# Familial pulmonary fibrosis: state of the art

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# Conflict of Interest Declaration

**Raphael Borie**

Grants/Research Support

Boehringer INgelheim, Ferrer, Sanofi

Payment

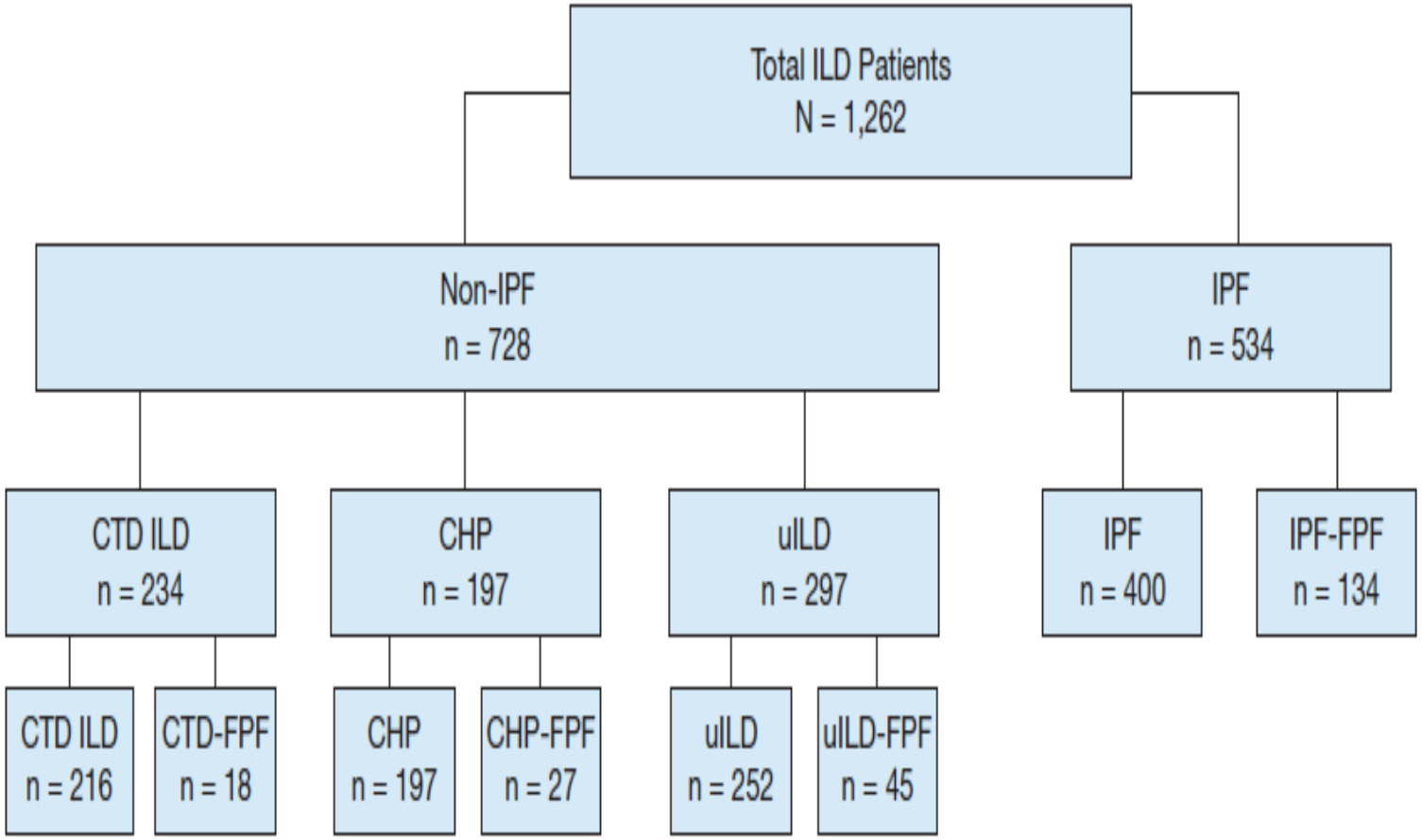
Boehringer INgelheim, Ferrer, Sanofi

# EVIDENCE FOR A GENETIC PREDISPOSITION : FAMILIAL PULMONARY FIBROSIS (FPF)

ERS Taskforce statement
- At least 2 members
- 1 or 2 degree of relationship
- Not limited to idiopathic ILD

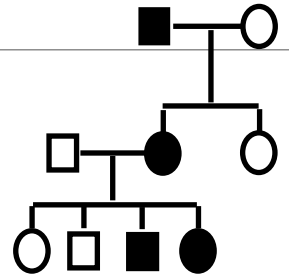
Frequency uncertain: ≈5-25%
- 25% in IPF?
- 12.5% non-IPF ILD?

Suggest a genetic background




Steele, AJRCCM 2005; Cutting, Chest, 2021, Borie, ERJ, 2023

# Heterogeneity of familial pulmonary fibrosis



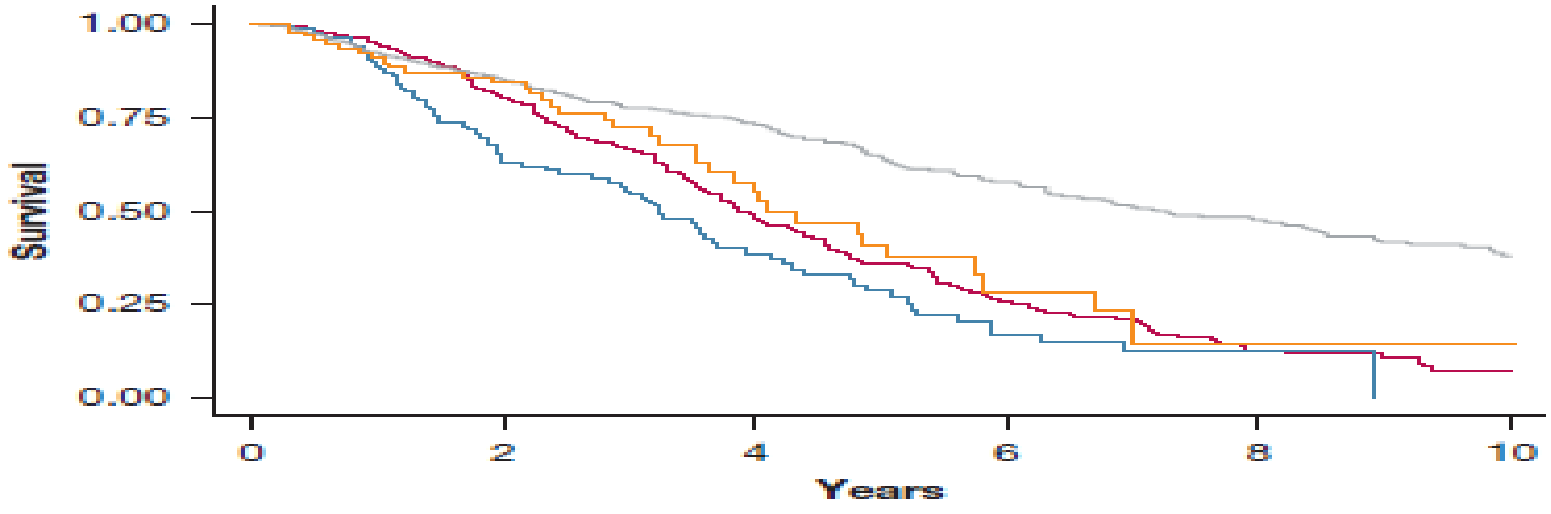
| | *Scanner* | *Histologique* |
|---|---|---|
| | Probable ($n$ = 231) | Definite ($n$ = 78) |
| IPF/UIP | 181 (78.4) | 67 (85.9) |
| NSIP | 12 (5.2) | 8 (10.3) |
| COP | 0 | 2 (2.6) |
| Centrilobular nodules | 1 (0.4) | 0 |
| Unclassified ILD | 37 (16.0) | 1 (1.3) |

**Heterogeneity in 45% of the family**

**UIP + unclassifiable *(60%)***
**UIP + NSIP *(30%)***
**UIP + COP *(very rare)***
**UIP + RB-ILD *(very rare)***

*Steele, AJRCCM, 2005*

# What is known about the natural history of FPF? FPF impacts the prognosis



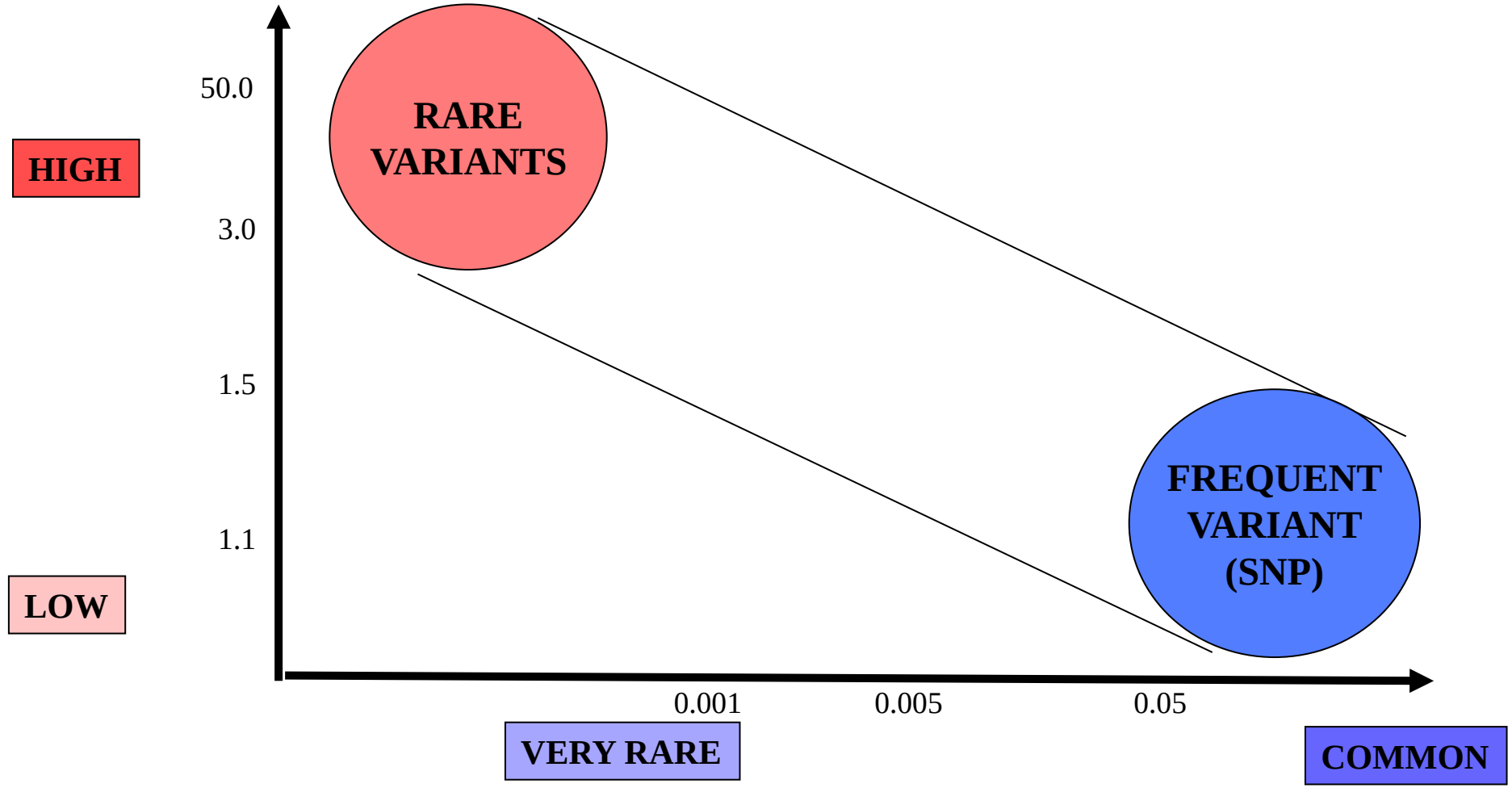

| Number at risk | | | | | | |
|---|---|---|---|---|---|---|
| Sporadic IPF | 400 | 230 | 89 | 39 | 14 | 6 |
| Familial IPF | 134 | 67 | 27 | 9 | 3 | 0 |
| Sporadic non-IPF ILD | 638 | 364 | 185 | 114 | 76 | 46 |
| Familial non-IPF ILD | 90 | 58 | 22 | 6 | 3 | 2 |

Sporadic IPF — Familial IPF
Sporadic non-IPF ILD — Familial non-IPF ILD

Cutting, Chest, 2021

# MENDELIAN DISEASE OR GENETIC RISK FACTOR

**Power of the effect**

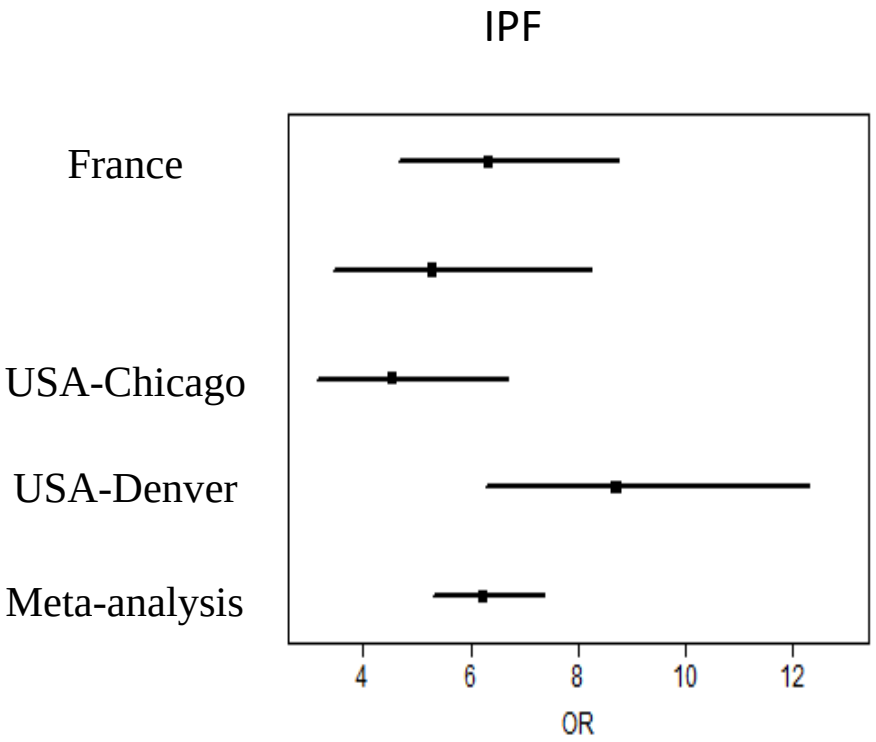



Manolio, Nature, 2009

Allele Frequency

# Presence of the T allele in the of *MUC5B* promoter x6 the risk of IPF in the white population

## INCREASED RISK OF IPF WITH THE *MUC5B* POLYMORPHISM

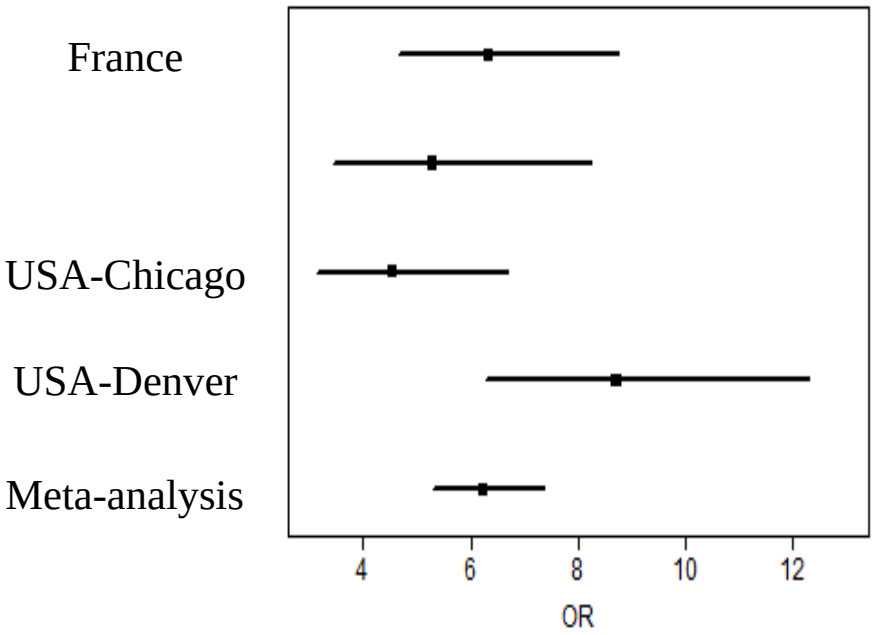



Borie, Plos One, 2013

# Presence of the T allele in the of *MUC5B* promoter x6 the risk of IPF/UIP in the white population

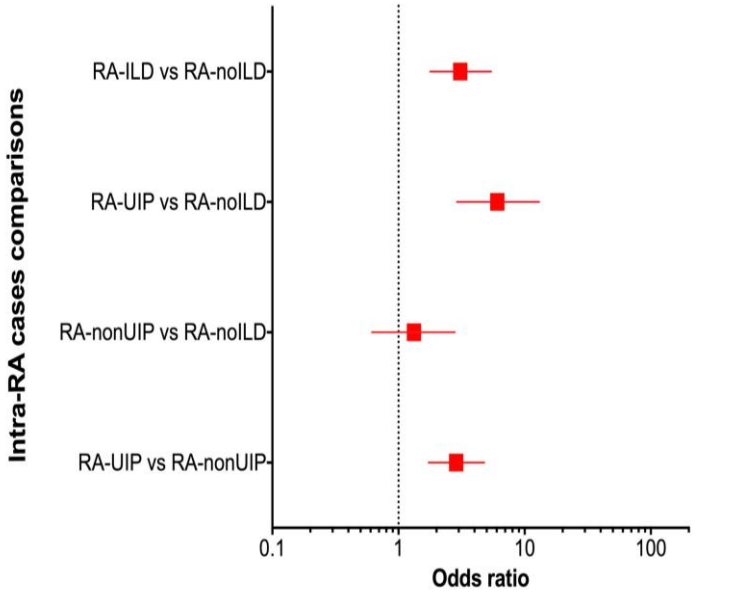
## INCREASED RISK OF IPF/UIP WITH THE *MUC5B* POLYMORPHISM

IPF




Borie, Plos One, 2013

RA-ILD

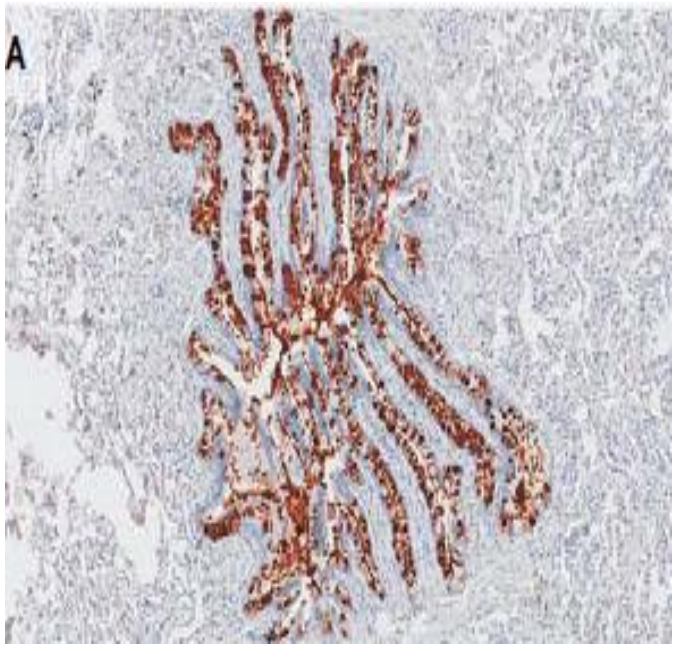



Juge, Nejm, 2018

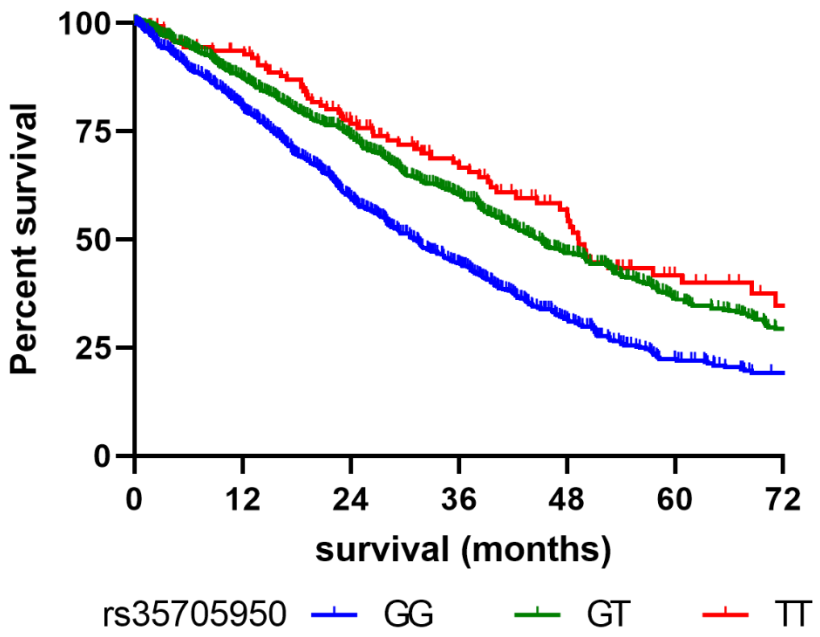
| | Asbestosis (n=78) | Controls (n=300) |
|---|---|---|
| GG* | 36 | 239 |
| GT* | 38 | 58 |
| TT* | 4 | 3 |
| MAF (%) | 29 | 11 |
| OR (95% CI) | 3.5 (2.4-5.1) | na |
| P-value | $5.1*10^{-11}$ | na |

Platenburg, ERJ, 2020

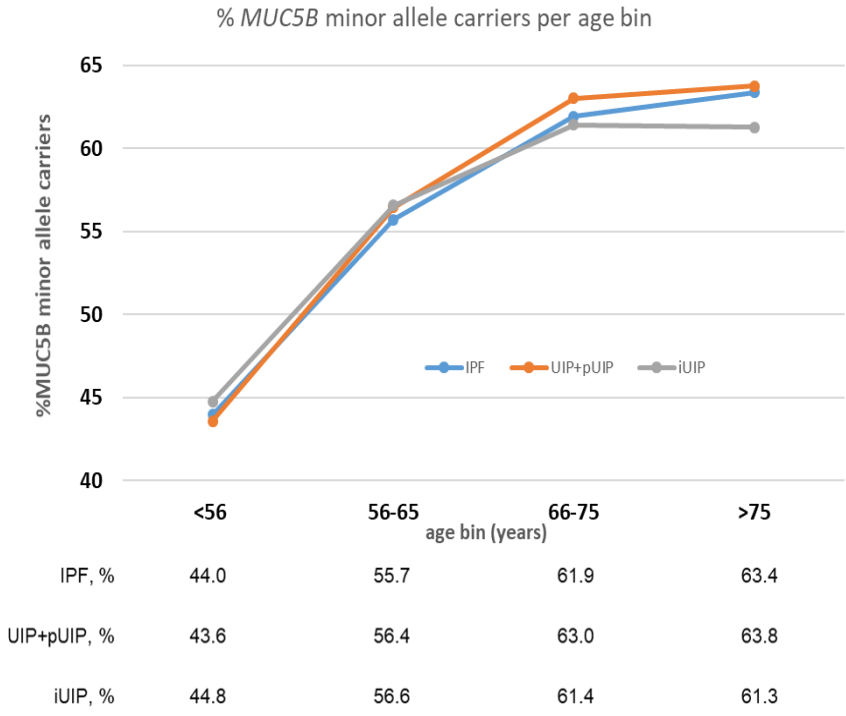
# MUC5B paradoxes




Epithelial Expression




Better survival

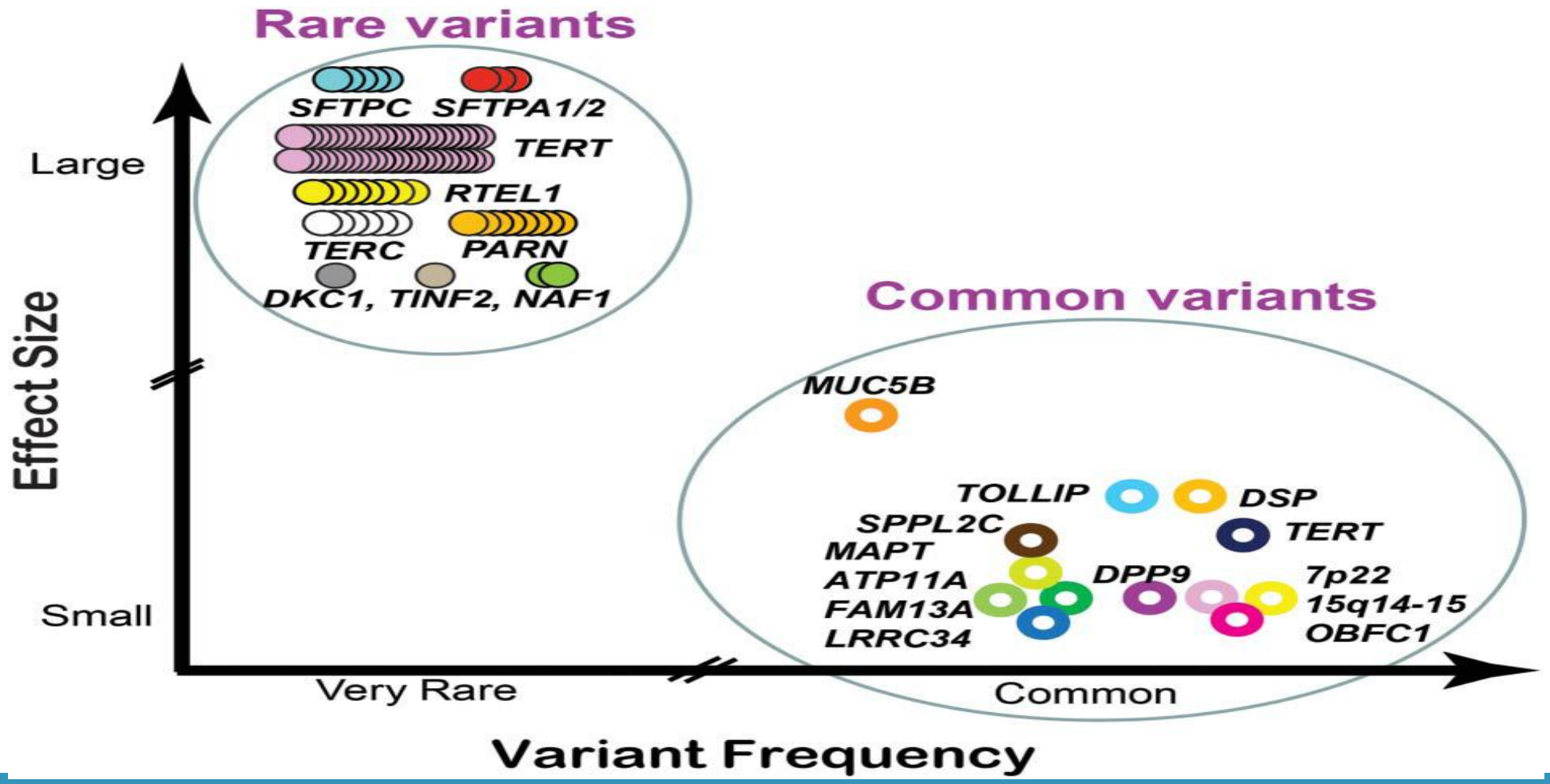



| | <56 | 56-65 | 66-75 | >75 |
|---|---|---|---|---|
| IPF, % | 44.0 | 55.7 | 61.9 | 63.4 |
| UIP+pUIP, % | 43.6 | 56.4 | 63.0 | 63.8 |
| iUIP, % | 44.8 | 56.6 | 61.4 | 61.3 |

Same prevalence in familial and sporadic pulmonary fibrosis

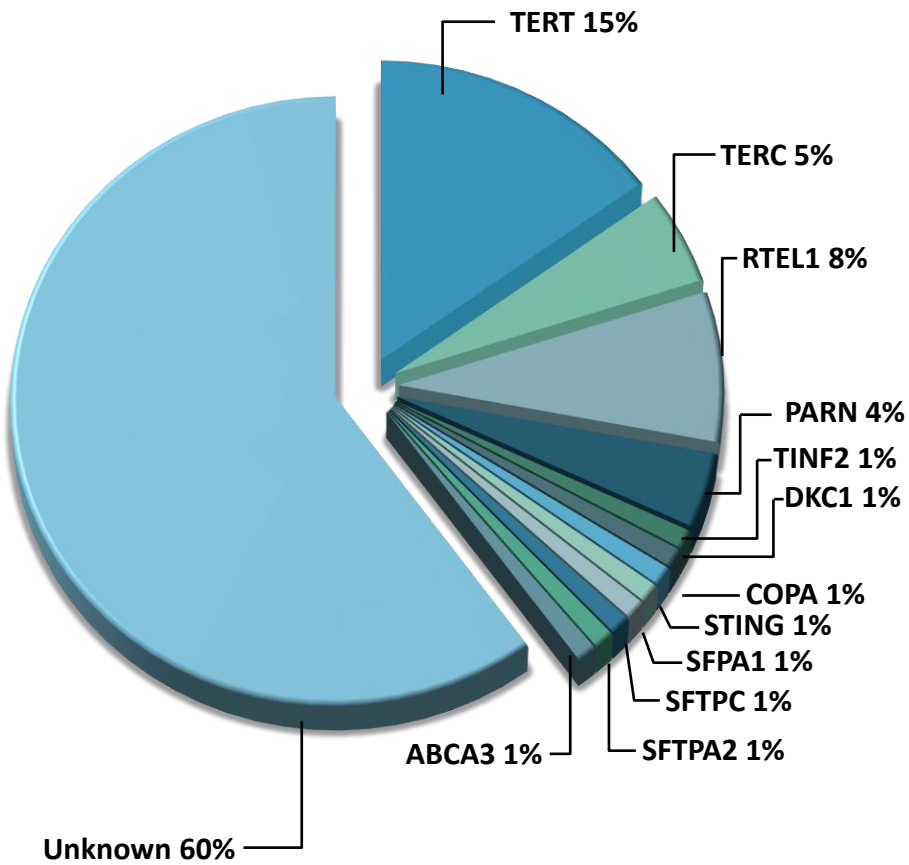
Seibold, NEJM, 2011, Peljto, JAMA, 2013, van der Vis, Respirology, 2023

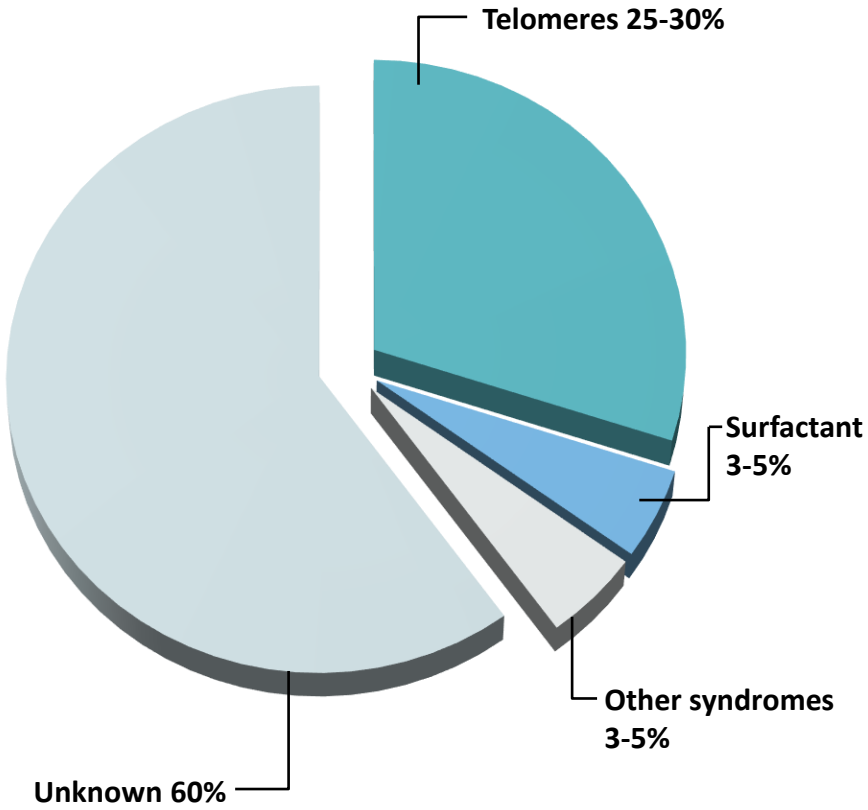
# MENDELIAN DISEASE OR GENETIC RISK FACTOR

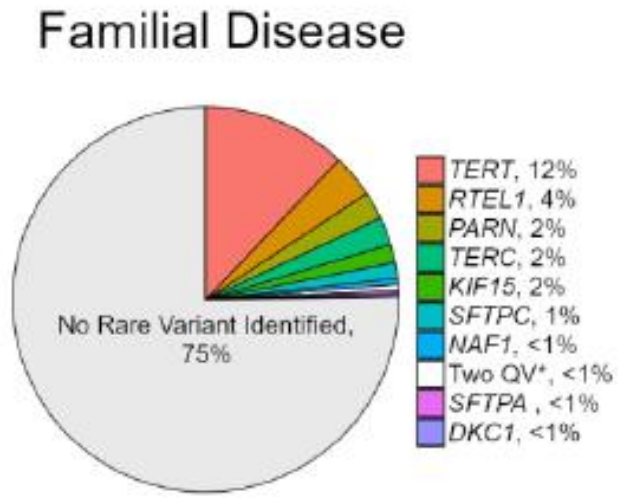


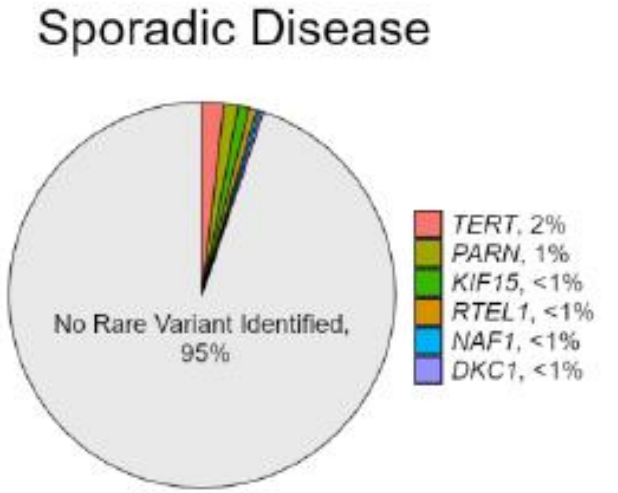

Mathai, Thorax, 2016

# SO MANY GENES



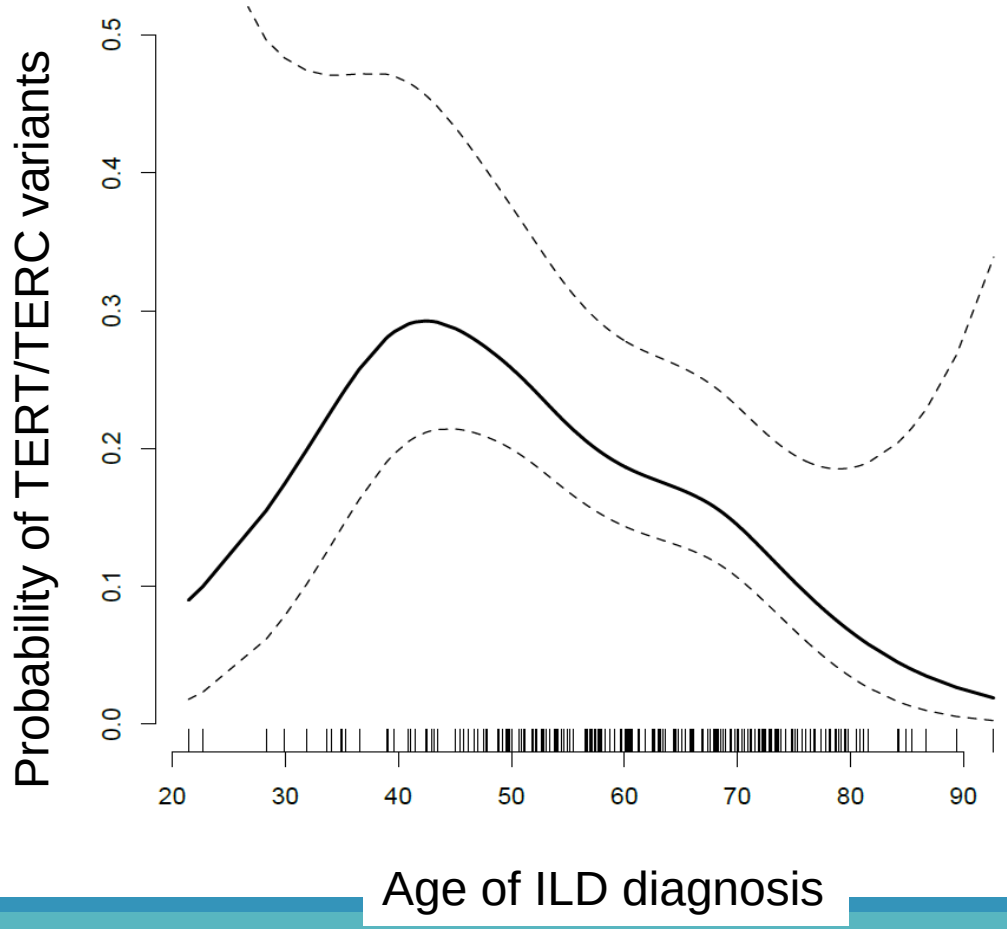




Borie, ERJ, 2023; Zhang, ERJ, 2022

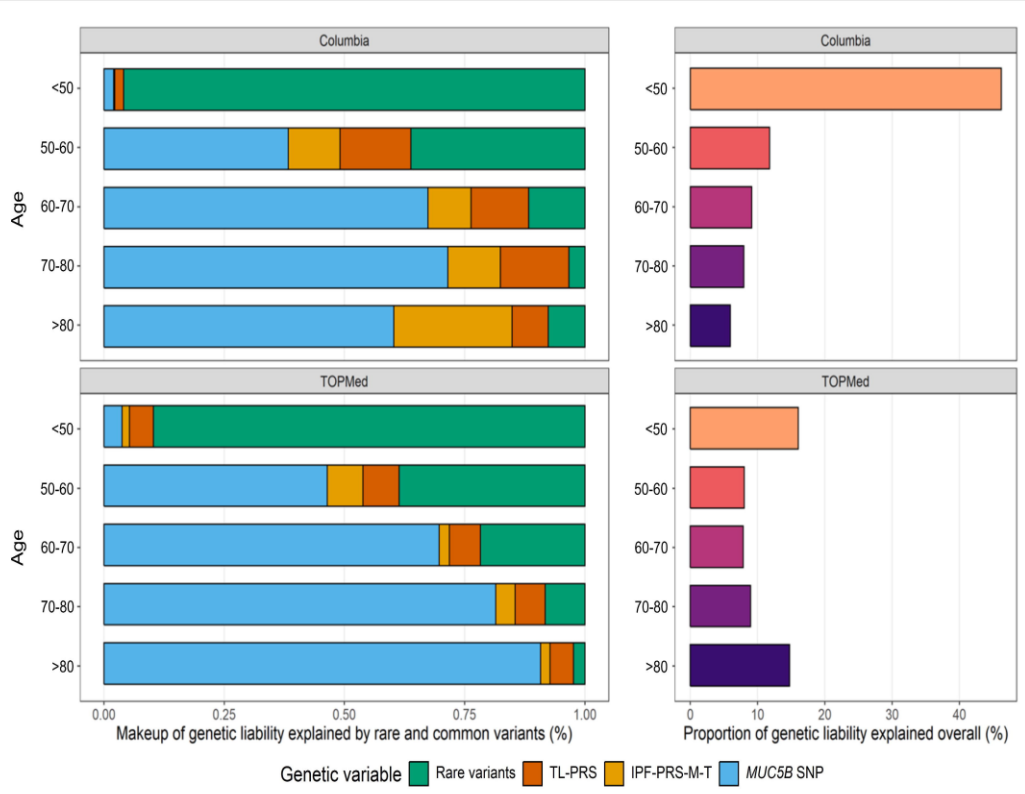
# Genetic backgound vary with age



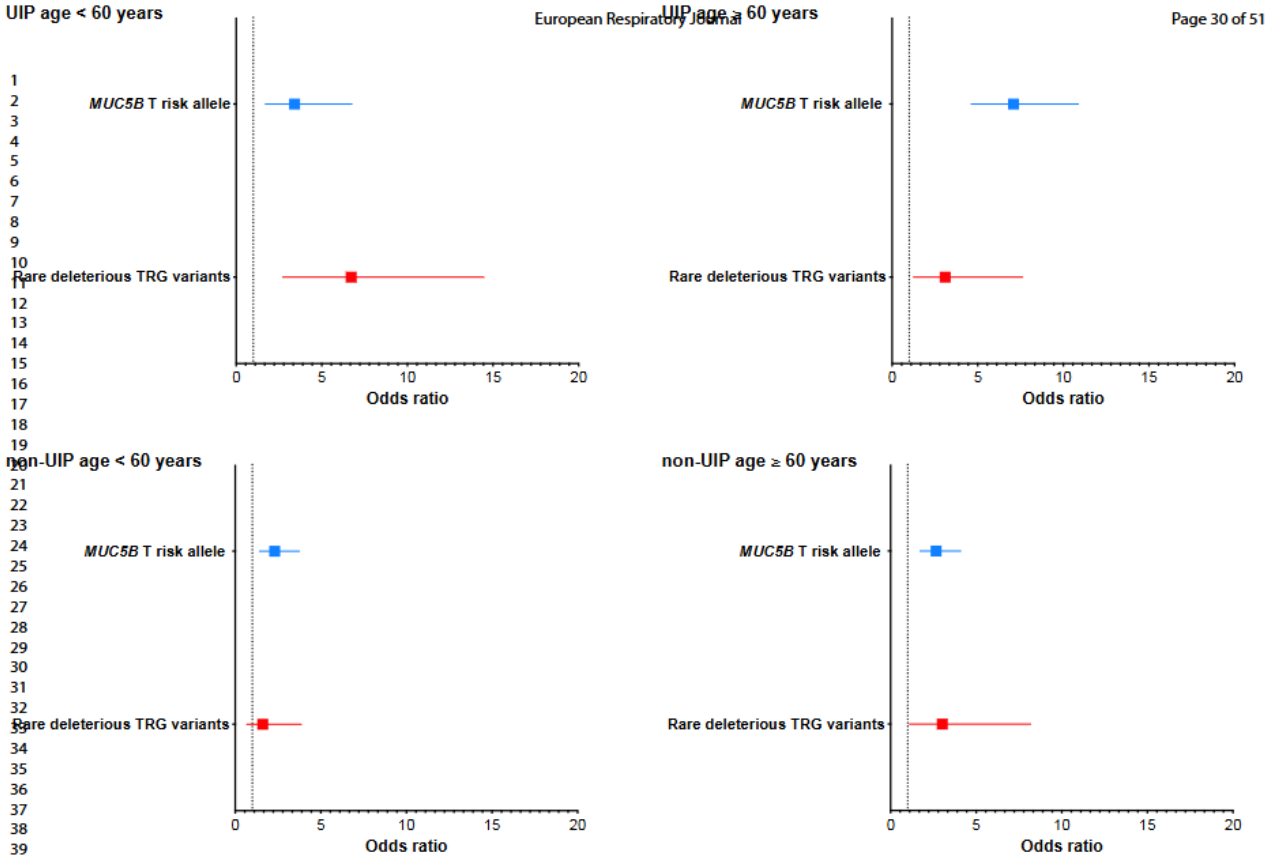

| | Transplanted (n = 149) | Non-transplanted (n = 282) |
|---|---|---|
| Age at diagnosis | 60 (37-74) | 70 (39-85) |
| Male | 112 (75%) | 194 (67.7%) |
| FPF | 17 (11.4%) | 24 (8.5%) |
| Variant TRG rare (%) | 36 (24.2%) | 33 (11.7%) |
| TERT | 9* | 9 |
| TERC | 5** | 2 |
| RTEL1 | 12 | 14 |
| PARN | 9 | 6 |
| NAF1 | 4 | 2 |
| Pathogenic variant | 20 (13.4%) | 11 (3.9%) |
| Telomere length <10$^{th}$% | 32 (25.2%) | 18 (6.8%) |

*Borie, ERJ, 2016; Alder, Jhlt, 2022*

## *IPF*




## *RA-ILD*



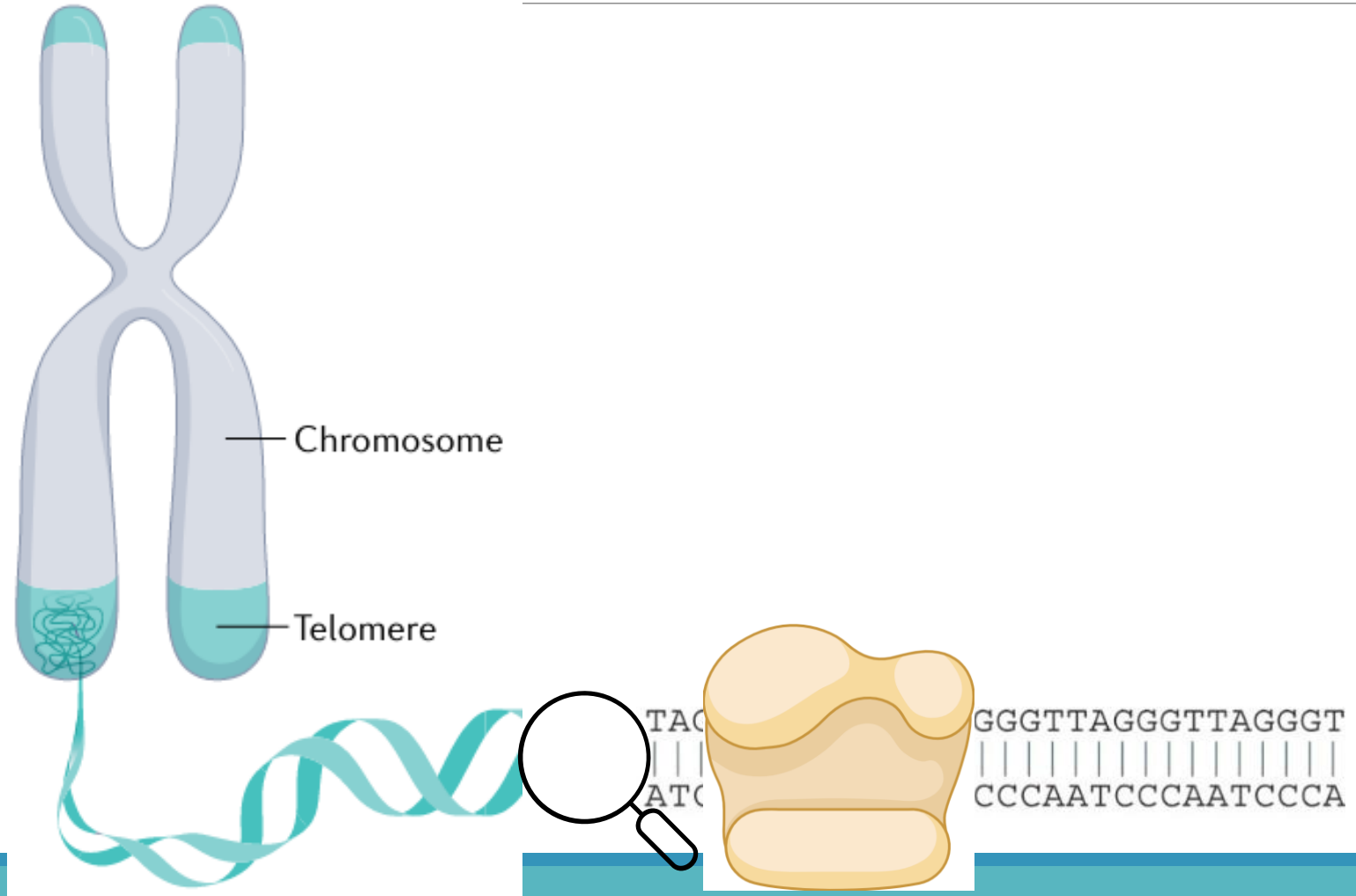



*Zhang MedRxiv; Juge, submitted*

| Disease | Genes | Hematological involvement | Hepatic involvement | Skin involvement | Other non Pulmonary involvement |
|---|---|---|---|---|---|
| **Telomeropathies** | TERT, TERC, RTEL1, PARN, DKC1, TINF2, NOP10, NHP2, ACD, NAF1, ZCCHC8, RPA, POT1 | Thrombocytopenia<br>Myelodysplastic syndrome<br>Acute Leukemia | Hepatopulmonary syndrome | Canitia<br>Dyskeratosis Congenita | |
| **Hermansky–Pudlak syndrome** | HPS1, AP3B1 / HSP2, HPS4 | Spontaneous bleeding | | Albinism | |
| **Interferonopathy** | STING1/TMEM173, COPA, OAS1, ZNFX1 | | | Vasculopathy dermatitis | Auto-inflammatory features Arthralgia kidney disease Fever inflammatory bowel disease, |
| **Aminoacyl-tRNA synthetases** | MARS, FARS1 | Anemia | liver dysfunction hepatomegaly | | Feeding difficulties, failure to thrive, Neurological findings, muscular and vascular abnormalities. |
| **Fibrosis, neurodegeneration, and cerebral angiomatosis (FINCA)** | NHLRC2 | | | | Neurodegeneration and cerebral angiomatosis |
| **Acid Sphingomyelinase Deficiency (ASMD)** | SMPD1 | Thrombocytopenia | Hepatomegaly<br>Splenomegaly | | |
| **GATA2 deficiency** | GATA2 | Monocytopenia<br>Myelodysplastic syndrome | | | Mycobacterial infection |
| **Poikilodermia lung fibrosis** | FAM111B | | | | Hereditary Fibrosing Poikiloderma with Tendon Contractures, Myopathy, Exocrine pancreatic dysfunction, pancreatic cancer |
| **Prolidase deficiency** | PEPD | | | Ulcerations | Mental retardation, facial dysmorphism |
| **Lysinuric protein intolerance** | SLC7A7 | leukopenia | hepatomegaly, diffuse cirrhosis, | | metabolic S: vomiting, diarrhea, failure to thrive, low blood urea, hyperammonemia |
| **Mitochondrial respiratory chain complex deficiency : Fanconi renotubular syndrome 5** | NDUFAF6 | | | | renotubular syndrome, interstitial renal fibrosis; |
| **Werner** | WRN | | | Scleroderma-like skin changes, and premature aged facies | cataract, subcutaneous calcification, premature arteriosclerosis, diabetes |

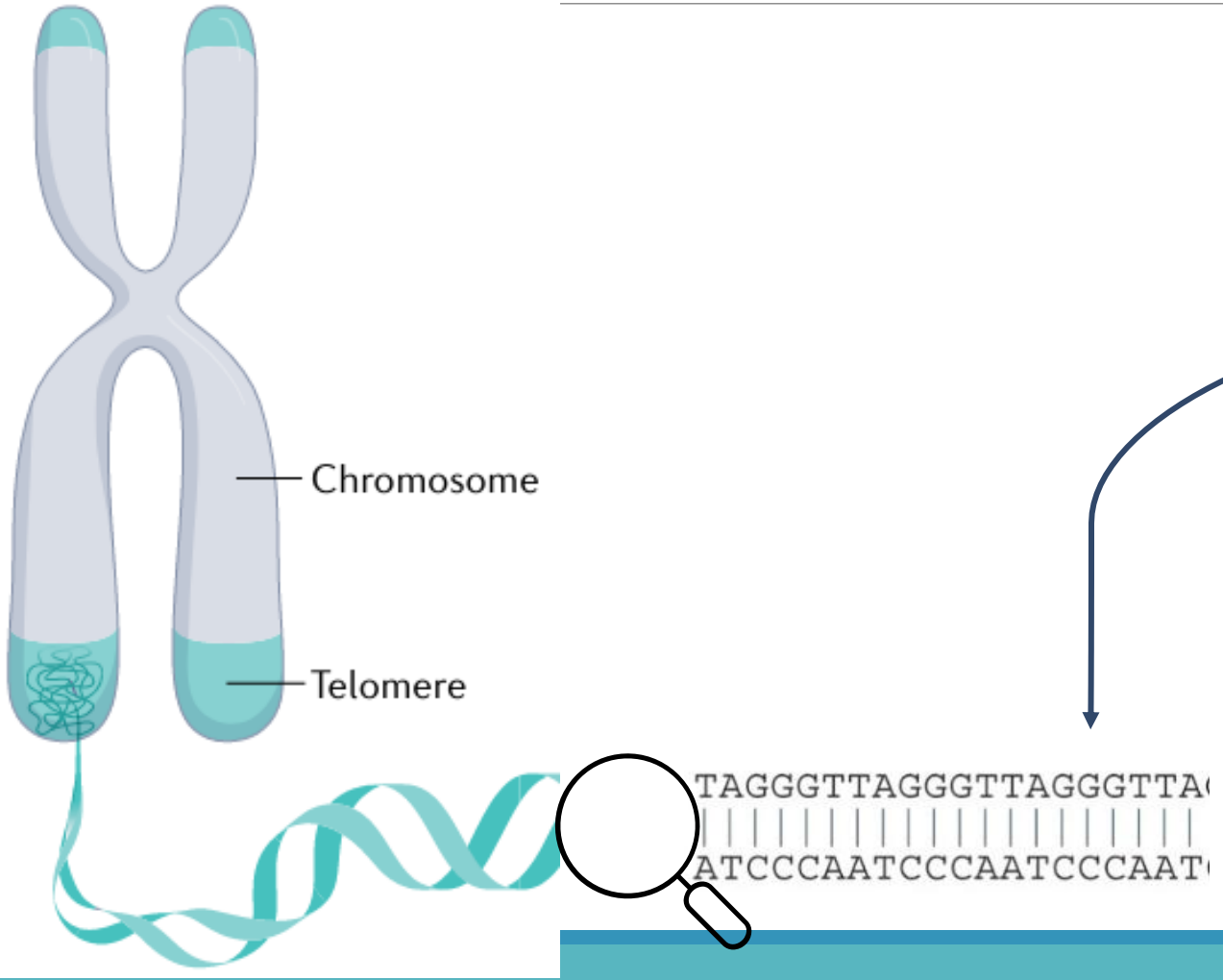
*Borie, ERJ, 2023, ERR, 2024*
*Borie, COPM, 2024*

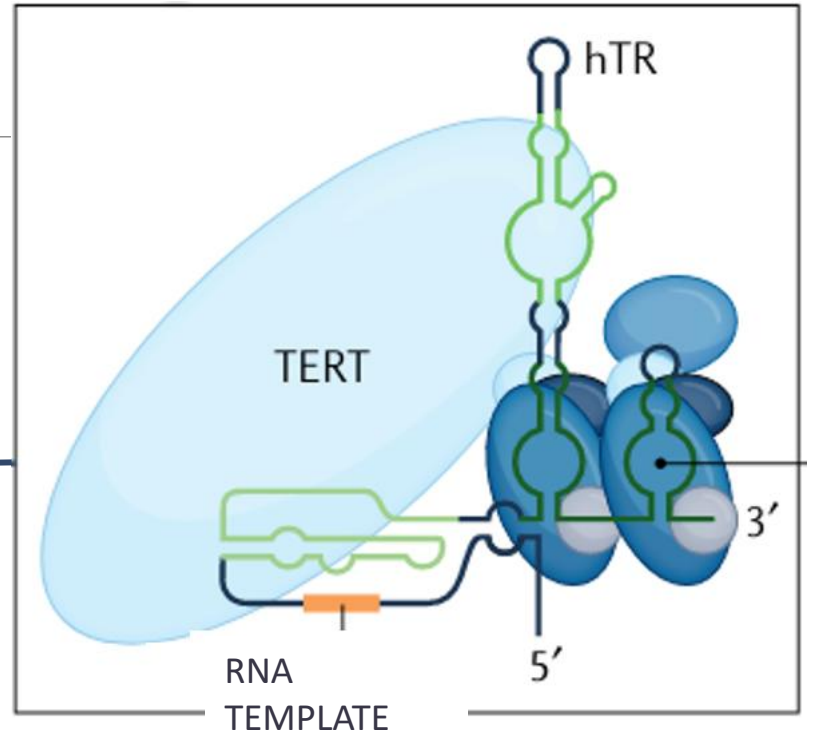
# TELOMERES




*F Maillet, Révy, Nature, 2023, Savage, Hematology, 2022*

# TELOMERASE

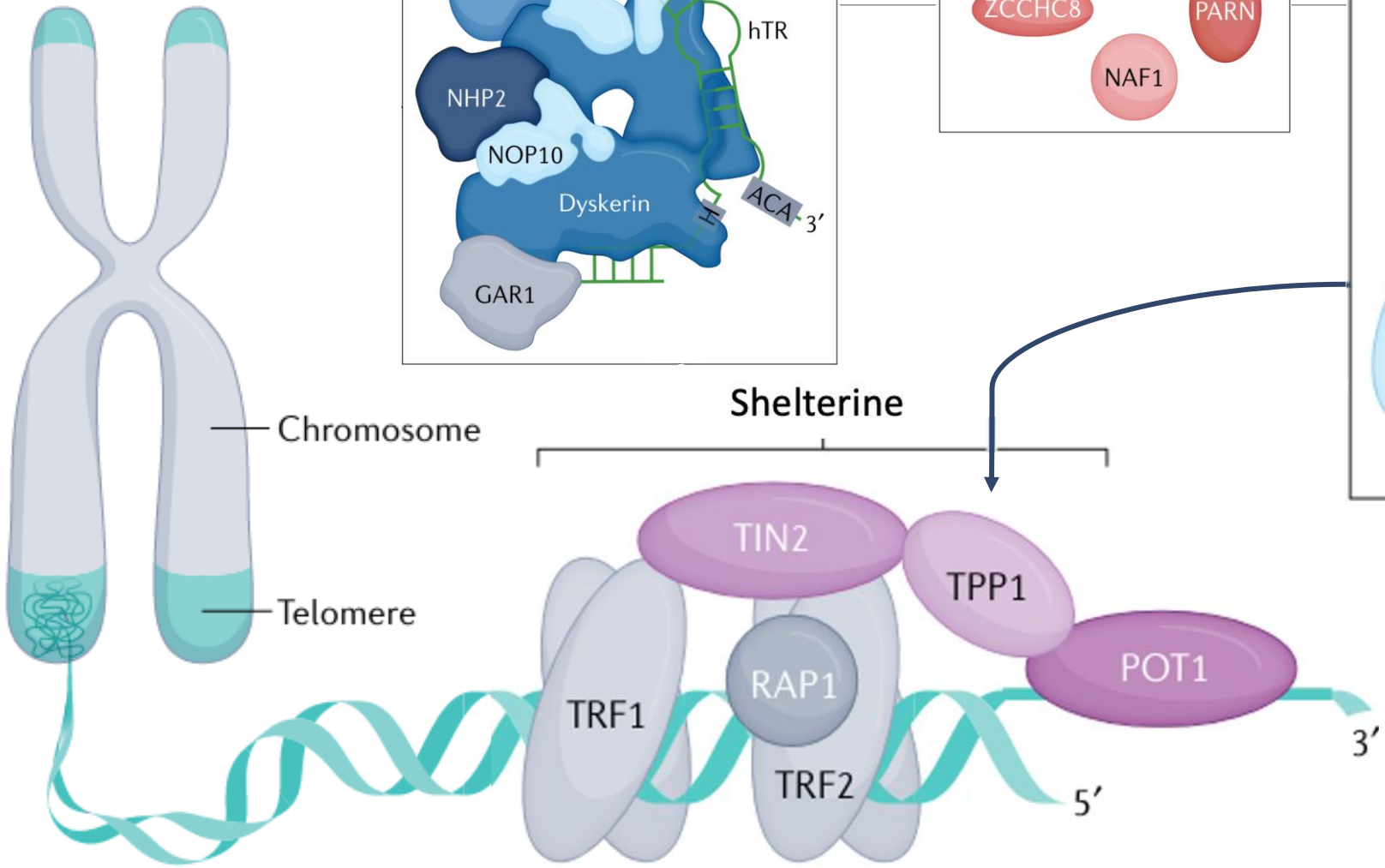



*F Maillet, Révy, Nature, 2023, Savage, Hematology, 2022*

# TELOMERE RELATED GENES

22 genes

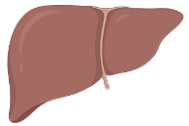



*F Maillet, Révy, Nature, 2023, Savage, Hematology, 2022*

# TELOMERE BIOLOGY DISORDERS (TBD)

Telomere related gene
Pathogenic Variant

TELOMERE BIOLOGY DISORDERS

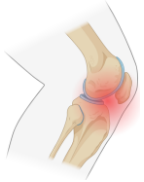


Cirrhosis
Portal Hypertension

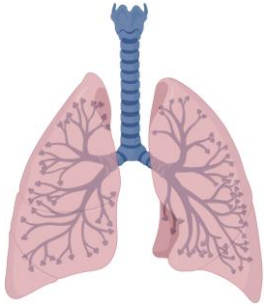
Premature grey hair
Dyskeratosis congenita

Acute Leukemia
Myelodysplasia

Microcephalia



Osteoporosis



Pulmonary Fibrois

Lymphopenia
Hypogammaglobulinemia

Retinal disease

Cancers

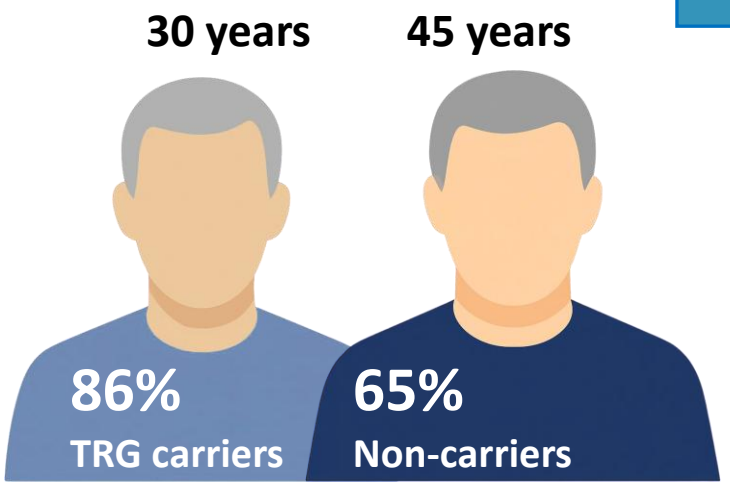
Savage, Hematology, 2022, Borie, ERJ, 2026

# Premature Hair Graying Predicts Pathogenic Variants in Telomere related genes in patients with Pulmonary Fibrosis

## Clinical Observation

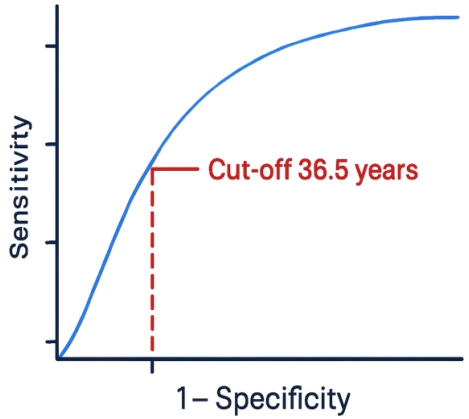
### Premature Hair Graying

Median age onset




## Predictive Value

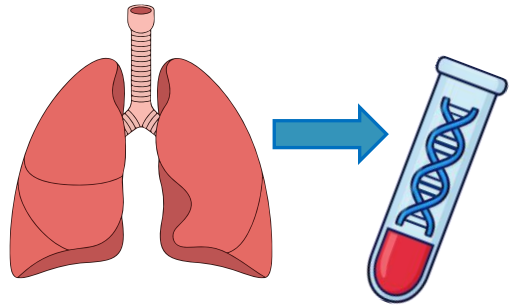
### Age< 36.5 years




- Sensitivity: **79%**
- Specificity: **63%**
- NPV: **88%**

## Clinical Implication

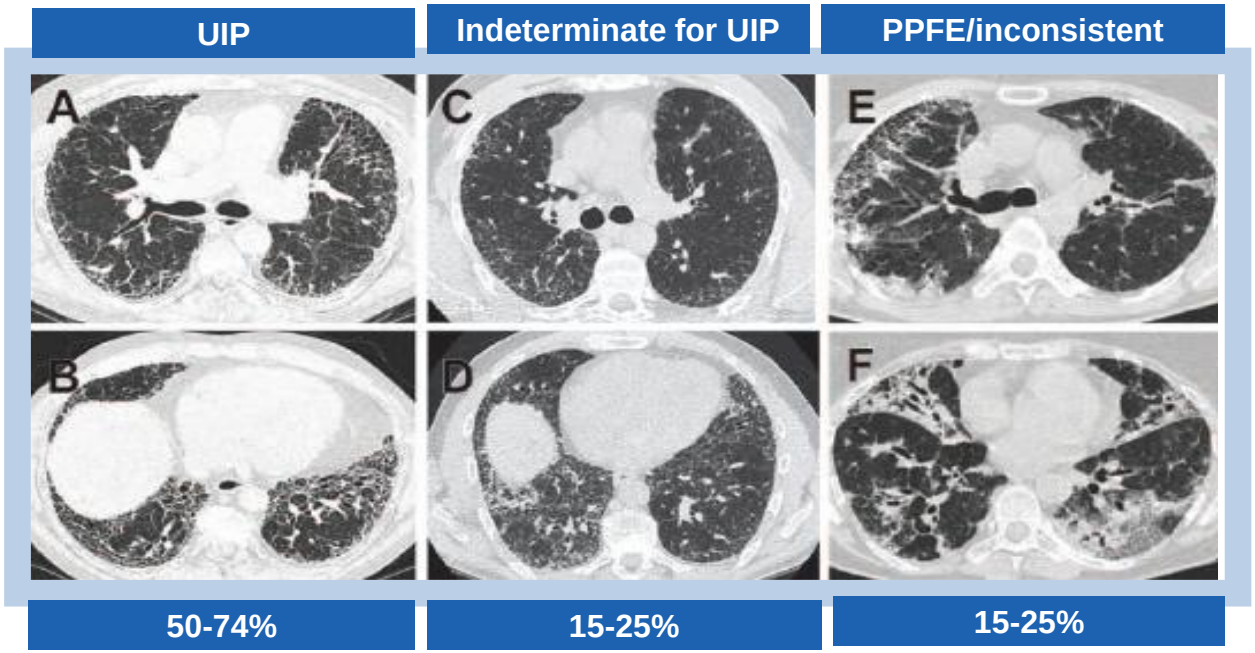
### Screen for TRG Mutations



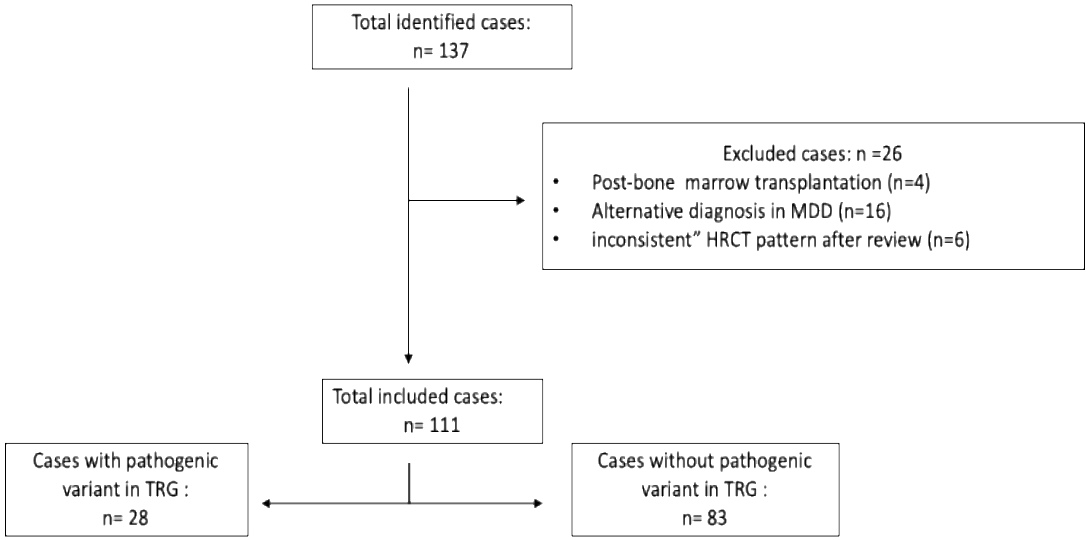
In Pulmonary fibrosis patients with **early hair graying**

**Prioritize** TRG genetic testing

# PPFE may be a specific pattern associated with TRG

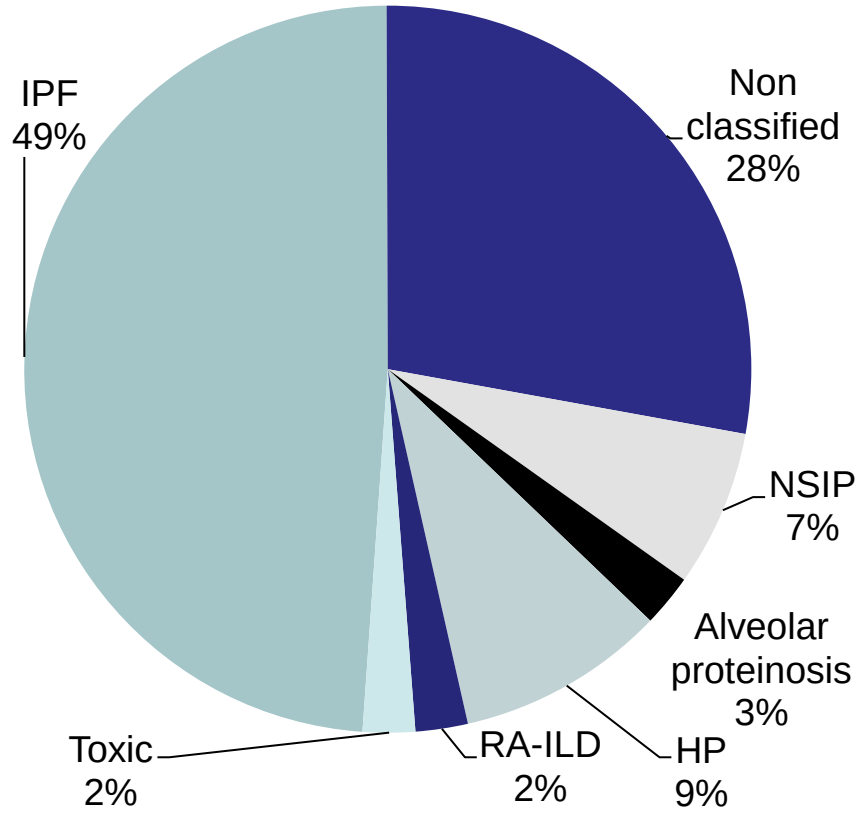



PPFE




*Diaz de Leon, PLoS One 2010, Borie, ERJ, 2016, Newton, ERJ, 2016, Gorgy, Chest, 2015,, Camboulive, ERS, 2023, submitted*

# PULMONARY DIAGNOSIS OF TBD



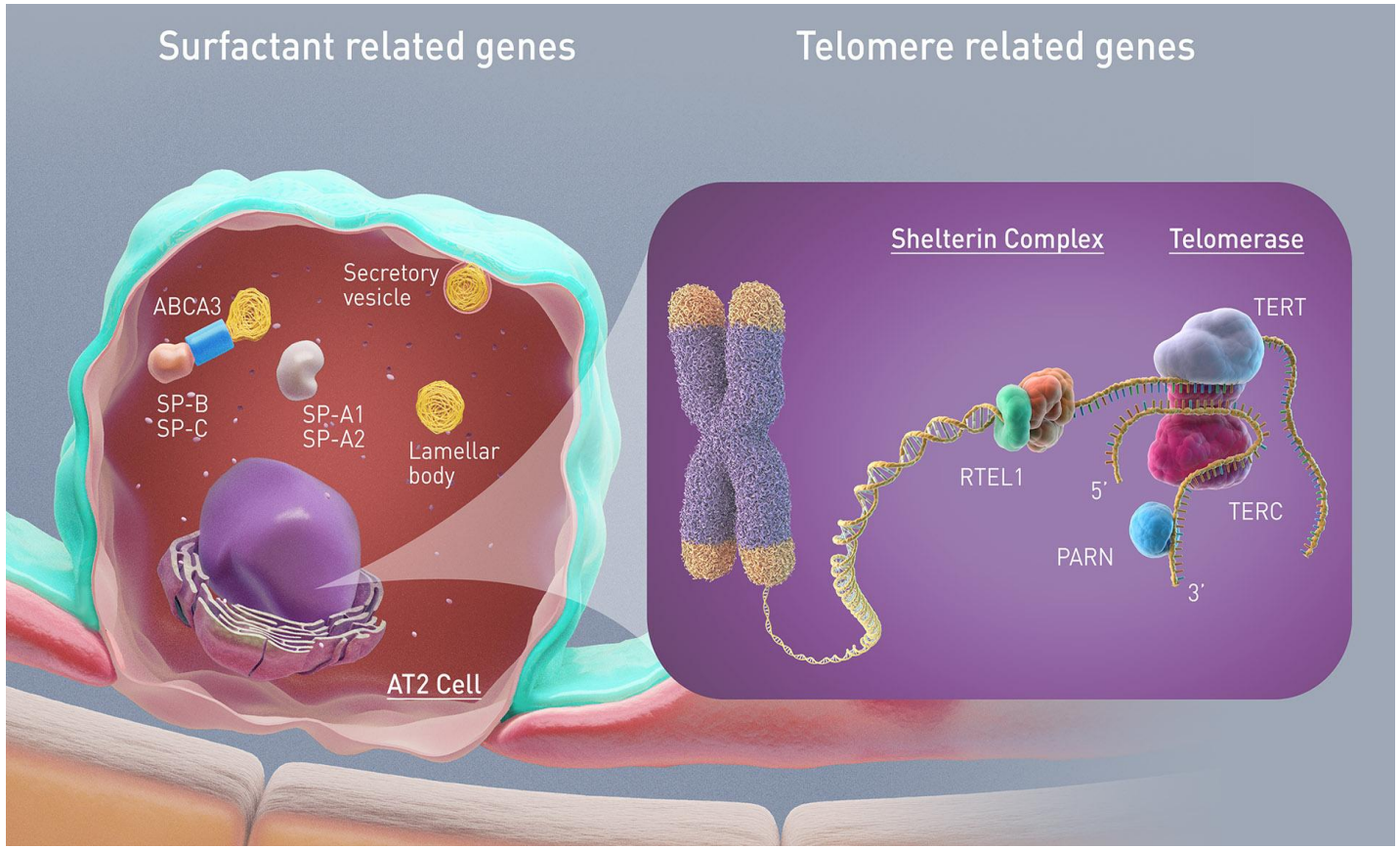

Secondary ILD 13%

| Diagnosis | 77 |
|---|---|
| IPF | 35 (45.5) |
| NSIP | 3 (2.6) |
| DIP | 1 (1.3) |
| PPFE | 8 (10.4) |
| Unclassifiable | 15 (19.5) |
| HP | 9 (11.7) |
| CTD-ILD | 2 (2.6) |
| IPAF | 5 (6.5) |

Borie, ERJ, 2016

Newton, ERJ, 2016

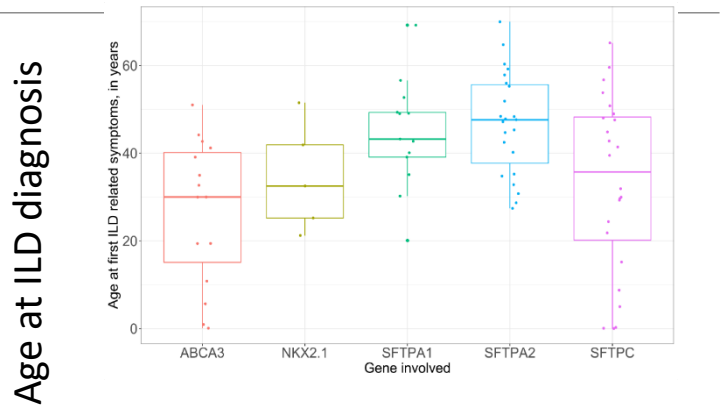
# Surfactant related genes

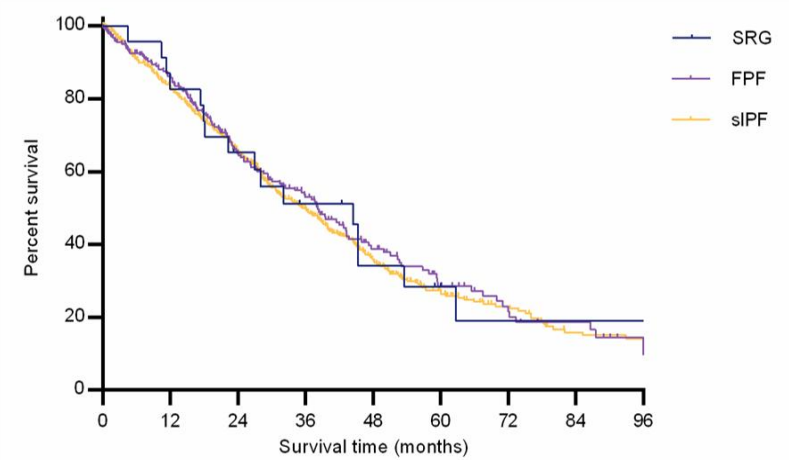


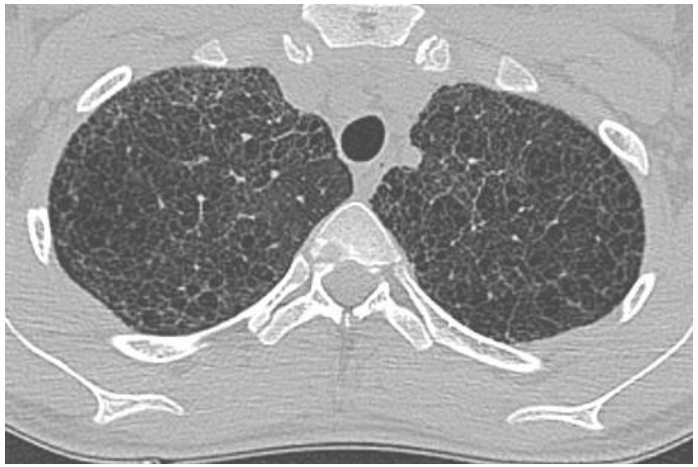

*Hurley, ebiolmed, 2024*

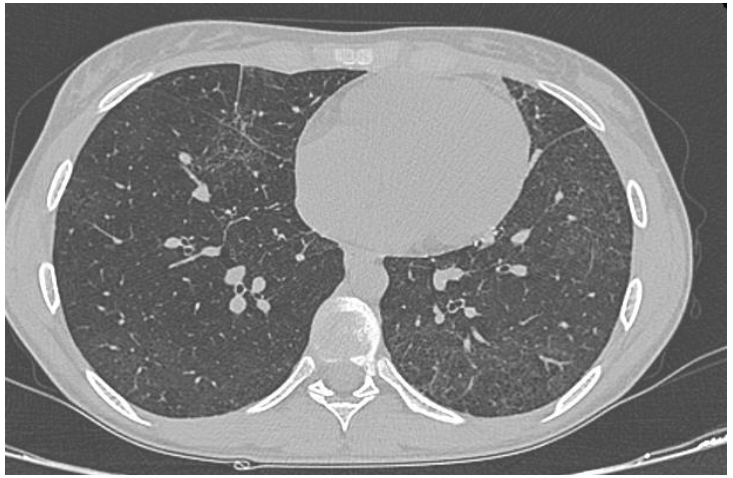
# SURFACTANT RELATED GENES

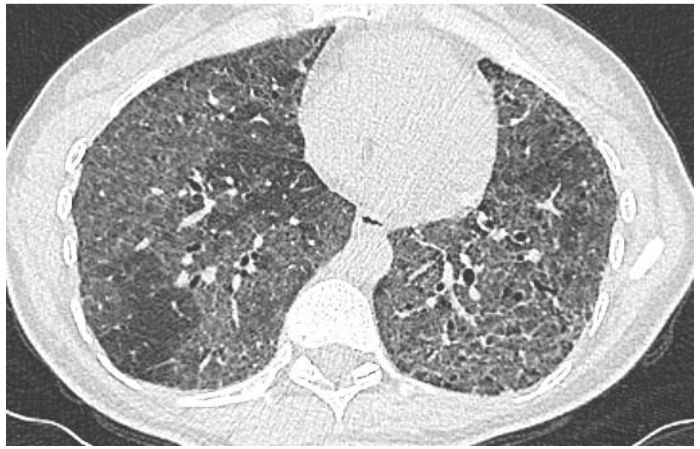
- Children or young adults
- HRCT : Lung cysts, Ground glass,
- Thoracic deformation
- ILD-SRG in adults are severe



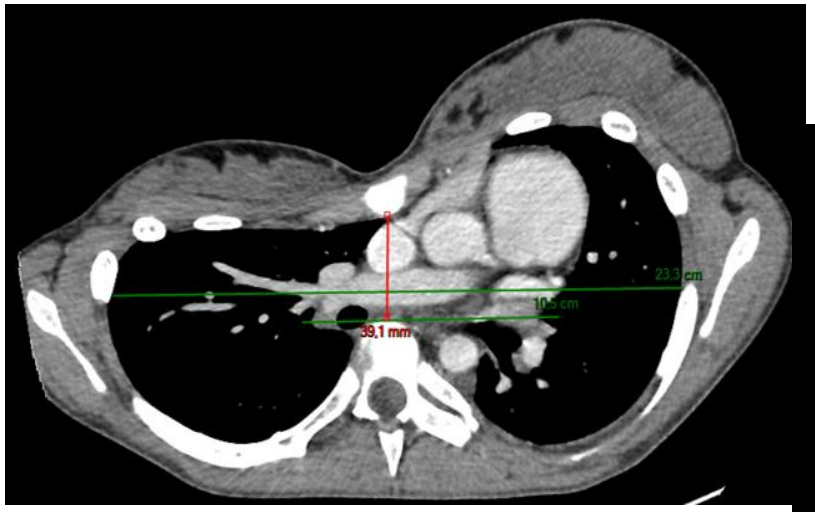



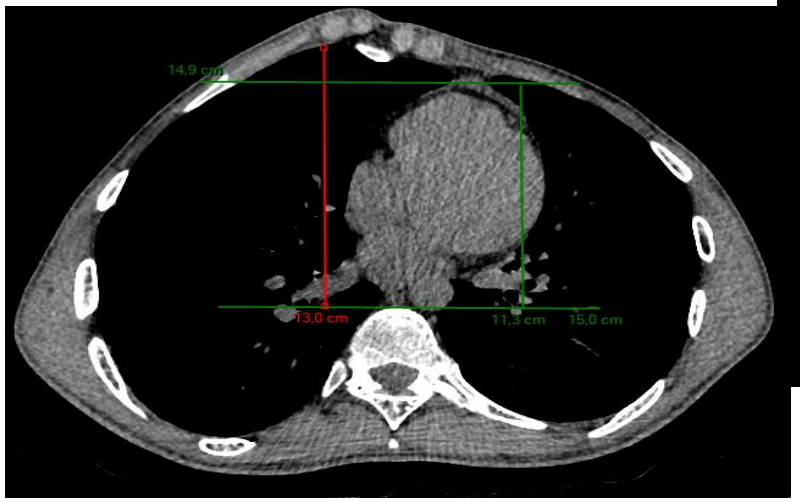


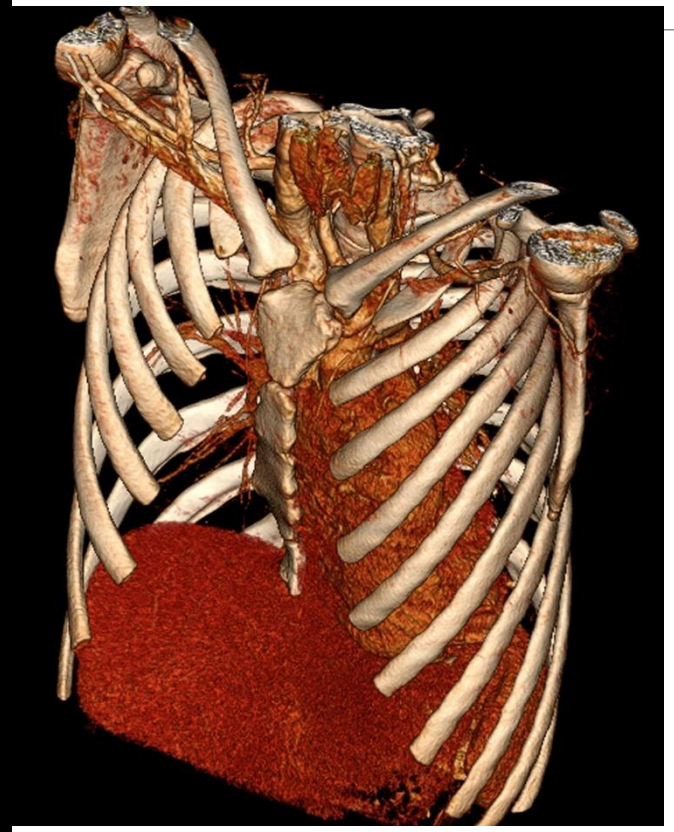


Klay, Chest, 2024; Diesler, Respirology, 2024; Bermudez, ERJOR, 2023, Brudon, ERJ, 2024

# Thoracic deformation

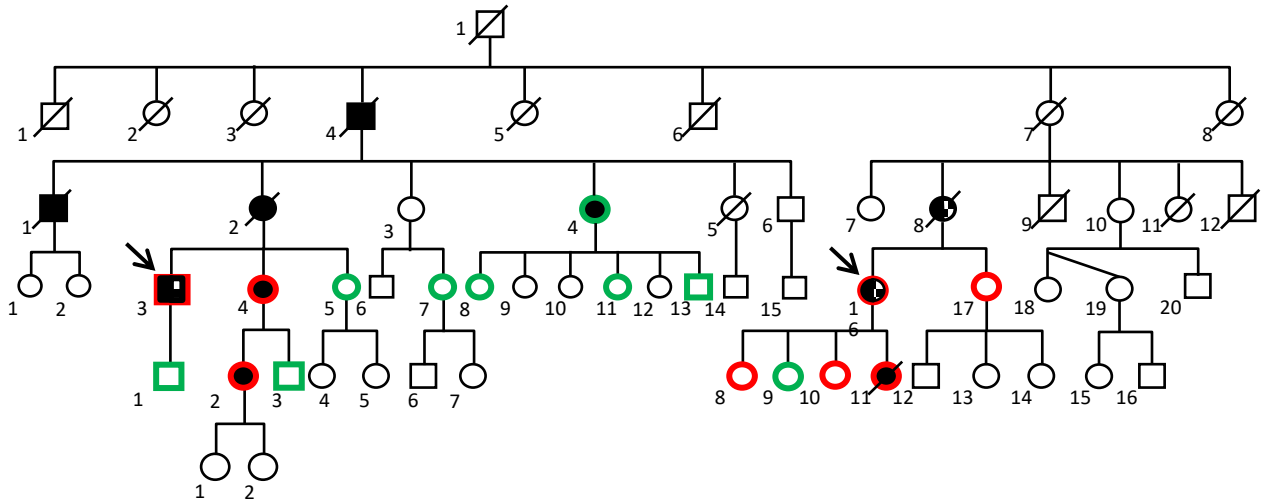


*Diesler, respirology, 2024, Lebrun, ERJOR, 2024*

# *SFTPA1/SFTPA2* the last of the surfactants?

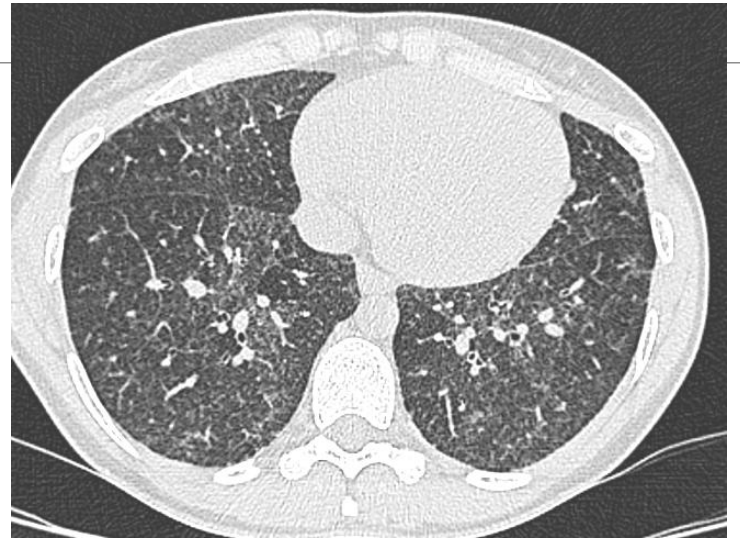


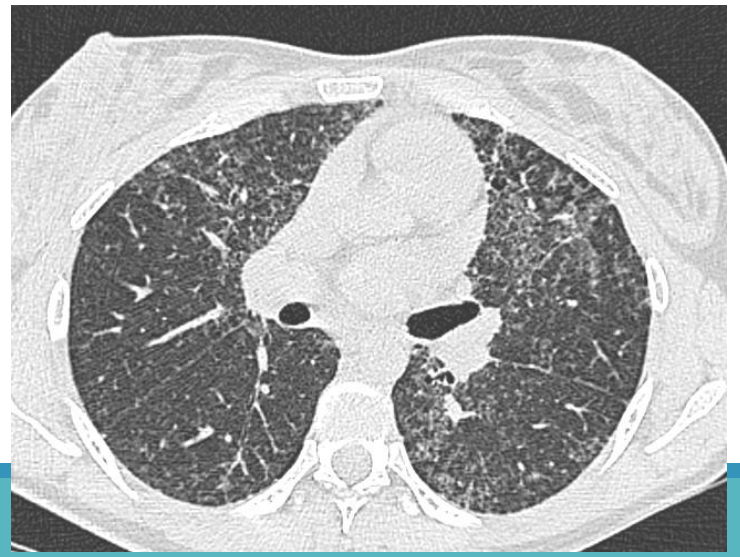
**SFTPA1 W211R +/-**

**No *SFTPA1* mutations**

**ILD**

**ILD and lung adenocarcinoma**





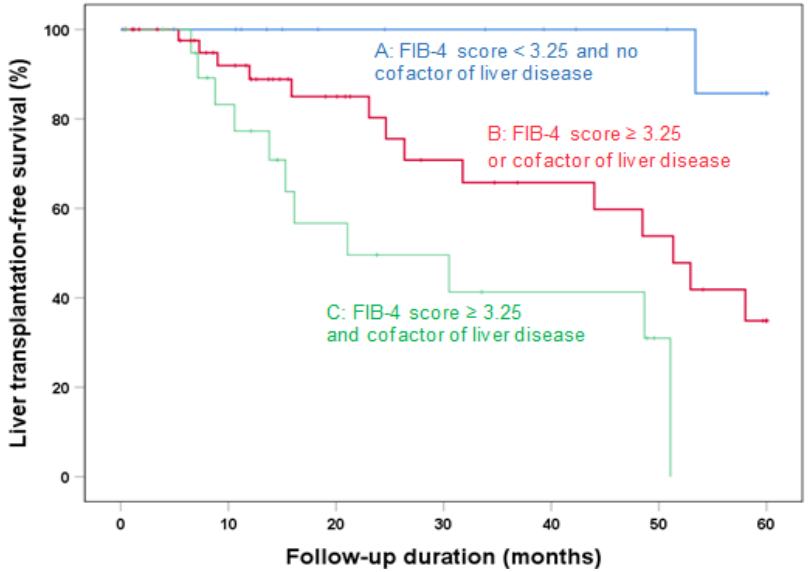
*Nathan, Hum, Mol Genet, 2016, Wang, Am J Med Genet, 2009; von Moorsel, AJRCCM, 2015*

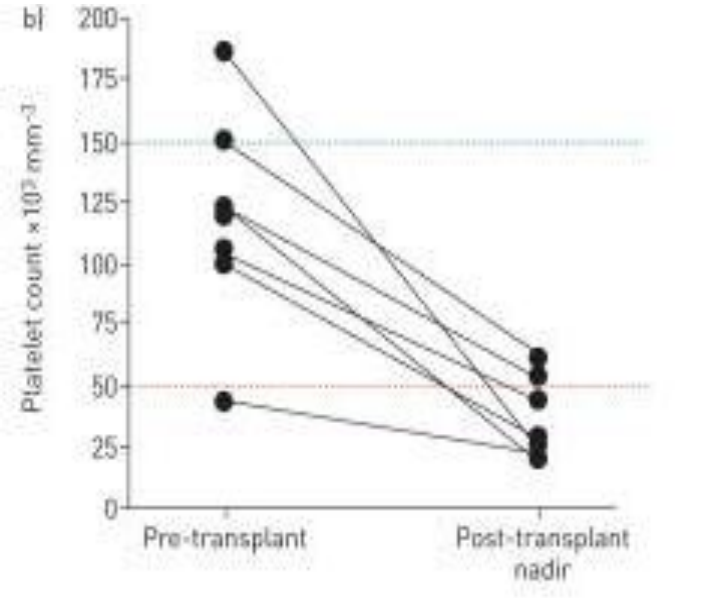
# GENES/ENVIRONNEMENT INTERACTION IN TBD

| Lung | N | Smoking |
|---|---|---|
| Diaz de Leon | 53 | 63% |
| French cohort | 43 | 52% |

- Liver:
  - Increased risk death in patients with cirrhosis and TRG if alcool or viral infection

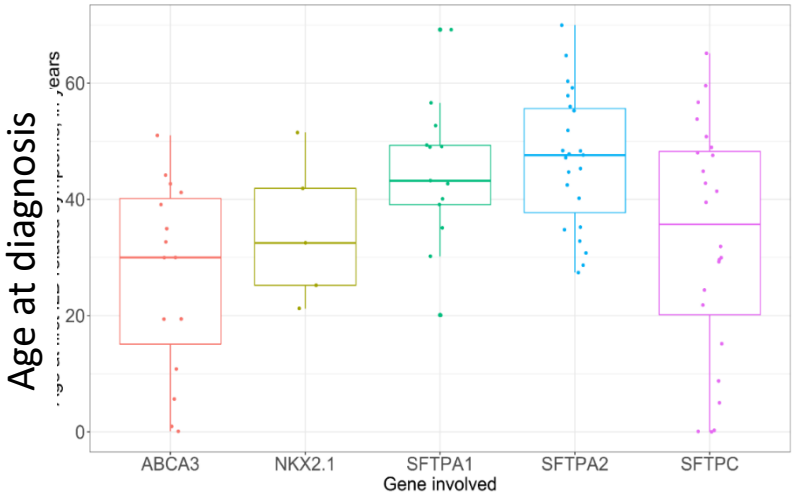
- Blood
  - Hematological complications after lung transplantation and use of cytotoxic drugs

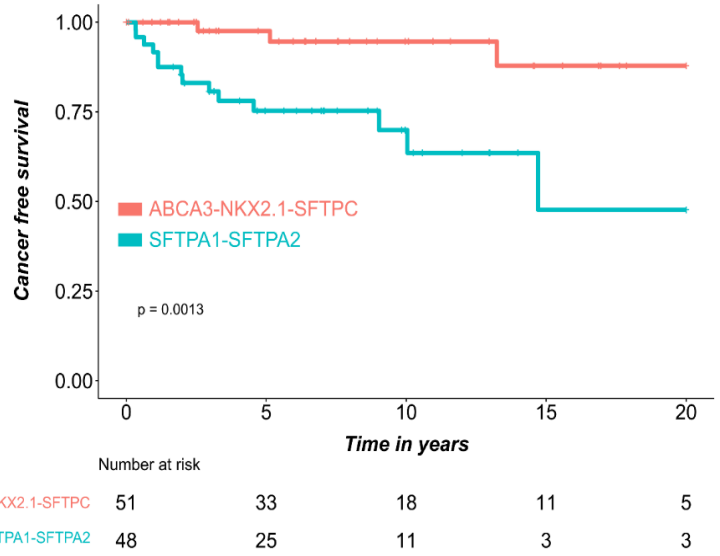


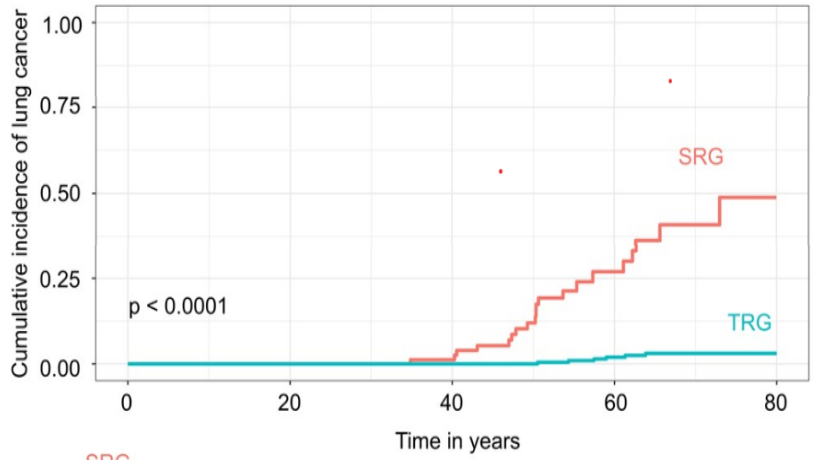




Diaz de Leon, P One, 2010; Calado, Hepatology, 2011;
Silhan, ERJ, 2010; Borie, ERJ, 2016, Sidali, J Hepatol, 2023

# Environment is also important with other genes: Lung cancer and Surfactant



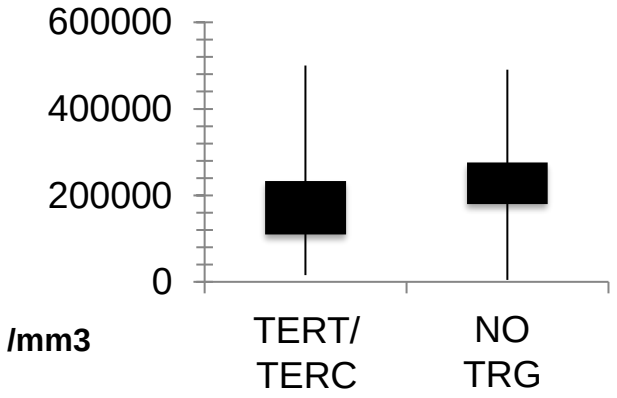

| | No cancer | Cancer | | |
|---|---|---|---|---|
| | | | OR | p |
| **Patients** | 81 | 19 | | |
| **Smoking** | 10 (12.3%) | 15 (79%) | 19.9 [6.2-73,6] | <0.001 |

*Brudon, ERJ, 2024*

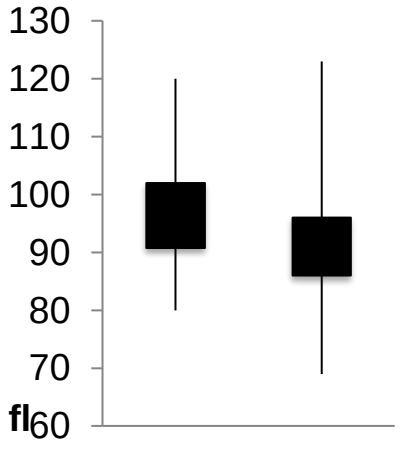
# Hematological manifestations of TBD

TERT/TERC and ILD

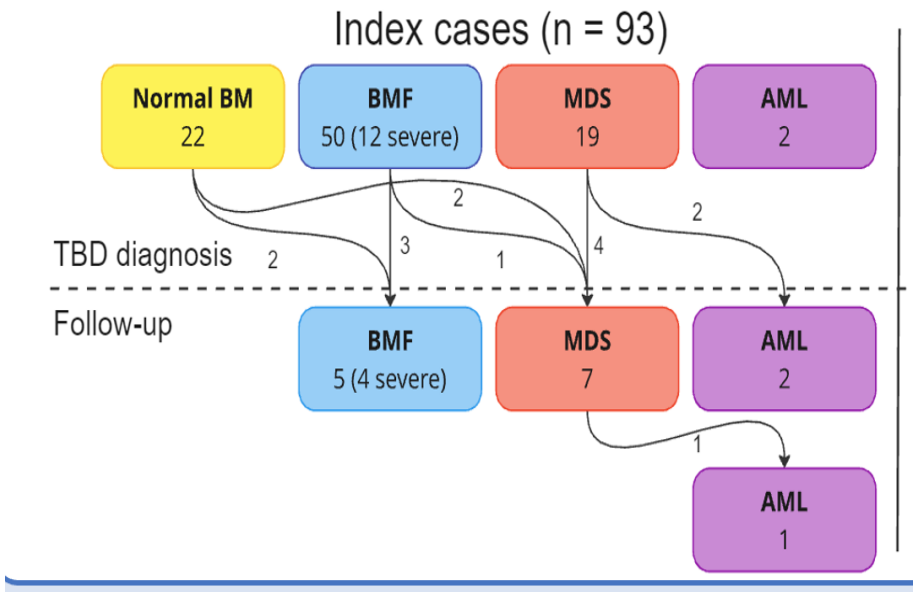
Platelet

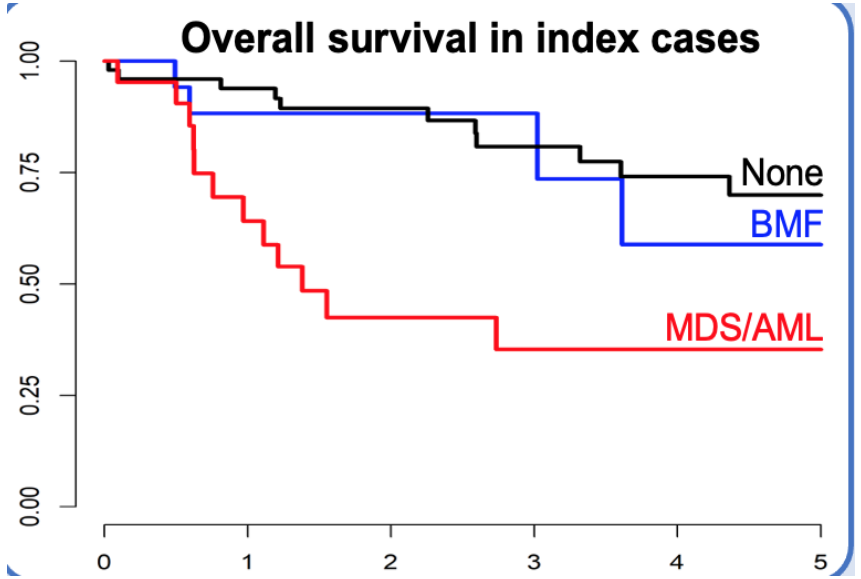



MCV




Hematological cohort




## HSCT

17 patients (13.4%)

9 MDS, 8 AML

5/9 (55.6%) relapse (2 AML)

## Androgenes

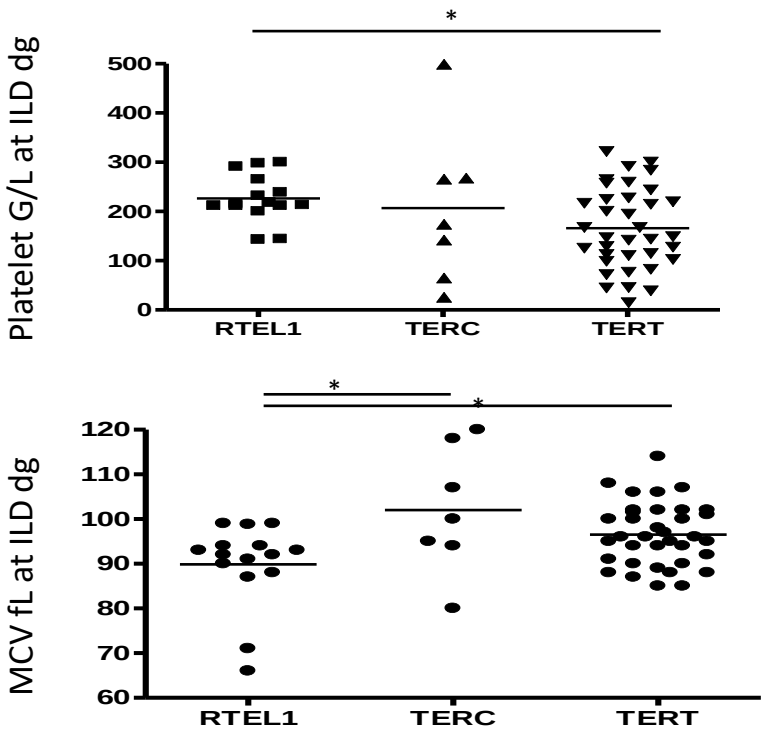
27 patients (21.3%)

22 AML, 3 MDS

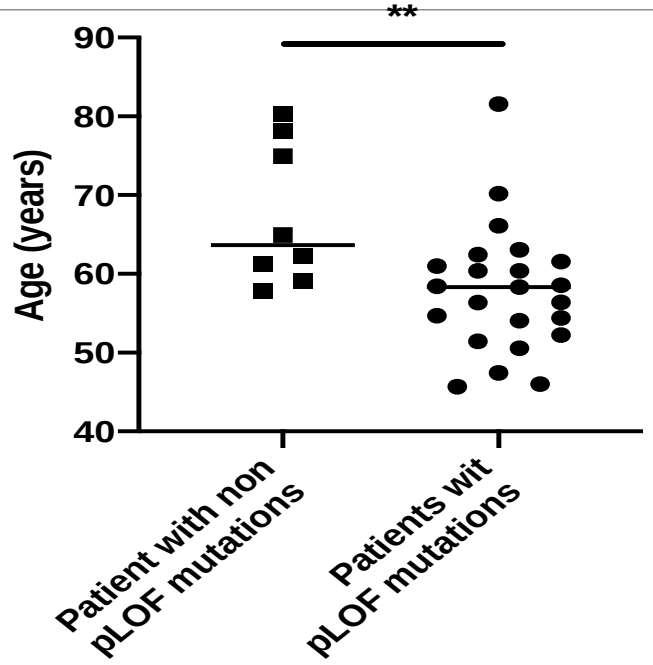
Response: 8/14 (57.1%)

*Borie, ERJ, 2016; Hussain-Agha, BMT, 2024 F Maillet, BJH, 2024*

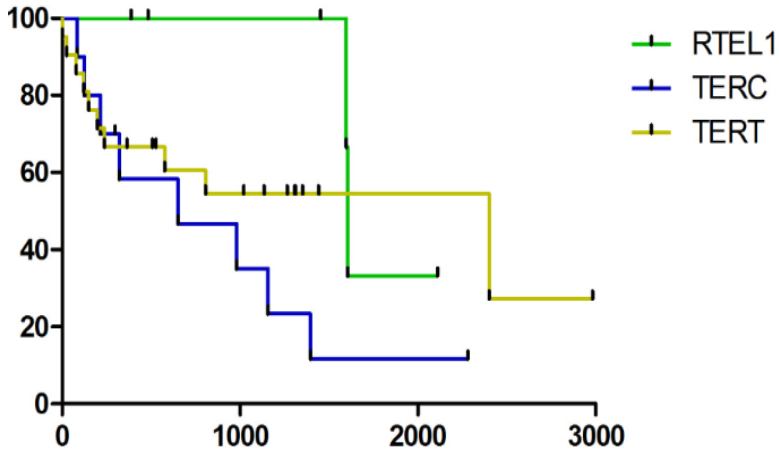
# Are all TRG associated with the same phenotype?



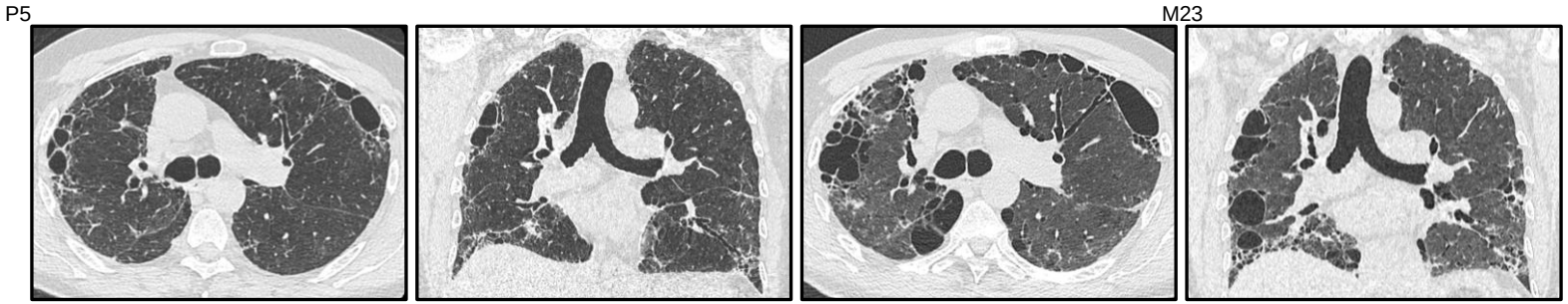

PARN and ILD




Survival after lung transplantation



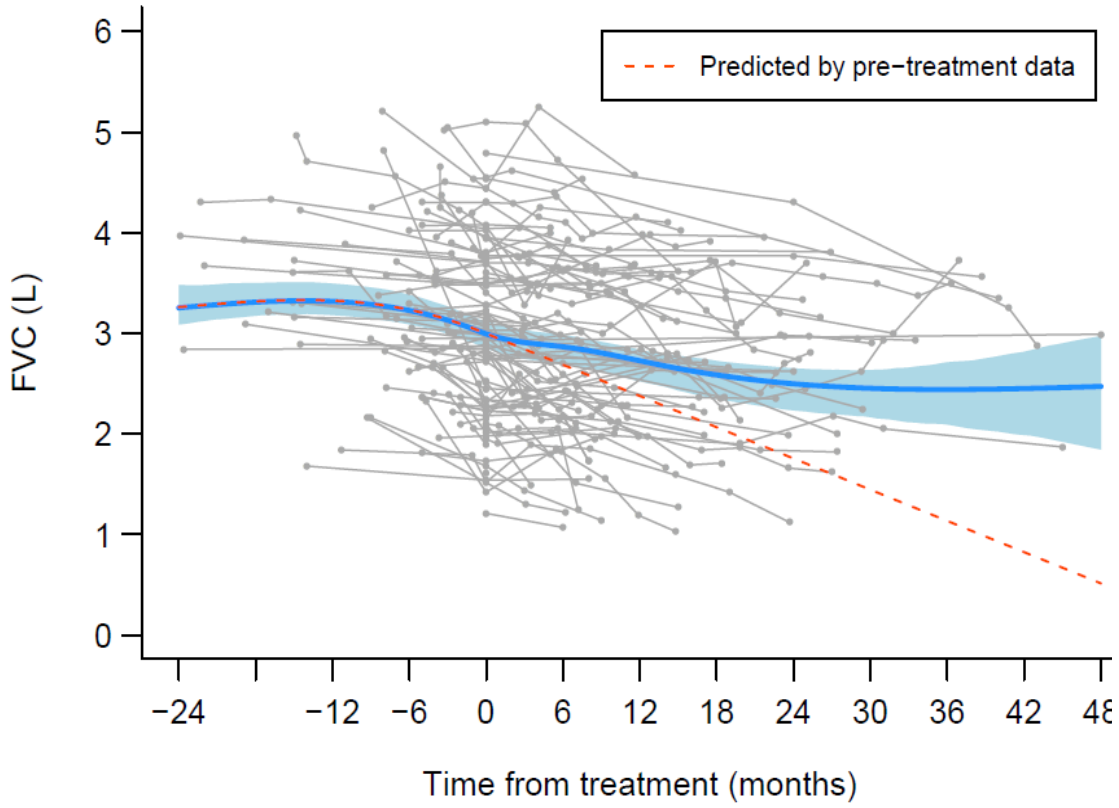

CPFE with DKC1 variants?




*Borie, ERJ, 2019, Phillips, AM J Transplant, 2021; Newton, ERJ, 2016, Philippot, respirology, 2022, Evrard, ERJOR, 2025*

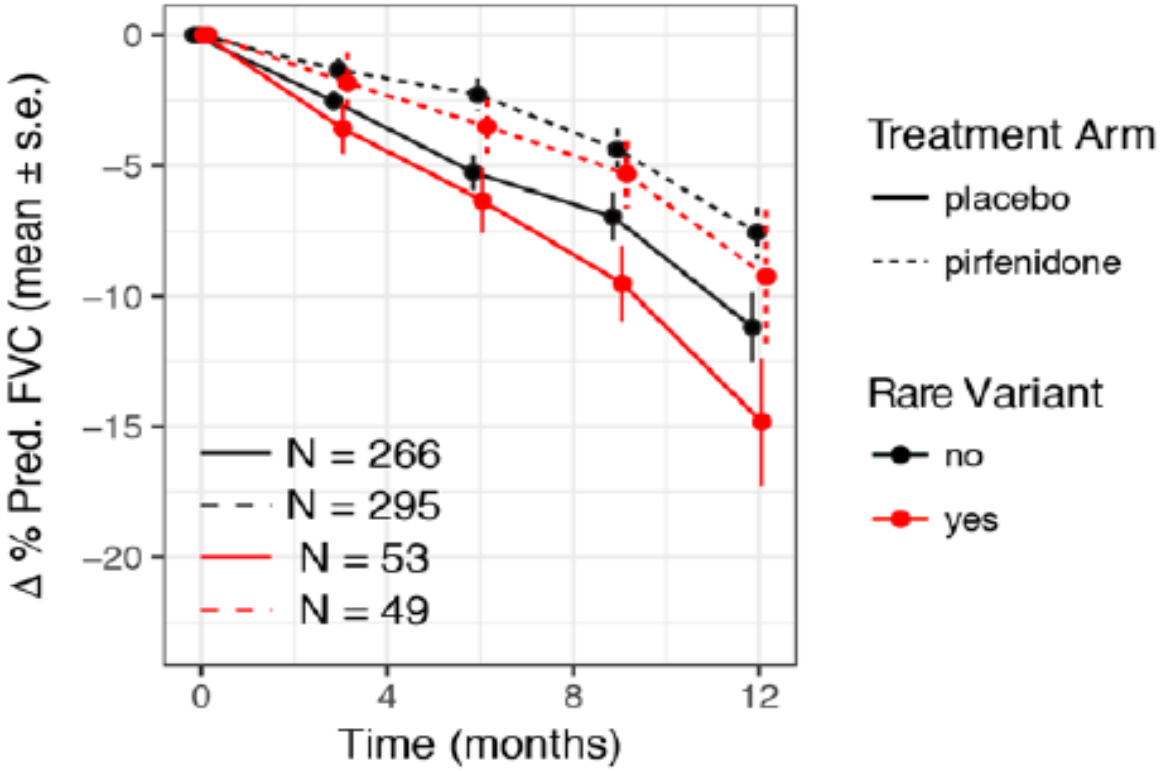
# ANTIFIBROTIC TREATMENT CAN BE USED IF INDICATED

Retrospective Adult IPF-TRG cohort




Justet, ERJ, 2020

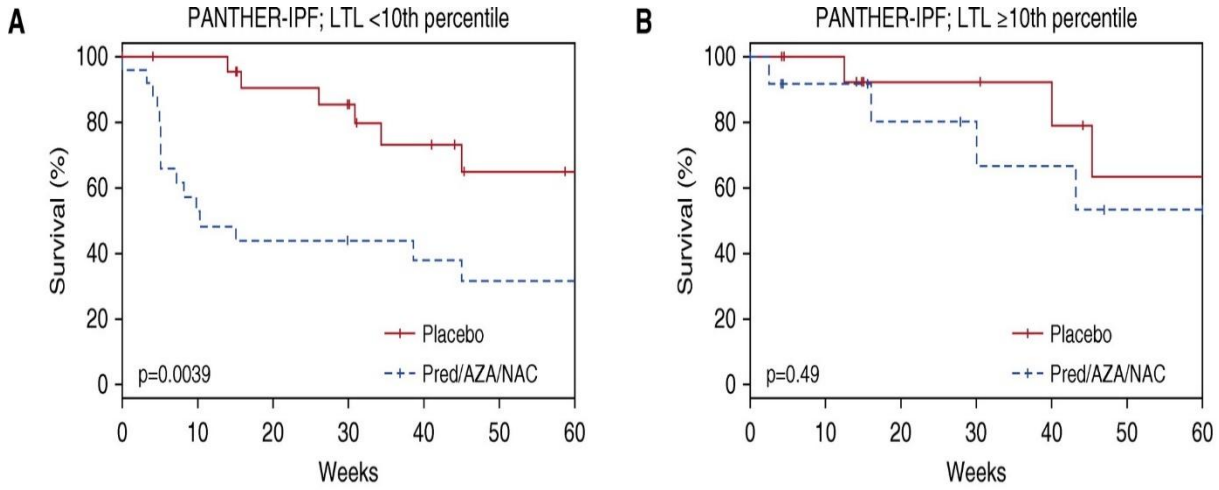
post-hoc analysis, pirfenidone in TRG

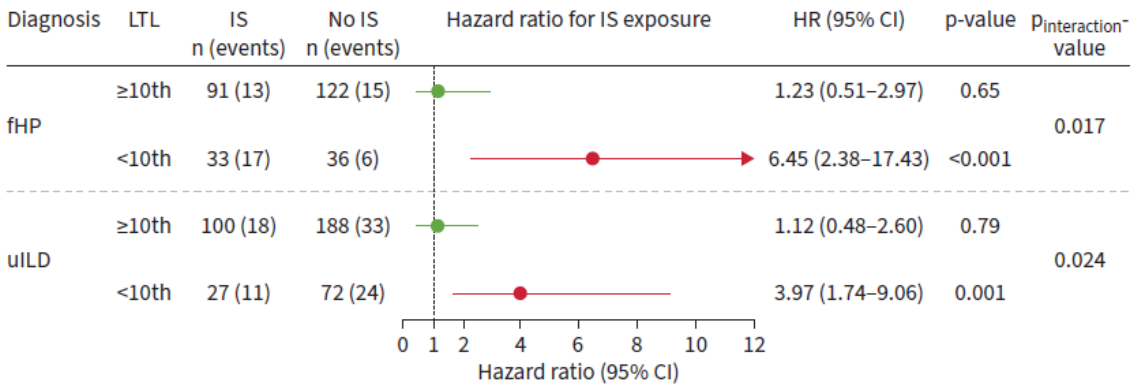



Dressen, Lanc Res Med, 2018

# SHOULD IMMUNOSUPPRESSIVE BE AVOIDED ACCORDING TO TELOMERE LENGTH ?

- Particular harm of AZA/Pred in IPF with TL<10th
- Hazard of pred/MMF in unclassifiable fibrosis or HP with TL<10th

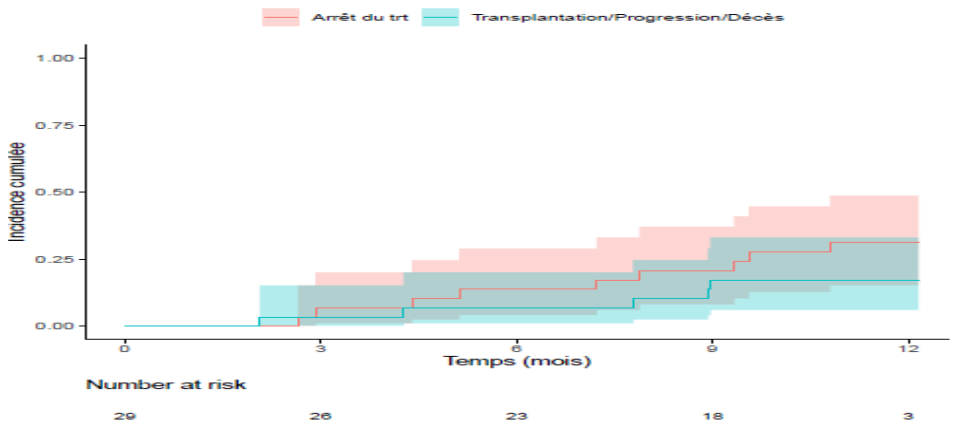


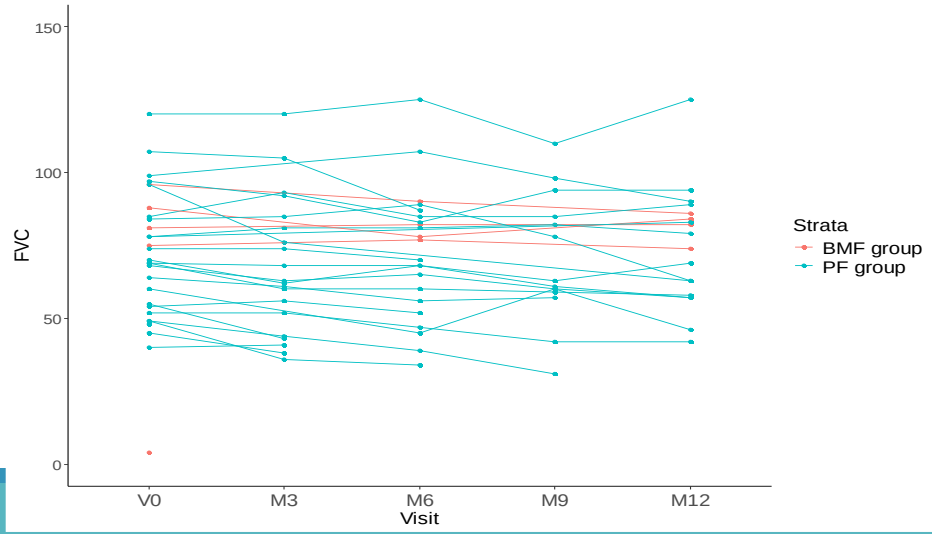




Newton, AJRCCM, 2018; Adegunsoye, ERJ, 2021, Zhang, ERJ, 2023

# Targeted therapy ?
# ANDROTELO: a phase 2 study with Danazol for TBD

| N | 25 |
|---|---|
| Age | 62.5 y [36.5-80.5] |
| Men/women | 16/9 |
| FVC (L) | 2.4 [1.4-9.1] |
| FVC (%) | 69 [40-120] |
| DLCO (%) | 44 [29-84] |
| TRG | |
| TERT | 12 |
| TERC | 6 |
| PARN | 2 |
| RTEL1 | 6 |



# Specific therapy for SRG

Pediatric use

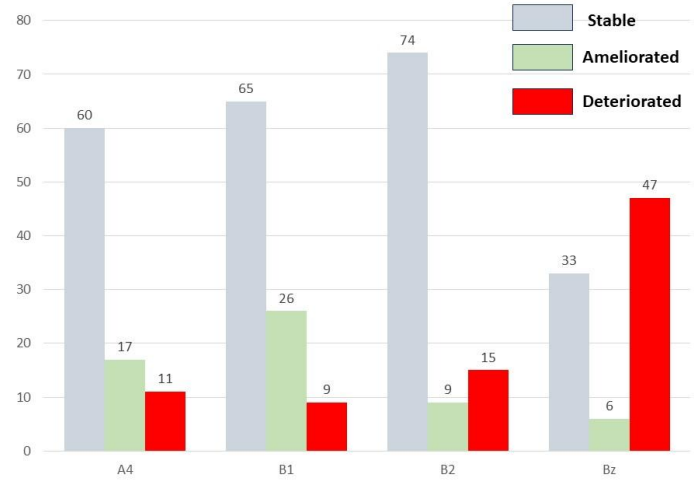
- Steroids/Macrolides (azithromycin) up to 1/3 improvement
- Hydroxycholoroquine
  - up to negative prospective pediatric trial
    → RCT TIPS to come!

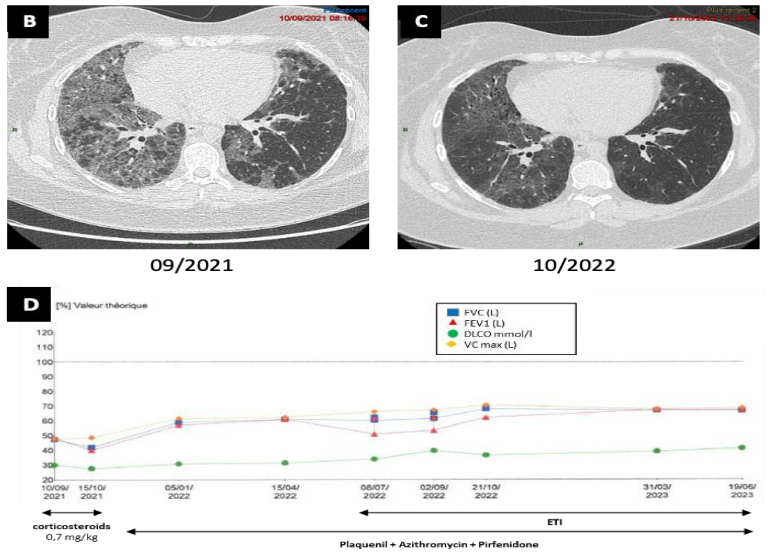
- Possible lung transplantation

Off-label Ivacaftor or cyclosporine active on certain *ABCA3* mutations in vitro

Possible prescription of nintedanib in children

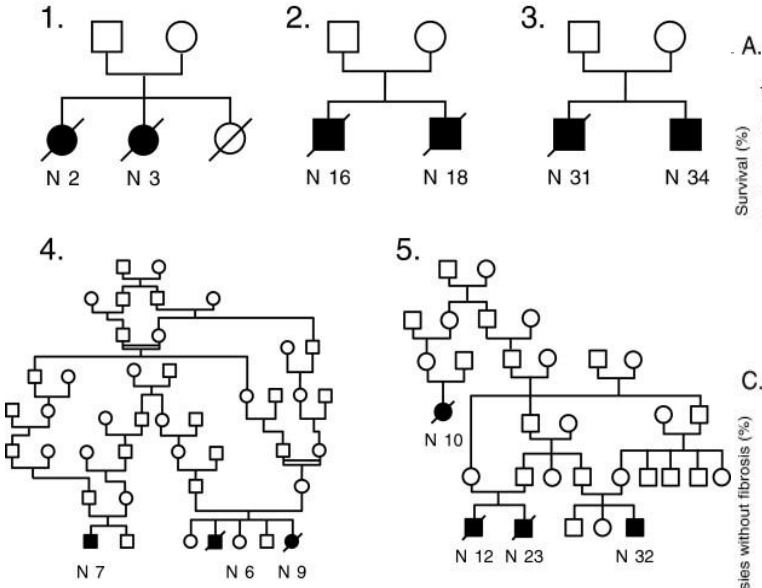
Children ILD transition to adults

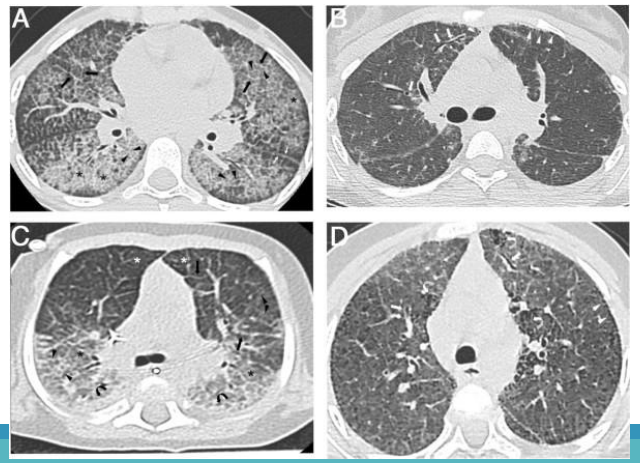


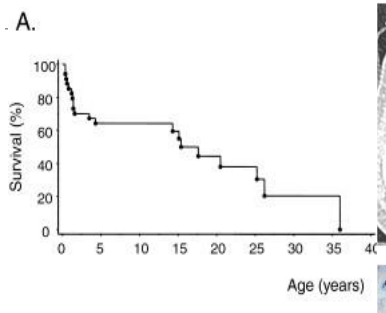



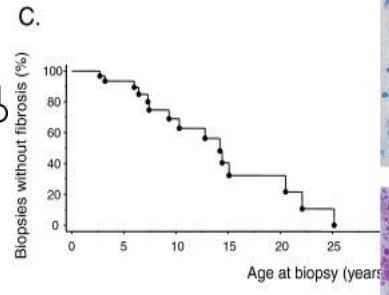

*Kroner, ERJ, 2016; Deterding ERJ, 2022, Bermudez, ERJOR, 2023, Lebrun, ERJOR, 2024, Manali, ERJ, 2025*

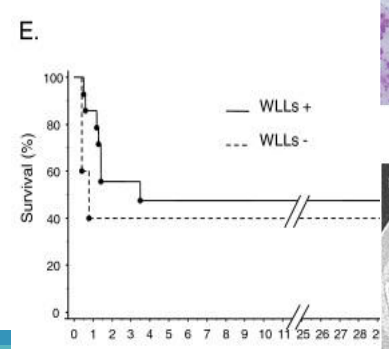
# SOME VERY RARE GENETIC ILD ARE ELIGIBLE TO TARGETED THERAPY
# e.g. *MARS1*

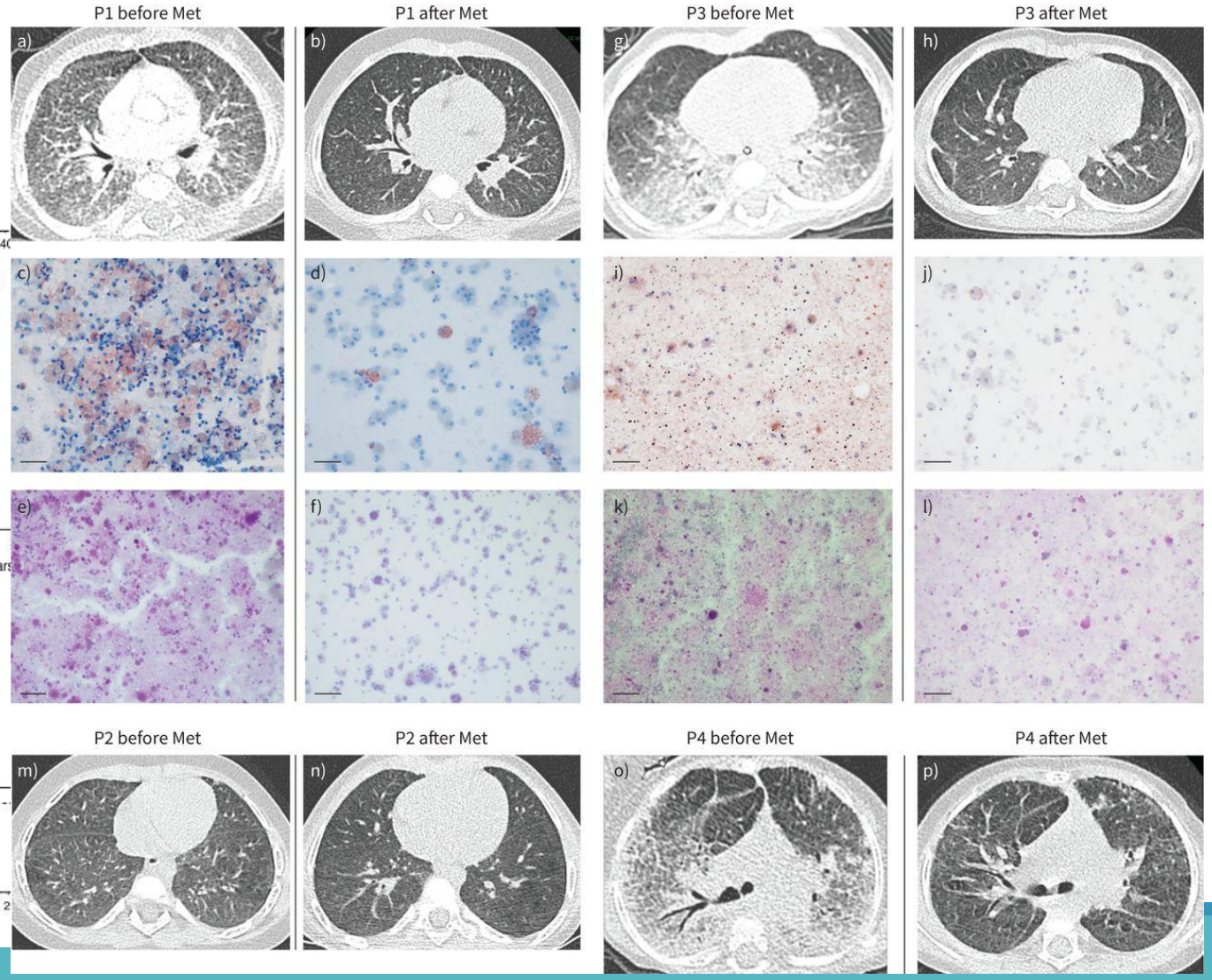


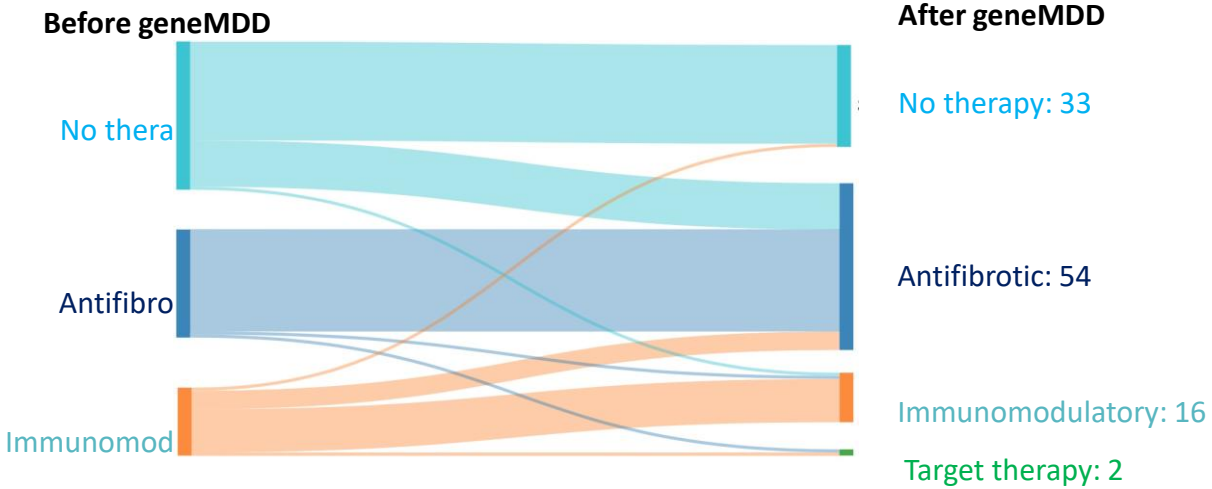



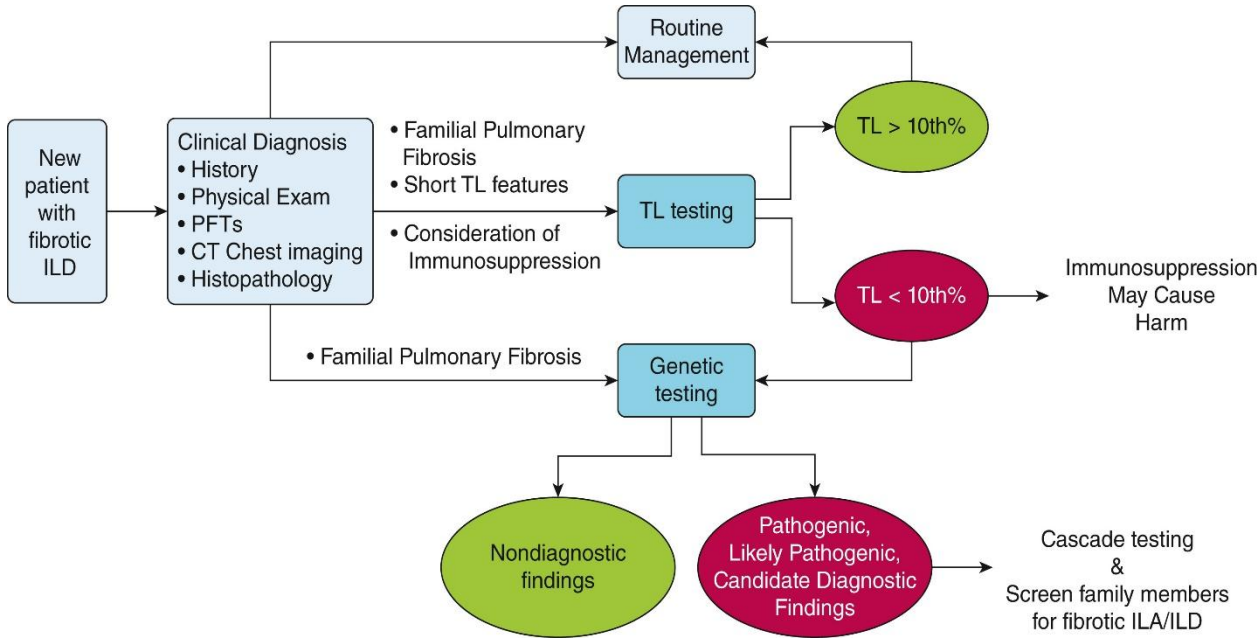




Hadchouel, ERJ, 2022

# WHAT DOES GENETIC TESTING CHANGE?



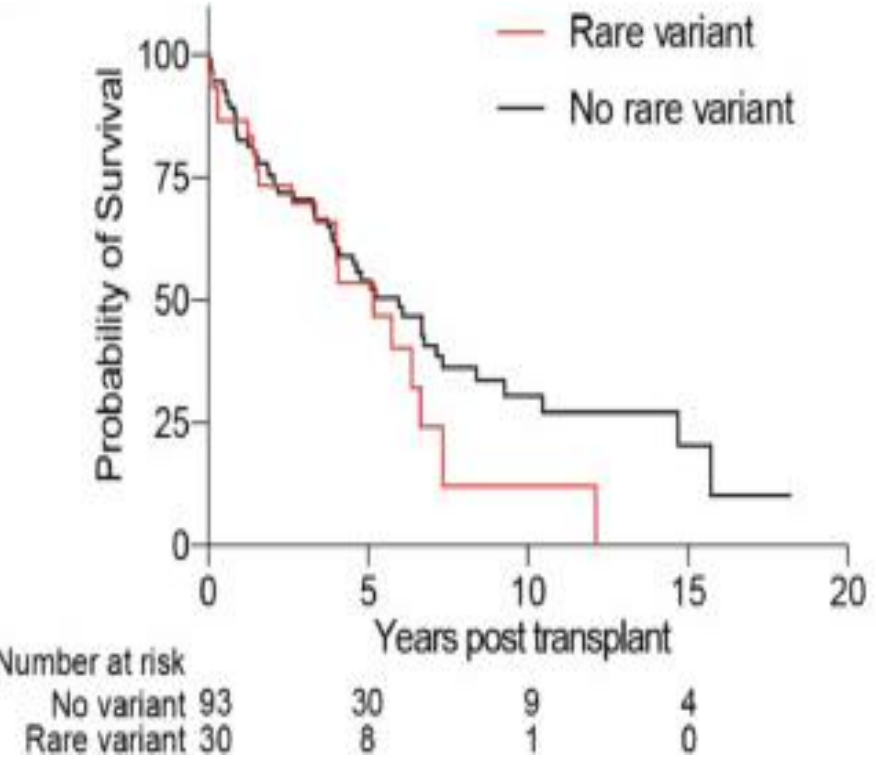

| Variable | Univariate regression analysis | | |
|---|---|---|---|
| | Hazard ratio | CI | p-value |
| **Age** | 0.98 | 0.96 – 0.99 | 0.036 |
| **IPF diagnosis** | 0.27 | 0.08 – 0.73 | 0.009 |
| **Genetic analysis** | | | |
| **Negative** | Ref | Ref | Ref |
| **Ongoing** | 42.5 | 5.88 – 271.6 | <0.001 |
| **SRG** | 9.57 | 1.87 – 96.7 | 0.005 |
| **TRG** | 6.41 | 1.44 – 60.9 | 0.012 |
| **Other** | 1.26 | 0.01 – 26.6 | 0.89 |

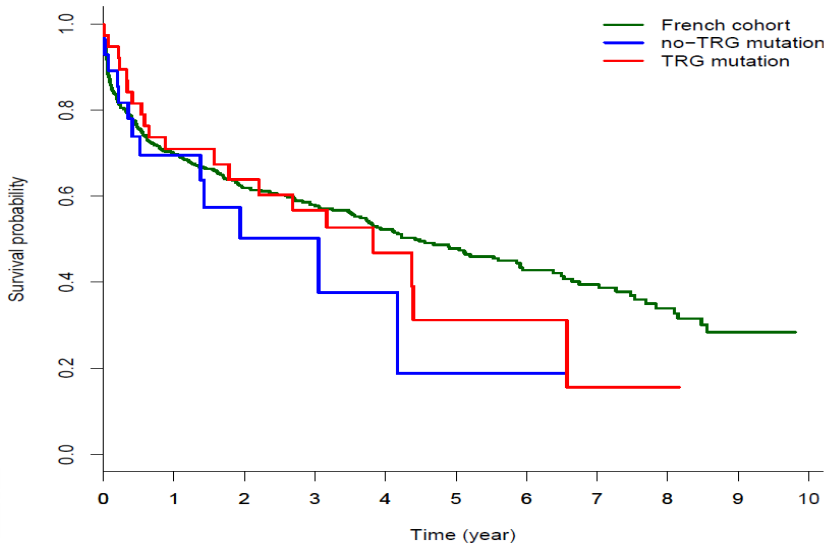



*Franco, Respirology, 2025, Zhang, Chest, 2024*

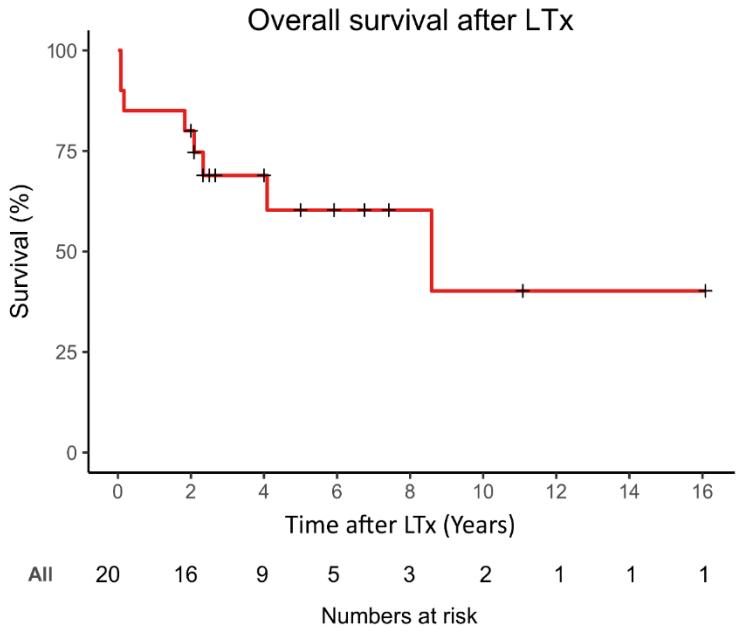
# GENETIC ANALYSIS DOES NOT IMPACT SURVIVAL AFTER LUNG TRANSPLANTATION

TELOMERE




SURFACTANT




*Alder, jhlt, 2022; Phillips, Am J Transplant, 2021; Bermudez, ERJOR, 2023*

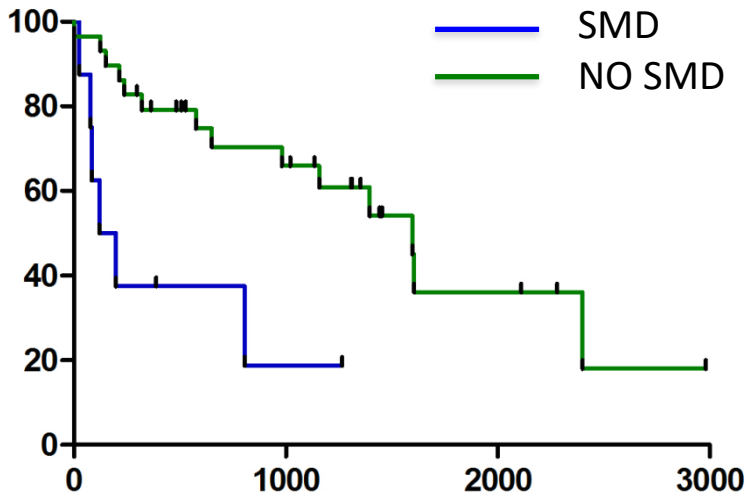
# Strict evaluation before lung transplantation ISHLT guidelines

Recommendations ISHLT:

The diagnosis of STS, by itself, should not be considered a contraindication to lung transplant evaluation.

The presence of STS-related advanced lung disease warrants additional testing:

- Hematologic conditions
- Hepatic conditions

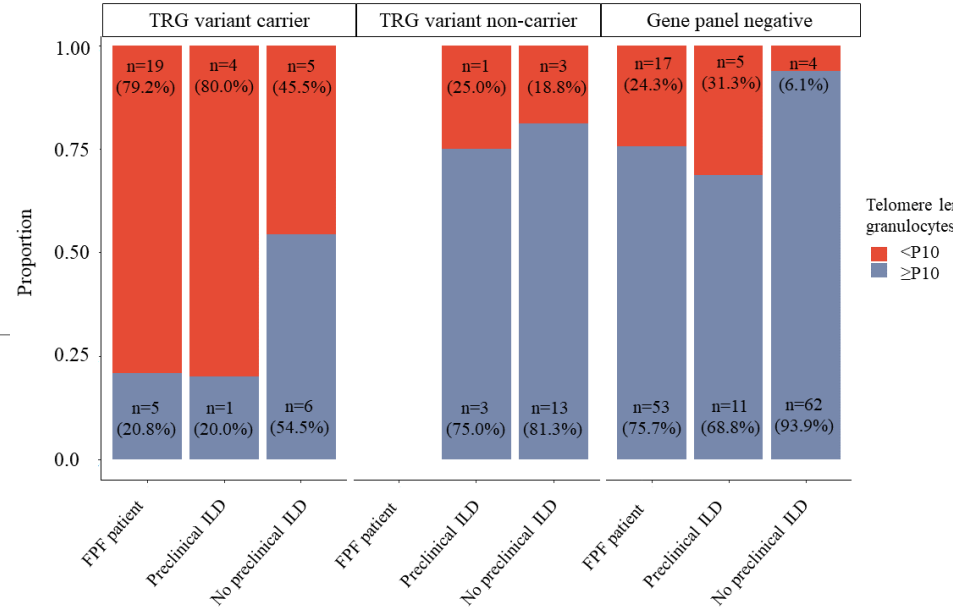



*Phillips, Am J Transplant, 2021, Courtwrigth, JHLT, 2026*

# Risk of ILD in FPF Relatives

- 830 asymptomatic relatives of FPF
- 15-30% early-onset ILD (ALI)
- 10-22% risk of progression or onset of ILD within 5 years

| | ODDS RATIO |
|---|---|
| Age | 1.1/1year |
| Gender | +/- |
| Smoking | 2.3 |
| Other expositions | |
| Aluminium | 11.5 |
| Moist | 3.2 |
| MUC5B | ↑ |
| Telomere length | 0.7 |




*Goos, submitted*

| | Asymptomatic relatives | Variant carriers | Non carriers | P |
|---|---|---|---|---|
| | N=81 | N=46 | N=35 | |
| Mean age | 47 (18) | 46 (18) | 50(18) | 0.413 |
| Male | 32 (40%) | 19 (41%) | 13 (37%) | 0.881 |
| Current smoker | 8 (10%) | 5 (11%) | 3 (9%) | 1.000 |
| Past smoking | 28 (35%) | 19 (41%) | 9 (26%) | 0.220 |
| Ever exposed to occupationnal exposure | 11 (14%) | 7 (15%) | 4 (11%) | 0.749 |
| Ever exposed to environnmental exposure | 43 (53%) | 25 (54%) | 18 (51%) | 0.971 |
| Number of exposures cumulated | 1.96 (1.36) | 2.20 (1.42) | 1.66 (1.24) | 0.073 |
| Behavioral changes [$] | **25 (31%)** | **16 (35%)** | **9 (26%)** | **0.527** |
| Currently exposed | 53 (65%) | 32 (70%) | 21 (60%) | 0.509 |

*Salisbury, AJRCCM, 2020; Mathai, Thorax, 2019, Steele, AJRCCM 2022*

*Sese, ERJOR, 2026*

# French Flowchart for relatives

Clinical evaluation

Biological evaluation

PFT

Abdominal US

**Indication for CT scan**

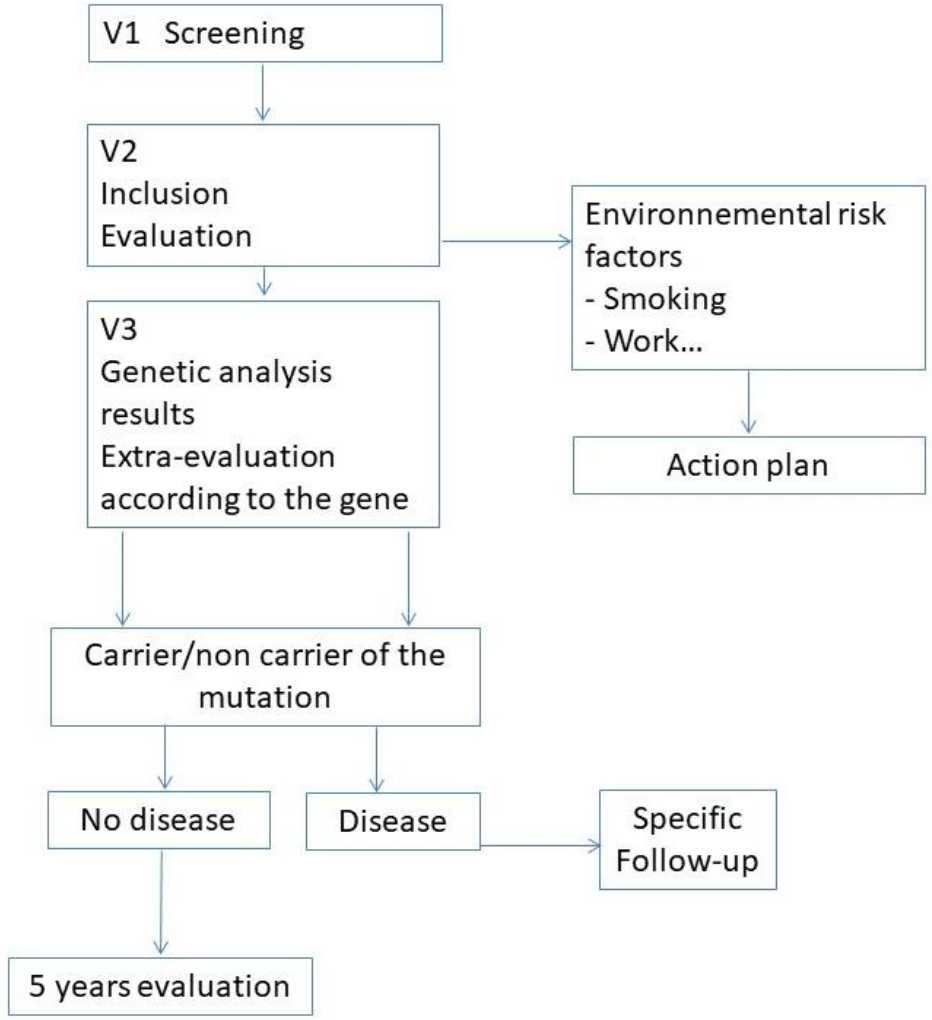
Symptoms, crackles

Or >40 years old

Or 10 years before the age of onset in the proband

**Frequency?**

Unknown, every 5 years?




*Newton, Chest, 2022, Borie, ERJ, 2023*

# Characteristics of asymptomatic relatives of TRG mutation carrier

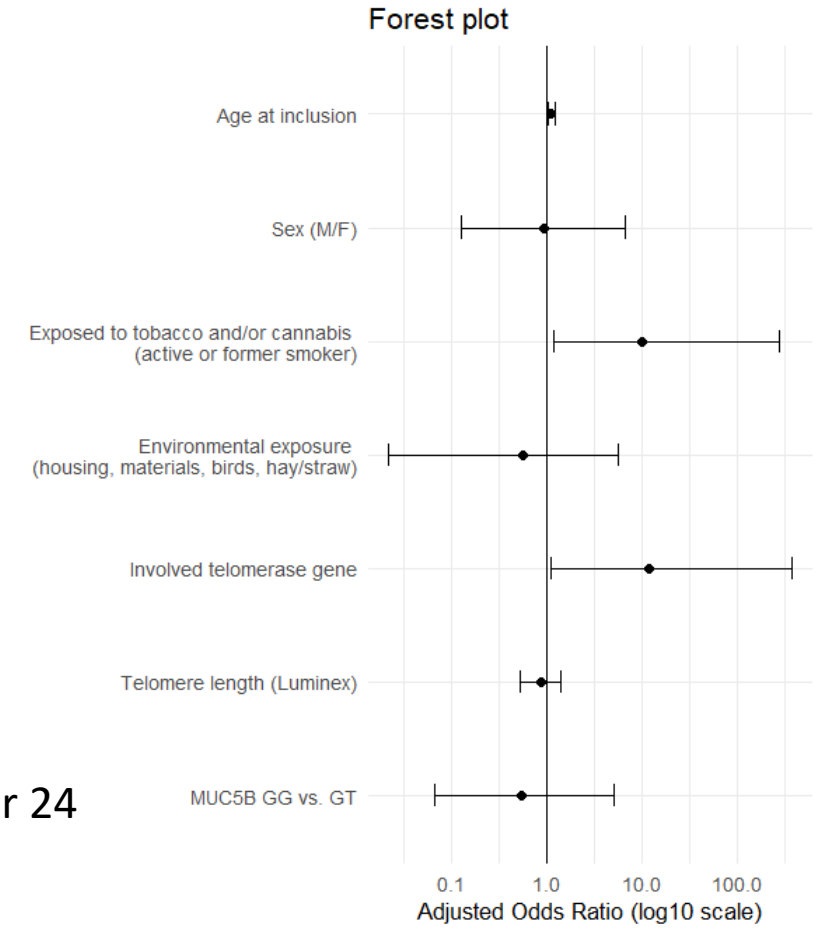
| | Total | Carriers | Non carriers | p |
|---|---|---|---|---|
| Age, years | 46.4 ± 15.1 (n=181) | 44.2 ± 14.8 (n=98) | 46.9 ± 16.5 (n=44) | 0.31* |
| Female sex | 108/182 (59.3%) | 58/98 (59.2%) | 24/44 (54.5%) | 0.62 |
| Tobacco exposure | 92/182 (50.4%) | 51/96 (53.1%) | 20/44 (45.5%) | 0.41 |
| Environmental exposure | 37/182 (20.4%) | 21/98 (21.4%) | 9/44 (20.5%) | 0.91 |

| Variable | Total | Carriers | Non-carriers | p |
|---|---|---|---|---|
| Fibrotic features | 10/106 (9.4%) | 9/65 (13.9%) | 1/28 (3.6%) | 0.12 |
| Non-fibrotic abnormalities | 31/105 (29.5%) | 18/64 (28.1%) | 9/28 (32.1%) | 0.68 |
| Emphysema | 13/96 (13.5%) | 9/55 (16.4%) | 2/28 (7.1%) | 0.21 |
| | | | | |
| PFT performed | | | | |
| FVC % predicted | 106.34 (16.10) (n=185) | 106.41 (15.40) (n=94) | 104.19 (15.90) (n=40) | 0.47 |
| DLCO % predicted | 85.41 (14.78) (n=175) | 84.19 (14.86) (n=92) | 86.15 (12.96) (n=40) | 0.46 |
| KCO% predicted | 90.32 (14.06) (n=160) | 89.46 (14.38) (n=84) | 92.85 (12.34) (n=39) | 0.24 |

*Guerin, ERS, 2024*

# TRG are associated wiht fibrotic ILA but not wiht non fibrotic

| | OR [IC95%] | p-value |
|---|---|---|
| Age at inclusion | 1.13 [1.05-1.25] | 0.004 |
| Sex (M/F) | 0.94 [0.13-6.65] | 0.947 |
| tobacco | 10.11 [1.18-277.23] | 0.077 |
| Environmental exposure | 0.56 [0.02-5.60] | 0.657 |
| Presence of the variant | 12.06 [1.11-384.99] | 0.078 |
| Telomere length (Luminex) | 0.88 [0.52-1.42] | 0.617 |
| MUC5B GG vs. GT | 0.56 [0.07-5.20] | 0.577 |




DROP FPF:
Double blind, randomized, placebo-controlled of nerandomilast over 24 months in ILA and a family history of pulmonary fibrosis

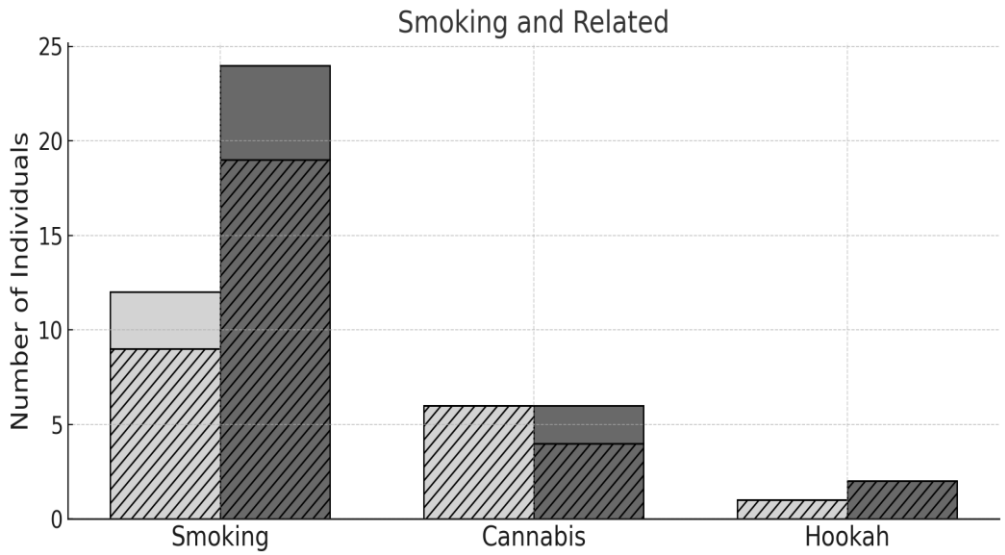
# Reduced environemental exposure in asymptomatic relatives

81 relatives surveyed

- 75% at-risk exposures
- 45% smokers
- 27% live within 200 m of a busy road

41% change in exposures after the consultation unrelated to being a carrier of the variant

No move or career change (yet?)




*Sese, ERJOR, 2026*

# Conclusion

GENETIC DIAGNOSIS INDICATIONS:

- Familial forms of ILD
- Suspected telomere biology disorders (liver, lung, skin, hematoma)
- Idiopathic ILD <50 years

IMPACT OF GENETIC DIAGNOSIS

- (almost) none currently for the patient
- Reduction of immunosuppressants if TRG?
- Immunosuppressants if SRG?

Genetic counseling and reduction of risk exposures?