Big data vs. the individual liver from a regulatory perspective

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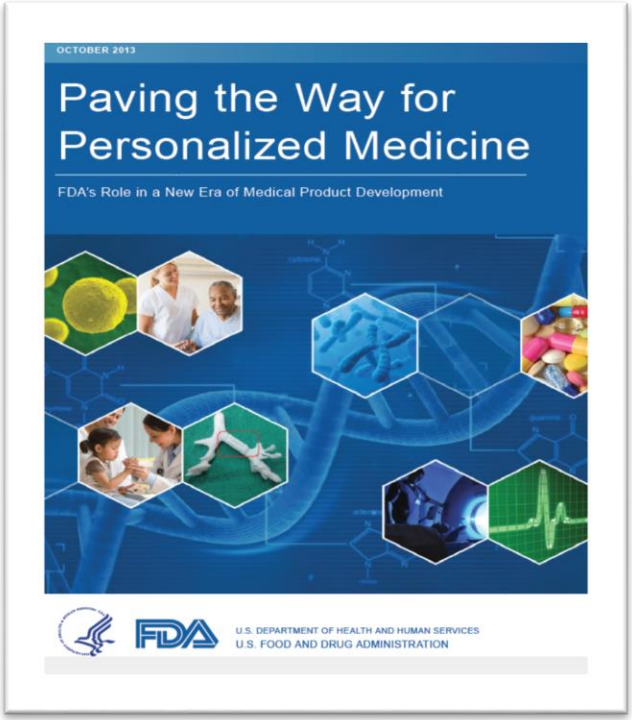
Disclosures

- 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



http://www.fda.gov/scienceresearch/specialtopics/personalizedmedicine/default.htm

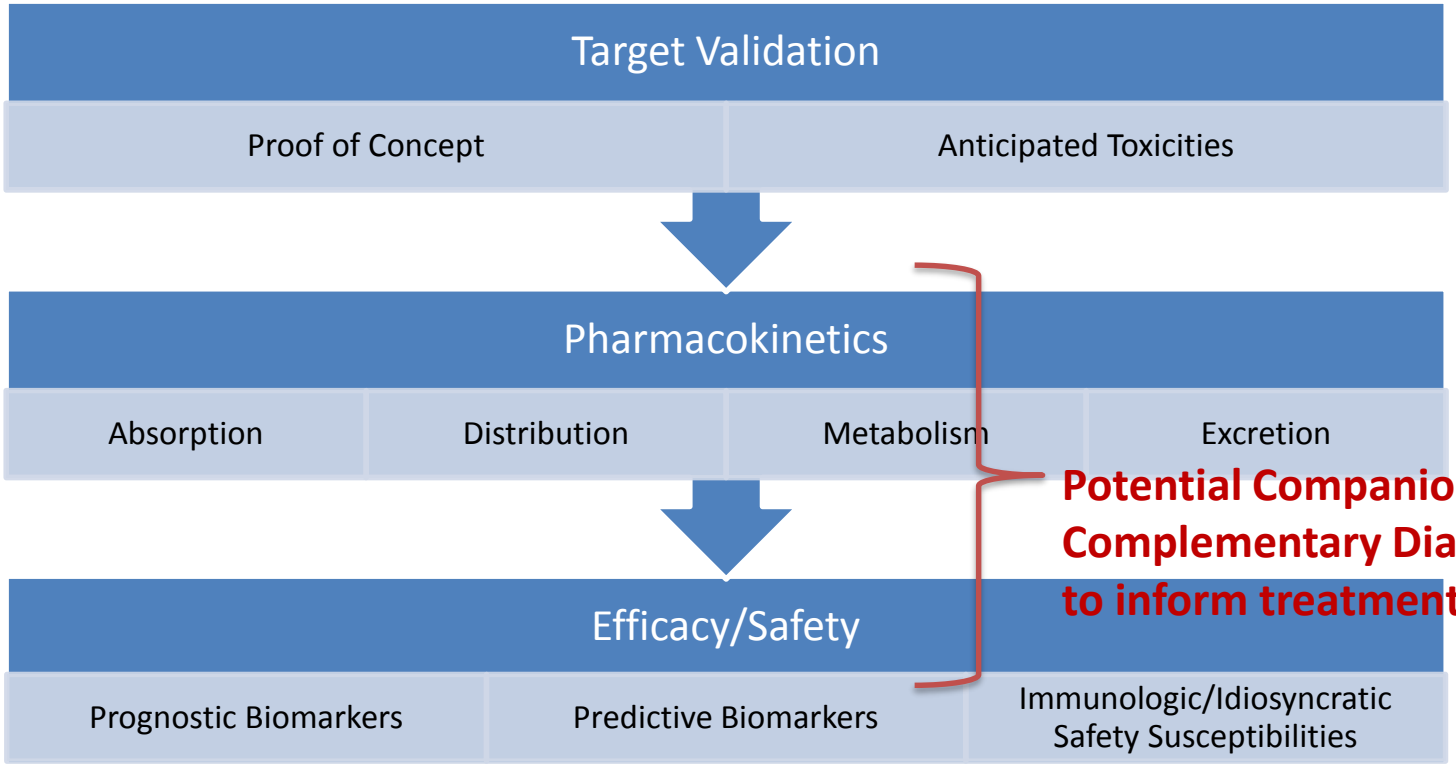
- Public-private partnerships
  - Several collaborative research initiatives
- Regulatory science research
  - Major focus of internally funded projects
- Biomarker Qualification program
  - Formal program to garner CDER-wide acceptance
- Product review
  - Case-by-case determinations
- Outreach
  -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

FDA Resources - Biomarker Development

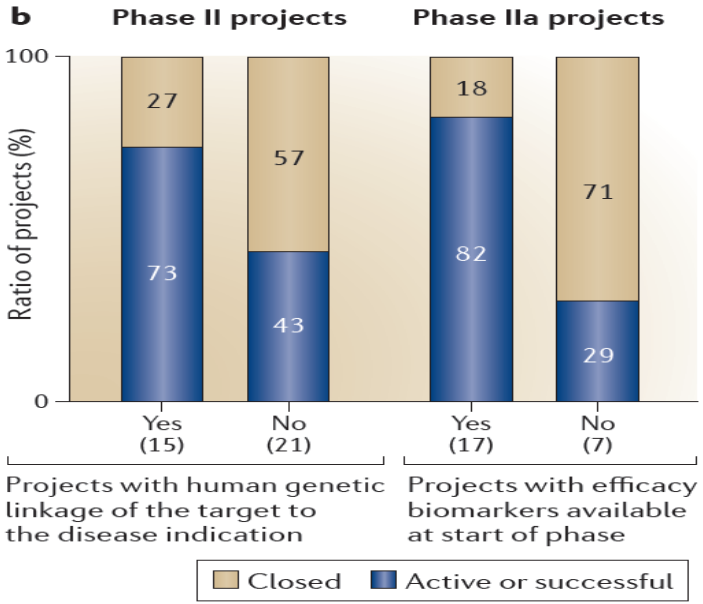
2005	Guidance on PG Data Submissions
	Concept Paper on Drug-Diagnostic Co-Development
2007	Companion Guidance on PG Data Submissions
	Guidance on PG Tests and Genetic Tests for Heritable Markers
2008	ICH E15 Definitions in Pharmacogenetics/Pharmacogenomics
2010	ICH E16 Qualification of Genomic Biomarkers
	Guidance on Qualification Process for Drug Development Tools
2012	Guidance on Clinical Trial Designs Employing Enrichment Designs
2013	Guidance on Clinical PG: Premarketing Evaluation in Early Phase Clinical Studies
	Rule: Orphan Subsets of a Common Disease
2014	Guidance on in vitro Companion Diagnostic Devices
	Guidance on Laboratory Developed Tests
2016	Guidance on Drug-Diagnostic Co-development
	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
	ICH E18 Genomic Sampling Methodologies
In Process	Complementary Diagnostics

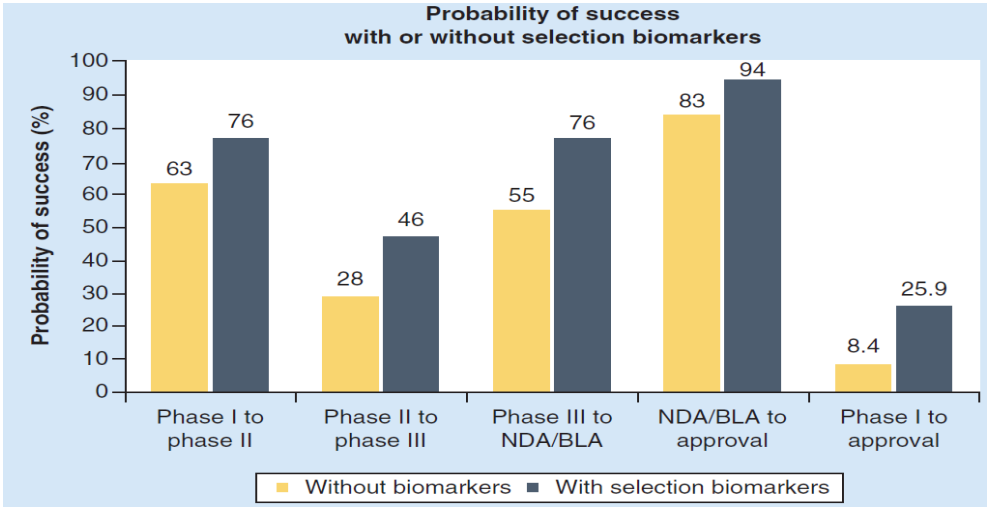
http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083374.htm
http://www.fda.gov/RegulatoryInformation/Guidances/default.htm

Potential Uses of Omic Data



Success Rate is Higher When Genetics is Included During Drug Development





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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

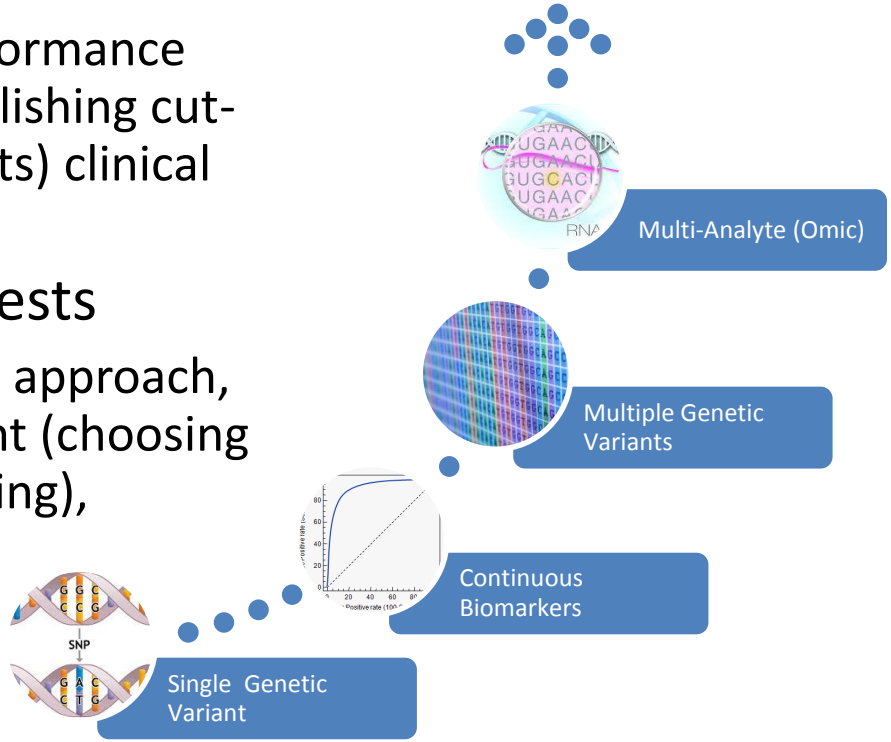
Summary of Selected Diagnostic Tests

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

*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

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

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

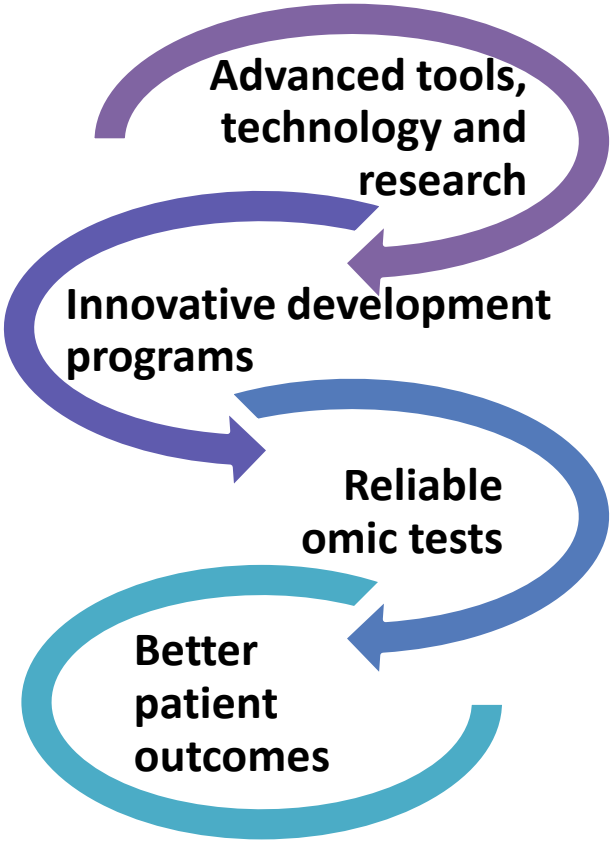
Selected FDA Cleared or Approved Omic Tests

Test	Disease	Biomarker(s)	Intended Use
MammaPrint	Breast cancer	70 gene expression profile in breast cancer tissue	Assess a patient's risk for distant metastasis within 5 years
Cologuard	Colon cancer	Epigenetic changes, mutational markers, occult hemoglobin	Detection of colorectal neoplasia associated DNA markers …(may indicate presence of colorectal cancer)
Allomap	Heart transplantation	RNA expression of 20 genes in PBMCs (11 informative, 9 control)	Aid in the identification of heart transplant recipients with stable allograft function who have a low probability of Moderate / severe acute cellular rejection
xTAG Cystic Fibrosis 60 Kit v2	Cystic Fibrosis	60 mutations and 4 variants in the *CFTR* gene	Carrier testing in adults of reproductive age, as an aid in newborn screening, and in confirmatory diagnostic testing in newborns and children

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