COPD Comorbidities
UNT Health Science Center
Grand Rounds

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Disclosure

- I have no financial interests related to this presentation
Plan

• Why do comorbidities matter?
• What is a comorbidity?
• Strengths and Limitations of Comorbidity Research
• Individual COPD Comorbidities
  – Frequency
  – Mechanisms
  – Clinical Implications
FEV\textsubscript{1} is cornerstone for diagnosis and progression

Casanova C. AJRCCM 2011; 184: 1015

FEV\textsubscript{1} is just one determinant of FEV\textsubscript{1} progression

Agusti A. Resp Res 2010; 11: 122

FEV\textsubscript{1} insufficient descriptor of disease experience

Agusti A. Resp Res 2010; 11: 122

FEV\textsubscript{1} insufficienlly describe disease experience

Agusti A. Resp Res 2010; 11: 122
**FEV, insufficiently describe disease experience**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Population</th>
<th>Factors included</th>
<th>Explained var.</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGRO total</td>
<td>146</td>
<td>FEV1, TLC, PaO2, MMRC, AE COPD</td>
<td>52%</td>
</tr>
<tr>
<td>de Torres 2006</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMRC de Torres 2007</td>
<td>100 women</td>
<td>BM, DLCO, PaO2, Po2/Plmax</td>
<td>30%</td>
</tr>
<tr>
<td>SGRO</td>
<td>60 men</td>
<td>FEV1, apo, FFM, SpO2, MMRC, 6MWD</td>
<td>42%</td>
</tr>
<tr>
<td>Ferrari 2010</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SF-36</td>
<td>163</td>
<td>FEV1, cough, phlegm, dyspnea, age, smoking status</td>
<td>39%</td>
</tr>
<tr>
<td>van Manen 2001</td>
<td>1,617</td>
<td>DLCO, FEV1, UCSD SOB, 6MWD</td>
<td>28%</td>
</tr>
<tr>
<td>SF-36 Moy 2009</td>
<td>4,475</td>
<td>FEV1, apo, MMRC, AE COPD, CB, TLC, smoking</td>
<td>54%</td>
</tr>
<tr>
<td>Martinez 2012</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Disease experience (QOL) impacted by other respiratory factors

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**No disease comes alone**

- Medicare beneficiaries
  - 83% at least one chronic condition
  - 23% have ≥ 5 chronic conditions
    - Visit ≥ 13 physicians
    - Fill ≥ 50 prescriptions
- Changing over time
  - Overall increase number of conditions
  - CHF, CAD, stroke declining
  - COPD, CKD, DM, MSK increasing

**Americans with COPD**

- Average 4 additional diseases
- Among those on Medicare 68% ≥ 4 additional conditions
- Between 5-10 prescribed medications

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**...and bringing company is expensive**

- RR of utilization by comorbidities
- Out-of-pocket payment by comorbidities

---

<table>
<thead>
<tr>
<th>Medicare annual cost by comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schneider KM. Health QOL Outcomes 2009;7:82</td>
</tr>
</tbody>
</table>
Question
• Is it possible for coexistent diseases to impact disease experience?
  – Symptoms
  – Exacerbations
  – Quality of life
• Is it possible for diseases to share pathogenic pathways?
  – Opportunities to develop treatment
• Could one disease treatment or prevention impact the other?
  – Specific or personalized treatment protocols

Why does this matter?
Comorbidities matter
• An additional opportunity to:
  – Explain burden of symptoms
  – Explain COPD outcomes
  – Improve quality of care
  • Diagnosis
  • Treatment
  • Readmissions
  – Understand COPD development and progression
  • Pathogenic mechanisms
  • Associations
  • Targets for interventions

Why does this matter?
Currently part of COPD definition
• Common preventable and treatable disease
• Characterized by airflow limitation that is usually progressive
• Associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases
• Exacerbations and comorbidities contribute to the overall severity in individual patients
Why does this matter?
“You die with COPD, not by COPD”
• A 64 year-old male with mild COPD is admitted for the first time in 1 year...
  – 42% of admissions are for cardiovascular disease
• The same patient, now 65 year-old is admitted again, ...
  – 48% of readmissions are for cardiovascular disease
  – Comorbidities are the strongest association with readmission
• The TORCH experience
  – Cvasc 27%, Resp 35%, Cancer 21%
  – AECOPD 21%. COPD named in less than 50% certificates
  Drummond. 2010. McGarvey. 2007

Plan
• Why do comorbidities matter?
• What is a comorbidity?
• Strengths and Limitations of Comorbidity Research
• Individual COPD Comorbidities
  – Frequency
  – Mechanisms
  – Clinical Implications

What is a comorbidity?
• Recent reports show association between COPD and skin wrinkles
  J. Unreal Research
• Coexistent diseases vs. Comorbid interactions
• Coexistent disease
  – Similar age distribution
  – Shared additional risk factors (e.g., tobacco)
  – Common mechanistic pathways include “systemic inflammation and abnormal repair”
  – Treatment of one condition does not impact the other
  Martinez. JCODF 2014
What is a comorbidity?

• Three possible criteria
  – Mutual impact on other disease’s progression and management
    • Discover unique physiologic pathways
    • Identify treatment interactions
  – Frequency and impact on mortality surpasses the expected in the general population
    • Set research and healthcare priorities
  – The disease is part of a unique phenotype
    • Discover physiologic pathways
    • Unique treatment opportunities

Martinez. JCPDF 2014

Comorbidity occurrence is not random

Comorbidities and mortality
Comorbidities and QOL

Comorbid disease

Wrinkles
- Frequency √
- Impact on COPD outcomes X
- Impact of COPD on comorbid disease X
- Associated phenotypes √
- Mechanistic pathways √

Erectile dysfunction
- Frequency X
- Impact on COPD outcomes √
- Impact of COPD on comorbid disease X
- Associated phenotypes X
- Mechanistic pathways √

What is a comorbidity?
- Frequency
  - Higher than in general population
  - Increasing with worsening COPD
- Impact
  - Symptoms, exacerbations, QOL
  - Treatment of one disease affects the other
- The disease is part of a unique phenotype
  - Comorbid disease more frequent in a subgroup of COPD
    - Chronic bronchitis, emphysema, frequent exacerbator

Martinez. JCPDF 2014
Plan

• Why do comorbidities matter?
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Research on COPD comorbidities:
Source of information matters

<table>
<thead>
<tr>
<th>Info provided</th>
<th>Chart review</th>
<th>RCTs</th>
<th>Prospective cohorts</th>
<th>Admin data</th>
<th>National surveys</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD severity</td>
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<td></td>
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<tr>
<td>Comorbidity</td>
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<tr>
<td>Demo: SES</td>
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<tr>
<td>Short-term outcomes</td>
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<tr>
<td>Mortality</td>
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<tr>
<td>Cost</td>
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<tr>
<td>Bio samples</td>
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<tr>
<td>External validity</td>
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</thead>
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<td>COPD severity</td>
<td>PFTs</td>
<td>PFTs</td>
<td>PFTs</td>
<td>O2 use, steroids</td>
<td>?</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>Objective</td>
<td>Self-report</td>
<td>Self-report</td>
<td>ICD codes</td>
<td>Self-report</td>
</tr>
<tr>
<td>Demo: SES</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
<td>?</td>
<td>Some</td>
</tr>
<tr>
<td>Short-term outcomes</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>ICD codes</td>
<td>?</td>
</tr>
<tr>
<td>Long-term outcomes</td>
<td>?</td>
<td>?</td>
<td>+/-</td>
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<td>Linked</td>
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<td>Mortality</td>
<td>?</td>
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<td>+</td>
<td>Linked</td>
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<tr>
<td>Cost</td>
<td>+</td>
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<td>?</td>
<td>+</td>
<td>Linked</td>
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<tr>
<td>Bio samples</td>
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<tr>
<td>External validity</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>+</td>
</tr>
</tbody>
</table>

### Research on COPD comorbidities:
#### The way comorbidities are counted matters

<table>
<thead>
<tr>
<th>Method</th>
<th>Example</th>
<th>Predicts</th>
<th>Preferred use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weighted</td>
<td>Charlson</td>
<td>Mortality</td>
<td>Admin. data</td>
</tr>
<tr>
<td>COPD specific</td>
<td>Elixhauser</td>
<td>Mortality, Cost</td>
<td>Admin. Data, Cohorts</td>
</tr>
<tr>
<td>COPD specific</td>
<td>COTE</td>
<td>Mortality</td>
<td>Cohorts</td>
</tr>
<tr>
<td>COPD specific</td>
<td>COMCOLD</td>
<td>QOL</td>
<td>RCTs, Cohorts</td>
</tr>
<tr>
<td>COPD specific</td>
<td>MCI</td>
<td>Mortality, QOL</td>
<td>Cohorts, Admin data</td>
</tr>
<tr>
<td>COPD specific</td>
<td>COPDGene</td>
<td>AECOPD, QOL</td>
<td>Cohorts</td>
</tr>
</tbody>
</table>


### COPD comorbidities in two contemporary cohorts. An example

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>COPDGene N=3,690</th>
<th>SPIROMICS N=853</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Heart disease (CHD)</td>
<td>668 (18)</td>
<td>177 (21)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>482 (13)</td>
<td>114 (13)</td>
</tr>
<tr>
<td>Congestive heart failure (CHF)</td>
<td>198 (5)</td>
<td>21 (2)</td>
</tr>
<tr>
<td>Stroke</td>
<td>220 (6)</td>
<td>35 (4)</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>764 (21)</td>
<td>246 (29)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>640 (17)</td>
<td>107 (13)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1868 (51)</td>
<td>428 (50)</td>
</tr>
<tr>
<td>High Blood pressure</td>
<td>1529 (42)</td>
<td>NA</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease (GERD)</td>
<td>1154 (30)</td>
<td>254 (30)</td>
</tr>
<tr>
<td>Stomach ulcers*</td>
<td>373 (11)</td>
<td>NA</td>
</tr>
<tr>
<td>Obesity</td>
<td>1227 (33)</td>
<td>270 (32)</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>631 (17)</td>
<td>139 (16)</td>
</tr>
<tr>
<td>Hay fever</td>
<td>980 (24)</td>
<td>236 (28)</td>
</tr>
<tr>
<td>Peripheral Vascular Disease (PVD)</td>
<td>126 (3)</td>
<td>NA</td>
</tr>
</tbody>
</table>
### Summary (so far)

- Respiratory factors are not sufficient explanation for COPD progression and experience
- Chronic diseases frequently coexist
- Coexistence is different from comorbid interaction
- Source of information on comorbidities matter

### Plan

- Why do comorbidities matter?
- What is a comorbidity?
- Strengths and Limitations of Comorbidity Research
- Individual COPD Comorbidities
  - Frequency
  - Mechanisms
  - Clinical Implications
Cardiovascular disease is frequent in COPD

Established COPD, clinical CVD

Mannino DM, ERJ 2008

Early COPD, subclinical CVD

Iwamoto, H. Am J Respir Crit Care Med 2009

How strong are the associations?

• Yes, obesity, age, socioeconomic status and tobacco use are shared risk factors
• However, risk of cardiovascular disease persists after controlling for those factors
• Two-fold increase in the odds of cardiovascular disease (OR2·46; 95% CI 2·02–3·00)
• Gradient: higher than in general population, higher than among smokers without COPD, higher as lung function declines
• For some conditions (sudden death, MI) risk is higher shortly after diagnosis or exacerbation, and higher in frequent exacerbation phenotype, CB and non-emphysematous

Cardiovascular disease impacts COPD outcomes

• More frequent exacerbations
• Exacerbations among COPD subjects with cardiovascular disease take longer to recover.
• Increased mortality: HR 1.3
• Poor QOL: OR 3.8
• Increased risk of cardiovascular mortality after COPD exacerbation:
  – MI RR 3
  – CHF OR 10

Martinez CH, J COPDF 2014

Cardiovascular medications impact COPD

Simvastatin for the prevention of exacerbations in moderate-to-severe COPD

Simvastatin 40 mg/day; 885 participants; Rx 641 days
Exacerbations/year 1.38 (s.d. 1.63) vs. 1.39 (s.d. 1.73), p=0.54
Time to exacerbation: 223 vs. 231 days, p=0.34
Beta-blockers are associated with a reduction in COPD exacerbations
COPDGene cohort, 3,264 GOLD 2-4
Incidence risk ratio: 0.73 (95% CI 0.60, 0.90) for exacerbations
0.67 (0.48, 0.93) for severe
Greater effect in severe disease and GOLD B.
No mortality difference.

Bhatt S, Thorax 2016; 71:8

Risk of cardiovascular events with LAMA/LABA

Diabetes
• DM and COPD outcomes
  − Mortality 1.5X (gradient by FEV1)
• COPD increases risk of diabetes
  − Increased risk incident DM:
    • RR 1.4-1.8
  − Yes, it is associated with ICS use:
    • DM (RR 1.0, 1.3)
Diabetes
• Associated phenotypes
  – CB or non-emphysematous
• Mechanistic pathways
  – Visceral fat
  – High IL-6 and PAI-1, low adiponectin
• Clinical implications
  – Screening or vigilance for DM and metabolic syndrome
  – Particularly among CB patients
  – Monitor glycemic control during exacerbations
    • Attention to ICS

Osteoporosis
• Bone health in COPD
  – High Risk Osteoporosis (1.3-2.4)
  – Osteopenia (1.3-1.7)
  – Vertebral fractures (1.1-2.7)

Osteoporosis
• Associated phenotypes
  – Emphysema predominant
• Mechanistic pathways
  – High TNF-alfa and IL-6 increase osteoclast activity
• Clinical implications
  – Screening for osteopenia early in COPD
  – Particularly among men
  – COPD increases mortality after hip fracture repair
Sleep apnea

- Frequency?
  - All-comers: Similar to general population
  - 65% among moderate-severe COPD
- Impact on COPD outcomes
  - Increased mortality
  - Early, out-of-proportion pulmonary HTN
  - Treatment implications
- Impact of COPD on comorbid disease
- Associated phenotypes
  - CB
- Mechanistic pathways?
- Clinical implications
  - Use screening tools in your clinic
  - Stress CPAP use, if indicated

GERD

- Impact of GERD on COPD outcomes
  - AECOPD (OR 2.7), even controlling for Rx (OR 1.4)
  - QOL, Symptoms
  - PPIs impact QOL, not exacerbations
- Impact of COPD on GERD
  - Risk of GERD after COPD diagnosis (RR 1.46)
- Associated phenotypes?
- Mechanistic pathways
  - ?
- Clinical implications
  - PPIs associated with better QOL
  - PPIs not associated with less exacerbations

Anxiety and depression

- Impact on COPD outcomes
  - Mortality (OR 2.0), QOL, 6MWD (only in depression)
  - Depression: younger, women, smokers
  - Anxiety: women
  - Incident COPD after a diagnosis of A/D (RR 1.6, 1.8, 2.0)
- Impact of COPD on Anx/Dep
  - Risk of Depression (RR 1.8) first year after COPD diagnosis
- Associated phenotypes
  - Anxiety: CB
- Mechanistic pathways?
- Clinical implications
  - Screen and refer
  - Limited evidence about what works

References:
- Soler X. Ann ATS 2015; 12: 1219
- Wang TY. Sleep Med 2015; 16: 1123
- Marin JM. Am J Respir Crit Care Med 20110; 182: 325
- Martinez CH. Respir Res 2014
- Anxiety and depression

1/4/2016
Body composition in COPD

High muscle area

<table>
<thead>
<tr>
<th>Panel</th>
<th>Muscle Area</th>
<th>FEV1 % pred.</th>
<th>Exacerbations last year</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>49.8 cm²</td>
<td>90%</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>49.8 cm²</td>
<td>39%</td>
<td>0</td>
</tr>
</tbody>
</table>

Low muscle area

<table>
<thead>
<tr>
<th>Panel</th>
<th>Muscle Area</th>
<th>FEV1 % pred.</th>
<th>Exacerbations last year</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>15.8 cm²</td>
<td>53%</td>
<td>4</td>
</tr>
<tr>
<td>D</td>
<td>15.3 cm²</td>
<td>15%</td>
<td>3</td>
</tr>
</tbody>
</table>

Representative images of pectoralis muscle area from different participants in COPDGene. Muscle area seems to be associated with outcomes, regardless of spirometric severity.

Cachexia and muscle wasting

- Impact on COPD outcomes
  - Body composition associated with functional status; e.g., 6MWD
  - Increased cardiovascular events
- Associated phenotypes
  - Emphysematous. Association with severity
- Mechanistic pathways
  - Disproportionate loss of fat-free tissue, especially muscle
  - Increased visceral fat
  - Decreased appetite, increased cost of breathing, low O2 (?)
  - Myocytes change into type II, less oxidative ability, prone to apoptosis
- Clinical implications
  - Cachexia doesn't affect rehabilitation outcomes
  - Nutritional support
    - Experimental evidence that physical activity decrease systemic and airway inflammation

If we are aging and COPD is increasing:
What about ability to self-care and tailor treatment?
Common impact of disease is more than a count?

- Activities of daily living
- Geriatric conditions (syndromes,)
- Frailty
- Disability

Infrequently measured in pulmonary medicine.
Let’s examine each one, and how can they affect process of care...
### Functional descriptors of Americans age ≥53 years by COPD status

<table>
<thead>
<tr>
<th>COPD Status</th>
<th>Cognitive Function (%)</th>
<th>Mild Cognitive Impairment (%)</th>
<th>Dementia (%)</th>
<th>p‐value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No COPD (n=15,723)</td>
<td>82.5</td>
<td>10.0</td>
<td>4.4</td>
<td>0.001</td>
</tr>
<tr>
<td>COPD (n=1,812)</td>
<td>77.5</td>
<td>13.5</td>
<td>5.85</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Geriatric Conditions and Dependencies Impact COPD Outcomes**

**Geriatric Conditions**
- Cognitive impairment
- Vision problems
- Hearing problems
- Urinary incontinence
- Falls

**Dependences**
- One or more ADL dependencies
- One or more IADL dependencies

Data from the Health and Retirement Study, 2006-2008

**Patient Complexity**

*Using functional descriptors to identify groups at risk.*

To identify ability to self-manage.

- **Relatively healthy** (RH) group <2 comorbidities, normal cognition, and dependency for ≤1 ADL or IADL.
- **Difficulty in self-management** (DSM) group >3 comorbidities, mild cognitive impairment (MCI), severe vision impairment, or ≥2 IADL dependencies.
- **Limited benefit** (LB) group from self-management programs, defined as dementia or >2 ADL dependencies.

Blauw C. Med Care. 2010;48: 327
Clinical complexity in COPD

Data from the Health and Retirement Study, 2006-2008

Summary

• Respiratory factors are not sufficient explanation for COPD progression and experience
• Chronic disease frequently coexists
• Coexistence is different from comorbid interaction
• Source of information on comorbidities matter
• Some comorbidities are clustered with phenotypes
  – CB: cardiovascular, metabolic, anxiety
  – Emphysematous: osteoporosis, sarcopenia
• Comorbidity knowledge offers opportunities to improve COPD care:
  – Beta-blockers are not contraindicated
  – Preserve bone health, in particular among men
  – CPAP for OSA decreases mortality in COPD
  – Review nutritional status
  – Physical activity (and rehabilitation) equally efficacious even if low BMI
  – Diagnose and treat GERD
  – Early referral to mental health professional
  – More attention to functional status

Thanks, and greetings from the Big House