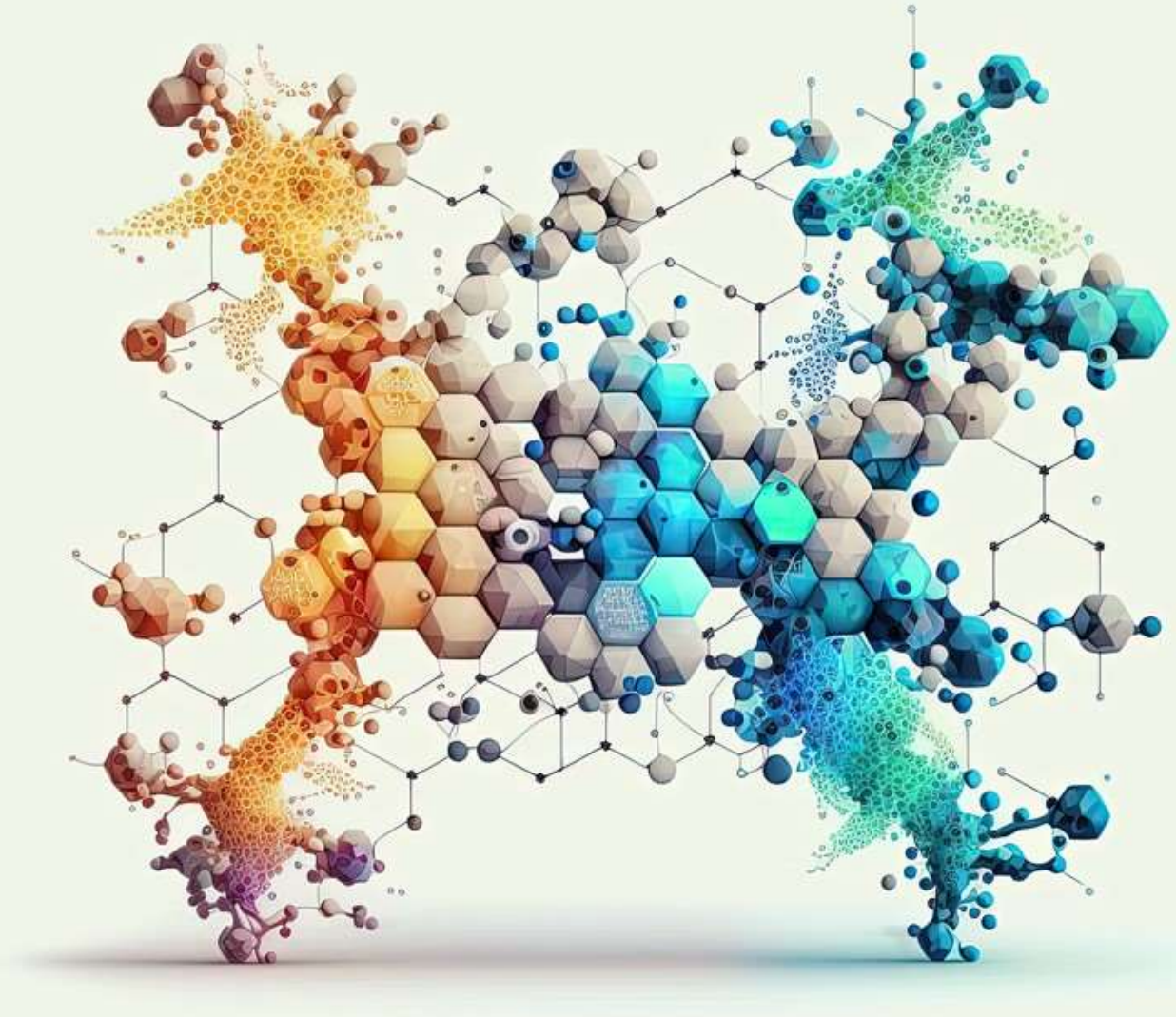
Clinical proteome analysis

Paradigm shift
in diagnostics
and therapy



mosaiques

Outline

Non-communicable diseases

- Current challenges and need for changes

Clinical proteome analysis to revolutionize medicine

- Why use proteomics?
- How we can measure the proteome?
- Collaborative approach and Mosaiques' scientific excellence

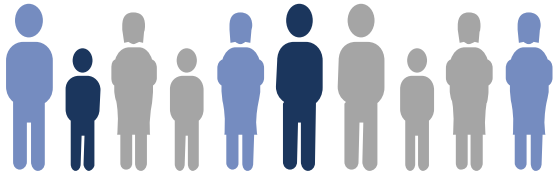
Available diagnostic tests

- How to order proteomics tests (sample collection and shipment)
- Chronic diseases and oncology

Non-communicable diseases

The leading cause of death

41
MILLION
deaths each year



7 out of 10 deaths worldwide

77% deaths are in low- and middle-income countries

- **17 million people die before age 70**
- **86% of premature deaths occur in low- and middle-income countries**

Cardiovascular: 17.9 million

Diabetes, kidney disease: 2.0 million

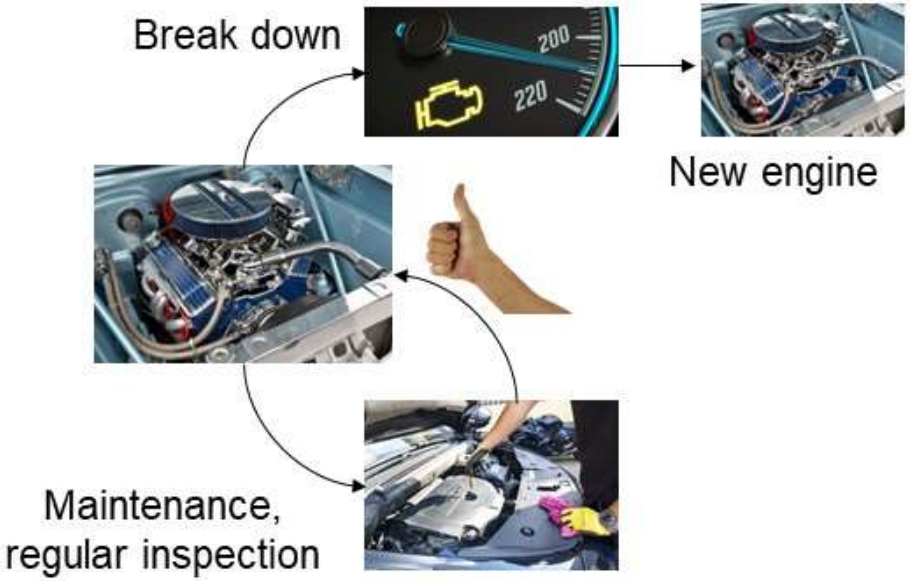
Cancer: 9.3 million

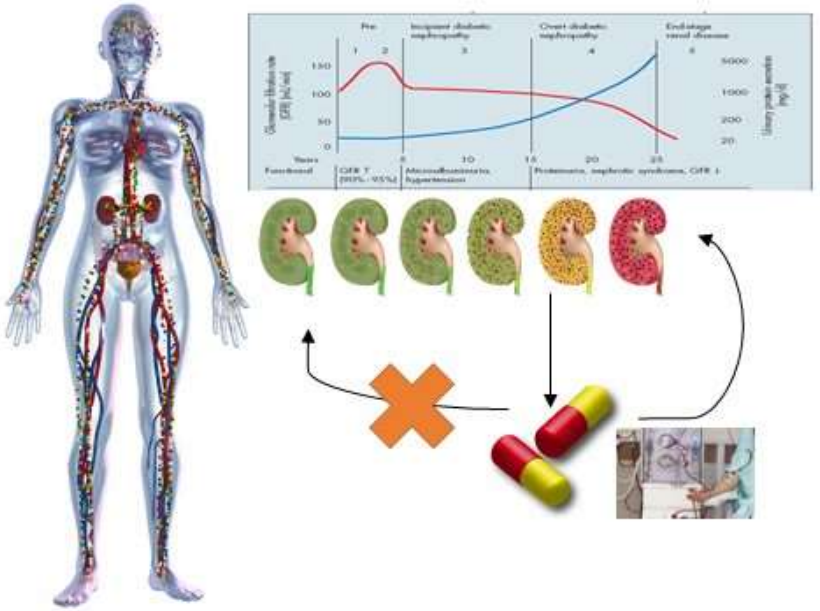
https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases

Non-communicable diseases

Current Challenge: Late Diagnosis

The human body compared with a car engine





For your car:

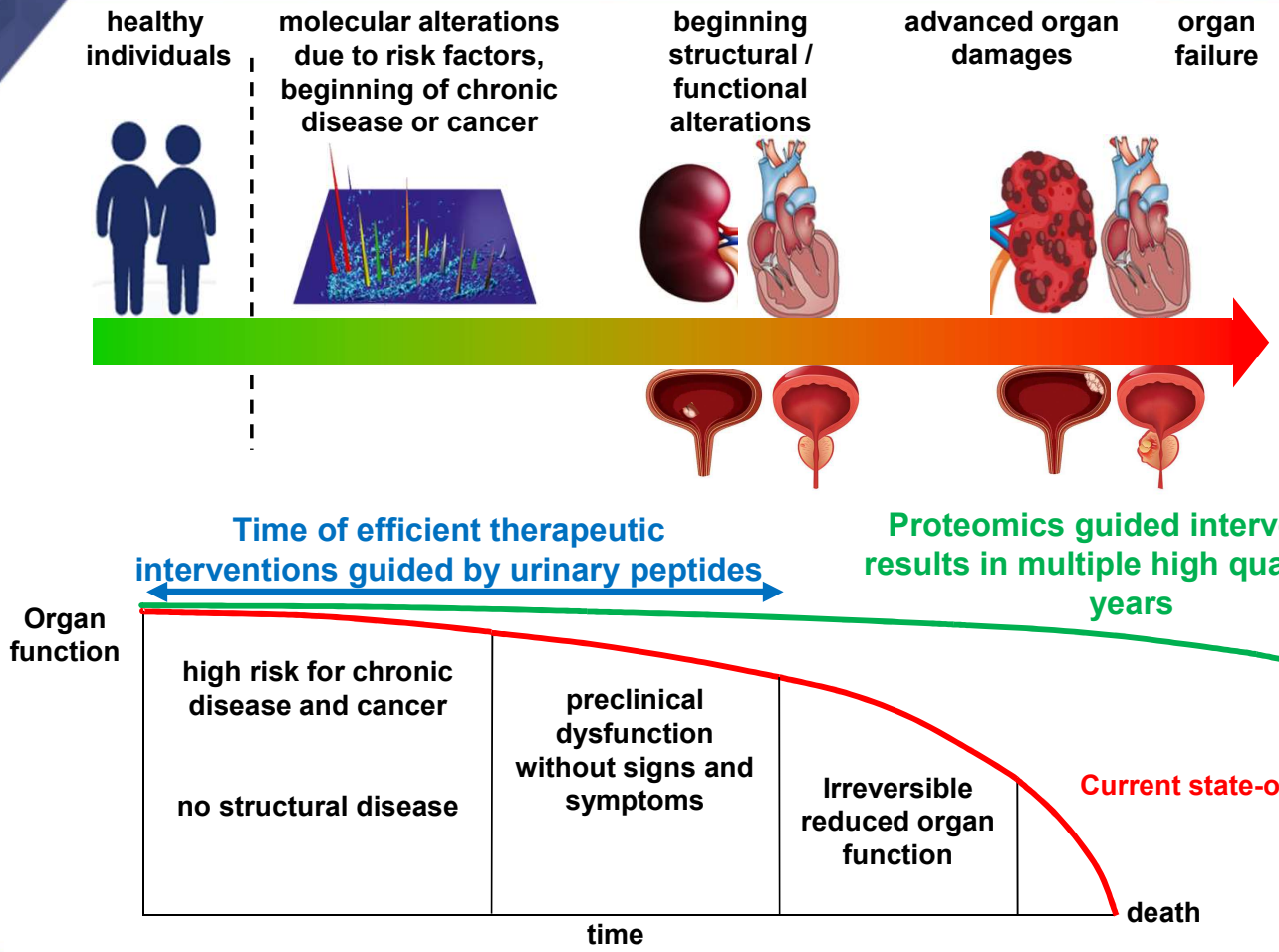
You don't wait for the engine to break down; apply regular inspections and timely action. However, if engine fails, at worst, it can be replaced.

For your body:

No regular inspections, wait until disease is detectable (after ~**50% loss** of the organ's function) before starting therapy. By then, it is too late for effective treatment. The option to replace organ is limited or non-existing.

Non-communicable diseases

Time to act to protect the human life!



Change is needed

From treatment of established disease (of note: chronic disease does not meet curative treatment, at best prevention of further progression) to personalized prevention of disease development.

Solution

Detection and assessment of initial individual changes in specific proteins, followed by timely intervention based on individual molecular features.

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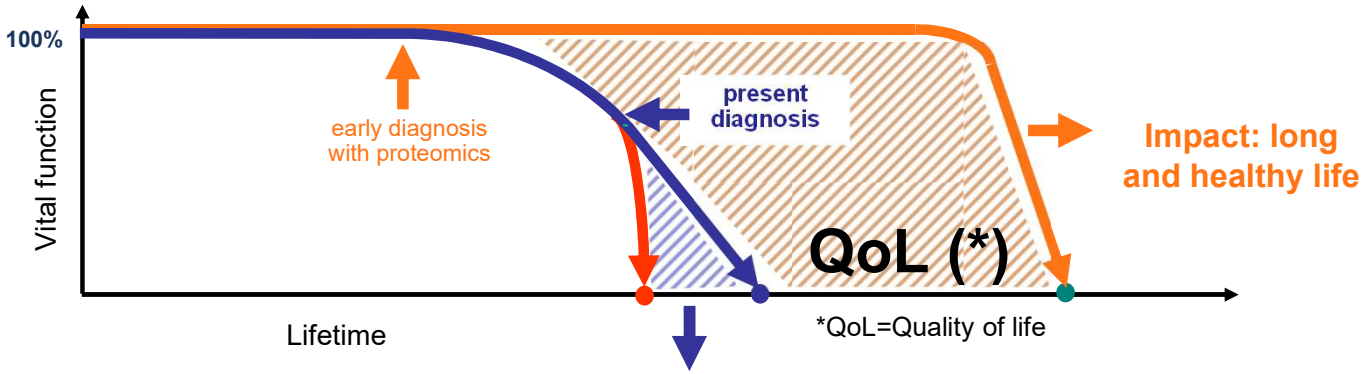
Clinical proteome analysis

Revolution in medicine

Molecular disease definition and early detection: The key to a long and healthy life



The past

A lack of understanding about diseases and ineffective treatments led to many deaths.

The presence

Advanced medical practices exist, but diseases are detected too late, based on irreversible organ damage, making interventions ineffective.

The proteomics diagnosis

Analyzing proteome changes enables early detection of disease before irreversible organ damage occurs, maximizing the efficacy of interventions and enabling disease prevention.

Clinical proteome analysis

Why proteins & proteomics?

- **Proteins and peptides** are active **key players in every organism** that enable and control life, normal and pathological development.
- Proteins are **responsible for all disease-specific processes**, initiate disease on the molecular level, **long before symptoms appear**, and are the target for drugs.
- **Knowledge of the proteome/peptidome**, the **entirety** of all proteins/peptides, **enables accurate assessment of (patho)physiology on an individual level**, in the context of disease enabling **optimal and personalized patient management.**

Clinical proteome analysis

How we can measure the proteome (1)

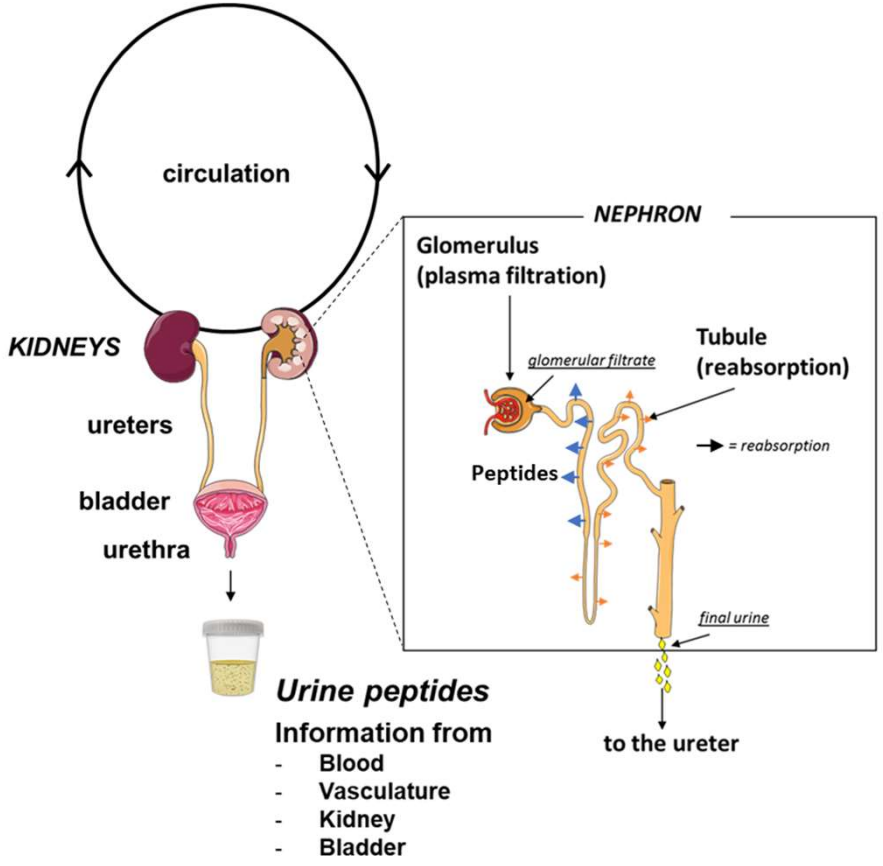
Analysis of endogenous peptide content (protein degradation products, <20 kDa) in urine

Urine:

- obtained non-invasively, easily accessible, in large quantities

Urinary peptides:

- Display the systemic/ peripheral disease associated changes
- Stable → comparable datasets



Adapted from Decramer S et al. Mol Cell Proteomics. 2008; 7(10):1850-62.

Clinical proteome analysis

How we can measure the proteome (2)

Capillary electrophoresis - mass spectrometry (CE-MS):

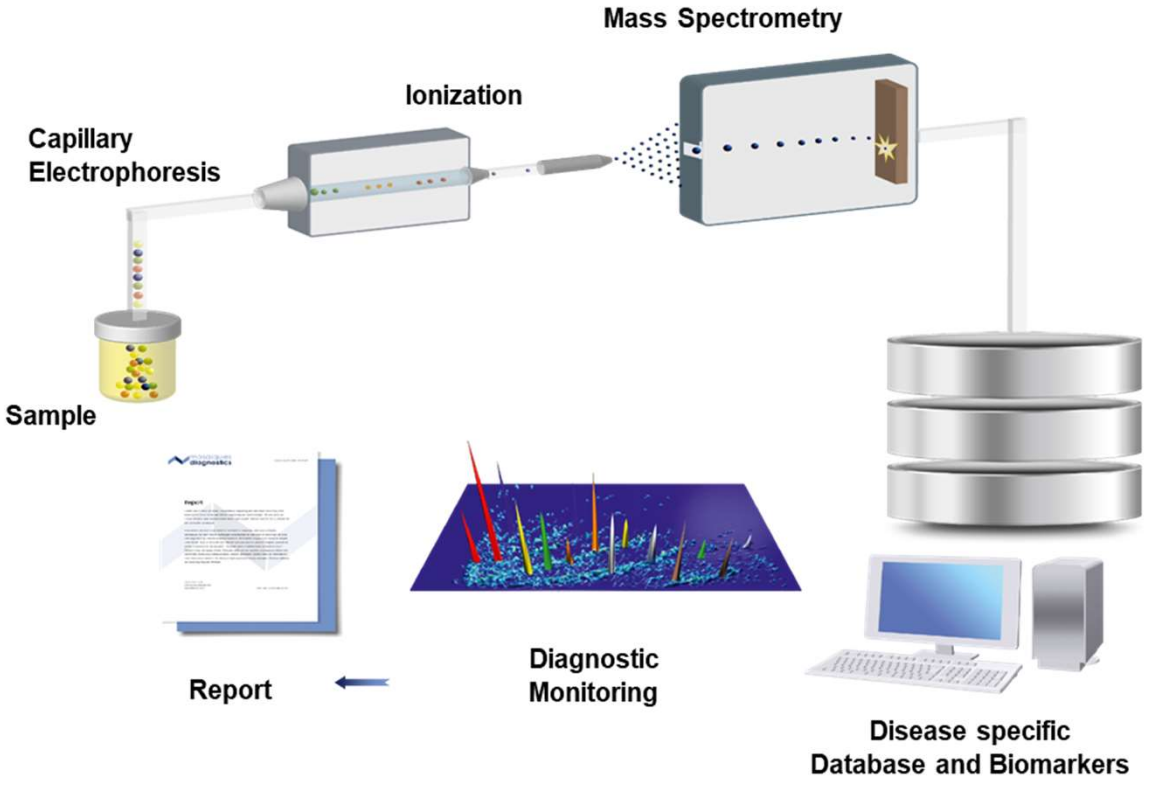
>8000 small proteins and peptides

Run time ~60 min

High reproducibility

High-throughput

Low sample consumption (0.7 ml)

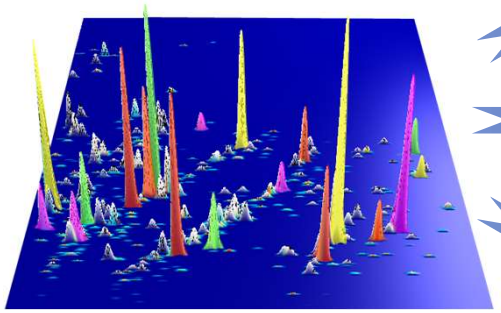


Latosinska et al. Proteomics Clin Appl. 2021,15(1):e2000027;
Adapted from: Pontillo et al. Clin Kidney J. 2017;10(2):192-201

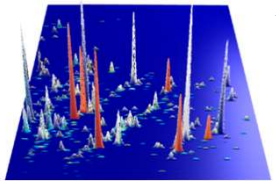
Clinical proteome analysis

One sample = Multiple diagnoses

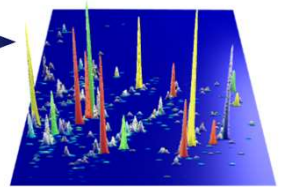
Personal Proteome



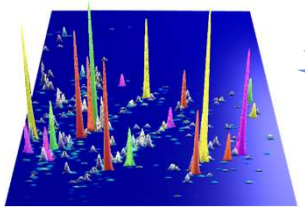
From each sample, the entire proteome (all proteins) is analyzed qualitatively and quantitatively.



Kidney Differential Diagnosis



Heart Check-Up



Bladder/Prostate Check-Up, Status Management

Kidney disease

- CKD
- diabetic nephropathy
- Nephrosclerosis
- IgA Nephropathy
- Lupus erythematodes
- Minimal-Change-Glomerulonephritis

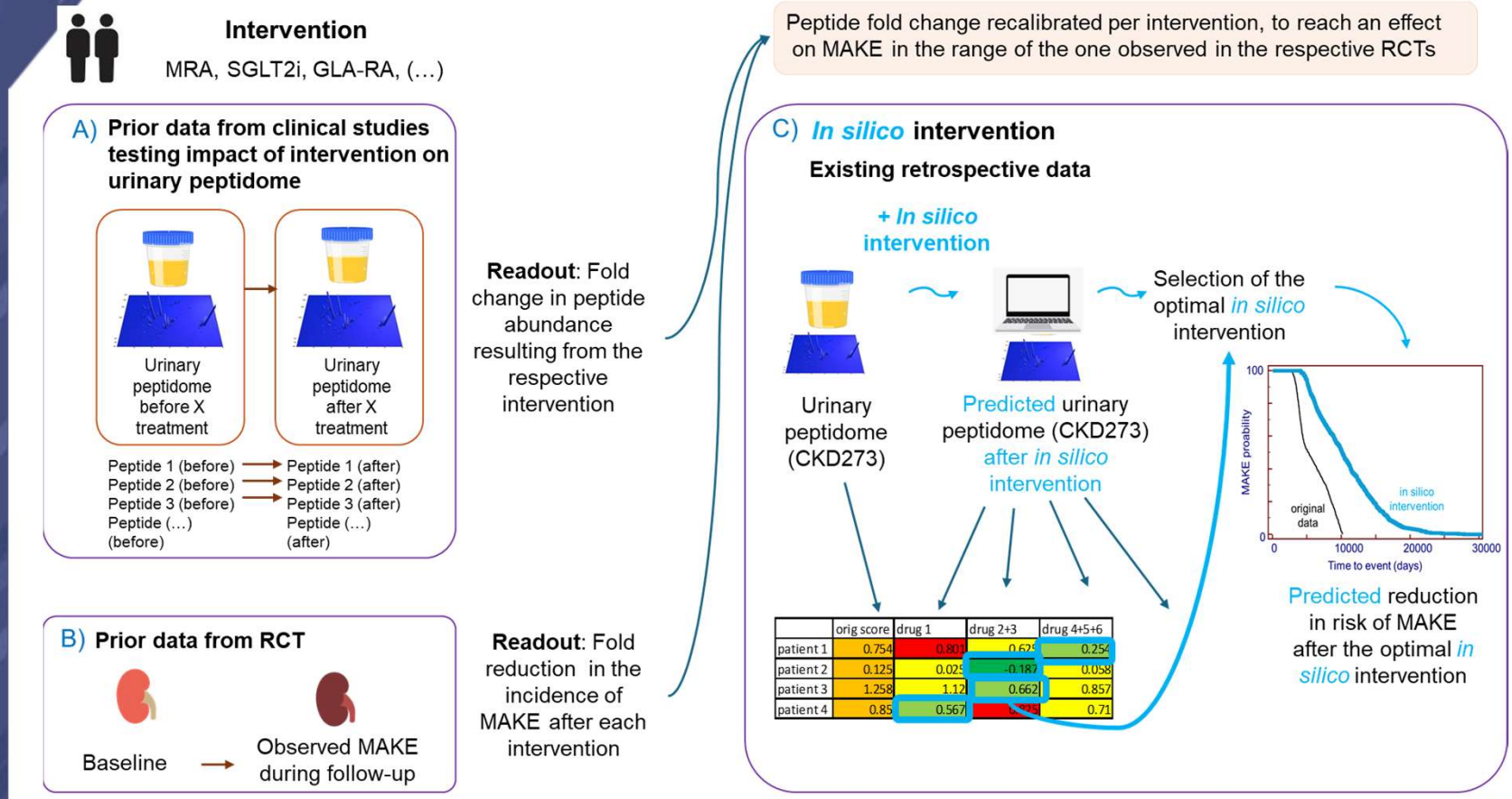
Cardiovascular

- Heart failure
- Coronary artery disease
- Myocard infarction

Cancer

- Bladder cancer
- Prostate cancer

Guiding personalized intervention



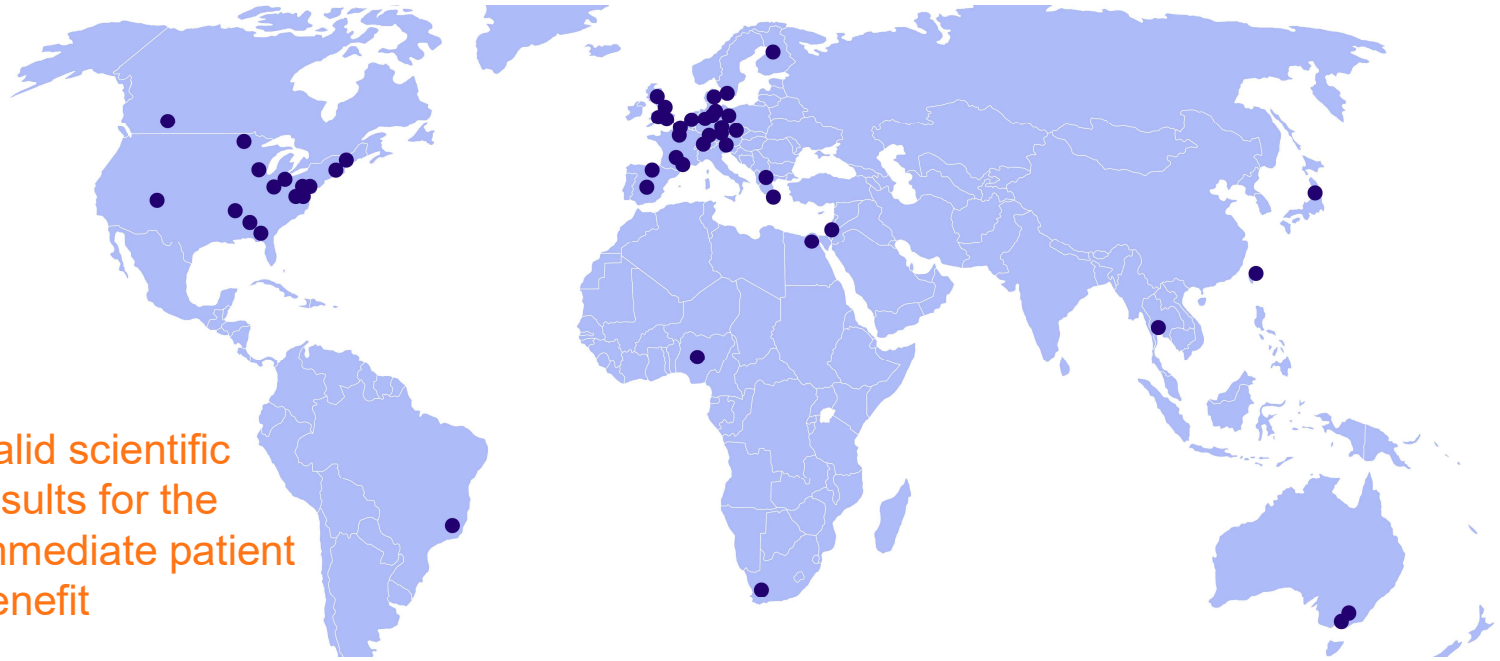
Patent applications

Singapore 11202409015V
Australia 2023288785
Canada CA 3,259,874
USA 18/876,322
Europe EP 23734620.0

Proteome data are used to predict the optimal personalized combination of drugs (out of 93 combinations) to prevent disease progression.

Collaboration

The basis of Mosaiques' proteomics approach



Valid scientific results for the immediate patient benefit

expertise of currently > 1,200 renowned scientists and physicians at > 100 institutes worldwide

> 100 clinical studies	**> 400 scientific publications**	**> 34,000 citations**

Collaboration

The basis of Mosaiques' proteomics approach

Collaboration

Some results of ongoing collaborations with African scientists

DOI: 10.1002/pmic.202200444

RESEARCH ARTICLE

Proteomics

Identifying a urinary peptidomics profile for hypertension in young adults: The African-PREDICT study

Urinary peptidomics and hypertension

Dalene De Beer[1] | Catharina M.C. Mels[1,2] | Aletta E. Schutte[1,2,3] | Christian Delles[4] | Sheon Mary[4] | William Mullen[4] | Agnieszka Latosinska[5] | Harald Mischak[5] | Ruan Kruger[1,2]

Original Articles

Urinary proteomics combined with home blood pressure telemonitoring for health care reform trial: rational and protocol

Lutgarde Thijs, Kei Asayama, Gladys E. Maestre, Tine W. Hansen, Luk Buyse, Dong-Mei Wei, Jesus D. Melgarejo, Jana Brguljan-Hitij, Hao-Min Cheng, Fabio de Souza, Natasza Gilis-Malinowska, Kalina Kawecka-Jaszcz, Carina Mels, Gontse Mokwatsi, Elisabeth S. Muxfeldt, Krzysztof Narkiewicz, Augustine N. Odili, Marek Rajzer, Aletta E. Schutte, Katarzyna Stolarz-Skrzypek, Yi-Wen Tsai, Thomas Vanassche, Raymond Vanholder, Zhen-Yu Zhang, Peter Verhamme, Ruan Kruger, Harald Mischak, Jan A. Staessen, The UPRIGHT-HTM Investigators, Coordinating, Logistic, Recruiting, and, Urinary Proteomics Centres, & Advisors

Pages 269-281 | Received 08 Jun 2021, Accepted 01 Jul 2021, Published online: 30 Aug 2021

Cite this article | https://doi.org/10.1080/08037051.2021.1952061

THE JOURNAL OF CLINICAL HYPERTENSION

ORIGINAL ARTICLE | Open Access

Urinary proteomics combined with home blood pressure telemonitoring for health care reform trial—First progress report

Babangida S. Chori MSc, De-Wei An MD, PhD, Dries S. Martens PhD, Yu-Ling Yu MD, Natasza Gilis-Malinowska MD, PhD, Sani M. Abubakar MD, Etubi A. Ibrahim MD, Ojonojima Ajanya MD, Olugbenga O. Abiodun MD, Tina Anya MD, Iyidobi Tobechukwu MD, Godsent Isiguzo MD, PhD, Hao-Min Cheng MD, PhD, Chen-Huan Chen MD, PhD, Chia-Te Liao MD, PhD, Gontse Mokwatsi MD, PhD, Katarzyna Stolarz-Skrzypek MD, PhD, Wiktoria Wojciechowska MD, PhD, Krzysztof Narkiewicz MD, PhD, Marek Rajzer MD, PhD, Jana Brguljan-Hitij MD, PhD, Tim S. Nawrot PhD, Kei Asayama MD, PhD, Peter Reyskens DVM, Harald Mischak PhD, Augustine N. Odili MD, PhD, Jan A. Staessen MD, PhD, the UPRIGHT-HTM Investigators

First published: 06 May 2023 | https://doi.org/10.1111/jch.14664

Article | Published: 17 November 2022

A urinary peptidomics approach for early stages of cardiovascular disease risk: The African-PREDICT study

Dalene de Beer, Catharina M. C. Mels, Aletta E. Schutte, Christian Delles, Sheon Mary, William Mullen, Harald Mischak & Ruan Kruger

Hypertension Research **46**, 485–494 (2023) | Cite this article

ORIGINAL ARTICLE

Multiple urinary peptides are associated with hypertension: a link to molecular pathophysiology

Mavrogeorgis, Emmanouil[a,b,*]; Kondyli, Margarita[c,*]; Mischak, Harald[a]; Vlahou, Antonia[d]; Siwy, Justyna[a]; Rossing, Peter[e,f]; Campbell, Archie[g]; Mels, Carina M.C.[h,i]; Delles, Christian[j]; Staessen, Jan A.[k]; Latosinska, Agnieszka[a]; Persu, Alexandre[l,m]

Author Information

Journal of Hypertension ():10.1097/HJH.0000000000003726, March 29, 2024. | **DOI:** 10.1097/HJH.0000000000003726

Journal of proteome research

pubs.acs.org/jpr

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Article

Urinary Peptidomics and Pulse Wave Velocity: The African-PREDICT Study

Dalene de Beer, Catharina MC Mels, Aletta E Schutte, Christian Delles, Sheon Mary, William Mullen, Harald Mischak, and Ruan Kruger*

Degenaar *et al. BMC Nephrology* (2023) 24:96
https://doi.org/10.1186/s12882-023-03100-w

BMC Nephrology

RESEARCH Open Access

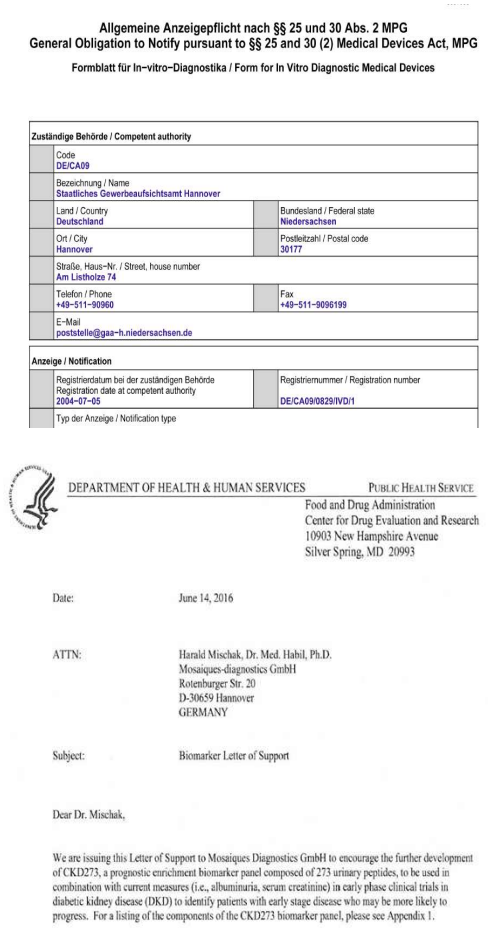
Cardiovascular risk and kidney function profiling using conventional and novel biomarkers in young adults: the African-PREDICT study

A Degenaar[1], A Jacobs[1,2], R Kruger[1,2], C Delles[3], H Mischak[3,4] and CMC Mels[1,2*]

Available diagnostic tests

IVD registration and FDA Letter-of-support

- All proteomic tests are registered as in-vitro diagnostics (IVD) in Germany.
- Letter-of–support from the US-FDA for the kidney disease test.
- Since February 1st 2024, our diagnostic tests are reimbursed by the first statutory health insurance company in Germany.



Allgemeine Anzeigepflicht nach §§ 25 und 30 Abs. 2 MPG
General Obligation to Notify pursuant to §§ 25 and 30 (2) Medical Devices Act, MPG

Formblatt für In-vitro-Diagnostika / Form for In Vitro Diagnostic Medical Devices

Zuständige Behörde / Competent authority	
Code: DE/CA09	
Bezeichnung / Name: Staatliches Gewerbeaufsichtsamt Hannover	
Land / Country: Deutschland	Bundesland / Federal state: Niedersachsen
Ort / City: Hannover	Postleitzahl / Postal code: 30177
Straße, Haus-Nr. / Street, house number: Am Listholze 74	
Telefon / Phone: +49-511-90960	Fax: +49-511-9096199
E-Mail: poststelle@gaa-h.niedersachsen.de	

Anzeige / Notification	
Registrierdatum bei der zuständigen Behörde / Registration date at competent authority: 2004-07-05	Registriernummer / Registration number: DE/CA09/0829/IVD/1
Typ der Anzeige / Notification type	

DEPARTMENT OF HEALTH & HUMAN SERVICES — PUBLIC HEALTH SERVICE
Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: June 14, 2016

ATTN: Harald Mischak, Dr. Med. Habil, Ph.D.
Mosaiques-diagnostics GmbH
Rotenburger Str. 20
D-30659 Hannover
GERMANY

Subject: Biomarker Letter of Support

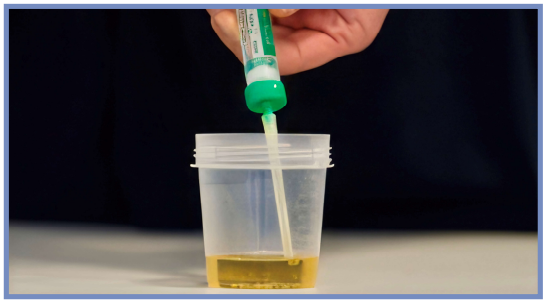
Dear Dr. Mischak,

We are issuing this Letter of Support to Mosaiques Diagnostics GmbH to encourage the further development of CKD273, a prognostic enrichment biomarker panel composed of 273 urinary peptides, to be used in combination with current measures (i.e., albuminuria, serum creatinine) in early phase clinical trials in diabetic kidney disease (DKD) to identify patients with early stage disease who may be more likely to progress. For a listing of the components of the CKD273 biomarker panel, please see Appendix 1.

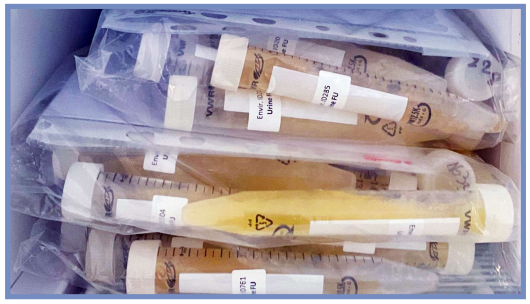
Available diagnostic tests

Sampling and shipment

Urine sampling (second morning urine, midstream).



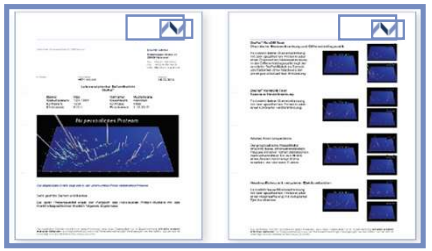
Transfer urine into monovette.



Collection and storage (-20°C).

Collective or individual sample shipping.

Proteomics analysis (CE-MS).



Report of results within three working days after receiving a sample.

Diagnostic tests: Chronic diseases

Who are the tests for?

The the urinary peptide test for early detection of chronic kidney and cardiovascular disease should be performed in the presence of risk factors, e.g.:

- Age
- Diabetes,
- Obesity,
- Hypertension,
- High cholesterol,
- Familiy history,
- Smoking

Enabling personalized therapy, targeted prevention of disease onset and progression

Diagnostic tests: Chronic diseases

Registered in-vitro diagnostic (IVD) tests for chronic diseases

Test name	HCU (Heart Check-Up)	CRS (CardioRenal Status)	KDD (Kidney Differential Diagnosis)
Function	Detection and prediction of coronary artery disease (CAD) and congestive heart failure (HF)	Prediction of major complications of diabetes mellitus and hypertension (CKD; CAD, HF)	Prediction of chronic kidney diseases (CKD) and differential diagnosis of common CKD subtypes
Accuracy (AUC and hazard ratio (HZ))	CAD AUC 83 % [1], HR 1.72 [2] HF AUC 94 % [3],HR 2.59 [2]	CKD AUC 96 % [1], HR 4.19 [2] CAD AUC 83 % [3], HR 1.72 [2] HF AUC 94 % [4], HR 2.59 [2]	CKD AUC 96 % [1] Differential diagnosis AUC 77–95 % (DN, MGN, MCD, IgAN, FSGS, LN, vasculitis) [2] IgANprogression AUC 72 % [3]
Reference	[1] Wei D, et al. Eur J Prev Cardiol. 2023, 00: 1–10. [2] Jaimes Campos MA, et al. Pharmaceuticals 2023, 16(9): 1298 [3] Campbell RT, et al. ESC Heart Fail. 2020, 7(4):1595 Zhang et al. J Am Heart Assoc. 2017, 6(8):e005432 Htun et al. PLoS One. 2017, 12(3):e0172036 He et al. Clin Transl Med. 2021, 11(1):e267	[1] Good DM, et al. Mol Cell Proteomics 2010, 9(11):2424 [2] Jaimes Campos MA, et al. Pharmaceuticals 2023, 16(9), 1298 [3] Wei D, et al. Eur J Prev Cardiol. 2023, 00: 1–10. [4] Campbell RT, et al. ESC Heart Fail. 2020, 7(4):1595 Tofte et al. Lancet Diabetes Endocrinol. 2020. 8(4):301-312	[1] Good DM, et al. Mol Cell Proteomics 2010, 9(11):2424 [2] Siwy J, et al. Nephrol Dial Transplant. 2017, 32(12):2079 [3] Rudnicki M, et al. Nephrol Dial Transplant. 2021;37(1):42-52 Peters et al., Nephrol Dial Transplant. 2023;38(12):2826-2834 Catanese et al. Clin Kidney J. 2023, 17(2), sfad296 Mavrogeorgis E, et al. Nephrol Dial Transplant. 2024;39(3):453-462

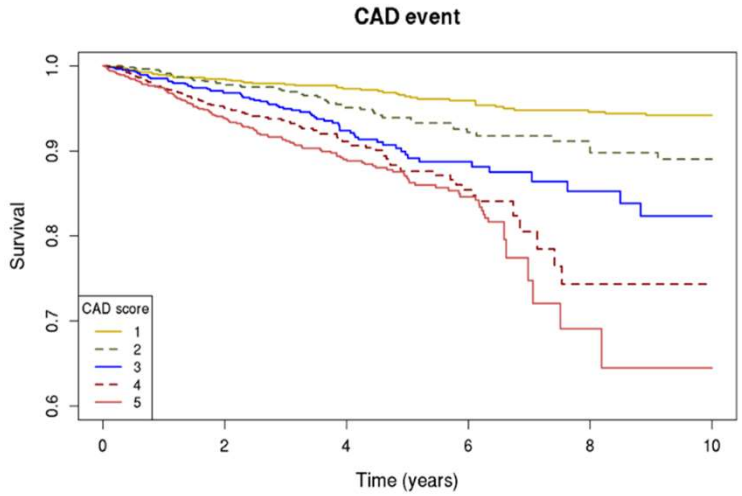
Kidney

Heart

Diagnostic tests: Chronic diseases

Scientific evidence and added value in early diagnosis of CVD

- The **HCU test** enables early detection of the most relevant cardiovascular diseases: coronary artery disease (CAD) and diastolic LV dysfunction / heart failure (HF). This allows early and personalized therapy and thus prevention of serious illnesses or death.



Kaplan-Meier survival analysis of proteomic CAD prediction:
Hazard Ratio = 1.72 (±0.050); p < 0.0001

The new classifier further improved the risk reclassification of CAD on top of the **Framingham or SCORE2 risk scores** (net reclassification index: 0.61, 95% CI: 0.25–0.95, P = 0.001; 0.64, 95% CI: 0.28–0.98, P = 0.001, correspondingly).

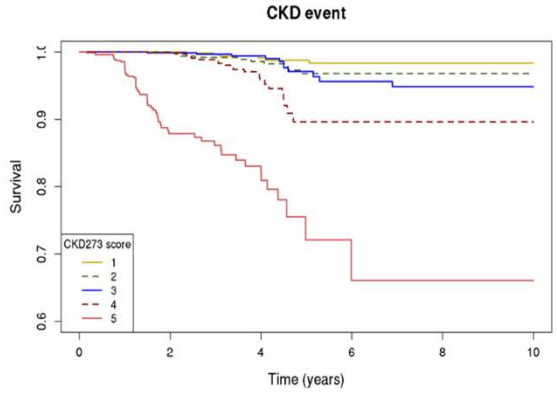
Jaimes Campos MA, et al. Pharmaceuticals 2023, 16(9), 1298
Wei D, et al. Eur J Prev Cardiol. 2023, 00: 1–10
Zhang et al. J Am Heart Assoc. 2017, 6(8):e005432
Htun et al. PLoS One. 2017, 12(3):e0172036
Zhang et al. Hypertension. 2015 Jul;66(1):52-60.
He et al. Clin Transl Med. 2021, 11(1):e267

Proteomics identifies patients at risk of developing CVD event.

Diagnostic tests: Chronic diseases

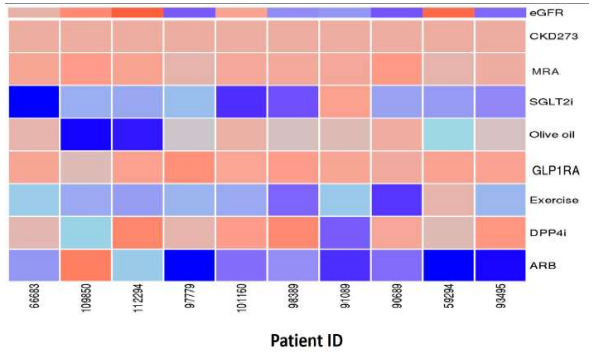
Scientific evidence and added value in early diagnosis of kidney diseases

- The **KDD test** enables early detection of CKD and differentiation between the most common subtypes, guiding personalized therapy at early stage, ideally preventing onset of clinically evident CKD.



Kaplan-Meier survival analysis of proteomic prediction of chronic kidney disease progression :
Hazard Ratio = 4.19 (±0.094); p < 0.0001

In silico prediction of individual response to specific intervention (blue=response, red=no response)



Current used albuminuria detect kidney disease when there is massive organ damage.

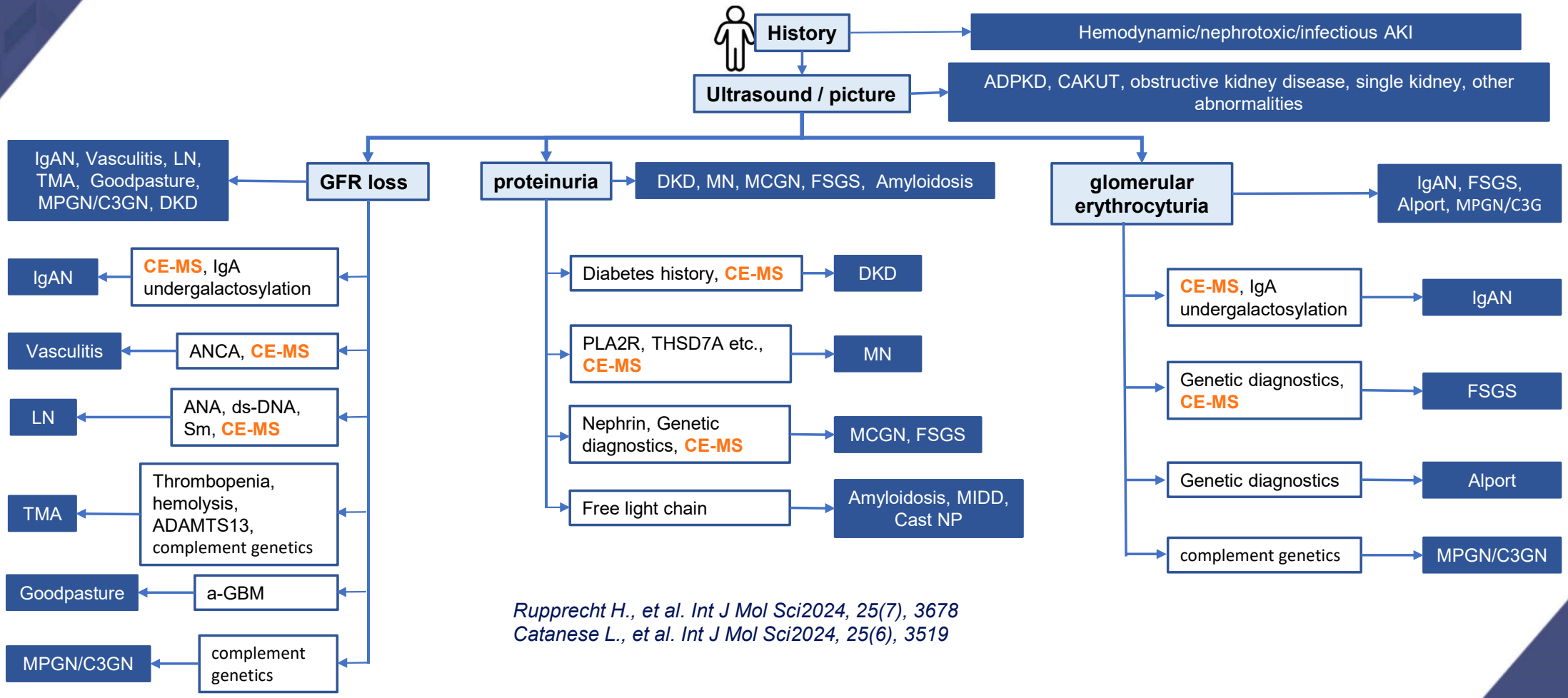
KDD is the only test worldwide that demonstrated early detection in prospective clinical trial!

Jaimes Campos et al., Pharmaceuticals 2023, 16(9), 1298
Tofte et al. Lancet Diabetes Endocrinol. 2020. 8(4):301-312
Pontillo et al. Nephrol Dial Transplant. 2017 Sep 1;32(9):1510

Proteomics identifies patients who will develop CKD in advance to albuminuria.

Diagnostic tests: Chronic diseases

Recommendation for biomarkers in the management of kidney diseases



Rupprecht H., et al. Int J Mol Sci2024, 25(7), 3678
Catanese L., et al. Int J Mol Sci2024, 25(6), 3519

Diagnostic tests: Oncology

Who are the tests for?

The the urinary peptide test for detection of bladder and prostate cancer should be performed by the presence of risk factors, e.g.:

- Hematuria
- Painful urination
- Back pain (bladder cancer)
- Frequent infection (bladder cancer)
- Family history (prostate cancer)
- Increased PSA (prostate cancer)

For non-invasive early detection, monitoring, and guiding therapy

Diagnostic tests: Onclology

Registered in-vitro diagnostic (IVD) tests for tumour detection

Testname	PCU (Prostate Check-Up)	PSM (Prostate Status Management)	BCU or BSM (Bladder Check-Up or Management)
Function	Prostate cancer diagnosis after increased PSA-value	Diagnosis of significant prostate cancer	Detection of primary bladder cancer Monitoring for recurrence of bladder cancer
Accuracy (AUC)	81 % [1]	82 % [1]	85 or 82 % +cytology [1]
Reference	[1] Frantzi M, et al. Cancers (Basel). 2023 Feb 11;15(4):1166. Schiffer E, et al. Int J Urol. 2012, 19(2):118	[1] Frantzi M, et al. Br J Cancer 2019, 120(12):1120 Frantzi M, et al. World J Urol. 2022, 40(9):2195	[1] Mengual L, et al. Br J Cancer 2022, 127(11):2043 Frantzi M, et al. Clin Cancer Res, 2016, 22(16):4077

Bladder

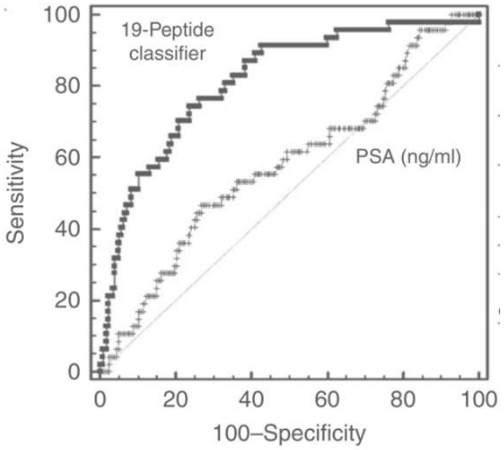
Prostate

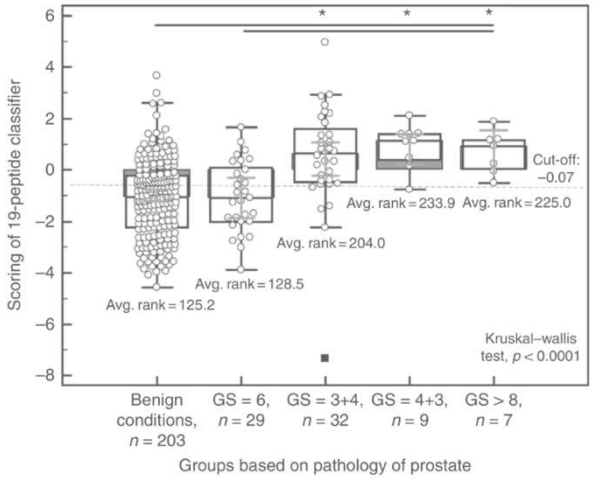
Diagnostic tests: Oncology

Scientific evidence and added value in early diagnosis of prostate cancer

- Detection of prostate cancer (PCa) using the non-invasive urine based **PCU test**.
- Discrimination between significant (requiring treatment) and indolent (no treatment required) PCa using the non-invasive **PSM test**.

Pairwise comparison	
19-Peptide classifier (AUC)	0.82 (0.76–0.86)
PSA (ng/ml) (AUC)	0.58 (0.52–0.64)
p value	<0.0001
Sample size (*n*)	274
Case/ control group(*n*)	47/227





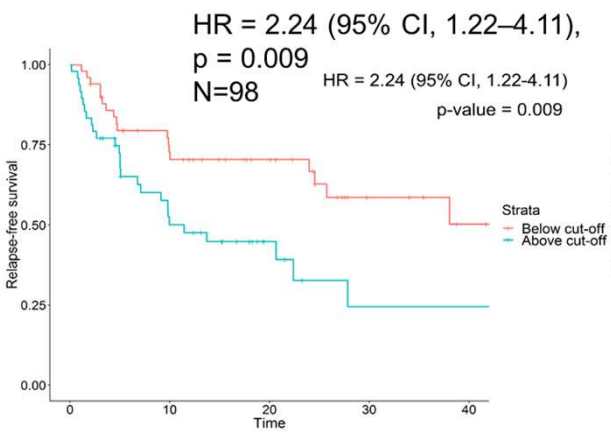
Frantzi et al. World J Urol. 2022, 40(9):2195-2203
Frantzi et al. Br J Cancer. 2019, 120(12):1120-1128
Frantzi M, et al. Cancers (Basel). 2023 Feb 11;15(4):1166.

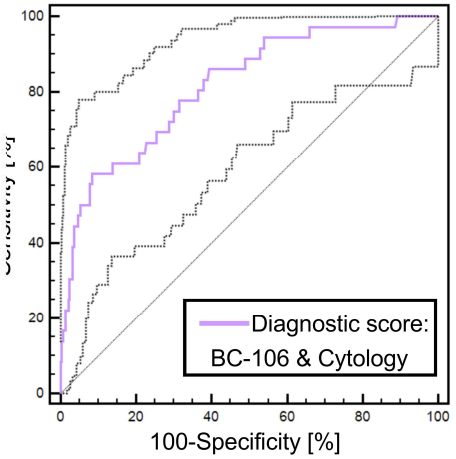
Proteomics identify prostate cancer more accurate and earlier.

Diagnostic tests: Oncology

Scientific evidence and added value in diagnosis of bladder cancer

- The **BCU test** can detect Bladder cancer (BC) early and non-invasively. This gives the opportunity for timely initiation of appropriate treatment.
- BC has a high recurrence rate of more than 50 %. Therefore, monitoring for recurrence of BC is necessary. The **BSM test** enables non-invasive monitoring.





ROC curve	*BC-106 & Cytology*
Recurrent cohort	*n= 318*
Cases / Controls	*n= 36 / 282*
AUC	*0.82*
95% CI	*0.77 – 0.86*
Significance P	*<0.0001*

Frantzi et al. Clin Cancer Res 2016, 22(16):4077-86,
Krochmal et al. Sci Rep. 2019;9(1):7635
Mengual et al. Br J Cancer. 2022, 127(11):2043-2051

Proteomics biomarkers enables detection of primary and recurrent BC

Why choose our diagnostic method?

The technology and the clinical application have been:

- developed during the last **20 years**
- published in **>400 scientific articles** that have been **cited >20000 times**
- proven in **>100 clinical studies**
- based on **>85000 proteome datasets**
- containing information on **>100 million individual measurements**
- generated together with **>1200 scientists** worldwide

"Exploring the Future: Do You Have Questions?"

Harald Mischak
Prof. PhD MD Dipl.-Ing.

- Co-founder of mosaiques

Maria Franzi
PhD

- oncology

Agnieszka Latosinska
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- cardiology

Justyna Siwy
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