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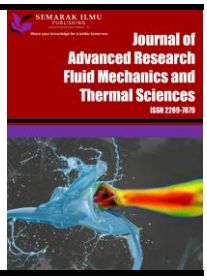


# Smart Microfluidic Devices for Point-Of-Care Applications

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**ABSTRACT**

Microfluidics is an emerging technology vital in the bio-medical sector, encompassing Lab-On-Chip (LOC), drug delivery, maladies diagnostic, and various healthcare fields. Additionally, its day-by-day research studies on drug discovery, cell sorting, and manipulation enrich bio-medical applications. This article provides an overview of the widely used microfluidic devices that are readily available for the commercial sector, improving medical diagnostics with the optimal transduction approaches for Point-Of-Care (POC) applications. On the other hand, some devices still in the development stage are discussed, along with their challenges in commercialization.

## 1. Introduction

Microfluidics is rapidly fledgling as the most in-demand medical diagnosis and treatment field because of its potential to bring out small and portable diagnostic kits. This cutting-edge technology utilizes fluid mechanics principles to precisely control and manipulate minimal amounts of fluids. Its remarkable accuracy paves the way for widespread applications in medical diagnosis, drug delivery, biotechnology, healthcare, and research and development [1,2]. Integrating microfluidics facilitates the development of medical diagnostic tools in the patient's vicinity, resulting in the development of a potent device popularly referred to as POC. POC devices offer a more efficient alternative to conventional clinical laboratories, ensuring quick diagnosis, real-time data processing, and intelligent decision-making capabilities at either the patient's side by non-experts or even in remote locations, thus aptly referred to as "smart microfluidic devices." It stands out for its short analysis time and portability. At the crux of any POC diagnosis is the LOC microfluidic technology, which combines and automates various medical testing processes while consuming less reagent and enabling controlled mixing and particle manipulation [3-5]. Moreover, the microdevices can be integrated into a single microfluidic operational unit, incorporating microchannels, microvalves, micropumps, microneedles, and various other components. This integrated system performs multiple assays and harnesses the advantages of each device, culminating in an efficient POC device, particularly in the context of

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Polymerase Chain Reaction (PCR), allowing for targeted and quick nucleic acid amplification for precise and prompt molecular diagnosis [6-8]. An innovatory POCT platform transforming diagnostics, a DropLab, is developed based on magnetic digital microfluidics. It allows for the simultaneous execution of four Enzyme-Linked Immunosorbent Assays (ELISAs), considerably improving diagnostic sensitivity and accuracy [9]. Microfluidics POCT devices extend their advantage beyond disease detection, which are extensively used in medical treatment, particularly drug delivery. For continuous monitoring of the targeted biomarkers in the concentration of biofluids, personalized drug administration is highly possible with wearable microfluidic devices [10-12]. Recent advances in microfluidic-based wearable sensors like skin-contact-based biofluidic-based sensors have improved remote healthcare monitoring. These biosensors are electrochemical and optical based on their transduction approaches [13,14]. Other emerging POCT applications include nanomaterial synthesis and DNA analysis, which help upgrade diagnostic accuracy, therapeutic interventions, and fundamental research in the field of healthcare [15].

The fluidic behavior at the micro and nanoscale is quite peculiar from the macro scale; this is the key attention in microfluidics [16]. Unlike in the macroscale, where inertial forces due to gravity are the dominant factor, surface forces, frictional, and viscous forces become dominant in the microscale, which means that fluid flow is much slower and more laminar [17]. Thus, various surface forces typically not felt very strongly at macroscopic scales may play significant roles in regulating the functionality of microfluidic devices. This brings out the capability of impacting the multidisciplinary field from optics and information technology to interface physics, surface chemistry, chemical synthesis, and biological analysis [18]. However, the critical concepts of microfluidics seem to revolve around the transport phenomena and flow physics in micro and nano-scale systems [19]. Droplet microfluidics relies significantly on surface forces influencing droplet formation and stability. Interfacial forces and wettability are parameters that control the precise generation of droplets and optimize the sensitivity of POC assays. Highly sensitive assays and a lesser chance of cross-contamination are possible because of the ability of microfluidic platforms to break down individual cells or biomolecules within separate droplets. Because of its accuracy, early and precise diagnoses are feasible to identify specific disease markers [20].

Microfluidics devices are employed in various commercial applications, including medicines, biotechnology, and diagnostics. Medical diagnostics using LOC technology is a prominent commercial application [21-23]. Still, the urge to develop near-at-care devices for the healthcare sector is ever-growing and challenging. These devices use microfluidic channels to perform small-scale assays and tests, making them ideal for Point-Of-Care Testing (POCT) in distant or resource-limited environments [24]. POC-based microfluidics holds versatile potential for many medical applications; however, the products are still at the preliminary research stage due to the complexity of production challenges [25]. In academic research, microfluidics devices aid researchers in understanding biological and chemical systems. By controlled manipulation of fluids at the microscale, researchers can study cells, tissues, and biomolecules and carry out a wide range of experiments. For instance, the study of individual cells and cell-to-cell interactions is conducted using microfluidics devices, which enable researchers to see cellular behavior in real-time [26,27]. They are also used to examine drug delivery, enabling researchers to test the efficacy and toxicity of new drugs [28]. Future pre-clinical research findings could benefit greatly from the increased adaptability and accuracy of microfluidic devices, which could lead to their commercialization.

This comprehensive review delves into the imperative of integrating microfluidics into real-time Point-of-Care (POC) applications renowned for their rapid response. While some microfluidics-based POC devices have successfully transitioned into fully developed commercial products for various disease diagnostics, a multitude of non-commercialized microfluidic devices remain in the early

stages of development. Despite extensive academic research on various technologies, the commercialization of these micro-scale devices proves challenging, grappling with substantial production costs and market acceptance issues [29]. Furthermore, the review provides an insightful exploration of optimal transduction techniques for Point-of-Care Testing (POCT) applications in subsequent sections.

## 2. Transduction Techniques in Microfluidics Devices

In the intricate framework of a microfluidic system, a key component is biosensors. A microfluidic biosensor is an analytical device that utilizes chemical and biological reactions to sense and quantify a specific analyte or event. The mixture of microfluidic technology with biosensing capabilities provides multiple benefits, including reduced sample volume, rapid analysis, compact design, and on-chip integration. Due to this, such devices have active applications such as medical diagnosis and POCT, promoting enhanced speed and sensitivity for analytics processes. The nature of analytes or biomarkers that are targeted for specific diseases determines the transduction method used by microfluidic biosensors [30]. The integral components of biosensors include bio-sensing elements, transducers, microfluidic channels, and signal-processing units. Among them, transducers are crucial elements that convert one signal form to another. Although the fluid behavior in microfluidics is advantageous, there is still a requirement for optimal transducers that can transform biological signals into quantifiable electronic signals like current, voltage, light intensity, wavelength, etc. Electrochemical and optical approaches are the two primary categories under the transduction techniques, which are frequently utilized in POC devices [31]. These detection methods are advantageous because they are simple to gel up with microfluidic devices. Electrochemical methods draw attention for their simple design, low-cost detection, and quick analysis of a variety of analytes. Additionally, in optical detecting techniques, the fluidic feature aids in selecting the suitable optical signal and processing it in optoelectronic read-out circuitry, which provides excellent sensitivity, dependability, and real-time detection.

### *2.1 Electrochemical Methods*

In microfluidics, electrochemical transduction is a technique used to transform a chemical signal into an electrical signal. Easy manufacture, integration, and miniaturization of electrodes within microfluidic devices are benefits of electrochemical detection. Due to its several advantages, it is commonly used in POC applications [32]. Numerous microfluidic technologies employ this technique, such as microfluidic fuel cells, LOC systems, and biosensors. It relies on the properties of electrochemical reactions and uses electrodes to detect the signal. Electrochemical transduction can be subdivided into three based on the measured electrical parameters: amperometric, potentiometric, and conductometric, as shown in Figure 1.

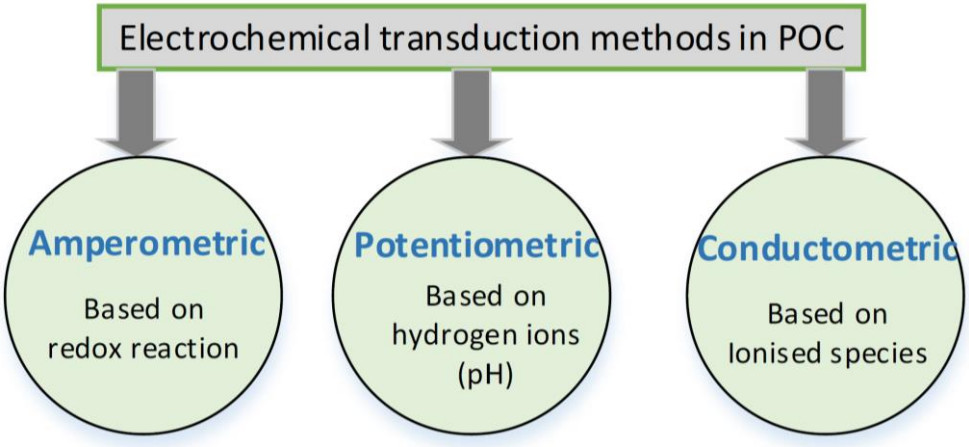


**Fig. 1.** Electrochemical transduction methods opted in POC applications

### *2.1.1 Amperometric detection*

In amperometric transduction, the measurement of electric current to the concentration of the analyte at fixed potential is carried out. If the electroactive species can be reduced or oxidized, then amperometric transduction is employed in suitable such microfluidic devices. The electrons flow to or from the electrodes depending on the redox reactions of molecules. Due to its simplicity, it has become an effective method for the detection, monitoring, and reporting of biochemical analytes relevant to a wide range of diseases [33-35]. The detection of glucose; glucometer is an example of a commercially available amperometric biosensor. A glucose oxidase enzyme was used as a catalyst to measure substrate depletion or product yield during the reaction in the initial generation of glucose biosensors. The Cottrell equation explains the relationship between the current and concentration of the analyte, as shown in Eq. (1).

$$i = \frac{nFAc_0\sqrt{D}}{\sqrt{\pi t}} \quad (1)$$

where the current, i (A); the number of electrons, n (to reduce/oxidize one molecule of analyte); the Faraday constant F, taken as F= 96,487 C $mol^{-1}$; the area of planar electrode, A ($cm^2$); the initial concentration of the analyte, $c_0$ (mol $mL^{-1}$); the diffusion coefficient, D ($cm^2$ $s^{-1}$); and the time elapsed, t (s).

A microfluidic patch device is developed to examine salt levels and sweat secretion rates across body regions when exercising and discover that there is often a positive correlation between the two measures across participants and regions. This patch uses electrochemical sensors to evaluate the presence of N+ and K+ ions in the sweat Figure 2 [36].

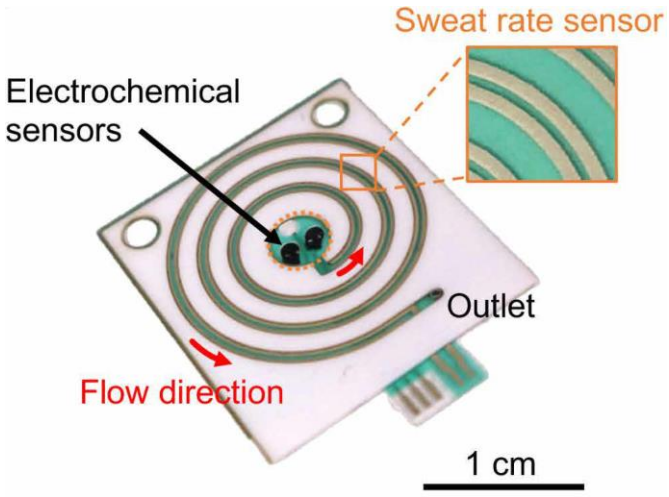


**Fig. 2.** Circular microfluidic sweat rate sensor [36]

### *2.1.2 Potentiometric detection*

Potentiometric transduction is another approach to detect chemical signals in microfluidics. This technique measures the potential difference between two electrodes when an analyte is present, and the potential difference is proportional to the concentration of the analyte. A microfluidic channel with two electrodes is used for microfluidic potentiometric transduction. The first electrode acts as a reference electrode with a constant potential, while the second electrode serves as a sensing electrode that can detect the analytes. When the analyte interacts with the sensing electrode, it generates a potential difference between the two electrodes, which is measured using a voltmeter. Using a calibration curve, the potential difference is then related to the analyte concentration. Ion-sensitive field-effect transistors (ISFETs) and pH-sensitive field-effect transistors (pH-FETs) are two forms of potentiometric transduction mechanisms utilized in microfluidics. The potential difference between two electrodes varies with the number of present ions in ISFETs, while the potential difference between two electrodes varies with changes in the pH of the solution in pH-FETs. Therefore, the pH meter is the best example of potentiometric transduction [37]. This transduction is often used in microfluidic devices such as LOC and POC platforms, where it provides a simple, rapid, and cost-effective method of detecting a wide range of analytes.

The Light-Addressable Potentiometric Sensor (LAPS), in contrast to conventional electrochemical sensors, is easy to integrate, miniaturize, and capable of quantitative label-free detection, preventing the adverse effects of fluorescent reagents on the analytical solutions [38].

### *2.1.3 Conductometric detection*

The ability to detect both electroactive and electroinactive organisms makes conductometric detection a preferable method in microfluidic POC devices. The conductivity electrodes may be either directly in contact with the solution or isolated from it by a thin layer of material. Thus, it can be classified into contact-mode and contactless conductivity detection. In contact-mode conductivity detection, the sensing electrodes are in direct contact with the sample, which results in high sensitivity but at the expense of electrode degradation. As a result, contactless detection is employed, which uses a thin insulating layer between the sample and the buffer. To ensure a good connection, however, the insulation should be the smallest possible. Detection of conductivity is most typically connected to capillary electrophoresis. Also, the conducting polymers are used in

conductivity-based detection due to its advantages such as compatibility with biomolecules, easy processibility, and coating to the desired surface [39,40].

In particular, myoglobin (Myo), cardiac troponin I (cTnI), creatine kinase-MB (CK-MB), and b-type natriuretic peptide (BNP), some of the cardiac biomarkers are detected using Polyaniline (PANI) nanowire biosensors. Utilizing the conductometric method of detection, multiple single PANI nanowire-based biosensors are employed to assess various concentrations of cTnI and compare their sensitivity, as shown in Figure 3 [41]. With the miniaturization of suitable components, this device can be made available for POC.

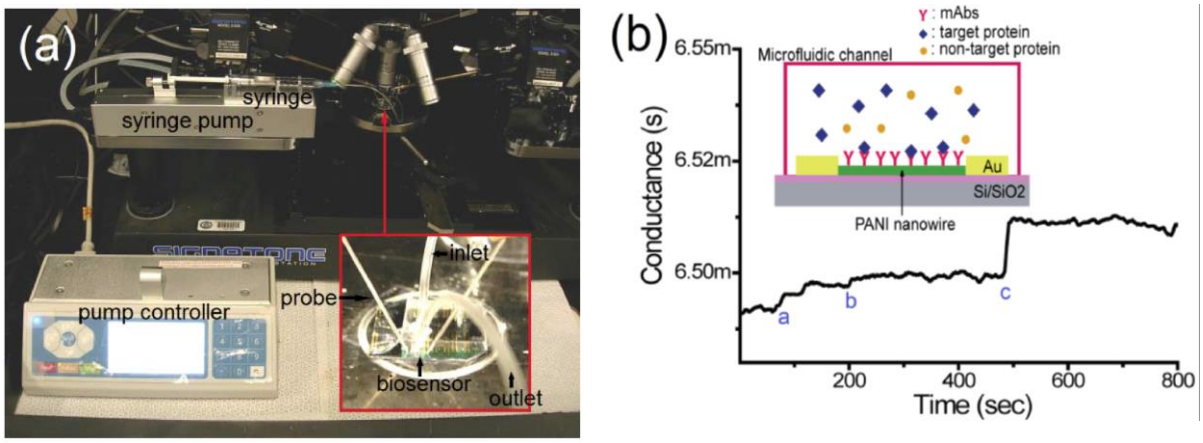


**Fig. 3.** (a) A set-up of microfluidic channel adhered with biosensor (b) The various changes in conductance are demonstrated by the injections of PBS (mark a), BSA (mark b), and cardiac biomarker (mark c) [41]

### *2.2 Optical Methods*

Another popular technique in microfluidics for detecting chemical signals based on their interactions with light is optical transduction. This method can be referred to as the on-chip detection approach. Optical transduction techniques are helpful for a variety of applications, including biosensors, LOC devices, and microfluidic imaging, because they are non-invasive and can deliver real-time measurements with great sensitivity [30].

Surface plasmon resonance (SPR) spectroscopy, absorbance spectroscopy, fluorescence spectroscopy, Interferometry, and Raman spectroscopy are a few of the optical detection techniques employed in microfluidics shown in Figure 4. As sensing systems get more compact in microfluidic systems, transduction problems start to appear. The number of analytes that may be detected decreases when the sample volume is decreased, making detection more challenging. Thus, sensitivity and scalability to micro-scale dimensions are the two key factors that influence the selection of the detection method for microfluidic devices [42]. Therefore, it is desirable to connect and include optical components in microfluidic systems. The majority of the optical parts utilized in these detectors are gradient refractive index lenses, diffractive elements, optical fibers, Light Emitting Diodes (LEDs) or laser diodes as light sources.

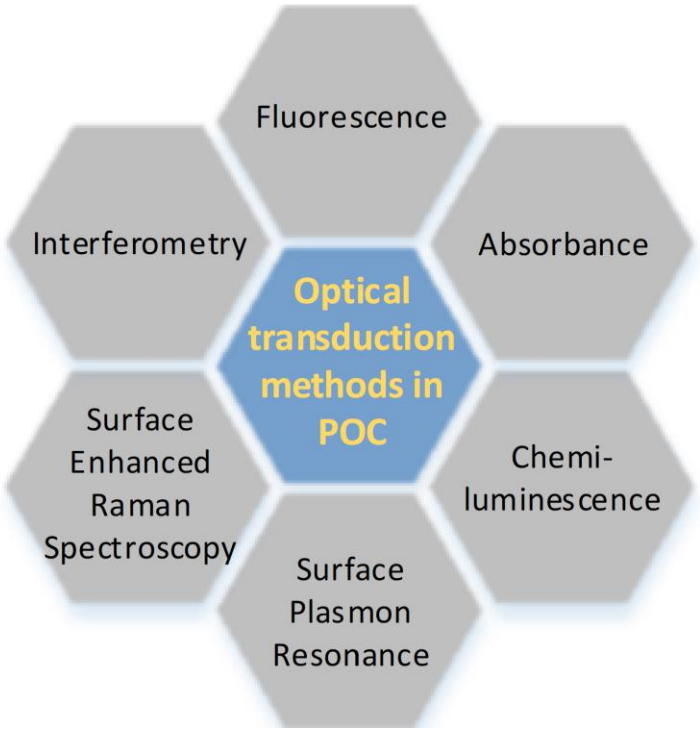


**Fig. 4.** Various optical methods opted in POC applications

One of the examples of optical transduction was developed by Alves *et al.,* [43] shown in Figure 5, a short-path micromixer and an optical circuit for colorimeter detection are integrated onto a PDMS microfluidic device where target RNA samples, gold-nanoprobe (Au-nanoprobe) and salt were mixed. To demonstrate the usefulness of this microfluidic system for molecular diagnostics, BCR-ABL1 (Ph chromosome) fusion transcript (RNA), which is the molecular indication of Chronic Myeloid Leukaemia (CML), was detected using gold-nanoprobe assays by UV spectroscopy. By developing and inserting a mechanical pump into the microfluidic chip and reducing its optical path length, the setup itself can also be made more suitable for POC [43]. Thus, in order to identify the target object, the transduction mechanism has to be chosen appropriately. Table 1 lists various microfluidic devices with optical and electrochemical transduction mechanisms that are intended for medical applications.

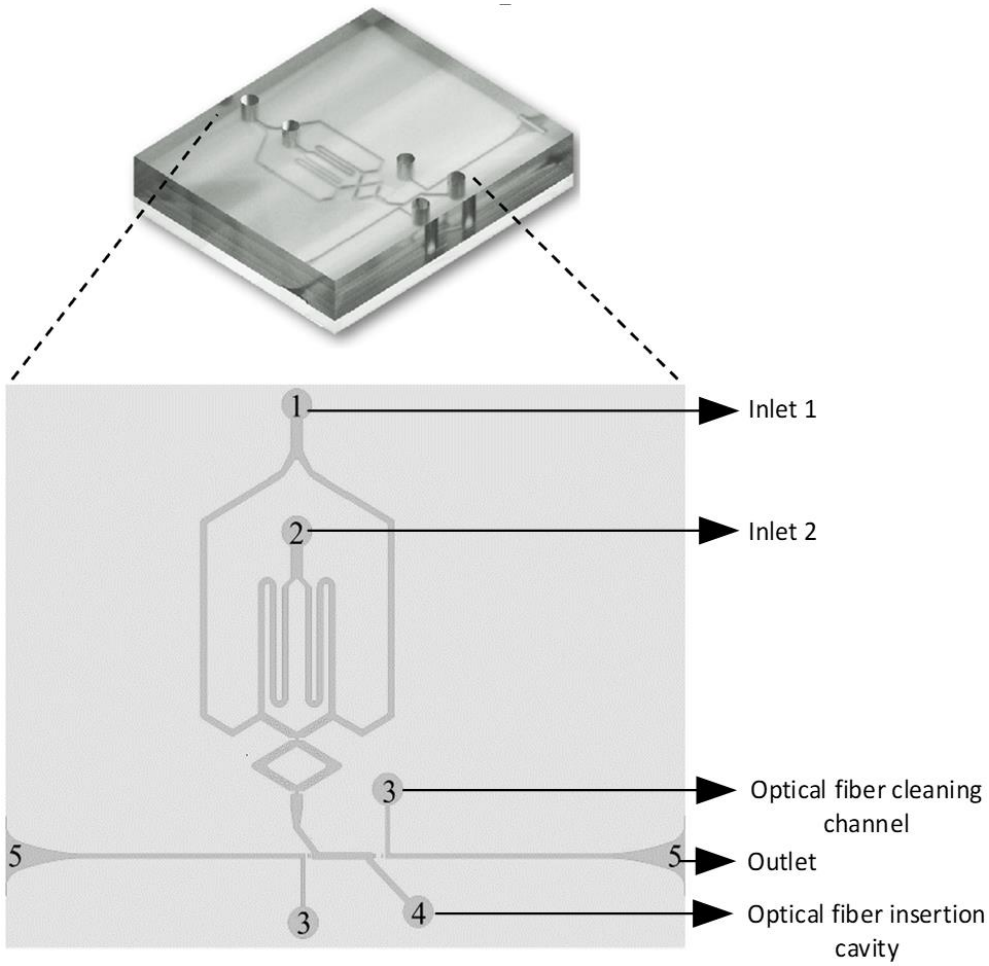


**Fig. 5.** A Microfluidic chip design for CML detection using UV spectroscopy [43]

**Table 1**
Microfluidic POC devices following different transduction methods for various applications

| Reference | Material used for microchannel | Transduction method opted | Application |
|---|---|---|---|
| Nyein *et al.,* [36] | Polyethylene terephthalate (PET) | Electrochemical | Sweat rate analysis on the human body |
| Fava *et al.,* [44] | Paper microfluidics-Whatman filter paper | Electrochemical | Glucose determination in urine |
| Chin *et al.,* [45] | Injection-molded plastic | Optical | HIV diagnostics |
| Alves *et al.,* [43] | Polydimethylsiloxane (PDMS) | Optical | Detection of chronic myeloid leukaemia |
| Glatz *et al.,* [46] | Polyimide substrate, SU8 | Electrochemical | Measuring meropenem antibiotics |
| Hu *et al.,* [47] | Polydimethylsiloxane (PDMS) | Optical | Detection for C-reactive protein (CRP) |
| Lee *et al.,* [41] | Polydimethylsiloxane (PDMS) | Electrochemical | Detection of Cardiac Biomarkers |

## 3. Market Ready Microfluidic POC Devices

In recent years, microfluidics devices endured a notable surge in manufacturing and deployment of POC applications. Developments in material research, production methods, and the integration of cutting-edge sensor technologies have put microfluidic POC devices at the forefront of timely and easily accessible medical solutions. The healthcare industry is focused on developing diagnostic kits (cardiac functions, diabetic study) that deliver results quickly and precisely [48]. For instance, the Siloam Biosciences' TROVA POCT Platform, as shown in Figure 6, is an open-source POCT system based on Optimizer microfluidic technology [49]. It is developed to achieve an ultra-high sensitivity that can be tuned for desired results with the existing reagents. Cardiac troponin (HS cTnI) is a significant biomarker for the diagnosis of acute myocardial infarction [50]. This POCT system can detect HS cTnI by performing assays in 20 minutes, having a limit of detection of 0.04 ng/mL. Also, it is designed to operate for the wide dynamic range, which tests β-hCG levels in 15 minutes by carrying out multiple assays with an operating range of 5 IU/L to 68,500 IU/L.

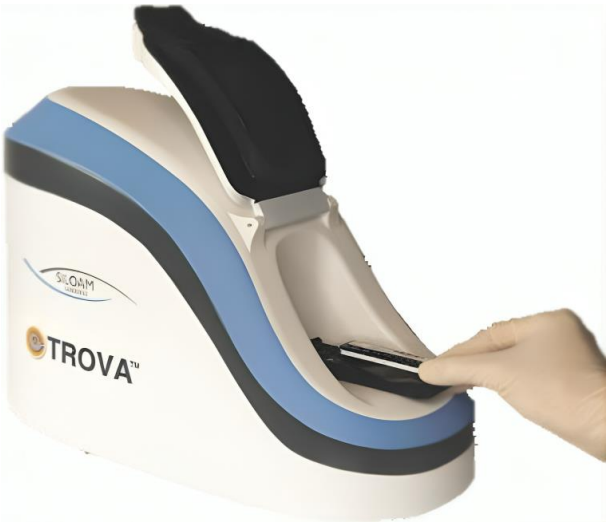


**Fig. 6.** TROVA POCT Platform [49]

Diabetes mellitus (DM) is a significant metabolic disease leading to high blood sugar levels in the human body. This causes attrition to other organs when pertained for a prolonged period [50,51]. Some of the expected long-term microvascular consequences of DM patients' persistently uncontrolled high blood sugar levels include diabetic foot, diabetic retinopathy, and diabetic kidney disease. The glycosylated hemoglobin A1c (HbA1c) level measurement is a diagnostic tool for DM, recognizing it as the most predictable biomarker. One such microfluidic device in the market is LumiraDx, shown in Figure 7, which is a high-performance microfluidic system that meets all of the needs of POCT in a tiny, portable instrument with superior low-cost test strips and seamless digital connectivity [52]. The microfluidic immunoassay performed in this system is rapid and simple-to-use that intends to accurately measure HbA1c levels in fingerstick and venous whole blood at the POC within 7 minutes.


**Fig. 7.** LumiraDx POCT device [52]

Another technology, the Spinit HbA1c instrument shown in Figure 8, performs quantitative assays for the computation and analysis of HbA1c levels in whole blood [53]. It takes venous or capillary blood sample volume of 8 µL in a Spinit microfluidic disc, which is fed into the Spinit system to achieve results in less than 6 minutes. Thus, it gives more precise and rapid results with minimal sample volume in contrast to the LumiraDx system, which requires a sample volume of 15 µL with a processing time of less than 7 minutes. Consequently, the Spinit system is substantially quicker.


**Fig. 8.** Spinit HbA1c microfluidic system [53]

## 4. Non-Market Ready Microfluidic POC Devices

The early diagnosis of any medical concern is a critical focus area for researchers to come up with new innovations for mitigating health-related issues. POC devices stand out as a promising example with their advantage of reliability and accessibility. In microfluidic technology, various laboratory tasks are combined into a single chip, as shown in Figure 9. It combines all the processes, including sample preparation, sample processing, and target detection [54]. The LOC devices are extended to include POC functionality after suitable development. Therefore, there are multiple applications for these microfluidic devices in a wide range of industries, such as biological diagnostics, drug development, environmental monitoring, and chemical analysis. Though these devices are

prototyped, the development of devices as end-user products is still vague due to the challenges of complexity and integration issues, manufacturability, and cost. The most efficient methods for pathogen identification are primarily based on molecular diagnostics in microfluidic devices. For the purpose of diagnosing cancer, researchers have investigated a wide range of applications. In the majority of these systems, there are microfluidic channels with a particular shape that is intended to separate the various analytes from the blood cells present in the sample (such as whole blood), such as circulating tumor cells (CTCs), De-oxyribo Nucleic Acid (DNA) and proteins. In the past decade, molecular analysis microfluidic devices, as shown in Figure 10, have made great strides and they have become a viable alternative to more conventional methods. In terms of assay repeatability, reagent immobilization, shelf life, or production cost, they still have room for development [55]. In summary, microfluidic devices have shown a variety of uses for molecular diagnostics, and it's time to explore their potential for functional diagnostics. Despite the tremendous progress in molecular analysis, especially in cancer diagnosis, there are hurdles in making it a market-ready product.

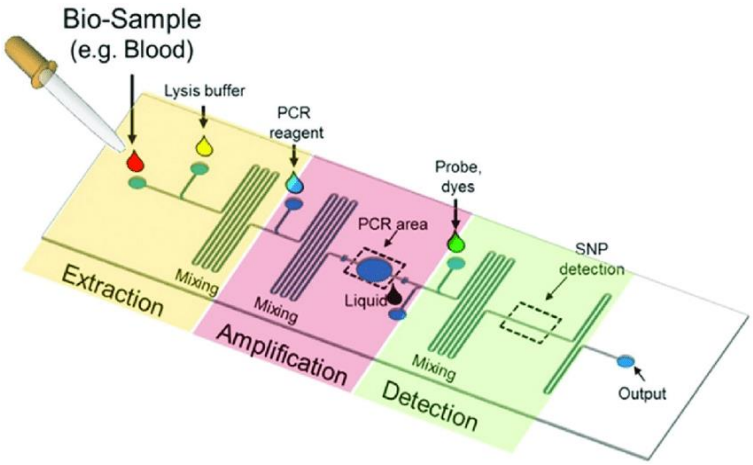


**Fig. 9.** Microfluidic chip as LOC application [54]

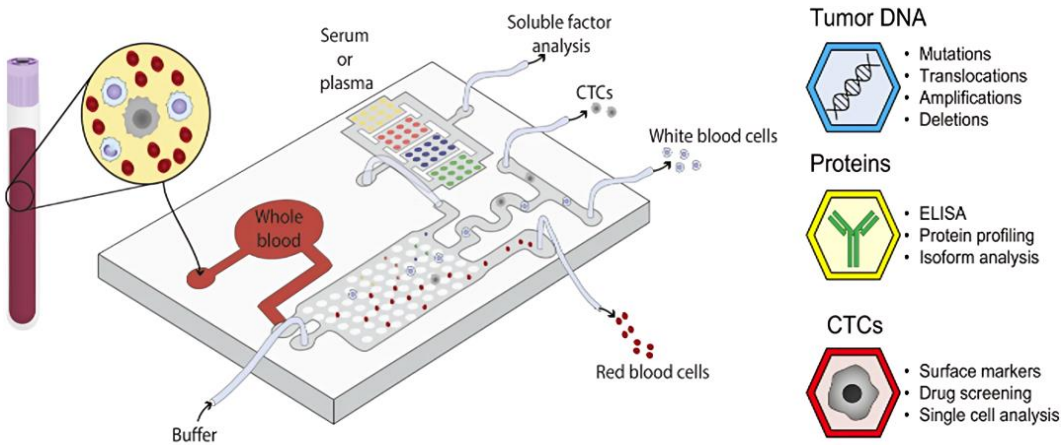


**Fig. 10.** Theoretical device design for parallel investigation of CTCs, circulating proteins, and DNA in whole blood [55]

Liquid biopsy is another instance of microfluidic diagnostic application. It has made significant advancements over the last decade because it offers a potentially novel remedy to various shortcomings of conventional cancer management. It has a number of benefits over traditional tissue biopsies by focusing on a minimally invasive study of analytes that circulate in physiological fluids after leaving the tumor site. Using a microfluidic device and its app-assisted results in smartphones,

a liquid biopsy can help detect pancreatic cancer early and simplify the diagnosis process [56]. Microfluidics can be exploited toward POC personalized medicine for the management of cancers. Though awaiting commercialization, these devices have great potential detection methods. These devices have great potential for moving from pre-clinical to commercially viable stages in the future due to their increasing versatility and precision. Future improvements to align with mass production standards, such as simplified design and material choice, enable the achievement of 'commercial grade' microfluidic devices.

## 5. Conclusion

This review summarizes the latest advances in microfluidics-based POC medical diagnostics for diseases using rapid, cost-effective, and portable devices in industrial outlooks and from academic perspectives. The growth of microfluidics can be accelerated by synchronizing the industrial demands with the academic research plans. Moreover, created microfluidic kits must be made available to the end-user at a price that is substantially lower than that of clinical tests. Furthermore, the transduction concepts that are utilized in current POCT microfluidic devices are explored. To address the severity of several common diseases, there is still plenty of space for microfluidic advancement. The conventional technologies are optimized but still involve numerous steps and frequent switching of platforms in the last stages of development. Thus, making it difficult in practice. So, the development of fully integrated microfluidics kits, which include sampling, sensing, and signaling modules, is irresistible. These kits can serve near the patient's vicinity, performing on-site diagnosis.

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