ORIGINAL ARTICLE

Pathology update to the Manchester Scoring System based on testing in over 4000 families

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ABSTRACT

Background While the requirement for thresholds for testing for mutations in *BRCA1/2* is being questioned, they are likely to remain for individuals unaffected by a relevant cancer. It is still useful to provide pretesting likelihoods, but models need to take into account tumour pathology.

Methods The Manchester Scoring System (MSS) is a well-used, simple, paper-based model for assessing carrier probability that already incorporates pathology data. We have used mutation testing data from 4115 unrelated samples from affected non-Jewish individuals alongside tumour pathology to further refine the scoring system.

Results Adding additional points for high-grade serous ovarian cancer <60 (HGSOC=+2) and adding grade score to those with triple-negative breast cancer, while reducing the score for those with HER2+ breast cancer (−6), resulted in significantly improved sensitivity and minor improvements in specificity to the MSS. Sporadic HGSOC <60 years thus reached a score of 15–19 points within the 10% grouping consistent with the 15/113–13.2% that were identified with a *BRCA1/2* pathogenic variant. Validation in a population series of ovarian cancer from Cambridge showed high sensitivity at the 10% threshold 15/17 (88.2%).

Conclusions The new pathology-adjusted Manchester score MSS3 appears to provide an effective and simple-to-use estimate of the 10% and 20% thresholds for *BRCA1/2* likelihood. For unaffected individuals, the 20-point (20%) threshold in their affected first-degree relative can be used to determine eligibility at the 10% threshold.

INTRODUCTION

In the general population, the frequency of pathogenic mutations in the breast cancer susceptibility genes *BRCA1* and *BRCA2* is estimated to be 0.05% and 0.068%, respectively.[1] As this is a per-allele frequency, it predicted that around 1 in 423 women carries a pathogenic mutation in either one of these genes. Women are usually given a personal probability of carrying a *BRCA1/2* mutation along with her risk of developing breast and/or ovarian cancer based on her personal and family history when seen in the genetics clinic. Several statistical methods have been developed in order to predict the probability of a woman carrying a *BRCA1/2* mutation. Generally, genetic testing has been undertaken when the probability of carrying a mutation is 10% or greater.[2] This threshold was in place primarily when mutation testing was largely performed to develop tests in families for unaffected relatives rather than to inform personal decision making for people with cancer. With the onset of personalised treatments such as PARPi in ovarian cancer[3] and platinum-based chemotherapy for *BRCA1/2* mutation carriers with breast cancer,[4] together with cheaper and more rapidly available results from genetic testing, such thresholds are being lowered. Nevertheless, thresholds for genetic testing in public health systems like the UK remain at 10%.[2] Furthermore, a substantial portion of testing of *BRCA1/2* of affected individuals occurs after primary treatment when treatment options for that individual are not the main driver for testing.

Various models have been developed over the years to determine the likelihood of *BRCA1/2* mutations[5] including the Frank1 and two (Myriad) models,[6] BRCAPRO[7] and BOADICEA.[8] We developed the Manchester Breast Cancer Scoring System[9] in 2004 as a simple-to-use, paper-based model that compares well with other more complicated computer-based models.[10] In 2009, adjustments were made to the Manchester Scoring System[11] (MSS) to account for the absence of mucinous and borderline ovarian tumours[12] in BRCA carriers and the higher rates of triple negative and lower rates of HER2+ breast cancers.[11] Further recent information on the high frequency of *BRCA1/2* mutations in sporadic high-grade serous ovarian cancer[13] and triple-negative breast cancer[14] as well as very low rates of HER2+ breast cancer in our own data has prompted us to revisit the pathology adjustments to further refine the Manchester Breast Cancer Scoring System.

METHODS

MSS is based on empirical data gathered from the Manchester mutation-screening programme.[9] Each individual and family characteristic (from one side of the family only) is given a numerical weight and these are added to give a score for each of the two genes, *BRCA1* and *BRCA2*. This score can be converted into a percentage chance of finding a mutation in an individual affected by breast or ovarian cancer. While a 10-point score was originally denoted as a 10% chance of finding a mutation in each specific gene, the combined score is now used given that sequential screening for *BRCA1* and *BRCA2* is rare, with both generally being tested together. In our practice, a combined score of 15–19 equates to the 10% threshold and a score

of 20 points to the 20% threshold.[15] The weights in the original scoring system (MSS1) are shown in the first 12 rows in table 1 and did not include any adjustment for pathology. As a result of further available data on the pathology of ovarian tumours[12] and rates of *BRCA1/2* based on breast cancer pathology, the scoring system was updated in 2009 (MSS2).[11] This included an uplift of 4 points for the *BRCA1* score for triple-negative breast cancer and a reduction of 4 points for true HER2 amplification (table 1). Reductions were also made for ductal carcinoma in situ and lobular histology as well as grade 1 pathology and ER positivity. Thus,high-grade (grade 3) and ER-negative pathology resulted in an uplift (table 1).

New MSS adaptations (MSS3)

A reassessment of the pathology adjustment was made based on further testing carried out in Manchester particularly for women with high-grade serous ovarian cancer and triple-negative breast without a family history of breast/ovarian cancer or second primary when referred (sporadic cases). Since 2013,[2] both apparently sporadic cases of high-grade serous ovarian cancer diagnosed less than 60 years of age and grade 3 triple-negative breast cancer diagnosed less than 40 years of age have been offered testing. Fifteen points was used as the minimum threshold to reach the 10% likelihood of a mutation; results from other large unselected series were also taken into account.[12 13] The new scores in MSS3 were modelled by upward adjustment of 1, 2, 3 or 4 points for triple-negative cancers and high-grade serous ovarian and by downward adjustments for 1–4 points for HER2+ breast cancers.

Table 1 The Manchester Scoring System with pathology adjustment[9 15 16]

Cancer, age at diagnosis	*BRCA1*	*BRCA2*
FBC, <30	6	5
FBC, 30–39	4	4
FBC, 40–49	3	3
FBC, 50–59	2	2
FBC, >59	1	1
MBC, <60	5	8
MBC, >59	5	5
Ovarian cancer, <60	8	5
Ovarian cancer, >59	5	5
Pancreatic cancer	0	1
Prostate cancer, <60	0	2
Prostate cancer, >59	0	1
Breast cancer path adjustment in index case		
Grade 3	2	0
Grade 1	−2	0
ER positive	−1	0
ER negative	1	0
Triple negative	4	0
HER2+	−6	0
Ductal carcinoma in situ	−2	0
Lobular	−2	0
Ovarian cancer adjustment – any case in family*		
Mucinous germ cell or borderline tumours	No score, that is, score as 0	No score, that is, score as 0
High grade serous <60	+2	0
Adopted no known status in blood relatives	+2	+2

*As long as not related to index case through more than one unaffected woman aged >60 years.
FBC, female breast cancer; MBC, male breast cancer.
Changes from the previous system:
Grade 3 ER score 3 (6, +2, +1)
Grade 2 ER+ score 7 (6, +0, 1)
Grade 1 ER+ score 9 (6, 2, 1)
1. HER2+ moves from 4 to 6; should in addition include grade and ER score.
2. Score grade in addition to triple negative, that is, grade.
3. Triple negative =+6 3. Add +2 for high-grade serous ovarian cancer <60, that is, sporadic tumour <60 now scores 15 points (8, +5, +2).

Pathology

Breast cancer and ovarian cancer pathology was obtained from hospital records, pathology reports and the North West Cancer Intelligence Service. Data on ER status were not widely available prior to 1995 and HER2 status prior to 2005. Even though most tumour diagnoses were confirmed in the index case and family members, full pathology reports were found in 71% of cases. Some cases were only confirmed from cancer registries with only the date and invasive status of the cancer identified.

Mutation testing

Until 2013, testing involved Sanger sequencing of all coding exons and intron/exon boundaries as well as Multiplex Ligation dependent Probe Amplification (MLPA) to test for large rearrangements. Since 2013, testing has involved next-generation sequencing analysis of the coding sequences of both genes plus MLPA.

Data analysis

Two-sided χ^2 tests with Yates correction were used to assess differences in sensitivity and specificity at the 10% level. Receiver operator curves (ROC) were used to assess the trade-off between sensitivity and specificity using the C statistic.

A population-based series of epithelial ovarian cancer from Cambridge (Genetic Testing in Epithelial Ovarian Cancer study) was used as a validation

Ethics approval is in place approved by the North Manchester Research Ethics Committee (reference 08/H1006/77), although the study reflects an audit of BRCA testing with no patient identifiable information.

RESULTS

Diagnostic *BRCA1/2* testing in the Manchester series

Results were available on 4115 primary *BRCA1/2* screens on non-Jewish individuals affected by either or both breast and ovarian cancer or another BRCA-related cancer (eg, pancreas, prostate). Pathology including at least grade of breast cancer was available on 2485/3511 (71%); hormone receptor status for ER, on 1946 (55.6%); and HER2, on 1323 (37.7%). table 2 shows the outcome of BRCA testing in 151 sporadic ovarian cancers and 340 sporadic breast cancers. Of these, 129/151 (85%) ovarian cancers were high-grade serous and 142/340 (42%) breast cancers were high-grade triple negative. A high proportion of sporadic breast cancers were tested as a result of population-based testing in women diagnosed at age 30 years or younger.[16] In sporadic high-grade serous ovarian cancer, pathogenic mutations were identified in *BRCA1* or *BRCA2* in 15/113 (13.3%) aged <60 years but none in 16 aged ≥60 years. In contrast, of those with high-grade, triple-negative breast cancer, only those diagnosed <30 years reached the 10% threshold −4/26 (15.4%) with only 4/87 (4.6%) of those aged 30–39 years having a mutation. Only 11/142 (7.7%) of women with sporadic

Table 2 Proportion of sporadic ovarian/HGS and sporadic breast cancer/triple negative with *BRCA1/2* mutations

Age of diagnosis		Sporadic ovarian	Sporadic HGS ovarian	Sporadic breast cancer	Sporadic TNT
<30	Mutation	0	0	5	4
	Number tested	6	2	80	26
BRCA1/2	%	0.0	0.0	6.25	15.4
30–39	Mutation	1	1	7	4
	Number tested	12	8	179	87
	%	8.3	12.5	3.9	4.6
40–49	Mutation	5	5	2	2
	Number tested	51	43	54	24
	%	9.8	11.6	3.7	8.3
50–59	Mutation	9	9	1	1
	Number tested	64	60	24	4
	%	14.1	15.0	4.2	25.0
60+	Mutation	0	0	0	0
	Number tested	18	16	3	1
	%	0.0	0.0	0.0	0.0
	Total mutated	15	15	15	11
	Total tested	151	129	340	142
	%	9.9	11.6	4.4	7.75
BRCA1		11	11	10	10
%		7.28	8.5	2.9	7.0
BRCA2		4	4	5	1
%		2.65	3.1	1.5	0.7

2/8 adopted patients with triple-negative breast cancer with *BRCA1* mutations were excluded from the analysis.
HGS, high-grade serous; TNT, triple-negative tumour.

triple-negative breast cancer (table 2) had a mutation with 10/11 (91%) in *BRCA1*. Of the remaining 198 sporadic breast cancers that were not triple negative, only four *BRCA2* mutations were found (2%) despite 146 being <40 years at diagnosis. We identified two *BRCA1* mutations in women with triple-negative breast cancer aged 40–49 years who were adopted. These were not included in the main analysis as they could not be shown to have an 'absent' family history.

The relevant results from two large unselected series of ovarian cancer[12] and triple-negative breast cancer[13] are shown in table 3. These show that, in the whole population, unselected non-mucinous epithelial ovarian cancers aged ≤60 years have a likelihood of a mutation of greater than 10% as 17.1% of those diagnosed aged 51–60 years had a mutation. Although the rates in sporadic ovarian cancer ≤60 years did not meet the 10% threshold, as the majority of mutations detected were in high-grade serous tumours, these were almost certain to have had a >10% likelihood as found in our series. For triple-negative breast cancer, unselected for family history rates were >10% for those aged up to 49 years.

Adjustments made to MSS3

Women with the high-grade, triple-negative breast tumours and a combined score of 15–19 in Manchester clearly met the 10% threshold and thus no additional adjustments to these were made (table 1). However, it is necessary to add in the score for grade. As such, a grade 3 triple negative <30 years would score (BRCA1-(6+)BRCA2-(5+), grade 3-(2+), triple negative-(4+)=17 points). An adjustment of +4 points (two for each gene) for adopted individuals means that a high-grade, triple-negative breast cancer aged 40–49 years would score (3+3+2+4+4=16 points). This tallies with the population-based estimates showing rates of >10% for those unselected <50 years of age[14] (table 3). Although further upward adjustment of triple negative of 1 point would mean that those with sporadic triple-negative breast cancer aged 30–39 years would hit 15 points, this was

Table 3 Previous results from large population-based series of breast or ovarian cancer cases

Age of diagnosis		All ovarian (Alsop *et al*[12])	Sporadic ovarian (Alsop *et al*[12])	Age of diagnosis	All TNT (Couch *et al*[13])	Sporadic TNT (Couch *et al*[13])
	Mutation	–	–	<35	34	18
	Number tested				156	91
	%				21.8	19.8
≤40*	Mutation	7		35–39	44	23
	Number tested	45			230	149
	%	15.6			19.1	15.4
41–49	Mutation	37		40–49	47	18
	Number tested	153			368	209
	%	24.2			12.8	8.6
51–60	Mutation	59		50–59	35	18
	Number tested	346			366	241
	%	17.1			9.6	7.5
61+	Mutation	38	16	60+	12	6
	Number tested	457	250		388	279
	%	8.3	6.4*		3.1	1.4

*Personal communication (Gillian Mitchell). By inference, as 62/749 with no ovarian cancer and no family history had a *BRCA1/2* mutation, 46/499 (9.2%) of those aged ≤60 years had a mutation. Therefore, only sporadic high-grade serous ovarian cancer aged ≤60 years was likely to have breached the 10% threshold.
TNT, triple-negative tumour.

Table 4 Application of original MSS1, current MSS2 and new pathology-adjusted Manchester score MSS3 to 4113 index cases from unrelated families affected by breast/ovarian cancer

Manchester score	<15			15–19			20–24			25–29			30+			Total mutation	Total tested	%	*BRCA1*	%	*BRCA2*	%
	BRCA1/2	Number tested	%	*BRCA1/2*	Number tested	%	*BRCA1/2*	Number tested	%	*BRCA1/2*	Number tested	%	*BRCA1/2*	Number tested	%							
ER– HER2+ original MSS1	0	19	0.0	0	10	0.0	2	10	20.0	2	6	33.3	2	3	66.7	6	48	12.5	4	8.3	2	4.2
ER– HER2+ current MSS2	0	28	0.0	2	9	22.2	1	6	16.7	2	4	50.0	1	1	100.0	6	48	12.5	4	8.3	2	4.2
ER– HER2+ new MSS3	0	26	0.0	2	11	18.2	1	6	16.7	2	4	50.0	1	1	100.0	6	48	12.5	4	8.3	2	4.2
ER+ HER2+ MSS1	1	48	2.1	1	28	3.6	3	28	10.7	1	17	5.9	0	9	0.0	6	130	4.6	1	0.8	5	3.8
ER+ HER2+ MSS2	2	72	2.8	3	32	9.4	1	16	6.3	0	5	0.0	0	5	0.0	6	130	4.6	1	0.8	5	3.8
ER+ HER2+ MSS3	2	80	2.5	3	28	10.7	1	13	7.7	0	8	0.0	0	1	0.0	6	130	4.6	1	0.8	5	3.8
TNT MSS1	32	250	12.8	33	89	37.1	30	66	45.5	23	31	74.2	41	47	87.2	159	483	32.9	125	25.9	34	7.0
TNT MSS2	11	137	8.0	24	119	20.2	37	101	36.6	30	57	52.6	57	69	82.6	159	483	32.9	125	25.9	34	7.0
TNT MSS3	7	112	6.3	13	86	15.1	39	126	31.0	29	69	42.0	71	90	78.9	159	483	32.9	125	25.9	34	7.0
TNT<30	0	0	0.0	4	24	16.7	2	4	50.0	3	8	37.5	13	14	92.9	22	50	44.0	19	38.0	3	6.0
TNT 30–39	3	75	4.0	3	20	15.0	14	46	30.4	10	20	50.0	30	38	78.9	60	199	30.2	53	26.6	7	3.5
TNT 40–49	3	28	10.7	5	27	18.5	15	39	38.5	9	23	39.1	22	27	81.5	54	144	37.5	40	27.8	14	9.7
TNT 50+	1	9	11.1	2	15	13.3	8	36	22.2	6	19	31.6	6	11	54.5	23	90	25.6	13	14.4	10	11.1
HGSOC MSS2+	15	140	10.7	7	43	16.3	10	24	41.7	3	8	37.5	3	5	60.0	38	220	17.3	29	13.2	9	4.1
HGSOC MSS3+	0	24	0.0	20	155	12.9	5	20	25.0	10	17	58.8	3	4	75.0	38	220	17.3	29	13.2	9	4.1
All ovarian case MSS3	3	96	3	30	255	11.8	31	114	27.2	39	110	35.5	87	139	62.6	190	714	26.6	123	17.2	67	9.4
All ovarian MSS1*	18	206	8.7	34	253	13.4	65	266	24.4	66	234	28.2	182	308	59.1	365	1267	28.8	227	17.9	138	10.9
Ovarian MSS2*	18	248	7.3	23	244	9.4	69	266	25.9	68	205	33.2	187	304	61.5	365	1267	28.8	227	17.9	138	10.9
All ovarian* MSS3	3	134	2.2	37	349	10.6	56	247	22.7	78	224	34.8	191	313	61.0	365	1267	28.8	227	17.9	138	10.9
Ovarian path adjusted only confirmed ovarian cancer	9	214	4.2	38	357	10.6	66	237	27.8	83	209	39.7	169	250	67.6	365	1267	28.8	227	17.9	138	10.9
Breast-only MSS1	65	1372	4.7	74	700	10.4	89	441	20.2	55	185	29.7	70	151	46.4	352	2849	12.4	157	5.5	195	6.8
Breast-only MSS2	49	1316	3.7	74	789	9.4	89	396	22.5	58	191	30.4	83	157	52.9	353	2849	12.4	157	5.5	195	6.8
Breast-only MSS3	43	1292	3.3	66	757	8.7	95	434	21.9	56	194	28.9	93	172	54.1	353	2849	12.4	157	5.5	195	6.8

Continued

Table 4 Continued

Manchester score	<15			15–19			20–24			25–29			30+			Total mutation	Total tested	%	*BRCA1*	%	*BRCA2*	%
	BRCA1/2	Number tested	%	*BRCA1/2*	Number tested	%	*BRCA1/2*	Number tested	%	*BRCA1/2*	Number tested	%	*BRCA1/2*	Number tested	%							
Breast MSS3 with path avail	33	920	3.6	63	625	10.1	103	411	25.1	84	243	34.6	180	287	62.7	463	2486	18.6	131	5.3	144	5.8
Breast/ovarian path avail MSS1	73	1165	6.3	92	709	13.0	126	525	24.0	103	325	31.7	207	361	57.3	601	3085	19.5	335	10.9	266	8.6
Breast/ovarian path avail MSS2	56	1130	5.0	82	789	10.4	128	486	26.3	109	312	34.9	226	368	61.4	601	3085	19.5	335	10.9	266	8.6
Breast/ovarian path avail MSS3	35	995	3.5	88	859	10.2	124	509	24.4	114	330	34.5	240	392	61.2	601	3085	19.5	335	10.9	266	8.6

*All ovarian cases and those with ovarian cancer family history. Only cases with proven high grade were included where no further ovarian cancers were present in the family. +HGSOC, high-grade serous ovarian cancer; path avail, pathology available; TNT, triple-negative tumour.

not supported by the Manchester data. Furthermore, adding this score substantially reduced the detection rates below 10% in those with scores of 15 points.

For high-grade serous ovarian cancer, an addition of 2 points meant that a sporadic case <60 years would meet the threshold (8-BRCA1+5-BRCA2+2 additional score=15 points). Additionally, any non-mucinous epithelial ovarian cancer aged <60 years in an adopted individual or high grade serous at any age would score at least 15 points. An addition of +1 for high grade serous ≥60 years was considered as two serous ovarian cancers without known grade with *BRCA2* mutations had a score of 14 points. If all serous with unknown grade were converted into high grade, then two further mutations would have been identified for 15 further samples to test. However, as the grade was not known, this was not employed.

For HER2+ breast cancers, the previous reduction of 4 points was insufficient for an accurate score as we have previously shown.[12] However, the rates of detection were higher in ER− HER2+ breast cancers for *BRCA1* with 4/48 (9%) having a mutation compared with only 1/130 (0.8%) in ER+ HER2+. A further reduction of 2 points for HER2+ (to −6 points) with incorporation of the scores for grade and ER produced the best fit. Although this lost minor sensitivity at the 10% threshold (table 4) compared with the unadjusted pathology score with one mutation carrier falling below the threshold, this was as a result of testing 37 fewer cases. There was no loss of sensitivity compared with the previous pathology adjustment with five fewer cases requiring testing.

For grade 3 triple-negative breast cancer, sensitivity improved with the new score identifying a further 25 mutation carriers from testing 138 extra cases (detection rate in extras, 25/138=18%), thereby increasing the sensitivity rate from 80% to 95.6% compared with MSS1. Four further *BRCA1/2* carriers were found by testing 25 further sporadic cases compared with the previous pathology-adjusted score (MSS2).

The greatest gain in sensitivity compared with MSS2 was from testing in ovarian cancer. Fifteen additional mutations were identified in sporadic high-grade serous ovarian cancer cases by testing 113 further women. However, compared with MSS1, this is based on testing only 72 additional samples.

There were 137 women with pathology-confirmed serous ovarian cancer without information regarding grade. A total of 29/137 (21%) had a *BRCA1/2* mutation with three with a Manchester score of <15. However, if all serous ovarian cancers including high grade >59 years of age were included, this still fell below the 10% threshold (3/40%–7.5%).

Overall, using MSS3, 37 extra *BRCA1/2* mutations were found in 152 extra samples to test at 10% threshold with an improvement in sensitivity compared with MSS1 from 88.4% (634/717) to 93.6% (671/717) and for 136 extra samples compared with MSS2, with 21 extra mutations improved from 90.7% (650/717). Specificities for the MSS1, MSS2 and MSS3 were 94.7%, 95.7% and 96.8%, respectively, at the 10% threshold. Improvements from MSS1 (2004) were significant for sensitivity (p=0.0008) and specificity (p=0.004) but it only reached significance for sensitivity (p=0.05) compared with the MSS2 (2009). The C statistic from ROC was significantly improved from 0.766 (95% CI 0.745 to 0.787) for MSS1 to 0.813 (95% CI 0.795 to 0.832) for MSS3 (figure 1), but not compared with MSS2.

To determine whether scores just below the threshold of 15 points approach the 10% threshold, an assessment of scores of 13–14 points was made. A combined Manchester score of 13–14 in MSS3 identified only 23/473 (4.9%) with a *BRCA1/2* mutation. This is significantly less than 10% (p=0.004). Even

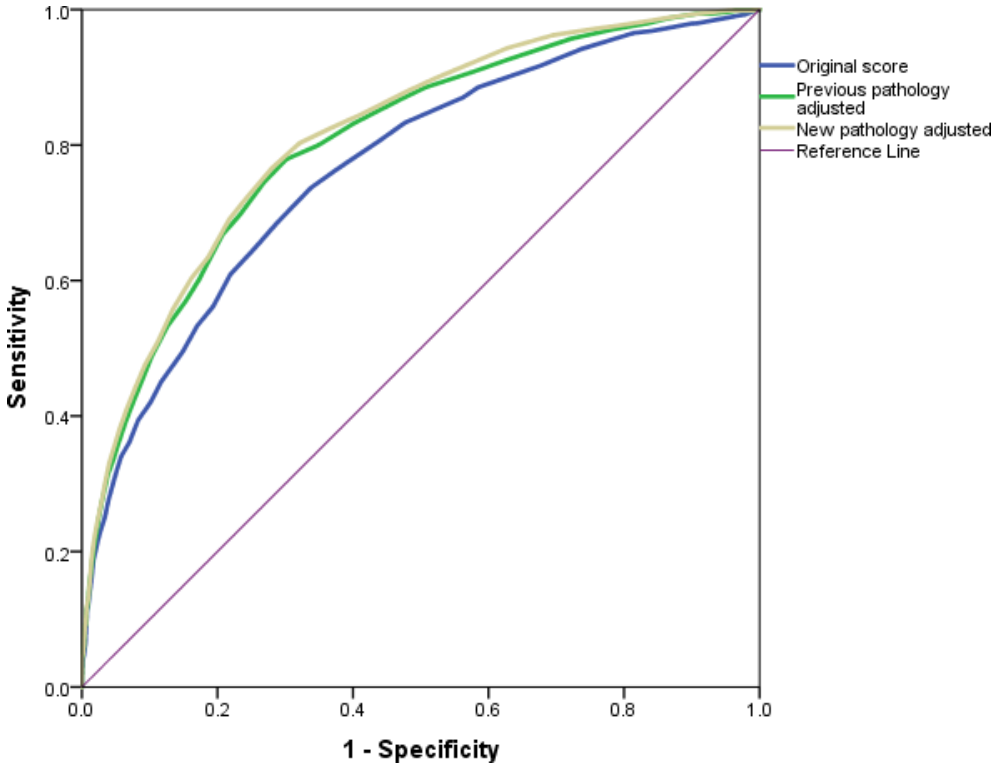

Figure 1 Receiver operator curves comparing the original Manchester score, previous pathology-adjusted score and new pathology-adjusted score.

when only those with available pathology were used, this was still significant, −18/364 (4.9%) (p=0.015). The MSS3 score of 12 identified only 6 (3%) mutations in 196 individuals.

A population-based series of epithelial cancer at any age from Cambridge was used as a validation cohort. Sensitivity improved from 12/17 (70.6%) using MSS2 to 15/17 (88.2%) with MSS3 while also improving specificity with the three extra mutations detected by testing only 37 extra cases. MSS3 was significantly better than BOADICEA (p=0.0013; table 5)

DISCUSSION

Additional changes made to the pathology-adjusted MSS have resulted in significant improvements in sensitivity of *BRCA1/2* mutation detection at the 10% threshold, with minor non-significant improvements in specificity. Overall, the C statistic from the ROC was significantly further improved from the original score (MSS1). The improvements are largely driven by the increased identification of mutations in sporadic cases of high-grade serous ovarian cancer and, to a lesser extent, triple-negative breast cancer. Using MSS3 identified 37 more mutations than MSS1[9 15] and 21 more mutations than MSS2.[16] Despite these changes, the specificity in familial cases remains unchanged. The Manchester score specifically excludes the Jewish population: the only significant founder population in Manchester.[9 17] While the 15-point (10%) threshold and the 20-point (20%) threshold hold true for the tested population in North West England, adjustments may need to be made in populations with higher prevalence of *BRCA1/2* mutations and/or lower penetrance for breast cancer in carriers and the general population. The 10% threshold in such populations may be only 13 points, which is equivalent to a 5% threshold in Manchester. Furthermore, given the reported 10% detection rate in apparently sporadic triple-negative breast cancers from a large multicentre study in women aged 30–39 years of age,[14] exceptions may need to be made to the 15-point score even in the UK where testing of all triple-negative breast cancer <40 years of age is already sanctioned.[2] Nonetheless, it is still possible that other outbred populations with high breast cancer incidence and no founder effect will result in women with apparently sporadic triple-negative breast cancer >30 years of age having <10% likelihood of having a *BRCA1/2* mutation.

There is a clear need for pathology adjustment of existing scoring algorithms. Assessment for BRCAPRO in 589 patients with ovarian cancer showed that if patients with BRCAPRO scores <10% had not been tested, 51 (28%) of 180 mutations would have been missed.[18] Indeed, overall detection rates were substantially higher in this study than those predicted by BRCAPRO, particularly with mutation likelihoods of <40% with 93 mutations found whereas only 34 were expected.

Table 5 Validation of the Manchester Scoring System using samples from the Genetic Testing in Epithelial Ovarian Cancer study from Cambridge

Manchester score	0–14 (0%–9.9%)	15–19 (10%–19.9%)	20–24	25+	Sensitivity at 10% (15–19) threshold	Specificity at 10% threshold
Previous MSS2	5/170 (2.9%)	0/23 (0%)	7/26 (27%)	5/12 (41.7%)	12/17 (70.6%)	97.1%
New MSS3	2/133 (1.5%)	3/56 (5.4%)	6/24 (25%)	6/18 (33%)	15/17 (88.2%)	98.5%
BOADICEA*	0%–9.9%	10%–19.9%	20%–29.9%	30%+	Sensitivity at 10% threshold	Specificity
	12/221 (5.5%)	2/3 (67%)	1/3 (33%)	2/2 (100%)	5/17 (29.5%)	94.5%

*Two cases without mutations did not generate a BOADICEA score.

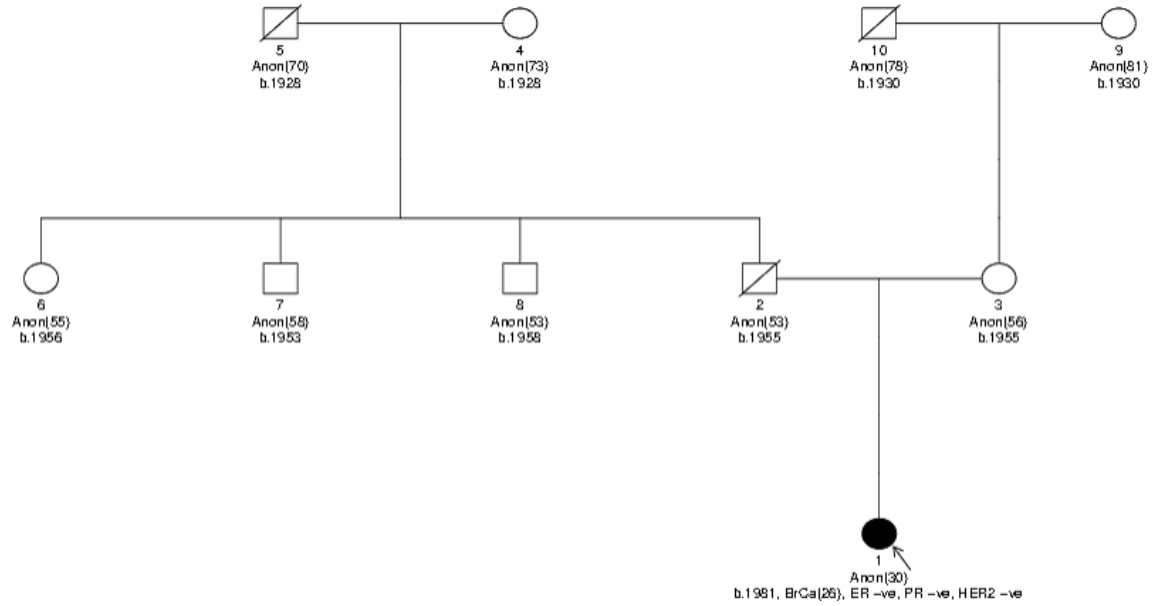

Figure 2 BOADICEA example with pathology adjustment for the youngest sporadic triple negative with a *BRCA1* mutation.

BRCAPRO particularly underpredicted for high-grade serous ovarian cancer.[18] In contrast, only three cases (3%) with ovarian cancer were missed using the new MSS at the 10% threshold out of 103 with a score of <30 points (which is equivalent to the <40% BRCAPRO score). Although the Manchester population of 714 ovarian cancers does not represent population screening, it does represent a similar genetics referral population to the US study,[17] and for the last 3 years, it has been close to population screening aged <60 years as sporadic cases have been tested. In that period, all 67/332 (20.2%) *BRCA1/2* mutations have been identified at the 10% threshold, producing a similar detection rate to the 22% for high grade serous in the Australian study.[13] Although pathology-adjusted BRCAPRO[18 19] and BOADICEA[19 20] have been presaged, these are not yet available other than inclusion of HER2 and hormonal receptor status (but not grade) for breast cancer in BOADICEA.[21] However, there is no pathology adjustment for ovarian cancer. Inputting all four of the sporadic triple-negative grade 3 breast cancers <30 within the Manchester dataset (aged 26, 27, 28 and 29 years, 3 *BRCA1*, 1 *BRCA2*) into BOADICEA resulted in risk estimations of below 10% even with the triple-negative status was applied (figure 2 for an example). Similarly, all 15 sporadic high-grade serous ovarian cancers which meet the 10% threshold of 15 points in the new MSS (MSS3) had mutation probabilities below 5% in BOADICEA, although there was no entry site for pathology. As such, it appears that neither current online versions of BOADICEA nor BRCAPRO reflect the >10% chance of identifying a *BRCA1/2* mutation in sporadic triple-negative breast cancer <30 years nor in sporadic high-grade serous ovarian cancer aged <60 years.

A full-scale comparison with either BOADICEA or BRCAPRO would not be appropriate as the dataset in this Manchester series was used to adapt the Manchester score. Therefore, for any full comparisons, a new large dataset would be required. Nevertheless, the data presented here on the new pathology-adjusted Manchester score suggest that this will be useful in many populations and could be adjusted to allow for higher frequencies of *BRCA1/2* or lower penetrance by reducing the points required in other populations for the 10% threshold.

While thresholds are likely to be further lowered or even abandoned for people with a relevant cancer (breast, ovary, prostate, pancreas), it is still useful to provide an individual with the likelihood they will test positive. Despite debate about population testing for *BRCA1/2*, this is unlikely to be covered by publicly funded healthcare systems without thresholds in unaffected people as there are still significant testing costs. For the 10% threshold in an unaffected relative, a score of ≥20 points in their affected first-degree relative would qualify them as per NICE recommendations in the UK.[2] This would drop to 15–19 points if the threshold drops to 5% (given the variant-of-uncertain-significance rate of >5%, further threshold reduction seems unlikely[2]). Using the score in the affected first-degree relative circumvents the difficult situation where sisters of different ages could fall either side of the threshold taking into account the reduced likelihood of carrying the mutation with age.

There was a good validation of the new MSS (MSS3) in a population-based cohort of epithelial ovarian cancer[22] with 15/17 (88.2%) being detected at the 10% (15-point) threshold.

Although panel testing for an extended set of genes for breast/ovarian cancer that include other high-risk genes such as *STK11*, *PTEN*, *TP53*, *CDH1* and *PALB2* and moderate-risk genes such as *ATM*, *NF1* and *CHEK2* (breast cancer) and *RAD51C*, *RAD51D* and *BRIP1*, these only add limited additional information[23] with only other high-risk genes being clearly actionable.[24] Testing will remain likely to be driven largely by the likelihood of *BRCA1/2* for some time. Tumour testing may also replace testing of germline DNA in lymphocytes due to the small but important rate of somatic mutations that can affect treatment options particularly for ovarian cancer.[25]

In summary, the new Manchester pathology-adjusted scoring system MSS3 has improved sensitivity significantly compared with the previous pathology-adjusted score MSS2 without any loss of specificity.

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