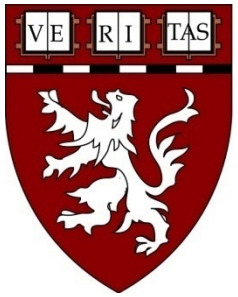
Current and Future Burden of CKD

Julie R. Ingelfinger, M.D.
Professor of Pediatrics, Harvard Medical School
Senior Consultant in Pediatric Nephrology, Mass General for Children at MGB
Deputy Editor, the New England Journal of Medicine

BUT, a better title might be



Preventing the Future Burden of CKD

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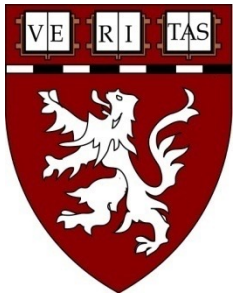


Disclosure

- I am an editor at the New England Journal of Medicine, for which I receive a salary.
- Editorial work my lead to intellectual bias.

CKD Prevalence: High and Increasing

- KNOWN FOR YEARS:
- Trend for increased prevalence of CKD in the USA and select countries, irrespective of the calculation, implies persistent and rapid growth worldwide.
- Reported prevalence estimates across countries range broadly from approximately 2.0% to 44%.
- This broad range in prevalence exemplifies the differences in patient populations and unmet clinical, humanistic, and economic needs across the globe.
- Thus, reasons for differences are many.

LA Braun et al. International Journal of Nephrology and Renovascular Disease **2012**;5: 151-163.

Projecting the Epidemiological and Economic Impact of Chronic Kidney Disease Using Patient-Level Microsimulation Modelling: Rationale and Methods of Inside CKD

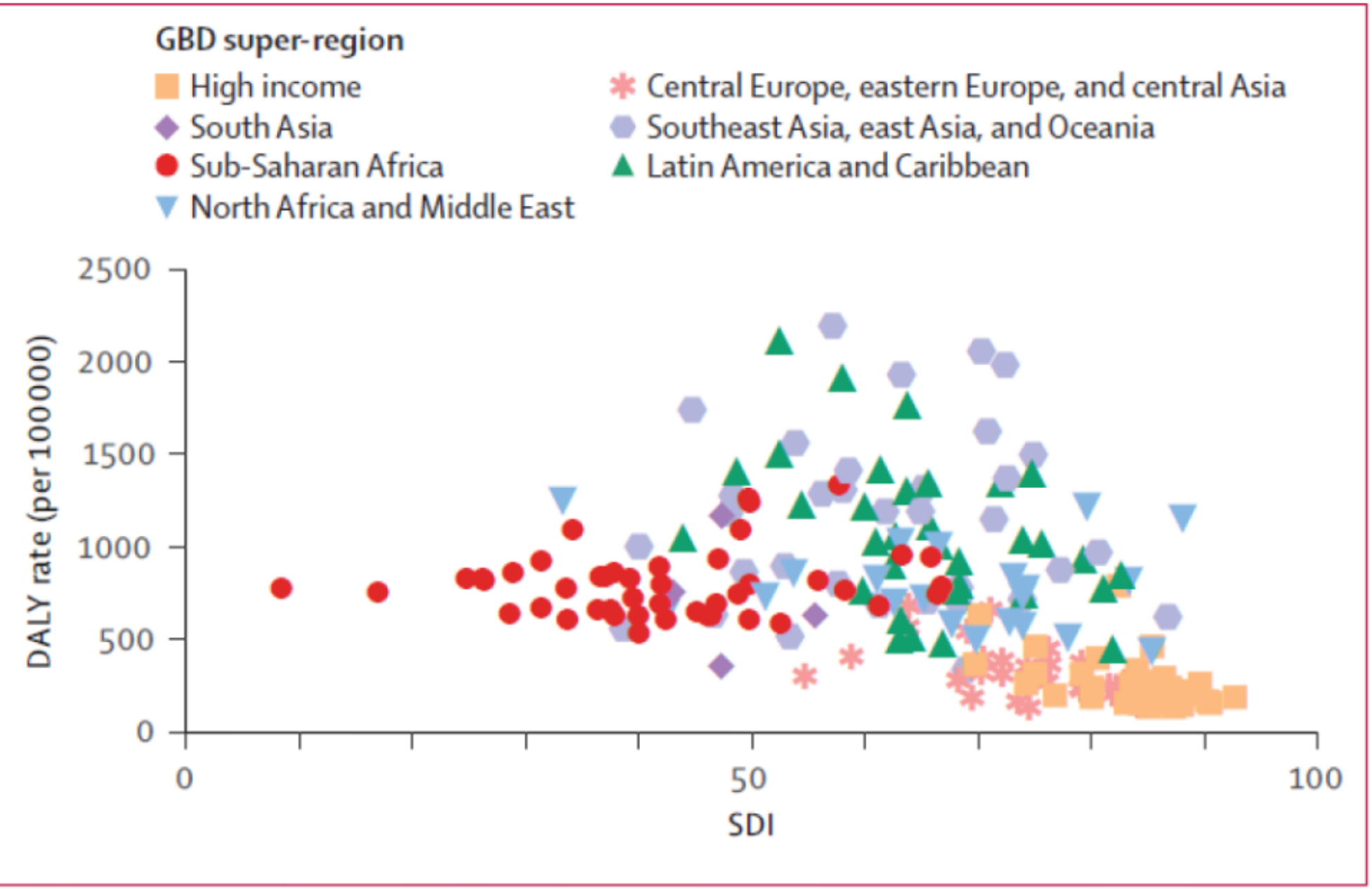
Tangri N, Chadban S, Cabrera C, Retat L, Gracia Sánchez JJ

CKD prevalence has increased by nearly 30% since 1990, with current prevalence estimates giving an approximate range between 8% and 16%.

Disease severity correlates with the extent of GFR reduction and albuminuria, which are used to classify the disease from CKD

stage 1 (mild disease) to CKD stage 5 (severe disease).

Adv Ther (2023) 40:265–281
https://doi.org/10.1007/s12325-022-02353-5



GBD, Global burden of Disease

DALY, disability-adjusted life years

SDI, Socio-demographic Index.

igure 1. Age-standardized DALY rates for each location by Socio-Demographic Index, both sexes ombined, 2019. Reprinted with permission from reference 23[20]

Global Burden of Disease 2019: GBD cause and risk summaries Chronic kidney Disease. *Lancet* 2020; **396:** S152-3.

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012				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
GFR categories (ml/min/1.73 m²) Description and range	**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			

Green, low risk (if no other marker of kidney disease, no CKD); Yellow, moderately increased risk; Orange, high risk; Red, very high risk. GFR; glomerular filtration rate

Kidney Health Issues We Often Miss

Lifespan issues!

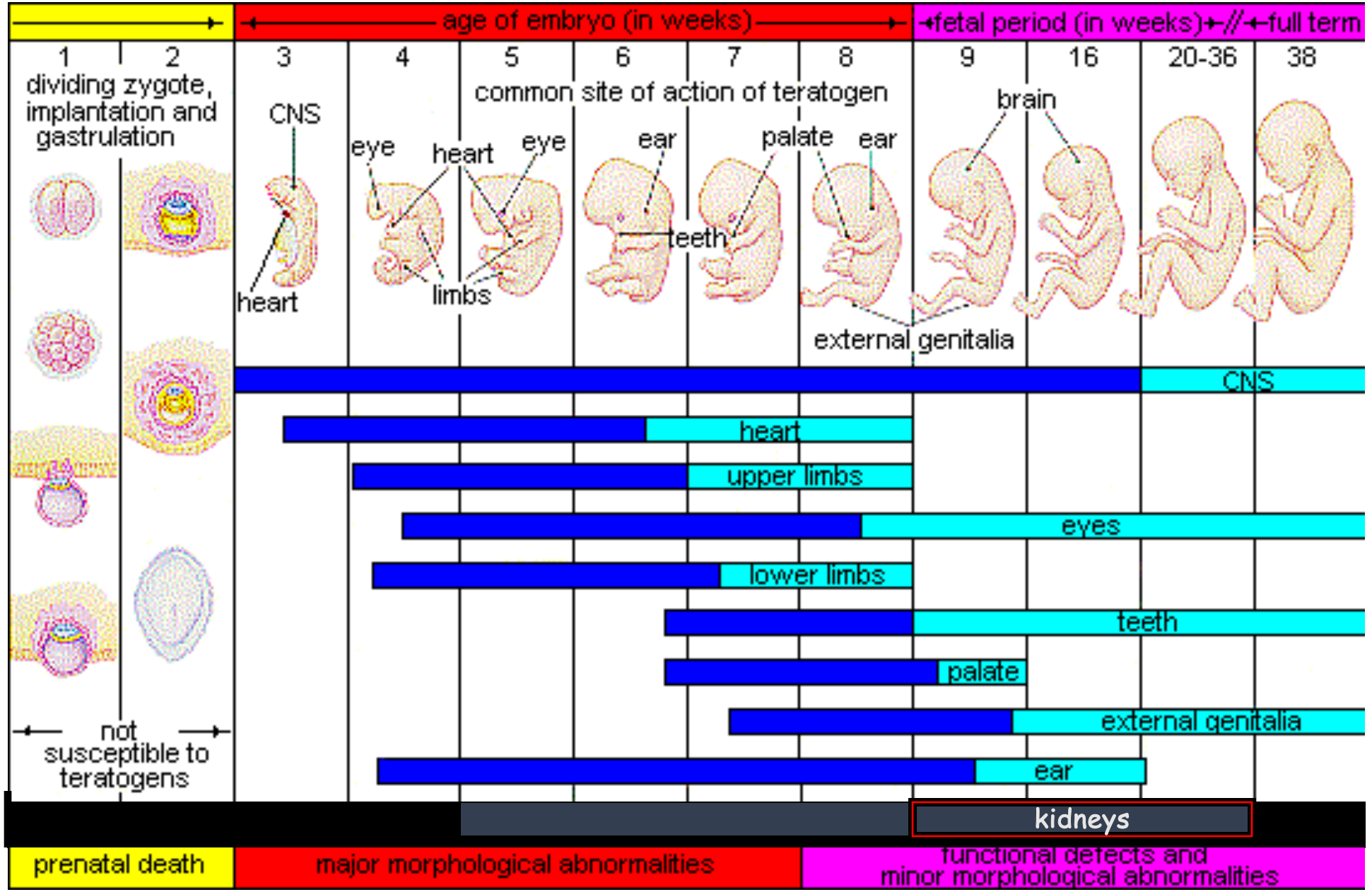
DOHaD in General

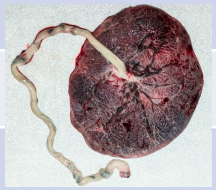
Intrauterine Dev

Kidney Endowment

Childhood Events

Critical Periods in Human Gestation



Maternal Factors		Pregnancy		Lactation	Childhood	Adulthood
Factors that → impaired fetal growth- undernutrition;↑glucocorticoids; uterine factors		Placenta	Fetus	Continued programming, esp. maturing immune system	Interactions with conventional risk factors. Importance of ACES (adverse Childhood experiences)	
Maternal overnutrition→ Obesity, hypercholesterolemia, diabetes, insulin resistance, proinflammatory states, increased oxidative stress Factors → Hypertension	→	Placental and placentation abnormalities	Beneficial or harmful effects Impaired organogenesis Genetic and epigenetic alterations Sensitivity to stressful events	→	Predictors of Kidney and Cardiovascular Risk Impaired endothelial fx and vascular reactivity Kidney insults- e.g., AKI, obesity, insulin resistance, Inflammation Decreased renal fxl reserve	**Clinical manifestations** **CKD** Htn Diabetes CVD
						

after Palinski W et al. J Cardiovasc Trans Res 2009; 2: 277-285.

HISTORICAL DATA

Renal Failure in NICU– associated with poor renal growth

(and also decreased GFR and tubular dysfunction)

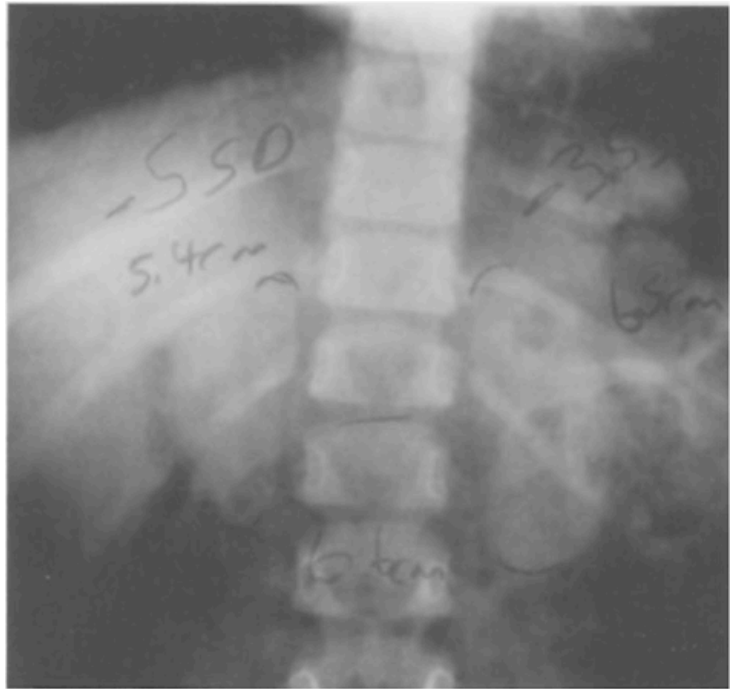


Fig. 2. Bilateral reduction in renal size is seen in this excretory urogram in a 5-year-old girl who had neonatal acute renal failure secondary to birth asphyxia. The length of the right kidney is 5 SD below the mean of normal and the length of the left kidney is 3.5 SD below the mean of normal. The reduction in renal mass is presumed to be the result of the perinatal renal insult.

Stapleton, Jones and Green. Acute renal failure in neonates: incidence, etiology and outcome. Pediatr. Nephrol 1987; 1: 314-320.

Hints from Historical Data

HUS in Argentina

Group 1- complete recovery 74 pts

Group 2- Proteinuria or proteinuria and Htn, but normal Ccr 21 pts

Group 3 Low Ccr plus proteinuria or proteinuria and Htn 19 pts

Group 4 ESRD after 6-20 years 4 pts

N=118

Spizzirri et al. Pediatr. Nephrol. 1997; 11: 156-60

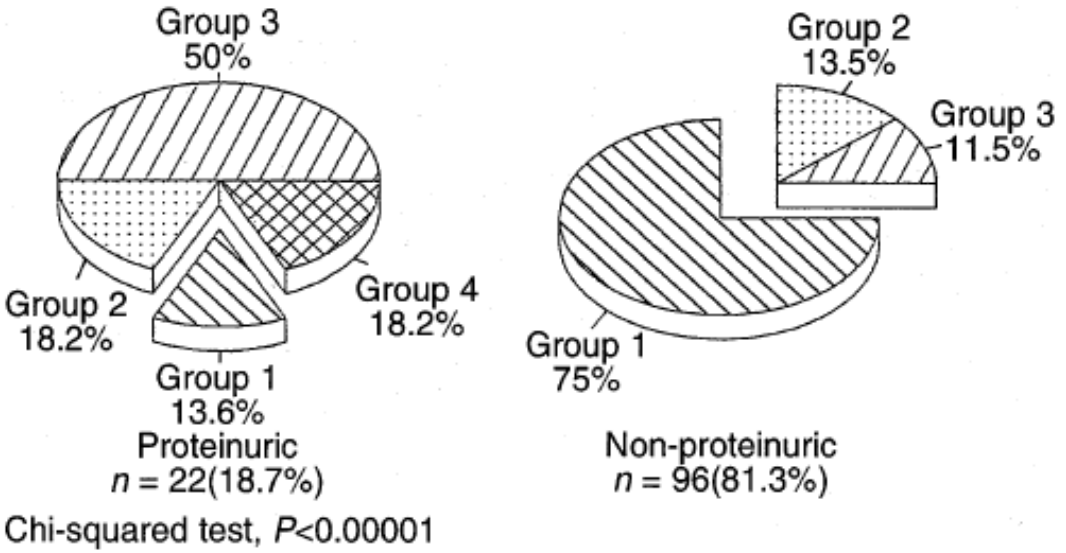


Fig. 3. Long-term evolution of HUS proteinuric and non-proteinuric patients at the 1-year control

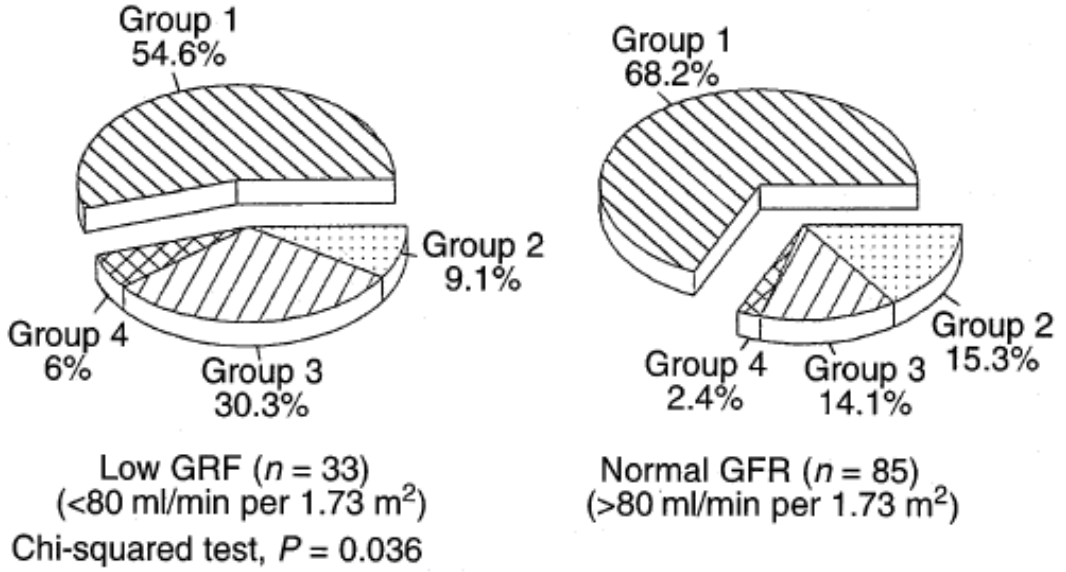


Fig. 4. Long-term evolution of HUS patients with low and normal glomerular filtration rate (*GFR*) at 1-year control

Long-term Risk of CKD in Children Surviving Episodes of Acute Kidney Injury in the Intensive Care Unit: A Prospective Cohort Study

Cherry Mammen, MD, MHSc[1], Abdullah Al Abbas, MD,[1] Peter Skippen, MD,[2] Helen Nadel, MD,[3] Daniel Levine, MD,[3] J.P. Collet, MD, PhD,[4] and Douglas G. Matsell, MD[1]

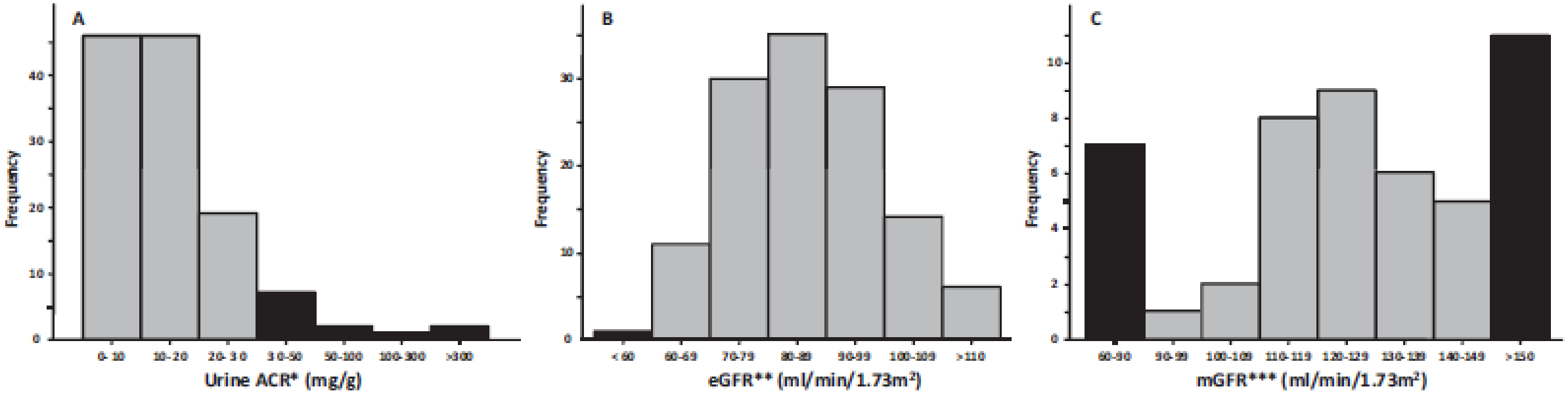
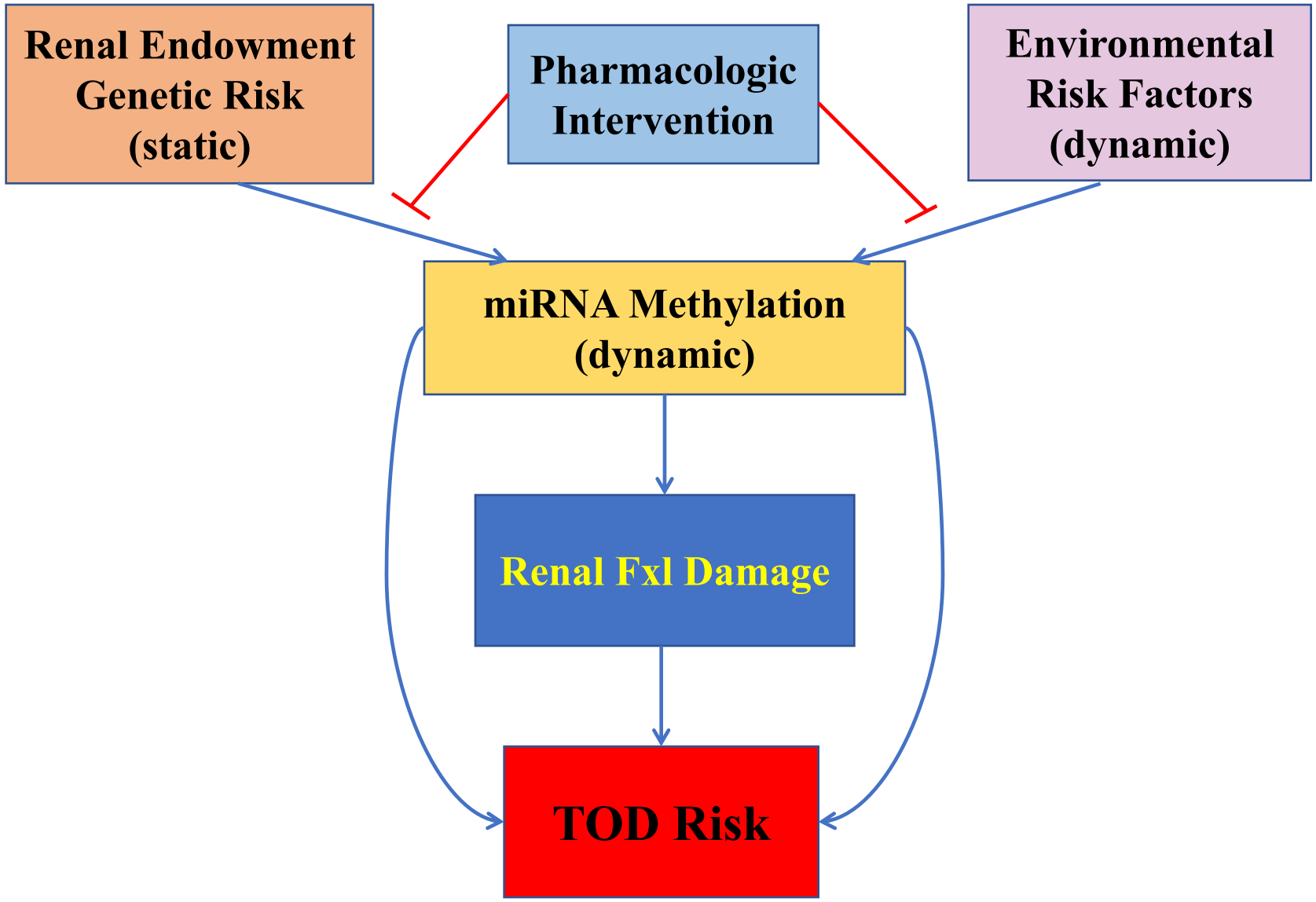
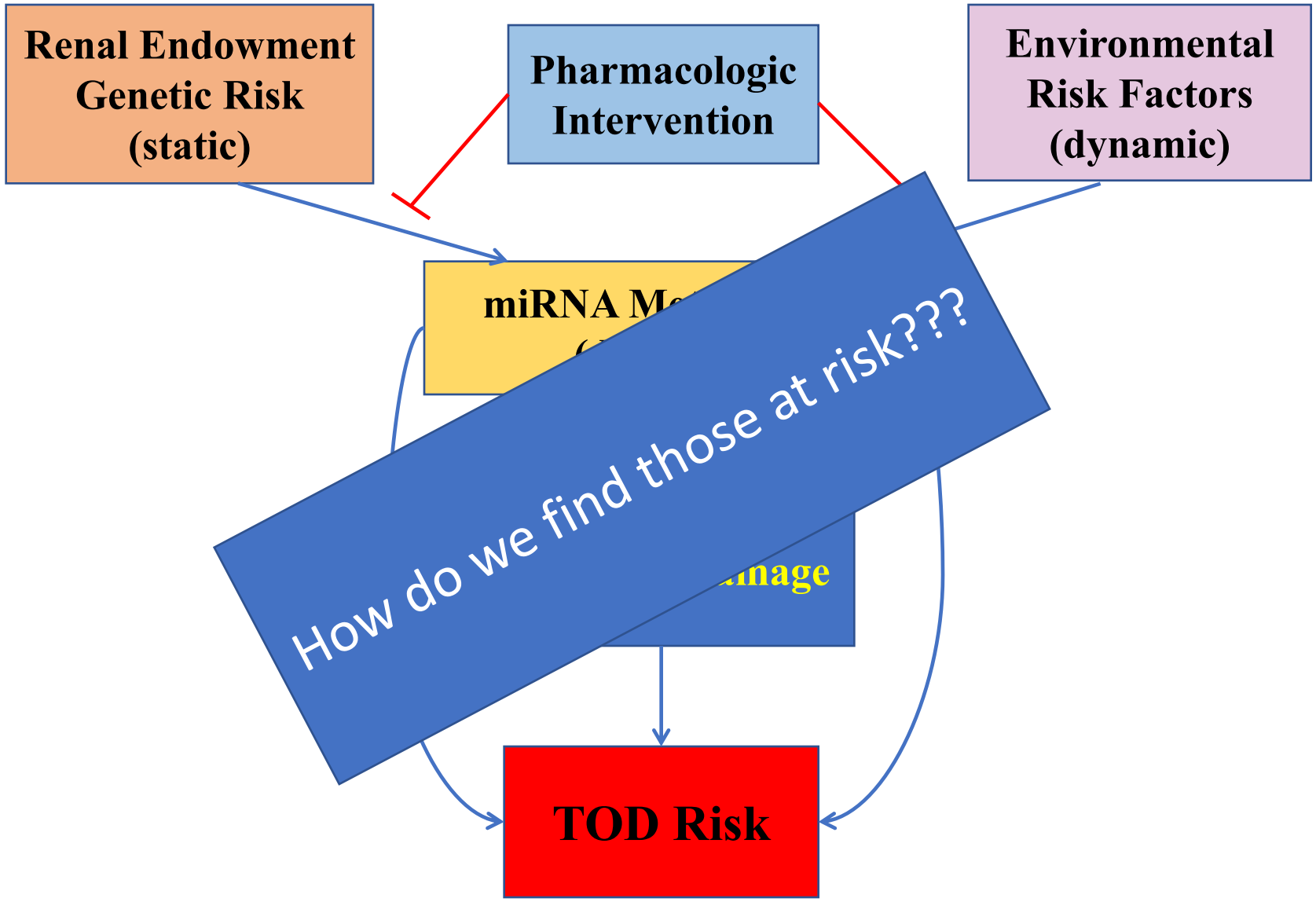


Figure 2. Histogram plots show the distribution of patients' (A) urine *albumin-creatinine ratio (ACR), (B) **estimated glomerular filtration rate (eGFR), and (C) ***measured GFR (mGFR). Black bars represent abnormal results.

Am J Kidney Dis. 59(4):523-530.


Renal Endowment Genetic Risk (static)
Pharmacologic Intervention
Environmental Risk Factors (dynamic)
miRNA Methylation (dynamic)
Renal Fxl Damage
TOD Risk


Renal Endowment Genetic Risk (static)
Pharmacologic Intervention
Environmental Risk Factors (dynamic)
miRNA M
How do we find those at risk???
nage
TOD Risk

Examples of New Surrogate Markers

- Renal functional reserve
- Nanoparticles in diagnosis
- New biomarkers
- New imaging techniques

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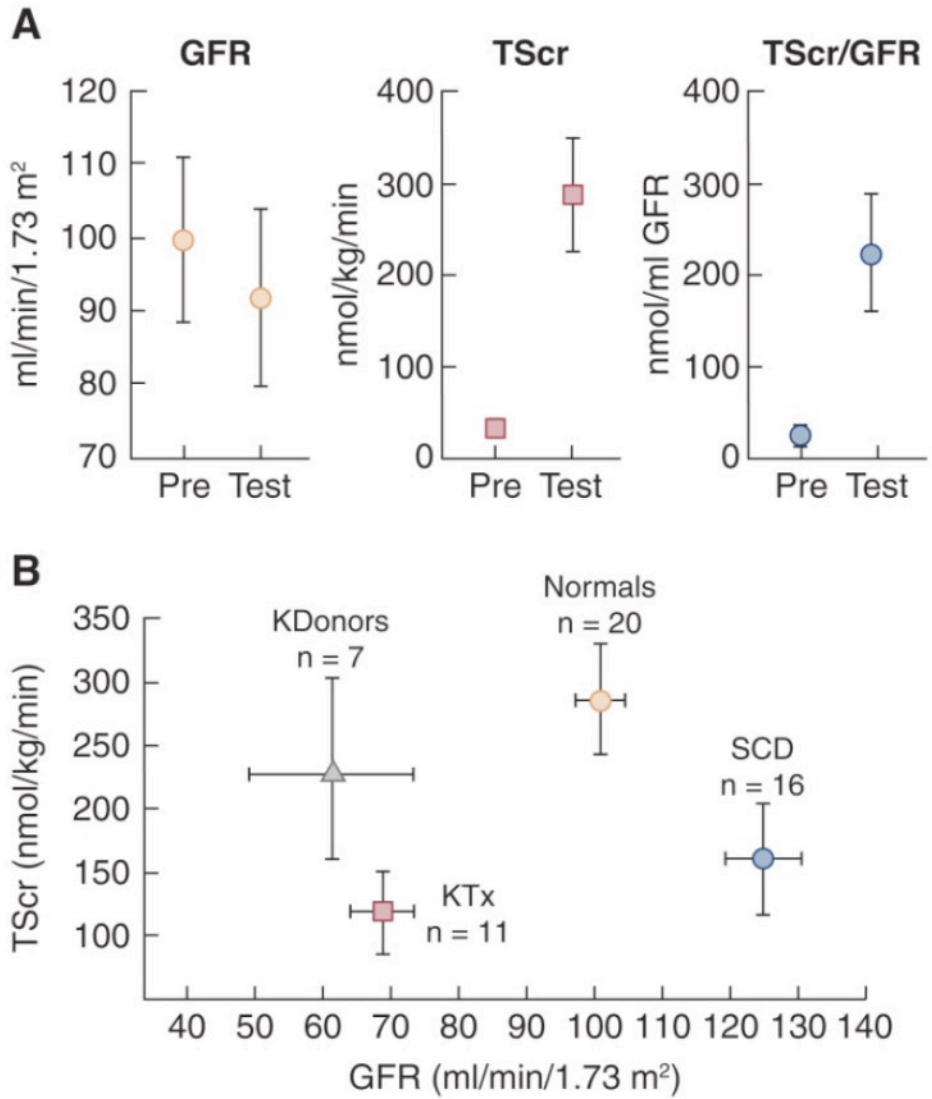
Stress Tests of Kidney Function – AKA Renal Functional Reserve Test Methods

TEST METHOD	ASSESSED RESPONSE	NORMAL RESPONSE	POTENTIAL USE
Oral protein or IV aa	Increase in GFR Change in tubular Cr. secretion	10%-30% increase	Estimate of single nephron fx.
U/P urea conc. ratio	Urea countercurrent X△	Urea U/P ratio ≥80 at copeptin levels of 11.9 pmol/L (IQR, 7.1-28.3)	
Oral NH4Cl (50 mEq) and U citrate/creat	Normal plasma bicarb	Ratio 187 (IQR, 125-277) mmol/mol	
Oral bicarb	H+ ion retention with normal plasma bicarb	3 ± 14 mmol H+ retention	Rx subclinical acidosis

Modified from Armenta Clin J Am Soc Nephrol. 2022 Mar; 17(3): 458–466.



Clin J Am Soc Nephrol. 2022 Mar; 17(3): 458–466.

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Use of Nanoparticles to Diagnose (and Treat) CKD

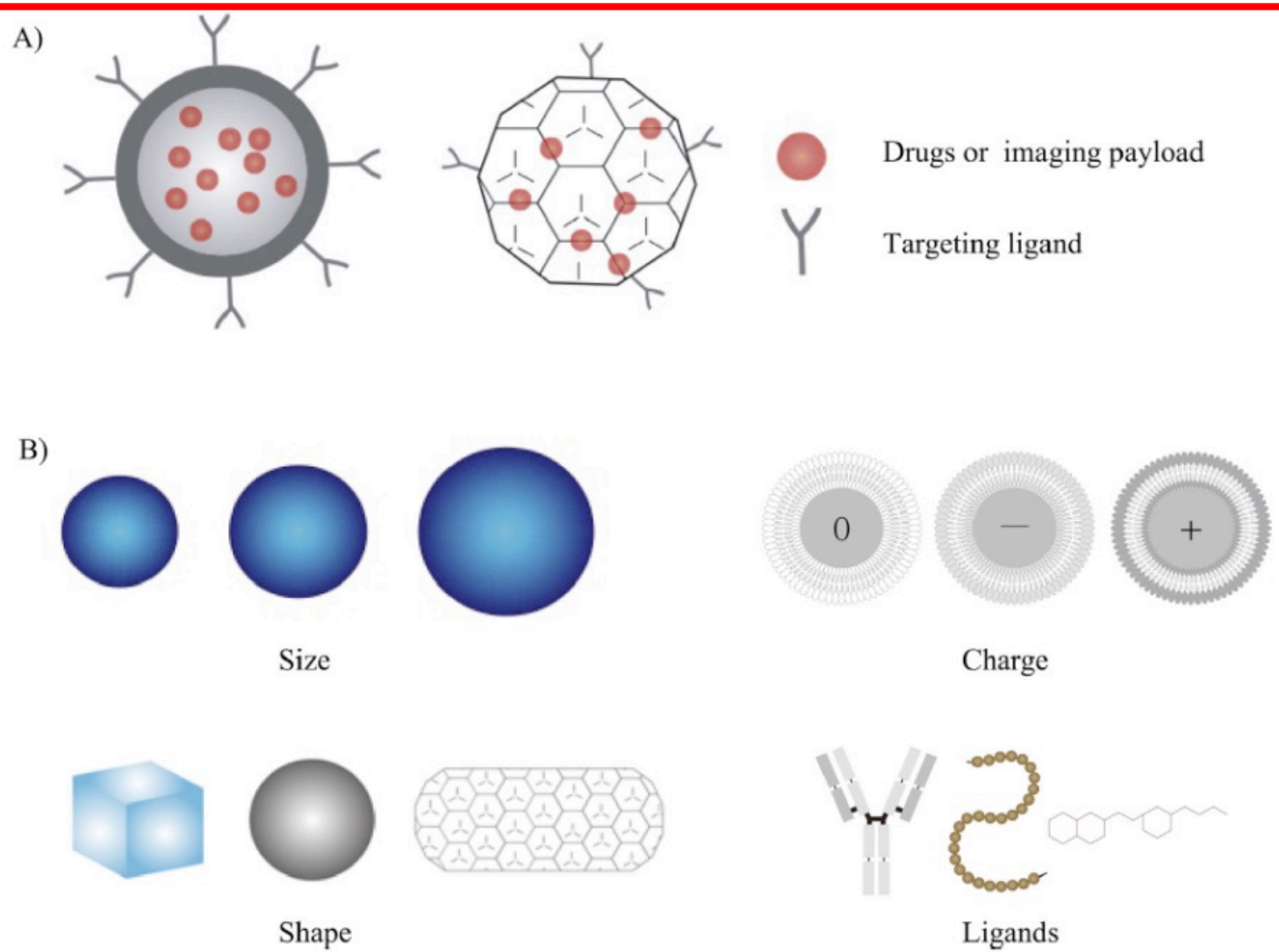

Fig. 1. The composition and properties of nanoparticles. A) Nanoparticles can serve as colloidal dispersions or a matrix structure; B) The features of NPs can be modified by size, charge, shape, and targeting ligands including antibody, peptide and small molecule.

Ma et al. *Bioactive Materials 5 (2020) 732–743*

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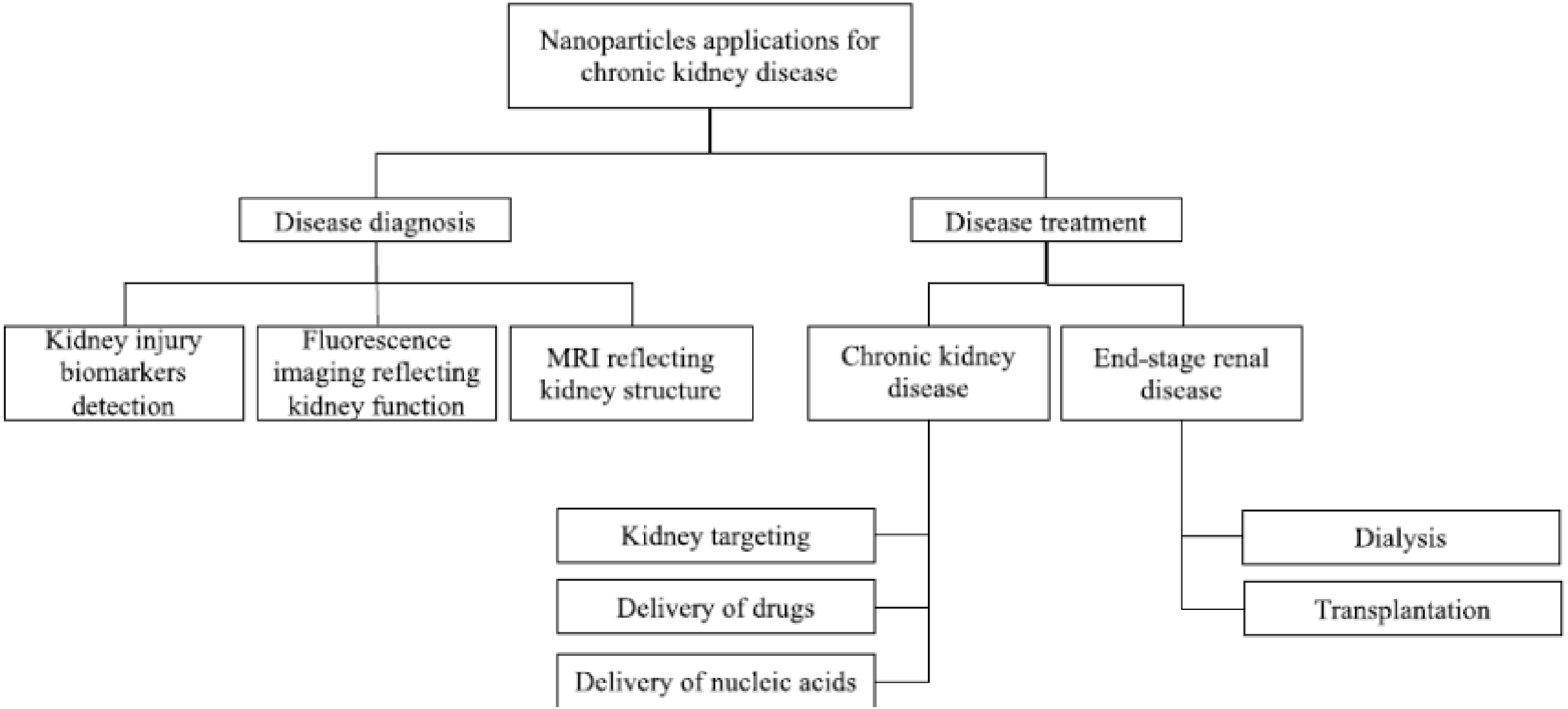

Ma et al. *Bioactive Materials 5 (2020) 732–743*

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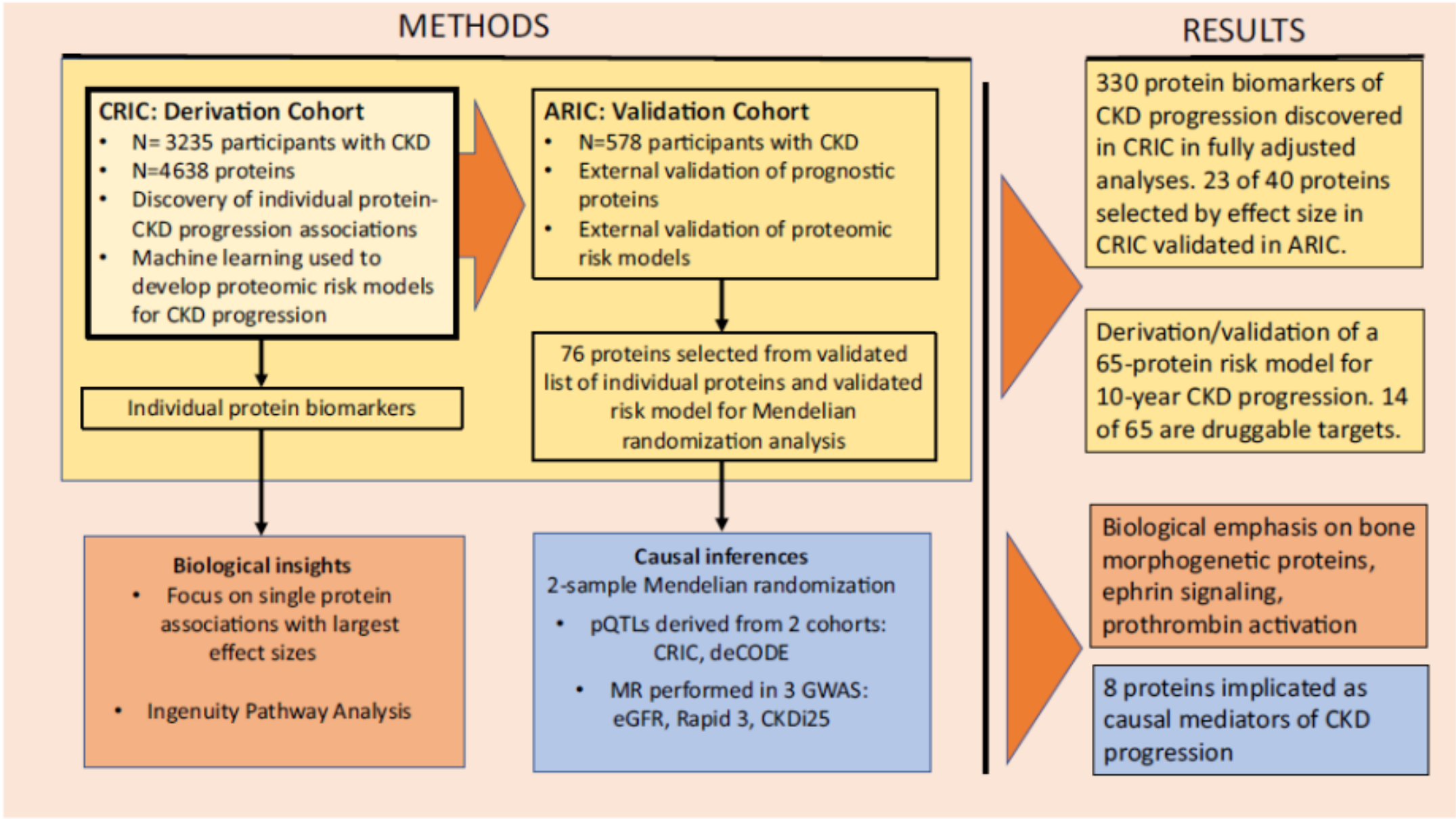
Dubin et al. *Proteomics of CKD Progression in CRIC*



Dubin et al. *Proteomics of CKD Progression in CRIC*

- Identified 100 circulating proteins associated with CKD
- Individual protein associations and pathway analyses led to
  - Bone morphogenic proteins, ephrin signaling, prothrombin activation
  - 65-protein risk model; 14/65 proteins are druggable; C-stat (95% CI) 0.862 (0.835-0.889)
  - Causes with 5 proteins, not previously known– EGFL9, LRP-11, MXRA7, IL-1sRII and ILT-2
- Finding protein risk markers may lead to drug development that may slow CKD progression

Nature Communications | (2023)14:6340 https://doi.org/10.1038/s41467-023-41642-7

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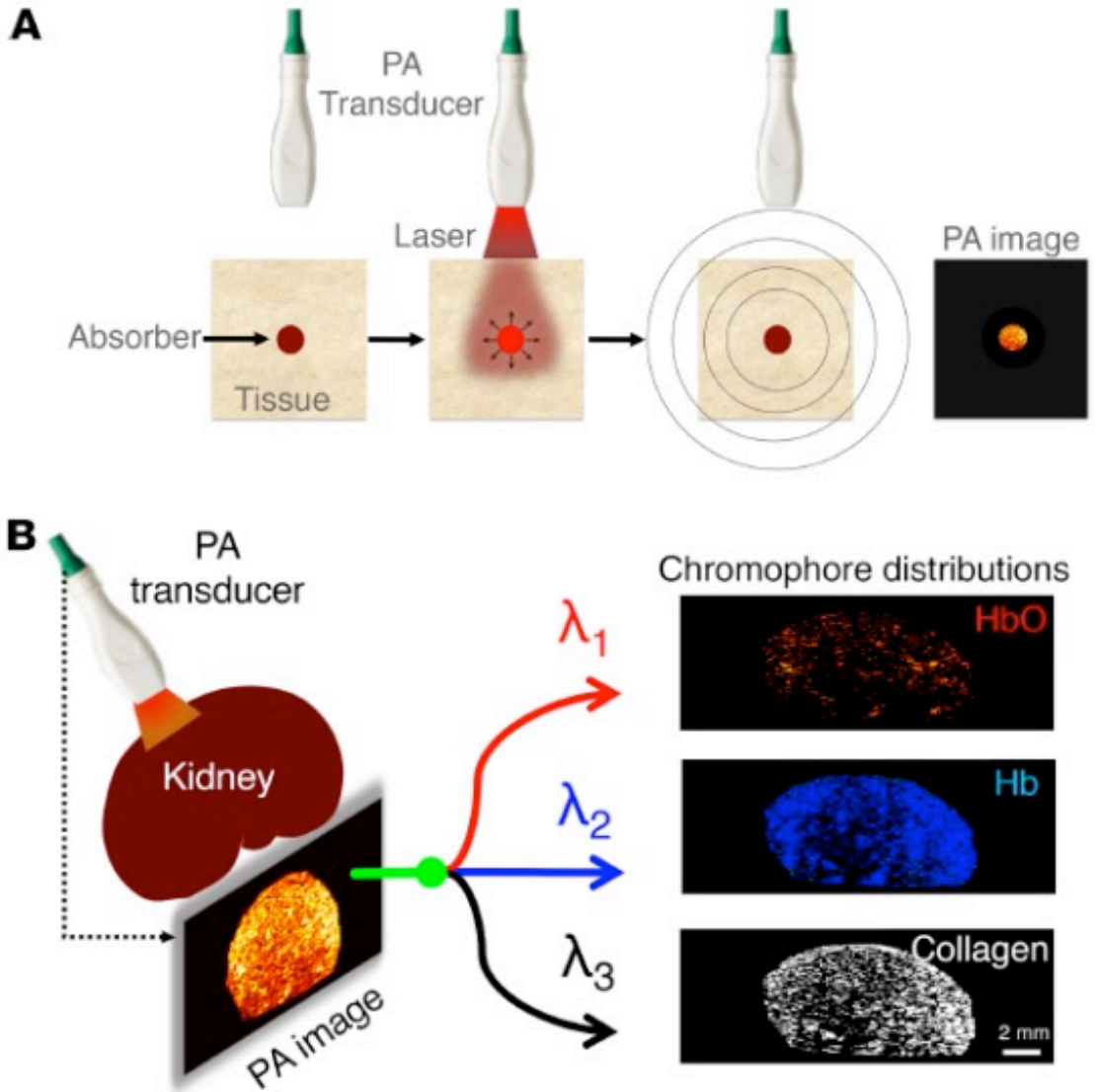

Photoacoustic imaging of kidney fibrosis for assessing pretransplant organ quality

Eno Hysi,[1,2] Xiaolin He,[2,3,4] Muhannad N. Fadhel,[1,2] Tianzhou Zhang,[3,4] Adriana Krizova,[4,5] Michael Ordon,[4,5,6] Monica Farcas,[4,5,6] Kenneth T. Pace,[4,5,6] Victoria Mintsopoulos,[4,7] Warren L. Lee,[4,7] Michael C. Kolios,[1,2] and Darren A. Yuen[2,3,4]

https://doi.org/10.1172/jci.insight.136995

Examples of New Medications and Management

- New antihypertensive agents
- New antidiabetic medications
- New antiinflammatory drugs
- Molecular approaches
- Other

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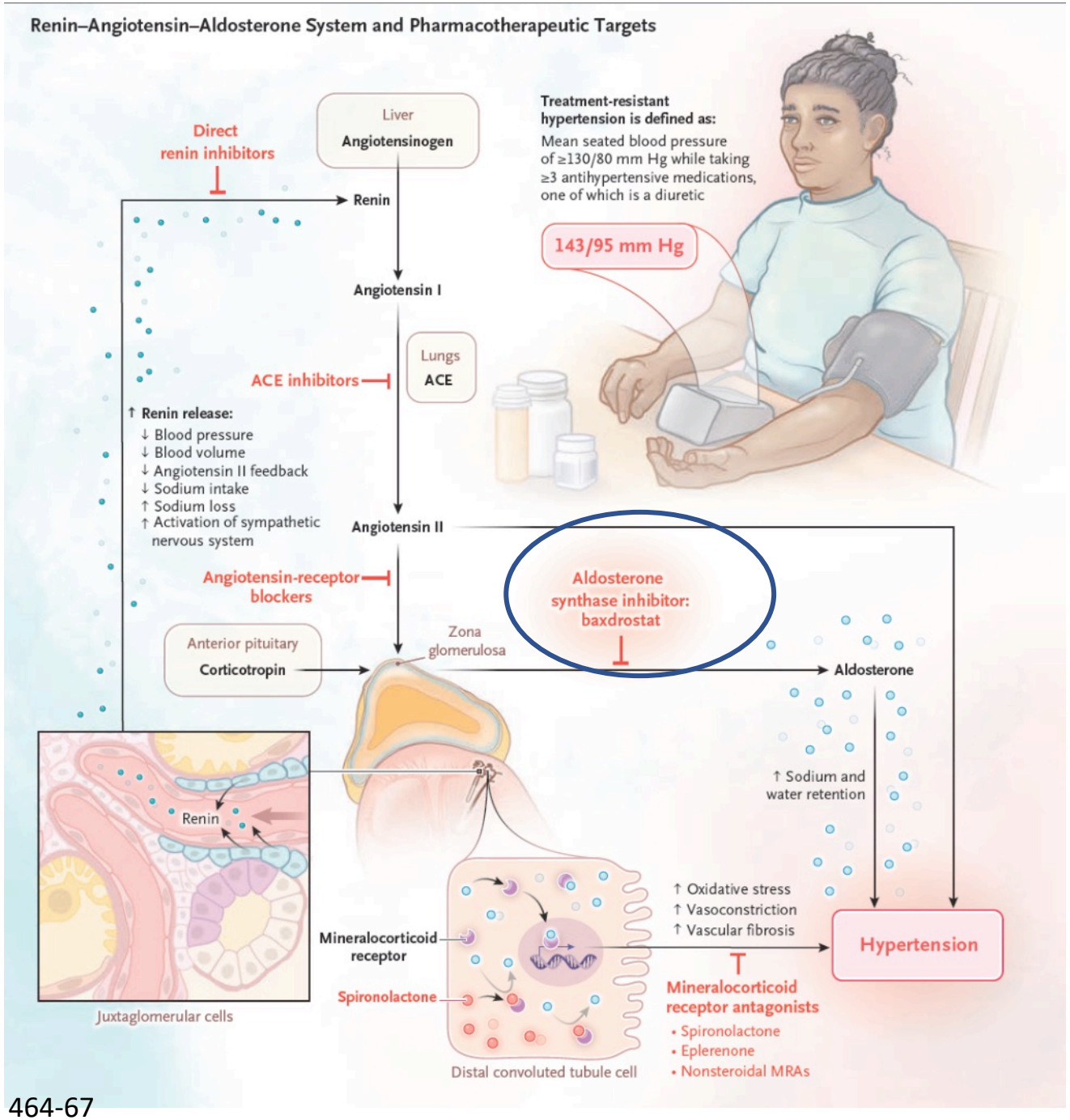

Leopold J and Ingelfinger JR. N Engl J Med 2023; 388: 464-67

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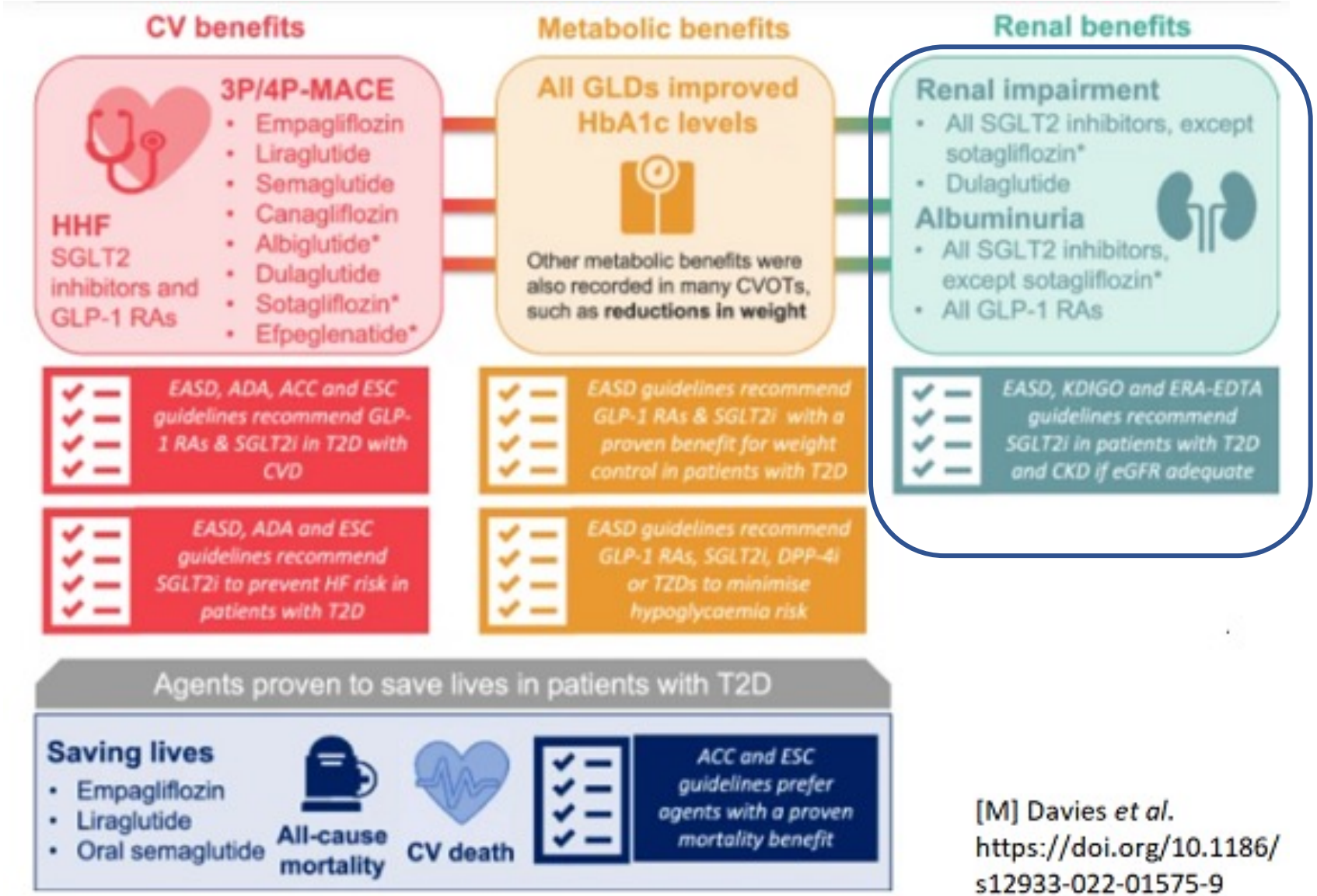
Novel Renoprotective Antidiabetic Medications



[M] Davies *et al.* https://doi.org/10.1186/s12933-022-01575-9

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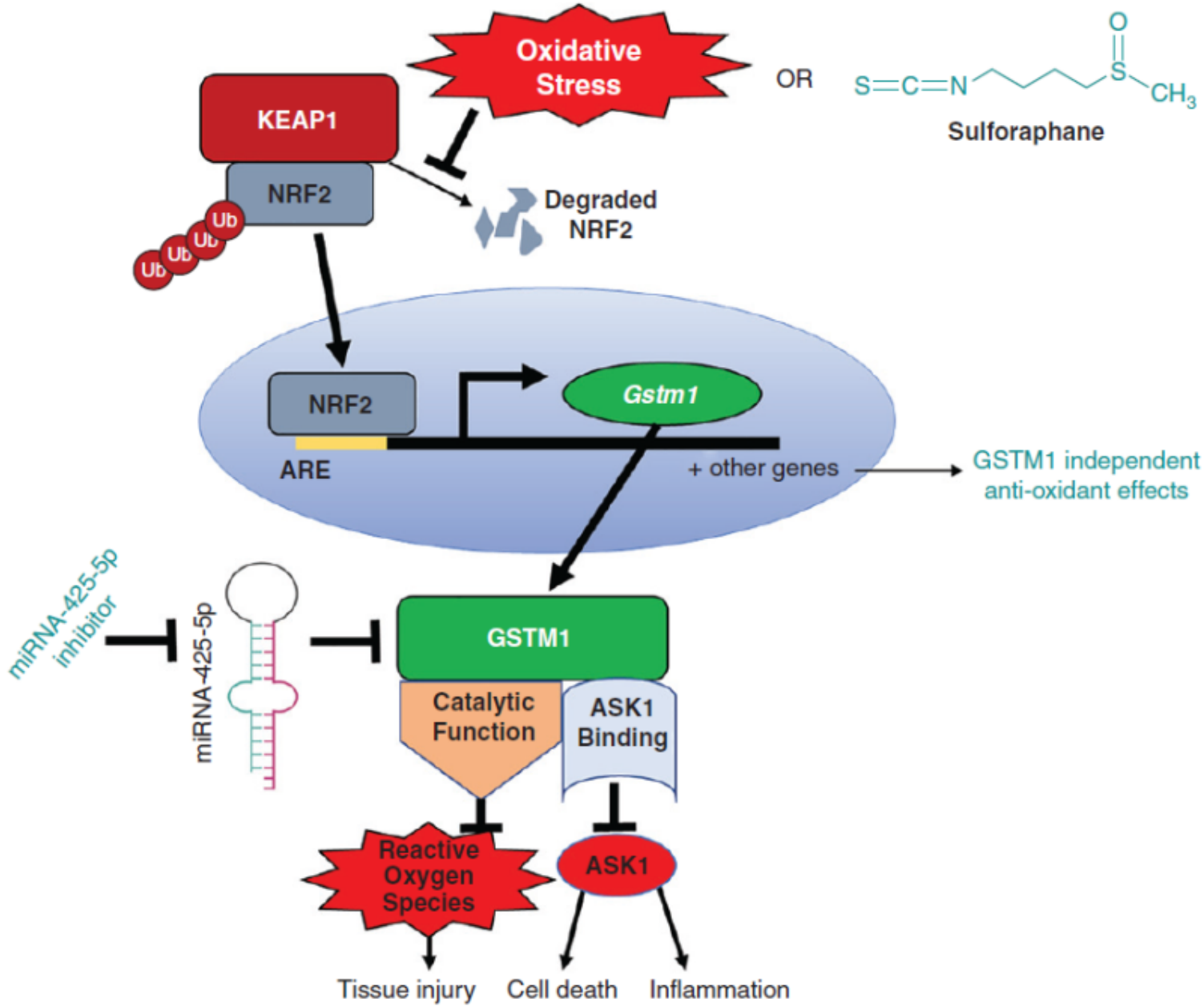


Figure 1. | Nrf2-GSTM1 pathway protects against oxidative stress and is a potential novel therapeutic target.

Patient-Centered Approach

- Studying representative patient groups
- Obtaining patient perspectives
- Considering all biological systems, not just the kidney
- Considering *in utero* development and childhood contributions
- Listening to patient responses continually

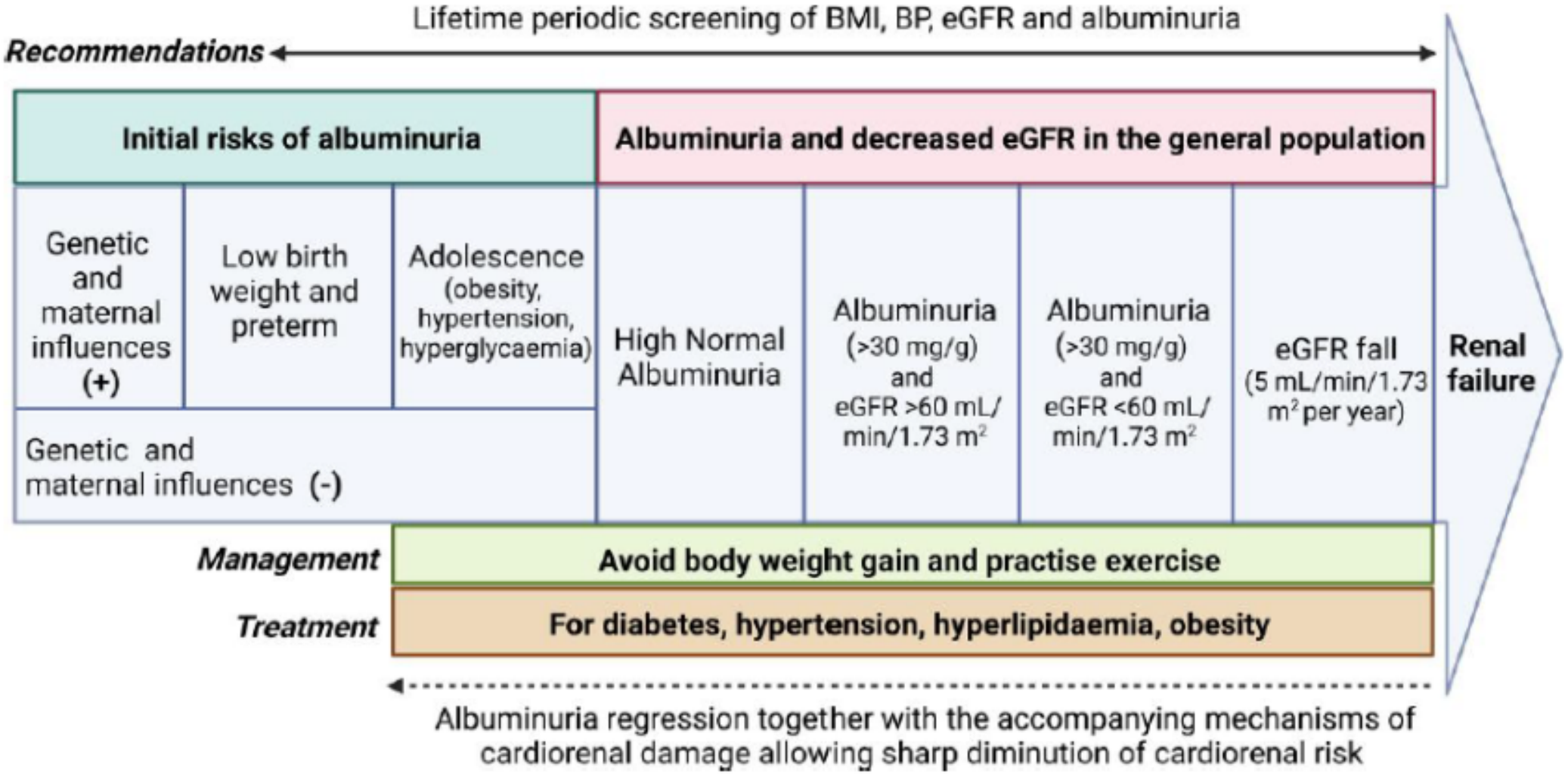
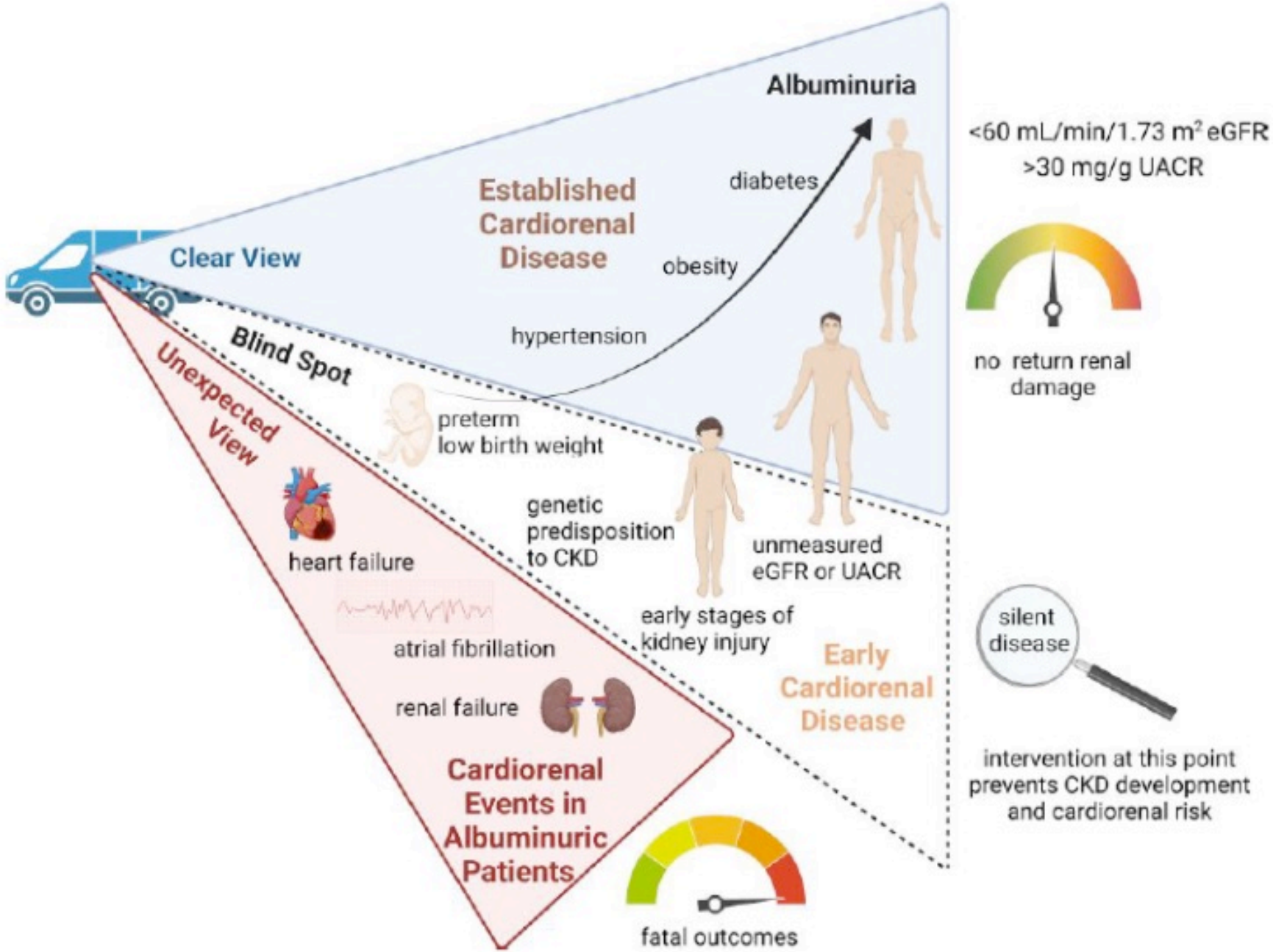


Figure 2 Different clinical settings linked to albuminuria development and evolution, and its adequate management.

European Heart Journal (2023) **44**, 1112–1123
https://doi.org/10.1093/eurheartj/ehac683



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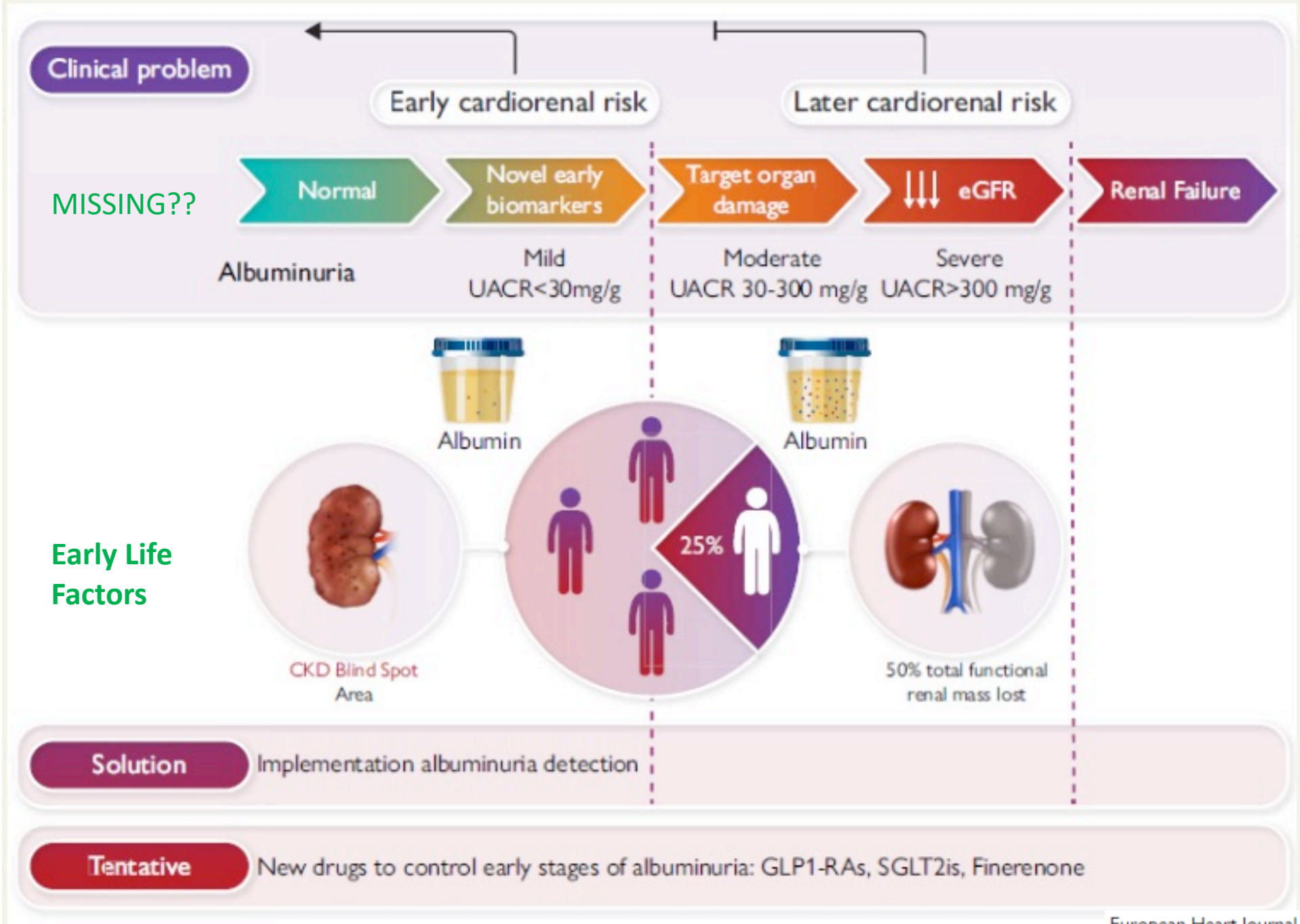

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THANK YOU!

Questions?

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