Genetics of parenchymal lung diseases

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General view on genetic testing

Physicians' perspective

+ Understand disease mechanisms
+ Refine diagnosis
+ Identify patients at risk
+ Genetic counselling, prevention
+ Theragnostic

Patients' perspective

+ Understand its own disease
+ Know whether relatives are at risk (planning)
+ Expected evolution/treatment results
↘ Burden, fear, feeling of guilt
↘ Socio-economic consequences

McGowan et al. *Pers Med* 2013

Patients' concerns on genetic testing

"It would be good in the fact that there may be things that you could do to help prevent it in the long term. T**Stress**ould be that you are constantly th it and worrying about 'Am I going to develop this? Am I going to get this?'"

"Well, I don't think anyone would want to know…I mean, it's not something you would sign up and say **Uncertainty** start having symptoms, Why is this happening? So if you had something, symptoms, ok do the test and just tell me what's going on."

"I would be very concerned about the consequences, my own personal consequences in the insura mean perso owing and e very worried about the medical profession sharing that information and it being out there."

Confidentiality

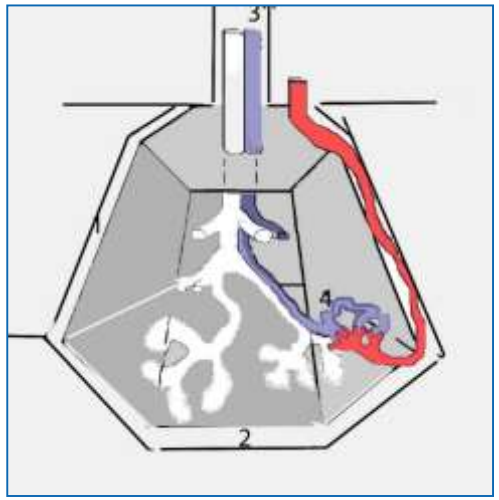
"Just because you say 'Yeah, it looks like you might be susceptible to all these genetically,' that doesn't mean f we know now, or possibly eve -released test, that it's a guaranteed thing. Nothing's really guaranteed until it happens."

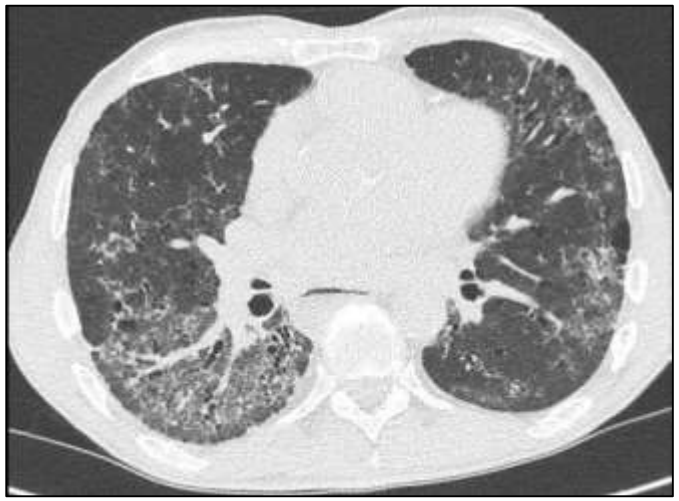
Reliability

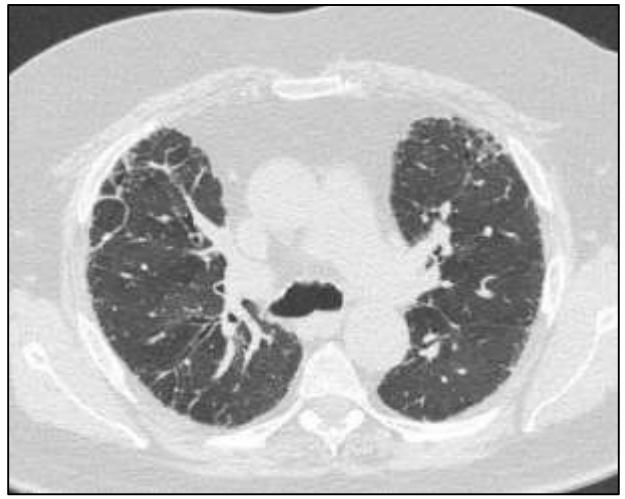
McGowan et al. *Pers Med* 2013

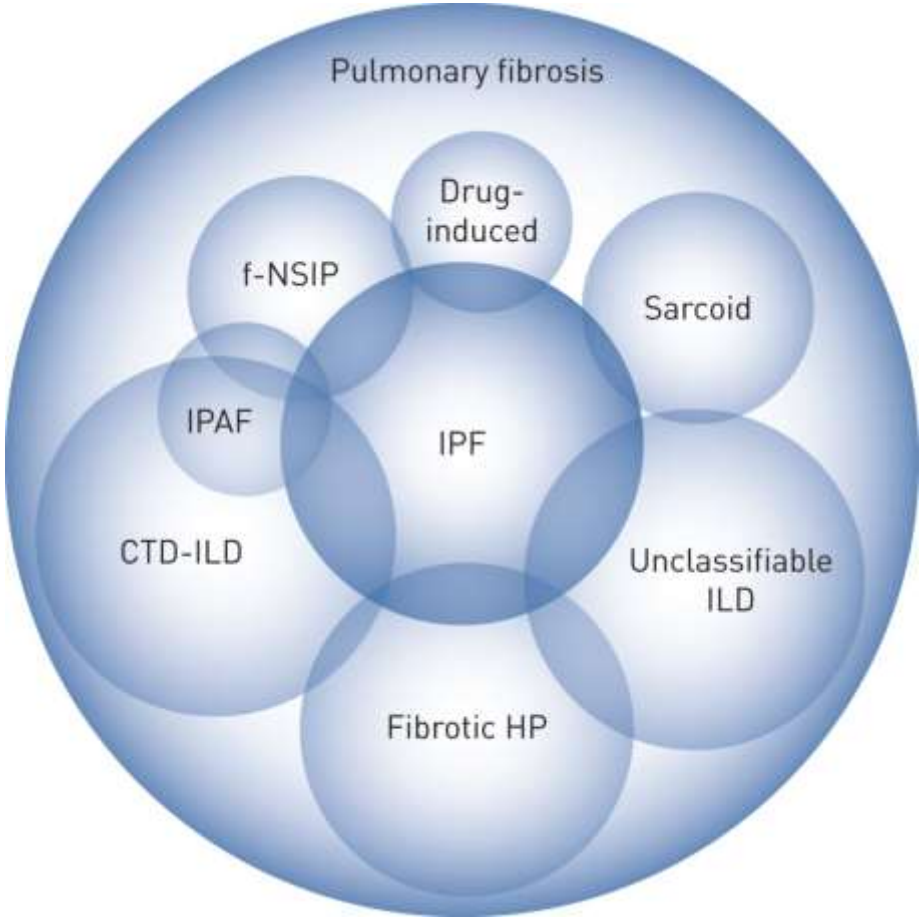
Familial pulmonary fibrosis

Pulmonary fibrosis



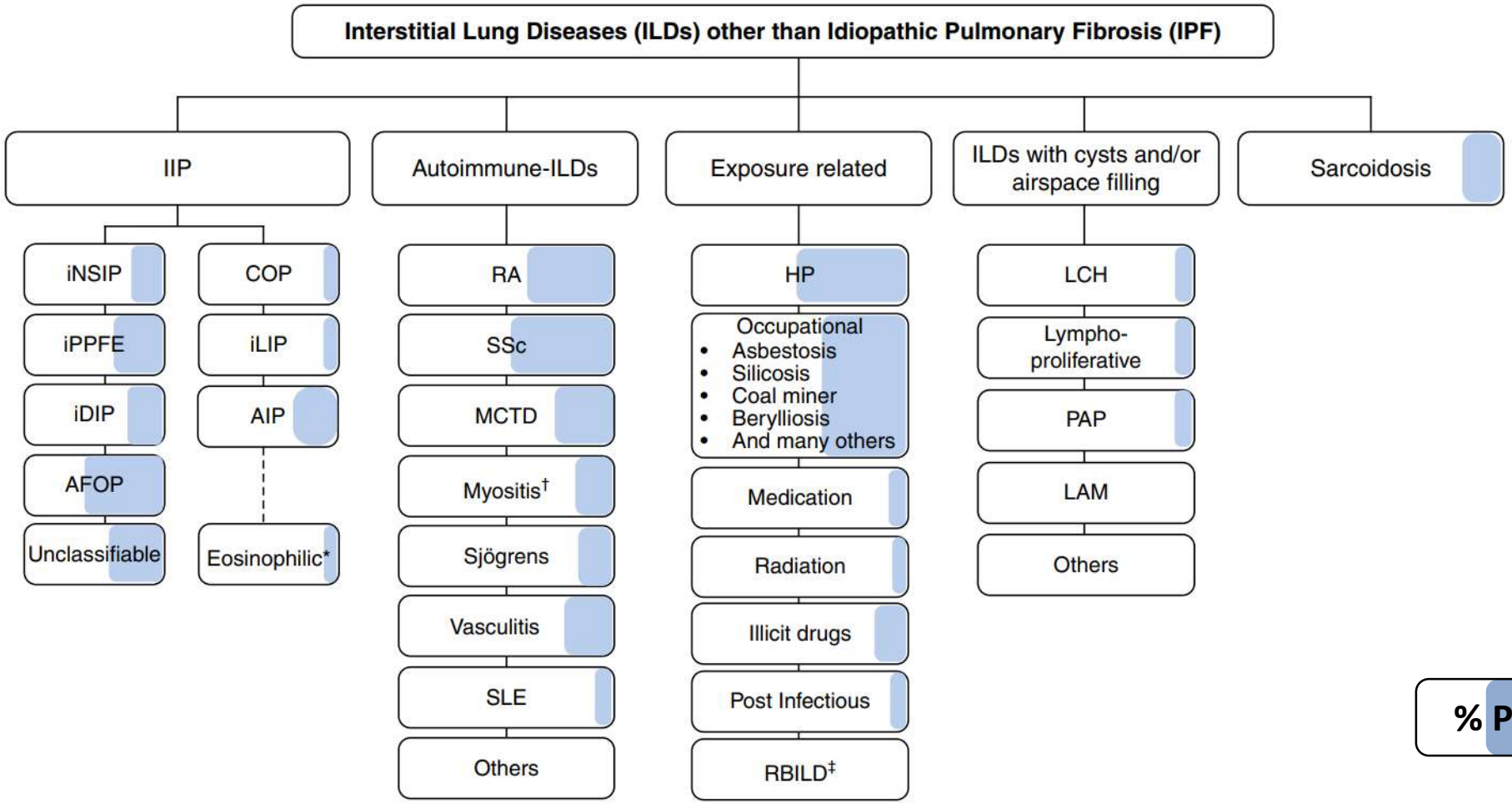






Wells et al. *Eur Respir J* 2018

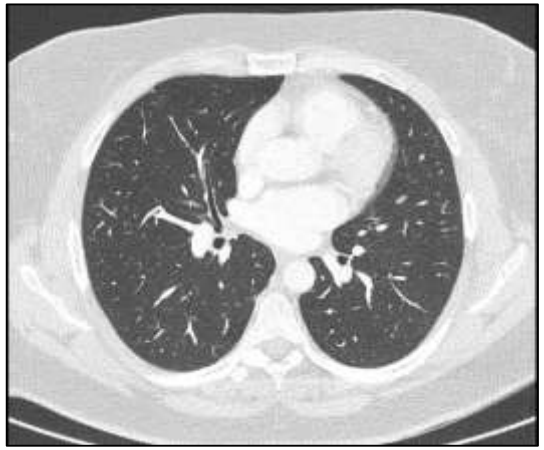
Interstitial lung diseases classification

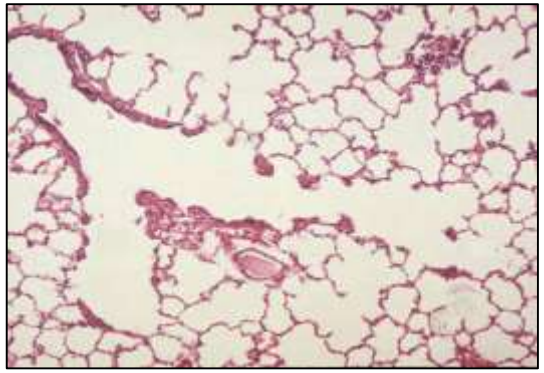


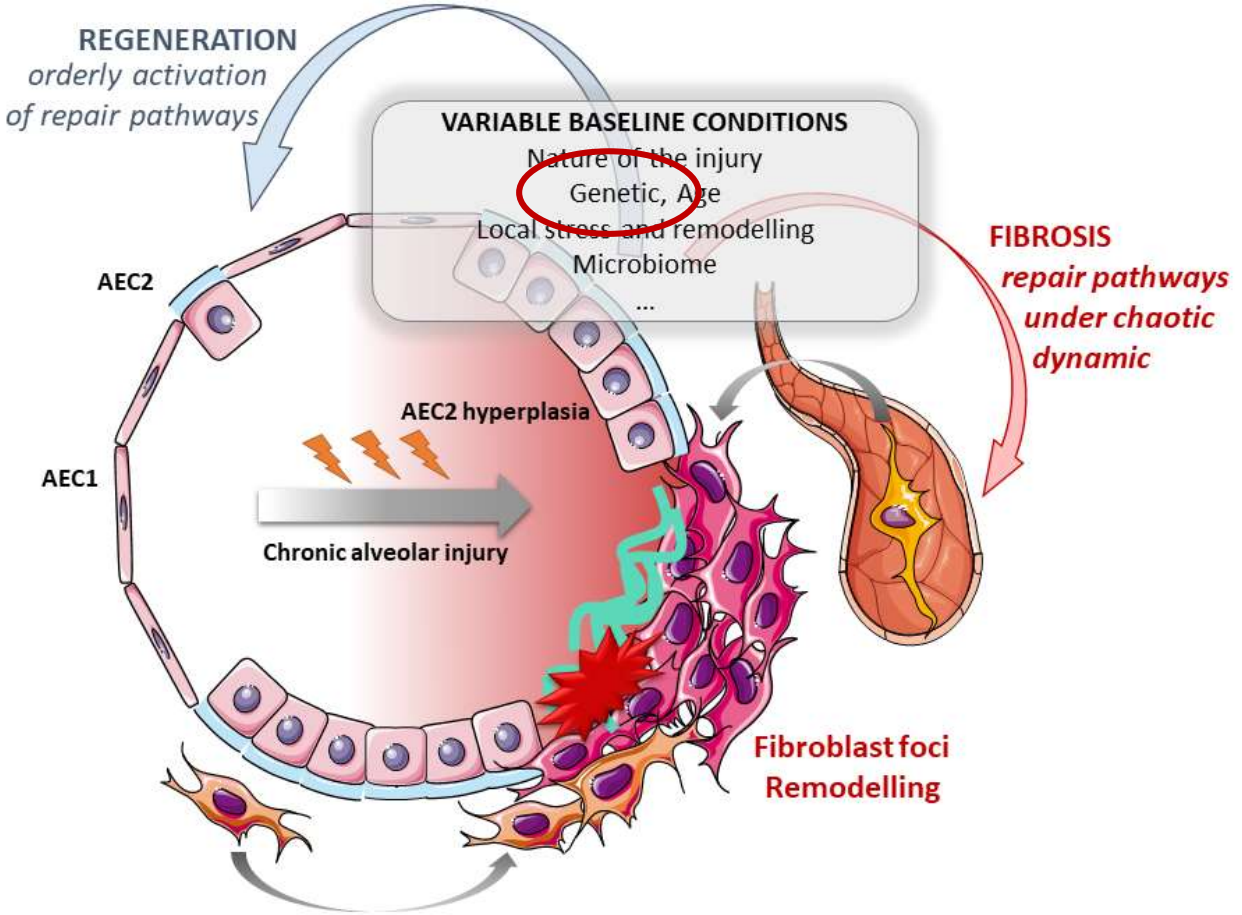
% PF-ILD

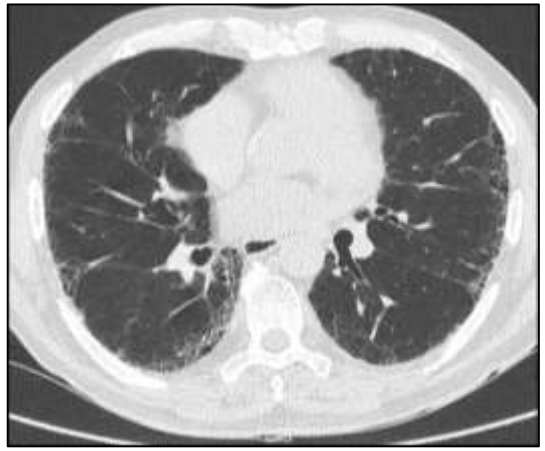
Raghu et al. *Am J Respir Crit Care Med* 2022

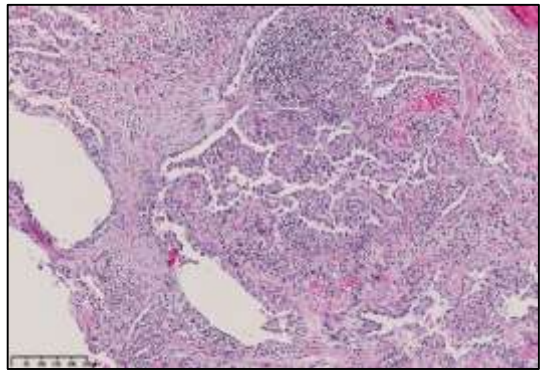
Pathophysiology of lung fibrosis





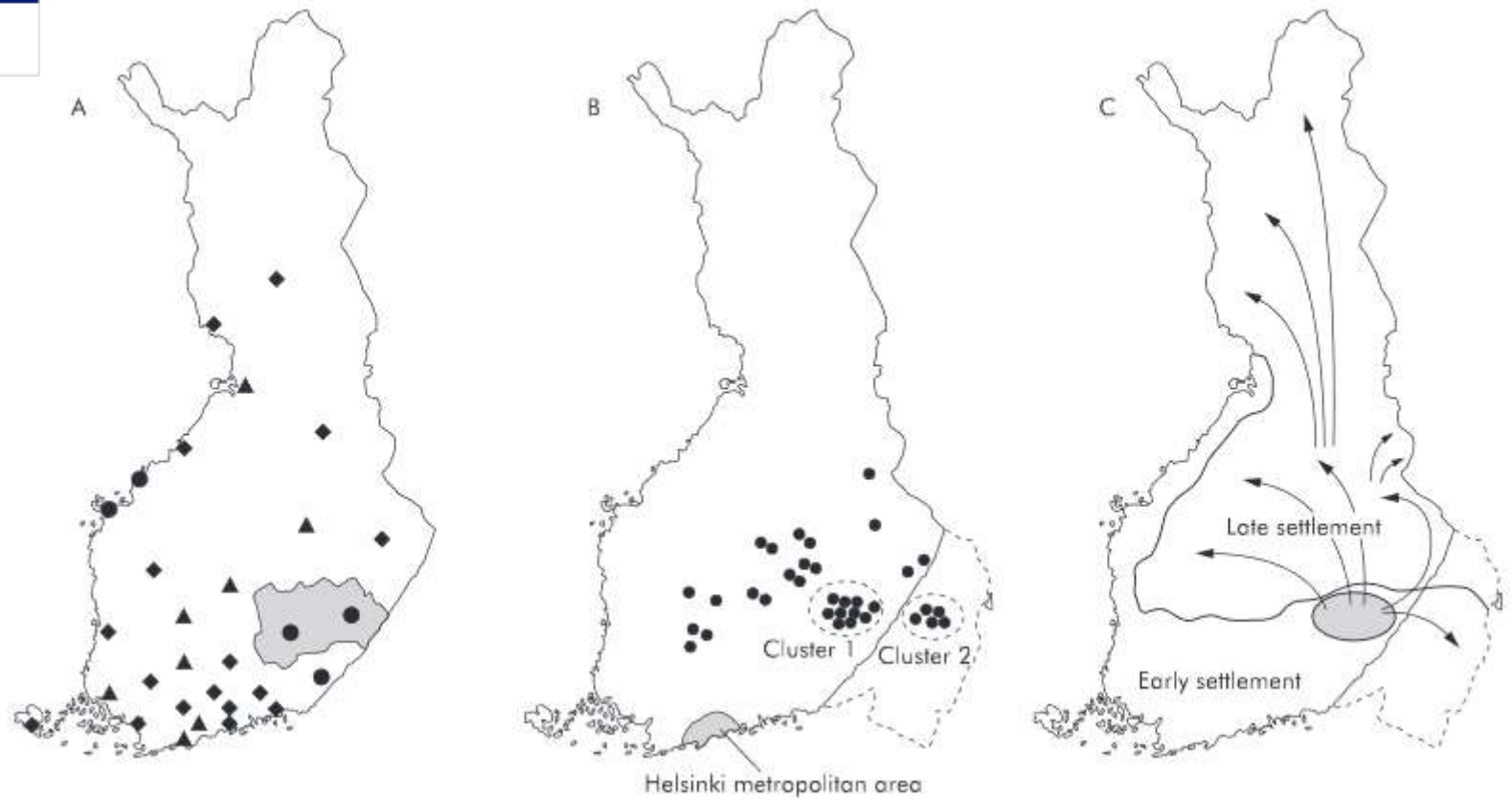






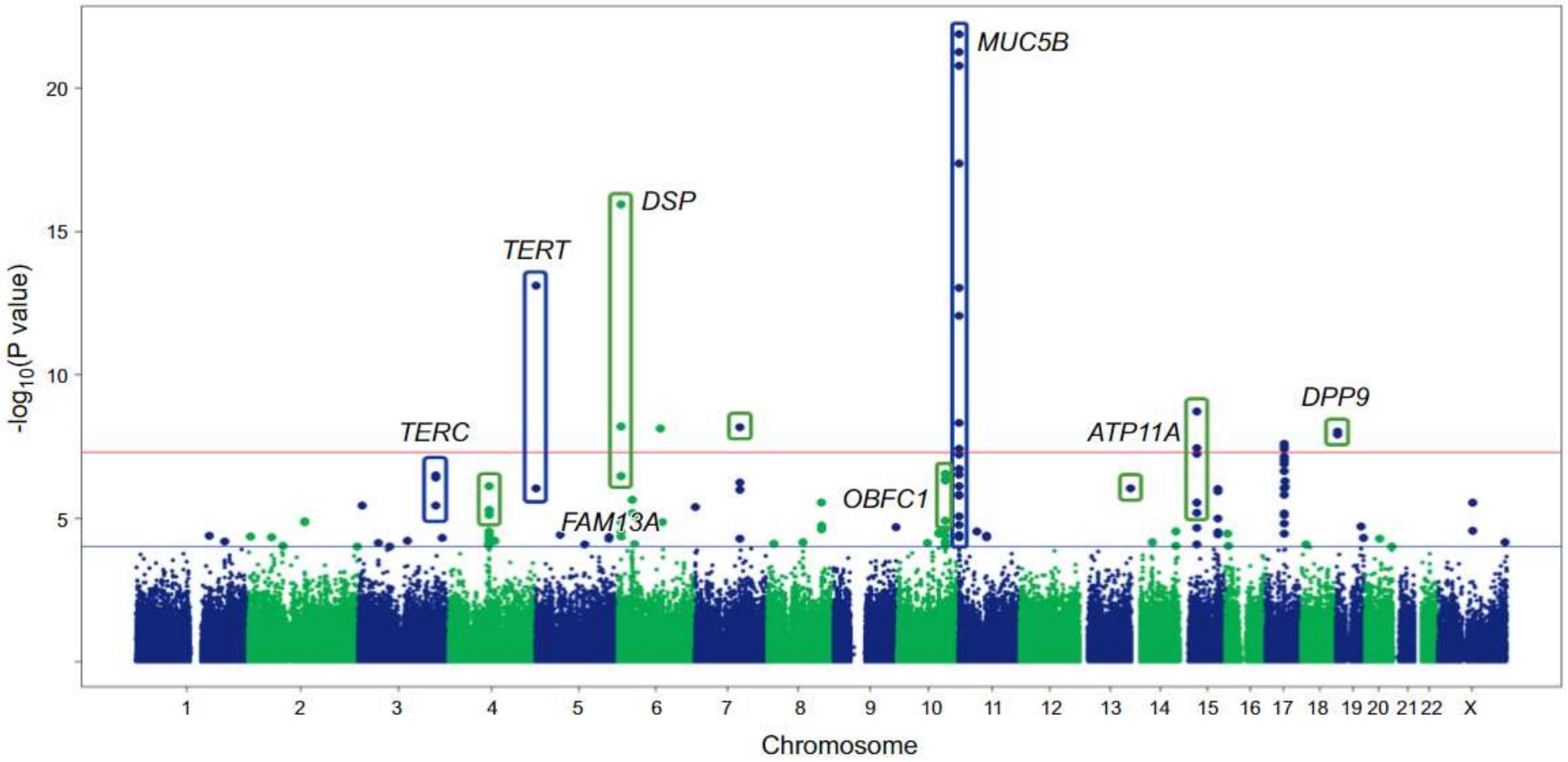
Froidure et al. *Eur Respir Rev* 2020

Evidence of familial clustering in IPF



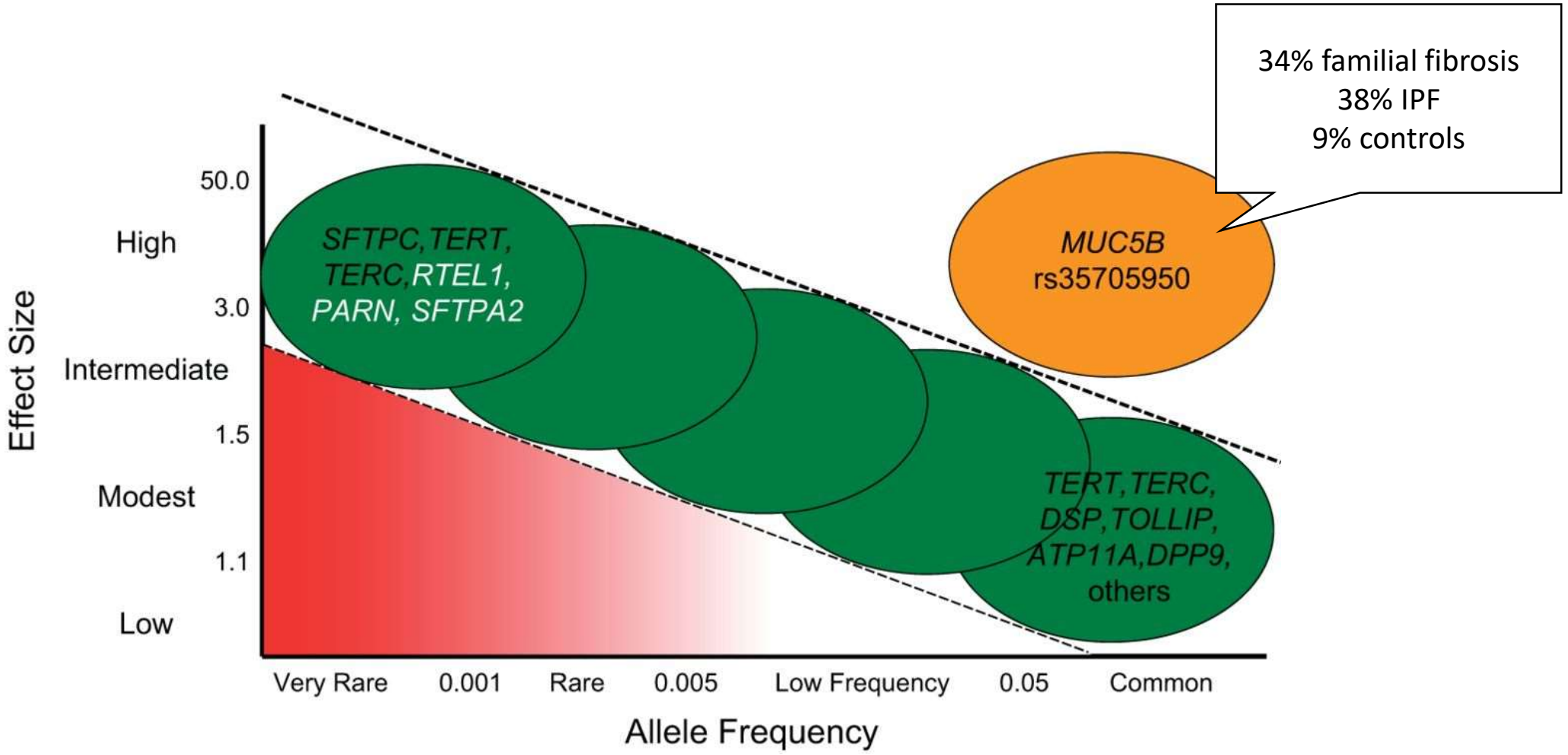
Hodgson et al. *Thorax* 2002

Allele frequency and effect on IPF



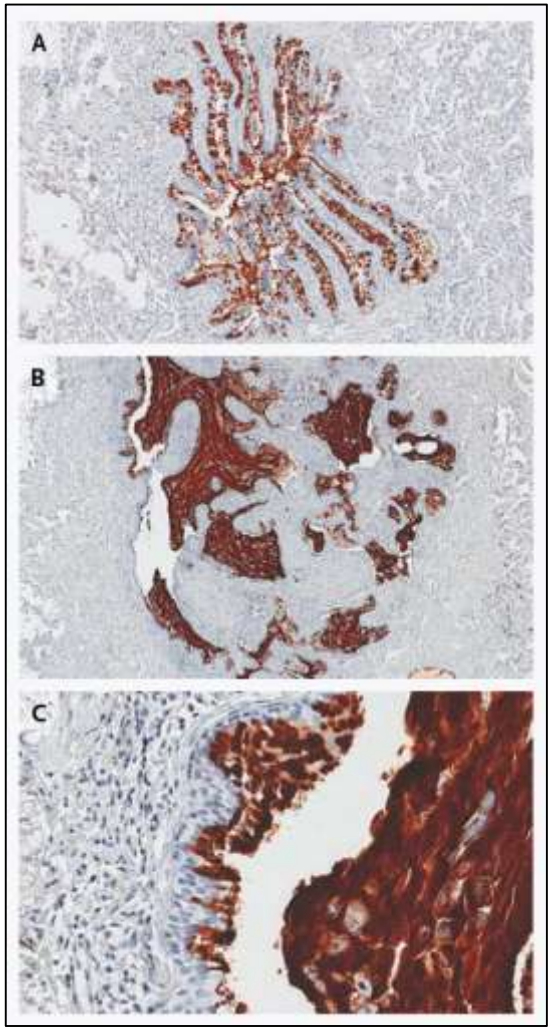
Figerlin et al. *Nat Genet* 2013
Evans et al. *Physiol Rev* 2016

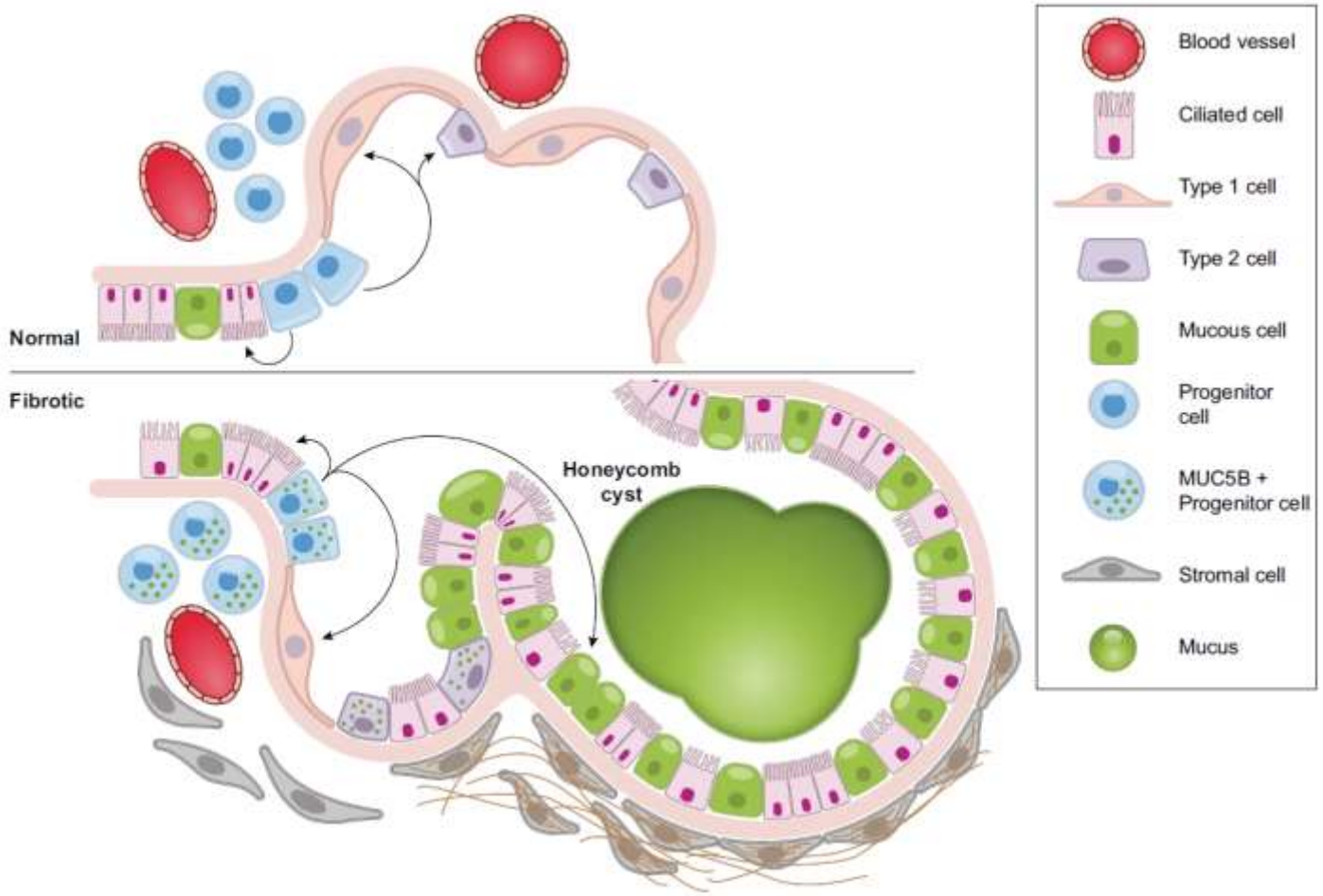
Allele frequency and effect on IPF



Evans et al. *Physiol Rev* 2016

Common variant of MUC5B promoter





Seibold et al. *New Engl J Med* 2013
Evans et al. Physiol Rev 2016

Familial pulmonary fibrosis (FPF)

EUROPEAN RESPIRATORY JOURNAL
ERS OFFICIAL DOCUMENTS
R. BORIE ET AL.

European Respiratory Society statement on familial pulmonary fibrosis

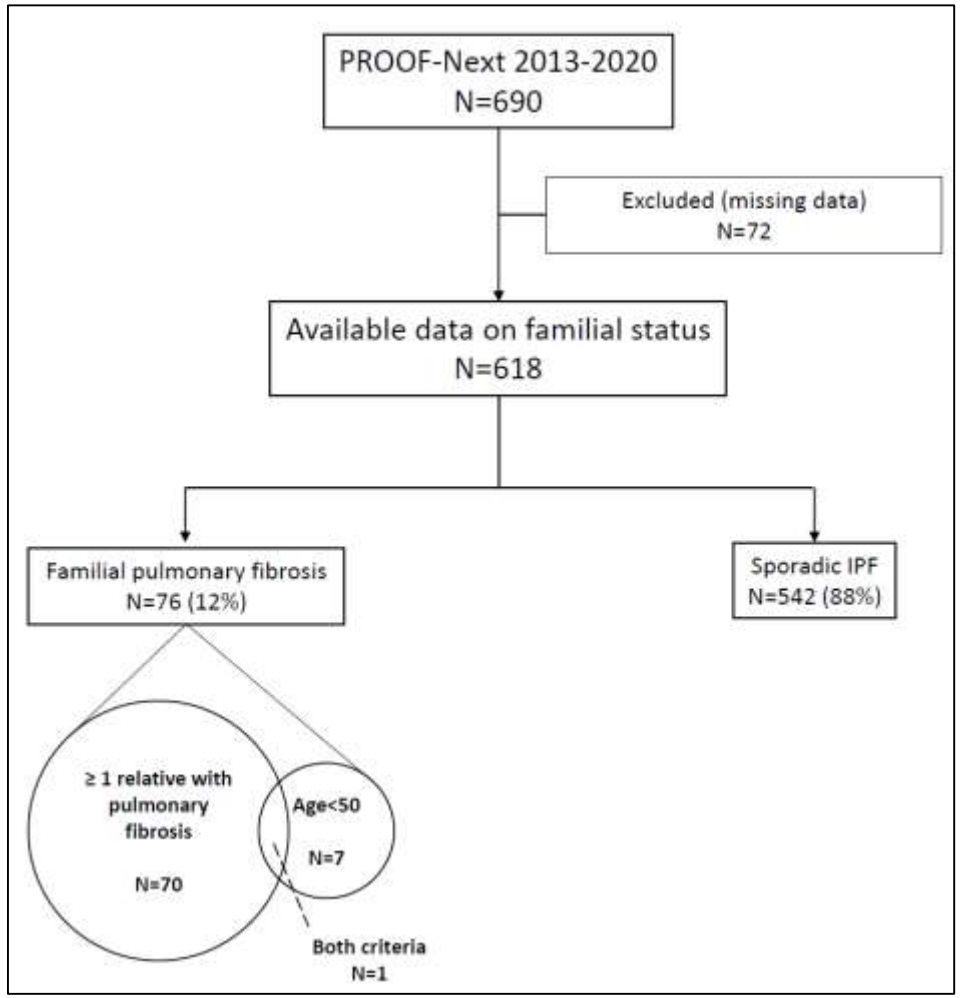
Raphael Borie[1], Caroline Kannengiesser[2], Katerina Antoniou[3], Francesco Bonella[4], Bruno Crestani[1], Aurélie Fabre[5], Antoine Froidure[6], Liam Galvin[7], Matthias Griese[8], Jan C. Grutters[9,10], Maria Molina-Molina[11], Venerino Poletti[12,13], Antje Prasse[14,15], Elisabetta Renzoni[16,17], Jasper van der Smagt[18] and Coline H.M. van Moorsel[9]

Narrative Question 1: Which patients may benefit from genetic sequencing and clinical counselling?

Statement

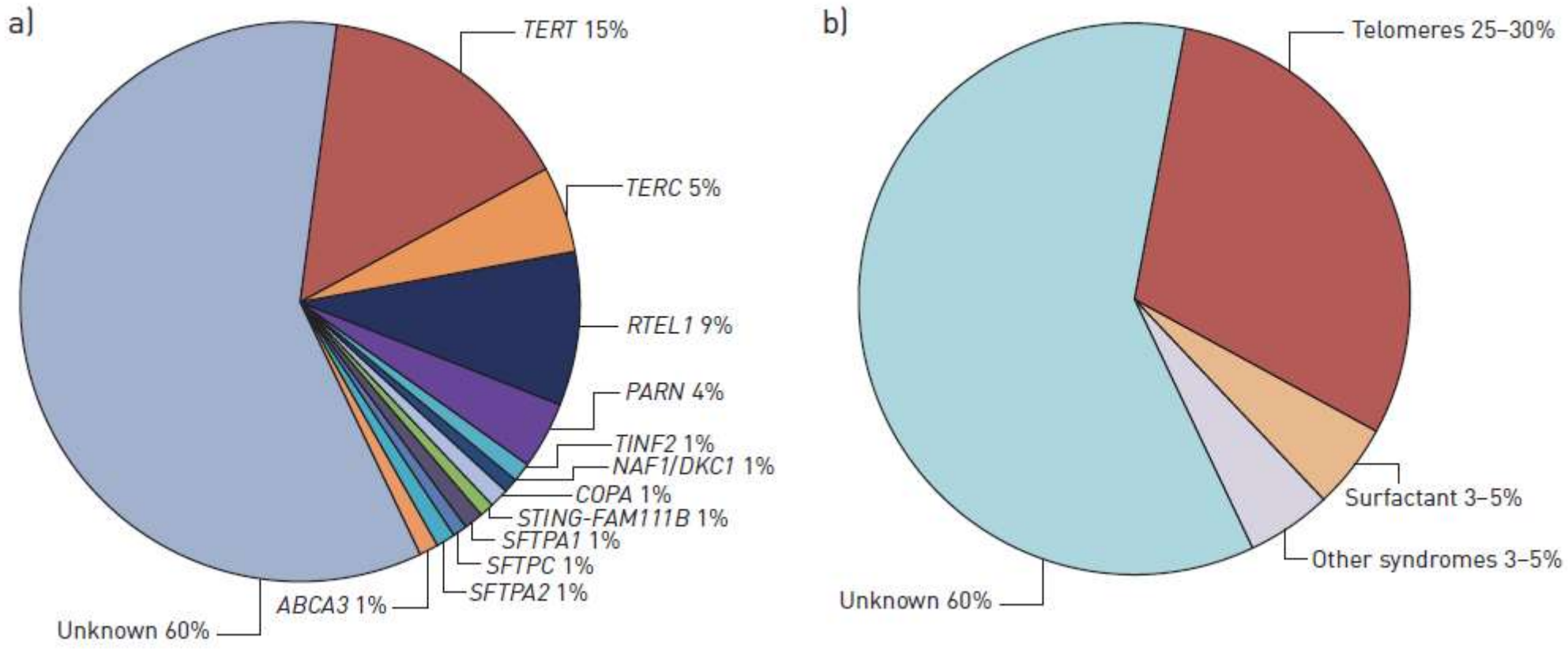
In the following clinical contexts, the Task Force members usually offer genetic sequencing:

- *Any patient with fibrotic ILD and one or more first- or second-degree family members with fibrotic ILD*
- *Any patient with a relative carrying a pathogenic/likely pathogenic variant known to cause ILD*
- *Any patient with suspected short telomere syndrome (table 3) [18]*
- *Any patient with an idiopathic fibrosing ILD before the age of 50 years*



Borie et al. *Eur Respir J* 2023
Froidure et al. *in prep*

Familial pulmonary fibrosis



Borie et al. *Eur Respir Rev* 2017

Genes associated with FPF

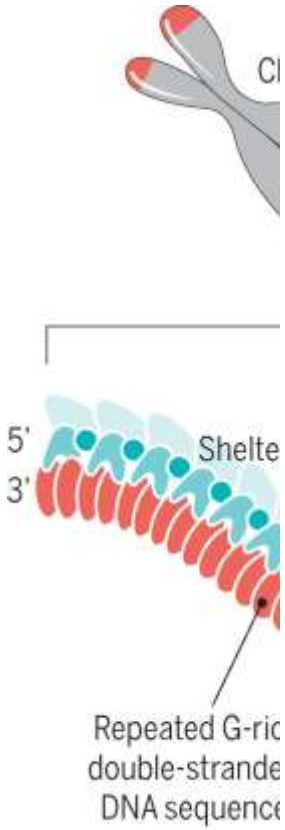
TABLE 1 Telomere- and surfactant-related genes associated with interstitial lung disease (ILD)

Gene	Mode of inheritance	Age of presentation of pulmonary symptoms	Non-ILD pulmonary and extrapulmonary phenotype	Frequency	Most frequent radiological patterns	Implication for management/therapy for pulmonary disease[#]	References
Telomere-related disease							
TERT	AD[¶]	>30 years in cases with ILD as single manifestation of short telomere syndrome	Mucocutaneous features: buccal leukoplakia, abnormal pigmentation, nail dystrophy, premature hair greying (canitia); aplastic anaemia, myelodysplastic syndrome, leukaemia; liver disease; osteoporosis	15–22%	UIP, NSIP, HP, PPFE or an indeterminate pattern	Antifibrotic drugs according to guidelines/market agreement. Lung transplantation may be considered with specific concern about haematological disease and cytomegalovirus infection.	[3, 8, 10, 58, 134–136]
TERC	AD[¶]			2–5%			
RTEL1	AD[¶]			5–10%			[3, 10, 21, 30, 88, 137, 138]
PARN	AD[¶]			1–5%			[10, 58, 88, 139, 140]
DKC1	X			Rare			[141, 142]
TINF2	AD			Rare			[143–145]
NOP10	AD			Ultra-rare			[146]
NHP2	AD			Ultra-rare			[147]
ACD	AD			Ultra-rare			[148]
NAF1	AD			Ultra-rare			[149]
ZCCHC8	AD			Ultra-rare			[150]
RPA	AD			Ultra-rare			[151]
POT1	AD			Ultra-rare			[152]
Surfactant-related disease							
SFTPA1	AD	All ages, rare in children	Lung cancer	<5%	Unclassifiable pulmonary fibrosis: predominant diffuse ground-glass opacities, septal thickening and bilateral cysts of variable size, with a preferential distribution in the upper lobes and in subpleural areas	Optimal treatment in childhood ILD may differ from adult ILD. No cohort evaluation of drug effects in adults. Steroids? Hydroxychloroquine? Macrolides? Antifibrotic drugs? Lung transplantation may be considered.	[11, 58, 80]
SFTPA2	AD	All ages, rare in children	Lung cancer	<5%			[11, 79, 81]
SFTPC	AD	All ages, more frequent in children		<5%			[73, 153]
NKX2.1	AD	All ages, mainly in children	Lung–brain–thyroid syndrome: chorea and hypothyroidism	Rare			[76, 154]
ABCA3	AR	All ages, mainly in children		Rare			[59, 61, 74, 75]

AD: autosomal dominant; AR: autosomal recessive; X: X-linked; UIP: usual interstitial pneumonia; NSIP: non-specific interstitial pneumonitis; HP: hypersensitivity pneumonitis; PPFE: pleuro-parenchymal fibroelastosis. [#]: see Narrative Question 6 for background information; [¶]: AR in severe cases.

Borie et al. *Eur Respir J* 2023

Telomeres



The Nobel Prize in Physiology or Medicine 2009

Photo: U. Montan

Elizabeth H. Blackburn

Prize share: 1/3

Photo: U. Montan

Carol W. Greider

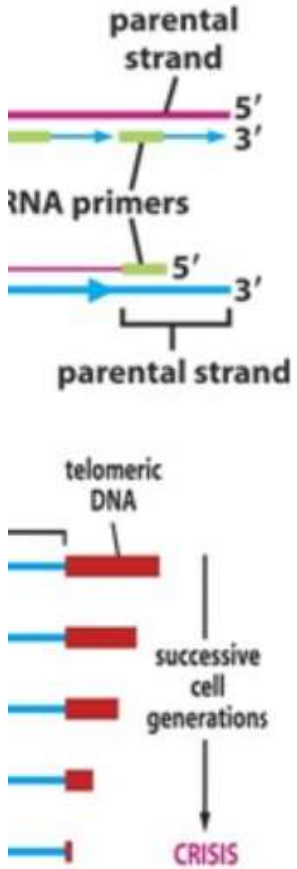
Prize share: 1/3

Photo: U. Montan

Jack W. Szostak

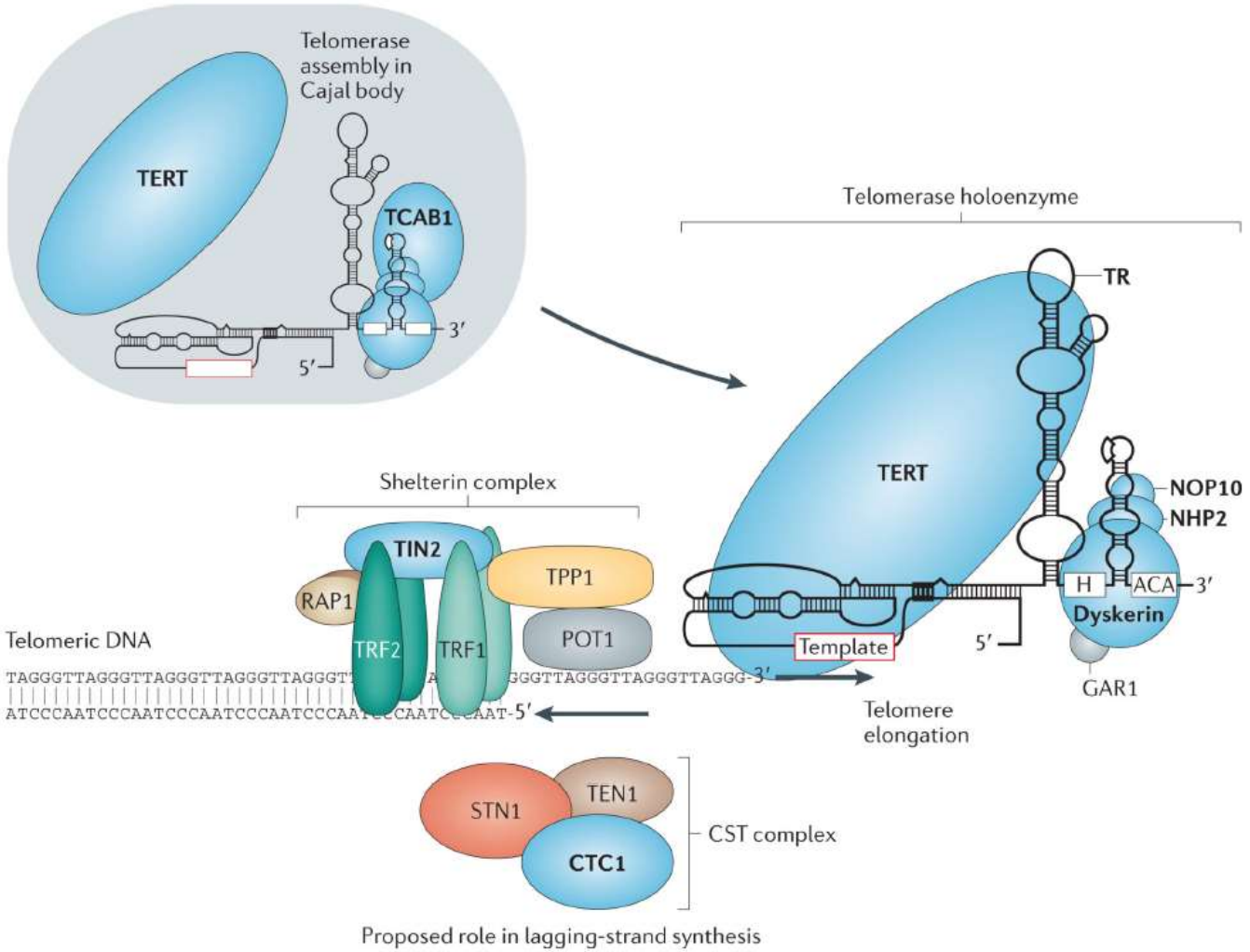
Prize share: 1/3

The Nobel Prize in Physiology or Medicine 2009 was awarded jointly to Elizabeth H. Blackburn, Carol W. Greider and Jack W. Szostak *"for the discovery of how chromosomes are protected by telomeres and the enzyme telomerase"*.



Blackburn, *Nature* 1991
Blackburn et al. *Science* 2015

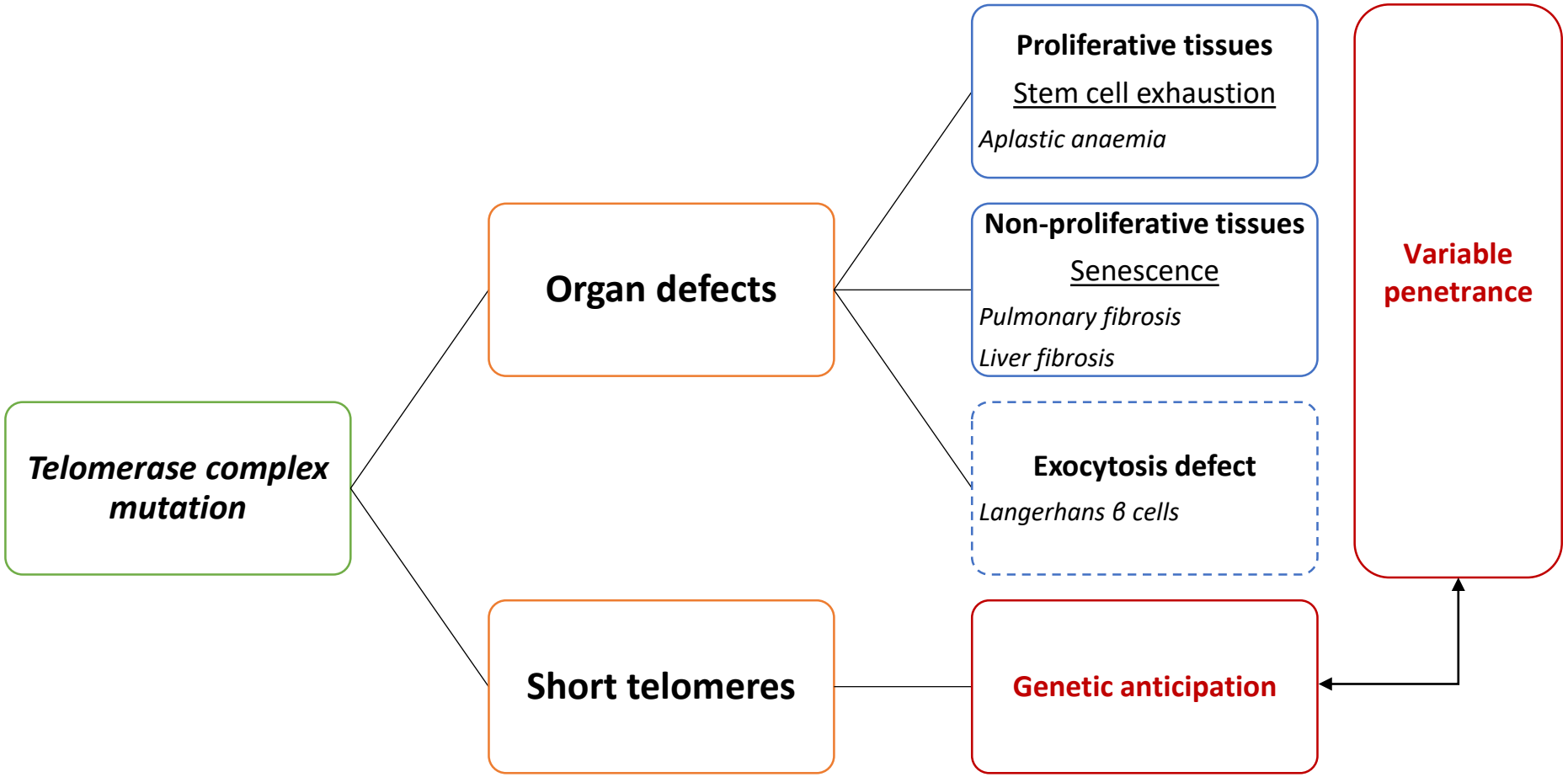
Telomerase complex



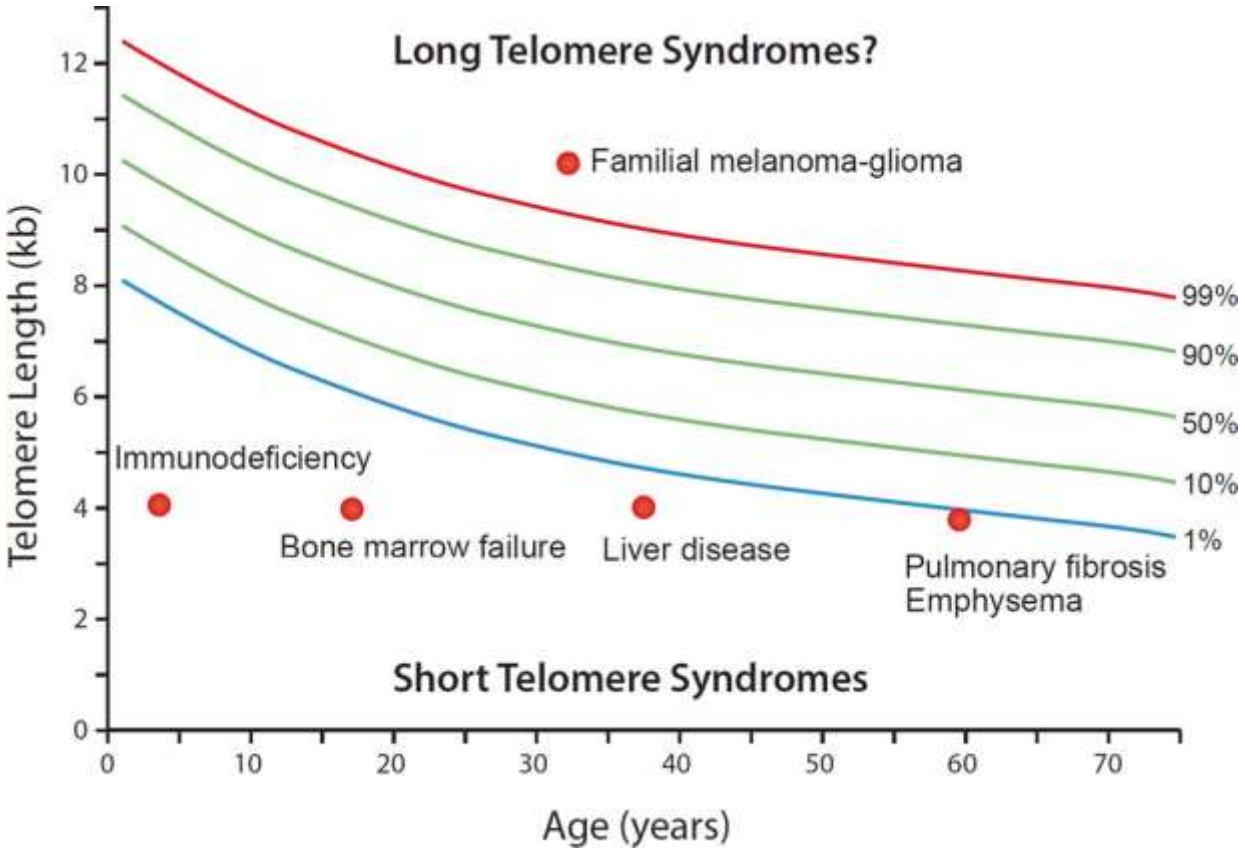
Gene name	***Protein***
TERC	Telomerase RNA component
TERT	Reverse transcriptase
RTEL1	Helicase
PARN	Poly-A specific ribonuclease
DKC	Dyskerin pseudouridin synthase

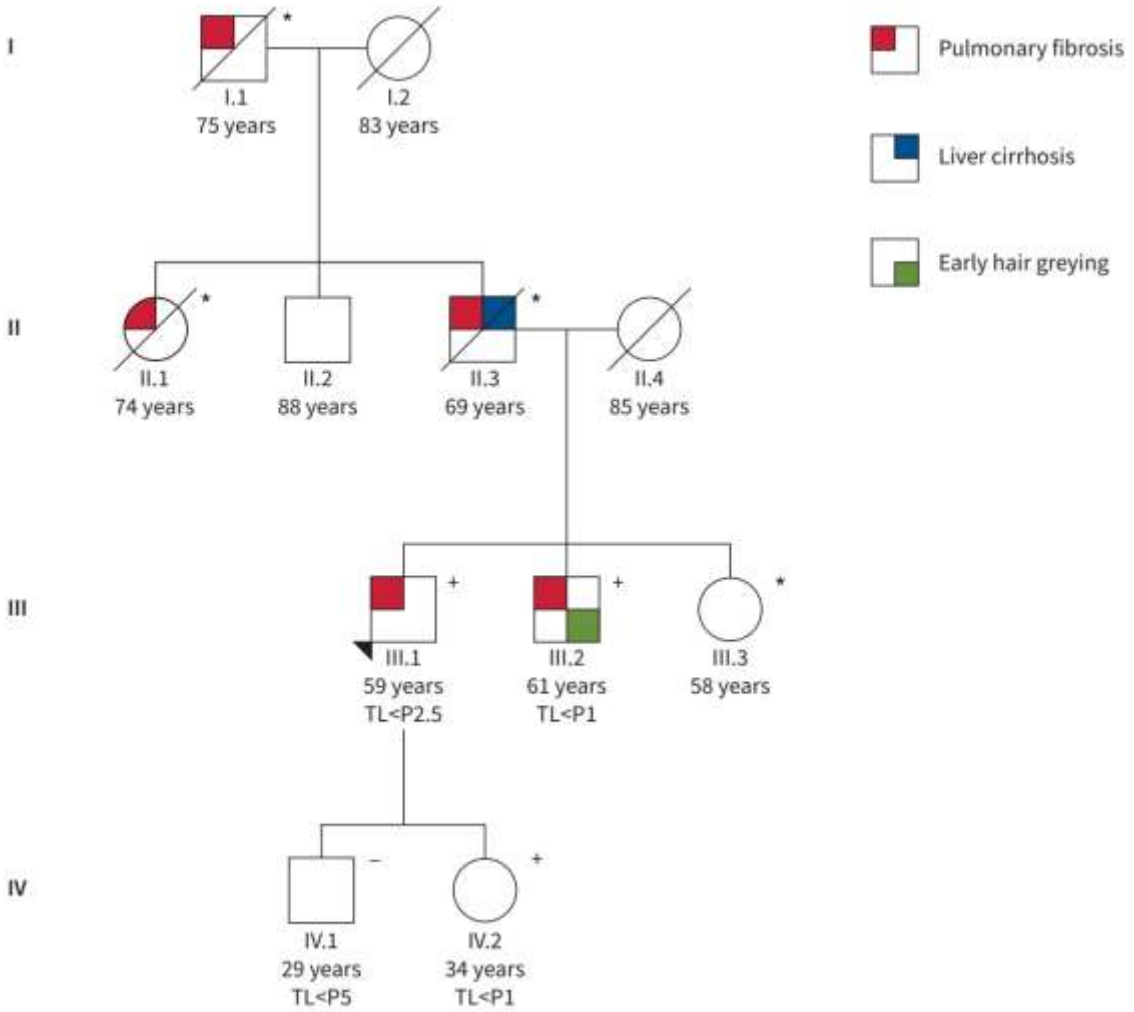
Armanios & Blackburn, *Nat Rev Genet* 2012

Short telomeres syndrome



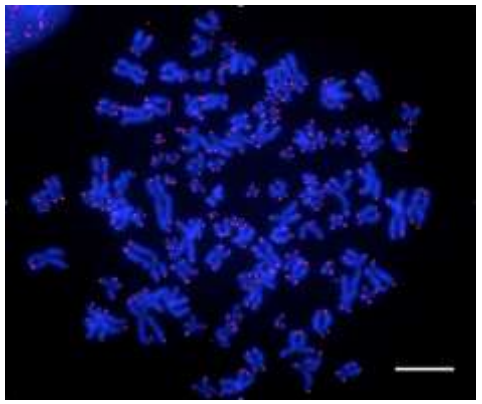
Short telomeres syndrome

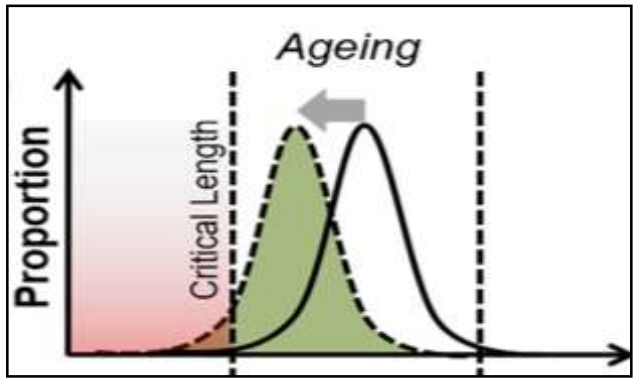


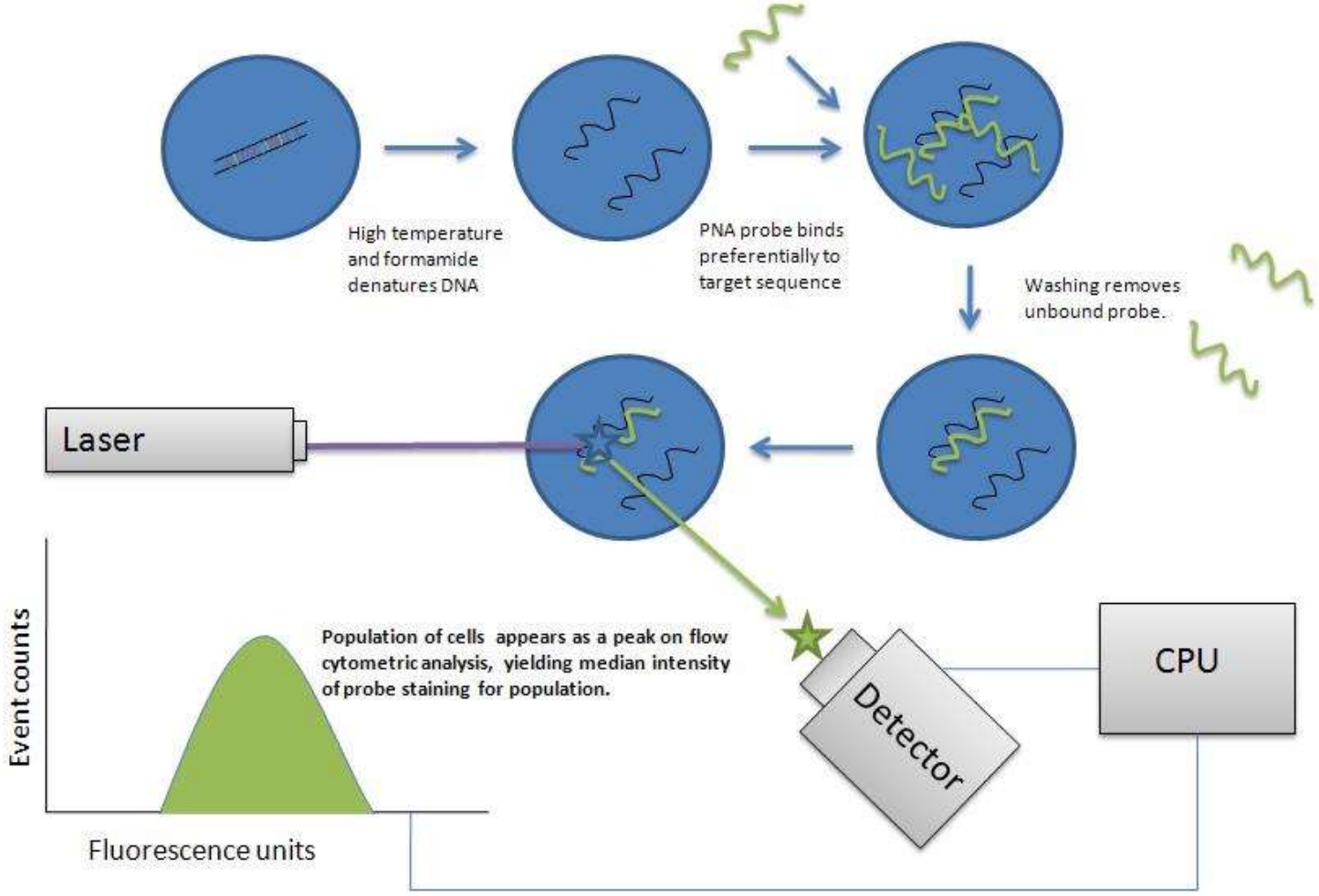


Stanley & Armanios, *Curr Opin Genet Dev* 2016
Borie et al. *Eur Respir J* 2023

Telomere length measurement

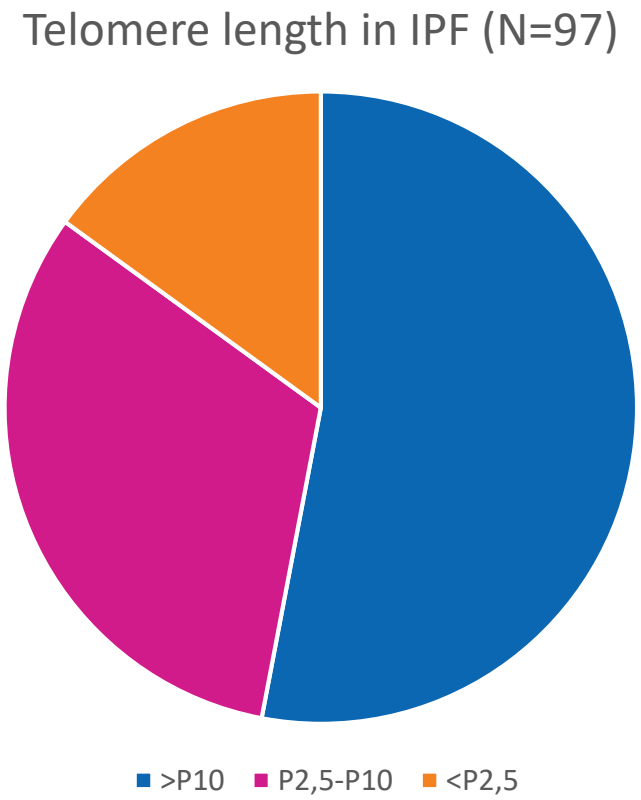


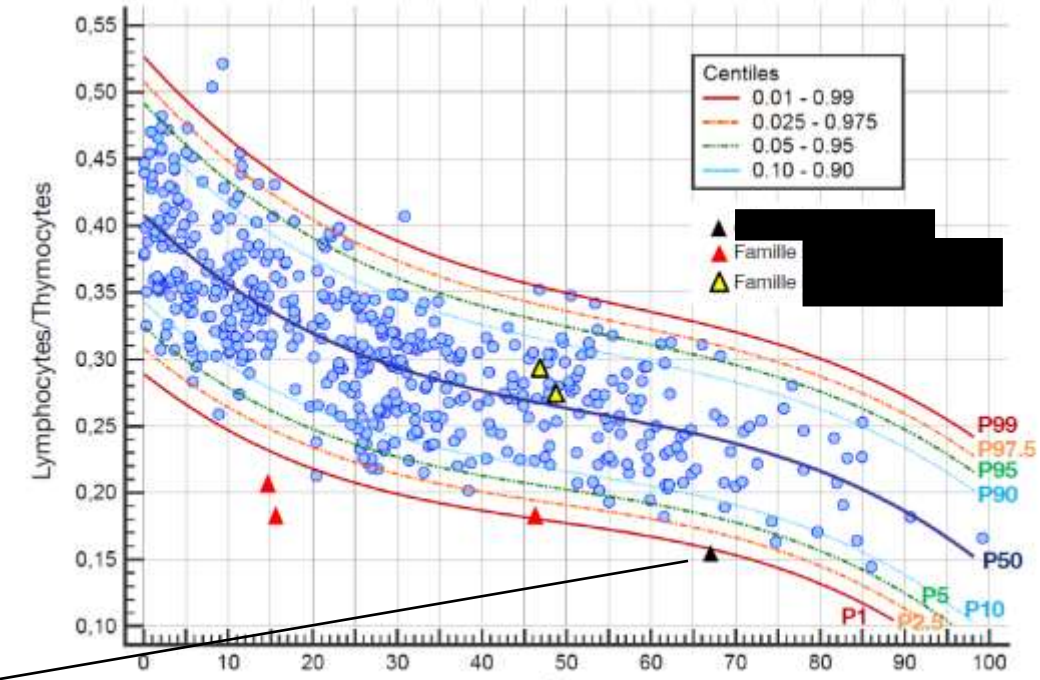




Beh et al, *Nucl Ac Research* 2018

Telomere length measurement





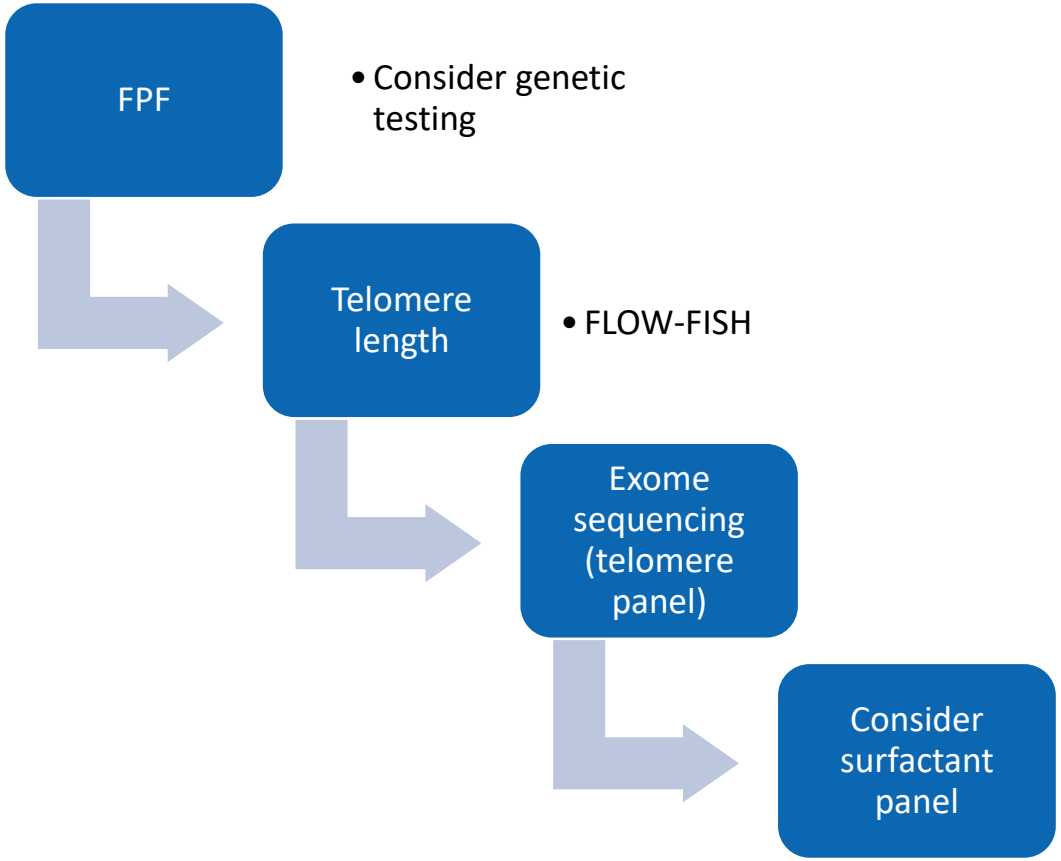
RESULTAT

Gène	Position	Exon	Mode de transmission	Statut	Classe
TERT (NM_198253.2)	c.2562T>G ; p.(Phe854Leu)	9	Autosomique dominant	Hétérozygote	V

Identification d'une substitution faux-sens à l'état hétérozygote: c.2562T>G (p.(Phe854Leu); pas de rs) dans l'exon 9 du gène *TERT*.

Muça et al. in prep.

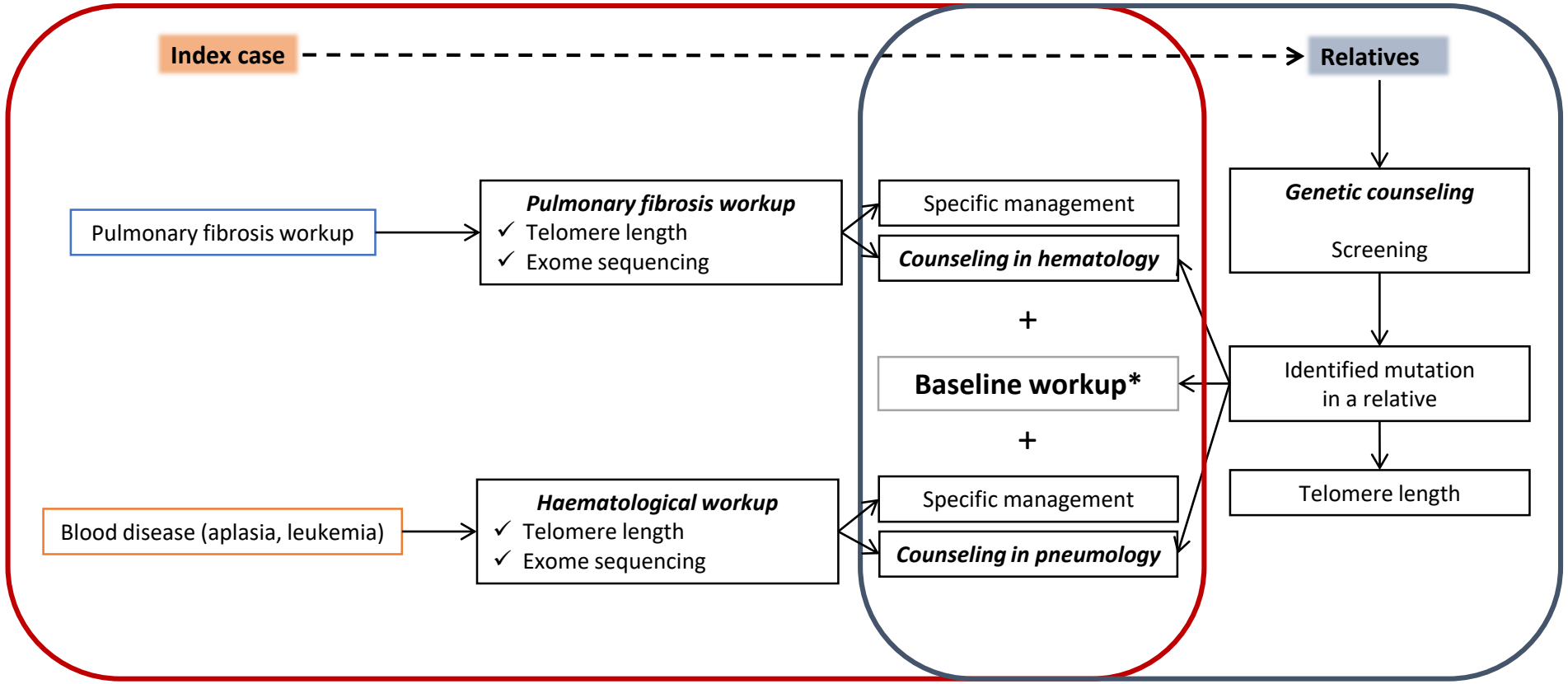
Practical patient management



Multidisciplinary management!
(European level)

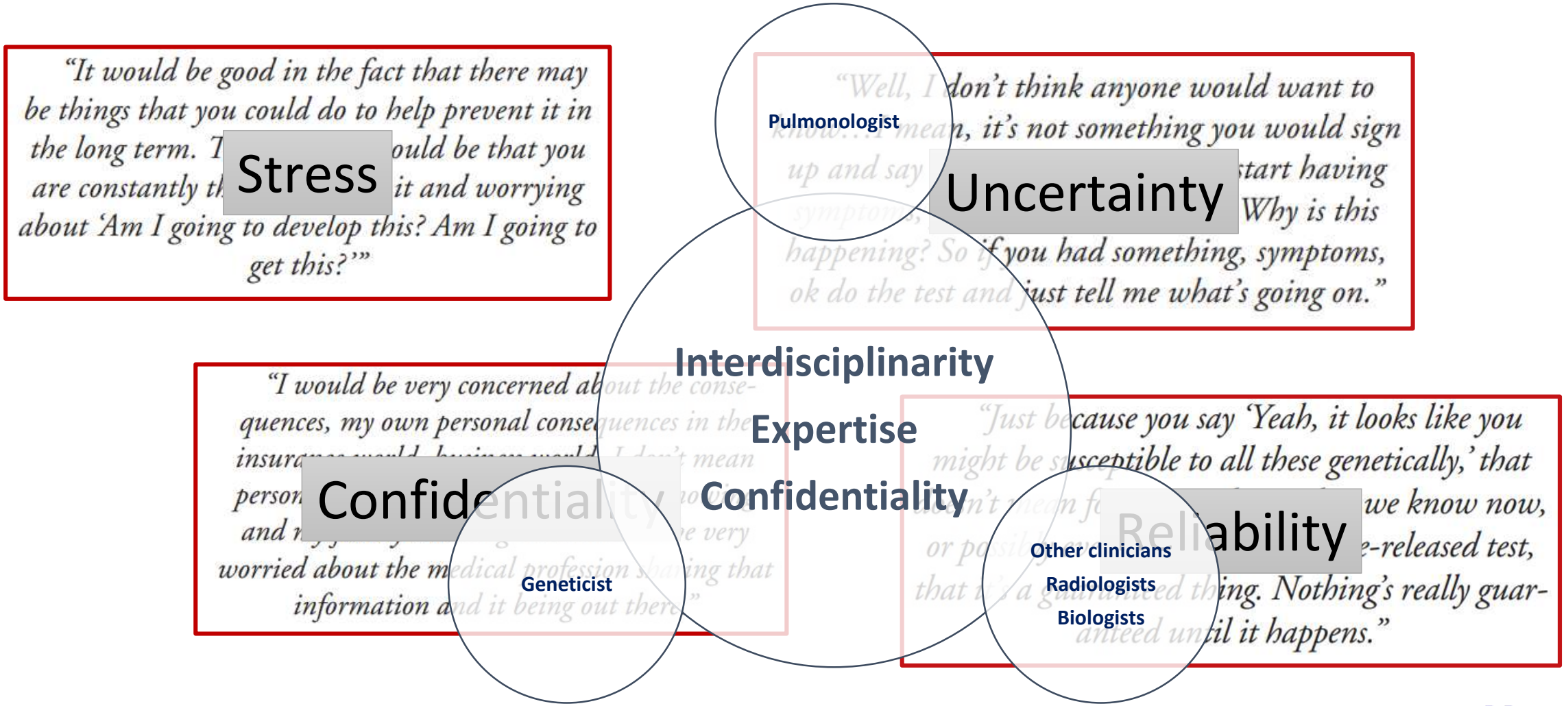
RespiFIL
Filière Maladies Respiratoires Rares

Genetic counselling



Baseline workup:
- ✓ Hemogram, liver enzymes
- ✓ Pulmonary function tests
- ✓ High resolution chest CT
- ✓ Fibroscan
- ✓ Lifestyle advices (smoking cessation, limitation of exposures…)

Tackling patients' concerns

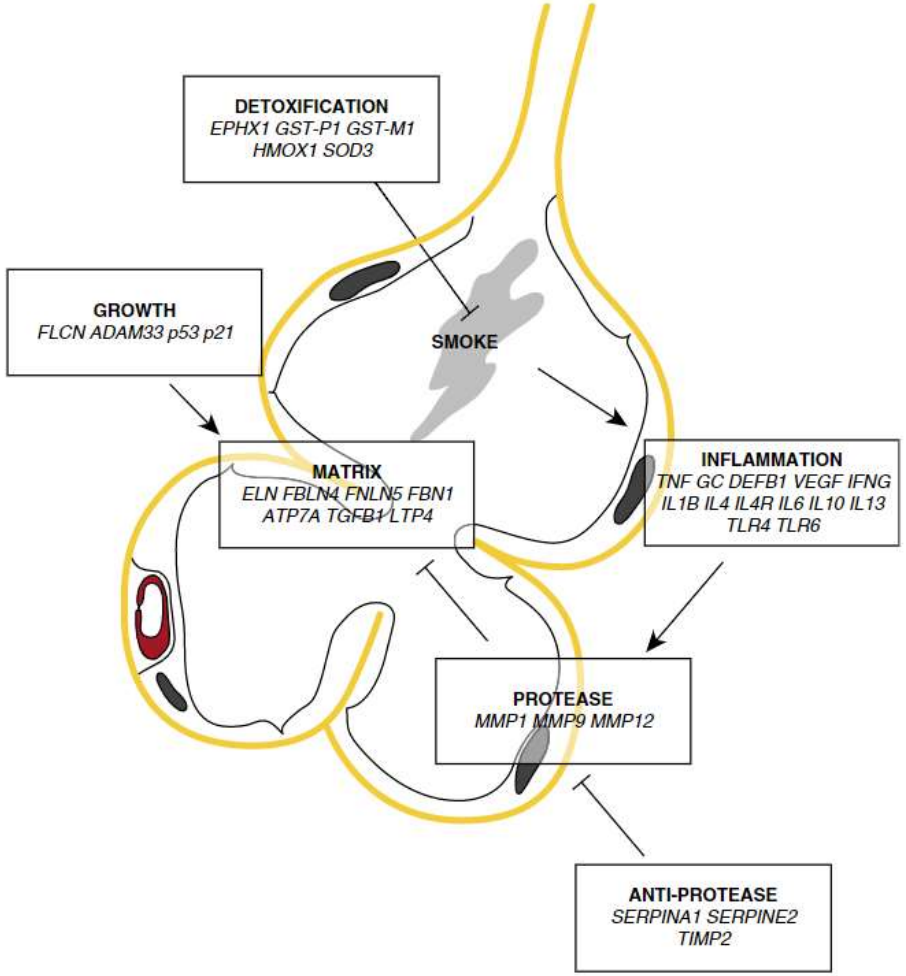


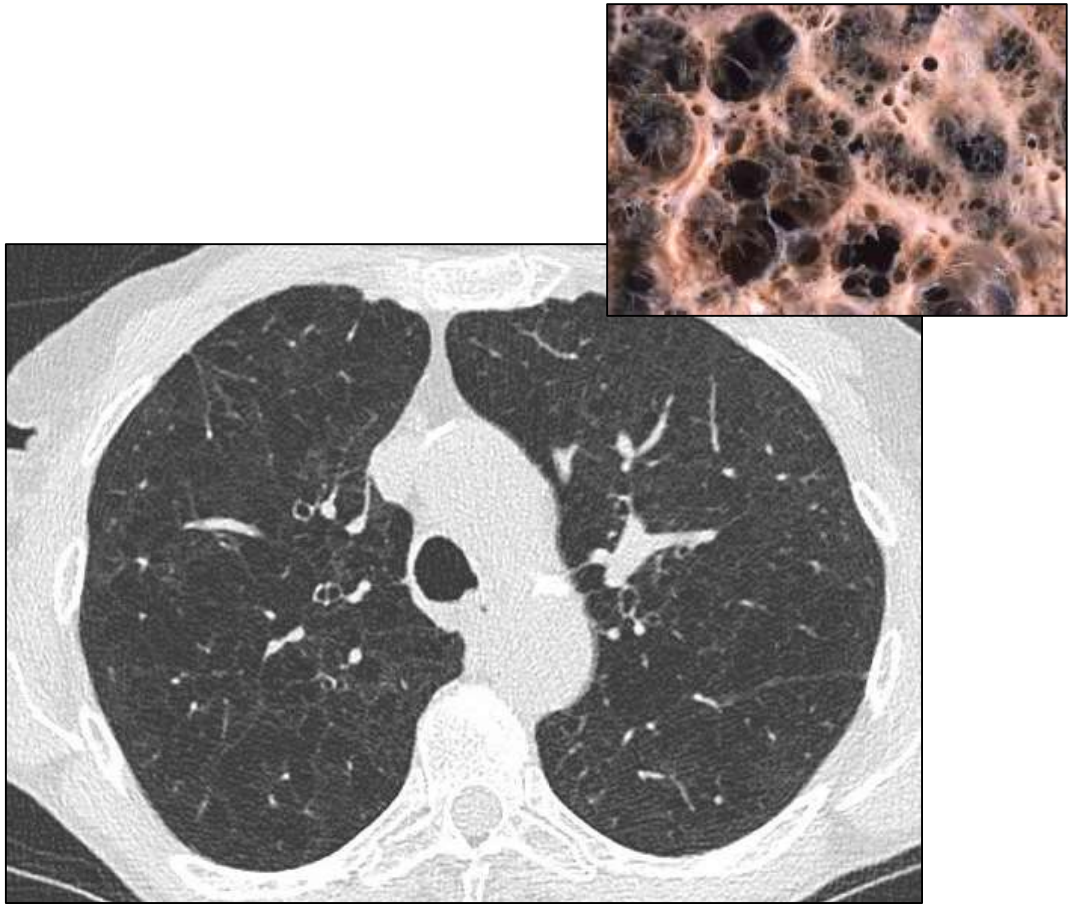
Conclusions

- 10% of patients with pulmonary fibrosis fulfill criteria for FPF
  - ✓ 1st or 2nd relative with pulmonary fibrosis
  - ✓ Fibrosis occuring <50
  - ✓ Signs of « short telomeres syndrome »
- Telomere-related genes variants are the most frequent
- Telomere length may serve as a screening tool
- Genetic counselling may be provided to relatives

Hereditary pulmonary emphysema

Emphysema

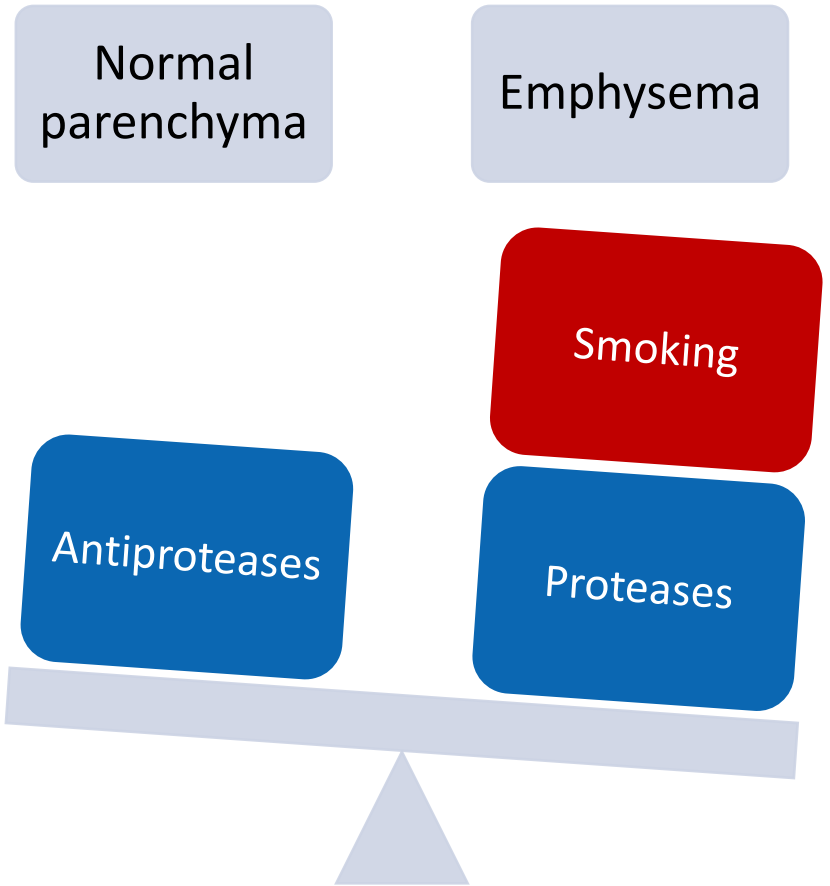




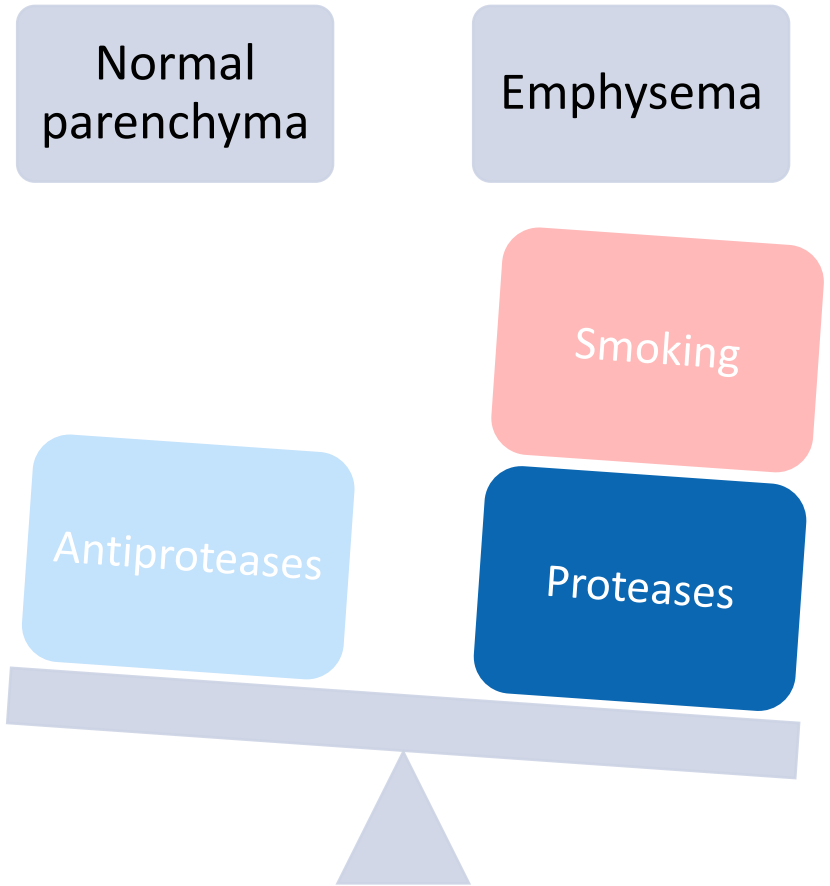
Lomas DA, *Ann Am Thorac Soc* 2016

α1-antitrypsin deficiency (AATD)

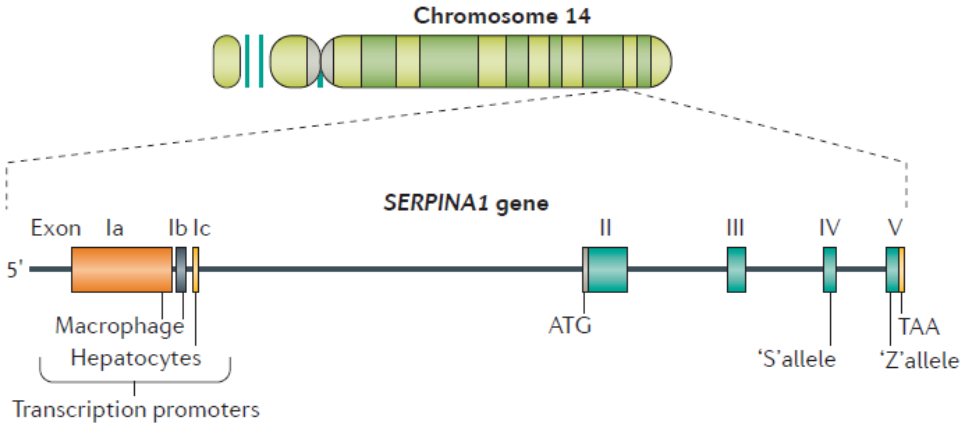
« Classical » emphysema



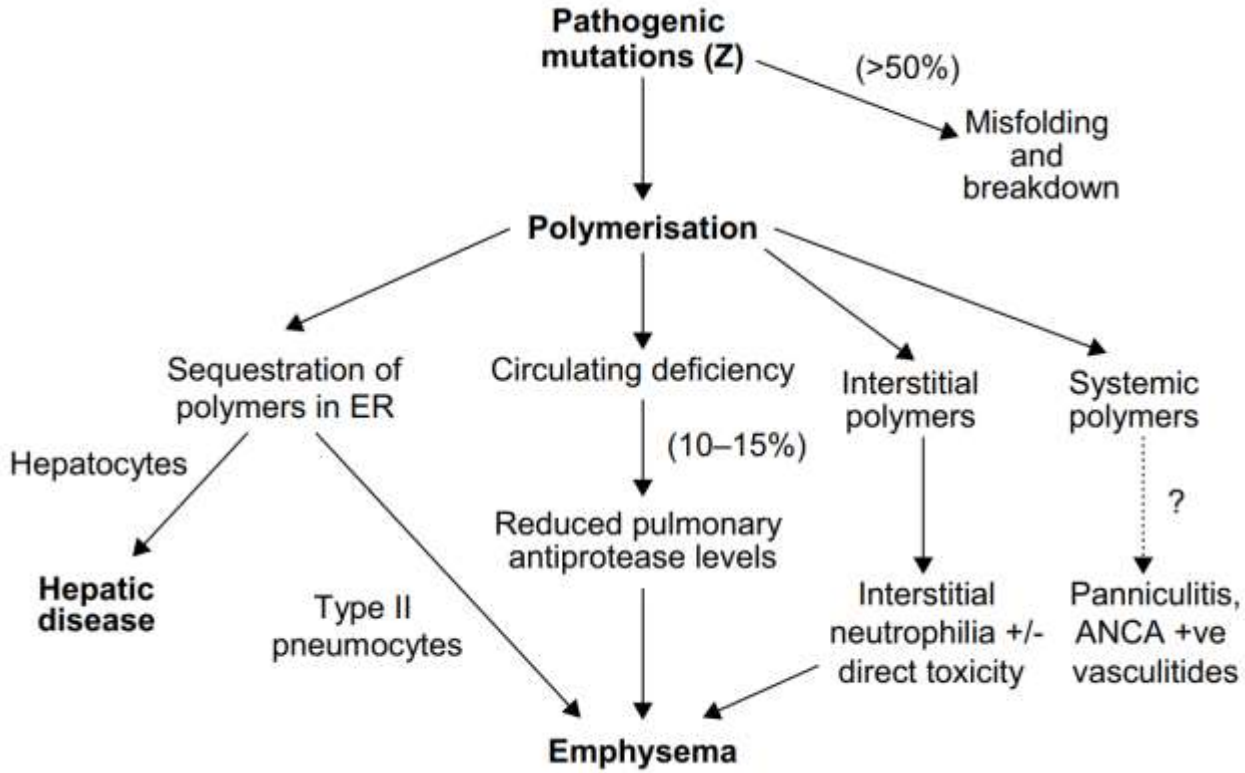
Antiproteases defect



Genetic mutations causing AATD

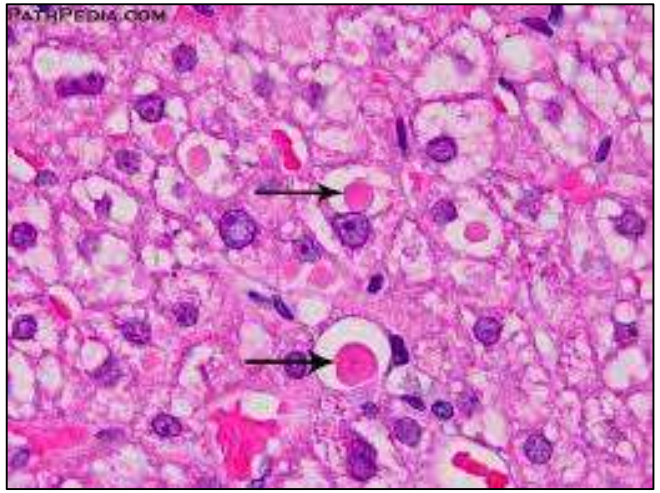


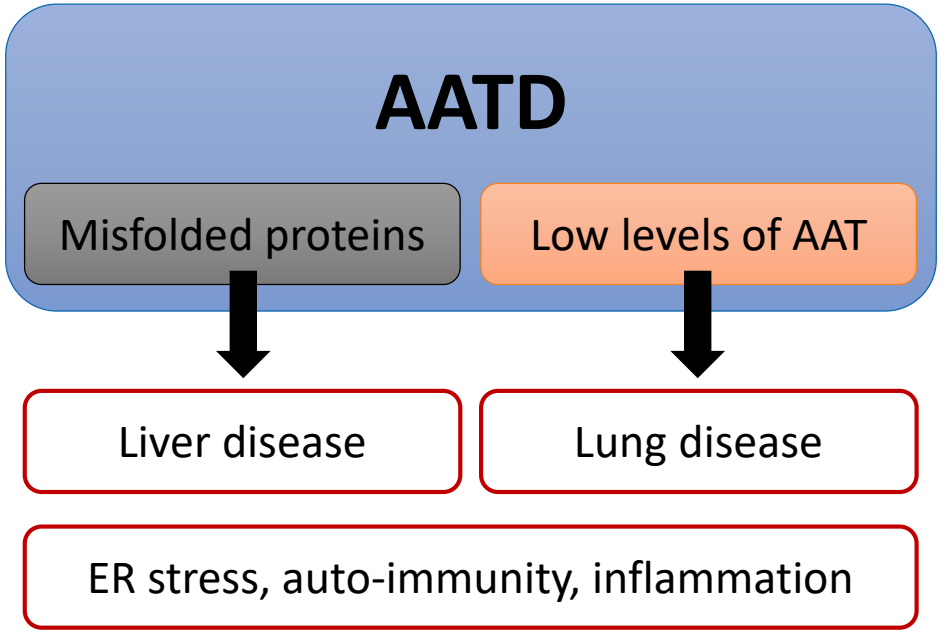
Genotype (co-dominance)	*Phenotype*	*Prevalence*
PI*MM	Normal	95%
PI*MZ, MS, M Null	↗ risk	4% caucasian
PI*ZZ, PI*ZS, PI*S Null, PI*Z Null	Disease	1/2000

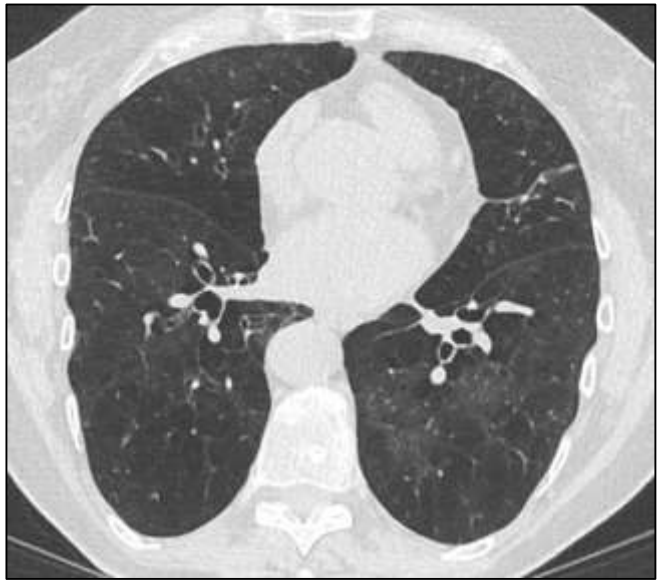


Greene et al. *Nat Rev Dis Primers* 2016
Gooptu et al. *Eur Respir J* 2009

Clinical spectrum of AATD

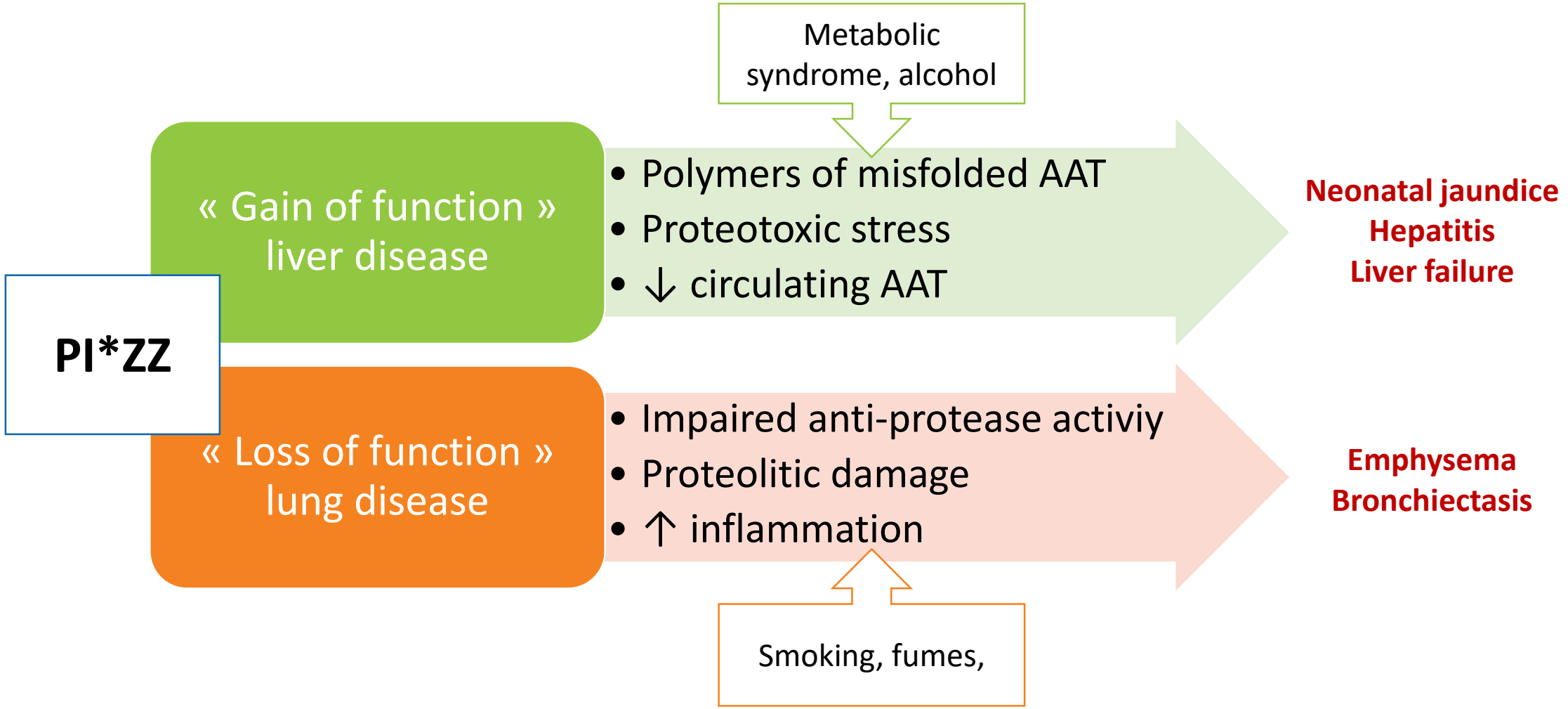






Pathpedia.com

Pathophysiology of AATD



Clinical spectrum of AATD

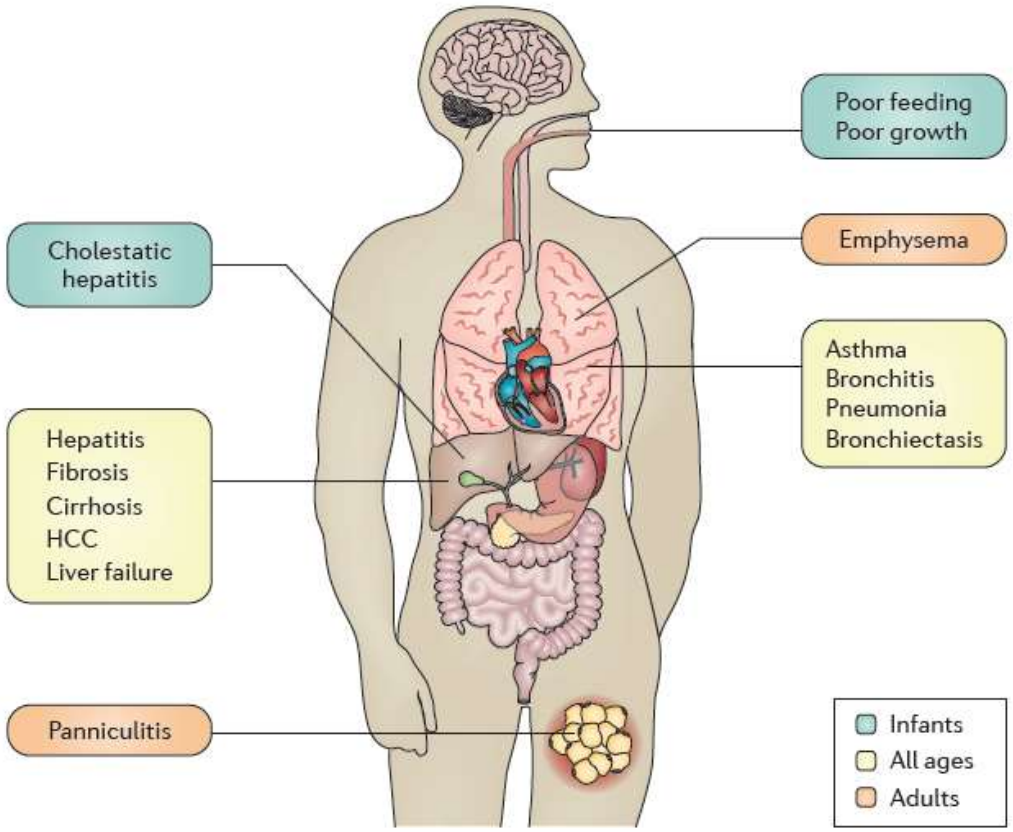


Table 2. Overview of Clinical Conditions Associated with AAT Deficiency.*

Disease	Odds Ratio (95% CI)		Study
	PI MZ	PI ZZ	
ANCA-associated vasculitis	2.9 (2.2–3.9)†	ND	Merkel et al.,[32] Rahmattulla et al.[33]
Gallstone disease	1.3 (1.3–1.4)	1.3 (0.7–2.5)	Ferkingstad et al.[34]
Emphysema (population-based studies)	1.4 (1.2–1.7)	28 (18–44)	Ferkingstad et al.[34]
COPD (population-based studies)‡	1–3	4.8 (3.0–7.9)	Ferkingstad et al.,[34] Foreman et al.[35]
COPD (case–control studies)‡	3–10	ND	Molloy et al.[36]
CFLD	5.0 (2.9–8.8)	ND	Bartlett et al.[37]
NAFLD cirrhosis	3–7	ND	Abul-Husn et al.[38]
Alcoholic liver cirrhosis	3.4–6	ND	Strnad et al.[39]
Advanced liver fibrosis (general population)	ND	9–20	Hamesch et al.[16]

* ANCA denotes antineutrophil cytoplasmic antibody, CFLD cystic fibrosis–associated liver disease with portal hypertension, CI confidence interval, COPD chronic obstructive pulmonary disease, NAFLD nonalcoholic fatty liver disease, ND not determined, PI MZ proteinase inhibitor genotype MZ, and PI ZZ proteinase inhibitor genotype ZZ.
† Higher odds ratios have been reported for vasculitis associated with proteinase 3–reactive ANCA with cytoplasmic staining (c-ANCA) and vasculitis associated with myeloperoxidase-reactive ANCA with perinuclear staining (p-ANCA).
‡ Higher odds ratios were reported for current and former smokers.

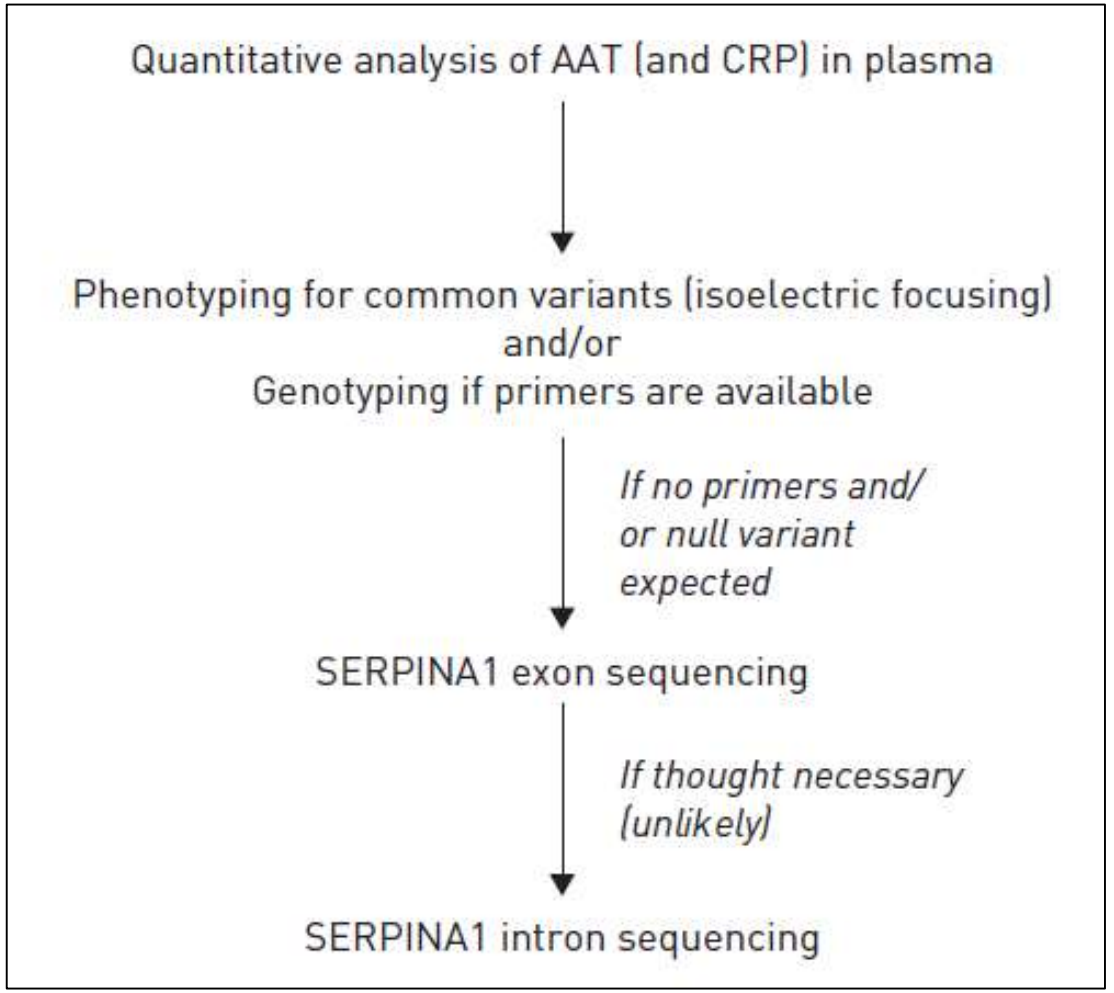
Greene et al. *Nat Rev Dis Primers* 2016
Strnad et al. *New Engl J Med* 2020

AATD diagnosis

- Underdiagnosed!!!
- We should test:
  - ✓ Emphysema (especially early-onset)
  - ✓ Non-responsive asthma
  - ✓ Bronchectasis
  - ✓ c-ANCA vasculitis
  - ✓ 1st-degree relatives of patients with AATD

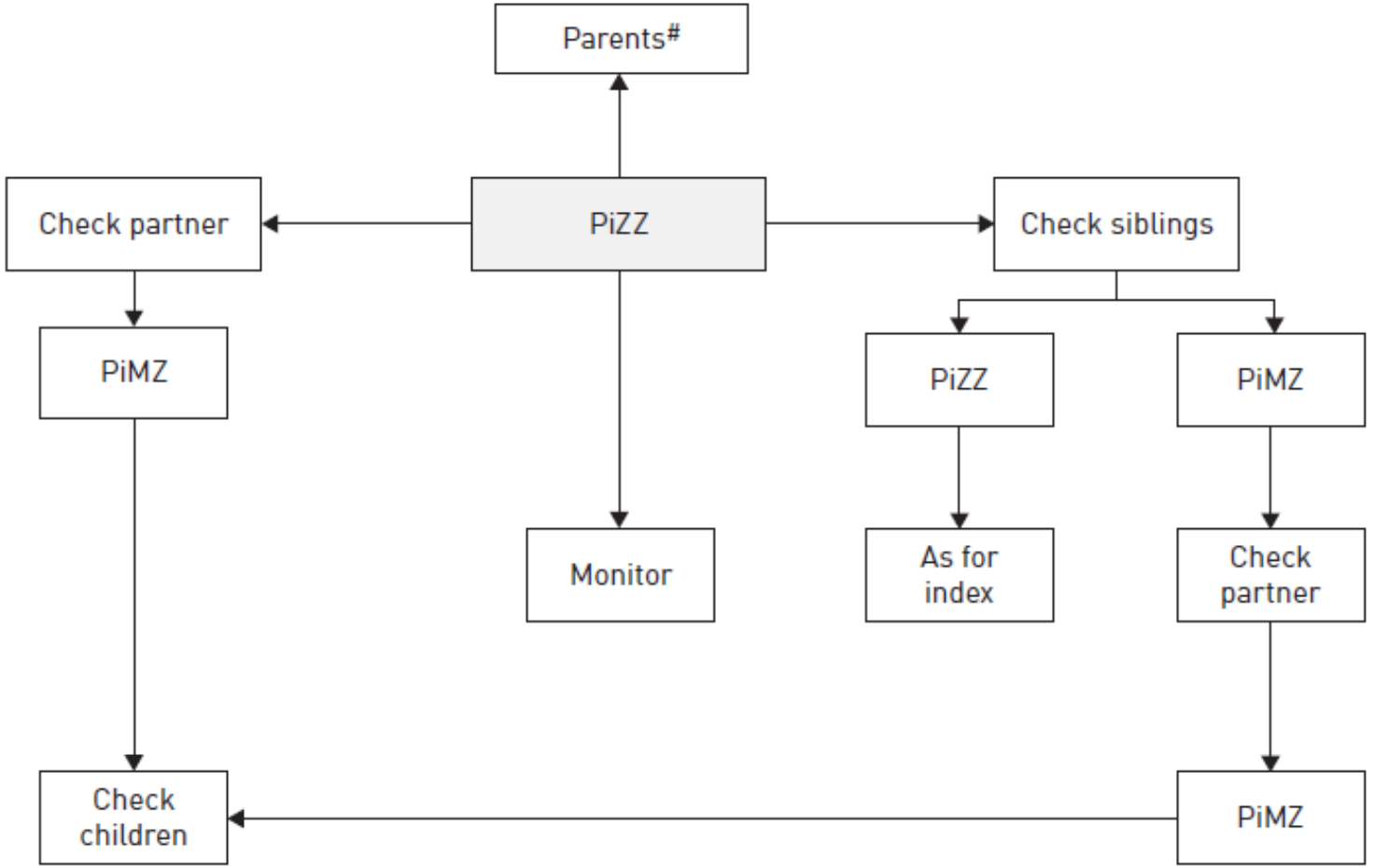
- First step: measurement of AAT serum level (+CRP)

  ➔ cut-off 1.1 g/L



Miravitlles et al. *Eur Respir J* 2017

Genetic counselling



Miravitlles et al. *Eur Respir J* 2017

Treatment of AATD

Control of risk factors

COPD treatment

AATD

Augmentation therapy

Organ transplantation

Conclusions

- AATD is the leading cause of genetic emphysema and is underdiagnosed.
- Diagnosis is based on measurement of serum AAT levels and genotyping;
- Homozygous patients develop early emphysema and liver fibrosis.
- Heterozygous patients are at risk for chronic lung, liver and systemic diseases.
- Treatment combines control of risk factors, augmentation therapy and organ replacement.

Thank you for your attention

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