Circulating Tumor Cells in brain metastatic patients

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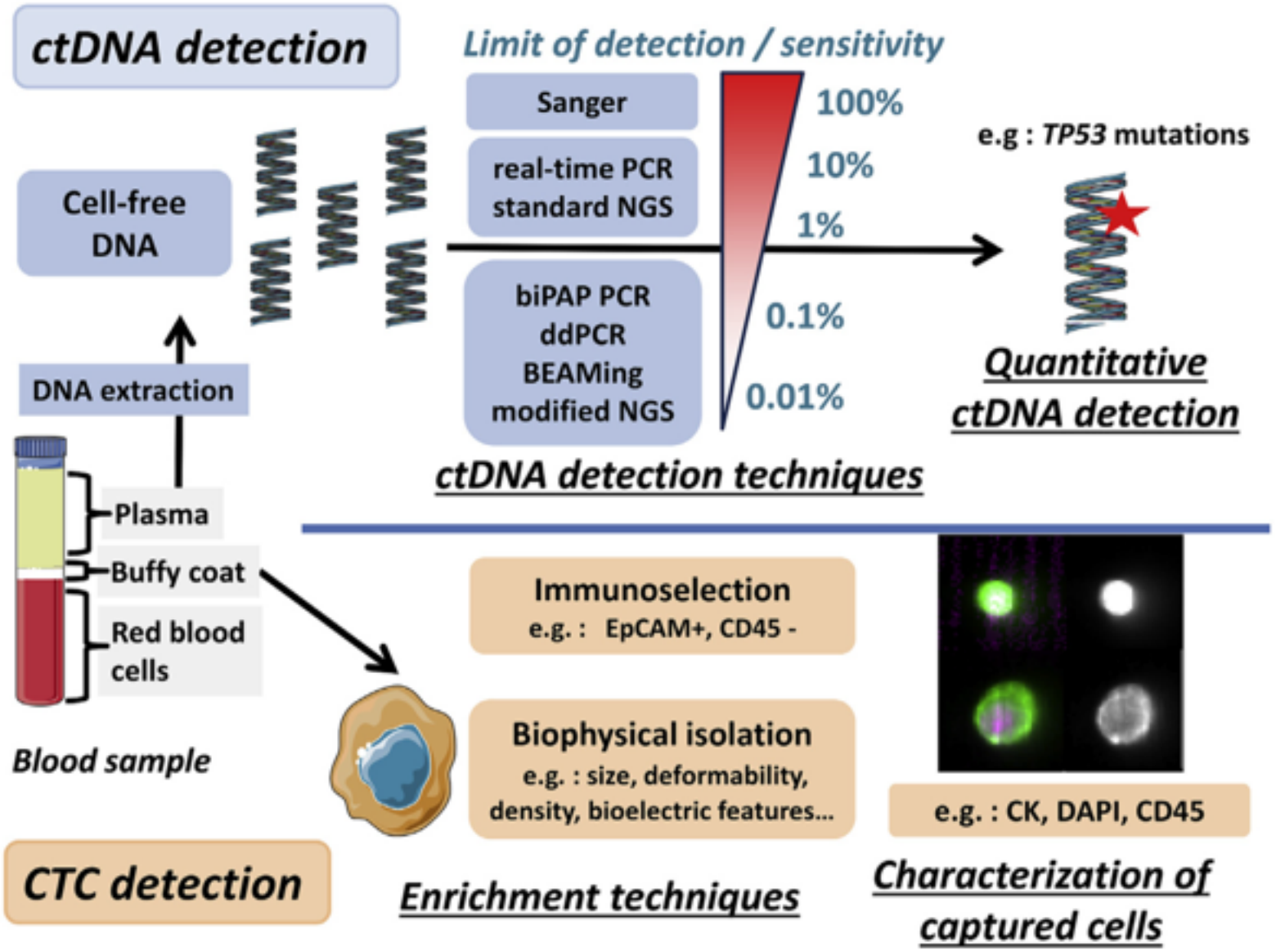
SiRIC Institut Curie Site de Recherche Intégrée sur le Cancer

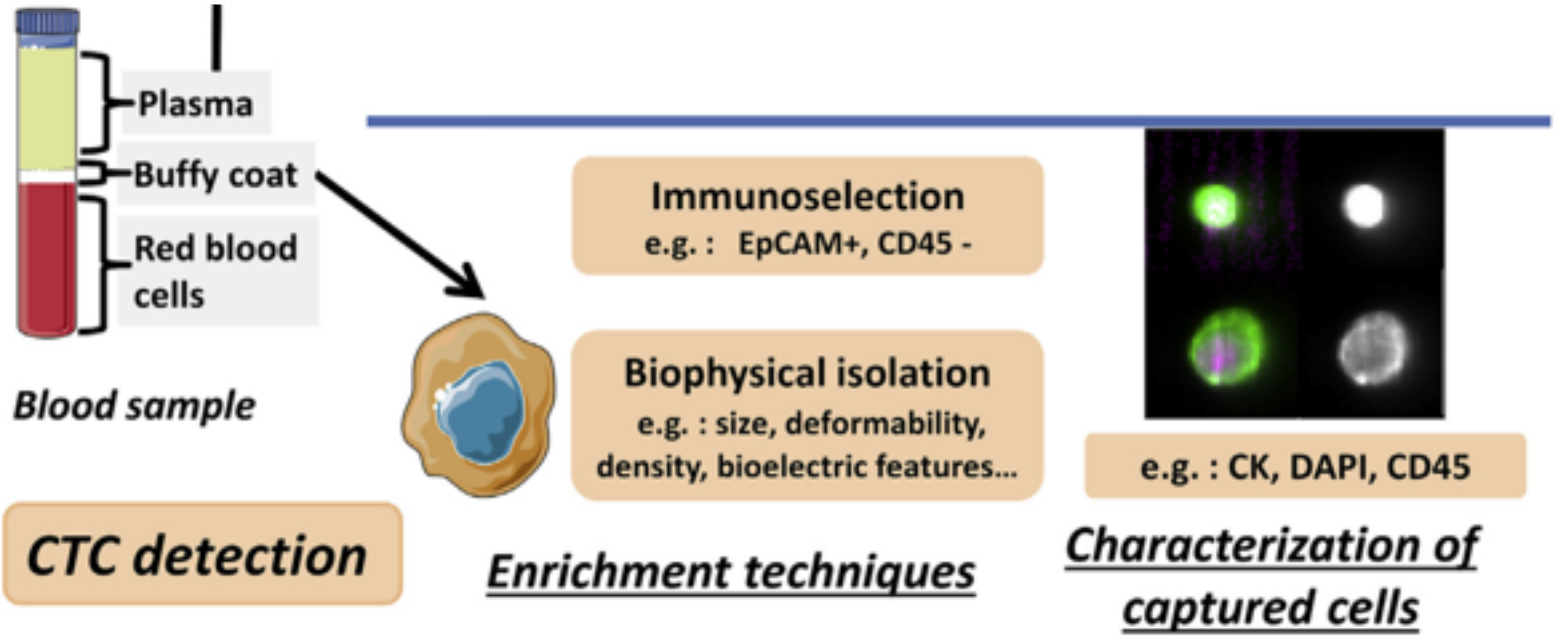
institutCurie

CTC and ctDNA detection



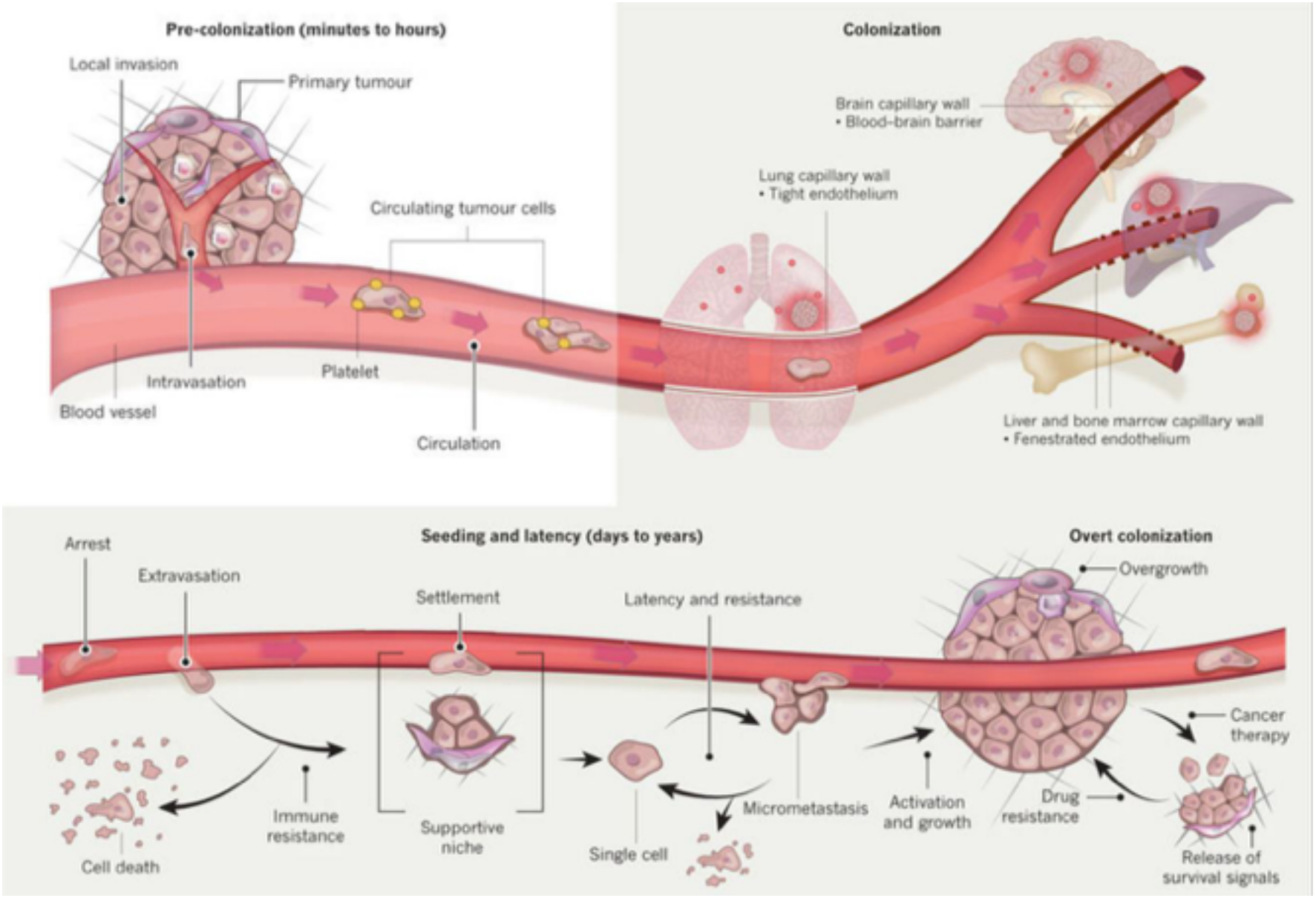
Cabel (…) Pierga, Bidard, EJSO 2017

CTC and ctDNA detection



Cabel (…) Pierga, Bidard, EJSO 2017

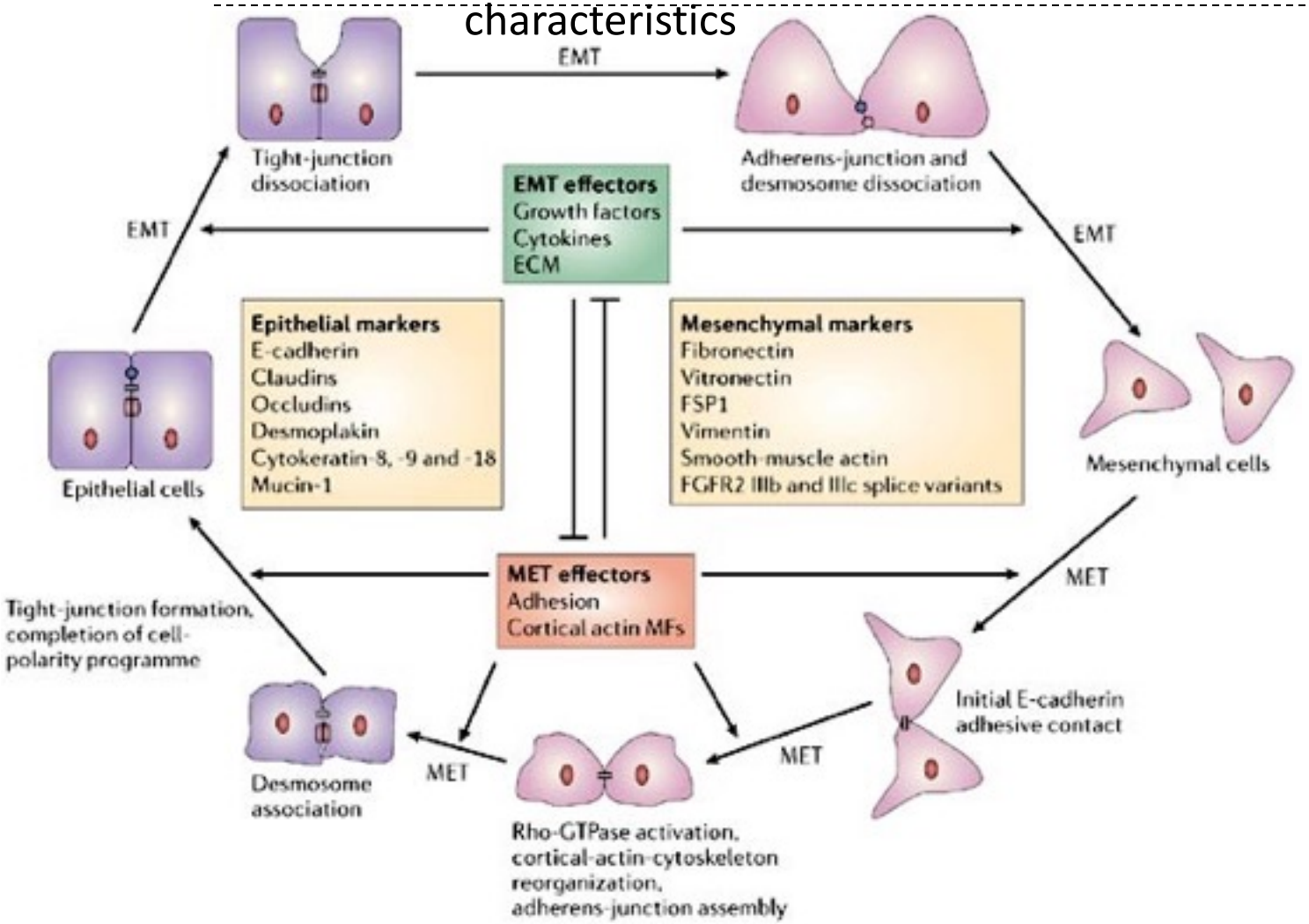
Metastatic process



Massague J. *et al.*, Nature, 2016

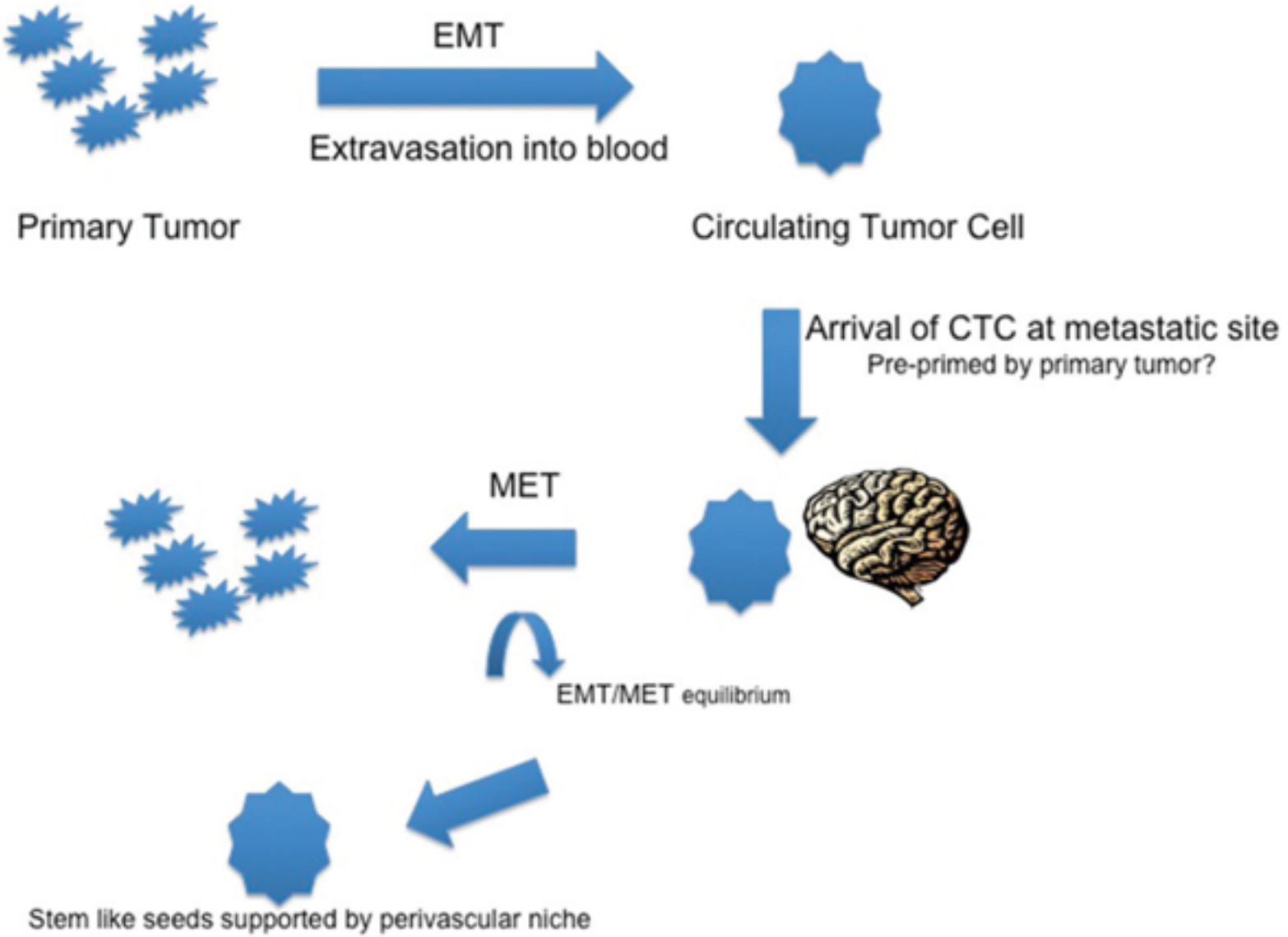
Epithelial-mesenchymal transition (EMT)

a process by which epithelial breast cancer cells acquire mesenchymal characteristics



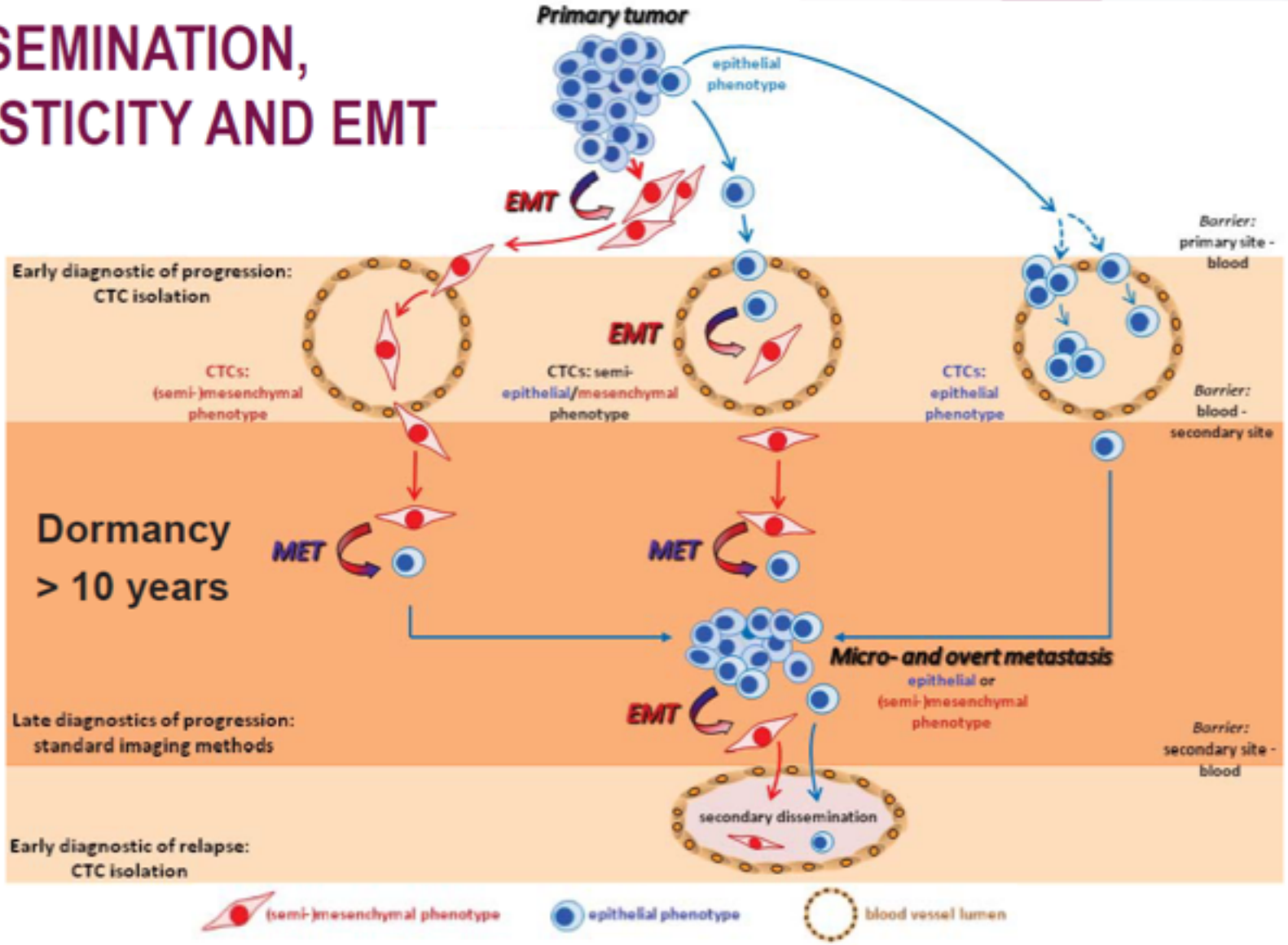
Thiery *et al. Nature Reviews Molecular Cell Biology* **7**, 131–142 (February 2006)

EMT/MET pathobiology of metastasis



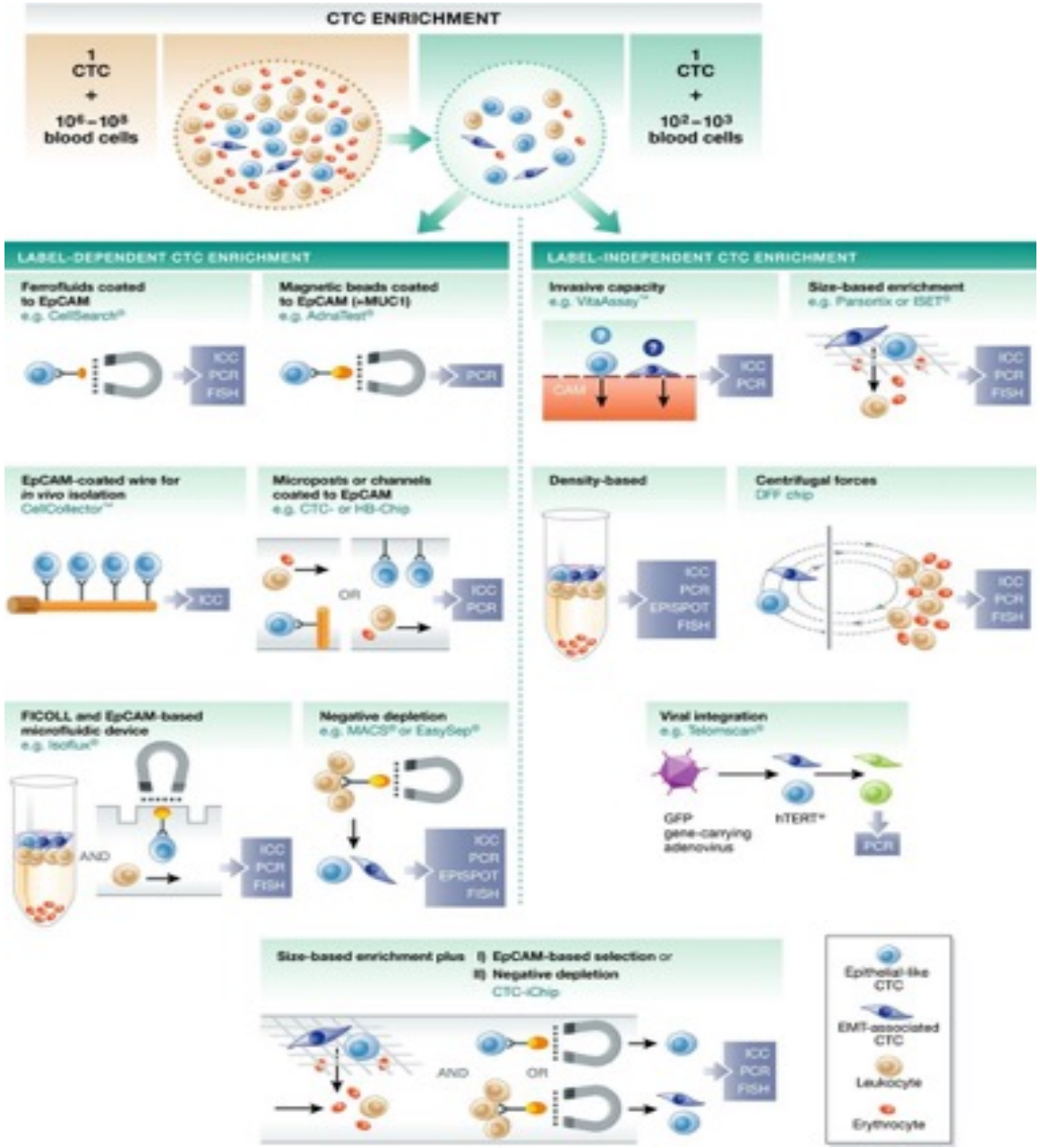
Ramakrishna R, Rostomily R. Seed, soil, and beyond: The basic biology of brain metastasis. Surg Neurol Int 2013;4:S256-64.

TUMOUR CELL DISSEMINATION, PLASTICITY AND EMT



Cancer Metastasis Rev, Plasticity of disseminating cancer cells in patients with epithelial malignancies, 2012; 31: 673–87. Bednarz-Knoll N, *et al.* © Springer Science+Business Media, LLC 2012. With permission of Springer; Kang Y & Pantel K, Cancer Cell 2013;23:573–81; Joosse SA, *et al.*, Individual cytokeratins can be downregulated and pan-cytokeratin antibody cocktail increases therefore the sensitivity of CTC assays. Clin. Cancer Res. 2012;18:993–1003; Yokobor T, *et al.*, Plastin-3 as new CTC marker not downregulated during EMT. Cancer Res 2013; 73:2059—69

CTC detection techniques

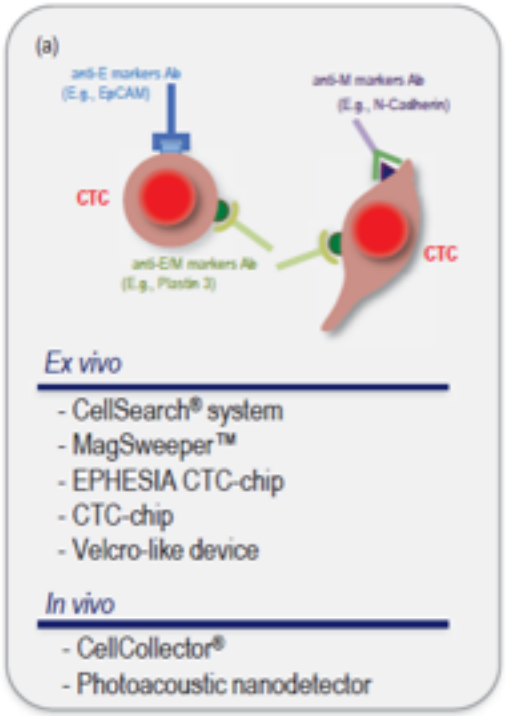


Simon A Joosse et al. EMBO Mol Med. 2015;7:1-11

CTC ENRICHMENT STRATEGIES

Biological properties
Protein expression

Positive selection



Ex vivo

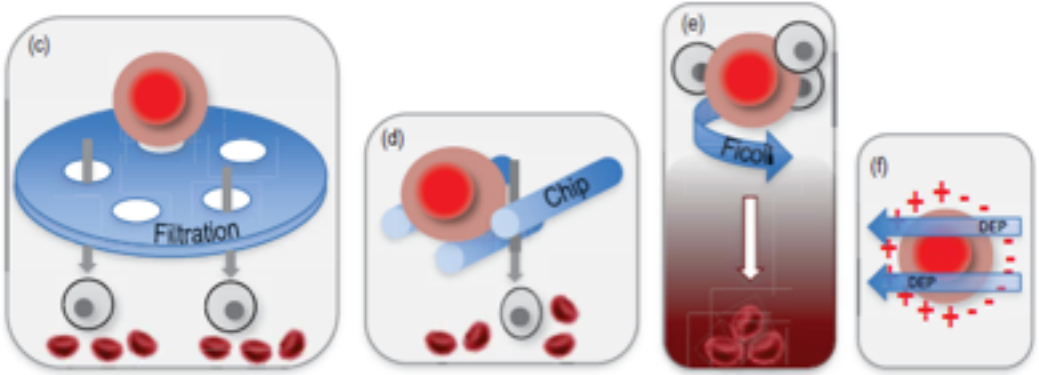
- CellSearch® system
- MagSweeper™
- EPHESIA CTC-chip
- CTC-chip
- Velcro-like device

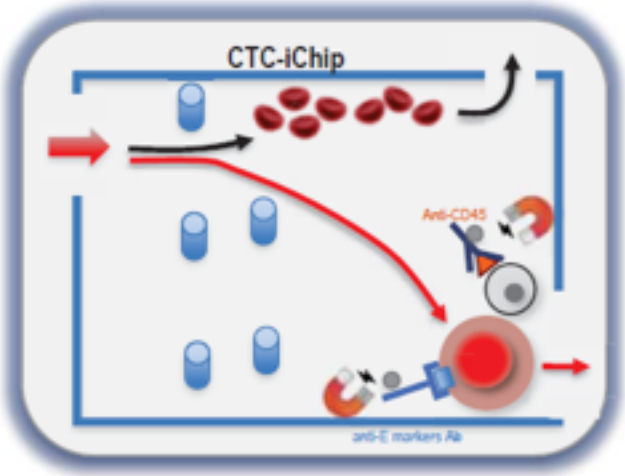
In vivo

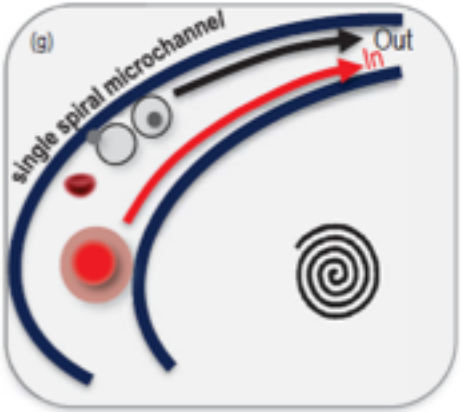
- CellCollector®
- Photoacoustic nanodetector

Negative selection

Physical properties
Label-free strategies





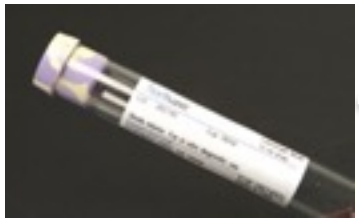


Alix-Panabieres C & Pantel K, Nature Rev.Cancer 2014;14:623–31
Images courtesy of Universitätsklinikum Hamburg Eppendorf

Circulating Tumor Cells Detection

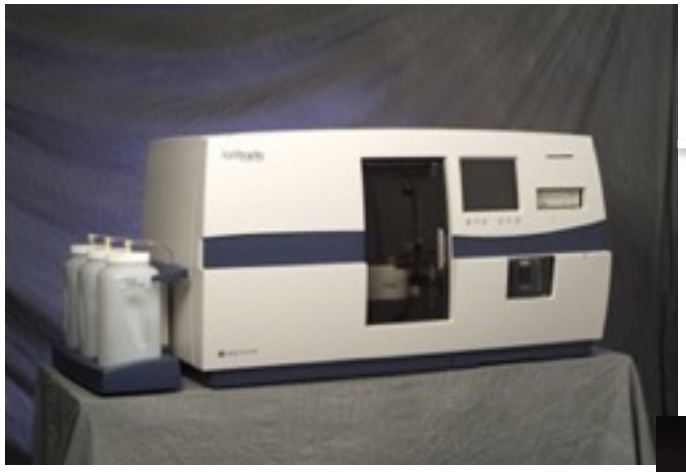
CellSearch™ System

cellsave Preservative Tube

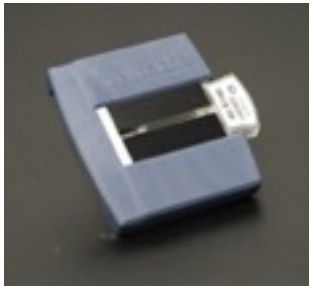


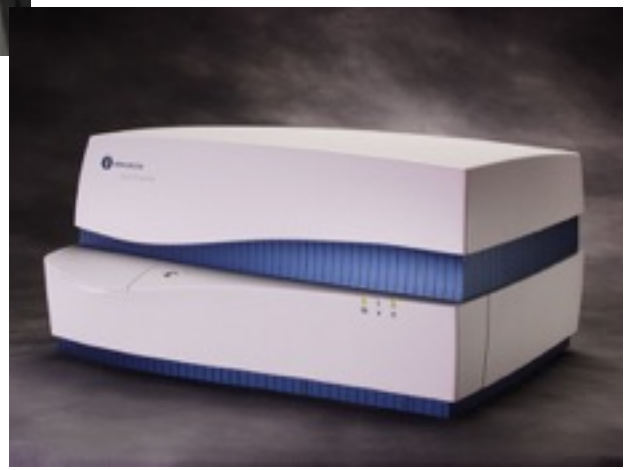
CellSearch™ Epithelial Cell

celltracks™ autoprep system



MagNest™



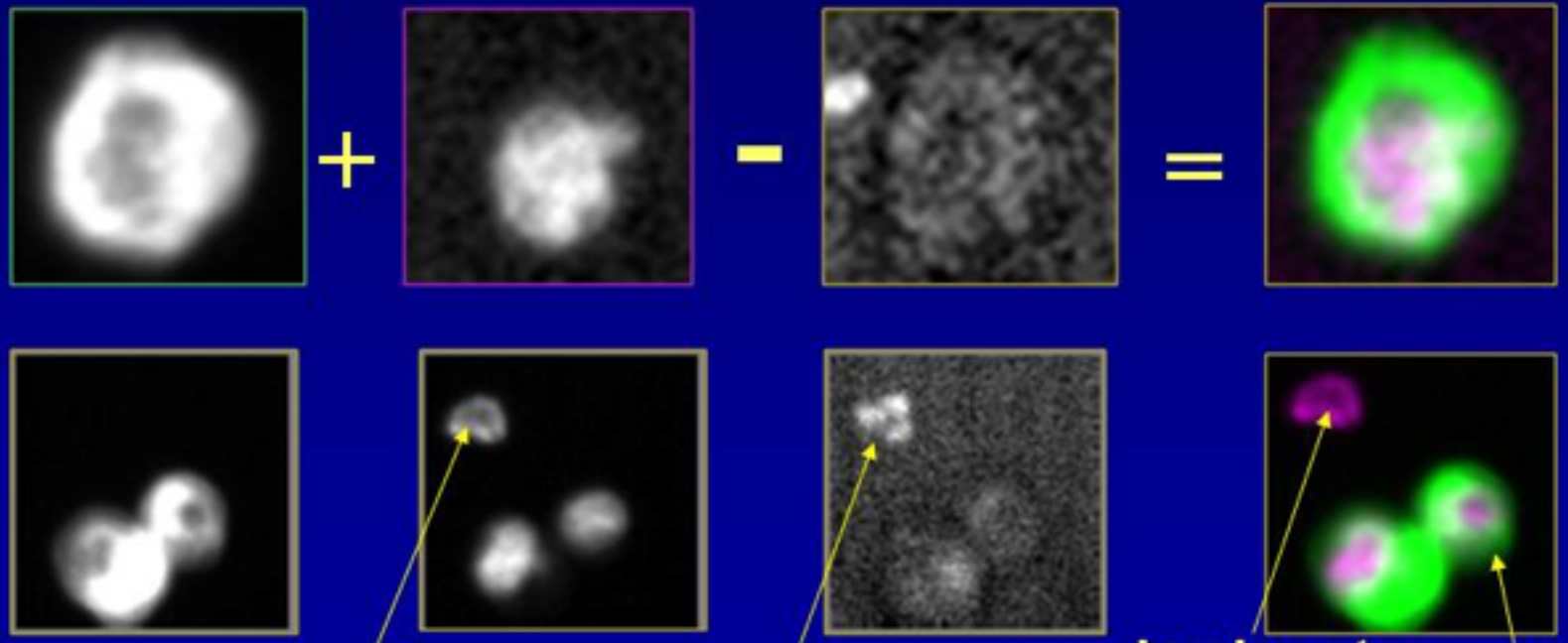


+ 3 channel capability

CellSearch™ System: Images of Tumor Cells

Cytoplasm Nucleus Cell Membrane Composite

CK-PE pos		DAPI pos		CD45-APC neg		Tumor Cell



EpCAM-based assays for epithelial tumor cell detection in cerebrospinal fluid

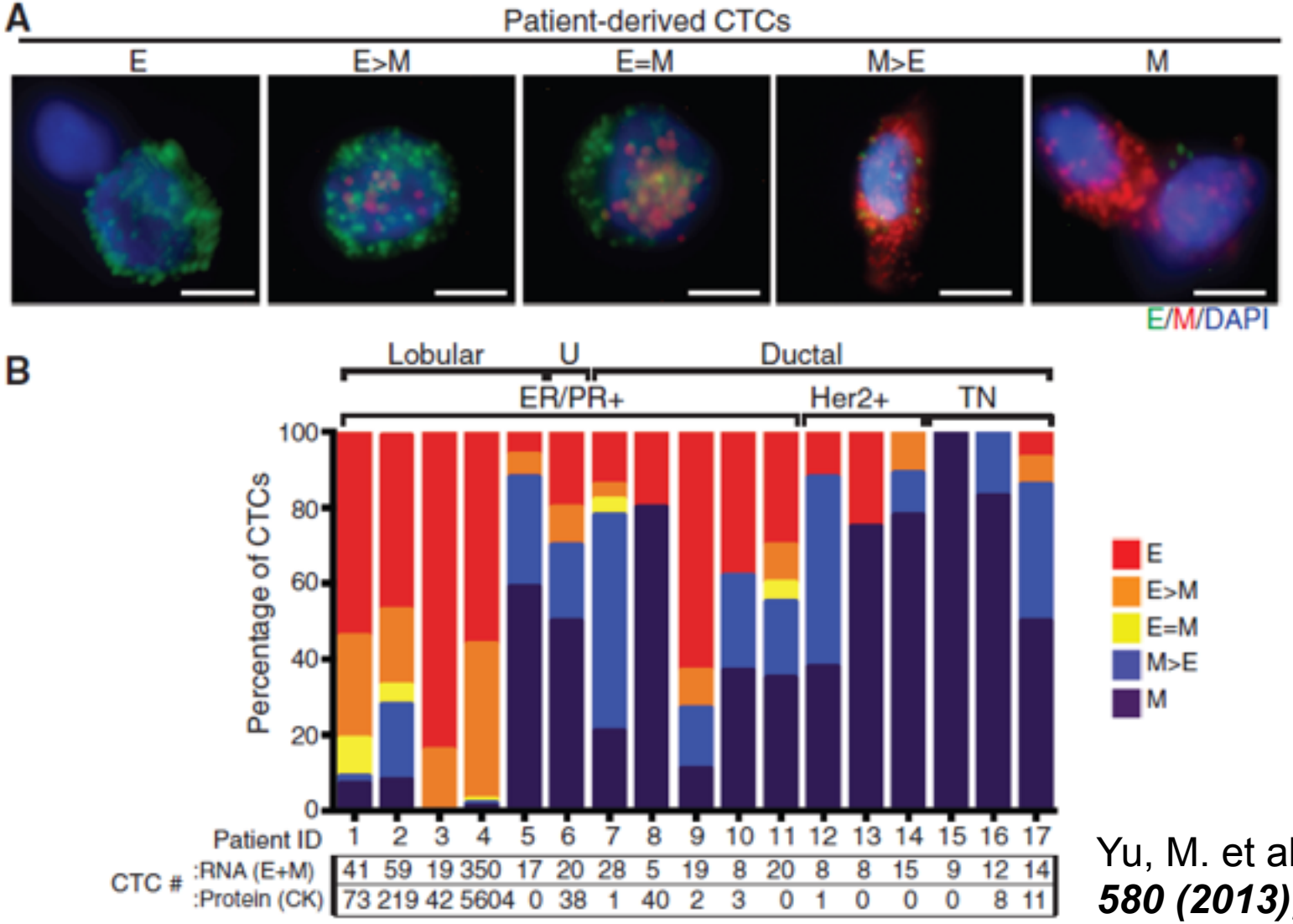
Table 2 Overview CELLSEARCH® and flow cytometry studies in CSF with reported sensitivity and specificity versus cytology

Study	Assay	N	Patient population	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI) cytology	Specificity (95% CI) cytology
Tu et al. [4]	C	18	MRI confirmed LM/lung cancer	77.8 (52.4–93.6)	100 (47.8–100)	44.4 (21.5–69.2)	Not reported
Lee et al. [5]	C	38	Confirmed LM/ suspected LM/ breast cancer	80.95 (58.1–94.4)	84.62 (54.5–97.6)	66.67 (43.04–85.35)	Used as gold standard 100%
Nayak et al. [6]	C	51	Clinical suspicion of LM/solid tumors (mainly NSCLC and breast cancer)	100 (78.1–100)	97.2 (85.4–99.9)	66.7 (38.3–88.1)	Used as gold standard
Jiang et al. [7]	C	21	NSCLC patients with suspected LM	95.2 (NA)	100 (NA)	57.1 (NA)	Not reported
Acosta et al. [26]	FC	6[a]	Clinical suspicion of LM previous diagnosed carcinoma	100% (NA)	100% (NA)	Not reported	Not reported
Milojkovic Kerklaan et al. [8]	FC	29	Clinical suspicion of LM but a negative or inconclusive MRI, previously diagnosed carcinoma	100 (75–100)	100 (79–100)	61.5 (32–86)	100 (79–100)
Subirá et al.[b] [10]	FC	144	Confirmed LM or clinically suspected LM	79.8 (NA)	84 (NA)	50 (NA)	100 (NA)
Subirá et al.[b] [9]	FC	78	Clinically suspected LM and previous diagnosis of epithelial-cell neoplasia	75.5 (63.5–87.6)	96.1 (88.8–100)	65.3 (52.0–78.6)	100 (100–100)

C CELLSEARCH®, *FC* flow cytometry, *95% CI* 95% confidence interval, *MRI* magnetic resonance imaging, *LM* leptomeningeal metastases, *NA* not available

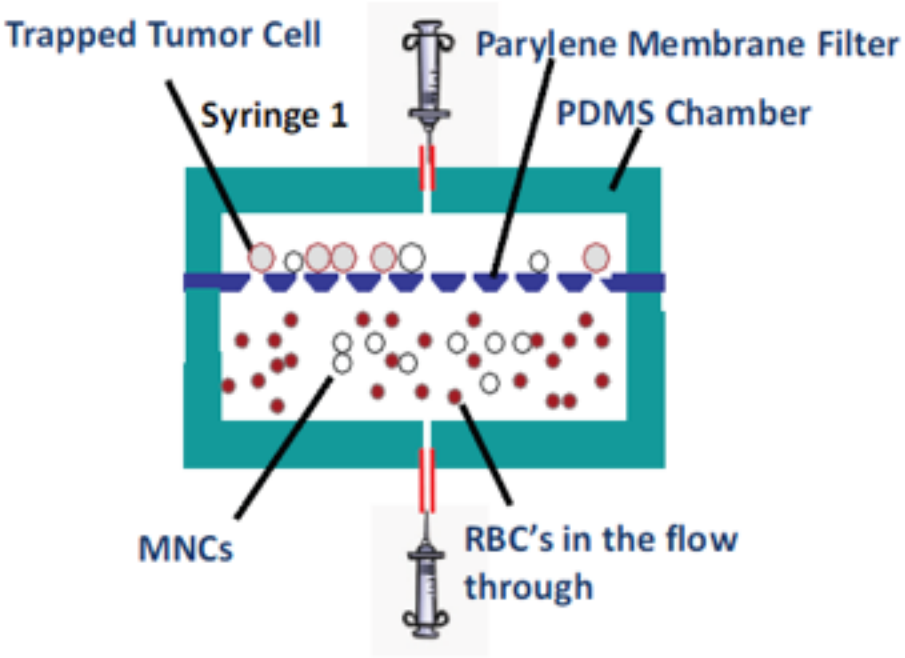
Mark T. J. van Bussel, Journal of Neuro-Oncology (2018) 137:1–10

Circulating Breast Tumor Cells Exhibit Dynamic Changes in Epithelial and Mesenchymal Compositio

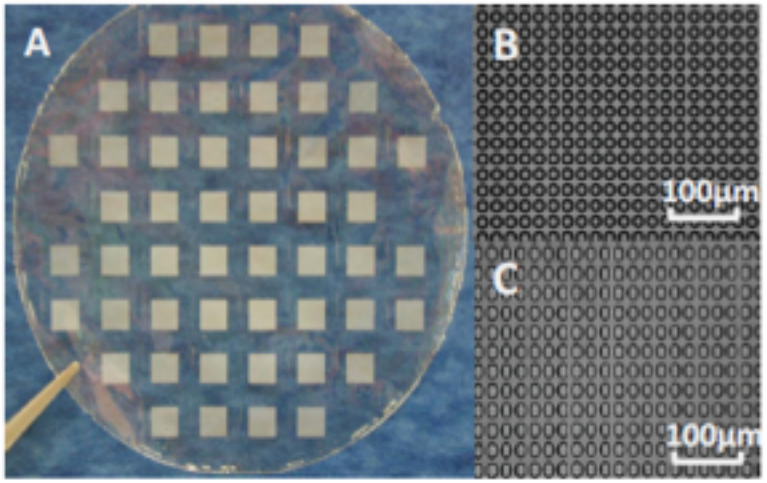


Yu, M. et al *Science* ***339, 580 (2013);***

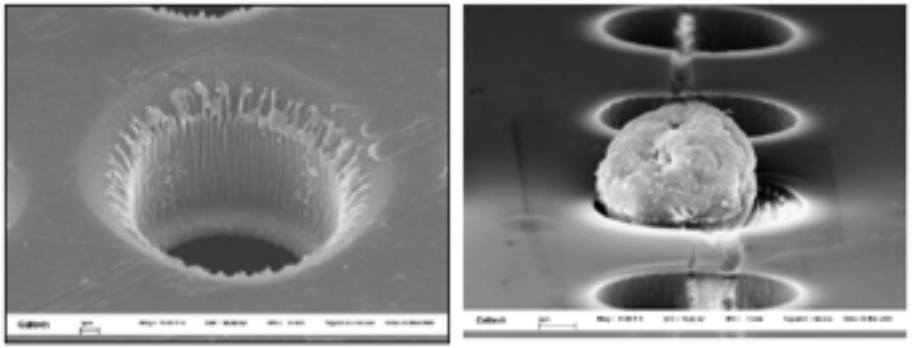
Microfluidics Based Cell Separation



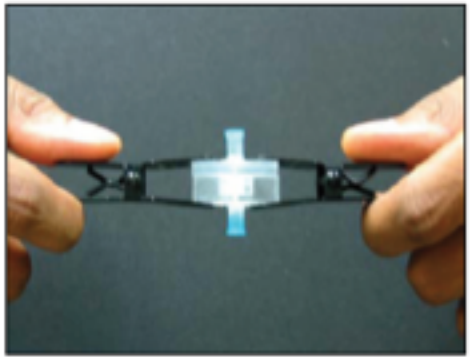
Parylene Filter Membrane



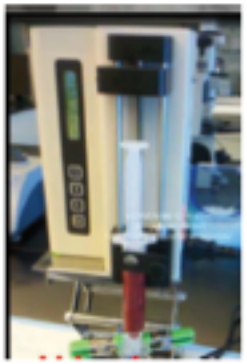
SEM of Cell Captured on filter



Assembled Filter Device

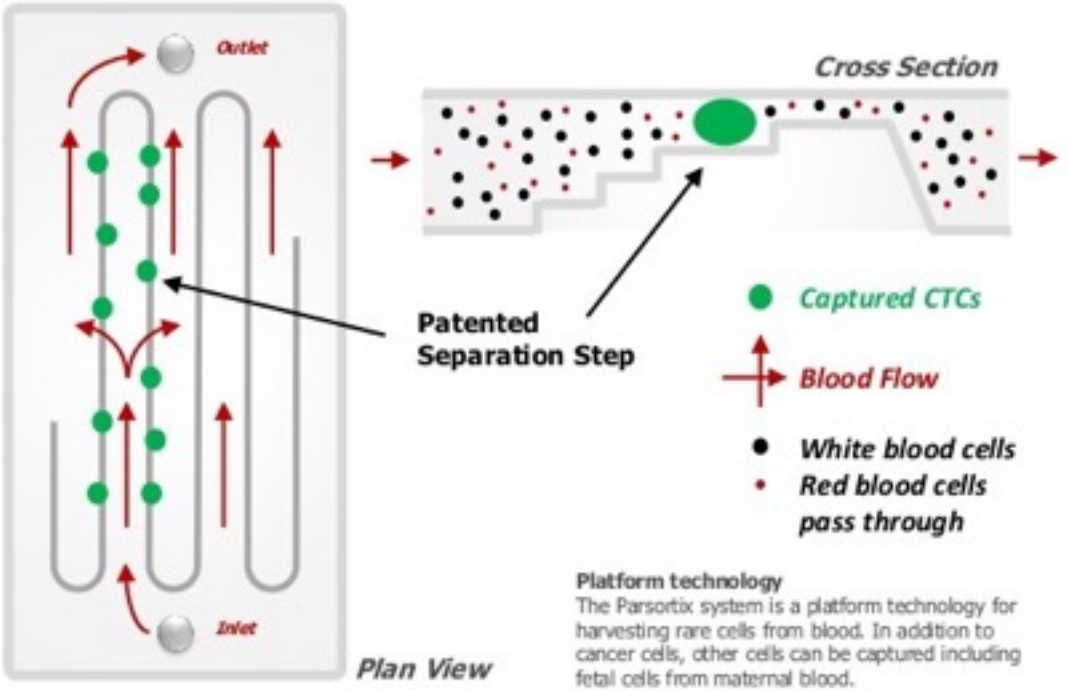


Automated Flow Device



R.Cote

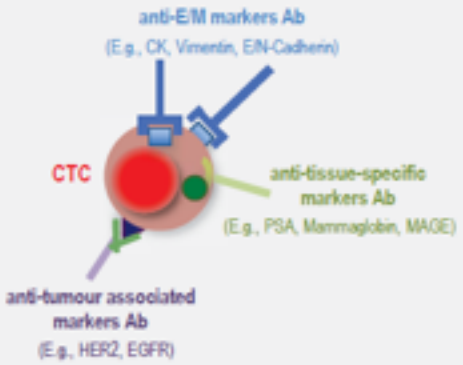
ANGLE's Parsortix system for capturing cancer cells



Platform technology
The Parsortix system is a platform technology for harvesting rare cells from blood. In addition to cancer cells, other cells can be captured including fetal cells from maternal blood.

APPROACHES FOR CTC DETECTION

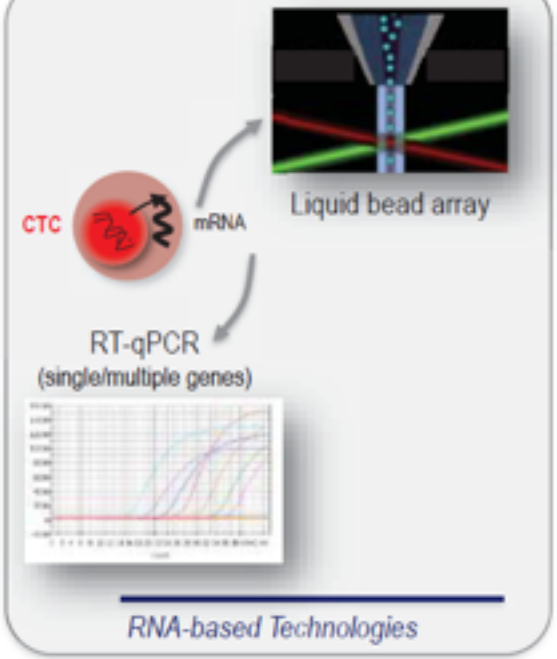
Immunocytological technologies



Technologies

- Immunocytochemistry
- CellSearch® system
- Flow Cytometry
- DEParray®

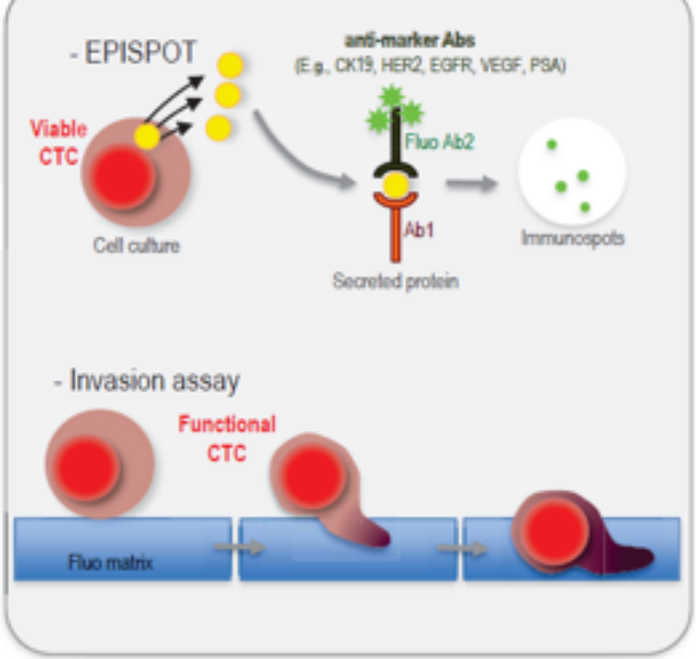
Molecular technologies



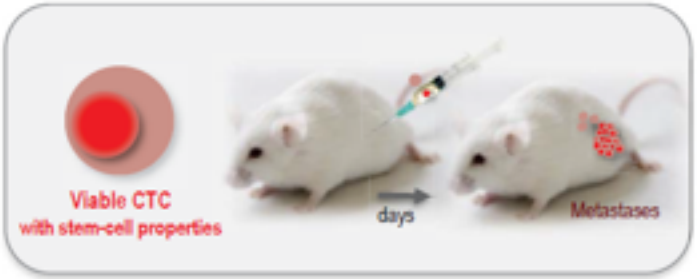
RNA-based Technologies

Functional assays

In vitro Cell Culture

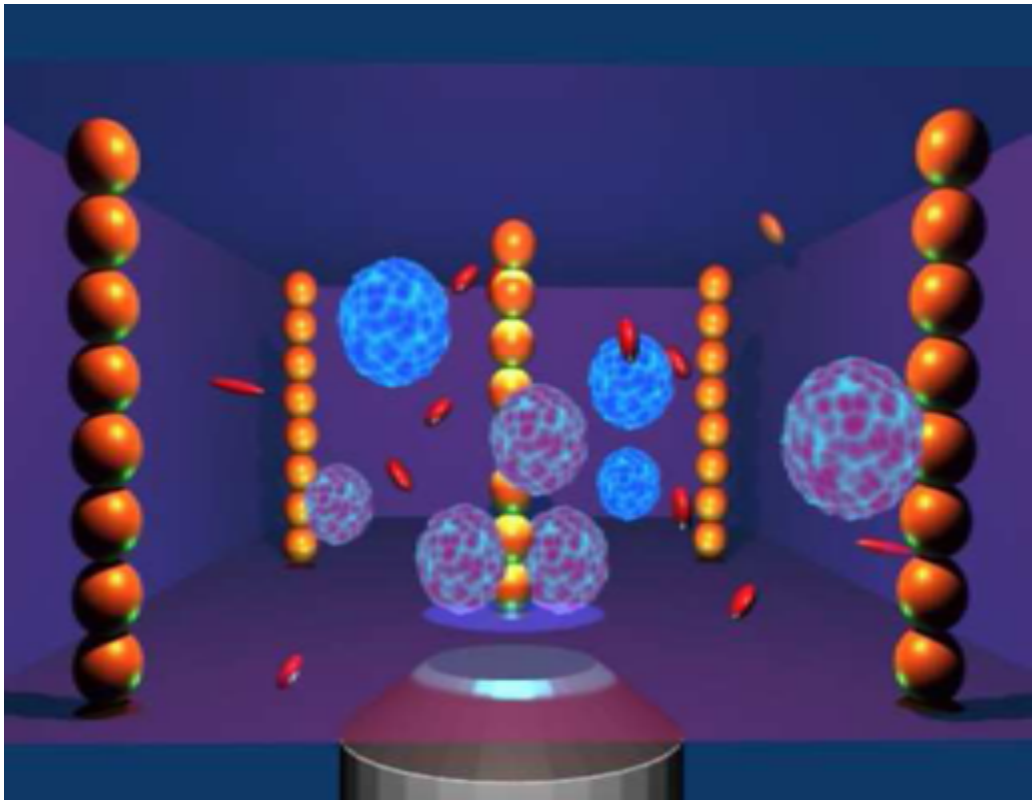


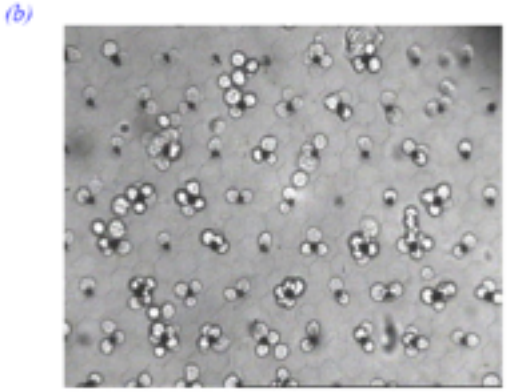
Xenotransplantation models (CDx)

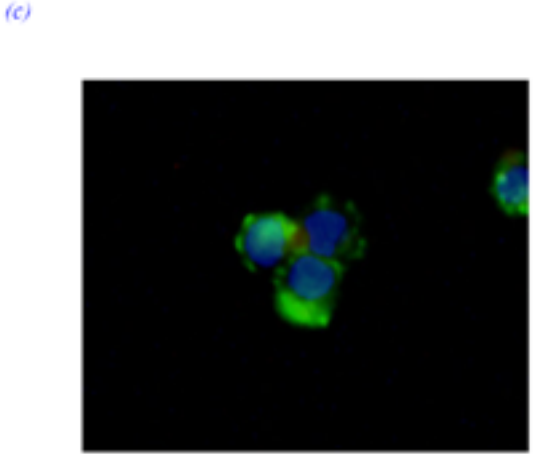


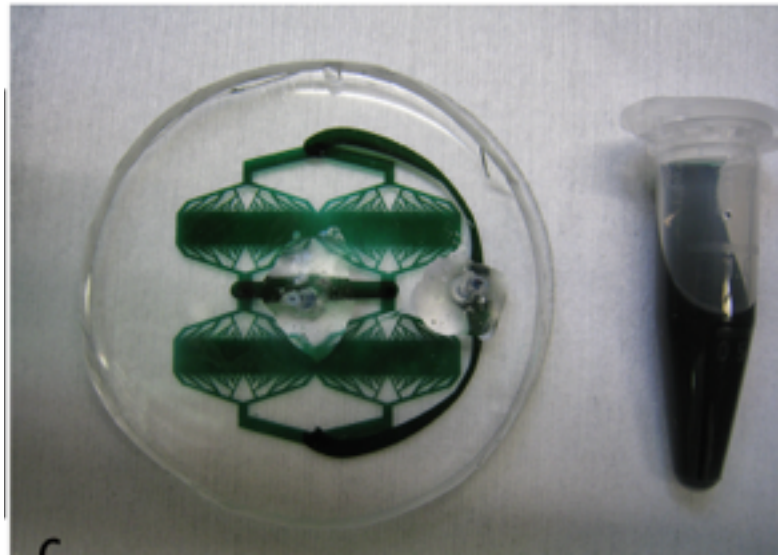
Alix-Panabieres C & Pantel K,.Nature Rev.Cancer 2014;14:623–31
Images courtesy of Universitätsklinikum Hamburg Eppendorf

MICROFLUIDIC EPHESIA







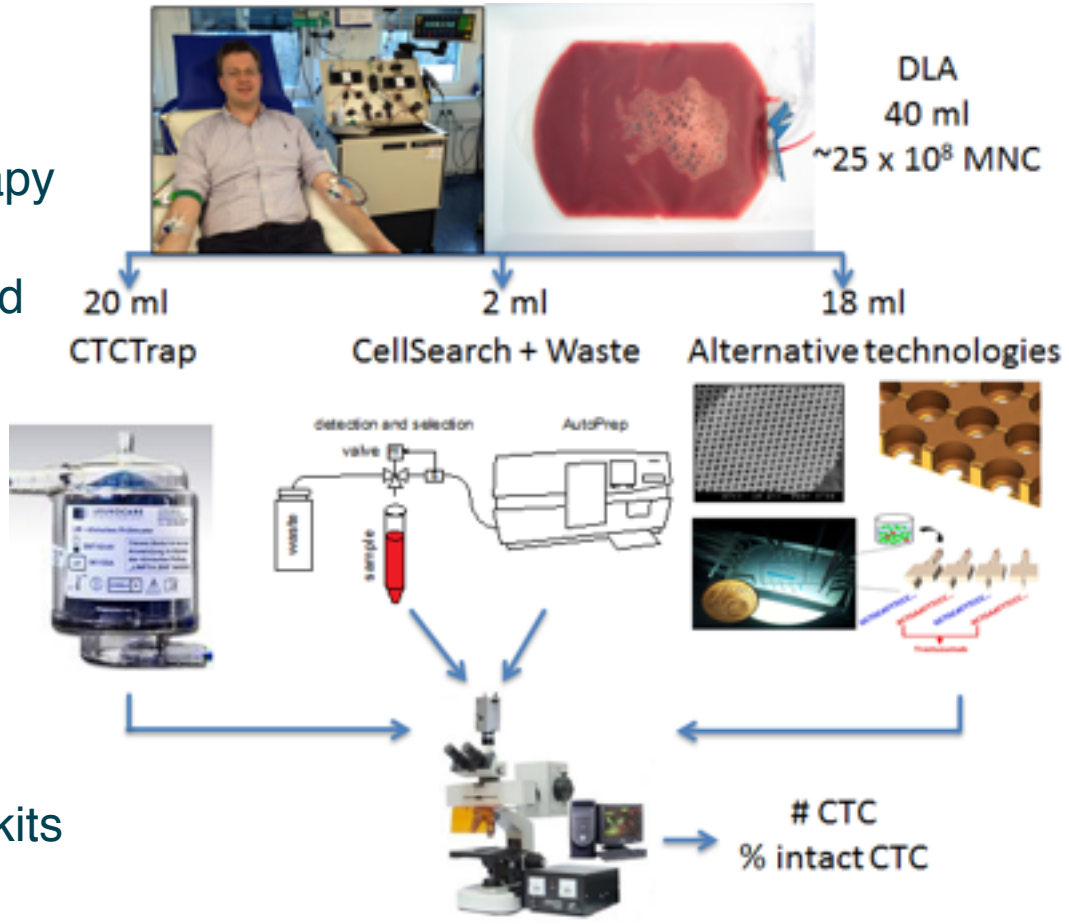


Saliba AE, L Saias, JL Viovy PNAS 2010
Laboratoire Physicochimie Curie, CNRS UMR 168
Autebert J Methods 2012

DLA as a Method for Expansion of Analysed Blood Volume

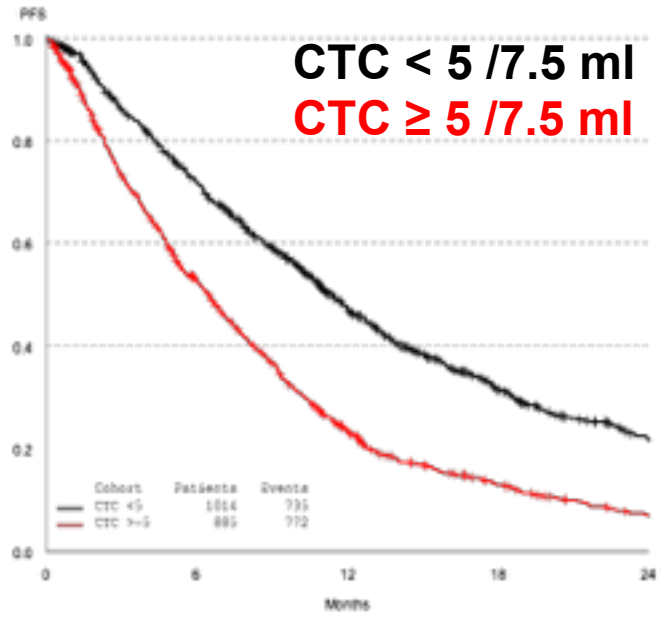
Diagnostic Leukapheresis (DLA):

- Safe, FDA approved procedure established in context of immunotherapy for prostate cancer
- Equivalent of 2.8 L of peripheral blood used for MNC enrichment, even 2-4x total blood volumes safe in solid tumor patients
- Well tolerated by patients
- Ethical approval at UDUS
- Enables liquid biopsy in patients with too few CTCs for analysis
- Costs reduced compared to use of a corresponding number of CellSearch kits



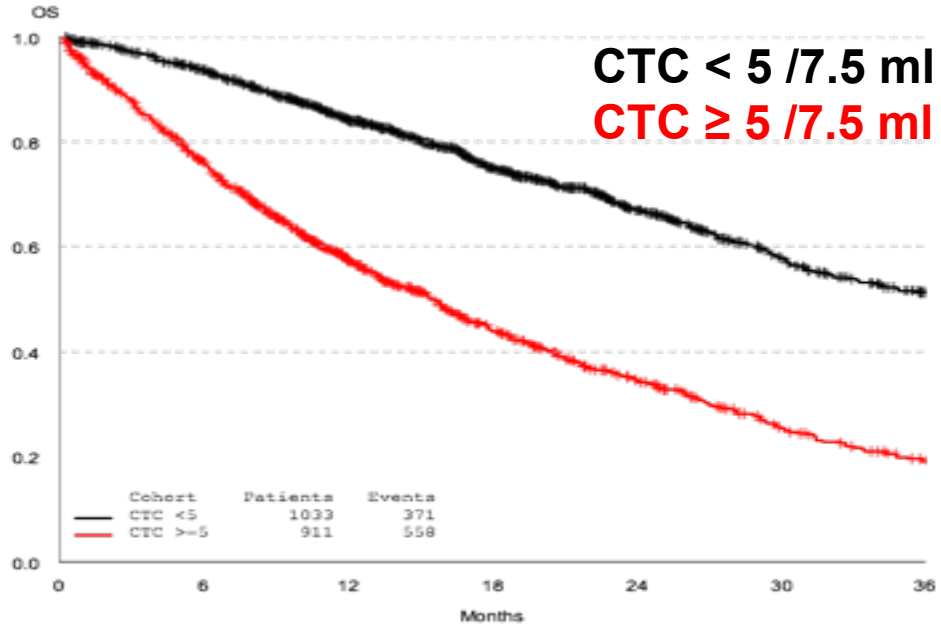
Clinical validity of circulating tumour cells in patients with metastatic breast cancer: a pooled analysis of individual patient data

Results - baseline



Progression-Free Survival

N= 1,899 patients
HR = 1.92
p<0.0001



Overall Survival

N= 1,944 patients
HR = 2.77
p<0.0001

Bidard FC, (…) Pantel K, Pierga JY, Michiels S.Lancet Oncol. 2014 Apr;15(4):406-14.

Essai LANDSCAPE - Bachelot et al, *Lancet Oncol 2012*

Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group phase 2 study

Thomas Bachelot, Gilles Romieu, Mario Campone, Véronique Diéras, Claire Cropet, Florence Dalenc, Marta Jimenez, Emilie Le Rhun, Jean-Yves Pierga, Anthony Gonçalves, Marianne Leheurteur, Julien Domont, Maya Gutierrez, Hervé Curé, Jean-Marc Ferrero, Catherine Labbe-Devilliers

Key Inclusion Criteria

- HER2+ MBC
- Newly diagnosed brain metastases, at least 1 cm in diameter (T1 gado. MRI)
- Not candidate for brain surgery or SRS
- Any previous treatment except WBR, lapatinib or capecitabine
- ECOG PS status 0-2

Treatment:

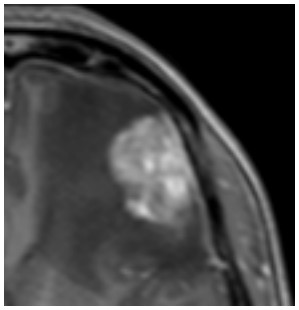
L: 1,250 mg/d, PO, continuous **C: 2,000 mg/m²/d, PO, d1–14 q3weeks**

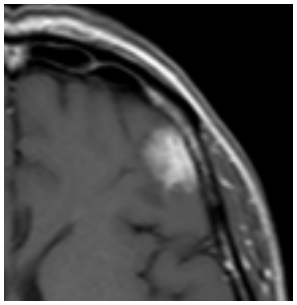
Primary endpoint:
CNS volumetric response

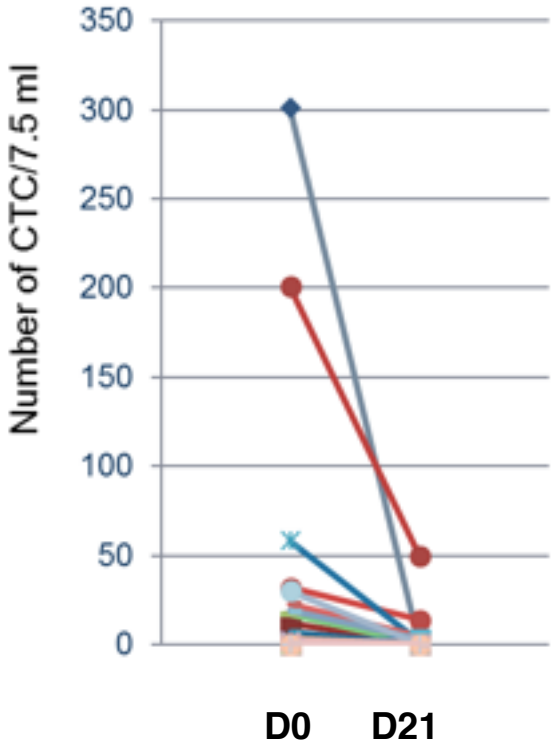
CNS Volumetric change	n = 44	%
CNS objective response	**29**	**65% (95% CI: 50.1-79.5)**
≥ 80% Reduction	**9**	**20%**
50- <80% Reduction	**20**	**45%**
20- <50% Reduction	**6**	**14%**
> 0- <20% Reduction	**2**	**5%**
Progression*	**7**	**16%**

*2 patients had extra-CNS disease progression

LANDSCAPE: a Unicancer phase II study with lapatinib and capecitabine in patients with brain metastases from HER2-positive metastatic breast cancer before whole brain radiotherapy







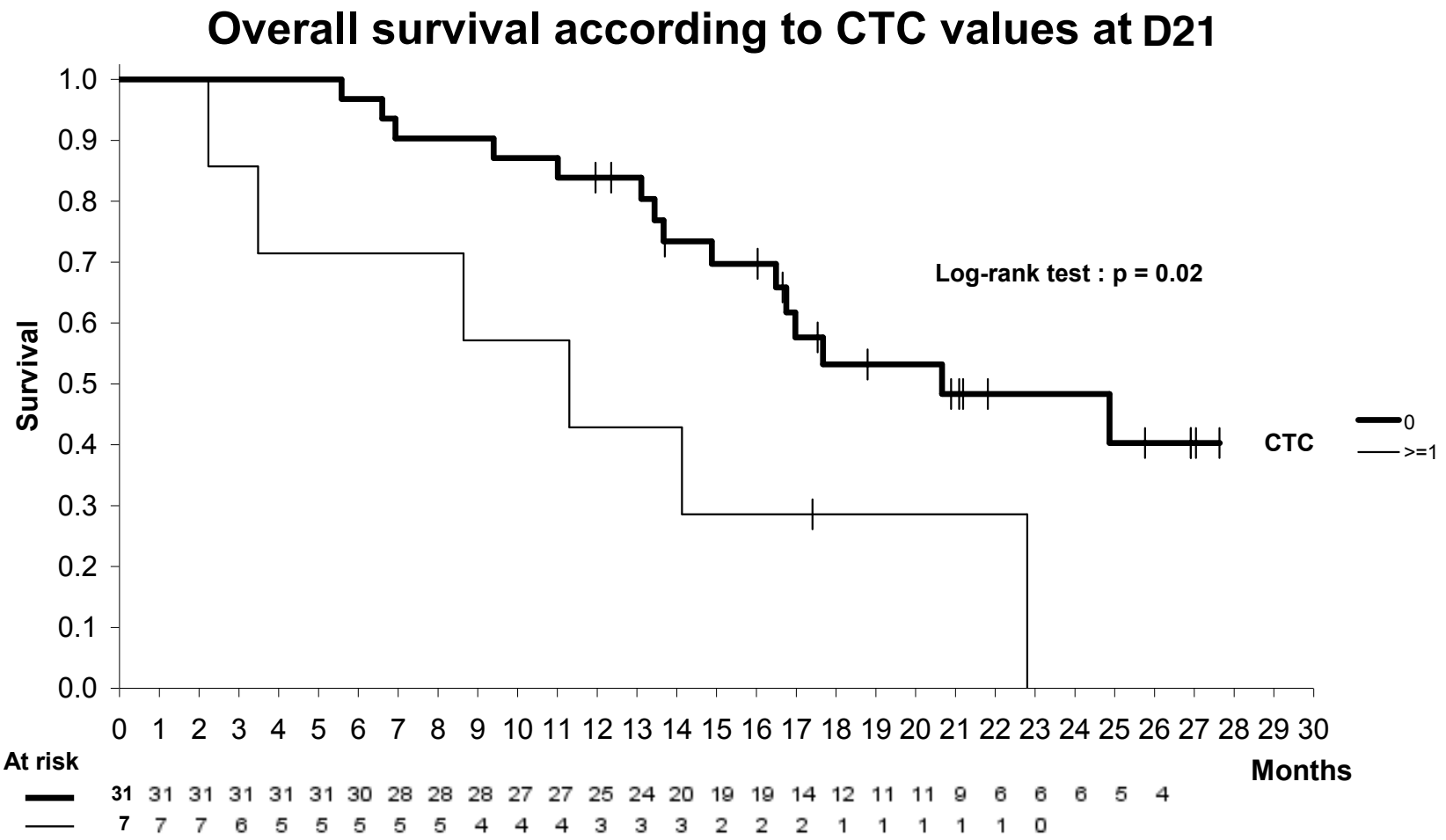
CTC/7.5ml at baseline and changes under treatment

Correlation with CNS-OR, (n=40)

Date of sampling	CTC Status	CNS-OR (%)	*p*
Baseline (n=41)	0 at baseline	(81)	*NS*
	≥ 1 at baseline	(57.9)	
Day 21 (n=38)	0 at day 21	(80.6)	*0.03*
	≥ 1 at day 21	(33.3)	

Pierga 2013 Ann Oncol

LANDSCAPE OS according to CTC at D21



Pierga 2013 Ann Oncol

Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group

(www.egappreviews.org/workingrp.htm)

- **Analytical performance**

  how accurately and reliably the test detects the analyte(s) of interest;

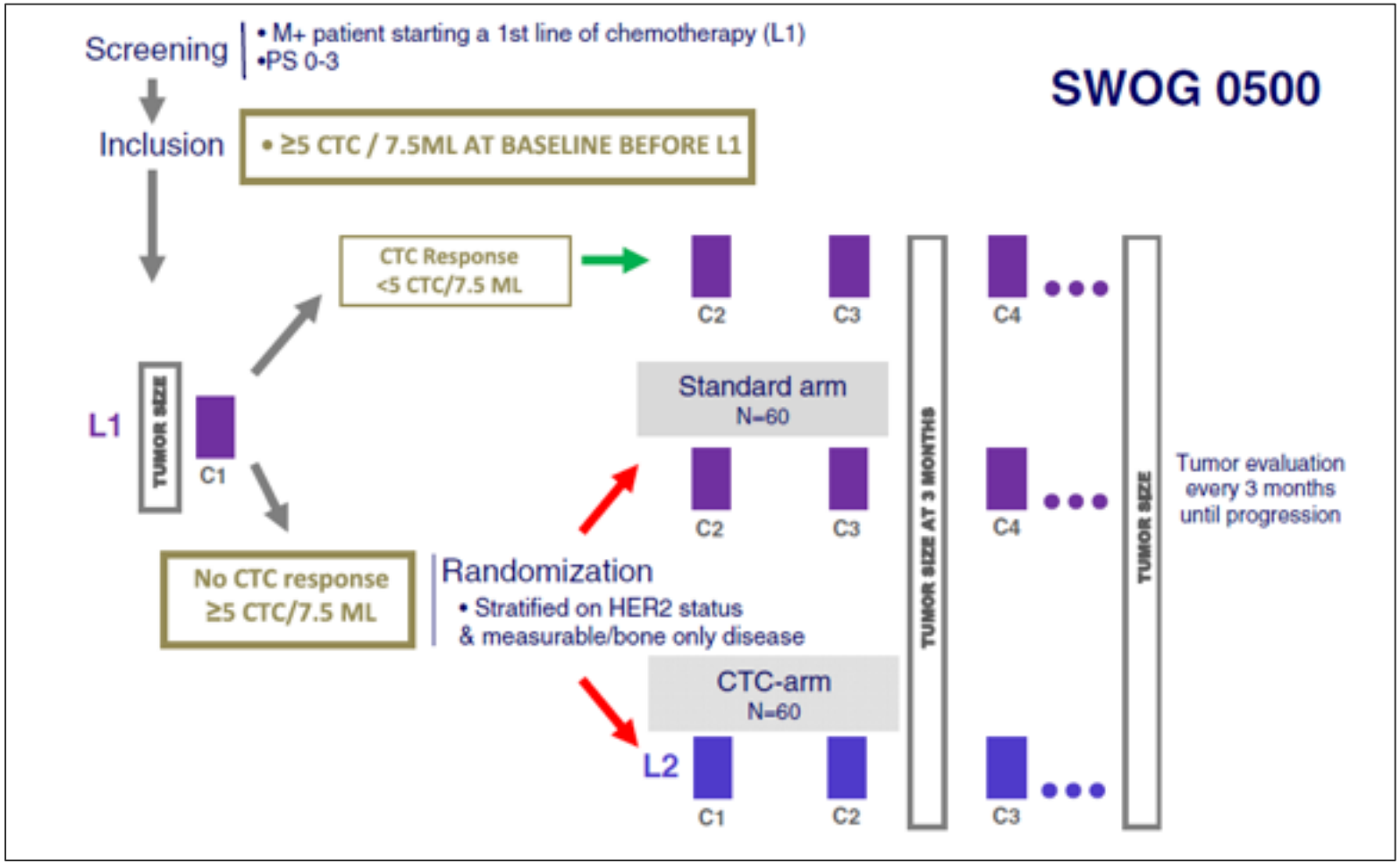
- **Clinical validity**

  how well the test relates to the clinical outcome of interest
  (such as survival or response to therapy);

- **Clinical utility**

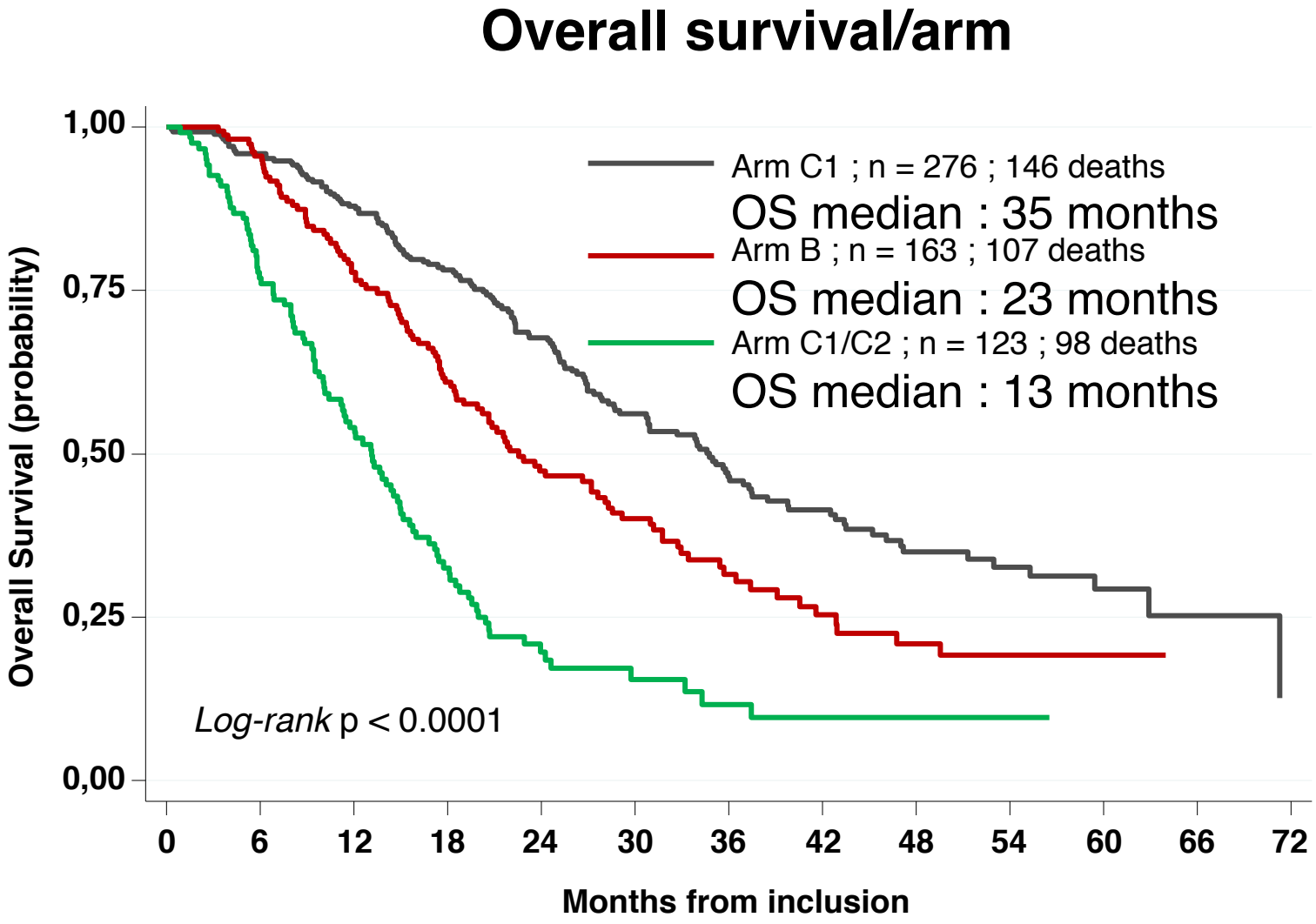
  Whether the results of the test provide information that contributes to and improves current optimal management of the patient's disease

The SWOG 0500 trial



reviewed in Bidard, Cancer Met Rev 2013

SWOG S0500 *Study*



Smerage JB et al., J Clin Oncol 2014

The SWOG 0500 trial

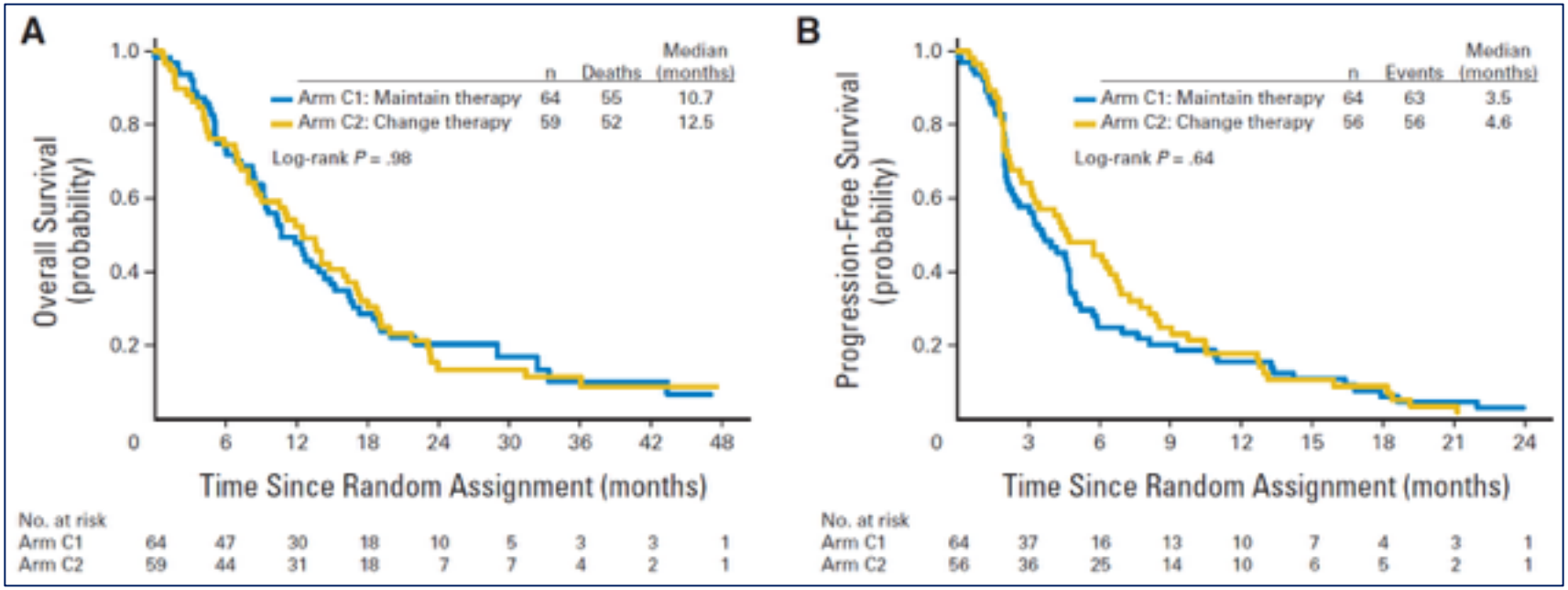
VOLUME 32 · NUMBER 31 · NOVEMBER 1 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Circulating Tumor Cells and Response to Chemotherapy in Metastatic Breast Cancer: SWOG S0500

Jeffrey B. Smerage, William E. Barlow, Gabriel N. Hortobagyi, Eric P. Winer, Brian Leyland-Jones, Gordan Srkalovic, Sheela Tejwani, Anne F. Schott, Mark A. O'Rourke, Danika L. Lew, Gerald V. Doyle, Julie R. Gralow, Robert B. Livingston, and Daniel F. Hayes



VOLUME 33 · NUMBER 24 · AUGUST 20 2015

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

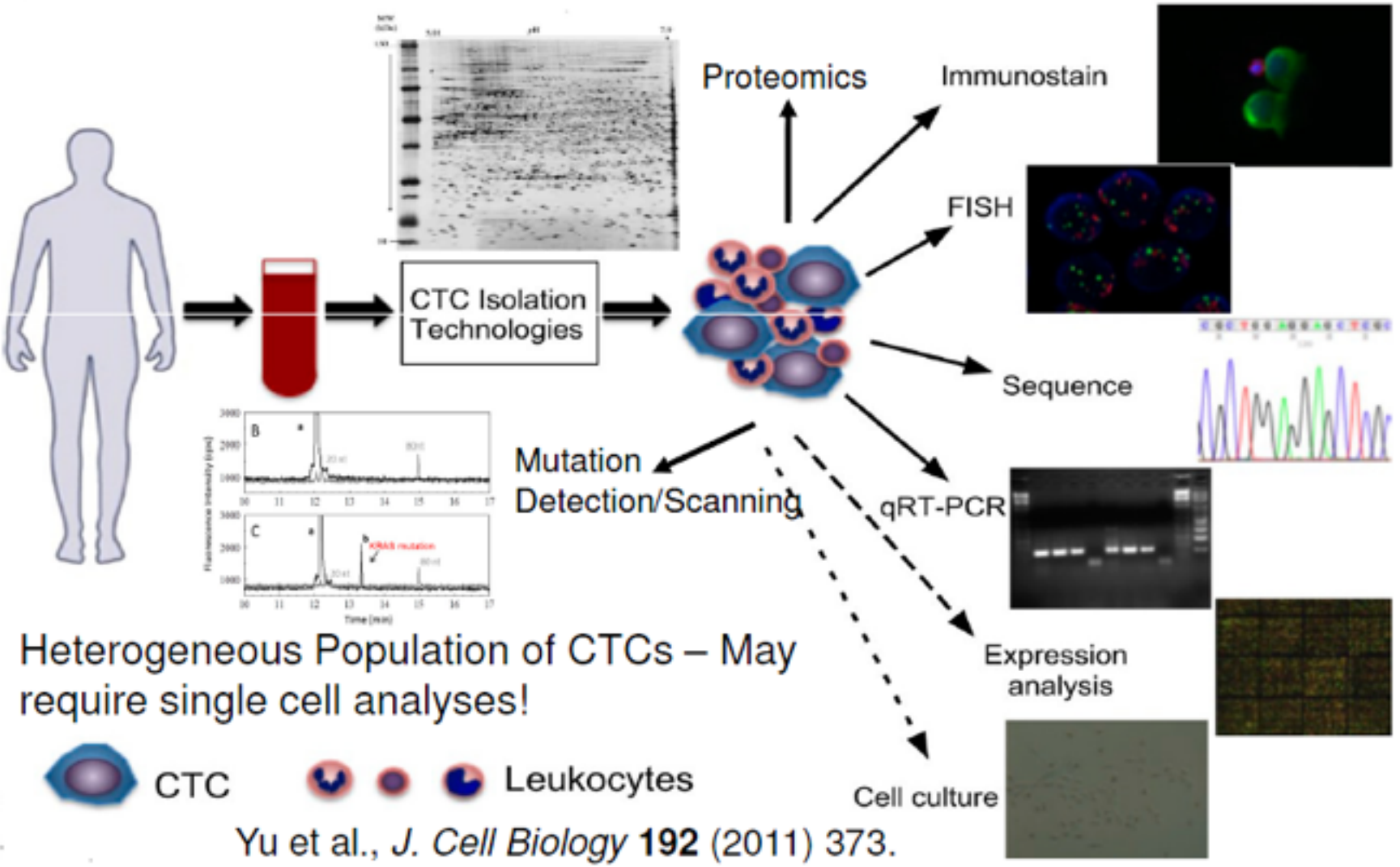
Use of Biomarkers to Guide Decisions on Systemic Therapy for Women With Metastatic Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline

Catherine Van Poznak, Mark R. Somerfield, Robert C. Bast, Massimo Cristofanilli, Matthew P. Goetz, Ana M. Gonzalez-Angulo, David G. Hicks, Elizabeth G. Hill, Minetta C. Liu, Wanda Lucas, Ingrid A. Mayer, Robert G. Mennel, William F. Symmans, Daniel F. Hayes, and Lyndsay N. Harris

Catherine Van Poznak and Daniel F. Hayes, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; Mark R. Somerfield, American Society of Clinical

- Data are insufficient to recommend use of CEA, CA 15-3, and CA 27-29 alone for monitoring response to treatment.
- The recommendation for use is based on clinical experience and Panel informal consensus in the absence of studies designed to evaluate the clinical utility of the markers.
- A number of studies have evaluated the role of CTCs in metastatic disease and have clearly shown that CTCs are associated with poor prognosis in this setting.
- However, none of the reviewed studies assessed predictive value using clinical utility guidelines, with one exception.

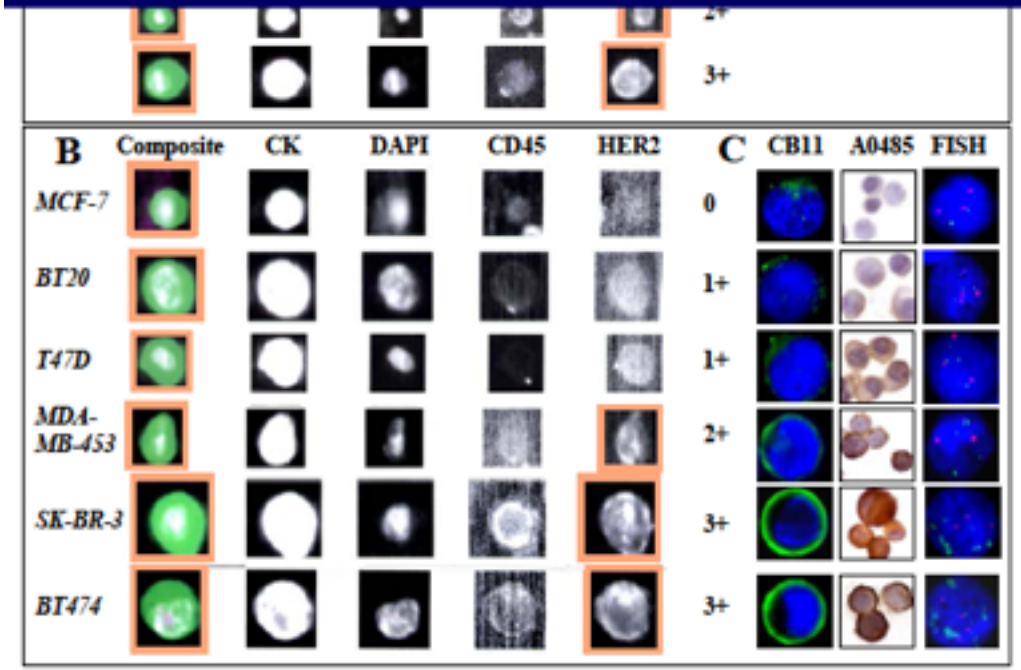
Dealing with Mass-Limited Samples – Don't Just Count, Analyze

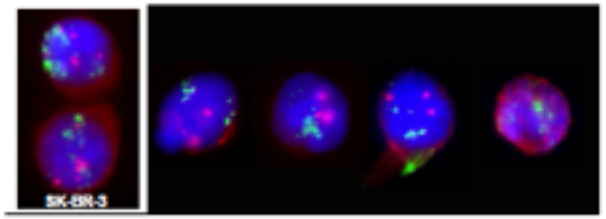


Yu et al., *J. Cell Biology* **192** (2011) 373.

Detection of therapeutic target molecules on CTC
Example: HER2 in breast cancer

Potential benefit from anti-HER2 therapy (e.g., trastuzumab) also in patients with „HER2-negative“ tumors (Paik *et al.*, NEJM 2008)





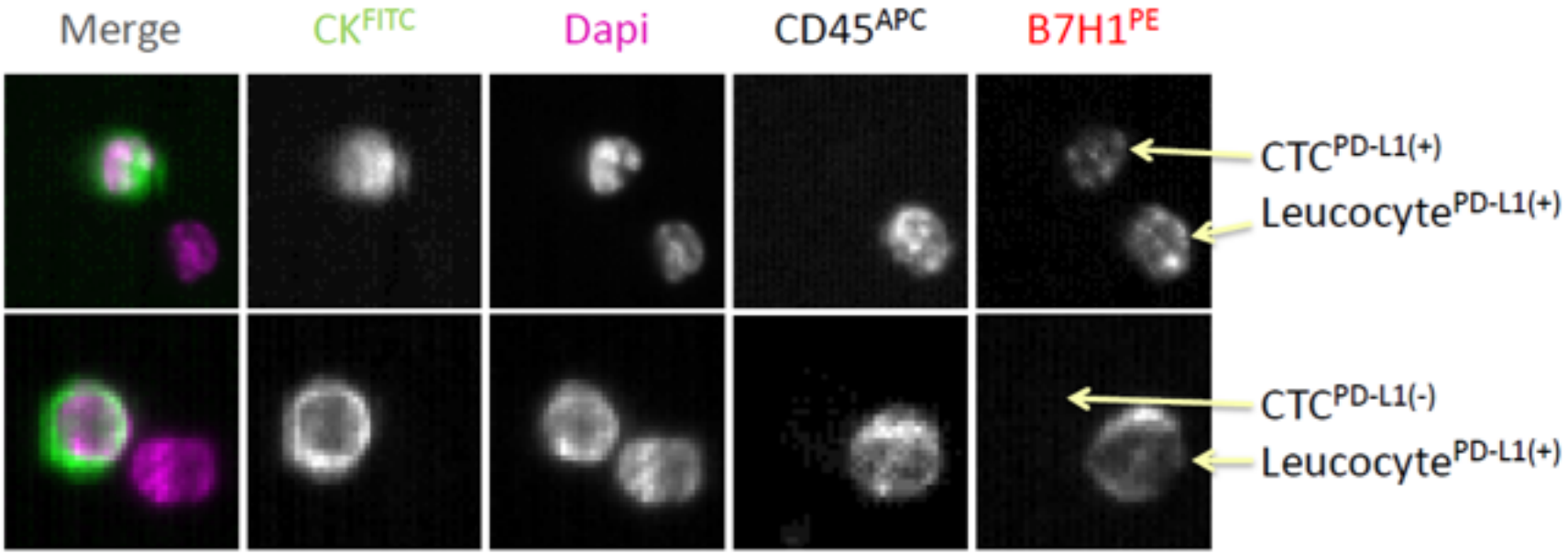
- **HER2-pos. CTC in pats w HER2-neg. primary tumors**
- **HER2-neg. & HER2-pos. CTC after trastuzumab**

Riethdorf/Pantel et al., Clinical Cancer Res 2010; Fehm/Pantel et al., Breast Cancer Res Treat 2010
Ignatiadis/Sotiriou et al, PlosONE, 2011

Frequent expression of PD-L1 on circulating breast cancer cells.

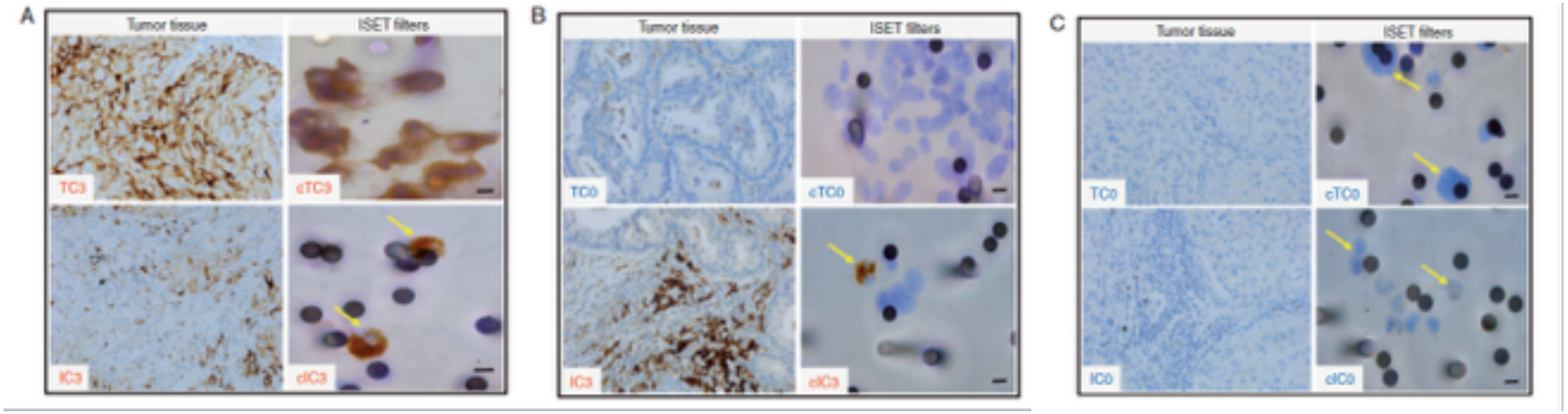
Sixteen patients with circulating tumor cells (CTCs) using the CellSearch® system: PD-L1(+) CTCs in 11 patients (68.8%).

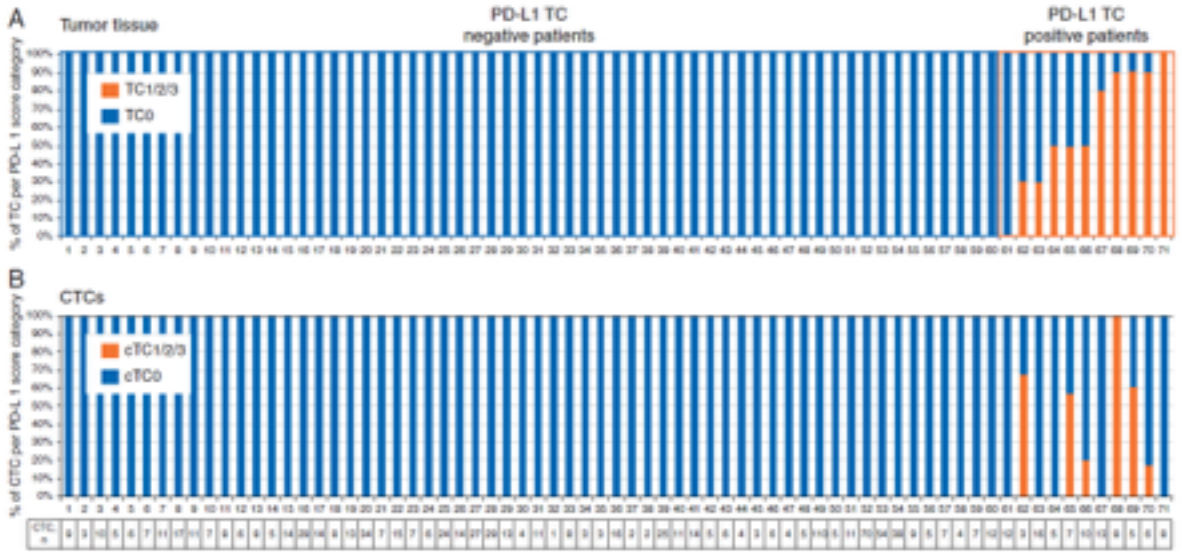
The fraction of PD-L1(+) CTCs varied from 0.2 to 100% in individual patients.



Mazel, M., Mol Oncol 2015

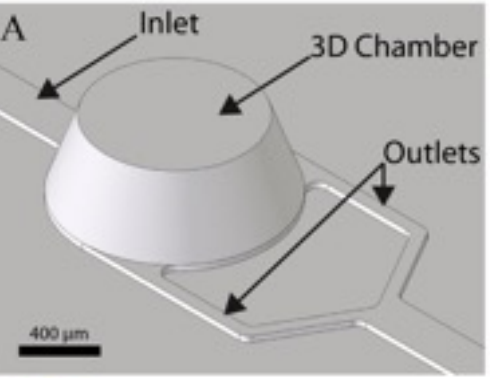
Concordant PD-L1 staining in tumor tissue and corresponding ISET filters from selected NSCLC patients.

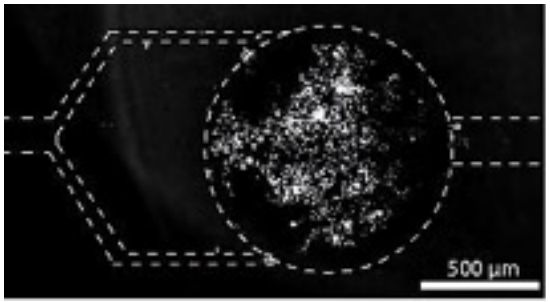


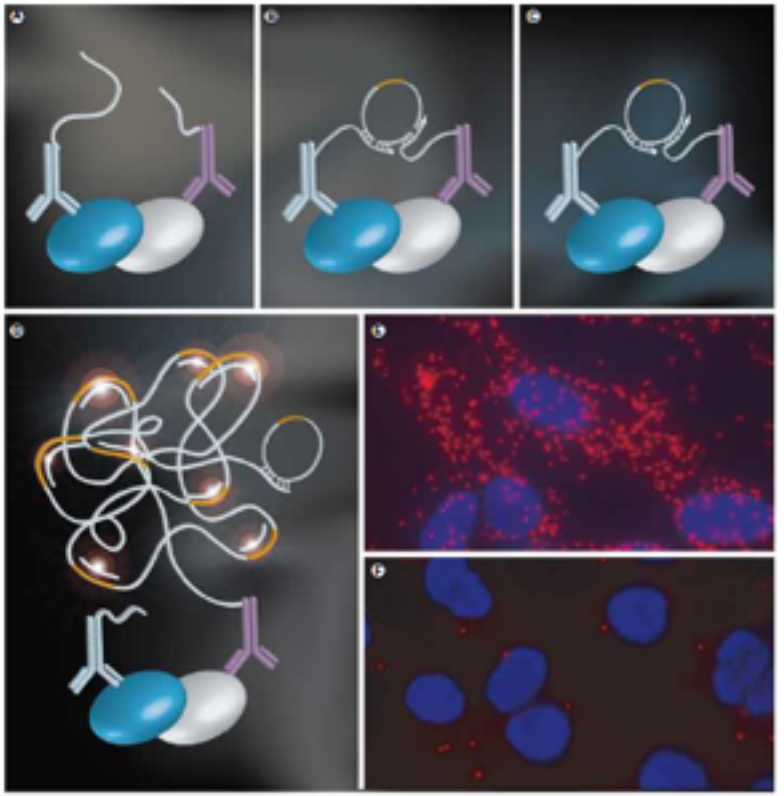


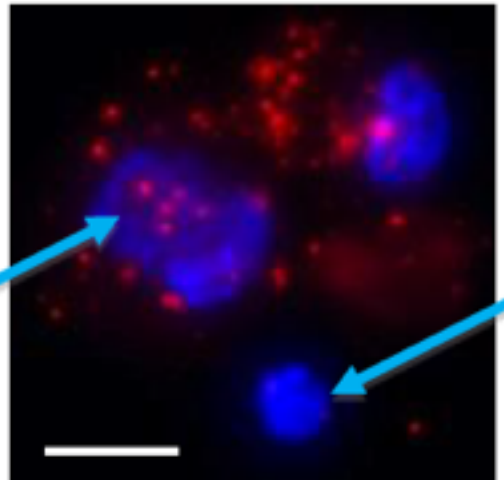
Illie, Annals of Oncology 29: 193–199, 2018

Proximity-Ligation Assay (PLA) HER2-HER3



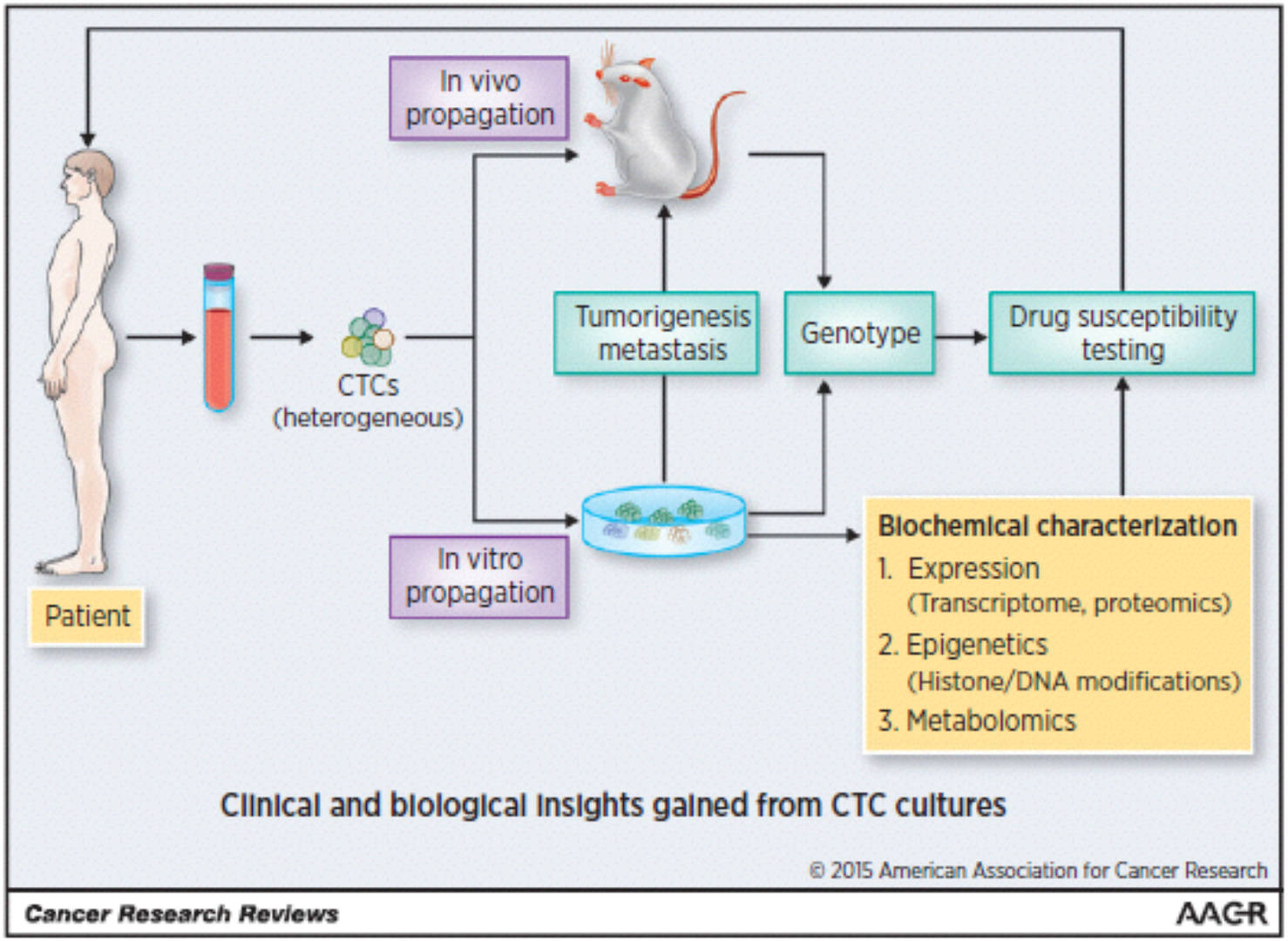




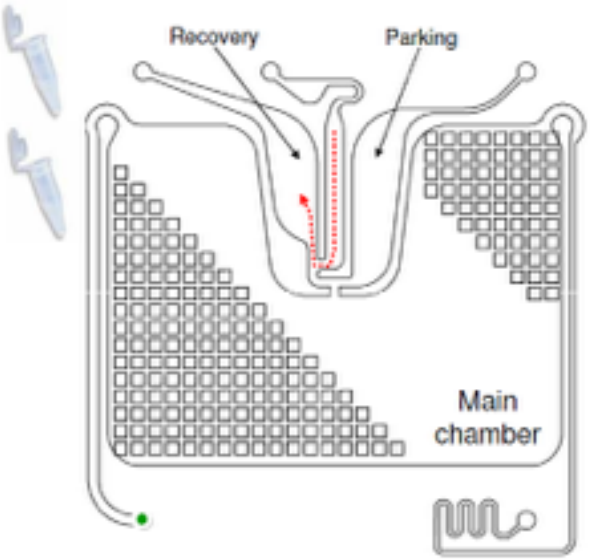


JL Viovy
S Descroix , I Hajji
Laboratoire Macromolécules et Microsystèmes en Biologie et Médecine **Institut Pierre-Gilles de Gennes**

Ex Vivo Culture of CTCs: An Emerging Resource to Guide Cancer Therapy



Maheswaran S Cancer Res; 75(12) June 15, 2015



DEPArray™ Delivers 100%-Pure CTCs

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Purity
1/1,000,000,000

Peripheral blood

Enrichment / Sample-Prep

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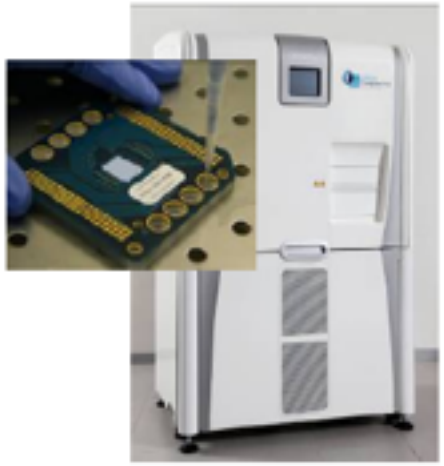
etc.

1/1,000-10,000

Enriched CTCs

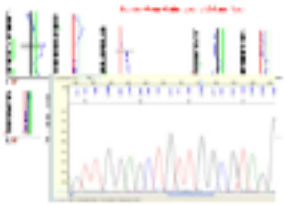
DEPArray™ Sorting



1/1

100% Pure CTCs

*Ampli*1™ WGA + Genetic Analysis

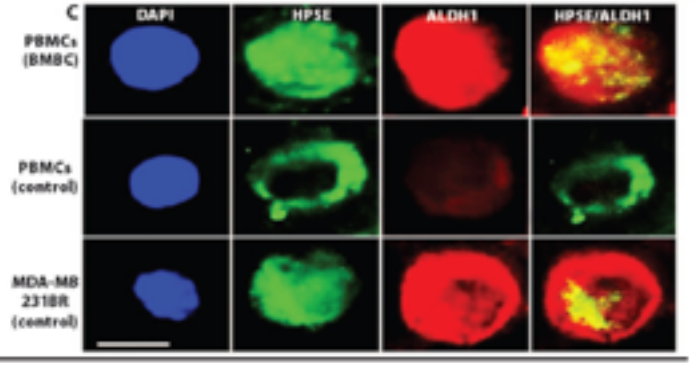


silicon biosystems

The Identification and Characterization of Breast Cancer CTCs Competent for Brain Metastasis

- CTCs isolated from peripheral blood mononuclear cells of patients with breast cancer and also develop CTC lines from three of these patients
- "brain metastasis selected markers

(BMSMs)" HER2+/EGFR+/HPSE+/Notch1+

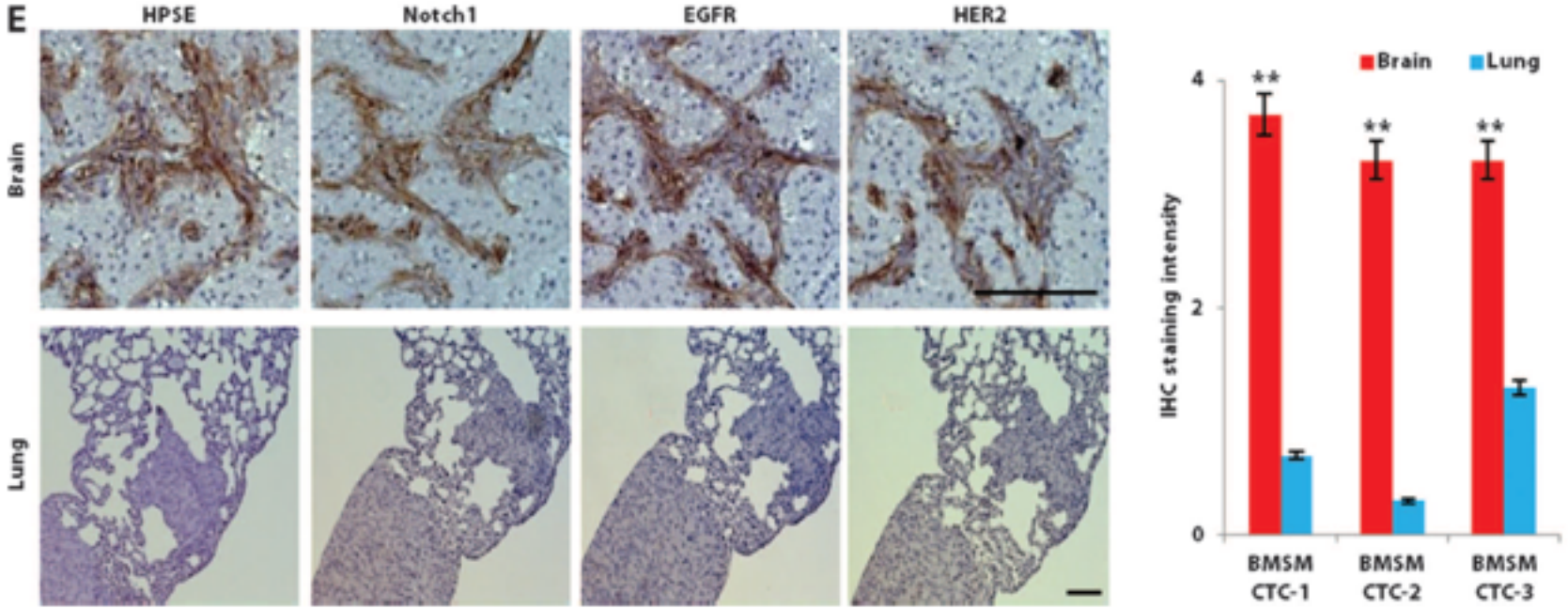


Cells injected	Pathology	Tumor incidence in lung (%)	*P* for lung	Tumor incidence in brain (%)	*P* for brain
CTC-1	Spindle perivascular	80	—	20	—
	Epithelioid micrometastases				
CTC-2	Spindle perivascular	60	—	0	—
CTC-3	Spindle perivascular	60	—	0	—
BMSM CTC-1	Spindle perivascular	100	<0.01 (compared to CTC-1)	80	<0.001 (compared to CTC-1)
	Epithelioid micrometastases				
BMSM CTC-2	Spindle perivascular	80	<0.01 (compared to CTC-2)	60	<0.001 (compared to CTC-2)
	Epithelioid micrometastases				
BMSM CTC-3	Spindle perivascular	80	<0.01 (compared to CTC-3)	60	<0.001 (compared to CTC-3)
PBMCs	No tumor	0	—	0	—

Lixin Zhang *et al. Sci Transl Med* ***5, 180ra48 (2013);***

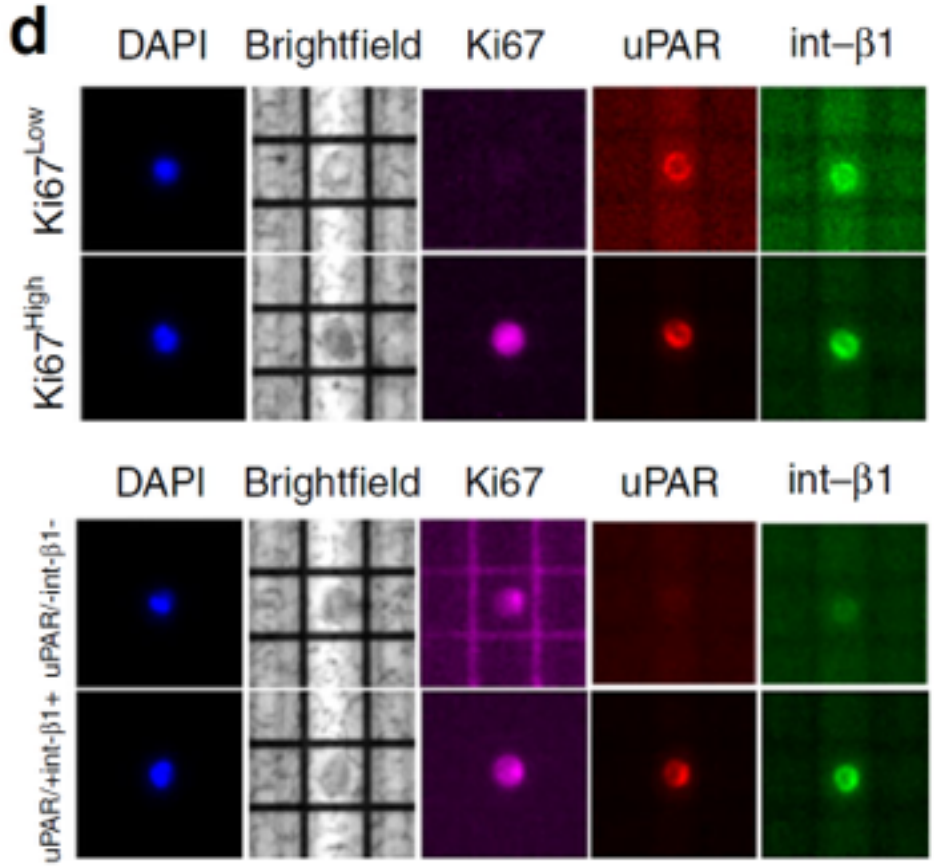
The Identification and Characterization of Breast Cancer CTCs Competent for Brain Metastasis

- murine brain and lung sections from animals injected with BMSM CTC-1 and analyzed for BMSM signature protein expression by immunohistochemistry



Lixin Zhang *et al. Sci Transl Med* ***5, 180ra48 (2013);***

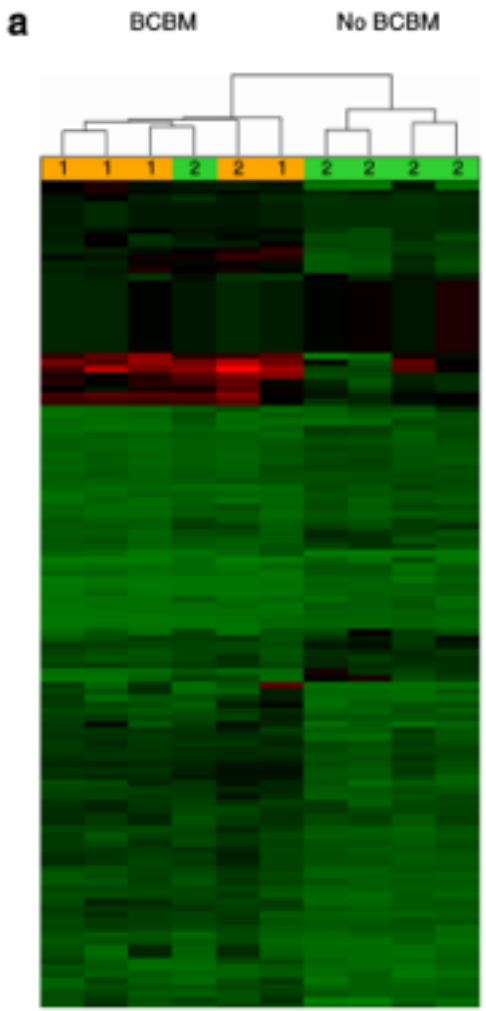
Molecular characterization of breast cancer CTCs associated with brain metastasis



- Demonstration of Ki67, uPAR, and int-β1 staining of single CTCs by DEPArrayTM.

Boral D. 2017 NATURE COMMUNICATIONSI8: 196

Molecular characterization of breast cancer CTCs associated with brain metastasis



- Deriving from a comprehensive analysis of CTC transcriptomes, a unique “circulating tumor cell gene signature” that is distinct from primary breast cancer tissues.
- This signature included enrichment of several genes associated with activation of Notch signalling, or with novel immune-evasion pathways.
- The validity of transcriptomic data was confirmed by the immunocytochemical detection of Notch 1 in 72% of CTCs from patients with confirmed BCBM, versus only 16% in CTCs from patients without BCBM.

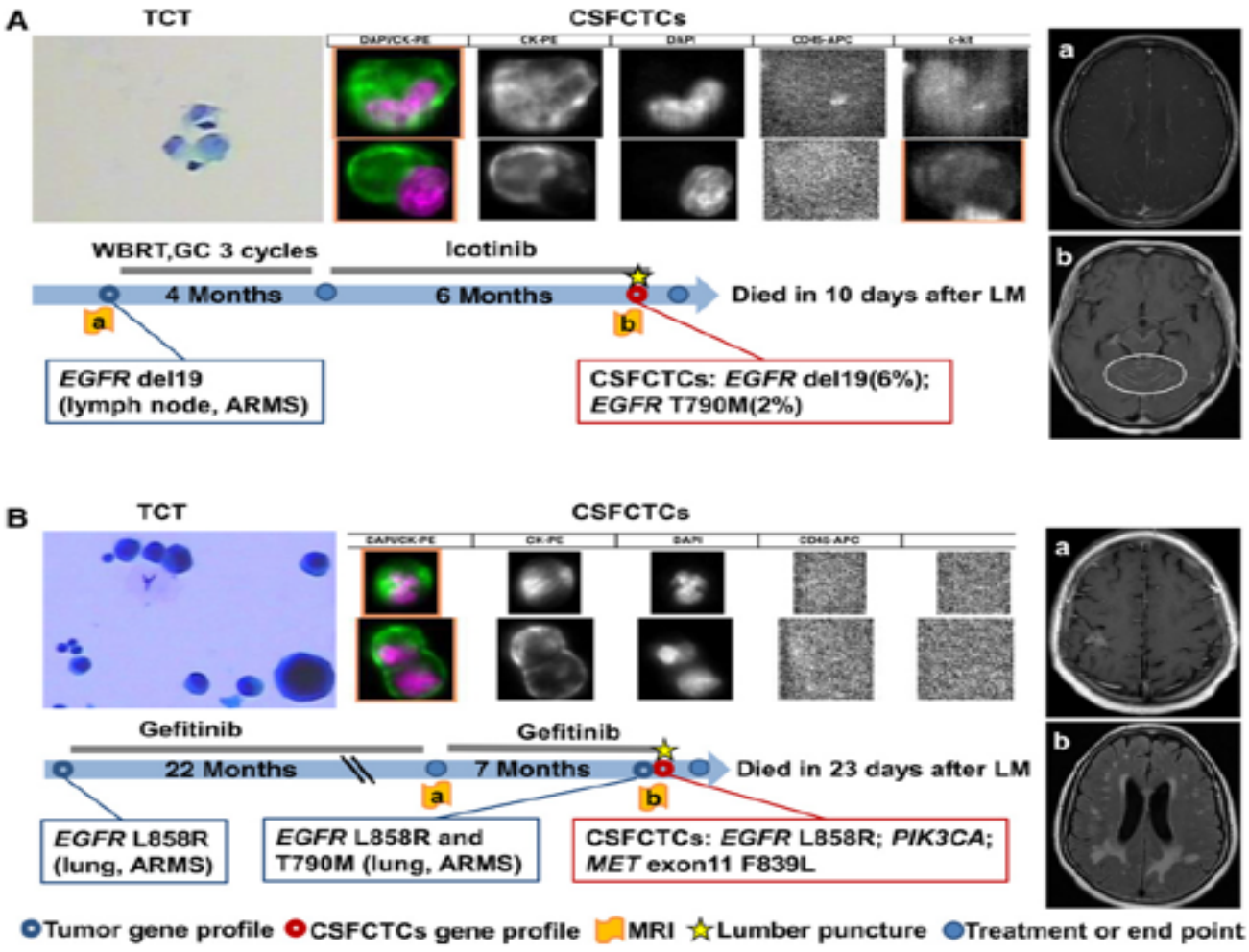
Boral D. 2017 NATURE COMMUNICATIONSl8: 196

Detection of Driver and Resistance Mutations in Leptomeningeal Metastases of NSCLC by Next-Generation Sequencing of Cerebrospinal Fluid Circulating Tumor Cells

No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Definitive LM	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CSFCTCs (cells/7.5 mL)	1310	2214	752	260	1283	72	2716	0	156	2300	1336	1009	252	4496	151	27	797	2060	929	14888	764
TCT	+	-	+	+	+	-	+	-	-	+	-	+	+	-	-	-	+	+	-	+	+
MRI	-	+	-	+	-	-	-	+	+	-	+	-	-	+	-	+	+	-	+	-	+
Combined MRI and TCT	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
CTCs (cells/7.5 mL)	2	2	0	0	2	0	4	0	0	0	0	2	0	0	UA	UA	UA	UA	UA	UA	UA

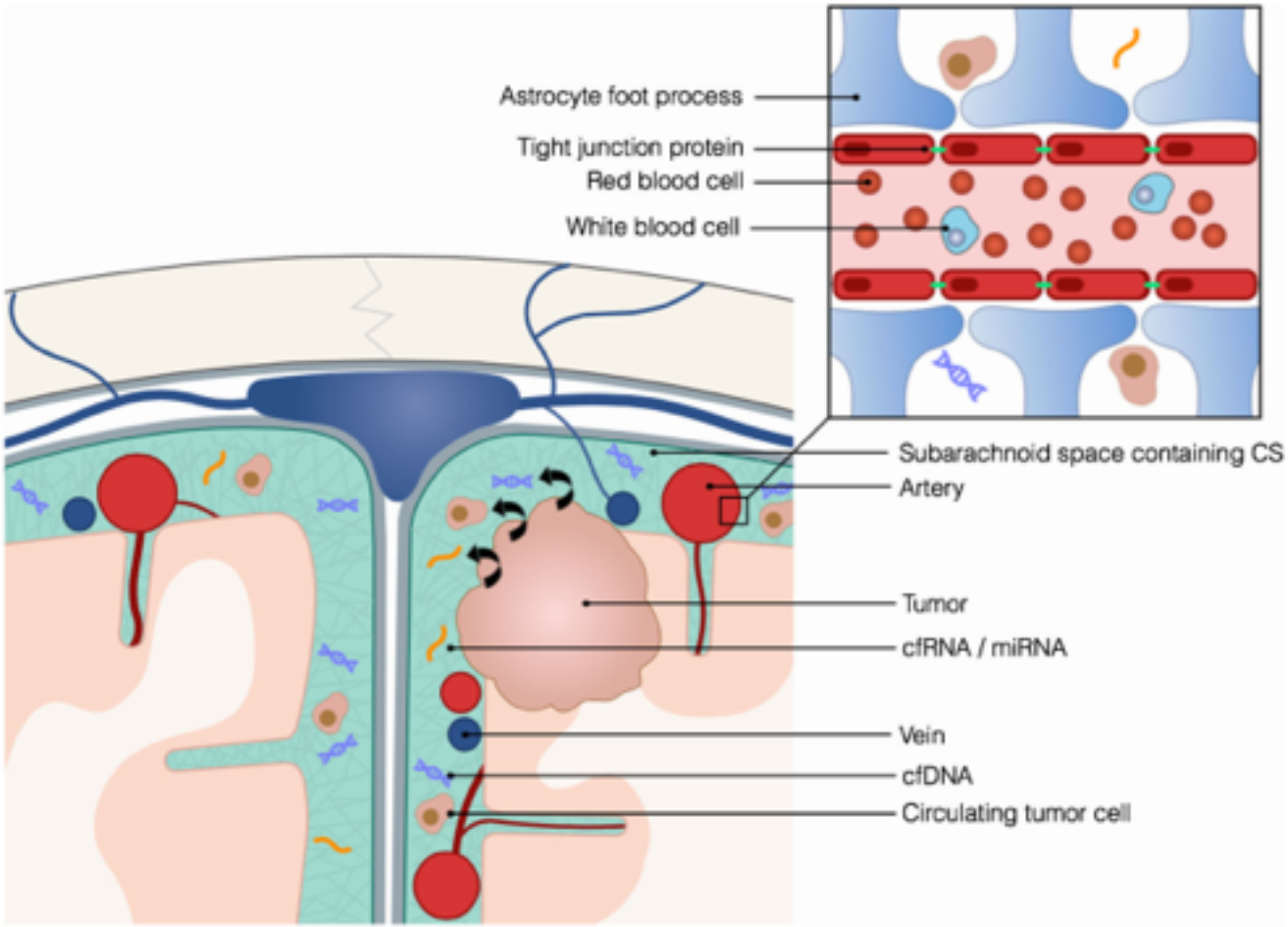
B.-Y. Jiang Clin Cancer Res; 23(18) September 15, 2017

Detection of Driver and Resistance Mutations in Leptomeningeal Metastases of NSCLC by Next-Generation Sequencing of Cerebrospinal Fluid Circulating Tumor Cells



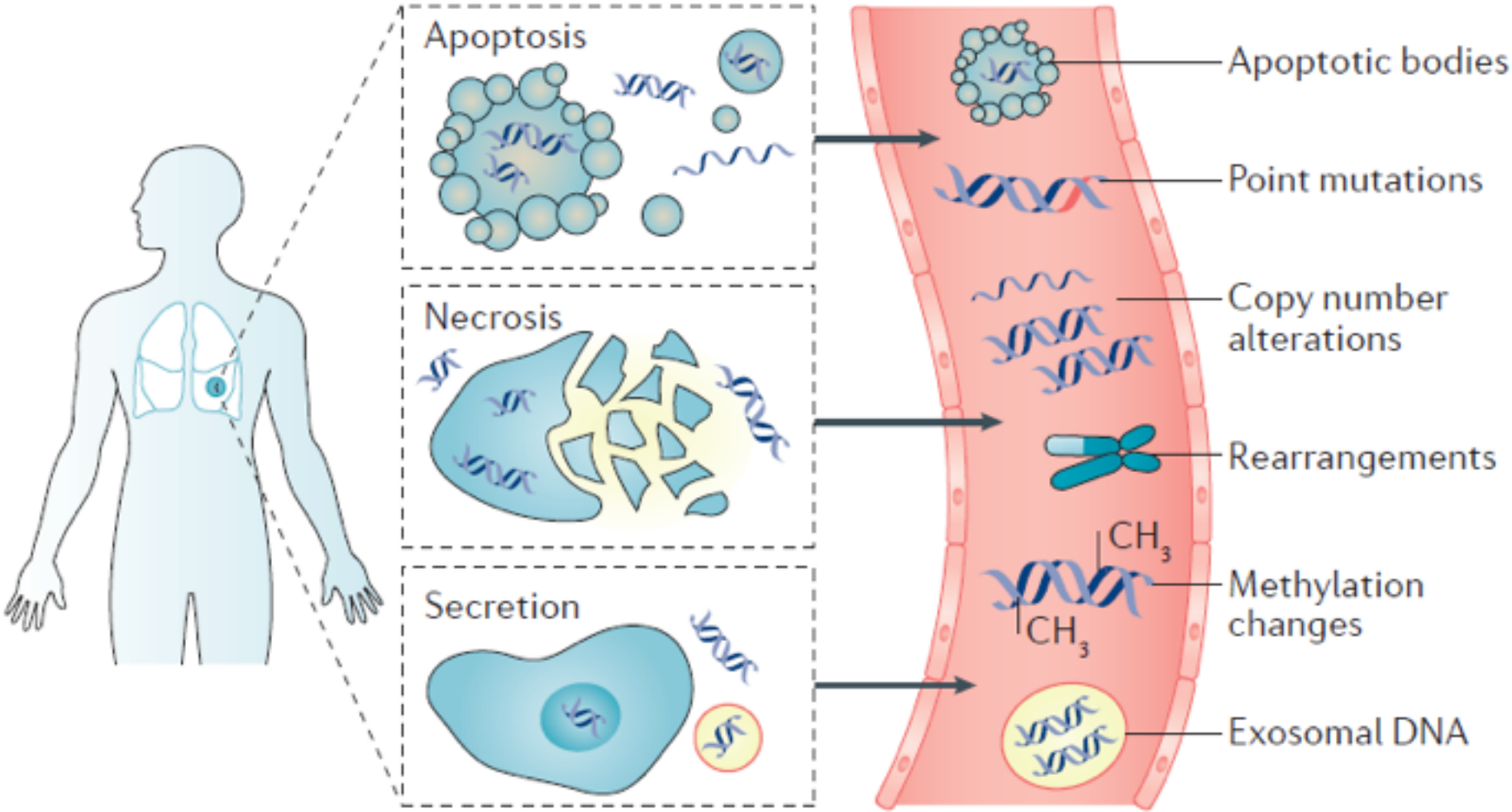
B.-Y. Jiang Clin Cancer Res; 23(18) September 15, 2017

CSF may be a more optimal source of tumor-derived circulating nucleic acids than blood which may have poorer signal-to-noise ratios due to the presence of the BBB and native blood cells



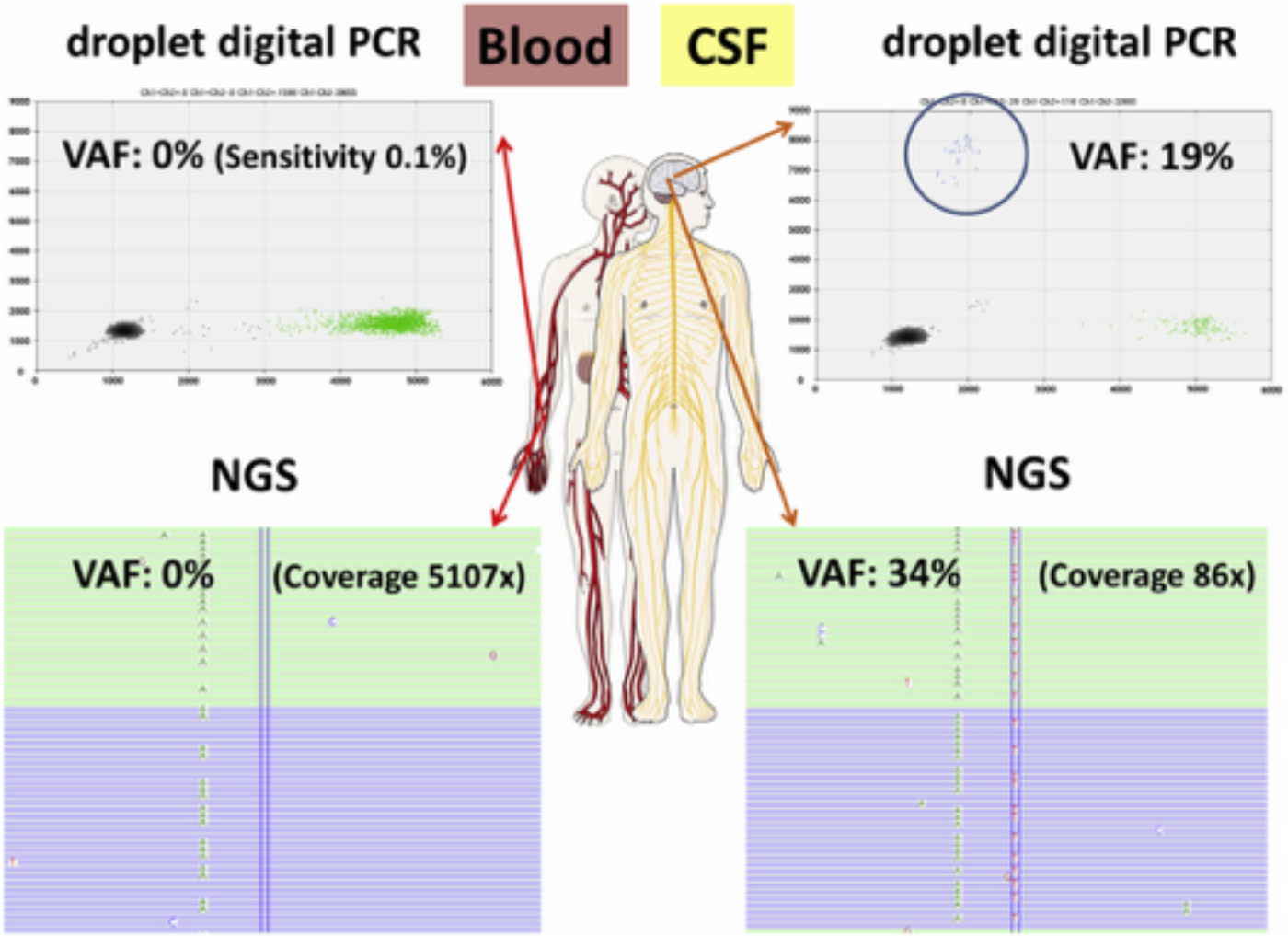
Connoly Curr Neurol Neurosci Rep (2016) 16: 25

Circulating tumor DNA ctDNA



J. C. M. Wan NATURE REVIEWS **CANCER** 17 ;2017 **223**

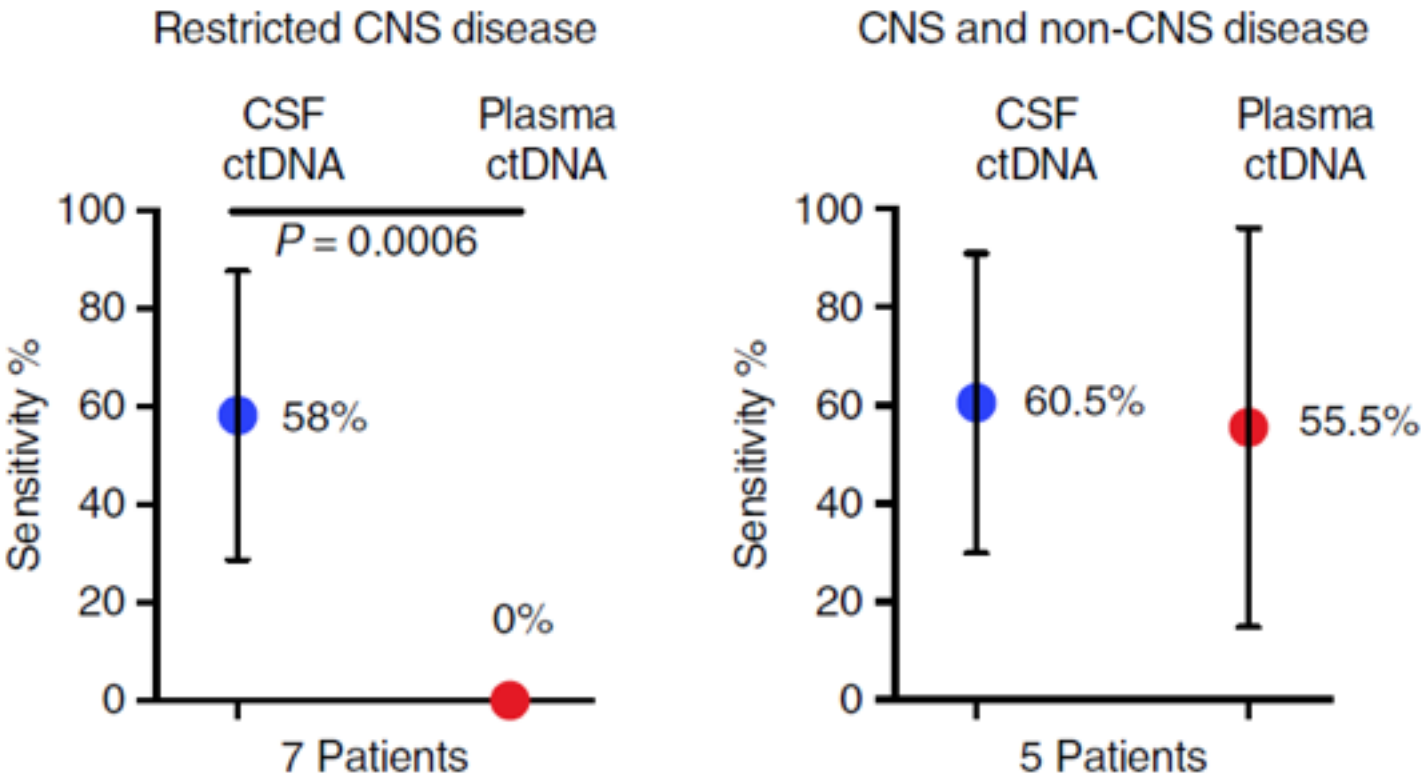
T790M EGFR Mutation Detection in Cerebrospinal Fluid and Response to Osimertinib in a Lung Cancer Patient with Meningeal Carcinomatosis



Gortais H 2017 Journal of Thoracic Oncology Vol. 12

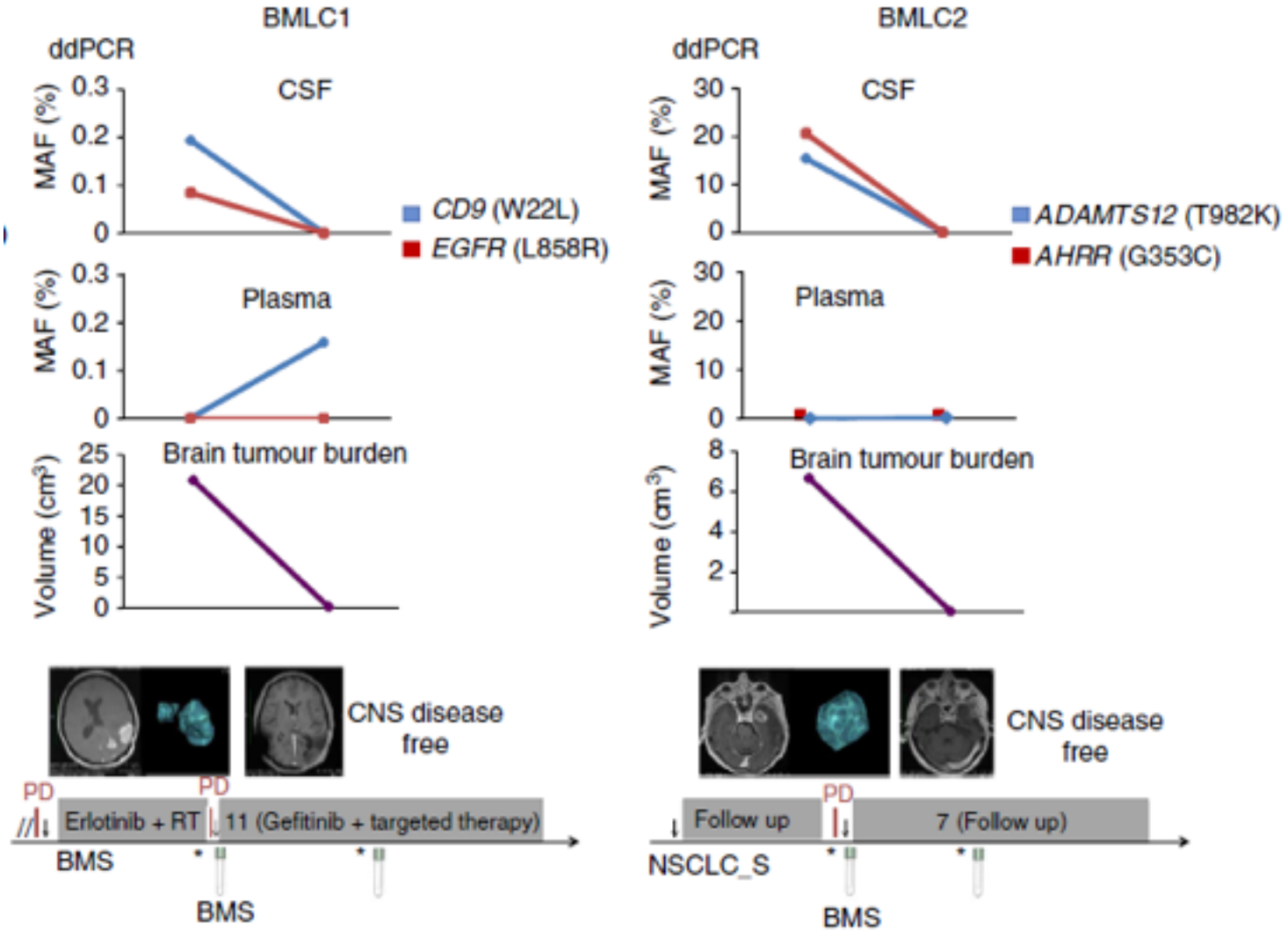
Cerebrospinal fluid-derived circulating tumour DNA better represents the genomic alterations of brain tumours than plasma

12 pa



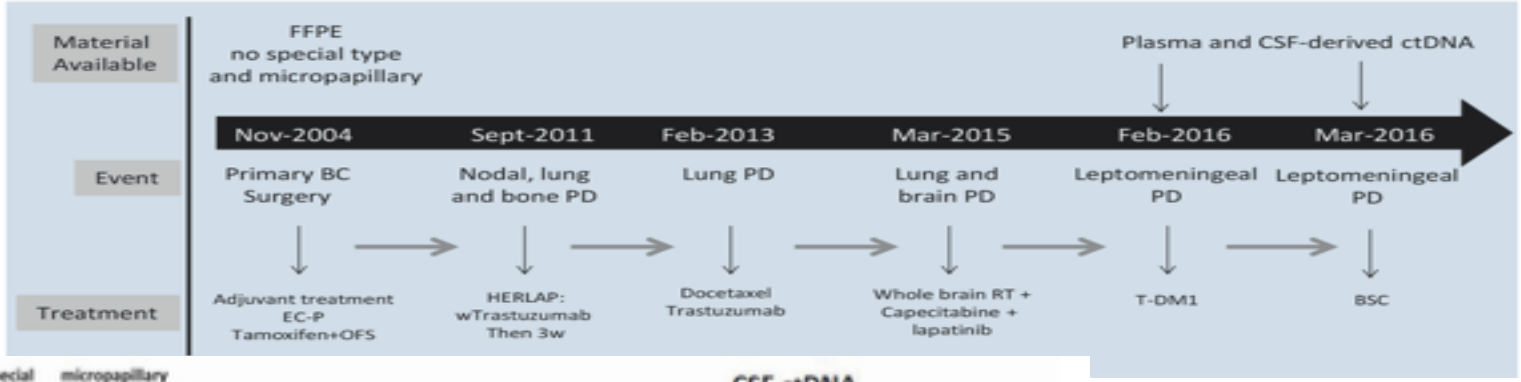
L De Mattos-Arruda NATURE COMM2015

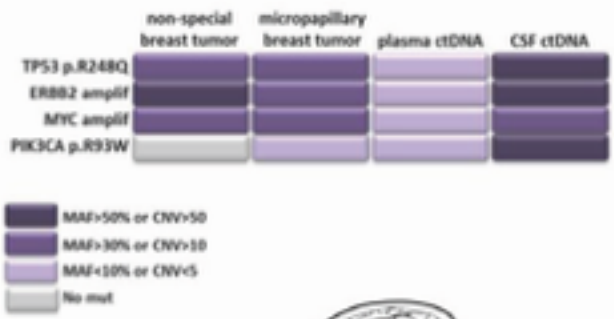
Cerebrospinal fluid-derived circulating tumour DNA better represents the genomic alterations of brain tumours than plasma

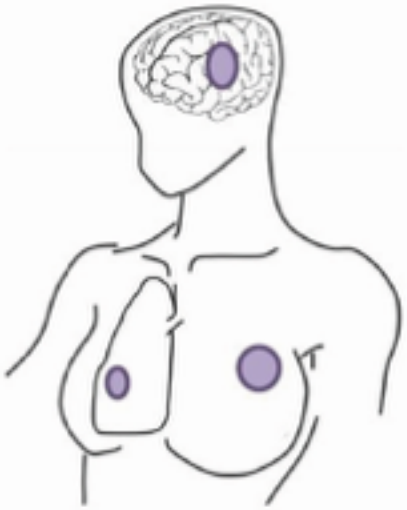


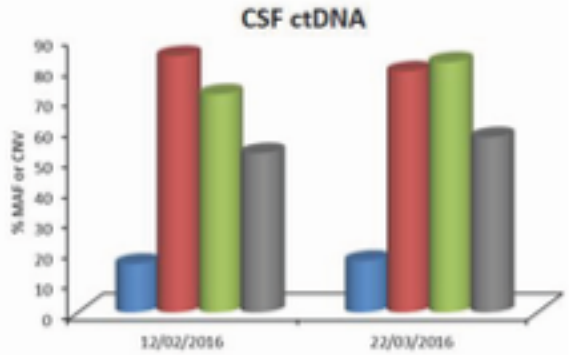
L De Mattos-Arruda NATURE COMM2015

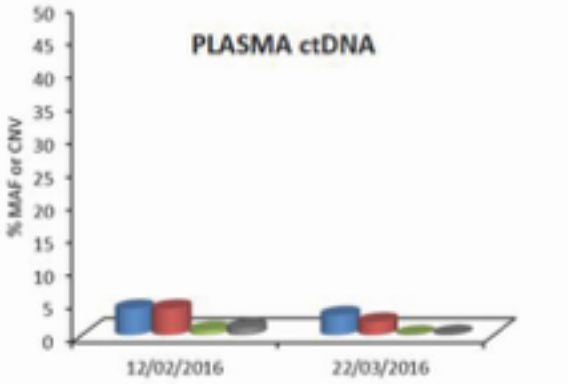
Genotyping tumour DNA in cerebrospinal fluid and plasma of a HER2-positive breast cancer patient with brain metastases





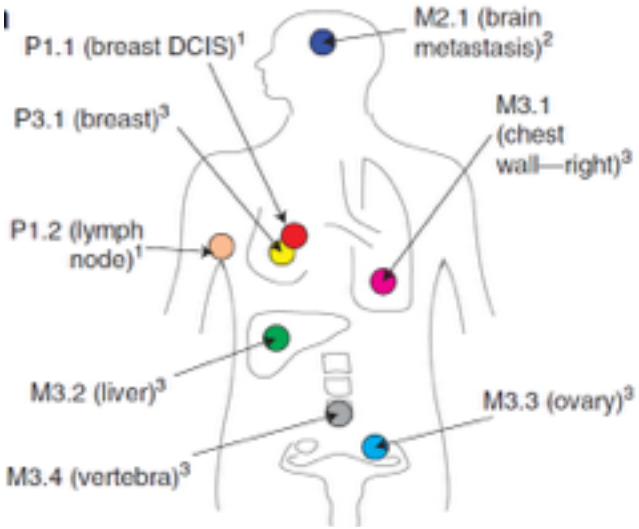


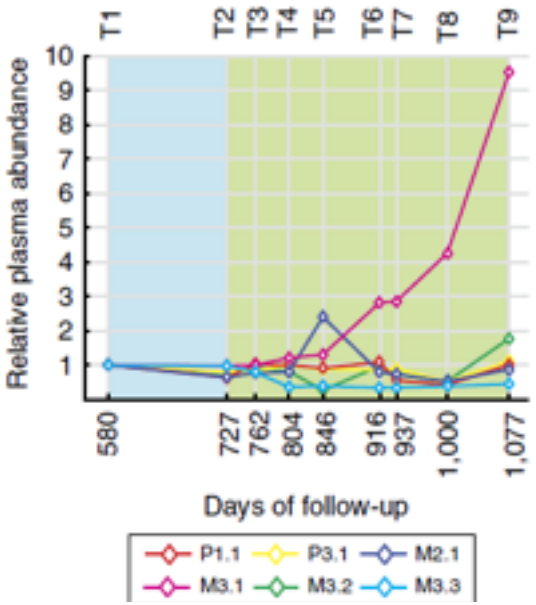


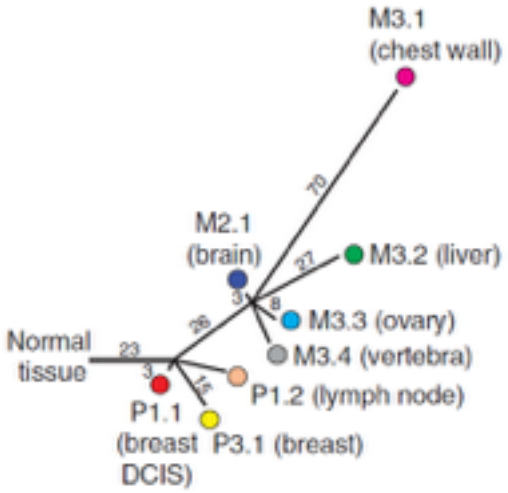


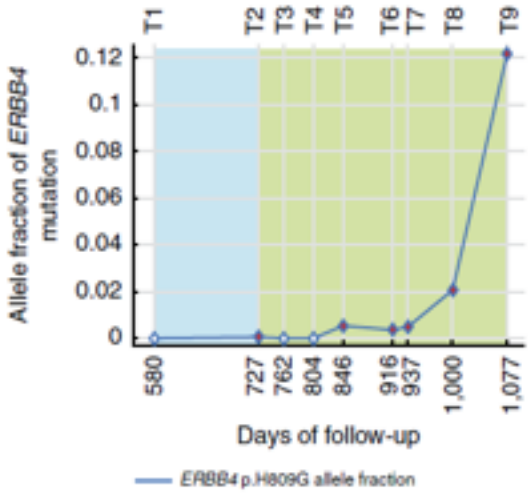
Siravegna G, *et al. ESMO Open* 2017;**2**:e000253.

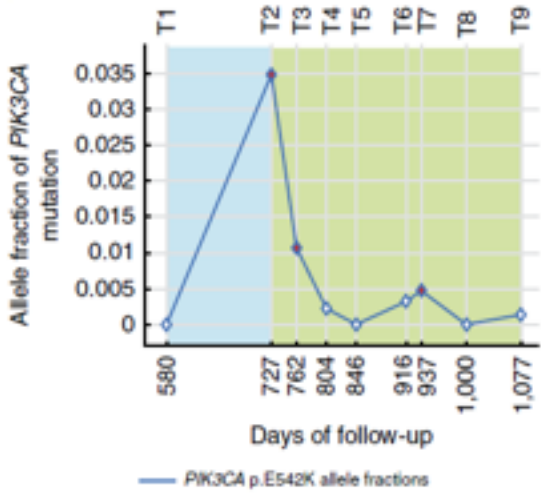
Multifocal clonal evolution characterized using circulating tumour DNA in a case of metastatic breast cancer (Murtaza et al, Nature Comm Nov 2015)



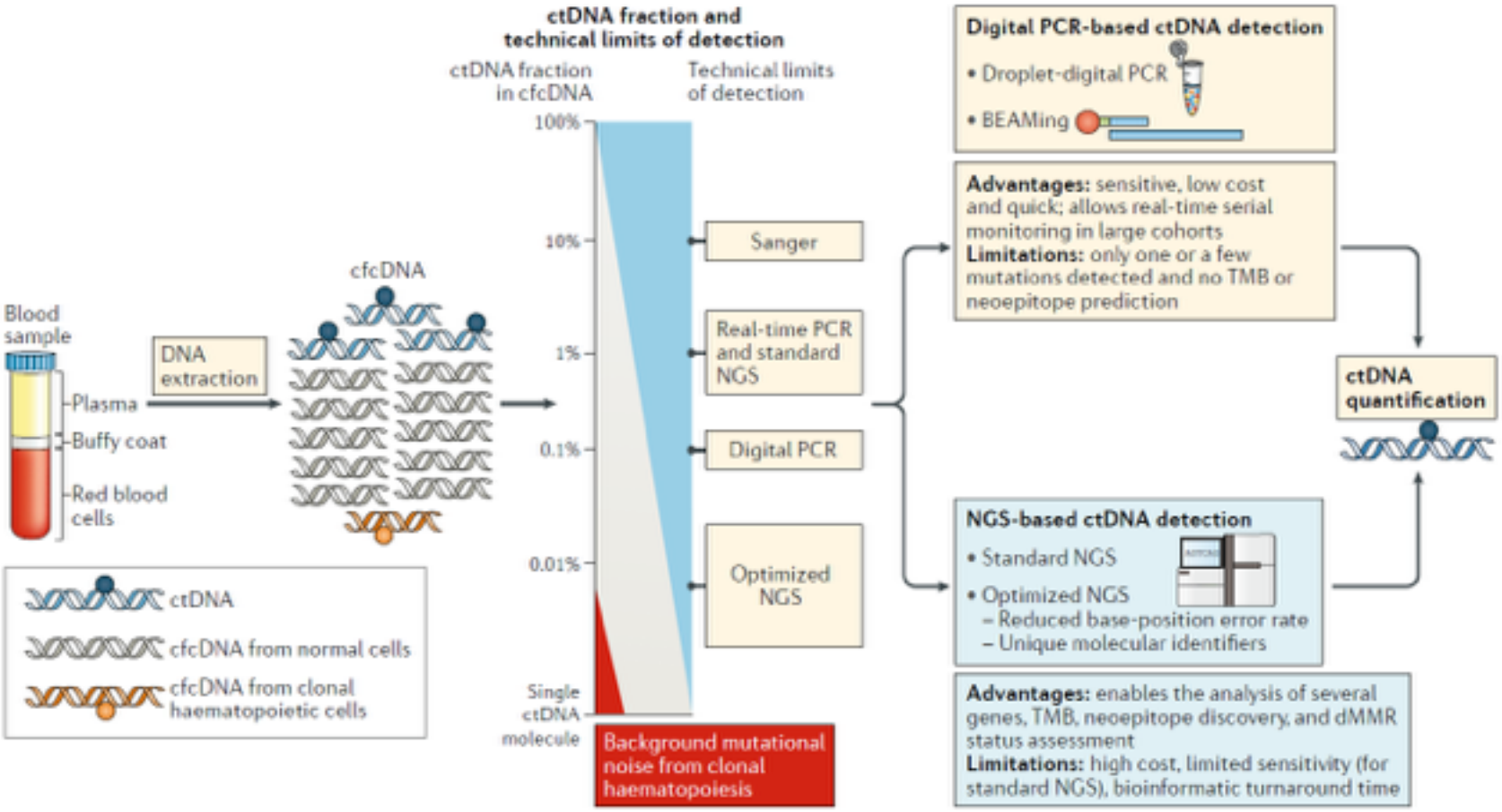








Analysis of ctDNA

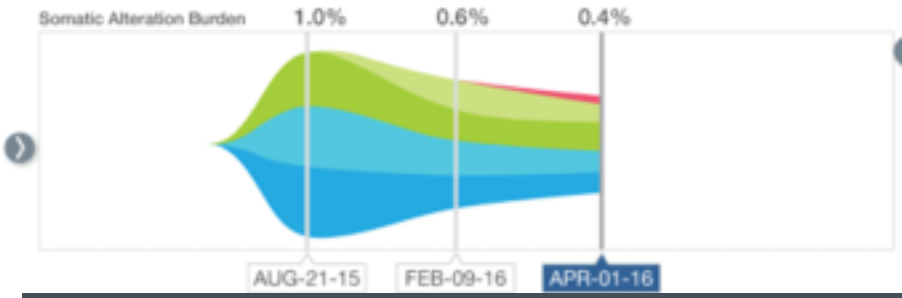


Cabel L, … Pierga JY & Bidard FC Nature Reviews **I Clinical Oncology 2018**

Tumor Response Map

Guardant360 Tumor Response Map

The Guardant360 Tumor Response Map illustrates the mutant allele percentage (% cfDNA) of observed somatic variants at each sample submission time point. The "Somatic Alteraton Burden" value below refers to the maximum % cfDNA detected at each time point. Amplifications are not plotted, and only the first and last four test dates are plotted. Please see the Physician Portal (https://portal.guardanthealth.com) for the Tumor Response Map with all test dates.



5 Total Somatic Alteration(s) Detected

3 with Associated Therapy
2 Associated with Lack of Response
Multiple Clinical Trials Available

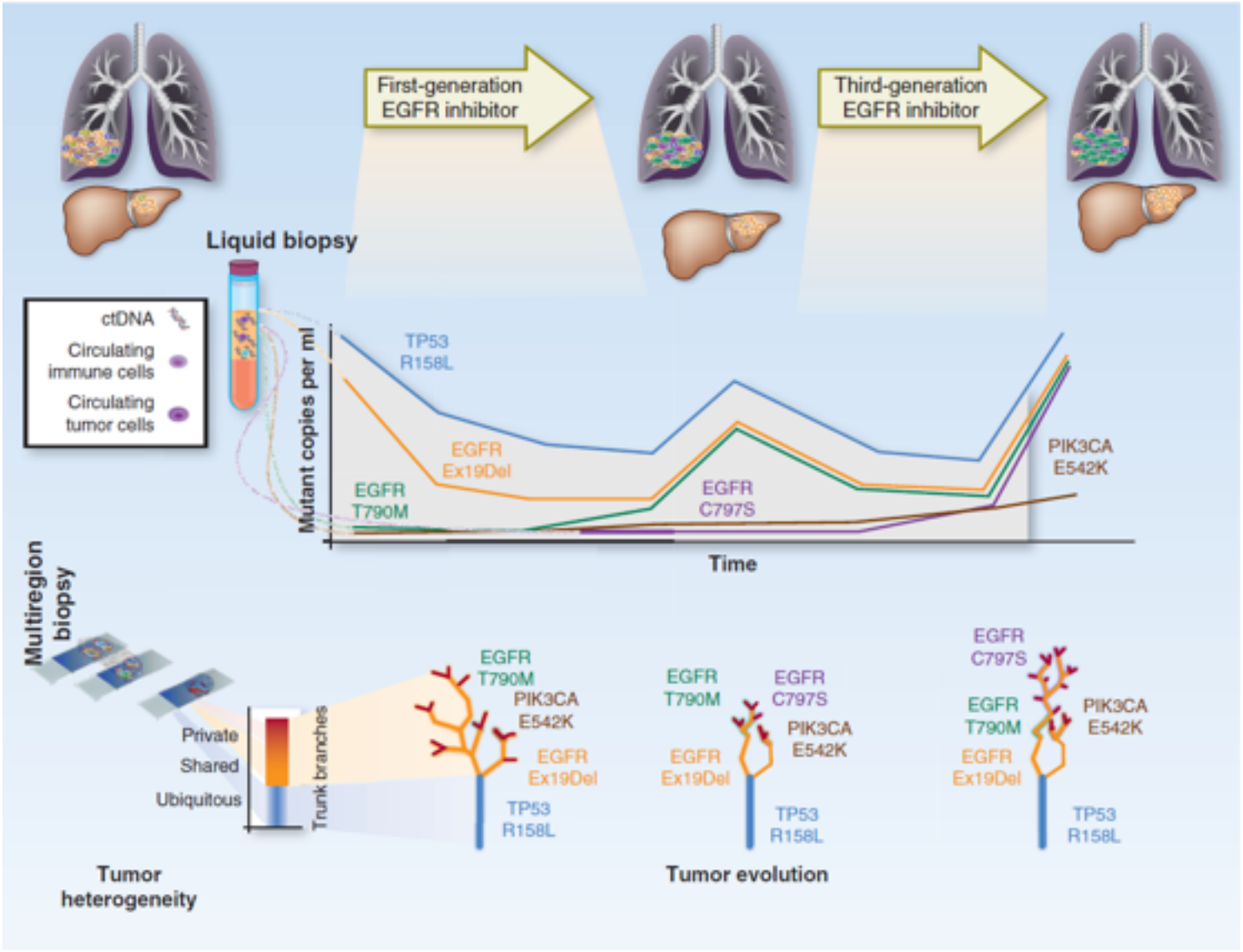
Alteration and Therapy List

Summary of Somatic Alterations & Associated Treatment Options

The percentage of altered cell-free DNA (% cfDNA) circulating in blood is related to the unique tumor biology of each patient. Factors that may affect the % cfDNA of detected somatic alterations include tumor growth, turn-over, size, heterogeneity, vascularization, disease progression, and treatment.

Alteration		Mutation Trend	% cfDNA or Amplification	FDA Approved in Indication see page 3	Available for Use in Other Indications see page 3	Clinical Drug Trials see page 10
Relevant for Therapy Selection						
EGFR	*L858R*		0.3	Afatinib Erlotinib Gefitinib	None	Trials Available
EGFR	*T790M*		0.25	Osimertinib Lack of Response: Erlotinib Gefitinib	Afatinib	Trials Available
EGFR	*C797S*		0.1	Erlotinib Lack of Response: Osimertinib	None	Trials Available
TP53	*Y220C*		0.3	None	None	Trials Available Nearby
Additional Alterations						
EGFR	*L392M*		0.4	The functional consequences and clinical significance of this gene variant are not established. Similar to other alterations in circulating cfDNA, the amount (% cfDNA) of this variant may reflect disease progression or response to treatment; clinical correlation is advised.		

Diagnostic approaches to measure the impact of cancer therapies on clonal evolution.



Nabil Amirouchene-Angelozzi *Cancer Discov* 2017;7:805-817

Circulating Tumor DNA Analysis in Patients With Cancer: American Society of Clinical Oncology and College of American Pathologists Joint Review

Jason D. Merker, Geoffrey R. Oxnard, Carolyn Compton, Maximilian Diehn, Patricia Hurley, Alexander J. Lazar, Neal Lindeman, Christina M. Lockwood, Alex J. Rai, Richard L. Schilsky, Apostolia M. Tsimberidou, Patricia Vasalos, Brooke L. Billman, Thomas K. Oliver, Suanna S. Bruinooge, Daniel F. Hayes, and Nicholas C. Turner

Some ctDNA assays have demonstrated clinical validity and utility with certain types of advanced cancer; however, there is insufficient evidence of clinical validity and utility for the majority of ctDNA assays in advanced cancer.

Evidence shows discordance between the results of ctDNA assays and genotyping tumor specimens and supports tumor tissue genotyping to confirm undetected results from ctDNA tests.

There is no evidence of clinical utility and little evidence of clinical validity of ctDNA assays in early-stage cancer, treatment monitoring, or residual disease detection.

There is no evidence of clinical validity and clinical utility to suggest that ctDNA assays are useful for cancer screening, outside of a clinical trial.

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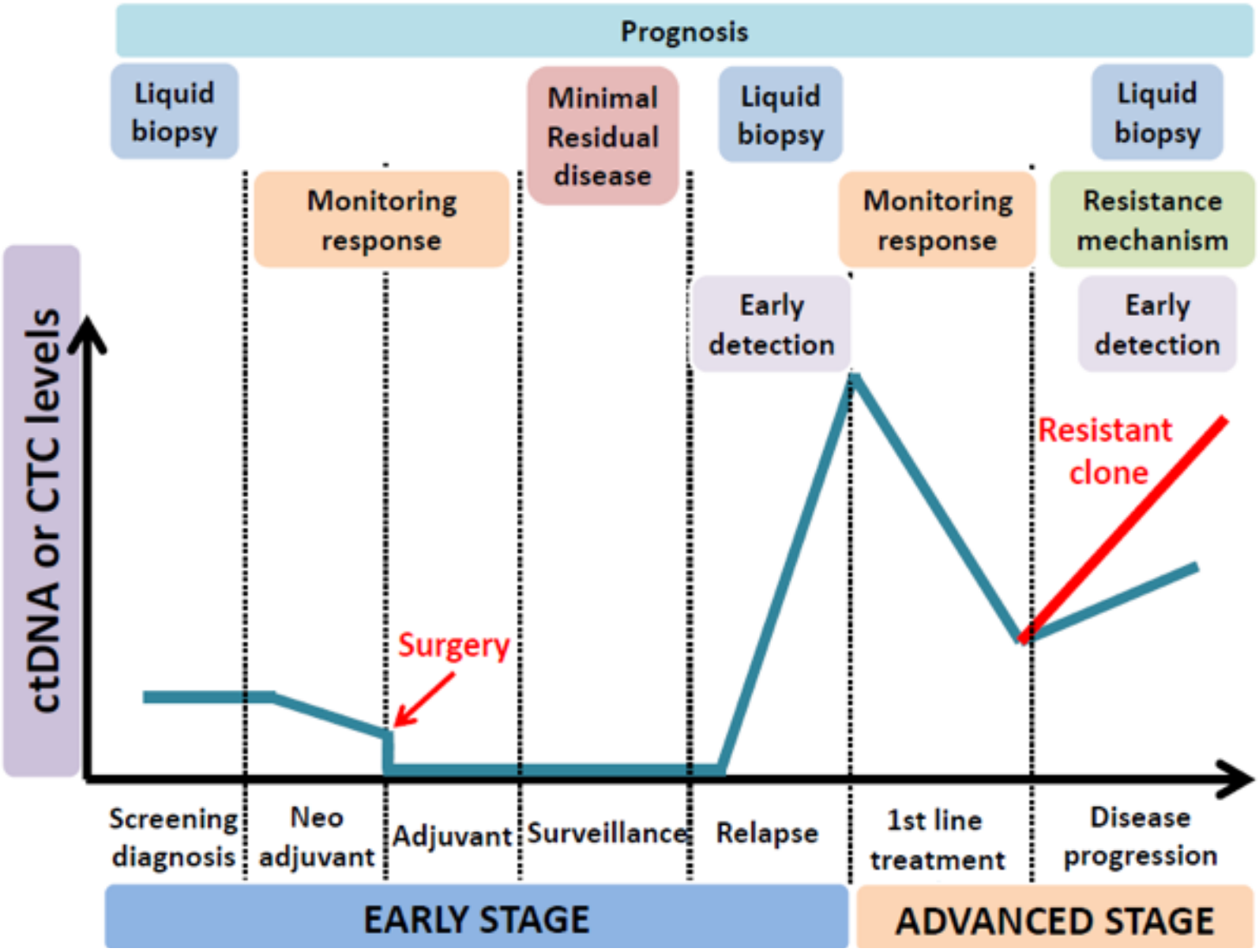
To recapitulate…



Cabel *et al*, Int J Clin Oncol 2017

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CANCER-ID Partners

EFPIA

Clinical sites

Academic institutions

Prof. Klaus Pantel

Prof. Leon Terstappen

UNIVERSITEIT TWENTE.

SMEs

Non-profit organizations

Non-EFPIA/ non-SME

32 partners:

- 6 EFPIA companies (lead **Bayer**, co-lead Menarini)
- 17 academic/clinical sites
- 6 SMEs
- 2 non-profit organizations
- 1 non-SME/non-EFPIA