Big data vs. the individual liver from a regulatory perspective

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Food and Drug Administration
Disclosures

• The speaker has nothing to disclose
• This presentation reflects the views of the speaker and should not be construed to represent FDA’s policies
Biomarker Development at FDA

- Public-private partnerships
  - Several collaborative research initiatives
- Regulatory science research
  - Major focus of internally funded projects
- Biomarker Qualification program
  - Formal program to garner CDER-wide acceptance
- Product review
  - Case-by-case determinations
- Outreach
  - Safe harbor stakeholder meetings

http://www.fda.gov/scienceresearch/specialtopics/personalizedmedicine/default.htm
<table>
<thead>
<tr>
<th>Year</th>
<th>Resource</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>Guidance on PG Data Submissions</td>
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<tr>
<td></td>
<td>Concept Paper on Drug-Diagnostic Co-Development</td>
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<tr>
<td>2007</td>
<td>Companion Guidance on PG Data Submissions</td>
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<td></td>
<td>Guidance on PG Tests and Genetic Tests for Heritable Markers</td>
</tr>
<tr>
<td>2008</td>
<td>ICH E15 Definitions in Pharmacogenetics/Pharmacogenomics</td>
</tr>
<tr>
<td>2010</td>
<td>ICH E16 Qualification of Genomic Biomarkers</td>
</tr>
<tr>
<td></td>
<td>Guidance on Qualification Process for Drug Development Tools</td>
</tr>
<tr>
<td>2012</td>
<td>Guidance on Clinical Trial Designs Employing Enrichment Designs</td>
</tr>
<tr>
<td>2013</td>
<td>Guidance on Clinical PG: Premarketing Evaluation in Early Phase Clinical Studies</td>
</tr>
<tr>
<td></td>
<td>Rule: Orphan Subsets of a Common Disease</td>
</tr>
<tr>
<td>2014</td>
<td>Guidance on in vitro Companion Diagnostic Devices</td>
</tr>
<tr>
<td></td>
<td>Guidance on Laboratory Developed Tests</td>
</tr>
<tr>
<td>2016</td>
<td>Guidance on Drug-Diagnostic Co-development</td>
</tr>
<tr>
<td></td>
<td>Guidance on NGS-based In Vitro Diagnostics (IVDs) for Diagnosing Germline Diseases, Use of Public Human Genetic Variant Databases to Support Clinical Validity for NGS-based IVDs</td>
</tr>
<tr>
<td></td>
<td>ICH E18 Genomic Sampling Methodologies</td>
</tr>
<tr>
<td></td>
<td>Complementary Diagnostics</td>
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</tbody>
</table>

http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083374.htm
http://www.fda.gov/RegulatoryInformation/Guidances/default.htm
Potential Uses of Omic Data

Prognostic Biomarkers | Predictive Biomarkers | Immunologic/Idiosyncratic Safety Susceptibilities
---|---|---
Absorption | Distribution | Excretion
Target Validation | Anticipated Toxicities

Potential Companion or Complementary Diagnostics to inform treatment decisions
Success Rate is Higher When Genetics is Included During Drug Development

PMID: 24833294, 27548825
Current State of Genomic Biomarker Testing in Clinical Practice

“Classical” Pharmacogenomics

• CYP2D6
  – Codeine
• CYP2C9
  – Warfarin
• CYP2C19
  – Clopidogrel
• NAT2
  – ISDN/hydralazine

“Targeted” Therapies

• Drugs developed for a molecular subset of a disease
• Mechanism of action is often directly linked to a molecular alteration
• Examples (not exhaustive):
  – Nivolumab
  – Pembrolizumab
  – Vemurafenib
  – Gefitinib
  – Afatinib
  – Erlotinib
  – Olaparib
  – Rucaparib
  – Ivacaftor
  – Mepolizumab
### Summary of Selected Diagnostic Tests

<table>
<thead>
<tr>
<th>Drug</th>
<th>Disease</th>
<th>Biomarker(s) Detected by Diagnostic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vemurafenib</td>
<td>Melanoma</td>
<td>BRAF V600E mutation</td>
</tr>
<tr>
<td>Afatinib</td>
<td>Non-small cell lung cancer (NSCLC)</td>
<td>Specific <em>EGFR</em> exon 19 deletions and exon 21 (L858R) substitution mutations</td>
</tr>
<tr>
<td>Erlotinib</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gefitinib</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nivolumab</td>
<td>NSCLC</td>
<td>PD-L1 protein in NSCLC tissue (as a Complementary Diagnostic)</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>NSCLC</td>
<td>PD-L1 protein in NSCLC tissue (as a Companion Diagnostic)</td>
</tr>
<tr>
<td>Rucaparib*</td>
<td>Ovarian cancer</td>
<td>Deleterious mutations in <em>BRCA1</em> or <em>BRCA2</em></td>
</tr>
<tr>
<td>Olaparib</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note: rucaparib companion diagnostic is next generation sequencing based*
Test Development Challenges Increase with Increasing Test Complexity

- Challenges common to all tests
  - Pre-analytical factors, analytical performance characteristics, reproducibility, establishing cut-points (for continuous biomarker tests) clinical validity, clinical utility

- Challenges associated with omic tests
  - Limited statistical power for agnostic approach, data quantity, algorithm development (choosing analytes, defining cut-points, weighting), unknown biological relevance
Challenges Associated with Omic Tests in Clinic

• Access to next-generation technologies

• Costs associated with testing
  – Reimbursement

• Interpretation of results
  – Actionability

• Incidental findings (if test reports all data)
Benefits of Omic Tests

Drug-Development

• Target Validation
  – Important in disease?
  – Toxicities anticipated?
• Dose finding
  – Explain variability
  – Stratified dosing if necessary
  – PD assessments
• Patient selection
  – Predictive/prognostic biomarkers
    • Smaller clinical trials
  – Identify high-risk subsets
    • E.g., HLA genotypes

Clinical Use

• Risk assessment
• Diagnosis
• Prognosis assessment
• Inform most appropriate therapy for individual patients
• Dose selection
## Use of Omic Strategies in Clinical Trials

<table>
<thead>
<tr>
<th>Disease/Drug</th>
<th>Biomarker(s)</th>
<th>Biomarker Purpose</th>
<th>ClinicalTrials.gov Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple myeloma / not drug specific</td>
<td>92 gene signature</td>
<td>Prognostic (to guide treatment decisions)</td>
<td>NCT02911571</td>
</tr>
<tr>
<td>Systemic lupus erythematosus (SLE) / IFN-K</td>
<td>Interferon gene signature</td>
<td>PD Endpoint (primary outcome for phase 2 study)</td>
<td>NCT02665364</td>
</tr>
<tr>
<td>Ovarian cancer / rucaparib</td>
<td>homologous recombination repair deficiency</td>
<td>Predict drug response</td>
<td>NCT01891344</td>
</tr>
<tr>
<td>Metastatic cancer / multiple drugs</td>
<td>Tumor molecular profiling</td>
<td>Treatment assignment (umbrella/basket trial enrollment)</td>
<td>NCT02152254</td>
</tr>
<tr>
<td>SLE / anifrolumab</td>
<td>Interferon signature high</td>
<td>Predictive Enrichment (trial enrollment)</td>
<td>NCT02962960</td>
</tr>
</tbody>
</table>

Studies identified by searching clinicaltrials.gov for “gene signature” and “gene expression signature”, April 2017.
Implementing Omics in Clinical Practice

Incorporate Omic Testing
- Genomics
- Transcriptomics
- Proteomics

Inform Treatment
- Diagnosis
- Therapy selection
- Dose

Improve Outcomes
- Morbidity
- Mortality
- Quality of life
<table>
<thead>
<tr>
<th>Test</th>
<th>Disease</th>
<th>Biomarker(s)</th>
<th>Intended Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>MammaPrint</td>
<td>Breast cancer</td>
<td>70 gene expression profile in breast cancer tissue</td>
<td>Assess a patient’s risk for distant metastasis within 5 years</td>
</tr>
<tr>
<td>Cologuard</td>
<td>Colon cancer</td>
<td>Epigenetic changes, mutational markers, occult hemoglobin</td>
<td>Detection of colorectal neoplasia associated DNA markers ...(may indicate presence of colorectal cancer)</td>
</tr>
<tr>
<td>Allomap</td>
<td>Heart transplantation</td>
<td>RNA expression of 20 genes in PBMCs (11 informative, 9 control)</td>
<td>Aid in the identification of heart transplant recipients with stable allograft function who have a low probability of Moderate / severe acute cellular rejection</td>
</tr>
<tr>
<td>xTAG Cystic Fibrosis 60 Kit v2</td>
<td>Cystic Fibrosis</td>
<td>60 mutations and 4 variants in the <em>CFTR</em> gene</td>
<td>Carrier testing in adults of reproductive age, as an aid in newborn screening, and in confirmatory diagnostic testing in newborns and children</td>
</tr>
</tbody>
</table>
How do we Move Forward?

• High-throughput exploration in early-phase trials

• Data sharing to promote validation of findings from exploratory studies

• Well-planned and executed codevelopment strategies

• Access to next-generation technologies in the clinic
Summary

Advanced tools, technology and research

Innovative development programs

Reliable omic tests

Better patient outcomes