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Città della Salute e della Scienza di Torino

SC FORMAZIONE PERMANENTE
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WORKSHOP

CPO
Centro di Riferimento per l'Epidemiologia
e la Prevenzione Oncologica in Piemonte

rete oncologica

PREVENZIONE PIEMONTE

REGIONE PIEMONTE

14 DICEMBRE 2023

CRPT- PROGRAMMA REGIONALE DI SCREENING
PER IL TUMORE DELLA MAMMELLA

PREVENZIONE SERENA

LO SCREENING PER LA MAMMELLA

Livia Giordano

SSD Epidemiologia e Screening – AOU Città della Salute e della Scienza
CPO Piemonte

Un punto luce su: blood cancer tests

Blood cancer tests/Liquid biopsy

Liquid biopsy is an all-encompassing term used to describe the testing of bodily fluids including, blood, urine, cerebrospinal fluid, and saliva. Definitions of liquid biopsy within the cancer diagnostics field tend to focus on tests that target specific biomarkers.

The National Cancer Institute states that a liquid biopsy is; *"A test done on a sample of blood to look for cancer cells from a tumor that are circulating in the blood or for pieces of DNA from tumor cells that are in the blood"*

Nell'arco di un decennio, l'idea che le molecole di origine tumorale che circolano nel sangue e in altri fluidi corporei possano essere sfruttate per rivelare la presenza del cancro e monitorarne il decorso è diventata un importante oggetto di ricerca

L'utilità dei biomarcatori circolanti per la sorveglianza della malattia e per guidare le decisioni terapeutiche è ormai diffusa.

I test di biopsia liquida finora approvati dalla Food and Drug Administration statunitense possono essere utilizzati per identificare l'idoneità a determinati trattamenti mirati, valutare la risposta alla terapia e monitorare la progressione della malattia in pazienti affetti da tumori del polmone, della mammella, della prostata, del colon-retto, delle ovaie e altri tumori solidi.

Affascinante l’ipotesi che possano essere utilizzati come test di diagnosi precoce

Ma a che punto siamo?

Liquid biopsies offer a real-time, minimal-invasive method to detect cancer in the blood through circulating tumor biomarkers

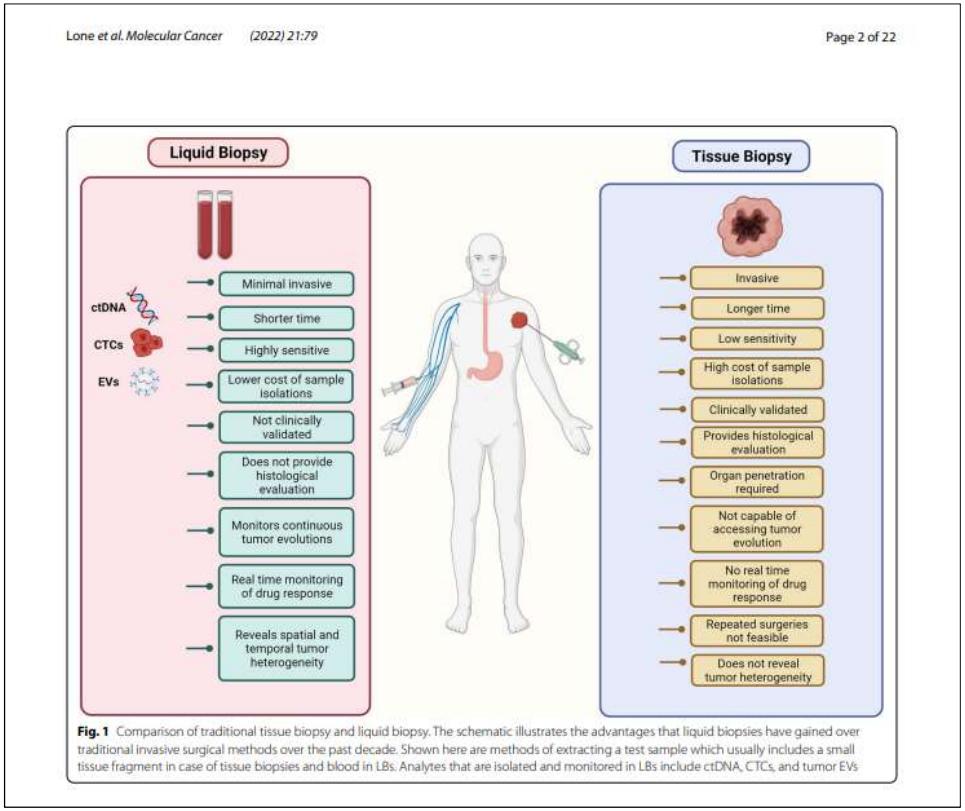


Fig. 1 Comparison of traditional tissue biopsy and liquid biopsy. The schematic illustrates the advantages that liquid biopsies have gained over traditional invasive surgical methods over the past decade. Shown here are methods of extracting a test sample which usually includes a small tissue fragment in case of tissue biopsies and blood in LBs. Analytes that are isolated and monitored in LBs include ctDNA, CTCs, and tumor EVs

Liquid biopsies have been proposed as a novel method for the early detection of cancer.

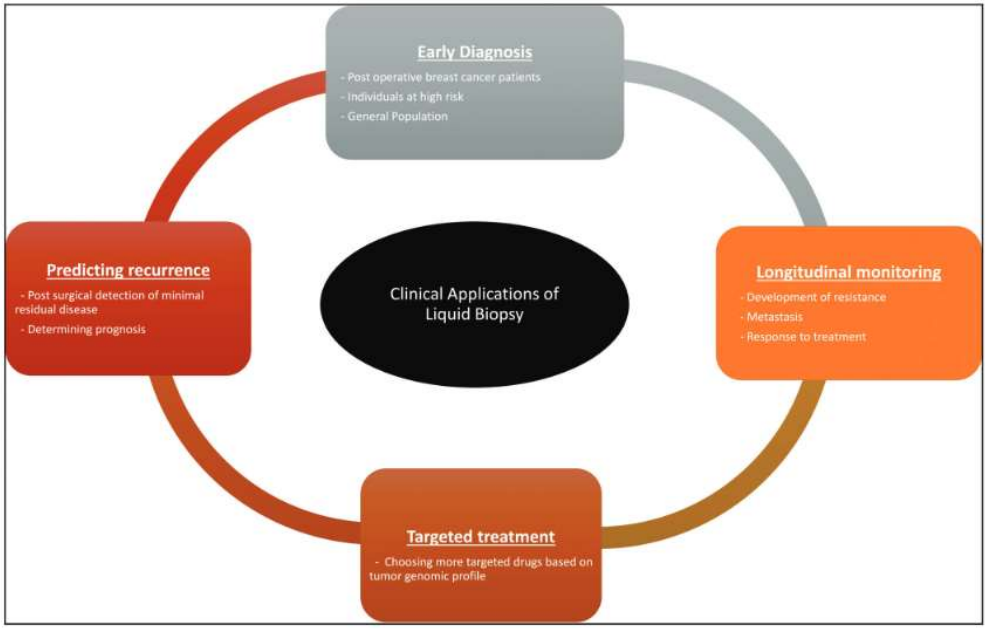


FIGURE 2 Clinical applications of liquid biopsy. Samples can be analyzed for biomarkers in primary or metastatic breast cancer for early diagnosis or detection of recurrence. Longitudinal monitoring is enhanced, because liquid biopsy is a non-invasive approach which enables serial sampling in patients. Additionally, liquid biopsy captures the entire tumor genome, which can be utilized to identify novel genetic markers and design comprehensive individualized gene panels for the purpose of patient stratification and tailored drug therapy

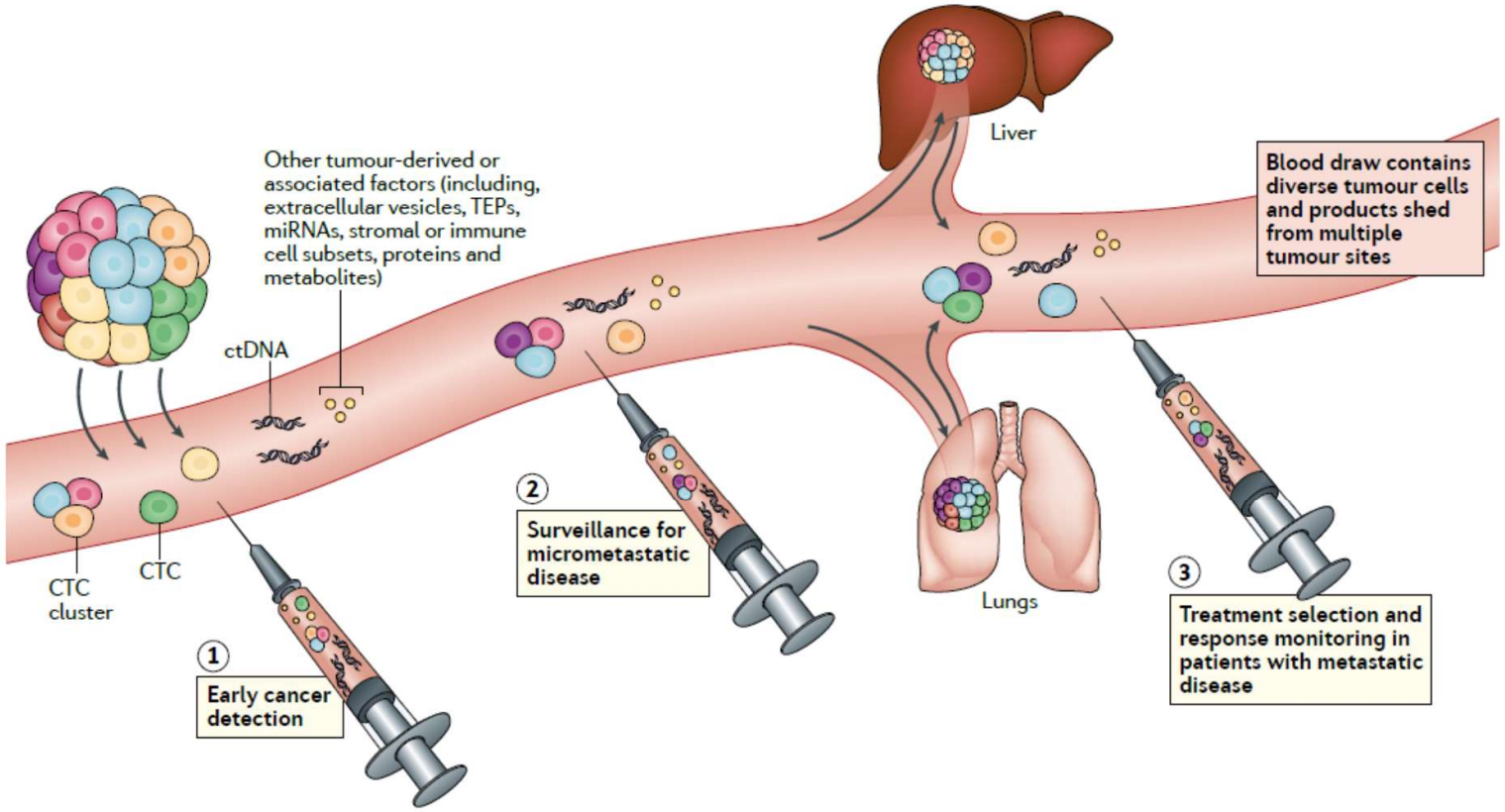
CLINICAL GENETICS WILEY

REVIEW

Liquid biopsy in breast cancer: A comprehensive review

Sahar Alimirzaie[1,2] | Maryam Bagherzadeh[1,3] | Mohammad R. Akbari[1,3,4]

LIQUID BIOPSY



It has been reported that non-invasive body fluid-based tests, including circulating carcinoma antigens (CAs), circulating tumor cells (CTCs), circulating cell-free tumor nucleic acids (DNA or RNA), circulating microRNAs (miRNAs), circulating extracellular vesicles (EVs) in the peripheral blood, nipple aspirate fluid (NAF), sweat, urine, and tears, as well as volatile organic compounds (VOCs) in exhaled breath, have the potential to supplement current clinical approaches to earlier detection of breast cancer.

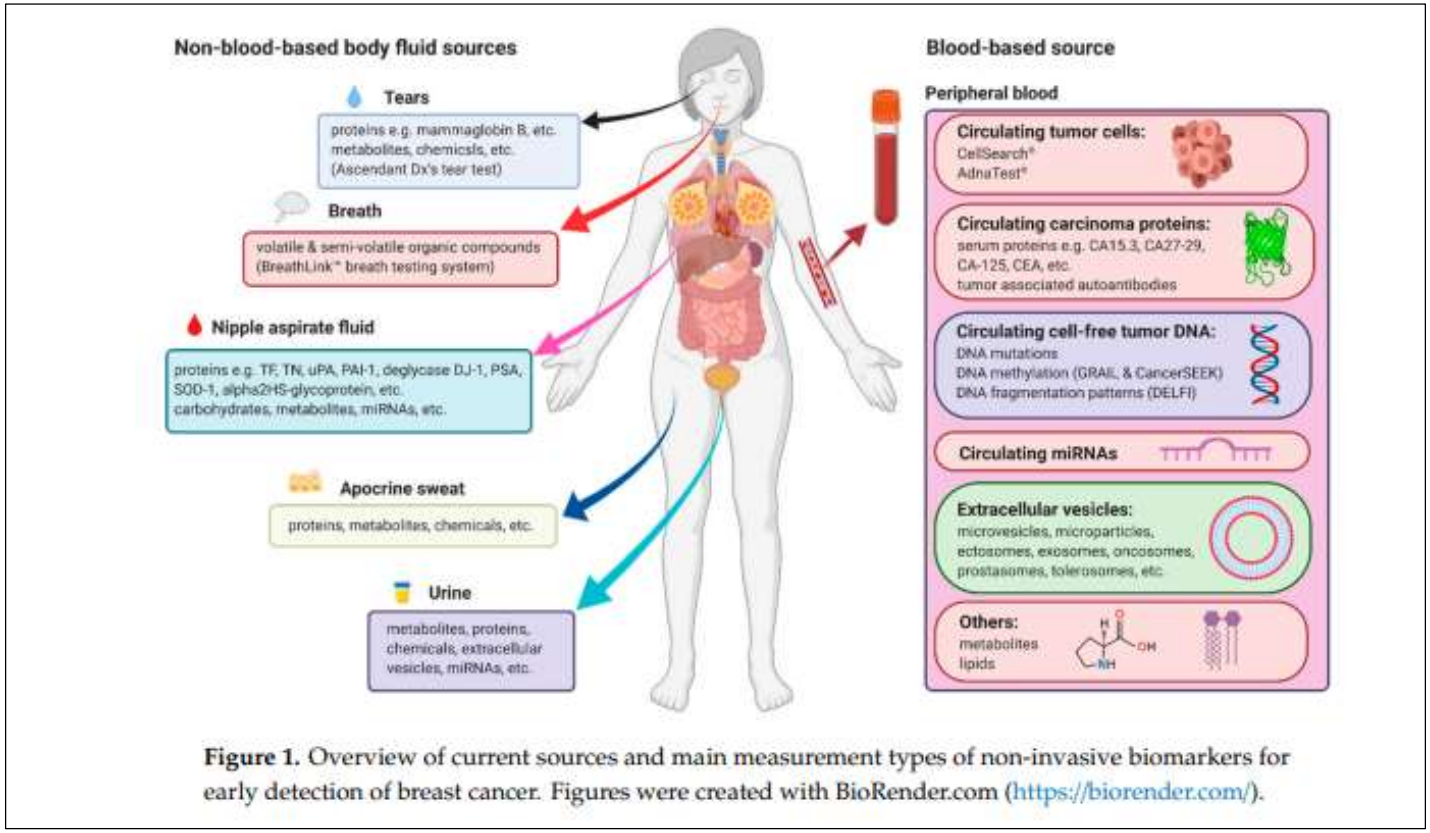


Figure 1. Overview of current sources and main measurement types of non-invasive biomarkers for early detection of breast cancer. Figures were created with BioRender.com (https://biorender.com/).

Un punto luce su: blood cancer tests

I test di biopsia liquida approvati si basano essenzialmente sul rilevamento e sull'analisi di :

Circulating tumor cells: le cellule tumorali circolanti (CTC), che vengono rilasciate dai tumori primari e viaggiano nel flusso sanguigno verso siti distanti;

Cell-free DNA/circulating tumor DNA: il DNA tumorale circolante (ctDNA), che viene rilasciato nel flusso sanguigno dalle cellule tumorali o dalle CTC in fase di morte cellulare e rappresenta una frazione del DNA libero da cellule (cfDNA) normalmente presente nel sangue

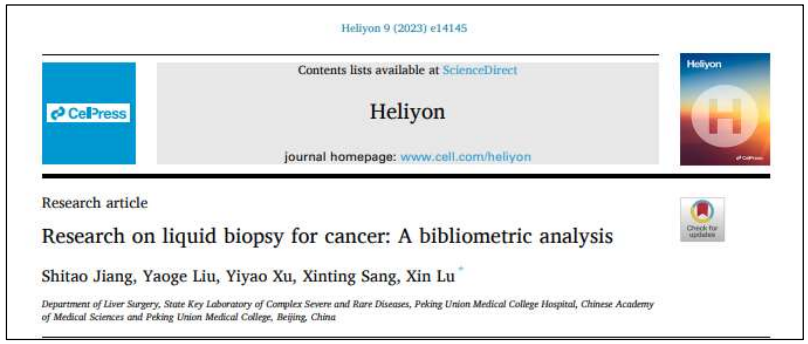
Methylation markers: la metilazione del DNA, che occorre normalmente nell'organismo, se presenta dei patterns anomali è indice di malattie come i tumori

Extracellular vesicles: mediatori della comunicazione intercellulare, rilasciate da tutti i tipi cellulari dell'organismo e, di conseguenza, sono presenti in tutti i fluidi corporei. Si possono suddividere i tre tipologie: gli **esosomi**, le **microvescicole**, i **corpi apoptotici**,

Proteins: come PSA, CA 125

....

Un interesse scientifico (solo?...) crescente



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Research article

Research on liquid biopsy for cancer: A bibliometric analysis

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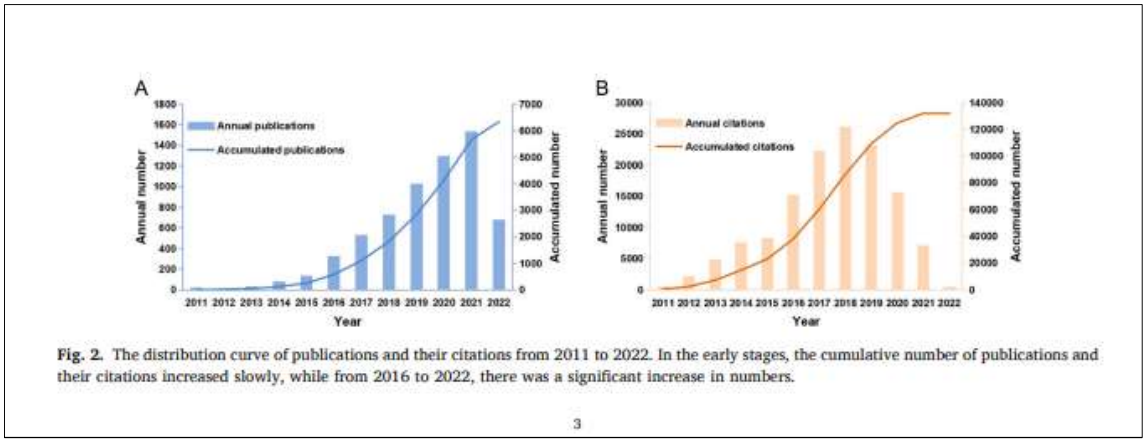

Fig. 2. The distribution curve of publications and their citations from 2011 to 2022. In the early stages, the cumulative number of publications and their citations increased slowly, while from 2016 to 2022, there was a significant increase in numbers.

3

The first publication was published in 2011 with the title “DNA Methylation of Tumor Suppressor and Metastasis Suppressor Genes in Circulating Tumor Cells.” The distribution of publications (Fig. 2A) and their citations (Fig. 2B) by year from 2011 to 2022. The field did not progress or develop significantly during the initial phase. **Citations did not exceed 10,000 until 2014, while publications did not exceed 500 until 2016.**

However, from 2017 to 2021, there was a clear qualitative leap in the cumulative numbers, indicating that research on cancer liquid biopsy was becoming a popular and intriguing topic, and numerous significant breakthroughs were made.

Table 1
The top 10 cited publications.

Rank	Title	Year, Journal	First author	Total citations	TC per Year
1	Liquid Biopsies: Genotyping Circulating Tumor DNA	2014, J CLIN ONCOL	DIAZ LA	1353	150.33
2	Non-invasive analysis of acquired resistance to cancer therapy by sequencing of plasma DNA	2013, NATURE	MURTAZA M	1158	115.80
3	Liquid biopsies come of age: towards implementation of circulating tumour DNA	2017, NAT REV CANCER	WAN JCM	1119	186.50
4	Tumour heterogeneity and resistance to cancer therapies	2018, NAT REV CLIN ONCOL	DAGOGO-JACK I	1072	214.40
5	Liquid biopsy: monitoring cancer-genetics in the blood	2013, NAT REV CLIN ONCOL	CROWLEY E	1060	106.00
6	Integrating liquid biopsies into the management of cancer	2017, NAT REV CLIN ONCOL	SIRAVEGNA G	912	152.00
7	The biology and function of exosomes in cancer	2016, J CLIN INVEST	KALLURI R	872	124.57
8	Noninvasive Identification and Monitoring of Cancer Mutations by Targeted Deep Sequencing of Plasma DNA	2012, SCI TRANSL MED	FORSHEW T	859	78.09
9	Clinical Applications of Circulating Tumor Cells and Circulating Tumor DNA as Liquid Biopsy	2016, CANCER DISCOV	ALIX-PANABIERES C	799	114.14
10	Challenges in circulating tumour cell research	2014, NAT REV CANCER	ALIX-PANABIERES C	770	85.56

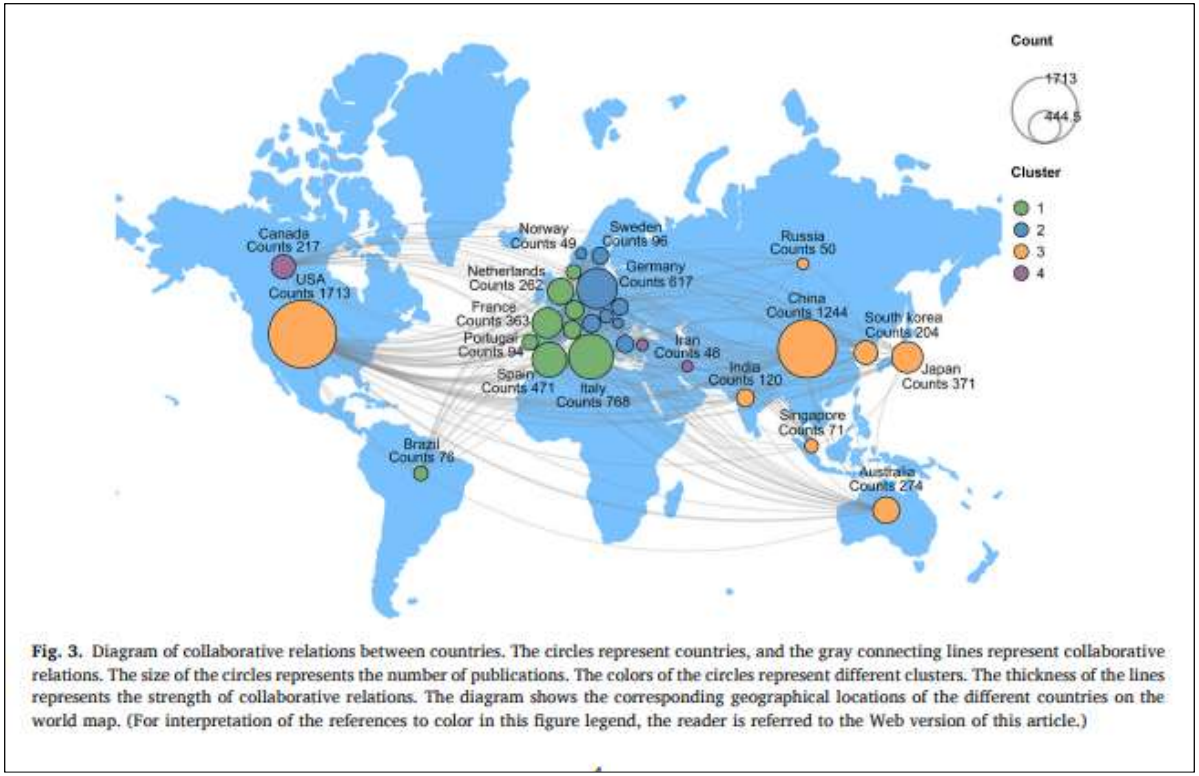

Fig. 3. Diagram of collaborative relations between countries. The circles represent countries, and the gray connecting lines represent collaborative relations. The size of the circles represents the number of publications. The colors of the circles represent different clusters. The thickness of the lines represents the strength of collaborative relations. The diagram shows the corresponding geographical locations of the different countries on the world map. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

According to the co-operative analysis, **the University of Texas** MD Anderson Cancer Center was the most active institution out of 7004 with 129 publications and collaborating with 47 other institutions. Based on the institution's highly cited publications, their research themes focused on applying liquid biopsy to multiple cancers. The carriers of liquid biopsy techniques that they focused on were primarily circulating tumor DNA and exosomes.

Ninety-five countries had collaborative studies on liquid biopsy for cancer. Of these, the United States was the country with the highest number of publications, with 1713 papers and collaborations with 41 other countries, followed by China (1244), Italy (768), Germany (617), and Spain (451).

It is worth noting that from 2015 to 2019, the United States experienced a sudden increase in scientific results. A similar phenomenon occurred in China (2016–2021), Italy (2015–2021), Germany (2014–2020), and Spain (2015–2021). "Burst" can occur when breakthroughs in the field lead to this sudden growth. Additionally, four of the top ten institutions are located in the US, suggesting a vital role for the US in cancer liquid biopsy research.

ICSN
International Cancer
Screening Network

ICSN2023

Cancer screening: in the present, the future

The future depends on what you do today
M. Gandhi

June 21-23, 2023 | **Turin (Italy)**

JUNE 21, 2023

AUDITORIUM HELDER CAMARA - CONCURRENT ROOM 1

17:00-18:30 **CONCURRENT SESSION 1: BLOOD/MULTI-CANCER TEST**

Chairs: **Robert Smith, Ruth Etzioni**

SALONE DELLA PACE - CONCURRENT ROOM 2

17:00-18:30 **CONCURRENT SESSION 2: SCREENING AS A RESEARCH PLATFORM**
(Screening as an opportunity to Contribute to Research)

Chairs: **Carlo Senore, Chyke Doubeni**

- Can India hit the target? Cervix Cancer Control Program in Tamil Nadu State as a case study
  Malliga J Subramanian
- Interval cancers after two rounds of population-based Fecal Immunochemical Test screening in Sweden with gender-specific cut-off levels
  Hanna Ribbing Wilén
- Can we kill three birds with one stone? A cluster-randomised study offering self-sampling for cervical- and colorectal cancer screening to women attending breast cancer screening
  Anne Dorte Lerche Helgestad

PLENARY ROOM - AUDITORIUM HELDER CAMARA

19:00-19.30 Lecture
Art and screening
Alfonso Frigerio

19:30 Welcome Reception

TABLE 1 Comparison of six liquid biopsy components and their application in breast cancer management

	Characteristics	Isolation/Analytical techniques	Applications	Limitations
CTC	• Released from tumor Various types and forms (ie, small and large ar CTC, intact cells	• Size selection (via MOFF) Surface marker enrichment (via CellSearch platform)	• Early detection • Prognosis • Monitor treatment Prediction of recurrence	• Low plasma concentration • Difficulty differentiating between primary tumor and metastatic tumor CTC origin
ctDNA	• ctDNA is a sub population cfDNA • Apoptotic ctDNA is significantly smaller in size and concentration (166 base pairs) • ctDNA mirrors the profile of the tum	litative analysis of tions ted/non-targeted ncing techniques via molecular barcoding)	• Early diagnosis with improved specificity and sensitivity (CanserSEEK) • MRD detection • Longitudinal screening • Metastasis prediction and recurrence • Primary tumor localization Detection of heterogeneity	• Low ctDNA:cfDNA ratio at early-stage cancer • Lack of adequate isolation techniques at low allele frequencies • Inability to analyze RNA and proteins
cfDNA	• Concentration in with cancer • Differing levels in various bodily fluids (1 /mL) • Higher in con than CTC	• Quantitative analysis of concentration (via ddPCR, molecular barcoding)	rly diagnosis ease stage and prognosis	• Limited research on its origin, function and biological relativity • Low sensitivity and specificity
cfRNA	• mRNA and miRNA sned from tumor • Found in various parts (ie, platelets, CTCs and EVs) • Higher in concentration than ctDNA	• Quantitative an (RT-qPCR) • Qualitative ana (microarrays ar	Determination of the genetic expression profile of tumor • Epigenetic	• Inability to analyze intergenic DNA • Difficulty in isolation due to size limitations ack of reliable methods for practical and reproducible application in the clinic
TEP	• Devoid of a nucleus • Harbor mRNA/miRNA • Protect tumor components • Guide and stabilize the secondary lesions in endothelium at metastatic sites • Secrete factors to promote angiogenesis • Facilitate intravasation of metastatic tumor cells	• Quantitativ • Qualitative a (TEP-RNA sequencing)	• Potential use for early cancer detection	imited research in the field Difficulty differentiating between TEPs and platelets due to other non-cancerous and inflammatory diseases • Lack of reliable methods for practical and reproducible application in the clinic
Exosome	• Shed via exocytosis of MVBs in tumor cells/ healthy non-neoplastic cells • Carriers of signals for intercellular communication (role in metastasis) • Contains large amounts of lipid rafts, ctDNA, and tumor mRNA and miRNA	• Analysis of gene expression profile of tumors, at the level of cfNAs, miRNA and mRNA (qRT-PCR, microarrays)	• Metastas or growth	• Inability to differentiate between tumor-derived and healthy exosomes • Lack of reliable methods for practical and reproducible application in the clinic

Abbreviations: cfDNA, cell-free DNA; cfNA, cell-free nucleic acid; cfRNA, cell-free RNA; CTC, circulating tumor cells; ctDNA, circulating tumor DNA; ddPCR, digital droplet-PCR; EV, extracellular vesicles; MOFF, multi-orifice flow fractionation; MRD, minimal residual disease; MVB, multivesicular bodies; NGS, next-generation sequencing; PCR, polymerase chain reaction; RT-qPCR, quantitative reverse transcription PCR; TEP, tumor-educated platelets.

- Bassa concentrazione ematica
- Problematiche tecniche inerenti l'isolamento del biomarcatore
- Falsi positivi (presenza anche in altre condizioni)
- Riproducibilità bassa
- Costi alti
- Problemi di sensibilità e specificità

Cureus

Biomarker	Characteristics	Advantages	Limitations
CTCs	Circulating tumor cells	Captures tumor heterogeneity	Rarity of CTCs, challenging isolation
ctDNA	Fragments of tumor DNA	Reflects genetic alterations	Low abundance in early-stage cancers, limited mutation detection
Exosomes	Small extracellular vesicles	Carry tumour-specific molecules	Heterogeneous composition, isolation challenges
microRNAs	Small non-coding RNA molecules	Stable in biofluids, reflects tumor state	Non-specific to tumors, influenced by other conditions

TABLE 1: Characteristics, advantages, and limitations of biomarkers in liquid biopsies

[1,4,28-33]

The table was created by the authors themselves.

CTC
- Bassa concentrazione ematica

In early-stage cancers, the low and variable amount of biomarkers raises the simple problem that different blood samples from the same individual might yield different results. **Low biomarker amounts also dictate that liquid biopsy techniques must be highly sensitive; however, the high sensitivity needed to detect ctDNA—or other biomarkers—can affect the specificity of the test. There is a concern that benign mutations could well trigger false-positive results**

CTC/ctDNA
- Costi alti
- Problemi di sensibilità e specificità

Currently, the cost of sequencing would also be prohibitive for utilisation as a screening tool. New ways of increasing sensitivity need to be developed for the potential of liquid biopsies in screening and early detection to be reached. **There are several promising avenues of research on this front—alternate methods of ctDNA analysis including novel epigenetic assay methods examining fragmentation patterns or combining ctDNA with other molecular marker types such as circulating proteins**

CTC
- Bassa concentrazione ematica

Extracellular vesicles (EVs) are membrane-wrapped particles that are released by most cell types and carry different types of molecules, including proteins, lipids, and nucleic acids. Originally considered a means to eliminate cellular waste, EVs play critical roles in cell-to-cell communication, serving as tiny packages the cells send to each other to exchange information and material. Given that tumors shed EVs in the blood, their molecular cargo is being evaluated as a source of tumor-derived material.

The use of EVs for liquid biopsy applications has some advantages over CTCs and ctDNA. EVs are **more abundant in the blood circulation than CTCs and, thanks to their structural features, remain stable even in harsh tumor microenvironment conditions. I**n addition, their cargo molecules reflect the physiologic state of the cells of origin.

One significant challenge in the application of EVs for liquid biopsy is their **complex isolation**. Researchers are investigating new methods to isolate EVs, to distinguish EVs of tumor origin from those derived from normal cells, and to profile their contents.

IMPROVING THE SENSITIVITY OF LIQUID BIOPSIES

One challenge that limits the application of liquid biopsies in the clinic is the very low amount of cfDNA in the blood. Research presented at the AACR Annual Meeting 2023 showed that cfDNA recovery might be boosted through the use of a priming agent given before blood collection. This agent consisted of engineered monoclonal antibodies that persist in the circulation and bind cfDNA, protecting it from being quickly cleared from the blood. In tumor-bearing mice, this priming strategy led to a 19-fold increased ctDNA recovery, improving the sensitivity of cancer detection and suggesting that priming agents could represent a viable strategy to boost the sensitivity of liquid biopsies and expand their applications.

Table 1. Summary of potential non-invasive biomarkers using liquid biopsy for early detection of breast cancer.

Study, Year	Sample	N	Stage of Disease	Biomarker	Sensitivity (%)	Specificity (%)	Accuracy (%)	Detection Method	Ref.
Kamel et al., 2016	Plasma	95	I–IV	cf-DNA	85.3	100	-	RT-qPCR	[26]
Li et al., 2016	Plasma	86	I–II	cf-DNA	75.6–94.2	30.4–53.3	66–75	Microfluidic PCR and Bisulfite Sequencing Technology	[27]
Cohen et al., 2018	Plasma	54	I–III	ct-DNA	33	99	73	Multiplex-PCR, NGS and CancerSEEK	[28]
Beaver et al., 2014	Plasma	29	I–III	ct-DNA	93.3	100	96.7	ddPCR	[29]
Kruspe et al., 2017	Plasma	29	IV	CTCs	-	-	-	RT-qPCR	[30]
Shimomura et al., 2016	Serum	1206	I–IV	miRNA	97.3	82.9	89.7	Microarray and RT-qPCR	[31]
Erbes et al., 2015	Serum and urine	24	Early	miRNA	83.3	87.5	88.7	RT-qPCR	[32]
Hirschfeld et al., 2020	Urine	69	Early	miRNA	98.6	100	99.9	RT-qPCR	[33]
Zhong et al., 2020	Serum	50	I–IV	lncRNA	87	70.6	87	RT-qPCR	[37]
Best et al., 2015	Blood	39	I–IV	TEPs	-	-	71	mRNA sequencing	[39]
Zhang et al., 2010	Saliva	40	I–IV	mRNA and proteins	83	97	92	Microarray, RT-qPCR, and immunoblot	[40]
López-Jornet et al., 2021	Saliva	91	I–IV	Proteins	67.5	66.7	-	Biochemical analyses	[41]
Kure et al., 2021	Urine	110	I–II	VOCs	93.3	83.3	88.3	GCMS	[42]

cfDNA, cell-free DNA; CTCs, circulating tumor cells; miRNA, microRNA; lncRNA, long non-coding RNAs; TEPs, tumor-educated platelets; VOCs, volatile organic compounds; mRNA, messenger RNA; NGS, next-generation sequencing; RT-qPCR, reverse transcription quantitative real-time PCR; GCMS, gas chromatography–mass spectrometry; ddPCR, droplet digital polymerase chain reaction.

Open Access Review

Liquid Biopsy as a Tool for the Diagnosis, Treatment, and Monitoring of Breast Cancer

by Ana Julia Aguiar de Freitas [1], Rhafaela Lima Causin [1], Muriele Bertagna Varuzza [1], Stéphanie Calfa [1], Cassio Murilo Trovo Hidalgo Filho [2], Tatiana Takahasi Komoto [1], Cristiano de Pádua Souza [3] and Márcia Maria Chiquitelli Marques [1,4,*]

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[3] Barretos Cancer Hospital, Barretos 14784-400, Brazil
[4] Barretos School of Health Sciences, Dr. Paulo Prata–FACISB, Barretos 14785-002, Brazil
* Author to whom correspondence should be addressed.

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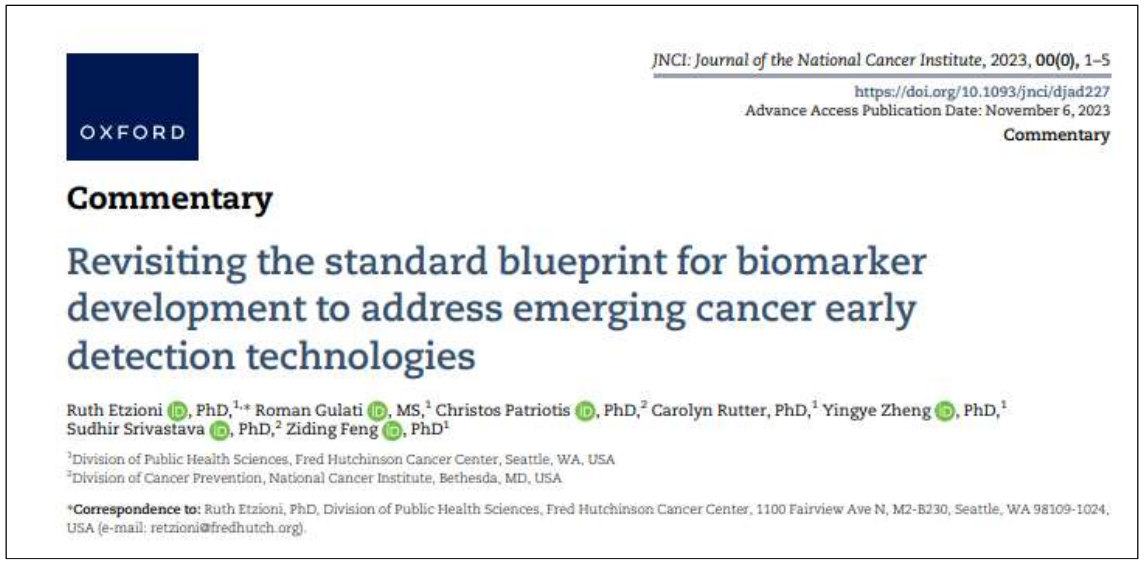
Cambierà la valutazione di impatto?



JNCI: Journal of the National Cancer Institute, 2023, 00(0), 1–5
https://doi.org/10.1093/jnci/djad227
Advance Access Publication Date: November 6, 2023
Commentary

OXFORD

Commentary

Revisiting the standard blueprint for biomarker development to address emerging cancer early detection technologies

Ruth Etzioni, PhD,[1,*] Roman Gulati, MS,[1] Christos Patriotis, PhD,[2] Carolyn Rutter, PhD,[1] Yingye Zheng, PhD,[1] Sudhir Srivastava, PhD,[2] Ziding Feng, PhD[1]

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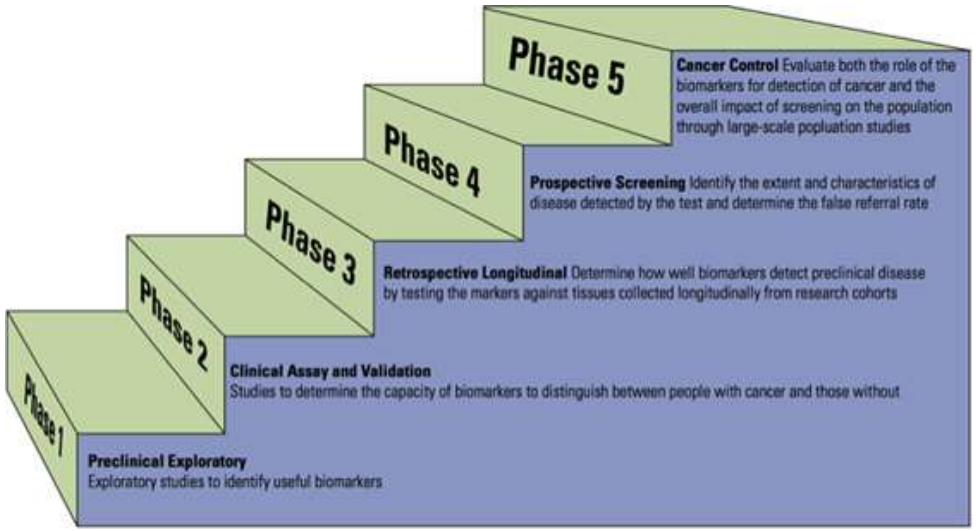
Establishing that a new test meets these 3 requirements while also controlling adverse outcomes, such as unnecessary biopsies and overdiagnosis, involves a corresponding sequence of studies that typically take many years to complete.

1. **test sensitivity in a prospective screening setting must be adequate**
2. **the shift to early curable stages must be meaningful**
3. **any stage shift must translate into clinically significant mortality benefit.**



The 5 phases of biomarkers development widely accepted by the biomarker research community.

- Phase 1: Preclinical exploratory studies.
- Phase 2: Clinical Assay Development for Clinical Disease.
- Phase 3: Retrospective Longitudinal Study.
- Phase 4: Prospective Screening Studies.
- Phase 5: Cancer Control Studies (RCT)

In the past, determining mortality benefit has required lengthy randomized screening trials, but interest is growing in expedited trial designs with shorter-term endpoints. Whether and how best to use such endpoints in a manner that retains the rigor of the PBD remains to be determined. We discuss how **computational disease modeling** can be harnessed to learn about screening impact and meet the needs of the moment

cancers

MDPI

Article

The Early Detection of Breast Cancer Using Liquid Biopsies: Model Estimates of the Benefits, Harms, and Costs

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Abstract: Breast cancer screening is associated with harms, such as false-positives and overdiagnoses, and, thus, novel screen tests can be considered. Liquid biopsies have been proposed as a novel method for the early detection of cancer, but low cell-free DNA tumor fraction might pose a problem for the use in population screening. Using breast cancer microsimulation model MISCAN-Fadia, we estimated the outcomes of using liquid biopsies in breast cancer screening in women aged 50 to 74 in the United States. For varying combinations of test sensitivity and specificity, we quantify the impact of the use of liquid biopsies on the harms and benefits of screening, and we estimate the maximum liquid biopsy price for cost-effective implementation in breast cancer screening at a cost-effectiveness threshold of USD 50,000. We investigate under what conditions liquid biopsies could be a suitable alternative to digital mammography and compare these conditions to a CCGA substudy. Outcomes were compared to digital mammography screening, and include mortality reduction, overdiagnoses, quality-adjusted life-years (QALYs), and the maximum price of a liquid biopsy for cost-effective implementation. When liquid biopsies are unable to detect DCIS, a large proportion of overdiagnosed cases is prevented but overall breast cancer mortality reduction and quality of life are lower, and costs are higher compared to digital mammography screening. Liquid biopsies prices should be restricted to USD 187 per liquid biopsy depending on test performance. Overall, liquid biopsies that are unable to detect ductal carcinoma in situ (DCIS) need to be able to detect small, early-stage tumors, with high specificity, at low costs in order to be an alternative to digital mammography. Liquid biopsies might be more suitable as an addition to digital mammography than as an alternative.

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

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Screening asymptomatic populations for cancer

The ultimate application of ctDNA for cancer care is the potential for identifying early-stage cancers and precancerous conditions in asymptomatic individuals with a view to take actions to increase cure rates or even prevent invasive cancer development. Large population studies are required to provide sufficient level of evidence for this concept to become a reality. A requisite for a standardised and reliable screening tool is to achieve high levels of specificity while maintaining clinically useful levels of sensitivity. This remains technically challenging using ctDNA, particularly as early-stage cancers shed low amounts of ctDNA. Ideally, ctDNA-based screening should also be informative of the cancer tissue of origin, which is far from optimal at this stage.

Sensitivity mainly depends on the ability to detect ctDNA confidently at very low purity, with no prior knowledge of mutations present in the cancer, and with an ability to discriminate population level single nucleotide polymorphisms and CHIP mutations.[32] Large efforts have been conducted in this field so far, with studies demonstrating high specificity and encouraging sensitivity with error-corrected sequencing[116] that may be combined with protein biomarkers,[117] genome-wide fragmentation patterns[118] and methylation-based ctDNA assays.[119] Data are awaited from large studies conducted in true screening populations, to assess ctDNA assays as a multi-cancer screening tool, but at this point screening cannot be considered as a validated use for ctDNA assays.

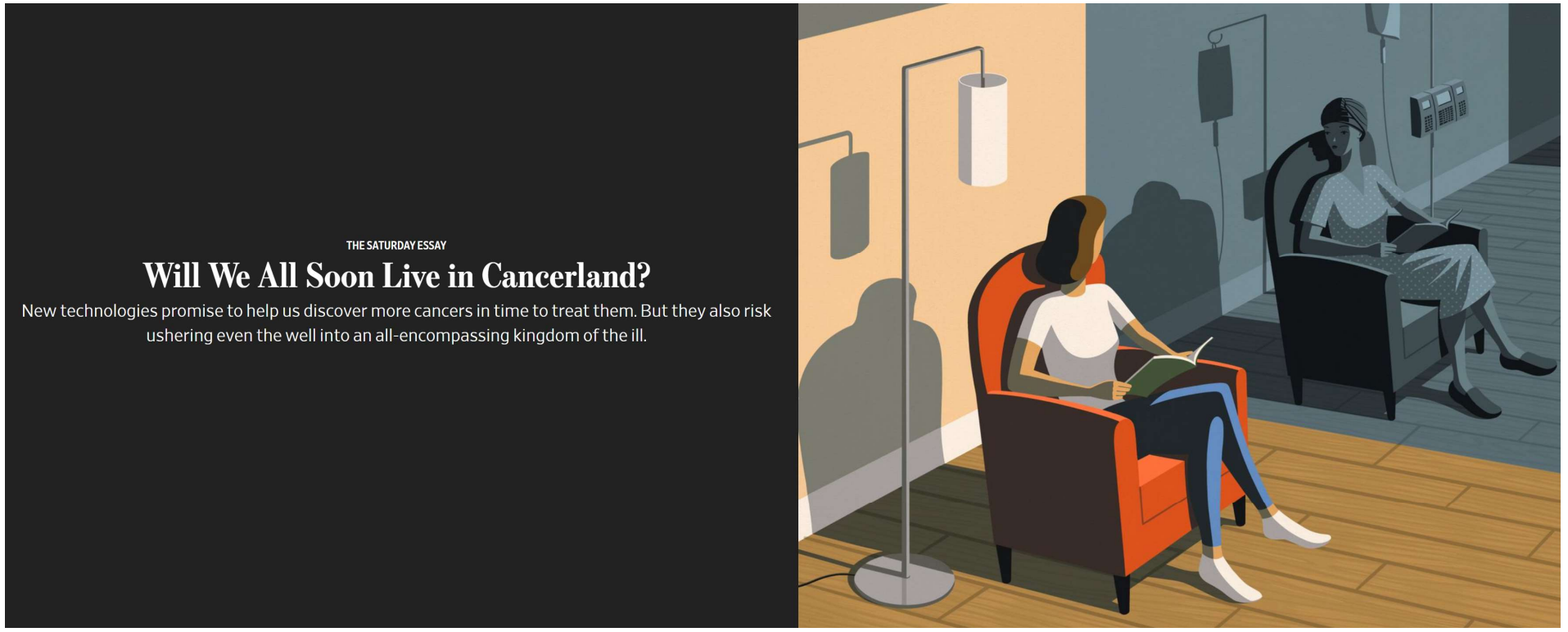
UPDATES

Circulating tumour DNA (ctDNA) assays conducted on plasma are rapidly developing a strong evidence base for use in patients with cancer. The European Society for Medical Oncology convened an expert working group to review the analytical and clinical validity and utility of ctDNA assays. For patients with advanced cancer, validated and adequately sensitive ctDNA assays have utility in identifying actionable mutations to direct targeted therapy, and may be used in routine clinical practice, provided the limitations of the assays are taken into account. Tissue-based testing remains the preferred test for many cancer patients, due to limitations of ctDNA assays detecting fusion events and copy number changes, although ctDNA assays may be routinely used when faster results will be clinically important, or when tissue biopsies are not possible or inappropriate. Reflex tumour testing should be considered following a non-informative ctDNA result, due to false-negative results with ctDNA testing. In patients treated for early-stage cancers, detection of molecular residual disease or molecular relapse, has high evidence of clinical validity in anticipating future relapse in many cancers. Molecular residual disease/molecular relapse detection cannot be recommended in routine clinical practice, as currently there is no evidence for clinical utility in directing treatment. Additional potential applications of ctDNA assays, under research development and not recommended for routine practice, include identifying patients not responding to therapy with early dynamic changes in ctDNA levels, monitoring therapy for the development of resistance mutations before clinical progression, and in screening asymptomatic people for cancer. Recommendations for reporting of results, future development of ctDNA assays and future clinical research are made.

Key words: circulating tumour DNA (ctDNA), liquid biopsy, precision medicine

Take home messages

- **Importanza per gli operatori di screening di avere la consapevolezza di quello che sta emergendo nella comunità scientifica e come questo influenzi le aspettative delle persone**
- **Essere pronti a dare delle risposte adeguate ed aggiornate**
- **L'argomento, per quello che riguarda lo screening, rimane confinato nel campo della ricerca**
- **La scienza procede più lentamente rispetto agli interessi industriali … necessaria cautela**
- **Rimane una sfida molto intrigante che probabilmente potrà rivoluzionare il nostro approccio futuro allo screening mammografico (e non solo…)**
- **Il rigore e la precauzione che ha sempre accompagnato l'introduzione di nuovi protocolli di screening deve essere mantenuto come paradigma imprescindibile anche da un punto di vista etico**
- **Il mondo degli screening è un mondo dinamico (come tutti gli altri mondi…) e noi dobbiamo essere pronti a collaborare e ad accettare nuove sfide**



By Siddharta Mukherjee (Columbia University - Pulitzer 2011 for General non Fiction)

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