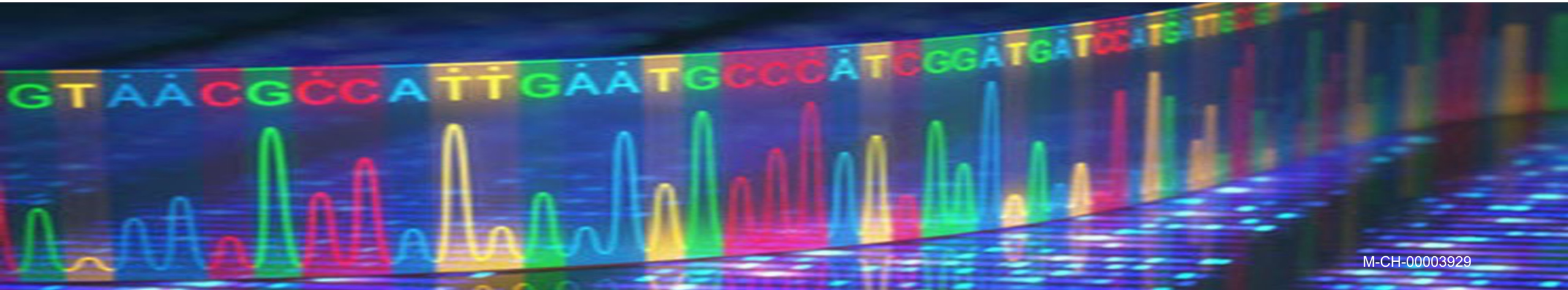
USZ Universitäts Spital Zürich

Erste Erfahrungen: Blut-basiertes umfassendes genomisches Profiling für solide Tumore

Martin Zoche, Universitätsspital Zürich

Jan 19, 2024



M-CH-00003929

Disclosures

Martin Zoche receives research grants from F. Hoffmann-La Roche Ltd. and consulting fees from Astra Zeneca, Bayer, GSK and the Swiss Government.

Disclaimers

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ESR1 Mutations in F1LiquidCDx
Patient Case: f/60y, Breast Cancer

F1Liquid CDx - Result table

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Blood Tumor Mutational Burden - 5 Muts/Mb	No therapies or clinical trials. See Biomarker Findings section
Microsatellite status - MSI-High Not Detected	MSI-High not detected. No evidence of microsatellite instability in this sample (see Appendix section).
Tumor Fraction - Elevated Tumor Fraction	Tumor fraction is considered elevated when ctDNA levels are high enough that aneuploidy can be detected. There is higher sensitivity for identifying genomic alterations and a lower risk of false negative results in specimens with elevated tumor fraction; the positive percent agreement observed between liquid and tissue for defined short variants is ≥ 90% (Li et al., 2021; AACR Abstract 2231) (see Biomarker Findings section).

GENOMIC FINDINGS		VAF %	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)		THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)	
ESR1 -	Y537N	29.1%	Abemaciclib + Fulvestrant	1	None	
	E380Q	2.6%	Palbociclib + Fulvestrant	1		
			Ribociclib + Fulvestrant	1		
			Fulvestrant	2A		
			Anastrozole	⊗		
			Exemestane	⊗		
			Letrozole	⊗		
10 Trials see p. 29						
PIK3CA -	E453_I459>D	16.8%	Alpelisib + Fulvestrant	1	Everolimus	2A
					Temsirolimus	
10 Trials see p. 34						

⊗ *Extensive evidence showing variant(s) in this sample may confer resistance to this therapy*

☐ *NCCN category*

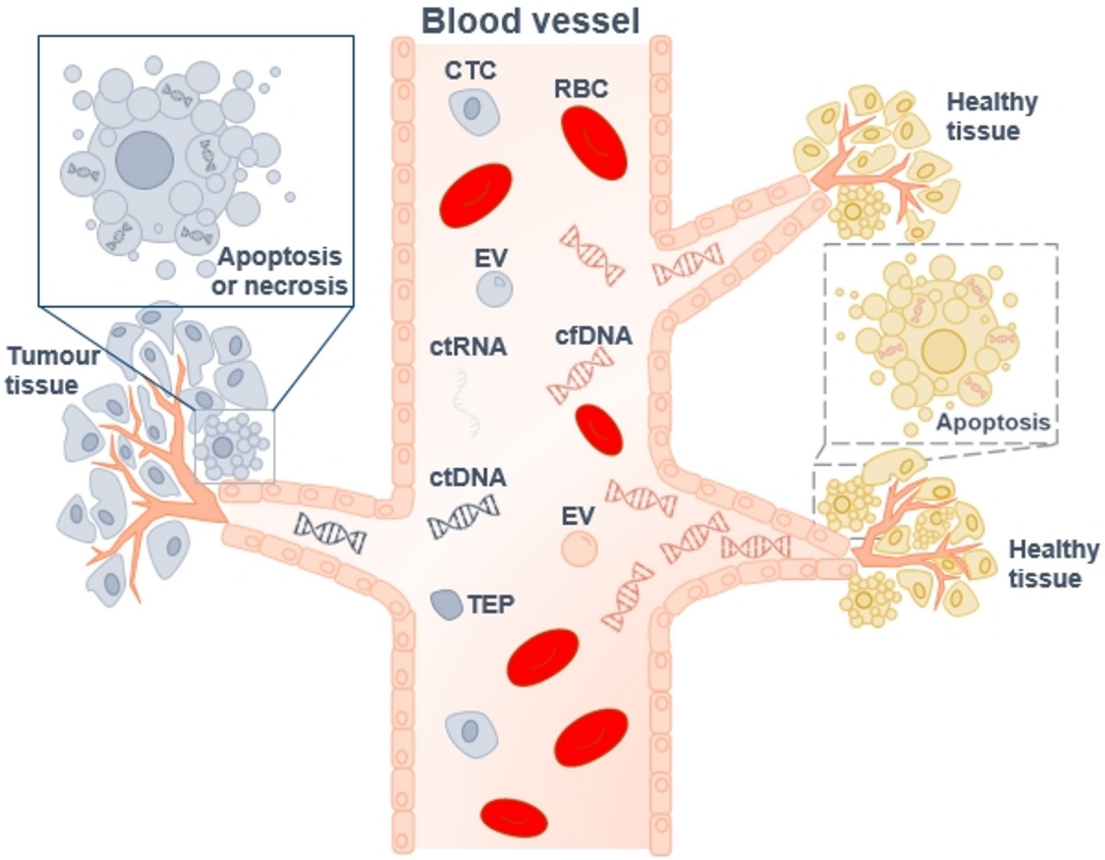
F1CDx 2022
Specimen Breast, TC 89%
TMB: 5, MSstable
LOH: 14%

F1LiquidCDx 2023
Specimen Blood, TF 23%
TMB: 5, MSstable
LOH: n.a.

F1CDx 2022	F1LiquidCDx 2023
ALOX12B (VUS) N178D (...) (7)	ALOX12B (VUS) N178D (...) (48)
ARID1A G95fs*1 (31%)	**ARID1A G95fs*1 (14%)**
ARID1A Q372fs*28 (...) (40)	ARID1A Q372fs*28 (...) (19)
BCOR (VUS) P1614L (...) (8)	ATM V1569fs*32 (...) (0)
BRD4 (VUS) E559Q (11%)	CDH1 splice site 1565+1G>A (...) (31)
CDH1 splice site 1565+1G>A (...) (82)	CDK12 (VUS) H381N (0%)
ESR1 Y537N (86%)	ERBB3 (VUS) A1023V (...) (4)
FANCA (VUS) A1215D (...) (92)	**ESR1 E380Q (3%)**
KDR (VUS) V136L (48%)	**ESR1 Y537N (29%)**
MYC amplification (x7)	FANCA (VUS) A1215D (...) (63)
NOTCH3 (VUS) V1470L (...) (51)	KDR (VUS) V136L (49%)
PALB2 (VUS) I813T (64%)	MLH1 (VUS) R9W (0%)
PIK3CA E453_I459>D (...) (43)	NOTCH3 (VUS) V1470L (...) (48)
RAD21 amplification (x7)	PALB2 (VUS) I813T (54%)
RB1 Q504* (83%)	PIK3CA (VUS) E453_I459>D (...) (17)
ROS1 (VUS) ROS1 rearr. (5 reads)	**RB1 Q504* (2%)**
ZNF217 (VUS) N696S (...) (52)	ZNF217 (VUS) N696S (...) (50)

Legend: **Green** - retained alteration | **Orange** - novel alteration | **Bold** - pathogenic alteration

Blood Provides a Rich Source of Tumour-derived Material



Circulating tumours cells (CTCs) are shed into circulation from primary tumour and metastases[3,4]

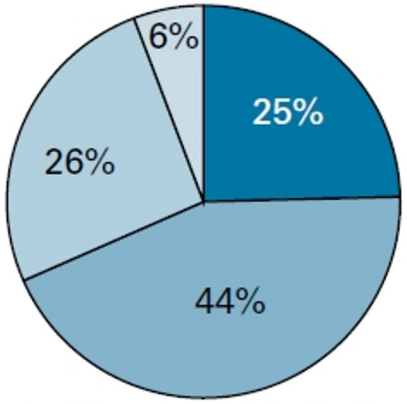
Healthy and tumour tissue release **cell-free DNA and RNA** into circulation through apoptosis, necrosis and lysis of circulating cells[3,5,6]

Membrane-encapsulated **extracellular vesicles** (EVs) are released from healthy and tumour cells[3]

Tumour-educated platelets (TEPs) may contain tumour-derived RNA and alternatively spliced transcripts[3]

cfDNA: cell-free DNA; ctDNA: circulating tumour DNA; ctRNA: circulating tumour RNA; CTC: circulating tumour cell; EV: extracellular vesicle; TEP: tumour-educated platelet; RBC: red blood cell. Figure adapted from references 1-3. 1. Dahl et al. (2015) Pathologe 36:572-8; 2. Crowley, E., et al. (2013) Nat Rev Clin Oncol 10:472-84; 3. De Rubis, G., et al. (2019)Trends Pharmacol Sci 40:172-86; 4. Yu, M., et al. (2011) J Cell Biol 192:373-82; 5. Francis, G. & Stein, S. (2015) Int J Mol Sci 16:14122-42; 6. Bettegowda, C., et al. (2014) Sci Transl Med 6:224ra24

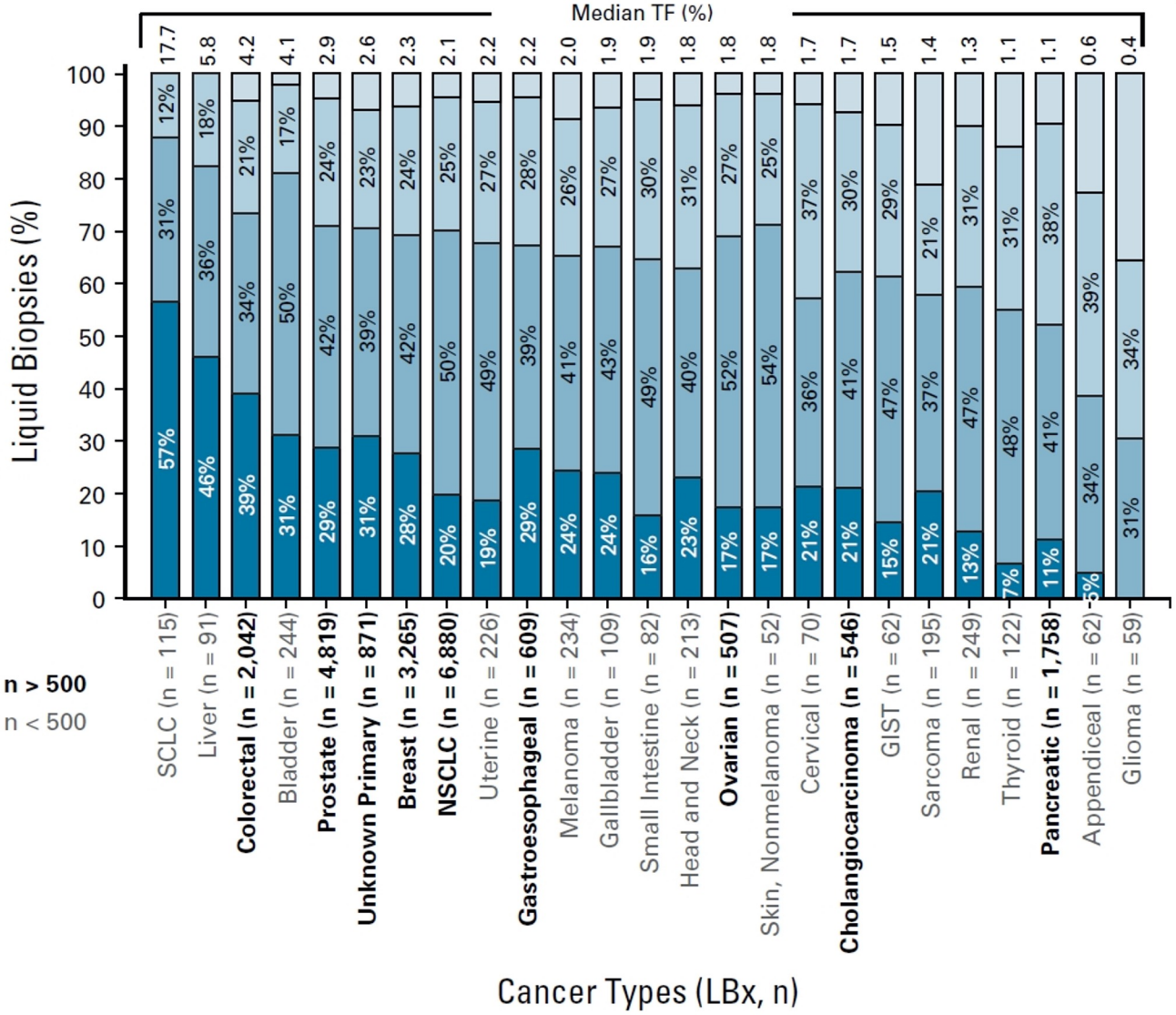
Variable ctDNA Shed across Tumour Types



Entire cohort (23,482)

ctDNA fraction

- ≥ 10%
- (1%-10%)
- (0%-1%)
- Not detected

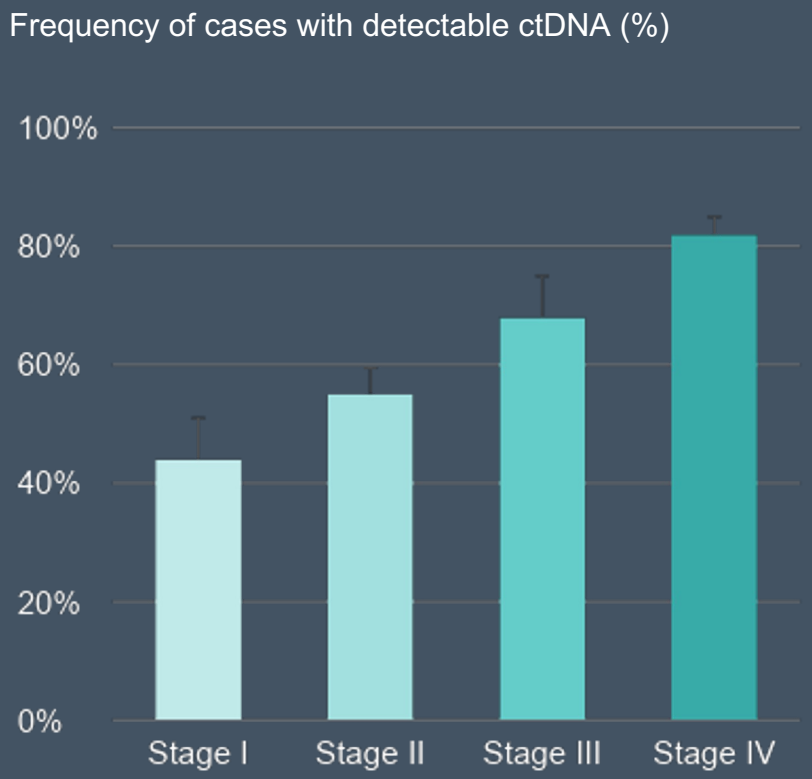


ctDNA: circulating tumour DNA

Husain, H., et al. (2022) Tumor Fraction Correlates With Detection of Actionable Variants Across > 23,000 Circulating Tumor DNA Samples. JCO Precis Oncol 6, e2200261.

ctDNA is Detectable but Variable in Patients with Different Stages of Cancer

- ctDNA was analyzed in 640 patients with a range of solid tumors
- ctDNA levels increased with stage of cancer and tumor burden
- ctDNA was detectable in **55%** of patients with localized disease (stages I-III)
- ctDNA was detectable in **>80%** of patients with metastatic disease (stage IV)
- ctDNA may be particularly useful in tumors such as prostate and breast that tend to metastasize to bone, which can be challenging to biopsy

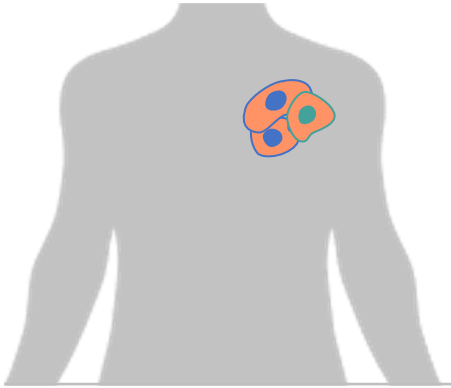


Bettegowda C, et al. *Sci Transl Med*. 2014;6(224):224ra224.
ctDNA = circulating tumor DNA

Slide kindly provided by Roche

Tissue biopsy may not capture the genomic landscape of a patient's entire tumour burden

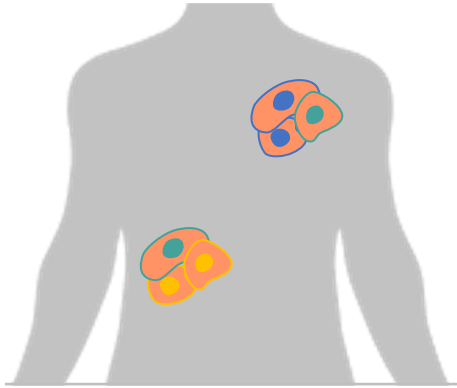
Intratumour Heterogeneity



The genomic landscape **within a single tumour manifestation** may not be uniform

Tissue biopsy may not capture subclonal populations of tumour cells with distinct alterations

Intrapatient Heterogeneity



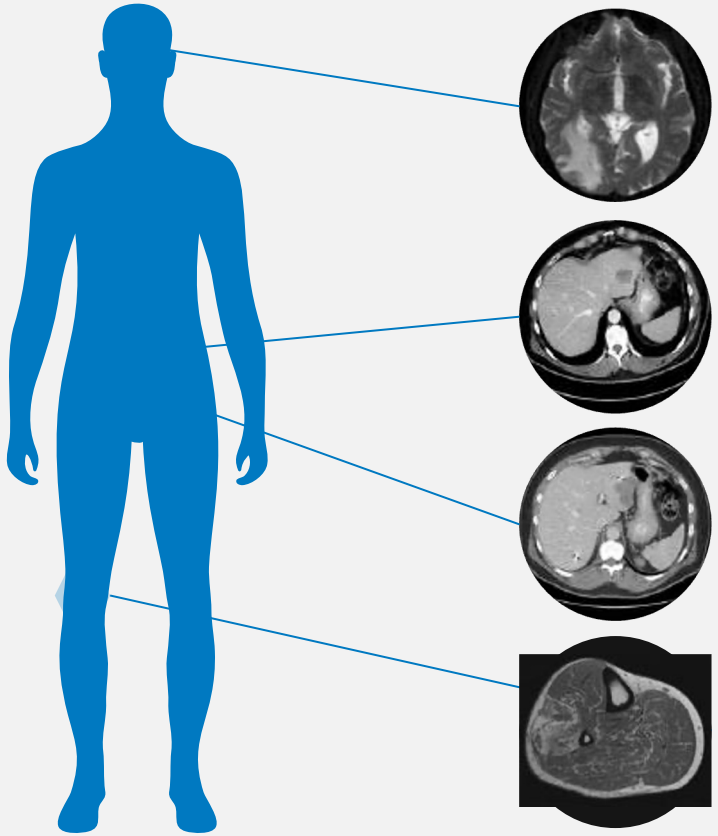
The genomic landscape may **differ between tumour sites** within a patient

Tissue biopsy from a single lesion will miss alterations unique to other lesions

Scherer, F. (2020) in *Recent Results in Cancer Research: Tumor Liquid Biopsies.* Springer.

Tumor Heterogeneity: ctDNA Can Capture Multiple Mechanisms of Acquired Resistance in mCRC

Multiple tissue biopsies show diverging resistance mechanisms in different metastases in a patient with advanced BRAF V600E CRC



Brain lesion
BRAF V600E, AF 54.7%
EGFR amp
KRAS G12S not detected
NRAS Q61R not detected

Liver biopsy 1
BRAF V600E, AF 36.4%
EGFR amp, not detected
KRAS G12S, AF 6.4%
NRAS Q61R, AF 3.1%

Liver biopsy 2
BRAF V600E, AF 61.6%
EGFR amp, not detected
KRAS G12S, AF 22.4%
NRAS Q61R, not detected

Subcutaneous lesion
BRAF V600E, AF 45.4%
EGFR amp, not detected
KRAS G12S, AF 0.2%
NRAS Q61R, not detected

Multiple solid tumor biopsies show diverging resistance mechanisms in different metastases in a patient with advanced *BRAF* V600E CRC

Liquid biopsy captured all 4 resistance mechanisms

ctDNA

BRAF V600E, AF 24%
EGFR amp
KRAS G12S, AF 2.1%
NRAS Q61R AF 0.6%

AF: allelic fraction, ctDNA: circulating tumor DNA, mCRC: metastatic colorectal cancer.
Parikh AR, et al. *Nat Med*. 2019;25(9):1415-1421.

Tumor Content of Liquid Biopsy cannot be Assessed Visually

Overall tumour content is important when assessing biopsy

Solid tumour assays utilise both visual (pathology) and computational assessments of overall tumour fraction (purity)

Assessments in liquid biopsy cannot be made visually

Various computational strategies for assessing tumour fraction in liquid biopsy have been developed, each based on a set of biological assumptions

Hypothetical biopsy 1:
High tumour content

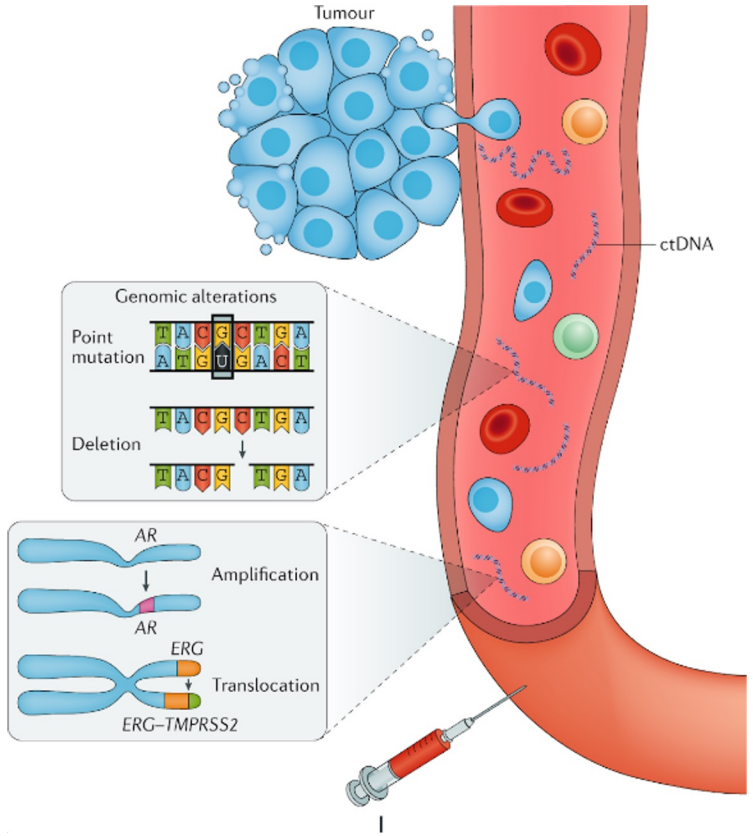
Hypothetical biopsy 2:
Low tumour content

Hypothetical biopsy 3:
Unknown tumour content

Foundation Medicine, Inc. (2020) Data on file.

Why is the Tumor Fraction (TF) an Important Biomarker?

- A key limitation of liquid biopsy is that sensitivity for detection of genomic alterations in ctDNA is impaired when tumor content is low.
- TF provides an estimate of the percentage of circulating-tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample.
- TF can potentially inform sensitivity of ctDNA genomic profiling to provide confidence to oncologists.

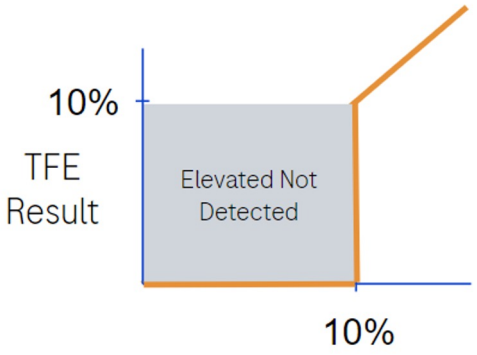


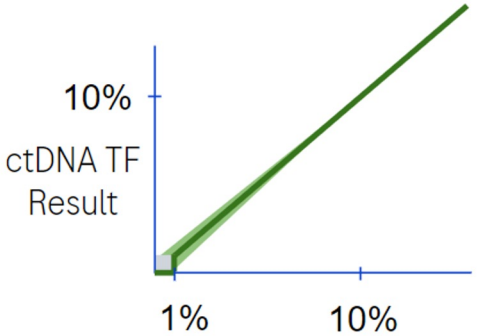
Maia et al. Harnessing cell-free DNA: plasma circulating tumour DNA for liquid biopsy in genitourinary cancers, 2020; 32203306

FMI's Tumor Fraction Algorithm

FMI updated the algorithm to improve sensitivity

Tumor Fraction Estimate (2021- 2023 Oct) → **ctDNA Tumor Fraction (2023 Nov- new algorithm)**

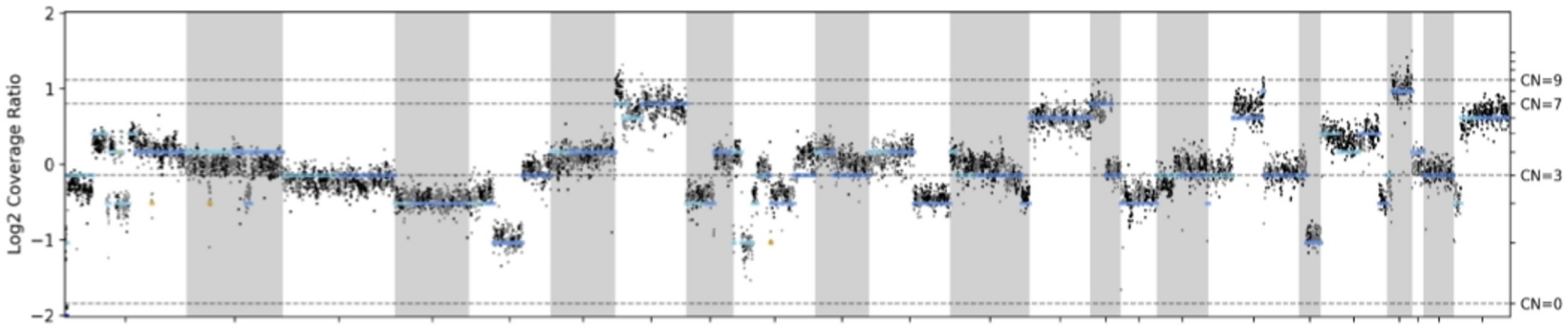




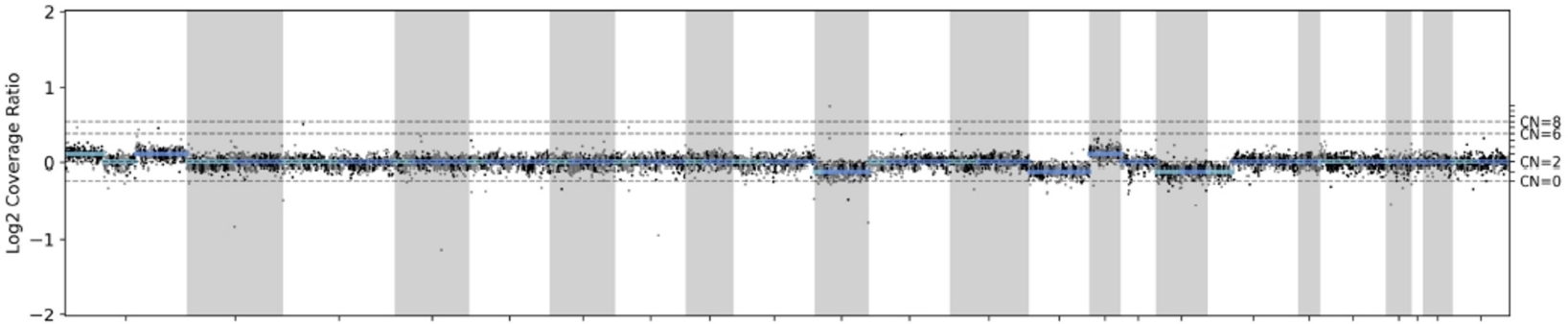
Input	**Aneuploidy**	**Aneuploidy** **Fragmentomics (CH)** **Maximum somatic allele frequency**
Output (TF Cut off level)	**Tumor Fraction Estimate Level at 10%** Elevated Tumor Fraction Elevated (≥10%) Elevated Tumor Fraction not detected	**ctDNA Tumor Fraction cutoff at 1%** Tumor Fraction - High (≥1% TF) Tumor Fraction - Low (0-0.99% TF)

Tumor Fraction is calculated from Copy Number Plot

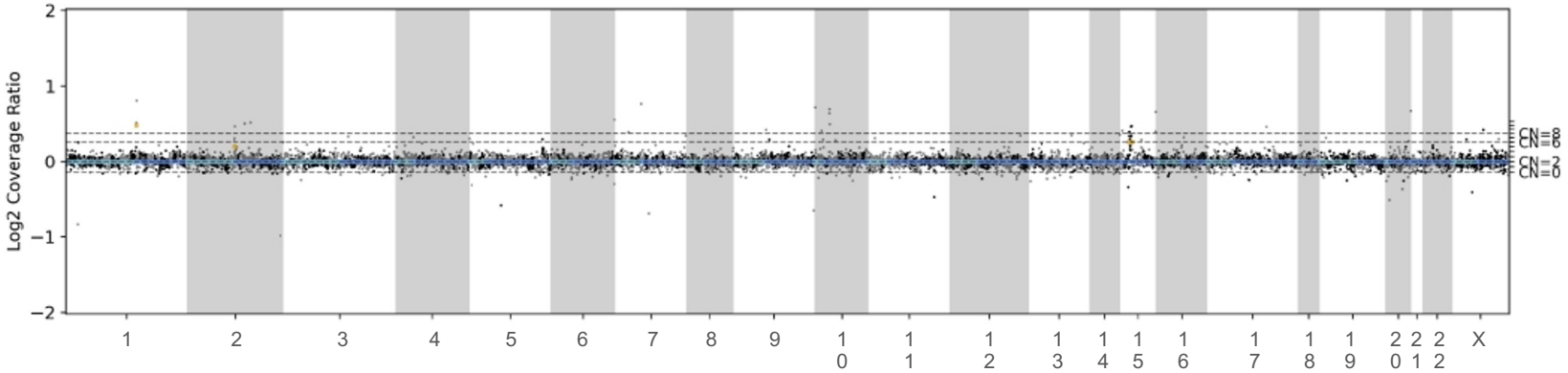
Tumor Fraction High ≥1%



Tumor Fraction Low <1%

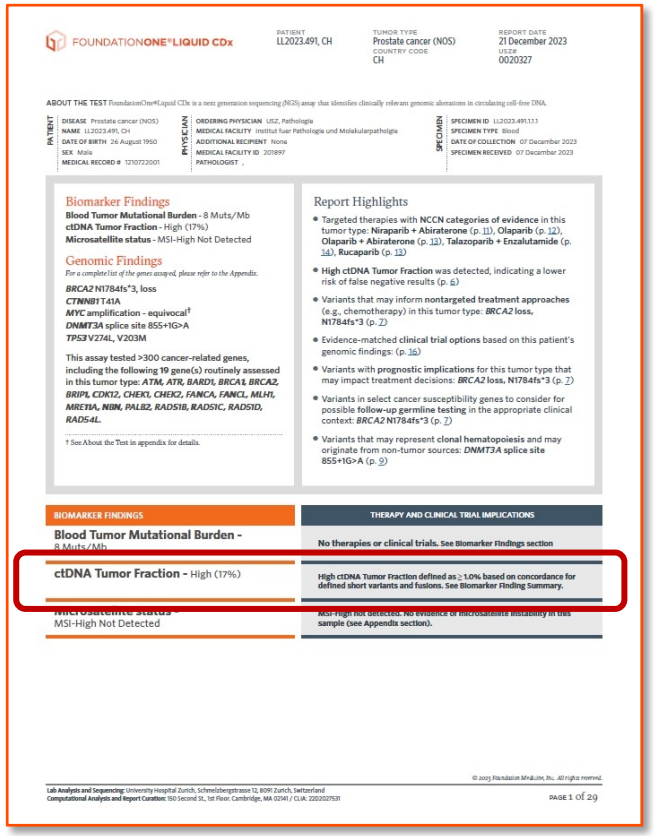


Tumor Fraction can not determined



Tumor Fraction in a F1LiquidCDx Report

Tumor Fraction cut-off at 1%



FOUNDATIONONE®LIQUID CDx

PATIENT LL2023.491, CH | TUMOR TYPE Prostate cancer (NOS) | COUNTRY CODE CH | REPORT DATE 21 December 2023 | USZIP 0020327

ABOUT THE TEST FoundationOne®Liquid CDx is a next generation sequencing (NGS) assay that identifies clinically relevant genomic alterations in circulating cell-free DNA.

PATIENT
DISEASE Prostate cancer (NOS)
NAME LL2023.491, CH
DATE OF BIRTH 26 August 1950
SEX Male
MEDICAL RECORD # 1210722001

PHYSICIAN
ORDERING PHYSICIAN USZ, Pathologie
MEDICAL FACILITY Institut fuer Pathologie und Molekularpathologie
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 201897
PATHOLOGIST ,

SPECIMEN
SPECIMEN ID LL2023.491.1.1.1
SPECIMEN TYPE Blood
DATE OF COLLECTION 07 December 2023
SPECIMEN RECEIVED 07 December 2023

Biomarker Findings
Blood Tumor Mutational Burden - 8 Muts/Mb
ctDNA Tumor Fraction - High (17%)
Microsatellite status - MSI-High Not Detected

Genomic Findings
For a complete list of the genes assayed, please refer to the Appendix.
***BRCA2* N1784fs*3, loss**
***CTNNB1* T41A**
***MYC* amplification - equivocal†**
***DNMT3A* splice site 855+1G>A**
***TP53* V274L, V203M**

This assay tested >300 cancer-related genes, including the following 19 gene(s) routinely assessed in this tumor type: ***ATM, ATR, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCA, FANCL, MLH1, MRE11A, NBN, PALB2, RAD51B, RAD51C, RAD51D, RAD54L.***

† See About the Test in appendix for details.

Report Highlights
- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Niraparib + Abiraterone** (p. 11), **Olaparib** (p. 12), **Olaparib + Abiraterone** (p. 12), **Talazoparib + Enzalutamide** (p. 14), **Rucaparib** (p. 13)
- **High ctDNA Tumor Fraction** was detected, indicating a lower risk of false negative results (p. 6)
- Variants that may inform **nontargeted treatment approaches** (e.g., chemotherapy) in this tumor type: ***BRCA2* loss, N1784fs*3** (p. 7)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 16)
- Variants with **prognostic implications** for this tumor type that may impact treatment decisions: ***BRCA2* loss, N1784fs*3** (p. 7)
- Variants in select cancer susceptibility genes to consider for possible **follow-up germline testing** in the appropriate clinical context: ***BRCA2* N1784fs*3** (p. 7)
- Variants that may represent **clonal hematopoiesis** and may originate from non-tumor sources: ***DNMT3A* splice site 855+1G>A** (p. 9)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Blood Tumor Mutational Burden - 8 Muts/Mb	**No therapies or clinical trials. See Biomarker Findings section**
ctDNA Tumor Fraction - High (17%)	**High ctDNA Tumor Fraction defined as ≥ 1.0% based on concordance for defined short variants and fusions. See Biomarker Finding Summary.**
Microsatellite status - MSI-High Not Detected	**MSI-High not detected. No evidence of microsatellite instability in this sample (see Appendix section).**

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Lab Analysis and Sequencing: University Hospital Zurich, Schmelzbergstrasse 12, 8091 Zurich, Switzerland
Computational Analysis and Report Curation: 150 Second St., 1st Floor, Cambridge, MA 02141 / CLIA: 22D2027531

ctDNA Tumor Fraction - High (17%)

High ctDNA Tumor Fraction defined as ≥ 1.0% based on concordance for defined short variants and fusions. See Biomarker Finding Summary.

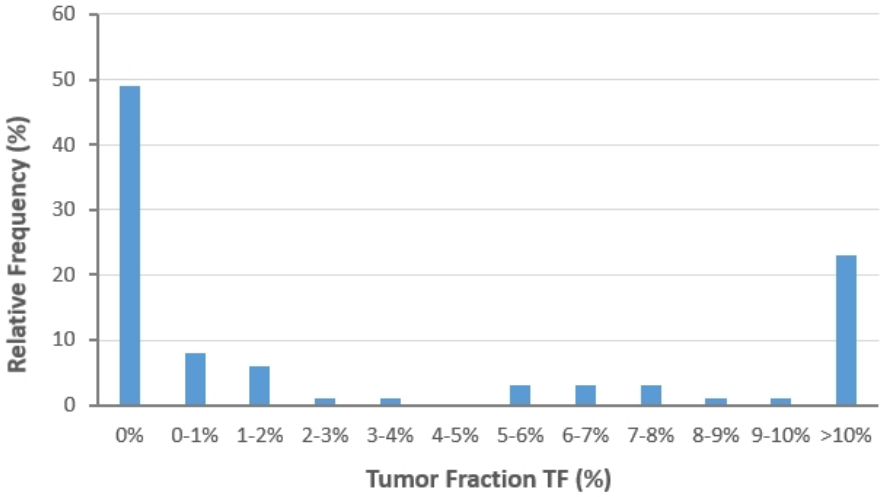
ctDNA Tumor Fraction - Low (< 1.0%)

Low ctDNA Tumor Fraction. This result does not compromise confidence in any reported alterations. See Biomarker Finding Summary.

Tumor Fraction - Cannot Be Determined

The tumor fraction estimate in this sample could not be determined with confidence. However, this result does not compromise confidence in any reported alterations or exclude the presence of ctDNA (see Biomarker Findings section).

Tumor Fraction Distribution



- with the new TF algorithm lower amounts of ctDNA can be determined very precisely.

cohort sample: 124 pat.

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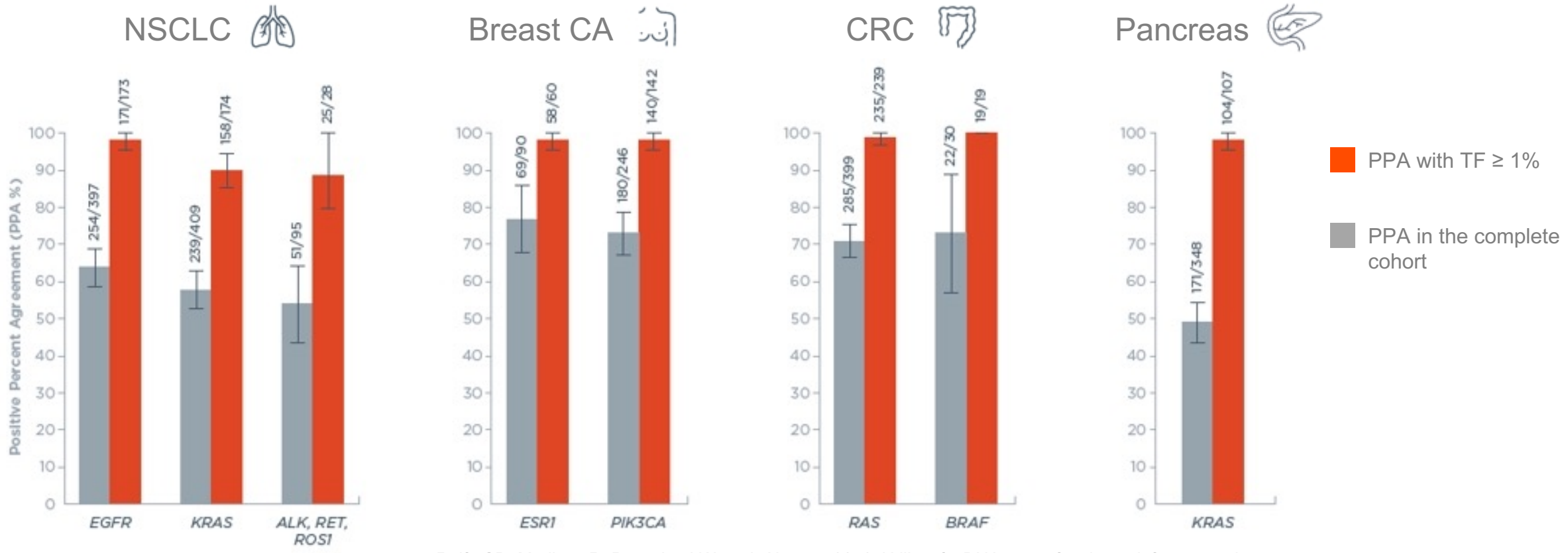
Concordance between Tissue-based F1CDx and blood-based F1LCDx

An elevated tumor fraction (TF) results in a high concordance for pathogenic alterations shown for different tumor types



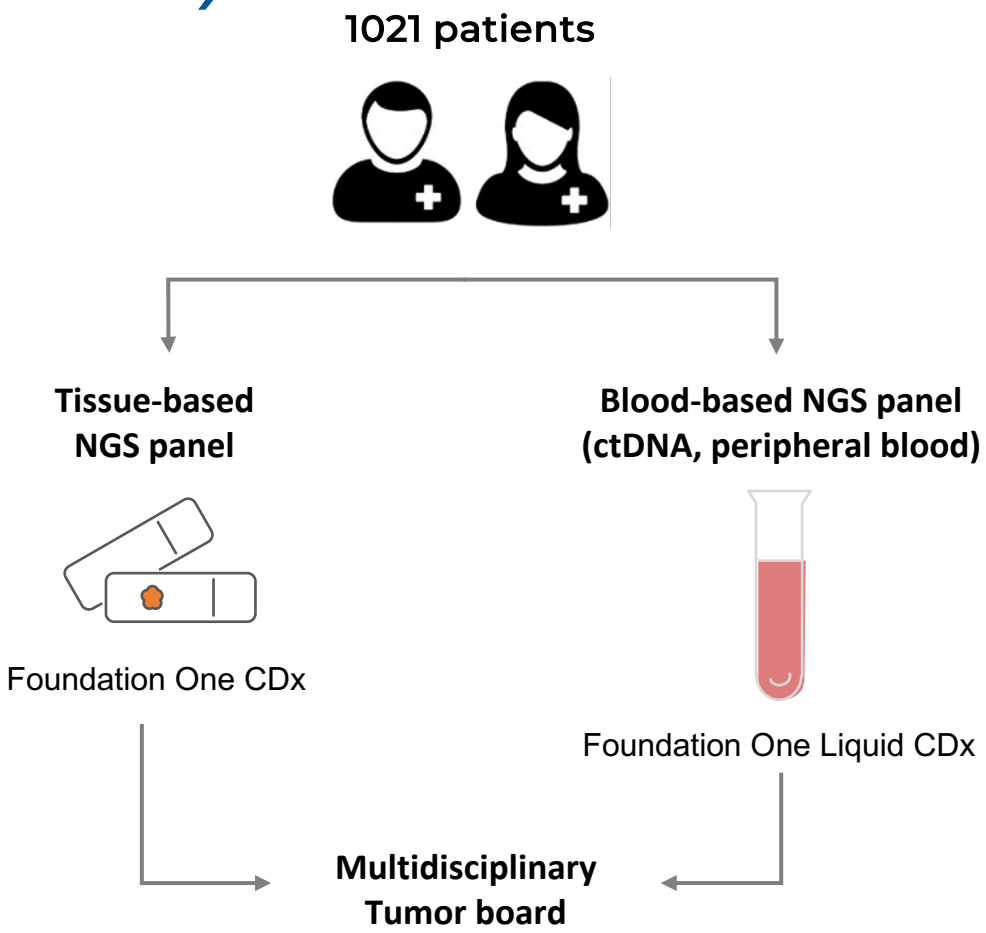
*PPA: Positive Percentage Agreement

Rolfo CD, Madison R, Pasquina LW et al, Abstract 9076, Utility of ctDNA tumor fraction to inform negative liquid biopsy (LBx) results and need for tissue reflex in advanced non-small cell lung cancer (aNSCLC). 2023 ASCO Annual Meeting. https://ascopubs.org/doi/abs/10.1200/ JCO.2023.41.16_suppl.9076 [Access October 18, 2023]

Slide kindly provided by Roche

Systematic Comparison of ctDNA vs. Tissue Sequencing

A study from the French National Center for Precision Medicine (PRISM)



Aim: Comparison of the efficiency of liquid vs tissue for tailoring therapies in cancer patients with solid tumors

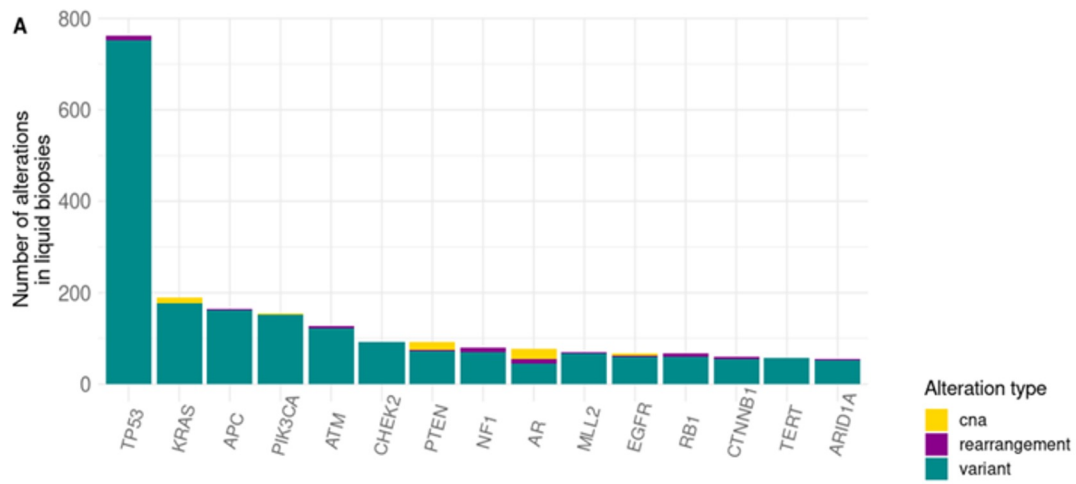
- 324 genes, tumor mutational burden [TMB], microsatellite instability status
- Review and discussion of each genomic report at regular MTB
- ESCAT used for classification of actionable targets leading to molecular-based treatment suggestions if possible

Bayle, A. *et al*. Liquid versus tissue biopsy for detecting actionable alterations according to ESCAT in patients with advanced cancer. Annals Oncol (2022). *pre-publication*. doi.org/10.1016/j.annonc.2022.08.089

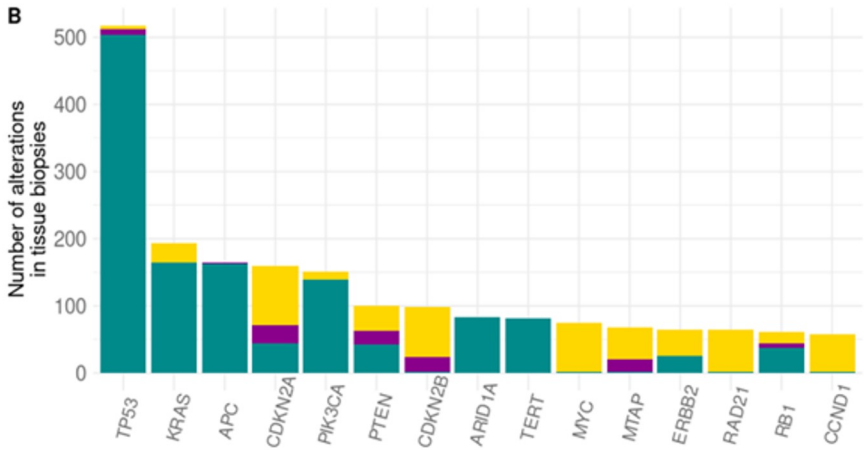
Systematic Comparison of ctDNA vs. Tissue Sequencing

Proportion of alterations in liquid and tissue biopsy

Liquid Biopsy (F1LiquidCDx)



Tissue Biopsy (F1CDx)

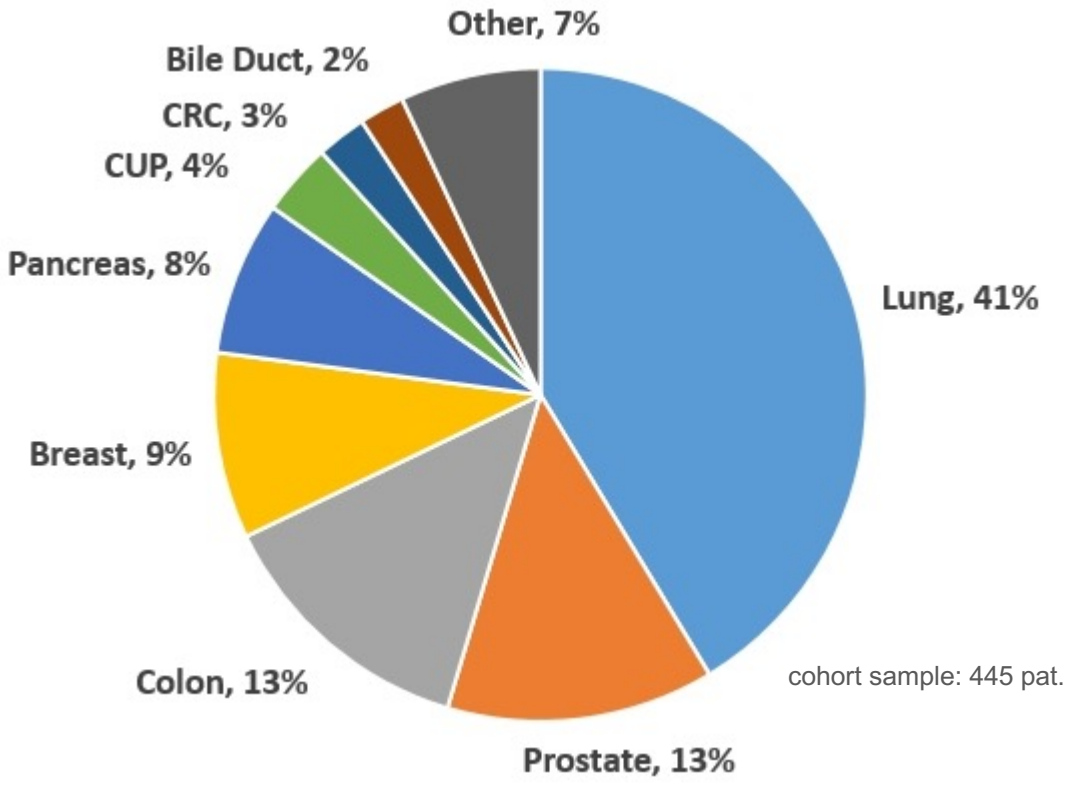


- Total number of cancer-related alterations and variants of unknown significance were 4704 and 11673 vs 4645 and 7481 for ctDNA and tissue, respectively.
- ctDNA is able to detect similar number of cancer related alterations than tissue (with lower sensitivity for copy number alterations).

Bayle, A. *et al*. Liquid versus tissue biopsy for detecting actionable alterations according to ESCAT in patients with advanced cancer. Annals Oncol (2022). *pre-publication*. doi.org/10.1016/j.annonc.2022.08.089

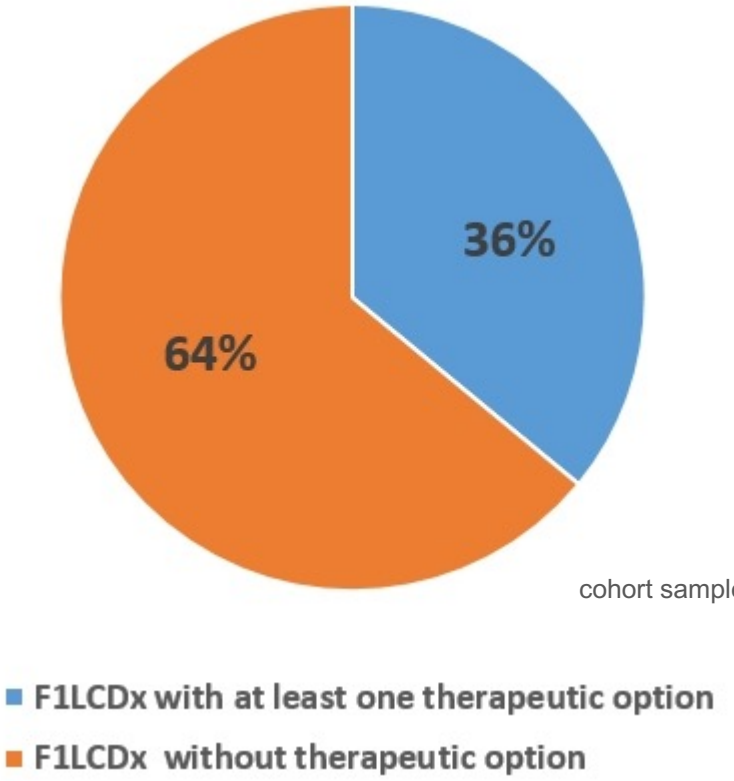
Liquid Biopsy - First Experience at the USZ

Top 8 Tumor Types in Liquid Biopsy



cohort sample: 445 pat.

Therapeutic Options



cohort sample: 517 pat.

The Patient Journey through Oncology Treatment

Each stage of the tumor disease has specific technical requirements for molecular analysis

Use broad panels *at baseline to define and treat each patient's unique disease,*
use personalised, narrow panels *for ultra-sensitive monitoring of recurrence and resistance*[1-3]

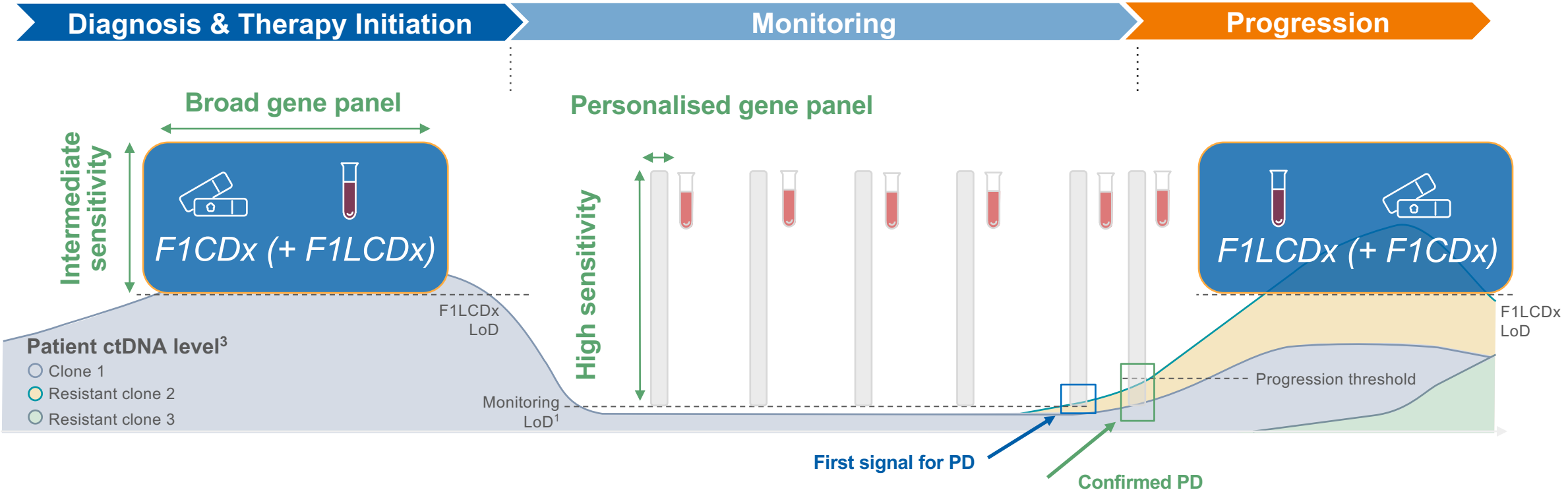


Illustration adapted from 1. Krebs, M.G. et al. Practical Considerations for the Use of Circulating Tumor DNA in the Treatment of PatientsWith Cancer. JAMA Oncology, Oct 20, 2022, doi: 10.1001/jamaoncol.2022.4457. 2. Corcoran, R.B. and Chabner, B.A. (2018) N Engl J Med 379:1754-65; 3. Wan, J.C.M., et al. (2017) Nat Rev Cancer 17:223-38.
ctDNA: circulating tumour DNA; F1(L)CDx: FoundationOne (Liquid) CDx; LoD: limit of detection; PD: progressive disease.

Patient Case, f/44y Breast Carcinoma

F1LiquidCDx

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Blood Tumor Mutational Burden - 4 Muts/Mb	**No therapies or clinical trials.** See Biomarker Findings section
Microsatellite status - MSI-High Not Detected	MSI-High not detected. No evidence of microsatellite instability in this sample (see Appendix section).
Tumor Fraction - Elevated Tumor Fraction Not Detected	Tumor fraction is considered elevated when ctDNA levels are high enough that aneuploidy can be detected. The fact that elevated tumor fraction was not detected in this specimen indicates the possibility of lower levels of ctDNA but does not compromise confidence in any reported alterations. However, in the setting of a negative liquid biopsy result, orthogonal testing of a tissue specimen should be considered if clinically indicated (see Biomarker Findings section).

GENOMIC FINDINGS		VAF%	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)		THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
BRCA1 -	Q1756fs*74	51.5%	Olaparib	1	Niraparib
	rearrangement intron 12	3.0%	Talazoparib	1	Rucaparib
10 Trials see p. 13					

GENOMIC FINDINGS		VAF%	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)		THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
PIK3CA -	Q546R	2.5%	Alpelisib + Fulvestrant	1	None
10 Trials see p. 15					

NCCN category

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING IN SELECT CANCER SUSCEPTIBILITY GENES

Findings below have been previously reported as pathogenic germline in the ClinVar genomic database and were detected at an allele frequency of >30%. See appendix for details.

BRCA1 - Q1756fs*74 ..... p. 6

This report does not indicate whether variants listed above are germline or somatic in this patient. In the appropriate clinical context, follow-up germline testing would be needed to determine whether a finding is germline or somatic.

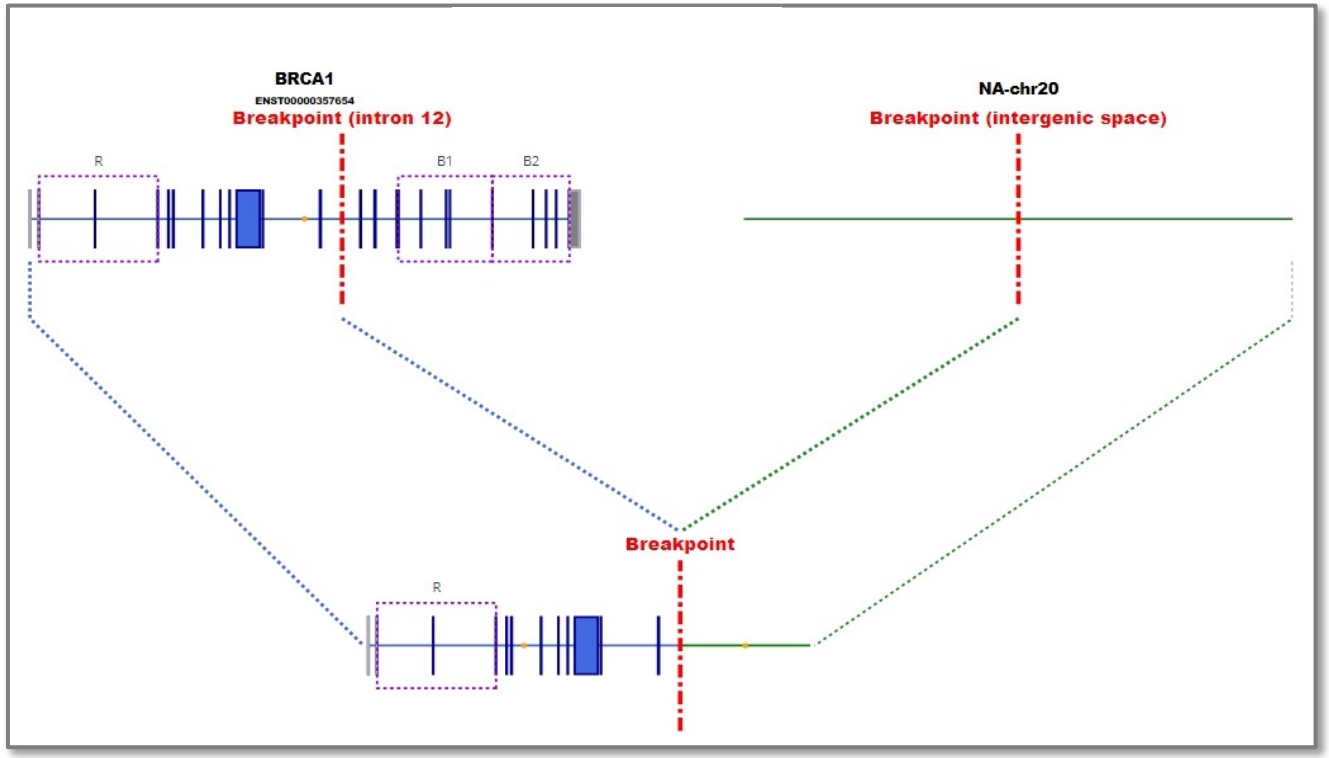
F1CDx 2022	F1LiquidCDx 2023
Specimen Breast, TC 73%	Specimen Blood, TF 0%
TMB: 8, MSstable	TMB: 4, MSstable
LOH: 38%	LOH: n.a.

F1CDx 2022	F1LiquidCDx 2023
ASXL1 (VUS) P873L (40%)	ASXL1 (VUS) P873L (50%)
BAP1 (VUS) (...) (6)	**BRCA1 N/A rearr. (221 reads)**
BRAF amplification (x7)	BRCA1 Q1756fs*74 (...) (52)
BRCA1 N/A rearr. (134 reads)	**PIK3CA Q546R (2%)**
BRCA1 Q1756fs*74 (...) (89)	SETD2 (VUS) Q1343K (...) (49)
CTNNB1 (VUS) (...) (7)	TP53 S149fs*21 (...) (3)
FGF12 (VUS) S223* (20%)	
MYC amplification (x8)	
NBN (VUS) (...) (9)	
PARK2 N/A rearr. (21 reads)	
PARP3 (VUS) (...) (6)	
PIK3CA Q546R (54%)	
PRKAR1A (VUS) (...) (6)	
SETD2 (VUS) Q1343K (...) (85)	
SNCAIP (VUS) (...) (6)	
TGFBR2 (VUS) (...) (7)	
TP53 S149fs*21 (...) (77)	
WT1 (VUS) (...) (6)	

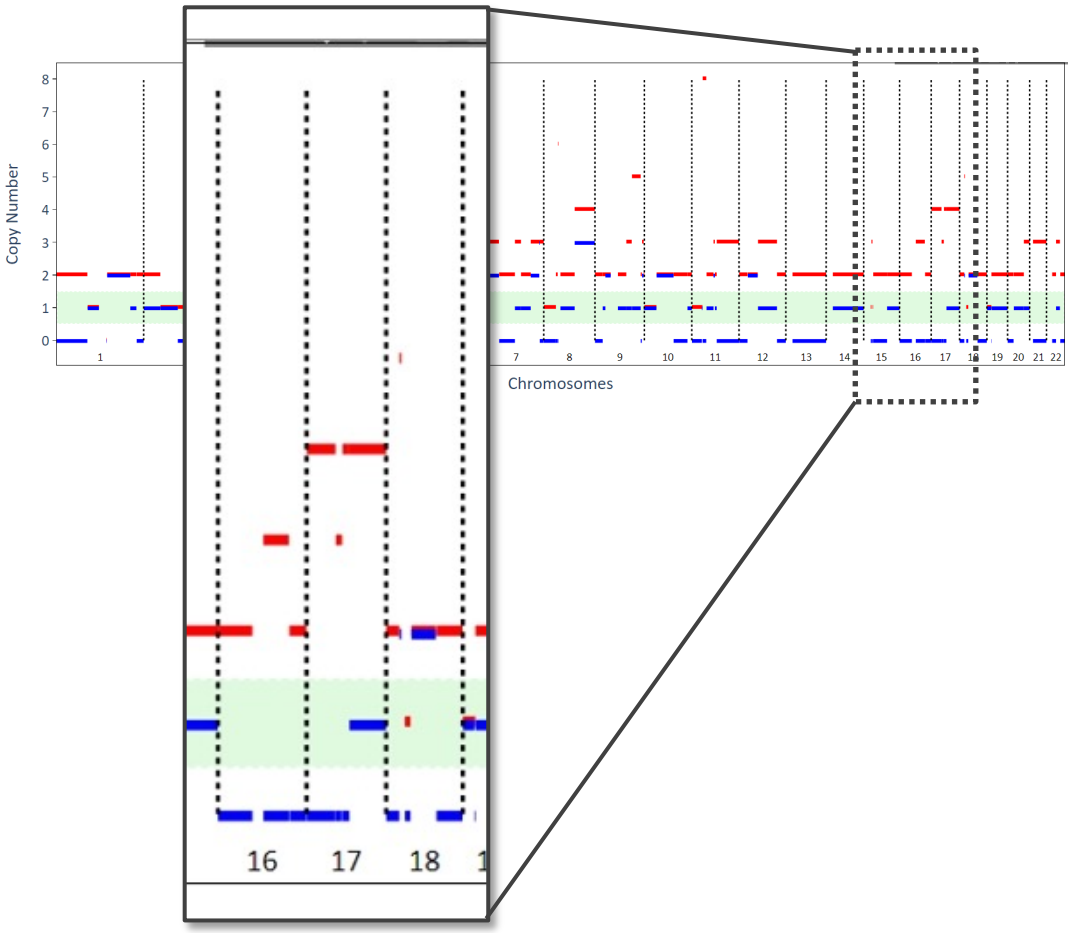
Legend: **Green** - retained alteration | **Orange** - novel alteration | **Bold** - pathogenic alteration

Patient Case, f/44y Breast Carcinoma

BRCA1::NA-chr20-fusion



CNV Plot



Where molecular tumor profiling leads oncology to best patient care

USZ Universitäts Spital Zürich

ESMO Liquid Biopsy Guidelines
Summary

1. Reflex testing may not be required if the presence of sufficient ctDNA in the sample can be confirmed (high tumor fraction).
2. A negative liquid biopsy result for an actionable variant should prompt reflex tissue testing.
3. All oncology physicians should have access to a **molecular tumor board** to ensure correct interpretation of results and for discussion of complex cases.

Pascual J, et al. *Ann Oncol*. 2022;33(8):750-768.

Patients Who May Benefit From Liquid Biopsy

1

Patients in whom traditional biopsy is inaccessible or impractical

- Anatomically inaccessible/unacceptable risk[1]
- Resource-limited settings (e.g. leading to delayed biopsy)[2]

2

Patients in whom traditional biopsy is insufficient

- Tissue exhausted by immunohistochemistry, PD-L1 or other molecular tumor-specific panels[1]
- Highly necrotic tumor with inadequate nucleated tumor cells[3]
- Low tumoral content in specimen[1]

3

Patients who have disease progression or relapse on targeted therapies[1]

- Detection of suspected resistance mutations

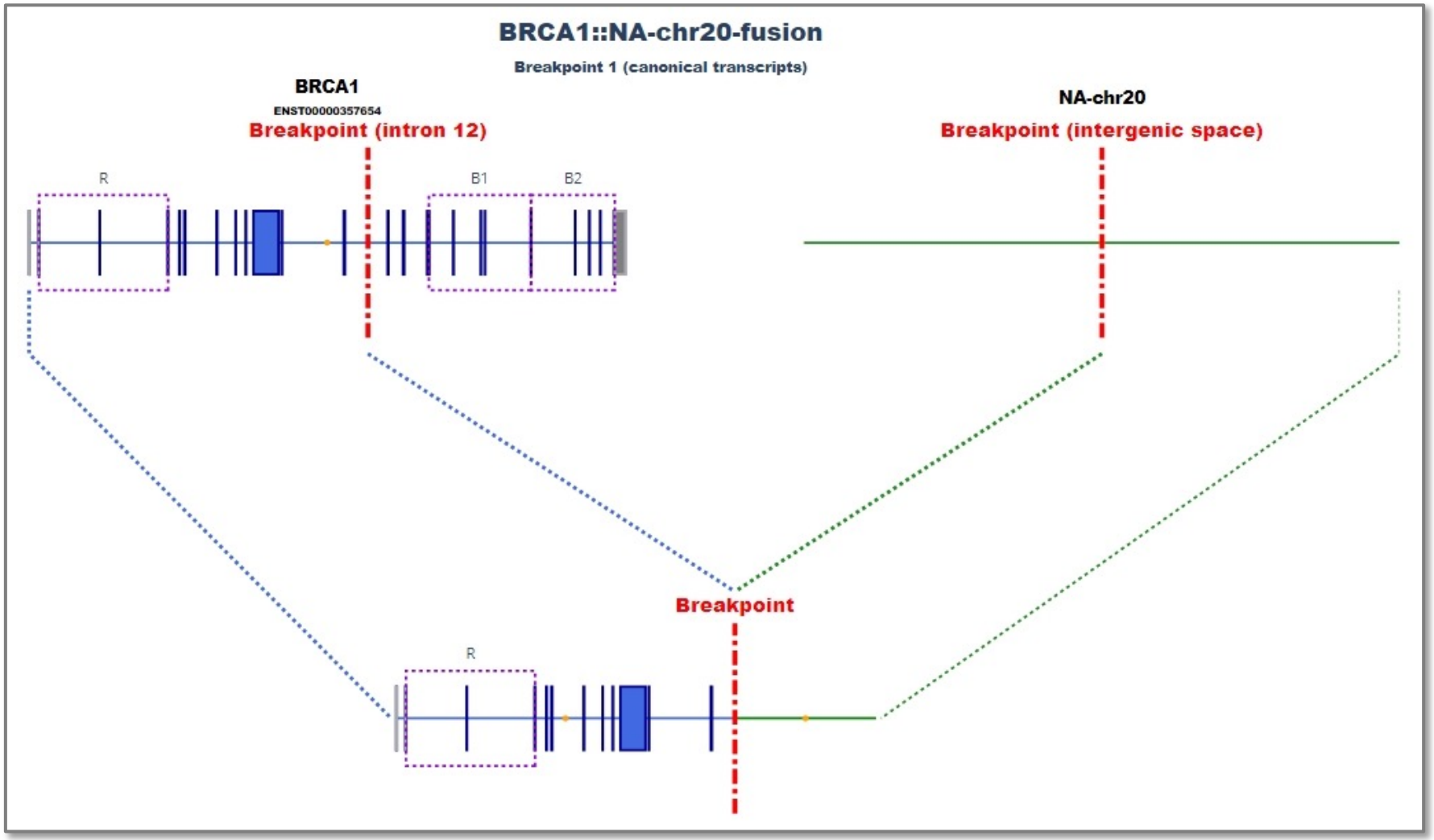
1. Rolfo C, et al. *J Thorac Oncol.* 2018;13(9):1248-1268; 2. Anderson B, et al. *Lancet Oncol.* 2011;12(4):387-398; 3. Sepulveda AR, et al. *J Clin Oncol.* 2017;35(13):1453-1486.

Complementary FDA-Approved Genomic Profiling Tests for Blood and Tissue Across All Solid Tumors

	FoundationOne®Liquid CDx*	FoundationOne®CDx
FDA-Approved	FDA approved CDx for 7 targeted therapies	FDA approved CDx for 24 targeted therapies
Target Tumor Types	All Solid Tumors	
Number of Genes Analyzed	324 (DNA)*	324 (DNA)
Genomic Signatures / Biomarkers	bTMB, MSI-High◊, Tumor Fraction*	TMB, MSI, HRD-status**,LOH**
Specimen	Peripheral Whole Blood	FFPE Tissue
Variant Types Identified	Point mutations, insertions/deletions, copy number alterations (amplifications and select deletions) and rearrangements	Point mutations, insertions/deletions, copy number alterations, selected rearrangements
Turnaround Time	Typically <14 days from receipt of specimen	

*FoundationOne®Liquid CDx is FDA-approved to report substitutions and indels in 311 genes, including rearrangements and copy number losses only in BRCA1/2. Comprehensive results across all 324 genes, including bTMB, MSI-H status, and tumor fraction are reported in the professional services section of the report. ◊MSI status will be reported for samples determined to have high microsatellite instability.
**LOH (loss of heterozygosity) and HRD status for ovarian cancer patients only. bTMB = blood tumor mutational burden, FFPE = formalin fixed paraffin embedded, MSI-High = microsatellite instability high.

References: 1. FoundationOne®Liquid CDx, Assay Specifications. Available at: https://www.foundationmedicine.qarad.eifu.online/foundationmedicine/foundationmedicine (last access: August 2023).
2.FoundationOne®CDx Specifications. Available at: https://www.foundationmedicine.qarad.eifu.online/foundationmedicine/foundationmedicine (last access: August 2023).

Slide kindly provided by Roche

Patient Case, f/44y Breast Carcinoma