

Additional file 3: Table S1-S13

Optimizing colorectal cancer screening through polygenic risk score-based risk stratification: evidence from a population-based cohort and screening trial

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Table S1. Construction of the healthy lifestyle index in the China Kadoorie Biobank cohort.

WCRF/AICR recommendations	HLI components	Categories	Score	Variable in China Kadoorie Biobank
1) Eat a diet rich in whole grains, vegetables, fruit and beans	Total fruit intake	Monthly/rarely/never	0	diet_freq_fresh_fruit
		1–3 days/week	0.25	
		4–7 days/week	0.5	
	Total vegetable intake	Monthly/rarely/never	0	diet_freq_fresh_veg
		1–3 days/week	0.25	
		4–7 days/week	0.5	
		Monthly/rarely/never	0	
	Soybean products	1–3 days/week	0.25	diet_freq_soybean
		4–7 days/week	0.5	
		>4 days/week	0	
2) Limit consumption of red meat	Red meat intake	1–3 days/week	0.5	diet_freq_meat
		Monthly/rarely/never	1	
		0	1	
		>0.0–14.0		
3) Limit alcohol consumption	Alcohol intake (g/day)	(female), >0.0–28.0	0.5	total_alc_typ_day_g
		(male)		
		>14.0		
		(female), >28.0	0	
4) Be physically active	Total moderate–vigorous physical activity (min/week)	<75	0	main_exercise_hours_x10; heavy_phys_hours_x10
		75–<150	0.5	
		≥150	1	
	BMI (kg/m ²)	18.5–24.9	0.5	bmi_calc
		25.0–29.9	0.25	
		≥30.0	0	
5) Be a healthy weight	Waist Circumference (cm)	<80 (female), <94 (male)	0.5	waist_mm
		80–<88 (female), 94–<102 (male)	0.25	
		≥88 (female), ≥102 (male)	0	
6) Smoking is not included in the WCRF/AICR guidelines	Smoking	Never smoked	1	smoking_category
		Former/Occasional smoker	0.5	
		Current smoker	0	

Table S2. Baseline characteristics of the China Kadoorie Biobank cohort based on colorectal cancer status.

Baseline characteristic	Health control (N = 99,409)¹	Colorectal cancer (N = 810)¹	P-value²
Age	54 (11)	60 (9)	<0.001
Sex			<0.001
Male	56,957 (57.3%)	401 (49.5%)	
Female	42,452 (42.7%)	409 (50.5%)	
Education			0.38
No formal school	19,924 (20.0%)	162 (20.0%)	
Primary School	32,882 (33.1%)	260 (32.1%)	
Middle School	26,651 (26.8%)	205 (25.3%)	
High School	14,060 (14.1%)	125 (15.4%)	
Technical school / college	3,460 (3.5%)	30 (3.7%)	
University	2,432 (2.4%)	28 (3.5%)	
Marital status			0.002
Married	88,703 (89.2%)	702 (86.7%)	
Widowed	8,429 (8.5%)	97 (12.0%)	
Separated / divorced	1,491 (1.5%)	8 (1.0%)	
Never married	786 (0.8%)	3 (0.4%)	
Household income			0.001
<2,500 yuan	3,885 (3.9%)	29 (3.6%)	
2,500-4,999 yuan	7,544 (7.6%)	39 (4.8%)	
5,000-9,999 yuan	19,488 (19.6%)	132 (16.3%)	
10,000-19,999 yuan	29,843 (30.0%)	257 (31.7%)	
20,000-34,999 yuan	22,903 (23.0%)	198 (24.4%)	
≥35,000 yuan	15,746 (15.8%)	155 (19.1%)	
Acoholol intake (g/day)	8 (24)	10 (24)	<0.001
BMI			<0.001
<25	66,090 (66.5%)	466 (57.5%)	
≥25 & <30	28,891 (29.1%)	280 (34.6%)	
≥30	4,422 (4.4%)	64 (7.9%)	
Smoking status			<0.001
Current smoker	27,401 (27.6%)	230 (28.4%)	
Former/Occasional smoker	12,361 (12.4%)	142 (17.5%)	
Never smoked	59,647 (60.0%)	438 (54.1%)	
HLI	4.03 (0.89)	3.77 (0.93)	<0.001

¹Mean (SD); n (%)

²Wilcoxon rank sum test; Pearson's Chi-squared test

Table S3. Summary of single nucleotide polymorphisms in the optimal polygenic risk score.

CHR	Postion	rsID	Effect allele	Other allele	Odds Ratio
1	222148822	rs12029332	T	C	0.89
1	38461319	rs61776719	C	A	1.05
1	55246035	rs12144319	C	T	1.02
1	55247852	rs12143541	G	A	1.08
1	62673037	rs7542665	C	T	1.08
1	183002639	rs6678517	A	G	1.06
1	222112634	rs17011141	G	A	1.03
2	48686695	rs7606562	T	A	1.10
2	159964552	rs448513	C	T	1.05
2	199601925	rs11893063	A	G	1.05
2	199781586	rs983402	T	C	1.05
2	200131695	rs7593422	T	A	1.02
2	219154781	rs992157	A	G	1.04
3	40915239	rs35470271	G	A	1.06
3	53088285	rs9831861	G	T	1.03
3	66365163	rs6781752	A	G	1.01
3	112916918	rs12635946	C	T	1.06
3	112999560	rs72942485	G	A	1.11
3	133701119	rs10049390	A	G	1.06
3	133748789	rs113569514	T	C	1.10
3	169492101	rs10936599	C	T	1.06
4	94938618	rs13149359	A	C	1.01
4	106048291	rs17035289	T	C	1.05
4	163333405	rs35509282	A	T	1.02
5	1296486	rs2735940	G	A	1.06
5	40102443	rs7708610	A	G	1.05
5	40280076	rs12514517	A	G	1.13
5	40281797	rs58791712	GT	G	1.11
5	125988175	rs12659017	G	A	1.09
5	134467751	rs639933	C	A	1.12
6	12292772	rs2070699	T	G	1.05
6	29809860	rs1476570	A	G	1.12
6	31449620	rs2516420	C	T	1.10
6	32191339	rs3830041	T	C	1.16
6	32593080	rs9271695	G	A	1.05
6	35528378	rs6906359	C	T	1.03
6	35569562	rs16878812	A	G	1.17
6	36623379	rs9470361	A	G	1.09
6	41692812	rs4711689	A	G	1.09

6	55714314	rs62404968	C	T	1.08
6	105966894	rs6928864	C	A	1.06
7	45136423	rs12672022	T	C	1.05
7	46887213	rs4308634	G	C	1.05
7	47511161	rs3801081	G	A	1.06
8	128395508	rs62513967	T	G	0.90
8	117671808	rs34007155	A	G	1.15
8	23664632	rs60911071	G	C	1.08
8	117629411	rs3133285	G	C	1.11
8	128413305	rs6983267	G	T	1.17
8	128571855	rs4313119	G	T	1.04
9	22110131	rs1412834	T	C	1.04
9	34039002	rs62558833	T	C	1.06
9	101679752	rs34405347	T	G	1.05
9	113671403	rs10980628	C	T	1.03
10	8739580	rs11255841	T	A	1.17
10	52648454	rs10821907	C	T	1.03
10	80819132	rs704017	G	A	1.09
10	101290301	rs6584283	C	T	1.09
10	101345366	rs1035209	T	C	1.07
10	104595248	rs4919687	G	A	1.07
10	114280702	rs12241008	C	T	1.11
10	114726843	rs11196172	A	G	1.13
11	213740	rs12226698	T	C	0.88
11	61552680	rs174537	G	T	1.10
11	74345550	rs3824999	G	T	1.07
11	101656397	rs2186607	T	A	1.00
11	111171709	rs3802842	C	A	1.07
12	113045654	rs11066359	T	C	0.91
12	4368607	rs35808169	C	T	1.12
12	4388271	rs3217810	T	C	1.07
12	4400808	rs3217874	T	C	1.06
12	6385727	rs10849432	T	C	1.08
12	6412036	rs10849438	G	T	1.03
12	6421174	rs2250430	T	A	1.04
12	6982162	rs11064437	C	T	1.04
12	12009741	rs2238126	G	A	1.04
12	43130624	rs2730985	G	A	1.08
12	51171090	rs12372718	G	A	1.05
12	57540848	rs7398375	C	G	1.07
12	96050887	rs11108175	A	G	1.08
12	115098094	rs9634162	A	G	1.06
12	115890835	rs72013726	C	CACA	1.05
12	115890922	rs7300312	C	T	1.04

12	117763309	rs55990915	A	C	1.05
13	34093518	rs10161980	C	G	1.03
13	37462010	rs7333607	G	A	1.07
13	73649152	rs45597035	A	G	1.02
13	73986628	rs1886450	G	A	1.10
13	78609615	rs1330889	C	T	1.06
14	51394480	rs8022952	T	C	1.09
14	54419106	rs35107139	C	A	1.08
15	32993111	rs16969681	T	C	1.08
15	33156386	rs17816465	A	G	1.19
15	67007813	rs4776316	A	G	1.02
15	67402824	rs56324967	C	T	1.04
15	68177162	rs10152518	G	A	1.03
16	68743939	rs9924886	A	C	1.06
16	80039621	rs4341754	G	C	1.09
16	86340448	rs2696839	G	C	1.04
16	86703949	rs62042090	T	C	1.05
17	809643	rs4968127	G	A	1.07
17	10707241	rs1078643	A	G	1.12
17	70413253	rs983318	A	G	1.03
17	81061048	rs75954926	G	A	1.08
18	46453156	rs11874392	A	T	1.21
19	33519927	rs28840750	T	G	1.21
19	41860296	rs1800469	G	A	1.05
19	49218602	rs12979278	T	C	1.02
19	59079096	rs73068325	T	C	1.06
20	6404281	rs961253	A	C	1.08
20	6603622	rs994308	C	T	1.03
20	6699595	rs4813802	G	T	1.10
20	6762221	rs28488	T	C	1.03
20	7812350	rs2423279	C	T	1.10
20	33173883	rs2295444	C	T	1.04
20	42660286	rs2179593	A	C	1.02
20	47340117	rs6066825	A	G	1.10
20	49057488	rs1810502	C	T	1.06
20	57475191	rs13831	G	A	1.08
20	60956917	rs6061231	C	A	1.18
20	62308612	rs2738783	T	G	1.03

Table S4. Interaction between genetic risk and healthy lifestyle index in the China Kadoorie Biobank cohort.

Lifestyle	Intermediate genetic risk				High genetic risk			
	Additive interaction			Multiplicative interaction	Additive interaction			Multiplicative interaction
	RERI (95%CI)	AP (95%CI)	SI (95%CI)	Multiplicative scale (95%CI)	RERI (95%CI)	AP (95%CI)	SI (95%CI)	Multiplicative scale (95%CI)
Moderate	-0.06 (-0.96, 0.83)	-0.04 (-0.53, 0.46)	0.92 (0.33, 2.57)	0.91 (0.44, 1.88)	1.31 (0.17, 2.44)	0.39 (0.06, 0.73)	2.29 (0.65, 8.02)	1.53 (0.68, 3.45)
Unfavorable	0.03 (-0.71, 0.77)	0.02 (-0.49, 0.54)	1.07 (0.17, 6.60)	1.13 (0.57, 2.25)	0.62 (-0.28, 1.52)	0.28 (-0.17, 0.73)	2.01 (0.30, 13.55)	1.56 (0.72, 3.37)

Abbreviations: RERI, relative excess risk due to interaction; AP, attributable proportion due to interaction; SI, the synergy index; CI, confidence interval.

Table S5. Baseline characteristics of the TARGET-C trial based on colorectal neoplasm status.

Baseline characteristic	Health control (N = 1,656)¹	Non-advanced adenoma (N = 750)¹	Advanced neoplasm (N = 415)¹	P-value²
Age				<0.001
<55	404 (24.4%)	144 (19.2%)	65 (15.7%)	
>=55 & <65	755 (45.6%)	363 (48.4%)	198 (47.7%)	
>=65	497 (30.0%)	243 (32.4%)	152 (36.6%)	
Sex				<0.001
Female	827 (49.9%)	287 (38.3%)	139 (33.5%)	
Male	829 (50.1%)	463 (61.7%)	276 (66.5%)	
Education				0.316
College & above	117 (7.1%)	52 (6.9%)	25 (6.0%)	
High school	288 (17.4%)	135 (18.0%)	60 (14.5%)	
Middle school	531 (32.1%)	251 (33.5%)	141 (34.0%)	
Primary school	513 (31.0%)	240 (32.0%)	146 (35.2%)	
No formal school	207 (12.5%)	72 (9.6%)	43 (10.4%)	
BMI				0.024
<25	108,3 (65.4%)	466 (62.1%)	244 (58.8%)	
>=25 & <30	528 (31.9%)	265 (35.3%)	151 (36.4%)	
>=30	45 (2.7%)	19 (2.5%)	20 (4.8%)	
Smoking status				<0.001
Non smoker	121,6 (73.4%)	488 (65.1%)	245 (59.0%)	
Current smoker	337 (20.4%)	208 (27.7%)	146 (35.2%)	
Past smoker	103 (6.2%)	54 (7.2%)	24 (5.8%)	
Family history of CRC				0.019
No	148,4 (89.6%)	655 (87.3%)	358 (86.3%)	
Unknown	40 (2.4%)	16 (2.1%)	5 (1.2%)	
Yes	132 (8.0%)	79 (10.5%)	52 (12.5%)	
APCS level				<0.001
High risk	441 (26.6%)	273 (36.4%)	174 (41.9%)	
Low risk	121,5 (73.4%)	477 (63.6%)	241 (58.1%)	

¹Mean (SD); n (%)

²Wilcoxon rank sum test; Pearson's Chi-squared test

Table S6. Baseline characteristic comparison between China Kadoorie Biobank and TARGET-C.

Baseline characteristic	China Kadoorie Biobank (N = 100,219) ¹	TARGET-C (N = 2,821) ¹	Standardized mean difference
Age	53.7 (11.0)	61.1 (6.3)	0.86
Sex			0.03
Male	57,358 (57.2%)	1,568 (55.6%)	
Female	42,861 (42.8%)	1,253 (44.4%)	
Education			0.25
No formal school	20,086 (20.0%)	322 (11.4%)	
Primary School	33,142 (33.1%)	899 (31.9%)	
Middle School	26,856 (26.8%)	923 (32.7%)	
High School	14,185 (14.2%)	483 (17.1%)	
College & above	5,950 (5.9%)	194 (6.9%)	
BMI			0.11
BMI < 25	66,557 (66.4%)	1,793 (63.6%)	
BMI ≥ 25 & <30	29,176 (29.1%)	944 (33.5%)	
BMI ≥ 30	4,486 (4.5%)	84 (3.0%)	
Smoking status			0.24
Current smoker	27,631 (27.6%)	691 (24.5%)	
Former/Occasional smoker	12,503 (12.5%)	181 (6.4%)	
Never smoked	60,085 (60.0%)	1,949 (69.1%)	
PRS₁₂₁	6.8 (0.5)	6.9 (0.5)	0.20

¹Mean (SD); n (%)

Table S7. Interaction between genetic risk and APCS categories in the TARGET-C.

Genetic risk	APCS high risk			
	AN and NAA vs normal	AN vs normal	AN vs NAA and normal	AN vs NAA
Intermediate risk				
Multiplicative scale (95% CI)	0.77 (0.56, 1.08)	0.65 (0.40, 1.07)	0.64 (0.41, 1.00)	0.75 (0.46, 1.22)
RERI (95% CI)	-0.28 (-0.61, 0.16)	-0.50 (-1.01, 0.23)	-0.54 (-1.07, 0.15)	-0.32 (-0.78, 0.33)
AP (95% CI)	-0.26 (-0.92, -0.03)	-0.45 (-1.68, -0.15)	-0.46 (-1.57, -0.13)	-0.31 (-1.46, -0.04)
SI (95% CI)	0.20 (0.00, 56.08)	0.20 (0.00, 28.26)	0.23 (0.01, 7.57)	0.07 (0.00, 844120304.28)
High risk				
Multiplicative scale (95% CI)	0.86 (0.55, 1.34)	1.01 (0.52, 1.97)	0.97 (0.53, 1.76)	1.26 (0.65, 2.45)
RERI (95% CI)	-0.17 (-1.05, 0.87)	0.56 (-1.26, 2.96)	0.17 (-1.00, 1.62)	0.42 (-0.53, 1.80)
AP (95% CI)	-0.09 (-0.78, 0.24)	0.17 (-0.61, 0.48)	0.08 (-0.69, 0.39)	0.23 (-0.59, 0.49)
SI (95% CI)	0.85 (0.35, 2.05)	1.31 (0.54, 3.20)	1.16 (0.43, 3.14)	2.01 (0.37, 10.98)

Abbreviations: APCS, Asia-Pacific Colorectal Screening Score; AN, advanced neoplasms; NAA, non-advanced adenoma; RERI, relative excess risk due to interaction; AP, attributable proportion due to interaction; SI, the synergy index; CI, confidence interval.

Table S8. Partial AUC results with 95% CIs for six individual predictors.

Comparison group	Patial AUC (95%CI)					
	PRS	Age	Sex	BMI	CRC family history	APCS
Advanced neoplasm vs normal	0.625 (0.587, 0.660)	0.513 (0.477, 0.557)	0.526 (0.484, 0.566)	0.544 (0.502, 0.584)	0.469 (0.427, 0.506)	0.501 (0.457, 0.546)
Advanced neoplasm and NAA vs normal	0.590 (0.563, 0.616)	0.499 (0.471, 0.533)	0.504 (0.475, 0.532)	0.522 (0.494, 0.555)	0.456 (0.430, 0.483)	0.510 (0.482, 0.538)
Advanced neoplasm vs NAA and normal	0.593 (0.559, 0.632)	0.517 (0.482, 0.554)	0.525 (0.483, 0.563)	0.543 (0.503, 0.583)	0.474 (0.437, 0.517)	0.497 (0.455, 0.541)
Advanced neoplasm vs NAA	0.550 (0.509, 0.592)	0.518 (0.473, 0.563)	0.524 (0.477, 0.567)	0.532 (0.491, 0.574)	0.479 (0.442, 0.520)	0.493 (0.446, 0.533)

Abbreviations: AUC, area under curve; CI, confidence interval; PRS, polygenic risk score; BMI, body mass index; CRC, colorectal cancer; APCS, Asia Pacific Colorectal Screening score; NAA, non-advanced adenoma.

Table S9. Predictors and performance of different risk factor combinations (Advanced neoplasm and NAA vs normal).

	Models, Odds Ratio (95% CI)					
	Age, Sex	Age, Sex, BMI	Age, Sex, BMI, FH	Age, Sex, BMI, FH, Smoking	Age, Sex, BMI, FH, Smoking, PRS	APCS, PRS
Predictors						
Age, per year increase	1.01 (0.99, 1.02)	1.01 (0.99, 1.02)	1.01 (0.99, 1.02)	1.01 (0.99, 1.03)	1.01 (1.00, 1.03)	
Sex						
Female	Reference	Reference	Reference	Reference	Reference	
Male	1.26 (1.02, 1.54)	1.19 (0.96, 1.46)	1.19 (0.97, 1.46)	1.06 (0.83, 1.35)	1.06 (0.83, 1.36)	
BMI (Continuous)		1.07 (1.03, 1.11)	1.07 (1.03, 1.11)	1.07 (1.03, 1.11)	1.07 (1.03, 1.10)	
Family history						
No			Reference	Reference	Reference	
Yes			1.10 (0.81, 1.49)	1.03 (0.75, 1.41)	0.98 (0.72, 1.35)	
Smoking						
Non smoker				Reference	Reference	
Past smoker				1.24 (0.92, 1.67)	1.26 (0.93, 1.70)	
Current smoker				1.24 (1.04, 1.48)	1.26 (1.05, 1.51)	
PRS (Continuous)					1.40 (1.27, 1.55)	1.41 (1.28, 1.56)
APCS, per point increase						1.14 (1.06, 1.22)
Model Performance						
Measures						
AUC (95%CI)	0.534 (0.506, 0.561)	0.562 (0.534, 0.589)	0.57 (0.542, 0.597)	0.584 (0.556, 0.611)	0.623 (0.597, 0.649)	0.606 (0.579, 0.633)

					0.65)	
<i>P</i> for difference	7.870E-08	8.749E-06	7.329E-05	9.675E-04	Reference	8.079E-03
IDI (95%CI)	-0.041 (-0.051, -0.032)	-0.033 (-0.041, -0.024)	-0.031 (-0.039, -0.022)	-0.026 (-0.034, -0.019)	Reference	-0.011 (-0.015, -0.006)
<i>P</i> for difference	0.000E+00	0.000E+00	0.000E+00	0.000E+00		1.000E-05
NRI (continuous) (95%CI)	-0.312 (-0.407, -0.217)	-0.307 (-0.402, -0.212)	-0.317 (-0.412, -0.222)	-0.261 (-0.357, -0.166)	Reference	-0.229 (-0.324, -0.133)
<i>P</i> for difference	0.000E+00	0.000E+00	0.000E+00	0.000E+00		0.000E+00
NRI (categorical) (95%CI)	-0.023 (-0.040, -0.006)	-0.024 (-0.041, -0.007)	-0.023 (-0.040, -0.006)	-0.023 (-0.039, -0.007)	Reference	-0.012 (-0.027, 0.004)
<i>P</i> for difference	8.830E-03	5.380E-03	7.570E-03	5.390E-03		1.346E-01

Abbreviations: NAA, non-advanced adenoma; BMI, body mass index; FH, family history; CI, confidence interval; APCS, Asia-Pacific Colorectal Screening Score; PRS, polygenic risk score; AUC, area under the curve; IDI, integrated discrimination improvement; NRI, net reclassification index.

Table S10. Predictors and performance of different risk factor combinations (Advanced neoplasm vs normal).

	Models, Odds Ratio (95% CI)					
	Age, Sex	Age, Sex, BMI	Age, Sex, BMI, FH	Age, Sex, BMI, FH, Smoking	Age, Sex, BMI, FH, Smoking, PRS	APCS, PRS
Predictors						
Age, per year increase	1.01 (0.99, 1.03)	1.01 (0.99, 1.03)	1.01 (0.99, 1.03)	1.02 (0.99, 1.04)	1.02 (0.99, 1.04)	
Sex						
Female	Reference	Reference	Reference	Reference	Reference	
Male	1.52 (1.12, 2.07)	1.36 (0.99, 1.86)	1.38 (1.01, 1.89)	1.23 (0.86, 1.76)	1.23 (0.85, 1.78)	
BMI (Continuous)		1.10 (1.05, 1.16)	1.10 (1.05, 1.16)	1.10 (1.05, 1.16)	1.09 (1.03, 1.14)	
Family history						
No			Reference	Reference	Reference	
Yes			1.33 (0.87, 2.02)	1.22 (0.79, 1.88)	1.17 (0.76, 1.81)	
Smoking						
Non smoker				Reference	Reference	
Past smoker				1.47 (0.94, 2.32)	1.46 (0.92, 2.32)	
Current smoker				1.28 (1.00, 1.65)	1.35 (1.04, 1.74)	
PRS (Continuous)					1.58 (1.36, 1.84)	1.60 (1.38, 1.86)
APCS, per point increase						1.22 (1.09, 1.35)
Model Performance Measures						
AUC (95%CI)	0.558 (0.519, 0.598)	0.599 (0.56, 0.639)	0.612 (0.573, 0.651)	0.626 (0.587, 0.664)	0.679 (0.641, 0.716)	0.652 (0.614, 0.69)
<i>P</i> for difference	1.329E-07	1.233E-05	1.000E-04	6.306E-04	Reference	4.352E-03

IDI (95%CI)	-0.059 (-0.074, -0.045)	-0.046 (-0.058, -0.033)	-0.041 (-0.053, -0.029)	-0.035 (-0.046, -0.024)	Reference	-0.018 (-0.025, -0.010)
<i>P</i> for difference	0.000E+00	0.000E+00	0.000E+00	0.000E+00		1.000E-05
NRI(continuous) (95%CI)	-0.447 (-0.582, -0.312)	-0.396 (-0.533, -0.260)	-0.399 (-0.535, -0.263)	-0.377 (-0.513, -0.241)	Reference	-0.262 (-0.400, -0.124)
<i>P</i> for difference	0.000E+00	0.000E+00	0.000E+00	0.000E+00		2.000E-04
NRI (categorical) (95%CI)	-0.172 (-0.246, -0.098)	-0.118 (-0.182, -0.055)	-0.098 (-0.159, -0.036)	-0.093 (-0.152, -0.035)	Reference	-0.061 (-0.108, -0.014)
<i>P</i> for difference	1.000E-05	2.600E-04	1.850E-03	1.860E-03		1.079E-02

Abbreviations: BMI, body mass index; FH, family history; CI, confidence interval; APCS, Asia-Pacific Colorectal Screening Score; PRS, polygenic risk score; AUC, area under the curve; IDI, integrated discrimination improvement; NRI, net reclassification index.

Table S11. Predictors and performance of different risk factor combinations (Advanced neoplasm vs NAA and normal).

	Models, Odds Ratio (95% CI)					
	Age, Sex	Age, Sex, BMI	Age, Sex, BMI, FH	Age, Sex, BMI, FH, Smoking	Age, Sex, BMI, FH, Smoking, PRS	APCS, PRS
Predictors						
Age, per year increase	1.01 (0.98, 1.03)	1.01 (0.99, 1.03)	1.01 (0.99, 1.03)	1.01 (0.99, 1.03)	1.01 (0.99, 1.04)	
Sex						
Female	Reference	Reference	Reference	Reference	Reference	
Male	1.43 (1.07, 1.92)	1.34 (1.00, 1.80)	1.35 (1.00, 1.82)	1.25 (0.89, 1.75)	1.25 (0.89, 1.77)	
BMI (Continuous)		1.08 (1.03, 1.13)	1.08 (1.03, 1.13)	1.08 (1.03, 1.13)	1.08 (1.03, 1.13)	
Family history						
No			Reference	Reference	Reference	
Yes			1.36 (0.92, 2.01)	1.28 (0.86, 1.91)	1.24 (0.83, 1.85)	
Smoking						
Non smoker				Reference	Reference	
Past smoker				1.19 (0.95, 1.51)	1.21 (0.96, 1.53)	
Current smoker				1.41 (0.92, 2.17)	1.43 (0.93, 2.20)	
PRS (Continuous)					1.38 (1.20, 1.58)	1.40 (1.22, 1.60)
APCS, per point increase						1.18 (1.07, 1.31)
Model Performance						
Measures						
AUC (95%CI)	0.549 (0.511, 0.587)	0.583 (0.545, 0.622)	0.594 (0.556, 0.631)	0.603 (0.566, 0.64)	0.642 (0.606,	0.618 (0.582, 0.655)

					0.679)	
<i>P</i> for difference	1.527E-05	3.008E-04	1.239E-03	3.584E-03	Reference	1.512E-02
IDI (95%CI)	-0.026 (-0.034, -0.018)	-0.019 (-0.026, -0.013)	-0.016 (-0.022, -0.010)	-0.013 (-0.019, -0.008)	Reference	-0.010 (-0.015, -0.005)
<i>P</i> for difference	0.000E+00	0.000E+00	0.000E+00	0.000E+00		8.000E-05
NRI(continuous) (95%CI)	-0.382 (-0.511, -0.253)	-0.284 (-0.415, -0.154)	-0.297 (-0.427, -0.167)	-0.307 (-0.437, -0.177)	Reference	-0.238 (-0.368, -0.107)
<i>P</i> for difference	0.000E+00	0.000E+00	0.000E+00	0.000E+00		3.600E-04
NRI (categorical) (95%CI)	-0.191 (-0.253, -0.129)	-0.115 (-0.178, -0.051)	-0.108 (-0.171, -0.045)	-0.079 (-0.141, -0.018)	Reference	-0.073 (-0.129, -0.017)
<i>P</i> for difference	0.000E+00	3.800E-04	7.900E-04	1.114E-02		1.096E-02

Abbreviations: NAA, non-advanced adenoma; BMI, body mass index; FH, family history; CI, confidence interval; APCS, Asia-Pacific Colorectal Screening Score; PRS, polygenic risk score; AUC, area under the curve; IDI, integrated discrimination improvement; NRI, net reclassification index.

Table S12. Predictors and performance of different risk factor combinations (Advanced neoplasm vs NAA).

	Models, Odds Ratio (95% CI)					
	Age, Sex	Age, Sex, BMI	Age, Sex, BMI, FH	Age, Sex, BMI, FH, Smoking	Age, Sex, BMI, FH, Smoking, PRS	APCS, PRS
Predictors						
Age, per year increase	1.00 (0.98, 1.03)	1.00 (0.98, 1.03)	1.01 (0.98, 1.03)	1.01 (0.98, 1.03)	1.01 (0.98, 1.03)	
Sex						
Female	Reference	Reference	Reference	Reference	Reference	
Male	1.31 (0.95, 1.81)	1.28 (0.93, 1.77)	1.28 (0.93, 1.78)	1.24 (0.84, 1.81)	1.24 (0.84, 1.81)	
BMI (Continuous)		1.05 (1.00, 1.11)	1.05 (1.00, 1.11)	1.06 (1.00, 1.11)	1.06 (1.00, 1.11)	
Family history						
No			Reference	Reference	Reference	
Yes			1.40 (0.90, 2.17)	1.36 (0.88, 2.13)	1.32 (0.85, 2.06)	
Smoking						
Non smoker				Reference	Reference	
Past smoker				1.10 (0.84, 1.43)	1.10 (0.85, 1.43)	
Current smoker				1.32 (0.82, 2.11)	1.35 (0.84, 2.16)	
PRS (Continuous)					1.18 (1.02, 1.37)	1.19 (1.02, 1.37)
APCS, per point increase						1.13 (1.01, 1.27)
Model Performance Measures						
AUC (95%CI)	0.536 (0.494, 0.578)	0.561 (0.519, 0.604)	0.569 (0.527, 0.611)	0.572 (0.53, 0.614)	0.594 (0.552, 0.635)	0.57 (0.529, 0.612)
<i>P</i> for difference	1.569E-02	6.560E-02	9.390E-02	7.526E-02	Reference	9.379E-02

IDI (95%CI)	-0.0163 (-0.025, -0.008)	-0.011 (-0.018, -0.004)	-0.008 (-0.014, -0.002)	-0.006 (-0.011, -0.001)	Reference	-0.009 (-0.015, -0.003)
<i>P</i> for difference	2.100E-04	1.360E-03	6.500E-02	2.093E-02		4.350E-03
NRI(continuous) (95%CI)	-0.266 (-0.411, -0.122)	-0.239 (-0.383, -0.094)	-0.117 (-0.262, 0.028)	-0.187 (-0.332, -0.042)	Reference	-0.173 (-0.318, -0.028)
<i>P</i> for difference	3.100E-04	1.230E-03	1.137E-01	1.133E-02		1.956E-02
NRI (categorical) (95%CI)	0.0108 (-0.016, 0.037)	0.011 (-0.016, 0.037)	0.013 (-0.010, 0.037)	0.013 (-0.009, 0.035)	Reference	0.011 (-0.012, 0.034)
<i>P</i> for difference	4.294E-01	4.294E-01	2.698E-01	2.503E-01		3.340E-01

Abbreviations: NAA, non-advanced adenoma; BMI, body mass index; FH, family history; CI, confidence interval; APCS, Asia-Pacific Colorectal Screening Score; PRS, polygenic risk score; AUC, area under the curve; IDI, integrated discrimination improvement; NRI, net reclassification index.

Table S13. Baseline characteristic comparison between FIT available and unavailable participants in TARGET-C.

Baseline characteristic	FIT available (N = 1,546)¹	FIT unavailable (N = 1,275)¹	Standardized Mean Difference
Age			0.27
<55	300 (19.4%)	323 (25.3%)	
>=55 & <65	685 (44.3%)	640 (50.2%)	
>=65	561 (36.3%)	312 (24.5%)	
Sex			0.25
Female	609 (39.4%)	663 (52.0%)	
Male	937 (60.6%)	612 (48.0%)	
BMI			0.12
BMI < 25	971 (62.8%)	825 (64.7%)	
BMI >= 25 & <30	541 (35.0%)	398 (31.2%)	
BMI >= 30	34 (2.2%)	54 (4.2%)	
Smoking status			0.22
Current smoker	421 (27.2%)	260 (20.4%)	
Non smoker	1010 (65.3%)	954 (74.8%)	
Past smoker	116 (7.5%)	61 (4.8%)	
Family history of CRC			0.21
No	1333 (86.2%)	1173 (92.0%)	
Unknown	42 (2.7%)	17 (1.3%)	
Yes	172 (11.1%)	85 (6.7%)	
PRS			0.00
	7.0 (0.5)	7.0 (0.5)	

¹Mean (SD); n (%)