Αντιμετώπιση και παρακολούθηση ιδιοπαθούς πνευμονικής ίνωσης

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- **No conflict of interest**

Outline

- Reconsider Diagnosis
- Monitoring
- Management

Reconsidering diagnosis

Usual interstitial pneumonia pattern in the diagnosis of idiopathic pulmonary fibrosis?

THE LANCET
Respiratory Medicine

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Lancet Respir Med. 2016;4(10):770-772

score of IPF applicable in clinical practice. The diagnosis of pulmonary embolism represents a characteristic example for which the clinical interpretation of the diagnostic test depends on a pretest probability score according to Bayes theorem; a similar approach should be used for the diagnosis of IPF. Thus, in patients with a high clinical likelihood of IPF, a possible UIP pattern will be considered diagnostic of UIP pathology and the term possible will no longer be needed.

Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society White Paper

David A Lynch, Nicola Sverzellati, William D Travis, Kevin K Brown, Thomas V Colby, Jeffrey R Galvin, Jonathan G Goldin, David M Hansell, Yoshikazu Inoue, Takeshi Johkoh, Andrew G Nicholson, Shandra L Knight, Suhail Raoof, Luca Richeldi, Christopher J Ryerson, Jay H Ryu, Athol U Wells

Lancet Respir Med 2018; 6: 138–53

	Typical UIP CT pattern	Probable UIP CT pattern	CT pattern indeterminate for UIP	CT features most consistent with non-IPF diagnosis
Distribution	Basal predominant (occasionally diffuse), and subpleural predominant; distribution is often heterogeneous	Basal and subpleural predominant; distribution is often heterogeneous	Variable or diffuse	Upper-lung or mid-lung predominant fibrosis; peribronchovascular predominance with subpleural sparing
Features	Honeycombing; reticular pattern with peripheral traction bronchiectasis or bronchiolectasis*; absence of features to suggest an alternative diagnosis	Reticular pattern with peripheral traction bronchiectasis or bronchiolectasis*; honeycombing is absent; absence of features to suggest an alternative diagnosis	Evidence of fibrosis with some inconspicuous features suggestive of non-UIP pattern	Any of the following: predominant consolidation, extensive pure ground glass opacity (without acute exacerbation), extensive mosaic attenuation with extensive sharply defined lobular air trapping on expiration, diffuse nodules or cysts

Taking a giant step in the diagnosis of idiopathic pulmonary fibrosis

*Vasilios Tzilas, Dominique Valeyre, Argyris Tzouvelekis, *Demosthenes Bouros*

THE LANCET
Respiratory Medicine

Lancet Respir Med. 2018 Feb;6(2):82-84.

Pretest Probablility

Older age (>60 years), being male, and an increased extent of fibrosis, increase the likelihood of IPF.[6-8] The Fleischner Society incorporates pretest probability into the diagnostic procedure. A clinical context that is typical for IPF includes being older than 60 years, and the exclusion of alternative diagnoses (eg, chronic hypersensitivity pneumonitis, collagen vascular diseases, drug-induced pulmonary toxicity, asbestosis). When the patient's clinical context is not typical of IPF, because of their age or evidence of alternative diagnoses, even the presence of a "definite UIP" pattern is not sufficient to secure a diagnosis of IPF. In such cases, a diagnostic biopsy is advised after multidisciplinary discussion.

Possible →Probable UIP

In the past 5 years, evidence has been mounting that, in the right clinical context, a possible UIP pattern carries enough positive predictive value to diagnose an underlying UIP pathology.[3-5] This increased confidence in CT differentiation of UIP is reflected in the Fleischner Review, since the possible UIP pattern, according to the 2011 guidelines,[2] has been upgraded to a "probable UIP" pattern. This so-called upgrade is not limited to nomenclature but has direct clinical implications. Honeycombing is no longer a prerequisite to avoid tissue biopsy confirmation. Even in the absence of honeycombing, the presence of traction bronchiectasis or bronchiolectasis in a peripheral distribution obviates the need for surgical lung biopsy in the appropriate clinical setting.

Reconsider diagnosis

- IPF diagnosis is a dynamic process
- Basic “silent mimickers”
  - Hypersensitivity pneumonitis
  - Connective Tissue Disease ILD (CTD-ILD)
  - Asbestosis
  - Drug toxicity

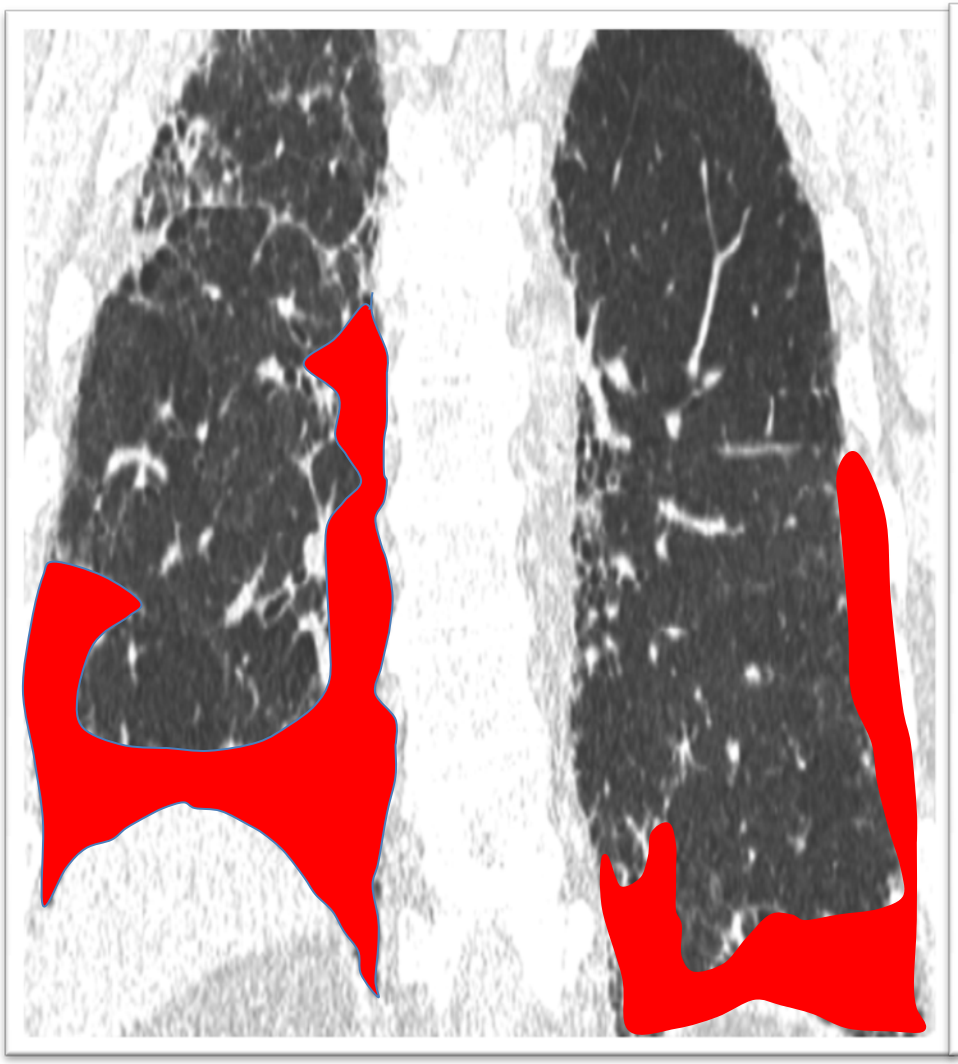
Sometimes the diagnosis is pretty obvious…..

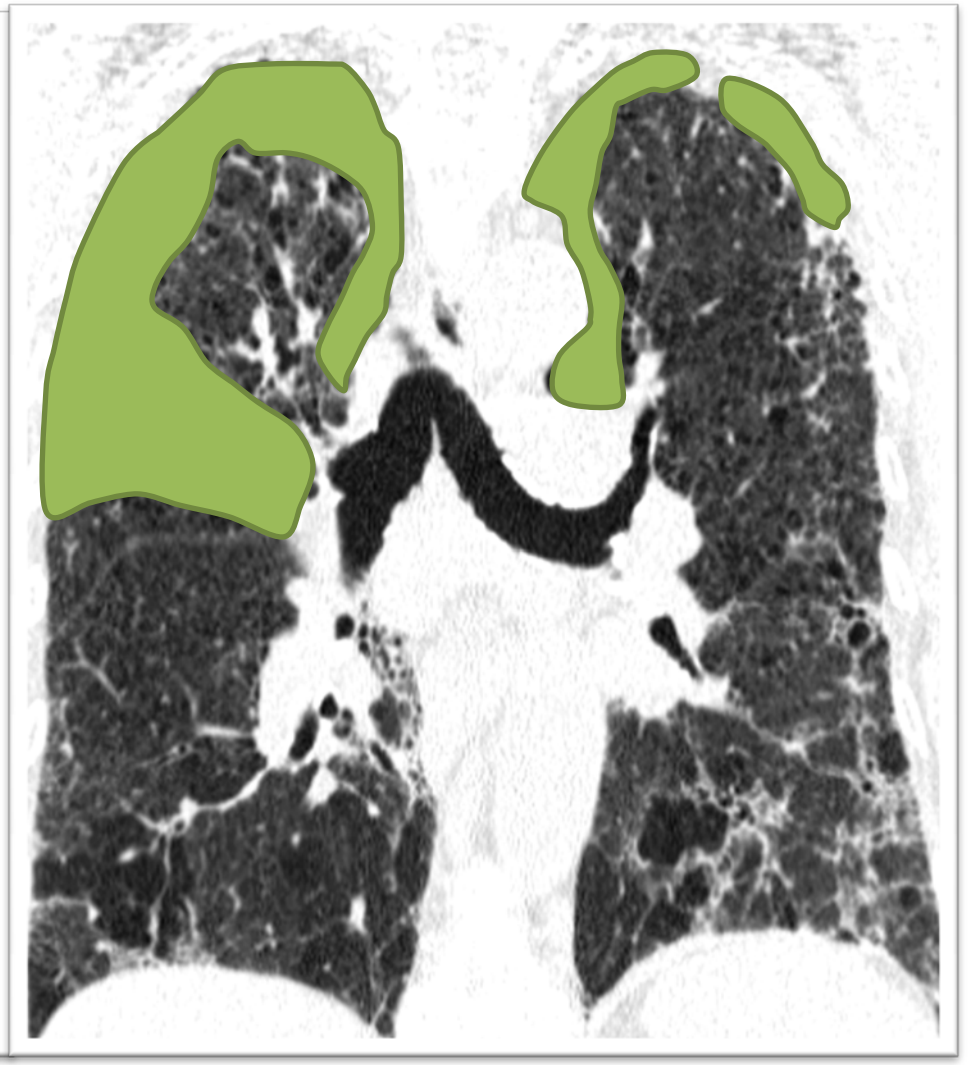
This is not always the case……

- Inciting Antigen is not identified in over 50% of cases
- Not identifying an Inciting Antigen is associated with shortened survival
- This highlights:
- Importance of antigen avoidance
- Difficulties in diagnosis

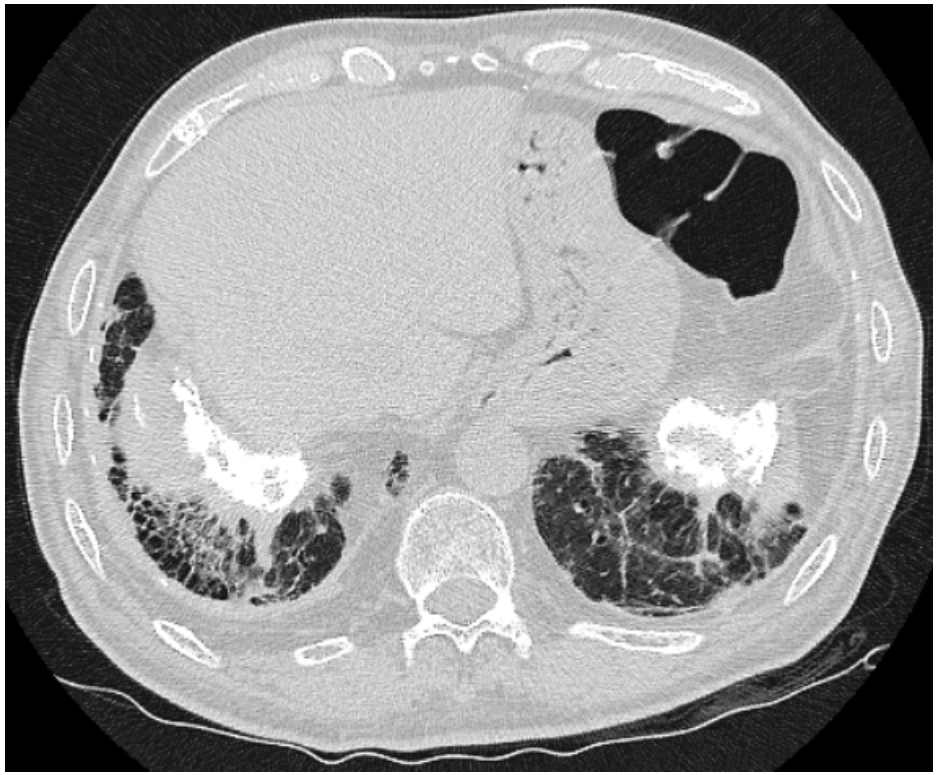
Fernández Pérez ER et al. Chest 2013;144(5):1644-1651.

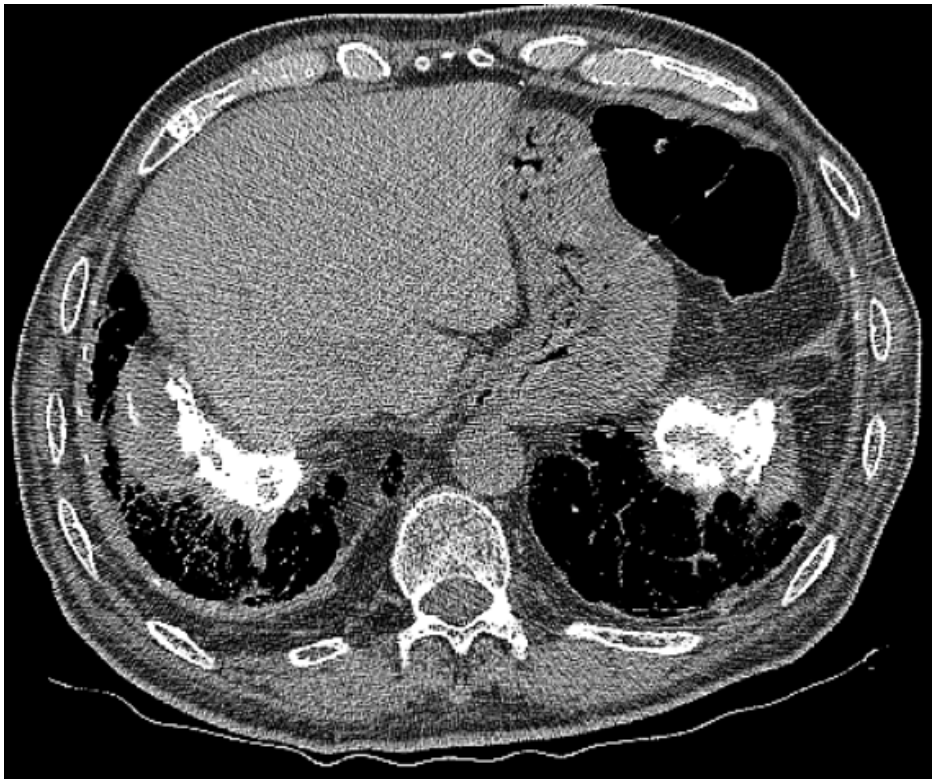
Distribution matters!





Looking outside the parenchyma…





CTD and ILD

- Rheumatoid arthritis (UIP)
- Systemic Lupus Erythematosus
- Scleroderma (f-NSIP)
- Polymyositis-Dermatomyositis (f-NSIP/OP)
- Sjogren syndrome
- Mixed CTD
- Undifferentiated CTD

- **ILD can be the presenting manifestation of CTD**
- **Usual time window: up to 2 years**

- **ANA (up to 1/160) and RF can be seen in IPF**

Monitoring

Patient monitoring

- **Monitoring is based on Pulmonary Function Tests (PFTs), every 3-6 months**

➢ **FVC**

➢ **DLco**

➢ **A decline in FVC ≥10% or DLCO ≥15% over 6 to 12 months predicts an increased risk of mortality**

The response to therapy is NOT monitored by HRCT

Tzilas V et al. Am J Med Sci 2009;338(6):481-5

Patient monitoring

- Clinical examination (3 month interval)
- PFTs (3 month interval)
- 6 minute walk test (3 month interval)

✓ Distance
✓ Desaturation
✓ Pulse Rate Recovery (PRR)

- Heart echo (every 6-12 months)

✓ TRV, RVSP

- Serology
- HRCT (annually)

Patients with IPF and lung cancer: diagnosis and management

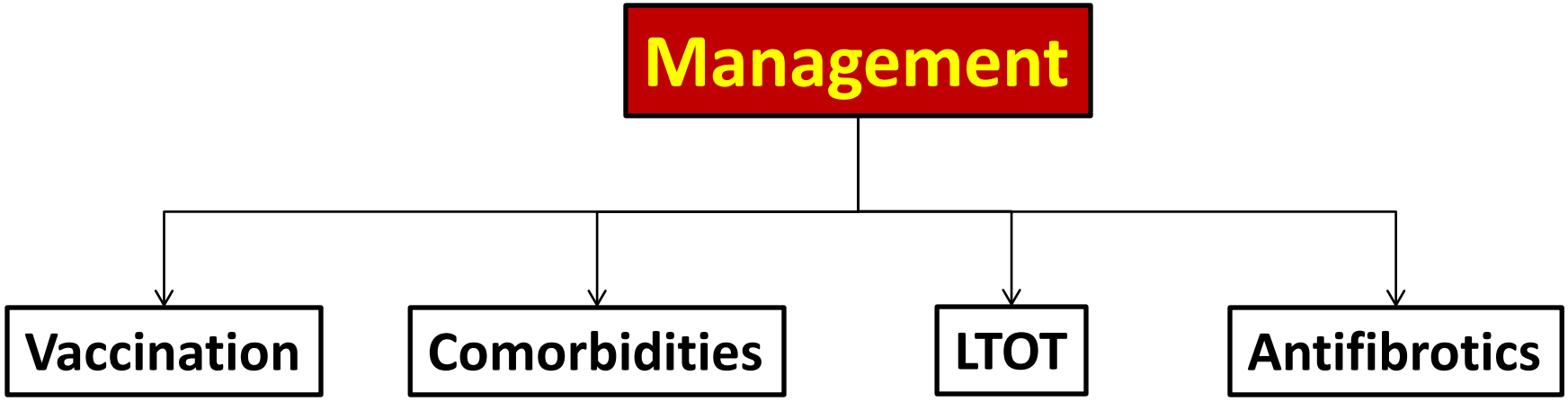
THE LANCET
Respiratory Medicine

*Argyris Tzouvelekis, Paolo Spagnolo, Francesco Bonella, Carlo Vancheri, Vasilios Tzilas, Bruno Crestani, Michael Kreuter, Demosthenes Bouros

Lancet Respir Med. 2018;6(2):86-88

We suggest that patients with IPF should be considered at high risk for lung cancer. Close surveillance with yearly HRCT should be mandatory not only to monitor disease progression but also for early detection of malignancy.

Management


Management
Vaccination
Comorbidities
LTOT
Antifibrotics

Comorbidities in IPF

Pulmonary

1. Parenchymal
- Emphysema
- Cancer
- Infections
2. Vascular
- Pulmonary hypertension
- Thromboembolic disease
3. Other
- Sleep apnea

Extra-pulmonary

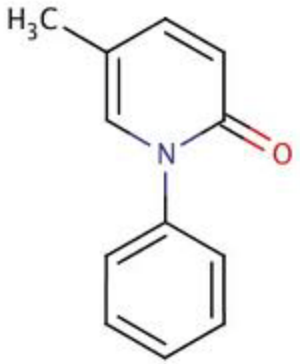
1. Cardiac
- CAD
- Diastolic/ischemic heart failure
2. Gastrointestinal
- GERD
- Nutrition
3. Psychiatric
- Anxiety/depression
4. Endocrine
- Diabetes
- Hypothyroidism
- Vitamin D insufficiency

Antifibrotics

- **Pirfenidone**
- **Nintedanib**
- **Slow disease progression**

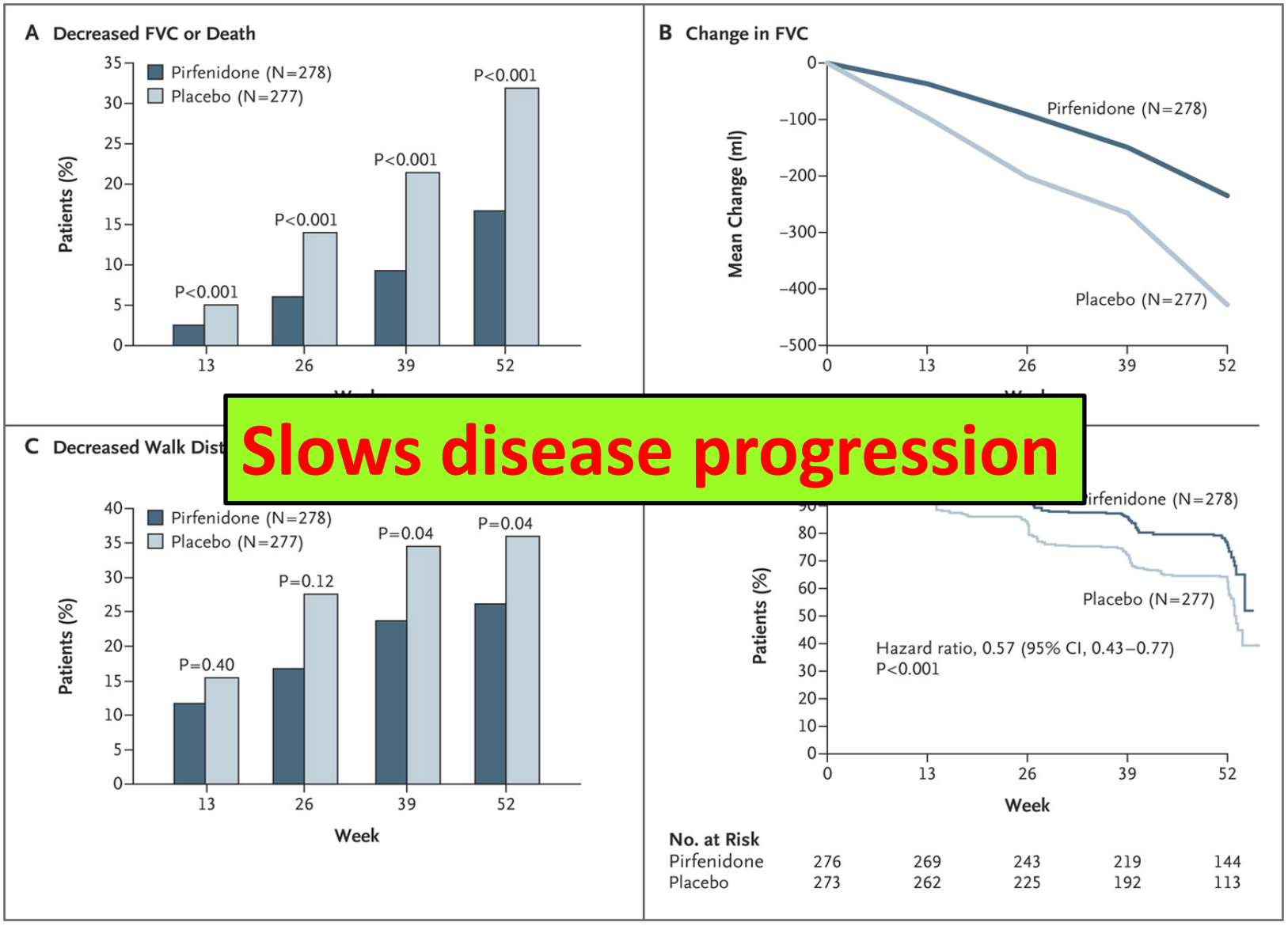
Pirfenidone

- **Primarily anti-fibrotic**
- **Inhibits experimental lung, heart, liver and kidney fibrosis**
- **Reduces *in vitro* fibroblast growth and collagen synthesis**
- **Inhibits production of a number of cytokines important in pulmonary fibrosis**



The precise mechanism of action has not been fully established

Pirfenidone-ASCEND



Slows disease progression

King TE Jr et al. N Engl J Med 2014

Pirfenidone

- **Form: 267 mg capsule**
- **Dose: 3 capsules three times daily (with meals)**

Important Side Effects:

- **Upset stomach, nausea, decreased appetite**
  - **Take pirfenidone with food**
- **Photosensitive rash**
  - **Sunblock with SPF 50 daily**
- **Hepatoxicity**
  - **Regular bloodwork**
  - **Reversible with dose reduction / discontinuation**

Pirfenidone-Drug interaction

- Metabolism is primarily in the liver, cytochrome P450 1A2 (CYP1A2).
- Strong CYP1A2 inhibitors should be avoided (fluvoxamine)
- Moderate CYP1A2 inhibitors (ciprofloxacin, amiodarone) can increase the levels of pirfenidone
- Inducers of CYPA12 (cigarette smoking, omeprazole) may reduce levels of pirfenidone and should be avoided

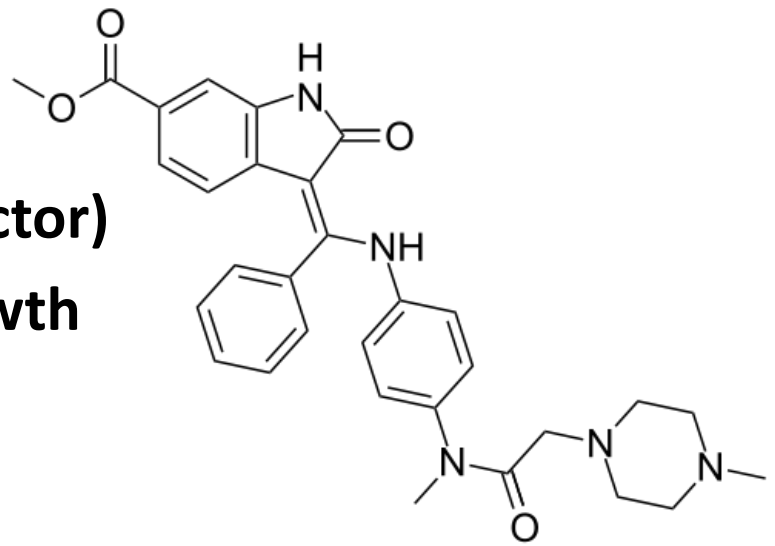
Longitudinal "Real-World" Outcomes of Pirfenidone in Idiopathic Pulmonary Fibrosis in Greece

Adverse event	*N* (%) (total = 80)
Photosensitivity/rash	20 (25)
Gastrointestinal	15 (18.8)
Liver toxicity	6 (7.5)
Nausea	6 (7.5)
Other	2 (2.5)
Discontinuation	18 (22.5)
Photosensitivity/rash	9 (11.2)
Gastrointestinal	6 (7.5)
Liver toxicity	4 (5)
Other	2 (2.5)

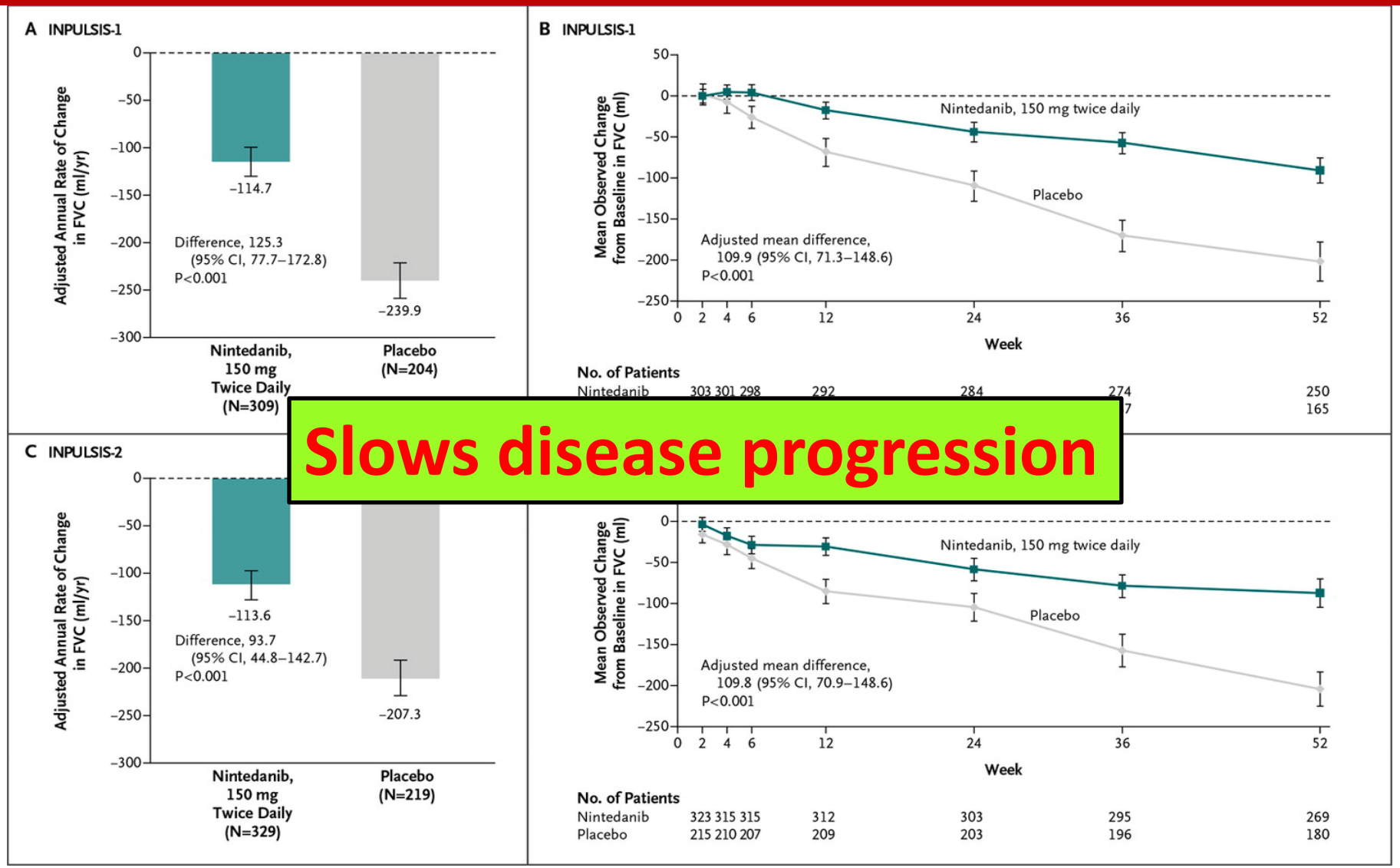
Tzouvelekis A. et al. Front Med (Lausanne). 2017;4:213.

Nintedanib

- **Nintedanib is a "triple kinase inhibitor" and acts on tyrosine kinase receptors for:**
  - **PDGF (platelet derived growth factor)**
  - **VEGF (vascular endothelium growth factor)**
  - **FGF (fibroblast growth factor)**
- **Inhibits fibroblast migration, proliferation, and myofibroblast transformation.**



Nintedanib-INPULSIS



Slows disease progression

Richeldi L et al. N Engl J Med 2014

Nintedanib

- **Form: 150 mg capsule + 100 mg capsule**
- **Dose: one 150 mg capsule twice per day with meals**

Important Side Effects:

- **Diarrhea**
  - **62% vs 18% placebo**
  - **Resulted in dose reduction in 10,7% and discontinuation in 4%**
  - **Loperamide**
- **Nausea, vomiting**
- **Hepatoxicity**
  - **Regular bloodwork**
  - **Reversible with dose reduction / discontinuation**

Safety and efficacy of nintedanib in idiopathic pulmonary fibrosis: A real-life observational study in Greece.

ADVERSE EVENT	N (%) (TOTAL=94)
Diarrhea	52 (55.3%)
Weight loss	19 (20.2%)
Decreased appetite	18 (19.1%)
Nausea	17 (18.1%)
Fatigue	17 (18.1%)
Vomiting	12 (12.7%)
Abdominal pain	9 (9.5%)
Upper respiratory tract infection	9 (9.5%)
Liver toxicity	5 (5.3%)
Headache	2 (2.1%)
Epistaxis	2 (2.1%)
Thromboembolic episode	1 (1%)
Total Discontinuation	37 (39.3%)

Tzouvelekis A et al. Pulm Pharmacol Ther. 2018 Apr;49:61-66

Nintedanib-Drug interaction

- Metabolism in the liver via cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp).
- Drugs that affect these enzymes can alter drug levels and exposure
- P-gp and CYP3A4 inhibitors (e.g., ketoconazole, erythromycin) may result in increased exposure to nintedanib.
- CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, and St. John's Wort) may result in decreased exposure to nintedanib

Bonus question….

- **What if the patient has Pulmonary Hypertension??**

Pharmaceutical management of PH-IPF. RCTs. The story so far…….

Therapy	Study	Year	Study population	Duration	Primary end point	Result
Bosentan	BUILD-1	2008	IPF-158 (1/1)	52 weeks	6MWD	Negative
Bosentan	BUILD-3	2011	IPF-616 (2/1)	52 weeks	Time to IPF worsening or death	Negative
Bosentan	B-PHIT	2014	Fibrotic IIP-60 (2/1)	16 weeks	Decrease in PVRi≥20%	Negative
Macitentan	MUSIC	2013	IPF-178 (2/1)	52 weeks	%change in FVC	Negative
Ambrisentan	ARTEMIS	2013	IPF-492 (75%) (2/1)	n/a	Time to IPF disease progression	Early termination
Sildenafil	STEP	2010	Adv. IPF-180 (1/1)	12 weeks	6MWD≥20%	Negative
Riociguat	RISE	2016	IIPs	26 weeks	6MWD	Early termination

Answer…

KEEP
CALM
AND
FIRST,
DO NO HARM

Drugs to avoid

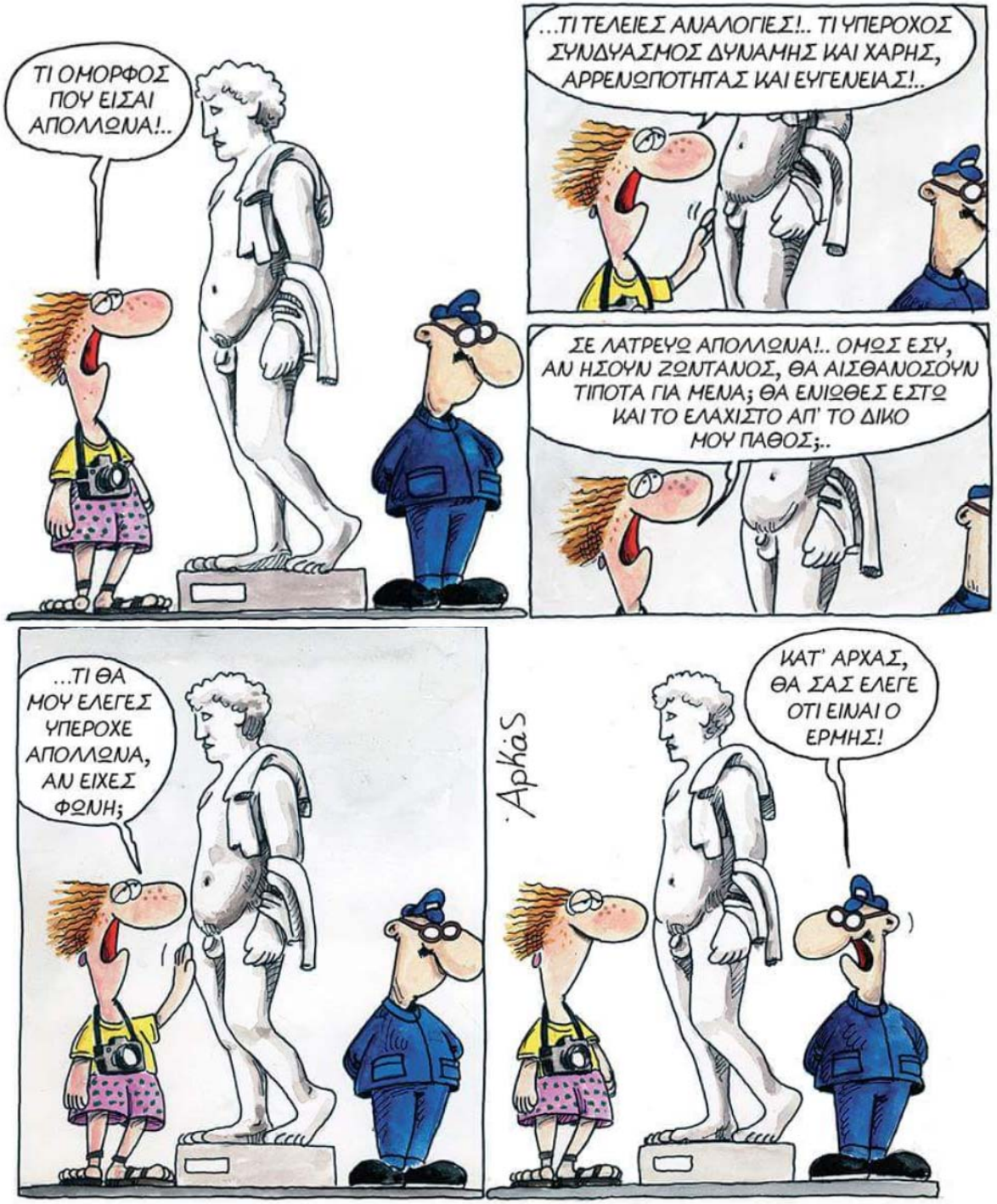
- **Immunosuppressants**
- **Warfarin**
- **Pulmonary vasodilators**

Clinical scenario: worsening dyspnea in IPF

Differential diagnosis	Recommended tests
• Pneumonia • Acute exacerbation of IPF • Pulmonary embolism • Pneumothorax • Cardiac ischemia • Congestive heart failure • Disease progression	• CBC, Chemistry panel, CRP, procalcitonin, d-dimers • Imaging (CXR, HRCT, CTPA) • Sputum, blood culture • BNP or NT-proBNP; • ECG, cardiac enzymes

Take home messages

- **Diagnosis of IPF is dynamic**
- **Monitor patient every 3 months**
- **Primary monitor tool: clinical examination, PFTs, 6MWT**
- **Holistic management**
  - **Antifibrotics**
  - **Vaccination**
  - **Comorbidities**
  - **LTOT**
  - **Palliative care**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ΚΑΤ' ΑΡΧΑΣ, ΘΑ ΣΑΣ ΕΛΕΓΕ ΟΤΙ ΕΙΝΑΙ Ο ΕΡΜΗΣ!
Aphas