Outcomes Following a False-Positive Multi-Cancer Early Detection Test: Results from DETECT-A, the First Large, Prospective, Interventional MCED Study

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ABSTRACT

Guideline recommended standard of care screening is available for four cancer types; most cancer-related deaths are caused by cancers without standard of care screening. DETECT-A is the first prospective interventional trial evaluating a multi-cancer early detection (MCED) blood test (CancerSEEK) in women without a history of cancer, providing the first opportunity to assess the long-term outcomes of individuals with false-positive (FP) MCED results. This prospective analysis of DETECT-A participants with FP results evaluates the performance of an imaging-based diagnostic workflow and examines cancer risk following a FP result. This analysis included all DETECT-A participants with a positive CancerSEEK test and subsequent flourine-18 fluorodeoxyglucose positron emission tomography-IV contrast-enhanced computed tomography (18-F-FDG PET-CT) imaging and clinical workup indicating no evidence of cancer within 1 year of enrollment ($n = 98$). Medical records, study interactions, and study surveys were used to assess cancer incidence, treatments, and clinical outcomes through August 2023. Ninety-five of 98 participants with a FP result remained cancer-free with a median follow-up of 3.6 years (IQR: 2.5–4.1) from determination of FP status. Three incident cancers were observed over the follow-up period. One bilateral stage IIIC ovarian cancer was diagnosed 1.9 years after determination of FP status; two stage I breast cancers were diagnosed 0.1 and 1.6 years from determination of FP status. The annual incidence rate of cancer during follow-up from FP determination was 1.0% (95% confidence interval, 0.2%–2.8%). Participants with a positive CancerSEEK test who underwent 18-F-FDG PET-CT and clinical workup without cancer findings had low risk for cancer over the following several years.

Prevention Relevance: This study provides multiyear clinical outcomes data following a false-positive multi-cancer early detection test for individuals participating in a prospective interventional trial. It provides a preliminary performance assessment of an imaging-based diagnostic workflow following a false-positive multi-cancer early detection test.

Introduction

More than 1.9 million new cancer cases and approximately 610,000 cancer deaths are predicted to occur in the United States in 2023 (1, 2). Cancers are often not diagnosed until patients report symptoms related to advanced stage disease, resulting in poor outcomes (1). Early detection of cancer is important as most cancers have a 5-year survival rate of less than 30% when diagnosed after they have metastasized (1).

Screening offers the opportunity to detect cancers in asymptomatic individuals and to identify cancers at an earlier stage. The U.S. Preventive Services Task Force recommends routine standard of care (SoC) screening for just four cancer types: breast (mammogram; ref. 3), cervical [Papanicolaou (Pap) test; ref. 4], colorectal (colonoscopy or stool-based modalities; ref. 5), and lung (low-dose computed tomography in individuals at elevated risk; ref. 6). Recommended SoC screening has improved the mortality rates for breast, colorectal, cervical, and lung cancers (7–10), but current SoC screening identifies less than 50% of all cancers, and approximately 63% of cancer-related deaths occur in cancer types for which no recommended screening paradigm exists (2, 11).

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Advances in sensitive multiomic technologies and the measurement of tumor-derived analytes in the blood enable the development of multi-cancer early detection (MCED) tests that have the potential to screen for multiple cancers concurrently in a single test, including many cancers for which no screening test currently exists. As MCED tests are screening tools, rather than diagnostic tests, positive MCED results are followed by a diagnostic evaluation that may include imaging to localize or rule out suspected cancer. Consequently, the performance of the diagnostic workflow following a positive MCED test result is central to accurate determination of cancer status and reduction of potential harms of screening. When false positives (FPs) occur in clinical practice, they require interpretation by physicians and patients. Concerns may arise about whether a cancer is actually present but was missed by the diagnostic workflow, or whether the positive MCED result indicates a higher risk for incident cancer in the subsequent months or years. Such concerns may result in patient anxiety as well as additional diagnostic procedures that may prove unnecessary. There is no published literature to date that chronicles outcomes following a FP MCED result. Detecting cancers Earlier Through Elective mutation-based blood Collection and Testing (DETECT-A) is the first prospective interventional trial to evaluate an MCED blood test (an early version of CancerSEEK that assessed circulating proteins and cell-free plasma DNA mutations; ref. 12), providing the first opportunity for longitudinal analysis of participants with FP MCED results. The present analysis evaluates multi-year cancer incidence among DETECT-A participants with FP results, enabling assessment of the imaging-based diagnostic workflow performance and an indication of whether FP results may be associated with increased cancer risk.

Materials and Methods

Study participants

DETECT-A is an ongoing prospective, interventional study to evaluate the performance of CancerSEEK, an early version of the Exact Sciences Corporation MCED test currently in development. The study included 10,006 women in the age group of 65 to 75 years with no personal history of cancer and were followed for 5 years from their CancerSEEK blood test at the time of enrollment (1). The study was approved by the Institutional Review Boards for Human Research at the Geisinger Health System (Geisinger; #2017-0268) and the Johns Hopkins Medical Institutions (#00119844) and was compliant with U.S. Common Rule and The Health Insurance Portability and Accountability Act. Written, informed consent was obtained from all participants. Women with a current or previously known cancer were excluded from the study. Participants with a positive CancerSEEK test underwent a flourine-18 fluorodeoxyglucose positron emission tomography-IV (18-F-FDG PET-IV) contrast CT with follow-up procedures, when clinically indicated, to determine the presence and location of cancer.

Ninety-eight (1.0%) of the 9,911 participants had a positive CancerSEEK test followed by 18-F-FDG PET-IV contrast CT and clinical workup without a cancer or precancer diagnosis within 12 months of enrollment (**Fig. 1**; ref. 1). These participants were considered to have a FP result. Three additional participants with positive CancerSEEK tests that led to precancerous findings within 12 months of enrollment were excluded from this analysis. Among the 98 participants with FP CancerSEEK results, cancer was ruled out by 18-F-FDG PET-CT alone in 63 cases, while 35 participants had further noninvasive or minimally invasive procedures to rule out cancer or to investigate the 18-F-FDG PET-CT findings. This study evaluated longitudinal cancer incidence and outcomes among these 98 participants with a presumed FP CancerSEEK test. Informed consent was provided as part of the original DETECT-A study.

Data collection and analyses

Enrolled participants were entered into a clinical database and underwent longitudinal follow-up. For participants who left the Geisinger Health System during or after the active study period, efforts were made to access any available records to supplement available study surveys and study interactions. Clinical data were obtained from a combination of electronic medical records, study interactions (e.g., genetic counselor calls), and study surveys that asked about new cancer diagnoses. An analysis was conducted in August 2023 to determine the latest date at which the cancer status of each participant was reliably known. Collected data included demographics, diagnostic information about any incident cancers (e.g., cancer type, stage, date of diagnosis), cancer treatments, and clinical outcomes including all-cause and cancer-related mortality. Clinical follow-up data were restricted to a limited dataset and were protected in adherence to applicable privacy laws and/or regulations. For cancers diagnosed in the follow-up period, the original 18-F-FDG PET-CT images recorded during the study were reexamined by a radiologist uninvolved in DETECT-A to confirm that the malignancies were not appreciable at that time. FP status was formally determined 12 months after enrollment. Time to cancer diagnosis was calculated at the latest date at which cancer status was reliably known from medical records, study interactions, or study surveys, and censored at the date of death, study completion, or study withdrawal. Cancer incidence was evaluated over the follow-up period to assess the robustness of an imaging-first diagnostic workflow for resolving a positive MCED test, and to determine whether participants with FP results may have substantially elevated cancer risk. Cumulative cancer incidence was estimated using the Kaplan–Meier method.

Data availability

The data generated in this study are available upon request from the corresponding author.

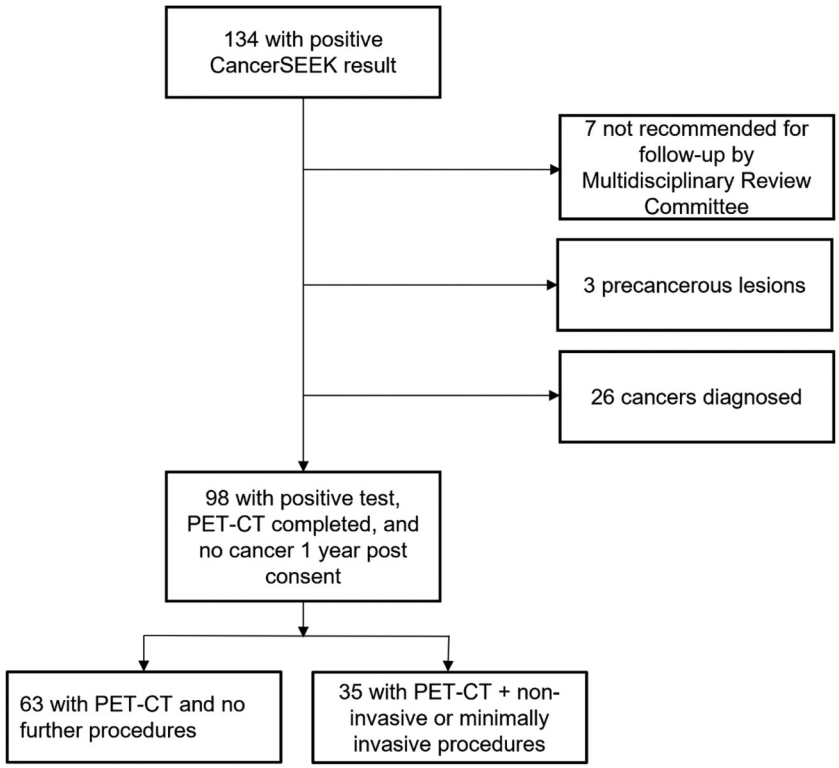

Figure 1.
Study diagram. Flow diagram for participants with positive CancerSEEK test results. For a comprehensive diagram for the DETECT-A study, see Lennon and colleagues (12).

Results

Among the 98 participants with a positive CancerSEEK test and no evidence of cancer or precancer within 12 months of enrollment, the mean and median follow-up time from the date when FP status was determined was 3.2 and 3.6 years (IQR: 2.5–4.1), respectively (12). Three incident cancers were observed over the follow-up period (**Table 1**). A bilateral stage IIIC ovarian cancer was diagnosed 1.9 years from determination of FP status after symptomatic presentation (case 1). Two stage I breast cancers were diagnosed through routine mammography screening 0.1 and 1.6 years from determination of FP status (case 2 and case 3, respectively). Independent radiology reviews of the initial 18-F-FDG PET-CT scans were conducted for case 1 and case 3 and were concordant with the observations and interpretations recorded at the time of the imaging. Re-review was not available for case 2, but the initial radiology review noted no observations potentially related to the breast cancer. The participant with ovarian cancer (case 1) underwent surgery and chemotherapy and died approximately 1 year after initial diagnosis. One participant with breast cancer (case 3) underwent surgery, radiation, and hormone therapy and was alive and cancer-free at the time of analysis. The other participant with breast cancer (case 2) reported undergoing surgery and radiation but declined to provide detailed medical records.

Among the 98 participants with a FP result, cumulative cancer incidence after determination of FP status was 1.0% (95% CI, 0.1%–7.2%) at 1 year and 3.4% (95% CI, 1.1%–10.1%) at 2, 3, and 4 years. Among the subset of 63 participants that had no further procedures immediately following 18-F-FDG PET-CT, cumulative cancer incidence after definition of FP status was 1.6% (95% CI, 0.2%–11.1%) at 1 year and 3.6% (95% CI, 0.9%–13.6%) at 2, 3, and 4 years. Overall annual cancer incidence was 1.0% (95% CI, 0.2%–2.8%).

Discussion

DETECT-A is the first study to provide multiyear clinical outcomes data following a FP MCED test for individuals participating in a prospective interventional trial. Cancer incidence among participants with FP results offers insight into the accuracy of the diagnostic workflow and whether participants with FP results are at an increased risk for developing cancer. During the first year of participation among all participants, the DETECT-A study identified 96 total cancers, an annual rate of 1.0% (12). Among the 98 participants with FP CancerSEEK results, three incident cancers were identified over the more than 3-year follow-up period from determination of FP status. The annual incidence rate of 1.0% from determination of FP status was consistent with the overall incidence in the first year of DETECT-A, and with the US Surveillance, Epidemiology, and End Results annual incidence rate of 1.5% for women age 65 to 74 (13), though these comparisons should be considered in light of the limited sample size of the current study. The low observed cancer incidence suggests patients with a positive

Table 1. Summary of incident cancers over the follow-up period among DETECT-A participants with FP CancerSEEK results.

Cancer information	^{18}F-FDG PET-IV contrast CT alone (n = 63)		^{18}F-FDG PET-IV contrast CT with additional noninvasive or minimally invasive procedures (n = 35)
	Case 1	Case 2	Case 3[a]
Time from determination of FP status to cancer diagnosis (years)	1.9	0.1	1.6
Cancer organ	Ovarian	Breast	Breast
Diagnostic indication	Symptomatic presentation	Routine mammogram	Routine mammogram
Cancer stage	IIIC	I	1A
Histological subtype	Serous surface papillary adenocarcinoma (compatible with Müllerian origin)	Unknown	Invasive ductal carcinoma
Treatment	Surgery and chemotherapy	Surgery and radiation	Surgery, radiation, and hormone therapy
Last known cancer status	Deceased	Unknown	Alive and cancer-free

[a]The participant underwent a colonoscopy based on a suspicious 18-F-FDG PET-CT observation, but no malignancy was identified.

CancerSEEK blood test and a negative clinical and 18-F-FDG PET-IV contrast CT diagnostic work-up are not at elevated risk for cancer. It is important to recognize that individuals should continue to adhere to SoC screening recommendations set forth by guideline bodies for breast, colorectal, cervical, and lung cancer even if they take an MCED test.

Nearly two-thirds of participants with a FP result had no additional follow-up procedures performed after the initial negative 18-F-FDG PET-IV contrast CT. The "rule out" performance of an 18-F-FDG PET-IV contrast CT workup alone following a positive MCED test result was 96.4% when defining a false negative as a cancer diagnosed within 2, 3, or 4 years of FP status. These results support the utility of an imaging-based clinical diagnostic workup to resolve a positive MCED test result. Imaging, often whole-body imaging, is routinely utilized in the clinic to localize and stage cancer. It is also well-suited to identify suspected cancer, especially when no localizing symptoms are present and a patient reports general symptoms that would prompt a suspicion of a cancer (14, 15). The imaging approach is efficient and feasible to implement broadly but does highlight the importance of access to imaging facilities and care pathways that facilitate the diagnostic evaluation initiated with a positive MCED test.

One of the most common concerns raised about MCED testing is that FP MCED results would trigger a complex cascade of follow-up diagnostic procedures that may impose significant physical and psychological burdens on healthy patients to definitively rule out cancer. Therefore, a better understanding of the diagnostic workups and patient outcomes following a MCED FP result will be important to guide physician decisions and alleviate patient anxiety. Although it is not possible to definitively determine whether the cancers were present at the time of evaluation following the positive CancerSEEK test or whether the cancers developed during the follow-up period, the results of this study demonstrate that an imaging strategy for resolving a positive MCED test appears effective. This is the first study to provide data to support the approach that patients who participate in MCED testing and receive a FP result can return to routine care if a clinical and imaging workup reveals no evidence of cancer. These results must be confirmed in prospective studies that include a broader age range, multiple genders, and a more racially/ethnically diverse cohort before they can be used to inform clinical practice. Further, they may not be generalizable to other MCED tests or different approaches to diagnostic resolutions. If confirmed in future studies, these results should provide reassurance to clinicians and to patients when no evidence of cancer is detected by diagnostic 18-F-FDG PET-IV contrast CT imaging following a positive MCED test result.

Authors' Disclosures

A.M. Lennon reports personal fees from Exact Science during the conduct of the study; in addition, A.M. Lennon has a patent for Patent issued and with royalties paid from Johns Hopkins University. A.H. Buchanan reports grants from Exact Sciences Corporation during the conduct of the study; grants from Freenome Holdings, Inc. outside the submitted work; and equity stake in MeTree and You, Inc. S.P. Rego reports employment and stock ownership at Exact Sciences Corporation. O.A. Choudhry employment and stock ownership at Exact Sciences Corporation. P.Z. Elias reportsemployment and stock ownership at Exact Sciences Corporation. J.R. Sadler reportsemployment and stock ownership at Exact Sciences Corporation. J. Roberta reportsemployment and stock ownership at Exact Sciences Corporation. Y. Zhang reports he is an employee of Exact Sciences Corporation and holds stocks of the company. D.D. Flake reportsemployment and stock ownership at Exact Sciences Corporation. A. Honushefsky reports grants from Exact Sciences Corporation during the conduct of the study; grants from Freenome Holdings, Inc. outside the submitted work. Z.M. Salvati reports grants from Exact Sciences Corporation during the conduct of the study. K. Sheridan reports grants from Exact Sciences Corporation during the conduct of the study; grants from Freenome Holdings Inc. outside the submitted work. E.S. Wagner reports grants from Exact Sciences

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Authors' Contributions

A.M. Lennon: Writing–review and editing. **A.H. Buchanan:** Conceptualization, investigation, methodology, project administration, writing–review and editing. **S.P. Rego:** Conceptualization, methodology, writing–original draft, writing–review and editing. **O.A. Choudhry:** Conceptualization, formal analysis, writing–original draft, writing–review and editing. **P.Z. Elias:** Formal analysis, writing–original draft, writing–review and editing. **J.R. Sadler:** Conceptualization, formal analysis, writing–review and editing. **J. Roberta:** Formal analysis, writing–review and editing. **Y. Zhang:** Formal analysis, writing–review and editing. **D.D. Flake:** Formal analysis, writing–review and editing. **A. Honushefsky:** Investigation, project administration, writing–review and editing. **Z.M. Salvati:** Investigation, project administration, writing–review and editing. **K. Sheridan:** Investigation, project administration, writing–review and editing. **E.S. Wagner:** Investigation, project administration, writing–review and editing. **E.K. Fishman:** Writing–review and editing. **N. Papadopoulos:** Writing–review and editing. **T.M. Beer:** Conceptualization, methodology, writing–original draft, writing–review and editing.

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