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COPDGene®

COPD Genetic Epidemiology

SPIROMICS

# COPD: Expanding The Diagnosis

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Supported by NHLBI R01 HL 089856 and 089897

# Disclosures

- Consultant: AstraZeneca, GlaxoSmithKline, Circassia, Spiration, Royalty Walters Knue, UpToDate and Boehringer Ingelheim
- Speaker: Sunovion
- Advisory Board: Verona

# Learning Objectives

- Describe the respiratory features in patients with a history of cigarette smoking and no airflow obstruction
- State the criteria of the COPDGene 2019 diagnosis of COPD

# COPDGene Major Entry Criteria

Inclusion criteria:

**Age 45 – 80**

**Non-Hispanic White and African American**

**≥ 10 pack-year cigarette smoking history**

Exclusion criteria: minimal to enhance recruitment

First or second degree relative

Recent COPD exacerbation

Lung surgery ≥ 1 lobe

Lung cancer

Other uncontrolled cancers

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# COPDGene Major Entry Criteria

**A Cohort of Current and Former Cigarette Smokers**

Inclusion criteria:

**Age 45 – 80**

**Non-Hispanic White and African American**

**≥ 10 pack-year cigarette smoking history**

Exclusion criteria: minimal to enhance recruitment

First or second degree relative

Recent COPD exacerbation

Lung surgery ≥ 1 lobe

Lung cancer

Other uncontrolled cancers

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# COPDGene Cohort Characteristics

| | Total | Percent |
|---|---|---|
| Gender | | |
| **Male** | **5345** | **53%** |
| **Female** | **4674** | **47%** |
| Race | | |
| **NHW** | **6887** | **69%** |
| **AA** | **3132** | **31%** |
| GOLD Spirometry Grade | | |
| **None** | **4380** | **44%** |
| **GOLD 1 & U** | **2000** | **20%** |
| **GOLD 2/3/4** | **3639** | **36%** |

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# GOLD 0

## GOLD 0 – At Risk

- No airflow limitation (FEV1/FVC ≥ 0.70)
- History of exposure (cigarette smoking)
- Chronic respiratory symptoms (cough, sputum)

Diagnosis, Management and Prevention of COPD. GOLD Guidelines, 2004. www.goldcopd.com

# GOLD 0

## GOLD 0: Why?

- GOLD objective: increase awareness of significance of symptoms
- Intervene when the disease is not yet a health problem
- Cough and sputum often precede the development of airflow limitation

Diagnosis, Management and Prevention of COPD. GOLD Guidelines, 2005. www.goldcopd.com

# Smokers Without Airflow Limitation

Original Investigation

## Clinical and Radiologic Disease in Smokers With Normal Spirometry

Elizabeth A. Regan, MD; David A. Lynch, MD; Douglas Curran-Everett, PhD; Jeffrey L. Curtis, MD; John H. M. Austin, MD; Philippe A. Grenier, MD; Hans-Ulrich Kauczor, MD; William C. Bailey, MD; Dawn L. DeMeo, MD; Richard H. Casaburi, PhD, MD; Paul Friedman, MD; Edwin J. R. Van Beek, MD; John E. Hokanson, PhD; Russell P. Bowler, MD; Terri H. Beaty, PhD; George R. Washko, MD; MeiLan K. Han, MD; Victor Kim, MD; Song Soo Kim, MD; Kunihiro Yagihashi, MD; Lacey Washington, MD; Charlene E. McEvoy, MD; Clint Tanner, MD; David M. Mannino, MD; Barry J. Make, MD; Edwin K. Silverman, MD; James D. Crapo, MD; for the Genetic Epidemiology of COPD (COPDGene) Investigators

*JAMA Intern Med*. doi:10.1001/jamainternmed.2015.2735
Published online June 22, 2015.

# No Airflow Obstruction Patients Are Similar to GOLD 1 Patients in COPDGene

| | GOLD 0 | GOLD 1 |
|---|---|---|
| Normal airflow, n | 4,388 | 794 |
| Chronic bronchitis; | 12.6%, | 15.7% |
| Severe exacerbations; | 4.3%, | 4.9% |
| Symptoms (SGRQ > 25); | 26.0%, | 28.5% |
| MMRC ≥ 2 dyspnea; | 23.5%. | 22.0% |
| 6MWD decrement (< 350 m); | 15.4%. | 13.7% |
| More airway disease (WA%); | 32.2%, | 34.2% |
| Less emphysema (> 5%); | 9.8%, | 34.4% |
| Respiratory medicine use; | 20.0%, | 29.1% |

More med use in symptomatic patients

# Impairment Definition

**Symptoms**

- Chronic bronchitis
- MMRC ≥ 2
- SGRQ > 25

**Functional**

- 6MWD < 350m

**AECOPD** history of ≥ 1 severe AECOPD in last year

**Radiologic** abnormalities

- Emphysema > 5%
- Gas trapping >20%

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# No Airflow Obstruction Patients Are Only Slightly Less Impaired Than GOLD 1

| | GOLD 0 (n = 4388) | GOLD 1 (n = 794) |
|---|---|---|
| Any Impairment | 2375 (54.1) | 585 (73.7) |
| 6 Impairments | 8 (0.2) | 6 (0.8) |
| 5 Impairments | 32 (0.7) | 17 (2.1) |
| 4 Impairments | 156 (3.6) | 65 (8.2) |
| 3 Impairments | 414 (9.4) | 92 (11.6) |
| 2 Impairments | 690 (15.7) | 204 (25.7) |
| 1 Impairment | 1089 (24.8) | 201 (25.3) |
| No Impairment | 1990 (45.4) | 209 (26.3) |

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# Smoking History With No Airflow Obstruction

**Frequently have:**

- **Respiratory symptoms: 25%**
- **Impaired health status: 25%**
- **Severe acute respiratory events (AECOPD): > 4%**
- **Functional impairment: 15%**
- **Have radiologic evidence of lung disease: 20%**
- **Are receiving respiratory medications: 20%**

# Smoking History
# With No Airflow Obstruction

- **Do they have NOCOPD?**
  **They have COPD!!**

- **"The Myth of the Healthy Smoker"**
- **Do they progress?**
- **How should they be treated?**

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 12, 2016 VOL. 374 NO. 19

# Clinical Significance of Symptoms in Smokers with Preserved Pulmonary Function

Prescott G. Woodruff, M.D., R. Graham Barr, M.D., Dr.P.H., Eugene Bleecker, M.D., Stephanie A. Christenson, M.D., David Couper, Ph.D., Jeffrey L. Curtis, M.D., Natalia A. Gouskova, Ph.D., Nadia N. Hansel, M.D., Eric A. Hoffman, Ph.D., Richard E. Kanner, M.D., Eric Kleerup, M.D., Stephen C. Lazarus, M.D., Fernando J. Martinez, M.D., Robert Paine, III, M.D., Stephen Rennard, M.D., Donald P. Tashkin, M.D., and MeiLan K. Han, M.D., for the SPIROMICS Research Group*

c/o MeiLan Han, MD

# SPIROMICS: longitudinal study of cigarette smokers and never smokers


n = 2736

Ever smokers (current or former) had ≥ 20 pack years

Respiratory symptoms assessed by COPD Assessment Test (CAT)

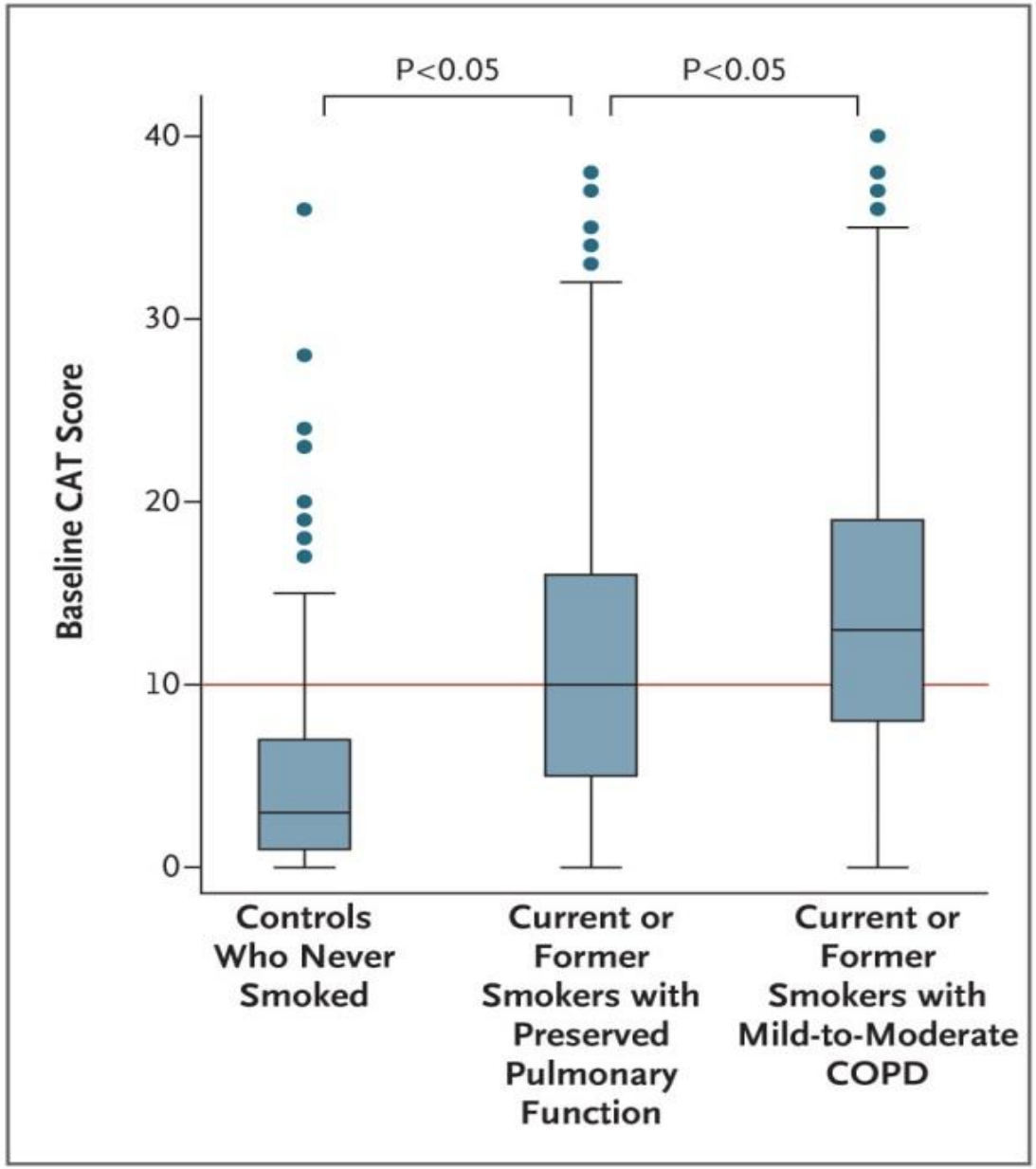
- CAT scores range from 0-40; higher score denotes greater impact
- GOLD: CAT score ≥ 10 - symptom threshold to assist treatment choice

Chest CT scan

Exacerbations collected prospectively

Spirometry

# Symptoms (CAT ≥10) are common in GOLD 0




849 GOLD 0 subjects

50% of GOLD 0 subjects have CAT ≥ 10

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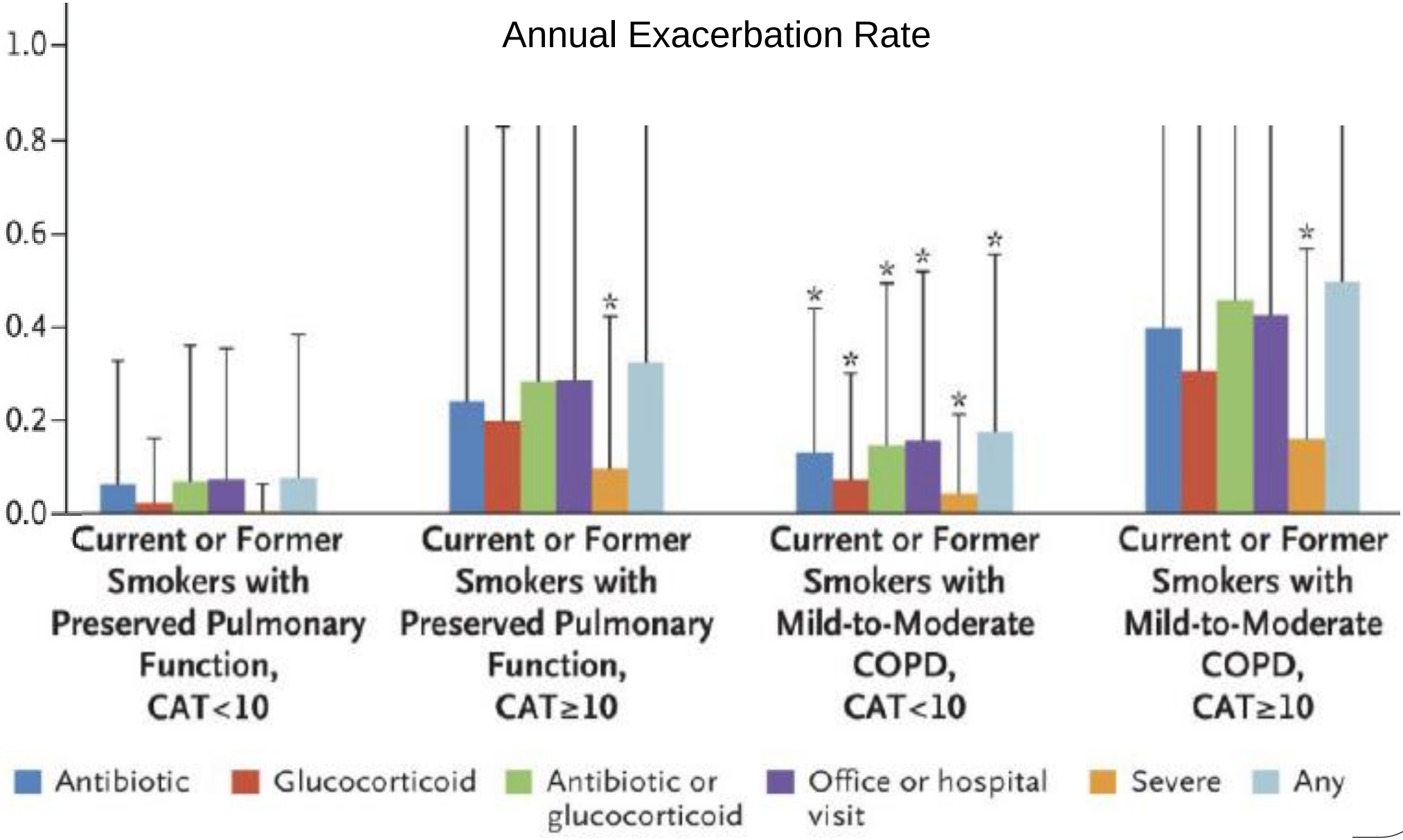
# Smokers with no airflow obstruction have acute respiratory exacerbations



# GOLD 0 Symptomatic Patients Compared to Mild COPD (GOLD 1 - 2)


- Similar acute respiratory events treated with antibiotics, steroids, hospitalizations
  - CAT is better predictor of AECOPD than FEV1
  - MRC dyspnea similar to CAT as predictor of AEOPD
- Similar airway thickening; less emphysema
- Similar decreases in 6-minute walk distance

- Lower $FEV_1$, FVC and inspiratory capacity (IC) than non-smokers

# Respiratory Medication Use

Symptomatic ever-smokers with no airflow obstruction

- 42% used bronchodilators
- 23% used inhaled corticosteroids

# COPD: COPDGene 2019

**Hypothesis:**

Integrated approach using

- environmental exposure,
- clinical symptoms,
- chest CT imaging and
- spirometry

better defines disease and

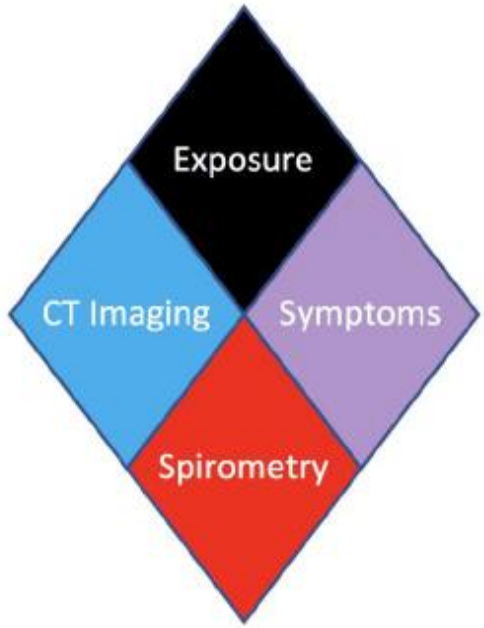
Identifies spirometric progression and mortality

Lowe KE et al. COPDGene 2019: Redefining the diagnosis of COPD. J COPD Fndn, submitted 2019

# COPD: COPDGene 2019

**Criteria for COPDGene 2019 diagnosis**

- Exposure: Cigarette smoking ≥ 10 pack-years
- Symptoms: mMRC dyspnea ≥ 2 and/or chronic bronchitis
- CT structural disease: >5% emphysema and/or >15% gas trapping
- Airflow obstruction: $FEV_1/FVC < 0.70$ and/or $FEV_1 < 80\%$ predicted




Lowe KE et al. Redefining the diagnosis of COPD. J COPDF, submitted 2019

# COPDGene 2019 COPD Subgroups

| Category | Description | Symbol | # of Disease Features |
|---|---|---|---|
| A | Exposure |  | 1 |
| B | Exposure + CT Abnormal |  | 2 |
| C | Exposure + Symptoms |  | 2 |
| D | Exposure + Spirometry Abnormal |  | 2 |
| E | Exposure + Symptoms + CT Abnormal |  | 3 |
| F | Exposure + Spirometry Abnormal + Symptoms |  | 3 |
| G | Exposure + Spirometry Abnormal + CT Abnormal |  | 3 |
| H | Exposure + Spirometry Abnormal + Symptoms + CT Abnormal |  | 4 |

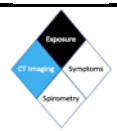
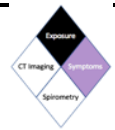
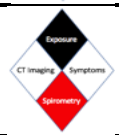
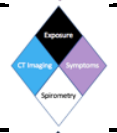
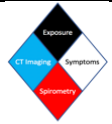
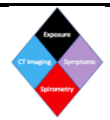
Lowe KE et al. Redefining the diagnosis of COPD. J COPDF, submitted 2019

# COPDGene 2019 COPD Subgroups

| Category | Description | Symbol | # of Disease Features | |
|---|---|---|---|---|
| A | Exposure |  | 1 | |
| B | Exposure + CT Abnormal |  | 2 | **Possible COPD** |
| C | Exposure + Symptoms |  | 2 | |
| D | Exposure + Spirometry Abnormal |  | 2 | |
| E | Exposure + Symptoms + CT Abnormal |  | 3 | |
| F | Exposure + Spirometry Abnormal + Symptoms |  | 3 | **Probable COPD** |
| G | Exposure + Spirometry Abnormal + CT Abnormal |  | 3 | |
| H | Exposure + Spirometry Abnormal + Symptoms + CT Abnormal |  | 4 | **Definite COPD** |

Lowe KE et al. Redefining the diagnosis of COPD. J COPDF, submitted 2019

# COPDGene 2019 COPD Progression & Mortality

| | Subgroup | Odds of change >350 ml in $FEV_1$ (OR [95% CI])* | Hazard Ratio for all-cause mortality (HR [95% CI])# | |
|---|---|---|---|---|
|  | **A** | 1.0 (ref.) | 1.0 (ref.) | **NO COP** |
|  | **B** | **1.31 (1.04-1.65)** | 1.05 (0.76-1.44) | **Possib COPD** |
|  | **C** | **1.42 (1.07-1.88)** | **1.55 (1.09-2.19)** | |
|  | **D** | 0.92 (0.64-1.30) | **1.48 (1.03-2.12)** | |
|  | **E** | **1.74 (1.28-2.36)** | **1.90 (1.33-2.71)** | **Probab COPD** |
|  | **F** | 1.02 (0.66-1.60) | **2.62 (1.84-3.72)** | |
|  | **G** | **2.11 (1.66-2.68)** | **1.76 (1.36-2.27)** | |
|  | **H** | **2.82 (2.18-3.66)** | **5.18 (4.15-6.48)** | **Definit COPD** |

Lowe KE et al. Redefining the diagnosis of COPD. J COPDF, submitted 2019

# COPDGene 2019 COPD Progression and Mortality

|  | Odds ratio for change in $FEV_1$ >350 ml* | Hazard ratio for all-cause mortality** | COPDGene 2019 Classification |
|---|---|---|---|
|  | 1.0 | 1.0 | Reference |
|  | **1.26 (1.03-1.53)** | 1.28 (0.99-1.66) | Possible COPD |
|  | **1.88 (1.52-2.32)** | **1.89 (1.48-2.41)** | Probable COPD |
|  | **2.88 (2.23-3.71)** | **5.21 (4.17-6.52)** | Definite COPD |

Lowe KE et al. Redefining the diagnosis of COPD. J COPDF, submitted 2019

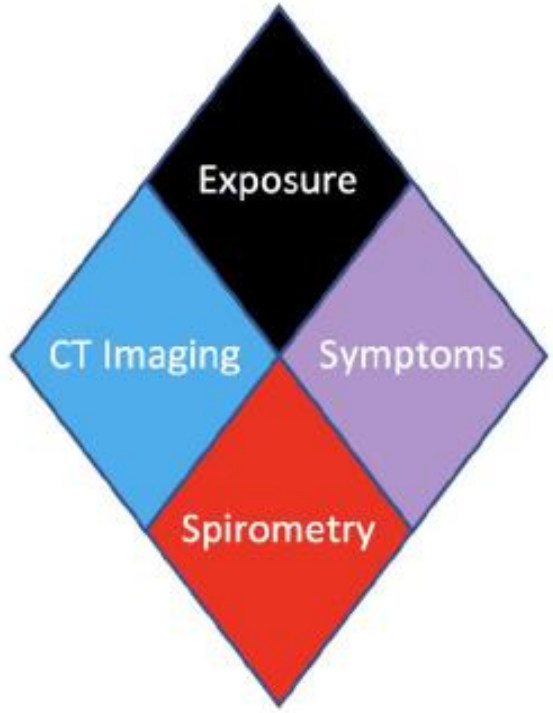
# COPD: COPDGene 2019

Integrated approach using

- environmental exposure,
- clinical symptoms,
- chest CT imaging and
- spirometry

better defines disease and

Identifies spirometric progression and mortality




Lowe KE et al. COPDGene 2019: Redefining the diagnosis of COPD. J COPD Fndn, submitted 2019

# COPD: COPDGene 2019

| | |
|---|---|
| Gloria Westney, MD, MS | Morehouse, Atlanta, GA |
| Ava Wilson | University of Alabama, Birmingham, AL |
| **Robert A. Wise, MD** | **Johns Hopkins University, Baltimore, MD** |
| Andrew Yen, MD | University of California, San Diego, CA |
| Kendra Young, MSPH, PhD | University of Colorado, Aurora, CO |
| Edwin K. Silverman, MD, PhD | Brigham and Women's Hospital, Boston, MA |
| James D. Crapo, MD | National Jewish Health, Denver, CO |

Lowe KE et al. Redefining the diagnosis of COPD. J COPDF, submitted 2019

# Summary

**Patients with history of cigarette smoking and normal airflow by GOLD criteria have**

- **Respiratory symptoms**
- **Impaired health status**
- **Severe acute respiratory events (AECOPD)**
- **Functional impairment**
- **Have radiologic evidence of lung disease**
- **Are receiving respiratory medications**

# COPDGene Investigators

**Program Directors: James D. Crapo, M.D. and Edwin K. Silverman, M.D., Ph.D.**
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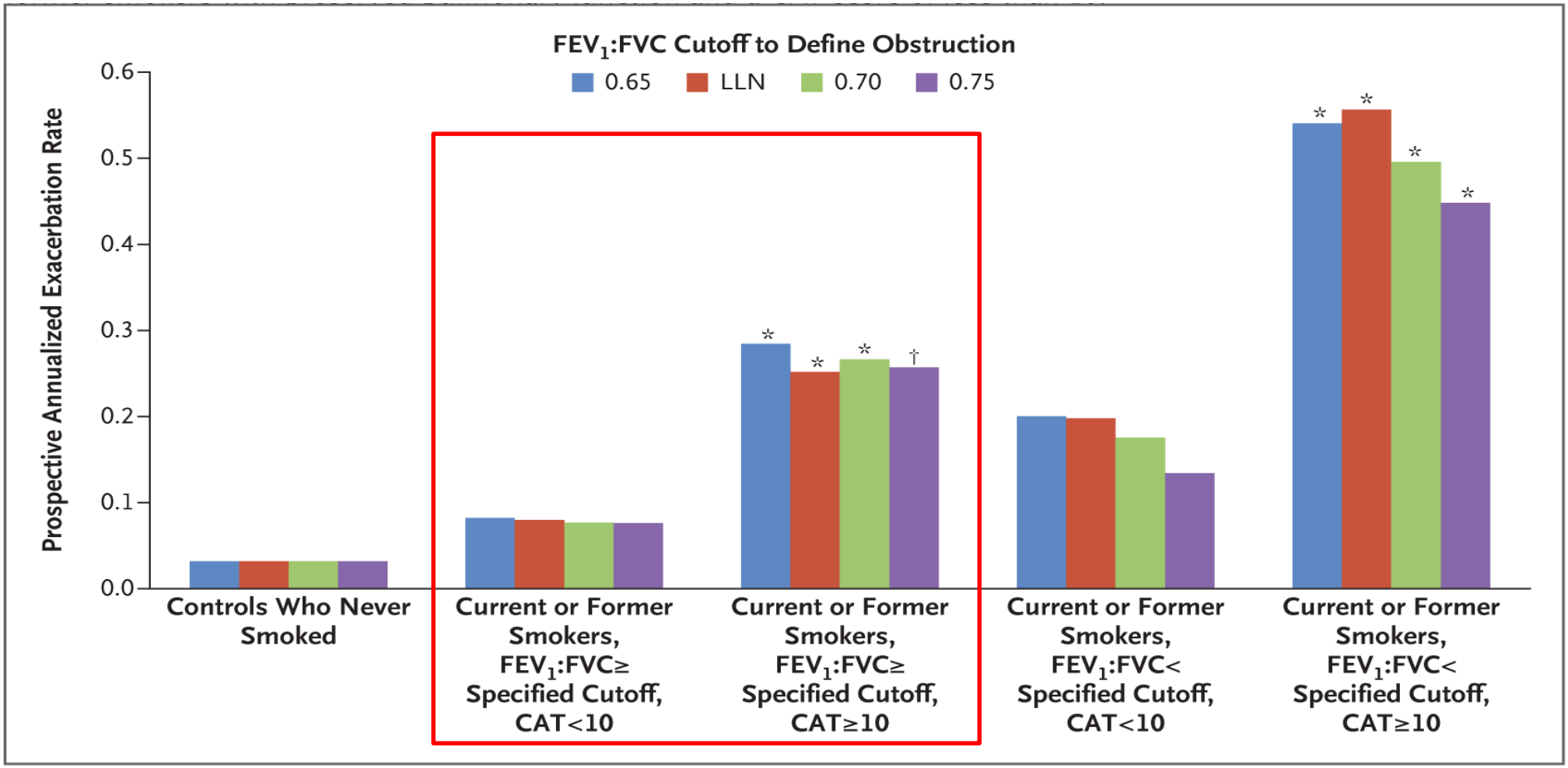
# Varying the definition of “obstruction” has little effect on exacerbations

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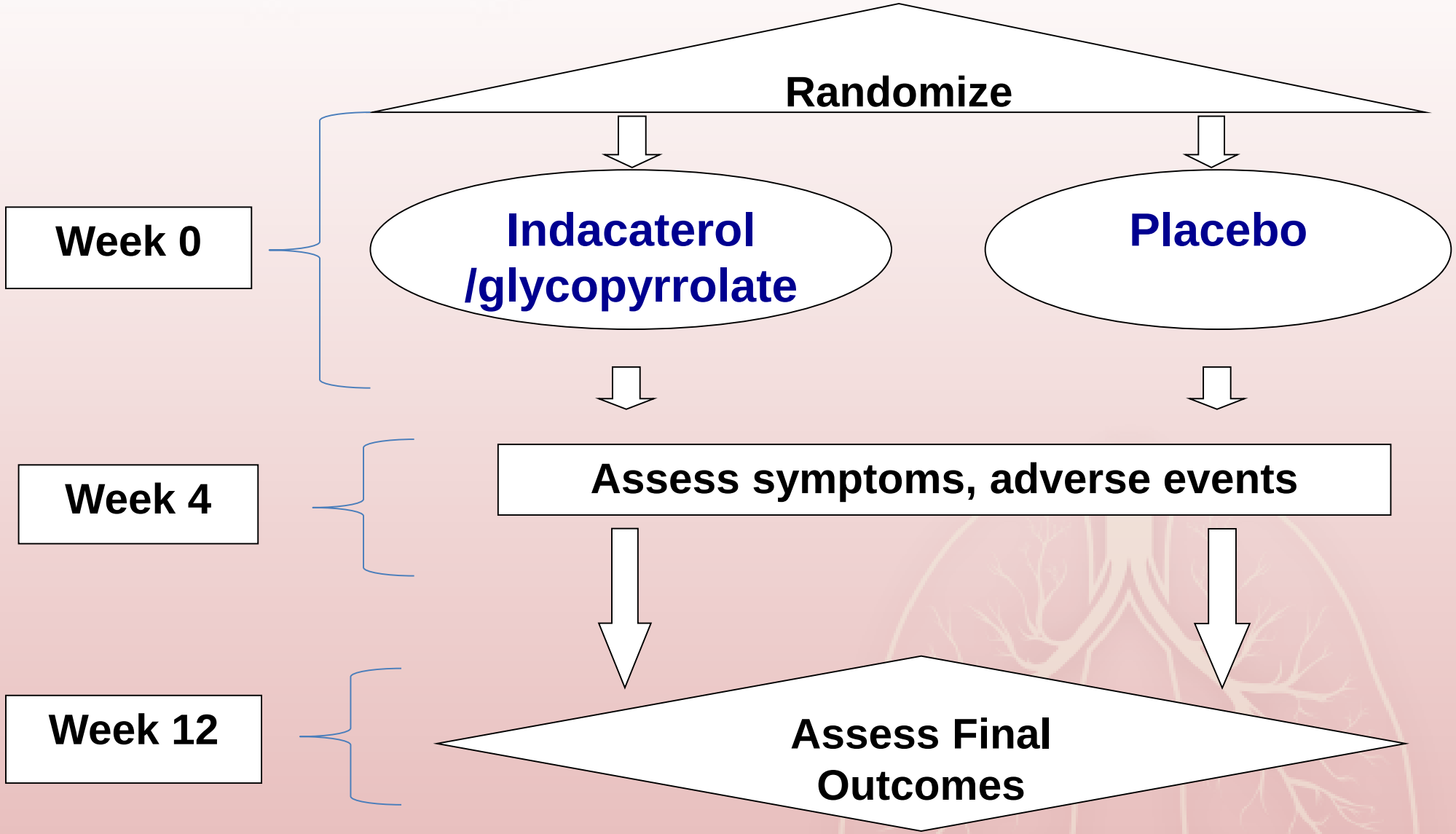
# STUDY AIMS

Hypothesis underlying this clinical trial:

- Current and former smokers with post-BD $FEV_1$/FVC ≥0.70 will derive symptomatic benefit from long-acting bronchodilator therapy

Study Objective:

- A 12-week treatment, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to assess the efficacy and safety of indacaterol / glycopyrrolate 27.5/15.6 mcg inhaled twice daily in symptomatic current and former smokers with preserved spirometry and respiratory symptoms as defined by CAT ≥ 10.


Randomize
Week 0
Indacaterol /glycopyrrolate
Placebo
Week 4
Assess symptoms, adverse events
Week 12
Assess Final Outcomes

# PRIMARY OUTCOME MEASURES

**Primary Outcome Measure:**

- **Proportion of individuals who experience a 4 unit improvement in SGRQ at 12 weeks and do not experience "treatment failure" during the 12 week treatment period.**

- ***Definition of treatment failure:*** **increase in respiratory symptoms necessitating treatment with active, long-acting inhaled bronchodilator and/or inhaled or oral corticosteroids.**