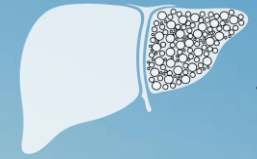


# AATD-associated liver disease

**UNIKLINIK  
RWTHAACHEN**



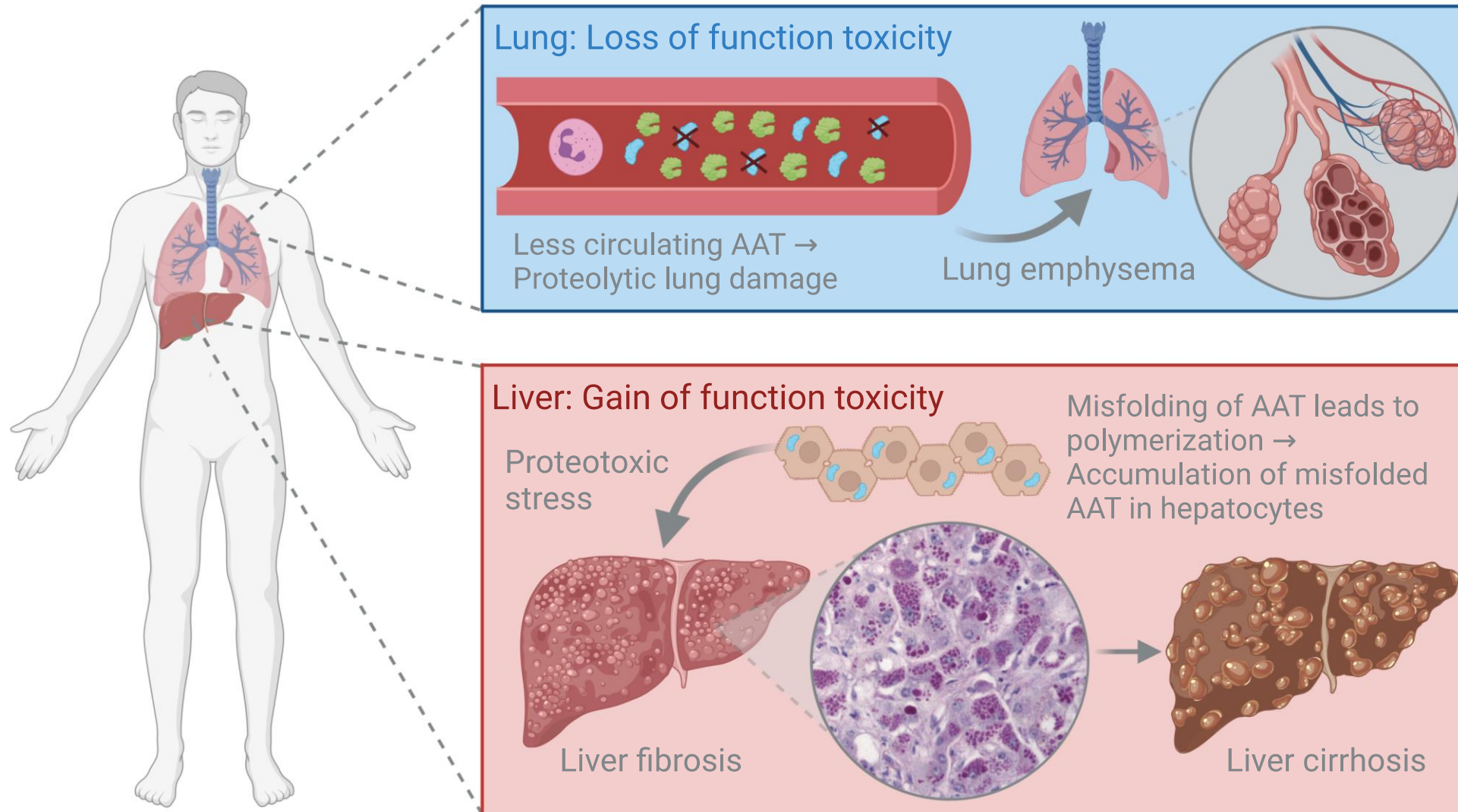
European  
AATD liver  
study group

Univ.-Prof. Dr. Pavel Strnad

05.11.2024

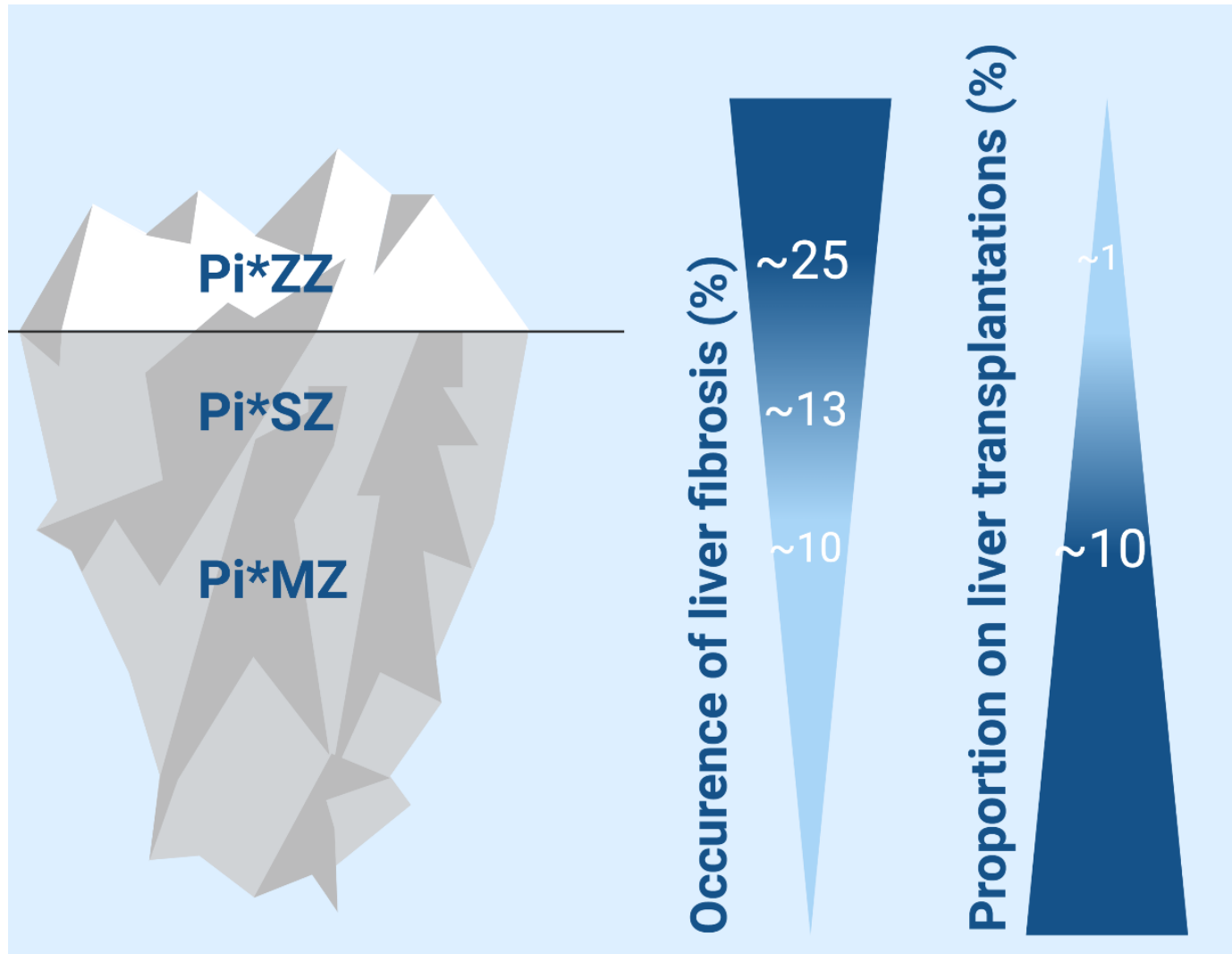
**Medizinische Klinik III –**  
Gastroenterologie, Stoffwechselkrankheiten  
und Internistische Intensivmedizin

# AATD: Lung and liver



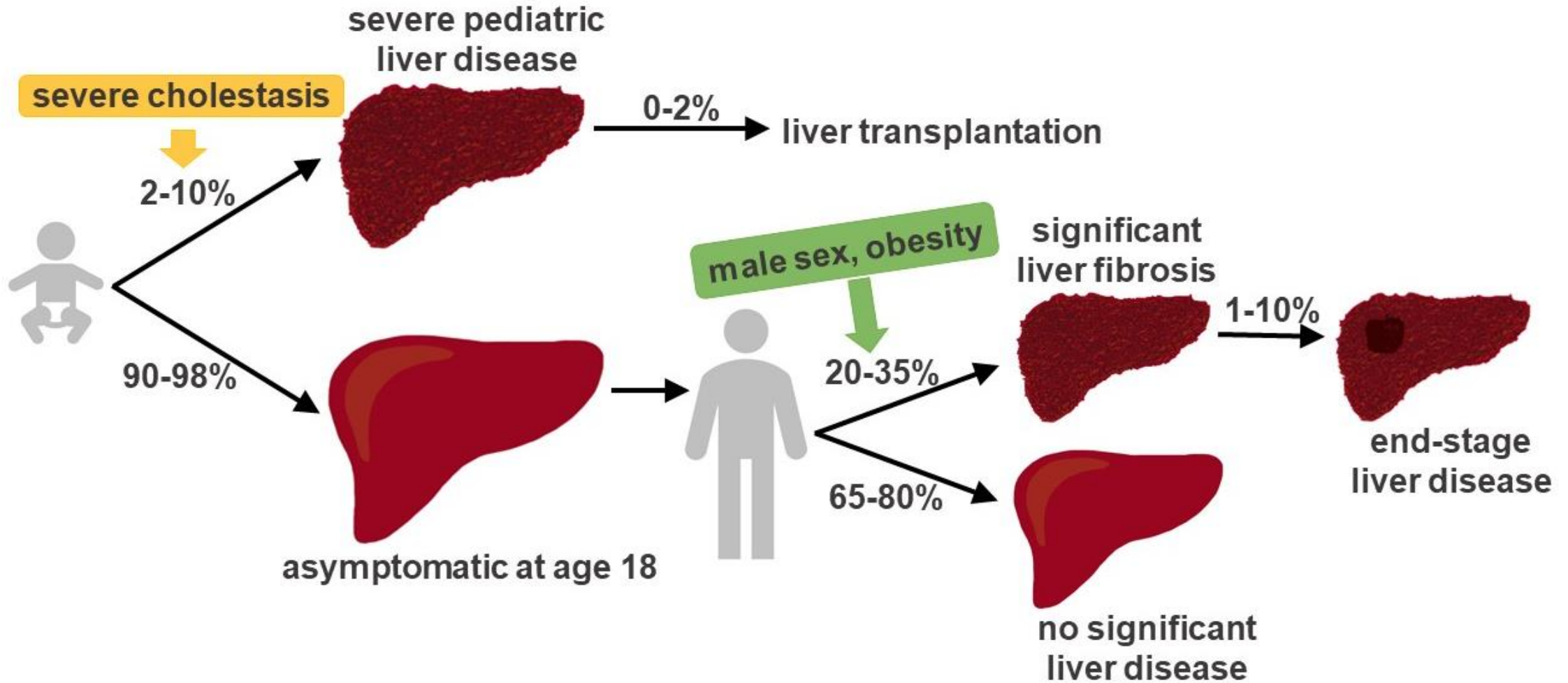
Strnad et al., *NEJM* 2020

# Liver disease in AATD

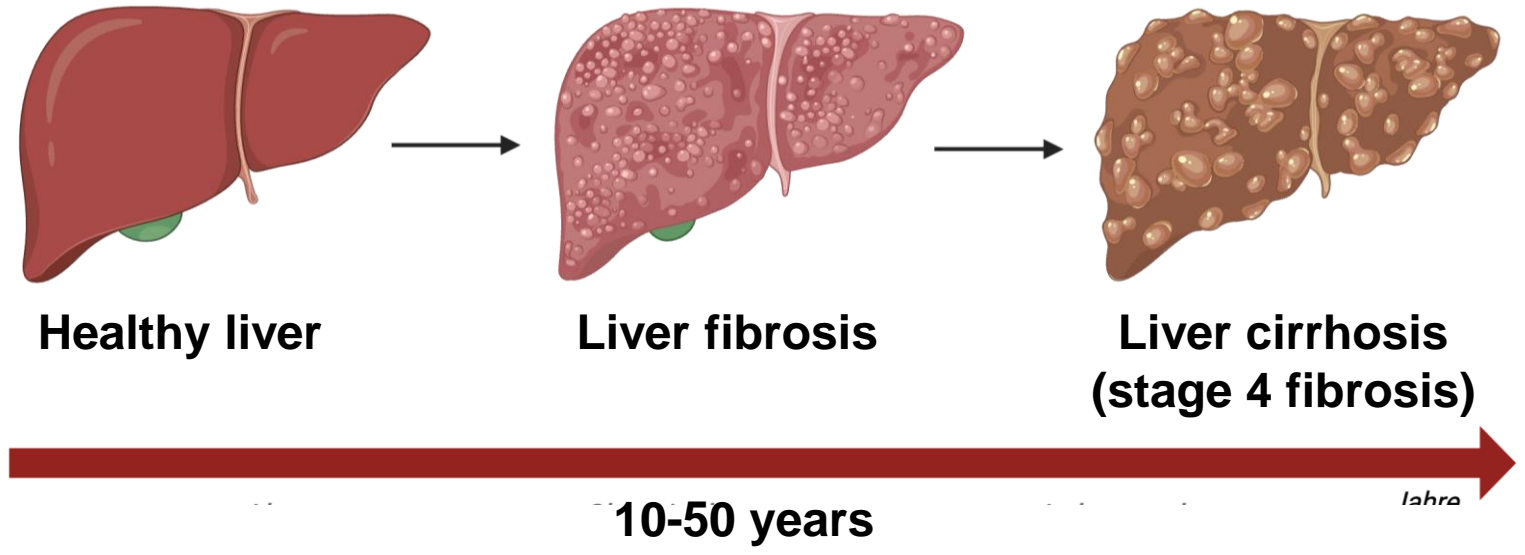


Strnad et al., Gut 2019; Hamesch....  
Strnad, Gastroenterology 2019;  
Kümpers... Strnad, J Hepatol 2019;  
Schneider.... Strnad, Gastroenterology  
2020, 2021; Fromme... Strnad Gut 2021

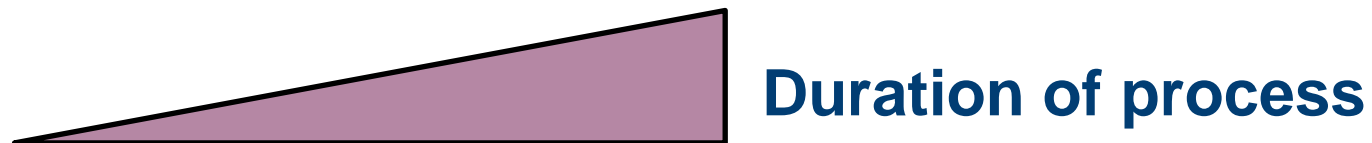
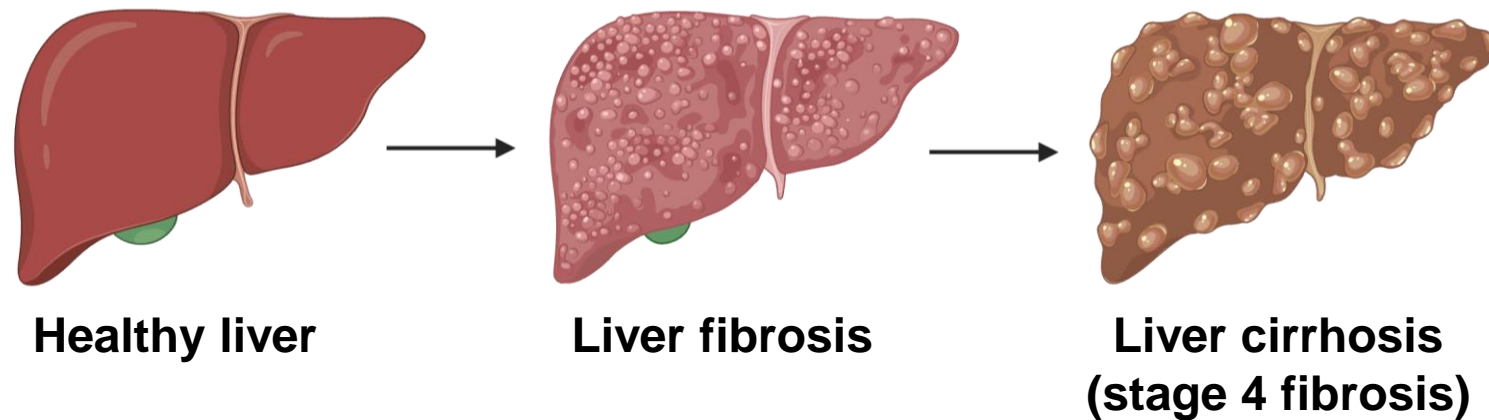
# Liver disease in Pi\*ZZ



# Chronic liver disease-a very slow process



# Chronic liver disease-a very slow process



# Liver function tests-“liver tears“

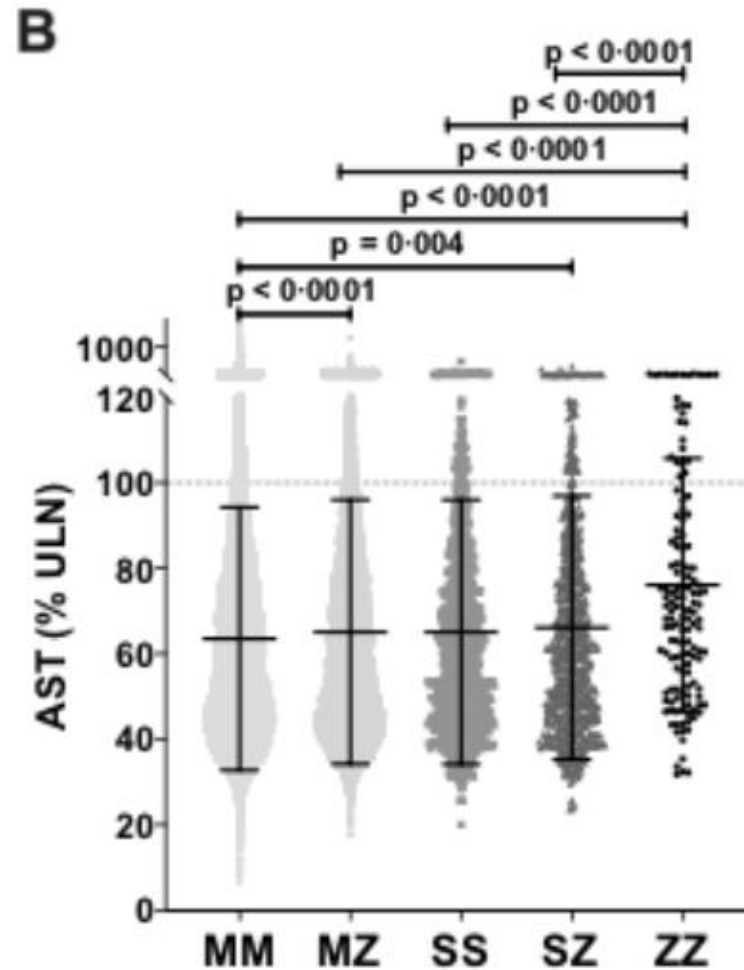
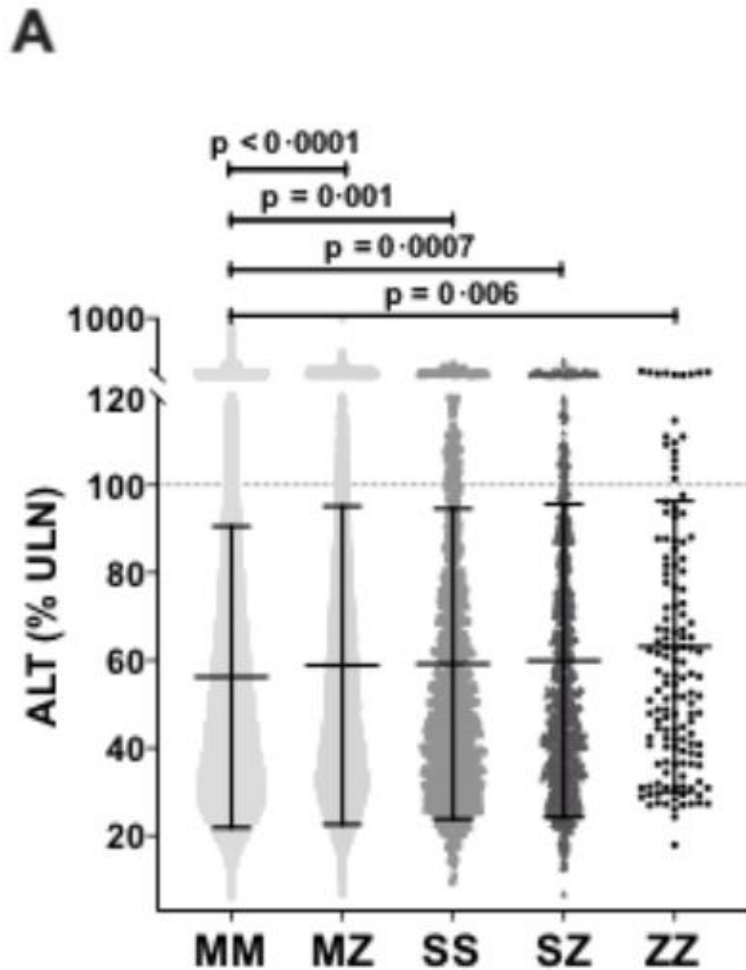


	Half-life
<b>AST=GOT</b>	<1d
<b>ALT=GPT</b>	~2d
<b>GGT</b>	7-10d



**Sensitive, but not specific (drugs, viral infections, alcohol etc.)**

# Liver function tests in AATD

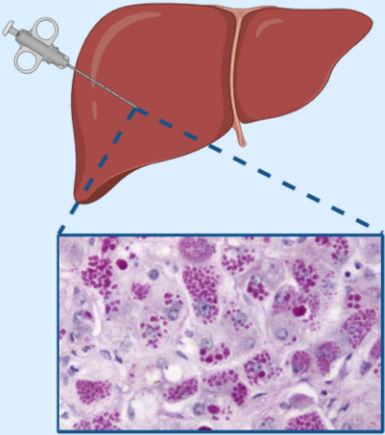


Genotyp	Pi*ZZ	Pi*SZ	Pi*MZ
Häufigkeit	~1:2000	~1:500	~1:50
AST ≥ ULN	15%	5%	5%
ALT ≥ ULN	11%	9%	7%

Elevated liver function tests should be examined!

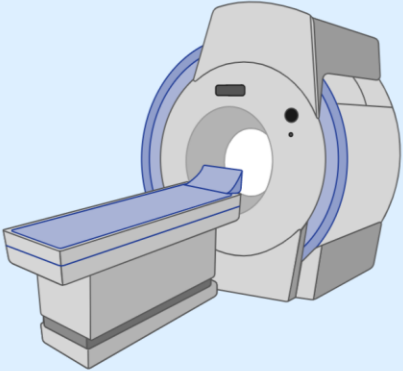


# Liver fibrosis



### Liver biopsy

Gold standard

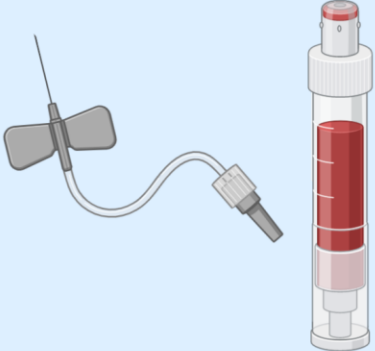


### MR Elastography



### Ultrasound

Transient Elastography  
Shear wave  
ARFI



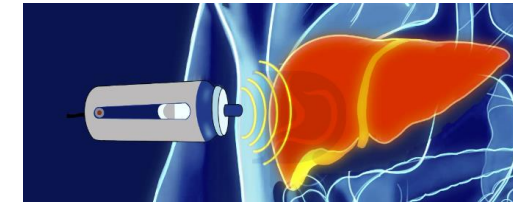
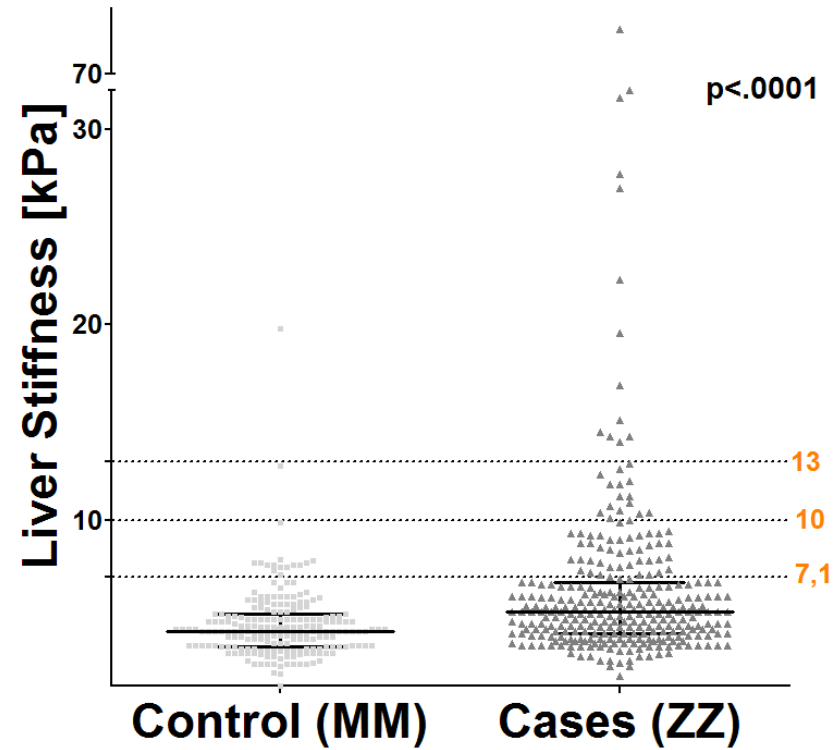
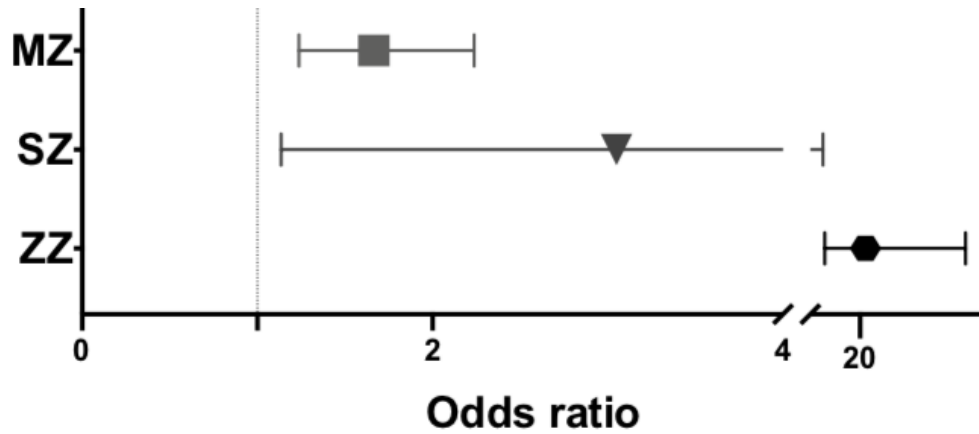
### Serum markers

Liver enzymes  
APRI40, Fib4  
HepaScore, ELF test



Fromme et al. Gut 2022

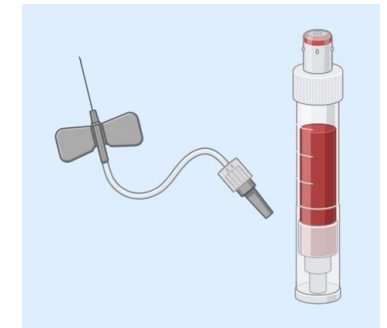
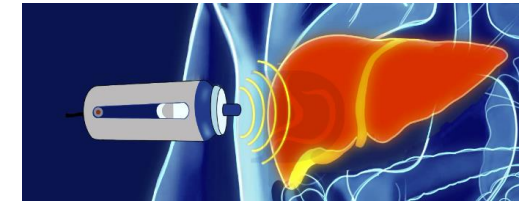
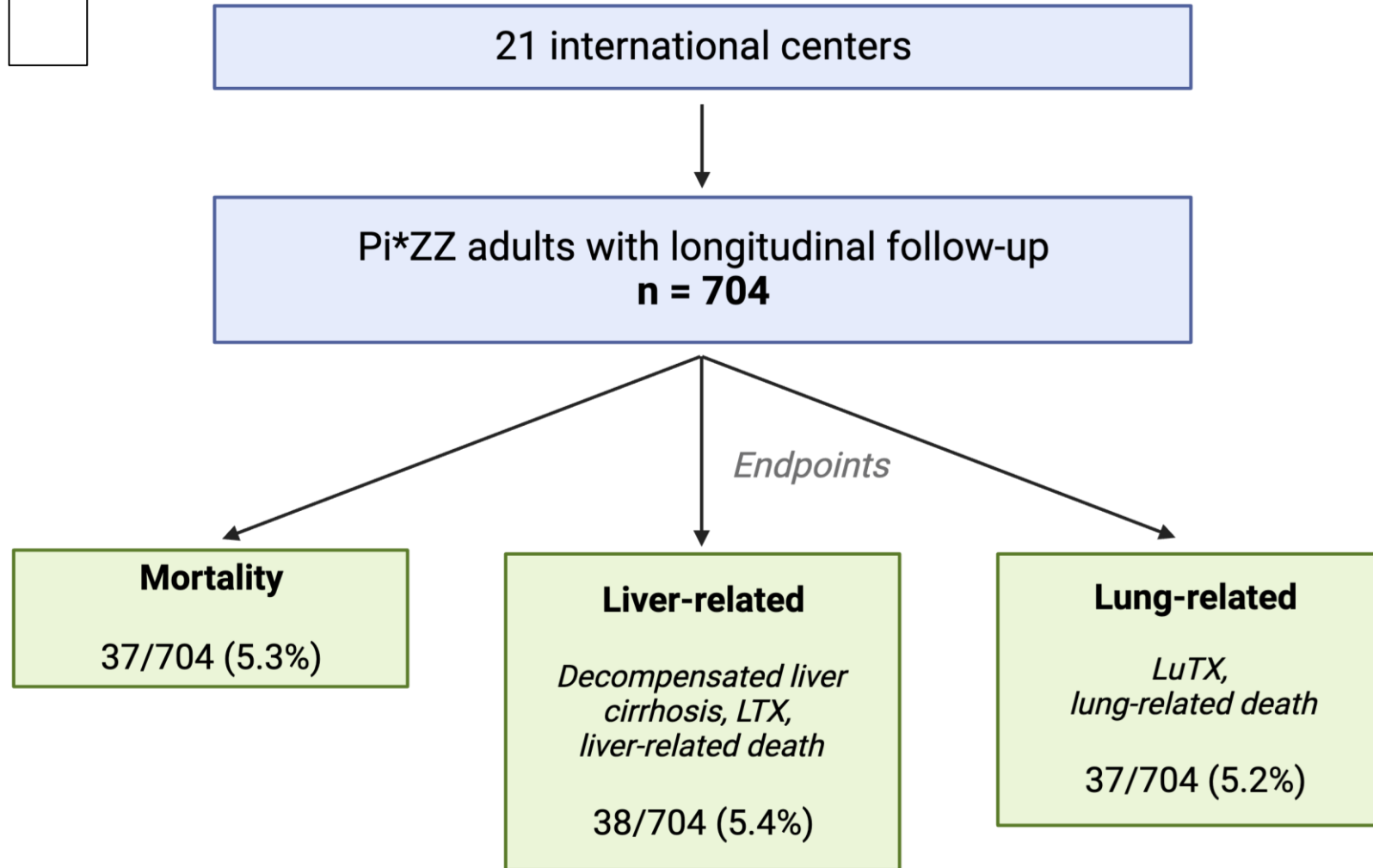
# Liver fibrosis in AATD



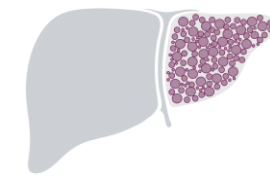
F $\geq$ 2 (moderate)	$\geq$ 7.1 kPa	22%
F $\geq$ 3 (severe)	$\geq$ 10.0 kPa	12%
F=4 (cirrhosis)	$\geq$ 13.0 kPa	5%

Hamesch et al., Gastro 2019; Fromme et al. Gut 2022

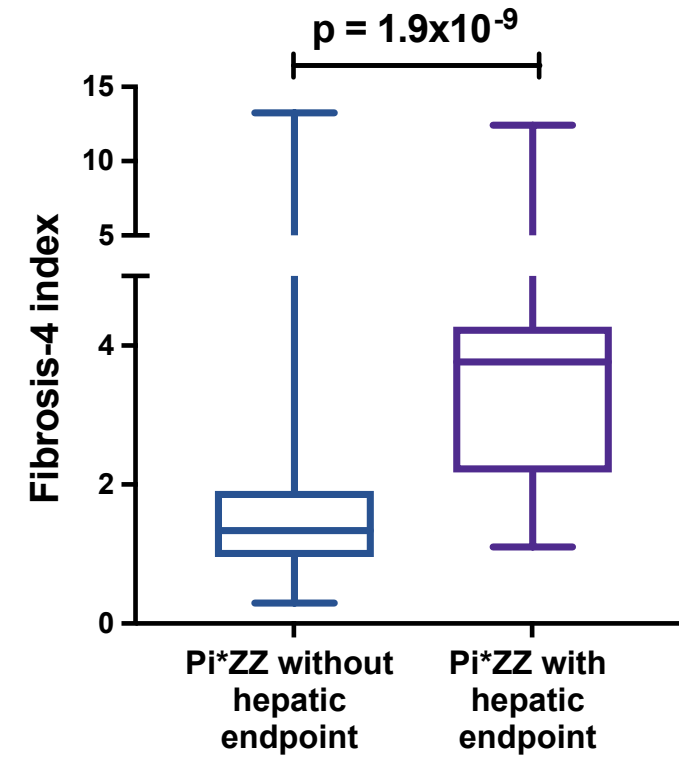
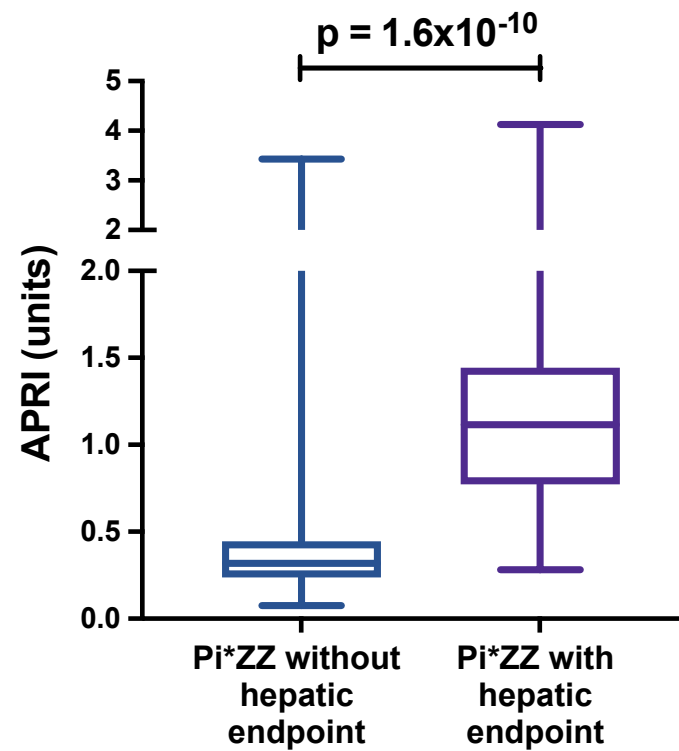
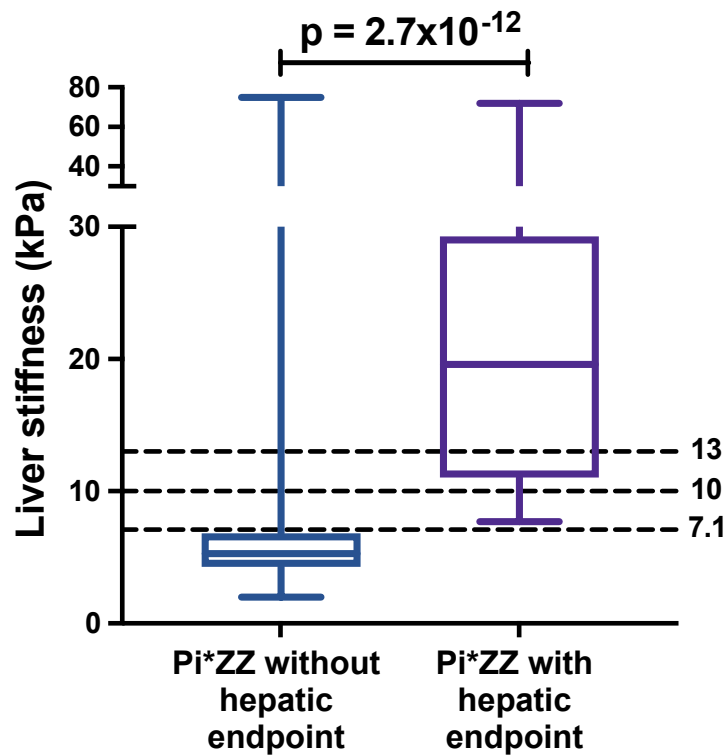
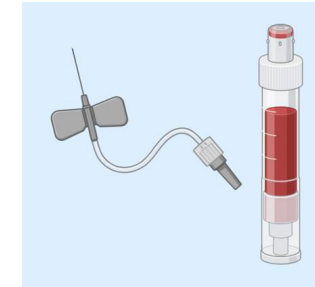
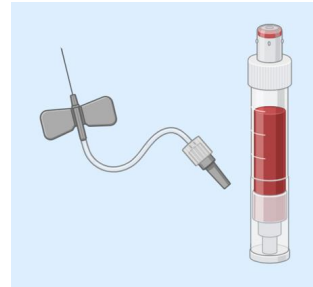
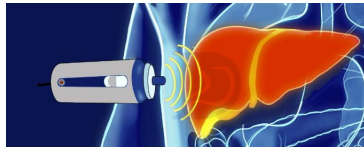
# Is evaluation of liver fibrosis helpful?



# Is evaluation of liver fibrosis helpful?

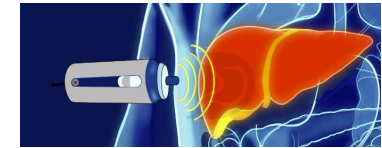


European  
AATD liver  
study group

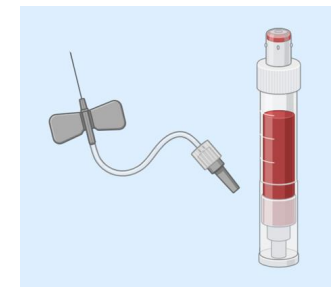


# Is evaluation of liver fibrosis helpful?

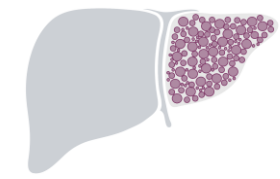
LSM (kPa)	n	Follow-up years	Liver-related endpoints	Endpoints/100 FU years
<7.1	540	1922.8	0	0
7.1 – 10	103	391.0	6	1.5
10.1 – 14.9	50	206.2	8	3.9
≥15	44	113.6	27	23.8



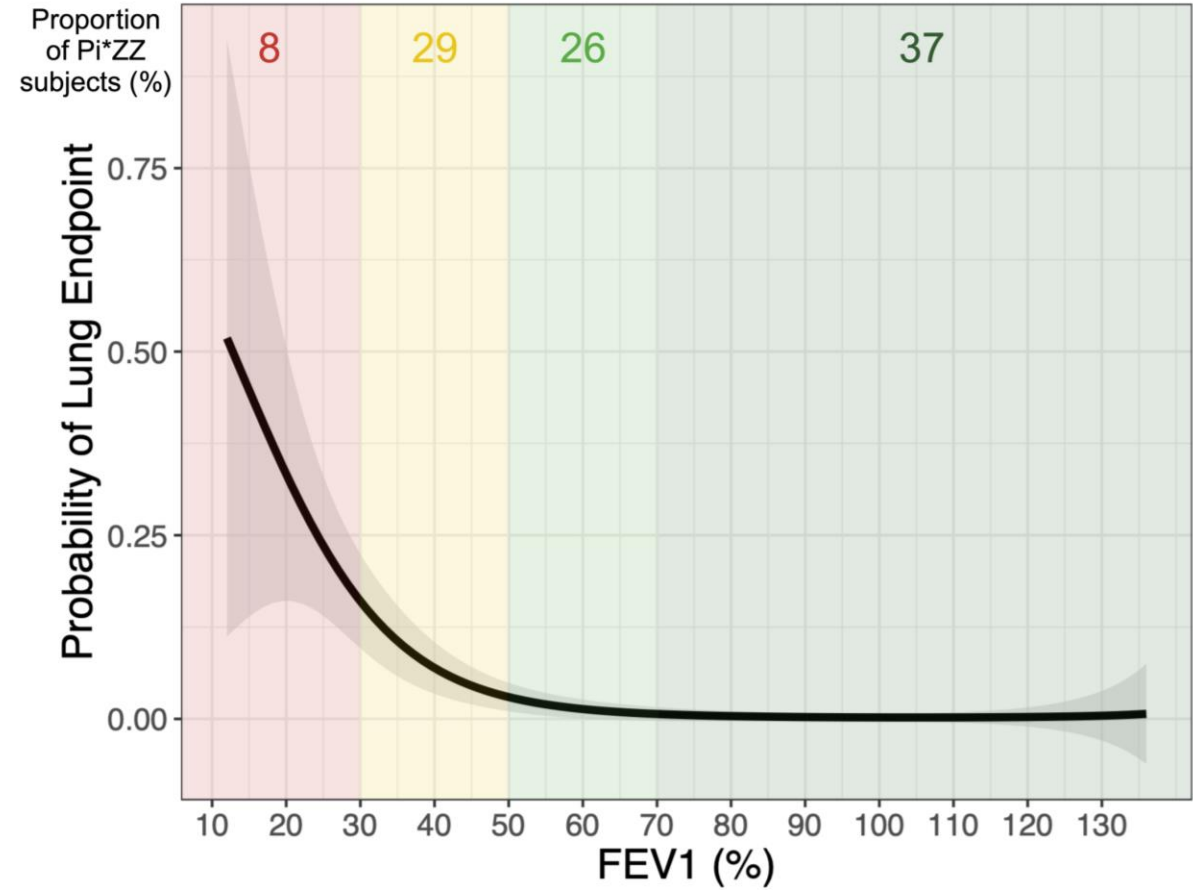
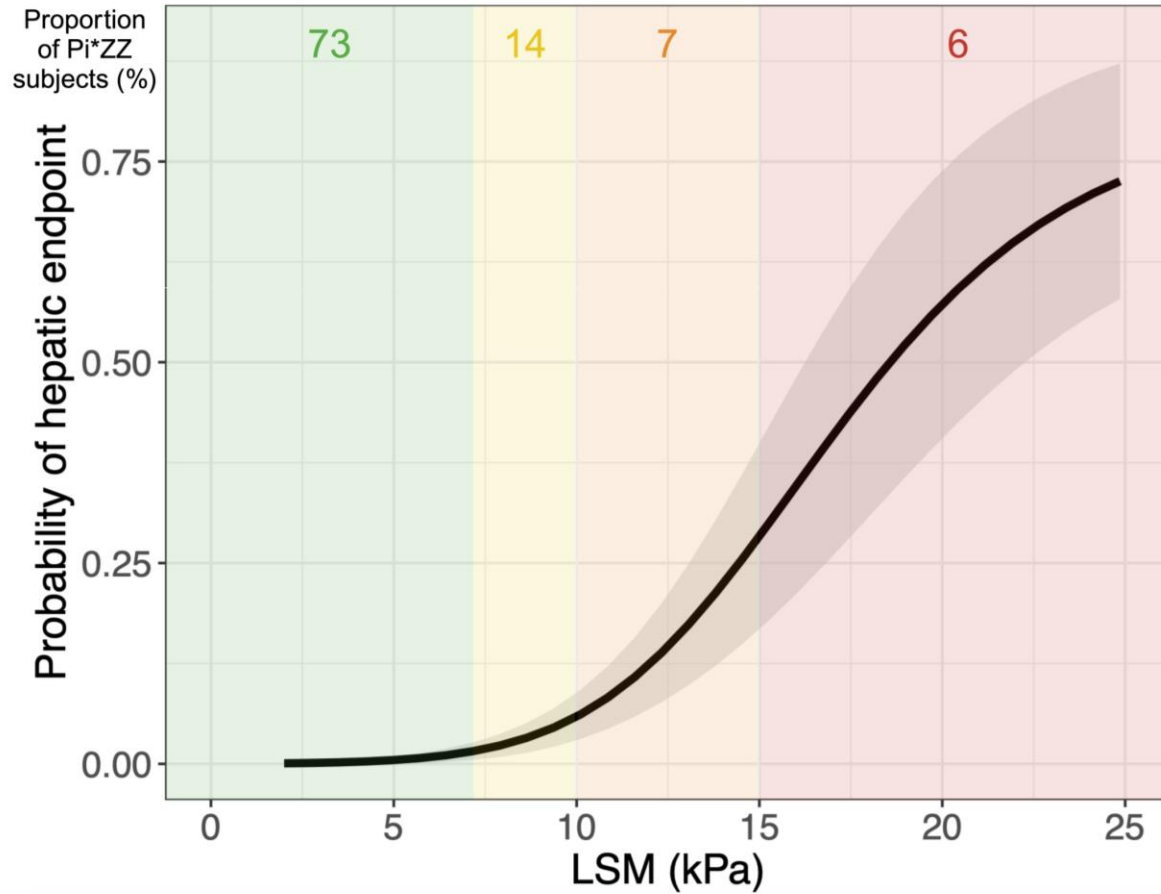
APRI (units)	n	Follow-up years	Liver-related endpoints	Endpoints/100 FU years
<0.5	545	1970.0	4	0.2
0.5 – 0.99	129	471.6	15	3.2
1.0 – 1.49	18	35.4	10	28.2
≥1.5	15	34.9	12	34.4



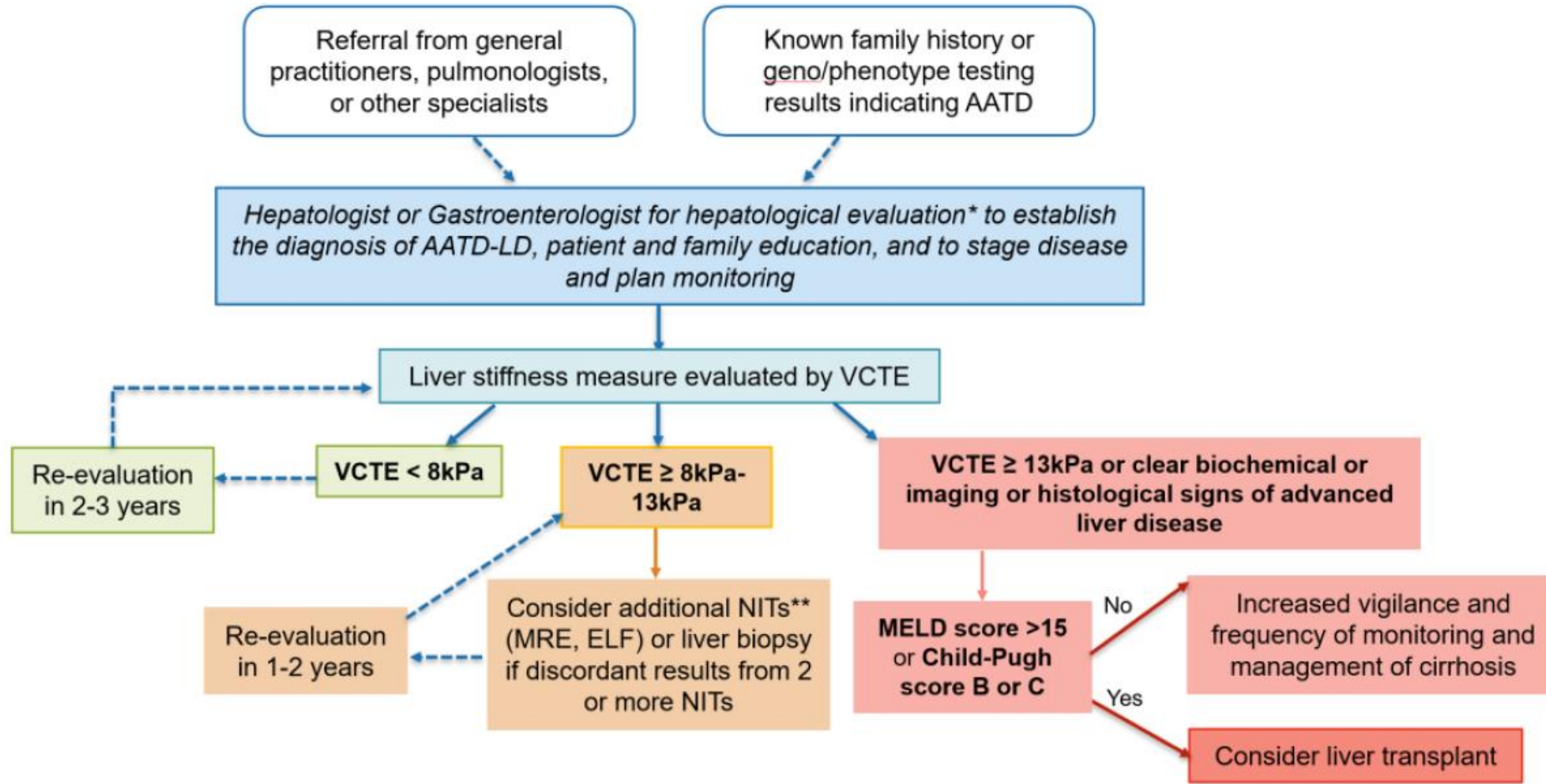
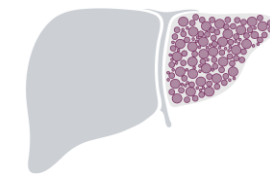
# Comparing lung and liver



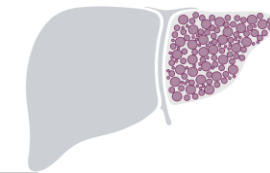
European  
AATD liver  
study group



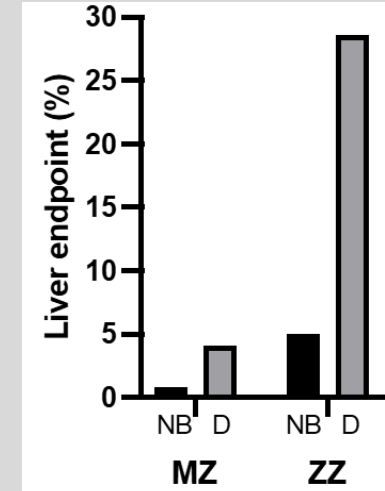
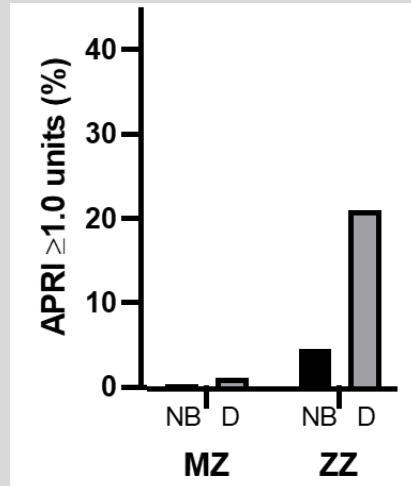
# Fibrosis and liver monitoring



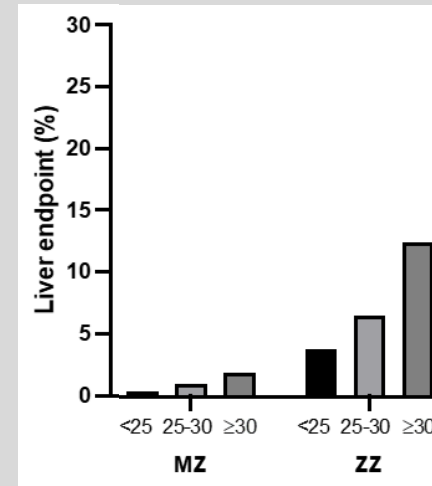
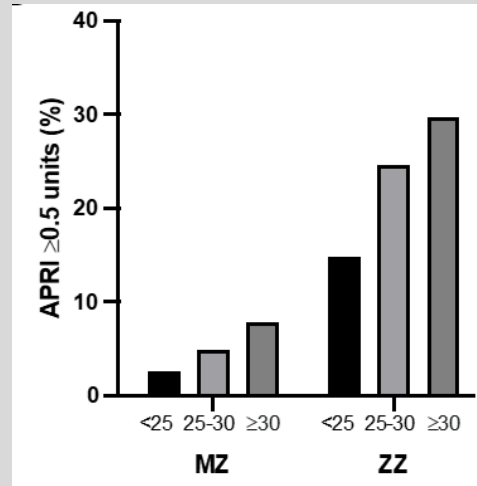
# Who is at risk?



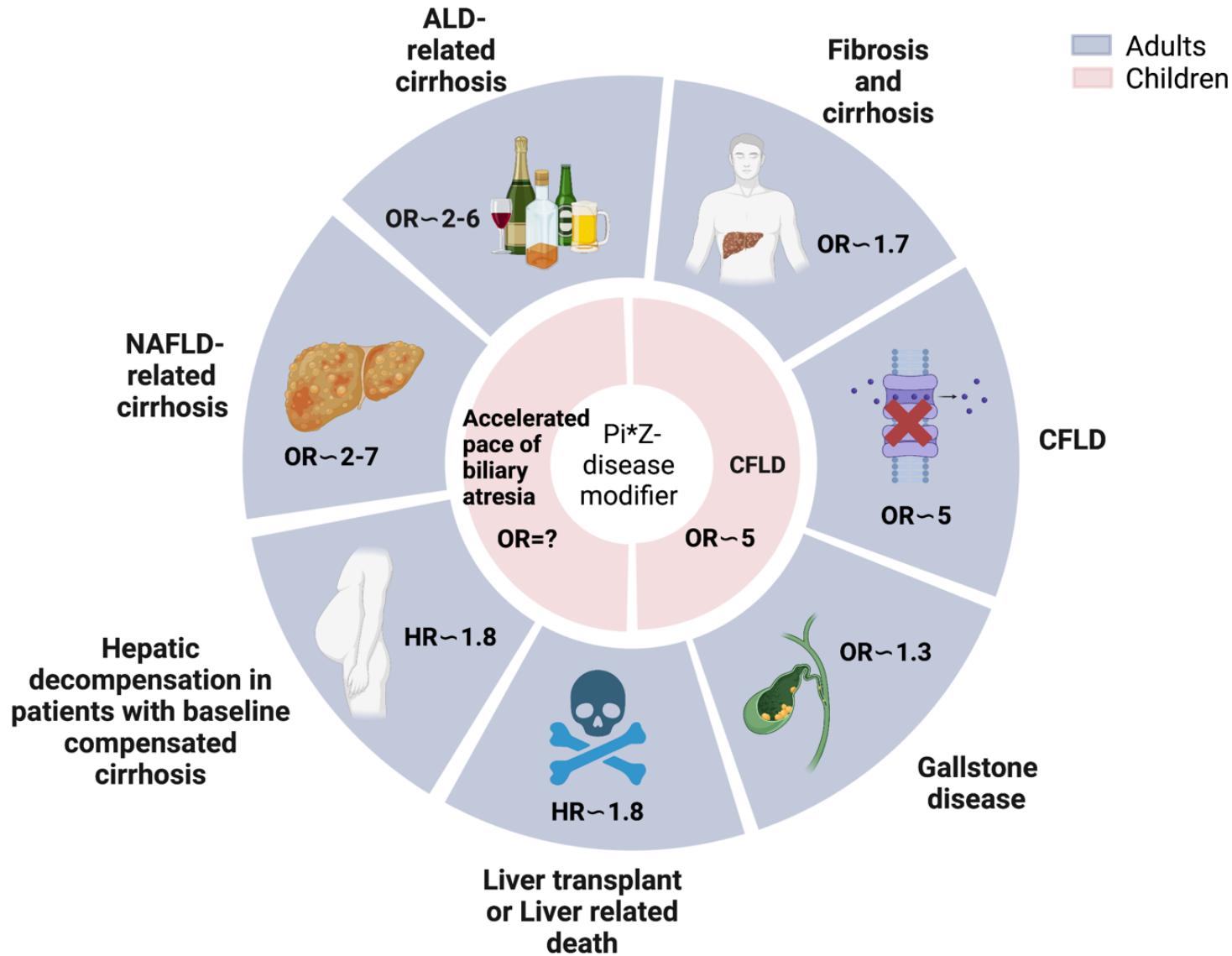
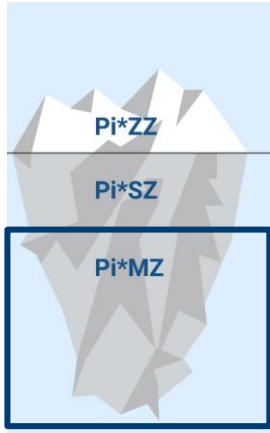
## Diabetes



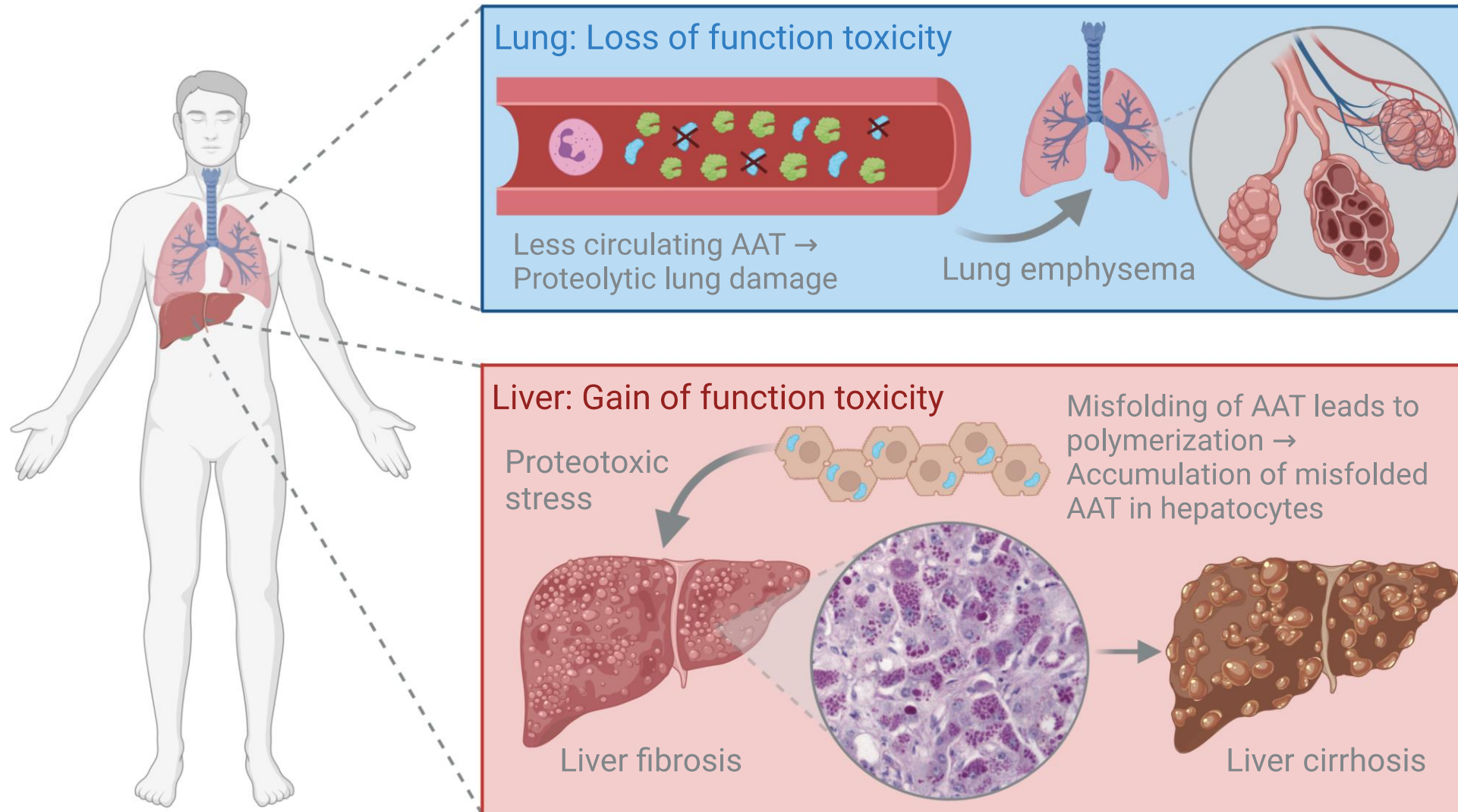
## Obesity



# Pi\*MZ-a disease modifier

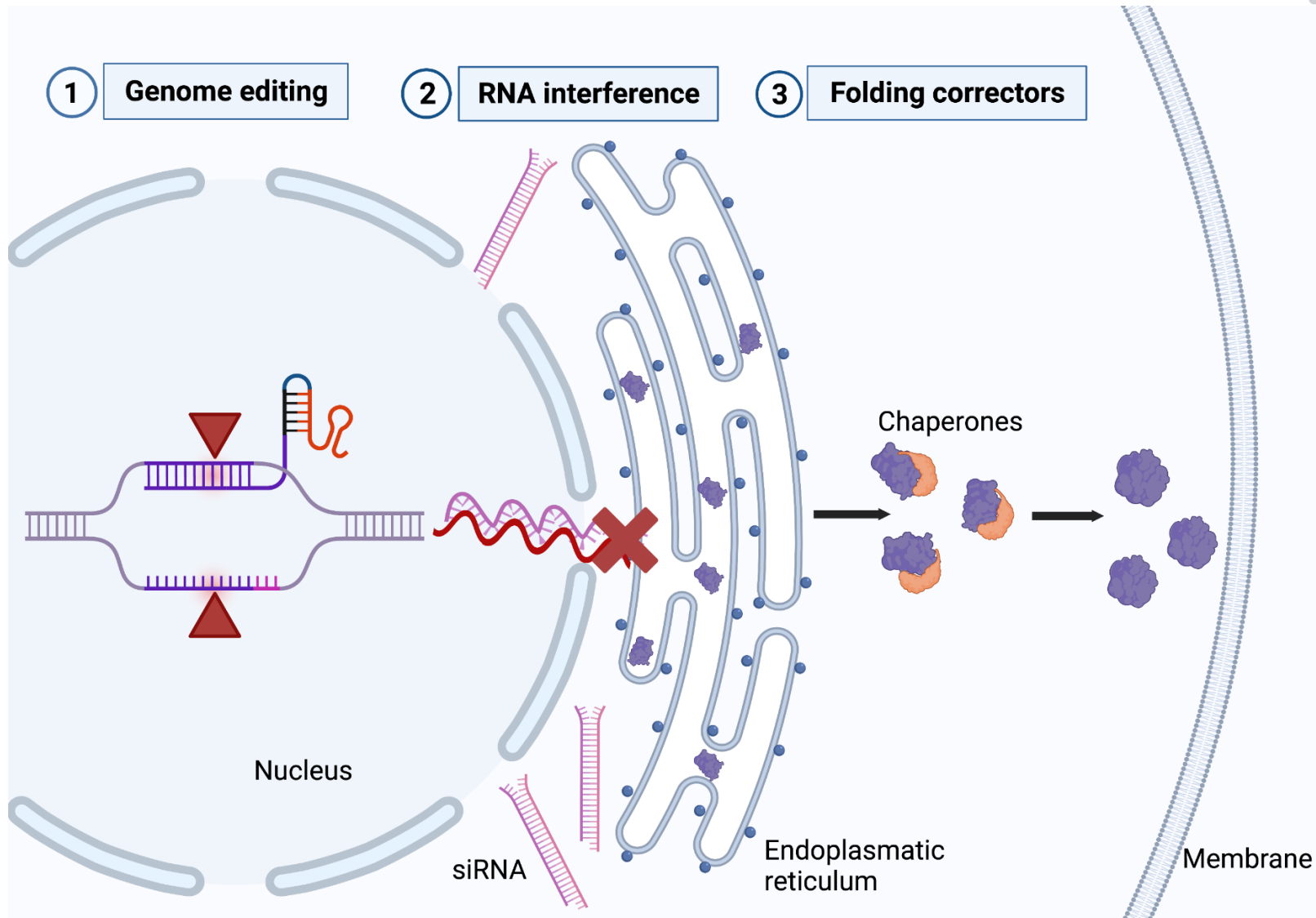


# How to treat liver disease?

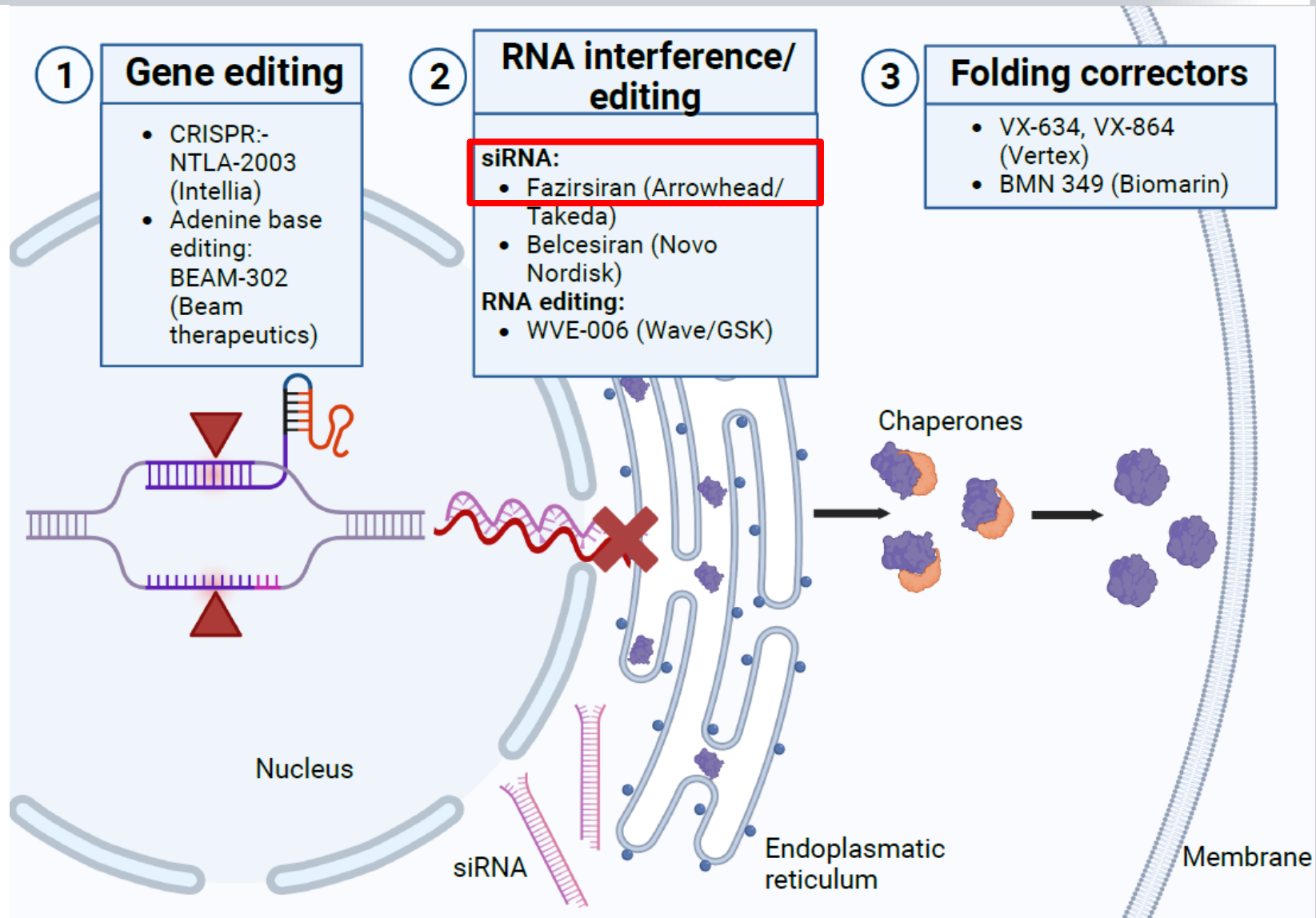


Strnad et al., *NEJM* 2020

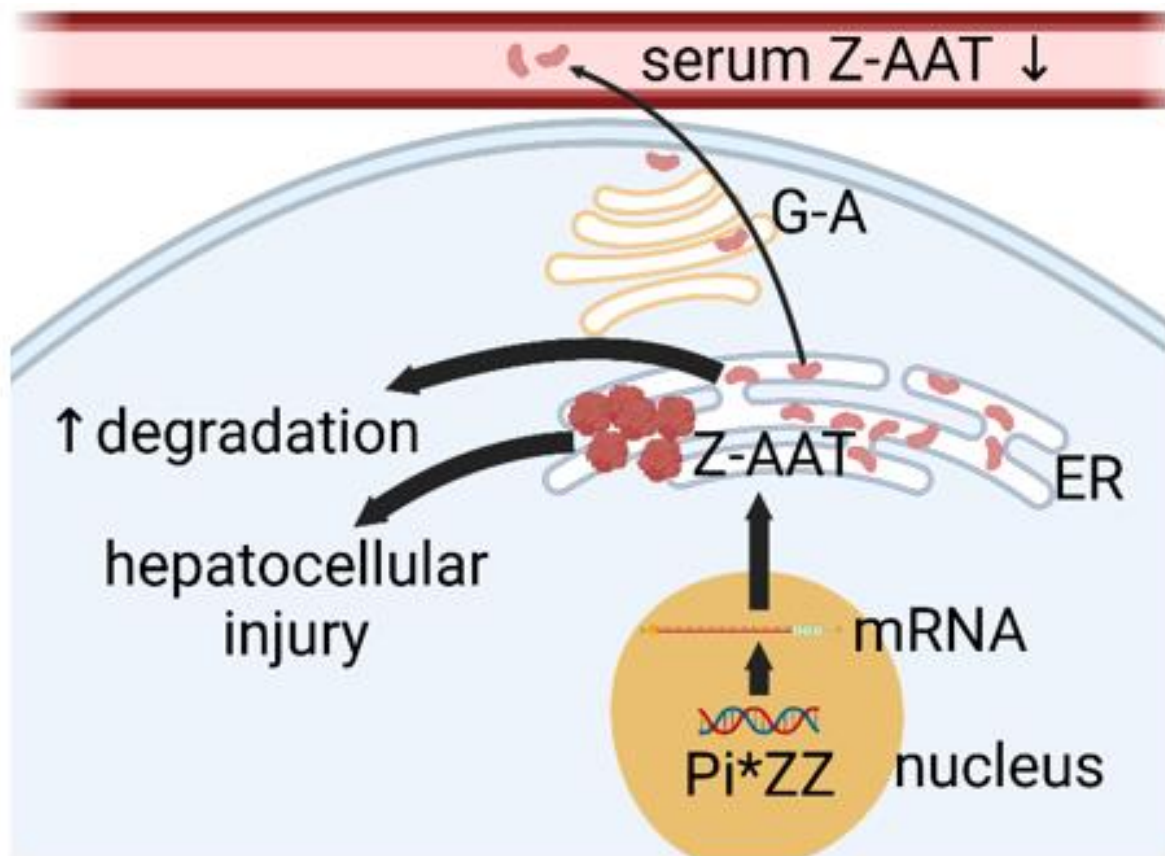
# How to treat liver disease?



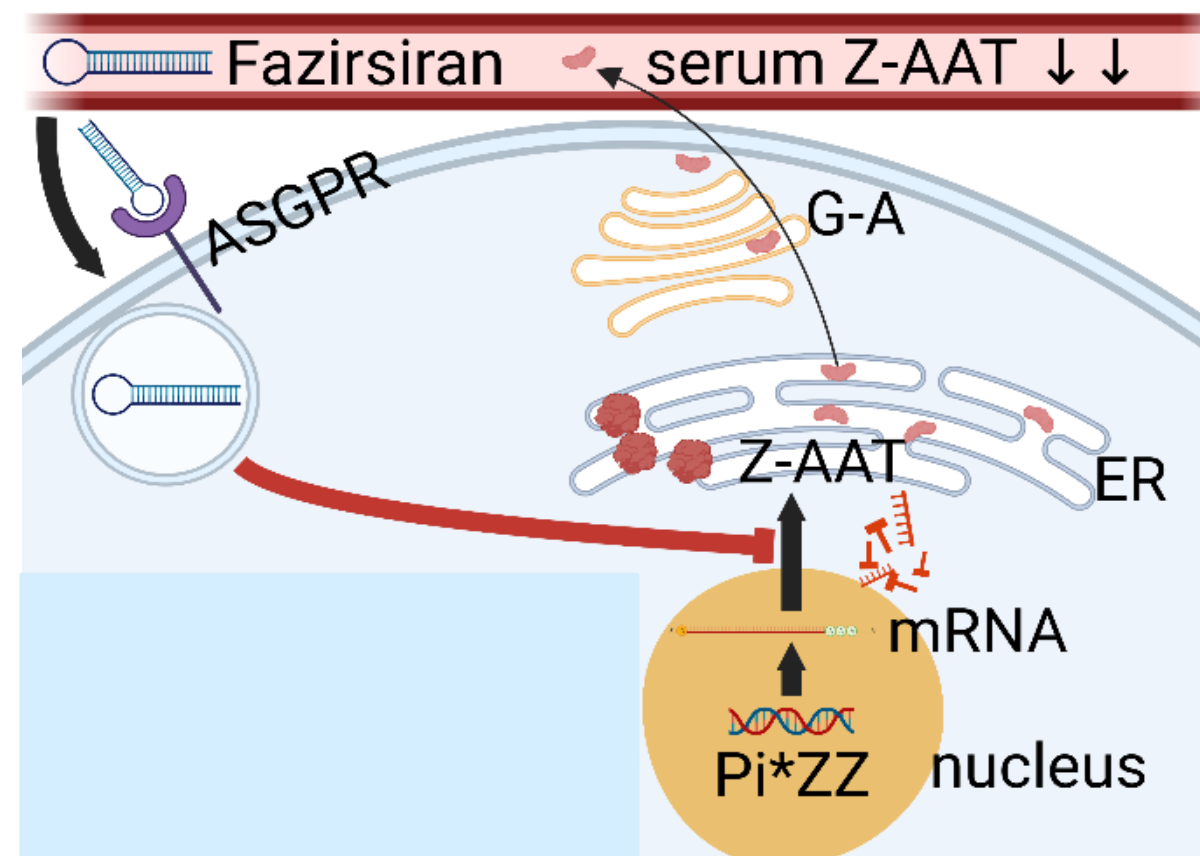
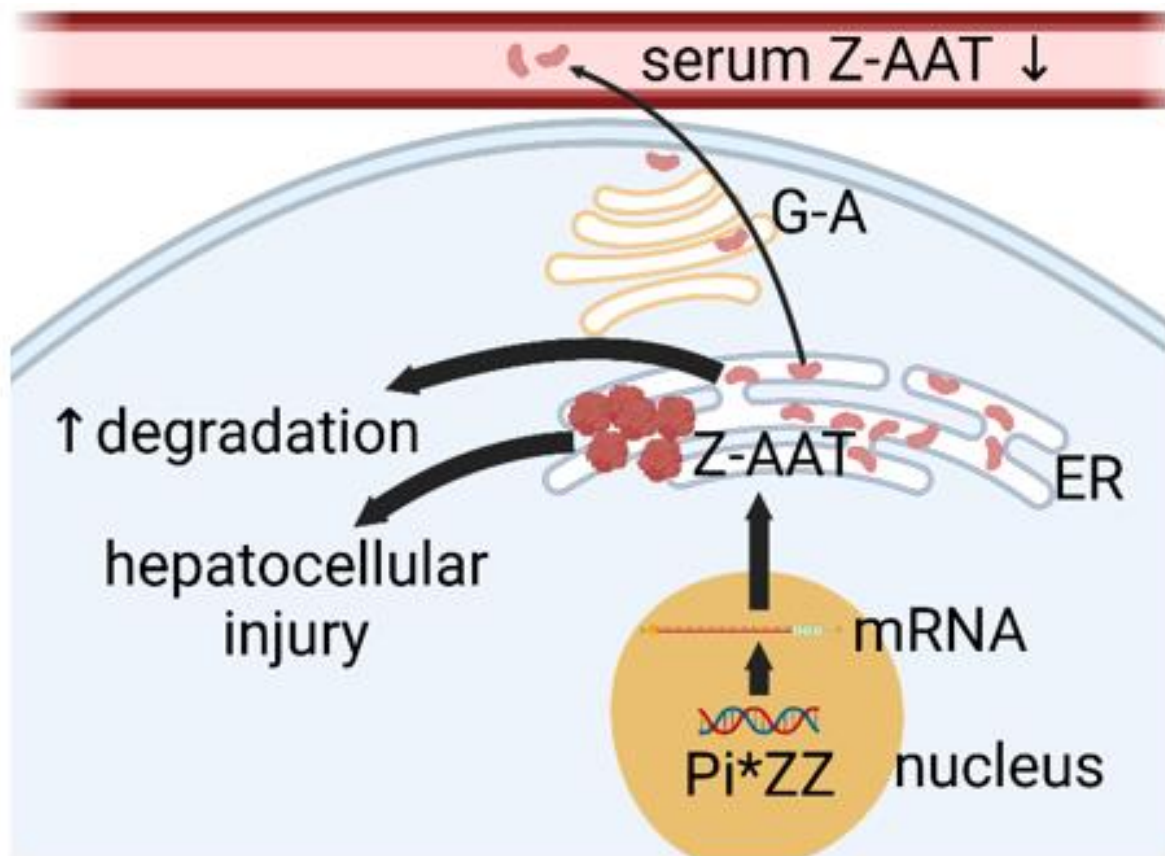
# How to treat liver disease?



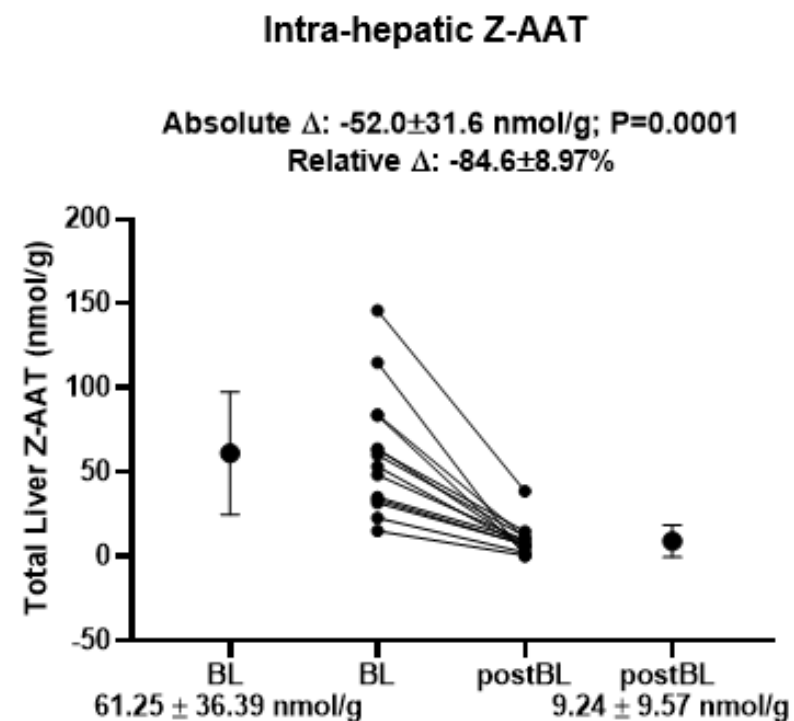
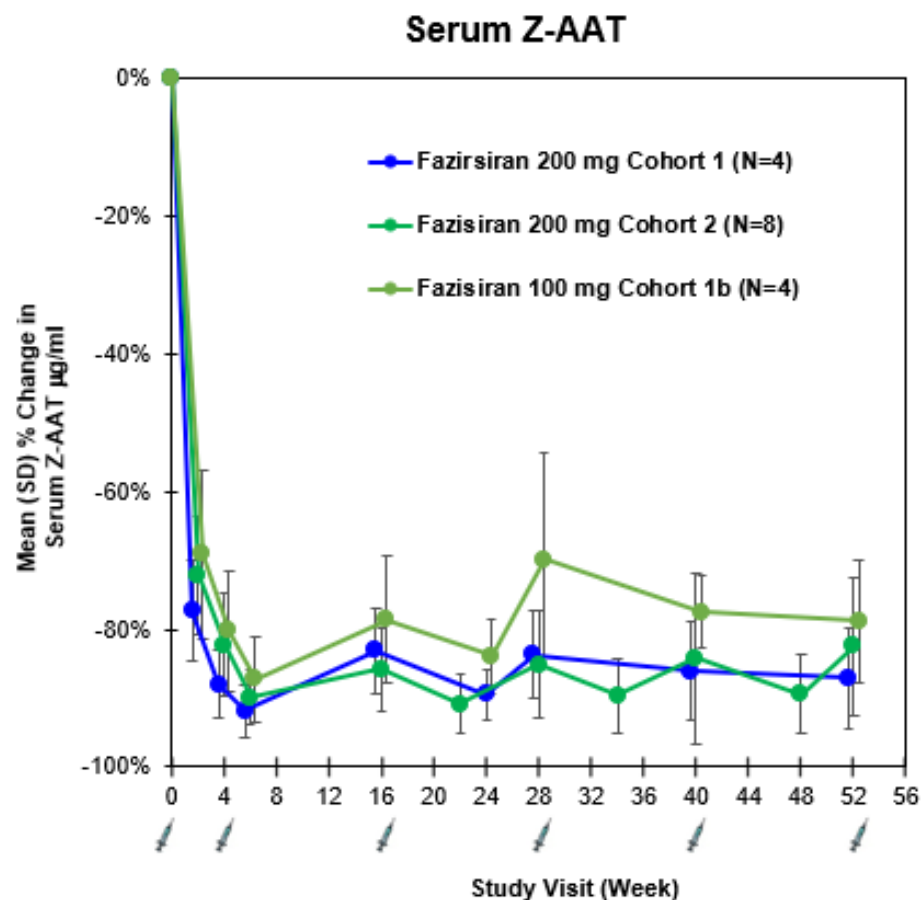
# Fazirsiran for Pi\*ZZ-associated liver disease



# Fazirsiran for Pi\*ZZ-associated liver disease



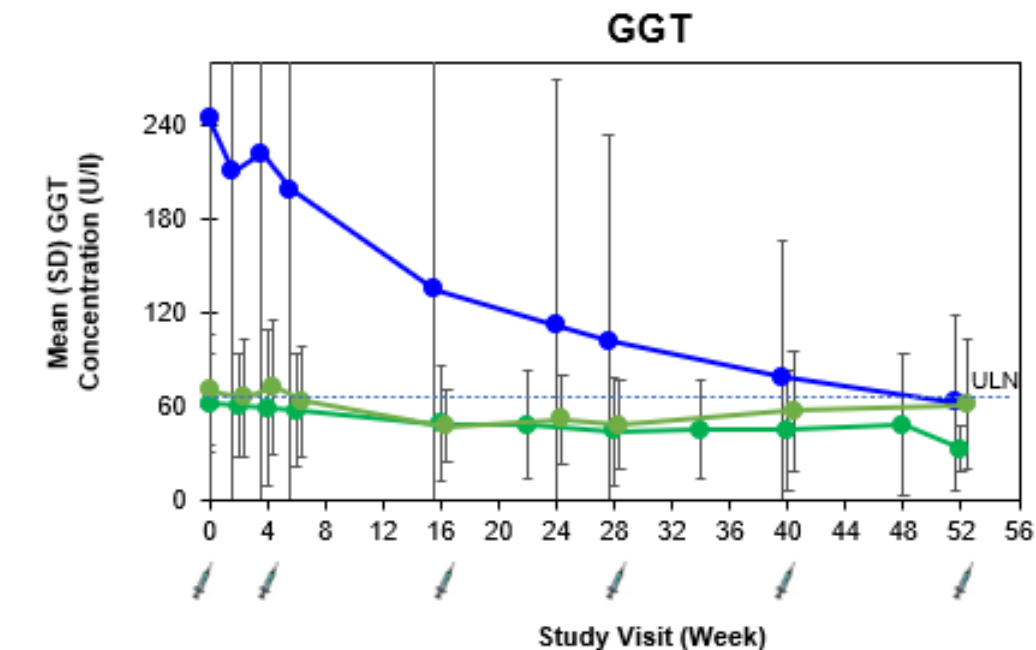
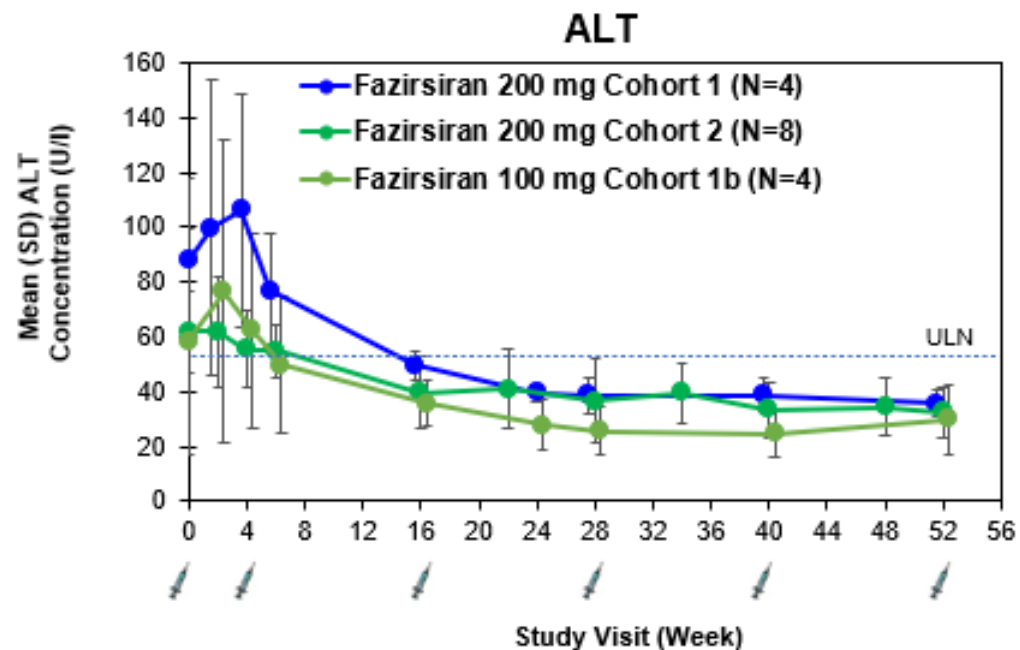
# Fazirsiran for Pi\*ZZ-associated liver disease



Two patients in Cohort 2 had insufficient liver biopsy samples for LC-MS/MS analysis.

BL denotes baseline, postBL postbaseline at Week 24 or 48  
Z-AAT = alpha-1 antitrypsin Z-mutant protein

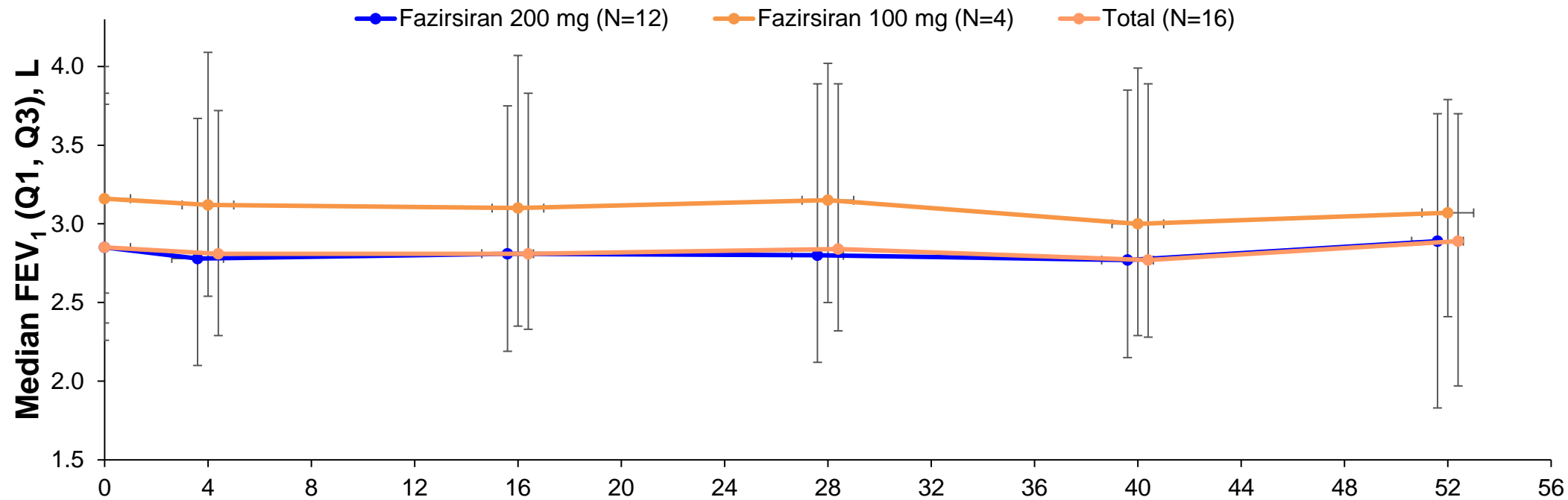
# Fazirsiran for Pi\*ZZ-associated liver disease



- Mean reduction in liver stiffness (VCTE)
  - Cohort 1: -18% at Week 24
  - Cohort 2: -15% at Week 48
  - Cohort 1b: -2% at Week 24

- Mean reduction in serum Pro-C3
  - Cohort 1: -36% at Week 28; -39% at Week 52
  - Cohort 2: -21% at Week 28; -17% at Week 52
  - Cohort 1b: +5% at last observation at Week 28

# Fazirsiran for Pi\*ZZ-associated liver disease



- No worsening of lung function

Strnad et al., *NEJM* 2022

# Fazirsiran for Pi\*ZZ-associated liver disease



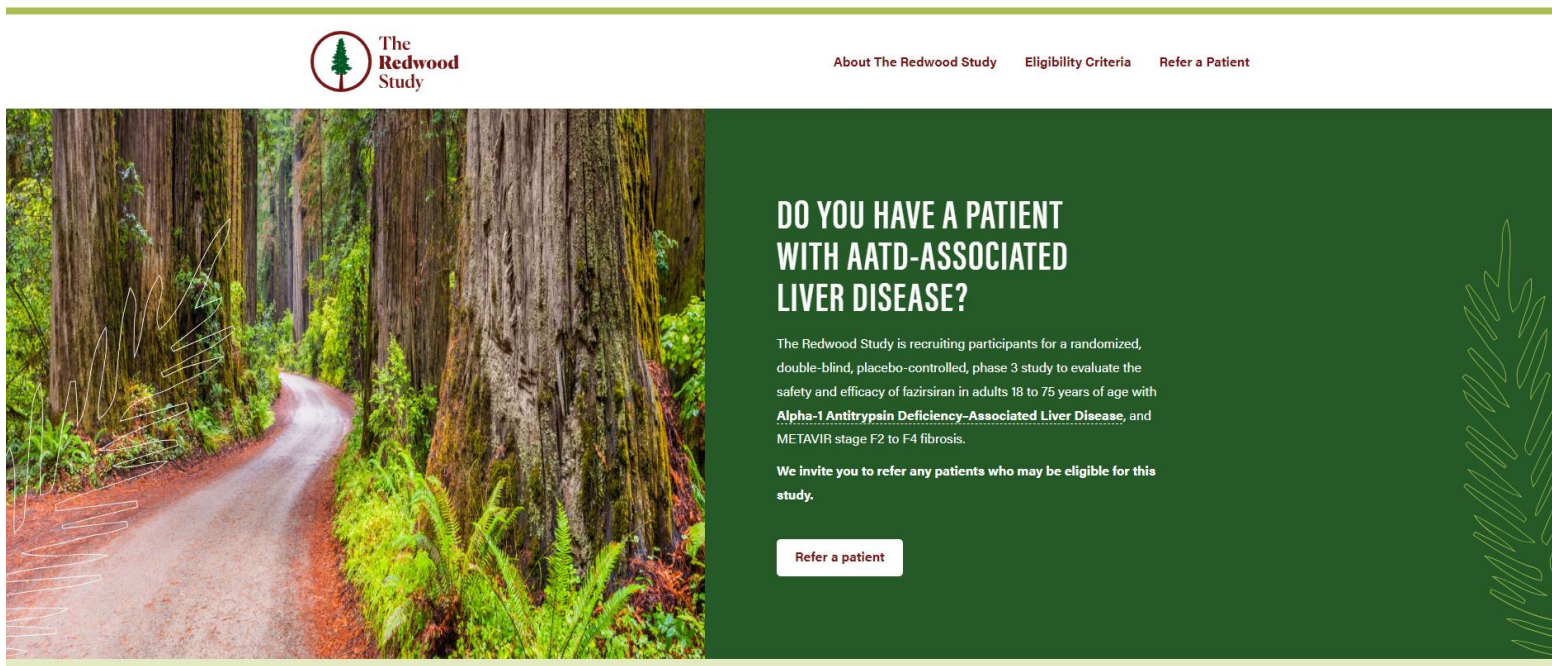
European  
AATD liver  
study group

Subject Incidence, n (%)	Fazirsiran 25 mg (N=9)	Fazirsiran 100 mg (N=8)	Fazirsiran 200 mg (N=9)	PBO (N=14)
Treatment-emergent AEs (TEAEs)	9 (100%)	8 (100%)	9 (100%)	13 (92.9%)
TEAEs in 4 or more subjects				
COVID19	0 (0%)	2 (25%)	6 (67%)	2 (14%)
Headache	4 (44%)	1 (13%)	2 (22%)	3 (21%)
Procedural pain	1 (11%)	0 (0%)	4 (44%)	3 (21%)
Arthralgia	2 (22%)	2 (25%)	0 (0%)	3 (21%)
Diarrhoea	1 (11%)	1 (13%)	0 (0%)	2 (14%)
Nausea	1 (11%)	0 (0%)	1 (11%)	3 (21%)
Back pain	1 (11%)	1 (13%)	2 (22%)	0 (0%)
Fatigue	1 (11%)	1 (13%)	0 (0%)	2 (14%)
Treatment-related TEAEs	2 (22%)	4 (50%)	3 (33%)	8 (57%)
Serious TEAEs	0 (0%)	0 (0%)	2 (22%)	3 (21%)
TEAEs leading to drug discontinuation, dose interruptions, or study withdrawal	0 (0%)	0 (0%)	0 (0%)	0 (0%)
TEAEs causing deaths	0 (0%)	0 (0%)	0 (0%)	0 (0%)

- No TEAE-related study drug discontinuation, dose interruptions, or premature study withdrawals
- 2 subjects with 2 TESAEs reported in the 200 mg cohort
  - Both were infective exacerbations of bronchiectasis (both with history of multiple pulmonary infections)
- 3 subjects with 6 TESAEs in PBO
  - One subject reported Influenza, Staph wound infection, and Acute pancreatitis
  - One subject reported PFT decreased and Hypertensive crisis
  - One subject reported Presyncope

- Australia
- Austria
- Belgium
- Brazil
- Canada
- France
- Germany
- Italy
- Poland
- Portugal
- Spain
- Switzerland
- UK
- US

For the full list of participating sites please visit the Redwood website:  
<https://redwoodclinicaltrial.com/hcp-participating-research-sites#hcp-full-list>



The Redwood Study

About The Redwood Study   Eligibility Criteria   Refer a Patient

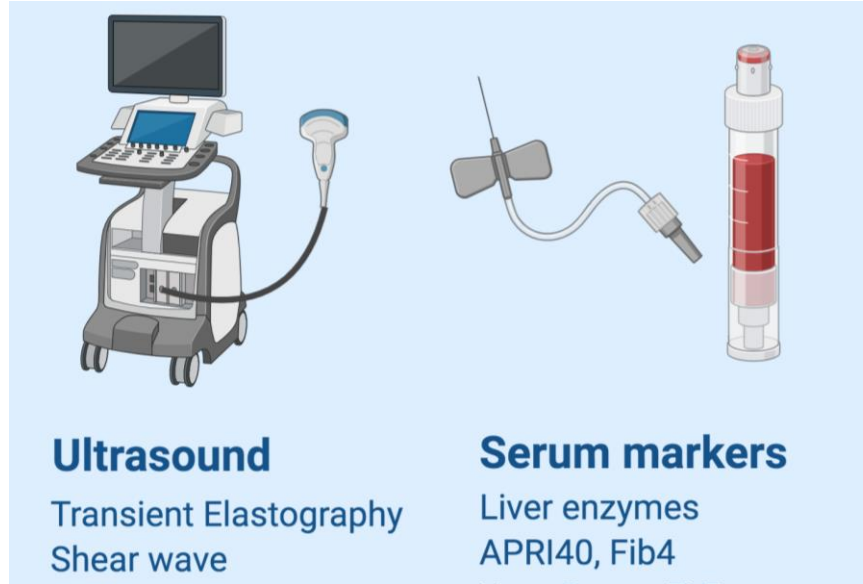
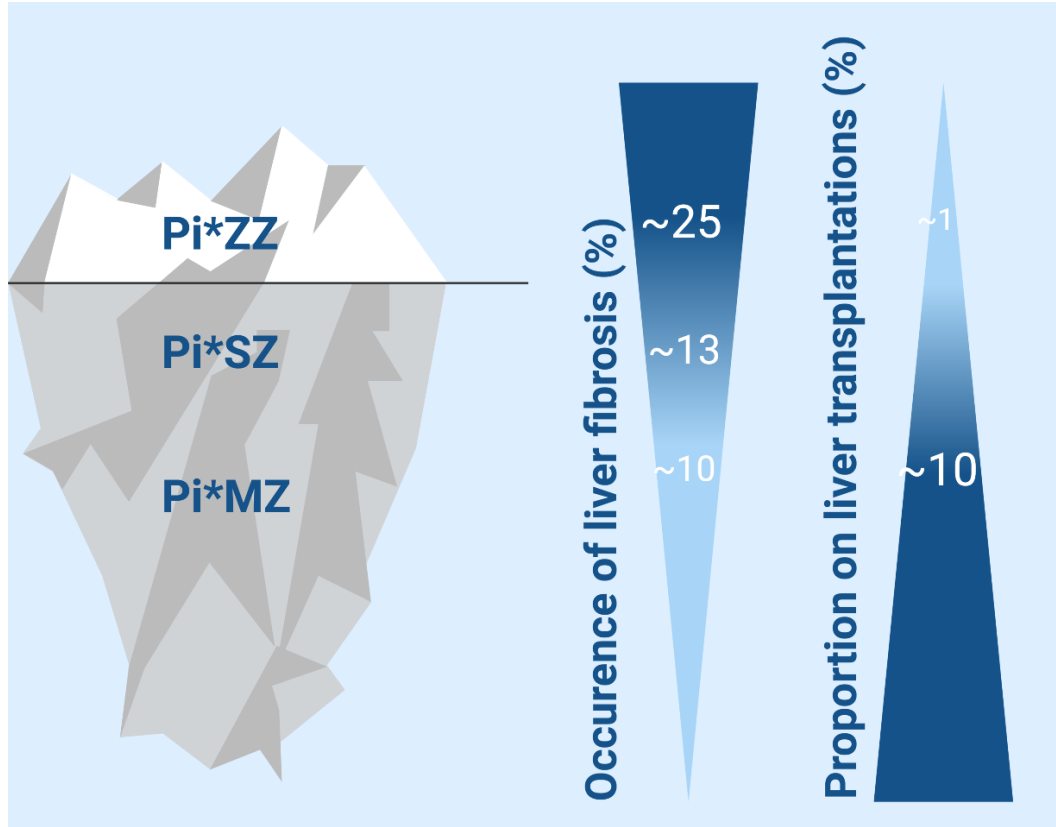
**DO YOU HAVE A PATIENT WITH AATD-ASSOCIATED LIVER DISEASE?**

The Redwood Study is recruiting participants for a randomized, double-blind, placebo-controlled, phase 3 study to evaluate the safety and efficacy of fazirsiran in adults 18 to 75 years of age with **Alpha-1 Antitrypsin Deficiency-Associated Liver Disease**, and METAVIR stage F2 to F4 fibrosis.

We invite you to refer any patients who may be eligible for this study.

[Refer a patient](#)

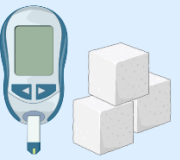



# Summary



**Ultrasound**  
Transient Elastography  
Shear wave

**Serum markers**  
Liver enzymes  
APRI40, Fib4

[alpha1@ukaachen.de](mailto:alpha1@ukaachen.de)

 <p>Diabetes mellitus</p>	 <p>Obesity, Metabolic syndrome</p>	 <p>Male sex</p>	 <p>Age ≥50 years</p>
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