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REVIEWS

Microfluidics engineering towards personalized oncology—a review

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Abstract
Identifying and monitoring the presence of cancer metastasis and highlighting inter-and intratumoral heterogeneity is a central tenet of targeted precision oncology medicine (POM). This process of relocation of cancer cells is often referred to as the missing link between a tumor and metastasis. In recent years, microfluidic technologies have been developed to isolate a plethora of different biomarkers, such as circulating tumor cells (CTCs), tumor-derived vesicles (exosomes), or cell/free nucleic acids and proteins directly from patients' blood samples. With the advent of microfluidic developments, minimally invasive and quantitative assessment of different tumors is becoming a reality. This short review article will touch briefly on how microfluidics at early-stage achievements can be combined or developed with the active vs passive microfluidic technologies, depending on whether they utilize external fields and forces (active) or just microchannel geometry and inherent fluid forces (passive) from the market to precision oncology research and our future prospectives in terms of the emergence of ultralow cost and rapid prototyping of microfluidics in precision oncology.

Keywords Microfluidics technologies · Precision oncology · Circulating tumor cells · Circulating DNA · Exosomes

Introduction

Genomic, cellular, and molecular cancer profiling allows the identification of improved and personalized disease diagnostics, monitoring, and treatment for cancer which will be the central idea of personalized cancer medicine. Microfluidic technology has great potential characterized by the micro-nano scale engineered manipulation of fluids and cells [1–4] and has therefore shown considerable promise as cancer prognostic devices at point-of-care monitoring [5–8]. Cancer diagnosis relies typically on clinical imaging modalities, genomic and molecular profiling [5, 9–14], and often in combination with invasive tumor solid biopsy [15] ("solid biopsy"). However, metastatic organotropism [16] has remained one of the tumor's greatest mysteries; hence, predicting successful cancer treatment remains difficult, due to its inter-and intra-tumoral heterogeneity [17]. Numerous technologies have been developed in the past decade to tackle the challenge of cancer diagnosis and monitoring [7, 18–20]. Among these, microfluidic technology provides a powerful platform for sample processing (e.g., separation, enrichment) platform to study bodily liquids [21, 22] (otherwise known as "liquid biopsy") which is a less invasive approach and can be taken numerous times directly from patients. The integration of microfluidics and biosensors offers a powerful tool to replace the bulky laboratory instruments that enable more sensitive detection with high-throughput detection at the micrometer scale, including a reduced sample volume and *reduced time and costs* [23, 24]. There is growing evidence that supports the cellular and molecular profiling [25–29] of cancer cell methodology which is fast becoming the preferred method of tumor grades classification and assessment of therapeutic efficacy. A detailed discussion on cellular and molecular profiling technologies was published in other precedents [9, 13, 21, 25, 26, 30]. In this short review, we focus on the impact of "personalized" solutions that utilize micro-and nanoscale integrated technologies to solve problems in diagnostics in cancer biology. Finally, we will discuss the emergence of ultra-low-cost rapid prototyping microfluidic in precision oncology (Fig. 1).

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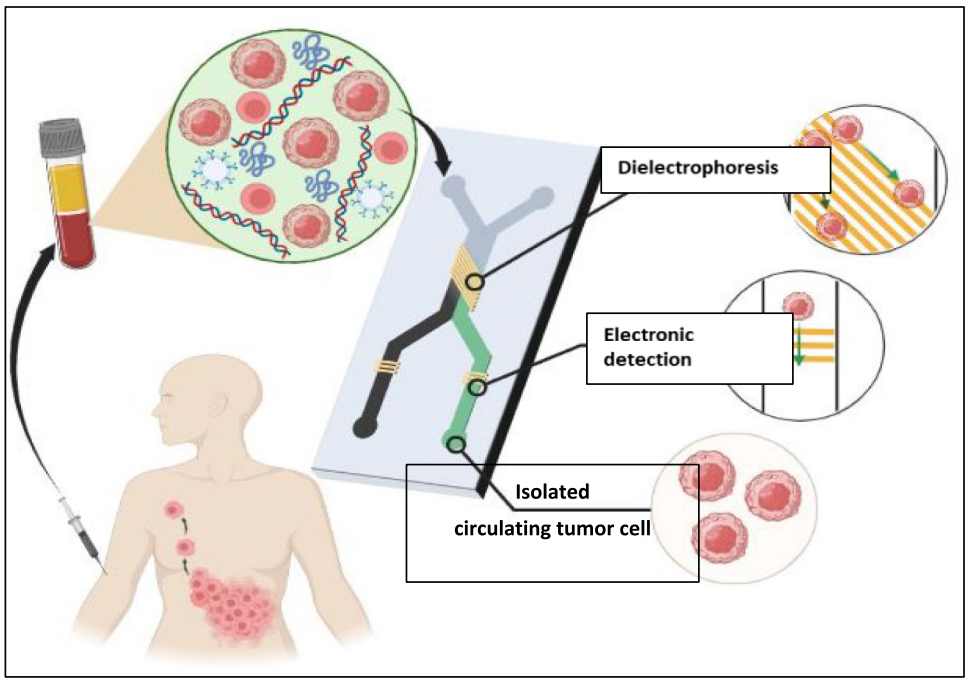

Fig. 1 Microfluidic devices address the limitations of personalized medicine. Schematic representation of a microfluidic device for capturing the markers circulating in the blood from the patient's blood

Search strategy and selection criteria in literature research

The search strategy of this review is based on the most recent research published in major medical and biomedical journals focusing on "Microfluidics," "circulating tumor cells" (CTCs), and related cancer studies. We used different search strategies: (1) literature databases such as PubMed, (2) customized Google search engines, and (3) targeted market search web links and relevant articles using the terms such as "microfluidics" and "circulating tumor cells." Our own research on the subject is also included in this review. The literature of the last 10 years was covered, but for more information, our literature search extended beyond the mentioned years (i.e., 2008 to the present). These literature search strategies were used to gather relevant information for this review, and we did not follow any exclusion criteria in the PubMed search.

Microfluidics design based on tumor cell parametrization

Characterizing the cellular, molecular, genetic, and functional heterogeneity of cancer at the single-cell level has become a major limitation for POM. In recent times, single cell-based assays reveal structural heterogeneities, cell function, composition, and genetic information of identical cells. An accurate analysis of biomolecules in cancer cells can help to improve a fundamental understanding of cancer biology at the cellular and molecular levels. But the present knowledge is mostly based on bulk experimental approaches, such as Western blotting or DNA sequencing which are performed in sample volume on a microliter scale. In recent years, microfluidics has emerged as an enabling powerful tool in cellular interactions to cancer diagnosis, and treatment such as multidrug resistance (MDR) modulation and cancer drug discovery due to their inherent miniaturization, low sample volume, integration, and portability. Researchers can take advantage of this scale and its intrinsic physical laws (such as laminar or dean flows), and the large surface area/volume ratio. Its further flexibility allows the relatively low-cost and rapid fabrication of devices with various geometries transforming precision oncology in new and unconventional ways [1, 3, 7, 31–34].

In addition, circulating tumor cells (CTCs) (Fig. 2) which are known as a liquid biopsy and present in low quantity in a complex blood sample have been confirmed to have a maximum level of heterogeneity in single-cell analysis experiments using live single-cell spectroscopic techniques integrated with microfluidic-based cell enrichments. Hence, cancer profiling at the single-cell level using microfluidics has gained large attraction.

In this context, microfluidics is a suitable tool to analyze complex body fluids (including peripheral blood, urine, stools, cerebrospinal fluid, tears, and saliva) in vitro. Currently, numerous emerging technologies have been demonstrated for the separation of rare cells obtained

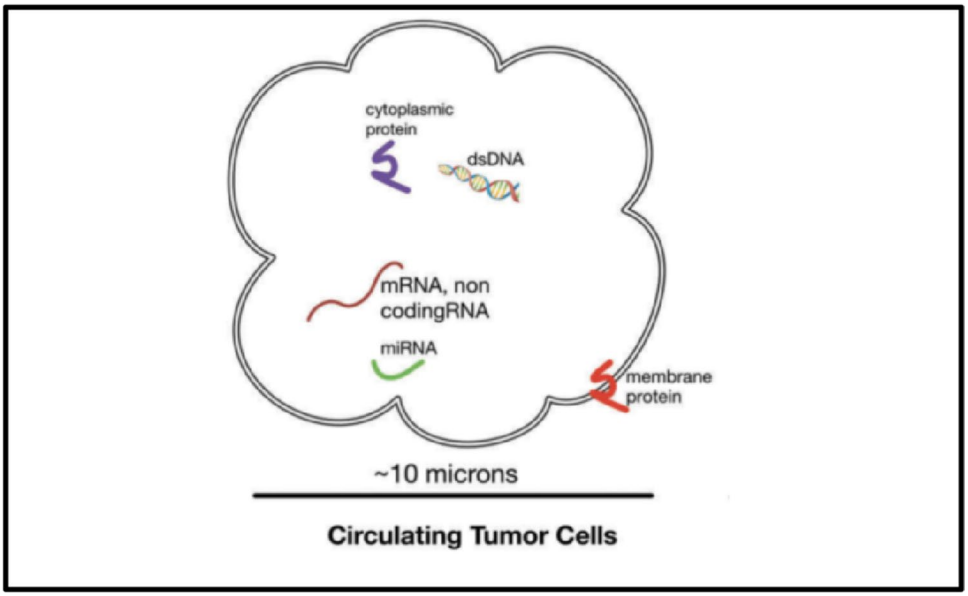

Fig. 2 Liquid biopsies of tumor-specific circulating CTCs containing cell-free fractions. circulating cell-free tumor nucleic acids and EVs

Table 1 Physical property-based CTC enrichment and separation

Method of separation	Characteristic	Capture efficiency (%)	Enrichment	Ref
Filtration-based	Size	NA	Positive, negative	[57]
Filtration-based	Size	~100	Positive, negative	[58]
Ratchet mechanism	Size, deformability	NA	Positive, negative	[51]
Microfiltration-based	Size	~90	Negative	[46]
Microfluidic labyrinth	Size	~90	Positive, negative	[59]
Force-based	Di-electrophoresis	~54	Positive	[47, 60–62]
Microfluidic system	Size, polarizability	~71	Positive	[57, 63]
Dielectrophoretic field-flow	Size, capillary action	~90	Positive	[47, 49, 61, 64, 65]
Metacell® tube	Size	NA	Positive	[66]
Isolation by size of epithelial tumor cells	Density centrifugation	67-78.3	Positive	[44, 67]
Gilupi cell collector™	Size	~71.5	Positive	[50, 68]
Parallel multi-orifice flow fractionation	Hydrodynamic force and size	~90.78	Positive	[68]

through liquid biopsy of cancer patients [27–29, 35–42] based on their physical and/or immunochemical characteristics. These techniques are based on different principles [35, 43–51] and target distinctive physical properties [52] (e.g., size and/or deformability harder), polarizability, density, and dielectric properties [53] (Tables 1 and 2). Another of the most widely used methods to isolate rare cells is based on the affinity of a specific immunocytochemical antigen (Table 3) expressed on the target cell surface to its corresponding antibody [54–56]. In this way, CTCs are trapped on the device surface specifically while most of the undesired billion blood cells are sorted out of extremely rare tumor cells that are found in the blood of cancer patients.

Table 2 Size range of the different cancer cells [69]

Cell type	Size (μm)	Range μm (min to max)	Circularity (%)	Ref
CLL	25	10 to 50	95	[70]
B16	28	1.2 to 38	93	[71]
K562	26	9 to 45	94	[72]
HeLa	23	15 to 50	94	[73]
A549	38	20 to 51	93	[74]
Colon-26	25	1.5 to 40	93	[75]
Jurkat	28	10 to 45	94	[76]
Molt-4	20	1.5 to 29	94	[77]
MDA-MB-468	22	10 to 45	94	[78]
MDA-MB-157	28	1.8 to 42	94	[79]
MC38	28	1.7 to 50	92	[80]

Table 3 Immuno-chemistry-based microfluidic chips for CTC separation

Principle/description	Immuno-chemistry	Capture efficiency (%)	Selectivity (%)	Enrichment type	Ref
Circulating tumor cells chip	anti-EpCAM	~99	~50	Positive, negative	[45, 81]
High-density membrane filter	EpCAM, HER2	89.1	NA	Positive, negative	[48]
Thermoresponsive system - chaotic mixer	EpCAM	NA	NA	NA	[82]
Geometrically enhanced mixing chip	anti-EpCAM	~94	~84	NA	[83]
EM chip with a herringbone patterned surface	CD24, anti-EpCAM	~78	~99	Positive	[33]
Immunomagnetic chip	anti-EpCAM	~100		Positive	[84]
Circular dual-immunopatterned chip	anti-63B6	~94		NA	[85]
Microfluidic immunosensor	anti-EpCAM	NA		NA	[86]
Graphene oxide-based immuno-affinity chip	Anti-bovine serum albumin	~90	NA	NA	[87]
NanoVelcro CTC Chip	anti-EpCAM antibody	~85		Positive	[82]
Microfluidic Cell Concentrator	anti-CD45	NA		Negative	[88]
μ - MixMACS chip	anti-EpCAM	~94		Positive	[89]
Automated extraction chip	anti-CD45	NA	NA	Positive, negative	[43]
PEG-functionalized graphene oxide chip	EpCAM	73 ± 32.4		Positive	[90]

Microfluidics for single-cell analysis cancer diagnosis and monitoring

The single cell is the fundamental component of biological phenomena. The advent of the microfluidic platform promptly introduced high-throughput techniques for isolating single cells by precise control, automation, and low volume from large populations with selectivity and sensitivity. The sensitivity of these microfluidics has become sufficiently large to enable the isolation of rare cells such as CTCs from complex media, cells shed from primary tumors into the whole blood [91]. Numerous tumors can be monitored for prognosis and their efficacy using the single CTCs extracted from circulating blood. Due to heterogeneity in cancer cells, current CTC detection technologies primarily rely on biomarker-intermediated technologies like magnetic beads, microfluidic chips, or size-sensitive microfiltration, which might reduce detection sensitivity [92]. The accurate enumeration and characterization for prognostic, diagnostic, and personalized therapeutic discovery, therefore, require high throughput characterization of CTCs at the microfluidic single-cell level. Recent work has provided high-throughput and label-free alternatives [93–95], and a significant number of microfluidic platforms have been developed for single-cell analysis based on polydimethylsiloxane (PDMS) [96, 97], glass [98], and paper [99–101] microfluidic platforms. Numerous geometries have been explored to isolate single cells, such as microwells, microvalves, and U-shaped micro dams [102–105]. Other active methods such as DEP [106, 107] have also been developed to isolate single cells on different microfluidic platforms.

Commercialized microfluidics technologies

The growing incidences of chronic diseases such as cancer have raised the need for effective early monitoring tools for the application of precision medicine in oncology. In the past, numerous technologies have been developed to tackle the challenge of capturing CTCs. Microfluidic technologies offer the tantalizing possibility of providing cost-effective rapid diagnostic results in a non-laboratory setup. The global microfluidics market is expected to reach 111.95 USD billion by 2023 (https://www.360marketupdates.com/global-microfluidics-market-12883671; Accessed on 16th June 2023). Commercialized microfluidics for CTC isolation and analysis is summarized in Table 4. Due to the unique nature of CTCs, microfluidics in precision oncology should be designed in a tubing-like manner. Avoiding CTC loss and complex programming to meet the needs of various users are the main factors to consider in designing automated microfluidic for personalized oncology in medicine. For example, Daktari Diagnostics Inc. has utilized microfluidic technology to integrate sample preparation and SERS detection.

However, this enabling technology has had a relatively limited number of consumer products and limited clinical acceptance for commercialization because of performance issues. Furthermore, existing commercial products have not been widely accepted due to their expensive equipment (~600,000 USD) [108], expensive consumables such as antibodies to capture the CTCs in the patient's blood, long detection time for each sample, complicated CTC enrichment step, very low purity of the captured CTCs (< 0.5%), because it cannot be used for phenotype identification and molecular analysis, and moreover, high false positive and

Table 4 Commercially available CTC technologies

Commercial status	Technology	Principle	Specifications	Limitations	Ref
GE Healthcare	Ficoll-Paque®	Density, size		Loss of CTCs	[1, 21, 25, 26, 33, 56, 109]
Menarini-Silicon Biosystems	CellSearch®	Immunoaffinity	EpCAM labelling, CD45 CK, DAPI staining	Loss of CTCs Loss of tumor cells	[67, 110, 111]
Miltenyi Biotec		Magnetic force	Recovery 87%		[112, 113]
Greiner Bio-One	OncoQuick®	Density, size			[114, 115]
Rare cells Diagnostics	ISET®	Size, filtration	Sensitivity: 1 CTCs/ 0.01L of blood	Loss of CTC	[44, 67, 116–119]
Clearbridge BioMedics	ClearCell®	Size	Sensitivity: 10,000×		[34, 120, 121]
Fluxion Biosciences	IsoFlux CTC	Immunomagnetic capture bead system	Enrichment of CTCs		[122, 123]
ANGLE plc	Parsortix™ system	Size	Enrichment of CTCs		[124]
ApoCell, Inc	ApoStream™	Dep	Detects independent of EpCAM expression		[40] [65]
Cynvenio	LiquidBiopsy®	Direct automated DNA analysis	Genetic Profiling of CTC		[125]
Silicon Biosystems	DEPArray™	Dielectrophoresis coupled with Sanger sequencing	Isolation of single CTCs		[126]
MetaCell Ltd.	MetaCell® system	Size	Allows post-capture analysis		[127]
Biocept	OncoCEE	Cell enrichment and extraction	High probability of CTC capture		[128]

false negative results, and none of the devices is standalone systems. Furthermore, using polymeric materials such as PDMS, the developed technologies are not suitable for scaling due to their cost. In addition, errors in the fabrication process and costs remain high.

Microfluidic devices for analysis of solid tumor biopsies

Traditional approaches, which require huge amounts of samples and reagents for each assay, are hampering the growth of "personalized medicine," where an increasing amount of biomarkers should be examined on the individual patient sample. Diagnosing solid tumor markers in sera at a low cost and with good accuracy and specificity has been a significant problem [141]. Many studies have been performed using microfluidic technology to build biosensors that are sensitive and perform rapid analysis of biomarkers of cancer like CTCs, DNA, proteins, miRNA, and exosomes [142]. Early detection of ovarian cancer (OC) and breast cancer (BC) can dramatically improve patient survival [143]. Microfabricated microfluidic–based biosensing devices continue to make significant strides in the precise and rapid detection of solid tumor biomarkers alongside aptamer (Ap)-dependent sensors. The Ap-based microfluidics utilizes Aps as targeting ligands and offers a novel method for the identification of single cells and in-depth studies [144]. Additionally, the combination of various SELEX (systematic evolution of ligands by exponential enrichment) as well as microfluidic approaches might enhance the screening of Aps against tumor markers and cancer cells while also offering on-chip SELEX methods for the automatic identification of strong-affinity Aps [145]. Hung et al. introduced a microfluidic method to study numerous OC cell lines and effective cell-SELEX to identify specific Aps that target OC cells [146]. They were able to identify 13 Aps that were active in the case of OC cells; 3 of them had a higher affinity for OC cells. The developed on-chip cell-SELEX system has a lot of potential for successful screening. They also highlighted the system's potential applicability in the individualized selection of Aps and the establishment of advantageous Aps-based diagnostic biosensors [146]. Similarly, Tsai et al. used the clinical tissue SELEX technique to design a microfluidic system with rapid and pre-programmed Aps screening. This study created tissue SELEX using an ssDNA library unique to the membrane of cancerous cells [145, 147]. HER2 amplification is found in 14–20% of patients with breast cancer, and consequent overexpression in breast cancer is related to an additional aggressive medical course [148]. Pretreatments like histological diagnosis, core needle biopsies, HER2 status, and hormone receptors are all used in the early diagnosis and risk classification of breast cancer. A qPCR is a reliable

option for HER2 evaluation methods in breast malignancies [148, 149]. Quake et al. created an RT-PCR using a microfluidic approach as droplet microfluidics that offers sensitivity to a single cell [150]. Later, the magnetic tweezer technique was used that facilitated the purification of mRNA from a raw sample to the world of droplet microfluidics. It includes a thermocycler that performs RT and pre-amplification cycles of PCR in droplets. This entire technique was set up as a succession of enclosed globules consisting of all necessary samples and reagents [151, 152]. Pekin et al. made an approach performing PCR in several millions of droplets in picolitre using a droplet-based microfluidic device. They described the development and validation of a digital PCR-based method with high sensitivity for screening of mutations in the KRAS oncogene in wild-type DNA sequences [153, 154]. DNA molecules with single target partitioned in droplets using validated clinical fluorescence-based TaqMan probes, particularly for mutated and wild-type KRAS [155], measured the ratio of mutant to wild-type DNA with the microfluidic system [153]. The following review [156–159] provides an overview of recent advances in the selection, isolation, and detection of biopsy markers for various solid tumors.

Microfluidic devices for analysis of tumor-derived exosomes

Exosomes are a type of extracellular vesicle that is released by diverse cells and detected in various physiological fluids. Exosomes, which indicate the state and source of the cell from where they are produced, have been used as markers to detect and evaluate therapeutic efficacy in a variety of disorders. There are many exosome isolation strategies based on microfluidics. Exosome separation based on physical features such as density and size or biomarker properties through antibody and antigen interactions is now the focus of microfluidic-based isolation approaches [160]. By altering the tumor microenvironment, exosomes have been demonstrated to have a role in cancer development, including tumor formation, proliferation, metastasis, and medication resistance. With microfluidic devices, it is now possible to manipulate individual components as well as incorporate complex compounds into the metastatic microenvironment for therapeutic target discovery and drug effect screening [20].

Compared to other methods such as ultracentrifugation, ultrafiltration, size exclusion chromatography (SEC), precipitation, and immunoaffinity-based capture for exosome isolation, microfluidic strategies offer efficient, rapid, high recovery and purity, and integrated isolation of exosomes from a small volume of samples. Because of these advantages, numerous microfluidic strategies for exosome isolation have been proposed, including antibody-based sensing, trapping-based isolation, magnetic isolation, acoustic isolation, and electroactive isolation. Protein and nucleic acid biomarkers from tumor-derived exosomes by microfluidic strategies are reviewed elsewhere [161].

Exosomal mRNAs and long non-coding RNAs in blood samples might be employed as biomarkers for colon and rectal cancer diagnosis, according to Dong et al. Furthermore, it was found that exosomes are a promising tool for cancer diagnostics since they contain considerably more RNA than apoptotic bodies and microvesicles [162]. When compared to traditional separation techniques, microfluidic devices can extract exosomes in a variety of samples with excellent selectivities and yields while reducing processing time, cost, and sample consumption [163]. Wu et al. used an acoustofluidic device (a mix of microfluidics and acoustics) to isolate an exosome sample from undiluted whole blood with high purity and yield. Fabricating microfluidic devices based on single exosome separation and analysis might be a significant tool for the diagnosis of cancer [164]. Zhang et al., on the other hand, created an integrated microfluidic device that used a layer of graphene oxide/polydopamine (GO-PDA) coating to achieve ultrasensitive exosome detection in plasma samples [165]. Exosomes have shown promise as individualized targeted medication delivery vehicles in addition to functioning as a source of biomarkers. Exosomes may be loaded with chemotherapeutic medicines like methotrexate to reduce tumor development in mouse cancer models, while paclitaxel loaded on macrophage-derived exosomes exhibited great anticancer activity in a murine model of pulmonary metastases [166, 167]. Using magnetic nanoparticles linked to the CD63 antibody, Fang et al. developed a lab-on-chip platform for identifying breast cancer-derived exosomes in patient plasma [168]. Plasma from breast cancer patients has been shown to contain more EpCAM-positive exosomes than plasma from healthy controls. Most lab-on-chip techniques use EpCAM to find CTCs. The EpCAM-based approach may be more accurate due to their variability and rarity in circulation [169]. In-depth analysis of microfluidic-assisted analysis of exosome-based liquid biopsy was reviewed in [161, 170].

Future perspectives

In this short review, we have introduced some recent microfluidic techniques for precision cancer medicine. Despite the many promising work already completed, microfluidic modules for personalized cancer medicine, paradigm translational shifts are still needed, and these translational steps will also be fuelled by new methodologies and applications. One of the main obstacles is the use of soft lithography which require access to cleanroom fabrication techniques that are costly and time-consuming. The original technique

was "borrowed" from the MEMS community. The earliest work of microfluidic performed using soft lithography [171, 172] can be traced back to the Whiteside group [173, 174]. The term "soft lithography" was first introduced back then, referring to a technique based on printing and replica molding using elastomeric soft materials and photomasks with the patterns of interest. The processes of soft lithography are well documented and therefore will not be elaborated on in this article [175–181].

Until recently, PDMS is a popular choice among researchers [182, 183] due to its biocompatibility, transparency (for optical detection), and low cost [184, 185]. The PDMS-based chip, however, is not the best choice for mass production due to issues in upscaling such as cost- and time-consuming in chip production in comparison to other non-lithographic methods (e.g., injection molding, embossing) [152] (Table 5).

Other non-lithographic methods were seen as more viable techniques for large-scale production, increasing the interest of the industrial and research community to develop simple, rapid, and low-cost microfluidic structures. The emergence of bench-top-sized equipment such as a 3D printer, laser ablation [186, 187], and milling system (Table 6) has since become the breeding ground for a new phenomenon for ultra-low-cost, rapid prototyping of microfluidic in a non-lithographic manner (Table 7). We argue that technological democratization has enabled a wide range of users from professional researchers to hobbyists whose wish is to embark on the same journey. Despite the exciting technological progress, there are some limitations due to the number of analytes in a single cell being very limited, and most current platforms for single-cell analysis focus on the detection of very limited biomolecules (DNA or RNA or proteins). However, exploring uncharted cancer biology will require integrating multiple characterization techniques for post-capture analysis of multiple analytes.

Microfluidic systems with simple steps for sample preparation (e.g., enrichment, isolation) have always been envisioned as a lab-on-a-chip. However, they are still always used in conjunction with large detection systems such as light/fluorescence microscopy. Moving forward, integrating microfluidic systems [188–190] with spectroscopic-based platforms (e.g., micro NMR [41, 191–193], SERS [194, 195], or electrochemical-based [196, 197] platform) is critical for its use as a point of care system. But we envision the integration of analysis in the same microfluidic device rather than doing off-chip analysis. The spectroscopic analysis allows deep phenotyping preferably in a label-free format of cell/tissue where acquiring information rapidly is vital in disease monitoring [198–200]. This will be covered in our upcoming reviews.

In conclusion, it is hoped that this short review will stimulate further developments in new microfluidics for precision oncology medicine and highlight some directions for clinical validation. Thus far, only CellSearch and a few other microfluidic systems have made the transition as a technology from exploratory to clinical decision-making status, and only for a few types of "War on Cancer." The newer microfluidic devices still face the challenges of development as accredited technologies for decision-making. At present, practical and marketable devices are needed rather than technical novelty. Although the

Table 5 Different fabrication techniques for microfluidic device fabrication

Techniques	Material compatibility	Production time	Production cost	Ref
Milling	Thermoplastics, metals, wax	< 1 h	Ultra-cheap	[129]
Embossing	Thermoplastics, metals	Days	Cheap	[129]
Stereolithography	Wafer (SU8)	Days	Expensive	[129]
Injection molding	Thermoplastics, metals, thermosets, elastomers	Days	Intermediate	[129]
Laser ablation	Metals, thermoplastics	<10 min	Cheap	[130]
3D printer	Thermoplastics, photocurable resin/polymer, hydrogels	< 1h	Cheap	[131]

Table 6 Manufacturing cost associated with microfluidic fabrication techniques

Type of machine	Substrate	Software	Cost of the machine, $	Cost per chip, $	Time, min	Precision, µm	Ref
Micro milling machine	PMMA	Fusion 360, makerCAM	NA	100	NA	50 µm	[129]
CNC milling	PDMS	Autodesk Fusion 360	20 to 200k	NA	20 min	< 28 µm	[132]
Milling	Plastics	CAD	NA	1	< 60 min	<25 µm	[129]
Micromachine	NA	NA	NA	< 100	NA	NA	[133]
Desktop machining	NA	NA	NA	NA	NA	NA	[134, 135]

Table 7 Cost-comparative methods for rapid prototyping of microfluidic devices

	Cost of machine	Advantages	Limitations	Ref
Laser ablation	entry: $200 intermediate: $1000 professional: $10,000	Cast/mold free Cleanroom free Mass production Ease of use High precision Manufacturing (> 25 µm)	Poor resolution Uneven channel widths and heights Surface roughness Defect formations Optics requires cleaning	[136, 137]
CNC micro machine	Entry: $100 Intermediate: $1000 Professional: $10,000	Cast/mold free Cleanroom free Low surface roughness Flexibility in design Quick prototyping	Low resolution High-cost accuracy CNC milling machine Mass production (difficult) Limited resolution (<250 µm) Requires tooling Skilled operator	[136]
3D printer	Entry: $250 Intermediate: $2000 Professional: $10,000	Low maintenance costs Wide choice of materials Low-temperature operation Design complexity (3D)	Low resolution Limited z-resolution Rough surface finish Low precision Surface roughness	[138–140]

nascent field of microfluidics for cancer cells/biomarkers is exciting and promising, there are gaps in our current knowledge of cancer pathogenesis that need to be filled alongside overcoming technical challenges to guide future advances. Multidisciplinary teams of bioengineers, biologists, and clinicians should work together in a strategic and integrated manner to find answers to, but not limited to, the following. For which cancer that is early in its growth or precancerous stage with lethal potential are the biology and pathogenesis sufficiently understood to advance the development of sensors?

How can machine learning and mathematical models support the identification of key features within complex biological datasets to achieve the predictive power for cancer biomarkers? How individualized/personalized medicine will benefit from early diagnosis? How can patient and tumor heterogeneity be overcome to ensure a more precise cancer diagnosis?

Like any new initiative, precision medicine faces many challenges. The large amounts of data that must be collected and analyzed not only represent an economic burden but also are labor-intensive and costly for technical know-how. Capacity building needs to happen at breakneck speed, especially with regard to the training of health workers and the availability of high-quality artificial intelligence, machine learning, and laboratory equipment. The search for precision-based treatments may put the health of the population at risk. However, microfluidic technology can enable advanced cell culture when intrinsic control over the patient's microenvironment is crucial, in ways that are not possible with traditional methods. POC devices and personalized medicine will make medical decisions and outcomes more timely and relevant to each patient, which will impact the choice of medical interventions and pharmacological therapies.

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Declarations

Competing interests The authors declare no competing interests.

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