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2/ 🚨 Our topic🚨: A Comprehensive Framework for Kidney Function Assessment: Summary of the NIDDKD Reimagining Kidney Function Assessment Workshop. There are no conflicts of interest.

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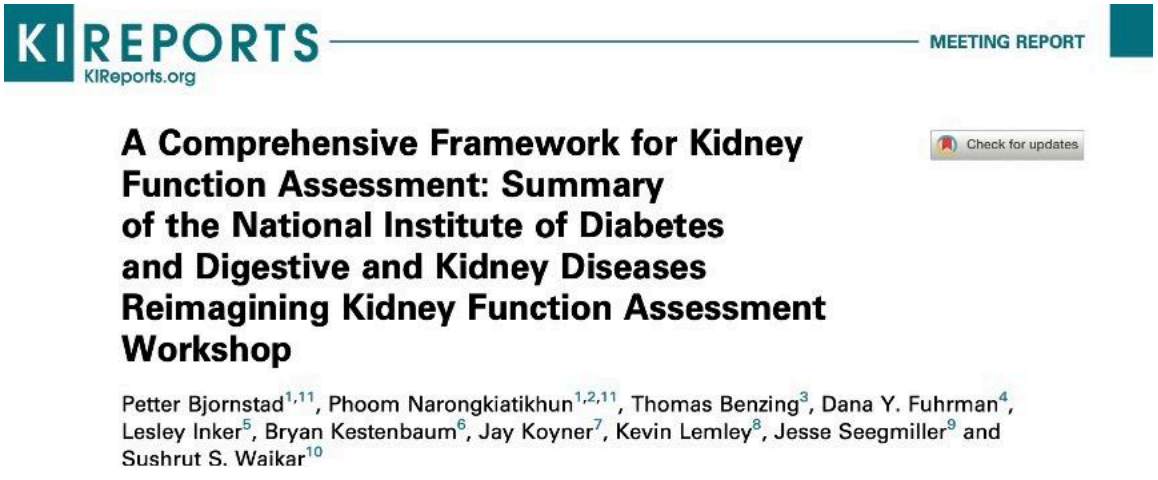
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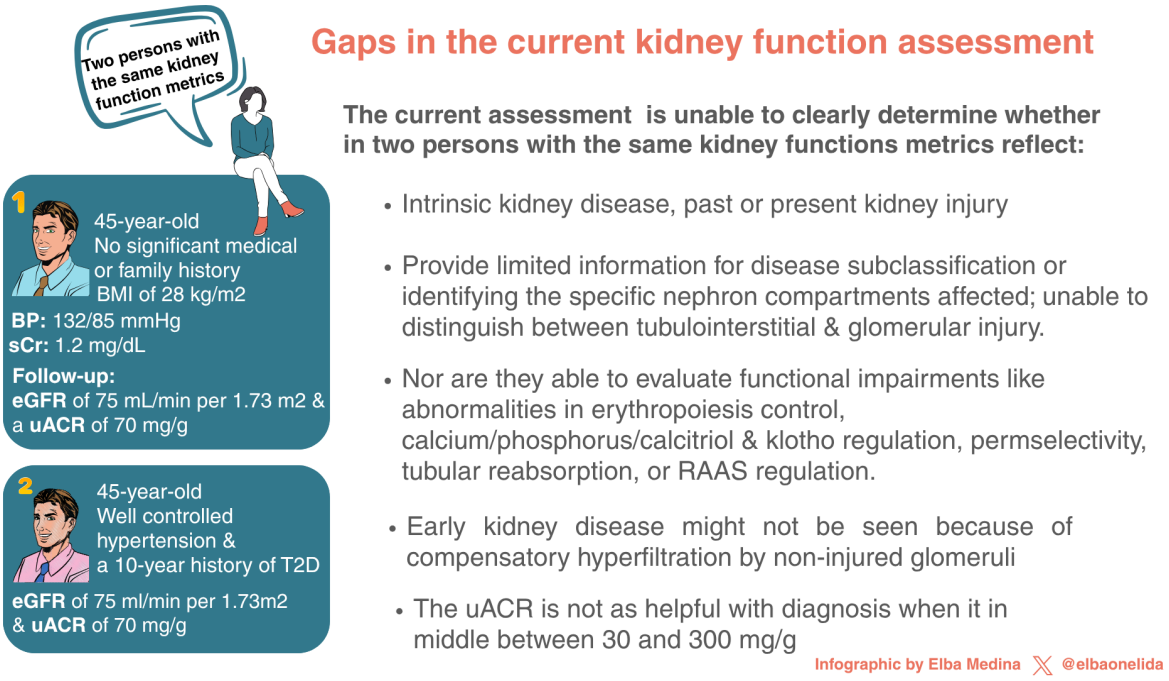
**A Comprehensive Framework for Kidney Function Assessment: Summary of the National Institute of Diabetes and Digestive and Kidney Diseases Reimagining Kidney Function Assessment Workshop**

Petter Bjornstad[1,11], Phoom Narongkiatikhun[1,2,11], Thomas Benzing[3], Dana Y. Fuhrman[4], Lesley Inker[5], Bryan Kestenbaum[6], Jay Koyner[7], Kevin Lemley[8], Jesse Seegmiller[9] and Sushrut S. Waikar[10]

3/ How about a quick quiz- 🧐🧐Which is the key limitation of current biomarkers (eGFR and uACR) for kidney function assessment?

a) They are highly specific
b) They are highly accurate
c) They lack specificity
d) They only measure tubular function

4/💡💥 The correct answer is C. Here is an example of two persons with the same kidney function metrics and the gaps in the current kidney function assessment🤩👀




5.- Read the executive summary and watch the meeting video for more information.
🔥🔥Start with the majors' key research questions🔥🔥

# Key Research Questions?

## How can.....

...standardizing iohexol plasma disappearance protocols improve the accuracy & reliability of measured GFR ?

...the glomerular selectivity index & permselective shunt parameter (ω0) predict kidney disease progression, assess tx. efficacy, & evaluate podocyte health?

...tubular secretory clearance measurements enhance kidney function assessment, early detection of tubular disorders, & optimization of drug dosing?

...eGFR assessment be improved by addressing variability & identifying biomarkers to better reflect true GFR across clinical scenarios ?

...KFR be quantified & applied to predict & prevent adverse kidney outcomes like AKI & CKD progression?

...the kidney's responses to stressors can be used to evaluate kidney health, identify functional limitations & affected compartments, determine disease subtypes, predict disease progression, & guide tx.?

...advanced functional imaging modalities be combined with clinical data to reliably assess kidney function, improve early detection, risk stratification, therapy monitoring, & guide clinical decisions while addressing challenges ?

...standardizing iohexol protocols improve the accuracy & reliability of measured GFR in clinical & research settings?

KFR, kidney functional Reserve

Infographic by Elba Medina @elbaonelida

# Key Research Questions?

## How can.....

standardizing iohexol plasma disappearance protocols improve the accuracy & reliability of measured GFR in both clinical practice & research settings?

the glomerular selectivity index & permselective shunt parameter (ω0) predict kidney disease progression, assess tx. efficacy, & evaluate podocyte health?

Glomerular Function & Biomarkers

eGFR assessment be improved by addressing variability & identifying biomarkers to better reflect true GFR across clinical scenarios?

Kidney Response to Stress & Comprehensive Assessment

tubular secretory clearance measurements enhance kidney function assessment, early detection of tubular disorders, & optimization of drug dosing?

KFR be quantified & applied to predict & prevent adverse kidney outcomes like AKI & CKD progression?

the kidney's responses to stressors can be used to improve diagnosis, predict disease progression, and guide tx. strategies?

Advanced Imaging & Clinical Data

advanced functional imaging modalities be combined with clinical data to reliably assess kidney function, improve early detection & personalized tx. planning?

KFR, kidney functional Reserve

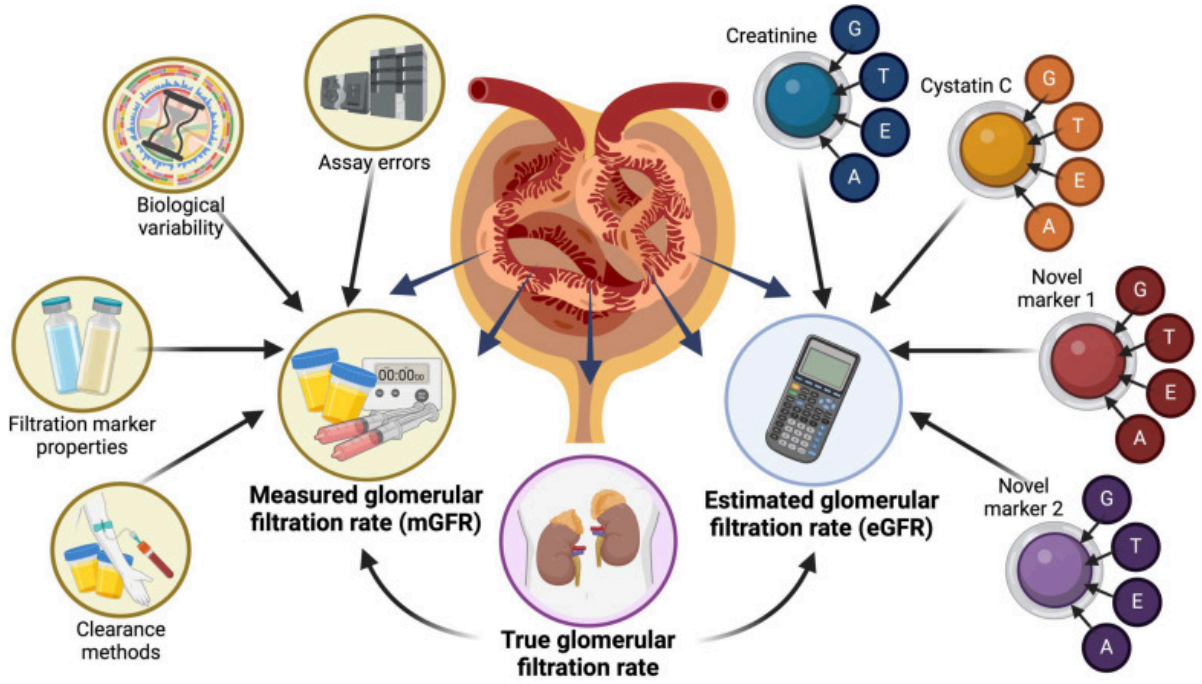
Infographic by Elba Medina @elbaonelida

06/ The CRIC study found that mGFR may not necessarily provide a better prediction of outcomes in CKD. There are differences between mGFR vs true GFR due: https://journals.lww.com/jasn/pages/articleviewer.aspx?year=2016&issue=07000&article=00034&type=Fulltext

🧵

- errors in clearance methods
- imperfect marker properties
- assay inaccuracies
- biological variability

07/ 👀Here are the factors influencing true, measured, and estimated glomerular filtration rate🫘



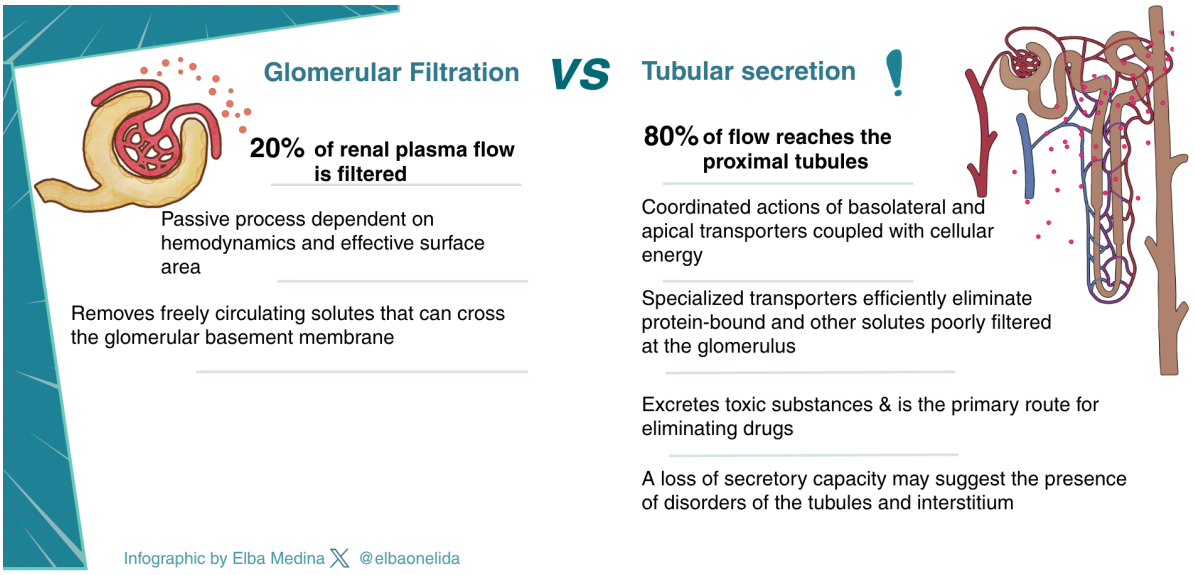

08/Serum creatinine and cystatin C measurements of eGFR can produce inconsistent results, which may be impacted by the non-GFR determinants unique to each marker.

**Effects of non-GFR determinants on creatinine and cystatin C as endogenous filtration markers**

| Factor | Creatinine | Mechanism of change | Cystatin C | Mechanism of change |
|---|---|---|---|---|
| Increasing age | ↓ | Decreased muscle mass | ↓ | Decreased total body cell mass |
| Female sex | ↓ | Less muscle mass compared to males | ↓ | Lower cell mass compared to males |
| African American ethnicity | ↑ | Higher average muscle mass compared to other ethnicities | - | - |
| Inflammation | - | - | ↑ | Increased cystatin C production |
| Hyperthyroidism | - | - | ↑ | Increased cystatin C production |
| Hypothyroidism | - | - | ↓ | Decreased cystatin C production |
| Smoking | - | - | ↑ | Increased cystatin C production due to inflammation |
| Vegetarian diet | ↓ | Reduced creatinine production | - | - |
| Consumption of meat or creatinine supplements | ↑ | Increased creatinine production (in some cases may show no change due to transient GFR increase) | - | - |
| Body builders or individuals with high muscle mass | ↑ | Increased creatinine production or from high protein intake | - | - |
| Low muscle mass (e.g., limb amputation) | ↓ | Decreased creatinine production or reduced protein intake | - | - |
| Malnutrition or muscle wasting due to chronic illness | ↓ | Decreased creatinine production | ↑ | Increased cystatin C production due to inflammation |
| Obesity | - | - | ↑ | Increased cystatin C production due to higher fat mass |
| Trimethoprim, cimetidine, fibric acid derivatives (except gemfibrozil) | ↑ | Inhibit tubular secretion of creatinine | No data | No data |

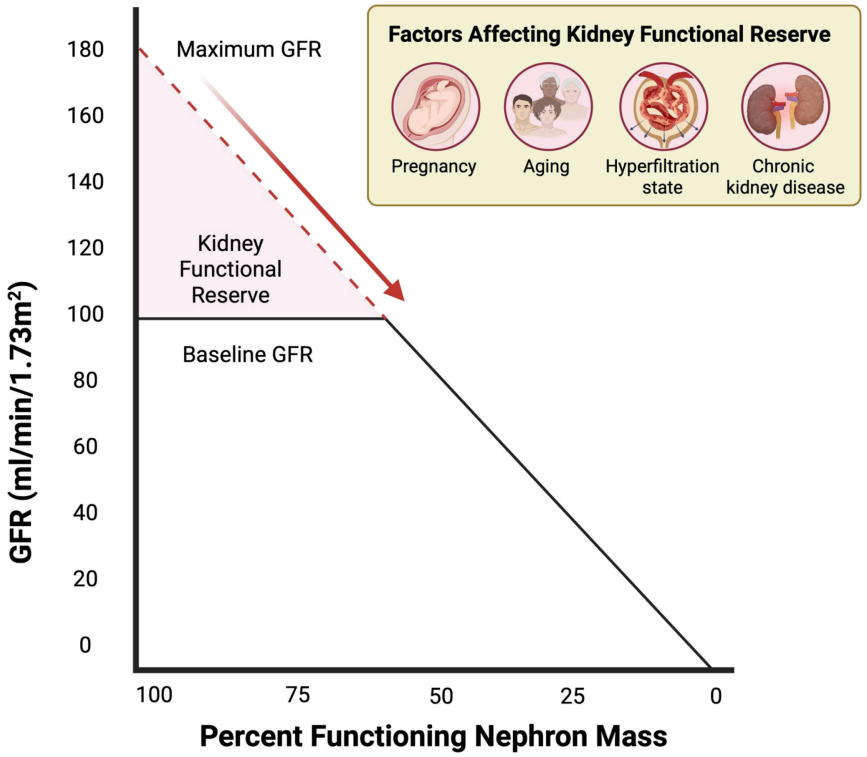
09/ Is there something that could be promising?
Researchers are exploring a novel fluorescent GFR tracer agent, relmapirazin, for real-time GFR monitoring. This could offer rapid, point-of-care assessment and reduce CKD misclassification (affecting up to 50% of patients) 👀

10/ Evaluating tubular function through dynamic physiological stress tests is essential for a comprehensive understanding of kidney function. e.g the furosemide stress test assesses renal tubular integrity




11/⬇️ in GFR commonly occur when RASi are initiated. A 📉 in eGFR of ≤13% over 3 months or ≤21% over 1 month has been associated with a lower risk of kidney failure. 🧍 who displayed preserved glomerular hemodynamic function experience the best clinical outcomes 🏅

12/Kidney filtration reserve ➡️ the capacity of the 🫘 to ⬆️ the GFR in response to increased demands or stress: A low KFR value <15ml/min/1.73m2 ➡️ increased likelihood of developing AKI or CKD.

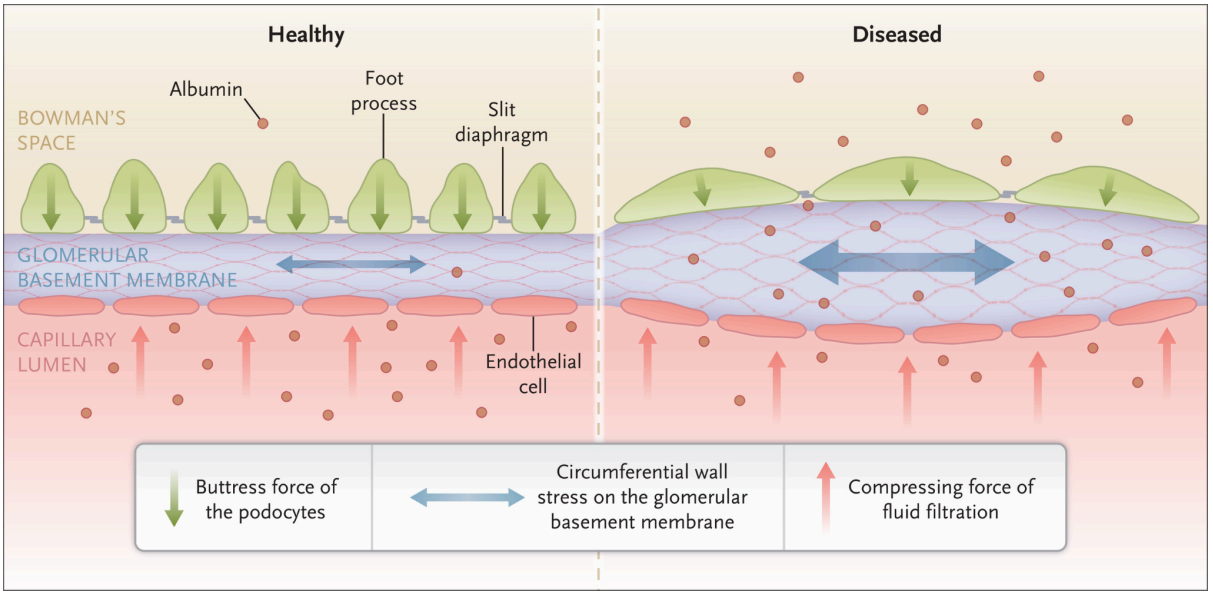



13/💥KFR:

- could be a promising tool for the early ☀️detection of subclinical kidney disease
- facilitating preemptive therapeutic interventions
- could be valuable for monitoring kidney recovery following AKI.

14/ The glomerulus filters extensively but restricts macromolecules. When KFR is depleted, stress directly impacts podocytes, as shown in the gel compression model:
👣 injury= simplified podocyte architecture
💥Slit-diaphragm length is reduced =📉 filtration area (⬇️🌊& solutes)
💥Excessive mechanical stress = podocytes detach

https://www.nejm.org/doi/pdf/10.1056/NEJMra1808786




15/The normal glomerular capillary wall acts as a sophisticated filter. Its unique structure restricts the passage of large proteins while allowing free filtration of water and small solutes🫧. 💥This crucial mechanism is known as permselectivity🎯it is associated with progression to kidney failure.

16/Permeselectivity is evaluated by two methods
💥1. Dextran sieving curves(ω0): characterize a change in glomerular permselectivity
💥2.The selectivity index: predicts steroid responsiveness & may detect early diabetic nephropathy

17/📉The dextran sieving curve:
💉IV dextrans & a reference filtration marker
🩸Simultaneous blood & 🥃urine samples.
🛑calculated by ratioing urine to plasma concentrations adjusted by the reference marker
💥a two-pore model is applied to estimate the parameter ω0

18/💥ω0 is the fraction of the total glomerular filtrate that passes through parts of the filtration barrier with essentially no restriction to the passage of large molecules. 📈 A 1 SD increase in ω0 raises the Hazard Ratio (HR) for kidney failure by 1.55.

19/💥The Proteinuria Selectivity Index is calculated by collecting simultaneous🩸serum and 🥃urine samples.
📏Concentrations of IgG & transferrin are measured & the ratio of clearance is then calculated
💥Selectivity index=IgG urine x transferrin serum/IgG serum x transferrin urine

20/💥The NIDDK suggested: 👀selectivity index might be a reasonable surrogate predictor of ω0, & a physical interpretation of the permselective shunt may reflect an early transient detachment of podocyte foot processes from the filtration surface 🫘👣

21/The selectivity index promises to be key.🔑🕵️🔍 ➡️ Its standardization & study as a predictor of could:
1️⃣Identify early pathogenesis.
2️⃣Classify clinically relevant subtypes of proteinuria.
3️⃣Improve the assessment of treatment response.💊

22/🎥Functional imaging studies have enhanced our understanding of physiology & pathology. 📸
However, most techniques are limited by variability in platforms, protocols, and image analysis. Standardization is crucial to unlock their full potential!🤳

**Summary of functional imaging modalities used in kidney assessment**

| Imaging modality | Principle | Measurement | Interpretation of parameters |
|---|---|---|---|
| **BOLD MRI** | Measures paramagnetic effects of deoxyhemoglobin to assess tissue oxygenation | Transverse relaxation rate (R2*) | • 1R2*: ↑ deoxyhemoglobin and ↓ tissue oxygenation<br>• R2* ↓ deoxyhemoglobin and ↑ tissue oxygenation |
| **Diffusion-weighted imaging (DWI) MRI** | Measures Brownian motion of water molecules reflecting tissue microstructure | Apparent diffusion coefficient (ADC) | • ↑ ADC: increased diffusion, normal tissue<br>• ↓ ADC: restricted water diffusion indicating fibrosis or inflammation |
| **T1 Mapping (magnetic resonance relaxometry)** | Quantifies longitudinal relaxation time to evaluate tissue composition and fibrosis | Longitudinal relaxation time (T1) | • ↑ T: increased fibrosis and edema<br>• ↓ T1: normal tissue structure |
| **Arterial spin labeling (ASL) MRI** | Uses magnetically labeled blood water as an endogenous tracer to quantify perfusion | Renal blood flow | • ↑ Perfusion: normal or increased flow<br>• ↓ Perfusion: impaired renal blood flow |
| **Positron emission tomography (PET)** | Uses radioactive tracers to measure renal blood flow, oxygen consumption, and metabolism | Tracer uptake rate, renal metabolic rate | • Altered tracer uptake indicates changes in perfusion or metabolic activity. * Altered tracer uptake indicates changes in perfusion or metabolic activity.<br>• Renal blood flow tracers (e.g. 150-H2O, 11C-acetate): uptake: ↑ renal blood flow; ↓ uptake: ↓ renal blood flow<br>• Oxygen consumption tracers (e.g. 1C-acetate): kinetics of 11C-acetate (K): ↑ K: ↑ oxygen consumption/ ↑ metabolic activity; ↓ K: ↓ oxygen consumption/ ↓ metabolic activity |
| **Contrast-enhanced ultrasound (CEUS)** | Uses microbubble contrast agents to visualize real- time blood flow in microvasculature | Contrast intensity, time-intensity curves | • Decreased contrast intensity or altered time-intensity patterns reflect reduced perfusion |

↑, increase; decrease; BOLD, blood oxygen level-dependent; MRI, magnetic resonance

Infographic by Elba Medina 𝕏 @elbaonelida

23/🥃Urinary biomarkers are revolutionizing kidney function assessment!
🔬Non-invasive & sensitive measures are complementing traditional tests.
🏹Challenges in standardization remain, multi-marker panels show promise for advancing precision nephrology & personalized patient care

## Summary of Established and Emerging Urine Biomarkers

| | Biomarker | Primary implications/ clinical association | Physiological basis/ mechanism | Key limitations |
|---|---|---|---|---|
| Biomarkers of glomerular integrity | Urinary transferrin (TRF) | Early glomerular charge barrier damage | • Glycoprotein<br>• Less negative charge than albumin<br>• Leaks earlier with charge barrier damage | Requires further clinical validation beyond early DKD studies. |
| | Urine IgG | Severe GBM damage | • High MW protein<br>• Indicates nonselective proteinuria | Reflects severe damage.<br>Not for early, subtle changes of glomerular or tubulointerstitial injury |
| | Urine α 2-macroglobulin (A2M) | Diabetic nephropathy progression | • Plasma proteinase inhibitor<br>• Involved in tissue repair & fibrosis | Requires further validation for routine clinical use |
| | Ferritin | Lupus nephritis (LN) activity<br>Tubulointerstitial lesions | • Large soluble protein<br>• Urinary presence indicates renal tubular epithelial cell origin | Primarily studied in LN.<br>Broader utility needs more research. |
| Tubular injury & reabsorption defects | Beta-2-microglobulin (B2M) | Proximal tubular damage/ dysfunction | • Low MW protein<br>• Filtered & extensively reabsorbed | Unstable in acidic urine (pH < 6) Suboptimal specificity (affected by proteinuria, chronic tubulopathies)<br>Poor for severe AKI prediction. |
| | Retinol-binding protein (RBP) | Proximal tubular injury or dysfunction (early marker) | • Low MW protein<br>• Filtered & extensively reabsorbed | Suboptimal specificity<br>(affected by proteinuria, chronic tubulopathies) |
| | N-acetyl-B-D-glucosaminidase (NAG) | Active renal tubular injury | • Lysosomal enzyme from proximal tubular cells<br>• Large MW prevents glomerular filtration | Suboptimal specificity for AKI in some settings (e.g., CKD, diabetes, and hypertension) can increase without clinical AKI |
| | Alpha-1-microglobulin (A1MG) | Tubular damage or reabsorptive defects (drug-induced kidney damage) | • Glycoprotein<br>• Filtered & extensively reabsorbed by tubules | Suboptimal specificity<br>(affected by proteinuria, chronic tubulopathies) |
| | Urinary cystatin C | Tubular reabsorption defects (acute tubular damage) | • Low MW protein Freely filtered<br>• Completely reabsorbed & metabolized by proximal tubule | Suboptimal specificity<br>(affected by proteinuria, chronic tubulopathies) |
| AKI, early tubular damage | Neutrophil gelatinase associated lipocalin (NGAL) | Early tubular injury, AKI prediction/severity | • Earliest & most robustly induced gene/protein in kidney following ischemic/nephrotoxic injury | Reduced specificity in systemic inflammation<br>No standard cutoffs |
| | Kidney injury molecule-1(KIM-1) | Specific proximal tubule injury | • Transmembrane protein<br>• Elevated in proximal tubular cells following ischemic/nephro-toxic AKI | Influenced by CKD, and urinary tract infection |
| | Interleukin-18 (IL-18) | Diagnosing ATN, AKI duration/mortality | • Proinflammatory cytokine<br>• Induced &cleaved in proximal tubule following AKI | Varies by collection timing<br>Affected by inflammatory diseases |
| | Tissue inhibitor of metalloprotease-2 (TIMP-2) & insulin-like growth factor binding protein 7(IGFBP7) | AKI risk assessment (critically ill patients) | • Proteins involved in G1 cell cycle arrest<br>• Released during tubular epithelial cell stress | Nonkidney-specific elevations possible |
| | Na+/H+ exchanger isoform 3 (NHE3) | Differentiating AKI types | • Sodium transporter in proximal tubule and thick ascending limb Liberated into urine upon injury | Limited studies |

AKI, acute kidney injury; CKD, chronic kidney disease; ECM, extracellular matrix; eGFR, estimated glomerular filtration rate; GBM, glomerular basement membrane; MW, molecular weight;DKD, diabetic kidney disease

Infographic by Elba Medina @elbaonelida

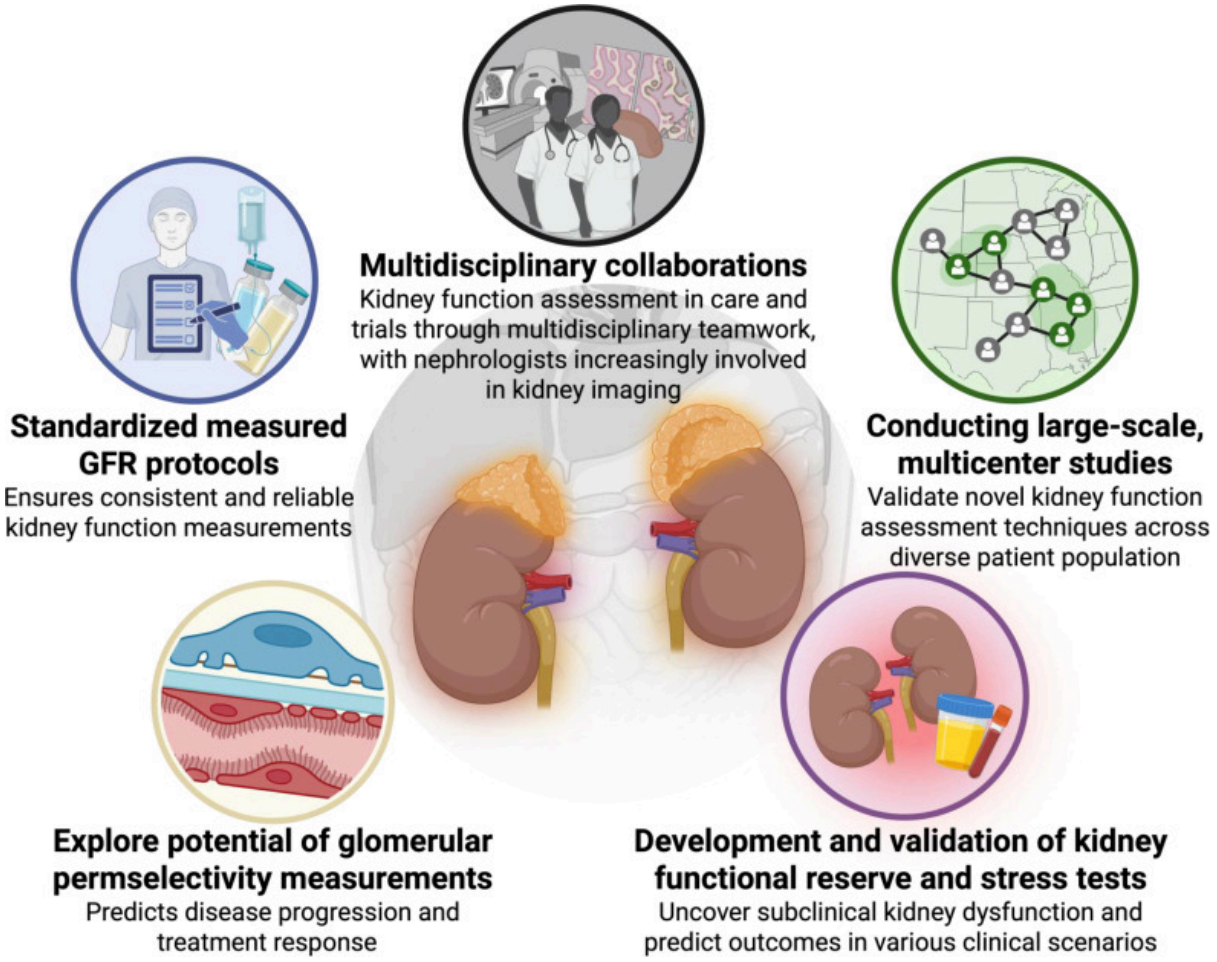
## Summary of established and emerging urine biomarkers

| | Biomarker | Primary implications/ clinical association | Physiological basis/ mechanism | Key limitations |
|---|---|---|---|---|
| CKD Progression | Trefoil factor 3 (TFF3) | • CKD progression<br>• Kidney transplant function monitoring | • Extensively produced in renal tubules<br>• Altered levels in disease states | Still under investigation |
| | Monocyte chemoattractant protein-1 (MCP-1) | • Tubular injury<br>• Kidney function decline | • Reflects maladaptive repair<br>• Recruits monocytes to inflammation/injury sites | Needs further validation |
| | Chitinase-3-like protein-1 | • Tubular injury<br>• Kidney function decline (adaptive repair) | • Glycoprotein involved in inflammation and tissue remodeling | Association with eGFR decline lost after albuminuria adjustment |
| | Dickkopf-related protein 3 (DKK-3) | • Tubulointerstitial fibrosis<br>• CKD progression | • Secreted glycoprotein from stressed tubular epithelia<br>• Implicated in Wnt signaling | Needs further validation |
| | Uromodulin (UMOD) / Tamm Horsfall protein | • Integrity of Henle's loop<br>• Tubulointerstitial fibrosis | • Most prevalent protein in healthy urine<br>• Exclusively expressed by thick ascending limb cells | Needs further validation |
| | Procollagen type III N-terminal propeptide (PIIINP) | • Renal fibrosis progression | • Indicates rate of collagen production<br>• Associated with ECM remodeling | Needs further validation |

AKI, acute kidney injury; CKD, chronic kidney disease; DKD, diabetic kidney disease; ECM, extracellular matrix; eGFR, estimated glomerular filtration rate; GBM, glomerular basement membrane; MW, molecular weight.

Infographic by Elba Medina @elbaonelida

24/🤩The workshop further emphasized the potential of glomerular permselectivity & molecular profiling as cornerstones of precision nephrology. Here are some key innovations and strategies for advancing kidney function assessment. GFR, glomerular filtration rate.🫘👀




25. This has been @elbaonelida with another @KIReports learning opportunity. Thank you! Please share this #tweetorial with your followers and friends!

Don't forget to check out KI Reports Community for more: http://kireportscommunity.org Thanks to @, @, @ for great feedback!