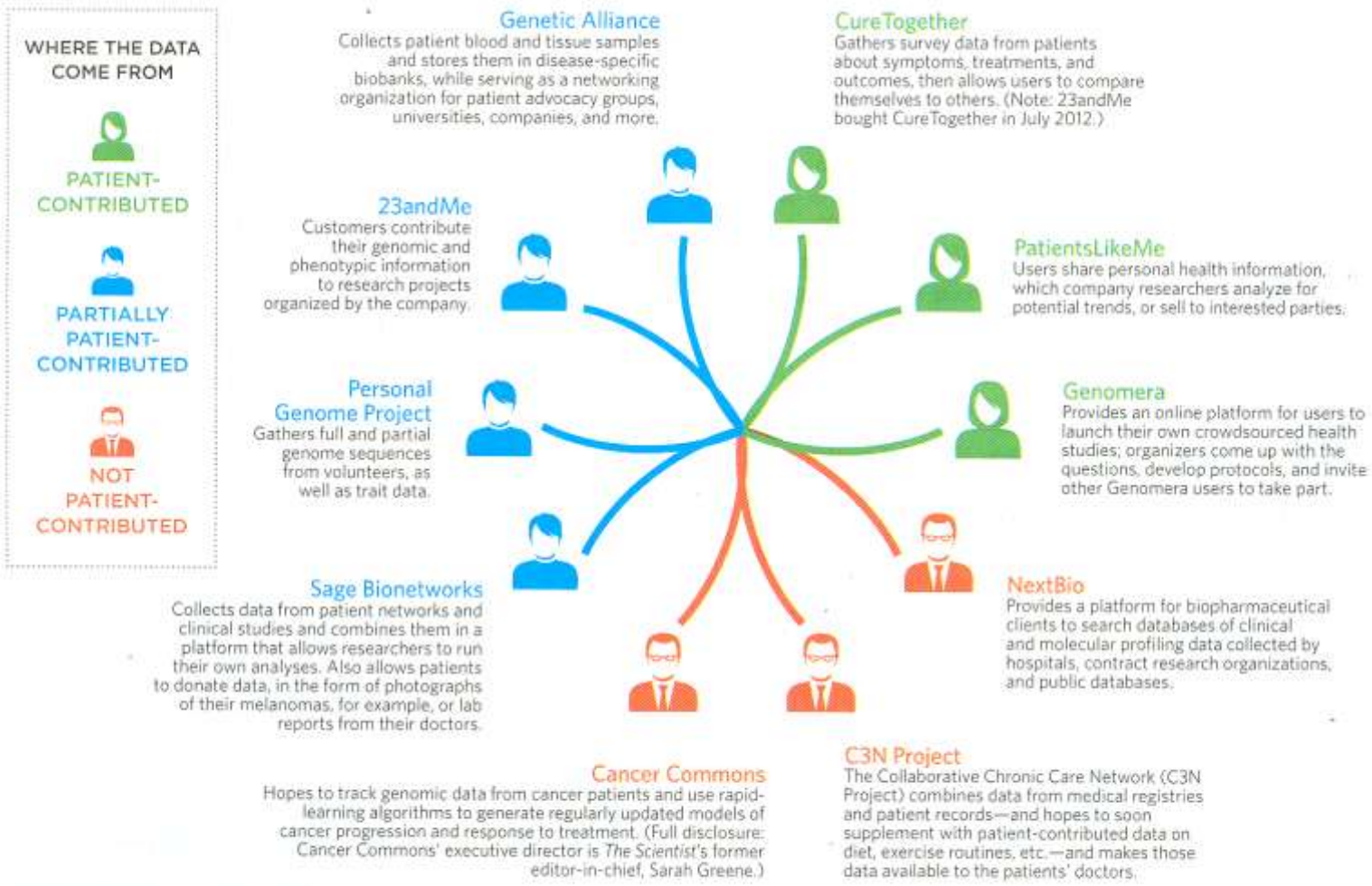
Go

Approved Drugs at FDA

Find a Clinical Trial

Ask the FDA

Patient-Driven Data: Registries, Clinical Trial Enrollment and Observational Outcomes Studies



From: The Scientist March 2013, p. 36

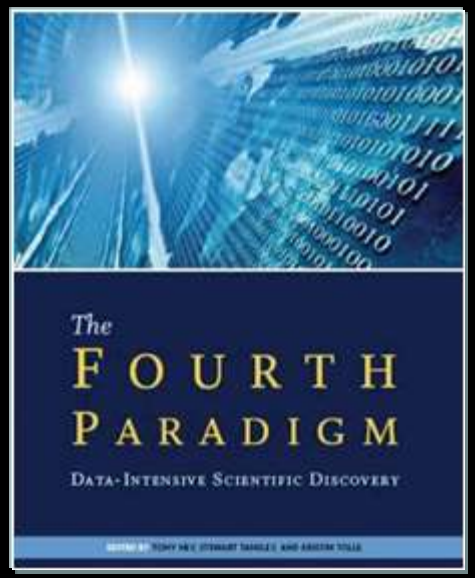
Social Behavior Becomes Quantifiable

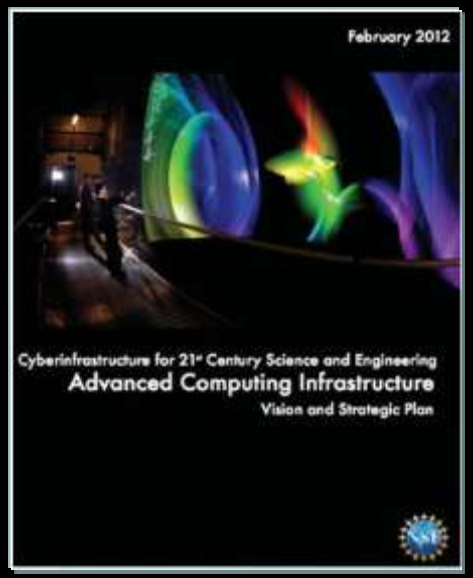
- who knows why people do what they do?
  - the fact is that they do!
- these actions can now be traced and measured with unprecedented precision
- with sufficient data, the numbers reveal increasingly predictable behavior individual risk patterns
- new business opportunities in multiple sectors including healthcare
- new ethical and legal issues regarding privacy and data security

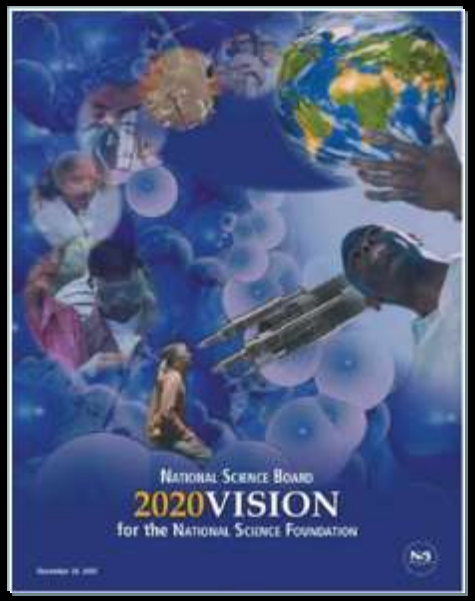
Web-Based Health Information and Research Uses: The Blurring of Informed Consent in Cyberspace

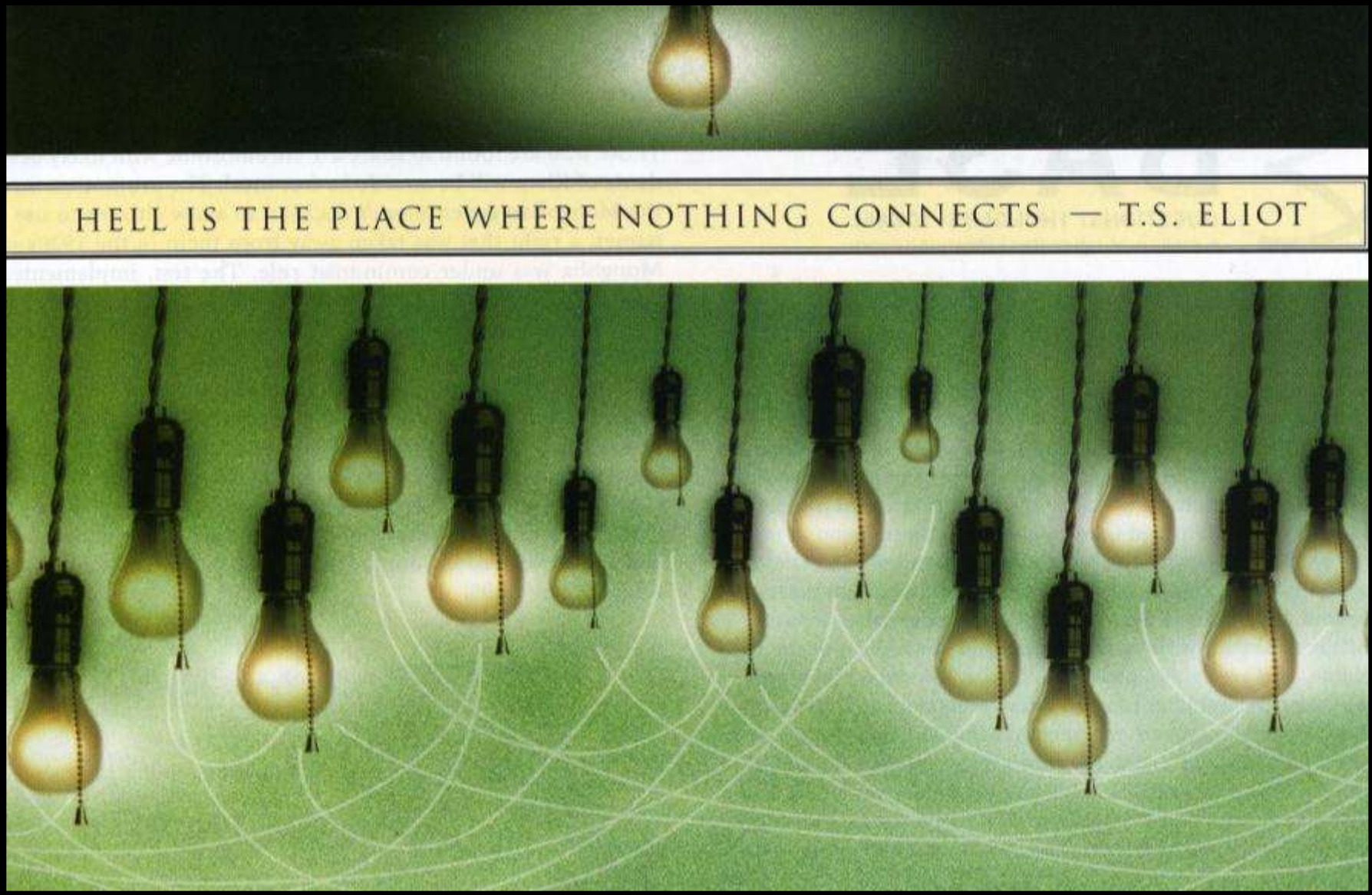
- information supplied by the user
  - medical history, genomic data, web posts
- personal information harvested in interaction with web sites
  - IP and e.mail addresses, searches, location data
- content that users provide becomes trading capital for web services providers
- do browsewrap disclosure agreements (click “I agree”) represent affirmative consent?

Data-Intensive Computing, Big Data and New Knowledge Networks in Biomedical R&D and Healthcare Delivery

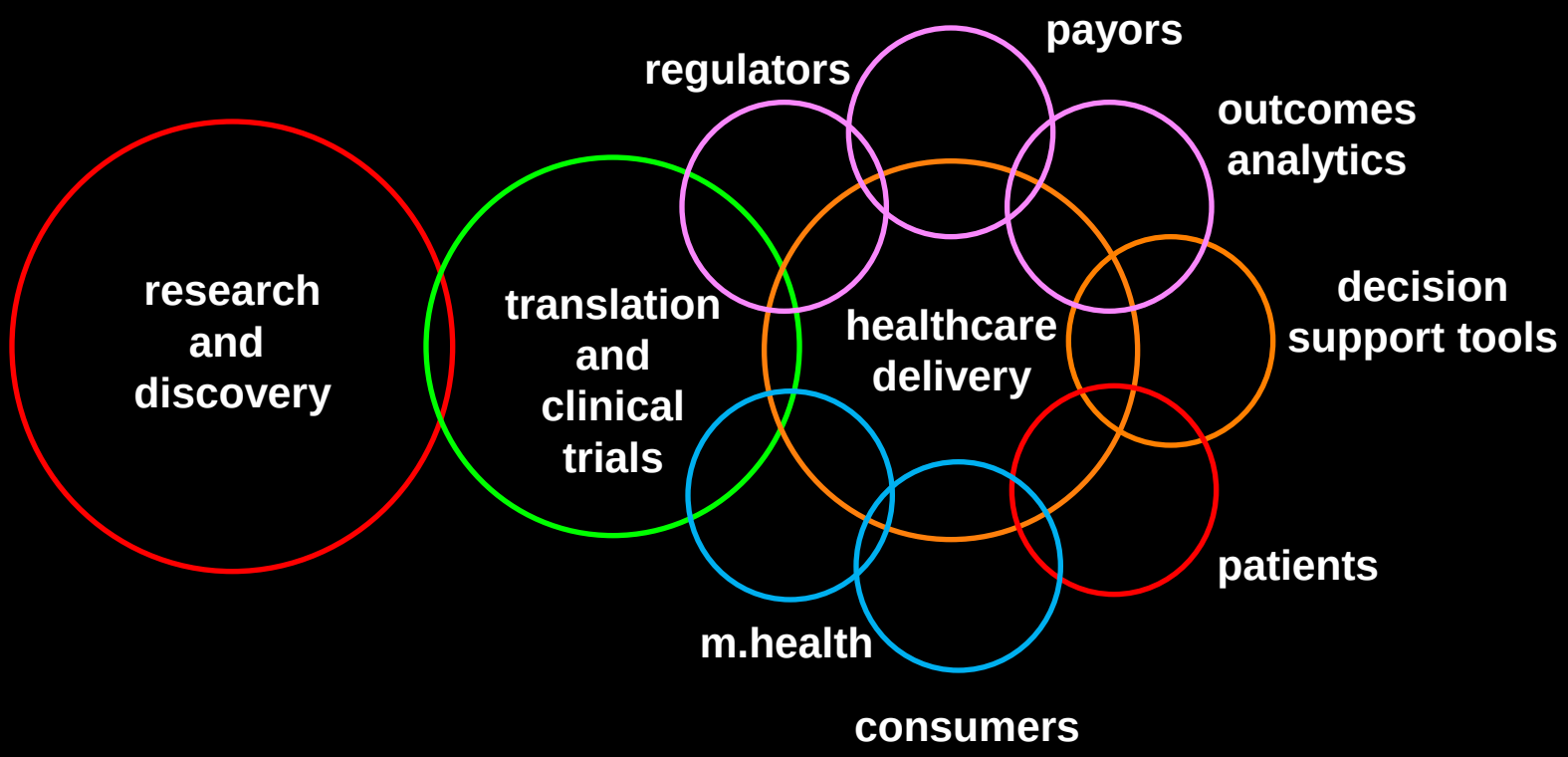







HELL IS THE PLACE WHERE NOTHING CONNECTS — T.S. ELIOT

The Need for Facile, Seamless Data Exchange Formats for Large Scale Biomedical Data Systems



Healthcare Data and EMR/EHRs Not Designed for Facile Mining or the Integration of New Data Classes (Omics)

Design of Agile EHR/EMR Formats for New Data Classes and Large Scale Data Mining

- EMR/EHR as e.replicant of paper records
- the vendor trap and incompatible formats
- rigid design formats and limited agility to integrate/mine new data classes (e.g. omics, social media)
- privacy and security protections as barriers to large scale mining and analytics, and of observational data

Formation of the CommonWell Health Alliance (March 2013)
A Major Step in the Interoperability in Health IT

McKESSON

Cerner

RelayHealth

GREENWAY

Allscripts

athenahealth

Health Outcomes Mining From Large Clinical Datasets

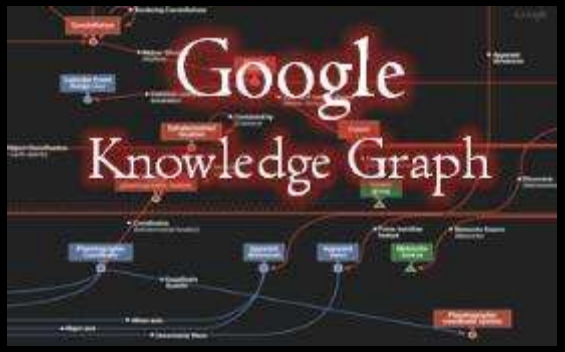
- 100 million claims records
- 5 million clinical records

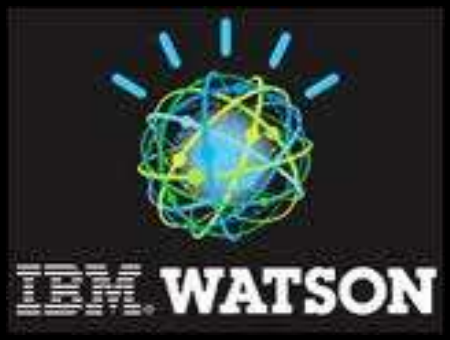
OPTUM™

MAYO CLINIC

UnitedHealth Group

Natural Language Processing, 'Trained Systems' and Big Data Analytics

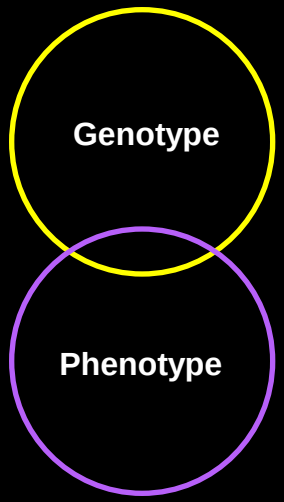


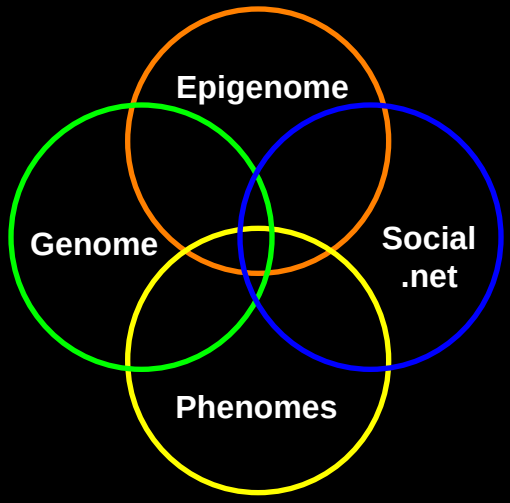


amazon.com

NETFLIX

Rich Data Will Drive Clinical Profiling to 'Interpreted Phenotypes'



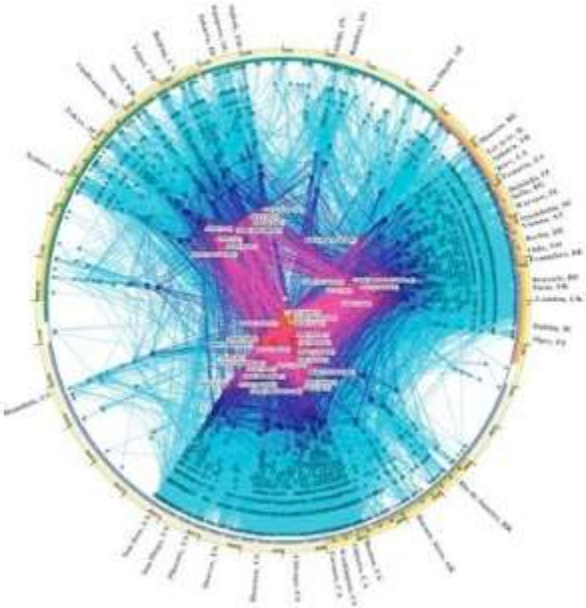


Observed Phenotype	Interpreted Phenotype and Phenomes Via Multi-Parameter Integration
• clinical annotation • EHR data mining	• large scale data analytics for "*robustness of match*" • reported clinical phenotype + integrated personal Omics profile + population EMR data mining + curated literature • automated decision-support

Data Changes the Questions That Can Be Asked

Isolated Data

Complex Networked Data

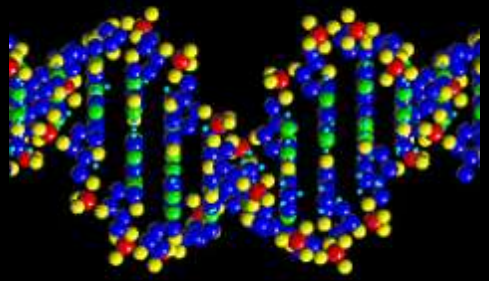


Complex Computational Data

The Omics Data Storage Challenge
(J. Starren et al. 2013 JAMA 309, 1237)

- typical EHR
  - 375 KB/patient
- radiologic picture archiving and communication system (PACS)
  - 104 MB/patient
  - x277 > EHR
- WGS
  - 3-10 million variants/individual
  - 5-10 GB/individual
  - x50 > imaging

"If the scientific community can justify
billions of dollars, 100MW of power
and thousands of staff in order
to fire tiny particles that most people
have never heard of around a big ring of magnets
for a fairly narrow science purpose
that most people will never understand…..



…..then how come we can't make
the case for facilities needing half the resources
that can do wonders for a whole range
of science problems and industrial applications?"

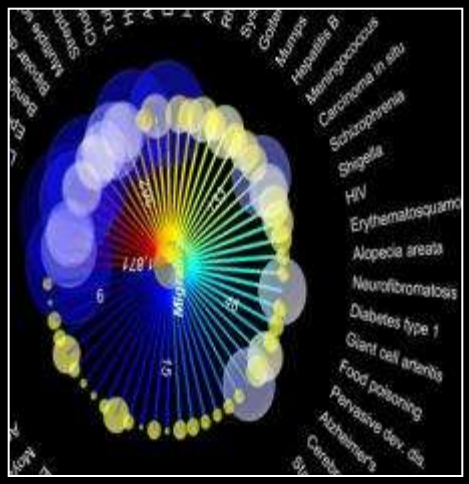
Andrew Jones
Vice-President, Numerical Algorithms Group
HPC Wire 29 August 2011

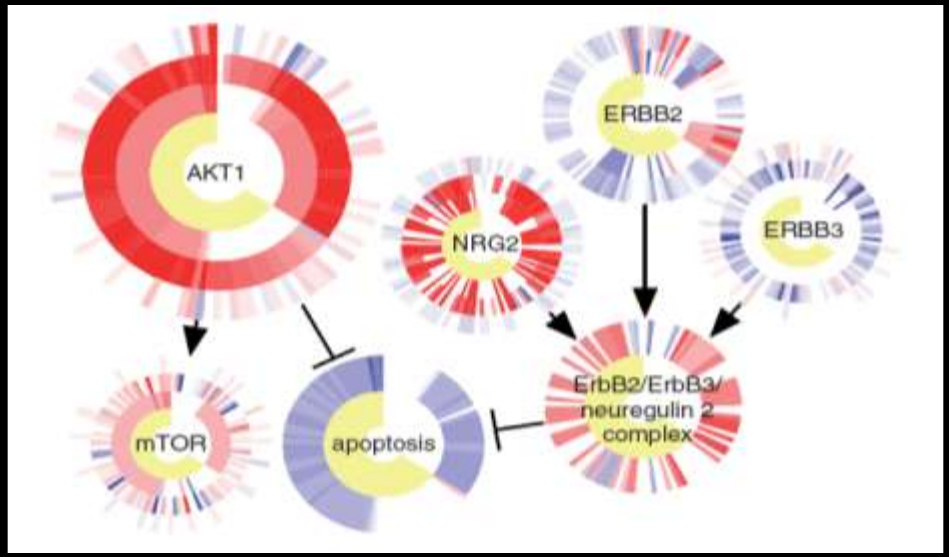
21st Century Knowledge Networks versus 20th Century Organizations

The Pending Era of Cognitive Systems: Overcoming the "Bandwidth" Limits of Human Individuals

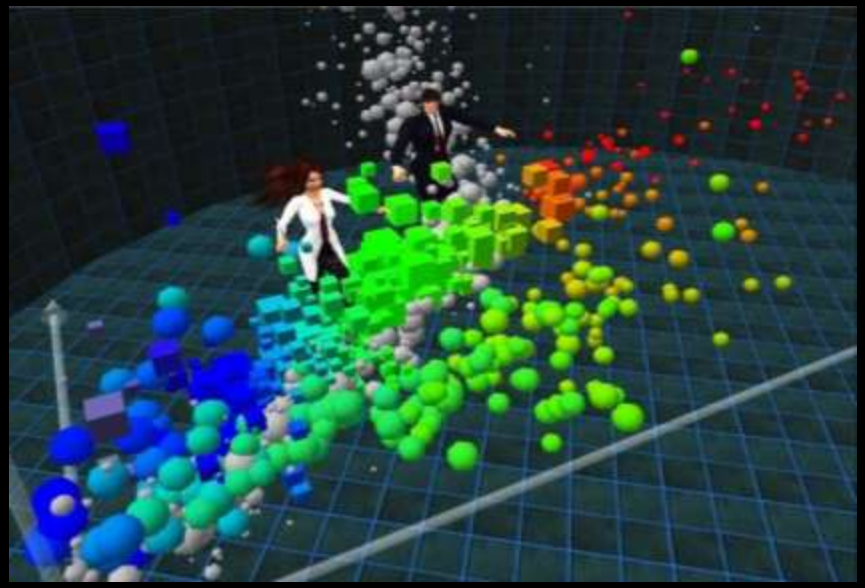
- limits to our expertise
- limits to our multi-dimensionality
- limits to our sensory systems
- limits to our experiences and perceptions
- limits to our objective decision-making

Data Customization and Visualization for EMRs





Computing Systems and Interactive Displays: From Defense to Gaming to Interactive Dynamics for R&D and Business Processes



Pervasive Computing: The Next Major Transition?

A Leap Forward:
3D Gestural Interfaces

LEAP MOTION

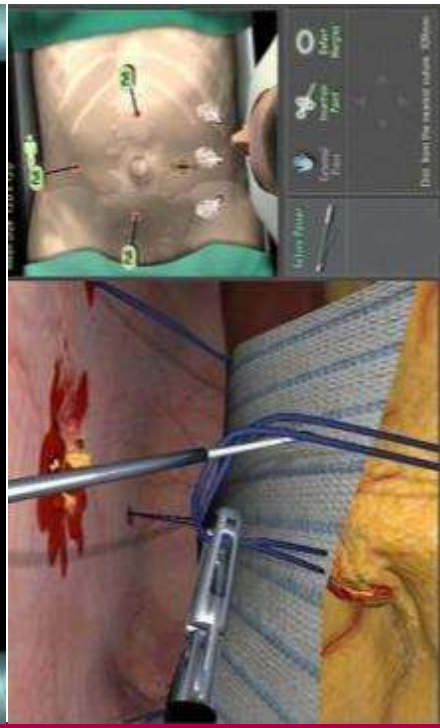
AUTODESK.

KINECT for Windows

Linden Lab

Project RED
virtual discharge
advocate

Simulation Training
in Surgery



Does Anyone Read Printed Journals Anymore?

PHILOSOPHICAL
TRANSACTIONS:
GIVING SOME
ACCOMPT
OF THE PRESENT
Undertakings, Studies, and Labours
OF THE
INGENIOUS
IN MANY
CONSIDERABLE PARTS
OF THE
WORLD

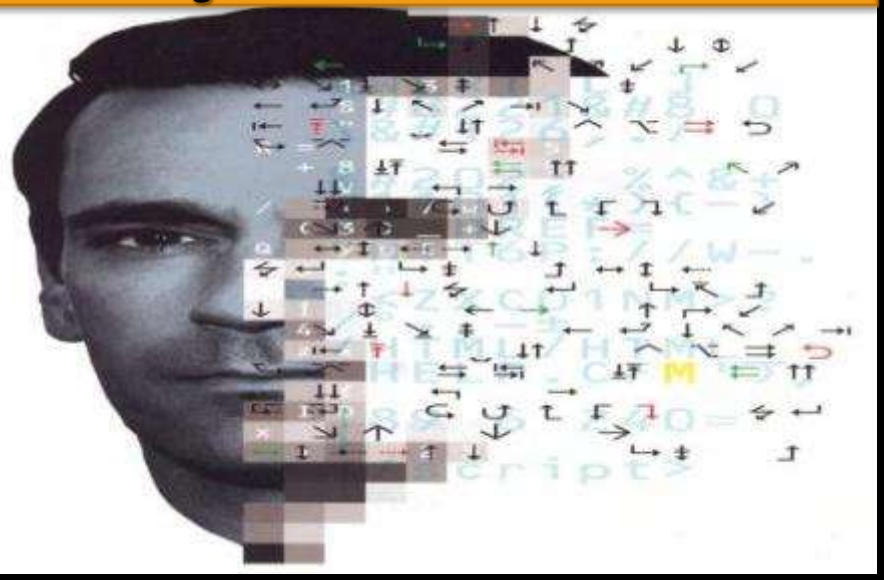
Vol I.
For Anno 1665, and 1666.

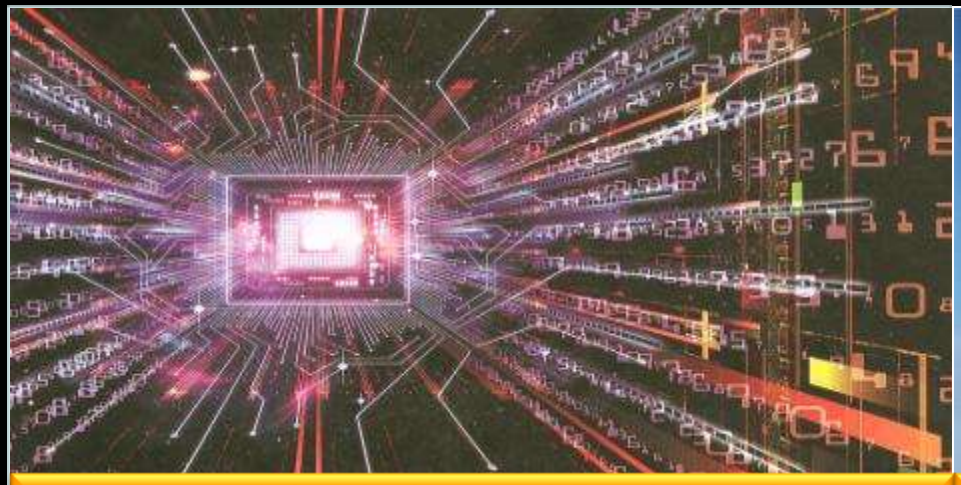
In the SAVOY,
Printed by T. N. for John Martyn at the Bell, a little without Temple-Bar, and James Allestry in Duck-Lane,
Printers to the Royal Society.

Technology Acceleration and Convergence: The Escalating Challenge for Professional Competency, Decision-Support and Future Education Curricula

Data Deluge

Cognitive Bandwidth Limits



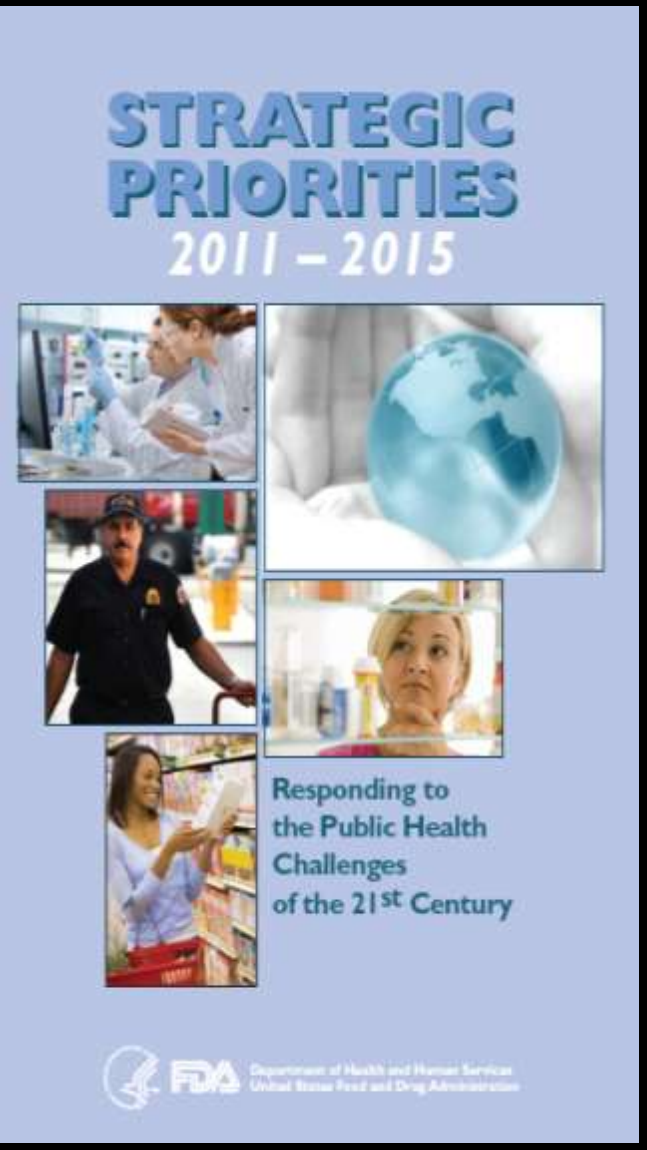


Automated Analytics and Decision Support

Facile Formats for Actionable Decisions

From Bench to Keyboard
For Second Opinion, Consult a Computer?

Regulatory Science



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

“Outside In” Data and Processes Will Intensify as Drivers of Disruptive Change in Healthcare Delivery

- from Rx product sales to optimizing Rx value in health outcomes/cost control
- patient engagement and loyalty
- integration with MDx, devices, m.health and real time remote health status monitoring
- health data aggregation and mining of large scale observational studies of real world use

Mastery of Technology Convergence, Big Data and Understanding Complex Networks

Building New Knowledge Networks: Who Knows Wins!

Building New Coalitions: Who Disrupts Current Pervasive Inefficiencies in Healthcare Wins!

Building New Rx Value Propositions: Who Integrates Rx With Other Healthcare Services More Proficiently Wins!

Transformational Technologies and New Value Propositions in Healthcare

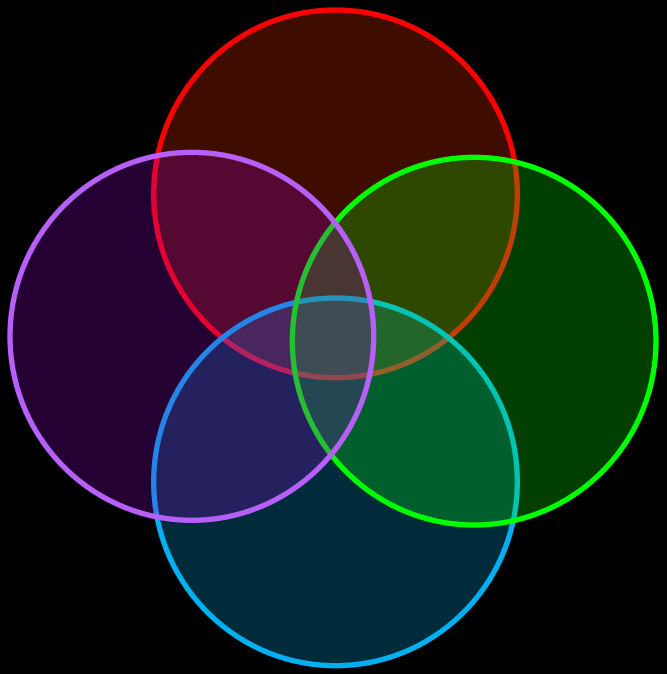
Technology

- understanding information patterns in complex systems
  - biological networks
  - care delivery networks
  - intelligent data networks
- integration of RX, MDx, sensors, devices and HIT

Value Drivers

- creating value outside the Rx product
- health outcomes, cost control
- consumer: patient engagement and loyalty
- the wellness premium
- increasing power of patients and payors

The Principal Forces Shaping Biomedical R&D and Healthcare Delivery



device-based medicine

- MDx, sensors

- remote health monitoring
- telemedicine

molecular (precision) medicine

- integrated analytics of biological networks

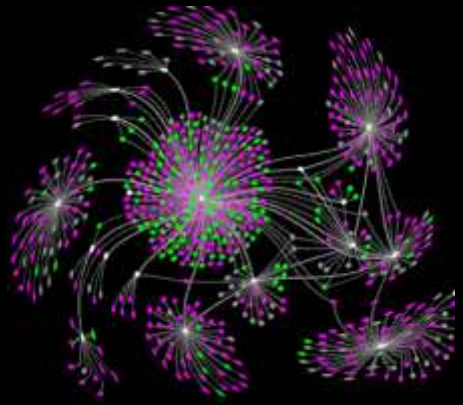
information-based healthcare

- m.health/e.health
- data- and evidence- based decisions and Rx selection

outcomes-based healthcare and sustainable health

new value propositions, new business models and services

Precision Medicine: Understanding Network Biology as the Intellectual Foundation for the Evolution of Robust Biological Knowledge and Rational Medicine



"Scienta potentia est" (Knowledge is power)

"Nullius in verba" (Take nobody's word for it)

"Omnis serta est" (Everything is connected)

00110101001l0…. (Code is power)

Experimental Design

Standards and Reproducibility

Mapping Network Dynamics

Precision Medicine

**“Oh, God help us!
We’re in the hands of
engineers.”**

**Dr. Ian Malcolm
‘Chaotician’: Jurassic Park**

Slides Available: http://casi.asu.edu/