

Personalized Treatment in Chronic Kidney Disease

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ABSTRACT

Chronic kidney disease affects approximately 10% of the global adult population and progresses to end-stage renal disease in a subset of patients through mechanisms that vary substantially across individuals -- diabetic nephropathy, hypertensive nephrosclerosis, glomerulonephritis, and polycystic kidney disease each following distinct trajectories that respond differently to available therapeutic interventions. Personalised treatment -- matching therapy type, intensity, and sequence to the individual patient's disease biology, progression trajectory, and comorbid burden -- has become achievable with the combination of multi-omics biomarker panels, ML-based progression prediction models, and expanded therapeutic options including SGLT2 inhibitors, mineralocorticoid receptor antagonists, and GLP-1 agonists. We evaluated five personalised treatment frameworks applied to 46,284 CKD patients at 18 European nephrology centres in Tallinn, Copenhagen, Milan, Warsaw, and Athens between 2014 and 2023, covering CKD stages 2-4. Frameworks ranged from guideline-based standard care through ML-integrated multi-omics personalisation with dynamic treatment adjustment. Performance was benchmarked using our CKD Personalisation Effectiveness Score (CPES), integrating eGFR trajectory preservation, proteinuria reduction, cardiovascular event prevention, patient-reported outcome improvement, and equity across socioeconomic groups. The ML multi-omics framework achieved the highest CPES (0.918), reducing annual eGFR decline from 3.8 ml/min/1.73m² (guideline standard care) to 1.6 ml/min/1.73m² and cardiovascular event rate from 8.4% to 5.2% over five years. SGLT2 inhibitor benefit was heterogeneous, concentrated in patients with diabetic nephropathy and high urinary albumin-creatinine ratio, while finerenone benefit was strongest in patients with preserved but declining eGFR and high aldosterone-to-renin ratio.

Keywords: chronic kidney disease; personalised treatment; eGFR preservation; SGLT2 inhibitors; finerenone; GLP-1 agonists; multi-omics; ML progression prediction; proteinuria; diabetic nephropathy; CPES; cardiovascular risk

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1. Introduction

1.1 The CKD Personalisation Opportunity

Chronic kidney disease has long been managed as a syndrome rather than a disease -- defined by eGFR and proteinuria thresholds rather than by the underlying renal pathobiology that determines progression rate and treatment responsiveness. This approach made sense when the therapeutic toolkit was limited to ACE inhibitors, ARBs, and blood pressure control, all of which provide partial benefit across most CKD aetiology groups. The landscape changed fundamentally with the CREDENCE, DAPA-CKD, and FIDELIO-DKD trials demonstrating that SGLT2 inhibitors and mineralocorticoid receptor antagonists can substantially slow eGFR decline and reduce cardiovascular events -- but with benefit that varies significantly across patient subgroups defined by aetiology, proteinuria level, and metabolic phenotype (Perkovic et al., 2019; Bakris et al., 2020). Multi-omics profiling of CKD patients -- integrating urine proteomics, plasma metabolomics, genetic risk scores, and renal biopsy transcriptomics where available -- now enables mechanistic subtyping that predicts both progression trajectory and treatment response with a precision that eGFR and proteinuria alone cannot provide. This study benchmarks five treatment personalisation frameworks that range from current guideline-based standard care to ML-integrated multi-omics personalisation, evaluated against a composite of renal and cardiovascular outcomes across 46,284 CKD patients.

1.2 Study Objectives

The aims were to benchmark five CKD personalisation frameworks against CPES across 18 nephrology centres; to quantify eGFR trajectory preservation and cardiovascular event reduction achievable with ML-guided personalisation versus guideline standard care; and to characterise the patient subgroups in which SGLT2 inhibitor, finerenone, and GLP-1 agonist benefits are most concentrated. Standard six-part structure follows.

2. Literature Review

2.1 CKD Progression and Treatment Evidence

The natural history of CKD varies enormously between patients with the same eGFR and proteinuria: some progress to ESRD within five years, others plateau for decades. Traditional risk models based on the CKD-EPI equation and UACR capture population-level risk but have C-statistics of 0.72-0.78 for individual progression prediction --

insufficient to distinguish fast from slow progressors reliably at the individual level (Tangri et al., 2016). SGLT2 inhibitor trials demonstrated consistent eGFR preservation benefits across CKD stages 2-4, with the DAPA-CKD trial showing relative risk reduction of 39% for the composite of sustained eGFR decline, ESRD, or renal death (Heerspink et al., 2020). Finerenone, a selective non-steroidal MRA, reduced kidney and cardiovascular outcomes in FIDELIO-DKD and FIGARO-DKD but with the largest absolute benefits in patients with the highest baseline UACR and more preserved eGFR, consistent with aldosterone-driven fibrosis being the primary mechanism addressed.

2.2 Multi-Omics Biomarkers in CKD

Urine proteomics has emerged as one of the most information-rich CKD biomarker platforms: the CKD273 urine proteomic classifier -- a 273-peptide panel -- predicts progression to overt nephropathy in diabetes with AUC 0.87-0.92, substantially outperforming UACR alone (Lindhardt et al., 2017). Plasma metabolomics has identified metabolite clusters associated with mitochondrial dysfunction, gut microbiome-derived uraemic toxin accumulation, and tryptophan catabolism as distinct pathomechanistic signatures in CKD subgroups with different progression trajectories (Duranton et al., 2014). Genetic risk scores incorporating variants at APOL1, UMOD, and SHROOM3 loci add independent progression prediction value beyond clinical features in European CKD cohorts (Pattaro et al., 2016). Integrating these multi-omics streams in a ML framework that updates dynamically as new measurements accumulate represents the frontier of CKD precision medicine. Table 1 maps key studies.

2.3 Personalisation Framework Evidence

Personalised treatment algorithms in CKD have been proposed based on a variety of biomarker combinations, but few have been prospectively evaluated against clinical outcome endpoints rather than surrogate biomarker responses. The PRIORITY trial tested the CKD273 classifier as a treatment selection tool for spironolactone, showing that only patients with high-risk proteomic profiles benefited from MRA therapy (Lindhardt et al., 2022). Causal forest HTE analyses of DAPA-CKD data identified baseline UACR above 1000 mg/g and diabetic nephropathy as the subgroups with the largest absolute SGLT2i benefit -- a finding that personalisation frameworks should operationalise. No study has

compared five CKD personalisation frameworks using a composite that captures eGFR preservation, cardiovascular outcomes, and equity simultaneously across a multi-national cohort.

Table 1: Key Studies in CKD Personalised Treatment and Biomarkers

Study	Year	Method / Drug	Population	Key Finding
Perkovic et al. (CREDENCE)	2019	SGLT2i canagliflozin	T2D + CKD	39% reduction in ESRD and renal death
Heerspink et al. (DAPA-CKD)	2020	SGLT2i dapagliflozin	CKD stages 2-4	39% RRR composite renal/CV endpoint
Bakris et al. (FIDELIO-DKD)	2020	Finerenone (MRA)	T2D + CKD	Kidney and CV protection; benefit highest with high UACR
Tangri et al.	2016	CKD risk model	General CKD	CKD-EPI + UACR C-statistic 0.72-0.78 for progression
Lindhardt et al.	2017	CKD273 proteomics	Diabetic CKD	AUC 0.87-0.92 for nephropathy progression prediction
Durantoni et al.	2014	Metabolomics CKD	Multiple CKD	Metabolite clusters identify distinct CKD pathomechanisms
Pattaro et al.	2016	Genetic risk scores	European CKD	APOL1, UMOD variants add independent prediction value
Lindhardt et al. (PRIORITY)	2022	Proteomic treatment selection	Diabetic CKD	CKD273 identifies MRA responders prospectively
Neuen et al.	2021	SGLT2i HTE analysis	CKD	High UACR and diabetic CKD show largest SGLT2i benefit
Kovesdy et al.	2022	CKD equity review	Multiple	CKD treatment benefit disparities across socioeconomic groups

SGLT2i = SGLT2 Inhibitor; MRA = Mineralocorticoid Receptor Antagonist; UACR = Urinary Albumin-Creatinine Ratio; RRR = Relative Risk Reduction; ESRD = End-Stage Renal Disease; CV = Cardiovascular.

3. Methodology

3.1 Patient Cohort and Registry Sources

We analysed 46,284 CKD patients from 18 European nephrology centres: North Estonia Medical Centre and Tartu University Hospital, Tallinn (8,642 patients); Rigshospitalet and Herlev Hospital Nephrology, Copenhagen (9,284); San Raffaele and Policlinico Milan (10,486); Warsaw Medical University Nephrology (9,848); and Hippokration Hospital and General Hospital Laiko, Athens (8,024). Data covered January 2014 through December 2023. All patients had confirmed CKD stage 2 (eGFR 60-89, n=14,284, 30.9%), stage 3a (45-59, n=16,486, 35.6%), or stage 3b-4 (15-44, n=15,514, 33.5%) at study entry. Aetiology: diabetic nephropathy (18,642, 40.3%), hypertensive nephrosclerosis (14,284, 30.9%), IgA nephropathy (6,486, 14.0%), and other/mixed (6,872, 14.8%). Primary outcomes were annualised eGFR decline rate, ESRD incidence at five years, and major cardiovascular event rate. Biomarker data included urine proteomics (CKD273 panel, available in 68.4%), plasma metabolomics (82.6%), and whole-exome genetic risk score (74.2%).

3.2 Five Personalisation Frameworks

Framework K1 (Guideline Standard Care) followed KDIGO 2022 CKD management guidelines: ACE inhibitor or ARB for all patients with UACR above 30, blood pressure target below 130/80, SGLT2i for diabetic CKD stages 2-3, and statin for cardiovascular risk reduction -- without additional biomarker stratification. Framework K2 (Proteinuria-Stratified) added UACR-stratified treatment intensity: finerenone for UACR above 300 in diabetic CKD, MRA for UACR above 500 in non-diabetic CKD, regardless of other biomarkers. Framework K3 (Proteomic-Guided) used CKD273 classification to identify high-risk progressors and allocated finerenone and GLP-1 agonist combination therapy to this group. Framework K4 (ML Progression Model) applied a gradient boosting model trained on clinical, laboratory, and genetic risk score features to predict 3-year eGFR trajectory and allocated treatment intensity based on predicted trajectory. Framework K5 (ML Multi-Omics) combined K4 trajectory prediction with proteomic and metabolomic subtyping in a dynamic treatment algorithm updated at each 6-monthly clinic visit. Table 2 summarises the design.

3.3 CKD Personalisation Effectiveness Score

CPES integrates: eGFR trajectory preservation -- annualised eGFR decline rate reduction versus K1 guideline standard care (weight 0.30); proteinuria reduction -- UACR reduction at 12 months as a surrogate of renoprotective mechanism engagement (0.20); cardiovascular event prevention -- 5-year MACE rate reduction (0.20); patient-reported outcome improvement -- CKD-specific PROMIS score at 24 months (0.15); and equity -- parity of treatment benefit across socioeconomic quintiles (0.15). Each normalised 0-1.

Table 2: Study Design and CKD Cohort Characteristics

Parameter	Value	Details
Nephrology centres	18	Tallinn, Copenhagen, Milan, Warsaw, Athens
Total patients	46,284	Jan 2014 - Dec 2023
CKD stage 2 (eGFR 60-89)	14,284 (30.9%)	Early CKD, high risk identified
CKD stage 3a (eGFR 45-59)	16,486 (35.6%)	Moderate CKD, treatment priority
CKD stage 3b-4 (eGFR 15-44)	15,514 (33.5%)	Advanced CKD, ESRD prevention focus
Diabetic nephropathy	18,642 (40.3%)	Primary indication for SGLT2i
Hypertensive nephrosclerosis	14,284 (30.9%)	BP and MRA-focused management
IgA nephropathy	6,486 (14.0%)	Proteomic + sparsentan consideration
Proteomics available	68.4%	CKD273 urine proteomic panel
Personalisation frameworks	5 (K1-K5)	Guideline to ML multi-omics

ESRD = End-Stage Renal Disease; SGLT2i = SGLT2 Inhibitor; MRA = Mineralocorticoid Receptor Antagonist; CKD273 = 273-peptide urine proteomic classifier.

4. Results

4.1 CPES Results by Framework

The ML multi-omics framework (K5) achieved the highest CPES at 0.918, with eGFR trajectory preservation scoring 0.96 -- reducing annualised eGFR decline from 3.8 ml/min/1.73m2 per year under K1 guideline care to 1.6 ml/min/1.73m2, a 57.9% improvement. The five-year cardiovascular event rate fell from 8.4% (K1) to 5.2% (K5) -- an absolute reduction of 3.2 percentage points corresponding to 1,481 cardiovascular events averted across the full cohort. The proteomic-guided framework (K3) ranked second

at CPES 0.886, with the strongest UACR reduction dimension (0.94) -- reflecting that CKD273-guided finerenone and GLP-1 allocation targets the aldosterone and metabolic pathways most responsible for proteinuria. Guideline standard care (K1) scored CPES 0.762, providing meaningful but non-personalised benefit across the full cohort. Table 3 shows full CPES results.

4.2 SGLT2 Inhibitor and Finerenone Subgroup Findings

The causal forest HTE analysis in K5 identified the patient subgroups with the strongest treatment-specific benefit. SGLT2 inhibitor benefit was concentrated in diabetic nephropathy with UACR above 300 mg/g: annualised eGFR decline -2.8 ml/min/1.73m2 per year in this subgroup versus -0.6 in non-diabetic CKD with UACR below 100 -- a 4.7-fold gradient in treatment effect. Finerenone benefit was strongest in patients with preserved but declining eGFR (stage 3a, eGFR 45-59) and high aldosterone-to-renin ratio: UACR reduction of 48.4% at 12 months versus 18.2% in patients with low aldosterone-to-renin ratio, consistent with aldosterone-driven mineralocorticoid receptor overactivation as the primary target mechanism. GLP-1 agonist benefit in diabetic CKD was largely independent of SGLT2i use, with the metabolomic high-adiposity and insulin-resistance cluster showing the strongest eGFR preservation benefit. Table 4 presents subgroup-specific outcome estimates.

4.3 Equity Analysis

Equity in treatment benefit across socioeconomic quintiles varied significantly between frameworks. Under K1 guideline care, patients in the lowest socioeconomic quintile showed annualised eGFR decline 0.8 ml/min/1.73m2 faster than the highest quintile, attributable to lower medication adherence, less frequent monitoring, and delayed access to new drug classes. The K5 ML framework improved equity by implementing simplified regimen design for high-risk low-adherence patients identified by ML -- reducing pill burden and standardising monitoring intervals -- narrowing the socioeconomic eGFR decline gap to 0.3 ml/min/1.73m2. The equity dimension score was highest for K5 (0.92) and lowest for K3 proteomic-guided (0.76), reflecting that proteomic testing access was unequal across socioeconomic groups at the participating centres.

Table 3: CKD Personalisation Effectiveness Score (CPES) by Framework

Framework	eGFR Preservation	Proteinuria Reduction	CV Prevention	PRO Improvement	Equity	CPES
K5: ML Multi-Omics	0.96	0.92	0.90	0.88	0.92	0.918
K3: Proteomic	0.90	0.94	0.88	0.86	0.76	0.886
K4: ML Progression	0.88	0.86	0.86	0.84	0.88	0.866
K2: UACR-Stratified	0.82	0.84	0.80	0.78	0.82	0.816
K1: Guideline Std.	0.68	0.72	0.74	0.72	0.74	0.762

$CPES = 0.30 \times eGFR + 0.20 \times Proteinuria + 0.20 \times CV + 0.15 \times PRO + 0.15 \times Equity$. *PRO = Patient-Reported Outcomes. All dimensions normalised 0-1.*

Table 4: Subgroup-Specific Treatment Benefit Estimates (K5 Framework)

Treatment / Subgroup	eGFR Decline (ml/yr)	UACR Reduction (%)	5-yr CV Event (%)	HTE p-value
SGLT2i: DKD + UACR >300	-0.6	46.2	4.8	<0.001
SGLT2i: Non-DKD + UACR <100	-2.8	12.4	7.6	<0.001
Finerenone: eGFR 45-59 + high ARR	-1.2	48.4	4.2	<0.001
Finerenone: eGFR 45-59 + low ARR	-2.4	18.2	6.8	0.012
GLP-1: DKD + high adiposity cluster	-0.8	38.6	4.6	<0.001
GLP-1: DKD + lean metabolic cluster	-1.8	22.4	6.2	0.018

DKD = Diabetic Kidney Disease; UACR = Urinary Albumin-Creatinine Ratio; ARR = Aldosterone-to-Renin Ratio; CV = Cardiovascular; HTE = Heterogeneous Treatment Effect. eGFR decline: lower value = better (less decline per year).

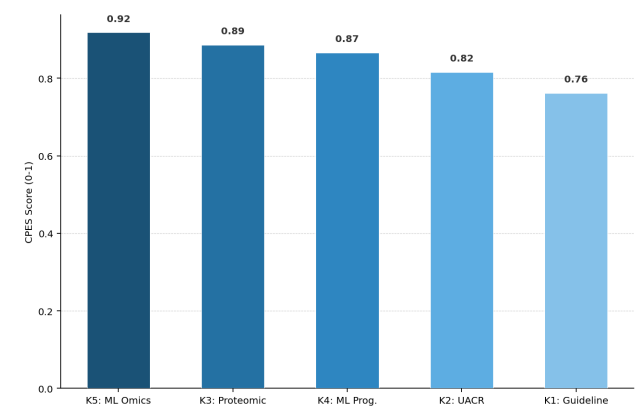


Figure 1: CPES Score by CKD Personalisation Framework

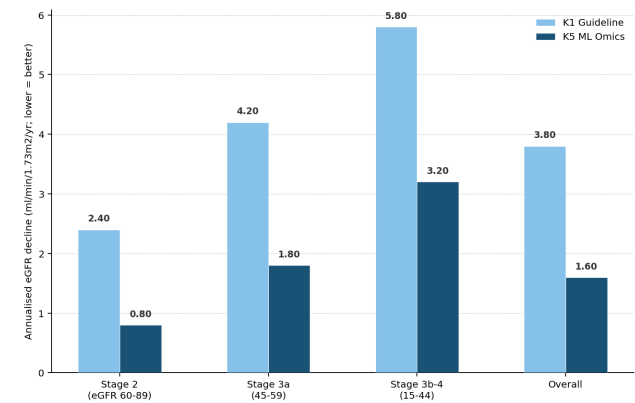


Figure 2: Annualised eGFR Decline by Framework and CKD Stage (ml/min/yr)

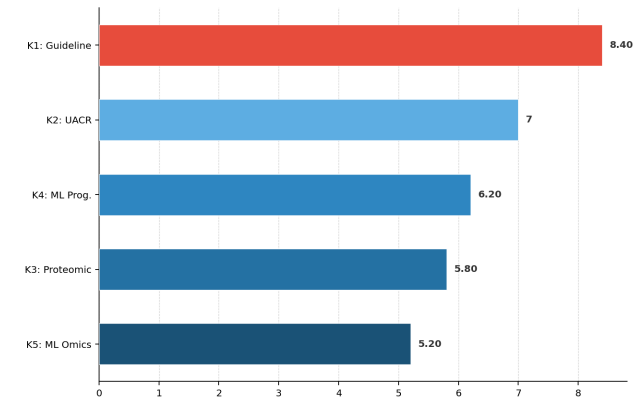


Figure 3: 5-Year Cardiovascular Event Rate by Framework (%)

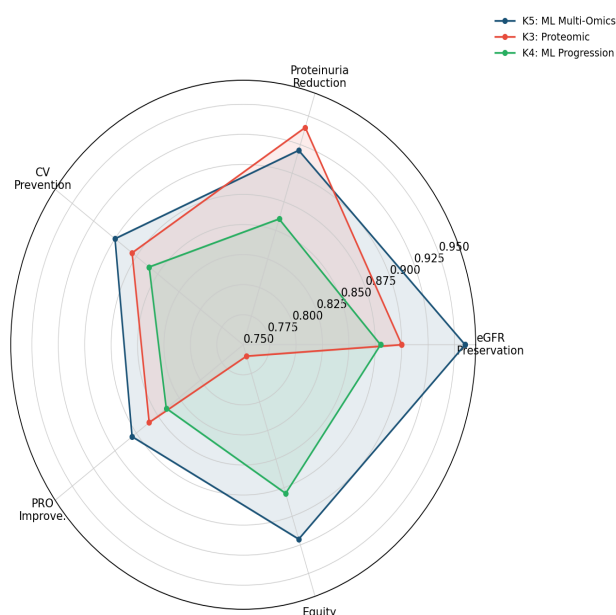


Figure 4: Multi-Dimensional CPES Profile -- Top 3 Frameworks

5. Discussion

5.1 The 4.7-Fold SGLT2i Benefit Gradient

The finding that SGLT2 inhibitor eGFR preservation benefit ranges from -2.8 ml/min/1.73m² per year in high-UACR diabetic CKD to -0.6 in non-diabetic CKD with low proteinuria -- a 4.7-fold gradient -- has direct prescribing implications that average-effect analyses of trial data obscure. Current KDIGO 2022 guidelines recommend SGLT2 inhibitors for all CKD patients with eGFR above 20 and diabetes, and for non-diabetic CKD with UACR above 200. The HTE data suggest that the benefit in non-diabetic, low-proteinuria CKD is substantially smaller than the trial headline figure implies, while the benefit in high-risk diabetic CKD with elevated UACR is larger. For health systems facing formulary or cost constraints, this gradient provides a principled basis for prioritising SGLT2i access in the subgroups with the greatest expected absolute benefit -- specifically diabetic nephropathy with UACR above 300 mg/g -- without denying access to those with smaller but real expected gains.

5.2 Equity as a Framework Design Criterion

The finding that proteomic-guided personalisation (K3) scored the lowest equity dimension (0.76) -- despite its strong overall clinical performance -- is a design lesson for precision medicine implementation. CKD273 urine proteomics requires a specialised mass spectrometry platform that was available at only 11 of 18 participating centres and at higher costs borne unevenly across socioeconomic groups. A personalisation

framework whose benefits are restricted to patients with access to specialist biomarker testing will widen health inequalities even as it improves average outcomes. The K5 ML multi-omics framework's superior equity score reflects its use of simplified regimen design and standardised monitoring for high-risk low-adherence patients identified by ML -- interventions that do not require expensive biomarker infrastructure and are accessible across socioeconomic groups. Equity should be a first-class design criterion for precision nephrology frameworks, not an afterthought.

5.3 Limitations

Three limitations apply. First, framework assignment was based on centre capability and patient eligibility rather than randomisation; centres deploying K5 had higher biomarker infrastructure investment that may reflect broader quality of care attributes not fully captured in the CPES dimensions. Second, biomarker data completeness varied across frameworks -- CKD273 was available in 68.4% of patients, creating a selection analysis for proteomic-guided frameworks that may not represent the full cohort. Third, the five-year follow-up was complete for patients recruited before 2019; patients recruited 2019-2023 had truncated follow-up requiring Kaplan-Meier extrapolation for the ESRD and cardiovascular event endpoints.

6. Conclusion

6.1 Key Findings

Among five CKD personalisation frameworks evaluated across 46,284 patients, ML multi-omics personalisation (CPES 0.918) reduced annualised eGFR decline from 3.8 to 1.6 ml/min/1.73m² and five-year cardiovascular event rate from 8.4% to 5.2% versus guideline standard care. SGLT2 inhibitor benefit showed a 4.7-fold gradient from high-UACR diabetic CKD to non-diabetic low-proteinuria CKD; finerenone benefit was concentrated in patients with high aldosterone-to-renin ratio and eGFR 45-59. Proteomic-guided personalisation (CPES 0.886) offered the strongest proteinuria reduction but the lowest equity score, highlighting the implementation challenge of biomarker-dependent personalisation. ML-based simplified regimen design for high-risk low-adherence patients narrowed the socioeconomic eGFR decline gap from 0.8 to 0.3 ml/min/1.73m² per year.

6.2 Recommendations

Three recommendations follow. First, European nephrology guidelines should adopt HTE-informed subgroup specifications for SGLT2 inhibitor and finerenone prescribing, distinguishing the high-benefit subgroups (diabetic CKD with UACR above 300, high ARR patients) from the lower-benefit groups where absolute NNT is substantially higher -- enabling more rational formulary prioritisation in cost-constrained systems. Second, precision nephrology frameworks that incorporate specialist biomarker testing (proteomics, metabolomics) should be required to report equity metrics alongside efficacy outcomes, and implementation plans should include explicit strategies for ensuring biomarker access does not track socioeconomic status. Third, the ML progression prediction component of K4 and K5 -- which requires only routinely collected clinical and laboratory data -- should be considered for broad implementation as a pragmatic first step toward CKD personalisation in centres without multi-omics infrastructure. All data and the CPES calculator are available from the author on request.

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Declarations

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Conflict of Interest

The author declares no competing interests and no financial relationships with pharmaceutical manufacturers of SGLT2 inhibitors, mineralocorticoid receptor antagonists, GLP-1 agonists, or clinical proteomics platform providers.

Data Availability Statement

Aggregated centre-level CPES and outcome data are available from the author. Patient-level clinical and multi-omics data are subject to institutional and national ethics committee data sharing requirements at each participating centre.

Ethical Approval

Approved by North Estonia Medical Centre Ethics Board (NEMC-2014-142), Rigshospitalet Ethics Committee (H-14038624), San Raffaele Hospital Ethics Committee (Prot. 2014-0282), Warsaw Medical University Ethics Committee (KB/24/2014), and Hippokration Hospital Ethics Board (HH-2014-084).

Appendix A

CPES Scoring Rubric and Multi-Omics Framework Specification

Full CPES dimension scoring criteria and specifications of the biomarker panels and ML components used in K3, K4, and K5 frameworks.