OPPORTUNITIES AND CHALLENGES IN THE DEVELOPMENT AND REGULATORY EVALUATION OF PRECISION MEDICINES

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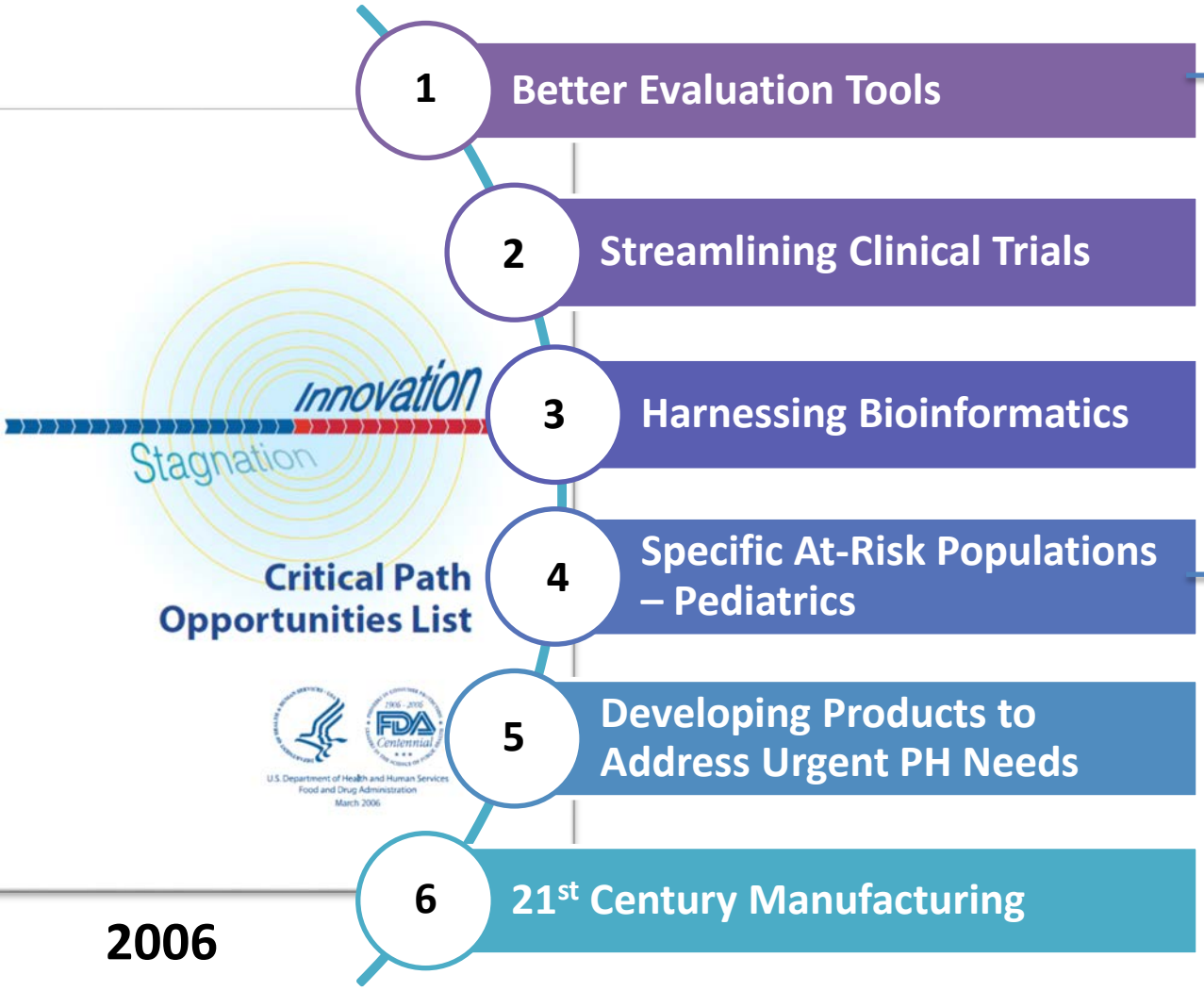
Overview

- Regulatory science and policy to date
- Trends in precision medicine
- Evolving areas and issues

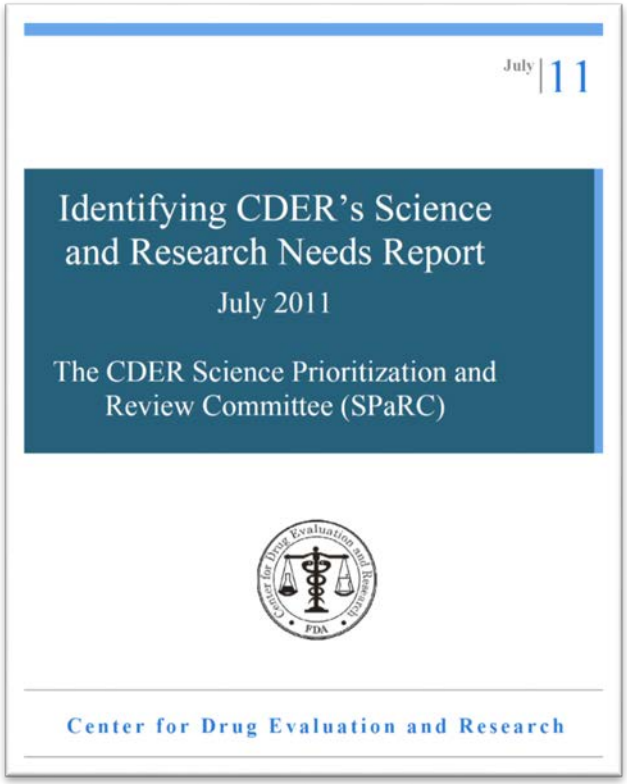
Precision Medicine on the Critical Path

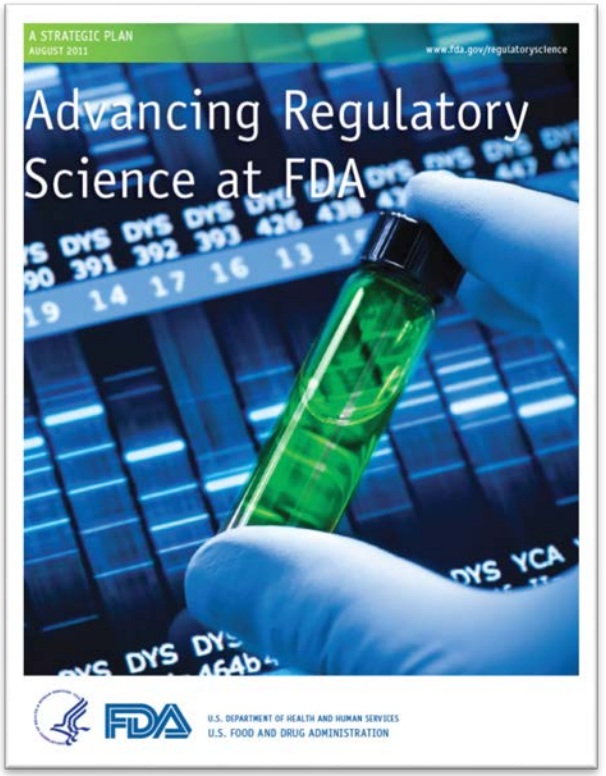


Rx/Dx Co-development
Omics reference standards
Pharmacogenetics
Enrichment designs
New trial designs
Predictive safety markers
Genotype-informed dosing
Disease subtyping

https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/UCM077258.pdf

Precision Medicine & Regulatory Science

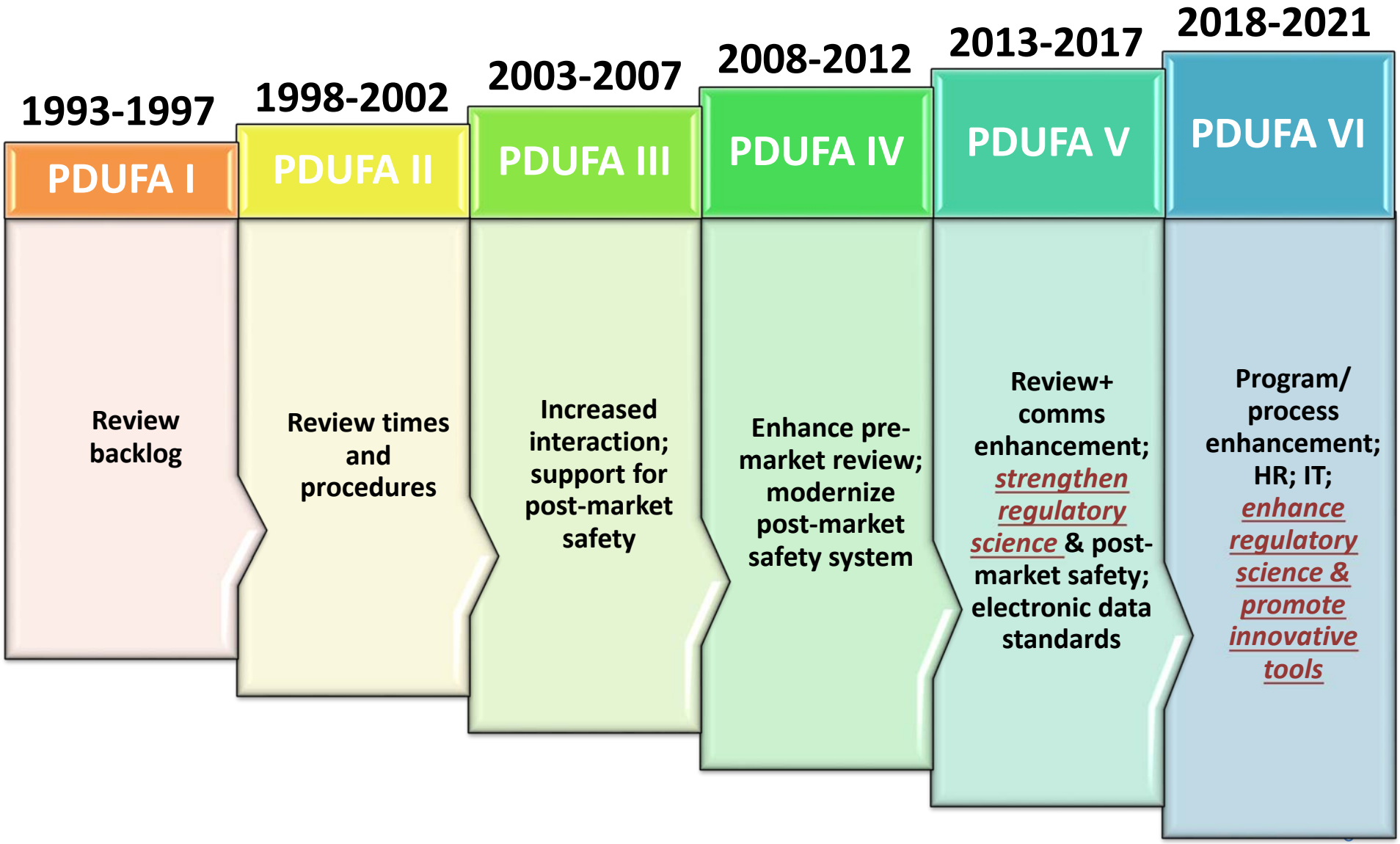




Enhance Individualization of Patient Treatment

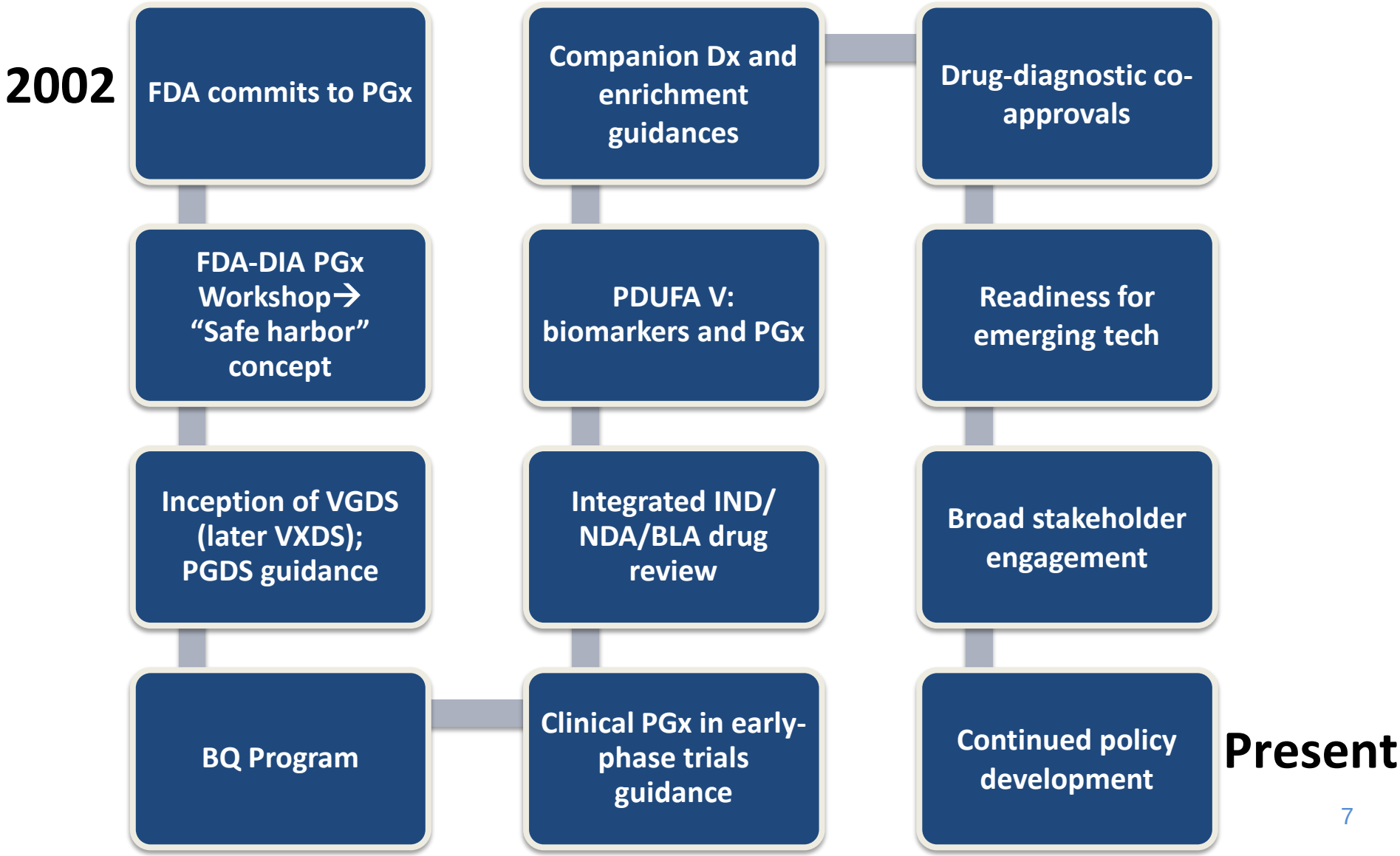
Stimulate Innovation in Clinical Evaluations and Personalized Medicine to Improve Product Development and Patient Outcomes

Regulatory Enhancements and Innovative Decision Tools

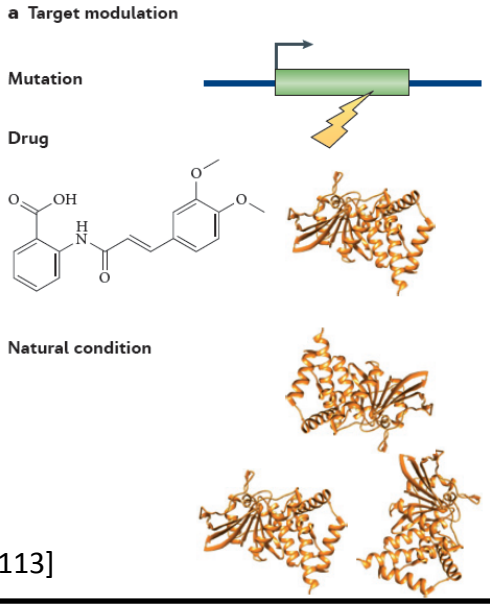


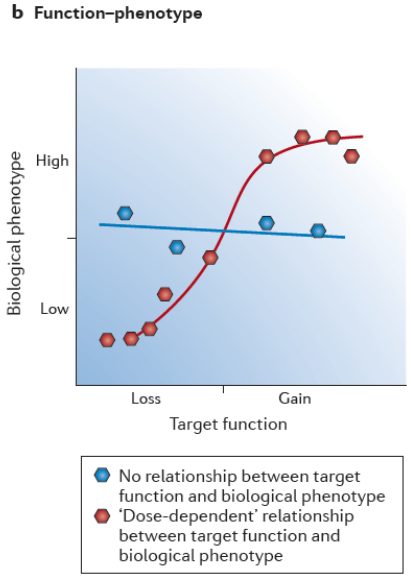
More info @ http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm | Modified from J. Barton, OSP/CDER/FDA

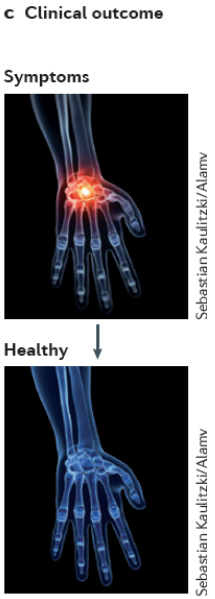
History of Precision Medicine at FDA



Precision Medicine Trends

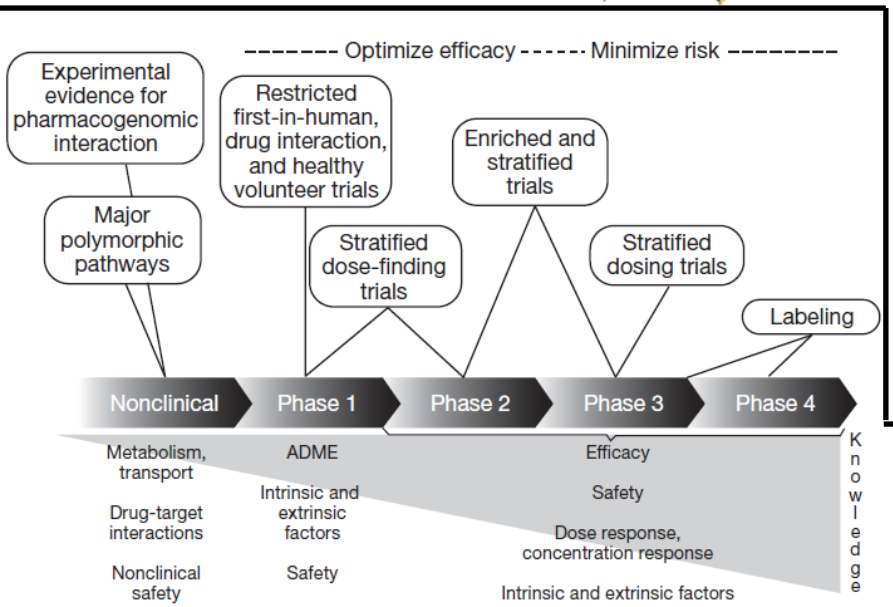






Plenge [PMID 23868113]

Nelson [PMID 26121088]



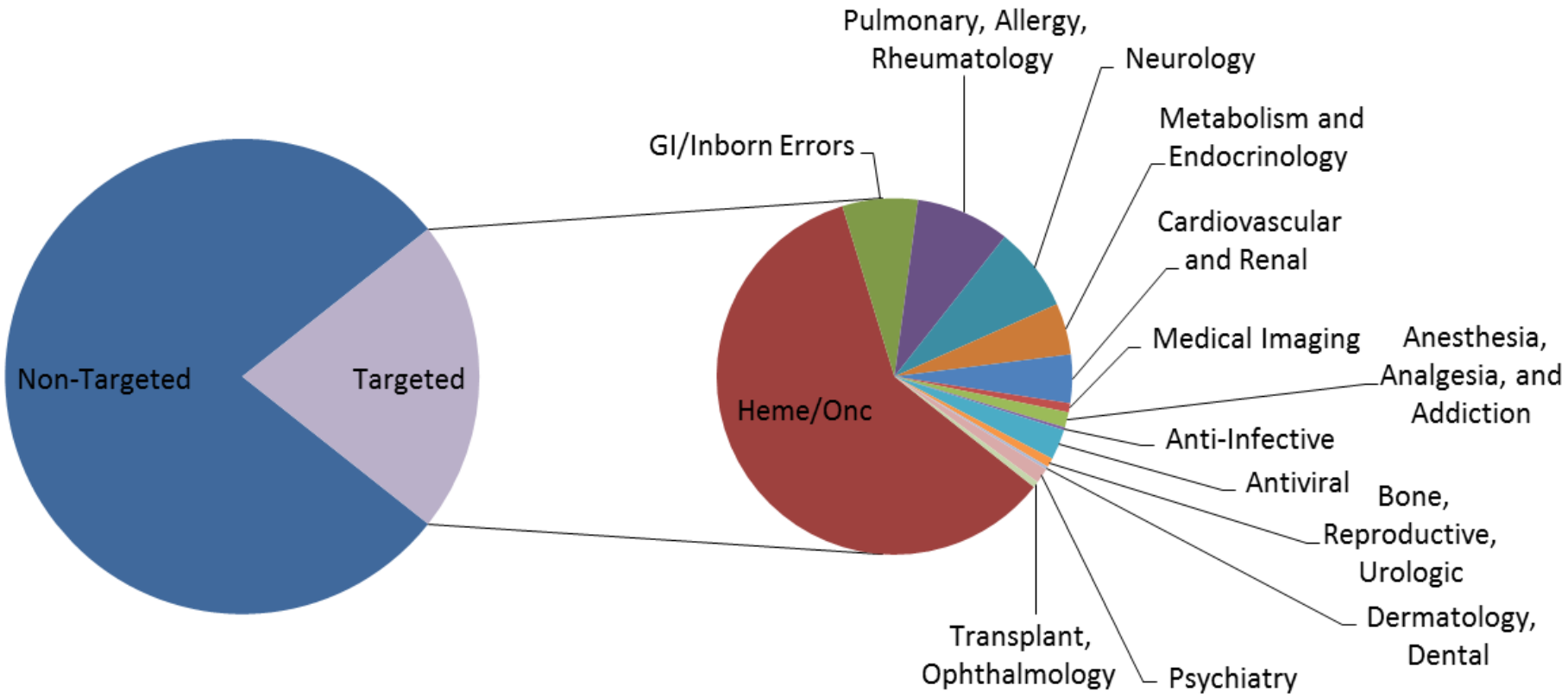
Progression	*p*(progress|genetic support)/(progress|no genetic support)		
	GWASdb and OMIM	GWASdb	OMIM
Phase I to phase II	1.2 (1.1–1.3)	1.2 (1.1–1.3)	1.2 (1.1–1.3)
Phase II to phase III	1.5 (1.3–1.7)	1.4 (1.2–1.7)	1.6 (1.3–1.9)
Phase III to approval	1.1 (1.0–1.2)	1.0 (0.8–1.2)	1.1 (0.9–1.3)
Phase I to phase III	1.8 (1.5–2.1)	1.8 (1.4–2.1)	1.9 (1.5–2.3)
Phase I to approval	2.0 (1.6–2.4)	1.8 (1.3–2.3)	2.2 (1.6–2.8)

Values give the ratio of the probability of a target-indication pair progressing given genetic support to the probability of progressing without genetic support; 95% confidence intervals are given in parentheses.

Guidances/White Papers in the double digits
PM strategies increasingly being used
Approvals increasing

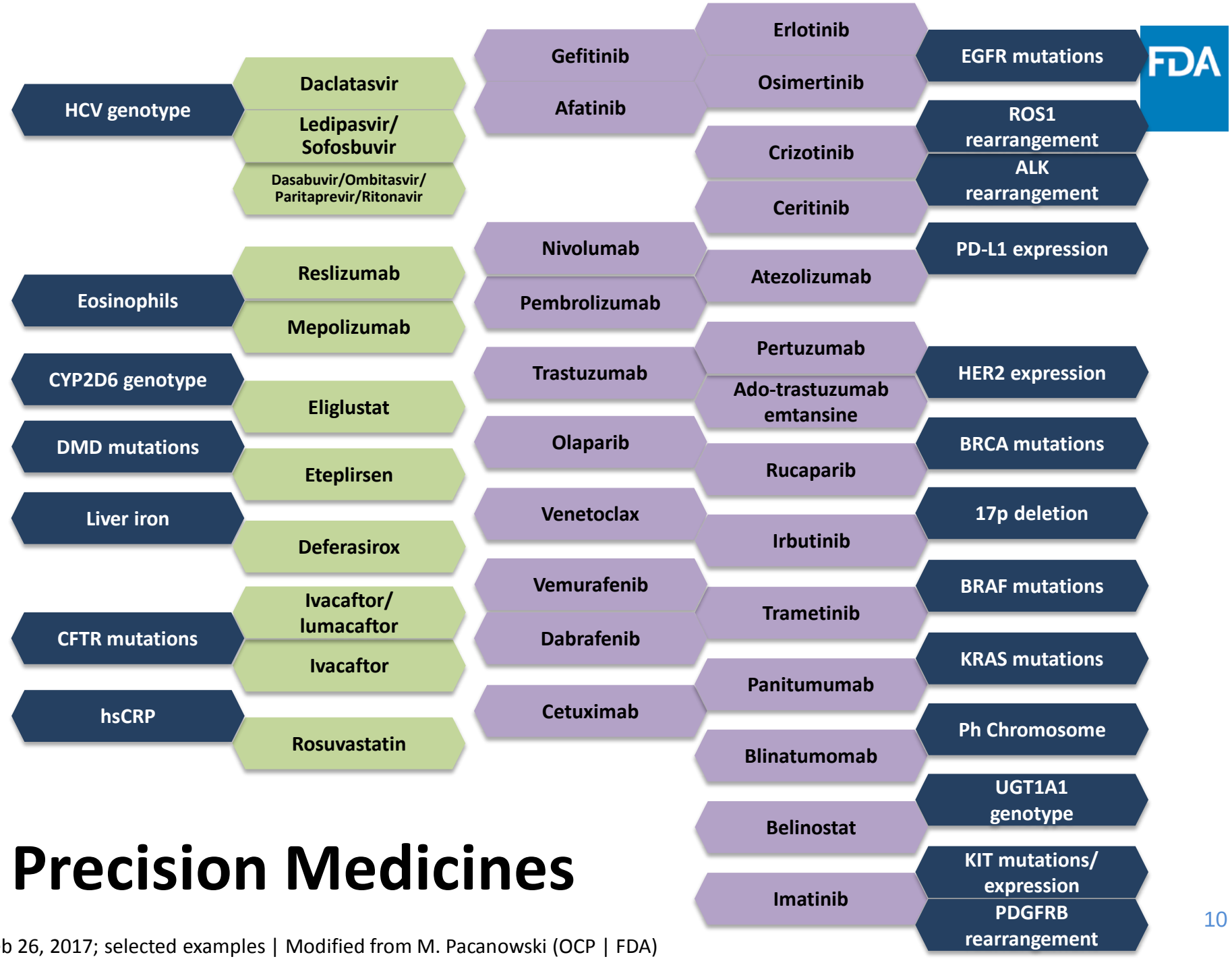
Zineh and Pacanowski [PMID 21923598]

Investigational Drug Landscape



Estimated volume of meeting packages and protocols with biomarker-based objectives (e.g., enrichment, stratification, endpoints) based on ~1700 electronic submissions, May 2014-Mar 2015

Courtesy Dr. Michael Pacanowski



Precision Medicines

Feb 26, 2017; selected examples | Modified from M. Pacanowski (OCP | FDA)

Regulations and Guidance

Year	Guidance, Guideline, or Other Regulatory Resource
2005	Pharmacogenomic Data Submissions
	Drug-Diagnostic Co-Development Concept Paper
2007	Pharmacogenomic Data Submission - Companion Guidance
	Pharmacogenomic Tests and Genetic Tests for Heritable Markers
2008	E15 Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data…
2010	E16 Genomic Biomarkers Related to Drug Response: Context, Structure, and Format of Qualification…
	Qualification Process for Drug Development Tools
2012	Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products
2013	Clinical Pharmacogenomics: Premarketing Evaluation in Early Phase Clinical Studies
	Rule: Orphan Subsets of a Common Disease
2014	Guidance on in vitro Companion Diagnostic Devices
2015	E18 Genomic Sampling Methodologies (Step 1)
2016	Use of Standards in FDA's Regulatory Oversight of Next Generation Sequencing (NGS)-Based [IVDs]…
	Use of Public Human Genetic Variant Databases to Support Clinical Validity for NGS)-Based [IVDs]
	Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product

Modified from Dr. Christian Grimstein (OCP | FDA)

The Evolving Regulatory Framework for Precision Medicines

Clinical Pharmacogenomics	**Collect DNA to facilitate biomarker development (sometimes drug development)**
Enrichment	**Use enrichment strategies to decrease noise (heterogeneity), increase event rates (prognostic), or enhance treatment effect (predictive)**
Companion Diagnostics	**IVD needed if essential for safe and effective use; need for pre-market review, risk-based regulation**
Co-development	**Process-oriented guidance on use and development of companion IVDs in a therapeutic trial context**

For more information on other related guidances, visit

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

Notable Observations to Date

- Major shift away from retrospective biomarker development
  - Better understood biology
  - Scientific and regulatory challenges to this approach
- Valid clinical trial and lab assays are important for defining analysis population (interpretation) and to-be-treated patients
- “Complementary” diagnostics are emerging as a new consideration for personalized medicine

Notable Observations to Date

- **"Indication", i.e. who the drug is approved for, often relates to the studied population(s)**
  - **"Ultra"-rare diseases are challenging this paradigm**
- **Knowledge gaps (e.g., trials in "marker-negative" patients) can be addressed after a drug's approval**
- **Re-defined disease (e.g., tissue-agnostic) and increasingly recognized genetic/molecular diversity *within* a disease are raising important issues:**
  - **Clinical trial design**
  - **Interpretation**
  - **Regulatory issues (approval population, labeling, post-approval needs)**

Drug Development Program Feature	Review/Policy Issue
Predictive enrichment (based on baseline enrichment factor measurement)	Need for enrolling patients without enrichment factor for safety and/or efficacy assessment
Enroll only biomarker (+) patients (high prevalence)	Question of need for Dx as part of indication if prevalence of diagnostic "positivity" is very high (e.g., >90%)
Enroll only biomarker (+) patients ("positive" comprised of several rare mutations with putative functional similarity)	Need/ability to adequately assess efficacy in each rare mutation group; how to appropriately label
Primary efficacy assessment in biomarker-defined subset (continuous or ordinal variable)	Pre-specification of diagnostic cut-off; post-hoc refinement of cut-off
Exclude genetic subgroup from first-in-human studies because of safety concerns (e.g., PMs)	Need for assessment of excluded subgroup later in development/post-approval; appropriate dosing and labeling; need for Dx
Variable drug exposure or dose/exposure/response in subgroups (e.g., genetic)	Strategy for dose optimization during/after development
In vitro diagnostic needed	Analytical issues; cross-center coordination; companion or complementary

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, mechanism, etc)
  - Specify hypothesis in overall population or homogenous subsets
  - Alternative (e.g., Bayesian) strategies
- 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, refine treatment population

Modified from Dr. Michael Pacanowski

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)

Public workshop/meeting date in parentheses

Summary

- **Precision medicine has been supported from regulatory science for over a decade**
- **Scientific advancement has led to progress in regulatory policy development and successful application of precision medicine principles in drug development**
- **New issues continue to emerge as new drug development gets more "precise" (i.e., targeted)**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Characteristics in Support of Targeted Drug Development

Biomarker is the major pathophysiological driver of the disease to be studied
Limited or adverse paradoxical activity of the drug is seen in a subgroup identified through in vitro or animal models (e.g., cell lines or animals without the biomarker)
The biomarker is the known molecular targeted of therapy
Preliminary evidence of harm from early phase clinical studies in patients without the biomarker
Preliminary evidence of lack of activity from early phase clinical studies in patients without the biomarker
Preliminary evidence of modest benefit in an unselected population, but the drug exhibits significant toxicity

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Draft Co-development 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