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# Diagnostic Journey Following a Multi-cancer Early Detection Test: A Retrospective Case Series of Gastrointestinal Cancers in the PATHFINDER Study

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## INTRODUCTION

- The USPSTF recommends screening for only a few select cancers (breast, cervical, colorectal, lung)[1]
- A blood-based multi-cancer early detection (MCED) test is available for use as a complement to existing single cancer screening modalities (Galleri®)[2]
- A multi-cancer approach to screening is novel, and healthcare providers may have questions on how, when, and in whom to implement the test, and what diagnostic follow up should be expected
- PATHFINDER (NCT04241796; enrollment complete, n=6662)[3] is a multi-center, prospective study in asymptomatic adults ≥50 years of age that returns MCED test results:
  - 'Signal not detected' or 'Signal detected'
  - For those with a signal detected, ≥1 cancer signal origin (CSO) prediction is included to direct diagnostic workup
- Interim data are available from the PATHFINDER study, allowing an assessment of participants who had their MCED test results shared as of the interim cut-off date
- A review of these participants with a cancer signal detected and CSO prediction that guided diagnostic workup to achieve a confirmed cancer diagnosis can provide early clinical insight
- The focus here is gastrointestinal (GI) cancers as they are common and contribute to roughly a third of all cancer-related deaths, but, with the exception of colorectal cancer, do not have USPTF-recommended screening options[4,5]

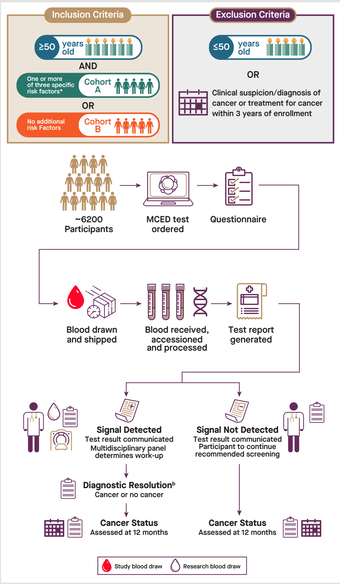
## OBJECTIVE

- To better understand challenges and opportunities following a signal detected result with an MCED test, GI case studies from the PATHFINDER study are presented

## METHODS

- A blood-based MCED test was evaluated in the PATHFINDER study by assessing extent of clinical evaluation required to achieve diagnostic resolution following a signal detected result (**Figure 1**)
  - Participants were adults ≥50 years and recruited into two cohorts:
    - With Additional Risk: a history of smoking, prior cancer treatment completed more than 3 years ago (excluding adjuvant hormone therapy), or genetic cancer predisposition
    - Without Additional Risk: all other participants
  - Treating physicians directed the diagnostic work-up based on their own clinical judgements and determined final cancer status
- Selection criteria were applied to identify participants for whom a more detailed view of diagnostic progression may provide early clinical insights on use of MCED testing
  - Participants from the interim PATHFINDER data set (data cutoff Mar-19-2021) were excluded from the current analysis based on any of the following criteria:
    - Diagnosed cancer was recurrent
    - Predicted CSO was "Indeterminate"
    - Staging information was unavailable
    - A predicted or diagnosed cancer was hematologic
    - Available clinical notes were incomplete
  - Participants must have had a confirmed new Clinical Stage I/II GI cancer
- Data for the 3 participants meeting these criteria were reviewed, and key diagnostic steps from signal detected (Day 1) to resolution are summarized

**Figure 1. Pathfinder Study Design**




*Previous history of cancer, smoking, and genetic risk; [b]Also collected at other timepoints during the study; [c]Defined as date when study team determines to end diagnostic evaluation triggered by a "signal detected" test result.
MCED, multi-cancer early detection.

## KEY RESULTS: MCED TESTING DETECTED CANCER SIGNAL AND DIRECTED DOWNSTREAM DIAGNOSTIC EVALUATION OF GI CANCERS, INCLUDING THOSE WITHOUT CURRENT SCREENING METHODS

### Individual 1

- Individual 1 was a female >60 y without additional cancer risk factors (CSO=Colon/Rectum, Upper GI Tract)

**Individual 1** — >60 | No Prior Cancer | Non-Smoker | No Genetic Cancer Predisposition | CSO prediction guided work-up | CSO 1 = Colon, Rectum; CSO 2 = Upper GI Tract

**Day 1** — Signal Detected

**Day 4** — Results Communicated and Multidisciplinary Panel Convened

**Day 7** — CT (Abdomen, Pelvis) With Contrast

Clinical Notes
- Unremarkable except for non-obstructing kidney stone

**Day 35** — GI referral

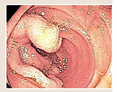
**Day 43** — Upper Endoscopy Colonoscopy, and Pathology

**Day 48** — Clinic Visit and Referral

Clinical Notes
- Upper Endoscopy: 2 cm hiatal hernia, 20 mm duodenal polyp (adenoma)
- Colonoscopy: 3 mm benign polyp ascending colon, 2 mm hyperplastic polyp rectum, diverticulosis

**Day 60** — Clinic Visit and EUS

Clinical Notes
- Endoscopic ultrasound: >4 cm duodenal mass in 3rd/4th portion. Pathology revealed invasive adenocarcinoma in a background of villous adenoma.



**Day 60**

**DIAGNOSIS:**
**Small Intestine Adenocarcinoma, Clinical Stage I (T2N0M0)**

**Treatment and Status**
- Surgery (Pathologic Stage III) and adjuvant chemotherapy
- Patient tolerated the treatment and remains disease free as of February 2022 (Day 709), though CT reveals new lung nodules that are concerning for metastases

### Individual 2

- Individual 2 was a male former smoker >65 y with a history of hepatitis C (CSO=Liver/Bile-duct)

**Individual 2** — >65 | No Prior Cancer | Former Smoker | No Genetic Cancer Predisposition | CSO prediction was correct | CSO 1 = Liver, Bile Duct

**Day 1** — Signal Detected

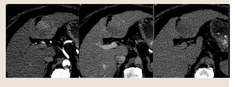
**Day 4** — Results Communicated and Multidisciplinary Panel Convened

**Day 36** — Chemistry Panel

Clinical Notes
- Glucose 188, Aspartate Aminotransferase 44

**Day 40** — Quad Phase wwo CT Abdomen and Chest CT With Contrast

Clinical Notes
- Cirrhotic liver with 6.4 cm LI-RADS 5
- Evidence of portal hypertension



**Day 45** — Referral to Liver Surgeon and Multidisciplinary Panel Convened

**Day 57** — Clinic Visit

**Day 57**

**DIAGNOSIS:**
**Liver tumor, Clinical Stage I (T1N0M0)**

**Treatment and Status**
- Treatment was declined following surgical referral and participant died <9 months post-test result (Day 225) from progression of cancer

### Individual 3

- Individual 3 was a male former smoker >70 y (CSO=Pancreas/Gallbladder, Lung)

**Individual 3** — >70 | No Prior Cancer | Former Smoker | No Genetic Cancer Predisposition | CSO prediction was correct | CSO 1 = Pancreas/Gallbladder; CSO 2 = Lung

**Day 1** — Signal Detected

**Day 3, Day 4** — Multidisciplinary Panel Convened and Results Communicated

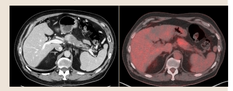
**Day 9** — Lab Work (Comprehensive Metabolic Panel and Tumor Markers)

Clinical Notes
- Comprehensive metabolic panel: no significant abnormalities
- Cancer Antigen 19-9: 167 u/mL

**Day 14** — CT Chest and Abdomen wwo Contrast

**Day 19** — PET-CT

Clinical Notes
- CT Chest: Right upper lobe spiculated lung nodule with air bronchograms, neoplasm not excluded
- CT Abdomen: Abnormal pancreas with low-attenuation non-enhancing mass in the proximal to mid body with obstruction of the dorsal duct
- PET-CT: Hypermetabolic pancreatic body mass with pancreatic duct dilatation with the atrophic tail, compatible with pancreatic adenocarcinoma
  - Suspicious mildly hypermetabolic left para-aortic lung nodule concerning for metastatic disease
  - Right apical lung nodule displays no radiotracer uptake



**Day 38** — CT-guided Core Biopsy

Clinical Notes
- Invasive adenocarcinoma, consistent with pancreatic primary tumor, moderately to poorly differentiated
- CK7+, weak nuclear CDX2; Negative for lung markers, TTF-1, Napsin A

**Day 38**

**DIAGNOSIS:**
**Pancreatic Adenocarcinoma, Clinical Stage IIb (T3N1M0)**

**Treatment and Status**
- Surgery revealed pathologic stage IIa disease
- Adjuvant chemotherapy followed
- Patient is disease free as of February 2022 (Day 520)

## CONCLUSIONS

- None of the cancers described here would have been identified through current recommended screening guidelines
- A multi-cancer screening approach is novel, and formal guidelines are not yet available to address best practices for integration of multi-cancer testing into clinical practice
- Individual participant data from the PATHFINDER study may provide valuable clinical insights on MCED test use and diagnostic follow up
  - The MCED test detected cancer signals and predicted CSOs that directed clinical follow-up leading to three individuals with Clinical Stage I or II GI cancer diagnoses
  - All three achieved diagnostic resolution within 2 months and were provided treatment recommendations with curative intent
  - Diagnostic testing prompted by MCED test results was consistent with existing clinical guidance and reflective of the steps and procedures that would be taken in any instance of suspicion of GI cancer with the corresponding patient attributes

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### Disclosures

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