The Manchester Scoring System in 2022: performances before and after raking in breast and ovarian cancer patients undergoing multigene panel testing

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INTRODUCTION

Recent recommendations from the USA state that most breast and ovarian cancer patients (BC/OC) should be offered germline testing. However, European oncogeneticists still have to select a subset of suggestive cases, as resources do not allow for near-universal testing. Scores, e.g. the Manchester Scoring System (MSS), prediction models, e.g. BOADICEA, or clinical criteria are used in this context. We have adapted the MSS to multigene panels and French practice (MSS-F), and report its performances in a large series of BC/OC cases.

MATERIAL AND METHODS

-We included 1220 BC/OC patients referred between 2016 and 2020 to the AP-HP.Sorbonne University Oncogenetics laboratory, Paris.

-Patients had undergone germline panel testing: *BRCA1, BRCA2, PALB2, TP53, RAD51C, RAD51D, ATM, CHEK2, PTEN, CDH1, MMR*.

-The MSS-F score was calculated prospectively for patients included from 2018 onwards, with a recommendation to test at the 12 point threshold, and to consider testing at the 9-point threshold

-MSS-F was calculated retrospectively for those who had genetic testing in 2016-2017, testing decision had been based on criteria.

-MSS-F correlation with the identification of pathogenic variants was assessed using AUC/ROC curves. For a subset of 210 patients, MSS-F was compared to BOADICEA.

-Curves were also re-calculated using the raking method as a correction, matching cases statistics to those of a series of unselected BC/OC cases.

-MSS-F was compared to MSS3, the most recent published version of the score.

Cancers in proband and 1st/2nd-degree relatives	Number	Points
Breast cancer F < 36 years		11
Breast cancer F 36-39 years		8
Breast cancer F 40-49 years		6
Breast cancer F 50-59 years		4
Breast cancer F > 59 years		2
Breast cancer M < 60 years		13
Breast cancer M ≥ 60 years		10
Ovarian cancer < 60 years		13
Ovarian cancer ≥ 60 years		10
Pancreatic cancer		1
Prostate cancer < 60 years		2
Prostate cancer ≥ 60 years		1
Ovarian cancer - pathology (proband or relatives)		
High-grade serous		2
Breast cancer - pathology (proband only)		
Grade 3		2
Grade 1		-2
Oestrogen receptor +		-1
Oestrogen receptor -		1
Triple-negative		4
Ductal *in situ*		-2
Familial data - other		
Adopted or one parent unknown		4
Ashkenazi origin		x2
Conclusion	**Total**	

The MSS-F score. The main adjustments to French practice and multigene panel testing were:
-suppression of the minus points associated with HER2 +++ and lobular breast cancers – as not to miss TP53 and CDH1 pathogenic variants
-modification of the age at breast cancer diagnosis associated with maximum points (<30→ <36 years)

RESULTS

-MMS-F performances were average, with an AUC of 0.61.

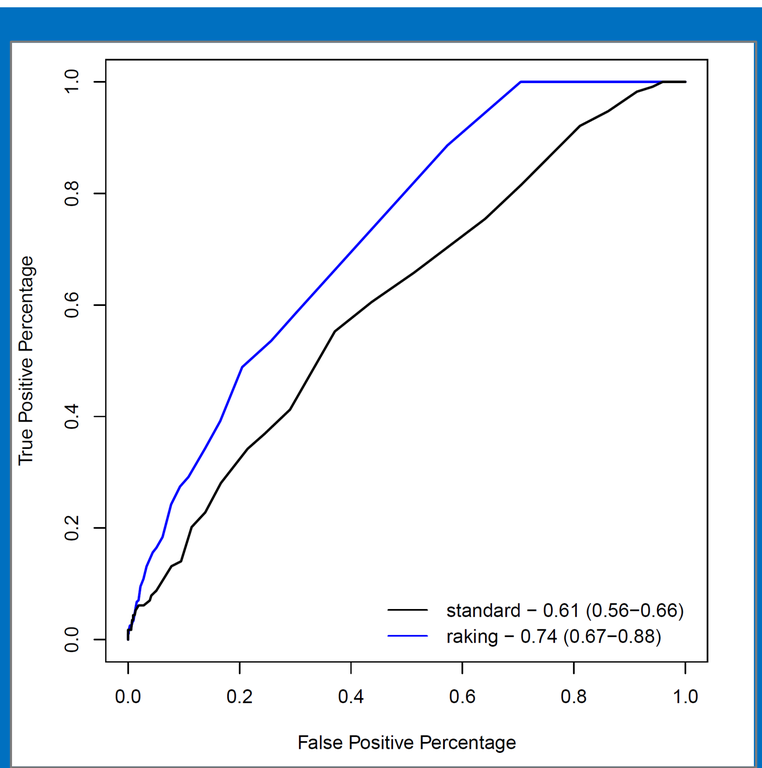
-Sensitivity was 0.95, 0.75 and 0.55 at the 9, 12 and 15-point thresholds. Specificity was 0.14, 0.36 and 0.63 at these thresholds, respectively.

-Negative and positive predictive values varied very little with thresholds, with estimations of 0.93-0.96 and 0.10-0.13, respectively.

-The BOADICEA AUC on a subset of cases was similar to MSS-F (0.61).

-MSS-F performances, though, were improved after raking, with an AUC of 0.74.

-Statistics were similar for MSS3 and MSS-F.



MSS-F ROC Curves based on 1220 BC/OC cases, before and after adjustment for the fact that analyses were based on selected cases (raking)

Testing threshold	9	12	15
sensitivity	0.947	0.754	0.553
specificity	0.138	0.359	0.629
PPV	0.102	0.108	0.133
NPV	0.962	0.934	0.932

MSS-F statistics at different genetic testing thresholds

CONCLUSION

-Improved performances after raking suggest that MSS-F should actually be used by in unselected BC/OC cases upstream the oncogenetics referral.

-Nevertheless, its performances remain limited. As are those of more complex mathematical models. There should therefore be a Europe-wide effort to promote access to genetic counseling and germline genetic testing for the majority of BC/OC cases.

-The approval of PARP-inhibitors for BC patients with germline *BRCA1/BRCA2* pathogenic variants makes it even more urgent to remove barriers to germline testing.

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