

Clinical Evaluation of Cancer Signal Origin (CSO) Prediction and Diagnostic Resolution Following Multi-Cancer Early Detection Testing

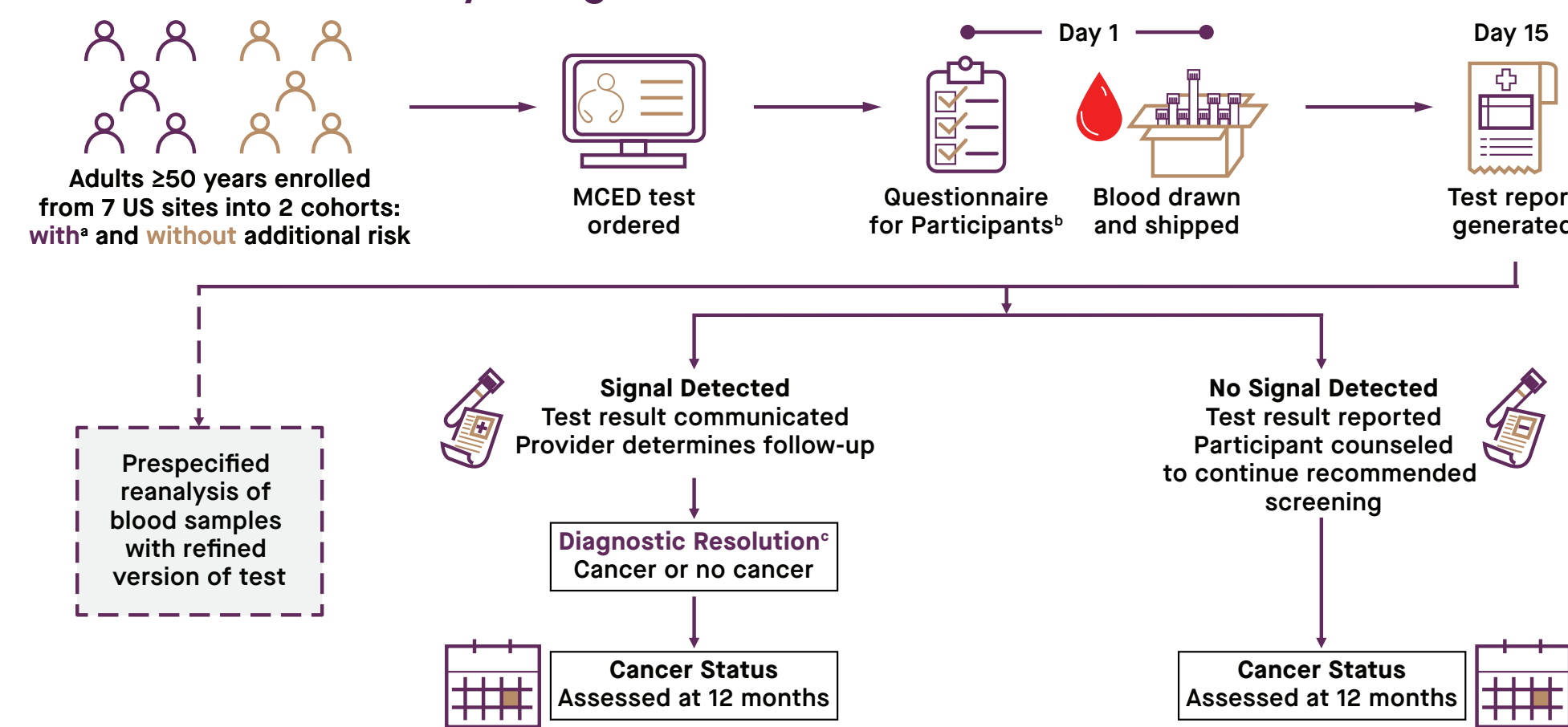
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INTRODUCTION

- United States Preventive Services Task Force-recommended cancer screening tests have reduced cancer-related mortality but are only available for a few cancer types¹⁻⁵ that represent less than 25% of cancer deaths in the US⁶
- Multi-cancer early detection (MCED) blood tests that detect a cancer signal from circulating cell-free DNA can complement existing single-cancer screening tests and serve as a screening test for cancers for which no screening options are available⁷⁻⁹
- The MCED test used in the PATHFINDER study (NCT04241796) was developed and validated in the Circulating Cell-Free Genome Atlas study (CCGA; NCT02889978)^{8,9}
- The prospective cohort PATHFINDER study (Figure 1) enrolled 6,662 participants from 7 US institutions between December 2019 and December 2020 to assess the feasibility of implementing MCED testing in outpatient settings for adults without clinical suspicion of cancer aged ≥50 years¹⁰
- For those with a cancer signal detected from an early MCED test version, a predicted CSO(s) was reported to help guide diagnostic evaluations
- Diagnostic evaluations were not prescribed by the protocol and were performed at the discretion of the ordering provider at the sponsor's cost
- Duration and extent of diagnostic evaluations were assessed
- Blood samples were retrospectively analyzed with a refined MCED test version; these results were not returned to participants
- Here, we report an analysis of PATHFINDER study results for those participants that had a cancer signal detected by MCED testing

Figure 1. PATHFINDER Study Design



*Previous history of cancer, smoking, and genetic risk. †Also collected at other time points during the study. ‡Defined as date when ordering physician determines to end diagnostic evaluation triggered by a cancer signal detected test result. MCED, multi-cancer early detection.

OBJECTIVES

- Retrospective analysis of whether the diagnostic evaluations in PATHFINDER were appropriately directed by CSO predictions using prespecified criteria (see **Methods**)
- Assessment of the residual risk of cancer after negative or equivocal initial evaluation
- Utility of WBI in diagnostic evaluation
- Evaluation of the number of imaging tests and diagnostic procedures needed to reach diagnostic resolution for true positive and false positive results

METHODS

- Analysis included participants with a cancer signal detected result from the two versions of an MCED test (early and refined MCED test versions) evaluated in PATHFINDER
- The refined MCED test was developed for clinical use as a screening tool based on training and validation data from the third and final CCGA substudy⁹
- The refined MCED test reduced detection of hematologic malignancies with relatively indolent natural history
- There was no maximum number of CSO predictions reported with the early MCED test; the refined test reports a maximum of 2 CSO predictions
- The refined MCED test results were not returned to physicians or participants and did not influence diagnostic evaluation
- All test elements, including assay processing, classifier, and CSO classification, were locked prior to sample processing for both test versions

- Initial diagnostic evaluation/workup is defined as any diagnostic procedure conducted prior to diagnostic resolution or prior to a time interval of 3 months or longer without any workup, whichever occurs first
- Additional diagnostic evaluation/workup is defined as diagnostic procedures conducted after a time interval of 3 months or longer without any workup
- Prespecified criteria blinded to study results were used to define expected diagnostic evaluations by CSO prediction
- Diagnostic testing (such as molecular analysis of blood, urine, stool, any imaging beyond plain films, endoscopy of any kind requiring a scope beyond an otolaryngology scope or light source alone, and tissue sample or cytology) was classified as directed or broad testing for each participant
- Directed testing: A single procedure interrogating one region of the body or one imaging field, molecular analysis of urine or stool

- Broad testing: Multiple procedures at same time, interrogating different organs or organ systems or imaging of multiple imaging fields in parallel or serially or functional imaging of the entire body (PET-CT), molecular analysis of blood
- CSOs with localization (such as lung or head & neck) were expected to receive directed diagnostic testing, and CSOs with no localization (hematologic or indeterminate) were expected to receive broad diagnostic testing
- These criteria were then used to judge if the type of the first diagnostic test (direct vs broad) was consistent with that expected for the given top CSO prediction
- An end of study cancer status assessment was conducted 12 (±1) months after enrollment and included an electronic health record review to confirm the presence or absence of cancer
- Date of diagnostic resolution was determined by the ordering physician
- WBI was defined as PET/CT or CT chest/abdomen/pelvis

KEY TAKEAWAYS

- Diagnostic Resolution was Achieved in 82% of Participants After Initial Diagnostic Evaluation, and CSO-Directed Initial Evaluation led to Diagnostic Resolution in the Majority (78%) of Cases**
- Although Whole-Body Imaging (WBI) was Useful for Non-Localizing CSOs (Hematologic or Indeterminate), WBI did not Contribute to Diagnostic Resolution in 51% of Participants**
- All Participants Reached Diagnostic Resolution, Including Those who Required Additional Workup Following Initial Evaluation**
- A Similar Number of Imaging Tests and Diagnostic Procedures Were Performed in True Positive and False Positive Participants**

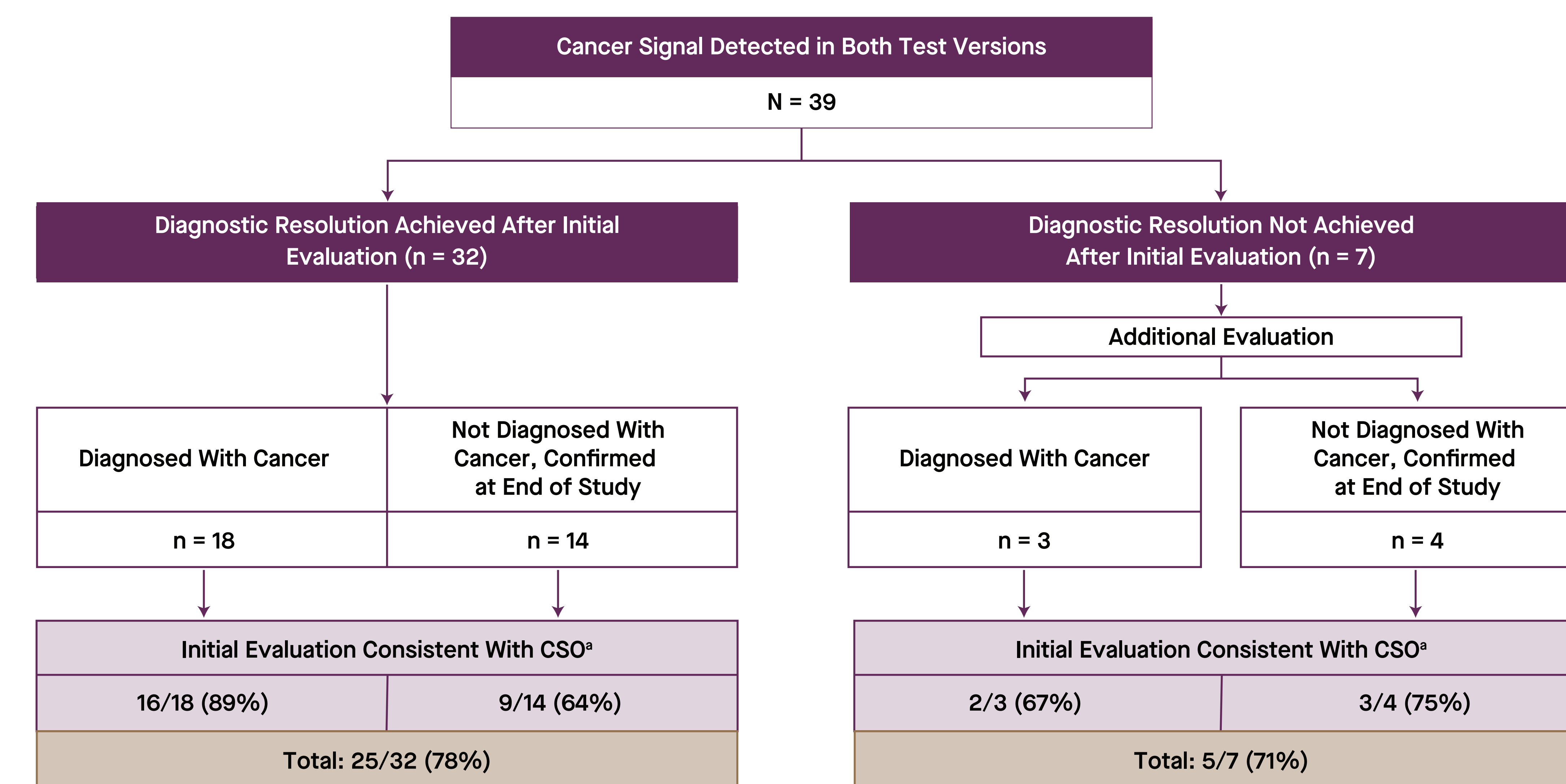
Diagnostic Resolution

- Ninety-two participants in PATHFINDER had a cancer signal detected by an early version of the MCED test
- This *retrospective analysis* was limited to the 39 participants who had cancer signal detected results by both MCED test versions (early version used in PATHFINDER and refined version now commercially available) and diagnostic evaluation triggered by MCED test results (Figure 2)
- Diagnostic resolution was achieved in 32/39 (82%) participants after initial evaluation, while 7/39 (18%) required additional workup before achieving diagnostic resolution
- Additional workup of the 7 participants not achieving initial diagnostic resolution was based on persistent clinical suspicion of cancer due to prior cancer history (n=1) or abnormal/equivocal findings on initial evaluation (n=6)
 - Additional workup led to diagnostic resolution in all 7 cases (3 with cancer and 4 with no cancer, confirmed at end of study) (Figure 2)

Consistency of Initial Diagnostic Evaluations With CSO Predictions

- Diagnostic resolution after initial evaluation was achieved in 25/32 (78%) by CSO-directed *initial* evaluation (Figure 2)

Figure 2. Diagnostic Resolution in Participants With Cancer Signal Detected by Both MCED Test Versions and Breakdown of the Consistency of Initial Diagnostic Evaluations With CSO Predictions

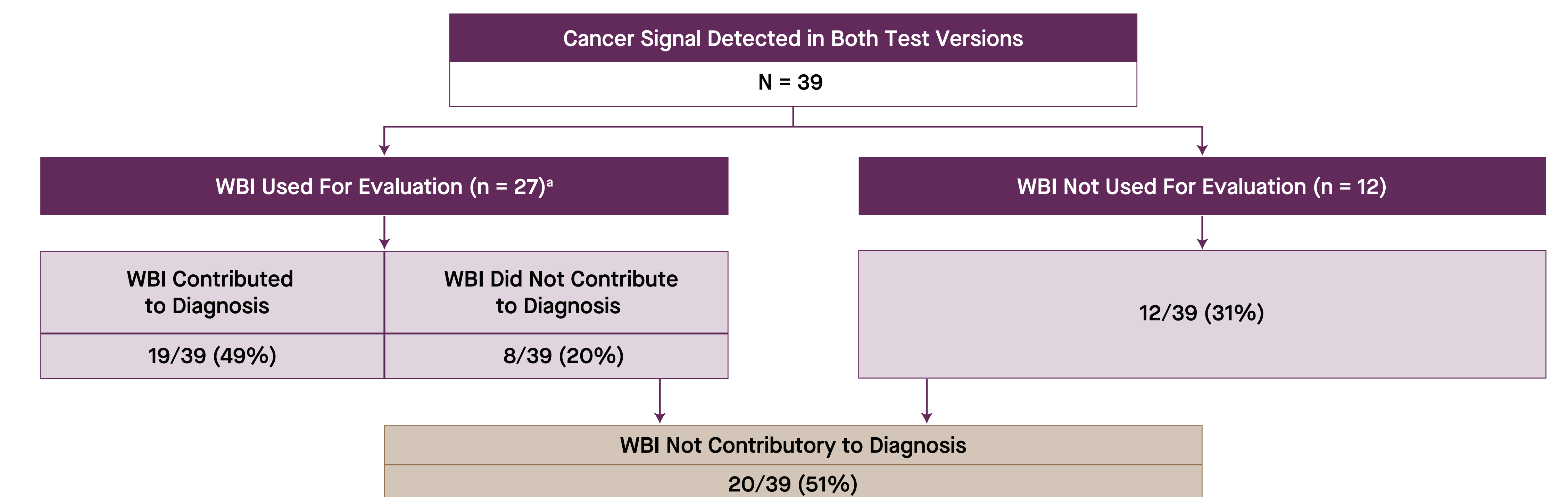


^aConsistency with CSO prediction, regardless of cancer diagnosis. CSO, cancer signal origin.

WBI

- WBI was ordered for specific indications in 27 cases, including 9 with a prior cancer history, 10 with non-localizing CSO (9 hematologic and 1 indeterminate), and 1 with both (Figure 3)
- WBI imaging was funded by the study sponsor
- WBI did not contribute to diagnostic resolution in 20/39 (51%) of participants

Figure 3. Detailed Breakdown of the Use of WBI



^aWBI was used for evaluation in these 27 cases for the following reasons: prior cancer history (n=9), non-localizing CSO (n=10), prior cancer history and non-localizing CSO (n=1), confirmatory testing (n=2), confirmatory testing and staging (n=1), and no reason identified (n=4). WBI, whole-body imaging.

Diagnostic Evaluation by Cancer Status and CSO Accuracy

- The mean number of imaging tests and diagnostic procedures required to reach diagnostic resolution was similar in true positives (2.8) and false positives (2.6) (Table 1)

Table 1. Diagnostic Evaluation by Cancer Status and CSO Accuracy

	Number of Imaging Tests and Diagnostic Procedures		
	Mean (SD)	Median (IQR)	Min, max
Participants with cancer signal detected by both test versions (N=39)	2.7 (1.9)	2 (1, 3)	0, 8
True positive ^a (n=21)	2.8 (1.9)	3 (2, 3)	0, 8
True positive & accurate CSO (n=18)	2.8 (2)	2.5 (2, 3)	0, 8
True positive & inaccurate CSO (n=3)	3 (1)	3 (2.5, 3.5)	2, 4
False positive ^b (n=18)	2.6 (2.1)	2 (1, 3.8)	0, 8

^aCancer signal detected and diagnosed with cancer. ^bCancer signal detected but not diagnosed with cancer. CSO, cancer signal origin; IQR, interquartile range; SD, standard deviation.

CONCLUSIONS

- Among participants who achieved diagnostic resolution after initial diagnostic evaluation, CSO-directed initial evaluation led to diagnostic resolution in the majority (78%) of cases
- Additional workup was required to achieve diagnostic resolution in participants with either a cancer history and negative initial evaluation or an equivocal initial evaluation
 - Cancer was diagnosed in some participants after additional workup
- Although WBI was useful when the CSO reflected the presence of a non-localized cancer (hematologic or indeterminate CSO), it did not contribute to diagnostic resolution in more than half of participants
- Participants with true positive and false positive MCED test results underwent a similar number of imaging tests and diagnostic procedures

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Disclosures

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