Systems and proactive P4 medicine—making blood a window into health and disease: A tipping point that is transforming healthcare

Predictive, Preventive, Personalized and Participatory

Lee Hood
Institute for Systems Biology, Seattle
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Conflict statement

I am a cofounder, have stock and am on the board of Integrated Diagnostics—a blood diagnostic company.
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 6 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 and an infrastructure for systems biology.
- **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.
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
Systems Medicine Is at a Tipping Point

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

Cancer genome sequencing—identifying driver mutations

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
Three stories about systems-driven blood diagnostics—desirable features—require multiparameter blood panels

- Distinguish normal individuals from diseased
- Early disease diagnosis
- Follow progression of disease
- Follow response to therapy
- Follow disease reoccurrences
- Stratification of disease
Dynamic approaches to prion-induced neurodegeneration in mice—implications for blood diagnostics—story 1
Global and Subtractive Brain Transcriptome Analysis—Differentially Expressed Genes (DEGs)

Inoculate w/ Prions

Prion strains:
- RML
- 301V

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

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

Prion infected brain

RNA from brain homogenate

Uninfected brain

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

- **Prion accumulation**
  - Cholesterol transport
  - Sphingolipid synthesis
  - Lysosome proteolysis

- **Glial Activation**
  - Reactive Astrocytes
  - Leukocyte extravasation
  - *Arachidonate metab./Ca⁺ sig.

- **Synaptic Degeneration**
  - Na⁺ channels
  - Cargo transport

- **Neuronal Cell Death**
  - Caspases

Clinical Signs:
- 0 wk
- 7 wk
- 18~20 wk
- 22 wk
10 Disease-Perturbed Dynamical Networks in Prion Disease Explain Virtually all of the Pathophysiology of the Disease in Mice
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

Synaptic vesicle transport

Calcium mediated signaling

Anatomical structure development

Cellular differentiation

GPCR signaling

Synaptic Transmission

Neurogenesis

Cell surface receptor signaling

RGS4, PEA15, CAMKII, RASGRF1, NR1

MAP1A, SPTBN, SPTBN4, FOXG1, EPHA5, N CAM2, ELAVL3

GNAQ1, GNA13, GABBR1, GLUR1, GRIA1

NEUROMOD, ULIN, HUC, CAMKII, RIN, SYNAPSIN1, RGS4, PEA15, RASGRF1, NR1

KINESIN, MAP1B, SYT3, CTNN1

CAMKII, PCLO, GRIA4, GLUR3, NSF, ANK2, ENO2, DOCK3, SCG3

L1CAM, CTF1, ARF3, ANK3, MAP3K12, CTNNA2, KIF3A, GFA, P, CTN1, ENC1, CRMP2, SYNAPSIN1

APLP1, SNAP25, LG1, NACM1, CLSTN2

Synaptic vesicle transport

Calcium mediated signaling

Nerve growth factor signaling

Anatomical structure development

Cellular differentiation

GPCR signaling

Synaptic Transmission

Neurogenesis

Cell surface receptor signaling

200 Brain-Specific Blood Proteins Reflect Key Networks
Targeted MS Proteomics: Human Selective Reaction Monitoring (SRM) Atlas

ISB has developed SRM/MRM assays for most of the known 20,333 human proteins

Analyze 100-200 proteins quantitatively in 1 hour

Heavy isotope peptides for Q3 analyses allow precise quantification
15 Brain-Specific Blood Proteins Reflect the Early Disease Detection and Progression of Prion Disease-Perturbed Networks

- Cholesterol transport
- Sphingolipid synthesis
- Lysosome proteolysis

Prion accumulation

Glial Activation
- Apod*
- Scg3
- Ctnn2*
- Ttc3*
- Reactive Astrocytes
- Leukocyte extravasation
- *Arachidonate metab./Ca^+ sig.

Synaptic Degeneration
- Gria3*
- Gfap*
- L1cam
- Na^+ channels
- Cargo transport
- Mapt*
- Snap25*
- Myo5a*
- Kif5a
- Grin1*
- Prkar1b*

Neuronal Cell Death
- Caspases
- Gria1*
- Bcas1

Clinical Signs

0 wk

18~20 wk

22 wk

* indicates brain-specific blood proteins
Organ-specific blood proteins allow one to study the dynamics of biological processes in humans through the blood window.

- Development
- Physiology
- Aging
- Wellness
- Disease dynamics (diagnostics)
- Disease stratification
- Drug toxicity
- Multi-organ responses to disease
Examples of mouse model diseases that have been studied dynamically revealing disease-perturbed networks correlating with pathophysiology

- Prion-induced neurodegeneration
- Frontal temporal dementia
- Huntington’s disease
- Post traumatic stress disorder (PTSD)
- Liver toxicity
- 4 models of glioblastoma—mimic Grade II, III, and IV human disease
A systems driven strategy: systems diagnostics--making blood a window into distinguishing health from disease—story 2
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
  - Proteins may be most effective blood biomarkers
  - Systems strategies for dealing with signal to noise
A systems approach 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

Look for cancer

Repeat CT studies

PET Scan

Needle Aspiration

Bronchoscopic Biopsy

Surgery for nodule removal

Cancer Risk

lower

intermediate

~0.8 – 2.0 cm

higher

“watchful waiting” threshold

surgery threshold

Systems Approach to Distinguishing Benign from Malignant Lung Cancer Nodules (with Integrated Diagnostics)

- 371 SRM assays for lung cancer tissue/190 detectable in the blood
  - Differentially secreted (normal vs. neoplastic)
  - Differentially shed from cell surface (normal vs. neoplastic)
  - Candidates captured from the literature
- Discovery samples—analyze all 190 detectable proteins
  - 72 cancer vs. 72 benign/four sites
- Discovery algorithm for “cooperative” proteins
  - Select the 32 (out of 190) best proteins for distinguishing nodules
  - A million random panels of 10 of 32 best proteins were scored
  - Identified 13 proteins that were highly “cooperative”—generally in most effective panels
- Validation study—13-protein panel
  - 52 cancer vs. 52 benign/from 4 sites plus 1 new site
- InDi commercialize the panel of 13 blood proteins in Q4 2013
- Published in Science Translational Medicine, Oct. 20, 2013
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 Essential Features--Multiparameter

• Distinguish normal individuals from diseased individuals
• Early diagnosis
• Follow progression
• Follow response to therapy
• Follow disease reoccurrences
• 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
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 contemporary 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
Understanding Health and Disease

How do we get there?

1. Scientifically validated metrics for wellness
2. Analyses at the initial stage of disease transition
3. Tracking disease progression from initiation to end
A Framingham-like P4 pilot project: digital-age study of wellness in 100,000 (100K project) patients longitudinally—20-30 years—story 3
Health: What do we really want to understand from 100,000 well patients?

Wellness

Disease transition

Time
Continuous Monitoring of Health & Data Collection

**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
2. Discovery
3. Personalize health information
4. Short and long term benefits
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
100 Pioneer Wellness Project: Started March 2014

AN EXAMINED LIFE
A nine-month study will collect data at daily and three-month intervals, and allow personalized interventions — such as changes in diet — as the study proceeds.

**BRAIN**
- **What’s measured:** Sleep patterns
- **Frequency:** Daily
- **Method:** Wrist sensor

**LIVER, LUNGS, BRAIN & HEART**
- 100 proteins to track organ health
- Every three months
- Blood sample

**HEART**
- Pulse, physical-activity level
- Daily
- Wrist sensor

**LYMPHATIC SYSTEM**
- Immune-cell activity
- Every three months
- Blood sample

**COLON**
- Microbiome ecology
- Every three months
- Stool sample

**INSULIN SENSITIVITY**
- Blood glucose
- Every three months
- Blood sample

**CHROMOSOMES**
- Whole-genome sequence
- At enrolment
- Blood sample
98% of the 107 Pioneers have actionable traits (1-4) 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

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Additional Comments on the 100K Project

• Collaboration with NIST to standardize sample collections and data types
• Individuals from 7 Countries have contacted us about initiating their own 100K projects
• Consideration of making 100K project a national (or international) initiative like the genome project
• Moore’s law will decrease dramatically the cost of the assays (and analytics)—100,000-fold decrease in cost DNA sequencing since 1985
• 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
Benefits and objectives of the 100,000 wellness person project
100K Project: Objectives/Benefits

• Identify vast array of actionable possibilities
• Optimize wellness and reduce disease for each individual patient and reduce the costs of healthcare
• Create a data base of wellness measurements to mine for the “multiparameter wellness metrics” — define fundamental human features
• Generate a data base from individuals that will allow us to follow transitions from wellness to disease for major diseases—cancer, diabetes and neurodegeneration
• Drive the development of improved old and new assays and analytics—parallelize, miniaturize, increase throughput, reduce cost, point of contact
• Bring P4 medicine into the healthcare system
How P4 medicine and the 100K project will transform healthcare
P4 medicine and the 100K project lead to five healthcare implications

• Digitalize medicine for the individual patient—a larger revolution than the digitization of information technologies and communication—patient-driven medicine and wellness—democratization of health

• Turn sharply around escalating costs of healthcare—democratization of healthcare

• Improve the quality of healthcare

• Force a revision of business plans of every sector of healthcare industry—enormous opportunities for innovation and economic gain

• Systems or P4 Medicine will create significant wealth—the emerging wellness industry
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