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PATHFINDER 2: A Prospective Study to Evaluate Safety and Performance of a Multi-Cancer Early Detection Test in a Population Setting

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INTRODUCTION

- Effective cancer screening is an important strategy for detecting early cancers and improving outcomes;[1] however, guideline-recommended screening is only available for a few cancer types
- Multi-cancer early detection (MCED) tests are being established as a novel approach to screen for multiple cancer types with one test
- It is increasingly recognized that certain demographic groups shoulder disproportionate cancer burdens while being historically underrepresented in cancer screening trials[2,3]
- Cancer screening trials should include diverse populations to evaluate generalizability of test clinical performance
- A blood-based MCED test using targeted methylation patterns in cell-free DNA to detect a shared cancer signal and predict a cancer signal origin (CSO) has previously demonstrated feasibility (CCGA [NCT02889978]; PATHFINDER [NCT04241796])[4,5]
- To further evaluate this MCED test, the PATHFINDER 2 study (NCT05155605) will evaluate safety and performance of the MCED test in a larger, more diverse population

OBJECTIVE

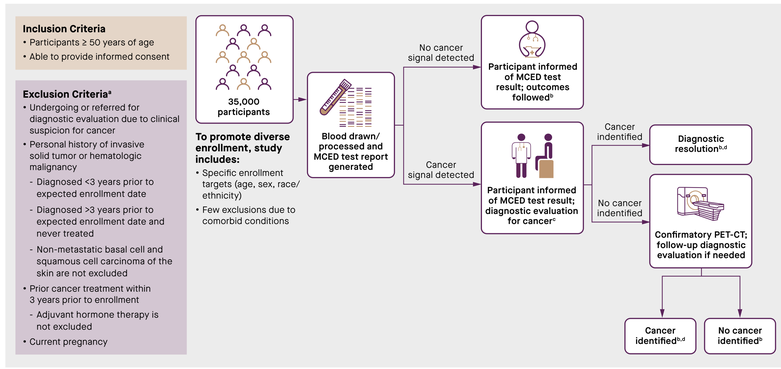
- The primary objectives of the PATHFINDER 2 study are to:
  - Evaluate the safety of the MCED test in terms of diagnostic testing triggered by the MCED test result
  - Evaluate performance of the MCED test in individuals eligible for cancer screening
- Secondary objectives include assessment of participant-reported outcomes (eg, anxiety), utilization of guideline-recommended cancer screening, the ability of PET-CT to detect cancer in cases for which CSO-directed workups do not result in cancer diagnoses, and others

PATHFINDER 2 IS A PROSPECTIVE, MULTI-CENTER, INTERVENTIONAL STUDY OF AN MCED TEST WITH STRATEGIES TO ENROLL A LARGE, DIVERSE POPULATION FROM HEALTHCARE SYSTEMS IN NORTH AMERICA

Assessing Safety and Performance of the MCED Test

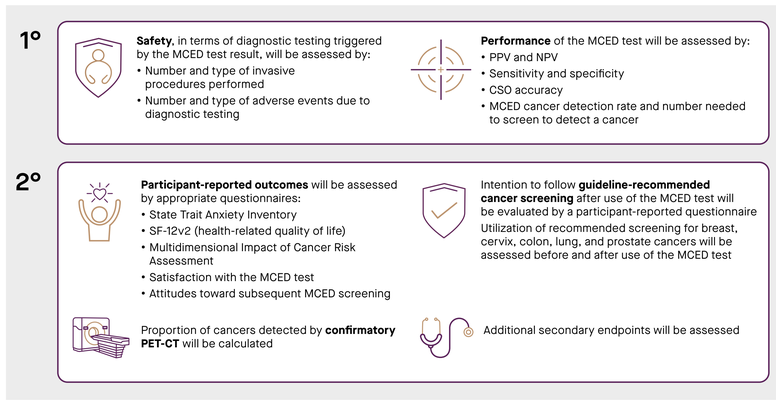
- PATHFINDER 2 is a prospective, multicenter, interventional study with planned enrollment of over 35,000 participants in North America over approximately 36 months (**Figure 1**)
- Enrolled participants will undergo a blood draw for MCED testing, and results will be returned to investigators to be shared with participants (**Figure 1**)
- If a cancer signal is detected, participants will undergo diagnostic evaluations directed by the CSO prediction; a confirmatory PET-CT scan will be performed if CSO-directed workups do not result in a cancer diagnosis (**Figure 1**)
- Participants will be followed for approximately 3 years

Figure 1. Study Design Overview.



[a]Additional exclusion criteria include individuals who cannot comply with protocol procedures, are not registered at participating centers, previously participated in a GRAIL-sponsored study, or are current employees/ contractors of GRAIL. [b]All participants will be actively followed by enrolled institutions for 3 years to assess cancer status and utilization of guideline-recommended cancer screening. [c]Diagnostic evaluations based on CSO are recommended in the protocol. [d]Clinical information including, but not limited to, cancer type, histology, and staging information will be captured.
CSO, cancer signal origin; MCED, multi-cancer early detection; PET-CT, positron-emission tomography-computerized tomography.

Figure 2. Study Endpoints.

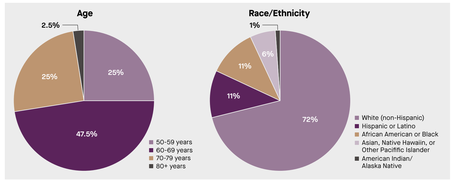


CSO, cancer signal origin; MCED, multi-cancer early detection; NPV, negative predictive value; PET-CT, positron-emission tomography-computerized tomography; PPV, positive predictive value.

Strategies to Enroll a Diverse Group of Participants Across North America

- PATHFINDER 2 aims to enroll a group of participants broadly representative of the United States (US) population
- Overall and site-specific enrollment targets for age, sex, and race/ethnicity were created. Race/ethnicity targets were derived from US Census data (**Figure 3**)

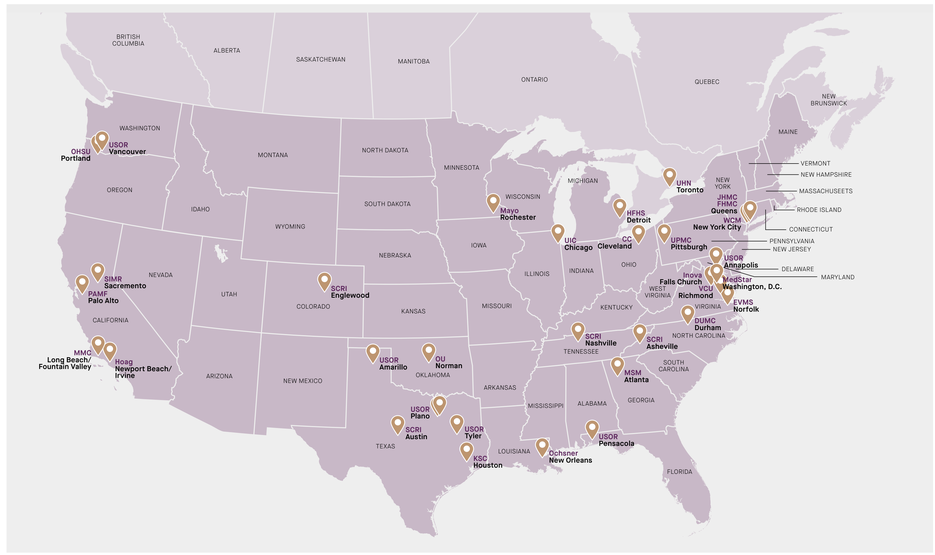
Figure 3. Enrollment Targets to Represent US Population.[a,b]



[a]Race/ethnicity categories are not mutually exclusive; thus, final study enrollment percentages may not add to 100%. [b]Sex targets are evenly distributed 1:1 per age group.

- Sites in the US and Canada were selected based on geographic location, catchment area demographics, and academic vs non-academic practice setting. PATHFINDER 2 is actively enrolling in 19 states, Washington, D.C., and 1 province in Canada (**Figure 4**)

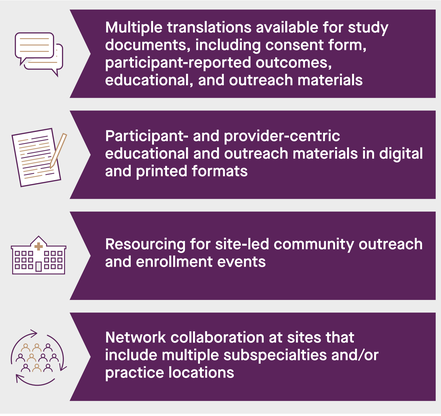
Figure 4. Enrollment Sites in the US and Canada.



CC, Cleveland Clinic; DUMC, Duke University Medical Center; EVMS, Eastern Virginia Medical School; FHMC, Flushing Hospital Medical Center; HFHS, Henry Ford Health System; Hoag, Hoag Hospital - Newport Beach and Irvine; Inova, Inova Fairfax Hospital; JHMC, Jamaica Hospital Medical Center; KSC, Kelsey-Seybold Clinic; Mayo, Mayo Clinic Comprehensive Cancer Center; MedStar, MedStar Washington Hospital Center and Montgomery Medical Center; MMC, Memorial Medical Center - Long Beach and Orange Coast; MSM, Morehouse School of Medicine; Ochsner, Ochsner Clinic Foundation locations in New Orleans, Baton Rouge, and Lafayette; OHSU, Oregon Health and Science University locations in Portland, Coos Bay, Salem, and Bend; OU, University of Oklahoma; PAMF, Sutter Health Palo Alto Medical Foundation; SCRI, Sarah Cannon Research Institute; SIMR, Sutter Institute for Medical Research; UHN, University Health Network; UIC, University of Illinois Chicago; UPMC, University of Pittsburgh Medical Center; USOR, US Oncology Research (Maryland Oncology Hematology; Northwest Cancer Specialists; Texas Oncology Plano East, Plano West, Tyler, and West Texas; Woodlands Medical Specialists); VCU, Virginia Commonwealth University; WCM, Weill Cornell Medicine.

- To meet enrollment targets, strategies to promote diverse recruitment are being implemented (**Figure 5**)

Figure 5. Strategies to Promote Diverse Recruitment.



CONCLUSIONS

- MCED testing is an emerging, potentially paradigm-changing strategy in cancer screening, and studies that characterize safety and performance in cancer screening-eligible populations are needed
- PATHFINDER 2 builds on the performance results of the MCED test from the first PATHFINDER study[5] by intentionally enrolling a broad, diverse group of participants who are representative of the US population
- Results from this study will contribute to data that inform safety, performance, and clinical implementation of the MCED test as a potential screening tool in diverse populations

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DISCLOSURES

Study funded by GRAIL, LLC. JAC and ML are employees of GRAIL, LLC. KVG has served on an advisory board (with honoraria provided to their institution) for Exact Sciences and Neogenomics, participated in research collaborations with Exact Sciences and Guardant Health, and received travel funding from GRAIL, LLC. MJD consulted for Loxo Lilly, Orphagen, Theralink, Bayer, TD2, OnCusp, Pfizer, and Aadi Biosciences and served on a data safety monitoring board for Loxo Lilly. SG has served on an advisory board for Merck, Mirati, AstraZeneca, Gilead, GSK, BMS, Genentech-Roche, Pfizer, AnHeart, Arcus, and Daiichi, received travel funding from Merck and Mirati, and served on an independent data monitoring committee for AstraZeneca. DK consulted for ER Squibb and Sons, LLC. MM consulted and served on speakers bureaus for AstraZeneca, Merck, BMS, Astellas, Eisai, Janssen, SeaGen, Exelixis, EMD Serono, Daiichi, Sankyo, Pfizer, and Novartis. CM consulted for GRAIL, LLC. NN consulted for GRAIL, LLC and Freenome. RHK, RM, DR, BR, and GS report no conflict of interest.

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