“Coming of Age” of Personalized Medicine

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Agenda

- State of Personalized Medicine
- Current challenges
  - Scientific
  - Policy
  - Logistical
  - Value-related
- Vision for the future

STATE OF PERSONALIZED MEDICINE

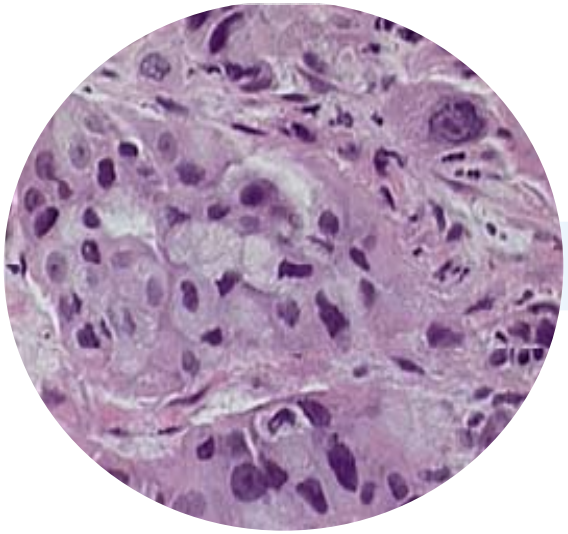
Targeted Therapies have Reached the Mainstream

- Drugs in development and approved drugs in many disease areas
- Cancer, genetic diseases, and infectious disease lead the way
- Many of the “Breakthrough” request for designation are for targeted drugs
- Ever-smaller subsets of disease are being identified

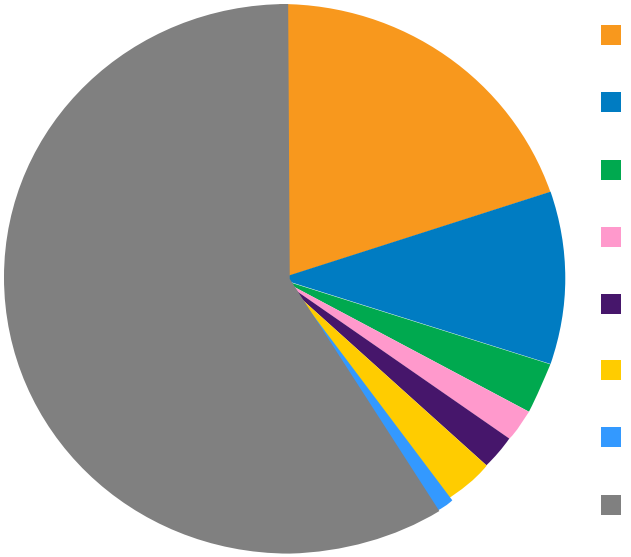
Addressing disease heterogeneity

Changing paradigms in identifying disease subsets
Understanding disease on a molecular basis

Adenocarcinoma 1999
Histology-driven selection



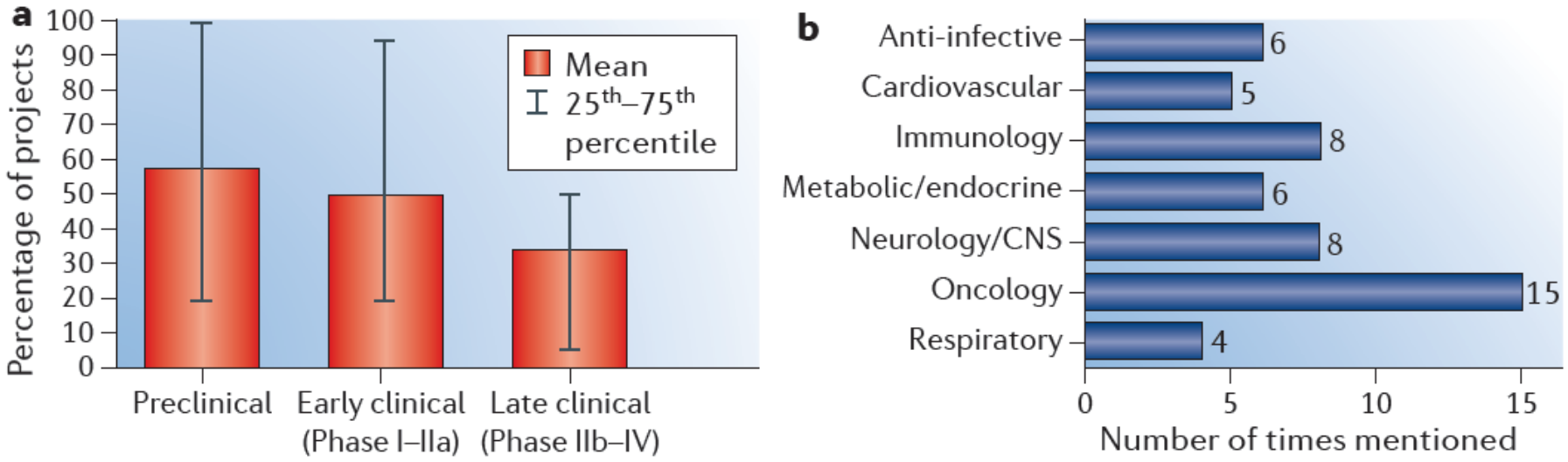
Adenocarcinoma 2010
Targeting oncogenic drivers



Examples of Drugs with Targeted Labels

Drug	Therapeutic Area	Biomarker	Label timing
Brentuximab Vedotin	Oncology	CD30	Pre-approval
Cetuximab, Panitumumab	Oncology	EGFR; KRAS	Pre-/Post-approval
Crizotinib	Oncology	ALK	Pre-approval
Exemestane, Fulvestrant, Letrozole	Oncology	ER/PR	Pre-approval
Imatinib	Oncology	C-Kit, PDGFR, FIP1L1	Pre-approval
Ivacaftor	Pulmonary	CFTR	Pre-approval
Lapatinib, Pertuzumab, Trastuzumab, Everolimus	Oncology	HER2	Pre-approval
Tositumomab	Oncology	CD20 antigen	Pre-approval
Vemurafenib	Oncology	BRAF	Pre-approval
Lenalidomide	Hematology	Chromosome 5q	Pre-approval
Maraviroc	Antivirals	CCR5	Pre-approval
Nilotinib, Dasatanib, Imatanib	Oncology	Ph Chromosome	Pre-approval
Arsenic Trioxide, Tretinoin	Oncology	PML/RARα	Pre-approval
Denileukin Diftitox	Oncology	CD25/IL2	Pre-approval
Capecitabine, Fluorouracil	Oncology	DPD	Post-approval
Pimozide, Aripiprazole, Iloperidone, Tetrabenazine, Thioridazine	Psychiatry, Neurology	CYP2D6	Post-approval
Celecoxib	Analgesics	CYP2C9	Pre-approval
Citalopram	Psychiatry	CYP2C19	Post-approval
Rasburicase	Oncology	G6PD	Pre-approval
Valproic Acid	Psychiatry	UCD	Post-approval

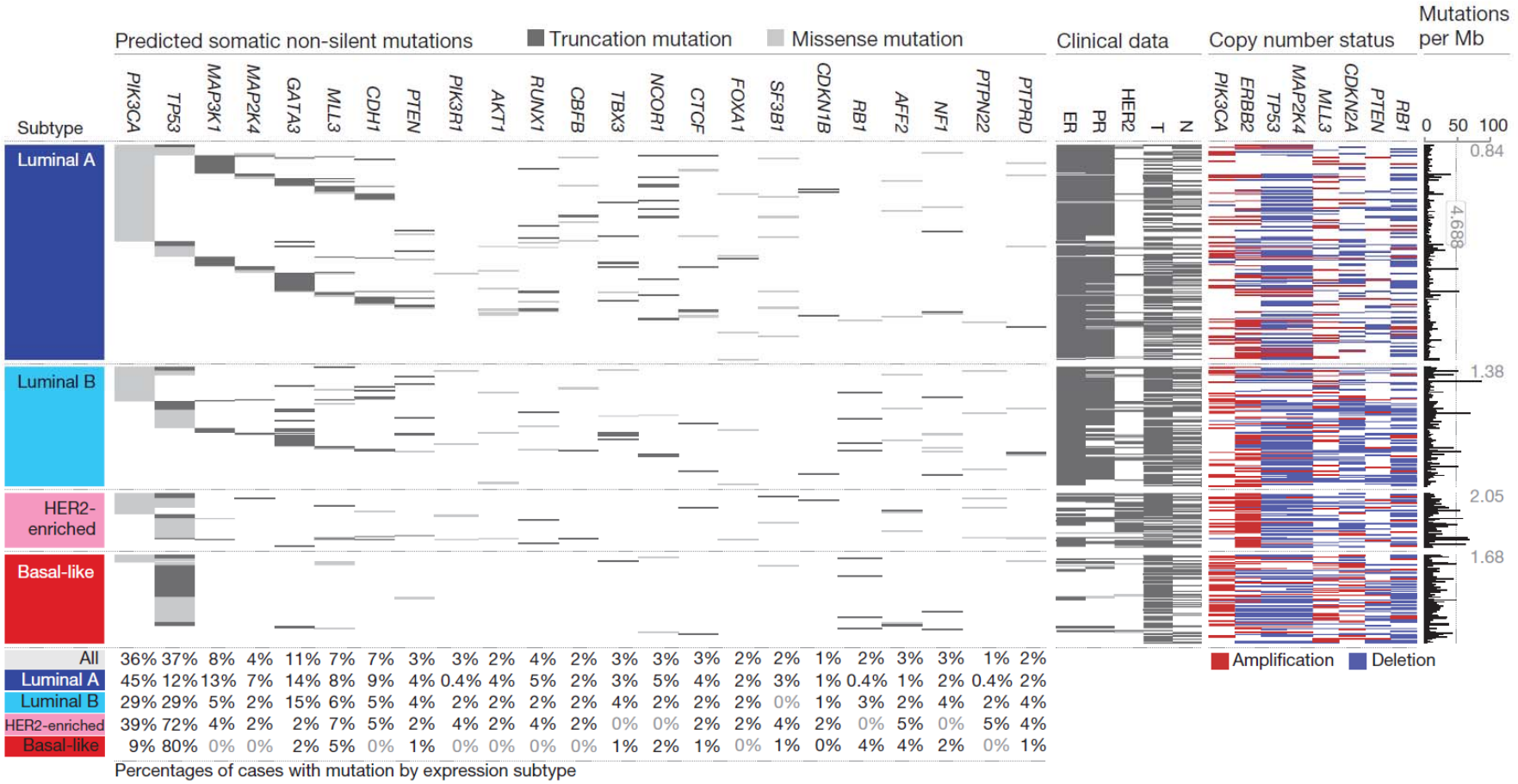
Personalized Medicine Strategies: Industry Survey



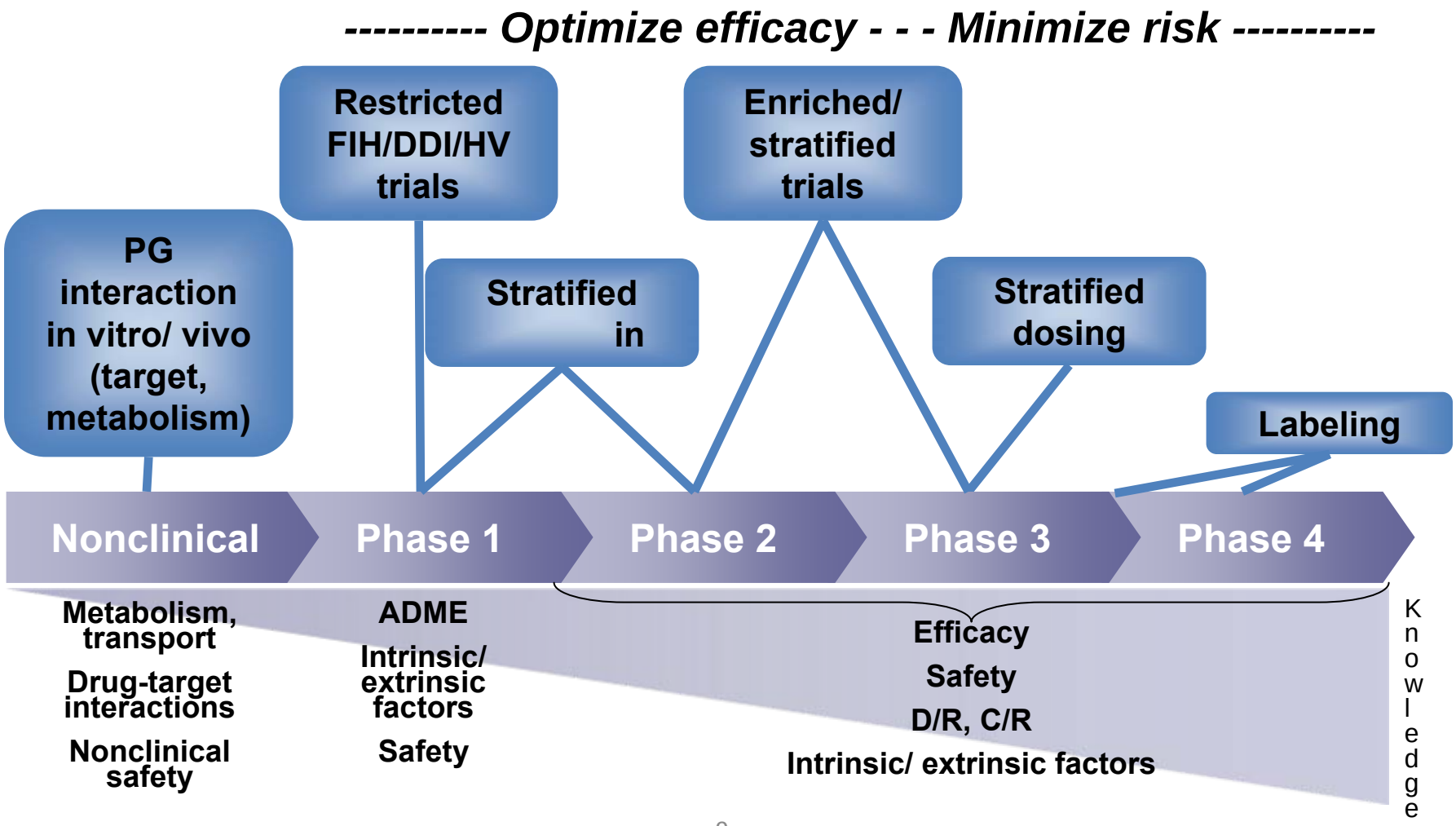
Comprise 12-50% of company pipelines

Our Future

Targeting the Molecular Basis of Disease

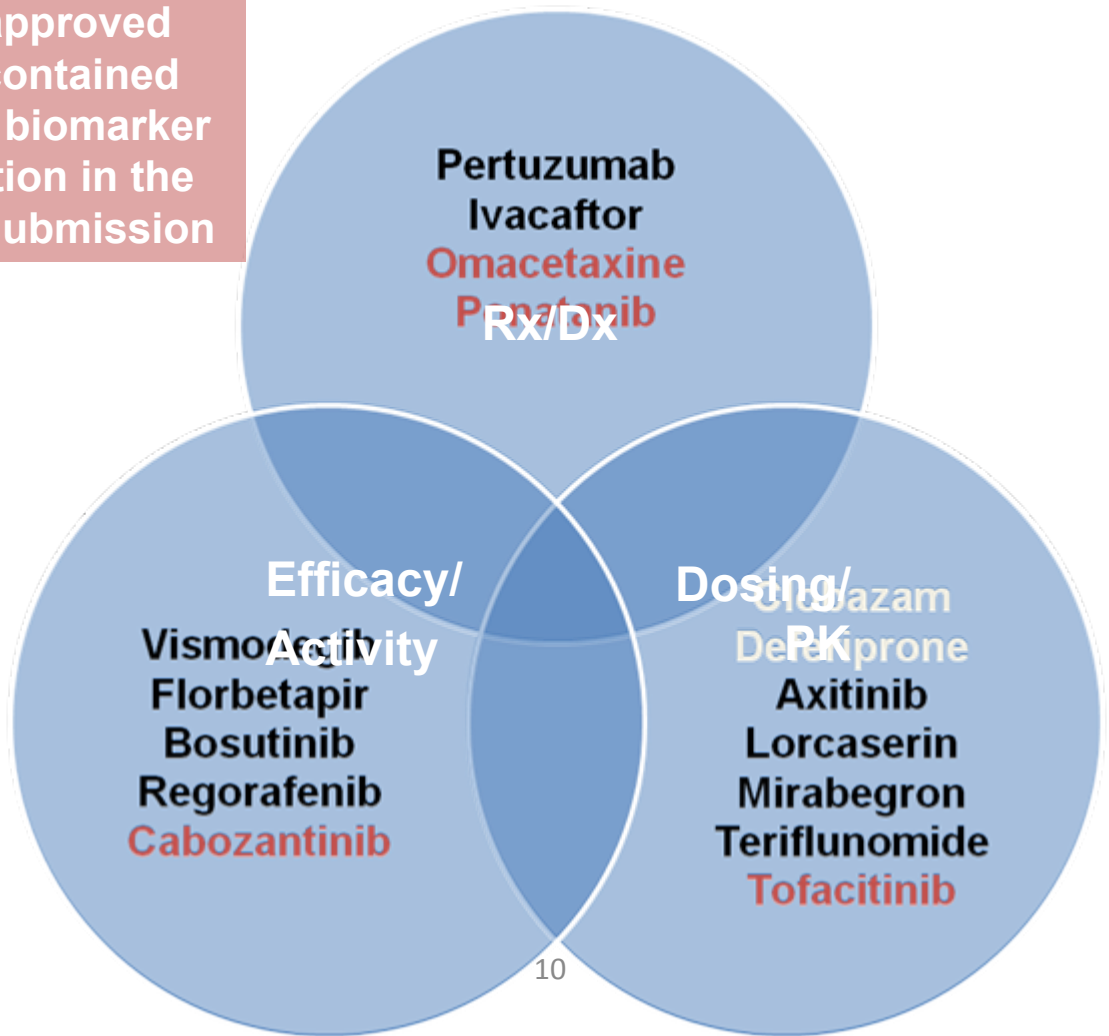


Subgroup-Driven Drug Development



NME Genomic Data Submissions
FY/CY2012

1/3 of approved NMEs contained genomic biomarker information in the original submission



1QFY12

4QCY12

Personalizing Dose by Genotype

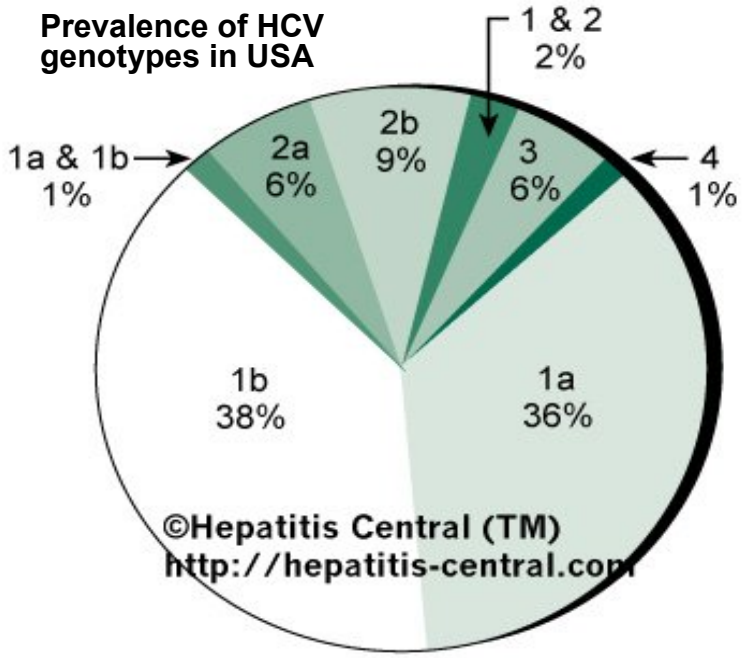
Tetrabenazine, a vesicular monoamine transporter 2 inhibitor indicated for the treatment of chorea associated with Huntington's disease

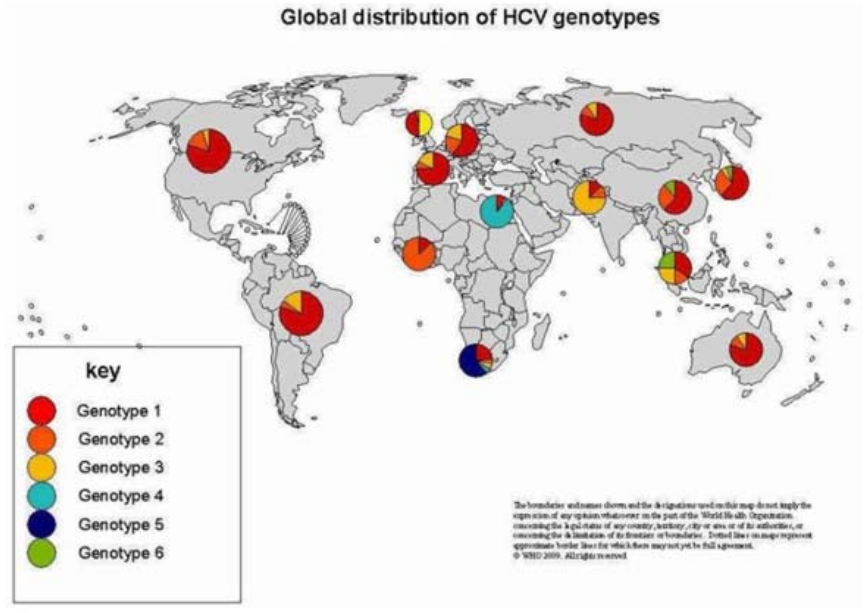
- **Patients who require doses of tetrabenazine greater than 50 mg per day should be first tested and genotyped to determine if they are poor metabolizers (PMs) or extensive metabolizers (EMs) by their ability to express the drug metabolizing enzyme, CYP2D6.**
- **The dose of tetrabenazine should then be individualized accordingly to their status as PMs or EMs.**
- **The maximum daily dose in PMs is 50 mg with a maximum single dose of 25 mg**
- **The maximum daily dose in EMs and intermediate metabolizers (IMs) 100 mg with a maximum single dose of 37.5 mg**

Hepatitis C

HCV virus is a RNA virus and infects liver
Chronic infection can lead to scarring of the liver and ultimately to cirrhosis
Earlier classification according to antigenic characteristics
Currently, genotypic classification through variations in the HCV genome

<u>Considerations in developing therapeutics for HCV</u>: Genotypes 2 and 3 are about 3 times more likely to respond to PEG-IFN and RBV than genotype 1





Global distribution of HCV genotypes

Who.int

Three GWAS Publications on IL28B SNP association to treatment outcome

Genetic variation in *IL28B* predicts hepatitis C treatment-induced viral clearance

USA

Dongliang Ge[1], Jacques Fellay[1], Alexander J. Thompson[2], Jason S. Simon[3], Kevin V. Shianna[1], Thomas J. Urban[1], Erin L. Heinzen[1], Ping Qiu[3], Arthur H. Bertelsen[3], Andrew J. Muir[2], Mark Sulkowski[4], John G. McHutchison[2] & David B. Goldstein[1]

IL28B is associated with response to chronic hepatitis C interferon-α and ribavirin therapy

Australia

Vijayaprakash Suppiah[1,2], Max Moldovan[3], Golo Ahlenstiel[4], Thomas Berg[5], Martin Weltman[6], Maria Lorena Abate[7], Margaret Bassendine[8], Ulrich Spengler[4], Gregory J Dore[9,10], Elizabeth Powell[11,12], Stephen Riordan[13], David Sheridan[8], Antonina Smedile[7], Vincenzo Fragomeli[6], Tobias Müller[5], Melanie Bahlo[3], Graeme J Stewart[2], David R Booth[2] & Jacob George[1], for the Hepatitis C Study[14]

Genome-wide association of *IL28B* with response to pegylated interferon-α and ribavirin therapy for chronic hepatitis C

Japan

Yasuhito Tanaka[1,18], Nao Nishida[2,18], Masaya Sugiyama[1], Masayuki Kurosaki[3], Kentaro Matsuura[1], Naoya Sakamoto[4], Mina Nakagawa[4], Masaaki Korenaga[5], Keisuke Hino[5], Shuhei Hige[6], Yoshito Ito[7], Eiji Mita[8], Eiji Tanaka[9], Satoshi Mochida[10], Yoshikazu Murawaki[11], Masao Honda[12], Akito Sakai[12], Yoichi Hiasa[13], Shuhei Nishiguchi[14], Asako Koike[15], Isao Sakaida[16], Masatoshi Imamura[17], Kiyoaki Ito[17], Koji Yano[17], Naohiko Masaki[17], Fuminaka Sugauchi[1], Namiki Izumi[3], Katsushi Tokunaga[2] & Masashi Mizokami[1,17]

Hepatitis C: Further considerations

- Protease inhibitors (telaprevir, boceprevir) approved 2 years ago, for Genotype 1
- Recent development of polymerase inhibitors
- Sofosbuvir recently reported in NEJM for Genotypes 2 and 3, among others
- Looking for sustained virologic response (surrogate EP, but very plausible)
- Beginning to target both organism and host characteristics

Treatment Selection based on Individual Molecular Characteristics Entering Mainstream

- Oncology undergoing exceeding rapid transition
- (Chronic) infectious diseases also
- Genetic disease not far behind
- Raises scientific, regulatory policy, logistical and reimbursement issues

ONGOING CHALLENGES

Scientific Issues

- “mutated gene” not site of action
- May be multiple sites where mutations occur in any given gene
- Variable functional impact: “molecular phenotype”, e.g.,
  - One mutation could drive cancer
  - A separate mutation might confer a better prognosis
  - Another mutation could confer resistance to therapy
  - Another mutation may have no impact
  - Current diagnostics may not discriminate adequately
- How to do drug development using such fine discrimination?

Scientific Issues

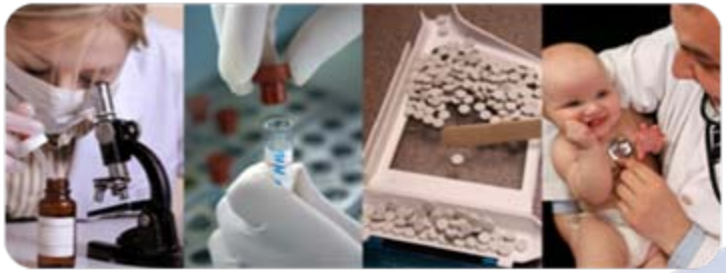
- Rapid evolution in diagnostic testing, particularly genomic testing
- Diagnosis is foundation of therapy—and of personalized medicine
- Need reliable diagnostics that relay understandable information to clinicians
- Making sense of large volume of information—e.g., from next-generation and beyond sequencing—will be challenging
- Other technologies will emerge that reflect a more integrated, functional view of the individual

POLICY ISSUES

FDA Policy Approach

- For over a decade, CDER has been urging adoption of pharmacogenomic strategies and pursuit of targeted therapies
- Reason: decrease variability of response; improve safety; increase size of treatment effect
- Began with proactive insertion of drug metabolizing enzyme information into existing drug dosing instructions
- For drugs under development, industry was concerned that CDER would cause delays if early genomic information was included in INDs
- Genesis of “safe harbor” concept: voluntary genomic data submission program

History of Genomics at FDA



Early 2002
Lesko & Woodcock commit to Pgx

2002
1st FDA-DIA Pgx Workshop ("Safe Harbor" concept introduced)

2003
Inception of VGDS program (later VXDS)

2004-2005
1st VDGS; GDS Guidance for Industry

2006
Guiding Principles for Joint FDA/EMA VGDS

2008 to Present
5th FDA-DIA Workshop
GG review infrastructure
Genomics review "Best Practices"
Knowledge management
Label updates
Investigator-initiated research
Collaborations

VXDS Impact on submission of novel biomarker data in INDs/NDAs/BLAs

- Ongoing process
- More than 50 VXDSs have been received since 2004
- Led to increasing numbers of regulatory submissions with novel biomarker data
- Helped development of policy at the FDA

Submission types

- "-omics"
- Pharmacogenomics
- Proteomics
- Metabolomics

Therapeutic areas

- Alzheimer's Disease
- Cancer
- Cardiovascular diseases
- Depression
- Diabetes
- HIV
- Obesity
- Rheumatoid Arthritis
- Sepsis
- Systemic Lupus Erythematosus

Issues Discussed

- Clinical/analytical
  - Clinical trial design/statistical issues
  - Genetic association to adverse events
  - Genetic variants and response to drugs
  - Use of biomarkers in stratification
  - Impact on labels
- Preclinical
  - Toxicology markers
  - Renal toxicity
  - Vascular toxicity
  - Hepatotoxicity

Policy and Guidance

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
2010	**ICH E16 Concept Paper on PG Biomarker Qualification: Format and Data Standards**
	Guidance on Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Agents for Treatment
	Guidance on Qualification Process for Drug Development Tools
2011	**Guidance on in vitro Companion Diagnostic Devices***
	Guidance on Clinical Trial Designs Employing Enrichment Designs*
2012	**Guidance on Clinical PG: Premarketing Evaluation in Early Phase Clinical Studies**
In Process	**Guidance on Drug-Diagnostic Co-development**

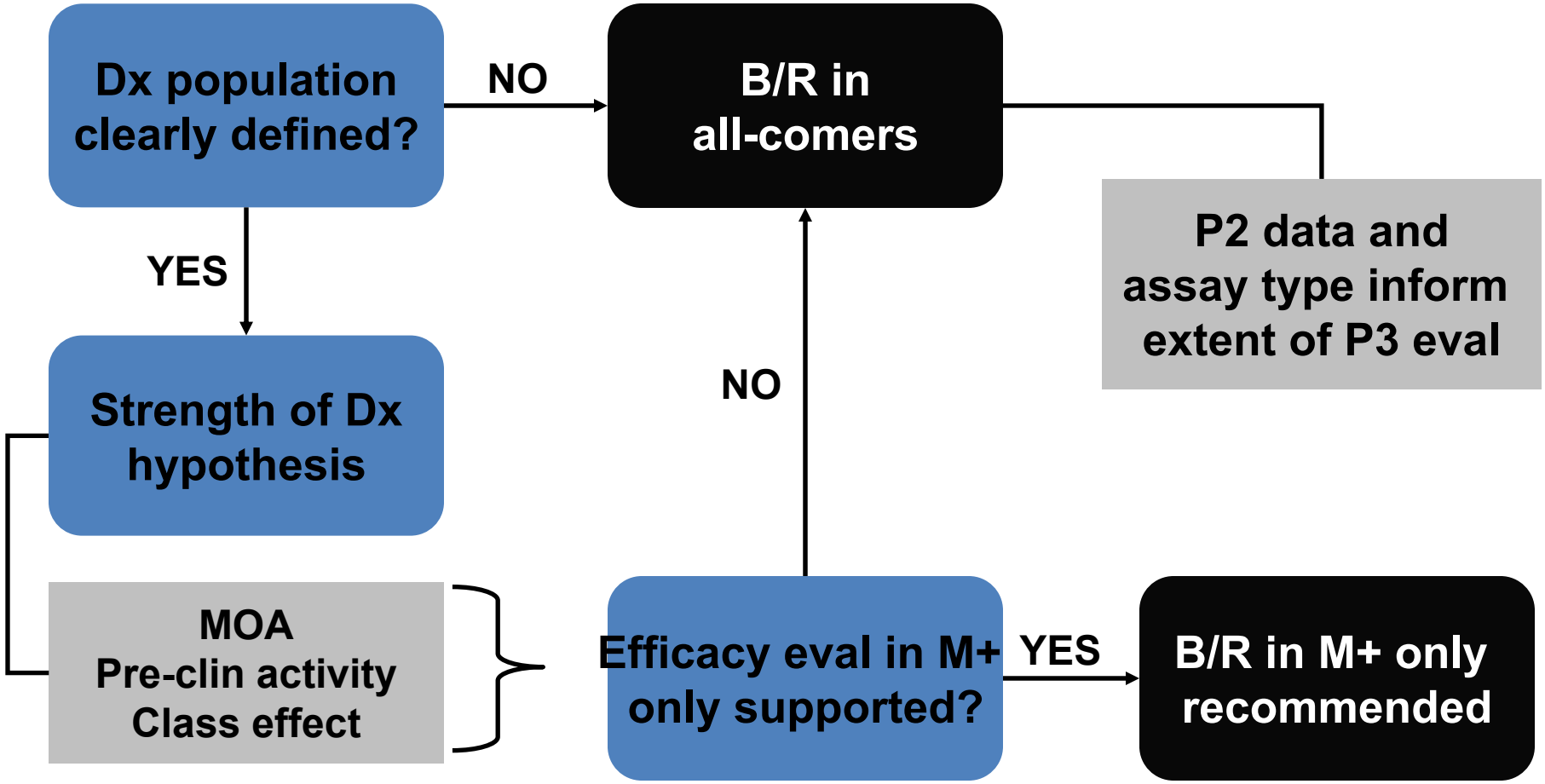
FDA Guidance: Companion Diagnostics

- Defines "companion diagnostic"
  - Test essential for safe and effective drug use
  - Prediction, prognosis, selection, dosing, monitoring
- Describes FDA's policies for approval and labeling of a therapeutic/diagnostic product pair
  - Pre-market review, risk-based regulation
  - Analytical validity of tests used for critical treatment decisions to be reviewed
- Does not describe how to co-develop products

Principles for Biomarker Use in Targeted Drug Development

Biomarker is the major pathophysiological driver of the disease
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)
Biomarker is the known molecular target 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

Need for Evaluating Marker-Negative Patients



Current Unresolved Policy Issues

- How to study rare genotypes
- Incorporation of functional information ("molecular phenotype") into development plan
- Dealing with rapid evolution of diagnostic technology (compared with pace of drug development)

LOGISTICAL ISSUES

Need for New Definition of "Clinical Trial"

- Personalized therapies are aimed at subsets of conventionally defined diseases
- Doing a single trial to answer each question raised by each marker/candidate therapeutic and combinations thereof is not feasible
- Need to "turn paradigm on its head"; set up ongoing trials with broad intake and many strata based on biomarkers
- Some trials ongoing (e.g., I-SPY 2); others being set up
- Other networks (e.g., cystic fibrosis) make rapid evaluation of genetic subsets feasible

Breakthrough Therapies

- Certain targeted therapies may have startling efficacy compared to conventional drugs
- FDASIA (passed 2012) sets up a designation program for “breakthrough therapies”
- Preliminary clinical evidence in serious disease of significant improvement over existing RX
- Voluntary; sponsor requests
- We have received quite a few submissions and will be granting additional designations

Breakthrough Therapies

- Designation allows sponsor to work very closely with FDA to design most efficient development path
- Early, separate meetings on manufacturing and scale-up to meet supply, if approved
- Based on current submissions, expect to see a growing category of (mostly) targeted, highly effective drugs for serious conditions
- Potentially very rapid development programs

VALUE RELATED CHALLENGES

Value-related Issues

- Rising healthcare costs around the world are leading to increased scrutiny of medical interventions and technology
- Most targeted interventions are considered “high tech” and “expensive”
- Reimbursement for diagnostics remains a challenge in development
- Seeing increasing resistance to reimbursement in some regions

Value-related Issues

- The new field of targeted therapy needs to raise its sights—focus on adding value
- Many of these new interventions have considerably greater efficacy for at least commensurate and sometimes improved safety
- Eventually, need to combine treatments or develop effective interventions that **cure** or **control** disease
- We are only in the early stages of this therapeutic revolution, but it is important to keep in mind the ultimate goal

The Future of Personalized Medicine

- Deliver new treatments at reasonable cost that have significant impact in treating or preventing human disease, and are
  - More effective
  - Less toxic
  - More cost-effective

--Than today's interventions

Then We can Say that Personalized Medicine is a Major Part of the Future of Healthcare