Pharmacogenomics

Personalizing Asthma and Allergy Therapy

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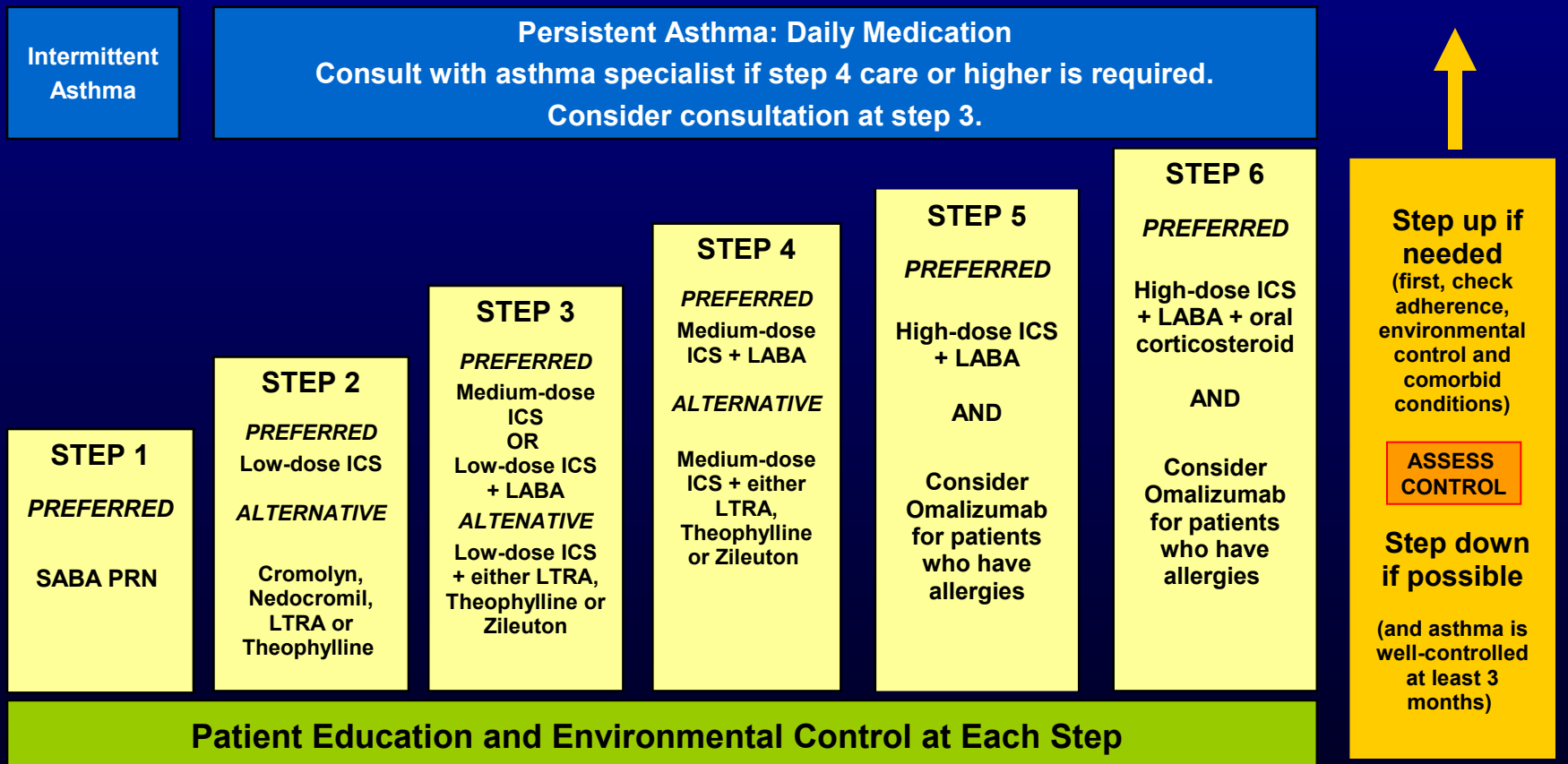
Too much of a good thing?

- 27 yo male with severe asthma with multiple hospitalizations
- Unable to reduce prednisone below 15 mg/d
- Uses nebulized and MDI beta-agonists 10-12 times a day
- Unable to tolerate inhaled corticosteroids because they make him wheeze
- Morbidly obese with scattered wheezes
- FEV1 70% predicted
- 7% eosinophils

- Switched to high dose ipratropium bromide (anticholinergic) and montelukast (leukotriene antagonist)
- Beta-agonists tapered
- 3 months later
  - Able to tolerate ICS
  - Off oral prednisone
- No hospitalizations in last 8 years

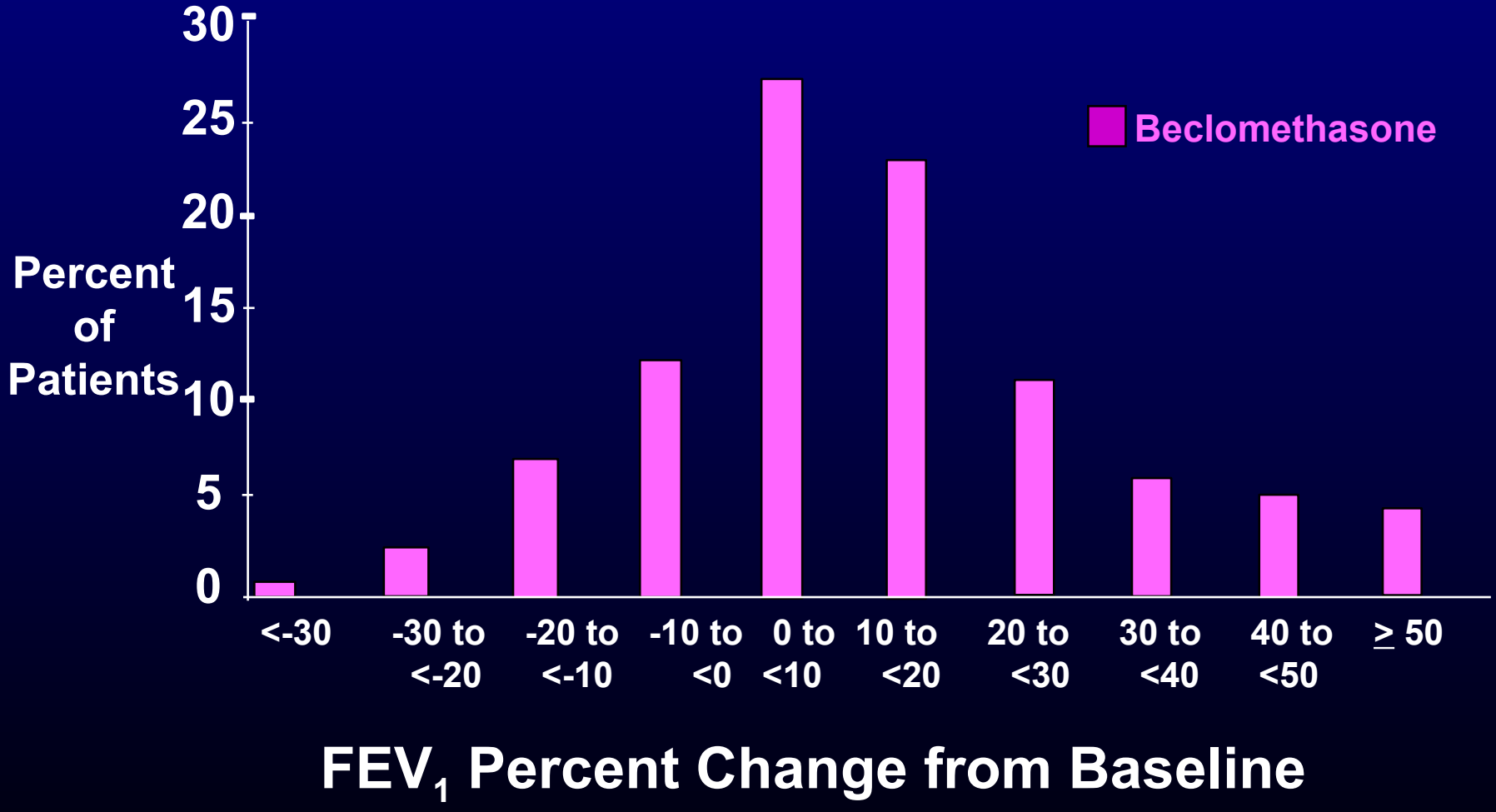
Stepwise Approach for Managing Asthma in Patients ≥ 12 Years of Age



- Quick-Relief Medication for All Patients:
- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of systemic oral corticosteroids may be needed.
- Caution: Increasing of β-agonist or use >2x/week for symptoms control indicates inadequate control and the need to step up treatment

NHLBI. National Asthma Education and Prevention Program. Expert Panel Report 3: page 517. Available at: http://www.nhlbi.nih.gov/guidelines/index.htm. Accessed 2.8.07.

45% of Patients Do Not Have an FEV_1 Response to ICS



Malmstrom et al. Ann Int Med 130: 487-95, 1999

GOAL

Bring you up to date on techniques that are allowing us to specify particular medications for individual patients

- Define pharmacogenomics and techniques
- Review developments in pharmacogenomics as they relate to use of beta agonists, leukotriene modifiers, and corticosteroids
- Review how we will use this information for treatment decisions in the future

PHARMACOGENOMICS

- Study of how genetic differences influence the variability in patients' responses (therapeutic and adverse) to drugs
  - 50-60% of genetic variability associates with variability in therapeutic responses

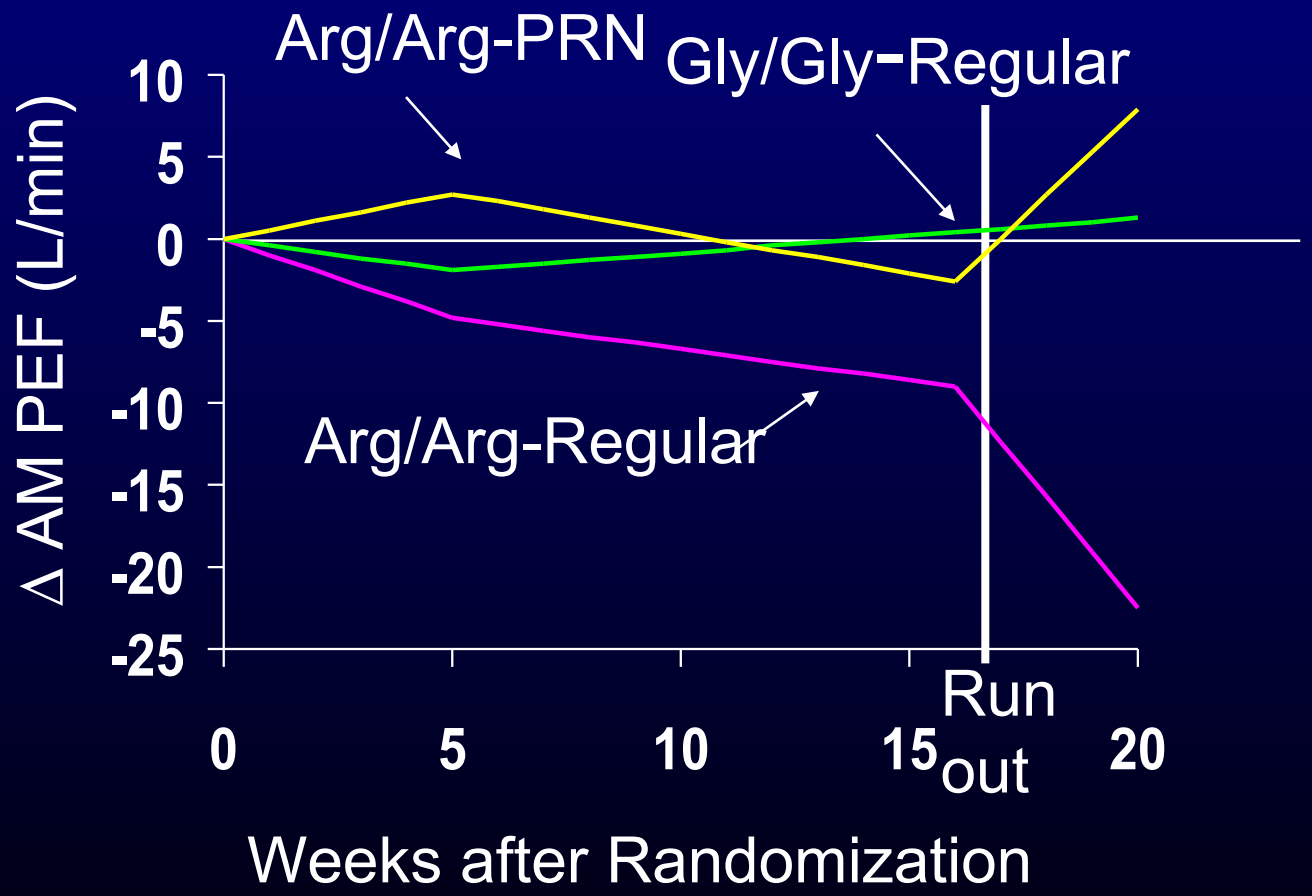
How Do We Look?

- Candidate Gene and Pathway Approaches
- GWAS
- Expression profiling in cells of responsive and non-responsive individuals

Beta-Agonists

BAGS Genetic Analysis

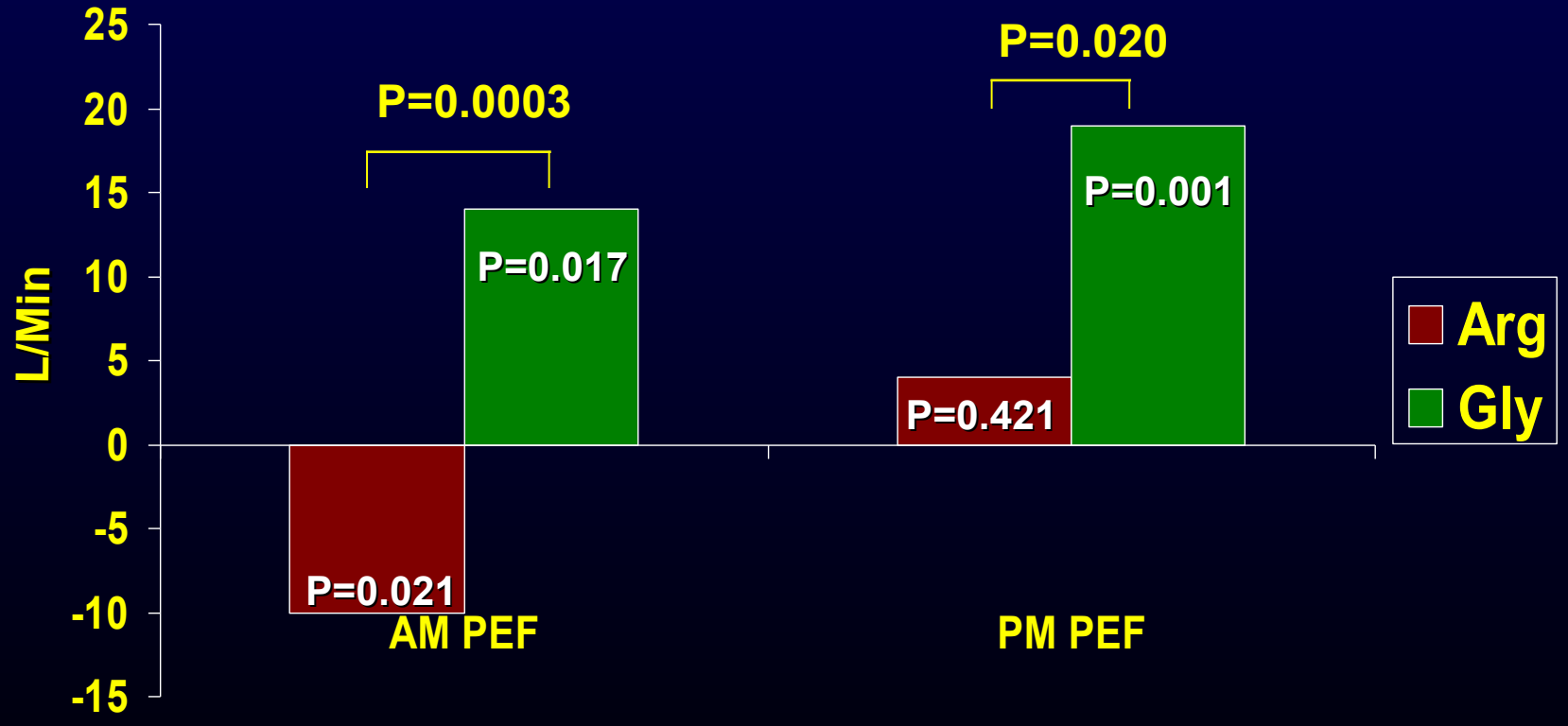
AA16 Locus



Israel E et al., AJRCCM; 2000

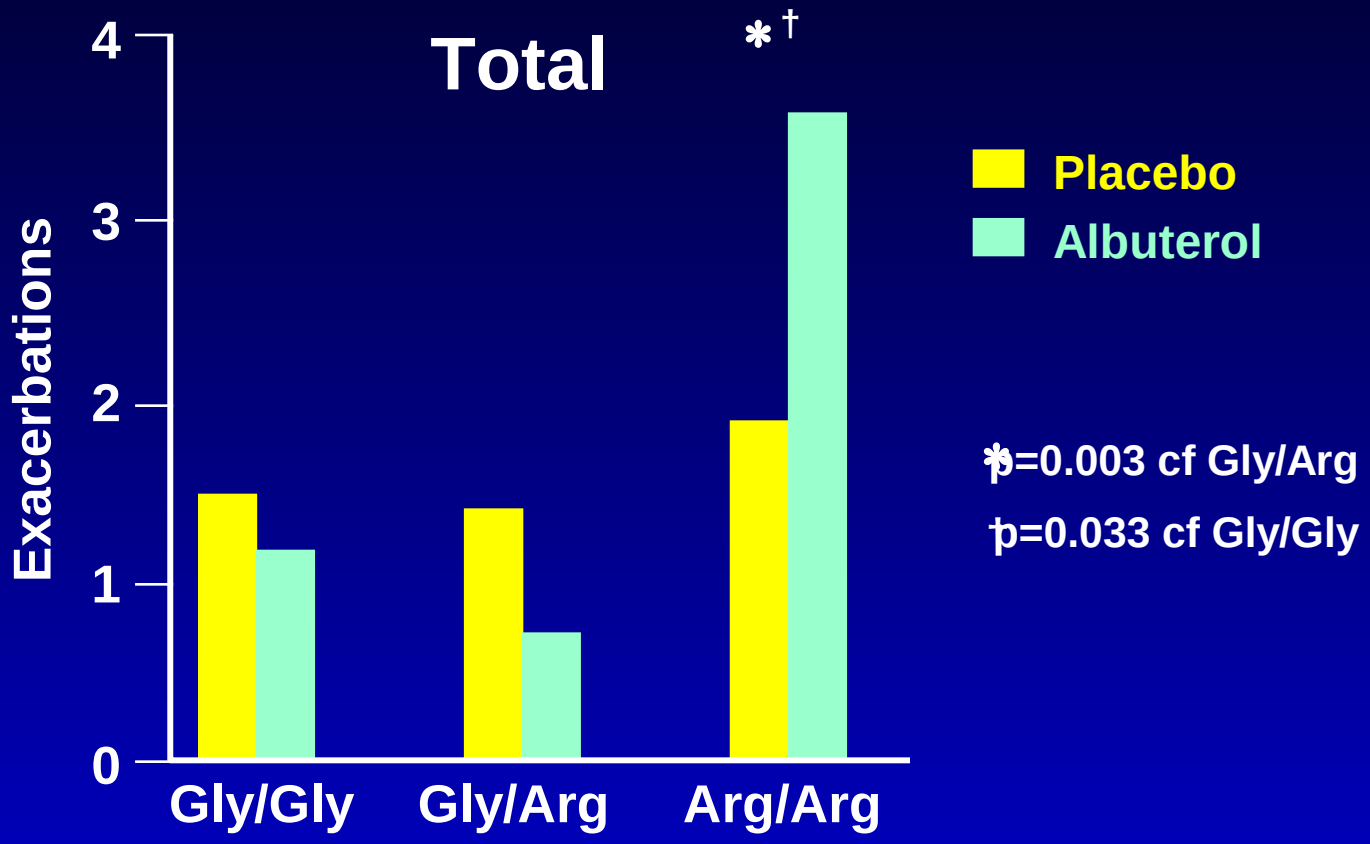
PEF

Difference between Regular vs. Placebo Treatment-induced Changes over 16 Wk



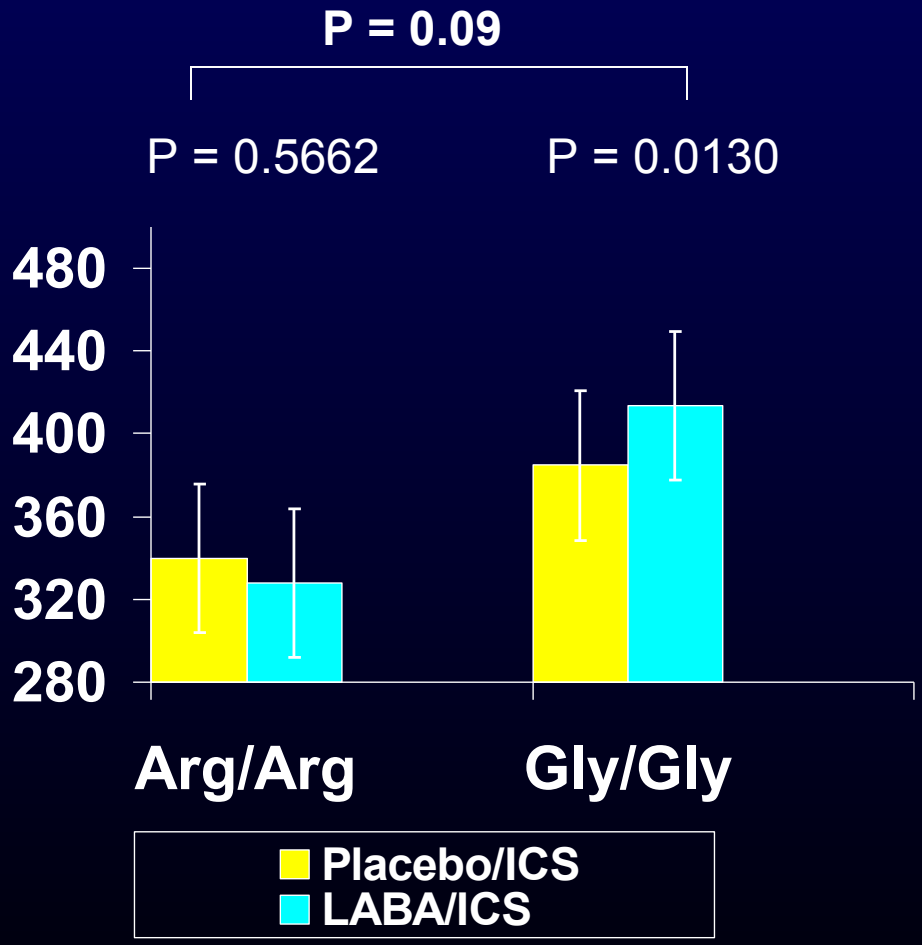
Israel E & the ACRN, The Lancet; 2004

Exacerbations/Subject/Year by Genotype

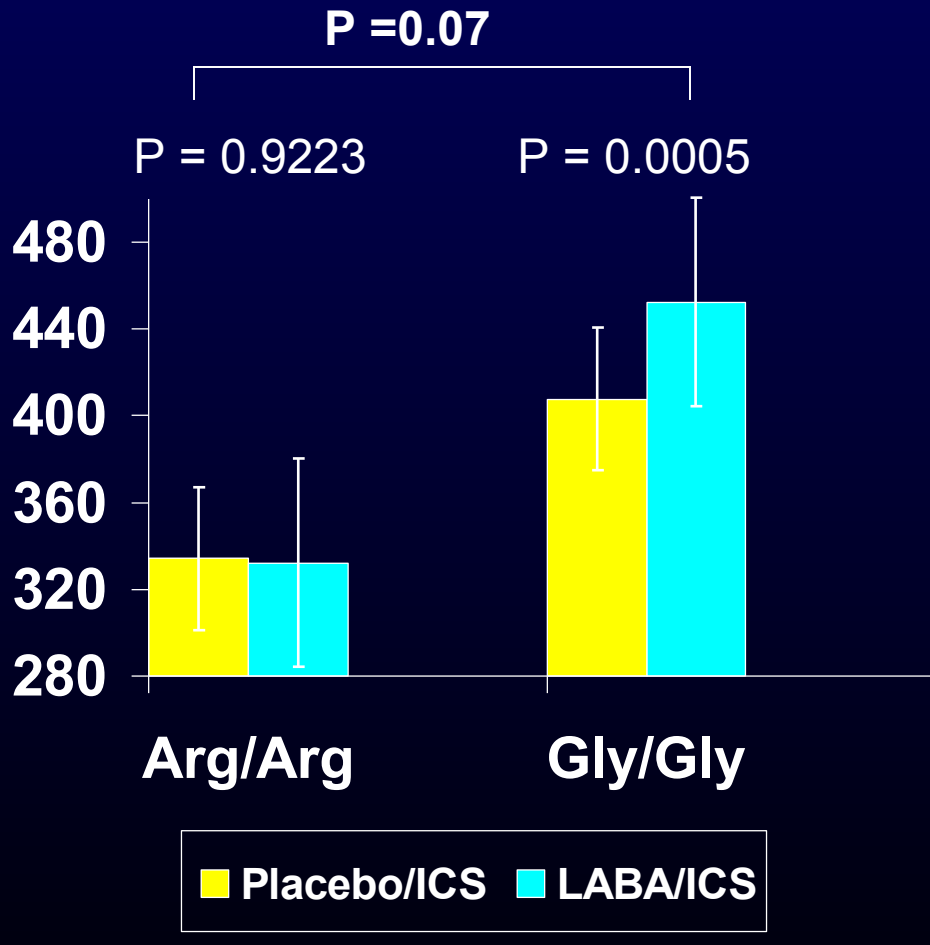


Taylor et al, Thorax, 2000

AM and PM PEF (Black/African Amer Subgroup, n= 8 vs. 8)



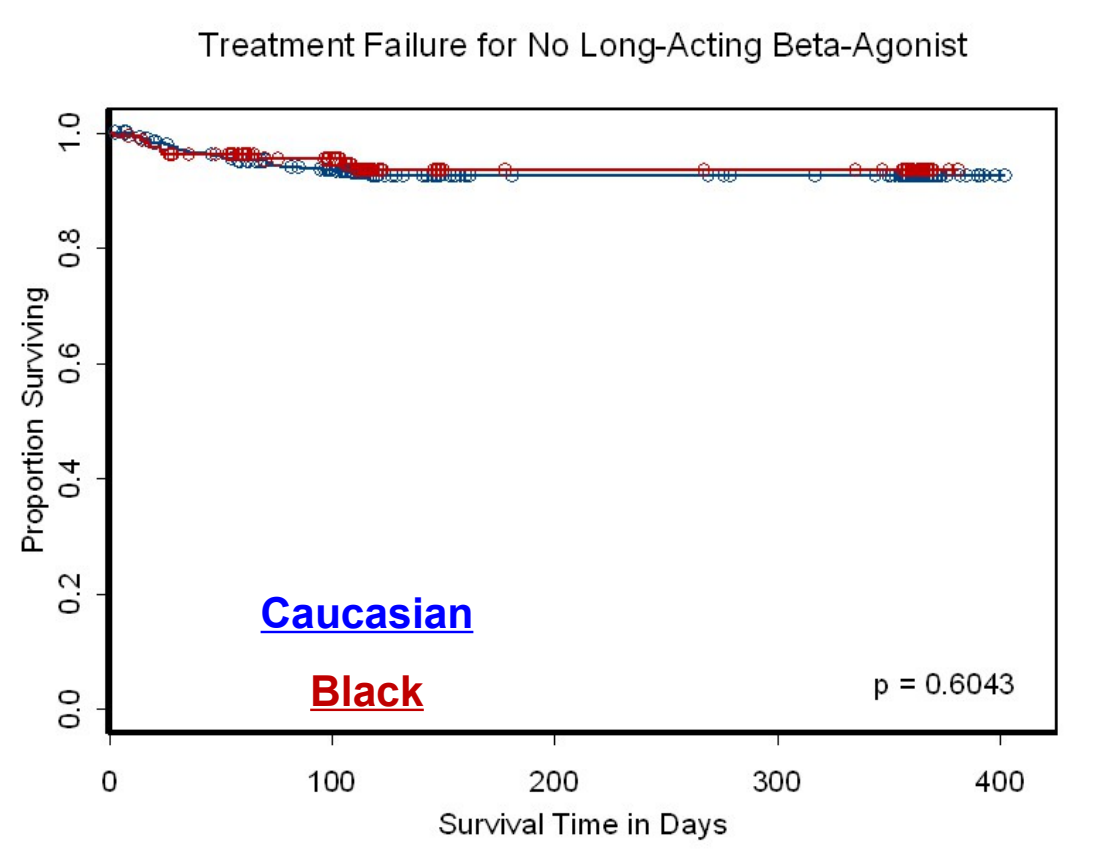
AM PEF (L/min)



PM PEF (L/min)

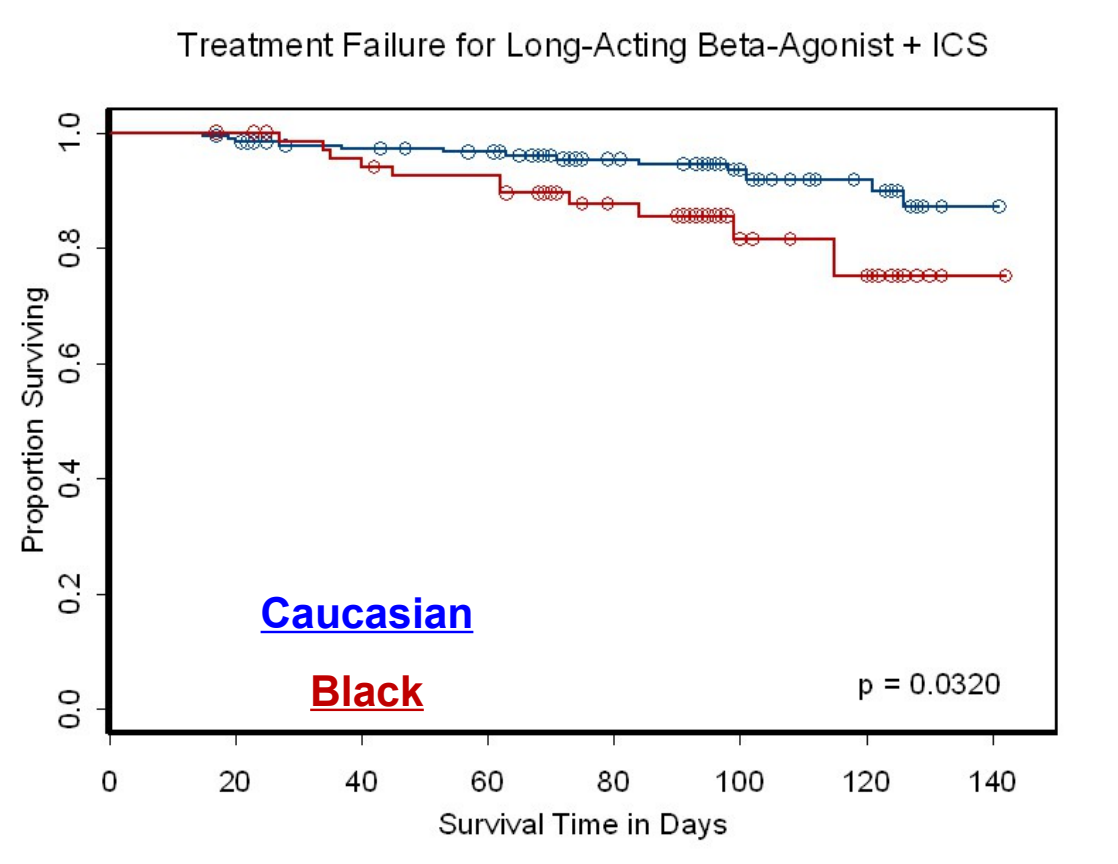
Wechsler et al, Lancet 2009

Treatment Failures in Subjects Not Taking LABA's Across ACRN



Wechsler & ACRN, AJRCCM, 2011

Treatment Failures in Subjects Taking LABA +ICS



Wechsler & ACRN, AJRCCM, 2011

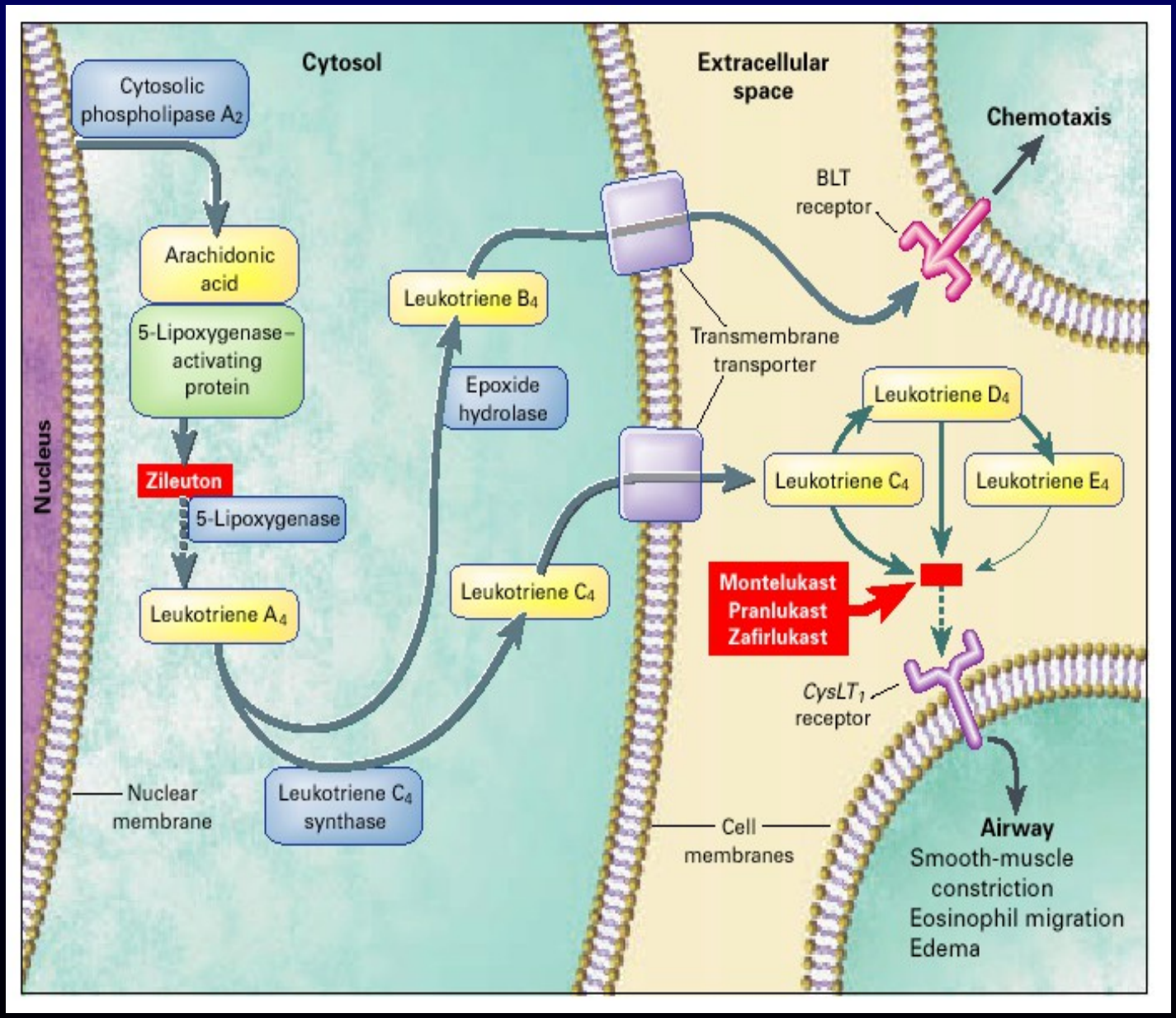
Table 1. LABA added to ICS are not as effective in Blacks: Effect of LABA Added on to ICS in Blacks vs. mixed populations

	Blacks Bailey 08	Blacks Spector 11	Blacks Brown 12	Mixed Shapiro 09	Mixed Ind 03	Mixed Kavuru 00
N	239	311	742	84	160	92
Duration	12 mo	3 mo	12 mo	3 mo	6 mo	3 mo
ICS dose (mcg/day)	200	640	640	500	500	200
Δ FEV1 L (Δ%)	0.11 (3%)		0.09 (4%)	0.23 (10%)	-	0.23 (10%)
Δ AM PEF L/min	16	18	10	38	25	35
Δ Rescue puffs/d	0.2 (ns)	.6		1.4	-	1.5
Δ% Sx free days	1.9 (ns)		1.9 (ns)	18.4	21	15.4

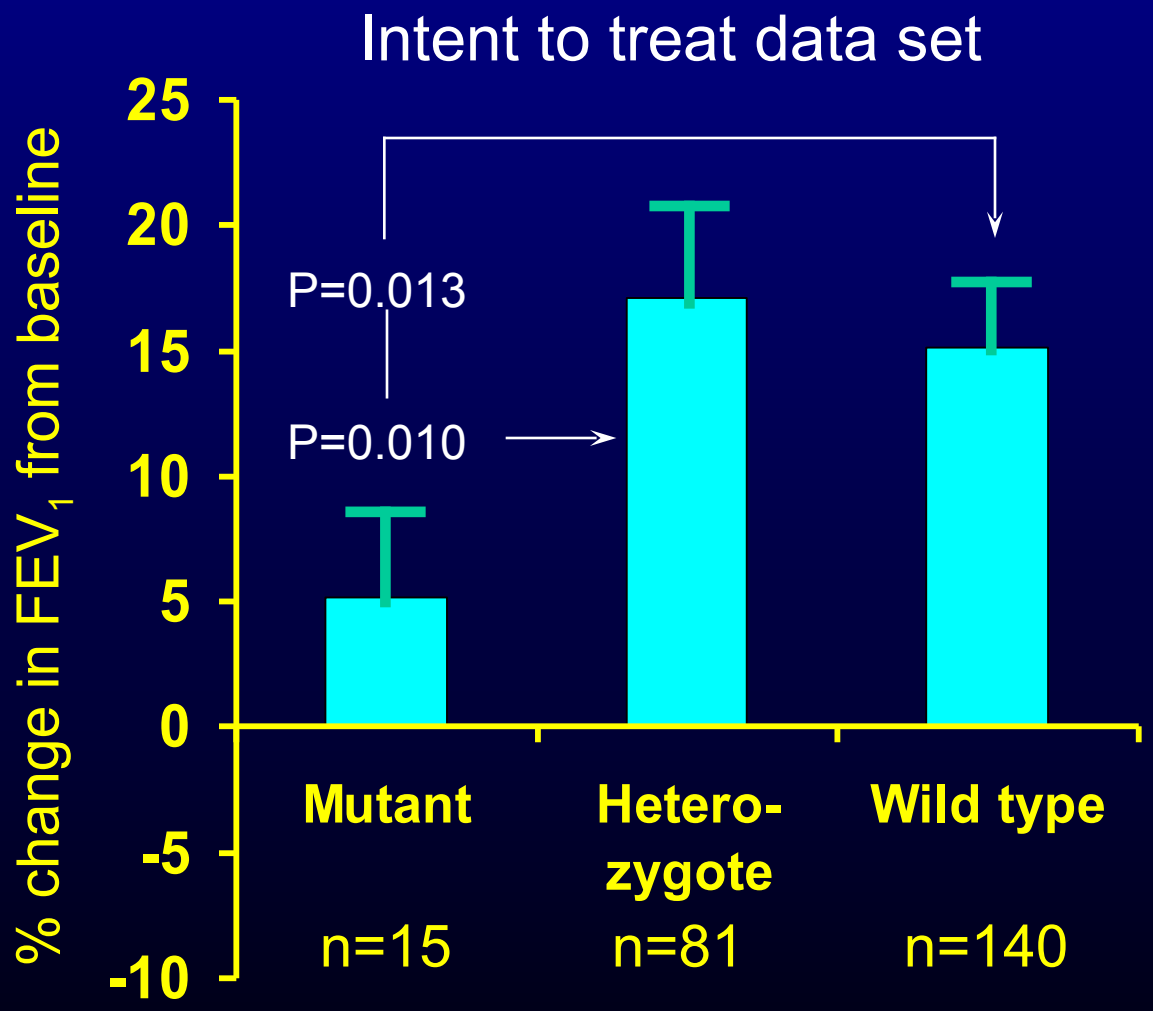
Conclusions

- Arg16Arg polymorphism identifies patients who may not do as well with regular beta-agonists
  - It may identify Blacks who do less well with LABAs
- Blacks may not realize as much benefit from LABAs as Caucasians

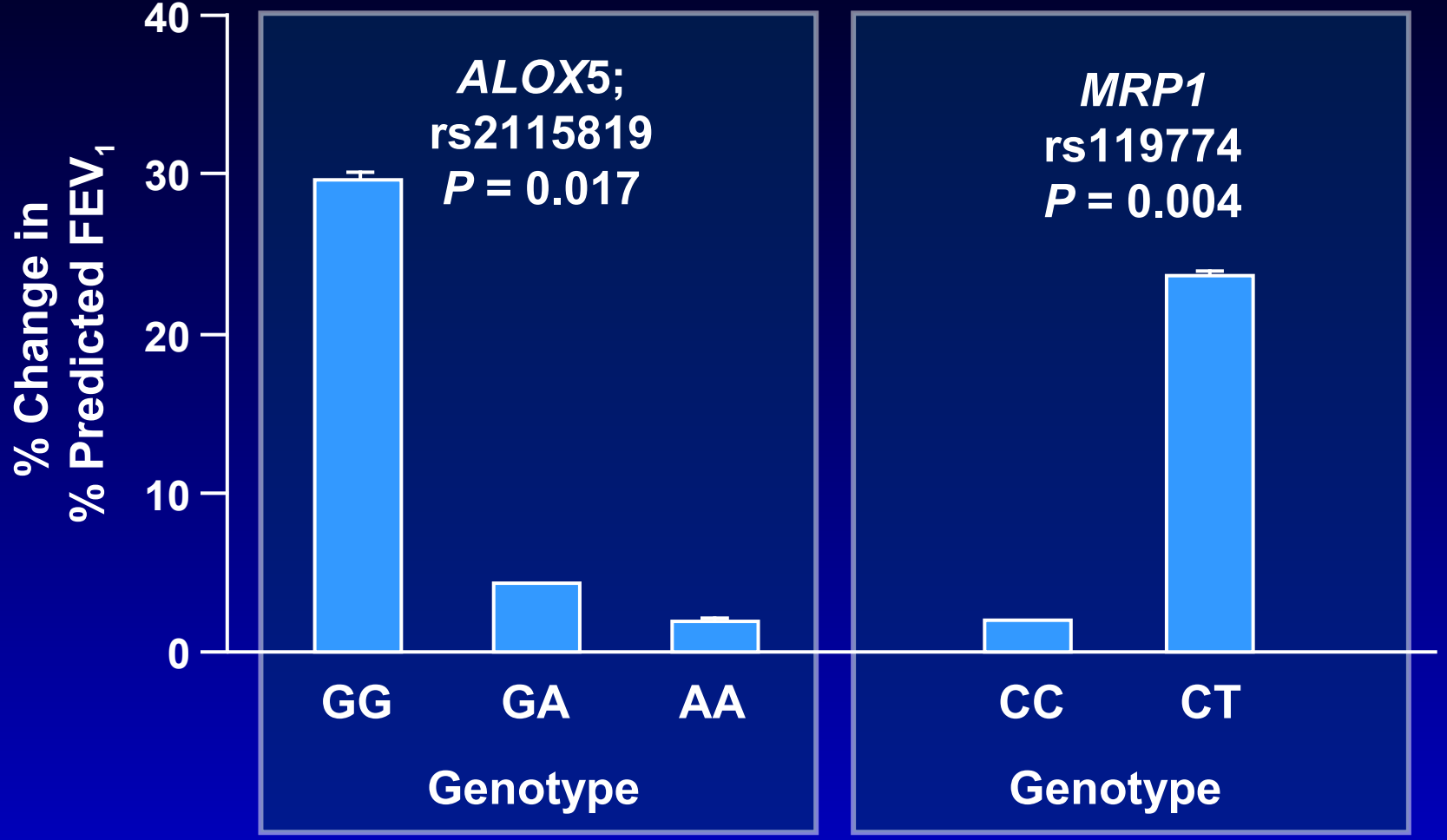
Leukotriene Modifiers


Cytosol
Extracellular space
Cytosolic phospholipase A_2
Arachidonic acid
5-Lipoxygenase–activating protein
Zileuton
5-Lipoxygenase
Leukotriene A_4
Leukotriene B_4
Epoxide hydrolase
Leukotriene C_4
Leukotriene C_4 synthase
Nuclear membrane
Nucleus
Transmembrane transporter
Leukotriene C_4
Leukotriene D_4
Leukotriene E_4
Montelukast
Pranlukast
Zafirlukast
BLT receptor
Chemotaxis
$CysLT_1$ receptor
Cell membranes
Airway
Smooth-muscle constriction
Eosinophil migration
Edema

Effect of promoter repeats of ALOX5 on the change in FEV_1 at end of active treatment with ABT-761



Influence of Genotype on Percentage Change in % Predicted $FEV_{1:}$ other SNPS



Minor allele freq: .47 ALOX5 and .07 MRP1

Lima JJ, et al. *Am J Respir Crit Care Med.* 2006;173:379-385.

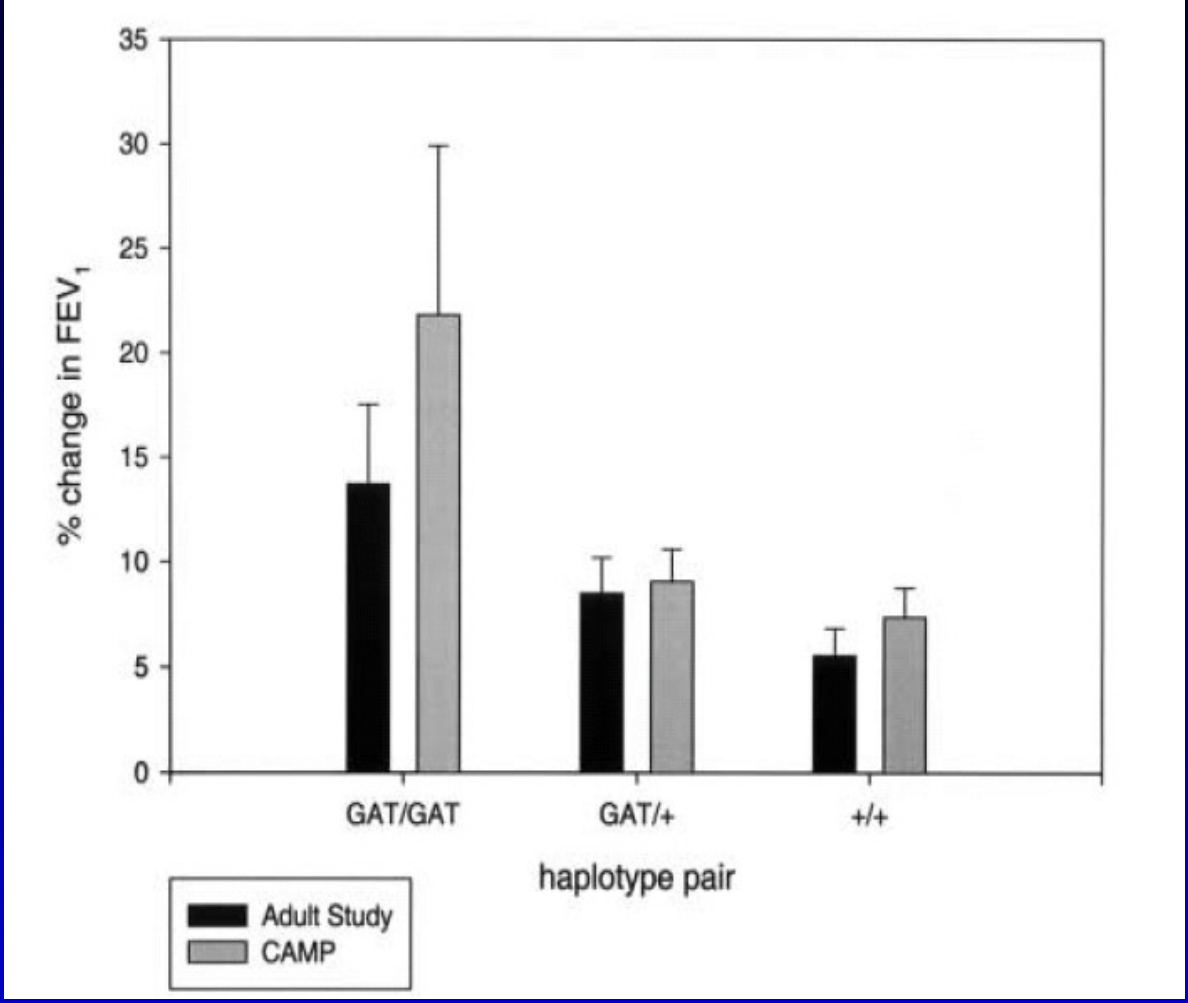
Influence of LT Pathway Polymorphisms on Asthma Exacerbation Risk

Gene (variant)	Genotype	Frequency (n)	Odds Ratio (95% CI)	*P* Value
ALOX5 (repeat variant)	5/5	0.64 (37)	1.0	0.045
	5/X	0.36 (21)	0.27 (0.08, 0.97)	
LTA4H (rs2660845)	AA	0.49 (28)	1.0	0.021
	AG	0.44 (25)	4.0 (1.23, 12.99)	0.133
	GG	0.08 (5)	4.5 (0.63, 31.95)	
LTC4S (rs730012)	AA	0.51 (30)	1.0	0.023
	AC	0.38 (22)	0.24 (0.07, 0.83)	0.106
	CC	0.11 (6)	0.16 (0.02, 1.49)	

Lima JJ, et al. *Am J Respir Crit Care Med.* 2006;173:379-385.

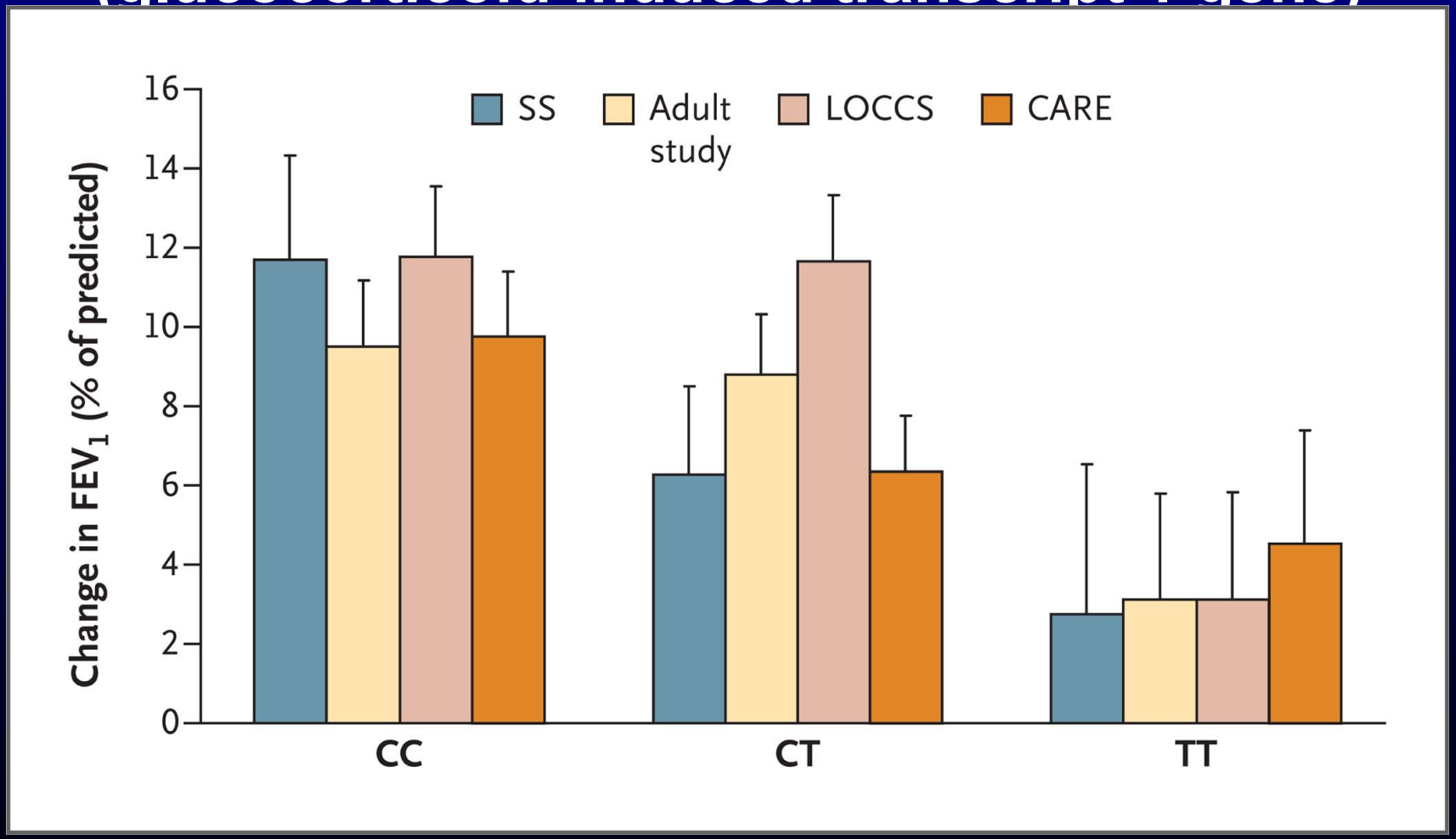
Corticosteroid Responses

Corticotropin Releasing Hormone Receptor-1 Haplotype and Response to ICS



Tantisara et al, Hum Mol Gen, 2004

Changes in Lung Function and GLCCI1 Polymorphism (glucocorticoid-induced transcript 1 gene)



Tantisira KG et al. N Engl J Med 2011

Biologics

- No polymorphisms that associate with altered responses
- However there are polymorphisms that associate with the biology
  - FCER1 gene polymorphisms and IgE levels (Palmer, Cin Exp All 1999)
  - IL6R polymorphisms and ciruculating IL6R (Bleecker, JACI, 2012)

Additional Methods to Discover Candidate Genes

- In vitro expression profiling of cells from responsive and non-responsive populations
  - NFKB - transcription factor activating transcription of cytokines, chemokines, growth factors, cellular ligands, and adhesion molecules associated with asthma (Chapman Mol Cell Endocrinol. 1995)
  - FK506 binding protein 51 gene (FKBP51) in bronchial epithelium (Woodruff PNAS 2007)

Conclusions

- Genetic polymorphisms do associate with differential responses to asthma medications

Potential Applicationns

- Predict responders
- Predict those with increased tendency for adverse effects
- Individualize dosing
- Allow introduction of medications that have effects in a predictable population

What prevents us from using this information now?

- Repeatable cross-sectional and prospective studies in **multiple** populations that will put the associations on a firm foundation of data

WHY?

- Gene-gene interactions
  - May modify associations so that they may differ significantly among different populations and ethnic groups
- Gene-environment interactions
  - May result in differences among populations and ethnic groups

SUMMARY

- While we have not yet reached the level of specificity seen in cystic fibrosis, where a drug is targeted to one specific polymorphism, we are beginning to identify patterns of genetic change which will predict responses (or adverse effects) to asthma medications.
- Combining multiple studies in multiple populations with informatics for physicians will allow us to bring this information to the practice setting