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Psychosocial Outcomes Associated With ctNA-Based Cancer Screening Test

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**PSYCHOSOCIAL OUTCOMES ASSOCIATED WITH A ctDNA-BASED CANCER
SCREENING TEST**

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ABSTRACT

Due to the increasing incidence of cancer diagnoses and lack of validated screenings for most types of cancer, cancer researchers continue to look for ways to improve cancer screening particularly for cancers that are difficult to detect early. One early detection technology being researched is blood-based testing looking for the presence of DNA from tumor cells, circulating tumor DNA (ctDNA). With any new cancer screening test there is a need to understand how participants respond, socially and psychologically, to abnormal results. Participants in Geisinger's DETECT study of a ctDNA test, CancerSEEK, who received positive ctDNA blood test results and opted to undergo a PET-CT scan, were interviewed to assess psychosocial outcomes of true positive and false positive blood test results. Qualitative data analysis of interviews of participants with true positive and false positive results using Atlas.ti identified 16 major themes. Results of the qualitative analysis revealed some differences between the negative and positive PET-CT groups. However, most participants, in both groups, reported a positive experience with the DETECT study and would recommend it to others. Results of the study suggest that the psychosocial outcomes associated with ctDNA-based cancer screening tests should continue to be explored in-depth to provide sufficient evidence for future usage.

Keywords: ctDNA, cancer screening, psychosocial outcomes, CancerSEEK, PET-CT

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All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients included in the study.

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INTRODUCTION

Cancer is defined as uncontrolled cell growth; malignant cells grow and divide rapidly leading to a diagnosis that is either localized or metastasized throughout tissues of the body. Cancer cells have six main features that distinguish them from healthy cells: independence of external growth signals, insensitivity to external anti-growth signals, ability to avoid apoptosis, ability to duplicate indeterminately, ability to activate angiogenesis and vascularize, and ability to attack tissues and create secondary tumors (Hanahan & Weinberg, 2000). Cancer is the second leading cause of death in the United States and each year the number of diagnoses and deaths increase worldwide. The chance to develop cancer depends on an individual's exposure, medical history, and genetic predisposition. The lifetime risk for a male to develop an invasive cancer is 42%, whereas for women it is 38%. While there has been a consistent decline in the death rate from cancer, by 1.4% in women and 1.8% in men annually from 2007 to 2016, it remains a serious public health concern. An estimated 1.7 million new cancer cases will arise in 2019 alone (Siegel et al., 2019).

Recommended Screening Guidelines, Risk Reduction Benefits, and Psychosocial Outcomes for Existing Cancer Screening Modalities

Several screening tests have been found to reduce cancer morbidity and mortality rates. Many organizations provide evidence-based recommendations about cancer screenings; however, these recommendations vary, making these preventive services more difficult for patients and providers to navigate. It is important to assess the societal and individual impact of these screenings in an effort to promote adherence. Adherence to screening recommendations provides the benefit of detecting cancer at earlier stages; nonadherence diminishes this benefit. When considering reasons for nonadherence, psychosocial harms of the screenings should be

explored. There is significant evidence of anxiety produced by cancer screening methods, especially when false positive results are the outcome (Brodersen & Siersma, 2013; Lipkus et al., 2000; Toft et al., 2019). The recommended screening guidelines, risk reduction benefits, and associated psychosocial harms are outlined for the following cancers: breast, colorectal, and lung.

Breast Cancer

The United States Preventive Services Task Force (USPSTF) recommends biennial mammography screening for women aged 50 to 74 years to maximize screening benefits. The USPSTF specifies that these guidelines are appropriate for average-risk women, who are at the general population risk to develop cancer. Prior to this, between ages 40 to 49, the decision to begin screening is on an individual basis. Lastly, the USPSTF provides no recommendations for screening women aged 75 and older (Siu et al., 2016). In contrast with the USPSTF, the National Comprehensive Cancer Network (NCCN) and other professional societies recommend annual mammography screening beginning at age 40 in average-risk women. Women who begin mammography screening in their 40s benefit from a reduction in breast cancer mortality. Early detection of breast cancer also leads to less aggressive treatment regimens and associated morbidities. The screening benefits outweigh the psychosocial harms associated with mammography, like anxiety due to false positive results and overdiagnoses. NCCN also addresses screening recommendations for women at increased risk of breast cancer (NCCN Guidelines Version 1.2019 Breast Cancer Screening and Diagnosis, 2019). Notably, the USPSTF does not provide screening recommendations for this group of high-risk women.

Women receiving false positive results report negative psychosocial harms such as breast-cancer specific worry, concern impacting mood and daily routines, lower cognitive

functioning, lower energy levels, and increased depression. Additionally, follow-up testing with negative results can cause persistent anxiety, continued breast-cancer specific worry, and distress for patients (Nelson et al., 2016). One study evaluated 12 psychosocial outcomes among 454 women with abnormal findings on mammography screening, using the Consequences of Screening in Breast Cancer Questionnaire. For every woman recruited with an abnormal finding, either true or false positive, two were enrolled that received normal mammogram screening results. Women with false positive results reported changes in existential values and inner calmness which were equivalent to responses reported by women with a diagnosis of breast cancer. In addition, women continuing to receive false positive results post-cancer diagnosis reported more negative psychosocial harms than women with normal mammogram screening results (Brodersen & Siersma, 2013).

Colorectal Cancer

To reduce colorectal cancer incidence and mortality, the USPSTF recommends screening in average-risk adults starting at age 50 years and continuing until age 75 years. The decision to screen for colorectal cancer in adults aged 76 to 85 is an individual one. Screening strategies include stool-based, direct visualization and serology tests, each with unique advantages and limitations (US Preventive Services Task Force, 2016). NCCN recommends starting screening earlier in adults at increased risk due to family history of cancer or pathogenic variants in colorectal cancer susceptibility genes. Shorter screening intervals are recommended for those at increased risk, compared to average-risk individuals who present for colonoscopy every 5-10 years (NCCN Guidelines Version 2.2019 Colorectal Cancer Screening, 2019).

Reported harms include unnecessary invasive follow-up testing for patients at low-risk and increased rates of anxiety, discomfort, and morbidity (US Preventive Services Task Force,

2016). One study assessed the psychosocial harms of receiving false positive screening results from an immunochemical fecal occult blood test (iFOBT), by interviewing 16 participants about their false positive results. Four main themes emerged: anxiety, discomfort, different self-perception/behavior, and views on active participation in screening. False positive results led to prolonged feelings of anxiety among some participants, resulting in an increase in existing anxiety and psychological impairments. Individuals may feel discomfort during a screening procedure, their self-perception may change upon experiencing the process, and they may demonstrate hesitancy towards diagnostic screening methods in the future (Toft et al., 2019).

Lung Cancer

The USPSTF recommends annual low-dose computed tomography (LDCT) for individuals who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years, and are aged 55 to 80. Annual LDCT screening serves as a benefit for high-risk individuals and can prevent lung cancer-related mortality. Lung cancer screening can be associated with negative psychosocial outcomes due to false positive results, false negative results, incidental findings, overdiagnosis, and increased radiation exposure leading to cancer (Moyer et al., 2014).

NCCN recommends LDCT testing after performing extensive risk assessment and categorizing risk status (high, moderate, or low-risk). Benefits of LDCT testing include decreased lung cancer mortality and discovery of other crucial health risks. A major benefit suggests an increase in quality of life by pursuing lung cancer screening, leading to the following: less morbidity related to the disease and treatment, aiding in a healthy lifestyle, and lessening anxiety/psychosocial harms. Psychosocial harms noted by NCCN include a decrease in

quality of life and anxiety of test findings (NCCN Guidelines Version 1.2020 Lung Cancer Screening, 2020).

Future Directions for Cancer Screening with ctDNA

Of the early detection technologies being researched, one of increasing interest is a blood-based testing looking for the presence of DNA from tumor cells. In contrast to many current cancer screenings, ctDNA-based screening offers an opportunity to screen for multiple cancers at once, including cancers for which no standard-of-care screenings exist, such as pancreatic and ovarian cancer. While a benefit of ctDNA-based cancer screening is that it is minimally invasive, requiring only a blood test, the psychosocial outcomes of abnormal ctDNA screening are unknown. As with any new screening modality, investigation into the psychosocial outcomes of abnormal results is important in understanding what may influence adherence, how it should be implemented clinically, and how it could positively or negatively impact care.

Historical Background of ctDNA

Documentation of the presence of circulating tumor cells goes back to the late 1800s when it was first observed in the blood of cancer patients (Neumann et al., 2018). Further evidence of the possibility of tumor DNA circulating in the blood came from a 1977 study comparing the level of free DNA in the serum of patients with different types of cancers to study participants without cancer (Leon et al., 1977). It was found that the levels of free DNA were increased in patients with cancer as compared to those without cancer; further differentiation found that those with metastatic cancers had significantly higher free DNA levels than those whose cancer was in situ. Significant decreases in the free DNA levels were found in the cancer patients who saw clinical improvements, like reduced tumor size, compared to patients who did not respond to cancer treatments and whose DNA levels were maintained throughout the study.

While the source of the additional free DNA was not fully understood in the study, the correlation of free DNA levels with the presence of cancer was indicative of some contribution of the tumor DNA to free DNA levels (Leon et al., 1977). More recently, expanded use of cell-free DNA (cfDNA) for prenatal screening provided further evidence of tumor DNA circulating in the bloodstream through cfDNA results that were discordant with the fetal karyotype. The discordance was explained by the presence of maternal malignancy during pregnancy (Bianchi et al., 2015).

Liquid Biopsy

A liquid biopsy is the analysis of tumor-derived components found in the bloodstream; these components include a combination of whole circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), RNA, proteins, and lipids that are shed from a tumor as apoptosis occurs (Palmirotta et al., 2018). The CTCs component of liquid biopsy are a stable, viable group of cells that can be purified from blood or particles on the surface of cells that differentiate them from typical blood cells. The ctDNA component is derived from lysed CTCs and consists of tiny fragments of free nucleic acids no longer associated with a cell (Olivi et al., 2014). Since the initial evidence of tumor analytes circulating in the blood, the use of liquid biopsy technology to detect these analytes has expanded to possibly become a fast, noninvasive, and low cost way of detecting cancer and monitoring disease status in response to treatment. It is believed that liquid biopsy circumvents challenges from biopsy of inaccessible tumors and biopsies that do not give a comprehensive picture of the tumor make up given metastasis or heterogeneity throughout the tumor tissue (Neumann et al., 2018). Proof of principle of how ctDNA works was established in a 2018 study done by Cohen et al., that used the ctDNA liquid biopsy, CancerSEEK, to successfully detect 70% of cancers that had already been clinically diagnosed. The specificity of

this liquid biopsy was more than 99% across the eight cancer types that it was used to confirm diagnosis in.

Benefits and Limitations of ctDNA Testing

ctDNA analysis has the potential to address a limitation of traditional tumor tissue biopsy - the oversight of possible driver mutations given the limited scope of biopsy and the heterogeneity of tumor tissue. This limitation results in a lack of information on the tumor profile. There is also the limitation of tumor tissue not always being accessible for biopsy or metastasis making a biopsy of all tumor tissue difficult (Stewart et al., 2018). Potential areas of application for ctDNA include tumor diagnosis to detect residual tumor after surgery, cancer treatment response and follow-up, and the molecular evolution of tumors resistant to treatment (Neumann et al., 2018). Despite these benefits, some studies have shown a rate of discordance between ctDNA assays and tumor testing. This could be the result of what cells are released from the tumor, where the tumor is, what barriers are present that prevent cells from entering the circulatory system and insufficient amounts of ctDNA being present in the blood sample. What tumor tissue testing shows, that ctDNA assays can fail to reveal, is a full picture of new cell variants within the tumor (Merker et al., 2018). Early detection of cancer is complicated with liquid biopsy by the mutation load being minimal or below the level of detection in early cancer stages. The proportion of ctDNA found in a blood sample is correlated to the tumor size; at early stages, when the tumor is small, the percentage of ctDNA present in the blood will be limited (Stewart et al., 2018). In early stage cancer, ctDNA can make up only 1% of cfDNA but that can increase to 40% in late stage cancer (Neumann et al., 2018). There are also limitations with the inability of liquid biopsy to determine the location of origin of the cancer (Cohen et al., 2018).

Psychosocial considerations

While there is limited data on the psychosocial impact of using ctDNA and liquid biopsy for cancer screening, there is significant evidence of the negative effect of other screening methods when false positive results are the outcome (Brodersen & Siersma, 2013; Lipkus et al., 2000; Toft et al., 2019). As part of understanding the clinical utility of ctDNA for screening, is a need for research into the psychosocial implications of screening. It is reasonable to suspect that different psychosocial effects may be present that are not seen in other screening methods. This is due to the limitation of liquid biopsy not being able to determine the location of origin of the cancer and the often further advanced stage of cancer that ctDNA is able to be detected. Further research into these areas could shed more light onto the utility and impact of this cancer detection technology.

MATERIALS AND METHODS

Sample Population

Study participants were recruited from among participants in Geisinger's DETECT (Detecting Cancers Earlier Through Elective Mutation-Based Blood Collection and Testing) research study. Inclusion criteria for DETECT study participants included women, ranging in age from 65-76, with no prior personal history of cancer. Of the DETECT participants, 97% are of Caucasian ancestry. Participants were from within the Geisinger catchment area, which covers central Pennsylvania.

Within the DETECT study, participants initially gave six tubes of blood. ctDNA and cancer biomarkers were analyzed using a "research marker panel test," called CancerSEEK. Participants in the DETECT study who received two consecutive positive blood test results were contacted by the DETECT study genetic counselor with the result disclosure and recommendation to have a follow-up PET-CT. Following the PET-CT, patient results were

disclosed by a DETECT study physician, either an oncologist or primary care physician (A. M. Lennon et al., 2020). DETECT study participants who opted to undergo a PET-CT scan were eligible for participation in this qualitative study. A list of DETECT participants who had a PET-CT was provided by the DETECT research study team.

Procedures

The DETECT study used the CancerSEEK blood test to interrogate the blood samples, from each participant, for 16 genes associated with cancer and levels of 11 protein markers, that can be elevated in individuals with cancer. CancerSEEK is expected to detect multiple cancer types, including pancreatic, ovarian, esophageal, liver, lung, breast, colorectal and stomach cancer. Participants were informed that their results might be used for research purposes beyond the DETECT research study.

Qualitative interviews, using an investigator-created interview guide informed by previous research on psychosocial outcomes of cancer screening tests, were conducted with eligible participants to assess psychosocial outcomes of having a positive ctDNA test. The interview guide began with general consent for participation, as well as consent for audio recording, and usage of data for research purposes in accordance with the study IRB. Interviews were conducted until saturation of responses was reached. There were five attempts to reach eligible participants before they were excluded from the study. Participant data were de-identified and stored with each participant interview case number for reference. All participant transcripts and audio recordings were saved on a Geisinger-protected desktop and were uploaded into the qualitative analysis program Atlas.ti. Qualitative analysis was conducted to assess participant views and psychosocial outcomes associated with a ctDNA-based cancer screening test. This study received an exemption from the Sarah Lawrence College Institutional Review

Board (IRB) in October 2019 along with approval from the Geisinger Health System IRB in April 2019.

Measures

The qualitative interview guide consisted of 9 stem questions, each followed by 0-10 probes to obtain additional nuance. Stem questions were aimed at assessing participants' rationale for joining the study, initial concerns regarding the possibility of detecting cancer, emotional response and coping strategies after the results of the CancerSEEK blood test and PET-CT scan, as well as response to discordant results (i.e., positive CancerSEEK followed by negative PET-CT), when applicable, previous cancer screening medical behaviors, and overall DETECT study satisfaction. Probe questions were aimed at gaining a better understanding of how participants coped with results, the negative and positive psychosocial outcomes they experienced, and their perception on the utility of the CancerSEEK blood test. Each participant was asked the 9 stem questions; probes were asked at the discretion of the interviewer based on the need for deeper or more comprehensive reflection.

Analysis

The codebook was created with the goal of identifying psychosocial themes that may have been present during the participants' contemplation of DETECT study participation, discovery of the CancerSEEK blood test results, discovery of PET-CT results, and post PET-CT experience. Themes and ideas stated in the interviews were identified as codes for the codebook. Codes were contributed by both study coders to capture the full range of psychosocial themes and emotions described by study participants. The codes are organized by major themes (Table 1) which allowed the coders to capture data relating to the most relevant psychosocial experiences expressed throughout the study. The codebook was established by consensus and

reviewed by the research supervisor. The final codebook contained 76 codes (Appendix B). Inclusion criteria were defined for each code to maintain consistency in applying the codebook to the interviews.

Complete List of 16 Major Themes

Theme Number	Major Themes
1	Awareness of Study Purpose
2	Rationale for Participation
3	Baseline Cancer Concern
4	CancerSEEK Emotional Reaction
5	CancerSEEK Coping
6	CancerSEEK Process Issue
7	PET-CT Emotional Reaction
8	PET-CT Process Issue
9	PET-CT Incidental Findings
10	PET-CT Understanding
11	PET-CT Coping
12	Emotional Reaction to Discordant Results

13	Coping with Discordant Results
14	Post Results Emotional Response
15	Previous Cancer Screening (Medical Behavior)
16	Study Satisfaction

Table 1. Complete List of 16 Major Themes.

Software analysis processing issues with Atlas.ti hindered the ability to establish inter-rater reliability between both coders. Atlas.ti was able to recognize that two individuals were coding separately; however, after running an analysis, the software counted the codes as one rather than two separate responses. This method would have hindered the overall data analysis; therefore, the coders addressed this issue through consensus coding.

Reliability of the codes was established through an iterative process. Both coders were randomly given two interviews to code separately and then compared. This process was repeated until both coders were consistently applying the appropriate codes to the themes found in the interviews. Once sufficient agreement on the usage of codes was reached, all 36 interviews were assessed by both coders together through consensus coding. Interviews were coded at the group level, with the intent to capture responses in both the negative and positive PET-CT groups. If a participant expressed similar statements multiple times throughout a transcript, the responses were repeatedly coded to collectively capture the psychosocial outcomes.

For the analysis of this study, participants with a negative PET-CT scan for cancer and a positive PET-CT scan for cancer were analyzed separately before being compared. Interviews from participants in both groups were analyzed for thematic content related to psychosocial

outcomes associated with the DETECT study. Comparisons using Atlas.ti were performed between and among participants in the positive and negative PET-CT groups.

Before analysis began, the data were normalized to account for differences in interviews of the negative and positive PET-CT participants. More negative PET-CT interviews were conducted and the number of coded statements in these interviews was greater than in the positive PET-CT interviews. Therefore, code percentages of the positive PET-CTs were normalized to account for the difference. The coding percentages for the positive PET-CT interviews were multiplied by 1.12, the quotient of the number of negative PET-CT and positive PET-CT interviews, $19/17 = 1.12$.

Once all interviews were coded, an analysis was run using the “Code Document Table” and “Code Co-Occurrence Tree” functions. The results represent significant findings outlined within the 16 major themes featured throughout the study, all of which highlight psychosocial outcomes associated with a ctDNA-based cancer screening test.

RESULTS

Participants

Eligible participants consisted of 21 individuals with negative follow-up PET-CT scan results, of which 19 participated, and 23 individuals with positive follow-up PET-CT scan results, of which 17 participated, an overall response rate of 82%. All of the positive PET-CT scan interview participants were diagnosed with cancer. Of the eligible women from the DETECT study, 3 declined to participate, 1 passed from cancer, 3 could not be reached after five phone call attempts and 1 was excluded due to inability to remember participation in the DETECT study. Of the study participants, 97% identified as Caucasian. A total of 36 participant

interviews were included in the study and subsequently analyzed for psychosocial outcomes associated with a ctDNA-based cancer screening test.

Code Document Table Results

Awareness of Study Purpose

In comparing DETECT study awareness among participants, women with negative PET-CTs were more likely to be aware of the study purpose and less likely to be uninformed of the study purpose as compared to women with positive PET-CTs (Figure 1).

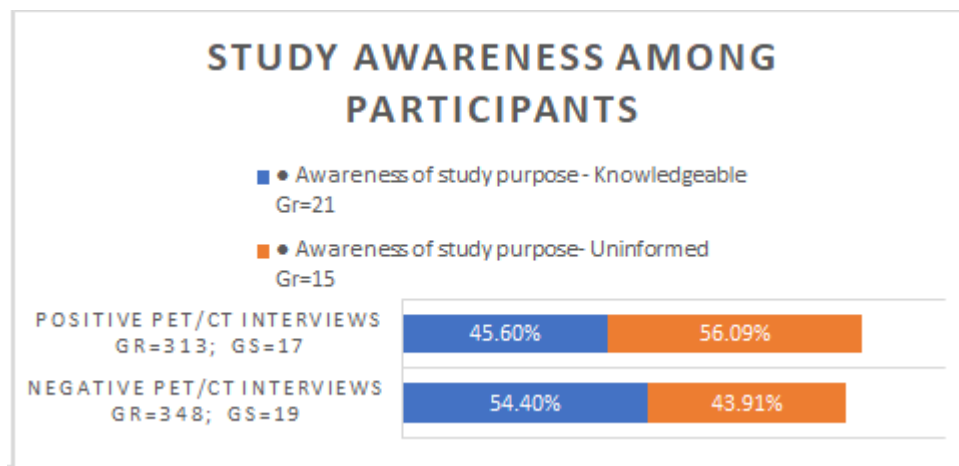


Figure 1. Study awareness among participants. Abbreviations: Gr=Groundedness of Codes (number of quotations attributed to a code), GS= Number of documents in a document group

Rationale for Participation

In regard to rationale for participation in DETECT among study participants, 40% of the overall responses among participants in both groups were coded as altruism. There was no significant difference between participants in the negative and positive PET-CT groups. Both envisioned their participation to be able to help future generations. Also expressed in about one-

quarter of responses, in both groups, was a desire to participate because of a family history of cancer and a desire to gain more personal health information for personal utility.

“In order for science or whatever to advance to help people, somebody has to volunteer, and I’m glad for other medicines that come up through studies, that I thought well maybe I should be the one this time to do the study.” (Negative PET-CT: Altruism)

*“Well, I figured that if I could help anyone it would be a plus for people everywhere.”
(Positive PET-CT: Altruism)*

Baseline Cancer Concern

Among women in the negative PET-CT interview group, the most commonly reported emotional response related to “the possibility that the test would lead to finding cancer” was acceptance at 46%. This is compared to 50% of responses in the positive PET-CT interview group that were unprepared for the possibility that testing would lead to a cancer diagnosis.

“Cancer was the farthest thing from my mind.” (Positive PET-CT: Unprepared)

“I didn’t think I had any possibility of having any cancer.” (Positive PET-CT: Unprepared)

CancerSEEK Emotional Reaction, Process Issues, and Coping

Participants mainly reported feelings of surprise and being upset in response to CancerSEEK. Participants reported confiding in someone after receiving their CancerSEEK blood test result. In both groups, some participants were dissatisfied with the timing and communication of study results.

In the positive PET-CT group, 33% of responses expressed being surprised by the results of the CancerSEEK blood test. The most prevalent emotional reaction for the negative PET-CT

group were feelings of being upset by the abnormal blood test, which was shared among 20% of the overall responses. Of note, 10% of participant responses in the negative PET-CT group emphasized feelings of being scared after receiving the CancerSEEK blood test result; however, this emotion was not expressed by any participants in the positive PET-CT group.

Dissatisfaction with timing and communication of DETECT study results was a logistical process issue associated with the CancerSEEK blood test. Eight responses by participants in the negative PET-CT group and five responses made by participants in the positive PET-CT group emphasized these challenges.

“I wish that [it] could be a shorter period of time so you’re not worrying for weeks and weeks about it.” (Negative PET-CT: Dissatisfaction)

“I would think they should be able to process it faster,” (Positive PET-CT: Dissatisfaction)

In regard to coping with the CancerSEEK blood test results, the most prevalent response was confiding with family members or close friends. Confiding accounted for 53% of negative PET-CTs interview responses and 68% of positive PET-CT interview responses. Of note, 17% of negative PET-CT responses for coping expressed relying on the DETECT genetic counselor for support; in comparison to positive PET-CT responses with 9%.

“I talked to a couple of close friends, my husband, my son and daughter... I told them I was concerned about it” (Negative PET-CT: Coping - Confiding)

“My significant [other] and my son I did tell, but they were real supportive.” (Positive PET-CT: Coping - Confiding)

“The counselor, he was very, very helpful and he assured me that, it does not mean I have

cancer.” (Negative PET-CT: Coping - GC)

“The genetic counselor that called me explained and answered all of my questions, so that was good.” (Positive PET-CT: Coping - GC)

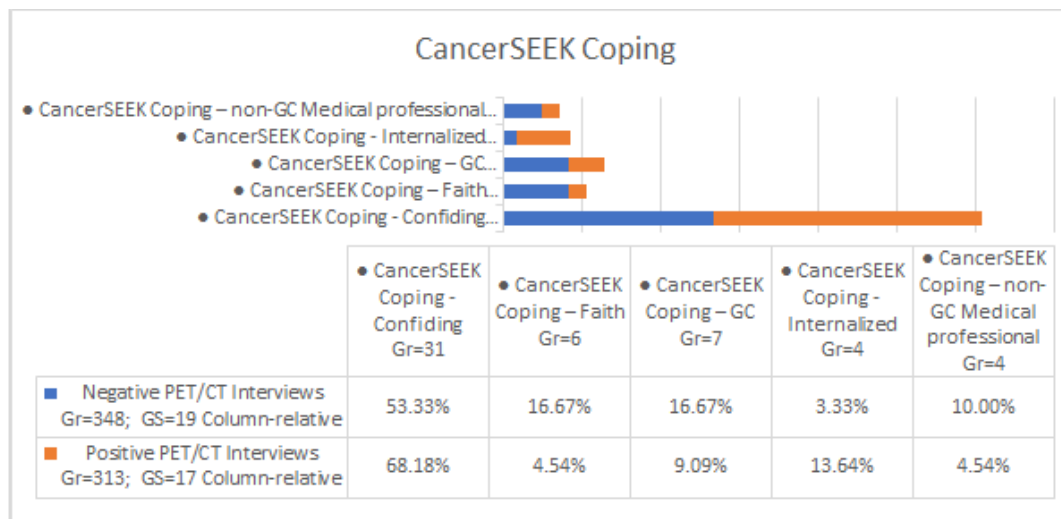


Figure 2. CancerSEEK coping strategies among participants. Abbreviations: Gr=Groundedness of Codes (number of quotations attributed to a code), GS= Number of documents in a document group

PET-CT Emotional Reaction, Process Issues, and Coping

As with responses to abnormal CancerSEEK blood test results, participants in both interview groups coped with the PET-CT results by confiding in others. Of note, the majority of positive PET-CT participants reported feeling confused by their results due to unclear result disclosure.

Similarly to the CancerSEEK blood test responses, the most common form of coping within the positive PET-CT interview group was confiding in family members or close friends, representing 36% of responses. For the negative PET-CT interview group responses, the most

common emotional reaction was anxiety, characterized by 36% of responses. Whereas for positive PET-CT responses, the most common emotional reaction was acceptance, characterized by 26% of responses.

Sixty percent of positive PET-CT interview responses described participants being confused by their results. This confusion was due to participants feeling inadequately informed of their results and being overwhelmed by the presented medical language, due to lack of clear result disclosure by the clinician. In addition to unclear results, 26% of responses expressed dissatisfaction with the timing of result disclosure. Significantly fewer responses in the negative PET-CTs interviews, 10%, expressed confusion regarding results. However, significantly more of these responses highlight dissatisfaction with the timing of the PET-CT.

“I have no clarity. I don’t know anything about what this now means, my odds of having cancer are or aren’t, and what I might need to be doing other than having the test again.”

(Positive PET-CT: Confusing Results)

“I couldn’t decipher it all because of course it’s in medical talk.” (Positive PET-CT: Confusing Results)

“That’s really scary when you’re waiting 5 and 6 weeks to find out what’s going on. I just had to say that. That would be my only complaint.” (Negative PET-CT: Dissatisfaction)

“They really need to speed this up because it’s just absolutely torture when you know there’s something wrong.” (Positive PET-CT: Dissatisfaction)

Psychosocial Reaction to Discordant CancerSEEK Results and PET-CT Findings

A crucial point of analysis is the psychosocial impact of discordant results for women with a false positive CancerSEEK blood test (i.e., positive CancerSEEK with subsequent

negative PET-CT scan). For women in the negative PET-CT group, 47% of responses expressed relief regarding the non-cancer incidental findings. Another 35% expressed neutral responses, in that they had no strong feelings about the non-cancer incidental findings. In comparing how women with discordant results coped, 88% of responses stated they confided in someone upon receiving the negative PET-CT scan result; while 11% of responses were in reference to relying on faith. While being found to be negative for a malignancy, 11 women in the negative PET-CT interview group had medically relevant non-cancer incidental findings reported from the PET-CT scan (e.g., hepatic cysts, pulmonary nodules, thyroid nodules, lung disease, and pericardial effusion). Of the six mentions of non-cancer incidental findings among the negative PET-CT interview group, five expressed responses of positive emotion regarding the findings.

“I felt that was OK, you know. Apparently something triggered it, and I’m glad they pursued it to make sure everything was OK.” (Negative PET-CT: Relief)

“I’m glad the CT scan didn’t show any tumors at the time.” (Negative PET-CT: Relief)

“I just didn’t get too concerned about it.” (Negative PET-CT: Neutral)

*“I just felt these things happen. I didn’t feel anything different one way or the other.”
(Negative PET-CT: Neutral)*

“I just relied on my faith that is all.” (Negative PET-CT: Faith)

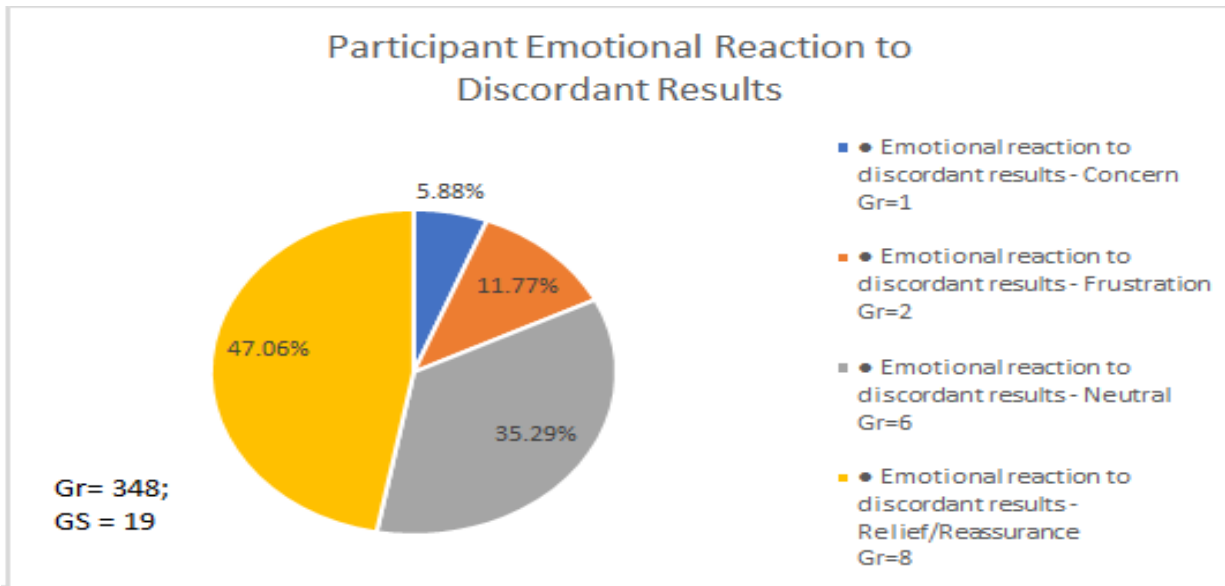


Figure 3. Emotional reaction to discordant results Negative PET-CT participants. Abbreviations:

Gr=Groundedness of Codes (number of quotations attributed to a code), GS= Number of documents in a document group

Study Satisfaction

The majority of study participant responses in the negative and positive PET-CT interview groups expressed that they would recommend the study to others and supported the idea of using the CancerSEEK blood test in routine care. Although anxiety was noted in both groups throughout the process, many commented on their appreciation and gratefulness for the DETECT study.

The overwhelming majority of participants expressed responses supporting the use of the CancerSEEK blood test in routine care; this sentiment was shared among 94% of responses in the negative PET-CT group and 88% of responses in the positive PET-CT group. Remaining responses expressed feelings of the DETECT study not yet being ready for use in routine care. Similar responses were shared in regard to participants' feelings of whether they would recommend the DETECT study to others; this consisted of 100% of responses in the negative

PET-CT interview group and 94% of responses in the positive PET-CT interview group. Only one response in the positive PET-CT interview group felt they would not recommend the study to others. In regard to the overall DETECT study, 20% of positive PET-CT participants (n=3) stated that they had a negative DETECT experience. Furthermore, 100% (n=19) of negative PET-CT interview participants and 80% (n=14) of positive PET-CT interview participants shared that they had a positive DETECT experience.

Some participants made suggestions as to what would make the DETECT study most useful in everyday care. Of these stipulations, cost was a major factor for participants in the positive PET-CT interview group. Twenty-three percent of responses emphasized that the CancerSEEK blood test should be available if it is financially accessible. As well as cost, 33% and 15% of negative and positive PET-CT interview responses, respectively, expressed feelings that males should be included in the study to have the best impact. The last criteria for inclusion participants expressed was that only individuals with a personal or family history should use the test in everyday care. This sentiment was expressed by 22% of negative PET-CT interview responses compared to 8% of positive PET-CT interview responses.

“Broaden the study to include not just females but males,” (Negative PET-CT: Include males)

“If it is affordable. I don’t know what the cost is, but it is probably expensive and people who don’t have insurance probably, you know, couldn’t do it.” (Positive PET-CT: Cost)

“I think if people have history, family history of it, it would be good for them.” (Positive PET-CT: Family history)

Regarding participants' emotional reactions to DETECT study satisfaction, in positive PET-CT participant interviews, 52% of responses expressed a sense of appreciation and

gratefulness for the DETECT study; in comparison to negative PET-CT participant interview responses accounting for 24%. Pertaining to negative psychosocial outcomes, 11% of positive PET-CT interview responses and 35% of negative PET-CT interview responses reported feelings of anxiety throughout the DETECT study. Of note, an important finding from our analysis showed that only positive PET-CT participant interview responses expressed feelings of trauma or being upset regarding study satisfaction, representing 7% in both categories.

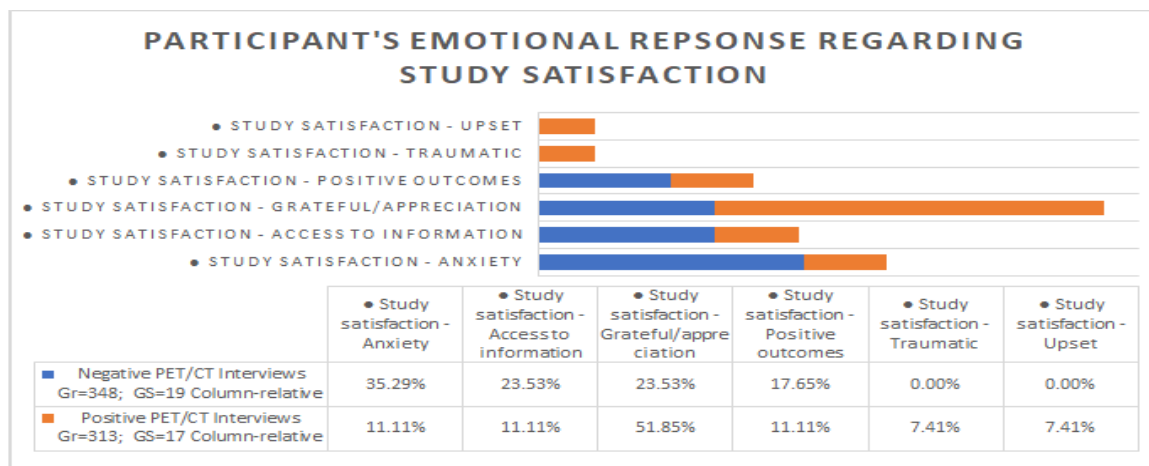


Figure 4. Emotional responses regarding study satisfaction among participants. Abbreviations:

Gr=Groundedness of Codes (number of quotations attributed to a code), GS= Number of documents in a document group

“To me, it was a wonderful experience and I was glad to know that if something had come up and I would have had to deal with a life or death situation that I wouldn’t stress out about it.”

(Negative PET-CT: Positive DETECT Experience)

“I’m grateful something was found and that it didn’t take long to schedule then, the further studies, and to move on with a plan.” (Positive PET-CT: Positive DETECT Experience)

“I’m so grateful to be part of that program and the whole procedure, I’m just very, very grateful. It’s something I would have never known about.” (Negative PET-CT:

Grateful/Appreciation)

“I am grateful that DETECT was there and asked me to participate in this program, because I found nothing.” (Positive PET-CT: Grateful/Appreciation)

DISCUSSION

This qualitative study was performed with the purpose of understanding the psychosocial outcomes associated with abnormal ctDNA testing to better understand how it could positively or negatively impact patient care. The research performed in this study analyzed participants’ emotional reactions and coping strategies, following DETECT study participation, through qualitative analysis rather than quantitative measurement. To date, studies of ctDNA for cancer detection have primarily been conducted using participants with a cancer diagnosis. The data collected from the interviews in this study aids in future understanding of the benefits, limitations, and usage of ctDNA-based screening tests in asymptomatic individuals.

Themes Shared Between Negative and Positive PET-CT Interview Groups

Between the negative and positive PET-CT interview groups, an overall response rate of 82% provides evidence of the findings being generalizable across DETECT participants.

The high percentage of responses supporting the use of the CancerSEEK blood test in routine care and the recommendation of DETECT to others, is evidence of the general acceptance of the DETECT study among participants, in both interview groups. In regard to routine care, 94% of negative PET-CT and 88% of positive PET-CT responses support the usage of the CancerSEEK blood test. This result gives support to the benefits of the CancerSEEK blood test, outweighing any negative psychosocial outcomes experienced among participants in both

groups. Regarding participants' emotional responses to study satisfaction, both groups emphasized finding value in having access to the information and of having a positive outcome from participation in the study. This holds true for participants who were given discordant CancerSEEK blood test results, suggesting that the discordant results and non-cancer incidental findings may not have lasting negative psychosocial impacts.

While there were certainly positive psychosocial outcomes associated with the CancerSEEK blood test found within the study, negative emotions were expressed by participants regarding the DETECT study logistics. Both the negative and positive PET-CT interview groups responses represented dissatisfaction with the timing and communication of the DETECT study results for the CancerSEEK blood test. They had anticipated a shorter wait time for return of results and were disappointed by the length of the process. Similar responses of dissatisfaction with the timing of result disclosure were expressed regarding the PET-CT scan, but a larger number of responses were reported as dissatisfaction with the timing of the PET-CT scan procedure. These responses are understandable as women in the DETECT study waited weeks to receive results for both the CancerSEEK blood test and PET-CT scan. Responses emphasized additional complaints regarding the PET-CT scan procedure and the importance of shortening wait times to allow for clear result disclosures in future trials of CancerSEEK.

Negative PET-CT Interview Themes

The negative PET-CT interview responses reported a higher percentage of study awareness than those in the positive PET-CT interview group. This could be due to these women being less overwhelmed by medical care following a cancer diagnosis, or to the anxiety of their discordant results, making them hyper-aware of the study purpose. The retrospective nature of the study likely created some bias in participant responses based on personal health outcomes,

which could explain this result. Participant responses in this group reported feelings of acceptance as their most common baseline concern for the possibility of the test detecting cancer. Their retrospective acceptance is likely the result of knowing, at the time of the interview, that they did not have cancer.

Feelings of being upset and scared were likely the most common emotional reaction to the discordant CancerSEEK blood test because participants were not expecting to receive a positive result. Regarding coping with discordant CancerSEEK blood test results, most responses reported confiding in a family member or friends. However, responses relying on faith, confiding in a GC, and confiding with a non-GC medical professional were all notably higher in the negative PET-CT interview group than participants in the positive PET-CT interview group.

Regarding emotional responses to PET-CT results, it is understandable that the most common reaction was nervousness or anxiety. Women in this group may have reported these emotions because of the discrepancy between the discordant CancerSEEK blood test and PET-CT results. However, this group expressed less confusion after they received their PET-CT scan results which provided confirmation that they fully understood that they were not being diagnosed with cancer. The women in this group were subsequently relieved or had no strong feelings upon receiving discordant CancerSEEK blood test results and/or non-cancer incidental findings. This could mean that there was not a lasting impact of negative psychosocial harms following the discordant CancerSEEK blood test results. Notably, all but one of the women in this group responded positively towards PET non-cancer incidental findings. This reaction towards the PET-CT scan results showed that even if the PET-CT scan did not identify cancer, they were grateful that it was capable of identifying other significant findings related to their health.

Every participant in the negative PET-CT interview group emphasized that they had an overall positive DETECT experience. This identification of study satisfaction is helpful for future expansion of the DETECT project. Responses in this group reported more feelings of anxiety throughout the DETECT study. It is understandable that women in the negative PET-CT group emphasized these responses because they received discordant results between the CancerSEEK blood test and the PET-CT that led to excessive worry, whereas for the positive group any worry would have been justified because they had cancer all along. To highlight inclusion criteria, more responses in the negative PET-CT interview group expressed that only individuals with a personal or family history of cancer should use the test in everyday care. This response may be emphasizing that utilizing average-risk individuals in cancer screening studies can result in negative psychosocial harms due to excessive worry.

Positive PET-CT Interview Themes

The increased lack of study awareness among women in the positive PET-CT interview group was an interesting finding. These women may have been overwhelmed by the medical care received after their cancer diagnosis, and less aware of the DETECT study as the reason for that diagnosis. This was surprising given that cancer had been diagnosed through study participation. It was assumed that more of these women would be aware of the DETECT study purpose.

Again, the retrospective nature of the study and the final health outcome of a cancer diagnosis may have created some recall bias among responses. In regard to baseline cancer concern before starting the study, it is understandable that the majority of responses by women in the positive PET-CT interview group had not considered the possibility of developing cancer. Had these women not been diagnosed with cancer, it is possible that they, retrospectively, would

have had more accepting responses towards that outcome. This sentiment is also seen in the responses of women in this group towards the results of the CancerSEEK blood test. Women were likely accepting of the result because with the benefit of hindsight they knew the results of the CancerSEEK test to be true.

This study highlighted the importance of having a support system in place. Over half of the responses to coping with results of the CancerSEEK blood test in the positive PET-CT group expressed confiding in family or close friends; in addition, one-third of responses in this group also expressed confiding as a way of coping with the results of the PET-CT scan. This shows that like other cancer screenings, people want to share their results with those they are close to for support. But it is interesting to note that many women in this group also internalized the results, not wanting to share until they had more information. This could be the result of not having a strong support system or needing confirmation before worrying others.

It is important to note the significant differences in responses in the positive PET-CT interview group that expressed being confused by the results of their PET-CT scan compared to those with negative PET-CT results. It is presumed that this confusion was due in part to participants feeling inadequately informed of their results and being overwhelmed by the medical language used. Clinicians can better communicate next steps, when a PET-CT is abnormal, by disclosing results in-person and having a GC present to help define complicated medical terminology. The presence of a GC would likely help alleviate the confusion and unclear results. In addition to confusing results, responses expressed dissatisfaction with wait time for disclosure of results; so much so that some women expressed discovering their cancer diagnosis by means outside of the study. In thinking about the routine use of the CancerSEEK blood test and the DETECT protocol, there is a need to address the time it takes for results to be released to patients

as well as how these results are communicated. Hence, the next trial of the DETECT study should help to address these issues.

It was postulated that there could be negative psychosocial outcomes for asymptomatic women in the study to be diagnosed with cancer, but the lack of responses regarding feelings of being upset or traumatized throughout study participation aids in disputing this thought. In contrast, responses in the positive PET-CT interview group expressed more positive psychosocial outcomes from study participation such as gratefulness and appreciation for being in the study. Women were grateful and appreciated participating in the study despite lacking the same level of study awareness of DETECT as participants in the negative PET-CT interview group. Responses expressed feelings of finding value in the information, given that the knowledge was used to make medically actionable decisions. It is reassuring for the possible future use of the CancerSEEK blood test that, among responses in this group, there was pervasive acceptance for routine use of the test and sentiments stating that participants would recommend the study to others.

Study Limitations

While the study was designed to capture the range of psychosocial experiences and be generalizable to larger populations, there are limitations of this study. While we maintain that the sample size of the study was appropriate for the type of research performed, because a saturation of themes was reached, studies in different populations (e.g., those with men or more racial diversity) could present different psychosocial themes. Furthermore, the sample size consisted of a comparison of responses for only two interview groups, the negative and positive PET-CTs for cancer. Further research is warranted to investigate the psychosocial outcomes of individuals with non-cancer incidental findings who are negative for cancer.

It is recognized as a study limitation that the length of the DETECT study process likely impacted recall, making it difficult for study participants to separate the CancerSEEK blood test results from the abnormal, or normal PET-CT scan responses. Also, the retrospective design is a limitation of the study. Participant responses were likely biased based on their personal health outcomes in the study. A future study to address this limitation could be designed using a pre-post test qualitative or quantitative approach, in which participants' baseline psychosocial state was captured prior to study intervention and diagnosis. Lastly, this study does not compare psychosocial outcomes of ctDNA cancer screening to currently utilized screening methods. A future study could compare outcomes in participants with discordant CancerSEEK blood test results to those with discordant results from routine cancer screenings such as mammography.

CONCLUSIONS

The goal of our study was to assess psychosocial outcomes associated with a ctDNA-based cancer screening test, by questioning whether the CancerSEEK blood test was acceptable to women with an abnormal result. It is clear from our analysis that distinct similarities and differences exist between the negative and positive PET-CT interview groups, highlighting the psychosocial outcomes. The results that most significantly informed psychosocial outcomes of CancerSEEK include:

1. Most notably, the majority of responses in both groups reported having a positive experience with the DETECT study and would recommend it to others. This is especially important to note for the negative PET-CT participants who received discordant CancerSEEK blood test results.
2. Among all responses in both groups, confiding in family and friends was the most commonly utilized coping strategy, following the results of the CancerSEEK blood test.

This emphasized the importance of a sufficient support system being available following screening.

3. For participants in the negative PET-CT group, who received non-cancer incidental findings, the most prevalent emotional response was relief about the findings. While anxiety was expressed regarding the false positive blood test, participants appreciated the knowledge of the non-cancer incidental findings.
4. Among responses in both groups, there was expression of dissatisfaction with the turnaround time for the CancerSEEK blood test and PET-CT results and the method in which these results were communicated. Issues surrounding result disclosure was a source of anxiety and concern based on study responses and needs to be further reviewed for an effective screening protocol.

While this research is reassuring in providing evidence of the acceptability of the CancerSEEK blood test as a screening method among those with an abnormal CancerSEEK result, continued research should be explored to expand on these findings and identify additional potential benefits of ctDNA testing. It is the hope that one day, a ctDNA cancer screen will be implemented for early detection of cancer, particularly for those cancers without valid screening modalities in place.

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Appendix A Qualitative Interview Guide

[Introduction Script] Hello, Ms. _____. My name is Gabby/Simone and I'm a Genetic Counseling Student working with Geisinger Health System. I am calling about the DETECT study that you are part of. We would like to know more about your experiences with the study. Would you be interested in answering some questions about your participation in the study?

[If no] Is there another time you would be available and interested in participating?

[If yes, discuss new time for interview and plan to re-contact the patient.]

[If no] Thank you for your time and thanks again for being in DETECT.

[If yes] These questions should take up to 15-20 minutes. Do you have time to answer them now?

[If yes] Thank you. Before we start, here are a couple of things to know about this interview. We are interviewing DETECT participants who had an abnormal result on the DETECT blood test. Your responses will help us learn more about what it is like to receive a result like yours. I will ask you some broad questions and then follow-up with some more specific questions about your experience with receiving results from the DETECT study. You can say whatever you want – nothing will hurt my feelings and nothing you say will have a negative effect on your care. Everything you tell me will be kept confidential. Your interview responses will only be shared with research team members and nothing will identify you if the information you share is used for future reports on the findings from this study. Participation in this interview is voluntary and you can stop at any time. Please remember: be honest with your responses and you do not have to answer anything you do not want to talk about. You can end the interview at any time. If you have any questions you can ask us during the interview or contact us afterwards at the following phone numbers: (570) 301-3014 or (336) 254-8378. Do you have any questions about this interview? Do you agree to participate in this study?

[If yes to participation] Before we begin, would you mind if I recorded this conversation so that I make sure I don't miss anything that you tell me? We will remove your name and any identifying information from the recording. Some of this information will be stored in a research record at Geisinger and they can be kept for up to 3 years.

[If no to participation] Thank you for your time and thanks again for being in DETECT.

[If no to recording] Okay, that's fine. I may need a little bit of extra time to make sure I write down what you tell me as completely as possible.

1) Do you remember why the DETECT study is being done?

[If yes] Can you tell me in your own words why they are doing the DETECT study?

[If no] The DETECT study uses a blood sample to look for cancer markers, either DNA from a tumor or elevated levels of proteins. You may recall having your blood drawn after consenting to be part of the project. The purpose of the DETECT study is to learn how well the blood test works at finding cancer early.

2) What motivated you to want to join the study?

1. Probe (if applies): What did you hope to get from being in the study?

2. Probe (if applies): Some participants expressed that they have a strong family history of cancer and maybe by participating in this study they might better understand their own cancer risk. Was this the case for you?

3. Probe: Others may want to help further scientific research and see if this technology can be helpful to future generations. Was this the case for you?

4. Probe (if applies): *If more than one motivation listed ask* “which one influenced you the most?”

3) When you joined the study, how did you feel about the possibility that the test would lead to finding cancer?

Narrative: We know that when someone is diagnosed with cancer, genetic material known as DNA is shed into their bloodstream. This specific type of genetic material is called circulating tumor DNA or ctDNA. As you recall, ctDNA or biomarkers looking for these specific cancers were detected in your bloodstream when we looked at your sample. This result did not necessarily mean that you had cancer, so the study team recommended that you have additional testing with a PET-CT scan.

4) How did you feel when the blood work results were abnormal indicating the possible presence of cancer?

1. Probe (if applies): Was this type of result something you were expecting?

2. Probe (if applies): Emotionally and psychologically, what did you experience after getting these results?

3. Probe: How did you feel about being asked to have a PET-CT scan?

4. Probe (if applies): Who did you lean on and communicate these results to?

5. Probe: Did you find that you needed more support than expected after receiving the results?

5) (For abnormal PET-CT scan) What do you remember about the results of the PET-CT scan?

1. Probe (if applies): What did you do medically to follow-up on the scan?

2. Probe (if applies): How did you feel about the results of the PET-CT scan?

3. Probe (if applies): Was this type of result something you were expecting?

4. Probe (if applies): Emotionally and psychologically, what did you experience after getting these results?

5. Probe (if applies): How are you dealing with a cancer diagnosis?

6. Probe (if applies): Does this result change any future management for you going forward?

7. Probe (if applies): Who did you communicate these results to?

8. Probe (if applies): Who did you lean on for emotional support?

9. Probe (if applies): Did you need more support than expected?

6) (For normal PET-CT scan) What do you remember about the results of the PET-CT scan?

1. Probe (if applies): What did you do medically to follow-up on the scan?

2. Probe (if applies): How did you feel about having an abnormal blood test but normal PET-CT scan?

3. Probe (if applies): Was this type of result something you were expecting?

4. Probe (if applies): Emotionally and psychologically, what did you experience after getting these results?

5. Probe (if applies): Who did you communicate these results to?

6. Probe (if applies): Who did you lean on for emotional support?

7. Probe (if applies): Did you need more support than expected?

7) How have your feelings toward the DETECT study changed since you received your PET-CT scan results?

1. Probe (if applies): *[If yes]* How?

2. Probe (if applies): *[If no]* Can you tell me more about why you did not feel any different about the DETECT study?

3. Probe: Would you recommend to friends or family members that they join DETECT?

8) How did cancer screening in this study compare to other cancer screening you have done?

1. Probe (if applies): What cancer screening do you routinely have?

9) What are your thoughts on whether the DETECT blood test should be part of everyday care?

1. Probe (if test should be part of everyday care): Before the test were offered in everyday care, what would you change about how the test is performed or followed up on?

2. Probe (if not ready for everyday care): What else needs to be done or studied before the test is ready for everyday care?

10) What other psychological, emotional or social outcomes from your participation in the study would you like to share?

Conclusion: Those are all of the questions I have. Thank you for your participation in this interview. I appreciate your time and responses. Your answers will help to better understand the expectations and experiences of study participants and may help improve how to better understand DETECT study results. Your responses will remain confidential. If you have any additional questions, please do not hesitate to contact us. Hope you have a wonderful day!

Appendix B
The Complete List of 76 Codes

Code Number	Major Themes - Code	Definition/Inclusion Criteria
1	Awareness of Study Purpose - Knowledgeable	Participant was actively able to recognize the purpose of the DETECT study
2	Awareness of Study Purpose- Uninformed	Participant was not actively able to recognize the purpose of the DETECT study
3	Rationale for Participation - Altruism	Participant used statement of wanting to help others and contribute to the current body of scientific research, including early cancer detection
4	Rationale for Participation - Family History	Participant used statement of family history of cancer
5	Rationale for Participation - Personal Utility	Participant wanted to know the information for their own health; early detection
6	Rationale for Participation - Unsure	Participant was not aware of a specific reason for enrollment
7	Rationale for Participation - Cure	Participant joined DETECT in the hope of finding a cure for cancer
8	Baseline Cancer Concern - Unprepared	Participant did not think about the possibility of cancer
9	Baseline Cancer Concern - Unconcerned/Not worried	Participant was not concerned about the possible thought of cancer
10	Baseline Cancer Concern - Acceptance	Participant applied statements of acceptance regarding cancer recognition
11	Baseline Cancer Concern - Distress	Participant felt upset, nervous, or anxious regarding the idea of cancer detection
12	Baseline Cancer Concern - Scared	Participant felt scared to learn about new information regarding a potential cancer diagnosis

13	CancerSEEK Emotional Reaction - Anxiety	Use when participant verbalizes statements of anxiety
14	CancerSEEK Emotional Reaction - Upset	Use when participant verbalizes statements of being upset
15	CancerSEEK Emotional Reaction - Concern	Use when participant verbalizes statements of concern
16	CancerSEEK Emotional Reaction - Scared	Use when participant verbalizes statements of being scared
17	CancerSEEK Emotional Reaction - Acceptance	Use when participant verbalizes statements of acceptance
18	CancerSEEK Emotional Reaction - Confusion	Use when participant verbalizes statements of confusion
19	CancerSEEK Emotional Reaction - Surprise	Use when participant verbalizes statements of not expecting result
20	CancerSEEK Emotional Reaction - Not surprised/Not worried	Use when participant verbalizes that the results did not have a significant impact on their quality of life
21	CancerSEEK Emotional Reaction - Control group	Use when participant verbalizes belief that they belonged to a different group within the study
22	CancerSEEK Coping - Internalized	Use when participant verbalizes that they dealt with results alone; did not communicate
23	CancerSEEK Coping - Confiding	Use when participant verbalizes that they dealt with result by confiding in someone
24	CancerSEEK Coping – Genetic Counselor	Use when participant expresses communication, reliance, or reassurance with a genetic counselor
25	CancerSEEK Coping – Non-GC Medical Professional	Use when participant verbalizes concern with a different medical professional other than a GC, relied on gaining information and communicating a with doctor

26	CancerSEEK Coping - Faith	Use when participant verbalizes that they relied on faith and prayer
27	CancerSEEK Process Issue - Dissatisfaction	Use when participant verbalizes statements of being dissatisfied with timing of results for CancerSEEK
28	PET-CT Emotional Reaction - Upset	Participant expresses statements of feeling upset
29	PET-CT Emotional Reaction - Concerned	Participant expresses statements of concern
30	PET-CT Emotional Reaction - Not Concerned	Participant expresses statements of no concern
31	PET-CT Emotional Reaction - Acceptance	Participant expresses statements of acceptance
32	PET-CT Emotional Reaction - Not Expecting Results	Participant expresses statements of not expecting results
33	PET-CT Emotional Reaction - Relief	Participant expresses relief after positive PET-CT results
34	PET-CT Emotional Reaction - Nervousness/Anxiety	Participant expresses statements of nervousness/anxiety
35	PET-CT Process Issue - Dissatisfaction	Participant expresses statements of being dissatisfied with the timing and communication of results for the PET-CT scan
36	PET-CT Process Issue - PCP Communication	Participant expresses problems reaching PCP after disclosure of PET-CT results
37	PET-CT Non-Cancer Incidental Findings - Positive Response to Non-Cancer Incidental Findings	Participant expresses positive emotion regarding secondary findings
38	PET-CT Non-Cancer Incidental Findings - Negative Response to Non-Cancer Incidental Findings	Participant expresses negative emotion regarding secondary findings

39	PET-CT Understanding - Confusing Results	Participant expresses statements of lack of understanding regarding the meaning of results
40	PET-CT Coping - Faith	Participant expresses they relied on faith and prayer
41	PET-CT Coping - Confiding	Use when participant verbalizes that they dealt with result by confiding in someone
42	Emotional Reaction to Discordant Results - Relief/Reassurance	Participant expresses relief after disclosure of results
43	Emotional Reaction to Discordant Results - Frustration	Participant expresses frustration that bloodwork was abnormal and PET-CT was normal
44	Emotional Reaction to Discordant Results - Concern	Participant expresses concern with the discordant results
45	Emotional Reaction to Discordant Results - Neutral	Participant expresses no strong emotions negatively or positively
46	Coping with Discordant Results - Confiding	Participant expresses that they dealt with discordant results by confiding in someone
47	Coping with Discordant Results - Faith	Participant expresses coping with discordant results by relying on faith and prayer
48	Post Results Emotional Response - Scared	Participant expressed statements of being scared following participation
49	Post Results Emotional Response - Self-Guilt	Participant expressed statements of guilt for poor personal habits
50	Post Results Emotional Response - Importance of Medical Care	Participant expressed statements of being more vigilant of medical needs/care
51	Previous Cancer Screening (Medical Behavior) - Similar Screening Comparison	Participant verbalized that previous cancer screening is comparable to other cancer screenings or no different

52	Previous Cancer Screening (Medical Behavior) - Different Screening Comparison	Participant verbalized that previous cancer screening is non-comparable to other cancer screenings
53	Previous Cancer Screening (Medical Behavior) - Ease of Process	Participant verbalized that the PET-CT and entire DETECT process was easier than other screenings
54	Previous Cancer Screening (Medical Behavior) - Inconvenient	Participant verbalized that cancer screening through DETECT is inconvenient/time consuming than other screenings
55	Previous Cancer Screening (Medical Behavior) - Comprehensive	Participant verbalized that cancer screening through DETECT is more in depth than other cancer screenings
56	Study Satisfaction - Include Males	Participant felt the inclusion criteria should have included males
57	Study Satisfaction - Personal/Family History	Participant felt that the study is useful if participant has an extensive medical/family history
58	Study Satisfaction - Cost	Participant verbalized that DETECT is useful if offered at the appropriate cost
59	Study Satisfaction - Study Outcomes	Participant verbalized that DETECT is useful based on overall study outcomes
60	Study Satisfaction - Prevention	Participant verbalized that DETECT is useful for prevention
61	Study Satisfaction - Positive DETECT Experience	Participant verbalized overall positive statements towards DETECT and the study process
62	Study Satisfaction - Negative DETECT Experience	Participant verbalized overall negative statements towards DETECT and the study process
63	Study Satisfaction - Use in Routine Care	Participant thinks DETECT should be used in routine care
64	Study Satisfaction - Not used in Routine Care	Participant does not think DETECT should be used in routine care

65	Study Satisfaction - Ease of Process	Participant felt the process for DETECT was easier than other screenings/simple way to detect cancers early
66	Study Satisfaction - Access to Information	Participant valued having access to the information
67	Study Satisfaction - Anxiety	Participant felt that parts of the process caused anxiety
68	Study Satisfaction - Upset	Participant verbalized statements of feeling upset
69	Study Satisfaction - Traumatic	Participant verbalized being emotionally traumatized from the experience
70	Study Satisfaction - Change in Feelings	Participant expressed change in attitude towards the study
71	Study Satisfaction - No Change in Feelings	Participant did not express change in attitude towards the study
72	Study Satisfaction - Grateful/Appreciation	Participant expressed statements of appreciation for study and getting results
73	Study Satisfaction - Recommend to Others	Participant would recommend the DETECT study to others
74	Study Satisfaction - Not Recommend to Others	Participant would not recommend the DETECT study to others
75	Study Satisfaction - Positive Outcomes	Participant expressed statements of positive experiences with medical professionals, rather than experiences with the DETECT project
76	Study Satisfaction – Lack of Care	Participant expressed wanting more care post getting results

Appendix C
Complete list of codes and frequency of use in negative PET-CT group

Codes	Negative PET-CT Interviews Gr=348; GS=19	
	Absolute Frequency	Table- relative Frequency
• Awareness of study purpose - Knowledgeable Gr=21	12	3.43%
• Awareness of study purpose- Uninformed Gr=15	7	2.00%
• Baseline Cancer Concern - Acceptance Gr=19	11	3.14%
• Baseline Cancer Concern - Distress Gr=2	2	0.57%
• Baseline Cancer Concern - Scared Gr=1	1	0.29%
• Baseline Cancer Concern - Unconcerned/Not worried Gr=8	6	1.71%
• Baseline Cancer Concern - Unprepared Gr=14	4	1.14%
• CancerSEEK Coping - Confiding Gr=31	16	4.57%
• CancerSEEK Coping - Faith Gr=6	5	1.43%
• CancerSEEK Coping - GC Gr=7	5	1.43%
• CancerSEEK Coping - Internalized Gr=4	1	0.29%
• CancerSEEK Coping - non-GC Medical professional Gr=4	3	0.86%
• CancerSEEK emotional reaction - Acceptance Gr=20	7	2.00%
• CancerSEEK emotional reaction - Anxiety Gr=6	5	1.43%
• CancerSEEK emotional reaction - Concern Gr=10	7	2.00%
• CancerSEEK emotional reaction - Confusion Gr=1	0	0.00%
• CancerSEEK emotional reaction - Control group Gr=1	0	0.00%
• CancerSEEK emotional reaction - Not surprised/Not worried Gr=6	3	0.86%
• CancerSEEK emotional reaction - Scared Gr=4	4	1.14%
• CancerSEEK emotional reaction - Surprise Gr=18	6	1.71%
• CancerSEEK emotional reaction - Upset Gr=10	8	2.29%
• CancerSEEK Process Issue - Dissatisfaction Gr=13	8	2.29%

• Coping with discordant results - Confiding Gr=17	15	4.29%
• Coping with discordant results - Faith Gr=2	2	0.57%
• Emotional reaction to discordant results - Concern Gr=1	1	0.29%
• Emotional reaction to discordant results - Frustration Gr=2	2	0.57%
• Emotional reaction to discordant results - Neutral Gr=6	6	1.71%
• Emotional reaction to discordant results - Relief/Reassurance Gr=8	8	2.29%
○ PET-CT coping - Confiding Gr=11	0	0.00%
• PET-CT Coping - Faith Gr=3	3	0.86%
• PET-CT emotional reaction - Acceptance Gr=13	5	1.43%
• PET-CT emotional reaction - Concerned Gr=2	2	0.57%
• PET-CT emotional reaction - Nervousness/anxiety Gr=8	8	2.29%
• PET-CT emotional reaction - Not concerned Gr=6	3	0.86%
• PET-CT emotional reaction - Not expecting results Gr=3	1	0.29%
○ PET-CT emotional reaction - Relief/Reassurance Gr=3	0	0.00%
• PET-CT emotional reaction - Upset Gr=3	0	0.00%
• PET-CT Process Issue - Dissatisfaction Gr=17	13	3.71%
• PET-CT Process Issue - PCP communication Gr=7	5	1.43%
• PET-CT Understanding - Confusing results Gr=11	2	0.57%
• PET-CT Non-Cancer incidental findings - Negative response to Non-Cancer incidental findings Gr=1	1	0.29%
• PET-CT Non-Cancer incidental findings - Positive response to Non-Cancer incidental findings Gr=5	5	1.43%
• Post results emotional response - Importance of medical care Gr=1	0	0.00%
• Post results emotional response - Scared Gr=1	0	0.00%
• Post results emotional response - Self-guilt Gr=2	2	0.57%
• Previous Cancer Screening (Medical Behavior) - Comprehensive Gr=8	2	0.57%
• Previous Cancer Screening (Medical Behavior) - Different screening comparison Gr=6	1	0.29%
• Previous Cancer Screening (Medical Behavior) - Ease of process Gr=3	1	0.29%

• Previous Cancer Screening (Medical Behavior) - Inconvenient Gr=4	3	0.86%
• Previous Cancer Screening (Medical Behavior) - Similar screening comparison Gr=13	10	2.86%
• Rationale for participation - Altruism Gr=25	13	3.71%
• Rationale for participation - Cure Gr=3	3	0.86%
• Rationale for participation - Family history Gr=16	9	2.57%
• Rationale for participation - Personal utility Gr=14	7	2.00%
• Rationale for participation - Unsure Gr=5	1	0.29%
• Study satisfaction - Study outcomes Gr=1	1	0.29%
• Study satisfaction - Anxiety Gr=9	6	1.71%
• Study satisfaction - Change in feelings Gr=1	1	0.29%
• Study satisfaction - Cost Gr=3	0	0.00%
• Study satisfaction - Ease of process Gr=3	0	0.00%
• Study satisfaction - Access to information Gr=7	4	1.14%
• Study satisfaction - Grateful/appreciation Gr=18	4	1.14%
• Study satisfaction - Include males Gr=5	3	0.86%
• Study satisfaction - Lack of care Gr=3	0	0.00%
• Study satisfaction - Negative DETECT experience Gr=5	0	0.00%
• Study satisfaction - No change in feelings Gr=29	20	5.71%
• Study satisfaction - Not recommend to others Gr=1	0	0.00%
• Study satisfaction - Not used in routine care Gr=3	1	0.29%
• Study satisfaction - Personal/family history Gr=3	2	0.57%
• Study satisfaction - Positive DETECT experience Gr=33	13	3.71%
• Study satisfaction - Positive outcomes Gr=6	3	0.86%
• Study satisfaction - Prevention Gr=5	4	1.14%
• Study satisfaction - Recommend to others Gr=33	17	4.86%
• Study satisfaction - Traumatic Gr=2	0	0.00%
• Study satisfaction - Upset Gr=2	0	0.00%

• Study satisfaction - Use in routine care Gr=31	16	4.57%
Totals	350	100.00%

Appendix D
Complete list of codes and frequency of use in positive PET-CT group

Codes	Positive PET-CT Interviews Gr=313; GS=17	
	Absolute Frequency	Table- relative Frequency
• Awareness of study purpose - Knowledgeable Gr=21	9	2.96%
• Awareness of study purpose- Uninformed Gr=15	8	2.63%
• Baseline Cancer Concern - Acceptance Gr=19	8	2.63%
• Baseline Cancer Concern - Distress Gr=2	0	0.00%
• Baseline Cancer Concern - Scared Gr=1	0	0.00%
• Baseline Cancer Concern - Unconcerned/Not worried Gr=8	2	0.66%
• Baseline Cancer Concern - Unprepared Gr=14	10	3.29%
• CancerSEEK Coping - Confiding Gr=31	15	4.93%
• CancerSEEK Coping - Faith Gr=6	1	0.33%
• CancerSEEK Coping - GC Gr=7	2	0.66%
• CancerSEEK Coping - Internalized Gr=4	3	0.99%
• CancerSEEK Coping - non-GC Medical professional Gr=4	1	0.33%
• CancerSEEK emotional reaction - Acceptance Gr=20	13	4.28%
• CancerSEEK emotional reaction - Anxiety Gr=6	1	0.33%
• CancerSEEK emotional reaction - Concern Gr=10	3	0.99%
• CancerSEEK emotional reaction - Confusion Gr=1	1	0.33%
• CancerSEEK emotional reaction - Control group Gr=1	1	0.33%
• CancerSEEK emotional reaction - Not surprised/Not worried Gr=6	3	0.99%
• CancerSEEK emotional reaction - Scared Gr=4	0	0.00%
• CancerSEEK emotional reaction - Surprise Gr=18	12	3.95%
• CancerSEEK emotional reaction - Upset Gr=10	2	0.66%
• CancerSEEK Process Issue - Dissatisfaction Gr=13	5	1.65%

• Coping with discordant results - Confiding Gr=17	2	0.66%
• Coping with discordant results - Faith Gr=2	0	0.00%
• Emotional reaction to discordant results - Concern Gr=1	0	0.00%
• Emotional reaction to discordant results - Frustration Gr=2	0	0.00%
• Emotional reaction to discordant results - Neutral Gr=6	0	0.00%
• Emotional reaction to discordant results - Relief/Reassurance Gr=8	0	0.00%
○ PET-CT coping - Confiding Gr=11	11	3.62%
• PET-CT Coping - Faith Gr=3	0	0.00%
• PET-CT emotional reaction - Acceptance Gr=13	8	2.63%
• PET-CT emotional reaction - Concerned Gr=2	0	0.00%
• PET-CT emotional reaction - Nervousness/anxiety Gr=8	0	0.00%
• PET-CT emotional reaction - No recall of PET-CT Gr=0	0	0.00%
• PET-CT emotional reaction - Not concerned Gr=6	3	0.99%
• PET-CT emotional reaction - Not expecting results Gr=3	2	0.66%
○ PET-CT emotional reaction - Relief/Reassurance Gr=3	3	0.99%
• PET-CT emotional reaction - Upset Gr=3	3	0.99%
• PET-CT Process Issue - Dissatisfaction Gr=17	4	1.32%
• PET-CT Process Issue - PCP communication Gr=7	2	0.66%
• PET-CT Understanding - Confusing results Gr=11	9	2.96%
• PET-CT Non-Cancer incidental findings - Negative response to Non-Cancer incidental findings Gr=1	0	0.00%
• PET-CT Non-Cancer incidental findings - Positive response to Non-Cancer incidental findings Gr=5	0	0.00%
• Post results emotional response - Importance of medical care Gr=1	1	0.33%
• Post results emotional response - Scared Gr=1	1	0.33%
• Post results emotional response - Self-guilt Gr=2	0	0.00%
• Previous Cancer Screening (Medical Behavior) - Comprehensive Gr=8	6	1.97%
• Previous Cancer Screening (Medical Behavior) - Different screening comparison Gr=6	5	1.65%

• Previous Cancer Screening (Medical Behavior) - Ease of process Gr=3	2	0.66%
• Previous Cancer Screening (Medical Behavior) - Inconvenient Gr=4	1	0.33%
• Previous Cancer Screening (Medical Behavior) - Similar screening comparison Gr=13	3	0.99%
• Rationale for participation - Altruism Gr=25	12	3.95%
• Rationale for participation - Cure Gr=3	0	0.00%
• Rationale for participation - Family history Gr=16	7	2.30%
• Rationale for participation - For a lost friend or significant other Gr=0	0	0.00%
• Rationale for participation - Personal utility Gr=14	7	2.30%
• Rationale for participation - Unsure Gr=5	4	1.32%
• Study satisfaction - Study outcomes Gr=1	0	0.00%
• Study satisfaction - Anxiety Gr=9	3	0.99%
• Study satisfaction - Change in feelings Gr=1	0	0.00%
• Study satisfaction - Cost Gr=3	3	0.99%
• Study satisfaction - Ease of process Gr=3	3	0.99%
• Study satisfaction - Access to information Gr=7	3	0.99%
• Study satisfaction - Grateful/appreciation Gr=18	14	4.61%
• Study satisfaction - Include males Gr=5	2	0.66%
• Study satisfaction - Lack of care Gr=3	3	0.99%
• Study satisfaction - Negative DETECT experience Gr=5	5	1.65%
• Study satisfaction - No change in feelings Gr=29	9	2.96%
• Study satisfaction - Not recommend to others Gr=1	1	0.33%
• Study satisfaction - Not used in routine care Gr=3	2	0.66%
• Study satisfaction - Personal/family history Gr=3	1	0.33%
• Study satisfaction - Positive DETECT experience Gr=33	20	6.58%
• Study satisfaction - Positive outcomes Gr=6	3	0.99%
• Study satisfaction - Prevention Gr=5	1	0.33%
• Study satisfaction - Recommend to others Gr=33	16	5.26%

• Study satisfaction - Regrets participation Gr=0	0	0.00%
• Study satisfaction - Traumatic Gr=2	2	0.66%
• Study satisfaction - Upset Gr=2	2	0.66%
• Study satisfaction - Use in routine care Gr=31	15	4.93%
Totals	304	100.00%