



Microsoft Research

Faculty
Summit

2014 15TH ANNUAL



Microsoft Research

Faculty Summit

2014 15TH ANNUAL

Systems Medicine and Proactive P4 Medicine: Revolutionizing Healthcare

Predictive, Preventive, Personalized and Participatory

Lee Hood
Institute for Systems Biology





The grand challenge for biology and medicine is deciphering biological complexity

I participated in five paradigm changes in biology to deal with complexity over 40 years

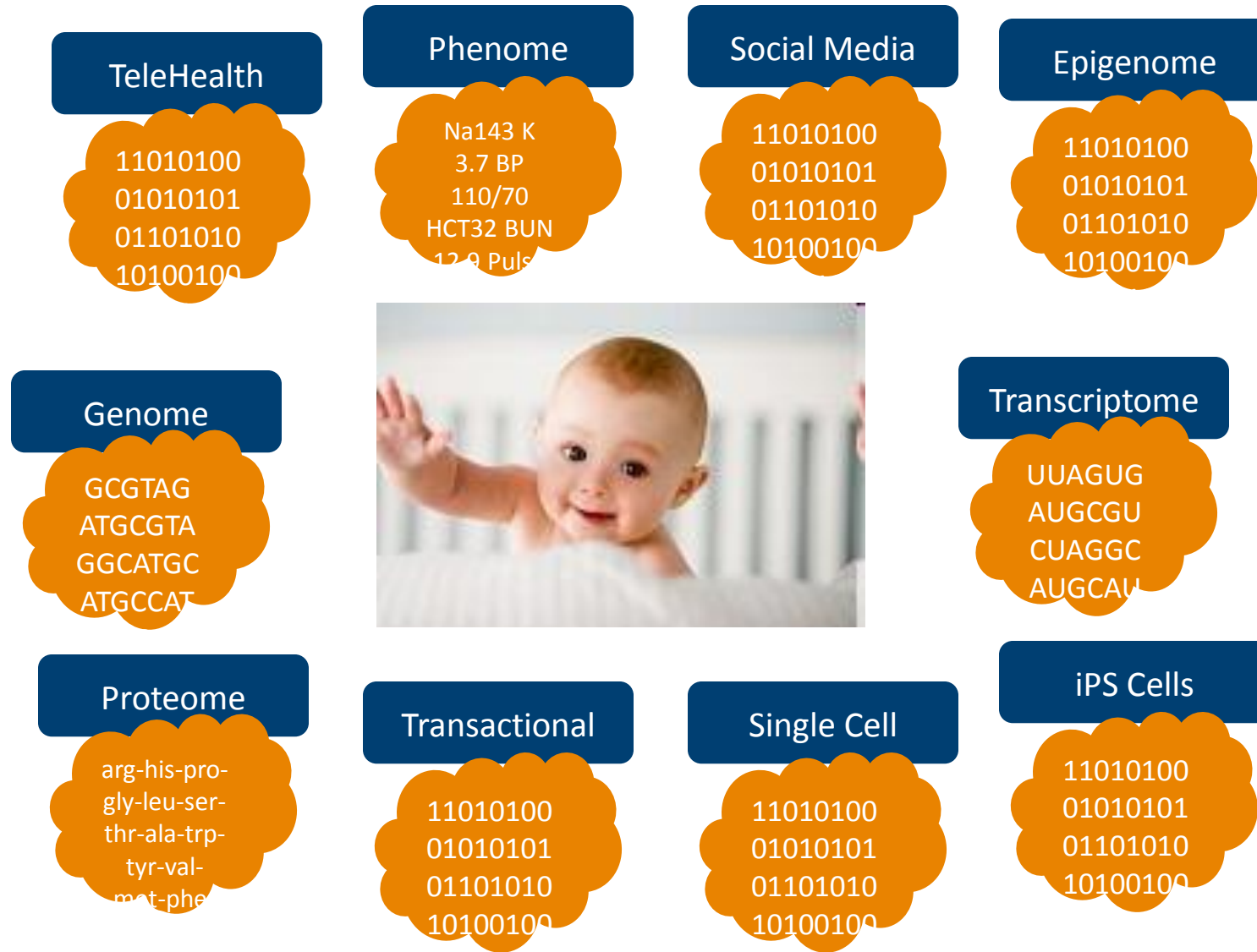


- **Bringing engineering to biology**—developed 5 instruments that led to high throughput biology and big data in biology
- **The human genome project**—invented enabling technology that provided a parts list for human genes (and proteins)
- **Cross-disciplinary biology**—created 1st department—enabled technology development
- **Systems biology**—created 1st institute—deciphering biology complexity
- **Systems medicine and the emergence of proactive P4 medicine**—early advocate and pioneer—transform healthcare



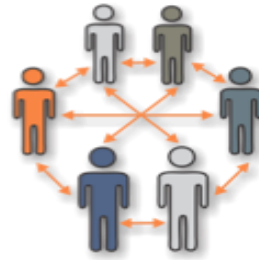
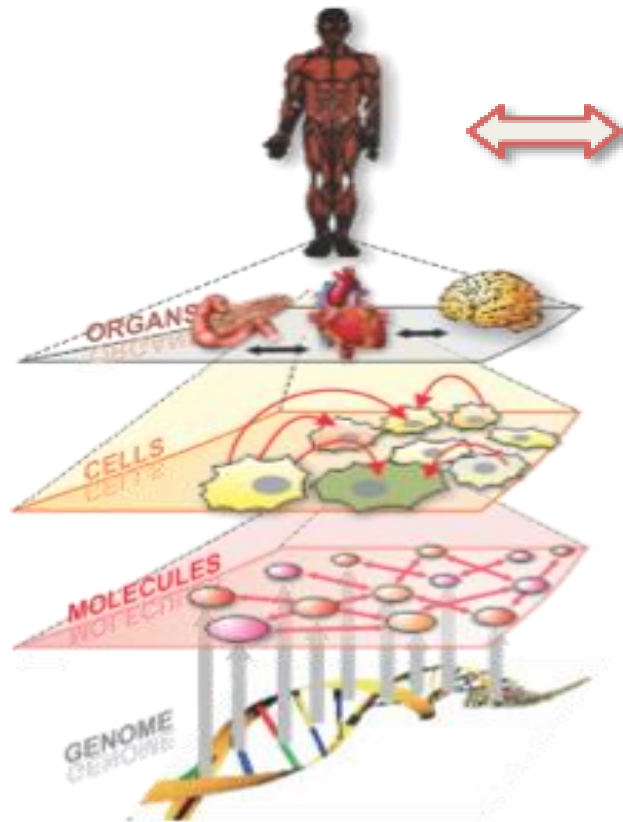
Central features of systems medicine

Big data is one essence of systems medicine: Soon each individual will be surrounded by a virtual cloud of billions of multi-scale data points—big data



Systems Medicine

Disease-perturbed network of networks



- Integration of patient data will reveal **biological networks** that specify health and are altered in disease
- Understanding differences in normal and disease-perturbed networks will provide fundamental insights into **disease mechanisms**
- These insights are essential for developing **more effective diagnostic and therapeutic approaches**

Systems features of big data: dealing with biological complexity



- **Global analyses** of all components—DNA, RNA protein, etc.
- **Dynamics** of systems (networks)—temporal and spatial
- **Integration** of different data types from the system
- Large data sets reflect two types of **noise**—
biological and technical

A Systems Medicine is the Key for Dealing with Disease Complexity—Two Conceptual Pillars



- 1. Holistic, dynamical systems experimental approaches** enables deep insights into disease mechanisms and new approaches to diagnosis and therapy
- 2. Emerging technologies and systems strategies** provide large-scale data acquisition and permit us to explore new dimensions of patient data space



Dynamic approaches to prion-induced neurodegeneration in mice

Global and Subtractive Brain Transcriptome Analysis— Differentially Expressed Genes (DEGs)



Time-course array analysis: subtrative analyses to DEGs

Prion strains:

- RML
- 301V

Mouse strains:

- C57BL/6J
- FVB/NCr
- BL6.I
- FVB/B4053

Inoculate w/ Prions



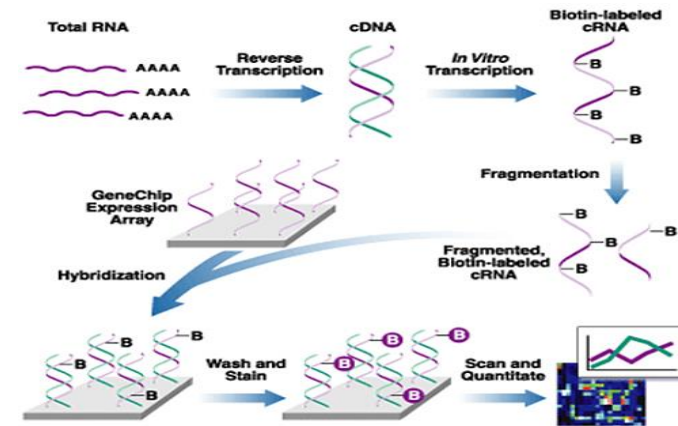
Prion infected brain



Uninfected brain

RNA
from brain
homogenate

- **C57BL/6J-RML:** 12 time points
- **FVB/NCr-RML:** 11 time points
- **BL6.I-301V:** 9 time points
- **FVB/B4053-RML:** 8 time points



Mouse Genome array:

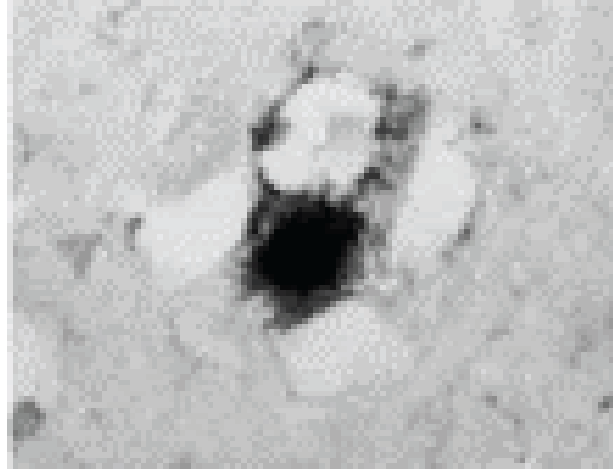
45,000 probe sets
~22,000 mouse genes.

7400 DEGs—signal to noise issues---biological/technical—deep biology--
300 DEGs encode the prion neurodegenerative response

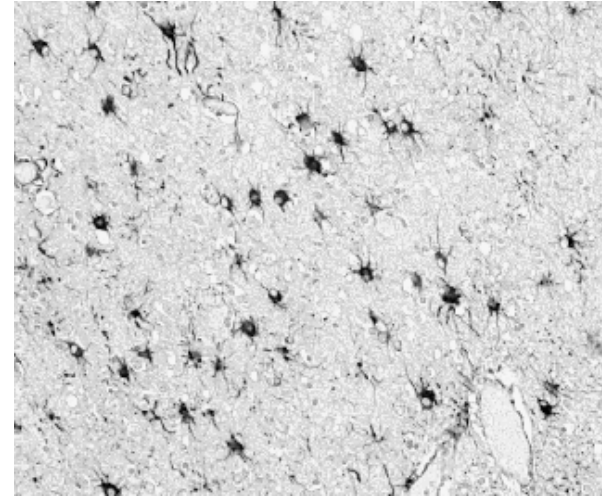
Neuropathology Identifies 4 Major Disease-Perturbed Networks for Prion Disease



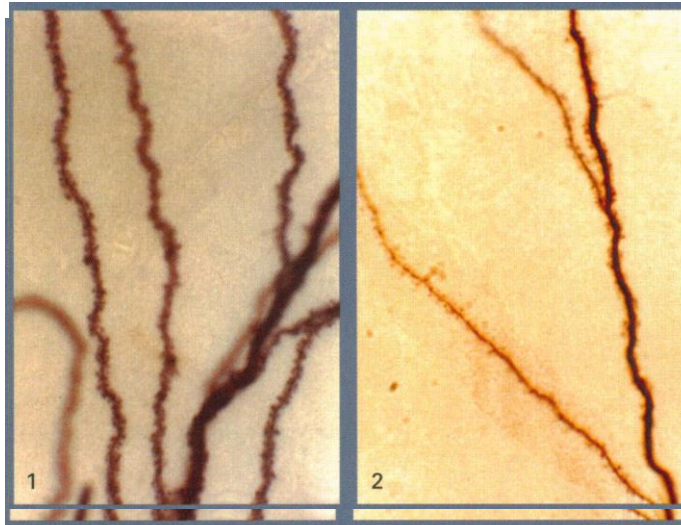
PrP replication/accumulation



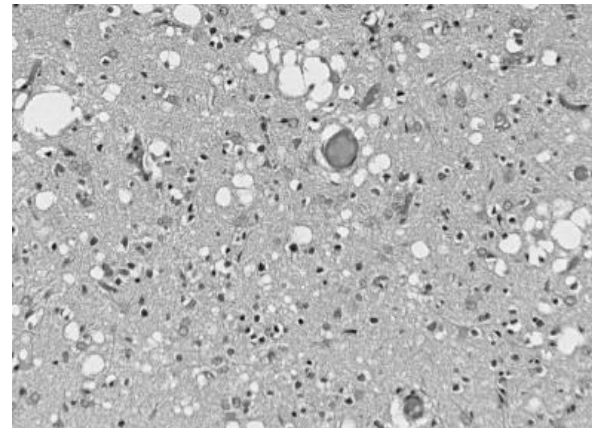
Microglia/astrocyte activation



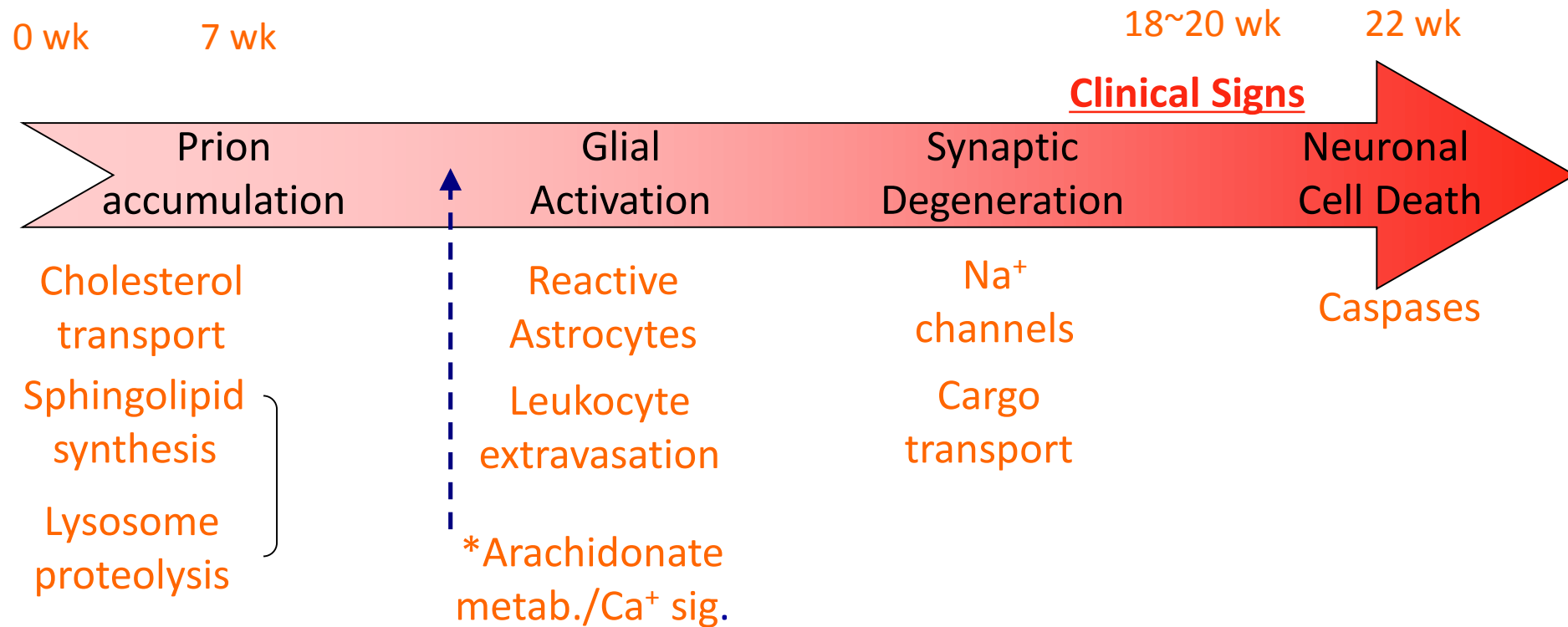
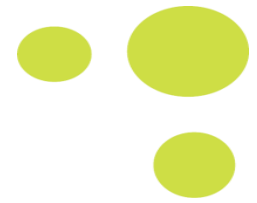
Synaptic degeneration



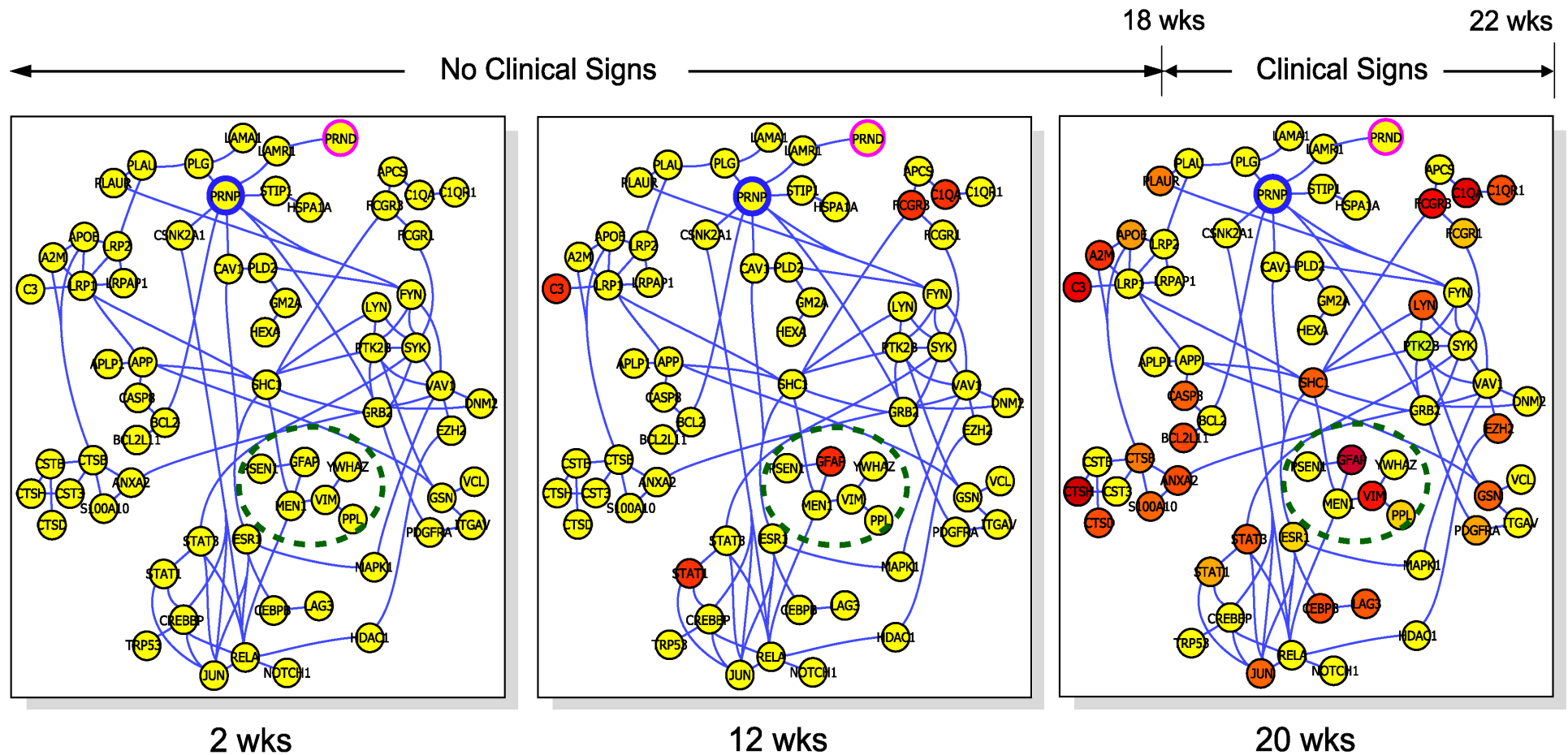
Nerve cell death



Sequential Disease-Perturbation of the Four Major Networks of Prion Disease



10 Disease-Perturbed Dynamical Networks in Prion Disease Explain Virtually all of the Pathophysiology of the Disease in Mice



Systems Strategies for Systems Medicine



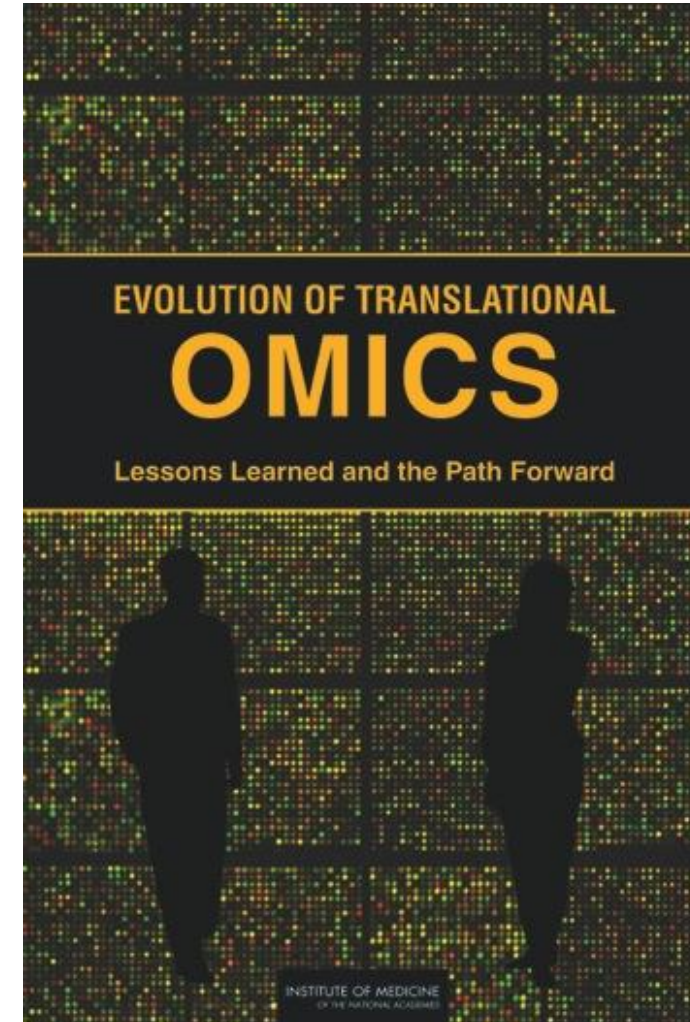
- A **systems-driven approach to blood diagnostics**—making blood a window into health and disease—prion disease, lung cancer and posttraumatic stress disorder
- A **futuristic global wellness assay** using microfluidics and peptide protein-capture agents and smart phones
- A **digital-age, longitudinal study of 100,000 well people** for 20-30 years



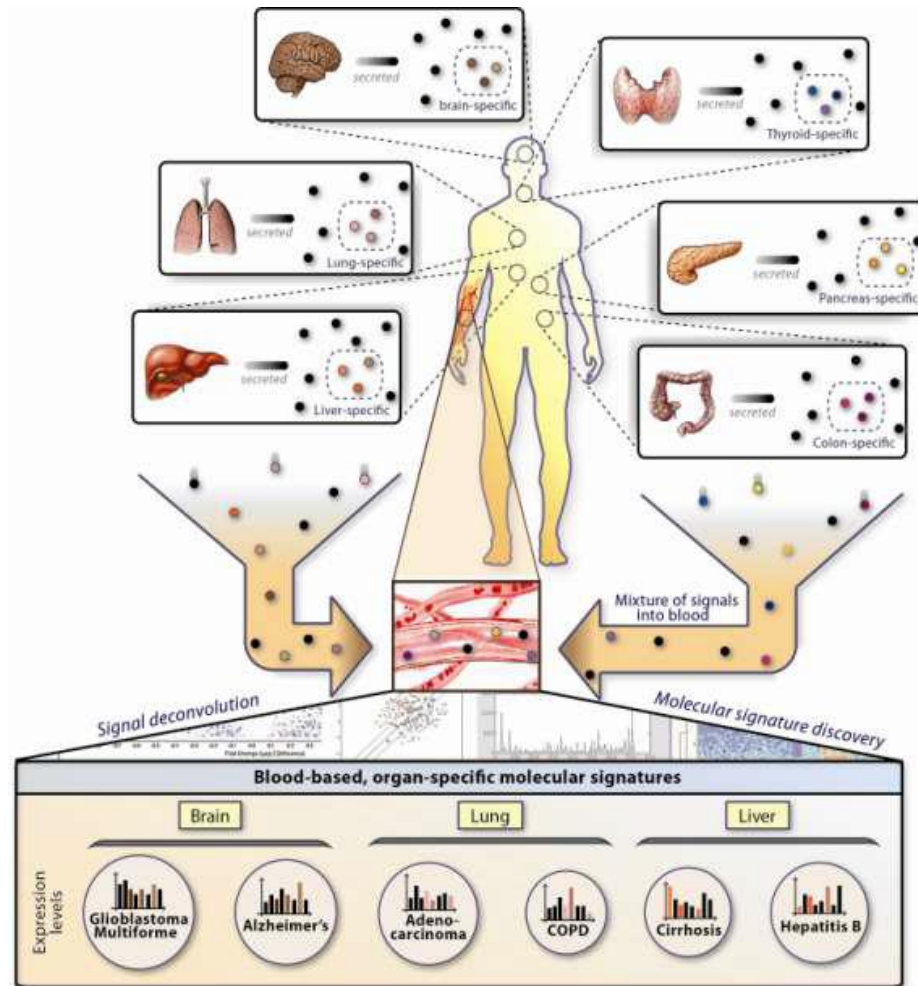
A systems driven strategy: systems
diagnostics--making blood a window into
distinguishing health from disease

High-throughput technologies set the stage for **information-rich systems medicine**

- Key issues include:
 - Many published, highly promising results that don't hold up for conversion to useful clinical assays
 - Need for systems analysis for extracting signal from noise--knowledge from data
 - Genetic diversity means must carry out assays in different geographical locations
- Report on best-practices released in 2012



Blood as a Window to Health and Disease



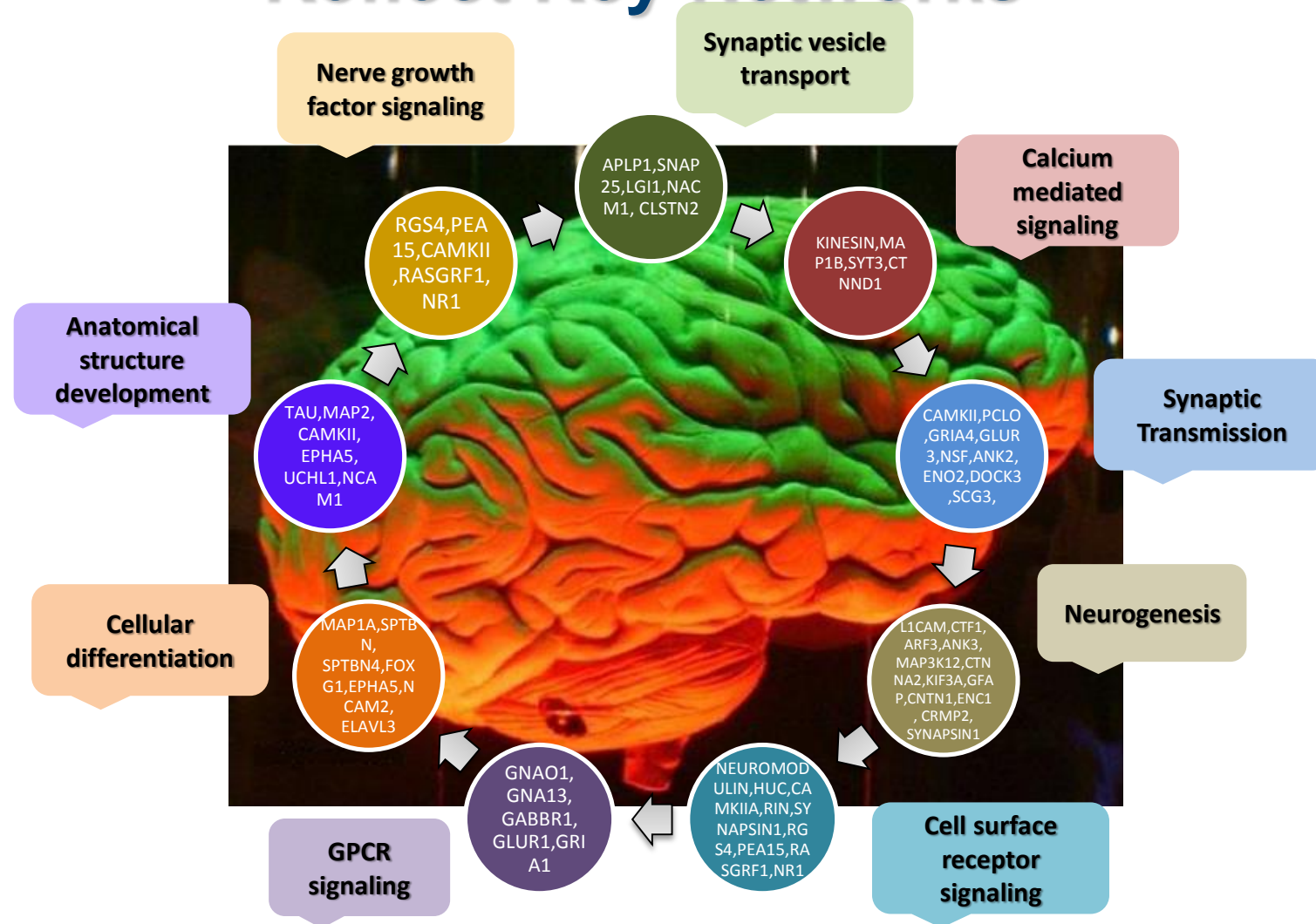
- **Systems decoding health and disease signals from the body**


- Blood is the key window as it bathes all organs
- Longitudinal analyses
- Multiparameter panels
- Quantitative analyses—targeted mass spectrometry
- Proteins may be most effective blood biomarkers
- Systems strategies for dealing with signal to noise
 - Organ-specific blood proteins
 - Systems filtering approaches in blood



Dynamics of prion-induced
neurodegeneration in mice as seen through
the blood with **brain-specific blood proteins**

200 Brain-Specific Blood Proteins Reflect Key Networks



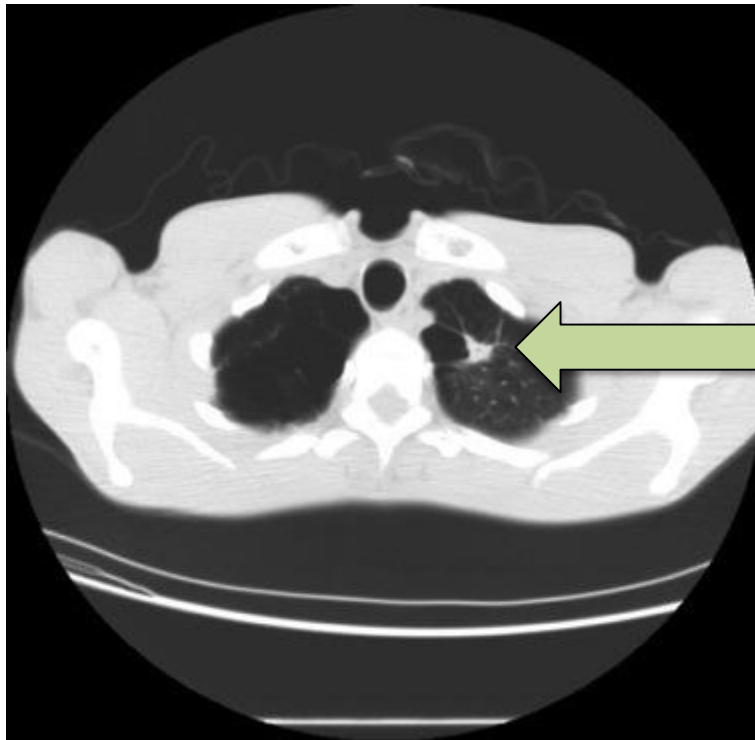
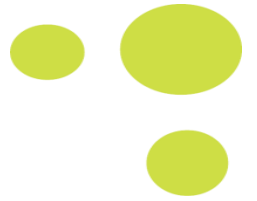


A **systems-filtering approaches** to blood diagnostic for identifying benign lung nodules in human lung cancer

Integrated Diagnostics—Paul Kearney, Xiao-jun Li, etc.

X. Li et.al. Science Translation Medicine: 5, 207, 2013

Indeterminate Pulmonary Nodules

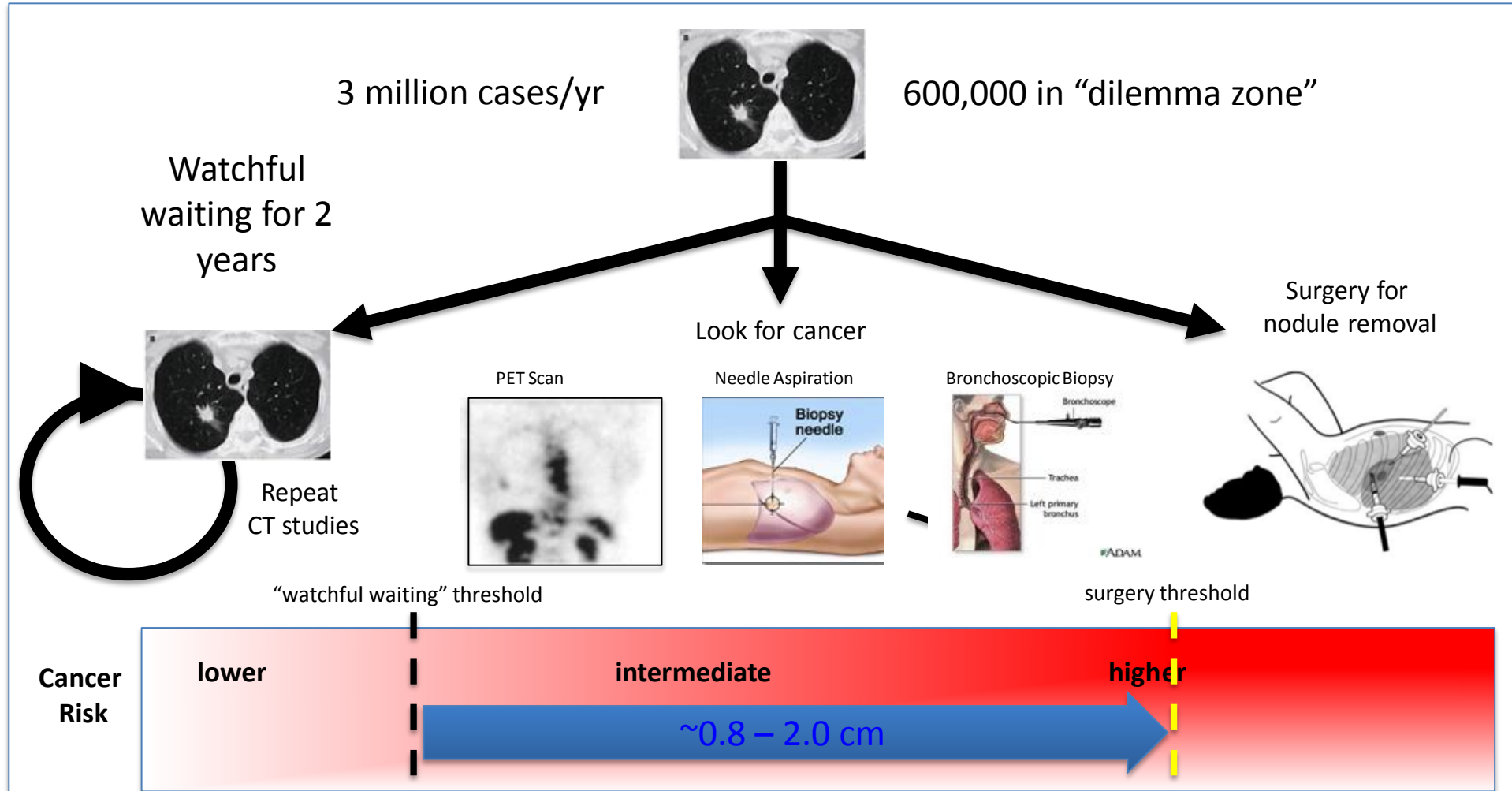


Is this cancer?

~3 million cases
annually in the USA

Patrick Nana-Sinkham, MD Ohio State University

Lung Nodules Found by CT Scan in USA

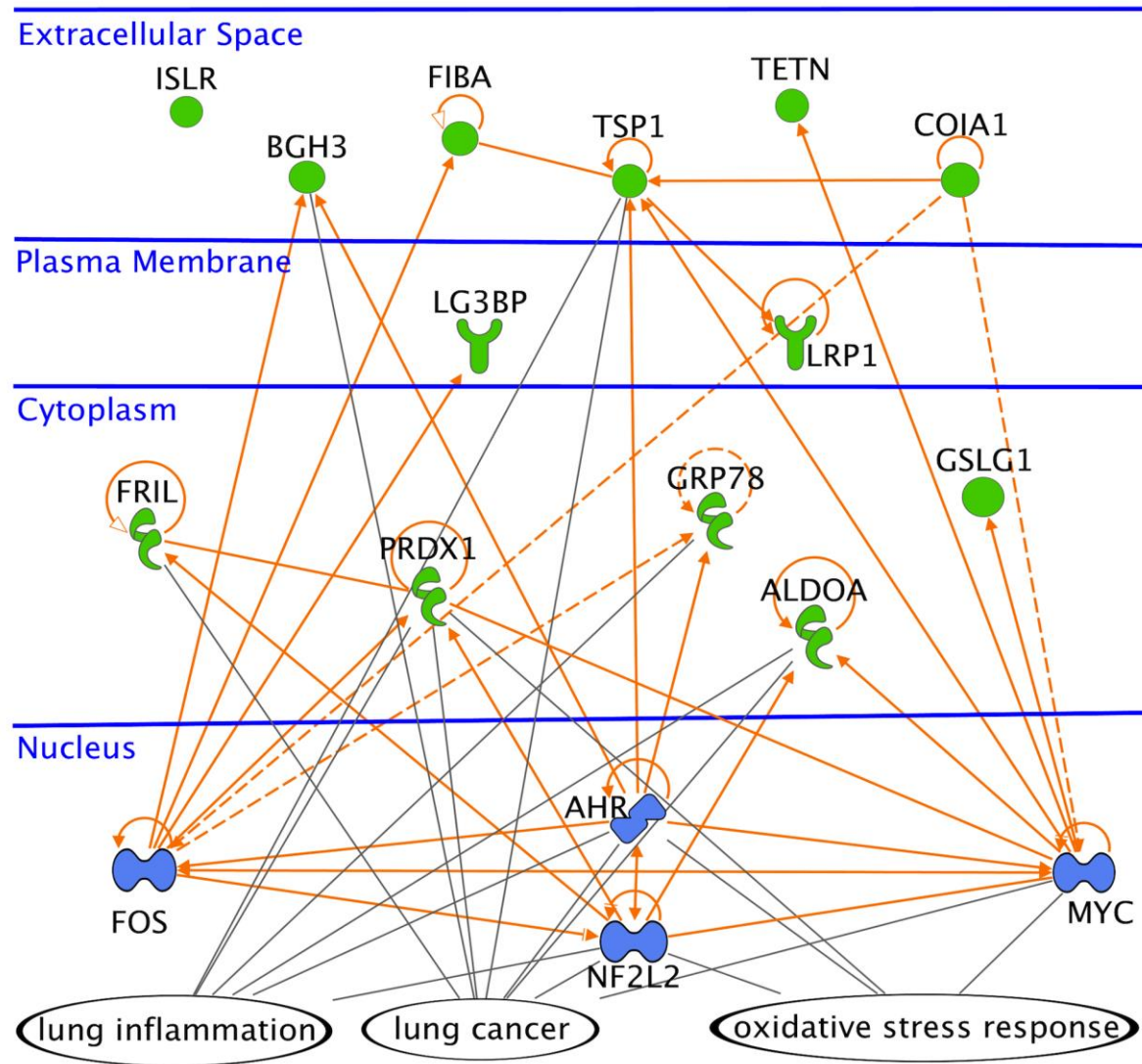
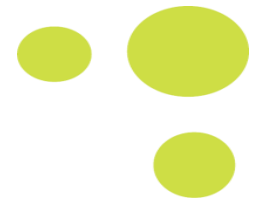


(Ost DE and Gould MK. Decision Making in the Patient with Pulmonary Nodules. Am. J. Respir. Crit. Care Med. October 6, 2011 as doi:10.1164/rccm.201104-0679C)

Lung cancer blood biomarker panel

- Rule out for surgery about 40% of the benign nodules with 90% specificity—prevent 1/3rd of unnecessary surgeries
- Save the healthcare system in US about \$3.5 billion per year
- Bring “peace of mind” to many patients
- Panel is independent of 3 classical criteria for lung cancer—age, smoking history and size of lung nodule

Three Lung Cancer Networks Monitored: 12/13 biomarkers map to these networks



Blood Biomarker Panels for Detecting Disease—Seven Features

- Distinguish normal individuals from diseased individuals
- Early diagnosis
- Follow progression
- Follow response to therapy
- Detect re-occurrence of disease
- Reveal disease-perturbed networks which suggest mechanisms of disease and candidate drug targets
- Stratification of disease into different subgroups for impedance match against effective drugs—and proper prognosis

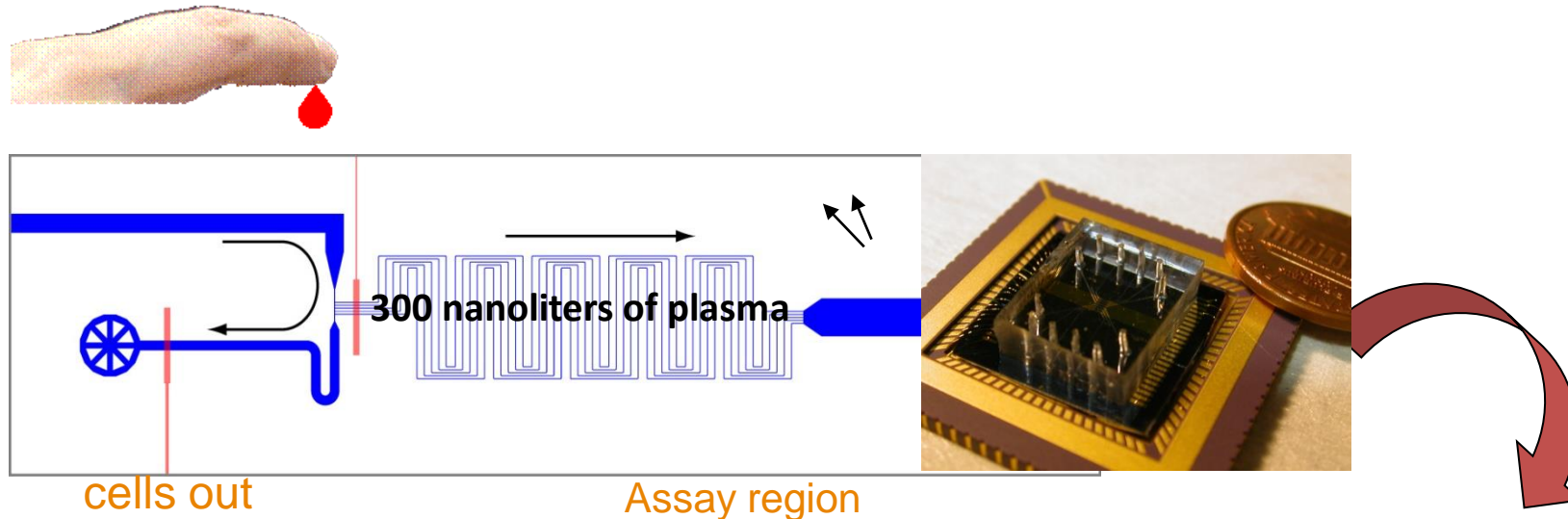


A futuristic wellness assay from a fraction of a droplet of blood in 5 minutes at home: a microfluidic platform, 2500 organ-specific blood proteins and ELIZA assays with peptide protein-capture agents fed into a smart phone

Making Blood a Window into Health and Disease for 100s millions of patients:

50 organ-specific blood proteins from each of 50 organs—measure 2500 blood proteins

Integrated nanotech/microfluidics platform



1. Uses fraction of droplet of blood
2. Assay takes 5 minutes to measure 50 proteins
3. Mid amole level of sensitivity
4. Already being used in hospitals
5. Bring it to the smart phone

Jim Heath, et al



Systems medicine has reached a tipping point and is changing the practice of healthcare

Systems Medicine Is Transforming Healthcare



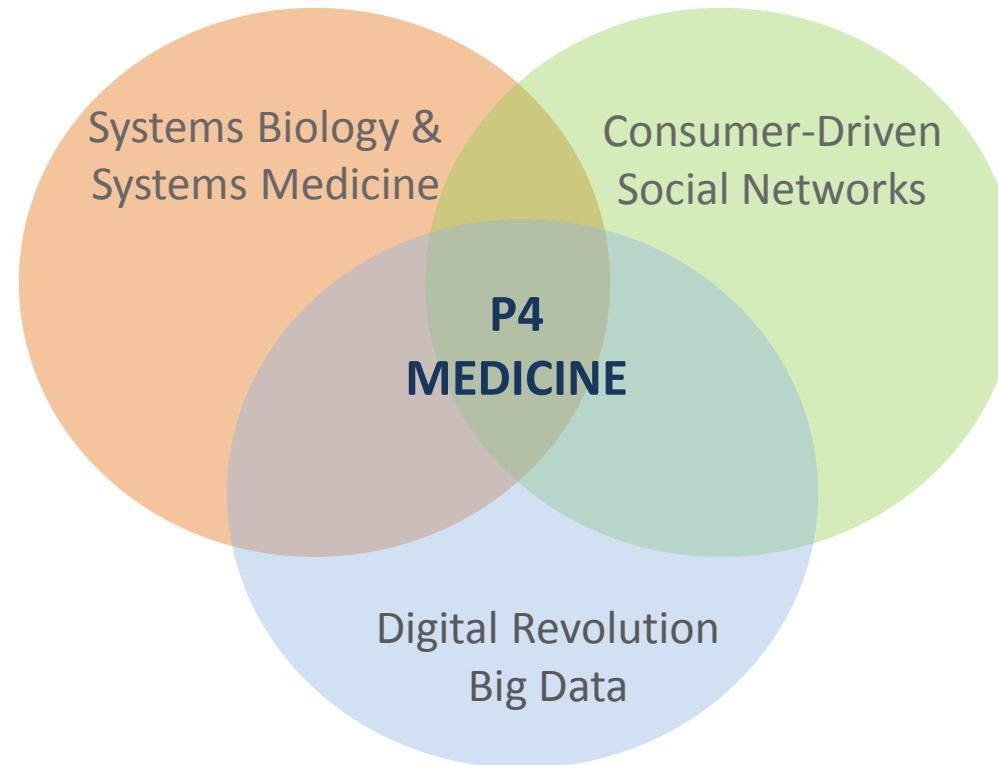
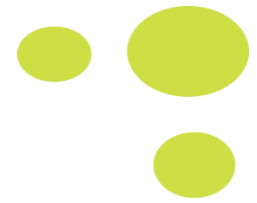
- Provide **fundamental insights** into **dynamical disease-perturbed networks**
 - Enable mechanistic insights, diagnosis, therapy and prevention for the individual patient
- **Family genome sequencing—identifying disease genes**
 - Identify disease, wellness genes and drug-intolerant genes. For the identification for each individual of 300 actionable genes
- Transform **blood into a window to distinguish health from disease**
 - Disease diagnostics, assess drug toxicity, assess wellness
 - Human examples: lung cancer, PTSD, liver toxicity, liver hepatitis
- **Stratify diseases** into their distinct subtypes
 - For impedance match with appropriate drugs
 - Human example: various cancers
- **Stratify patients**—drug adverse reactions, modifier genes to disease mechanisms, eg, early and late onset of Huntington's disease, Variant genes increase mercury susceptibility in kids
- Permit a **multi-organ approach** to the study of disease
 - Unraveling the complexity of the individual patient's disease with organ-specific blood proteins
- Enable a **new computational approaches to pioneering drug reuse and drug target discovery**
 - Re-engineer disease-perturbed networks to normalcy with drugs, Repurpose drugs. faster and cheaper, drugs that prevent networks from becoming disease-perturbed
- **Large-scale, multiparameter, digital-age, longitudinal, Framingham-like clinical trials** for preterm birth, cardiovascular disease, wellness, etc



P4 medicine arises from a convergence of three thrusts in healthcare

The Emergence of P4 Medicine

Predictive, Preventive, Personalize, Participatory



Converging Megatrends

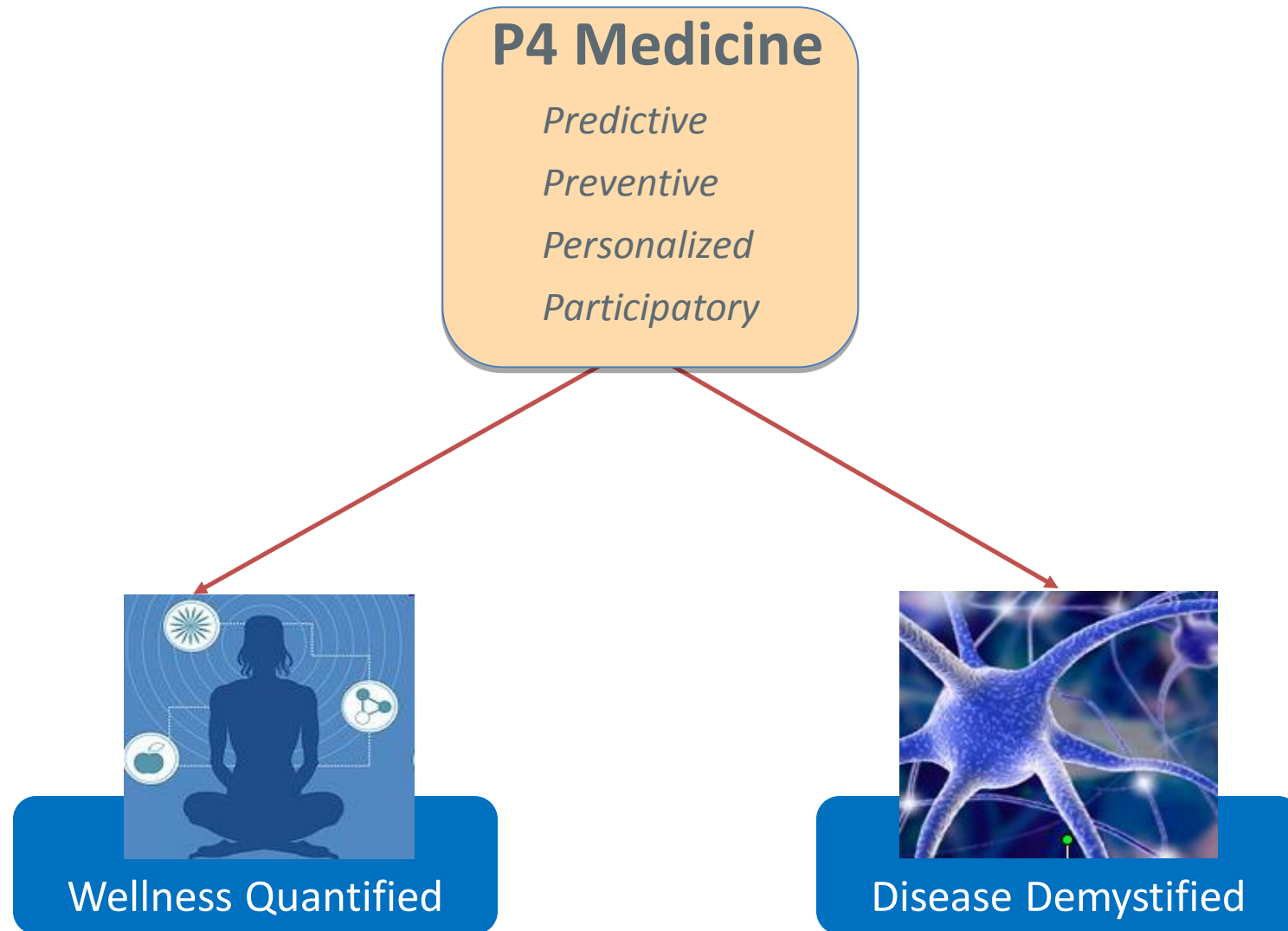
Driving the transformation of healthcare for patients

How P4 medicine differs from population-based medicine



- Proactive
- Focus on Individual
- Focus on Wellness
- Generate, mine and integrate the individual patient data clouds to produce predictive and actionable models of wellness/disease
- Clinical trials--large patient populations analyzed at single individual level (not population averages!) to generate quantized stratification of patient populations and create the predictive medicine of the future. **N=1 experiments.**
- Patient-driven social networks are a key to driving the acceptance of P4 medicine. The emergence of the quantified self networks in many cities demonstrates crowd sourcing and the ability to drive physician to start learning about wellness.

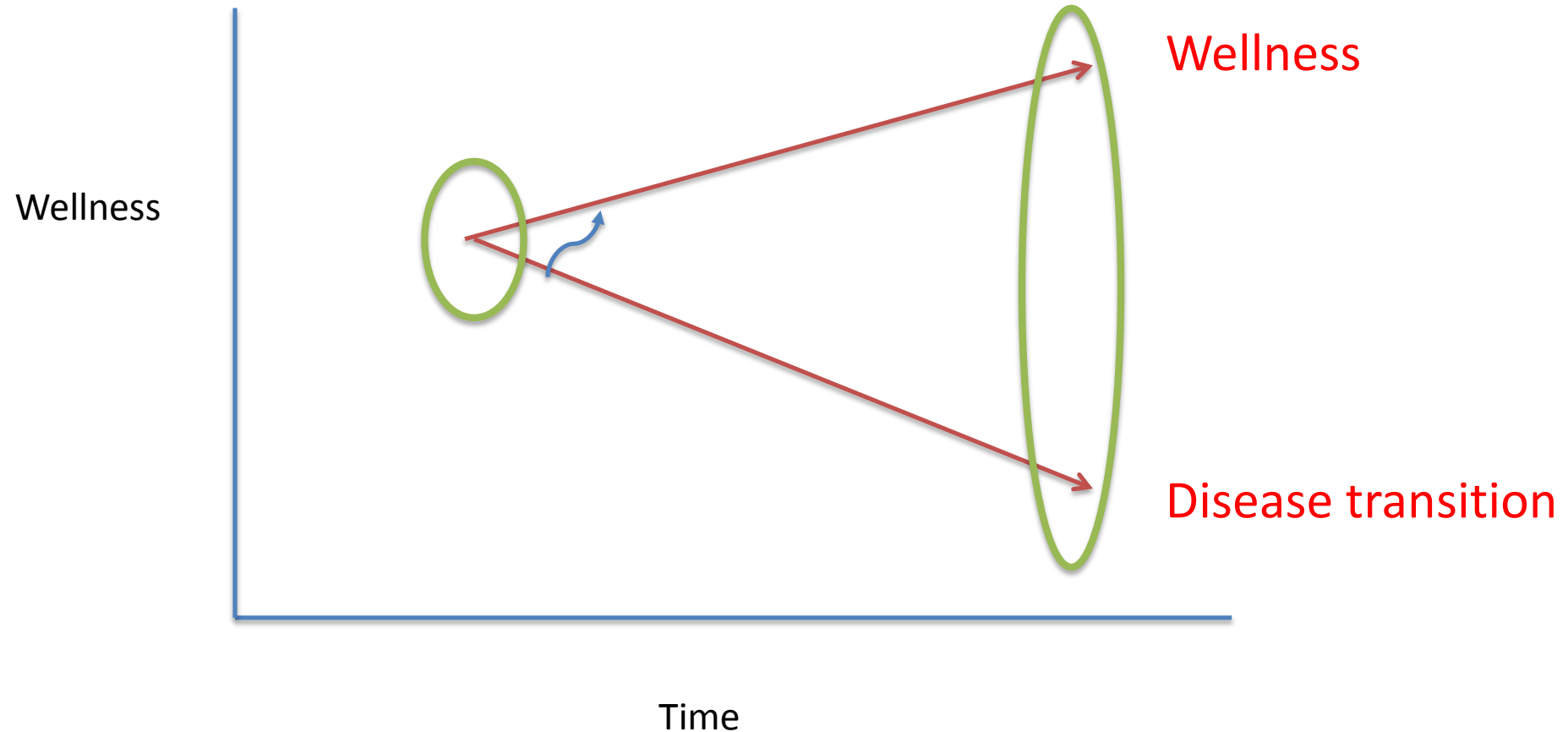
Conceptual Themes of P4 Medicine





A Framingham-like P4 pilot project: digital-age study of wellness in 100,000 (100K project) patients longitudinally—20-30 years

Health: What do we really want to understand from 100,000 well patients?



Personal Trait Data

- Collection of personal and family phenotypes
- Indicators of behavior
- Biomarkers of health

Genomics

- Genome sequencing—300-500 actionable variants
- Disease predisposition - personalized interventions to reduce disease
- Pharmacogenomic analysis to optimize medication choices & dosages
- Nutrigenomic analysis to optimize nutrition

Blood/Urine/Saliva Monitoring

- Clinical chemistries—focus on nutrition
- Personalized and molecular feedback from changes in behavior
- Blood metabolites--1200

Self-Tracking (Quantified Self)

Health monitoring through self-tracking: physical activity, heart rate, sleep patterns, weight, blood pressure, etc

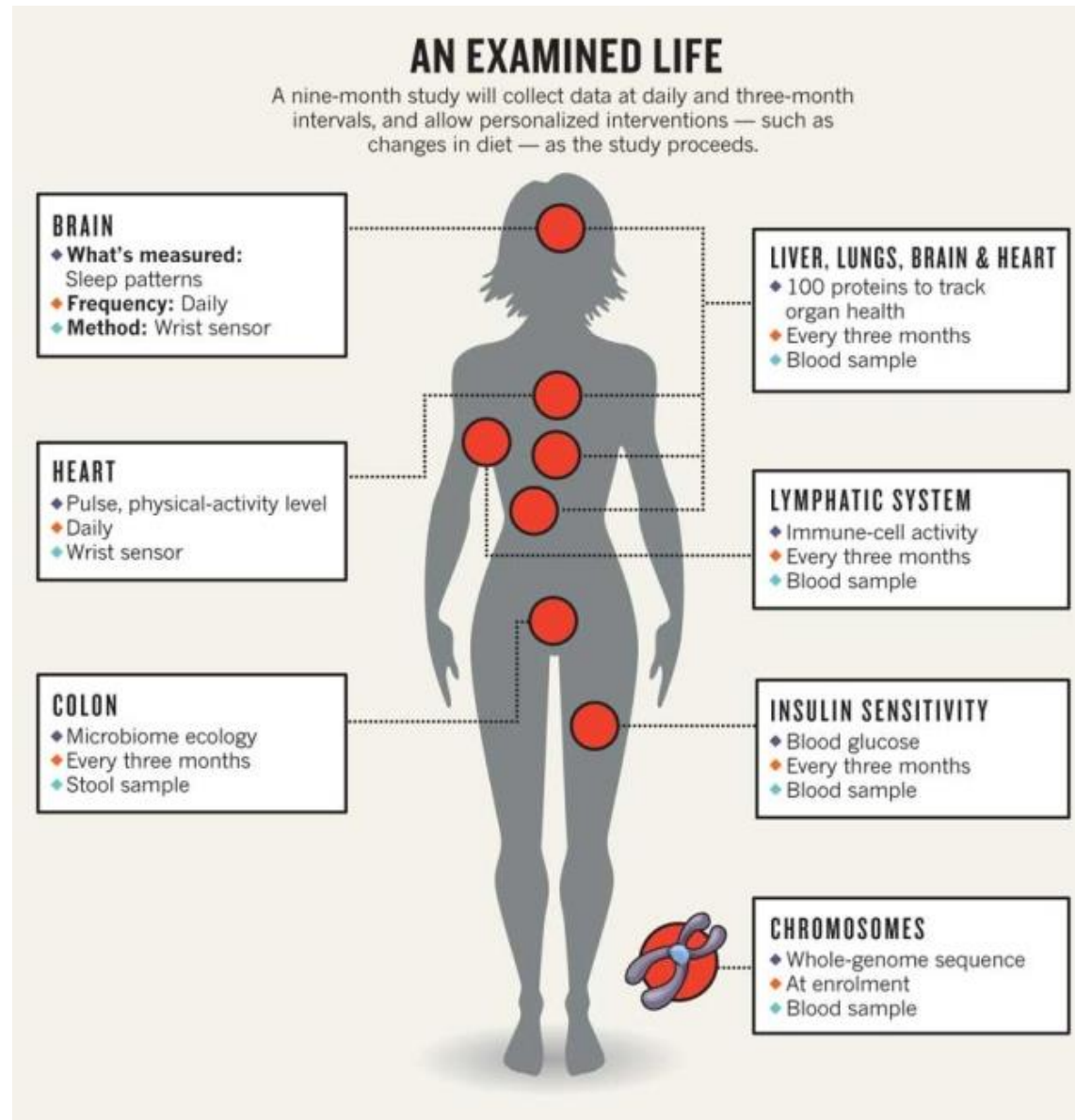
Emerging Novel Biomarkers

- Methylation of WBC DNAs.
- Microbiome: track ecology of major microbial species in the gut
- Organ-specific blood proteins to monitor wellness to disease transitions in brain, heart and liver.

Big Data / Analytics

1. Collection, integration
1. Discovery
2. Personalize health information
3. Short and long term benefits

100 Pioneer Wellness Project: Started March 2014

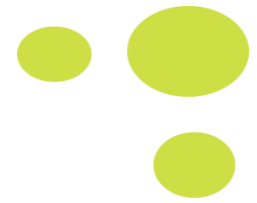




Actionable traits

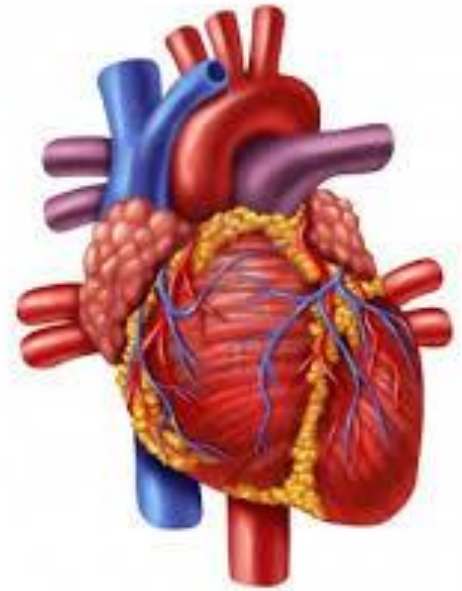
- From individual data types
- From integrated data types
- Coaches with MD advisors for bringing actionable opportunities to each individual
- Social networks—crowd sourcing, learning and driving change in the healthcare system

Actionable Patterns in 100 Pioneers



Cardiovascular Pattern
(abnormal lipids, particle size or density)

Prevalence= 59% (N=62)

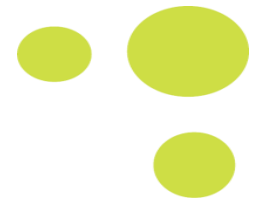


Prediabetes Pattern
(elevated glucose, insulin, HbA1c or HOMA)

Prevalence= 54% (N=50)



Actionable Patterns in 100i Labs



Inflammation Pattern
(elevated hs-CRP, IL-6, IL-8,
TNF-alpha, PAI-1)
Prevalence= 68% (N=63)

Nutrient Insufficiency Pattern
(decreased levels of key nutrients)
Prevalence= 91% (N=87)



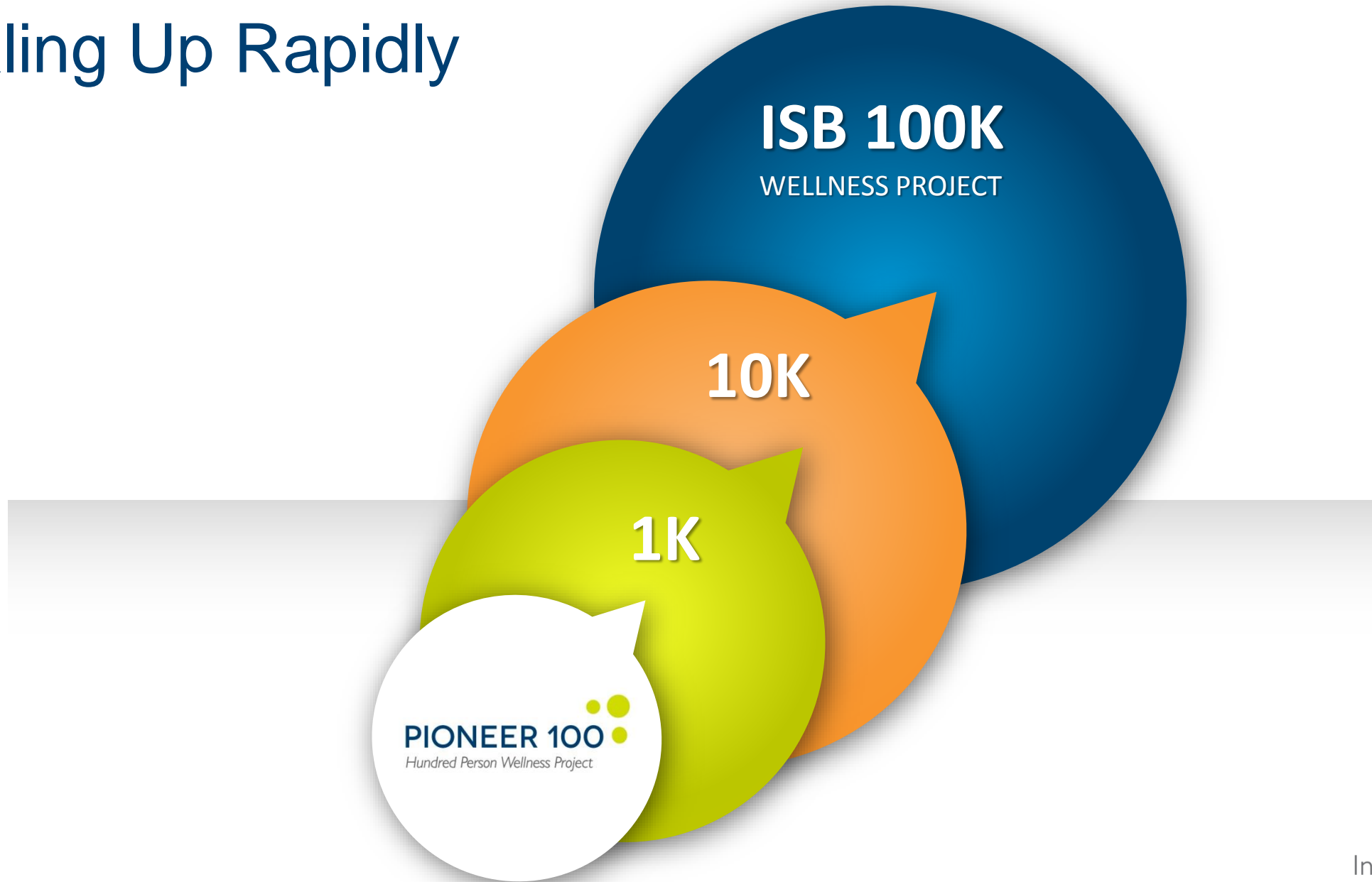


100% of the 100 Pioneers have actionable traits by examining just one type of data—hence virtually every person will have multiple actionable traits—and these will change as the environment changes



How will we proceed?

Scaling Up Rapidly



Additional Comments on the 100K Project



- Collaboration with NIST to standardize sample collections and data types
- Individuals from about 15 Countries have contacted us about initiating their own 100K projects
- Consideration of making 100K project a national (or international) initiative like the genome project
- Two wellness strategies going forward
 - 100K discovery project—discover the effective features of P4 medicine and bring it into the healthcare system
 - Wellness company—scalability, exportability to the developed and under-developed worlds and the democratization of healthcare
- Moore's law will decrease dramatically the cost of the assays (and analytics)—100,000-fold decrease in cost DNA sequencing since 1985



Benefits of 100K wellness project

Benefits of 100K/P4 program



- **Dynamical personal data clouds**—optimize wellness/minimize disease
- **Comprehensive catalogue of actionable possibilities**
- **Metrics for wellness**—revealing fundamental human features—stress, resilience, physiological age, etc.
- Delineate mechanisms for the **transitions from wellness to disease**—how to stop disease early—early disease mechanism, early diagnostics, therapeutics
- **Drive smart phone measurement technologies for assays and coaching**—do it at home—digitization of medicine and the democratization of healthcare
- **Drive and develop integrative analytical software**
- **Bring P4 medicine to the healthcare system**
 - Improve the quality of healthcare
 - Decrease the cost of healthcare
 - Introduce wellness as a central concept in healthcare
- Drive the **development of a healthcare industry** that is responding to the imperatives of P4 medicine—eliminate the company dinosaurs
- Drive the **development of a wellness industry** that will in 10-15 years exceed the market cap of the healthcare industry—create wealth

100K/P challenges regarding IT for healthcare

- Integrate the dynamical data of patient records, the omics, higher level phenotypes and in vivo imaging in a manner scalable to billions
- Education the patients, physicians and healthcare community as to the P4 revolution
- Medical records—security, de-identification, ethics, conform to regulatory policies
- Create and apply standards for evaluation of sample collections and all types of data
- Create IT for managing regulatory constraints
- Include “gold standards” web site for diagnoses accessible to patients and physicians
- Recognize that an enormous amount of domain expertise will be required to accomplish these goals

Proposal to Microsoft

- Create a pipeline for the data of the 100K (100 Pioneer) project that is scalable to millions of individuals.
- The pipeline should automate the aggregation of individual data, storage, analysis, integration, model building, inference, reporting, visualization, stratification of individuals into medically relevant groups, etc. Health Vault could be extremely useful in this regard.
- This would be a big step towards IT for healthcare in the coming P4 world of medicine.

Acknowledgements

Prion--Institute for Systems Biology

Daehee Hwang
Inyoul Lee
Hyuntae Yoo

Nanotechnology—protein chips, protein-capture agents--Jim Heath, Caltech, Indi Diagnostics, Inc

SRM protein assays and Human Proteome—R Moritz, R Aebersold, Y Zhou, Shizen Qin
Integrated Diagnostics, Inc. and Agilent

Single-cell analyses and iPS cells—Leslie Chen and Qiang Tian, M Shelton, K Trachana, R Bargaje

Mouse and human glioblastoms—R Bargaje, B Kutlu, L Chen, Q Tian, Terry van Dyke, NCI

Prion--McLaughlin Research Institute
Great Falls, Montana

Ranjit Giri
Douglas Spicer
Rajeev Kumar
Rose Pitstick
Rebecca Young
George A. Carlson

Family genome project—G. Glussman, J Roach, S Ament, Complete Genomics

P4 medicine and 100K project—
Mauricio Flories, Nathan Price, Kristen Brogaard, , Clayton Lewis, M Ashida, G Glussman, Sean Bell

Single protein analysis—Chris Lausted

Brain imaging—Nathan Price (ISB)



Save the planet and return
your name badge before you
leave (on Tuesday)

