

Supplemental Material

	Age 5-39	Age 40-49	Age 50-59	Age 60+
All counselees (N = 784)				
Model Performance				
Leiden	0.66 (0.57, 0.75)	0.84 (0.77, 0.90)	0.80 (0.70, 0.88)	0.65 (0.49, 0.77)
MMRpro	0.72 (0.64, 0.79)	0.85 (0.78, 0.91)	0.75 (0.63, 0.85)	0.66 (0.53, 0.77)
MMRpro+	0.76 (0.69, 0.83)	0.88 (0.83, 0.93)	0.79 (0.68, 0.88)	0.67 (0.55, 0.78)
PREMM ₅	0.73 (0.65, 0.80)	0.85 (0.78, 0.91)	0.79 (0.68, 0.89)	0.65 (0.53, 0.77)
Improvement Frequency Across Bootstrap Replicates ^a				
MMRpro > MMRpro+	0.011	0.020	0.075	0.331
MMRpro > PREMM ₅	0.511	0.609	0.165	0.592
MMRpro > Leiden	0.965	0.709	0.197	0.569
MMRpro+ > PREMM ₅	0.873	0.943	0.531	0.668
MMRpro+ > Leiden	0.993	0.931	0.459	0.631
PREMM ₅ > Leiden	0.952	0.614	0.421	0.478
CRC Affected counselees (N = 413)				
Model Performance				
Leiden	0.65 (0.56, 0.74)	0.82 (0.74, 0.90)	0.75 (0.59, 0.89)	0.56 (0.29, 0.82)
MMRpredict	0.70 (0.62, 0.78)	0.79 (0.69, 0.87)	0.71 (0.51, 0.88)	0.55 (0.27, 0.80)
MMRpro	0.73 (0.64, 0.80)	0.83 (0.73, 0.92)	0.68 (0.47, 0.86)	0.56 (0.27, 0.82)
MMRpro+	0.76 (0.68, 0.84)	0.86 (0.79, 0.93)	0.79 (0.62, 0.93)	0.62 (0.39, 0.84)
PREMM ₅	0.72 (0.62, 0.80)	0.85 (0.77, 0.93)	0.70 (0.47, 0.88)	0.55 (0.29, 0.81)
Improvement Frequency Across Bootstrap Replicates ^a				
MMRpro > MMRpro+	0.056	0.014	0.015	0.062
MMRpro > PREMM ₅	0.748	0.135	0.336	0.633
MMRpro > Leiden	0.990	0.482	0.130	0.598
MMRpro > MMRpredict	0.816	0.838	0.334	0.650
MMRpro+ > PREMM ₅	0.936	0.708	0.927	0.828
MMRpro+ > Leiden	0.995	0.837	0.709	0.796
MMRpro+ > MMRpredict	0.943	0.991	0.869	0.926
PREMM ₅ > Leiden	0.943	0.730	0.170	0.442
PREMM ₅ > MMRpredict	0.638	0.965	0.378	0.480
Leiden > MMRpredict	0.085	0.796	0.743	0.500

Table S1. C-statistics stratified by age interval for all counselees and affected counselees.

^aImprovement frequency is defined as the proportion of replicates for which model 1 had a higher c-statistic than model 2 across 1000 bootstrap replicates.

	CU	JHU	MDA	MSKCC	DFCI	CCFR	All Centers
Total counselees	55 (100)	59 (100)	143 (100)	201 (100)	326 (100)	2729 (100)	3513 (100)
Male counselees	24 (43.64)	24 (40.68)	69 (48.25)	74 (36.82)	89 (27.3)	1298 (47.56)	1578 (44.92)
counselees with CRC	29 (52.73)	42 (71.19)	131 (91.61)	104 (51.74)	107 (32.82)	2509 (91.94)	2922 (83.18)
Male counselees with CRC	15 (27.27)	15 (25.42)	65 (45.45)	49 (24.38)	48 (14.72)	1234 (45.22)	1426 (40.59)
Female counselees with CRC	14 (25.45)	27 (45.76)	66 (46.15)	55 (27.36)	59 (18.1)	1275 (46.72)	1496 (42.58)
Female counselees with EC	7 (12.73)	2 (3.39)	5 (3.5)	25 (12.44)	68 (20.86)	72 (2.64)	179 (5.10)
Counselees with no cancer	21 (38.18)	17 (28.81)	8 (5.59)	57 (28.36)	102 (31.29)	135 (4.95)	340 (9.68)
Counselees with an extra-colonic cancer ϑ	9 (16.36)	0 (0)	22 (15.38)	27 (13.43)	64 (19.63)	0 (0)	122 (3.47)
Counselees with multiple primary cancers ψ	17 (30.91)	1 (1.69)	77 (53.85)	34 (16.92)	64 (19.63)	633 (23.2)	826 (23.51)
Counselees with a previous adenoma(s) ξ	14 (25.45)	2 (3.39)	0 (0)	79 (39.3)	149 (45.71)	0 (0)	244 (6.95)
Number of known proximal tumors	9 (16.36)	15 (25.42)	15 (10.49)	0 (0)	0 (0)	0 (0)	39 (1.11)
Number of known distal tumors	8 (14.55)	14 (23.73)	24 (16.78)	0 (0)	0 (0)	0 (0)	46 (1.31)
Number of tumors with unknown location	12 (21.82)	13 (22.03)	92 (64.34)	104 (51.74)	107 (32.82)	2509 (91.94)	2837 (80.76)
MSI+ δ	0 (0)	12 (20.34)	1 (0.7)	48 (23.88)	26 (7.98)	649 (23.78)	736 (20.95)
MSI-, Germline tested	0 (0)	0 (0)	0 (0)	46 (22.89)	64 (19.63)	831 (30.45)	941 (26.79)
MSI-, Not germline tested	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Not MSI tested	55 (100)	47 (79.66)	142 (99.3)	107 (53.23)	236 (72.39)	1249 (45.77)	1836 (55.11)
MLH1+	19 (34.55)	11 (18.64)	29 (20.28)	25 (12.44)	15 (4.6)	228 (8.35)	327 (9.31)
MLH1 tested	31 (56.36)	59 (100)	109 (76.22)	157 (78.11)	311 (95.4)	2425 (88.86)	3092 (88.02)
MSH2+	15 (27.27)	7 (11.86)	39 (27.27)	43 (21.39)	13 (3.99)	274 (10.04)	391 (11.13)
MSH2 Tested	24 (43.64)	59 (100)	103 (72.03)	194 (96.52)	312 (95.71)	2268 (83.11)	2960 (84.26)
MSH6+	0 (0)	0 (0)	0 (0)	4 (1.99)	14 (4.29)	83 (3.04)	101 (2.88)
MSH6 tested	0 (0)	0 (0)	0 (0)	11 (5.47)	300 (92.02)	808 (29.61)	1119 (31.85)
Total positive	34 (61.82)	18 (30.51)	68 (47.55)	68 (33.83)	42 (12.88)	584 (21.4)	814 (23.17)
Median family size	133	19	19	44	33	33	33
Mean age onset CRC	43.0	43.4	41.8	46.0	47.4	51.3	50.3
Mean age CRC (Males)	42.7	41.1	40.4	46.5	47.9	50.8	49.9
Mean age onset CRC (Females)	43.2	44.6	43.2	45.6	47.1	51.8	50.8
Mean age onset EC (Females)	46.6	54.0	44.4	49.0	49.6	49.5	49.3

Table S2. Clinical information of counselees in the additional analysis by center.

N (%) for count data for each participating data center

ϑ Extra-colonic cancers include those in the Revised Bethesda Guidelines

ψ Includes individuals with colon cancers in different sites and cancers in multiple organs. Recurrences of the same cancer are not included.

ξ Information about previous adenomas and/or colonic polyps was not available for all individuals.

δ All counselees who were MSI positive were germline tested.

	C-Statistic	Observed to Expected Ratio	PPV †	PPV ‡	NPV †	NPV ‡	Brier Score
All counselees (N = 3513) §							
Model Performance							
Leiden	0.79 (0.78,0.81)	1.52 (1.44,1.62)	0.38 (0.36,0.41)	0.33 (0.31,0.35)	0.91 (0.89,0.92)	0.92 (0.91,0.94)	0.15 (0.14,0.16)
MMRpro	0.82 (0.8,0.84)	1.09 (1.03,1.15)	0.44 (0.41,0.47)	0.38 (0.36,0.4)	0.91 (0.9,0.92)	0.92 (0.91,0.93)	0.14 (0.13,0.15)
MMRpro+	0.85 (0.83,0.86)	1.02 (0.96,1.06)	0.45 (0.43,0.48)	0.4 (0.37,0.42)	0.93 (0.92,0.94)	0.93 (0.92,0.94)	0.13 (0.12,0.14)
PREMM ₅	0.81 (0.79,0.83)	2.11 (1.99,2.24)	0.47 (0.44,0.5)	0.37 (0.35,0.39)	0.9 (0.89,0.91)	0.92 (0.9,0.93)	0.15 (0.14,0.16)
Improvement Frequency Across							
Bootstrap Replicates ^a							
MMRpro > MMRpro+	0	0.183	0.064	0.007	0	0.001	0
MMRpro > PREMM ₅	0.996	1	0	0.997	1	0.887	1
MMRpro > Leiden	1	1	1	1	0.962	0.376	0.992
MMRpro+ > PREMM ₅	1	1	0.023	1	1	0.996	1
MMRpro+ > Leiden	1	1	1	1	0.999	0.871	1
PREMM ₅ > Leiden	0.973	0	1	1	0.125	0.085	0.016
CRC Affected counselees (N = 2339)							
Model Performance							
Leiden	0.81 (0.79,0.83)	1.63 (1.53,1.73)	0.4 (0.37,0.42)	0.33 (0.31,0.35)	0.92 (0.9,0.93)	0.94 (0.92,0.95)	0.14 (0.13,0.15)
MMRpredict	0.84 (0.82,0.86)	0.81 (0.76,0.85)	0.34 (0.32,0.36)	0.3 (0.28,0.32)	0.95 (0.94,0.97)	0.96 (0.95,0.97)	0.14 (0.13,0.14)
MMRpro	0.85 (0.83,0.87)	0.99 (0.94,1.06)	0.45 (0.42,0.47)	0.38 (0.36,0.41)	0.93 (0.91,0.94)	0.94 (0.92,0.95)	0.13 (0.12,0.13)
MMRpro+	0.88 (0.87,0.9)	0.92 (0.87,0.97)	0.46 (0.43,0.49)	0.4 (0.37,0.42)	0.94 (0.93,0.95)	0.95 (0.94,0.96)	0.12 (0.11,0.13)
PREMM ₅	0.85 (0.83,0.86)	1.89 (1.77,2)	0.48 (0.45,0.51)	0.36 (0.34,0.39)	0.93 (0.91,0.94)	0.94 (0.93,0.95)	0.14 (0.13,0.15)
Improvement Frequency Across							
Bootstrap Replicates ^a							
MMRpro > MMRpro+	0	0.971	0.174	0.010	0	0	0
MMRpro > PREMM ₅	0.876	1	0.002	0.998	0.806	0.474	0.995
MMRpro > Leiden	1	1	1	1	0.968	0.583	0.985
MMRpro > MMRpredict	0.966	1	1	1	0	0	0.991
MMRpro+ > PREMM ₅	1	1	0.038	1	1	0.994	1
MMRpro+ > Leiden	1	1	1	1	1	0.981	1
MMRpro+ > MMRpredict	1	1	1	1	0.086	0.141	1
PREMM ₅ > Leiden	1	0	1	1	0.912	0.644	0.390
PREMM ₅ > MMRpredict	0.844	0	1	1	0	0	0.410
Leiden > MMRpredict	0.001	0	1	1	0	0.002	0.451
Unaffected counselees (N=554)							
Model Performance							
Leiden	0.69 (0.63,0.74)	1.22 (1.06,1.38)	0.34 (0.3,0.39)	0.34 (0.3,0.39)	0.83 (0.78,0.87)	0.85 (0.81,0.9)	0.22 (0.19,0.24)
MMRpro	0.69 (0.63,0.74)	1.69 (1.49,1.94)	0.41 (0.36,0.47)	0.38 (0.33,0.44)	0.83 (0.78,0.87)	0.83 (0.78,0.87)	0.21 (0.18,0.23)
MMRpro+	0.71 (0.66,0.76)	1.65 (1.46,1.91)	0.42 (0.37,0.49)	0.39 (0.34,0.45)	0.83 (0.79,0.87)	0.83 (0.79,0.87)	0.2 (0.17,0.22)
PREMM ₅	0.67 (0.62,0.71)	3.77 (3.21,4.4)	0.43 (0.36,0.49)	0.39 (0.33,0.45)	0.78 (0.74,0.82)	0.81 (0.77,0.86)	0.24 (0.21,0.27)
Improvement Frequency Across							
Bootstrap Replicates ^a							
MMRpro > MMRpro+	0.223	0.736	0.046	0.112	0.764	0.832	0.236
MMRpro > PREMM ₅	0.985	1	0.196	0.203	0.998	0.866	1
MMRpro > Leiden	0.743	0	0.978	0.899	0.673	0.173	0.806
MMRpro+ > PREMM ₅	0.987	1	0.385	0.355	0.998	0.752	1
MMRpro+ > Leiden	0.801	0	0.998	0.952	0.586	0.095	0.878
PREMM ₅ > Leiden	0.162	0	0.988	0.968	0.015	0.043	0.002

Table S3. Combined c-statistic, observed to expected ratio, and positive and negative predictive value results across centers, with 95% bootstrap confidence intervals for the additional analysis

†PPV: Proportion of individuals with a probability or score above 5% who have a pathogenic homozygous or heterozygous LS variant; NPV: Proportion of individuals with a probability or score below 5% who do not have a pathogenic homozygous or heterozygous LS variant

#PPV: Proportion of individuals with a probability or score above 2.5% who have a pathogenic homozygous or heterozygous LS variant; NPV: Proportion of individuals with a probability or score below 2.5% who do not have a pathogenic homozygous or heterozygous LS variant

§Includes all counselees who had germline testing.

^aImprovement is defined as follows: higher c-statistic, O/E ratio closer to 1, higher PPV, higher NPV, and lower Brier score.

	C-Statistic	Observed to Expected Ratio	PPV †	PPV ‡	NPV †	NPV ‡	Brier Score
All counselees (N = 784) §							
Model Performance							
MMRpro (v2.1-5)	0.79 (0.75,0.82)	0.93 (0.84,1.03)	0.42 (0.37,0.46)	0.38 (0.34,0.42)	0.89 (0.85,0.92)	0.89 (0.85,0.93)	0.18 (0.16,0.2)
MMRpro+ (v2.1-5)	0.81 (0.77,0.84)	0.96 (0.88,1.06)	0.45 (0.41,0.5)	0.41 (0.37,0.46)	0.9 (0.87,0.93)	0.91 (0.87,0.94)	0.17 (0.15,0.19)
MMRpro (v2.1-6)	0.78 (0.74,0.82)	0.95 (0.86,1.04)	0.42 (0.38,0.47)	0.39 (0.34,0.43)	0.87 (0.84,0.91)	0.88 (0.84,0.91)	0.18 (0.16,0.21)
MMRpro+ (v2.1-6)	0.80 (0.77,0.84)	0.98 (0.89,1.08)	0.46 (0.41,0.51)	0.42 (0.38,0.46)	0.88 (0.85,0.91)	0.88 (0.85,0.92)	0.17 (0.15,0.19)
Improvement Frequency Across							
Bootstrap Replicates ^a							
MMRpro(v2.1-6) > MMRpro(v2.1-5)	0.319	0.465	1	1	1	1	1
MMRpro (v2.1-6) > MMRpro+ (v2.1-5)	0.098	0.440	1	1	1	1	1
MMRpro+ (v2.1-6) > MMRpro (v2.1-5)	0.622	0.645	1	1	1	1	1
MMRpro+ (v2.1-6) > MMRpro+ (v2.1-5)	0.346	0.605	1	1	1	1	1
MMRpro (v2.1-5) > MMRpro+ (v2.1-5)	0.004	0.456	0.912	0.754	0.984	0.940	0.353
CRC Affected counselees (N = 413)							
Model Performance							
MMRpro (v2.1-5)	0.78 (0.73,0.82)	0.86 (0.77,0.96)	0.47 (0.42,0.53)	0.44 (0.39,0.49)	0.82 (0.74,0.89)	0.82 (0.71,0.9)	0.22 (0.19,0.25)
MMRpro+ (v2.1-5)	0.81 (0.77,0.85)	0.90 (0.8,0.99)	0.52 (0.46,0.58)	0.5 (0.44,0.55)	0.88 (0.82,0.93)	0.92 (0.86,0.97)	0.20 (0.16,0.23)
MMRpro (v2.1-6)	0.77 (0.72,0.82)	0.88 (0.78,0.98)	0.49 (0.43,0.55)	0.45 (0.4,0.51)	0.79 (0.72,0.86)	0.79 (0.7,0.87)	0.23 (0.19,0.26)
MMRpro+ (v2.1-6)	0.81 (0.77,0.85)	0.92 (0.82,1.02)	0.55 (0.48,0.61)	0.51 (0.45,0.57)	0.85 (0.79,0.9)	0.86 (0.79,0.92)	0.20 (0.17,0.24)
Improvement Frequency Across							
Bootstrap Replicates ^a							
MMRpro(v2.1-6) > MMRpro(v2.1-5)	0.398	0.472	1	1	1	0.991	1
MMRpro (v2.1-6) > MMRpro+ (v2.1-5)	0.103	0.327	1	0.999	1	0.999	1
MMRpro+ (v2.1-6) > MMRpro (v2.1-5)	0.806	0.634	1	1	1	1	1
MMRpro+ (v2.1-6) > MMRpro+ (v2.1-5)	0.421	0.485	1	1	1	1	1
MMRpro (v2.1-5) > MMRpro+ (v2.1-5)	0.001	0.286	0.579	0.616	0.558	0.686	0.274
Unaffected counselees (N=371)							
Model Performance							
MMRpro (v2.1-5)	0.75 (0.68,0.82)	1.18 (0.94,1.46)	0.27 (0.21,0.34)	0.27 (0.21,0.34)	0.92 (0.88,0.96)	0.92 (0.88,0.96)	0.14 (0.11,0.16)
MMRpro+ (v2.1-5)	0.74 (0.67,0.81)	1.19 (0.94,1.45)	0.26 (0.2,0.33)	0.26 (0.2,0.33)	0.90 (0.86,0.94)	0.90 (0.86,0.94)	0.13 (0.11,0.16)
MMRpro (v2.1-6)	0.75 (0.68,0.82)	1.18 (0.95,1.46)	0.31 (0.24,0.39)	0.28 (0.21,0.34)	0.92 (0.88,0.96)	0.92 (0.88,0.96)	0.13 (0.11,0.16)
MMRpro+ (v2.1-6)	0.74 (0.66,0.81)	1.20 (0.95,1.47)	0.31 (0.24,0.39)	0.27 (0.2,0.34)	0.91 (0.87,0.94)	0.90 (0.86,0.94)	0.13 (0.11,0.16)
Improvement Frequency Across							
Bootstrap Replicates ^a							
MMRpro(v2.1-6) > MMRpro(v2.1-5)	0.404	0.465	1	0.997	0.996	0.994	0.999
MMRpro (v2.1-6) > MMRpro+ (v2.1-5)	0.550	0.530	0.999	0.999	0.998	1	0.999
MMRpro+ (v2.1-6) > MMRpro (v2.1-5)	0.284	0.423	0.997	0.989	0.989	0.971	0.999
MMRpro+ (v2.1-6) > MMRpro+ (v2.1-5)	0.403	0.477	0.997	0.995	0.996	0.991	0.998
MMRpro (v2.1-5) > MMRpro+ (v2.1-5)	0.887	0.643	0.759	0.865	0.852	0.907	0.847

Table S4. Combined c-statistic, observed to expected ratio, and positive and negative predictive value results across centers, with 95% bootstrap confidence intervals comparing the MMRpro version 2.1-5 to the MMRpro version 2.1-6.

†PPV: Proportion of individuals with a probability or score above 5% who have a pathogenic homozygous or heterozygous LS variant; NPV: Proportion of individuals with a probability or score below 5% who do not have a pathogenic homozygous or heterozygous LS variant

‡PPV: Proportion of individuals with a probability or score above 2.5% who have a pathogenic homozygous or heterozygous LS variant; NPV: Proportion of individuals with a probability or score below 2.5% who do not have a pathogenic homozygous or heterozygous LS variant

§Includes all counselees who had germline testing.

^aImprovement frequency is defined as the proportion of replicates for which model 1 had a higher c-statistic than model 2 across 1000 bootstrap replicates.

Model	NRI (MMRpro+)	NRI (PREMM ₅)	Log loss
MMRpro+			0.67 (0.55, 0.82)
PREMM ₅			0.52 (0.46, 0.58)
LR	-0.99 (-1.14, -0.84)	-0.21 (-0.42, -0.05)	0.42 (0.39, 0.45)
Spline	-0.84 (-1.00, -0.65)	0.21 (-0.18, 0.70)	0.47 (0.41, 0.56)
RF	-0.69 (-0.92, -0.47)	0.13 (-0.16, 0.34)	0.79 (0.51, 1.22)

Table S5. Net reclassification indices and log loss values for MMRpro+, PREMM₅, and several model combination techniques combining MMRpro+ and PREMM₅ on the data. All metrics are obtained through Monte Carlo cross-validation, with 100 iterations splitting the data into half for training and half for testing. LR refers to logistic regression, Spline refers to generalized additive model with multivariate smoothing splines, and RF refers to random forest. NRI (MMRpro+) refers to the net reclassification index when comparing to MMRpro+, and NRI (PREMM) refers to the net reclassification index when comparing to PREMM₅.

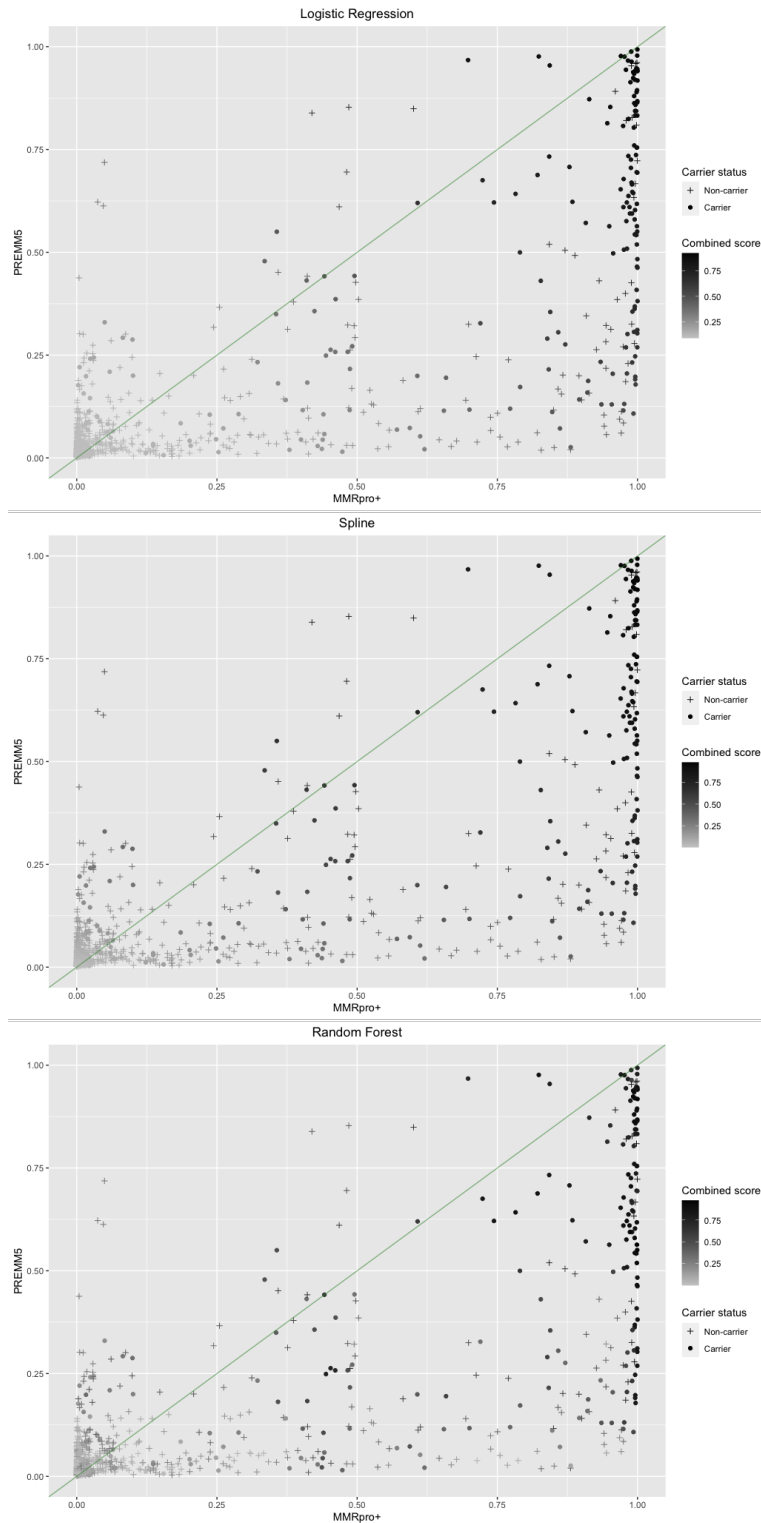


Figure S1. Plots comparing the MMRpro+ and PREMM₅ score. The dots represent individuals with a pathogenic homozygous or heterozygous LS variant, and the pluses represent individuals without a pathogenic homozygous or heterozygous LS variant. The points are shaded based on the scores for the combined models (logistic regression,

generalized additive models with multivariate smoothing splines, and random forests).