

Enhancing the diagnostic performance of a multi-cancer early detection test with patient characteristics, symptoms, and standard laboratory test results

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Background & Aims

- The prospective observational SYMPLIFY study reported the diagnostic accuracy of the Galleri® multi-cancer early detection (MCED) test in symptomatic patients referred for cancer testing^[1].
- Mean (SD) age of the 5,461 participants was 62.1 years (13.8), 3,609 (66.1%) were female, and 368 (6.7%) had cancer within 9 months.
- MCED performance (95% CI) for 9-month cancer detection was:
 - sensitivity 66.3% (61.2-71.1)
 - specificity 98.4% (98.1-98.8)
 - positive predictive value (PPV) 75.5% (70.5-80.1)
 - negative predictive value (NPV) 97.6% (97.1-98.0)
- This exploratory study assessed whether combining MCED results with patient characteristics, symptoms and blood test results enhances cancer risk stratification.

Methods

- Blood was taken for MCED testing at baseline and cancer signal detected (yes/no) result included in this analysis. Demographic, referral pathway and symptoms arranged into symptom clusters meeting referral criteria at enrolment and cancer outcomes within 9 months (yes/no) after enrolment were collected.
- Sites collated continuous blood test results performed around the referral.
- MCED + other factors:** sensitivity, specificity, PPV and NPV (with 95% CIs) of the MCED test was calculated in subgroups of patient data. The discriminative ability of the MCED, alone and in combination with patient data, was explored with the AUC (95% CI) using logistic regression and ROC curves.
- Prediction model:** an exploratory logistic regression prediction model for 9-month cancer detection included the MCED test, age, and sex and used backward selection for symptoms using a p<0.05 removal threshold. Interval validation: bootstrapping (100 samples) was used to identify and correct for optimism^[2].
- False positive analysis:** logistic regression was used to identify factors associated with a positive MCED test result in cancer-free participants. A two-sided 5% significance level was used.

AUC of MCED with other factors

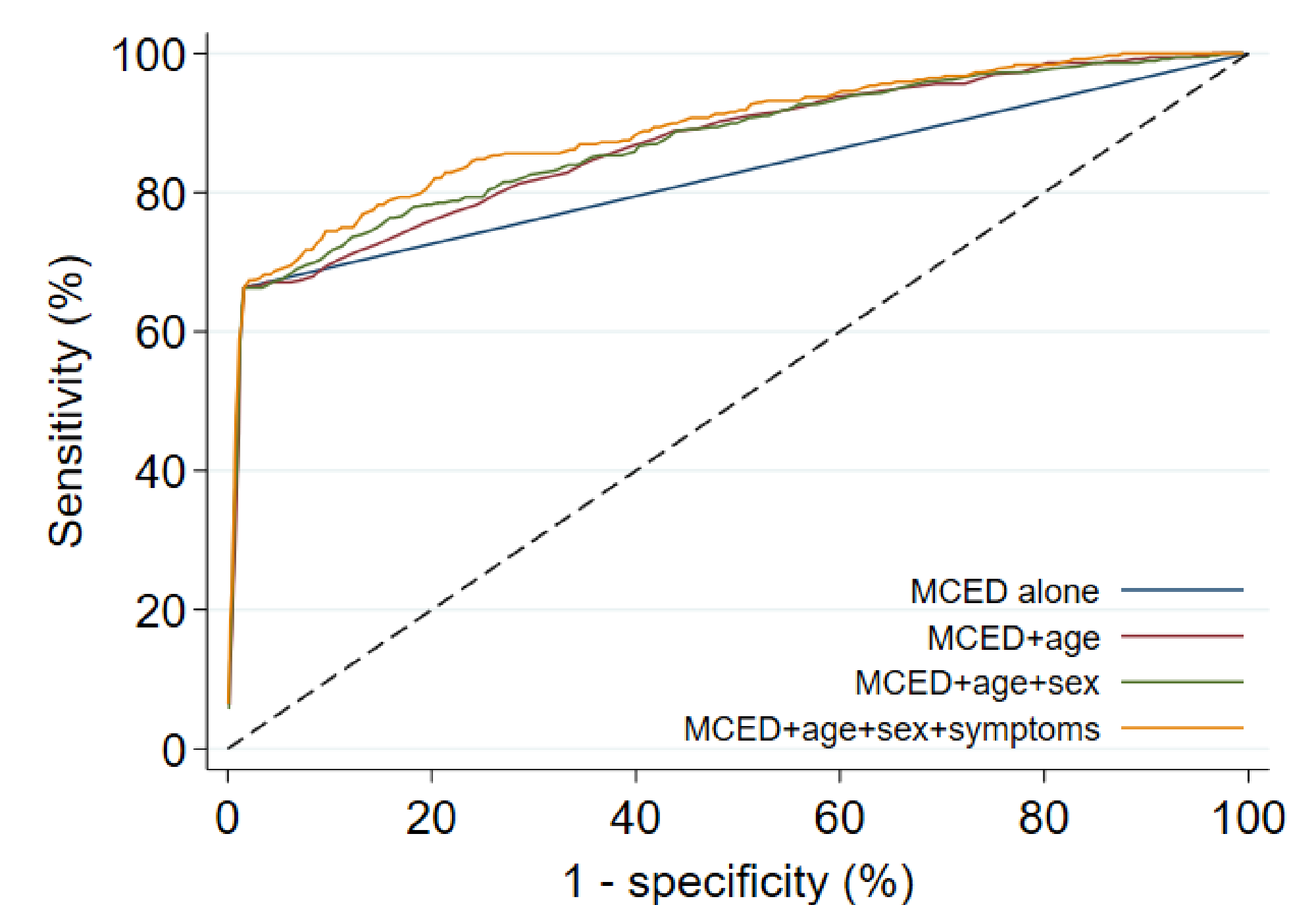
- The addition of age increased the AUC (0.87, 95% CI: 0.85-0.89) compared to that of the MCED alone (Table 1). The further addition of sex did not further increase the AUC.
- The AUC increased further with the addition of individual blood tests (0.88 AST to 0.90 albumin) and symptoms (0.87-0.88) to age, sex, and the MCED test result.
- The AUC improved further with: MCED test, age, sex, and all blood tests (0.92, 95%CI: 0.89-0.95) and MCED test, age, sex, and all symptoms (0.89, 95%CI: 0.87-0.91).
- The ROC curves (Figure 1) highlight how sensitivity changes at a fixed specificity and vice versa. For example, at 80% sensitivity, specificity increased with the addition of each of age, sex, and symptoms.

Table 1. AUC of MCED alone and combined with age, sex, symptom clusters, and blood test results, overall by clinical pathway in this exploratory analysis

Variables	Overall		Lung		Gynae		Upper GI		Lower GI		RDC	
	n/N	AUC (95% CI)	n/N	AUC (95% CI)	n/Ns	AUC (95% CI)	n/N	AUC (95% CI)	n/N	AUC (95% CI)	n/N	AUC (95% CI)
MCED alone	368/5461	0.82 (0.80, 0.85)	89/299	0.83 (0.79, 0.88)	54/1446	0.73 (0.66, 0.80)	46/1021	0.89 (0.83, 0.95)	143/2202	0.84 (0.80, 0.88)	36/493	0.77 (0.69, 0.85)
Participant characteristics												
MCED, age	368/5461	0.87 (0.85, 0.89)	89/299	0.86 (0.80, 0.91)	54/1446	0.83 (0.77, 0.90)	46/1021	0.85 (0.77, 0.94)	143/2202	0.88 (0.84, 0.92)	36/493	0.78 (0.68, 0.87)
MCED, sex	368/5461	0.84 (0.82, 0.87)	89/299	0.85 (0.79, 0.90)	54/1446	0.73 (0.66, 0.80)	46/1021	0.92 (0.87, 0.97)	143/2202	0.86 (0.82, 0.90)	36/493	0.81 (0.72, 0.90)
MCED, age, sex	368/5461	0.87 (0.85, 0.90)	89/299	0.86 (0.81, 0.91)	54/1446	0.83 (0.77, 0.90)	46/1021	0.90 (0.84, 0.97)	143/2202	0.89 (0.86, 0.92)		0.82 (0.72, 0.91)
Participant characteristics and symptom clusters												
MCED, age, sex, lung symp. ¹	368/5461	0.88 (0.85, 0.90)	89/299	0.91 (0.87, 0.95)								
MCED, age, sex, gynae symp. ²	368/5461	0.87 (0.85, 0.89)			54/1446	0.83 (0.76, 0.90)						
MCED, age, sex, upper GI symp. ³	368/5461	0.88 (0.86, 0.90)					46/1021	0.94 (0.90, 0.98)				
MCED, age, sex, lower GI symp. ⁴	368/5461	0.88 (0.85, 0.90)							143/2202	0.89 (0.86, 0.93)		
MCED, age, sex, NSS symp. ⁵	368/5461	0.88 (0.86, 0.90)									36/493	0.81 (0.71, 0.90)
MCED, age, sex, RDC symp. ⁶	368/5461	0.87 (0.85, 0.90)									36/493	0.80 (0.70, 0.90)
Participant characteristics and all symptoms*												
MCED, age, sex, all symptoms*	368/5461	0.89 (0.87, 0.91)	89/299	0.88 (0.84, 0.93)	54/1446	0.83 (0.76, 0.90)	46/1021	0.93 (0.87, 0.98)	143/2202	0.89 (0.86, 0.93)	36/493	0.81 (0.73, 0.90)
Participant characteristics, symptom clusters, and blood tests												
MCED, age, sex, bloods ⁷ , lung symp. ¹	147/159	0.91 (0.88, 0.94)	57/135	0.92 (0.86, 0.97)								
MCED, age, sex, bloods ⁷ , gynae symp. ²	147/159	0.90 (0.86, 0.93)			8/224	0.99 (0.97, 1.00)						
MCED, age, sex, bloods ⁷ , upper GI symp. ³	147/154	0.90 (0.87, 0.94)					13/226	1.00 (0.99, 1.00)				
MCED, age, sex, bloods ⁷ , lower GI symp. ⁴	147/159	0.90 (0.87, 0.93)							47/694	0.94 (0.90, 0.98)		
MCED, age, sex, bloods ⁷ , NSS symp. ⁵	147/155	0.90 (0.87, 0.93)									22/257	0.89 (0.79, 0.99)
MCED, age, sex, bloods ⁷ , RDC symp. ⁶	147/159	0.90 (0.87, 0.93)									22/257	0.89 (0.79, 0.99)
Participant characteristics, all symptoms and all blood tests												
MCED, age, sex, all blood tests, symptoms.	147/152	0.93 (0.91, 0.96)	57/135	0.95 (0.91, 0.98)	8/206	1.00 (1.00, 1.00)	13/222	1.00 (1.00, 1.00)	47/693	0.96 (0.94, 0.99)	22/257	0.92 (0.84, 0.99)

¹Lung symptoms: Appetite Loss, Cough, Fatigue, Haemoptysis, Shortness of Breath, Weight Loss; ²Gynae symptoms: Abdominal Pain, Bloating, Post-menopausal Bleed; ³Upper GI symptoms: Abdominal Mass, Abdominal Pain, Anaemia, Appetite Loss, Dyspepsia, Dysphagia, Early Satiety, Nausea, Reflux, Vomiting, Weight Loss; ⁴Lower GI symptoms: Abdominal Mass, Abdominal Pain, Anaemia, Bloating, Change in Bowel Habit, Rectal Bleed, Weight Loss; ⁵Non-specific symptoms (NSS): Abdominal Pain, Anaemia, Appetite Loss, Back Pain, Bloating, Dyspepsia, Fatigue, GP Gut Feeling, Nausea, Pain, Weight Loss; ⁶Rapid Diagnostic Centre (RDC) symptoms: Abdominal Mass, Appetite Loss, Bloating, Fatigue, GP Gut Feeling, Nausea, Weight Loss; ⁷Blood tests: Haemoglobin, MCH, MCV, Platelets, WBC, ALP, Albumin, Bilirubin; ⁸the 15 most common symptoms prompting referral with at least ten cancers diagnosed

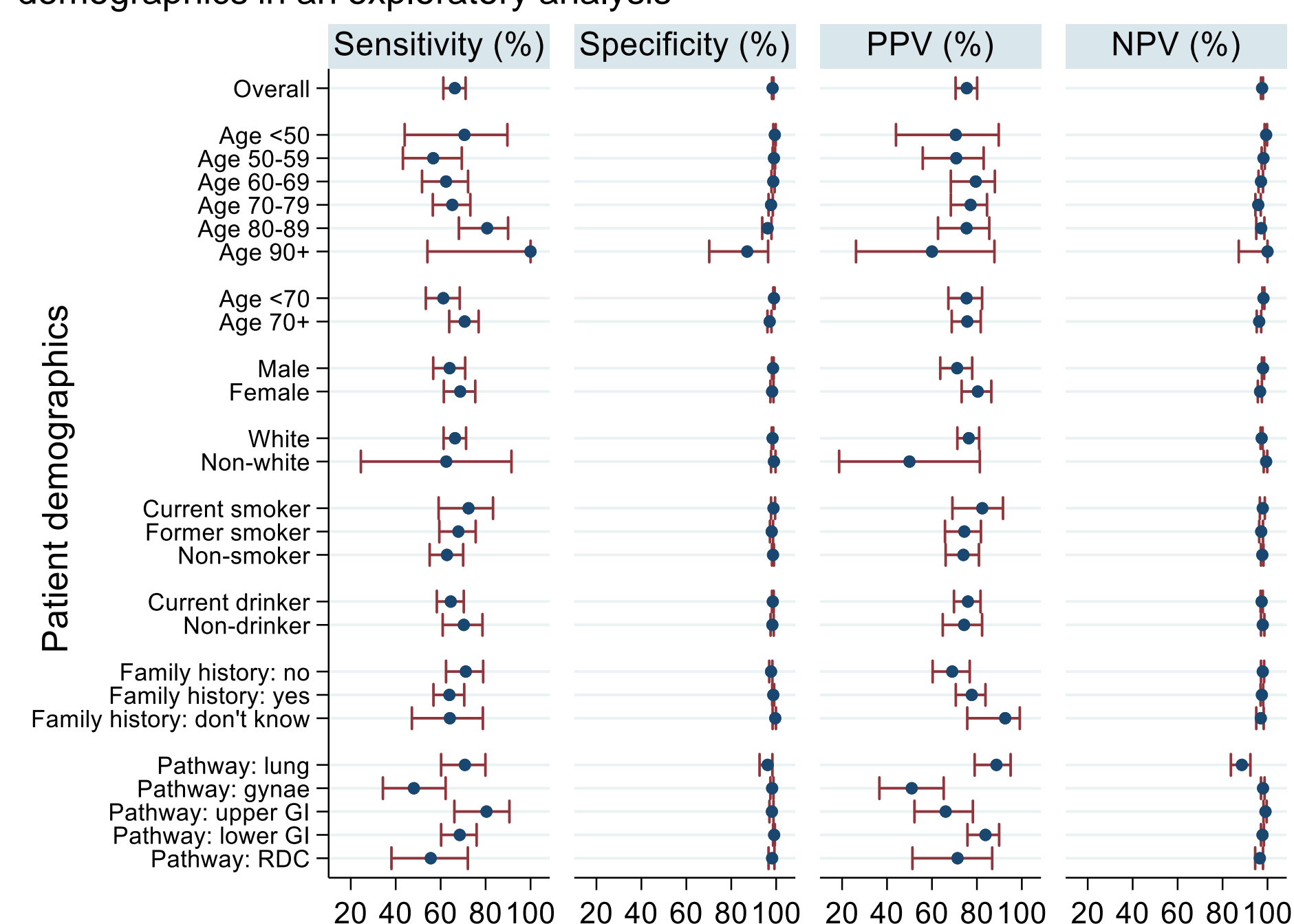
Figure 1. ROC curves of the MCED alone and combined with other patient data



MCED performance in subgroups

- Diagnostic accuracy of the MCED in subgroups is in Figure 2.

Figure 2. Diagnostic accuracy of the MCED in subgroups of patient demographics in an exploratory analysis



False positive analysis

- Age appeared to be the strongest predictor of a false positive MCED test result in this exploratory analysis (Table 2).
- An increasing age appeared to increase the likelihood of a false positive MCED test.
- Sex, ethnicity, and smoking status were not associated with a false positive MCED in this exploratory analysis.

Table 2. Association between patient demographics and a false positive MCED test in an exploratory analysis

Predictor	Odds ratio (95% CI)
Age	1.06 (1.04, 1.08)
Sex male (ref=female)	1.01 (0.63, 1.61)
Ethnicity non-white (ref=white)	0.81 (0.32, 2.00)
Smoking former (ref=smoker)	1.07 (0.50, 2.30)
Smoking non-smoker (ref=smoker)	0.81 (0.38, 1.71)

Prediction model

- Pain, cough, and dysphagia were selected by backward selection in an exploratory prediction model (Table 3).
- There was little optimism in the performance measures (Table 4).
- The AUC improved with then inclusion of the MCED: 0.71 to 0.88

Table 3. Prediction model for 9-month cancer detection

Predictor	Odds ratio (95% CI)	p-value
MCED+ (ref=-)	107.52 (77.93, 148.34)	<0.001
Age	1.02 (1.01, 1.03)	<0.001
Sex male (ref=female)	1.57 (1.16, 2.12)	0.003
Pain (ref=no)	1.61 (1.05, 2.48)	0.029
Cough (ref=no)	2.48 (1.26, 4.90)	0.009
Dysphagia (ref=no)	0.35 (0.18, 0.69)	0.002
Constant	0.00 (0.00, 0.01)	<0.001

Table 4. Performance measures of the prediction model

Performance measure (95% CI)	Apparent performance	Optimism-corrected	When the MCED is excluded from the model
AUC	0.88 (0.86, 0.91)	0.88	0.71 (0.68, 0.73)
Observed/expected	1.00	1.00	1.00
Calibration-in-the-large	0.00 (-0.15, 0.15)	0.00	0.00 (-0.11, 0.11)
Calibration slope	1.00 (0.93, 1.07)	1.00	1.00 (0.85, 1.15)

Discussion & Conclusions

- Results of our exploratory analysis show that predictive performance of the MCED test could be impacted by a complex set of factors, such as patient characteristics, symptoms, and blood test results, and this has been reported with other cancer detection tests. Considering further patient data with the MCED test may offer improved cancer risk stratification.
- Further work is required to understand what is driving the improvements observed in the AUC.
- Our findings support the prospective collection of clinical and blood test data in future MCED evaluations to assess their combined performance with MCED test results.

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References

- [1] Brian D. Nicholson *et al* (2023). Multi-cancer early detection test in symptomatic patients referred for cancer investigation in England and Wales (SYMPLIFY): a large-scale, observational cohort study. *The Lancet Oncology*. DOI: [https://doi.org/10.1016/S1470-2045\(23\)00277-2](https://doi.org/10.1016/S1470-2045(23)00277-2).
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