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Inside CKD: Cost-Effectiveness of Multinational Screening for CKD

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Introduction: Early detection of chronic kidney disease (CKD) could slow its progression; however, most patients in earlier stages remain undiagnosed. Our study objective was to assess the cost-effectiveness of multinational CKD screening strategies from the payer perspective across general and higher-risk populations.

Methods: Using the published Inside CKD microsimulation, we projected virtual closed populations to assess CKD screening strategies in 31 countries or regions over a lifetime horizon. We considered people aged ≥ 65 or ≥ 45 years in the general population and in high-risk subgroups (type 2 diabetes [T2D], hypertension, or cardiovascular disease [CVD]). Simulated populations could receive 2 serum creatinine (SCr) tests assessing estimated glomerular filtration rate (eGFR), "2 eGFR only", or an additional urinary albumin-to-creatinine ratio test (UACR), "2 eGFR and 1 UACR", versus current practice. Eligible patients received renin-angiotensin system inhibitors (RASi).

Results: Screening the general population aged ≥ 45 years for CKD was cost-effective versus current practice in all countries or regions using the "2 eGFR and 1 UACR" strategy, and cost-effective in all but 1 country using the 2 eGFR only strategy. The 2 eGFR and 1 UACR strategy showed consistently higher cost-effectiveness. Screening general populations aged ≥ 45 years increased projected CKD diagnosis rates per 100,000 persons eligible for screening from 459 by current practice to 7475 patients using 2 eGFR only, or 14,392 using 2 eGFR and 1 UACR. Similar trends in cost-effectiveness and diagnosis rates were observed in persons aged ≥ 65 years.

Conclusion: CKD screening may be cost-effective in general populations worldwide, including in populations aged ≥ 45 years. Our analysis corroborates global guideline recommendations for simultaneous eGFR and UACR testing if considered in the context of local factors.

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CKD has an estimated prevalence of 8% to 14% worldwide[1–4] and is a major concern to public health because prevalence increases in tandem with T2D, hypertension, CVD, and aging populations.[5] The burden of CKD increases substantially upon progression, particularly at kidney failure.[6,7] Advanced CKD severely affects health-related quality of life and leads to increased rates of mortality and complications such as myocardial infarction, heart failure, and stroke,[8] further compounding the pressure on healthcare systems.[9] CKD disproportionally affects vulnerable populations, including lower socioeconomic groups, who experience higher prevalence, limited access to treatments, and poorer outcomes.[10] Access to kidney

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replacement therapies (KRTs) is often limited, especially in low-or middle-income countries, leading to an estimated 2.3 to 7.1 million premature deaths in adults annually worldwide.[11-13]

Early detection could slow CKD progression by raising disease awareness and facilitating earlier intervention[14]; however, approximately 95.5% of patients with CKD stage G3 remain undiagnosed.[15] When diagnosing CKD, it is recommended that multiple patient-specific factors are considered, including the eGFR—based on SCr levels, age, race, and gender—as well as chronicity and the presence of albuminuria.[16] However, whereas routine eGFR and albuminuria testing is recommended in the T2D population, UACR is not routinely tested in any population in real-world clinical practice.[17]

A scoping review of available identification programs demonstrated a paucity of available policies to guide early identification of CKD worldwide, particularly in low-or middle-income countries.[18] Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference participants agreed that CKD meets the World Health Organization principles of screening for disease; early CKD is asymptomatic and there are accurate, low-cost diagnostic tests and effective treatments for early stages.[10]

The cost-effectiveness of screening for CKD has been assessed at the national-level in over 20 analyses incorporating variable scopes and/or modelling approaches.[19] These have reported mixed results dependent on intervention (testing for eGFR via and/or UACR via urinary albumin testing), considered populations, and methodological differences.[19] No published study has assessed the value of screening from a multinational perspective, and relatively few studies consider screening interventions outside of higher-risk subpopulations. Therefore, a validated, comprehensive global model is required to support robust evidence-based healthcare decision-making.

The Inside CKD program projects the prevalence and burden of CKD and can simulate hypothetical strategies at the population-level in medium-or high-income nations worldwide using a validated microsimulation model.[20] Our objective was to estimate the cost-effectiveness of systematic, early screening strategies to identify patients with CKD within the general population and higher-risk subpopulations from multinational payer perspectives.

METHODS

Model Overview

The Inside CKD microsimulation model projects virtual populations based on demographic, epidemiological, and economic data sources; detailed methodology, including sensitivity analyses and validation, has been published.[20] Our analysis assesses early screening, intervention upon CKD diagnosis, and progression rates at national population levels across 31 medium-or high-income countries worldwide. We present the epidemiological effects of screening over 10 years (2022–2032), evaluating health economic outcomes over a lifetime horizon. A schematic of the study framework is provided in Supplementary Figure S1, with a comprehensive schematic of the model published previously.[20]

Study Population

Simulated closed cohorts are representative of the total population for each country or region, exclusively including patients without diagnosed CKD at baseline because study interventions or comparators would not be applied to diagnosed patients and would therefore have no influence upon incremental results. We considered screening strategies in 2 age-defined general population cohorts: aged ≥ 65 years and ≥ 45 years. The general population aged ≥ 65 years comprises a typically higher-risk cohort, representing a more conservative approach (i.e., often more cost-effective).[21] General populations aged ≥ 45 years were assessed to investigate earlier intervention in a younger population. We also conducted subgroup analyses in higher-risk patients with comorbid hypertension, T2D, or CVD across age groups.

We ascribed demographic characteristics to individuals within a virtual population, including age and biological sex, comorbidities (T2D, hypertension), complications (myocardial infarction, stroke, and heart failure), and baseline eGFR and UACR values; baseline characteristics for the general populations aged ≥ 65 years and ≥ 45 years are defined in Supplementary Tables S1 and S2, respectively. Where available, we sourced characteristics from published local databases, identifying suitable imputed proxy data according to published algorithms if local data were unavailable.[20] Data sources for population parameters are published separately.[22]

These characteristics were used to assign individuals with a KDIGO-defined CKD stage, labelled as:

- No CKD
- CKD (stage G1–5, A1–3) by laboratory testing of eGFR and UACR; clinically undiagnosed
- CKD (stage G1–5, A1–3); clinically diagnosed.

Individuals with diagnosed or undiagnosed CKD were "tagged" with CKD-related comorbidity statuses (T2D, hypertension, or CVD).

Intervention and Comparators

We assessed 2 CKD screening strategies:

1. "2 eGFR only": 2 SCr tests in the index year to estimate a person's eGFR. Because eGFR is tested more commonly, it is more aligned to current the practice, and may be considered pragmatic.
2. "2 eGFR and 1 UACR": 2 SCr tests plus 1 urinary albumin test in the index year. The "gold standard" approach to CKD screening; testing for multiple disease markers is more likely to identify previously undiagnosed patients, based on KDIGO criteria or research.

We assumed both SCr tests were required to return a positive result for a diagnosis according to the "2 eGFR only" strategy (Supplementary Figure S2). For the "2 eGFR and 1 UACR" strategy, both eGFR tests or the UACR test were required to return a positive result (Supplementary Figure S3). We considered both strategies in pairwise analyses versus current practice, estimated according to published national diagnosis rates by CKD stage if available, otherwise imputed via relevant proxy data as described previously.[22] Background diagnosis rates were applied in the current practice setting and the systematic screening strategies. Undiagnosed persons may be diagnosed according to current practice every year. Individuals already diagnosed with CKD are not screened for CKD.

Sensitivities and specificities for eGFR and UACR tests were based on data for ENDORSE testing devices,[23] with true and false positives progressing to treatment; further details are available in the supplementary materials.

Disease Progression and Modelling of Pharmacological Treatment

We quantified CKD progression using eGFR trajectories derived from the DISCOVER CKD database.[20,24] As published previously, these estimates were adapted for the Inside CKD microsimulation model to assign eGFR trajectories to individual patients based on clinical characteristics or tags, and updated annually.[19] The microsimulation accounts for patients that experience CKD progression and cardiovascular complications in the same competing risk framework as mortality. Individuals with CKD stage 5 might also be subject to KRT (hemodialysis, peritoneal dialysis, or kidney transplant).

Modelling of CKD treatment was aligned to KDIGO 2012 guidelines, the most up-to-date guidance at the time of model development.[25] We assigned RASi treatment (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers) accordingly:

- Patients with CKD and hypertension, regardless of UACR value
- Patients with CKD and T2D with UACR $\geq$ 30 mg/g
- Patients with CKD with or without comorbidities, if UACR $\geq$ 300 mg/g.

Patients could already be receiving treatment because of other preexisting conditions; however, individuals who met the eligibility criteria but were not yet enrolled could be initiated on RASi. The effects of treatment, including slowed eGFR decline and reduced mortality, are based on a published meta-analysis of randomized controlled trials.[26]

Further details on the dynamics of disease progression and RASi treatment are provided in the Supplementary Material, with data sources for disease progression and cardiovascular risk detailed in a separate publication.[22]

Cost and Health Care Resource Use

We considered national health care system payer perspectives, so only direct costs were incorporated. We derived country- or region-specific direct healthcare costs applied to modeled health states (defined by CKD stage, KRT modality, and complication events) from a published review.[7] This review identified costs in cooperation with local research organizations via pragmatic literature searches for the Inside CKD research program. Local clinical experts validated cost data in conjunction with the Inside CKD scientific steering committee (Supplementary Table S3); further details on health state cost parameters are detailed in the Supplementary Material. The cost of screening and RASi treatment were derived from local costs for urinary albumin tests, primary care visits, SCr tests, and nurse consultations (Supplementary Tables S4 and S5). We expressed cost estimates in local currency units adjusted to 2022 prices according to the gross domestic product deflator data from the International Monetary Fund, accounting for purchasing power parity.[27] We applied discount rates for costs aligned to current practice in each counter or region, validated by local experts (Supplementary Table S6).

Health-Related Quality of Life

We estimated universal utility weights for all countries or regions, based on EQ-5D, for patients dependent on their CKD stages and comorbidities or complications (Supplementary Table S7).[28-32] We employed a minimum algorithm by which a patient with multiple comorbidities or complications would be assigned the lowest utility weight of these disease states. Quality-adjusted life years (QALYs) were determined by applying this utility weight to the life years gained by intervention. We applied discount

rates for benefits aligned to current practice in each country/region, validated by local experts (Supplementary Table S6).

Analysis

Modeled clinical outcomes included CKD diagnosis rates after 1 year and incremental epidemiological outcomes (vs. current practice) 10 years postscreening:

- Prevalence of people receiving KRT
- Cumulative incidence of progression through eGFR-defined CKD stages
- Cumulative incidence of cardiovascular complications.

Clinical outcomes and benefits were presented as averages across the 31 countries or regions, providing ranges where possible, scaled to 100,000 people not previously diagnosed with CKD eligible for screening. Outcomes represent the entire cohort of 100,000 people, regardless of whether they are screened in the first year, thus capturing people who do not visit a primary care physician in the year of screening and those who do not agree to CKD testing.

Principal economic outcomes were pairwise incremental cost-effectiveness ratios for "2 eGFR only" and "2 eGFR and 1 UACR" strategies versus current practice, calculated over a lifetime horizon based on the net difference between incremental costs incurred divided by the QALYs gained. The "willingness-to-pay" (WTP) thresholds were aligned to current practice based on local expert opinion and publications (Supplementary Table S6); conservative values were applied if specific guidelines were unavailable. To consider the relative value of "2 eGFR only" and "2 eGFR and 1 UACR" strategies, we calculated the net monetary benefit (NMB, incremental QALYs gained multiplied by the WTP threshold and then subtracting the incremental total lifetime cost per person). A positive NMB indicates that the intervention is cost-effective versus current practice at the specified WTP threshold, with the more positive value estimated for each scenario indicative of better value.

Sensitivity analyses have been carried out in previous publications on eGFR slopes, relative risks, diagnosis rates, and KRT incidence rates that demonstrated that model outcomes were robust to alterations to applied disease progression parameters.[20] Given previous validation exercises, prior assessment of key model parameters, broad scope of analyses, further parametric sensitivity analyses specific to the presented cost-effectiveness analysis were limited to the assessment the bidirectional impact of a 10% variance for cost and utility inputs.

RESULTS

Diagnosis Rates

Screening by "2 eGFR only" or "2 eGFR and 1 UACR" was expected to substantially increase the incidence rate of CKD diagnoses versus current practice in 31 countries/regions across both general populations (Table 1; Supplementary Table S8 for outcomes by country/region).

In the general populations aged ≥ 65 years, testing via "2 eGFR only" identified a mean of 13,260 incident cases of CKD per 100,000 eligible persons in year 1, versus 629 if detected only by current practice. Of incident cases, 7774 persons who were untreated at baseline were initiated with RASi therapy. If screened via "2 eGFR and 1 UACR", a mean of 22,554 cases were identified per 100,000 eligible persons, of whom 13,553 were subsequently treated with RASi therapy.

Screening the general population aged ≥ 45 years was expected to lead to a lower proportion of CKD diagnoses per 100,000 people, due to the age-associated risk of CKD. We estimated screening via "2 eGFR only" to lead to a mean of 7475 patients diagnosed per 100,000 eligible persons, versus 459 patients according to current practice alone. Of these, 3973 patients otherwise untreated would receive RASi treatment. Screening via "2 eGFR and 1 UACR" led to 14,392 mean incident cases of CKD per 100,000 eligible persons; 8111 were eligible to receive RASi treatment.

Disease Progression

The increased diagnosis rates from screening in the general population led to higher overall prevalence of diagnosed CKD in both age-defined populations and current practice. Patients with diagnosed and treated CKD experienced slower disease progression and longer life expectancy, contributing to greater prevalence of CKD in the modeled populations over time through reduced mortality. There was an incremental decrease in the prevalence of KRT initiation in the initial years after screening (Figure 1), which began to reverse because more patients who survived as a result of screening progressed to kidney failure in the longer-term. The effect was more sustained in populations screened with "2 eGFR and 1 UACR", due to increased rates of early diagnosis.

Both screening strategies led to higher cumulative incidence of progression to stages 3b and 4 from earlier stages over the initial 10 years through higher rate of diagnosis in earlier stages and lower rates of mortality in combination with progression despite RASi treatment (Supplementary Figure S4). In line with estimates shown in Figure 1, progression to stage 5 was reduced for both strategies in general populations aged ≥ 65

Table 1. Mean (range) diagnosis rates per 100,000 members of the general population eligible for screening across 31 countries/regions in the year of screening

Outcome	Current practice	2 eGFR only	2 eGFR and 1 UACR
General population aged ≥ 65 yrs			
Diagnosed via strategy			
RASi	N/A	7774 (2430–15,872)	13,553 (3531–22,638)
Untreated	N/A	5008 (853–9454)	8575 (1294–15,329)
Diagnosed via current practice	629 (214–1,056)	470 (166–811)	419 (108–736)
Screened, positive	629 (214–1,056)	13,260 (3714–22,581)	22,554 (5236–38,142)
Screened, negative	N/A	57,773 (14,881–81,076)	48,478 (13,361–64,886)
General population aged ≥ 45 yrs			
Diagnosed via strategy			
RASi	N/A	3973 (1076–8715)	8111 (2151–14,799)
Untreated	N/A	3111 (882–8296)	5944 (2064–10,608)
Diagnosed via current practice	459 (155–748)	391 (90–686)	337 (120–649)
Screened, positive	459 (155–748)	7475 (2603–17,101)	14,392 (4399–25,350)
Screened, negative	N/A	64,878 (31,253–91,132)	57,961 (26,178–82,986)

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; RASi, renin-angiotensin system inhibitor; UACR, urine albumin to creatinine ratio.
The simulated cohort comprised only people without a CKD diagnosis who are eligible for screening and not all patients are assumed to undergo screening. After enrolment of screening in year 1, these values will correspond to all incident patients subsequently diagnosed with CKD. Hence, the smaller values relating to current practice will reflect new diagnoses according to current pathways for diagnosis in each country or region and will not include the prevalent population diagnosed with CKD before the simulation.

and those aged ≥ 45 years. In populations screened via "2 eGFR and 1 UACR," progression through earlier CKD stages (1–3a) also varied over the initial 10 years versus current practice, because of increased diagnosis rates of patients with milder eGFR impairment and elevated UACR.

Cardiovascular Burden

Despite higher CKD diagnosis rates achieved via "2 eGFR only" and "2 eGFR and 1 UACR" strategies, the rates of heart failure, myocardial infarction, and stroke were not predicted to decrease. In most countries or regions, rates slightly increased per 100,000 eligible persons in the 10 years after screening (Table 2), equating to a mean increase of 0% to 2% versus current practice, despite increased initiation of RASi treatment in eligible patients who were not already enrolled at baseline. Prolonged life expectancy through improved management of CKD, in tandem with the residual cardiovascular risk despite RAS blockade,[33] led to similar outcomes with "2 eGFR only" or "2 eGFR and 1 UACR" as compared with the current practice.

Health Economic Outcomes

Health Benefits

Accrual of incremental life years and QALYs over time versus current practice is presented in Figure 2, with modest increases for both "2 eGFR only" and "2 eGFR and 1 UACR" strategies when averaged across general populations. The benefits to life expectancy and QALYs were typically realized over 10 to 15 years after screening in the general population aged ≥ 65 years, with benefits accrued more slowly in the general population aged ≥ 45 years.

Per person aged ≥ 65 years screened via "2 eGFR only," we observed an incremental increase in life expectancy (mean: 0.07, range: 0.02–0.14 years) versus current practice, increasing further if screened via "2 eGFR and 1 UACR" (mean: 0.12, range: 0.03–0.22 years). This effect was observed to a lesser extent in the general population aged ≥ 45 years after screening through either "2 eGFR only" (mean: 0.03, range: 0.01–0.06 years) or "2 eGFR and 1 UACR" (mean: 0.08, range: 0.03–0.14 years) strategies versus current practice, due to the lower prevalence of CKD in this population at baseline.

Similarly, mean incremental QALYs per member of the general population aged ≥ 65 years were 0.05 (range: 0.01–0.09 years) and 0.08 (range: 0.02–0.14 years) if screened via "2 eGFR only" and "2 eGFR and 1 UACR" strategies, respectively. In the general population aged ≥ 45 years, mean incremental QALYs were 0.02 (range: 0.00–0.04 years) and 0.05 (range: 0.02–0.10 years) for "2 eGFR only" and "2 eGFR and 1 UACR" strategies, respectively, versus current practice.

Measures of Cost-Effectiveness

In the general population aged ≥ 65 years, screening was considered cost-effective in all countries or regions and all populations versus current practice for both the "2 eGFR only" and "2 eGFR and 1 UACR" strategies (Figure 3a). Incremental cost-effectiveness ratios were consistently lower if patients were screened via the "2 eGFR and 1 UACR" strategy versus the "2 eGFR only" strategy (Table 3).

In the general population aged ≥ 45 years, screening according to "2 eGFR and 1 UACR" was considered cost-effective in all countries or regions at the defined WTP thresholds versus current practice. The "2 eGFR

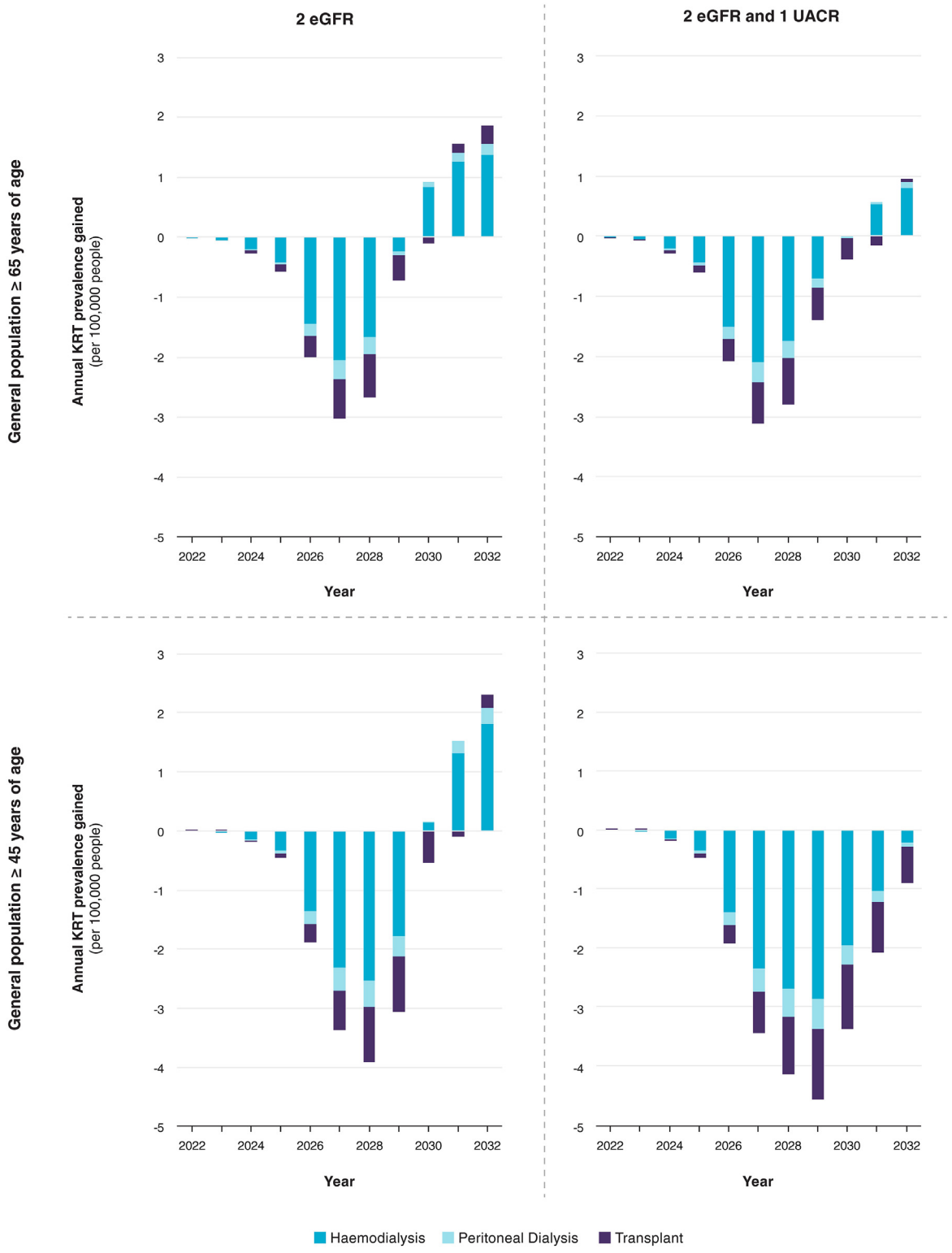

Figure 1. Incremental change in kidney replacement therapy (KRT) prevalence by modality in the general population per 100,000 people by screening strategy (unweighted average across considered 31 countries or regions). The simulated cohort comprised only people without a CKD diagnosis who are eligible for screening and not all patients are assumed to undergo screening. Negative values indicate an incremental decrease in the number of individuals initiating KRT resulting from a screening strategy compared to current practice. CKD, chronic kidney disease; eGFR: estimated glomerular filtration rate; KRT, kidney replacement therapies; UACR: urine albumin-to-creatinine ratio.

only" strategy was considered cost-effective in all countries except Saudi Arabia, driven partly by lower average age, lower RASi eligibility, and higher screening and healthcare costs than other countries or regions. In cost-effective scenarios, the NMB of "2 eGFR and 1 UACR" was consistently greater than that

Table 2. Mean incremental cardiovascular events gained per 100,000 members of the general population across 31 countries *or* regions by strategy received

	2 eGFR only, mean (range)		2 eGFR and 1 UACR, mean (range)	
Outcome	*n*	%	*n*	%
General population aged ≥ 65 yrs				
HF	65.3 (0.0–169.0)	0.93% (0.00%–2.27%)	102.0 (0.0–238.3)	1.48% (0.00%–2.84%)
MI	47.5 (0.5–128.1)	0.84% (0.18%–1.63%)	72.2 (2.2–173.9)	1.29% (0.51%–2.10%)
Stroke	48.6 (1.1–103.9)	0.91% (0.16%–1.86%)	77.5 (2.0–156.6)	1.48% (0.23%–2.79%)
General population aged ≥ 45 yrs				
HF	24.8 (−1.6 to 69.3)	0.52% (−0.04% to 1.35%)	40.4 (1.0–106.1)	0.85% (0.05%–1.86%)
MI	17.6 (0.1–51.7)	0.40% (0.05%–0.97%)	28.4 (1.1–63.3)	0.64% (0.17%–1.28%)
Stroke	18.2 (0.8–45.1)	0.50% (0.11%–1.08%)	30.1 (3.0–68.7)	0.83% (0.16%–1.55%)

eGFR, estimated glomerular filtration rate; HF, heart failure; IQR, interquartile range; MI, myocardial infarction; UACR, urine albumin to creatinine ratio.

of "2 eGFR only" (Table 3, Figure 3b) versus current practice, indicating "2 eGFR and 1 UACR" may represent better value to healthcare systems.

We present health economic outcomes over a lifetime horizon by country or region in the supplementary materials for the general populations aged ≥ 65 years (Supplementary Table S9) and those aged ≥ 45 years (Supplementary Table S10).

Subgroup Analysis

In patients with preexisting T2D, hypertension, or CVD, both screening strategies would be considered

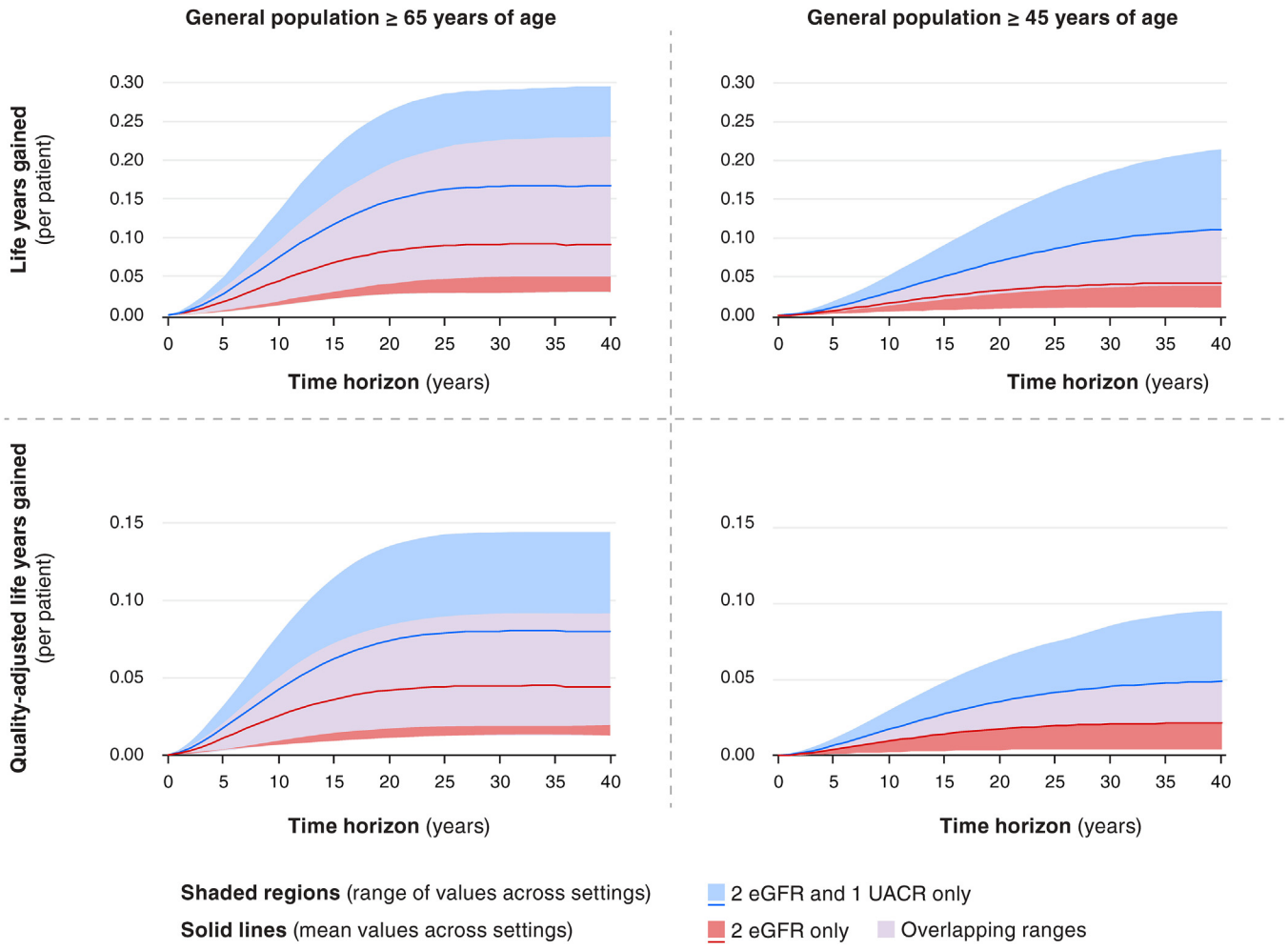

Figure 2. Incremental per-patient accrual of LYs and QALYs in the general population after screening for CKD. Solid lines represent the mean value across 31 countries or regions, the shaded regions pertain to the range of values observed in the base case analyses across countries. LY, life years; QALY, quality-adjusted life year.

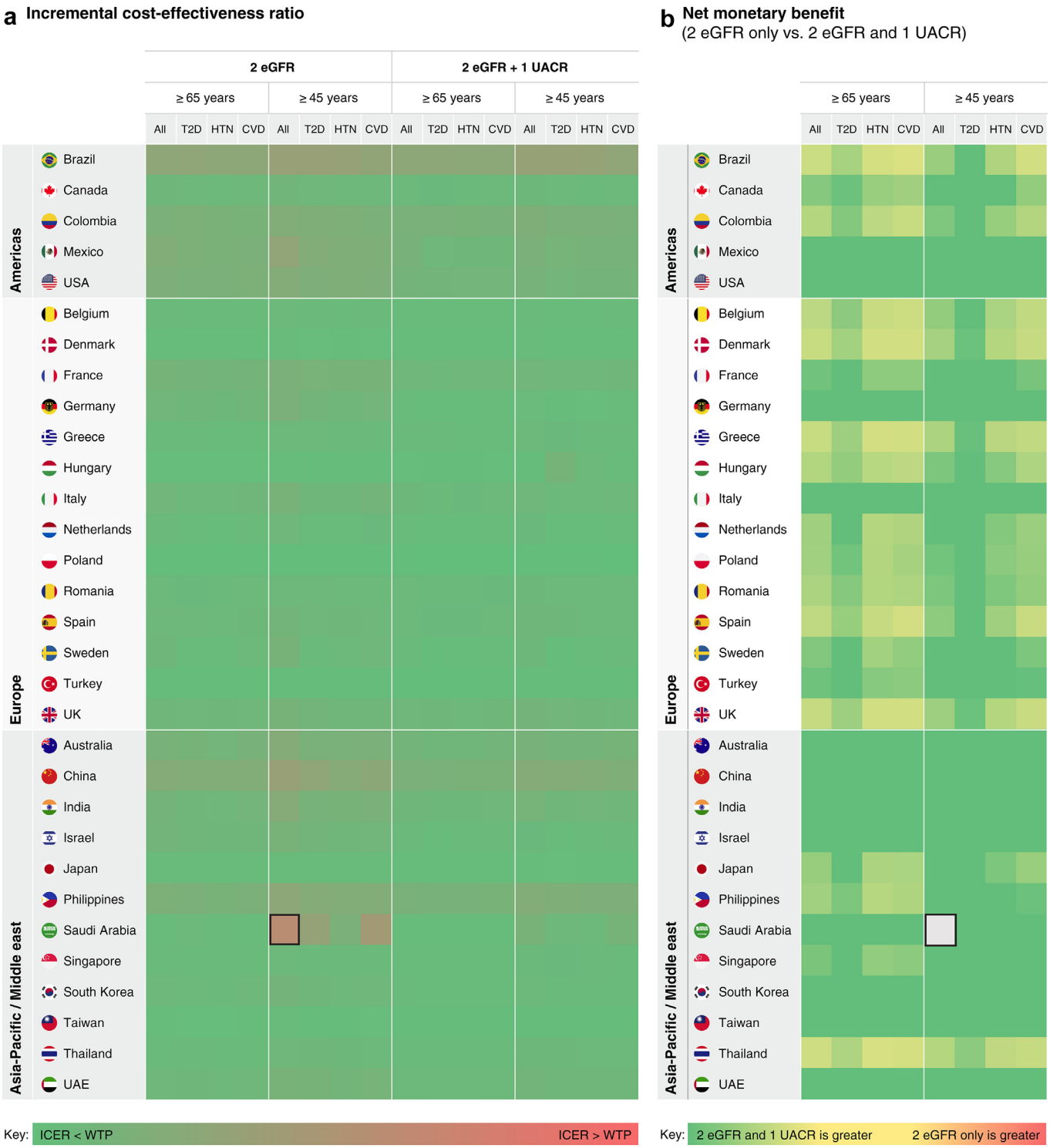

Figure 3. Cost-effectiveness of screening, in general population and high-risk subgroups, across 31 countries or regions, expressed as (a) pairwise ICERs as a function of WTP threshold versus current practice, (b) incremental net monetary benefit between the pairwise analyses. Green color indicates an incremental cost-effective ratio that is below the *WTP* threshold meaning that the strategy would be considered cost-effective according to the study criteria, with bordered squares indicating analyses that were not considered cost-effective. The net monetary benefit characterizes the relative value of cost-effective screening interventions and suits evaluation of pairwise analyses. Green color indicates that the net monetary benefit of the "2 eGFR and 1 UACR" is at least double the "2 eGFR only" strategy, yellow color indicates that they are comparable, and red indicates that "2 eGFR only" strategies are better value. CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HTN, hypertension; ICER, incremental cost-effectiveness ratio; T2D, type 2 diabetes; WTP, willingness-to-pay threshold; UACR, urine albumin-to-creatinine ratio; UAE, United Arab Emirates; UK: United Kingdom; USA: United States of America.

Table 3. Primary health economic outcomes in the general population

		General population aged ≥ 65 yrs				General population aged ≥ 45 yrs			
		2 eGFR only		2 eGFR and 1 UACR		2 eGFR only		2 eGFR and 1 UACR	
Country or region (currency)	WTP	ICER (/QALY)	NMB	ICER (/QALY)	NMB	ICER (/QALY)	NMB	ICER (/QALY)	NMB
Australia (AUS, $)	50,000	15,306	883	11,359	2158	22,991	311	15,349	1137
Belgium (EUR, €)	35,950	3889	2355	3292	3392	4755	1201	3623	2034
Brazil (BRL, R$)	36,635	21,438	1392	20,781	1867	26,356	364	25,638	600
Canada (CAD, $)	50,000	8480	2468	6475	4392	10,668	1139	7237	2624
China (CNY, ¥)	67,304	16,702	688	12,098	2552	25,585	168	16,845	1201
Colombia (COP, $)	17,000,000	5,795,830	150,048	5,349,321	222,298	7,441,001	168,597	6,514,030	309,009
Denmark (DKK, kr.)	426,762	27,823	29,549	25,804	40,322	34,817	14,091	31,152	22,302
France (EUR, €)	21,686	5511	824	3982	1584	7158	396	4578	992
Germany (EUR, €)	30,000	6335	546	2419	2173	9923	235	2822	1544
Greece (EUR, €)	17,140	1787	839	1712	1142	2220	405	2097	629
Hungary (HUF, Ft.)	7,382,730	335,696	468,442	299,152	704,749	410,026	226,494	354,162	416,771
India (INR, ₹)	668,314	166,160	6525	112,990	23,216	320,388	1486	170,748	10,058
Israel (ILS, ₪)	135,660	30,156	3793	15,192	13,399	40,163	1612	16,103	9417
Italy (EUR, €)	30,000	6287	547	4351	1280	8962	245	5315	749
Japan (JPY, ¥)	5,000,000	415,171	133,723	316,964	223,289	450,030	74,583	330,947	154,896
Mexico (MXN, $)	204,893	84,352	3030	60,487	8162	127,249	775	68,338	5003
Netherlands (EUR, €)	20,000	2242	941	1774	1526	3528	442	2382	888
Philippines (PHP, ₱)	120,000	41,887	2795	37,240	4486	69,189	583	51,879	1634
Poland (PLN, zł)	166,758	3276	6481	3347	10,401	4473	3241	4401	6184
Romania (RON, lei)	69,401	9103	1135	8618	1751	10,808	758	10,175	1398
Saudi Arabia (SAR, ر.س)	90,000	7448	3403	4963	8580	103,753	−306	26,895	4576
Singapore (SGD, S$)	101,288	10,166	6663	9245	12,366	12,739	2566	11,860	6292
South Korea (KRW, ₩)	25,000,000	4,024,976	400,427	2,367,052	1,188,912	6,242,044	190,559	3,180,216	753,236
Spain (EUR, €)	30,000	4659	1753	3973	2473	6570	746	5102	1282
Sweden (SEK, kr)	702,000	115,739	18,597	74,416	33,486	192,966	8375	101,268	20,503
Taiwan (NTD, $)	2,985,272	177,421	55,869	120,172	247,007	229,486	31,259	156,490	185,833
Thailand (THB, ฿)	160,000	17,117	12,005	16,095	15,815	25,937	5917	23,582	8764
Turkey (TRY, ₺)	257,016	8584	17,047	6874	32,942	10,140	6492	8084	21,049
UAE (AED, د.إ)	133,255	24,847	6309	18,594	16,522	40,560	2866	28,629	10,073
UK (GBP, £)	20,000	3954	1057	3678	1451	5462	449	4851	733
USA (USD, $)	50,000	18,615	1583	12,115	4555	22,737	726	13,303	3334

eGFR, estimated glomerular filtration rate; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALY, quality-adjusted life year; UACR, urine albumin-to-creatinine ratio; UAE, United Arab Emirates; UK, United Kingdom; USA, United States of America; WTP, willingness-to-pay threshold.

cost-effective compared to current practice in populations aged ≥ 65 years or those aged ≥ 45 years (Figure 3a). In line with general population analyses, NMB was consistently greater if patients were screened via "2 eGFR and 1 UACR" over "2 eGFR only" (Figure 3b), particularly in T2D subpopulations.

Scenario Analysis

Generally, cost-effectiveness of "2 eGFR only" and "2 eGFR and 1 UACR" versus current practice was realized within 5 to 10 years from baseline (Figure 4) and was faster in the general population aged ≥ 65 years.

Sensitivity Analysis

Model outcomes were generally most sensitive to variations in RASi treatment costs in subsequent years after screening, costs relating to patients who were screened but RASi-ineligible, and utility parameters relating to patients aged ≥ 65 years and those with hypertension. However, variation of individual parameters did not affect cost-effectiveness outcomes.

DISCUSSION

Early screening for CKD can lead to optimized disease management and facilitate earlier therapeutic intervention to improve patient outcomes. Correspondingly, there is a need to consider the value of screening strategies by SCr testing alone or with UACR assessments, per international guidelines.[16] Our analyses indicate that population-level screening may be cost-effective, despite increased lifetime costs in all settings because of the cost of screening, with all strategies considered to be cost-effective in both age groups in middle-income countries. Incremental cost-effectiveness ratios were proportionally closer to WTP thresholds than in high-income countries, indicating that affordability and healthcare service delivery may be more challenging. We note that conclusions are subject to change as new WTP thresholds are specified

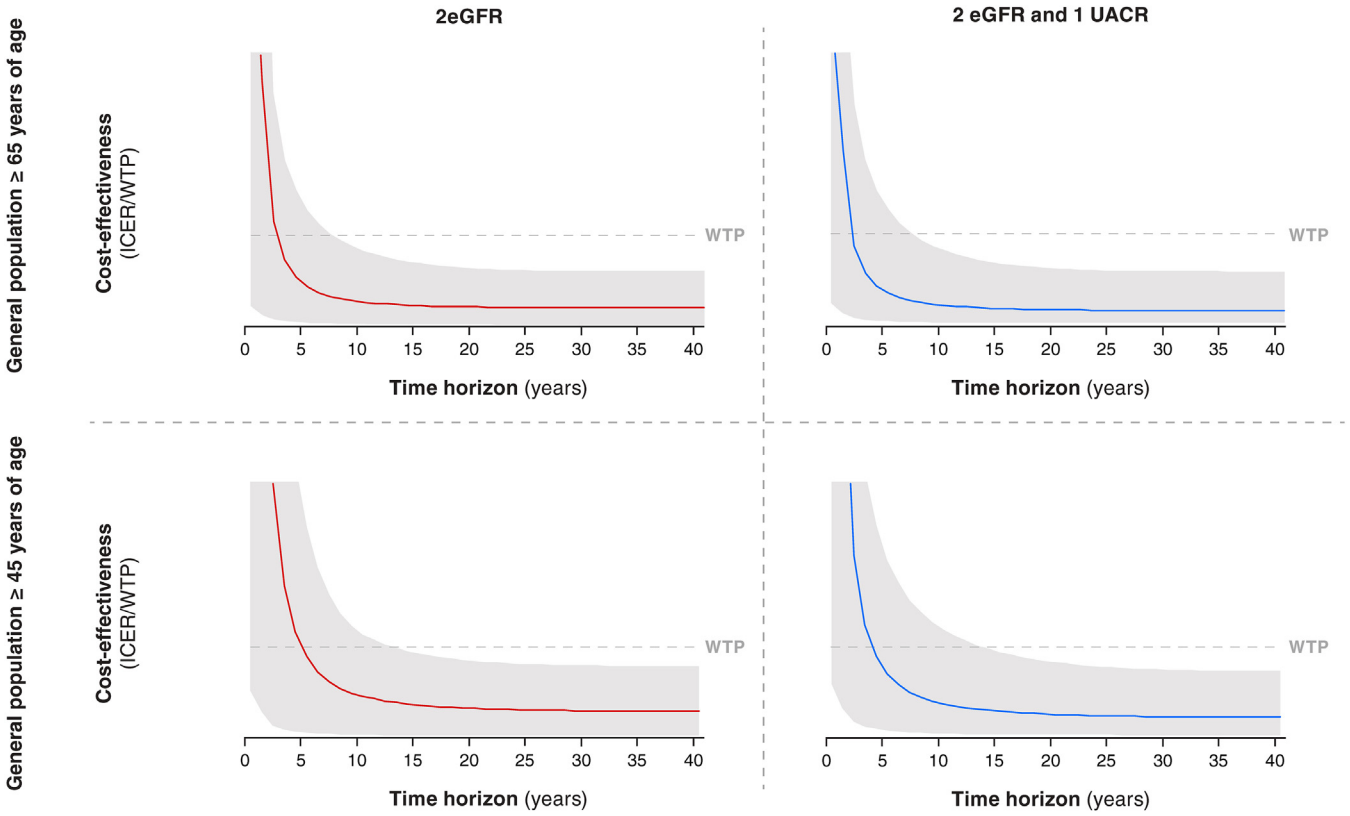

Figure 4. Evolution of the cost effectiveness of screening over time for the "2 eGFR only" (red) and "2 eGFR and 1 UACR" (blue) strategies in the general population across 31 countries or regions. Solid lines indicate the mean value across countries or regions; the grey shaded area indicates the range of estimates across the 31 countries or regions; the grey dotted line indicates the WTP threshold, with cost-effective estimates falling below the line. Screening occurs in the index year, with outcomes assessed in subsequent years. eGFR, estimated glomerular filtration rate; ICER, incremental cost-effectiveness ratio; UACR, urine albumin to creatinine ratio; WTP, willingness-to-pay threshold.

(e.g., for Saudi Arabia[34] and the United Arab Emirates).[35]

In all countries, measuring UACR in addition to eGFR was cost-effective in the general population aged ≥ 65 years and aged ≥ 45 years and in all subgroups. Most were cost-effective if only assessing eGFR, however urinary albumin testing consistently led to better outcomes and greater NMB versus current practice, driven by diagnosis of more patients with milder eGFR impairment still at risk of progression, in whom early intervention is critical. This approach is aligned to international guidelines,[16] and supports implementation as standard practice for CKD detection and management. There are greater considerations for earlier testing in certain populations, such as Hispanics and Pacific Islanders in Mexico, who are subject to additional risk factors and are otherwise unlikely to be diagnosed.[36,37]

The study findings demonstrate the importance of timely diagnosis of interconnected complications in patients with CKD, T2D, hypertension, and CVD, and subsequent adherence to treatment guidelines, with previous studies showing inconsistent application of pharmacological therapy in line with treatment guidelines.[38–42] Extended life expectancy through enrolment on RASi therapies and improved management of CKD in diagnosed patients contributed to improving patient health-related quality of life. However, QALY gains averaged across the general population were modest due to the continued presence of CKD and increased life expectancy in which cardiorenal complications occurred, broadly in alignment with previous analyses.[21,43–47] This highlights the necessity for improvements to current practice by treating eligible patients beyond RASi alone to address cardiovascular risk and improve glycemic management (in T2D), with a recent analysis demonstrating that treating newly diagnosed patients with sodium-glucose cotransporter 2 inhibitors can be cost-effective in the US.[48]

According to a recent systematic review, published analyses of screening interventions were generally cost-effective for comorbid disease populations and higher-risk or vulnerable ethnic populations, with less consistent agreement in the general population.[19] Disparities may be attributed to differences in screening interventions, methodological inconsistencies, and modeling approaches. For example,

screening was not cost-effective in the US general population[45] but was in people with diabetes,[45] hypertension,[43] and obesity.[47] A Canadian analysis of SCr testing was cost-effective in a T2D population,[21] whereas another Canadian analysis showed urinary albumin testing was cost-effective.[44] Population-level urinary albumin testing in Japan and Netherlands was considered cost-effective, including in patients aged < 65 years.[46,49] A previous analysis has focused specifically upon rural indigenous populations in Canada. In this vulnerable population, remote communities with less access to care showed greater cost-effectiveness of screening strategies, highlighting the importance of tailored local strategies that account for access to care to be cost-effective.[44]

The presented modeling analysis is subject to certain limitations, including reliance on published data that are associated with uncertainty. The analysis only considers historical standard therapy and did not account for emerging therapies, which should be assessed in future analyses. Identification of patients with CKD can improve access to cardiorenal protective therapies with or without T2D, including emerging treatment options such as sodium-glucose cotransporter 2 inhibitors, or mineralocorticoid receptor antagonists for diabetic kidney disease.[50-52] Furthermore, the influence of RASi on the cost-effectiveness of screening was not considered in sensitivity analyses. Incorporating cystatin C testing can lead to more accurate GFR estimation[53]; however, it was not incorporated because it is not systematically used and may lead to prohibitive additional costs in low- or middle-income countries.[54] A paucity of adequate reporting in the literature of uncertainty on input data, and complexity and nonlinearity of the microsimulation, meant conducting probabilistic sensitivity analyses was not feasible.[7,55] Local evaluations may differ from country-level cost-effectiveness results due to factors such as access to screening, the presence of vulnerable populations, or local budget constraints, and these present as limitations to the analysis. Inequities exist in the treatment of CKD, which can affect access to care[56]; these were not considered in the present analysis. Country-specific data on access to care were used within the model, however the local numbers may differ from the country averages. Finally, it should be noted that cost-effectiveness should not be considered as a binary assessment, rather a probability of cost-effectiveness at a specified WTP threshold. Therefore, cost-effectiveness is limited when considered in isolation of other factors such as local budgets that may not follow established WTP thresholds and service delivery.[57]

Conclusion

We report the largest international cost-effectiveness analysis of CKD screening conducted to date, using a validated microsimulation model.[20] Our analyses show that screening could be cost-effective in the general population aged ≥ 65 years, and in people as young as 45 years in most settings. In addition, our analysis supports albuminuria testing in addition to SCr testing, showing greater NMB when UACR testing is included across settings. Outcomes are supportive of the KDIGO "case for early identification and intervention of CKD."[10] Improvements to historical standard of care could improve cardiorenal outcomes further, with emerging therapies contributing to the alleviation of the substantial healthcare burden of CKD.

DISCLOSURE

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DATA AVAILABILITY STATEMENT

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at: https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

AUTHOR CONTRIBUTIONS

LR and JJGS conceptualized and designed the study. LR, JC-G and TC were responsible for data analysis. NT, K-HO, JC, MJ, JÄ, MB, CFC, GC, LR, JC-G, TC, SB, SN, and JJGS contributed to interpretation of the results, preparation and review of the manuscript, as well as approval of the final manuscript for publication.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Supplementary References.

Figure S1. Analytical framework.

Figure S2. Screening intervention "2 eGFR only": 2 serum creatinine tests per year.

Figure S3. Screening intervention "2 eGFR and 1 UACR": 2 serum creatinine tests and one urinary albumin test per year.

Figure S4. Incremental progression to eGFR-defined CKD stages in the general population per 100,000 screened participants by screening strategy across 31 countries or regions.

Table S1. Baseline characteristics for undiagnosed population eligible for screening (general population aged ≥ 65 years), by country or region, per 100,000 people.

Table S2. Baseline characteristics for undiagnosed population eligible for screening (general population aged ≥ 45 years), by country/region, per 100,000 people.

Table S3. Inside CKD Scientific Steering Committee.

Table S4. Input costs for screening and treatment.

Table S5. Total screening and treatment costs per patient.

Table S6. Country- or region-specific health economic parameters.

Table S7. Health state utility weights by CKD stage, comorbidity, and complication.

Table S8. Diagnosis and treatment rates by country or region, per 100,000 people eligible for screening over 10 years.

Table S9. Health economic outcomes in the overall population aged ≥ 65 years.

Table S10. Health economic outcomes in the overall population aged ≥ 45 years.

CHEERS Checklist.

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