Evaluating Baseline ctDNA Measurements Across Cancer Types and Stages

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Friends of Cancer Research

Initial data presented on behalf of the Baseline ctDNA Working Group

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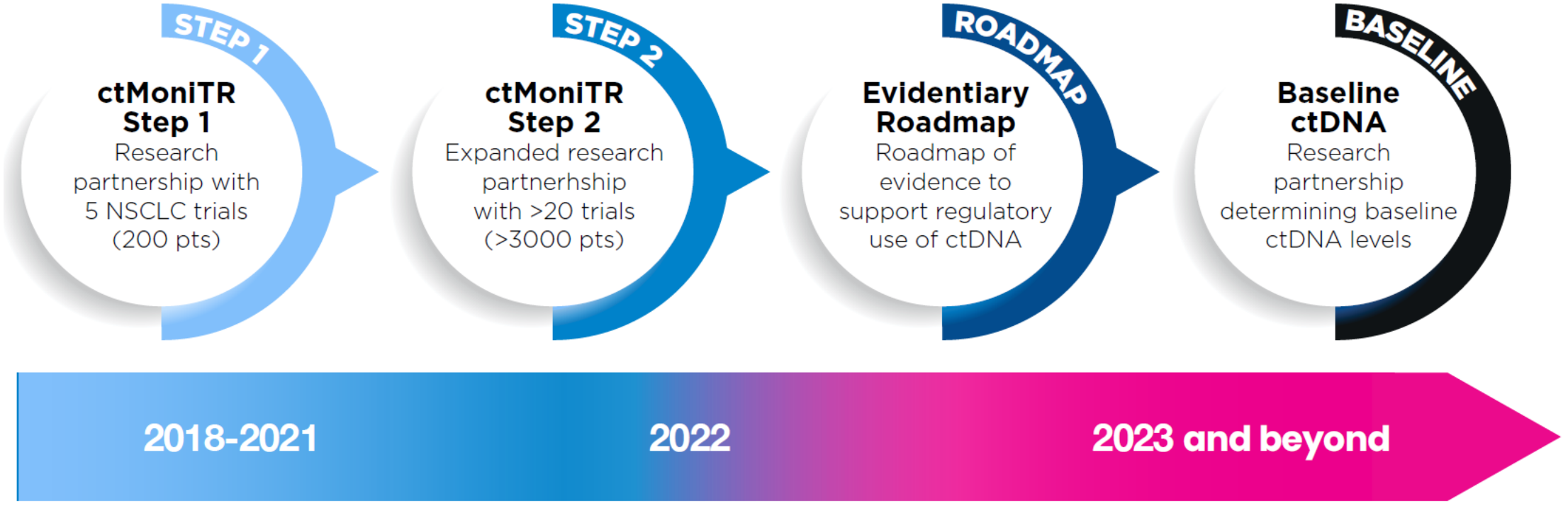
Friends' ctDNA Portfolio



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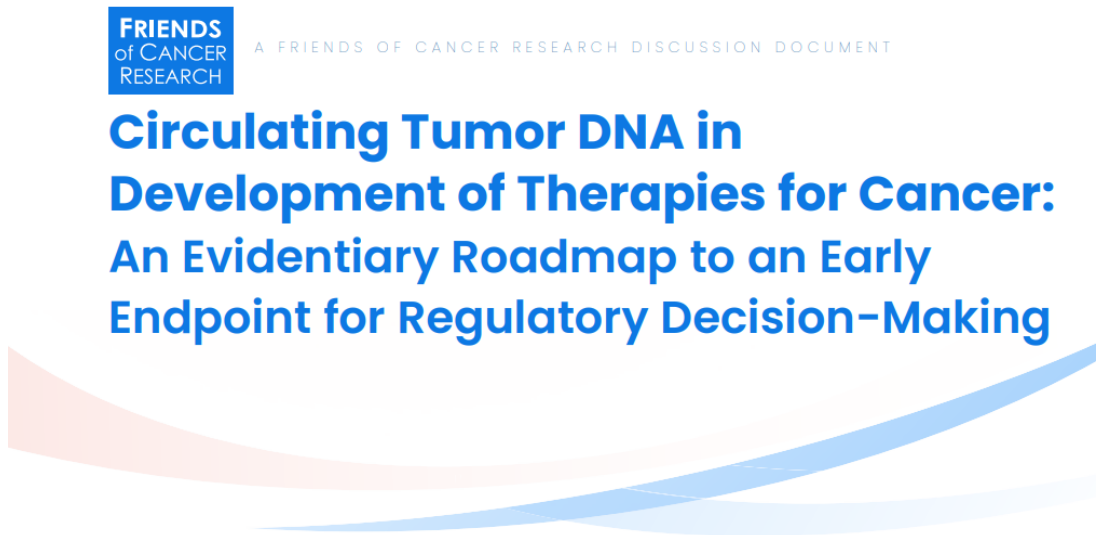
An Evidentiary Roadmap



Friends assembled a multi-stakeholder group to develop an aligned strategy for generating data and evidence to support using the measurement of ctDNA levels in patients with solid tumors for regulatory purposes

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Knowledge Gaps: Baseline ctDNA

The Challenge:
Baseline ctDNA Levels

- Current baseline ctDNA data in the metastatic setting are variable across different cancer types.
- There is a dearth of data on baseline ctDNA shed rates in early-stage cancers.
- Data is disparate across ctDNA technologies, making pooled analyses across studies challenging.

The Solution:
Baseline ctDNA Project

- Establish evidence of baseline ctDNA levels by cancer type and stage across assays through a collaborative effort with multiple assay developers.
- Comparing different assay outputs will build an evidence foundation across cancer types to support use of ctDNA and identify key questions to support harmonization across assays.

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Baseline ctDNA Project Objectives

- Compare baseline ctDNA level trends:
  - Across cancer types in early-stage disease
  - Across cancer types in late-stage disease
  - Across stages within the same cancer type
  - Across assays within the same cancer type and disease setting
- Develop considerations/lessons learned for data harmonization efforts across assays

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Baseline ctDNA Project Objectives

- Compare baseline ctDNA level trends:
  - Across cancer types in late-stage disease
    - NSCLC, Breast, Bladder, Prostate, HNSCC
  - Across stages within the same cancer type
    - Early-Stage vs. Late-Stage NSCLC
  - Across assays within the same cancer type and disease setting
    - 3/8 assays with data from all five late-stage cancer types
- Develop considerations/lessons learned for data harmonization efforts across assays

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ctDNA Assay Characteristics

Assay Type

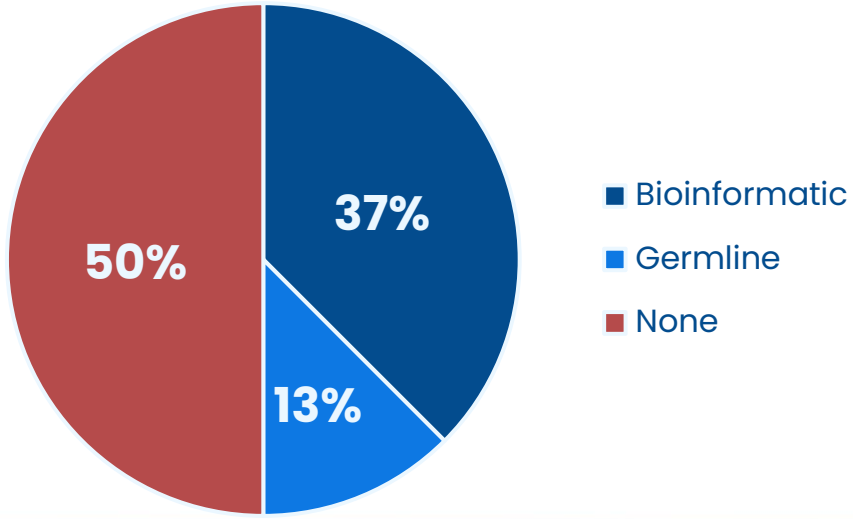
5/8 Tumor-Informed

3/8 Tumor-Naïve

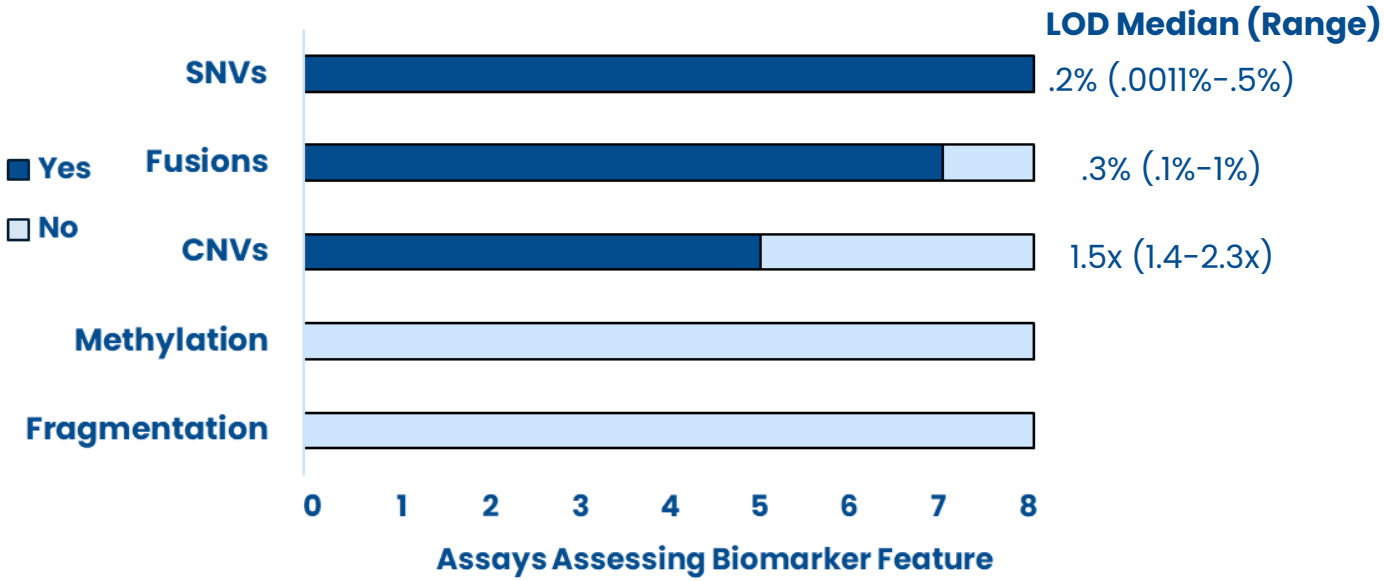
7/8 NGS

1/8 ddPCR

CHIP Filtering



Biomarker Features Assessed and LOD



All assays met pre-analytical specifications of cfDNA minimal technical data elements proposed by BloodPAC.*

*Febbo, *et al. J Clin Pharm Ther*. Feb 2020. https://doi.org/10.1002/cpt.1747

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Sample Characteristics

2,327 Early-Stage NSCLC Cancer Samples

87,209 Late-Stage Cancer Samples Across 5 Cancer Types

Late-Stage Cancer Type	Total Samples
NSCLC	63,127
Breast	10,532
Bladder	1,359
Prostate	11,235
HNSCC	956

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Sample Characteristics

		EARLY-STAGE NSCLC					LATE-STAGE NSCLC					
		A	B	D	E	I	A	B	C	D	F	G
	N (Samples)	245	1873	679	78	131	1232	31889	23157	2452	264	4000
Age	Median, years	70	70	70	Unkn	63	69	67	68	Unkn	70	73
Gender	Female	48	49	49	49	35	49	50	52	49	52	53
	Male	52	51	51	51	65	51	50	48	51	49	47
Clinical Stage	I	5	19	15	53	48	0	0	0	0	0	0
	II	2	15	17	28	17	0	0	0	0	0	0
	III	11	29	68	19	35	5	1	0	0	15	0
	IV	0	0	0	0	0	13	7	0	100	82	0
	Unknown	82	37	0	0	0	82	92	100	0	3	100

Unknown characteristics across most cohorts:

- Prior anti-cancer treatments
- Recurrence/progression status
  - Type of recurrence

In early-stage NSCLC, the proportion of samples in each clinical stage varies across cohorts, which may impact cross-assay comparisons

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Sample Characteristics

		EARLY-STAGE NSCLC					LATE-STAGE NSCLC						Breast			Bladder			Prostate			HNSCC		
		A	B	D	E	I	A	B	C	D	F	G	C	D	G	C	D	G	C	D	G	C	D	G
N (Samples)		245	1873	679	78	131	1232	31889	23157	2452	264	4000	2572	1020	6940	500	282	577	1100	633	9502	274	136	546
Age	Median, years	70	70	70	Unkn	63	69	67	68	Unkn	70	73	62	61	64	72	71	73	70	68	74	64	62	64
Gender	Female	48	49	49	49	35	49	50	52	49	52	53	98	100	99	29	26	25	0	0	0	22	24	23
	Male	52	51	51	51	65	51	50	48	51	49	47	2	0	1	71	74	75	100	100	100	78	76	77
Clinical Stage	I	5	19	15	53	48	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	II	2	15	17	28	17	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	III	11	29	68	19	35	5	1	0	0	15	0	0	0	0	0	0	0	0	0	0	0	0	0
	IV	0	0	0	0	0	13	7	0	100	82	0	0	100	0	0	100	0	0	100	0	0	100	0
	Unknown	82	37	0	0	0	82	92	100	0	3	100	100	0	100	100	0	100	100	0	100	100	0	100

Unknown characteristics across most cohorts:

- Clinical stage (I-IV)
- Prior anti-cancer treatments
- Recurrence/progression status
  - Type of recurrence

Due to unknown clinicopathological factors, significant cohort heterogeneity may bias comparisons across cohorts

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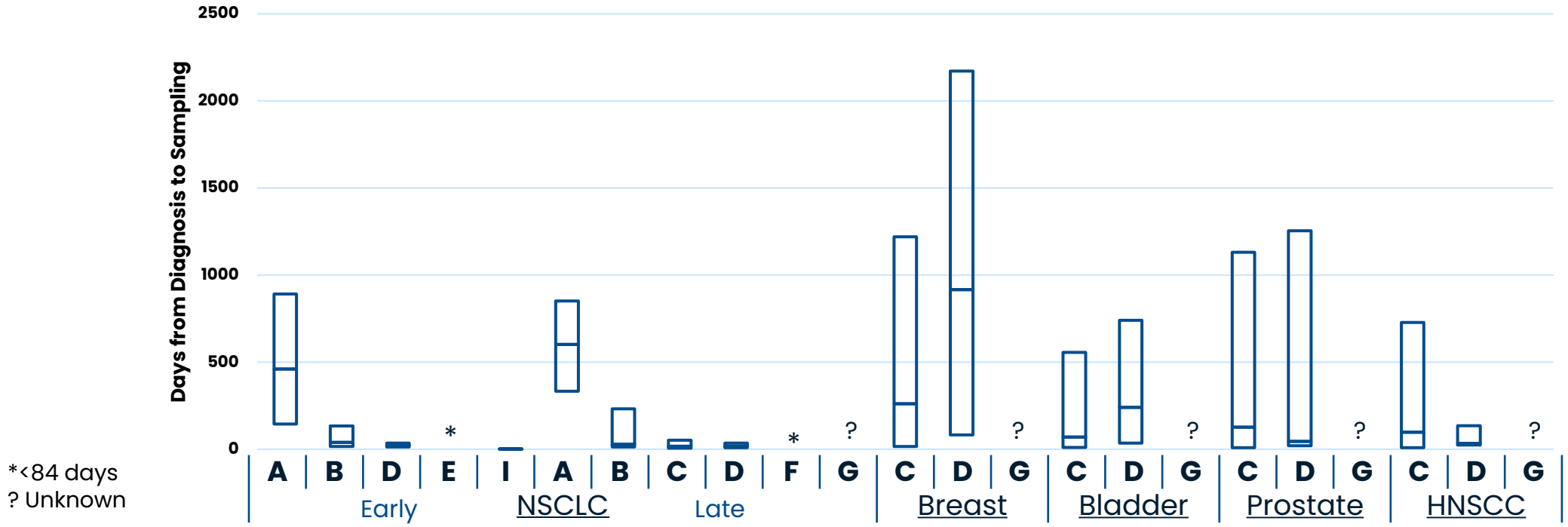
Timing of Sampling Relative to Diagnosis



Timing of sampling relative to diagnosis varies across datasets, which may be impacted by the intended use of the test or limited access to clinical data other than initial diagnosis

Boxes depict IQ1, Median, IQ3

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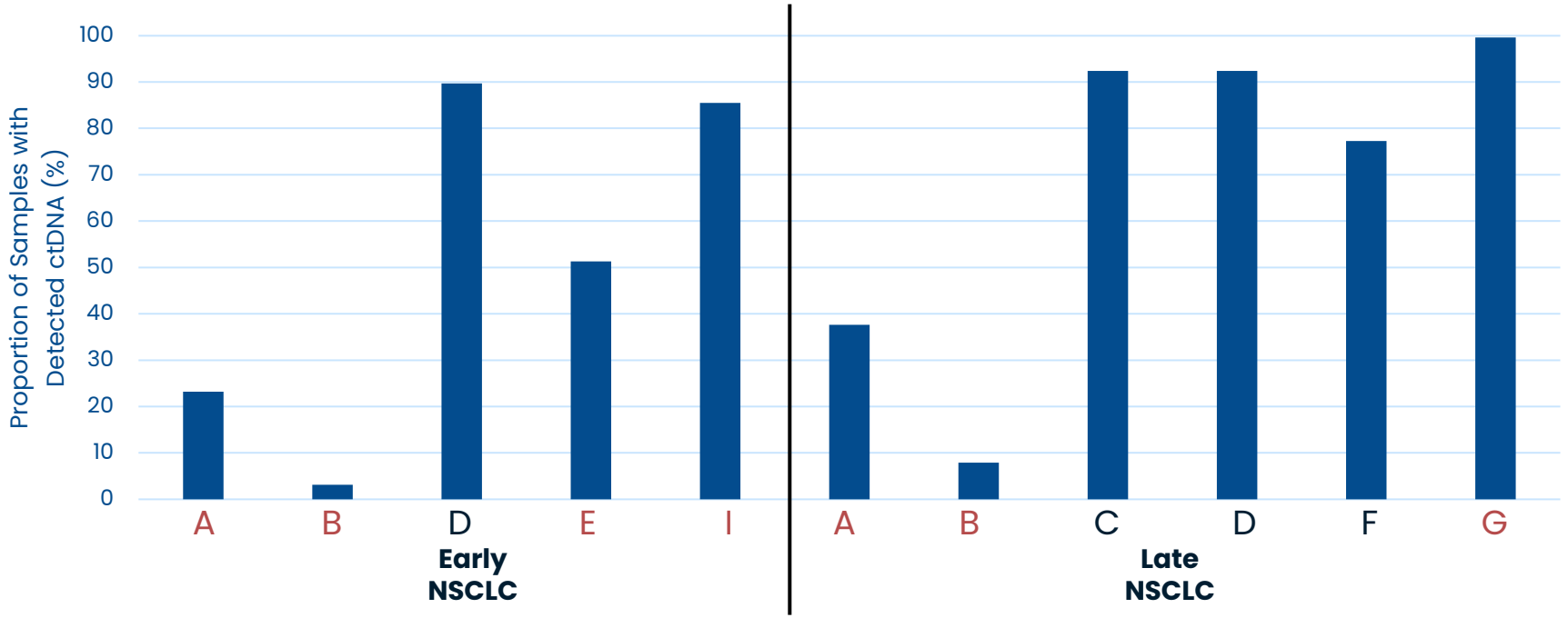
Frequency of ctDNA Detection in NSCLC



Frequency of detection varies across datasets, with late-stage NSCLC generally having a higher proportion of samples with detected ctDNA than early-stage

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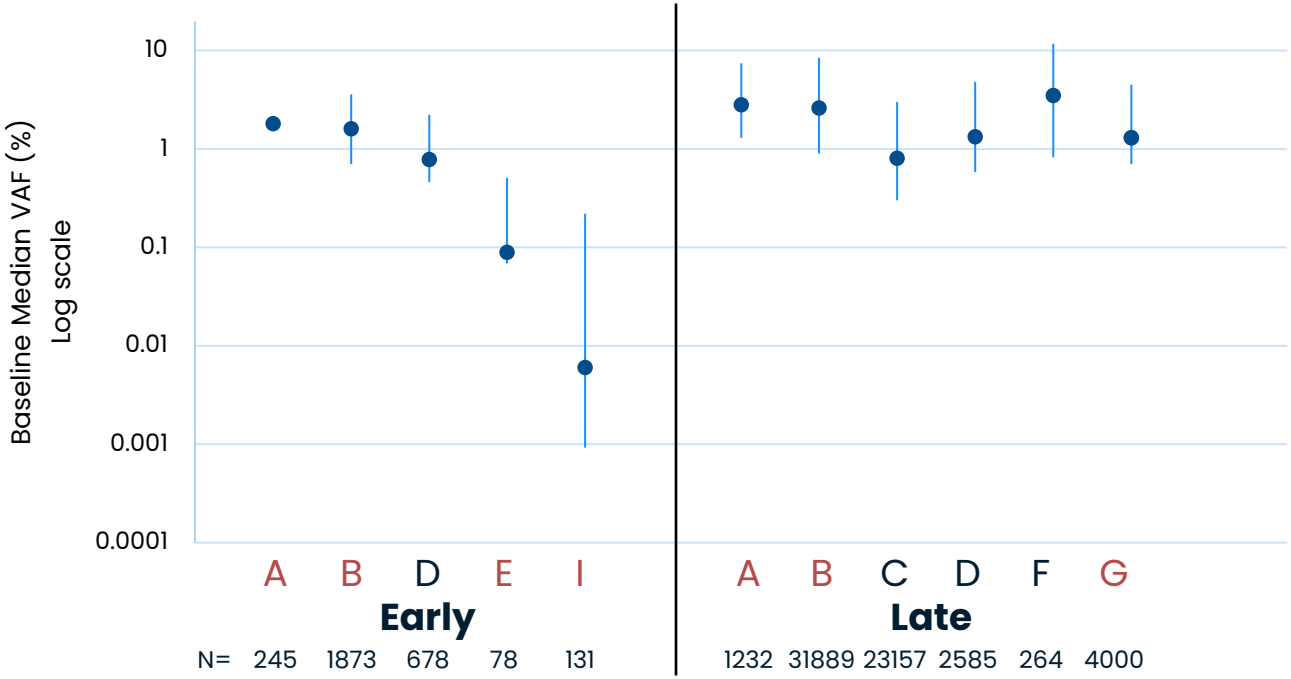
NSCLC Baseline ctDNA Median VAFs

Median VAF= the median of VAF values from all somatic tumor-derived variants



Late-stage NSCLC samples with detected ctDNA generally have higher ctDNA levels than early-stage samples, with assay variability

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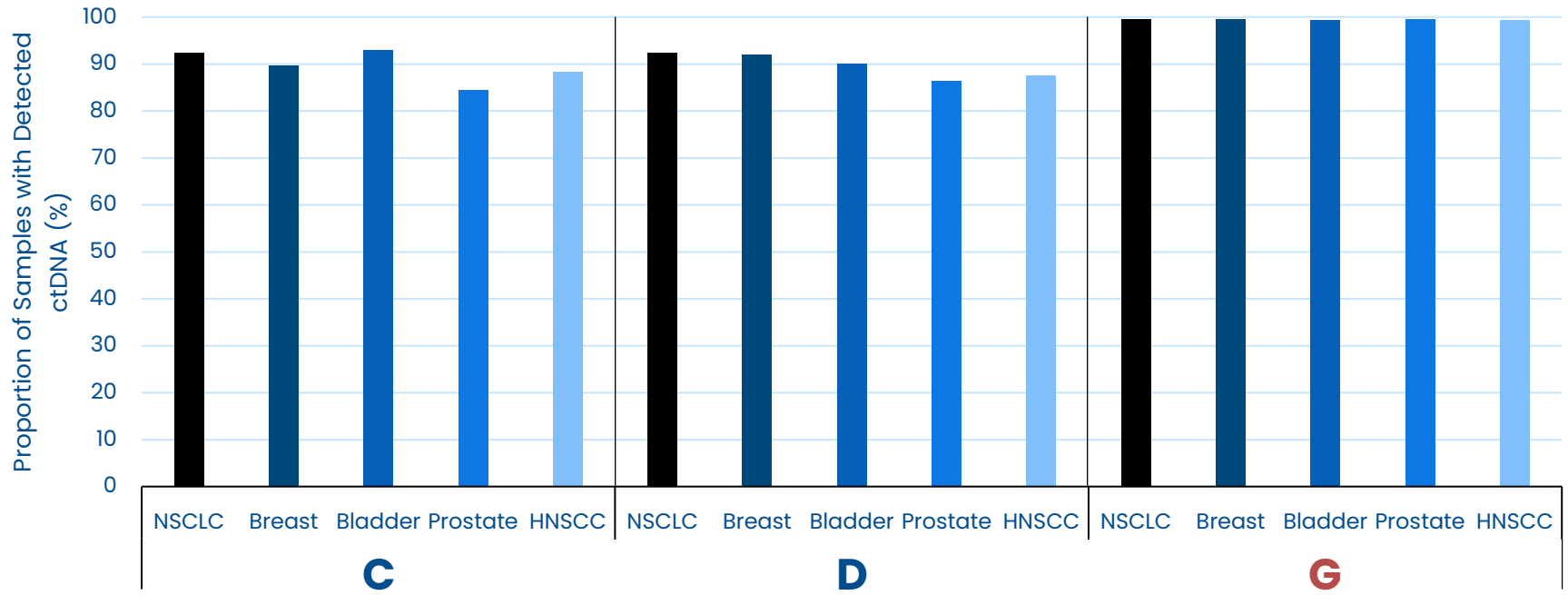
Frequency of ctDNA Detection in Late-Stage Cancers



Baseline ctDNA is similarly detected across late-stage cancer types.

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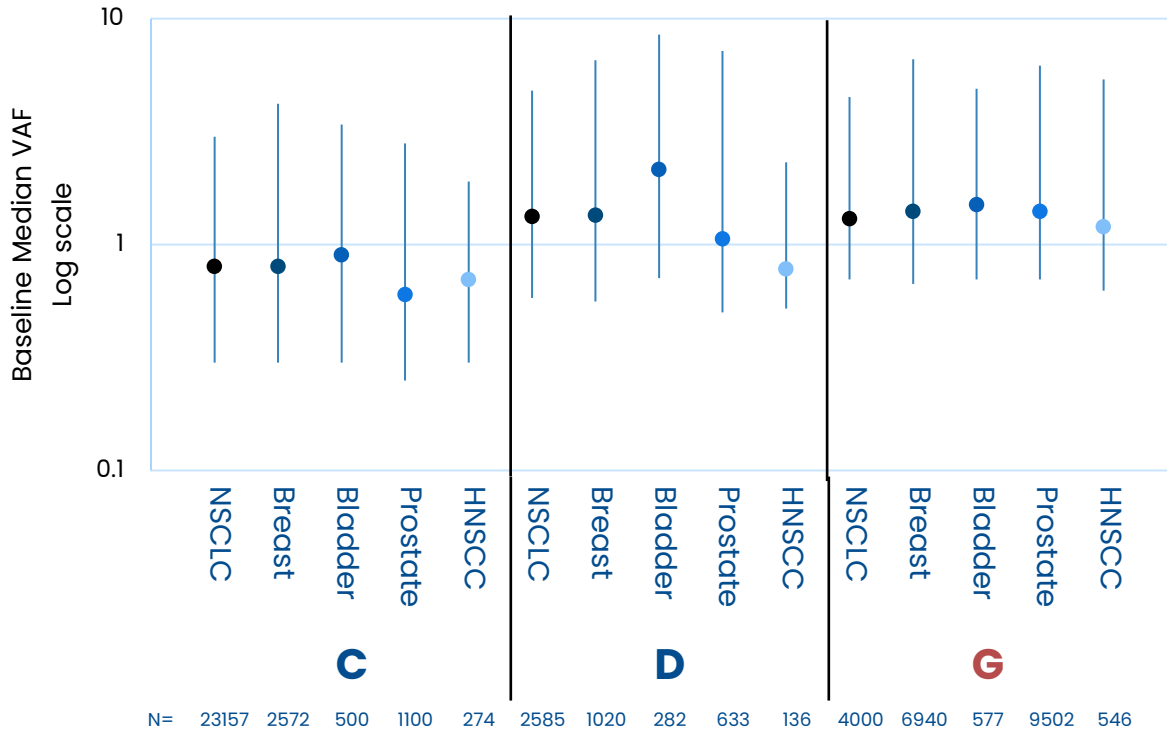
Late-Stage Median VAF by Assay



Baseline ctDNA levels are similar for late-stage cancer types across assays.

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Key Conclusions

- Overall trends were observed:
  - Late-stage NSCLC samples had higher proportion of detected ctDNA and ctDNA levels than early-stage samples.
  - Baseline ctDNA was similarly detected across most late-stage cancer samples, and across assays
- Assay characteristics and available clinicopathological data are heterogeneous, leading to difficulties in interpreting aggregated data.
- Additional data and development of common data standards are needed to make more robust comparisons and support future harmonization efforts.

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Baseline ctDNA Project Partners

- Biodesix
- Burning Rock
- Foundation Medicine, Inc.
- Guardant Health, Inc.
- NeoGenomics Laboratories
- Predicine
- Tempus Labs, Inc.
- Exact Sciences Corp.
- Illumina, Inc.
- Personal Genome Diagnostics (Labcorp)
- U.S. Food and Drug Administration (FDA)

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