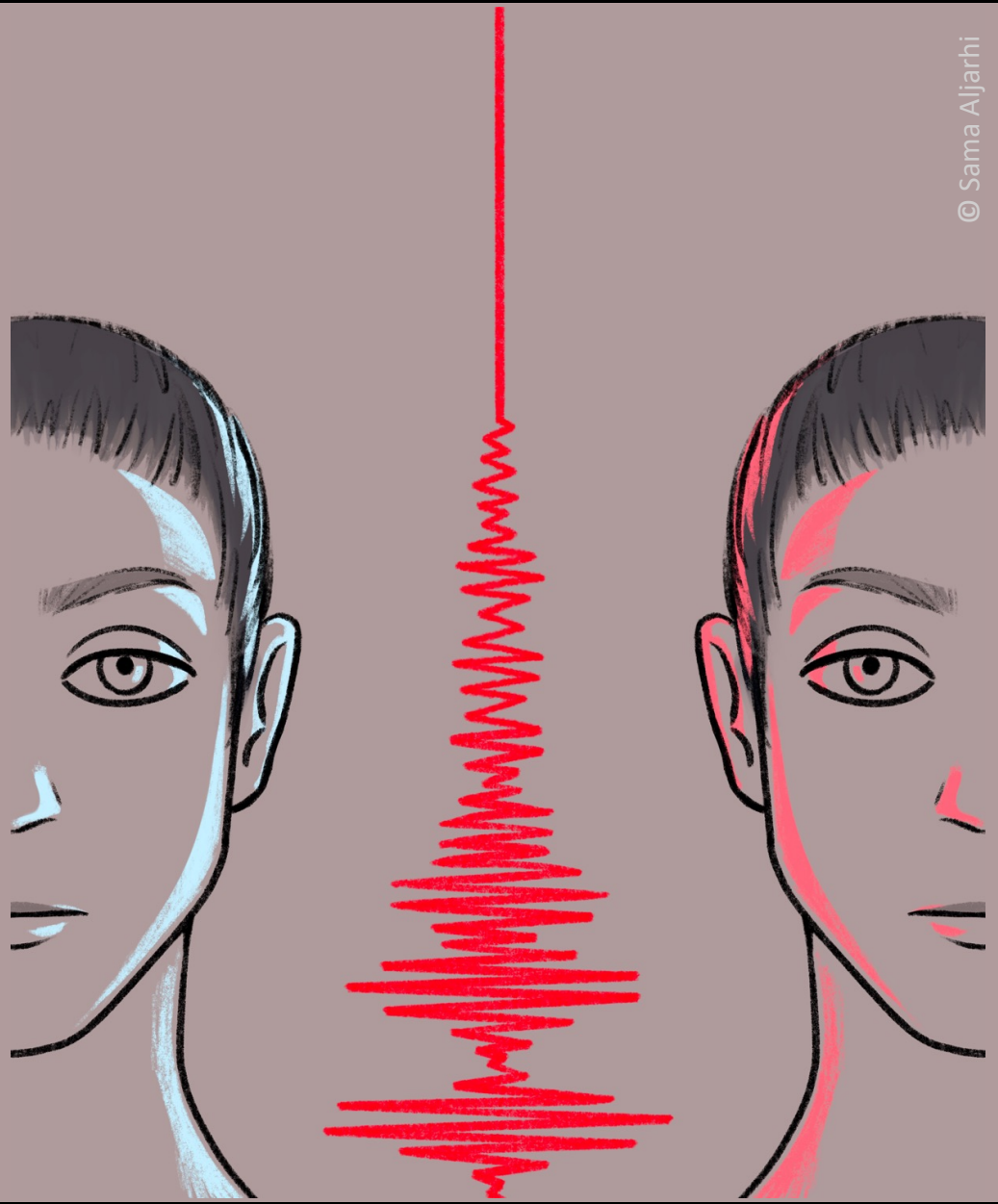
LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

MAX PLANCK INSTITUTE
OF QUANTUM OPTICS

Infrared molecular spectroscopy to better understand human health and disease

Mihaela Žigman



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Broadband InfraRed Diagnostics, *BIRD*

- Establish and apply ***infrared molecular spectroscopy*** and analytics to quantify system-level physiology.
- Profiling multi-molecular, health and cross-disease patterns, to identify strategies that improve patient outcomes.

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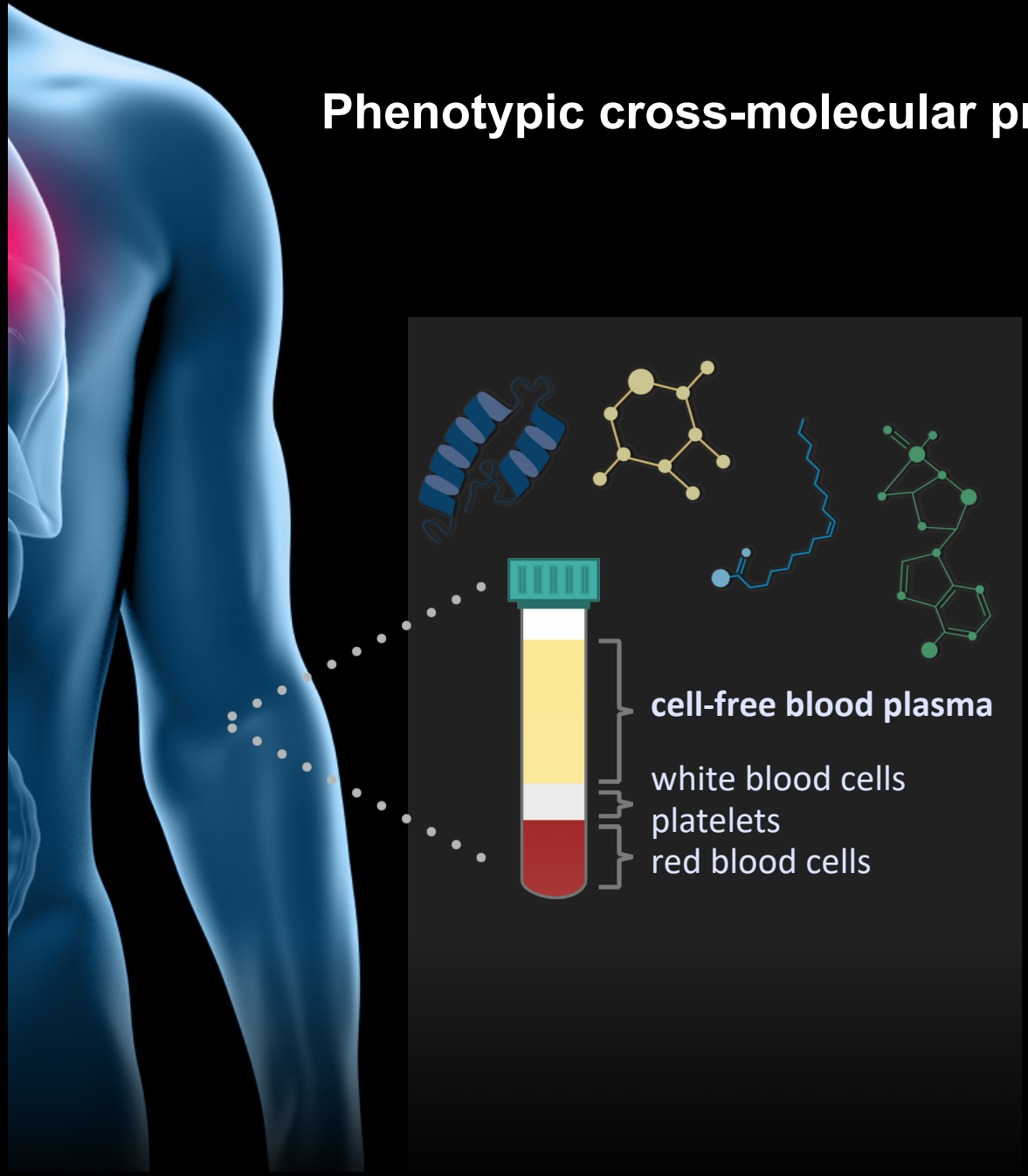
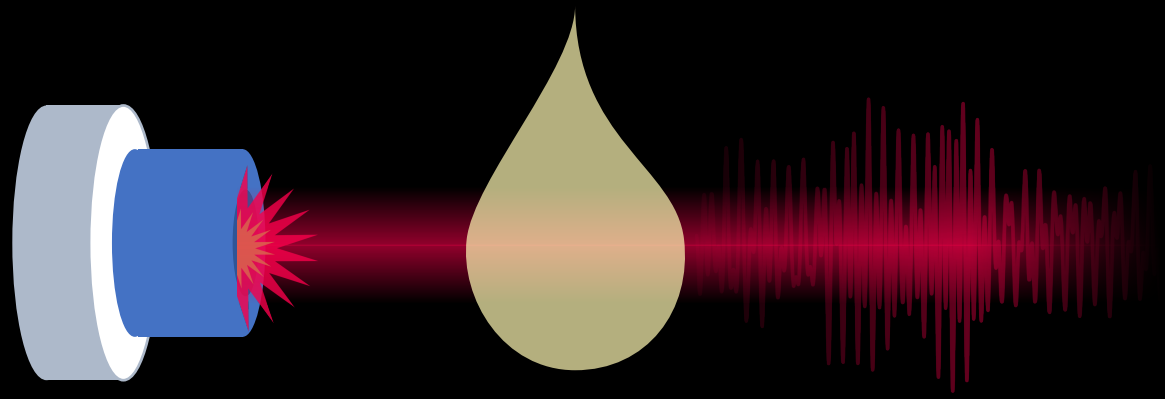
Phenotypic cross-molecular probing for *in vitro* medical diagnostics

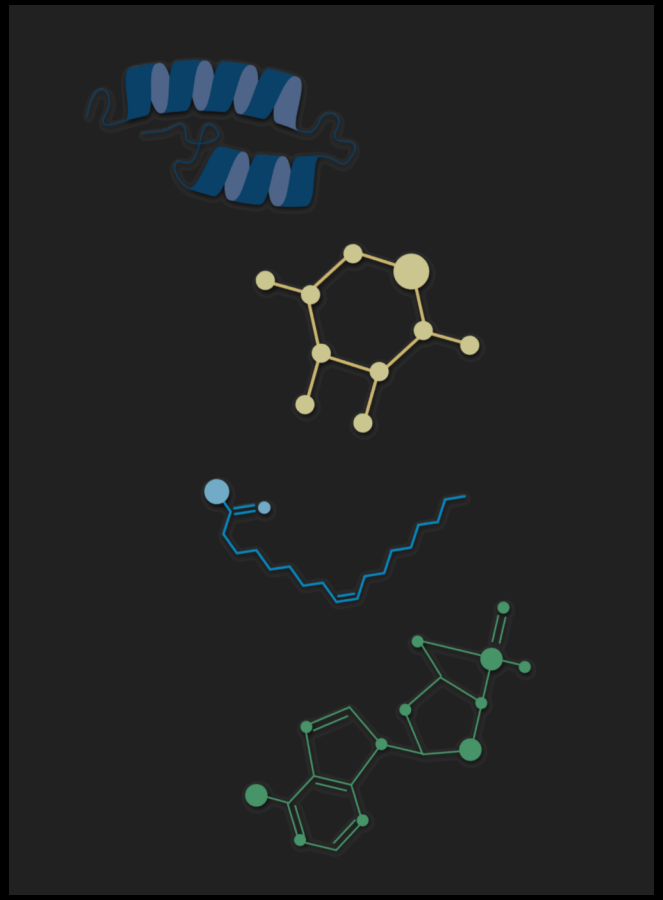


BROADBAND midIR VIBRATIONAL SPECTROSCOPY



- combination of patterns >> INFRARED MOLECULAR FINGERPRINT
- amplitude > quantity of bonds
- positioning > chemical bond identity

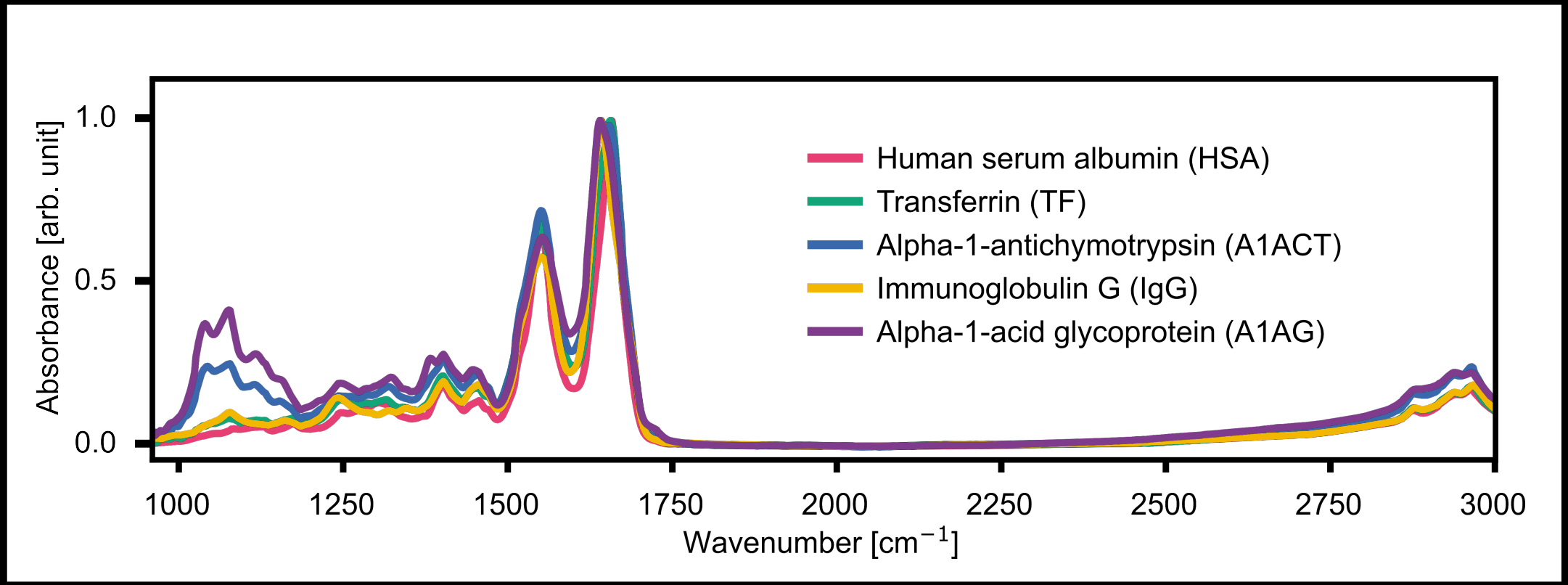
Molecular complexity of human blood-based matrices



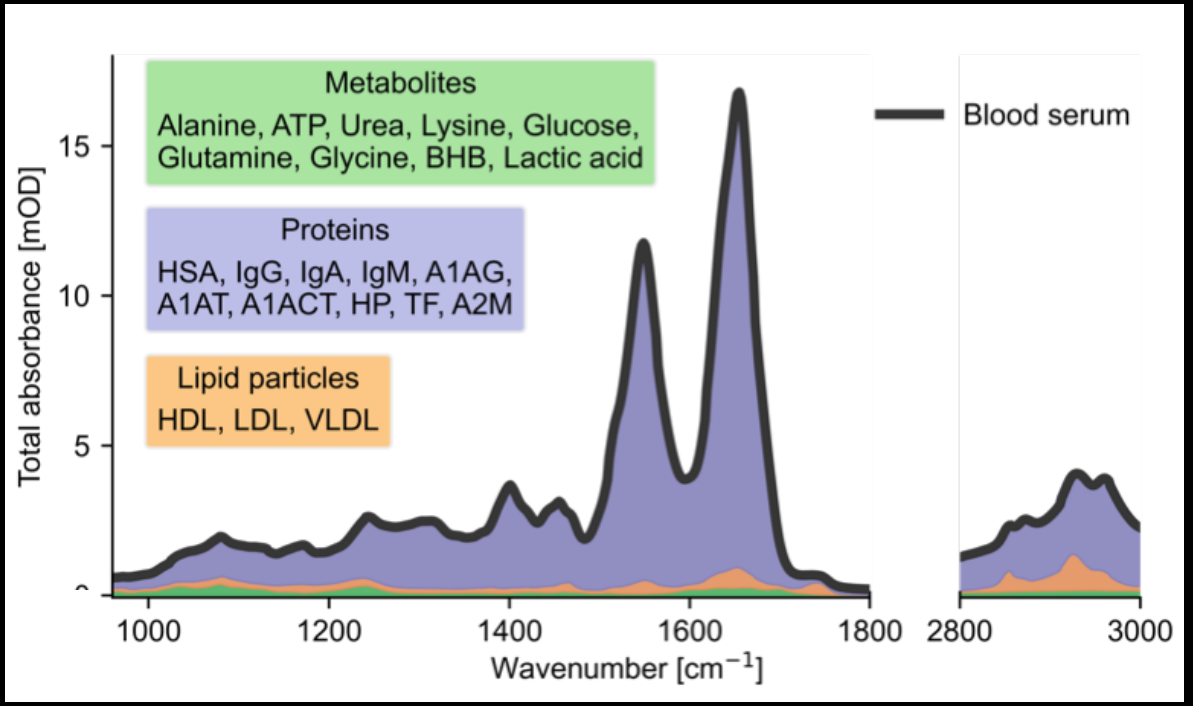
	PROTEINS	GLYCO-PROTEINS	METABOLITES	LIPIDS	GLYCANS
estimate (total)	75.000 (millions of isoforms)	>7.000	200.000 (millions of isoforms)	3.000	≥7.000
detected in **blood plasma**	12.000	2.000	18.000	590	>300

Molecular complexity of human blood-based matrices

Proteins



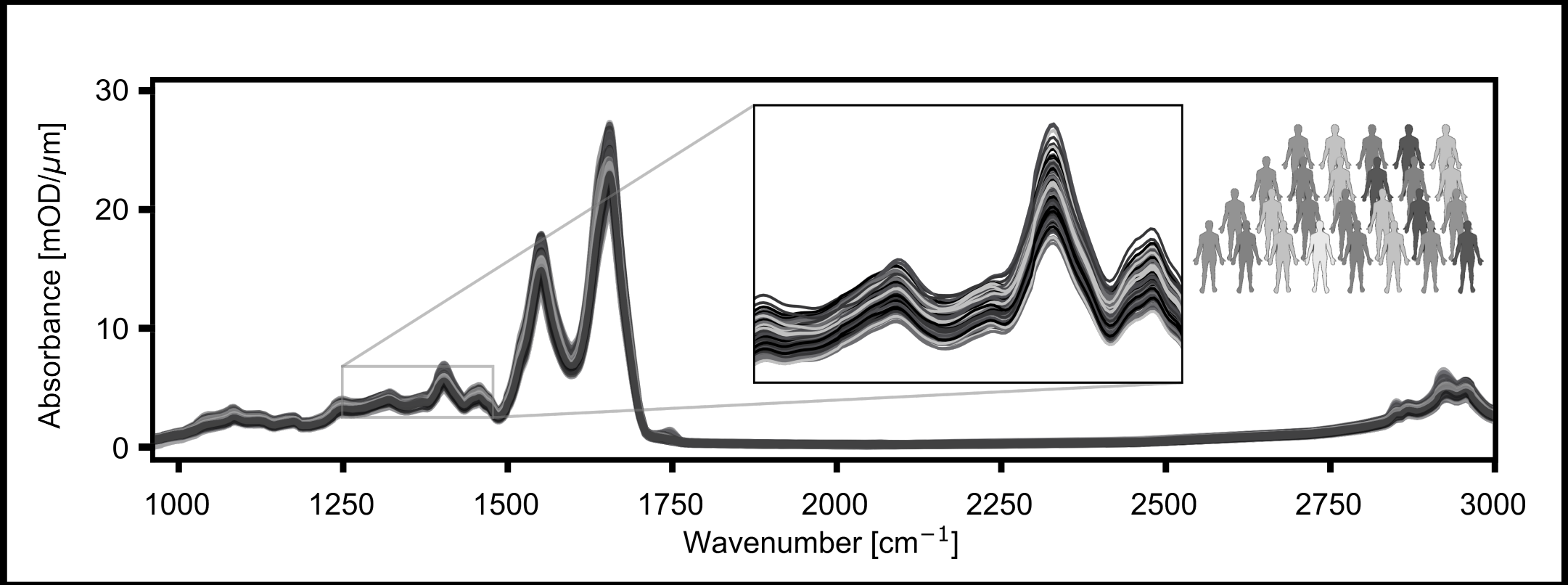
Decoding & Understanding of infrared molecular fingerprints



Eissa et al., Zigman. ***Angewandte Chemie**, Sept 2024*

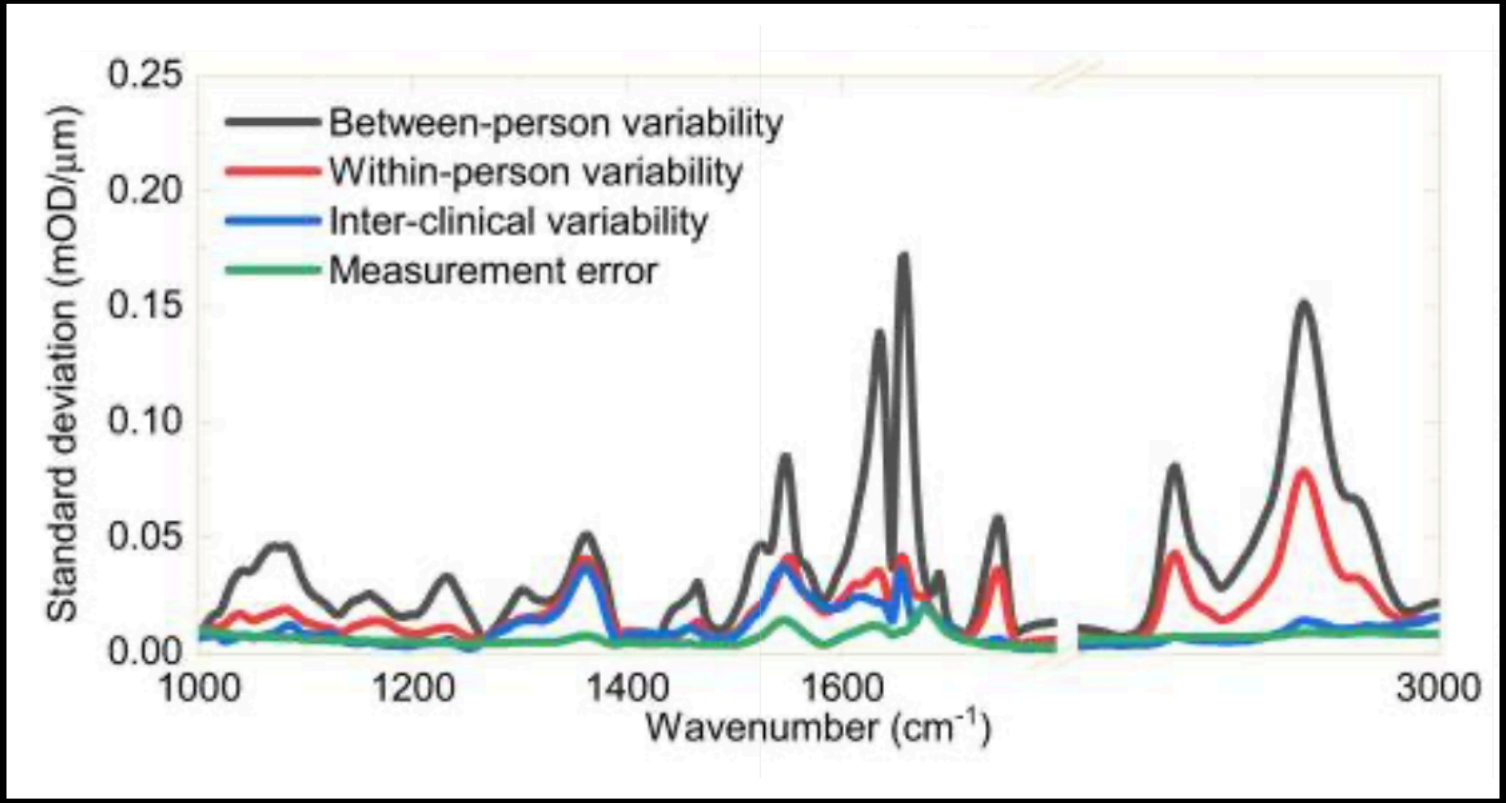
Infrared spectroscopy to probe complex multi-molecular matrices

probing crude human blood plasma



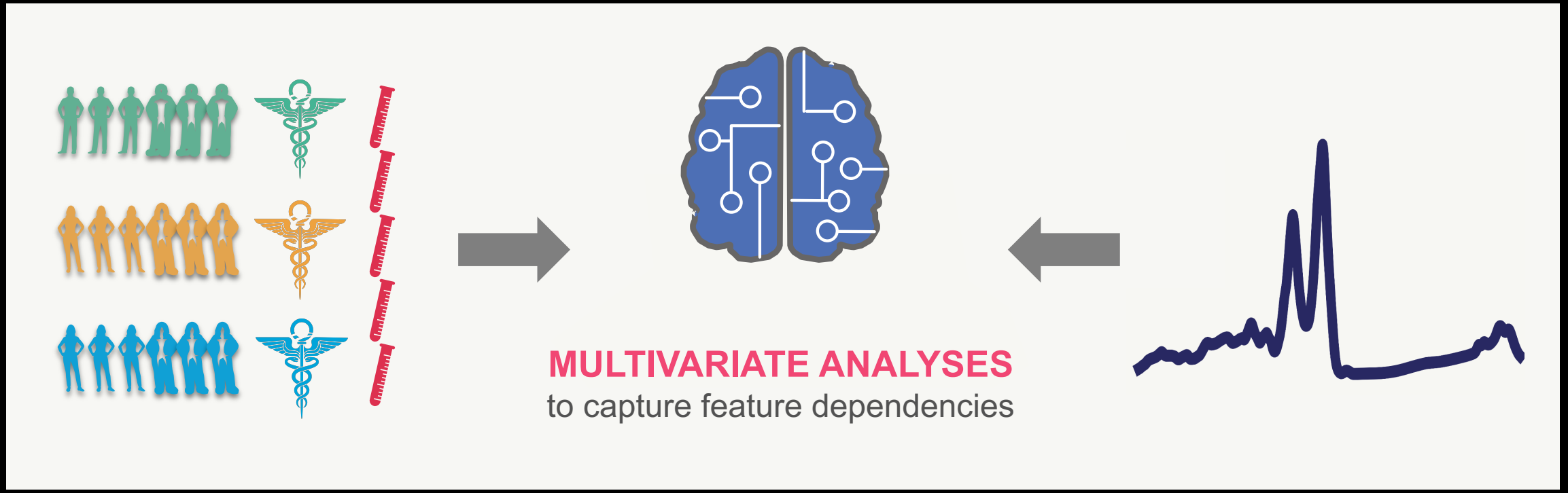
Infrared spectroscopy to probe complex multi-molecular matrices

probing crude human blood plasma



Huber et al., Zigman. ***Nature Communications****, 2021*

Transforming IR fingerprints into medical insights with predictive analytics



CLINICAL STUDIES

INFRARED SPECTROSCOPY

Molecular interrogation of clinical health-to-disease quantification

Lasers4Life (L4L)
LMU Munich, BIRD team

>6.300 volunteers enrolled
cross-sectional, multi-centric, case-control study

Health4Hungary (H4H)
CMF Hungary

>13.500 volunteers enrolled with
already > 5 longitudinal follow ups, multi-centric, 10 years

KORA study
Helmholtz Institute, Munich

>5.500 samplings studied with IR spectroscopy
populational longitudinal follow ups, 3-5 year intervals

Biomarkers of Personalised Medicine (BioPersMed)
University Graz, Austria

44 volunteers enrolled with already > 330 samplings
longitudinal follow ups, over 8 years already IR analyzed

CAD - CHIP study
Deutsches Herzzentrum München

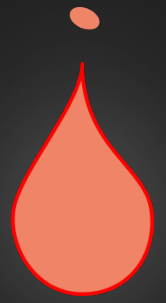
1.341 CAD patients studied with IR spectroscopy
longitudinal follow ups up to 11 years

Biomarkers of Early Lung Cancer
University of Navarra, Pamplona, Spain

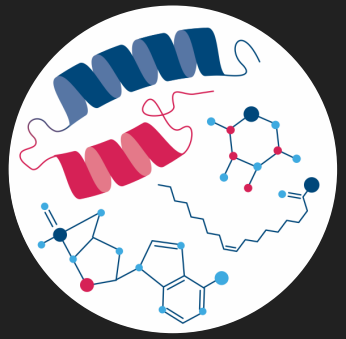
>500 high-risk volunteers followed in LDCT cancer screening
longitudinal follow ups, over 15 years

Why infrared spectroscopy?

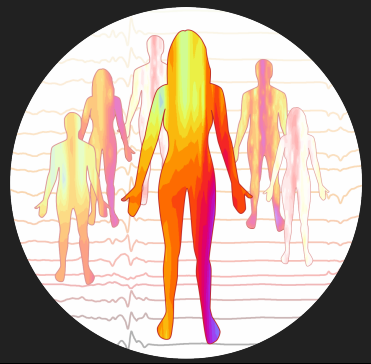
minimally invasive, small sample volume



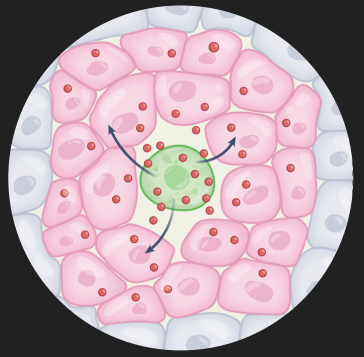
cross-molecular fingerprinting



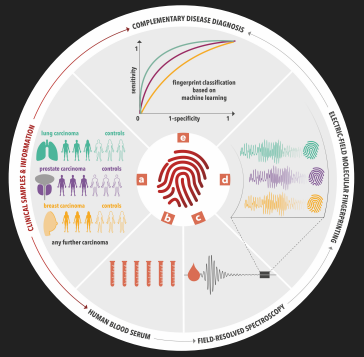
detecting multimorbid physiologies



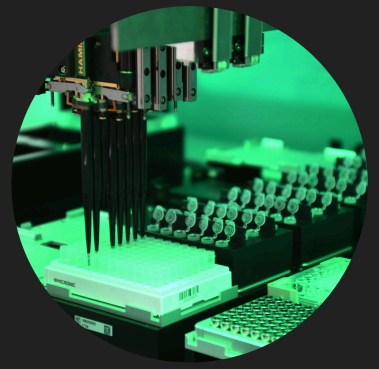
not dependent on tumor-shed analytes



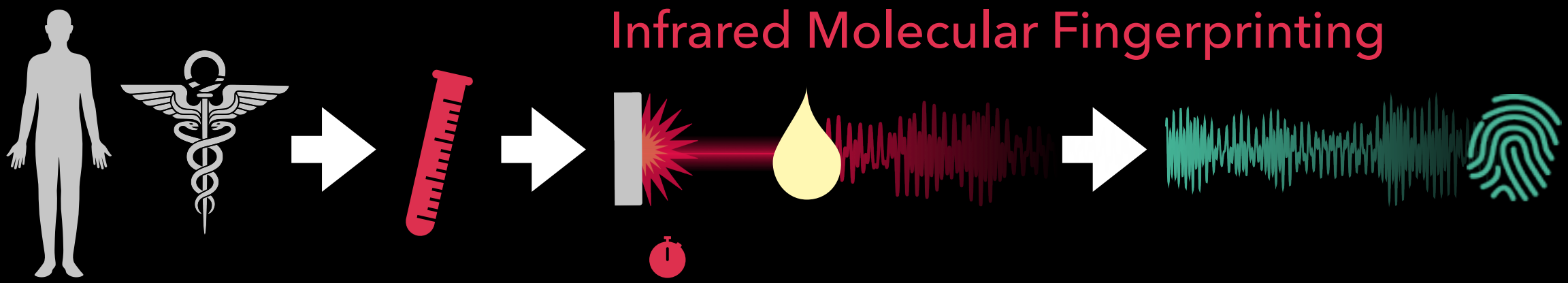
phenotype-agnostic fingerprinting



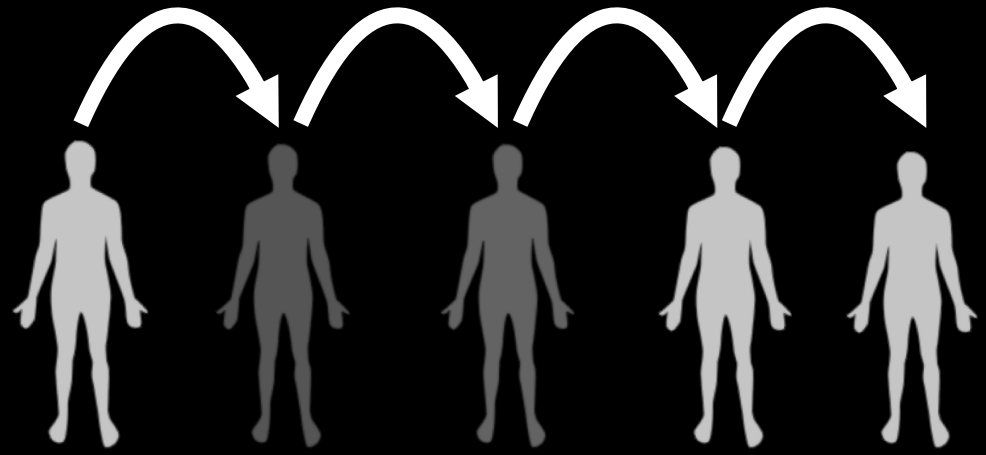
high-throughput, cost-effective



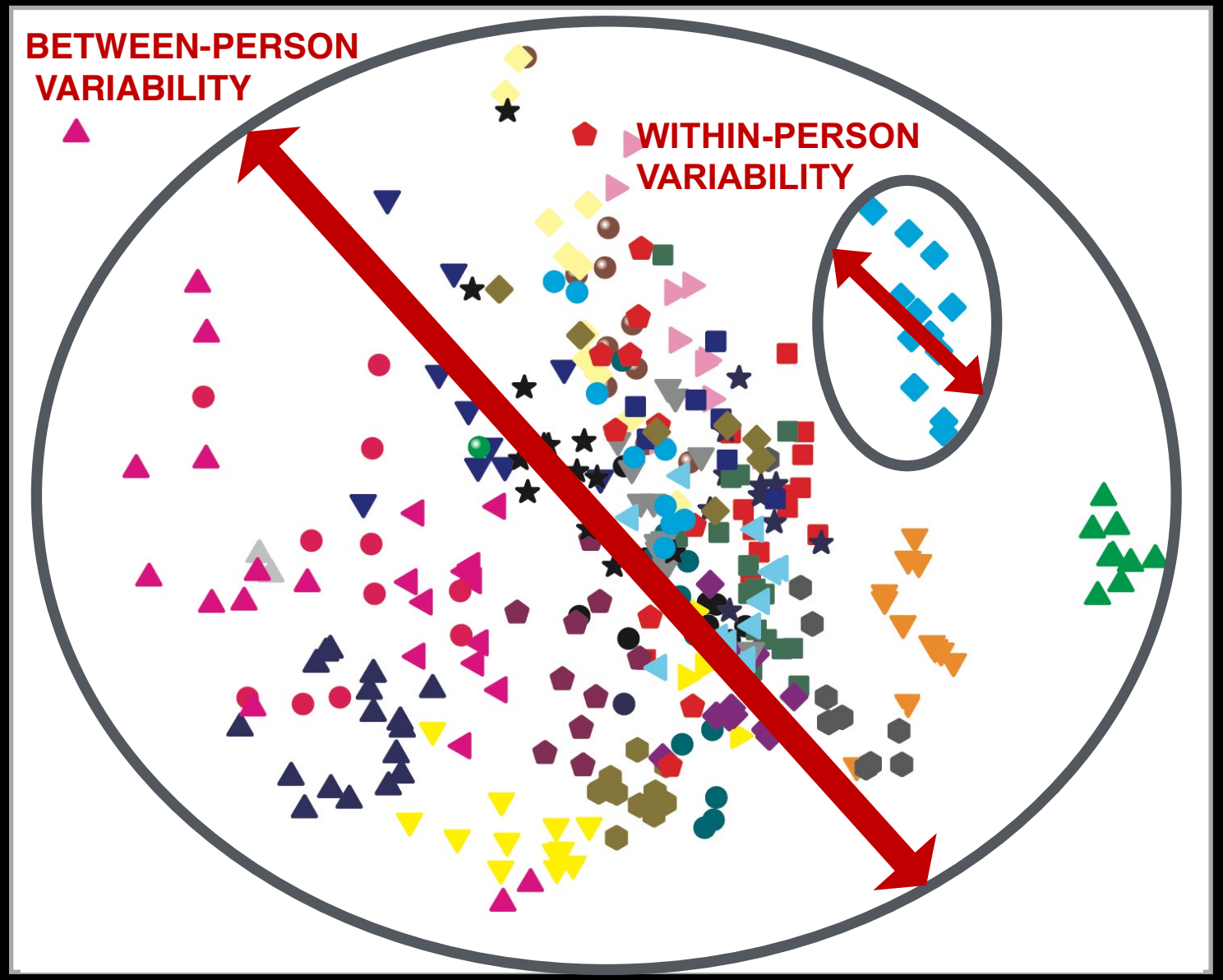
Profiling health physiologies using optical spectroscopy



How to molecularly capture clinically meaningful physiological changes?



Infrared fingerprinting can robustly profile healthy phenotypes over time, longitudinally

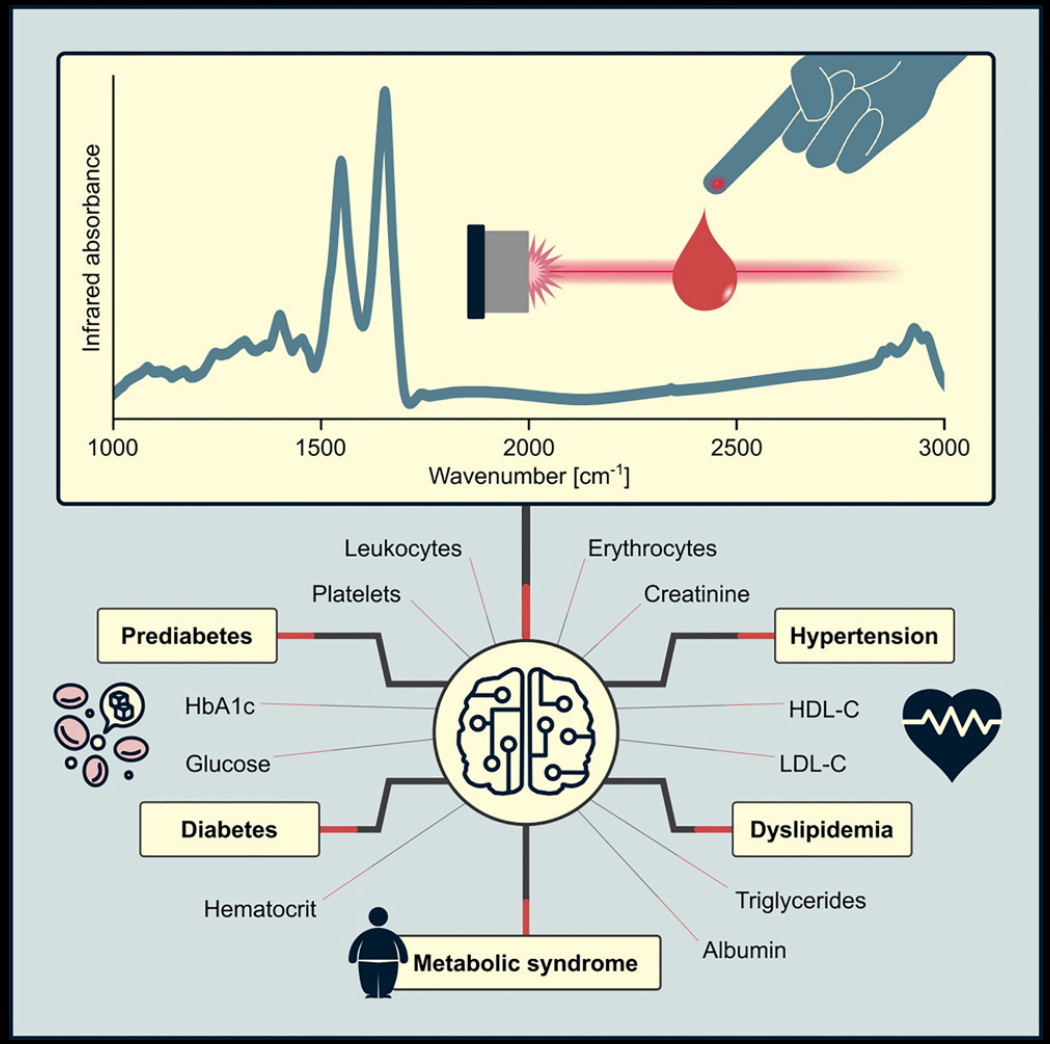


Huber et al., Zigman. ***Nature Communications****, 2021*

Eissa et al., Zigman. ***PNAS Nexus,*** *2024*

What health deviations can be profiled with infrared spectroscopy?

Infrared spectroscopy of blood plasma can :



- **Detect common Non-Concomitant Disease** (NCD)
  (*Cell Rep Medicine 2024*)
- **Distinguish different comorbid physiologies: Metabolic Syndrome** (MetS)
  (*Cell Rep Medicine 2024*)
- **Profile & distinguish between Common Cancers**
  (*eLife 2021, ACS Central Science 2024*)
- **Effectively phenotype large-scale heterogenous cohorts & populations**
  (*Nat Comms 2021, Cell Rep Medicine 2024, unpublished*)
- **Predict patient's outcomes** (e.g., NSCLC, MetS)
  (*BMC Medicine 2024, unpublished*)
- **Distinguish relevant multimorbid states (with/without MetS, Cancer)**
  (*manuscript unpublished*)
- **Risk stratify Coronary Artery Disease** (CAD)
  & Clonal hematopoiesis of indeterminate potential (CHIP)
  (*manuscript unpublished*)

In vitro diagnostics of common cancers

Lasers4Life

LMU Munich, BIRD team
> 6.700 now enrolled

therapy naïve pre-metastatic cancer detection

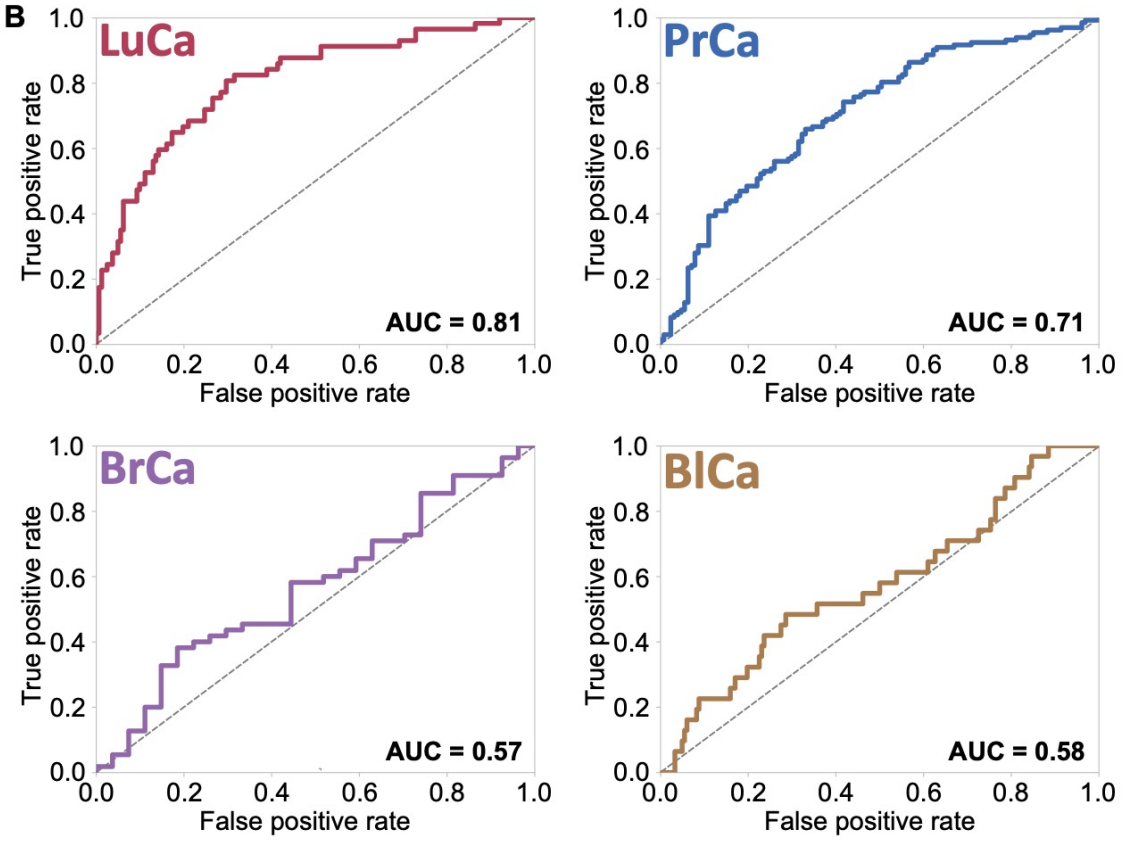
training data

Group	# Individuals	Age (years)	% Female	BMI (kg/m²)
Lung Cancer Training Cohort				
Cases	471	68 ± 9	46	26 ± 5
Controls	471	62 ± 10	59	26 ± 5
Prostate Cancer Training Cohort				
Cases	296	64 ± 10	0	27 ± 4
Controls	296	59 ± 15	0	27 ± 5
Breast Cancer Training Cohort				
Cases	144	60 ± 14	100	26 ± 5
Controls	144	60 ± 13	100	26 ± 6
Bladder Cancer Training Cohort				
Cases	183	72 ± 10	22	26 ± 4
Controls	183	71 ± 9	20	27 ± 5

test data

Group	# Individuals	Age (years)	% Female	BMI (kg/m²)
Lung Cancer Test Cohort				
Cases	57	68 ± 9	42	26 ± 6
Controls	162	66 ± 10	28	27 ± 5
Prostate Cancer Test Cohort				
Cases	132	67 ± 9	0	27 ± 4
Controls	127	67 ± 9	0	27 ± 4
Breast Cancer Test Cohort				
Cases	27	60 ± 14	100	25 ± 5
Controls	55	63 ± 13	100	26 ± 5
Bladder Cancer Test Cohort				
Cases	31	69 ± 10	26	25 ± 5
Controls	182	66 ± 11	30	27 ± 5

analysis involving 2.533 matched individuals



Huber et al., Zigman. ***eLife,*** Oct. 2021

Kepesidis et al., Zigman. ***ACS Central Science,*** April 2025

Towards early disease detection

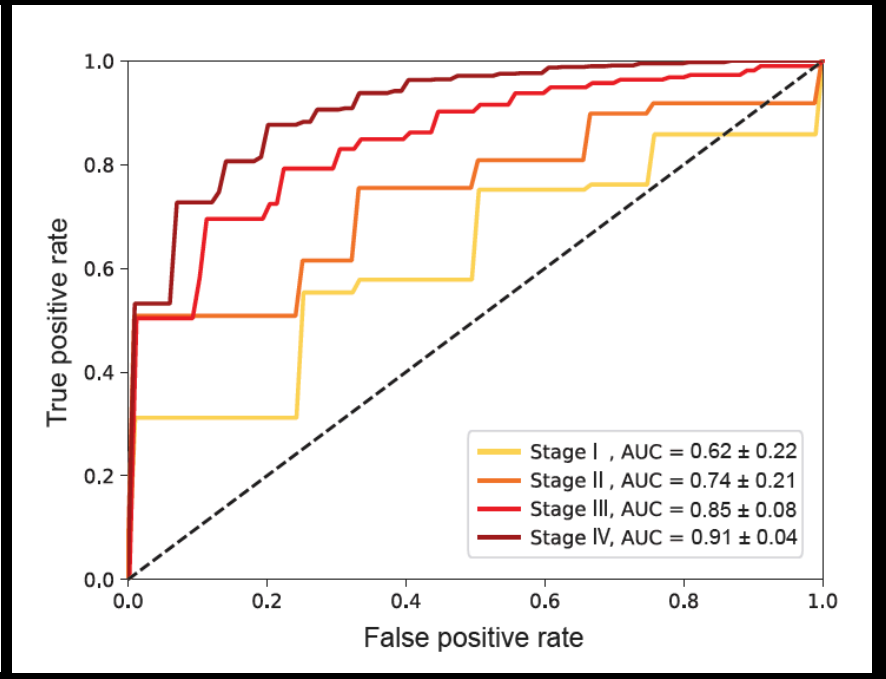
Lasers4Life

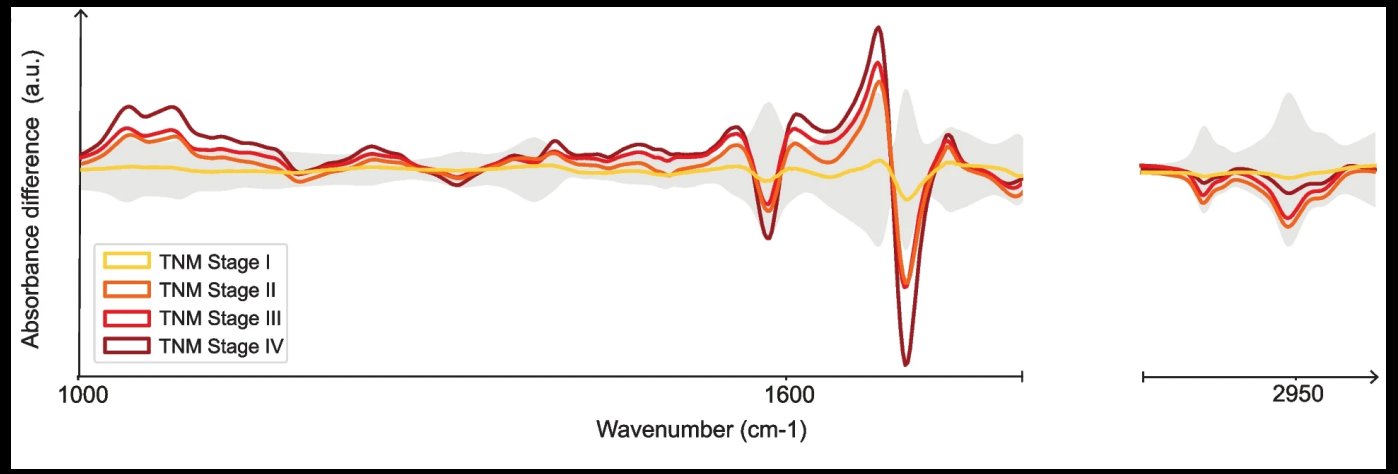
		Stage I
Group	# individuals	Age (years)
Cases	39	70 ± 9
Controls	39	70 ± 9

		Stage II
Group	# individuals	Age (years)
Cases	33	69 ± 8
Controls	33	69 ± 8

		Stage III
Group	# individuals	Age (years)
Cases	94	68 ± 10
Controls	94	68 ± 10

		Stage IV
Group	# individuals	Age (years)
Cases	151	68 ± 9
controls	151	68 ± 9



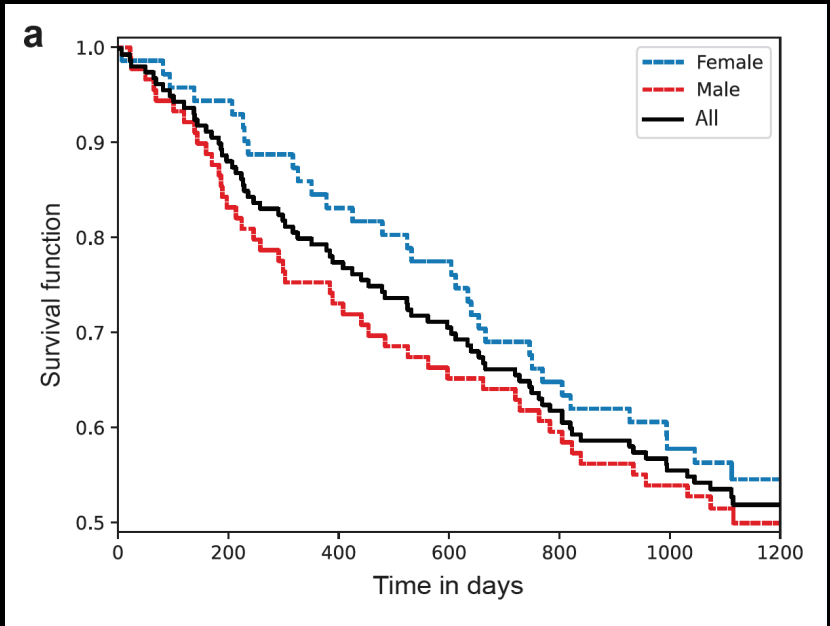


Kepesidis et al., Zigman. ***BMC Medicine**, March 2025*

Prognostication of disease development

Lasers4Life

> FORECASTING SURVIVAL in Lung Cancer patients - within 4.5 years after primary diagnosis



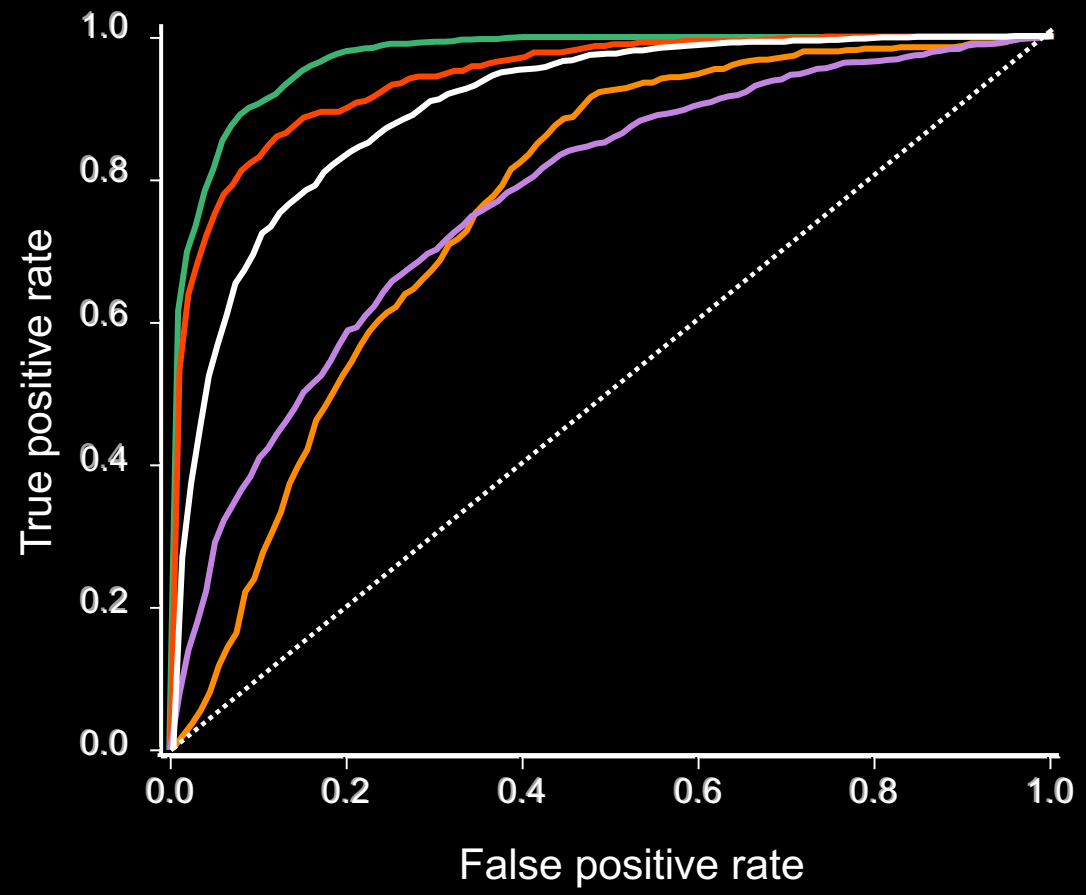
Parameter	C-index Markers	C-index IMFs	# Patients
IMFs		0.63 ± 0.12	160
Stage	0.67 ± 0.16	0.68 ± 0.12	95
NSE	0.64 ± 0.15	0.65 ± 0.12	132
CEA	0.59 ± 0.18	0.66 ± 0.12	147
CYFRA-21-1	0.72 ± 0.10	0.68 ± 0.10	144
Hemoglobin	0.57 ± 0.10	0.64 ± 0.09	159
Leukocytes	0.63 ± 0.12	0.64 ± 0.09	159
CRP	0.34 ± 0.15	0.63 ± 0.12	160

Kepesidis et al., Zigman. ***BMC Medicine**, March 2025*

Profiling common medical outcomes with IR fingerprinting

in collaboration with HELMHOLTZ MUNICH

> binary classifications in a naturally heterogenic population (5.184 samplings)



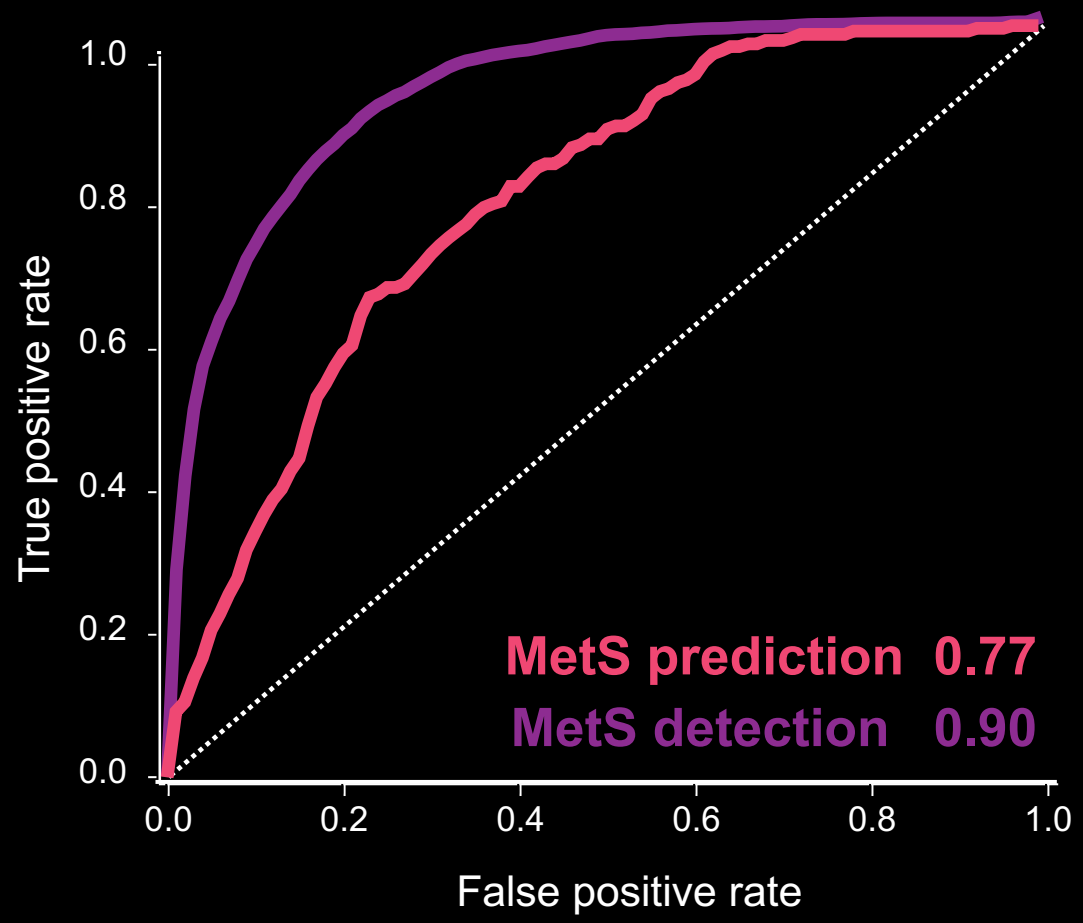
	Independent testing (AUC)
Dyslipidemia	0.97 ± 0.00
Type 2 diabetes	0.94 ± 0.01
Prediabetes	0.76 ± 0.04
Hypertension	0.77 ± 0.02
HEALTHY	0.90 ± 0.01

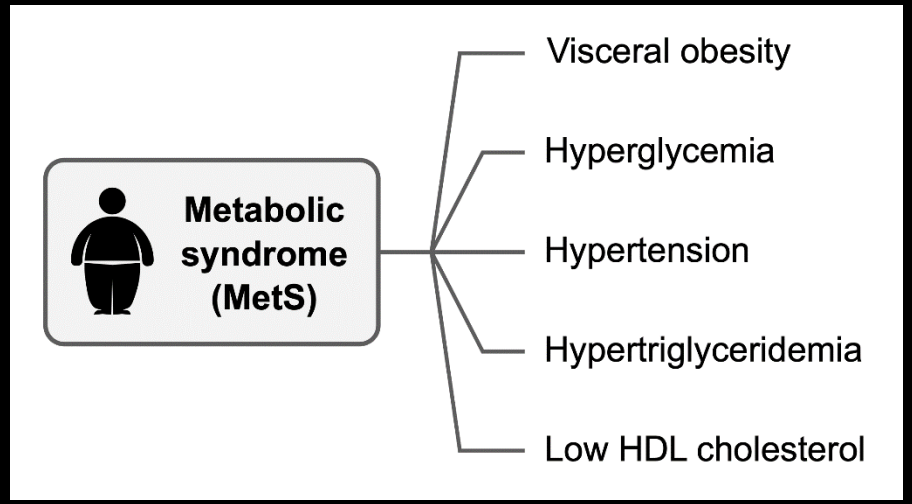
Eissa et al., Zigman. ***Cell Reports Medicine, July 2024***

Forecasting the development of Metabolic Syndrome - upcoming 6.5 years

in collaboration with HELMHOLTZ MUNICH

Predictive power for stratifying health risk

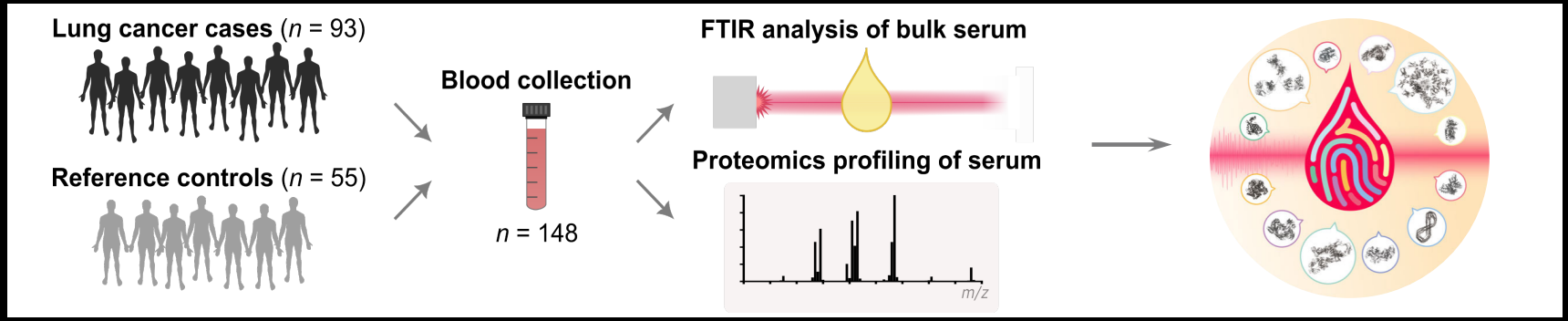


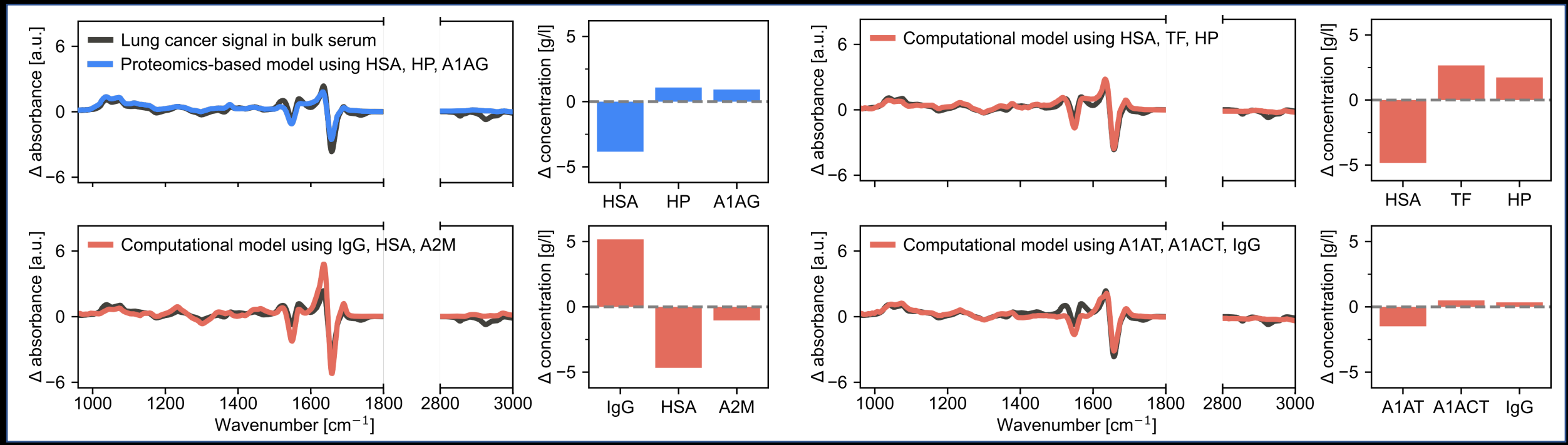


Eissa et al., Zigman. ***Cell Reports Medicine, July 2024***

What molecules encode infrared fingerprints?

Decoding & Understanding of infrared molecular fingerprints

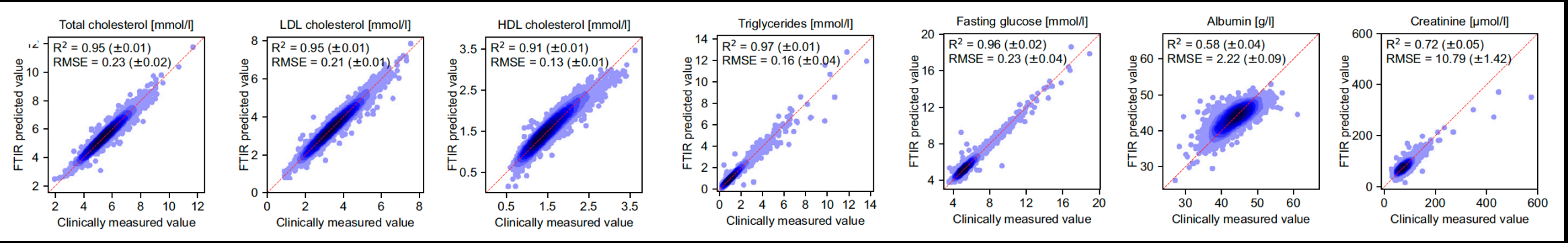




add I.) molecular interpretability

Voronina L., et al., Zigman M. ***Angew Chem Int Ed***, July 2021; Eissa T., et.al., Zigman M. ***Angew Chem Int Ed***, Nov. 2024

Uncovering the information content of multi-omic infrared profiling

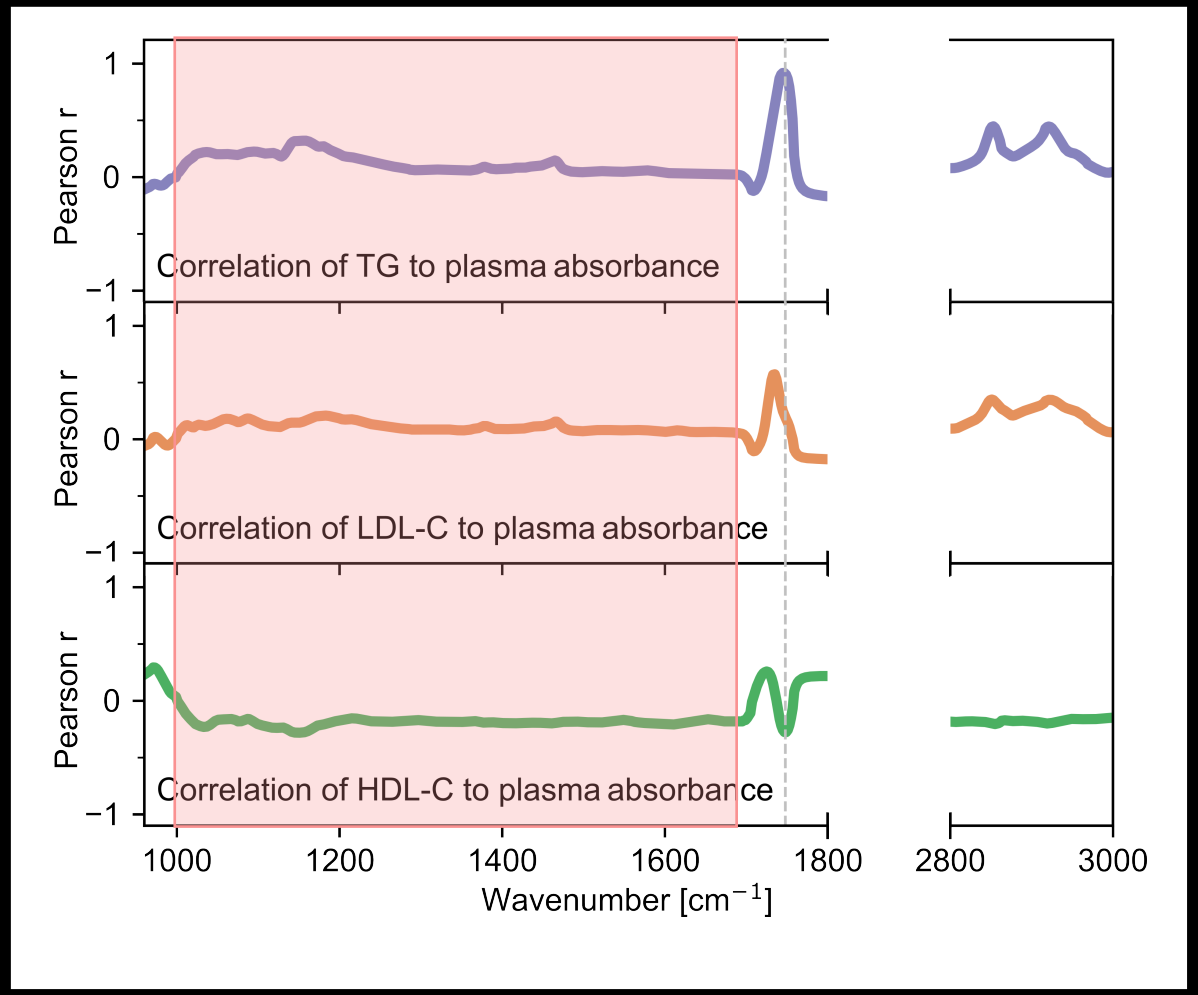


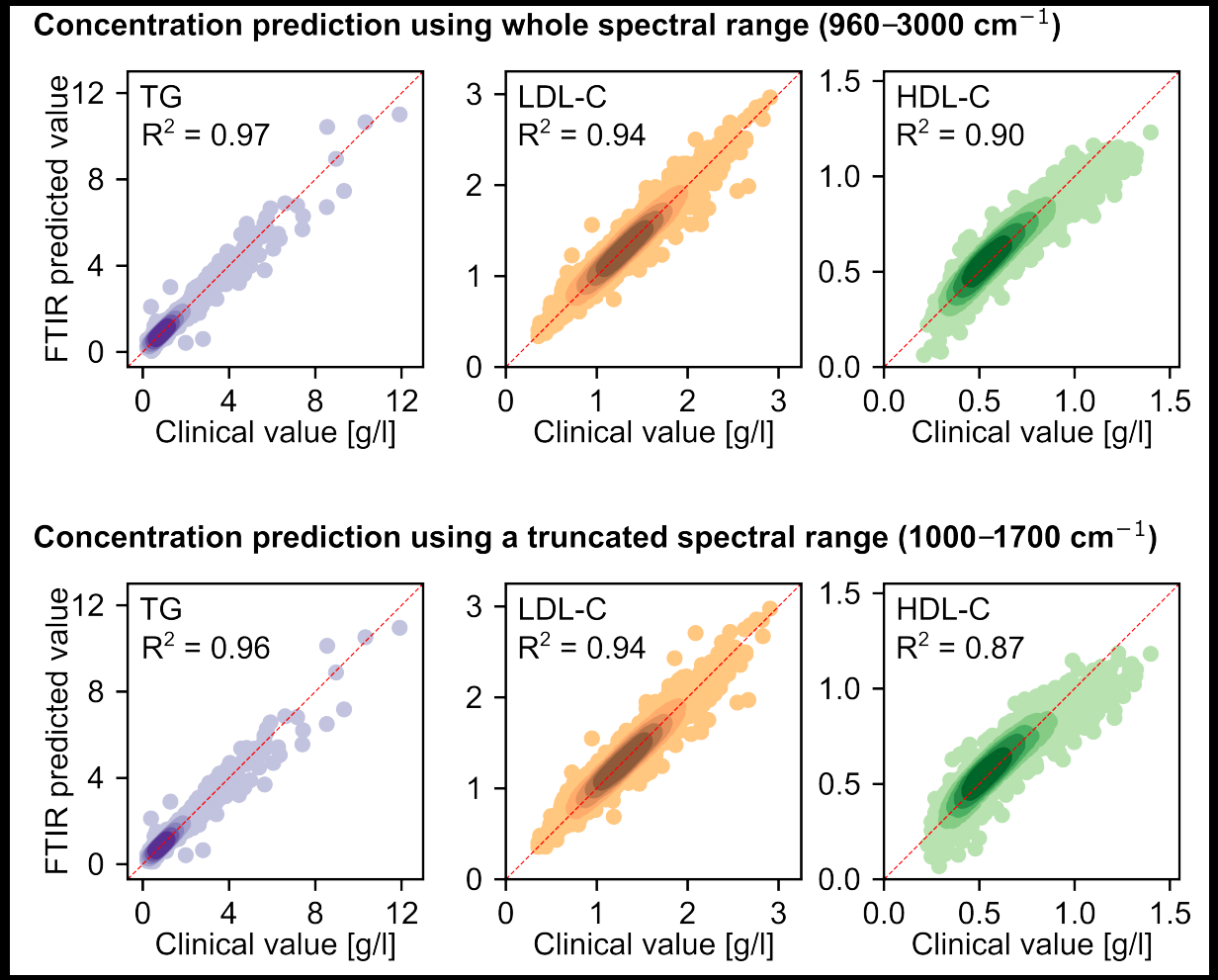
Eissa et al., Zigman. ***Cell Reports Medicine***, *July 2024*

add II.) medical & molecular interpretability

Quantifying the concentrations of analytes in molecularly complex spectra

Using a ridge regression algorithm





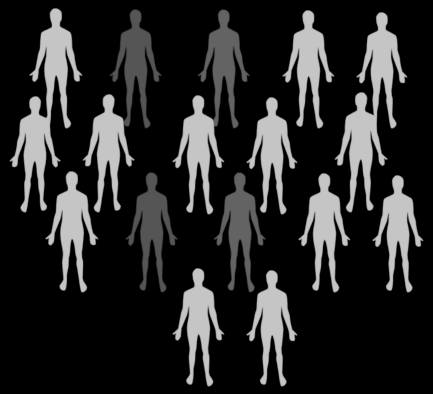
→ **Multivariate analysis can uncover masked spectral signals.**

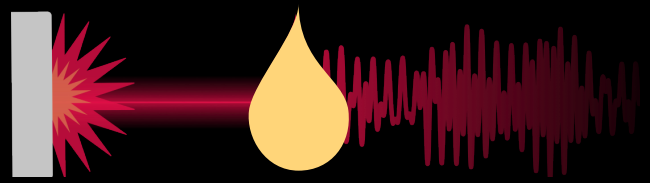
→ **There is a lot of redundant data in IR spectra, with many possible feature combinations yielding similar results.**

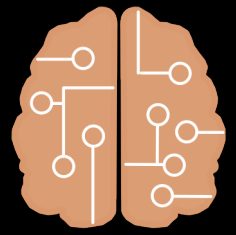
Eissa et al., Zigman. ***Angewandte Chemie Int. Ed.***, 2024.

>>> from exploratory measurements >>> to medical implementation:

PRE-ANALYTICS | **SPECTROSCOPIC MEASUREMENTS** | **POST-ANALYTICS** | **CLINICAL USE**







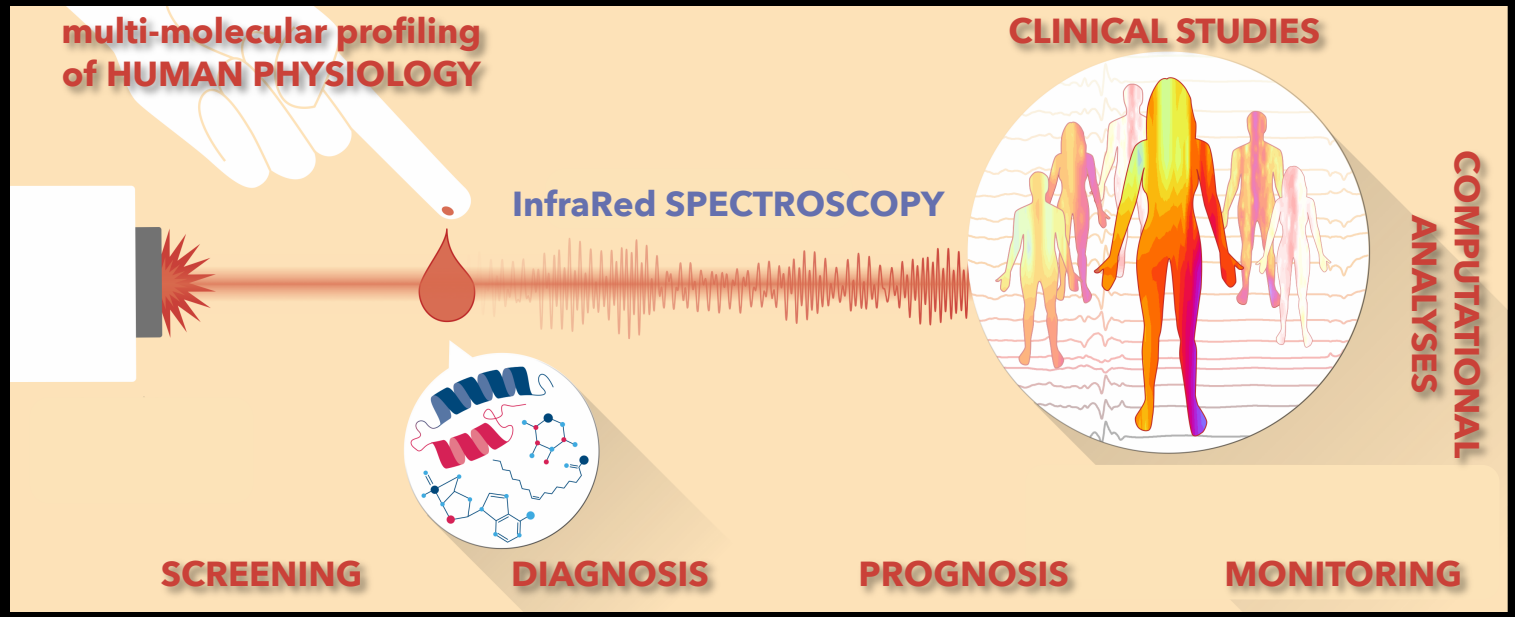
- hypotheses
- cross-disciplinary collaborations
- natural variation
- design study population
- medical data
- blood collection
- databases
- plasma preparation - quality (timings, centrifugation, freeze/thaw,)

- sensitivity, S/N, spectral coverage
- measurement reproducibility
- reference materials
- quality control samples
- analytical design, batches
- thawing
- spectrometric measurements

- raw data quality control
- quantitation
- batch /drift effects
- standardization, normalization
- pattern recognition
- machine learning & prediction
- independent testing

- cross-study clinical validation
- regulations
- countries/populations
- privacy/security
- ethics
- data sharing

Infrared Molecular Fingerprinting



- Ability to molecularly profile complex human biological matrices
- Feasible monitoring of health states and tracking person-specific changes over time
- Assesses individual risk for health deviations (e.g., metabolic, cardiovascular)
- Detects single and multimorbid -*medically relevant*- phenotypes and health states
- Forecasts and predicts future physiological deviations
- Enabling affordable, molecule-agnostic, disease-independent, high-throughput *in vitro* diagnostics

ACKNOWLEDGEMENTS

Broadband InfraRed Diagnostics team (BIRD)

All study volunteers

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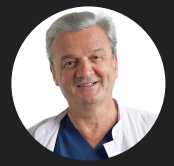

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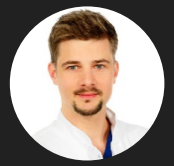

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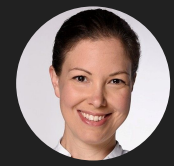

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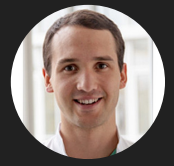

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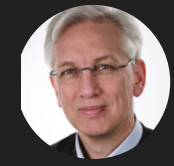

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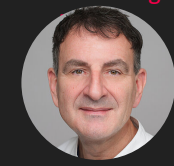

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THANK YOU !

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