GOLD 0 should we bring it back? NO

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Johns Hopkins University School of Medicine
Baltimore, MD

Eastern Pulmonary Conference, Sept 2019

Conflicts of Interest

- AstraZeneca
- Boehringer-Ingelheim
- Contrafect
- Pulmonx
- Roche
- Sunovion
- Novartis
- Merck
- GlaxoSmithKline
- Verona
- Mylan
- Theravance
- Propeller Health
- AbbVie

Learning objectives

- To describe GOLD 0
- To explain the natural history of GOLD 0
- To realize that one should not use the diagnosis “GOLD 0”

Definition of GOLD 0

Medical Definition of **GOLD-0**

GOLD-0 is stage **0** in the **GOLD** classification of **COPD** and indicates "at risk" for **COPD**. **GOLD-0** is characterized by chronic cough and sputum production. Lung function, as measured by spirometry (a test of the air capacity of the lungs),is still normal.

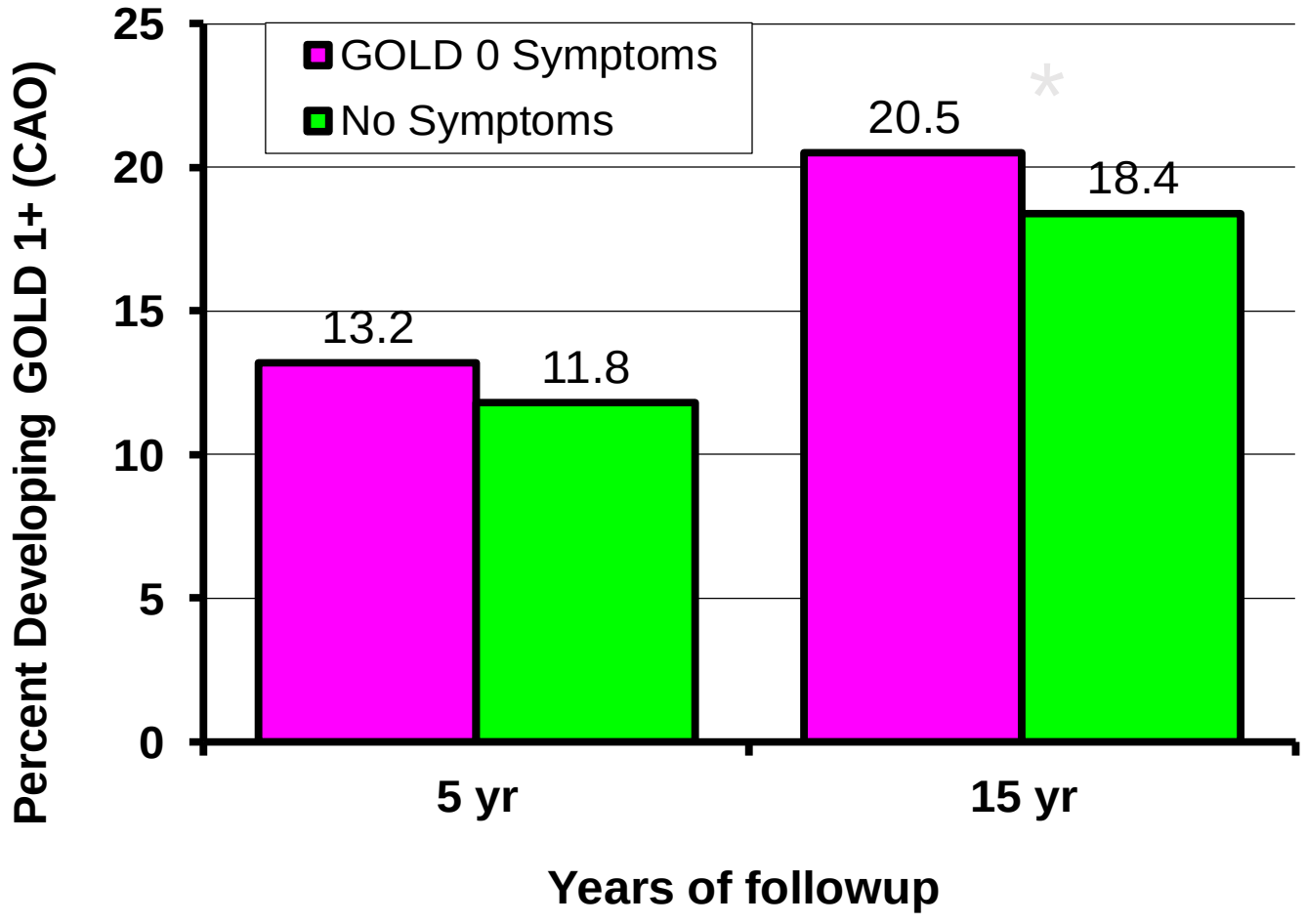
Definition of GOLD-0 - MedicineNet

https://www.medicinenet.com/script/main/art.asp?articlekey=39634

Main Questions about GOLD 0

- Is there such a thing?
- Is it important?
- Do we need to do something about it?

Does cough & phlegm predict smokers at risk for COPD if spirometry is normal?



Copenhagen City Study
16,000 general population
15 year follow-up

Vestbo & Lange. Can GOLD Stage 0 Provide Information of Prognostic Value in COPD? AJRCCM 166:329-332, 2002

GOLD 0 is not a stable condition over time

- After 5 years 39.6% of GOLD 0 individuals no longer reported cough and phlegm
- After 15 years 51.0% of GOLD 0 individuals no longer had cough and phlegm and had normal lung function

Vestbo & Lange. Can GOLD Stage 0 Provide Information of Prognostic Value in COPD? AJRCCM 166:329-332, 2002

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. Woo
David Couper, Ph
Richard E. Kanne
Stephen Rennar

Conclusion

Smokers with current respiratory symptoms are more likely to have future respiratory symptoms…

But the risk is small.

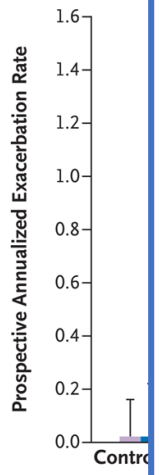


Figure 2. Prevalence of Symptoms and Risk of Respiratory Exacerbations, According to Study Group.

Prospective respiratory exacerbations were defined as respiratory events that were treated with antibiotics or oral glucocorticoids, those associated with health care utilization (office visit, emergency department visit, or hospitalization), those that were considered to be severe exacerbations (i.e., that led to an emergency department visit or hospitalization), or any exacerbation (any of the above). T bars indicate 1 SD. Asterisks indicate a P value of less than 0.05, with Bonferroni correction for multiple comparisons, for the comparison with current or former smokers with preserved pulmonary function and a CAT score of less than 10.

vith

ars

rs

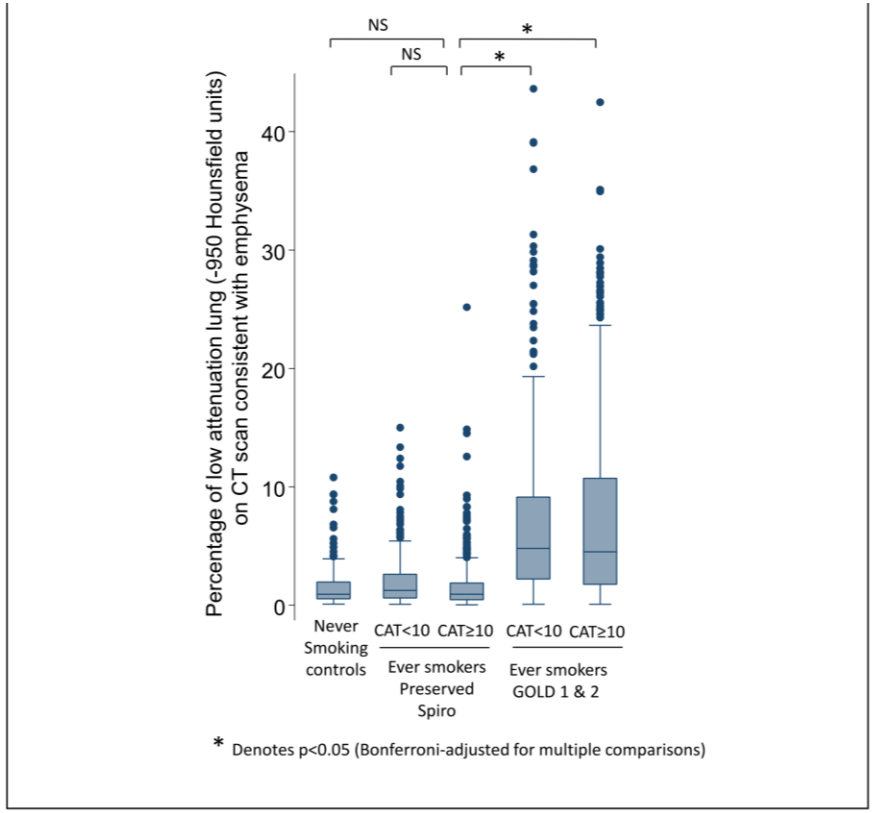
vith

n 2.5 years

n 0.5 – 1

year

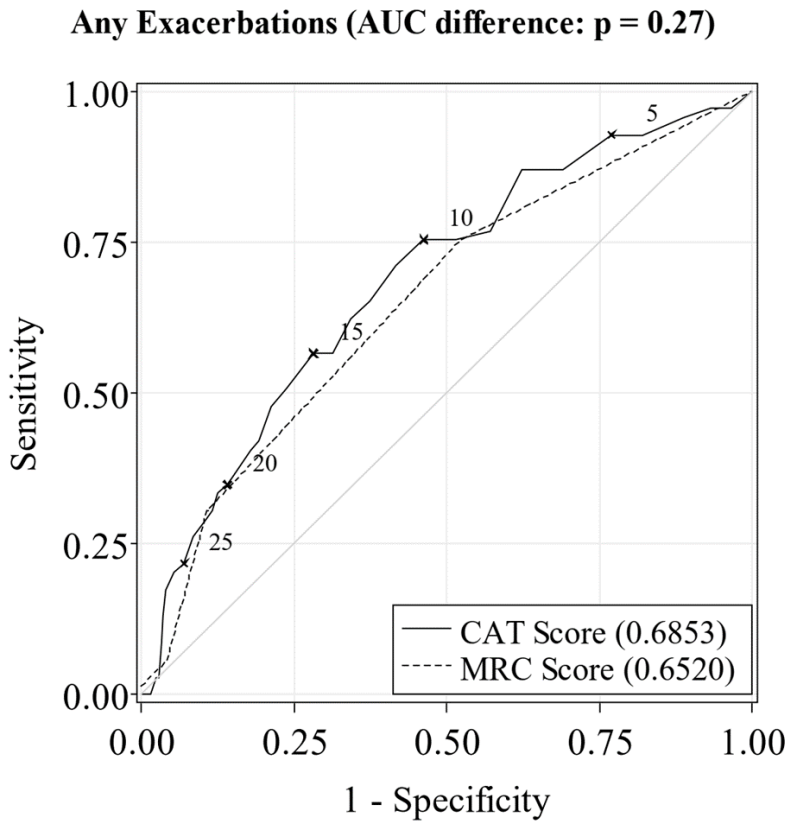
Emphysema is not increased in smokers with normal spirometry and symptoms (CAT > 10)



Woodruff PG et al and SPIROMICS Research Group. Clinical Significance of Symptoms in Smokers with Preserved Pulmonary Function. N Engl J Med. 2016 May 12;374(19):1811-21

Is the CAT score a good test for 1-year exacerbation in smokers with normal PFT?

Figure S8. ROC analysis of CAT score as compared to the Medical Research Council (MRC) score for predicting the occurrence of any exacerbation over the first year of follow-up in ever-smokers with preserved spirometry. CAT was similar to MRC score for prediction of any exacerbation. Participants with < 1 year of follow-up were excluded.

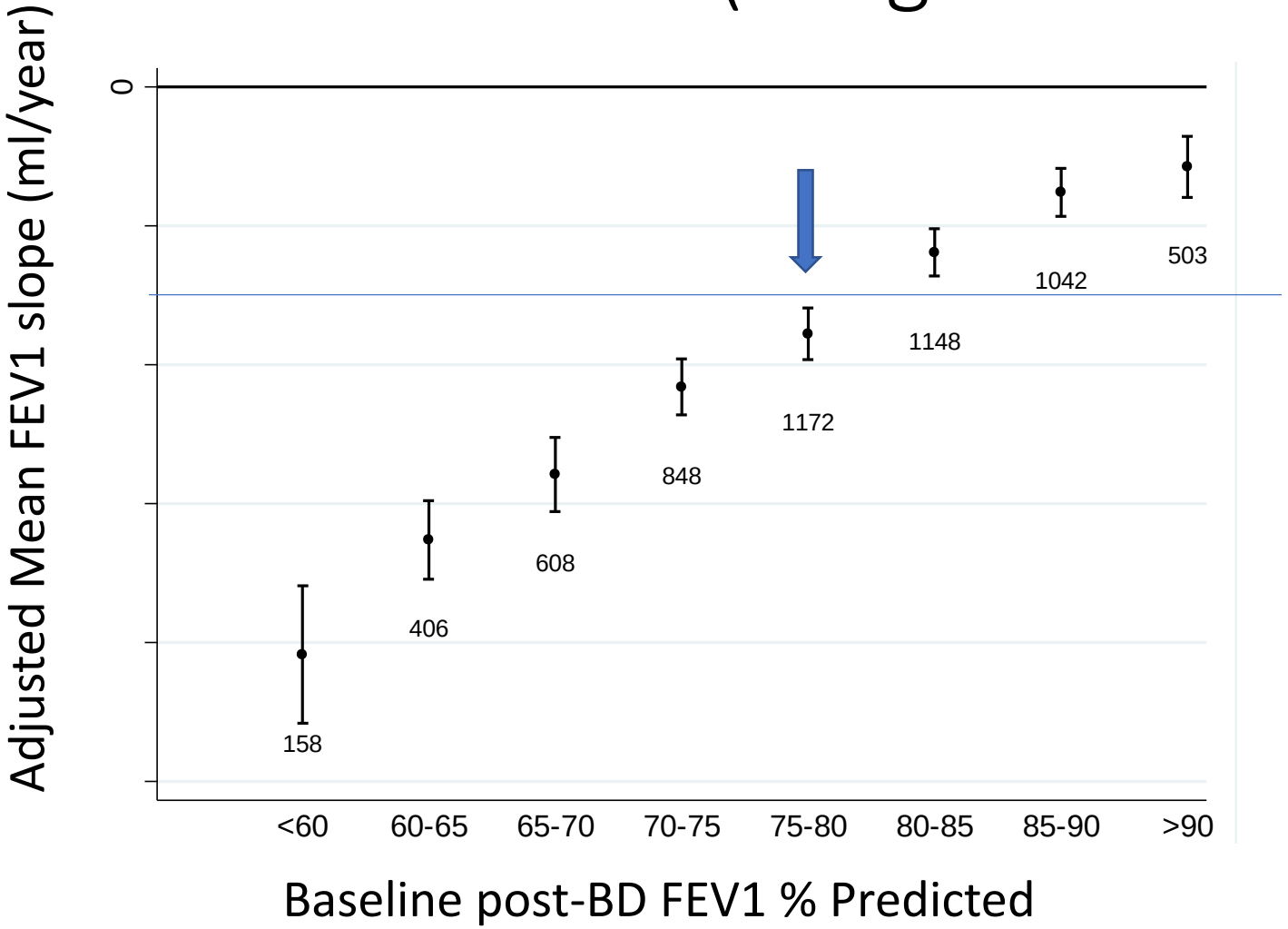


- .90-1 = excellent (A)
- .80-.90 = good (B)
- .70-.80 = fair (C)
- .60-.70 = poor (D)
- .50-.60 = fail (F)

ROC area 0.68

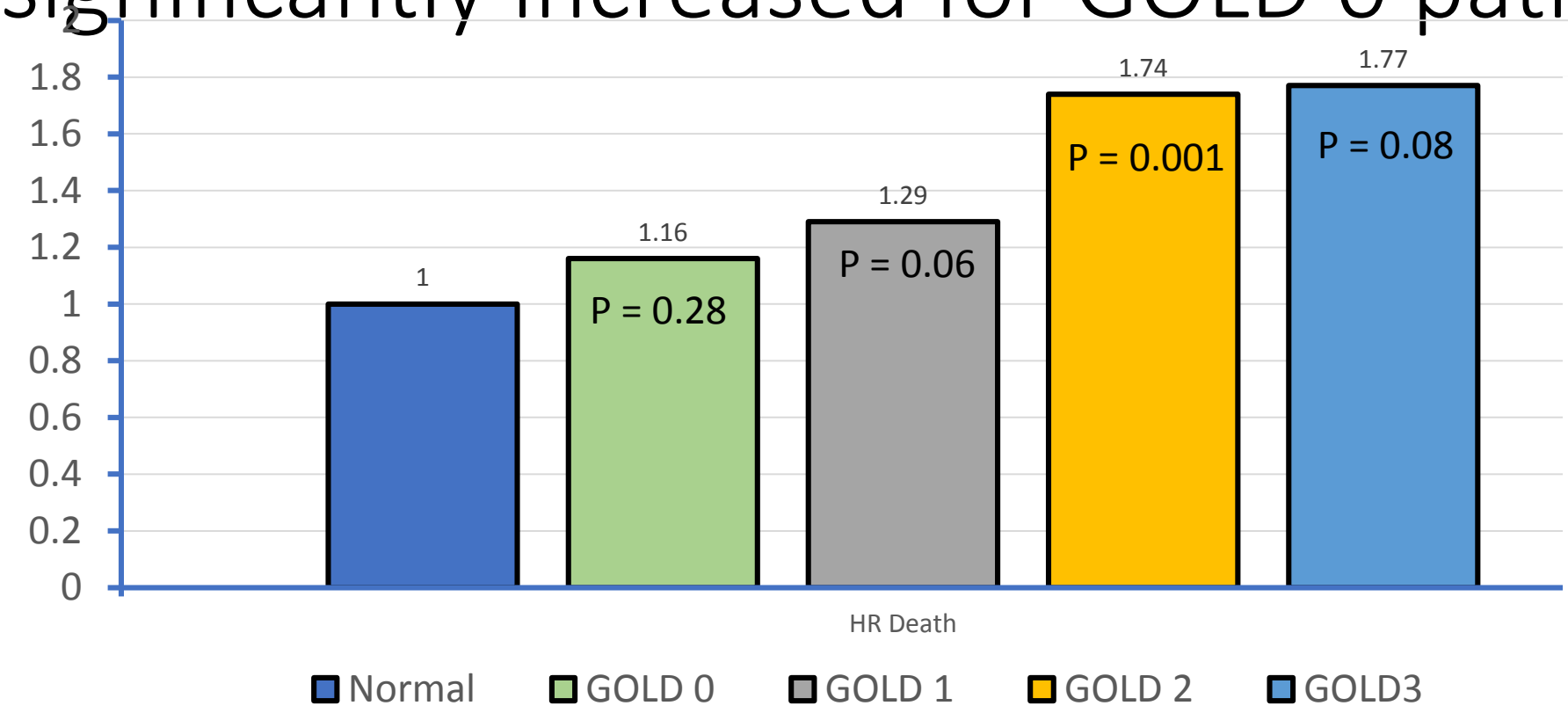
Woodruff PG et al and SPIROMICS Research Group. Clinical Significance of Symptoms in Smokers with Preserved Pulmonary Function. N Engl J Med. 2016 May 12;374(19):1811-21

Smokers with normal baseline FEV1 do not have accelerated decline in FEV1 (Lung Health Study)



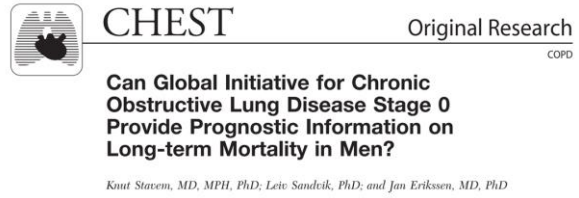
Drummond MB, Hansel NN, Connett JE, Scanlon PD, Tashkin DP, Wise RA. Spirometric predictors of lung function decline and mortality in early chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2012 ;185(12):1301-6.

Risk of death in 25 year follow up is not significantly increased for GOLD 0 patients



n = 1,623 Men
Norway cohort
25 year followup
92.4% smokers
GOLD 0 = cough and phlegm with normal spirometry

Stavem K, Sandvik L, Erikssen J. Can global initiative for Chronic Obstructive Lung Disease stage 0 provide prognostic information on long-term mortality in men? Chest. 2006 Aug;130(2):318-25.



GOLD 0 (normal spirometry in smokers) in COPDgene have normal mortality

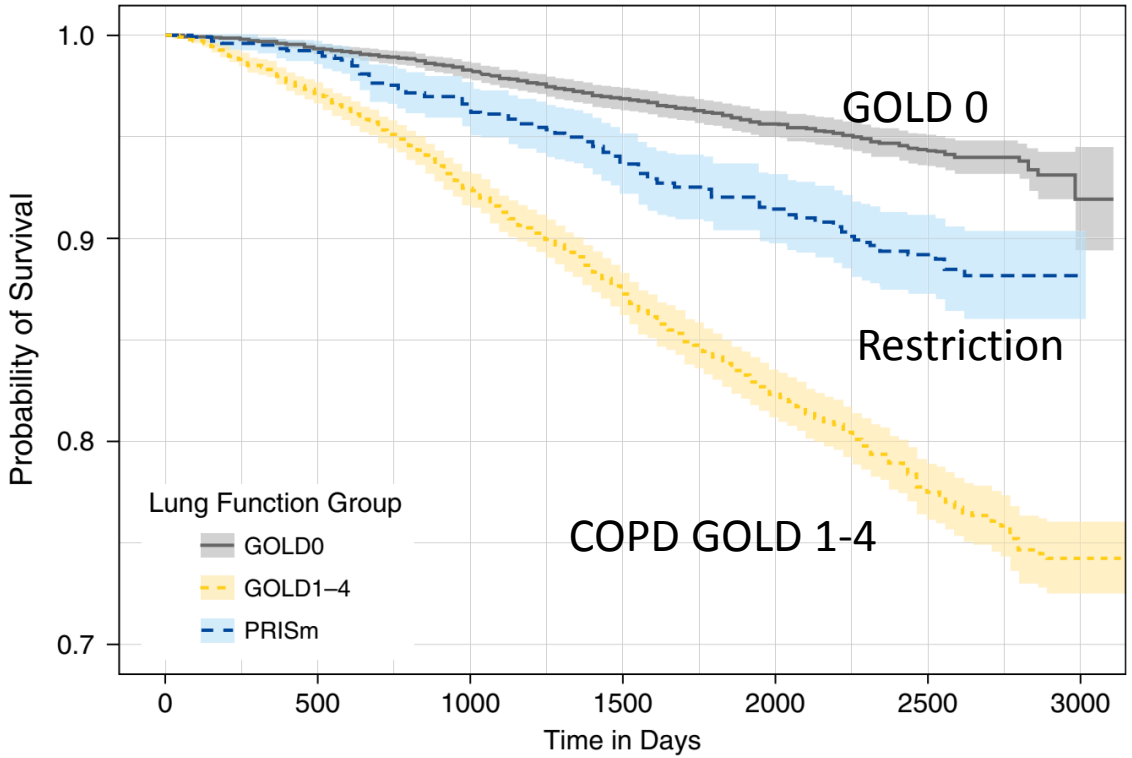


Figure 1. Kaplan-Meier plot of mortality by lung function category in the COPDGene cohort ($n_{GOLD0} = 3{,}783$, $n_{PRISm} = 1{,}058$, $n_{GOLD1–4} = 3{,}959$). PRISm: $FEV_1/FVC \geq 0.7$ and $FEV_1 < 80\%$ predicted; GOLD0: $FEV_1/FVC \geq 0.7$ and $FEV_1 \geq 80\%$ predicted; GOLD1–4: $FEV_1/FVC < 0.7$. GOLD = Global Initiative for Chronic Obstructive Lung Disease; PRISm = Preserved Ratio Impaired Spirometry.

Am J Respir Crit Care Med Vol 198, Iss 11, pp 1397–1405, Dec 1, 2018

ORIGINAL ARTICLE

Longitudinal Phenotypes and Mortality in Preserved Ratio Impaired Spirometry in the COPDGene Study

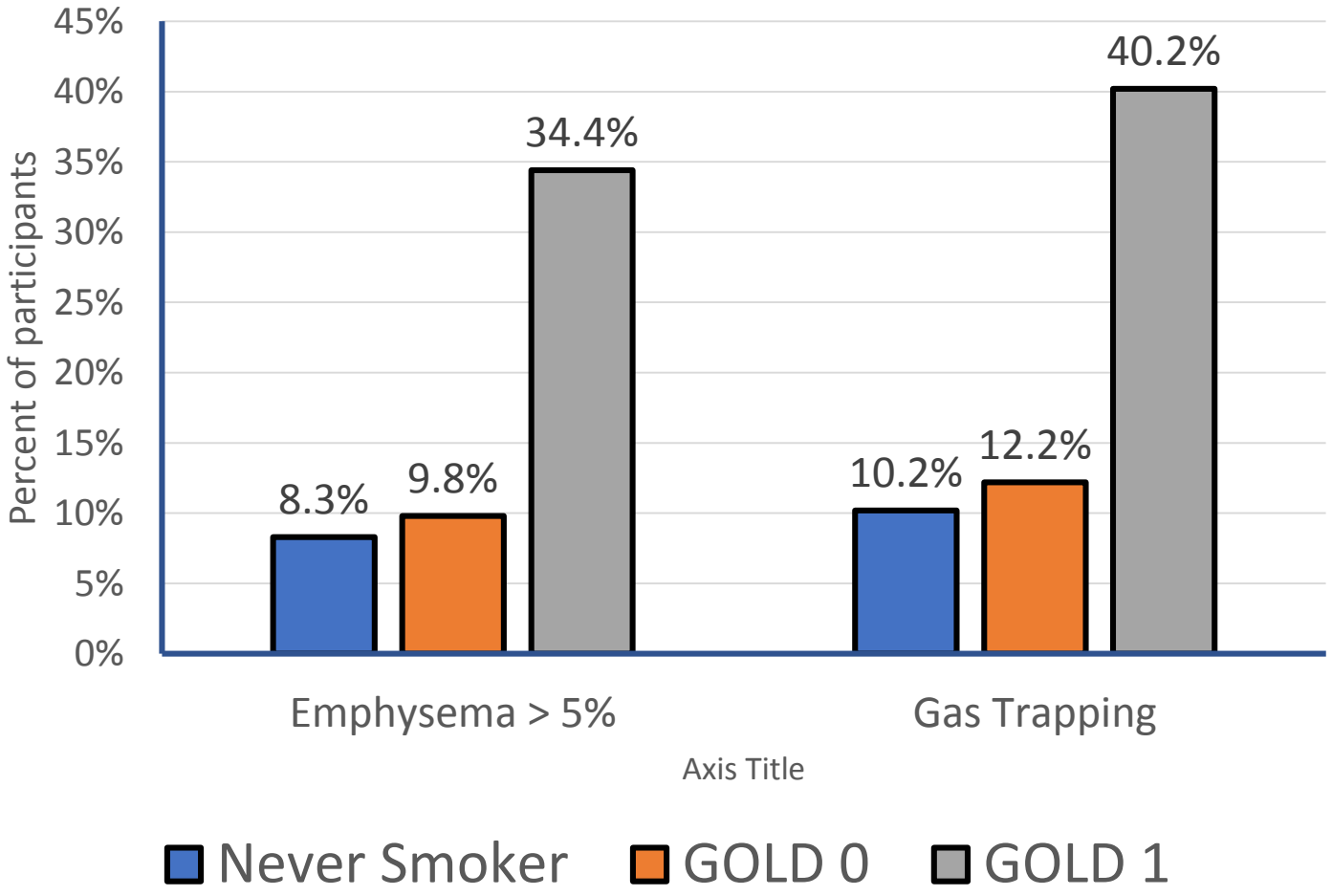
Emily S. Wan[1,2], Spyridon Fortis[3], Elizabeth A. Regan[4], John Hokanson[5], MeiLan K. Han[6], Richard Casaburi[7], Barry J. Make[4], James D. Crapo[4], Dawn L. DeMeo[1], and Edwin K. Silverman[1]; for the COPDGene Investigators

Table 3. Characteristics of Subjects with Preserved Ratio Impaired Spirometry at Phase 1 by Lung Function Category at Phase 2

	Lung Function Category at Phase 2		
	PRISm (*n* = 360)	GOLD0 (*n* = 152)	GOLD1–4 (*n* = 172)
Months between phase 1 and phase 2 visits	67.6 (9.6)	67.5 (9.4)	67.3 (9.0)
Age, yr	56.7 (8.1)*†	58.6 (8.1)	59.3 (8.8)
Female sex, *n* (%)	200 (55.6)	94 (61.8)	89 (51.7)
African American race, *n* (%)	141 (39.2)	61 (40.1)	69 (40.1)
BMI, kg/m^2	32.7 (7.7)†	32.4 (6.7)	31.2 (7.2)
Current smoker, *n* (%)	219 (60.8)*	77 (50.7)	97 (56.4)
Pack-years	40.4 (22.3)†	38.8 (20.6)‡	45.9 (25.0)
FEV_1% predicted, baseline	69.5 (8.1)*	74.8 (5.5)‡	68.2 (8.8)
FVC% predicted, baseline	70.2 (8.9)*†	75.0 (6.8)‡	71.9 (9.7)
TLC_{CT} % predicted§	79.3 (13.2)†	80.5 (13.9)‡	84.2 (15.0)
Chronic bronchitis, *n* (%)	63 (17.5)*	15 (9.9)	28 (16.3)
mMRC	1.4 (1.4)	1.4 (1.4)	1.4 (1.4)
SGRQ	28.1 (23.2)	25.2 (19.5)	29.1 (23.5)
6MWD, m	402.1 (111.4)	401.7 (102.6)	384.4 (106.6)
Percent emphysema§	1.5 (3.2)†	1.6 (2.1)‡	2.2 (2.9)
Percent gas trapping‖	8.2 (6.6)†	9.7 (7.6)‡	12.6 (8.2)
Pi10, mm**	3.72 (0.12)	3.72 (0.12)	3.71 (0.14)
Acute respiratory events/yr††	0.3 (0.6)†	0.3 (0.8)	0.4 (0.8)
ΔFEV_1, ml/yr	−27.2 (42.2)*†	28.0 (44.5)‡	−42.9 (53.8)
ΔFVC, ml/yr	−32.6 (56.8)*†	35.7 (59.4)‡	−2.6 (75.2)
ΔBMI, kg/m^2	0.0 (3.8)*	−1.3 (3.8)‡	−0.4 (3.5)
ΔAdjusted lung density, g/L‡‡	−0.2 (12.5)	−2.4 (11.2)	−2.7 (12.1)

Definition of abbreviations: 6MWD = 6-minute-walk distance; BMI = body mass index; CT = computed tomography; GOLD = Global Initiative for Chronic Obstructive Lung Disease; mMRC = modified Medical Research Council; P1 = phase 1; P2 = phase 2; Pi10 = square root of the wall area (in mm) of a hypothetical airway with an internal perimeter of 10 mm; PRISm = Preserved Ratio Impaired Spirometry; SGRQ = St. George's Respiratory Questionnaire; TLC_{CT} = total lung capacity by computed tomography.
Data are expressed as mean (SD) unless otherwise noted. Data are shown for subjects with lung function data at P1 and P2.
*$P < 0.05$ between PRISm-P2 and GOLD0 spirometry at P2.
†$P < 0.05$ between PRISm-P2 and GOLD1–4 spirometry at P2.
‡$P < 0.05$ between GOLD0 and GOLD1–4 at P2.
§Subjects with quantitative CT imaging available for analysis: PRISm = 331, GOLD0 = 138, GOLD1–4 = 154.
‖Subjects with quantitative CT imaging available for analysis: PRISm = 272, GOLD0 = 112, GOLD1–4 = 122.
**Subjects with quantitative CT imaging available for analysis: PRISm = 329, GOLD0 = 138, GOLD1–4 = 152.
††Subjects with longitudinal follow-up data on acute respiratory events as assessed by interview every 6 months: PRISm = 341, GOLD0 = 142, GOLD1–4 = 166.
‡‡Subjects with change in CT lung density data: PRISm = 250, GOLD0 = 108, GOLD1–4 = 116.

CT abnormalities in GOLD 0 (Normal Spirometry) vs GOLD 1

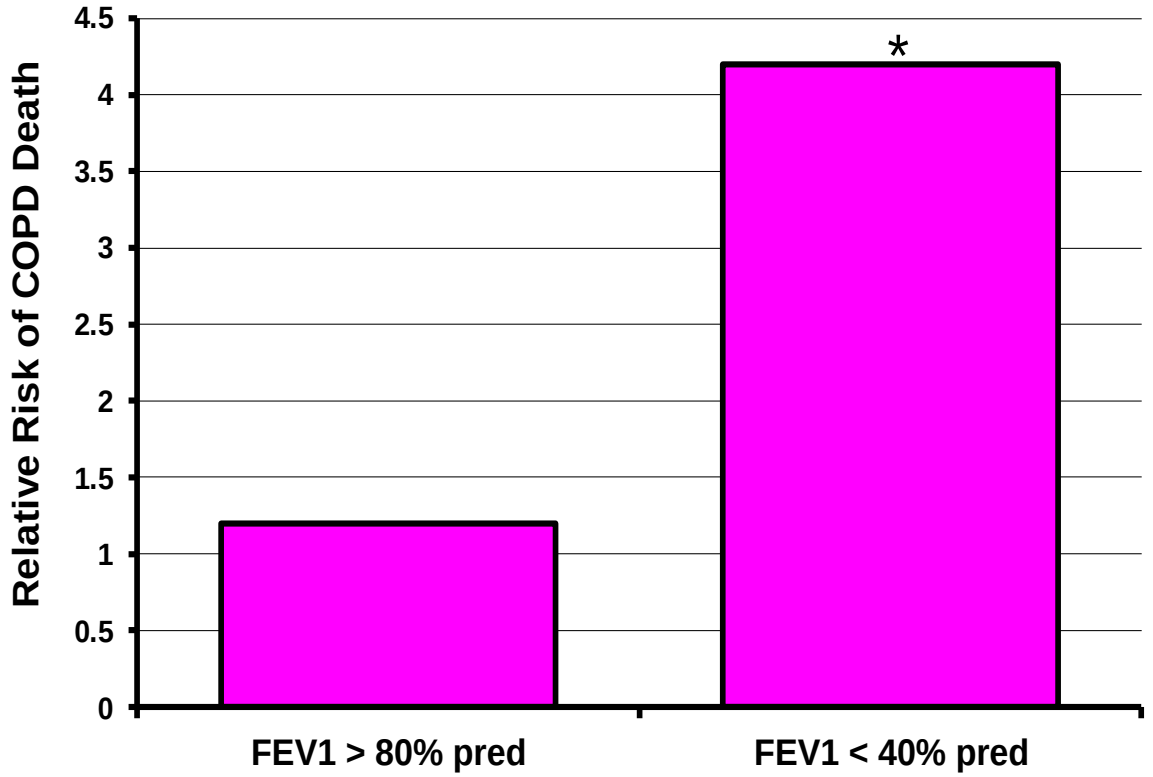


GOLD 0 defined as smokers with normal spirometry

12.6% with chronic bronchitis

Regan EA et al; Genetic Epidemiology of COPD (COPDGene) Investigators. Clinical and Radiologic Disease in Smokers With Normal Spirometry. JAMA Intern Med. 2015 Sep;175(9):1539-49.

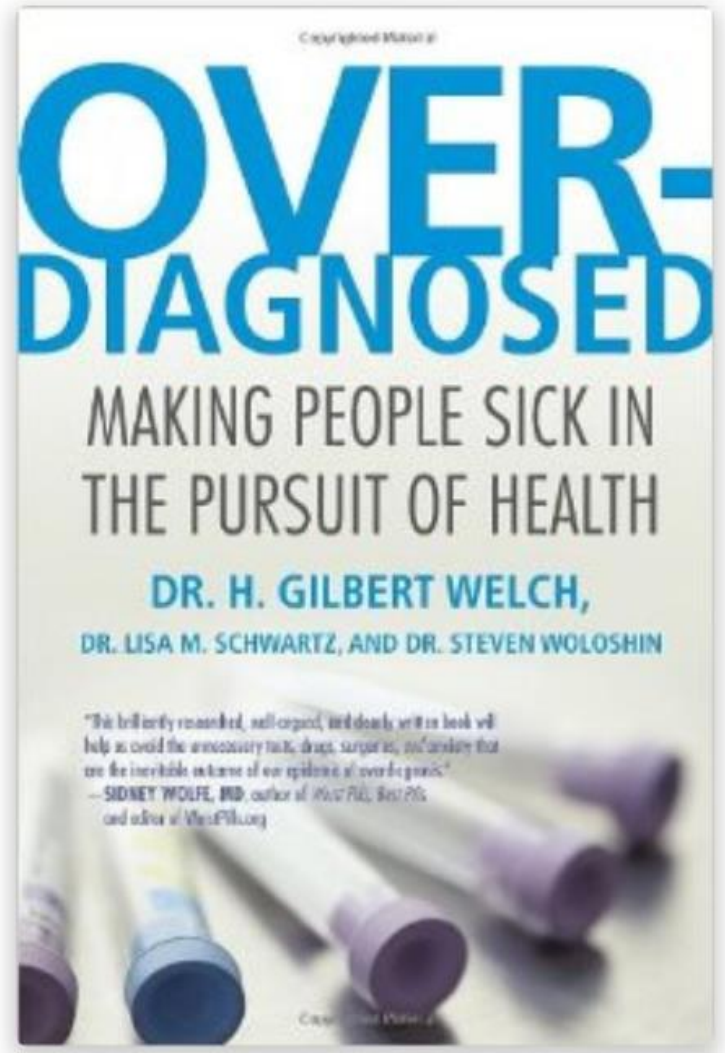
Cough and Phlegm predict respiratory mortality only in people who have abnormal spirometry

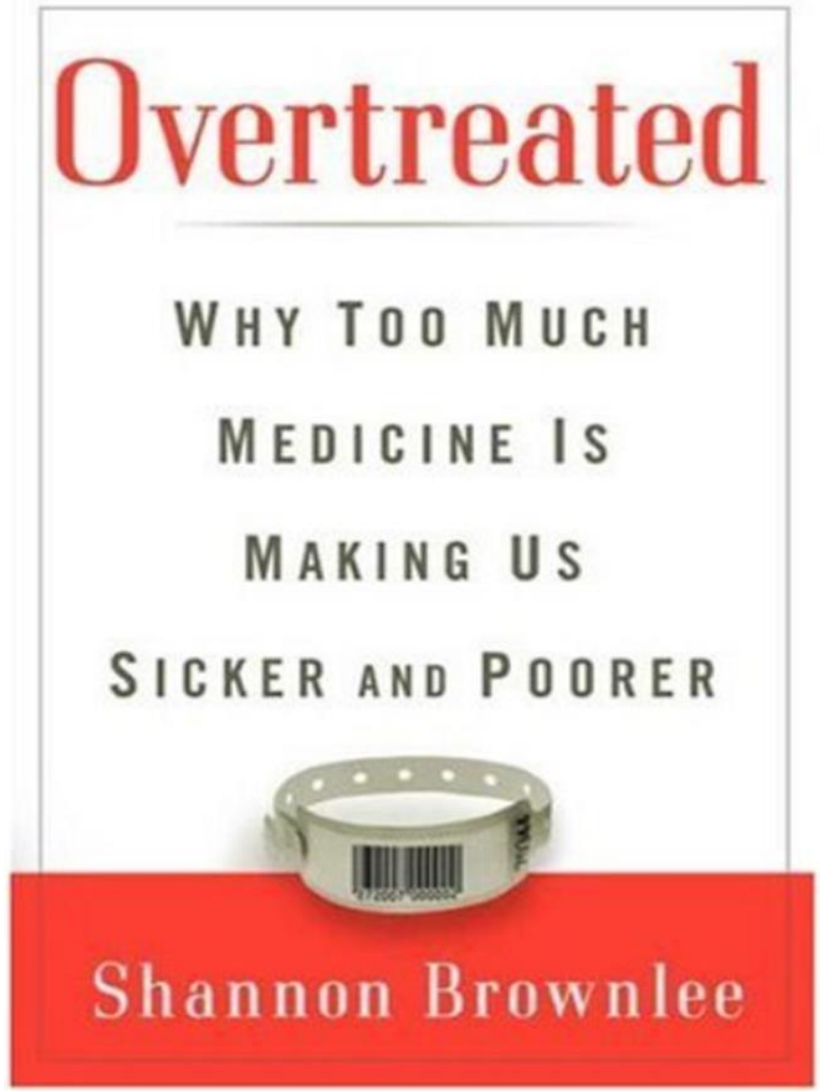


Effect on all-cause mortality non-significant.

Effect on non-COPD mortality NS for pts with low PFT

Lange P et al. Relation of ventilatory impairment and of chronic mucus hypersecretion to mortality from obstructive lung disease and from all causes. Thorax. 1990;45:579-85.


OVER-
DIAGNOSED
MAKING PEOPLE SICK IN THE PURSUIT OF HEALTH
DR. H. GILBERT WELCH,
DR. LISA M. SCHWARTZ, AND DR. STEVEN WOLOSHIN


Overtreated
WHY TOO MUCH MEDICINE IS MAKING US SICKER AND POORER
Shannon Brownlee

Overdiagnosis

- **Overdiagnosis** occurs when a disease is diagnosed correctly, but the diagnosis is irrelevant. A correct diagnosis may be irrelevant because treatment for the disease is not available, not needed, or not wanted.

Wikipedia: “Overdiagnosis”, accessed Oct 24, 2014

Widening definitions of disease

- 16 guidelines on 14 common conditions
- 10/16 proposed widening definition of disease
- 1/14 proposed narrowing definition of disease
- Widening definitions
  - Defining “Pre-Disease”
  - Lowering diagnostic thresholds
  - Earlier, different diagnostic methods
- None addressed potential harms of proposed changes
- 75% of members had industry ties, median = 7 ties

Moynihan RN, et al. Expanding disease definitions in guidelines and expert panel ties to industry: a cross-sectional study of common conditions in the United States. PLoS Med. 2013 Aug;10(8):e1001500.

Conflict of Interests or Confluence of Interests?

- Doctors want to make diagnoses and treat diseases
- Patients want explanatory diagnoses and prescriptions
- Pharmaceutical companies want to develop and market treatments
- Researchers want more funding for their disease targets

“Never ask a barber if you need a haircut.”

— Warren Buffett

OPEN ACCESS

ESSAY

52,218

VIEWS

Bigger and Better: How Pfizer Redefined Erectile Dysfunction

Joel Lexchin

Published: April 11, 2006 • DOI: 10.1371/journal.pmed.0030132 • Published in *PLOS Medicine*

On its Web site, Pfizer states that “in fact, more than half of all men over 40 have difficulties getting or maintaining an erection”

Question: “I don't have ED because the problem doesn't happen often. Does this mean that VIAGRA is not for me?”
Answer: “Even if erection problems happen only once in a while, VIAGRA can help. You should know that most men with ED only experience problems some of the time. In one study, VIAGRA helped 87% of men with mild-to-moderate ED have better erections versus 36% of men taking a sugar pill”

Lexchin J. Bigger and better: how Pfizer redefined erectile dysfunction. PLoS Med. 2006 Apr;3(4):e132. Epub 2006 Apr 11.

STEPH

4K

The war on 'prediabetes' could be a boon for pharma—but is it good medicine?

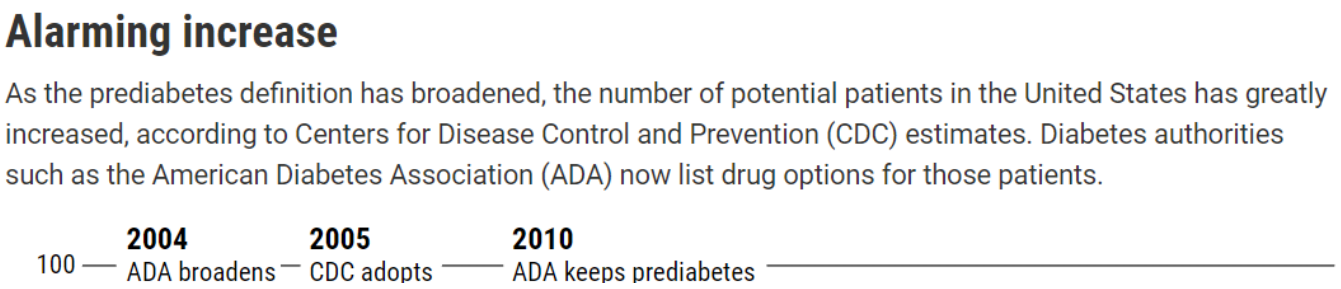
By **Charles Piller** | Mar. 7, 2019 , 2:00 PM

Piller C. The war on pre-diabetes could be a boon for pharma – but is it good medicine. Science 08 Mar 2019: Vol. 363, Issue 6431, pp. 1026-1031

The war on “Pre-Diabetes”

Pre-diabetes has increased from 12 million Americans to 80 million in the past 15 years

<2% of pre-diabetics progress to diabetes / year



> **It seems counterintuitive to take a medicine in order to prevent something for which you would take that medicine.**
>
> *Gojka Roglic, World Health Organization*

increased from $66M to $173M between 2010 and 2017 (262%)

Piller C. Science 08 Mar 2019: Vol. 363, Issue 6431, pp. 1026-1031
Diabetes Prevention Research Group: N Engl J Med 2002; 346: 393-403
Diabetes Prevention Program Research Group. Lancet Diabetes 2015 3(11); 866-875

So…Is GOLD 0 a thing?

Smoking, Not COPD, as the Disease

Leonardo M. Fabbri, M.D.

Thank you