

### Small Airways (SAW) Symposium: Asthma Treatment Issues

#### New Bronchodilator for Asthma: A Patient-Centric Approach for Treating Asthma

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Immunologic Diseases  
Wake Forest School of Medicine

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### Stephen P. Peters, MD, PhD Disclosure

- **Basic and Clinical Research**
  - NHLBI (AsthmaNet, SARP, SPIROMICS)
  - ALA (ACRC)
- **Book Chapters**
  - UpToDate
  - Merck Manuals
- **Pharmaceutical Trials**
  - Actelion, Amgen, AstraZeneca, Boehringer-Ingelheim, Centocor, Cephalon, Genentech, GlaxoSmithKline, Forest, Medimmune, Sanofi-aventis
- **Advisory Boards**
  - Array Biopharma, AstraZeneca, Aerocrine, Airsonett AB, Boehringer-Ingelheim, Experts in Asthma, Gilead, GlaxoSmithKline, Merck, Novartis, Ono Pharmaceuticals, Pfizer, PPD Development, Quintiles, Sunovion, Saatchi & Saatchi, Targacept, TEVA, Theron
- **Speakers' Bureaus**
  - Integrity CE
- **Editorial Boards**
  - Resp Med, Assoc Editor,
  - Resp Research, Assoc Ed
  - J Allergy
  - Case Reports in Medicine
  - US Resp Disease
  - J Pulm Resp Medicine
  - Clin Exp Med Sciences
  - JACI: *In Practice*

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### Goals and Learning Objectives

- **Discuss the use of Patient Characteristics to Guide Asthma Treatment with respect to**
  - Characteristics of Inflammation
  - Smoking
  - *Hyperinflation*
  - Airflow Limitation
  - **N of 1 Approaches as an Adjunct**

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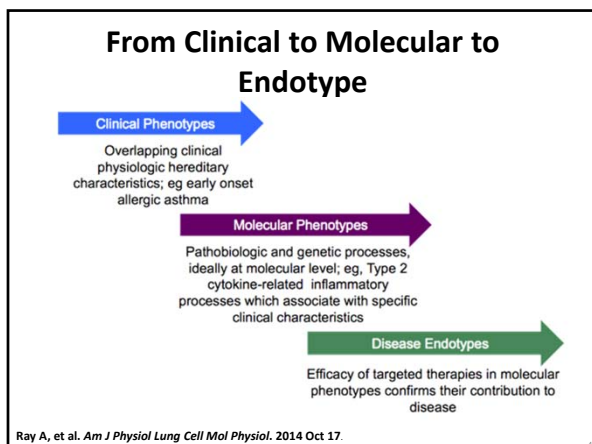
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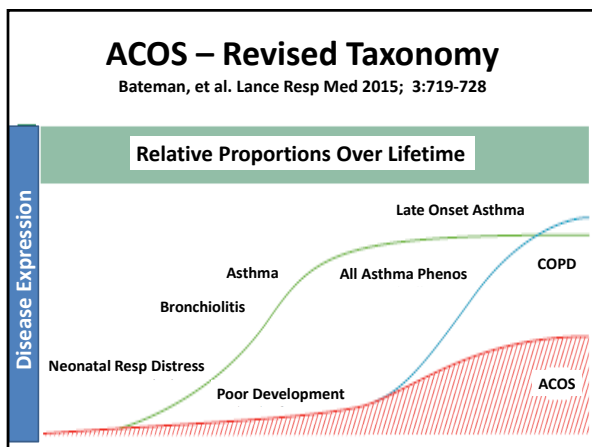
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- ### Drugs for COPD and Asthma
- **LABAs**
    - Salmterol (GSK)
    - Formoterol (MSD)
    - Arformoterol (Sunovion)
    - Indacaterol (Novartis) *Arcapta*
    - Olodaterol (BI) *Striverdi*
  - **LAMAs**
    - Tiotropium (BI)
    - Aclidinium (Actavis) *Tudorza*
    - Umeclidinium (GSK) *Incruse*
  - **LAMA/LABAs**
    - Umeclidinium/Vilanterol (GSK) *Anoro*
    - Tiotropium/Olodaterol (BI) *Stiolto*
  - **ICS/LABAs**
    - Fluticasone pro/Salmterol (GSK)
    - Budesonide/Formoterol (AZ)
    - Mometasone/Formoterol (MSD)
    - Fluticasone fur/Vilanterol (GSK) *Breo*
  - **PDE Inhibitors**
    - Theophylline
    - Roflumilast
  - **Leukotriene Modifiers**
    - Montelukast
  - **Antibiotics**
    - Azithromycin
  - **Biologics**

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### Patient Characteristics to Guide Therapy

- Characteristics of Inflammation
- Smoking Without or With COPD
- Air Trapping
- Airflow Limitation
  - With Reversibility
  - Persistent Obstruction

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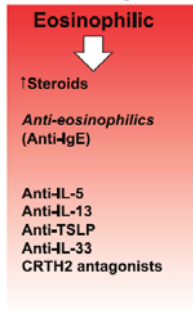
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### Characteristics of Inflammation

Barnes. J Allergy Clin Immunol 2015; 136:531-545  
"Th2 high"



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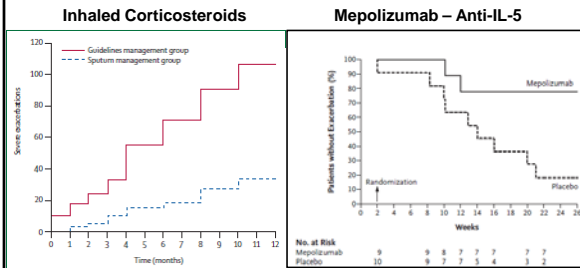
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### Targeting Sputum Eosinophils in Asthma



Green RH, et al. Lancet 2002;360:1715-1721.  
Nair P, et al. NEJM. 2009;360:985-993.

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### Characteristics of Inflammation

Barnes. J Allergy Clin Immunol 2015; 136:531-545  
"Th2 low"

<b>Neutrophilic</b>	<b>Paucigranulocytic</b>
↓	↓
<b>Steroid-resistant</b>	<b>Steroid-resistant</b>
<i>Anti-neutrophilics</i> <b>Macrolides</b>	<b>LAMA</b> <b>LAMA+LABA combo</b> <b>Triple combo</b>
<b>CXCR2 antagonists</b> <b>Anti-TNF</b> <b>Anti-IL-1</b> <b>Inflammasome inhibitors</b> <b>Anti-IL-17/23</b> <b>p38 MAPK inhibitors</b> <b>PDE4 inhibitors</b>	<b>Bronchial thermoplasty</b>

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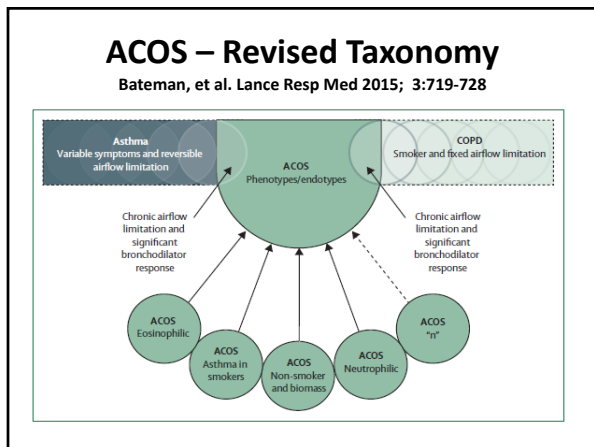
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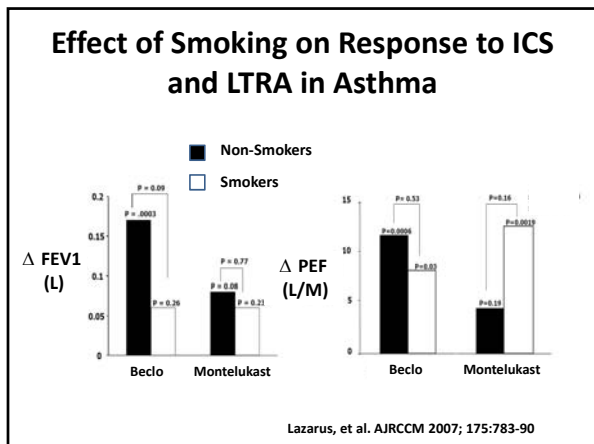
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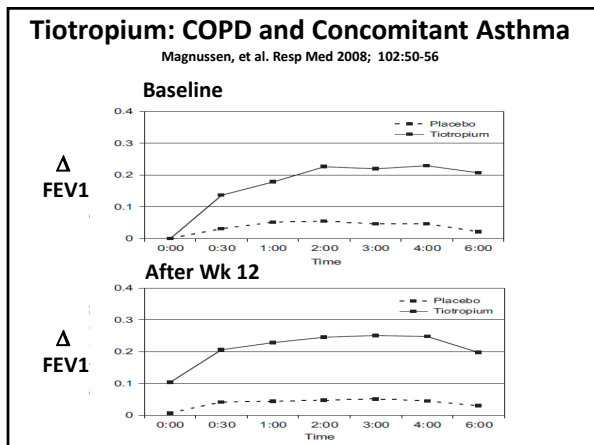
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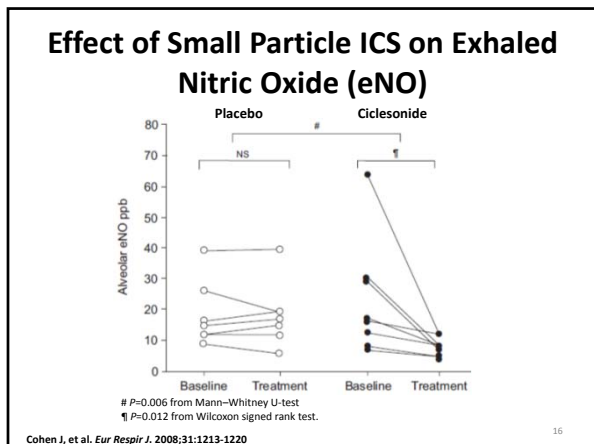
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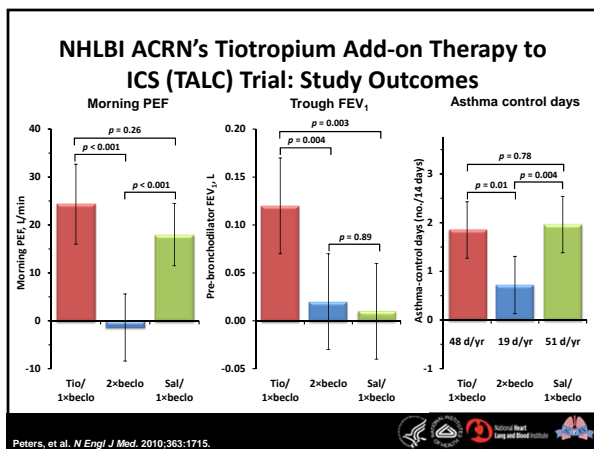
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### Predictors of Response to Tiotropium: Summary

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

Peters, et al., J Allergy Clin Immunol 2013; 132:1068-1074

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### Exploratory Predictors Not Associated with Response to Tiotropium

- Ethnicity
- Gender
- Atopy (skin test +)
- IgE Level (ln)
- Sputum Eosinophils
- FeNO (ln)
- Asthma Duration
- BMI

Peters, et al., J Allergy Clin Immunol 2013; 132:1068-1074

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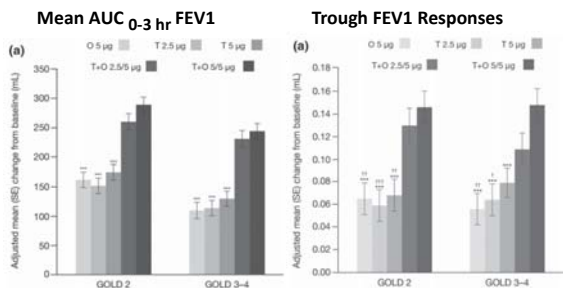
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### Combination Tiotropium & Olodaterol Therapy in COPD



Ferguson, et al. Adv Ther 2015; 32:523-536

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## Time for one-person trials

Precision medicine requires a different type of clinical trial that focuses on individual, not average, responses to therapy, says **Nicholas J. Schork**.



Nature 2015; 250:609-611

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### IMPRECISION MEDICINE

For every person they do help (blue), the ten highest-grossing drugs in the United States fail to improve the conditions of between 3 and 24 people (red).

**1. ABILIFY (aripiprazole)**  
Schizophrenia



**2. NEXIUM (esomeprazole)**  
Heartburn



**3. HUMIRA (adalimumab)**  
Arthritis



**4. CRESTOR (rosuvastatin)**  
High cholesterol



Nature 2015; 250:609-611

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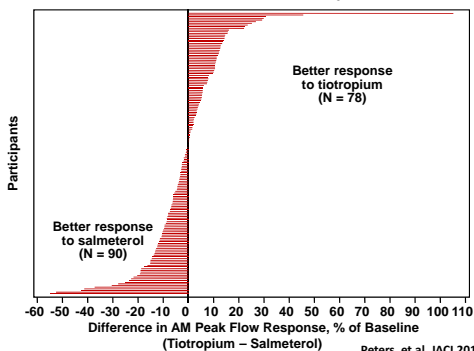
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### Differential Response to Tiotropium vs Salmeterol: PEF<sub>am</sub>



Peters, et al. JACI 2013;132:1068

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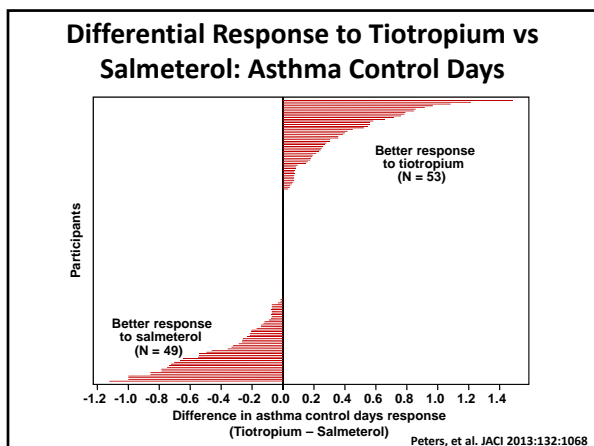
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### The N of 1 Clinical Trial: The Ultimate Strategy for Individualizing Medicine?

**Do n-of-1 trials have a role in clinical science?**

- N-of-1 trials that **focus exclusively on the objective, empirically determined optimal intervention for a single patient** are compatible with the ultimate end point of clinical practice: the care of individual patients.
- **Meta-analyses of the outcomes of multiple n-of-1 trials** could be compared with standard treatment regimens and help put into context the utility and practicality of n-of-1 trials.

**Design issues in n-of-1 clinical trials**

- **Randomization of treatment order, carryover effects, washout periods and blinding** are key design elements that need to be considered in n-of-1 trials.

**The analysis of n-of-1 clinical trials**

- **Methods that account for serial correlation** in comparing the response to two or more treatments, such as certain time-series analyses, are necessary.
- **More research** into how to identify and accommodate **carryover effects** in n-of-1 trials is clearly needed.

Per Med 2011; 8:161-173

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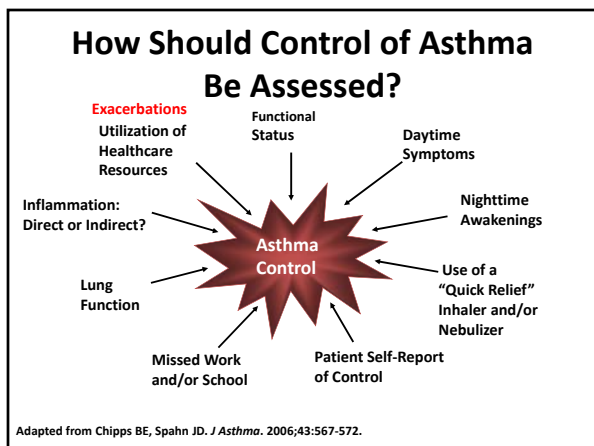
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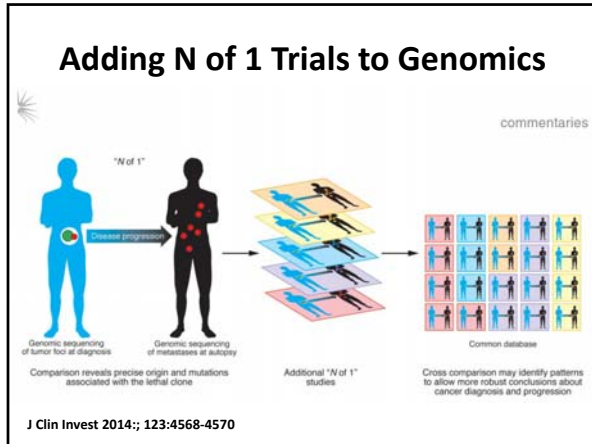
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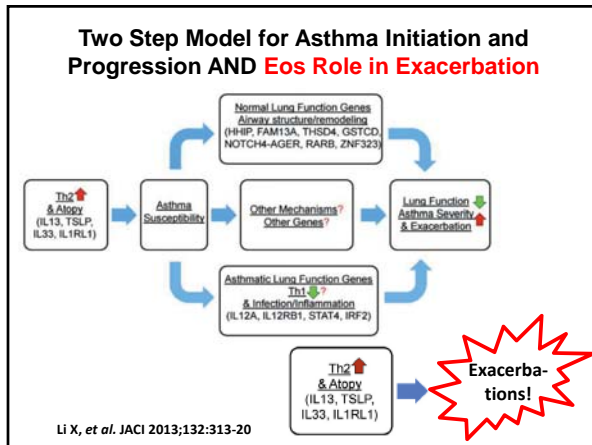
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Questions?

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