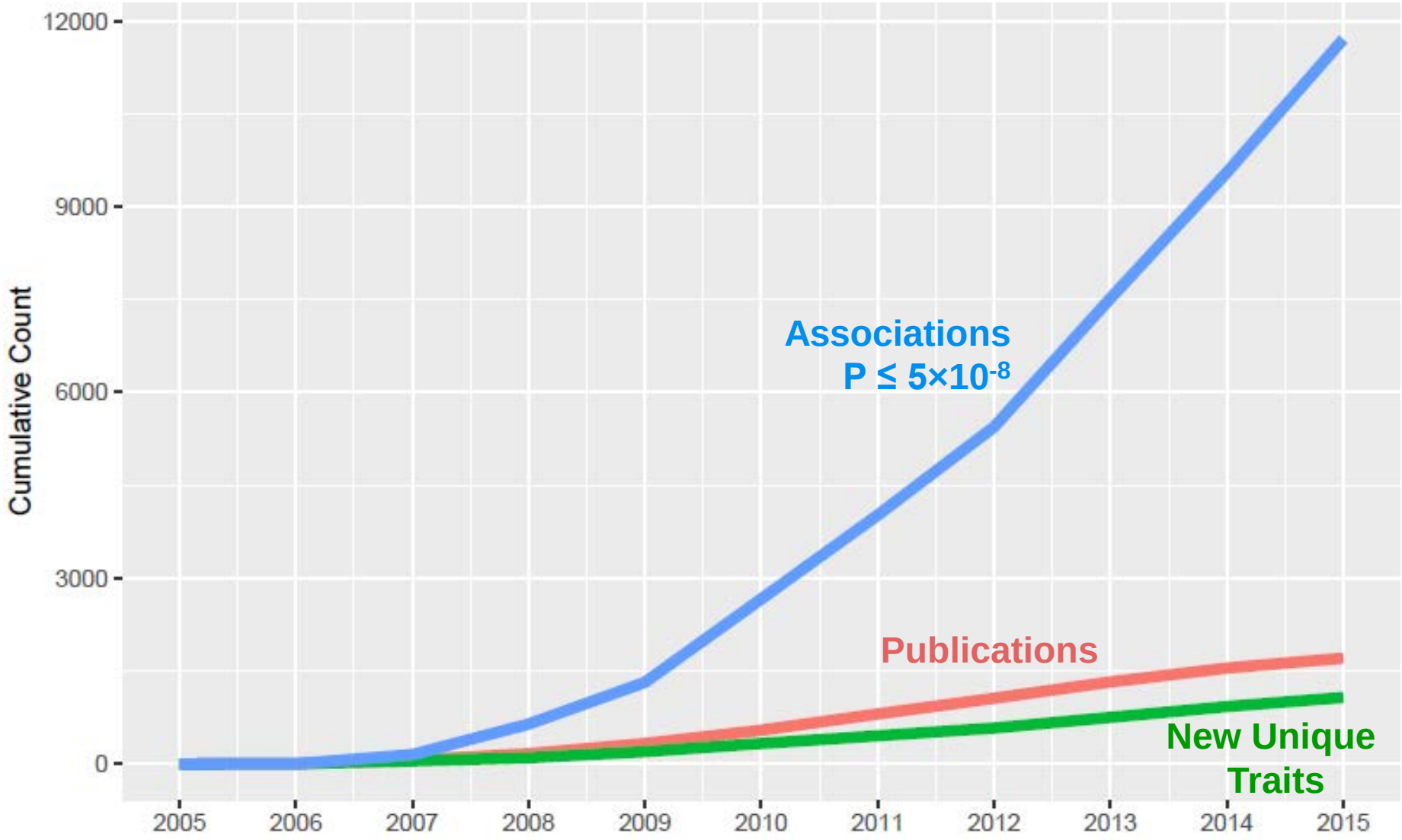
Potential Advantages and Pitfalls to Using Genetics in Drug Development for Complex Diseases

Matthew R. Nelson

March 8, 2017

Genome-wide association studies have identified thousands of variants that influence complex human traits



Source: NHGRI/EBI GWAS Catalog, September 1, 2016

Early reasons to be optimistic about PGx in PM
Abacavir hypersensitivity reaction (HSR) and *HLA-B**57:01

In 2001, an analysis of a retrospective case/control study identified *HLA-B**57:01 to be strongly associated with HSR risk

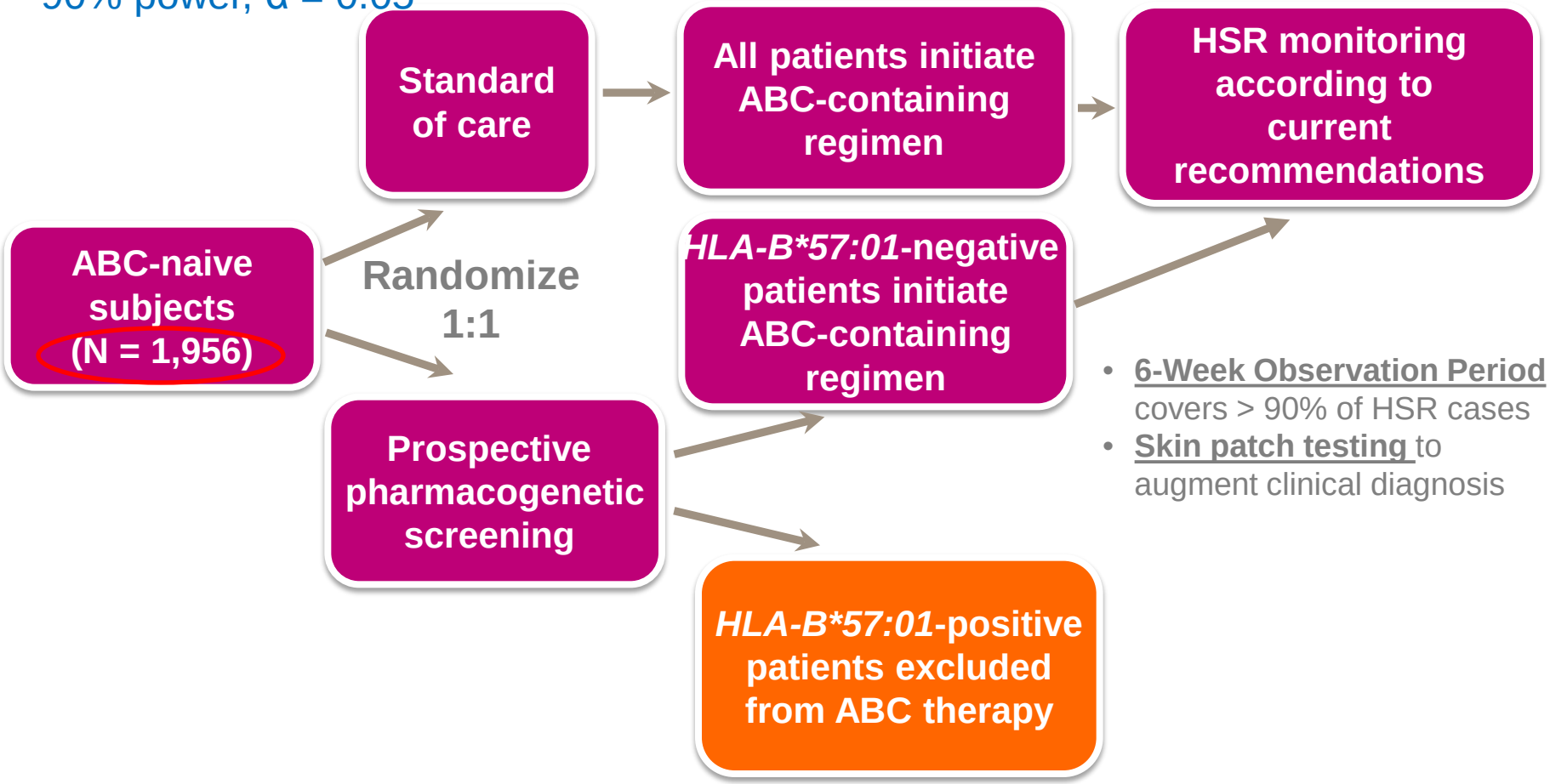
	Cases (n=84)	*Controls (n=113)*	*p-value*
HLA-B57 Present	39 (46%)	4 (4%)	<0.0001
HLA-B57 Absent	45 (54%)	109 (96%)	

The presence of HLA-B57 is more common in cases (46%) than controls (4%)

Hetherington et al. (2001) Lancet 359: 1121–2

PREDICT-1 study design

Hypothesized HSR rate **7.3%**
Post-screening HSR rate **3.8%**
90% power, α = 0.05



Hughes S *et al*. (2007) Pharmaceut. Statist. 7: 121-9

PREDICT-1 trial demonstrated screening utility

Table 4. Performance Characteristics of HLA-B*5701 Screening for Hypersensitivity Reaction to Abacavir in the Control Group.*

Subgro… …ristic …action

Immun

Total p…

Hyp… …100)

No… …98.0)

White s…

Hyp… …100)

No… …97.6)

WARNING: HYPERSENSITIVITY REACTIONS, and LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY

See full prescribing information for complete boxed warning.

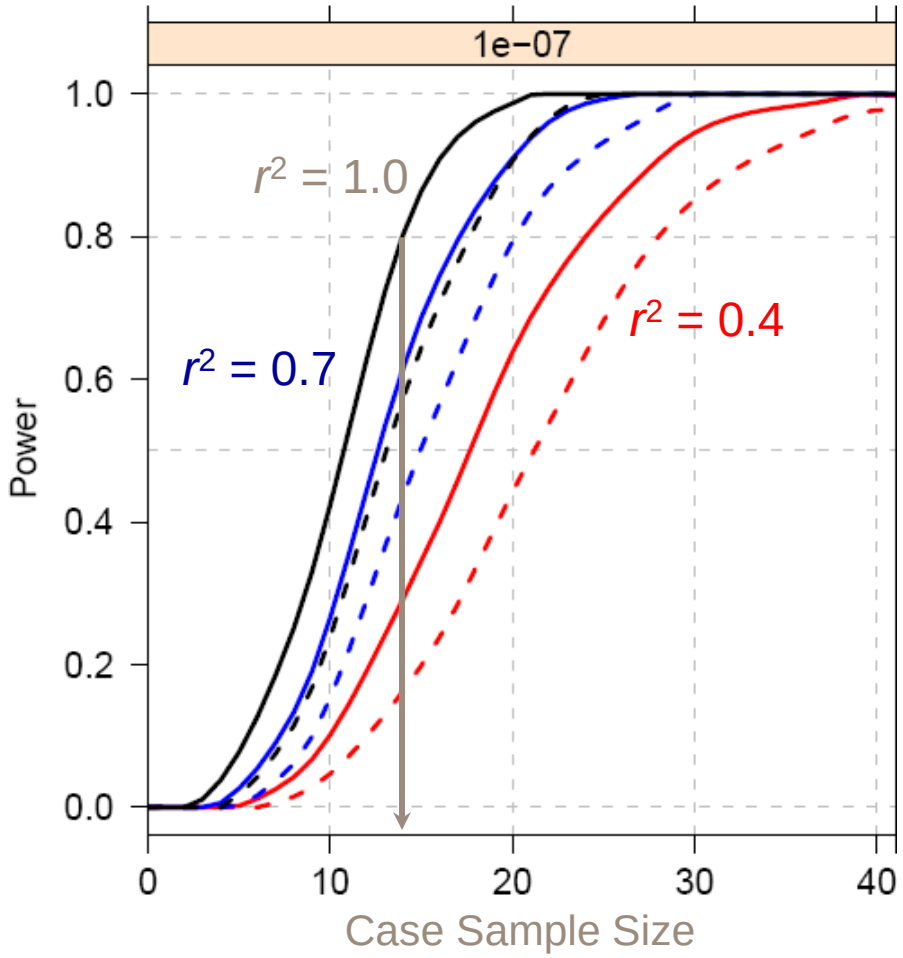
Hypersensitivity Reactions

- **Serious and sometimes fatal hypersensitivity reactions have occurred with ZIAGEN (abacavir). (5.1)**
- **Hypersensitivity to ZIAGEN is a multi-organ clinical syndrome. (5.1)**
- **Patients who carry the HLA-B*5701 allele are at a higher risk of experiencing a hypersensitivity reaction to abacavir. (5.1)**
- **ZIAGEN is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients. (4)**
- **Discontinue ZIAGEN as soon as a hypersensitivity reaction is suspected. Regardless of HLA-B*5701 status, permanently discontinue ZIAGEN if hypersensitivity cannot be ruled out, even when other diagnoses are possible. (5.1)**
- **Following a hypersensitivity reaction to ZIAGEN, NEVER restart ZIAGEN or any other abacavir-containing product. (5.1)**

PPV: 46.8 (32.1–61.9)
NPV: 100 (99.4–100)

Mallal *et al.* NEJM (2008) 358:568-79

Power to Detect Abacavir HSR HLA-B*5701-like Effect



Adjustment for 500,000 hypothesis tests for an experiment-wide α = 0.05 yields a test-wise significance level of 10^{-7}

200 clinical controls

200 population controls

From Nelson et al. (2009) *Pharmacogenomics J* 9:23-33

	Non-iSAEC Findings			iSAEC-related Findings		
	Drug	Risk Allele	OR	Drug	Risk Allele	OR
Liver Injury						
	Pazopanib	***HLA-B*57:01***	2	**Augmentin**	***HLA-DRB1*15:01***	3
	Nevirapine	***HLA-DRB1*01***	3	**Augmentin**	*HLA-A*02:01*	2
	Ximelagatran	***HLA-DRB1*07:01***	4	**Augmentin**	*PTPN22 R620W*	2
	Lapatinib	***HLA-DRB1*07:01***	19	**Flucloxacillin**	***HLA-B*57:01***	81
	Lumiracoxib	***HLA-DRB1*15:01***	13	**Methyldopa**	***HLA-A*33:01***	98
	Ticlopidine	*HLA-A*33:03*	36	**Fenofibrate**	***HLA-A*33:01***	51
				Terbinafine	***HLA-A*33:01***	37
				Sertraline	***HLA-A*33:01***	22
				Erythromycin	***HLA-A*33:01***	10
				Cyprofloxacin	*HLA-B*50:02*	11
				Minocyclin	*HLA-B*35:02*	28
				Valproic Acid	***HLA-DRB1*10:01***	14
				Atorvastatin	***HLA-DRB1*10:01***	11
				Simvastatin	*HLA-B*13:02*	8
Skin Injury						
	Nevirapine	*HLA-B*35*	2	**Carbamazepine**	*HLA-A*31:01*	26
	Nevirapine	*HLA-C*04*	3			
	Phenytoin	*CYP2C9*3*	12			
	Phenytoin	***HLA-B*15:02***	6			
	Allopurinol	*HLA-B*58:01*	678			
	Carbamazepine	***HLA-B*15:02***	>1000			
AHSS/HSR						
	Dapsone	*HLA-B*13:01*	21	**Penicillins**	***HLA-DRB1*10:01***	3
	Abacavir	***HLA-B*57:01***	>1000	**Augmentin**	***HLA-DRB1*10:01***	3
				Amoxicillin	***HLA-DRB1*10:01***	3
Other						
	Statin myopathy	*SLCO1B1*5*	5	**Thiopurine pancreatitis**	***HLA-DRB1*07:01***	3
	Anthracycline cardiotox	*SLC28A3 rs7853758*	5	**5-ASA nephrotoxicity**	*HLA-DRB1*03:01*	2
	Anthracycline cardiotox	*UGT1A6 rs6759892*	3	**Clozapine agranulocytosis**	*HLA-DQB1 126H*	5
	Pazopanib hyperbilirubin	*UGT1A1*28*	13	**Clozapine agranulocytosis**	*HLA-B 158T*	3
	Cisplatin ototoxicity	*TPMT rs12201199*	17			
	Cisplatin ototoxicity	*COMT rs9332377*	5			
	Thiopurine leukopenia	*NUDT15* Arg139Cys	35			
	Irinotecan neutropenia	*UGT1A1*28*	28			
	Tranilast hyperbilirubin	*UGT1A1*28*	48			
	Clopidogrel CV events	*CYP2C19*2/3/4/5*	3			

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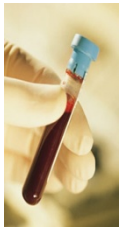
Gene Categories
HLA
ADME
Immune-related

Pharmacogenetics timeline at GSK

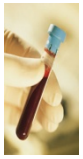
Several notable successes, but where's the impact on efficacy?

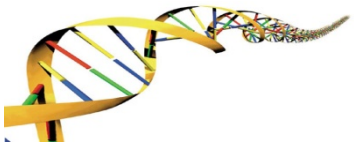
Abacavir HSR HLA-B*57:01 (2001)
Tranilast Bilirubin UGT1A1*28 (2003)
Pazopanib Bilirubin UGT1A1*28 (2005)
Lapatinib DILI HLA-DRB1*07:01 (2007)
Pazopanib DILI HLA-B*57:01 (2009)
2011
2013
2015.....



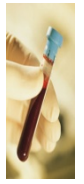
Collected and hold blood for later use

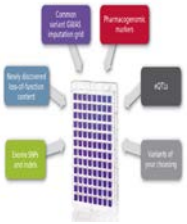
~$10





DNA extracted real time and banked -
~$50 DNA extraction & banking





Genome	$1000-3000
Exome	$600-1,500
NGS Panels	$200-400
GWAS	$80-100
HLA	$400
Imputation	$0

DNA extracted as required

3wks to ship and extract

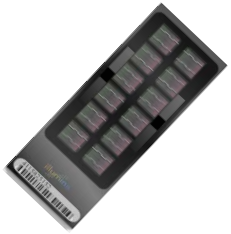
~$40 per extraction

Custom genotyping

~$1-5 per SNP (Taqman, Sanger Seq)
~$500 GWAS (600K), ~$1000 HLA
~$400 Roche Amplichip (CYP2D6)

Bespoke GT

~$30 candidate SNPs
~$400 GWAS (1M)
~$350 ADME arrays
~$700 HLA



Many Candidate Gene Studies Published Implicating Genes in Steroid Treatment Response in Asthma Subjects

Association between *WDR21A* polymorphisms and airway responsiveness to inhaled corticosteroids in asthmatic patients

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 29, 2011 VOL. 365 NO. 13

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Mechanisms of allergy and clinical immunology

The glucocorticoid receptor heterocomplex gene *STIP1* is associated with improved lung function in asthmatic subjects treated with inhaled corticosteroids

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Human Molecular Genetics, 2004, Vol. 13, No. 13 *1353–1359*
DOI: 10.1093/hmg/ddh149
Advance Access published on May 5, 2004

Corticosteroid pharmacogenetics: association of sequence variants in *CRHR1* with improved lung function in asthmatics treated with inhaled corticosteroids

Kelan G. Tantisira[1,2], Stephen Lake[1], Eric S. Silverman[2], Lyle J. Palmer[3], Ross Lazarus[1], Edwin K. Silverman[1,2], Stephen B. Liggett[4], Erwin W. Gelfand[5], Lanny J. Rosenwasser[5], Brent Richter[1], Elliot Israel[2], Michael Wechsler[1,2], Stacey Gabriel[6,8], David Altshuler[6,7,8], Eric Lander[6,8], Jeffrey Drazen[2] and Scott T. Weiss[1,*]

PNAS

***TBX21*: A functional variant predicts improve in asthma with the use of inhaled corticoste**

Kelan G. Tantisira*†‡, Eun Sook Hwang§, Benjamin A. Raby*†, Eric S. Silverman†§, Stephen L. Lake*, Brent G. Richter*, Stanford L. Peng¶, Jeffrey M. Drazen†§, Laurie H. Glimcher§, and Scott T. Weiss*

*Channing Laboratory and †Pulmonary Division, Brigham and Women's Hospital and Harvard Medical School, Bost Health and Harvard Medical School, Boston, MA 02115; and ¶Washington University School of Medicine, St. Louis,

Contributed by Laurie H. Glimcher, November 17, 2004

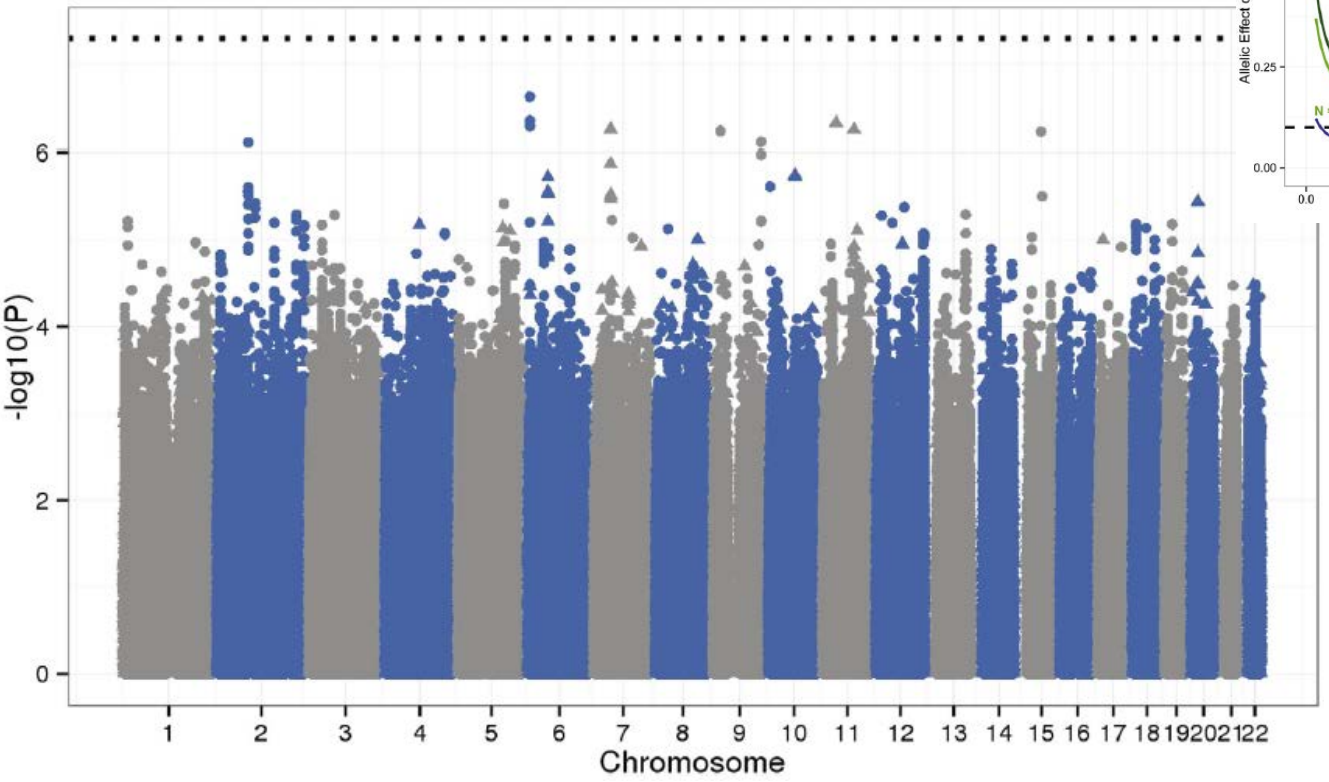
TBX21 encodes for the transcription factor T-bet (T-box expressed rolled in the Childhood

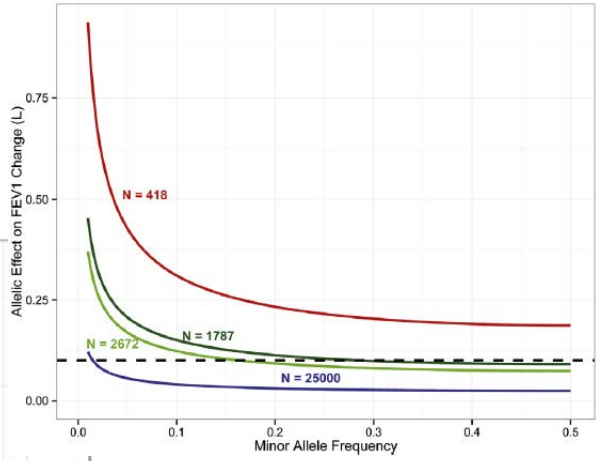
Asthma and lower airway disease

Genetic predictors associated with improvement of asthma symptoms in response to inhaled corticosteroids

Heung-Woo Park, MD, PhD,[a,b] Amber Dahlin, PhD, MMSc,[a] Szeman Tse, MDCM, MPH,[a] Qing Ling Duan, PhD,[a] Brooke Schuemann, BS,[a] Fernando D. Martinez, MD,[c] Stephen P. Peters, MD, PhD,[d] Stanley J. Szefler, MD,[e] John J. Lima, PharmD,[f] Michiaki Kubo, MD, PhD,[g] Mayumi Tamari, MD, PhD,[g] and Kelan G. Tantisira, MD, MPH[a,h]
Boston, Mass, Seoul, Korea, Tucson, Ariz, Winston-Salem, NC, Denver, Colo, Jacksonville, Fla, and Kanagawa, Japan

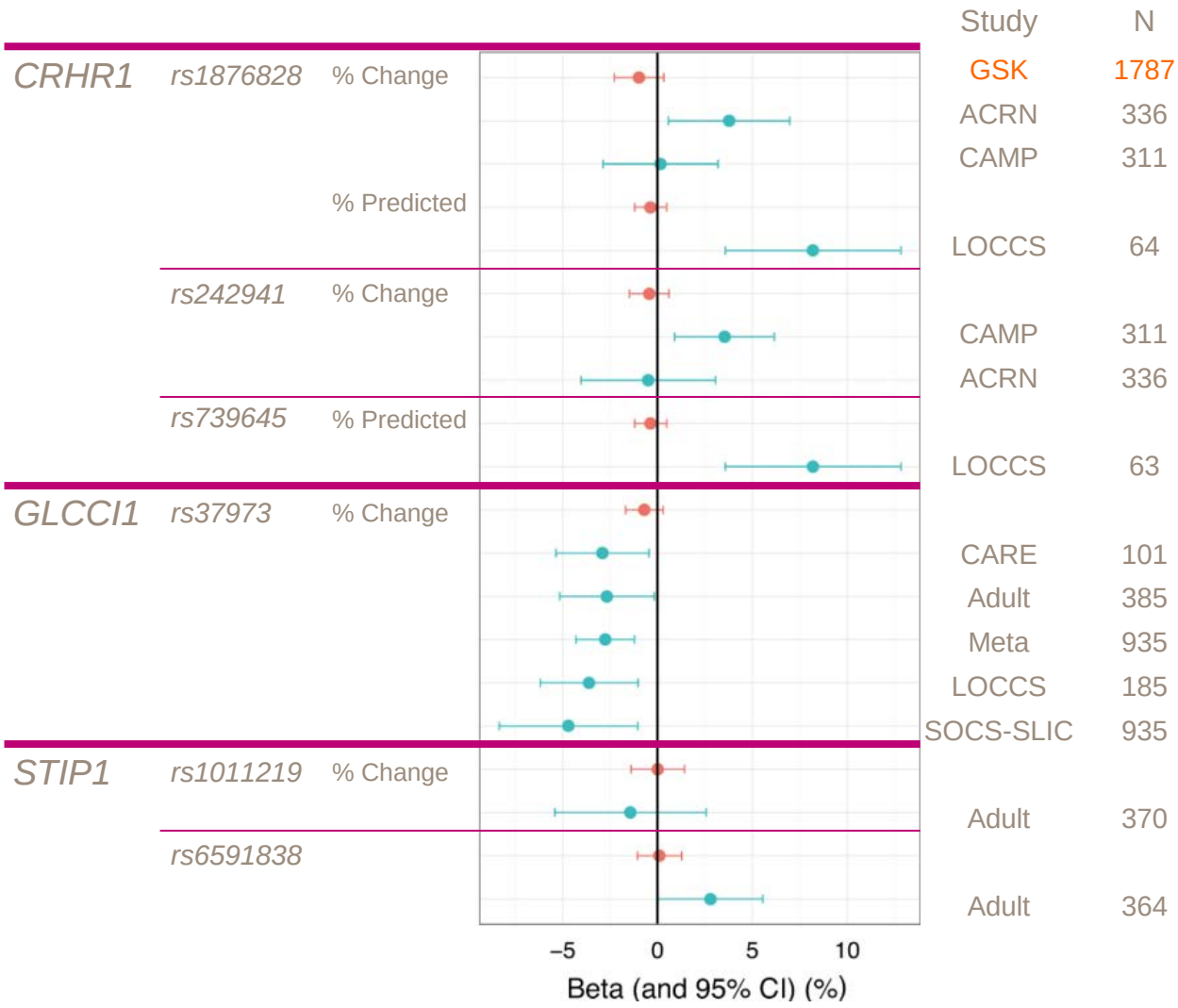
Study of Patient Response to Inhaled Corticosteroids across 7 Clinical Trials in 2672 patients (1787 European)





Mosteller et al. JACI 2016

No Previously Reported Associations with Steroid Response were Statistically Significant at P<0.05



Mosteller et al. JACI 2016

Several GWAS for drug efficacy have been conducted and many high confidence associations found

2,223 GWAS reported in NHGRI/EBI GWAS Catalog as of July, 2015

76 (3.4%) GWAS of drug efficacy

- 41 different drugs, drug classes or combinations

13 (17%) GWAS of drug efficacy with high confidence associations

- 6 of 41 (15%) different drugs, drug classes or combinations

13 high confidence efficacy associations for five drug classes identified by GWAS

Drug	Efficacy Trait	Gene (Allele)
Warfarin	Maintenance dose	*VKORC1* *CYP2C9* (*3, *2, other) *CYP4F2*
Clopidogrel	Platelet aggregation, CV events	*CYP2C19* (*2)
Rosuvastatin	Change in LDL-C	*ABCG2*
Statins	Change in LDL-C	*LPA* *APOE* *SORT1* *SLCO1B1*
Metformin	HbA1c below 7%	*ATM*
Peg-Interferon	Sustained virologic response	*IL28B*

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Compelling candidate gene drug efficacy associations

11 additional associations for 7 drugs not identified or confirmed by GWAS

Drug	Efficacy Trait	Gene (Allele)
Codeine	Pain tolerance	*CYP2D6* (PM)
Tamoxifen	Disease-free survival (inv)	*CYP2D6* (PM)
Eculizumab	Hemolytic activity	*C5*
EGFR TKIs	NSCLC progression	*BIM*
Platinum-based chemotherapy	Ovarian cancer progression and survival	*BRCA1* *BRCA2*
Olaparib	Ovarian cancer complete response	*BRCA1* *BRCA2*
Sulfonylureas	HbA1c/glucose control	*KCNJ11* *ABCC8* *HNF1A*

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Efficacy associations fall into three functional mechanisms

Though with some ambiguity based on current understanding

ADME
<200 genes

Warfarin–*CYP2C9*
Warfarin–*CYP4F2*
Clopidogrel–*CYP2C19*
Rosuvastatin–*ABCG2*
Statin-*SLCO1B1*
Codeine–*CYP2D6*
Tamoxifen–*CYP2D6*

Drug Target
~350 genes

Warfarin–*VKORC1*
Eculizumab–*C5*
Sulfonylureas–*KCNJ11*
Sulfonylureas–*ABCC8*

Disease Mechanism
>>2000 genes

Statin–*LPA*
Statin–*APOE*
Statin–*SORT1*
Metformin–*ATM*
Peg Ifn–*IL28B*
Platinums–*BRCA1/2*
Olaparib–*BRCA1/2*
EGFR TKIs–*BIM*
Sulfonylureas–*HNF1A*

Significant excess of ADME gene associations (OR = 5.5) and underrepresentation of disease gene associations (OR = 0.24; p = 0.001)

What have we learned about the role of genetics in drug safety and efficacy?

- **Drug Safety**
  - Mechanisms primarily through HLA and ADME genes
  - Most HLA genetic risk factors are drug and SAE specific
  - Common genetic risk factors (*alone*) do not accurately predict patient risk for rare SAEs
  - <50% of drug SAEs appear to have *major* genetic risks

- **Drug Efficacy**
  - Mechanisms primarily through ADME, drug targets, and disease genes
  - We expect ~10% of drugs to have genetic predictors of drug efficacy that could influence clinical decision making

Implications for Drug Development

- Probability of success can be improved with tailored analysis strategies
  - Where possible, take advantage of sensitive, quantitative biomarkers of response
  - Balance hypothesis-driven and hypothesis-free approaches
  - Combine data across trials of same or similar drugs
  - Don’t shy away from investigating very effective drugs; this is where the best opportunities are
- With proper consent or secondary use, anonymized clinical trial data could advance understanding of disease genetics

PGx in Drug Development: Advantages and Pitfalls

Advantages

- Cost effective strategies to consent and screen routinely
- Discover early, *hopefully* validate pre-submission
- Opportunity to develop companion diagnostics
- Quickly respond to regulatory and academic questions
- Use unique clinical resources to advance discovery and development

Pitfalls

- Limitations in statistical power and strong temptation to over interpret "suggestive" or just significant findings
- Tendency to focus on trials demonstrating poor efficacy
  - Lowest probability of success
- Low "success" rates require a long view
- Cost

iSAEC Acknowledgments

Scientific Management Committee

- Co-chairs: Matt Nelson (GSK) & **Sally John** (Pfizer)
- Anahita Bhathena & Jeff Warring (Abbott)
- Scott Patterson (Amgen)
- Martin Armstrong & Fredrik Nyberg (Astra-Zeneca)
- Mark Hoffman (Cerner)
- Joe Walker (Daiichi Sankyo)
- Vincent Mooser (GSK)
- Rebecca Blanchard and Ke Hao (Merck)
- Steve Lewitzky (Novartis)
- Clay Stephens (Pfizer)
- Steven Kovacs (Sanofi)
- Leonardo Sahelijo (Takeda)
- Panos Deloukas (Wellcome Trust/Sanger Centre)
- Jan Johannessen (FDA)

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- **Tom Urban** (Duke & UNC)
- Munir Pirmohamed (Liverpool)

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- **Yufeng Shen**
- Aris Floratos
- **Paola Nicoletti**
- Andrea Califano

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- Scott Patterson [Amgen]
- Rick Scheyer & Joe Walker (Daiichi Sankyo)
- Vincent Mooser (GSK)
- Peter Shaw (Merck)
- Joanne Meyer (Novartis)
- Aidan Power (Pfizer)
- Robert Dix (Sanofi)
- Leonardo Sahelijo (Takeda)
- Michael Dunn (Wellcome Trust)

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- EUDRAGENE -- Mariam Molokhia (Kings College, UK)
- ITCH -- Munir Pirmohamed (Liverpool, UK)
- TdP -- Elijah Behr (SGUL) & Dan Roden (Vanderbilt)
- IBD –- Tariq Amend (Exeter, UK)
- DIRECT – Ravi Mehta (UCSD)

DILIN

- Paul Watkins (Hamner)

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GSK

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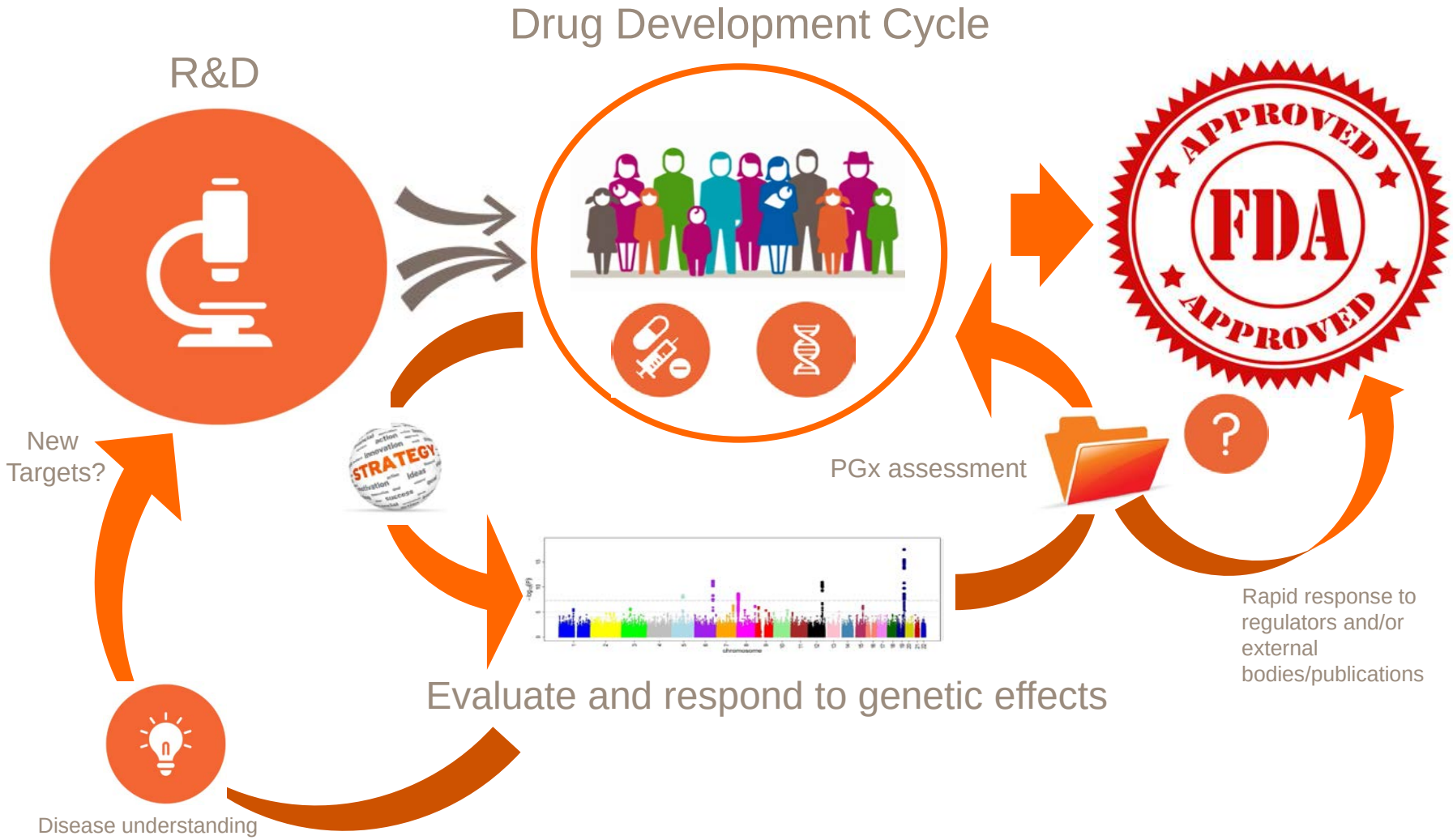
- Arlene R. Hughes (currently at PAREXEL)
- Charlie Cox
- Stephanie L. Chissoe
- Chun-Fang Xu
- **Dawn M. Waterworth**

Our PGx vision: To identify genetic predictors of response and safety in time to inform medicine development decision making

Driven by asset specific strategies, targeting key impact points



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PNAS

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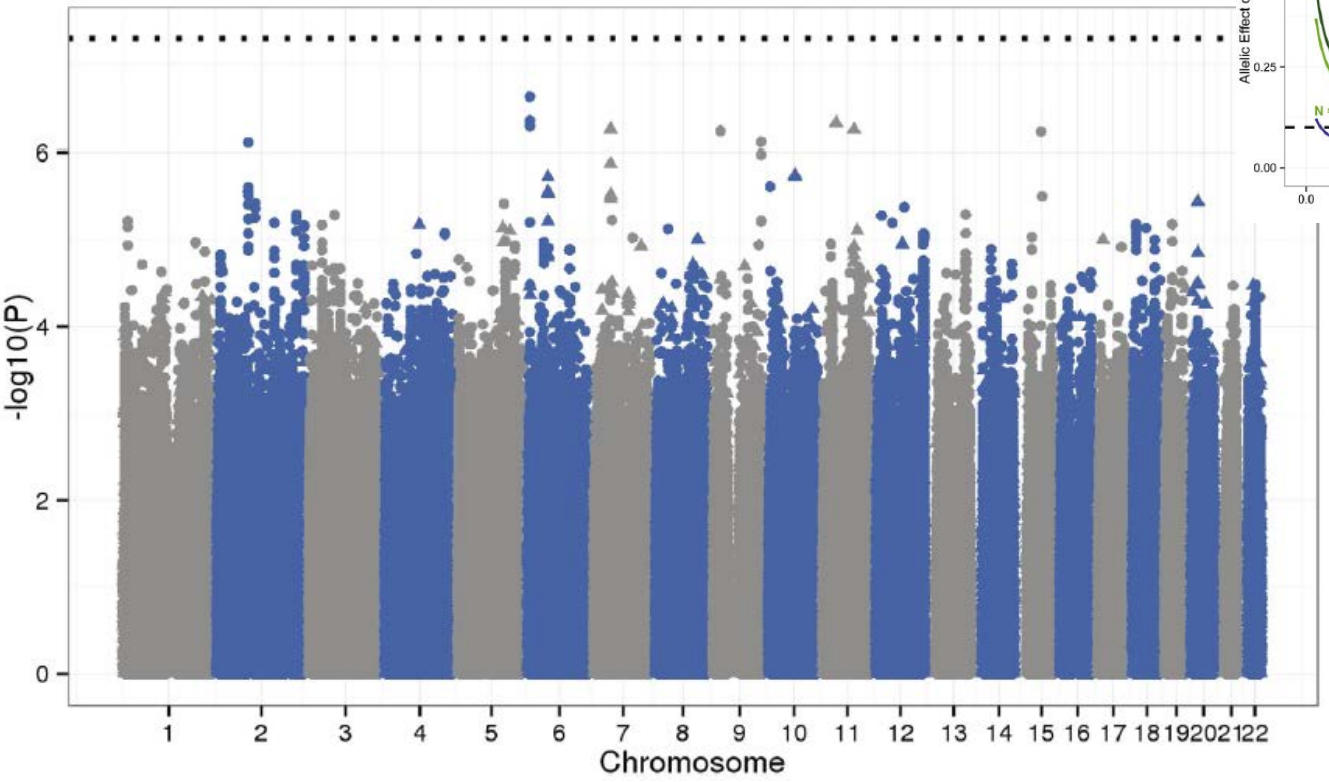
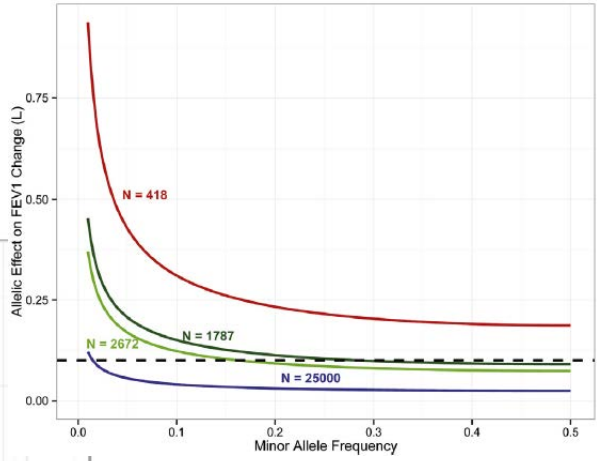
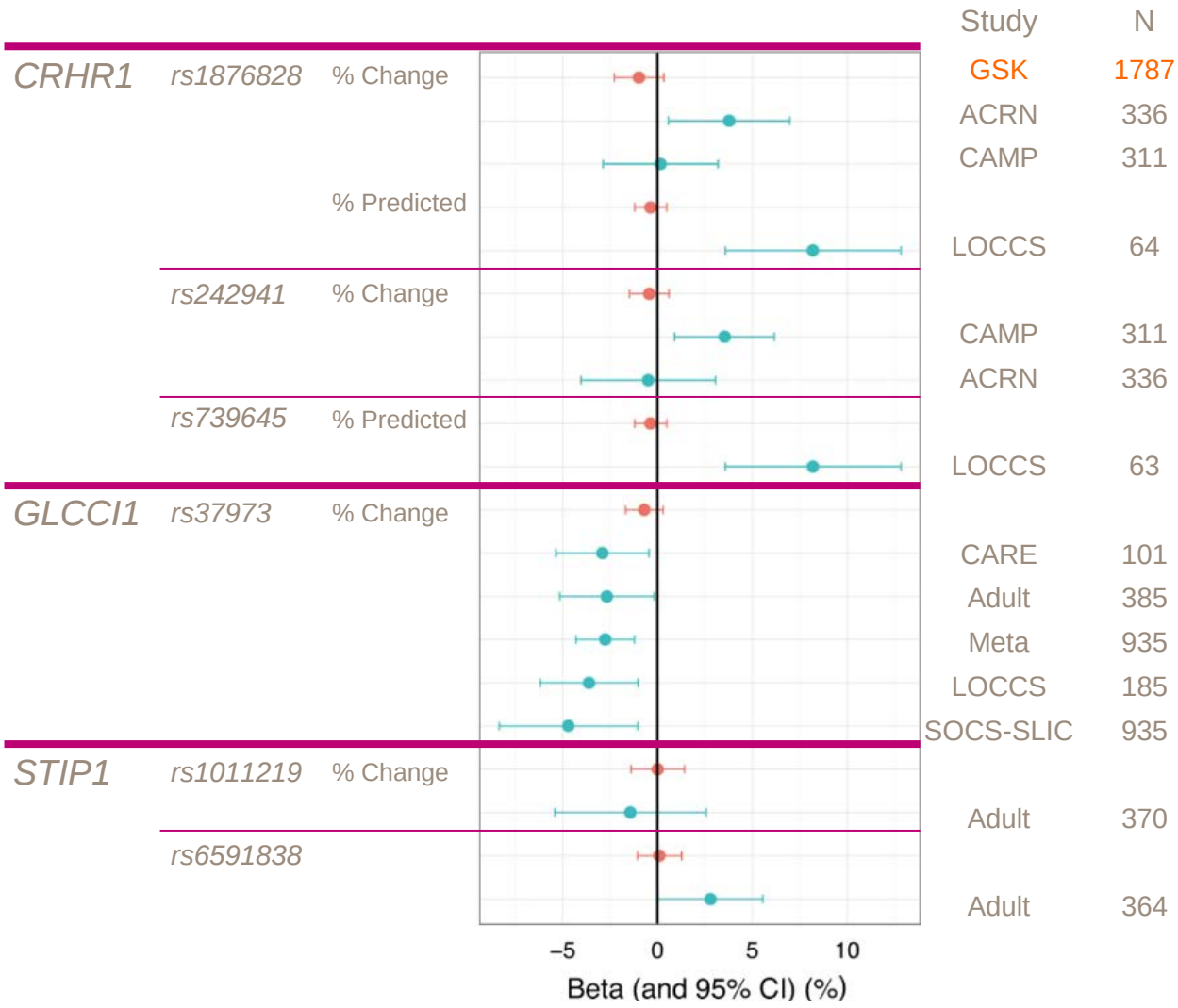
Study of Patient Response to Inhaled Corticosteroids across 7 Clinical Trials in 2672 patients (1787 European)





Mosteller et al. JACI 2016

No Previously Reported Associations with Steroid Response were Statistically Significant at P<0.05



Mosteller et al. JACI 2016

How often do we expect drugs to have efficacy genetic effects with potential to inform patient treatment?

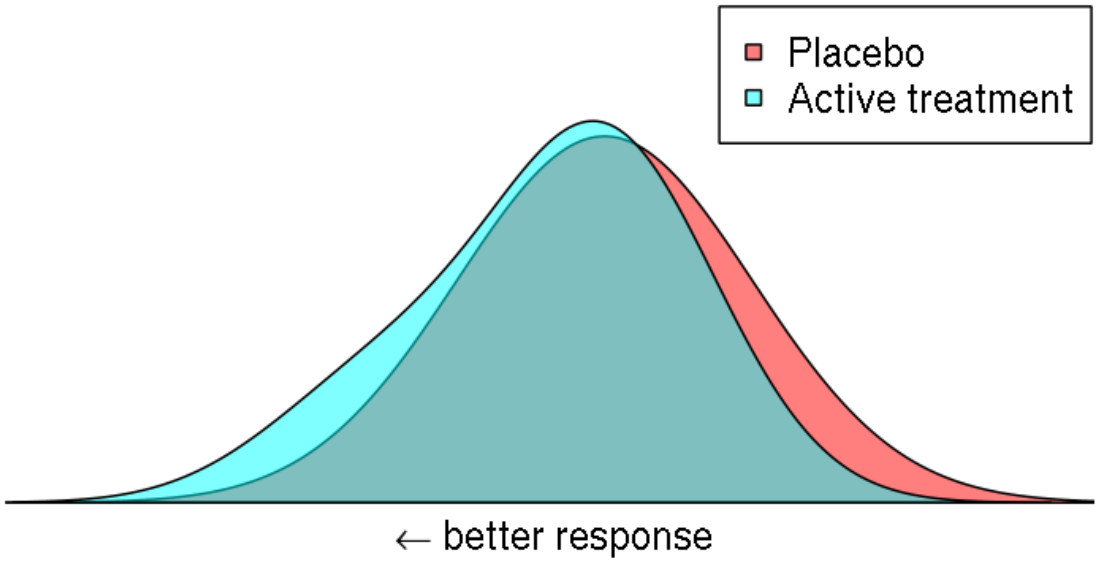
15% × 64% = 8.1% (2.0–17.1%)

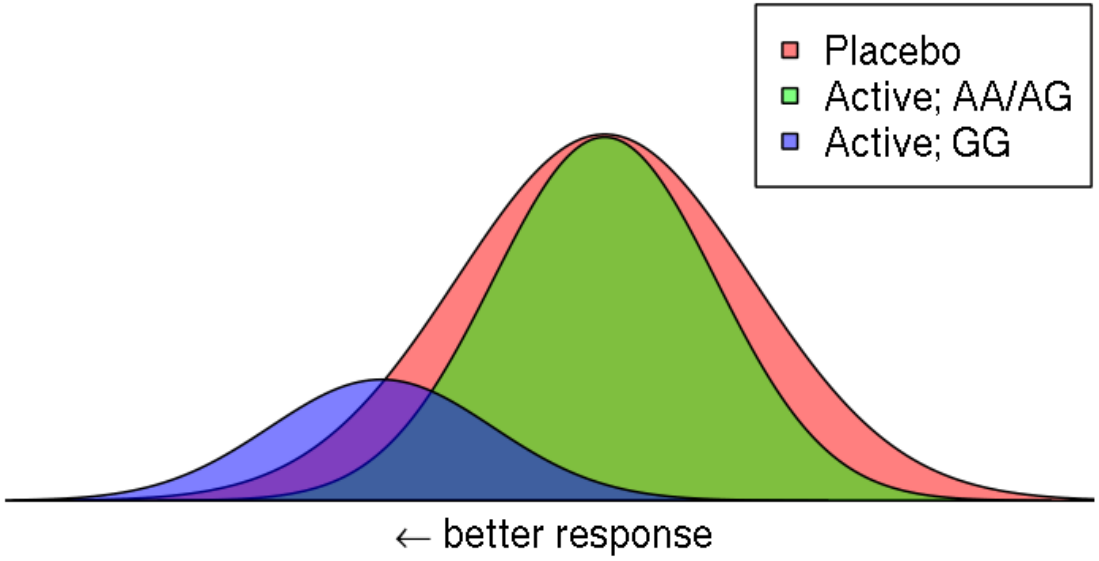
6/41 drugs/classes with effect found by GWAS

5/9 drugs/classes with common genetic effects with *potential* clinical utility

Expected drugs having genetic effects with *potential* clinical utility

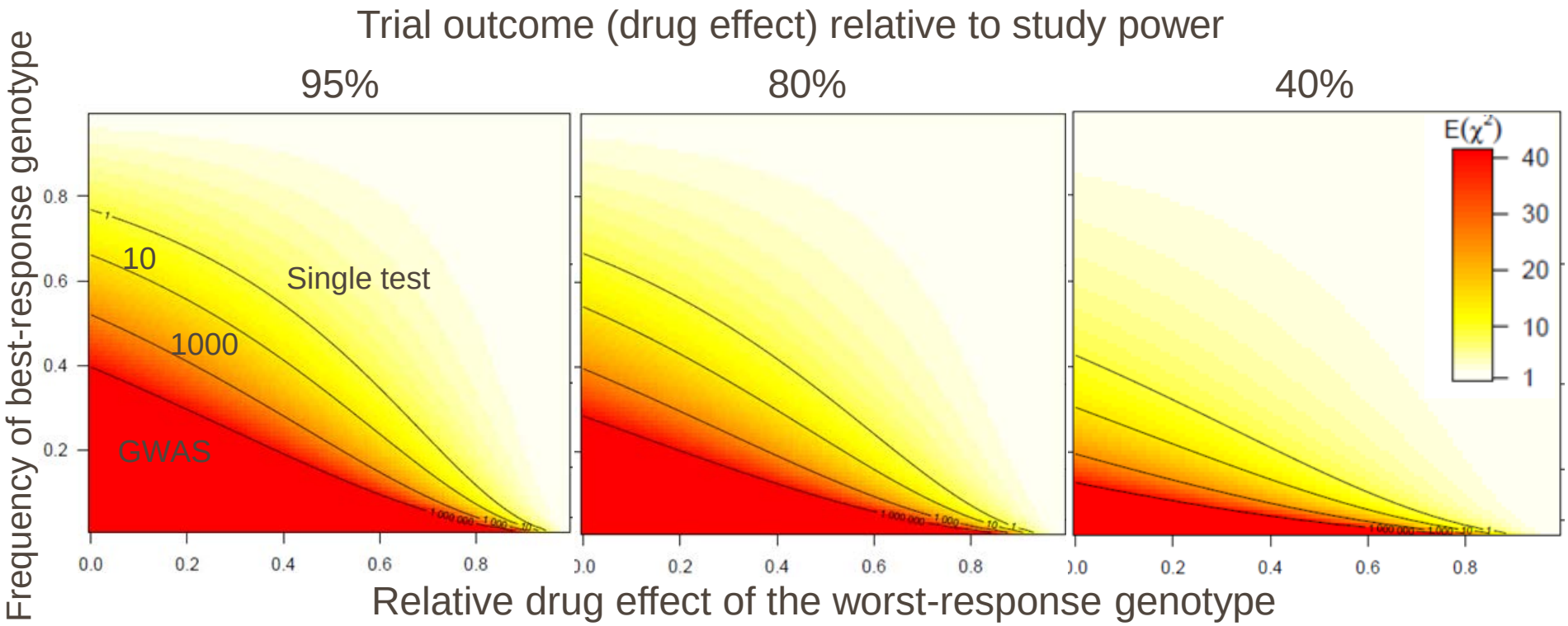
Efficacy effects, and the power to identify them, are constrained by drug effect sizes observed in trials





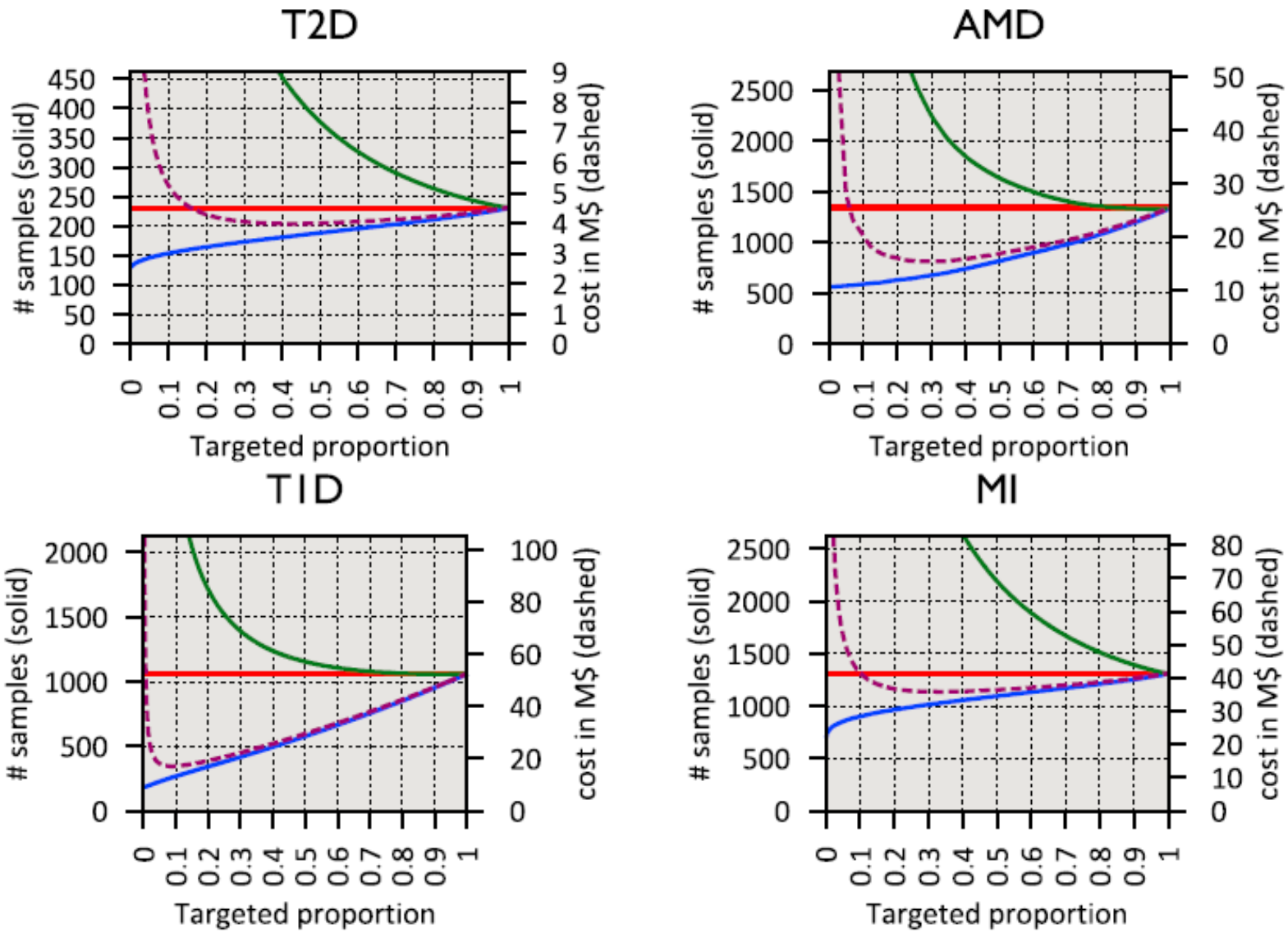
Efficacy effects, and the power to identify them, are constrained by drug effect sizes observed in trials

$$\mathrm{NCP}_{\mathrm{PGx}} \leq \mathrm{NCP}_{\mathrm{treatment}} \times 2\frac{1-p_{\mathrm{carrier}}}{p_{\mathrm{carrier}}}$$



1. We should be mindful how we pay our multiple test penalities
2. Very few situations where PGx will rescue a failed trial
3. ~~Trials with larger drug~~ effects have more power to find efficacy PGx
4. Combine data across trials to increase PGx power

Enrichment by genetic risk can result in more efficient preventive clinical trials



The role of Genetics in drug response

Drug Safety

- Important role for genetics in immune-mediated and exposure-related adverse events
- 5 key discoveries within GSK
- External discoveries for 2 GSK drugs

Drug Exposure

- Expectations from regulators that PGx studies will be conducted to understand PK variability
- Avoidance of key polymorphic enzymes have reduced risk

Drug Efficacy*

- 5-20% of drugs estimated to have clinically meaningful PGx effects
- Known mechanisms focus on ADME, drug targets, and disease genes
- Larger effects can be

Be patient focused

*"*The genetics of drug efficacy: opportunities and challenges*": Nelson, M. *et al.*, **Nat Rev Genet (2016) 17: 197**