Scenario #1

- Your precocious high-school child is going to the third-world to gain experience and bolster her chances of getting into medical school
- She plans to open an Asthma Clinic, because asthma is a common problem
- She wants simple guidelines to treat patients

Question #1:
Which of the Following do You Tell Her?

1. Most asthma is well-controlled
2. All asthmatics can be managed by a simple "step-care" algorithm
3. Because asthma is an eosinophilic disease, steroids always work
4. All of the Above
5. None of the Above
Key Points/Outline: Asthma-1

- Prevalence continues to increase in the US
- ~1/3 of asthmatics take long-term controllers
- There is a role for:
  - Inhaled corticosteroids
  - Leukotriene modifiers
  - Long-acting β2-agonists (LABAs)
  - Long-acting Muscarinic antagonists (LAMAs)
- Intermittent or prn treatment may work for some patients

Key Points/Outline: Asthma-2

- Asthma is a heterogeneous disease
- Response to treatments varies
- Clinical phenotypes differ
- Eosinophilia is not ubiquitous
- Non-eosinophilic asthma is not steroid responsive
- Phenotyping & Genotyping may offer “Personalized Asthma Management”

Los Angeles Times | SCIENCE

U.S. asthma rates at all-time high, CDC says

Asthma Prevalence in the US 2008-2010

May 15, 2012

Nat Ctr for Health Statistics Data Brief No 94, May 2012
Asthma Prevalence in the US 2001-2009 Adults

2 separate studies:
- PARSIFAL
  - N = 6,843 Bavarian Children
  - Mattress Dust
  - Vacuum Cleaner
- GABRIELA
  - N = 9,668 Bavarian Children
  - Settled Dust
  - Electrostatic Dust Collector

Relationship Between Microbial Exposure and Probability of Asthma

Asthma Characteristics US 2008

Ege et al

MMWR 60:647, 2011
The CHOICE Survey:
High Rates of Persistent and Uncontrolled Asthma in the United States

- National Telephone Survey
- Random
- Self-Reported Asthma
- Symptoms or Meds in 12 months

N = 1000
Age ≥ 12
(2008)

490/1000 = 49% were on NO CONTROLLER

Asthma Control in 510 patients taking Controllers

Asthma Severity (EPR3) and Asthma Control (self-reported) in 490 patients not taking Controllers

EPR-3, NHLBI, 2011

Figure 4-5. Stepwise Approach for Managing Asthma in Youths ≥12 Years of Age and Adults
One Size Fits All

Doesn’t Work for Asthma!

Symposium in Personalized Medicine in Cystic Fibrosis & Asthma

Scenario #2

- 48 year old female
- BMI 42
- Onset asthma at age 46
- FEV1 50% of predicted
- Fluticasone/Salmeterol 500/50 BID
Question #2:
What do you do next?

1. Increase her inhaled steroid dose a little
2. Increase her inhaled steroid a lot
3. Add tiotropium
4. Add prednisone

Patients (≥15 Years) Not Controlled on PRN Beta-Agonists

FEV₁: Distribution of Individual Patient Responses

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>FEV₁ Percent Change From Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone (n=246)</td>
<td>Montelukast (n=375)</td>
</tr>
</tbody>
</table>

Figure 1. Heterogeneity of response to inhaled corticosteroids at 8 weeks (Adult Study and CAMP) and 6 weeks (ACRN).


Human Molecular Genetics, Vol. 13, No. 13 © Oxford University Press 2004; all rights reserved
**Identification of Asthma Phenotypes Using Cluster Analysis in the Severe Asthma Research Program**

N = 726

**CLUSTER 1**
- 15% of subjects
- Young, F > M
- Childhood onset
- Atopic
- Normal Lung Function
- ≤ 2 controllers
- Low HCU

**CLUSTER 2**
- 44% of subjects
- Older, 66% F
- Childhood onset
- Atopic
- Normal to Normal Lung Function
- Reverse to Normal to Normal
- ≥ 2 controllers
- Higher dose ICS
- Low HCU

**CLUSTER 3**
- 8% of subjects
- Older F, high BMI
- Late onset
- Less Atopy
- Lower Lung Function
- Less Reversibility
- 50% ≥ 3 controllers
- HD ICS, oral steroids
- High HCU

**CLUSTER 4**
- 17% of subjects
- M = F
- 72% Childhood onset
- Atopy (83%)
- Low Lung Function
- Reversibility
- 50% ≥ 3 controllers
- HD ICS, oral steroids
- High HCU; 40% ICU

**CLUSTER 5**
- 16% of subjects
- 63% F
- 69% Late onset
- Less Atopy (66%)
- V Low Lung Fxn
- Less Reversibility
- 50% ≥ 3 controllers
- HD ICS, oral steroids
- High HCU; 40% ICU

---

**How do we personalize medications for asthma?**

---

**A Patient with Asthma Seeks Medical Advice in 1828, 1928, and 2012**

Erika von Mutius, M.D., and Jeffrey M. Drazen, M.D.

"...the presence of eosinophils in the blood and sputum makes the diagnosis virtually certain"


---

**A Large Subgroup of Mild-to-Moderate Asthma Is Persistently Noneosinophilic**

- Asthma is a heterogeneous disease
- ~50% of asthmatics – poor response to steroids
- Eosinophilic airway inflammation not ubiquitous
- Prior ACRN data (n=995; 2.7 SI; ≥2% eos):
  - No ICS
  - ICS

**Sputum Eosinophil Percentage (No ICS)**

![Graph showing eosinophil percentage over time.](image)


**SIENA: Steroids In Eosinophil Negative Asthma**

![Diagram of SIENA study design.](image)

What is Pharmacogenetics?

"Pharmacogenetics is the study of the role of genetic determinants in the variable response to therapy"

Palmer, Silverman, Weiss, Drazen Am J Respir Crit Care Med 165:861, 2002

**IMPACT (Boushey et al NEJM 352: 1519-28, 2005)**

**PICT - Period of Intense Combined Therapy:**
- Prednisone, 0.5 mg/kg/day x 10-14 days
- Budesonide, 800 mcg BID x 10-14 days
- Zafirlukast, 20 mg BID x 10-14 days

<table>
<thead>
<tr>
<th>%Δ in FEV₁ (L)</th>
<th>Non-Eosinophil</th>
<th>Intermittent</th>
<th>Persistent</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-to Post-PICT</td>
<td>-0.2</td>
<td>4.7</td>
<td>8.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Post-PICT to Max Rev</td>
<td>10.1</td>
<td>12.1</td>
<td>13.5</td>
<td>0.32</td>
</tr>
</tbody>
</table>

**Pharmacogenetic Targets in Asthma**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome</th>
<th>Potential Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>β₂-adrenoreceptor</td>
<td>5q31.32</td>
<td>β₂ agonists</td>
</tr>
<tr>
<td>ALOX5</td>
<td>10q11.12</td>
<td>5-LOX Inhibitors</td>
</tr>
<tr>
<td>ALOX5AP (FLAP)</td>
<td>13q12</td>
<td>LTRAs</td>
</tr>
<tr>
<td>LTC₄ Synthase</td>
<td>5q35</td>
<td></td>
</tr>
<tr>
<td>CysLT₂</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>M₂ (CHRM2)</td>
<td>7q35.36</td>
<td>Ipratropium</td>
</tr>
<tr>
<td>M₃ (CHRM3)</td>
<td>1q43.44</td>
<td>Tiotropium</td>
</tr>
<tr>
<td>GR</td>
<td>5q31</td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td>STIF1</td>
<td>Various</td>
<td></td>
</tr>
<tr>
<td>NR3C1</td>
<td>Various</td>
<td></td>
</tr>
<tr>
<td>NF-kb</td>
<td>1p31</td>
<td></td>
</tr>
<tr>
<td>PDE₄A</td>
<td>19p13.2</td>
<td>Theophylline</td>
</tr>
<tr>
<td>PDE₄B</td>
<td>1p31</td>
<td>PDE₄ Inhibitors</td>
</tr>
<tr>
<td>PDE₄C</td>
<td>19p13.1</td>
<td></td>
</tr>
<tr>
<td>PDE₄D</td>
<td>5q12</td>
<td></td>
</tr>
<tr>
<td>CYP450</td>
<td>Various</td>
<td></td>
</tr>
</tbody>
</table>

**Summary Pharmacogenetics**

- Risk of SABAs (not LABAs) appears to segregate by genotype
- SNPs in ALOX5 and LTC₄ Synthase determine response to Leukotriene modifiers
- GLCCI1 is associated with decreased glucocorticoid response

**Anti-IL5 (Mepolizumab) in Persistent Asthma**


**New England Journal of Medicine**

Genomewide Association between GLCCI1 and Response to Glucocorticoid Therapy in Asthma

Anti-IL5 (Mepolizumab) in Persistent Asthma

Flood-Page et al
Am J Respir Crit Care Med 176:1062, 2007

Anti-IL5 (Mepolizumab) in Persistent Asthma with Persistent Eosinophilia

Nair et al

Anti-IL5 (Reslizumab) for Poorly Controlled, Eosinophilic Asthma

Castro et al
Am J Respir Crit Care Med 184:1125, 2011

Anti-IL5 (Reslizumab) for Poorly Controlled, Eosinophilic Asthma

Castro et al
Am J Respir Crit Care Med 184:1125, 2011
Tiotropium Step-Up for Uncontrolled Asthma

Peters et al.

Alternatives to LABAs?

Tiotropium Bromide Step-Up Therapy for Adults with Uncontrolled Asthma

Stephen P. Peters, M.D., Ph.D., Susan J. Kunselman, M.A.
Nikolina Icicovic, M.A.S., Wendy C. Moore, M.D., Rodolfo Pasquali, M.D.
Bill T. Ameredes, Ph.D., Homer A. Bourey, M.D., William J. Calhoun, M.D.
Mario Castro, M.D., Reuben M. Cherniack, M.D., Timothy Craig, D.O.
Loren Derlinger, M.D., Ph.D., Linda L. Engle, B.S., Emily A. DiMango, M.D.
John V. Fahy, M.D., Elliot Israel, M.D., Nizar Jaujour, M.D.
Shamsah D. Kuzni, M.D., Monica Kraft, M.D., Stephen C. Lazarus, M.D.
Robert F. Lemanske, Jr., M.D., Njira Lugogo, M.D., Richard J. Martin, M.D.
Deborah A. Meyers, Ph.D., Joe Ramsdell, M.D., Christine A. Sorkness, Pharm.D.
E. Rand Sutherland, M.D., Stanley J. Szefler, M.D., Stephen I. Wasserman, M.D.
Michael J. Walter, M.D., Michael E. Wechsler, M.D., Vernon M. Chinchilli, Ph.D.
and Eugene R. Blecker, M.D., for the National Heart, Lung, and Blood Institute
Asthma Clinical Research Network

Peters et al.
Tiotropium Step-Up for Uncontrolled Asthma

TALC Conclusions

- Tiotropium step-up therapy demonstrated efficacy (asthma control) equivalent to a LABA (salmeterol) in patients inadequately controlled on low-dose ICS.
- Further studies are required to establish the efficacy of tiotropium in reducing asthma exacerbations, and to establish long-term safety in patients with asthma.

Predictors of Response to Tiotropium

- Higher Cholinergic Tone (Lower Resting Heart Rate)
- Greater Airway Obstruction (Lower FEV1/FVC ratio)
- Positive Short-Acting Bronchodilator Response (Albuterol > Ipratropium)
- Younger Age (Asthma Control Days)

Maximizing Tiotropium Responsiveness in Patients with Uncontrolled Asthma

- Evaluate Asthma Control with Patient on ICS
- If Uncontrolled
  - FEV1 ≤ 70% pred
  - Symptomatic 6-7 days/wk
- Perform Spirometry Before and After Albuterol
- Positive Tiotropium Response More Likely if
  - FEV1/FVC Ratio is Low
  - Positive Response to Albuterol
N = 17 Severe Persistent Asthma
Budesonide 800 – 1600 mcg/day ± LABA

Iwamoto et al

Key Points/Outline: COPD
• COPD is a leading cause of death worldwide, and mortality is increasing
• Exacerbations are the major complication of COPD
• Exacerbations are associated with accelerated loss of lung function
• Anxiety/Depression are common and associated with decreased performance status and QoL
• Peak VO2 = most significant predictor of mortality
• Hospitalization for COPD predicts mortality
• There are effective strategies for decreasing exacerbations

Leading Causes of Deaths
U.S. 1998→2009

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Heart Disease</td>
<td>724,269</td>
</tr>
<tr>
<td>2. Cancer</td>
<td>538,947</td>
</tr>
<tr>
<td>3. Cerebrovascular disease (stroke)</td>
<td>158,060</td>
</tr>
<tr>
<td>4. Respiratory Diseases (COPD)</td>
<td>114,381</td>
</tr>
<tr>
<td>5. Accidents</td>
<td>94,828</td>
</tr>
<tr>
<td>6. Pneumonia and influenza</td>
<td>93,207</td>
</tr>
<tr>
<td>7. Diabetes</td>
<td>64,574</td>
</tr>
<tr>
<td>8. Suicide</td>
<td>29,264</td>
</tr>
<tr>
<td>9. Nephritis</td>
<td>26,295</td>
</tr>
<tr>
<td>10. Chronic liver disease</td>
<td>24,936</td>
</tr>
<tr>
<td>11. All other causes of death</td>
<td>469,314</td>
</tr>
</tbody>
</table>

Percent Change in Age-Adjusted Death Rates (US, 1965-1998)

Proportion of 1965 Rate

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>-59%</td>
<td>-64%</td>
<td>-35%</td>
<td>+163%</td>
<td>-7%</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other CVD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All other causes</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Scenario #3

• 73 year old man with exacerbation-prone COPD, on oxygen at 2LPM 24/7

• Tiotropium, Fluticasone/Salmeterol, Azithromycin, Roflumilast

• Extremely anxious, depressed

• Unable to walk more than across the room

Question #3: What do you do?

1. Simplify his medical regimen
2. Counsel him to accept his anxiety and depression
3. Tell him to give up the dream of walking without dyspnea
4. All of the Above
5. None of the Above

Anxiety is a BIG PROBLEM in COPD

(N = 1828 patients in the NETT trial)

Anxiety associated with:

• Worse 6 MWD $P < 0.001$
• Worse Peak Workload $P < 0.04$
• Worse Q of L $P < 0.001$
• More Dyspnea $P < 0.001$

Giardino et al
Respiratory Research 11:29, 2010

Functional Status (exercise) predicts mortality in COPD

Oga et al
Am J Respir Crit Care Med 167:544, 2003
Hospitalized Severe AECOPD and Mortality: Severity of AECOPD

- 1. no AECOPD
- 2. AECOPD ED
- 3. AECOPD Hosp
- 4. AECOPD Readmit

N = 305 men with COPD x 5 years

Soler-Cataluna Thorax 2005

Lung Function & Hospitalizations Predict Mortality

≥ 1 COPD Admission
HR 14.3 (13.15.7; p<0.001)

Garcia-Aymerich et al
Thorax 66:585-590, 2011

Increased Mortality Associated with Prior Hospitalizations is Similar for All GOLD Stages

Garcia-Aymerich et al
Thorax 66:585-590, 2011
**Prevention of Exacerbations**

- Immunizations (Influenza, Pneumococcal)
- Inhaled Corticosteroids
- Long-acting Beta-adrenergic Agonists (LABA)
- Long-acting anticholinergics
- LABA + Inhaled Corticosteroids
- Macrolide antibiotics
- Statins?

**Effects of Inhaled Corticosteroids in COPD: Meta-Analysis**

*Relative Risk of Exacerbations in Patients With COPD Treated With Inhaled Corticosteroids vs Placebo*

<table>
<thead>
<tr>
<th>Author</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vestbo et al</td>
<td></td>
</tr>
<tr>
<td>Bourbeau et al</td>
<td></td>
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<tr>
<td>Burge et al</td>
<td></td>
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<tr>
<td>Lung Health Study</td>
<td></td>
</tr>
<tr>
<td>Weir et al</td>
<td></td>
</tr>
<tr>
<td>Paggiaro et al</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
</tr>
</tbody>
</table>


**COPD Exacerbations (Lung Health II)**

- Placebo: 28.2 Respiratory Exacerbations (per 100 person-years)
- Triamcinolone: 21.1 Respiratory Exacerbations (per 100 person-years)

*p = 0.005*

**Salmeterol reduces rate of COPD Exacerbations**

Tiotropium Reduces Exacerbations and Hospitalizations vs Ipratropium


Tiotropium vs Salmeterol for the Prevention of Exacerbations of COPD

**Tiotropium in Combination with Placebo, Salmeterol, or Fluticasone-Salmeterol for COPD**

Randomized, DB, PC Trial
N = 449
Moderate or Severe COPD

Tiotropium + PBO vs Tiotropium + Salmeterol 50 mcg BID vs Tiotropium + Fluticasone/Salmeterol 500/50 BID X 1 year

Aaron et al

---

**Tiotropium in Combination with Placebo, Salmeterol, or Fluticasone-Salmeterol for COPD**

Randomized, DB, PC Trial
N = 660
Moderate or Severe COPD

Tiotropium + PBO vs Tiotropium + Budesonide/Formoterol 320/9 BID X 12 weeks

Welte et al
Am J Respir Crit Care Med 180:741, 2009
Tiotropium in Combination with Budesonide/Formoterol for COPD

Rate Ratio 0.38 (0.24-0.57; p < 0.001)

Welte et al
Am J Respir Crit Care Med 180:741, 2009

The MACRO Study
(Azithromycin 250mg/day x 1 year)

- NHLBI - COPD Clinical Research Network
- N = 1130
- Moderately-severe COPD
  \( \text{FEV}_1/\text{FVC} < 70\%; \text{FEV}_1 < 80\% \)
- "Exacerbation Prone"
- Primary Outcome: Time to first AECOPD

The NEW ENGLAND JOURNAL of MEDICINE

AUGUST 25, 2011

Azithromycin for Prevention of Exacerbations of COPD

Richard K. Albert, M.D., John Connett, Ph.D., William C. Bailey, M.D., Richard Casaburi, M.D., Ph.D., J. Allen D. Cooper, Jr., M.D., Gerard J. Criner, M.D., Jeffrey L. Curtis, M.D., Mark T. Dransfield, M.D., Melan K. Han, M.D., Stephen C. Lazarus, M.D., Barry Make, M.D., Nadhanan Marchetti, M.D., Fernando J. Martinez, M.D., Nancy E. Maldinger, M.D., Charlene McEvoy, M.D., M.P.H., Dennis E. Niewoehner, M.D., James Persaz, M.D., Ph.D., Connie S. Price, M.D., John Reilly, M.D., Paul D. Scanlon, M.D., Frank C. Scirica, M.D., Steven M. Shapiro, M.D., Ph.D., George R. Washko, M.D., Prescott G. Woodruff, M.D., M.P.H., and Nicholas R. Anthonisen, M.D., for the COPD Clinical Research Network

Time to First AECOPD

P < 0.001

Log-rank

Median = 266 days

Median = 174 days

HR = 0.73 (95% CI 0.63, 0.84), P < 0.0001

NEJM 365:689-98, 2011
STATCOPE: SimvaSTATin in the Prevention of COPD Exacerbations
(Simvastatin 40mg/day x 1 year)

- NHLBI - COPD Clinical Research Network
- N = 1130; Simvastatin + Usual Care vs Usual Care
- Moderately-severe COPD
  \( \text{FEV}_1/FVC < 70\%; \text{FEV}_1 < 80\% \)
- "Exacerbation Prone"
- Primary Outcome: Time to first AECOPD

Tiotropium Step-Up for Uncontrolled Asthma

**Number and Rates of AECOPD**

- **Number (N)**
  - Azithro: 900
  - Placebo: 600

- **Rates (N/patient-yr)**
  - Azithro: 1.48
  - Placebo: 1.83

**P < 0.001 (Chi-Square)**

**P < 0.008 (Poisson, Neg Binomial)**

**Rates of AECOPD/Patient-Year**

- **Participants (N)**
  - 200
  - 150
  - 250
  - 100
  - 50

- **Rates of AECOPD/patient-year**
  - P = 0.008 by Negative Binomial or Poisson

**Treatment Effects**

- **Hospitalized (all cause)**
  - Azithro: 175
  - Placebo: 110

- **Hospitalized (COPD-related)**
  - Azithro: 140
  - Placebo: 11

- **ED/Urgent Care Visits**
  - Azithro: 237
  - Placebo: 14

- **Unscheduled Office Visits**
  - Azithro: 249
  - Placebo: 11

- **Intubations**
  - Azithro: 322
  - Placebo: 14

**P = 0.13**

**P = 0.06**

**P = 0.47**

**P = 0.48**

**P = 0.03**