ISLB 2024

Liquid biopsy detection of gene copy number (CN) losses including existing and emerging clinical targets

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BACKGROUND

- Homozygous copy number (CN) losses of *PTEN*, *BRCA1/2*, *PALB2* and other homologous recombination repair genes are established biomarkers in breast, ovarian, and prostate cancers, and additional CN losses including *MTAP, NF1, SPOP,* and *STK11* are being investigated in clinical trials.
- Detection of these alterations is imperative for therapy selection and trial enrollment. However, reliability of blood-based assays to detect CN loss is uncertain, and tissue remains the preferred testing method.
- We studied the prevalence of CN loss in liquid biopsies and assessed concordance with paired tissue.

MATERIALS AND METHODS

- CGP results from 57,612 liquid (FoundationOne® Liquid CDx) and 439,560 tissue (FoundationOne® or FoundationOne® CDx) biopsies were queried for CN loss.
- Copy number alterations (gene amplifications and homozygous losses) were assessed for 324 genes on both assays and were determined from a genome-wide copy number model generated from normalized target coverage and single nucleotide polymorphism (SNP) allele frequencies.
- Patient paired tissue and liquid (plasma) samples collected <1 year apart were used to assess concordance of liquid CN loss calling compared to tissue.
- ctDNA tumor fraction (TF) was quantified using a combination of aneuploidy and variant allele frequencies of genomic alterations, while excluding clonal hematopoiesis mutations and aneuploidy using fragmentomic signal from cell free DNA

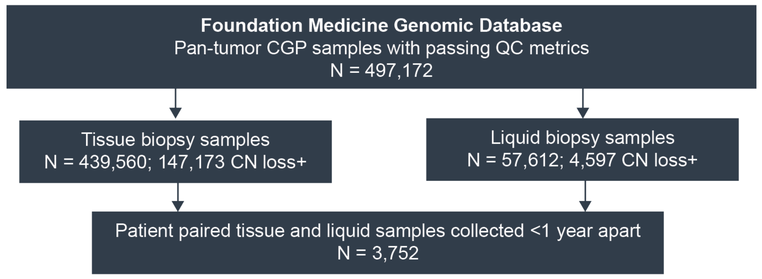


FIGURE 1: Consort diagram

RESULTS: Median ctDNA TF was 34% for samples harboring a CN loss

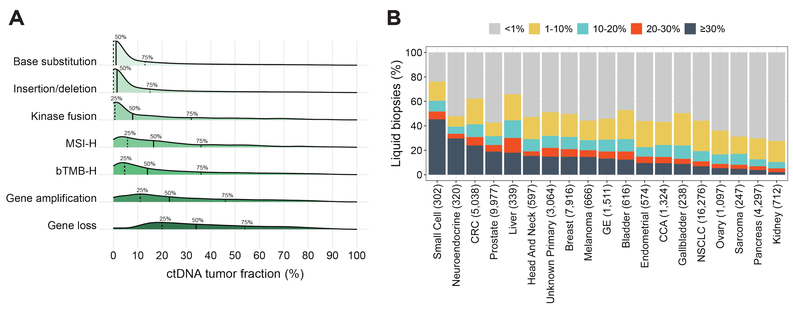
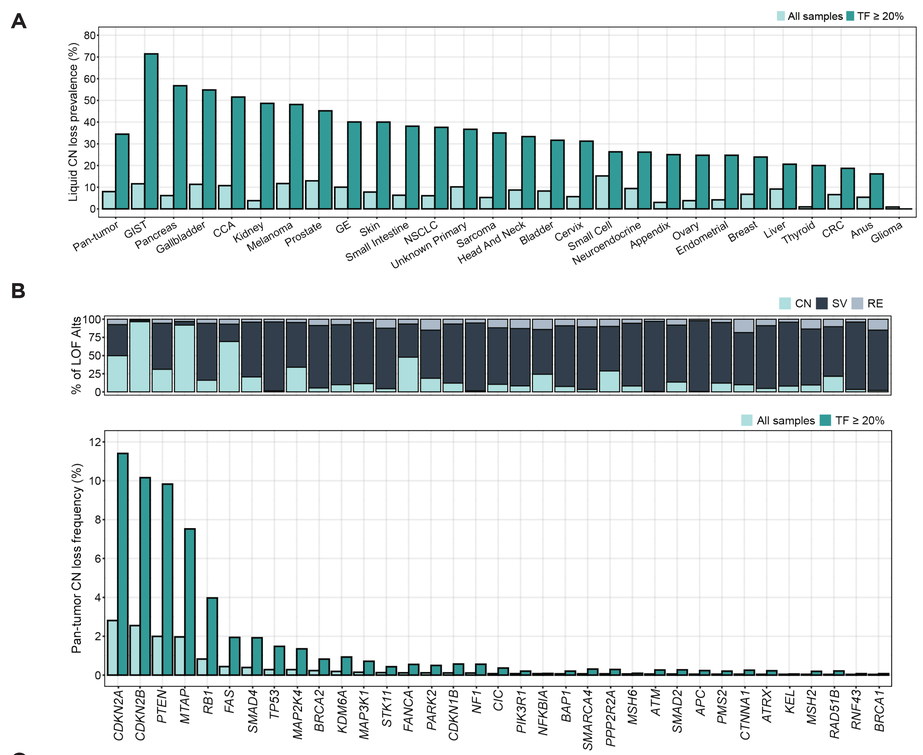


FIGURE 2: ctDNA tumor fraction distribution across alteration and cancer types
(A) Distribution of TF across alteration types detected in liquid samples. The median TF of CN loss+ sample was 34% (IQR 20-54%).
(B) Distribution of TF by cancer type.

RESULTS: Homozygous CN losses were detected in 8% of liquid pan-tumor samples



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	CDKN2A	*CDKN2B*	*RB1*	*TP53*	*MTAP*	*STK11*	*CDK12*	*PTEN*	*NF1*	*MAP2K4*	*MAP3K1*	*BRCA2*	*BRCA1*	*PALB2*	*ATM*
All	2.8 / 11.4%	2.5 / 10.2%	0.8 / 4%	0.3 / 1.5%	2 / 7.5%	0.1 / 0.4%	<0.1 / <0.1%	2 / 9.8%	0.1 / 0.6%	0.3 / 1.4%	0.1 / 0.7%	0.2 / 0.8%	<0.1 / <0.1%	<0.1 / 0%	<0.1 / 0.3%
NSCLC	3.5 / 21.5%	3.2 / 19%	0.8 / 5.8%	0.1 / 1.2%	2.5 / 14.3%	0.2 / 1.1%	0 / 0%	0.5 / 3.4%	<0.1 / 0.6%	<0.1 / 0.6%	0 / 0%	<0.1 / 0.1%	<0.1 / 0.1%	0 / 0%	<0.1 / 0%
Prostate	0.6 / 2.3%	0.6 / 2.2%	1.4 / 5.3%	0.7 / 2.8%	0.5 / 1.8%	<0.1 / <0.1%	<0.1 / <0.1%	7.7 / 27.8%	<0.1 / <0.1%	0.1 / 0.5%	0.8 / 2.8%	0.9 / 3.1%	<0.1 / <0.1%	0 / 0%	0.2 / 0.7%
Breast	1.6 / 6%	1.5 / 5.7%	0.7 / 2.9%	0.2 / 0.9%	1.1 / 4.1%	0.2 / 0.4%	0 / 0%	1.1 / 4.6%	0.3 / 1.4%	1.0 / 4%	<0.1 / 0.1%	0.2 / 0.2%	<0.1 / 0.2%	<0.1 / 0%	<0.1 / 0.2%
CRC	0.7 / 2%	0.6 / 1.9%	0.2 / 0.6%	0.3 / 0.8%	0.5 / 1.5%	<0.1 / <0.1%	0 / 0%	1.3 / 4.1%	0.1 / 0.4%	0.5 / 1.2%	0 / 0%	<0.1 / 0%	<0.1 / <0.1%	0 / 0%	<0.1 / 0.2%
Pancreas	4.4 / 42.2%	4 / 37.5%	0.4 / 4.1%	<0.1 / 0.3%	3.4 / 30.4%	0 / 0%	0 / 0%	0.1 / 1.4%	<0.1 / 0.7%	0.4 / 4.4%	0 / 0%	<0.1 / 0%	<0.1 / 0.3%	0 / 0%	<0.1 / 0.3%
Unknown Primary	6 / 20.5%	5.6 / 18.6%	0.8 / 3.7%	0.4 / 1.6%	4 / 12.6%	0.3 / 1.0%	0 / 0%	1.1 / 4.9%	<0.1 / 0.3%	0.2 / 0.7%	<0.1 / 0.3%	<0.1 / 0.1%	0 / 0%	0 / 0%	<0.1 / 0.3%
GE	5.6 / 22%	4.8 / 18.5%	0.4 / 1.4%	0.2 / 1.0%	3.6 / 12.9%	0.3 / 1.4%	0 / 0%	1.0 / 3.8%	0 / 0%	0.5 / 2.1%	0 / 0%	0.1 / 0%	<0.1 / 0%	0 / 0%	0 / 0%
CCA	7.9 / 39.1%	7.4 / 37%	0.5 / 2.6%	0.5 / 2.6%	5.8 / 27.6%	0 / 0%	0 / 0%	0.5 / 3.1%	0.2 / 1.0%	0.2 / 0.5%	0 / 0%	0.2 / 0%	0 / 0%	0 / 0%	0 / 0%
Ovary	0.6 / 4.1%	0.4 / 2.1%	0.5 / 5.2%	<0.1 / 1.0%	0.5 / 2.1%	<0.1 / 0%	0 / 0%	0.4 / 4.1%	0.5 / 4.1%	0 / 0%	<0.1 / 1.0%	0 / 0%	0.2 / 0%	0 / 0%	0 / 0%
Kidney	2.8 / 40.5%	2.5 / 35.1%	0.1 / 0%	0 / 0%	1.8 / 27%	0 / 0%	0 / 0%	0.3 / 2.7%	0 / 0%	0 / 0%	0 / 0%	0 / 0%	0 / 0%	0 / 0%	0 / 0%
Melanoma	7.7 / 31.6%	6 / 23.3%	0.2 / 0.8%	0 / 0%	4.2 / 15%	0.3 / 1.5%	0 / 0%	2.4 / 10.5%	0.3 / 1.5%	0 / 0%	0 / 0%	0.2 / 0%	0 / 0%	0 / 0%	0 / 0%
Bladder	6.2 / 23.9%	5.4 / 20.5%	0.6 / 2.6%	0 / 0%	4.4 / 15.4%	0.2 / 0.9%	0 / 0%	0.5 / 2.6%	0 / 0%	0 / 0%	0 / 0%	0 / 0%	0 / 0%	0 / 0%	0 / 0%
Head And Neck	3.4 / 12.3%	2.3 / 8.8%	0.5 / 2.6%	0 / 0%	0.8 / 3.5%	0.2 / 0%	0 / 0%	1.8 / 7.9%	0 / 0%	0 / 0%	0 / 0%	0 / 0%	0 / 0%	0 / 0%	0.2 / 0%
Endometrial	0.2 / 0%	0.2 / 0%	1.7 / 11.8%	0.2 / 1.2%	0.2 / 0%	0 / 0%	0 / 0%	1.0 / 7.1%	0.2 / 1.2%	0 / 0%	0 / 0%	0.2 / 1.2%	0 / 0%	0 / 0%	0 / 0%
Liver	3.2 / 6.9%	3.2 / 6.9%	1.8 / 3.9%	0.6 / 2%	2.1 / 4.9%	0 / 0%	0 / 0%	2.1 / 5.9%	0 / 0%	0.3 / 1.0%	0 / 0%	0 / 0%	0.3 / 0%	0 / 0%	0.3 / 1.0%
Neuroendocrine	4.1 / 11.2%	3.4 / 9.3%	0.9 / 1.9%	0.3 / 0.9%	3.4 / 9.3%	0 / 0%	0 / 0%	0.3 / 0.9%	0 / 0%	0.3 / 0.9%	0 / 0%	0 / 0%	0 / 0%	0 / 0%	0 / 0%
Small Cell	1.3 / 1.3%	1.3 / 1.3%	8.3 / 14.7%	0.7 / 1.3%	0.7 / 0.6%	0 / 0%	0 / 0%	2.3 / 4.5%	0.3 / 0.6%	0 / 0%	0 / 0%	0 / 0%	0 / 0%	0 / 0%	0 / 0%
Sarcoma	1.6 / 5%	1.2 / 5%	1.2 / 10%	1.2 / 15%	1.6 / 5%	0 / 0%	0 / 0%	1.2 / 10%	0 / 0%	0 / 0%	0 / 0%	0 / 0%	0 / 0%	0 / 0%	0 / 0%
Gallbladder	7.6 / 35.5%	7.1 / 32.3%	1.3 / 9.7%	0.4 / 3.2%	5 / 22.6%	0 / 0%	0 / 0%	0.8 / 0%	0 / 0%	0.4 / 0%	0 / 0%	0 / 0%	0 / 0%	0 / 0%	0 / 0%

FIGURE 3: Prevalence of CN losses in liquid samples pan-tumor and across tumor types
(A) The prevalence of losses in pan-tumor liquid samples was 8.0% and increased to 34% among samples with TF ≥ 20%, which is comparable to the 33% prevalence observed in our tissue cohort.
(B) The most commonly detected losses in liquid samples were *CDKN2A/B, PTEN, MTAP,* and *RB1*. CN loss also represented the most common loss-of-function alteration in *CDKN2B* and *FAS*.
(C) Heatmap of disease-specific CN loss prevalence (prevalence across all samples/prevalence in samples with TF ≥ 20%). *CDKN2A/B* and *MTAP* losses were prevalent across tumor types. Disease-specific enrichments were observed with *RB1* losses in small cell lung and *PTEN* losses in prostate.

RESULTS: MTAP losses were detected in 2% of pan-tumor samples

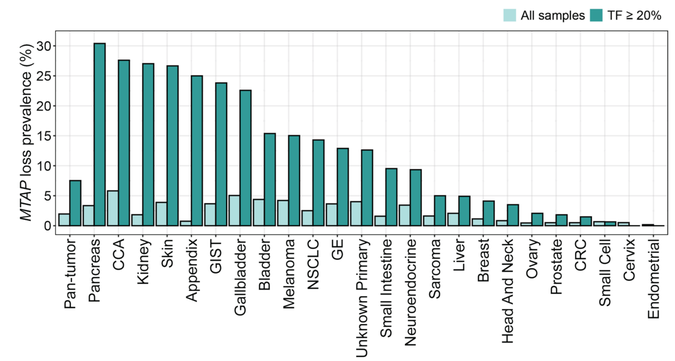

FIGURE 4: Prevalence of *MTAP* loss across tumor types
MTAP losses were present in 2.0% of pan-tumor liquid samples and in 7.5% of samples with TF≥20%. They were most prevalent in pancreas (3.4% overall/30% in TF≥20%), cholangiocarcinoma (5.8%/28%), and kidney (1.8%/27%).

RESULTS: High sensitivity of loss detection observed in samples with TF ≥ 20%

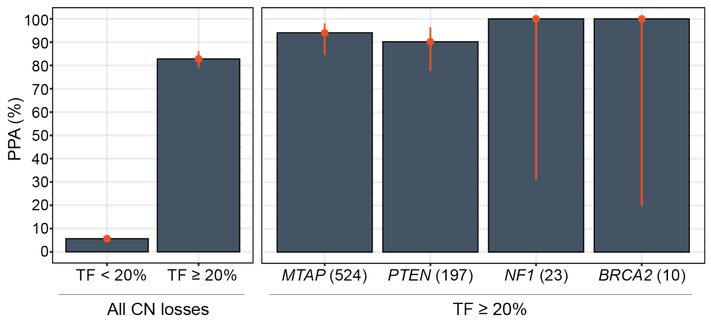

FIGURE 5: Concordance of liquid CN loss detection compared to tissue
Sensitivity of CN loss detection in liquid biopsy compared to tissue was 83% in samples with TF ≥ 20% vs. 5.7% in samples with TF < 20%. Among samples with TF ≥ 20%, high sensitivity of *MTAP, PTEN, NF1,* and *BRCA2* loss detection was observed (PPA 90-100%).

CONCLUSIONS

- FoundationOne® Liquid CDx is able to detect and report homozygous CN losses in 324 genes including established and emerging targets such as *PTEN, MTAP, RB1*, and *BRCA1/2*.
- Sufficient ctDNA TF is needed for CN loss detection in liquid and is critical to distinguish true negatives and inform reflex to tissue testing.

CGP = comprehensive genomic profiling; CN = copy number; LOF = loss-of-function; TF = tumor fraction