Auto-immune serology in interstitial lung disease diagnostics

Valerie Adam

Pulmonologist

OLV hospital Aalst-Asse-Ninove

Reflection Network, UZ leuven

Conflict of interest

Research granted in cooperation with

Diagnostic companies:

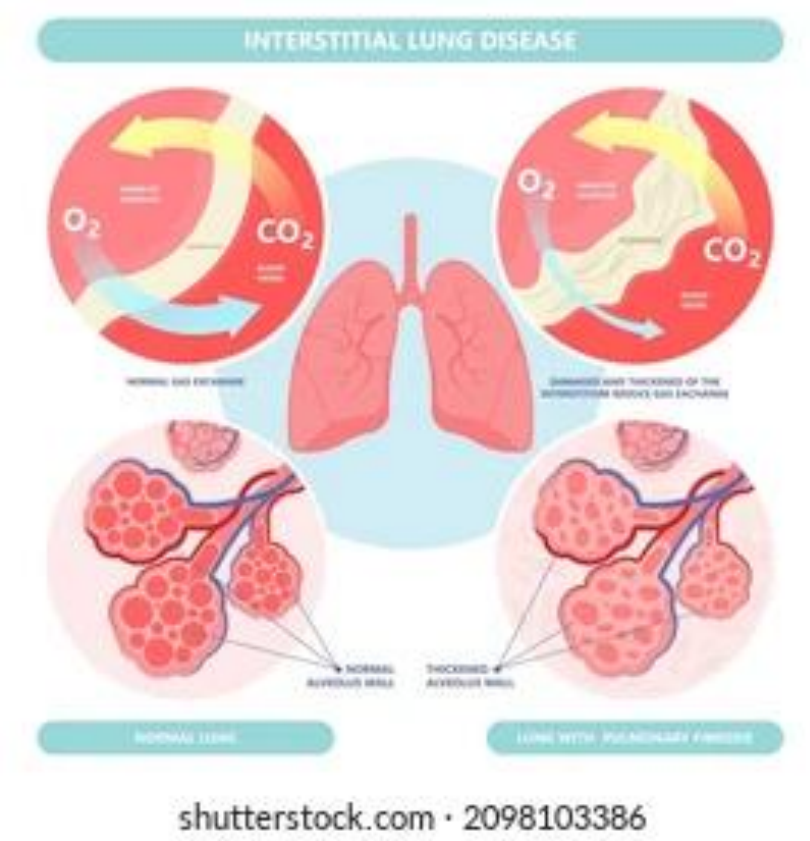
Thermo Fisher Scientific

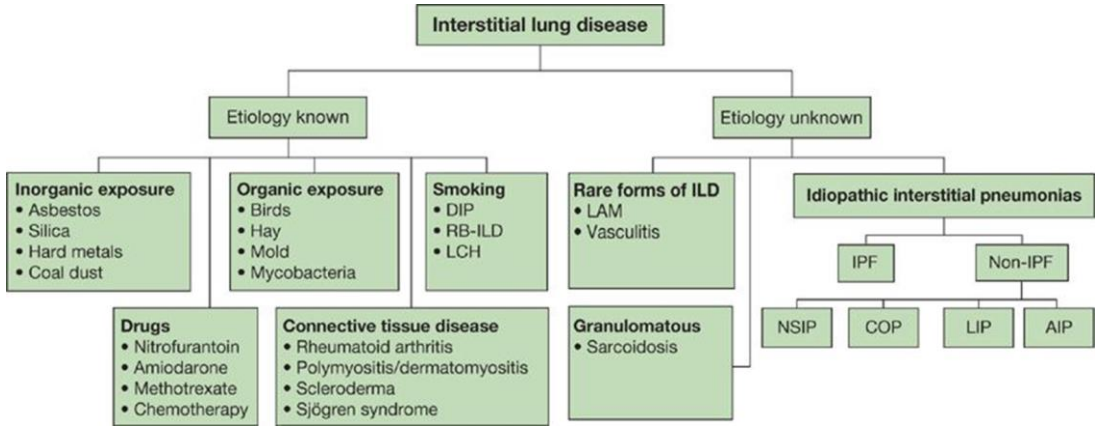
Werfen BeNeLux

Pharmaceutic companies:

Boehringer Ingelheim

Interstitial lung diseases: a crash course

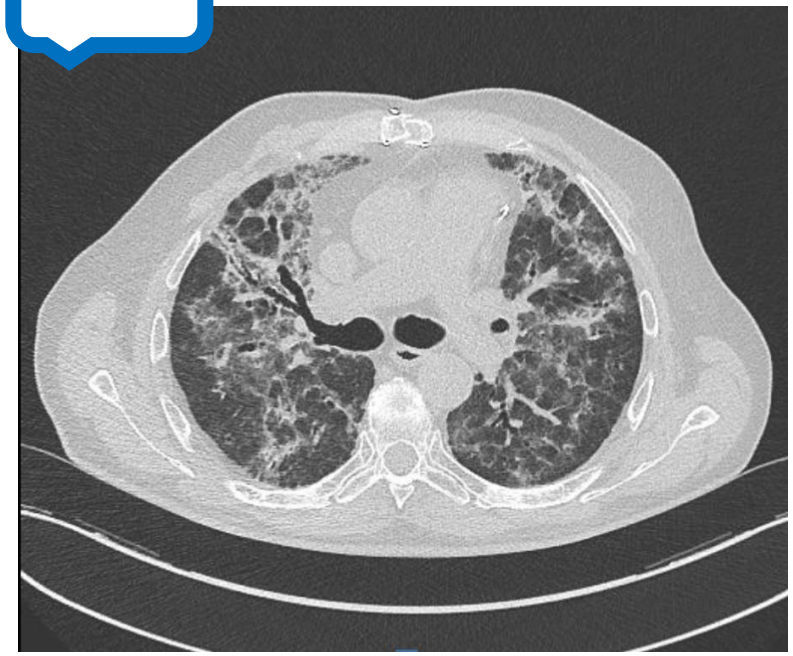




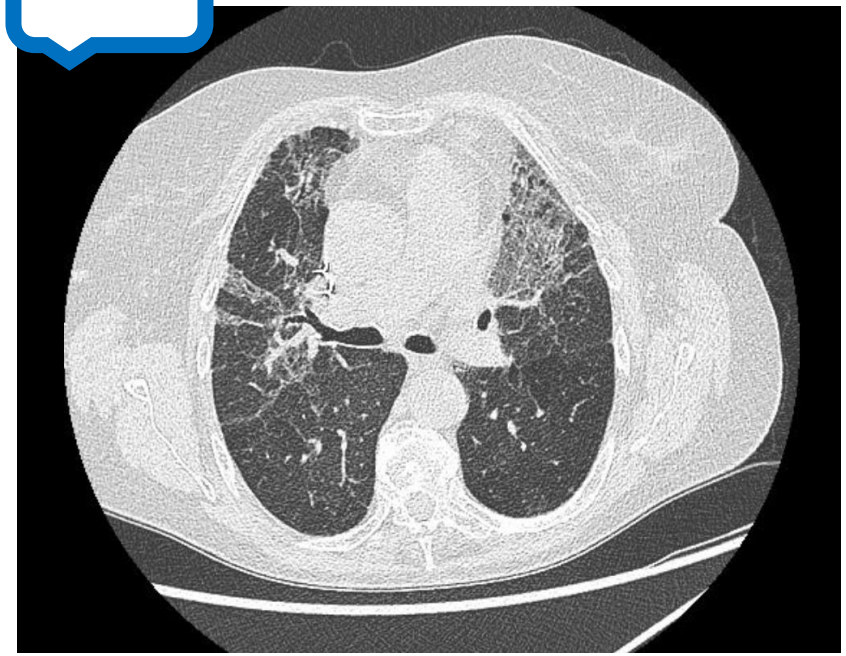
ATS/ESR classification, 2001; Travis *et al*. Am J Respir Crit Care Med 2013; 188: 733-748

Differential diagnosis in ILD: a bit of a pickle

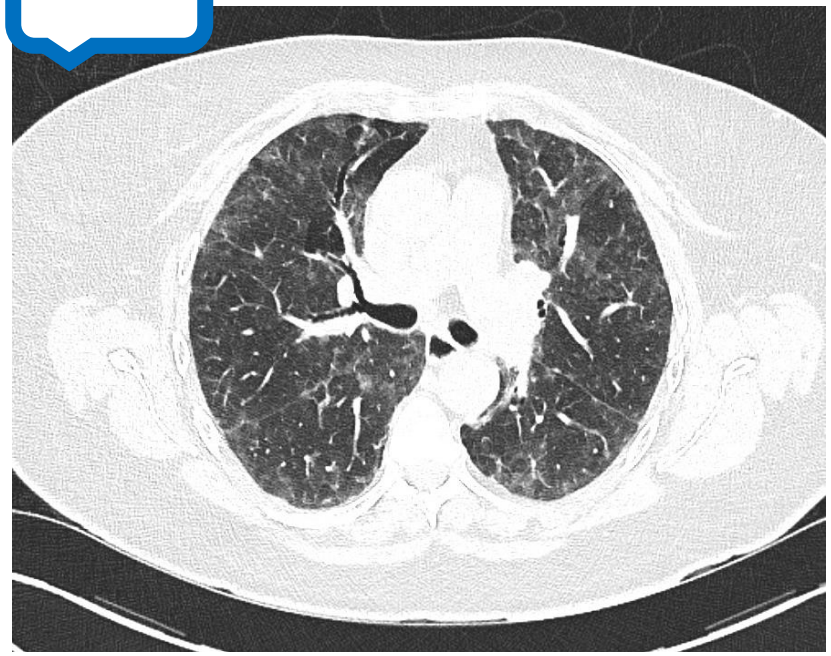
FPF



ASS



IPAF



Patient 1
Negative auto-immune serology
clubbing
Sister with Idiopathic Pulmonary Fibrosis

Patient 2
ANF 1/160, homogenous pattern
Discrete mechanic hands

Patient 3
ANF 1/1280, gespikkeld patroon
Reumatologic examination completely normal

Interstitial pneumonia with auto-immune features (IPAF)

TABLE 1 Classification criteria for "interstitial pneu

1. Presence of an interstitial pneumonia (by HRCT or sur
2. Exclusion of alternative aetiologies *and*,
3. Does not meet criteria of a defined connective tissue d
4. At least one feature from at least two of these domain
   A. Clinical domain
   B. Serologic domain

A. Clinical domain

1. Distal digital fissuring (mechanic hands)
2. Distal digital tip ulceration
3. Inflammatory arthritis or polyarticular morning joint stiffness >60 min
4. Palmar telangiectasia
5. Raynaud's phenomenon
6. Unexplained digital oedema
7. Unexplained fixed rash on the digital extensor surfaces (Gottron's sign)

B. Serologic domain

1. ANA ⩾1:320 titre, diffuse, speckled, homogeneous patterns *or*
   a. ANA nucleolar pattern (any titre) *or*
   b. ANA centromere pattern (any titre)
2. Rheumatoid factor ⩾2× upper limit of normal
3. Anti-CCP
4. Anti-dsDNA
5. Anti-Ro (SS-A)
6. Anti-La (SS-B)
7. Anti-ribonucleoprotein
8. Anti-Smith
9. Anti-topoisomerase (Scl-70)
10. Anti-tRNA synthetase (*e.g.* Jo-1, PL-7, PL-12; others are: EJ, OJ, KS, Zo, tRS)
11. Anti-PM-Scl
12. Anti-MDA-5

C. Morphologic domain

1. Suggestive radiology patterns by HRCT (see text for descriptions):
   a. NSIP
   b. OP
   c. NSIP with OP overlap
   d. LIP

Fischer *et al.* Eur Respir J 2015; 46: 976-987

Differential diagnosis in ILD: a bit of a pickle

- Most recent guidelines on diagnosis of IPF (2018):
  - Perform routine serological testing in all patients with newly identified ILD.
  - far less agreement about which serological tests to perform:
    - CRP (C-reactiveprotein), erythrocyte sedimentationrate, antinuclear antibodies (byimmunofluorescence), rheumatoid factor, myositis panel, and anti–cyclic citrullinatedpeptide.
    - Other detailed tests to be performed on a case-by-case basis according to associated symptoms and signs:
      - muscle enzymes (creatininephosphokinase, myoglobin, and aldolase),
      - antisynthetase antibodies (Jo-1 and others if available),
      - anti–MDA5 (melanomadifferentiation-associated protein 5),
      - anti-PM/Scl75(polymyositis/scleroderma 75),
      - anti-PM/Scl100
      - anti-Ku
      - If systemic sclerosis(i.e., scleroderma) is suspected, additional tests include: anti–Scl-70/topoisomerase-1,anti-centromere, anti-RNA polymerase III,anti-U1RNP, anti-Th/To, anti-PMScl, U3RNP (fibrillarin), and anti-Ku.
      - If Sjogrensyndrome is suspected, additional testsinclude: anti-SSA/Ro (Sj¨ogren-specificantibody A) and anti-SSB/La.
      - If vasculitis is suspected, an additional test includes anti-cytoplasmic antibodies.
    - A small minority ofthe panelists include all of the detailed testslisted above as an“ILD panel”at initialscreening/baseline evaluation

G Raghu et al, Am J Respir Crit Care Med Vol 198, Iss 5, pp e44–e68, Sep 1, 2018

Study goal

- Optimize the diagnostic work-up of OLV patients with ILD

Impact of additional (SSc and AIM) serology on ILD classification

Impact of HRCT pattern on added value of addional serology

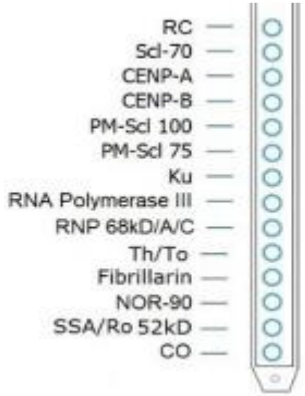
Materials and methods

ILD patients (n=181), presenting at OLV hospital Aalst (Belgium)
from 02/2018-08/2022 with **UIP** (n=110)**, NSIP** (n=48) and **OP** (n=23)

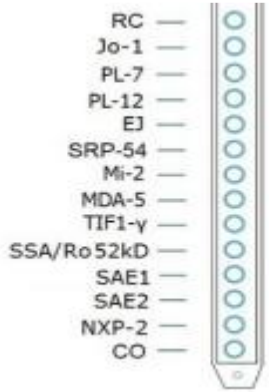
MTD 1:
standard serology:

RF IgM, ACPA IgG (Phadia 250, Thermo Fisher Scientific)
ANA IFA (NOVA View, Werfen) + ENA/dsDNA IgG (ANA profile 3, Euroimmun)
ANCA IFA (Euroimmun) + MPO/PR3 IgG (BIO-FLASH, Werfen)

MTD 2:
additional SSc and AIM serology:



SCL12DIV-24 Immunodot
(D-tek, Werfen)

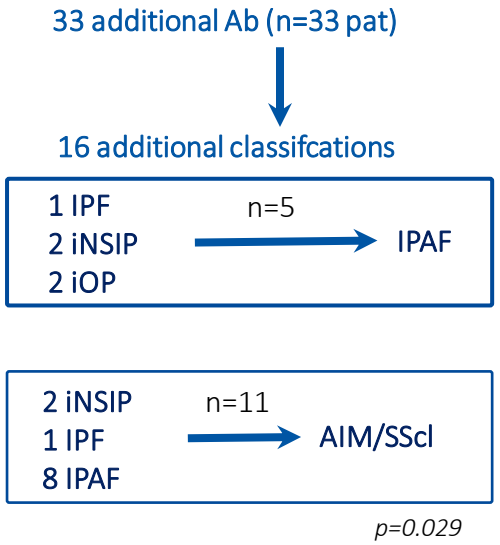


MYO12DIV-24 Immunodot
(D-tek, Werfen)

Results

- Impact on CTD/IPAF classification

	ILD classification	MTD1 (%)	MTD2 (%)
Idiopathic ILD	Idiopathic pulmonary fibrosis (IPF)	85 (47.0)	83 (45.9)
	Idiopathic non-specific interstitial pneumonia (iNSIP)	12 (6.6)	8 (4.4)
	Idiopathic organizing pneumonia (iOP)	8 (4.4)	6 (3.3)
	Total	**105 (58.0)**	**97 (53.6)**
Non-idiopathic ILD	Hypersensitivity pneumonitis	12 (6.6)	12 (6.6)
	Interstitial pneumonia with autoimmune features (IPAF)	38 (21.0)	35 (19.3)
	ANCA associated small vessel vasculitis	1 (0.6)	1 (0.6)
	Rheumatoid arthritis	14 (7.7)	14 (7.7)
	Systemic sclerosis (SSc)	6 (3.3)	7 (3.9)
	Antisynthetase syndrome/polymyositis (AIM)	3 (1.7)	13 (7.2)
	Sjögren syndrome	2 (1.1)	2 (1.1)
	Total	**76 (42.0)**	**84 (46.4)**



Results

Impact of HRCT on additional CTD/IPAF classification

HRCT pattern	MTD1	MTD2	Additional serology
UIP	IPF	IPAF	Anti-RNA polymerase III (+++)
	IPF	AIM-ILD	Anti-PM-Scl75 (+)
	IPAF	SSc	Anti-PM-Scl75 (+++)
	IPAF	AIM-ILD	Anti-PL-12 (+++)
NSIP	IPAF	AIM-ILD	Anti-SRP (+)
	IPAF	AIM-ILD	Anti-PL-7 (+++)
	IPAF	AIM-ILD	Anti-EJ (+++)
	IPAF	AIM-ILD	Anti-Th/To (+++)
	iNSIP	IPAF	Anti-Th/To (+++)
	iNSIP	IPAF	Anti-PM-Scl100 (+)
	iNSIP	AIM-ILD	Anti-PL-7 (+++)
	iNSIP	AIM-ILD	Anti-EJ (+++)
OP	IPAF	AIM-ILD	Anti-PL-12 (+++)
	IPAF	AIM-ILD	Anti-PL-12 (+++)
	iOP	IPAF	Anti-SAE-1 (+)
	iOP	IPAF	Anti-SAE-2 (+)

C. Morphologic domain
1. Suggestive radiology patterns by HRCT (see text for descriptions):
   a. NSIP
   b. OP
   c. NSIP with OP overlap
   d. LIP

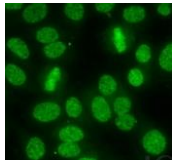
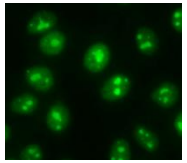
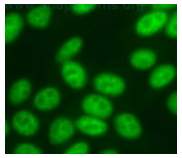
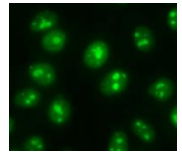
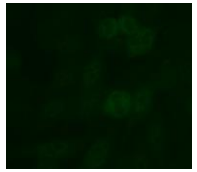
UIPAF?

Sambataro et al, J Clin Med 2024; 13(2):369

Results

Accuracy of newly identified Ab

HRCT pattern	MTD1	MTD2	Additional serology
UIP	IPF	IPAF	Anti-RNA polymerase III (+++)
	IPF	AIM-ILD	Anti-PM-Scl75 (+)
	IPAF	SSc	Anti-PM-Scl75 (+++)
	IPAF	AIM-ILD	Anti-PL-12 (+++)
NSIP	IPAF	AIM-ILD	Anti-SRP (+)
	IPAF	AIM-ILD	Anti-PL-7 (+++)
	IPAF	AIM-ILD	Anti-EJ (+++)
	IPAF	AIM-ILD	Anti-Th/To (+++)
	iNSIP	IPAF	Anti-Th/To (+++)
	iNSIP	IPAF	Anti-PM-Scl100 (+)
	iNSIP	AIM-ILD	Anti-PL-7 (+++)
	iNSIP	AIM-ILD	Anti-EJ (+++)
OP	IPAF	AIM-ILD	Anti-PL-12 (+++)
	IPAF	AIM-ILD	Anti-PL-12 (+++)
	iOP	IPAF	Anti-SAE-1 (+)
	iOP	IPAF	Anti-SAE-2 (+)

ANA IFA obtained	ANA IFA expected
 AC-2 (1:320) AC-18,19,20 (1:320)	 **AC-8,9,10**
 AC-4,5 (1:80)	 **AC-8,9,10**
 AC-0	

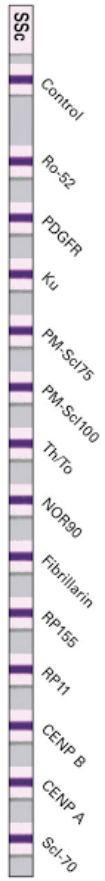
www.anapatterns.org

Bonroy *et al*. CCLM 2023; 61: 1167-1198

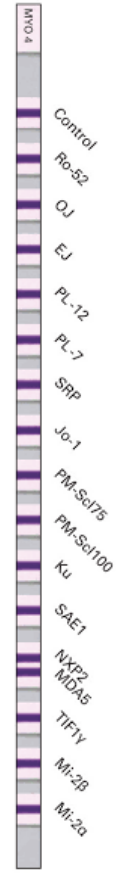
Results

Accuracy of newly identified Ab

HRCT pattern	MTD1	MTD2	Additional serology
UIP	IPF	IPAF	Anti-RNA polymerase III (+++)
	IPF	AIM-ILD	Anti-PM-Scl75 (+)
	IPAF	SSc	Anti-PM-Scl75 (+++)
	IPAF	AIM-ILD	Anti-PL-12 (+++)
NSIP	IPAF	AIM-ILD	Anti-SRP (+)
	IPAF	AIM-ILD	Anti-PL-7 (+++)
	IPAF	AIM-ILD	Anti-EJ (+++)
	IPAF	AIM-ILD	Anti-Th/To (+++)
	iNSIP	IPAF	Anti-Th/To (+++)
	iNSIP	IPAF	Anti-PM-Scl100 (+)
	iNSIP	AIM-ILD	Anti-PL-7 (+++)
	iNSIP	AIM-ILD	Anti-EJ (+++)
OP	IPAF	AIM-ILD	Anti-PL-12 (+++)
	IPAF	AIM-ILD	Anti-PL-12 (+++)
	iOP	IPAF	Anti-SAE-1 (+)
	iOP	IPAF	Anti-SAE-2 (+)



Systemic sclerosis (Profile (IgG) (EuroImmun, Germany)



Autoimmune Inflammatory Myopathies (IgG) (EuroImmun, Germany)

Results

Accuracy of newly identified Ab

HRCT pattern	MTD1	MTD2	Additional serology
UIP	IPF	IPAF	Anti-RNA polymerase III (+++)
	IPF	AIM-ILD	Anti-PM-Scl75 (+)
	IPAF	SSc	Anti-PM-Scl75 (+++)
	IPAF	AIM-ILD	Anti-PL-12 (+++)
NSIP	IPAF	AIM-ILD	Anti-SRP (+)
	IPAF	AIM-ILD	Anti-PL-7 (+++)
	IPAF	AIM-ILD	Anti-EJ (+++)
	IPAF	AIM-ILD	Anti-Th/To (+++)
	iNSIP	IPAF	Anti-Th/To (+++)
	iNSIP	IPAF	Anti-PM-Scl100 (+)
	iNSIP	AIM-ILD	Anti-PL-7 (+++)
	iNSIP	AIM-ILD	Anti-EJ (+++)
OP	IPAF	AIM-ILD	Anti-PL-12 (+++)
	IPAF	AIM-ILD	Anti-PL-12 (+++)
	iOP	IPAF	Anti-SAE-1 (+)
	iOP	IPAF	Anti-SAE-2 (+)

IP-MS

Vulsteke *et al*. Ann Rheum Dis 2023; 82: 546-555

Results

Co-occurence of Ro52 Ab

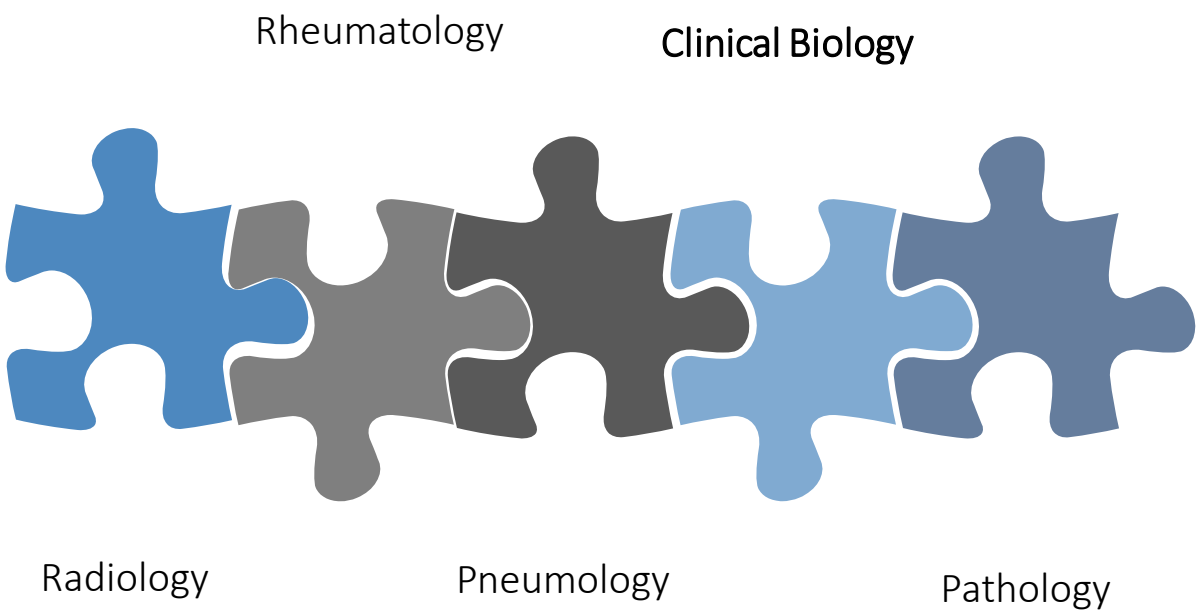
HRCT pattern	MTD1	MTD2	Additional serology
UIP	IPF	IPAF	Anti-RNA polymerase III (+++)
	IPF	AIM-ILD	Anti-PM-Scl75 (+)
	IPAF	SSc	Anti-PM-Scl75 (+++)
	IPAF	AIM-ILD	Anti-PL-12 (+++)
NSIP	IPAF	AIM-ILD	Anti-SRP (+)
	IPAF	AIM-ILD	Anti-PL-7 (+++)
	IPAF	AIM-ILD	Anti-EJ (+++)
	IPAF	AIM-ILD	Anti-Th/To (+++)
	iNSIP	IPAF	Anti-Th/To (+++)
	iNSIP	IPAF	Anti-PM-Scl100 (+)
	iNSIP	AIM-ILD	Anti-PL-7 (+++)
	iNSIP	AIM-ILD	Anti-EJ (+++)
OP	IPAF	AIM-ILD	Anti-PL-12 (+++)
	IPAF	AIM-ILD	Anti-PL-12 (+++)
	iOP	IPAF	Anti-SAE-1 (+)
	iOP	IPAF	Anti-SAE-2 (+)

In 6 of 16 additional classifications!

Ro52 Ab occurence should trigger further AIM/SSc Ab analyses

Concluding remarks

- ILD diagnosis requires multidisciplinary team discussions



Concluding remarks

- Newer biomarkers have to be adopted into clinical practice and the availability of commercial assays can help achieve this
- Differences in specificity/sensitivity between manufacturers
- Anti-Ro52 Ab have been associated with more severe forms of ILD. Their presence in patients with ILD should trigger subsequent testing for additional SSc and AIM Ab
- Independent of the HRCT pattern, serological testing for SSc and AIM Ab can have added value in CTD-ILD classification
- Revision of clinical guidelines (e.g. IPAF classification-guidelines) is required, implementing increasing insights in radiology and new SSc/AIM Ab and other biomarkers

Thank You

- Lieve Van Hoovels
- Bert Vander Cruyssen
- Bo Massa
- Stefanie Van Den Bremt
- Lieven Van Hoe
- Xavier Bossuyt
- Wim Wuyts
- Thermo Fisher Scientific, Werfen BeNeLux, Boehringer Ingelheim

KU LEUVEN

UZ LEUVEN

olv Top in Zorg.