

# Navigating the Regulatory Pathway for Genetic Tests and Biomarkers in Clinical Drug Development

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*Enabling Precision Medicine: The Role of Genetics in Clinical  
Drug Development*

*National Academies of Science, Engineering and Medicine*

*March 8, 2017*

**This speech reflects the views of the speaker and should not be construed to represent FDA's policies**



# Key Questions

- **What are the issues that need to be considered with regard to the regulatory pathway for genetic tests and biomarkers used in clinical drug development?**
- **How can these be addressed during the development process?**
- **Is there a need to examine/enroll biomarker-negative populations in addition to biomarker-positive populations?**
- **What is the best path forward from a GWAS finding to a Phase 3 trial?**

# Agenda



- General considerations
- Rare, genetic diseases
- Common, complex diseases

# Uses of Genomics in Drug Development



## Preemptive

- Validate target
- Predict toxicities
- Define target population

## Retrospective

- Explain variability
- Identify (non-)responders or toxic responders
- Characterize drug interactions

## Prospective

- Control exposures
- Minimize noise
- Increase event rates
- Select responders

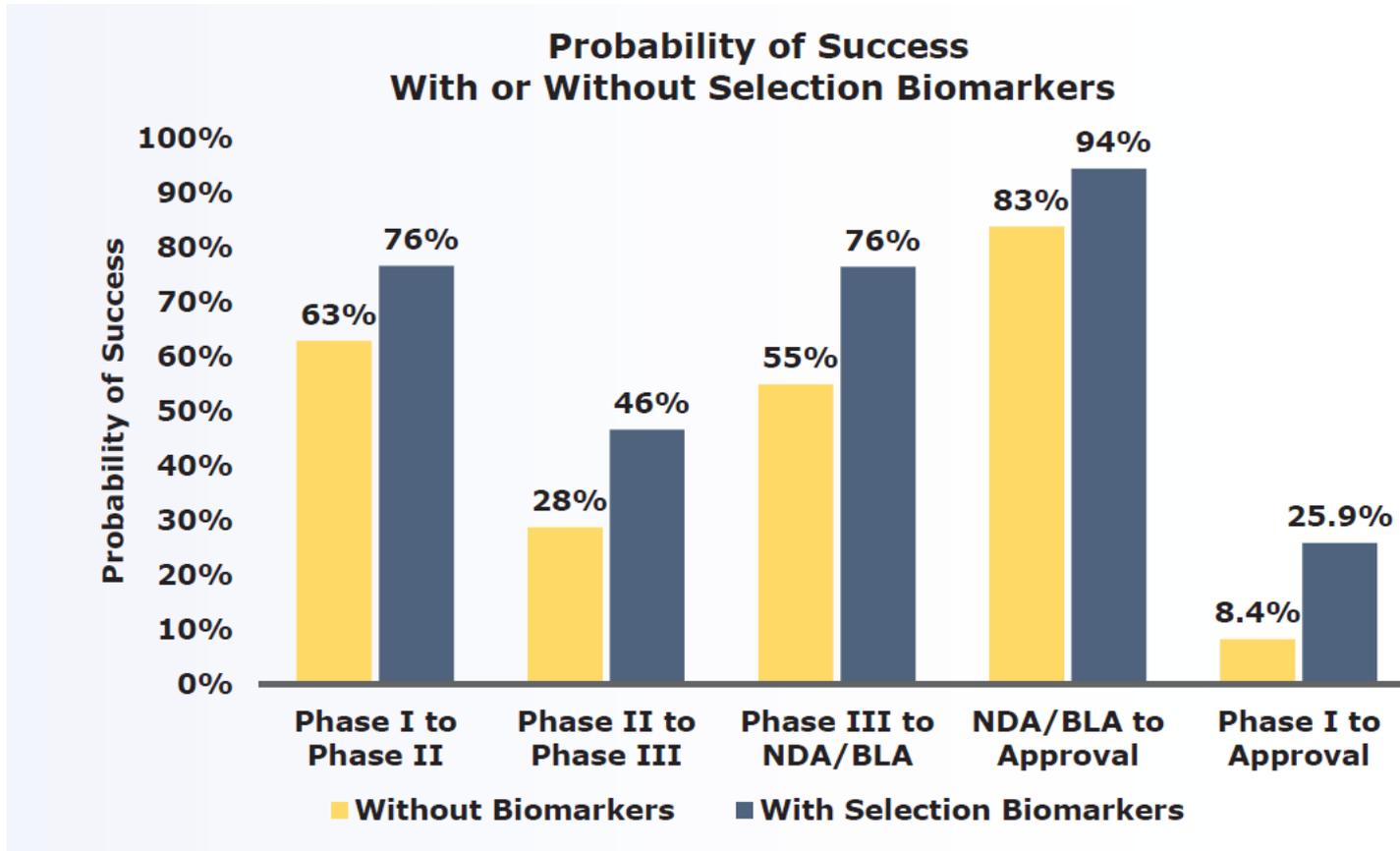
## “Precision Medicines”\*

- Drug or biologic intended for use with a genomic, proteomic, or other specific biomarker that identifies patients within a clinically-defined disease who are eligible for treatment, aids in determining the appropriate dose, or allows for monitoring of responses to individualize therapy
- Biomarkers may have diagnostic, prognostic, predictive, or other value; mechanistically related to the drug of interest in most cases

# Why?



## *Success Rates Tend to be Higher with Patient Selection Biomarkers*





Feb 26, 2017; selected examples

\* Approved companion or complementary dx

† Not "essential"

# Setting the Stage for Targeted Drug Development



- Drivers of targeted development
  - Biomarker is in causal pathway or the primary drug target
  - Nonclinical studies show limited or paradoxical activity in gene/protein variants
  - Clinical studies show large benefit, harm, or lack of activity in biomarker-defined subgroups
- Considerations for biomarker-based indications
  - Confidence in the biomarker: predictive utility, novel vs. established, intrinsic properties (e.g., assay, variability)
  - Nature of the disease: morbidity, mortality, available treatments
  - Therapeutic properties: magnitude and nature of benefit, toxicities, dosing approach (e.g., titration)

## Past Experience

- Evidence for retrospectively identified biomarkers depends on context; incomplete biospecimen sampling can be problematic
- An unreliable clinical trial assay can alter the analysis population and affect interpretation of the trial results
- A reliable test is needed to identify the to-be-treated population in the clinic
- Complementary diagnostics can provide useful information to assess individual benefits/risks if a drug is effective overall
- Trials in “marker-negative” patients can occur post-marketing
- Disease microheterogeneity may exist among “marker-positive” patients
- Indications often relate to the studied population(s)

# The Evolving Regulatory Framework for Precision Medicines



<b>Clinical Pharmacogenomics</b>	<b>Collect DNA to facilitate biomarker development (sometimes it is needed)</b>
<b>Enrichment</b>	<b>Use enrichment strategies (via trial design or patient selection) to decrease noise, increase event rates, or enhance treatment effect</b>
<b>Companion Diagnostics</b>	<b>IVD needed if essential for safe and effective use; need for pre-market review, risk-based regulation</b>
<b>Codevelopment</b>	<b>Process-oriented guidance on use and development of companion IVDs in a therapeutic trial context</b>

For more information on other related guidances, visit

<http://www.fda.gov/ScienceResearch/SpecialTopics/PersonalizedMedicine/ucm372544.htm>

# Draft Codevelopment Guidance: Key Points



- Determine what IDE requirements apply to investigational IVDs
- Complete analytical validation studies before using IVD in trials
- Use an IVD with “market-ready” performance in pivotal trials
- Use a single testing protocol for clinical trial assays and do not manipulate during the trial
- Establish preanalytical operating procedures, and qualify sites if decentralized
- Characterize prescreening bias, evaluate intent-to-diagnose population
- Bank specimens in sufficient quantity to support analytical validation and bridging
- Submit marketing applications for contemporaneous review (letters of authorization); modular PMA advised

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# Molecular Diversity of Genetic Diseases

Unknown molecular etiology



Known molecular etiology in most, single pathological variant



Known molecular etiology in most, multiple pathological variants, some rare



Known molecular etiology in most, multiple rare pathological variants, all rare



Shared molecular etiology, with permutations on diversity above



# Who Should Be Enrolled in Confirmatory Trials?



Disease/ Mechanism	Drug	Indicated Subset
NSCLC/ EGFR inhibitor	<u>Erlotinib</u>	EGFR exon 19 deletions or exon 21 L858R substitution*
	<u>Afatinib</u>	
	<u>Gefitinib</u>	
	Osimertinib	EGFR T790M mutation*
Melanoma/ BRAF inhibitor	<u>Vemurafenib</u>	BRAF V600E mutation*
	Dabrafenib	
Melanoma/ MEK inhibitor	Trametinib	BRAF V600E/K mutations*
Ovarian cancer/ PARP inhibitor	<u>Olaparib</u>	Deleterious or suspected deleterious germline BRCA mutations*
	Rucaparib	Deleterious germline and/or somatic BRCA mutations*
Colorectal cancer/ EGFR inhibitor	<u>Cetuximab</u>	KRAS wild-type* (not RAS mutations)
	Panitumumab	KRAS wild-type (exon 2)* (not RAS mutations)
Cystic fibrosis/ CFTR potentiator	Ivacaftor	Heterozygous CFTR G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, R117H
Cystic fibrosis/ CFTR potentiator/corrector	Ivacaftor/ lumacaftor	Homozygous CFTR F508del mutation
Duchenne muscular dystrophy/ exon skipper	Eteplirsen	Exon 51 skipping amenable

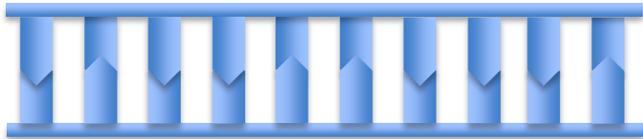
\* As detected by an FDA-approved test

# Approaches to Manage Molecular Diversity



- Enrollment strategy
  - Therapeutic risk/benefit or ability of trial to detect a drug effect may differ across subtypes (defined by allele, locus, gene, pathway, etc)
  - Mechanistic, nonclinical or clinical data may inform baseline grouping
  - Enroll diverse subtypes that are expected to respond similarly
- Trial analysis and interpretation
  - Unable to infer treatment effects in small or unstudied subsets; build case on totality of evidence (e.g., nonclinical models)
  - Specify hypothesis in overall population or homogenous subsets
- Conditions for use
  - Indications may be based on individual mutations, codons, genes, pathways, or functional groupings thereof
  - Breadth of to-be-treated population depends on enrollment criteria, benefit (e.g., unmet need), risk, and IVD design
  - Post-marketing studies may be used to monitor outcomes

# Synthetic Oligonucleotides and Other Genetically Targeted Therapies



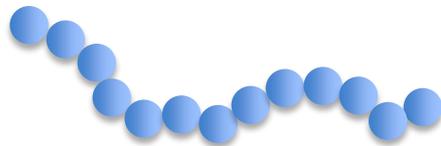
DNA

CRISPR/Cas9



RNA

Antisense (**mipomersen**)  
Splice-altering (**eteplirsen**, **nusinersen**)  
siRNA  
microRNA  
mRNA replacement



Protein

Aptamers (**pegatinib**)  
CpG/TLR

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# Translating GWAS Results (and Other SNP Markers) to Confirmatory Trials

- Targeted drug development for common diseases tends to focus on stratification using well-established biomarkers (drug metabolism and disease markers like APOE)

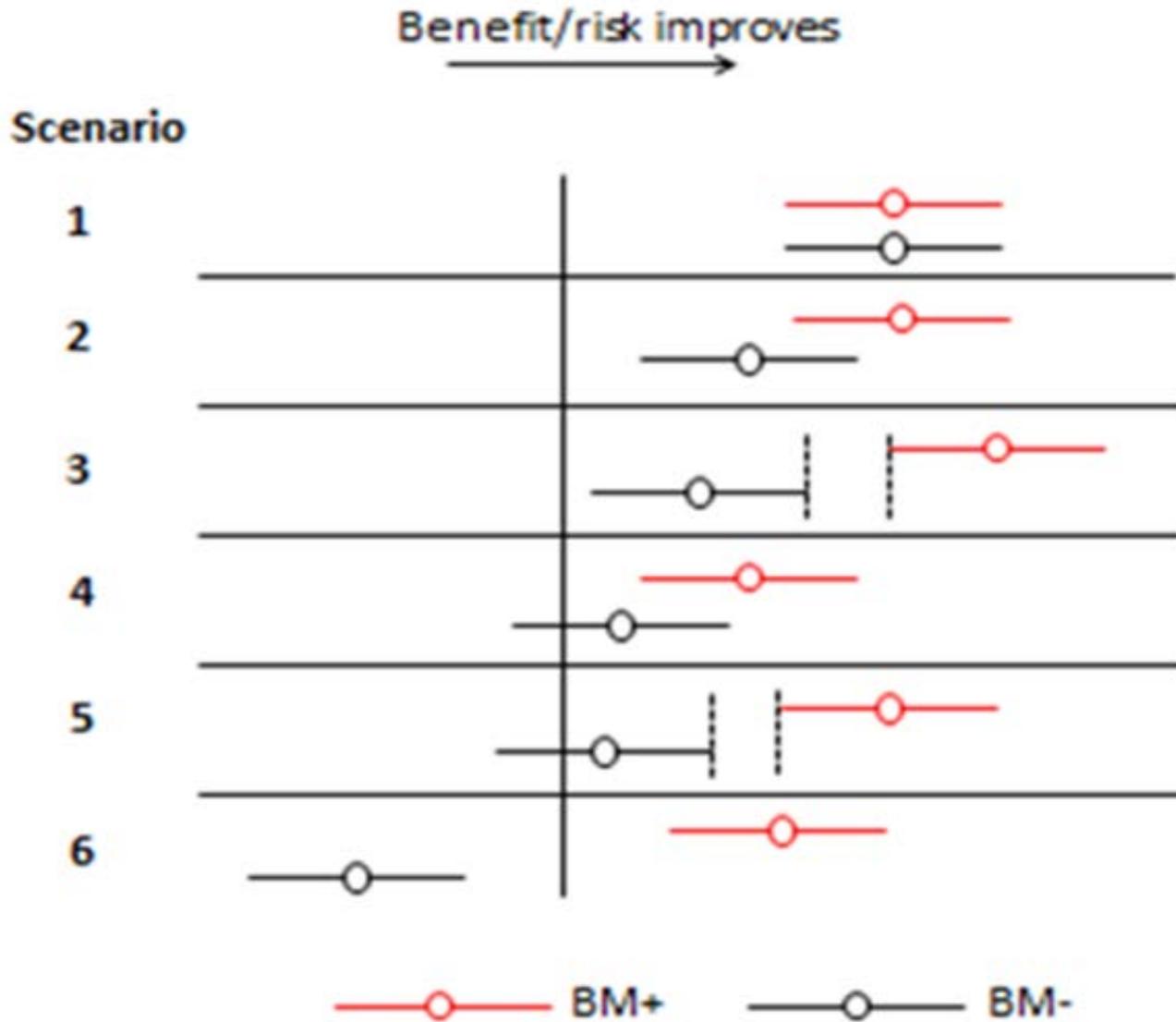
## Discovery Challenges

- Small sample size
- Incomplete sampling, bias
- Homogenous populations
- Marginal p-values, contrived analyses
- Inconsistency between early- and late-phase trial endpoints
- Lack of mature efficacy/safety data

## Strengthening Validity

- Establish statistical gene x drug interaction
- Focus on large effect sizes
- Identify causal locus
- Perform functional studies
- Plan to enroll marker-positive and -negative patients in pivotal trials
- Examine ethnically diverse populations

# Possible Outcomes



# Investigational New Drug and Marketing Application Review Issues



- What biomarkers/genetic factors need to be prospectively assessed? (*disease, target, pathway, disposition*)
- Are biomarker/genomic studies needed to resolve variability in exposure or response? (*variability, race effects; certain AEs*)
- Do genetic studies indicate a potential for target-based toxicities? (*genetic epidemiology of drug target or pathway*)
- Is the target population appropriate? (*well-defined population, rare subsets*)
- Is review of the investigational or to-be-marketed in vitro diagnostic needed? (*enrichment/stratification; codevelopment*)
- Are different dosing or patient selection recommendations needed on the basis of differences in exposure or response across biomarker subgroups? (*benefit-risk*)

# Summary

- **What are the issues that need to be considered with regard to the regulatory pathway for genetic tests and biomarkers used in clinical drug development?**
  - Strength of evidence to support biomarker-directed development, managing microheterogeneity, need for an IVD
- **How can these be addressed during the development process?**
  - Use a development strategy that provides evidence for the drug and biomarker, plan ahead for the IVD, engage IVD partner and FDA early
- **Is there a need to examine/enroll biomarker-negative populations in addition to biomarker-positive populations?**
  - Some data in marker-negative patients is usually desirable, particularly when the merits and limitations of the biomarker are unknown
- **What is the best path forward from a GWAS finding to a Phase 3 trial?**
  - Use robust methods, perform supportive experiments, address ethnic diversity

## Areas of Ongoing Discussion

- **Informatics architecture for NGS** (Sep 14)
- **Evidence generation for small subsets** (Dec 14)
- **Laboratory-developed tests** (Jan 15)
- **Regulatory framework for NGS** (Feb 15)
- **Harmonizing co-Dx across a drug class** (Mar 15)
- **Analytical performance of NGS platforms** (Nov 15)
- **Databases to establish clinical relevance** (Nov 15)
- **NGS panels** (Feb 16)
- **Complementary biomarkers/diagnostics**
- **Evidentiary criteria for biomarker qualification**  
(Aug 15, Oct 15, Dec 15, Apr 16)

