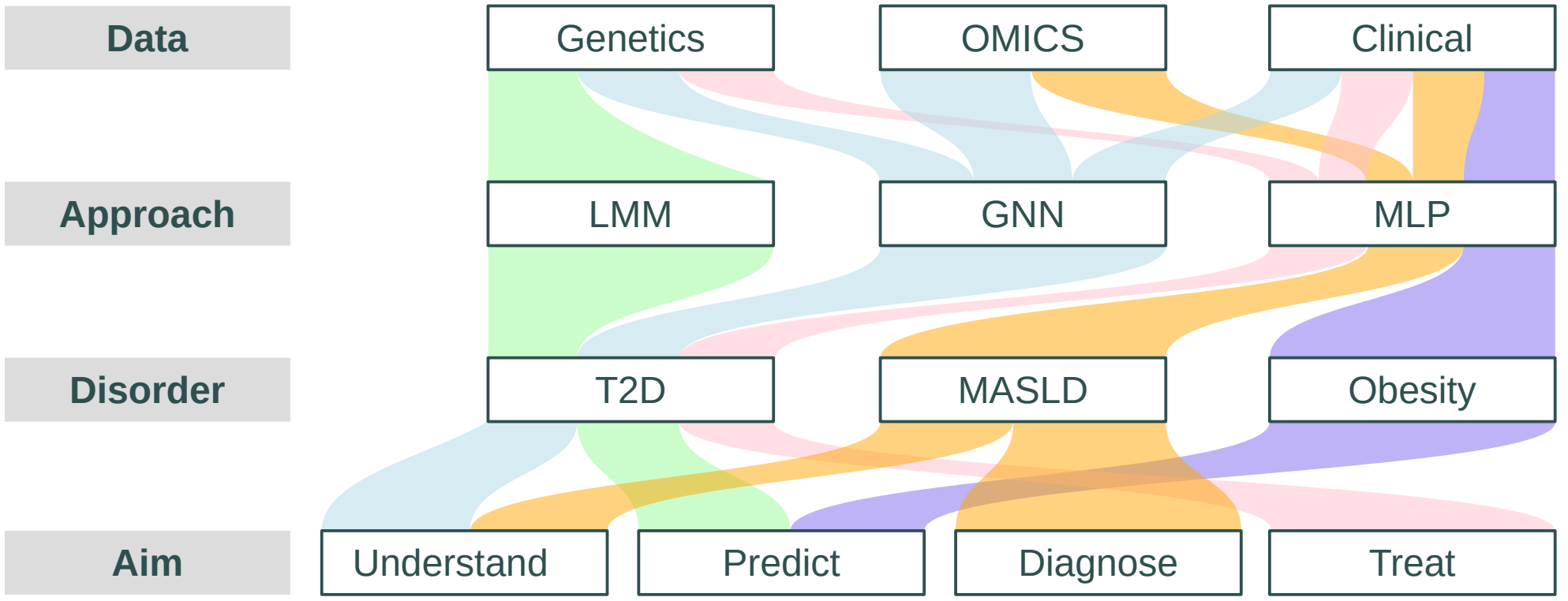
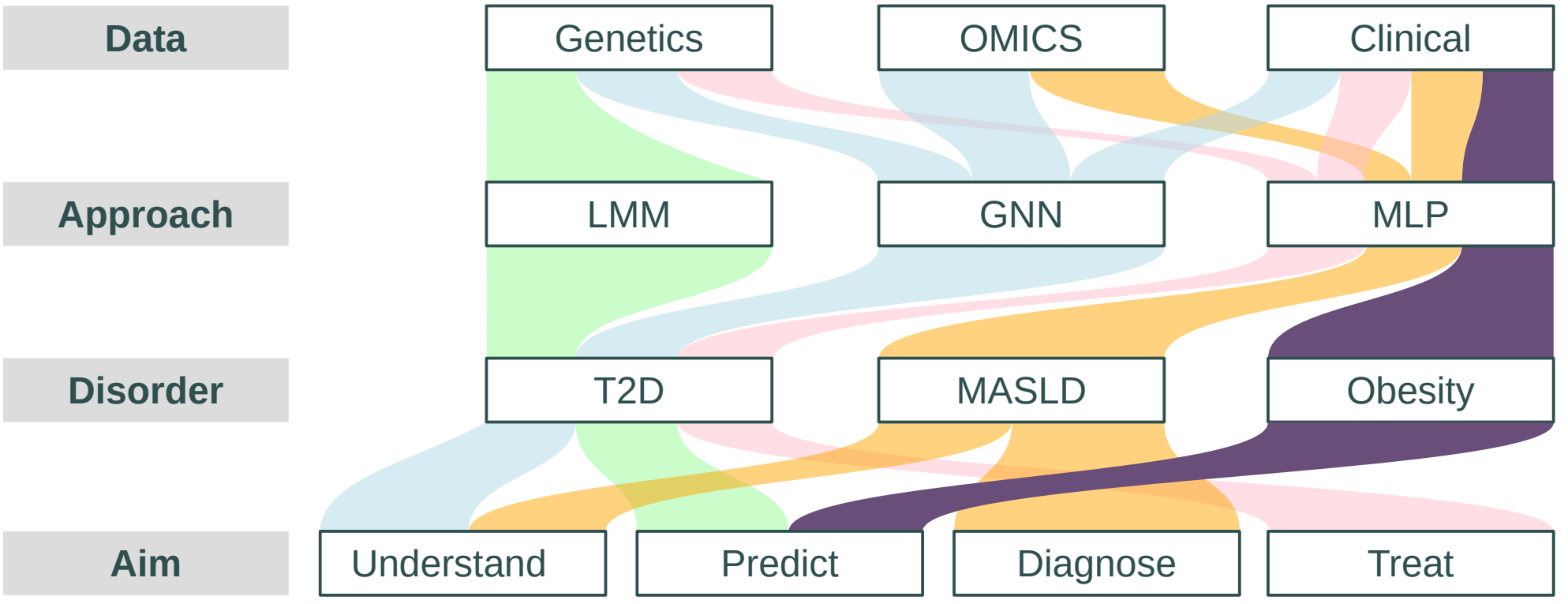
IA @ Egenodia


Steatosis
Diabetes
Artificialintelligence
Obesity
Deeplearning
Neuralnetwork
Encoderdecoder
Inflammation
Attention
Mash
Gru
Tensor
Gemini
Neuralnetwork
Lstm
Chatgpt
Cnn
Dnn
Artificialintelligence
Transformer
Predict
Fullyconnected
Treatment
Largelanguagemodel
Rnn
Encoderdecoder
Vae
Diagnosis
Prognosis
Deeplearning
Ssm
Llama
Autoencoder
Convolutional
Dense
Claude
Masld
Cluster
Tensor
Lmm
Transformer
Ssm
Claude
Steatosis
Dnn
Treatment
Rnn
Inflammation

Artificial Intelligence for the precision medicine of cardiometabolic disorders (AImedCMD)

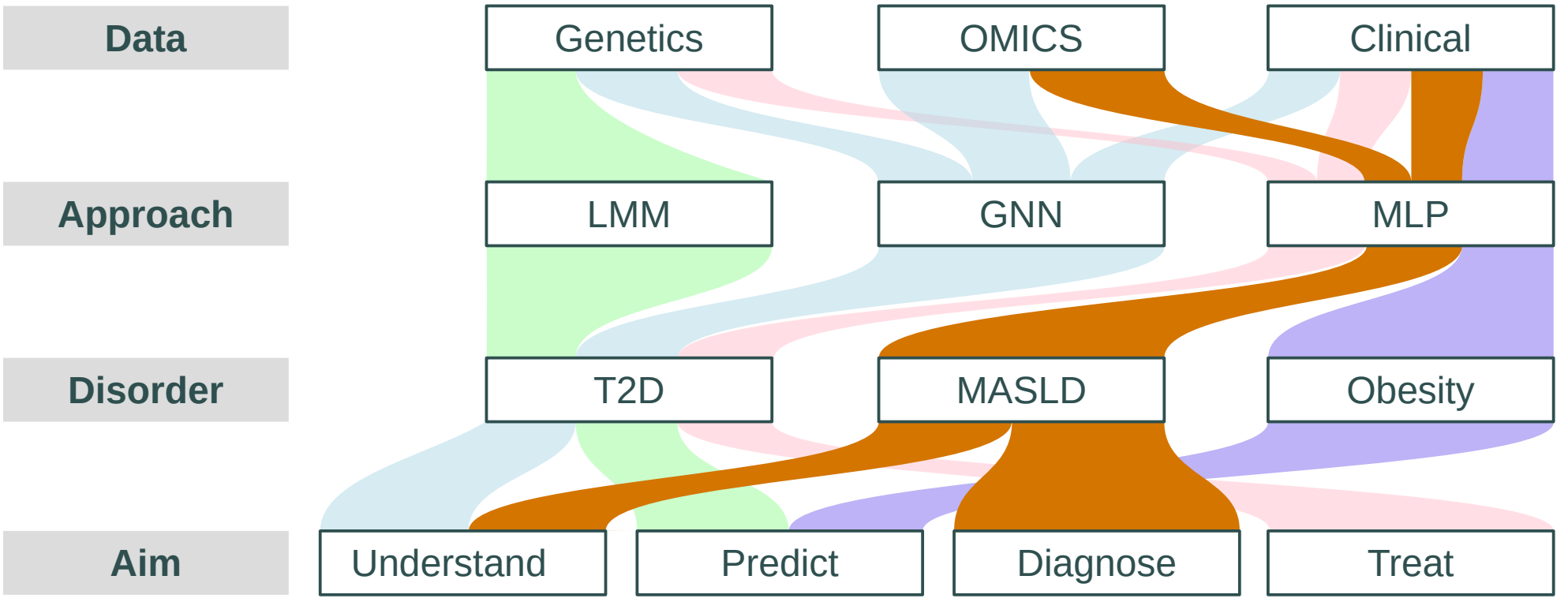



Sami Le Guilcher



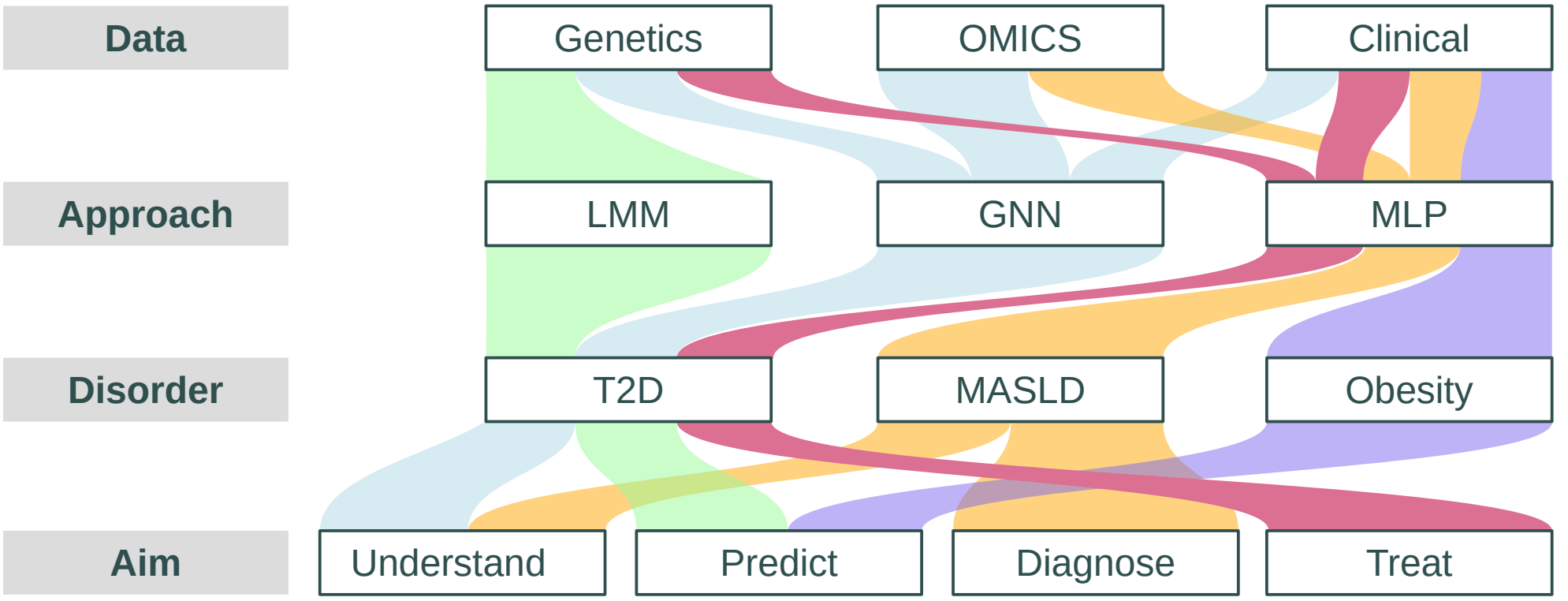
horizon europe

Obelisk



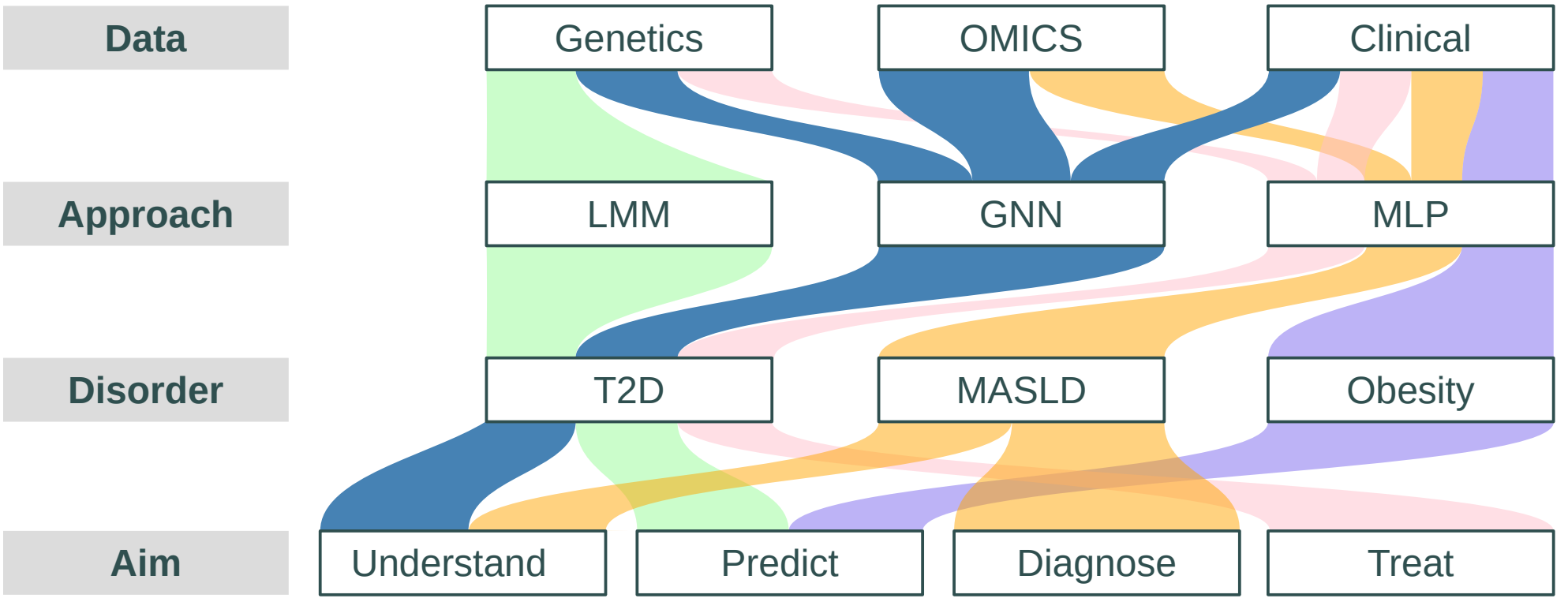
PreciNASH
recherche hospitalo-universitaire

Marwa Afnouch   Arthur Six

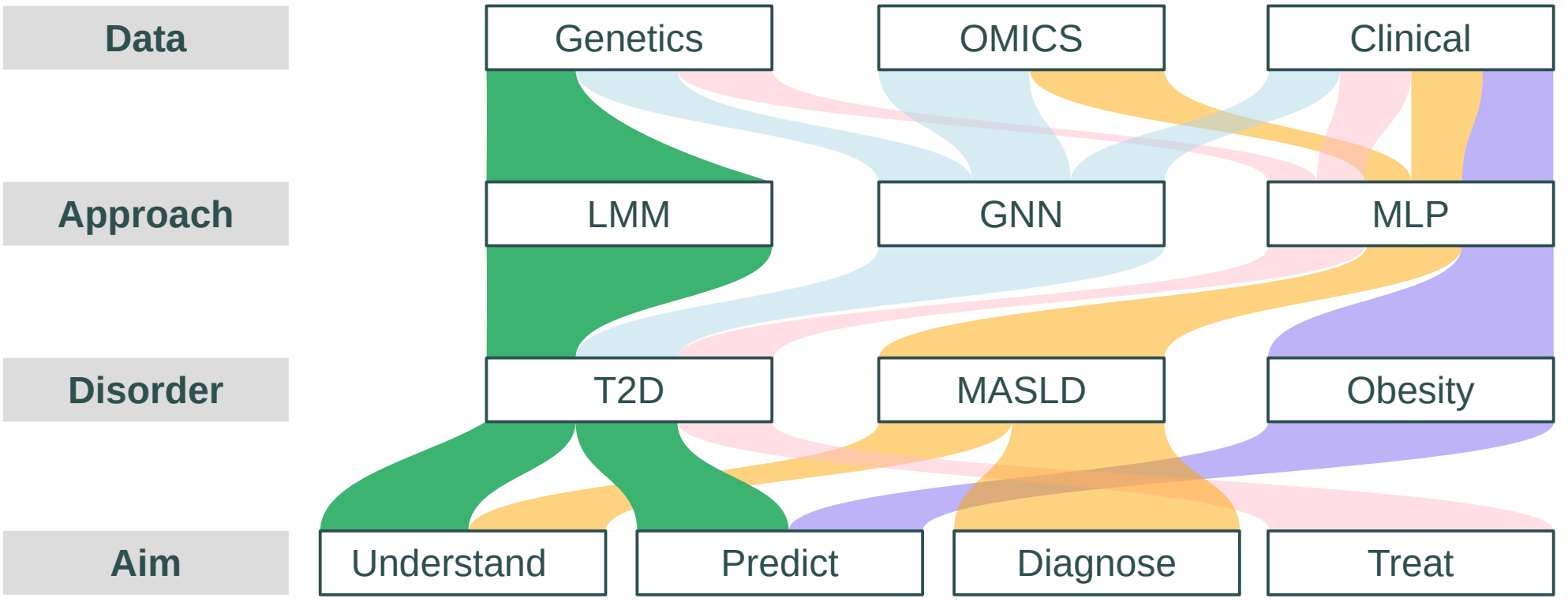


PreciDIAG
Precision Diagnosis
for Type 2 Diabetes

Amna Khamis   Omaima Binan



Smaïn Fettem

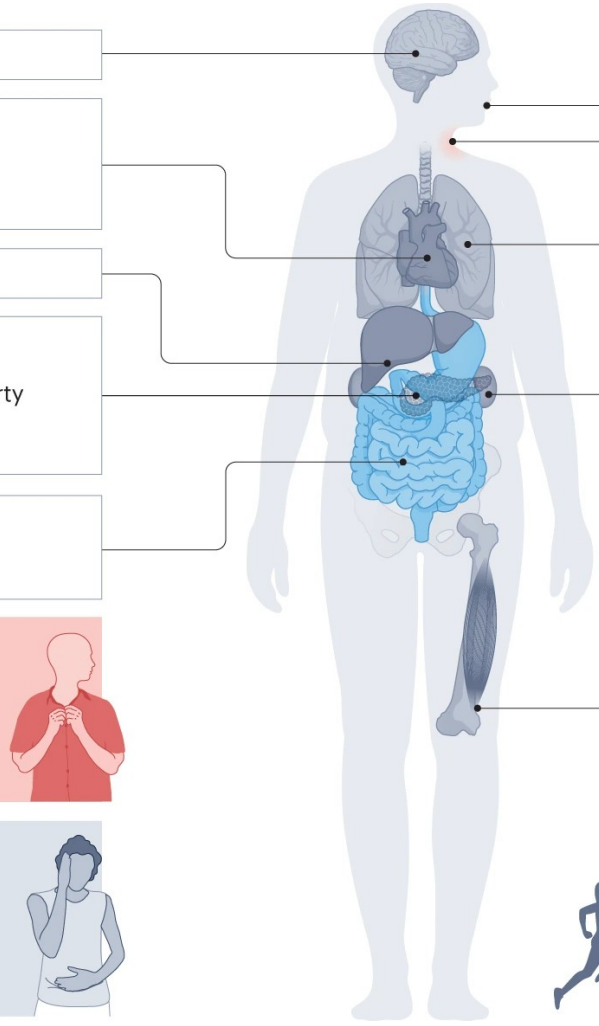


PreciDIAB
National Center for
Precision Diabetic Medicine

Childhood obesity triggers health problem throughout life

In adults

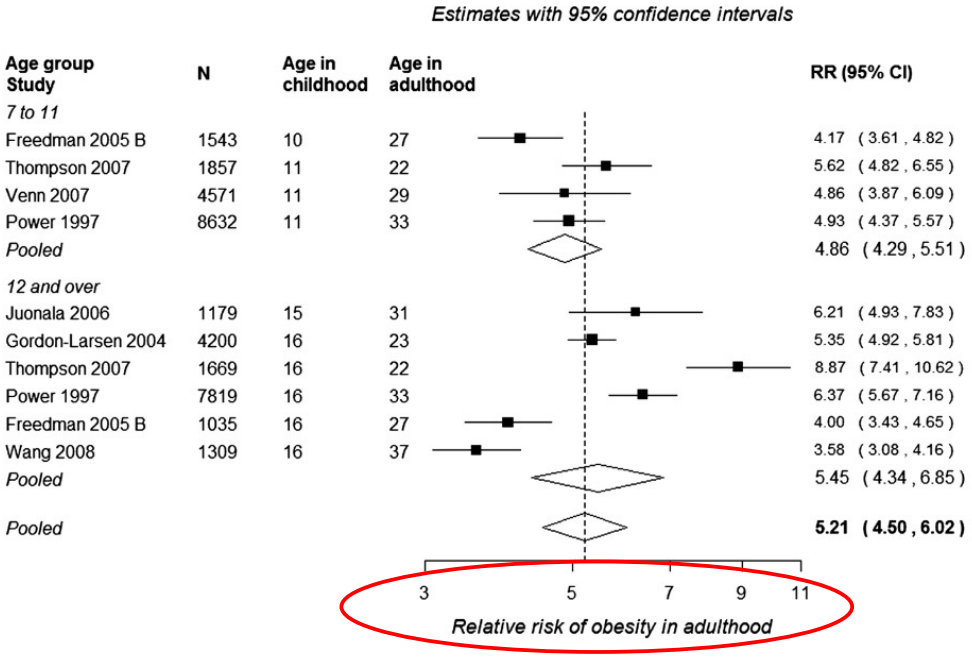
- Intracranial hypertension
- Hypertension
- Dyslipidaemia
- Endothelial dysfunction
- Left ventricular hypertrophy
- Fatty liver disease
- Impaired glucose tolerance
- Polycystic ovary syndrome
- Delayed or accelerated puberty
- Metabolic syndrome
- Type 2 diabetes mellitus
- Gastro-oesophageal reflux
- Constipation
- Micronutrient deficiencies
- Coronary artery disease
- Some cancers
- Infertility
- Osteoarthritis
- Type 2 diabetes mellitus
- Adult obesity
- Reduced self esteem
- Depression
- Anxiety
- Disordered eating
- Internalizing disorders
- Body dissatisfaction

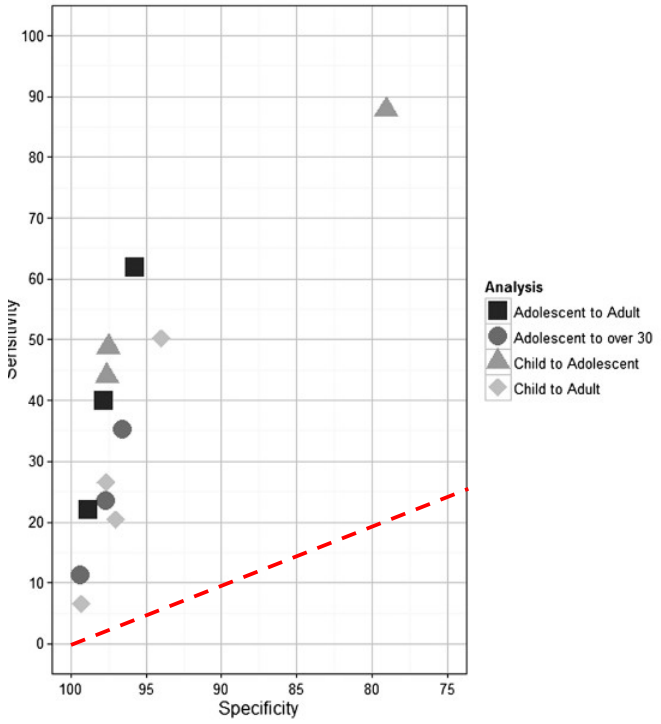


- Periodontal disease, caries
- Acanthosis nigricans, psoriasis
- Asthma
- Obstructive sleep apnoea
- Impaired exercise tolerance
- Sleep disordered breathing
- Sleep disorders
- Poor outcomes of viral infection
- Hypoventilation syndrome
- Glomerulosclerosis, enuresis
- Pain
- Acute injuries
- Impaired balance and coordination
- Impaired muscle strength
- Gait deviations
- Postural malalignment
- Fractures
- Slipped capital femoral epiphysis
- Blount disease
- Impaired motor skill and competency
- Fatigue
- Impaired functional mobility
- Reduced health-related quality of life
- Reduced moderate–vigorous physical activity level

Lister *et al* (2023)
Child and adolescent obesity.
Nat Rev Disease Primer, 9: 24.
https://doi.org/10.1038/s41572-023-00435-4

Childhood obesity as a predictor of adult obesity





Simmonds *et al* (2016) Predicting adult obesity from childhood obesity: a systematic review and meta-analysis. *Obesity Reviews*, 17: 95-107. https://doi.org/10.1111/obr.1233

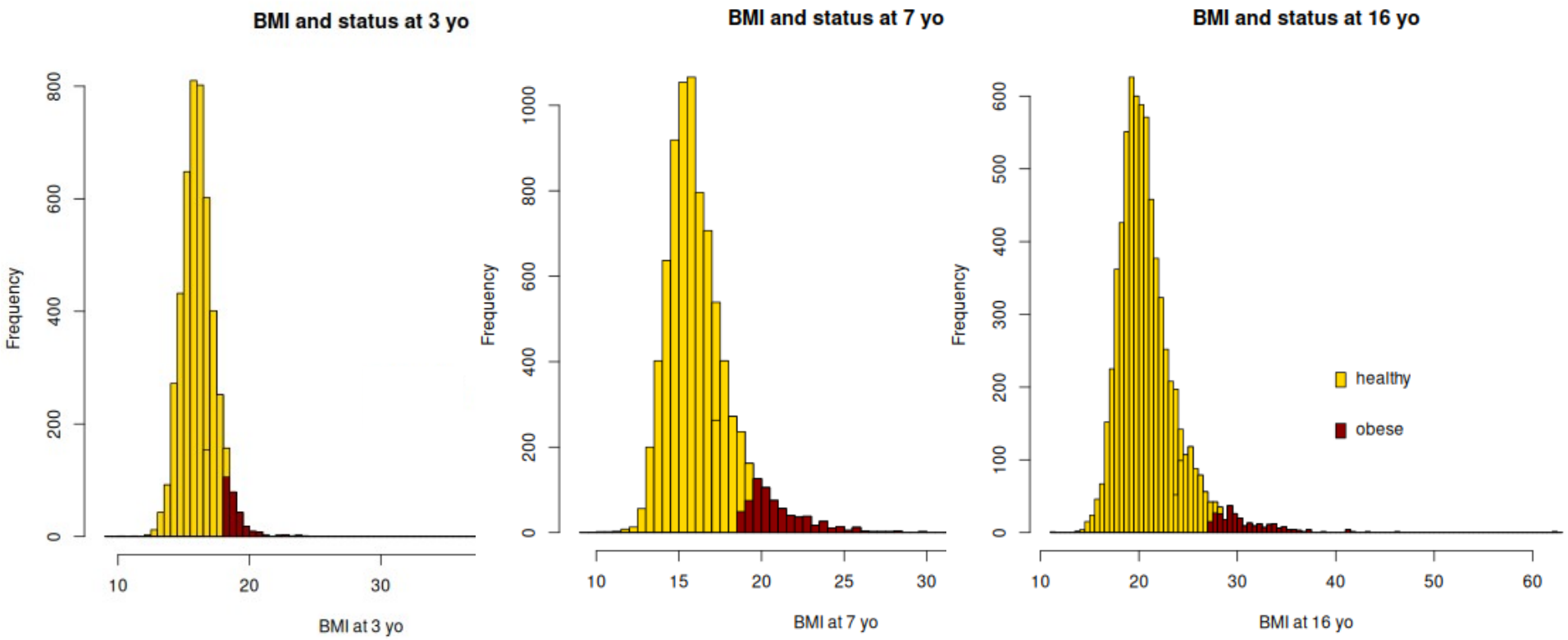
SOA: Morandi *et al* 2012, biological and socioeconomics variables

	AUROC when term is added
Childhood Overweight-Obesity	
Maternal BMI	*0.63 (0.60–0.65)*
Paternal BMI	*0.65 (0.62–0.67)*
N of household members	*0.66 (0.64–0.68)*
Gestational weight gain	*0.66 (0.64–0.69)*
Birth weight	*0.67 (0.65–0.69)*
Maternal smoking	**0.67 (0.65–0.69)**

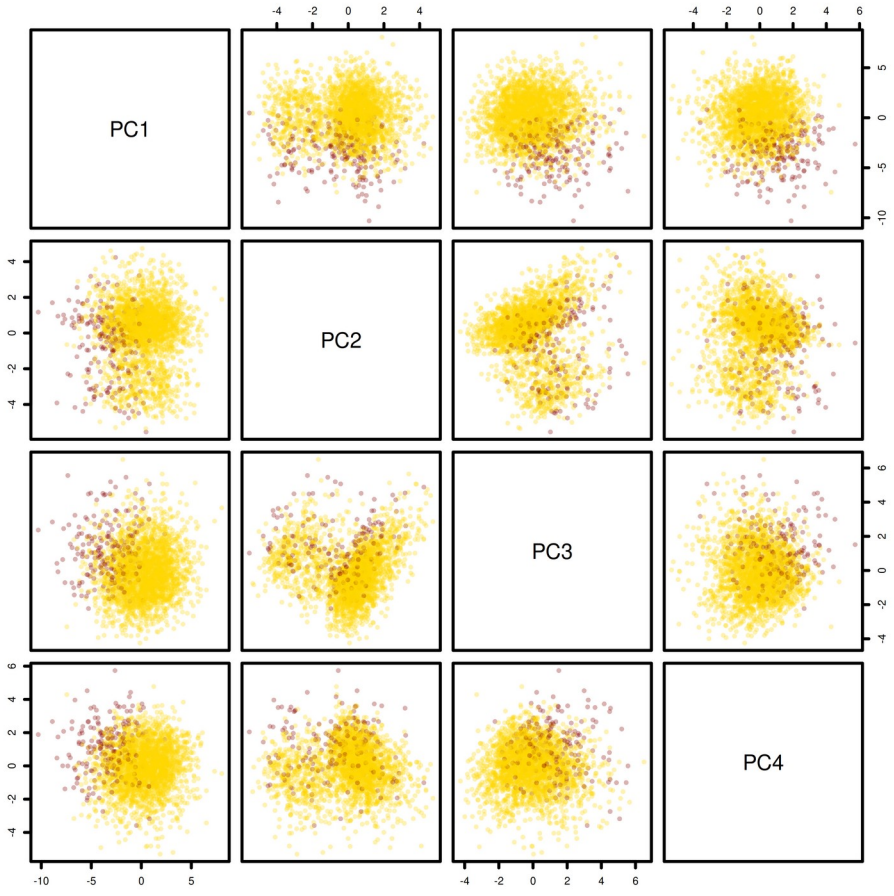
	AUROC when term is added
Childhood Obesity	
Paternal BMI	*0.68 (0.64–0.73)*
Maternal BMI	*0.74 (0.70–0.78)*
N of household members	*0.77 (0.73–0.80)*
Birth weight (kg)	*0.77 (0.73–0.80)*
Maternal occupation	*0.77 (0.73–0.81)*
Gestational smoking	**0.78 (0.74–0.82)**

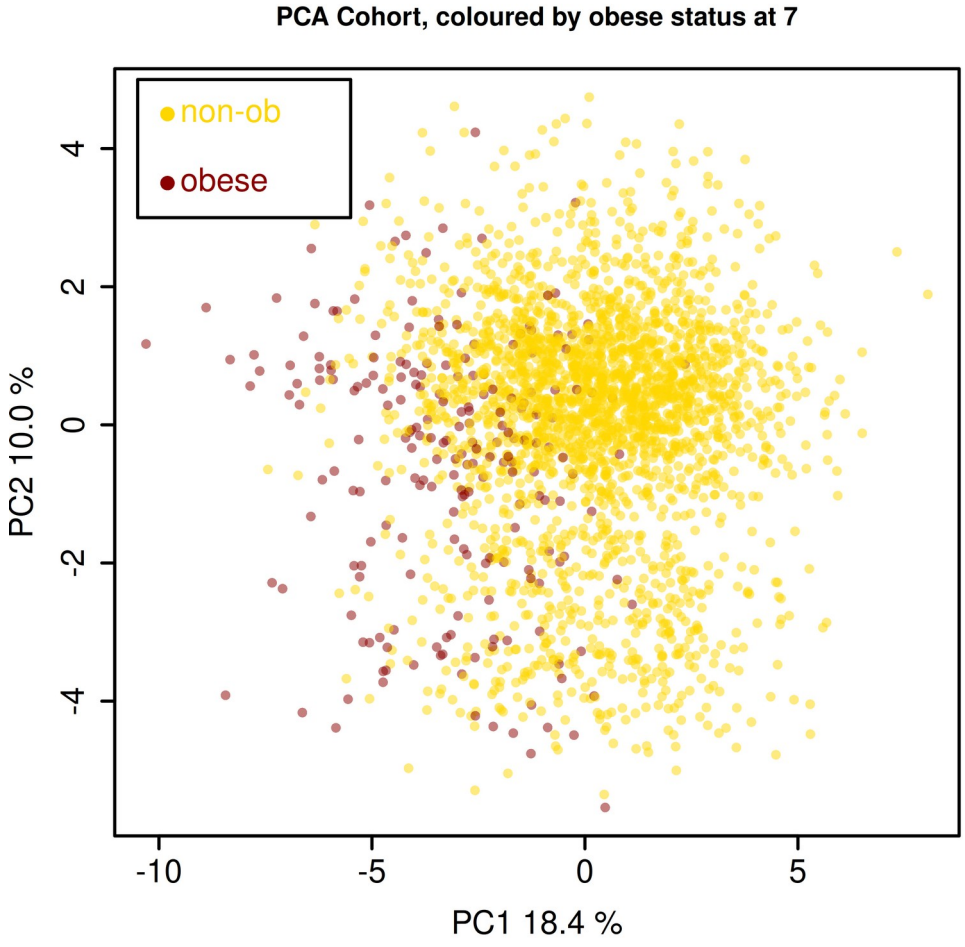
Morandi A, Meyre D, Lobbens S, Kleinman K, Kaakinen M, Rifas-Shiman SL, Vatin V, Gaget S, Pouta A, Hartikainen AL, Laitinen J, Ruokonen A, Das S, Khan AA, Elliott P, Maffeis C, Gillman MW, Järvelin MR, **Froguel P** (2012) Estimation of Newborn Risk for Child or Adolescent Obesity: Lessons from Longitudinal Birth Cohorts. *PLoS ONE* **7**(11): e49919. https://doi.org/10.1371/journal.pone.0049919

The Finn youth population is reasonably fit

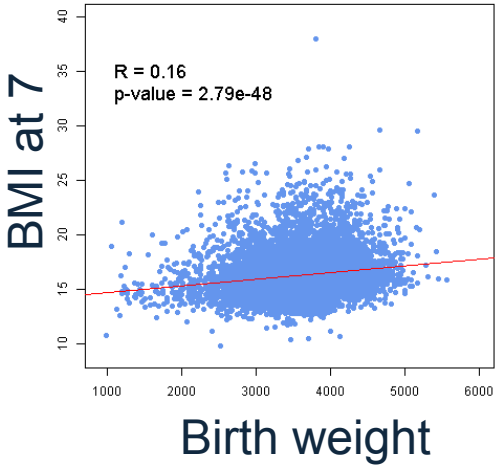


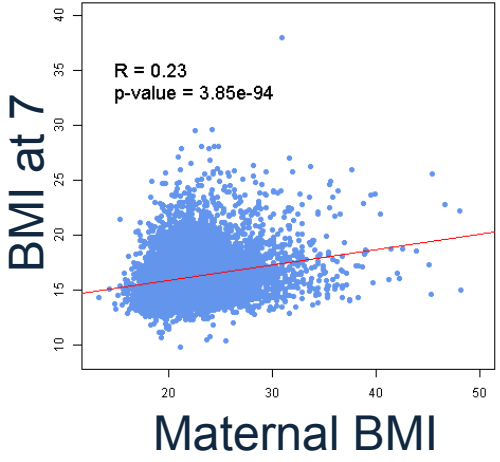
Obese *vs* non-obese differ but clusters are not well defined

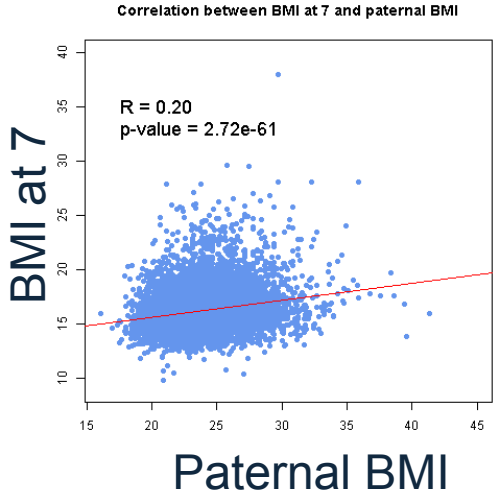




Few quantitative variables clearly correlate with obesity



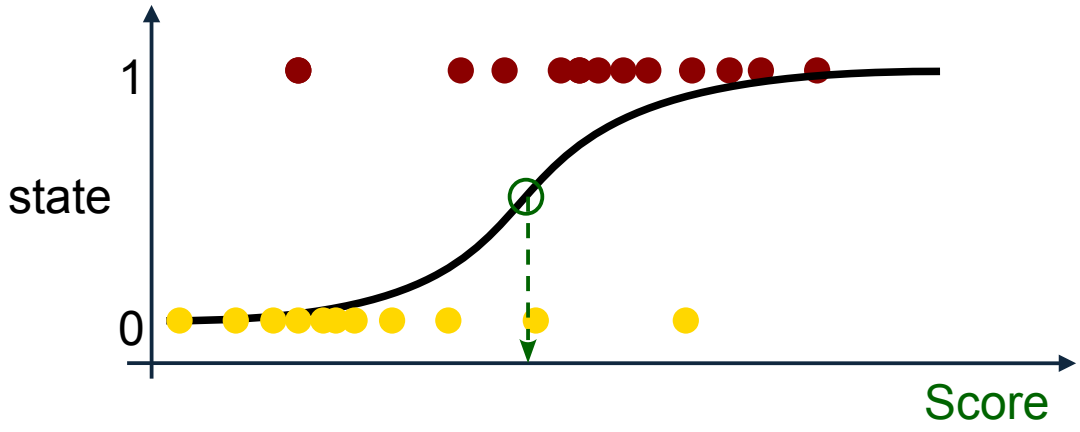




Morandi *et al* 2012, logistic regression

$$p(X) = \frac{1}{1 + e^{-(\beta_0 + \beta_1 V_1 + \beta_2 V_2 + \ldots)}}$$

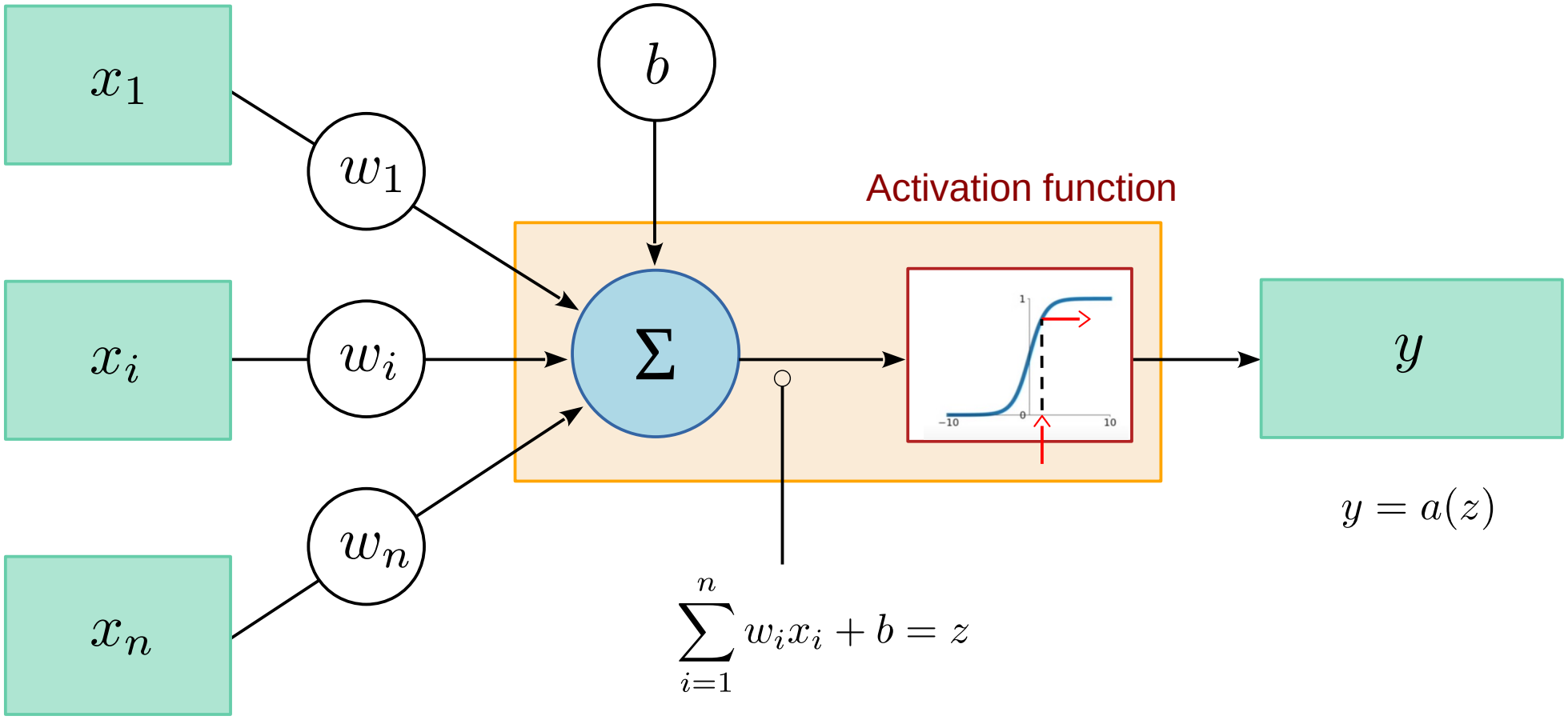
linear regression



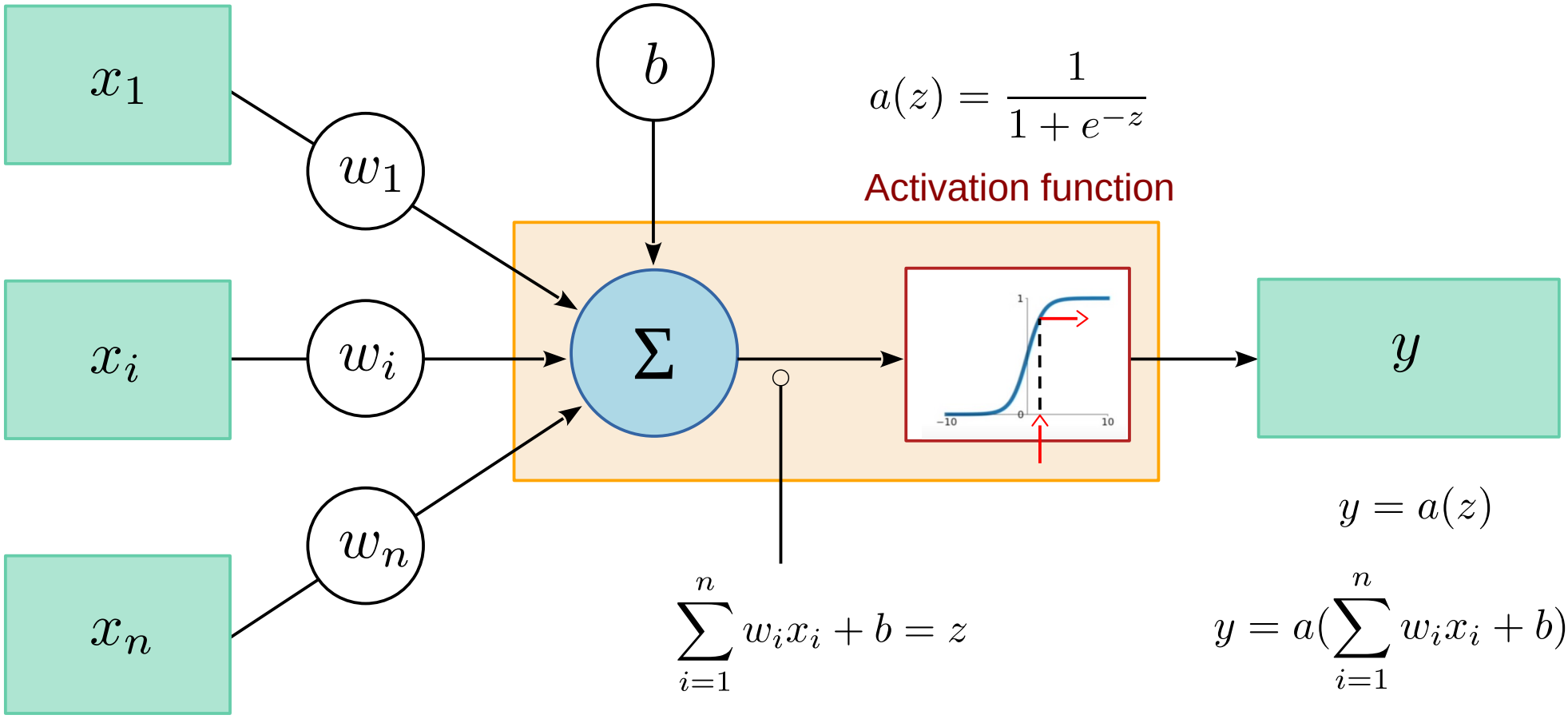
NFBC·1986:¶

Risk·for·childhood·obesity = e^(-10.61+0.12·x·maternal·BMI+·0.18·x·paternal·BMI·-0.31·x·number·of·household·members·-·0.69·x·maternal··occupation·+·0.61·x·gestational·smoking*·+·0.75·x·birth·weight)·/·(1·+·e^(-10.61+0.12·x·maternal·BMI·+·0.18·x·paternal·BMI·-0.31·x·number·of·household·members·-·0.69·x·maternal··occupation·+·0.61·x·gestational·smoking*·+·0.75·x·birth·weight))¶

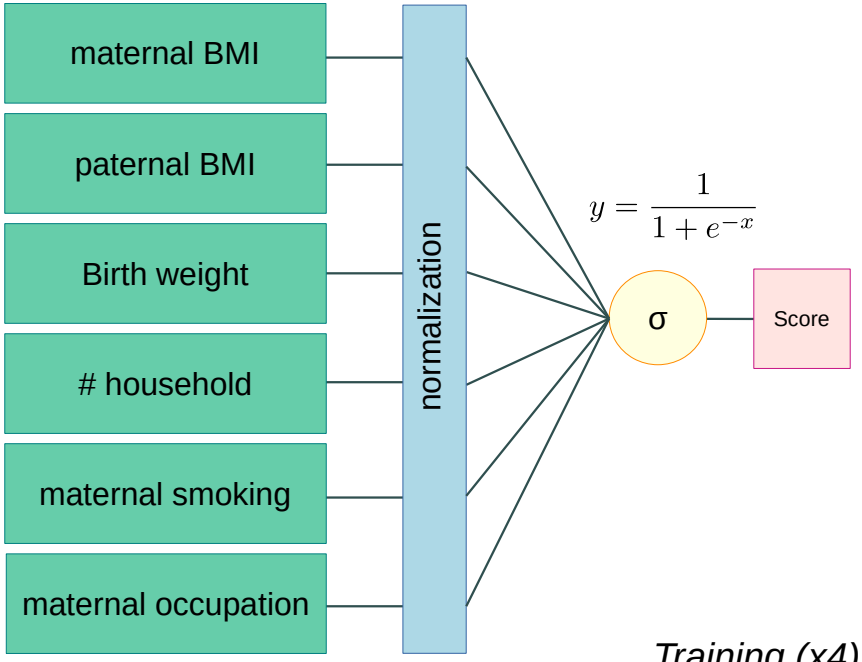
logistic regression ≈ 1 artificial neuron



logistic regression ≈ 1 artificial neuron



Let’s retrain Morandi



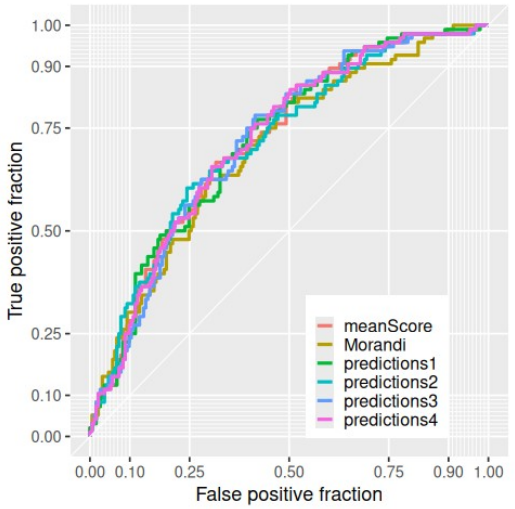
NB:
Maternal occupation
1 = unskilled/apprentice/unemployed
2 = skilled manual
3 = skilled non manual
4 = entrepreneur/professional

Training (x4)
290 obese
580 non-obese

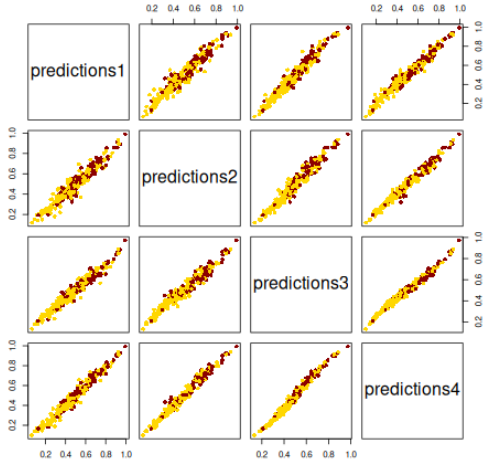
Test and Validation
96 obese
192 non-obese

AUC
Morandi = 0.701
Now = 0.72
Sensitivity = 64.6

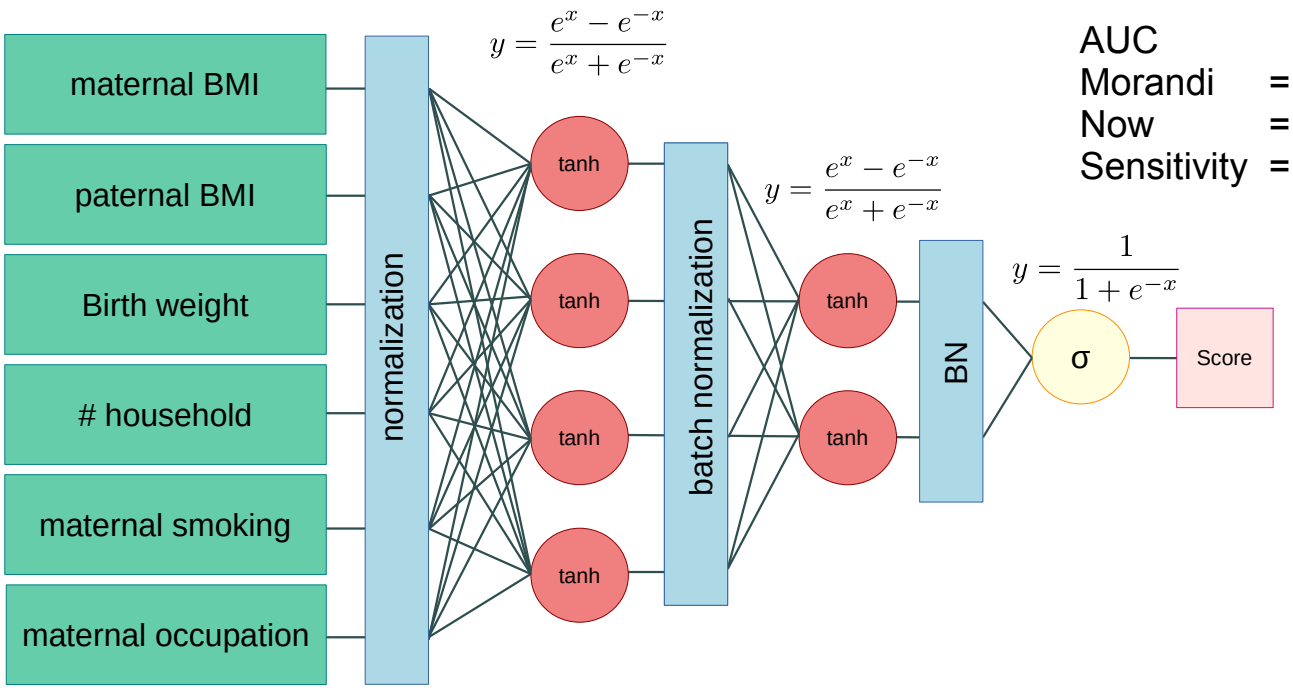
Validation set



Comparison models’ scores

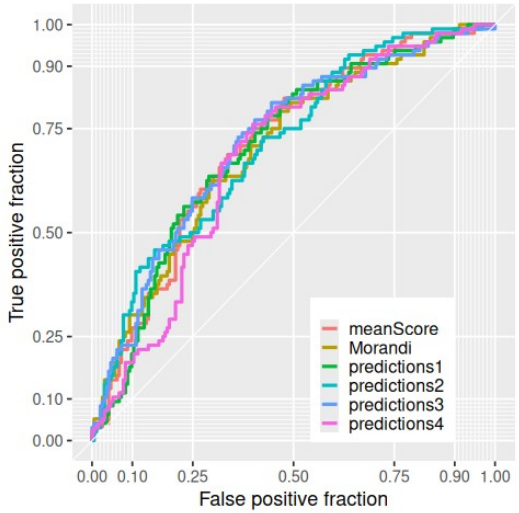


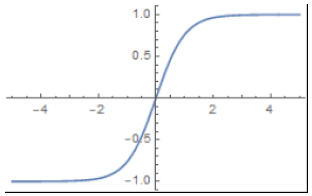
Can we improve on that?



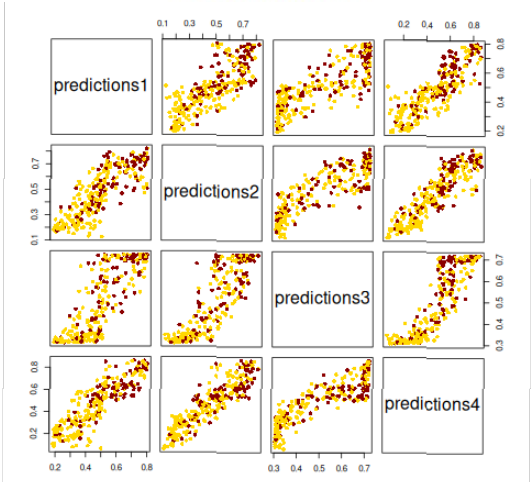
AUC
Morandi = 0.701
Now = 0.726
Sensitivity = 67.7

Validation set

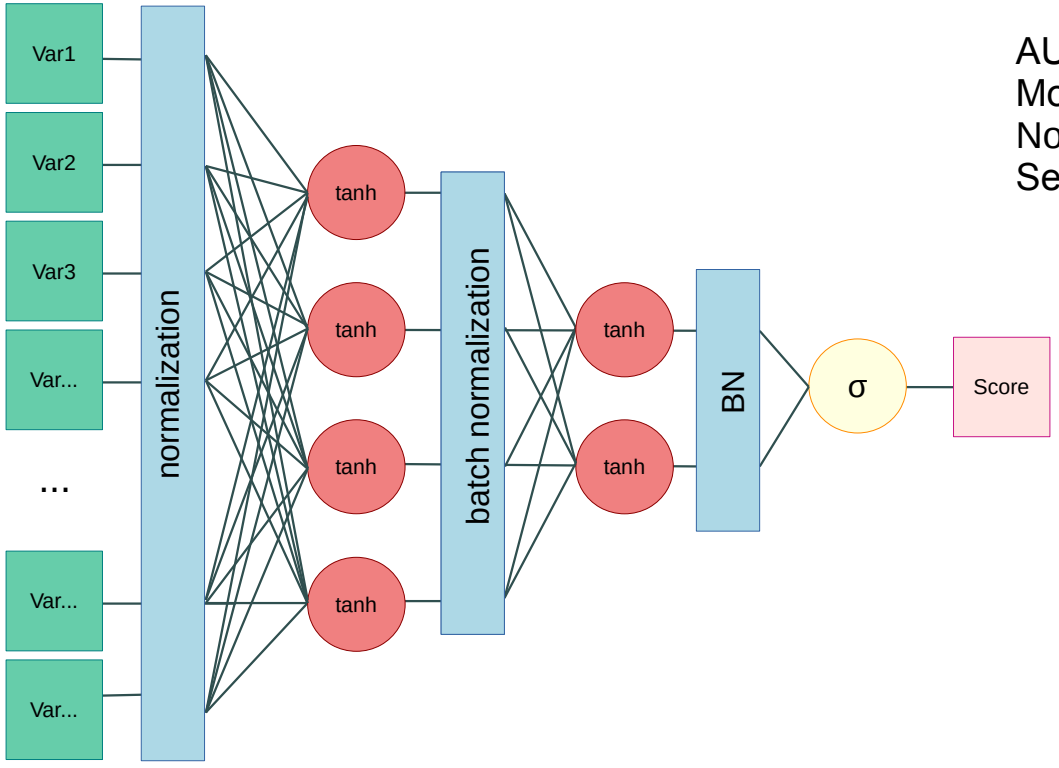




Comparison models' scores

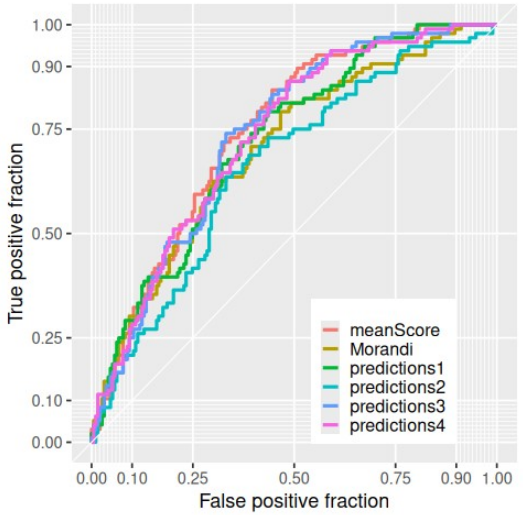


Increasing the number of variables

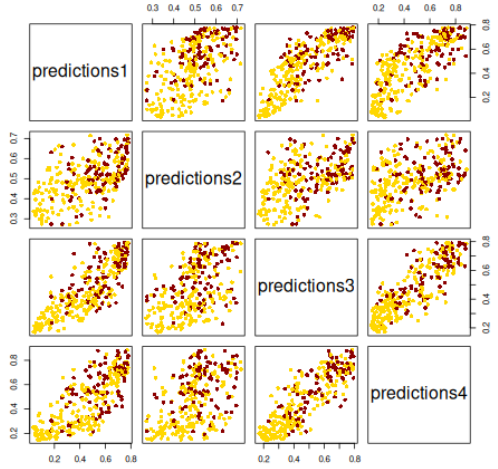


AUC
Morandi = 0.701
Now = 0.745
Sensitivity = 69.8

Validation set



Comparison models' scores

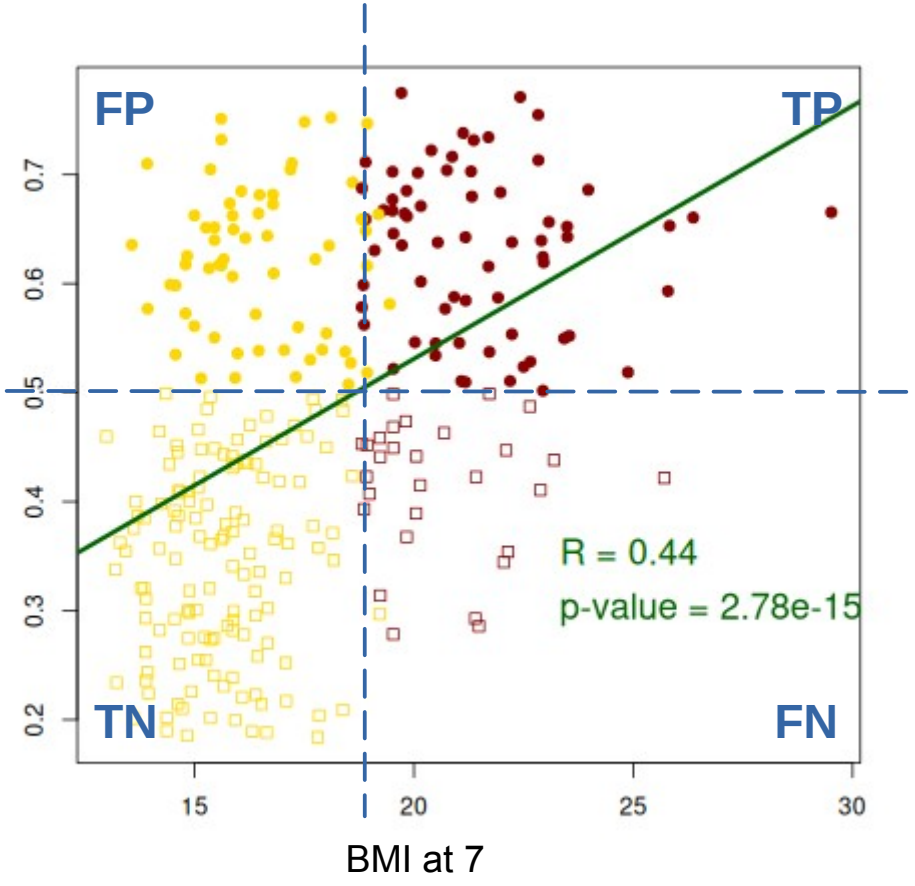


Variables =
gender, birth weight, BMI mat, BMI pat, gestational weight gain, # household, maternal smoking (2nd month), maternal and paternal alcohol, maternal and paternal education, maternal and paternal occupation

4 levels based on ISCED

How good is the prediction?

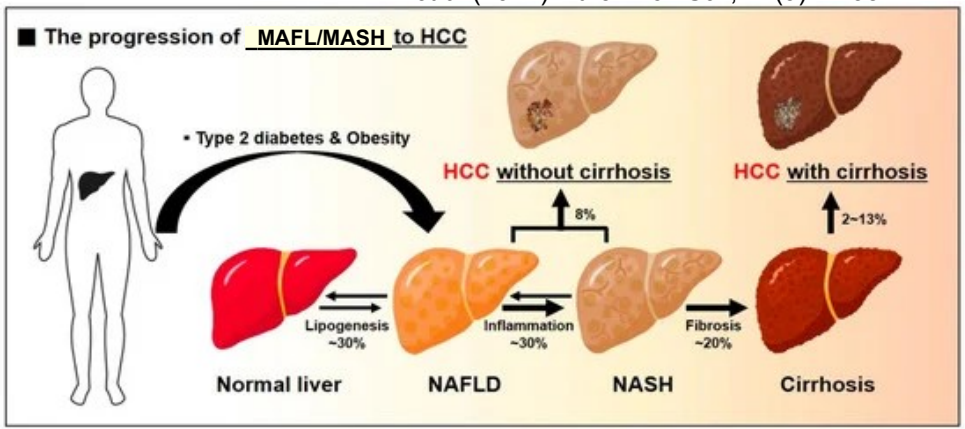
Over-zealous:
Stigmatising?

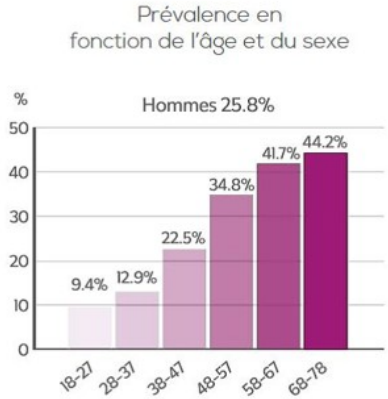


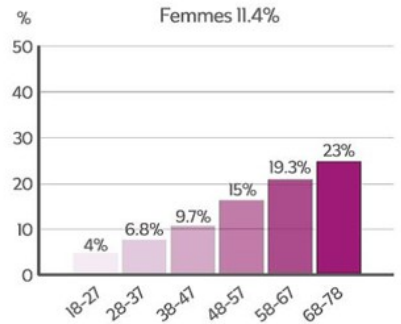
Missed:
Failure to duty?

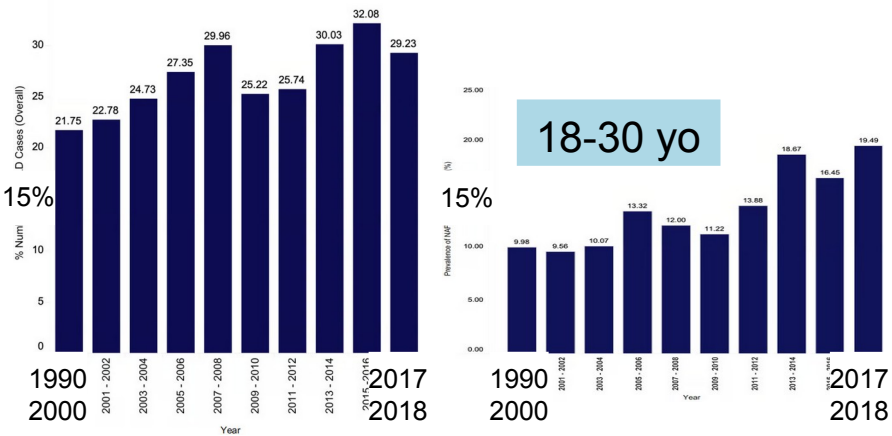
Omics data: recognising MASLD severity

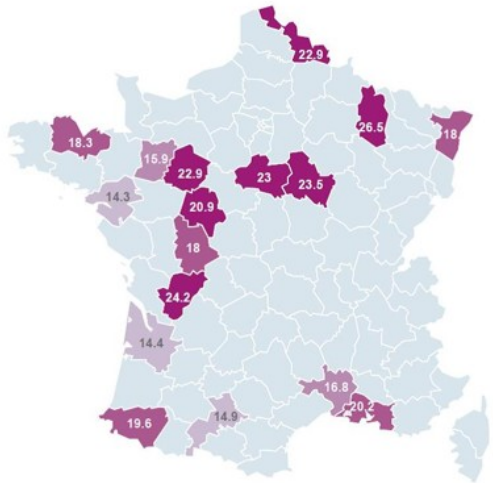
Kim *et al* (2021) *Int. J. Mol. Sci.*, 22(9): 4495











Répartition par régions

NASH
(now MASH)

Paris MASH Meeting

(11-12 juillet 2019)

Kim *et al* (2022) *Met. Target Organ Damage*, 2: 19

NALFD (now MASLD)

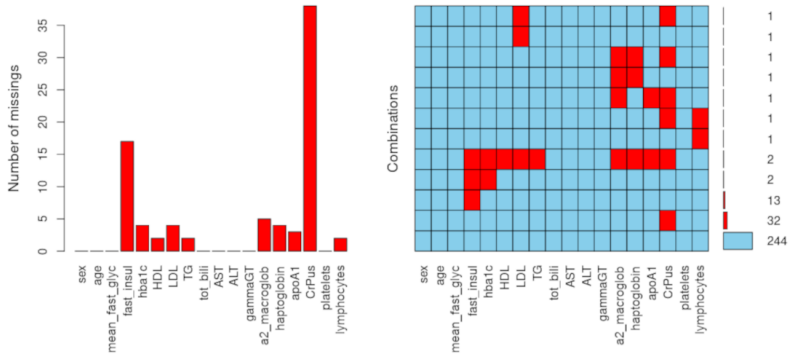
Biological and clinical variables

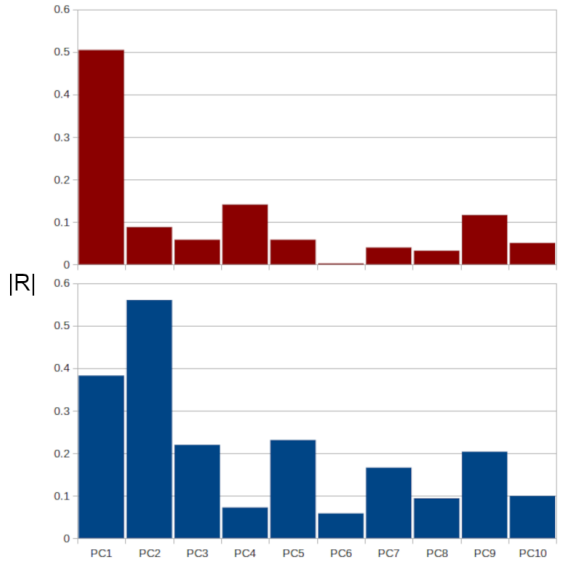
Definition	Type	Range; mean (SD)
Biological sex	Categorical (M, F)	Converted into {0, 1}
Age at the time of intervention	Quantitative	18-65; 4.56 (11.81)
Mean fasting glycaemia (mmol/l)	Quantitative	4.26-18.89; 7.24 (3.10)
Fasting insulinaemia (pmol/l)	Quantitative	11.11-7952.03; 238.83 (638.39)
Glycated haemoglobin (%)	Quantitative	4.4-14; 6.65 (1.76)
HDL cholesterol (mmol/l)	Quantitative	0.41-1.86; 1.11 (0.25)
LDL cholesterol (mmol/l)	Quantitative	0.85-6.44; 3.03 (0.89)
Triglycerides (mmol/l)	Quantitative	0.41-16.01; 1.87 (1.53)
Total bilirubin (mg/l)	Quantitative	1.5-14; 4.76 (2.14)
Aspartate transaminase (UI/l)	Quantitative	8-113; 31.36 (16.23)
Alanine transaminase (UI/l)	Quantitative	8-161; 40.15 (24.91)
Gamma-glutamyltransferase (UI/l)	Quantitative	7-380; 54.41 (56.01)
α2 macroglobulin (g/l)	Quantitative	0.31-3.7; 1.78 (0.56)
Haptoglobin (g/l)	Quantitative	0.27-5.08; 2.02 (0.73)
Apolipoprotein A1 (g/l)	Quantitative	0.77-2.48; 1.46 (0.24)
Ultrasensitive CRP (mg/l)	Quantitative	0.17-11.1; 6.70 (3.09)
Platelets (10^9/l)	Quantitative	130-460; 272.06 (60.86)
Lymphocytes (10^9/l)	Quantitative	0.3-5.4; 2.43 (0.72)

Among 66 available, ignoring redundant, overlapping, and irrelevant ones

Biological and clinical variables

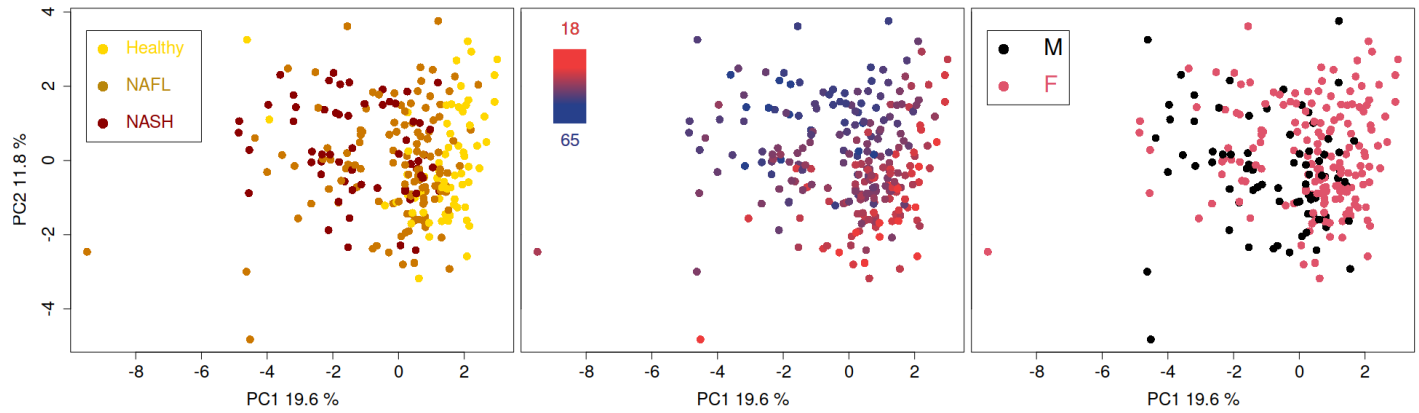
Missing data
→ Imputation





PCA, correlation with severity

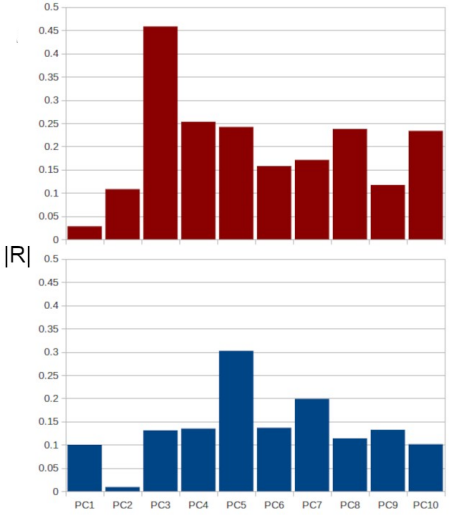
PCA, correlation with age

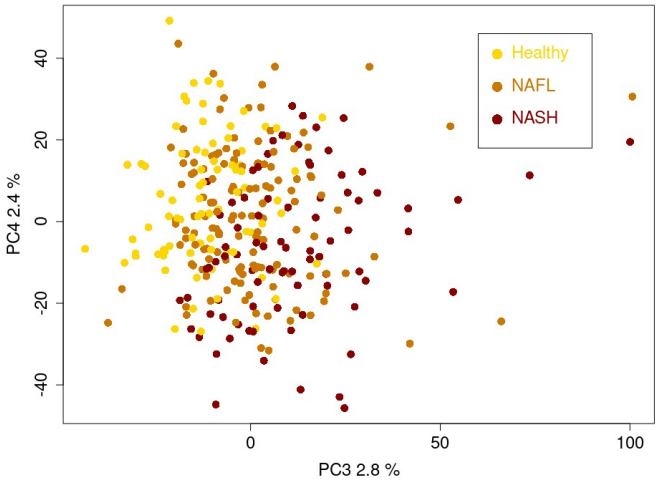


Omics features: RNA-seq

PCA, correlation with severity

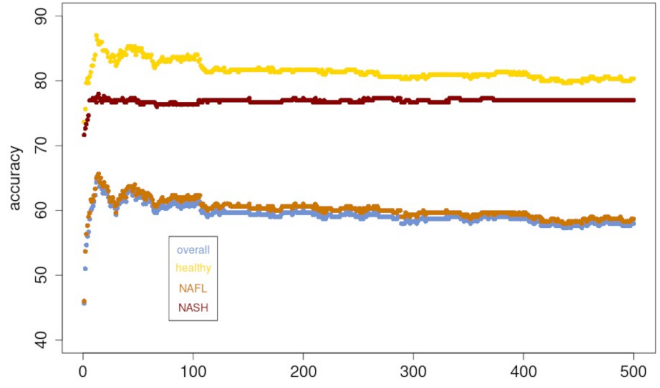
PCA, correlation with age

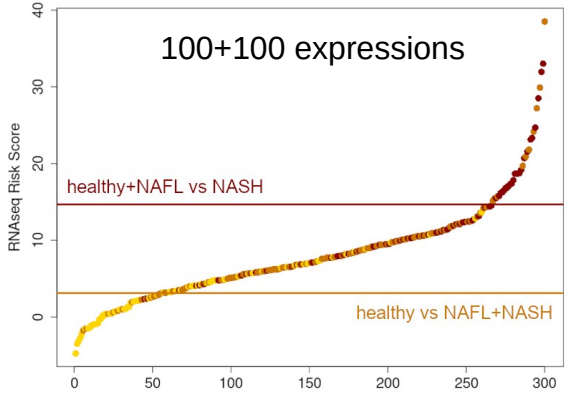




Logistic regressions on RNA score

$$\sum_{i=1}^{n} log(CPM_i + 1) \times PC3\text{load}_i$$



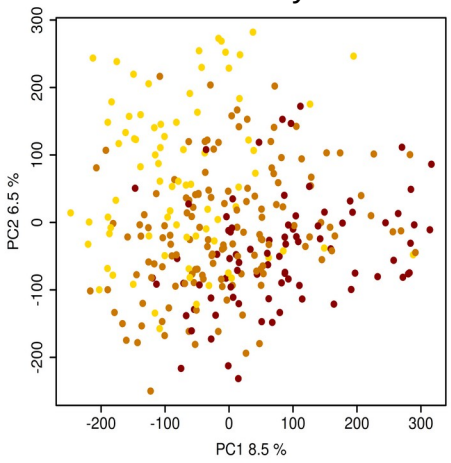


Subjects ranked by RNA scores

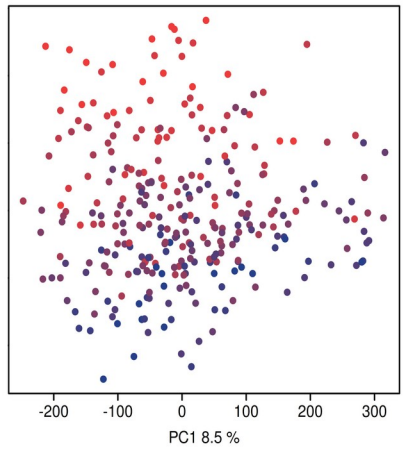
Omics features: DNA methylation

Before correction

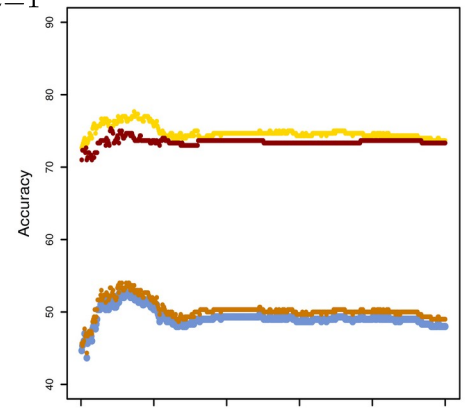
Severity



Age



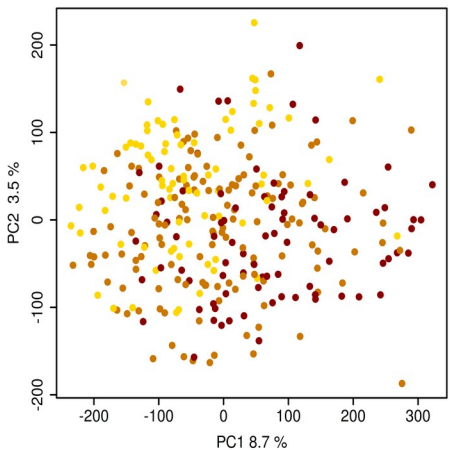
$$\sum_{i=1}^{\#\mathrm{CpGs}} \mathrm{Methyl}(\mathrm{CpG_i}) \times \mathrm{PC1load}(\mathrm{CpG_i})$$

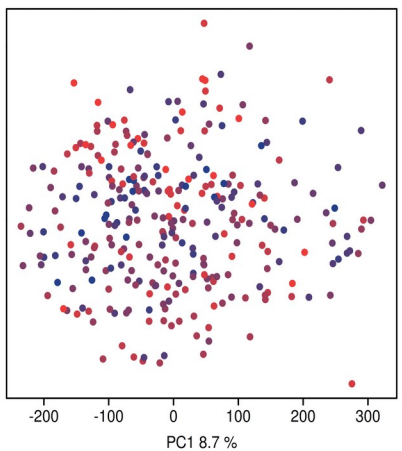


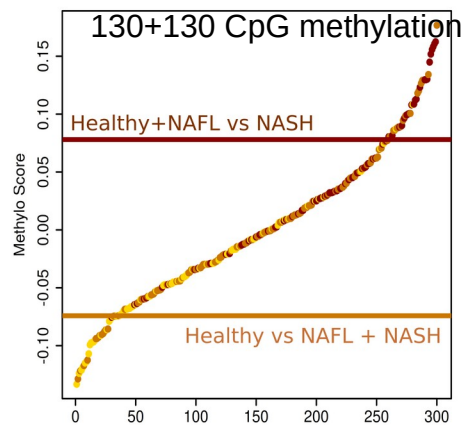
Correction for age:
For each CpG

$$\hat{M}_i = a_0 + a_1 \times age_i + \varepsilon_i$$

After correction

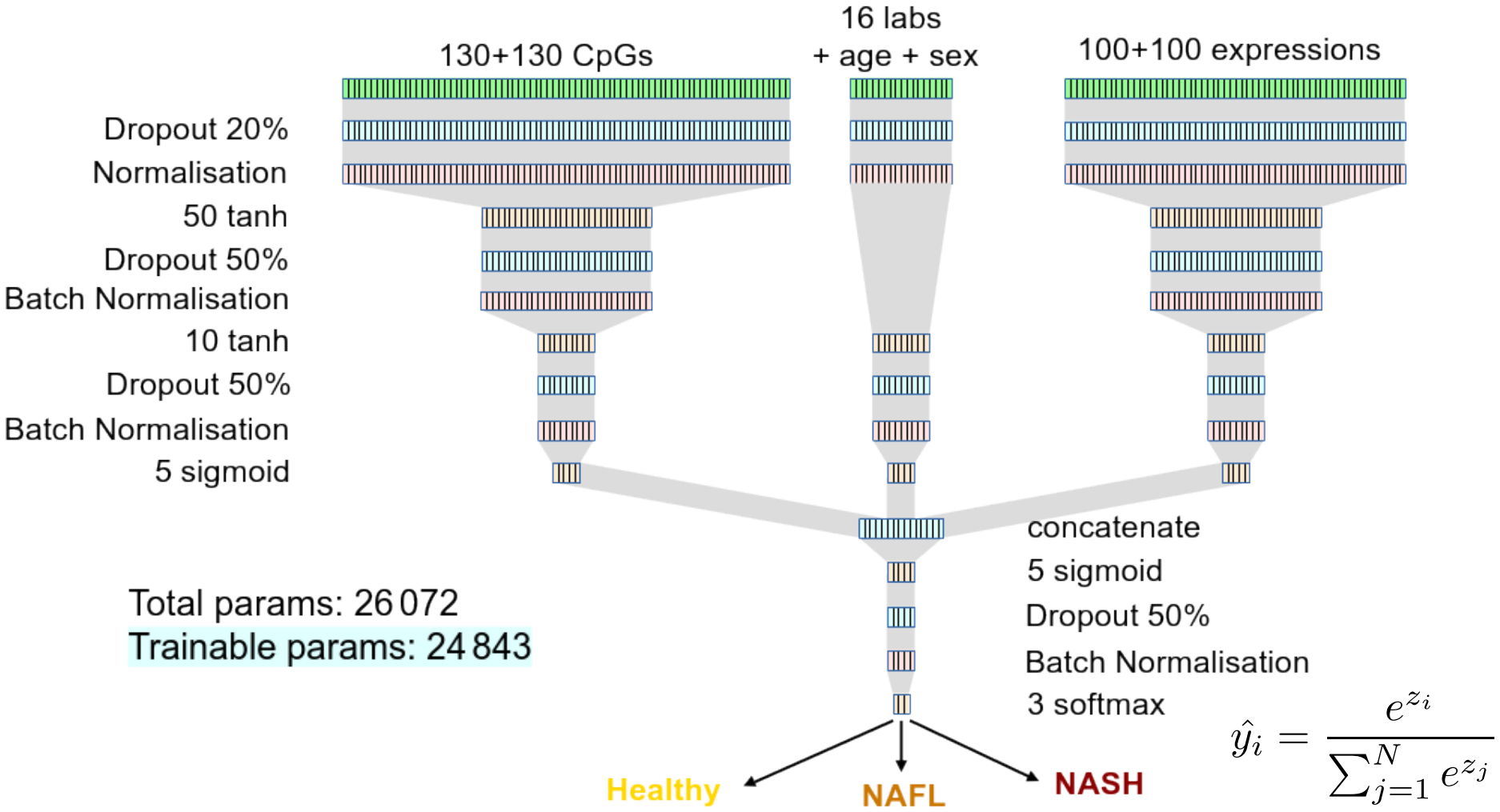






Subjects ranked by methylation scores

Multi-module multilayer perceptron

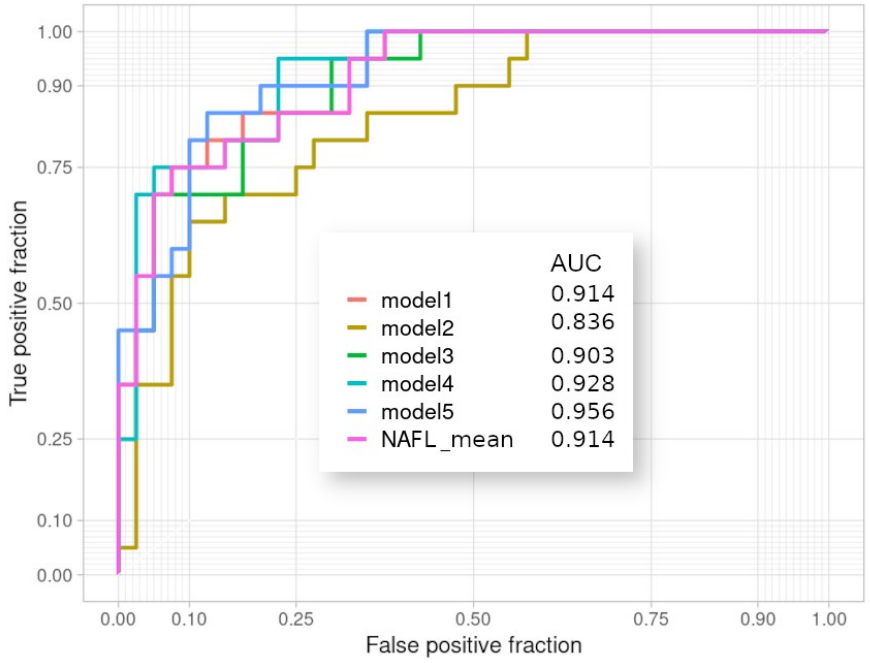


Total params: 26 072
Trainable params: 24 843

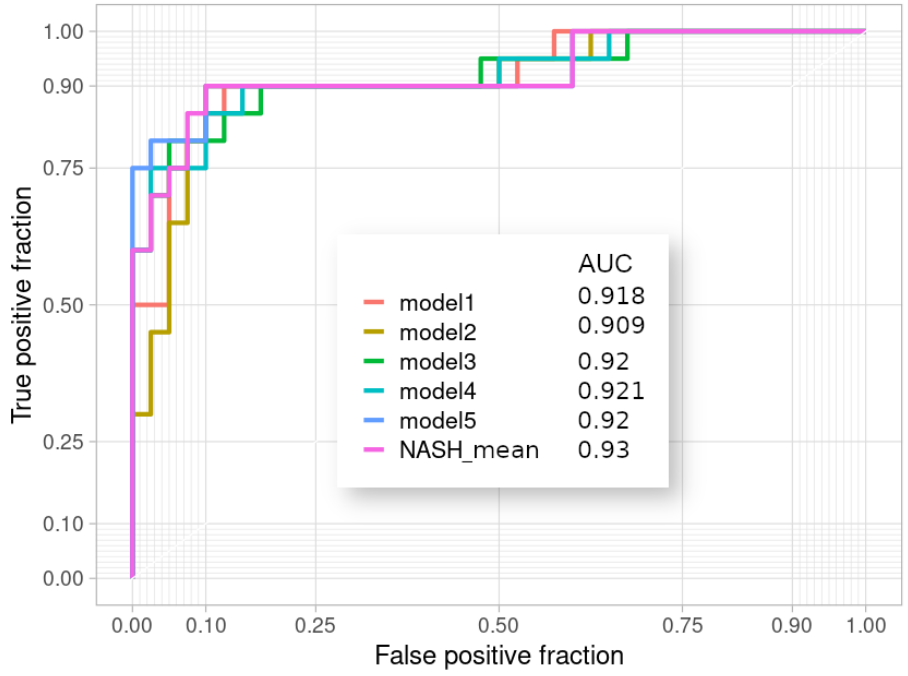
$$\hat{y}_i = \frac{e^{z_i}}{\sum_{j=1}^{N} e^{z_j}}$$

Performance on validation set: AUC > 0.9 for NAFL and NASH

sensitivity

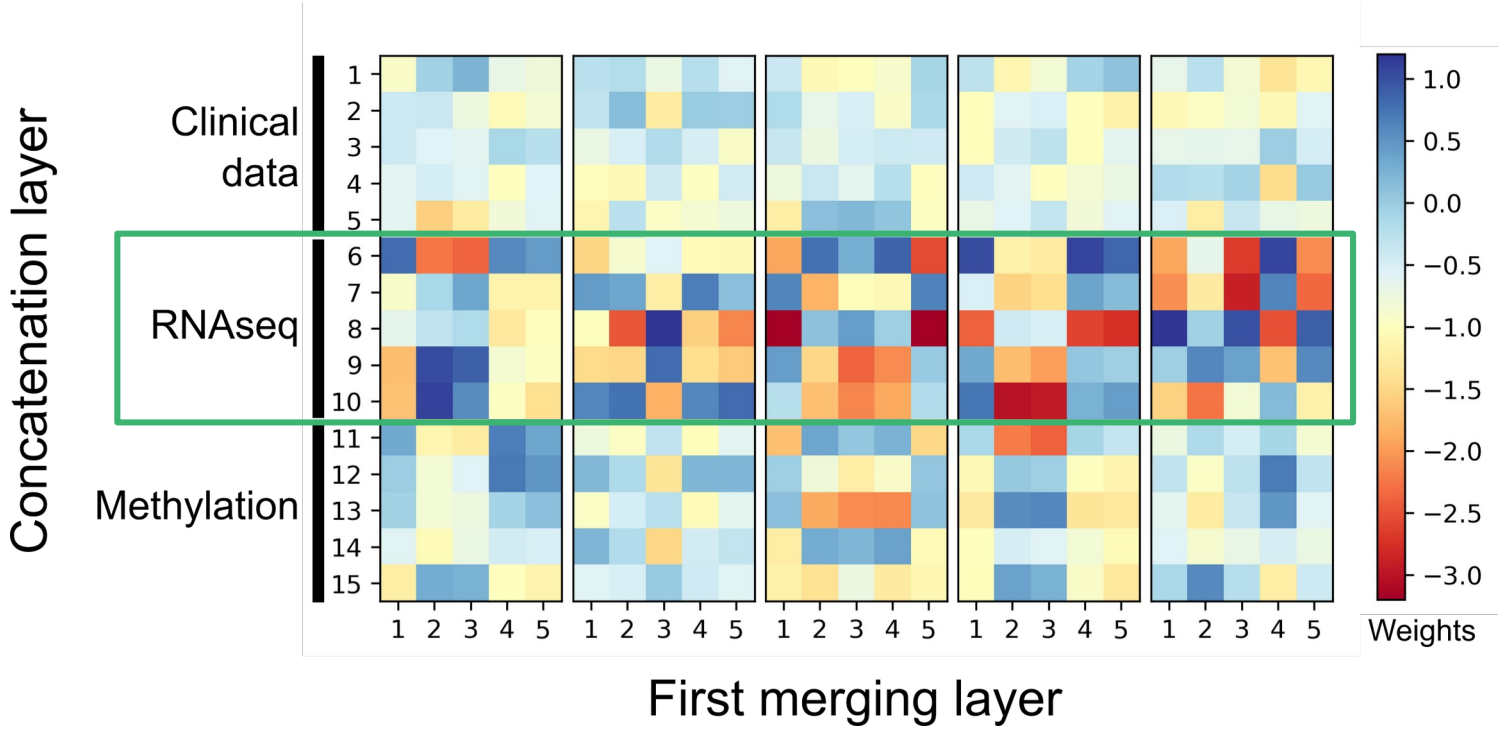


1 - specificity

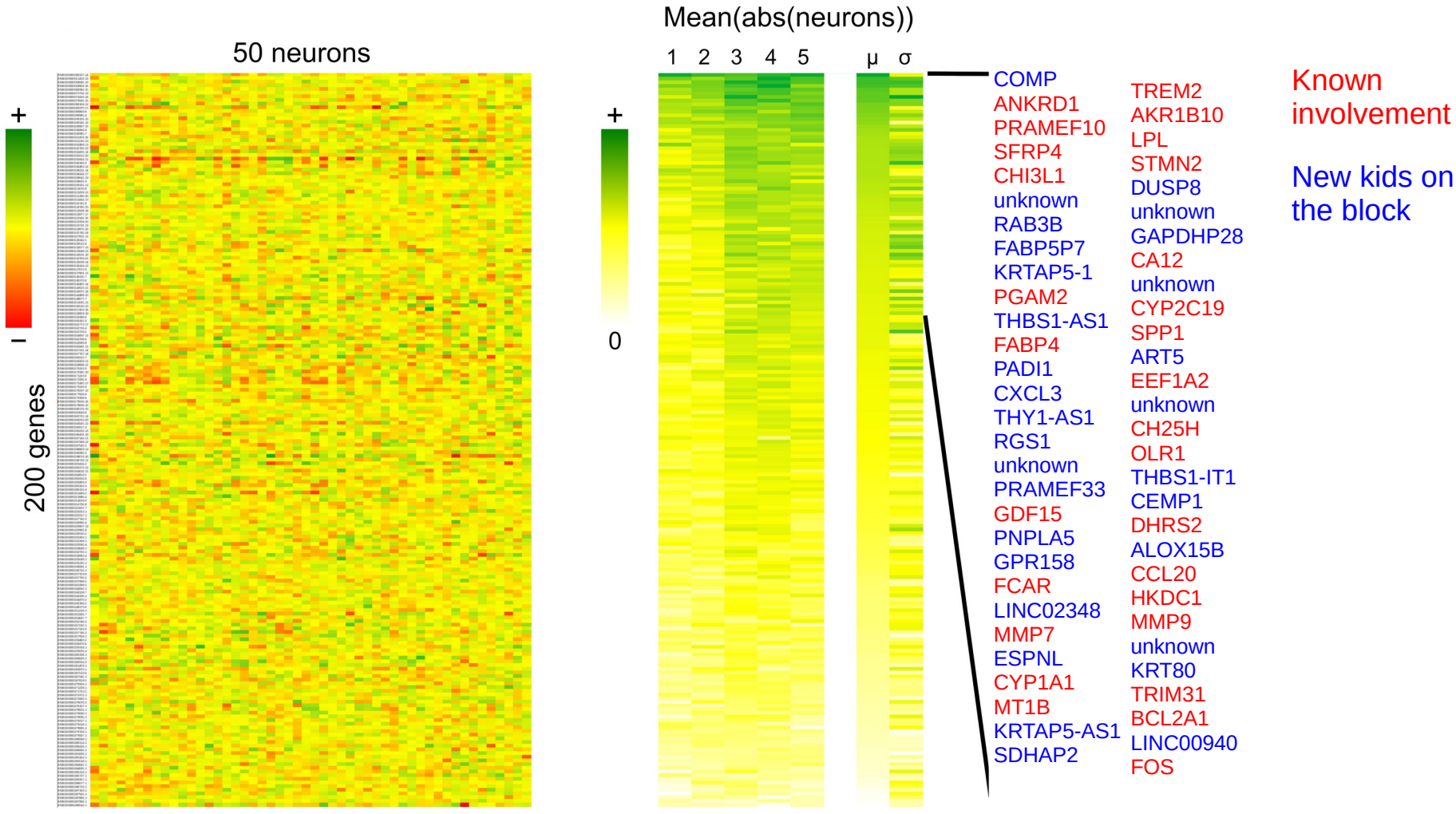


1 - specificity

Peeping into the black box: RNA-seq is key



What are the most impactful genes; old culprits, new faces

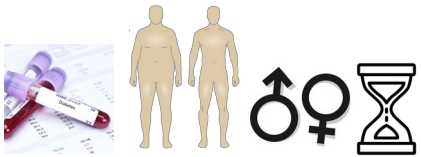


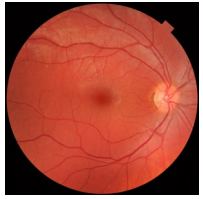
Coming collaborations

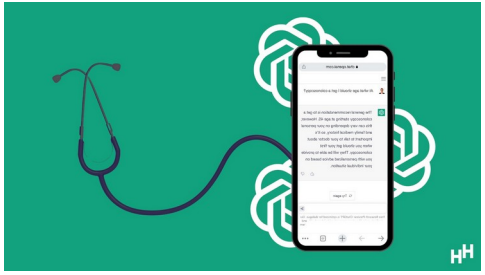
- Dark metabolome
  - Collaboration with Francesc Puig-Castellvi
  - Liquid Chromato-High Rex Mass Spec Metabolomics
  - **Aim:** Increase the annotated metabolites and unravel their role
- Biological clocks
  - Collaboration with Marc-Emmanuel Dumas
  - ECG, DNA methylation, metabolomes
  - **Aim:** Comparing cardiac, epigenetic, and metabolic aging
- Adiposity, physical activities and cardiometabolic diseases
  - Collaboration with CHUV, Colaus cohort
  - Genetic, clinical and demographic data,
    plus adiposity and physical activity. Longitudinal over 25 years
  - **Aim:**Predict disease trajectories, anticipate comorbidities
- Cardiometabolic diseases
  - Collaboration with Inria and University of Evry (multi-cohorts)
  - Digital twins:
    Genetic foundation models + Graph neural networks
  - **Aim:** better understand underpinning molecular pathways

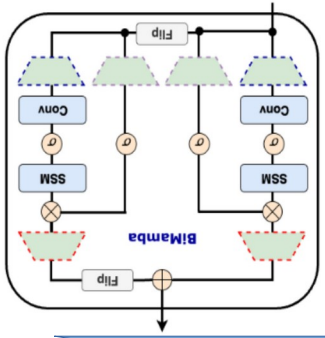
Next-Gen AI for CMDs: multi-modality

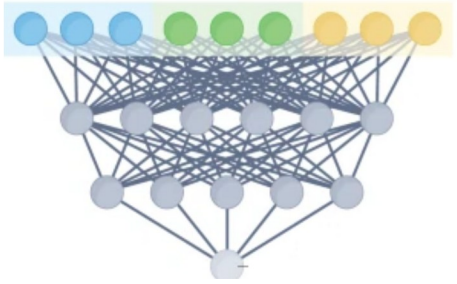
rs4661310	CC
rs4920461	GA
rs11249215	GG
rs12116935	TA
...	

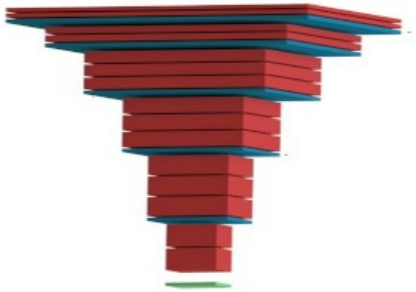












How, what, when, who, why
Understand, predict, prevent, cluster, care better

Acknowledgments

The group
Smaïn Fettem
Marwa Afnouch
Omaima Binan
Sami Le Guilcher

The tools
R package developers
(*VIM*, *MICE*, *DESEq2*, *ChAMP*)

Python package developers
(*Tensorflow/Keras*, *Numpy*, *Pandas*, *Scikit-learn*)

Egenodia
Philippe Froguel
Amélie Bonnefond

Mathilde Boissel
Mehdi Derhourhi
Emma Henriques
Stefan Gaget
ShuangShuang Geng
Anne-Sophie Ledoux
Vincent Massy
Lijiao Ning

Marc-Emmanuel Dumas
Amna Khamis
Francesc Puig-Castellvi

Hélène de Gavre
Mélanie Hocquet

PreciNASH
François Pattou
Violetta Raverdy

Obelisk
Anita Morandi
Rozenn Nedelec
Susanna Pätsi
Sylvain Sebert

PreciDIAG
Marjorie Fadeur
Nicolas Paquot

PreciDIAB
National Center for Precision Diabetic Medicine

cnrs

Université de Lille

UMR 1283 8199
Functional (Epi)genomics and Mechanisms of Type 2 Diabetes and Related Diseases

anr

Région Hauts-de-France