Genome-wide polygenic score with APOL1 risk genotypes predicts chronic kidney disease across ancestries

Supplementary Information

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Supplementary Tables

Supplementary Table 1: Association of candidate polygenic scores with CKD in the first UKBB optimization dataset (70% of UKBB Europeans). Odds ratio (OR) per standard deviation (SD) of each risk score, and area under the receiver-operator curve (AUC) were calculated in the UKBB optimization dataset of 177,208 Europeans with adjustment for age, sex, diabetes, first four principal components of ancestry and genotyping batch; AUC crude and variance explained are calculated for the risk score component alone without any covariates; r^2: linkage disequilibrium pruning threshold; ρ-tuning parameter to model the proportion of variants assumed to be causal; the best performing score is highlighted in red. Variance explained is estimated as a Nagelkerke pseudo R^2 and refers to the variance in case-control status. The best model is highlighted in bold.

Method	Parameter	N variants	OR* per SD of GPS	P-value	AUC (Adjusted*)	AUC (Crude)	Variance Explained
P+T	P=1.0E-01	89,880	1.85	P<1.00E-300	0.8383	0.6505	0.0436
P+T	P=1.0E-02	21,764	1.84	P<1.00E-300	0.8391	0.6516	0.0440
P+T	P=1.0E-03	7,486	1.79	P<1.00E-300	0.8371	0.6443	0.0404
P+T	P=1.0E-04	3,598	1.78	P<1.00E-300	0.8366	0.6419	0.0393
P+T	P=1.0E-05	2,111	1.76	P<1.00E-300	0.8357	0.6393	0.0376
P+T	P=1.0E-06	1,407	1.75	P<1.00E-300	0.8355	0.6383	0.0369
P+T	P=1.0E-07	1,028	1.75	P<1.00E-300	0.8352	0.6380	0.0367
P+T	P=1.0E-08	753	1.73	P<1.00E-300	0.8343	0.6354	0.0352
P+T	**P=3.0E-02**	**41,426**	**1.86**	**P<1.00E-300**	**0.8391**	**0.6524**	**0.0448**
P+T	P=3.0E-03	11,918	1.82	P<1.00E-300	0.8383	0.6490	0.0427
P+T	P=3.0E-04	4,971	1.79	P<1.00E-300	0.8370	0.6434	0.0400
P+T	P=3.0E-05	2,675	1.76	P<1.00E-300	0.8360	0.6401	0.0383
LDPred	ρ=1.0E+00	5,440,627	1.83	P<1.00E-300	0.8377	0.6506	0.0430
LDPred	ρ=1.0E−01	5,440,627	1.20	P=1.14E-44	0.8159	0.5470	0.0039
LDPred	ρ=1.0E−02	5,440,627	1.16	P=1.06E-29	0.8153	0.5390	0.0025
LDPred	ρ=1.0E−03	5,440,627	1.14	P=1.36E-23	0.8148	0.5326	0.0020
LDPred	ρ=3.0E−01	5,440,627	1.72	P<1.00E-300	0.8330	0.6345	0.0341
LDPred	ρ=3.0E−02	5,440,627	1.12	P=1.01E-18	0.8146	0.5285	0.0015
LDPred	ρ=3.0E−03	5,440,627	1.17	P=1.25E-31	0.8152	0.5385	0.0027

* Adjusted for age, sex, diabetes, the first four principal components of ancestry and genotyping batch.

Supplementary Table 2: Mutually-adjusted effects for *APOL1* risk genotype and the best GPS from the first optimization cohort when tested in the second optimization cohort of African ancestry for association with CKD stage 3 or above.

Model *	Effect (β)	OR (95% CI)	P-value
Standardized GPS	0.15	1.16 (1.09-1.24)	P=1.0E-04
APOL1 risk genotype	0.17	1.19 (1.01-1.38)	P=4.0E-02
GPS and *APOL1* risk genotype interaction	0.09	1.09 (0.93-1.28)	P=0.29 (NS)

* adjusted for age, sex, diabetes, four principal components of ancestry, and genotyping batch.

Supplemental Table 3: GPS performance meta-analysis for testing cohorts of European ancestry (14,201 cases and 82,849 controls in total)

Cohort	Case/control	OR per SD (95% CI), P-value	AUC (Crude)	PRS Threshold	Odds ratio (95% CI), P value
UKBB	2,759/72,968	1.82 (1.78-1.86), P=1.32E-190	0.84 (0.65)	Top 20% vs. other 80%	2.86 (2.78-2.94), P=3.19E-135
				Top 10% vs. other 90%	3.25 (3.15-3.35), P=6.43E-123
				Top 5% vs. other 95%	3.56 (3.44-3.68), P=5.09E-90
				Top 2% vs. other 98%	4.10 (3.92-4.28), P=2.92E-54
				Top 1% vs. other 99%	4.95 (4.72-5.18), P=6.03E-41
eMERGE	10,572/8,030	1.38 (1.35-140), P=1.58E-83	0.77 (0.60)	Top 20% vs. other 80%	1.84 (1.69-2.00), P=1.54E-45
				Top 10% vs. other 90%	1.90 (1.70-2.14), P=5.87E-28
				Top 5% vs. other 95%	2.15 (1.83-2.54), P=7.49E-20
				Top 2% vs. other 98%	2.65 (2.02-3.48), P=1.35E-12
				Top 1% vs. other 99%	3.22 (2.17-4.78), P=6.80E-09
BioME	870/1,851	1.58 (1.46-1.70), P=2.50E-14	0.91 (0.65)	Top 20% vs. other 80%	2.42 (2.13-2.71), P=1.39E-09
				Top 10% vs. other 90%	2.31 (1.94-2.68), P=7.88E-06
				Top 5% vs. other 95%	1.99 (1.50-2.48), P=5.57E-03
				Top 2% vs. other 98%	3.39 (2.60-4.18), P=2.54E-03
				Top 1% vs. other 99%	5.87 (4.74-7.00), P=2.01E-03
Meta	14,201/82,849	1.46 (1.43-1.48), P<1.00E-300	0.81 (0.62)	Top 20% vs. other 80%	2.30 (2.17-2.44), P=1.65E-174
				Top 10% vs. other 90%	2.59 (2.40-2.78), P=1.27E-142
				Top 5% vs. other 95%	2.92 (2.65-3.21), P=2.64E-104
				Top 2% vs. other 98%	3.60 (3.11-4.17), P=4.26E-66
				Top 1% vs. other 99%	4.46 (3.66-5.44), P=7.82E-50

OR: Odds ratio for the model adjusted for age, sex, diabetes, principal components of ancestry and genotyping array or clinical site; SD: standard deviation of the GPS distribution in controls; AUC: area under the receiver-operator curve for the model adjusted for age, sex, diabetes, principal components of ancestry and genotyping array or clinical site (crude: AUC for GPS alone without any covariates).

Supplementary Table 4: Overall frequencies of *APOL1* G1 and G2 risk alleles and *APOL1* risk genotypes in African American, Admixed/Latinx and European cohorts included in the study.

Ancestry	Cohorts (cases and controls combined)	*APOL1* 1072A>G (rs73885319)	*APOL1* 1200T>G (rs60910145)	*APOL1* 1212-del6 (rs71785313)	*APOL1* computed risk genotype (G1G1, G1G2, or G2G2)
African	UKBB (N=7,158)	0.28	0.28	0.15	0.12
	eMERGE (N=2,743)	0.23	0.22	0.13	0.18
	BioMe (N=1,878)	0.23	0.23	0.13	0.14
	HyperGEN (N=728)	0.23	0.23	0.15	0.14
	REGARDS (N=5,369)	0.22	0.21	0.13	0.12
	GenHat (N=3,378)	0.21	0.2	0.13	0.12
	Warfarin (N=448)	0.25	0.24	0.14	0.18
Latinx	eMERGE (N=915)	0.05	0.05	0.04	0.03
	BioMe (N=2,710)	0.05	0.05	0.04	0.01
European	UKBB (N=75,727)	3.75E-05	1.96E-04	2.91E-05	<0.01
	eMERGE (N=18,602)	7.80E-04	7.80E-04	2.43E-04	<0.01
	BioMe (N=2,721)	7.35E-04	7.35E-04	3.68E-04	<0.01

Supplementary Table 5: GPS performance meta-analysis for testing cohorts of African ancestry (4,268 cases and 10,276 controls in total).

Cohort	Case/control	OR per SD (95% CI), P-value	AUC (Crude)	PRS Threshold	Odds ratio (95% CI), P value
eMEGRE	1,143/1,600	1.31 (1.09-1.56), P=1.30E-09	0.79 (0.57)	Top 20% vs. other 80%	1.56 (1.26-1.94), P=5.52E-05
				Top 10% vs. other 90%	1.71 (1.28-2.28), P=2.50E-04
				Top 5% vs. other 95%	2.16 (1.45-3.23), P=1.77E-04
				Top 2% vs. other 98%	2.60 (1.38-4.90), P=3.10E-03
				Top 1% vs. other 99%	2.51 (1.02-6.14), P=4.41E-02
BioME	729/1,149	1.44 (1.33-1.55), P=7.70E-11	0.81 (0.57)	Top 20% vs. other 80%	2.05 (1.78-2.32), P=2.00E-07
				Top 10% vs. other 90%	2.70 (2.34-3.06), P=6.00E-08
				Top 5% vs. other 95%	3.46 (2.97-3.95), P=8.00E-07
				Top 2% vs. other 98%	5.75 (4.96-6.54), P=1.00E-05
				Top 1% vs. other 99%	7.10 (5.93-8.27), P=1.00E-03
HyperGen	109/619	1.26 (1.01-1.57), P=3.79E-02	0.77 (0.56)	Top 20% vs. other 80%	1.37 (0.81-2.31), P=2.30E-01
				Top 10% vs. other 90%	1.91 (1.00-3.66), P=4.97E-02
				Top 5% vs. other 95%	1.92 (0.78-4.73), P=1.53E-01
				Top 2% vs. other 98%	1.64 (0.43-6.20), P=4.65E-01
				Top 1% vs. other 99%	1.28 (0.20-8.09), P=7.91E-01
REGARDS	1,055/4,314	1.22 (1.13-1.32), P=3.45E-07	0.77 (0.56)	Top 20% vs. other 80%	1.46 (1.23-1.75), P=2.04E-05
				Top 10% vs. other 90%	1.47 (1.16-1.85), P=1.03E-03
				Top 5% vs. other 95%	1.52 (1.11-2.07), P=7.49E-03
				Top 2% vs. other 98%	1.56 (0.97-2.59), P=6.52E-02
				Top 1% vs. other 99%	2.44 (1.29-4.58), P=5.54E-03
GenHat	924/2,454	1.39 (1.27-1.52), P=1.43E-12	0.75 (0.61)	Top 20% vs. other 80%	1.78 (1.47-2.17), P=5.18E-09
				Top 10% vs. other 90%	2.16 (1.68-2.78), P=2.05E-09
				Top 5% vs. other 95%	2.17 (1.54-3.05), P=8.69E-06
				Top 2% vs. other 98%	4.38 (2.56-7.50), P=6.80E-08
				Top 1% vs. other 99%	7.02 (3.20-15.3), P=1.08E-06
Warfarin	308/140	1.18 (0.94-1.46), P=1.45E-01	0.71 (0.53)	Top 20% vs. other 80%	1.76 (0.98-3.14), P=5.52E-02
				Top 10% vs. other 90%	1.24 (0.59-2.61), P=5.66E-01
				Top 5% vs. other 95%	3.52 (0.94-13.1), P=6.10E-02
				Top 2% vs. other 98%	1.59 (0.28-8.73), P=5.96E-01
				Top 1% vs. other 99%	-
Meta	4,268/10,276	1.32 (1.26-1.38), P=1.78E-33	0.78 (0.57)	Top 20% vs. other 80%	1.65 (1.49-1.82), P=1.17E-22
				Top 10% vs. other 90%	1.84 (1.61-2.09), P=9.26E-20
				Top 5% vs. other 95%	2.06 (1.72-2.47), P=2.11E-15
				Top 2% vs. other 98%	2.66 (2.01-3.51), P= 4.93E-12
				Top 1% vs. other 99%	3.51 (2.37-5.22), P=4.21E-10

OR: Odds ratio for the model adjusted for age, sex, diabetes, principal components of ancestry and genotyping array or clinical site; SD: standard deviation of the GPS distribution in controls; AUC: area under the receiver-operator curve for the model adjusted for age, sex, diabetes, principal components of ancestry and genotyping array or clinical site (crude: AUC for GPS alone without any covariates).

Supplementary Table 6: GPS performance meta-analysis for testing cohorts of Latinx/Hispanic ancestry (1,386 cases and 2,239 controls in total).

Cohort	Case/control	OR per SD (95% CI), P-value	AUC (Crude)	PRS Threshold	Odds ratio (95% CI), P value
eMERGE	382/533	1.33 (1.11-1.59), P=2.24E-03	0.86 (0.58)	Top 20% vs. other 80%	2.34 (1.51-3.61), P=1.35E-04
				Top 10% vs. other 90%	2.26 (1.28-4.01), P=5.16E-03
				Top 5% vs. other 95%	2.44 (1.11-5.34), P=2.28E-02
				Top 2% vs. other 98%	6.89 (1.60-29.07), P=9.78E-03
				Top 1% vs. other 99%	7.46 (1.18-47.10), P=3.26E-02
BioME	1,004/1,706	1.47 (1.35-1.59), P=8.00E-10	0.89 (0.63)	Top 20% vs. other 80%	1.74 (1.47-2.01), P=5.34E-05
				Top 10% vs. other 90%	2.26 (1.90-2.62), P=7.77E-06
				Top 5% vs. other 95%	2.77 (2.27-3.27), P=6.27E-05
				Top 2% vs. other 98%	4.48 (3.69-5.27), P=2.10E-04
				Top 1% vs. other 99%	6.30 (5.13-7.47), P=2.07E-02
Meta	1,386/2,239	1.42 (1.29-1.57), P=4.56E-12	0.88 (0.62)	Top 20% vs. other 80%	1.88 (1.50-2.37), P=5.46E-08
				Top 10% vs. other 90%	2.26 (1.66-3.06), P=1.56E-07
				Top 5% vs. other 95%	2.67 (1.75-4.07), P=4.96E-06
				Top 2% vs. other 98%	4.93 (2.46-9.89), P=6.69E-06
				Top 1% vs. other 99%	6.61 (2.46-17.75), P=1.77E-04

OR: Odds ratio for the model adjusted for age, sex, diabetes, principal components of ancestry and genotyping array or clinical site; SD: standard deviation of the GPS distribution in controls; AUC: area under the receiver-operator curve for the model adjusted for age, sex, diabetes, principal components of ancestry and genotyping array or clinical site (crude: AUC for GPS alone without any covariates).

Supplementary Table 7: GPS performance meta-analysis for testing cohorts of Asian continental ancestry (392 cases and 8,233 controls in total).

Cohort	Case/Control	OR per SD (95% CI), P-value	AUC (Crude)	PRS Threshold	Odds ratio (95% CI), P value
eMERGE (E.Asian)	96/97	1.76 (1.09-2.83), P=2.06E-02	0.92 (0.57)	Top 20% vs. other 80%	4.57 (1.35-15.40), P=1.47E-02
				Top 10% vs. other 90%	5.21 (1.24-21.90), P=2.44E-02
				Top 5% vs. other 95%	3.94 (0.57-27.40), P=1.68E-01
				Top 2% vs. other 98%	7.03 (0.27-182.0), P=2.38E-01
				Top 1% vs. other 99%	1.16 (.002-579.1), P=9.63E-01
UKBB (E.Asian)	26/1,525	1.64 (1.14-2.14), P=5.05E-02	0.98 (0.67)	Top 20% vs. other 80%	1.23 (0.04-2.42), P=7.30E-01
				Top 10% vs. other 90%	0.98 (-0.53-2.50), P=9.83E-01
				Top 5% vs. other 95%	1.14 (-0.72-3.00), P=8.91E-01
				Top 2% vs. other 98%	3.25 (1.02-5.48), P=3.10E-01
				Top 1% vs. other 99%	9.30 (6.69-11.90), P=9.48E-02
UKBB (SW Asian)	209/6,258	1.65 (1.49-1.81), P=4.03E-10	0.89 (0.61)	Top 20% vs. other 80%	2.43 (2.09-2.77), P=2.49E-07
				Top 10% vs. other 90%	2.89 (2.49-3.29), P=1.84E-07
				Top 5% vs. other 95%	3.86 (3.36-4.36), P=9.46E-08
				Top 2% vs. other 98%	3.39 (2.61-4.17), P=2.15E-03
				Top 1% vs. other 99%	7.77 (6.84-8.70), P=1.81E-05
BioMe (E. Asian)	61/353	1.89 (1.43-2.35), P=6.89E-03	0.89 (0.63)	Top 20% vs. other 80%	2.61 (1.66-3.56), P=4.83E-02
				Top 10% vs. other 90%	4.57 (3.41-5.73), P=1.05E-01
				Top 5% vs. other 95%	3.13 (1.11-5.15), P=2.65E-01
				Top 2% vs. other 98%	10.1 (7.71-12.5), P=5.78E-02
				Top 1% vs. other 99%	20.9 (18.3-23.5), P=2.26E-02
Meta	392/8,233	1.68 (1.45-2.06), P=7.11E-13	0.91 (0.61)	Top 20% vs. other 80%	2.42 (1.81-2.27), P=4.39E-09
				Top 10% vs. other 90%	2.95 (2.06-4.20), P=2.43E-09
				Top 5% vs. other 95%	3.56 (2.26-5.60), P=4.09E-08
				Top 2% vs. other 98%	3.81 (1.91-7.59), P=1.35E-04
				Top 1% vs. other 99%	8.46 (3.70-19.3), P=4.00E-07

OR: Odds ratio for the model adjusted for age, sex, diabetes, principal components of ancestry and genotyping array or clinical site; SD: standard deviation of the GPS distribution in controls; AUC: area under the receiver-operator curve for the model adjusted for age, sex, diabetes, principal components of ancestry and genotyping array or clinical site (crude: AUC for GPS alone without any covariates).

Supplementary Table 8: Pooled sensitivity, specificity, and prevalence-adjusted PPV and NPV for extreme tail cut-offs (95th and 98th percentile) of the GPS distribution in controls. Based on the most recent CDC data from 2021, the CKD prevalence in the U.S. was assumed to be 12.7% in European Americans, 16.3% in African Americans, 13.60% in Hispanic Americans, and 12.9% in Asian Americans.

Ancestry	GPS Tail Cut-off	Sensitivity	Specificity	Prevalence-adjusted PPV*	Prevalence-adjusted NPV*
European	Top 5% vs. other 95%	0.713	0.732	0.279	0.946
(14,201/82,849)	Top 2% vs. other 98%	0.711	0.731	0.277	0.945
African	Top 5% vs. other 95%	0.286	0.922	0.416	0.868
(4,268/10,276)	Top 2% vs. other 98%	0.160	0.972	0.526	0.855
Asian	Top 5% vs. other 95%	0.911	0.914	0.613	0.985
(392/8,233)	Top 2% vs. other 98%	0.928	0.817	0.439	0.987
Latinx	Top 5% vs. other 95%	0.735	0.826	0.330	0.964
(1,386/2,239)	Top 2% vs. other 98%	0.717	0.864	0.453	0.951

* PPV and NPV adjusted for race/ethnicity-specific CKD prevalence (CDC, 2021).

Supplementary Table 9: Comparison of the changes in GPS effects for the top 1%, 2%, and 5% tail cut-offs using different ancestry adjustment methods in the eMERGE-III dataset.

	eMERGE Cohorts	Unadjusted (Standardized using ancestry-matched controls)		Ancestry-adjusted (Method 1)		Ancestry-adjusted (Method 2)	
Cut-off	**Ancestry**	**Z-score**	**OR (95%CI)**	**Z-score**	**OR (95%CI)**	**Z-score**	**OR (95%CI)**
Top 5%	European	1.90	2.15 (1.83-2.54)	2.88	2.15 (1.99-2.31)	2.77	2.30 (2.13-2.47)
	African	1.80	2.16 (1.45-3.23)	2.76	2.12 (1.72-2.52)	3.18	1.91 (1.51-2.31)
	Latinx	1.88	2.44 (1.11-5.34)	2.74	1.91 (1.15-2.67)	2.58	1.68 (0.93-2.43)
	Asian	1.84	3.94 (0.57-27.40)	2.56	3.94 (2.00-5.88)	2.73	5.31 (3.49-7.13)
	Combined	1.85	2.07 (1.79-2.39)	3.27	2.13 (1.98-2.28)	2.82	2.17 (2.02-2.32)
Top 2%	European	2.38	2.65 (2.02-3.48)	3.89	3.16 (2.88-3.44)	3.21	2.92 (2.64-3.20)
	African	2.23	2.60 (1.38-4.90)	3.14	2.39 (1.76-3.02)	3.62	1.83 (1.21-2.45)
	Latinx	2.31	6.89 (1.60-29.70)	3.18	3.22 (1.82-4.02)	2.99	2.89 (1.70-4.08)
	Asian	2.27	7.03 (0.27-182.0)	2.98	7.03 (3.78-10.30)	3.18	4.95 (1.42-8.48)
	Combined	2.27	2.83 (2.22-3.60)	3.78	2.86 (2.61-3.11)	3.28	2.77 (2.53-3.01)
Top 1%	European	2.60	3.22 (2.17-4.78)	4.25	2.97 (2.58-3.36)	3.51	3.06 (2.66-3.46)
	African	2.51	2.51 (1.02-6.14)	3.39	3.29 (2.37-4.21)	3.91	1.46 (0.60-2.32)
	Latinx	2.59	7.46 (1.18-47.10)	3.47	5.31 (3.68-6.94)	3.27	5.31 (3.68-6.94)
	Asian	2.56	1.16 (.0002-579.0)	3.25	1.16 (-5.05-7.37)	3.47	1.16 (-5.05-7.37)
	Combined	2.55	3.35 (2.36-4.76)	4.13	3.06 (2.70-3.42)	3.57	2.89 (2.55-3.23)

Supplementary Table 10. GPS effects in the eMERGE-III cohorts defined by **(a)** genetic ancestry and **(b)** self-reported race/ethnicity, with comparison of CKD phenotypes defined using race-adjusted CKD-EPI equation vs. CKD-EPI 2021 (without race) equation. The numbers of cases and controls included in each analysis are provided after exclusion of G2, but including kidney failure patients with kidney transplant or on dialysis.

A. Genetic Ancestry

Genetic Ancestry	Phenotype	Case/Control	OR per SD (95% CI)	AUC (Crude)	Nagelkerke R2
European	CKD-EPI Race-adjusted Equation	10572/8030	1.38 (1.34-1.43), P=9.33E-84	0.771 (0.599)	0.022
	CKD-EPI 2021 (New) Equation	9435/12615	1.39 (1.35-1.43), P=3.69E-110	0.728 (0.596)	0.026
African	CKD-EPI Race-adjusted Equation	1143/1600	1.31 (1.20-1.43), P=1.27E-09	0.787 (0.568)	0.014
	CKD-EPI 2021 (New) Equation	1358/1401	1.37 (1.26-1.49), P=1.04E-12	0.780 (0.587)	0.019
Latinx	CKD-EPI Race-adjusted Equation	382/533	1.33 (1.11-1.59), P=2.24E-03	0.857 (0.580)	0.009
	CKD-EPI 2021 (New) Equation	359/1027	1.41 (1.20-1.66), P=2.65E-05	0.888 (0.599)	0.013
Asian	CKD-EPI Race-adjusted Equation	96/97	1.76 (1.09-2.83), P=2.06E-02	0.915 (0.573)	0.020
	CKD-EPI 2021 (New) Equation	93/178	1.60 (1.02-2.49), P=4.08E-02	0.908 (0.560)	0.012

B. Self-reported Race/Ethnicity

Self-report	Phenotype	Case/Control	OR per SD (95% CI)	AUC (Crude)	Nagelkerke R2
European	CKD-EPI Race-adjusted Equation	10344/7890	1.39 (1.34-1.43), P=6.95E-84	0.772 (0.600	0.022
	CKD-EPI 2021 (New) Equation	9358/12276	1.40 (1.36-1.44), P=1.42E-111	0.729 (0.597)	0.027
Black	CKD-EPI Race-adjusted Equation	1034/1619	1.34 (1.23-1.47), P=1.31E-10	0.785 (0.582)	0.016
	CKD-EPI 2021 (New) Equation	1305/1392	1.37 (1.25-1.50), P=6.00E-12	0.796 (0.596)	0.017
Hispanic	CKD-EPI Race-adjusted Equation	259/343	1.42 (1.13-1.79), P=2.30E-03	0.869 (0.618)	0.012
	CKD-EPI 2021 (New) Equation	330/603	1.44 (1.17-1.76), P=4.60E-04	0.896 (0.612)	0.010
Asian	CKD-EPI Race-adjusted Equation	105/147	1.42 (0.95-2.12), P=8.39E-02	0.902 (0.509)	0.008
	CKD-EPI 2021 (New) Equation	106/227	1.57 (1.08-2.27), P=1.76E-02	0.890 (0.501)	0.014

Supplementary Table 11. Comparison of the polygenic risk score published by Yu et al. with the present study: (a) summary of the design, optimization, and testing strategies; **(b)** comparison of the performance characteristics of the polygenic score published by Yu et al. with the score from the present study across the ancestry-defined eMERGE-III case-control cohorts. Adjusted AUC refers to the area under the receiver operating curve for the full model (PRS, age, sex, diabetes, and ancestry PCs). Crude AUC (in parenthesis) refers to the area under the receiver operating curve for the PRS predictor alone. Variance explained was estimated as a Nagelkerke pseudo-R^2 and refers to the variance in case-control status explained by the PRS predictor alone. Performance differences in the African-ancestry testing cohort highlighted in red.

A. Design, Optimization, and Testing Strategies

	Yu et al. (*JASN 2021*)	Khan et al. (*present study*)
Design		
GWAS summary statistics	CKDGen without ARIC + 90% of UKBB	CKDGen meta-analysis GWAS for eGFR
GWAS phenotype	Estimated GFR	Estimated GFR
GWAS sample size	N=1,159,871	N=765,348
GWAS ancestral composition	82% European 16% Asian 1.5% African <1% Hispanic	75% European 23% Asian 2% African <1% Hispanic
External LD reference	N=608 (1000G multiethnic subset)	N=2,504 (1000G all populations)
APOL1 risk genotype	Not included	Included under a recessive model
Covariates	Age, sex, diabetes, PCs of ancestry	Age, sex, diabetes, PCs of ancestry
Optimization		
Best performing model	LDpred (1.5M variants)	P+T (41K variants)
Optimization datasets	10% of UKBB (N=45,158)	70% UKBB European ancestry (N=177,208) AND 100% UKBB African ancestry (N=7,158)
Testing		
Overall Strategy	ARIC prospective cohort (total N=11,737)	15 Case-Control Cohorts (total N=123,844)
Outcome definition	Incident CKD (eGFR <60 mL/min/1.73 m2 plus ≥30% eGFR decline during follow-up).	CKD stage 3 or above (eGFR <60 mL/min/1.73) including ESRD (chronic dialysis, transplant)
European ancestry	ARIC Europeans (N=8,866)	3 European ancestry cohorts (N=97,050)
African ancestry	ARIC African Americans (N=2,871)	6 African ancestry cohorts (N=14,544)
Hispanic/Latinx ancestry	NA	2 admixed ancestry Latinx cohorts (N=3,625)
Asian ancestry	NA	4 Asian cohorts (N=8,625)

B. Performance Testing

Performance Metrics	Yu et al. (*JASN 2021*)	Khan et al. (*present study*)
Adjusted AUC (Crude AUC), Pseudo R^2		
European (N case/control = 10,572/8,030)	AUC 0.78 (0.61), R^2 0.035	AUC 0.77 (0.60), R^2 0.022
African (N case/control = 1,143/1,600)	AUC 0.78 (0.55), R^2 0.010	AUC 0.78 (0.57), R^2 0.014
Latinx (N case/control = 382/533)	AUC 0.86 (0.58), R^2 0.012	AUC 0.86 (0.58), R^2 0.009
Asian (N case/control = 96/97)	AUC 0.91 (0.56), R^2 0.009	AUC 0.92 (0.57), R^2 0.020
OR per SD (95% CI), P-value		
European (N case/control = 10,572/8,030)	1.51 (1.46-1.56), P=6.25E-129	1.38 (1.35-1.40), P=1.58E-83
African (N case/control = 1,143/1,600)	1.28 (1.17-1.41), P=1.07E-07	1.31 (1.09-1.56), P=1.30E-09
Latinx (N case/control = 382/583)	1.44 (1.18-1.76), P=4.27E-04	1.33 (1.11-1.59), P=2.24E-03
Asian (N case/control = 96/97)	1.44 (0.93-2.23), P=2.23E-01	1.76 (1.09-2.83), P=2.06E-02
OR for top 2% (95% CI), P-value		
European (N case/control = 10,572/8,030)	3.60 (2.70-4.79), P=1.25E-18	2.65 (2.02-3.48), P=1.35E-12
African (N case/control = 1,143/1,600)	1.92 (1.03-3.59), P=3.93E-02	2.60 (1.38-4.90), P=3.10E-03
Latinx (N case/control = 382/583)	1.55 (0.48-5.07), P=4.69E-01	6.89 (1.60-29.07), P=9.78E-03
Asian (N case/control = 96/97)	1.72 (0.02-145.0), P=8.02E-01	7.03 (0.27-182.0), P=2.38E-01