

# **Bridging the Gap: From Biomarker Discovery to Precision Medicine Implementation in CKD**

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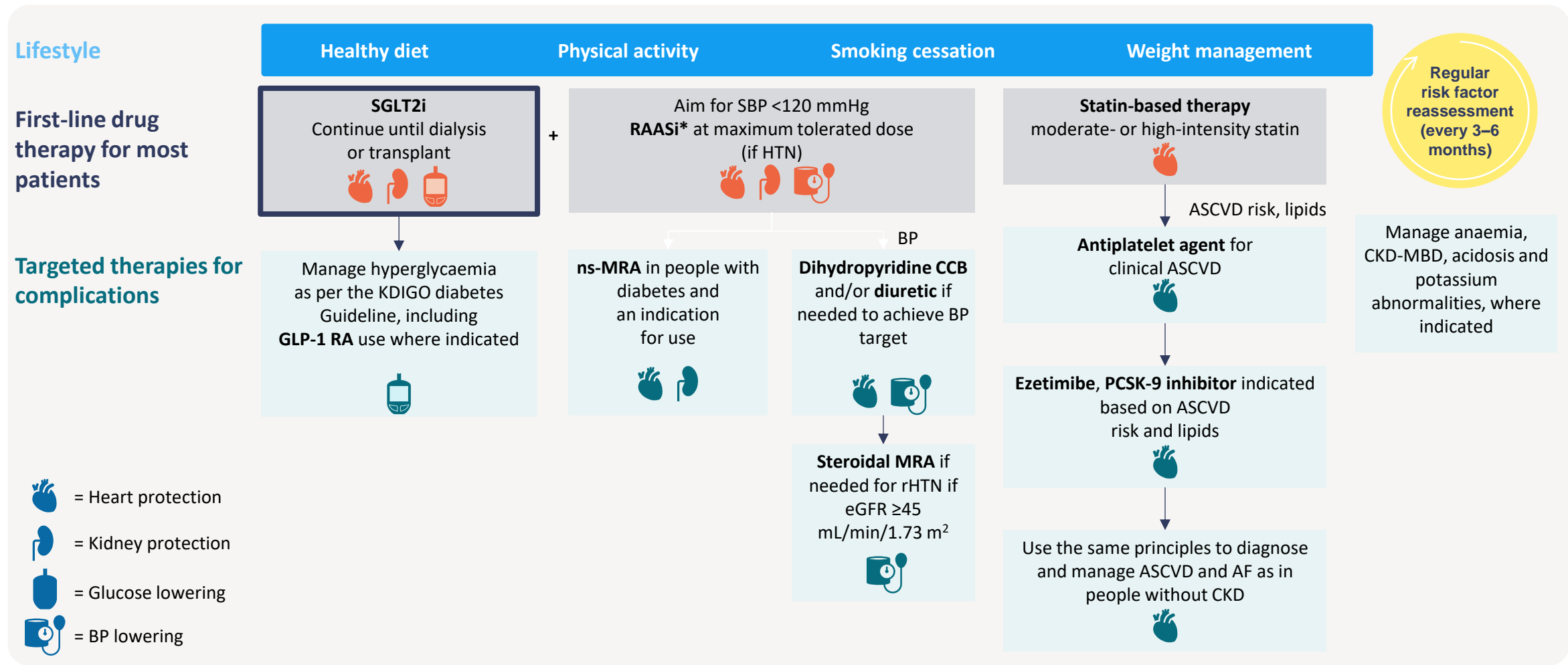
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# Disclosures

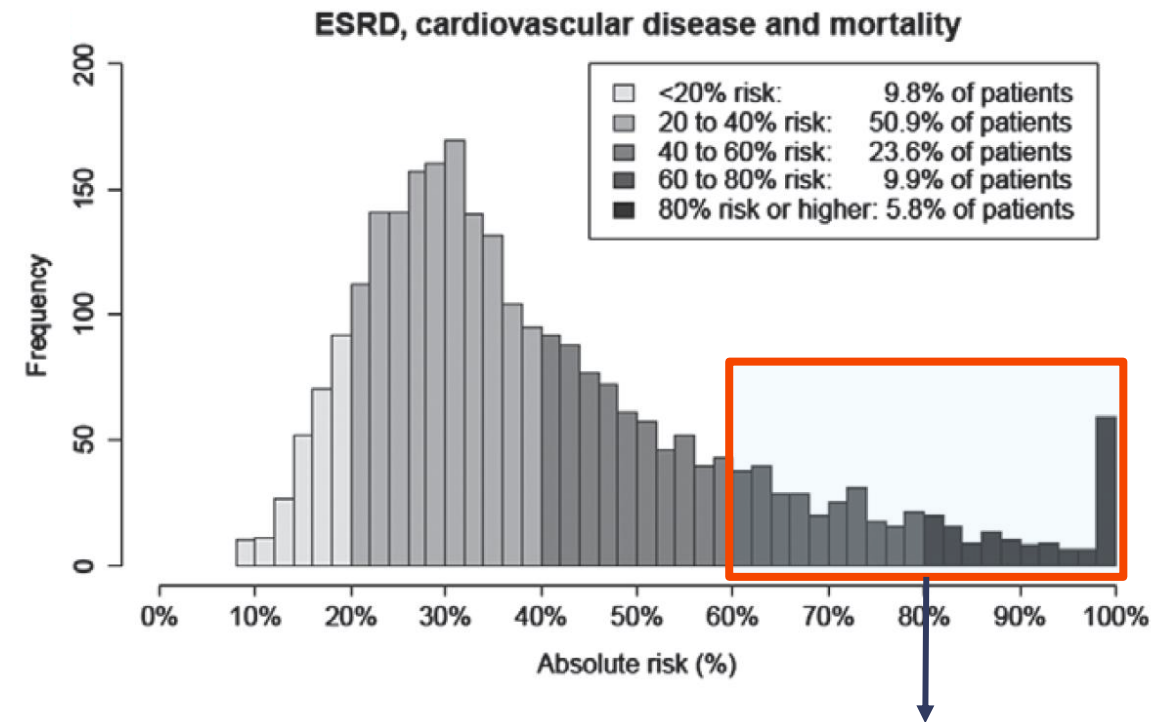
- HJLH is a consultant for AbbVie, AstraZeneca, Bayer, Boehringer Ingelheim, Chinook, CSL Behring, Eli-Lilly, Gilead, Janssen, Merck, NovoNordisk, and Traverre Therapeutics
- He has received research support from AstraZeneca, Boehringer Ingelheim, Janssen and NovoNordisk

# KDIGO 2024: Treatment recommendations

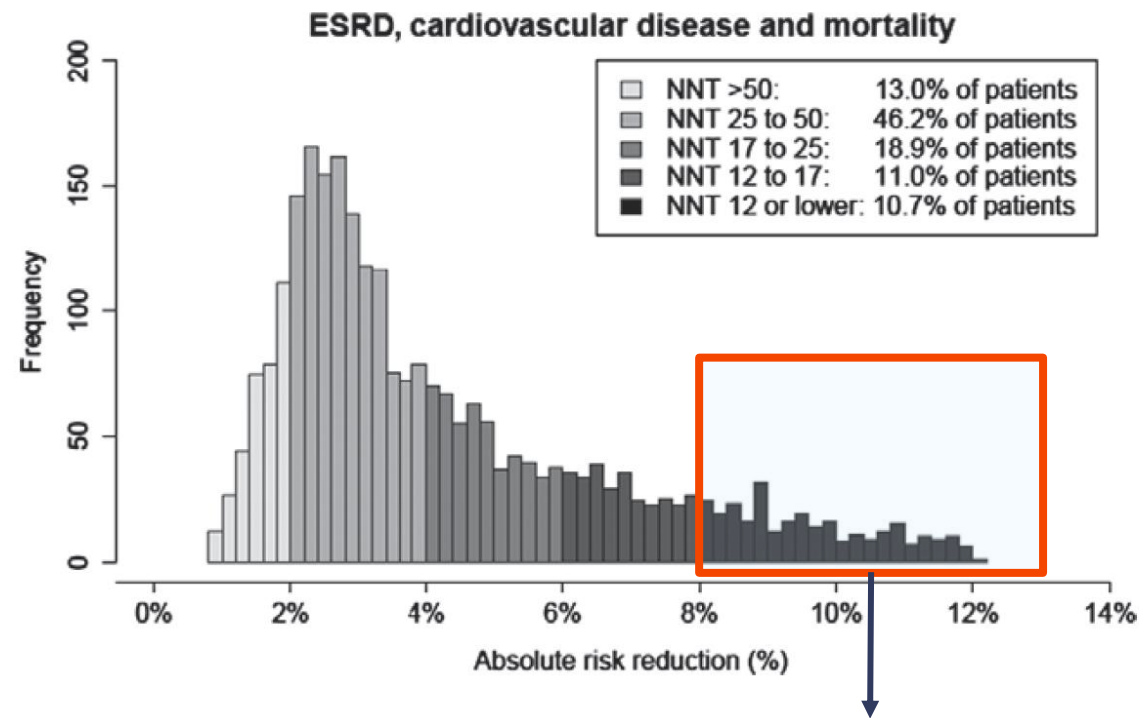


\*Angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker should be first-line therapy for BP control when albuminuria is present; otherwise dihydropyridine CCB or diuretic can also be considered. All 3 classes are often needed to attain BP targets. AF, atrial fibrillation; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CCB, calcium channel blocker; CKD(-MBD), chronic kidney disease(-mineral and bone disorder); eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; (r)HTN, (resistant)hypertension; KDIGO, Kidney Disease: Improving Global Outcomes; (ns-)MRA, (nonsteroidal) mineralocorticoid receptor antagonist; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; RAASI, renin-angiotensin-aldosterone system inhibitor; SBP, systolic blood pressure; SGLT2i, sodium-glucose co-transporter-2 inhibitor. Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2024;105:S117.

# Large variation in risk and response to guideline recommended therapies



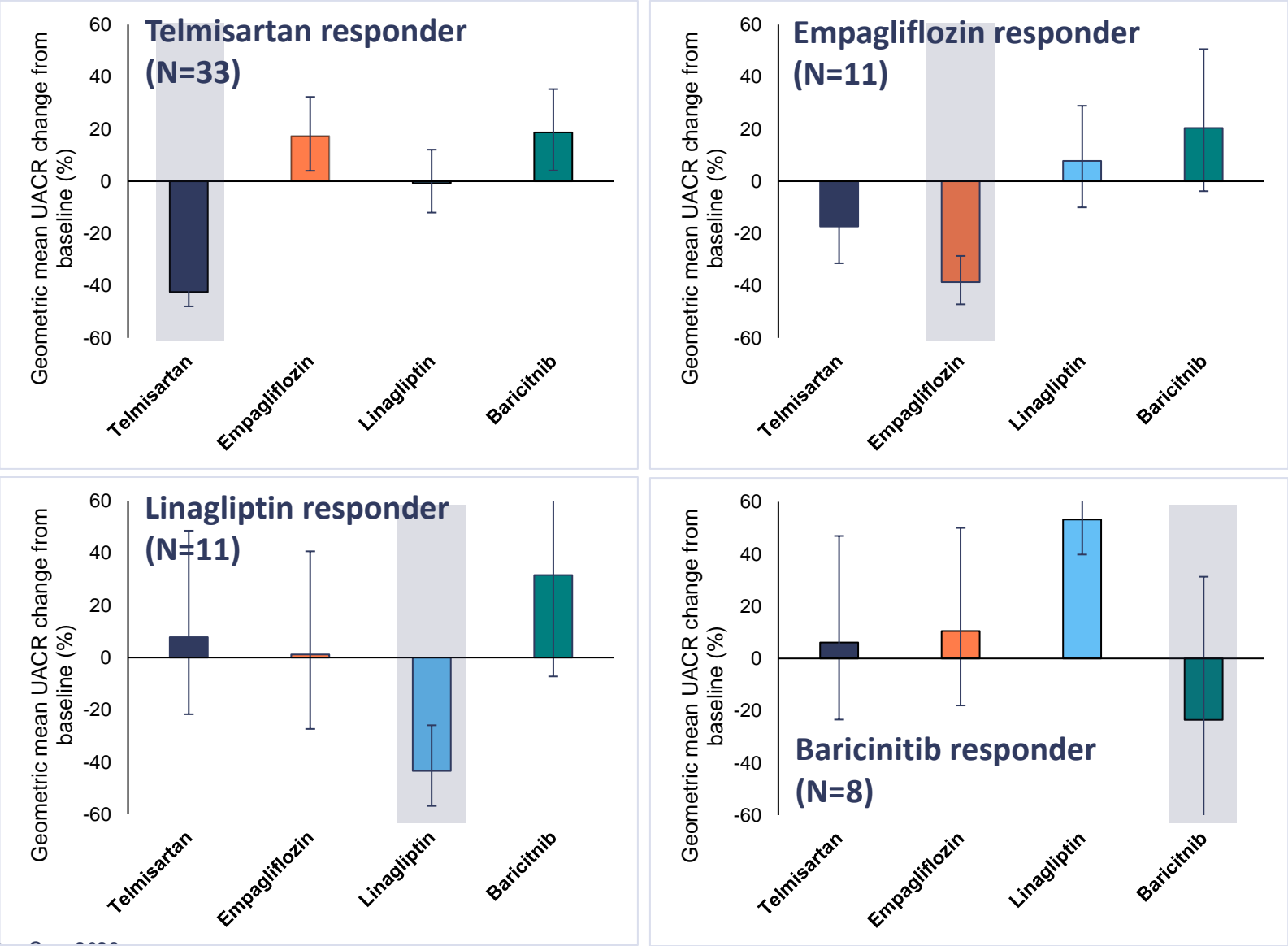
*Use biomarkers to identify individuals at high risk of morbidity and mortality*



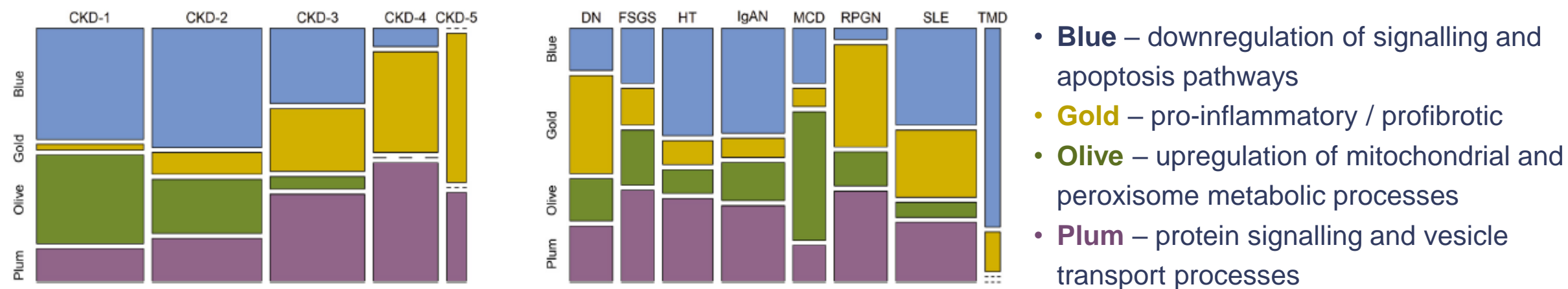
*Use biomarkers to tailor therapy to those who benefit most*

# Individual patients vary in their responses to different drugs

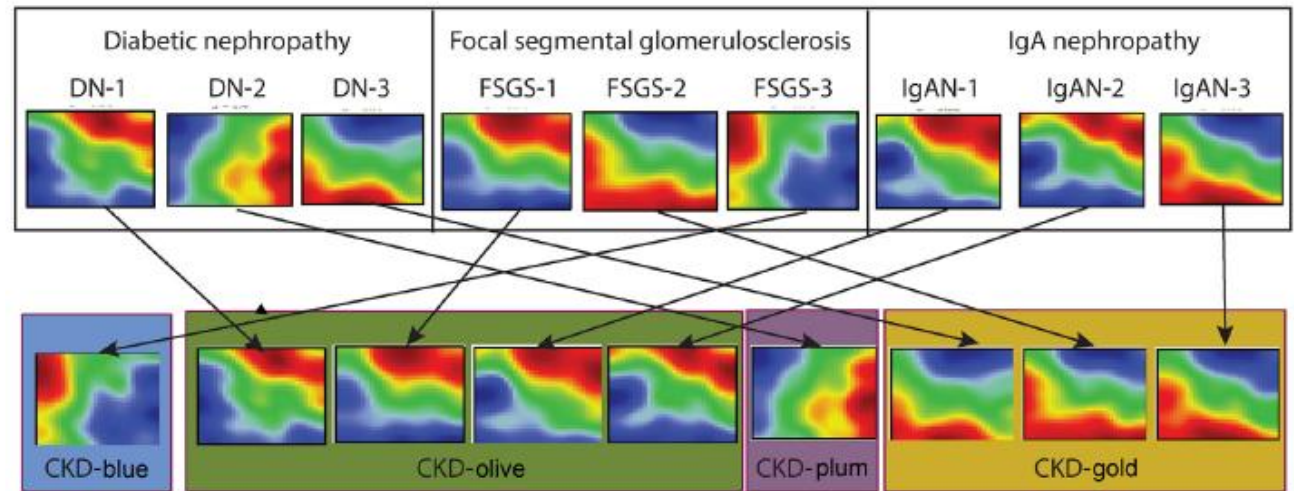
*Each individual has a preferred drug*



# Molecular stratification of CKD reveals large variation in underlying mechanisms in each CKD stage and etiology

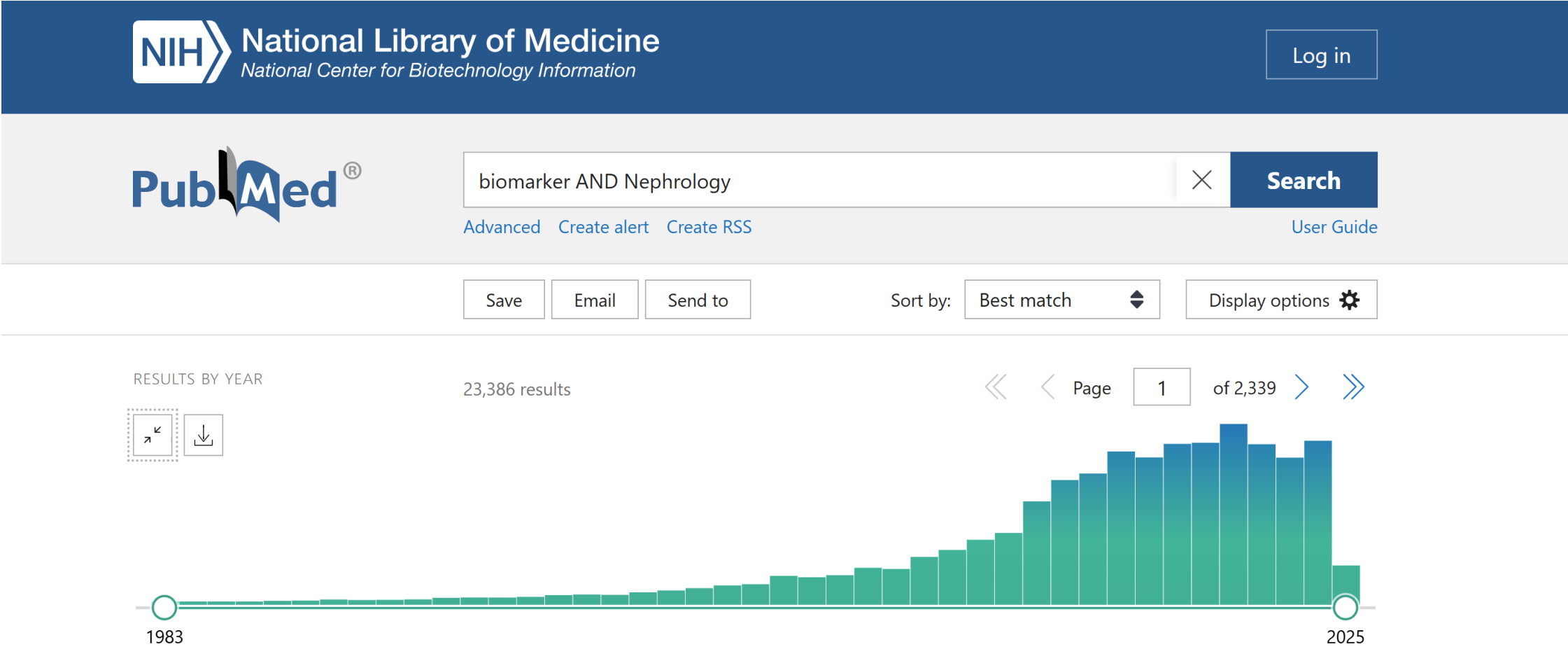


## Classification of histopathological diagnosis



## Classification of by molecular class

# The Gap between Biomarker Research and Clinical Implementation

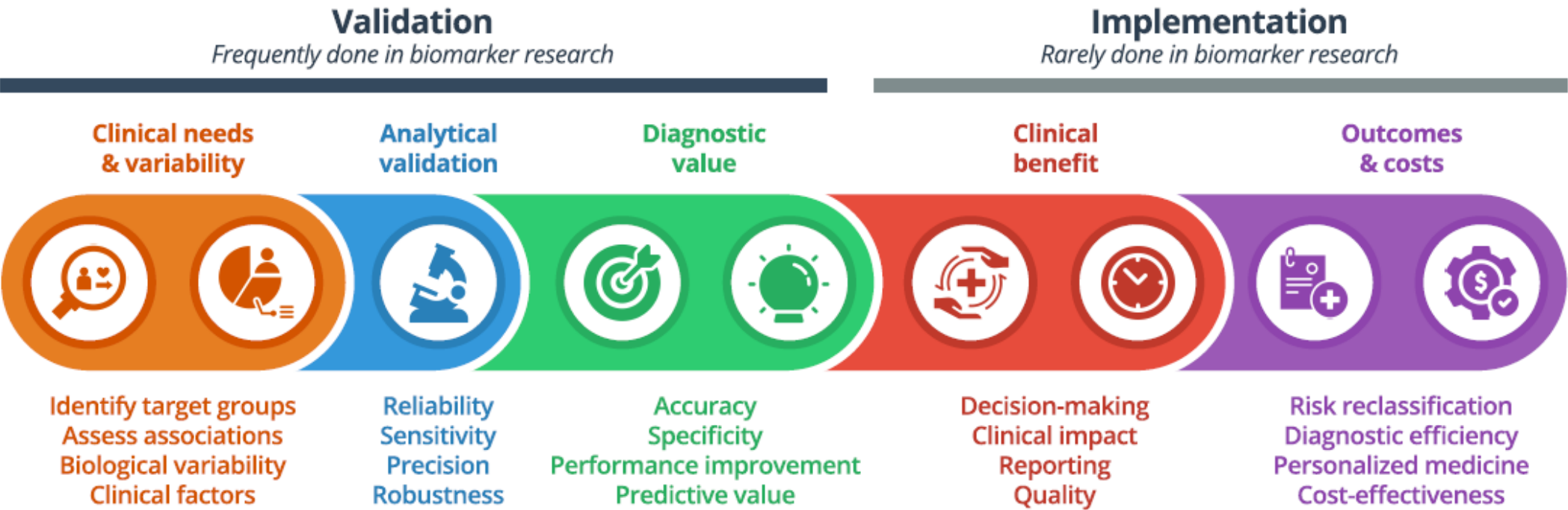


# Guidance for rational development of biomarkers





# Five phases of biomarker development: Implementation studies often not conducted

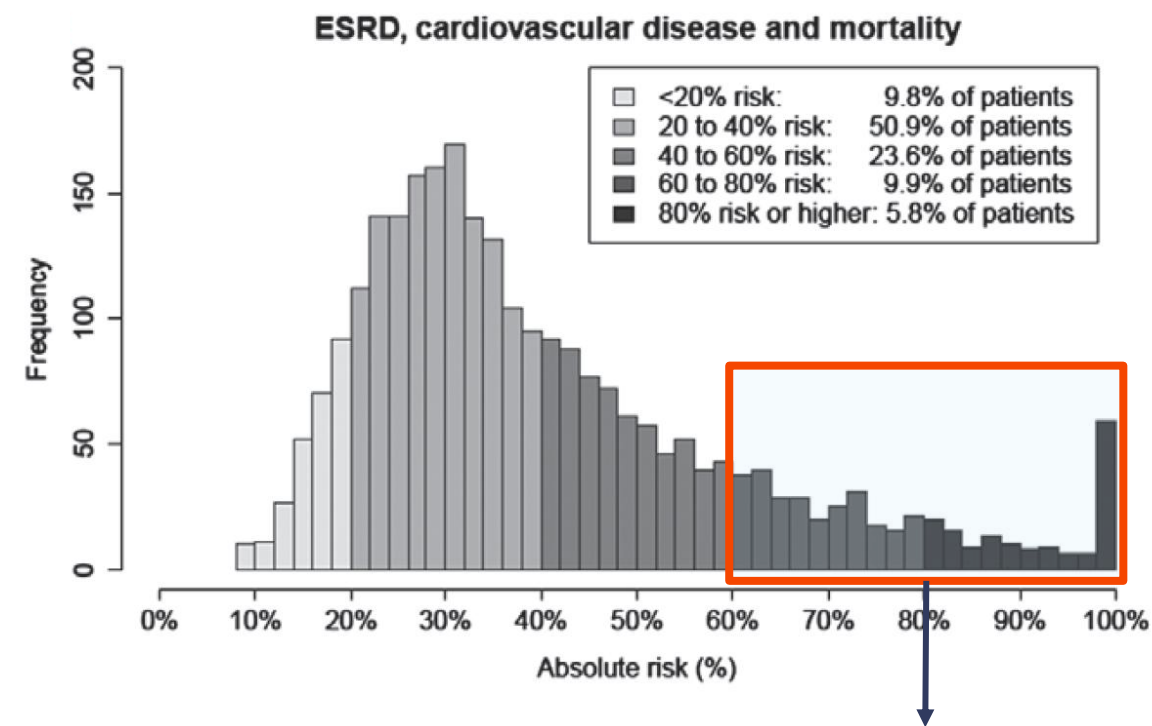


# Failures in Biomarker Pipeline:

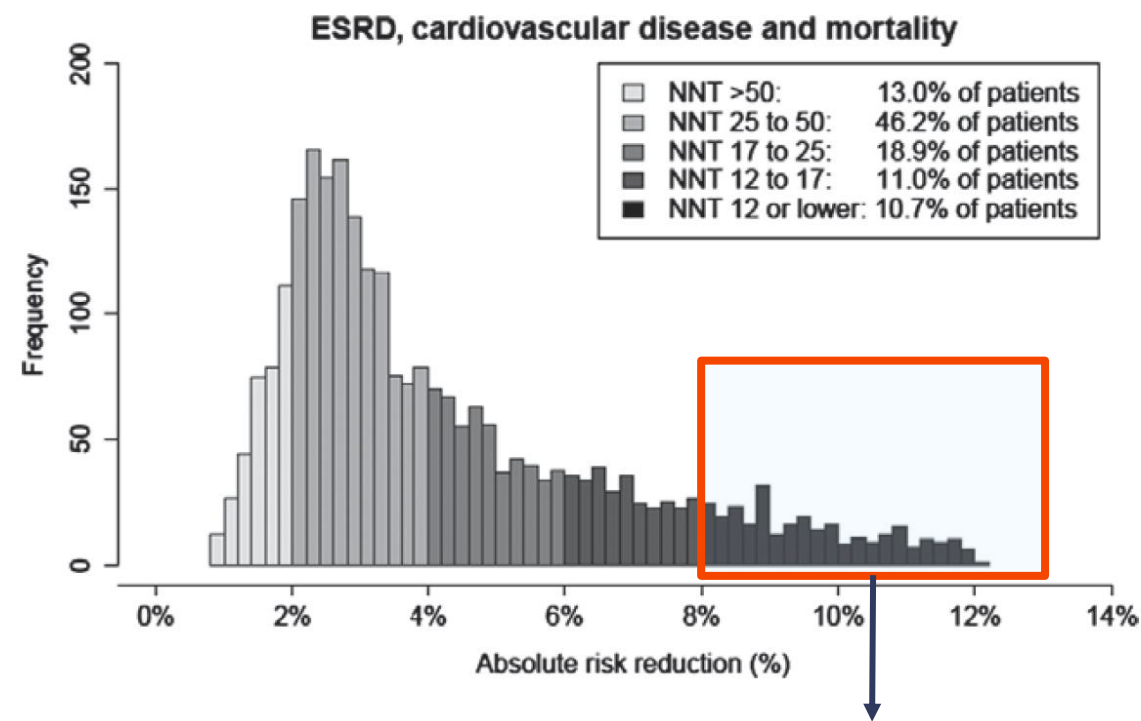
## *From Discovery to Implementation*

	Current Problem	Potential Solution
Discovery	Poor design conduct analysis	Methodological rigor
	Extreme case selection	Proper cohort selection
	Poor / selective reporting	Use reporting standards
Validation	Lack of replication efforts	Incentive for replication
	Inbred replication	More external replication
	Inflation in early small studies	Large collaborative validation studies
Evaluation	Few randomized biomarker trials	Promote randomized biomarker trials
	Improper use of subgroup analyses	Validation of utility of subgroup analysis
Implementation	Poor understanding use of biomarker in real-life	Incentive for implementation studies
	Not well defined regulatory landscape	Testing of utility of long-used biomarkers
	Lack of rigorous guidelines	Standardized nonconflicted guidelines

# Large variation in risk and response to guideline recommended therapies

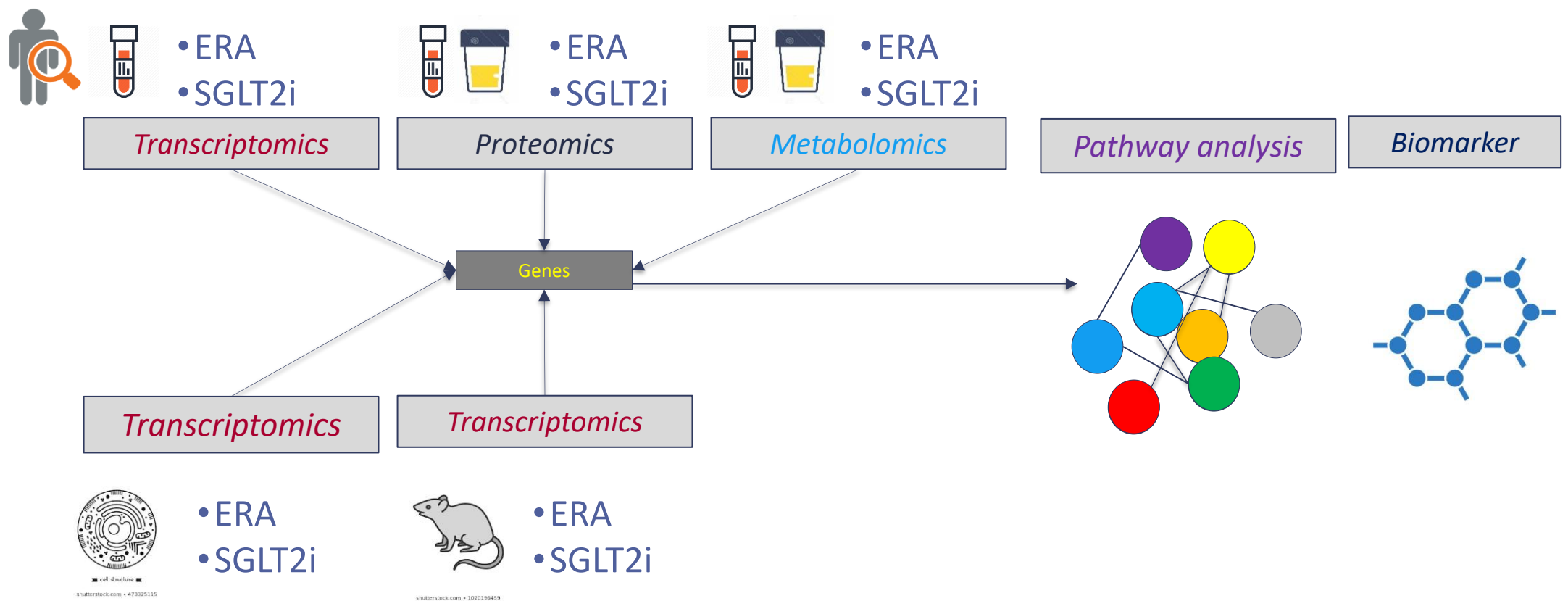


Use biomarkers to identify individuals at high risk of morbidity and mortality



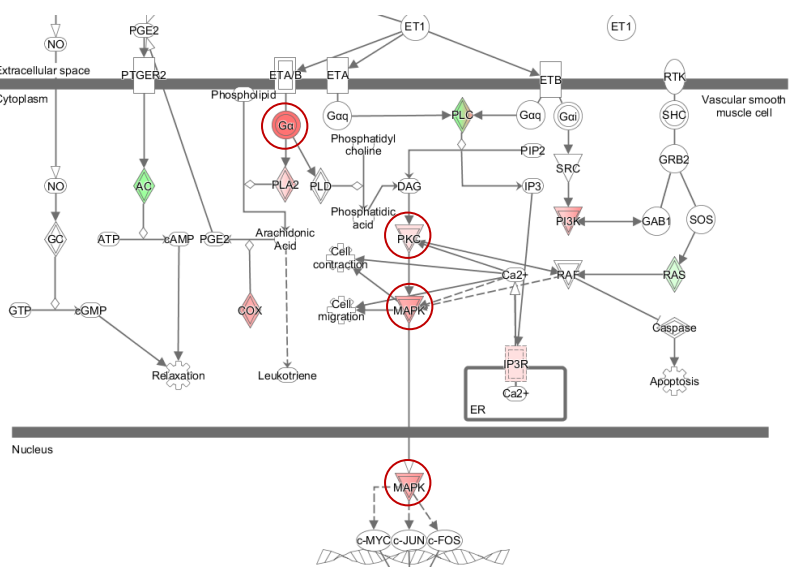
*Use biomarkers to tailor therapy to those who benefit most*

# BEAt-DKD: A multi-omics biomarker discovery approach for ERA drug response

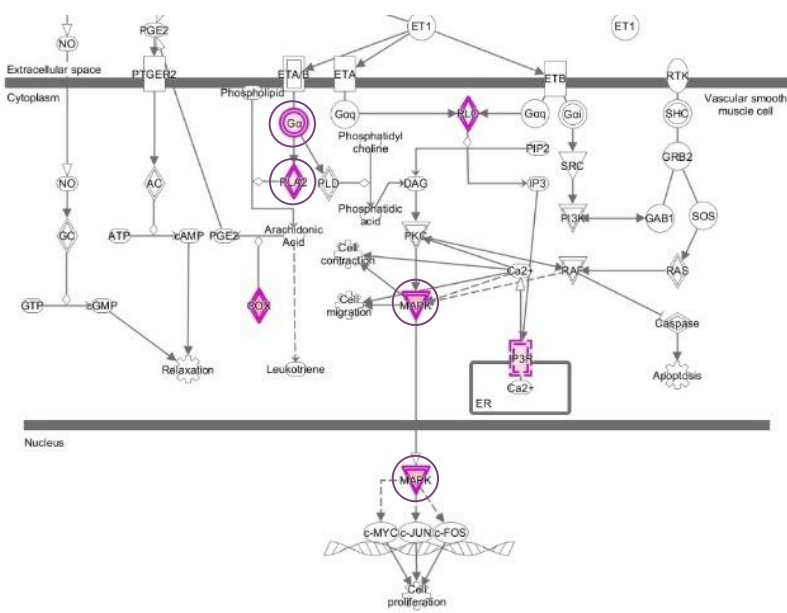


# Endothelin-1 signaling in experimental and human diabetic kidney disease and reversed by ET-1 receptor blockade

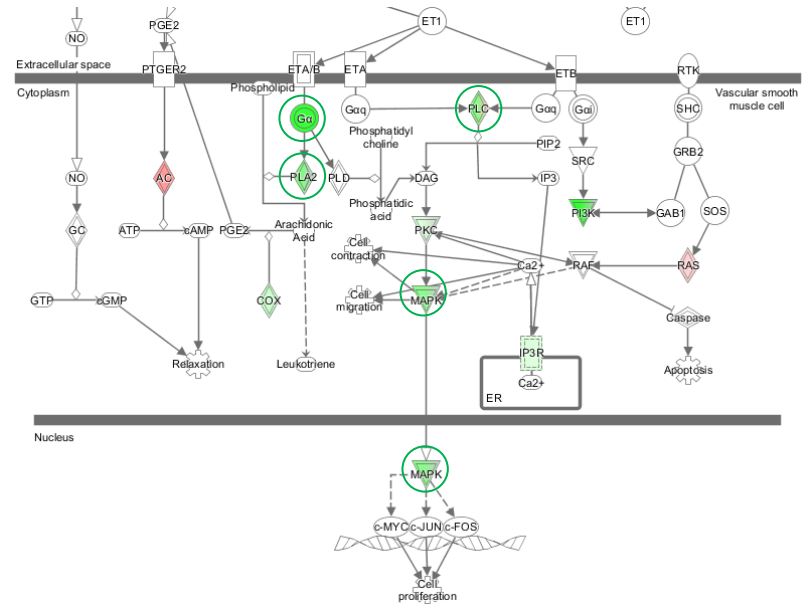
Endothelin-1 pathway activated in experimental animal model



The same endothelin-1 pathway activated in humans with DKD

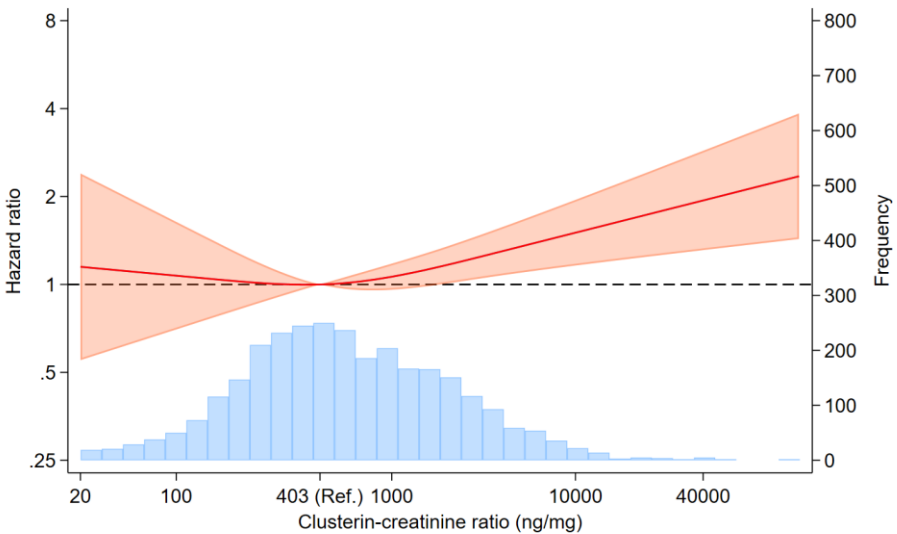


Endothelin-1 pathway activity reversed by atrasentan treatment

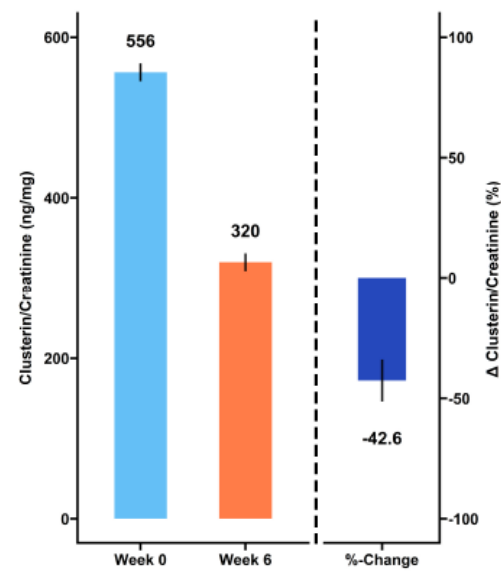


# Atrasentan reduces clusterin and its change is associated with kidney outcomes

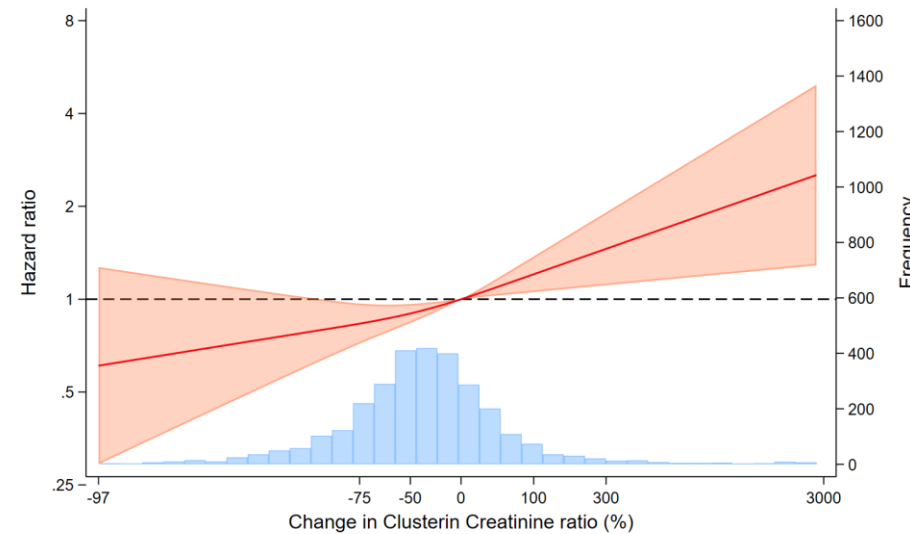
Baseline clusterin is associated with kidney outcomes



Atrasentan reduces Clusterin



Early change in clusterin is associated with kidney outcomes





# PRIME-CKD: From discovery to validation and implementation



## Clinical chemistry validation

- 1: **Technical performance of the assay**; sensitivity / specificity / linearity
- 2: **Pre-analytical factors**: Optimizing sample logistics / processing times
- 3: **Biological variation and clinical factors**: Circadian and day-to-day variation; Age, sex, race, weight; drugs and major surgery



## Clinical Validation

Does a biomarker guided treatment approach compared to care as usual improve kidney function



## Implementation

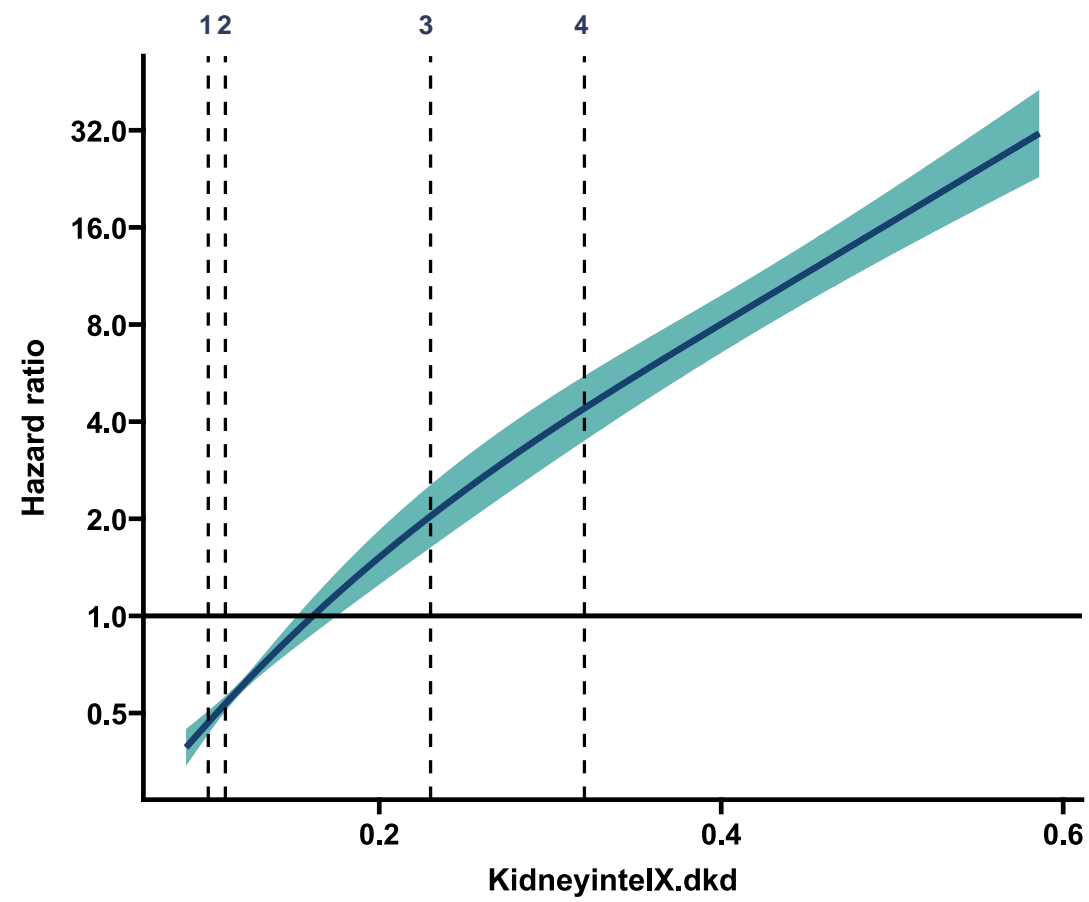
How to present results to patients and physicians

What is the turn-around time

Do patients accept more blood tests (and extra costs?)



# KidneyIntelX is associated with kidney failure in people with type 2 diabetes



- Analyses adjusted for age, sex cardiovascular risk factors, eGFR, UACR
- Vertical lines indicate KDIGO stages representing the mean KidneyIntelX score in each stage

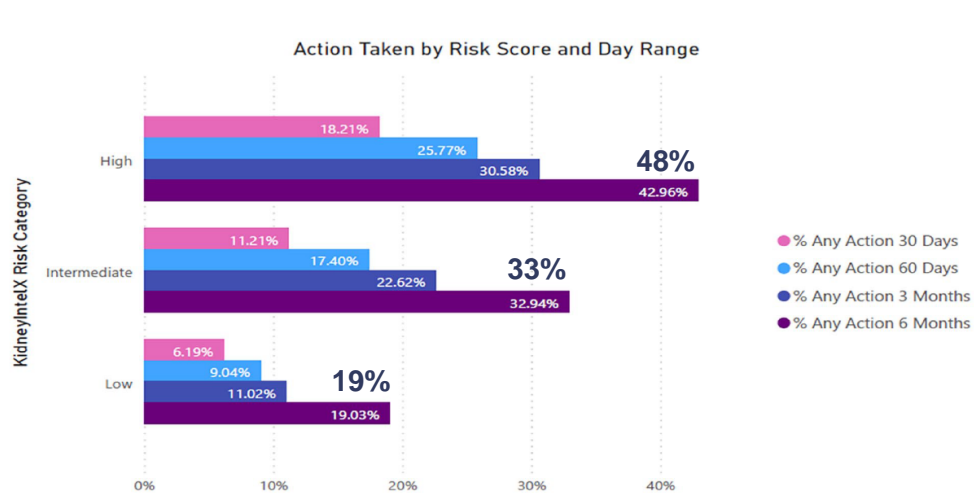




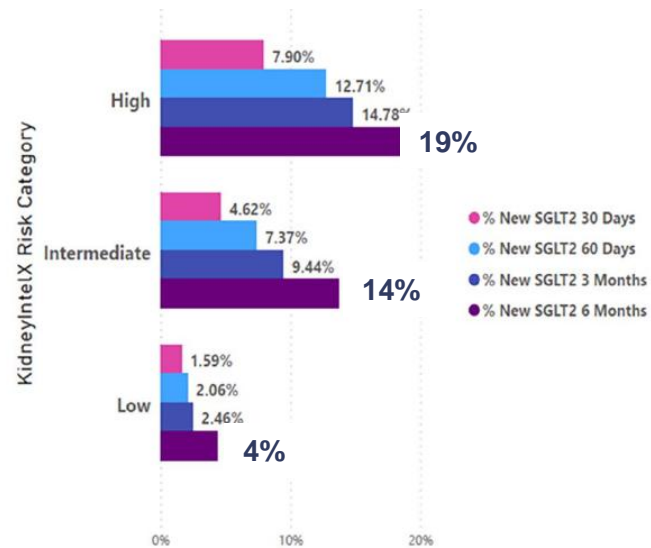
# Implementation of Kidney IntelX in Daily Practice

N=2569

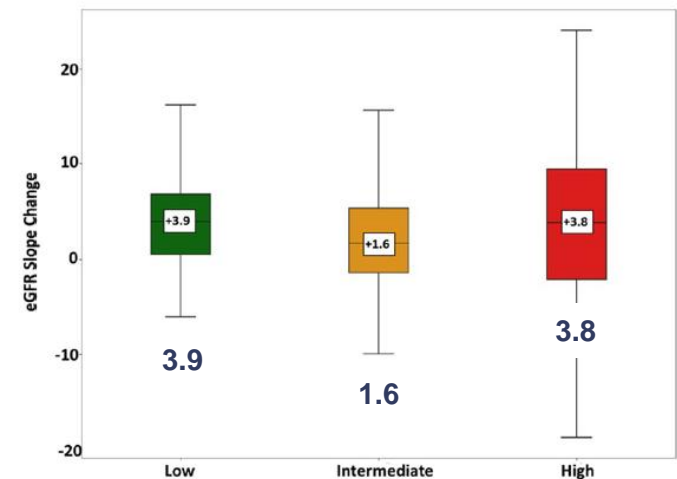
Clinical Action Taken by Risk Score and Day Range



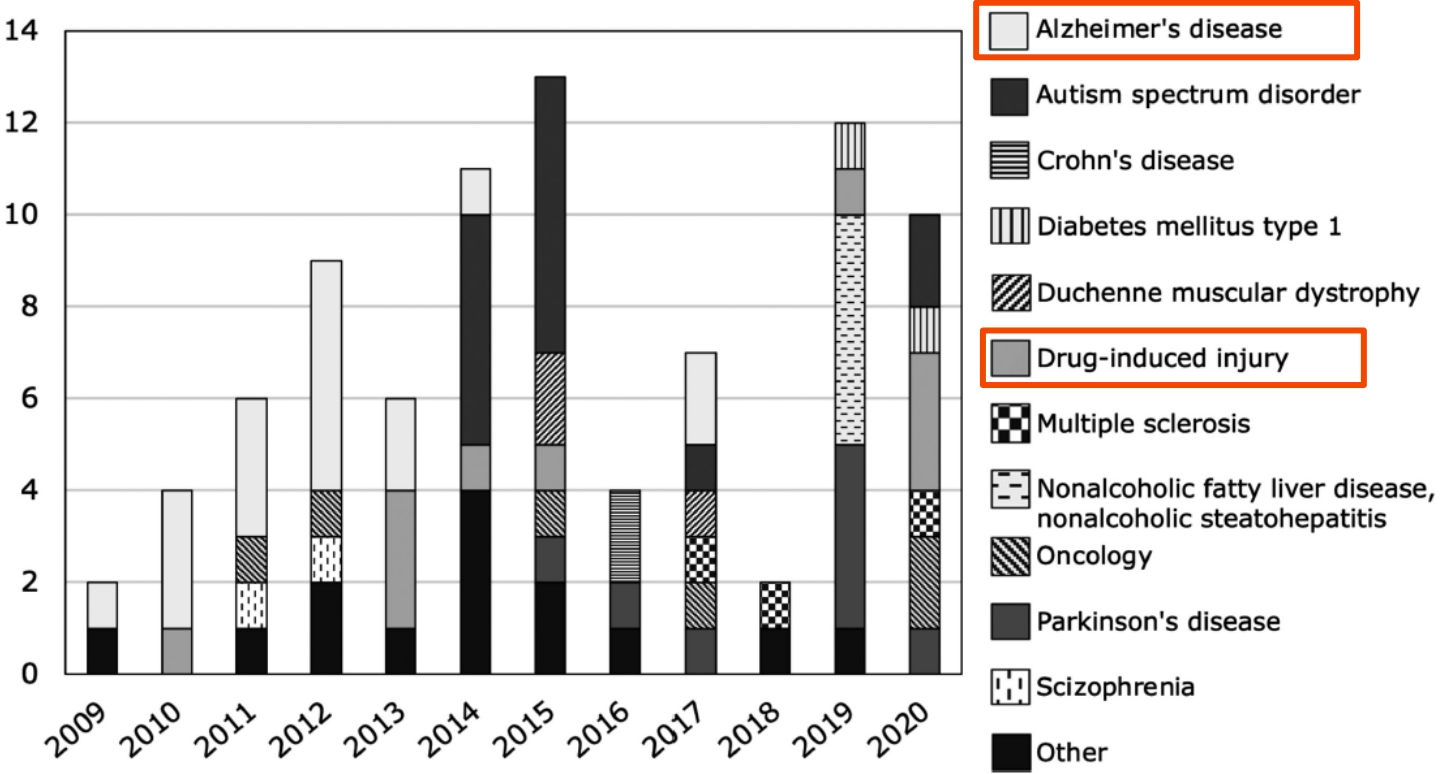
New SGLT2 prescription by Risk



eGFR slope change prior/post



# Biomarker qualification programs in Europe stratified by therapeutic/disease areas



*Very few if any new biomarker qualification programs initiated in Nephrology*



# Take Home Message

- Ongoing discovery and validation of new biomarkers predicting kidney failure
- Implementation studies to assess if the new biomarker improves daily practice and patient outcomes lacking
- Few known biomarkers that predict individual response to guideline recommended CKD therapies
- Existing consortia in Europe (BEAt-DKD, PRIME-CKD) and USA (KPMP) aim to advance and implement biomarker-based therapy approaches in CKD (both diabetes and non-diabetes)