Personalized (Precision) Medicine: Science, Law and Health Policy

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From Bench to Society: Law and Ethics at the
Frontier of Genomic Technology
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Slides available @ http://casi.asu.edu/
Healthcare: An Expensive Menu Without Prices

Managing the Demands of an Aging Society and Chronic Disease Burden in an Era of Economic Constraint

Shift From a “Do More, Bill More” Healthcare System to Managing Individual Risk for Improved Health Outcomes and Cost Control

Sustainable Health: Societal (Economic) and Individual (Wellness)
The Economic, Social and Clinical Benefits of Proactive Mitigation of Disease Risk and Chronic Disease Co-Morbidities

Health Status

Healthy/ Low Risk

At-Risk

High Risk

20% of the Population Generate 80% Cost

end-of-life care

chronic disease progression

chronic disease early stage

acute disease

multiple co-morbidities

Value

Cost
Medical Progress: From Superstitions to Symptoms to Signatures
Mapping The Molecular Signatures of Disease: The Intellectual Foundation of Rational Diagnosis and Treatment Selection

Genomics

Proteomics

Molecular Pathways and Networks

Network Regulatory Mechanisms

ID of Causal Relationships Between Network Perturbations and Disease

Patient-Specific Signals and Signatures of Disease or Predisposition to Disease
• personalized medicine is hyperbole
• personalized medicine will be so expensive as to be unaffordable
• personalized (precision) medicine is an inevitable outcome of outstanding disease at the level of alterations in molecular information networks
• precision medicine is the intellectual foundation for rational care, improved outcomes and cost control
Biomarkers and Biosignatures: The Primacy of Molecular Profiling in Monitoring of Health and Disease

Integrated 'Omics (iOmics): Building the Core Technical Foundation of Molecular Medicine and Improved Healthcare

The Journey to Integrative Personal Omics Profiling (iPOP)

Big Data: Molecular Medicine Meets Digital Medicine
Information-Based Services for Increased Precision in Managing Risk in Healthcare

- Earlier detection
- MDx, disease subtyping and rational Rx
- Health status monitoring
- Predisposition risk
- Optimized resource allocation

Integrated Personal ‘Omics Profile (iPoP)

- Profiling
- Analysis
- Informed decisions

Big data: volume, velocity, variety

Risk identification and mitigation + decision-support tools
Mapping Causal Perturbations in Molecular Pathways and Networks in Disease: Defining a New Taxonomy for Disease

“Omics” Profiling to Identify Disease Subtypes (+ or - Rx Target)

Altered Network Structure and ID of Molecular Targets for MDx and/or Rx Action
Biomarkers, Disease Subtyping and Targeted Therapy: Companion Diagnostics – the Right Rx for the Right Disease (Subtype)

- **Her-2+** (Herceptin) (Perjeta)
- **EML4-ALK** (Xalkori)
- **KRAS** (Erbitux) (Vectibix)
- **BRAF-V600** (Zelboraf)
- **CFTR-G551** (Kalydeco)
Molecular Medicine and Rational Therapeutics: Molecular Diagnostics and Targeted Rx

- companion therapeutics selected by precision diagnostics (nomenclature inversion!)
- opening era in linking disease molecular pathology to rational Rx via MDx-disease subtyping
- increasing payor, regulatory and public pressures for reliable ID of Rx-responsive patients
- demand for Dx-Rx combinations will intensify
- Dx-Rx combination will become an obligate element of NDA/BLA submission and product labeling
- development of Dx-Rx combinations as intrinsic components of R&D for investigational Rx
Mapping the Genetics of Drug Metabolism: Profiling Patient Risk to Adverse Drug Reactions

Right Rx for the Right Patient

- 1.5 to 3 million annual hospitalizations (US)
- 80 to 140 thousand annual deaths (US)
- est. cost of $30-50 billion

- Rx AE risk for “slow metabolizers”
  - genetic variation in type I/II drug metabolism enzymes
- HLA-related drug toxicities
- GI microbiome and metabolism of drugs/carcinogens
Pharmacogenetic Diagnostics (PGx) for Predisposition to Adverse Drug Reactions/Drug-Drug Interactions

- inadequate/erratic use of PGx testing
  - professional and payer knowledge gaps
- predictive value of PGx tests may be insufficient for clinical utility and/or cost-effectiveness
- physician obligations to offer PGx test and obligation to use results?
- new liabilities?
  - physicians, pharmacists, companies, payors?
● study of medical home primary care population at Vanderbilt Univ. Med. Center
  – records of 52,942 patients (pts) over 5 years
  – 64.8% and 11.9% pts exposed to at least 1-4 Rx across 56 medications with known AE risk alleles
  – for 6 medications with severe Rx attributable events 383 could have been prevented by pre-emptive genotyping

● merits of proactive multiplex genotyping data in EMR versus ‘reactive’ approach to patient safety

● do preventable AE events represent “high-priority events” under meaningful use provisions ACA 2010?
“Ideally, baseline DNA samples should be collected from all patients in all arms of clinical trials in all phases of drug development.”

Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling
The Evolution of Diagnostic Technologies for Precision (Personalized) Medicine

Anatomic pathology + single analyte MDx

Multiplex 'Omics' MDx

Whole exome sequencing (WES), whole genome sequencing (WGS), epigenome profiling

Clinical validation and adoption

Current

Emerging

?
Now Comes the Hard Part!
The Transition from Mapping Unigenic Events to Complex, Multigenic Late-Onset Adult Diseases

- variation in single gene/protein target
- monogenic (Mendelian) disorders
- Rx efficacy (pharmacodynamic)
- drug metabolism and AE risk (pharmacokinetic)

- multigenic, late-onset adult diseases
  - cancer
  - diabesity
  - neurodegen.
  - aging

- disease subtypes and heterogeneous perturbations in multiple molecular pathways
- expansion of molecular network perturbations with disease progression

germ line dominated

germ line + somatic variation + epigenetics + lifestyle
Analytical and Clinical Validation of Molecular Determinants of Disease, Treatment Options and Predisposition Risk

- Evidence standards for regulation/reimbursement
- Big data: volume, velocity, variety
- Disease biomarkers and molecular variants
- Clinical utility and adoption
- Value and reimbursement policies
Rigorous Selection of Specimen Donors and Specimen Collection

- poorly standardized tissues and erratic availability
- challenge of obtaining fresh tissue
- uncertain value of legacy tissue blocks

primacy of standardized clinical phenotyping and annotated health records and outcomes for biospecimen collection
disturbing low reproducibility of academic publications
poor access to rigorously annotated biospecimens from stringently phenotyped sources
insufficient control of pre-analytical parameters and variable analytical standards
idiosyncratic ‘lab-specific’ analytical methods
‘s’small N’ studies lacking statistical power
chaotic data reporting formats and poor dbase interoperability
pressure to publish and poor compliance with funding agency/journal policies on open data sharing
failure to work to (or understand) industry and regulatory standards
The Dismal Productivity of Biomarker R&D

The Complexity of iPOP Profiling and Multiplex Biomarker Discovery, Validation and Clinical Adoption is Comparable to (Bio) Pharmaceutical R&D

In Common With R&D for Drugs and Vaccines
Success Demands a Systems-Based Approach
Identification and Validation of Disease-Associated Biomarkers: Obligate Need for a Systems-Based Approaches

- Biospecimens and Analysis of Molecular Pathway/Network Perturbations
- Multiplex Assays and Complex Signal Deconvolution Algorithms
- Novel Instrumentation, Automation and Large Scale Informatics
- Patient Profiling, Rational Rx and Health Monitoring
Large Scale Biobanks and Patient Registries: A Crucial Resource for Biomedical Research

- impeccably curated samples and linkage to detailed health histories and data on genealogical pedigree, lifestyle and disease patterns
- blurring of boundaries between research and clinical datasets
- shift from consent for specific (narrow) research use to broad consent for range of unspecified future research
- shift from protection against physical harms to informational harms
Validation of Multiplex Assays for Use in Clinical Trials: A Multidisciplinary Task and New IRB Competencies
Will Low Cost Whole Genome Sequencing Change Everything?

1 million genomes x $1,000 = $1 billion

“It’s not even a scary number anymore!”

When Will WGS Become Just Another Laboratory Test Value?

How Will WGS Affect Patient Care?
What Standards of Accuracy Will Regulatory Agencies Require For Use of Whole Exome Sequencing (WES) and Whole Genome Sequencing (WGS) in Clinical-Decisions?

Storage of Large Scale WGS Datasets and Protected Health Information
The Complex Landscape of WGS: Standards, Clinical Utility, Reimbursement, Ethics and Big Data

- **correlation and causality analytics**
  - SNPs, haplotypes
  - CNVs rearrangements
  - non-coding regions
  - ethnic diversity
  - epistasis
  - epigenetics
  - other ‘omics’

- **clinical decision analytics**
  - Rx response/resistance - target(s), networks
  - Rx adverse event risk
  - prognosis/progression
  - predisposition to disease
  - environmental exposure/lifestyle confounders for predisposition

- **privacy and security**
  - technical standards
  - regulatory requirements
  - reimbursement
  - clinician education

- **technical standards**
- **regulatory requirements**
- **reimbursement**
- **clinician education**
Next-Generation Sequencing: Standardization of Clinical Testing (Next-StoCT Workgroup) (CDC convener)
College of American Pathologists (CAP) NGS checklist
New York State NGS checklist
FDA Sequencing Quality Control Project
NIST/NIH Genome-in-a-Bottle NGS reference materials
CDC Genetic Testing Reference Materials Coordination Program
Association of Biomolecular Resource Facilities

*see Nature Biotechnol. (2012) 30, 1033
The Imperative for Regulatory Clarity Regarding Test Classification and Analytical Standards for Molecular Diagnostics and WGS

- regulatory classification as LDTs vs. requirement for 510(k)/PMA submission?
- sequencers as Class III devices?
- FDA enforcement (21CFR820) of Quality Systems Regulations (QSRs)
  - laboratories and suppliers
  - already imposed on medical device industry and FDA-cleared IVD products
  - action to forbid RUO materials when QSR-grade available?
Presidential Commission for the Study of Bioethical Issues: Privacy and Progress in Whole Genome Sequencing

- risks new in kind
- risks new in degree
- regulatory gaps
- barriers to data sharing
- information exchange between researchers and clinicians
- proactive development of policies and practices for consent and security protections
Mapping the Human Variome: Defining the Molecular Taxonomy of Individuality

Mapping the Causal Variants for Phenotypic Traits, Disease Predisposition and Disease Patterns
“Our ignorance of the laws of variation is profound”

Charles Darwin

- humans are inherently variable ….. which is good for evolution
- but bad for biomarker discovery, drug discovery and predicting Rx efficacy
Disease Predisposition Risk Profiling (PDx)
hypotheses

- small number of common variants (>1-5% allele frequency) with large effects
- large number of common variants with small effects
- large number of rare variants (<0.001-0.0001% frequency) with small effects
Profiling Risk of Disease Predisposition

- over-hyped and slow evolution of robust evidence for multigenic diseases
- complex interplay between genes (epistasis) and genes and environment (epigenetic changes)
- interactions of multiple low prevalence gene variants each with low penetrance
- probabilistic rather than absolute risk
The Scale and Complexity of Human Genome Variation

- Individual genomes on average carry:
  - 3.5 - 4.0 million SNVs, 1000 CNVs (>450bp)
  - 3-4 hundred indels
  - 200-500,000 private SNVs
  - 20-400 loss-of-function variants

- Estimated up to 60 new inherited mutations/generation
  - Gender dependent transmission: maternal 15/paternal 25-45
  - Impact of paternal age at fertilization on transmitted mutation load?
The Overly Simplistic and Deterministic Dangers of a Genome-Sequence Centric Perspective

The Over-Simplified Perspective That Whole Exome-and Whole Genome-Sequencing Will Reveal the Full Etiology of Disease Pathogenesis
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

recognition of the complexity of genome organization and regulation

Cell-specific Molecular Interaction Networks

Perturbed Networks and Disease
The Evolutionary Lineage of Modern Hominids
Defining Genetic Variation in Human Populations: The Skewing of the Allele Frequency Spectrum Towards Rare and Private Genetic Variants

- **Distal (paleo-) ancestors**
- **clan**
- **pedigree**
- **individual**

- Common variants that segregate within large populations
- Rare-to-intermediate frequency variants arising in recent history (extended pedigree)
- Inherited rare variants arising in (G1, G^n) parental lineages
- De novo (private) mutations
Human Genetic Diversity and Evolutionary History

- Reduced historical population and genetic bottlenecks
- Increased migration and inter-breeding
- Distal (paleo-) ancestors
- Clan
- Pedigree
- Individual

- Population expansion and progressive reduction of geographic isolation
- Anthropogenic-relaxation of selection intensity (food, sanitation, Rx)
- Natural selection pressures (famine, pestilence)
- Population and genetic diversity
- The paleo-populations

Population and individual genetic diversity
Implications of Role of Rare/Private Variants in Disease for Identification and Validation Studies

- renewed focus on clan:pedigree cohorts to identify “recent” disease causal variants not yet purged by negative selection
- replication of findings across diverse populations will be limited (ancestry, geographic history)
- large scale profiling of random cohorts may be less productive in revealing genetic (epistatic) drivers of major diseases
Clinical Utility of Knowledge of Individual Genetic Variations

- immediately actionable
- known association/causation of disease but no Rx available
- unknown clinical significance
Molecular Medicine: Managing “The Incidentalome”

- identification of incidental disease risk factors during research and/or clinical omics profiling for a different purpose
- evidentiary standards and decision thresholds for follow-up/recontact research participants
- duties/obligations to recontact/reprofile based on new knowledge?
- consented vs. non-consented follow-up?
- obligations to inform extended biological pedigree of serious risk(s)?
214 Changes Over Seven Years in Risk Classification for Hypertrophic Cardiomyopathy (HCM) Risk Variants on 11 Genes on HCM CardioChip Test*

*S. J. Aronson et al. (2012) Genetics in Medicine 14, 713
Partners Health Care HCM Knowledge base: 1472 variants, 2279 family members, 4923 tests
Ancestry Matter!

Ancestry-Based Patterns in Recurrent Mutations

Ancestry-Informed Genetic Screening and Counseling
US Patents Referencing Race and/or Ethnicity in Diagnostic and/or Therapeutic Claims*

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<th>Patent Number 3</th>
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* C.C. Brinckenhoff. Genetic Engineering News 1 January 2012 p.8

- deleterious BRCA1 (124) and BRCA (63) mutations detected in 746 individuals with family history breast and/or ovarian cancer
- BRCA1 185 delAG mutation
  - founder mutation in Ashkenazi Jews
  - ancestry-origin via Spanish Conversos and Crypto-Jews?
- BRCA1 R71G
  - Spanish founder mutation
- BRCA1 ex9-12 del
  - Mexican founder mutation (not yet found in Spain/South America)
- BRCA1 R1443X
  - French-Canadian founder mutation but independent Hispanic origin via hypermutability of CG-TG
Genetic Markers of Ancestry Pedigree

- disease predisposition
- Rx response/resistance
- Rx safety
- communication of knowledge of disease risk/
  Rx response markers to extended biological cohort?
- forensics and law enforcement
Personal Privacy Protection and Individual Genome Identification in Research and/or Public Databases
“…it will be hard for anyone to find out anything about you personally from this research”

Informed Consent Form for the 1000 Genomes Project (2008)

“profiling Y chromosome (Y-STRs), recreational genetic genealogy databases and a combination of surname with other types of data, such as age and state, can be used to identify the target” (individual)

M. Gymrek et al. (2013) Science 339, 321
The Role of Two Other ‘Omes’ in Human Physiology and Pathology

The Epigenome

The Microbiome
Mapping The Spectrum of Human Genetic Variation: The Under-Explored Epigenome and the Chromatin Landscape

- Distal (paleo-) ancestors
- Clan
- Pedigree
- Individual

Epigenetics

- In utero and post-natal environmental effects ("exposome")
- Rare/private variants
- Fetal origins of disease hypothesis
- Trans-generational heredity of epigenome markers
Miniaturization of Analytical Technologies

“Lab-on-a-Chip”

“Lab-on-a-Tip”

“Lab-Always On” and “Lab-On-Me”
Invasion of the Body Trackers

Individual Biosignature Profiling Via On Body: In Body (OBIB) Sensors and Devices

“The Quantified Self”

Real Time, Remote Health Status Monitoring

Every Individual Become Their Own Control (Monitoring the Delta)
m. Health

Real Time Remote Health Monitoring and Chronic Disease Management

Lifestyle and Fitness

Information for Proactive Health Awareness (Wellness)
Siri, does this look malignant?
Interactive Patient-Centered Initiatives (PCIs)

- social media, patient advocacy and consumer/care-giver engagement
- new opportunities to capture, share, mine and integrate data
  - both research and clinical studies
- matchmaking for more proficient research studies/clinical trial recruitment
The Wellness Premium

Greater Engagement and Incentivization of Consumers/Patients in Care Decisions and Sustaining Wellness

Social Media, Patient Advocacy Group and New Opportunities for Observational Studies on Popular Health and Outcomes

Blurring the Boundaries Between Clinical Research and Clinical Care
If It Isn’t Billable, It Won’t Happen

Ambiguities and Lack of Transparency in Reimbursement Policies for MDx and Genome Sequencing

The Urgent Need for Streamlining Coding, Coverage and Payment Policies

Value-Based Reimbursement Policies to Reward Dx Innovation and Recover Escalating R&D Costs
Reimbursement for Omics Testing and Clinical Adoption

- Widespread coverage denials and case-by-case arbitration
- “Investigational and not medically necessary” (CMS)
- Validation of clinical utility and cost-effectiveness
- Payment for profiling markers that may affect future health but have no impact on immediate treatment decisions
- Continued uncertainty in reimbursement environment
  - CMS ‘gap fill’ action for new MDx codes 2013
  - Void for IVDMIAs/MAAAAs
Informed Consent and Medicare Coverage
With Evidence Development (CED)

- must CED program comply with HHS Common Rule?
- is consent coercive when it is required for participation in a registry mandated as a condition of insurance coverage?
Increasingly Granular Segmentation of Major Diseases by Molecular Profiling

Common Diseases: Are There Any?
Molecular Diagnostics and Identification of Responder/Non-Responder Patients for Rational Rx

“The problem with all these tests, soon I’ll have nothing (treatments) I can offer my patients”

“The Eminent Oncologist” (journal’s designation)

Frequencies of Molecular Alterations in CRC and Responsiveness to Cetuximab or Panitumumab

“malignant snowflakes”: each cancer carries multiple unique mutations and other genome perturbations

disturbing implications for development of new Rx
Initial Response (A/B) of BRAF-V600 Positive Metastatic Miliary Melanoma After 15 Weeks Therapy with Vemurafenib (Zelboraf® - Roche) Followed by Rapid Recurrence of Rx-Resistant Lesions with MEKI C1215 Mutant Allele After 23 Weeks Therapy

• targeted therapies, Yes but
• success requires targeting complex molecular networks not single/small N targets

From: N. Wagle et al. (2011) J. Clin. Oncol. 29, 3085

http://jco.ascopubs.org/content/29/22/3085.full.pdf+html
Should Low Incidence Cancer Subtypes (The Entirety of Cancer Cases?) be Accorded Similar Regulatory and Economic Privileges to Classic Orphan Diseases?
Three Different Scenarios for the Use (Value) of New Diagnostic Technologies for Early Detection of Disease and/or Disease Predisposition

- **Cancer Detection Before Metastasis**
- **Cardiovascular/Metabolic Diseases**
- **Neurodegenerative Diseases**

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- Early Diagnosis and Curative Surgery
- Lifestyle Changes and/or Rx to Limit Risk
- The Dilemma of Early Diagnosis Without Rx
The Healthcare Infocosm

From Fragmented Silos of Reactive, Incident-Centric Care to Integrated Continuity of Care and Proactive Management of Individual Risk

The Primacy of Health Information Systems in Driving Precision Medicine and Integrated Care Delivery
Silos Subvert Solutions: Protecting Turf and Sustaining the Status Quo
The Need for Healthcare to Transition to Data-and Computation-Intensive Processes

Current Era

- “silos” of research/clinical activities
- opinion-rich, information content-poor
- proliferation of poorly standardized and fragmented data, semantic anarchy and incompatible databases
- unacceptable levels of inaccurate clinical diagnoses, fragmented care provision and flawed clinical decisions
  - highly variable treatment practices and erratic clinical outcomes
- extravagant waste and risk to patients
The Need for Facile, Seamless Data Exchange Formats for Large Scale Biomedical Data Systems

- research and discovery
- translation and clinical trials
- healthcare delivery
- m.health
- consumers
- patients
- regulators
- payors
- outcomes
- analytics
- decision support tools
The Design Challenge for Next Generation HIT Systems

- todays EHRs not designed to support secondary use of data to inform research/translational medicine
- lack of harmonized data standards in different clinical specialties and provider organizations
- integration of new data classes
  - omics profiling (iPOP)
  - observational data from primary care providers and patient self-reported data
  - SEER (Surveillance, Epidemiology and End Results) data
  - m.health/sensor nets and remote data monitoring
Integration of iOmics Data Into Electronic Health Records and Clinical Decisions
The Growing Education and Knowledge Gaps in Comprehension of Molecular Medicine Concepts Among Healthcare Professionals
“We don’t teach (medical) students how to interpret lab results or how to pick them. We’re spending 61 to 302 hours in anatomic pathology and nine hours teaching laboratory medicine. To pass anatomic pathology you’ve got to pass a test. There are no tests for lab. medicine.”

Dr. M. Laposta MD. Ph.D.
Executive Vice-Chair of Pathology, Microbiology and Immunology
Vanderbilt Univ. School of Medicine
Member, CDC Clinical Laboratory Integration Into Healthcare Collaborative (CLIHC)

Technology Acceleration and Convergence: The Escalating Challenge for Professional Competency, Decision-Support and Future Education Curricula

Data Deluge

Cognitive Bandwidth Limits

Automated Analytics and Decision Support

Facile Formats for Actionable Decisions
Fundamental Questions

- when does failure to use/recommend molecular profiling tests represent:
  - failure to meet reasonable standard of care and minimal clinical competence?
  - negligent non-referral?
- how will evidentiary standards/guidelines be set for molecular profiling and precision medicine?
  - timely revision(s) of SOC guidelines
  - duty to act?
  - duty to warn?
  - duty to update (the evolving incidentalome)?
Precision Medicine is a Disruptive Technology

- conflicted incentives and practices of multiple constituencies in the $3 trillion healthcare ‘ecosystem’
  - providers, payors
  - regulators
  - vendors

- absent new incentives and pathways to sustain revenues and financial viability change will be opposed, protracted and inefficient

- patients/consumers not yet sufficiently well informed about availability/value of precision medicine to demand change in clinical practice
  - legal remedies (malpractice via neglect) as catalyst?
• incorporation of new technologies into old business models typically drives cost up without productivity gain(s)

• the disruptive technologies needed to transform massive inefficiencies in healthcare services will need to emerge from the outside
Precision Medicine and Charting a New Ecology for Healthcare: Managing Risk and Incentivizing the Wellness Premium

- Integrated Care, Continuity of Care
- Superior Decisions, Improved Outcomes, Lower Cost
- Digital Medicine: The Healthcare Infocosm
- Molecular Medicine: Precision Dx, Personalized Rx and Risk Mitigation
- Infrastructure and New Competencies in Integration
- Large Scale Data
- Mapping the Dysregulation of Molecular Networks in Disease
Slides available @ http://casi.asu.edu/

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