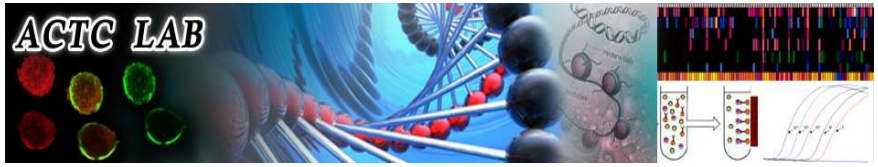
IX SIMPOSIO · SYMPOSIUM | 2024
BIOPSIA LÍQUIDA · LIQUID BIOPSY
EL CAMINO A LA ONCOLOGÍA DE PRECISIÓN · THE WAY TO PRECISION MEDICINE

25, 26 Y 27 DE ENERO · JANUARY 25th, 26th and 27th

European Initiatives to accredit the liquid biopsy based tests

Evi S. Lianidou, PhD
Professor of Analytical Chemistry and Clinical Chemistry
Analysis of Circulating Tumor Cells Lab,
Department of Chemistry,
University of Athens , Greece
Website: http://en.actc-lab.chem.uoa.gr/



Organizado por:
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Universidad Francisco de Vitoria UFV Madrid

Talk outline

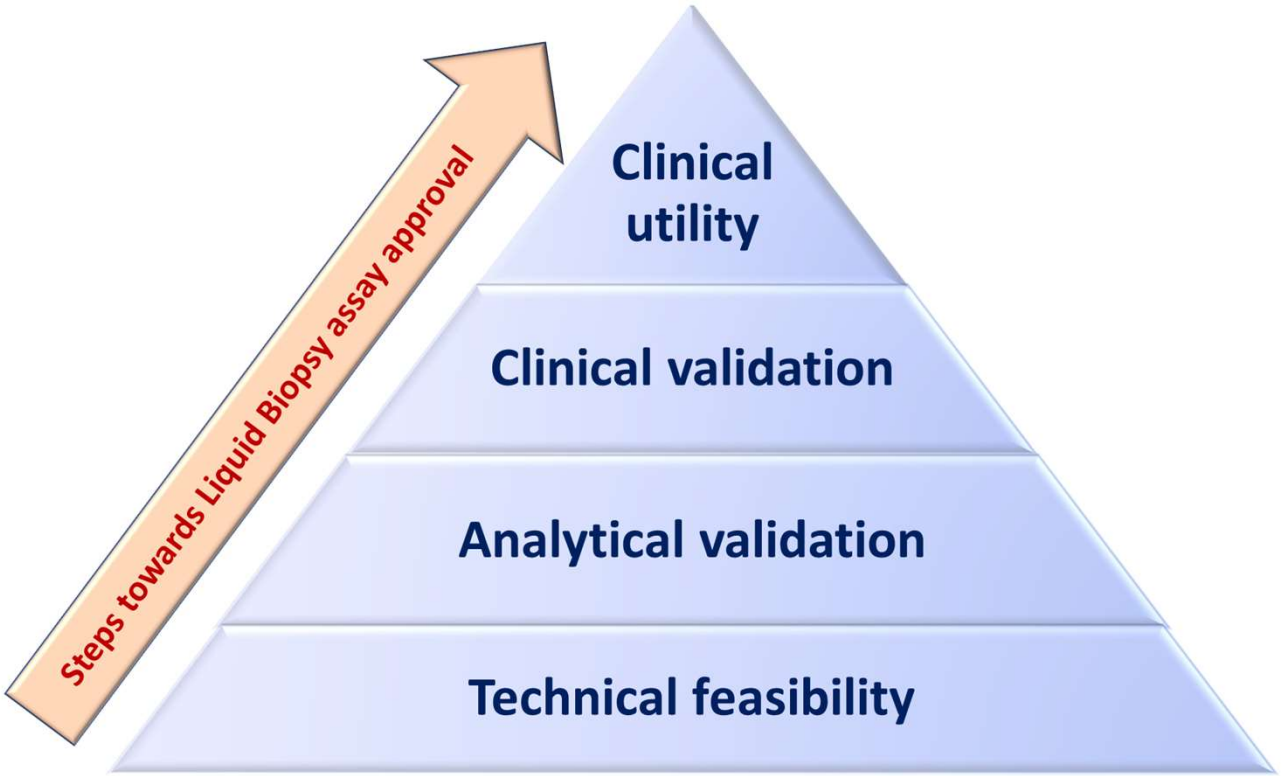
- **Standardization of liquid biopsy testing**
- **External Quality Control schemes (EQA)**
- **Accreditation : ISO-15189**
- **Conclusions**

LB tests: MAIN REQUIREMENTS FOR APPLICATION IN CLINICAL PRACTICE

•**Analytical validity** refers to the ability of a test to accurately and reliably detect the variant(s) of interest and includes measures of accuracy, sensitivity, specificity, and robustness.

•**Clinical validity** implies that the test may accurately detect the presence or absence of a pathologic state or predict outcomes for groups of patients whose test results differ.

•**Clinical utility** is documented when high levels of evidence exist to demonstrate that the use of the test improves patient outcomes compared with not using it.



Ntzifa A. & Lianidou E, Crit Rev Clin Lab Sci, 2023

FDA APPROVED LIQUID BIOPSY TESTS

Table 1. Liquid biopsy tests cleared by the FDA (up to March 2023).

Test	Company	Cancer type	Biomarkers	Intended use	Technology	Year	Matrix
CTC enumeration CellSearch®	Menarini Silicon Biosystems	Metastatic Breast Metastatic Colorectal Metastatic Prostate	CTC detection ($CK^+/DAPI^+/CD45^-$)	Prognostic significance	Ep-CAM based CTC enrichment & CTC detection with IF	2004 2007 2008	Whole blood
cobas® EGFR Mutation Test v2	Roche	Metastatic NSCLC	*EGFR* exon 19 deletions or exon 21 L858R	CDx for erlotinib (TARCEVA, Genentech) and osimertinib (TAGRISSO, AstraZeneca)	Real-time PCR	2016	Plasma
Epi proColon®	Epigenomics AG	Colorectal cancer	*Septin9* gene DNA methylation	Screening test	Bisulfite conversion & Real-time PCR	2016	Plasma
cobas® EGFR Mutation Test v2	Roche	Metastatic NSCLC	*EGFR* exon 19 deletions or exon 21 L858R	CDx for gefitinib (IRESSA, AstraZeneca)	Real-time PCR	2018	Plasma
therascreen® *PIK3CA* RGQ PCR Kit	Qiagen	Advanced or Metastatic Breast Cancer	*PIK3CA* mutations	CDx for alpelisib (PIQRAY, Novartis)	Real-time PCR	2019	Plasma
Guardant360® CDx assay	Guardant Health	Metastatic NSCLC	*EGFR* exon 19 deletions, L858R and T790M	CDx for osimertinib (TAGRISSO, AstraZeneca Pharmaceuticals LP)	NGS	2020	Plasma
Guardant360® CDx assay	Guardant Health	All Solid Cancers	SNVs. Indels, amplifications and fusions in 55 genes	Comprehensive genomic profiling (CGP)	NGS	2020	Plasma
FoundationOne® Liquid CDx	FoundationOne	Metastatic Castration Resistance Prostate Cancer (mCRPC)	*BRCA1* and/ or *BRCA2* mutations	CDx for rucaparib (RUBRACA, Clovis Oncology, Inc.)	NGS	2020	Plasma
FoundationOne® Liquid CDx	FoundationOne	Advanced or Metastatic Breast Cancer	*PIK3CA* mutations	CDx for alpelisib (PIQRAY, Novartis)	NGS	2020	Plasma
FoundationOne® Liquid CDx	FoundationOne	Metastatic NSCLC	*ALK* rearrangements	CDx for alectinib (ALECENSA, Genetech USA, Inc.)	NGS	2020	Plasma
FoundationOne® Liquid CDx	FoundationOne	Advanced Ovarian cancer	*BRCA1* and/ or *BRCA2* mutations	CDx for rucaparib (RUBRACA, Clovis Oncology, Inc.)	NGS	2020	Plasma
cobas® EGFR Mutation Test v2	Roche	Metastatic NSCLC	*EGFR* exon 19 deletions or exon 21 L858R	CDx for expanded EGFR TKIs: osimertinib (TAGRISSO, AstraZeneca), erlotinib (TARCEVA, Genentech), gefitinib (IRESSA, AstraZeneca), afatinib (GILOTRIF, Boehringer Ingelheim), and dacomitinib (VIZIMPRO, Pfizer)	Real-time PCR	2020	Plasma
FoundationOne® Liquid CDx	FoundationOne	Metastatic Castration Resistance Prostate Cancer (mCRPC)	*BRCA1*, *BRCA2* and *ATM* mutations	CDx for olaparib (LYNPARZA, AstraZeneca Pharmaceuticals LP)	NGS	2020	Plasma
Guardant360® CDx assay	Guardant Health	Locally Advanced or Metastatic NSCLC	*EGFR* Exon 20 Insertion Mutations	CDx for amivantamab-vmjw (RYBREVANT, Janssen)	NGS	2021	Plasma
Guardant360® CDx assay	Guardant Health	Locally Advanced or Metastatic NSCLC	*KRAS* G12C mutation	CDx for sotorasib (LUMAKRAS, Amgen Inc.)	NGS	2021	Plasma
FoundationOne® Liquid CDx	FoundationOne	Metastatic NSCLC	*MET* exon 14 skipping	CDx for capmatinib (TABRECTA, Novartis)	NGS	2021	Plasma
FoundationOne® Liquid CDx	FoundationOne	Metastatic NSCLC	*EGFR* exon 19 deletions or exon 21 L858R substitutions	CDx for erlotinib (TARCEVA, Genentech), osimertinib (TAGRISSO), and gefitinib (IRESSA)	NGS	2022	Plasma
therascreen®KRAS RGQ PCR kit	Qiagen	NSCLC	*KRAS* G12C mutation	CDx for adagrasib (KRAZATI, Mirati Therapeutics)	Real-time PCR	2022	Plasma
CTC isolation / enrichment	ANGLE	Metastatic Breast Cancer	*Different biomarkers*	CTC isolation	Size-based enrichment microfluidics	2022	Whole blood
FoundationOne® Liquid CDx	FoundationOne	Metastatic NSCLC	*ROS1* mutations or *NTRK* fusions	CDx for entrectinib (ROZLYTREK, Roche)	NGS	2023	Plasma
Guardant360® CDx assay	Guardant Health	Advanced or Metastatic Breast Cancer	*ESR1* mutations	CDx for elacestrant (ORSERDU, Menarini)	NGS	2023	Plasma

Ntzifa A. & Lianidou E, Crit Rev Clin Lab Sci, 2023

International efforts for standardization of LB-testing

Several organizations and committees worldwide are working towards the implementation of liquid biopsy in clinical practice covering various aspects of this multifaceted procedure. An important effort is guided by the International Liquid Biopsy Standardization Alliance (ILSA) that gathered organizations and foundations to systematically working towards the global use of liquid biopsy in oncology practice.

CURRENT GUIDELINES & STANDARDS FOR cfDNA ANALYSIS

SPIDIA4P

CANCER ID

- developing CEN (European Committee for Standardization) technical preanalytical standards, including those for ccfDNA (CEN/TC 16835-3, https://standards.cen.eu/).

BloodPAC

BLOOD PROFILING ATLAS IN CANCER

- 11 pre-analytical Minimal Technical Data Elements (MTDE) concerning factors most commonly associated with cell-free DNA (cfDNA) test design and development
- generic analytical validation protocols for NGS ctDNA analysis in collaboration with FDA
- the future steps - development of standards for analytical validation in multimarker testing, in MRD tests, and in blood tumor mutational burden (bTMB) tests

CURRENT GUIDELINES & STANDARDS FOR cfDNA ANALYSIS

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

What do we need to obtain high quality circulating tumor DNA (ctDNA) for routine diagnostic test in oncology? – Considerations on pre-analytical aspects by the IFCC workgroup cfDNA

R. Danesi[a], Y.M.D. Lo[b], M. Oellerich[c], J. Beck[d], S. Galbiati[e], M. Del Re[a], E. Lianidou[f], M. Neumaier[g], R.H.N. van Schaik[h,*]

Clin Cancer Res. 2020 July 01; 26(13): 3104–3109. doi:10.1158/1078-0432.CCR-19-3015.

Harmonizing cell-free DNA Collection and Processing Practices through Evidence-based Guidance

Sarah R. Greytak[1], Kelly B. Engel[2], Sonya Parpart-Li[3], Muhammed Murtaza[4], Abel J. Bronkhorst[5], Mark D. Pertile[6], Helen M. Moore[7,*]

ANNALS OF ONCOLOGY

SPECIAL ARTICLE

ESMO recommendations on the use of circulating tumour DNA assays for patients with cancer: a report from the ESMO Precision Medicine Working Group

J. Pascual[1], G. Attard[2], F.-C. Bidard[3,4], G. Curigliano[5,6], L. De Mattos-Arruda[7,8], M. Diehn[9], A. Italiano[10,11,12], J. Lindberg[13], J. D. Merker[14], C. Montagut[15], N. Normanno[16], K. Pantel[17], G. Pentheroudakis[18], S. Popat[19,20], J. S. Reis-Filho[21], J. Tie[22,23], J. Seoane[24,25], N. Tarazona[26,27], T. Yoshino[28] & N. C. Turner[19,20*]

CURRENT RECOMMENDATIONS FOR LB ANALYSIS IN SOLID TUMOURS

ELSEVIER

Critical Reviews in Oncology/Hematology

Volume 156, December 2020, 103112

European School of Oncology – Review

International liquid biopsy standardization alliance white paper

Dana Connors [a], Jeff Allen [b], J.D. Alvarez [c], Jennifer Boyle [d], Massimo Cristofanilli [e], Carolyn Hiller [c], Susan Keating [f], Gary Kelloff [g], Lauren Leiman [h], Robert McCormack [i], Diana Merino [b], Emily Morgan [a], Klaus Pantel [j], Christian Rolfo [k], Maria Jose Serrano [l], A. Pia Sanzone [d], Thomas Schlange [m], Caroline Sigman [f], Mark Stewart [b]

CURRENT RECOMMENDATIONS FOR ctDNA ANALYSIS IN SOLID TUMOURS

U.S. FOOD & DRUG ADMINISTRATION

GUIDANCE DOCUMENT

Use of Circulating Tumor Deoxyribonucleic Acid for Early-Stage Solid Tumor Drug Development; Draft Guidance for Industry; Availability

MAY 2022

The Food and Drug Administration (FDA or Agency) is announcing the availability of a **draft guidance for industry** entitled "Use of Circulating Tumor DNA for Early-Stage Solid Tumor Drug Development." This draft guidance is intended to help sponsors planning to use circulating cell-free plasma derived tumor deoxyribonucleic acid (**ctDNA) as a biomarker in cancer clinical trials conducted under an investigational new drug application (IND) and/or to support marketing approval of drugs and biological products for treating solid tumor malignancies in the early-stage setting.**

ELBS

EUROPEAN LIQUID BIOPSY SOCIETY

ACTUAL MEMBERS

ORGANIZATION TEAM

INDUSTRY CLINIC RESEARCH

CHAIRMAN | ELBS

Prof. Dr. med. Klaus Pantel
Director of the institute

Center for Experimental Medicine
Institute of Tumor Biology
pantel@uke.de
+49 (0) 40 7410 – 53503

PROJECT MANAGER | ELBS

Dr. Claudia Koch

Center for Experimental Medicine
Institute of Tumor Biology
c.koch@uke.de
+49 (0) 152 22830556
www.elbs.eu | LinkedIn

WORKING GROUPS

DISSEMINATION & EDUCATION
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MEET 2 TIMES A YEAR

TECHNOLOGY
MEET 4 TIMES A YEAR
- CTC WORK GROUP
- ctDNA WORK GROUP
- EV WORK GROUP

REGULATORY
MEET 2 TIMES A YEAR

European Liquid Biopsy Society, ELBS

The European LB Society (ELBS), as an extension to the CANCER-ID project, is currently working on the development of guidelines fostering LB research and interactions with industry.

Moreover, ELBS aims to organize ring studies across Europe using established standardized methods to achieve clinical implementation

One of ELBS main activities is also to encourage and support laboratories to fulfill the ISO15189 requirements regarding LB testing.

European Liquid Biopsy Society (ELBS)

European Liquid Biopsy Society Network

PRE-ANALYTICAL VARIABLES FOR ctDNA ANALYSIS

- **Plasma cfDNA** is released in blood circulation because of **cell death, apoptosis, or necrosis**, but can also arise from fetuses in pregnant women.
- **ctDNA** comprises a **small fraction of cfDNA** and originates **from active tumors** that constantly release their biological information into the bloodstream.
- Different tumor subclones may concurrently constitute the **heterogeneous tumor background of plasma**.
- The size of ctDNA significantly differs from that of cfDNA, **ranging between 160 and 180 bp**, and is packaged around nucleosomes in a specific manner that makes it distinguishable during fragmentation analysis.
- Its **short half-life, usually less than 2 h**, requires careful handling of samples and prompt transit to the laboratory.
- The **levels of ctDNA** in body fluids are affected by various factors such as **tumor stage** or **assigned treatments** that need to be considered during its analysis

PRE-ANALYTICAL VARIABLES FOR ctDNA ANALYSIS

OUTSIDE THE LAB

Blood sampling

avoid e.g. hemolyzed samples

~~Serum~~ or plasma?

Plasma is preferred to serum because clotting in serum increases gDNA

Blood collection tubes

EDTA tubes for immediate sample processing (<2h) or
Tubes with preservatives: anti-coagulant molecules and specific cell stabilizers to prevent cell lysis



or

Transportation

time

-Minimize time intervals between blood collection and sample processing.
-Sample transportation at RT

AT THE LAB

Centrifugation

Double centrifugation protocols: low to avoid cell lysis & higher for max purification

Plasma storage

At −80 °C for long term storage
aliquots to avoid freeze-thaw cycles

cfDNA extraction

commercially available kits or automated systems for high-throughput analysis and better repeatability (e.g. TETHIS)

cfDNA storage

At −20 °C for short term storage
At −80 °C for long term storage
Minimize freeze-thaw cycles

cfDNA quantity

PCR-based techniques are preferred to fluorometric methods

Preanalytical aspects for cfDNA and circulating miRNA analysis

Clinical Chemistry

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Volume 66, Issue 1
January 2020

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Multicenter Evaluation of Circulating Cell-Free DNA Extraction and Downstream Analyses for the Development of Standardized (Pre)analytical Work Flows

Rita Lampignano, Martin H.D Neumann, Sabrina Weber, Vera Kloten, Andrei Herdean, Thorsten Voss, Daniel Groelz, Anna Babayan, Marco Tibbesma, Martin Schlumpberger ...
Show more

Clinical Chemistry, Volume 66, Issue 1, January 2020, Pages 149–160,
https://doi.org/10.1373/clinchem.2019.306837
Published: 30 December 2019 **Article history**

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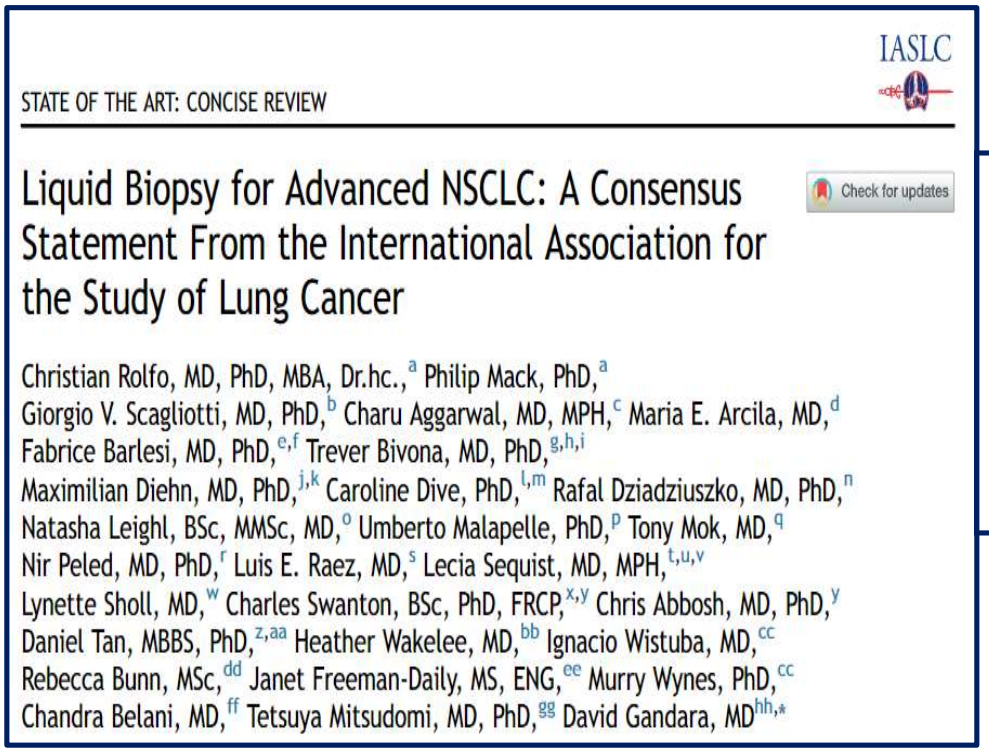
Multicenter Evaluation of Circulating Plasma MicroRNA Extraction Technologies for the Development of Clinically Feasible Reverse Transcription Quantitative PCR and Next-Generation Sequencing Analytical Work Flows

Vera Kloten, Martin H.D. Neumann, Francesca Di Pasquale, Markus Sprenger-Haussels, Jonathan M. Shaffer, Martin Schlumpberger, Andrei Herdean, Fay Betsou, Wim Ammerlaan, Taija af Hällström, Elina Serkkola, Tarja Forsman, Evi Lianidou, Robert Sjöback, Mikael Kubista, Sebastian Bender, Rita Lampignano, Thomas Krahn, Thomas Schlange, for the CANCER-ID consortium

DOI: 10.1373/clinchem.2019.303271 Published September 2019

RECOMMENDATIONS FOR ctDNA TESTING



IASLC

STATE OF THE ART: CONCISE REVIEW

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

Check for updates

Christian Rolfo, MD, PhD, MBA, Dr.hc.,[a] Philip Mack, PhD,[a] Giorgio V. Scagliotti, MD, PhD,[b] Charu Aggarwal, MD, MPH,[c] Maria E. Arcila, MD,[d] Fabrice Barlesi, MD, PhD,[e,f] Trever Bivona, MD, PhD,[g,h,i] Maximilian Diehn, MD, PhD,[j,k] Caroline Dive, PhD,[l,m] Rafal Dziadziuszko, MD, PhD,[n] Natasha Leighl, BSc, MMSc, MD,[o] Umberto Malapelle, PhD,[p] Tony Mok, MD,[q] Nir Peled, MD, PhD,[r] Luis E. Raez, MD,[s] Lecia Sequist, MD, MPH,[t,u,v] Lynette Sholl, MD,[w] Charles Swanton, BSc, PhD, FRCP,[x,y] Chris Abbosh, MD, PhD,[y] Daniel Tan, MBBS, PhD,[z,aa] Heather Wakelee, MD,[bb] Ignacio Wistuba, MD,[cc] Rebecca Bunn, MSc,[dd] Janet Freeman-Daily, MS, ENG,[ee] Murry Wynes, PhD,[cc] Chandra Belani, MD,[ff] Tetsuya Mitsudomi, MD, PhD,[gg] David Gandara, MD[hh,*]

Recommendations: "In patients with oncogene-addicted NSCLC, liquid biopsy is emerging as not only complementary to tissue-based analysis but also acceptable as the initial "plasma first" approach for biomarker evaluation at the time of diagnosis and for monitoring the efficacy of targeted therapies".

IASLC

Rolfo C, et al, J Thorac Oncol. 2021

Switch to fulvestrant and palbociclib versus no switch in advanced breast cancer with rising *ESR1* mutation during aromatase inhibitor and palbociclib therapy (PADA-1): a randomised, open-label, multicentre, phase 3 trial

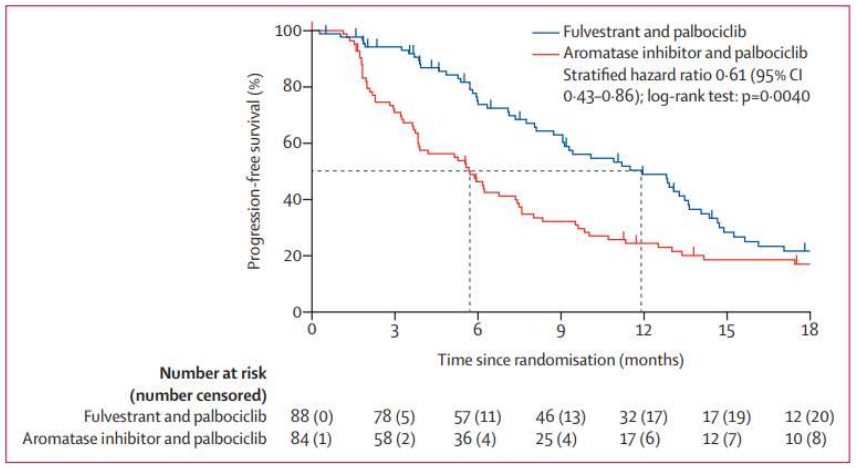
THE LANCET Oncology

François-Clément Bidard, Anne-Claire Hardy-Bessard, Florence Dalenc, Thomas Bachelot, Jean-Yves Pierga, Thibault de la Motte Rouge, Renaud Sabatier, Coraline Dubot, Jean-Sébastien Frenel, Jean Marc Ferrero, Sylvain Ladoire, Christelle Levy, Marie-Ange Mouret-Reynier, Alain Lortholary, Julien Grenier, Camille Chakiba, Laetitia Stefani, Jérôme Edouard Plaza, Florian Clatot, Luis Teixeira, Véronique D'Hondt, Hélène Vegas, Olfa Derbel, Claire Garnier-Tixidre, Jean-Luc Canon, Barbara Pistilli, Fabrice André, Laurent Arnould, Anne Pradines, Ivan Bièche, Céline Callens, Jérôme Lemonnier, Frédérique Berger, Suzette Delaloge, on behalf of the PADA-1 investigators

Summary

Background In advanced oestrogen receptor-positive, HER2-negative breast cancer, acquired resistance to aromatase inhibitors frequently stems from *ESR1*-mutated subclones, which might be sensitive to fulvestrant. The PADA-1 trial aimed to show the efficacy of an early change in therapy on the basis of a rising *ESR1* mutation in blood (b*ESR1*^{mut}), while assessing the global safety of combination fulvestrant and palbociclib.

Lancet Oncol 2022; 23: 1367–77
Published Online September 29, 2022
https://doi.org/10.1016/S1470-2045(22)00555-1



"PADA-1 is the first trial to demonstrate that, in most patients, resistance-associated mutations in the estrogen receptor gene can be detected and targeted before tumor progression through *ESR1* mutation monitoring in blood "

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

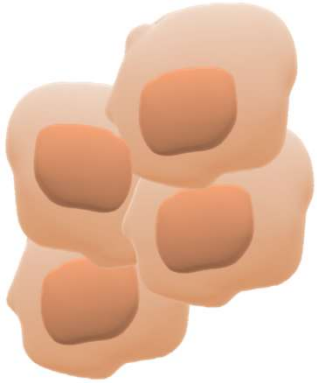
SPECIAL ARTICLE

ESMO recommendations on the use of circulating tumour DNA assays for patients with cancer: a report from the ESMO Precision Medicine Working Group

J. Pascual[1], G. Attard[2], F.-C. Bidard[3,4], G. Curigliano[5,6], L. De Mattos-Arruda[7,8], M. Diehn[9], A. Italiano[10,11,12], J. Lindberg[13], J. D. Merker[14], C. Montagut[15], N. Normanno[16], K. Pantel[17], G. Pentheroudakis[18], S. Popat[19,20], J. S. Reis-Filho[21], J. Tie[22,23], J. Seoane[24,25], N. Tarazona[26,27], T. Yoshino[28] & N. C. Turner[19,20*]

Recommendation: ESR1 mutations should preferentially be tested in ctDNA

PRE-ANALYTICAL VARIABLES FOR CTC ANALYSIS



- CTCs constitute a more difficult blood component in respect to ctDNA to handle pre-analytically
- CTCs possess unique characteristics that **reflect the origin of tumors** and make them distinguishable from normal blood cells
- CTCs can artfully be converted from one phenotypic state to another during **epithelial-to-mesenchymal transition (EMT)**
- Moreover, their scarcity in blood, with approximately **1 CTC at 10^7 peripheral blood mononuclear cells (PBMCs)**, often renders them hard to track down as LB components.
- CTCs are, in most types of cancer, **bigger in size** compared to the other blood cells and present **different deformability and electric properties**
- **Standardization** of pre-analytical variables that affect CTC analysis is at its infancy, and guidelines that regulate their processing are **still under investigation**.
- Nevertheless, some of the pre-analytical steps that precede sample processing are also essential for ensuring further CTC analysis. Different factors should be taken into account concerning the type of downstream CTC analysis: CTC counting or CTC molecular characterization on the transcriptomic, genomic, or proteomic level

PRE-ANALYTICAL VARIABLES FOR CTC ANALYSIS

Blood sampling

Discard the first 5 ml of blood draw to avoid contamination of skin epithelial cells, since cytokeratins are used for CTC detection and enumeration

Transportation

time

Transportation and time intervals are also important for the integrity of CTCs

Blood collection tubes

use of specific tubes for CTC staining and counting that contain preservatives, is required because intracellular proteins and cell surface antigens must be preserved for efficient antibody-based or label-independent enrichment and detection by immunofluorescence. However, these are inappropriate for gene expression analysis

or

CTC enrichment

the co-presence of peripheral blood cells significantly affects the sensitivity and specificity of results. The selection of the appropriate CTC enrichment technology is also a crucial step prior to CTC analysis

Preanalytical aspects for CTC analysis

Clinical Chemistry 64:10
1522–1533 (2018)

Cancer Diagnostics

Evaluation of Preanalytical Conditions and Implementation of Quality Control Steps for Reliable Gene Expression and DNA Methylation Analyses in Liquid Biopsies

Martha Zavridou,[1†] Sofia Mastoraki,[1†] Areti Strati,[1] Eleni Tzanikou,[1] Maria Chimonidou,[1] and Evi Lianidou[1*]

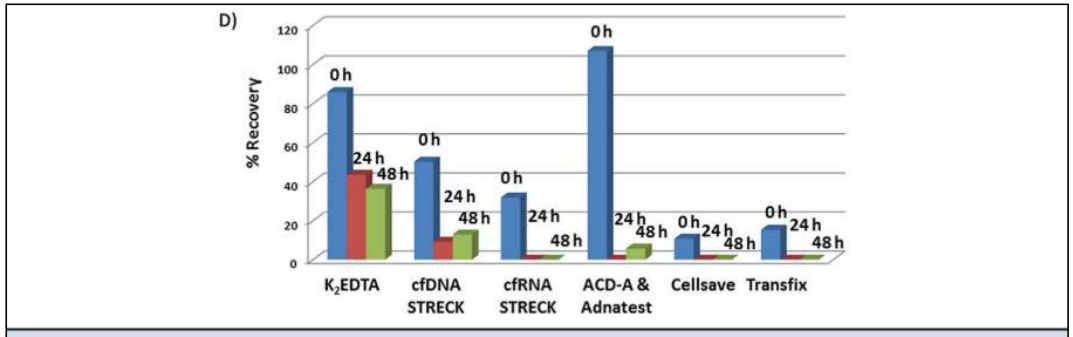


Fig. 4. Evaluation of CTC-RNA stability in 6 different commercially available BCTs at different time points and under different storage conditions.

In all, 100 MCF7 cells were used as recovery control (100%), and results are expressed as Cq values (RT-qPCR). *B2M* (A) and *CK19* (B) RT-qPCR; for *CK19* standard curve (C): Cq plotted vs log (cells/μL), as measured in triplicate, and percentage recovery of *CK19* mRNA transcripts as quantified by RT-qPCR at different time points (D).

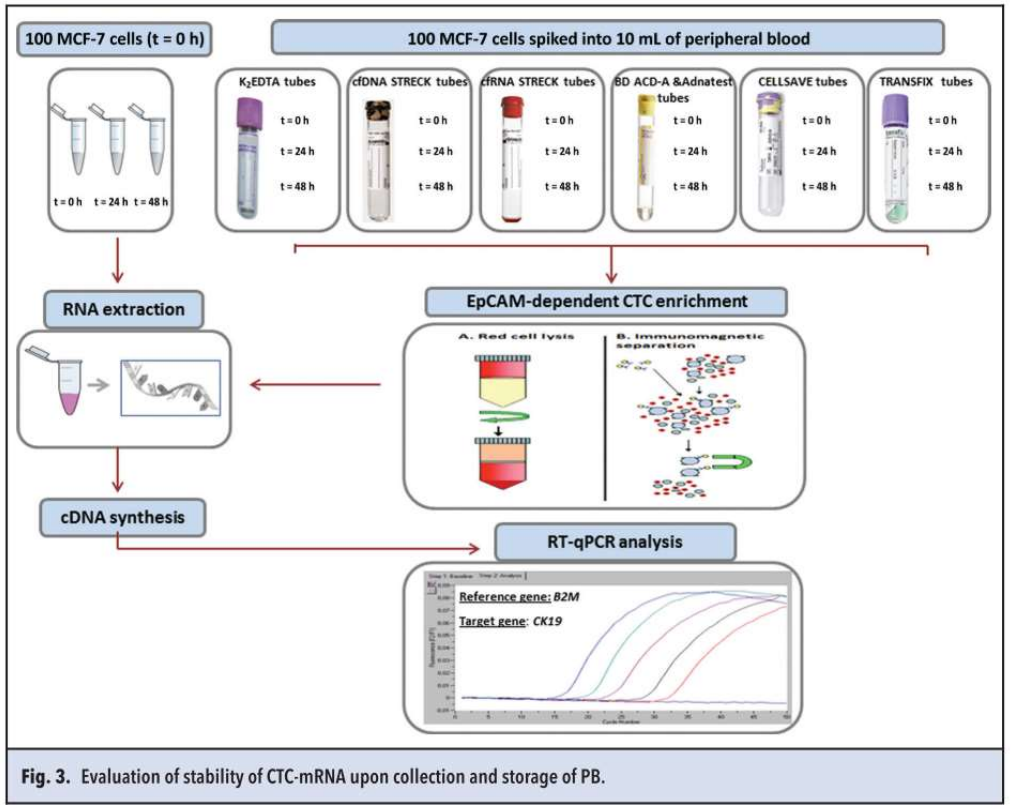


Fig. 3. Evaluation of stability of CTC-mRNA upon collection and storage of PB.

CANCER ID

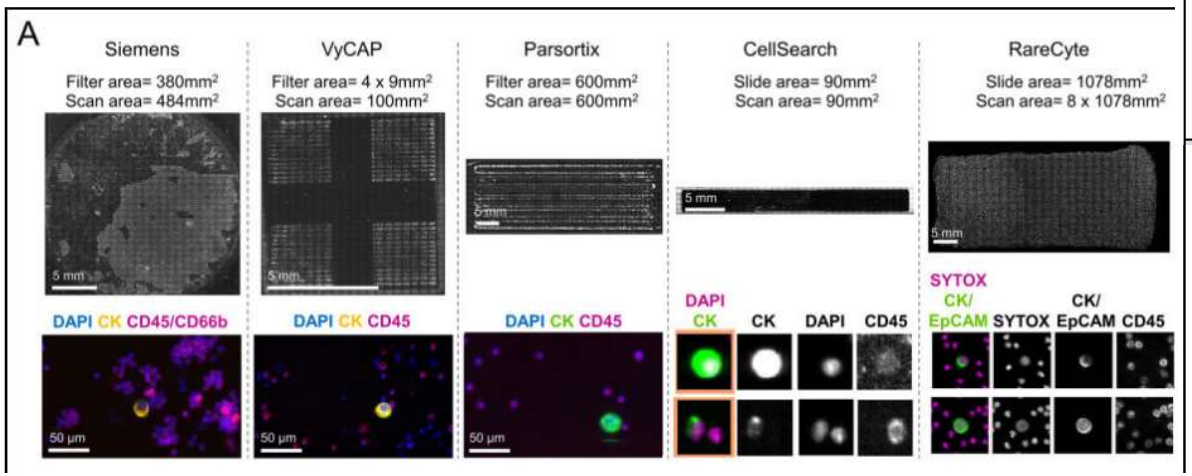
Preanalytical aspects for CTC analysis

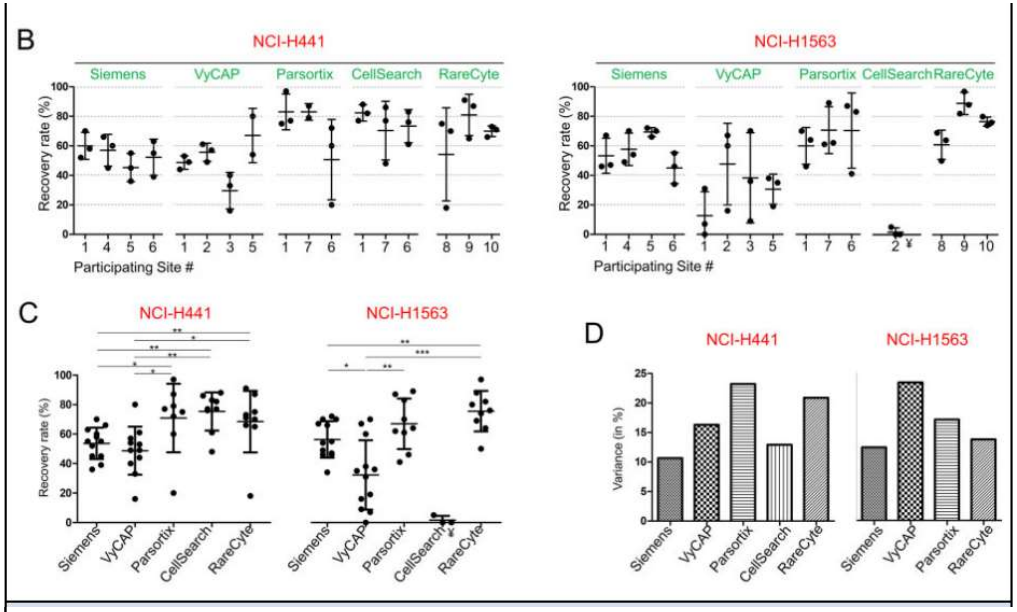
Clinical Chemistry 67:4
631–641 (2021)

Cancer Diagnostics

Proficiency Testing to Assess Technical Performance for CTC-Processing and Detection Methods in CANCER-ID

Rui P.L. Neves,[a,†] Wim Ammerlaan,[b,†] Kiki C. Andree,[c] Sebastian Bender,[d] Laure Cayrefourcq,[e] Christiane Driemel,[a] Claudia Koch,[f] Merlin Verena Luetke-Eversloh,[d] Marianne Oulhen,[g] Elisabetta Rossi,[h,i] Catherine Alix-Panabières,[e] Fay Betsou,[b] Françoise Farace,[g] Sabine Riethdorf,[f] Thomas Schlange,[d] Harriet Wikman,[f] Rita Zamarchi,[i] Klaus Pantel,[f] Leon W.M.M. Terstappen,[c] and Nikolas H. Stoecklein,[a,*] for the CANCER-ID Consortium





CANCER ID

Preanalytical aspects for CTC analysis

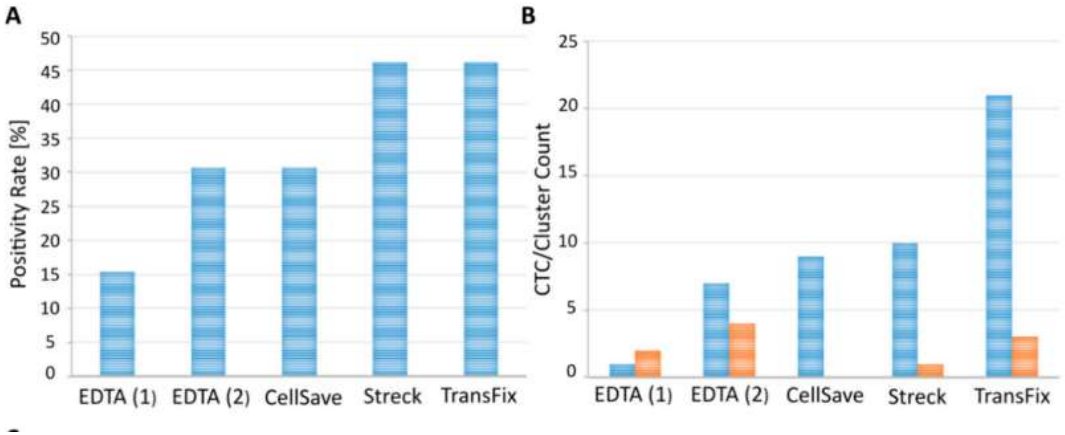
cancers

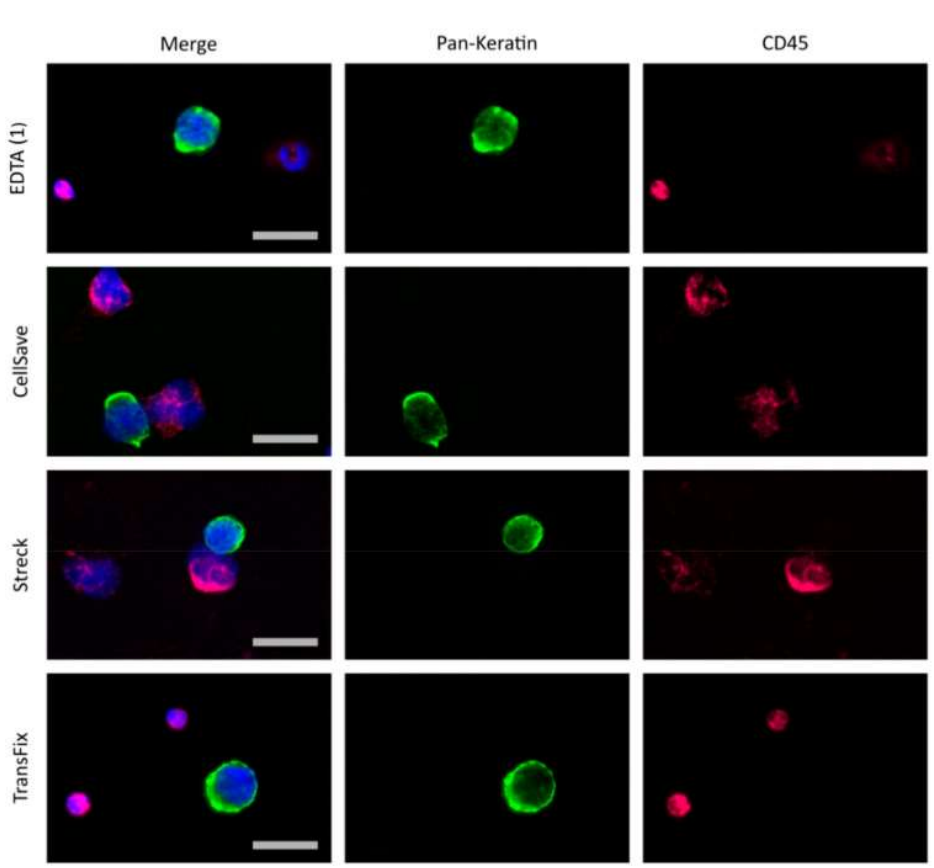
MDPI

Article

Pre-Analytical and Analytical Variables of Label-Independent Enrichment and Automated Detection of Circulating Tumor Cells in Cancer Patients

Claudia Koch [1], Simon A. Joosse [1,†], Svenja Schneegans [1,†], Okka J. W. Wilken [1,†], Melanie Janning [1,2], Desiree Loreth [1], Volkmar Müller [3], Katharina Prieske [3], Malgorzata Banys-Paluchowski [4,5], Ludwig J. Horst [1], Sonja Loges [1,2], Sven Peine [6], Harriet Wikman [1], Tobias M. Gorges [1] and Klaus Pantel [1,*]



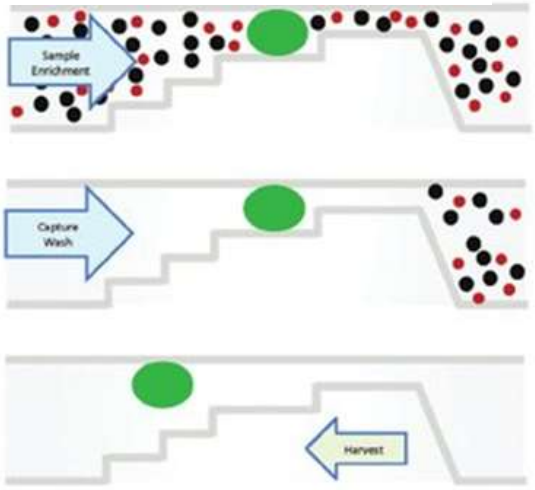


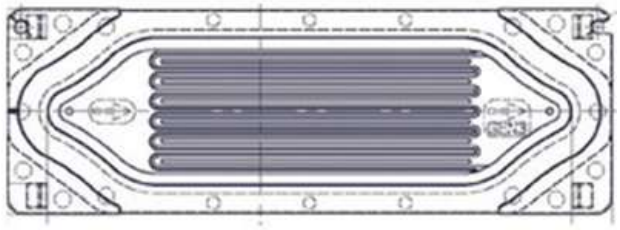
Koch et al, Cancers, 2020

Angle wins first FDA clearance for Parsortix liquid biopsy system

By Catherine Longworth May 26, 2022

U.K.'s Angle plc has become the first company to receive a U.S. FDA product clearance for harvesting intact cancer cells for analysis. Angle reported it scored FDA clearance for its Parsortix system for the capture and harvest of circulating tumor cells (CTCs) from metastatic breast cancer patient blood. Shares in the AIM-listed company soared by more than 50% following the news.





Talk outline

- Standardization of liquid biopsy testing
- **External Quality Control schemes (EQA)**
- Accreditation : ISO-15189
- Conclusions

EXTERNAL QUALITY ASSESSMENT SCHEMES

- Crucial for the harmonization and standardization of the processes by ensuring the evaluation and monitoring of the comparability of test results across different laboratories and over time.

- The purpose of EQA programs includes
  (a) the evaluation of laboratory performance for specific tests and its continuous monitoring,
  (b) the identification of interlaboratory differences,
  (c) the evaluation of method/diagnostic system performances,
  (d) the degree of comparability between methods/diagnostic systems and
  (e) the monitoring of the success of harmonization/standardization efforts for improving results comparability.

  (*Sciacovelli et al. Clin Chem Lab Med 2018; 56(10): 1644–1654*)

External Quality Assessment (EQA) SCHEMES

- Participation of laboratories in EQA schemes is equally important to the internal control assessment for **testing the good performance of molecular assays** in daily practice or as part of multicentered studies.

- Interlaboratory testing conducted **by accredited organizations (ISO17043)** compares genotyping results between diverse laboratories that use the same or alternative detection methodologies and aims **to improve quality and strengthen the awareness of any intra-laboratory deficiencies**

- An important aspect that is highlighted through all the above-mentioned inter-laboratory comparisons is the **genotyping inconsistencies observed between laboratories even when they are using exactly the same methodology**.

- **Inter-laboratory differences underline the urgent need for compliance to specific requirements and guidelines regarding the good clinical practice (GLP), especially in the field of liquid biopsy where standardization of the pre-analytical variants is significantly important.**

EXTERNAL QUALITY ASSESSMENT SCHEMES PROVIDERS

- IQNPATH
  http://www.iqnpath.org/

  EQA-European Society of Pathology
  http://lung.eqascheme.org/

  EMQN
  https://www.emqn.org/

EQA SCHEMES

Diagnostics (Basel). 2020 Oct 18;10(10):837. doi: 10.3390/diagnostics10100837.

Managing Deviating EQA Results: A Survey to Assess the Corrective and Preventive Actions of Medical Laboratories Testing for Oncological Biomarkers

Analysis in tissues

Cleo Keppens [1], Ed Schuuring [2], Elisabeth Mc Dequeker [1]

EQA participants from the European Society of Pathology between 2014 and 2018 for lung and colorectal cancer were contacted, if they had at least one analysis error or test failure in the provided cases, to complete a survey.

For 72.4% of 514 deviating EQA results, an appropriate action was performed, most often including staff training (15.2%) and protocol revisions (14.6%).

The majority of participants adhered to ISO 15189 and implemented suitable actions by designated staff, not limited to accredited laboratories.

However, for 27.6% of cases (by 20 laboratories) no corrective action was taken, especially for pre-analytic problems and complex techniques.

The surveys were feasible to request information on results follow-up and further recommendations were provided.

EQA SCHEMES - ctDNA

EMQN
The European Molecular Genetics Quality Network

GenQA GENOMICS QUALITY ASSESSMENT

IQNPath
International Quality Network for Pathology

EQA
European Society of Pathology

DE GRUYTER Clin Chem Lab Med 2017; aop

Verena Haselmann*, Parviz Ahmad-Nejad, Wolf J. Geilenkeuser, Angelika Duda, Merle Gabor, Romy Eichner, Simon Patton and Michael Neumaier*

Results of the first external quality assessment scheme (EQA) for isolation and analysis of circulating tumour DNA (ctDNA)

Virchows Archiv (2019) 474:681–689
https://doi.org/10.1007/s00428-019-02571-3

ORIGINAL ARTICLE

Check for updates

IQN path ASBL report from the first European cfDNA consensus meeting: expert opinion on the minimal requirements for clinical ctDNA testing

Zandra C. Deans[1] · Rachel Butler[2] · Melanie Cheetham[3] · Elisabeth M. C. Dequeker[4,5] · Jennifer A. Fairley[1] · Francesca Fenizia[6] · Jacqueline A. Hall[7] · Cleo Keppens[4] · Nicola Normanno[6] · Ed Schuuring[8] · Simon J. Patton[3]

Keppens et al. BMC Cancer (2018) 18:804
https://doi.org/10.1186/s12885-018-4694-x

BMC Cancer

RESEARCH ARTICLE Open Access

CrossMark

International pilot external quality assessment scheme for analysis and reporting of circulating tumour DNA

Cleo Keppens[1,2*], Elisabeth M. C. Dequeker[1,2], Simon J. Patton[3], Nicola Normanno[4], Francesca Fenizia[4], Rachel Butler[5], Melanie Cheetham[3], Jennifer A. Fairley[6], Hannah Williams[6], Jacqueline A. Hall[7,8], Ed Schuuring[2,9], Zandra C. Deans[6] and On behalf of IQN Path ASBL

Fairley et al. BMC Cancer (2022) 22:759
https://doi.org/10.1186/s12885-022-09849-x

BMC Cancer

RESEARCH Open Access

Check for updates

Results of a worldwide external quality assessment of cfDNA testing in lung Cancer

Jennifer A. Fairley[1*], Melanie H. Cheetham[2], Simon J. Patton[2], Etienne Rouleau[3], Marc Denis[4], Elisabeth M. C. Dequeker[5], Ed Schuuring[6], Kaat van Casteren[5], Francesca Fenizia[7], Nicola Normanno[8] and Zandra C. Deans[1]

The Journal of Molecular Diagnostics, Vol. 20, No. 4, July 2018

ELSEVIER

the Journal of Molecular Diagnostics
jmd.amjpathol.org

Check for updates

Detection of *EGFR* Variants in Plasma

A Multilaboratory Comparison of a Real-Time PCR EGFR *Mutation Test in Europe*

Cleo Keppens,* John F. Palma,† Partha M. Das,‡ Sidney Scudder,‡ Wei Wen,‡ Nicola Normanno,§ J. Han van Krieken,¶ Alessandra Sacco,§ Francesca Fenizia,§ David Gonzalez de Castro,‖** Selma Hönigschnabl,†† Izidor Kern,‡‡ Fernando Lopez-Rios,§§ Maria D. Lozano,¶¶ Antonio Marchetti,‖‖ Philippe Halfon,*** Ed Schuuring,††† Ulrike Setinek,‡‡‡ Boe Sorensen,§§§ Phillipe Taniere,¶¶¶ Markus Tiemann,‖‖‖ Hana Vosmikova,**** and Elisabeth M.C. Dequeker*

DE GRUYTER Clin Chem Lab Med 2018; aop

Letter to the Editor

Aliki Ntzifa, Christos Kroupis[a], Alexander Haliassos[b] and Evi Lianidou[c,*]

A pilot plasma-ctDNA ring trial for the Cobas® EGFR Mutation Test in clinical diagnostic laboratories

EQA SCHEMES - ctDNA

Keppens et al. BMC Cancer (2018) 18:804
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BMC Cancer

RESEARCH ARTICLE Open Access

International pilot external quality assessment scheme for analysis and reporting of circulating tumour DNA

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1st EQA in cfDNA testing in Greece

DE GRUYTER

Cln Chem Lab Med 2018; aop

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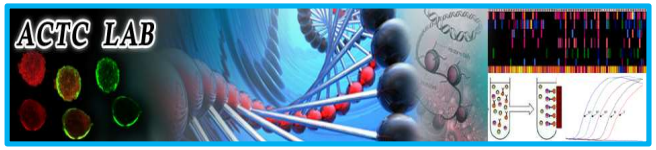
A pilot plasma-ctDNA ring trial for the Cobas® EGFR Mutation Test in clinical diagnostic laboratories

•**Organized by:**



ΕΣΕΑΠ

❖*ISO17043-accredited External Quality Assessment (EQA) organization*

•**Supported by:**

AstraZeneca

1st EQA in cfDNA testing in Greece - RESULTS

Table 1: Plasma *EGFR* mutation results for the eight participating laboratories.[a]

Horizon reference standards	Mutations and percentage in Horizon certified standards	Enrolled laboratories							
		1	2	3	4	5	6	7	8
#1	0.5% T790M	T790M	T790M	T790M	T790M	T790M, **Exon19 Del**	T790M	T790M	T790M
#2	5% T790M	T790M	T790M	**No mutation detected**	T790M	T790M	T790M	T790M	T790M
#3	0.5% L858R	L858R	L858R	L858R	L858R	L858R	**No mutation detected**	L858R	L858R
#4	0.05% E746-A750del	Exon19 Del	Exon19 Del	Exon19 Del	Exon19 Del	Exon19 Del	Exon19 Del	Exon19 Del	Exon19 Del
#5	0.5% E746-A750del	Exon19 Del	Exon19 Del	Exon19 Del	Exon19 Del	Exon19 Del	**No mutation detected**	Exon19 Del	Exon19 Del
#6	Wild type	Wild type	Wild type	Wild type	Wild type	Wild type	**T790M**	Wild type	Wild type
#7	0.5% T790M, L858R	T790M, L858R	T790M, L858R	T790M, L858R	T790M, L858R	T790M, L858R	T790M, L858R	T790M, L858R	T790M, L858R
#8	5% T790M, L858R	T790M, L858R	T790M, L858R	T790M, L858R	T790M, L858R	T790M, L858R	T790M, L858R	T790M, L858R	T790M, L858R
#9	0.5% T790M, E746-A750del	T790M, Exon19 Del	T790M, Exon19 Del	T790M, Exon19 Del	T790M, Exon19 Del	T790M, Exon19 Del	T790M, Exon19 Del	T790M, Exon19 Del	T790M, Exon19 Del
#10	5% T790M, E746-A750del	T790M, Exon19 Del	T790M, Exon19 Del	T790M, Exon19 Del	T790M, Exon19 Del	T790M, Exon19 Del	T790M, Exon19 Del	T790M, Exon19 Del	T790M, Exon19 Del

[a]Cobas® EGFR Mutation Test v2 offers only qualitative genotyping result and also does not refer to the exact nature of exon19 deletion (e.g. e746-750). In bold are the wrong results, that were not expected since these were not the correct answers according to the standards provided.

Ntzifa et al, Clin Chem Lab Med, 2018

1st EQA in cfDNA testing in Greece - Results

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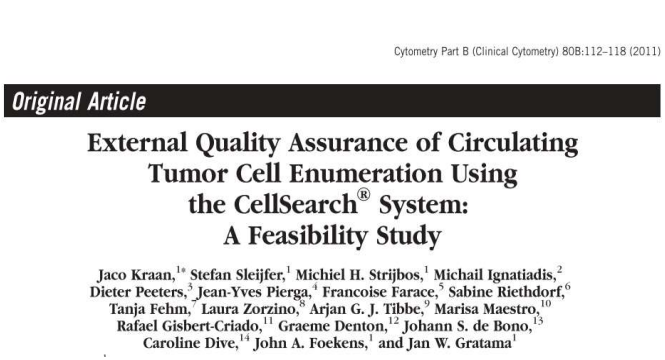
#2	5% T790M	T790M	T790M	**No mutation detected**	T790M	T790M	T790M	T790M	T790M
#3	0.5% L858R	L858R	L858R	L858R	L858R	L858R	**No mutation detected**	L858R	L858R
#4	0.05% E746-A750del	Exon19 Del	Exon19 Del	Exon19 Del	Exon19 Del	Exon19 Del	Exon19 Del	Exon19 Del	Exon19 Del
#5	0.5% E746-A750del	Exon19 Del	Exon19 Del	Exon19 Del	Exon19 Del	Exon19 Del	**No mutation detected**	Exon19 Del	Exon19 Del
#6	Wild type	Wild type	Wild type	Wild type	Wild type	Wild type	**T790M**	Wild type	Wild type
#7	0.5% T790M, L858R	T790M, L858R	T790M, L858R	T790M, L858R	T790M, L858R	T790M, L858R	T790M, L858R	T790M, L858R	T790M, L858R
#8	5% T790M, L858R	T790M, L858R	T790M, L858R	T790M, L858R	T790M, L858R	T790M, L858R	T790M, L858R	T790M, L858R	T790M, L858R
#9	0.5% T790M, E746-A750del	T790M, Exon19 Del	T790M, Exon19 Del	T790M, Exon19 Del	T790M, Exon19 Del	T790M, Exon19 Del	T790M, Exon19 Del	T790M, Exon19 Del	T790M, Exon19 Del
#10	5% T790M, E746-A750del	T790M, Exon19 Del	T790M, Exon19 Del	T790M, Exon19 Del	T790M, Exon19 Del	T790M, Exon19 Del	T790M, Exon19 Del	T790M, Exon19 Del	T790M, Exon19 Del

[a]Cobas® EGFR Mutation Test v2 offers only qualitative genotyping result and also does not refer to the exact nature of exon19 deletion (e.g. e746-750). In bold are the wrong results, that were not expected since these were not the correct answers according to the standards provided.

Ntzifa et al, Clin Chem Lab Med, 2018

EQA SCHEMES - CTCs

- ***To date, official bodies certified according to ISO17043 standard for organizing EQA schemes for CTC analysis do not exist***


Cytometry Part B (Clinical Cytometry) 80B:112–118 (2011)

Original Article

External Quality Assurance of Circulating Tumor Cell Enumeration Using the CellSearch® System: A Feasibility Study

Jaco Kraan,[1*] Stefan Sleijfer,[1] Michiel H. Strijbos,[1] Michail Ignatiadis,[2] Dieter Peeters,[3] Jean-Yves Pierga,[4] Francoise Farace,[5] Sabine Riethdorf,[6] Tanja Fehm,[7] Laura Zorzino,[8] Arjan G. J. Tibbe,[9] Marisa Maestro,[10] Rafael Gisbert-Criado,[11] Graeme Denton,[12] Johann S. de Bono,[13] Caroline Dive,[14] John A. Foekens,[1] and Jan W. Gratama[1]

Variations were observed between laboratories, between instruments and between operators

The main contributor to these inter-laboratory variations was the variability among reviewers of CellSearch images

Ignatiadis et al. Breast Cancer Research 2014, 16:R43
http://breast-cancer-research.com/content/16/2/R43

Breast Cancer RESEARCH

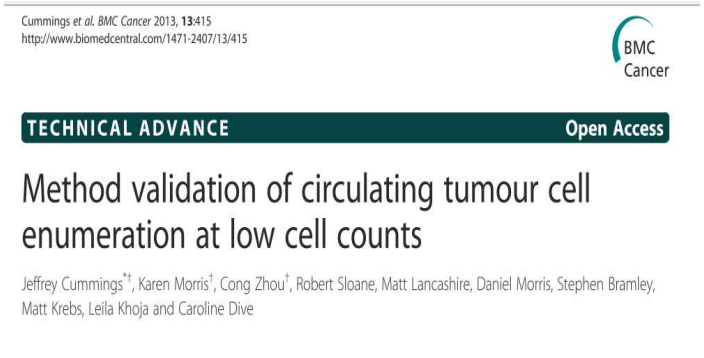
RESEARCH ARTICLE Open Access

International study on inter-reader variability for circulating tumor cells in breast cancer

Michail Ignatiadis[1,2*], Sabine Riethdorf[3], François-Clement Bidard[4], Isabelle Vaucher[4], Mustapha Khazour[4], Françoise Rothé[2], Jessica Metallo[2], Ghizlane Rouas[2], Rachel E Payne[5], Raoul Charles Coombes[5], Ingrid Teufel[6], Ulrich Andergassen[7], Stella Apostolaki[8], Eleni Politaki[8], Dimitris Mavroudis[8], Silvia Bessi[9], Marta Pestrin[9], Angelo Di Leo[9], Michael Campion[10], Monica Reinholz[10], Edith Perez[10], Martine Piccart[1,2], Elin Borgen[11], Bjorn Naume[12], Jose Jimenez[13], Claudia Monica Aura[13], Laura Zorzino[14], Maria Cristina Cassatella[14], Maria Teresa Sandri[14], Bianca Mostert[15], Stefan Sleijfer[15], Jaco Kraan[15], Wolfgang Janni[16], Tanja Fehm[17], Brigitte Rack[7], Leon Terstappen[18], Madeline Repollet[19], Jean-Yves Pierga[4], Craig Miller[19], Christos Sotiriou[1,2], Stefan Michiels[20] and Klaus Pantel[3]

Lower agreement was observed in the non-metastatic setting of M0 breast cancer patients in contrast to the metastatic setting

The lower number of CTCs or the presence of granular CTCs due to administration of therapy were two of the major contributors to inter-reader disagreement


Cummings et al. BMC Cancer 2013, 13:415
http://www.biomedcentral.com/1471-2407/13/415

BMC Cancer

TECHNICAL ADVANCE Open Access

Method validation of circulating tumour cell enumeration at low cell counts

Jeffrey Cummings*†, Karen Morris†, Cong Zhou†, Robert Sloane, Matt Lancashire, Daniel Morris, Stephen Bramley, Matt Krebs, Leila Khoja and Caroline Dive

The pivotal role of standardization of image interpretation through regular training of the readers and through well-designed external quality schemes

Talk outline

- Standardization of liquid biopsy testing
- External Quality Control schemes (EQA)
- **Accreditation : ISO-15189**
- Conclusions

ISO15189 STANDARD

ICS › 03 › 03.120 › 03.120.10

ISO 15189:2012

Medical laboratories — Requirements for quality and competence

- **Scope:** to guide laboratories to develop a quality management system that regulates the whole testing procedure, thus ensuring constant quality services of patient care.

- The ISO15189:2012 describes which procedures and aspects must be included regarding pre-analytical, analytical and post-analytical phase, in order to design a proper quality management system.

- This International Standard can be used by medical laboratories in developing their quality management systems and assessing their own competence. It can also be used for confirming or recognizing the competence of medical laboratories by laboratory customers, regulating authorities and accreditation bodies.

Accreditation of a lab according to the ISO-15189 standard

The **aim of ISO15189 standard** is

- to specify the requirements about the total testing procedure including pre-analytical, analytical and post-analytical phase,
- to give recommendations and
- to offer guidance to laboratories for improving their quality system.

The **two main components** of the ISO15189 standard are
a) the management and
b) the technical requirements,
the fulfilment of which ensures the generation of technically valid results.

- Laboratories are asked to develop and define **their own quality management system that meets ISO15189 requirements** adapted to their total testing process thus aiming to the **quality of services**. Undoubtedly, accredited laboratories often reach more optimal results in contrast to the labs that don't work under standardized procedures

- All the quality metrics mentioned above, including pre-analytical variables, quality control issues, regular participation to EQA schemes or conformity to recommendations about reporting and interpretation of results are well-defined in the requirements of the ISO15189 standard.

ISO15189 REPORTING OF RESULTS

- According to the ISO15189, the results shall be reported "**accurately, clearly, unambiguously, in accordance with any specific instruction**", sample quality/ suitability/adequacy shall be commented, and interpretive comments shall be included

- All reported recommendations suggest the use of "**mutation detected/not detected**" instead of "positive/ negative" result

- **False-positive results** could be attributed to the presence of clonal hematopoiesis or concurrent germline mutations. Therefore, it is advisable to **report the variants detected by the assay and underline genes that are commonly implicated in CHIP**

- **False-negative results** might be subjected to **pre-analytical variables** that could lead to insufficient ctDNA input or to the lower analytical sensitivity of the methodology used.

- **It is essential to include these quality control metrics regarding DNA yield or DNA quality and LOD of the assay in order to avoid over-interpretation of results.**

Accreditation of a LB lab according to the ISO-15189 standard

- In liquid biopsy, **harmonization to standardized procedures** can be achieved **through compliance to ISO15189 standard and laboratory accreditation.**
- ISO15189 certification to laboratories that offer liquid biopsy testing will **upgrade the quality systems** of the labs by enhancing the competence.
- ISO certification constitutes **a prerequisite for reimbursement** of liquid biopsy tests.
- One of the main activities of **European Liquid Biopsy Society (ELBS)** is to encourage and support laboratories to fulfil ISO15189 requirements regarding liquid biopsy testing (https://www.uke.de/english/departments-institutes/institutes/tumor-biology/european-liquid-biopsy-society-elbs/index.html).
- The **recent in vitro diagnostics regulation (IVDR)** included an important requirement regarding the use of laboratory-developed tests (LDT) that are limited **only to the laboratories compliant to the ISO15189 standard** to guarantee a proper validation of such tests

ISO 15189: REQUIREMENTS

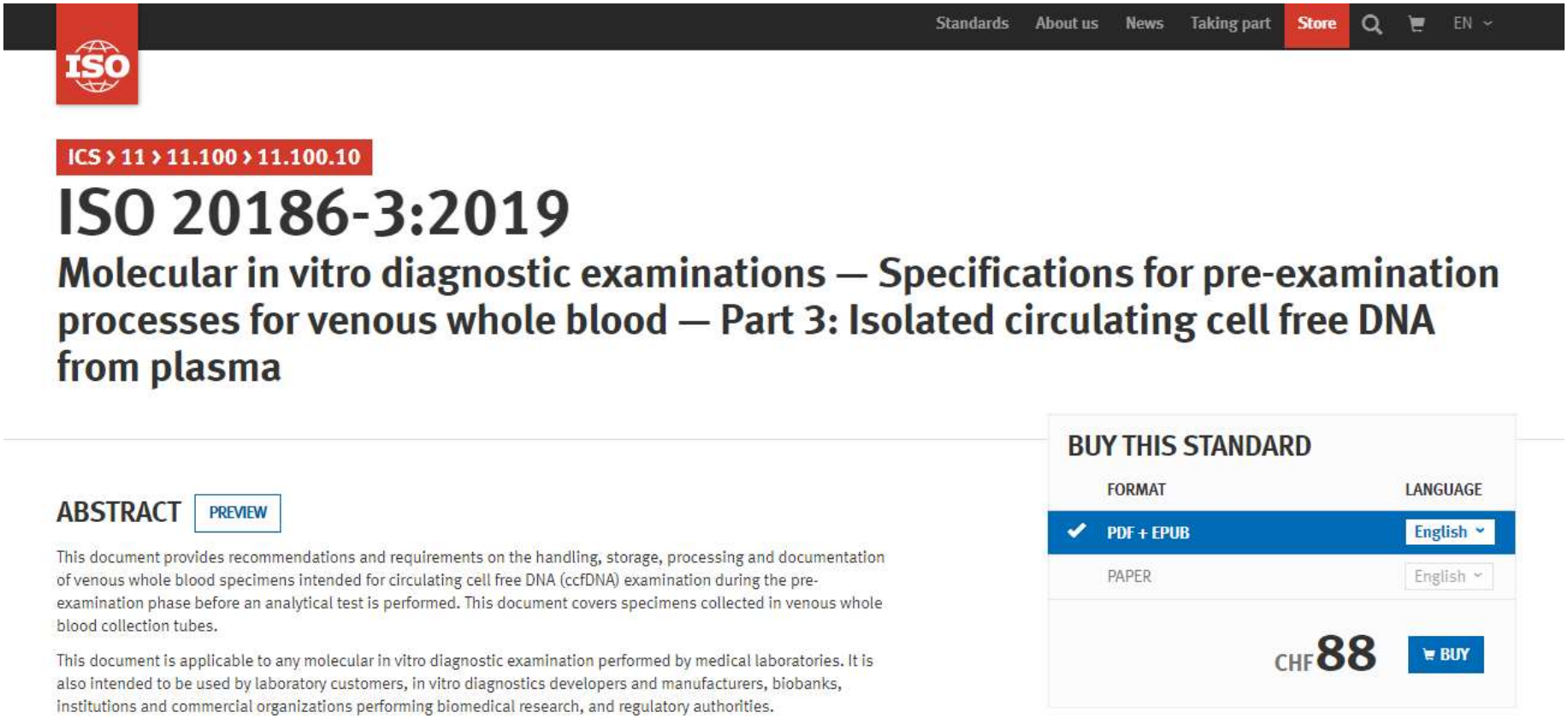
Management requirements

Organization and management responsibility
Quality management system
Document control
Service agreements
Examination by referral laboratories
External services and supplies
Advisory services
Resolution of complaints
Identification and control of nonconformities
Corrective action
Preventive action
Continual improvement
Control of records
Evaluation and audits
Management review

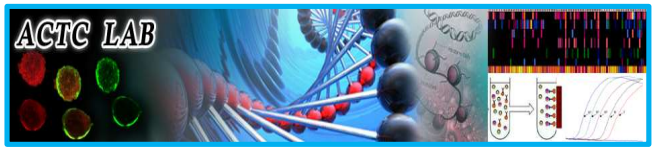
Technical Requirements

Personnel
Accommodation and environmental conditions
Laboratory equipment, reagents, and consumables
Pre-examination processes
Examination processes
Ensuring quality of examination results
Post-examination processes
Reporting of results
Release of results

https://www.iso.org/standard/69800.html



ACTC lab : ACCREDITATION IN LIQUID BIOPSY ANALYSIS



Κλινικές Δοκιμές
Αρ. Πιστ. 1108

ISO15189 certified for:

- **EGFR mutations in ctDNA in COBAS, ROCHE (FDA cleared assay)**

- **CTCs enumeration using the CellSearch system (FDA cleared)**

for metastatic:

- **Breast cancer**
- **Colorectal cancer**
- **Prostate cancer**

- ***PD-L1* mRNA expression in CTCs –Oncolipsy kit (Pharmassist)**

ACTC lab, ISO-15189 ACCREDITATION
CellSearch CTC enumeration

- **ACTC lab is accredited for the CTC enumeration using the CellSearch system according to ISO 15189:2012**

An example when EQA schemes for liquid biopsy analyses are not available

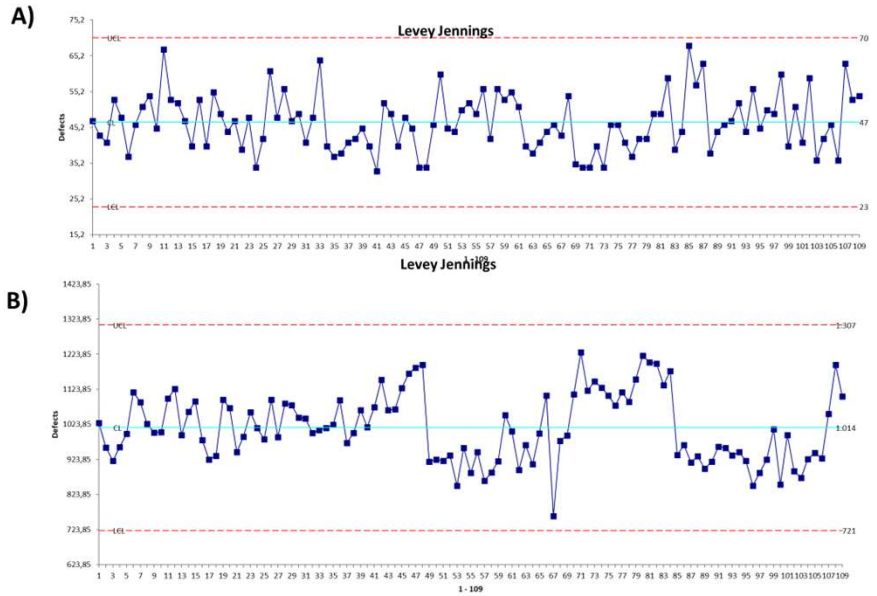
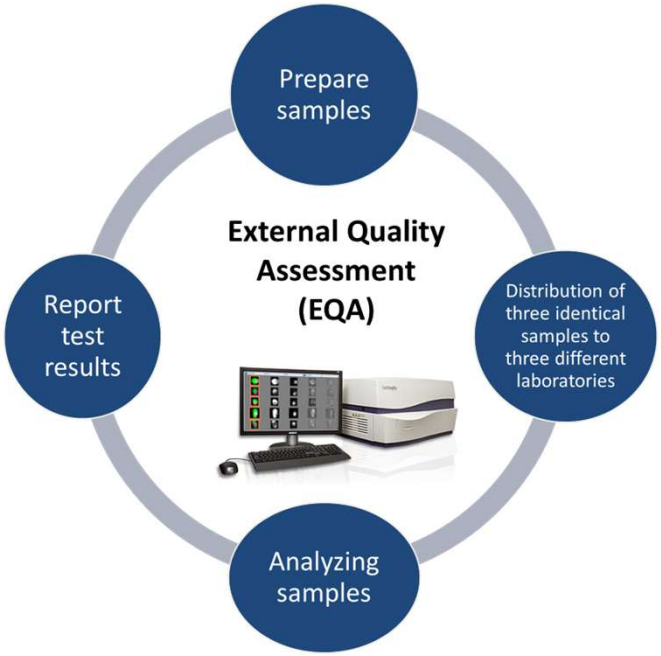


Figure 3. Quality control of CellSearch analysis (Levey–Jennings graphs): A) Low control, B) High Control



Day to day repeatability:
CellSearch® Circulating Tumor Cell Control

	Low CTC numbers			High CTC numbers		
Day	median	range	result	median	range	result
1	48	25-71	36	971	819-1123	927
2	48	25-71	46	971	819-1123	943
3	48	25-71	42	971	819-1123	925
4	48	25-71	36	971	819-1123	871
5	48	25-71	59	971	819-1123	890
6	48	25-71	41	971	819-1123	993
7	48	25-71	51	971	819-1123	853
8	48	25-71	40	971	819-1123	1010
9	48	25-71	60	971	819-1123	923
10	48	25-71	49	971	819-1123	886
11	48	25-71	50	971	819-1123	849
12	48	25-71	45	971	819-1123	920
13	48	25-71	56	971	819-1123	945
14	48	25-71	44	971	819-1123	935
15	48	25-71	52	971	819-1123	957
16	48	25-71	47	971	819-1123	960
Median value			47			924
Standard deviation (SD)			7,4			46
(CV%)			16			5,0

ACTC lab, ISO-15189 ACCREDITATION
CellSearch CTC enumeration

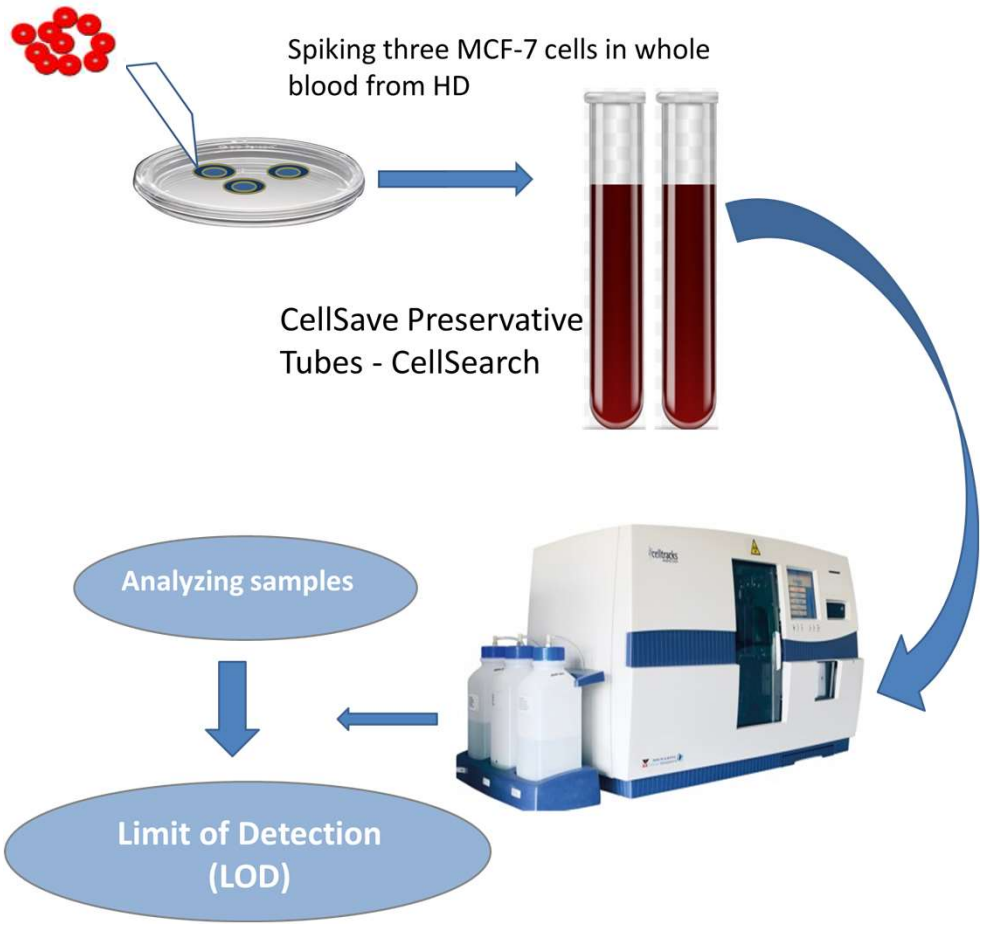


Table 1. Intra-operator repeatability for CTC enumeration

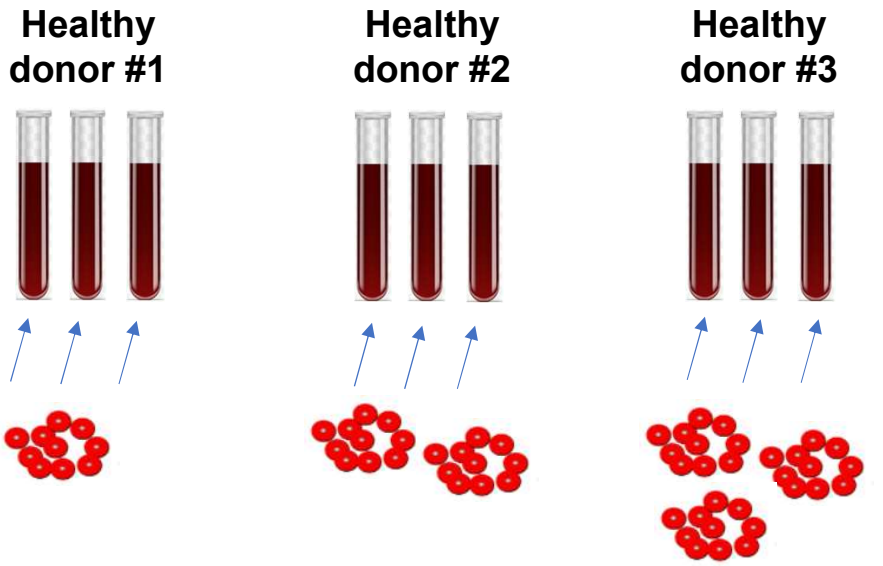
Number of spiked MCF-7 cells	Enumeration of CTCs	Recovery (%)
100	92	92%
100	80	80%
100	74	74%
Mean	82	
SD	9,2	
CV	11%	

Table 2. Validation of the LOD of the CellSearch System

Number of spiked MCF-7 cells	Enumeration of CTCs	Recovery (%)
3	3	100%
3	3	100%
Mean	3	

ACTC lab, ISO-15189 ACCREDITATION
CellSearch CTC enumeration

Preparation of samples: Spiking MCF-7 cells in healthy donors blood samples



EQA 2017 RESULTS

Participating labs: E. Lianidou, K. Pantel, L. Terstappen

Table 3. External Quality Assessment Schemes for CellSearch testing for the year 2017

Samples	Lab#1	Lab#2	Lab#3	Mean	SD	CV%
Sample 1	51	37	34	41	9,1	22,3
Sample 2	12	12	3	9	5,2	57,7
Sample 3	0	0	0	0	0,0	
Sample 4	90	64	62	72	15,6	21,7

EQA 2019 RESULTS

Participating labs: E. Lianidou, R. Zamarchi, N. Stoecklein

Table 4. External Quality Assessment Schemes for CellSearch testing for the year 2019

Samples	Lab#1	Lab#2	Lab#3	Mean	SD	CV%
Sample 1	7,0	0,0	4,0	3,7	3,5	95,8
Sample 2	3,0	2,0	1,0	2,0	1,0	50,0
Sample 3	9,0	7,0	8,0	8,0	1,0	12,5

ELBS EQA: CellSearch, CTC enumeration
(sponsored by Menarini Silicon Biosystems)
9 participating ELBS member sites (8 academic)

1. **Oncopole, Toulouse University Cancer Institute, Toulouse, France, *Anne Pradines / Laura Keller***
2. **Institute of Tumor Biology, UKE, Hamburg, Germany, *Sabine Riethdorf***
3. **Institut Curie, Paris, France, *Jean-Yves Pierga / Renault Shufang***
4. **Oslo University Hospital, Oslo, Norway, *Elin Faye Borgen / Hege Russnes***
5. **Translational Medical Oncology Group (Oncomet), Santiago de Compostela, Spain, *Laura Muinelo Romay***
6. **ACTC Lab, University of Athens, Athens, Greece, *Evi Lianidou***
7. **University Clinic Düsseldorf, Düsseldorf, Germany, *Nikolas Stoecklein***
8. **Erasmus University Medical Center, Rotterdam, Netherlands, *Jaco Kraan***
9. **Menarini HQ/Bologna lab**

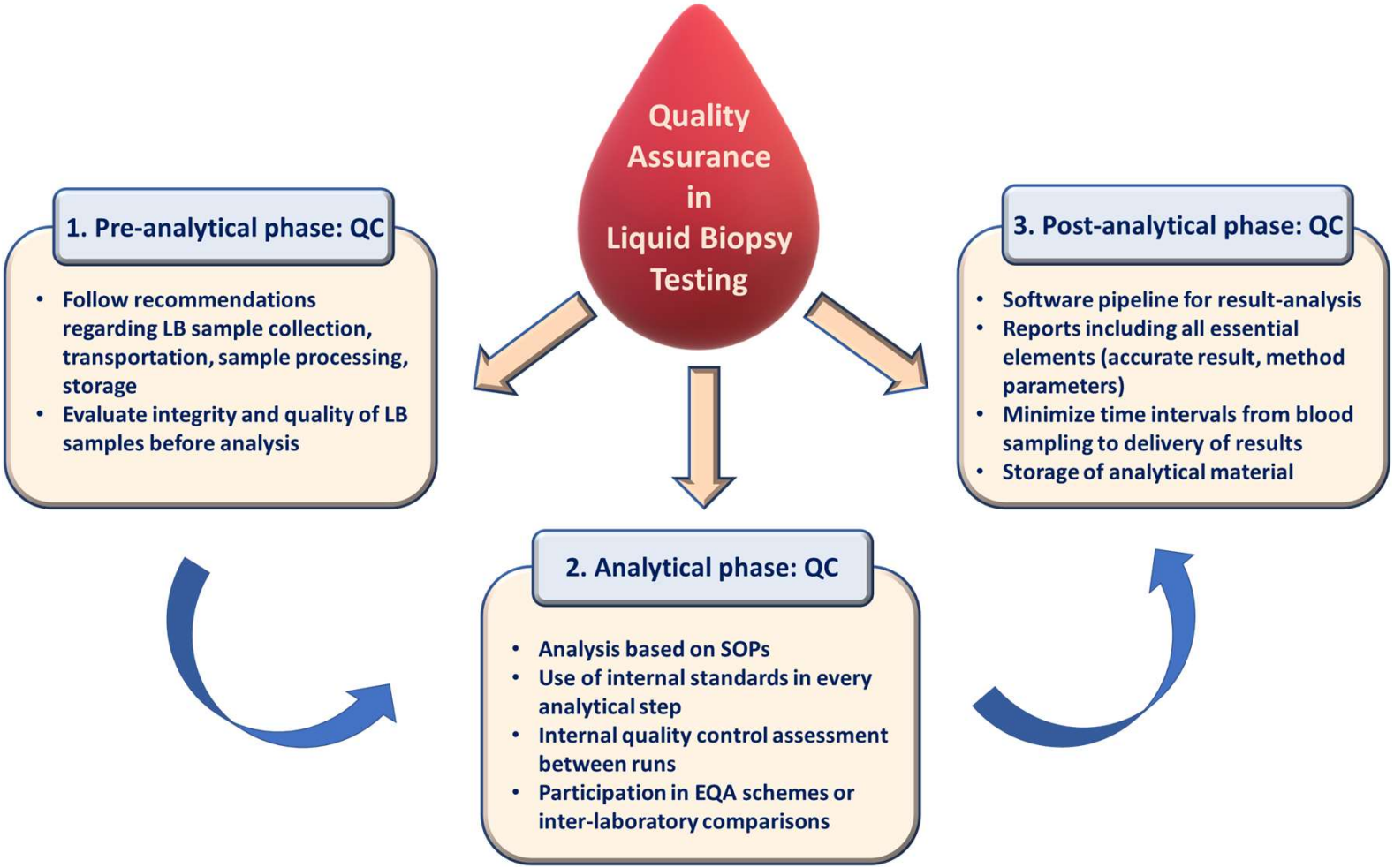
European Liquid Biopsy Society (ELBS)

European Liquid Biopsy Society Network

Talk outline

- Standardization of liquid biopsy testing
- External Quality Control schemes (EQA)
- Accreditation : ISO-15189
- **Conclusions**

QUALITY CONTROL ISSUES IN LIQUID BIOPSY TESTING



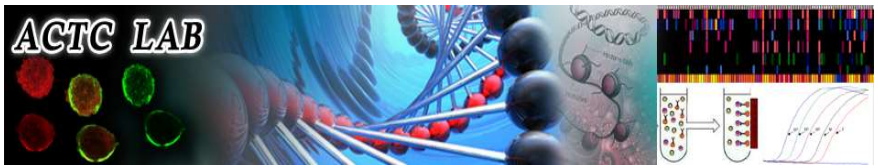
Ntzifa A. & Lianidou E, Crit Rev Clin Lab Sci, 2023

BENEFITS OF ISO-15189 ACCREDITATION

- **Harmonization of results for the same liquid biopsy assays in different labs that use exactly the same technology**
- **Highly important to establish a network of ISO-15189 certified labs for specific liquid biopsy tests within ELBS**
- **Validation of liquid biopsy protocols and their implementation in the clinical setting**
- **Reimbursement of liquid biopsy tests by the National Health System (example: AR-V7, Epic assay, USA)**
- **Evaluation of novel technologies by comparing results for the same samples in ISO-15189 labs**

CONCLUSIONS

- Liquid biopsy is a valuable tool for real-time monitoring of cancer patients during therapy, for treatment selection, and cancer diagnosis and prognosis
- To date, there are guidelines and recommendations mainly for ctDNA testing in solid cancers
- There are still technical challenges to overcome to achieve standardization of liquid biopsy testing and implementation to clinical practice
- Pre-analytical considerations and quality control issues are important steps to consider for the implementation of liquid biopsy assays
- Accreditation of laboratories according to ISO15189 standard is the best way to reassure valid and reliable results in favor of cancer patients



hslb

Hellenic Society of Liquid Biopsy

Muchas Gracias!!!

Thank you for your attention!