Long-term cancer registry follow-up of false positive multi-cancer early detection (MCED) test results from the SYMPLIFY study

Ashley Jackson[1,2], Pradeep S Virdee[1], Sharon Tonner[1],, Harpal Kumar[3], Sara Hiom[3], Kaveh Riahi[3], Jason Oke[1], Rafael Perera[1], Mark R Middleton[4], Brian D Nicholson[1].

[1]Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK
[2]Faculty of Medicine, University of Ottawa, Ottawa, ON
[3]GRAIL Bio UK, Ltd., London, UK
[4]Department of Oncology, University of Oxford, UK
brian.nicholson@phc.ox.ac.uk

Background & Aims

- The SYMPLIFY study was a prospective multicentre observational study evaluating the diagnostic performance of a methylation-based MCED test in symptomatic patients referred from primary care for urgent cancer investigation in England and Wales[1]
- Patients were followed in the SYMPLIFY study until diagnostic resolution or up to 9 months by research staff at each site and MCED predictions were compared with the diagnosis obtained by standard of care
- We aimed to follow-up the SYMPLIFY participants who were reported to have a false positive (FP) or true negative (TN) MCED test result in the original SYMPLIFY study for 24 months in the national cancer registry to determine how many developed cancer after the original study had concluded

Methods

- We followed all 5,461 patients enrolled in the SMPLIFY study in the National Cancer Registration Dataset (NCRD) and Welsh Cancer Intelligence and Surveillance Unit (WCISU) dataset for 24 months following their enrolment in the SYMPLIFY study to investigate for subsequent cancer diagnoses
- We compared the subsequent cancer rates among the 79 patients that were reported to have a FP MCED test result to the 5,014 patients that had a TN MCED test result in the original study o better understand the residual cancer risk in those with a FP MCED test result
- We additionally investigated the congruency between these subsequent cancer diagnoses and the presenting symptoms, referral pathway, and MCED test results to identify which cancers were likely related to the diagnosis, and which were more likely to be incidental findings

Cancer Diagnoses

There were 533 cancers diagnosed among the 5,461 patients enrolled in the SYMPLIFY study throughout the follow-up period. The median number of days between enrolment and diagnosis was 33 (IQR: 10-98).

Table 1. Characteristics of cancers diagnosed within 24 months of enrolment, based on standard of care investigations (CRF) and cancer registry data.

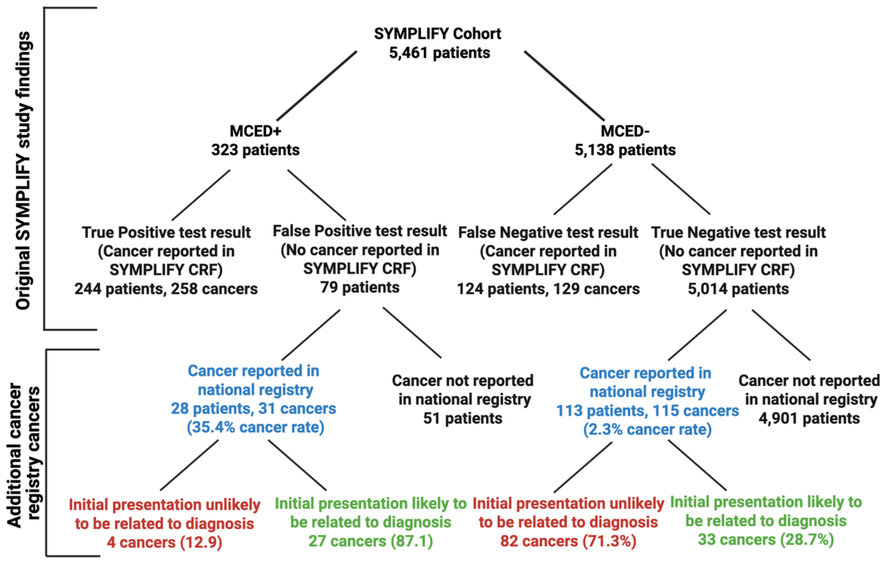
Characteristic	Number (%)	Median Days to Diagnosis (IQR)
Whole Cohort	533	33 (10-98)
Patient Demographics		
Age Group		
50-59	87 (16.3)	38 (9-132)
60-69	125 (23.5)	27 (10-86)
70-79	198 (37.2)	35 (11-108)
80-89	85 (16.0)	22 (9-91)
90+	12 (2.3)	63.5 (14.5-239)
<50	26 (4.9)	20 (6-71)
Sex		
Female	281 (52.7)	37 (12-110)
Male	252 (47.3)	29 (8-93)
Ethnicity		
Non-white	15 (2.8)	97 (42-540)
White	518 (97.2)	32 (10-95)
Cancer Characteristics		
Cancer Stage		
Stage I	163 (30.6)	59 (14-254)
Stage II	85 (16.0)	51 (15-106)
Stage III	138 (25.9)	21 (7-56)
Stage IV	106 (19.9)	18.5 (7-63)
Unknown	41 (7.7)	63 (27-228)
Referral Pathway		
Gynae 2WW	81 (15.2)	68 (17-157)
Lower GI clinic	213 (40.0)	29 (10-103)
Lung 2WW	104 (19.5)	14 (6-34)
Rapid diagnostic centre	49 (9.2)	51 (19-120)
Upper GI 2WW	86 (16.1)	53.5 (19-299)
Time to Diagnosis		
Within 28 days of enrolment	252 (47.3)	9 (1-16)
>28 days after enrolment	281 (52.7)	93 (56-362)
Present in CRF/Registry		
CRF only	45 (8.0)	21 (7-69)
Registry only	154 (28.9)	323.5 (90-548)
Both	334 (62.7)	20 (7-50)

Subsequent Cancer Diagnoses

We found that 28 (35.4%) of patients who had a False Positive MCED test in the original SYMPLIFY study ended up having a cancer reported in the national registry within 24 months of study enrolment, accounting for 31 cancers in total (Fig. 1). Only 113 (2.3%) of patients with a True Negative MCED test result had a cancer reported in the national registry, accounting for 115 total cancers.

Among the 31 total cancers reported in the False Positive patients, 27 (87.1%) were likely to be related to the initial presentation, based on symptoms, pathway, and MCED test congruency, compared to only 33 (28.7%) of the 115 cancers in the previous True Negative group.

Figure 1. Breakdown of patients and cancers in the original and following the addition of subsequent registry cancers



Analysis of FP Cancers

Of the 28 participants initially classified with a FP MCED that were subsequently reported to have a cancer diagnosed in the cancer registry, 15 (53.6%) were female. 16/28 (57.1%) were diagnosed with cancer within 9 months of enrolment. 8 of the 16 were diagnosed with cancers that were incongruent with the diagnostic pathway chosen based on their presenting symptoms but the MCED Cancer Signal Origin (CSO) call was correct. The other 8 were referred to the correct diagnostic pathway for the cancer diagnosed, suggesting the cancer was missed by standard of care investigations or data entry errors during SYMPLIFY. 12/28 (39.3%) were diagnosed with cancer 10-24 months following enrolment. 7 of the 12 were diagnosed with pathway incongruent cancers but the MCED CSO was correct. For the remaining 5, the pathway initially chosen was appropriate for the cancer registered, suggesting the cancer was undetectable on initial standard of care investigation.

Table 2. Line listing of patients initially deemed FP in original SYMPLIFY study who were later found to have cancer within 24 months.

Patient	Cancer Site	Stage	MCED CSO 1	MCED CSO 2	Congruency	Time to Dx (days)
1	Ovarian	stage 4	ovary	uterus	Symptoms, pathway, MCED	157
2	Ovarian	stage 1	ovary	uterus	Symptoms, pathway, MCED	503
3	Uterus	stage 1	uterus	NA	MCED only	95
4	Lung, trachea and bronchus	stage 4	lung	lung/NET	Symptoms, MCED	64
5	Pancreas	stage 4	pancreas/ gallbladder	NA	Symptoms, MCED	15
6	Colorectal	stage 4	colorectal	NA	Symptoms, pathway, MCED	460
7	Liver, Bile Duct	stage 3	liver/bile duct	NA	MCED only	553
8	Head and neck	stage 4	head/neck	lung	MCED only	35
9	Plasma Cell	stage 2	plasma cell	sarcoma	MCED only	727
10	Ovarian	stage 3	uterus	breast	Symptoms, pathway	156
11	Colorectal	stage 4	colorectal	NA	Symptoms, MCED	91
12	Colorectal	stage 2	colorectal	NA	Symptoms, MCED	380
13	Lung, trachea and bronchus	stage 2	lung	NA	Symptoms, pathway, MCED	15
14	Oesophagus	stage 4	Upper GI	NA	MCED only	548
15	Other	stage 2	lung	head/neck	Symptoms, pathway, MCED	21
16	Colorectal	stage 1	colorectal	prostate	Symptoms, pathway, MCED	0
17	Lung, trachea and bronchus	stage 1	lung	NA	Symptoms, pathway, MCED	0
	Lung, trachea and bronchus	stage 4	lung	NA	Symptoms, pathway, MCED	24
18	Colorectal	stage 2	lymphoid	colorectal	None	68
19	Lymphoid	stage 4	lymphoid	NA	MCED only	19
20	Oesophagus	unknown	colorectal	Upper GI	Symptoms, pathway	392
21	Plasma Cell	stage 3	plasma cell	liver/bile duct	Symptoms, pathway, MCED	120
22	Colorectal	stage 3	colorectal	NA	Symptoms, MCED	49
23	Ovarian	stage 4	ovary	uterus	Symptoms, pathway, MCED	114
	Melanoma of skin	stage 2	ovary	uterus	None	119
24	Lung, trachea and bronchus	stage 4	lung	NA	MCED only	546
25	Colorectal	stage 3	colorectal	NA	Symptoms, pathway, MCED	652
	Lung, trachea and bronchus	stage 1	colorectal	NA	None	684
26	Lung, trachea and bronchus	stage 4	lung/NET	lung	Symptoms, MCED	335
27	Liver, Bile Duct	unknown	lung	upper GI	Symptoms, pathway	362
28	Lung, trachea and bronchus	stage 3	head/neck	lung	None	423

Discussion & Conclusions

Summary

- We found that 35.4% of patients who had a FP MCED test result in the original SYMPLIFY study ended up having a cancer diagnosis recorded in the respective national cancer registries within two years of study enrolment, compared to only 2.3% of those with a TN MCED test result
- Based on these results there is a reduction in FPs from 79 to 51 and would result in the overall MCED PPV increasing from 75.5% (95% CI 70.5-80.1) to 84.2% (80.1-87.6)
- We found that most (87.1%) of the cancers diagnosed among the FP group were related to the initial presenting symptoms, referral pathway, and/or MCED test result, compared to only 28.7% of the TN

Conclusions

- Our results provide strong justification for proactive follow-up of positive MCED results where initial standard of care investigations do not identify cancer as approximately only third of these patients will be diagnosed with cancer within two years
- We outline an approach by which patients with symptoms concerning for cancer can be investigated based on presenting symptoms and MCED test results based on the findings of cancers diagnosed in this study (Fig. 2)

Figure 2. Proposed pathway for investigating positive MCED test results in symptomatic patients with theoretical proportions based on our study data.