Complex Adaptive Systems Forum:
Transformative CAS Initiatives in Biomedicine

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Creating CAS-Based Knowledge Networks to Enable Molecularly-Based Medicine

- State of Precision (Personalized Medicine)
- The National Biomarker Development Alliance (NBDA)
- A 21st Century *In Silico* Medicine Consortium
# Increasing Chronic Disease Burden: Looming Healthcare Crisis

<table>
<thead>
<tr>
<th>Disease</th>
<th>Current Burden</th>
<th>Projected Cost</th>
<th>Future Estimates</th>
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<tbody>
<tr>
<td>Alzheimer's</td>
<td>*5.4 million survivors</td>
<td>$130 billion/year</td>
<td>~16 million (Mid-century)</td>
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<td>(6th leading cause of death)</td>
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<tr>
<td>Cancer **</td>
<td>12 million survivors</td>
<td>$263 billion/year</td>
<td>~ 2.0 million new cases/year</td>
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<td>(1.5 million new cases/year)</td>
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<td>(30% in 20 Years)</td>
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<td>(2nd leading cause of death)</td>
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<td>Diabetes ***</td>
<td>25.8 million</td>
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<td>(18.8 M Diagnosed/ 7 M Undiagnosed)</td>
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<td>(7th leading cause of death)</td>
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* Alzheimer’s Association; ** ACS; *** Diabetes Association
Genomics: Establishing a Foundation for Precision (Personalized) Medicine

Vision: understanding genomic changes would enable targeted intervention

- **Since 2003:** Sequencing costs fell from ~$1.0 million in early 2001 to less than $10,000 per genome ($1000/genome possible); Numbers of genomes sequenced 2011 -~ 30,000 (NHGRI); Number of genomes projected end of 2014 - 1.0 million (NGRI); total cumulative global sequencing output (on a path to reach ~ 28PB by late 2014)
It’s RNA
It’s single gene changes
It’s Proteins
It’s Chromosome Changes
It’s Epigenomics
The Genomics Pipeline Today – from Raw Data to 1st Order Function

RAW DATA

GENOME ASSEMBLY

VARIANT IDENTIFICATION

FUNCTIONAL ANNOTATION

INTEGRATED ANALYSIS - IN SILICO MEDICINE

220 GB per sample

1000 GB/SAMPLE

100 MB/SAMPLE

Storage, Management and Transfer

Data Compression
Cancer is a Complex Evolving System (composed of multiple subsystems)

- chemical
- virus
- hormone
- nutrition

Co-Evolution of Information-Driven Communication Between Cancer Cells/networks and their Environment (In Context) Across Scales
Complex Diseases (e.g. Cancer) are CAS – All Share 2 Features

Genomic alterations (information) drive the development of new information that enables the emergence of many diseases – e.g., cancer is an emergent property of the interactions of elements/subsystems across scales.
Big DATA (Cancer is the Prime Example)

TCGA

- Sanger Institute
- ICGC
- International Sequencing Projects

Data - Data
Data - Data
Data – Data
(Issues: Public and Private – Quality, Access, Consents, Etc.)

Pharma/Bio

Individual investigators

Hospitals

NCI-Designated Cancer Centers – Academic Medical Centers
The CAS-Based Diseases will Require Theoretical Constructs that Utilize Information and Evolutionary Theory to Interrogate Multi-Dimensional Data

Information Theory

Evolutionary Theory

Claude Shannon

Charles Darwin

**Information Theory** - mathematical basis for describing/measuring information
Management/decision making in cancer (e.g., can defining changes in fitness (implies changes in information content) be used to predict future disease states?

**Evolutionary Theory** - Perhaps our best hope to predict evolution of resistant states in cancer (Prediction of most probable states)

“the Mind can not possibly grasp …the full effects of many slight variations, accumulated during an almost infinite number of generations – C. Darwin
The *In Silico* Medicine: Integration – and Analysis of Multi-Dimensional – “BIG DATA”
In silico Medicine Consortium Status

- Discussions of concept and construct began ~ 1 year ago with staff from Biodesign, Mayo Clinic, Intel and Others ("Big Data Project")

- Goal 1 is an *in silico* center that creates a high quality continuum in the genome sequencing space that maximizes functional information and minimizes noise.

- Goal 2 is to create an integrated in silico approach that aggregates and enables “big data” from the genome, phenome and exposome

- Goal 3 is a new generation of tools for physicians that maximize disease amelioration.

- Goal 4 is knowledge network that serves as a learning system to ensure that patients benefit from the system.

- Currently – developing partner agreements – initiating demonstration projects

- Seeking computational/modeling scientists from ASU
Genomic Changes, Pathways, Networks: Early in the Discovery Process = Biomarkers

Hanahan and Weinberg
Potential of Biomarkers

- New **target discovery** (understand underlying biology)
- Drug **development** – markers of toxicity, metabolism, etc. - **pharmacogenomics**
- **Early detection** (broad or specific detection / corroboration of specific disease stage)
- Identify **molecular basis of disease phenotypes**
- **Rational** choice of **treatments (patient stratification)**
- **Assessment** of treatment **effectiveness**
- **Prognostic biomarkers**
- **Prevention markers**
- **Surrogate endpoints for clinical trials**
Status of Protein-Based Biomarkers

Few biomarker candidates translating into clinical utility and at a steadily declining rate

- Well over 1260 putative protein biomarkers described in the literature
- Very few approved by FDA for clinical use
- Large numbers of biomarker publications and claims – but bias and lack of standards, reproducibility across labs and SOPs make discoveries questionable
- Molecular diagnostics business remains underdeveloped

Source: Based on data from FDA and Plasma Proteome Institute
Why is the Development of Biomarkers Slow and Difficult?

- Knowledge of the biological space is insufficient to understand how biomarkers reflect function – especially in populations (heterogeneity)
- Biomarkers are often developed without attention to biospecimen and technology standards
- Proteomics technologies (and others) are not standardized – often findings are not reproducible
- Biomarkers are not specifically developed for a specific function or test (i.e. FDA – fit for purpose)
- Biomarkers are not qualified before entering clinical trials
- Little understanding of what is required to develop a diagnostic test vs. using a biomarker for other uses
- Regulatory pathways not final – currently in development
- There is not end-to-end standards based system for biomarker development
NBDA: An end to End Standards Based System for Biomarker Development

Early Discovery (Biology Verified Patient Samples)

Translatable Discovery (Clinical Measure Established)

Assay Development (Analyte - Reagents-Technology – Robust)

Assay Performance (Analytical Validation)

Biomarker Qualification (“Fit for Clinical Purpose”)

Biomarker Validation (Clinical Validation)
NBDA: Description and Status

- Overall Description: Under the leadership of ASU over the last nine months, the respective strengths of ASU –especially Biodesign, C-Path, IGC (Founding Partners) and Collaborating Partners (Mayo Clinic) and (Several Partners in Discussion) have converged to create the NBDA.

- Goals: The NBDA will transition to become a 501C3 with an overall goal of developing the evidentiary standards needed for molecularly based and other biomarkers (agnostic in terms of diseases and classes of biomarkers) at each stage of the biomarker pipeline to ensure a predictable prospective path to clinical development and regulatory filing.

- Status: NBDA planning (and strategic plan completed; start up funds raised; workshop to begin standards identification and process held December 13-14, 2012; preliminary discussions with several pharmaceutical and diagnostic partners; discussions with FDA, NIH National Center for Advancing Translational Research, etc.)
NBDA Future Plans

- NBDA is underway – official launch with aggressive communications strategy in March 2013

- Case studies of approved biomarkers finalized to be submitted for publication 1st quarter 2013

- Overall development process- preliminary plan following December workshop

- Initial laboratory study completed – mid 2013 (DNA, expression, epigenomic results in fresh tissue vs. paraffin fixed patient materials)

- Precompetitive collaborative consortia with industry established – 2013

- Additional content focused workshops in 2013

- Additional fund raising underway

NBDA is the “ Poster-Child” for use-inspired Research to enable creation of a rational system for the development of precision medicine. Lots of opportunities for collaboration