Best Practice of Overcoming Personalised Medicine Implementation Barriers
co-funded ERA-PerMed Project 2018 Call *"Multidimensional stratification for treatment of acute kidney injury - Kidney Attack Project"* (Health Research Institute of Jiménez Díaz Foundation IIS-FJD)
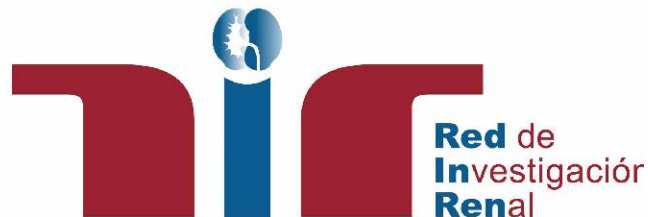
Alberto Ortiz, MD, PhD

Chief of Nephrology and Hypertension

Professor of Medicine

IIS-Fundacion Jimenez Diaz/Universidad Autonoma de Madrid

The issues

The ERA-PerMed Project

The barriers

Worldwide top projected causes of death by 2040

Leading causes 2016	Leading causes 2040	Mean % change number of YLLs
1 Ischaemic heart disease	1 Ischaemic heart disease	−3·6 (−43·1 to 40·9)
2 Stroke	2 Stroke	−10·7 (−40·1 to 31·9)
3 Lower respiratory infections	3 Lower respiratory infections	−24·8 (−47·9 to 3·4)
4 Diarrhoeal diseases	4 COPD	32·1 (−13·0 to 98·4)
5 Road injuries	**5 Chronic kidney disease**	**100·3 (8·3 to 302·1)**
6 Malaria	6 Alzheimer's disease	131·2 (90·9 to 196·6)
7 Neonatal preterm birth	7 Diabetes	76·7 (10·3 to 228·8)
8 HIV/AIDS	8 Road injuries	−18·3 (−31·7 to 8·5)
9 COPD	9 Lung cancer	20·7 (−9·0 to 60·5)
10 Neonatal encephalopathy	10 Diarrhoeal diseases	−39·7 (−76·5 to 47·0)
11 Tuberculosis	11 Self-harm	7·8 (−15·2 to 41·9)
12 Congenital defects	12 HIV/AIDS	−30·4 (−41·8 to −20·3)
13 Lung cancer	13 Liver cancer	69·6 (30·7 to 135·2)
14 Self-harm	14 Hypertensive heart disease	89·9 (6·3 to 358·7)
15 Diabetes	15 Colorectal cancer	59·1 (18·3 to 123·9)
16 Chronic kidney disease	16 Tuberculosis	−40·0 (−52·8 to −19·7)
17 Other neonatal	17 Congenital defects	−41·0 (−50·6 to −30·5)
18 Alzheimer's disease	18 Neonatal preterm birth	−57·0 (−66·4 to −48·9)

YLL: years of life lost

Foreman KJ et al. Lancet 2018; 392: 2052–90

What is AKI?

Acute
Kidney
Injury

What is CKD?

Currently missing

Either of the following for **>3 months**)

1. Markers of **kidney damage** (one)
- **Albuminuria** (**>30** mg/g creatinine)
- Abnormalities detected by histology
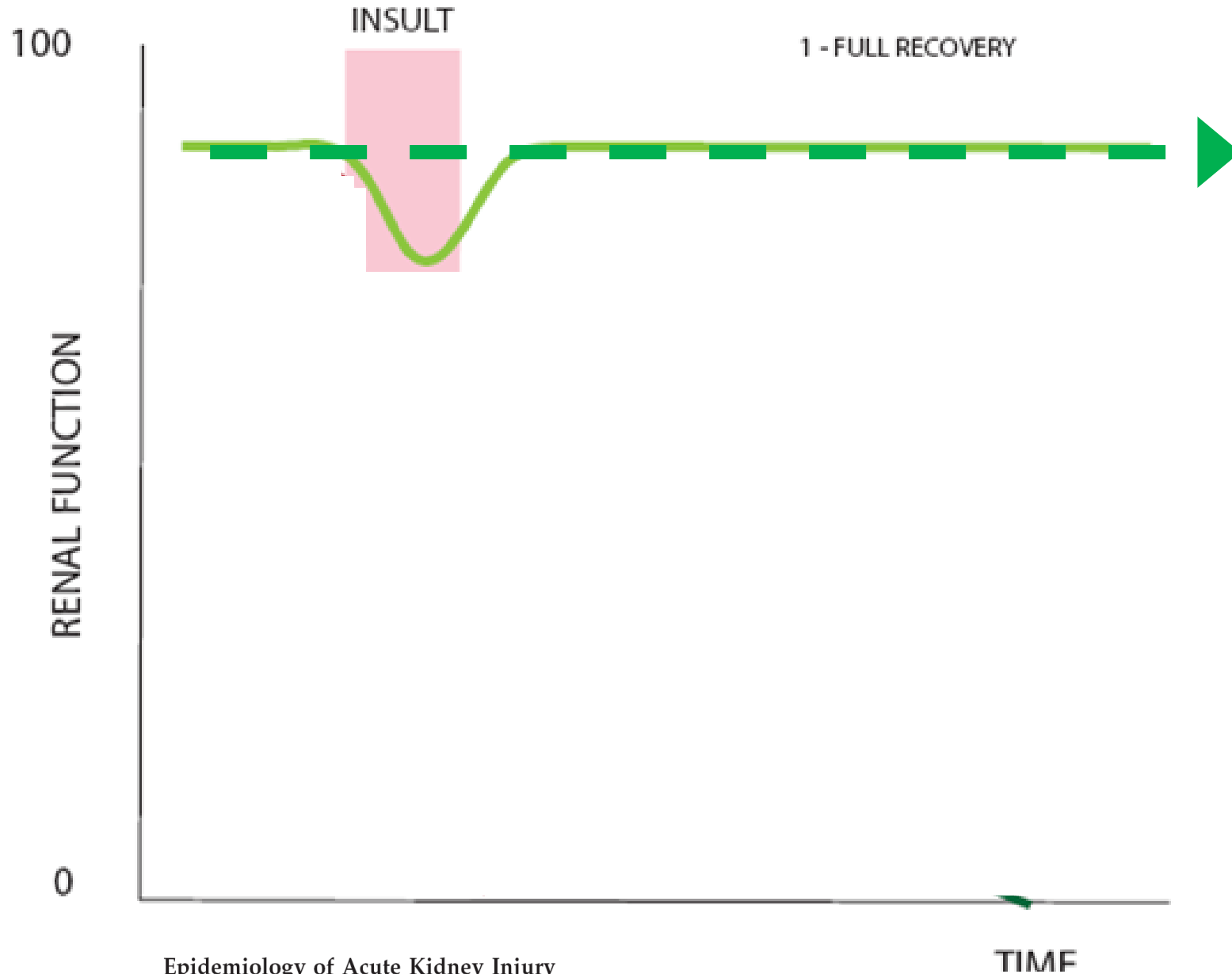- Other

or

Serum creatinine increases
≥0.3 mg/dl in **48**h

or

>50% in **7 days**

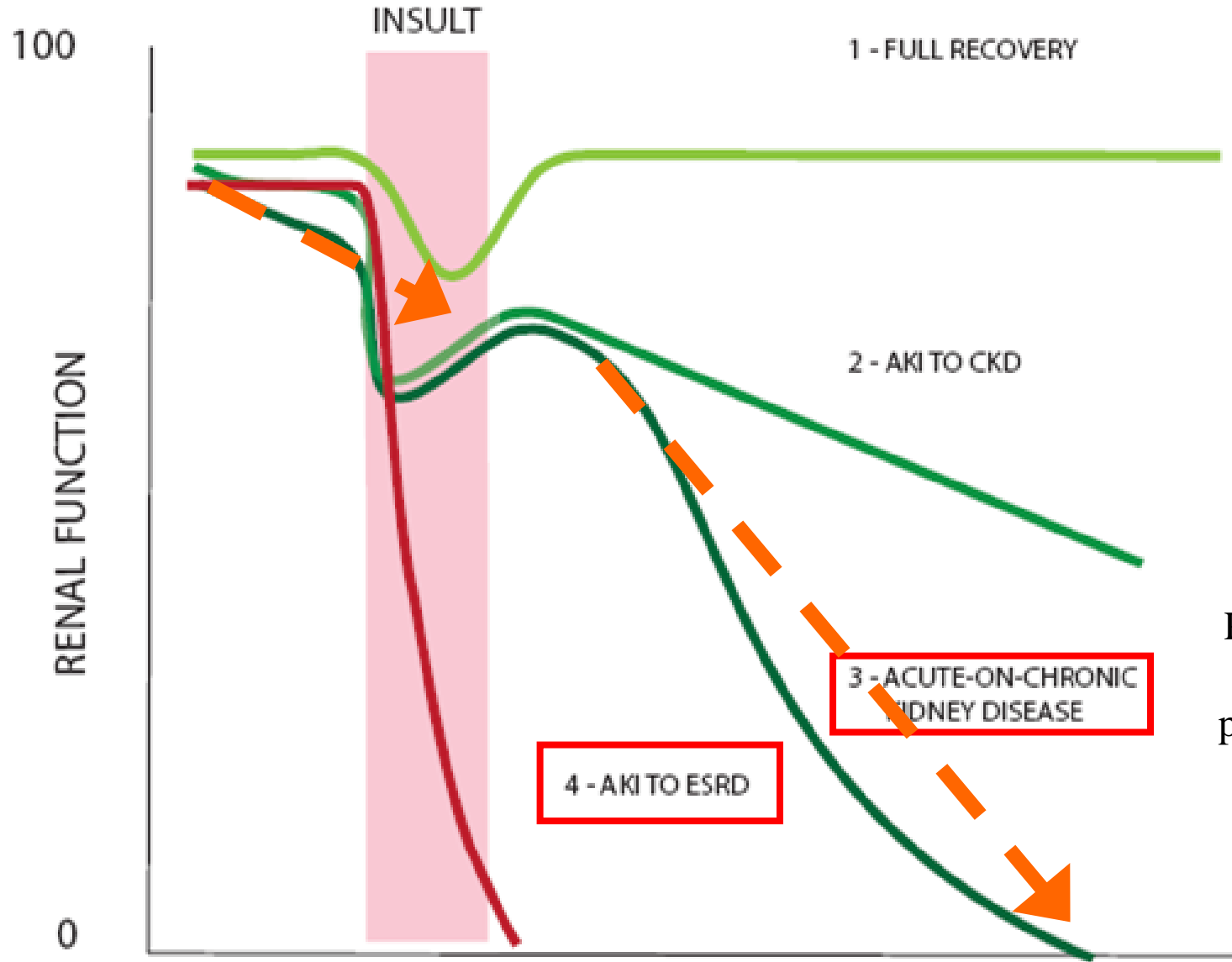**2. Decreased GFR** (**<60** ml/min/1.73 m^2)

AKI: the traditional view

Epidemiology of Acute Kidney Injury

Jorge Cerdá,* Norbert Lameire,† Paul Eggers,‡ Neesh Pannu,§ Sigehiko Uchino,‖ Haiyan Wang,¶ Arvind Bagga,** and Adeera Levin††

Clin J Am Soc Nephrol 3: 881-886, 2008

AKI

Probably the **most common, CKD** predisposes to AKI

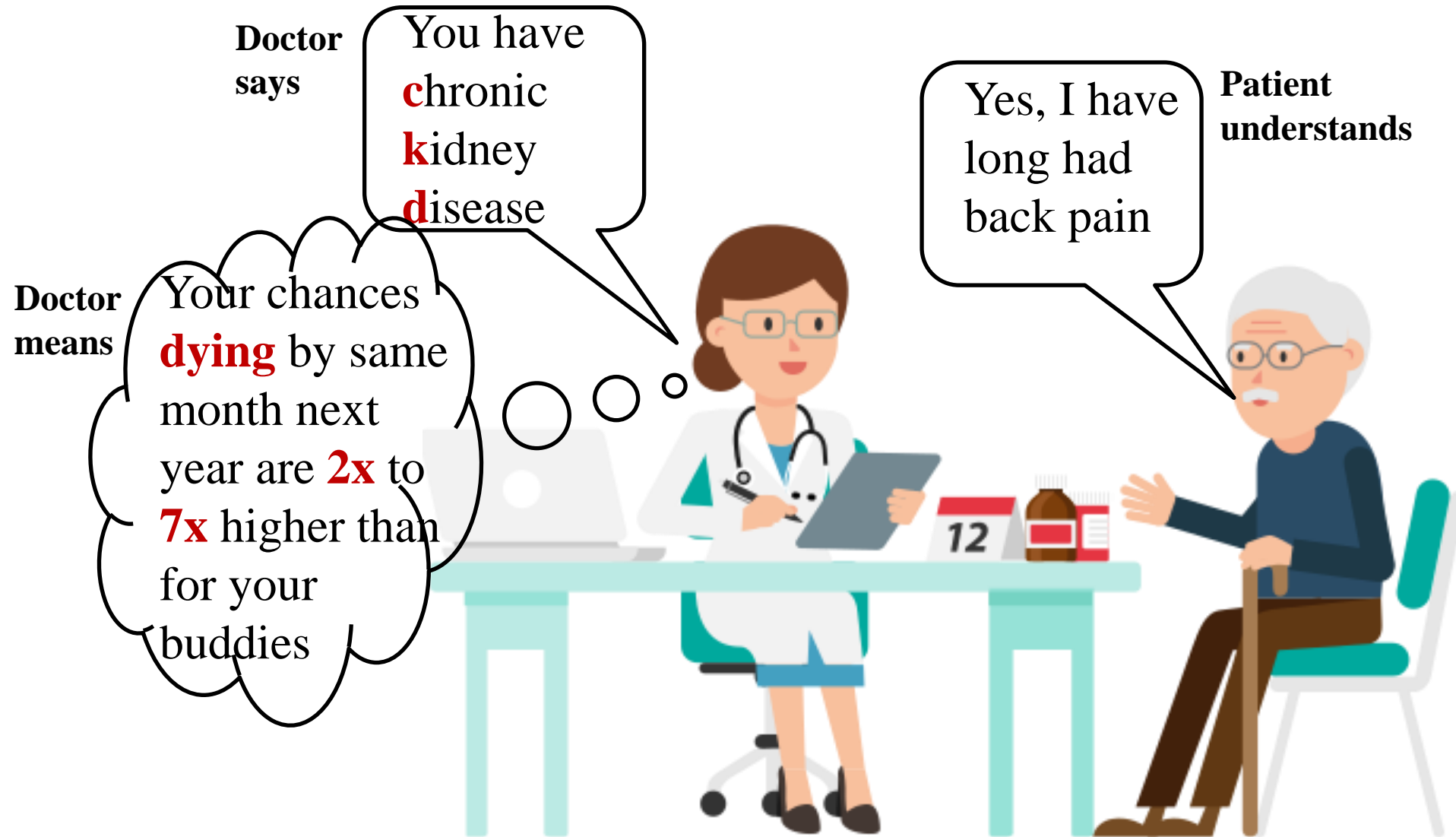# Where do the GFR and albuminuria **thresholds** come from?

Risk

- For CKD progression

- For all-cause and cardiovascular **death**

  - Death, the **ultimate outcome**

  - The issue is not if, but **when**

Premature!

A CKD diagnosis

https://commons.wikimedia.org/wiki/File:Doctor_with_Patient_Cartoon.svg

CKD is the risk factor associated with **highest** COVID-19 **mortality** after old age

Data: Williamson EJ et al. Nature. 2020;584:430-6; Graph Ortiz et al. NDT 2020

Figure 1

			Categories de albuminuria (CACo, mg/g)		
			A1	**A2**	**A3**
			<30	**30-299**	**≥300**
	G1	**>90**	0.9-1.5x*	1.7-2.3x	2.1-3.7x
	G2	**60-89**	1.0-1.4x*	1.6-2.0x	3.7-4.1x
	G3a	**45-59**	1.5-2.2x	2.8x	4.3x
	G3b	**30-44**	2.2-2.7x	3.4x	5.2x
	G4	**15-29**	7.9-14.1x	4.8x	8.1x
	G5	**<15**	+++	+++	+++
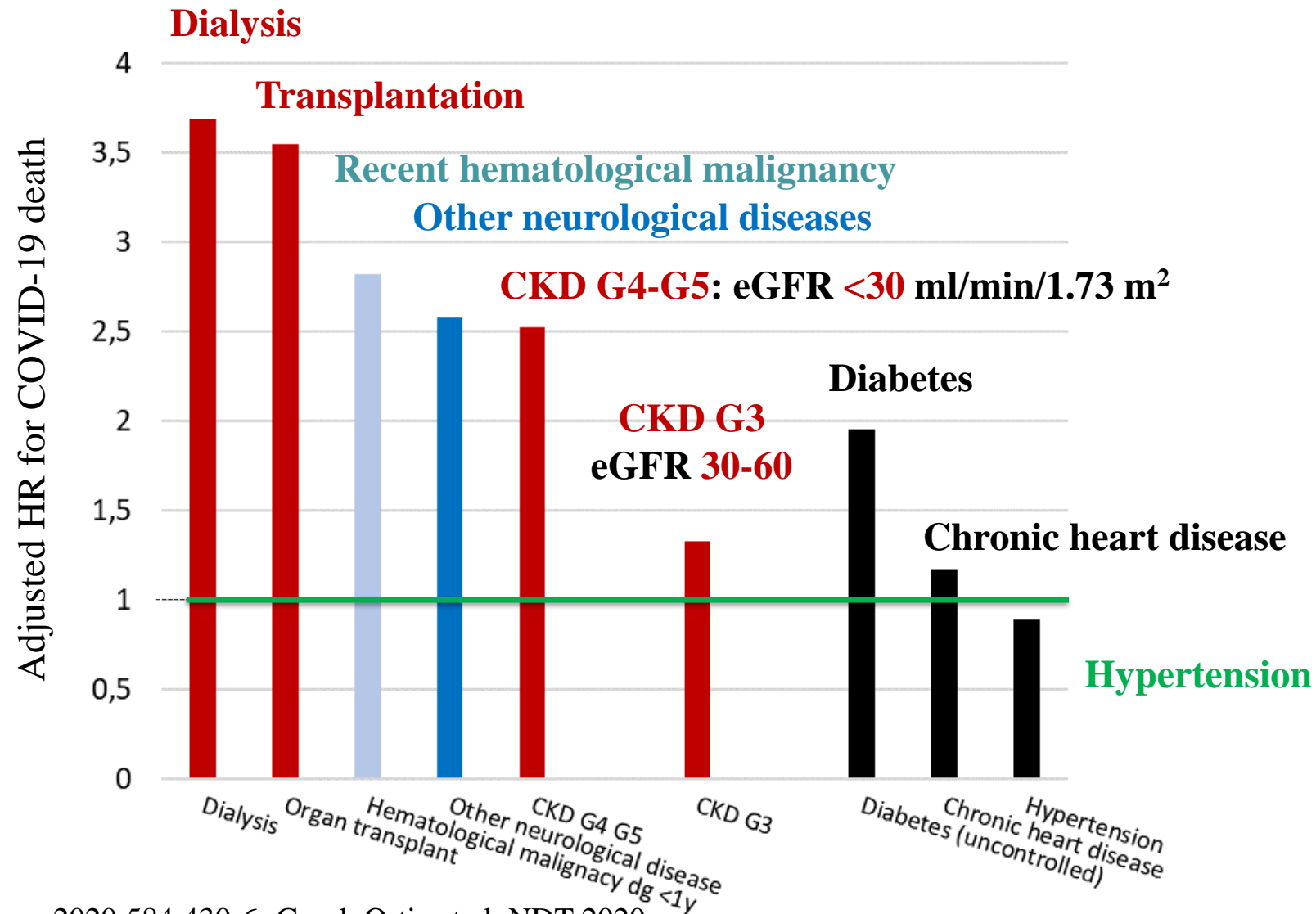
Risk of cardiovascular death

Categorias de FGe (mL/min/1.73 m²)

Gravedad de la ERC
- Mild CKD
- Moderate CKD
- Severe CKD

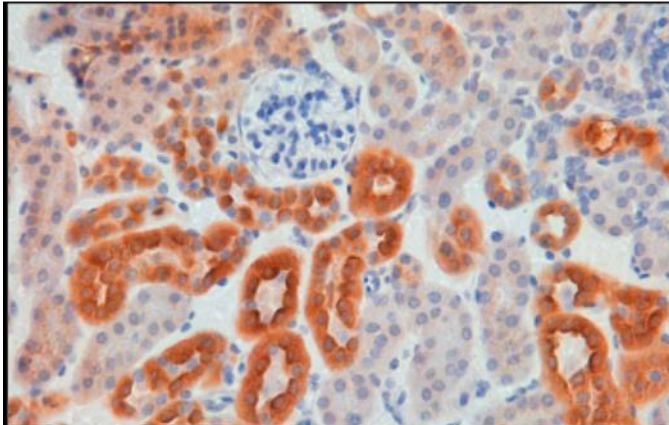**ESC 2021 riesgo de ECV**
- High CVD risk
- Very high CVD risk

SENEFRO (ms in preparation), based on KDIGO CKD 2012

2018

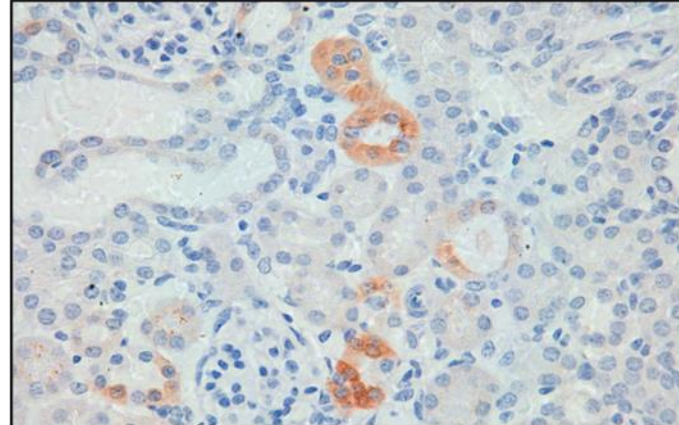# Albumin downregulates Klotho in tubular cells

Beatriz Fernandez-Fernandez[1,2,3,a], M. Concepcion Izquierdo[1,2,3,5,a], Lara Valiño-Rivas[1,2,3], Dimitra Nastou[4], Ana B. Sanz[1,2,3], Alberto Ortiz[1,3,b] and Maria D. Sanchez-Niño[1,2,3,b]

El Empacho

Control   Albuminuria

Current AKI definition

- **One size** fits all

Serum creatinine increases $\geq$**0.3** mg/dl in **48**h

Kidney injury

Nephrologist

Late diagnosis!

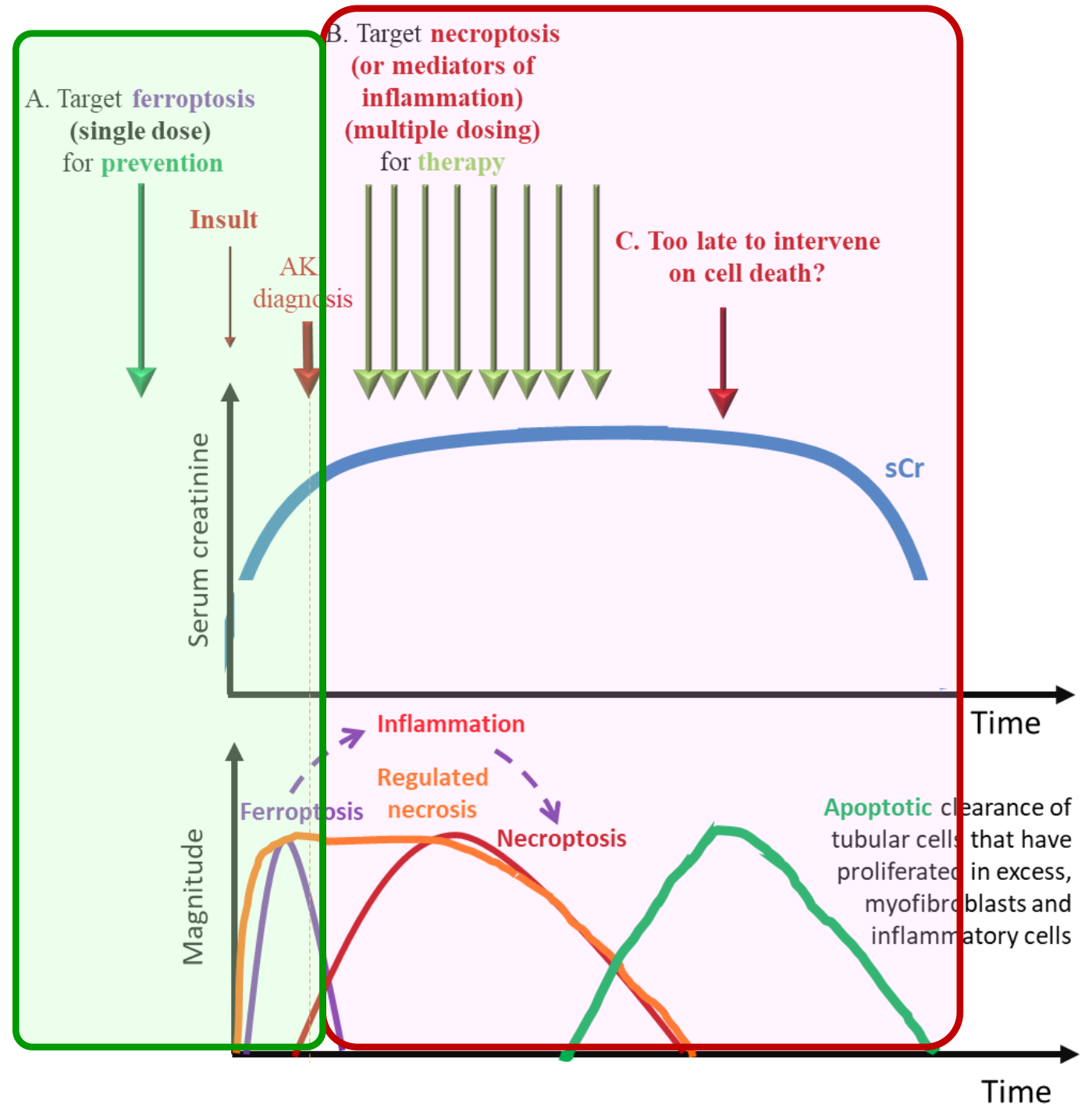AKI: closing the stable door after the horse has bolted

**There is
no treatment for AKI:**

**Earlier diagnosis of
AKI or of AKI risk
will allow well-
designed RCT
assessing treatment**

Sanz et at. Nat Rev Nephrol (under review)
Martin-Sanchez D et al. PNAS USA 2018
Martin-Sanchez D et al., JASN 2017

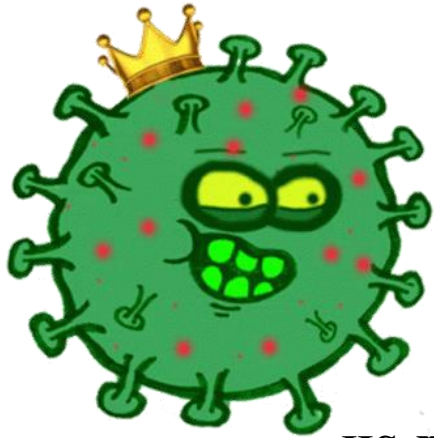The issues

The ERA-PerMed Project

The barriers

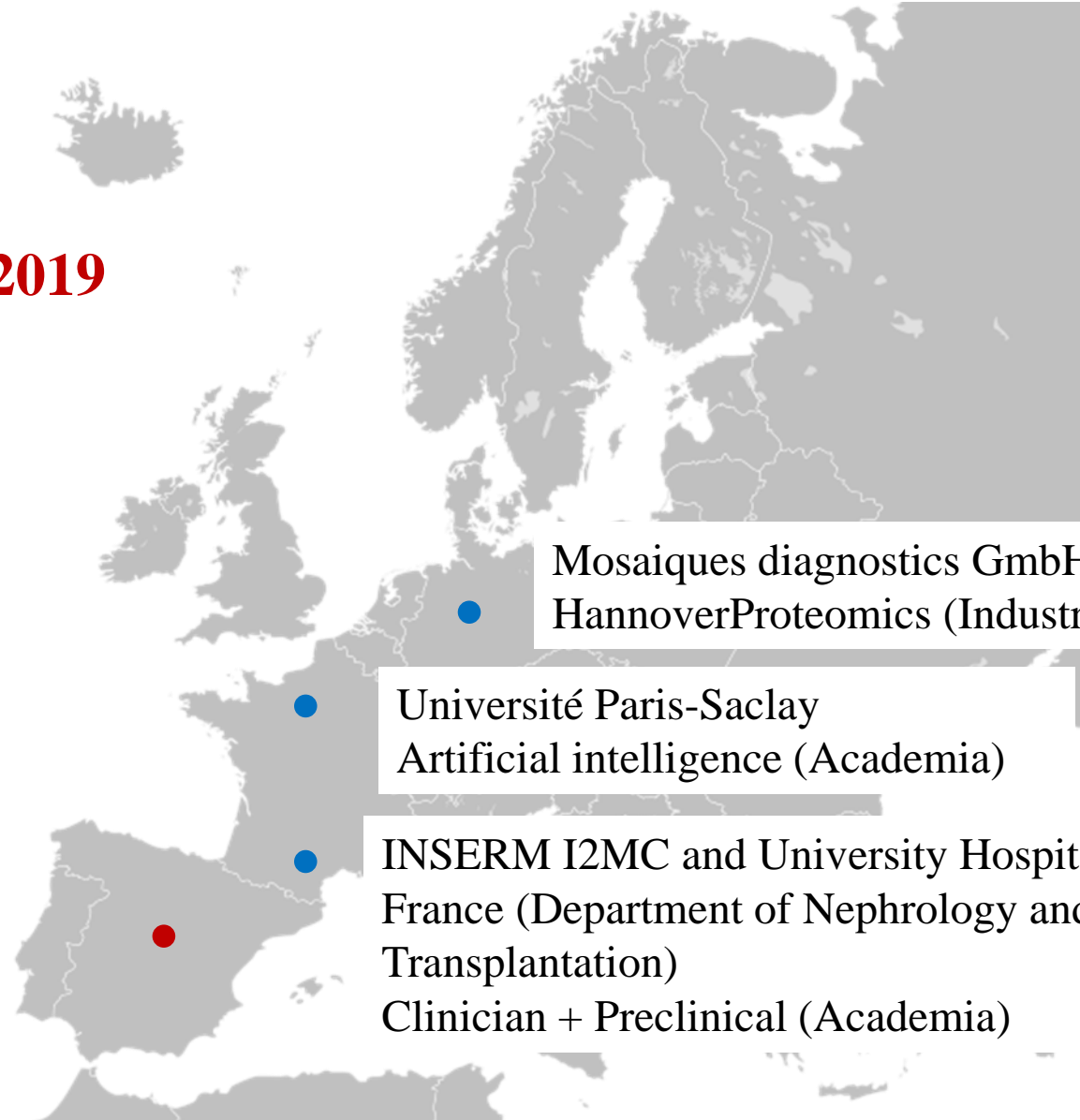# Multidimensional stratification for treatment of acute kidney injury
KIDNEY ATTACK
Coordinator Alberto Ortiz, IIS-FJD UAM, Madrid, Spain

Starting date   1 April **2019**

Mosaiques diagnostics GmbH
HannoverProteomics (Industry)

Université Paris-Saclay
Artificial intelligence (Academia)

IIS-FJD Madrid

Clinician +
Preclinical
(Academia)

INSERM I2MC and University Hospital of Toulouse,
France (Department of Nephrology and Organ
Transplantation)
Clinician + Preclinical (Academia)

Aims

• Assess the performance of **combination of multiomics** traits and clinical observations for **early stage stratification** of **cardiac surgery**-related AKI.

Recruitment **stopped March 2020**

• Select new compounds and drugs for AKI based on combination of existing database and literature data.

• Develop translational humanized readouts in animal models of AKI by integration of AKI-specific human and animal model omics signatures.

• Screen of novel AKI drugs with high translational value in preclinical AKI models based on humanized readouts.

Critical Care

RESEARCH   **Open Access**

Check for updates

A universal predictive and mechanistic urinary peptide signature in acute kidney injury

Alexis Piedrafita[1,2,3†], Justyna Siwy[4†], Julie Klein[2,3†], Amal Akkari[5], Ana Amaya-garrido[2], Alexandre Mebazaa[6], Anna Belen Sanz[7], Benjamin Breuil[2,3], Laura Montero Herrero[7], Bertrand Marcheix[3,8], François Depret[6], Lucie Fernandez[2], Elsa Tardif[9], Vincent Minville[3,9], Melinda Alves[2], Jochen Metzger[4], Kidney Attack Study Group, Julia Grossac[9], Harald Mischak[4], Alberto Ortiz[7], Stéphane Gazut[5], Joost P. Schanstra[2,3*†], Stanislas Faguer[1,2,3*†], Nicolas Mayeur[9], Audrey Casemayou[10] and François Labaste[9]
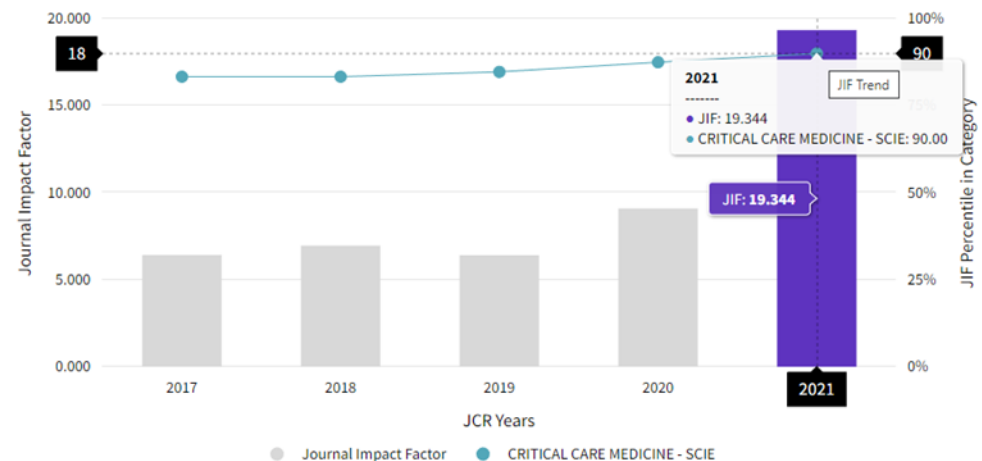
2021 JOURNAL IMPACT FACTOR

19.344

View calculation

JOURNAL IMPACT FACTOR WITHOUT SELF CITATIONS

18.780

View calculation

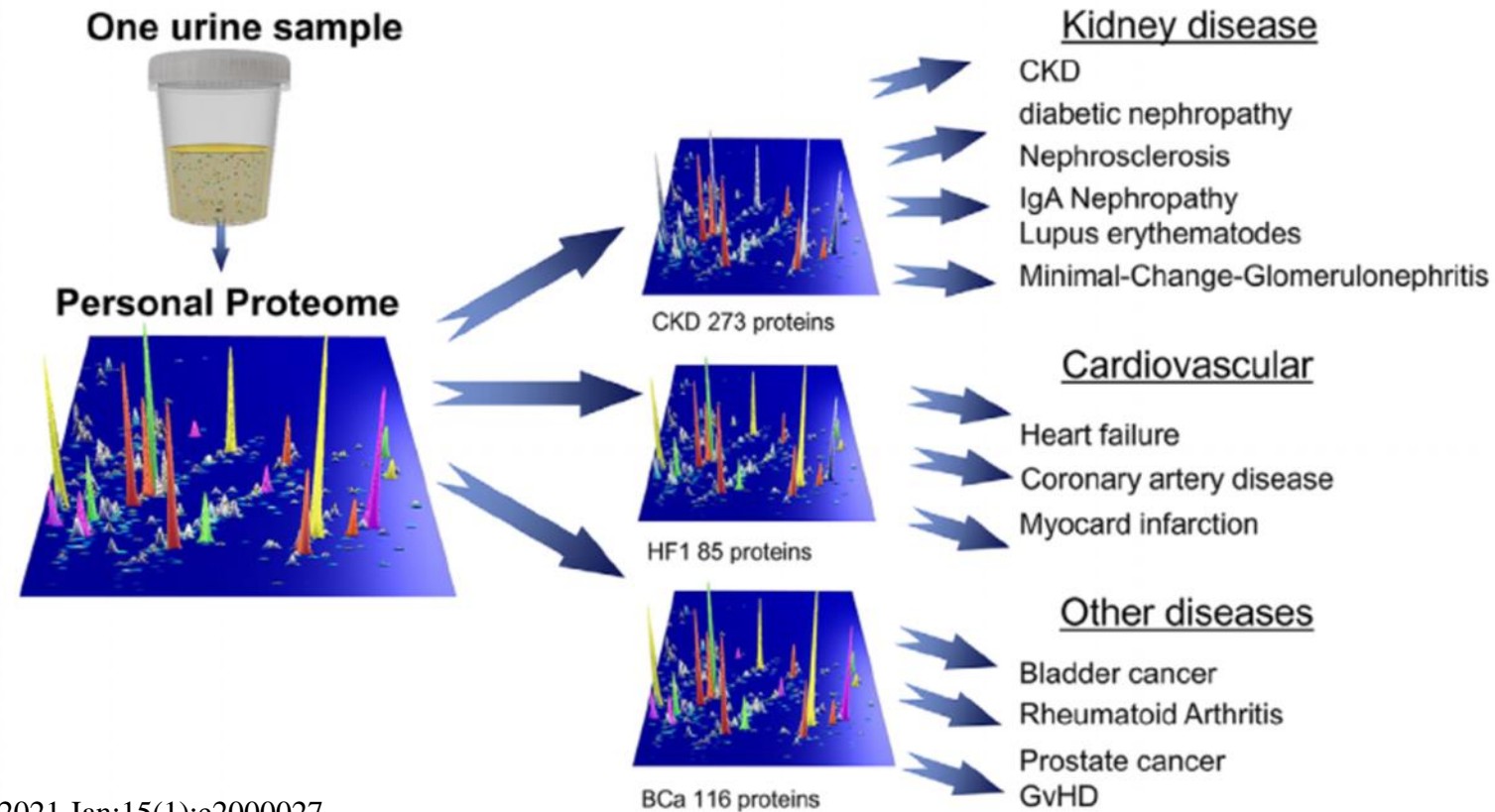**Journal Impact Factor Trend 2021**   ⬇ Export

2021

● JIF: 19.344
● CRITICAL CARE MEDICINE - SCIE: 90.00

JIF: 19.344

JIF Trend

● Journal Impact Factor   ● CRITICAL CARE MEDICINE - SCIE

Capillary electrophoresis–mass spectrometry (**CE-MS**)

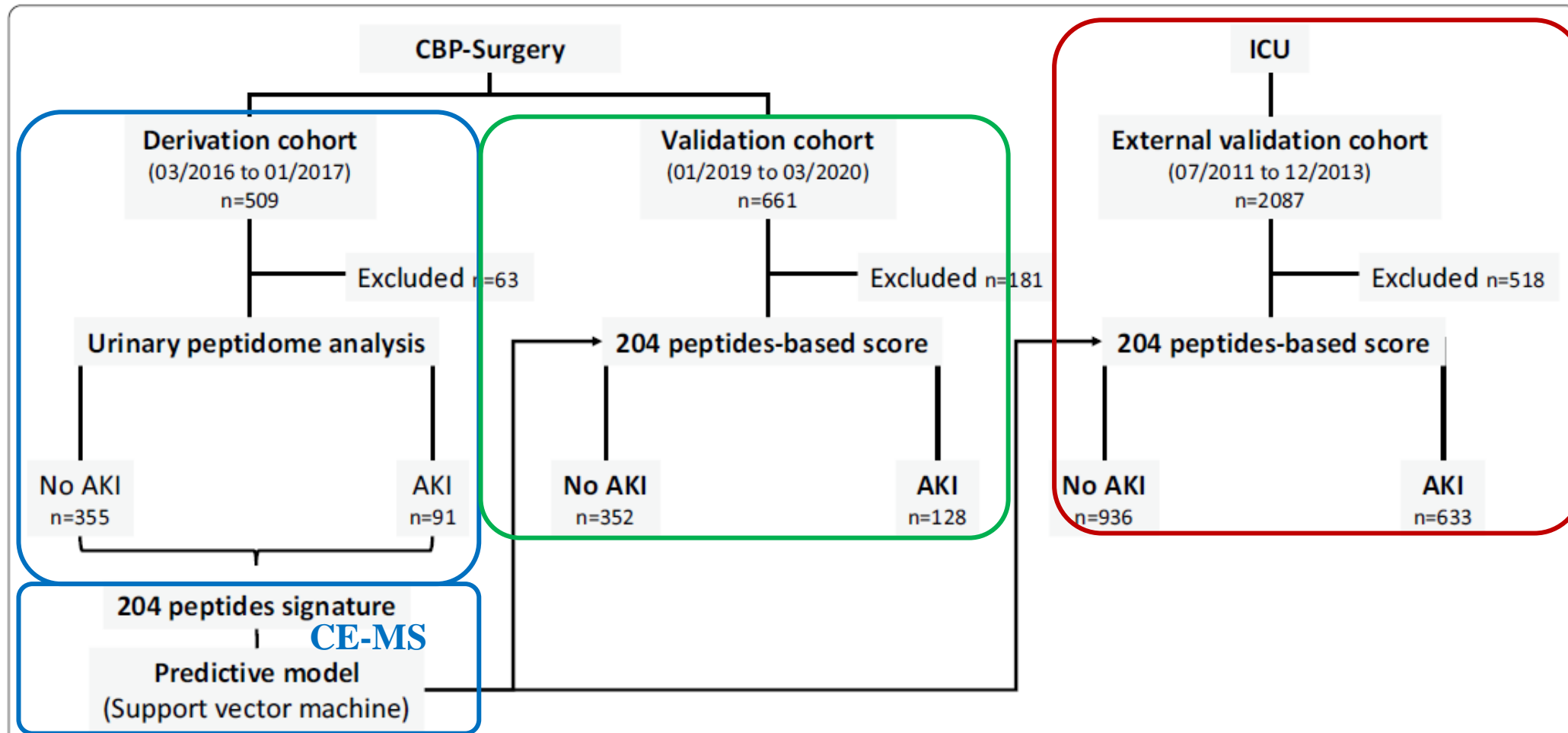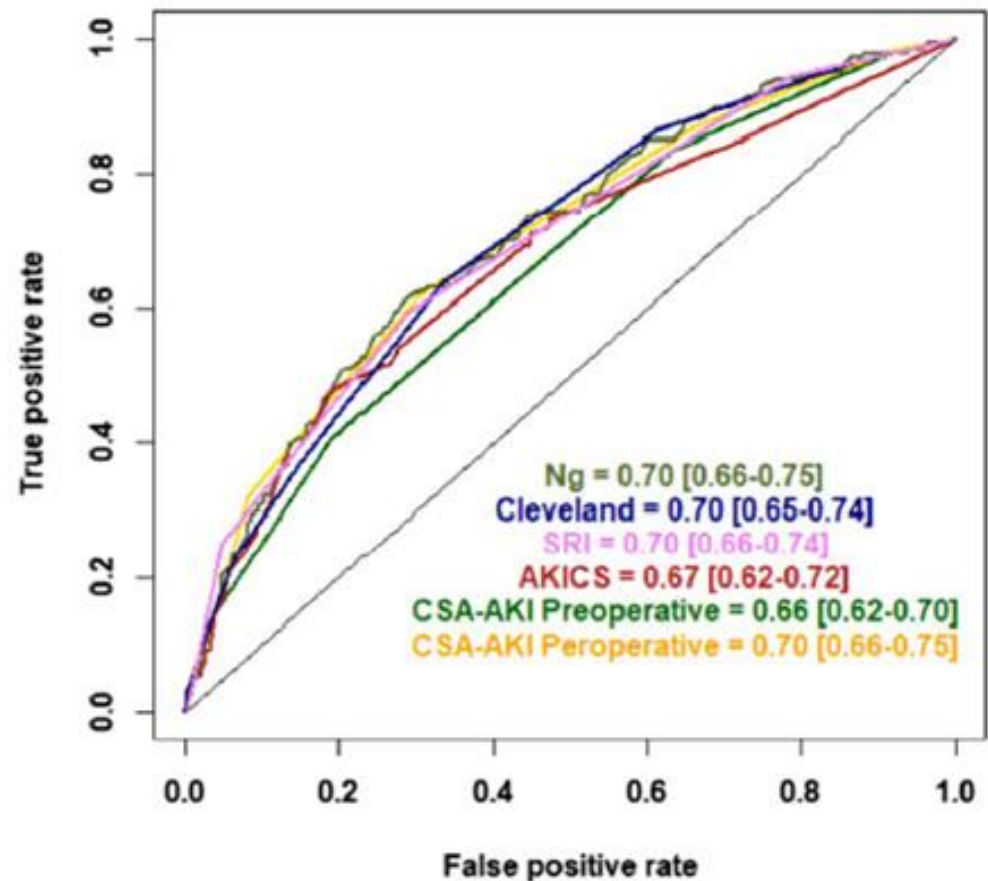Latosinska A, et al. Proteomics Clin Appl. 2021 Jan;15(1):e2000027

Fig. 1 Patient flowchart for the identification and validation of a predictive AKI urinary peptide signature. Three independent cohorts were used: a derivation CBP surgery cohort (n = 509), a validation CBP surgery cohort (n = 661)—both recruited in the University Hospital of Toulouse (France), but during different time periods—and an external ICU cohort (external ICU validation multicenter cohort [25], n = 2087). Sixty-three patients from the derivation and 181 from the validation CBP surgery cohorts were excluded because of missing urine samples or failure of the urinary peptidome analysis pipeline. Five hundred eighteen patients from the external ICU validation cohort were excluded because of missing urine samples, failure of the urinary peptidome analysis pipeline, or missing information with respect to the development or presence of AKI. *CBP surgery*, cardiac bypass surgery; *ICU*, intensive care unit
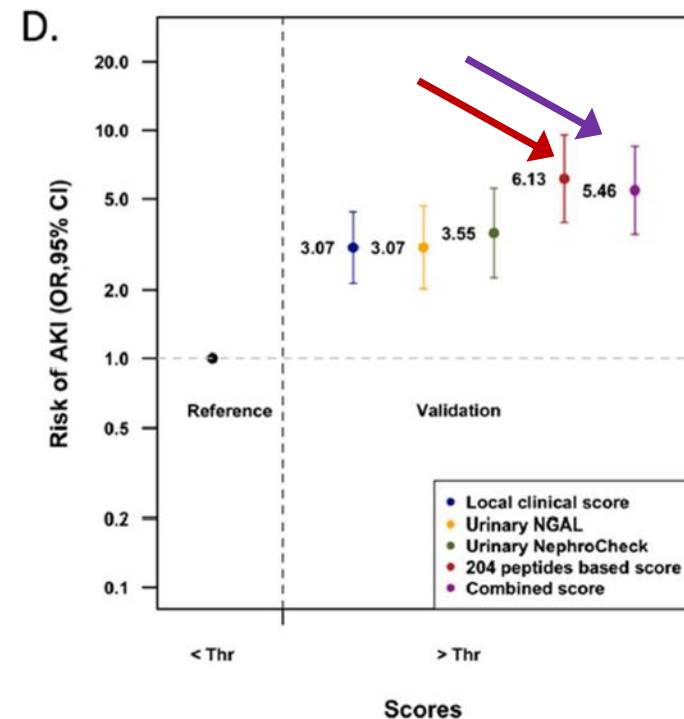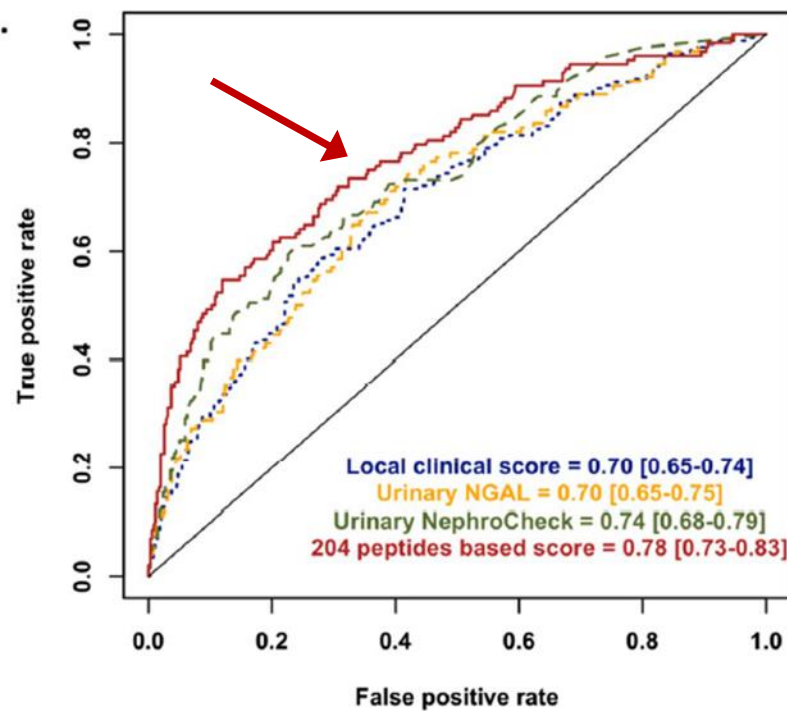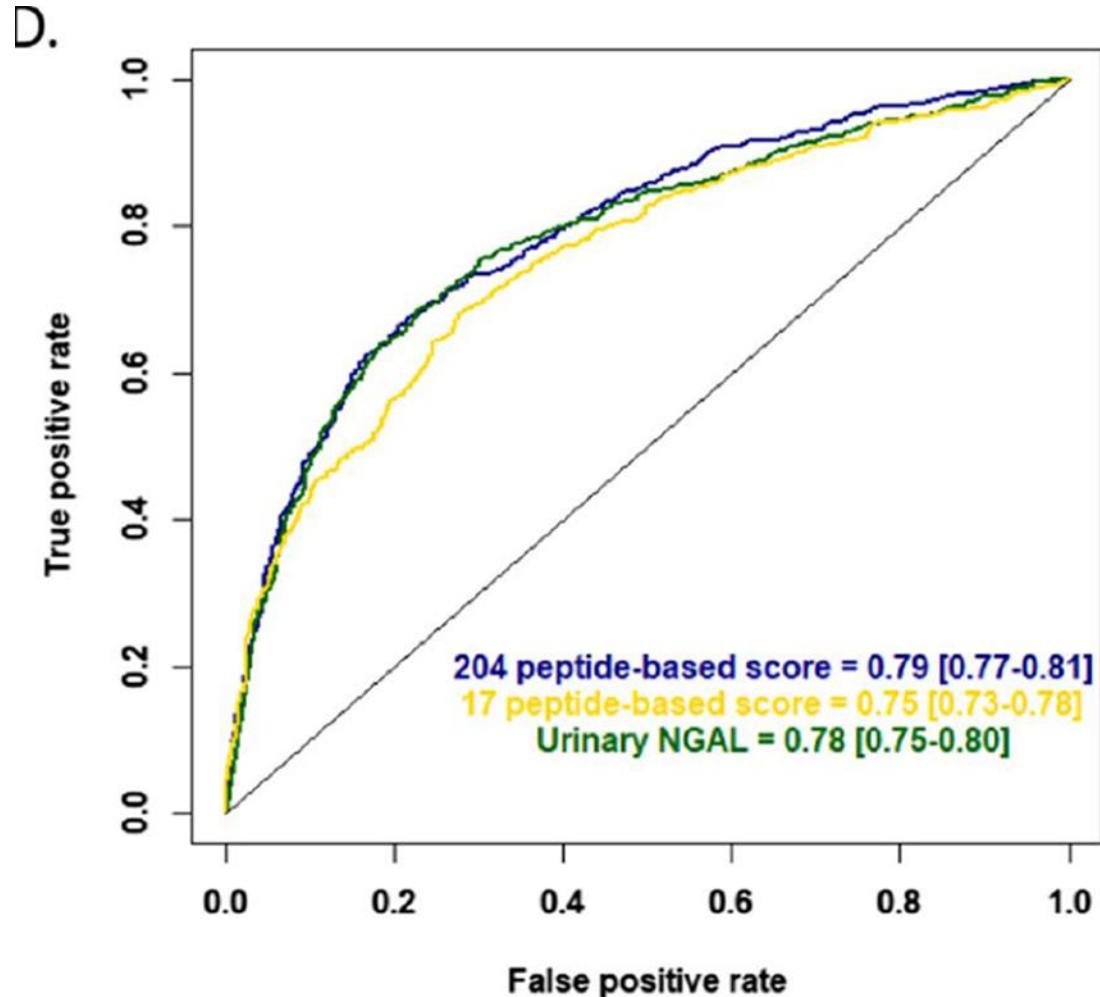
4 h:
Urine peptidomics:
6x risk AKI
Increased risk of death

Surgery

24-48-72 h:
AKI diagnosis
(increased serum creatinine)

24h

48h

Prediction of AKI

Heart surgery

Clinical risk scores

Ng = 0.70 [0.66-0.75]
Cleveland = 0.70 [0.65-0.74]
SRI = 0.70 [0.66-0.74]
AKICS = 0.67 [0.62-0.72]
CSA-AKI Preoperative = 0.66 [0.62-0.70]
CSA-AKI Peroperative = 0.70 [0.66-0.75]

U peptidonics vs current clinical risk scores or current biomarkers

Local clinical score = 0.70 [0.65-0.74]
Urinary NGAL = 0.70 [0.65-0.75]
Urinary NephroCheck = 0.74 [0.68-0.79]
204 peptides based score = 0.78 [0.73-0.83]

D.

- Local clinical score
- Urinary NGAL
- Urinary NephroCheck
- 204 peptides based score
- Combined score

Prediction of AKI

D.

204 peptide-based score = 0.79 [0.77-0.81]
17 peptide-based score = 0.75 [0.73-0.78]
Urinary NGAL = 0.78 [0.75-0.80]

Diagnosis	AUC [95%CI]	p-value
Cardiac Arrest (n = 140)	0.71 [0.62-0.80]	0.050
Hemodynamic (n = 193)	0.81 [0.75-0.88]	0.374
Septic (n = 378)	0.78 [0.74-0.83]	0.862
Post-Operative (n = 146)	0.86 [0.80-0.92]	0.024
Acute Respiratory Failure (n= 325)	0.72 [0.66-0.79]	0.025
Neurological failure (n = 240)	0.74 [0.64-0.84]	0.408
Others (n = 154)	0.74 [0.65-0.74]	0.189

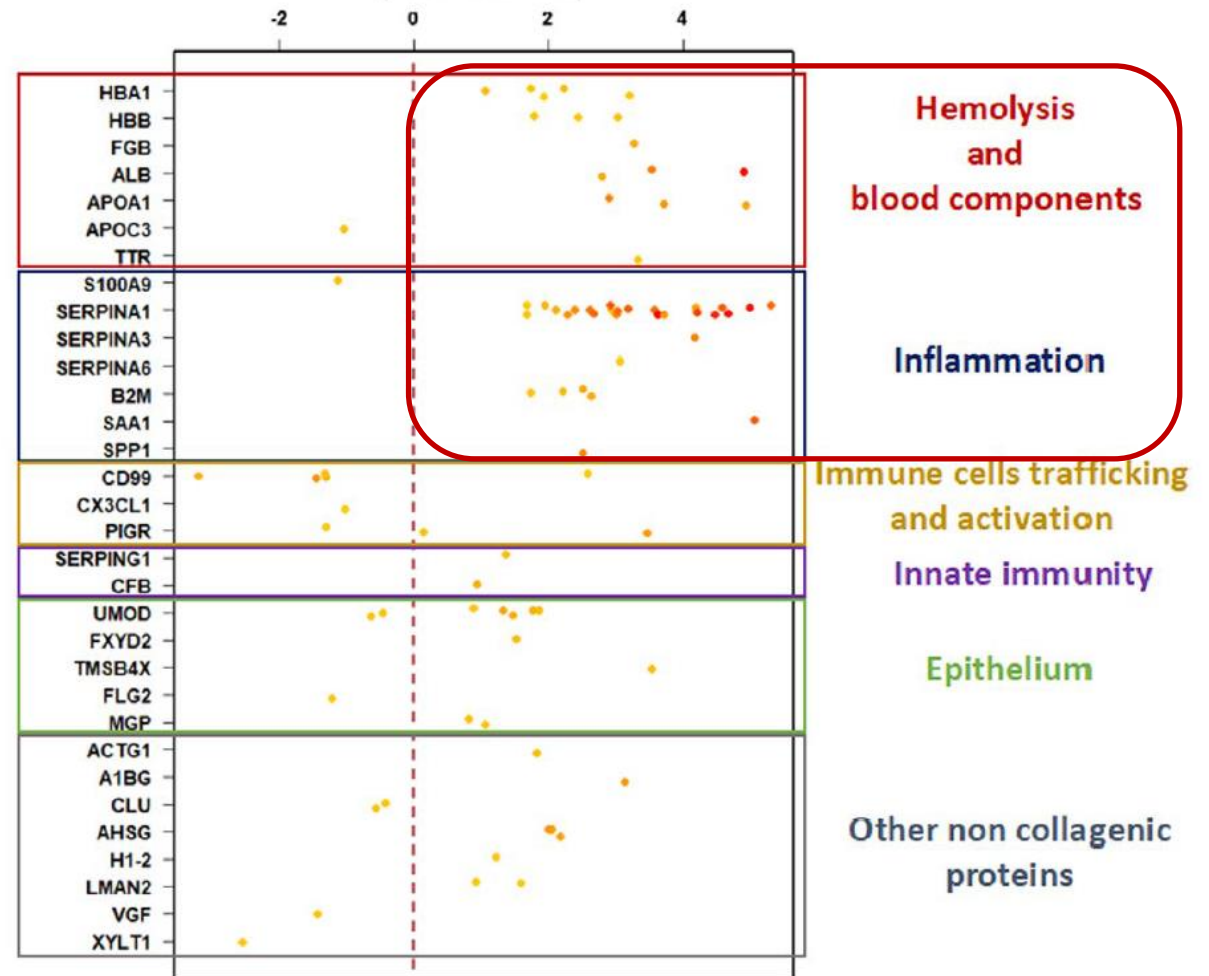Interpretation: **U peptidomics** main advantage is **early identification of kidney injury**

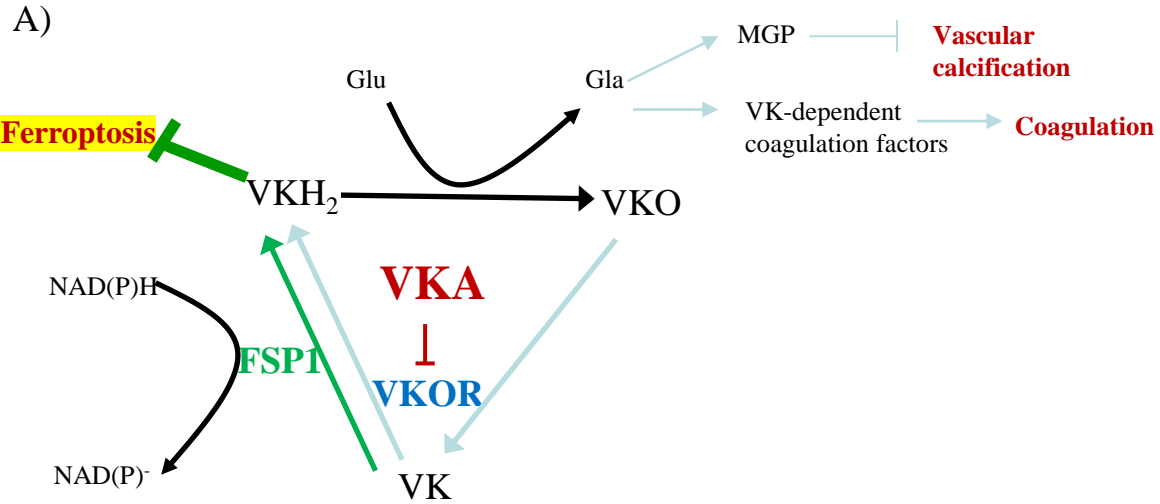# Urinary peptides
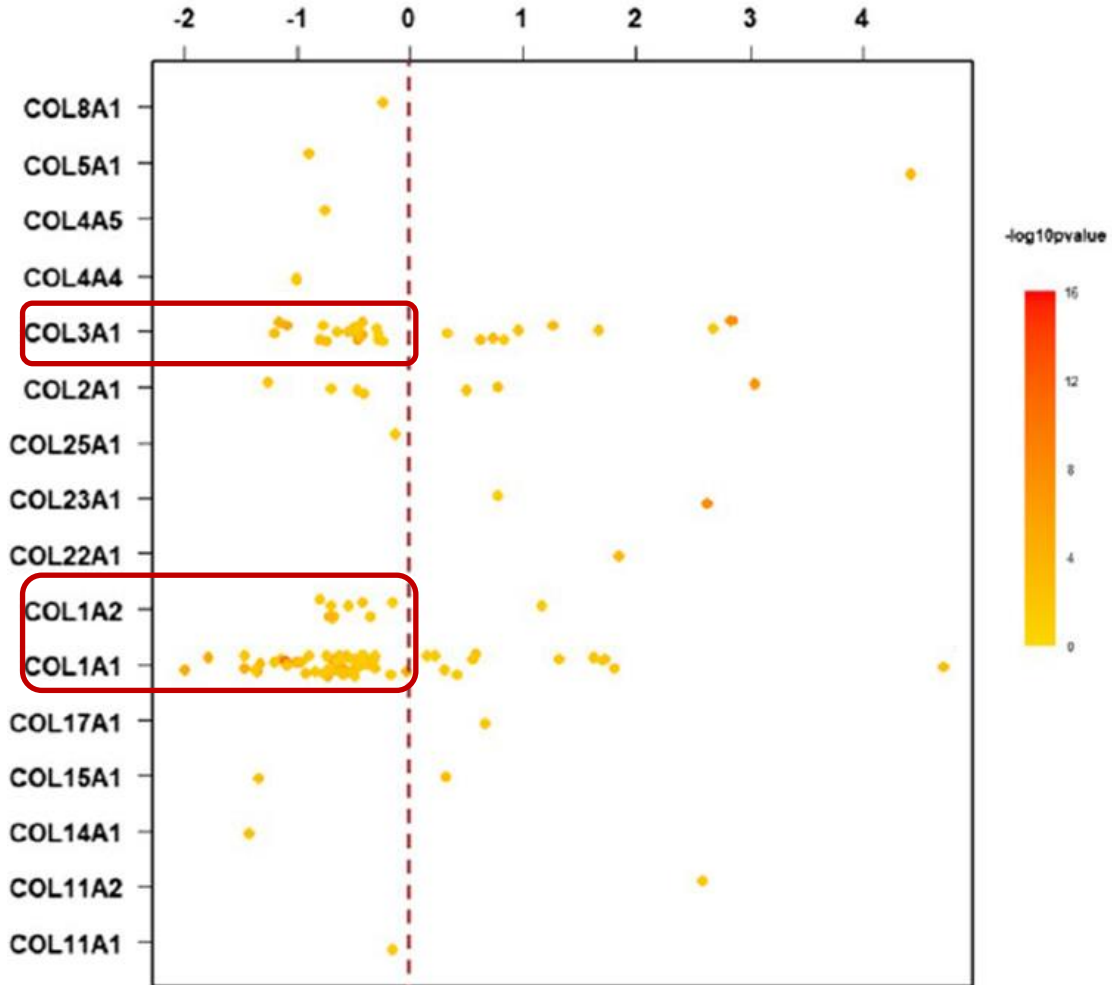
Urine metabolomics

Original Article

Ferrostatin-1 modulates dysregulated kidney lipids in acute kidney injury

Lucía Martín-Saiz, Juan Guerrero-Mauvecin, Diego Martín-Sanchez, Olatz Fresnedo, Manuel J Gómez, Susana Carrasco, Pablo Cannata-Ortiz, Alberto Ortiz ✉, José A Fernandez ✉, Ana B Sanz ✉
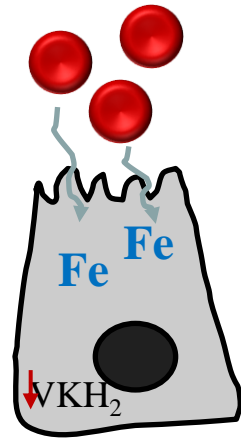
Vitamin K, ferroptosis and AKI

Sanz et al. Nat Rev Nephrol (under review)

The issues

The ERA-PerMed Project

The barriers

Clinical need: **Yes**

Industry partner can provide the product: **Yes**

Is the technology available and in clinical use: **Yes**

Does implementation result in improved outcomes: **do not know yet**

Is implementation cost-effective **do not know yet**

- **Pragmatic clinical trial** **Barrier: funding**
- **Decide** to initiate **therapy** early based on **u-peptidomics** results
- Assess impact on **outcomes** **Barrier: turn around time**
  Barrier: what drug

Early detection of diabetic kidney disease by urinary proteomics and subsequent intervention with spironolactone to delay progression (PRIORITY): a prospective observational study and embedded randomised placebo-controlled trial

Nete Tofte*, Morten Lindhardt*, Katarina Adamova, Stephan J L Bakker, Joachim Beige, Joline W J Beulens, Andreas L Birkenfeld, Gemma Currie, Christian Delles, Ingo Dimos, Lidmila Francová, Marie Frimodt-Møller, Peter Girman, Rüdiger Göke, Tereza Havrdova, Hiddo J L Heerspink, Adriaan Kooy, Gozewijn D Laverman, Harald Mischak, Gerjan Navis, Giel Nijpels, Marina Noutsou, Alberto Ortiz, Aneliya Parvanova, Frederik Persson, John R Petrie, Piero L Ruggenenti, Femke Rutters, Ivan Rychlík, Justyna Siwy, Goce Spasovski, Marijn Speeckaert, Matias Trillini, Petra Zürbig, Heiko von der Leyen, Peter Rossing, for the PRIORITY investigators†

Lancet Diabetes Endocrinol . **2020** Apr;8(

EU funded

U proteomics **correctly identified** fast progressors

The **intervention did not improve** outcomes

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes

George L. Bakris, M.D., Rajiv Agarwal, M.D., Stefan D. Anker, M.D., Ph.D., Bertram Pitt, M.D., Luis M. Ruilope, M.D., Peter Rossing, M.D., Peter Kolkhof, Ph.D., Christina Nowack, M.D., Patrick Schloemer, Ph.D., Amer Joseph, M.B., B.S., and Gerasimos Filippatos, M.D., for the FIDELIO-DKD Investigators*