CALIFORNIA THORACIC SOCIETY
NORTHERN CALIFORNIA
ANNUAL EDUCATIONAL CONFERENCE

SATURDAY, JANUARY 18, 2020

UPDATES ON PULMONARY HYPERTENSION AND HOT TOPICS IN PULMONARY MEDICINE

REGISTRATION/EXHIBITS

Saturday, January 18, 2020 – 7:00 a.m. – 8:00 a.m.

CTS Northern California Annual Educational Conference

PROGRAM SCHEDULE - SATURDAY, JANUARY 18, 2020

Updates on Pulmonary Hypertension and Hot Topics in Pulmonary Medicine

7:00 am – 8:00 am
Registration / Exhibits

8:00 am – 8:15 am
Welcome and Introductions; Pre-Test
Michelle Cao, DO

Updates on Pulmonary Hypertension

8:15 am – 9:15 am
2018 World Symposium Update: Diagnostic Classification/Hemodynamic Definitions
KEYNOTE SPEAKER: Nicholas Hill, MD

9:15 am – 10:00 am
Treating Group 1 PAH
Kristina Kudelko, MD

10:00 am –10:25 am
BREAK / EXHIBIT HALL OPEN

10:25 am – 11:10 am
Group 3 Pulmonary Hypertension: Diagnosis and When to Refer
Nicholas Kolaitis, MD

11:10 am – 11:55 am
Updates on CTEPH
Kim Kerr, MD

11:55 am – 12:15 pm
Panel Discussion (Questions/Answers with Nicholas Hill, MD; Kristina Kudelko, MD; Nicholas Kolaitis, MD; Kim Kerr, MD)

12:15 pm – 1:15 pm
LUNCH / EXHIBIT HALL OPEN

1:00 pm – 1:15 pm
CTS Annual Business Meeting
Lorriana E. Leard, MD

Hot Topics in Pulmonary Medicine

1:15 pm – 2:00 pm
Biologics in Asthma: A Personalized Approach
Stephen Lazarus, MD

2:00 pm – 2:45 pm
Advances in ILD
Justin Oldham, MD

2:45 pm – 3:10 pm
BREAK / EXHIBIT HALL OPEN

3:10 pm – 3:55 pm
Advances in Cystic Fibrosis
Doug Conrad, MD

3:55 pm – 5:05 pm
Updates on Lung Transplant: From Clinic to Surgery and Beyond
Lorriana Leard, MD; George Chaux, MD;
Doug Conrad, MD; Alyssa Perez, MD

5:05 pm – 5:20 pm
Panel Discussion
(Questions/Answers with Lorriana Leard, MD; George Chaux, MD; Doug Conrad, MD; Alyssa Perez, MD)

5:20 pm - 5:30 pm
Closing Remarks and Post Test
Michelle Cao, DO

6:00 pm – 8:30 pm
Post Saturday Program Special Event – Non-CME Event: SPARK! a gathering of CA women in pulmonary, critical care and sleep medicine

WELCOME AND INTRODUCTIONS
PRE-TEST

Michelle Cao, DO
Stanford University School of Medicine
Clinical Associate Professor
Pulmonary, Critical Care, and Sleep Medicine
Division of Neuromuscular Medicine and Division of Sleep Medicine

Saturday, January 18, 2020 – 8:00 a.m. – 8:15 a.m.

Michelle Cao, DO is a Clinical Associate Professor in the Division of Sleep Medicine and the Division of Neuromuscular Medicine, at the Stanford University School of Medicine. She is board certified in Pulmonary, Critical Care, and Sleep Medicine. She completed internal medicine residency at Loma Linda University in California, then went on to complete Pulmonary and Critical Care fellowship training at Harbor-UCLA Medical Center in Los Angeles, California. She then completed Sleep Medicine fellowship training at Stanford University. Her clinical expertise is in complex sleep-related respiratory disorders and home mechanical ventilation for chronic respiratory failure syndromes. Dr. Cao is the Director of the Adult Noninvasive Ventilation Program for the Neuromuscular Medicine Program at Stanford Health Care. She is actively engaged in training of house staff for Sleep Medicine fellowship and the Neuromuscular Medicine fellowship at Stanford University.

UPDATES ON PULMONARY HYPERTENSION

2018 World Symposium Update: Diagnostic Classification/Hemodynamic Definitions

KEYNOTE SPEAKER

Nicholas S. Hill, MD
Tufts Medical Center in Boston
Chief of the Division of Pulmonary, Critical Care and Sleep Medicine

Saturday, January 18, 2020 – 8:15 a.m. – 9:15 a.m.

NICHOLAS S. HILL, MD is Chief of the Division of Pulmonary, Critical Care and Sleep Medicine at Tufts Medical Center in Boston and Professor of Medicine at Tufts University School of Medicine. He received his M.D. from Dartmouth Medical School in 1975. He did his internship and residency in Medicine at Tufts-New England Medical Center. He did a fellowship in Cardiovascular Medicine at the University of Massachusetts Medical Center and in Pulmonary Medicine at Boston University School of Medicine. He is Board Certified in Internal Medicine, Pulmonary Diseases, and Critical Care Medicine. He has done extensive research and writing in the fields of noninvasive ventilation and pulmonary hypertension dating back over 35 years. He has edited several books related to these topics. He established the Pulmonary Hypertension Center at Tufts Medical Center. He is a Past President of the American Thoracic Society and has received a Distinguished Scholar Award in Critical Care from the Chest Foundation of the American College of Chest Physicians as well an Award for Excellence in Pulmonary Hypertension Care from the Pulmonary Hypertension Association.

Treating Group 1 PAH

Kristina Kudelko, MD
Stanford University
Clinical Associate Professor, Division of PCCM
Director of Education, Vera Moulton Wall Center of Pulmonary Vascular Disease

Saturday, January 18, 2020 – 9:15 a.m. – 10:00 a.m.

Kristina Kudelko, MD received her medical degree from the University of Pennsylvania. She trained in internal medicine and pulmonary and critical care medicine at New York Presbyterian Hospital-Cornell before she pursued a second fellowship in pulmonary hypertension at Stanford University in 2008-9. She is currently a Clinical Associate Professor in pulmonary and critical care medicine at Stanford and Director of Education of the Vera Moulton Wall Center for Pulmonary Vascular Disease.

An Update on the Treatment of Group I PAH

Kristina Kudelko MD
Clinical Associate Professor, Division of PCCM, Stanford University
Director of Education, Vera Moulton Wall Center of Pulmonary Vascular Disease

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Disclosures

- No financial conflicts or disclosures

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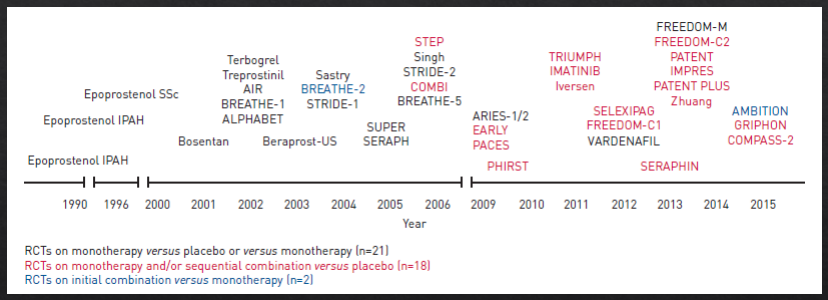

Galiè et al., ***Eur Respir J*** 2019

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TABLE 1 Summary of four registries assessing risk scores

	REVEAL [17–19]	Swedish PAH Register [6]	COMPERA [7]	French Pulmonary Hypertension Network [8]#
Required variables n	12–14	8	8	4
Patients at baseline n	2716	530	1588	1017
Patients at follow-up n	2529	383	1094	1017
Associated PAH included	Yes	Yes	Yes	No
Definition of low risk	≤6 REVEAL score	<1.5 average score	<1.5 average score	3–4 out of 4 low-risk criteria
1-year mortality by risk group (low/intermediate/high) %	≤2.6/7.0/≥10.7	1.0/7.0/26.0	2.8/9.9/21.2	1.0/NA/13.0–30.0

PAH: pulmonary arterial hypertension; NA: not available. #: incident patients only.

Galiè et al., ***Eur Respir J*** 2019

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TABLE 13 Risk assessment in pulmonary arterial hypertension

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15ml/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 <11 ml/min/kg (<35% pred.) VE/VCO_2 slope >45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/l	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 <60%

Galiè et al., ***Eur Respir J*** 2015

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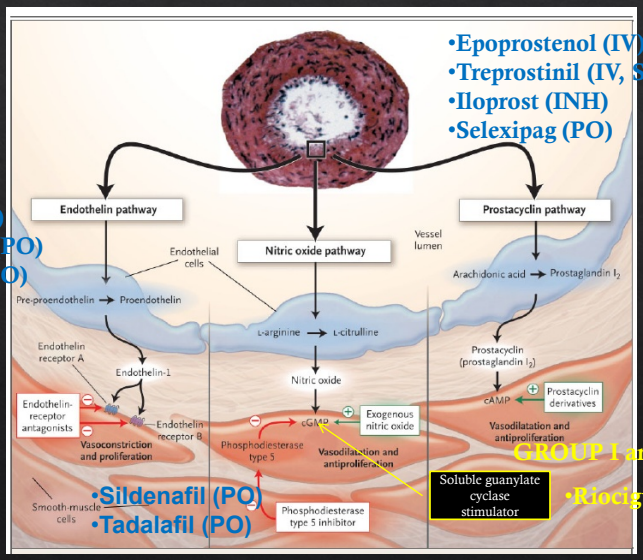
PAH FDA-Approved Drugs

(WHO Group I ONLY except…)



- •Epoprostenol (IV)
- •Treprostinil (IV, SQ, INH, PO)
- •Iloprost (INH)
- •Selexipag (PO)
- •Bosentan (PO)
- •Ambrisentan (PO)
- •Macitentan (PO)
- •Sildenafil (PO)
- •Tadalafil (PO)
- •Riociguat (PO)

GROUP I and IV CTEPH

Humbert M et al., ***NEJM*** 2004

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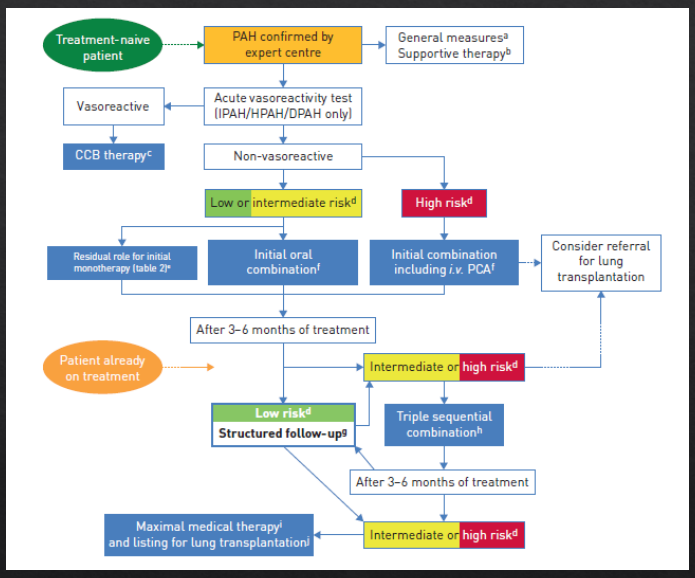

Galiè et al., *Eur Respir J* 2019

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TABLE 16 Recommendations for general measures

Recommendations	Class[a]	Level[b]	Ref.[c]
It is recommended that PAH patients avoid pregnancy	I	C	[160, 161]
Immunization of PAH patients against influenza and pneumococcal infection is recommended	I	C	
Psychosocial support is recommended in PAH patients	I	C	[168]
Supervised exercise training should be considered in physically deconditioned PAH patients under medical therapy	IIa	B	[153-157]
In-flight O_2 administration should be considered for patients in WHO-FC III and IV and those with arterial blood O_2 pressure consistently <8 kPa (60 mmHg)	IIa	C	
In elective surgery, epidural rather than general anaesthesia should be preferred whenever possible	IIa	C	
Excessive physical activity that leads to distressing symptoms is not recommended in PAH patients	III	C	

TABLE 17 Recommendations for supportive therapy

Recommendations	Class[a]	Level[b]	Ref.[c]
Diuretic treatment is recommended in PAH patients with signs of RV failure and fluid retention	I	C	[178]
Continuous long-term O_2 therapy is recommended in PAH patients when arterial blood O_2 pressure is consistently <8 kPa (60 mmHg)[d]	I	C	[179]
Oral anticoagulant treatment may be considered in patients with IPAH, HPAH and PAH due to use of anorexigens	IIb	C	[84, 171, 175–177]
Correction of anaemia and/or iron status may be considered in PAH patients	IIb	C	[184]
The use of angiotensin-converting enzyme inhibitors, angiotensin-2 receptor antagonists, beta-blockers and ivabradine is not recommended in patients with PAH unless required by co-morbidities (i.e. high blood pressure, coronary artery disease or left heart failure)	III	C	

Galiè et al., *Eur Respir J* 2015

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BREAK
EXHIBIT HALL OPEN

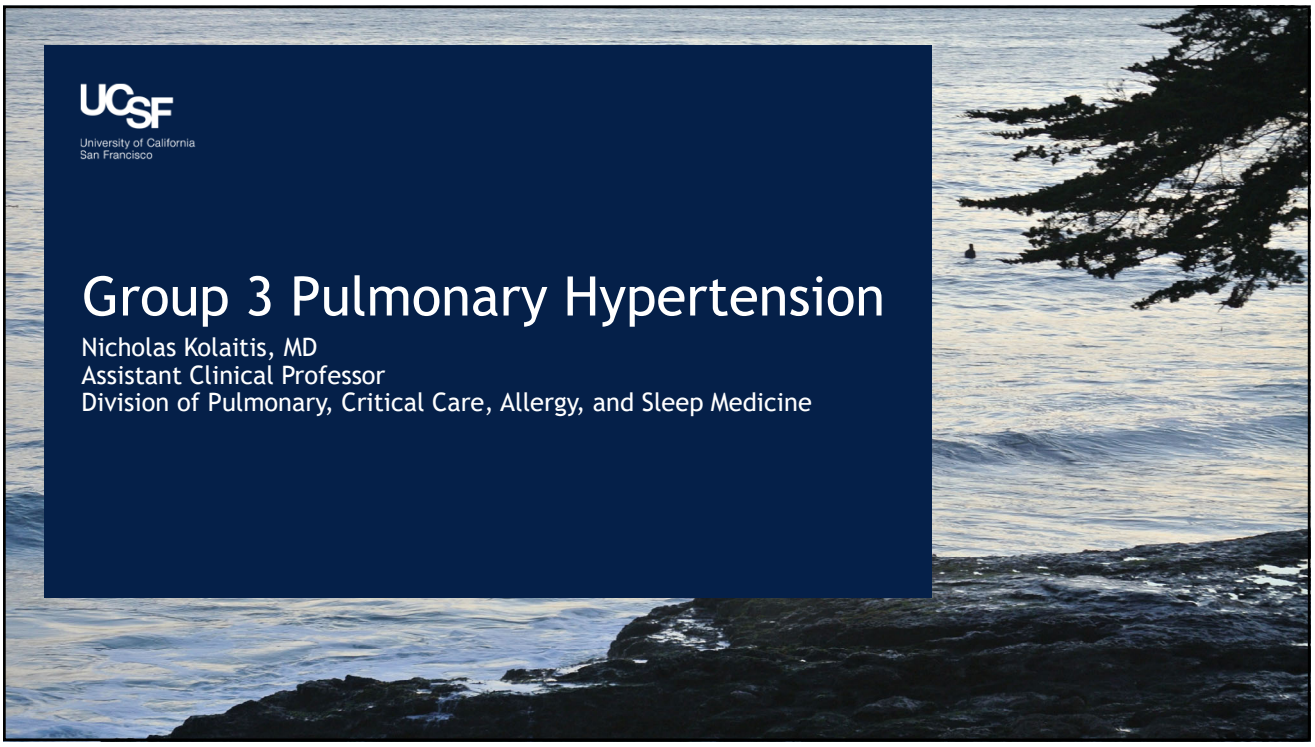
Saturday, January 18, 2020 – 10:00 a.m. – 10:25 a.m.

GROUP 3 PULMONARY HYPERTENSION: DIAGNOSIS AND WHEN TO REFER

Nicholas A. Kolaitis, MD
UC San Francisco
Assistant Clinical Professor of Medicine

Saturday, January 18, 2020– 10:25 a.m. – 11:10 a.m.

Nicholas A. Kolaitis, MD is an Assistant Clinical Professor of Medicine at the University of California, San Francisco. He cares for patients in the UCSF Lung Transplant Program and Pulmonary Hypertension Clinic. His research interests are in health-related quality of life and the systemic manifestations of lung disease. He is the chair of the CTS Career Development Committee and is a member of the CTS Board of Directors.



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Disclosures

- No Disclosures
- No Conflicts of Interest

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Background

- Pulmonary hypertension
  - Abnormal elevation in the pulmonary circulatory pressure
  - Elevated mean PAP >20 mm Hg *AND* PVR ≥ 3 wood units
- Group 3 pulmonary hypertension
  - Resting pulmonary hypertension in the setting of chronic lung disease, sleep-disordered breathing, or chronic high altitude exposure

Frost A et al. Eur Respir J 2018
Hoeper MM et al. J Am Coll Cardiol. 2013

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Goals for Today

- Epidemiology and clinical relevance of Group 3 pulmonary hypertension
- Diagnosis of pulmonary hypertension in chronic lung disease
- Treatment of pulmonary hypertension in chronic lung disease
- Focus on interstitial lung disease and chronic obstructive pulmonary disease
- Will not discuss pulmonary hypertension in the setting of acute exacerbations

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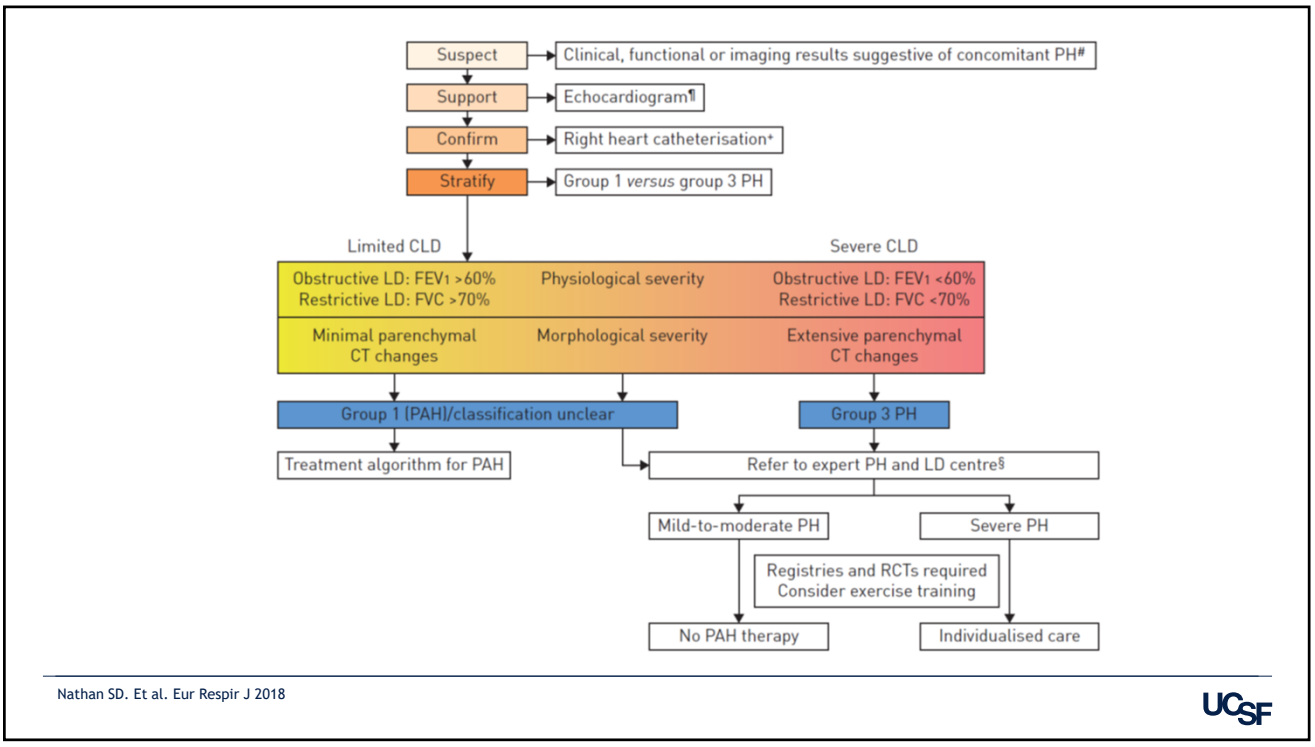

Nathan SD. Et al. Eur Respir J 2018

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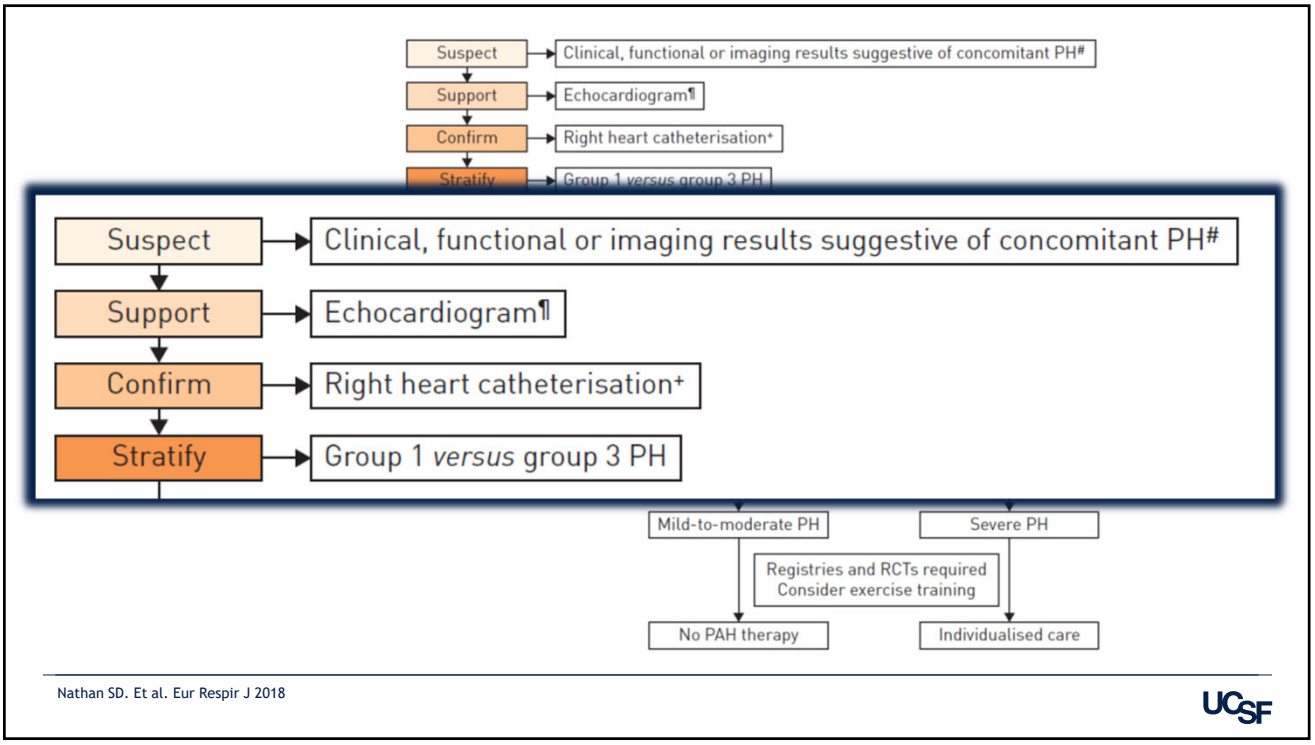

Nathan SD. Et al. Eur Respir J 2018

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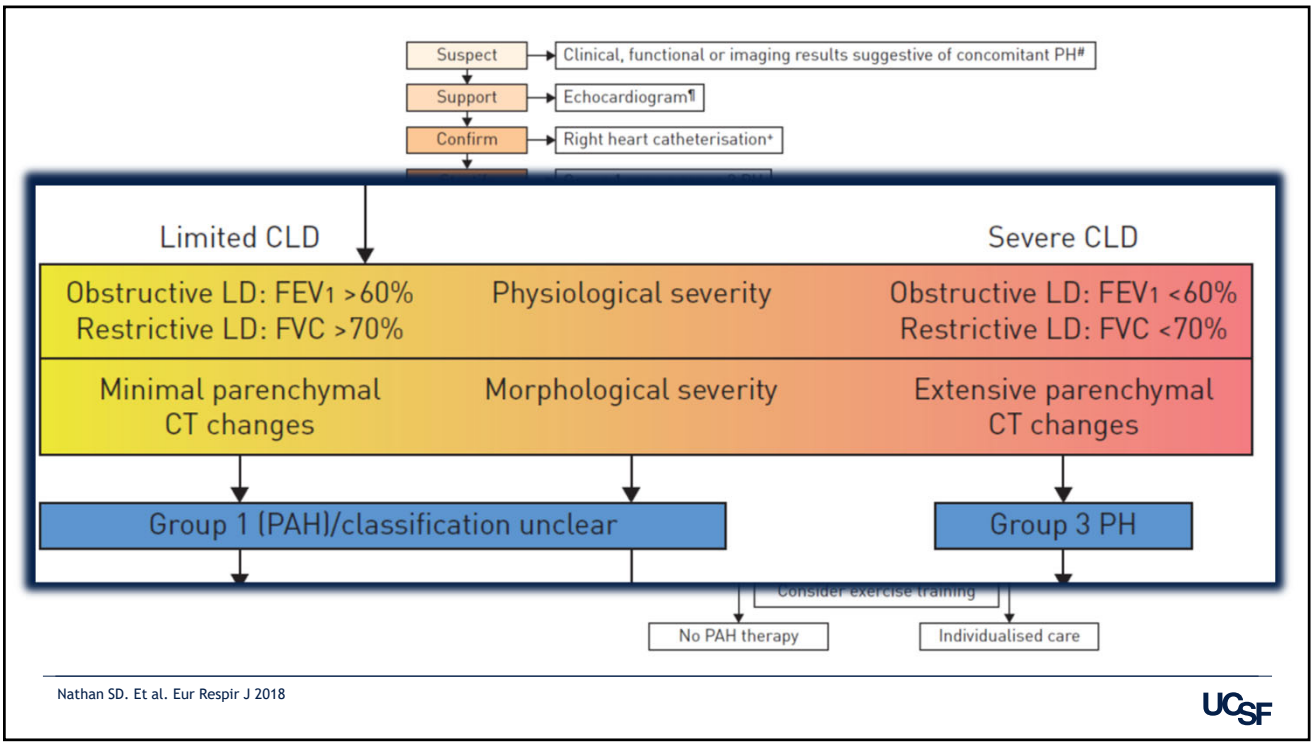

Nathan SD. Et al. Eur Respir J 2018

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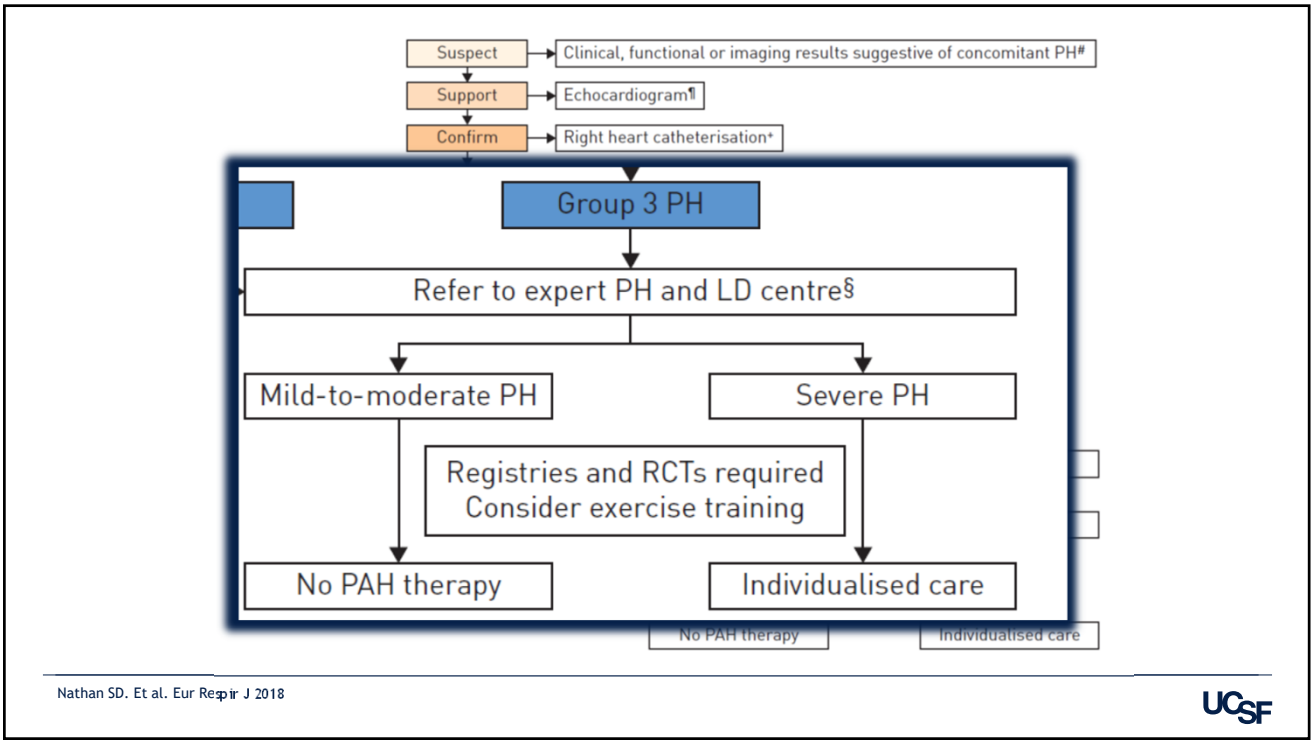

Nathan SD. Et al. Eur Respir J 2018

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Epidemiology and Clinical Relevance

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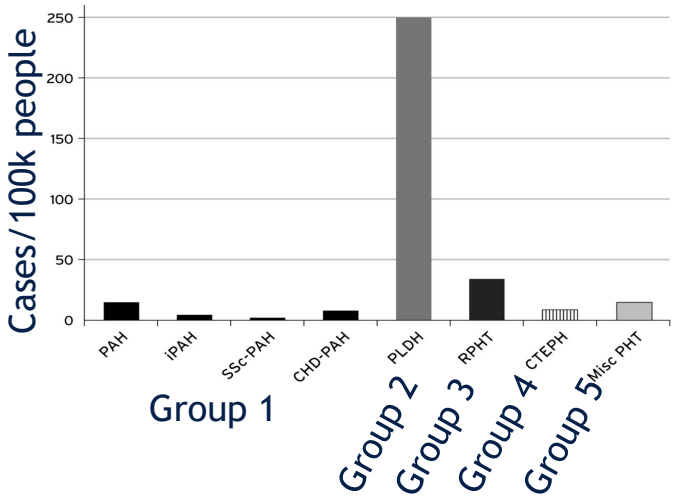
Group 3 PH is common

ECHO estimates of PH (ePASP>40 mmHg) in 6.2% of the surrounding population of Arnadale, Western Australia



Strange G et al. Heart 2012

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Group 3 PH is common

- Approximately 1–5% of all COPD patients have mPAP >35–40 mmHg at rest
  - Up to 90% of patients with GOLD Stage IV COPD have mPAP >20 mmHg
- Approximately 8-15% of IPF patients have mPAP ≥25 mmHg
  - 30-50% in advanced disease and >60% in end-stage disease
- Approximately 30-50% of patients with combined pulmonary fibrosis and emphysema have pulmonary hypertension

Nathan SD. Et al. Eur Respir J 2018

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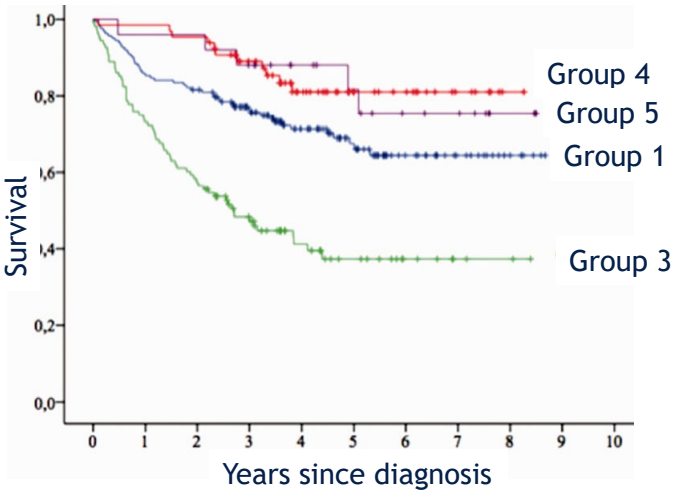
Group 3 PH is important

363 patients with pulmonary hypertension at a single center



Chebib N et al. Pulm Circ 2018

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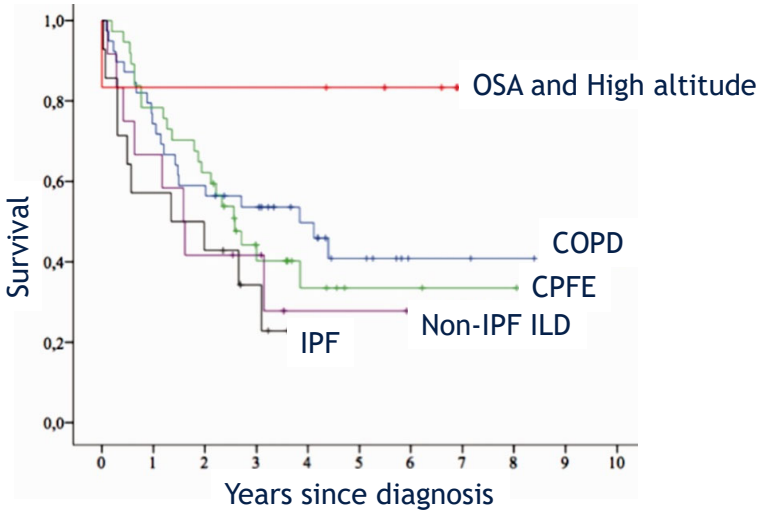
Group 3 PH is important

363 patients with pulmonary hypertension at a single center



Chebib N et al. Pulm Circ 2018

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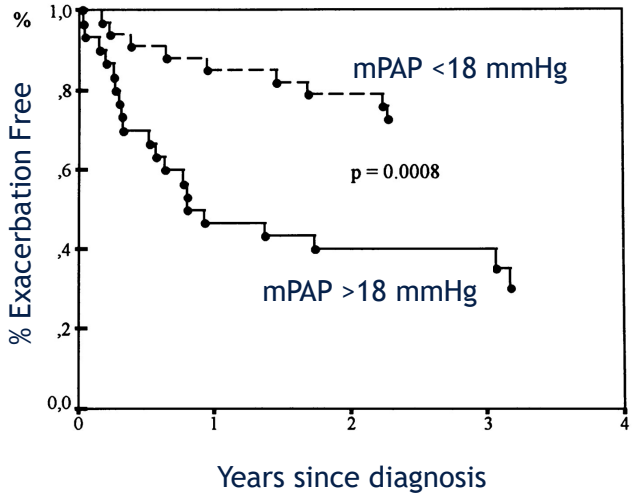
Group 3 PH is important in COPD

64 patients with COPD



Kessler R et al. Am J Respir Crit Care Med 1999

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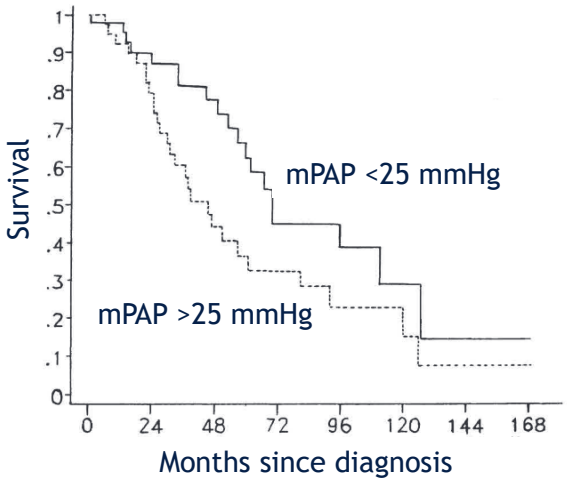
Group 3 PH is important in COPD

84 patients with COPD who underwent RHC before oxygen therapy



Oswald-Mammosser et al. Chest. 1995

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Group 3 PH is important in COPD

84 patients with COPD who underwent RHC before oxygen therapy

Table 2—*Estimated Survival at 5 Years in the Subgroups Divided According to the Level of Several Variables*

Age, yr		FEV_1, mL		PaO_2, mm Hg		$PaCO_2$, mm Hg		PAP, mm Hg	
≤63 (n=45)	>63 (n=39)	≤800 (n=39)	>800 (n=45)	≤52 (n=42)	>52 (n=42)	≤45 (n=42)	>45 (n=42)	≤25 (n=44)	>25 (n=40)
56.7%	36.8%*	47.7%	51.4%	43.0%	57.3%	49.2%	49.1%	62.2%	36.3%†

*p<0.05.
†p<0.001.

Table 3—*Prognostic Factors: Results of Cox's Regression Analysis in the 84 Patients*

Variables	RR*	CI†	Probability Value
PAP >25 mm Hg	2.17	1.14-3.78	0.016
Age >63 yr	2.18	1.15-4.11	0.018

*RR is the relative risk of dying.
†CI is the 95% confidence interval.

Oswald-Mammosser et al. Chest. 1995

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Group 3 PH is important in ILD

55 patients with IPF awaiting lung transplant

TABLE 3 Risk factors at initial assessment for acute exacerbation

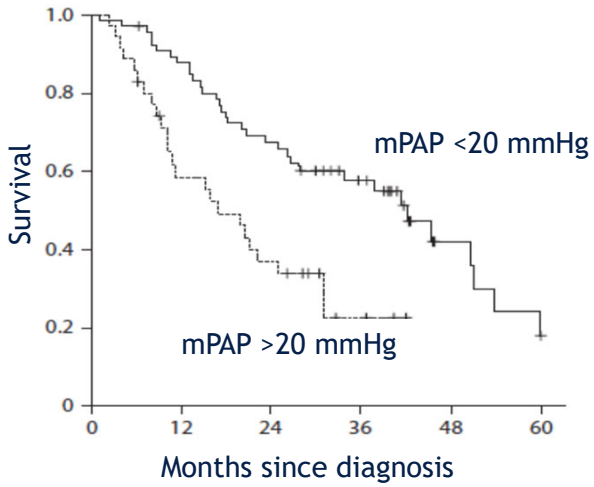
Parameter	HR (95% CI)	p-value
Multivariate Cox analysis		
Male	0.587 (0.398–1.139)	0.182
PH	2.510 (1.119–5.628)	0.026

Judge EP et al. Eur Respir J 2012

17

Group 3 PH is important in ILD

101 patients with IPF

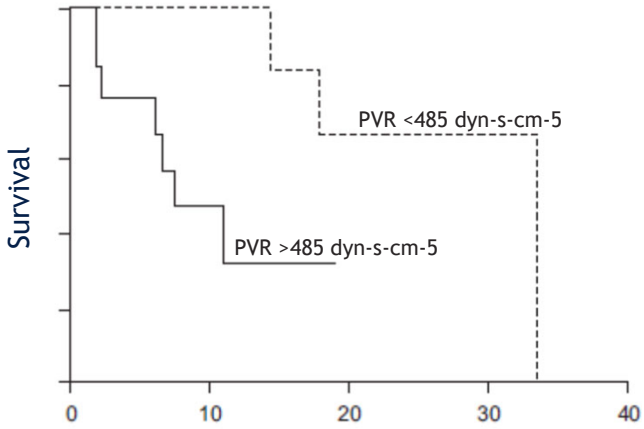


Kimura M et al. Respiration 2013

18

Group 3 PH is important in CPFE

40 patients with CPFE



Cottin V et al. Eur Respir J 2010

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Interim Summary

- Group 3 Pulmonary Hypertension is common
- Worst survival of all forms of pulmonary hypertension
- Associated with increased risk of acute exacerbations of COPD and IPF
- Associated with attenuation of survival

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Pathogenesis of Group 3 Pulmonary Hypertension

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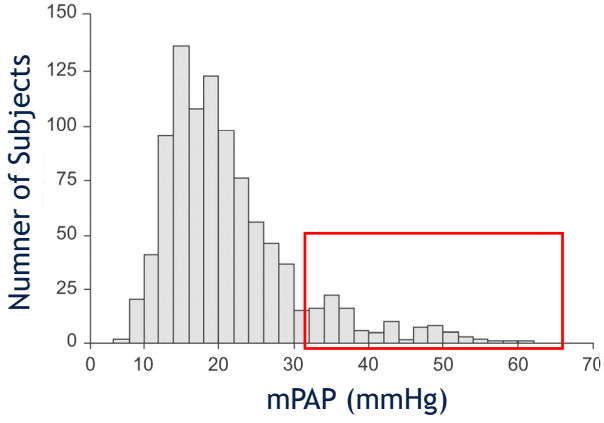
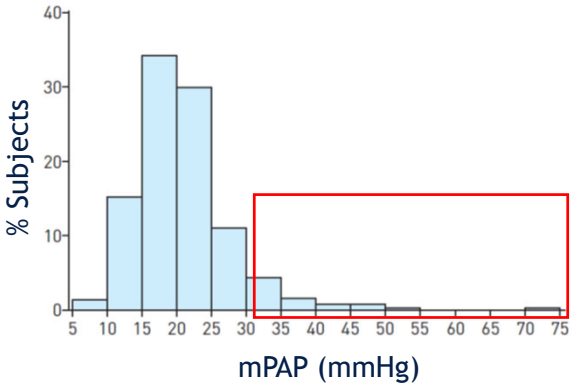
Distinct Phenotype



998 patients with COPD



488 patients with IPF

Chaouat A. et al. Eur Respir J 2008
Raghu G. et al. Eur Respir J 2015

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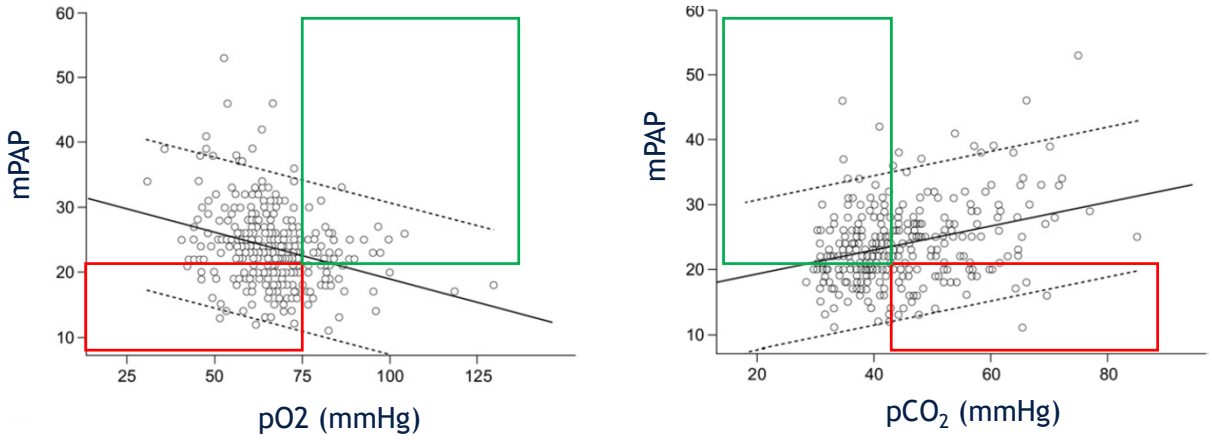
More than just end-stage COPD

409 patients with COPD



Andersen KH. J Heart Lung Transplant 2012

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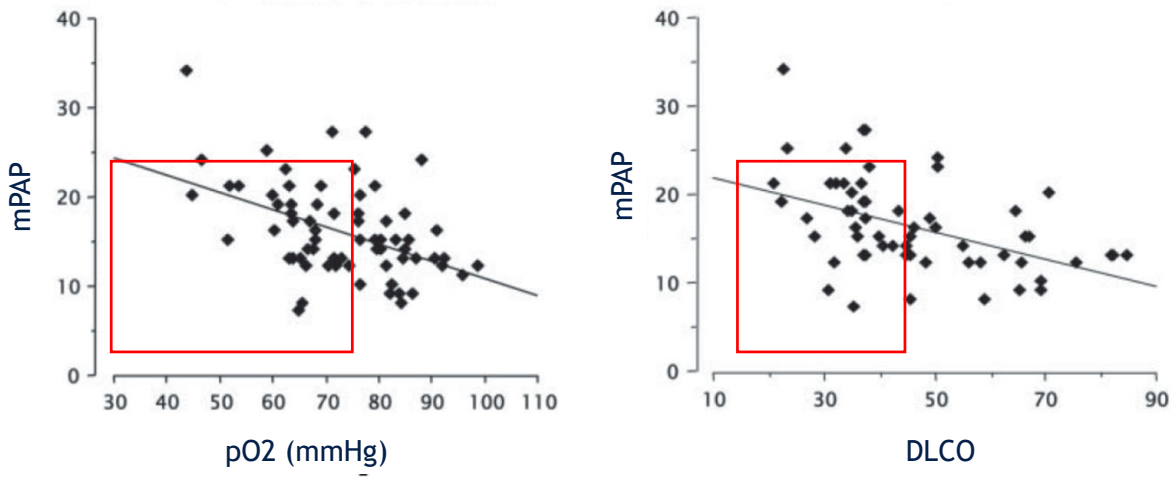
More than just end-stage in ILD

78 patients with IPF



Hamada K. Chest 2007

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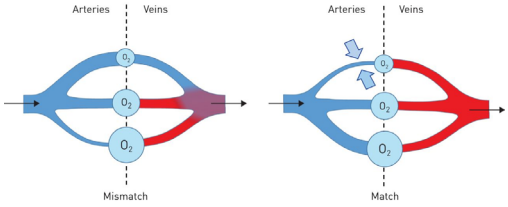
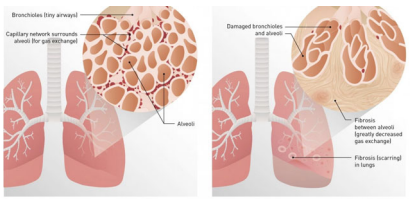
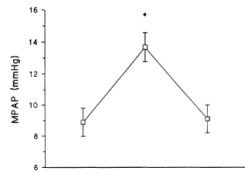
Pathogenesis is complicated

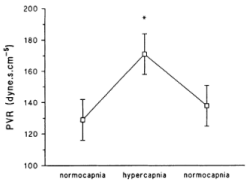


Hypoxemic pulmonary vasoconstriction

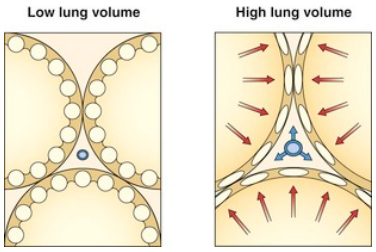


Destruction of capillary bed

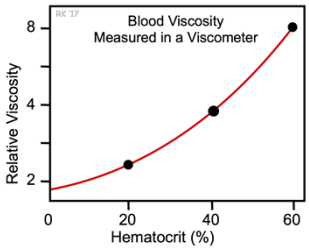




Hypercapnia induced



Compression of alveolar vessels



Increased blood viscosity

Sommer N et al. Eur Respir J 2016
Kiely DB et al. Chest 1996
Culver BH, The respiratory system 2006

Glassberg MK Am J Manag Care. 2019

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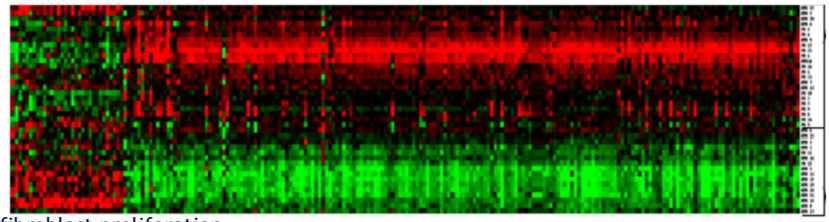
Pathogenesis is complicated

Microarray RNA analysis of 222 genes from explanted lungs in patients with pulmonary fibrosis

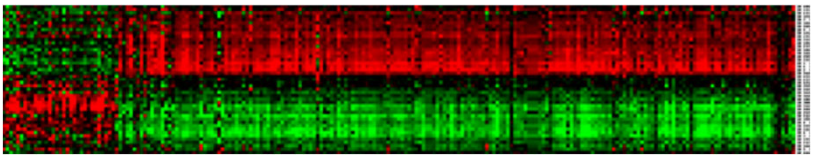


17 patients mPAP >40

22 patients mPAP <20

myofibroblast proliferation and vascular remodeling

proinflammatory



mPAP 23-39

Mura M et al. Chest 2012

26

Distinct Phenotype

Nathan SD. Et al. Eur Respir J 2018

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Interim Summary

- Group 3 Pulmonary Hypertension is more than just end stage disease
- Pathogenesis is complicated
- There is a pulmonary vascular phenotype

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Diagnosis of Group 3 Pulmonary Hypertension

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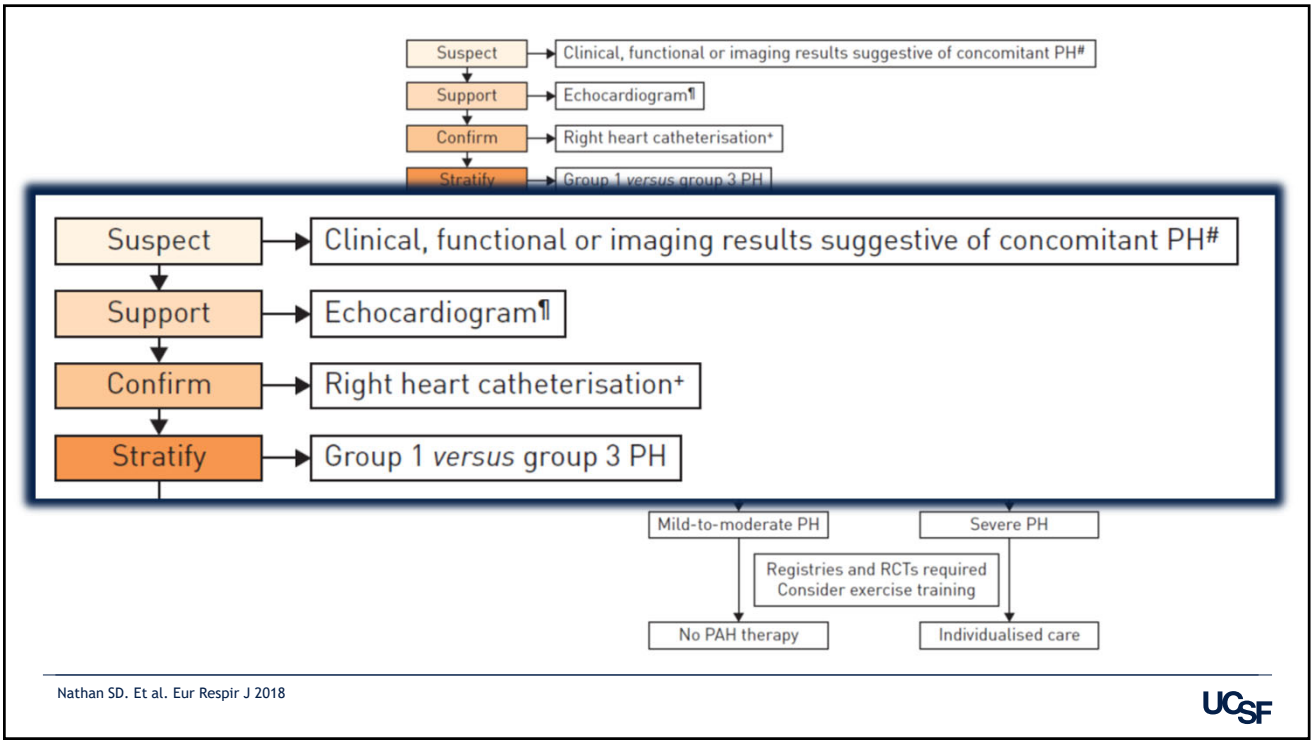
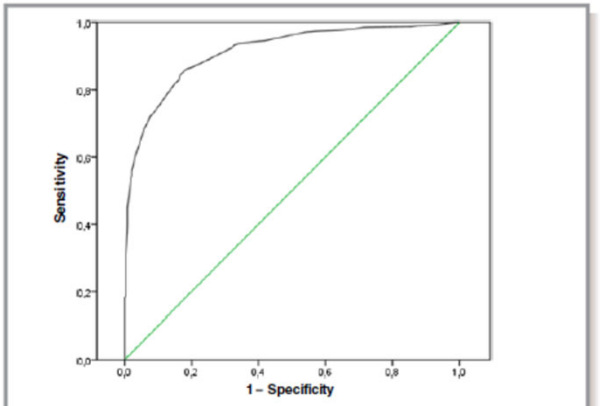


30

ECHO for diagnosis of PH in general population

1695 patients with paired ECHO and RHC



	AUC	p value	95% CI	Cut-off	Sensitivity	Specificity
sPAP	0.91	<0.001	0.90 – 0.93	36 mm Hg	87 %	79 %

eSPAP>36
Sensitivity 87%
Specificity 79%

Greiner S. J Am Heart Assoc 2014

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ECHO for diagnosis of Group 3 PH

$RVSP_{echo}$ (mmHg)	Diagnostic and 95% CI Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
$RVSP_{echo}$ > 35	86.4 (69.8-95.0)	28.9 (14.1-47.8)		
$RVSP_{echo}$ > 45	59.1 (38.7-76.8)	52.6 (33.5-69.8)	39.6	70.9
$RVSP_{echo}$ > 50	50.0 (30.7-69.3)	68.4 (48.3-82.9)	45.5	72.0
$RVSP_{echo}$ > 55	40.9 (23.2-61.3)	84.2 (60.4-91.6)	57.7	73.0
$RVSP_{echo}$ > 60	27.3 (12.9-48.4)	92.1 (73.9-98.9)	64.5	70.6

78 patients with IPF with paired RHC and ECHO

Nathan SD. Respir Med 2008

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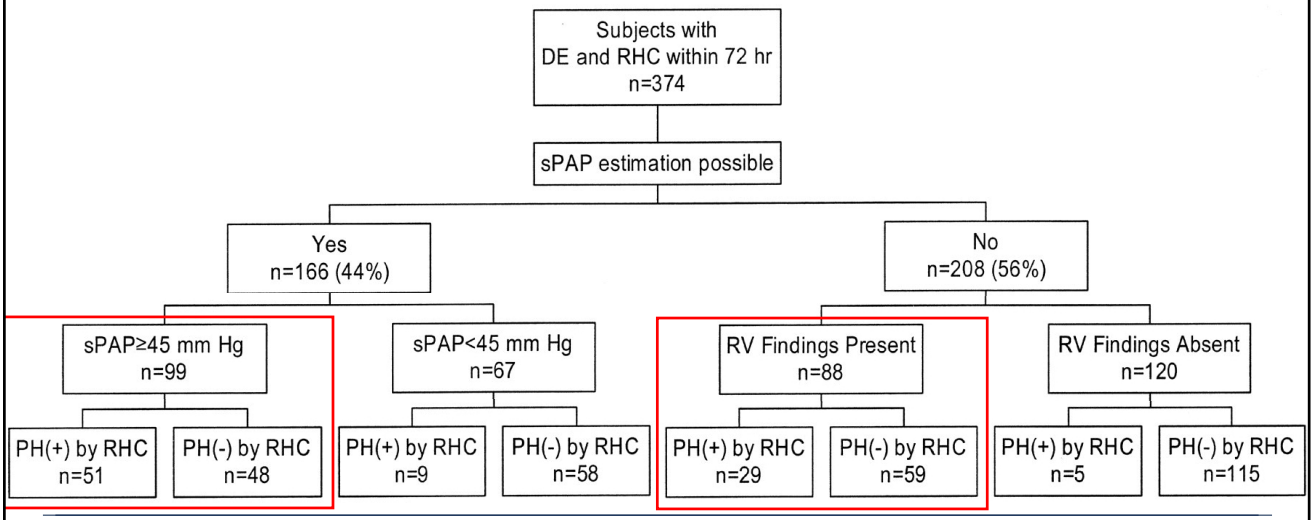
ECHO for diagnosis of Group 3 PH

374 patients with paired ECHO and RHC awaiting lung transplant



Arcasoy SM. Am J Respir Crit Care Med 2002

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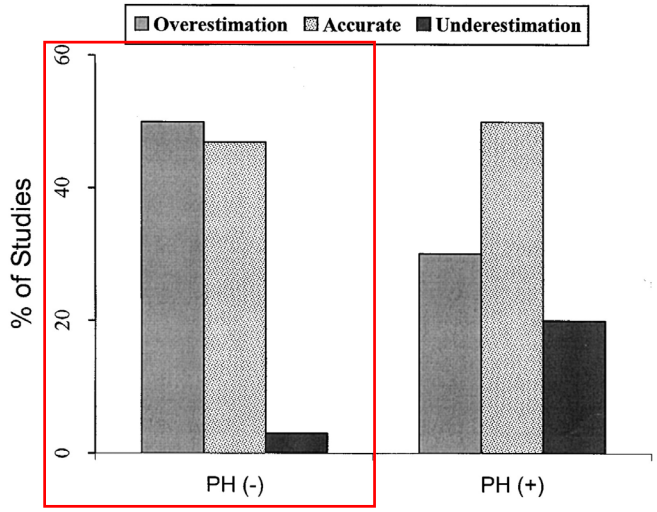
ECHO for diagnosis of Group 3 PH

374 patients with paired ECHO and RHC awaiting lung transplant



Arcasoy SM. Am J Respir Crit Care Med 2002

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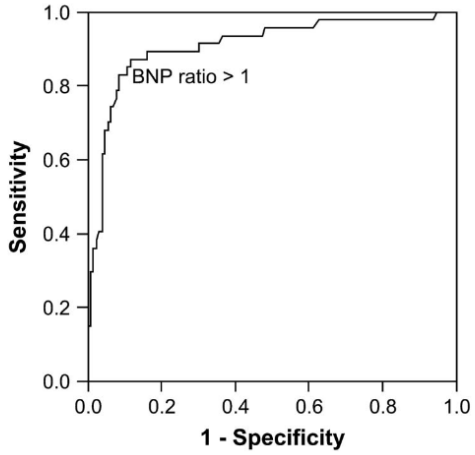
BNP for diagnosis of Group 3 PH

176 patients with various types of lung disease



Normalized BNP ratio
i.e., measured value>age & sex-specific value

Nathan SD. Respir Med 2008

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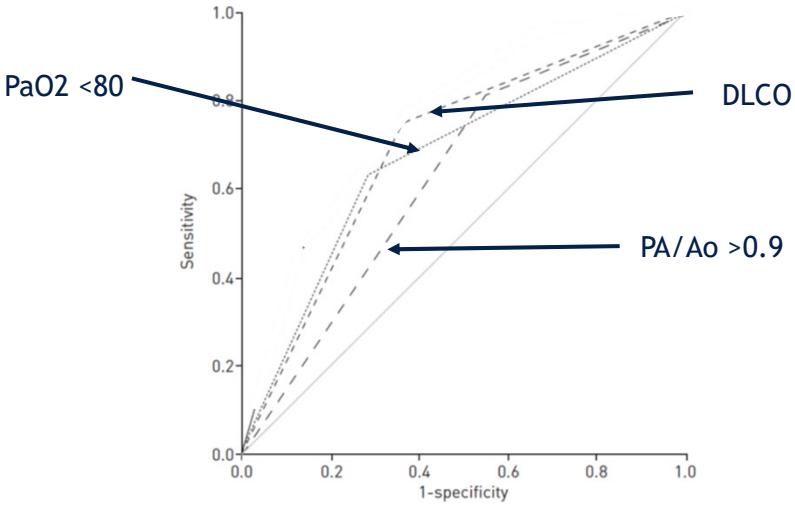
Other parameters for diagnosis of Group 3 PH

276 patients with IPF



Furukawa T. Eur Respir J 2018

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Right Heart Catheterization

- Right heart catheterization necessary to confirm diagnosis

2018 World Symposium Statement

*"RHC should be performed in patients with CLD when significant PH is suspected and the **patient's management will likely be influenced by RHC results**, including referral for transplantation, inclusion in clinical trials or registries, treatment of unmasked left heart dysfunction, or compassionate use of therapy."*

Nathan SD. Et al. Eur Respir J 2018

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Interim Summary

- ECHO overestimates presence of pulmonary hypertension in chronic lung disease
- Surrogate markers suggestive (BNP, DLCO, PaO2, PA/Ao)
- No substitute for RHC
- Perform when will change management

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Treatment of Group 3 Pulmonary Hypertension

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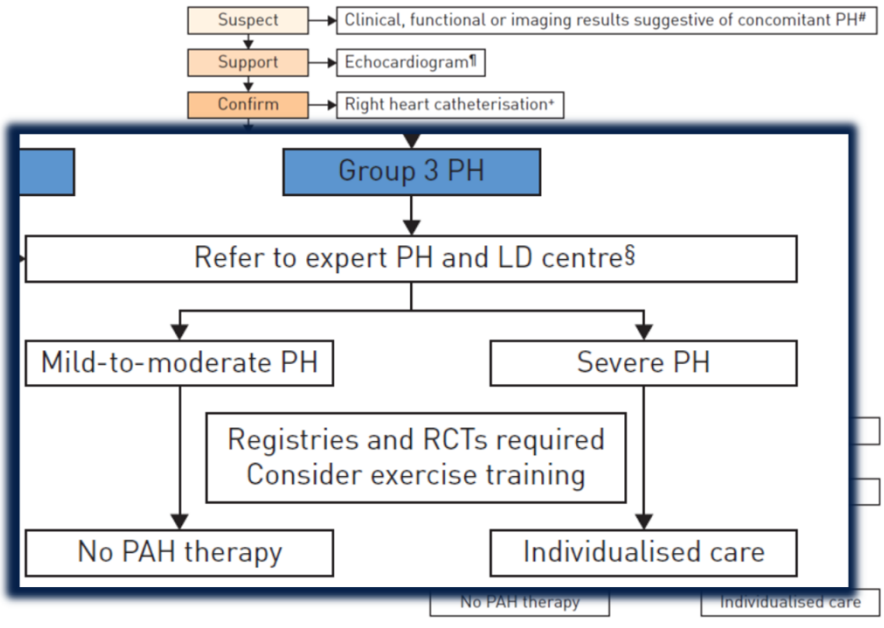

Nathan SD. Et al. Eur Respir J 2018

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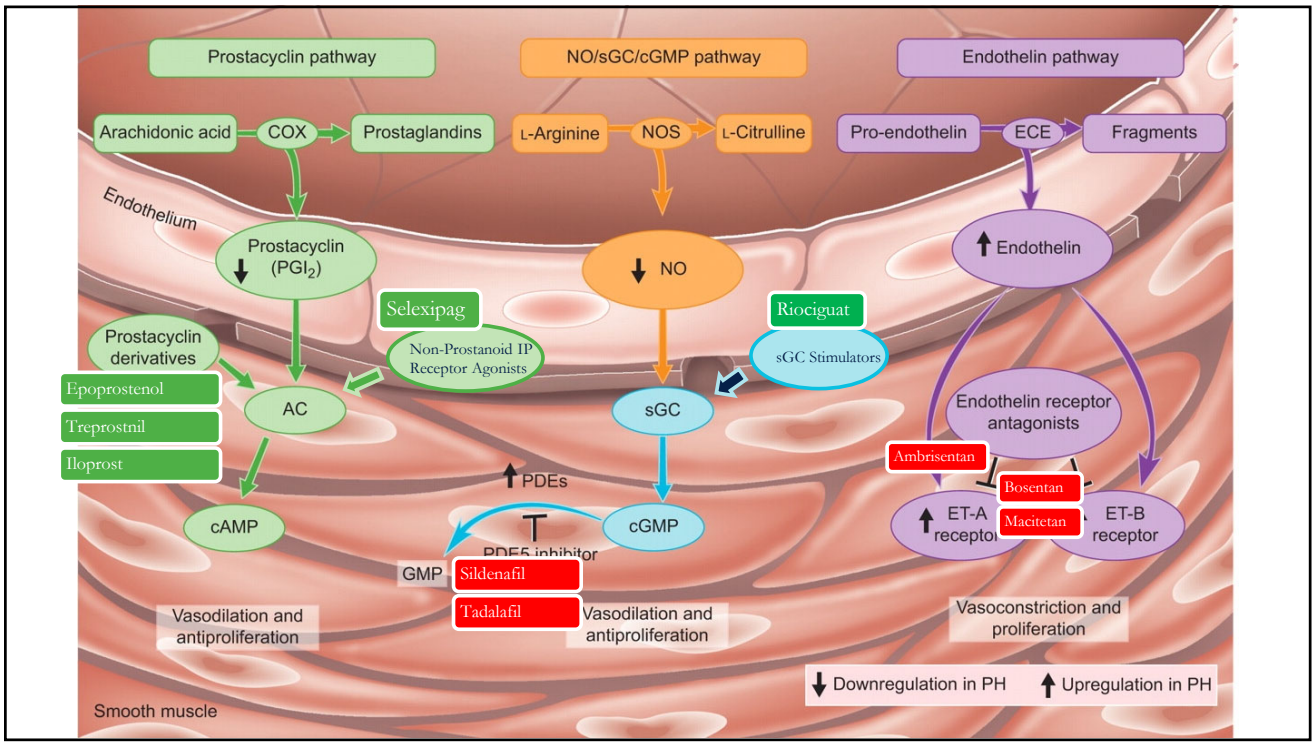

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Treatment of Group 3 Pulmonary Hypertension due to COPD

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Long Term Oxygen Therapy in COPD

203 paitents with COPD Nocturnal O2 vs Continuous O2

Table 3. Chronic Changes in Hemodynamic Levels in Patients with Hypoxemic Chronic Obstructive Pulmonary Disease After Six Months of Treatment*

	Nocturnal Oxygen Therapy			Oxygen Continuous Therapy		
	Rest	Legs Up	Exercise	Rest	Legs Up	Exercise
Mean right atrial pressure						
Mean ± SD, *mm Hg*	0 ± 3	0 ± 4	0 ± 6	0 ± 3	0 ± 5	−2 ± 7
Patients, *n*	56	34	40	58	31	42
p Value	0.52	0.77	0.77	0.68	0.73	0.15
Mean pulmonary artery pressure						
Mean ± SD, *mm Hg*	0 ± 7	−1 ± 9	−4 ± 13	−3 ± 11	−3 ± 9	−6 ± 14
Patients, *n*	57	40	50	61	40	54
p Value	0.57	0.52	0.03	0.02	0.03	0.005†
Pulmonary wedge pressure						
Mean ± SD, *mm Hg*	0 ± 5	−1 ± 6	−1 ± 9	0 ± 5	−1 ± 4	1 ± 10
Patients, *n*	51	35	39	54	31	41
p Value	0.55	0.24	0.56	0.89	0.13	0.65
Cardiac index						
Mean ± SD, *L/min · m²*	0.1 ± 0.7	...	0.1 ± 0.8	0.1 ± 0.7	...	0.3 ± 1.3
Patients, *n*	55	...	47	57	...	52
p Value	0.52	...	0.41	0.43	...	0.07
Stroke volume index						
Mean ± SD	0.4 ± 8.4	...	2.3 ± 8.5	2.4 ± 8.1	...	4.3 ± 9.8
Patients, *n*	54	...	46	53	...	48
p Value	0.70	...	0.07	0.04	...	0.004†
Pulmonary vascular resistance						
Mean ± SD, *dyne · s · cm⁻⁵*	−15.4 ± 116.9	...	−47.9 ± 117.8	−67.9 ± 174.0	...	−107.7 ± 190.7
Patients, *n*	49	...	35	52	...	38
p Value	0.36	...	0.02	0.007	...	0.001†

PASP improved

SVI improved

PVR improved

Timms RM. Ann Intern Med 1985

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Treatment of COPD-PH

TABLE 2 Randomised controlled trials (RCTs) with pulmonary arterial hypertension (PAH)-targeted therapy in lung disease

First author (year) [ref.]	Subjects n	Inclusion criteria	Study design	Diagnosis of PH	Baseline haemodynamics#	Baseline PFTs#	Therapy	Duration	Primary end-point result	Other outcomes
COPD										
Vonbank (2003) [86]	40	COPD on supplemental oxygen with PH by RHC	RCT (open label)	RHC: mPAP ≥25 mmHg	mPAP 27.6±4.4 mmHg, CI 2.7±0.6 L·min^{-1}·m^{-2}	FEV$_1$ 1.09±0.4 L, FEV$_1$/FVC 44.5%	"Pulsed" nitric oxide with oxygen *vs* oxygen	3 months	PVRI, improved	Improved mPAP, CO and PVR; no worsened hypoxaemia
Stolz (2008) [53]	30	GOLD III–IV; no haemodynamic requirement	RCT (2:1)	Echo	sPAP 32 (29–38) mmHg	Not reported	Bosentan 125 mg 2 times daily	12 weeks	6MWD, no change	Worsened hypoxaemia and health-related QoL
Valerio (2009) [50]	32	COPD with PH by RHC	RCT (open label)	RHC	mPAP 37±5 mmHg	FEV$_1$ 37±18%	Bosentan 125 mg 2 times daily	18 months	No defined primary	mPAP, PVR, BODE index and 6MWD improved
Rao (2011) [87]	33	GOLD III–IV	RCT	Echo: sPAP >40 mmHg	sPAP 52.7±11.9 mmHg	FEV$_1$ 32.5±11.1%	Sildenafil 20 mg 3 times daily	12 weeks	6MWD, increased 190 m	Decrease in sPAP
Blanco (2013) [88]	60	COPD with PH by RHC or echo	RCT	RHC: mPAP ≥25 mmHg; echo: sPAP ≥35 mmHg	sPAP 42±10 mmHg, mPAP 31±5 mmHg	FEV$_1$ 32±11%	Sildenafil 20 mg or placebo 3 times daily and PR	3 months	Exercise endurance time, no change	No change in 6MWD, peak V'_{O_2}, QoL or oxygenation
Goudie (2014) [89]	120	COPD with PH by echo	RCT	Echo: pulmonary acceleration time <120 ms or sPAP >30 mmHg	Echo: sPAP 42±10 mmHg	FEV$_1$ 41±16%	Tadalafil 10 mg daily	12 weeks	6MWD, no change	Decreased sPAP compared with placebo; no difference in QoL, BNP or S_{aO_2}
Vitulo (2016) [49]	28	COPD with PH by RHC	RCT (2:1)	RHC: mPAP >35 mmHg (if FEV$_1$ <30%), mPAP ≥30 mmHg (if FEV$_1$ ≥30%)	mPAP 39±8 mmHg, CI 2.4±0.5 L·min^{-1}·m^{-2}, PVR 7±2.6 WU	FEV$_1$ 54±22%, D_{LCO} 33±12%	Sildenafil 20 mg 3 times daily	16 weeks	PVR, decreased 1.4 WU	Improved CI, BODE scores and QoL; no effect on gas exchange

Nathan SD. Et al. Eur Respir J 2018

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Treatment of COPD-PH

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Nathan SD. Et al. Eur Respir J 2018

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Treatment of COPD-PH

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Nathan SD. Et al. Eur Respir J 2018

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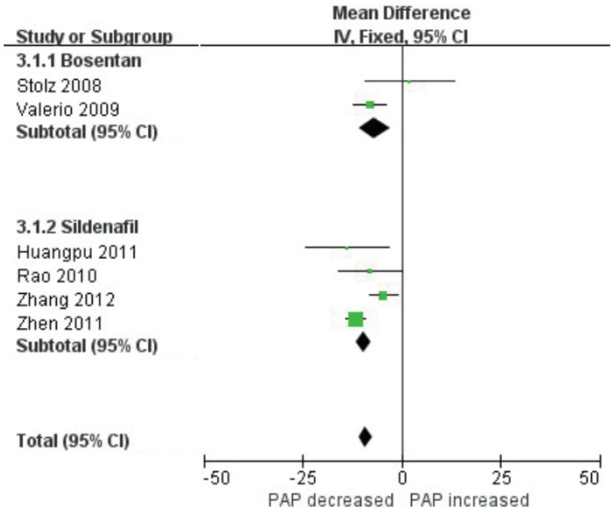
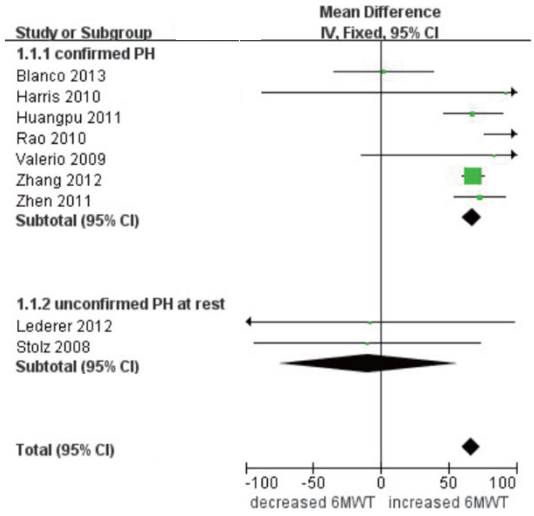
Treatment of COPD-PH



Chen X. et al. J Thorac Dis 2015

47

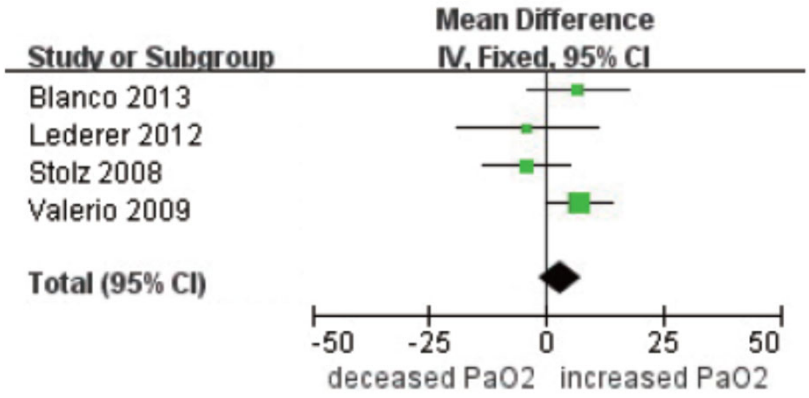
Treatment of COPD-PH



Chen X. et al. J Thorac Dis 2015

48

Treatment of COPD-PH



Chen X. et al. J Thorac Dis 2015

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Treatment of COPD-PH

2018 WSPH Statement

"Although preliminary evidence suggests that currently available vasoactive medications may have a benefit in COPD-PH patients with mPAP ≥35 mmHg, further studies are required before PAH therapies can be recommended"

Nathan SD. Et al. Eur Respir J 2018

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Upcoming Studies

- Inhaled prostacyclin vs placebo in COPD-PH
- Inhaled nitric oxide vs oxygen in COPD-PH

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Treatment of Group 3 Pulmonary Hypertension due to ILD

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Treatment of ILD-PH

TABLE 2 Randomised controlled trials (RCTs) with pulmonary arterial hypertension (PAH)-targeted therapy in lung disease

First author (year) [ref.]	Subjects n	Inclusion criteria	Study design	Diagnosis of PH	Baseline haemodynamics#	Baseline PFTs#	Therapy	Duration	Primary end-point result	Other outcomes
ILD										
Han (2013) [90]	119	IPF with echo available (66% of the whole cohort)	RCT	Echo: RVSD	Not available	FVC 57%, *D*LCO 26%	Sildenafil 20 mg 3 times daily	12 weeks	6MWD, less decline in patients with RVSD on sildenafil	Improvement in QoL in patients with RVSD
Corte (2014) [60]	60	IPF or idiopathic fibrotic NSIP	RCT (2:1)	RHC: mPAP ⩾25 mmHg	mPAP 37±9.9 mmHg, CI 2.2±0.5 L·min^{-1}·m^{-2}	FVC 55.7±20%, *K*CO 45±22%	Bosentan	16 weeks	PVRI decrease of 20%, negative	Secondary end-points all negative; no change in functional capacity or symptoms
Raghu (2015) [14]¶	68	IPF with group 2 PH (14% of whole cohort)	RCT (2:1)	RHC	mPAP 30±8 mmHg	FVC 67±12%, *D*LCO 39±15%	Ambrisentan 10 mg·day^{-1}	Event-driven study terminated early	Disease progression, unfavourable trend	More hospitalised ambrisentan arm
Nathan (2017) [57]	147	IIP, FVC >45%, mPAP >25 mmHg	RCT	RHC	mPAP 33.2±8.2 mmHg, CI 2.6±0.7 L·min^{-1}·m^{-2}	FVC 76.3±19%, *D*LCO 32±12%	Riociguat 2.5 mg 3 times daily	26 weeks	6MWD, no difference at study halt	Study stopped early for increased harm to riociguat arm (death and hospitalisation)
Nathan [2019]	229	IIP	RCT	RHC					6MWD	Increased mortality

Nathan SD. Et al. Eur Respir J 2018

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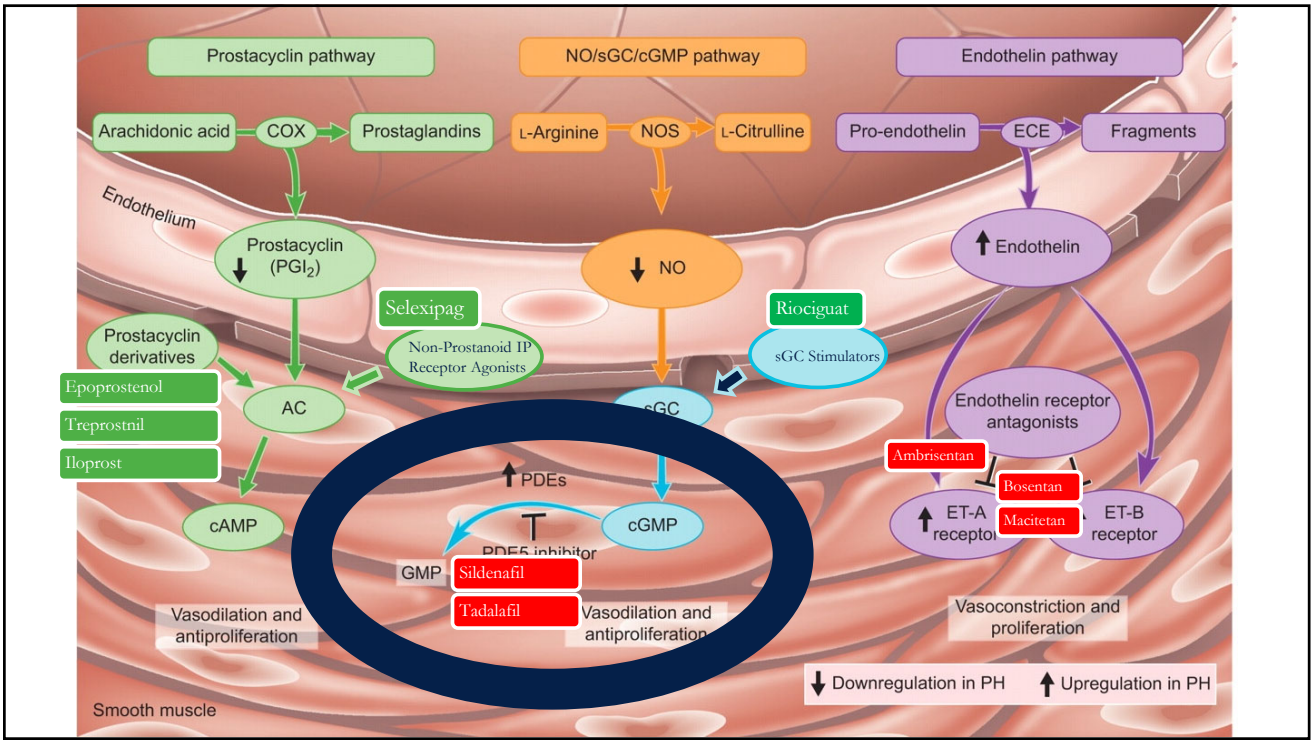

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Treatment of ILD-PH (STEP-IPF)

- 180 patients with IPF randomized to sildenafil vs placebo
- Inclusion criteria DLCO <35% predicted
- PRIMARY OUTCOME: Improvement in 6MWD of 20% or more
  - 10% of placebo group
  - 7% of sildenafil group

Zisman DA et al. N Engl J Med 2010

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Treatment of ILD-PH (STEP-IPF)

180 patients with IPF randomized to sildenafil vs placebo

Table 2. Change in Prespecified Secondary Outcomes at 12 Weeks.*

Characteristic	Sildenafil (N=89)	Placebo (N=91)	Absolute Difference†	P Value
	mean change (95% confidence interval)			
Dyspnea				
Score on Borg Dyspnea Index after walk test‡	0.04 (−0.30 to 0.37)	0.37 (0.04 to 0.70)	−0.34 (−0.81 to 0.14)	0.16
Shortness of Breath Questionnaire‡	0.22 (−3.10 to 3.54)	6.81 (3.53 to 10.08)	−6.58 (−11.25 to −1.92)	0.006
Quality of life				
St. George's Respiratory Questionnaire‡				
Total score	−1.64 (−3.91 to 0.64)	2.45 (0.17 to 4.72)	−4.08 (−7.30 to −0.86)	0.01
SF-36§				
Aggregate physical score	−0.51 (−1.86 to 0.83)	−0.35 (−1.68 to 0.99)	−0.17 (−2.06 to 1.73)	0.86
Aggregate mental score	1.30 (−0.59 to 3.18)	3.02 (1.15 to 4.89)	−1.72 (−4.38 to 0.93)	0.20
Score on EQ-5D§				
Self-report questionnaire	−0.01 (−0.06 to 0.03)	−0.03 (−0.08 to 0.01)	0.02 (−0.04 to 0.08)	0.54
Visual-analogue scale	0.48 (−3.10 to 4.06)	−1.81 (−5.34 to 1.73)	2.28 (−2.75 to 7.32)	0.37

Zisman DA et al. N Engl J Med 2010

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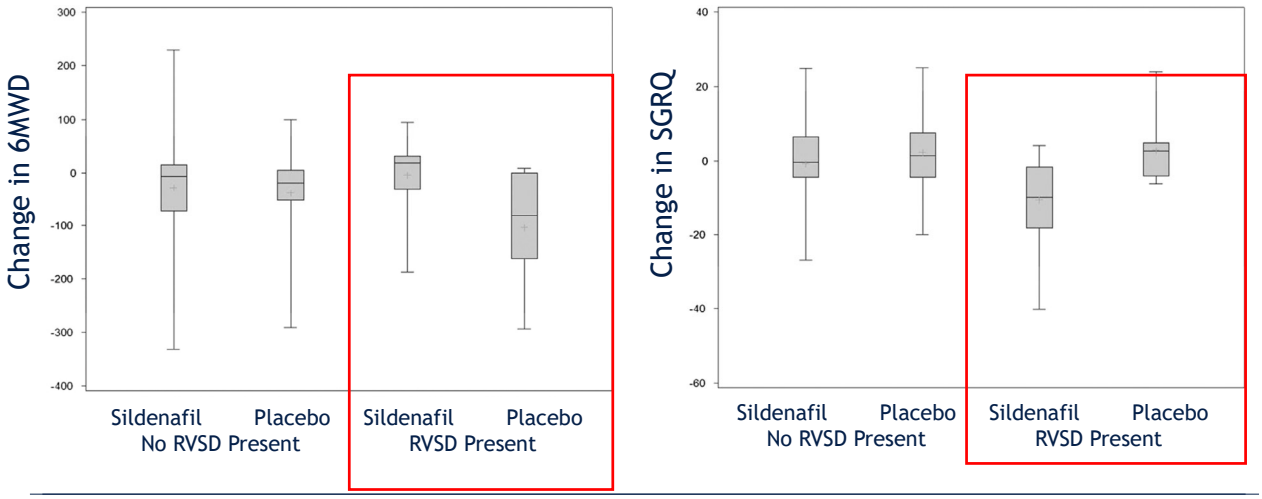
Treatment of ILD-PH (STEP-IPF)

Subgroup analysis of 119 subjects in Step-IPF with ECHO



Han MK et al. Chest 2013

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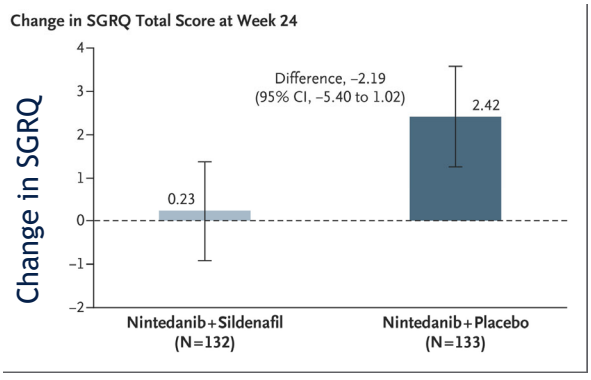
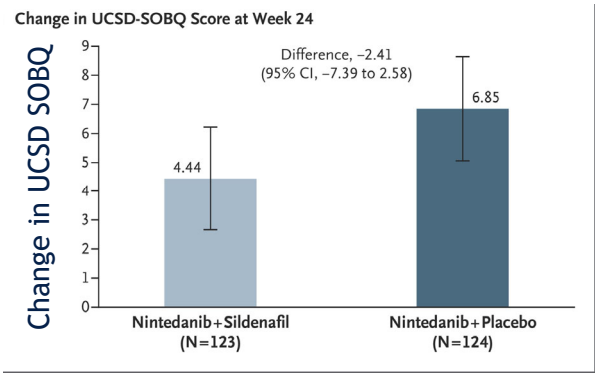
Treatment of ILD-PH (INSTAGE)

274 Patients with IPF and DLCO<35% predicted

PRIMARY END POINT: Change in St. George Respiratory Questionnaire



Higher scores indicating worse HRQL



Higher scores indicating more dyspnea

Kolb M et al. N Engl J Med 2018

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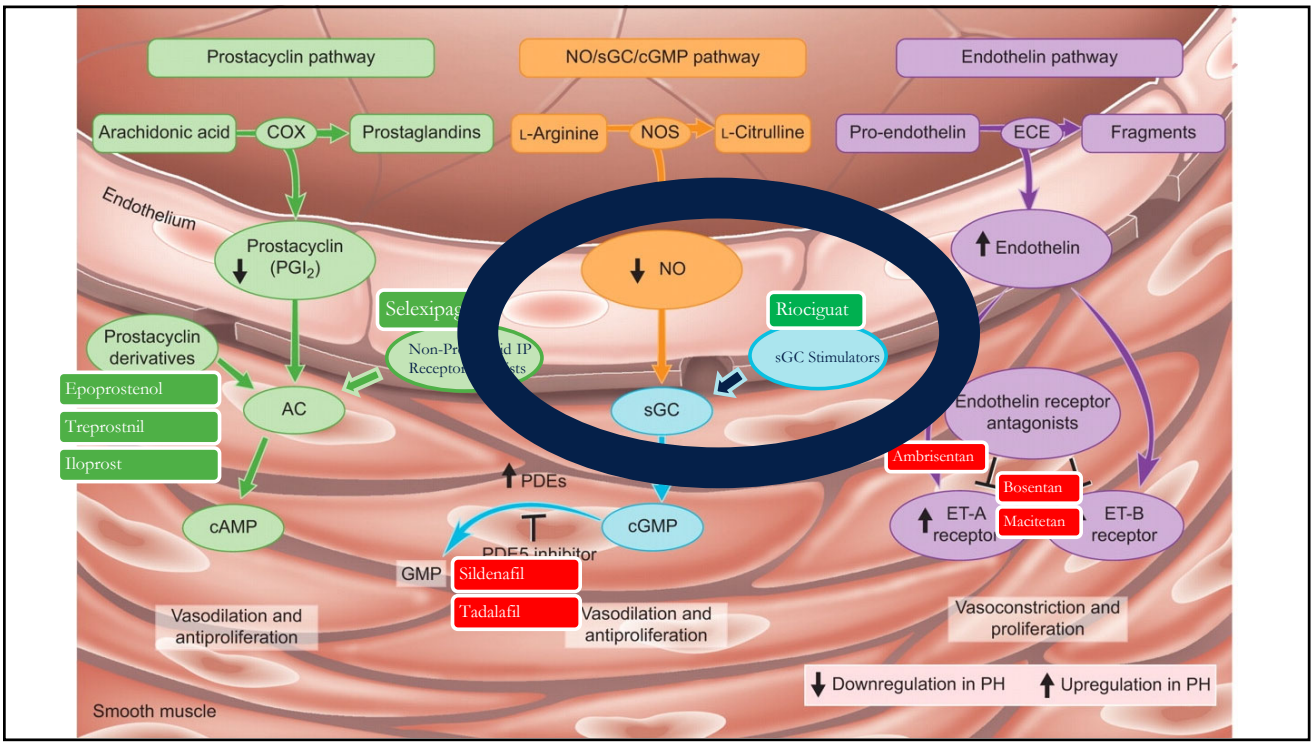

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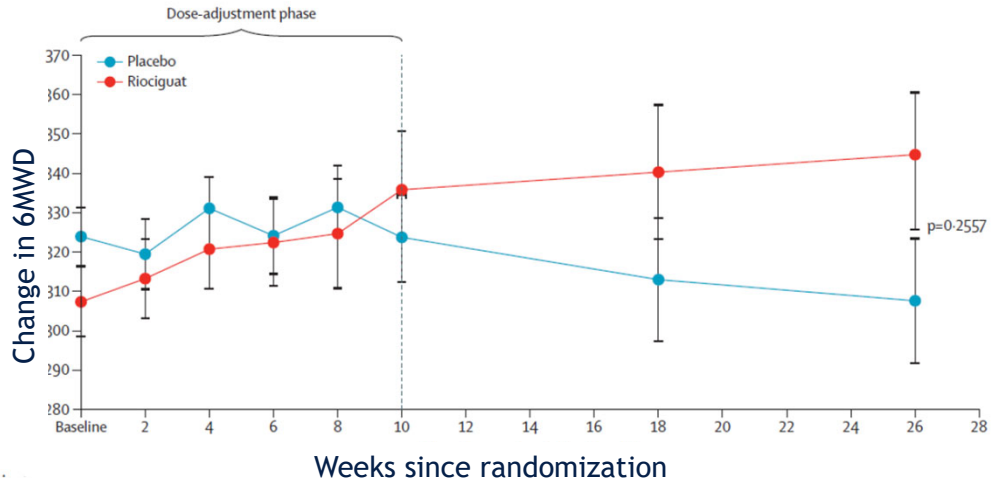
Treatment of ILD-PH (RISE-IIP)

229 patients with ILD and PH by RHC



Nathan SD. Lancet Repir Med 2019

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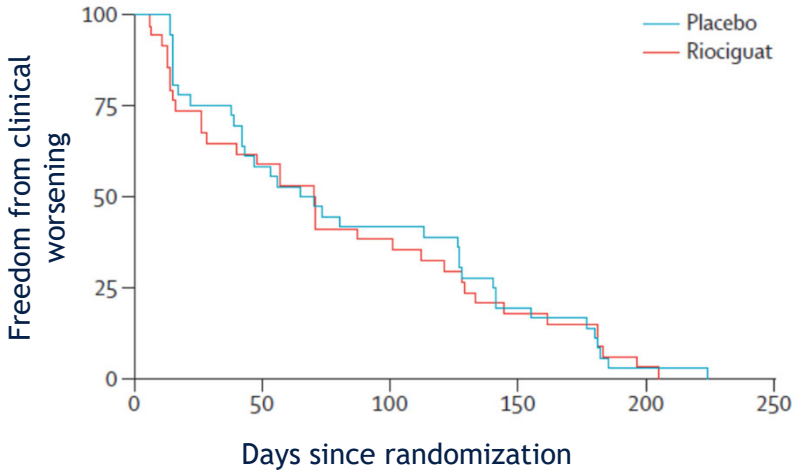
Treatment of ILD-PH (RISE-IIP)

229 patients with ILD and PH by RHC



Nathan SD. Lancet Repir Med 2019

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Treatment of ILD-PH (RISE-IIP)

229 patients with ILD and PH by RHC

	Main phase	
	Riociguat up to 2·5 mg (n=73)	Placebo (n=74)
Any AE	65 (89%)	64 (86%)
Study drug-related AEs	29 (40%)	28 (38%)
AEs leading to study drug discontinuation	11 (15%)	3 (4%)
Any SAE	27 (37%)	17 (23%)
Study drug-related SAEs	5 (7%)	4 (5%)
SAEs leading to study drug discontinuation	10 (14%)	1 (1%)
Deaths	8 (11%)	3 (4%)

No deaths attributed directly to drug

Nathan SD. Lancet Repir Med 2019

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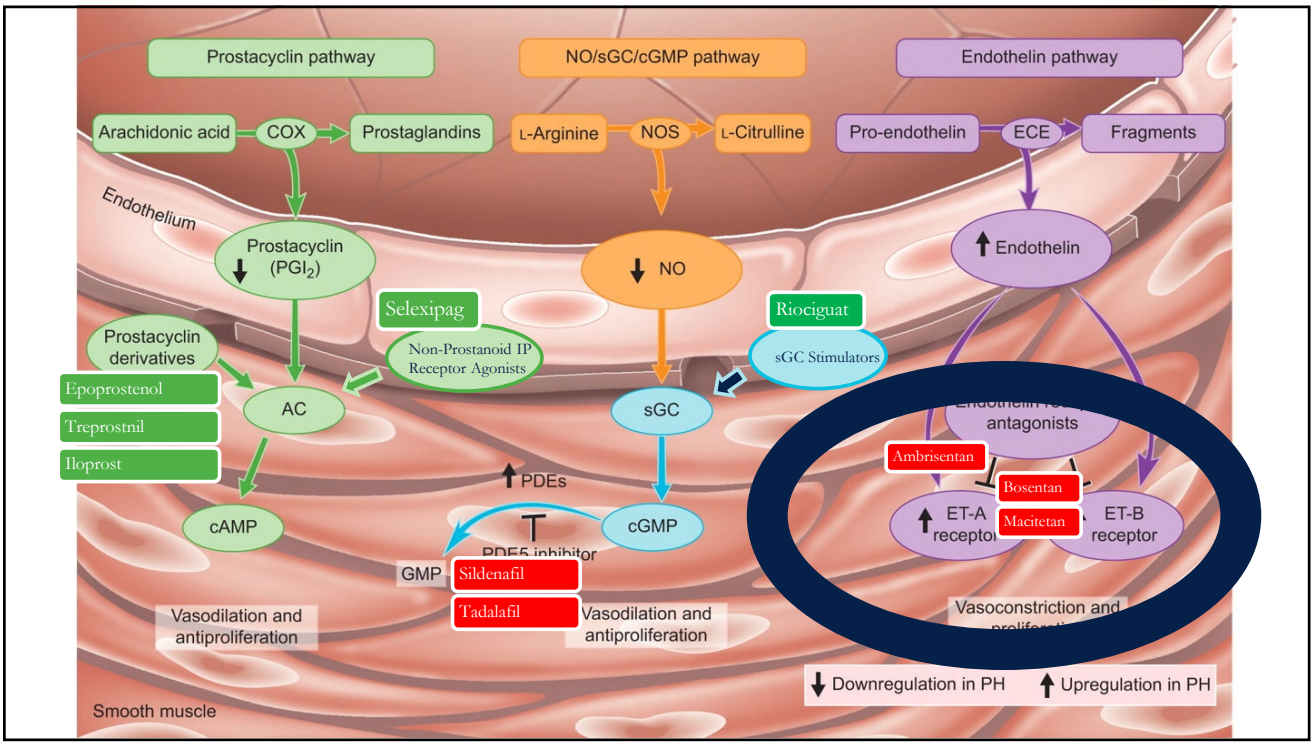
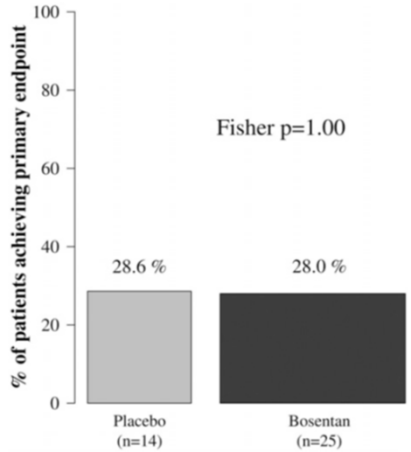


63

Treatment of ILD-PH (BPHIT)

60 patients with fibrotic ILD and mPAP ≥25mmHg
PRIMARY ENDPOINT: Change in PVRI from 20% of baseline

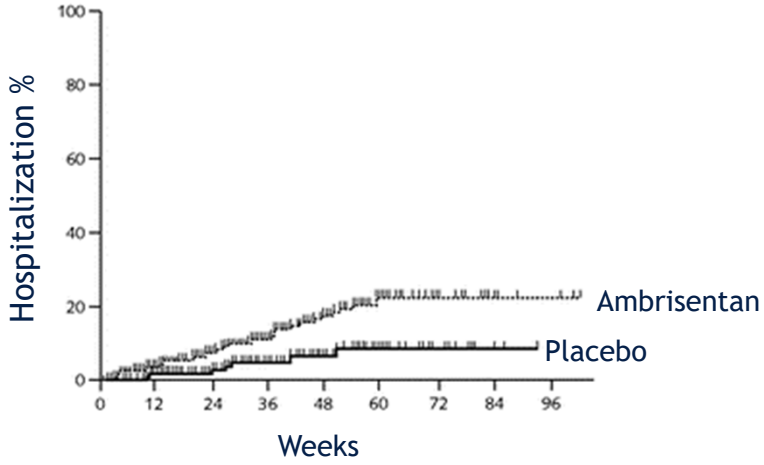


Corte TJ et al. Am J Respir Crit Care Med 2014

64

Treatment of ILD-PH (ARTEMIS-IPF)

492 patients with mild-moderate IPF - No PH inclusion criteria



Raghu G et al. Ann Intern Med. 2013

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Treatment of ILD-PH (ARTEMIS-IPF)

Table 1. **Baseline Characteristics of Study Participants**

Characteristic	Placebo (n = 163)	Ambrisentan (n = 329)
Pulmonary hypertension, *n (%)**	16 (9.8)	32 (9.7)
Mean pulmonary arterial pressure (SD), *mm Hg*	20.6 (8.0)	20.3 (6.3)

Subgroup analysis on adverse outcomes with patients who had PH was not significant, although the point estimates were similar to primary model

Raghu G et al. Ann Intern Med. 2013

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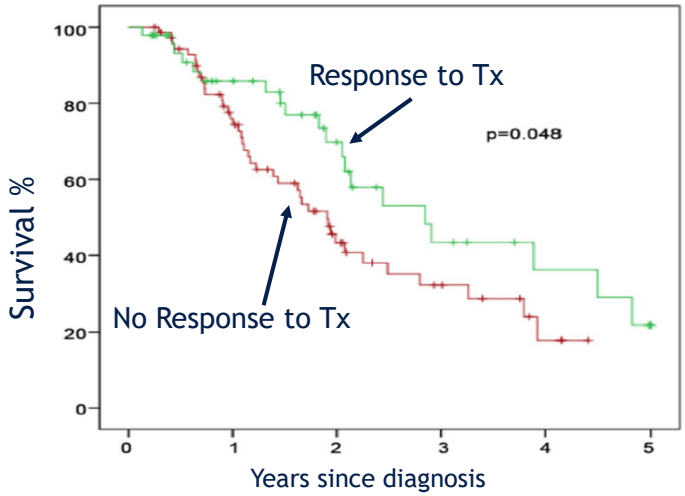
66

Treatment of ILD-PH

115 patients with ILD started on PAH-therapy



Hoeper MM et al. PLOS 2015

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Treatment of ILD-PH

2018 WSPH Statement

*"**Riociguat and ambrisentan are both contraindicated in IIP-PH**. There is no evidence of benefit for other endothelin receptor antagonists in IIP-PH. **Data on the use of sildenafil in IIP-PH is conflicting**, while evidence for prostanoid therapy is too limited for any current recommendations."*

Nathan SD. Et al. Eur Respir J 2018

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Upcoming Studies

- Inhaled prostacyclin vs placebo in ILD-PH
- Sildenafil with pirfenidone in ILD-PH

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Interim Summary

- No approved drugs for Group 3 PH
- Treat underlying lung disease
- More promising data in COPD than ILD
- Treatment should be performed in select patients with clinically relevant pulmonary hypertension
  - Ideally in expert centers
  - Ideally under the context of a clinical trial

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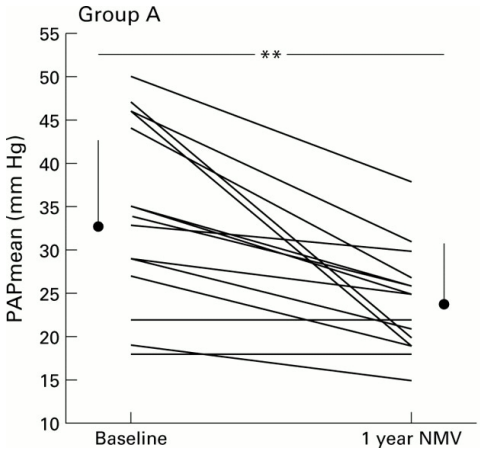
Treatment of Group 3 Pulmonary Hypertension from OSA

71

OSA/OHS-PH

- Pulmonary hypertension common in obstructive sleep apnea and obesity hypoventilation syndrome
- Treatment of OSA is underlying therapy
- No indication for PAH-specific therapy



Schonhofer B. et al. Thorax 2001

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San Francisco

Conclusion

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Conclusions

- Group 3 Pulmonary Hypertension is common and important
- Associated with attenuation of survival
- Pathogenesis is complex and likely represents a different phenotype than end-stage lung disease
- No approved drugs for Group 3 pulmonary hypertension
- Treat underlying lung disease
- Hope for treatment remains

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Thank You

nicholas.kolaitis@ucsf.edu

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Right Heart Catheterization – PH Severity

Severity	PAP (mmHg)	PVR (WU)	CI
Without	mPAP <21		
Without	mPAP 21-24	PVR <3	
With	mPAP 21-24	PVR ≥3	
With	mPAP 25-34		
Severe	mPAP ≥35	PVR ≥3	
Severe	mPAP 21-24		<2

Nathan SD. Et al. Eur Respir J 2018

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UPDATES ON CTEPH

Kim M. Kerr, MD
UC San Diego
Clinical Professor of Medicine and Vice Chief of the Division of Pulmonary, Critical Care & Sleep Medicine

Saturday, January 18, 2020– 11:10 a.m. – 11:55 a.m.

Kim M. Kerr, MD is Clinical Professor of Medicine and Vice Chief of the Division of Pulmonary, Critical Care & Sleep Medicine at the University of California San Diego. She has been a member of the UCSD Pulmonary Vascular Program since 1993 and her clinical research is focused on pulmonary vascular disease including predictors of surgical outcomes and interventional trials to prevent reperfusion edema following pulmonary thromboendarterectomy. She currently serves as the Principle Investigator and Steering Committee Chair of the United States CTEPH Registry, a multi-center, prospective, longitudinal registry of patients with chronic thromboembolic pulmonary hypertension.

PANEL DISCUSSION

Questions/Answers with
Nicholas Hill, MD; Kristina Kudelko, MD;
Nicholas Kolaitis, MD;
Kim Kerr, MD

Saturday, January 18, 2020– 11:55 a.m. – 12:15 p.m.

Nicholas S. Hill, MD
Tufts Medical Center in Boston
Chief of the Division of Pulmonary, Critical Care and Sleep Medicine

NICHOLAS S. HILL, MD is Chief of the Division of Pulmonary, Critical Care and Sleep Medicine at Tufts Medical Center in Boston and Professor of Medicine at Tufts University School of Medicine. He received his M.D. from Dartmouth Medical School in 1975. He did his internship and residency in Medicine at Tufts-New England Medical Center. He did a fellowship in Cardiovascular Medicine at the University of Massachusetts Medical Center and in Pulmonary Medicine at Boston University School of Medicine. He is Board Certified in Internal Medicine, Pulmonary Diseases, and Critical Care Medicine. He has done extensive research and writing in the fields of noninvasive ventilation and pulmonary hypertension dating back over 35 years. He has edited several books related to these topics. He established the Pulmonary Hypertension Center at Tufts Medical Center. He is a Past President of the American Thoracic Society and has received a Distinguished Scholar Award in Critical Care from the Chest Foundation of the American College of Chest Physicians as well an Award for Excellence in Pulmonary Hypertension Care from the Pulmonary Hypertension Association.

Kristina Kudelko, MD
Stanford University
Clinical Associate Professor, Division of PCCM
Director of Education, Vera Moulton Wall Center of Pulmonary Vascular Disease

Kristina Kudelko, MD received her medical degree from the University of Pennsylvania. She trained in internal medicine and pulmonary and critical care medicine at New York Presbyterian Hospital-Cornell before she pursued a second fellowship in pulmonary hypertension at Stanford University in 2008-9. She is currently a Clinical Associate Professor in pulmonary and critical care medicine at Stanford and Director of Education of the Vera Moulton Wall Center for Pulmonary Vascular Disease.

Nicholas A. Kolaitis, MD
UC San Francisco
Assistant Clinical Professor of Medicine

Nicholas A. Kolaitis, MD is an Assistant Clinical Professor of Medicine at the University of California, San Francisco. He cares for patients in the UCSF Lung Transplant Program and Pulmonary Hypertension Clinic. His research interests are in health-related quality of life and the systemic manifestations of lung disease. He is the chair of the CTS Career Development Committee and is a member of the CTS Board of Directors.

Kim M. Kerr, MD
UC San Diego
Clinical Professor of Medicine and Vice Chief of the Division of Pulmonary, Critical Care & Sleep Medicine

Kim M. Kerr, MD is Clinical Professor of Medicine and Vice Chief of the Division of Pulmonary, Critical Care & Sleep Medicine at the University of California San Diego. She has been a member of the UCSD Pulmonary Vascular Program since 1993 and her clinical research is focused on pulmonary vascular disease including predictors of surgical outcomes and interventional trials to prevent reperfusion edema following pulmonary thromboendarterectomy. She currently serves as the Principle Investigator and Steering Committee Chair of the United States CTEPH Registry, a multi-center, prospective, longitudinal registry of patients with chronic thromboembolic pulmonary hypertension.

LUNCH
EXHIBIT HALL OPEN

Saturday, January 18, 2020 – 12:15 p.m. – 1:15 p.m.

CTS ANNUAL BUSINESS MEETING

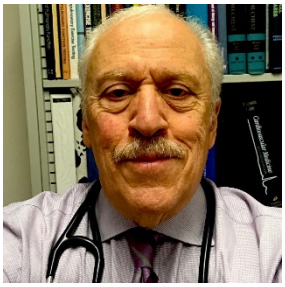
Saturday, January 18, 2020 – 1:00 p.m. – 1:15 p.m.

HOT TOPICS IN PULMONARY MEDICINE

BIOLOGICS IN ASTHMA:
A PERSONAL APPROACH

Stephen C. Lazarus, MD, FCCP, FERS
UC San Francisco
Professor of Medicine
Division of Pulmonary & Critical Care Medicine
Senior Investigator, Cardiovascular Research Institute

Saturday, January 18, 2020 – 1:15 p.m. – 2:00 p.m.



Stephen C. Lazarus, MD, FCCP, FERS is an inbred product of the University of California, having trained at Berkeley, Irvine, and San Francisco. He served as Fellowship Director at UCSF for 18 years, as well as Clinic Chief and Division Chief. His clinical and research focus is airway disease, and he's been PI of the NHLBI-sponsored Asthma Clinical Research Network, AsthmaNet, the COPD Clinical Research Network, the DOD ß-Blockers in COPD network, and the ALA Airway Clinical Research Centers Network. He was a member of the NAEPP Coordinating Committee 2001-2017. Dr. Lazarus is an Editor of the Murray & Nadel Textbook of Respiratory Medicine, and has authored more than 200 original research papers, review articles, and book chapters.

Biologics in Asthma: A Personalized Approach

Stephen C. Lazarus, MD, FCCP, FERS
University of California San Francisco

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Disclosures

- No interactions with Pharma or Industry

- Member NAEPP Coordinating Committee
- PI NHLBI Asthma Clinical Research Network (ACRN)
- PI NHLBI AsthmaNet
- PI NHLBI COPD Clinical Research Network (CCRN)
- Co-Investigator NHLBI SPIROMICS Network
- PI ALA Airway Clinical Research Centers Network

2

(All Asthma is not the same!)

3

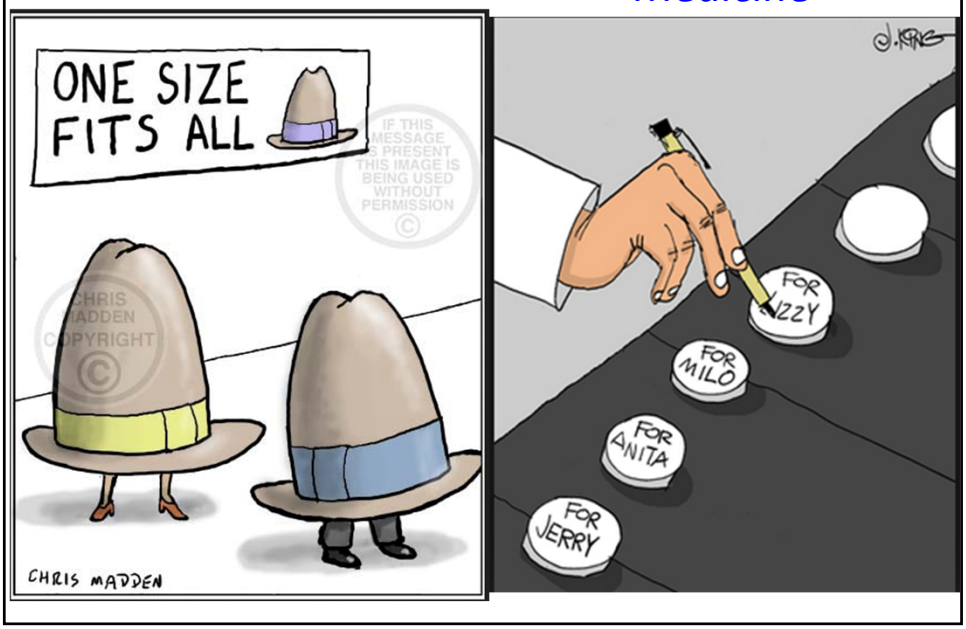
Phenotypes vs Endotypes

- ***Phenotype***: Any observable characteristic or trait, without implication for mechanism
- ***Endotype:*** A disease subtype defined by a distinct functional or pathobiological mechanism

Anderson, GP
Lancet 372:20-26, 2008

4

Precision Medicine



5

Evidence That Severe Asthma Can Be Divided Pathologically into Two Inflammatory Subtypes with Distinct Physiologic and Clinical Characteristics

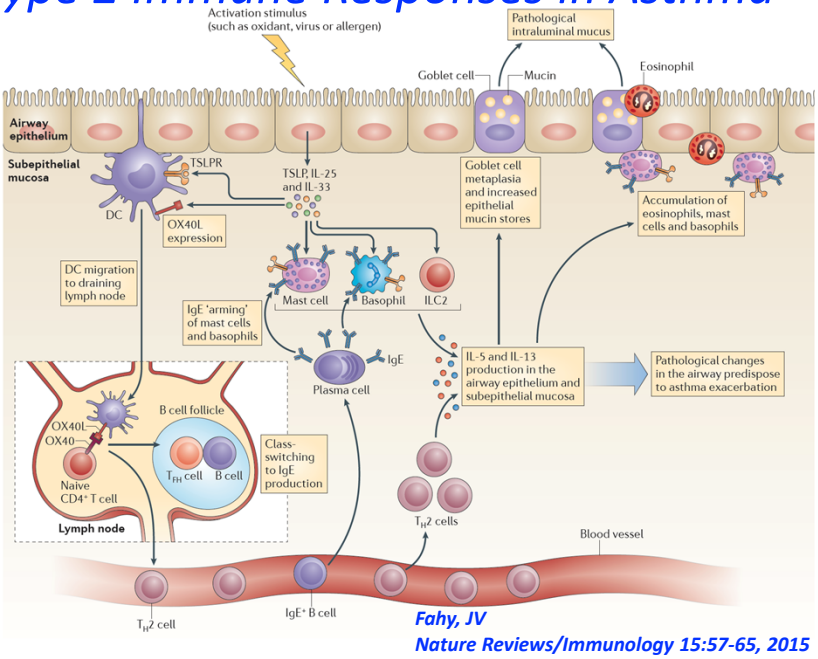
SALLY E. WENZEL, LAWRENCE B. SCHWARTZ, ESTHER L. LANGMACK, JANET L. HALLIDAY, JOHN B. TRUDEAU, ROBYN L. GIBBS, and HONG WEI CHU

- N = 34 Severe Asthma
- Endobronchial Biopsies
- 59% (20/34) Eosinophil Positive
- 41% (14/34) Eosinophil Negative

Am J Respir Crit Care Med 160:1001-8, 1999

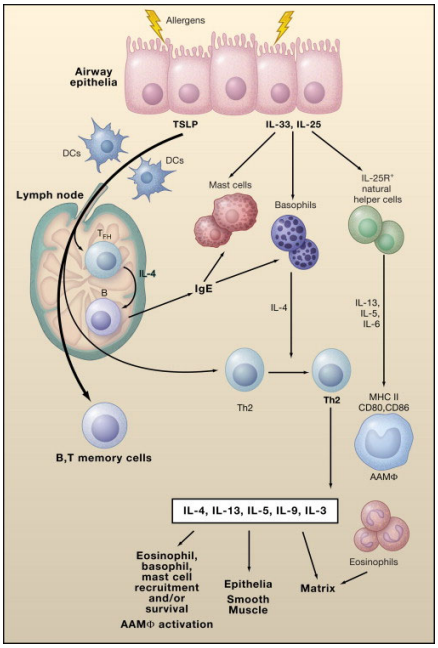
6

Type 2 Immune Responses in Asthma



Fahy, JV
Nature Reviews/Immunology 15:57-65, 2015

7



Locksley Cell 2010

IL13 and IL5 comprise distinct components of type 2 inflammation:

- IL5 directly promotes eosinophilia
- IL13 has direct effects on lung structural cells, promotes IgE class switching and indirectly promotes eosinophilia

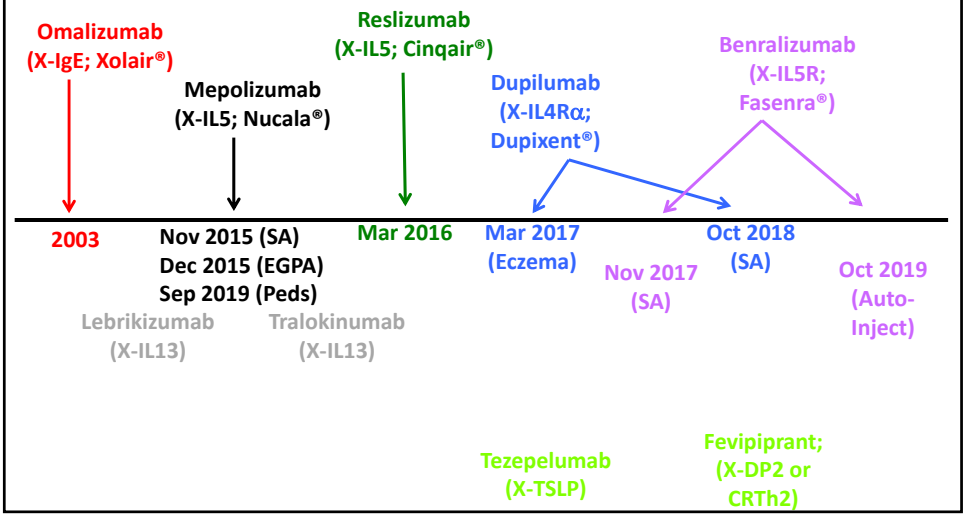
Blood and sputum eosinophilia reflect the effect of IL5

Periostin and inducible NO synthetase are induced in structural cells by IL13

Optimal choice of biomarker may depend on what aspect type 2 inflammation you are choosing to target

8

Timeline for Asthma Biologics



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Inhibiting IgE for Asthma

- Omalizumab (Anti-IgE)
- FDA approved 2003
- Indications: Mod-severe allergic asthma
  Chronic idiopathic urticaria
- Binds IgE and prevents binding to FcεR1
- Approved for 6-11 and ≥12
- Administered SC, q2-4 weeks

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Cochrane Library

Cochrane Database of Systematic Reviews

Omalizumab for asthma in adults and children (Review)

Normansell R, Walker S, Milan SJ, Walters EH, Nair P

- N = 25 clinical trials; moderate or severe asthma
- Reduced risk of exacerbations (26% → 16%)
- Reduced risk of hospitalization (3% → 0.5%)
- Small (significant) decrease in ICS dose
- Increased likelihood of eliminating ICS (40% vs 21%)
- No reduction in OCS

11

Annals of Internal Medicine | ORIGINAL RESEARCH

Omalizumab in Severe Allergic Asthma Inadequately Controlled With Standard Therapy

A Randomized Trial

Nicola A. Hanania, MD, MS; Oral Alpan, MD; Daniel L. Hamilos, MD; John J. Condemi, MD; Imarie Reyes-Rivera, PhD; Jin Zhu, PhD; Karin E. Rosen, MD, PhD; Mark D. Eisner, MD, MPH; Dennis A. Wong, MD; and William Busse, MD

- N = 850, randomized, 12 months
- 25% reduction in exacerbations (0.88 to 0.66)
- Improved AQLS (0.29 points; 0.15 to 0.43)
- Decreased daily albuterol (-0.27 puffs; -0.49 to -0.04)
- Decreased mean Asthma Symptom Score (-0.26; -0.42 to -0.10)

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Original article

The oral corticosteroid-sparing effect of omalizumab in children with severe asthma

Malcolm Brodlie,[1,2] Michael C McKean,[2] Samantha Moss,[2] David A Spencer[2]

Arch Dis Child 2012;**97**:604–609.

- N = 34 children, prospective, not randomized, 4 months
- Median prednisolone reduced 20 to 5 mg (p<0.0001))
- Improved AQLQ, 3.5 to 5.9 (p<0.0001)
- Improved ACT, 12 to 20 (p<0.0001)

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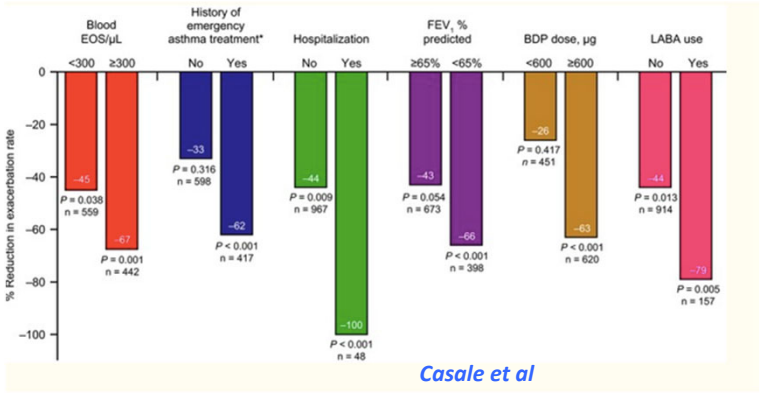
Blood Eosinophils and Clinical Markers of Asthma Severity Predict Response to Omalizumab

2 Phase III trials
N=1071
Omalizumab
Vs
Placebo

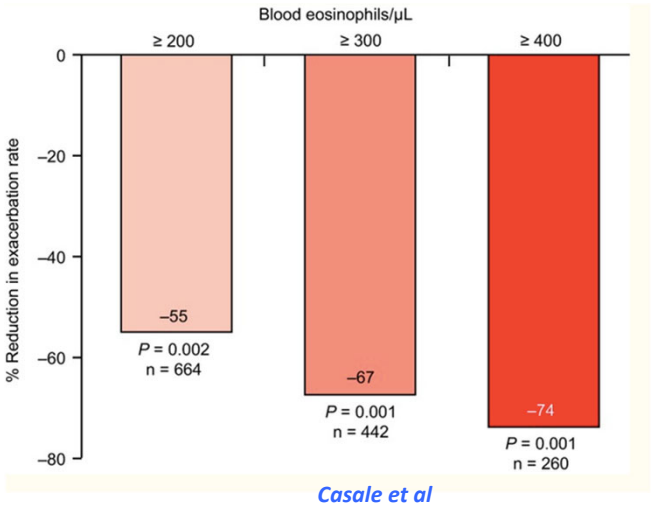


Casale et al
Allergy, 2018; 73:490-97

14

Omalizumab is More Effective in Patients with Robust T2 Signal

2 Phase III trials
N=1071
Omalizumab
Vs
Placebo



Casale et al
Allergy, 2018; 73:490-97

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Inhibiting IL-5 for Asthma

- Mepolizumab (Anti-IL5)*
- Reslizumab (Anti-IL5) **
- Benralizumab (Anti-IL5Rα) +++

*FDA-approved 11/15 for Asthma (SA) Add-on Maintenance and
in 12/15 for EGPA
in 09/19 for Pediatric SA

**FDA-approved 3/16 for Asthma (SA) Add-on Maintenance

+++FDA-approved 11/17 for Asthma (SA) Add-on Maintenance

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Inhibiting IL-5 for Asthma

- Mepolizumab (Anti-IL-5)
- FDA approved 2015
- Indications: Severe allergic asthma
  EGPA
- Binds IL-5
- Approved for ≥6 - 11 and ≥12
- Administered SC, qMonth
  (in office, then at home)

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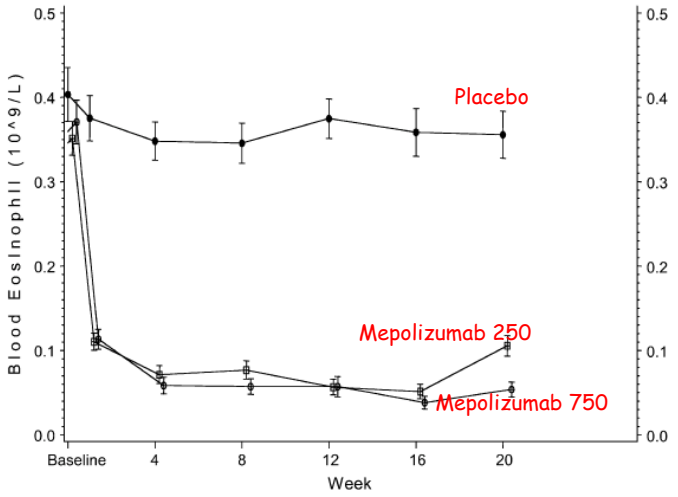
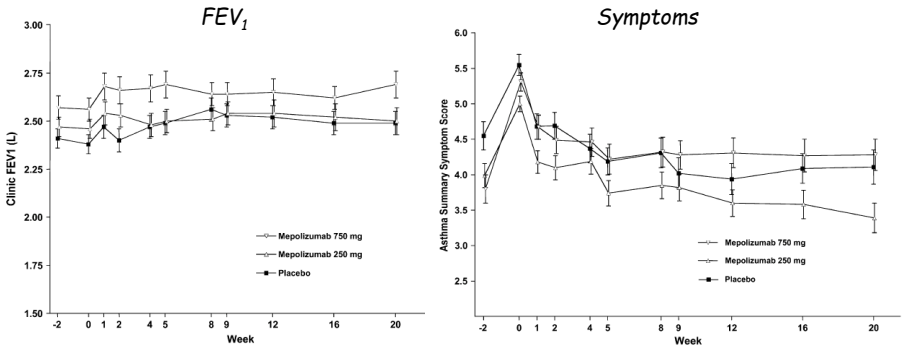
Anti-IL5 (Mepolizumab) in Persistent Asthma



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

18

Anti-IL5 (Mepolizumab) in Persistent Asthma



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

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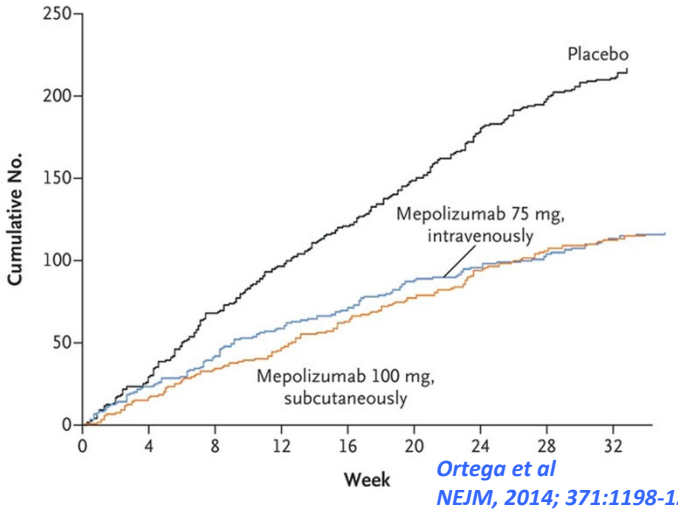
The NEW ENGLAND JOURNAL of MEDICINE

Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma

Hector G. Ortega, M.D., Sc.D., Mark C. Liu, M.D., Ian D. Pavord, D.M., Guy G. Brusselle, M.D., J. Mark FitzGerald, M.D., Alfredo Chetta, M.D., Marc Humbert, M.D., Ph.D., Lynn

A Asthma Exacerbations

N=575
Mepolizumab IV
Vs
Mepolizumab SQ
Vs
Placebo



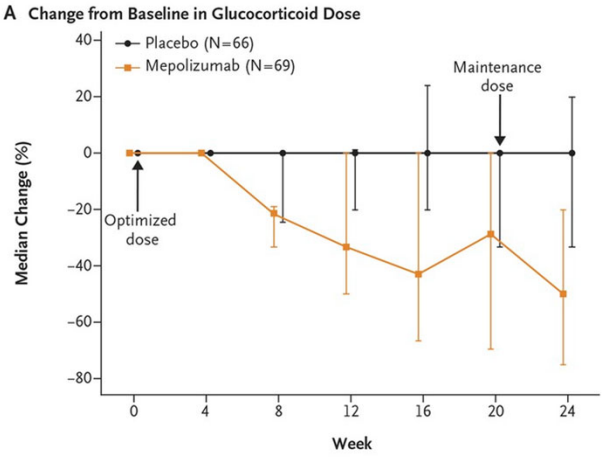
Ortega et al
NEJM, 2014; 371:1198-1207

20

The NEW ENGLAND JOURNAL of MEDICINE

Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma

Elisabeth H. Bel, M.D., Ph.D., Sally E. Wenzel, M.D., Philip J. Thompson, M.D., Charlene M. Prazma, Ph.D., Oliver N. Keene, M.Sc., Steven W. Yancey, M.Sc., Hector G. Ortega, M.D., Sc.D., and Ian D. Pavord, D.M. for the SIRIUS Investigators*



Bel et al
NEJM, 2014; 371:1189-1197

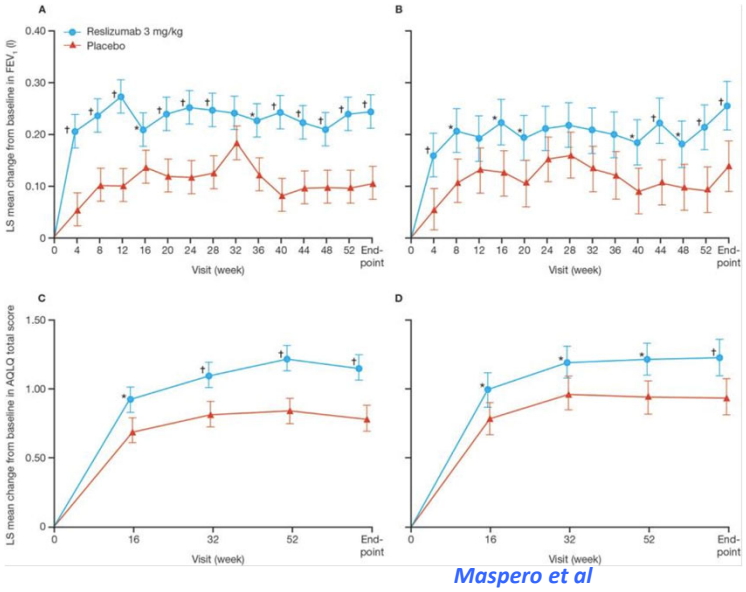
21

Inhibiting IL-5 for Asthma

- Reslizumab (Anti-IL-5)
- FDA approved 2016
- Indications: Severe allergic asthma
- Binds IL-5
- Approved for ≥18 year old
- Administered IV, qMonth
- Weight-based (3mg/kg)

22

Changes in FEV_1 and AQLQ over 52 weeks in patients receiving reslizumab or placebo in 2 Studies (Castro et al; Lancet Respir Med 2015; 3: 355–66)



Maspero et al
Ther Adv Respir Dis 2017; 11:311-25

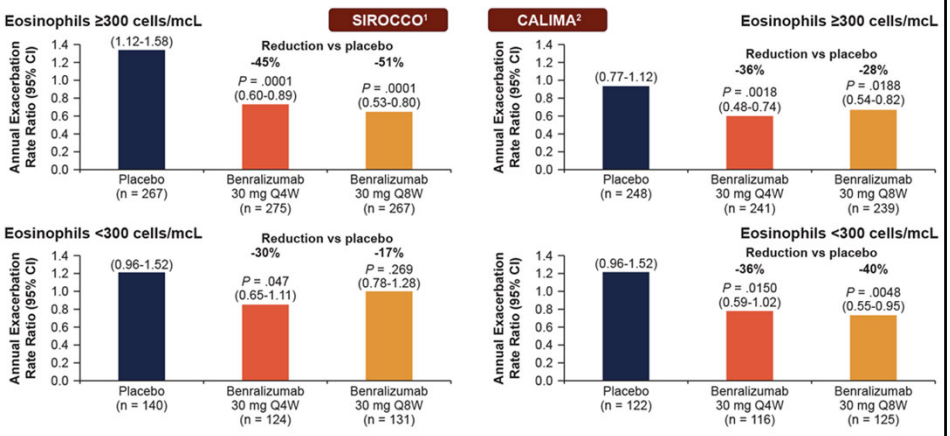
23

Inhibiting IL-5 for Asthma

- Benralizumab (Anti-IL-5Rα)
- FDA approved 2017
- Indications: Severe allergic asthma
- Binds IL-5Rα, blocks IL-5 inflammation; kills eosinophils
- Approved for ≥12 year old
- Administered SC qMonth x 3, then q8 weeks

24

Patients with ≥300 Eos/mcL had greater reduction in exacerbations with Benralizumab



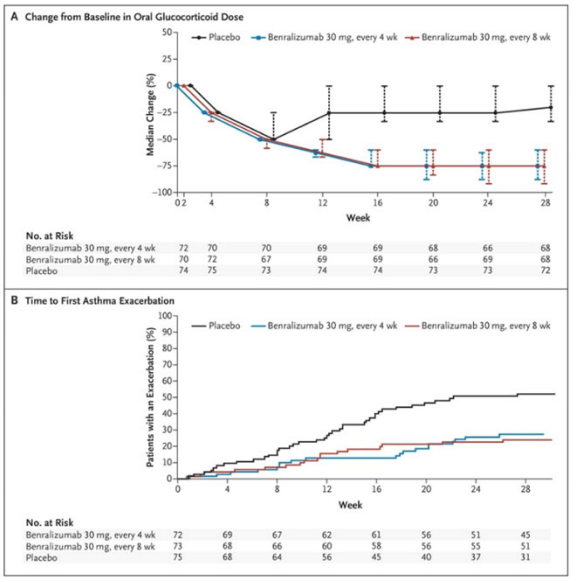
Bleecker et al
Lancet 2016; 388:2115-2127

Fitzgerald et al
Lancet 2016; 388:2128-2141

25

Oral Glucocorticoid–Sparing Effect of Benralizumab in Severe Asthma

Parameswaran Nair, M.D., Ph.D., Sally Wenzel, M.D., Klaus F. Rabe, M.D., Ph.D., Arnaud Bourdin, M.D., Ph.D., Njira L. Lugogo, M.D., Piotr Kuna, M.D., Ph.D., Peter Barker, Ph.D., Stephanie Sproule, M.Math., Sandhia Ponnarambil, M.D., and Mitchell Goldman, M.D. for the ZONDA Trial Investigators*



The NEW ENGLAND JOURNAL of MEDICINE
2017; 376:2448-2458

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Inhibiting IL-4 and IL-13 for Asthma

- Dupilumab (Anti-IL-4Rα)
- FDA approved 2018
- Indications: Severe allergic asthma, steroid dependent asthma, atopic dermatitis
- Binds IL-4Rα, a shared component of IL-4 and IL-13 receptors
- Approved for ≥12 year old
- Administered SC q2 Weeks

27

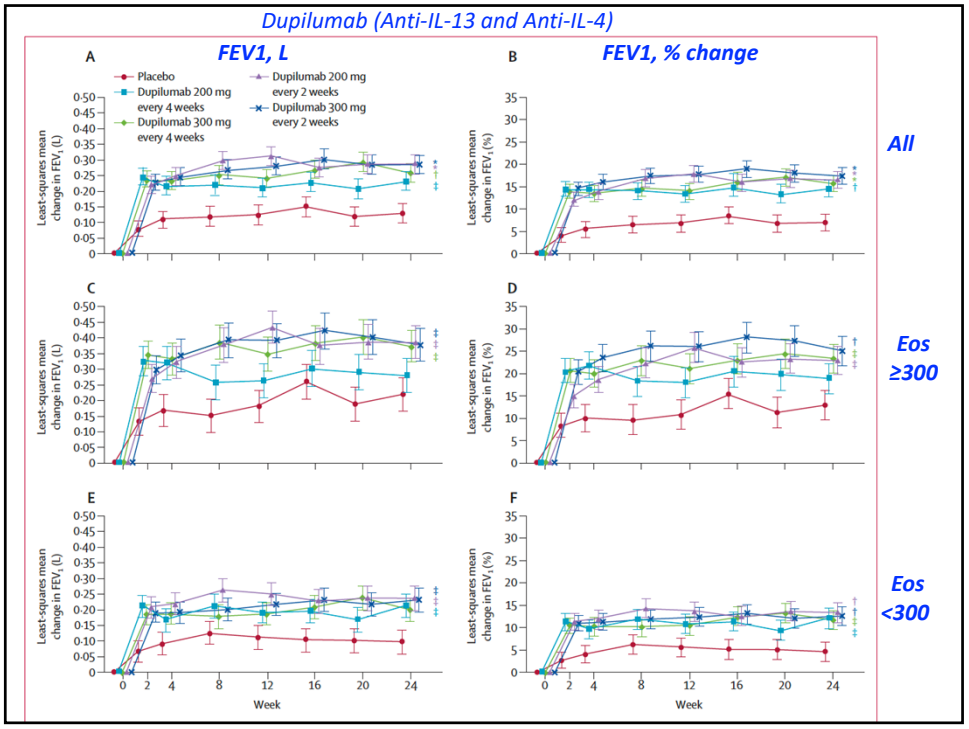
Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β_2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial ***(Anti-IL-13 and Anti-IL-4)***

Sally Wenzel, Mario Castro, Jonathan Corren, Jorge Maspero, Lin Wang, Bingzhi Zhang, Gianluca Pirozzi, E Rand Sutherland, Robert R Evans, Vijay N Joish, Laurent Eckert, Neil M H Graham, Neil Stahl, George D Yancopoulos, Mariana Louis-Tisserand, Ariel Teper

- Phase 2b, N = 769
- Severe uncontrolled asthma
- Dupilumab Q2 or 4 wks x 24 weeks

Lancet, 388:31-44, 2016

28



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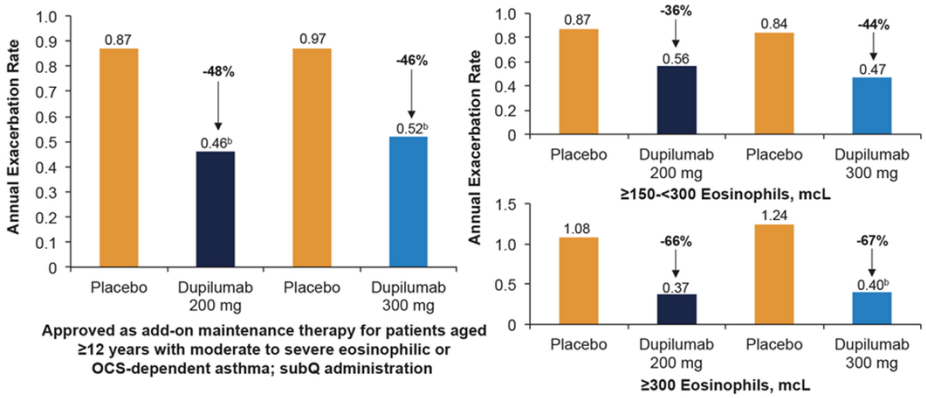
Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma

Mario Castro, M.D., Jonathan Corren, M.D., Ian D. Pavord, M.D., Jorge Maspero, M.D., Sally Wenzel, M.D., Klaus F. Rabe, M.D., William W. Busse, M.D., Linda Ford, M.D., Lawrence Sher, M.D., J. Mark FitzGerald, M.D., Constance Katelaris, M.D., Yuji Tohda, M.D., et al.

The NEW ENGLAND JOURNAL of MEDICINE
2018 378:2486-96

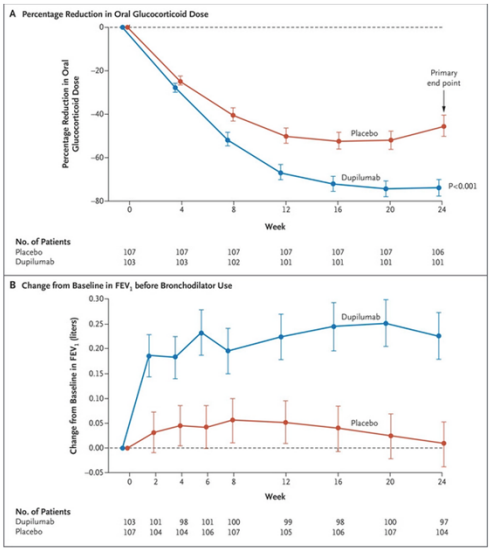
N = 1902; ≥12 years old
Uncontrolled despite:
FP ≥500 mcg/day + LABA or LTRA



30

Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma

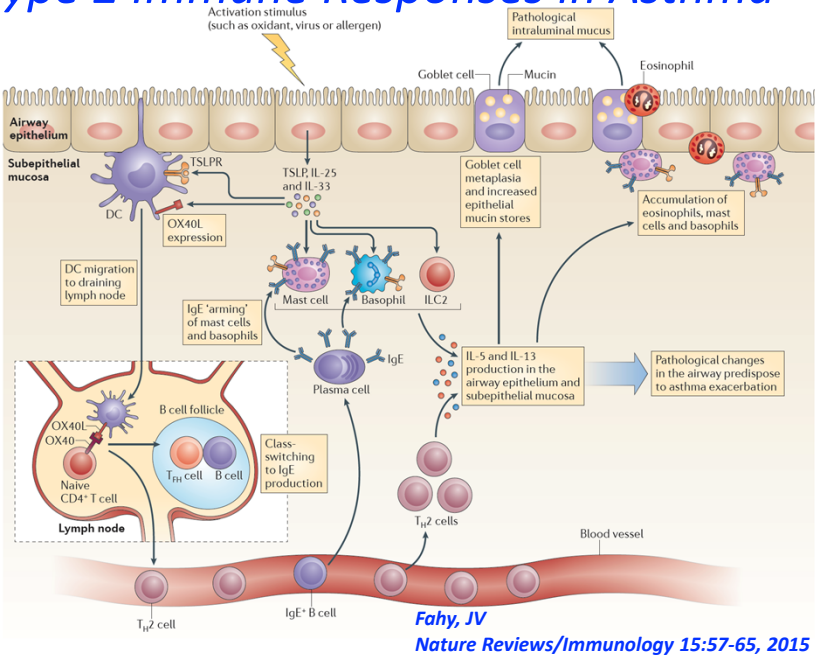
Klaus F. Rabe, M.D., Ph.D., Parameswaran Nair, M.D., Ph.D., Guy Brusselle, M.D., Ph.D., Jorge F. Maspero, M.D., Mario Castro, M.D., Lawrence Sher, M.D., Hongjie Zhu, Ph.D., Jennifer D. Hamilton, Ph.D., Brian N. Swanson, Ph.D., Asif Khan, M.B., B.S., M.P.H., Jingdong Chao, Ph.D., Heribert Staudinger, M.D., Ph.D., et al.



The NEW ENGLAND JOURNAL of MEDICINE
2018 378:2475-2485

31

Type 2 Immune Responses in Asthma



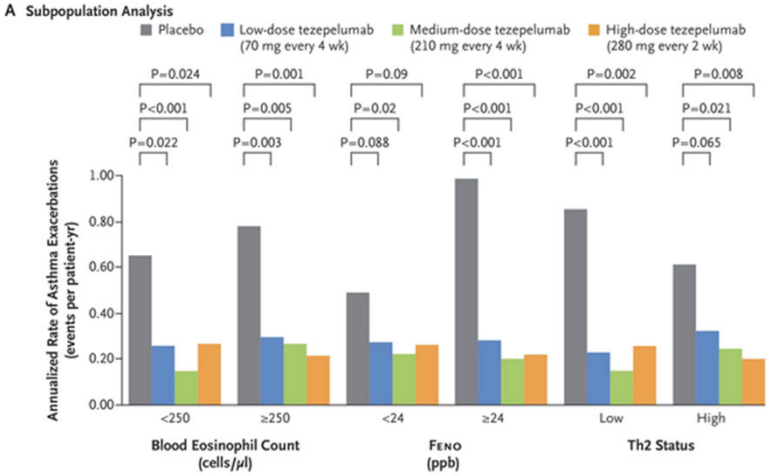
Fahy, JV
Nature Reviews/Immunology 15:57-65, 2015

32

Tezepelumab in Adults with Uncontrolled Asthma

Jonathan Corren, M.D., Jane R. Parnes, M.D., Liangwei Wang, Ph.D., May Mo, M.S., Stephanie L. Roseti, A.P.N., M.S.N., Janet M. Griffiths, Ph.D., and René van der Merwe, M.B., Ch.B.

The NEW ENGLAND JOURNAL of MEDICINE
2017; 377:936-46

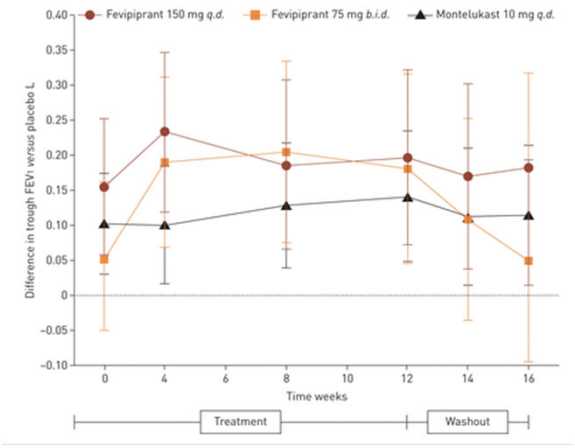


33

EUROPEAN RESPIRATORY *journal*
FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Fevipiprant, an oral prostaglandin DP_2 receptor (CRTh2) antagonist, in allergic asthma uncontrolled on low-dose inhaled corticosteroids

Eric D. Bateman, Alfredo G. Guerreros, Florian Brockhaus, Björn Holzhauer, Abhijit Pethe, Richard A. Kay, Robert G. Townley
European Respiratory Journal 2017 50: 1700670; **DOI:** 10.1183/13993003.00670-2017



34

EUROPEAN RESPIRATORY *journal*
FLAGSHIP SCIENTIFIC JOURNAL OF ERS

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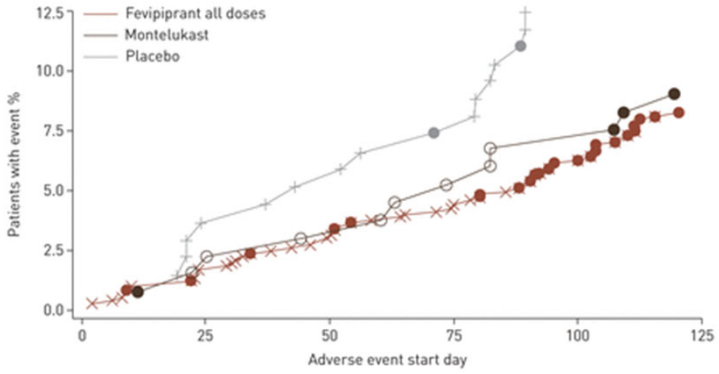
European Respiratory Journal 2017 50: 1700670; **DOI:** 10.1183/13993003.00670-2017



35

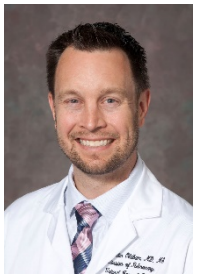
	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
FDA Approval	2003	2015	2016	2017	2018
Patient Age	6-11 ≥12	6-11 ≥12	≥18	≥12	≥12
Route of Administration	SC	SC	IV	SC	SC
Dosing	Q 2-4 weeks (BMI + IgE)	Q month (office-home)	Q month 3mg/kg	Q month x 3; Q 8 weeks	Q 2 weeks
Eosinophils per mcL	-- (more effective with higher levels)	≥150	≥400	>300	≥150 (studied all)
IgE, IU/ml	30-700	--	--	--	--
Indications	Mod-Severe Allergic Asthma; Chr Urticaria	Severe Allergic Asthma; EGPA	Severe Allergic Asthma	Severe Allergic Asthma	Severe Allergic Asthma; Steroid Dependent Asthma; Atopic Dermatitis

36

Advances in ILD

Justin Oldham, MD
UC Davis
Assistant Professor of Medicine

Saturday, January 18, 2020 – 2:00 p.m. – 2:45 p.m.



Justin Oldham, MD is an Assistant Professor of Medicine at UC-Davis, where he directs the Interstitial Lung Disease Program. He attended medical school at the University of Colorado, then completed his residency at UC-Davis and pulmonary/critical care fellowship at the University of Chicago, where he completed an additional two-year ILD fellowship. He was recruited back to UC-Davis in 2016 to lead the ILD program and is currently funded by the National Institutes of Health to study biomarkers of IPF progression and treatment response.

Interstitial Lung Disease: An Update

Justin Oldham, MD MS
Assistant Professor of Medicine
Director, Interstitial Lung Disease Program
University of California at Davis

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1

Disclosures

- Grants to study Interstitial Lung Disease
  - National Institutes of Health (NHLBI)
    - K23 (Oldham) – Genomic determinants of IPF outcomes
    - R01 (Chen) – MARCKS signaling in IPF
    - R01 (Fernandez-Perez) - Transcriptomic signature of hypersensitivity pneumonitis
    - R01 (Noth/Martinez) - PRECISIONS IPF clinical trial and genomic sequencing
  - CA Tobacco Related Disease Research Program
    - MARCKS signaling in IPF (Chen)
- ILD/IPF Speaking and Consulting
  - Genentech
  - Boehringer Ingelheim

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2

Objectives

- Review ILD diagnostic classification and provide overview of common ILDs
- Present data from recently published ILD clinical trials and propose a new paradigm in ILD classification
- Highlight challenges ahead in the treatment of patients with ILD

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3

Part I

ILD diagnostic classification and common ILDs

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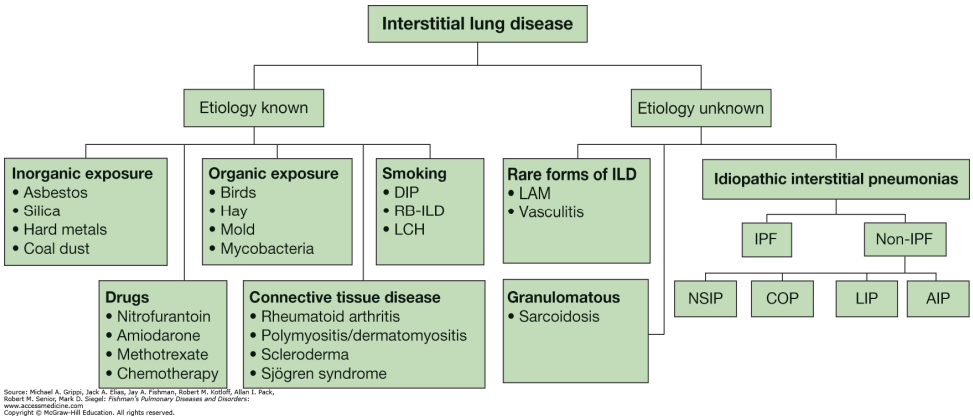
4

Interstitial Lung Disease Classification – The Textbook



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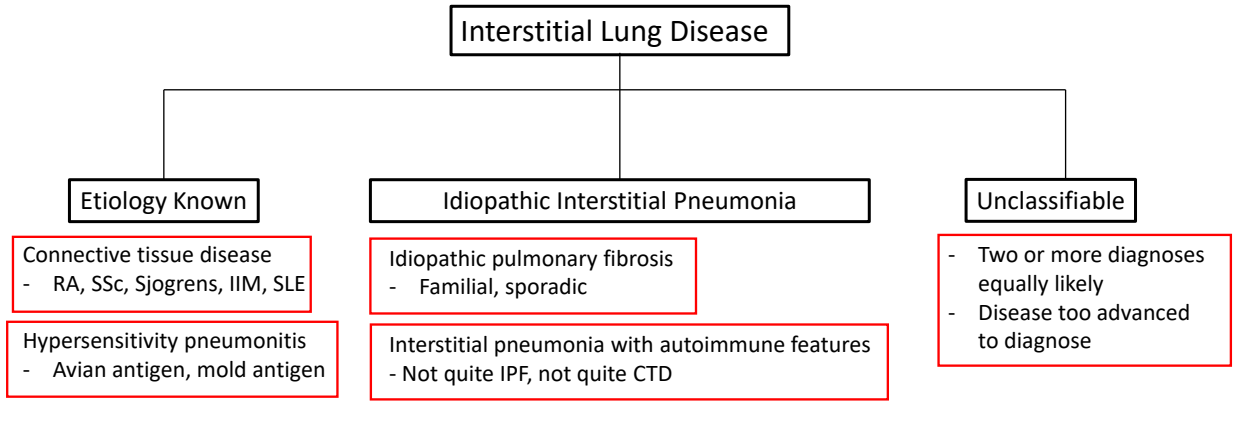
Grippi et al. Fishman's Pulmonary Diseases and Disorders

5

Interstitial Lung Disease Classification – Cliff Notes



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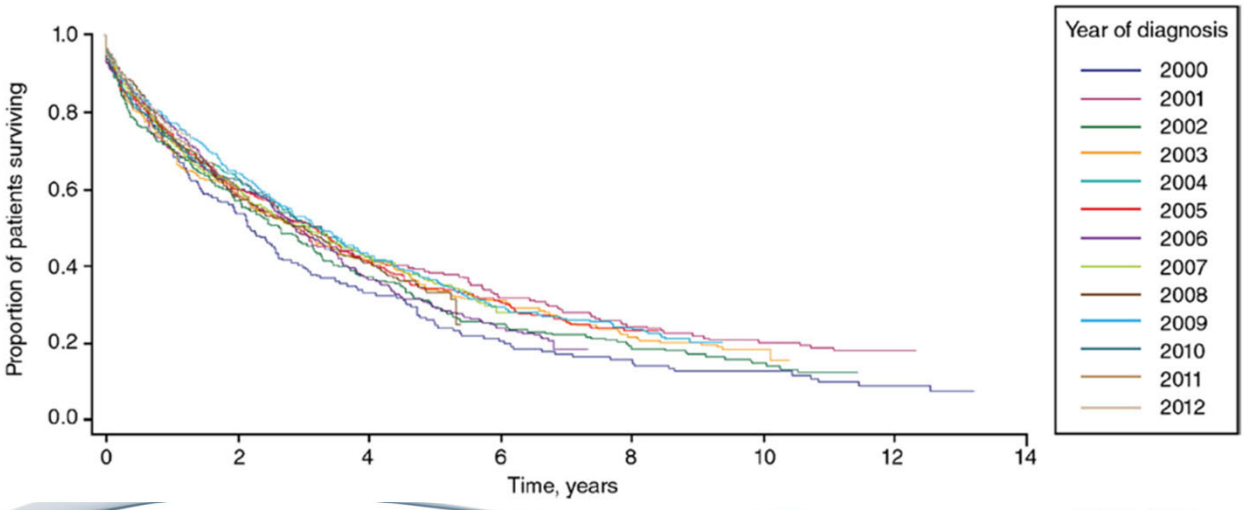
Idiopathic Pulmonary Fibrosis



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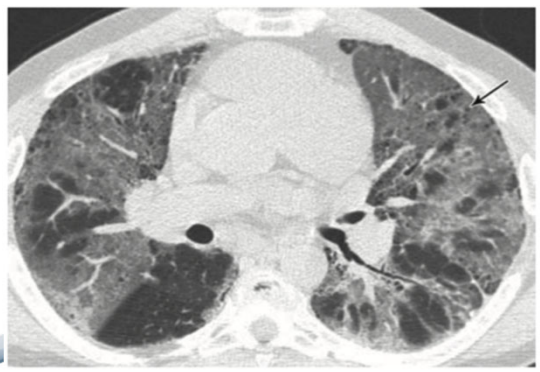
Oldham and Noth. Res Med 2012
Maher and Strek. Res Res 2019

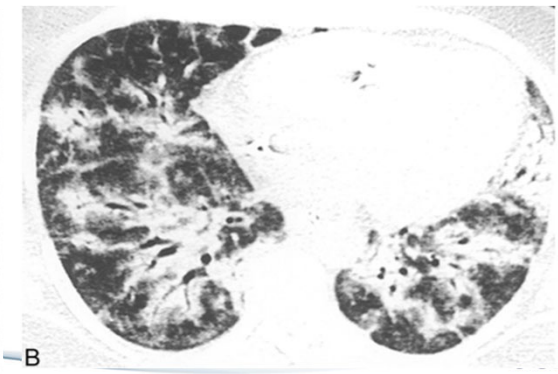
7

CTD-associated ILD

- Most common causes are rheumatoid arthritis, idiopathic inflammatory myopathy and systemic sclerosis
- Inflammatory changes often precede the development of pulmonary fibrosis



Non-specific interstitial pneumonia

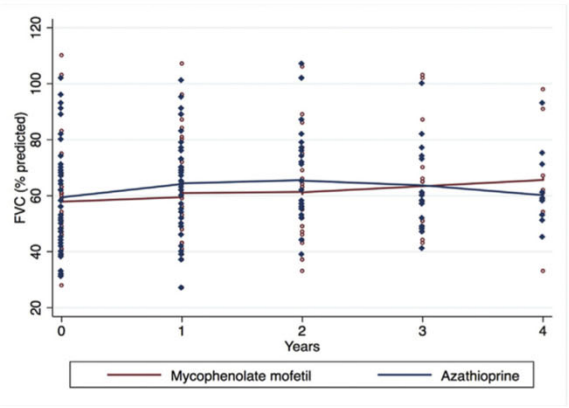


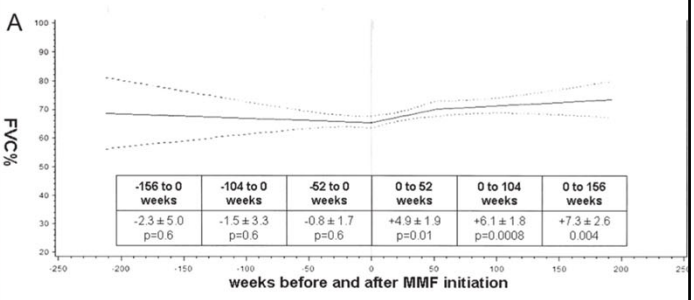
Organizing Pneumonia

Kligerman et al.Radiographics 2009
Travis et al. AJRCCM 2013

8

Immunosuppressive therapy generally effective in treating CTD-ILD





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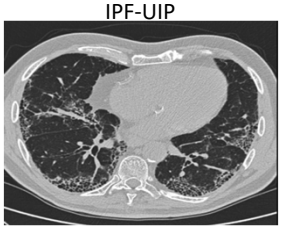
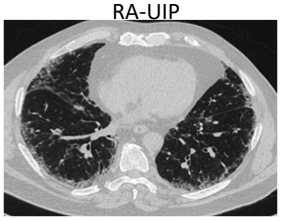
Oldham et al. Res Med 2016
Fischer et al. J Rheum 2013

9

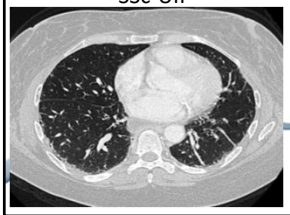
IPF-UIP



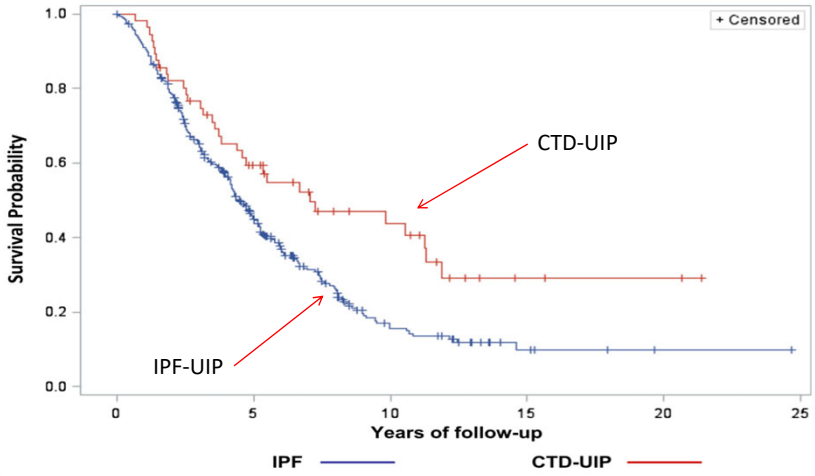
RA-UIP



SSc-UIP



CTD Patients UIP often follow IPF-like trajectory



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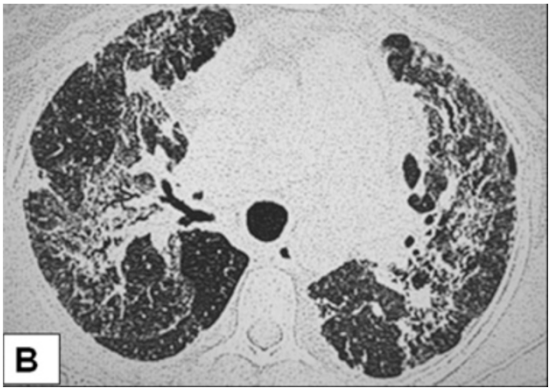
Strand et al. Chest 2015

10

Chronic Hypersensitivity Pneumonitis

- Inhalational disease characterized by inflammation and fibrosis
- Organic antigens are most common etiology
  - avian, fungal, agricultural
- Failure to identify an antigen is associated with worse outcome
- High lymphocyte count on bronchoalveolar lavage is suggestive



Airway-centric fibrosis with ground glass opacity and air trapping

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Selman et al. AJRCCM 2012

11

Use of Mycophenolate Mofetil or Azathioprine for the Management of Chronic Hypersensitivity Pneumonitis

CrossMark

Julie Morisset, MD; Kerri A. Johannson, MD; Eric Vittinghoff, PhD; Carlos Aravena, MD; Brett M. Elicker, MD; Kirk D. Jones, MD; Charlene D. Fell, MD; Helene Manganas, MD; Bruno-Pierre Dubé, MD; Paul J. Wolters, MD; Harold R. Collard, MD, FCCP; Christopher J. Ryerson, MD; and Brett Ley, MD

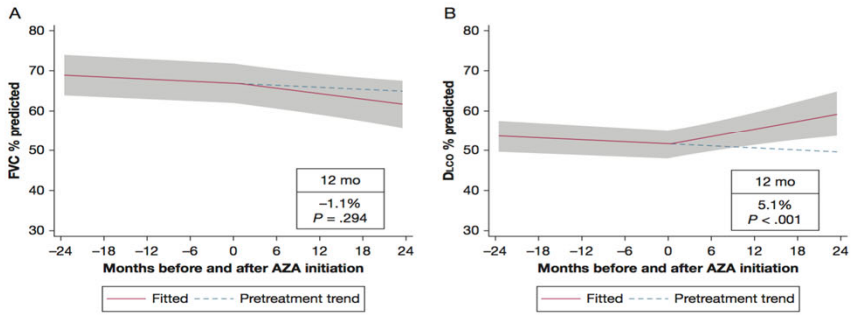

Figure 4 – *Mixed-effects model estimates for FVC % predicted and DLCO % predicted before and after initiation of azathioprine. The gray shading indicates the 95% CI. See Figure 1 and 2 legends for expansion of abbreviations.*

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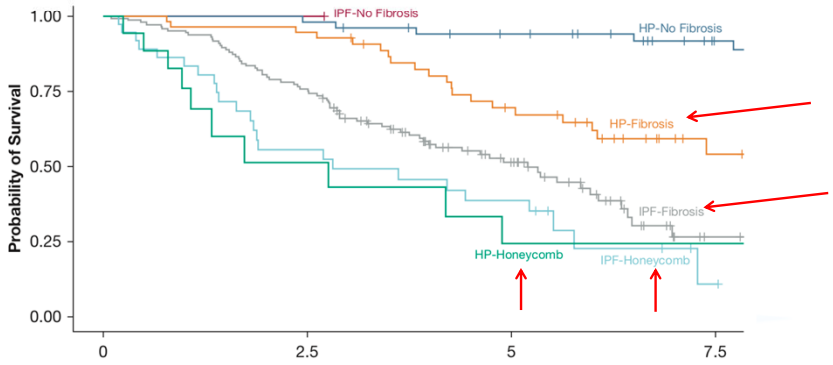
Morisset et al. Chest 2017

12

Hypersensitivity Pneumonitis

Radiologic Phenotypes Are Associated With Distinct Survival Time and Pulmonary Function Trajectory

Margaret L. Salisbury, MD; Tian Gu, MS; Susan Murray, ScD; Barry H. Gross, MD; Aamer Chughtai, MBBS; Mohamed Sayyouh, MBBCh; Ella A. Kazerooni, MD; Jeffrey L. Myers, MD; Amir Lagstein, MD; Kristine E. Konopka, MD; Elizabeth A. Belloli, MD; Jamie S. Sheth, MD; Eric S. White, MD; Colin Holtze, MD; Fernando J. Martinez, MD; and Kevin R. Flaherty, MD



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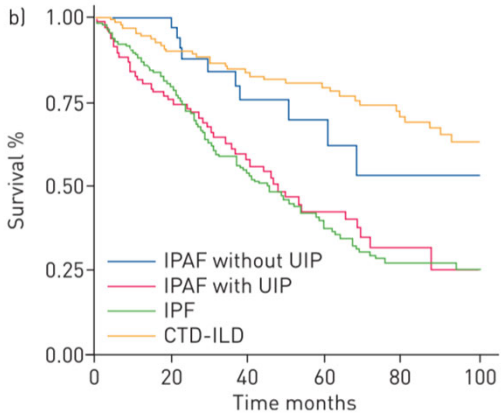
Interstitial Pneumonia with Autoimmune Features (IPAF)

- Patients with ILD having features of CTD but failed to meet established CTD criteria
  - Clinical features
  - Serologic features
  - Morphologic features
- Variable degree of inflammation and fibrosis on imaging/path
- Treatment strategies not defined
- Survival marginally better than IPF but largely influenced by morphologic pattern



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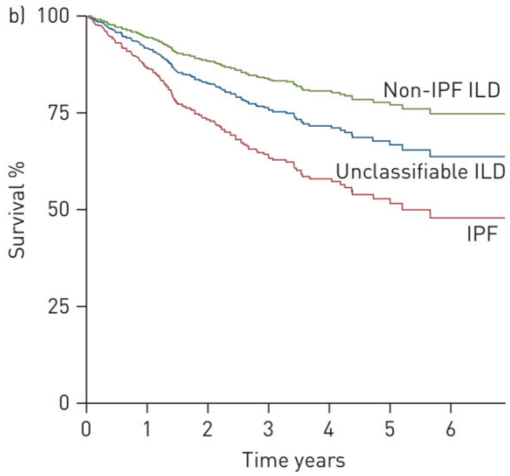
Oldham et al. ERJ 2016

14

Unclassifiable ILD

- Patients for whom a confident ILD diagnosis cannot be reached
- Variable degree of inflammation and fibrosis on imaging and pathology
- Treatment strategy not defined
- Survival better than IPF but worse than non-IPF ILD



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Ryerson et al. ERJ 2012

15

Patient presenting with fibrotic interstitial lung disease

PULMONARY PERSPECTIVE

A Standardized Diagnostic Ontology for Fibrotic Interstitial Lung Disease

An International Working Group Perspective

Christopher J. Ryerson[1,2], Tamera J. Corte[3,4], Joyce S. Lee[5], Luca Richeldi[6], Simon L. F. Walsh[7], Jeffrey L. Myers[8], Jürgen Behr[9,10,11], Vincent Cottin[12], Sonye K. Danoff[13], Kevin R. Flaherty[14], David J. Lederer[15], David A. Lynch[16], Fernando J. Martinez[17], Ganesh Raghu[18], William D. Travis[19], Zarir Udwadia[20,21], Athol U. Wells[22], and Harold R. Collard[23]

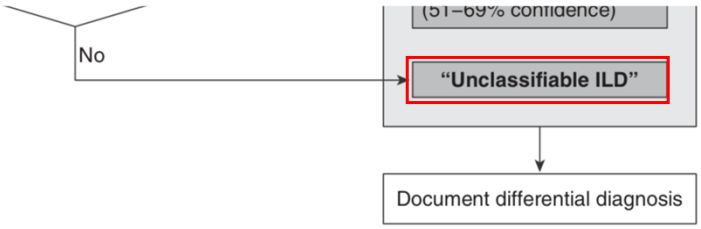

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Figure 1. Proposed approach to the classification of fibrotic interstitial lung disease (ILD).

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Part II

Data from recent ILD clinical trials and introduction to a new paradigm in ILD classification

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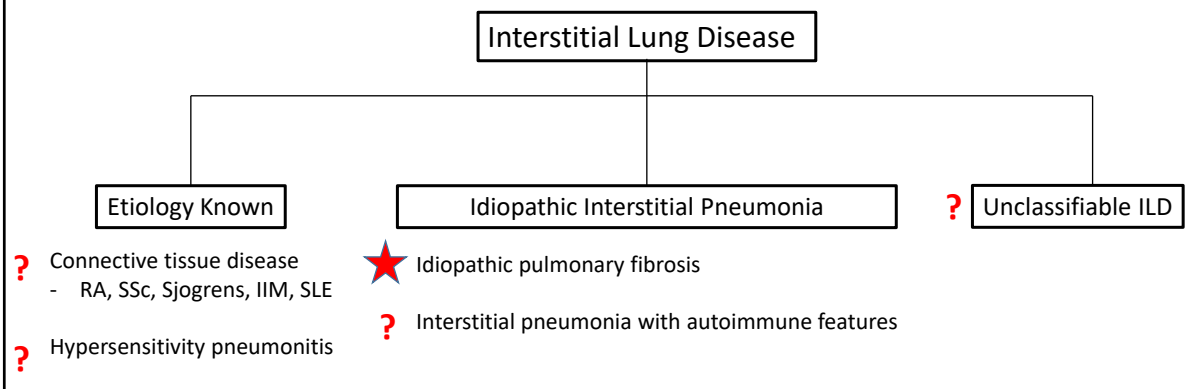
Interstitial Lung Disease Classification



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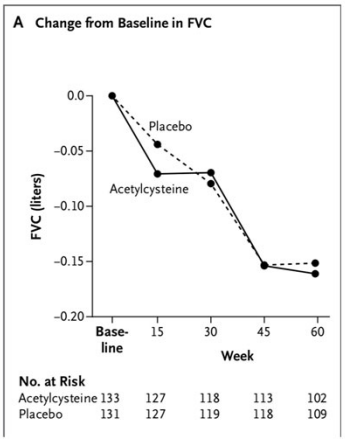
ORIGINAL ARTICLE

Randomized Trial of Acetylcysteine in Idiopathic Pulmonary Fibrosis

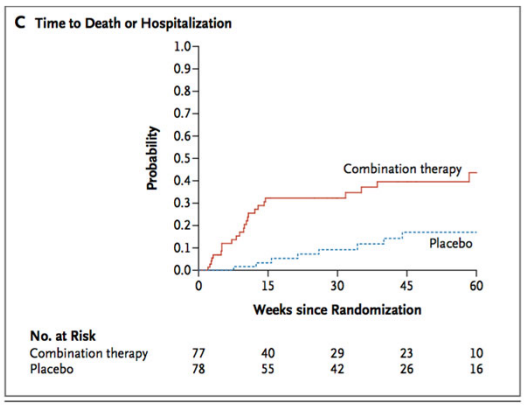
The Idiopathic Pulmonary Fibrosis Clinical Research Network*



ORIGINAL ARTICLE

Prednisone, Azathioprine, and *N*-Acetylcysteine for Pulmonary Fibrosis

The Idiopathic Pulmonary Fibrosis Clinical Research Network*



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Raghu et al. NEJM 2012
Martinez et al. NEJM 2014

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 29, 2014 VOL. 370 NO. 22

Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

Luca Richeldi, M.D., Ph.D., Roland M. du Bois, M.D., Ganesh Raghu, M.D., Arata Azuma, M.D., Ph.D., Kevin K. Brown, M.D., Ulrich Costabel, M.D., Vincent Cottin, M.D., Ph.D., Kevin R. Flaherty, M.D., David M. Hansell, M.D., Yoshikazu Inoue, M.D., Ph.D., Dong Soon Kim, M.D., Martin Kolb, M.D., Ph.D., Andrew G. Nicholson, D.M., Paul W. Noble, M.D., Moisés Selman, M.D., Hiroyuki Taniguchi, M.D., Ph.D., Michèle Brun, M.Sc., Florence Le Maulf, M.Sc., Mannaïg Girard, M.Sc., Susanne Stowasser, M.D., Rozsa Schlenker-Herceg, M.D., Bernd Disse, M.D., Ph.D., and Harold R. Collard, M.D., for the INPULSIS Trial Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis

Talmadge E. King, Jr., M.D., Williamson Z. Bradford, M.D., Ph.D., Socorro Castro-Bernardini, M.D., Elizabeth A. Fagan, M.D., Ian Glaspole, M.B., B.S., Ph.D., Marilyn K. Glassberg, M.D., Eduard Gorina, M.D., Peter M. Hopkins, M.D., David Kardatzke, Ph.D., Lisa Lancaster, M.D., David J. Lederer, M.D., Steven D. Nathan, M.D., Carlos A. Pereira, M.D., Steven A. Sahn, M.D., Robert Sussman, M.D., Jeffrey J. Swigris, D.O., and Paul W. Noble, M.D., for the ASCEND Study Group*

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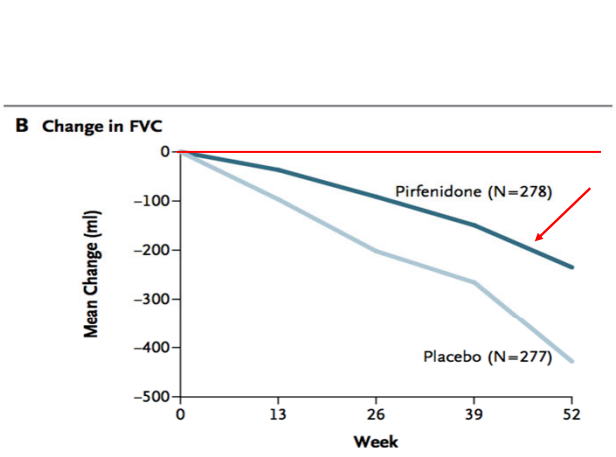

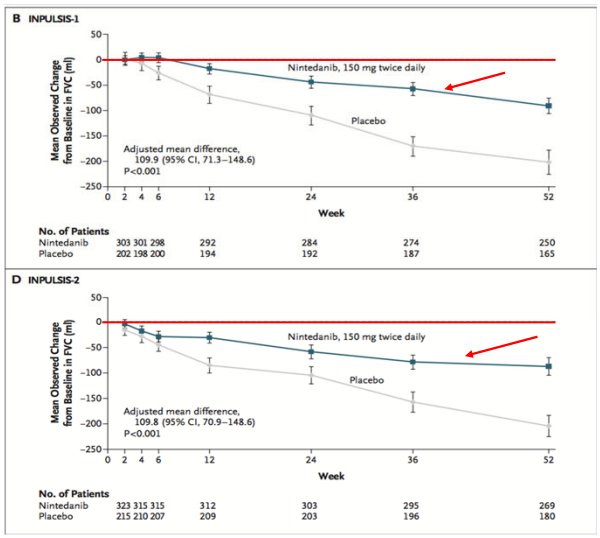

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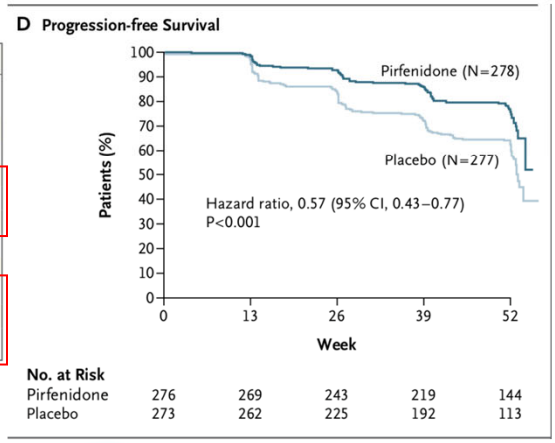
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis

Table 2. Mortality in the ASCEND and CAPACITY Trials.*

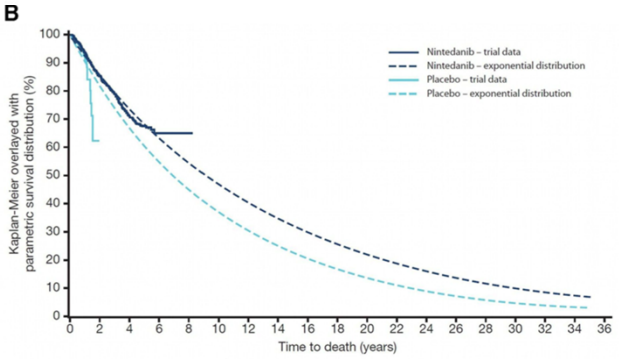
Variable	Pirfenidone	Placebo	Hazard Ratio (95% CI)†	P Value‡
ASCEND trial				
No. of patients	278	277		
Death — no. (%)				
From any cause	11 (4.0)	20 (7.2)	0.55 (0.26–1.15)	0.10
Related to idiopathic pulmonary fibrosis§	3 (1.1)	7 (2.5)	0.44 (0.11–1.72)	0.23
Pooled data from ASCEND and CAPACITY trials				
No. of patients	623	624		
Death — no. (%)				
From any cause	22 (3.5)	42 (6.7)	0.52 (0.31–0.87)	0.01
Related to idiopathic pulmonary fibrosis§	7 (1.1)	22 (3.5)	0.32 (0.14–0.76)	0.006



22

Safety and survival data in patients with idiopathic pulmonary fibrosis treated with nintedanib: pooled data from six clinical trials

Lisa Lancaster,[1] Bruno Crestani,[2] Paul Hernandez,[3] Yoshikazu Inoue,[4] Daniel Wachtlin,[5] Lazaro Loaiza,[6] Manuel Quaresma,[6] Susanne Stowasser,[6] Luca Richeldi[7]



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ORIGINAL ARTICLE

Pirfenidone Reduces Respiratory-related Hospitalizations in Idiopathic Pulmonary Fibrosis

Brett Ley[1], Jeffrey Swigris[2], Bann-mo Day[3], John L. Stauffer[3], Karina Raimundo[3], Willis Chou[3], and Harold R. Collard[1]

[1]Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, University of California, San Francisco, San Francisco, California; [2]Interstitial Lung Disease Program, Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, National Jewish Health, Denver, Colorado; and [3]Genentech, Inc., South San Francisco, California

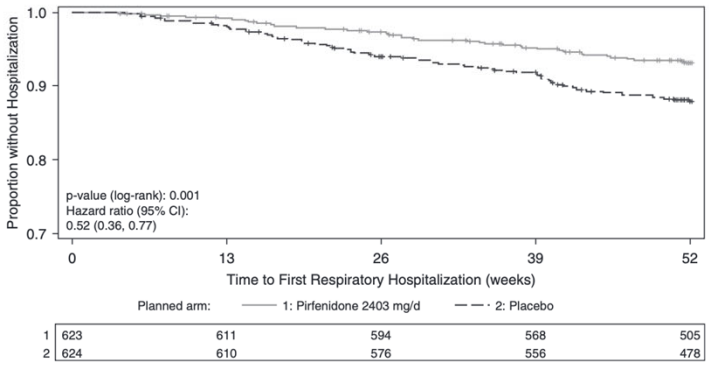

Figure 2. Kaplan-Meier plot for time to first nonelective respiratory-related hospitalization in pirfenidone-treated patients compared with placebo-treated patients. CI = confidence interval.

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Acute exacerbations in the INPULSIS trials of nintedanib in idiopathic pulmonary fibrosis

Harold R. Collard[1], Luca Richeldi[2,3], Dong Soon Kim[4], Hiroyuki Taniguchi[5], Inga Tschoepe[6], Maurizio Luisetti[†7], Jesse Roman[8], Gregory Tino[9], Rozsa Schlenker-Herceg[10], Christoph Hallmann[11] and Roland M. du Bois[12]

TABLE 2 Risk prediction models for investigator-reported and adjudicated confirmed or suspected acute exacerbations

Step	Risk factor analysis			Final model
	Model variable[#]	p-value[¶]	AIC[+]	HR (95% CI)[§]
Investigator-reported acute exacerbations	FVC % predicted at baseline[f]	<0.0001	830.217	0.67 (0.55–0.80)
	Supplemental oxygen use at baseline	0.0018	824.565	2.47 (1.37–4.47)
	Antacid medication use at baseline	0.0873	823.706	1.50 (0.91–2.47)
	Randomisation to nintedanib	0.1150	823.271	0.66 (0.40–1.08)
Adjudicated confirmed or suspected acute exacerbations	FVC % predicted at baseline	0.0006	483.723	0.67 (0.53–0.86)
	Randomisation to nintedanib	0.0010	475.169	0.33 (0.16–0.66)
	Antacid medication use at baseline	0.0676	473.938	1.78 (0.92–3.43)
	Former or current smoker	0.0938	472.805	2.13 (0.89–5.13)
	Supplemental oxygen use at baseline	0.1322	472.870	1.85 (0.80–4.29)

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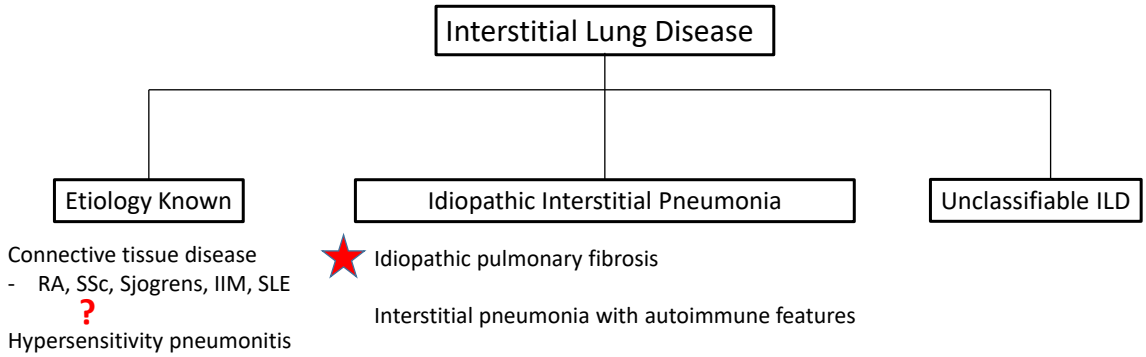
Interstitial Lung Disease Classification



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Phase III

ORIGINAL ARTICLE

Nintedanib for Systemic Sclerosis–Associated Interstitial Lung Disease

Oliver Distler, M.D., Kristin B. Highland, M.D., Martina Gahlemann, M.D., Arata Azuma, M.D., Aryeh Fischer, M.D., Maureen D. Mayes, M.D., Ganesh Raghu, M.D., Wiebke Sauter, Ph.D., Mannaig Girard, M.Sc., Margarida Alves, M.D., Emmanuelle Clerisme-Beaty, M.D., Susanne Stowasser, M.D., Kay Tetzlaff, M.D., Masataka Kuwana, M.D., and Toby M. Maher, M.D., for the SENSCIS Trial Investigators*

- Inclusion Criteria
  - Established diagnosis of SSc with ≥10% fibrosis on HRCT
  - First non-Raynaud's SSc symptoms within 7 years of enrollment
  - FVC ≥40% and DLCO ≥30% predicted
- Allowed background prednisone (up to 10mg) and immunosuppression (MMF or MTX) if on stable dose for >6 months prior to enrollment

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Table 1. Baseline Characteristics of the Patients.*

Characteristic	Nintedanib (N=288)	Placebo (N=288)
Female sex — no. (%)	221 (76.7)	212 (73.6)
Age — yr	54.6±11.8	53.4±12.6
Diffuse cutaneous systemic sclerosis — no. (%)	153 (53.1)	146 (50.7)
Years since the onset of the first non-Raynaud's symptom		
Median	3.4	3.5
Range	0.3–7.1	0.4–7.2
Extent of fibrosis of the lungs on high-resolution CT — %	36.8±21.8	35.2±20.7
FVC — ml	2459±736	2541±816
FVC — % of predicted value	72.4±16.8	72.7±16.6
DL_{CO} — % of predicted value†	52.9±15.1	53.2±15.1
Antitopoisomerase antibody positive — no. (%)‡	173 (60.1)	177 (61.5)
Modified Rodnan skin score§	11.3±9.2	10.9±8.8
Patients with diffuse cutaneous systemic sclerosis	17.0±8.7	16.3±8.9
Patients with limited cutaneous systemic sclerosis	4.9±4.2	5.4±4.1
Total score on the SGRQ¶	40.7±20.2	39.4±20.9
Score on the HAQ-DI‖	0.65±0.70	0.55±0.58
Scaled score on the FACIT-Dyspnea questionnaire**	47.01±9.64	45.67±9.90
Receiving mycophenolate — no. (%)	139 (48.3)	140 (48.6)
Receiving methotrexate — no. (%)	23 (8.0)	15 (5.2)

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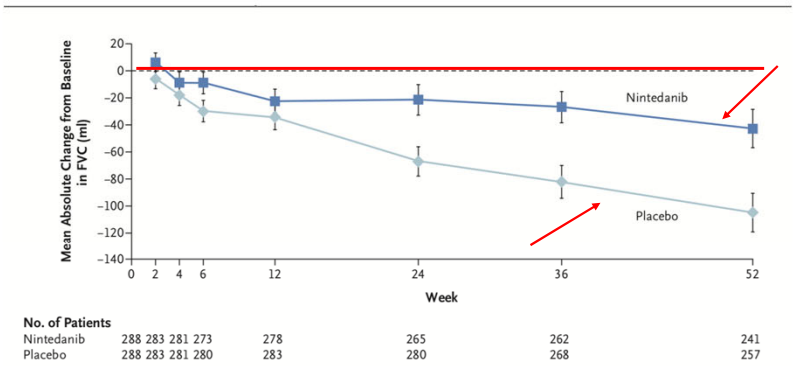
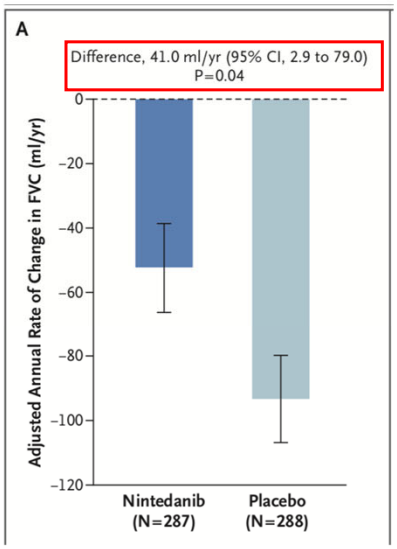
Primary Endpoint – Change in FVC over time





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Secondary Endpoints

Table 2. Primary and Secondary Efficacy End Points.*

End Point	Nintedanib	Placebo	Difference (95% CI)
Primary end point			
Annual rate of decline in FVC assessed over 52 weeks — ml/yr	−52.4±13.8	−93.3±13.5	41.0 (2.9 to 79.0)†
Key secondary end points			
Absolute change from baseline in modified Rodnan skin score at week 52	−2.17±0.27	−1.96±0.26	−0.21 (−0.94 to 0.53)‡
Absolute change from baseline in total score on the SGRQ at week 52	0.81±0.88	−0.88±0.87	1.69 (−0.73 to 4.12)§
Other secondary end points			
Absolute change from baseline in FVC at week 52 — ml	−54.6±13.9	−101.0±13.6	46.4 (8.1 to 84.7)§
Annual rate of decline in FVC — % of predicted value	−1.4±0.4	−2.6±0.4	1.2 (0.1 to 2.2)§
Absolute change from baseline in DL_{CO} at week 52 — % of predicted value	−3.21±0.54	−2.77±0.54	−0.44 (−1.94 to 1.06)§
Absolute change from baseline in net digital ulcer burden at week 52	0.03±0.05	0.06±0.04	−0.03 (−0.16 to 0.09)§
Patients with an absolute decline from baseline in FVC of >5 percentage points of the predicted value at week 52 — no./total no. (%)	59/287 (20.6)	82/288 (28.5)	0.65 (0.44 to 0.96)§¶
Patients with an absolute decline from baseline in FVC of >10 percentage points of the predicted value at week 52 — no./total no. (%)	20/287 (7.0)	24/288 (8.3)	0.82 (0.44 to 1.52)§¶
Patients with a relative decline from baseline in FVC, measured in milliliters, of >5% at week 52 — no./total no. (%)	95/287 (33.1)	125/288 (43.4)	0.65 (0.46 to 0.91)§¶
Patients with a relative decline from baseline in FVC, measured in milliliters, of >10% at week 52 — no./total no. (%)	48/287 (16.7)	52/288 (18.1)	0.91 (0.59 to 1.41)§¶

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Table 3. Adverse Events.*

SSc-ILD

Event	Nintedanib (N = 288)	Placebo (N = 288)
	no. of patients (%)	
Any adverse event	283 (98.3)	276 (95.8)
Most common adverse events†		
Diarrhea	218 (75.7)	91 (31.6)
Nausea	91 (31.6)	39 (13.5)
Skin ulcer	53 (18.4)	50 (17.4)
Vomiting	71 (24.7)	30 (10.4)
Cough	34 (11.8)	52 (18.1)
Nasopharyngitis	36 (12.5)	49 (17.0)
Upper respiratory tract infection	33 (11.5)	35 (12.2)
Abdominal pain	33 (11.5)	21 (7.3)
Fatigue	31 (10.8)	20 (6.9)
Weight decrease	34 (11.8)	12 (4.2)
Severe adverse event‡	52 (18.1)	36 (12.5)
Serious adverse event§	69 (24.0)	62 (21.5)
Fatal adverse event	5 (1.7)	4 (1.4)
Adverse event leading to discontinuation of the intervention	46 (16.0)	25 (8.7)

Table 3. Adverse Events.

IPF

Event	INPULSIS-1	
	Nintedanib (N = 309)	Placebo (N = 204)
		number of p
Any adverse event	298 (96.4)	181 (88.7)
Any adverse event, excluding progression of idiopathic pulmonary fibrosis*	296 (95.8)	179 (87.7)
Most frequent adverse events†		
Diarrhea	190 (61.5)	38 (18.6)
Nausea	70 (22.7)	12 (5.9)
Nasopharyngitis	39 (12.6)	34 (16.7)
Cough	47 (15.2)	26 (12.7)
Progression of idiopathic pulmonary fibrosis*	31 (10.0)	21 (10.3)
Bronchitis	36 (11.7)	28 (13.7)
Upper respiratory tract infection	28 (9.1)	18 (8.8)
Dyspnea	22 (7.1)	23 (11.3)
Decreased appetite	26 (8.4)	14 (6.9)
Vomiting	40 (12.9)	4 (2.0)
Weight loss	25 (8.1)	13 (6.4)
Severe adverse events‡	81 (26.2)	37 (18.1)
Serious adverse events‡	96 (31.1)	55 (27.0)
Fatal adverse events	12 (3.9)	10 (4.9)
Adverse events leading to treatment discontinuation§	65 (21.0)	22 (10.8)

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SENSCIS Trial Conclusions

- Nintedanib slows FVC decline compared to placebo in patients with SSc-ILD
  - Treatment effect less than observed with IPF, but overall progression was less than is observed in IPF
- No significant treatment effect on skin scores or QOL scores
- Similar side effect profile in SSc-ILD as with IPF, but with more diarrhea (76%)
  - Need to consider in patients with significant SSc-related lower GI involvement

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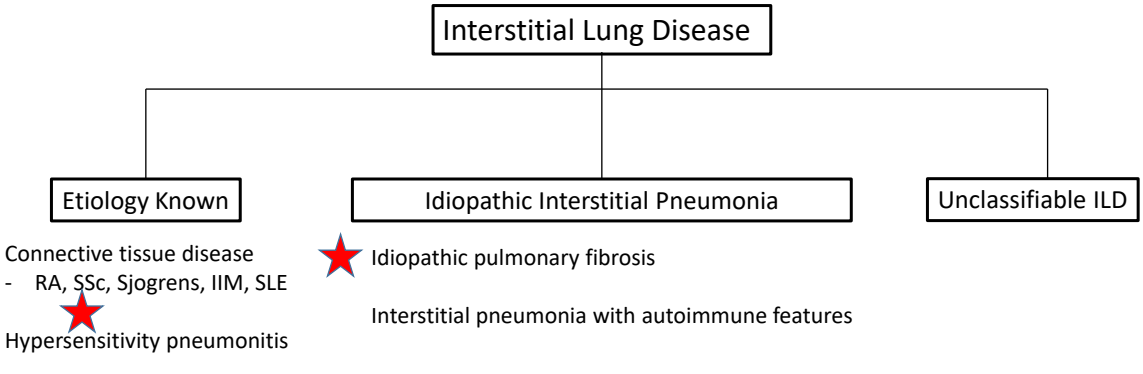
Interstitial Lung Disease Classification



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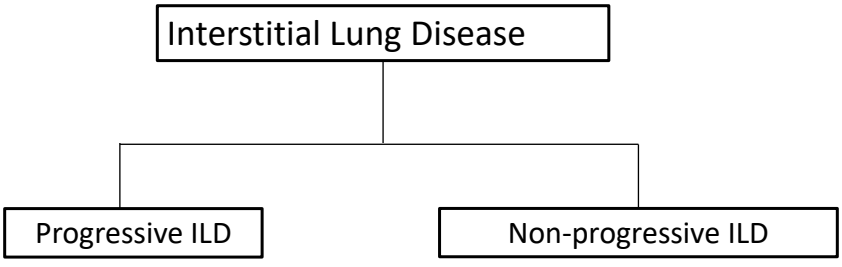
Interstitial Lung Disease Classification
A new paradigm



Idiopathic pulmonary fibrosis
Progressive fibrosing ILD
- SSc-ILD
- RA-ILD
- Other CTD-ILD (myositis, SLE, Sjogrens)
- CHP
- IPAF
- uILD
- other progressive ILDs

- SSc-ILD
- RA-ILD
- Other CTD-ILD
- CHP
- IPAF
- uILD
- other non-progressive ILDs

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Phase III

ORIGINAL ARTICLE

Nintedanib in Progressive Fibrosing Interstitial Lung Diseases

K.R. Flaherty, A.U. Wells, V. Cottin, A. Devaraj, S.L.F. Walsh, Y. Inoue, L. Richeldi, M. Kolb, K. Tetzlaff, S. Stowasser, C. Coeck, E. Clerisme-Beaty, B. Rosenstock, M. Quaresma, T. Haeufel, R.-G. Goeldner, R. Schlenker-Herceg, and K.K. Brown, for the INBUILD Trial Investigators*

- Inclusion Criteria
  - Non-IPF ILD diagnosis with ≥10% pulmonary fibrosis on HRCT
  - Progressive fibrosing phenotype within 2 years of enrollment
    - ≥10% relative decline in FVC in two years prior to enrollment
    - 5-10% relative decline in FVC and worsening symptoms or extent of fibrosis on HRCT
    - Worsening symptoms and extent of fibrosis on HRCT
  - ≥45% predicted FVC and >30% predicted DLCO
- Background immunosuppression (including prednisone ≥20mg) not allowed (but could be initiated after 6 months for clinical worsening)

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Table 1. Characteristics of the Overall Population at Baseline.*

Characteristic	Nintedanib (N=332)	Placebo (N=331)
Male sex — no. (%)	179 (53.9)	177 (53.5)
Age — yr	65.2±9.7	66.3±9.8
Former or current smoker — no. (%)	169 (50.9)	169 (51.1)
UIP-like fibrotic pattern on high-resolution CT — no. (%)	206 (62.0)	206 (62.2)
Criteria for disease progression in previous 24 mo — no. (%)		
Relative decline in FVC of ≥10% of predicted value	160 (48.2)	172 (52.0)
Relative decline in FVC of 5% to <10% of predicted value plus worsening of respiratory symptoms or increased extent of fibrosis on high-resolution CT	110 (33.1)	97 (29.3)
Worsening of respiratory symptoms and increased extent of fibrosis on high-resolution CT	62 (18.7)	61 (18.4)
FVC		
Mean value — ml	2340±740	2321±728
Percent of predicted value	68.7±16.0	69.3±15.2
Diffusing capacity for carbon monoxide†		
Mean value — mmol/min/kPa	3.5±1.2	3.7±1.3
Percent of predicted value	44.4±11.9	47.9±15.0
Total score on K-BILD questionnaire‡	52.5±11.0	52.3±9.8

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ILDs Included

Table S2: Clinical ILD diagnoses (grouped) in the overall population

	Nintedanib (n=332)	Placebo (n=331)
Hypersensitivity pneumonitis	84 (25.3)	89 (26.9)
Autoimmune ILDs	82 (24.7)	88 (26.6)
Rheumatoid arthritis-associated ILD	42 (12.7)	47 (14.2)
Systemic sclerosis-associated ILD	23 (6.9)	16 (4.8)
Mixed connective tissue disease-associated ILD	7 (2.1)	12 (3.6)
Other autoimmune ILDs	10 (3.0)	13 (3.9)
Idiopathic non-specific interstitial pneumonia	64 (19.3)	61 (18.4)
Unclassifiable idiopathic interstitial pneumonia	64 (19.3)	50 (15.1)
Other ILDs*	38 (11.4)	43 (13.0)

Data are no (%) of patients.

*Included sarcoidosis, exposure-related ILDs and selected other terms in "Other fibrosing ILDs".

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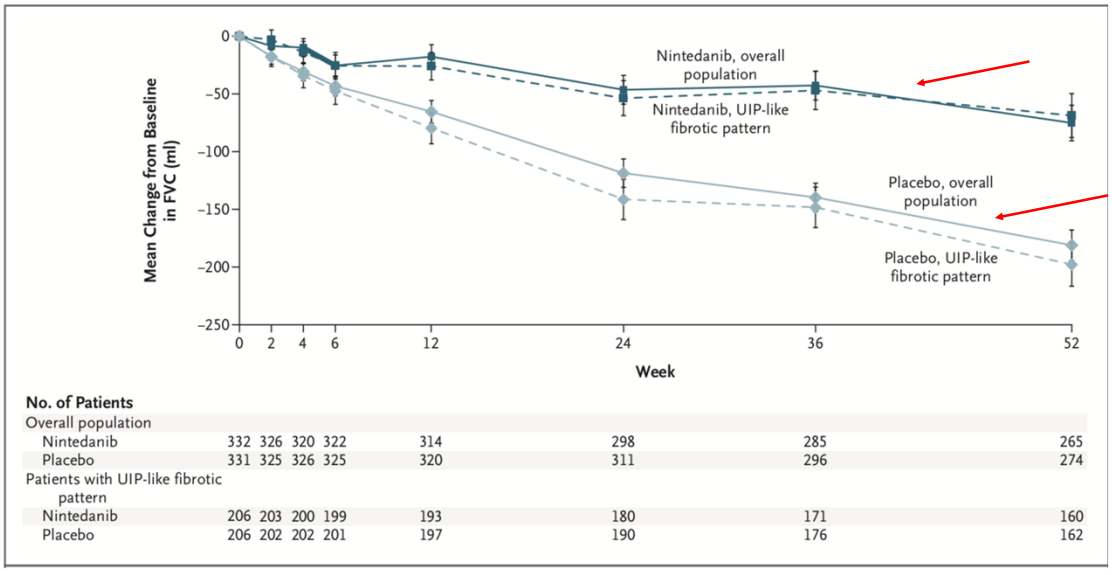
Primary Endpoint – Change in FVC over time



No. of Patients								
Overall population								
Nintedanib	332	326	320	322	314	298	285	265
Placebo	331	325	326	325	320	311	296	274
Patients with UIP-like fibrotic pattern								
Nintedanib	206	203	200	199	193	180	171	160
Placebo	206	202	202	201	197	190	176	162

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Secondary Endpoints

Table 2. Efficacy End Points.*

End Point	Nintedanib (N=332)	Placebo (N=331)	Difference (95% CI)
Primary end point			
Rate of decline in the FVC at 52 wk — ml/yr†			
Overall population	−80.8±15.1	−187.8±14.8	107.0 (65.4 to 148.5)‡
Patients with a UIP-like fibrotic pattern	−82.9±20.8	−211.1±20.5	128.2 (70.8 to 185.6)‡
Patients with other fibrotic patterns	−79.0±21.6	−154.2±21.2	75.3 (15.5 to 135.0)§
Main secondary end points			
Absolute change from baseline in total score on K-BILD questionnaire at 52 wk¶			
Overall population	0.55±0.60	−0.79±0.59	1.34 (−0.31 to 2.98)§
Patients with a UIP-like fibrotic pattern	0.75±0.80	−0.78±0.79	1.53 (−0.68 to 3.74)§
Acute exacerbation of interstitial lung disease or death at 52 wk — no. with event/total no. (%)			
Overall population	26/332 (7.8)	32/331 (9.7)	0.80 (0.48 to 1.34)§‖
Patients with a UIP-like fibrotic pattern	17/206 (8.3)	25/206 (12.1)	0.67 (0.36 to 1.24)§‖
Death at 52 wk — no. with event/total no. (%)			
Overall population	16/332 (4.8)	17/331 (5.1)	0.94 (0.47 to 1.86)§‖
Patients with a UIP-like fibrotic pattern	11/206 (5.3)	16/206 (7.8)	0.68 (0.32 to 1.47)§‖
Additional end points assessed during period until first database lock			
Acute exacerbation of interstitial lung disease or death — no. with event/total no. (%)			
Overall population	41/332 (12.3)	59/331 (17.8)	0.68 (0.46 to 1.01)§‖
Patients with a UIP-like fibrotic pattern	28/206 (13.6)	44/206 (21.4)	0.61 (0.38 to 0.98)§‖
Death — no. with event/total no. (%)			
Overall population	27/332 (8.1)	38/331 (11.5)	0.70 (0.43 to 1.15)§‖
Patients with a UIP-like fibrotic pattern	20/206 (9.7)	31/206 (15.0)	0.63 (0.36 to 1.10)§‖

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INBUILD Trial Conclusions

- Nintedanib slows FVC decline compared to placebo in patients with diverse forms of progressive fibrosing ILD
- No significant treatment effect on QOL measures
- Trend towards reduced mortality and hospitalization in nintedanib treated patients
- Safety and tolerability data similar to IPF and SSc-ILD

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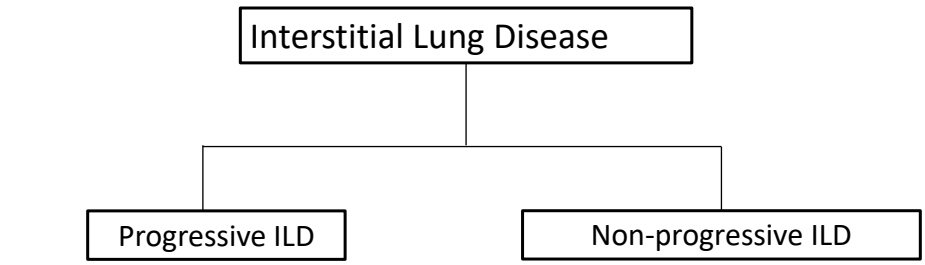
Interstitial Lung Disease Classification
A new paradigm



Idiopathic pulmonary fibrosis
Progressive fibrosing ILD
- SSc-ILD
- RA-ILD
- Other CTD-ILD (myositis, SLE, Sjogrens)
- CHP
- IPAF
- uILD
- other progressive ILDs

- SSc-ILD
- RA-ILD
- Other CTD-ILD
- CHP
- IPAF
- uILD
- other non-progressive ILDs

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Phase II

Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: a double-blind, randomised, placebo-controlled, phase 2 trial

Toby M Maher, Tamera J Corte, Aryeh Fischer, Michael Kreuter, David J Lederer, Maria Molina-Molina, Judit Axmann, Klaus-Uwe Kirchgaessler, Katerina Samara, Frank Gilberg, Vincent Cottin

- Inclusion Criteria
  - Established diagnosis of progressive fibrosing unclassifiable ILD by local investigators
    - Inability to provide high or moderate confidence ILD diagnosis
    - ≥10% fibrosis on HRCT
    - >5% absolute decline in % predicted FVC or significant symptomatic worsening within the prior 6 months (excluding non-cardiac causes)
  - FVC ≥45% and DLCO ≥30% predicted
- Allowed background immunosuppression

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	Pirfenidone (n=127)	Placebo (n=126)
Age at screening, years	70·0 (61·0–76·0)	69·0 (63·0–74·0)
Sex		
Men	70 (55%)	69 (55%)
Women	57 (45%)	57 (45%)
Race		
White	120 (94%)	123 (98%)
Black	1 (1%)	2 (2%)
Asian	5 (4%)	0
Native American or Alaskan Native	1 (1%)	0
Other	0	1 (1%)
Body-mass index, kg/m^2	28·6 (26·5–32·9)	29·3 (26·2–32·7)
Previous surgical lung biopsy	40 (31%)	48 (38%)
Percent predicted FVC	71·0% (59·0–87·3)	71·5% (58·0–88·0)
Percent predicted DLco	44·6% (36·9–53·5)	48·0% (38·4–59·0)
Percent predicted FEV$_1$	75·0% (62·0–88·0)	76·0% (62·0–92·7)
FEV$_1$/FVC ratio	0·82 (0·78–0·86)	0·84 (0·78–0·87)
6MWD, m	372·0 (303·0–487·0)	395·0 (325·0–472·0)
Concomitant treatment with mycophenolate mofetil	23 (18%)	22 (17%)
IPAF diagnosis	15 (12%)	18 (14%)
Concomitant treatment with mycophenolate mofetil	6 (5%)	6 (5%)
Unclassifiable ILD diagnosis		
Low-confidence rheumatoid arthritis-ILD	0	0
Low-confidence systemic sclerosis-ILD	0	1 (1%)
Low-confidence undifferentiated connective tissue disease-ILD	3 (2%)	2 (2%)
Low-confidence chronic hypersensitivity pneumonitis-ILD	10 (8%)	9 (7%)
Low-confidence idiopathic non-specific interstitial pneumonia-ILD	4 (3%)	3 (2%)
Low-confidence sarcoidosis-ILD	0	0
Low-confidence myositis-ILD	0	0
Low-confidence other defined ILD	1 (1%)	0
Unclassifiable ILD	93 (73%)	93 (74%)

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Primary Endpoint – change in FVC over time using home spirometry

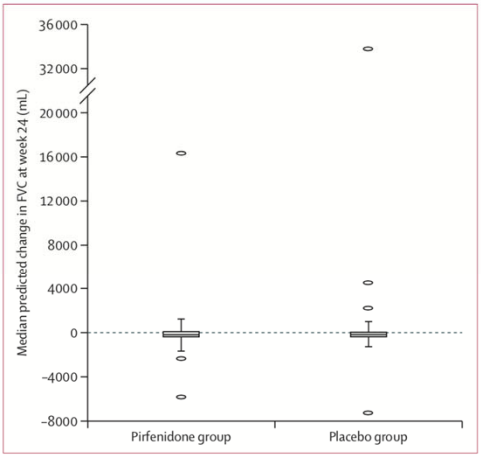

Figure 2: **Median predicted FVC change from baseline at week 24 measured using daily home spirometry in the ITT analysis set (n=253)**
The median change in FVC from baseline was –87·7 mL (Q1–Q3 –338·1 to 148·6) in the pirfenidone group and –157·1 mL (–370·9 to 70·1) in the placebo group. Horizontal lines within the rectangle show the median; the outer lines of the rectangle show the Q1 and Q3 values; the whiskers show the minimum and maximum values, excluding outliers; and circles show the outliers. FVC=forced vital capacity. ITT=intention-to-treat.

- Required single daily spirometry from patients using home spirometer
- Substantial variability in measures observed at study conclusion
- Resulted in inability to conduct hypothesis testing of primary endpoint
- Spirometers had internal controls to detect variability, but required >2 daily measures

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Secondary Endpoints

	Pirfenidone (n=127)	Placebo (n=126)	Pirfenidone *vs* placebo	p value*
Predicted FVC change from baseline measured by site spirometry, mL				
Mean (95% CI)	−17·8† (−62·6 to 27·0)	−113·0‡ (−152·5 to −73·6)	95·3 (35·9 to 154·6)	0·002
Median (Q1–Q3)	−7·5 (−185·4 to 112·3)	−125·8 (−238·2 to 2·2)	118·3	..
FVC change from baseline measured by site spirometry, % predicted				
Rank analysis of covariance	..	..	..	0·038
Patients with >5% decline in FVC	47 (37%)	74 (59%)	0·42 (0·25 to 0·69)§	0·001
Patients with >10% decline in FVC	18 (14%)	34 (27%)	0·44 (0·23 to 0·84)§	0·011
DLco change from baseline, % predicted				
Rank analysis of covariance	..	..	..	0·09
Patients with >15% decline in DLco¶	3 (2%)	11 (9%)	0·25 (0·07 to 0·93)§	0·039
6MWD change from baseline, m				
Rank analysis of covariance	..	..	..	0·040
Patients with >50 m decline in 6MWD¶	36 (28%)	35 (28%)	1·03 (0·59 to 1·78)§	0·92

Data are n (%), unless otherwise specified. FVC=forced vital capacity. DLco=carbon monoxide diffusing capacity. 6MWD=6-min walk distance. *p values for secondary endpoints are not adjusted for multiplicity and are provided for descriptive purposes only. †n=118; only patients with a baseline measurement and at least two post-baseline measurements were included in the analysis. ‡n=119; only patients with a baseline measurement and at least two post-baseline measurements were included in the analysis. §Odds ratio (95% CI). ¶Prespecified exploratory outcome.

Table 2: **Secondary and prespecified exploratory outcomes at week 24 in the intention-to-treat population (n=253)**

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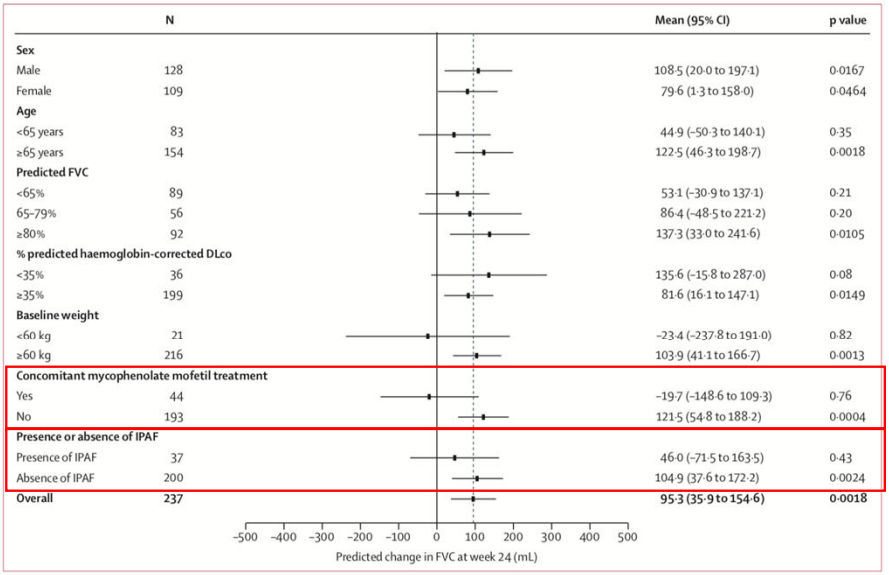

Figure 3: **Subgroup analysis of mean change in FVC from baseline at week 24 measured by site spirometry in all patients who had site spirometry at week 8 (n=237)**

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Safety and tolerability

	Pirfenidone (n=127)	Placebo (n=124)
Any treatment-emergent adverse events	120 (94%)	101 (81%)
Any treatment-related treatment-emergent adverse events	90 (71%)	57 (46%)
Any serious treatment-emergent adverse events*	18 (14%)	20 (16%)
Any severe treatment-emergent adverse events	29 (23%)	28 (23%)
Any treatment-related, severe treatment-emergent adverse events	6 (5%)	2 (2%)
Treatment-emergent adverse events of special interest†	0	0
Treatment-emergent adverse events leading to death	1 (1%)	1 (1%)
Treatment-related, treatment-emergent adverse events leading to death	0	0
Treatment-emergent adverse events leading to treatment discontinuation	19 (15%)	5 (4%)
Treatment-related, treatment-emergent adverse events leading to treatment discontinuation	16 (13%)	1 (1%)
Treatment-related treatment-emergent adverse events known to be associated with pirfenidone		
Gastrointestinal disorder‡	60 (47%)	32 (26%)
Photosensitivity§	10 (8%)	2 (2%)
Rash¶	13 (10%)	9 (7%)
Dizziness	10 (8%)	4 (3%)
Weight decrease	10 (8%)	1 (1%)
Fatigue	16 (13%)	12 (10%)

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Study Conclusions

- Pirfenidone slowed FVC decline compared to placebo in patients with progressive, unclassifiable ILD
  - Based on secondary endpoints of standardized site-spirometry
  - Primary endpoint of home-based spirometry could not be assessed due to significant inter- and intra-subject variability
- Treatment effects consistent across diverse subgroups
  - Exception appears to be those treated concurrently with MMF
- Safety and tolerability similar to IPF
- Support phase III trial of pirfenidone in this group (other other progressive ILDs)

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Part III

Our challenges ahead in ILD therapeutics

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Challenges Ahead

First we must actually treat!

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Table 1. Baseline patient characteristics overall and by IPF vs Non-IPF*

Variable	IPF N=834	Non-IPF N=627	P-Value#
Age, years	71 (8)	64 (12)	<0.0001
Male	615 (74%)	275 (44%)	<0.0001
Never smoker	302 (37%)	321 (52%)	<0.0001
Former smoker	519 (63%)	292 (48%)	<0.0001
Consented for Biorepository	752 (90%)	562 (90%)	0.74
Pulmonary Function			
FEV1, L	2.2 (0.6)	2.0 (0.7)	<0.0001
FEV1, % pred	72 (18)	70 (20)	0.03
FVC, L	2.7 (0.8)	2.5 (0.9)	<0.0001
FVC, % pred	68 (17)	68 (20)	0.99
DLCO, mL/mmHg/min	12.0 (5.4)	12.5 (5.6)	0.11
DLCO, % pred	41 (18)	45 (18)	0.0001
Supplemental home oxygen use	354 (43%)	253 (41%)	0.42
Comorbidity			
GERD	517 (62%)	357 (57%)	0.05
OSA	220 (26%)	154 (25%)	0.42
Depression	135 (17%)	115 (19%)	0.23
Anxiety	83 (10%)	81 (14%)	0.06
CAD	199 (25%)	84 (14%)	<0.0001
Cardiac Arrhythmia	88 (11%)	52 (9%)	0.17
CHF	34 (4%)	32 (5%)	0.32
COPD	69 (9%)	52 (9%)	0.93
Medical Therapy			
Immunosuppression, any	44 (5%)	353 (56%)	<0.0001
Anti-fibrotic	512 (62%)	40 (6%)	<0.0001
N-acetyl Cysteine	20 (2%)	6 (1%)	0.04

Pulmonary Fibrosis FOUNDATION

~40% of patients with IPF are not taking anti-fibrotic therapy

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Flaherty et al. ERS Abstract 2018

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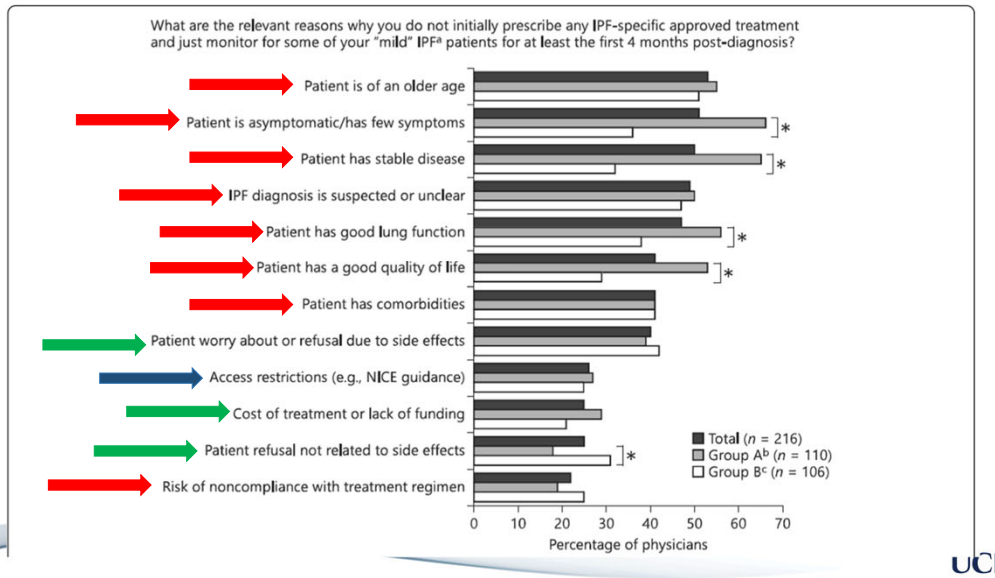
Reasons patients are not being treated



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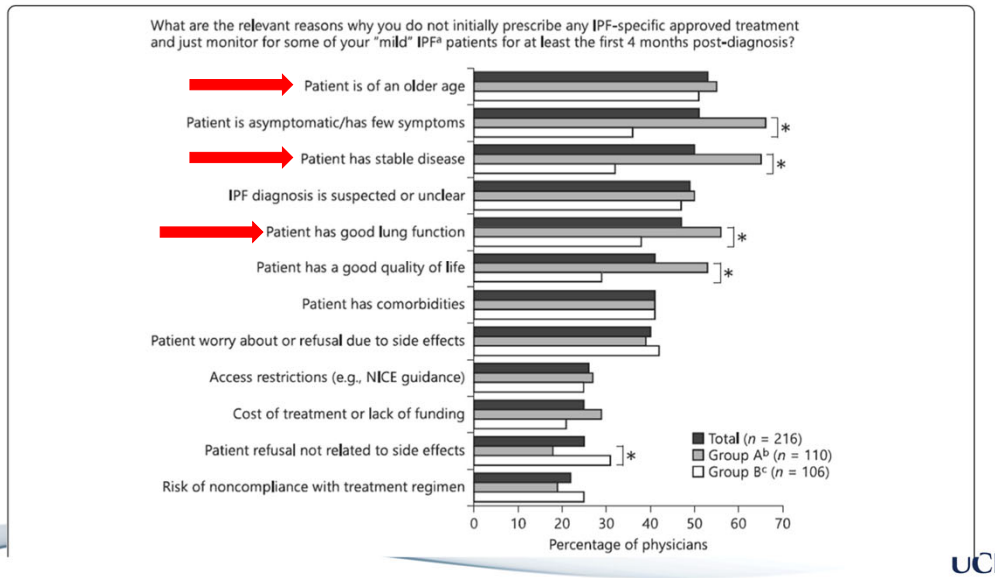
Maher et al. Respiration 2018

52

Reasons patients are not being treated



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Maher and Strek Res Res 2019

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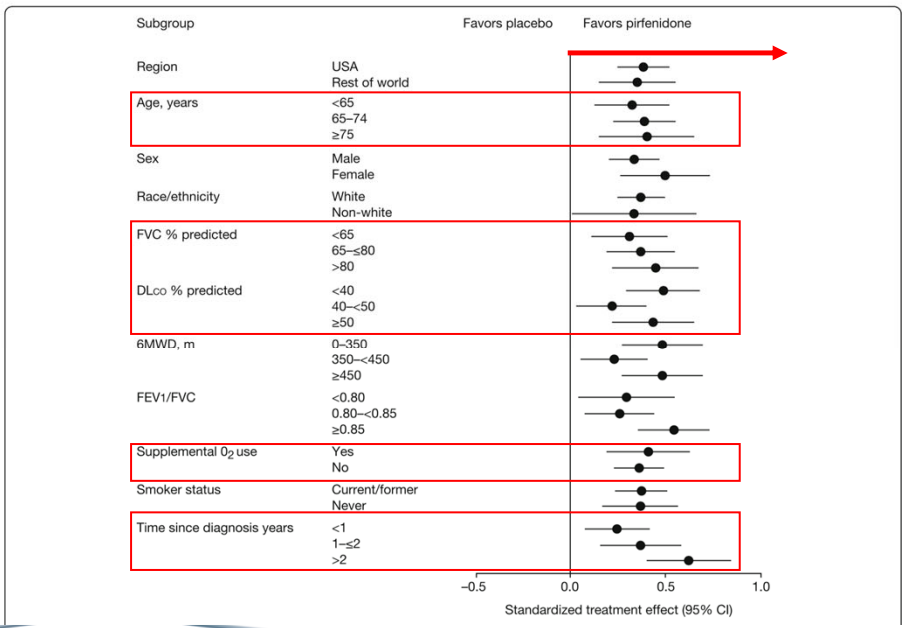

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Maher and Strek. Res Res 2019

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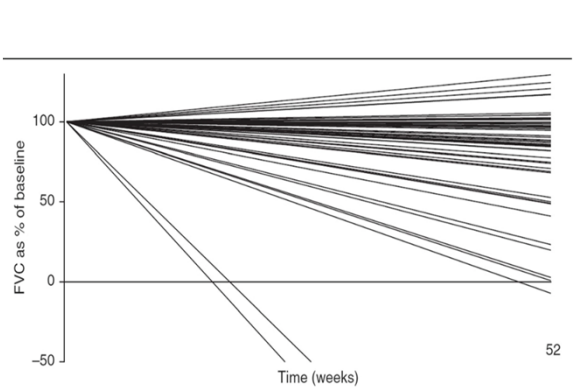
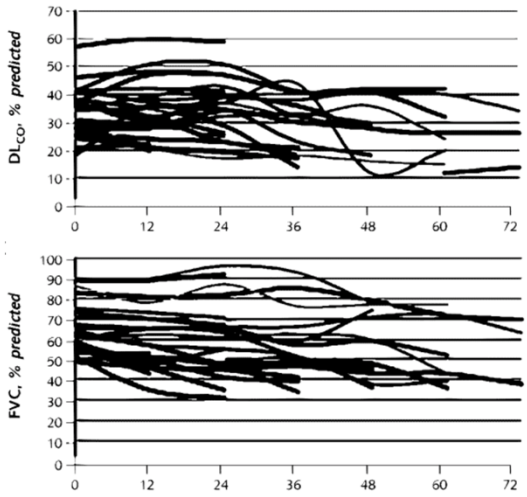
Stable IPF cannot be predicted with lung function





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Russell et al. AJRCCM 2018
Martinez et al. Ann Int Med 2005

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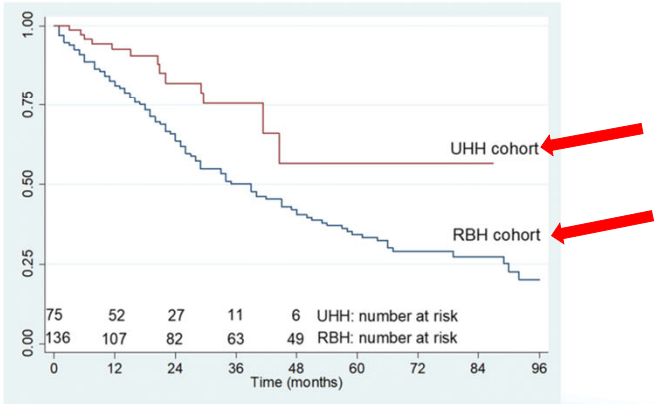
Research article | Open Access | Open Peer Review | Published: 23 November 2018

Pirfenidone improves survival in IPF: results from a real-life study

George A. Margaritopoulos, Athina Trachalaki, Athol U. Wells, Eirini Vasarmidi, Eleni Bibaki, George Papastratigakis, Stathis Detorakis, Nikos Tzanakis & Katerina M. Antoniou



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Clinical Effectiveness of Antifibrotic Medications for Idiopathic Pulmonary Fibrosis

Timothy M. Dempsey[1], Lindsey R. Sangaralingham[2,3], Xiaoxi Yao[4], Darshak Sanghavi[3], Nilay D. Shah[2,4], and Andrew H. Limper[1,2]

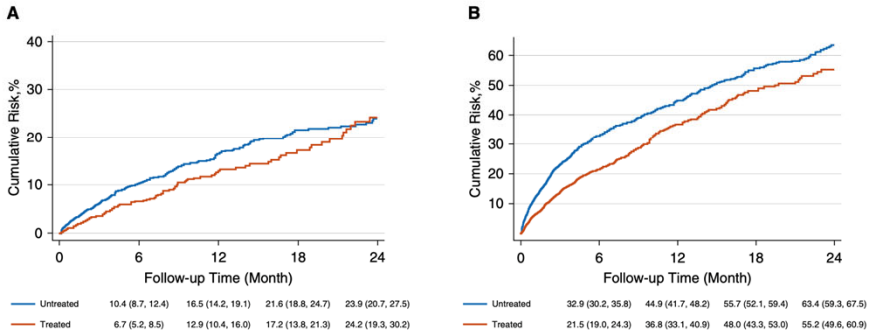

Figure 1. (*A*) Mortality cumulative risk (percent). The cumulative risk of all-cause mortality in patients on treatment for idiopathic pulmonary fibrosis (IPF) (treated) compared with an untreated IPF matched cohort (untreated) during a 24-month follow-up is shown. For the number of patients at risk during each time interval, *see* Table E5. (*B*) Hospitalization cumulative risk (percent). The cumulative risk of acute hospitalizations in patients on treatment for IPF (treated) compared with an untreated IPF matched cohort (untreated) during a 24-month follow-up is shown. For the number of patients at risk during each time interval, *see* Table E5.

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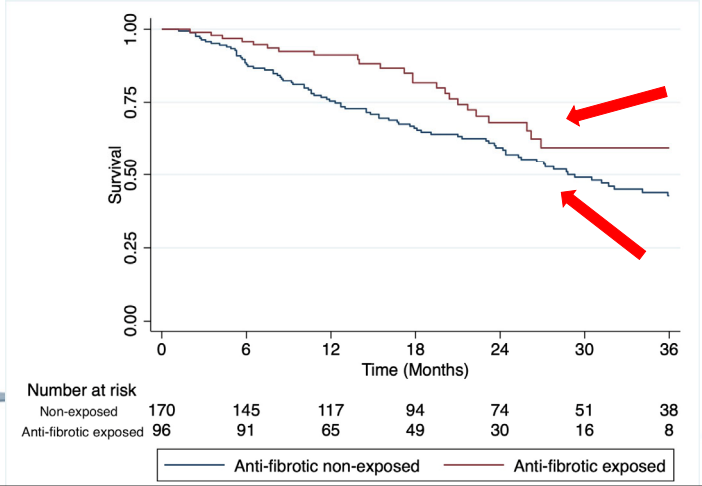
Modulation of Prognostic Plasma Biomarkers by Anti-fibrotic Therapy in Patients with Idiopathic Pulmonary Fibrosis

Ayodeji Adegunsoye*[1], MD MS; Shehabaldin Alqalyoobi*[2], MD; Cathryn T. Lee[1], MD; Willis S. Bowman[3], MD, Janelle Vu Pugashetti[3], MD; Angela Linderholm[3], PhD; Shwu-Fan Ma,[4] PhD; Angela Haczku[3], MD PhD; Anne Sperling[1], PhD; Mary E Strek[1], MD; Imre Noth[4], MD; Justin M. Oldham[3], MD MS



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Manuscript Under Review

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REVIEW

Antifibrotic therapy for idiopathic pulmonary fibrosis: time to treat

Toby M. Maher[1,2*] and Mary E. Strek[3]

Imperial College
Royal Brompton Hospital

Univ of Chicago

Antifibrotic therapy for progressive fibrosing interstitial lung disease: time to treat

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Challenges Ahead

Interstitial Lung Disease

Progressive ILD

Idiopathic pulmonary fibrosis
Progressive fibrosing ILD
- SSc-ILD
- RA-ILD
- Other CTD-ILD
- CHP
- IPAF
- uILD
- other progressive ILDs

We need to identify progressive fibrosing ILD before it becomes progressive

60

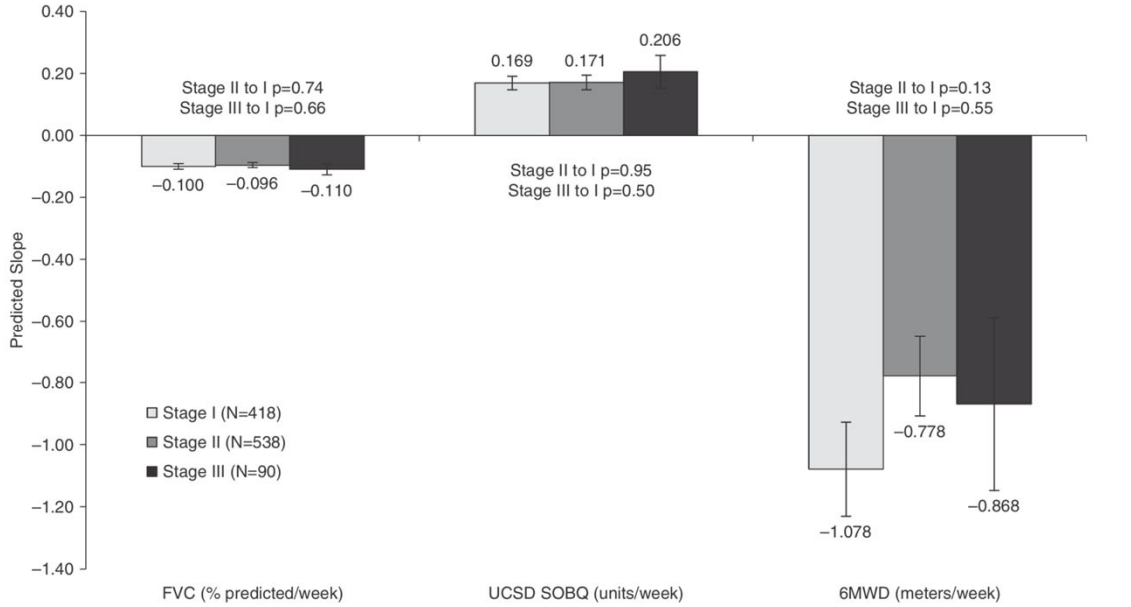

Figure 2. Mean ± SE disease progression per week by Gender-Age-Physiology stage at study baseline. FVC change is in percent predicted per week, UCSD SOBQ change is in units per week, and 6MWD change is in meters per week. 6MWD = 6-minute-walk distance; UCSD SOBQ = University of California, San Diego Shortness of Breath Questionnaire.

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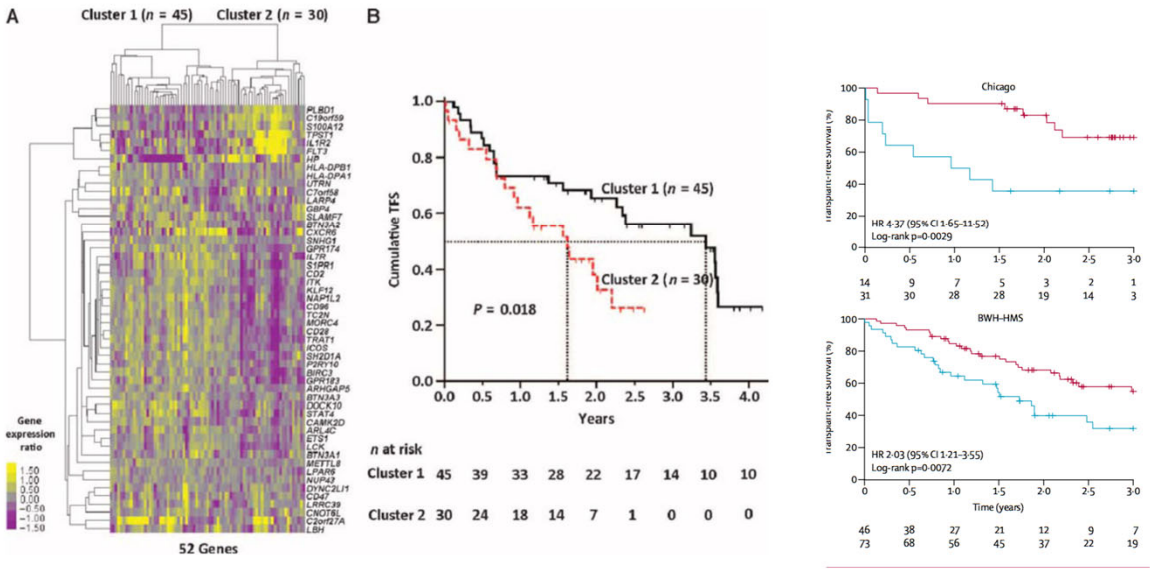
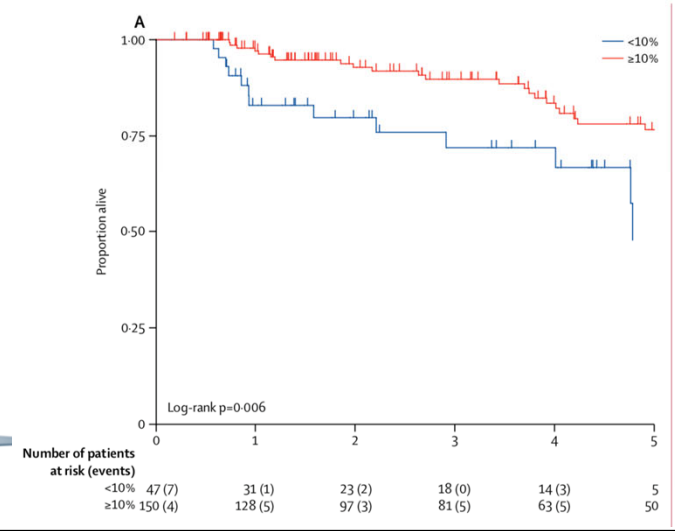
Peripheral Blood Mononuclear Cell Gene Expression Profiles Predict Poor Outcome in Idiopathic Pulmonary Fibrosis



62

The *MUC5B* promoter polymorphism and telomere length in patients with chronic hypersensitivity pneumonitis: an observational cohort-control study

Brett Ley, Chad A Newton, Isabel Arnould, Brett M Elicker, Travis S Henry, Eric Vittinghoff, Jeffrey A Golden, Kirk D Jones, Kiran Batra, Jose Torrealba, Christine Kim Garcia, Paul J Wolters



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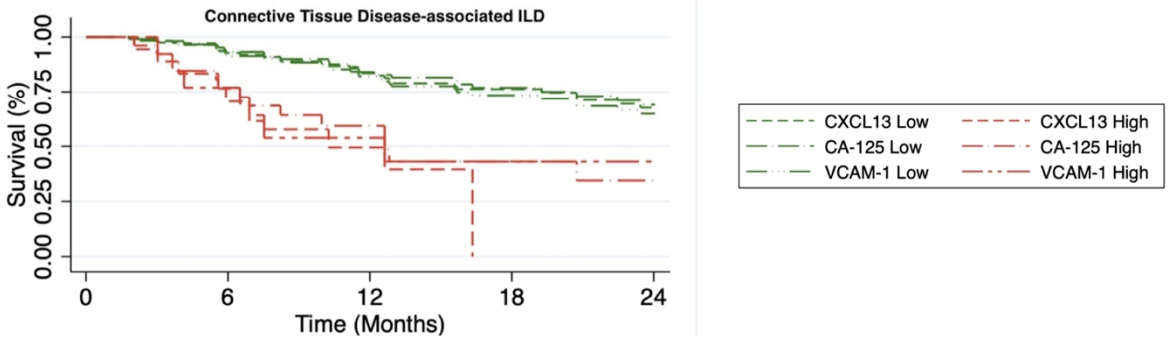
Circulating Plasma Biomarkers of Progressive Interstitial Lung Disease

Shehabaldin Alqalyoobi , Ayodeji Adegunsoye , Angela Linderholm , Cara Hrusch , Claire Cutting , Shwu-Fan Ma , Anne Sperling , Imre Noth , Mary E. Strek , and **Justin M Oldham**

\+ Author Information

https://doi.org/10.1164/rccm.201907-1343LE **PubMed:** 31524503

Received: September 10, 2019 Accepted: September 13, 2019 Published Online: September 16, 2019



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Circulating Plasma Biomarkers of Progressive Interstitial Lung Disease

Shehabaldin Alqalyoobi , Ayodeji Adegunsoye , Angela Linderholm , Cara Hrusch , Claire Cutting , Shwu-Fan Ma , Anne Sperling , Imre Noth , Mary E. Strek , and Justin M Oldham
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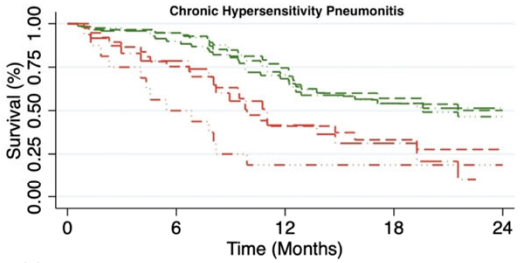
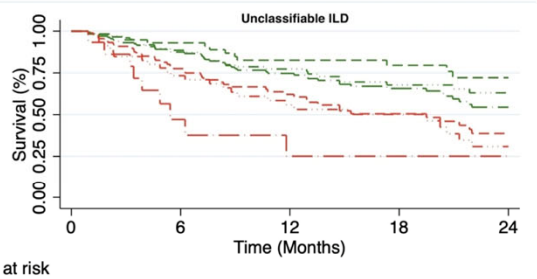


Number at risk					
CXCL13 Low	59	51	31	18	10
CXCL13 High	39	26	13	7	5
MMP7 Low	74	60	36	21	15
MMP7 High	24	17	8	4	0
VCAM-1 Low	82	69	41	23	14
VCAM-1 High	16	8	3	2	1



Number at risk					
CXCL13 Low	63	47	35	25	14
CXCL13 High	96	59	40	26	13
CA-125 Low	144	101	73	49	25
CA-125 High	15	5	2	2	2
MMP7 Low	113	75	54	36	22
MMP7 High	46	31	21	15	5

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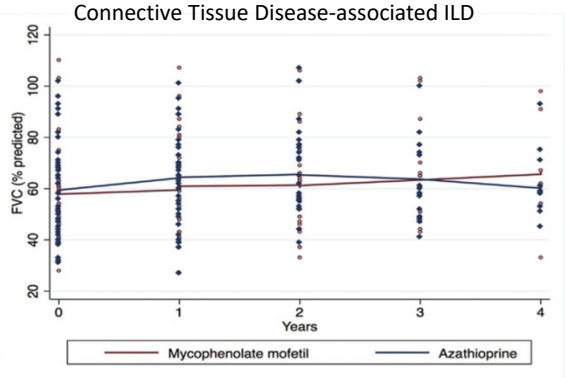
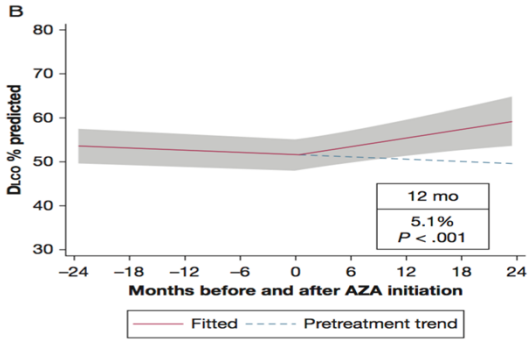
Challenges Ahead

Some ILDs are probably better treated with immunosuppression than anti-fibrotic therapy

Connective Tissue Disease-associated ILD



Chronic Hypersensitivity Pneumonitis



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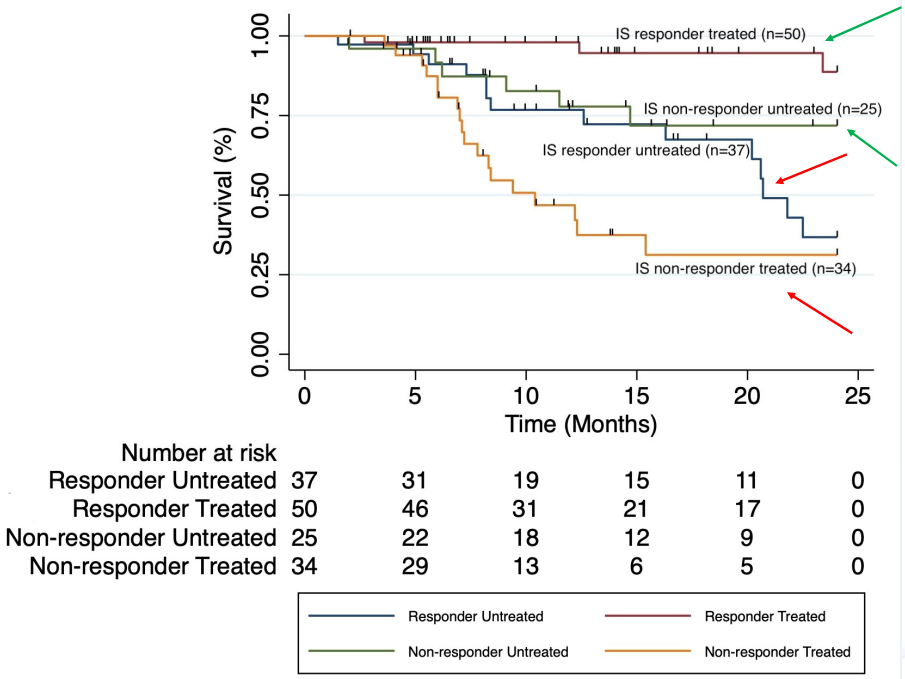

Composite risk score comprised of :

Age
DLCO
Four proteins

Can predict treatment response in patients with CTD-ILD

Immunosuppressive (IS) treatment in responsive endotype
= favorable outcome
First line therapy: immunosuppressant

Immunosuppressive (IS) treatment in nonresponsive endotype
= poor outcome
First line therapy: anti-fibrotic?

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Oldham et al. Unpublished data

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Summary

- 2019 was an exciting year that showed anti-fibrotic therapy is effective for progressive ILD, irrespective of subtype
- BUT…ILD remains a complex disease without a one size fits all treatment
  - Some ILDs will better respond to immunosuppression while others will be better suited to receive an anti-fibrotic
- Biomarker investigations provide a path forward in discriminating progressive from non-progressive ILD and identifying those who should receive an immunosuppressant versus anti-fibrotic

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Thank You!

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BREAK
EXHIBIT HALL OPEN

Saturday, January 18, 2020 – 2:45 p.m. – 3:10 p.m.

ADVANCES IN CYSTIC FIBROSIS

Douglas Conrad, MD
UC San Diego
Director, Adult CF program
Pulmonary Critical Care Clinical Service Chief

Saturday, January 18, 2020 – 3:10 p.m. – 3:55 p.m.

Douglas Conrad, MD received his Medical Degree from Case Western Reserve University. His post graduate studies include Internal Medicine training at the University of Minnesota Affiliated Hospitals and Pulmonary/Critical Care and research training at the University of California San Francisco. Currently he is the director of the UC San Diego Adult CF program, serves as the UCSD Pulmonary Critical Care Clinical Service Chief. His research interests include CF airway inflammation and airway microbiome, CF related airway infection phage therapy, and is the UCSD site principal investigator for the COPD Gene Network. He is Professor of Medicine at UC San Diego.

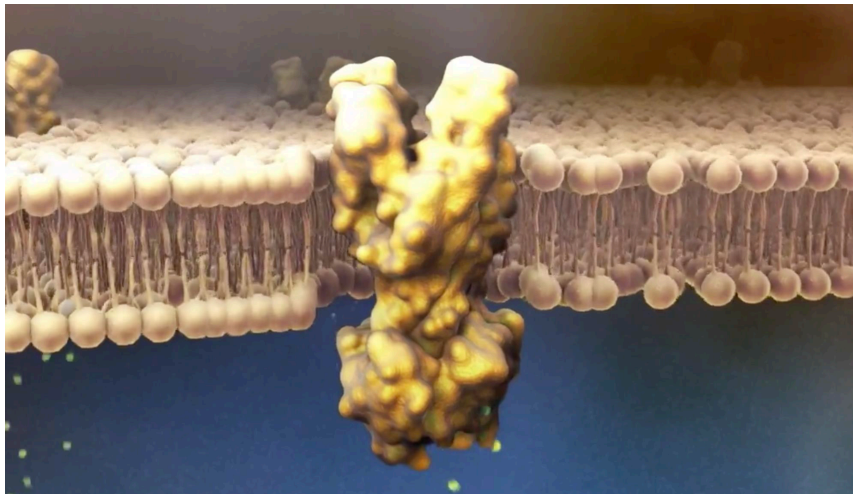
Advances in Cystic Fibrosis: 2020

Douglas Conrad MD

Professor of Medicine

California Thoracic Society

January 2020



Disclosures

- There are no conflicts of interest to disclose
  - Local site investigator for Vertex Pharmaceuticals, Sound in CF
  - Boehringer-Ingelheim, GSK
  - NIH: COPD Gene Investigator, RO1 x2
  - CF Foundation

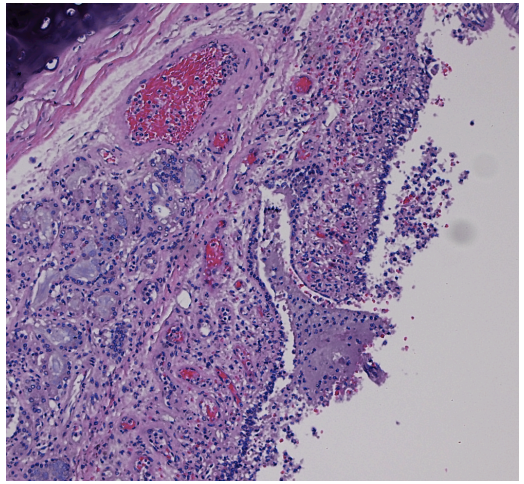
- There will be discussion of off-label use of anti-infective therapies

- Acknowledgements:
  - Slides from publicly available plenary session: NACFC Jane Davies MD
  - Forest Rohwer, Chip Schooley

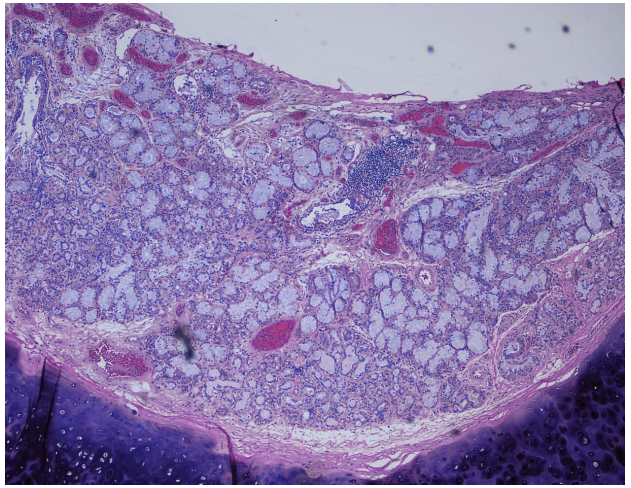
Outline

- Diagnostic Challenges
- Diagnosing CF and the Effects of Newborn Screening Program
- CFTR Modulator Therapy Review
- Update in treatment of complex airway infection
  - Nontuberculous Mycobacteria
  - Fungi
  - Phage Therapy

Cystic Fibrosis



- Most common genetic disease associated with a decreased lifespan in Caucasians
- 30,000 in US; 70,000 worldwide.
- 3-4% North American carrier rate
- Caused by mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene



- Disrupts anion (chloride and bicarbonate) transport in organs throughout the body resulting in mucus dysfunction
- Results in chronic polymicrobial sino-pulmonary lung infection, pancreatic insufficiency, hepatic cirrhosis and bowel obstruction.

Cystic Fibrosis Systemic Manifestations

Median predicted survival age for people with CF in the US was 43.6 years*, but median age at death was 30.7 years[1]

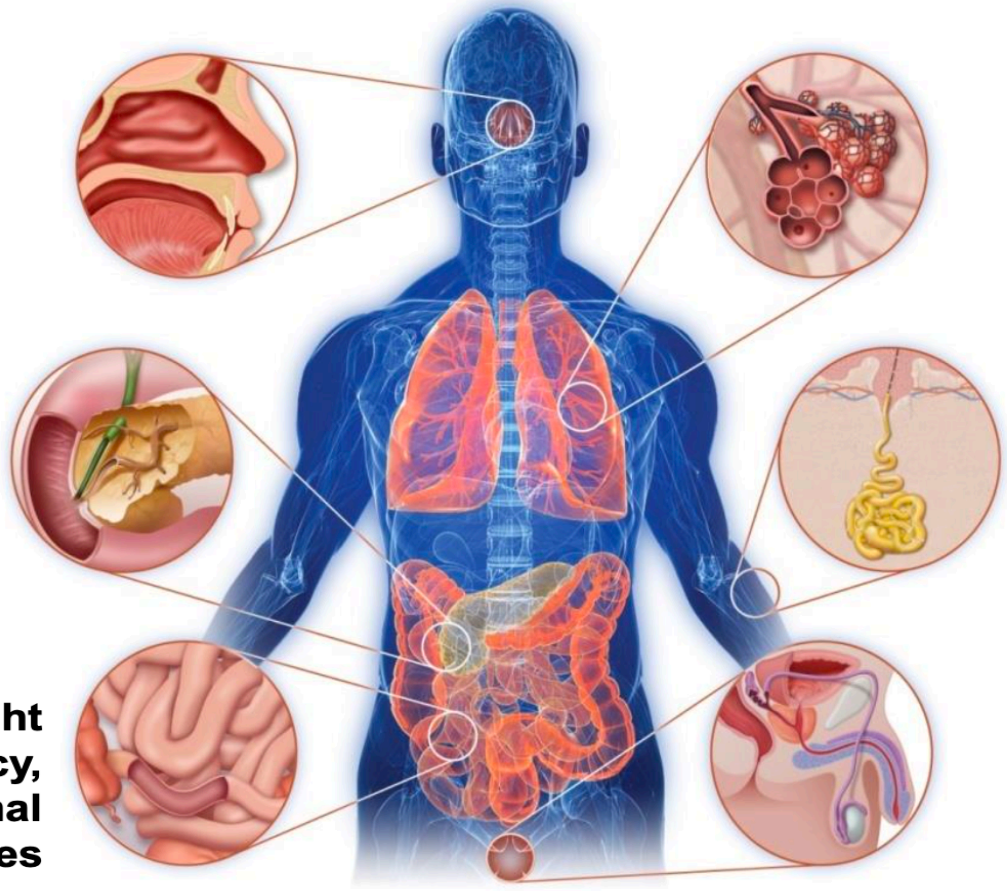
Sinus infections

Nasal polyps

Exocrine pancreatic insufficiency and resulting malnutrition

Endocrine pancreatic insufficiency and resulting CF-related diabetes

Failure to thrive/gain weight due to pancreatic insufficiency, digestive problems, and intestinal blockages



Reduced lung function

Frequent lung infections, inflammation, and progressive lung disease

Elevated Sweat Chloride

Reproductive Tract

- **Infertility**
- **Congenital bilateral absence of the vas deferens (CBAVD) in men**

Cystic Fibrosis-Laboratory Confirmation

Sweat chloride concentration-Pilocarpine iontopheresis

- Operator dependent. Experience and quality control are important

- Requires 100 mg sweat sample.

- Values: < 30 meq/l normal
  > 60 meq/l positive

- Repeat all positive and borderline test and those with a classical clinical presentation

Cystic Fibrosis-Laboratory Confirmation

CFTR Genetic mutation screening

- Standard CFTR genetic screens assesses
  - •F508del. If homozygous then stop.

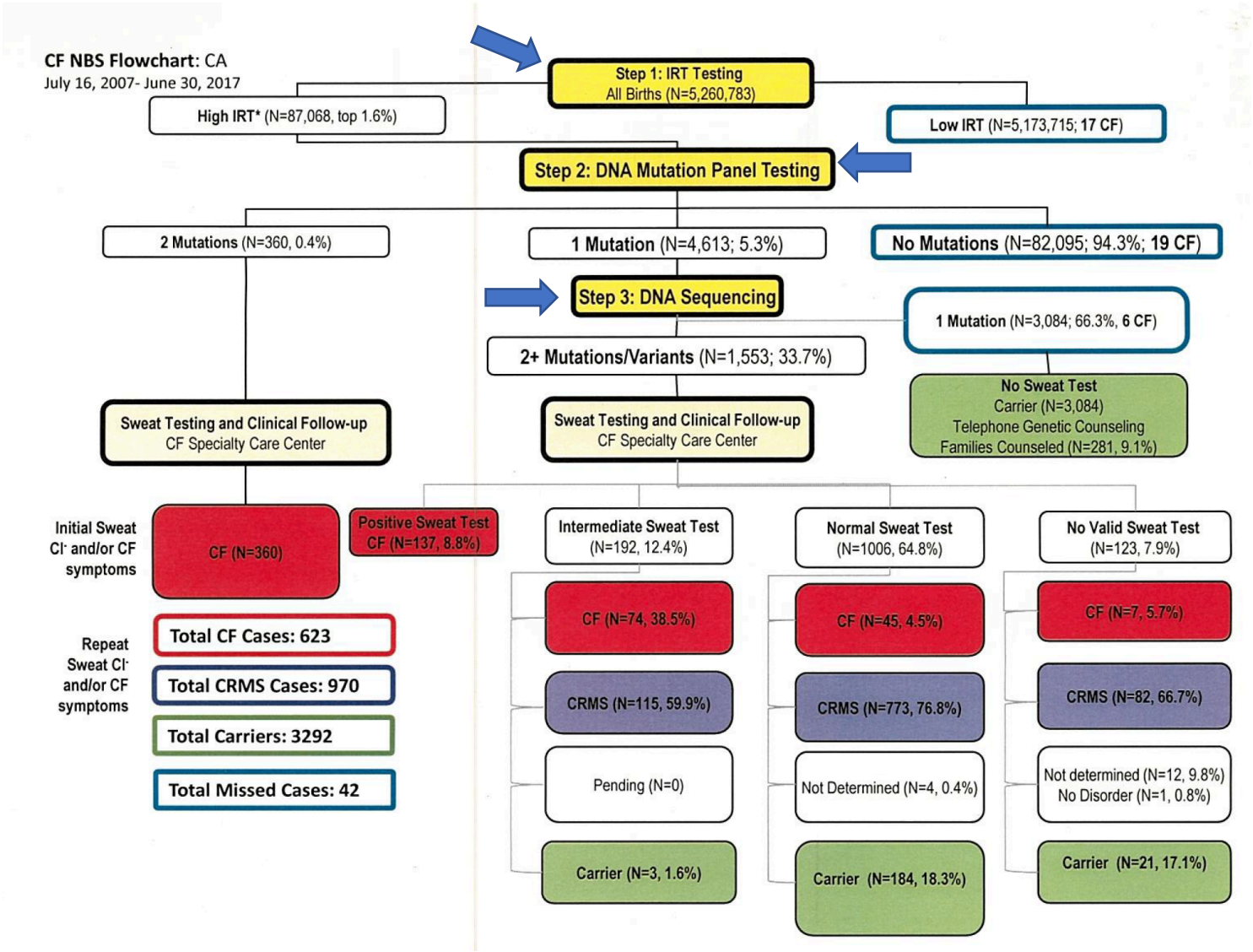
- Next step: 32-200 most frequent mutations in North America which account for 90% of the mutated alleles

- Full CFTR Gene Sequencing (Exome sequencing with selected intron information
  - •Atypical CF cases have a high frequency of rare mutations not identified in the screens
  - •Duplications and Deletions: ~ 1% of general population
    - Not identified by sequencing
    - Require specialized techniques to identify.
  - •Avoid “Bronchiectasis screens”

Newborn Screening

- Early identification results in initiation of therapies associated with much improved long-term medical outcomes
  - Nutritional
  - Early initiation of pulmonary specific therapies
- Advantages of long-term effects outweigh the disadvantages
- Statewide programs vary but most are designed to identify 90-99% of the most severe cases
- California uses a “three step screening process”

California Newborn Screening



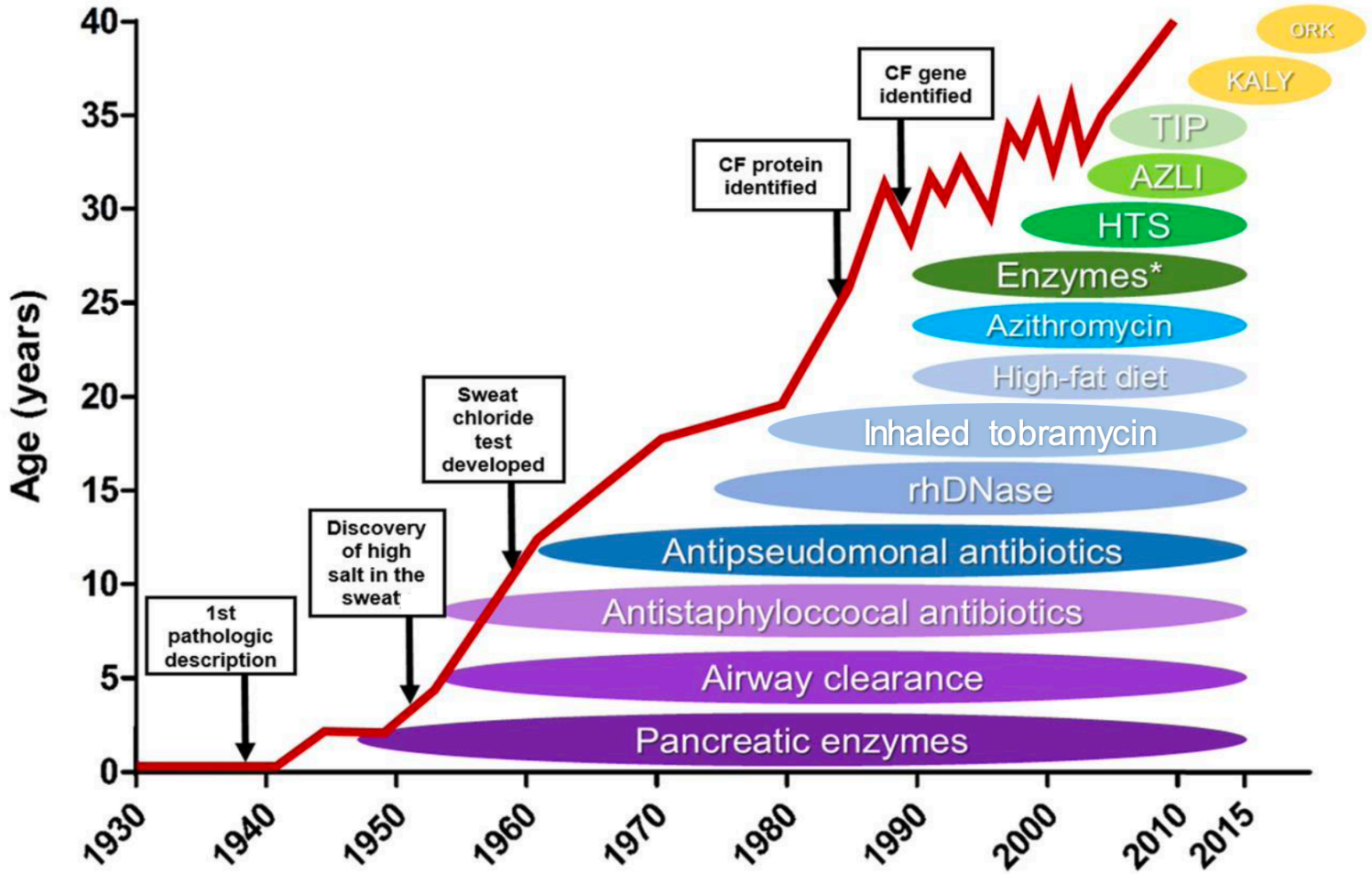
Newborn Screening Challenges

- **Pediatric Pulmonary Providers**
  - **Screen positive, asymptomatic subjects**

- **Adult Pulmonary Providers**
  - **California newborn screening has a sensitivity of about 92 %**
  - **Missed subjects may have less severe or atypical disease**
  - **Missed subjects are more likely to present in adulthood**
  - **Program was initiated in July 2007**

  - ***Adult pulmonologists need to maintain awareness of CFTR related disease in their patients with diffuse bronchiectasis.***

Cystic Fibrosis Therapeutics: Where we have been



CFTR Modulator Therapy

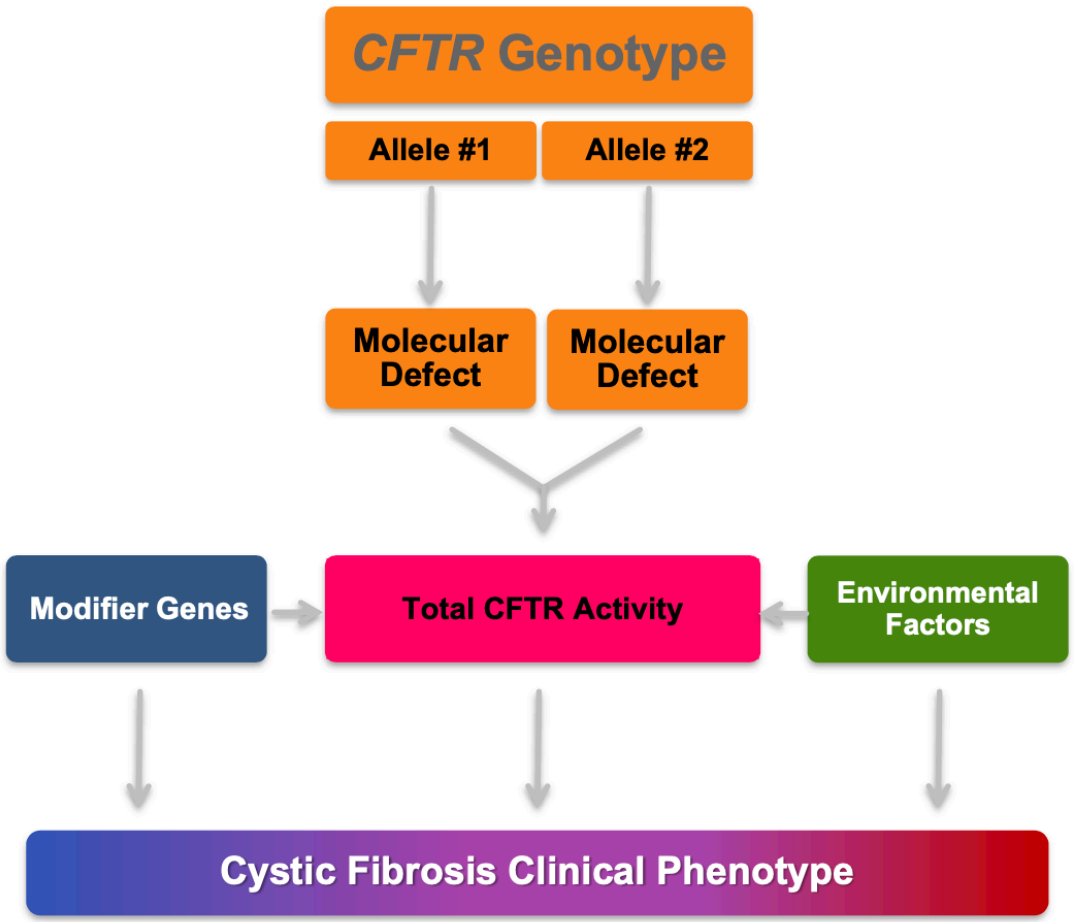
- **Small, orally bioavailable medications that directly increase (i.e. “modulate”) CFTR activity**
- **High-throughput robotic screening of CFTR in primary airway epithelial cells**
- ***Potentiators:*** **Increase open probability of CFTR channel**
  - **Ivacaftor**
- ***Correctors:*** **Improves F508del polypeptide folding and maturation**
  - **Lumacaftor**
  - **Tezacaftor**
  - **Elexacaftor**
- **Others**

Clinical Phenotype Is Influenced by Multiple Factors

- ***CFTR* Genotype and the resulting amount of total CFTR Activity[1,2]**
  Generally, 2 mutations with little or no CFTR activity are associated with a more classic phenotype. The presence of a complex allele (more than 1 mutation in a single allele) may also contribute to reduction in CFTR activity

- **Modifier Genes[3]**
  Many modifier genes have been identified that affect function of various organs and have an impact on CF disease manifestations

- **Environmental Factors[4]**
  Exposure to cigarette smoke and other toxins; pulmonary bacterial colonization and infection may affect phenotype and longevity



1. DeGracia J et al. Thorax. 2005;60-558-563.
2. Castellani C et al. J Cyst Fibros. 2008;7:179-196.
3. Cutting GR et al. Nat Rev Genet. 2015;16:45-56.
4. Cutting GR. Annu Rev Genomics Hum Genet. 2005;6:237-260.

Ivacaftor with G551D

- Potentiator

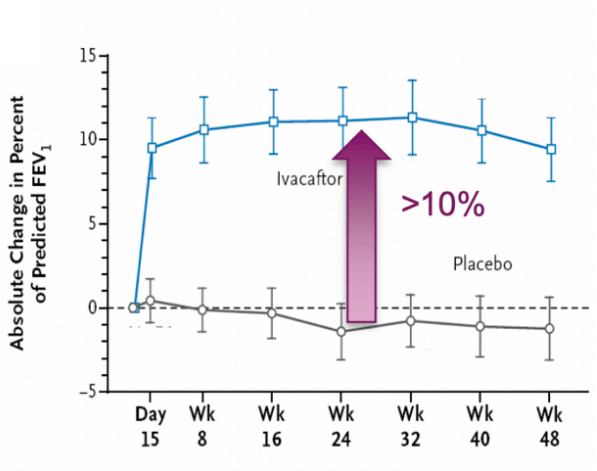
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 3, 2011 VOL. 365 NO. 18

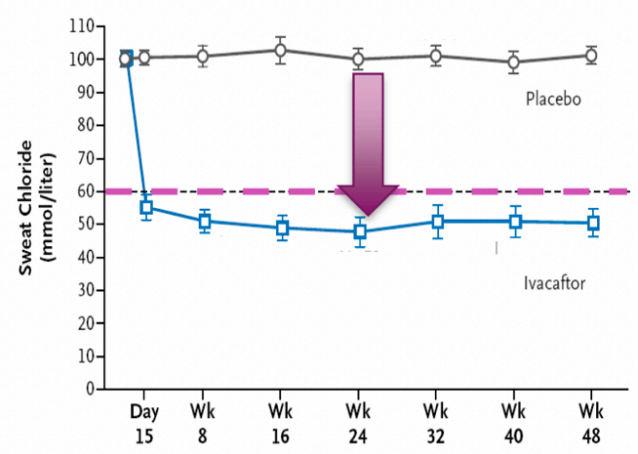
A CFTR Potentiator in Patients with Cystic Fibrosis and the *G551D* Mutation

Bonnie W. Ramsey, M.D., Jane Davies, M.D., M.B., Ch.B., N. Gerard McElvaney, M.D., Elizabeth Tullis, M.D., Scott C. Bell, M.B., B.S., M.D., Pavel Dřevínek, M.D., Matthias Griese, M.D., Edward F. McKone, M.D., Claire E. Wainwright, M.D., M.B., B.S., Michael W. Konstan, M.D., Richard Moss, M.D., Felix Ratjen, M.D., Ph.D., Isabelle Sermet-Gaudelus, M.D., Ph.D., Steven M. Rowe, M.D., M.S.P.H., Qunming Dong, Ph.D., Sally Rodriguez, Ph.D., Karl Yen, M.D., Claudia Ordoñez, M.D., and J. Stuart Elborn, M.D., for the VX08-770-102 Study Group*

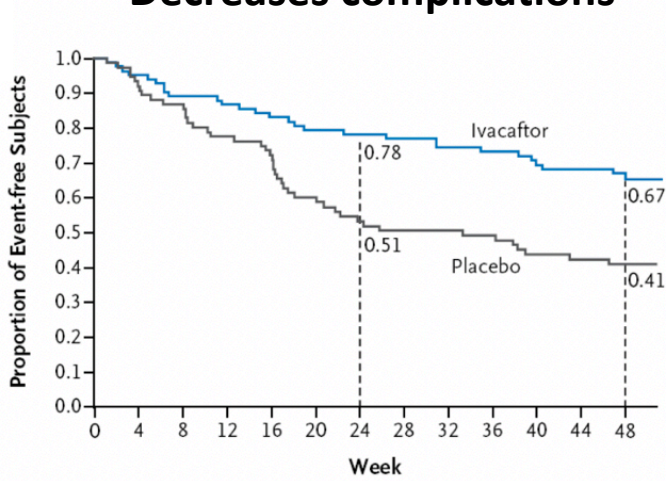
Improves lung function



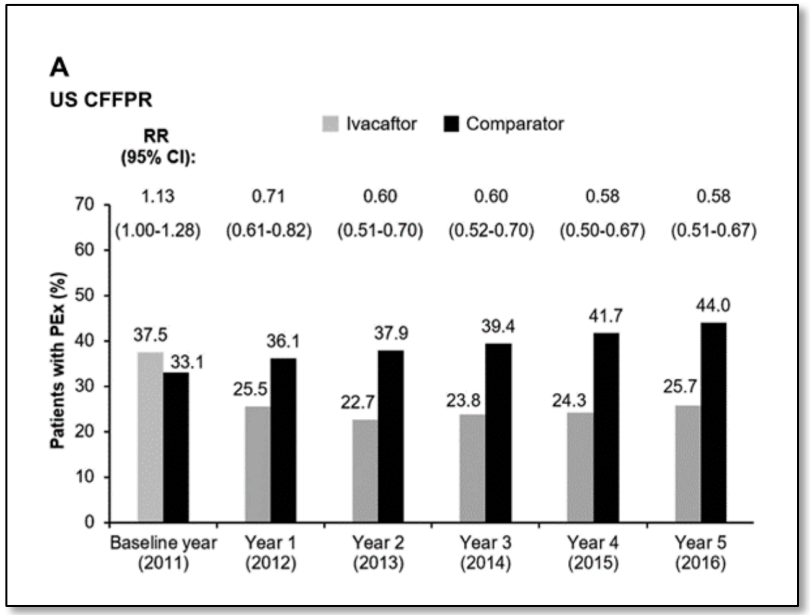
Improves sweat chloride

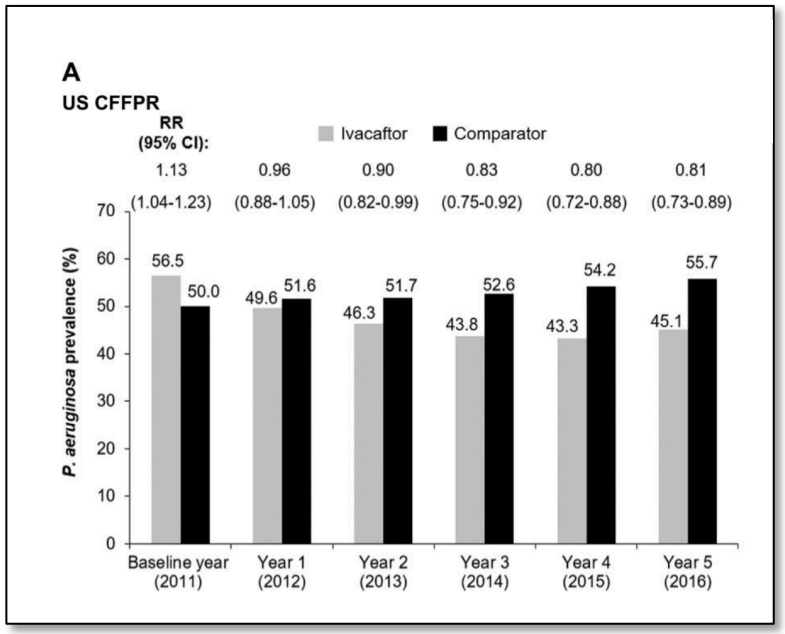


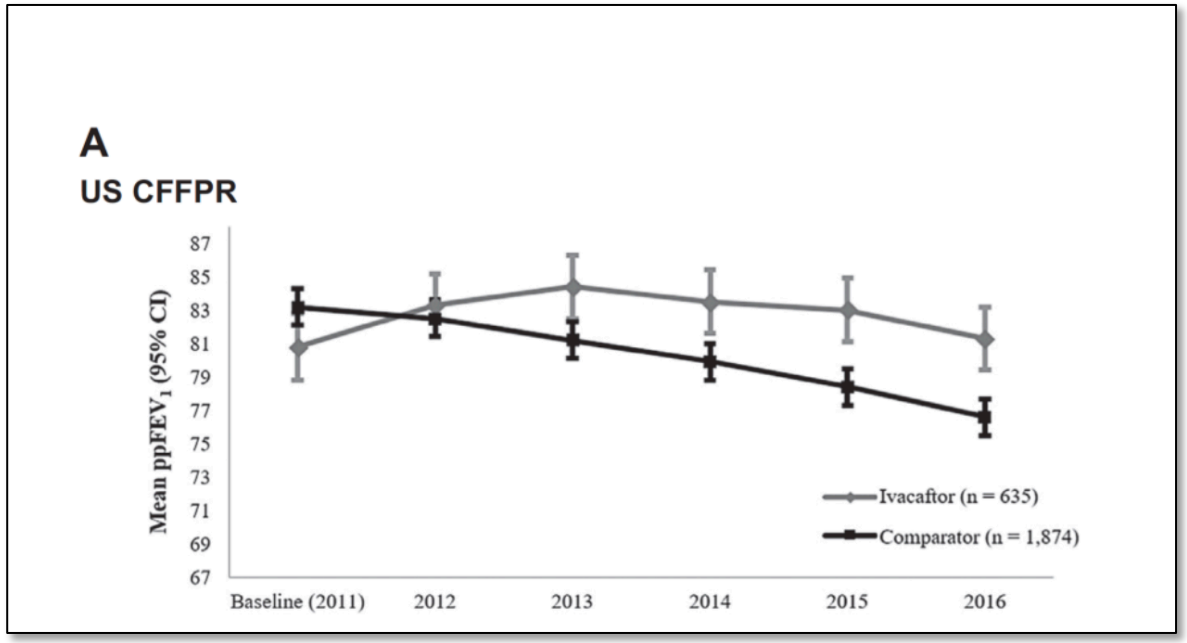
Decreases complications



Long-term effects of ivacaftor

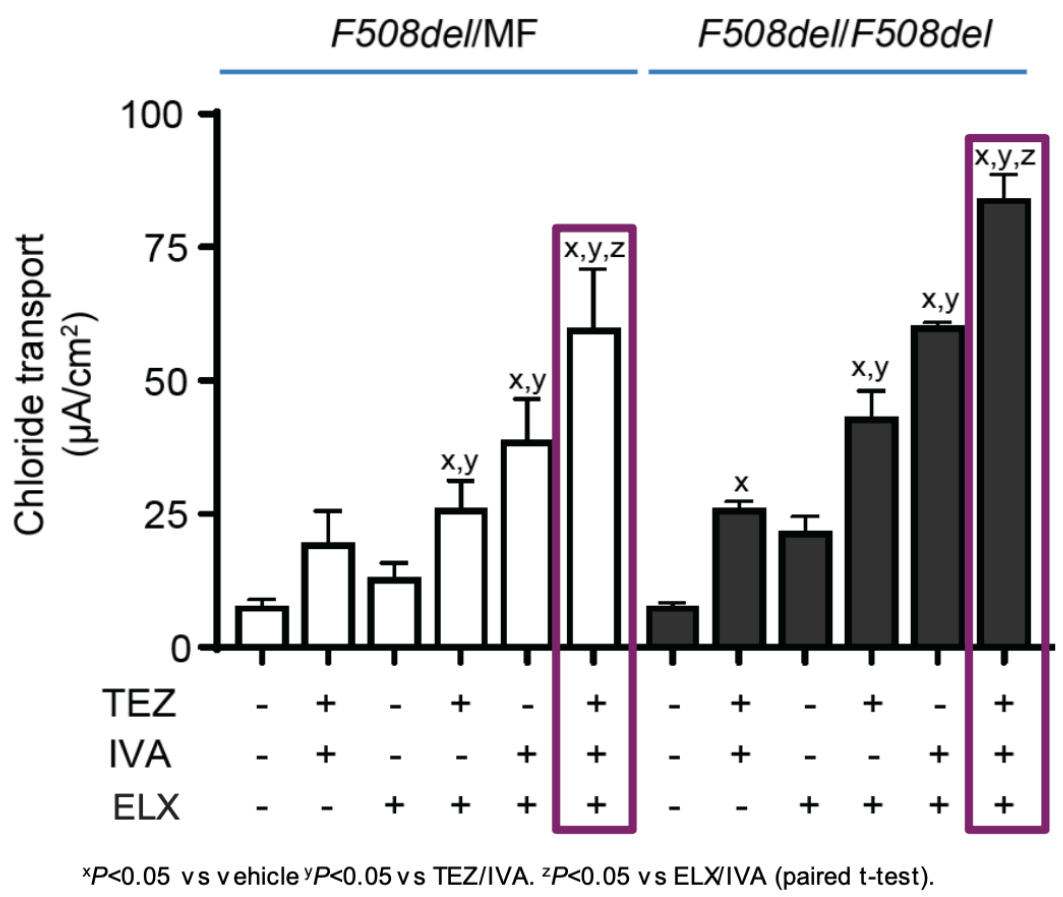






J Cyst Fibros. 2019 Jun 10. pii: S1569-1993(19)30767-2.

Triple combination modulator therapy



$^{x}P<0.05$ vs vehicle $^{y}P<0.05$ vs TEZ/IVA. $^{z}P<0.05$ vs ELX/IVA (paired t-test).

Ivacaftor (Potentiator)

Tezacaftor (Corrector)

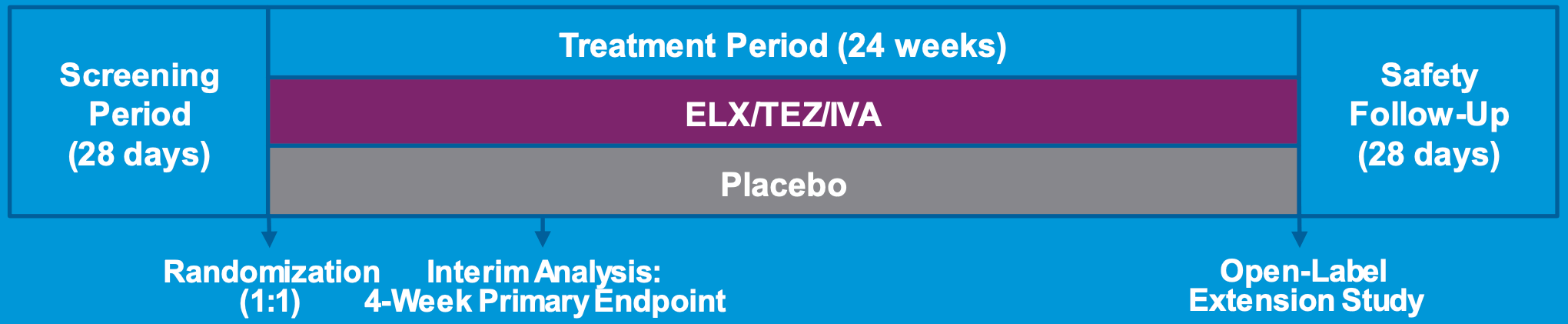
Elexacaftor (Corrector)

- ***in vitro*** **effects on primary bronchial epithelial cell chloride transport**

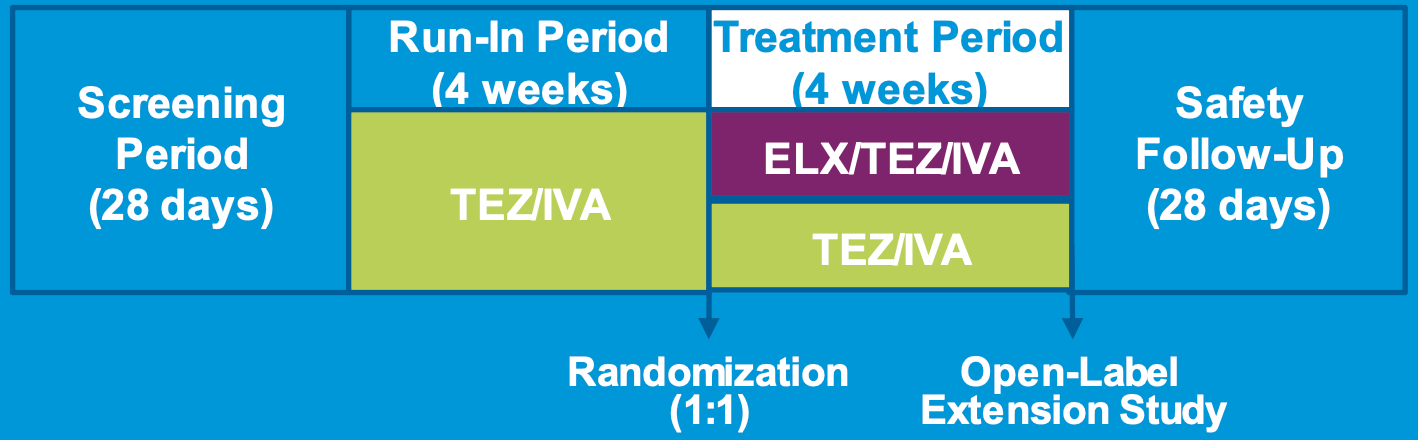
Keating D, et al. N Engl J Med. 2018;379:1612-1620.

Study Designs: Participants With *F*/MF and *F*/*F* Genotypes

VX17-445-102 (*F*/MF):



VX17-445-103 (*F*/*F*):



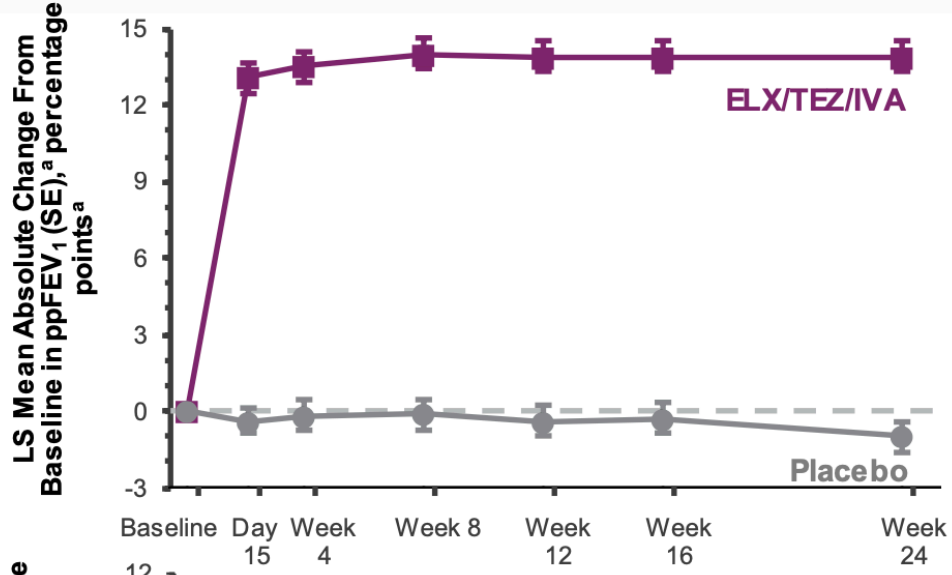
N Engl J Med 2019;381:1809-19.
Lancet. 2019 Nov 23;394(10212):1940-1948

Primary endpoint for both studies: absolute change from baseline in $ppFEV_1$ at Week 4

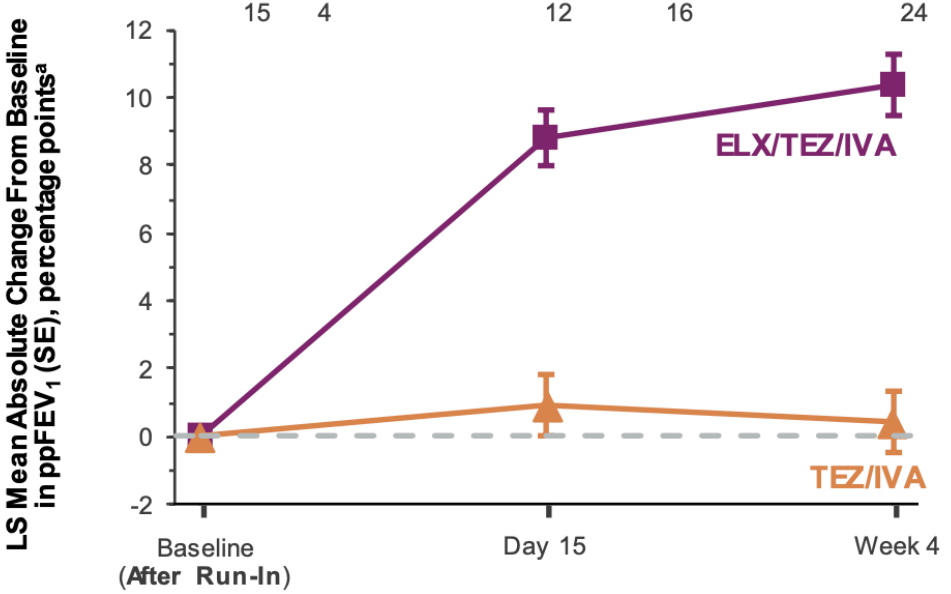
MF, minimal function; $ppFEV_1$, percent predicted forced expiratory volume in 1 second.

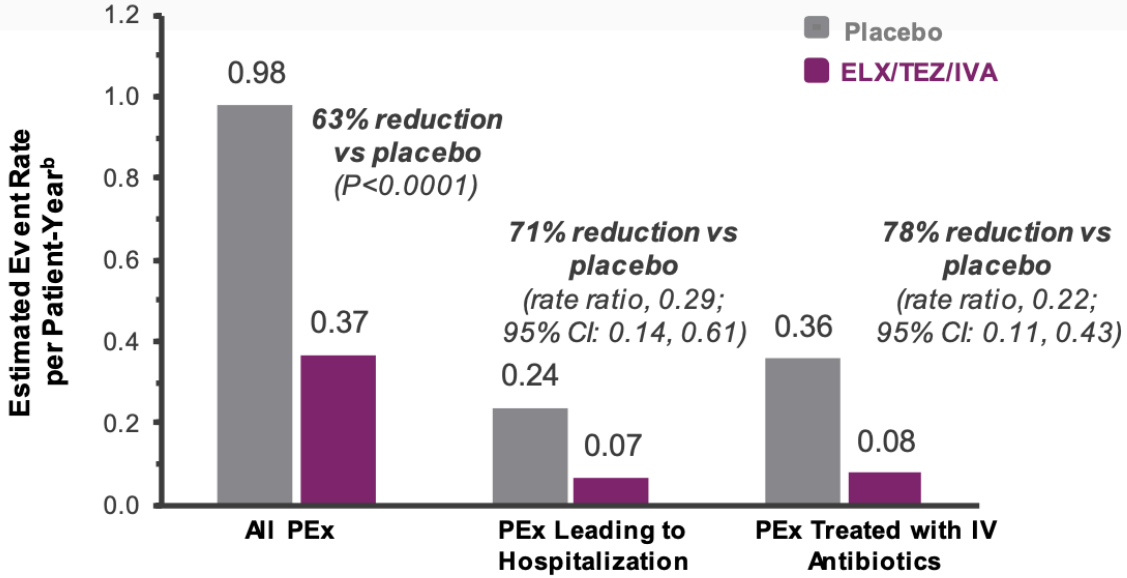
Substantial Improvements in Lung Function and Rate of Pulmonary Exacerbations

Study 102, F/MF



Study 103, F/F





N Engl J Med 2019;381:1809-19.
Lancet. 2019 Nov 23;394(10212):1940-1948

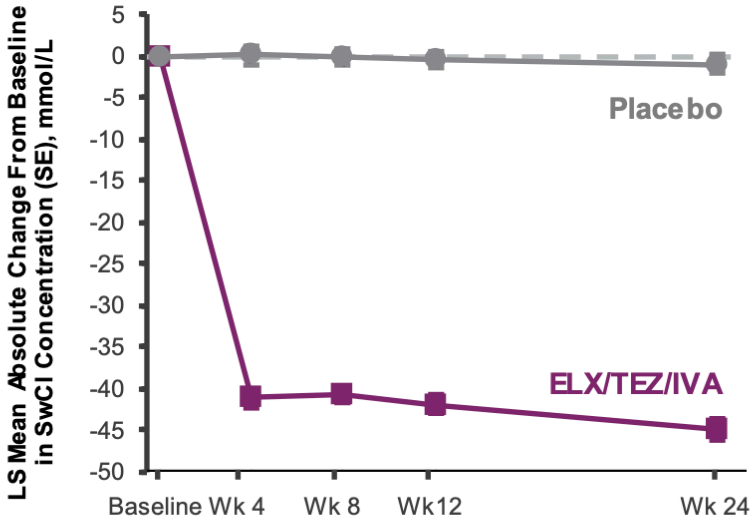
Significant Improvements in Sweat Chloride, CFQ-R Respiratory Domain Score and BMI

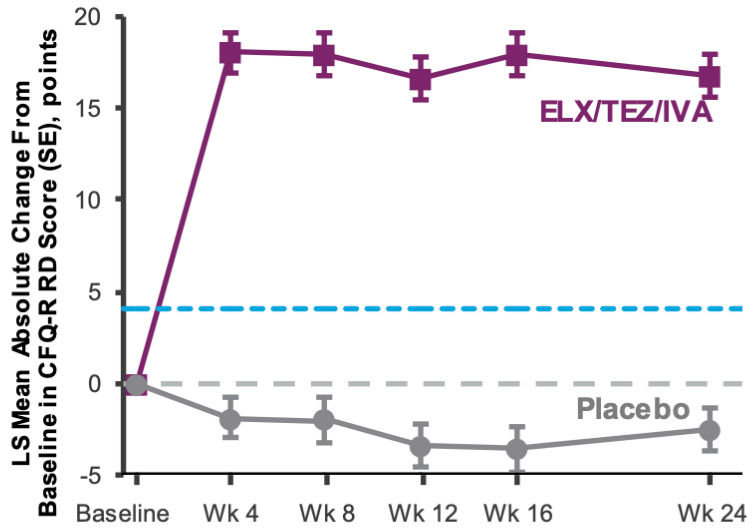
SwCl CONCENTRATION

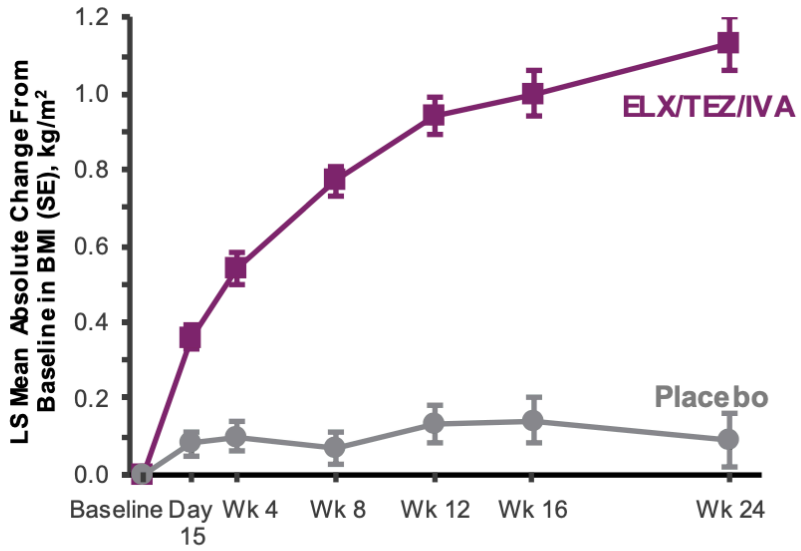
CFQ-R RD SCORE

BMI

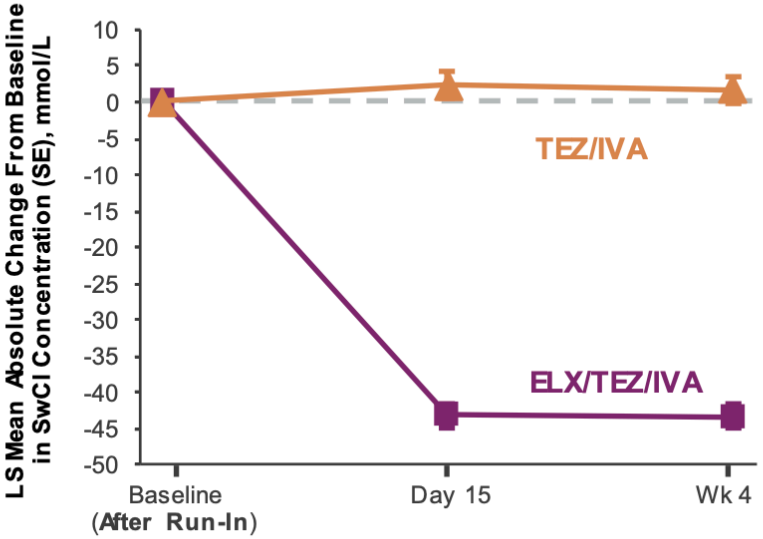
Study 102, *F/MF*

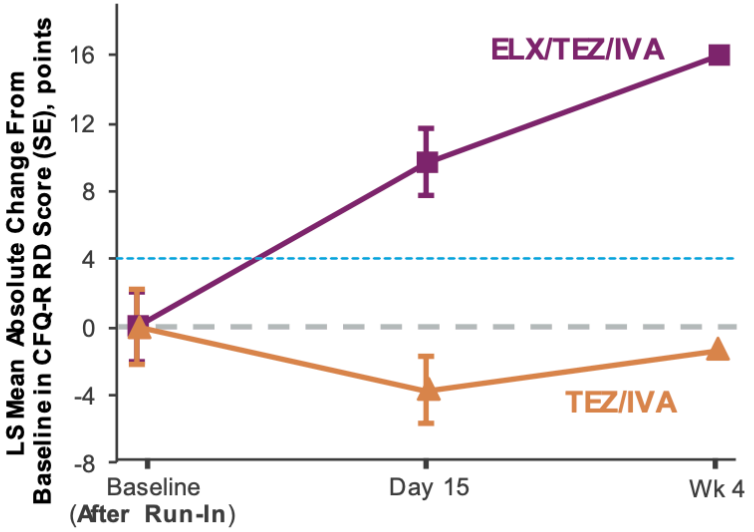






Study 103, *F/F*



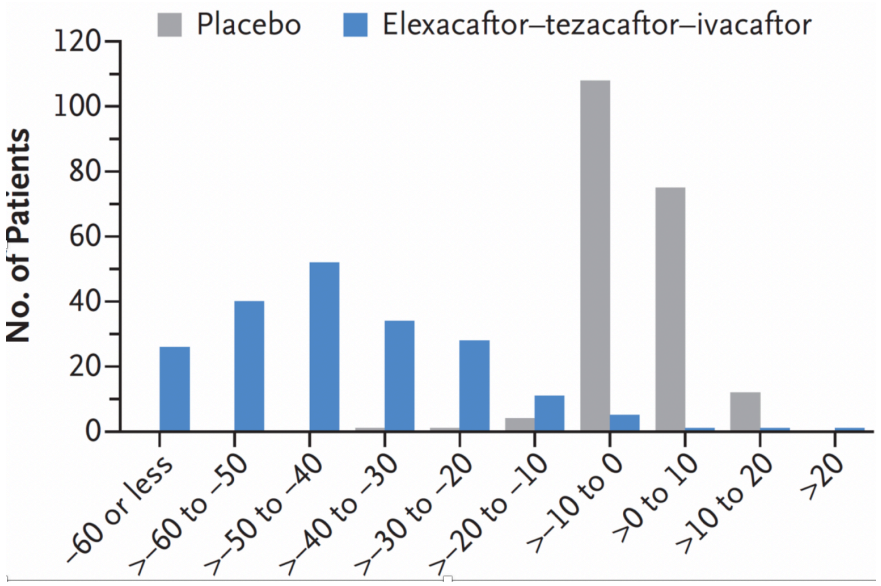


N Engl J Med 2019;381:1809-19.
Lancet. 2019 Nov 23;394(10212):1940-1948

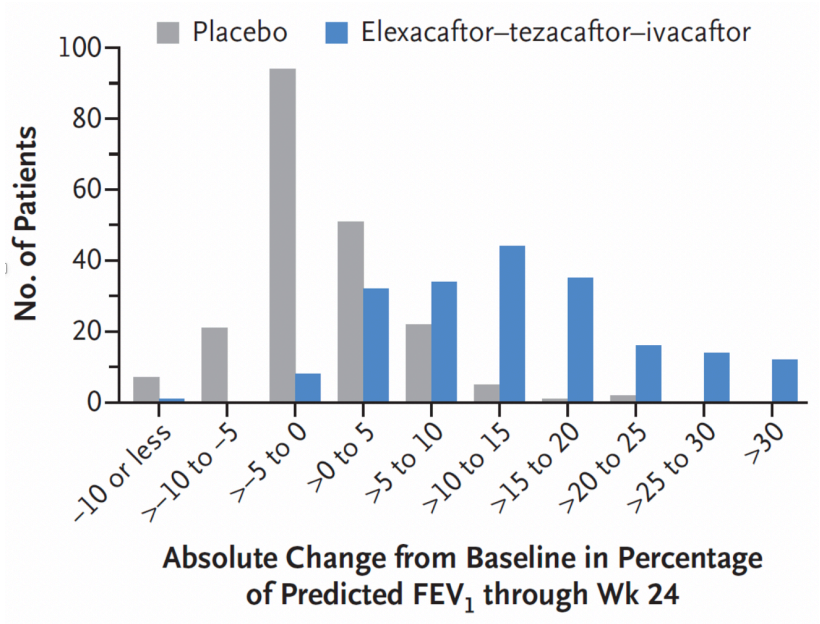
BMI, body mass index; LS, least squares; CFQ-R RD, cystic fibrosis questionnaire-revised respiratory domain; MF, minimal function; MMRM, mixed-effects model for repeated measures; SwCl, sweat chloride.
Data are LS means based on an MMRM; dotted blue line indicates a change in 4 points, which is the minimal clinically important difference for pwCF with stable disease.[1] **1.** Quittner AL, et al. *Chest* 2009; 135: 1610-1618.

Individual Responses to Elexacaftor-Tezacaftor-Ivacaftor

Sweat Chloride



Change in ppFEV1



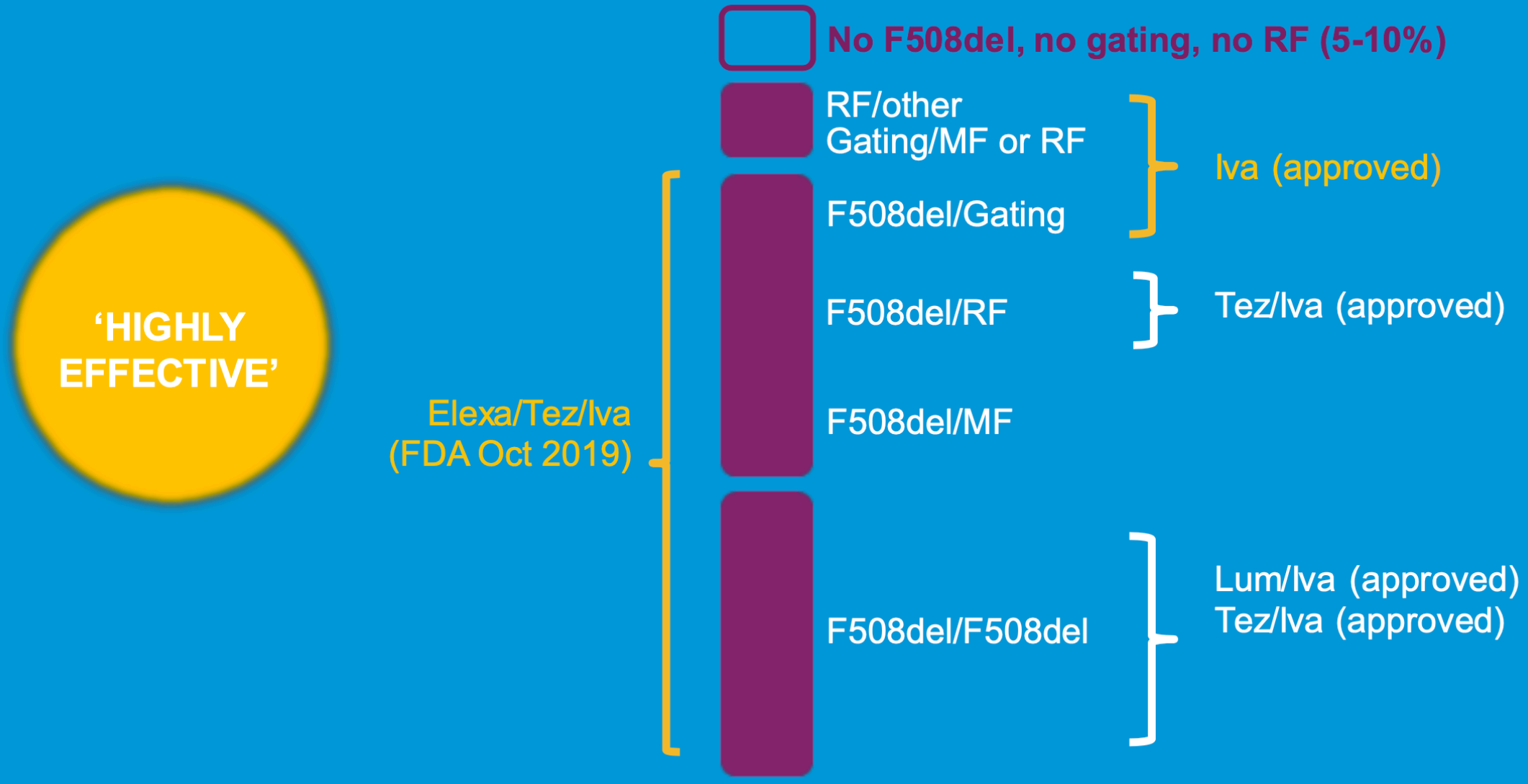
N Engl J Med 2019;381:1809-19.
Lancet. 2019 Nov 23;394(10212):1940-1948

Adverse Events: Elexacaftor-Tezacaftor-Ivacaftor

Most Common (≥10%) AEs			SAEs, Discontinuations, Deaths			Other Events		
	Placebo (N=201),[a] %	ELX/TEZ/IVA (N=202),[a] %		Placebo (N=201), %	ELX/TEZ/IVA (N=202), %		Placebo (N=201), %	ELX/TEZ/IVA (N=202), %
Infective PEx	47.3	21.8	**SAEs (≥2 pts in either arm)**	20.9	13.9	**ALT/AST AEs**	4.0	10.9
Sputum increased	19.4	19.8	Infective PEx	16.4	5.4	**ALT/AST elevations**		
Headache	14.9	17.3	Influenza	0	1.5	>3× ULN	5.5	7.9
Cough	38.3	16.8	Rash events[b]	0.5	1.5	>5× ULN	1.5	2.5
Diarrhea	7.0	12.9	Hemoptysis	1.5	1.0	>8× ULN	1.0	1.5
URTI	10.9	11.9	**Discontinuations due to AEs**	0	1.0	**Rash events[b]**	6.5	10.9
Nasopharyngitis	12.9	10.9	Rash	0	0.5	**AEs of creatine kinase elevation**	4.5	9.9
Oropharyngeal pain	12.4	9.9	Portal Hypertension	0	0.5			
Hemoptysis	13.9	5.4	**No deaths in either arm**					
Fatigue	10.0	4.5						

N Engl J Med 2019;381:1809-19.
Lancet. 2019 Nov 23;394(10212):1940-1948

Modulator Landscape



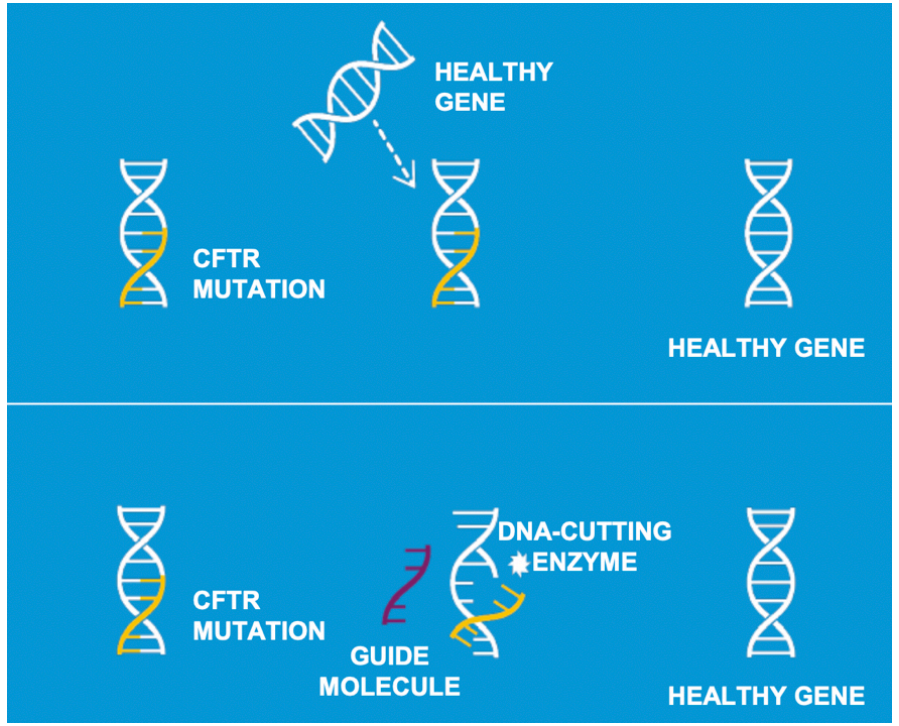
MF = minimal function
RF = residual function

What's next?

- Screening for Nonsense Mutations (premature translational stop codons such as W1282X or G542X)
  - High throughput/robotic screening of over 1,300,000 compounds
  - Modified Aminoglycosides (Phase 2 Trials)

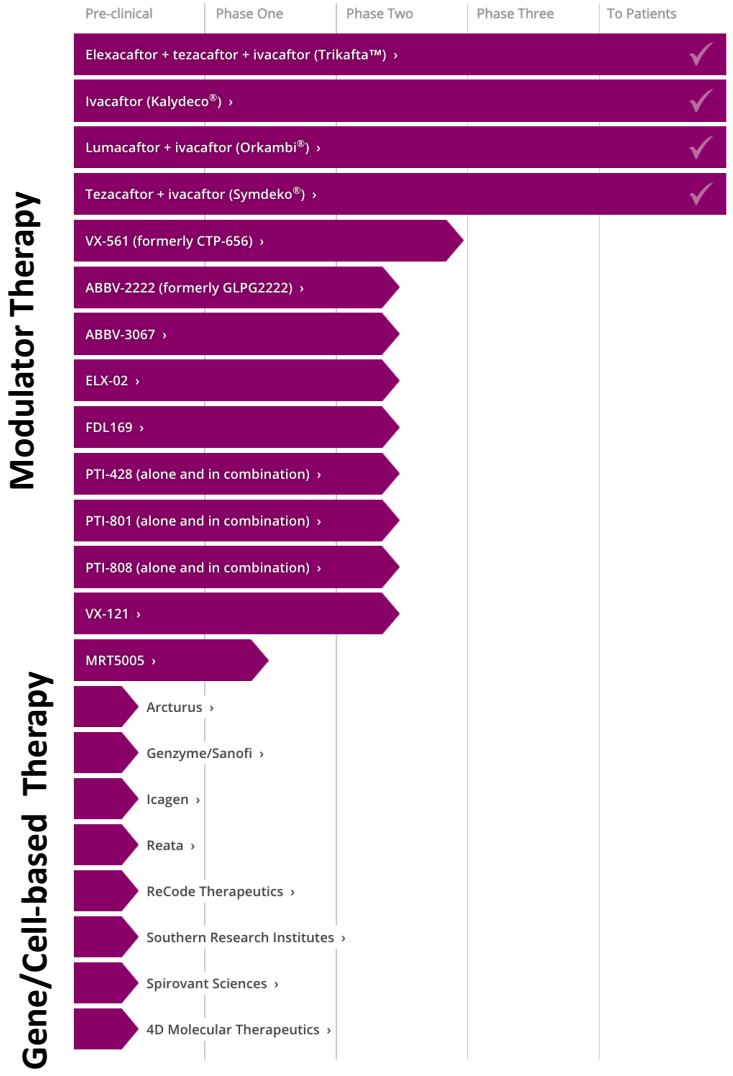
- RNA-based Therapy (All patients potentially benefit)
  - tRNA
  - mRNA (upcoming Phase I trial)
  - Anti-sense oligonucleotides

- Gene Therapy and Gene Editing
  - -Transferring and expressing a normal CFTR gene to appropriate airway cells
  - Repairing CFTR mutations in a patients own cells with CRISPR-CAS9 and other technologies
  - Challenges:
    - Optimal vector for transfer: AAV, Adenovirus, Lentivirus, non-viral
    - Immune Tolerance of the vector and corrected protein



CF Therapy Pipeline

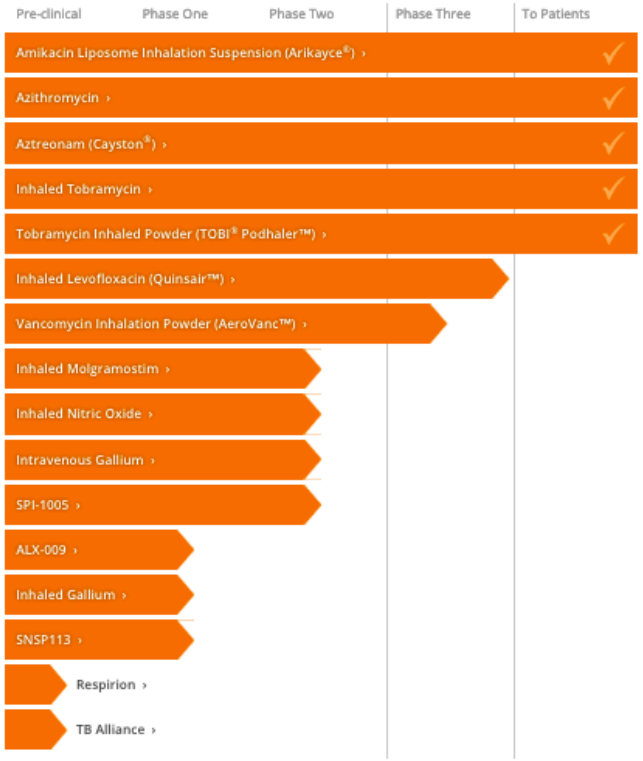
Restore CFTR Function



Mucociliary Clearance

Anti-inflammatory

Anti-infective



Nutritional-GI-Other

Anti-Infective Therapy

Anti-fungal therapy

Non-tuberculous mycobacteria

Phage Therapy

CF airway fungal infections

- *Aspergillus spp* are associated with accelerated loss of lung function
- Allergic Bronchopulmonary Aspergillus
- The decision to treat CF airway fungal infection uses a similar approach as NTM
  - Recurrent positive culture
  - Radiographic evidence
  - *Clinical Instability*
  - Treat underlying CF aggressively
- Therapy guidelines do not exist
  - When possible use drug levels to guide therapy
  - Drug susceptibility testing (association with medical outcomes are not established).
  - Consider synergistic combinations between azoles, echinocandins, amphotericin and terbinafine
  - Induction therapy for 1-2 months (2-3 drugs)
  - Consolidation:
    - Minimum of 4-6 months of azole or terbinafine +/- inhaled amphotericin

In vitro susceptibility of fungi to common anti-fungals

	Fluc	Itra	Vori	Posa	Isavu	Echino	Ampho B	Terb
C. albicans, parapsilosis, tropicalis	+	+	+	+	+	+	+	+
C. glabrata	±	±	+	+	+	+	+	+
C. Krusei	-	±	+	+	+	+	+	+
C. auris	-	-	-	-	-	+	±	+
A. fumigatus, flavus, niger	-	+	+	+	+	+	+	+
A. terrus	-	+	+	+	+	+	-	+
S apiospermium	-	±	+	+	+	-	±	+
S. prolificans	-	-	±	±	-	-	-	+
Penicillium spp	±	±	±	±	+	+	±	+
Exophiala spp	-	+	+	+	+	±	+	+
Trichosporin spp	±	+	+	+	+	-	-	+

Non-tuberculous Mycobacteria

MAC/MAI: Standard Therapy. 3 Requried

Severe Disease (almost all CF patients fall into this category) consider qd dosing and not TIW
Consider 4-12 weeks of Amikacin IV (TIW) for severe disease.

First line selections

Rifampin	Cannot by used in conjunction with CFTR modulators
Ethambutol	
Azithromycin	

Second line selections

Clofazimine	Preferred agent if rifampin is not used.
Amikacin Inh	
Bedaquiline PO	
Tedizolid (IV or PO)	
Moxifloxacin PO	
Amikacin (IV or Inh)	

Non-tuberculous Mycobacteria

M. abscessus induction (4 reaquired *ssp abscessus;* 3 required for *ssp massillense)*

Length of induction: At least one month

Selections are based on tolerance and in vitro susceptibility when available.

First line selections

Amikacin IV	Consider nebulized form for contraindications
Imipenem IV	
Azithromycin (IV or PO)	
Linezolid IV	

Second line selections

Amikacin Inh	
Cefoxitin IV	
Tigecycline IV	
Eravacycline IV	
Omadacycline IV or PO	Possibly better tolerated than tigecycline
Tedizolid (IV or PO)	Prefered over linezolid if tolerated and available.
Clofazimine PO	
Bedaquiline PO	
Moxifloxacin PO	

Non-tuberculous Mycobacteria

M. abscessus continuation (4 reaquired *ssp abscessus;* 3 required for *ssp massillense)*

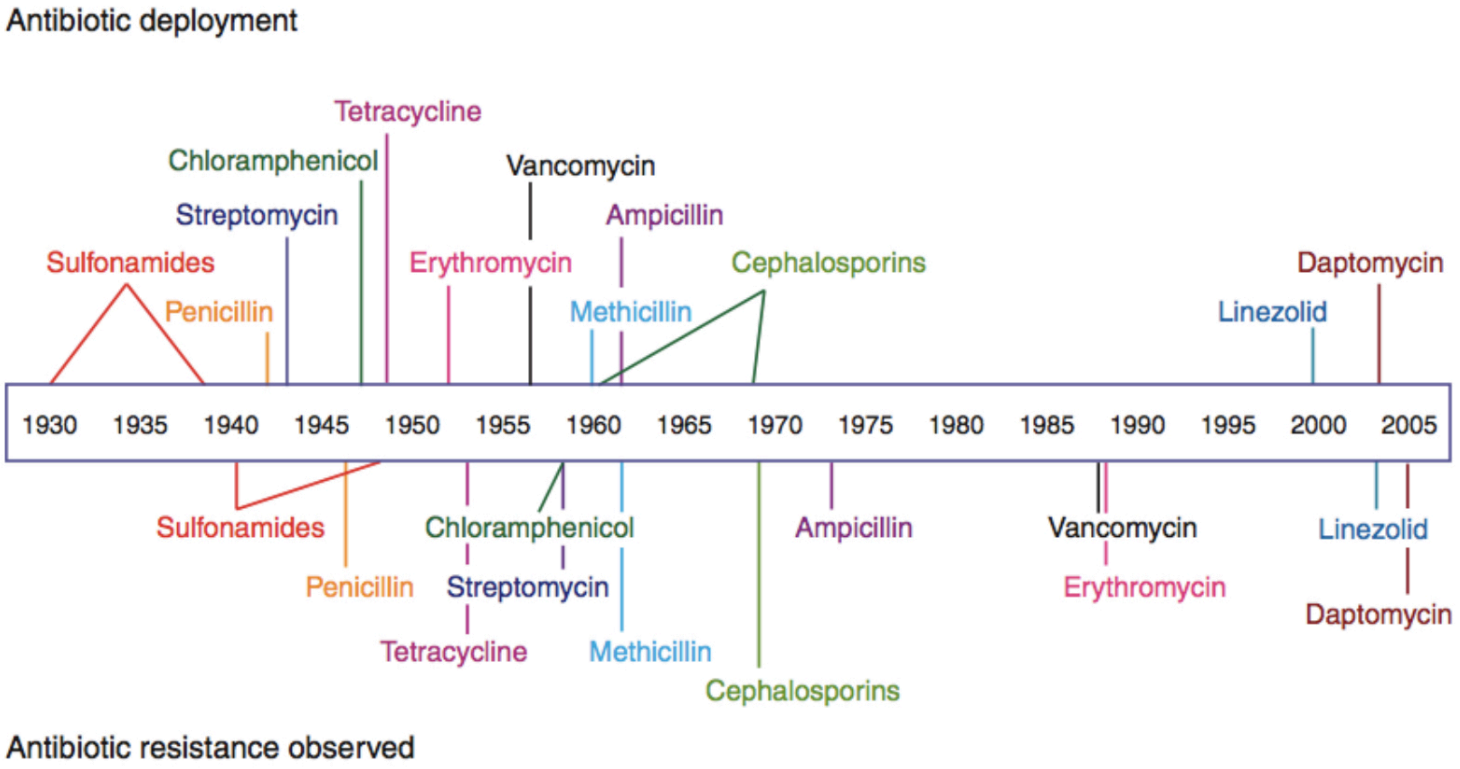
First line selections

Amikacin Inh
Azithromycin (IV or PO)
Linezolid IV
Moxifloxacin PO

Second line selections

Clofazimine PO
Bedaquiline PO
Tedizolid (IV or PO)
Minocycline PO
Omadacycline IV or PO
Imipenem IV
Cefoxitin IV
Tigecycline IV
Eravacycline IV

No Fundamentally New Antibiotics Have Been Discovered for 20 Years



1934 Commissioned JAMA Report

BACTERIOPHAGE THERAPY

REVIEW OF THE PRINCIPLES AND RESULTS OF THE USE OF BACTERIOPHAGE IN THE TREATMENT OF INFECTIONS

MONROE D. EATON, M.D.
AND
STANHOPE BAYNE-JONES, M.D.
NEW HAVEN, CONN.

The purpose of this report is (*a*) to present summaries and discussions of (1) the experimentally determined facts relating to the bacteriophage phenomenon, (2) the laboratory and clinical evidence for and against the therapeutic usefulness of bacteriophage and (3) the relation of so-called antivirus to materials containing bacteriophage, and (*b*) to serve as a basis for a survey of the status of some of the commercial preparations. As it is impossible to include in this article an abstract of the whole voluminous and contradictory literature on these subjects, we have summarized only the papers and reviews that have appeared to us to be the most significant.

1941: Second AMA report further discredits the "d'Herelle" phage theory

Council on Pharmacy and Chemistry

BACTERIOPHAGE THERAPY: II.

IN 1934 THERE WAS PUBLISHED IN THE JOURNAL UNDER THE AUSPICES OF THE COUNCIL A SERIES OF ARTICLES ON THE STATUS OF BACTERIOPHAGE THERAPY, BY DRS. EATON AND BAYNE-JONES. RECENTLY THE COUNCIL FELT THAT SUBSEQUENT DEVELOPMENTS IN THIS FIELD MIGHT WARRANT A RESTUDY OF THIS SUBJECT. DR. A. P. KRUEGER, PROFESSOR OF BACTERIOLOGY AT THE UNIVERSITY OF CALIFORNIA AND HIS COLLEAGUE, DR. E. JANE SCRIBNER, KINDLY AGREED TO MAKE THE NECESSARY STUDY AND TO WRITE A REPORT. THEIR REPORT, WHICH FOLLOWS, HAS BEEN ADOPTED BY THE COUNCIL AND AUTHORIZED FOR PUBLICATION. IN AUTHORIZING THE PUBLICATION, THE COUNCIL EXPRESSES ITS GRATITUDE TO DRS. KRUEGER AND SCRIBNER FOR THEIR EXCELLENT STATUS REPORT.

OFFICE OF THE COUNCIL.

THE BACTERIOPHAGE

ITS NATURE AND ITS THERAPEUTIC USE

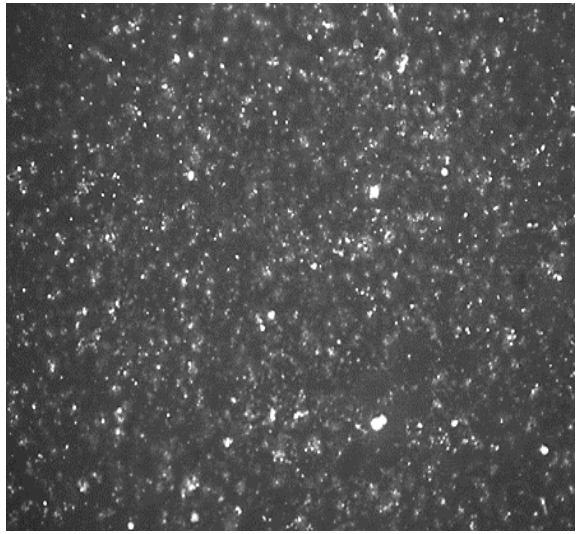
ALBERT PAUL KRUEGER, M.D.
AND
E. JANE SCRIBNER, PH.D.
BERKELEY, CALIF.

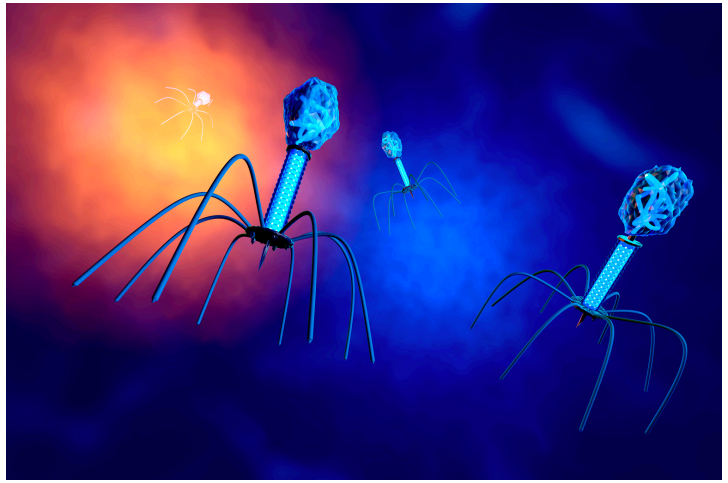
There appeared in THE JOURNAL during December 1934 a series of articles on bacteriophage therapy by Drs. M. D. Eaton and Stanhope Bayne-Jones.[1] The phases of the subject covered included the experimentally determined facts relating to the bacteriophage phenomenon, the laboratory and clinical evidence for

Courtesy of Ryland Young, Texas A&M University

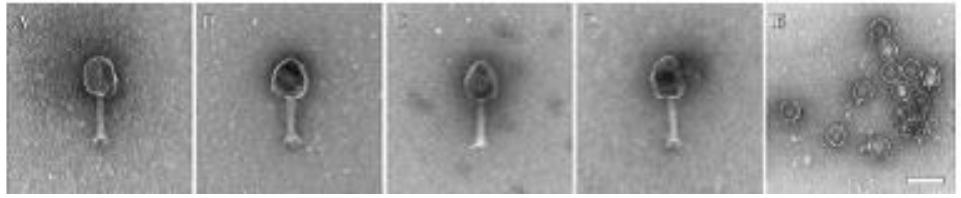
Bacteriophage

Epifluorescence: Light Microscopy





Electron Microscopy

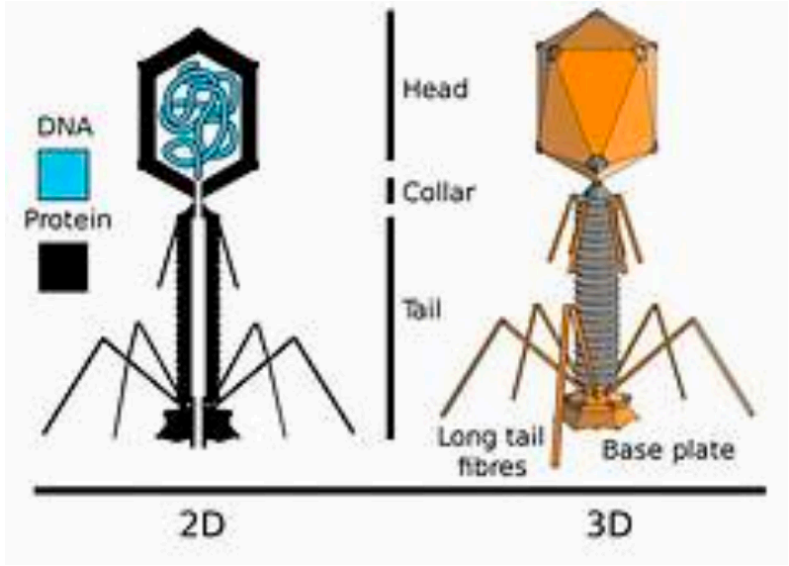


AbΦ1 AbΦ4 AbΦ71 AbΦ97 AbTP3Φ1

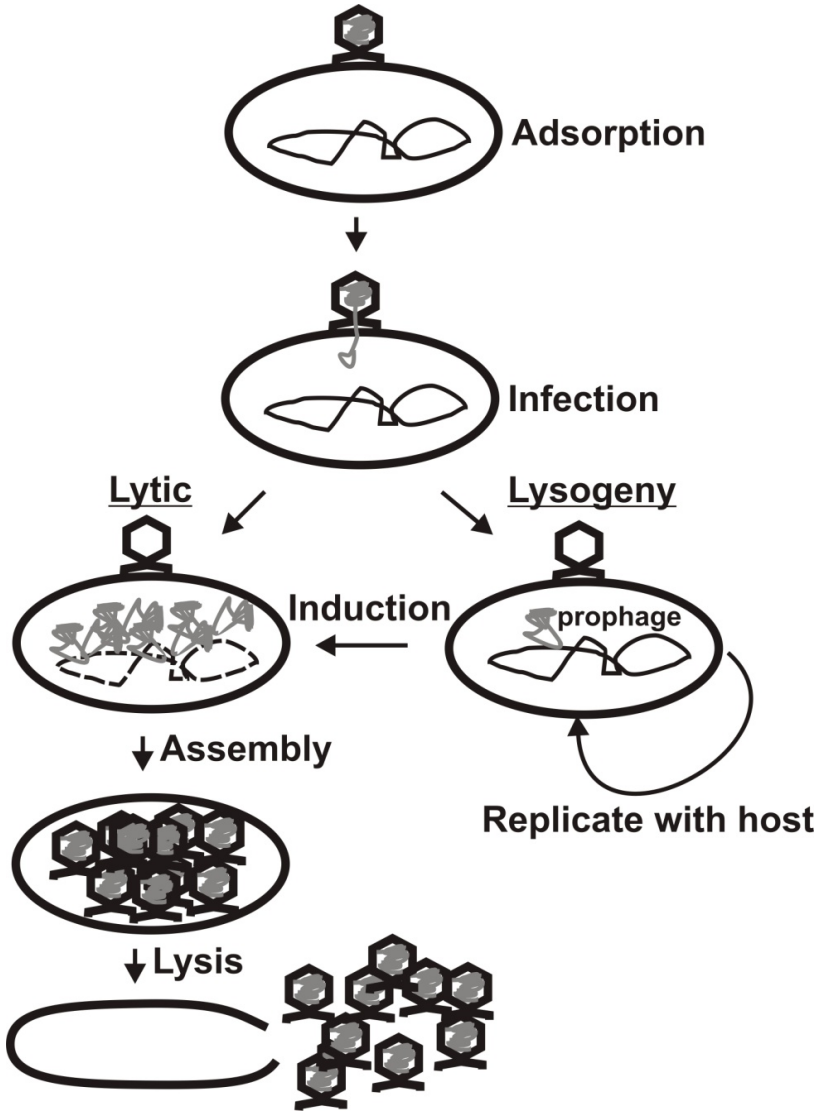
Myophages

Podophage

Schooley, et. al.,Antimcrob Ag Chemother, 2017



Phage Therapy: Bacteriophage Life Cycle

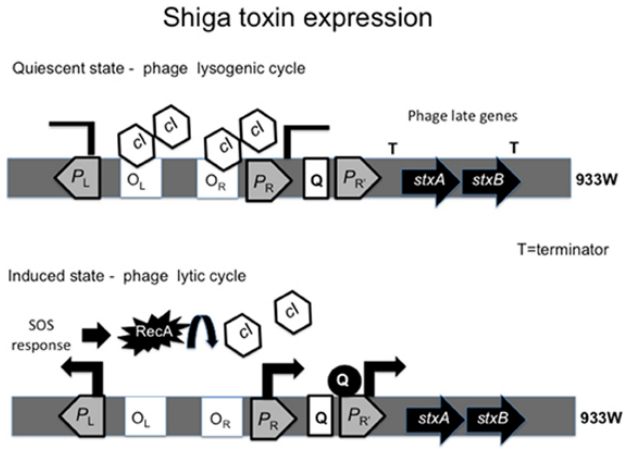


a lysogen is a cell containing a prophage/provirus

majority of bacterial pathogens are lysogens

bacteria in high density ecosystems are often lysogens (Knowles, Silveira *et al.* 2016)

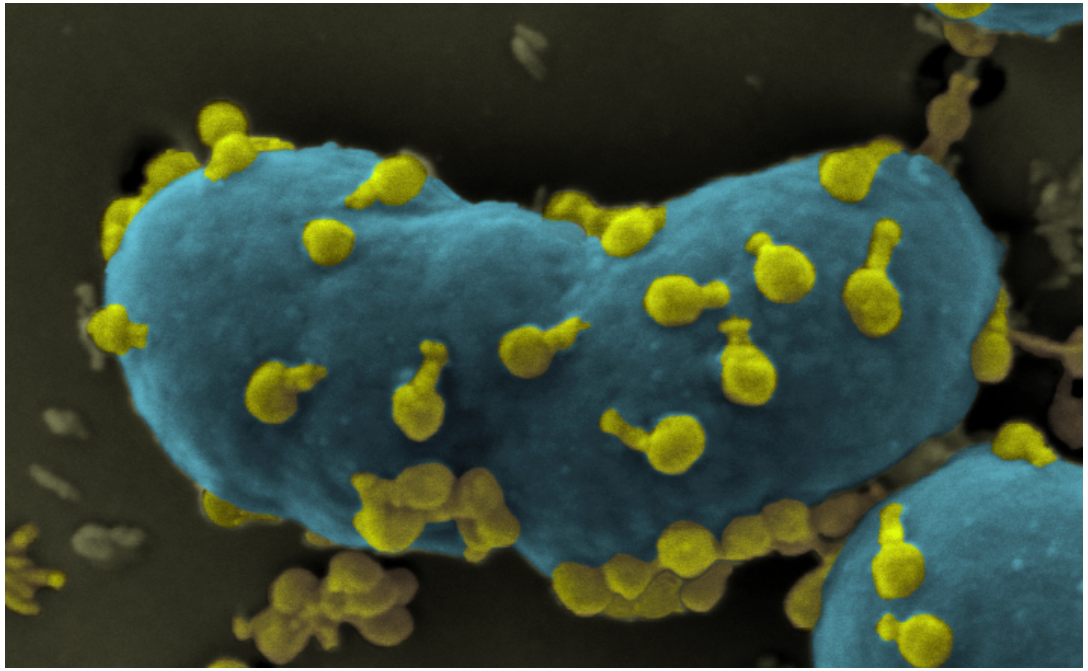
prophage carry virulence factors



https://doi.org/10.3389/fcimb.2012.00081

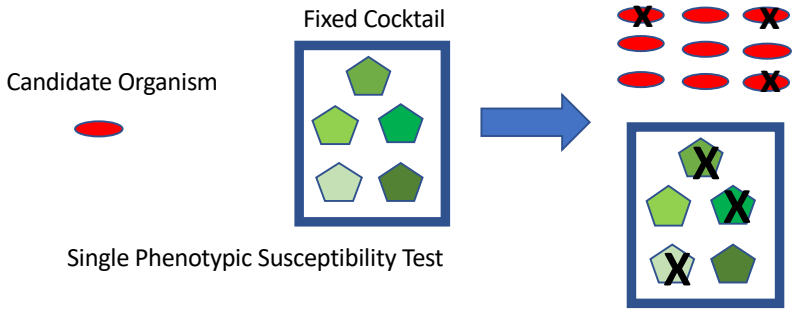
What Other Factors Might Contribute to Phage Therapy Success

- Synergistic or additive activity with antibiotics
- Capsular changes resulting in reduced invasiveness
- Enhancement of pathogen specific immune responses
- Biofilm disruption
- Phage Library Availability
  - *Staphylococcus spp*
  - *Pseudomonas spp*
  - *E. Coli spp*
  - *Acinetobacter spp*
  - *Achromobacter spp*
  - *M abscessus*



Bacteriophage Approaches

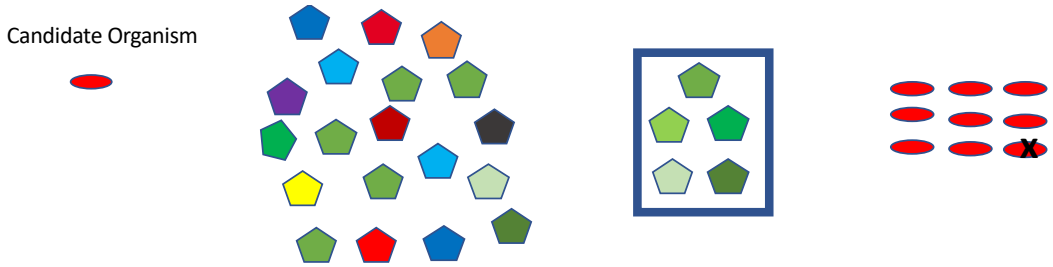
Fixed Phage Cocktails



Advantages
Phage cocktail is pre-prepared and ready to administer

Disadvantages
Not all organisms will be susceptible to the fixed cocktail
Limited to organisms with broad host range phage (*S. aureus/P. aeruginosa*)
Not all phage in the cocktail are active against any given bacterium
When resistance develops there is no backup plan

Custom Phage Cocktails



Advantages
Broader spectrum of bacteria can be approached
Every phage in the cocktail is active
Second generation phage cocktail can be. created for resistance

Disadvantages
Requires more time to prepare
May be more expensive

Phage: Biological Challenges as Therapeutic Agents

- **Lysogeny: shuffle bacterial resistance and/or pathogenicity genes**

- **High degree of specificity for bacterial targets**
  - **Species specific**
  - **Each phage kills only a subset of the bacteria in a given species**

- **Ecological considerations in complex lung infections**
  - **What microbial population (bacterial, fungal) will fill in the niche vacated by the lysed populations?**

- **Selection of bacteria for phage resistance**
  - **Receptor changes by bacteria**
  - **Destruction of phage nucleic acid by endonuclease.**

- **Unknown Unknowns**

Questions?

Identification of the Cystic Fibrosis Gene: Chromosome Walking and Jumping

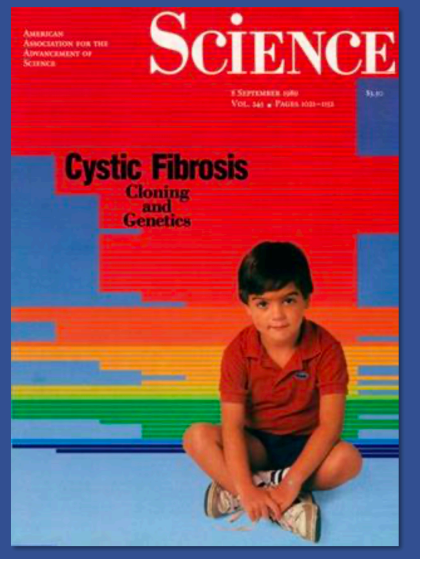
Johanna M. Rommens, Michael C. Iannuzzi, Bat-sheva Kerem, Mitchell L. Drumm, Georg Melmer, Michael Dean, Richard Rozmahel, Jeffery L. Cole, Dara Kennedy, Noriko Hidaka, Martha Zsiga, Manuel Buchwald, John R. Riordan, Lap-Chee Tsui, Francis S. Collins

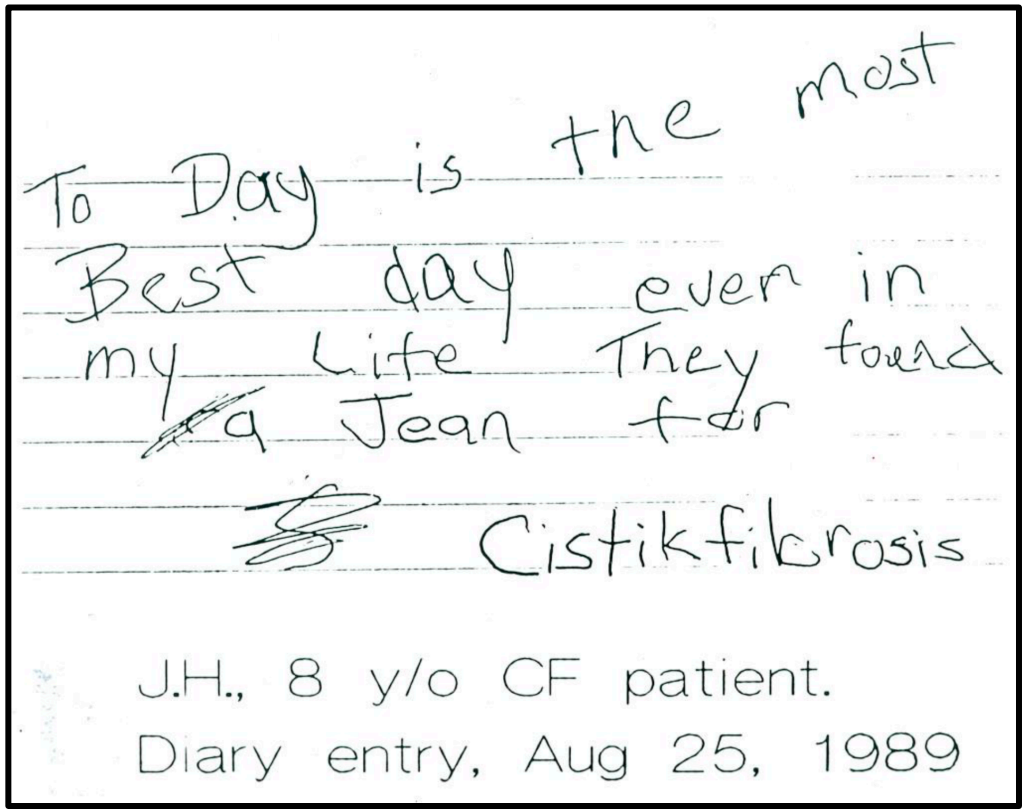
Identification of the Cystic Fibrosis Gene: Cloning and Characterization of Complementary DNA

John R. Riordan, Johanna M. Rommens, Bat-sheva Kerem, Noa Alon, Richard Rozmahel, Zbyszko Grzelczak, Julian Zielenski, Si Lok, Natasa Plavsic, Jia-Ling Chou, Mitchell L. Drumm, Michael C. Iannuzzi, Francis S. Collins, Lap-Chee Tsui

Identification of the Cystic Fibrosis Gene: Genetic Analysis

Bat-sheva Kerem, Johanna M. Rommens, Janet A. Buchanan, Danuta Markiewicz, Tara K. Cox, Aravinda Chakravarti, Manuel Buchwald, Lap-Chee Tsui





UPDATES ON LUNG TRANSPLANT: FROM CLINIC TO SURGERY AND BEYOND

Lorriana Leard, MD
UC San Francisco
Professor of Clinical Medicine

George E. Chaux, MD, FCCP
Cedars Sinai Medical Center
Medical Director, Lung Transplant Program

Doug Conrad, MD
UC San Diego
Director, Adult CF program
Pulmonary Critical Care Clinical Service Chief

Alyssa Perez, MD
UC San Francisco
Fellow, Pulmonary and Critical Care Medicine

Saturday, January 18, 2020 – 3:55 p.m. – 5:05 p.m.

Lorriana Leard, MD
UC San Francisco
Professor of Clinical Medicine

Lorriana Leard, MD is Professor of Clinical Medicine at the University of California San Francisco. She received her undergraduate degree from Stanford University and her M.D. from the University of California San Diego. After completing her Internal Medicine residency at the University of Texas Southwestern in Dallas, she came to the University of California San Francisco for her Pulmonary and Critical Care Fellowship where she also completed an additional subspecialty fellowship in Advanced Bronchoscopy and Lung Transplantation. She is currently the Vice Chief of Clinical Operations for the UCSF Division of Pulmonary, Critical Care, Allergy, and Sleep Medicine and has an emphasis in medical education. She specializes in the care of patients with lung cancer and advanced lung diseases who are candidates for lung transplants. Dr. Leard is the current president of the California Thoracic Society. She serves on Item Review Committees for the National Board of Medical Educators and is an Editorial Board Consultant for the Journal of Heart and Lung Transplantation.

George E. Chaux, MD, FCCP
Cedars Sinai Medical Center
Medical Director, Lung Transplant Program

George E. Chaux, MD, FCCP is Medical Director of the Lung Transplant Program at Cedars- Sinai Medical Center. Board certified in internal medicine, Dr. Chaux has specialized certification in pulmonary medicine and in critical care medicine. His primary areas of research and clinical interest involve state-of-the-art diagnosis, treatment and postoperative management strategies for lung transplant patients and individuals with pulmonary arterial hypertension and idiopathic pulmonary fibrosis. In addition, he is actively involved in developing the interventional pulmonology program at Cedars-Sinai Medical Center which includes the advanced use of rigid bronchoscopy with laser treatment of airway tumors, stenting of airway strictures and the introduction of new technologies such as SuperDimension for the biopsy of peripheral lung lesions and endobronchial ultrasound for the biopsy of mediastinal lymph nodes.

Dr. Chaux has made numerous presentations at professional symposia, and he has written articles for peer-reviewed publications, including *Circulation*, *Clinical Infectious Diseases*, *Critical Care Medicine, Transplantation, The Lancet, The Annals of Thoracic Surgery and the Annals of the American Thoracic Society*. He is a fellow of the American College of Chest Physicians and a member of the American College of Physicians, American Thoracic Society, California Thoracic Society and International Society of Heart and Lung Transplantation.

Dr. Chaux received his bachelor's degree from Bowdoin College in Brunswick, Maine and his medical degree from Boston University School of Medicine. At the University of California, San Diego Medical Center, he completed an internship and residency in internal medicine, serving

as Chief Resident, and a fellowship in pulmonary and critical care medicine. He also served as Medical Director of the Lung and Heart-Lung Transplant Program at UCSD following his training and before coming to Cedars-Sinai Medical Center.

Over the past twelve years, the lung transplant program at Cedars-Sinai Medical Center has grown tremendously under the direction of Dr. Chaux. The program is now averaging more than twenty lung transplants a year with excellent outcomes. We are a Medicare certified program and a number of third party payers such as Kaiser Permanente and Blue Cross are now contracted with Cedars-Sinai Medical Center as a center of excellence for lung transplantation which has increase our volume even further. A second new faculty member was added to the program in 2006 and a third new faculty member was added to the program in subsequent years. We also have a pulmonary fellow assigned to the lung transplant service for every month of the year thereby improving the training of our fellows in pulmonary and critical care medicine. With the growing volume of lung transplants that are being done, there is now ample opportunity to launch new clinical investigations. Current studies that being carried out or that are being planned include outcomes of combined lung and kidney transplantation, an investigation into the impact of non-HLA antibodies on the acute rejection process in lung transplantation and an investigation into the impact of auto-antibodies on the acute rejection process in lung transplantation.

Dr. Chaux has been actively involved in Medicine and Pulmonary Grand Rounds, teaching of medical students, residents and interns and in the education of nursing staff regarding the care of patients who are candidates for and have received lung transplants. He has been invited to give numerous lectures at other academic institutions such as UC Irvine and Harbor UCLA. He was recently invited to deliver a lecture at a symposium of an international meeting of the Latin-American Association of Thoracic Medicine in Colombia. He actively participates in the annual meeting of the International Society for Heart and Lung Transplantation. In addition, Dr. Chaux is an active member of the Heart-Lung Committee of the local organ procurement organization, OneLegacy, and he is involved in community outreach programs that raise donor organ awareness and promote Cedars-Sinai Medical Center as a leader in the care of patients with advanced lung disease.

Doug Conrad, MD

UC San Diego

Director, Adult CF program

Pulmonary Critical Care Clinical Service Chief

Douglas Conrad, MD received his Medical Degree from Case Western Reserve University. His post graduate studies include Internal Medicine training at the University of Minnesota Affiliated Hospitals and Pulmonary/Critical Care and research training at the University of California San Francisco. Currently he is the director of the UC San Diego Adult CF program, serves as the UCSD Pulmonary Critical Care Clinical Service Chief. His research interests include CF airway inflammation and airway microbiome, CF related airway infection phage therapy, and is the UCSD site principal investigator for the COPD Gene Network. He is Professor of Medicine at UC San Diego.

Alyssa Perez, MD

UC San Francisco

Fellow, Pulmonary and Critical Care Medicine

Alyssa Perez received her BA from Haverford College in 2007 with a major in Religion and minor in Spanish. She completed her pre-medical requirements at the University of Pennsylvania in 2009. She received her MD and graduated summa cum laude from Jefferson Medical College in 2013. She went to Brigham and Women's hospital for Internal Medicine Residency. Following residency, she was the 3rd Nancy and Elliot Comenitz Fellow in Medical Education at Brigham and Women's Hospital. As part of this fellowship, she received her EdM from Harvard Graduate School of Education in 2017. She is currently a third-year fellow in Pulmonary and Critical Care Medicine at the University of California San Francisco. She is interested in cystic fibrosis and lung transplant and is currently spending a dedicated year of training in lung transplant and CF.

CALIFORNIA THORACIC SOCIETY
A chapter of the American Thoracic Society

CF and Lung Transplant

Alyssa A. Perez MD, EdM
Lung Transplant and Advanced Lung Disease Fellow
University of California, San Francisco

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Disclosures

- I have no disclosures

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The Case

- A 24F with a history of CF (delta F508/1717-1-G-T) diagnosed at age 2 (FEV_1 0.77L, 25% predicted)
- At age 11, she had her first hospitalization
- At age 12, she was diagnosed with *Mycobacterium Abscessus* and has been on/off antibiotic therapy since this time
- She requires frequent antibiotics for pseudomonas
- She developed dyspnea about 5 years ago

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The Case

- She has trouble maintaining her weight and had a PEG placed this year for supplemental tube feeds.
  - BMI currently 19
- At age 24, she developed a spontaneous pneumothorax with persistent air leak requiring VATS with pleurodesis and bleb resection
- She started supplemental oxygen following the pneumothorax

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When should patients with CF be referred for Lung Transplant (LTx)?

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What are the contraindications to LTx in this patient?

- A: BMI
- B: She is too early for lung transplant
- C: *M abscessus* infection
- D: History of pleurodesis
- E: No absolute contraindications

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What are the contraindications to LTx in this patient?

- A: BMI
- B: She is too early for lung transplant
- C: *M abscessus* infection
- D: History of pleurodesis
- **E: No absolute contraindications**

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Lung Transplant and *M Abscessus*

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Care of CF patients after LTx

9

Conclusions

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Questions?

- Alyssa.Perez@ucsf.edu

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PANEL DISCUSSION

Questions/Answers with:
Lorriana Leard, MD
George Chaux, MD
Doug Conrad, MD
Alyssa Perez, MD

Saturday, January 18, 2020 – 5:05 p.m. – 5:20 p.m.

CLOSING REMARKS AND POST TEST

Michelle Cao, DO
Stanford University School of Medicine
Clinical Associate Professor
Pulmonary, Critical Care, and Sleep Medicine
Division of Neuromuscular Medicine and Division of Sleep Medicine

Saturday, January 18, 2020 – 5:20 p.m. – 5:30 p.m.

Michelle Cao, DO is a Clinical Associate Professor in the Division of Sleep Medicine and the Division of Neuromuscular Medicine, at the Stanford University School of Medicine. She is board certified in Pulmonary, Critical Care, and Sleep Medicine. She completed internal medicine residency at Loma Linda University in California, then went on to complete Pulmonary and Critical Care fellowship training at Harbor-UCLA Medical Center in Los Angeles, California. She then completed Sleep Medicine fellowship training at Stanford University. Her clinical expertise is in complex sleep-related respiratory disorders and home mechanical ventilation for chronic respiratory failure syndromes. Dr. Cao is the Director of the Adult Noninvasive Ventilation Program for the Neuromuscular Medicine Program at Stanford Health Care. She is actively engaged in training of house staff for Sleep Medicine fellowship and the Neuromuscular Medicine fellowship at Stanford University.