

# Positive MCED test results associated with subsequent cancer diagnosis in participants in the SYMPLIFY study

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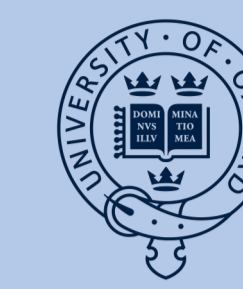
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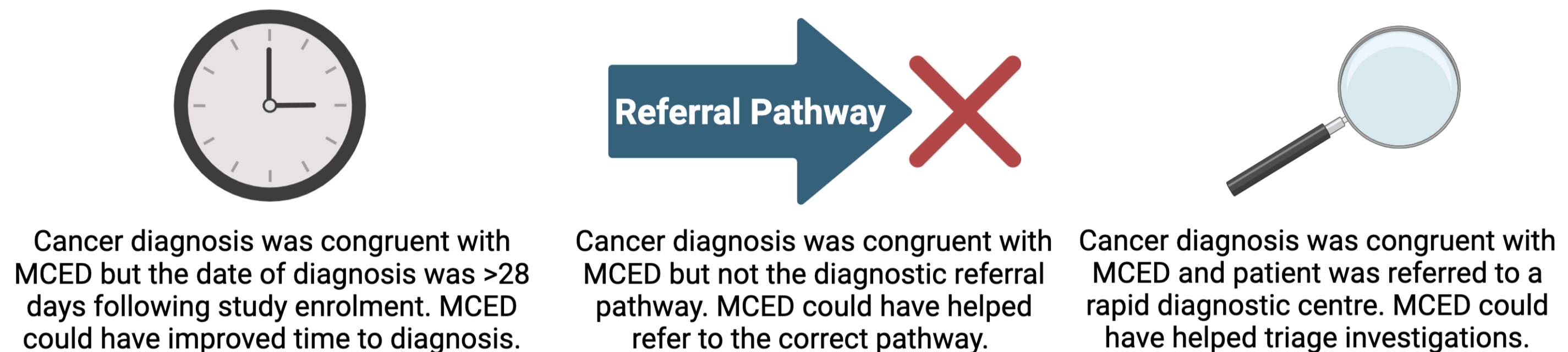
## Background & Aims

- The SYMPLIFY study demonstrated positive findings regarding the feasibility of using a multi-cancer early detection (MCED) test in a symptomatic population<sup>1</sup>
- However, further investigation is necessary to determine how MCED tests may aid the cancer diagnostic pathway and support the Faster Diagnosis Standard set out by NHS England, which aims for patients to receive a cancer diagnosis within 28 days of urgent referral<sup>2</sup>
- We were also interested in seeing how many patients who did not have cancers detected by standard of care investigations (SYMPLIFY) ended up having a cancer reported in the respective national registries, following recent evidence that patients who undergo urgent referral for investigation of cancer have an increased risk of receiving a cancer diagnosis in the following five years<sup>3</sup>
- We aimed to use data from SYMPLIFY and the respective national cancer registries to determine all cancers diagnosed among patients from the SYMPLIFY study and to highlight areas where an MCED test could have aided the diagnostic evaluation

## Methods

- We reviewed all cancers that were diagnosed among patients enrolled in the SYMPLIFY study, including those identified in the case report form, and those diagnosed in the respective national registries within 12 months of study enrolment
- Each cancer diagnosis was evaluated for congruence between the cancer site and the symptoms, diagnostic referral pathway, and MCED test cancer signal origin (CSO)
- Cancers were further characterised based on these congruency groupings and the time between enrolment and diagnosis to determine whether the MCED test may have provided an added benefit in the diagnostic process (Fig. 1)
- Additional analyses were conducted on cancers that were not detected by standard of care investigations (SYMPLIFY) but were reported in the respective national registries

Figure 1. Classifications of potential MCED benefit.



## MCED Benefit

There were 462 cancers diagnosed among the 5,461 patients enrolled in the SYMPLIFY study throughout the follow-up period. The average number of days between enrolment and diagnosis was 50.0 (SD = 68.6, range = 0-362). Of these, 254 (55.0%) cancers were diagnosed within 28 days of enrolment. Among the total cancers, 280 (60.6%) were diagnosed in patients with a positive MCED test, and 93 (20.1%) of the total cancers may have derived an additional benefit from the MCED test result. Table 1 outlines the breakdown of MCED test results and the cancers that may have benefitted from the use of the MCED test result in the diagnostic evaluation.

Table 1. Breakdown of MCED test results and benefit for all cancers.

Characteristic	Number (% of all cancers)
<b>MCED result</b>	
Negative	182 (39.4)
Positive	280 (60.6)
<b>MCED benefit</b>	
No benefit	369 (79.9)
Benefit	93 (20.1)
Diagnosed >28 days after enrolment	41 (8.9)
Wrong referral pathway	34 (7.4)
RDC referral	18 (3.9)

## Understanding Potential MCED Benefit

Table 2. Characteristics of cancers that may have benefitted from the MCED test result, based on the various congruency groupings. Presented as the number of MCED benefit cancers with each characteristic.

**Legend**  
0 cancers  
1 to 10 cancers  
11 to 20 cancers  
21 to 30 cancers  
>30 cancers

The cancer types that had the most benefit were colorectal (n=31), of which 11 cases occurred in patients whose MCED test and symptoms were congruent with the diagnosis but were incorrectly referred to a different diagnostic pathway (Table 2).

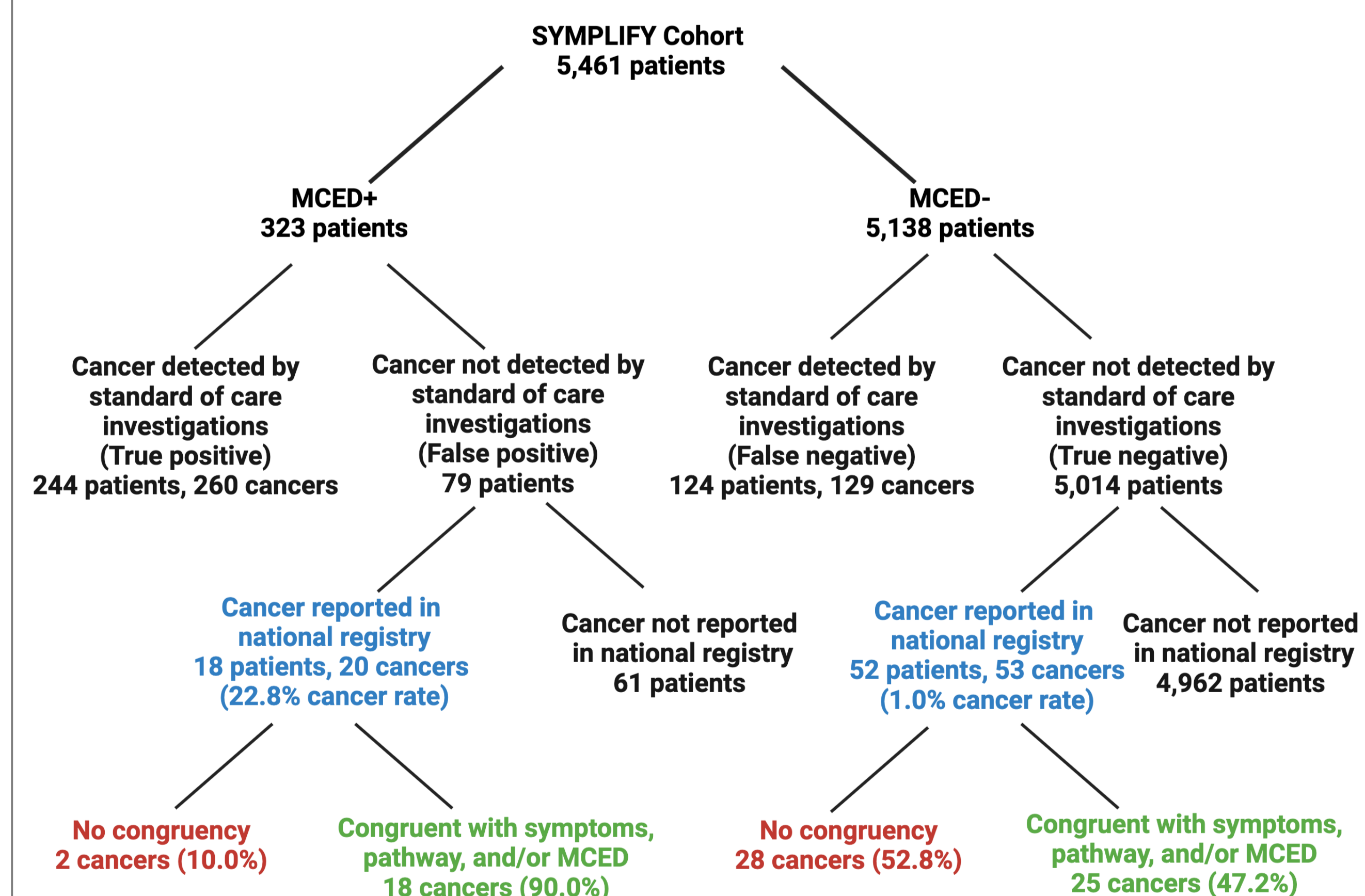
The symptom that was most common among cancers with a potential MCED benefit was unexplained weight loss, of which 23 were referred to the correct diagnostic referral pathway but were diagnosed >28 days after enrolment. Meanwhile, 9 cases were congruent with the symptoms and the MCED but were not referred to the correct pathway. Change in bowel habit (CIBH), abdominal pain, and anaemia were other common symptoms among cases of potential MCED benefit.

Cancer Characteristic	Symptoms, pathway, and MCED congruent but diagnosed >28 days or referred to RDC		Symptoms, MCED congruent	Only MCED congruent	Total MCED benefit
<b>Cancer Site</b>					
Bladder & urothelial tract	2	0	1	3	
Breast, female	1	1	2	4	
Cancer of unknown primary	2	0	0	2	
Colorectal	20	11	0	31	
Gallbladder	1	0	0	1	
Head and neck	0	0	1	1	
Liver, bile duct	2	0	0	2	
Lung, trachea, and bronchus	6	2	1	9	
Lymphoid	4	3	1	8	
Oesophagus	0	1	0	1	
Other	1	0	1	2	
Ovarian	6	0	1	7	
Pancreas	6	5	0	11	
Plasma cell	1	0	0	1	
Prostate	0	0	1	1	
Uterus	7	0	2	9	
<b>Stage</b>					
Stage 1	10	1	1	12	
Stage 2	14	4	1	19	
Stage 3	15	6	2	23	
Stage 4	17	11	6	34	
Unknown	3	1	1	5	
<b>Referral Pathway</b>					
Gynae 2WW	13	4	0	17	
Lower GI clinic	17	4	7	28	
Lung 2WW	5	4	2	11	
Rapid diagnostic centre	18	0	0	18	
Upper GI 2WW	6	11	2	19	
Abdominal pain	10	0	1	11	
Anaemia	6	3	1	10	
Appetite loss	6	0	0	6	
Bloating	2	3	0	5	
CIBH	8	3	3	14	
Cough	2	2	0	4	
Dyspepsia	1	3	0	4	
Dysphagia	0	1	1	2	
Fatigue	5	0	0	5	
IDA	0	2	2	4	
Pain	7	1	0	8	
PMB	7	0	0	7	
Rectal bleeding	6	0	2	8	
Upper abdominal pain	4	2	0	6	
Weight loss	23	9	3	35	

## Subsequent Cancer Diagnoses

We found that 18 (22.8%) of patients who had a positive MCED test with no cancer detected by standard of care investigations (SYMPLIFY) ended up having a cancer reported in the national registry (Fig. 2). Among the 20 cancers reported in these patients, 16 (80.0%) were congruent with the MCED CSO. Only 52 (1.0%) of patients with a negative MCED test with no cancer detected by standard of care investigations had a cancer reported in the national registry. Among these 53 cancers, 28 (52.8%) were not congruent with the symptoms or pathway associated with the initial referral. Including subsequent registry diagnoses resulted in a sensitivity of the MCED test of 59.8% (95% CI: 58.5-61.1), specificity of 98.8% (98.5-99.1), positive predictive value of 81.1% (80.1-82.2), and negative predictive value of 96.6% (96.1-97.1).

Figure 2. Breakdown of all cancers diagnosed among patients in the SYMPLIFY study either through standard of care investigations (SYMPLIFY) or through long-term registry follow-up.



## Discussion & Conclusions

### Summary

- We found that 20.1% of cancers diagnosed among patients from the SYMPLIFY study could have benefitted from using the MCED test result in the diagnostic work up of potential cancer, particularly in patients with non-specific symptoms that may be associated with multiple cancers
- We describe patients with a positive MCED test who were diagnosed with cancer several months after the initial referral and a higher rate of subsequent cancer diagnoses among patients with a positive MCED test than those with a negative result

### Conclusions

- MCED tests may assist clinicians with decision making regarding diagnostic referral routes and triaging investigations
- As a result, MCED tests have the potential to reduce diagnostic delays in some cases and may help in improving the number of cancer diagnoses that meet the Faster Diagnosis Standard

## References

- Nicholson BD, Oke J, Virdee PS, Harris DA, O'Doherty C, Park JE, et al. Multi-cancer early detection test in symptomatic patients referred for cancer investigation in England and Wales (SYMPLIFY): a large-scale, observational cohort study. *Lancet Oncol*. 2023;24(7):733-43.
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