Pharmacogenomics

Treating the Individual Asthma Patient

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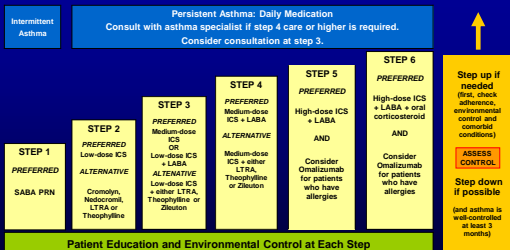Partners' Asthma Center

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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
- Not working and rarely leaving the house

- On exam: Morbidly obese with scattered wheezes
- FEV1 70% predicted
- 7% eosinophils
- Sinus CT mucosal thickening
- pH probe mild reflux

- 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

Intermittent Asthma

Persistent Asthma: Daily Medication
Consult with asthma specialist if step 4 care or higher is required.
Consider consultation at step 3.

STEP 1	STEP 2	STEP 3	STEP 4	STEP 5	STEP 6
PREFERRED	PREFERRED	PREFERRED	PREFERRED	PREFERRED	PREFERRED
SABA PRN	Low-dose ICS	Medium-dose ICS OR Low-dose ICS + LABA	Medium-dose ICS + LABA	High-dose ICS + LABA	High-dose ICS + LABA + oral corticosteroid
	ALTERNATIVE	ALTERNATIVE	ALTERNATIVE	AND	AND
	Cromolyn, Nedocromil, LTRA or Theophylline	Low-dose ICS + either LTRA, Theophylline or Zileuton	Medium-dose ICS + either LTRA, Theophylline or Zileuton	Consider Omalizumab for patients who have allergies	Consider Omalizumab for patients who have allergies

Step up if needed
(first, check adherence, environmental control and comorbid conditions)

ASSESS CONTROL

Step down if possible
(and asthma is well-controlled at least 3 months)

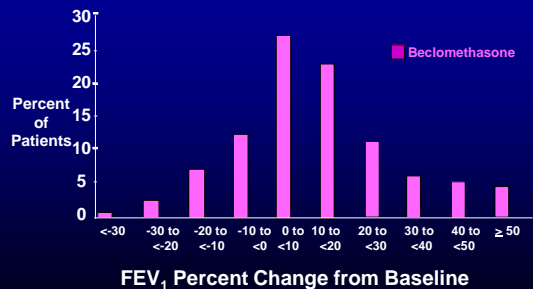**Patient Education and Environmental Control at Each Step**

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

Percent of Patients / FEV$_1$ Percent Change from Baseline — Beclomethasone

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

OUTLINE

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

What Polymorphisms Do We Look For?

- SNPs- Single Nucleotide Polymorphisms eg Guanine to Cytosine
- Insertions-additional gene sequences
  – CNVs- Copy Number Variants
    • Change in the number of repeats of a sequence
- Deletions-removal of a nucleotide or nucleotides
- Genomic/Non-Genomic
  – Genomic- in areas of the gene that are know to code for or regulate a gene
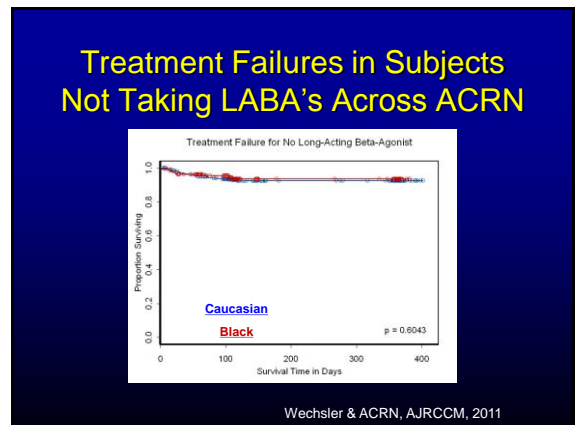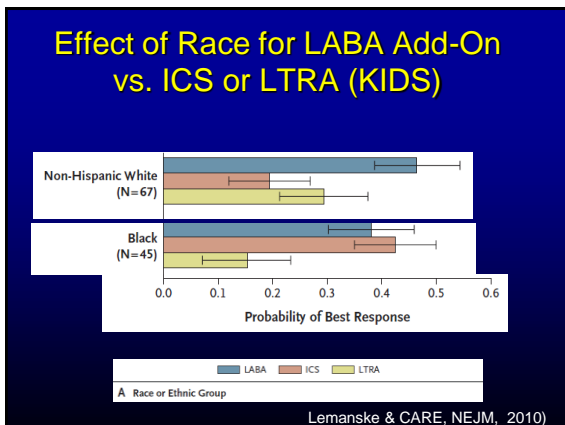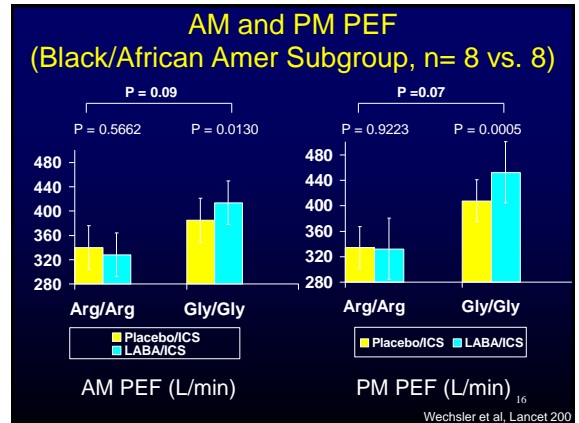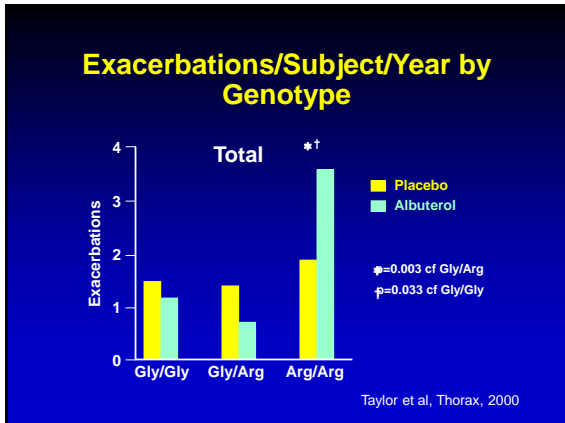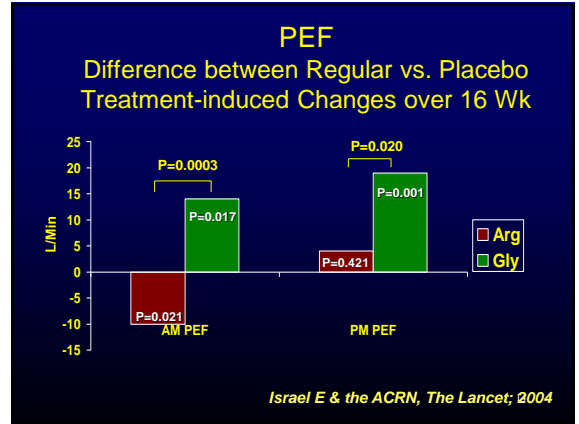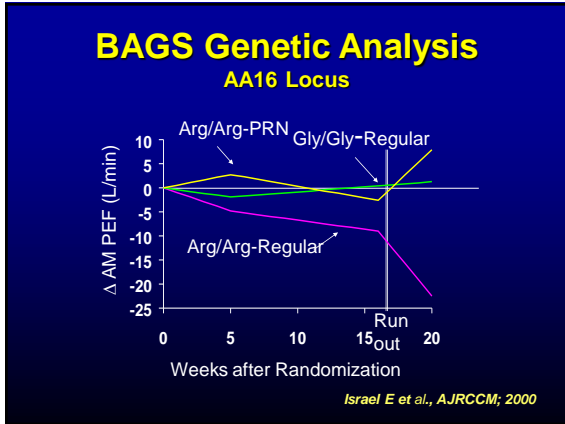- Macro-level – Race

How Do We Look?

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

How Do We Confirm?

- Prospective studies
  – Labor-intensive
  – Less subject to confounding
- Association studies
  – Require large numbers
  – Allow easy replication in multiple populations

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)

Wechsler et al, Lancet 200

Effect of Race for LABA Add-On
vs. ICS or LTRA (KIDS)

Lemanske & CARE, NEJM, 2010)

Treatment Failures in Subjects
Not Taking LABA's Across ACRN

Wechsler & ACRN, AJRCCM, 2011

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Treatment Failures in Subjects Taking LABA's Across ACRN

Treatment Failure for Long-Acting Beta-Agonist

Caucasian
Black
p = 0.0014

Wechsler & ACRN, AJRCCM, 2011

Treatment Failures in Subjects Taking LABA +ICS

Treatment Failure for Long-Acting Beta-Agonist + ICS

Caucasian
Black
p = 0.0320

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

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Leukotriene Modifiers

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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

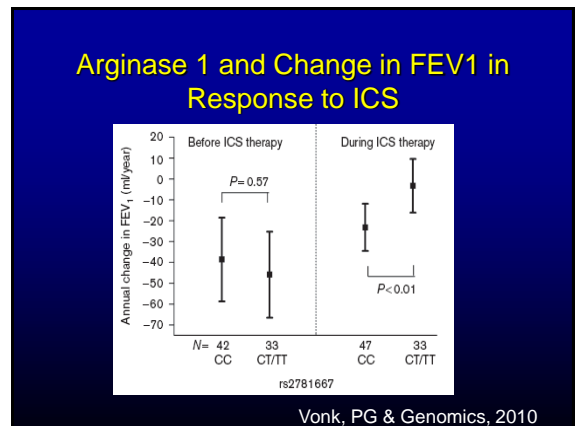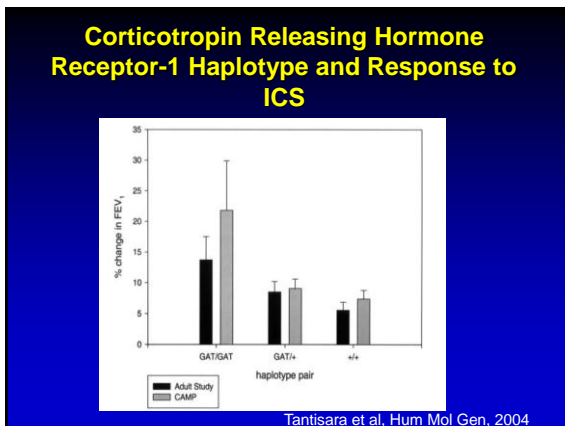Minor allele freq: .47 ALOX5 and .07 MRP1 Lima JJ, et al. *Am J Respir Crit Care Med.* 2006;173:379-385.

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

Arginase 1 and Change in FEV1 in Response to ICS

Vonk, PG & Genomics, 2010

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## Additional Associations with Corticosteroid Responses

- TBX21 - encodes the transcription factor T-bet (induction of Th1 and suppression of Th2)
  - associated with large improvement in airway hyperresponsiveness in response to corticosteroid therapy. (Tantisira PNAS 2004 and Ye J Clin Pharm Ther. 2009)
  - Only 5% frequency
- Adenyl Cyclase 9 (AC9) -activated by ADRB2
  - SNP associated with improved bronchodilator response with ICS (Tantisira, Hum Mol Genet. 2005 and Kim, J Clin Pharm Ther. 2011)

Changes in Lung Function and GLCCI1 Polymorphism (glucocorticoid-induced transcript 1 gene)
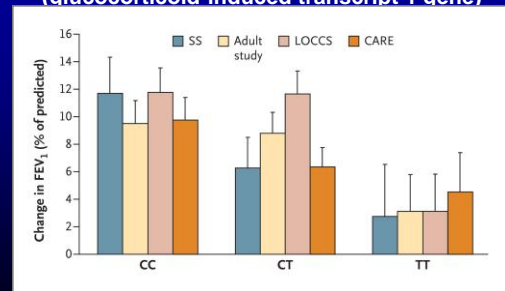
Tantisira KG et al. N Engl J Med 2011

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 circulating 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

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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