Design and enrollment for a classifier development study for a blood-based multi-cancer early detection (MCED) test

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Background

The aim of the Ascertaining Serial Cancer patients to Enable New Diagnostic 2 (ASCEND 2) study is to develop a classifier algorithm for a refined version of a multi-analyte blood-based MCED test.

Here, we report the study design, enrollment, and sample selection from the ASCEND-2 study.

Study Design

ASCEND 2 is a multi-center, prospective, case-control study of clinically characterized participants.

One hundred fifty-one sites within the US and Europe were engaged for subject enrollment.

Samples consisted of blood collected using LBgard® tubes for plasma and buffy samples.

The study population includes male and female subjects ≥50 years old with known cancer, suspicion of cancer, and controls without suspicion of cancer. All subjects provided informed consent and were assessed for study participation eligibility.

Enrollment

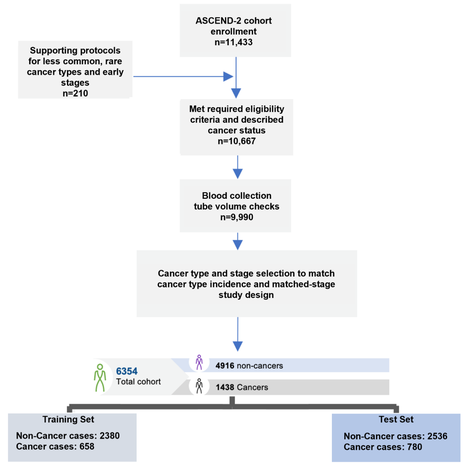
Over 11,000 subjects were enrolled in this study.

A subset of 6354 samples was selected to develop and refine a multi-analyte cancer detection classifier. The subset includes 1438 cancer subjects, from 21 organ sites (Enrollment and SEER Incidence Table) reflective of US cancer incidence by tumor type[1], and 4916 age-matched subjects without suspicion of cancer. Demographics are reported in the Demographics Table.

Relative to SEER incidence, the study enriched for lung cancers. Similarly, breast and prostate cancers were de-prioritized. These adjustments reflect cfDNA shedding rates and the expected clinical utility for MCED in these cancer types[2,3,4].

Cancer types were selected in approximately equal proportions for stage I-IV to power cancer staging performance assessment.

Study Enrollment Diagram



Allocation to training and testing sets:
The samples were partitioned into training and independent test sets. The performance of one or more locked cancer detection models developed in the training phase will be tested.
Cancer types with enrollment below incidence targets were allocated to the test set over the training set.
A subset of participants enrolled at unique sites were included in the test set but not the training set.

Demographics Table

Variable	Training Set (N=3,038)	Test Set (N=3,316)
Non-Cancer cases	2,380	2,536
Cancer Cases	658	780
Age (years)		
Mean (SD)	65.3 (8.3)	65.6 (8.4)
Sex, n (%)		
Female	1,705 (56.1%)	1,871 (56.4%)
Male	1,333 (43.9%)	1,445 (43.6%)
Race, n (%)		
White	2,467 (81.2%)	2,724 (82.1%)
Black/African American	410 (13.5%)	407 (12.3%)
Asian	110 (3.6%)	93 (2.8%)
American Indian/Alaskan Native	12 (0.4%)	17 (0.5%)
Native Hawaiian or Other Pacific Islander	3 (0.1%)	3 (0.1%)
Multiracial	4 (0.1%)	9 (0.3%)
Unknown*	32 (1.1%)	63 (1.9%)
Ethnicity, n (%)		
Hispanic/Latino	416 (13.7%)	412 (12.4%)
Not Hispanic/Latino	2,592 (85.3%)	2,853 (86.0%)
Unknown*	30 (1.0%)	51 (1.5%)
Region, n (%)		
Midwest	612 (20.1%)	576 (17.4%)
Northeast	405 (13.3%)	428 (12.9%)
South	1,328 (43.7%)	1,731 (52.2%)
West	563 (18.5%)	510 (15.4%)
Outside US	105 (3.5%)	55 (1.7%)
Unknown	25 (0.8%)	16 (0.5%)
Cigarette Smoking Status,** n (%)		
Current	29 (1.0%)	36 (1.1%)
Former	25 (0.8%)	37 (1.1%)
Never	2,978 (98.0%)	3,236 (97.6%)
Unknown*	6 (0.2%)	7 (0.2%)
Cancer Stage, n (%)		
Stage I	199 (30.2%)	197 (25.3%)
Stage II	127 (19.3%)	171 (21.9%)
Stage III	182 (27.7%)	193 (24.7%)
Stage IV	136 (20.7%)	183 (23.5%)
Unknown*	14 (2.1%)	36 (4.6%)

*Participants with missing/unknown information are grouped under Unknown category. ** Self-reported smoking status.

Training and test set demographics represented a racially, ethnically, and geographically diverse cohort

Enrollment and SEER Incidence[1]

Cancer Type	% of total (number of samples)	Normalized SEER Incidence %[a]
anus	1.9% (28)	0.6%
bladder and urinary	4.5% (65)	3.0%
Breast*	11.5% (165)	17.7%
cervix uteri	1.5% (22)	0.6%
colon and rectum	11.2% (161)	9.9%
esophagus	3.7% (53)	1.3%
head and neck	5.4% (78)	4.3%
kidney	5.6% (80)	4.6%
liver and bile duct	3.5% (50)	2.9%
lung and bronchus**	24.2% (348)	15.8%
multiple myeloma***	0.1% (1)	2.0%
non-Hodgkin's lymphoma***	0.6% (9)	5.0%
ovary	2.5% (37)	1.4%
pancreas	5.3% (76)	3.8%
Prostate*	4.6% (66)	17.5%
small intestine	0.8% (12)	0.7%
stomach	4.0% (58)	1.9%
testis	0.1% (2)	0.1%
thyroid	1.7% (25)	2.3%
uterus	5.6% (81)	4.2%
vulva	1.5% (21)	0.4%

[a] Normalized SEER proportions are adjusted to account only cancer types included in this study. Values do not account for incidence o 7 rare cancer types listed in SEER but not this study. *Breast[2] and prostate[3] selection was de-prioritized due to low expected cfDNA shedding. **Lung and bronchus cancer selection was enriched because of high expected cfDNA shedding and potential clinical utility[4]. ***Hematological cancer cases were lower than SEER incidence rates due to a lower-than-expected enrollment rate.

Target enrollment, including rare cancers, (based on SEER incidence rates) was achieved for most cancer types

The ASCEND 2 study selected cancer types in an incidence-targeted manner, including rare and common cancers and evenly distributed stages

The ASCEND-2 study represents a racially, ethnically, and geographically diverse cohort for MCED test development

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Disclosure: Christopher Douville is an inventor on some technologies. Licenses to these technologies are or will be associated with equity or royalty payments to the inventors as well as to Johns Hopkins University. CD is a consultant with Exact Sciences. The terms of these arrangements are being managed by Johns Hopkins University in accordance with its conflict-of-interest policies. He is also the founder of Belay Diagnostics.