Practical look at liquid biopsy

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2/9/2022

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Objectives

- Understand the principles of liquid biopsy as the method of sampling tumor genome with its advantages and disadvantages
- Identify different categories of liquid biopsy assays currently available on the market and their limitations
- Discuss different clinical scenarios where the use of liquid biopsy may be beneficial in the workup of cancer patients

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Introduction to liquid biopsy

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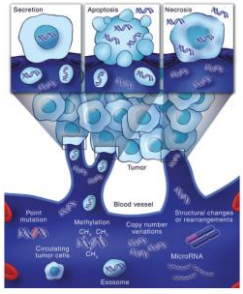
What is liquid biopsy?

- Minimally invasive method of sampling cancer genome using blood sample
- Circulating analytes
  - » Circulating tumor cells (CTCs)
  - » Cell-free DNA (cfDNA)
    - Circulating tumor DNA (ctDNA)



J Clin Oncol. 2014;32(6):579-86.

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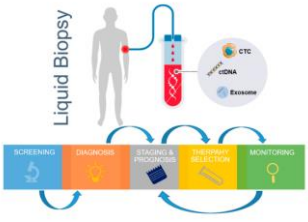
Applications of liquid biopsy



Micromachines. 2018; 9(8): 397.

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Collection

- Whole blood in Streck Cell-Free DNA BCT
  - » **Two tubes** of blood, yielding approximately 7-10mL of plasma should be collected from each patient
  - » Mix by gentle inversion
  - » Stability: ambient or refrigerated 5-7days
- Plasma separation
- cfDNA extraction

https://www.streck.com/products/stabilization/cell-free-dna-bct-ivd/

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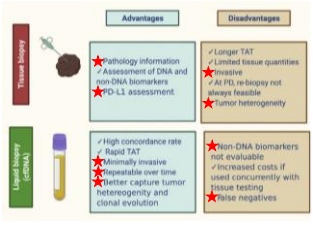
Liquid vs tissue biopsy



J Thorac Oncol 2021 Oct;16(10):1647-1662.

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Types of liquid biopsy assays

	Single-gene	Targeted/Small comprehensive	Large comprehensive
# of genes	1 (may include few hotspots)	<100 (e.g. 73)	Lots (e.g. >324)
Methodology	qPCR, ddPCR, other	NGS	NGS
Types of alterations detected	SNV +/- indels	SNV, indels, CNV, and rearrangements	SNV, indels, CNV, rearrangements, bTMB, MSI, and tumor fraction
FDA approved assay*	- Cobas *EGFR* Mutation Test v2 (Roche) - Therascreen *PIK3CA* RGQ PCR Kit (Qiagen)	Guardant360® CDx	FoundationOne® Liquid CDx
Other assay examples	ddPCR assay detecting *BRAF* V600E mutation	Assay to detect alterations in NSCLC	Assay to detect pan-cancer alterations

* I have no commercial ties to these companies

SNV – single nucleotide variant; **Indel** – insertion/deletion variant; **CNV** – copy number variant; **bTMB** – blood tumor mutation burden; **MSI** – microsatellite instability

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Case 1: Young Asian female, non-smoker

- Diagnosed with lung adenocarcinoma on small tissue biopsy
  - » Few stains were performed to confirm diagnosis
  - » No tumor left in the tissue block
- Clinician is requesting molecular work-up

- Questions:
  - » Is re-biopsy necessary since diagnosis is already established?
  - » Can liquid biopsy be used in the setting of primary molecular workup?
  - » If yes, which type of liquid biopsy assay should be used?

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Liquid biopsy in NCCN guidelines (1.2022)

- Plasma cf/ctDNA testing should not be used to diagnose NSCLC
- cfDNA can be used in specific circumstances if:
  - » The patient is not medically fit for invasive tissue sampling
  - » There is insufficient tissue for molecular analysis and follow-up tissue-based analysis will be done if an oncogenic driver is not identified
- Careful consideration is required to determine whether cfDNA findings reflect a true oncogenic driver or an unrelated finding (e.g. clonal hematopoiesis of indeterminate potential (CHIP))

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How does liquid bx perform in this setting?

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TABLE 1. The 2-×2 Table: Tissue as the Testing Standard

Testing Result	Tissue Positive	Tissue Negative
Plasma positive	TP	FP
Plasma negative	FN	TN

NOTE. Sensitivity = TP / (TP + FN); specificity = TN / (TN + FP); PPV = TP / (TP + FP); NPV = TN / (TN + FN)

Abbreviations: FN, false negative; FP, false positive; NPV, negative predictive value; PPV, positive predictive value; TN, true negative; TP, true positive.

JCO Precis Oncol. 2019 Apr 25;3:PO.18.00299.

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Clinical Utility of Comprehensive Cell-free DNA Analysis to Identify Genomic Biomarkers in Patients with Newly Diagnosed Metastatic Non-small Cell Lung Cancer ☆

Natasha B. Leighl[1], Ray D. Page[2], Victoria M. Raymond[3], Davey B. Daniel[4], Stephen G. Divers[5], Karen L. Reckamp[6], Miguel A. Villalona-Calero[7], Daniel Dix[8], Justin I. Odegaard[9], Richard B. Lanman[9], and Vassiliki A. Papadimitrakopoulou[8]

- Multicenter, prospective
- 282 patients with biopsy proven, previously untreated, non-squamous mNSCLC (stage IIIB/IV) undergoing physician discretion standard of care tissue genotyping were included in final analysis
  - » All patients underwent cfDNA testing
- Eight guideline-recommended biomarkers were evaluated: *EGFR* mutations, *ALK* fusions, *ROS1* fusions, *BRAF* V600E mutation, *RET* fusions, *MET* amplification and *MET* exon 14 skipping variants, and *ERBB2 (HER2)* mutations
  - » Tissue genotyping may include NGS, PCR "hotspot" testing, FISH and/or IHC, or Sanger sequencing
  - » cfDNA genotyping by 73 gene NGS panel

Clin Cancer Res. 2019;25:4691–700.

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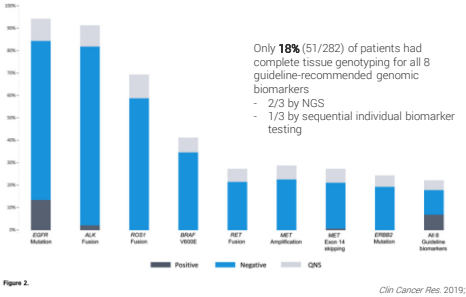

Figure 2.

Only **18%** (51/282) of patients had complete tissue genotyping for all 8 guideline-recommended genomic biomarkers
- 2/3 by NGS
- 1/3 by sequential individual biomarker testing

Clin Cancer Res. 2019;25:4691–700.

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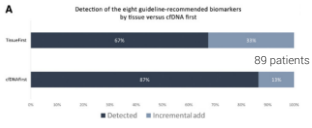
Table 2A. Guideline-recommended genomic biomarker positivity by sample type

Guideline-recommended biomarker positivity by sample type		Tissue		
		Positive	Negative	Total
cfDNA	Positive	48	29	77
	Negative	12	193	205
	Total	60	222	282

For tissue, negative includes samples that were negative for all biomarkers of interest, QNS for all biomarkers, and/or biomarkers were not assessed.



89 patients

- Biomarker detection in tissue vs cfDNA:
  - 21.3% vs. 27.3%; P < 0.0001 for noninferiority
- Clinical sensitivity **80%** (48/60)
- Adding cfDNA increased detection by 48%, from 60 to 89 patients
- cfDNA median TAT was significantly faster than tissue (9 vs. 15 days)

Clin Cancer Res. 2019;25:4691–700.

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Prospective Clinical Validation of the InVisionFirst-Lung Circulating Tumor DNA Assay for Molecular Profiling of Patients With Advanced Nonsquamous Non–Small-Cell Lung Cancer

- Multicenter, prospective study of 264 patients with untreated advanced NSCLC (stage IIIB/IV)
  - » 178 patients underwent plasma and tissue profiling (within 12 weeks)
  - » 86 patients underwent only plasma profiling
- Looked at clinically relevant gene mutation hotspots: ***EGFR*** exons 18-21, ***BRAF*** V600, ***MET*** exon 14, ***ERBB2*** ins 20, ***KRAS***, and ***ALK*** and ***ROS1*** structural variants, and ***STK11***
  - » Plasma profiling was done by NGS panel detecting genomic alterations in 36 commonly mutated genes
  - » Tissue profiling was done by 592 gene NGS panel or when tissue insufficient by other methods

JCO Precis Oncol. 2019 Apr 25;3:PO.18.00299.

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- Tissue genotyping for at least one genomic alteration was successful in 67% (178/264) patients
- Tissue genotyping for all 8 genes was successful in 36% (95/264) patients

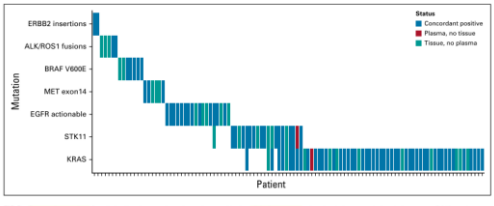

FIG 2. Concordance data for clinically relevant alterations detected in the eight key genes when both tissue and circulating tumor DNA testing was successful. EGFR, epidermal growth factor receptor.

JCO Precis Oncol. 2019 Apr 25;3:PO.18.00299.

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TABLE 3. Summary of Tissue Concordance Data

Alteration	Tissue and Plasma	Tissue Only	Plasma Only	No Call	PPV	NPV	Sensitivity	Specificity
ALK/ROS1 fusions	2	3	0	292	100.0	99.0	40.0	100.0
BRAF V600E	5	2	0	140	100.0	98.6	71.4	100.0
EGFR (exons 18-21)	13	5	0	146	100.0	96.7	72.2	100.0
ERBB2 exon 20 insertions	2	0	0	137	100.0	100.0	100.0	100.0
KRAS	48	12	1	86	98.0	87.8	80.0	98.9
*MET*Δex14	3	3	0	133	100.0	97.8	50.0	100.0
STK11	15	6	1	93	93.8	93.9	71.4	98.9
Key eight genes*	88	31	2	1,027	97.8	97.1	73.9	99.8
All genes	156	65	32	4,135	83.0	98.5	70.6	99.2

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.
*Key eight genes refers to the combination of all directly actionable mutations (*ALK/ROS1* fusions, *BRAF* V600E, *EGFR* exons 18-21, *ERBB2* insertions, *MET* exon 14 splice) and *KRAS* and *STK11* variants.

JCO Precis Oncol. 2019 Apr 25;3:PO.18.00299.

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TABLE 4. Summary of Actionable and Rule-Out Status Using the Liquid Biopsy Data (N = 264)

Class	Subclass	Plasma (No.)	Plasma (%)	Tissue (No.)	Tissue (%)
Actionable		48	18.18	38	14.39
	EGFR exons 18-21	26	9.85	18	6.82
	ALK/ROS1 fusions	5	1.89	5	1.89
	ERBB2 exon 20 insertions	4	1.52	2	0.76
	BRAF V600E	6	2.27	7	2.65
	MET exon 14 splice	7	2.65	6	2.27
KRAS/STK11 and no actionable mutations		94	35.61	70	26.52
Testing complete		264	100.00	178	67.42

- 18.2% of patients tested by liquid biopsy had an actionable change detected
- Additional 35.6% had genomic alteration generally mutually exclusive with actionable alterations
- 53.8% of patients had an informative result that could prevent the need for additional invasive biopsies **(rule-in/rule-out approach)**

JCO Precis Oncol. 2019 Apr 25;3:PO.18.00299.

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JAMA Oncology | Original Investigation

Clinical Implications of Plasma-Based Genotyping With the Delivery of Personalized Therapy in Metastatic Non-Small Cell Lung Cancer

- Single-center, prospective study of 323 patients with stage IV NSCLC (histologically confirmed)
- Looked at alterations detected with plasma and tissue NGS
  - » Therapeutically targetable: ***EGFR***, ***ALK***, ***MET***, ***BRCA1***, ***ROS1***, ***RET***, ***ERBB2***, or ***BRAF***
  - » Clinically relevant: above + ***KRAS***
- Patients had plasma testing ordered as part of routine clinical management
  - » Plasma was analyzed by 73 (70) gene commercial NGS panel
  - » Tissue was analyzed by various NGS panels
    - 15 at outside institution, 64 by in-house 153 (47) gene panel, 49 by in-house 20 gene panel

JAMA Oncol. 2019;5(2):173-180.

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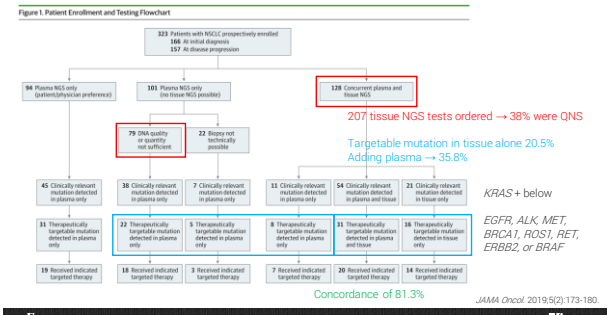

JAMA Oncol. 2019;5(2):173-180.

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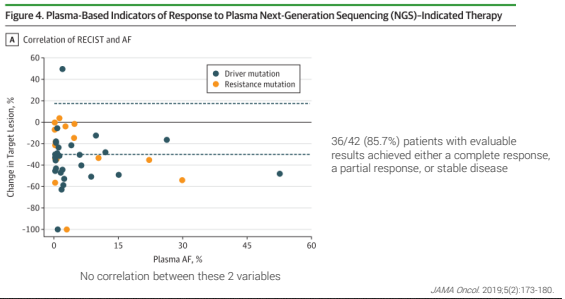

JAMA Oncol. 2019;5(2):173-180.

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Conclusions from these studies

- Comprehensive, sensitive, and specific cfDNA test identifies guideline-recommended biomarkers at a rate, at least, as high as standard of care tissue testing and returns these results significantly faster and for a significantly higher proportion of the population (Leighl)
- The liquid biopsy NGS assay demonstrated excellent concordance with tissue profiling and its use led to the detection of 26% more actionable alterations compared with standard of care tissue testing (Pritchett)
- Liquid biopsy can improve delivery of therapy and, consequently, outcomes (Aggarwal)

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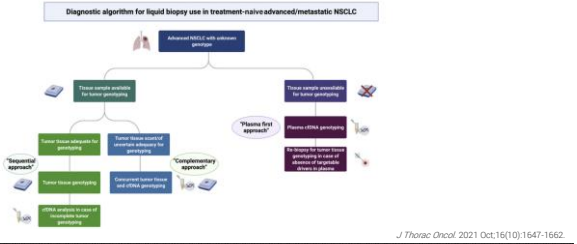
STATE OF THE ART: CONCISE REVIEW

Liquid Biopsy for Advanced NSCLC: A Consensus Statement From the International Association for the Study of Lung Cancer



J Thorac Oncol. 2021 Oct;16(10):1647-1662.

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Case 1: Young Asian female, non-smoker

- Liquid biopsy is ordered (comprehensive panel)
  - » *EGFR* exon 19 deletion is detected
- Patient receives TKI therapy with good clinical response

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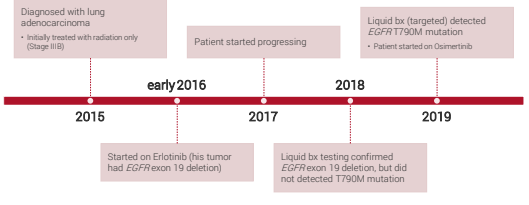
Case 2: 50-year-old male



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How does liquid bx perform for resistance mutation detection?

Detection of T790M, the Acquired Resistance *EGFR* Mutation, by Tumor Biopsy versus Noninvasive Blood-Based Analyses

Tikhe K. Sundaresan[1,2], Lecia V. Sequist[3,4], John V. Heymach[5], Gregory J. Riely[6], Pasi A. Jänne[3,4], Walter H. Koch[7], James P. Sullivan[1], Douglas B. Fox[7], Robert Maher[1,2], Alona Muzikansky[1], Andrew Webb[8], Hai T. Tran[1], Lima Giri[1], Martin Fleisher[9], Helena A. Yu[6], Wen Wei[6], Bruce E. Johnson[3,4], Thomas A. Barber[10], John R. Walsh[10], Jeffrey A. Engelman[3,4], Shannon L. Stott[1,2], Ravi Kapur[10], Shyamala Maheswaran[1,2], Mehmet Toner[1,2,11], and Daniel A. Haber[1,2,12]

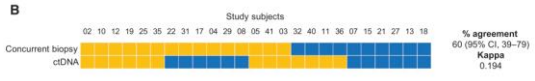

Figure 2.

The resistance-associated mutation was detected in 47% to 50% of patients using each of the genotyping assays, with concordance among them ranging from 57% to 74%.

Clin Cancer Res. 2016 Mar 1;22(5):1103-10.

Plasma ctDNA Analysis for Detection of the *EGFR* T790M Mutation in Patients with Advanced Non-Small Cell Lung Cancer

Sunber Jenkins, DPhil,[1,2] James C-H. Yang, M.B.B.S., MD,[3] Suresh S. Ramalingam, MD, PhD,[1] Karen Yu, BA,[1] Sabina Patel, PhD,[4] Susie Weston, BSc,[4] Rachel Hodge, MSc,[4] Mireille Cantarini, MD,[4] Pasi A. Jänne, MD, PhD,[5] Tetsuya Mitsudomi, MD, PhD,[6] Glenwood D. Goss, MD[7]

Table 2. Percent Agreement of the cobas Plasma Test with the cobas Tissue Test as a Reference Method for the Detection of *EGFR* T790M, L858R, and Exon 19 Deletion

	Percent Agreement (95% CI)								
	T790M			L858R			Exon 19 Deletion		
	AURA Extension (n = 210)	AURA2 (n = 341)	Pooled AURA Extension and AURA2 (n = 551)	AURA Extension (n = 210)	AURA2 (n = 341)	Pooled AURA Extension and AURA2 (n = 551)	AURA Extension (n = 210)	AURA2 (n = 341)	Pooled AURA Extension and AURA2 (n = 551)
PPA	64 (57-71)	59 (52-65)	61 (57-66)	75 (61-85)	76 (67-84)	76 (69-82)	88 (81-93)	83 (77-88)	85 (81-89)
NPA	–[a]	80 (72-87)	79 (70-85)	99 (95-100)	98 (95-99)	98 (96-99)	98 (92-100)	98 (94-100)	98 (95-100)
OPA	65 (58-71)	66 (61-71)	65 (61-69)	92 (88-96)	90 (86-93)	91 (88-93)	91 (86-94)	89 (86-93)	90 (87-92)

[a]Not calculated because of the low number of samples (total <20).
PPA, positive percent agreement (sensitivity); NPA, negative percent agreement (specificity); OPA, overall percent agreement (concordance).

J Thorac Oncol. 2017 Jul;12(7):1061-1070.

Table 4. NGS Results for T790M Mutation Detection Using Tissue and Plasma Samples for the AURA Extension and AURA2 Cases in Which T790M was Detected with the Plasma Test but Not Detected with the Tissue Test

Study	T790M Detected with cobas Plasma Test but Not Detected with cobas Tissue Test	NGS Tumor Tissue T790M Status		NGS Plasma T790M Status	
		Positive	Negative	Positive	Negative
AURA extension	5	3[a] of 5	1 of 5	5 of 5	0 of 5
AURA2	22	8 of 22	14 of 22	18[b] of 22	3 of 22
Pooled AURA extension and AURA2	27	11 of 27	15 of 27	23 of 27	3 of 27

[a]One AURA extension tissue sample had invalid NGS test.
[b]One AURA2 plasma sample not tested by NGS.
NGS, next-generation sequencing.

J Thorac Oncol. 2017 Jul;12(7):1061-1070.

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Study (reference)	Number of patients	Assay	Sensitivity n. (%)	Specificity n. (%)	PPV n. (%)	NPV n. (%)
Ishii *et al.*[18]	18	Droplet dPCR	9/11 (81.8)	6/7 (85.7)	9/10 (90)	6/8 (75)
Thress *et al.*[19]	65	RT-PCR (cobas) BEAMing dPCR	30/41 (73) 33/41 (81)	16/24 (67) 14/24 (58)	30/38 (79) 33/43 (76.7)	16/27 (59.3) 14/22 (63.6)
Karlovich *et al.*[20]	95	RT-PCR (cobas) BEAMing dPCR	21/33 (64) 33/45 (73)	61/62 (98) 9/18	21/22 (95.5) 33/42 (78.6)	61/73 (83.6) 9/21 (42.9)
Oxnard *et al.*[17]	216	BEAMing dPCR	111/158 (70.3)	40/58 (69)	111/129 (86)	40/87 (46)
Reckamp *et al.*[21]	105	NGS	38/41 (93)	60/64 (94)	38/42 (90.5)	60/63 (95.2)
Sacher *et al.*[22]	54	Droplet dPCR	27/35 (77)	12/19 (63)	27/34 (79.4)	12/20 (60)
Sundaresan *et al.*[23]	25	RT-PCR (cobas)	6/10 (60)	9/15 (60)	6/12 (50)	9/13 (69.2)
Takahama *et al.*[24]	41	Droplet dPCR	20/31 (65)	7/10 (70)	20/23 (87)	7/18 (38.9)
Paweletz *et al.*[25]	14	NGS	8/10 (80)	2/4 (50)	8/10 (80)	2/4 (50)
Seki *et al.*[26]	10	Droplet dPCR	5/7 (71)	3/3 (100)	5/5 (100)	3/5(60)
Thompson *et al.*[27]	50	NGS	2/4 (50)	40/46 (87)	2/8 (25)	40/42 (95.2)
Suzawa *et al.*[28]	59	Droplet dPCR	9/21 (36)	37/38 (97)	9/10 (90)	37/49 (75.5)
Jenkins *et al.*[29]	543	RT-PCR (cobas)	255/416 (61.4)	100/127 (78.6)	255/282 (90.4)	100/261 (38.3)
Wang *et al.*[30]	16	Droplet dPCR	6/9 (66.7)	5/7 (71.4)	6/8 (75)	5/8 (62.5)
Mellert *et al.*[31]	55	Droplet dPCR	13/15 (87)	40/40 (100)	13/13 (100)	40/42 (95.2)
Kasahara *et al.*[32]	20	Chip-based dPCR	5/7 (71	7/13 (54)	5/11 (45.5)	7/9 (77.8)
Yoshida *et al.*[33]	21	PNA-LNA PCR	4/10 (40)	11/11 (100)	4/4 (100)	11/17 (64.7)
Wu *et al.*[34]	24	RT-PCR	7/17 (41)	5/7 (71)	7/9 (77.8)	5/15 (33.3)
Buder *et al.*[35]	45	Droplet dPCR	28/34 (82)	2/11 (18)	28/37 (75.7)	2/8 (25)

Table 1. Characteristics of Trials Included in the Meta-Analysis. RT-PCR: real-time PCR; dPCR: digital-PCR; NGS: next-generation sequencing; CI: confidence intervals; PPV: positive predictive value; NPV: negative predictive value.

The diagnostic accuracy of circulating tumor DNA for the detection of EGFR-T790M mutation in NSCLC: a systematic review and meta-analysis

Sci Rep. 2018 Sep 6;8(1):13379.

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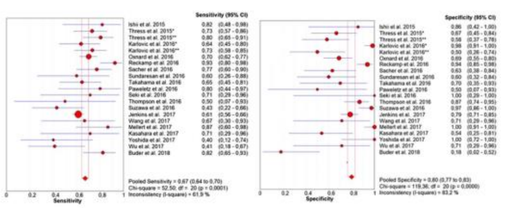

Figure 2. Forest plots of sensitivity and specificity of ctDNA for the detection of EGFR-T790M mutation; *RT-PCR; **dPCR.

Sci Rep. 2018 Sep 6;8(1):13379.

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Case 3: 36-year-old male

- No significant past medical history
- Presents with enlarged L supraclavicular lymph node (present for 2 months)
- Excisional biopsy (L deep cervical lymph node) at outside hospital:
  - » Malignancy with features consistent with metastatic melanoma
  - » IHC stains positive for Mart1, MITF and HMB45, variably positive for S100 and CD117, and negative for pan-cytokeratin, p16, CD45 and PAX8

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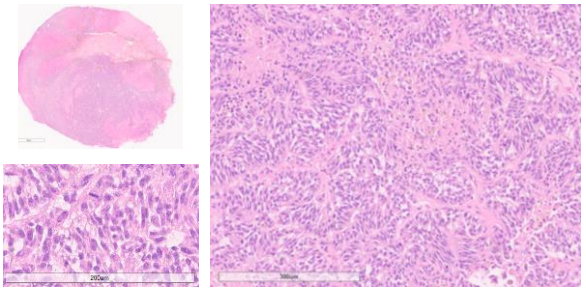

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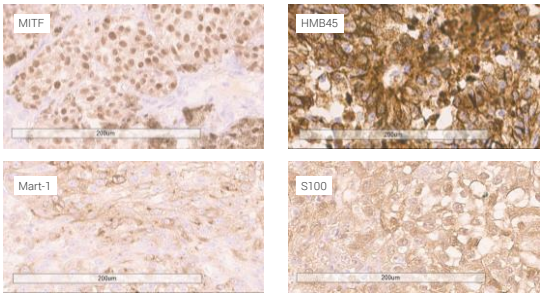

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Case 3: 36-year-old male

- Patient presents to HCH for a second opinion and to establish care
  - » Abdominal pain, nausea/vomiting and anorexia
- Staging PET-CT (outside)
  - » Numerous hypermetabolic left-sided lymph nodes, metastatic disease in the liver, spleen, bone and the left psoas muscle. Brain MRI showed no intracranial metastasis.
- *BRAF* testing was not done on the tumor at the outside facility. *BRAF* cfDNA liquid biopsy is ordered with the following treatment plan:
  - » If *BRAF* positive: pembrolizumab/dabrafenib/trametinib
  - » If *BRAF* negative: nivolumab/ipilimumab

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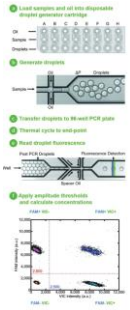
ddPCR



- Many thousands discrete independent measurements
- Absolute quantification (absolute count of target DNA copies per input sample)
- Great precision (reliable measurement of small fold differences)
- No calibration standards (for standard curve) required

Anal Chem. 2011 Nov 15;83(22):8604-10.

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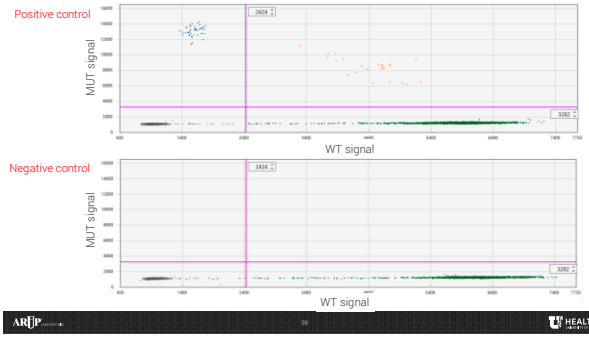

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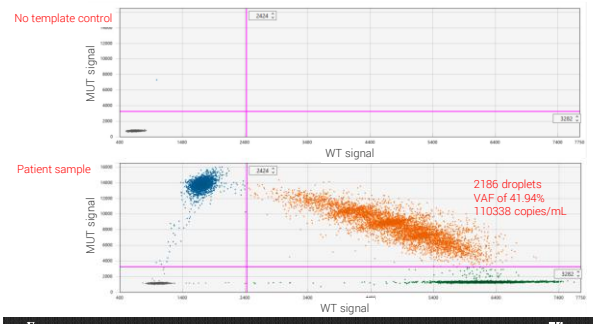

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Case 3: 36-year-old male

- The same day test result come back patient starts therapy with dabrafenib/trametinib
  - » Patient starts pembrolizumab few days later
  - » Symptoms improved
- Year later he continues therapy and has relatively stable disease

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What if his test came back negative?

- Know the limitation of the assay ordered i.e. which *BRAF* mutations are detectable with a given design:
  - » E.g. assay performed in this case only detects *BRAF* V600E
  - » In negative cases retesting with an assay designed to detect other *BRAF* V600 variants (K/R/M/D/G) is recommended
- NCCN guidelines (v1.2022) for cutaneous melanoma
  - » Molecular testing on tumor tissue is preferred, but may be performed on peripheral blood (liquid biopsy) if tumor tissue is not available

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Case 4: 2-year-old girl

- Established diagnosis of multisystem Langerhans cell histiocytosis (LCH)
  - » *BRAF* V600E positive on tissue (outside result)
- She underwent multiple cycles of chemotherapy and is now for the first time in remission based on radiology (question of residual CNS involvement)
- The test was ordered to access the mutation burden
  - » If negative, she was going to be done with chemo for now
  - » If positive, she has an option of starting off-label BRAF inhibitor (already approved by insurance)

Molecular basis of LCH

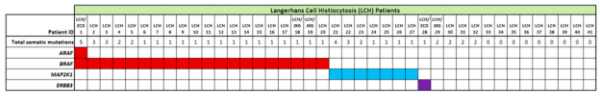


Figure 1. Key genetic alterations identified in MAPK pathway genes in LCH patients.

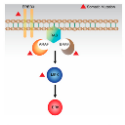
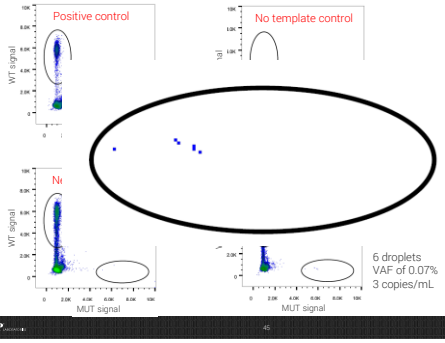


Figure 2. MAPK pathway mutations identified in LCH patients.

Blood. 2014;124(19):3007-3015.



Case 4: 2-year-old girl

- Discussed this result with an ordering physician as very low positive/borderline
- The physician plans on monitoring this patient in the future with this assay

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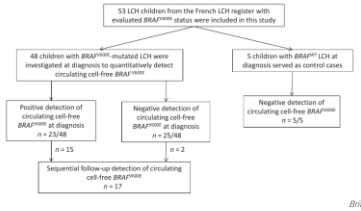
bjh research paper

Circulating cell-free *BRAF*^{V600E} as a biomarker in children with Langerhans cell histiocytosis



British Journal of Haematology. 2017;178:457–467.

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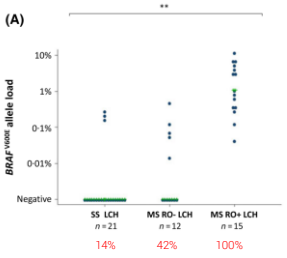

- After first-line vinblastine-steroid induction therapy, 7/7 (100%) of the non-responders remained positive for ccf BRAF V600E compared to 2/4 (50%) of the partial-responders and 0/4 of the complete responders
- Six children treated with vemurafenib showed a clinical response that was associated with a decrease in the ccf BRAF V600E load at day 15
- ccf BRAF V600E is a promising biomarker for monitoring the response to therapy for children with RO+ MS LCH or RO- LCH resistant to first-line chemotherapy

British Journal of Haematology. 2017;178:457–467.

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Case 4: 2-year-old girl

Collection date	Result	Mutant Allele Frequency %	Mutant Copies/mL plasma
12/2019	See note*	0.07	3
6/2020	Detected	0.22	18
2/2021	Not detected		
8/2021	Not detected		
11/2021	Not detected		

* An extremely low level of BRAF V600E mutation was detected in the BRAF gene. This result should be interpreted with caution and in the context of all other clinical data.

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Summary

- Liquid bx can be suitable alternative sample source when:
  - » Tissue is unavailable for molecular testing
    - Will identify patients who can avoid re-biopsy
    - Negative results must be confirmed by tissue-based testing
  - » Fast results are needed, especially if there is no tissue in house
  - » For monitoring to avoid repeat invasive biopsies
- Liquid bx has problematic clinical sensitivity, but great specificity
- There are different types of liquid bx assays, know what you are looking for before ordering

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ARUP is a nonprofit enterprise of the University of Utah and its Department of Pathology.

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