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INNOVATIONacademy

Application of Genetics to support Personalised Medicine

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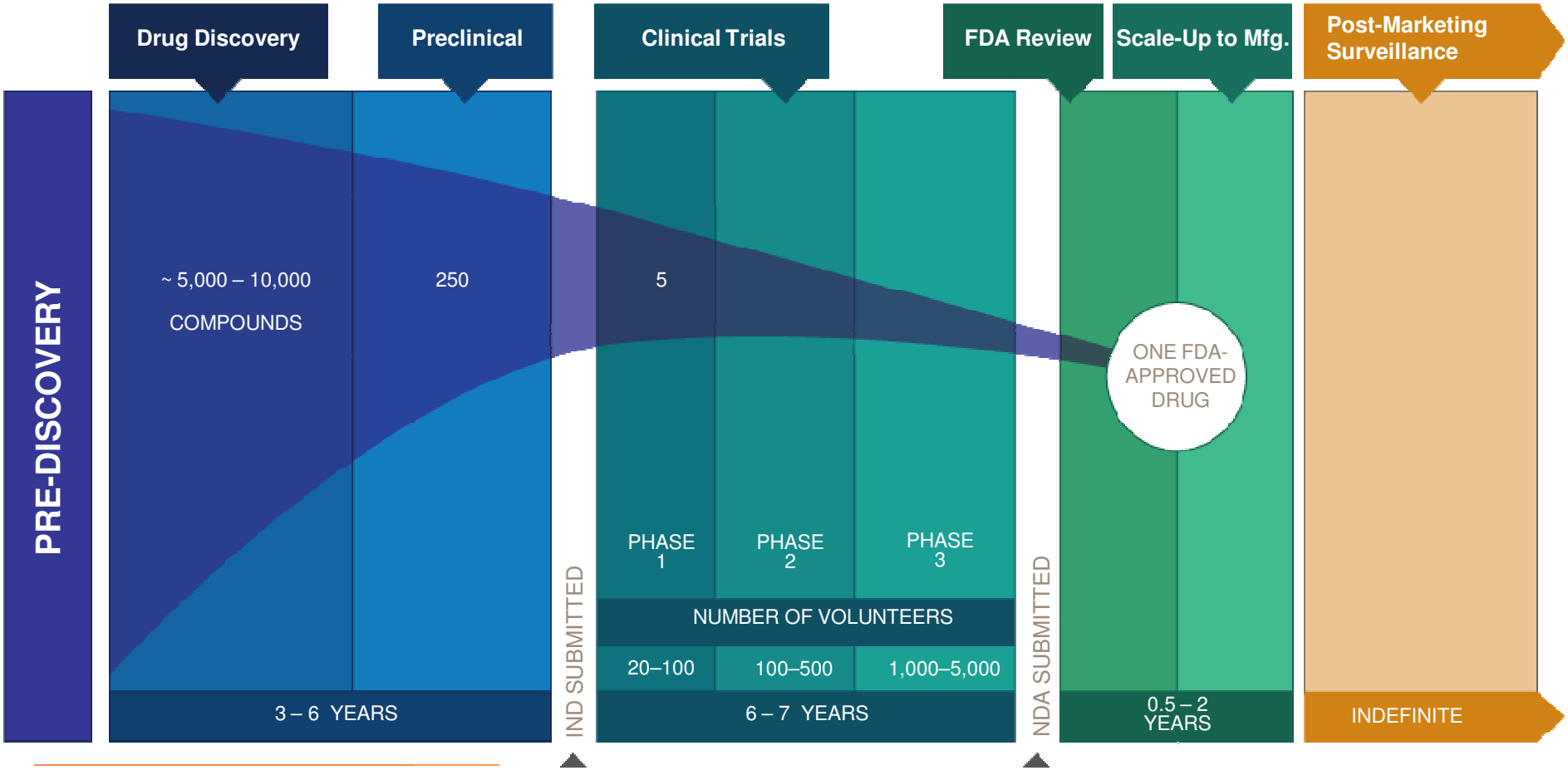
Overview

- Human genetics in the drug lifecycle
- Pharmacogenetic examples
  - Efficacy: clopidogrel and CYP2C19
  - Safety: lapatinib and HLA-DRB1*07:01
- Clinical translation of pharmacogenetics
- Challenges and opportunities

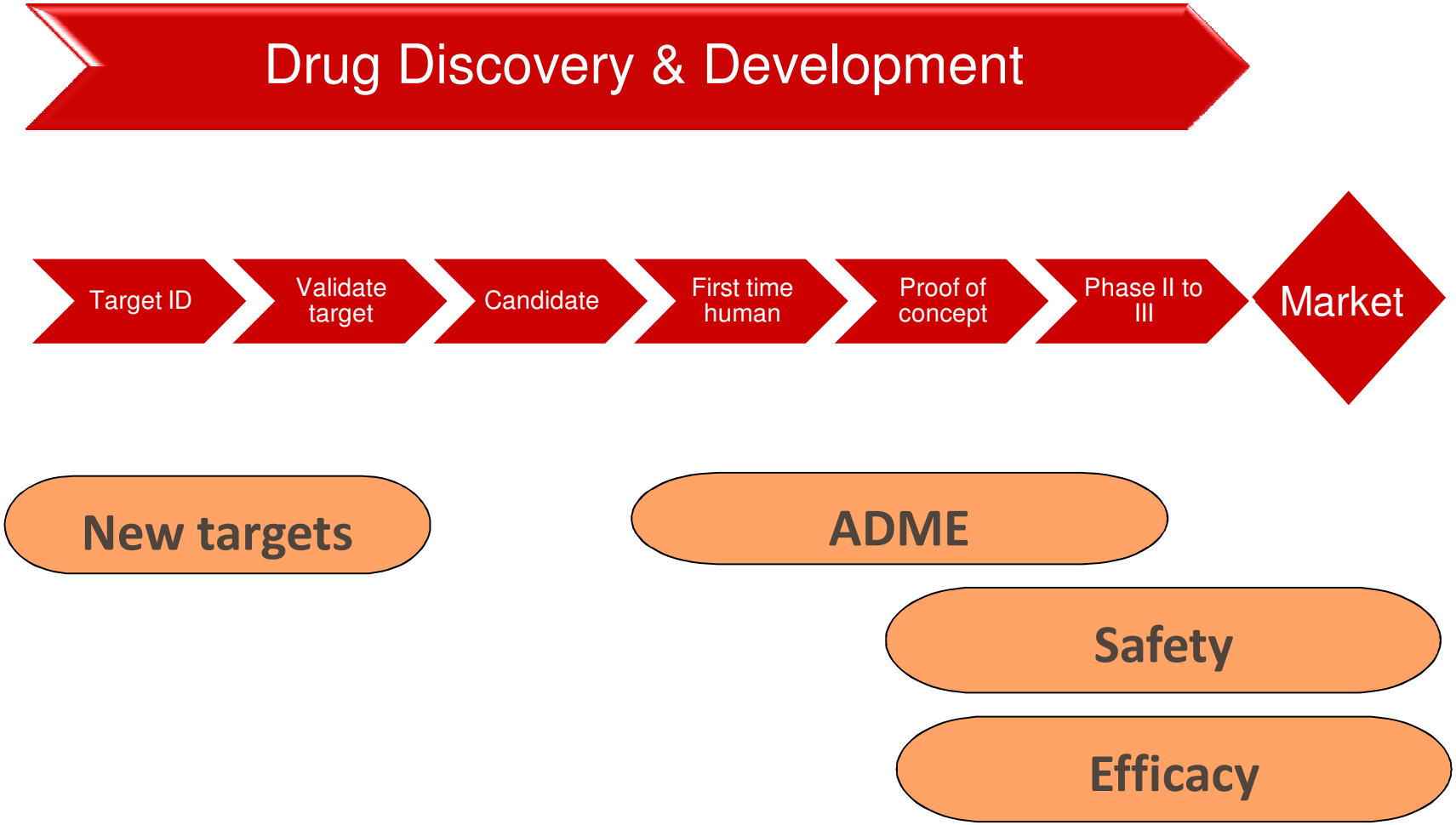
Drug Discovery & Development

Developing a new medicine takes an average of 10–15 years
Relatively few drugs survive the clinical trial process

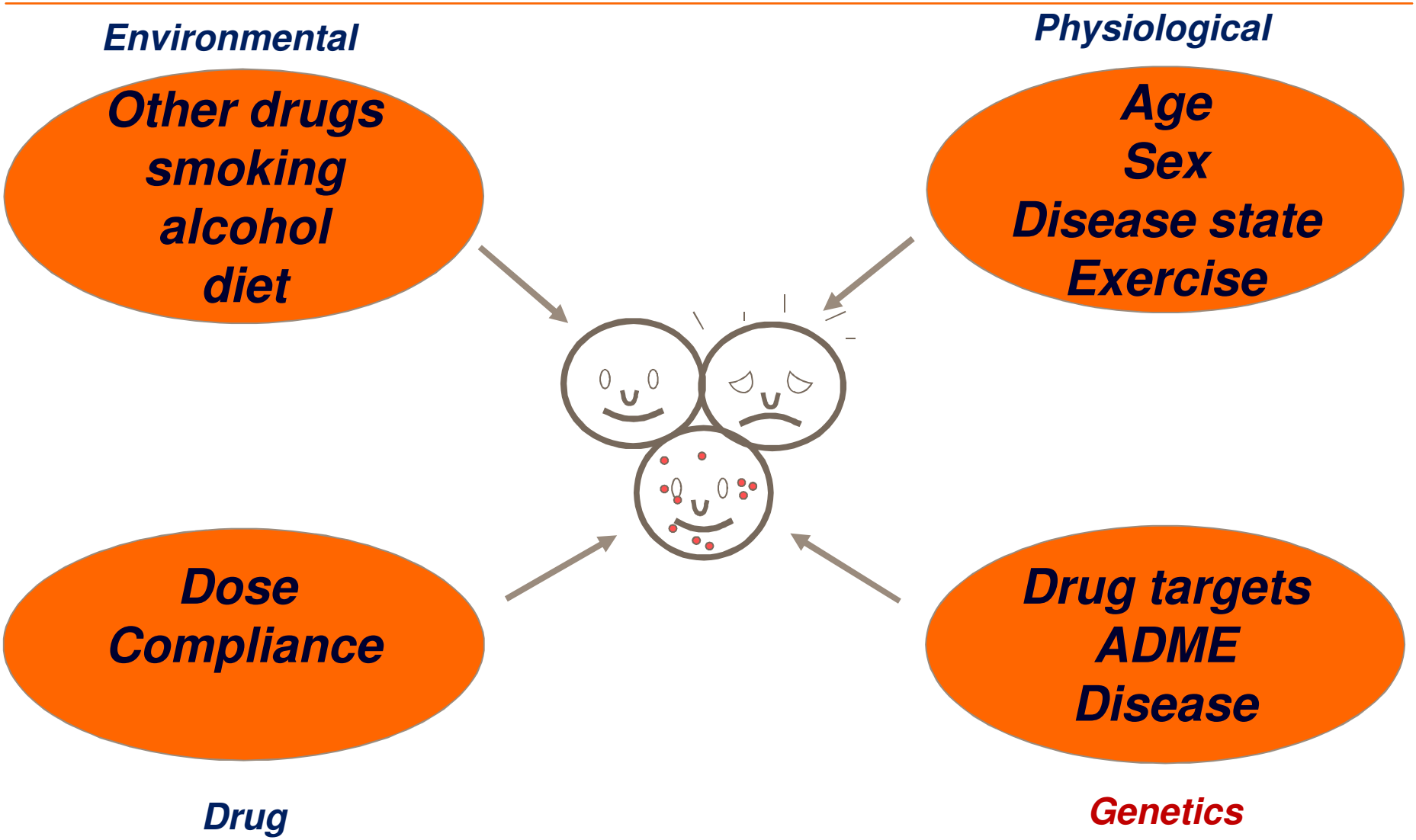


Sources: Drug Discovery and Development: Understanding the R&D Process, www.innovation.org; CBO, *Research and Development in the Pharmaceutical Industry*, 2006.

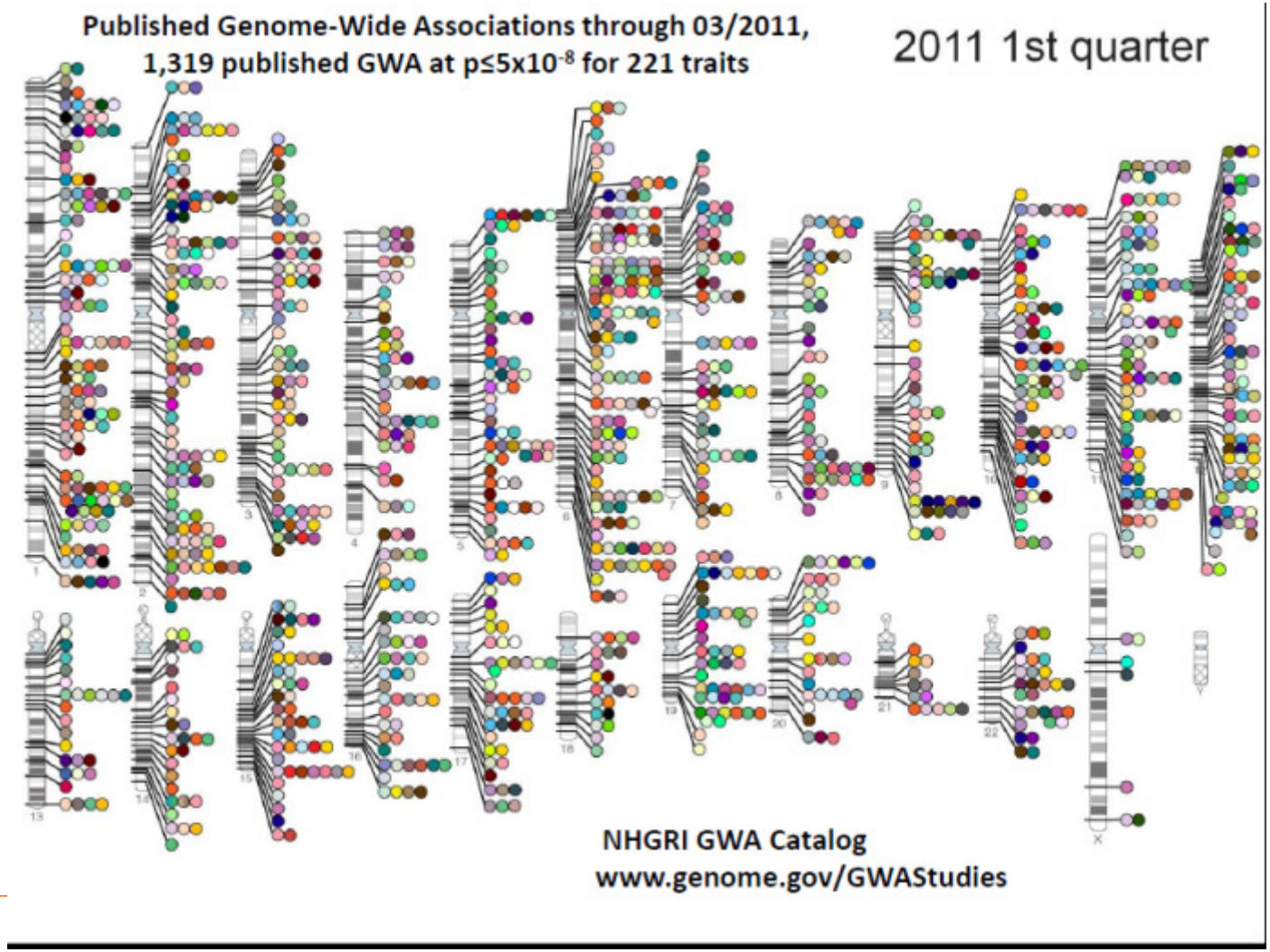
Human genetics opportunities for differentiation in drug discovery and development



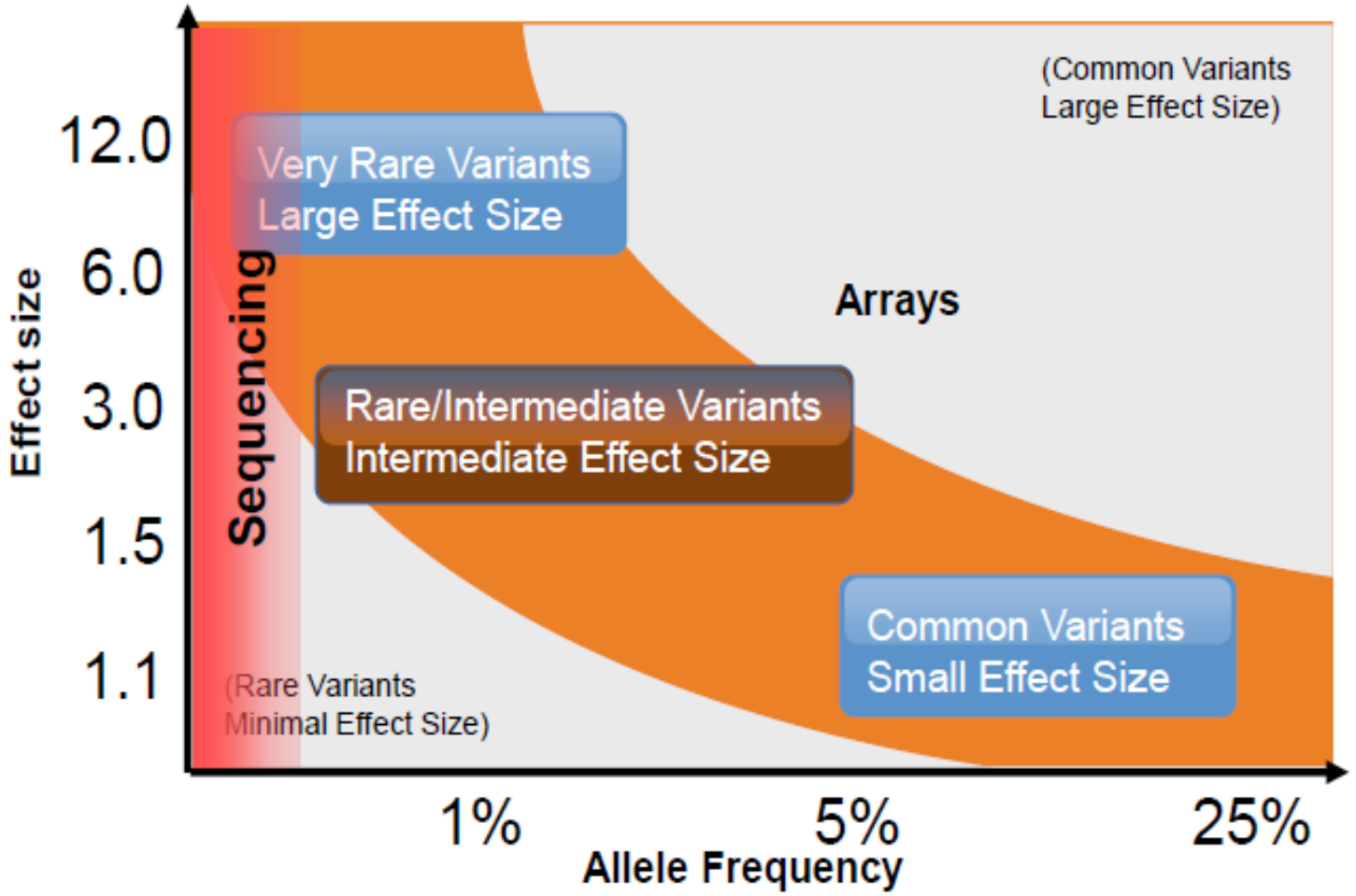
Many factors influence drug response



Genome-Wide Association Study of disease susceptibility

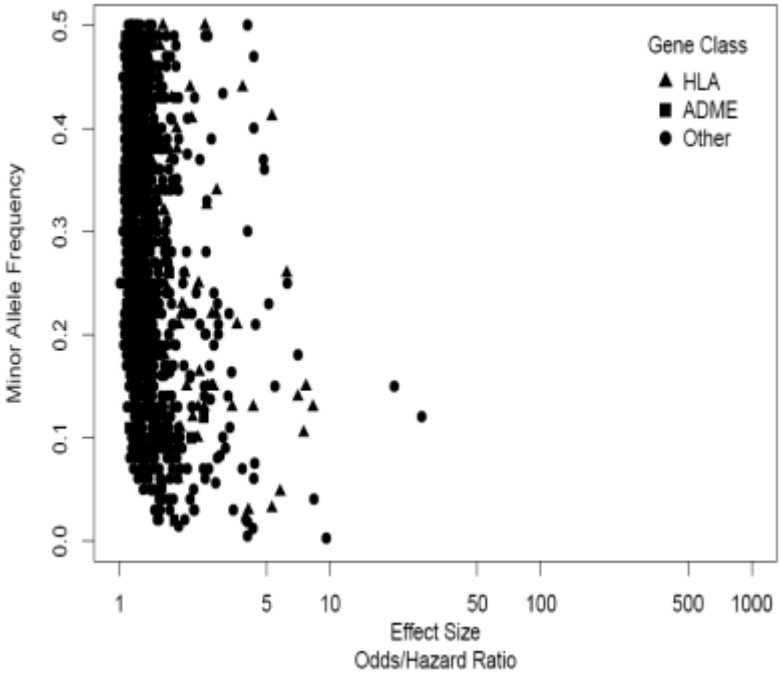


Genotyping landscape

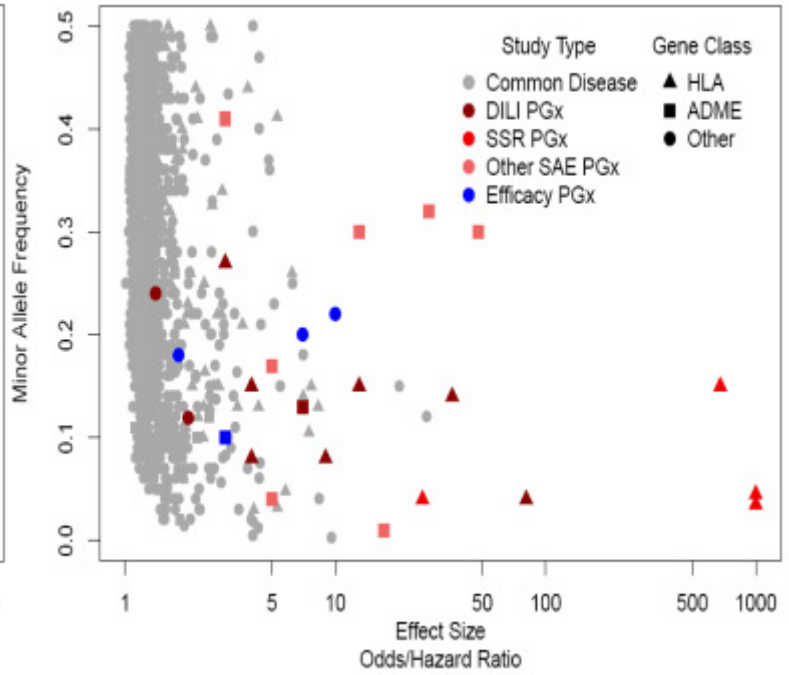


Pharmacogenetic effects tend to be large

Disease-related associations in NHGRI GWAS Catalog



Pharmacogenetic effects

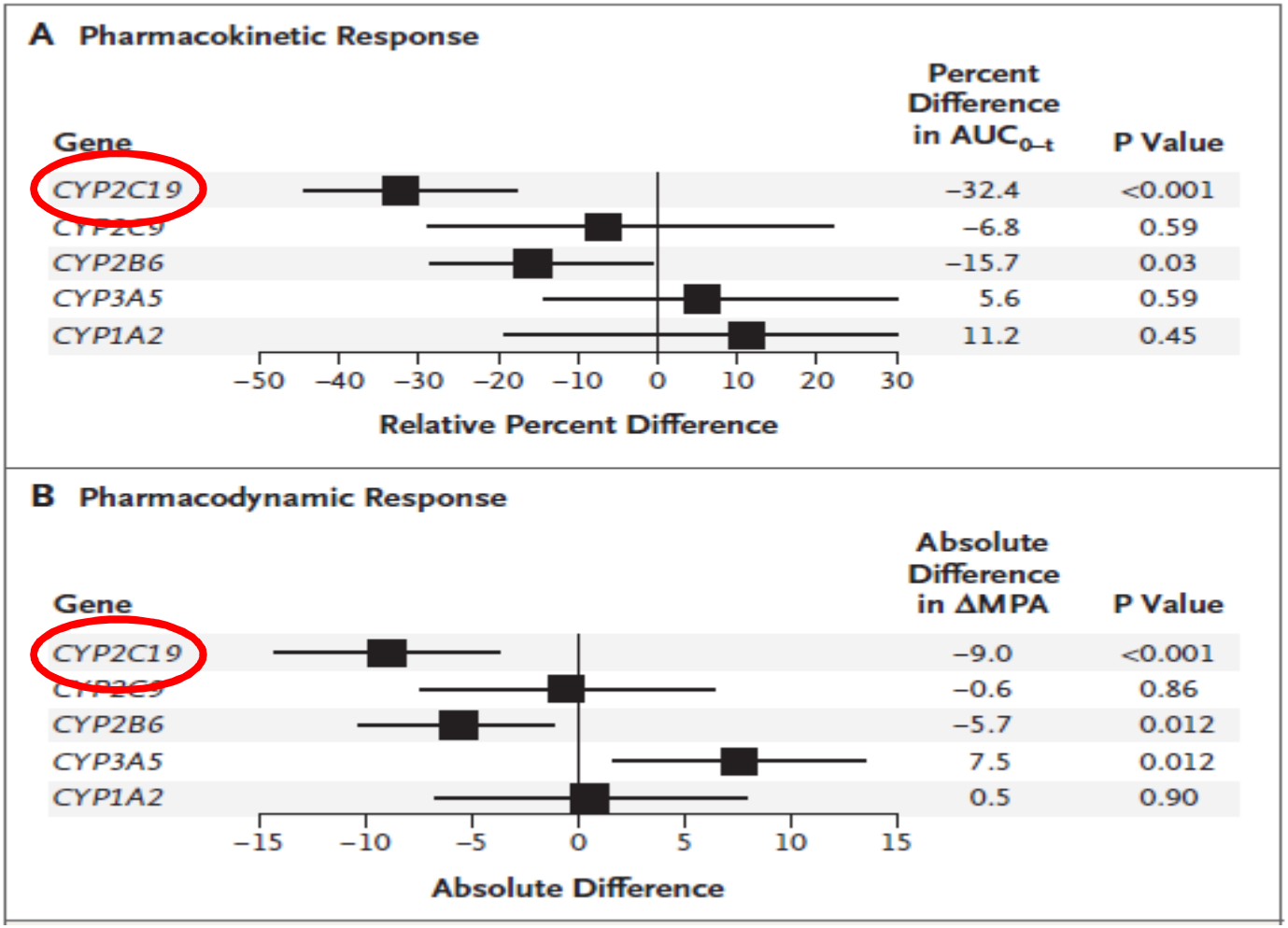


From http://www.genome.gov/gwastudies

Efficacy: Clopidogrel and *CYP2C19* variation

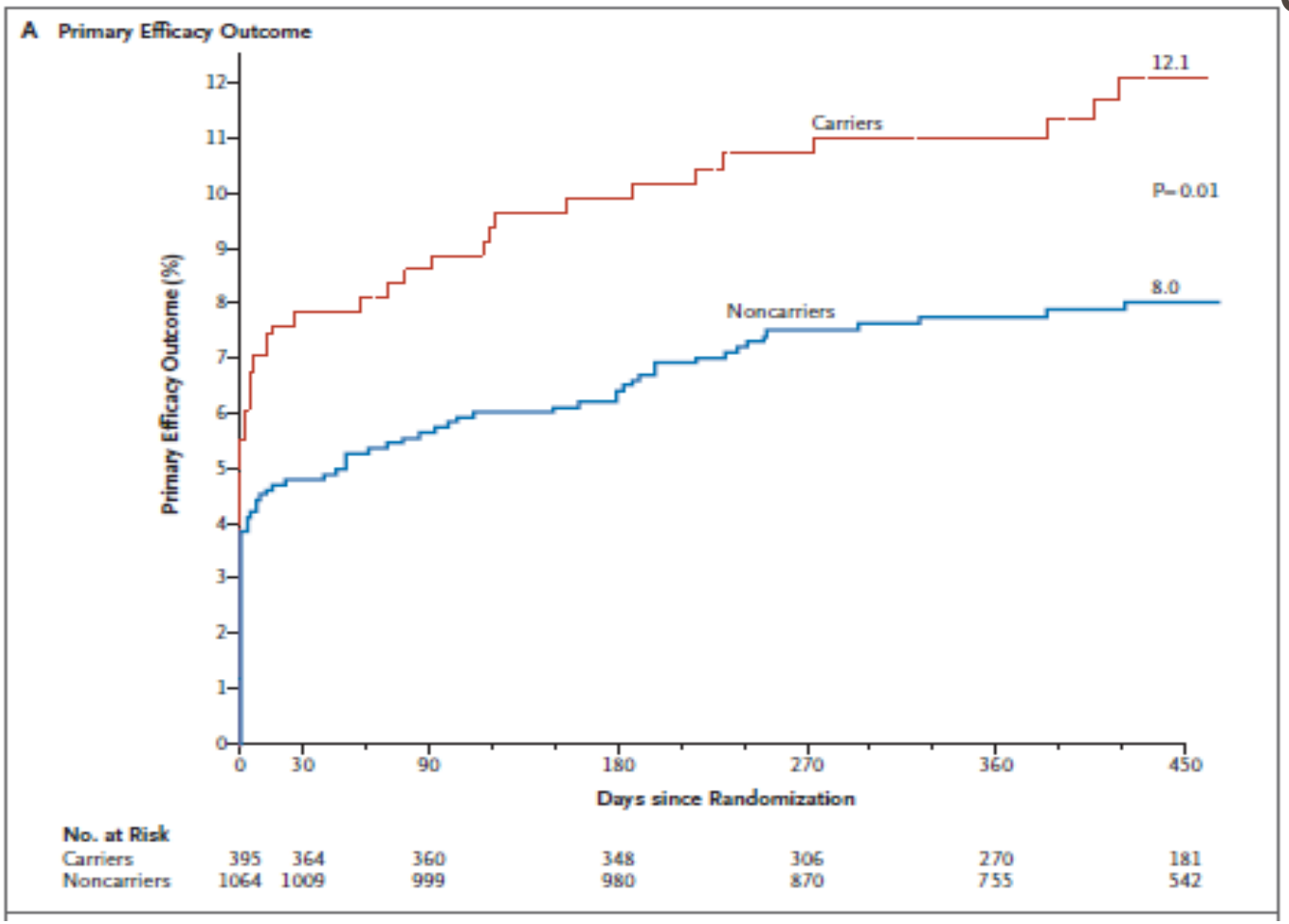
- Clopidogrel is a $P2Y_{12}$ antagonist anti-thrombotic
- Alternative to warfarin for thrombosis prevention in patients with coronary syndromes
- Clopidogrel is a prodrug, activated by *CYP2C19*
- *CYP2C19* has common loss of function variants
  - *CYP2C19*2*
  - 25% Whites, 30% African Americans, 50% Asians

CYP Loss of Function variants and clopidogrel pharmacokinetics & pharmacodynamics



Mega, JL, et al (2009), *New England Journal of Medicine* 360: 354-362

Effect of CYP LOF variants on clopidogrel efficacy (risk of death from CV causes)

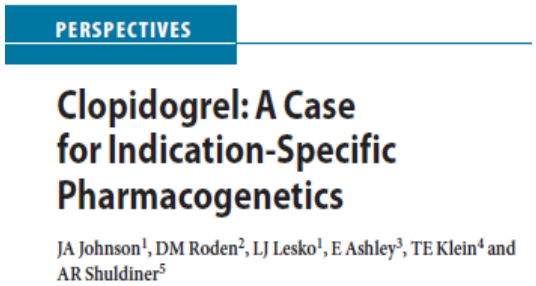


Carriers have at least one copy of *2C19* LOF variant (30% of study population)

Mega, JL, et al (2009), *New England Journal of Medicine* 360: 354-362

However.....

- CYP2C19*2 loss of function allele is associated with reduced generation of active metabolites of clopidogrel
- Meta-analyses have both supported or discounted the impact of genotype on adverse CV outcomes during clopidogrel therapy
- Evidence supports a differential genotype effect on protection from major adverse CV outcomes following percutaneous coronary intervention (PCI), but not for other clopidogrel indications


PERSPECTIVES

Clopidogrel: A Case for Indication-Specific Pharmacogenetics

JA Johnson[1], DM Roden[2], LJ Lesko[1], E Ashley[3], TE Klein[4] and AR Shuldiner[5]

Clin Pharmac Ther (2012): 91; 774-776

HLA Influence on Adverse Drug Reaction Risk
Selected Examples

Drug	Adverse Drug Reaction		Genetic Risk Factor		
	Reaction	Prevalence	Risk Allele	MAF	Rel. Risk
Ximelagatran	Hepatotoxicity	0.08	*DRB1*07:01*	0.14	4
Augmentin	Hepatotoxicity	<0.001	*DRB1*15:01*	0.15	4
		<0.001	*A*02:01*	0.27	3
Lapatinib	Hepatotoxicity	0.03	*DRB1*07:01*	0.14	14
Lumiracoxib	Hepatotoxicity	0.013	*DRB1*15:01*	0.15	13
Ticlopidine	Hepatotoxicity	<0.001	*A*33:03*	0.14	36
Flucloxacillin	Hepatotoxicity	<0.001	*B*57:01*	0.04	81
Allopurinol	SCAR	<0.001	*B*58:01*	0.15	678
Abacavir	Hypersensitivity reaction	0.05	*B*57:01*	0.04	>1000
Carbamazepine	SCAR - Taiwanese	0.003	*B*15:02*	0.04	>1000
	SCAR - European	<0.001	*A*31:01*	0.04	26

Frequency of the ADR is typically much lower than the frequency of the HLA allele associated with the ADR

Clinical Utility: HLA biomarker characteristics

Abacavir (HIV), Allopurinol (hyperuricemia) and Carbamazepine (epilepsy)

HLA-mediated ADRs: Severe skin reactions – SJS, TEN, HSR

Clinical utility defined by:

- Predictive value (PPV & NPV)
- Number needed to test (NNT)

Benefit/Risk considerations:

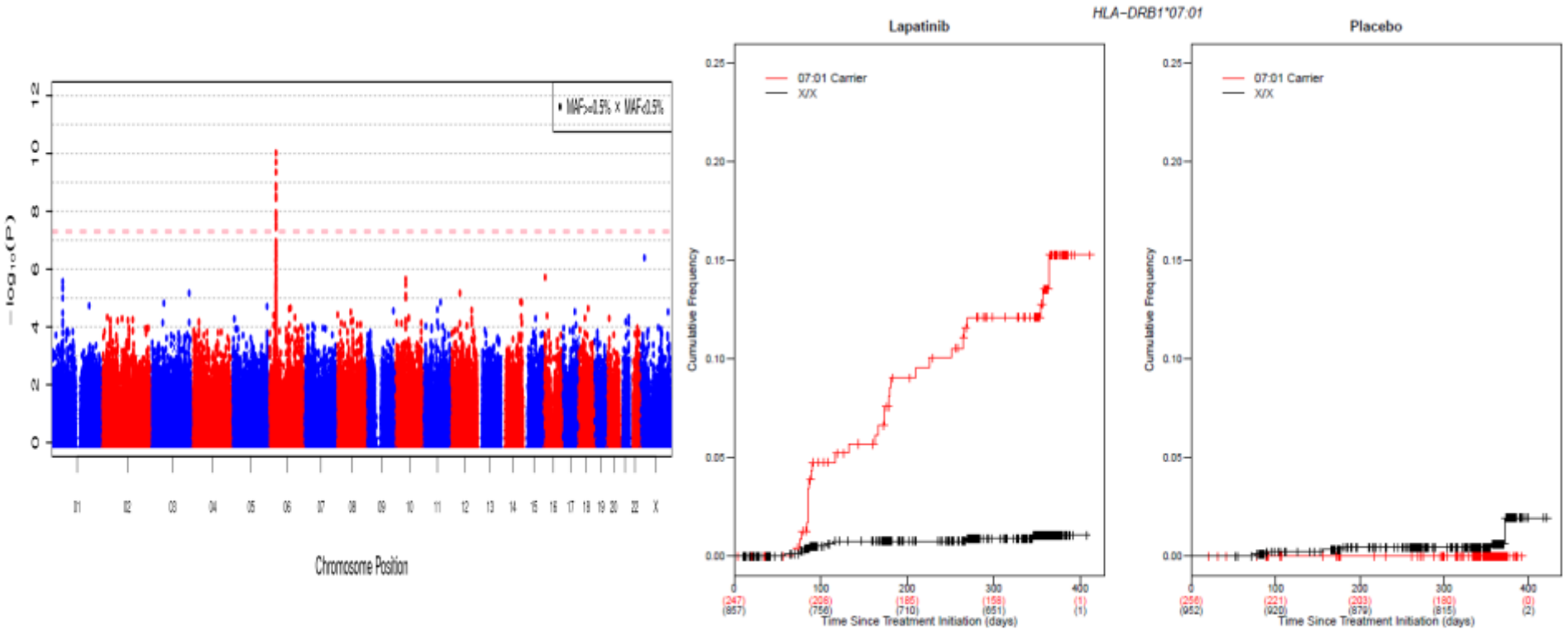
- Life threatening – Yes/No
- Treatment options – Yes/No

Drug	HLA allele	Carrier rate	Prevalence diagnosis	Approx NNT to prevent 1 case	PPV/NPV (%)
Abacavir	B*5701	6-8% Cauc	8%	13	55/100
Allopurinol	B*5801	9-11% Han Ch	1-4 in 1000	250	2.7/100
Carbamazepine	B*1502	10-15% Han Ch	<1-6 in 1000	1000	3.1/100

Adapted from Phillips and Mallal, Pharmacogenomics 2010

Lapatinib induced liver toxicity

ALT elevations >3x ULN



Drug	HLA allele	Carrier rate	Prevalence diagnosis	Approx NNT to prevent 1 case	PPV/NPV (%)
Lapatinib	DRB1* 07:01	20% Cauc (1% Japan)	2%	38	8/99.8

Spraggs et al, SABCS 2012

Clinical PGx translation success, in some areas.....

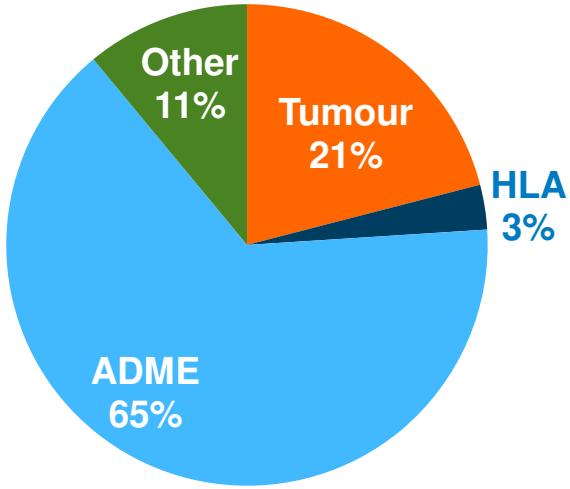
- Somatic mutations & gene expression direct **cancer** treatment
  - Ph+, EGFR+, HER2+/-, KRASwt, BRAFmt,
- Heritable mutations provide mechanisms to diagnose & treat **Mendelian diseases** (e.g. CFTR G551D - Invacaftor)
- Viral/microbial genomes provide taxonomy & provide **pathogen resistance** profiles prospectively (e.g. HIV, HCV)

Limited translation in others….

PGx biomarkers with Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines

- Regulatory guidances are proactive & encouraging
- Drug exposure/PK PGx translation not reflected in the number of ADME labels

Drug (s)	Gene(s)	Issue
Thiopurines	TPMT	Safety
Codeine	CYP2D6	Safety
Abacavir	HLA-B*57:01	Safety
Simvastatin	SLCO1B1	Safety
Allopurinol	HLA-B*58:01	Safety
Clopidogrel	CYP2C19	Efficacy/safety
Warfarin	VKORC1/CYP2C9	Efficacy/safety
Tricyclic antidepressants	CYP2D6/CYP2C19	Efficacy
Peg-IFNα	IL28B	Efficacy



Genomics in FDA drug labels (N=120)

Challenges & Opportunities for PGx clinical translation

Enhance discovery & validation

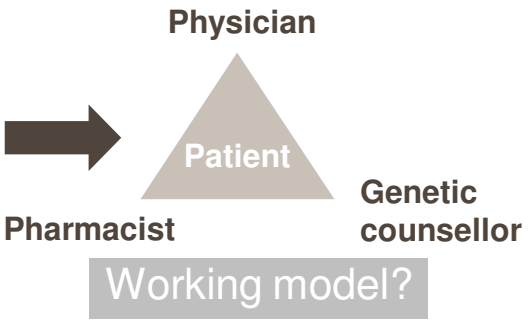
- Improve science
- Demonstrate clinical utility

Implementation in clinical practice

- Point-of-care testing
- Pre-emptive PGx testing
- Companion diagnostics
- PGx integration & education

Re-imbursement

- PGx test cost : benefit
- Clinical consultation



Working model?

PGx testing programs in academic medical centres – understanding the possibilities

- **TPMT** genotyping for 6-mercaptopurine for acute lymphoblastoid leukemia - St Jude's Hospital
- **CYP2C19** genotyping for clopidigrel treatment of patients underoing percutaneous coronary intervention – Scripps, Vanderbilt, Uni Florida
- **CYP2D6** genotyping to guide treatment for anti-psychotics and antidepressants – Mayo Clinic

Conclusions

- Genetics has the potential to influence clinical decision making - there are many challenges, but also opportunities
- Determining genetic biomarker performance characteristics is crucial for determining clinical utility
- Embedding PGx testing into clinical practice will require:
  - Solid science - supporting robust discovery & validation
  - Education, integration and improved logistics
  - Demonstration of cost-benefit (re-imbursable)
  - Change in clinical paradigm to support personalised medicine