Molecular Diagnostics: Multiplexity, Complexity and Ambiguity

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Medical Progress:
From Superstitions to Symptoms to Signatures
The Path to Precision (Personalized) Medicine
### Mapping The Molecular Signatures of Disease: The Intellectual Foundation of Rational Diagnosis and Treatment Selection

#### (Epi)Genomics

[Image of human face with genomics data overlay]

#### Proteomics

[Image of molecular structures and proteins]

#### Molecular Pathways and Networks

[Image of a complex network diagram]

#### Network Regulatory Mechanisms

[Image of regulatory pathways involving RNA and proteins]

<table>
<thead>
<tr>
<th>ID of Causal Relationships Between Network Perturbations and Disease</th>
<th>Patient-Specific Signals and Signatures of Disease or Predisposition to Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Image of a genomics data chart]</td>
<td>[Image of a patient with disease signs]</td>
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</table>
Mapping Molecular (Information) Signaling Pathways in Health and Disease

**Complex Biosignature Profiling: panOmics**

<table>
<thead>
<tr>
<th>(epi)genomics</th>
<th>proteomics</th>
<th>immunomics</th>
</tr>
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<tbody>
<tr>
<td><img src="epi_genomics.png" alt="Image" /></td>
<td><img src="proteomics.png" alt="Image" /></td>
<td><img src="immunomics.png" alt="Image" /></td>
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**Signature Detection, Deconvolution and Multivariate Analysis**

- automated, high throughput multiplex assays
- novel test formats and devices (POC)
- new algorithms for complex signal/deconvolution
Progressive Migration of Diagnostic Profiling from Centralized Large Laboratories to Decentralized POC/PON Platforms and Settings

Centralized Testing and Large Capital Base Instrumentation

Economies of Scale for Genome Sequencing

Desktop Integrated Dx

On-Body: In-Body Sensors

Remote (Virtual) Care

Increasingly Distributed and Diversified Data Feeds and Real-Time Health Status Monitoring

Mobile and Handheld Devices
Precision (Personalized) Medicine

- Molecular Profiling
  - Molecular diagnostics and disease subtyping
  - Improved outcomes and lower cost
  - Multiplex biomarkers and targeted therapies

Platforms

Rx selection

Impact

New analytical and computational technologies
A New Taxonomy for Disease Classification

Revealing the Underlying Complexity and Diversity of Disease Mechanisms

Disease Subtypes, Different Molecular Pathway Perturbations and the Phenotypic and Clinical Diversity of Disease Pathology, Progression and Rx Responses
Molecular Biomarkers in NSCLC

- KRAS: 15-25%
- EGFR: 10-35%
- ALK
- HER2
- MET
- BRAF
- PI3K
- FGFR1
- ROS1
- MEK
- KIF5B-RET
- AKT1
“malignant snowflakes”: each cancer carries multiple unique mutations and other genome perturbations

disturbing implications for Rx and development of new Rx
Are We There Yet?
Personalized (Precision) Medicine: Seemingly Always on the Threshold of Mainstream Adoption
What Applications of NGS/panOmics Profiling Technologies Are Ready Now for Routine Clinical Adoption?
The Central Challenge in the Validation/Qualification of Multiplex Biomarkers, panOmics Profiling and Molecular Diagnostics
Genome Sequencing: A Disruptive Technology

Clinical Utility: Not If, but When, What and How
Use of NGS and Clinical Care

- because we can?
- because it is useful?

Meeting the ‘Fit-for-Purpose’ Standard

The Urgent Imperative to Define Analytical and Interpretation Standards for Clinical Grade Genome Sequencing
“Failure of such tests to perform as intended can lead to patients receiving inappropriate and potentially harmful treatments or, alternatively, not receiving a treatment that has the potential to benefit them.”

“These are significant risks in reporting tumor or genetic variants as being “actionable” in association with non-FDA-approved indications, or those which are not listed in CMS-approved compendia.”

“Such reports have the potential to mislead physicians and expose patients to undue risk.”
Current Issues Related to the Accuracy and Quality of WGS for Clinical Applications

- error rate
- sequence completeness
- sequencing depth
- instrument platform variation
- base calling algorithms
- aligning real algorithms
- adequacy of reference genomes
- annotation, analysis and curation of large scale data

Lack of Consistent Technical Standards and Ill-Defined Regulatory Frameworks
Accuracy of Identification of Sequence Variation Calls in Next Generation Sequencing

- NGS in its current incarnation(s) estimated to make high-confidence calls for 78% of the human genome
- c.80% concordance between cells made using different sequencing platforms
  - CAP Today March 2015, p.16
- extensive disagreement between different bioinformatics programs in calling variants on same sequencing data
Seeking the ‘Needle’ of Actionable Clinical Value in the ‘Haystack’ of Large Scale PanOmics Data

- estimated 3-4 million variants in genome of any individual
- estimated 8-15 protein coding region variants provide ‘actionable’ information based on current knowledge
- vast majority are Variants of Unknown Significance (VUS)
- anticipated dramatic expansion of individual variant space with resolution of non-coding regions and their regulatory elements
- normal mutation rate will continue to generate a nearly infinite spectrum of genetic variation
  - current population, future generations
Rx safety adverse events

Monogenic, high-penetrance alleles

Monogenic, high-penetrance alleles

Oligogenic, high or intermediate penetrance alleles

Complex epistatic interaction of multiple low penetrance alleles

Autoimmunity

Prenatal fetal aneuploidy

HLA transplant immunotyping

Late-onset multigenic diseases
- cancer
- neurodegeneration
- diabesity
- aging

Mental illness/ neurodevelopmental

High disease frequency

Low disease frequency

Actionable data
Genes for....
The Over-Simplified Perspective That Whole Exome-and Whole Genome-Sequencing Will Reveal the Full Etiology of Disease Pathogenesis and Transform Treatment Options

- other ‘omes’ matter - the current black box of genome-phenotype relationships
- the epigenome and environmental effects
- the yet unknown dimension of epistatic complexity
- hype, hubris and herd mentalities in uncritical acceptance of value of NGS data in isolation
Individual Variation, Genome Complexity and the Challenge of Genotype-Phenotype Predictions

Junk No More: Pervasive Transcription
- alternate transcription/translation/(co)splicing
- SNPs, CNVs
- pseudogenes
- indels, SVs
- ncRNAs
- phasing
- epistasis
- imprinting
- silencing
- miRNAs/ceRNAs/circRNAs

Cell-specific Molecular Interaction Networks

Perturbed Networks and Disease

recognition of genome organizational and regulatory complexity
Large Scale Imputation of Epigenomic Datasets for Systematic Annotation of Diverse Human Tissues

The Need for New Diagnostic Assays to Assess Immunophenotypes

- Early evidence indicates that immune checkpoint modulation may offer major PFS gains in several malignancies.
- What markers characterize immunorestorative (positive Rx response) and immunoevasive (Rx-resistant) phenotypes?
• at least four Rx companies with proprietary assays
• different antibody clones
• different staining protocols
• different scoring methods
multiple drugs acting on same target
multiple companion diagnostics (CDx) and LDT assays
multiple FDA-approved CDx for same drug class but each Rx-specific (and proprietary)
  – cost to providers to offer all CDx
  – confusion for MDs/HCPs
different ‘cut-off’ points in assay interpretation
scarce biopsy tissue as obstacle to running multiple tests to ID best-in-class Rx recommendation
Patient Stratification by Molecular (panOmics) Profiling, Rx Selection and Need for New Clinical Trial Designs
the demise of the “all-comers” RCT design?
new trial designs based on biomarker-selected patient cohorts and Rx response evaluation
  – enrichment trials, adaptive trials, basket trials
  – multi-agent trials and more agile shifts in combination Rx
statistical sophistication of protocol design and criteria for switching between trial arms
proactive regulatory engagement in trial design
new regulatory policies for review of Rx^n:MDx^n combination dossiers and labeling issues
The Internet of Things
Expanding the Diversity and Scale of Multiplex Signatures

On-Body: In-Body Sensors, Mobile Health and Telemedicine

Real-time Transmission of Multiplex Signatures on Health Status and Treatment Compliance

New Challenges in Clinical Monitoring, Health Records, Regulation and Reimbursement
From Static Population-Based Indices of Diagnostic Ranges to Dynamic Longitudinal Monitoring of Individuals Who Each Serve as Their Own Controls
The Imminent Arrival of the Zettabyte ($10^{21}$) Era
Integration of Multiplex panOmics Data into Electronic Medical Records

Standards for Data, Formatting, Database Architecture and Analytics

Design of Facile Interfaces for Cross Vendor, Cross-Institution Data Interoperability!
Data Access Will Become a Critical Factor in the Accuracy and Safety of Clinical Decisions Using NGS and panOmics Patient Profiling Platforms

- anticipated expansion of data profiles on millions of individuals
- value will reside in robust correlation with individual risk and clinical outcomes and demonstration of clinical utility
- escalating complexity of informatics and algorithms for data mining with concomitant improvements in risk management and outcomes
  - transitioning from the current VUS black box to increased capture of clinically actionable information
Missing Metrics in Linking NGS Data and Clinical Phenotypes

For much of the genomic data obtained for nearly 14,000 patients by the International Cancer Genome Consortium, key clinical information is missing.

<table>
<thead>
<tr>
<th>Metric</th>
<th>Missing</th>
<th>Collected</th>
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<tbody>
<tr>
<td>Proportion of tumour cells in sample</td>
<td>92%</td>
<td></td>
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<tr>
<td>Relapse type</td>
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<td></td>
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<tr>
<td>Length of disease-free interval</td>
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<td></td>
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<tr>
<td>Tumour stage at diagnosis</td>
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<tr>
<td>Survival time</td>
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<tr>
<td>Clinical tumour stage</td>
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<tr>
<td>Tumour grade</td>
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<td>Age when sample was taken</td>
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<tr>
<td>Type of tissue</td>
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<tr>
<td>Disease status at last follow up</td>
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<tr>
<td>Age at last follow up</td>
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<tr>
<td>Vital status (alive or dead)</td>
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<td>Diagnosis</td>
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<td>Age when diagnosed</td>
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<tr>
<td>Sex</td>
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Data Access Will Become a Critical Factor in the Accuracy and Safety of Clinical Decisions Using NGS and panOmics Patient Profiling Platforms

- how to establish open-source ‘data commons’ of requisite scale?
- major implications for viability of single segment (data-poor) versus integrated (systems) entities
  - clinical decisions and patient safety
  - database standards and inter-operability
  - scale matters!
  - IP
  - competitive business models
“The present framework for regulating the genetic testing industry does not address the need for competing providers of test-related services to have access to data resources to support state-of-the-art interpretation of genetic tests.”

Barbara J. Evans,
University of Houston Law Center
J. Law Med. Ethics Supplement Fall 2014, p.51
**“Modularity”**

The Economic and Regulatory Framework for Access to Complementary Products and Services

- markets with mix of integrated and single segment providers
  - telecommunications, public utilities, natural gas industry
- market structure able to interoperate through public, non-discriminatory and well-understood interfaces

Assimilation of Concepts of Molecular Medicine into Routine Clinical Practice and Health Records
### Technology Acceleration and Convergence: The Escalating Challenge for Professional Competency, Decision-Support and Future Education Curricula

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<th>Data Deluge</th>
<th>Cognitive Bandwidth Limits</th>
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<tr>
<td>Automated Analytics and Decision Support</td>
<td>Facile Formats for Actionable Decisions</td>
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Living in a World Where the Data Analytics and Interpretation Algorithms Are Obscure to the End User

- ceding decision authority to computerized support systems
- culturally alien to professionals in their expertise domain but accept in all other aspects of their activities
- who will have the responsibility for diligence and oversight of critical assumptions used in decision tree analytics?
Analytical and Clinical Validation of Molecular Determinants of Disease (Subtypes) and Treatment Options

- Multiplex disease biomarkers and molecular variants
- Massive data: volume, velocity, variety, veracity
- Evidentiary standards for regulation
- Outcomes, value, and reimbursement
- Clinical utility and adoption
Anticipated Details of the Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories

Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)

This document provides the anticipated details of the Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories; Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs) that FDA intends to issue in 60 days, and is being provided to Congress pursuant to section 1143 of the Food and Drug Administration Safety and Innovation Act of 2012

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
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Reimbursement for Molecular Diagnostics and Emerging Molecular Profiling Tests

• current payment policies based on earlier era of comparatively simple (low technical complexity) tests
  – cost-based pricing: time and materials used to conduct test

• no premium for cost recovery for escalating technical complexity/R&D investment need to qualify panOmics profiling tests

• failure of CPT coding to match pace of technical advances in MDx/WES/WGS

• inadequate HTA/reimbursement/business models for value-based pricing of next-generation diagnostic platforms as value drivers of improved clinical outcomes and cost savings
Precision Medicine is a Disruptive Technology

- conflicts with systems, incentives and practices of multiple constituencies in the healthcare ‘ecosystem’
  - providers
  - regulators
  - payors
- absent new incentives and alternatives to sustain financial viability these groups “won’t vote themselves off the Island”
- patients/consumers not yet sufficiently well informed about availability/value of precision medicine to demand faster adoption
Building Knowledge Networks to Improve Individual Health and Sustainable Healthcare Delivery

Data Analytics and Clinical Decision Tools for Improved Outcomes and Cost Control

Precision Medicine

New Competencies for Mastery of Data-Intensive Biomedicine

mHealth and remote health status monitoring

eHealth: mining large scale population databases

panOmics sensors/devices

molecular profiling of patients

mapping the dysregulation of biological networks in disease
Slides available @ http://casi.asu.edu/