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Beyond disease progression – Item response theory modelling to gain structural insights into disease facets underlying clinical score assessments

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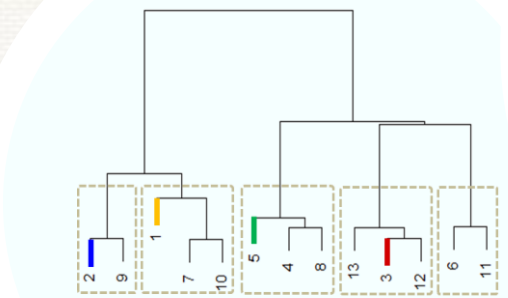
29th PAGE Meeting, September 7th, 2021



Kon K., Shutterstock ID: 769634155

*opinions expressed in this presentation do not necessarily represent the views of Boehringer Ingelheim

Complex, multi-faceted diseases

- Multiple factors
- Different manifestations

→ Multi-factorial assessment

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Complex, multi-faceted diseases

- Multiple factors
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https://vcresearch.berkeley.edu/sites/default/files/inline-images/puzzlebrain750px.jpg

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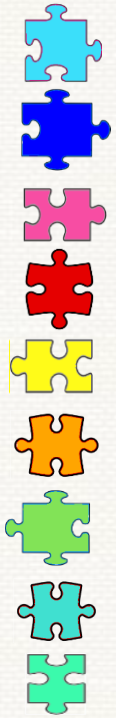
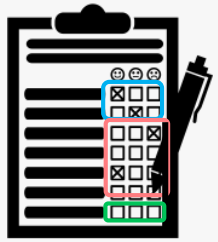
Assessment of complex diseases

Items
(symptoms etc.)



Questionnaire



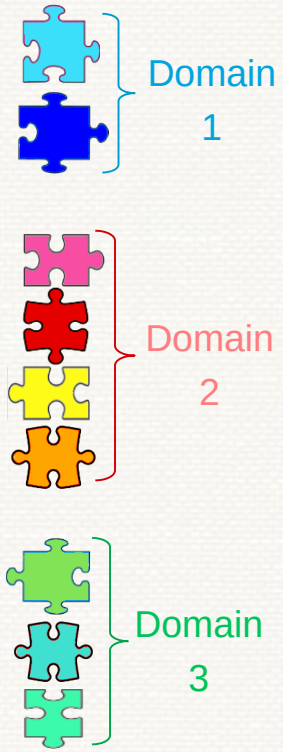
- Patient-reported outcomes
- Healthcare professionals

Clinical scores
(discrete data)

Decision making

Assessment of complex diseases

Items
(symptoms etc.)



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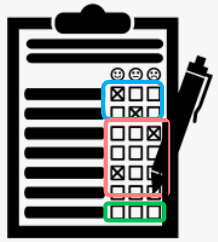

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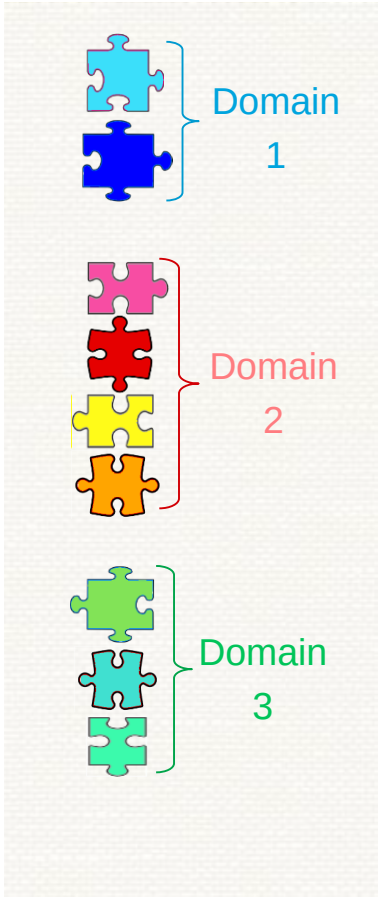

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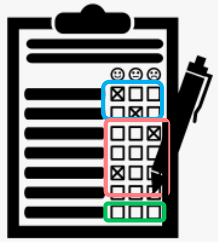

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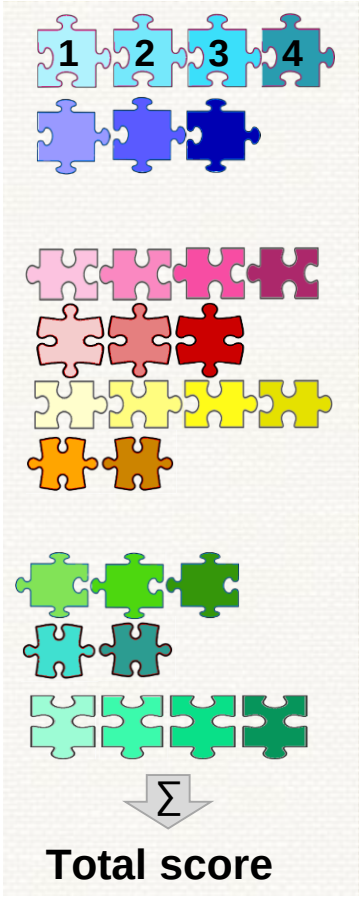

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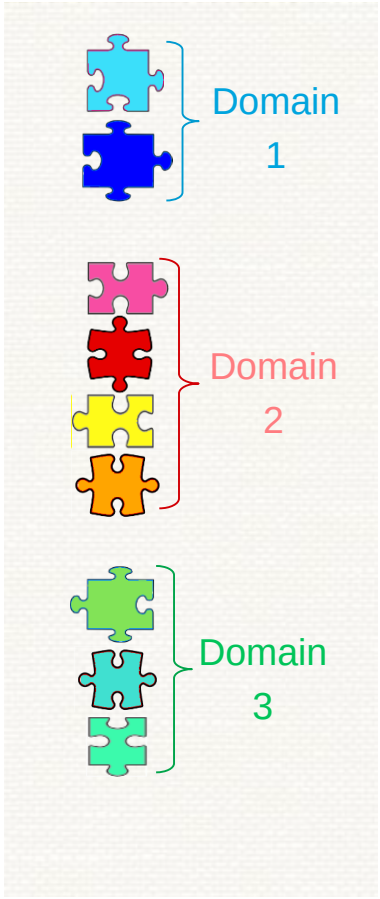

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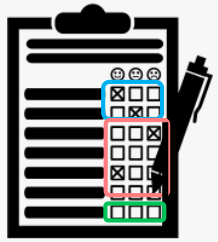

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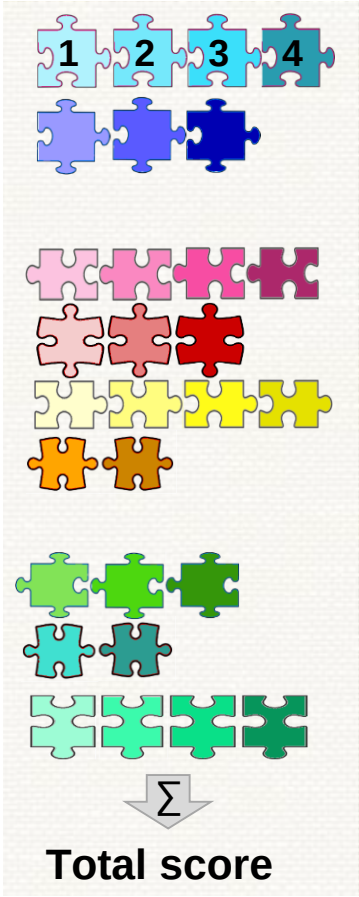

Decision making

Clinical studies

Treatment

Development

Assessment of complex diseases

Items
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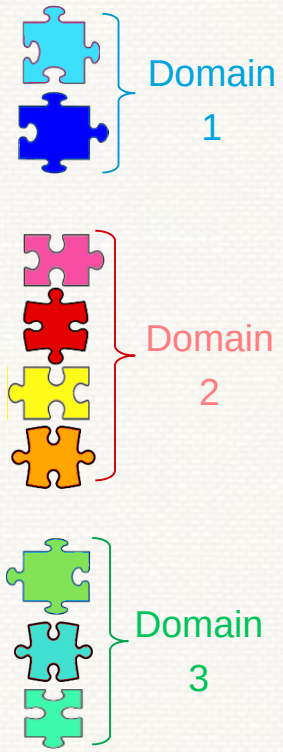

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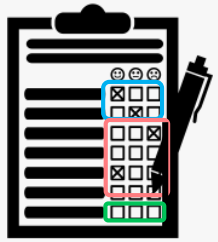

- Patient-reported outcomes
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Clinical scores
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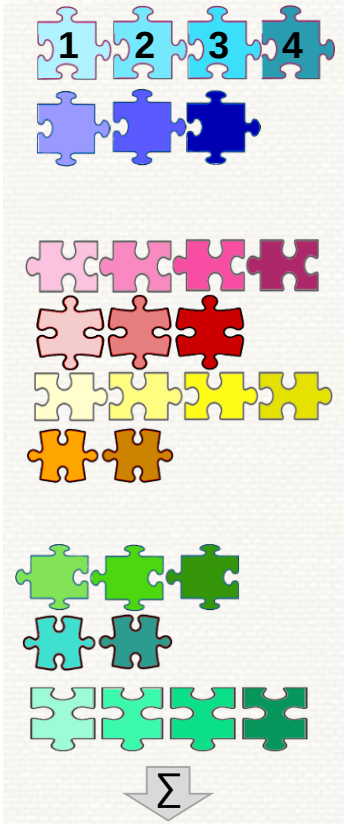


Modelling

- Data simplification
  - Total scores
  - Information loss
- **Item response theory (IRT) models**
  - Consider each score component

Decision making

Clinical studies

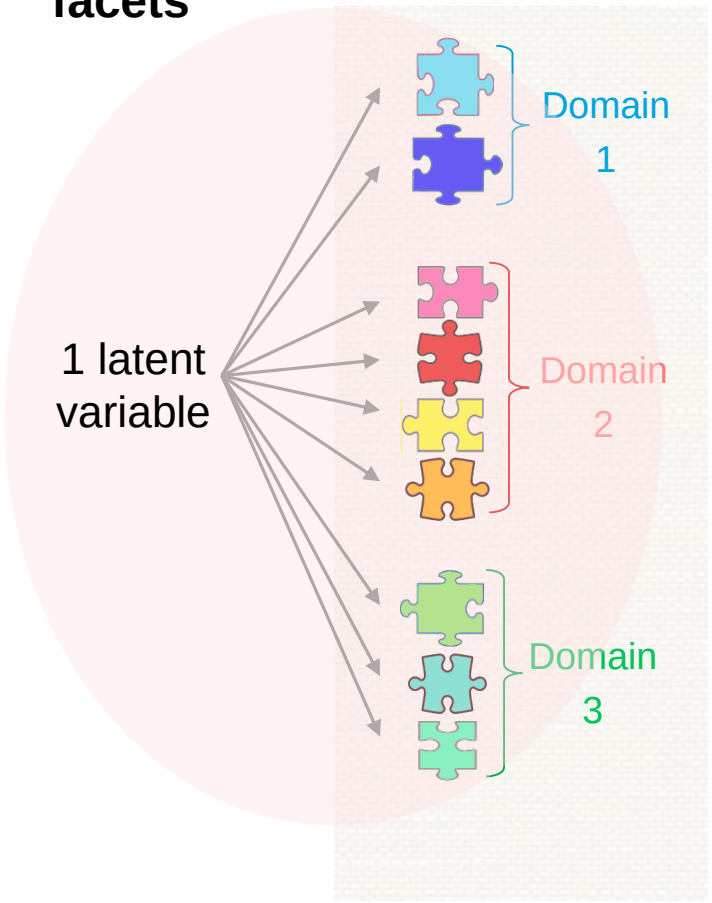
Treatment

Development

Previous IRT models

Latent disease facets

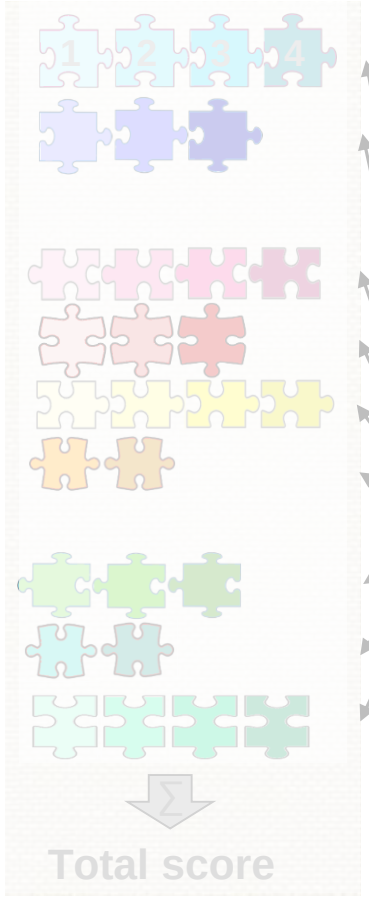
Items (symptoms etc.)



Questionnaire

- Patient-reported outcomes
- Healthcare professionals

Clinical scores (discrete data)



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Decision making

- Clinical studies
- Treatment
- Development

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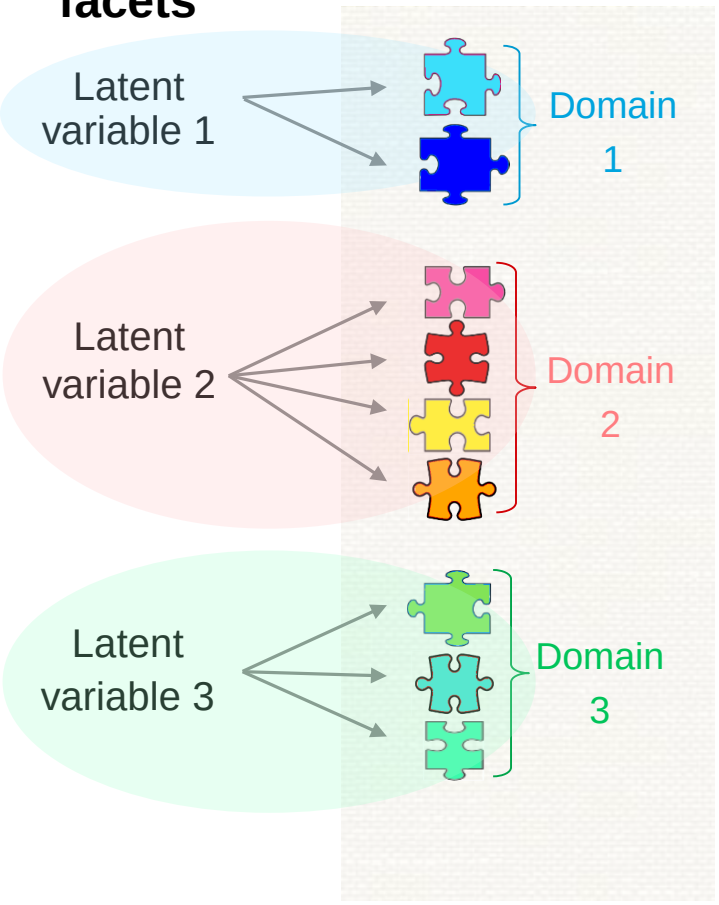

Questionnaire

- Patient-reported outcomes
- Healthcare professionals

Clinical scores (discrete data)

Modelling

- Data simplification
  - Total scores
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- **Item response theory (IRT) models**
  - Consider each score component

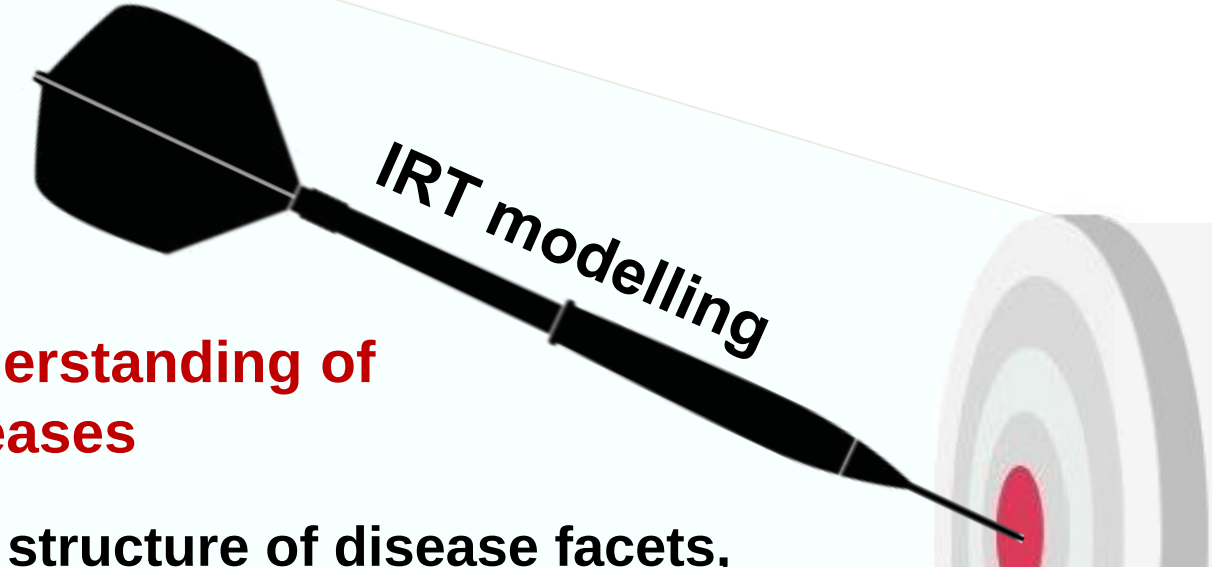
Decision making

Clinical studies

Treatment

Development

Objectives



Enhance understanding of complex diseases

- **Explore structure of disease facets, *guided by complex clinical score data***
- Identify association of covariates with disease facets

➡ Nonalcoholic fatty liver disease

Previously:

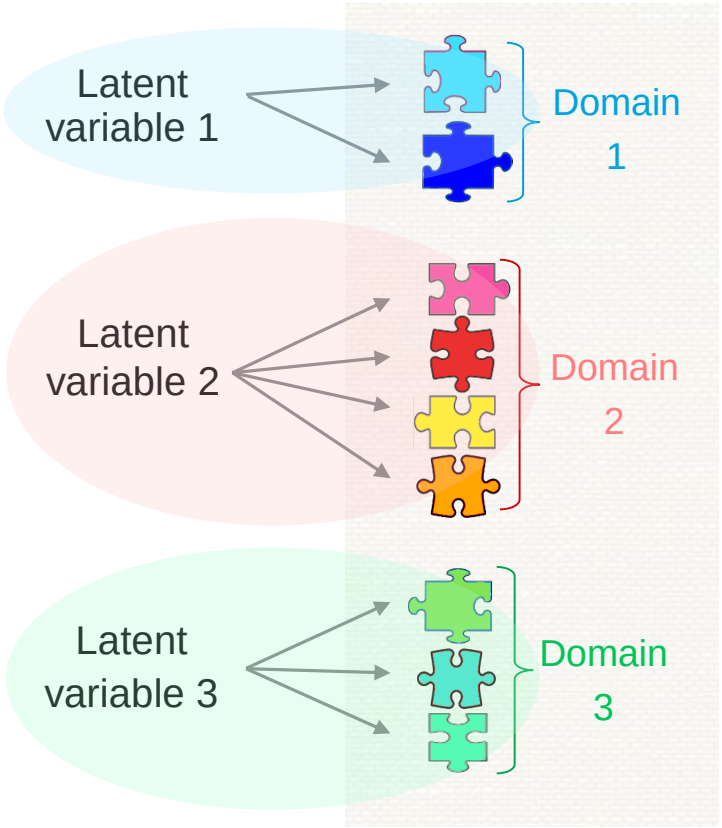
Focus on

- Disease progression

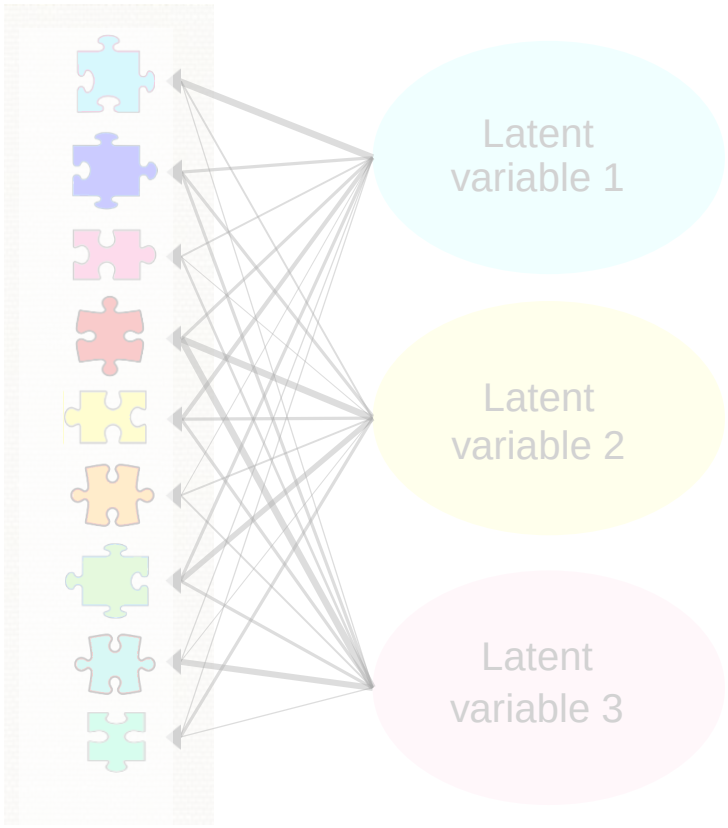
istockphoto, id1017677230

Structure of IRT model

Questionnaire-driven



Data-driven

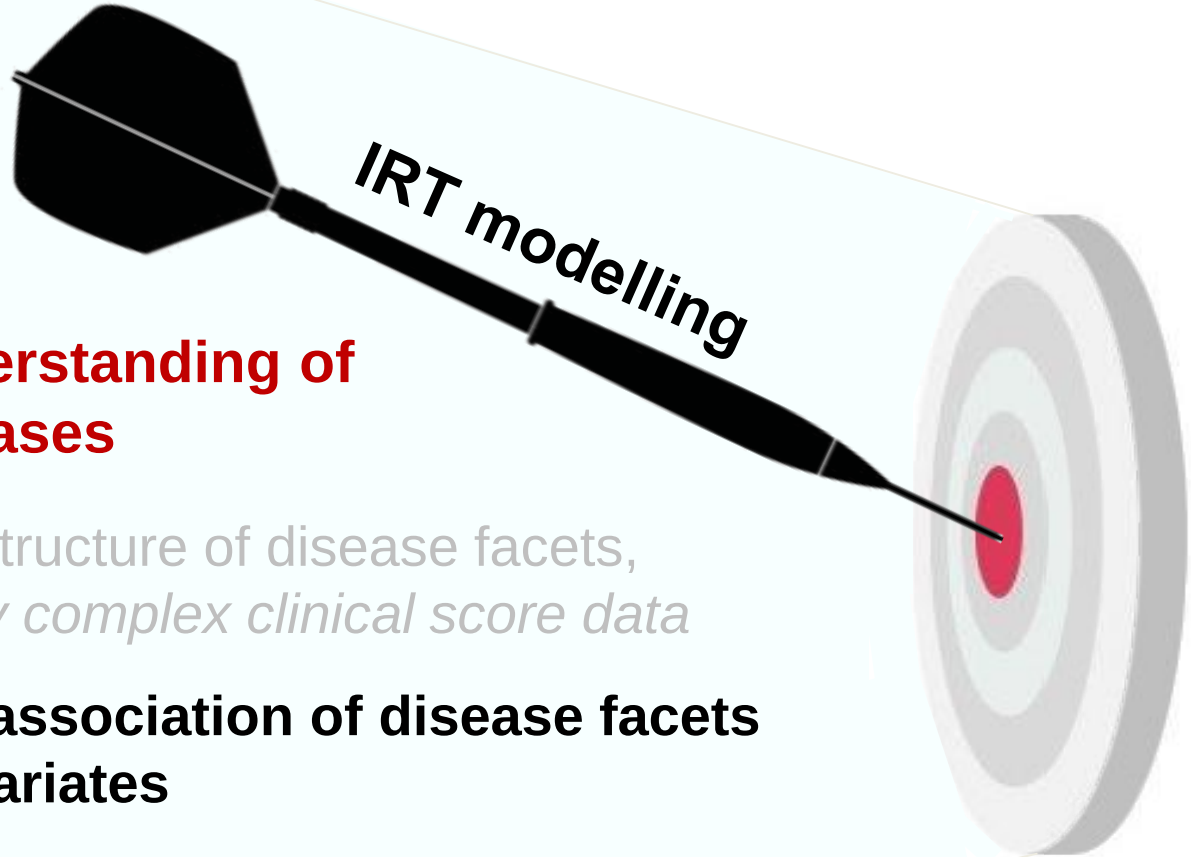


Structure of IRT model

Questionnaire-driven

Data-driven

Objectives



Enhance understanding of complex diseases

- Explore structure of disease facets, *guided by complex clinical score data*
- **Explore association of disease facets with covariates**

➡ **Nonalcoholic fatty liver disease**

istockphoto, id1017677230

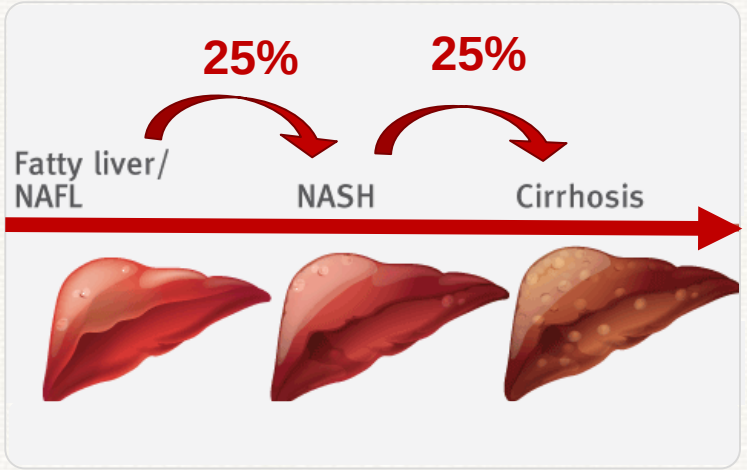
Nonalcoholic fatty liver disease (NAFLD)

Non**A**lcoholic **F**atty **L**iver

- Minimum of 5% hepatic **steatosis**

4 'key features' of NAFLD

Spectrum



Non**A**lcoholic **S**teato**H**epatitis

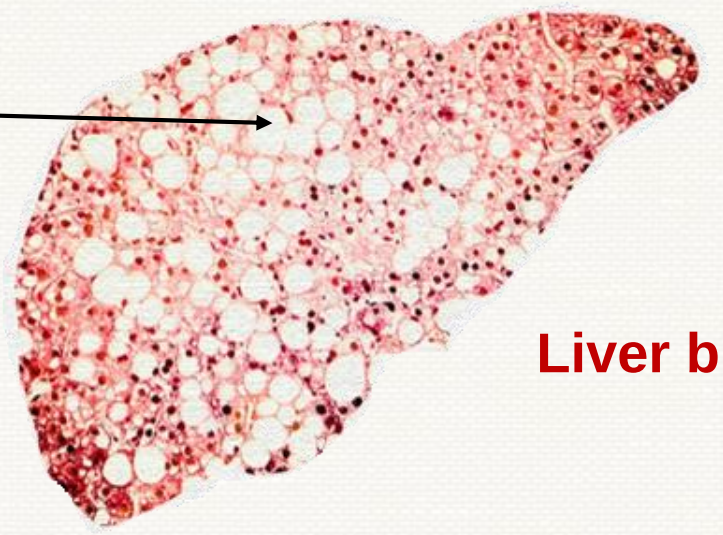
+ **Inflammation** (hepatitis)
+ Hepatocyte injury (**ballooning**)
+/- **Fibrosis**

- **Common**
  - Prevalence 20-40%
- **No approved drugs**
- **Complex**
  - Pathophysiology
  - Diagnosis

Nonalcoholic fatty liver disease (NAFLD)

Non**A**lcoholic **F**atty **L**iver

- Minimum of 5% hepatic **steatosis**



Liver biopsy

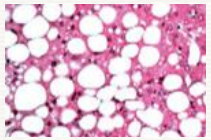
- **Common**
  - Prevalence 20-40%
- **No approved drugs**
- **Complex**
  - Pathophysiology
  - **Diagnosis**

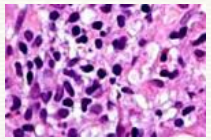
Kon Kateryna. Shutterstock ID: 769634155 (2020)

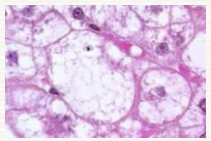
Histological scoring system for NAFLD

Key metrics (of 14 features)

NAFLD activity score (NAS)

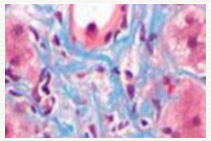






Histological feature	Score
Steatosis	0
	1
	2
	3
Lobular inflammation	0
	1
	2
	3
Hepatocellular ballooning	0
	1
	2
NAS	**0-8**

Fibrosis stage



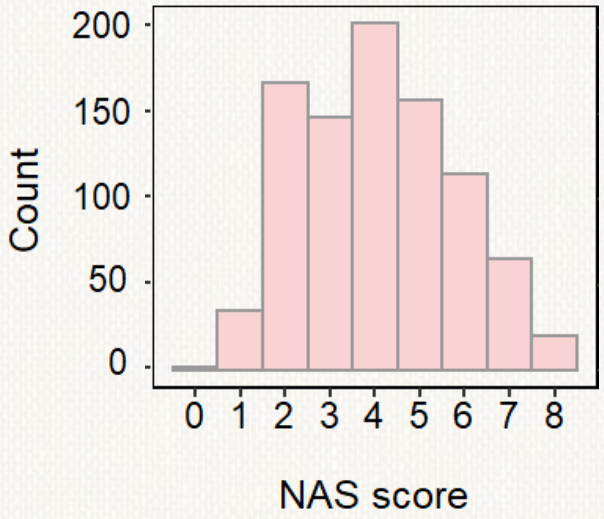
Fibrosis	Score
None	**0**
Perisinusoidal or periportal	1
Mild, zone 3, perisinusoidal	1A
Moderate, zone 3, perisinusoidal	1B
Portal/periportal	1C
Perisinusoidal and portal/periportal	2
Bridging fibrosis	3
Cirrhosis	**4**

Strongest predictor of adverse clinical outcomes (liver transplantation, death)

Kleiner et al. Hepatology 41 (2005); Trovato et al. EPMA J 5 (2014)

Public NAFLD Adult database

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

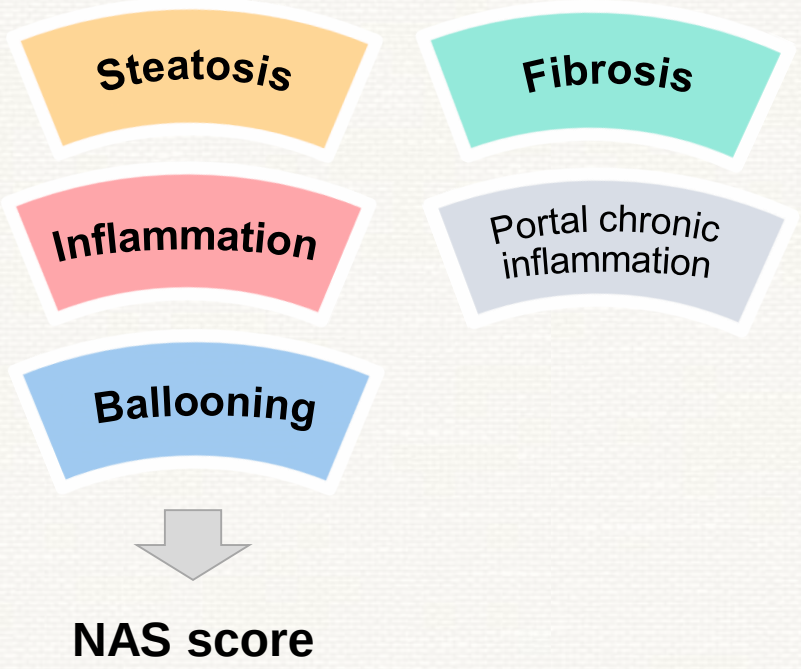


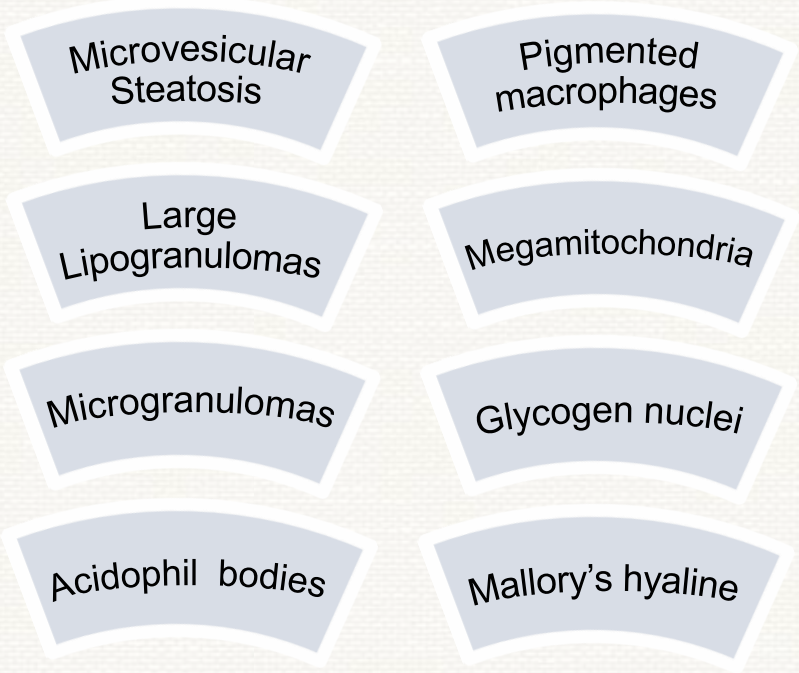
- **17 questionnaires**, i.a.
  - **Histological liver scores**
    → **Full spectrum of NAFLD**
  - **Patient characteristics** (laboratory results, etc.)

- **>900 adult IDs** (biopsy + laboratory data)
- Models based on **1 biopsy/patient**

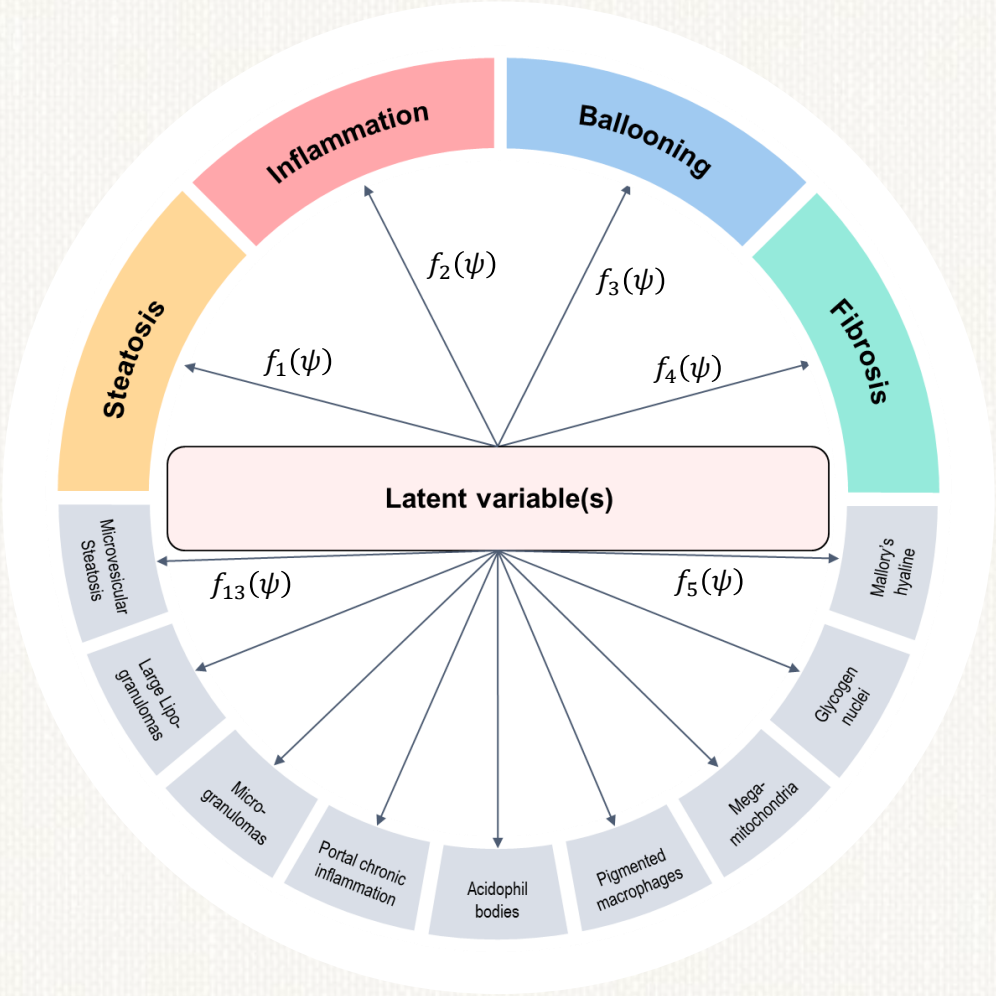
Histological liver scores (items)

- **5 ordered categorical** features
- **8 binary** features





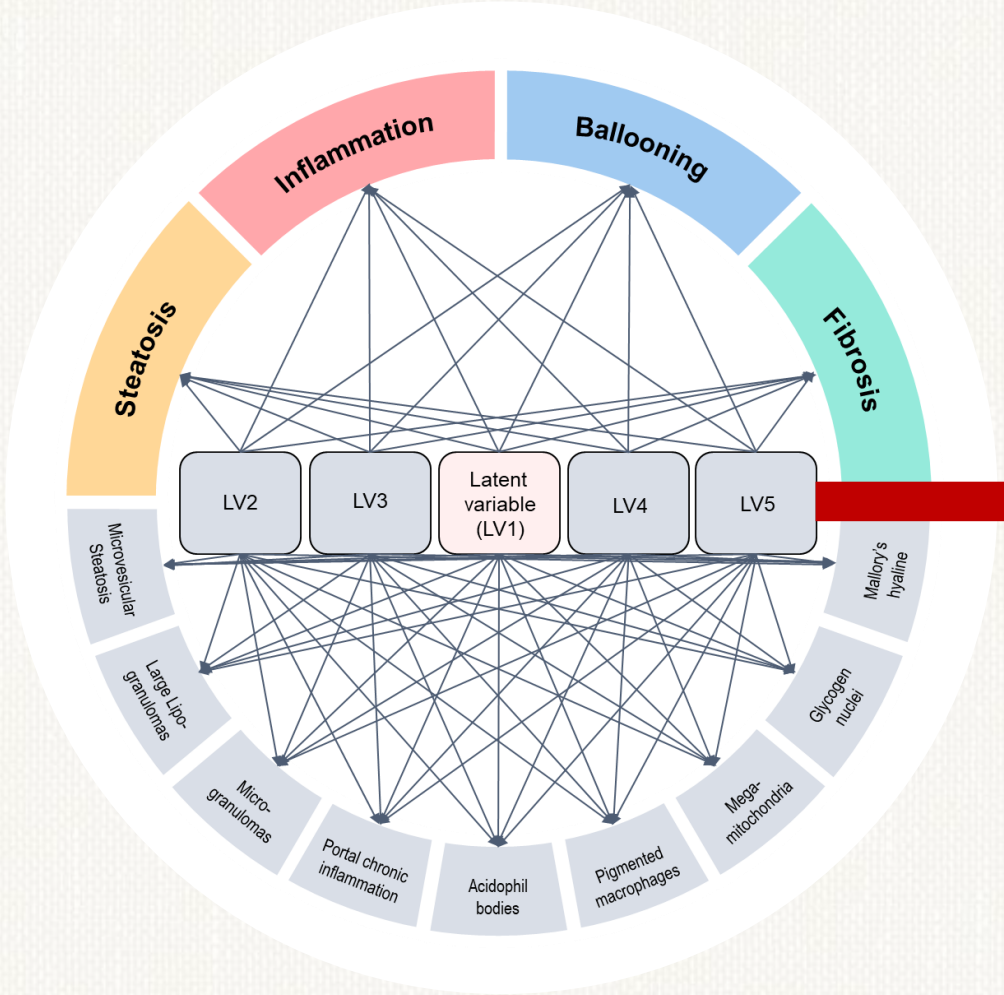
IRT modelling



- **13 histological liver scores** (items)
- **Probability of the outcome of each item** related to ≥1 **latent variable(s)**
  - **Ordered categorical** features: Graded-response models
  - **Binary** features: 2-parameter logit models
- **package mirt**

  (**m**ultidimensional **i**tem **r**esponse **t**heory)

Exploratory models

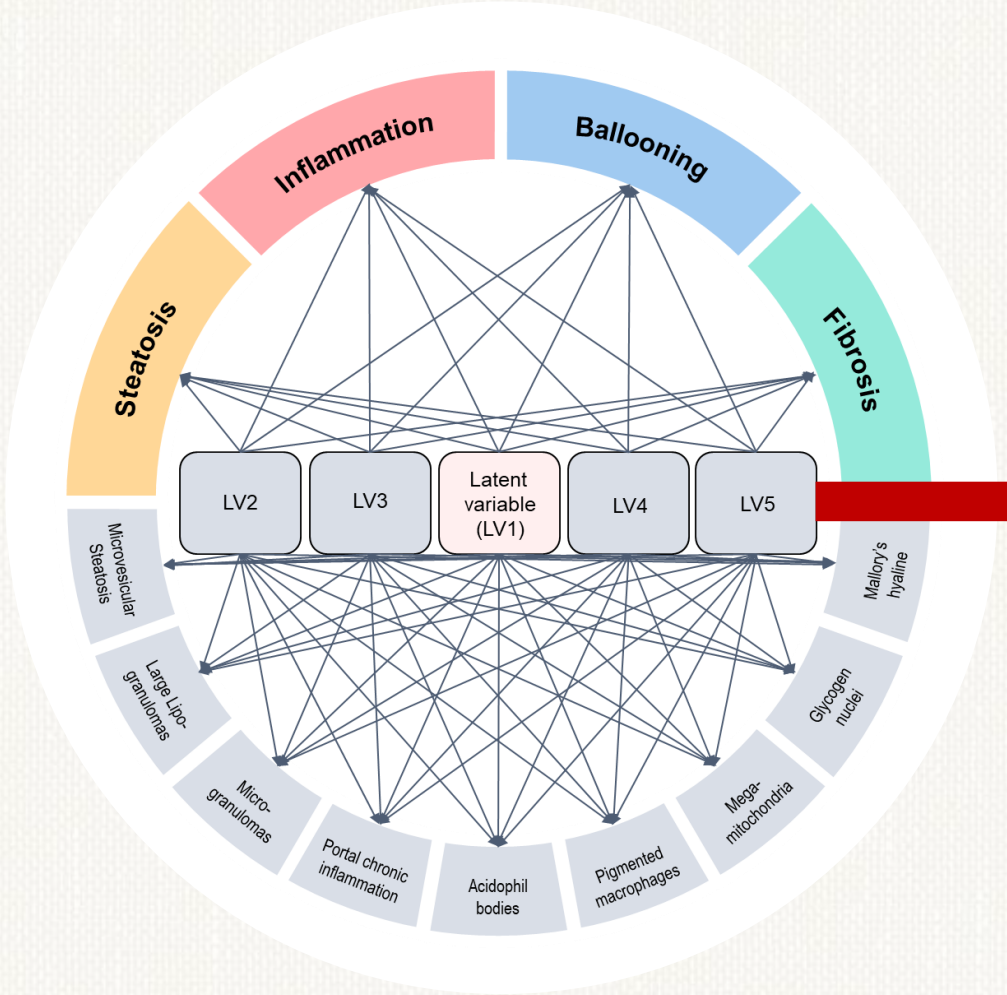


- No clear hypothesis about the structure of the item response data

What are the different facets of NAFLD detectable in the data?

How many latent variables (LVs) represent the data?

Exploratory models



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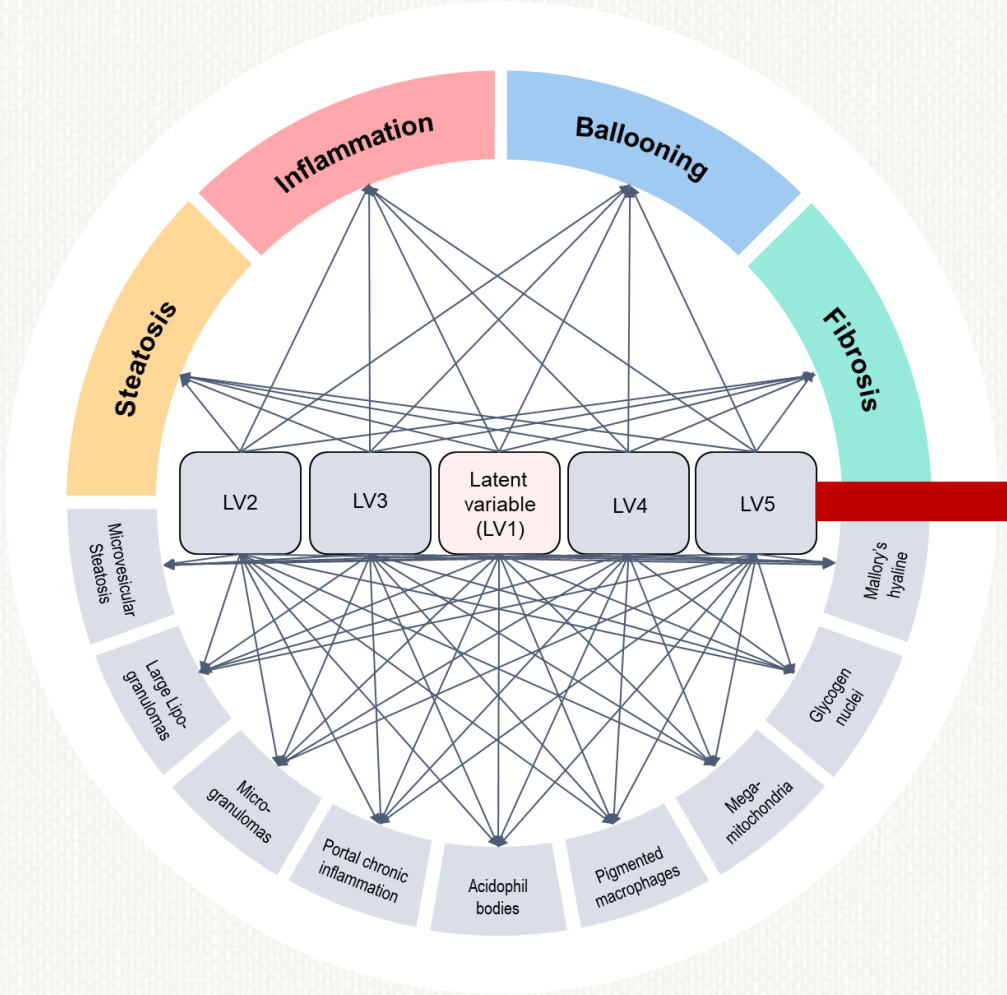
- Item-specific parameters (a_{1j}, a_{2j}, d_j)
- Subject-specific parameters $(\boldsymbol{\psi_{1i}}, \boldsymbol{\psi_{2i}})$

Exploratory models



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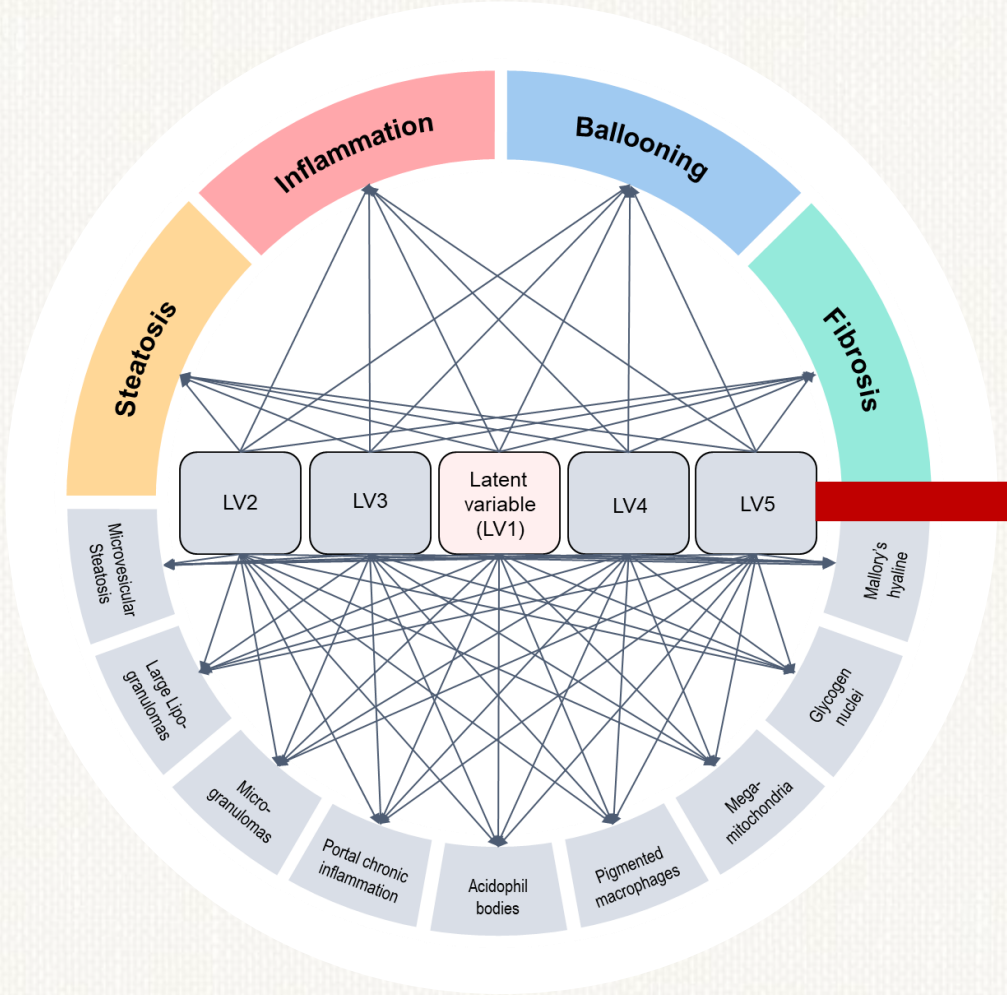

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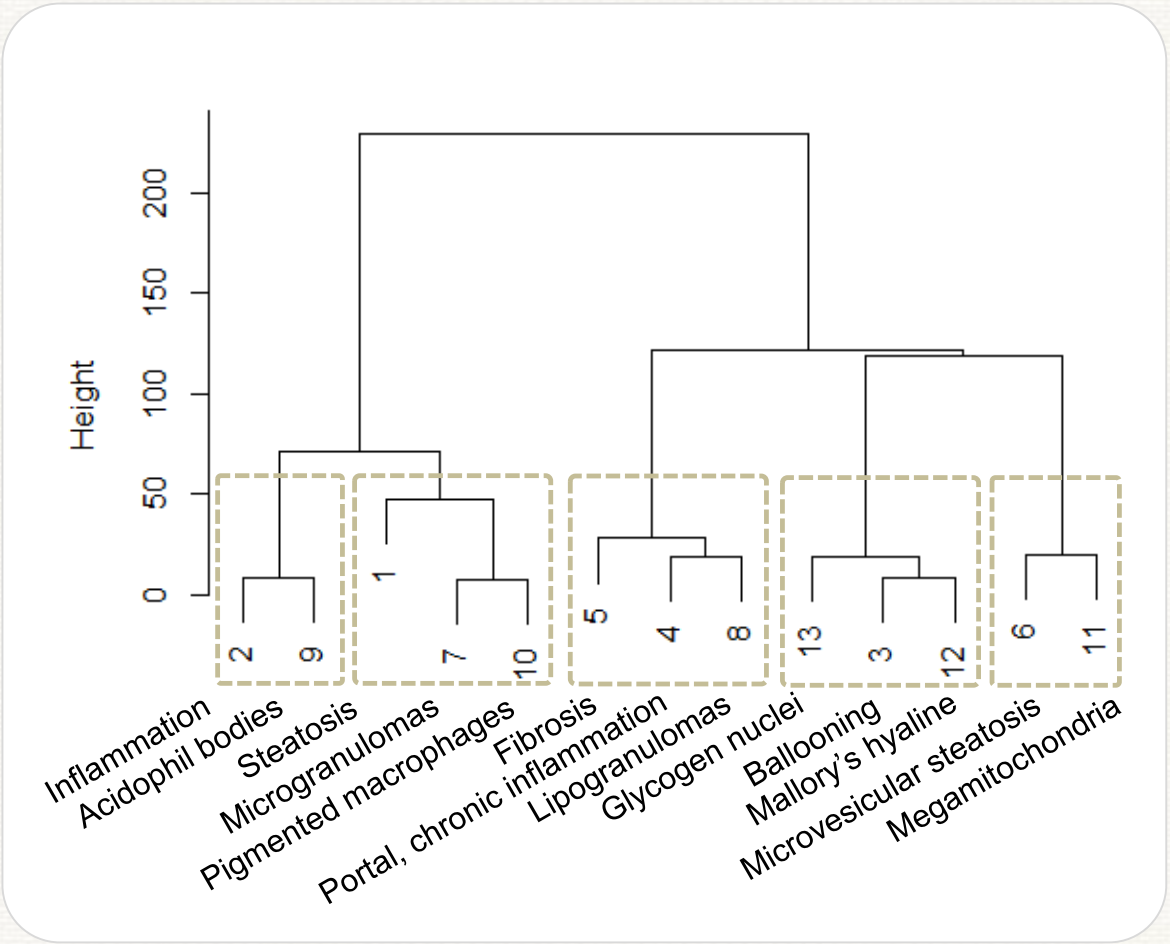
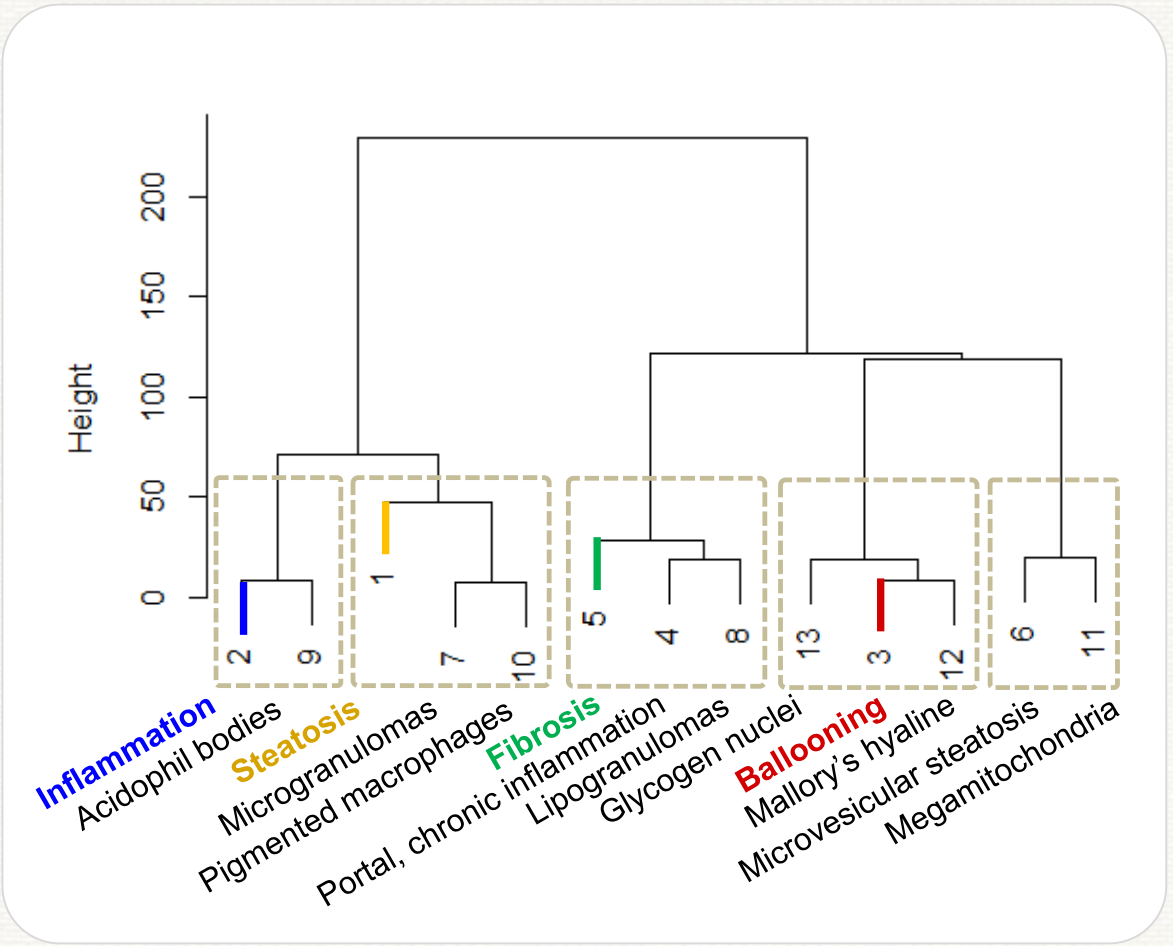
Cluster analysis

- Visualise associations of items



Cluster analysis



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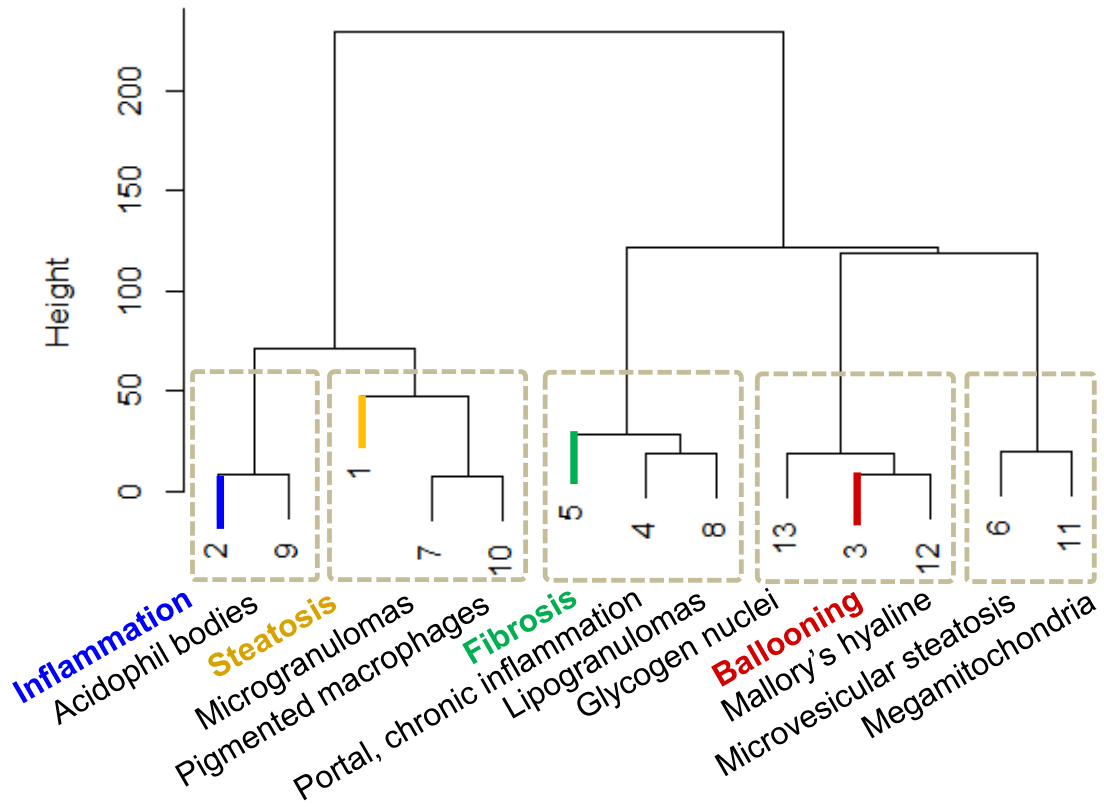
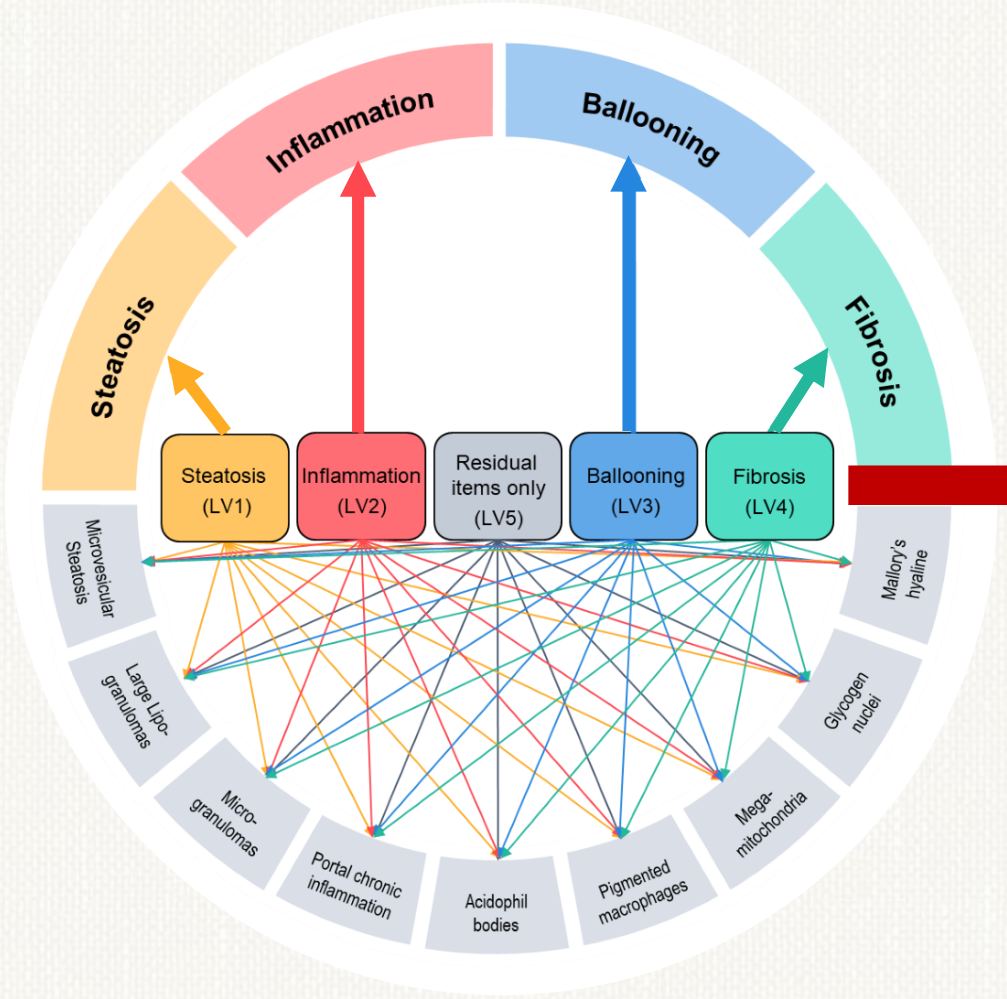


Different disease facets
(i.e. separate latent variables)
underlying the 4 key features of NAFLD

- **Confirmatory models**

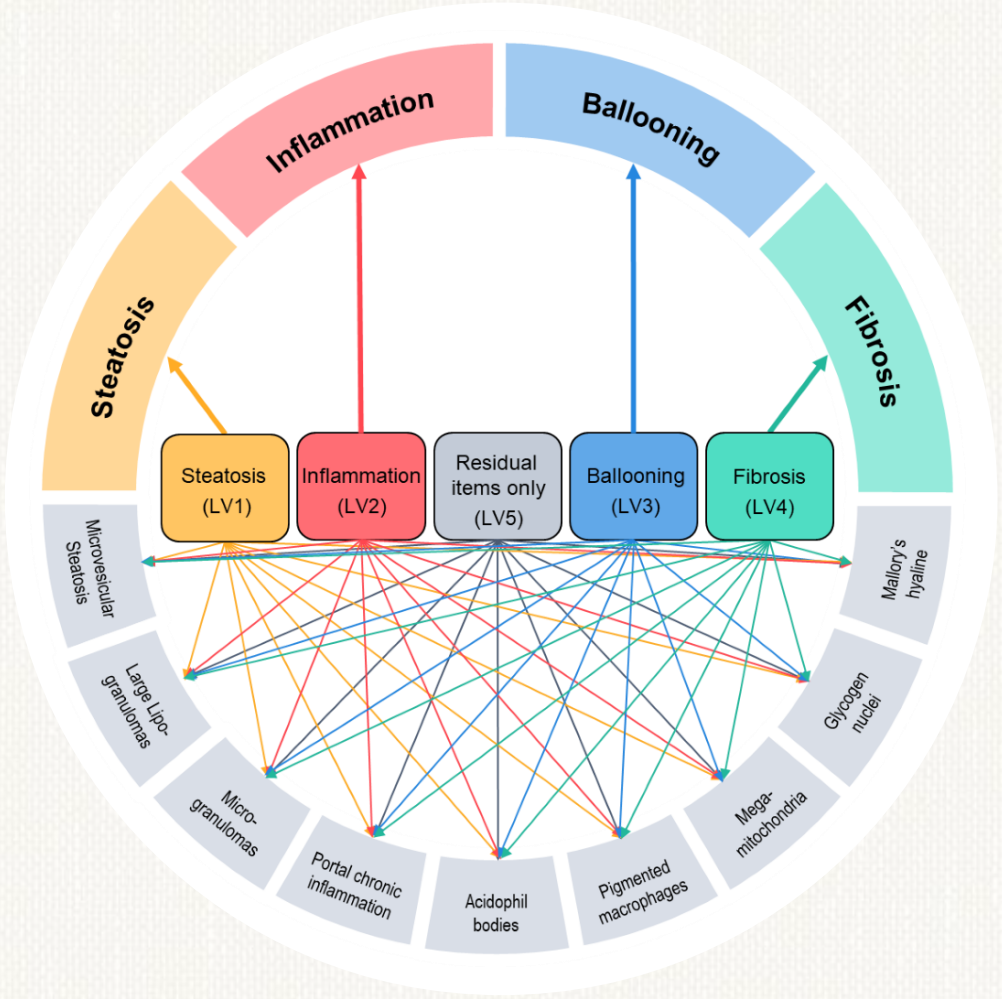
  Model items assigned to specific latent variables

Confirmatory models



- Structure informed by cluster analysis
- 5 latent variables (LVs)
  - **Different LVs for 4 'key features'** of NAFLD

Histological liver score model

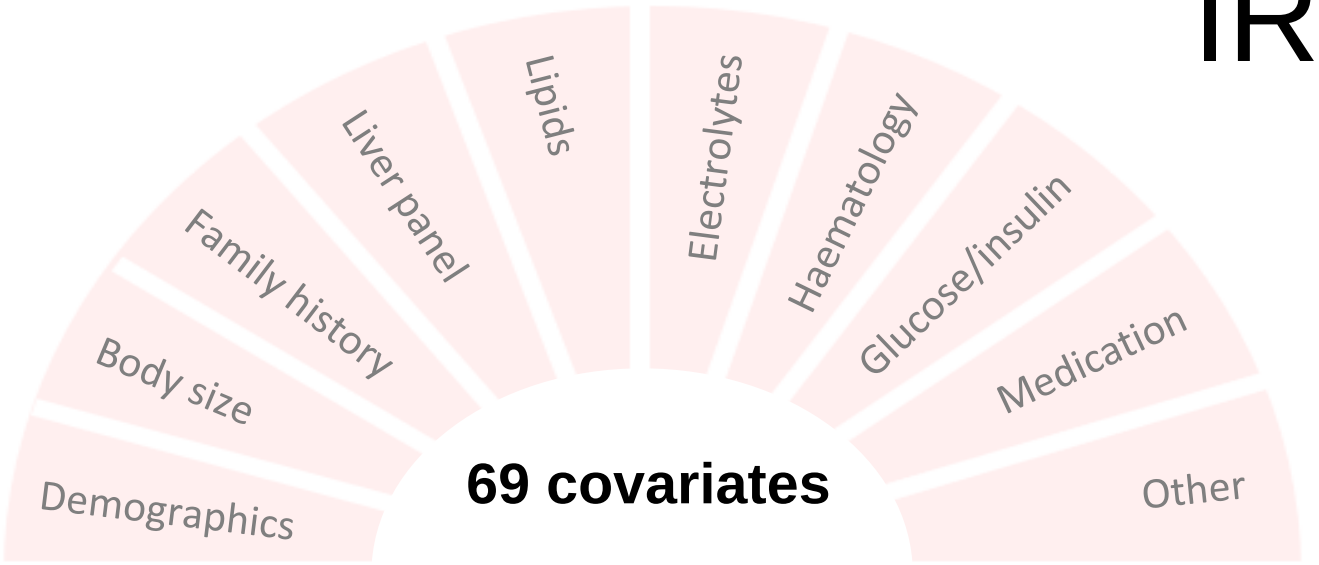


- Which **covariates** ↔ latent variables, i.e. **disease facets?**

- Which **noninvasive biomarkers** ↔ **biopsy-based scores?**

  – Considerable limitations of liver biopsies, biopsy-based screening, treatment endpoints, etc.

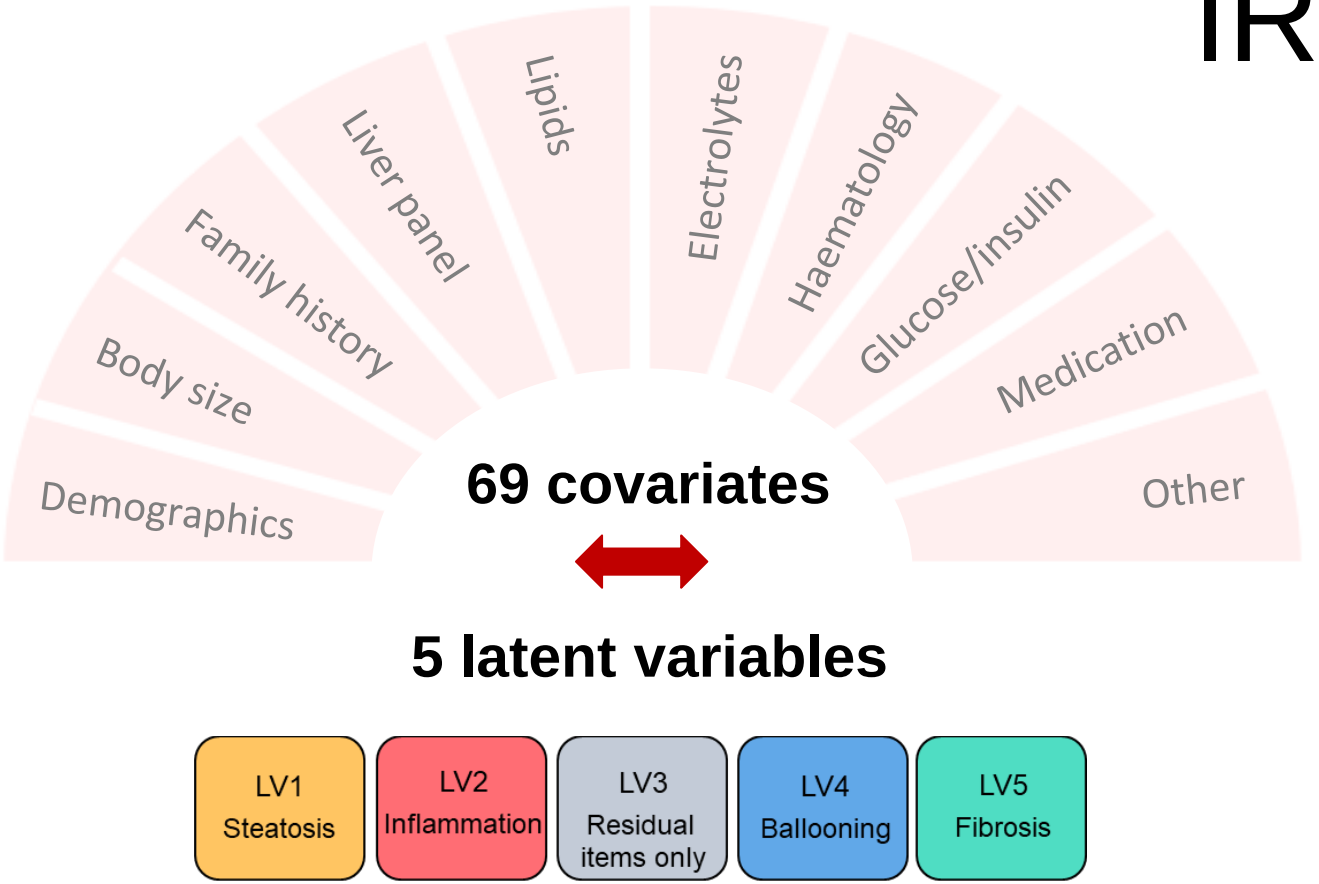
IRT-FREM



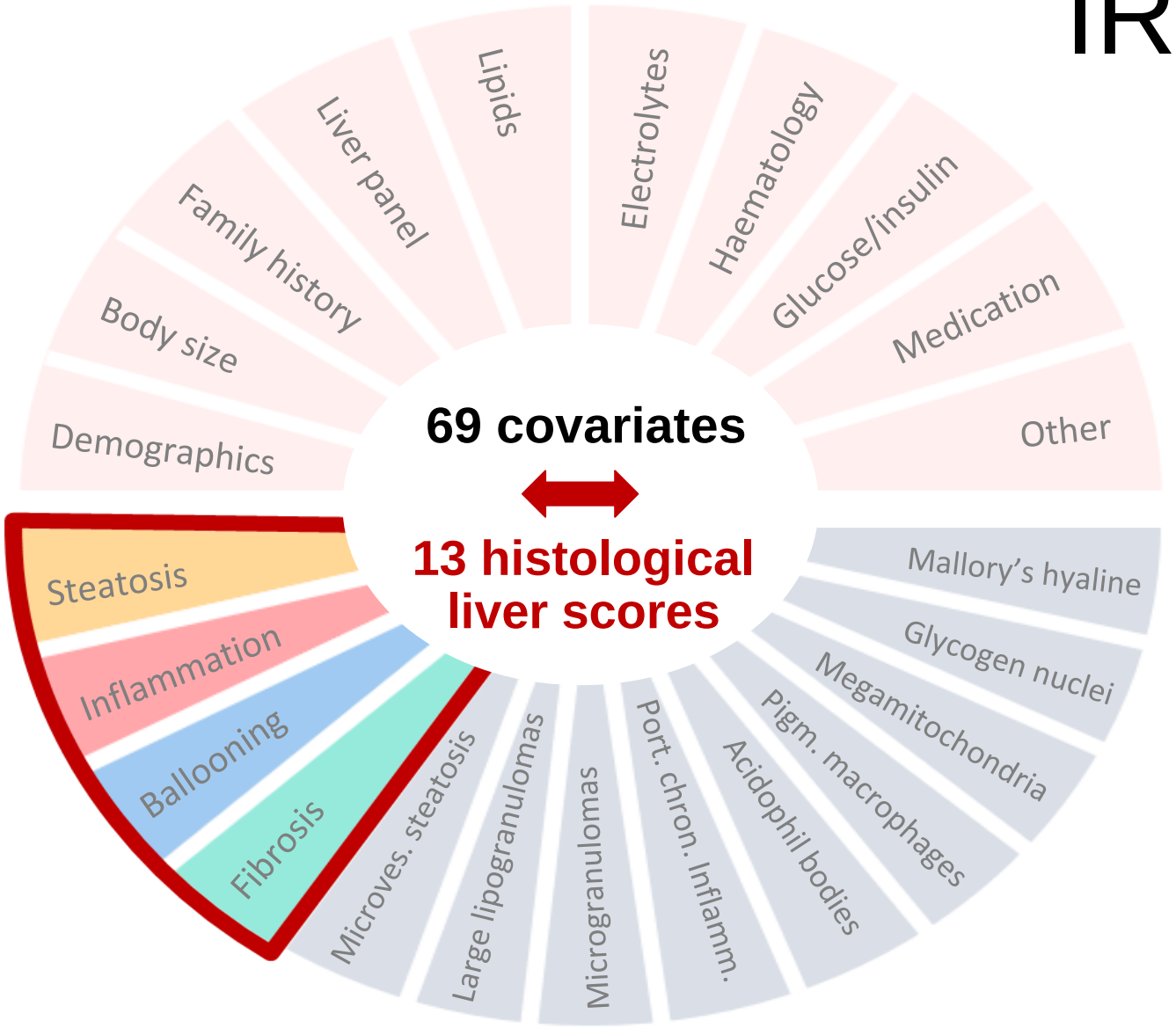
- **Abundant** and **correlated** covariates
- **Missing** covariate values

Full random effects modelling (FREM)
(NONMEM® and PsN)

IRT-FREM

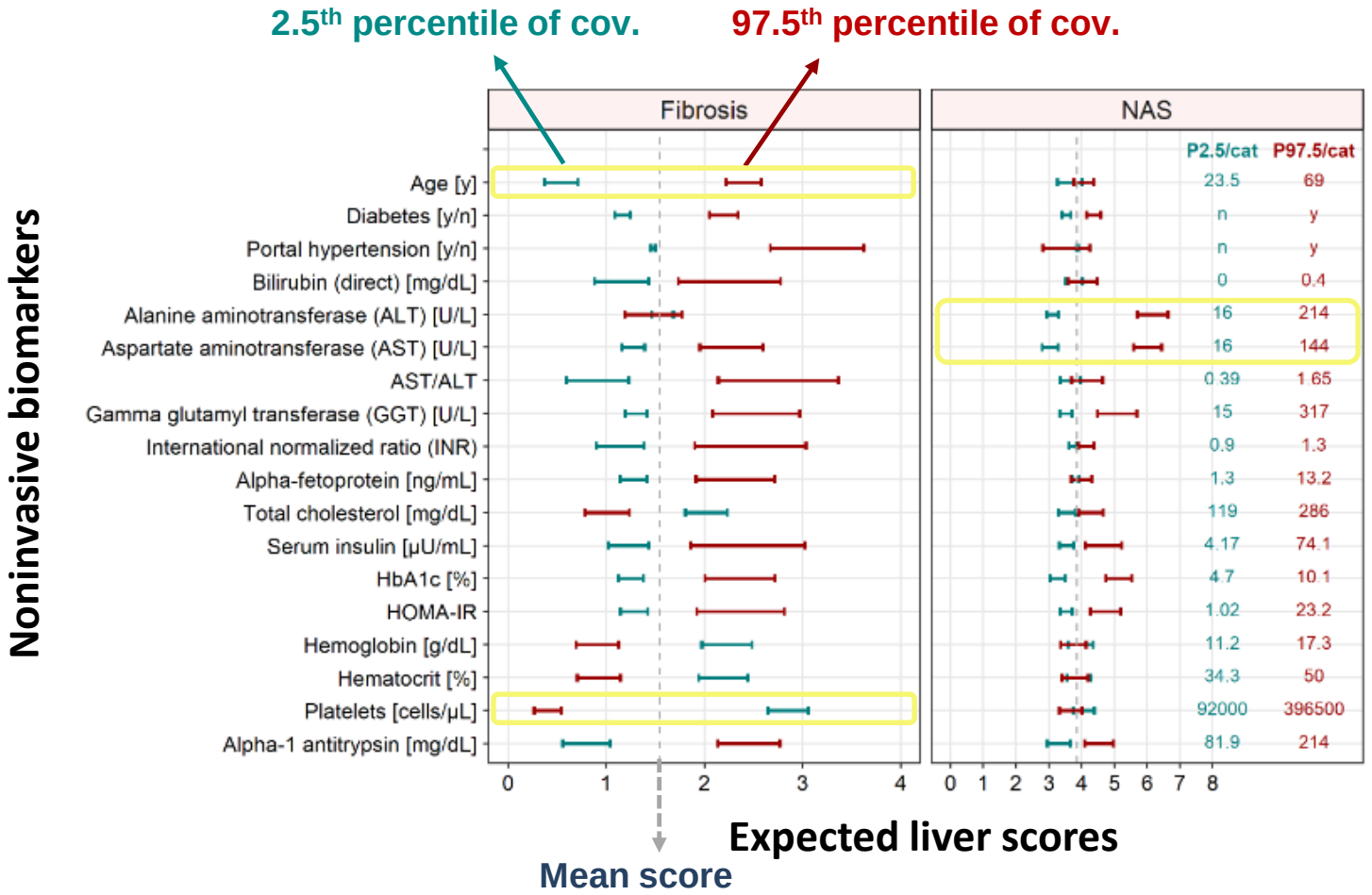

Demographics
Body size
Family history
Liver panel
Lipids
Electrolytes
Haematology
Glucose/insulin
Medication
Other
69 covariates
5 latent variables
LV1 Steatosis
LV2 Inflammation
LV3 Residual items only
LV4 Ballooning
LV5 Fibrosis

IRT-FREM



➡ Compute **expected liver scores** conditional on **specific covariate values**

Noninvasive biomarkers best reflecting fibrosis and NAS



HOMA-IR: homeostatic model assessment for insulin resistance

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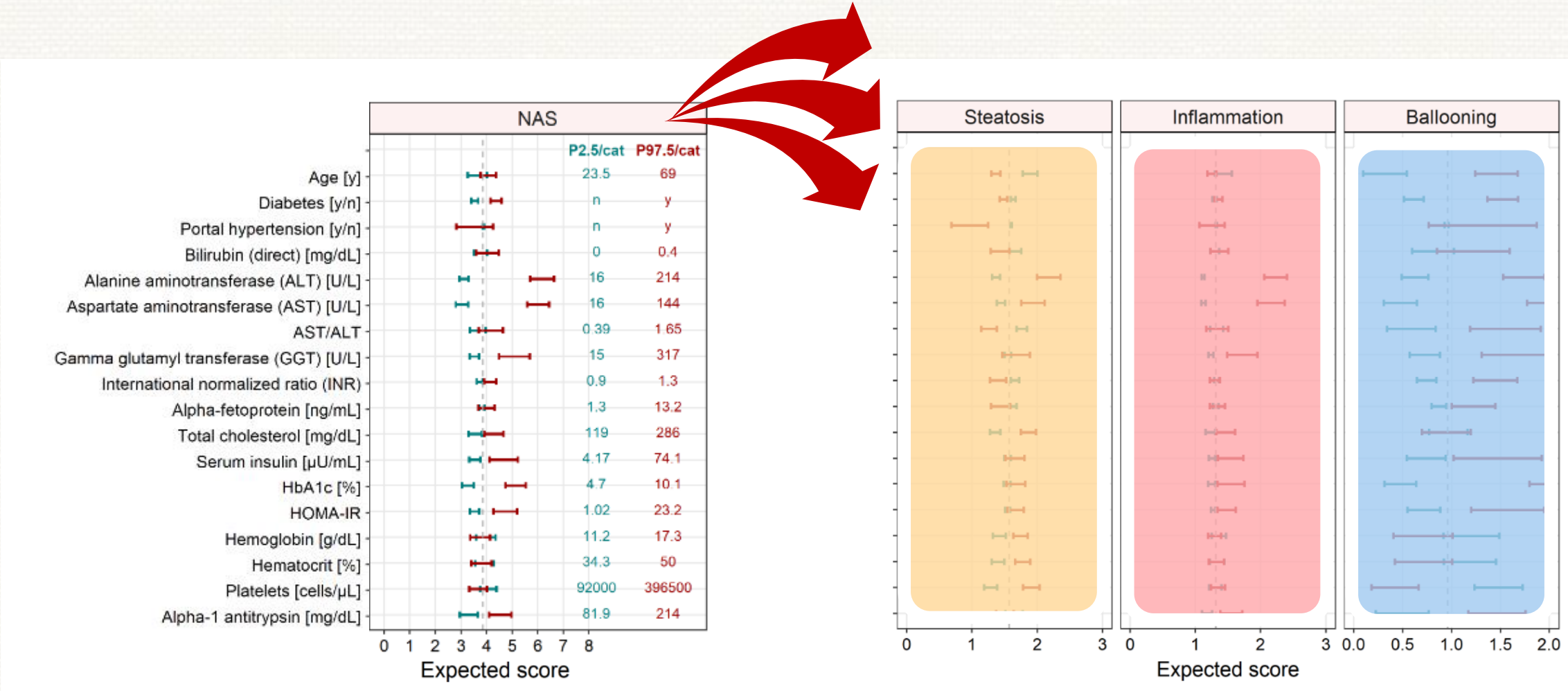
Contributions of **NAS items** to the results of the overall NAS score



HOMA-IR: homeostatic model assessment for insulin resistance

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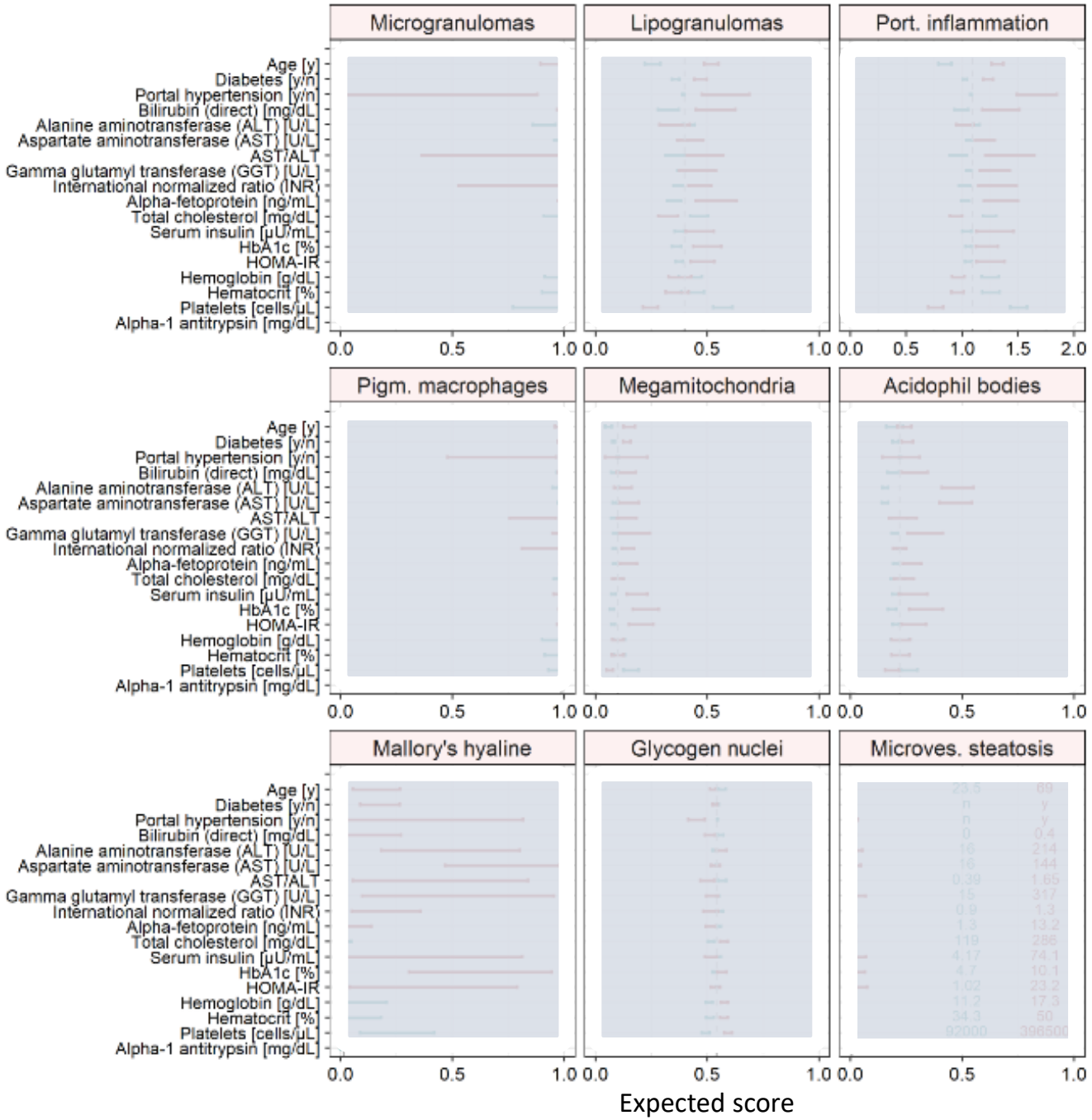
IRT-FREM



13 histological scores

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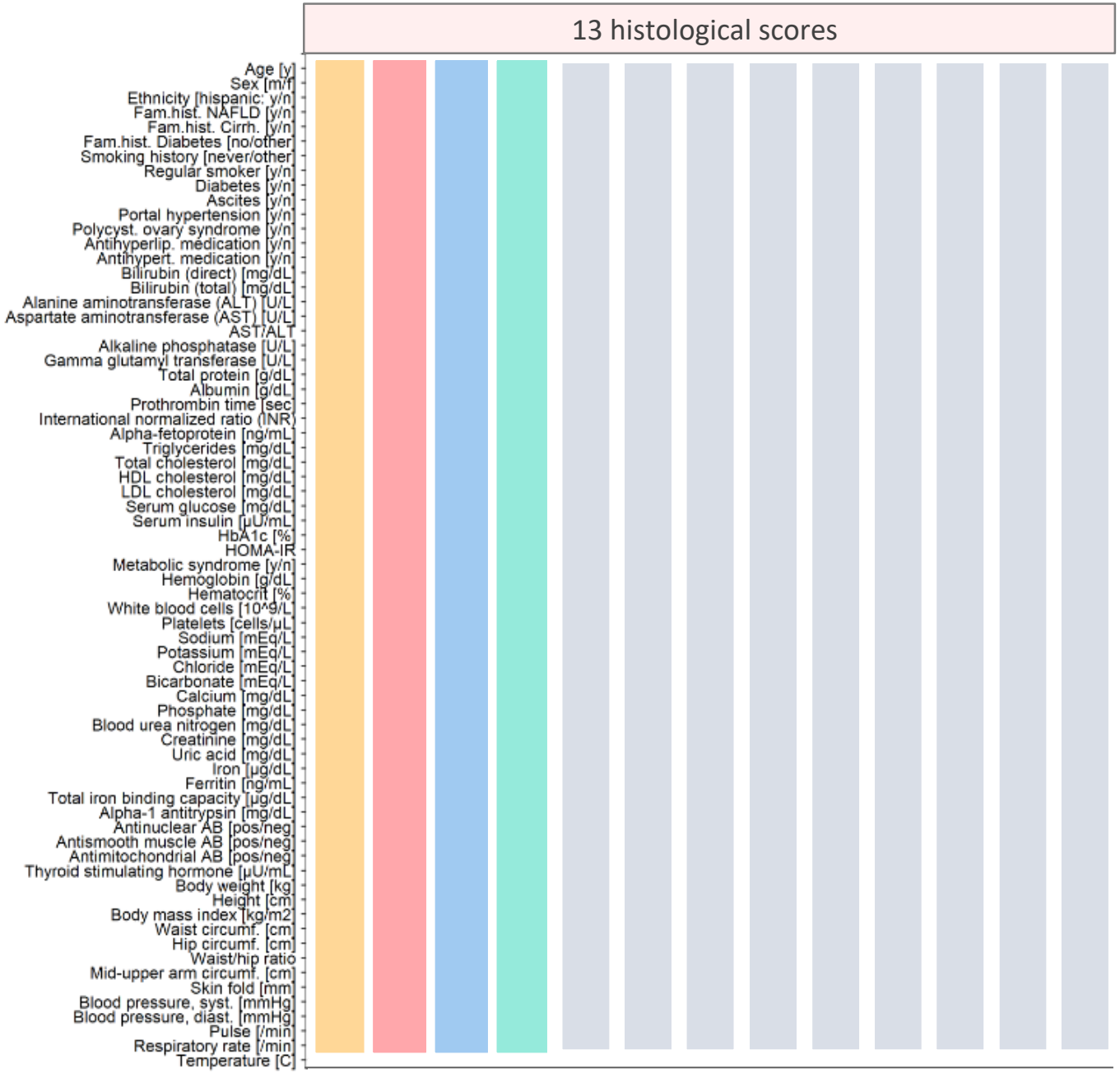
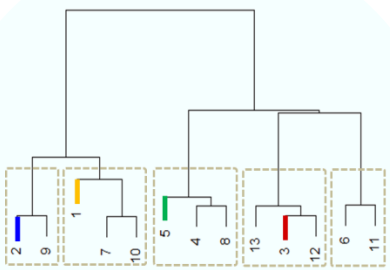
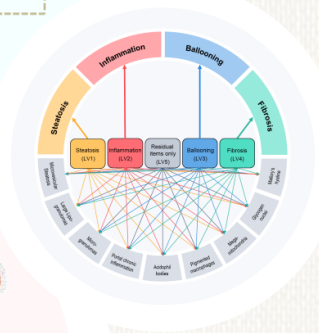
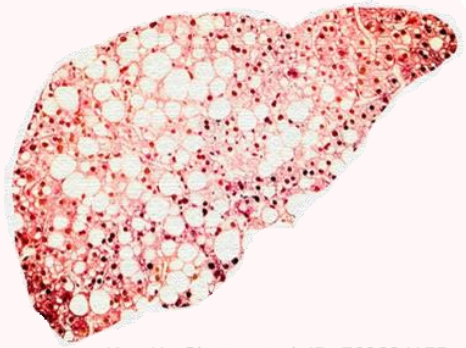


- **13 histological scores**
- **69 covariates**

Conclusion







- **Holistic IRT modelling approach**
  - Quantitative insights into the **structure of different facets underlying complex diseases**
    - Guided by clinical score data, irrespective of predefined item categorisation
- **IRT-FREM framework**
  - Expected clinical scores conditional on specific covariate values
    - Noninvasive biomarkers → biopsy-based scores

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