Precision Medicine in Nephrology

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Precision Medicine in Nephrology might improve

- Diagnosis of CKD
- Prediction of CKD progression
- Tailored, individualized treatment

Diagnosis and Prognosis of CKD

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

GFR categories (ml/min per 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

eGFR and albuminuria for

CKD diagnosis

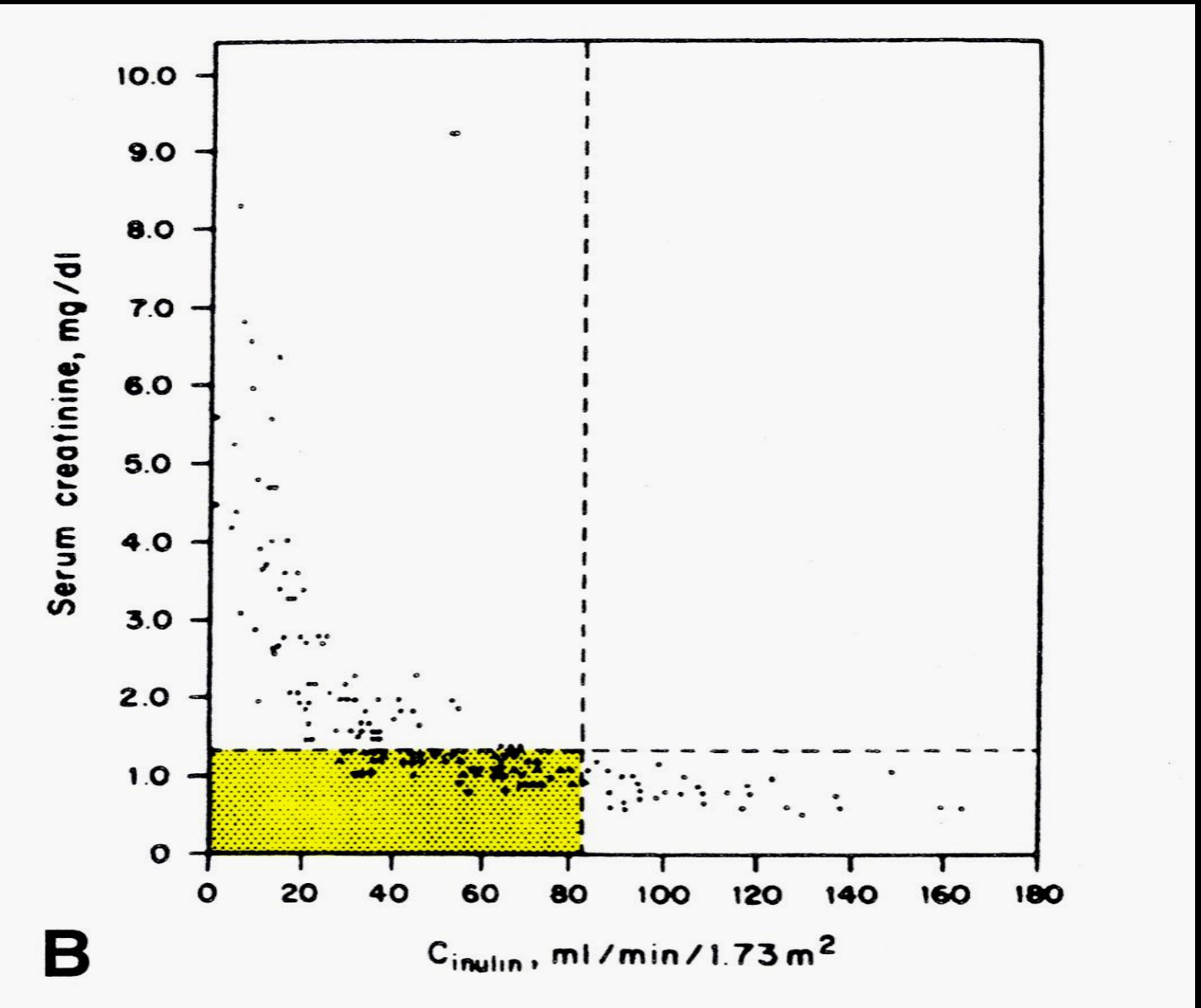
Assessment of **progression risk**

KDIGO . Kidney Int Suppl 2013

Diagnosis and Prognosis of CKD

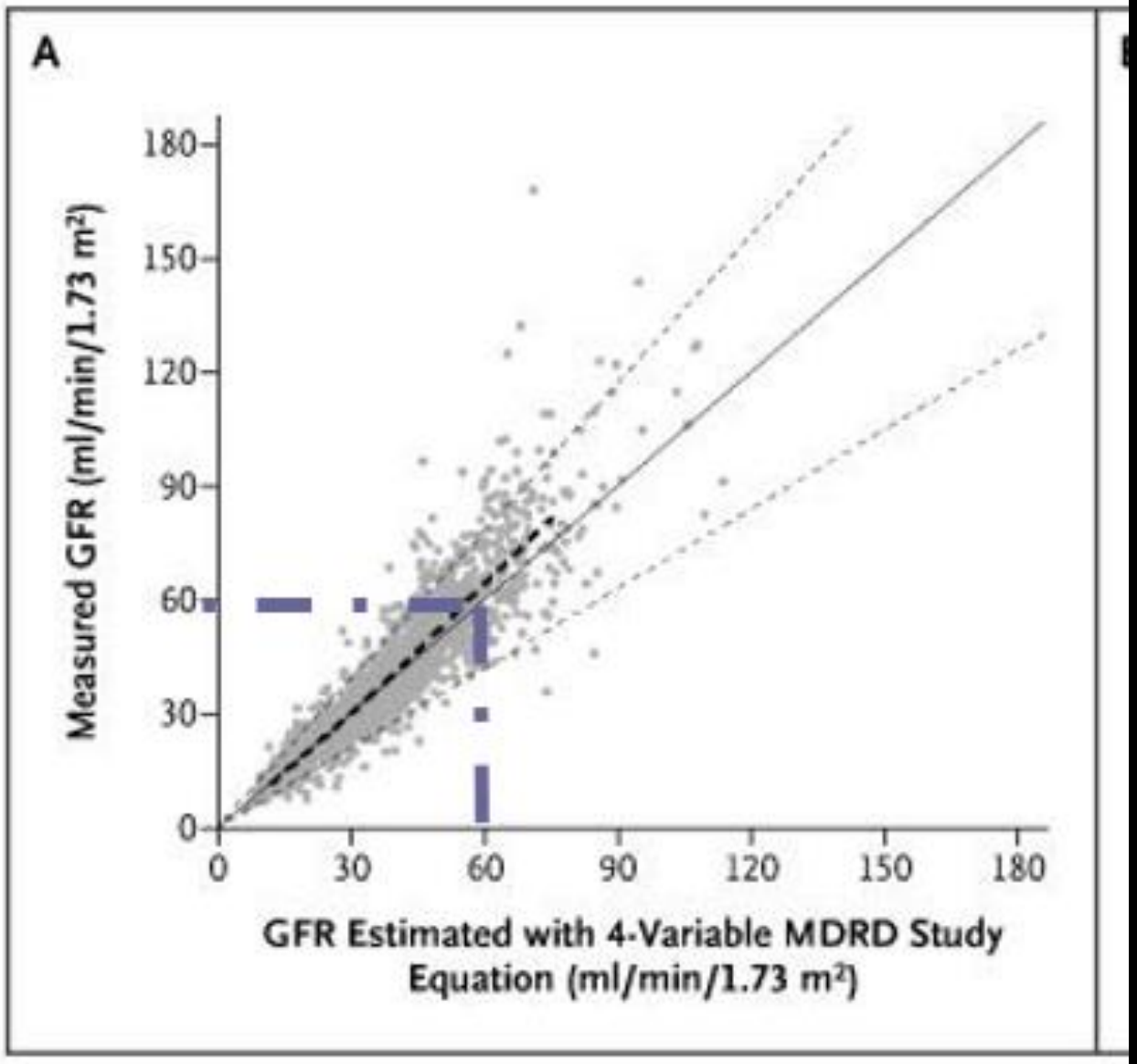
eGFR and albuminuria for CKD diagnosis????

Limitations of creatinine for CKD diagnosis

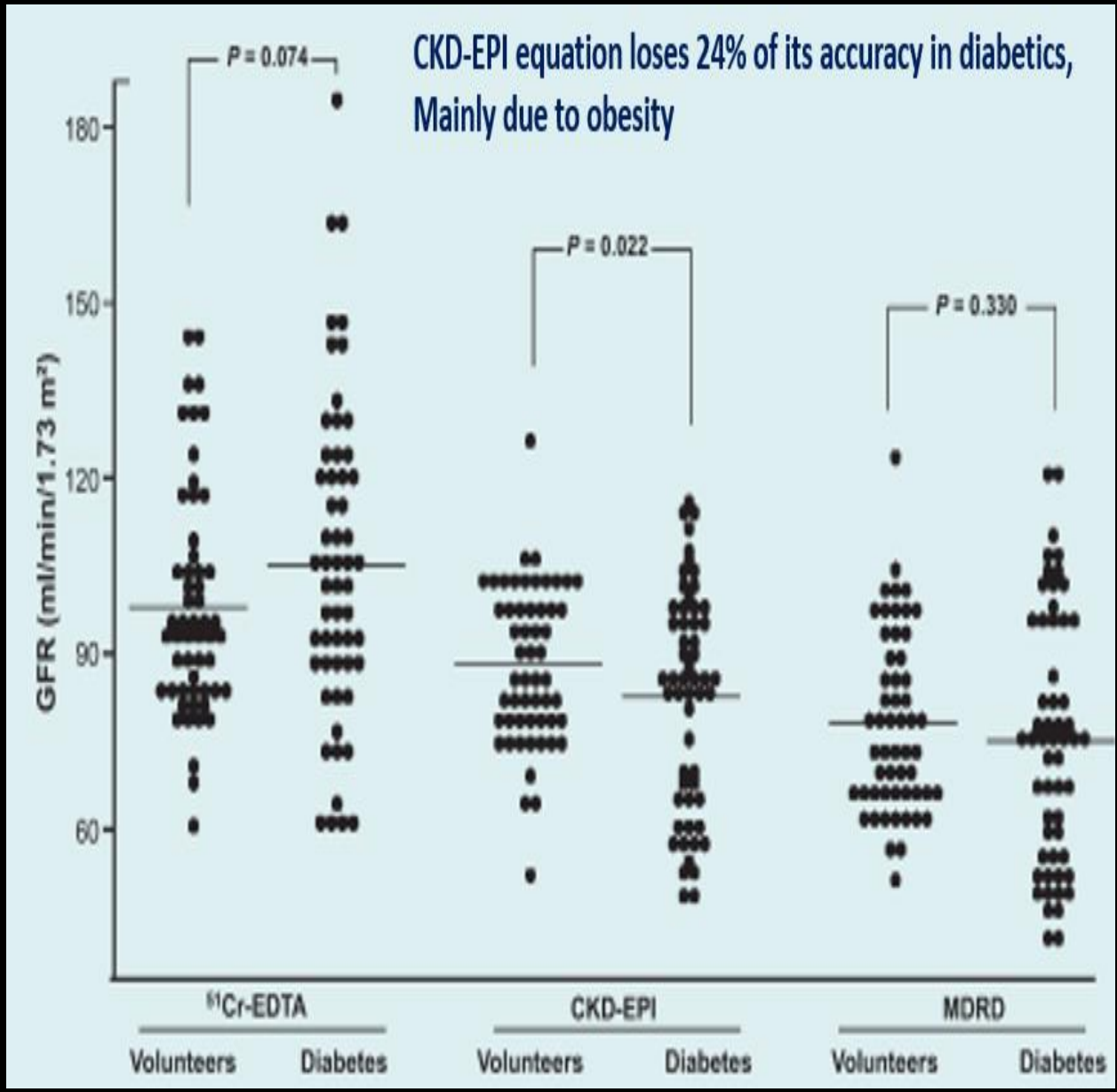


40% of patients with decreased eGFR have serum creatinine levels within the normal range

MDRD equation underestimates Clcre at eGFR>60 ml/



Stevens L et al. N Engl J Med 2006;354:2473-2483



Camargo EG et al. Diabet Med 2011;28(1):90-5

Limitations of albuminuria for CKD/DKD diagnosis

There are several reasons unrelated to CKD that can trigger albuminuria

-Stress

-Diet

-Fever

-Congestive heart failure

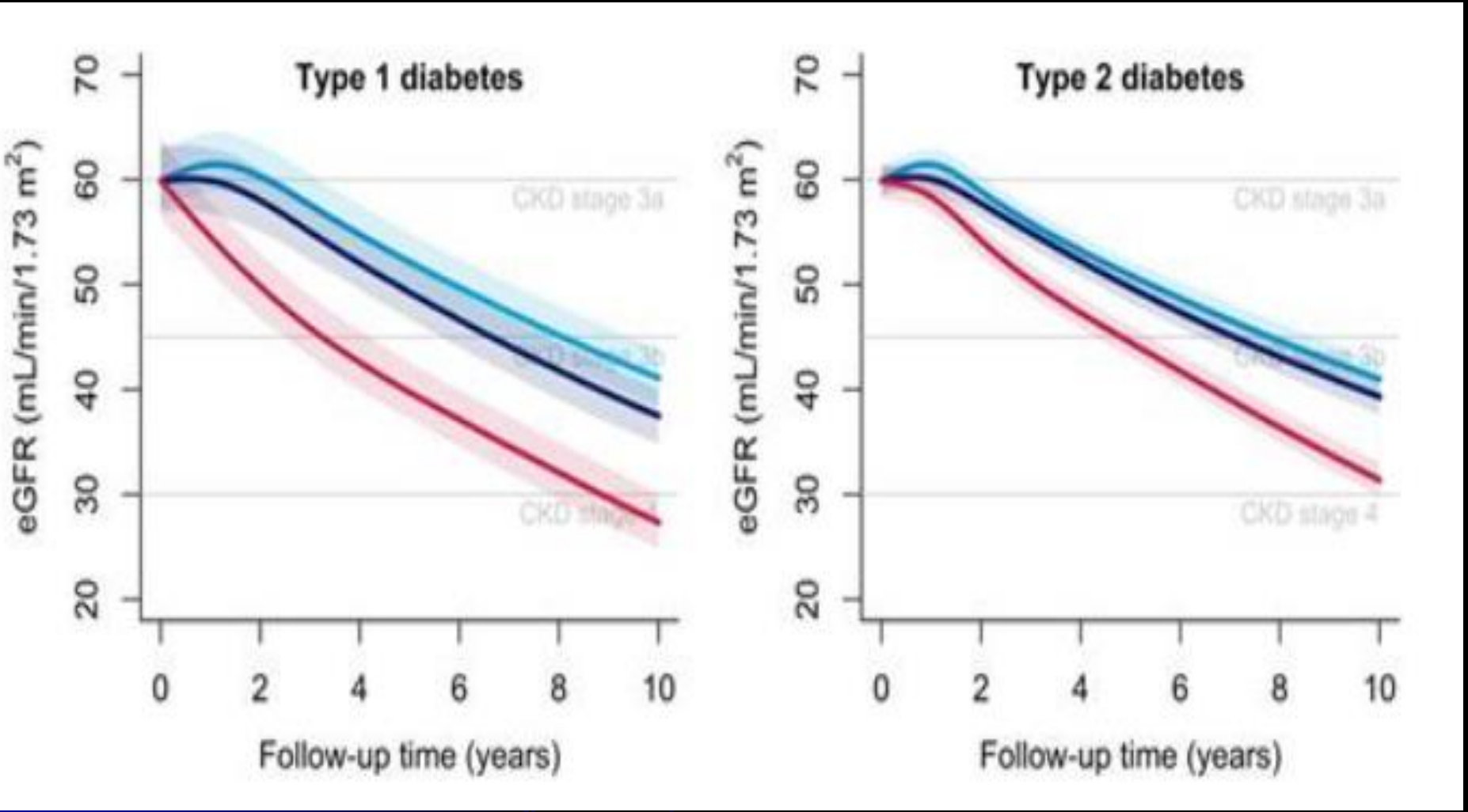
-Poor management of Glc or BP

-Exercise

-Infection

Roumeliotis, S., et al. (2023) In: Blood Pressure Disorders in Diabetes Mellitus. Updates in Hypertension and Cardiovascular Protection. Springer, Cham

Non albuminuric Diabetic CKD has 30% prevalence and is continuously increasing



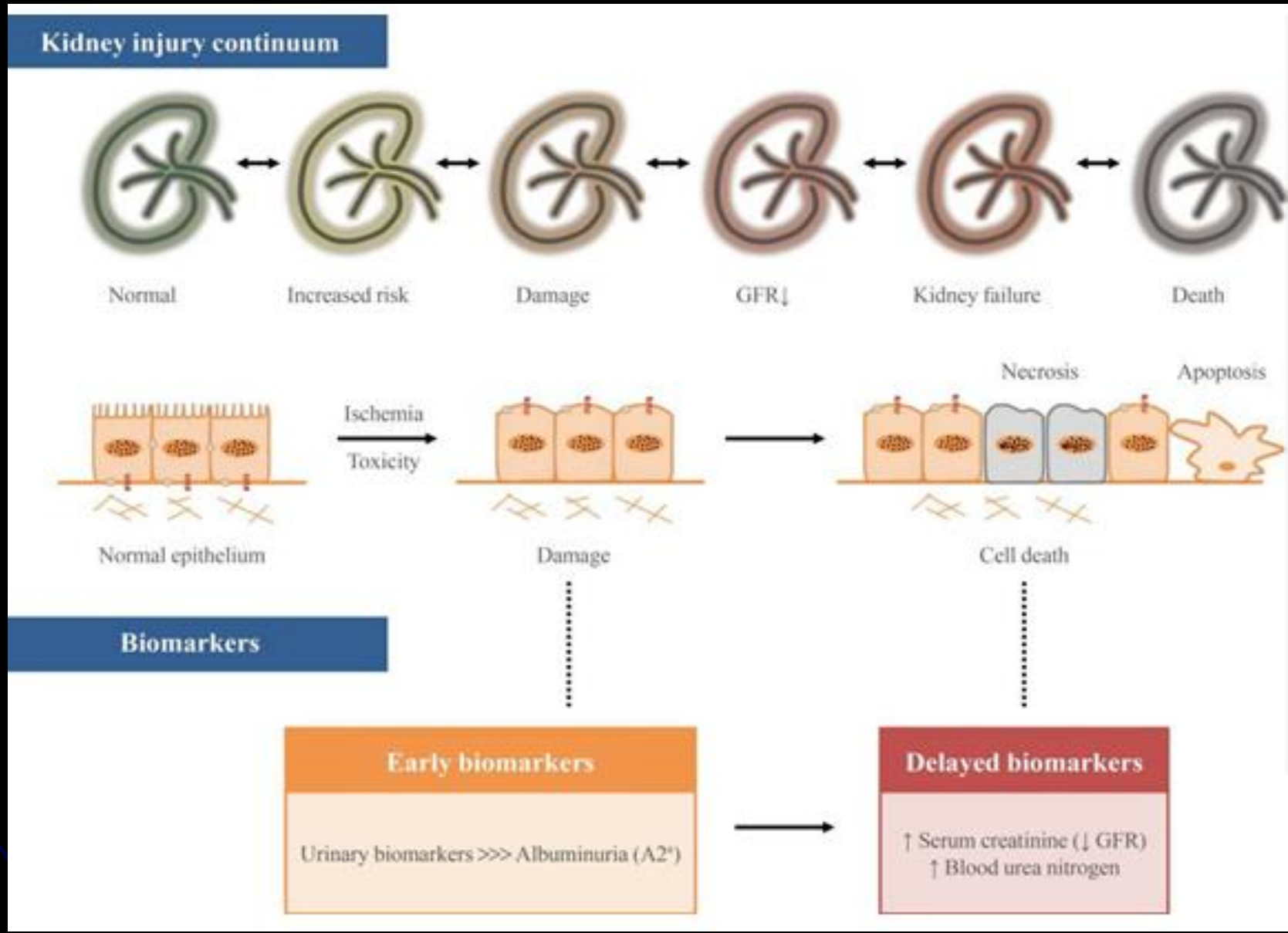
Vistisen D. et al. Diabetes Care 2019;42(10):1886–1894

EGFR and albuminuria as early markers of CKD diagnosis

Increased variability
Low accuracy

Not causally associated with **molecular injury** or **pathogenetic mechanisms**

These markers are the result, not the CAUSE of kidney damage



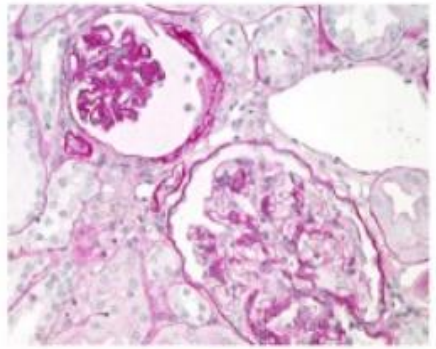
Diagnosis and Prognosis of CKD

eGFR and albuminuria for assessment of progression risk?

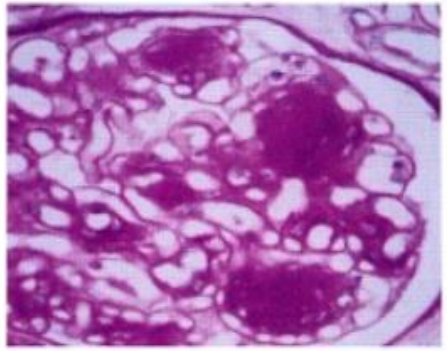
Progression of CKD depends on
-Cause
-Co-morbidities (HT, T2DM)
-Concomitant treatment

Progression of CKD is highly variable

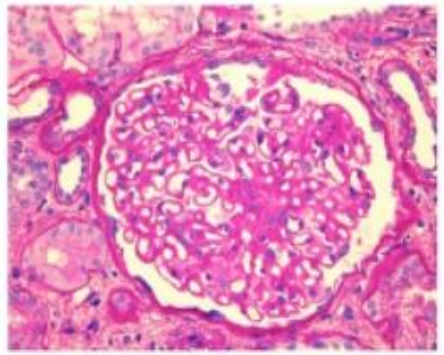
82-year-old white female
Otherwise healthy
Creatinine: 1.2 mg/dl



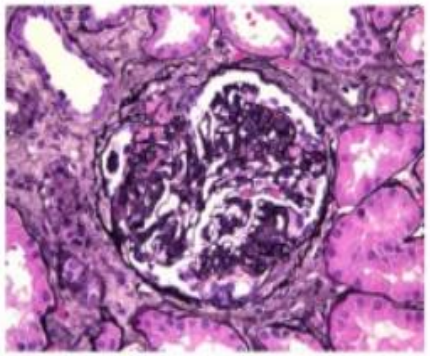
55-year-old Hispanic female
Type 2 diabetes
Multiple comorbidities
Creatinine: 1.3 mg/dl



22-year-old white male
Biopsy proven membranous nephropathy
Creatinine: 2.0 mg/dl



30-year-old black male with hypertension
Homozygous APO-L1 risk alleles
Creatinine: 2.2 mg/dl



Images courtesy of C. Alpers, K. Tuttle and R. Wiggins

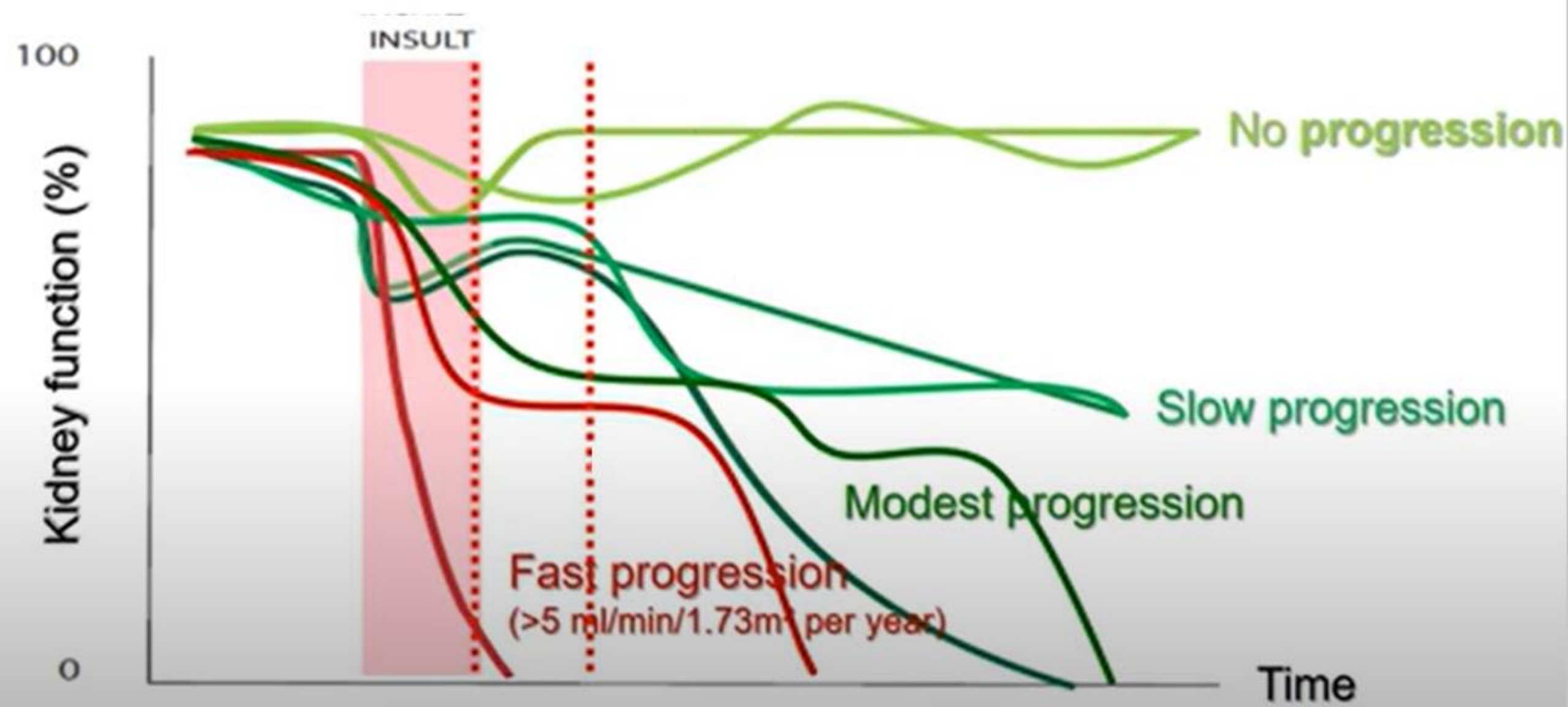
Hypothetical CKD case scenarios illustrating the clinical heterogeneity NOT captured by the CKD classification system

These 4 individuals have similar eGFR and CKD classification CLASS but differ widely in

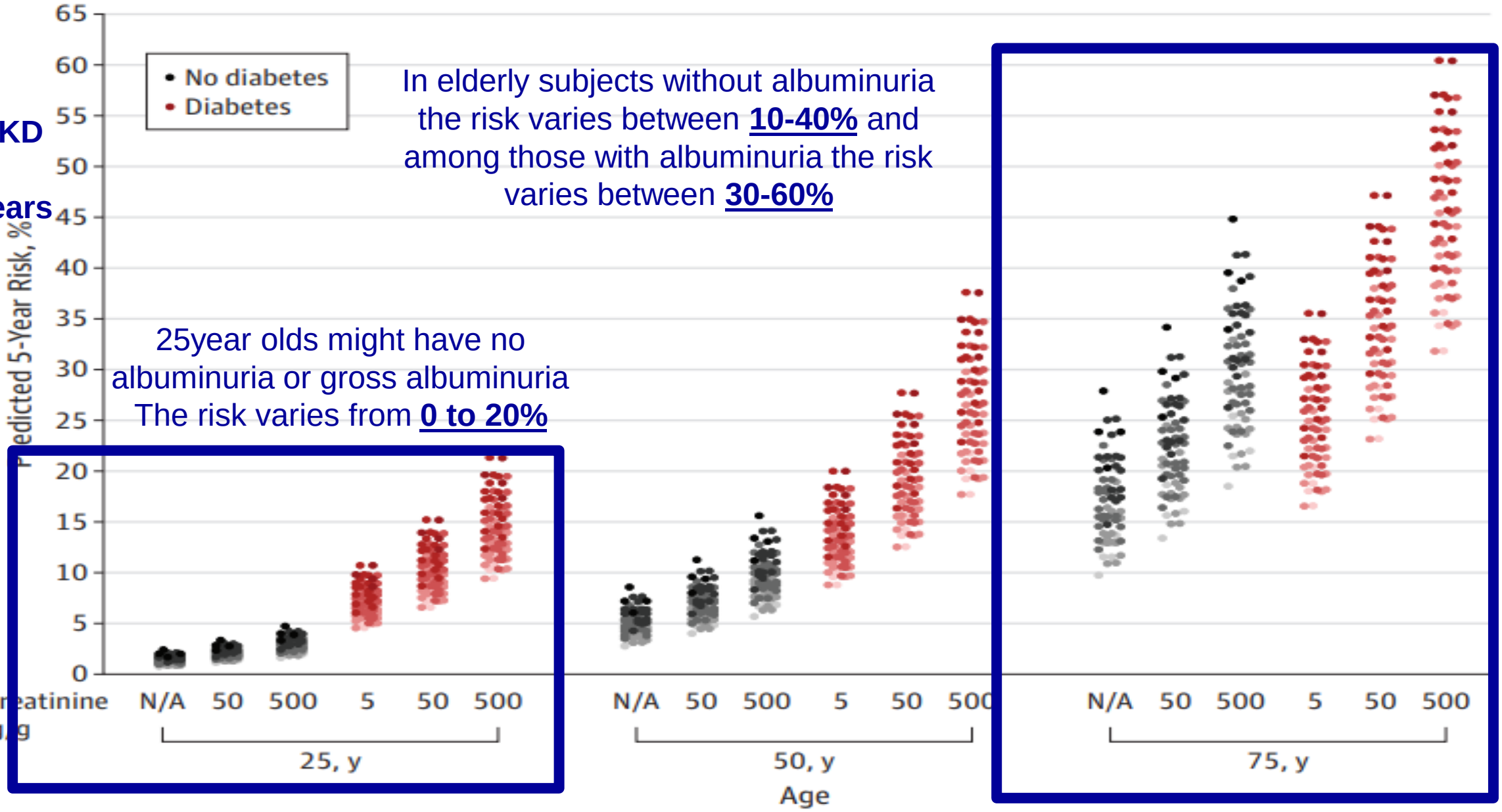
- **prognosis**
- **ordering diagnostic tests**
- **frequency of required follow-up**
- **appropriate treatment recommendations**

Hall, Himmelfarb. CJASN 2017

Progression patterns of CKD



incident CKD eGFR<60 within 5 years

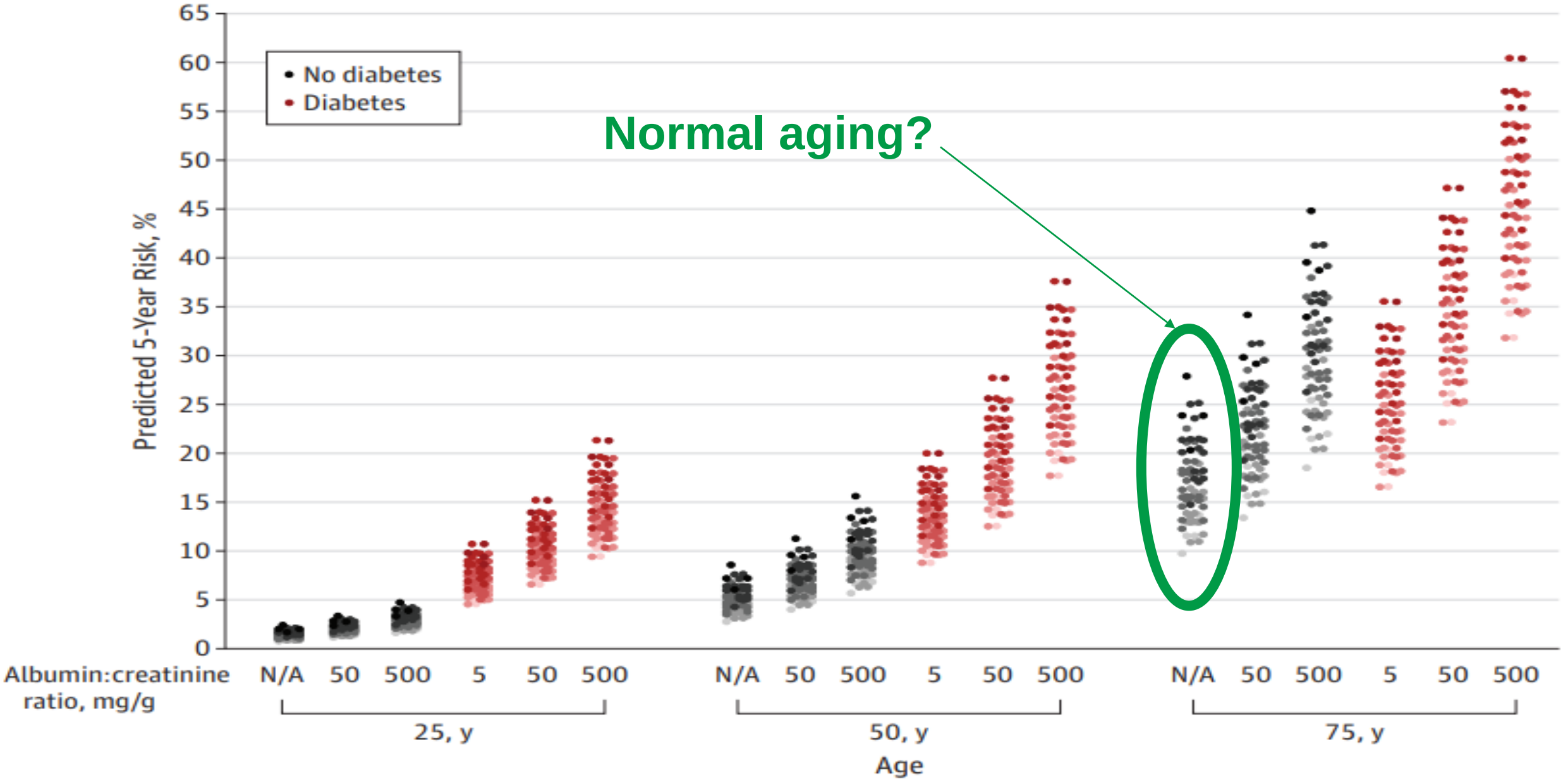


In elderly subjects without albuminuria the risk varies between **10-40%** and among those with albuminuria the risk varies between **30-60%**

25year olds might have no albuminuria or gross albuminuria The risk varies from **0 to 20%**

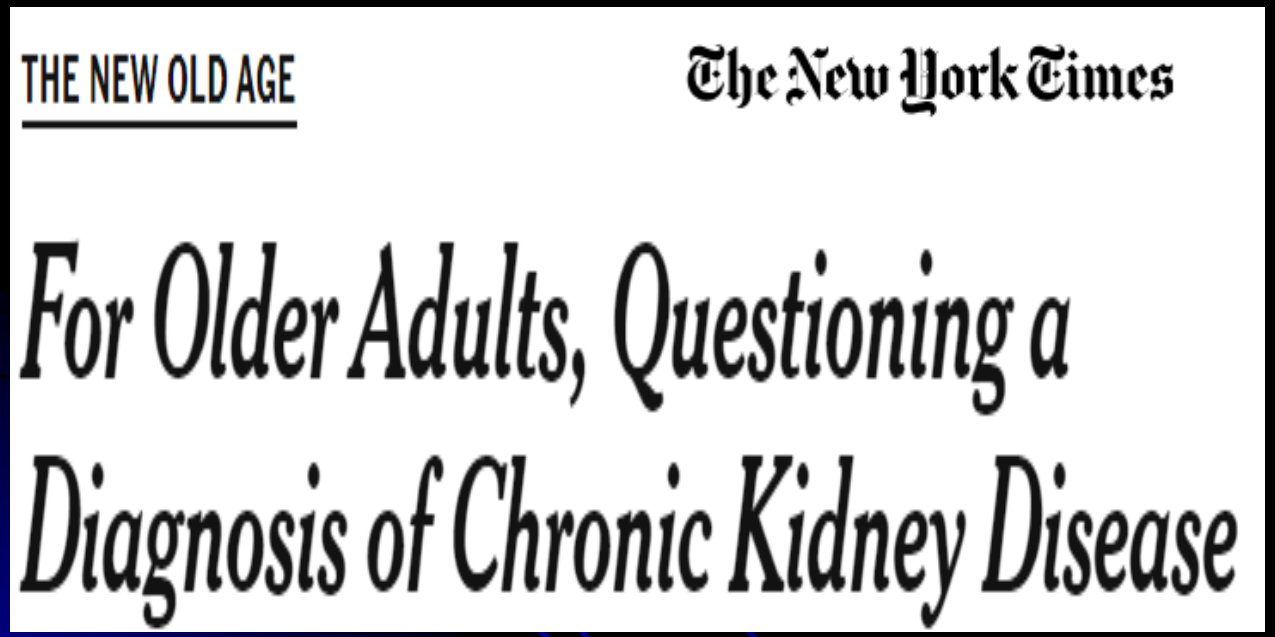
Nelson et al., JAMA 2019

Progression of CKD is highly variable



Chronic Renal Confusion

- Terminology
- Is it really possible that half of the population older than 70 has CKD?



THE NEW OLD AGE

The New York Times

For Older Adults, Questioning a Diagnosis of Chronic Kidney Disease

An Age-Calibrated Classification of Chronic Kidney Disease

Richard Glassock, MD[1]; Pierre Delanaye, MD, PhD[2]; Meguid El Nahas, MD, PhD, FRCP[3]

» Author Affiliations

JAMA. 2015;314(6):559-560. doi:10.1001/jama.2015.6731

Current guidelines should be recalibrated by age

The 2015 Precision Medicine Initiative

"Tonight I am launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes-and to give all of us access to the personalized information we need to keep ourselves and our families healthier."

An emerging approach advocating that disease prevention and treatment strategies must take individual variability into account

Precision Medicine in Nephrology

Emerging approach that characterize diseases based on pathogenetic molecular mechanisms

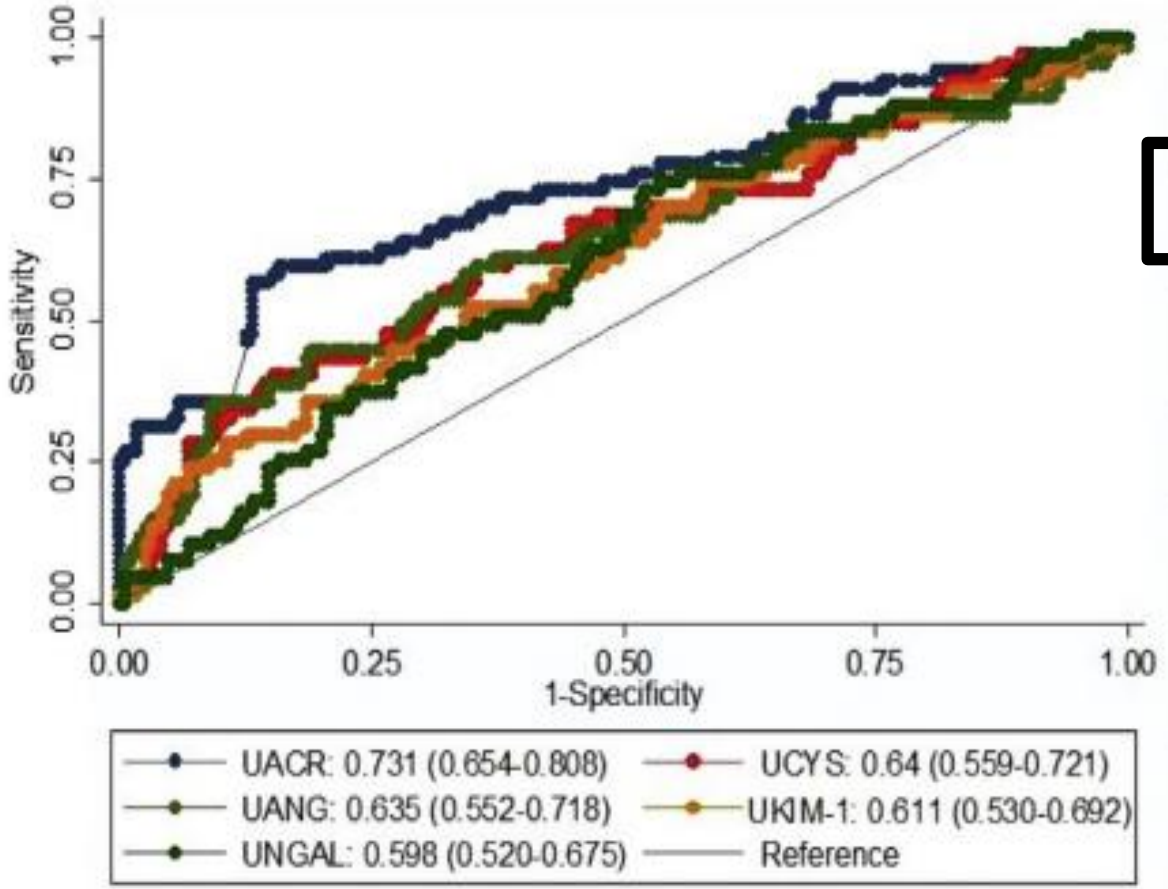
Identify highly sensitive, not-specific biomarkers and tailored therapeutic targets to optimize patient outcomes

The opportunity to offer the
-right drug
-for the right patients
-for the specific condition
-at the right time and
-in the right dosage

Wyatt et al., Kidney Int 2016

Even combined, urine biomarkers do not add anything on top of UACR for prediction of CKD Progression

A



B

Biomarkers	AUC	95% CI	P value
UACR	0.731	0.65 – 0.81	<0.001
UACR+UCYS	0.744	0.67 – 0.82	<0.001
UACR+UNGAL	0.745	0.67 – 0.82	<0.001
UACR+UCYS+UNGAL	0.748	0.68 – 0.82	<0.001
UACR+UANG+UNGAL	0.751	0.68 - 0.82	<0.001
UACR+UCYS+UANG+UNGAL	0.745	0.67 - 0.82	<0.001

Satirapoj B., et al. J Diabetes Complications. 2019 Sep;33(9):675-681

The “OMICS” might reflect early molecular changes before actual injury

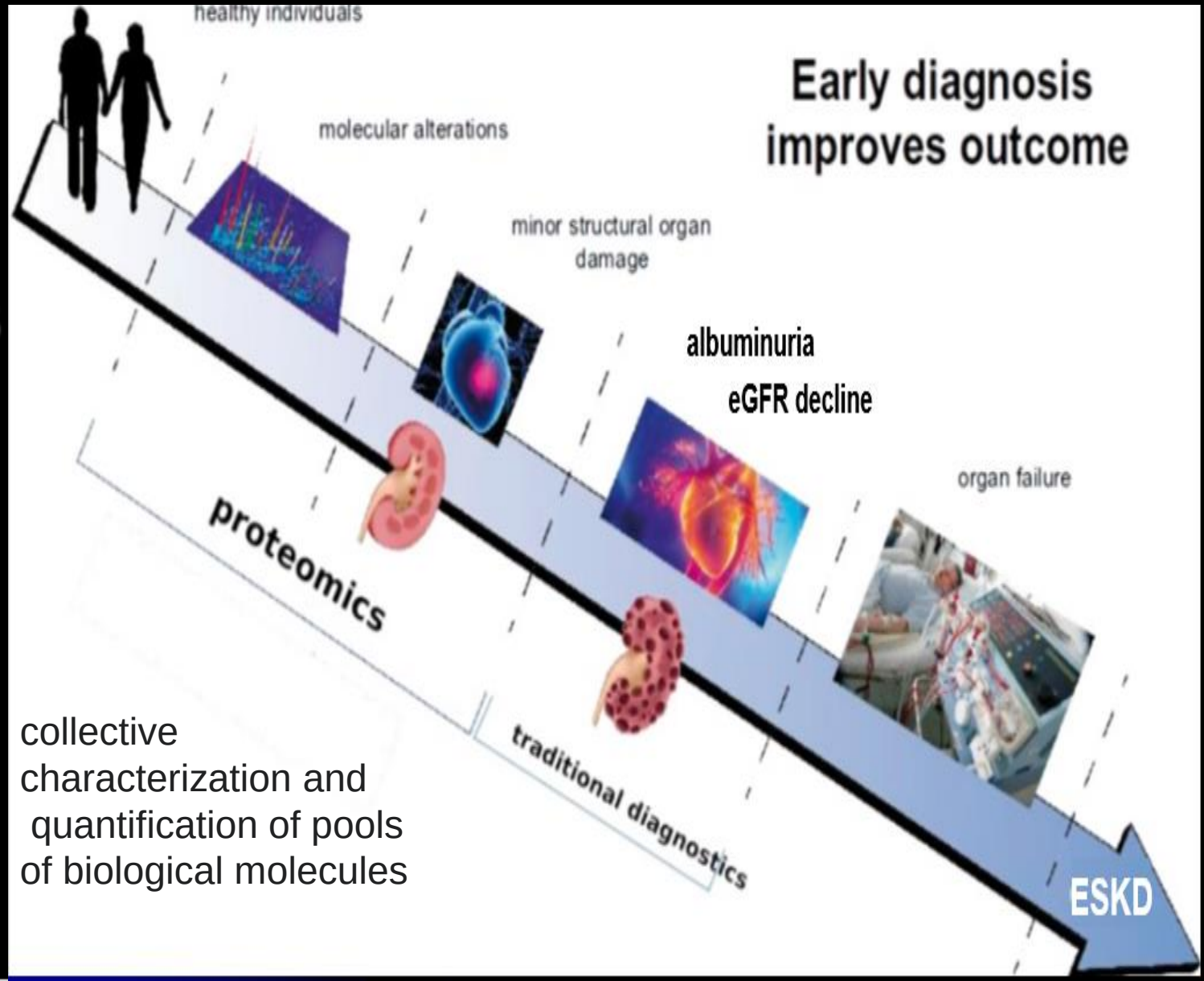
DNA — Genomics

RNA — Transcriptomics

Proteins — Proteomics

Bio chemics — Metabolomics

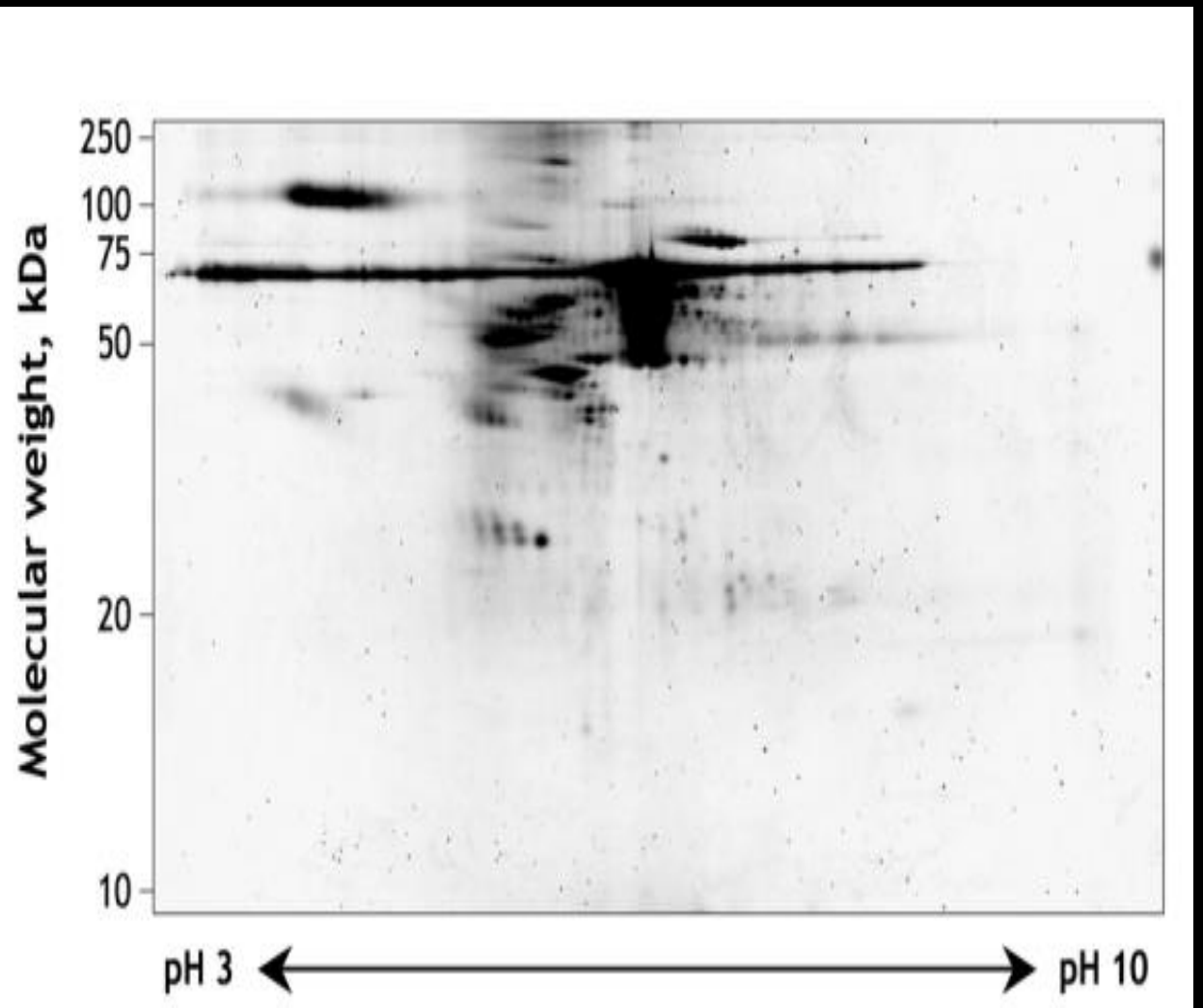
Individual biological Phenotype

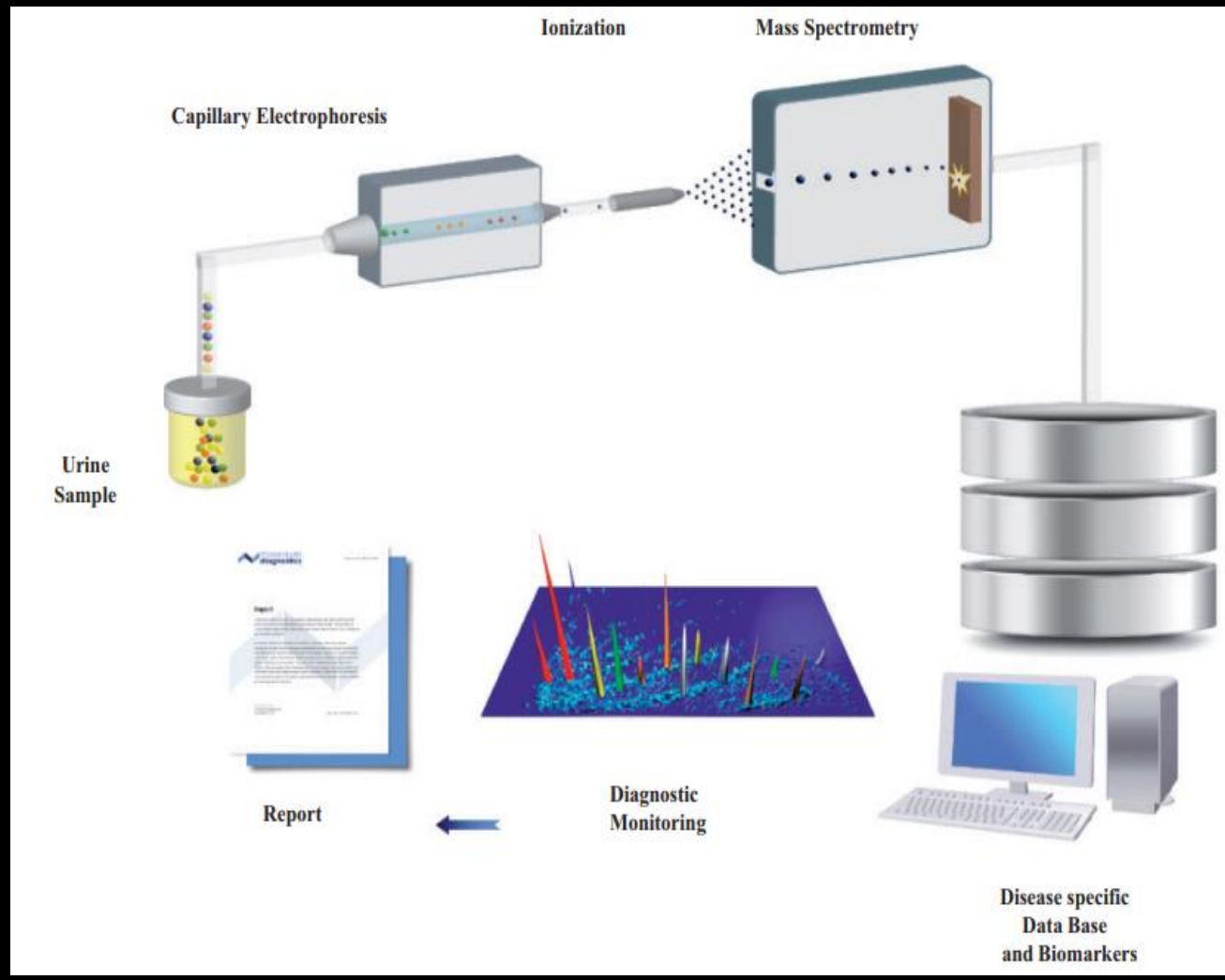


collective characterization and quantification of pools of biological molecules

Urine biomarker discovery: the future

There are 2 principal approaches to the discovery of new urine biomarkers. The first involves the study of candidate biomarkers (usually tubular proteins, cytokines, growth factors and inflammatory mediators) in specific diseases where laboratory studies have suggested a pathological link. The second involves biomarker discovery studies in which urine is screened for disease-associated proteins using an array of technologies, predominantly based on mass spectrometry.





CKD273 prognosis classifier: towards clinical application in CKD

Panel of 273 urine peptides ↑↑early and significantly before incidence of CKD

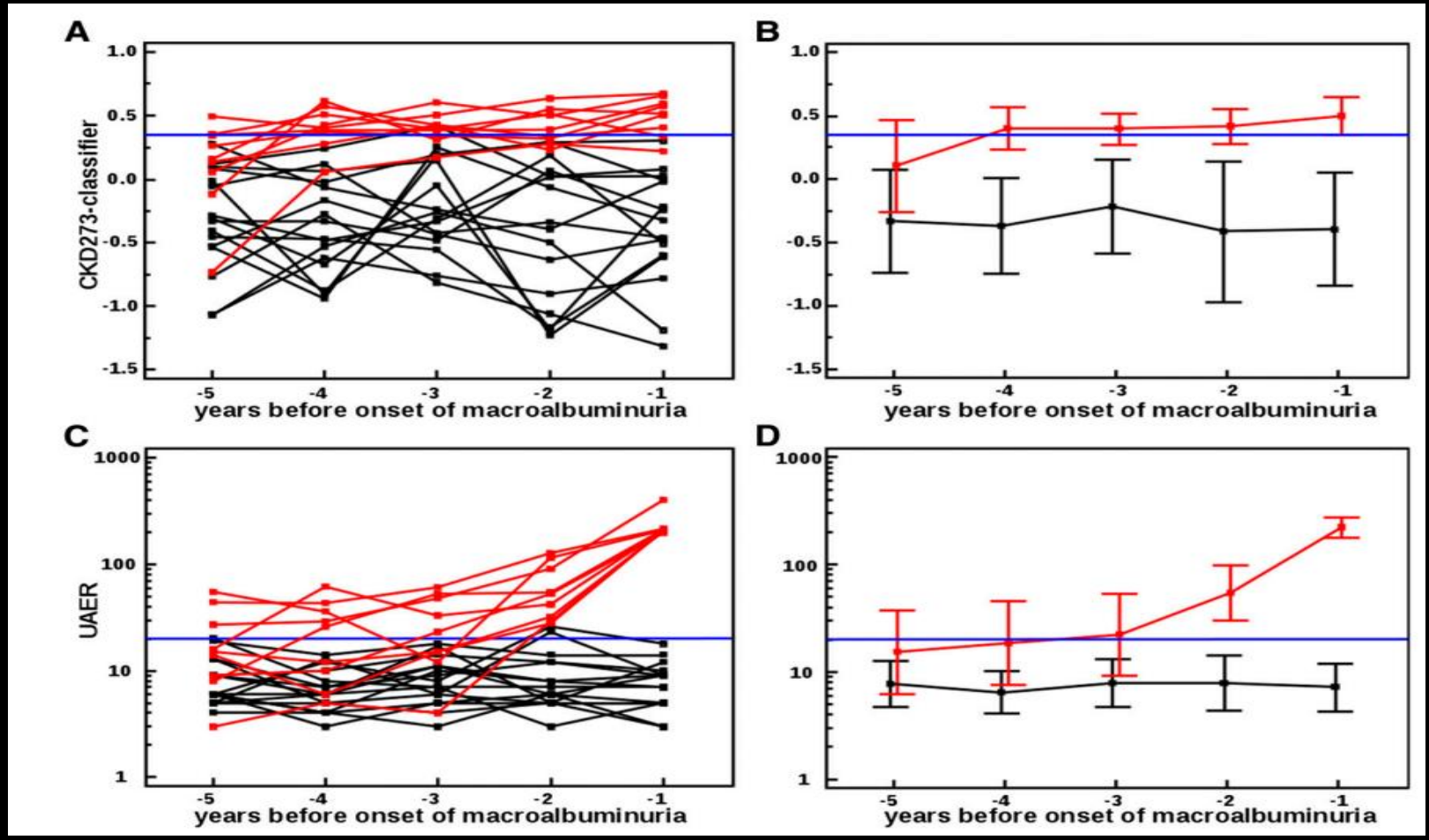
-Collagen fractures(74%)

-peptides associated with inflammation and fibrosis

-α1-antitrypsin (6.6%)

-Fibrinogen (1.8%)

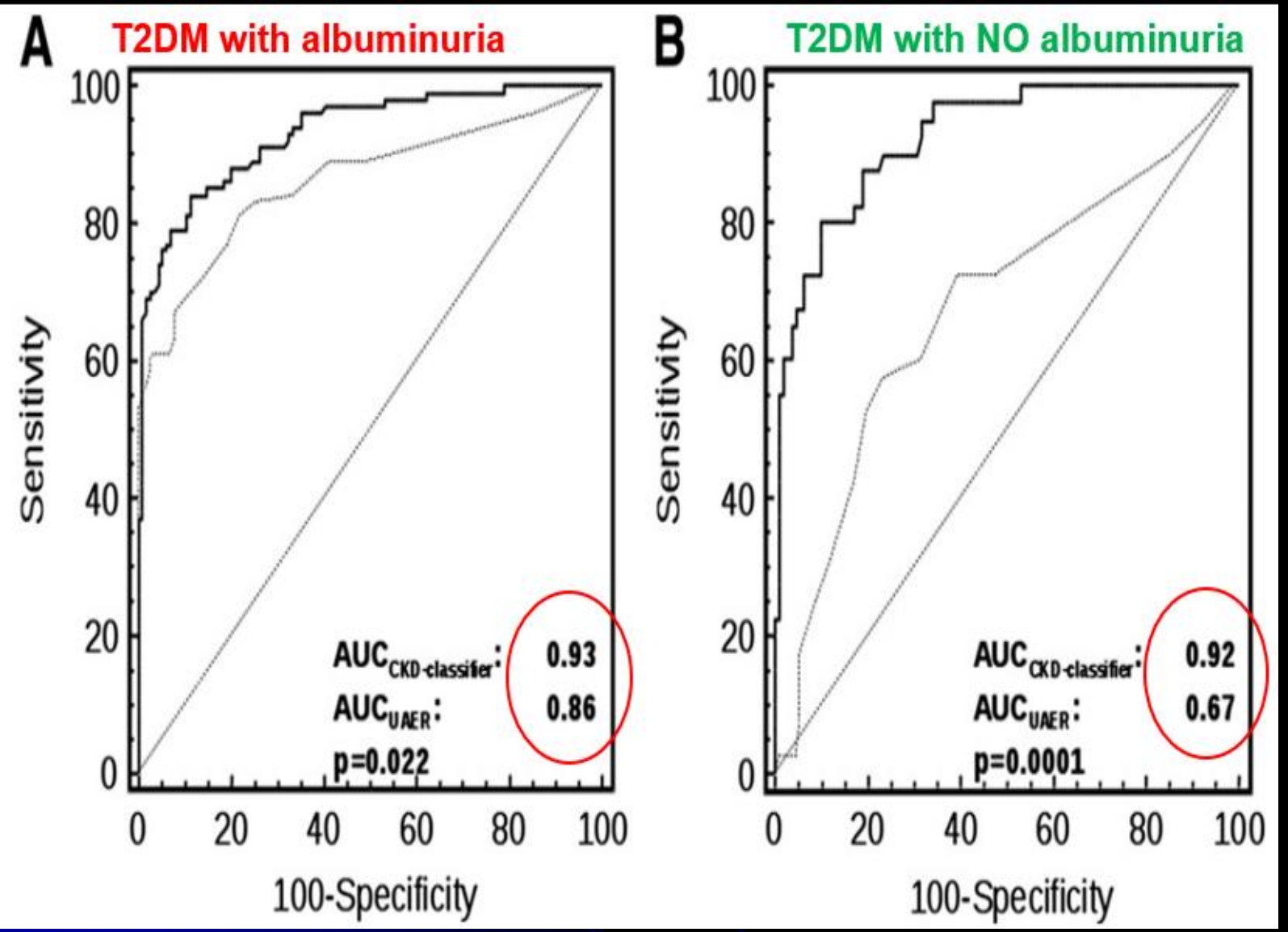
CKD273 predicted the incidence macro-albuminuria 1.5 years BEFORE the onset of micro-albuminuria in diabetics



Pontillo C., et al. Clin Kidney J 2017;10(2):192-201

Zurbig P., et al. Diabetes 2012;61(12):3304-13

CKD273 is a better predictor of macro-albuminuria than micro-albuminuria



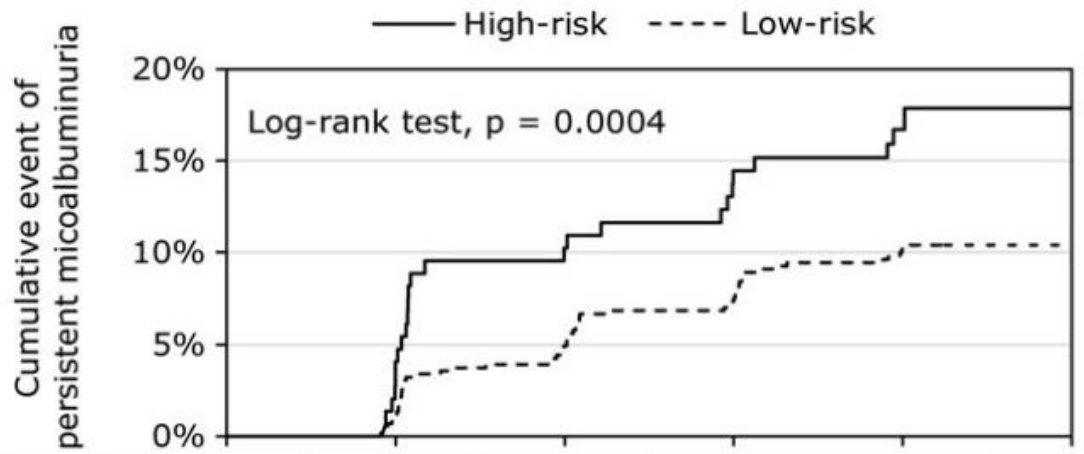
CKD273 predicted the incidence macro-albuminuria

With better discriminatory ability Compared to micro-albuminuria

7% better in albuminuric T2DM

25% better in NON-albuminuric T2DM

DIRECT-protect2 study



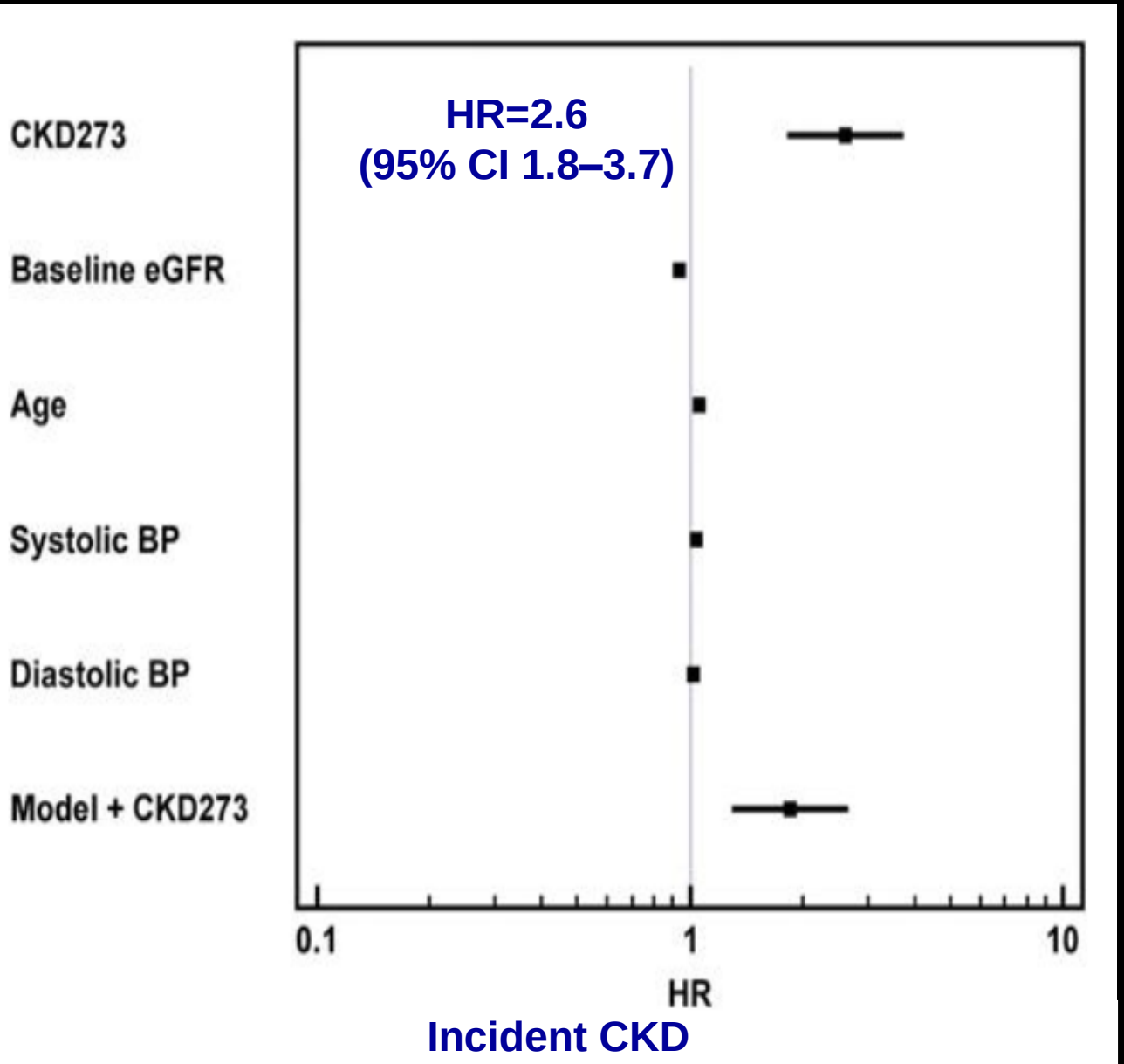
Follow-up (years)	0	1	2	3	4	5
High-risk (n)	72	68	60	56	42	7
Low-risk (n)	665	655	625	597	502	100

CKD273 predicts incident micro-albuminuria in normotensive, normoalbuminuric T2DM with normal kidney function

Model	Model covariates[a]	HR for the CKD273-classifier in the model (95% CI; P-value)	Area under ROC (95% CI; P-value)
1[b]	CKD273-classifier	2.64 (1.57–4.43; 0.0002)	0.56 (0.52–0.60; 0.007)
2[c]	CKD273-classifier, UAER, eGFR,	2.72 (1.61–4.6; 0.0002)	0.76 (0.70–0.81; <0.0001)
3[d]	CKD273-classifier, UAER, eGFR, age, HDL	2.78 (1.64–4.72; 0.0001)	0.79 (0.74–0.83; <0.0001)
4[e]	CKD273-classifier, UAER, eGFR, age, HDL, systolic blood pressure, HbA_{1c}, smoking, gender, antihypertensive treatment	2.47 (1.42–4.32; 0.0015)	0.79 (0.75–0.84; <0.0001)

Lindhartd, M et al. Nephrol Dial Transplant 2017

CKD273 predicts incident CKD in diabetics with normal kidney function and no albuminuria



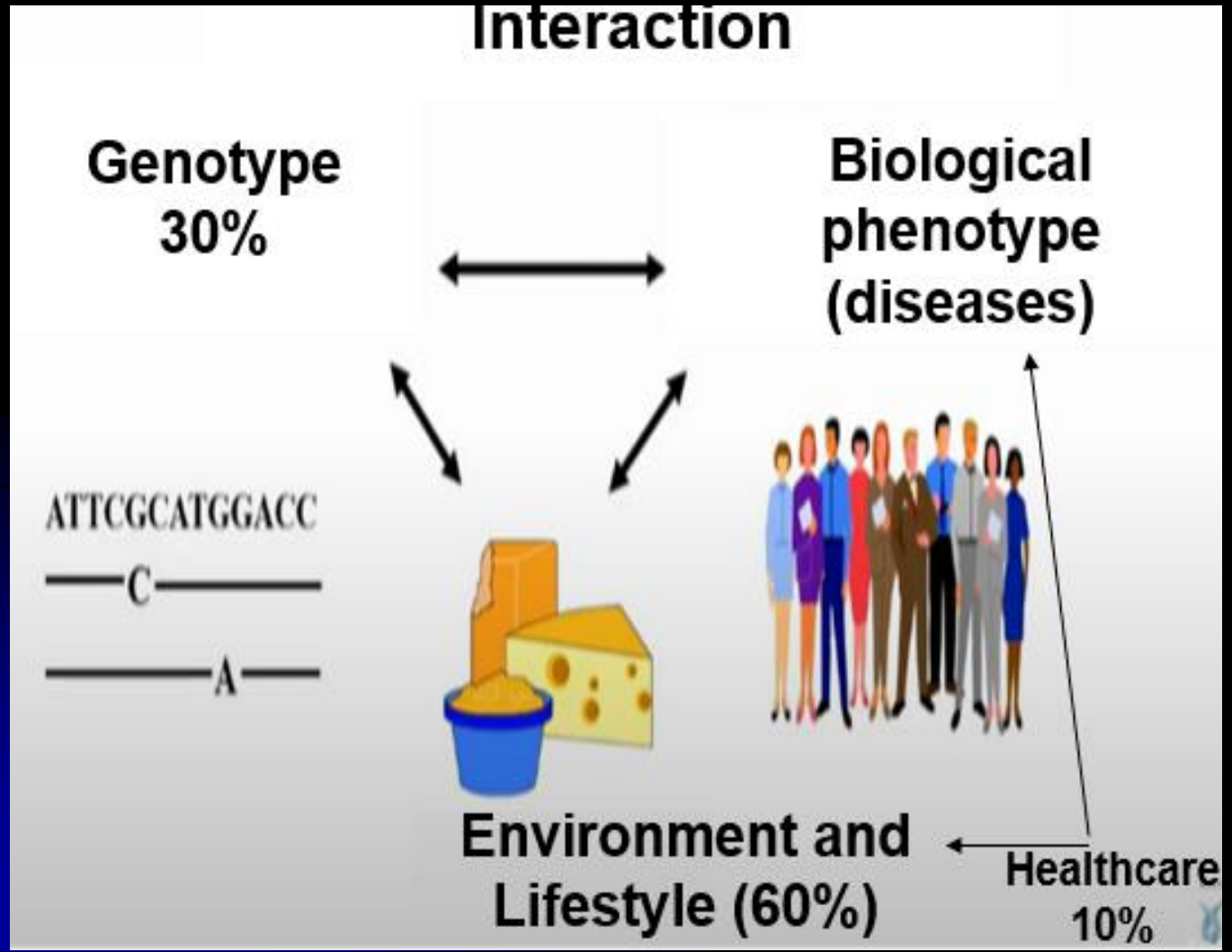
1014 T2DM and T1DM

Normal baseline eGFR ≥70 mL/min, urinary albumin excretion of <20 µg/min

Incident CKD-eGFR<60ml/min over a follow-up time of 6 years

Zurbig P. et al., Diabetes Care 2019

Genomics in CKD



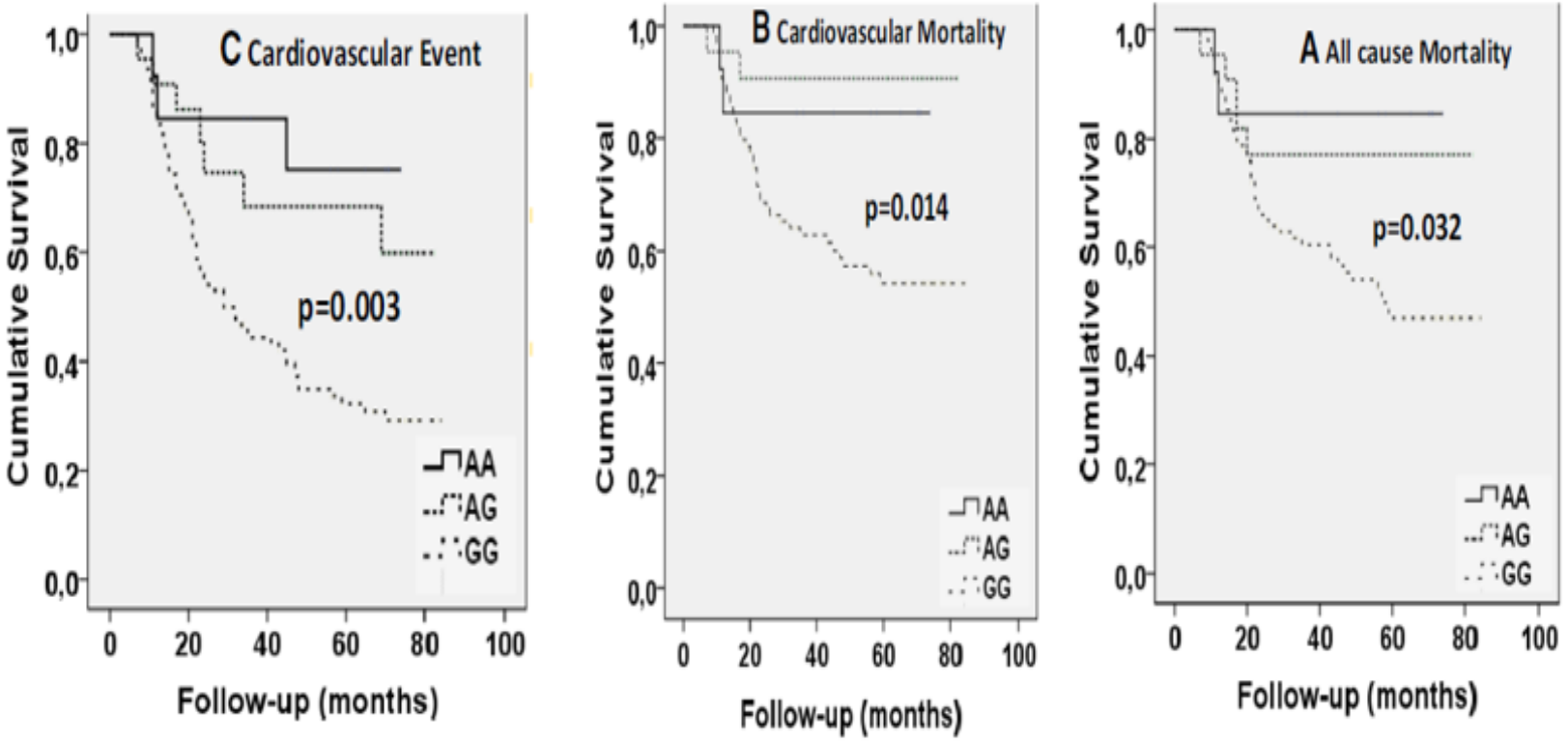
GR-DIAGENES Consortium

International Urology and Nephrology
https://doi.org/10.1007/s11255-017-1755-z

NEPHROLOGY - ORIGINAL PAPER

Association of ALOX12 gene polymorphism with all-cause and cardiovascular mortality in diabetic nephropathy

Athanasios K. Roumeliotis[1] · Stefanos K. Roumeliotis[1] · Stylianos A. Panagoutsos[1] · Fotis Tsetsos[2] · Marianthi Georgitsi[4] · Vangelis Manolopoulos[3] · Peristera Paschou[2] · Ploumis S. Passadakis[1]

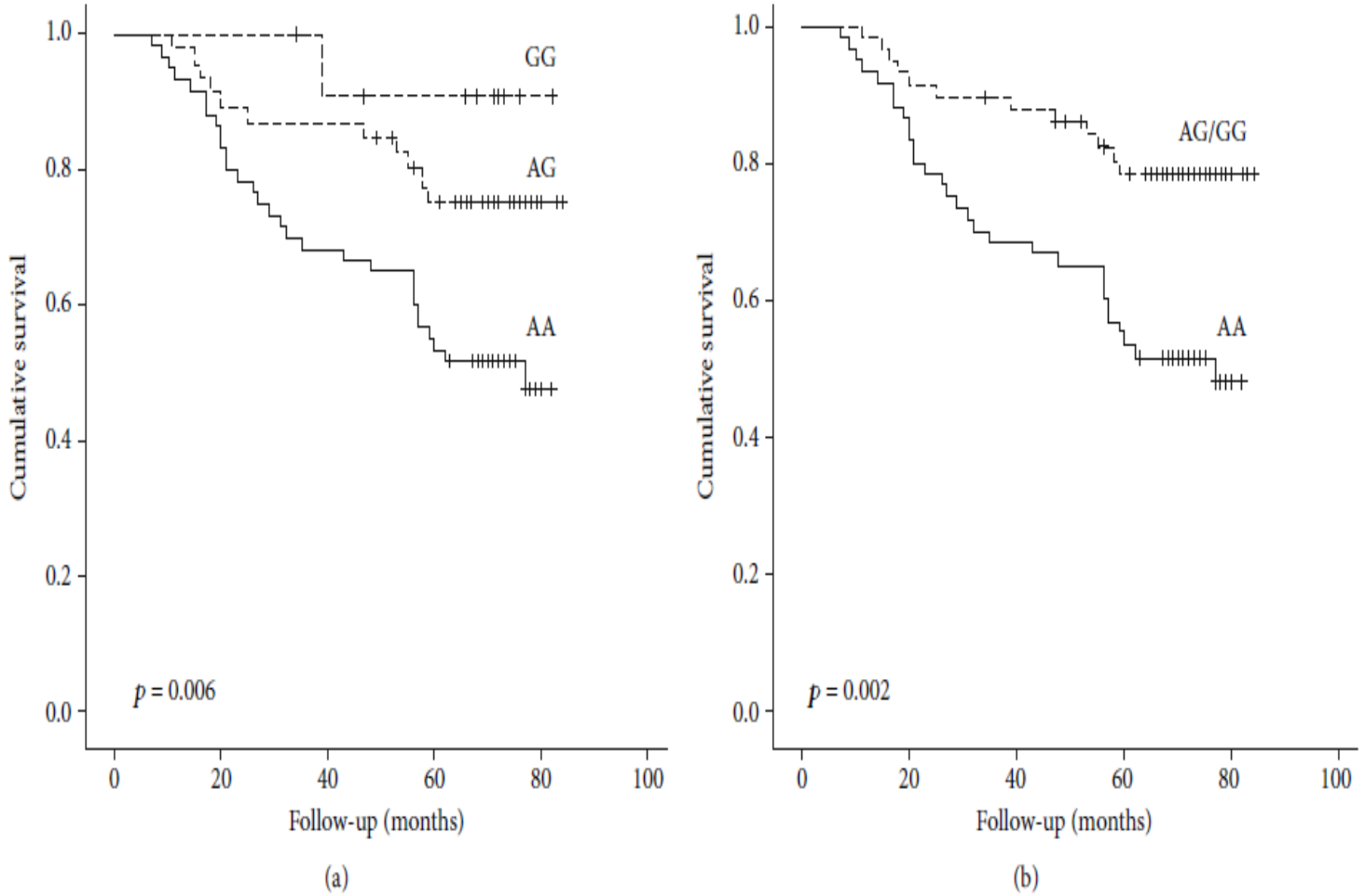


860 with established diabetic nephropathy

and 650 controls

Genome-wide association study (GWAS)

A novel SNP of human soluble epoxide hydrolase was associated with Ox-LDL and mortality in DKD



	HR	CI	p
All-cause mortality			
Model 1[a]			
rs11780592 EPHX2	2.74	1.40-5.35	**0.003**
rs2741335 EPHX2	0.85	0.58-1.26	0.42
Model 2[b]			
rs11780592 EPHX2	2.61	1.32-5.17	**0.006**
CV events (fatal and nonfatal)			
Model 1[a]			
rs11780592 EPHX2	1.10	0.72-1.69	0.67
rs2741335 EPHX2	0.77	0.54-1.11	0.16

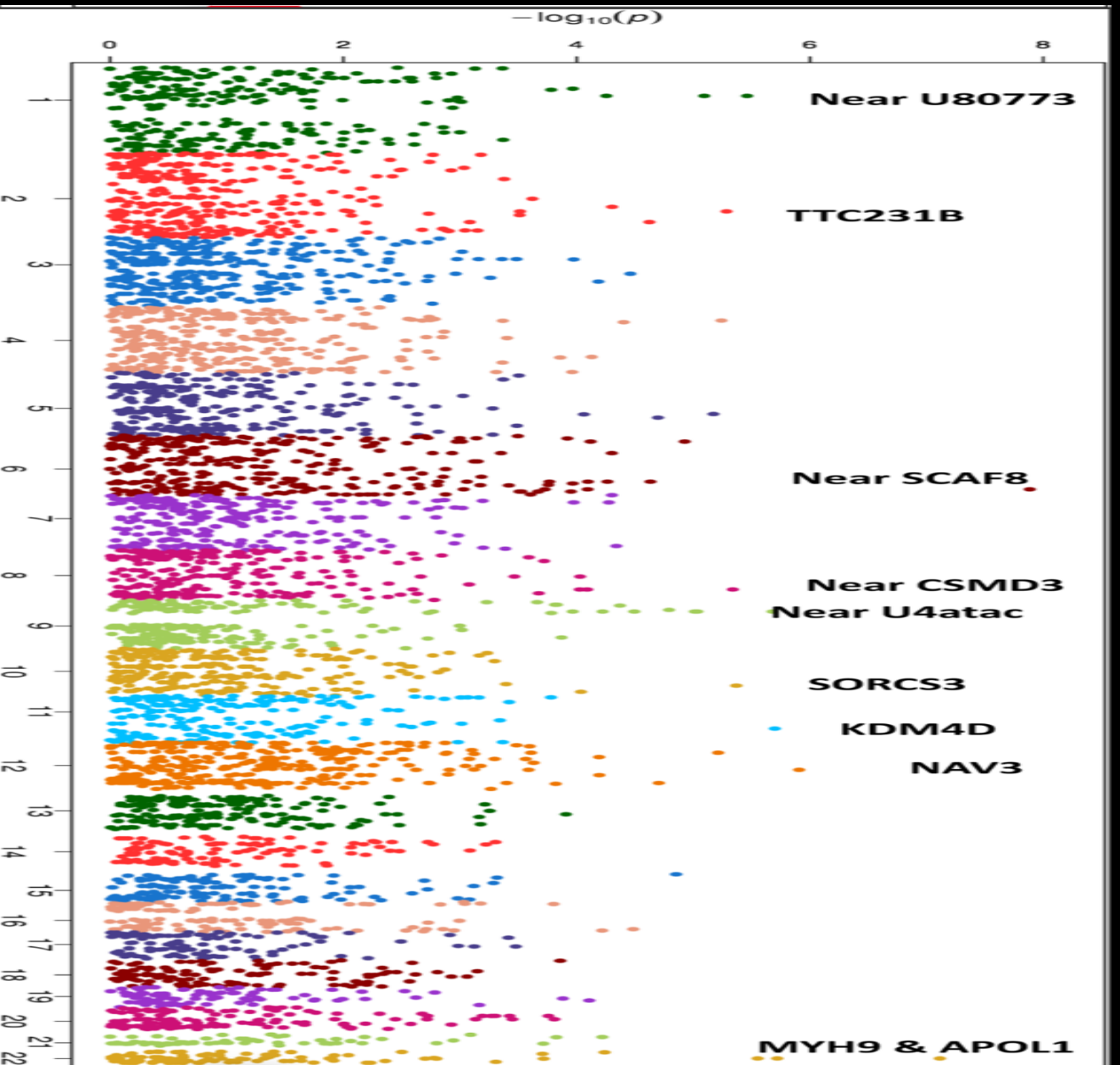
Roumeliotis S. et al., Oxid Med Cell Longev 2021:8817502

16 SNPs in the pathway of Oxidative stress that had never been identified before increased the risk for DKD

Chromosome	SNP-gene	Minor allele	% of minor allele in case group patients	% of minor allele in control group patients	Major allele	χ^2	p value	Odds ratio (OR) (CI: confidence interval)	Standard error (SE)
5	rs8177413-GPX3	C	1.653	0.2294	G	4.308	0.037	7.311 (0.8125-65.78)	1.121
8	rs7824574-CLU	A	5.785	10.45	C	4.243	0.039	0.5259 (0.2829-0.9778)	0.3164
22	rs12106549-TXNRD2	T	25.62	18.86	G	4.257	0.039	1.482 (1.019-2.155)	0.1911
17	rs14309-ALOX12	A	7.438	12.5	G	4.186	0.04	0.5625 (0.3222-0.9819)	0.2843
6	rs1293928-IPCEF1	G	30.58	38.41	A	4.174	0.041	0.7063 (0.5057-0.9866)	0.1705
6	rs6905523-GSTA7P	G	26.03	19.32	A	4.143	0.041	1.47 (1.013-2.133)	0.1898
8	rs10087808-OXR1	G	22.31	29.55	A	4.144	0.042	0.6849 (0.4753-0.9871)	0.1864
6	rs35062161-GPX6	T	3.719	1.364	A	4.027	0.044	2.794 (0.9824-7.946)	0.5333
8	rs10109171-OXR1	A	38.43	30.82	G	4.048	0.044	1.401 (1.008-1.947)	0.1678
2	rs2465661-AOX1	T	38.02	45.91	C	3.966	0.046	0.7226 (0.5246-0.9954)	0.1634
7	rs6947821-NOS3	C	29.75	37.27	T	3.902	0.048	0.7128 (0.5091-0.998)	0.1717
8	rs10108813-OXR1	C	22.73	29.77	T	3.907	0.048	0.6938 (0.4823-0.9979)	0.1855
6	rs72944451-GSTA4	T	2.479	68.18	G	3.874	0.049	3.703 (0.9179-14.94)	0.7117
8	rs1503573-OXR1	G	42.15	50	A	3.862	0.049	0.7286 (0.531-0.9996)	0.1614
17	rs11652709-EPX	C	37.6	30.23	G	3.851	0.049	1.391 (1-1.935)	0.1685
20	rs6052780-PRNP	A	1.65	4.545	G	3.848	0.049	0.3529 (0.1192-1.045)	0.5537

Roumeliotis A., Roumeliotis S. et al., Oxid Med Cell Longev 2021:2531062

FIND GWAS and meta-analysis



Several GWAS studies reported new SNPs increasing the risk for DKD, but all focused in only one race/ethnicity

15.000 diabetics

1st study showing

novel DKD susceptibility locus

Across all races/ethnicities

Iyengar et al, Plos Genetics, 2015

SNP in CUBN gene is associated with T2DM risk and lower 25(OH)D concentrations

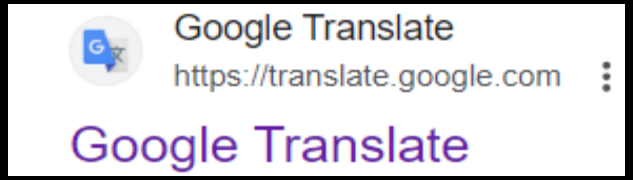
GR-DIAGENES
@GRDIAGENES

Table 3. Polymorphisms in *CUBN* gene significantly correlated with T2DM risk

SNP	Major >> Minor allele	P_{perm}	OR	Lower 95% CI	Upper 95% CI
rs11254375	T>>G	.00049	1.482	1.192	1.844
rs6602175	T>>G	.01697	0.822	0.697	0.970
rs1801224	T>>G	.02462	0.830	0.705	0.976
rs4366393	G>>A	.02841	0.829	0.706	0.973
rs7071576	G>>A	.04293	1.219	1.018	1.460

Megalin and cubilin (encoded by CUBN gene), are endocytic receptors in the proximal tubule

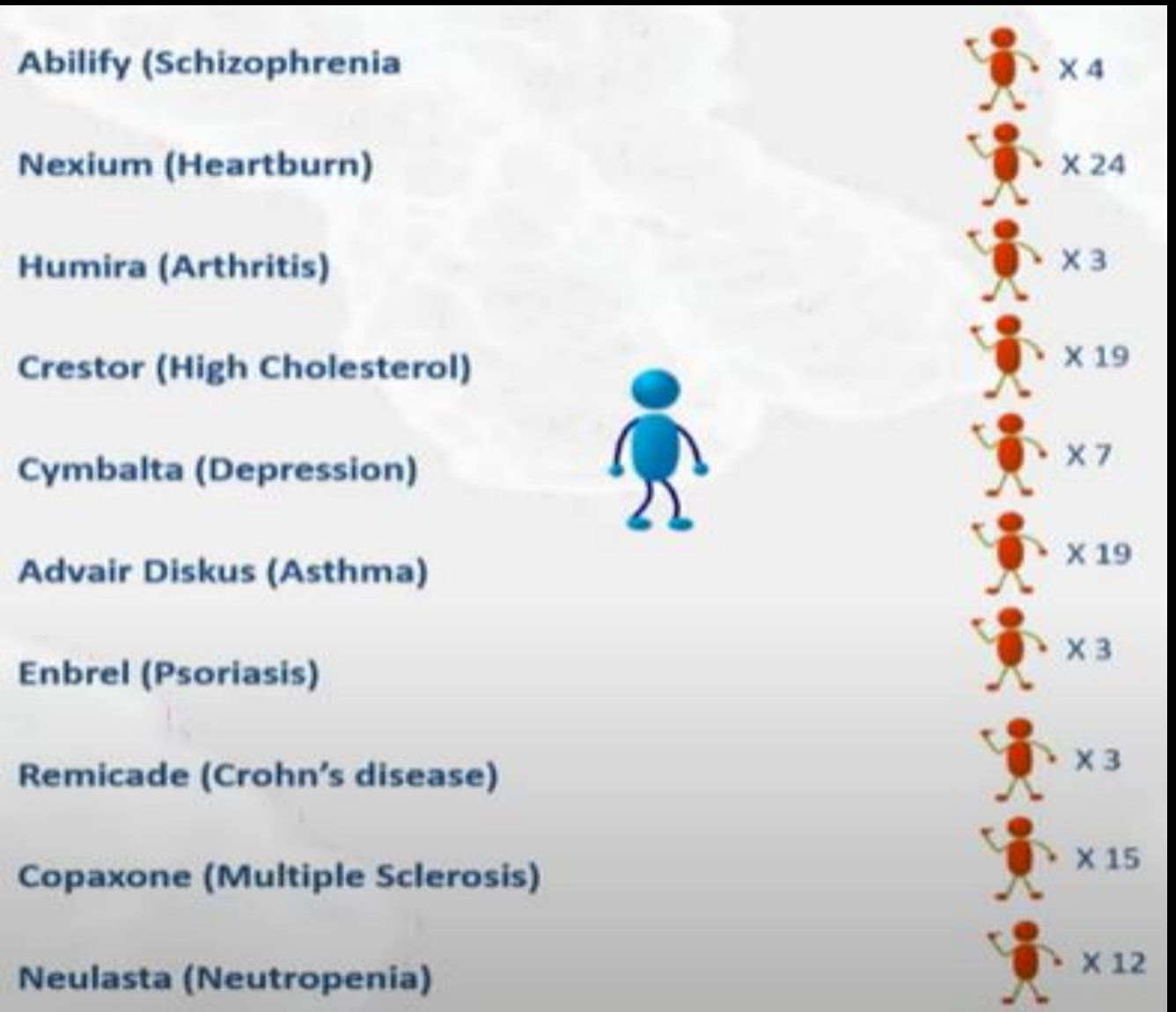
CUBN SNPs was strongly associated with lower 25(OH)D concentration



Patients having this polymorphism might need HIGHER vit.D doses to achieve optimal levels

Tsekmekidou X. et al. J Steroid Biochem Mol Biol. 2020

FDA: For every patient benefitting from a drug in the top-10 list, there are other 3-24 not getting beneficial effect

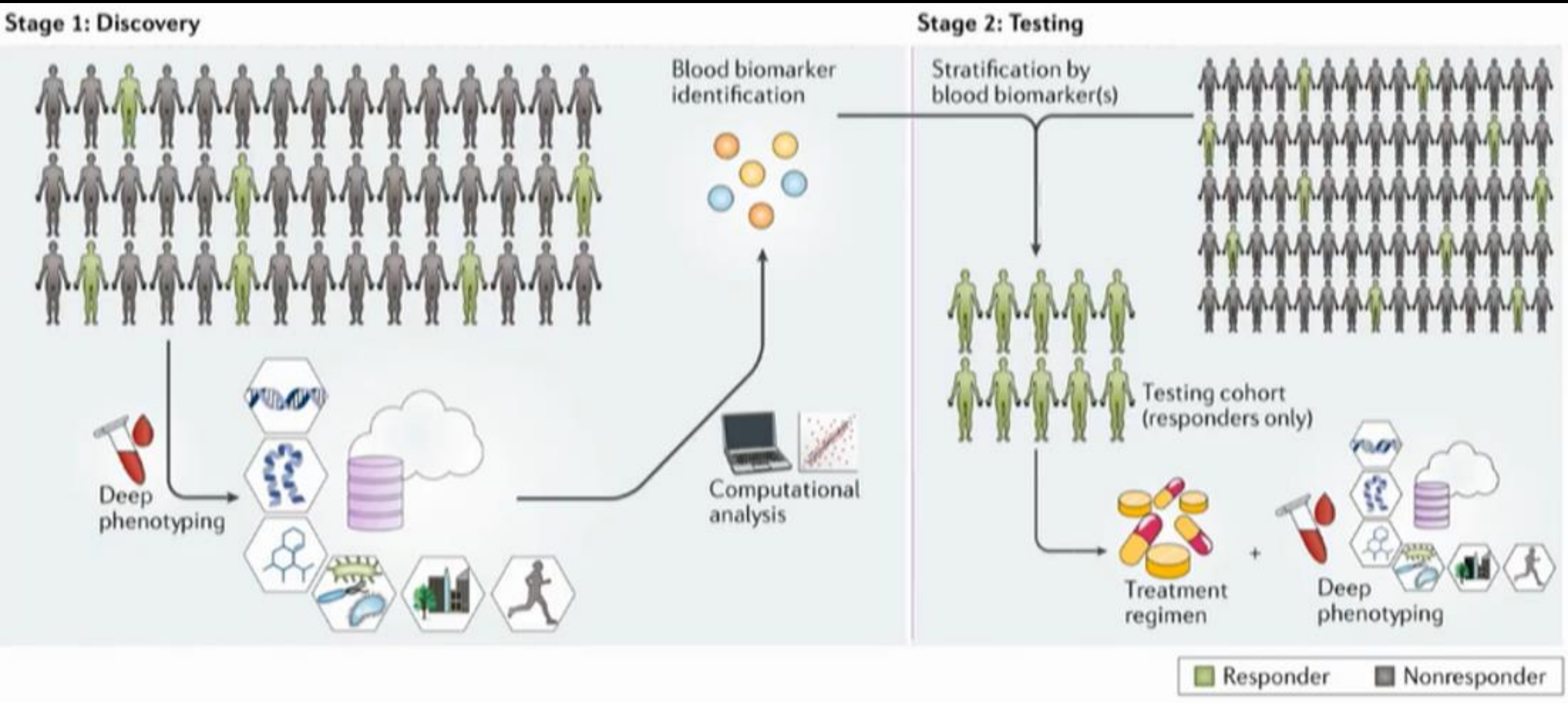


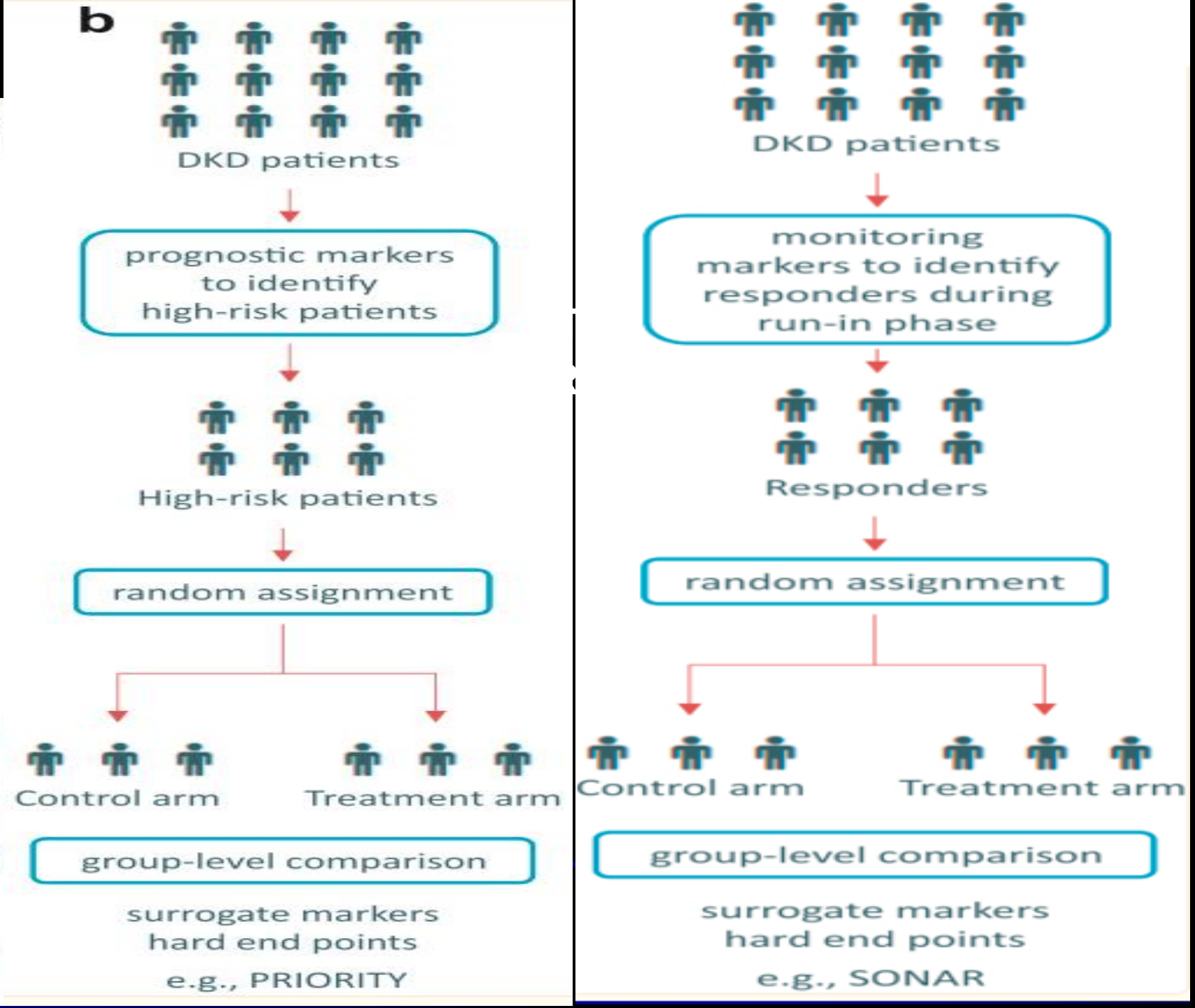
Most RCTs included white populations with normal kidney function

Until 2006, 75% of RCTs had CKD among exclusion criteria

Participants in RCTs are patients receiving healthcare and should not be considered
as “average” subjects

RCT Design for targeted therapies



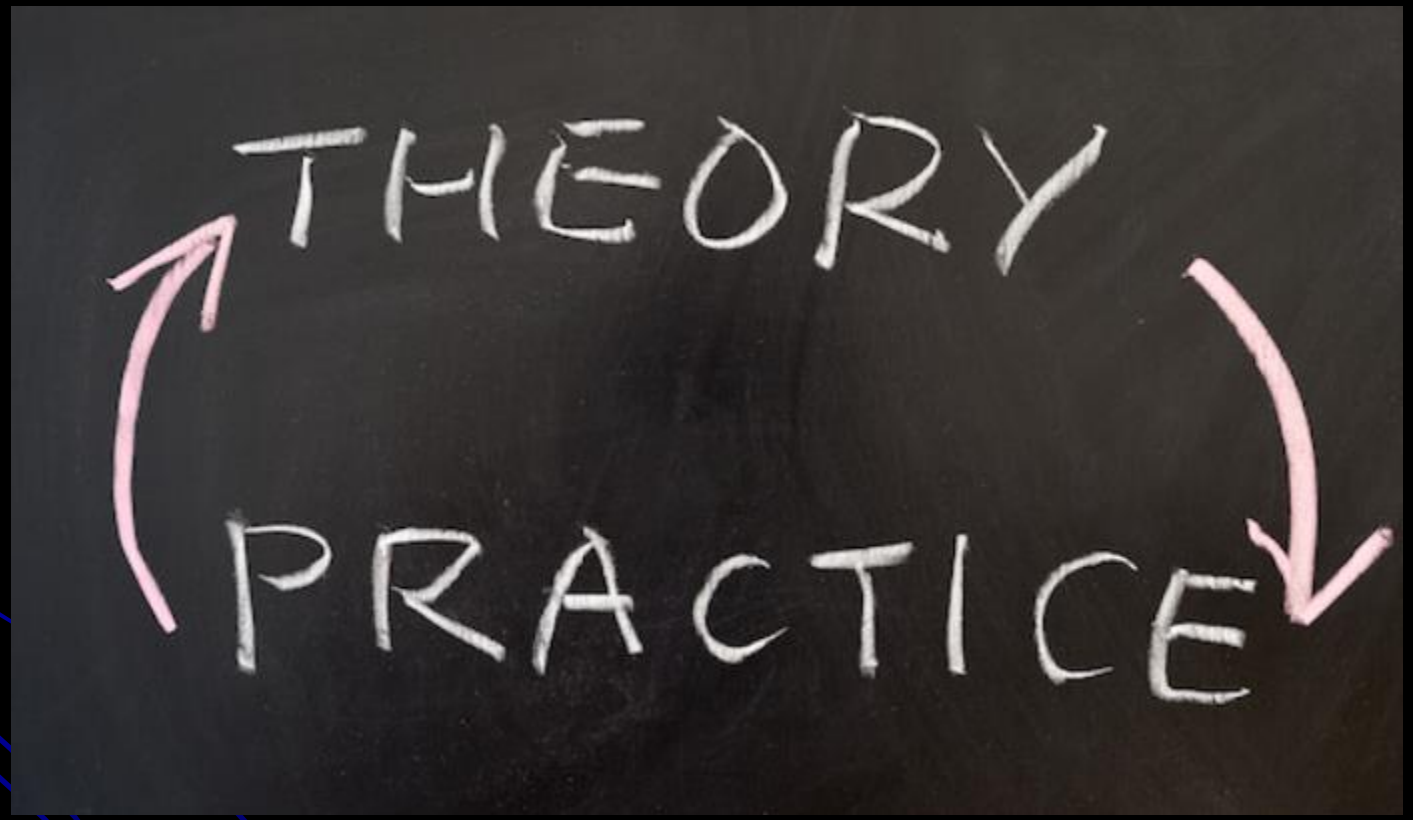


strategies enrolling populations that are more likely to respond to the new intervention

After a run-in phase, there was a strategy to separate atrasentan responders from nonresponders based on the level of reduction in UACR (>30% decrease)

Albuminuria was not used as a prognostic marker but rather to **describe treatment efficacy**

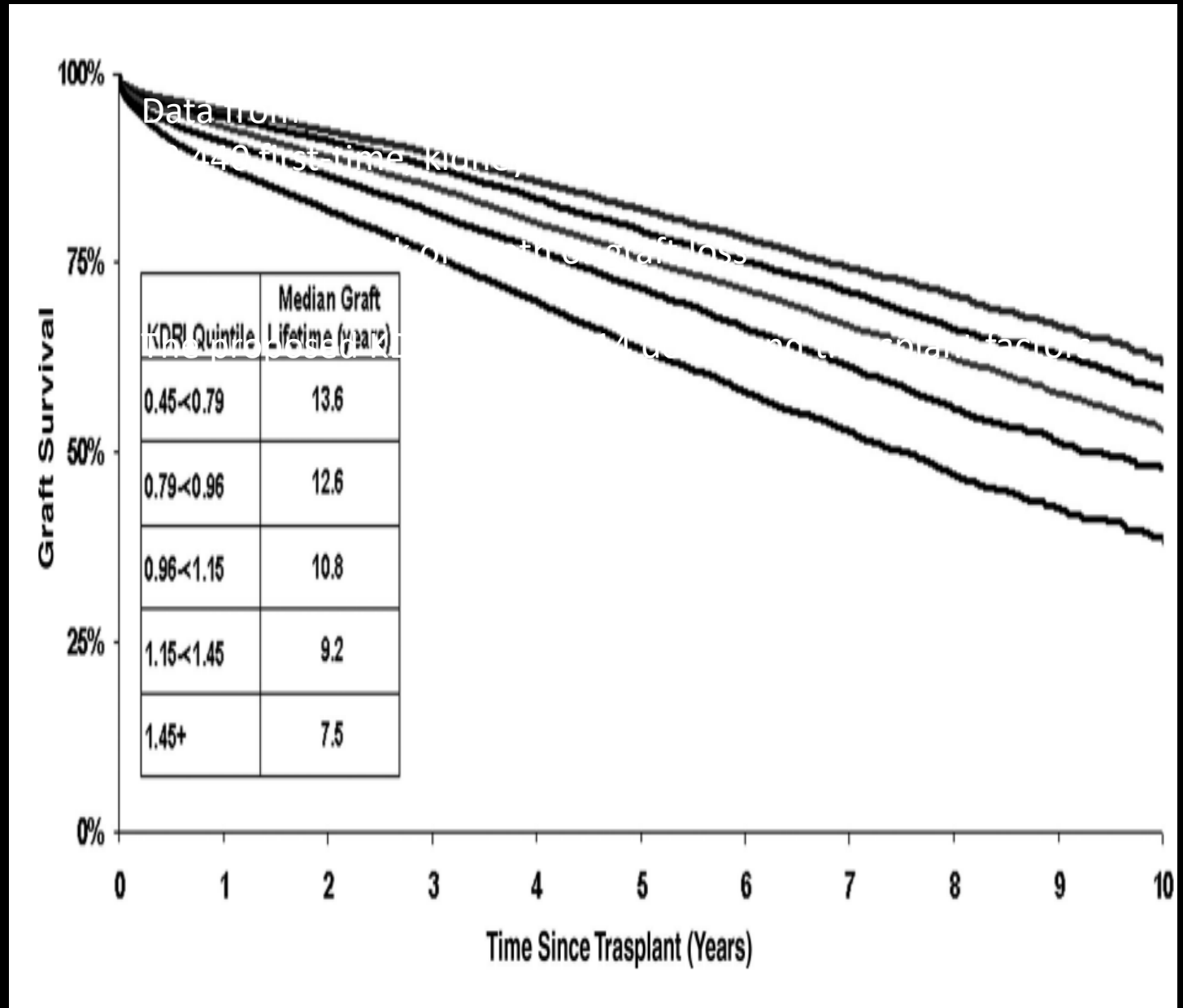
Precision Medicine in Nephrology: are we there yet?



Kidney donor risk index (KDRI)

TABLE 2. Calculating KDRI: examples

Donor factor	Reference donor	Example 1	Example 2	Example 3
Age (yr)	40	21	45	65
Race	Non-Black	Non-Black	Non-Black	Non-Black
Hypertensive	No	No	No	No
Diabetic	No	No	No	No
Serum creatinine (mg/dL)	1.0	1.0	1.0	1.0
Cause of death	Nonstroke	Nonstroke	Nonstroke	Nonstroke
Height (cm)	170	183	183	183
Weight (kg)	80	80	80	80
Donation after cardiac death	No	No	No	No
Hepatitis C	No	No	No	No
Number of B mismatch	2	2	2	0
Number of DR mismatch	1	2	2	0
Cold time (hr)	20	18	18	18
Enbloc kidney transplant	No	No	No	No
Double kidney transplant	No	No	No	No
KDRI	1.00	0.79	1.07	1.22



APOL1 Long-term Kidney Transplantation Outcomes Network (APOLLO): Design and Rationale

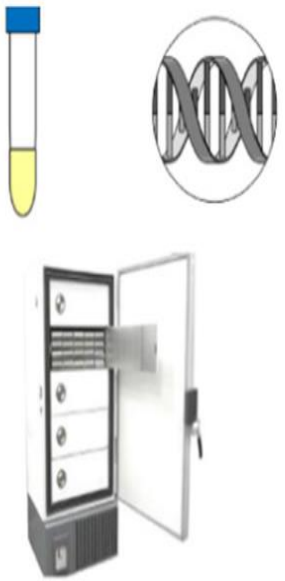
APOLLO

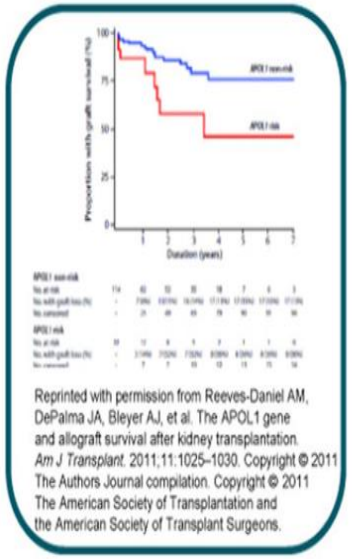
DNA extraction for *APOL1* testing & bio-sample collection

Transplant outcomes based on UNOS data

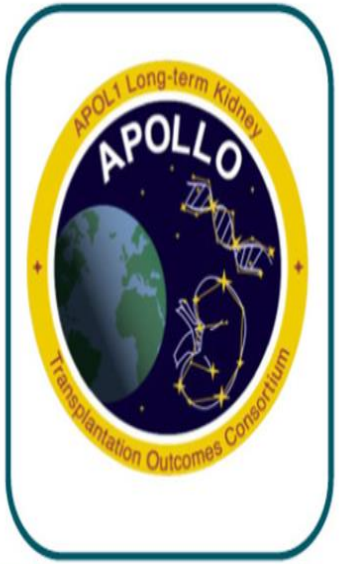
APOL1 effects on kidney transplant recipients & donors

- 2,614 DDKT pairs
- 550 LD pairs
- 260 Transplant Programs
- 58 OPOs
- 66 HLA labs





Reprinted with permission from Reeves-Daniel AM, DePalma JA, Bleyer AJ, et al. The APOL1 gene and allograft survival after kidney transplantation. *Am J Transplant*. 2011;11:1025–1030. Copyright © 2011 The Authors Journal compilation. Copyright © 2011 The American Society of Transplantation and the American Society of Transplant Surgeons.



CONCLUSION:

The NIH APOLLO Consortium including 260 transplant programs, 58 OPOs and 66 HLA labs will assess effects of *APOL1* in deceased and living donor kidney transplantation.

KI REPORTS
KIReports.org

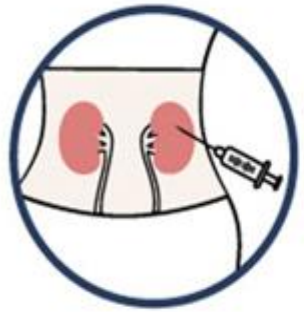
Freedman BI *et al.*, KI Reports

APOL1 polymorphism is associated with a **30-fold increased risk** for CKD progression and CV mortality in patients of African ancestry

Genovese G. et al., Science 2010

Friedman D.J, et al., CJASN 2021

Rationale and design of the Kidney Precision Medicine Project.



KPMP Kidney Biopsy

Study populations:

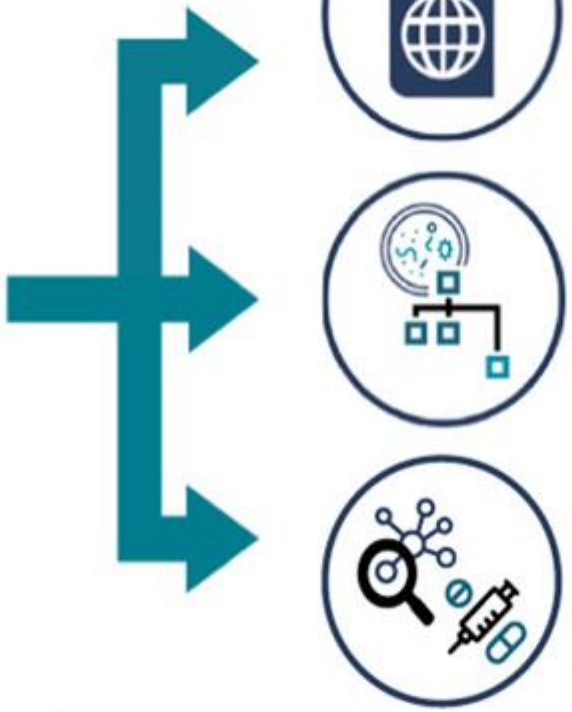
Diabetes & CKD
Hypertension & CKD
Acute kidney injury

Clinical Presentation

Traditional & Digital Pathology

Omics & Imaging Integration

Clinical Outcomes



Create reference kidney tissue atlas

Develop mechanism-based disease subtypes

Identify critical cells, pathways, and targets for novel therapies

CONCLUSION:

The KPMP seeks to redefine and reclassify common kidney diseases by combining deep molecular phenotyping with clinical characteristics, innovative digital pathology, and clinical outcomes.

ISN kidney INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

de Boer et al for the KPMP, 2020

Ongoing studies building biopsy banks

European Renal cDNA Bank (15 years)

Cohen C.D. et al. Kidney Int 2002

Nephrotic Syndrome Study Network (NEPTUNE)

Gadegbeku CA. Kidney Int. 2013

Clinical Phenotypic and Resource Biobank (C-PROBE)

Troost JP,. Kidney Int Rep. 2018

KOrea Renal biobank NEtwoRk System TOward NExt-generation analysis (KORNERSTONE)

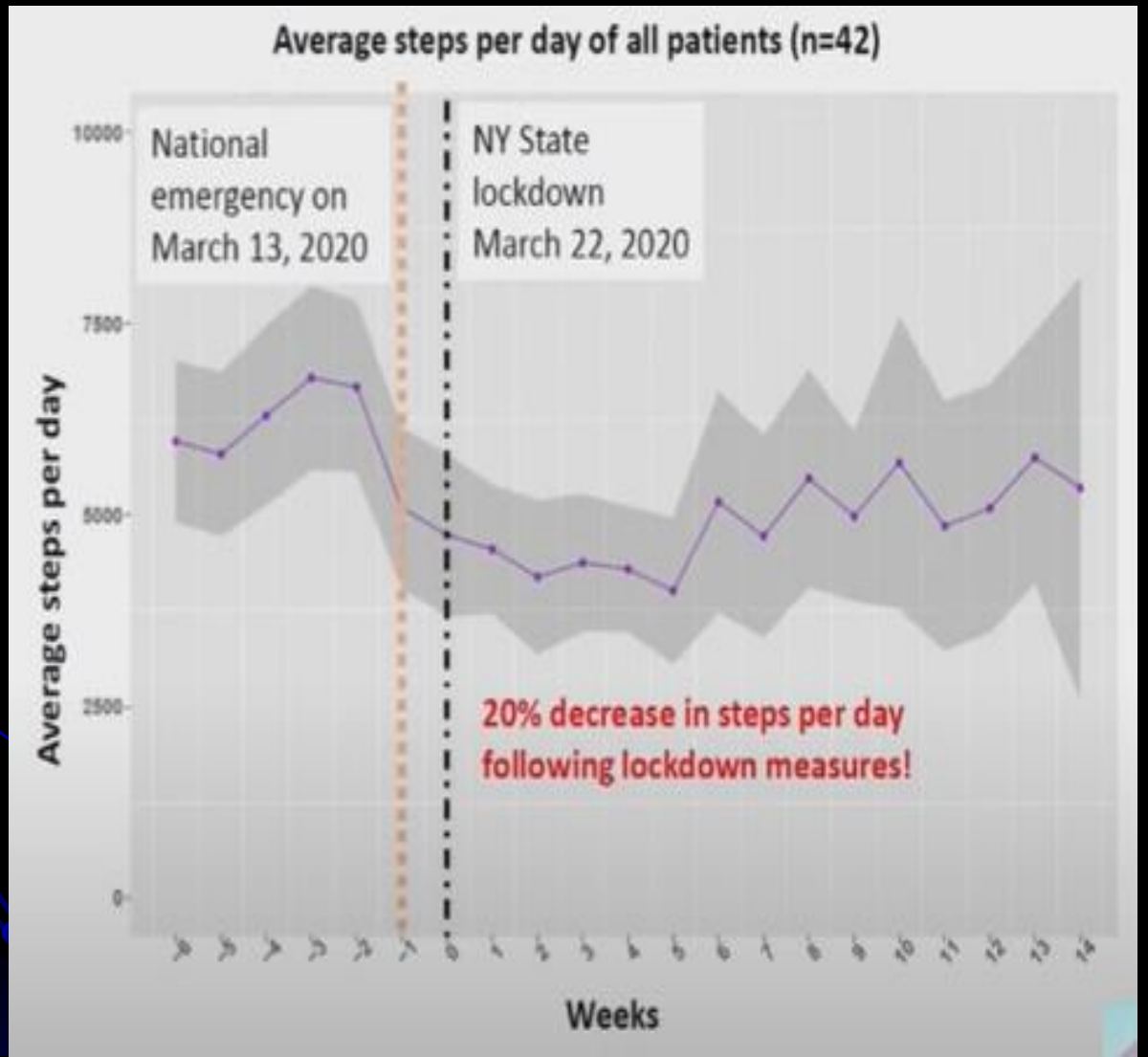
Kang E. et al., BMC Nephrol 2020

Prospective RRI Interdialytic Activity Monitoring Exploration (PRIME)

RENAL RESEARCH INSTITUTE

Fit bit device
The largest database of wearables data in HD

- Steps
- heart rate
- sleep indicators

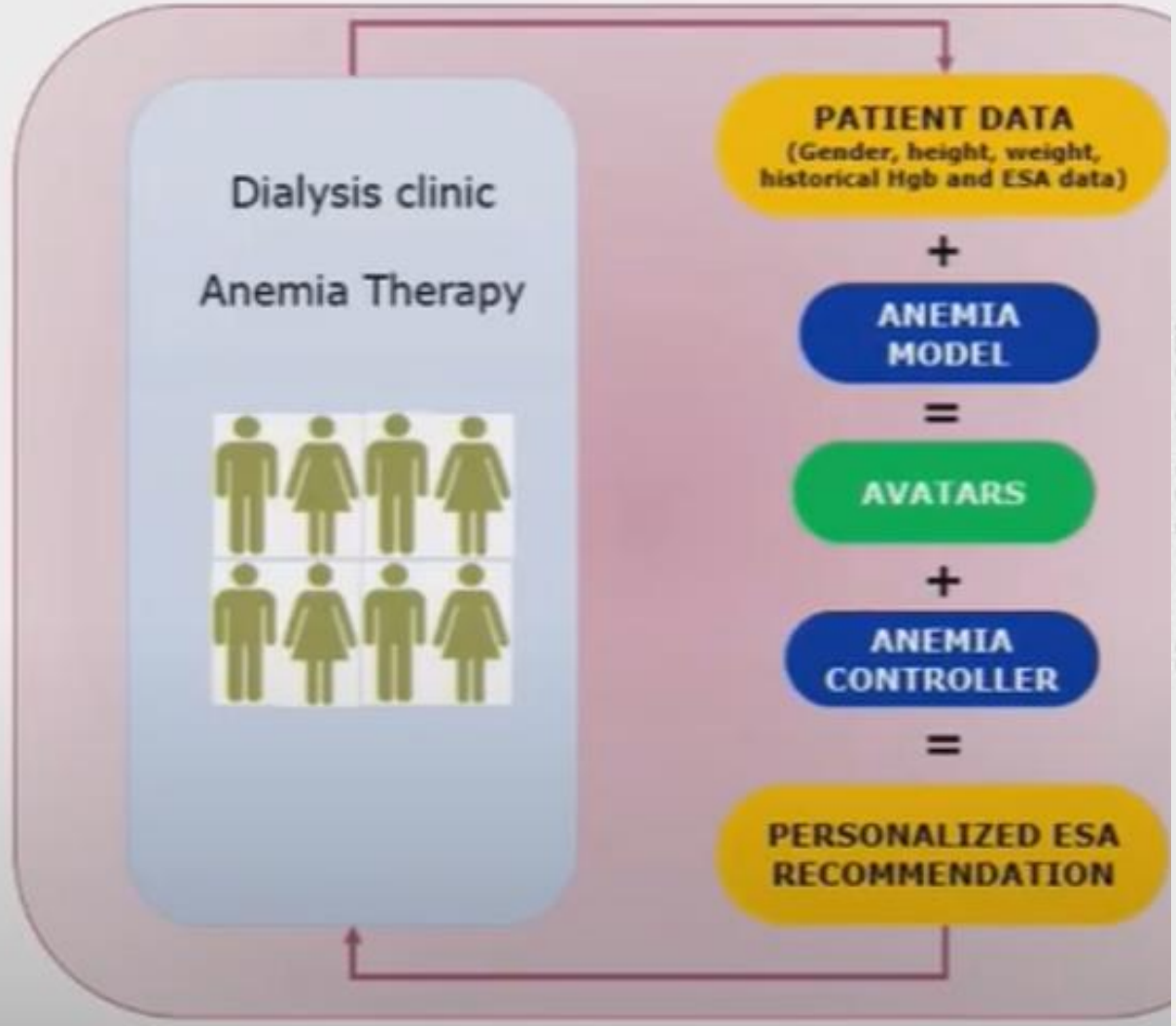


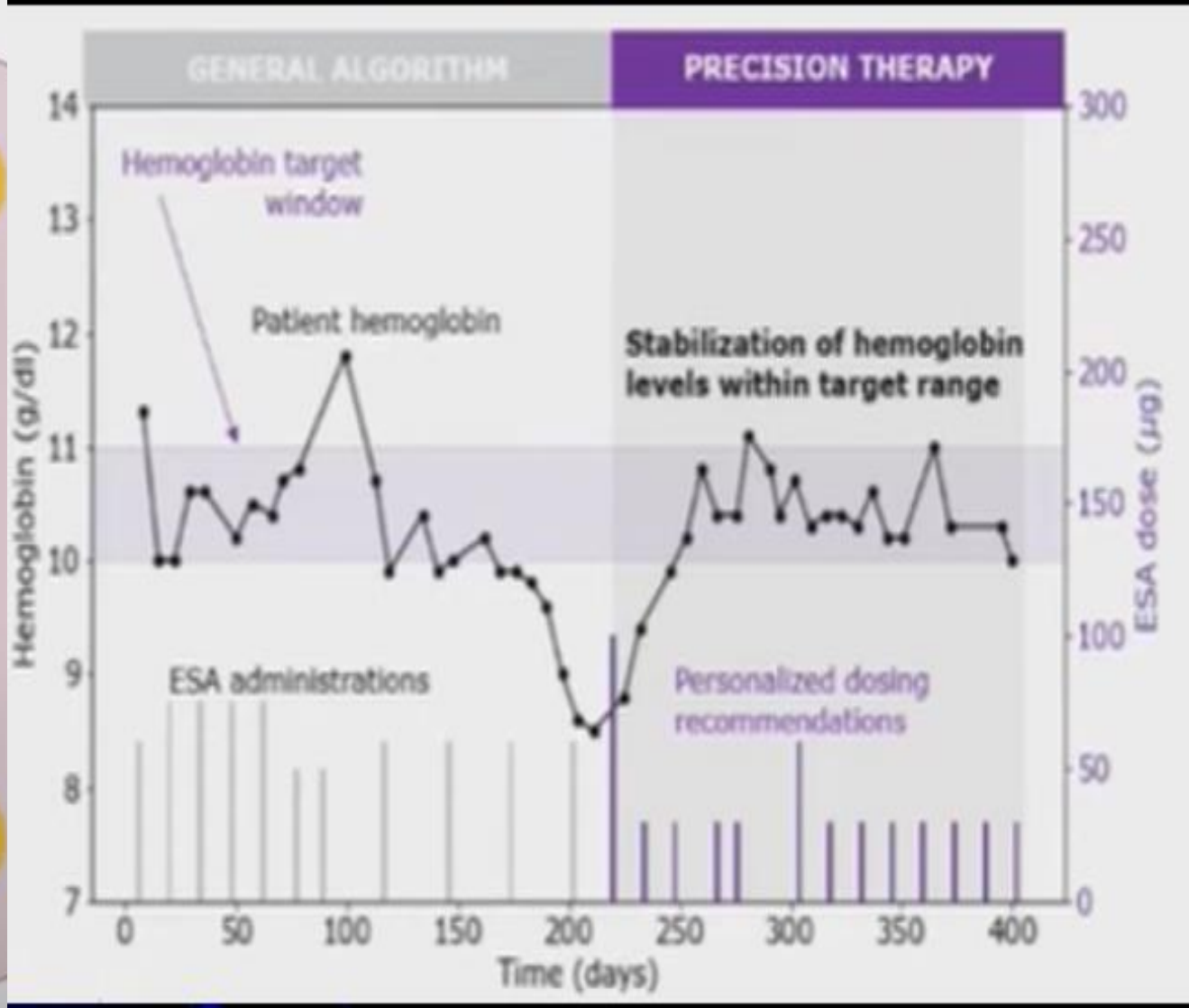
83% of patients with COVID19 had **increased physical activity in two weeks prior** to COVID diagnosis

Personalized Anemia Therapy Through Creation of a Patient's Mathematical Twin ("Avatar")

RENAL RESEARCH INSTITUTE

RCT of Personalized Anemia Care: Interim Results Show Improved Control





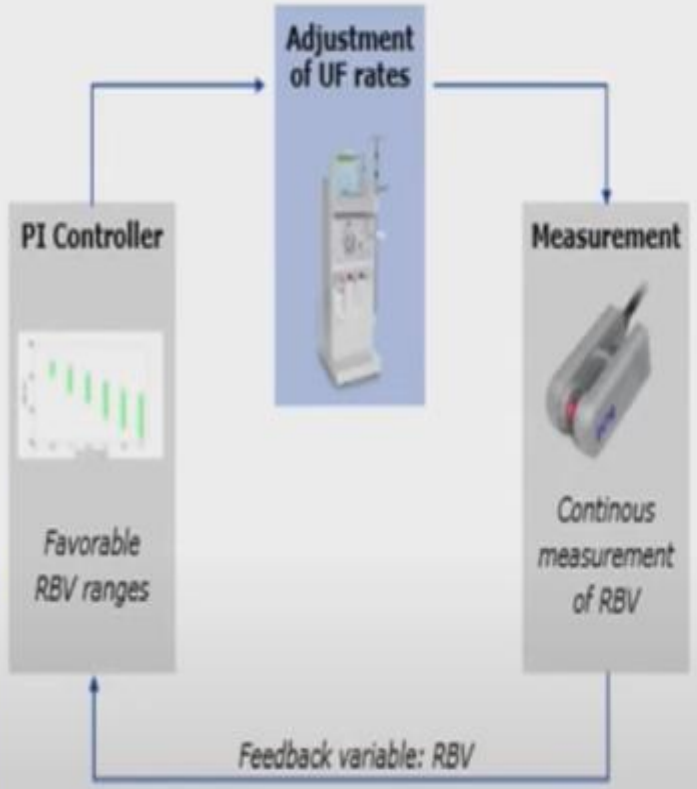
Adaptive Ultrafiltration-A step towards Personalized Fluid Management

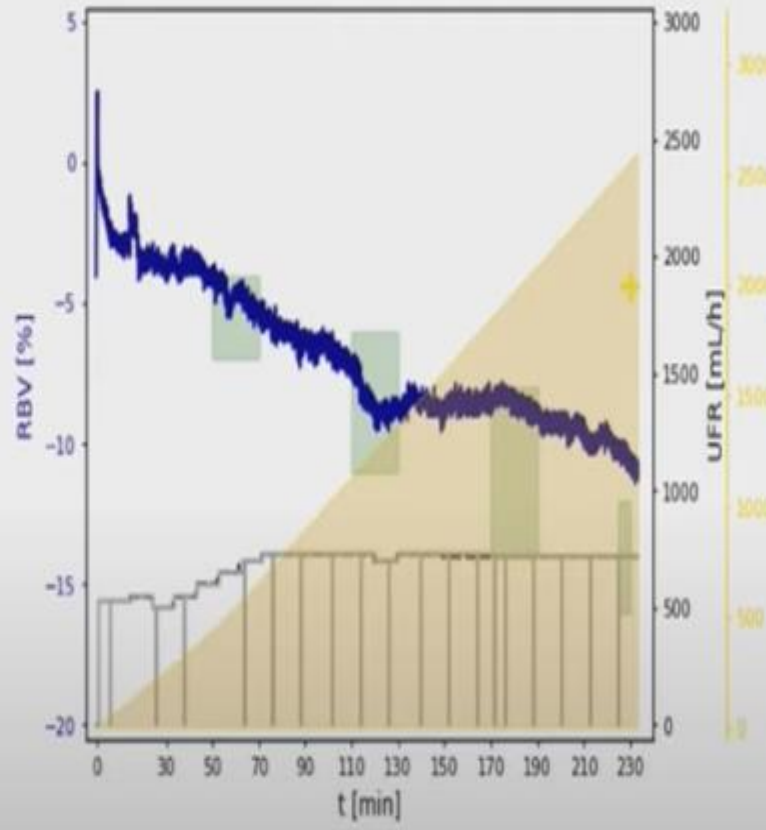
Identified relative blood volume (RBV) ranges associated with improved patient survival

Manually steering the patients into these targets would require incessant, iterative adjustments of the UF rate by the nurse during the treatment

Not feasible in routine practice

WE DEVELOPED AN ADAPTIVE UF CONTROLLER THAT GUIDES RBV INTO THOSE FAVOARLE RANGES WHILE CONSIDERING OTHER CONSTRAINTS





Precision medicine in kidney disease: the patient's view

Keith D. Brown, Catherine Campbell and Glenda V. Roberts

NATURE REVIEWS | NEPHROLOGY VOLUME 16 | NOVEMBER 2020 | 625

of course, the concern about the privacy of an individual's genetic information

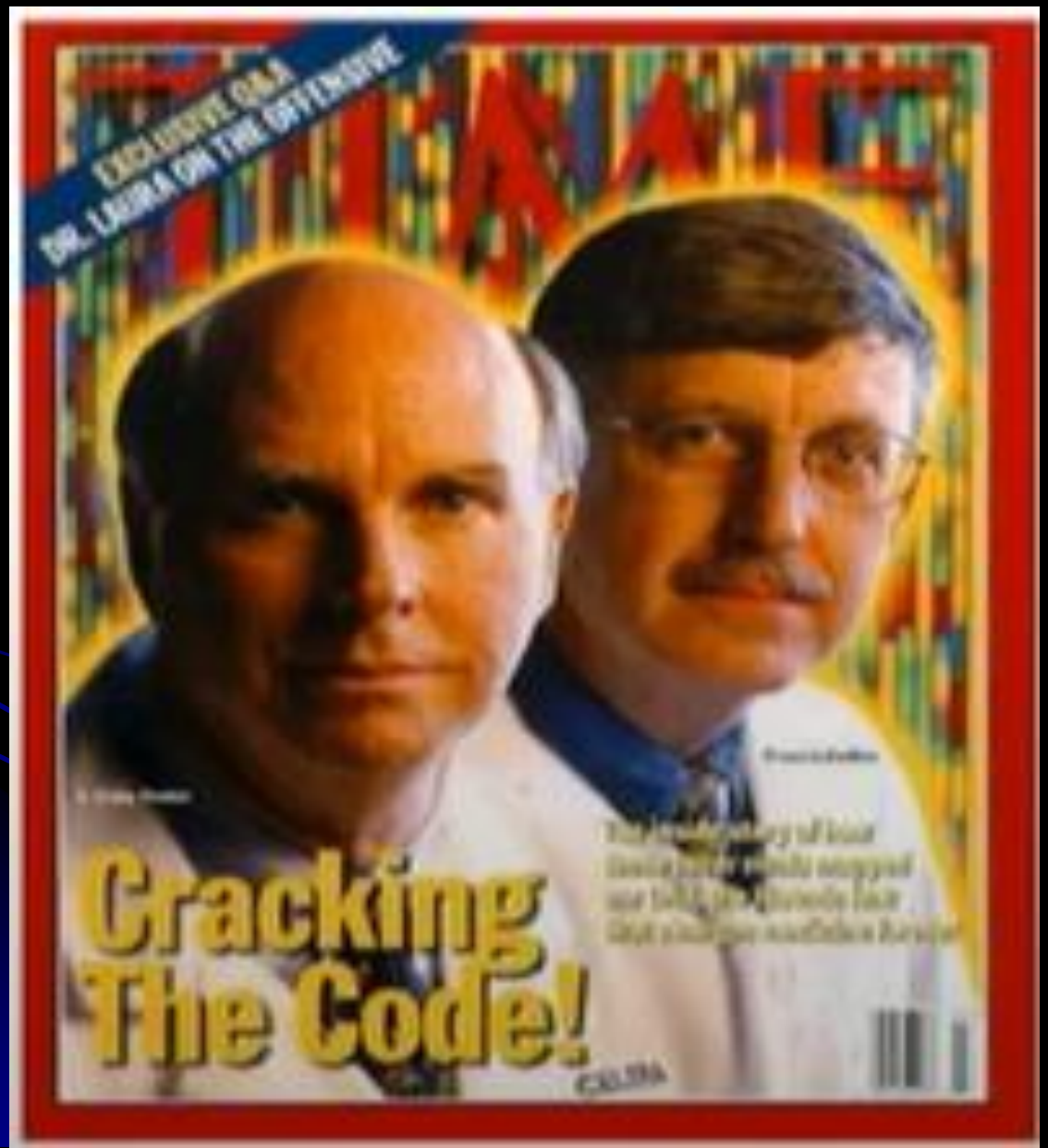
worry about things like insurability and employability if certain genetic information is revealed

For example, family members who might have inherited these genetic predispositions to kidney disease will be faced with decisions about whether or not they want to undergo genetic testing.

insurance companies, I think that some people will be reluctant to get a personalized diagnosis because it might be viewed as a pre-existing condition.

Patients should have an active role throughout this ethical, transparent research process

Human Genome Project



2000 - 90%

2004 - 99%

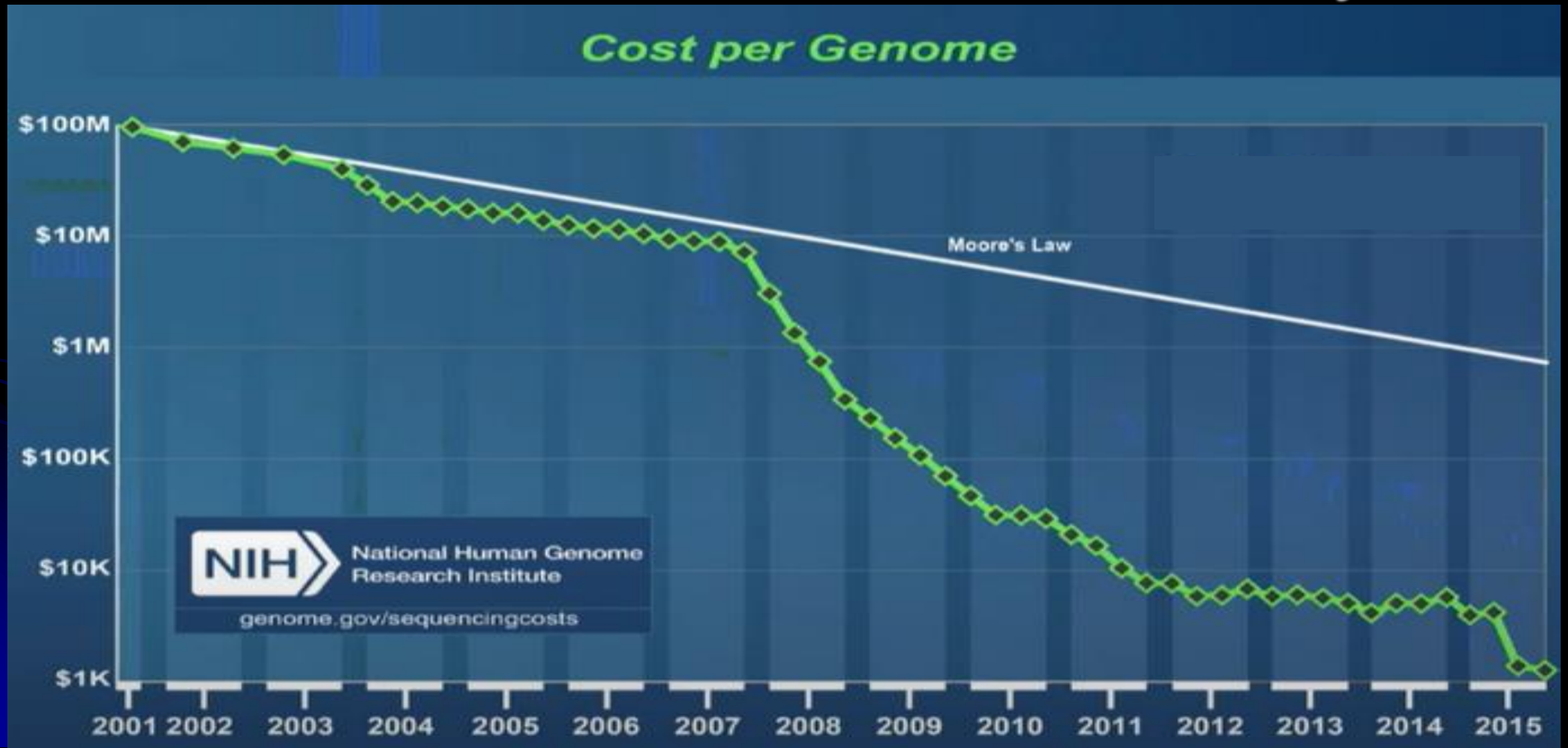
Francis Collins, 10 years later (Nature 2010;464:674-5)

Has the revolution arrived?

The consequences for clinical medicine, however, have thus far been modest.

«we invariably overestimate the short-term impacts of new technologies and underestimate their longer-term effects».

Analyze Human Genome sequence: from 100.000.000 in 2000 to 600$ today



Precision Medicine in Nephrology

- **There are no diseases, but patients**
- **Or Categories of patients depending on genes, lifestyle, environment who may benefit from specific treatments**
- **<u>One size DOES not fit all</u>**

G&K & IWG Working Groups

e-seminars G&K & IWG

Precision medicine and hierarchy of diagnostics and treatment in haematuria/proteinuria

Speaker:
Bertrand Knebelmann, France

Speaker:
Elion Hoxha, Germany

Panellist:
Daniel Gale, UK

Panellist:
Peter Boor, Germany

Moderator:
Jan Halbritter, Germany

Moderator:
Annette Bruchfeld, Sweden

17 OCT

Tuesday, October 17, 2023
From 5:00 to 6:00 PM (CEST)

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“It is what we think we know already that often prevents us from learning.”

Dr. Claude Bernard, physiologist

**“The good physician treats the disease
The great physician treats the patient.”**

Sir William Osler, 1903

Thank you


ΑΧΕΠΑ
ΠΑΝΕΠΙΣΤΗΜΙΑΚΟ ΓΕΝΙΚΟ ΝΟΣΟΚΟΜΕΙΟ ΘΕΣΣΑΛΟΝΙΚΗΣ ΑΧΕΠΑ