Systems Medicine and Proactive P4 Medicine: Revolutionizing Healthcare
Predictive, Preventive, Personalized and Participatory

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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)

Prion strains:
- RML
- 301V

Mouse strains:
- C57BL/6J
- FVB/NCr
- BL6.I
- FVB/B4053

Inoculate w/ Prions

Prion infected brain

RNA from brain homogenate

Uninfected brain

Time-course array analysis: subtractive analyses to DEGs

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

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

Mouse Genome array: 45,000 probe sets ~22,000 mouse genes.
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

0 wk  7 wk  18~20 wk  22 wk

Clinical Signs

Prion accumulation

Glial Activation

Synaptic Degeneration

Neuronal Cell Death

Cholesterol transport

Sphingolipid synthesis

Lysosome proteolysis

Reactive Astrocytes

Leukocyte extravasation

Na⁺ channels

Cargo transport

*Caspases

*Arachidonate metab./Ca⁺ sig.
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 baths 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

- **Nerve growth factor signaling**
  - APLP1, SNAP25, LG1, NAC M1, CLSTN2
  - KINESIN, MA P1B, SYT3, CT NND1
  - CAMKII, PCLO, GRIA4, GLUR3, NSF, ANK2, ENO2, DOCK3, SCG3, L1CAM, CTF1, ARF3, ANK3, MAP3K12, CTNNA2, KIF3A, GFA P, CNTN1, ENC1, CRMP2, SYNAPSIN1
  - NEUROMODULIN, UNL, HUC, CAMKII, RIN5, SYNAP1, RGSGF3, 3

- **Synaptic vesicle transport**
  - TAU, MAP2, CAMKII, EPHA5, UCHL1, NCA M1
  - MAP1A, SP1, N, SP2, N4, EPHA5, G1, EPHA5, N, CAM2, ELAVL3
  - GNAO1, GNA13, GABBR1, GLUR1, GRI A1
  - NEUROMODULIN, UNL, HUC, CAMKII, RIN5, SYNAP1, RGSGF3, 3

- **Calcium mediated signaling**
  - Synaptic Transmission
    - Synaptic Transmission
  - Neurogenesis
  - Cell surface receptor signaling
    - GPCR signaling
    - Anatomical structure development
    - Cellular differentiation

- **200 Brain-Specific Blood Proteins Reflect Key Networks**
15 Brain-Specific Blood Proteins Reflect the Early Detection and Progression of Prion Disease-Perturbed Networks

**Clinical Signs**

- 0 wk
- 18~20 wk
- 22 wk

<table>
<thead>
<tr>
<th>Prion accumulation</th>
<th>Glial Activation</th>
<th>Synaptic Degeneration</th>
<th>Neuronal Cell Death</th>
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<tbody>
<tr>
<td>Cholesterol transport</td>
<td>Reactive Astrocytes</td>
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<td>Caspases</td>
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<tr>
<td>Sphingolipid synthesis</td>
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<td>Gria1*</td>
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<td>Lysosome proteolysis</td>
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<td>Snap25*</td>
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<td>Apod*</td>
<td>Gfap*</td>
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<td>Cntn2*</td>
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<tr>
<td>Ttc3*</td>
<td>Prkar1b*</td>
<td></td>
<td>Bcas1</td>
</tr>
</tbody>
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* indicates brain-specific blood proteins
A systems-filtering approaches to blood diagnostic for identifying benign lung nodules in human lung cancer

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

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

3 million cases/yr

600,000 in “dilemma zone”

Watchful waiting for 2 years

PET Scan

Repeat CT studies

Needle Aspiration

Bronchoscopic Biopsy

Look for cancer

Surgery for nodule removal

“watchful waiting” threshold

Cancer Risk

~0.8 – 2.0 cm

intermediate

~lower

higher

600,000 in “dilemma zone”

Lung cancer blood biomarker panel

• Rule out for surgery about 40% of the benign nodules with 90% specificity—prevent 1/3\textsuperscript{rd} 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

P4 Medicine

*Predictive*
*Preventive*
*Personalized*
*Participatory*

Wellness Quantified

Disease Demystified
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?
Continuous Monitoring of Health & Data Collection

**Clinical chemistries**
- Focus on nutrition

**Blood metabolites**
- 1200 Blood/Urine/Saliva Monitoring

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.

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

Big Data / Analytics
1. Collection, integration
2. Personalize health information
3. Short and long term benefits

Personal Trait Data
- Collection of personal and family phenotypes
- Indicators of behavior
- Biomarkers of health
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

ISB 100K
WELLNESS PROJECT

10K

1K

PIONEER 100
Hundred Person Wellness Project
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.
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Single protein analysis—Chris Lausted

Brain imaging—Nathan Price (ISB)
Save the planet and return your name badge before you leave (on Tuesday)

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