U.S. FOOD & DRUG ADMINISTRATION

Precision Medicine: The New Normal

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Office of Clinical Pharmacology
Center for Drug Evaluation and Research

ASCPT Annual Meeting
March 22, 2018

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

Thank You!

Genomics and Targeted Therapy Group Staff/Fellows/Affiliates/Alumni

- Christian Grimstein, Rosane Charlab Orbach, Padmaja Mummaneni, Jeff Kraft, Sarah Dorff, Anu Ramamoorthy, Bart Rogers, Bob Schuck, Kate Drozda, Jillian Sun, Oluseyi Adeniyi, Spencer, Todd
- **Issam Zineh***, Shashi Amur†, Li Zhang*, Silvana Borges†, Federico Goodsaid*, Felix Frueh*, Lyle Canida†, Stacy Shord, Eli Pfuma, Kim Maxfield

Office of Clinical Pharmacology

- Everyone!!!, **Issam Zineh**, Shiew Mei Huang, Darrell Abernathy, Gil Burckart, Vikram Sinha*, Larry Lesko*, Karen Graves, Raj Madabushi, Jeff "midi-"Florian†

Office of New Drugs

- Chris Leptak, John Jenkins*, Patrick Frey, many more…

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Center for Drug Evaluation and Research

- Janet Woodcock, Bob Temple, Bob Guidos, Rich Moscicki*

Office of In Vitro Diagnostics and Radiologic Health

- Liz Mansfield*, Bob Becker, David Litwack, Pam Bradley, et al.

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- John Wagner, Deanna Kroetz, Sarah Robertson, Naoto Uemura, Mark Dresser, Valentina Shakhnovich, Nina Isoherranen, Chris Austin, Sharon Terry
- Emma Shumeyko, Rachel Taylor, Julie Vo, Elise Laffman Johnson, Sharon Swan
- Editorial board and peer-reviewers

Collaborators/Contractors/Fellows/Students

- Russ Altman, Kathy Giacomini, Alan Shuldiner, Richard Horenstein, Howard McLeod, Bob Meyer, Stephan Schmidt, Danny Gonzalez, Doug Figg, Cody Peer, Jennifer Wilson, Chakri Lagishetty
- Many, many more…

Bassett Healthcare

- **Joe Bertino***, Guy Amsden, Anne Nafziger*, Thomas Gregory*, many excellent doctors

University of Florida

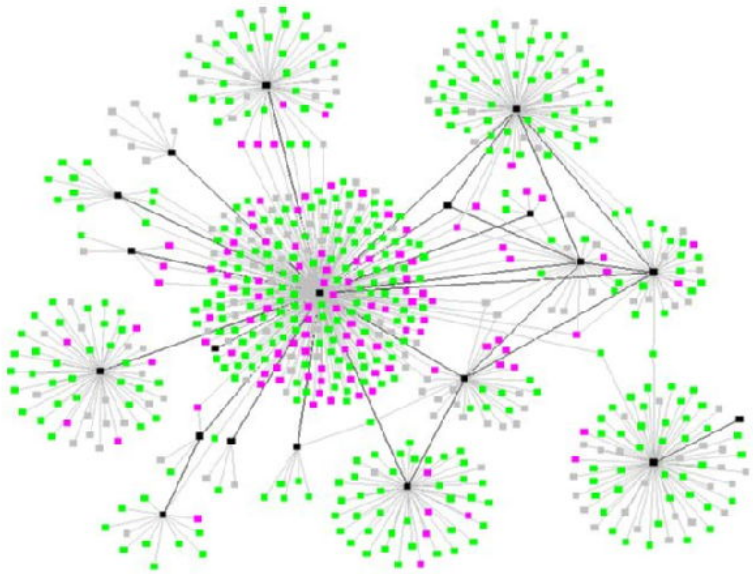
- **Julie Johnson**, Taimour Langaee, Amber Beitelshees*, Yan Gong, Anne Schentrup, Max Lobmeyer*, Elvin Price*, Jaekyu Shin*, Heather Davis*, Mariellen Moore*, Ben Burkley, Lynda Stauffer, Greg Welder*, **Issam Zineh***, My Phuong Le, Hrishi Navare, Julio Duarte*, Jason Karnes*, Tobi Gerhard*

My family

- Erica, Ari, Khyla, Abuela, Lita, Gigi, Grandpa, Granny, Chris, Moe, Carlos, Steve, John Paul, Crystal, Brian, Adam, Uncle Tom, Linda, Mike, Megan, Matt, Brendan, Cooper, Griffin, Gavin, Liam, Brynna, Teagan, Helen, Lucy, Shammy

* Former position; † At FDA in a different organization than is listed

A personal vision of the future…



Genomic information will be universally accessible and portable

Patient care and clinical research will be more seamless, and mechanistically-driven

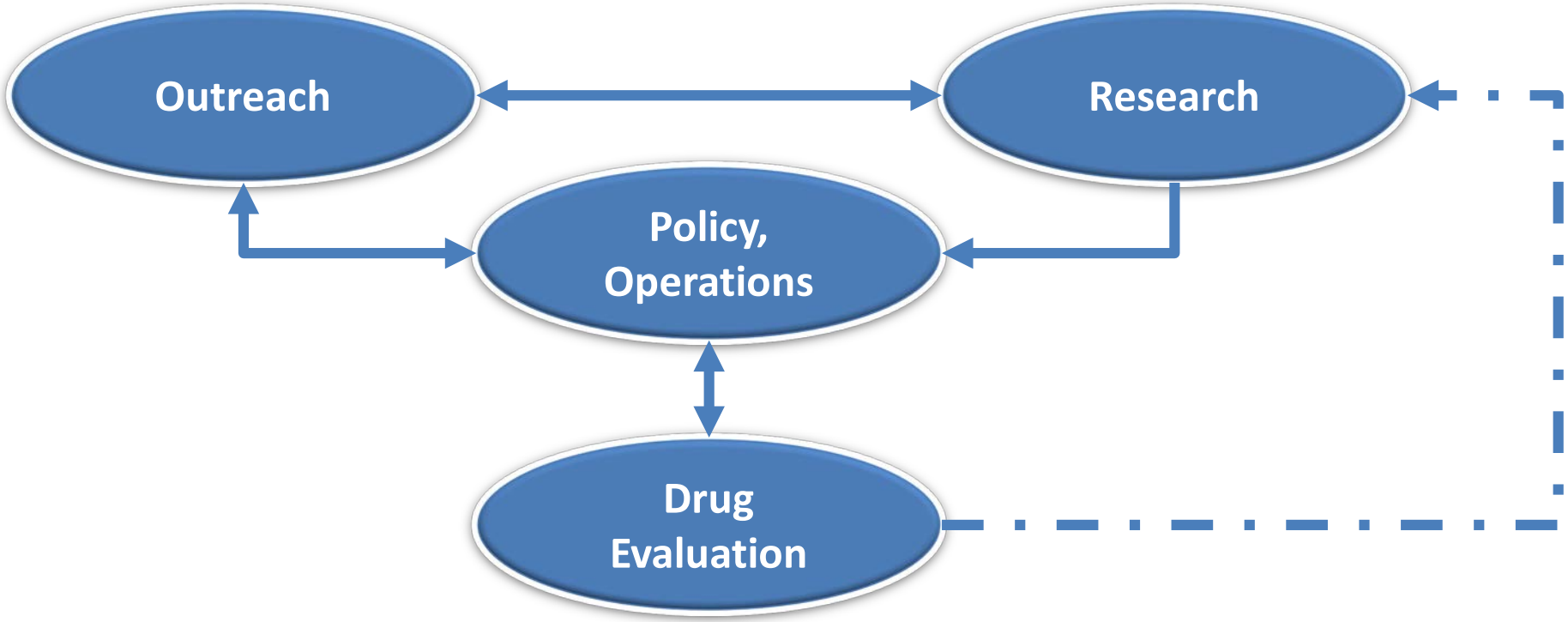
Real-time synthesis of evidence from patient experience will support clinical decision-making

Realizing the Vision

- ***In post-approval therapeutic optimization…***
  - Access to reliable “next-generation” technologies in the clinic
  - Health record infrastructure to absorb dense information
  - Common data architecture for pooling and analysis across platforms

- ***In new drug development…***
  - Knowledge and exploitation of molecular pathology/pharmacology
  - High-throughput exploration to resolve response variability
  - Robust biomarker to detect drug effects

The "Virtuous Circle" of FDA's Genomics and Targeted Therapy Group



Promote the rational application of biomarkers to support the targeted development and use of drugs through regulatory review, policy development, and research

Agenda

- Optimizing benefits and risks of marketed drugs
- Proactive management of the investigational pipeline
- Building a regulatory science toolkit

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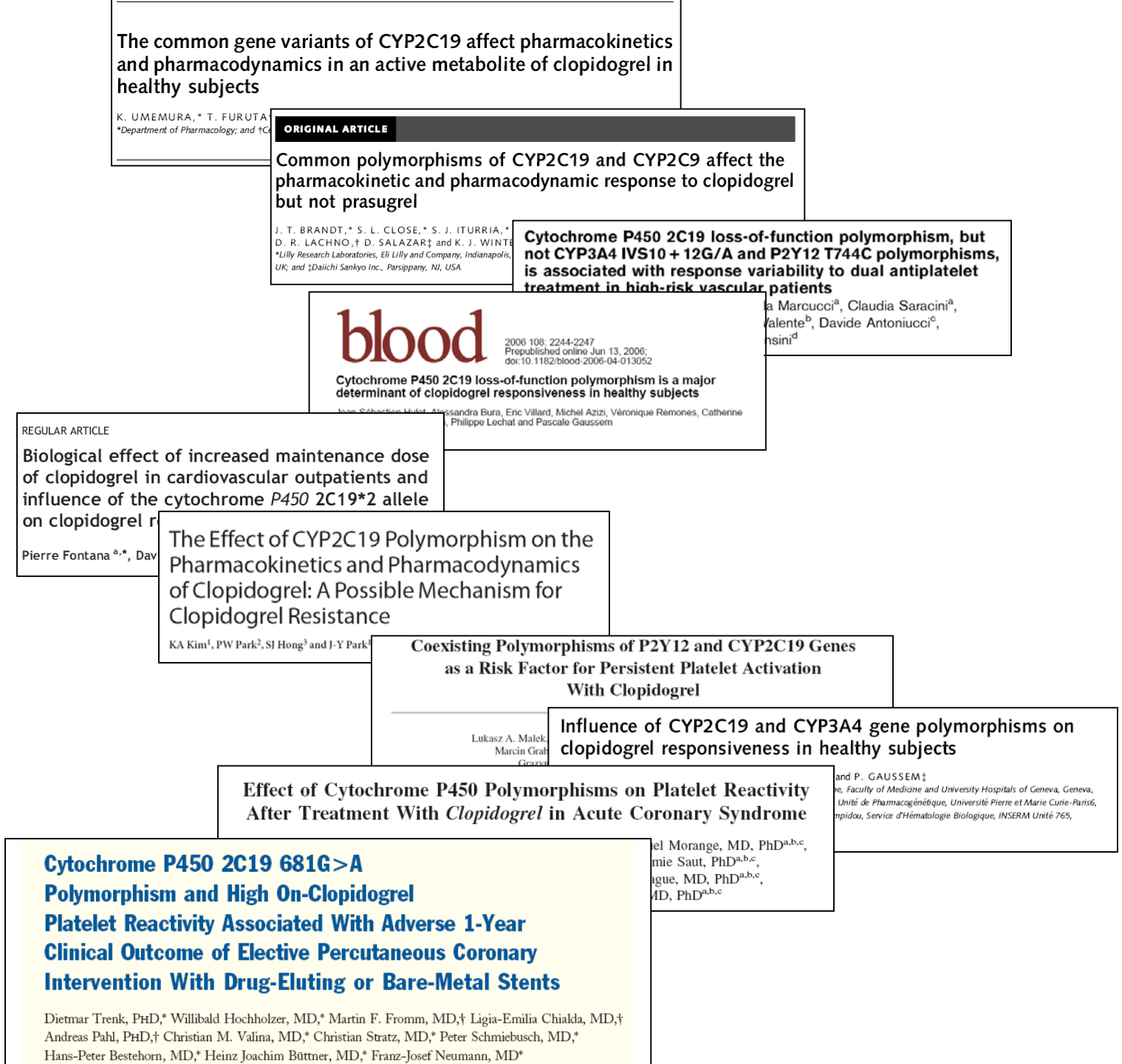


The common gene variants of CYP2C19 affect pharmacokinetics and pharmacodynamics in an active metabolite of clopidogrel in healthy subjects

K. UMEMURA,* T. FURUTA†

*Department of Pharmacology; and †Ce

ORIGINAL ARTICLE

Common polymorphisms of CYP2C19 and CYP2C9 affect the pharmacokinetic and pharmacodynamic response to clopidogrel but not prasugrel

J. T. BRANDT,* S. L. CLOSE,* S. J. ITURRIA,*
D. R. LACHNO,† D. SALAZAR‡ and K. J. WINTE

*Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, UK; and ‡Daiichi Sankyo Inc., Parsippany, NJ, USA

Cytochrome P450 2C19 loss-of-function polymorphism, but not CYP3A4 IVS10 + 12G/A and P2Y12 T744C polymorphisms, is associated with response variability to dual antiplatelet treatment in high-risk vascular patients

a Marcucci[a], Claudia Saracini[a],
Valente[b], Davide Antoniucci[c],
nsini[d]

blood

2006 108: 2244-2247
Prepublished online Jun 13, 2006;
doi:10.1182/blood-2006-04-013052

Cytochrome P450 2C19 loss-of-function polymorphism is a major determinant of clopidogrel responsiveness in healthy subjects

, Philippe Lechat and Pascale Gaussem

REGULAR ARTICLE

Biological effect of increased maintenance dose of clopidogrel in cardiovascular outpatients and influence of the cytochrome *P450* 2C19*2 allele on clopidogrel r

Pierre Fontana [a,*], Dav

The Effect of CYP2C19 Polymorphism on the Pharmacokinetics and Pharmacodynamics of Clopidogrel: A Possible Mechanism for Clopidogrel Resistance

KA Kim[1], PW Park[2], SJ Hong[3] and J-Y Park[

Coexisting Polymorphisms of P2Y12 and CYP2C19 Genes as a Risk Factor for Persistent Platelet Activation With Clopidogrel

Lukasz A. Malek,
Marcin Grab
Grazyn

Influence of CYP2C19 and CYP3A4 gene polymorphisms on clopidogrel responsiveness in healthy subjects

and P. GAUSSEM‡
e, Faculty of Medicine and University Hospitals of Geneva, Geneva,
Unité de Pharmacogénétique, Université Pierre et Marie Curie-Paris6,
mpidou, Service d'Hématologie Biologique, INSERM Unité 765,

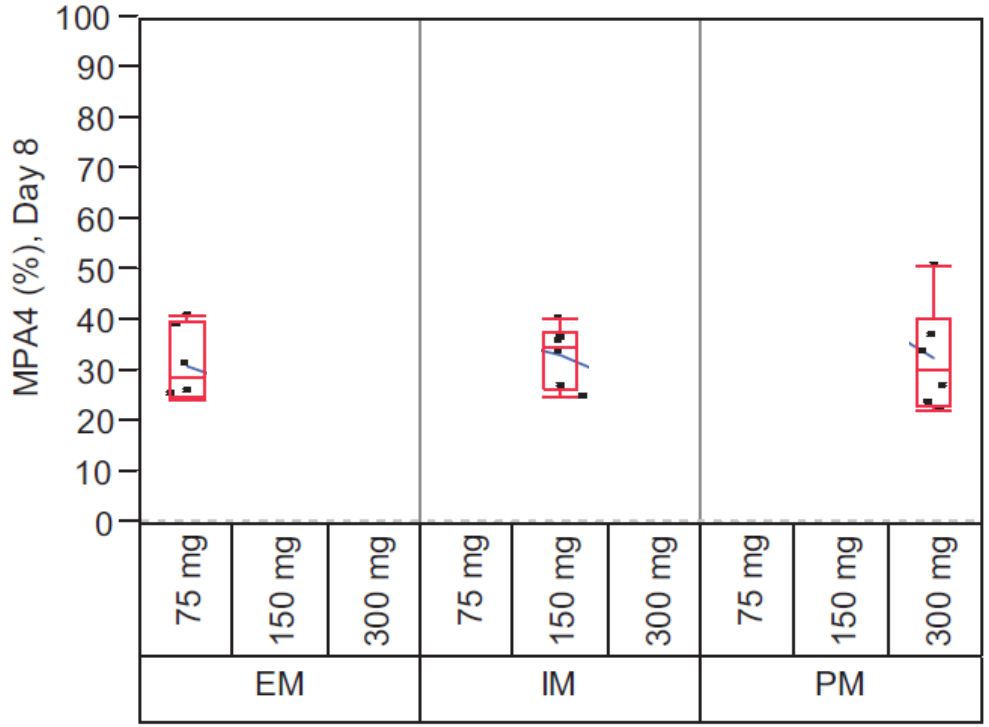
Effect of Cytochrome P450 Polymorphisms on Platelet Reactivity After Treatment With *Clopidogrel* in Acute Coronary Syndrome

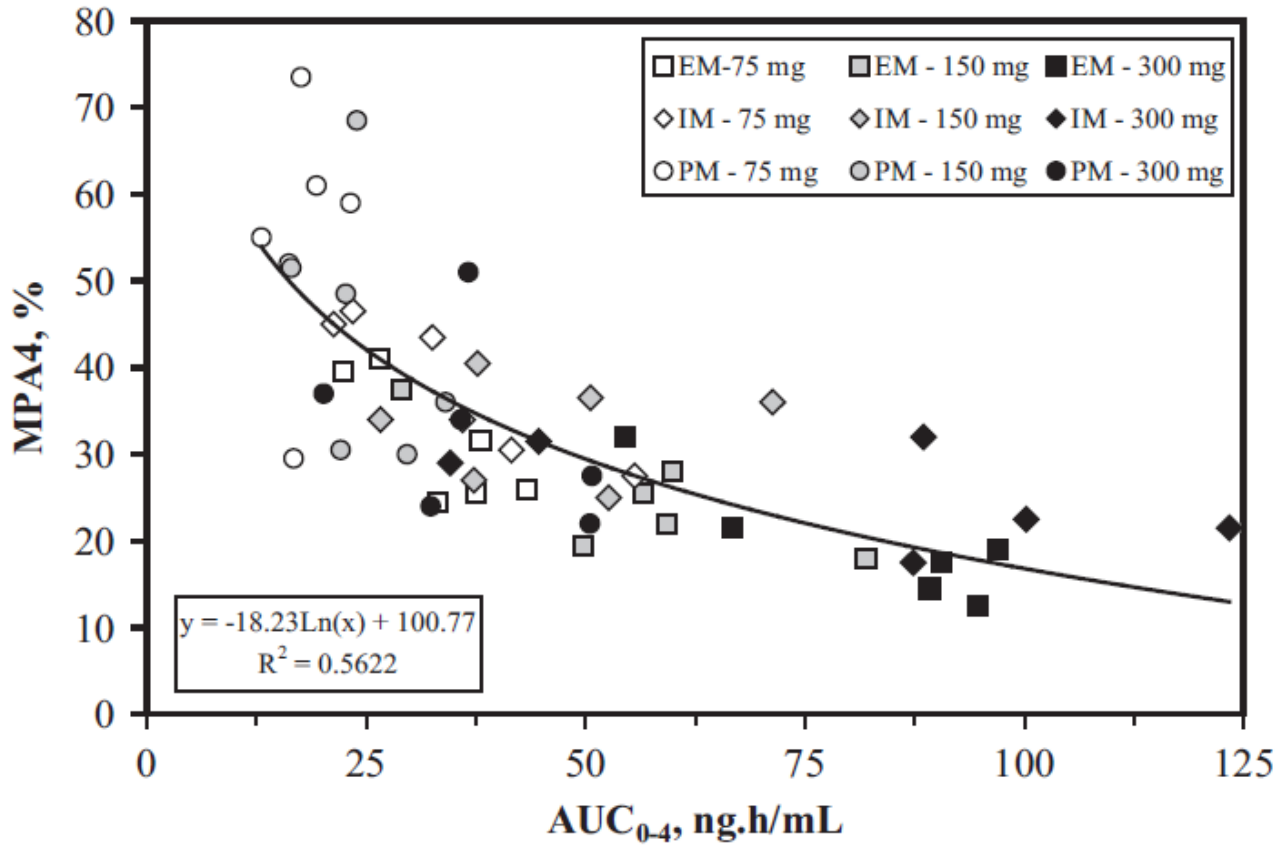
el Morange, MD, PhD[a,b,c],
mie Saut, PhD[a,b,c],
gue, MD, PhD[a,b,c],
MD, PhD[a,b,c]

Cytochrome P450 2C19 681G>A Polymorphism and High On-Clopidogrel Platelet Reactivity Associated With Adverse 1-Year Clinical Outcome of Elective Percutaneous Coronary Intervention With Drug-Eluting or Bare-Metal Stents

Dietmar Trenk, PHD,* Willibald Hochholzer, MD,* Martin F. Fromm, MD,† Ligia-Emilia Chialda, MD,† Andreas Pahl, PHD,† Christian M. Valina, MD,* Christian Stratz, MD,* Peter Schmiebusch, MD,* Hans-Peter Bestehorn, MD,* Heinz Joachim Büttner, MD,* Franz-Josef Neumann, MD*

Effectiveness of clopidogrel dose escalation to normalize active metabolite exposure and antiplatelet effects in CYP2C19 poor metabolizers





PMCID: PMC4113831

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Genetic Determinants of Response to Clopidogrel and Cardiovascular Events

Tabassome Simon, M.D., Ph.D., Céline Verstuyft, Pharm.D., Ph.D., Murielle Mary-Krause, Ph.D., Lina Quteineh, M.D., Elodie Drouet, M.Sc., Nicolas Méneveau, M.D., P. Gabriel Steg, M.D., Ph.D., Jean Ferrières, M.D., Nicolas Danchin, M.D., Ph.D., and Laurent Becquemont, M.D., Ph.D., for the French Registry of Acute ST-Elevation and Non–ST-Elevation Myocardial Infarction (FAST-MI) Investigators

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cytochrome P-450 Polymorphisms and Response to Clopidogrel

Jessica L. Mega, M.D., M.P.H., Sandra L. Close, Ph.D., Stephen D. Wiviott, M.D., Lei Shen, Ph.D., Richard D. Hockett, M.D., John T. Brandt, M.D., Joseph R. Walker, Pharm.D., Elliott M. Antman, M.D., William Macias, M.D., Ph.D., Eugene Braunwald, M.D., and Marc S. Sabatine, M.D., M.P.H.

Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study

Jean-Philippe Collet, Jean-Sébastien Hulot, Anna Pena, Eric Villard, Jean-Baptiste Esteve, Johanne Silvain, Laurent Payot, Delphine Brugier, Guillaume Cayla, Farzin Beygui, Gilbert Bensimon, Christian Funck-Brentano, Gilles Montalescot

WARNING: DIMINISHED ANTIPLATELET EFFECT IN PATIENTS WITH TWO LOSS-OF-FUNCTION ALLELES OF THE CYP2C19 GENE

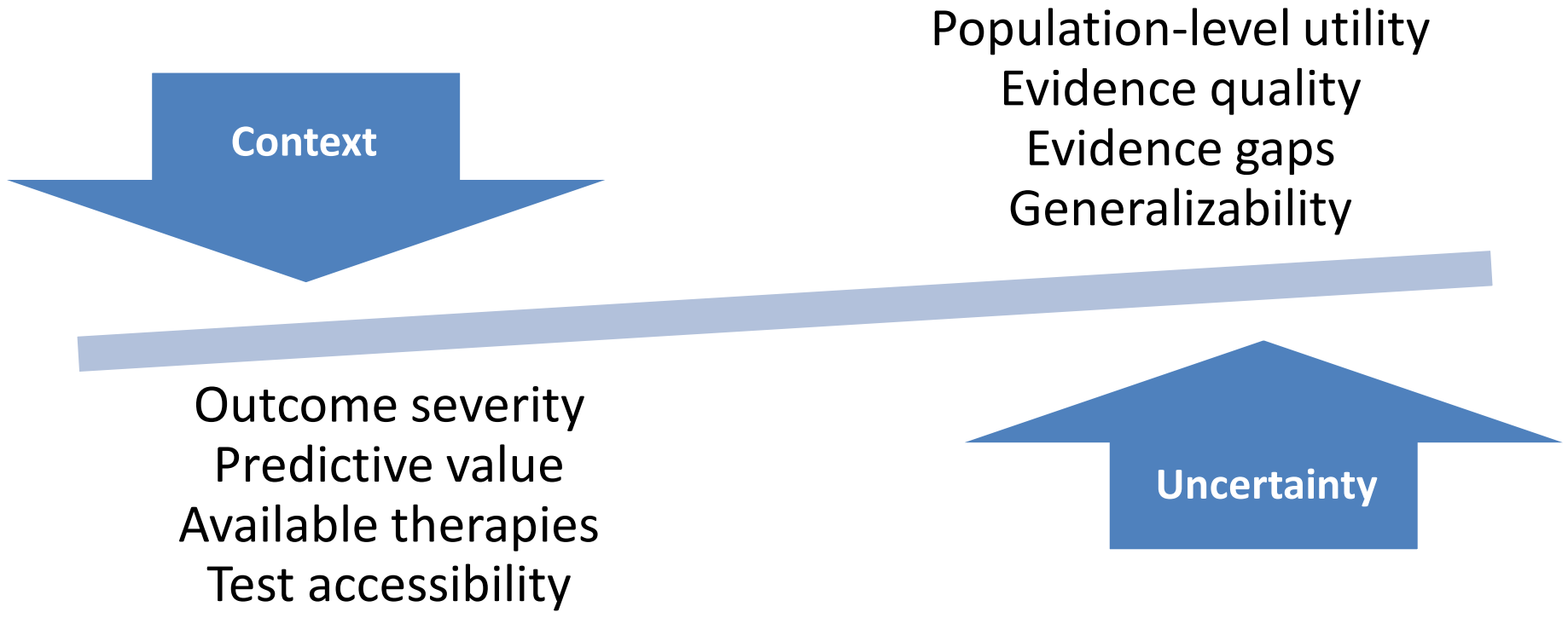
The effectiveness of Plavix results from its antiplatelet activity, which is dependent on its conversion to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19 *[see Warnings and Precautions (5.1), Clinical Pharmacology (12.3)]*. Plavix at recommended doses forms less of the active metabolite and so has a reduced effect on platelet activity in patients who are homozygous for nonfunctional alleles of the CYP2C19 gene, (termed "CYP2C19 poor metabolizers"). Tests are available to identify patients who are CYP2C19 poor metabolizers *[see Clinical Pharmacology (12.5)]*. Consider use of another platelet P2Y12 inhibitor in patients identified as CYP2C19 poor metabolizers.

Labeling version 9/16/16; Original update 3/12/10

Other Selected Post-Marketing Labeling Revisions

Valproic Acid	POLG	Liver failure	Contraindicated
Codeine/ Tramadol	CYP2D6	Respiratory depression	Contraindicated
Pimozide	CYP2D6	Sudden death	Dose cap/slow titration
Citalopram	CYP2C19	QT prolongation	Dose cap
Carbamazepine	HLA-B*1502, HLA-A*3101	Severe skin reactions	Warnings
Rosuvastatin	SLCO1B1	PK difference	Treat as usual

Factors Guiding the Strength of Prescribing and Testing Recommendations



Testing approaches

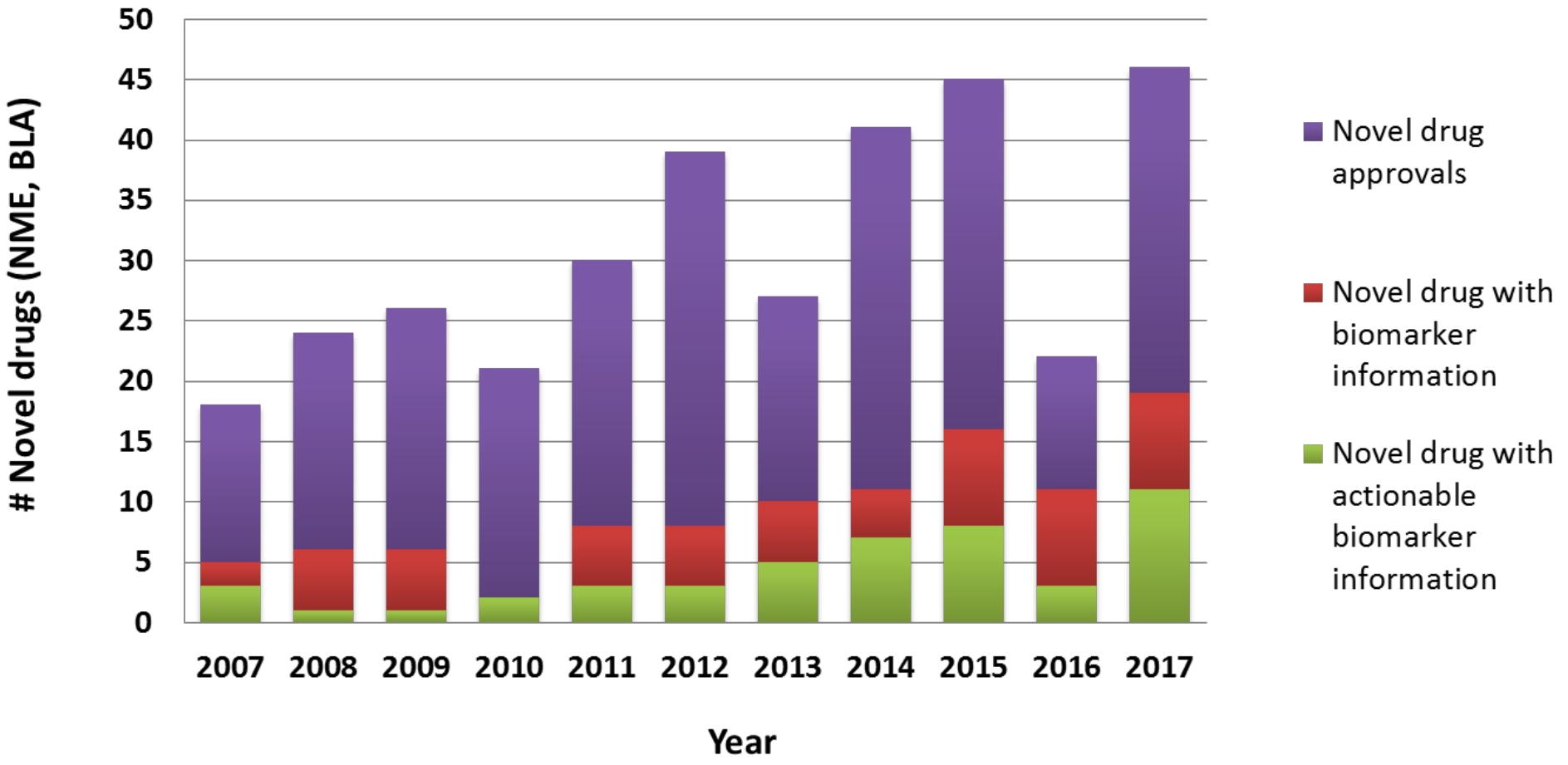
Silent / clinical judgement

Test at a certain threshold

Test a targeted, at-risk subset

Test everyone

Novel Drugs Approved (NME, BLA) with Genomic and other Selected Biomarker Information in Labeling



- Actionable biomarker: labeling includes a specific prescribing recommendation that is included in one of the following label sections: 1)Boxed Warning, 2) Indications and Usage, 3) Dosage and Administration, 4) Contraindications, or 4) Warnings and Precautions.
- Biomarkers may be any genomic biomarker or other selected protein biomarker that are used for patient selection.

Agenda

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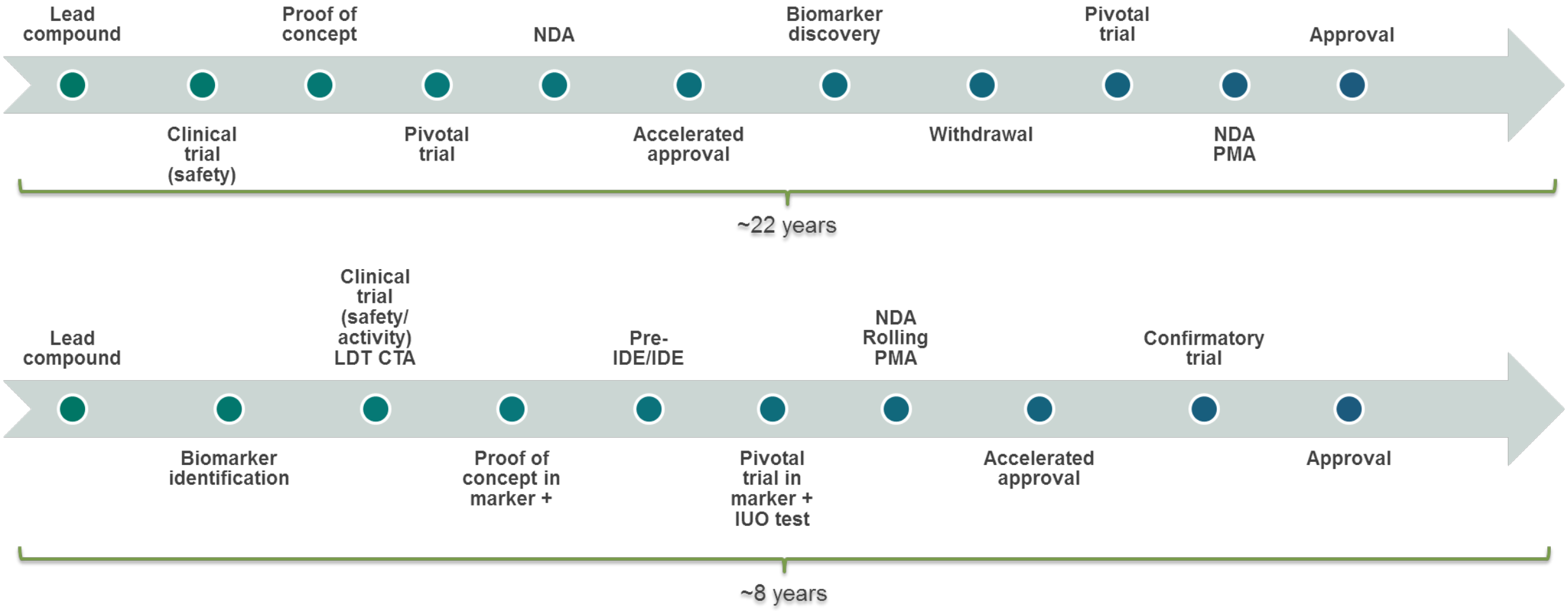
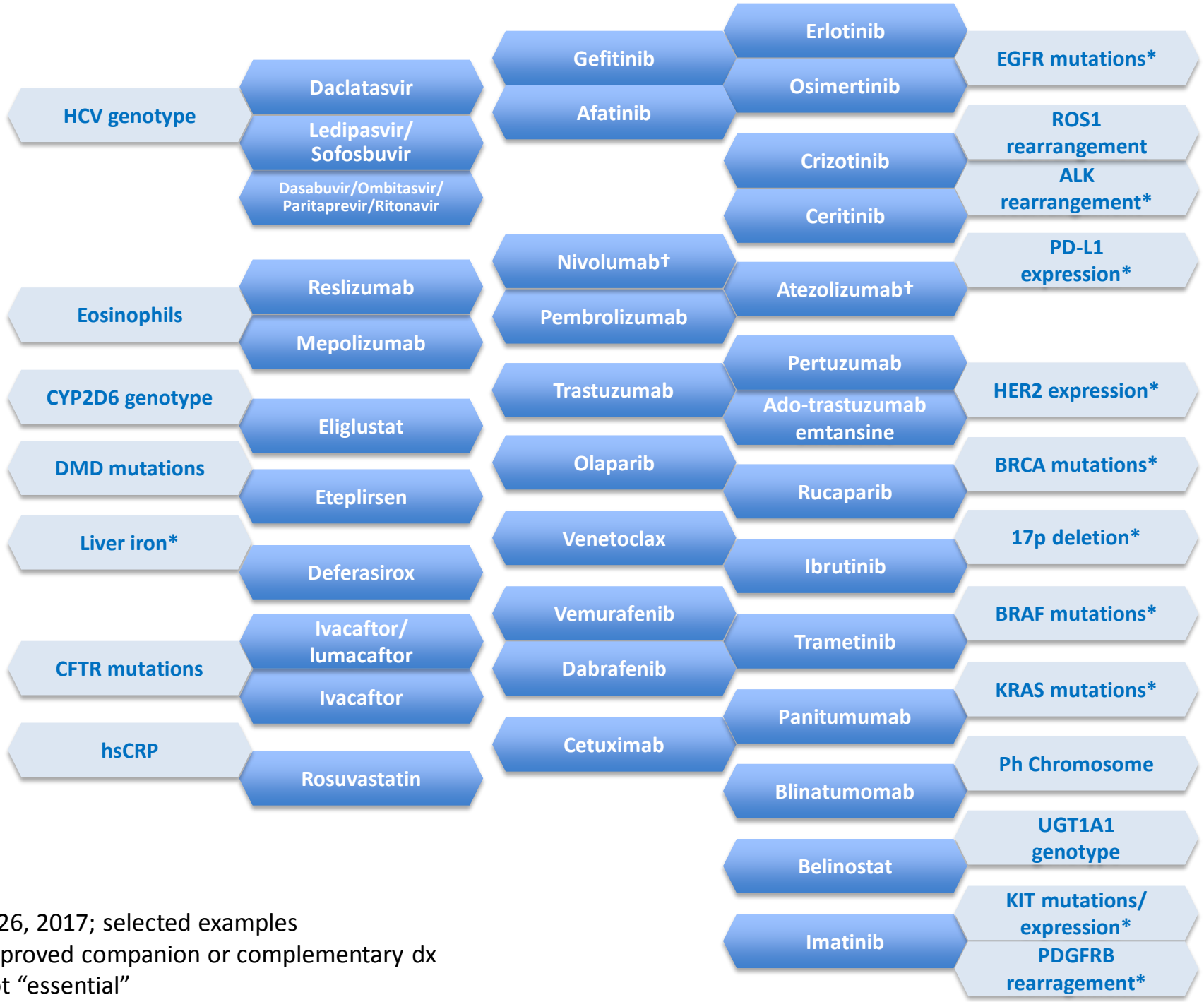
Uses of Genomics in Drug Development

Preemptive	• Validate targets for drug development • Predict drug toxicities • Define target population
Retrospective	• Explain variable responses to drug • Identify (non-)responders or patients with adverse reactions • Identify risk for serious drug interactions
Prospective	• Predict drug exposure • Minimize noise • Identify patients at risk for disease or event • Select patients likely to respond to drug

A Tale of Two Drugs





Feb 26, 2017; selected examples

* Approved companion or complementary dx

† Not “essential”

Innovations in Drug Development

Selected Examples

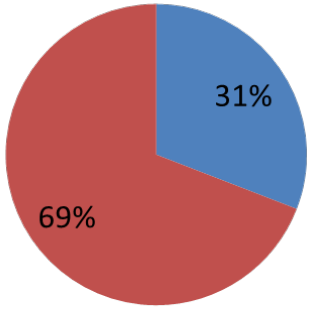
Disease/mechanism	Drug(s)	Indicated subset in FDA-approved labeling	Low-frequency molecular alteration(s) within disease
NSCLC/ EGFR inhibitor	Erlotinib	*EGFR* exon 19 deletions or exon 21 L858R substitution	Additional *EGFR* mutations including L861Q, G719A/C/S, and T790M
	Gefitinib		
	Afatinib	Non-resistant *EGFR* mutations[a]	
Melanoma/BRAF inhibitor	Vemurafenib	*BRAF* V600E mutation[b]	*BRAF* V600K/D/R
	Dabrafenib		
Melanoma/MEK inhibitor	Trametinib	*BRAF* V600E/K mutations	*BRAF* V600D/R
Ovarian cancer/PARP inhibitor	Olaparib	Deleterious or suspected deleterious germline *BRCA* mutations	Most individual *BRCA1* and *BRCA2* mutations occur at low frequency in ovarian cancer
	Rucaparib	Deleterious germline and/or somatic BRCA mutations	
Colorectal cancer/EGFR inhibitor	Cetuximab	*KRAS* wildtype (not *RAS* mutations)[c]	Low-frequency *KRAS* mutations outside of exon 2, other *RAS* family mutations
	Panitumumab	*KRAS* wildtype (exon 2) (not *RAS* mutations)[c]	
Cystic fibrosis/CFTR potentiator	Ivacaftor	*CFTR* mutations that are responsive to ivacaftor based on clinical and/or in vitro assay data[a]	
Duchenne muscular dystrophy/ exon skipper	Eteplirsen	*DMD* exon 51 skipping amenable	All individual mutations occur at low frequencies

Schuck, et al. CPT 2018

Precision Drug Development Practices: Cardiometabolic Disorders

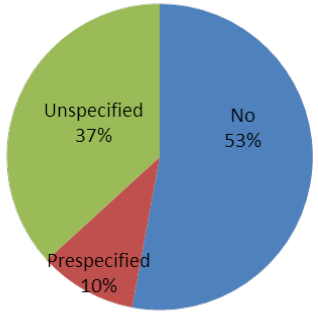
134 …Phase 2 or 3 development programs for cardiac and metabolic diseases

31% …of drug targets (n=86) have a genetic association supporting the corresponding indication



* drug targets publicly disclosed by the sponsors

47% …of clinical trial protocols (n=155), covering 66 programs, have exploratory aims to study genomic biomarkers

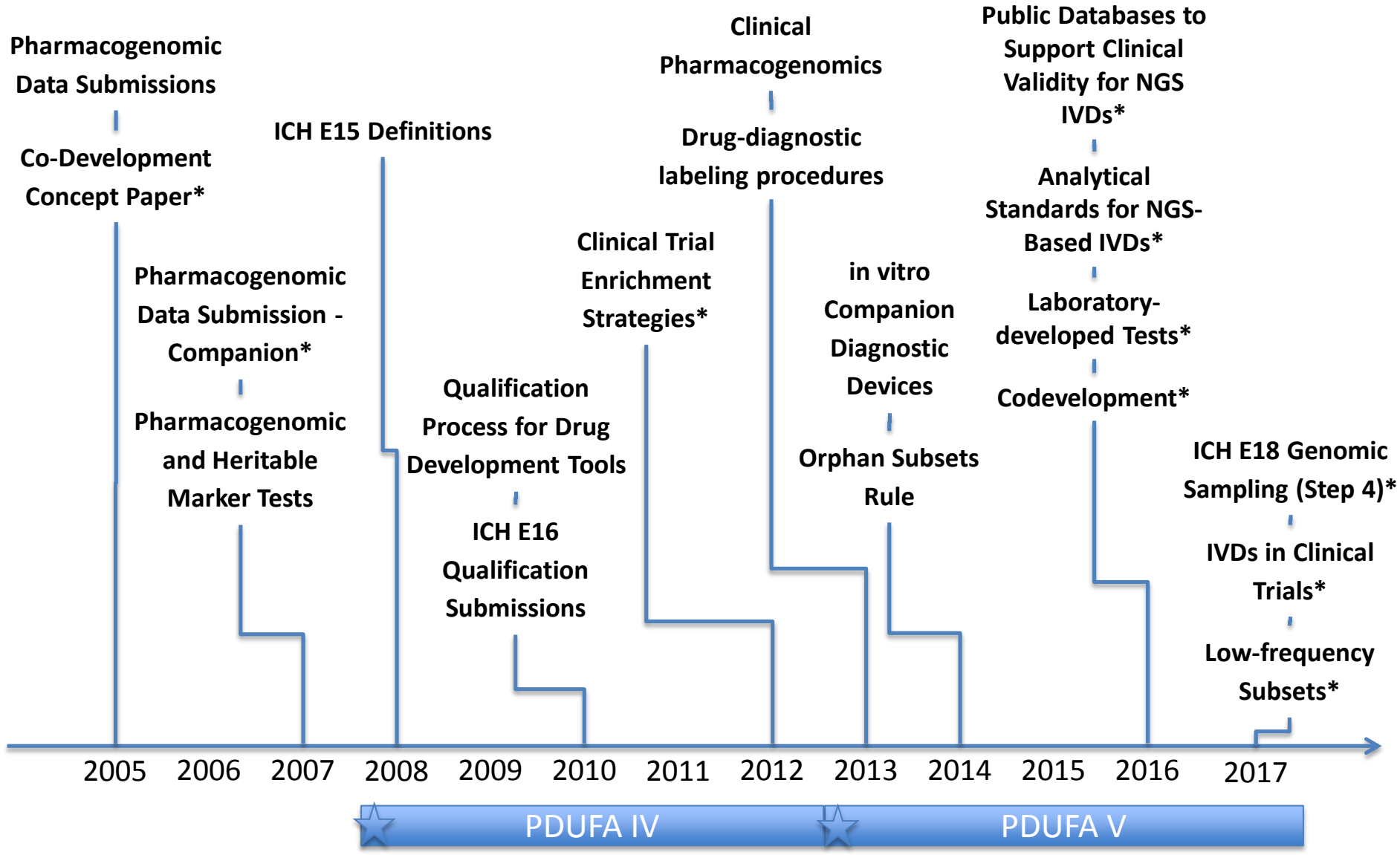


1/155 …clinical trial protocols use genomic biomarkers <u>prospectively</u> in

- Patient selection
- Patient stratification
- Subgroup hypothesis testing

O. Adeniyi

Guidance and Policy



* Draft

Agenda

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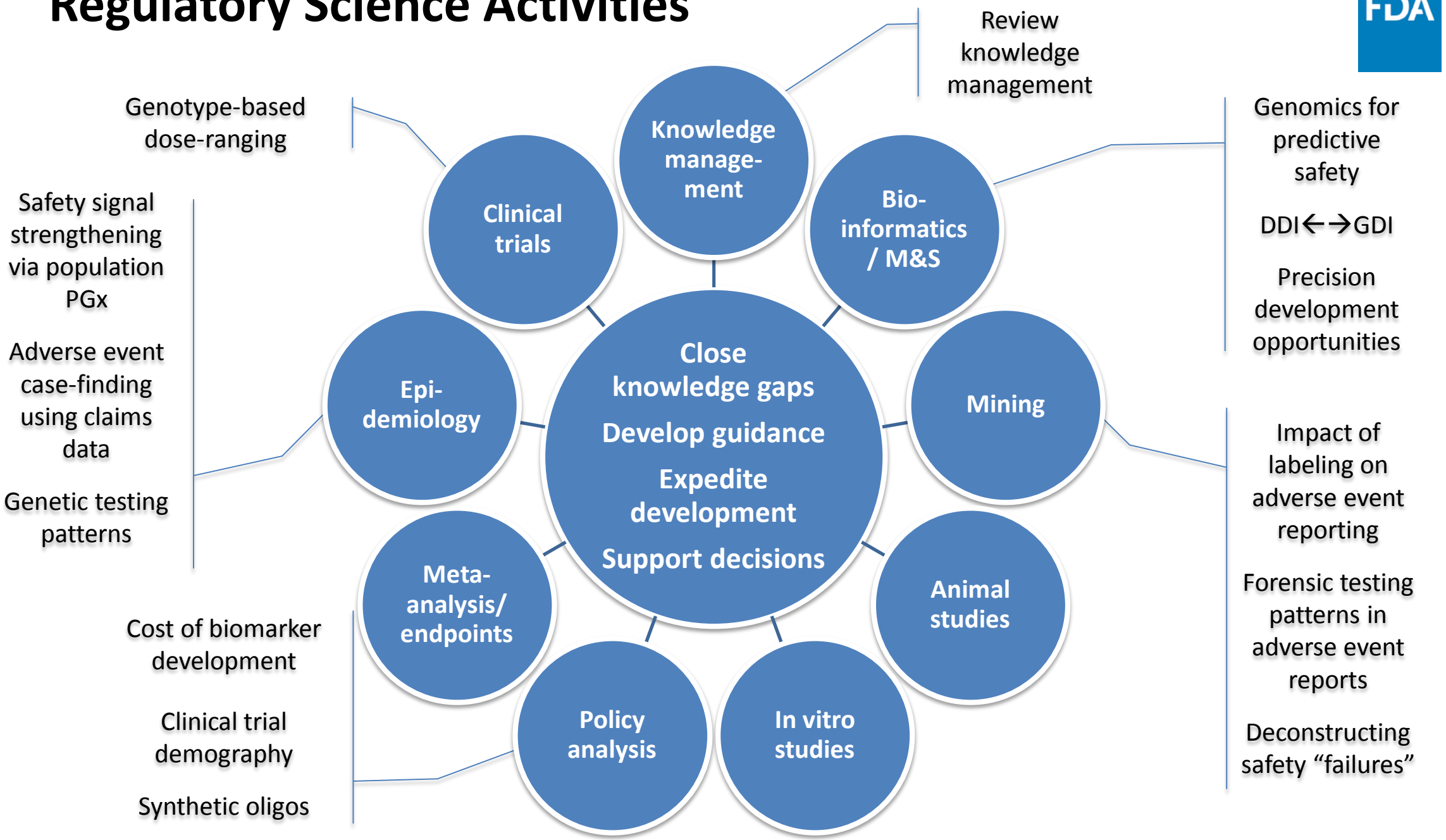
365
ORGANIC
Cane Sugar

Regulatory Science Activities



Summary

- Diverse data streams and resource are required to inform decision-making
- Investigational and new drugs have benefitted from precision medicine principles
- Medicine (clinical pharmacology) is an art, information is a medium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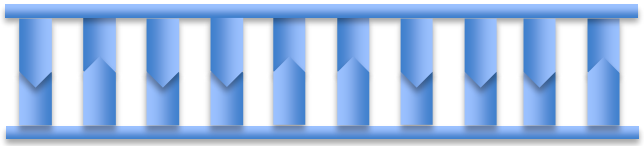
Post-Marketing Commitments and Requirements

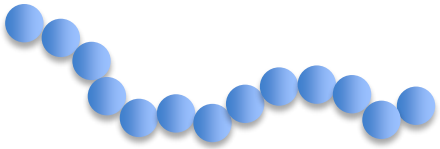
Validation	
Clopidogrel	CYP2C19 effects on PK/PD
Ipilimumab	CD86 effects on immune-related AEs
Prasugrel	CYP450 genotype effects on outcomes
Belinostat	Safety and PK by UGT genotype
Discovery	
Telaprevir	Exploratory GWAS for skin reactions
Deferiprone	DNA banking for agranulocytosis
Infliximab	DNA banking for HSTCL
Agalsidase alfa	Mutation effects on renal disease
Eslicarbazepine	DNA banking for skin reactions

Synthetic Oligonucleotides and Other Genetically Targeted Therapies



DNA

RNA



Protein

CRISPR/Cas9

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

Aptamers (pegatinib)
CpG/TLR

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?
  - (*molecular diversity, marker-negatives*)
- 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?