protexam

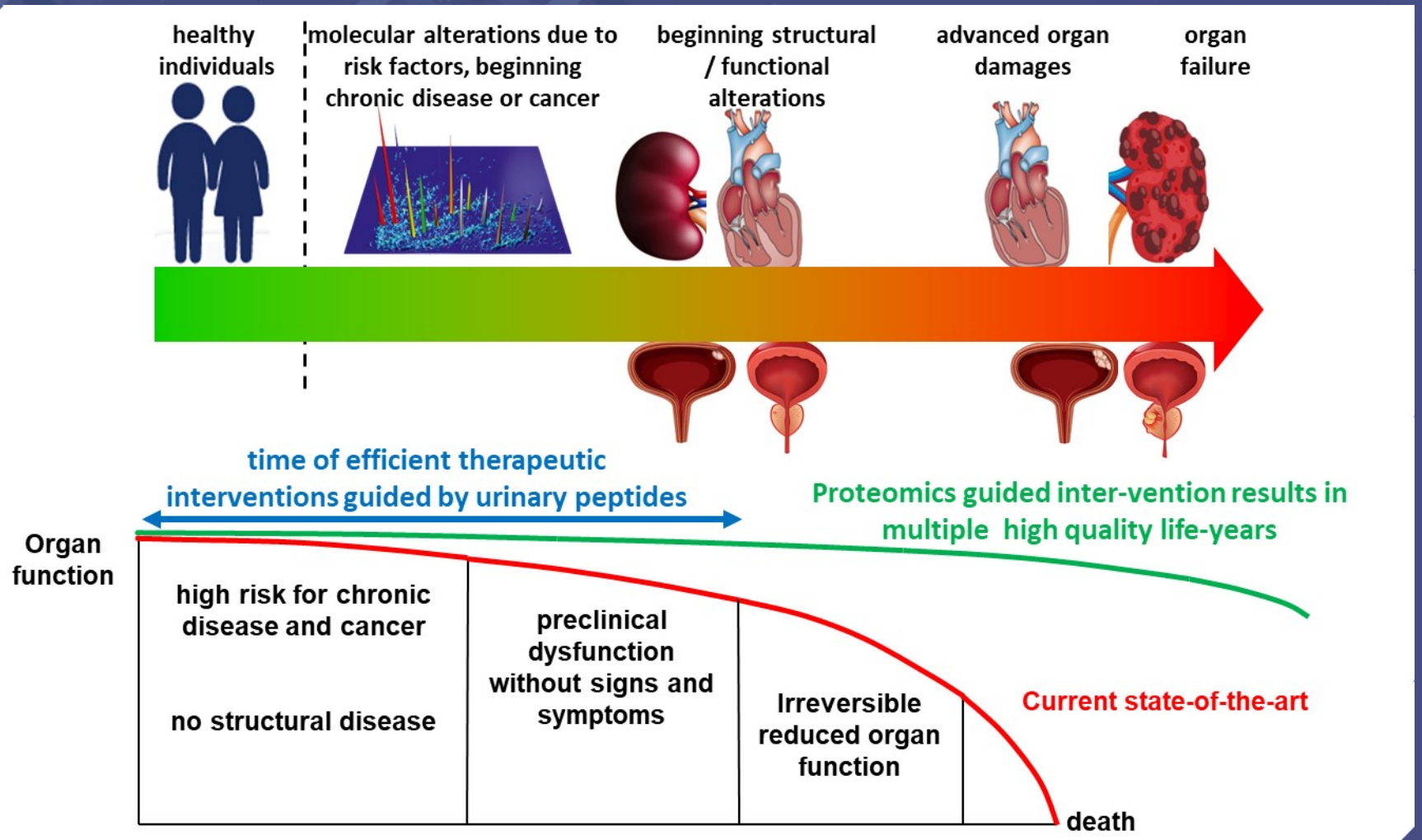
Diagnostic biomarker tests

Ready-to-use tests with IVD registration

Clinical proteome analysis
The power of protexam CE-MS technology

Time to act

to protect the human life!



... we detect diseases before organ damage

...

Chronic diseases

The the urinary peptide test for early detection of chronic kidney and cardiovascular diseasee should be performed by 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

Oncology

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

Sampling and shipment

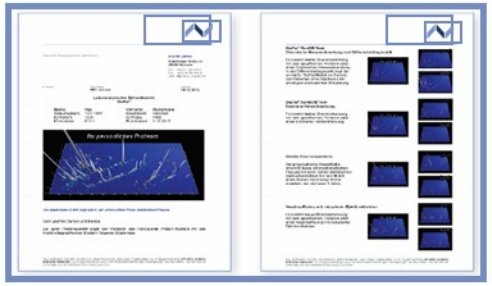
Urine sampling (second morning urine, midstream)

Transfer urine into monovette

Collection and storage (-20°C)

Collective or individual sample shipping

CE-MS analysis



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

IVD registration and FDA Letter-of-support

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.

IVD

All proteomic tests are registered as in-vitro diagnostics (IVD) in Germany.
Letter-of–support from the US-FDA for the CKD273 test.

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, x, in press [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, x, in press [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 (2020) 1–11 Peters et al., Nephrol Dial Transplant, 2023, 0, 1–9 Catanese et al. Clinical Kidney Journal, submitted Mavrogeorgis E, et al. Nephrol Dial Transplant (2020), accepted

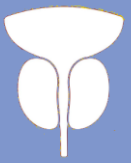
Kidney

Heart

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

Testname	PCU (Prostate Check-Up)	PSM (Prostate Status Management)	BCU (Bladder Check-Up)	BSM (Bladder Status Management)	BPA-CC and UPA-CC (Bile/Urine Proteome Analysis-CC)
Function	Prostate cancer diagnosis after increased PSA-value	Diagnosis of significant prostate cancer	Detection of primary bladder cancer	Monitoring for recurrence of bladder cancer	Early detection of a cholangiocarcinoma (CC)
Accuracy (AUC)	81 % [1]	82 % [1]	85 % +cytology [1]	82 % +cytology [1]	96 % (bile/urine) 93 % (urine)
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	[1] Mengual L, et al. Br J Cancer 2022, 127(11):2043 Frantzi M, et al. Clin Cancer Res, 2016, 22(16):4077	Voigtländer T, et al. United European Gastroenterol J. 2017, 5(5):668

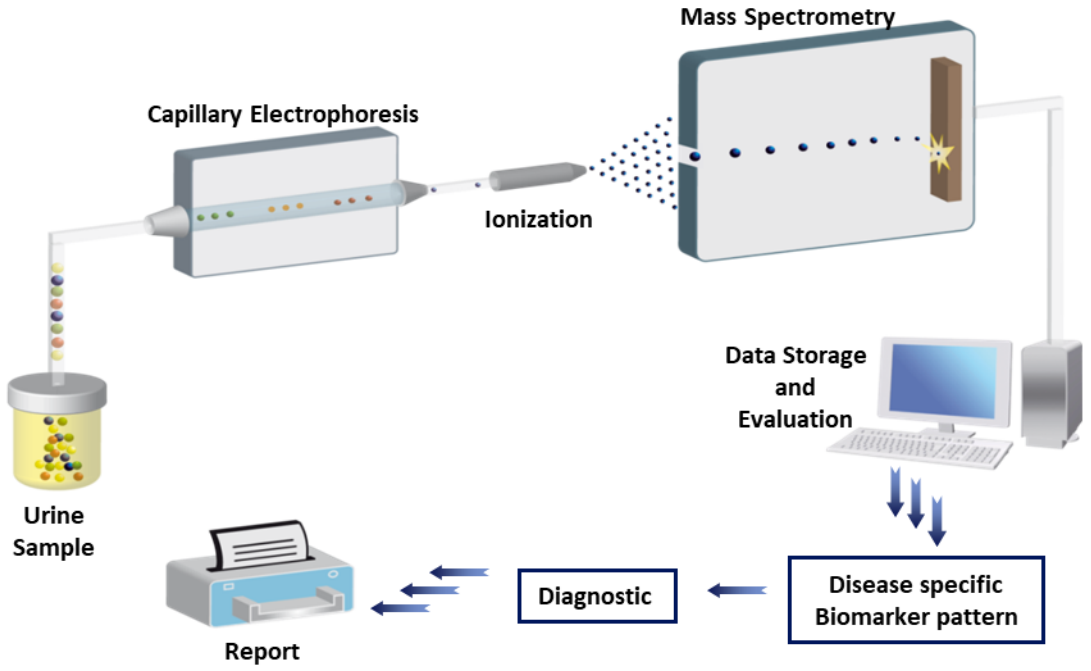
Bladder



Prostate

Technology background

Capillary Electrophoresis coupled to Mass Spectrometry (CE-MS)

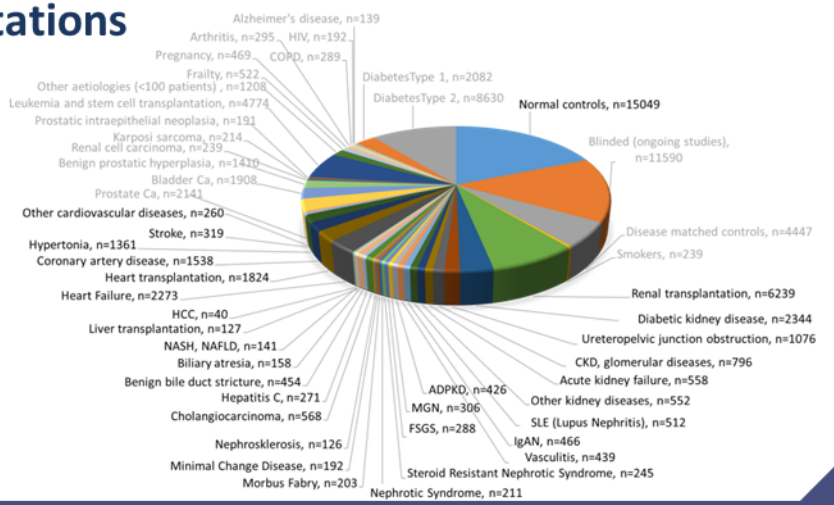


Separation and analysis of proteins and peptides (typically 2000-5000)

Run time ~**60 min**

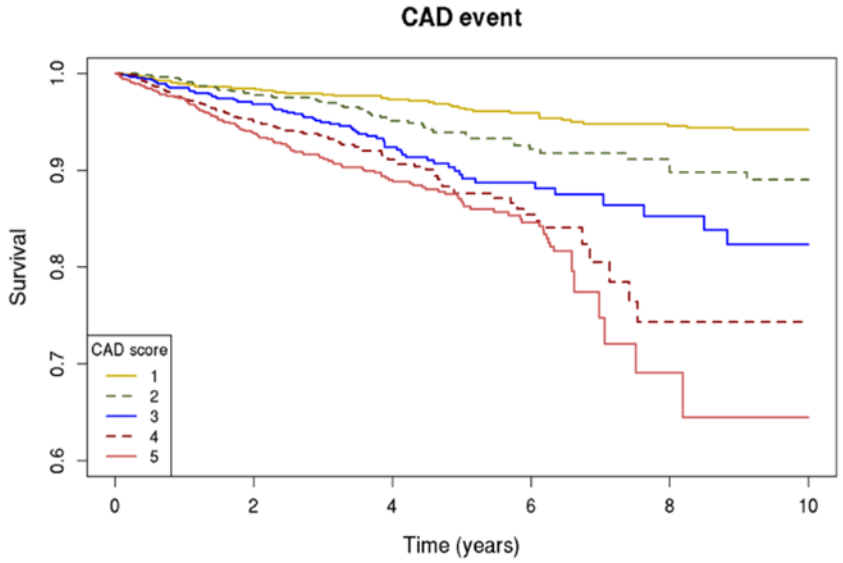
Our know-how

- full proteome (quality and quantity)
- **> 85.000 human data**
- > 20.000 proteins and peptides
- patents for procedure and key technology (no claims from third parties)
- compehensive approach
  ➔ **no limitations**



Scientific evidence and added value in early diagnosis of heart diseases I

- Cardiovascular diseases (CVD) are the leading cause of death worldwide.
- 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

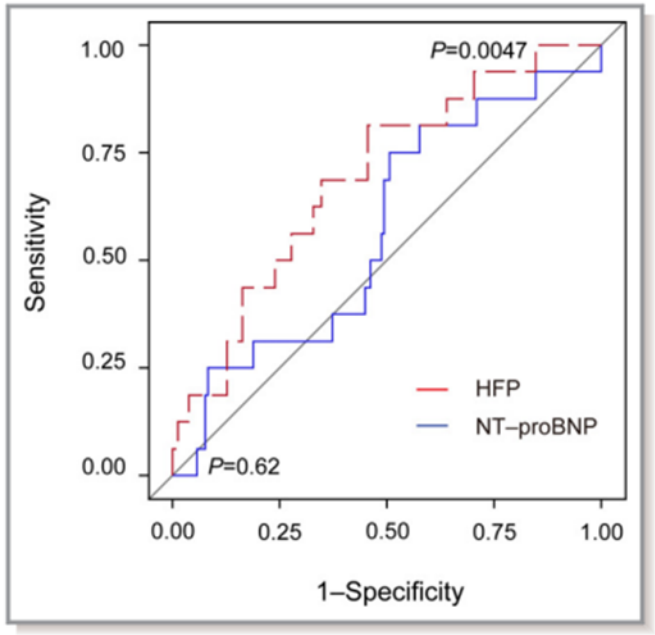
The new classifier further improved the risk reclassification of CAD on top of the **Framingham or SCORE2 risk scores** (net reclassification index: 0.61, 95% CI: 0.25–0.95, P = 0.001; 0.64, 95% CI: 0.28–0.98, P = 0.001, correspondingly).

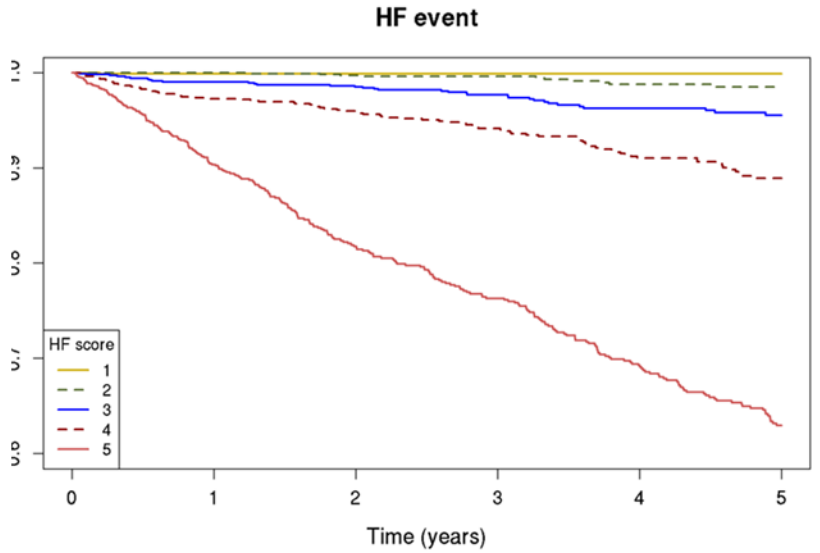
Jaimes Campos MA, et al. Pharmaceuticals 2023, 16, x, in press
Wei D, et al. Eur J Prev Cardiol. 2023, 00: 1–10
Zhang et al. J Am Heart Assoc. 2017, 6(8):e005432
Htun et al. PLoS One. 2017, 12(3):e0172036
Zhang et al. Hypertension. 2015 Jul;66(1):52-60.
He et al. Clin Transl Med. 2021, 11(1):e267

Proteomics identifies patients at risk of developing CVD event (myocard infarct)

Scientific evidence and added value in early diagnosis of heart diseases II

- Early detection of heart failure (HF) enables targeted intervention to ideally prevent onset of clinically relevant disease. This is possible based on specific changes in urinary peptides





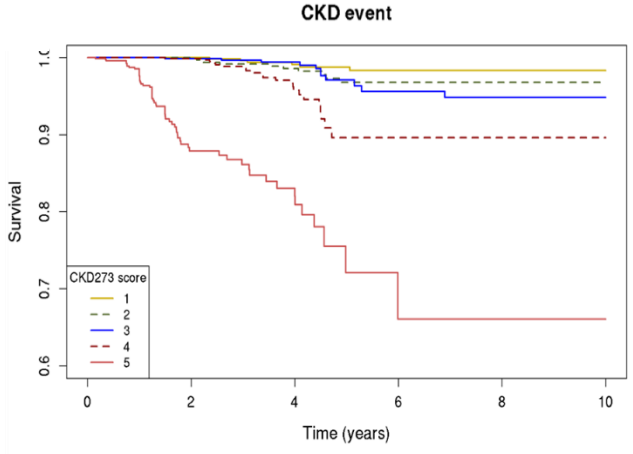
Kaplan-Meier survival analysis of proteomic HF prediction:
Hazard Ratio = 2.59 (±0.047); p < 0.0001

Jaimes Campos et al., Pharmaceuticals 2023, 16, in press
Campbell RT, et al. ESC Heart Fail. 2020, 7(4):1595
Zhang et al. J Am Heart Assoc. 2017, 6(8): e005432.

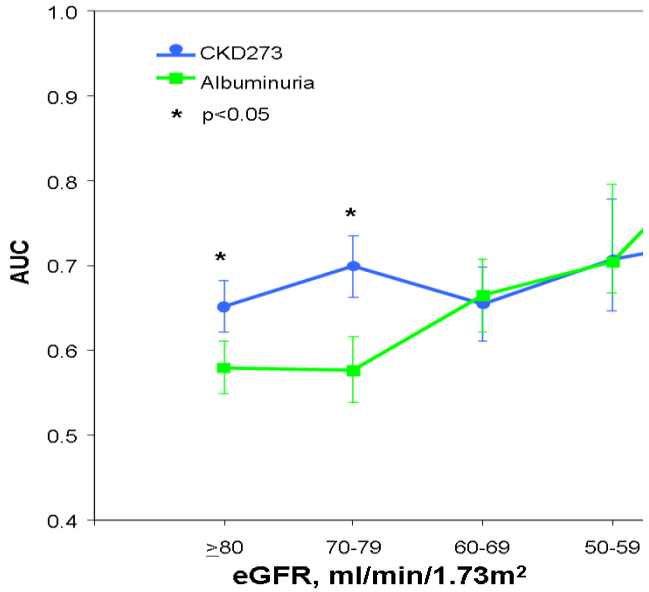
Proteomics predicts progression to heart failure more accurate than a research-optimized NT-proBNP

Scientific evidence and added value in early diagnosis of kidney diseases

- About 10 % of the worlds population suffers from chronic kidney disease (CKD), which will progress to end-stage renal disease, requiring dialysis or transplantation to avoid death.
- 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



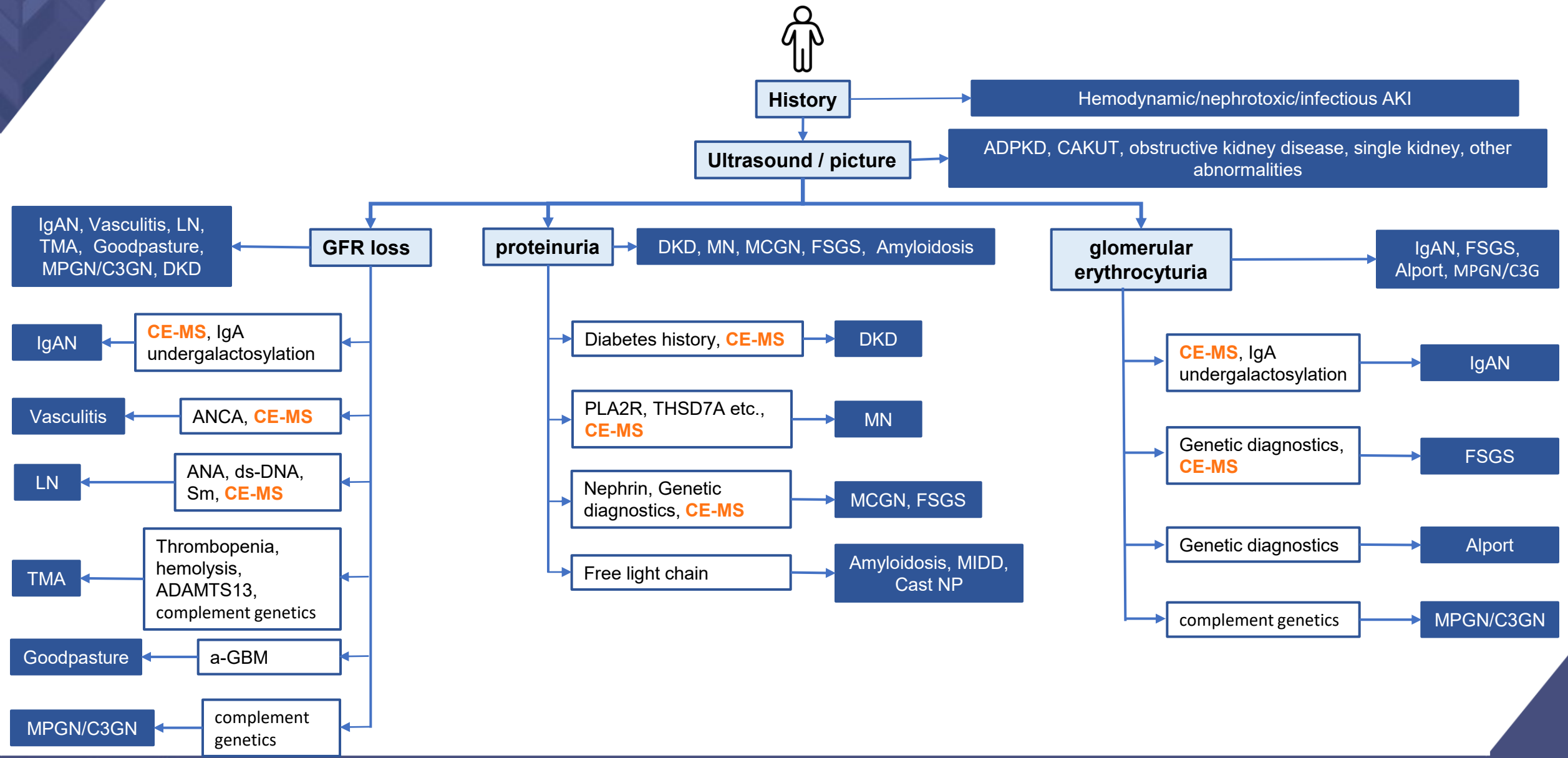
Current used albuminuria detect kidney disease when there is massive organ damage

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

Jaimes Campos et al., Pharmaceuticals 2023, 16, in press
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

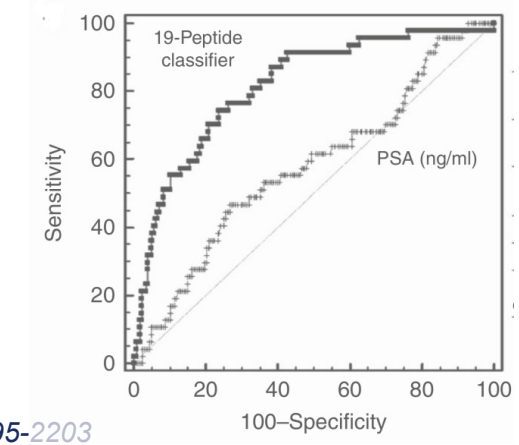
Application of proteomics (CE-MS) biomarkers for detection and classification of kidney diseases

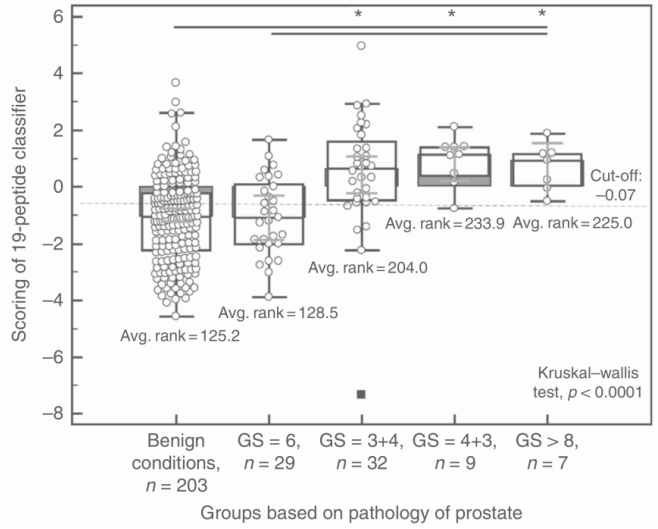


Scientific evidence and added value in early diagnosis of prostate cancer

- The **PCU test** offers patients with elevated PSA levels a non-invasive approach to determine whether prostate cancer (PCa) is present or absent.
- PCa is one of the most common types of cancer in men. It is important to distinguish between indolent (does not require treatment) and significant tumor that requires treatment to reduce unnecessary treatments. The **PSM test** enables non-invasive differentiation between indolent and significant PCa.

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

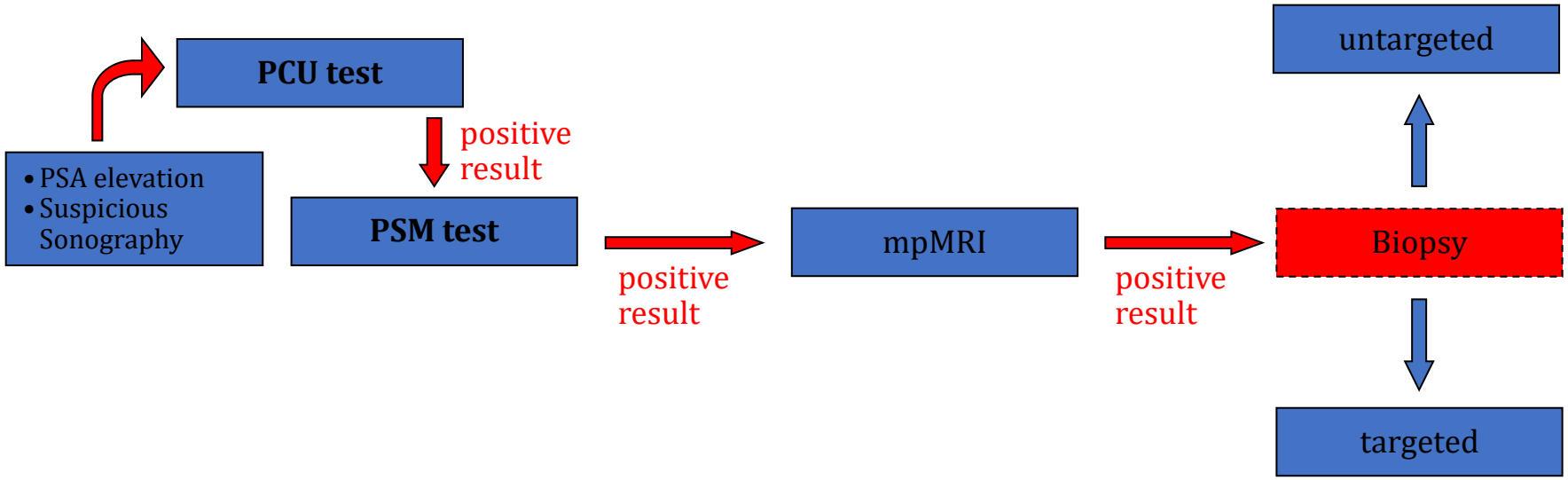




Frantzi et al. World J Urol. 2022, 40(9):2195-2203
Frantzi et al. Br J Cancer. 2019, 120(12):1120-1128
Frantzi M, et al. Cancers (Basel). 2023 Feb 11;15(4):1166.

Proteomics identify prostate cancer more accurate and earlier

Application of proteomics (PCU/PSM) biomarkers for detection and monitoring of prostate cancer



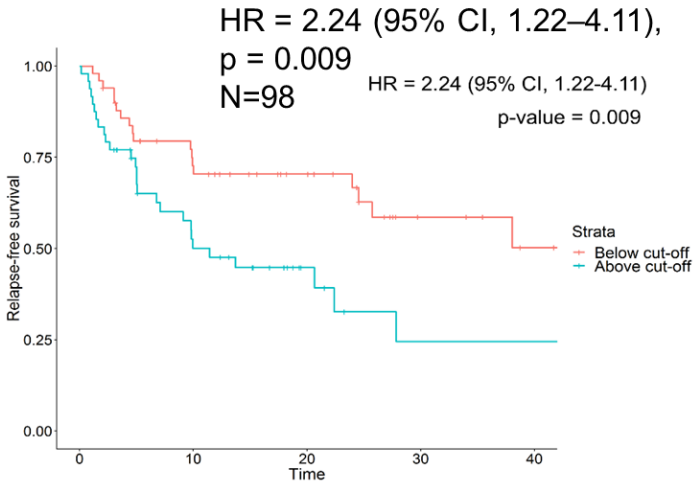
After the examination with the PSA value, a **PCU test** should be carried out if the result is positive. If this is also positive, then the **PSM test** should be carried out afterwards.

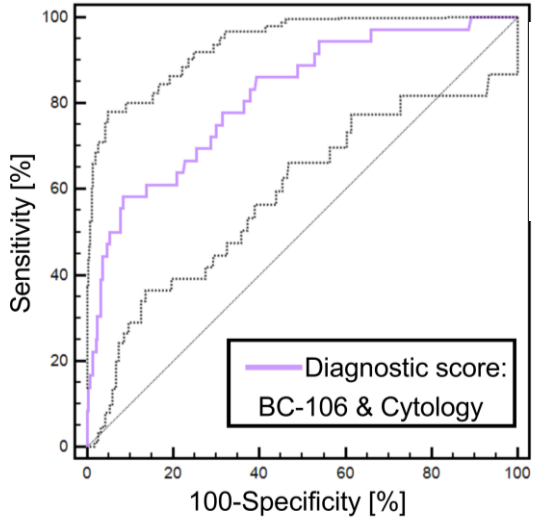
If the test result indicates an aggressive tumour, then an mpMRI examination is recommended. This can then be used to localise the tumour. This examination is more cost-intensive than the **PCU test** and therefore only makes sense if the proteome test is positive. The **PSM test** also increases the accuracy of the mpMRI result because it confirms the tissue abnormality as a cancer finding solely molecularly with assured further medical treatment measures.

Advantages: NON-INVASIVE tests, there is no need for prior digital rectal examination and/or prostate massage, these tests reduce the unnecessary biopsies by correcting false positive PSA tests, the tests can identify prostate cancer more accurate and earlier so that appropriate intervention can be initiated.

Scientific evidence and added value in diagnosis of bladder cancer

- Bladder cancer (BC) is the second leading cause of death among urogenital tumors. The **BCU test** can detect 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 bladder cancer is necessary. The **BSM test** enables non-invasive monitoring.



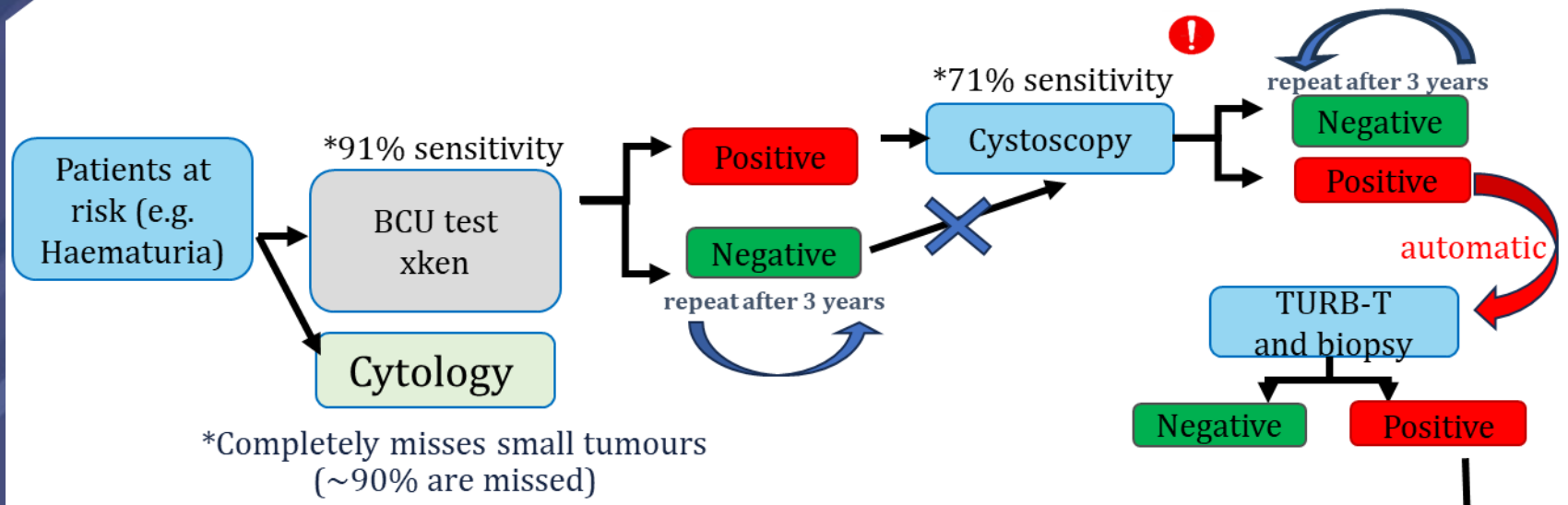


ROC curve	BC-106 & Cytology
Recurrent cohort	n= 318
Cases / Controls	n= 36 / 282
AUC	0.82
95% CI	0.77 – 0.86
Significance P	<0.0001

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 BCa

Application of proteomics (BCU/BSM) biomarkers for detection and monitoring of bladder cancer



- The **BCU test** significantly reduces the number of cystoscopies required (70% to 80%).
- The **BSM test** reduce the number of cystoscopies required per bladder cancer recurrence to 60%.
- The **BSM test** also detects carcinomas in the upper urothelial tract and in the urethra at an early stage - in 30% of cases and in severe cases!
- The cancer cells are excreted in the urine! Thus, the **BSM urine test** detects cancers even outside the bladder!

Revolutionize your diagnostic pipeline with Mosaiques' expertise in proteomics!

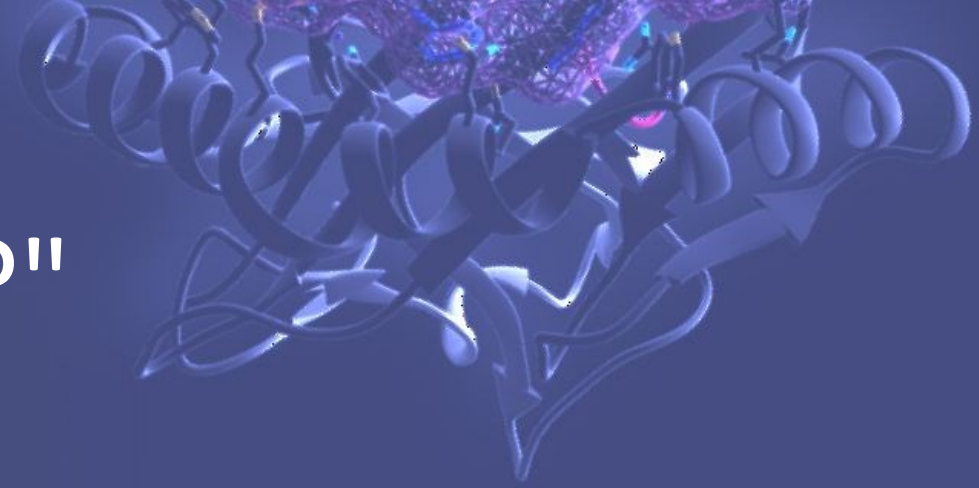
Why choose our diagnostic method?

- ✓ Robust and reproducible method with an extensive track record
  - > 100 clinical studies
  - > 400 publications
- ✓ FDA Letter of Support
- ✓ Easily obtainable/ non-invasive
- ✓ Can be repeated multiple times and enables monitoring
- ✓ Is superior to other established parameters (e.g. albuminuria, eGFR)
- ✓ Enables early detection of disease, can guide early intervention, and significantly improve outcome

Explore our diagnostic service for

- ✓ Early diagnosis
- ✓ Prediction of disease progression
- ✓ Prediction of recurrence
- ✓ Prediction of drug response
- ✓ Therapy guidance
- ✓ Treatment monitoring

"Exploring the Future:
Do You Have Questions?"



Harald Mischak
Prof. PhD MD Dipl.-Ing.

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- oncology

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