Overview of Regulatory and Reimbursement Challenges for Molecular Diagnostics and Precision (Personalized) Medicine

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ASU Workshop on Molecular Diagnostics:
Reimbursement and Regulation
Arizona State University
3 April 2014
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 Future of Healthcare Delivery: Managing Risk

- risk detection (assessment)
- risk mitigation (management)
  - pre-emption
  - earlier detection (MDx, IMx)
  - selection of optimum response (Rx, etc.)
  - behavior (compliance, guidelines)
  - reducing R&D risk and costly clinical trial failures
  - regulatory and reimbursement risk and ROI on increasingly long and costly R&D
- the real ROI: return on actionable information
Medical Progress:
From Superstitions to Symptoms to Signatures
Precision Medicine: Integrated “Omics” Profiling and Mapping Disruption of Molecular Networks in Disease

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

Precision (Personalized) Medicine

- right Dx for right disease classification (precision)
- right Rx for right disease subtype (efficacy)
- right Rx for right patient (adverse event/AE reduction)
- right behavior to meet treatment guidelines (compliance)
- identification and mitigation of disease risk predisposition (prevention)
- agile regulatory and reimbursement systems to keep pace with technological advances (sophistication and speed)
- dynamic health technology assessment tools (value)
Heterogeneity of Driver Oncogenes in NSCLC

<table>
<thead>
<tr>
<th>Target</th>
<th># Patients Screened</th>
<th># Eligible Patients</th>
<th># Centers</th>
<th># Countries</th>
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</thead>
<tbody>
<tr>
<td>EML4 ALK+: lung cancer</td>
<td>1500</td>
<td>82</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>HER2+: gastric cancer</td>
<td>3803</td>
<td>549</td>
<td>122</td>
<td>24</td>
</tr>
</tbody>
</table>

* E.L. Kwak et al. (2010) NEJM 363, 1693  
** Y. Bang et al. (2010) Lancet 376, 687
Precision Medicine and Escalating Technical Complexities

The Need for Agile, Adaptive Regulatory and Reimbursement Policies
The Evolution of Clinical Diagnostic Testing in The Pending ‘Omics Era and New Device Technologies

Unianalyte Tests

Multianalyte Biomarkers

Whole Genome Sequencing

New Regulatory and Reimbursement Policies

On-Body: In-Body Sensors

Portable, Point of Need Diagnostic Devices

Centralized Testing, Large Capital Base Instrumentation

Increasingly Distributed Data Feeds and Real Time Health Monitoring
The Evolution of Diagnostic Tests

- Laboratory Developed Tests (LDTs) and CLIA oversight
  - analytical validity/competency
  - originated in era of single analyte/simple analyte tests
- ‘Omics’ technologies
  - multiplex profiling (signatures)
  - high dimensionality problem in analytical validation
  - algorithm based endpoints (IVDMIAs/MAAAs)
  - the looming data deluge from WGS without adequate standards

Technology Has Outpaced Regulation and Reimbursement Policies
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
Next-Generation “Omics” Diagnostic Tests

- dramatic increase in technical complexity, development time and cost versus traditional LDTs
- requires skillsets, resources and business risk foreign to historical unianalyte test development and industrial investment in diagnostics R&D
- complex probabilistic endpoints versus binary decisions
Will Whole Genome Sequencing (WGS) Change Everything?

Will WGS Become Just Another Laboratory Test Value?

Will WGS Affect Patient Care?
• The $1000 (or less) Whole Genome Sequence (WGS)

• The $ ? Interpreted WGS

• The $ ? Reimbursed WGS for Clinical Use

• Techno-optimism and the Seduction of New Technologies: Hype and Herd Mentalities
Whole Exome Sequencing (WES) and Whole Genome Sequencing (WGS)

- regulatory issues
  - accuracy, instrumentation, reagents
  - analytical algorithms and evidentiary standards
- reimbursement
  - value (economic and clinical)
- education
  - massive information gap (analysis) and education gap (clinical practice)
- legal and ethical issues
Novel, Actionable Information: The Key Value Driver in Genome Sequencing

- immediately actionable
- known association/causation of disease but no Rx available
- informative (biological plausibility and likely causal but not actionable)
- unknown clinical significance
high disease frequency

- monogenic, high-penetrance alleles
- prenatal fetal aneuploidy
- HLA transplant immunotyping
- monogenic rare diseases/inborn errors of metabolism
- Rx safety adverse events

low disease frequency

- oligogenic, high or intermediate penetrance alleles
- complex epistatic interaction of multiple low penetrance alleles
- late-onset multigenic diseases
  - cancer
  - neurodegeneration
  - diabetes
  - aging
- mental Illness/neuro-developmental
- autoimmunity

actionable data
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)
- declining guarantees for anonymity, privacy and confidentiality
WGS and Claims Outstripping Current Analytical Capabilities
Disease Predisposition Risk Profiling (PDx)
“FDA is concerned about the public health consequences of inaccurate results from the (Personal Genome Service) device; the main purpose of compliance with FDA’s regulatory requirements is to ensure that the tests work.”

Alberto Gutierrez
Director of the FDA’s Office of In Vitro Diagnostics and Radiological Health,
in a letter to 23andMe CEO Ann Wojcicki
telling her company that the company must stop marketing its genomic testing kits or face FDA sanctions
November 22, 2013
Genes For ....
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 and Transform Treatment Options
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 genome organizational and regulatory complexity**

**Cell-specific Molecular Interaction Networks**

**Perturbed Networks and Disease**
The Need for Multi Molecular Diagnostic Platforms to Maximize the Number of Actionable Drug: Target Associations to Guide Therapeutic Decisions

- FISH = fluorescent in situ hybridization
- CISH = chronogenic in situ hybridization
- IHC = immunohistochemistry

FISH = fluorescent in situ hybridization
CISH = chronogenic in situ hybridization
IHC = immunohistochemistry

- trastuzumab
- lapatinib
- pertuzumab
- T-DM1
- everolimus
- afatinib
- cetuximab
- erlotinib
- gefitinib
- imatinib
- panitumumab
- crizotinib
- everolimus
- lapatinib
- T-DM1
- trastuzumab
- dabrafenib
- trametinib
- vemurafenib
- afatinib
- cetuximab
- erlotinib
- gefitinib
- imatinib
- panitumumab
- crizotinib
- everolimus
- lapatinib
- T-DM1
- trastuzumab
- everolimus
- hormone therapy
- lapatinib
- pertuzumab
- T-DM1
- trastuzumab
Invasion of the Body Trackers
Miniaturization of Analytical Technologies

“Lab-on-a-Chip”

“Lab-on-a-Tip”

“Lab-Always On”
and
“Lab-On-Me”
Individual Biosignature Monitoring
Via
On Body: In Body (OBIB) Sensors and Devices

Remote Health Status Monitoring
Real Time Remote Health Monitoring and Chronic Disease Management

Lifestyle and Fitness

Information for Proactive Health Awareness (Wellness)

mHealth
Mobile Devices, Wireless Technologies, Big Data and Increasingly Patient-Centric Delivery Channels

- extend reach and continuity in care
- each individual becomes their own control
- better real time patient-specific data and decision-support tools
- new patterns (touch points) of patient engagement with the health system
  - AORTA: Always-On-Real Time Access
  - new delivery channels and services
  - the changing ‘care space’
  - targeted care and ability to monitor larger number of patients
We Are Not Alone!

The Growing Recognition of the Importance of the Body’s Commensal Bacterial Population in Health and Disease
We Are Not Alone: The “Frenemy Within” Variation in the Human Microbiome as a Potential Factor in Health and Disease
Commensal Microbiomes: The “Frenemy Within”
An Additional Dimension to Biomarker Profiling

Metagenome-wide Association Studies (MGWAS)

- Immune-Mediated GI Diseases
- Type 2 Diabetes Profile
- Aging Metabolism and Fragility
- Metabolic Activation of Carcinogens/Pollutants

Immune-Mediated GI Diseases
Type 2 Diabetes Profile
Aging Metabolism and Fragility
Metabolic Activation of Carcinogens/Pollutants
Regulation of Human Fecal Transplants: Biological Drug or Cell Therapy or Tissue?

C. difficile infection and refractory infection
Nature (2014) 506, 290
Information-Based Services for Increased Precision in Managing Risk in Healthcare

Profiling

Analysis

Informed decisions

data curation and analysis

risk identification and mitigation + decision-support tools

earlier detection of disease
rational Rx
monitoring of health status
predisposition risk
risk pre-emption

gene

lifestyle

phenomes

exposome

curation and analysis

profiling

analysis

informed decisions
Keeping Pace With Technical Advances

- Regulatory Science
- Health Technology Assessment
- Clinical Guidelines and Standard-of-Care (SOC)
- Reimbursement
- Defining Value
If You Build It, Will They Pay?
If It Isn’t Billable, It Won’t Happen!

● #1 will test alter patient management?
  – reduce cost of care
  – improve outcomes
● #2 what additional resources/services/training are affected by test adoption?
● #3 perception of RCT as only ‘gold standard’
  – narrow interpretation that discounts value of observational studies
● #4 payer demand for regulatory approval to be eligible for reimbursement or CED
● #5 mindset of ‘lab data’ as low cost (<1% total cost) despite role in most treatment decisions (>85%)
  – unianalyte versus multiplex tests
  – outdated US reimbursement codes
<table>
<thead>
<tr>
<th>Cancer Detection Before Metastasis</th>
<th>Cardiovascular/ Metabolic Diseases</th>
<th>Neurodegenerative Diseases</th>
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<tbody>
<tr>
<td>Early Diagnosis and Curative Surgery</td>
<td>Lifestyle Changes and/or Rx to Limit Risk</td>
<td>The Dilemma of Early Diagnosis Without Rx</td>
</tr>
</tbody>
</table>

Three Different Scenarios for the Use (Value) of New Diagnostic Technologies for Early Detection of Disease and/or Disease Predisposition
“When I grow up, I want to go into medicine and help people who can pay out of pocket.”
Educating Payors on the Value of Biomarkers in Healthcare: Shift from Cost-Based Pricing to Value-Based Reimbursement to Incentivize Biomarker R&D
A Study in Reimbursement Policy Contrasts: Targeted Therapeutics (Rx) Versus Molecular Diagnostics (MDx) in Oncology
# The Projected Increase in US Cancer Cases (2010 to 2020)

<table>
<thead>
<tr>
<th>Site</th>
<th># People (thousands)</th>
<th>2010</th>
<th>2020</th>
<th>% change</th>
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<tbody>
<tr>
<td>Breast</td>
<td></td>
<td>3461</td>
<td>4538</td>
<td>31</td>
</tr>
<tr>
<td>Prostate</td>
<td></td>
<td>2311</td>
<td>3265</td>
<td>41</td>
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<tr>
<td>Colorectal</td>
<td></td>
<td>1216</td>
<td>1517</td>
<td>25</td>
</tr>
<tr>
<td>Melanoma</td>
<td></td>
<td>1225</td>
<td>1714</td>
<td>40</td>
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<tr>
<td>Lymphoma</td>
<td></td>
<td>639</td>
<td>812</td>
<td>27</td>
</tr>
<tr>
<td>Uterus</td>
<td></td>
<td>588</td>
<td>672</td>
<td>15</td>
</tr>
<tr>
<td>Bladder</td>
<td></td>
<td>514</td>
<td>629</td>
<td>22</td>
</tr>
<tr>
<td>Lung</td>
<td></td>
<td>374</td>
<td>457</td>
<td>22</td>
</tr>
<tr>
<td>Kidney</td>
<td></td>
<td>308</td>
<td>426</td>
<td>38</td>
</tr>
<tr>
<td>Leukemia</td>
<td></td>
<td>263</td>
<td>240</td>
<td>29</td>
</tr>
<tr>
<td>All Sites</td>
<td></td>
<td>13,772</td>
<td>18,071</td>
<td>32</td>
</tr>
</tbody>
</table>

Non-responders to Oncology Therapeutics Are Highly Prevalent and Very Costly
Cost of Recently Approved Anti-Cancer Drugs

- brenfuximab (Adcetris) $216,000/course
- ipilimab (Yervoy) $123,000/year
- cabazitaxel (Jevtana) $96,000/year
- sipuleucel-t (Provenge) $93,000/year
- vismodegib (Erivedge) $75,000/course
- petuzumab (Perjeta) $70,800/year
- vemurafenib (Zelboraf) $61,000/year
- abiraterone (Zimiga) $60,000/year
- premetrexed (Alimta) $30,000/course
Conflicts and Contrasts in Reimbursement Policies and Clinical Utilization of Molecular Diagnostics (MDx) and Therapeutics (Rx) in Oncology

- MDx and Omics Profiling
- SOC Rx guidelines

- MDx profiling to ID Rx response/resistance

- Segmentation of major cancers into ever smaller cohorts

- ‘one size-fits all’ Rx regimens
  - multi-line Rx versus palliation
  - aggressive end-of-life Rx
Conflicts and Contrasts in Reimbursement Policies and Clinical Utilization of Molecular Diagnostics (MDx) and Therapeutics (Rx) in Oncology

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- aggressive end-of-life Rx

Segmentation of major cancers into ever smaller cohorts

Foundation for Precision Diagnosis and Rational Treatment Selection

Propagation of Irrational Therapeutic Strategies With Limited Effectiveness
Conflicts and Contrasts in Reimbursement Policies and Clinical Utilization of Molecular Diagnostics (MDx) and Therapeutics (Rx) in Oncology

MDx and Omics Profiling

Cost-Based Versus Value-based Pricing

Uncritical Acceptance of Rx Pricing

Barriers to Innovation and Recovery of Increasing R&D Cost

Incentives to Sustain Inadequate Rx Discovery Strategies
Reimbursement for Molecular Diagnostics and Related Omics Profiling Tests

- current payment policies based on earlier era of comparatively simple (low technical complexity) tests
  - time and materials used to conduct test
  - no premium for cost recovery for escalating test complexity/R&D investment for next-generation “Omics” 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
“CMS.....believes that the lessons learned during the initial implementation of CED can inform its more frequent use and create predictable incentives for innovation while providing great assurance that new technologies in fact fulfill their initial claims of benefit.”

National Bioeconomy Blueprint
The White House, April 2012
Reimbursement for Multi-Analyte Algorithmic Tests

- FDA: In Vitro Diagnostic Multivariate Index Assay (IVDMIAs)
- AMA/CMS: Multi-Analyte Assays with Algorithmic Analysis/(MAAA)

“Medicare does not recognize a calculated or algorithmically derived rate or result as a clinical laboratory test since the derived rate or result alone does not indicate the presence or absence of a substance or organism in the body.”

Segmentation (Stratification) of Patient Cohorts by Molecular Profiling and Clinical Trials

Can Large Scale, “All Comers”, Randomized Clinical Trials Be Justified in an Era of Clinical Profiling?

New Regulatory and Reimbursement Issues

Design of Post-Approval/Observational Studies to Support Reimbursement Decisions
Heterogeneity of Driver Oncogenes in NSCLC

Enrichment and Adaptive Trials Using MDx-Stratified Patients: Consequences of Foregoing Phase III RCTs

- faster trials and patient access to promising Rx (terminal diseases)
- less definitive evidence regarding safety and efficacy (smaller ‘N’)
- accelerated approval should require reciprocal agreement for market withdrawal if confirmatory trials are negative
  - “fast on, fast off”
  - lessons from Avastin
The Challenge of Escalating Technical Complexity and Massive Data Streams

“In God we trust, all others must bring data”

W. Edwards Deming, Statistician

- validated data
- actionable data
- accessible data
- integrated data for knowledge-driven decisions
Silos Subvert Solutions: Protecting Turf and Sustaining the Status Quo

HELL IS THE PLACE WHERE NOTHING CONNECTS — T.S. ELIOT
WELCOME TO BIOMEDICAL RESEARCH AND PATIENT MEDICAL RECORDS
The Need for Facile, Seamless Data Exchange Formats for Large Scale Biomedical Data Systems
The Pending Zettabyte Era
1,000,000,000,000,000,000,000

Managing Big Data in Biomedicine is Not a Simple Extrapolation from Current Practices

Current Institutional Structures and Competencies Are Ill-Prepared for Pending Disruptive Change
● typical EHR
  – 375 KB/patient

● radiologic picture archiving and communication system (PACS)
  – 104 MB/patient
  – x277 > EHR

● WGS
  – 3-10 million variants/individual
  – 5-10 GB/individual
  – x50 > imaging
The Growing Education and Knowledge Gaps in Comprehension of Molecular Medicine Concepts Among Healthcare Professionals
Education in Molecular (Precision) Medicine and a Looming Skills Gap

- Clinical specialists with panOmics expertise
  - Molecular genetics, pathology, genetic counseling
  - “Molecular medicine 101” and CME for healthcare professionals
- Informaticians
  - Informatics (analytics)
  - Database design and curation for optimized data flows for clinical decisions
  - Data customization and visualization for different end-users
- Social media and medical apps.
Technology Acceleration and Convergence:
The Escalating Challenge for Professional Competency,
Decision-Support and Future Education Curricula
The Principal Forces Shaping Biomedical R&D and Healthcare Delivery

- Device-based medicine
  - Sensors and m.health
  - Remote health monitoring

- Molecular medicine
  - PanOmics

- Information-based healthcare
  - M.health/e.health

Outcomes-based healthcare and sustainable health

New value propositions, new business models and services
Analytical and Clinical Validation of Molecular Determinants of Disease, Treatment Options and Predisposition Risk

disease biomarker and molecular variants

massive data: volume, velocity, variety, veracity

evidentiary standards for regulation/reimbursement

clinical utility and adoption

value
Identification and Validation Biomarkers: A Complex, Multi-Dimensional Challenge

OPTIMIZED DECISIONS FOR IMPROVED OUTCOMES AT LOWER COST

- biomarker profiling technologies
- multi-disciplinary data integration
- clinical utility and adoption
- value and reimbursement