ALPHA ONE INTERNATIONAL REGISTRY

A. I. R.

L U M C

Screening for Alpha-1-antitrypsin deficiency Why?

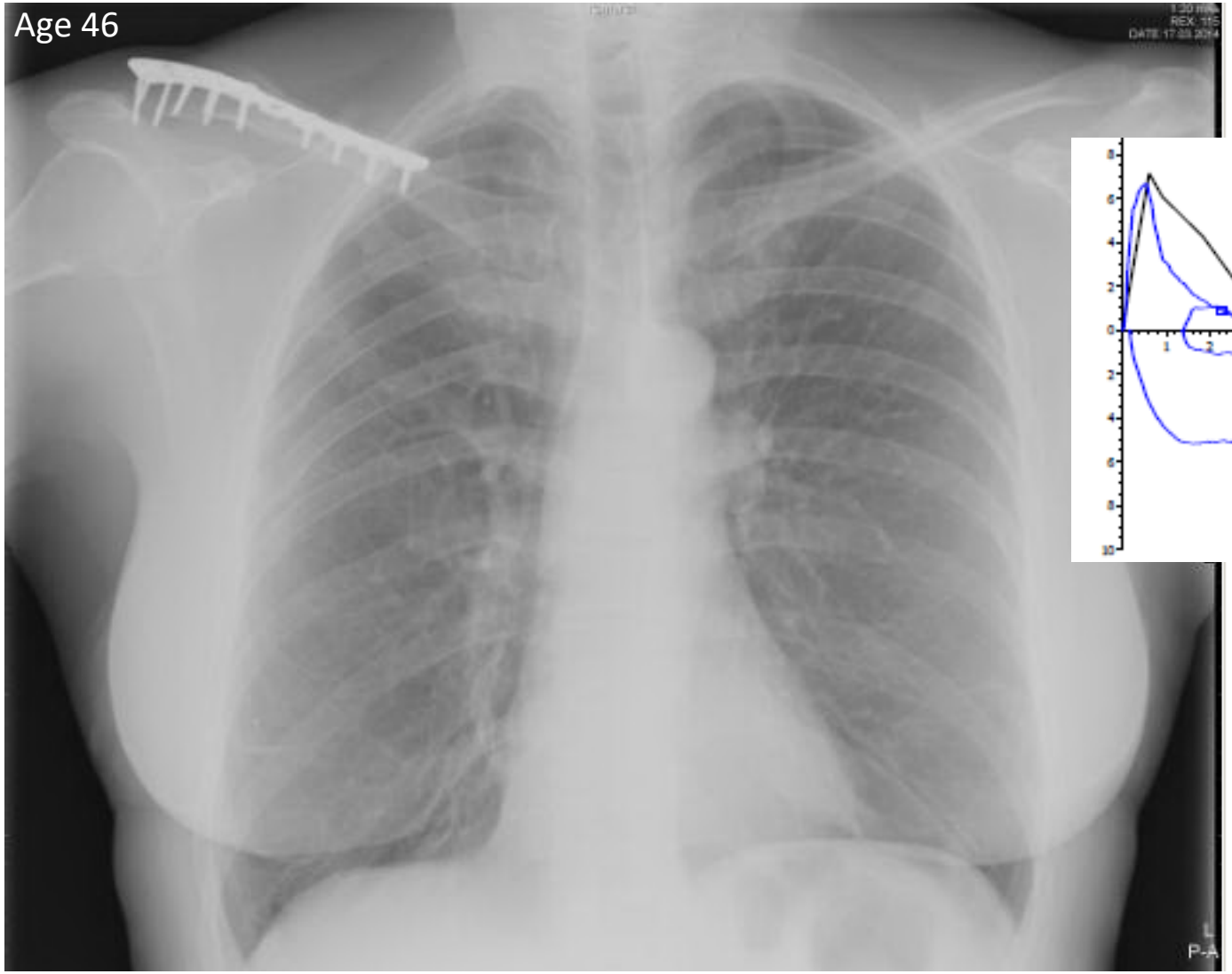
In memory of Prof. Maurizio Luisetti

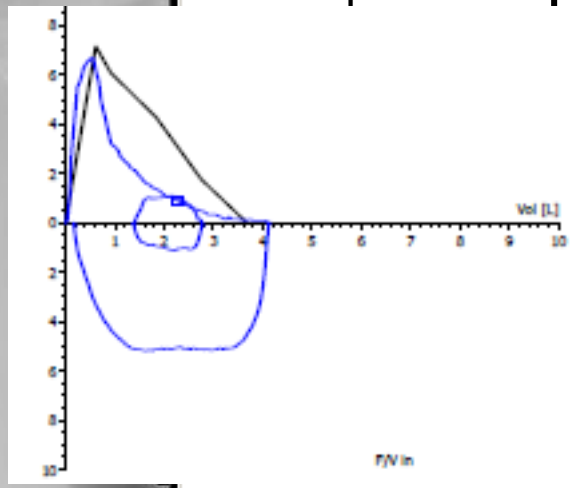
Jan Stolk
Department of Pulmonology

Conflict of Interest

None for this topic

A typical case that requires screening?



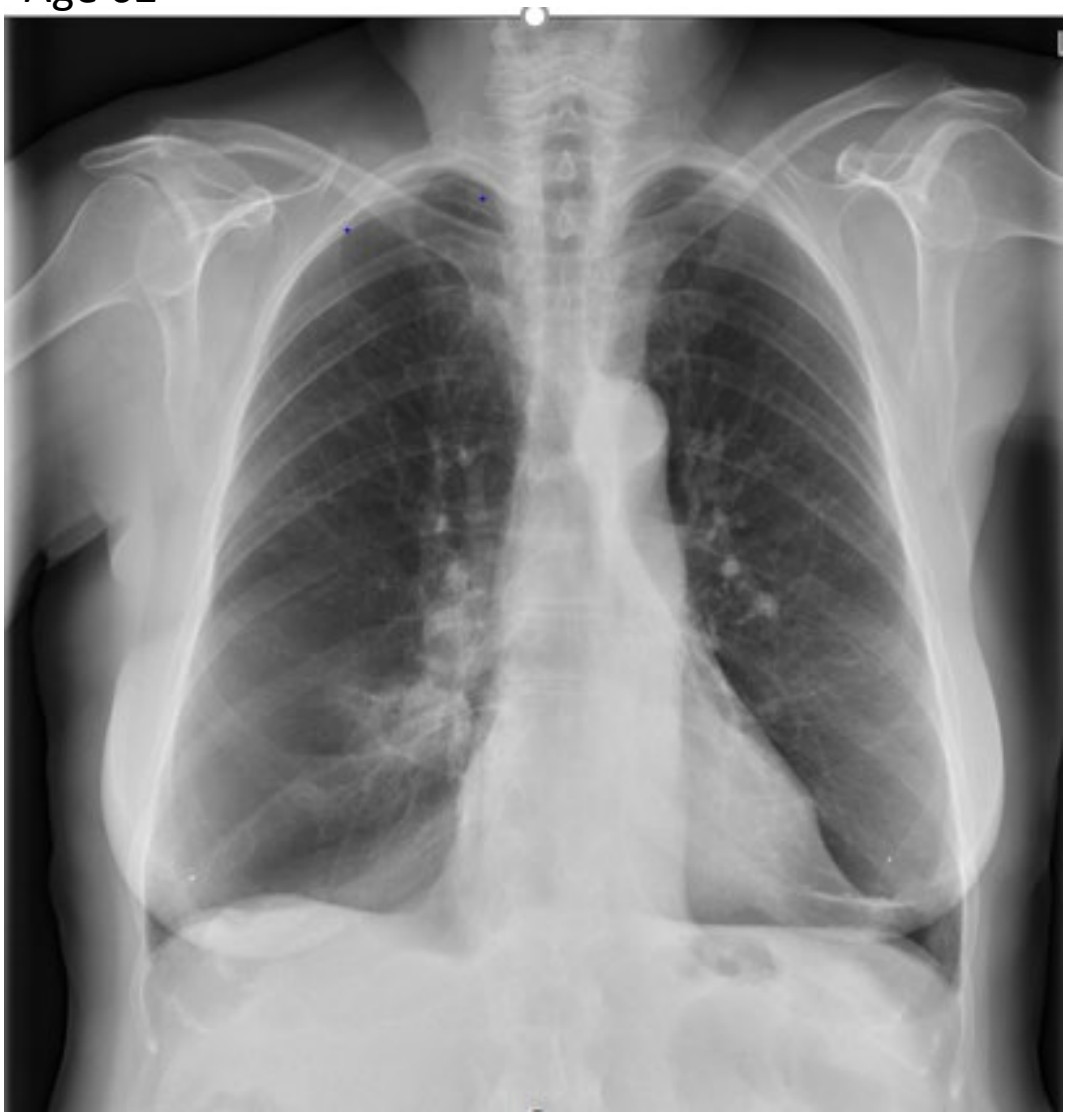


FEV_1: 76% pred

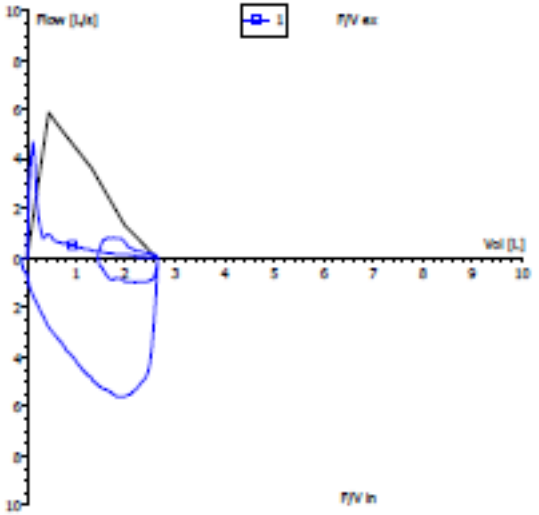
DLCO: 53% pred

This case certainly does require screening!

Age 62



FEV_1: 36% pred



DLCO: 32% pred

My introduction to AATD

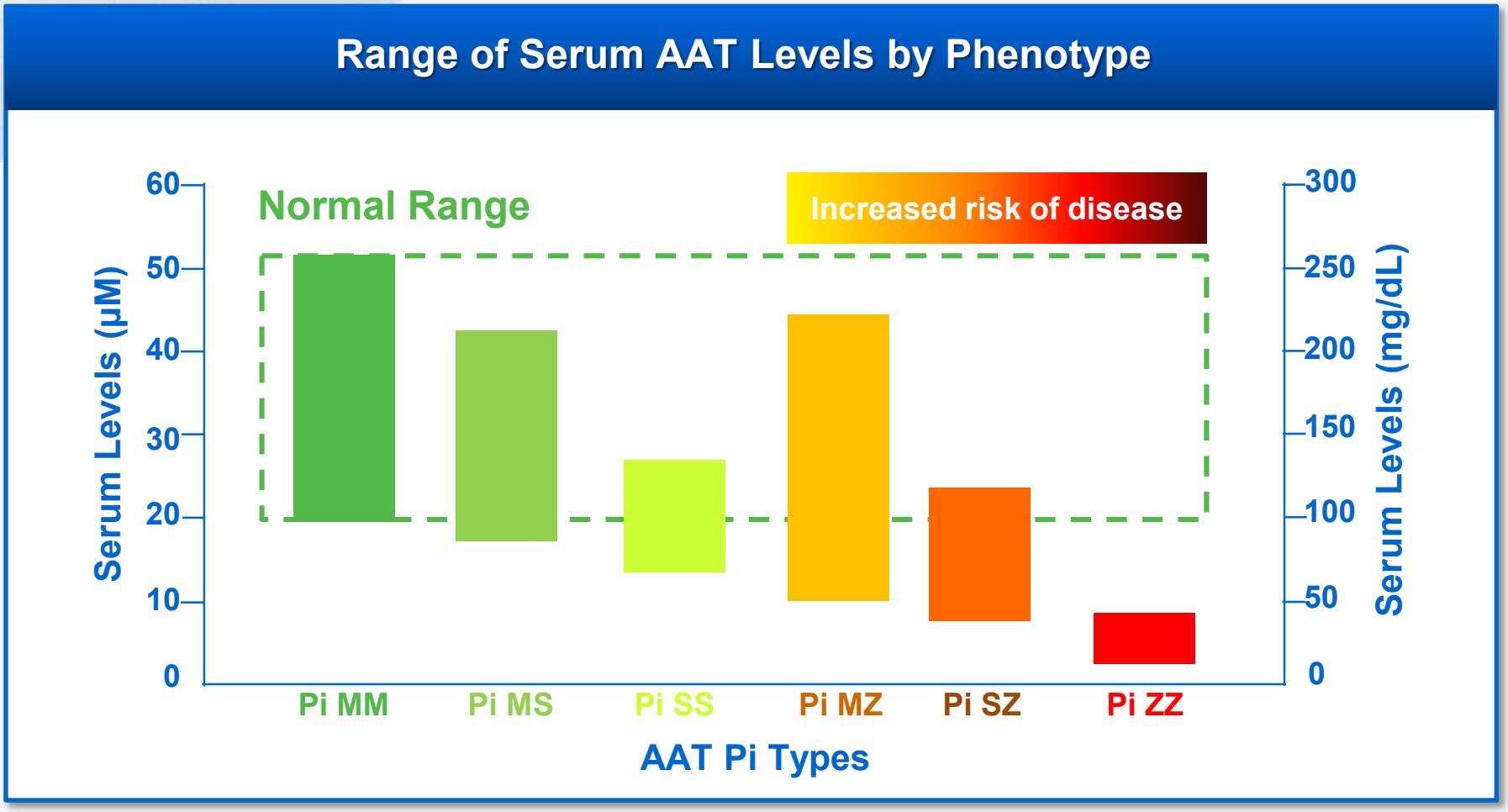
- 1996 in Portugal: UK, NL, SE, DK, D
- WHO document was starting point
- Scientific driven or patient driven?
- Only European?
- Role of Pharmaceutical Industry?

Alpha$_1$-antitrypsin Deficiency (AATD)

- ***Autosomal, codominant genetic disorder characterised by reduced serum level of AAT***
- ***Highest prevalence in Northern Europeans and in Populations with northern european background***

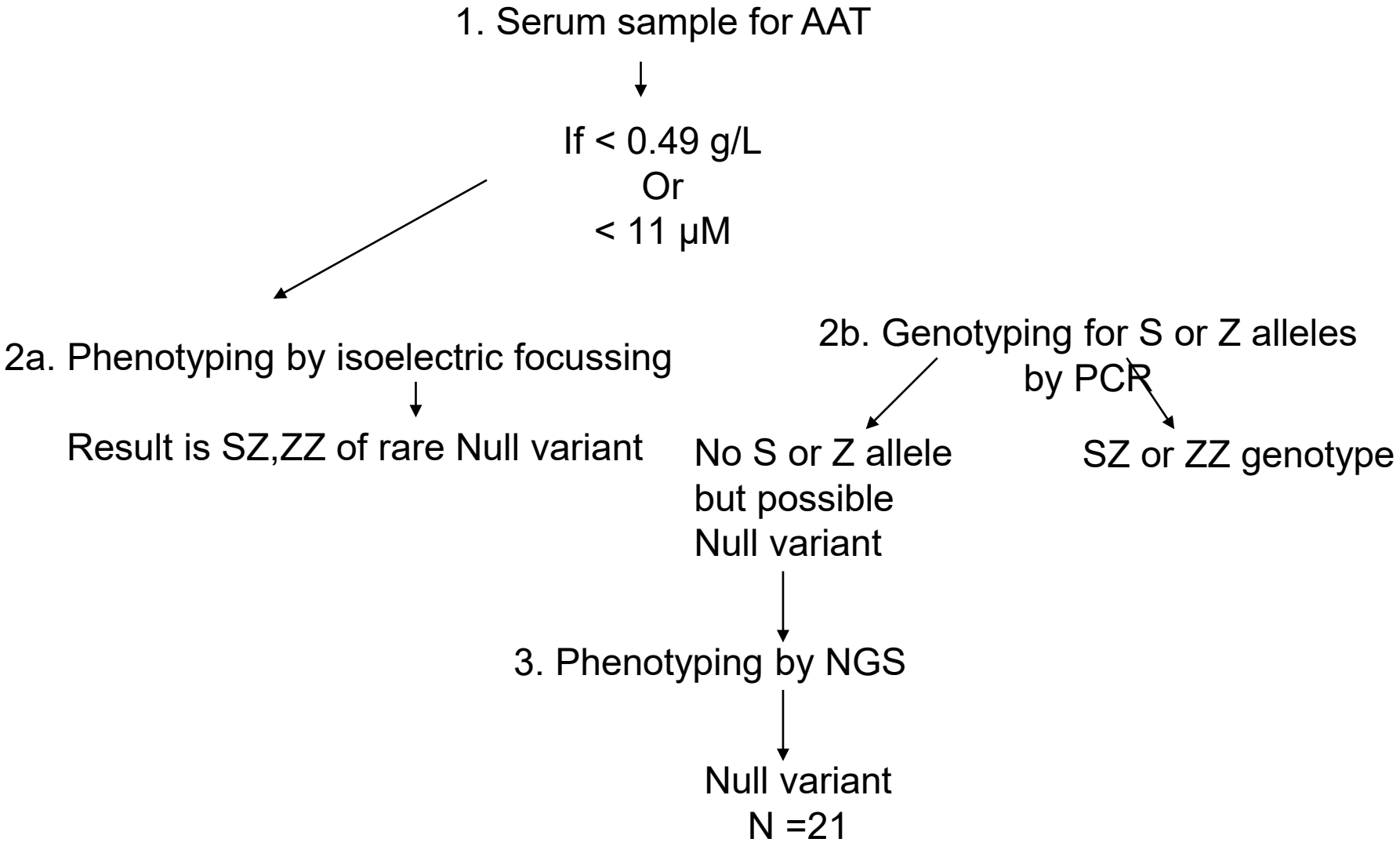
  (prevalence in Western Europe 1:1,500 – 1:5,000)
- ***Increased risk of developing COPD (mostly pulmonary emphysema) early in life and chronic liver disease in later phases***

Serum Level Alone is NOT a Diagnostic Tool

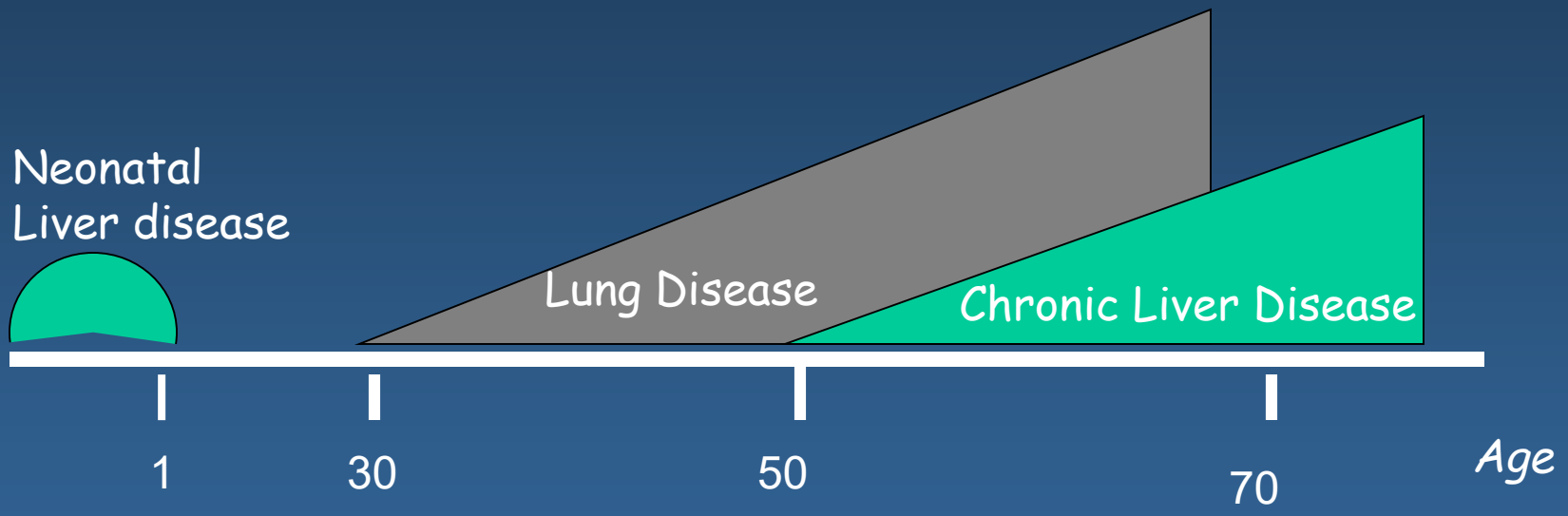


Data on file, Grifols.

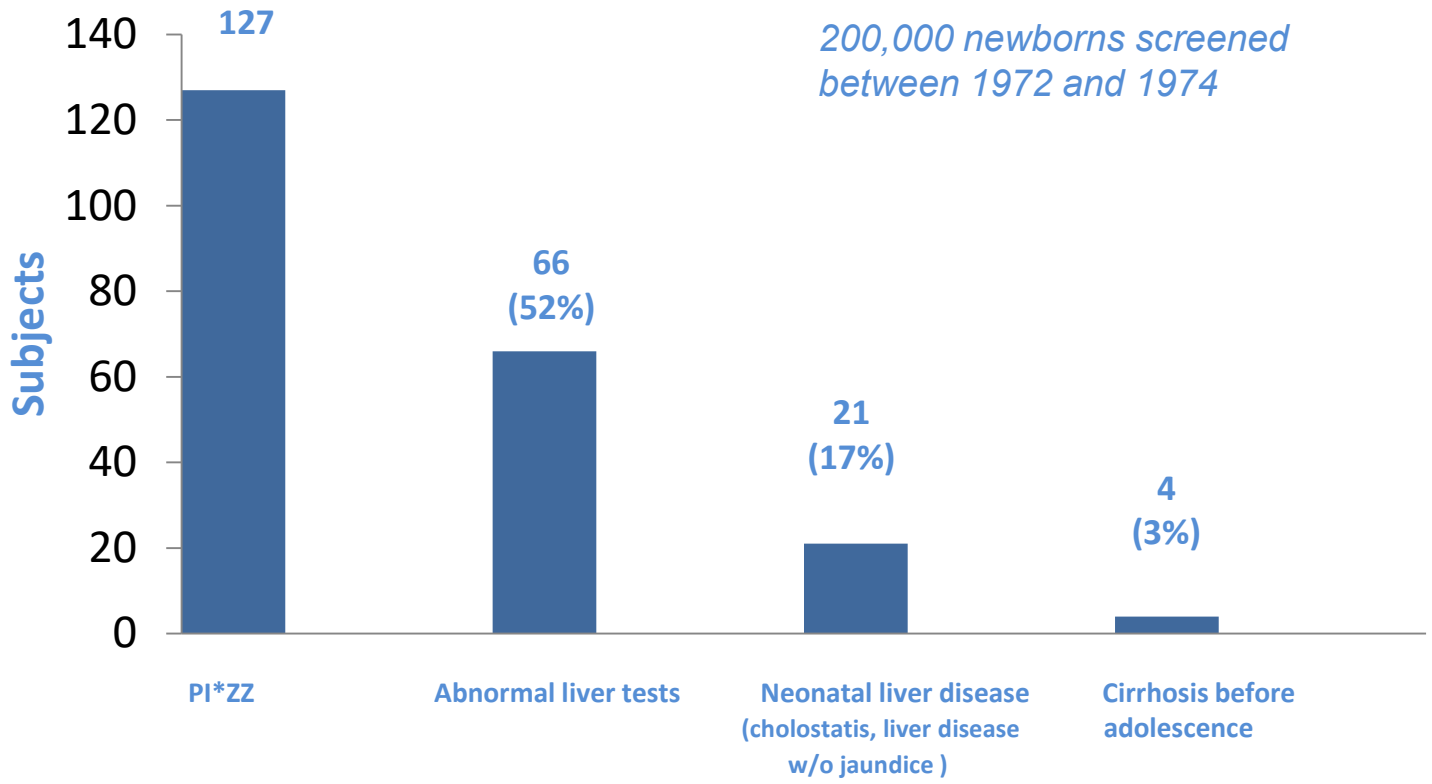
Alpha-1-antitrypsin testing algorithum



LIFE CYCLE OF AATD ASSOCIATED CONDITIONS



Liver disease in the Swedish Newborn Screening



Sveger T N Engl J Med 1976;294:1316

Hepatology 1995;22:514

Why screening for AATD?

The Swedish cohort patients at age 38

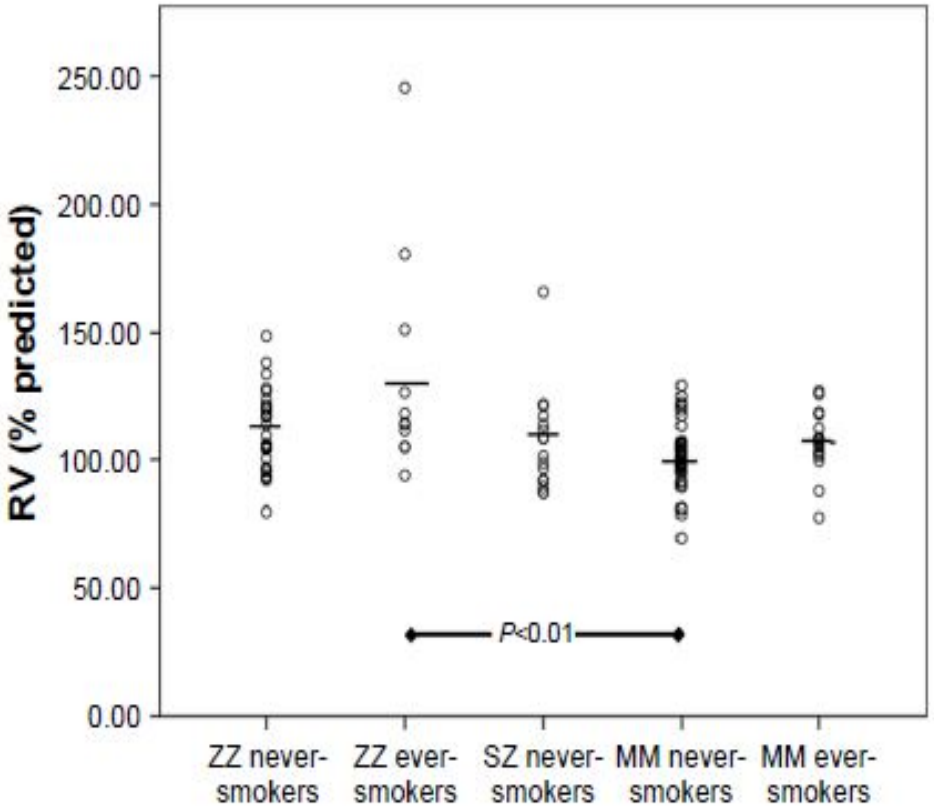


Figure 1 The RV % predicted in Pi-smoking categories.

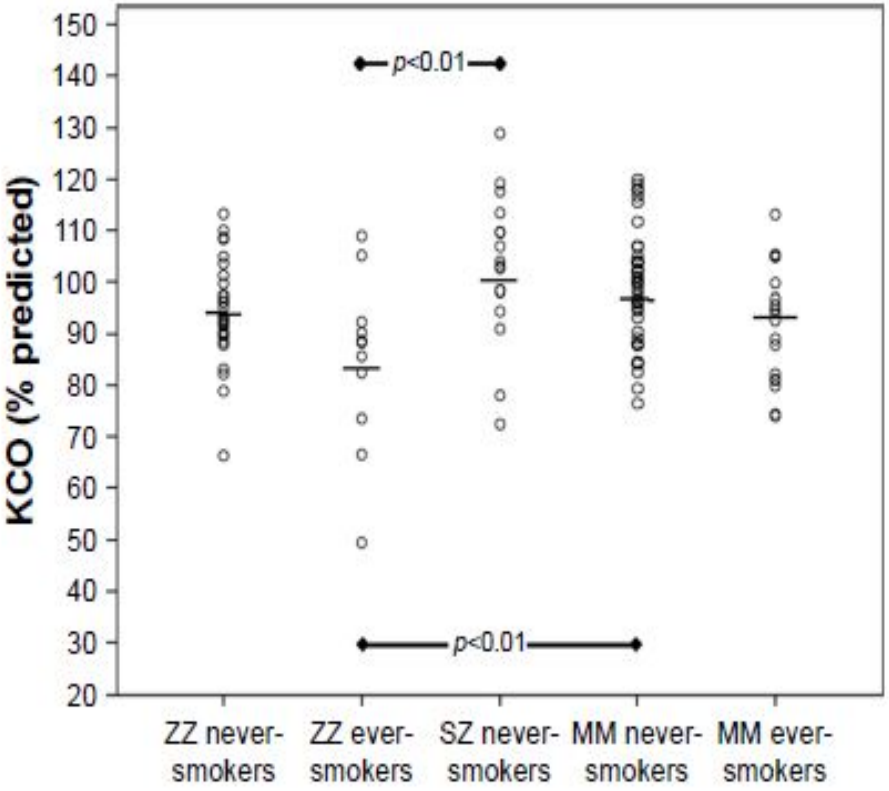


Figure 2 The *Kco* % predicted in the Pi-smoking categories.

Counseling to not start smoking helps!

Why screening for AATD?

in extended Swedish registry

Liver disease	At identification ($N = 55$)	At inclusion ($N = 53$)	At study end ($N = 155$)
Liver cirrhosis	45	49[a]	103
Fatty liver	4	2	17
Unspecific hepatitis	2	Recovered	6
Hepatocellular carcinoma	2	2	29[b]
Neonatal cholestasis	2	Recovered	–

[a]Includes 2 patients with fatty liver who developed liver cirrhosis before inclusion in the register

[b]Includes 13 patients with liver cirrhosis who developed hepatocellular carcinoma during the follow-up

Liver fibroscan for cirrhosis or liver MRI for HCC is recommended

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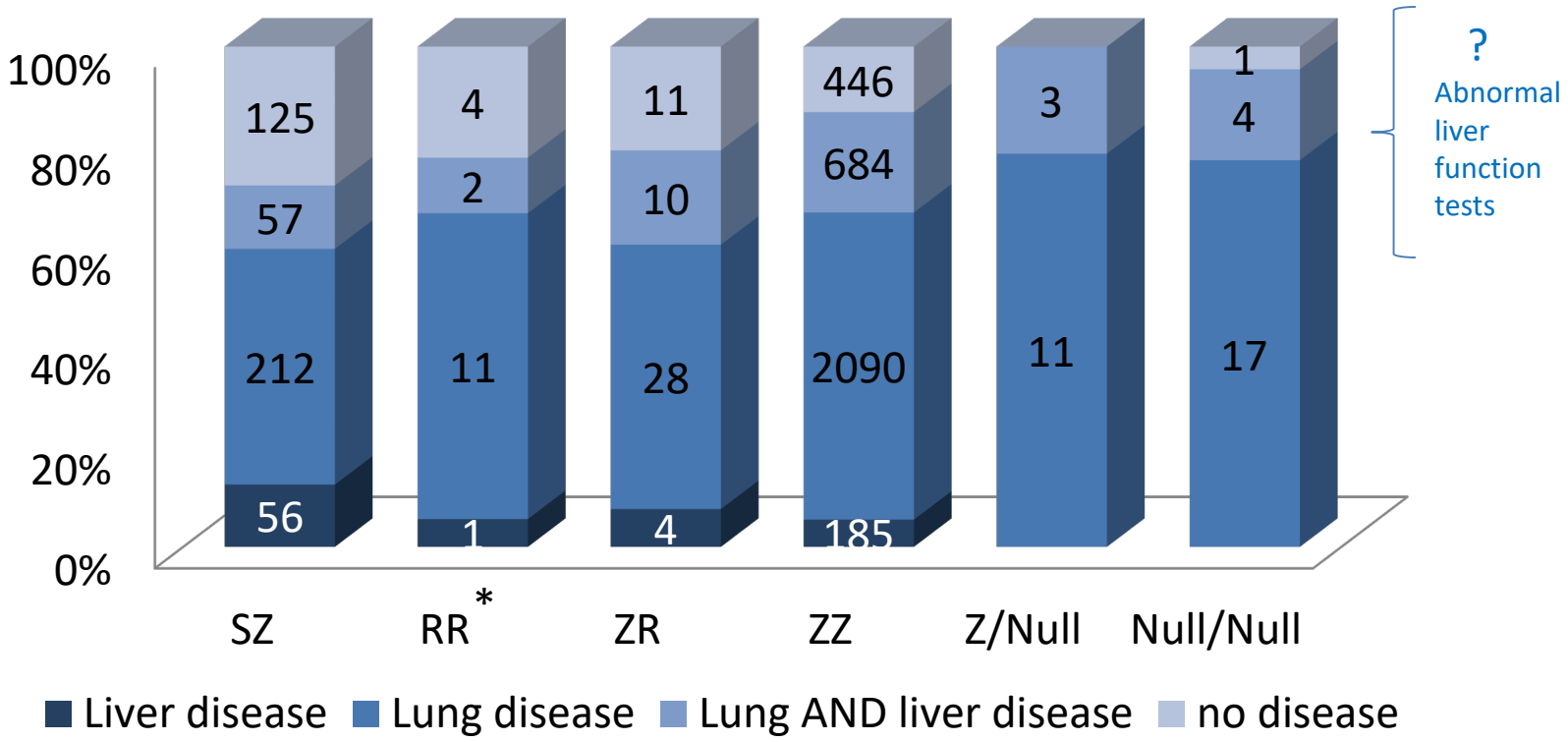
Frequency of lung and/or liver disease at diagnosis according to different genotypes



** R denotes non-Z and non-S deficiency variants*

What is the protective level of AAT to aim for?

- Luisetti & Sapaldia study for AAT threshold: *Plos One* 2012; 7(8): e42728
- population-based study showed that neither PiMS, nor PiMZ carriers have a substantial impact on change in lung function. This **suggests** that the 11 uM (0,5 g/L) threshold is a clinically relevant one.

Alpha-1-antitrypsin deficiency: optimal therapeutic regimen based on population pharmacokinetics

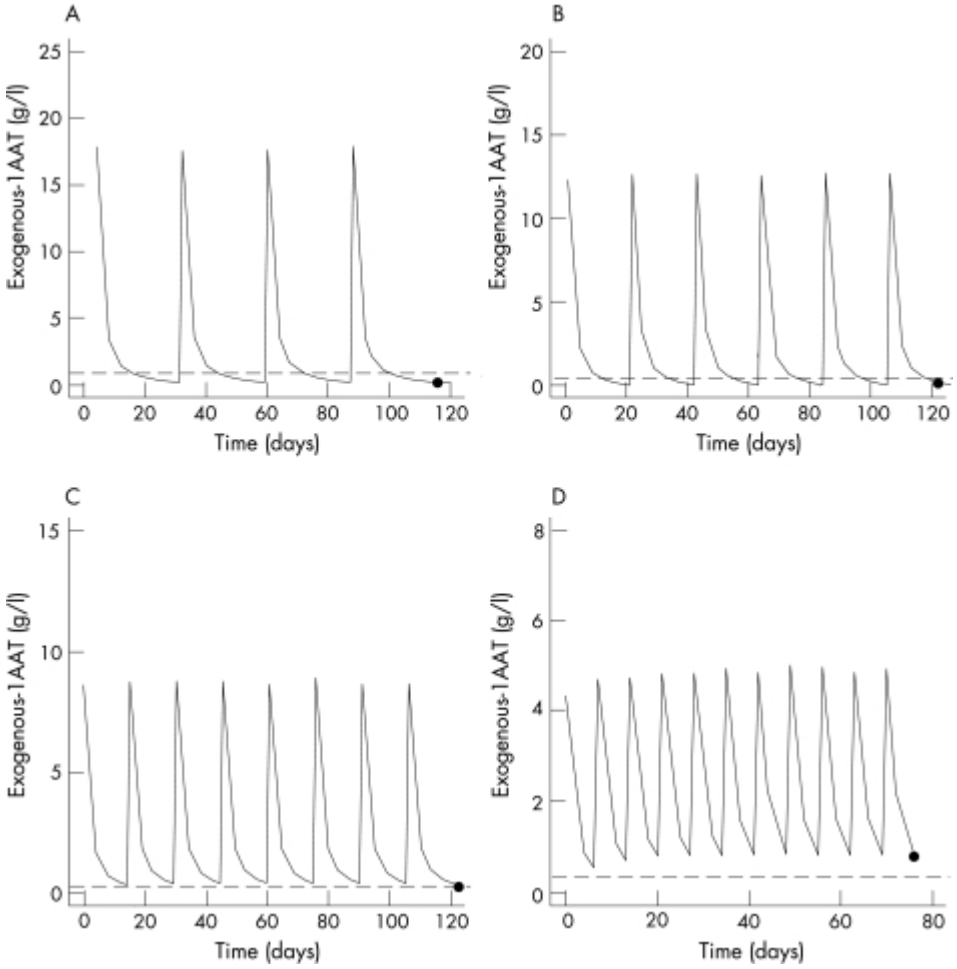
D Soy, C de la Roza, B Lara, C Esquinas, A Torres, and M Miravitlles

Thorax. 2006; 61(12): 1059–1064.

To address the question:

If so, at what dose and at what rhythm?

If so, at what dose and at what rhythm?



A: 180mg/kg every 28 days result in AAT trough concentration of 0.19 g/l far from the 0,5 g/L AAT target level.

B: 180mg/kg every 21 days: Trough AAT level at 0,23 g/L.

C: 120mg/kg every 14 days: Trough level AAT at 0,58 g/L

D: 60 mg/kg every 7 days: Trough AAT level at 0,73 g/L

We don't know the relation between dose and elastase inhibition capacity in vivo

Change of FEV_1 from baseline

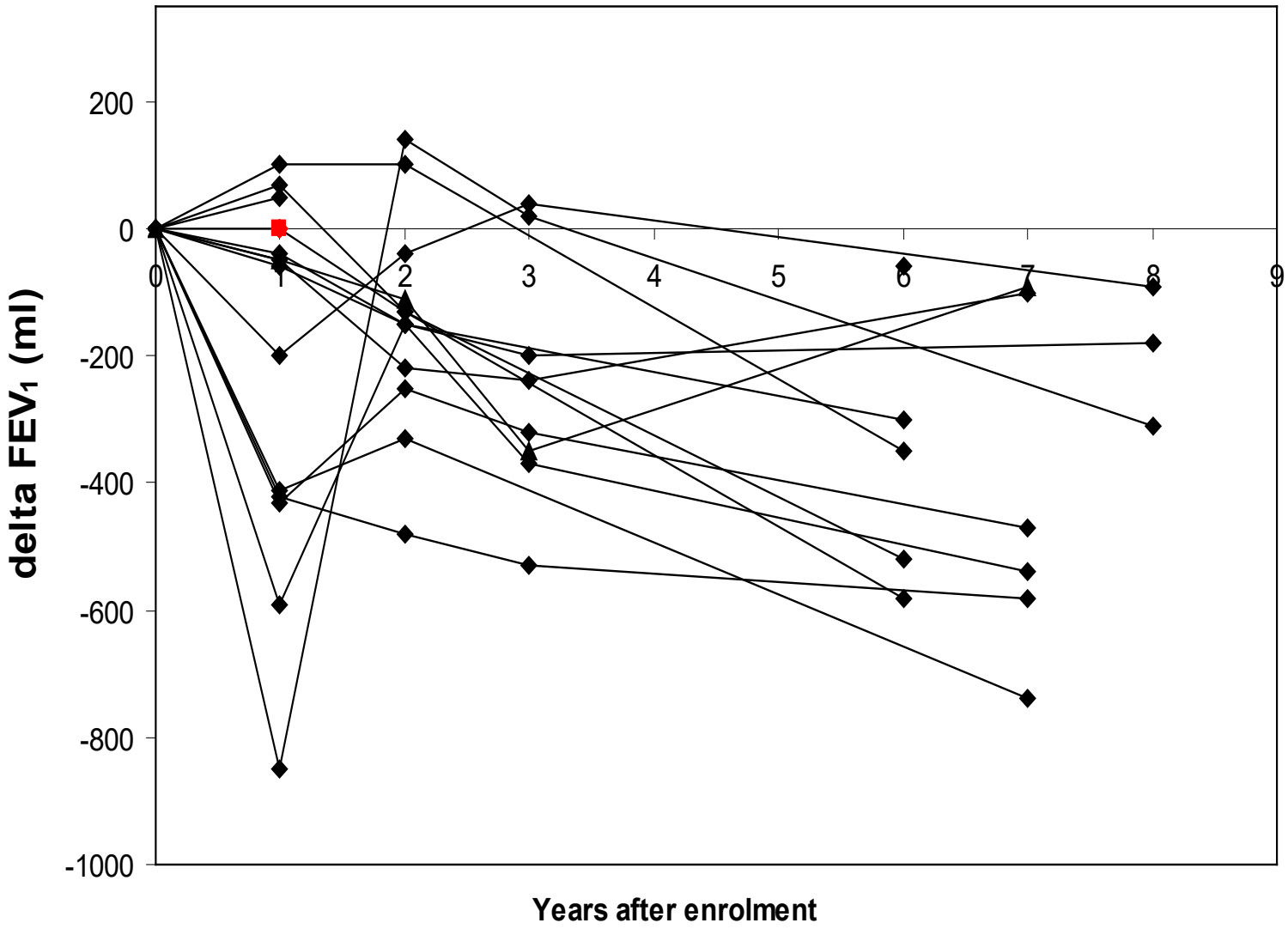


TABLE 3

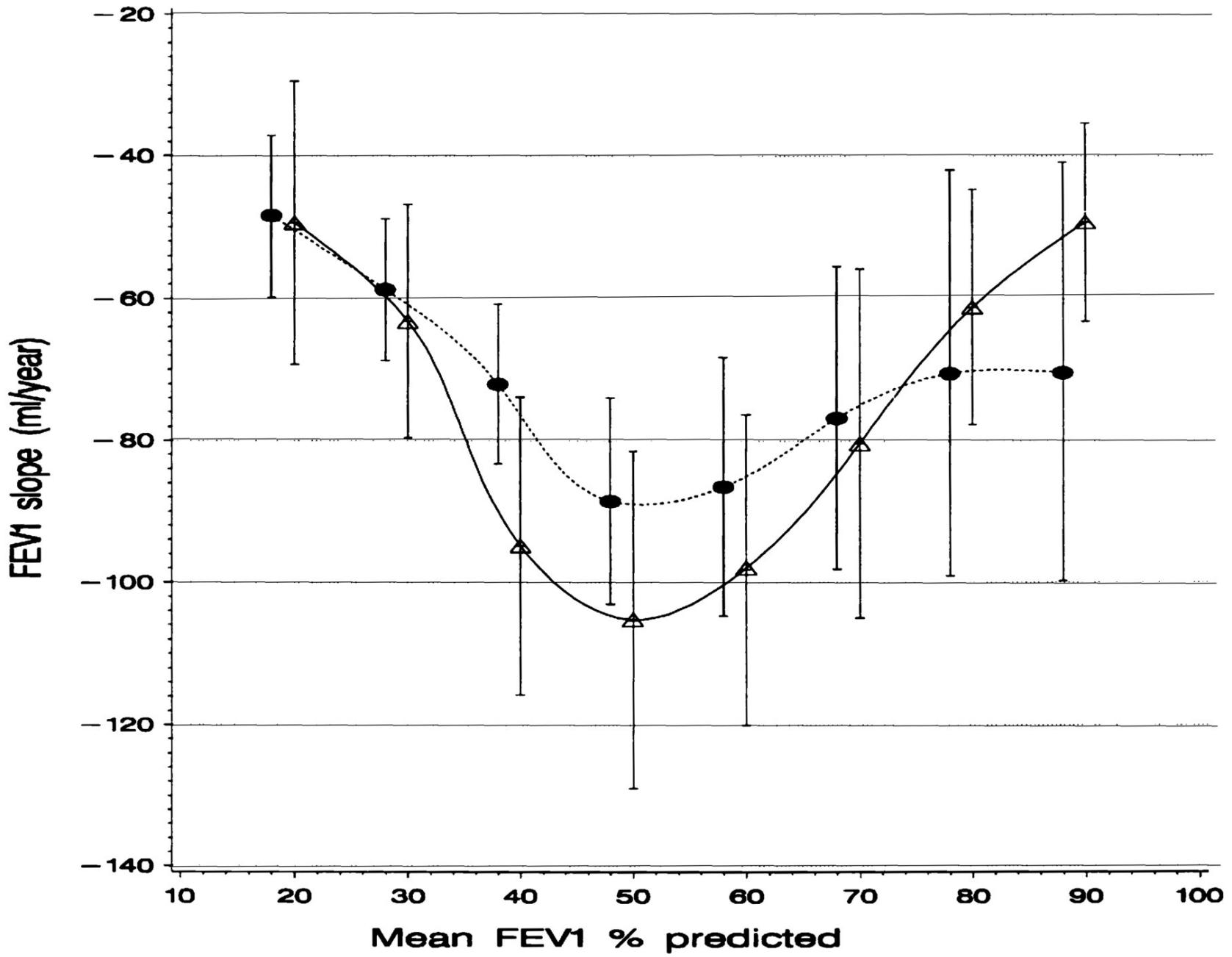
MULTIVARIATE ANALYSIS OF FEV_1 DECLINE: MEAN FEV_1 DECLINE (ml/yr) BY FEV_1% PREDICTED AND AUGMENTATION THERAPY STATUS*

	Not Receiving Augmentation Therapy		Receiving Augmentation Therapy		Difference Receiv
Mean FEV_1% Predicted	Mean	SE	Mean	SE	Estimate
$FEV_1 < 35\%$	−46.5	6.2	−43.9	3.4	2.6
FEV_1 35–49%	−93.2	11.1	−66.4	5.0	26.8
FEV_1 50–79%	−81.2	8.9	−73.7	6.8	7.5
$FEV_1 \geq 80\%$	−39.2	5.6	−63.0	12.8	−23.8
Pooled categories†					
All subjects	−56.0	3.8	−51.8	2.7	4.2
35–79%	−83.5	7.6	−69.9	4.1	13.6

* Reported means are least-squares means that adjust for other factors included in the model. The multivariate model for change in FEV age, bronchodilator responsiveness, FEV_1% predicted (categorized as < 35%, 35–49%, 50–79%, ≥ 80%), augmentation-therapy status dicted and augmentation-therapy status. Reported means are the average estimated rates of FEV_1 decline with and without augmentation dicted, averaged across the levels (categories) of the other factors (smoking status, age, bronchodilator responsiveness), using weights ba in the overall cohort.

† A positive difference in slopes implies a slower rate of decline for subjects receiving augmentation therapy compared with those not slopes with and without augmentation therapy were estimated using cumulative time on augmentation therapy as a time-varying covaria section).

‡ Estimates for pooled categories are obtained from a model fit to the entire cohort or to the specific subgroup, with interaction terms be therapy excluded from the model.


A. Mean FEV1 decline
FEV1 slope (ml/year)
-20
-40
-60
-80
-100
-120
-140
10
20
30
40
50
60
70
80
90
100
Mean FEV1 % predicted

Take home message

- In AATD the AAT genotype is the clinical characteristic that determines outcome of lung disease
- The ATS-ERS guidelines from 2003 state that baseline FEV_1 should be between 35 and 65% pred. at start of AAT iv treatment.
- There is a poor correlation between ΔFEV_1 and Δ change CT scan lungdensity score.
- The impact of liver fibroscanning is currently being evaluated.