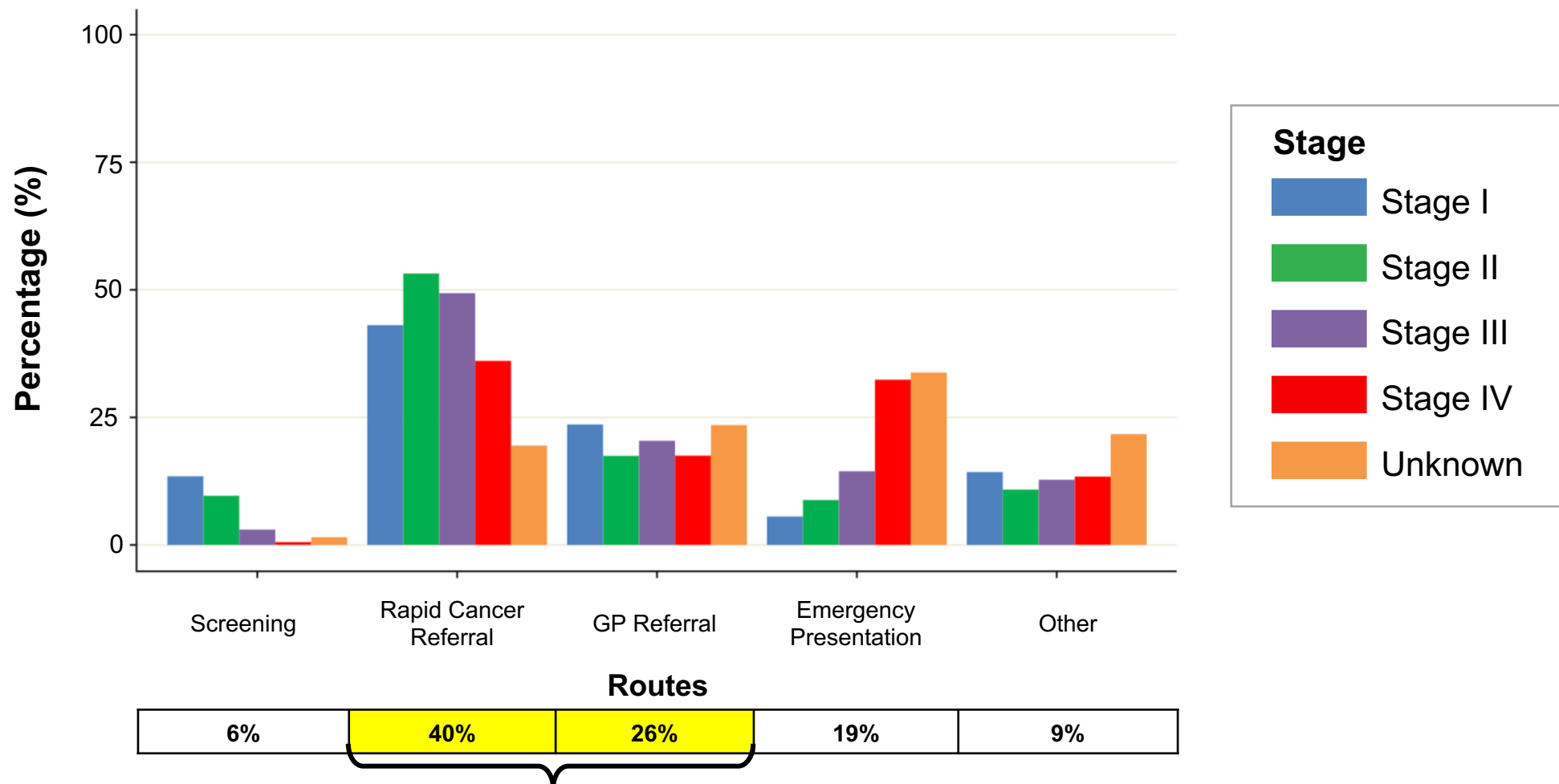


Large-scale observational prospective cohort study of a multi-cancer early detection (MCED) test in symptomatic patients referred for cancer investigation.

SYMPLIFY

Dr Brian D Nicholson, Associate Professor
Nuffield Department of Primary Care Health Sciences, University of Oxford, UK.

Routes to Cancer Diagnosis



GP, general practitioner.

<https://www.cancerdata.nhs.uk/covid-19/rcrd>

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Majority of Patients Diagnosed With Cancer Present With Symptoms

Red Flag Symptoms



Cough, Haemoptysis



Dysphagia



Rectal bleeding, Haematuria



Breast lump

Nonspecific Signs and Symptoms



Unexplained weight loss



Abdominal pain








Fatigue or exhaustion








Fever






Urgent Cancer Pathways Based on National Guidelines

Cancer Pathways and Sites			
	Gynaecological	<ul style="list-style-type: none">• Cervical• Endometrial• Ovarian	<ul style="list-style-type: none">• Vaginal• Vulval
	Lower Gastrointestinal	<ul style="list-style-type: none">• Anus• Colon	<ul style="list-style-type: none">• Rectum
	Upper Gastrointestinal	<ul style="list-style-type: none">• Gallbladder• Liver	<ul style="list-style-type: none">• Oesophago-gastric• Pancreas
	Lung	<ul style="list-style-type: none">• Lung	
	Rapid Diagnostic Centre	<ul style="list-style-type: none">• NA	

Symptoms by Pathway

Cancer Pathways and Sites			Symptoms
	Gynaecological	<ul style="list-style-type: none"> • Cervical • Endometrial • Ovarian 	<ul style="list-style-type: none"> • Abdominal mass • Change in bowel habit • Iron deficiency anaemia • Positive Fecal Immunochemical Test • Rectal bleeding • Weight loss and abdominal pain
	Lower Gastrointestinal	<ul style="list-style-type: none"> • Anus • Colon 	
	Upper Gastrointestinal	<ul style="list-style-type: none"> • Gallbladder • Liver 	
	Lung	<ul style="list-style-type: none"> • Lung 	
	Rapid Diagnostic Centre	<ul style="list-style-type: none"> • NA 	

Symptoms by Pathway

Cancer Pathways and Sites			Symptoms
	Gynaecological	<ul style="list-style-type: none"> • Cervical • Endometrial • Ovarian 	<ul style="list-style-type: none"> • Dysphagia • Weight loss and dyspepsia • Weight loss and reflux • Weight loss and upper abdominal pain
	Lower Gastrointestinal	<ul style="list-style-type: none"> • Anus • Colon 	
	Upper Gastrointestinal	<ul style="list-style-type: none"> • Gallbladder • Liver 	
	Lung	<ul style="list-style-type: none"> • Lung 	
	Rapid Diagnostic Centre	<ul style="list-style-type: none"> • NA 	
		<ul style="list-style-type: none"> • Vaginal • Vulval 	
		<ul style="list-style-type: none"> • Rectum 	
		<ul style="list-style-type: none"> • Oesophago-gastric • Pancreas 	

Symptoms by Pathway

Cancer Pathways and Sites				Symptoms
	Gynaecological	<ul style="list-style-type: none"> • Cervical • Endometrial • Ovarian 	<ul style="list-style-type: none"> • Vaginal • Vulval 	<ul style="list-style-type: none"> • Appetite loss • Fatigue • GP “gut feeling” • Nausea • Pain • Unexplained laboratory test results • Weight loss
	Lower Gastrointestinal	<ul style="list-style-type: none"> • Anus • Colon 	<ul style="list-style-type: none"> • Rectum 	
	Upper Gastrointestinal	<ul style="list-style-type: none"> • Gallbladder • Liver 	<ul style="list-style-type: none"> • Oesophago-gastric • Pancreas 	
	Lung	<ul style="list-style-type: none"> • Lung 		
	Rapid Diagnostic Centre	<ul style="list-style-type: none"> • NA 		

Most Common Symptoms Overall

Cancer Pathways and Sites		
	Gynaecological	<ul style="list-style-type: none"> • Cervical • Endometrial • Ovarian • Vaginal • Vulval
	Lower Gastrointestinal	<ul style="list-style-type: none"> • Anus • Colon • Rectum
	Upper Gastrointestinal	<ul style="list-style-type: none"> • Gallbladder • Liver • Oesophago-gastric • Pancreas
	Lung	<ul style="list-style-type: none"> • Lung
	Rapid Diagnostic Centre	<ul style="list-style-type: none"> • NA

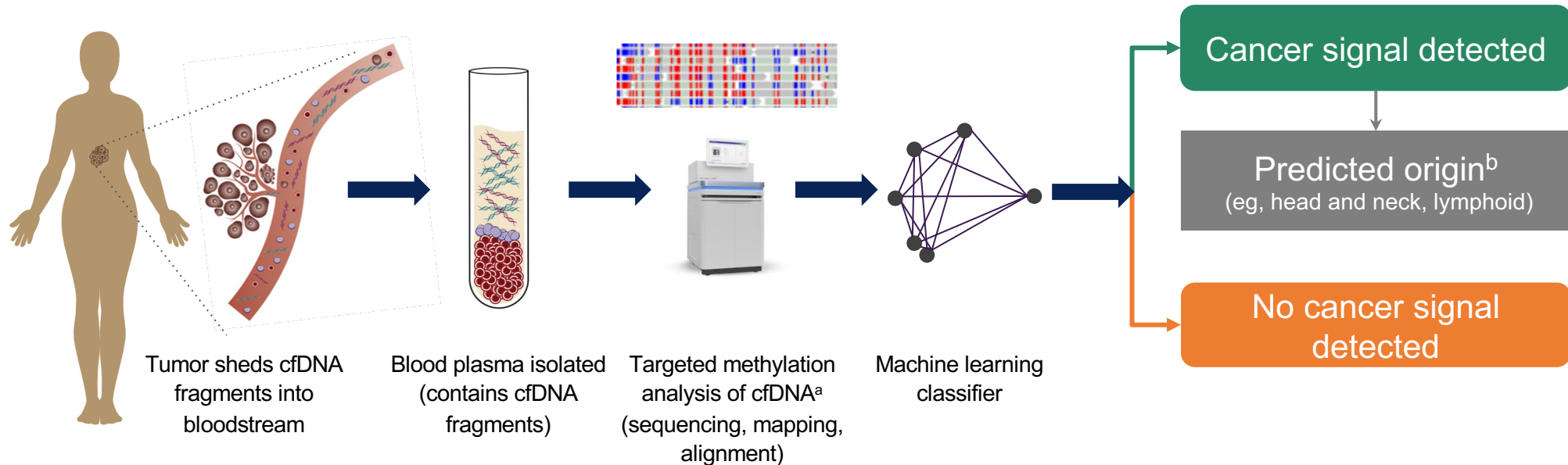
Most Common Symptoms

- Abdominal pain
- Anaemia
- Appetite loss
- Bloating
- Change in bowel habit
- Cough
- Dyspepsia
- Dysphagia
- Fatigue
- Iron deficiency
- Pain
- Postmenopausal bleeding
- Rectal bleeding
- Upper abdominal pain
- Weight loss

An MCED Test Developed for Asymptomatic Population

MCED testing uses a targeted methylation, next-generation sequencing (NGS)-based assay to:

- Detect and analyze cfDNA in the bloodstream
- Deploy machine learning to detect a cancer signal
- Predict the likely cancer signal origin (CSO)



cfDNA, cell-free DNA; MCED, multi-cancer early detection.

^aBisulfite treatment; targeted probes pull out fragments matching regions of interest. ^bFor a detected signal, the MCED test predicts 1-2 cancer signal origins (CSO) that can be either an anatomic site (eg, colorectal) or a cellular lineage (eg, lymphoid). Adapted from Liu MC, et al. Ann Oncol. 2020;31(6):745-759. PMID: 33506766

SYMPLIFY Study Design

- Prospective observational cohort study
- 44 hospital centres in England and Wales
- 6,240 patients in 5 months
- Symptomatic patients referred to one of five Cancer Pathways by their Family Doctor
- Each participant consented to:
 - An additional blood draw
 - Follow-up in NHS records and registries



NHS, National Health Service.

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Participants Baseline Demographics

5,461

participants reached diagnostic resolution and had an evaluable MCED test

Referral Pathway

1446



Gynaecological

2202



Lower GI

1021



Upper GI

299



Lung

493



RDC

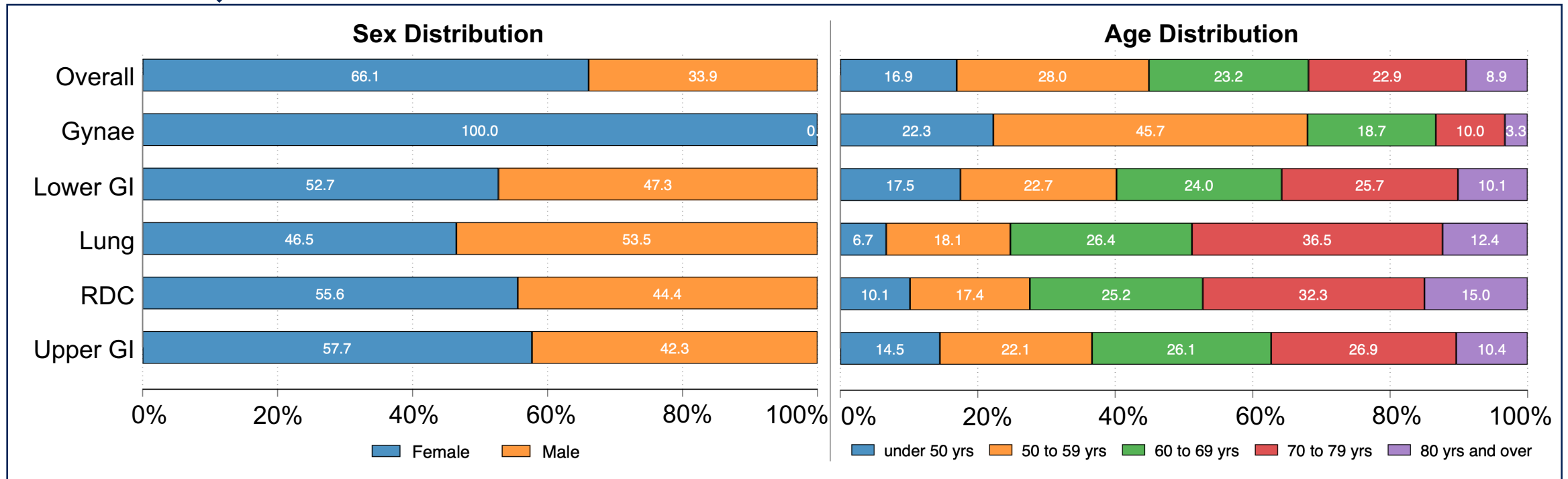
GI, gastrointestinal; MCED, multi-cancer early detection test; RDC, rapid diagnostic centre.

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Participants Baseline Demographics

5,461

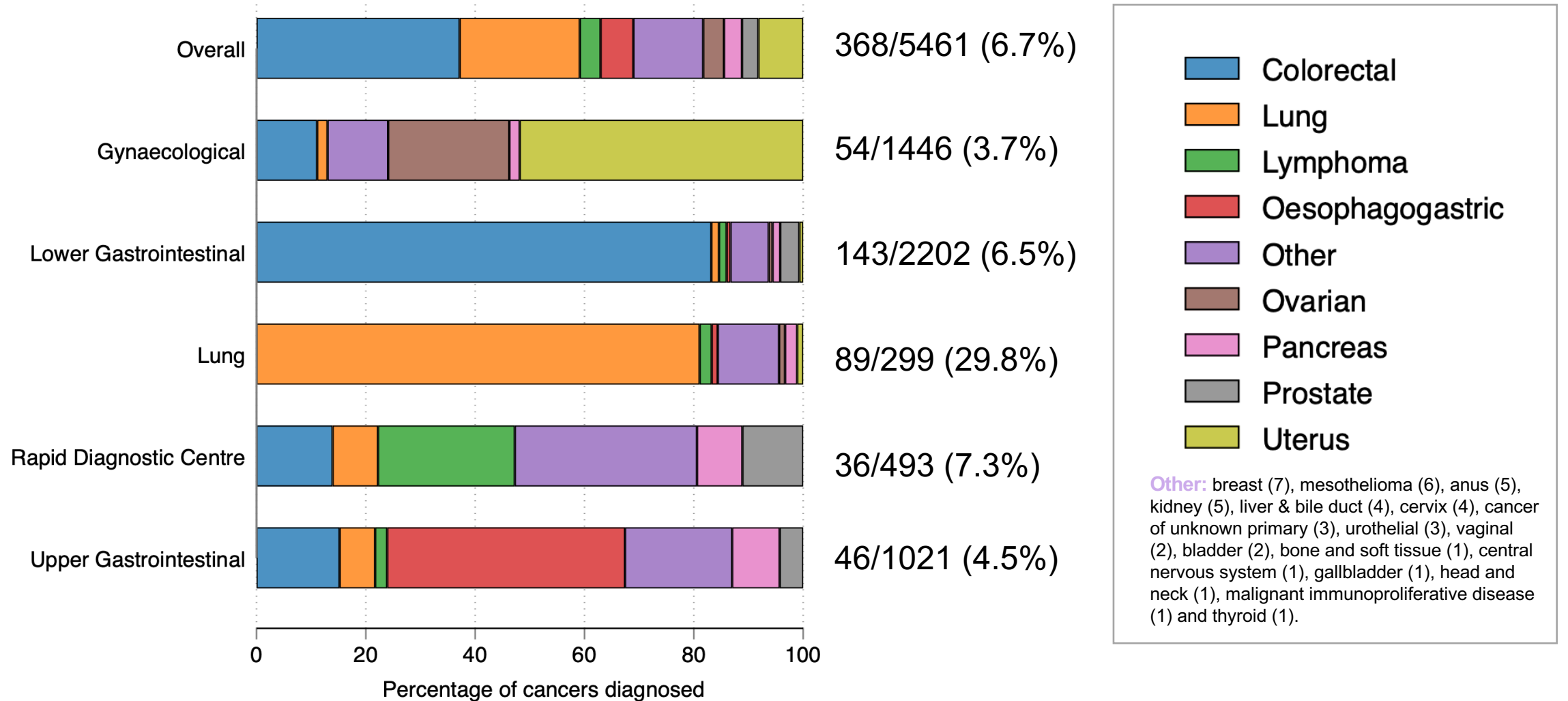
participants reached diagnostic resolution and had an evaluable MCED test



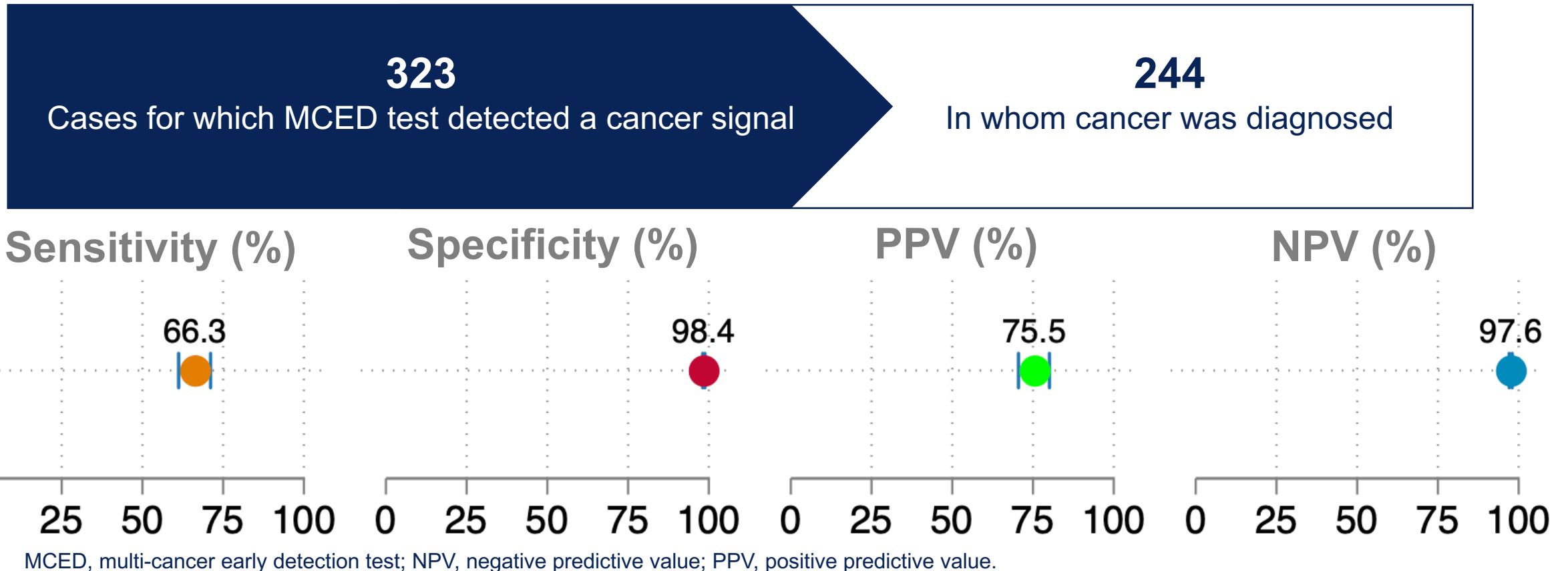
GI, gastrointestinal; MCED, multi-cancer early detection test; RDC, rapid diagnostic centre.

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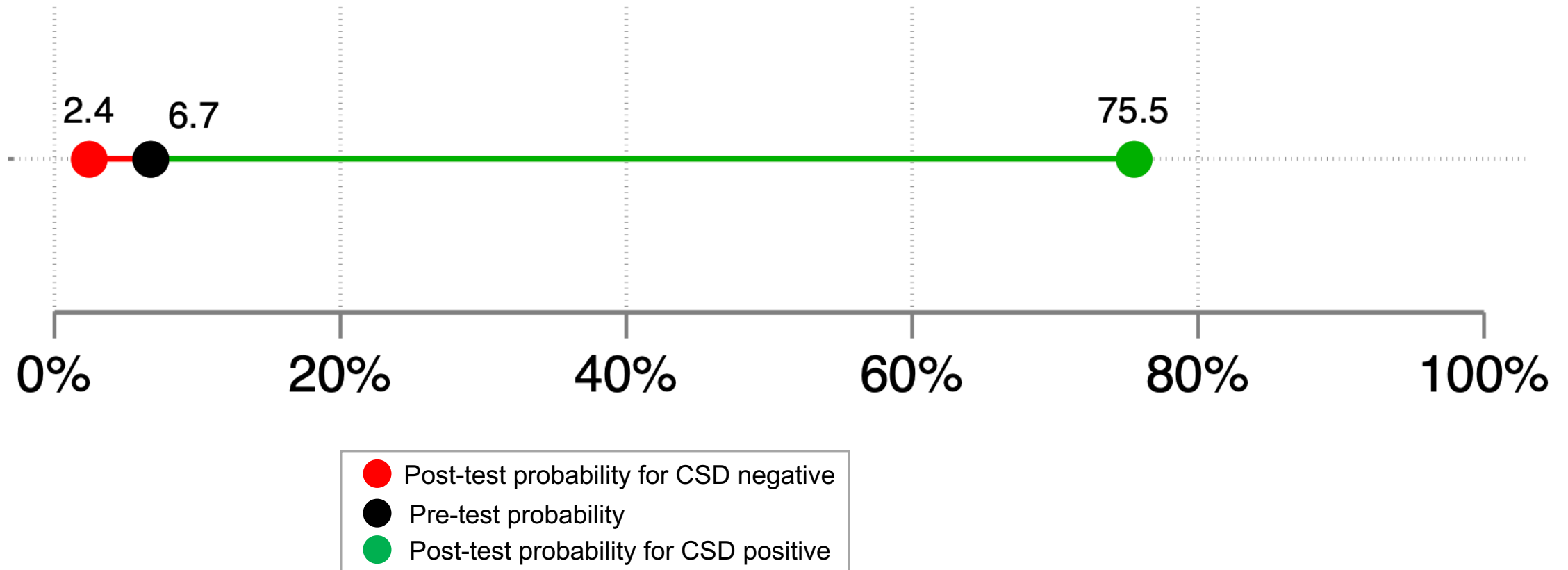
Cancers Diagnosed by Cancer Pathway



Primary Objective: To evaluate the performance of a MCED test for the detection of invasive cancer.



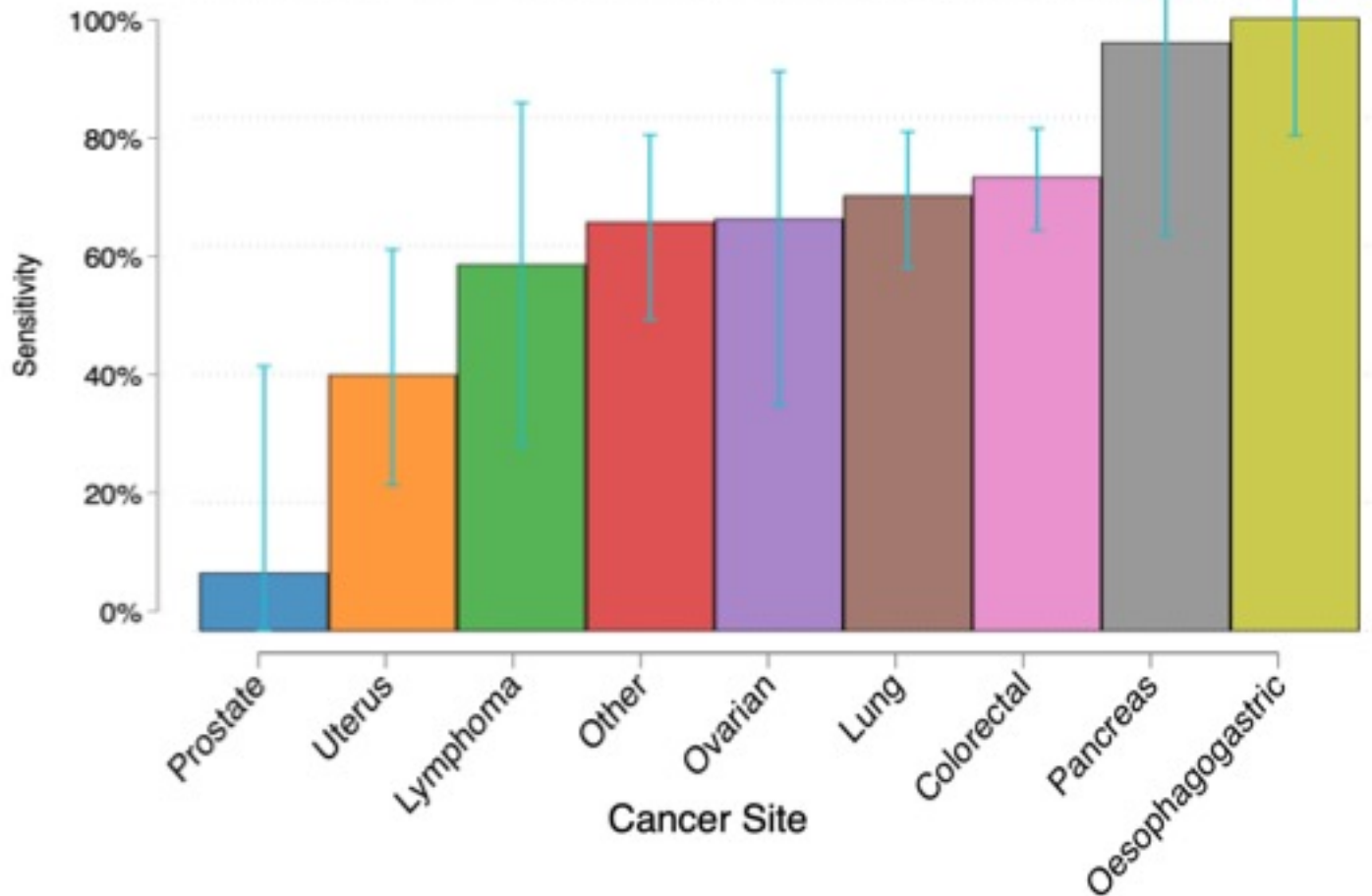
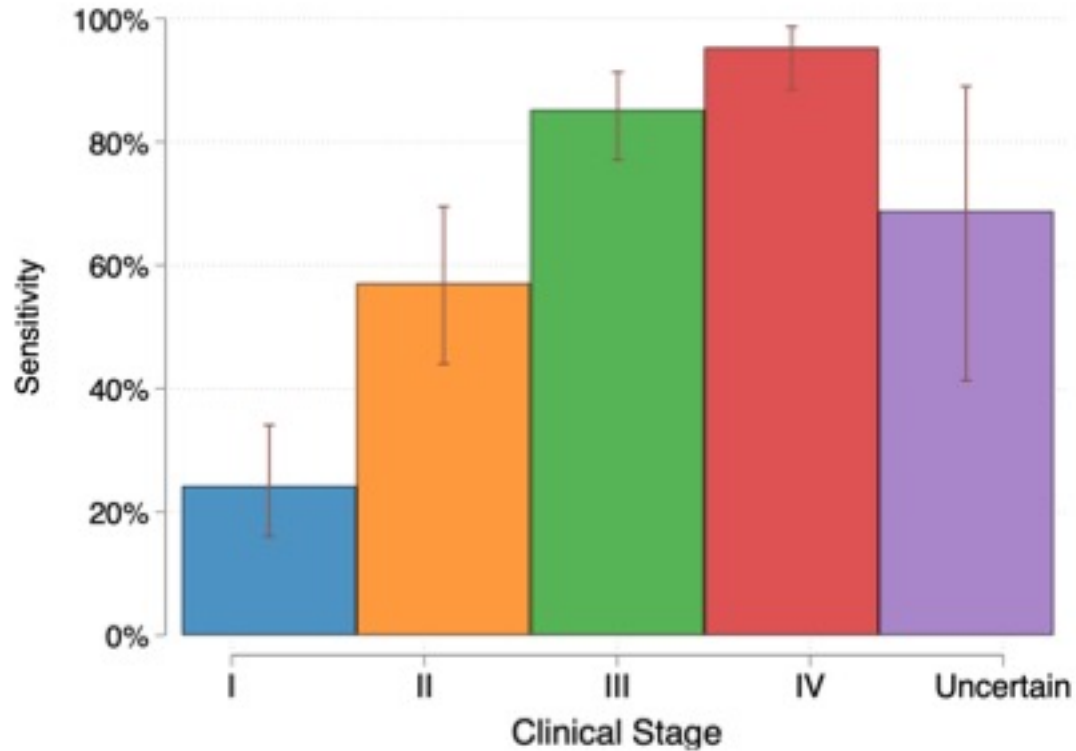
Primary Objective: To evaluate the performance of a MCED test for the detection of invasive cancer.



CSD, cancer signal detected; MCED, multi-cancer early detection test.

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Secondary Objective: To evaluate the performance of a MCED test by cancer stage and site.

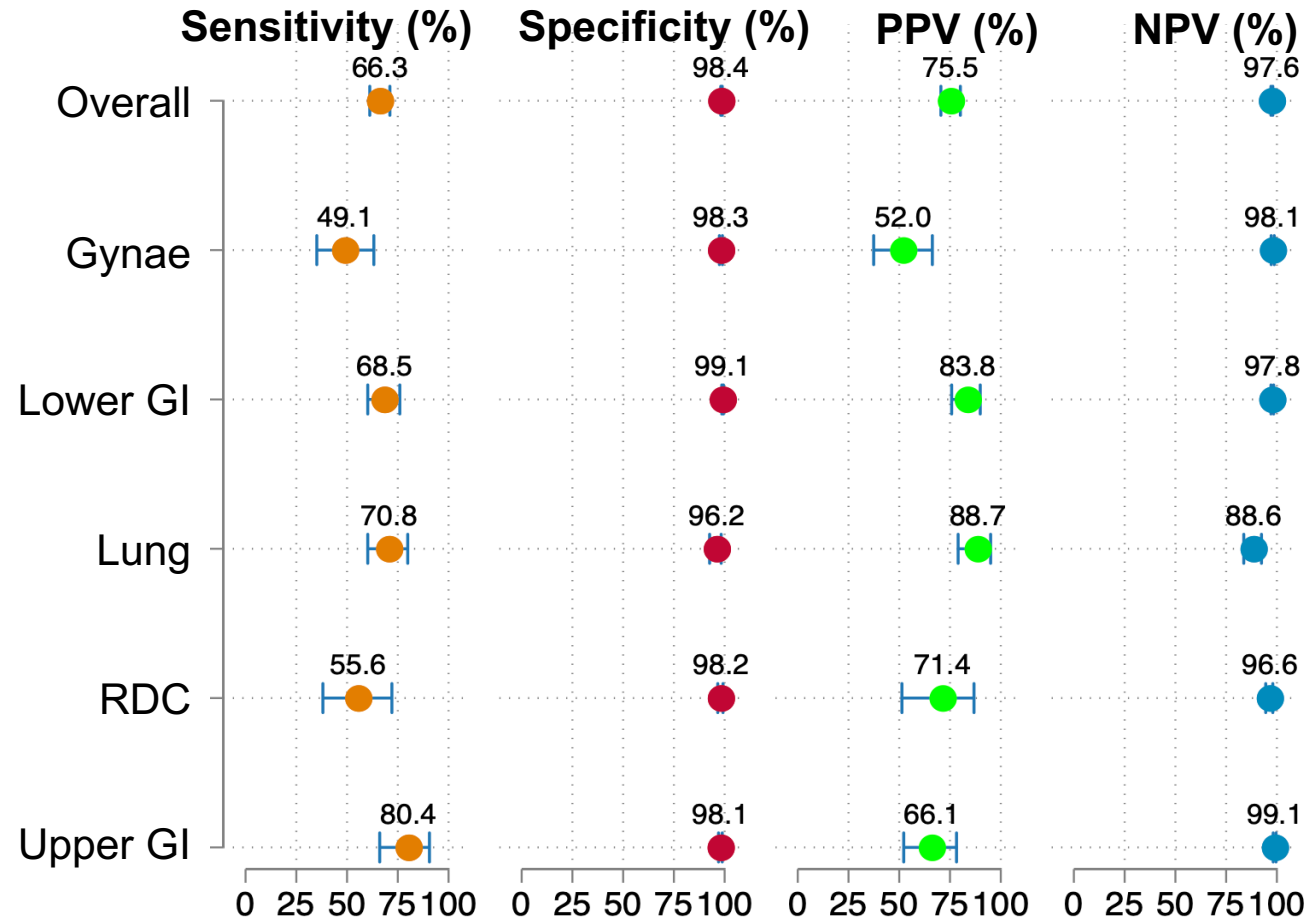


MCED, multi-cancer early detection test.

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Diagnostic Accuracy of Cancer Signal Detected

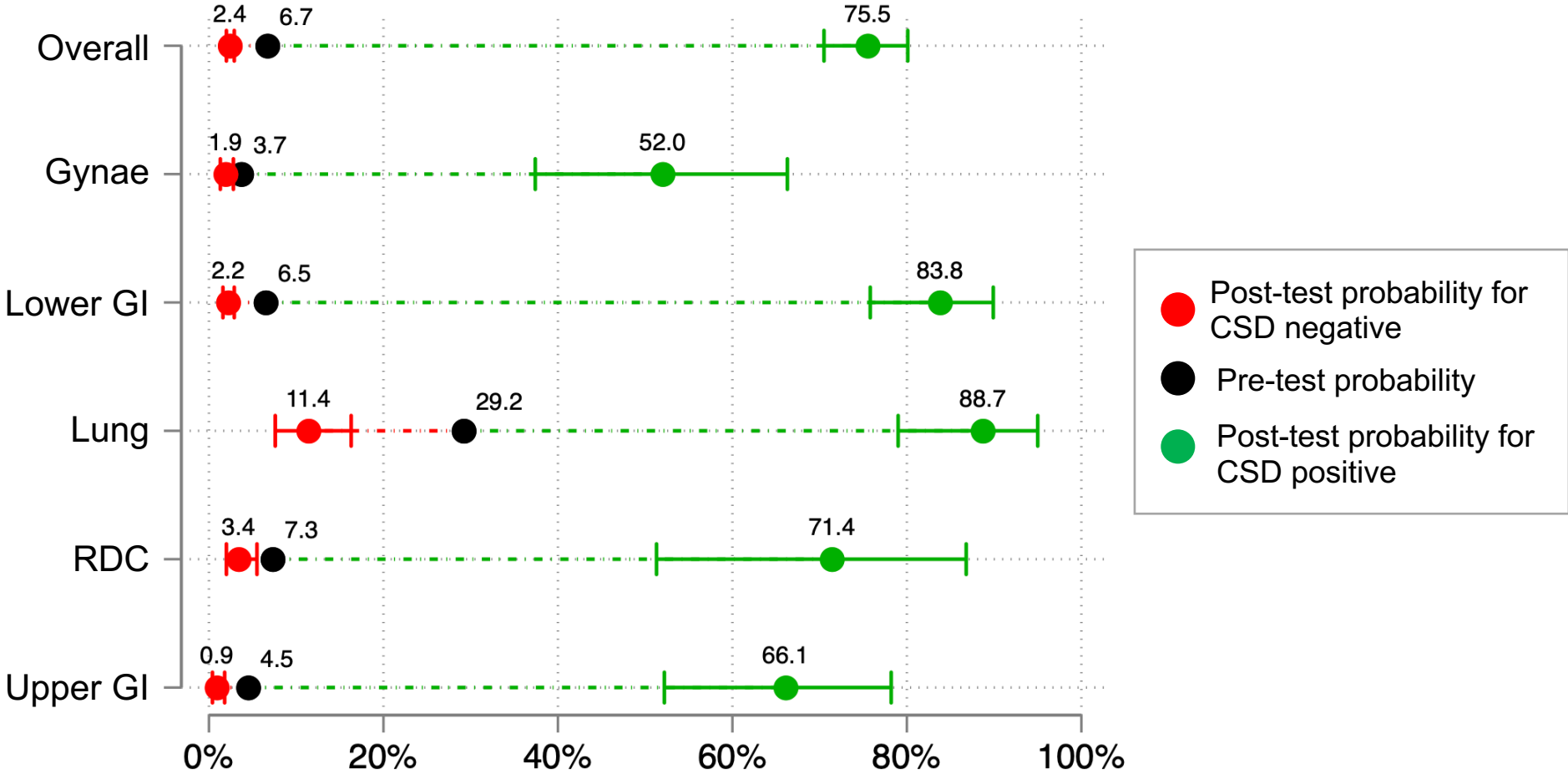
Cancer Referral Pathways



GI, gastrointestinal; RDC, rapid diagnostic centre.

Cancer Risk Following Cancer Signal Detected Result

Cancer Referral Pathways

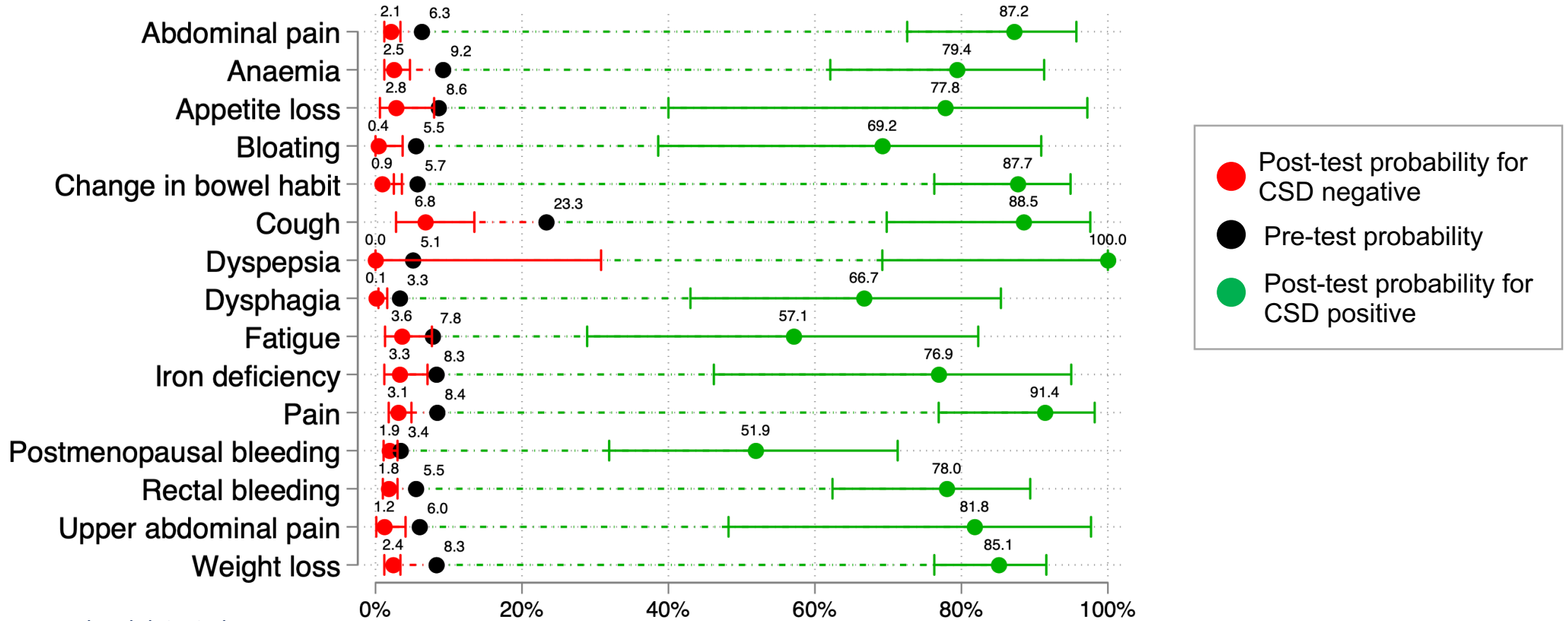


CSD, cancer signal detected, GI, gastrointestinal; RDC, rapid diagnostic centre.

Cancer Risk Following Cancer Signal Detected Result

Symptoms

Secondary care referred cancer pre-test probability

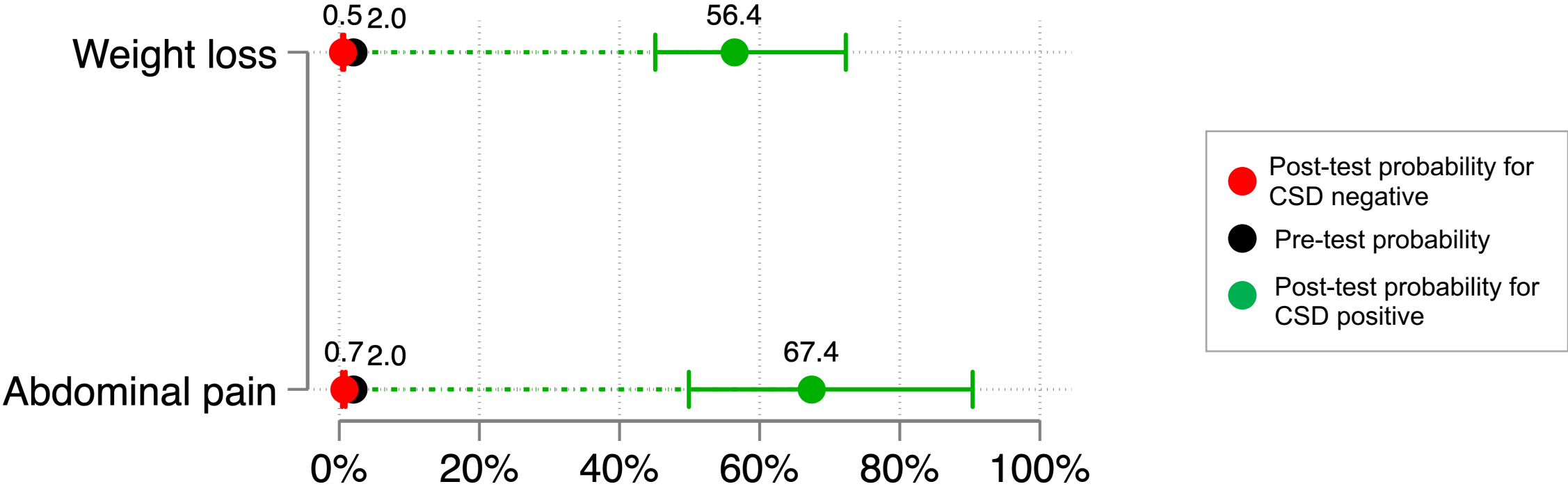


CSD, cancer signal detected.

Cancer Risk Following Cancer Signal Detected Result

Symptoms

Primary care pre-referral cancer pre-test probability



CSD, cancer signal detected.

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Accuracy of Predicted Cancer Signal Origin

Predicted Cancer Signal Origin	Anus	Blad/Uro	Bone & ST	Breast	Cervix	Colorectal	H&N	Kidney	Liver/BD	Lung	Lymphoid	Melanoma	Myeloid	NET	Oes/Sto	Ovary	Panc/GB	Plasma	Prostate	Thyroid	Uterus	CNS	CUP	Other	No Cancer
CSD -																									
Uterus					1											1					12				4
Thyroid																									
Prostate										1										1					5
Plasma																									6
Panc/GB															1		1	11							2
Ovary										2						6									4
Oes/Sto															17										3
NET										4					6										2
Myeloid																									
Melanoma																									
Lymphoid						2					7						1							1	9
Lung	1				1				1	36	1				3	2		1							3
Liver/BD									3															2	2
Kidney								1																	1
H&N	4				1					1						1									1
Colorectal						94				2					1										14
Cervix																									
Breast				4						1															5
Bone & ST																									
Blad/Uro		2																							
Anus	1																								

**Accuracy of cancer signal origin prediction:
85.2% (79.8% to 89.3%)**

Concluding Points

- Large-scale rapid studies of MCED tests in symptomatic patients are feasible in routine clinical practice.
- The current MCED test showed increased sensitivity for cancer detection with increasing cancer stage, with variation in accuracy by referral pathway, and for individual symptoms.
- High overall specificity and positive predictive values indicate that if positive, the current MCED test could be used to confirm that referred patients should be investigated for cancer.
- Moderate overall sensitivity suggests that a negative result would not currently be sufficient to de-escalate referred patients from further investigation, except for the upper GI pathway.
- Many cancers were “off-target” to those inferred by the symptoms that led to referral demonstrating the benefit of a Cancer Signal Origin prediction with high accuracy.

MCED, multi-cancer early detection test.

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Implications

- Once the algorithm is optimised for NPV in symptomatic patients using our data it should have greater utility to inform decisions about cancer investigation.
- Testing symptomatic patients with lower pre-test probabilities for cancer in primary care before referral could permit both the use of a positive MCED result to confirm referral was indicated and a negative result to reassure about a decision not to refer.
- Large interventional studies of the MCED test are required to ascertain the impact on time to diagnosis, stage at diagnosis, and the resources used to achieve that diagnosis as early readouts, and on overall survival and mortality in the longer term.

MCED, multi-cancer early detection test; NPV, negative predictive value.

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Acknowledgements

Thank you!

All participants: for consenting and taking part.

- **Study Team: Chief Investigator:** Professor Mark Middleton; **Oxford University:** Jason Oke, Pradeep S Virdee, Sharon Tonner, Monika Vargova, Lazarina Engonidou, Ly-Mee Yu, Clare Freestone, Sarah Pearson, FD Richard Hobbs, Rafael Perera; **GRAIL:** Kaveh Riahi, Ying Luan, Sara Hiom, Harit Nandani, Kate Kurtzman, Harpal Kumar; **NIHR Clinical Research Network:** Pippa Corrie, Teresa Lockett, Mark Dolman.
- **Recruiting sites:** **University Hospital Southampton NHS Foundation Trust** - Mr Zaed Hamady (PI); **Buckinghamshire Healthcare NHS Trust** - Dr XingWu Zhu (PI); **Oxford University Hospitals NHS Foundation Trust** - Dr John Park (PI); **Royal Berkshire NHS Foundation Trust** - Dr Gelareh Eslamian (PI); **Mid and South Essex NHS Foundation Trust** - Dr Catherine O'Doherty (PI); **Torbay & South Devon Foundation Trust** - Dr Louise Medley (PI); **Royal Cornwall Hospital NHS Trust** - Dr Duncan Wheatley (PI); **Royal Free London NHS Foundation Trust** - Dr Anant Patel (PI); **University College London Hospitals NHS Foundation Trust** - Dr Vinay Seghal (PI); **North Middlesex University Hospital NHS Trust** - Dr Andrew Millar (PI); **York & Scarborough Teaching Hospitals NHS Foundation Trust** - Dr James Turvill (PI); **Hull University Teaching Hospitals NHS Trust** - Dr Shagufta Mirza (PI); **Chelsea and Westminster Hospital NHS Foundation Trust** - Dr Abhijit Gill (PI); **Velindre NHS Trust** - Professor Dean Harris (PI).

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