Pharmacogenomics Translation: From Discovery to Confirmation to Clinical Utility

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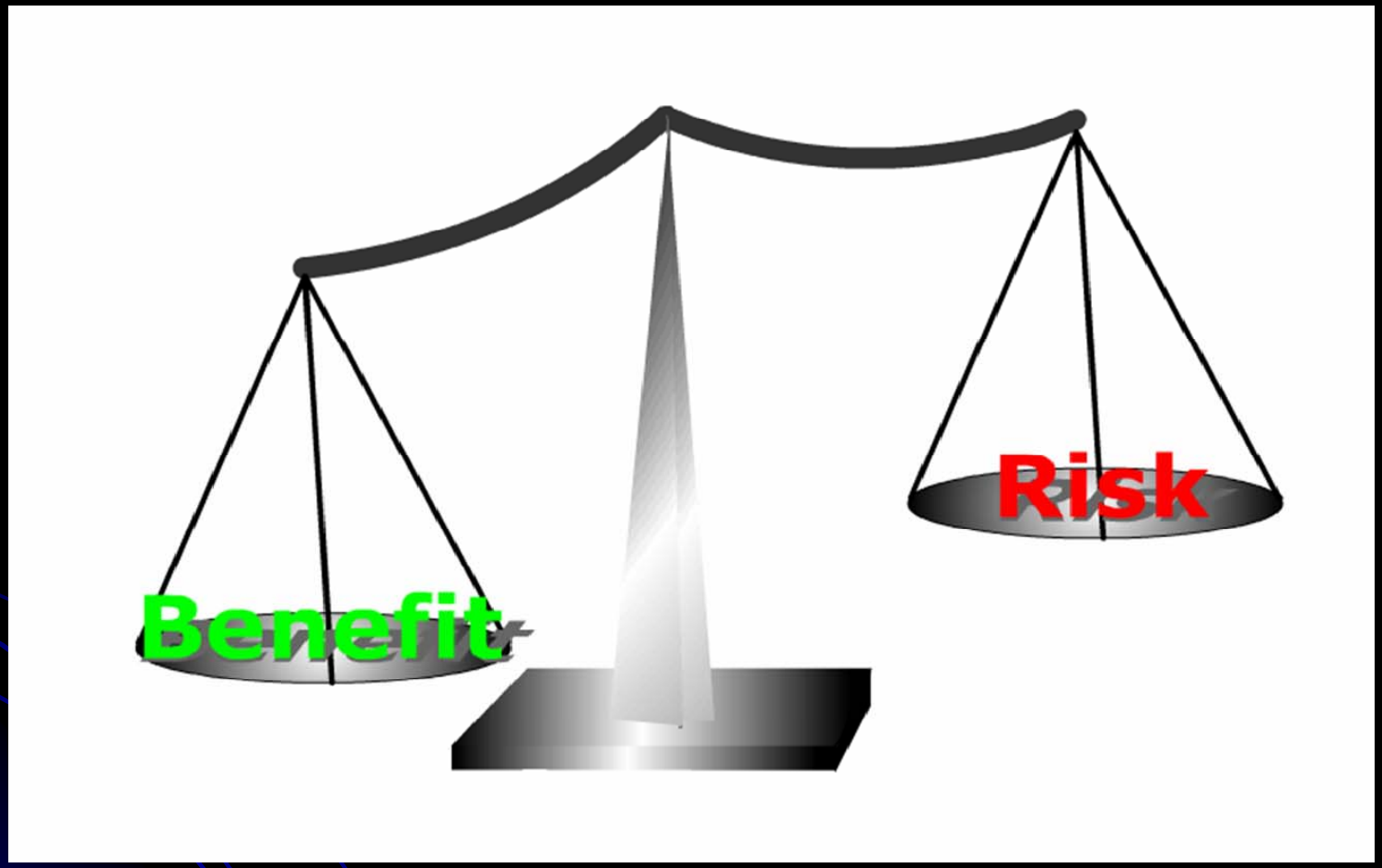
Public Health Genomics Interest Group, Feb 25, 2009

Pharmacogenomics (PGx)

- Improve patient outcome by maximizing response and minimizing adverse events *using an individual's genetic profile*

Goal of Pharmacogenomics



Optimize Therapy So Benefits Outweigh the Risks

Adverse Drug Reactions (ADRs) in Drug Therapy

- More than 2 million people in the U.S each year experience ADRs resulting in over 100,00 deaths
- Types of ADRs
  - dose-related (Type A)
  - non-dose-related (Type B)
- Many ADRs are associated with variants in the sequence of metabolizing enzymes, resulting in fast or slow metabolizers.
- It is now possible to identify other genomic markers that are associated with specific ADRs
  - Safety Pharmacogenomics

Abacavir (ABC)

- A nucleoside analog reverse transcriptase inhibitor used to treat HIV and AIDS
- Available under the trade name Ziagen (GlaxoSmithKline)
- Used in combination formulations
  - Trizivir (abacavir, zidovudine and lamivudine)
  - Kivexa/Epzicom (abacavir and lamivudine)
- Approved by the FDA on December 18, 1998

Hypersensitivity Syndrome (HSR)

- 5 - 8% of patients receiving ABC develop HSR
- Symptoms include fever, rash, GI, lethargy and malaise
- Can be severe and life threatening
- Usually occur within 6 weeks
- Resolves on stopping ABC
- HSR reappears on rechallenge (contraindicated)

Risk Factor Analysis

Case-control design

- 5332 patients exposed to ABC; 197 (3.7%) cases of HSR

Compared demographic, clinical and laboratory characteristics:

- HSR among black patients was lower compared with other ethnic groups (OR = 0.59; 95% CI, 0.38-0.91)
- HSR among patients who received previous therapy for HIV-1 infection was lower compared with those receiving therapy for the first time (OR = 0.58; 95% CI, 0.44-0.78)

- The only characteristics identified as prognostic factors for HSR were previous antiretroviral treatment status and black race

Cutrell et al. Ann Pharmacother 2004

Genetic Risk Factors

- 150 PGx markers in 12 candidate genes implicated in immune response and drug metabolism
- HLA-B*5701 was identified

Table 2 Association of *HLA-B*5701* with ABC HSR in GSK study CNA30027[9] and Western Australian HIV cohort[10] (2002)

	White		*Black*		*Other*	
	Cases (N)	*Controls or ABC-tolerant patients*[a] (N)	*Cases* (N)	*Controls* (N)	*Cases* (N)	*Controls* (N)
GSK study CNA30027	55% (36/65)	1% (1/80)	0 (0/9)	0 (0/18)	10% (1/10)	NA
Western Australian HIV cohort	78% (14/18)	2%[b] (4/167)				

Abbreviations: ABC, abacavir; GSK, GlaxoSmithKline; HLA, human leukocyte antigen; HSR, hypersensitivity; NA, not applicable.
[a]GSK CNA30027 was a case–control investigation, whereas the Western Australian HIV investigation was an observational cohort study of clinically suspected ABC HSR cases and patients who received ABC without evidence of ABC HSR.
[b]20% of ABC-tolerant patients in the Western Australian HIV cohort were of non-Caucasian ancestry (all cases were Caucasian).

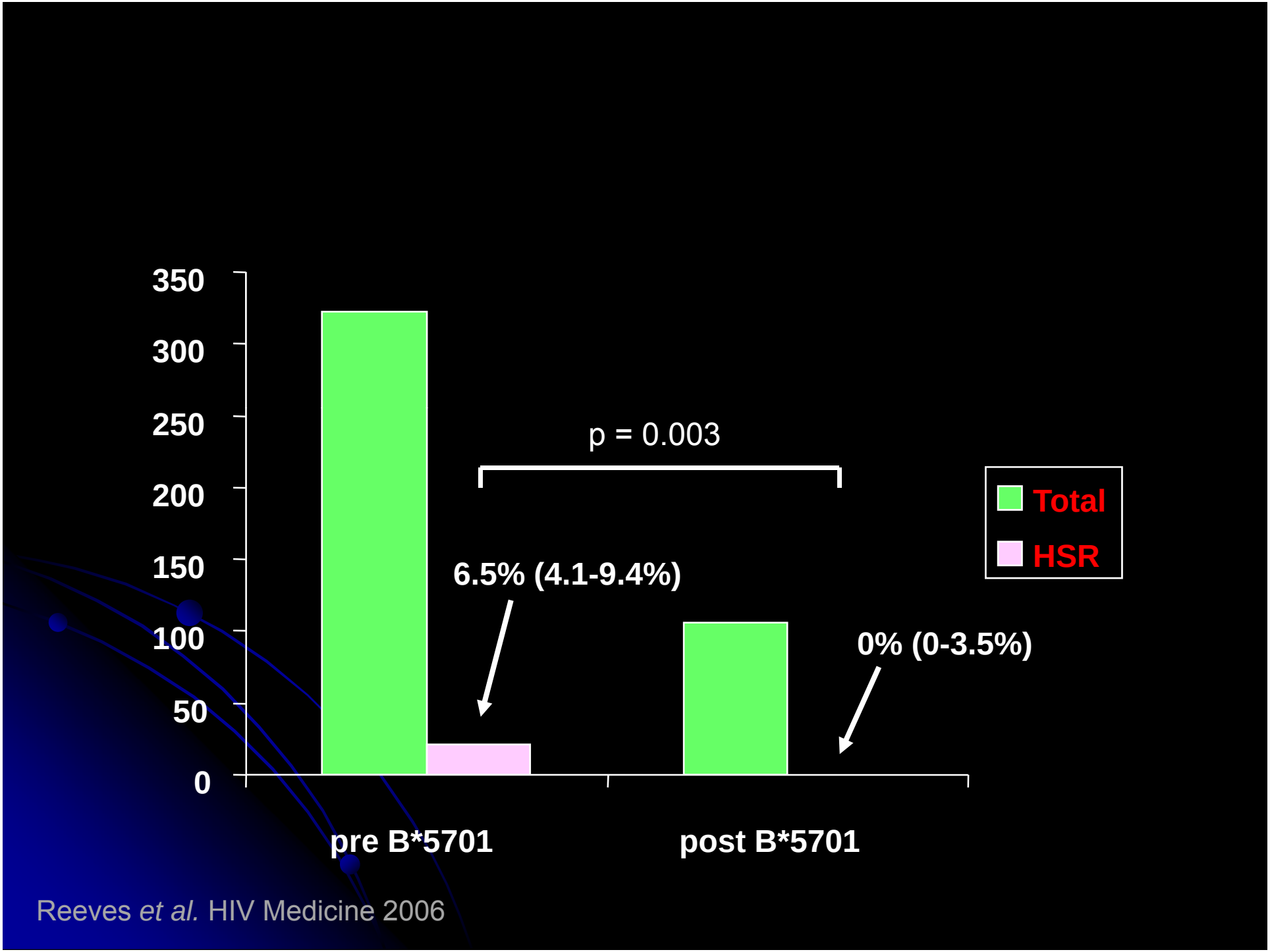
Hetherington et al. Lancet 2002 359;1121-22.
Mallal et al. Lancet 2002:359, 727–732.

Table 3 Performance characteristics of *HLA-B*5701* in combined GSK data sets: clinically diagnosed ABC HSR

	Cases (N)	*Controls (N)*	*Genotypic P-value*	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*	*Odds ratio*	*Odds ratio, 95% CI*
White standard	444	486	7.53×10^{-73}	50	98	53	97	42.1	(22.8, 77.8)
Black standard	50	67	0.162	8	99	14	96	4.3	(0.7, 28.3)
Hispanic standard	63	70	1.22×10^{-5}	22	100	67	95	41.3	(2.4, 708.7)
Thai standard	7	102	6.29×10^{-6}	57	100	87	98	263.6	(11.8, 5909.1)

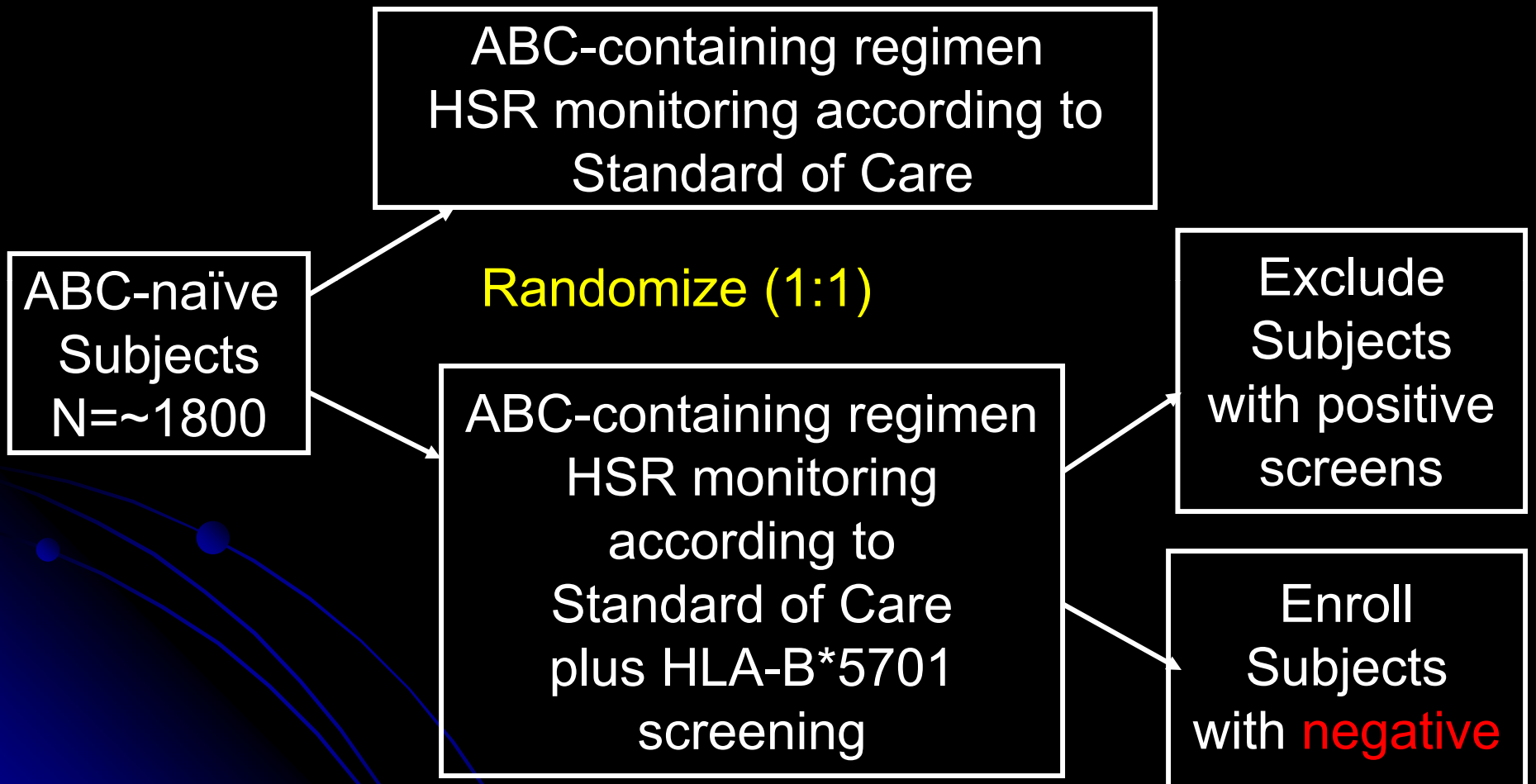
Abbreviations: ABC, abacavir; CI, confidence interval; GSK, GlaxoSmithKline; HLA, human leukocyte antigen; HSR, hypersensitivity; NPV, negative predictive value; PPV, positive predictive value.
Includes subjects from GSK studies CNA30027, CNA30032, CNA30021, CNA30024 and EPV40001.

Hughes et al. Pharmacogenomics Journal 2008

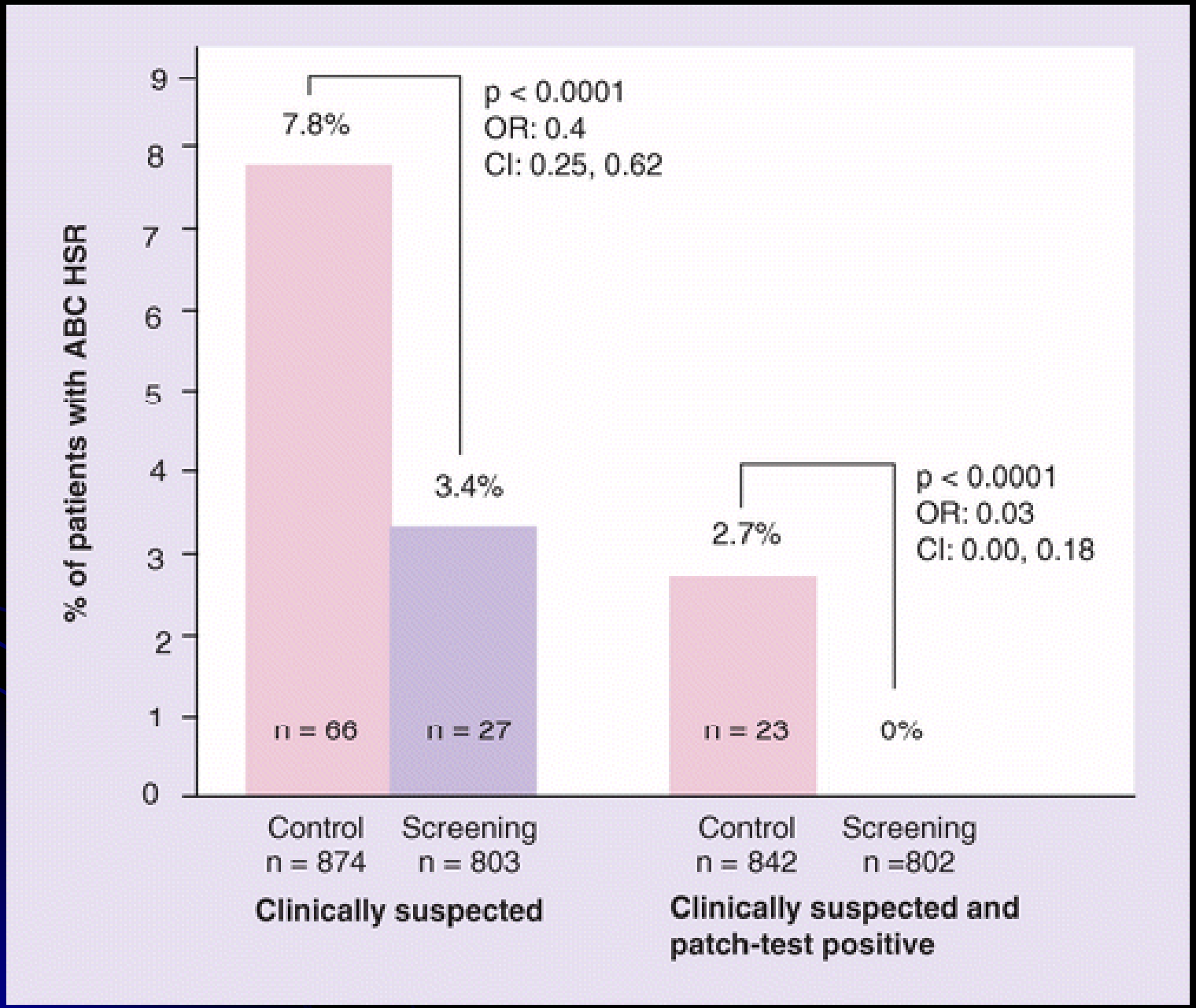


Reeves *et al.* HIV Medicine 2006

PREDICT-1 Prospective PGx Randomized Clinical Trial



Mallal et al. NEJM 2008


% of patients with ABC HSR
9
8
7
6
5
4
3
2
1
0
7.8%
p < 0.0001
OR: 0.4
CI: 0.25, 0.62
3.4%
2.7%
p < 0.0001
OR: 0.03
CI: 0.00, 0.18
n = 66
n = 27
n = 23
0%
Control
n = 874
Screening
n = 803
Control
n = 842
Screening
n =802
Clinically suspected
Clinically suspected and
patch-test positive

- GSK SHAPE
- Retrospective, case control in white and black subjects
- 40 white and 40 black clinically-suspected cases of HSR
- 200 white and 200 black controls
- Primary endpoint
  - Sensitivity of HLA-B*5701 among subjects with
    - clinically-suspected HSR
    - skin patch test positive HSR

Saag et al. Clin Infect Dis 2008

Table 4 Sensitivity and specificity of *HLA-B*5701* in US white and black HIV patients (SHAPE study)

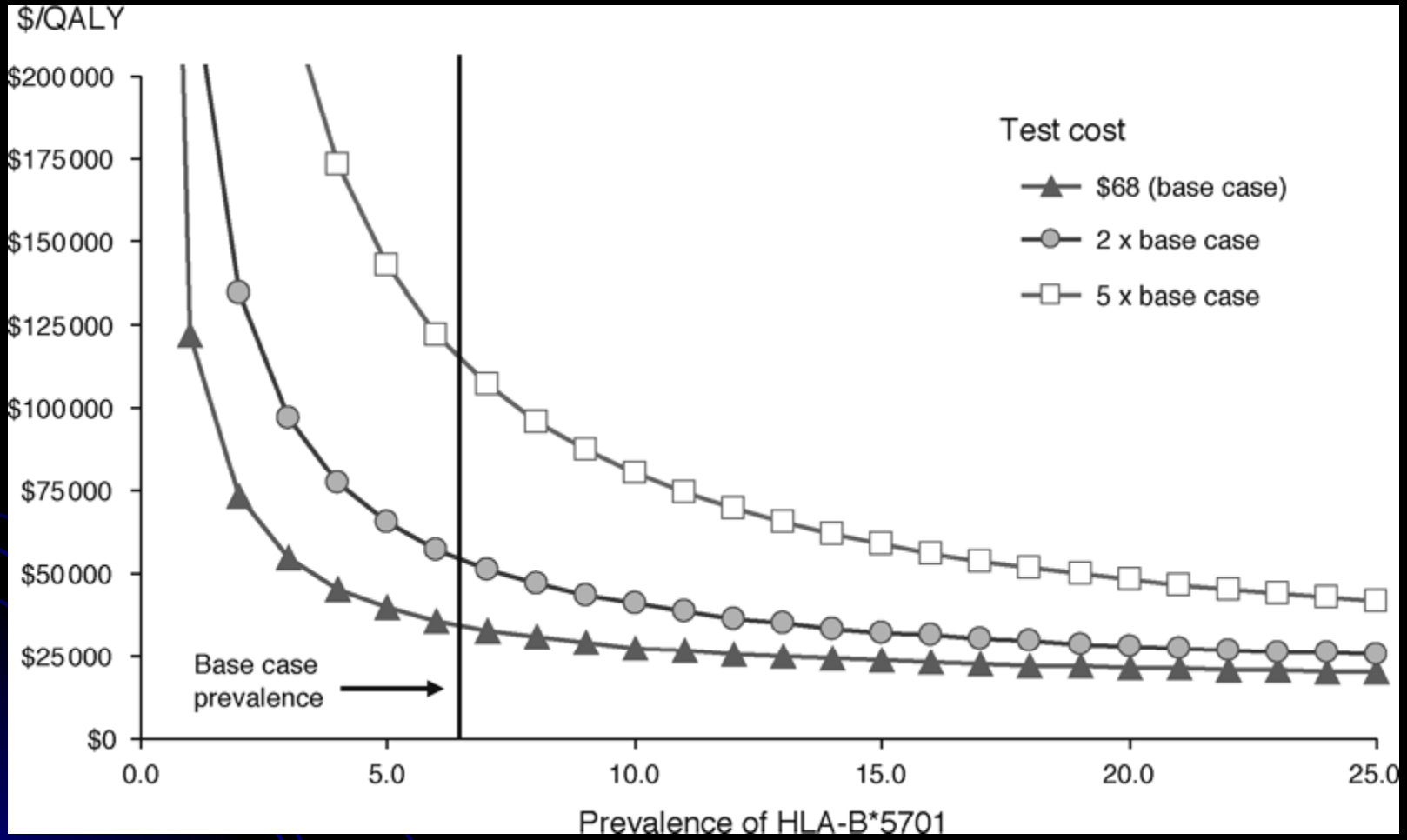
	White	*Black*
Sensitivity: clinically suspected HSR (*N*)	44% (56/127) (95% CI: 35, 53)	14% (10/69) (95% CI: 7, 25)
Sensitivity: immunologically confirmed HSR[a] (*N*)	100% (42/42) (95% CI: 92, 100)	100% (5/5) (95% CI: 48, 100)
Specificity (*N*)	96% (194/202) (95% CI: 92, 98)	99% (204/206) (95% CI: 97, 100)

Saag et al. Clin Infect Dis 2008

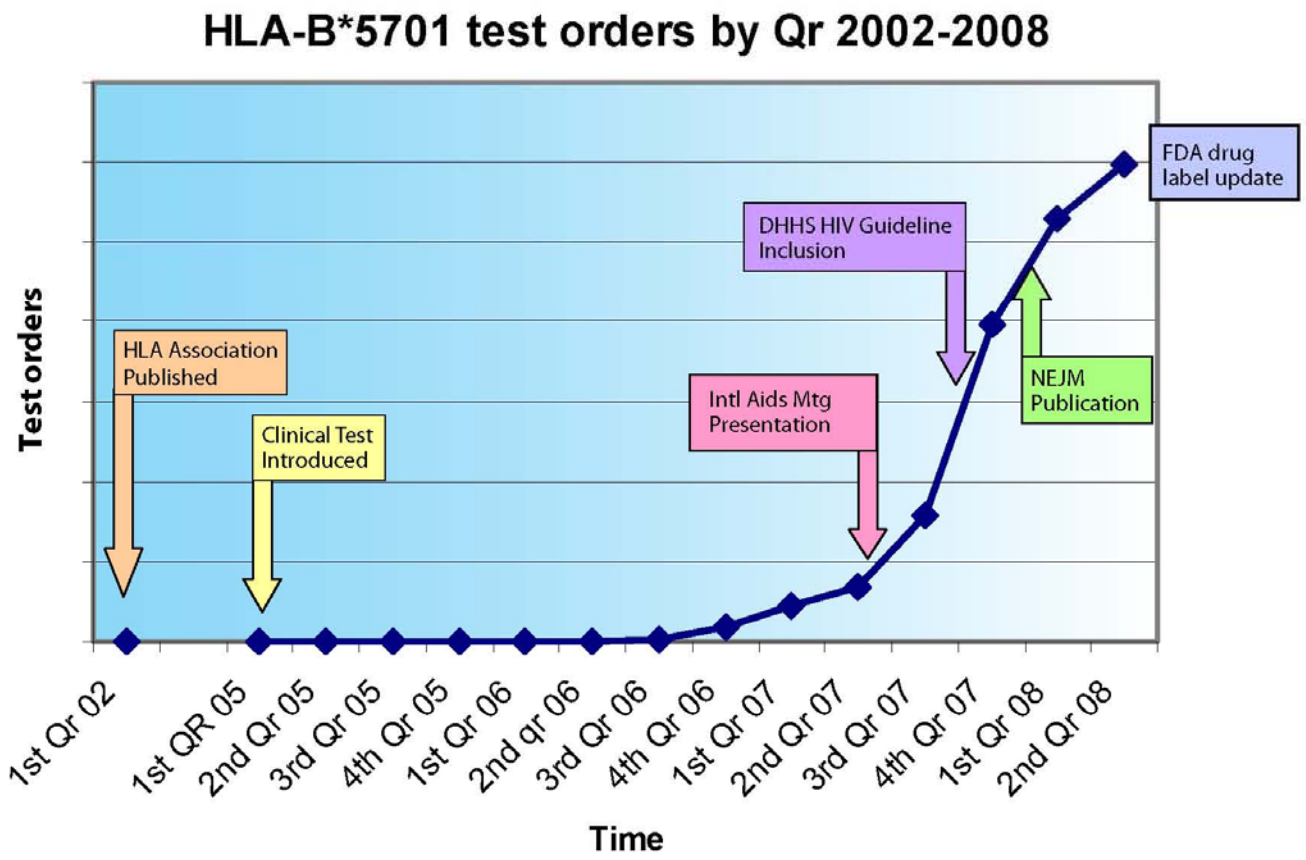
WARNING: HYPERSENSITIVITY REACTIONS/LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY

See full prescribing information for complete boxed warning.

- **Serious and sometimes fatal hypersensitivity reactions have been associated with ZIAGEN (abacavir sulfate). (5.1)**
- **Hypersensitivity to abacavir is a multi-organ clinical syndrome. (5.1)**
- **Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir. (5.1)**
- **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 abacavir, NEVER restart ZIAGEN or any other abacavir-containing product. (5.1)**
- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues. (5.2)**



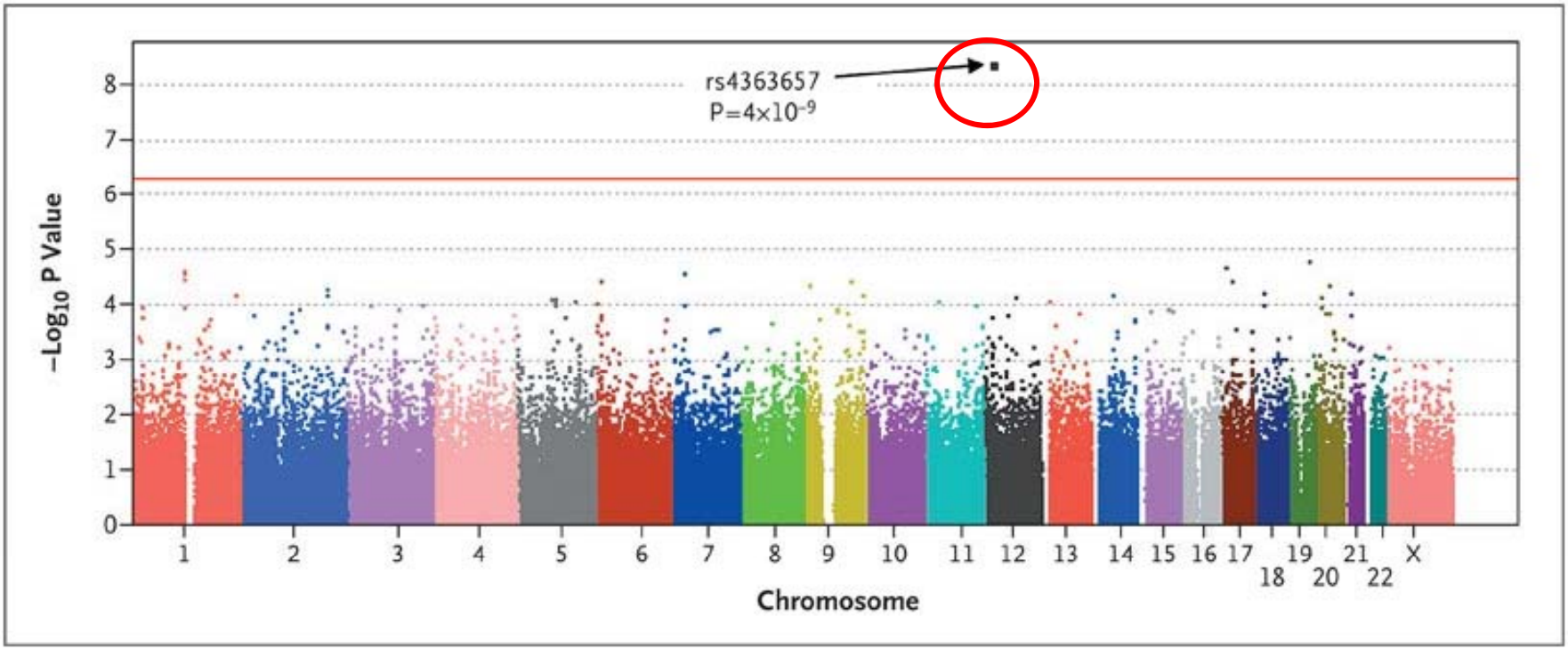
Schackman BR et al. AIDS. 2008 Oct 1;22(15):2025-33.



Lai-Goldman M and Faruki H. Genetics in Medicine 2008

PGx Statin-Induced Myopathy

GWAS, 85 simvastatin myopathy patients and 90 matched controls



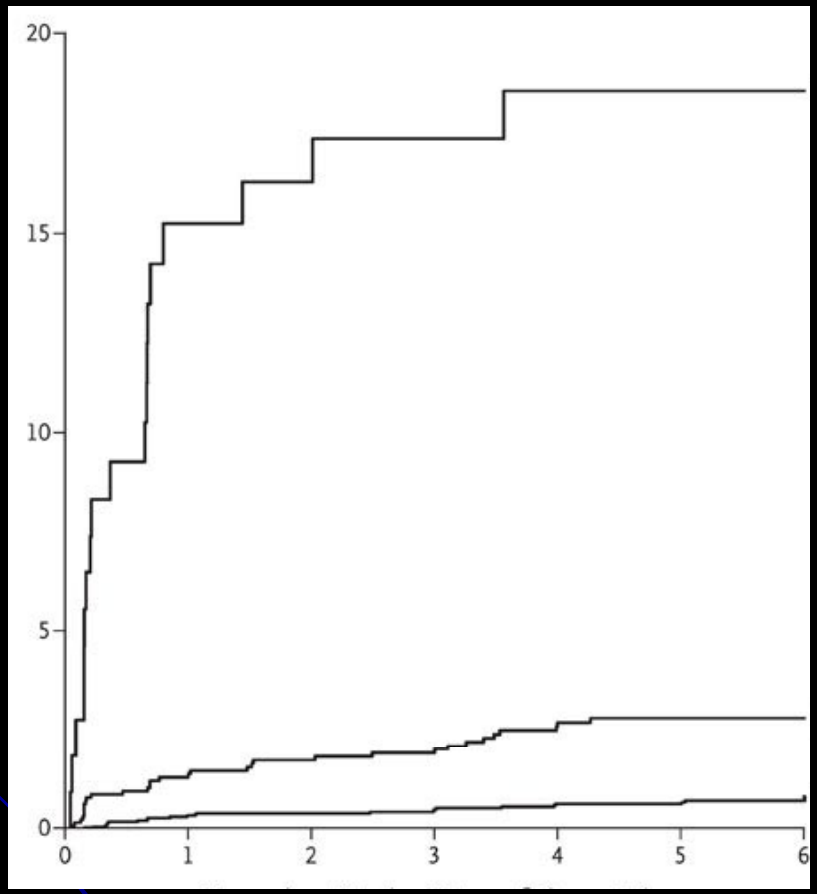
The SEARCH Collaborative Group. NEJM 2008

PGx of Statin-Induced Myopathy

- *SLCO1B1* SNP rs4363657, $p = 4 \times 10^{-9}$ (Minor Allele Frequency ~15%)
- OR for myopathy
  - 4.5 (CI 2.6-7.7) for one C allele
  - 16.9 (CI 4.7-61.1) for CC allele
- ~60% of myopathy cases explained by this allele

The SEARCH Collaborative Group. NEJM 2008

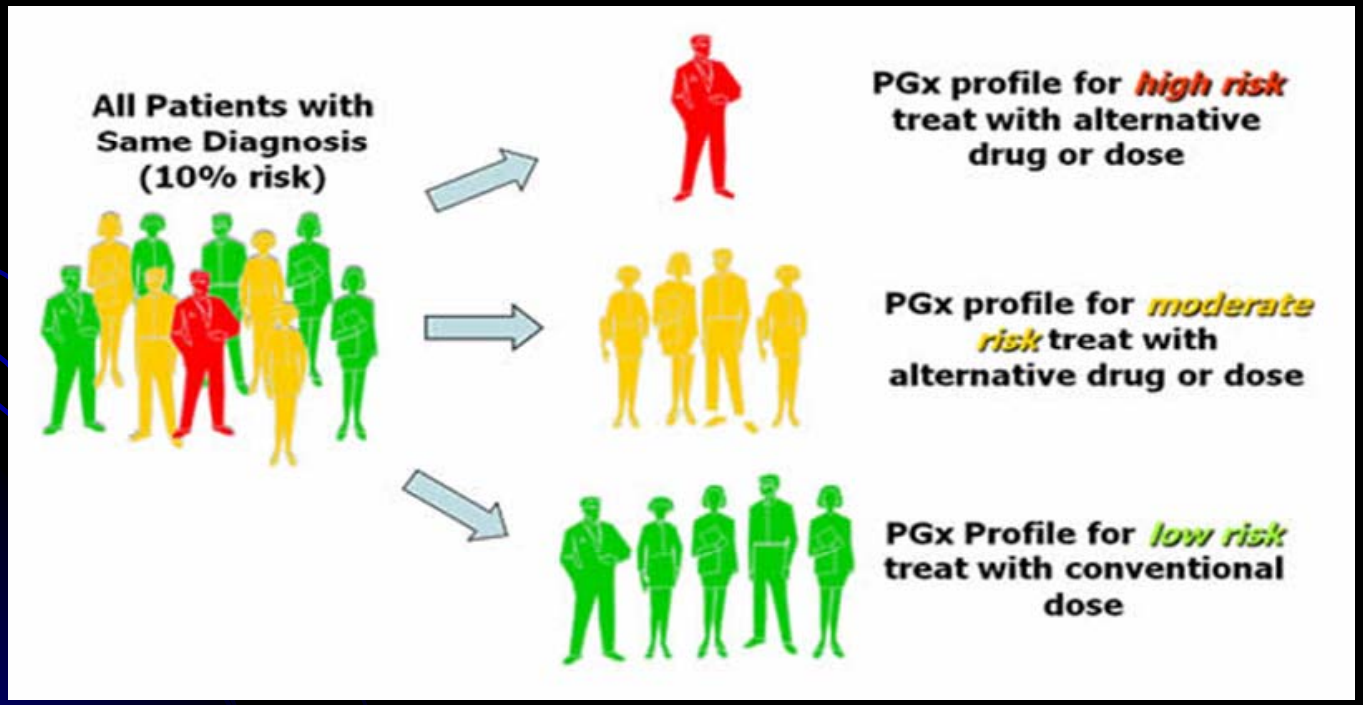
PGx of Statin-Induced Myopathy



The SEARCH Collaborative Group. NEJM 2008

Trans-NCI Pharmacoepidemiology and Pharmacogenomics Working Group (PPWG)

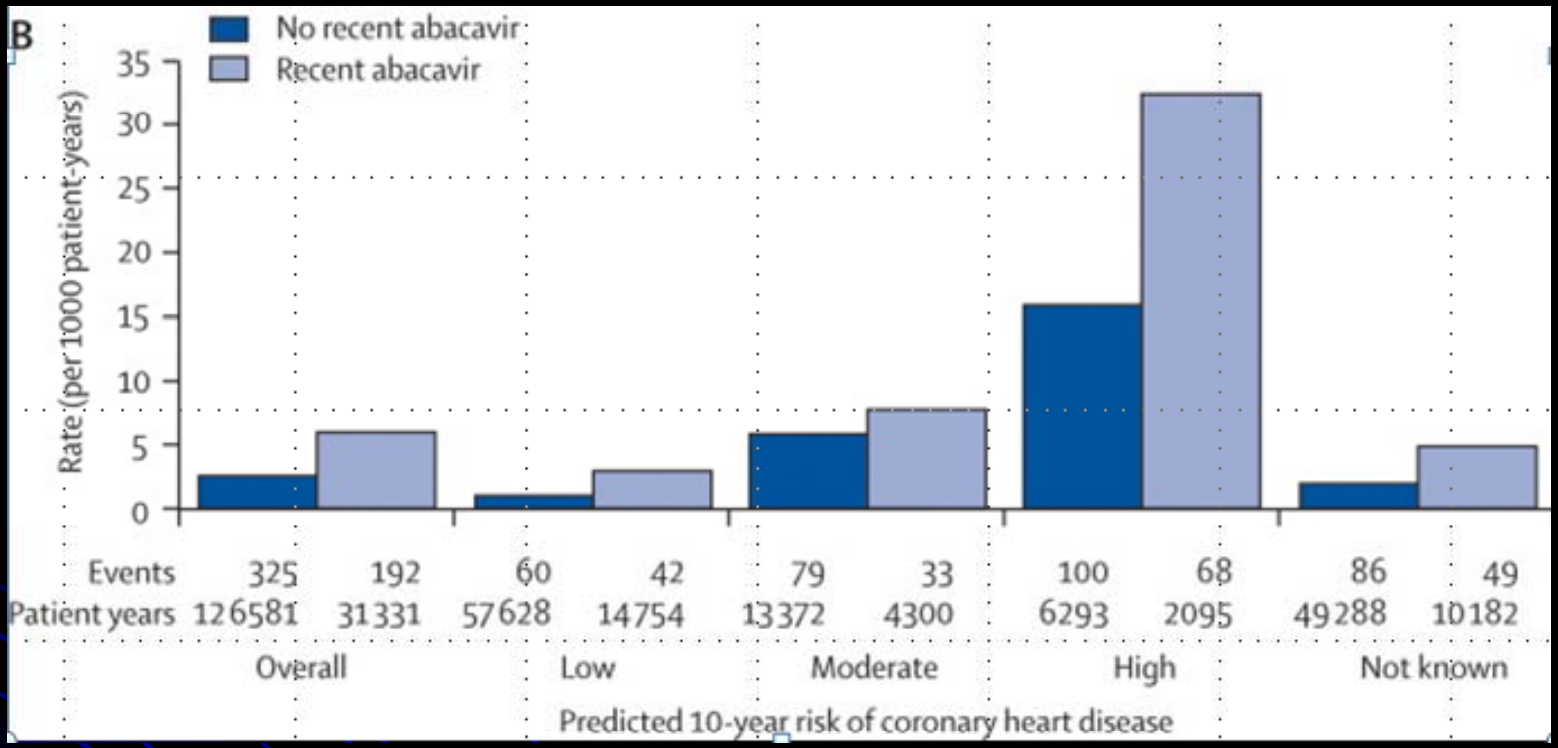
Identify specific epidemiologic, clinical, and genomic profiles that could enhance response to therapy and minimize toxicity



Summary

- We can identify and translate PGx markers of drug safety into clinical practice
  - RCTs and observational studies may be needed
  - This can be done throughout all phases of drug development and post-approval
- PGx marker evidence for physicians ≠ guideline committees ≠ regulators ≠ payers

Abacavir and Myocardial Infarction RR=1.90 (1.47-2.45)



D:A:D Study Group. Lancet 2008

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