Overview of Presentation

• IOM Report on Recommended Pathway for Omics Test Evaluation Framework

• College of American Pathologists Evaluation of Genomics

• Genomics from a Molecular Pathologist’s Perspective
Recommended Framework for Evaluation of Omics Tests from Discovery to Test Validation and Clinical Utility Assessment

**Discovery and Test Validation Stage**
- **Discovery Phase**
  - Product is a fully specified candidate omics-based test with locked down computational procedures.
  - See Chapter 2

- **Test Validation Phase**
  - Analytical and Clinical/Biological Validation
  - Product is a fully specified and locked down omics-based clinical test.
  - See Chapter 3

**Evaluation for Clinical Utility and Use Stage**

Three Potential Pathways (IRB Approval and FDA Consultation)

- **Prospective/Retrospective Study with Archived Specimens**
- **Prospective Clinical Trial; Test Does NOT Direct Patient Management**
- **Prospective Clinical Trial; Test Directs Patient Management**

IDE Needed?
- No
- No
- Yes

- FDA Approval/Clearance or LDT Process for Clinical Test
- Additional High Quality Evidence to Evaluate Clinical Utility of the Test
- Practice Guidelines and Reimbursement
- Clinical Use
Understanding of the Human Genome Combined with Sequencing Technology Advances are Moving Us Toward Genomic Medicine

Genomic Medicine is made possible by ability to analyze individual patient genomes.
Genomic Medicine is Driving a Strong Global Molecular Diagnostics Market with Estimated Annual Growth of 13.6%

Source: ‘Valuation of Carried Intangible Assets’, Acuity Technology Management, June 2011
Genetics & Oncology Show Highest Growth with Continued Growth in Infectious Diseases in North American Market

USD MM

---|---|---|---|---|---|---
Genetics | 214 | 288 | 334 | 388 | 450 | 522
Oncology | 211 | 293 | 346 | 408 | 481 | 568
Infectious Diseases | 857 | 1,048 | 1,159 | 1,284 | 1,423 | 1,577

The Cost of Genome Sequencing Is Decreasing Rapidly and Driving Clinical Adoption of Genomic Analysis

Cost per Genome Data Generation, 2001 – 2011

Cost for genome sequence data generation today is <$3,000

Source: National Human Genome Research Institute
Advances in Sequencing Technology is Driving Adoption of Clinical Genomic Analysis in Molecular Pathology Laboratories

<table>
<thead>
<tr>
<th>Sequencers</th>
<th>1st Genome</th>
<th>Research/ Clinical</th>
<th>Clinically Relevant Cost &amp; TAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABI</td>
<td>Hundreds</td>
<td>HiSeq</td>
<td>MiSeq</td>
</tr>
<tr>
<td>Instrument Price</td>
<td>$ 250,000</td>
<td>$ 750,000</td>
<td>$ 125,000+</td>
</tr>
<tr>
<td>Time</td>
<td>Years</td>
<td>Weeks</td>
<td>27 hours</td>
</tr>
<tr>
<td>Output</td>
<td>NA</td>
<td>~50 Gb</td>
<td>2 Gb</td>
</tr>
<tr>
<td>Genomic Analysis</td>
<td>Single Genes</td>
<td>Gene Panels, Exome, Genome</td>
<td>Gene Panels</td>
</tr>
</tbody>
</table>

**TIME**

Clinical Genomics is possible today & technology continues to advance
Genomic Testing by Next Gen Sequencing is Being Used in Molecular Pathology Practice Today

Past and Continuing Molecular Pathology Tests

- Single/Few Mutations
- Single Gene/Pathogen
- Few Genes/Pathogens

Genomic Analysis: Clinically Useful Now

- Gene Panels
- Exome

Genomic Analysis: Research & Future Potential

- Genome
- Transcriptome

Research will increase clinical use

Next Gen Sequencing is the newest Molecular Pathology technology and is being used now
Some Molecular Tests Will Move to Next Generation Sequencing While Others Will Remain on Current Platforms

Current Molecular Pathology Testing Examples
- Viral Loads
- Bone Marrow Engraftment Analysis
- Deafness Genetic Testing
- EGFR Mutations
- KRAS Mutations
- BRAF Mutations

Genomic Analysis
- Gene Panels
  - Cancer
  - Specific inherited disorders
- Exome
  - Cancer
  - Unidentified inherited disorders
Opportunities Exist for *ALL* Pathologists to Play Key Roles Within Genomic Medicine

- **Pre-Analytical**
  - All Pathologists

- **Sequence Data Generation**
  - Molecular Pathologists, Molecular Geneticists, Industry & Others with strong molecular biology or genetics knowledge

- **Sequence Data Interpretation**
  - All Pathologists

- **Reporting & Billing**
  - All Pathologists

- **Clinical Consultation**
Early Adopters Identify Clinical Grade Databases and Bioinformatics Tools as a High Priority Need

- **Clinical Database(s):**
  - Require significant time & money
  - Need to define quality & submission standards
  - Need to define access & IP issues

- **Software Tools for Interpretation and Clinical Usefulness:**
  - Require significant time & money
  - Many software tools being developed
  - No interoperability standards
  - Will facilitate role for ALL pathologists in Genomic Medicine

*Pathologists should be at the table in the development of bioinformatics tools & should learn to use tools as developed*
Opportunities Exist for *ALL* Pathologists to Play Key Roles Within Genomic Medicine

What is the landscape for *ALL* Pathologists in the Pre-Analytical & Clinical Consultation Phases for Genomic Testing?

- Pre-Analytical
- Sequence Data Generation
- Sequence Data Interpretation
- Reporting & Billing
- Clinical Consultation
Clinical Decision Support Tools Can Assist **ALL** Pathologists with the Pre-analytical and Clinical Consultations for Genomic Medicine

<table>
<thead>
<tr>
<th>Source: Grail Analysis</th>
<th>My Cancer Genome</th>
<th>Ariadne</th>
<th>Reactome</th>
<th>Interactive Biosoftware</th>
<th>Ingenuity</th>
<th>CollabRx</th>
<th>Omicia</th>
<th>Cartagenia</th>
<th>GeneGo</th>
<th>Biobase</th>
</tr>
</thead>
</table>

**Biobase**

**GeneGo**

**CollabRx**

**Omicia**

**Cartagenia**

**Ingenuity**

**Interactive Biosoftware**

**Reactome**

**Ariadne**

**My Cancer Genome**
### Speed of Clinical Adoption Hinges on Several Factors

| Decreasing Costs                  | • Cost of genome analysis is rapidly decreasing  
|                                  | • Sequencing instruments now are clinically affordable  |
| Increasing Speed                 | • Can generate sequencing data in 10-36 hours  
|                                  | • Clinically relevant TAT available today for data generation  |
| Bioinformatics                   | • Need clinical quality databases and software tools  
|                                  | • Pathologists must participate in development  |
| Clinical Usefulness              | • Genomic Analysis is in clinical use now (small but growing)  
|                                  | • Research/discovery will increase clinical applications  |
| Payment Uncertainty              | • Currently, no specific CPT codes exist for Genomic Analysis  
|                                  | • Payers do not understand Genomic Analysis  |
| Regulatory Uncertainty           | • Federal regulatory uncertainty today  
|                                  | • Quality standards being led by CAP with AMP & ACMG  |
Current GA Reporting and Payment Environment is Uncertain

- No IT standards for reporting in LIS, EHR & PHR
  - Interoperability standards
  - Terminology standards
- Molecular CPT Codes under revision
- No GA CPT Codes available
- Payers do not understand GA
- Early adopters negotiating coverage & reimbursement with each payer for each patient by early adopters
Current GA Regulatory Environment is Uncertain

- FDA held meeting to understand early clinical users needs & concerns
- No FDA position/guidance
- No CLIA standards for GA
- CAP Next Generation Sequencing (NGS) Work Group
  - NGS Checklist questions
  - PT Exchange

Pre-Analytical

Sequence Data Generation

Sequence Data Interpretation

Reporting & Billing

Clinical Consultation
Pathologists Have an Opportunity to Lead the Medical Community in Genomic Medicine

- No single medical specialty is well informed about Genomic Medicine
- Pathologists have an opportunity to be leaders in Genomic Medicine as another diagnostic testing modality
- While genomic technology is rapidly advancing, the discovery process for clinical genomics applications will be an evolution rather than a revolution
- Pathologists can lead in the application of genomic testing as evidence for clinical applications and utility develops
Thoughts on Genomics from a Molecular Pathologist

• Genomics is the next adventure for Molecular Pathology

• Need quality guidelines for data generation and bioinformatics

• Standards hard to develop when everyone still learning ad technology changing so rapidly

• Basic accreditation standards developed for 2012 (CAP, ACMG, AMP) and will evolve as we develop standards/guidelines

• PT is complicated but is coming (CAP)

• Appropriate billing codes needed

• Need to train next generation for genomics
Many Thanks to IOM & CAP Committee Colleagues