Supplementary Materials

Supplementary Methods

Here we describe the methods for obtaining the overall sensitivity, specificity, AUC, PVP, and PVN of the two-stage approach. First, we obtain the overall sensitivity and specificity as follows. Denote the cutoffs used at the first and second stages as c_1 and c_2, and P(AnyBRCA) at these two stages as Pr_1 and Pr_2, respectively. Consider a specific first-stage tool and denote its sensitivity and specificity at c_1 as $Se.1 = P(Pr_1 > c_1|$ positive genetic test) and $Sp.1 = P(Pr_1 < c_1|$ negative genetic test). Further, denote the sensitivity and specificity of the second stage at c_2 given the results of the first stage as Se.2|1 and Sp.2|1, respectively. These can be estimated by evaluating the subsample of patients with $Pr_1 > c_1$ who undergo the second stage. A counselee will be considered at high risk overall, and referred for genetic testing, only if $Pr_1 > c_1$ and $Pr_2 > c_2$. Thus, the sensitivity Se.O and the specificity Sp.O of the overall two-stage procedure can be calculated as

$Se.O = P(Pr_2 > c_2|Pr_1 > c_1,$ positive genetic test) $* P(Pr_1 > c_1|$ positive genetic test) $= Se.2|1 * Se.1$, and

$Sp.O = P(Pr_1 < c_1|$ negative genetic test) $+ P(Pr_2 < c_2|Pr_1 > c_1,$ negative genetic test) $* P(Pr_1 > c_1|$ negative genetic test) $= Sp.1 + Sp.2|1 * (1 - Sp.1)$.

By varying the values of c_1 and c_2, we can get a range of sensitivities and specificities for the two-stage approach. Next, we plot the Se.O versus 1-Sp.O over the range of c1 and c2 to obtain an empirical ROC curve, and estimate the AUC using trapezoidal rule. Also, we calculate the overall predictive values, PVP.O and PVN.O from Se.O and Sp.O values by using the Bayes rule. We obtain 95% CI for overall sensitivity, specificity, and predictive values using the bootstrap method [1]. For AUC, we use an asymptotic CI [2,3].

References

1. Efron B, Tibshirani R: An Introduction to the Bootstrap. Chapman and Hall/CRC 1994.
2. Pepe M: The Statistical Evaluation of Medical Tests for Classification and Prediction. Oxford University Press, 2004
3. Hanley JA, McNeil BJ: The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology. 143:29-36, 1982

Supplement Table 1: First Stage Results (with CI) for NWH data

	Cutoff	BRCAPRO	BRCAPROLYTE	BRCAPROLYTE-Plus	BRCAPRO-Simple
Sensitivity	0.001	0.97 (0.93, 0.99)	0.99 (0.97, 1)	0.96 (0.92, 0.99)	0.97 (0.93, 0.99)
Specificity		0.07 (0.05, 0.08)	0 (0, 0.01)	0.09 (0.07, 0.1)	0.06 (0.04, 0.07)
Sensitivity	0.003	0.92 (0.87, 0.96)	0.97 (0.93, 0.99)	0.91 (0.86, 0.96)	0.93 (0.88, 0.97)
Specificity		0.17 (0.15, 0.19)	0.05 (0.04, 0.07)	0.18 (0.15, 0.2)	0.1 (0.08, 0.12)
Sensitivity	0.005	0.89 (0.83, 0.94)	0.97 (0.93, 0.99)	0.86 (0.79, 0.92)	0.9 (0.85, 0.95)
Specificity		0.22 (0.2, 0.24)	0.07 (0.05, 0.08)	0.26 (0.24, 0.28)	0.14 (0.13, 0.16)
Sensitivity	0.007	0.84 (0.77, 0.9)	0.96 (0.92, 0.99)	0.8 (0.73, 0.87)	0.89 (0.83, 0.94)
Specificity		0.27 (0.25, 0.3)	0.08 (0.06, 0.09)	0.33 (0.3, 0.36)	0.21 (0.19, 0.23)
Sensitivity	0.01	0.8 (0.73, 0.87)	0.93 (0.88, 0.97)	0.76 (0.68, 0.83)	0.83 (0.76, 0.89)
Specificity		0.33 (0.3, 0.35)	0.1 (0.08, 0.12)	0.4 (0.37, 0.42)	0.29 (0.27, 0.32)
Sensitivity	0.03	0.63 (0.55, 0.71)	0.84 (0.77, 0.9)	0.54 (0.46, 0.63)	0.6 (0.51, 0.69)
Specificity		0.54 (0.51, 0.57)	0.29 (0.27, 0.32)	0.61 (0.58, 0.64)	0.53 (0.5, 0.55)
Sensitivity	0.05	0.54 (0.45, 0.62)	0.7 (0.61, 0.78)	0.49 (0.4, 0.58)	0.54 (0.45, 0.62)
Specificity		0.64 (0.61, 0.66)	0.41 (0.39, 0.44)	0.71 (0.68, 0.73)	0.64 (0.61, 0.67)
Sensitivity	0.1	0.46 (0.37, 0.54)	0.57 (0.48, 0.66)	0.39 (0.31, 0.48)	0.43 (0.34, 0.52)
Specificity		0.75 (0.72, 0.77)	0.56 (0.53, 0.59)	0.83 (0.81, 0.85)	0.79 (0.77, 0.81)
Sensitivity	0.2	0.39 (0.31, 0.48)	0.46 (0.37, 0.54)	0.32 (0.24, 0.4)	0.34 (0.25, 0.42)
Specificity		0.86 (0.84, 0.88)	0.74 (0.72, 0.77)	0.9 (0.88, 0.92)	0.88 (0.86, 0.9)
PVP	0.001	0.1 (0.08, 0.11)	0.09 (0.08, 0.11)	0.1 (0.08, 0.11)	0.1 (0.08, 0.11)
PVN		0.95 (0.9, 0.99)	0.83 (0.5, 1)	0.95 (0.91, 0.99)	0.95 (0.89, 0.99)
PVP	0.003	0.1 (0.08, 0.12)	0.09 (0.08, 0.11)	0.1 (0.08, 0.12)	0.1 (0.08, 0.11)
PVN		0.95 (0.93, 0.98)	0.94 (0.88, 0.99)	0.95 (0.92, 0.98)	0.93 (0.88, 0.97)
PVP	0.005	0.1 (0.09, 0.12)	0.1 (0.08, 0.11)	0.11 (0.09, 0.13)	0.1 (0.08, 0.12)
PVN		0.95 (0.92, 0.97)	0.95 (0.9, 0.99)	0.95 (0.92, 0.97)	0.94 (0.9, 0.97)
PVP	0.007	0.11 (0.09, 0.13)	0.1 (0.08, 0.11)	0.11 (0.09, 0.13)	0.1 (0.09, 0.12)
PVN		0.94 (0.92, 0.97)	0.95 (0.9, 0.99)	0.94 (0.92, 0.96)	0.95 (0.92, 0.97)
PVP	0.01	0.11 (0.09, 0.13)	0.1 (0.08, 0.11)	0.11 (0.09, 0.14)	0.11 (0.09, 0.13)
PVN		0.94 (0.92, 0.96)	0.93 (0.89, 0.97)	0.94 (0.92, 0.96)	0.94 (0.92, 0.97)
PVP	0.03	0.12 (0.1, 0.15)	0.11 (0.09, 0.13)	0.13 (0.1, 0.15)	0.12 (0.09, 0.14)
PVN		0.93 (0.92, 0.95)	0.95 (0.92, 0.97)	0.93 (0.91, 0.95)	0.93 (0.91, 0.95)
PVP	0.05	0.13 (0.1, 0.16)	0.11 (0.09, 0.13)	0.15 (0.11, 0.18)	0.13 (0.1, 0.16)
PVN		0.93 (0.91, 0.95)	0.93 (0.91, 0.95)	0.93 (0.91, 0.95)	0.93 (0.91, 0.95)
PVP	0.1	0.16 (0.12, 0.2)	0.12 (0.09, 0.14)	0.19 (0.14, 0.24)	0.17 (0.13, 0.22)
PVN		0.93 (0.91, 0.95)	0.93 (0.91, 0.94)	0.93 (0.91, 0.94)	0.93 (0.92, 0.95)
PVP	0.2	0.22 (0.17, 0.28)	0.15 (0.12, 0.19)	0.25 (0.18, 0.32)	0.22 (0.16, 0.28)
PVN		0.93 (0.92, 0.95)	0.93 (0.91, 0.95)	0.93 (0.91, 0.94)	0.93 (0.91, 0.94)
AUC		0.65 (0.59, 0.70)	0.63 (0.57, 0.68)	0.64 (0.59, 0.7)	0.64 (0.58, 0.7)
O/E		125/146.45 = 0.85 (0.71, 1)	125/228.94 = 0.55 (0.46, 0.64)	125/113.98 = 1.10 (0.91, 1.3)	125/135.37 = 0.92 (0.77, 1.09)

Supplement Table 2: Numbers of referrals made at each stage using a two-stage approach, as compared to using BRCAPRO only on all probands for CGN+MDA data. For each combination of c_1 and c_2, three numbers are provided – number of probands with first stage probability exceeding c_1 (n_1), out of n_1, the number of probands with second stage probability exceeding c_2 (n_2), and out of n_2, the number of probands tested positive for BRCA mutation.

BRCAPROLYTE

c_1 (%)	c_2 (%) = 1	3	5	10
1	2584	2584	2584	2584
	2070	1624	1361	1036
	548	498	458	414
3	2255	2255	2255	2255
	2012	1620	1359	1035
	541	496	456	413
5	2028	2028	2028	2028
	1881	1576	1350	1031
	526	494	456	413
10	1632	1632	1632	1632
	1559	1410	1276	1023
	490	472	447	412

BRCAPROLYTE-Plus

c_1 (%)	c_2 (%) = 1	3	5	10
1	2003	2003	2003	2003
	1909	1582	1340	1029
	532	494	456	413
3	1477	1477	1477	1477
	1470	1429	1280	1006
	471	468	444	409
5	1244	1244	1244	1244
	1240	1231	1191	980
	438	438	429	401
10	903	903	903	903
	902	902	898	867
	379	379	378	372

BRCAPROLYTE-Simple

c_1 (%)	c_2 (%) = 1	3	5	10
1	2300	2300	2300	2300
	2044	1619	1359	1036
	546	497	457	414
3	1789	1789	1789	1789
	1725	1536	1330	1024
	509	483	454	412
5	1522	1522	1522	1522
	1494	1415	1299	1018
	484	472	450	412
10	1167	1167	1167	1167
	1160	1141	1100	978
	426	423	415	399

BRCAPRO

c_2 (%) = 1	3	5	10
2070	1624	1361	1036
548	498	458	414

Supplement Table 3: Numbers of referrals made at each stage using a two-stage approach, as compared to using BRCAPRO only on all probands for NWH data. For each combination of c_1 and c_2, three numbers are provided – number of probands with first stage probability exceeding c_1 (n_1), out of n_1, the number of probands with second stage probability exceeding c_2 (n_2), and out of n_2, the number of probands tested positive for BRCA mutation.

BRCAPROLYTE

c_1 (%)	c_2 (%) = 1	c_2 (%) = 3	c_2 (%) = 5	c_2 (%) = 10
1	1212	1212	1212	1212
	921	641	509	363
	100	79	67	57
3	969	969	969	969
	836	636	504	360
	98	79	67	57
5	803	803	803	803
	729	592	500	357
	83	76	67	57
10	608	608	608	608
	585	513	448	347
	71	68	61	54

BRCAPROLYTE-Plus

c_1 (%)	c_2 (%) = 1	c_2 (%) = 3	c_2 (%) = 5	c_2 (%) = 10
1	831	831	831	831
	795	623	500	356
	91	77	66	56
3	540	540	540	540
	540	510	450	339
	68	67	61	53
5	416	416	416	416
	416	414	389	312
	61	61	58	51
10	256	256	256	256
	256	256	252	239
	49	49	48	47

BRCAPROLYTE-Simple

c_1 (%)	c_2 (%) = 1	c_2 (%) = 3	c_2 (%) = 5	c_2 (%) = 10
1	964	964	964	964
	849	635	506	362
	99	78	67	57
3	651	651	651	651
	634	542	470	349
	74	72	64	55
5	506	506	506	506
	502	468	417	326
	67	67	60	53
10	309	309	309	309
	307	303	290	253
	54	54	52	48

BRCAPRO

c_2 (%) = 1	c_2 (%) = 3	c_2 (%) = 5	c_2 (%) = 10
922	642	510	363
100	79	67	57