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Point-of-care testing based on smartphone: The current state-of-the-art (2017–2018)

Junjie Liu[a], Zhaoxin Geng[a,*], Zhiyuan Fan[b,d], Jian Liu[c,d], Hongda Chen[b,d]

[a] School of Information Engineering, Minzu University of China, Beijing 100081, China
[b] State Key Laboratory of Integrated Optoelectronics, Institute of Semiconductors, Chinese Academy of Sciences, Beijing 100083, China
[c] State Key Laboratory of Superlattices and Microstructures, Institute of Semiconductors, Chinese Academy of Sciences, Beijing 100083, China
[d] Center of Materials Science and Optoelectronics Engineering, University of Chinese Academy of Sciences, Beijing 100049, China

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ABSTRACT

Smartphone-based point-of-care testing (POCT) is rapidly emerging as a potential alternative to the traditional laboratory-based diagnostic testing owing to economic considerations and availability of medical equipment especially in resource-limited areas. A smartphone, combined with a biosensor and other related accessories, can offer high accuracy and sensitivity for medical testing. Moreover, the ubiquity of smartphone has propelled the development considerably, and accordingly research in recent years has shown promising progress in POCT. Here, we used samples (blood, urine, sweat, saliva and tears) of liquid biopsy as the standard for classification of smartphone-based POCT devices, considering that these samples contain multiple biomarkers of serious diseases. The colorimetric, fluorescent, brightfield, and electrochemical methods were utilized to examine these samples. We performed a comprehensive review of the development of smartphone-based POCT devices over the past two years (2017–2018) and assessed their relative merits and drawbacks. Based on the progress of POCT development, it illustrates that the various technological and economical requirements are urgent and tremendous. The tendency of high-quality, low-cost smartphone-based POCT devices, feature of biosensors (paper-based sensor, flexible device, microfluidic chip, et al.) currently widely used in POCT and recommendations of future works were summarized.

1. Introduction

With the integration of micro-and nanotechnology, computer technology, signal processing, biotechnology, and microelectronics, medical diagnosis technology is undergoing a transformation as its operational base is gradually shifting from centralized medical centers to individual homes driven by the growing need for a continuous real-time monitoring. Traditionally, and even today, laboratory-based testing remains the most preferred diagnostic method, involving infrastructure facilities related to biochemistry, electrochemistry, hematology, and so on (John and Price, 2014). Generally, a laboratory-based test center is an expensive setup since it requires not only large benchtop analyzers but also professionally trained operators. Accordingly, patients wait for several days for test results because of the time-consuming preparation of reagents and clinical samples (Anderson et al., 2011; Jung et al., 2015). In addition, there is usually a large gap between the availability of medical care facilities and the demand especially in developing countries due to inadequate health care budgets, resulting in frequent outbreaks of chronic infectious diseases that have limited medical solutions (Khan et al., 2017). Even in developed countries such as the United States and Germany, diagnostics accounts only for 2.3% and 1.4% of their medical expenditures, respectively (Rohr et al., 2016). Therefore, developing inexpensive, effective and rapid portable diagnostic devices as a replacement for the traditional laboratory-based ones has become a hot research topic.

Point-of-care testing (POCT), which is a rapidly developing discipline in medical diagnosis, is emerging as a modern testing method for diagnostic analysis and other clinical applications (Luppa et al., 2011). Compared with laboratory-based testing, POCT enables quicker yet more accurate results at more economical rates. Accordingly, POCT is an effective alternative to laboratory-based testing in resource-limited areas.

The unique advantages of POCT are as follows: (1) simpler operation without the need for professionally trained operators; (2) less analysis time and quicker test results; (3) simpler and cost-effective fabrication of POCT devices; (4) convenience of use especially in

* Corresponding author.
E-mail address: zxgeng@muc.edu.cn (Z. Geng).

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limited-resource areas (Chan et al., 2017); (5) low consumption of energy and reagents (Arduini et al., 2016). These features of POCT are valuable in global health care programs, especially those related to non-ideal conditions where rapid medical decisions are needed. Thus, POCT-based diagnostics is a critical tool in reducing disease morbidity and mortality, thereby improving the overall quality of life (Urdea et al., 2006). Accordingly, organizations such as the US Global Health Initiative, the UK Department for International Development, etc. are investing in research and development of POCT (Chan et al., 2017).

Many commercial non-mobile-based POCT systems have been developed over the past decade, however, most of them are still not established in the market extensively (Drain et al., 2014; Pai et al., 2015). The important reason for this result is insufficient integration and automation of current commercial POCT (Syedmoradi et al., 2017a). The advent of smartphones, which are must-have tools for everyone, has changed this situation (Kanchi et al., 2018). Smartphone is very suitable for incorporation into promising technology to generate moveable diagnostic and monitoring systems for POCT, including paper-based sensors, microfluidic chips and flexible electronics etc. For example, Martinez et al. proposed the first case of using a mobile phone for telemedicine and off-site diagnosis (Martinez et al., 2008). Since then, there has been an increase in the number of POCT applications based on smartphones owing to their high visibility, data-processing capabilities, and better performance of sensors (Geng et al., 2017). It is usually used either as an independent device or in combination with other accessories such as a data display device, a detector, or a data processor. Biologically derived materials such as enzymes, cells, nucleic acids, antigen–antibodies, and microorganisms could be tested using smartphones (Geng et al., 2017). The detection methods include brightfield, colorimetry, fluorescence, and electrochemistry. Consequently, smartphones integrated with sensors and other hardware, together with related test methods, can provide accurate diagnosis and meet numerous clinical needs especially in resource-limited areas.

Many researchers have surveyed and discussed the developments in POCT (Jung et al., 2015; Luppa et al., 2011; Chan et al., 2017; Drain et al., 2014; Hernández-Neuta et al., 2018; Dhiman et al., 2017; Tian et al., 2018; Ozcan, 2014; Zhu et al., 2013; Kaur and Toley, 2018; Majors et al., 2017; Lee et al., 2018b; Ha et al., 2018; Shin et al., 2018; Zarei, 2018), most of them pertain to technical principles of testing, while others are on biomarkers or the advantages and relevance of POCT. For example, Syedmoradi et al. summarized the development of nanotechnology in POCT in detail (Syedmoradi et al., 2017b). Simultaneously, the current problems and future direction of POCT based on nanotechnology were also discussed. According to category of sensors and role of smartphone, Xu and co-workers reviewed five types of smartphone-based microfluidic biosensor systems for POCT (Xu et al., 2018). These reviews give researchers and engineers to specify problems and future direction for POCT field. However, it is also important to know which diseases can be diagnosed by the collected samples, which is more helpful for medical personnel who directly face patients. It is significant to diagnose diseases via samples that can be directly taken from human body, especially for resource-limited areas, because human tissue fluids or metabolites can be directly used as test samples without any preparations, and sample collection is also convenient for the users. With rapid advances in smartphones (hardware and software), researchers are exploring their use as standalone platforms for POCT especially for healthcare interventions in resource-limited areas. Smartphone-based liquid biopsy is particularly appropriate for use in a resource-limited area without costly reagents and large medical devices. In this review, therefore, we use liquid biopsy samples (blood, urine, sweat, saliva and tears) as the basis for classification, as shown in Fig. 1 and Table 1. In addition, combined with the detection principles to diagnose diseases, we critically review the development of smartphone-based POCT in the past two years (2017–2018). Finally, we propose the requirements and future prospects of smartphone-based POCT systems.

2. Blood

Blood, including serum and plasma, is a widely as specimens in routine clinical analysis. The levels of molecular components in the blood such as proteins, nucleic acids, and metabolites are directly related to the physiological states of the body (Gutierrez et al., 2004). Furthermore, blood is not only readily available but also simple to process. Therefore, blood contains targets that can be detected on smartphones using detection theories selected based on the specific target. The details regarding smartphone-based POCT devices listed in this section are shown in Table 2.

2.1. Brightfield test

Brightfield technology is the simplest optical microscopy technique, therefore, it can easily be developed on smartphone to form a small POCT device. The working principle is described in Table 1. Because of simple principle, it facilitates easy observation of living cells or large biomolecules in a blood sample. Based on this merits, a typical smartphone-based microfluidic chip for CD4 detection under a brightfield was reported (Kanakasabapathy et al., 2017a), as shown in Fig. 2. The device consisted of a microfluidic chip and a series of optical accessories. A custom-built smartphone application (App) was designed to perform image capturing, processing, and estimation of quantity of cells in the field of view. The entire image detection was completed within 10 s. A resolution of 33 cells per μL was achieved. Compared with large commercial devices, this POCT system is inexpensive (less than USD 10), and it can easily be implemented in resource-limited areas. In addition, the device can detect other living cells. In another case, the device, after a simple modification, was used for estimation of the amount of sperms in semen (Kanakasabapathy et al., 2017b). If the illumination source, focusing attachments, and complementary metal–oxide–semiconductor (CMOS) image sensor were combined together with the computational methods (convolution, super-resolution algorithms, and machine learning) in the App's software, the error of outcome would be reduced significantly. This work illustrates that, if the microfluidics, optical sensing accessories, and advances in consumer electronics, especially smartphone capabilities were integrated together, brightfield test can make remote sample quality testing accessible to people in any countries who have access to smartphones.

2.2. Colorimetric test

Colorimetry is a biochemical assay for assessing the change in absorbance or reflectance of an analyte-reagent complex. Usually, a nanostructure shape can affect the wavelength of plasmon resonance that gives rise to the optical properties in the sample, thereby changing its color. A simple smartphone-based colorimetric test needs only illumination and image processing. In addition, high sensitivity of the biosensor is also important. With the integration of a CMOS image sensor, an optical grating, and a spectrum processing technique, a complex smartphone-based POCT was developed, which included small lenses, separate lighting sources, and a biosensor chip with microfluidics (McCracken and Yoon, 2016).

Although this section only reviews the progress of colorimetric testing during 2017–2018, a typical work (testing blood) performed earlier in 2016 compared it with the latest works. For example, a device based on colorimetric detection of vitamin B_{12} has emerged (Lee et al., 2016). As shown in Fig. 3 Panel 1, the blood from the finger was directly dropped onto the test strip. Once the sample was competitively bound to the gold nanoparticles-anti-B_{12} conjugate on the test strip, the colorimetric signal was enhanced by silver. After the custom-built App captured and processed the image, the concentration of vitamin B_{12} was calculated based on a comparison with a predetermined calibration curve. This study group also proposed a device for detecting serum ferritin in 2018, as shown in Fig. 3 Panel 2 (Srinivasan et al., 2018). The

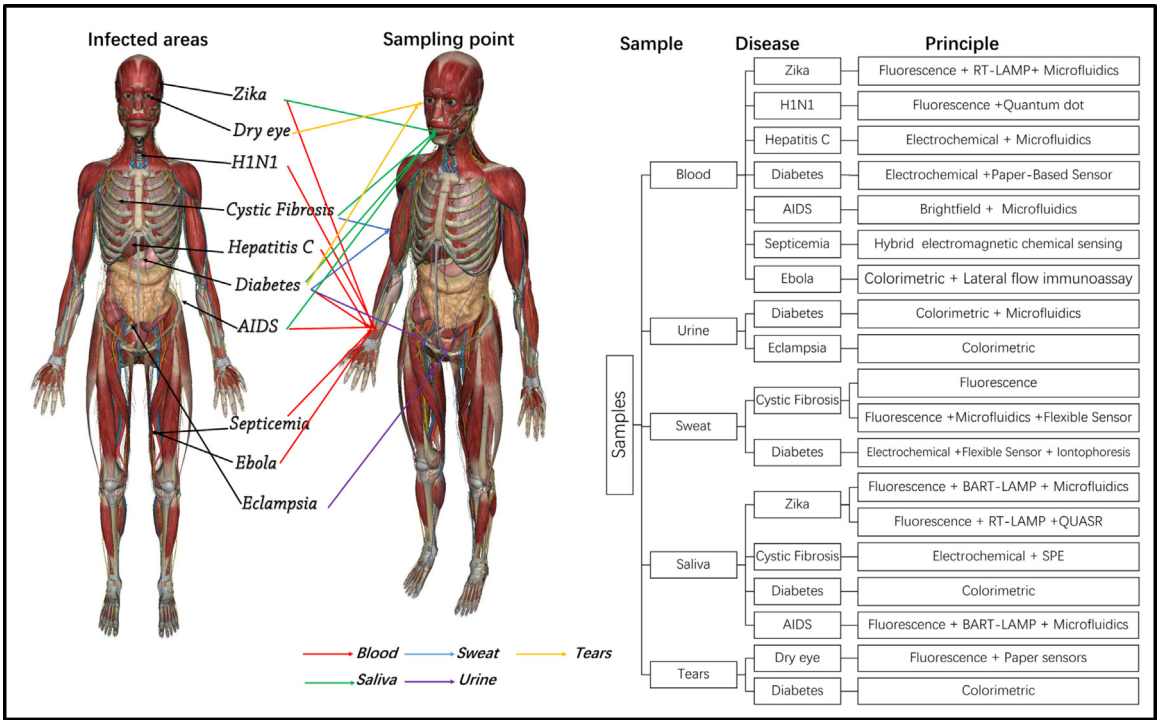

Fig. 1. The correlation between disease and test sample that can be diagnosed by a smartphone-based POCT. Left: Different diseases in body; **Middle**: Sampling point for liquid biopsy detection; **Right:** Different detection principles and tested samples. RT-LAMP: reverse-transcription loop-mediated isothermal amplification. BART-LAMP: bioluminescent assay in real-time and loop-mediated isothermal amplification. SPE: screen-printed electrode. QUASR: quenching of unincorporated amplification signal reporters.

detection principle is similar to the above. The system exhibits good scalability and reusability. Multiple analytes can be detected by replacing the test strips and upgrading the App. Thus, the direction for future work is to develop different kinds of test strips and modularize the custom-built App. If parallel detection technology of multiple copies is developed in colorimetric detection, also with development of online medical technology and big data technology, colorimetric test has the potential to enable highly sensitive home-use test kits as well as testing in field and survey settings for ID. And the test results can upload online real time, which will help enrich centralized electronic health records database.

Recently, a POCT device for the rapid detection of IgG antibodies against Ebola by blood testing was proposed (Brangel et al., 2018). As shown in Fig. 3 Panel 3, the complete system includes an immunochromatographic strip and a smartphone. When the serum containing Ebola virus antibody is dropped onto the reagent strip, a red-purple line appears on the reagent strip. Then, the custom-built App computes the relative strength of the test line and determines the result (positive or negative). The entire process takes less than 15 min; therefore, this device with low-cost and rapid smartphone-based lateral flow-based assay can be particularly used in places with limited medical resources. In addition, it helps disease control departments to formulate policies in favor of patients because the App has user-friendly features such as saving the location information of a patient. However, the POCT device has a limitation in that the results are likely to be affected by the ambient light.

Similarly, a smartphone-based optical platform for colorimetric analysis of blood hematocrit was proposed, as shown in Fig. 3 Panel 4 (Kim et al., 2017b). The researchers used a disposable microfluidic device to hold the blood sample and a smartphone camera to take a photograph of blood in the microchannel. The image was analyzed by using a custom-built App. The most important module of the system was the light diffusing device inside the white imaging box, which could avoid the image burning caused by the flash of phone and the interference caused by external light. The device could calculate hematocrit levels in the range of 10–65%. The limit of detection (LOD) obtained from the platform is 0.1% hematocrit. In 2017, a method for detecting antibodies to HIV and treponema pallidum infections was also

Table 1
Main testing principles used for different diseases.

Principle	Description	Disease
Brightfield test	The sample is illumined from below by white light, and the light is transmitted through the sample. The contrasts in the sample are caused by attenuation of the transmitted light in dense areas of the sample (Drey et al., 2013).	AIDS[1]; Infertility …
Colorimetric test	Colorimetric test is often used to measure the concentration of a chemical element or compound in a solution or a test strip with the aid of a color reagent, and it is based on changes in the absorbance or reflected intensity of analyte-reagent complexes (Heo et al., 2014).	Ebola; AIDS; Syphilis; Diabetes; Preeclampsia …
Fluorescence test	Fluorescence is the emission of light produced by a substance that has absorbed light or other electromagnetic radiation. It is directly proportional to the intensity of excitation (Moerner and Fromm, 2003).	Zika; H1N1[2]; Cystic fibrosis; AIDS …
Electrochemical test	A chemical reaction caused by an external current, or an electric current caused by a spontaneous chemical reaction; it is called electrochemical reaction (Bahadır and Sezgintürk, 2015).	Diabetes; Hepatitis C; Septicemia; Cystic fibrosis …

Note: 1 Acquired Immune Deficiency Syndrome; 2 Highly Sensitive Influenza Virus.

Table 2
The information of blood sample POCT device.

Theory	Detect Target	Accessories	Time	LOD	Disease	Ref.
Brightfield	$CD4^+$ T cells	Microfluidic chip, light source, lenses	< 10 s	≥ 60 cells per μL	AIDS	(Kanakasabapathy et al., 2017a)
Colorimetric	Vitamin B_{12}	Case, battery, LED, lens, test strip	15 min	92 pmol/L	–	(Lee et al., 2016)
Colorimetric	Ferritin	Test strip, test strip reader	< 7 min	15.0 μg/L	Iron deficiency	(Srinivasan et al., 2018)
Colorimetric	Ebola virus	Lateral flow strip	15 min	200 ng/mL	Ebola	(Brangel et al., 2018)
Colorimetric	Red blood cell	Light diffuser, microfluidic device, custom-built box	–	0.1% of hematocrit	Restless leg syndrome, Headache etc.	(S. C. Kim et al., 2017b)
Colorimetric	HIV, Treponema pallidum	HRDR-200 reader	–	–	AIDS, Syphilis	(Herbst de Cortina et al., 2017)
Fluorescence	Zika, Chikungunya, Dengue	Microfluidic chip, battery, lens, long pass filter, heater, LED	~30 min	1.56×10^5 PFU/mL	Zika, Chikungunya, Dengue	(Ganguli et al., 2017)
Fluorescence	Red blood cells, Cancer cells	Lens, permanent magnets, battery, switch, resistor, emission filter set	–	935 cells/mL	Cancer	(Knowlton et al., 2017)
Fluorescence	H1N1 virus	LED, custom-built chamber, biosensor	40 min	138 pg/mL (idea sample) 600 ng/mL (real sample)	H1N1	(N. Lee et al., 2018a)
Electrochemical	Glucose	Capacitor, transformer, USB connector, earphone jack, switch	~2 min	–	Diabetes	(Fujimoto et al., 2017)
Electrochemical	Glucose	Electrodes, wireless potentiometer	< 80 s	0.1 mM	Diabetes	(Cánovas et al., 2017)
Electrochemical	Glucose	Custom-built case, sensor strip, stylus	Few seconds	60–125 mg/dL	Diabetes	(Bandodkar et al., 2018)
Electrochemical	Blood ketone	Medic dongle, test strip	Few seconds	0.001 mmol/L	Diabetes Ketoacidosis, Diabetic Ketosis Acid	(Guo, 2017)
Electrochemical	Cholesterol	test strip, embedded circuit	~1 min	–	Cardiovascular Disease	(Fu and Guo, 2018)
Electrochemical	White blood cell	Battery, power regulator, micro-controller, analog to digital converter, digital-to-analog converter, potentiostat, sensor	< 1 min	100 /μL	Leukocytosis, Leukopenia	(Xinhao Wang et al., 2017c)
Electrochemical	IL-3	Battery, magnetic pipet, magneto-electrochemical sensor	< 1 h	10 pg/mL	Septicemia	(Min et al., 2018)

proposed (Herbst de Cortina et al., 2017) (Fig. 3 Panel 5). This method needed an electronic reader (Mudanyali et al., 2015). The experiments showed that the specificity of this method could reach ~95%.

As seen from the aforementioned cases, a smartphone-based POCT device is emerging as an important tool to detect the biomarkers of a serious disease. Thus, it can be considered as a potential indicator of a revolution in medical testing equipment.

2.3. Fluorescence test

Fluorescence analysis has the characteristics of high sensitivity, simple operation, and strong specificity. It is commonly used in biochemistry to detect antibodies or nucleic acids in blood. For example, Zika, chikungunya, and dengue are not only highly contagious but also difficult to make an effective diagnosis during clinical testing (Lessler et al., 2016). These infectious diseases may break out quickly as in recent years, therefore, there is a need to develop a novel POCT platform for urgent, sensitive, and portable testing. To solve this problem, a device based on the reverse-transcription loop-mediated isothermal amplification (RT-LAMP) and fluorescence for rapid detection of Zika, chikungunya, and dengue was proposed (Ganguli et al., 2017). Fig. 4 Panel 1 shows a diagnostic card containing two modules. The module A is a microfluidic chip for processing samples. The module B is introduced via the outlet port of module A. Only the channels of the pathogen-specific primers in the blood sample illuminate over time, while the fluorescence of other channels remains at the initial baseline level. The sample does not require any additional processing; therefore, this device can multiplex detect viral and other nucleic acid targets on a portable point-of-care setup from whole blood samples. The system is also capable of printing other viral primers on the chip for other tests, and therefore it is cost-effective compared to a commercial device. Similarly, researchers developed a device based on fluorescence method for screening cells for identification of cell types and activities according to density-based principle (Knowlton et al., 2017), which is shown in Fig. 4 Panel 2. The author imaged a mixture of red blood cells and calcein-stained cancer cells under bright- and dark-fields, respectively.

Under bright-field, the two groups are spatially separated in the magnetic field due to their different densities. In the fluorescence imaging mode, only cancer cells can be observed. The proposed device is portable; therefore, it can be used in different situations. With advances in detection technology, more biomarkers of disease can be detected, which make it more convenient for use. For example, a highly sensitive influenza virus (H1N1) assay resolved the above difficulties effectively (Lee et al., 2018a). As shown in Fig. 4 Panel 3, the method utilizes the synergy of quantum dot (Qdot)-aptamer beacons and emission light guides to perform signal enhancement based on three-dimensional photonic crystal biosensor. The authors used the switch ("ON-OFF") measurement theory to realize detection of the biomarker. In a pre-prepared solution for detection of influenza A (H1N1) virus, the energy from Qdot is transferred by fluorescence resonance energy transfer to a dark quencher conjugated to guard DNA (G-DNA). Together, the fluorescence emission level of Qdot is in the "OFF" state, which is extremely low. If the target H1N1 influenza is present, the biosensor would enter "ON" state. Compared with a commercial POCT, the sensitivity of this device is higher because the fluorescence signal is enhanced by the three-dimensional photonic crystal. The experimental results showed that the LOD could reach 600 ng/mL in a real sample. In addition, the entire experimental process needs only ~40 min. Based on the three cases mentioned above, there are some important directions for future developments: (1) Expanding the compatibility of this device to both nuclear and surface stains is expected to broaden its applications greatly to live/dead assays, immunostaining; (2) Expanding the use of fluorescence detection in whole blood samples, especially for some infectious agents; (3) The acquired sensing information can be easily transmitted and analyzed through integration of information

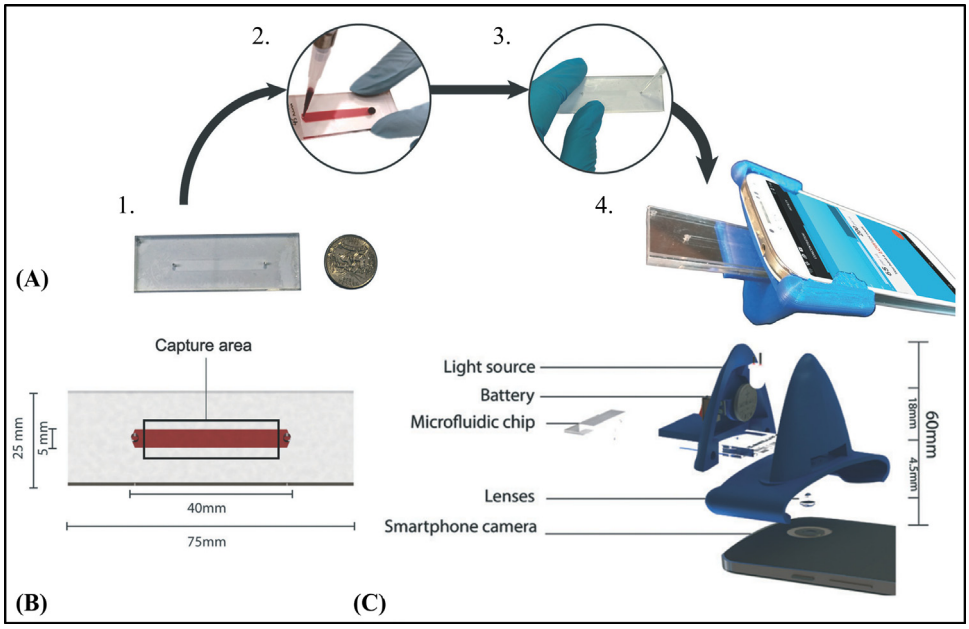

Fig. 2. Smartphone for detecting CD4 under brightfield. (A) Process flow showing the steps involved in performing the assay; **(B)** Dimensions of the disposable microfluidic chip; **(C)** Exploded images of the smartphone attachments and the relevant dimensions. Reproduced from Kanakasabapathy et al. (2017a).

technologies such as smartphones and online databases for real-time analysis and in-time diagnosis.

2.4. Electrochemical test

A chemical reaction caused by electricity is called an electrochemical reaction. A POCT device with an electrochemical sensor exhibits high precision, fast response, low cost, and portability (Yu et al., 2016b, 2016a). It is widely used in medical testing, industrial analysis, and environmental evaluation. This method has been applied to detect important analytes. It is an ideal detection method, especially for protein biomarkers (Q. Zhang et al., 2018a). The important research progresses (2017–2018) of this technology, which were based on smartphone that acts as a portable platform to record, analyze, control, and display the results, are briefly reviewed below.

A smartphone-based electrochemical detection device and paper-based biosensor were developed and used to measure the concentration of β-D-glucose in phosphate-buffered saline (Fujimoto et al., 2017). As shown in Fig. 5 Panel 1, the device transmits data through an audio jack. The detecting principle of glucose concentration is based on chronoamperometry method. This experiment is aimed at detection of the targets in whole blood for diabetes. Improved reliability should extensively justify this cost-effective sensing system. Similarly, a paper-based sensor for detecting glucose was developed (Cánovas et al., 2017). The system combines a paper-based working electrode and a reference electrode to build the potentiometer unit (Fig. 5 Panel 2). The system calculates the concentration of glucose in the sample by detecting the hydrogen peroxide produced by an enzymatic reaction. However, the system currently requires further improvements in sensitivity and linear range. Paper-based biosensor, as cost-effective biosensor, paper-based biosensors have been widely used to analyze ions, metabolites, proteins, nucleic acids, etc. (Wang et al., 2017d). Therefore, a combination of paper-based equipment and smartphones have also become a trend. Another system for detecting glucose may be more suitable for large-scale industrial production (Bandodkar et al., 2018). It is composed of a custom-designed smartphone case with a permanently exposed sensor strip, a stylus with enzyme-carbon composite particles, and a sensor meter circuitry (Fig. 5 Panel 3). The testing process is simple, and the entire testing takes only a few seconds. Compared with the previous two works, this device has the advantage of repeated usage. Moreover, the glucose oxidase in the reaction is easy to transport and easy to preserve owing to simple packaging. Therefore, the system may have the potential of commercial production.

Blood-based electrochemical POCT is not limited to glucose detection. For example, a real-time monitoring method for blood β-ketone was proposed (Fig. 5 Panel 4) (Guo, 2017). The researchers used a disposable test strip and a medical dongle powered by a smartphone to detect biomarkers in blood. The device has merits such as compact structure, high sensitivity, and less time-consuming. Moreover, the device has the ability to detect other biomarkers in blood. Another study of the group showed that the device is capable of detecting blood lipid level, which has a positive effect on prevention of cardiovascular disease (Fu and Guo, 2018). However, the hematocrit of blood has a negative impact on the measurement results. Therefore, it is necessary to perform compensation in the algorithm to improve the detection results. In 2017, a smartphone-based white blood cells (WBC) counter was proposed as shown in Fig. 5 Panel 5 to obtain detailed information in rapid diagnosis (Wang et al., 2017c). When the membrane electrode was covered by the trapped cells, there was a response in current. The system could quantify WBC concentrations covering the physiological and pathological ranges. Further developments in smartphone-based portable devices helped detect more diseases. For example, sepsis, which is an important illness causing death from infection, has recently been explored on a smartphone-based platform (Min et al., 2018). As shown in Fig. 5 Panel 6, the platform utilized the pathophysiological role of the cytokine interleukin-3 (IL-3) in early sepsis and an electrochemical sensor for IL-3 detection. The platform could provide testing results from natural blood samples within 1 h. Compared with the traditional enzyme-linked immunosorbent assay (ELISA), the performance is improved by more than 5 times, and the sensitivity is increased by more than 10 times. The experimental results show that the detection sensitivity and specificity are 91.3% and 82.4%, respectively. The cases mentioned above illustrate that compact and fast test devices could be a practical clinical kit for timely diagnosis and proactive treatment of disease.

The rapid development of research on the smartphone-based electrochemical sensor platform indicates some important trends: (1) a variety of major disease samples are tested; (2) devices based on smartphone sensor platform or sensor components are increasingly miniaturized and becoming portable; (3) the signal processing time of

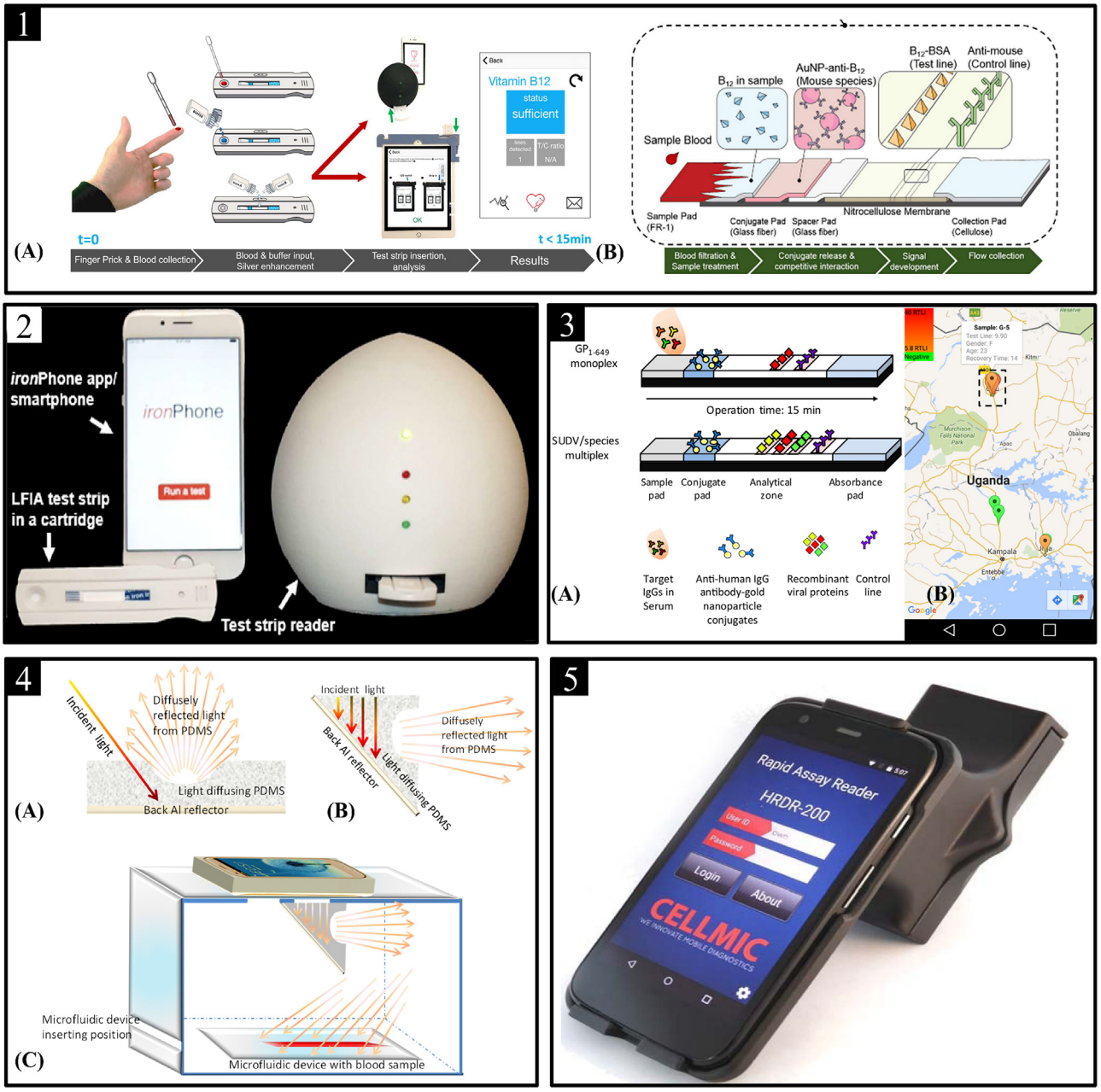

Fig. 3. Colorimetric test method for POCT in blood samples. Panel 1: (A) Equipment instructions and test processes; **(B)** Schematic of the Vitamin B_{12} test strip. Reproduced from Lee et al. (2016). **Panel 2:** System overview of device. Reproduced from Srinivasan et al. (2018). **Panel 3: (A)** Schematic of the working principle of the lateral flow test paper used to detect the Ebola virus IgG; **(B)** Map generated after on-site testing of the collected Ebola survivors; red indicates positive and green indicates negative. Reproduced from Brangel et al. (2018). **Panel 4: (A)** and **(B)** Description of light diffusing effect of u-shaped PDMS; **(C)** Schematic side view of the smartphone-based optical analysis platform. Reproduced from Kim et al. (2017b). **Panel 5:** Cellmic HRDR-200 smartphone-based electronic reader. Reproduced from Herbst de Cortina et al. (2017).

testing is shorter.

3. Urine

Urine is another important sample commonly used in a medical treatment, and its constituents such as urinary hemoglobin, WBC, enzymes, electrolytes, etc. are critical for clinical diagnosis, judgment of efficacy, and prognosis (Kumar and Das, 2017). Unlike blood testing, urine testing has the advantage of being non-invasive (Coskun et al., 2013). The information related to the detection of urine using smartphone-based POCT devices are shown in Table 3.

3.1. Colorimetric test

A traditional system was used to detect protein in urine, which has high cost, low throughput, and long analysis time. To overcome these limitations, a smartphone platform based on colorimetric method was developed to detect multiple proteins in urine as shown in Fig. 6 Panel 1 (Wang et al., 2017a). The authors used different sodium chloride solutions to discriminate 12 kinds of proteins (shown in different colors) because gold nanoparticles exhibit an aggregation behavior that varies with the kind of protein. This device could considerably improve the efficiency of medical workers. However, it still suffered from low accuracy and false positives. Like proteins, glucose is another important target in urine. The concentration of glucose in urine is an indicator of

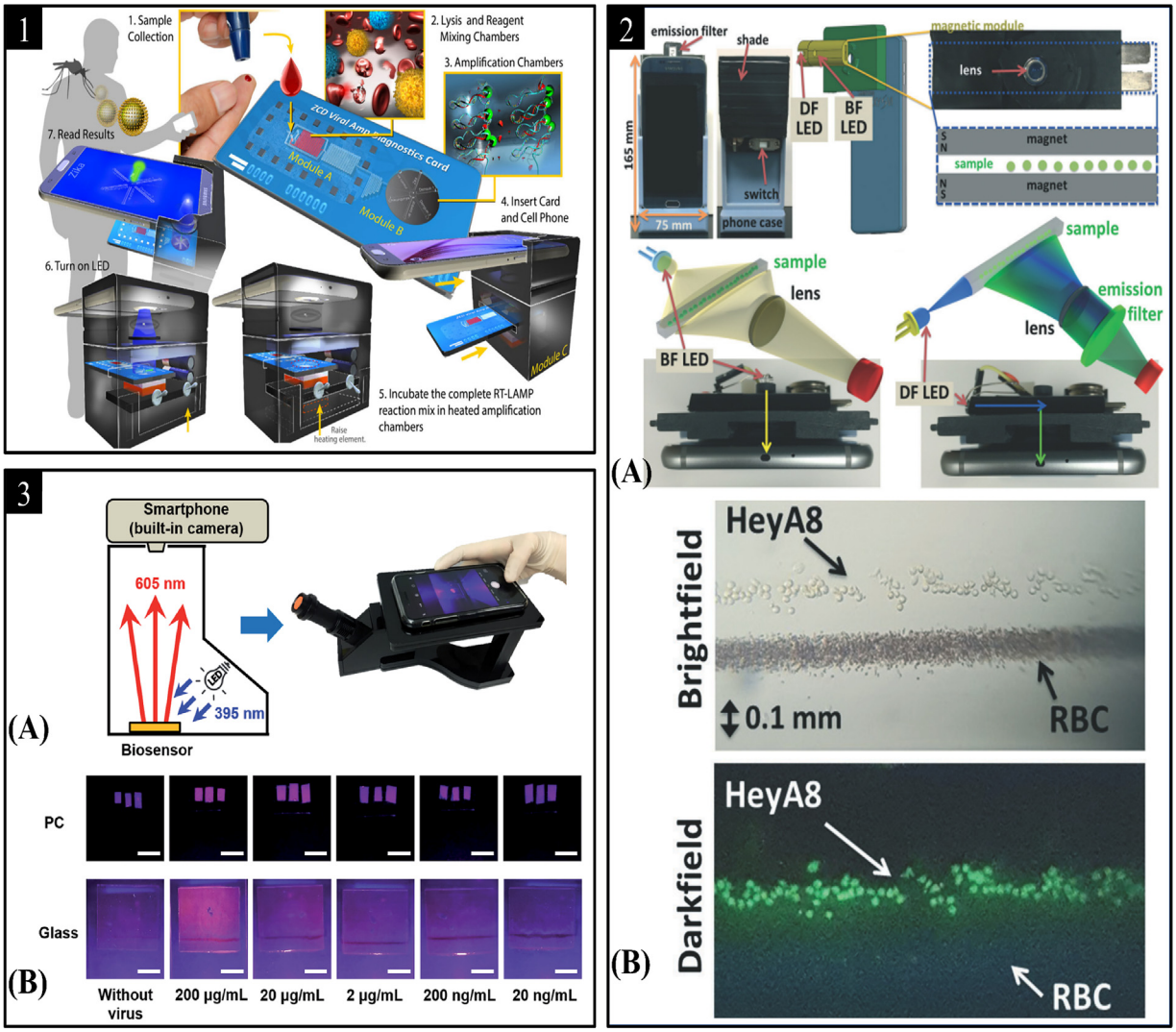

Fig. 4. Fluorescence test method for POCT in blood samples. Panel 1: Process flow for detection of the Zika, chikungunya, and dengue. Reproduced from Ref (Ganguli et al., 2017). **Panel 2: (A)** Image and schematic of 3D-printed fluorescence microscope system; **(B)** Images of a mixture of calcein-stained cancer cells and RBC in bright- and dark-field conditions. The darkfield has a shielding effect on the RBC. Reproduced from Knowlton et al. (2017). **Panel 3: (A)** Schematic and photograph of the device detecting H1N1 virus; **(B)** Fluorescent images of different concentrations of virus photographed by a smartphone on photonic crystal (PC) and glass, which show that photonic crystals have higher fluorescence intensity than glass. Reproduced from Lee et al. (2018a).

diabetes. Recently, two research teams reported smartphone-based methods for detecting glucose in urine. One was a wearable device as shown in Fig. 6 Panel 2 (Zhou and Dong, 2018) whereby the system includes a diaper with a self-sampling device and a smartphone. The device could analyze the collected samples of urine via a custom-built App. In this system, the colorimetric reaction can be stable for 20–480 min, which is critical for disabled users. The other one was a paper-plastic hybrid microfluidic device (Fig. 6 Panel 3) (Jalal et al., 2017). An array of commercial paper-based reagent test pads was embedded into the microchannel of a microfluidic device. A micropump was installed on the device for controlling the volume of reaction sample. Subsequent to the sampling, the smartphone was used for colorimetric analysis in conjunction with the imaging cartridge previously proposed by the team (Kim et al., 2017b). The hardware of this system was reasonably compact. The detection error is minor since the volume of urine is controlled. Zhou's work shows a unique advantage with respect to self-detection of samples from paralyzed patients. Many paraplegic patients are unable to control their urination, and, in some cases, they are not even aware that they have urinated. Therefore, retaining urine samples so as to avoid secondary pollution in Zhou's device was more suitable for self-diagnosis in the case of disabled people.

Detection of sodium ions in urine is an essential test in a POCT. Recently, researchers proposed a simple digital atomic emission spectrometer for the quantitative analysis of sodium in human urine samples (Debus et al., 2017). As Fig. 6 Panel 4 shows, the system was capable of operating without a power source. However, the need for a Bunsen burner is serious drawback of this system, considering that the operator is compelled to keep a safe distance from the system and that there is a risk of flame burning the top of the box, thereby affecting the experimental results.

It has always been difficult to organize an appropriate maternal care equipment in a resource-limited area. To overcome this problem, researchers proposed a system for indicating pre-eclampsia/eclampsia (Wirth et al., 2018). The system includes a module called uChek and a smartphone (Fig. 6 Panel 5). The uChek works on the principle of reflectance photometry that analyzes the intensity and color of the light reflected from the reagent areas of the urinalysis reagent strip. Thus, the system could compute the ratio of albumin to creatinine with a test strip. The ratio was critical for the diagnosis of pre-eclampsia. The device was tested in underdeveloped areas where no medical staff used the device. The final results showed that all medical staff considered the capability of the device to provide rapid results, while 90% of them

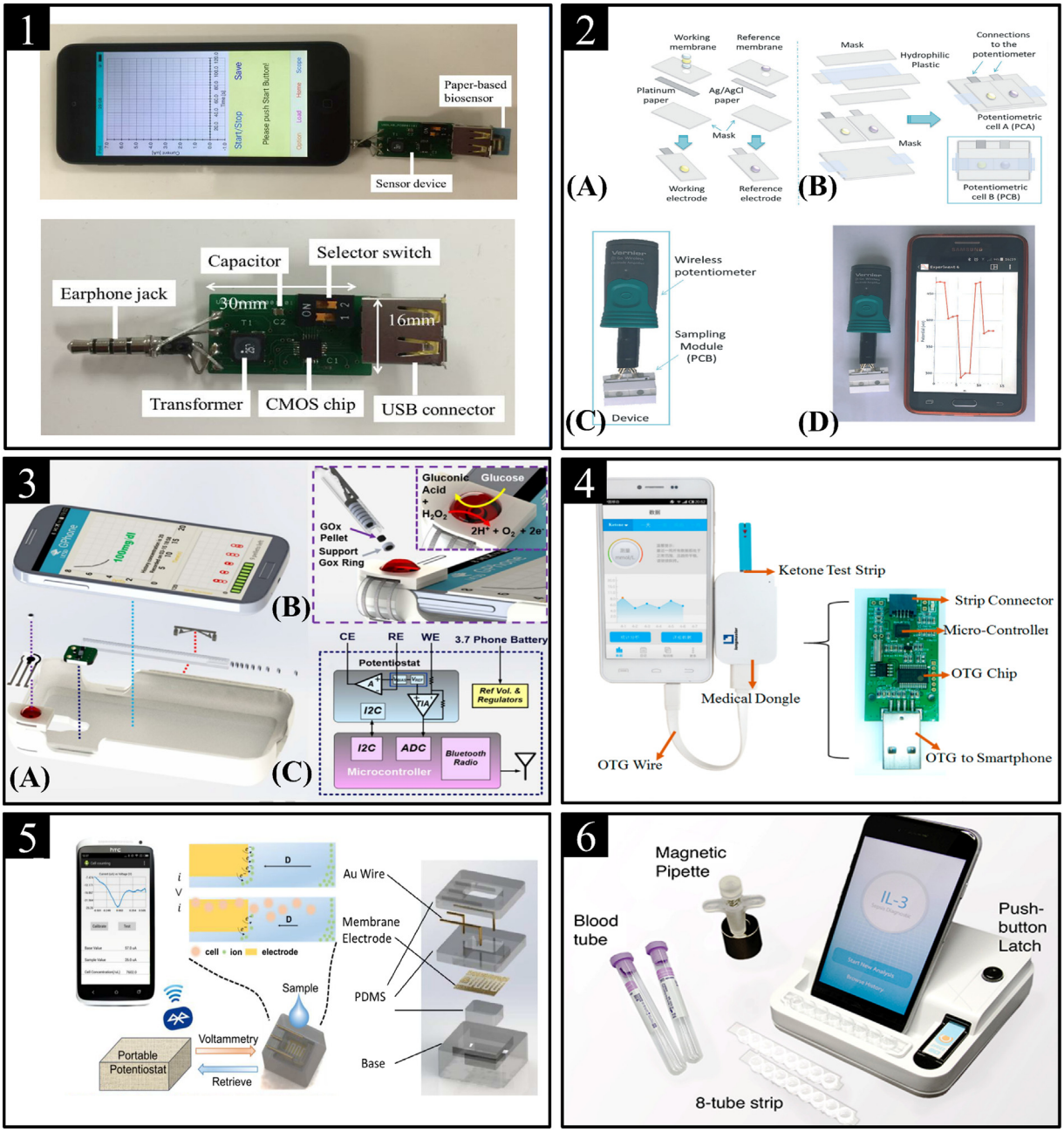

Fig. 5. Electrochemical method for POCT in blood samples. Panel 1: A photograph of the whole system. Reproduced from Fujimoto et al. (2017). **Panel 2: (A)** Preparation of reference electrodes and working electrodes; **(B)** Schematics of sensor and sampling unit; **(C)** A photograph of the integrated accessory; **(D)** A photograph of the entire system. The phone screen shows the results of sample measurement. Reproduced from Cánovas et al. (2017). **Panel 3: (A)** Schematic of the smartphone-based glucose sensing system; **(B)** The diagrammatic drawing of chemical reactions occurring at working electrodes; **(C)** Circuit diagram of the electronic readout circuit. Reproduced from Bandodkar et al. (2018). **Panel 4:** Image and composition diagram of the system. Reproduced from Guo (2017). **Panel 5:** The design and method of WBC system (Left) and explosive view of the sensor. **D** is diffusion coefficient; **i** is the electrochemical current. Reproduced from Wang et al. (2017c). **Panel 6:** A photograph of the whole system. Reproduced from Min et al. (2018).

agreed that the system reduced the risk of human error.

For colorimetric test, eliminating the effects of ambient light was critical. Thus, a method of smartphone-based POCT urinalysis under various conditions of illumination was proposed (Ra et al., 2018). The author modified the traditional reagent strip into a circular strip called donut-shaped nearness urine tester (DONUT). A set of DONUT contains 10 sub-modules for measuring 10 target substances (urobilinogen, glucose, bilirubin, ketones, specific gravity, red blood cells (RBC), pH, proteins, nitrites, and leukocytes), respectively (Fig. 6 Panel 6). The system not only used the naked eye directly to get results but also developed a solution for using the evaluation results of smartphone App. The shape of the strip helps avoid the interference of ambient light effectively. The merits of the strip are simplicity, uniqueness, robustness, and accuracy. In addition, the data processing algorithm has a great impact on POCT and in general paper-based analytical devices. This technology is expected to be very important for POCT in near future.

3.2. Fluorescence test

Human chorionic gonadotropin (HCG) detection in urine is a common POCT. However, current commercial HCG tests only provide

Table 3
The information of urine sample POCT device.

Theory	Detect Target	Accessory	Time	LOD	Disease	Ref
Colorimetric	Protein	96-well micro titer plates, colorimetric sensor array	–	–	Renal disease	(Wang et al., 2017a)
Colorimetric	Glucose, Leukocytes, Nitrite, Proteins	Self-sampling device, diaper	10 min	–	Urinary tract infections, Kidney-related diseases	(Zhou and Dong, 2018)
Colorimetric	Glucose, Protein, pH, Red blood cell	Acrylic imaging box, micropump	few minutes	Glucose: 0–350 mg/dL Protein: 0–2000 mg/dL pH: 5.25–7.5 RBC: 0–280 RBC/μL	Diabetes	(Jalal et al., 2017)
Colorimetric	Na^+	Case, Bunsen burner, silver wire loop	10 s	10.9 mmol/L	Diseases related	(Debus et al., 2017)
Colorimetric	Protein	Cuboid Reader, test strip	~3 min	–	Preeclampsia, Eclampsia	(Wirth et al., 2018)
Colorimetric	Urobilinogen, glucose, bilirubin, ketones, specific gravity, red blood cell, pH, protein, nitrite, leukocytes	urine test strip consists of porous matrices mixed with dried reagents on a carrier element	–	–	Many related diseases	(Ra et al., 2018)
Fluorescence	Sepsis pathogen	Hot plate, LED, cable, battery, cardboard box	~1 h	5×10^3 10^3 CFU/mL	Sepsis	(Barnes et al., 2018)
Fluorescence	Human chorionic gonadotropin	Lens, optical fiber bundle	few seconds	1.2 pM	Pregnancy	(Paterson et al., 2017)
Electrochemical	Ascorbic Acid, Dopamine, Uric Acid	Sensor, coin-sized detector	–	1.04 μmol/L, (ascorbic acid) 0.29 μmol/L, (dopamine) 5.4 μmol/L, (uric acid)	Hyperuricemia	(Ji et al., 2018a)

"yes" or "no" result. In 2017, a device, luminescent phosphor and smartphone flash as reporter and excitation source, respectively, was developed, which can quantitatively and rapidly detect HCG in urine (Fig. 7 Panel 1) (Paterson et al., 2017). LOD of this system for HCG is 10-fold better than that of traditional rapid-pregnancy-test device. If this device or method can be commercialized, it will enable pregnant women to have pregnancy tests at home at any time without having to wait in line at the hospital, which will become an important application direction of POCT and have a large market value.

In 2018, a smartphone-based pathogen diagnosis in urinary sepsis patients was proposed (Barnes et al., 2018). The entire workflow is shown in Fig. 7 Panel 2. The lysate sample is mixed with a pre-mixed LAMP reaction mixture that produces a fluorescent signal in response to amplification. Subsequently, the samples are placed in an apparatus consisting of a platform that can accommodate samples, a heat block, and an LED light source. The concentration of gDNA is computed by a custom-built App. The rough derivation algorithm that used is to calculate fluorescence intensity is robust and has high data repeatability. However, the working has two shortcomings. One is that a part of data still needs to be calculated using MATLAB on a personal computer. The other one is that the “OpenCV Manager” needs to be installed on users’ phone before using the custom-built App. These two shortcomings weaken the convenience of the working. This device was used to test pathogen in urinary sepsis, which presents the potential to deliver rapid diagnosis and treatment of urinary tract infections and urinary sepsis with a simple test being performed at low cost at the point-of-care. Especially, this technique can also be utilized in battlefield scenarios.

3.3. Electrochemical test

A portable device that can detect ascorbic acid, dopamine, and uric acid based on electrochemical technique was proposed (Ji et al., 2018a). The system consisted of a disposable sensor, a detector, and a smartphone (Fig. 8). The sensor was composed of a screen-printed electrode (SPE) modified with reduced graphene oxide and gold nanoparticles for recording analog signals. The detector further converts the analog signal into a digital signal. Finally, the smartphone converts the received data into a differential pulse volt–ampere curve and a cyclic volt–ampere curve. The overall system was compact and accurate. Moreover, this working has the potential to be further upgraded. In another case, this device was improved to detect levodopa in human serum (Ji et al., 2018b). The levodopa is a significant biomarker for diagnosing Parkinson's disease. However, the custom-built App in this working was not friendly enough because it required the users to set a series of electrical parameters, while it may be difficult to operate for an unskilled or a poorly educated person. Thus, there is immense potential for simplification of the App.

4. Sweat

Sweat is a vital metabolic waste, which contains uric acid, lactic acid, and various electrolytes (Xu and Yan, 2018). The electrolyte in sweat is mainly composed of sodium ions and chloride ions, as well as small amounts of potassium ions and calcium ions. In general, the concentrations of chloride, sodium, and potassium in human sweat are 4–60 mmol/L, 10–40 mmol/L, and 9 mmol/L, respectively. In recent years, the sweat-based POCT has been setting up a different way for health care because of the development of flexible electronic technology and wearable devices. The information of smartphone-based POCT devices discussed in this section are summarized in Table 4.

4.1. Fluorescence test

Cystic fibrosis is a hereditary disease caused by genetic flaws. The test of electrolyte levels in sweat is the gold standard for the determination of cystic fibrosis. However, the electrolyte in sweat is still tested

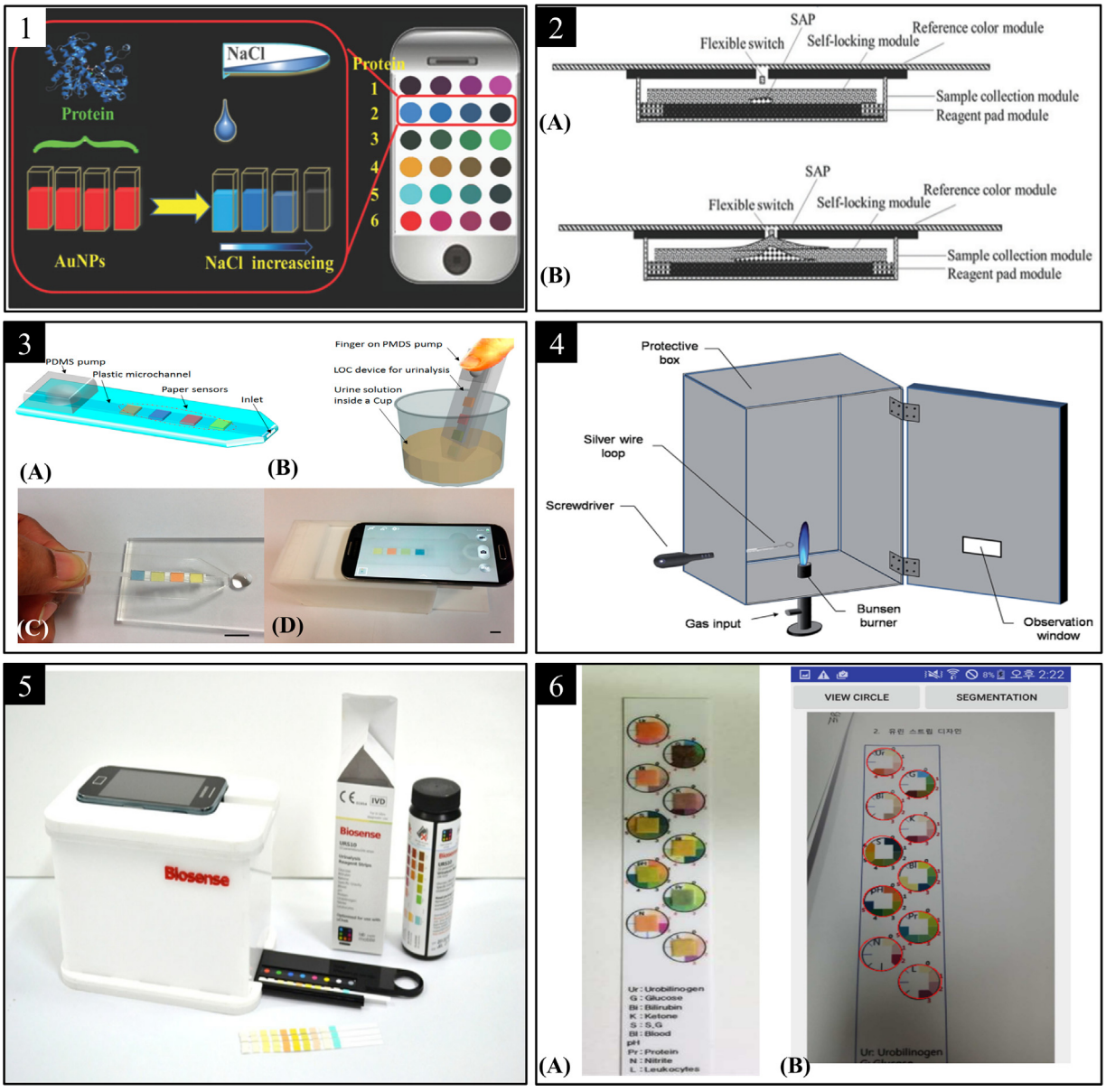

Fig. 6. Device employing colorimetric method for POCT in urine samples. Panel 1: Schematic of sensor array recognizing multiple proteins. Reproduced from Wang et al. (2017a). **Panel 2: (A)** Schematic of self-locking device without urine; **(B)** Schematic of self-locking device with urine. Reproduced from Zhou and Dong (2018). **Panel 3: (A)** Construction of microfluidic device; **(B)** A finger presses the microfluidic pump, and the device collects urine samples from the cup; **(C)** A photograph of microfluidic device; **(D)** A photograph of the whole system. Reproduced from Jalal et al. (2017). **Panel 4:** Scheme of platform for the determination of sodium content in urine, the sample in silver wire loop, smartphone placed in the observation window. Reproduced from Debus et al. (2017). **Panel 5:** A picture of uChek system. Reproduced from Ref (Wirth et al., 2018). **Panel 6: (A)** Captured image of DONUT under natural light conditions; **(B)** Load image interface of the custom-built App. Reproduced from Ra et al. (2018).

using a manual titration. Therefore, medical personnel urgently need an automated analyzer. To meet this need, as shown in Fig. 9 Panel 1, researchers proposed a smartphone-based chloridometer for diagnostics of cystic fibrosis (Zhang et al., 2017). The concentration of chloride ions was calculated by utilizing the characteristic that the fluorescence intensity of CA-Cysteine is decreased when it encounters chloride ions. However, the device did not detect electrolytes in sweat continuously, and components such as battery and LED also increased the complexity of the device. Wearable devices solved these problems effectively (Sekine et al., 2018). The microfluidic device consists of a detachable black shield, a cover layer, a microfluidic channel layer, and an adhesive layer (Fig. 9 Panel 2). The entire microfluidic device exhibits excellent resilience, which helps fit the device snugly against skin. The accessories contain excitation and emission filters which allow use of the smartphone flash as a source of excitation light. The device detects sodium, chloride, and zinc ions. Furthermore, the device does not need batteries and LED. The concentration of electrolyte in the sweat can be detected continuously for a long time. However, the data of zinc ions may be imprecise because its fluorescence intensity is relatively low. Although the detection sensitivity needs to be further improved, the results also shown the versatility of fluorescent-based imaging modalities in sweat microfluidics platforms. The cost-effective nature and concise application of this platform could expand its application field.

4.2. Electrochemical test

Electrochemical method also plays an important role in the detection of sweat samples, and detecting concentration of glucose in body

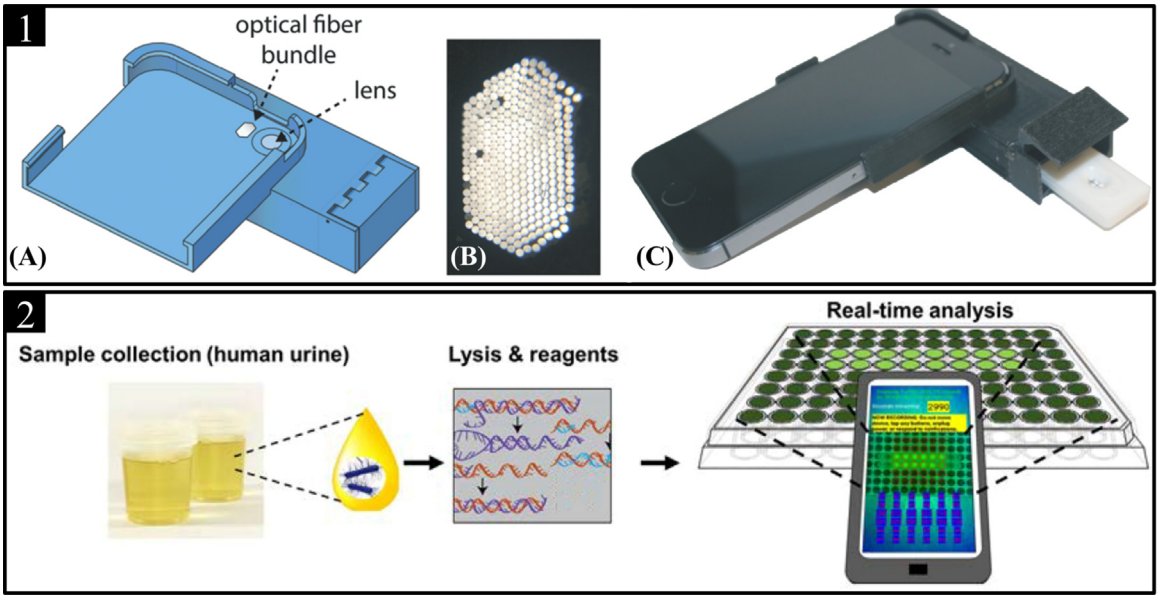

Fig. 7. Device employing fluorescence method for POCT in urine samples. Panel 1: (A) Schematic diagram of smartphone attachment; **(B)** Image of optical fibers; **(C)** Photograph of the whole system. Reproduced from Paterson et al. (2017). **Panel 2.** Assay schematic for the smartphone-based pathogen diagnosis in urinary sepsis, including sample collection, bacterial cell lysis/reagent addition, and real-time analysis. Reproduced from Barnes et al. (2018).

has always been a critical topic. Researchers proposed an electrochemical-based wearable sensor as shown in Fig. 10 Panel 1 (Zhu et al., 2018). The entire sensor was integrated in a wristband, which detects the concentration of glucose continuously and displays the results on the smartphone screen via Bluetooth. A salient feature was that it did not rely on the reaction with enzymes to avoid the effects of body temperature and pH. Furthermore, the potential of commercial implementation was greater because it can be integrated in a wristband. Similarly, based on principles of electrochemistry, an integrated wearable device for computing concentration of lactate was proposed

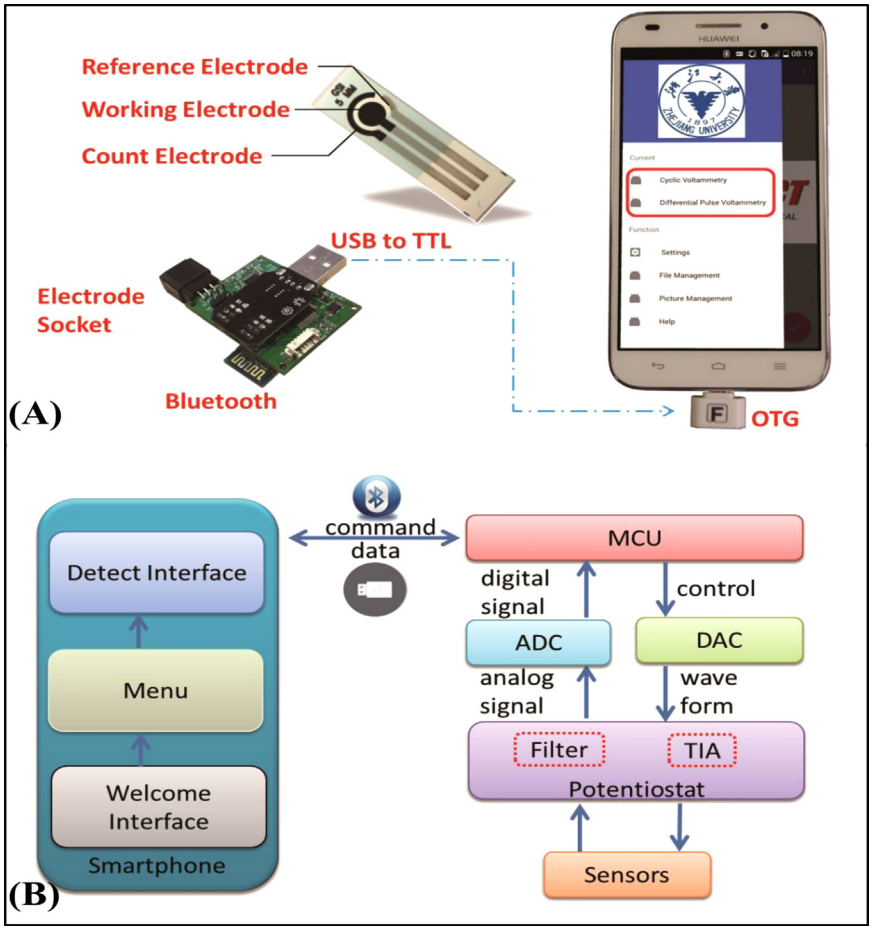

Fig. 8. The device using electrochemical method for POCT in urine samples. (A) A photograph and structure diagram of the whole system; **(B)** Schematic of the smartphone-based POCT for detecting ascorbic acid, dopamine, and uric acid. OTG: On the Go; MCU: microcontroller unit; ADC: analog-to-digital converter; DAC: digital-to-analog converter. Reproduced from Ji et al. (2018a).

Table 4
The information of sweat sample POCT device.

Theory	Detect Target	Accessory	Time	LOD	Disease	Ref
Fluorescence	Cl^-	LED, battery, filter, 3D-print case, chloride sensors	–	0.8–200 mM	Cystic fibrosis	(Zhang et al., 2017)
Fluorescence	Cl^-, Na^+, Zn^{2+}	Dark box with phone holder, sweat patch, emission/excitation filer	~20 min	5–100 mM (Cl^-) 1–20 μM (Zn^{2+}) 20 mM (Na^+)	Cystic fibrosis	(Sekine et al., 2018)
Electrochemical	Glucose	Three-electrode system, bluetooth chipset, lithium battery	30 min	15 μM	Diabetes	(Zhu et al., 2018)
Electrochemical	Lactate	Photoelectric biofuel cell, buckypaper, electrode	< 1 min	20–60 mM	–	(Yu et al., 2017)
Electrochemical	pH	RFID Antenna, pH sensor, transmission circuitry	< 8 s	5–9	–	(Dang et al., 2018)
Electrochemical	Glucose, Lactate, Na^+, K^+, Temperature	Battery, sensor array, electrode arrays, Bluetooth transceiver, microcontroller	~20 min	–	Hyponatremia, Hypokalemia	(Gao et al., 2016)
Electrochemical	Cl^-, Na^+, Glucose	Microcontroller, sensor array, electrode arrays, Bluetooth transceiver, battery	20–25 min	–	Cystic fibrosis, Diabetes	(Emaminejad et al., 2017)

(Yu et al., 2017). The system was powered by an environmentally friendly photoelectric biofuel cell that converts light energy and biomass energy into electrical energy (Fig. 10 Panel 2). The device could measure the concentrations of lactate in the range of 20–60 mM. pH value is another important target of sweat detection. Recently, researchers proposed a stretchable wireless system for sweat pH monitoring (Dang et al., 2018). As shown in Fig. 10 Panel 3, the entire device could be effectively attached to human skin. It could measure pH in the range of 5–9. However, the communication distance was only 2–3 cm; therefore, the phone should be placed close to the sensor, which causes inconvenience to a user in respect of actual experience.

Most of the equipment or methods described above could detect only one or two kinds of substances. However, simultaneous detection of multiple substances was the prevailing trend because it could diagnose a disease more accurately. Thus, an integrated wearable sensor array for a multiplexed in situ perspiration analysis has emerged (Fig. 10 Panel 4) (Gao et al., 2016). The plastic sensors and commercial chips were integrated into the wristband or headband. It could measure body temperature and concentrations of sodium, potassium, glucose, and lactate, simultaneously. The sensors in the system exhibited great selectivity and accuracy for each target analyte or proposed a compensation algorithm. This study also proposed a wearable device for analysis of cystic fibrosis and glucose (Emaminejad et al., 2017). A remarkable enhancement in this study, in response to a previous study, was iontophoresis for improving efficiency of sweat collection. As shown in Fig. 10 Panel 5C, the main principle of this method was that the ion current was directed to diffuse in a medium driven by an electric field. According to this principle, irritant agonists could be transmitted to the sweat glands to stimulate the secretion of sweat. The entire device was light and simple. It was used repeatedly; however, it did not cause a damage or discomfort to skin. Both devices could detect multiple targets in sweat. Moreover, the ability of using sweat was greatly improved due to the improvements in the method of collecting sweat.

From the aforementioned cases in this section, it can be concluded that most sweat-based POCT devices presently available in the market are based on flexible electronics. Compared with other test samples in this review, sweat collection is more cumbersome and the available sample capacity is more limited. Flexible electronics overcomes these limitations because the devices are wearable and continuously detectable. Therefore, the development of sweat-based POCT in the future depends largely on the progress of flexible electronics.

5. Saliva

Saliva is mainly secreted by the salivary glands, colorless and odorless, and the pH range is 6.6–7.1. Saliva is a complex mixture, including various enzymes, electrolytes, proteins, nucleic acids, etc. (Khan et al., 2017). A study has shown that saliva includes 1116 proteins (Denny et al., 2008), most of which can be found in both tears and blood. Compared with blood collection, saliva collection is safer, more convenient, and without risk of transmission of blood-borne diseases, by virtue of being non-invasive. Similarly, compared with urine and sweat samples, saliva has the advantage of being sampled in real time. Therefore, saliva may become a substitute for blood and urine testing, providing a new way for systemic examinations (Shetty and Yamaguchi, 2010). The information of smartphone-based POCT devices discussed in this section are summarized in Table 5.

5.1. Colorimetric test

In 2017, a non-invasive salivary glucose biosensor was presented (Soni and Jha, 2017). The authors immobilized glucose oxidase and bromocresol purple on a filter paper strip (Fig. 11 Panel 1). After the saliva was loaded onto the filter paper strip, the glucose in the saliva reacted with chemicals on the filter strip, thereby changing the color. Then the concentration of glucose in the test sample was estimated through a custom-built App. In 2018, this group also proposed an optical biosensor for the detection of urea in saliva (Soni et al., 2018). The principle of the whole system is similar to the previous one. The authors utilized urea and urease as reactants to produce ammonia and carbon dioxide (Fig. 11 Panel 2). Since ammonia is alkaline, the pH rises from ~6.8 to 8.2. Paper color-based detection performed by reflectance measurement is the most popular method. However, this method has the problem of poor detectability and reproducibility due to inhomogeneity of color development. A biosensor for oral fluid L-lactate detection offered an effective solution (Calabria et al., 2017). All the reagents were wrapped in a wafer-like bilayer film of polyelectrolyte. Simultaneously, the test strip was fixed at an appropriate distance by the custom attachment (Fig. 11 Panel 4). The phone flash was used as a control light source, and a cover-like accessory was placed in front of the flash for homogeneous illumination. Through the above measures, the LOD of the working could reach 0.1 mmol/L.

Machine learning, which has been an emerging field in recent years, has influenced the development of multiple industries considerably. More recently, as shown in Fig. 11 Panel 3, a system combined with machine learning for detecting alcohol in saliva has been proposed (Kim et al., 2017a). It includes linear discriminant analysis (LDA), support vector machines (SVMs), and artificial neural networks (ANNs). Four kinds of color spaces are integrated into the algorithm: RGB, HSV, YUV, and Lab. The system supports two computational models, which performs either an independent smartphone computing or uploading to the server. Server mode is more conducive for mass data collection and analysis. Nonetheless, smartphone mode may be more practical to implement in resource-limited or remote areas without the need for high

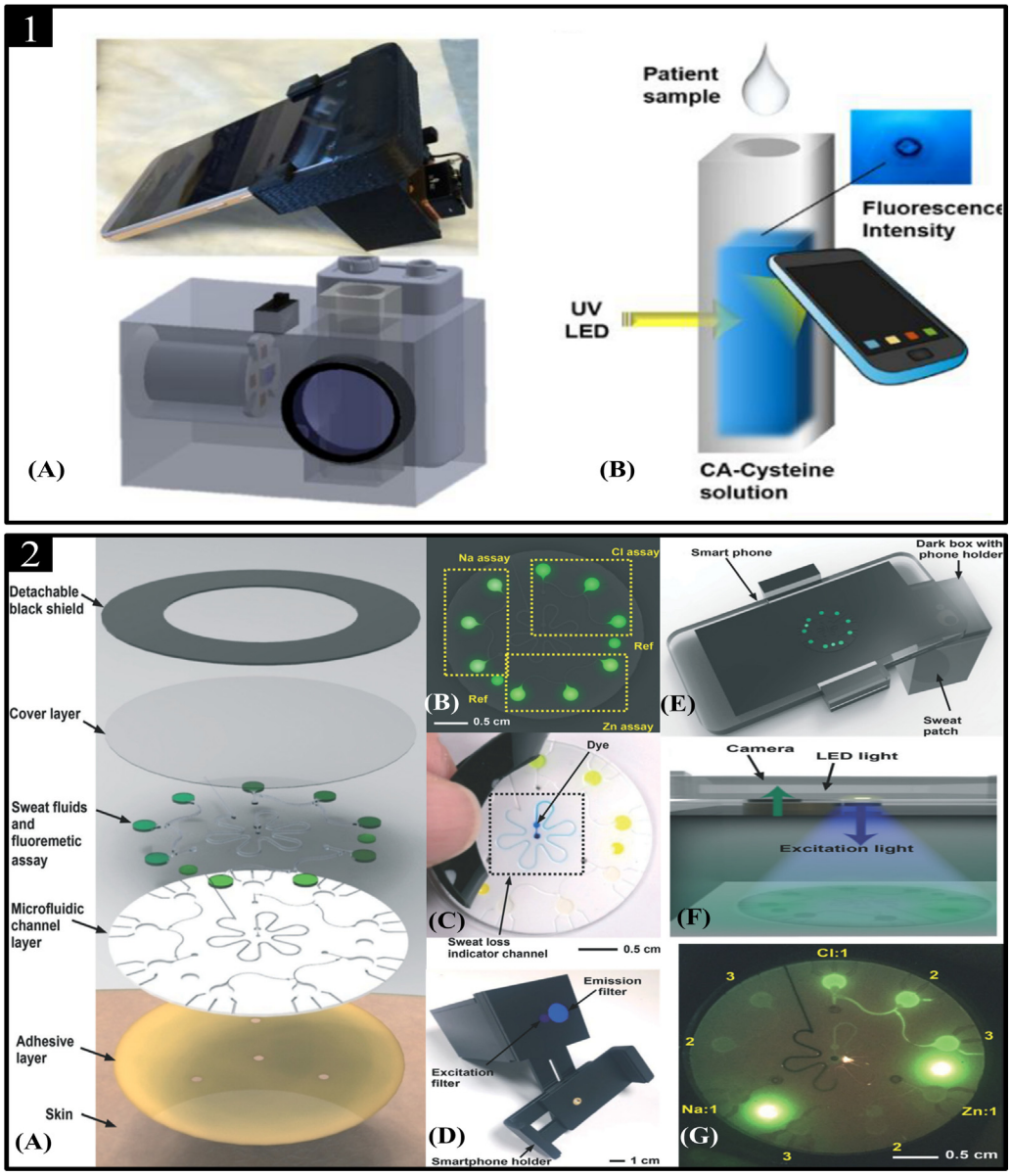

Fig. 9. Device using fluorescence method for POCT in sweat samples. Panel 1: (A) A photograph and a 3D perspective of the entire device; **(B)** Schematic of the system detection principle. Reproduced from Zhang et al. (2017). **Panel 2: (A)** Schematic exploded view of a microfluidic device; **(B)** Ions detection regions of the microfluidic chip; **(C)** An image of the microfluidic device with the black shield removed; **(D)** and **(E)** The overall schematic of the fluorescence-imaging system; **(F)** Working schematic of the entire system; **(G)** Fluorescent image captured by a smartphone. Reproduced from Sekine et al. (2018).

quality infrastructure. Although alcohol testing in saliva may not be more valuable for medical purposes, the system has the potential to be upgraded to detect glucose, ketones, and nitrites. Furthermore, the probability of misjudgment by human eyes is effectively reduced owing to the machine learning algorithms. This may be a direction for future developments in POCT.

5.2. Fluorescence test

Saliva is not a routine sample of Zika, dengue, and chikungunya (Meagher and Kousvelari, 2018). However, two research groups had proposed innovative POCT devices for detecting Zika, dengue, chikungunya by using saliva sample. One research group combined RT-LAMP and quenching of unincorporated amplification signal reporters (QUASR) (Priye et al., 2017). The working structure is as shown in Fig. 12 Panel 1. Compared to the traditional LAMP method, QUASR provides a brighter signal. In addition, the possibility of false positive amplification was greatly reduced. The device of another group was called smart-connected cup (SCC), which consists of a custom-built multifunctional isothermal amplification reactor (MIAR) chip, a thermos cup body, and a 3D-printed holder (Song et al., 2018) (Fig. 12 Panel 2). This second working employed bioluminescence method instead of the excitation source used in the first working and produced fluorescein by using the polymerase by-product as fuel. The entire device, except for the smartphone, did not need a battery because the heat supplied for amplification was provided by a Mg-Fe alloy bag. Thus, this device was more compact because of the elimination of the need for batteries, excitation sources, and optical filters. The more mature data management system, combined with big data and cloud computing, is expected to help the device play a greater role in disease control.

5.3. Electrochemical test

A cloth-based biosensor for detecting lactate was exploited (Yao

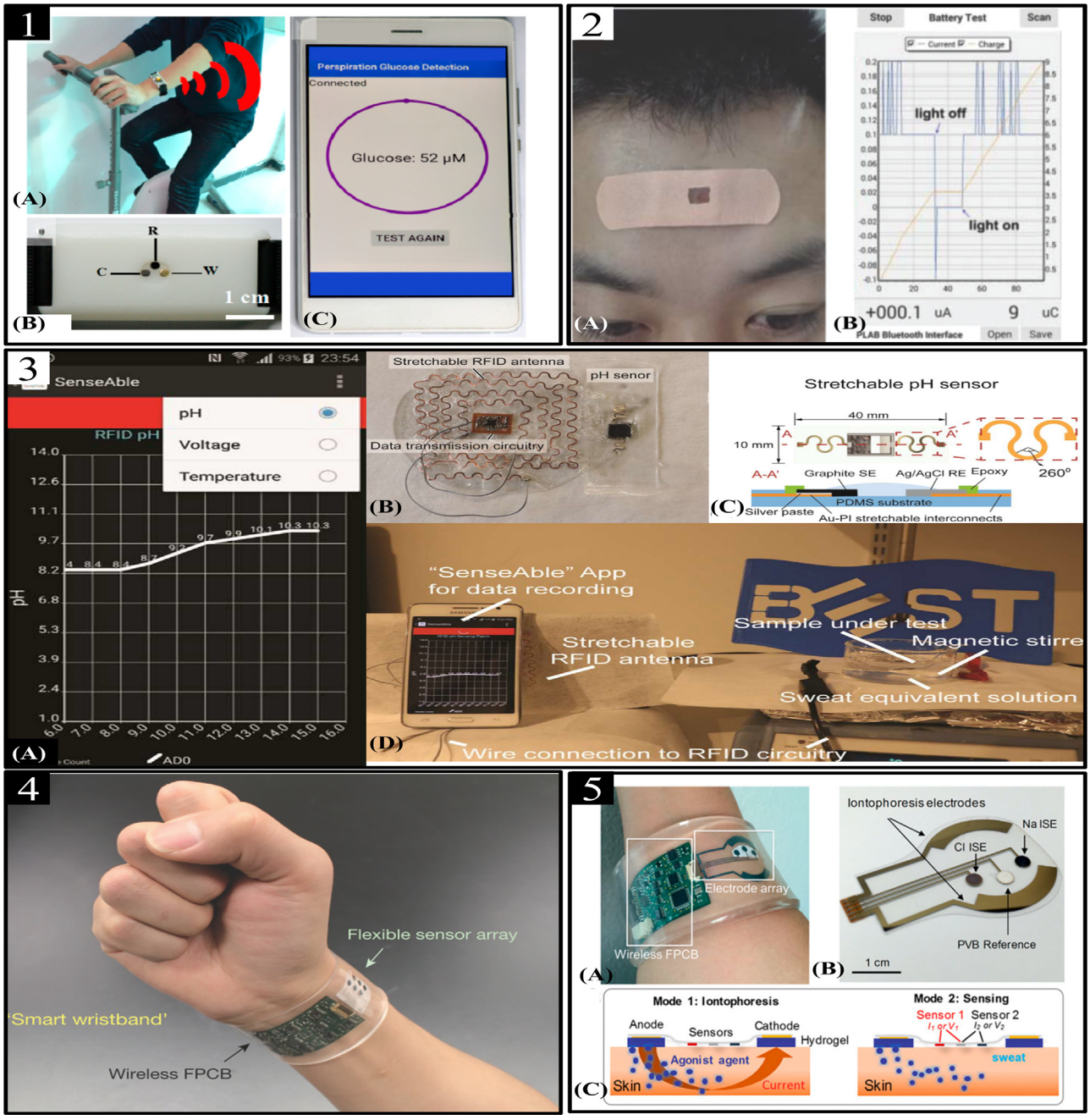

Fig. 10. The device using electrochemical method for POCT in sweat samples. Panel 1: (A) and **(B)** An image of the wristband for measuring glucose; **(C)** A photograph of the custom-built App. The sensor was connected to the phone via Bluetooth. Reproduced from Zhu et al. (2018). **Panel 2: (A)** Sensor attached to the forehead for measuring lactate; **(B)** A smartphone screenshot during the experiments. Reproduced from Yu et al. (2017). **Panel 3: (A) A** screenshot of custom smartphone App; **(B)** A photograph of stretchable wireless system; **(C)** Schematic of stretchable pH sensor; **(D)** A photograph of the whole system that includes a stretchable pH sensor in sweat equivalent solution, a stretchable antenna, and a monitor App. Reproduced from Dang et al. (2018). **Panel 4:** A photograph of the device on one's wrist, showing a wireless flexible printed circuit board (FPCB) and a multiplexed sweat sensor array. Reproduced from Gao et al. (2016). **Panel 5: (A)** A photograph of the device; **(B)** An image of sweat sensor electrodes for $Na^+$and Cl^- sensing; **(C)** Schematics of the iontophoresis and sensing modes. Reproduced from Emaminejad et al. (2017).

et al., 2017). The system was composed of a smartphone, cables, an instrument container, a potentiostat, a device for wireless transmission of electrochemiluminescence signal, a cloth-based device, and a personal computer (Fig. 13 Panel 1). The LOD of the whole system is 0.035 mM. The lactic acid could be detected in the range of 0.05–2.5 mM. However, the shortcomings of the work were obvious. The whole system was not compact enough because the smartphone only played the role of a camera, thereby wasting its original computing capacity greatly. The second shortcoming was that the system was expensive because of the use of a potentiostat. Therefore, it is necessary to further streamline the entire system by exploiting the computing capacity of smartphone and exploring a low-cost alternative to the potentiostat.

In 2017, a research team developed a POCT device for monitoring pulmonary exacerbations in cystic fibrosis (Sun et al., 2017). Since saliva samples were much easier to collect than sweat samples, the device could be used for continuous monitoring of patients with cystic fibrosis. The platform consisted of a smartphone, an electronic module

Table 5
The information of saliva sample POCT device.

Theory	Detect Target	Accessory	Time	LOD	Disease	Ref
Colorimetric	Glucose	Test strip, dark cardboard box	20 s	24.6 mg/dL	Diabetes	(Soni and Jha, 2017)
Colorimetric	Urea	Test strip, dark cardboard box	20 s	10.4 mg/dL	Many related diseases	(Soni et al., 2018)
Colorimetric	Alcohol	3D-print case; plano–convex lens, test strips, mirror, diffusers	few minutes	0.01%	Many related diseases	(H. Kim et al., 2017a)
Colorimetric	L-lactate	Analytical cartridge, mini dark box, cover-like accessory	1 min	0.1 mmol/L	Sepsis, Septic shock	(Calabria et al., 2017)
Fluorescence	Zika virus	Emission filters, Bluetooth microcontroller, reaction tubes, RGB excitation source, multi-pass filter, isothermal hot plate, battery	30 min	100 PFU/mL	Zika	(Priye et al., 2017)
Fluorescence	Zika virus, HIV	3D-printed holder, thermos cup body, chip	45 min	–	Zika, AIDS	(Song et al., 2018)
Electrochemical	Lactate	Instrument container, specified cables, potentiostat, computer	–	0.035 mM	Respiratory insufficiency, heart failure, systemic disorder	(Yao et al., 2017)
Electrochemical	pH	pH/Temperature sensor, potentiostat, power harvester, electrode	10 min	5.9–8.08	Cystic fibrosis	(Sun et al., 2017)

for measuring electrochemical pH value, a sample holder, and a modified SPE, as shown in Fig. 13 Panel 2. The accessory was connected to the smartphone via audio jack. In addition, the phone provides the electricity needed for the electrochemical reaction. The experiments showed that the device exhibited a maximum difference of 0.031 pH as compared to a commercial meter. The compact smartphone biosensor detection system provides an important platform for medical detections. With the development of biochip technology and biological expression technology, this smartphone-based testing platform is expected to become a standard part of a smartphone and also become the standard device for use in the individual homes, thus realizing the real POCT.

6. Tears

Tears contain a variety of biomarkers such as immunoglobulin, albumin, Na^+, K^+ and Cl^- ions. Thus, smartphone-based POCT for tears has attracted a great attention due to non-invasive, no pretreatment, low potential interference and direct correlation with biological fluids such as serum and blood (Lane et al., 2006). The information of smartphone-based POCT devices discussed in this section are summarized in Table 6.

6.1. Colorimetric test

Traditional paper-based colorimetric assays are limited in POCT due to their poor color uniformity and detection capabilities. To overcome this problem, a multilayer-modified paper test was proposed (Wang et al., 2018). As Fig. 14 Panel 1 shows, the paper-based biosensor is composed of chitosan, color reagent, horseradish peroxidase and specific oxidase. When the biochemical reaction happened, the color would change, which would will be captured and calculated through smartphone. The experiment results show that LOD of the paper-based biosensor is one order of magnitude lower than that of traditional paper-based sensors. However, ambient-light which affect the tested results is not to be filtered in this work. Therefore, to improve anti-interference maybe is the further improvement direction. In another work, ascorbic acid in tears was successfully measured, which is considered as an important biomarker for full-thickness injuries to the ocular surface (Misra et al., 2018). The researchers manufactured a reactive plasmonic biosensing material which composed of ionic gold interspersed through agarose gel scaffolding (Fig. 14 Panel 2). Once the material reacts with ascorbic acid in tears, colorimetric changes that correlates with the R value of RGB color space will be generated. Based on this theory, the concentration of ascorbic acid in tears can be quantitatively detected by colorimetric test App.

6.2. Fluorescence test

Current smartphone-based minimally-invasive rapid tears diagnosing system cannot effectively identify dry eye. In 2017, to solve this problem, a paper-based microfluidic system for detecting dry eye was proposed (Fig. 14 Panel 3) (Yetisen et al., 2017). The custom-built test strip is divided 4 branches at the end. And each branch is fixed with different fluorescence sensors for detecting Na^+, K^+, Ca^{2+} and pH value, respectively. The intensity of fluorescence is calculated via a custom-built App. The degree of dry eye syndrome is greatly related to concentration of electrolytes in tears, therefore, the device can effectively diagnose dry eye. Meanwhile, this microfluidic system also presented new potential for the diagnosis and differentiation of ocular disease.

From the researches mentioned in this section, it illustrated that the current smartphone-based POCT devices for biomarkers test in tears mainly focused on paper/cloth biosensors because these hydrophilic materials can make more effective use of tears samples. Nevertheless, paper/cloth biosensors have a defect that real-time monitoring cannot

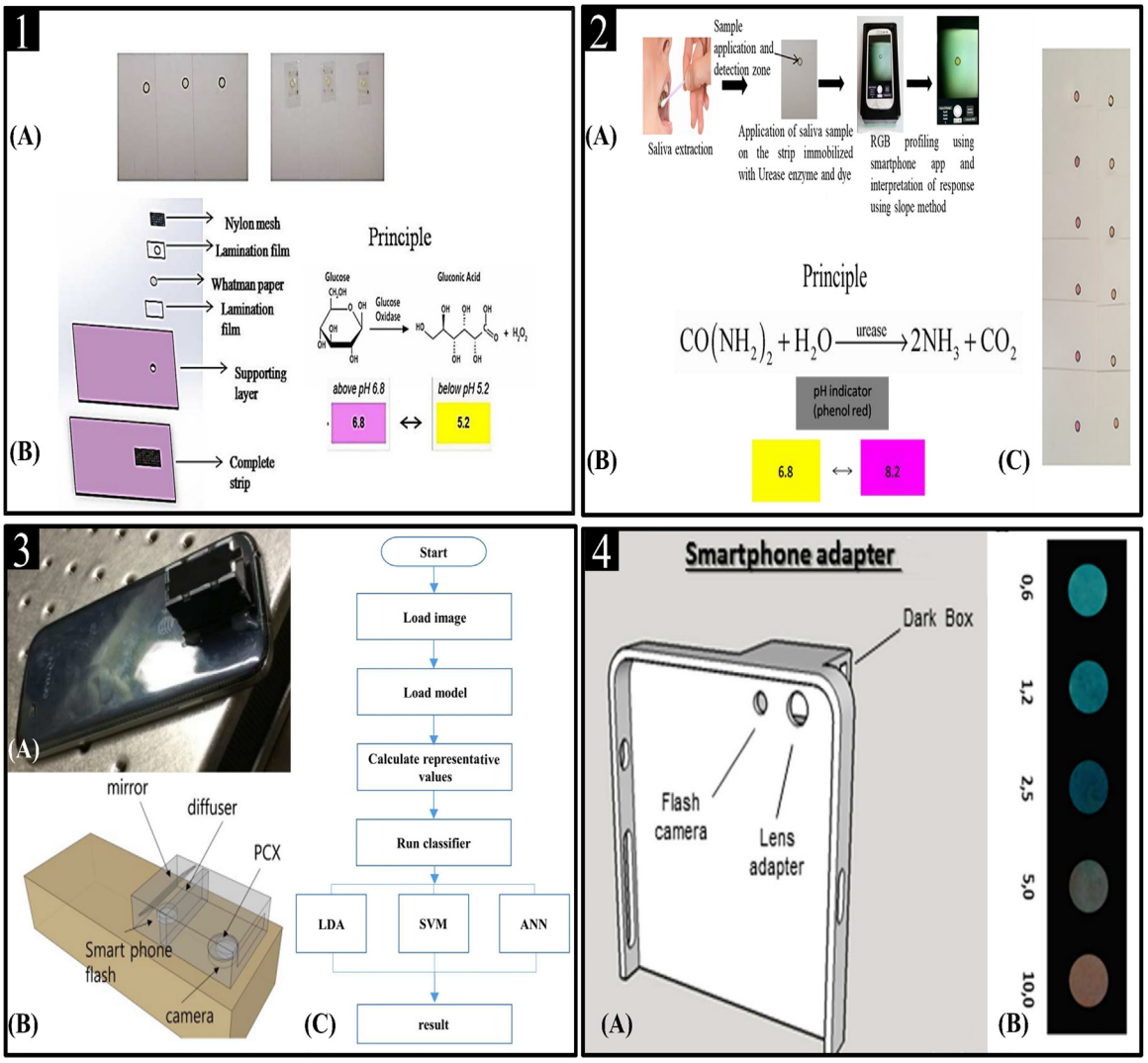

Fig. 11. Device using colorimetric method for POCT in saliva samples. Panel 1: (A) A photograph of biosensor strips. The left one represents front view of strips, and the other one represents back view; **(B)** Schematic of layered structure of a biosensor strip and the sensing principle of biosensor. The pH decreased from 6.8 to 5.2. Reproduced from Soni and Jha, (2017). **Panel 2: (A)** Procedures for the determination of urea in saliva; **(B)** The principle of the biosensor. The pH increased from 6.8 to 8.2; **(C)** Color change in the strips with increase in urea concentration (10–1000mgdL^{-1}). Reproduced from Soni et al. (2018). **Panel 3: (A)** and **(B)** Photograph and structure of the whole device; **(C)** A flow chart of the App. Reproduced from Kim et al. (2017a). **Panel 4: (A)** Structure schematic of custom attachment; (B) Color changes of the test paper under different concentrations of lactate (0.6–10.0 mmolL^{-1}). Reproduced from Calabria et al. (2017).

be realized. To overcome this problem, wearable biosensor on eyes have been able to monitor glucose in tears (Ascaso and Huerva, 2016). However, this work should to improve interference rejection, biocompatibility and service life, meanwhile, the readout circuits and wireless transmitting and receiving equipment need further improvement. And the tested results can transmit to smartphone. In conclusion, smartphone-based POCT device for biomarkers test in tears can classify two kinds: wearable testing real-time and non-real-time, offline, microfluidic sampling test.

7. Challenges and future direction

Here, we review the progress in smartphone-based POCTs during the past two years (2017–2018) based on the type of liquid biopsy. A smartphone-based POCT overcomes the limitations of the traditional laboratory-based testing effectively. However, there are several challenges that still need to be addressed for better development of the smartphone-based POCT: (1) The cost of smartphone-based POCT is an important factor. Reducing the cost of materials and consumption of reagents is the key to realize the democratization of health care. Owing to the emergence of 3D-print technology, the manufacturing costs of smartphone-based POCT devices have been greatly reduced. Sample processing is another critical factor. The cost of sample processing includes not only the cost of reagents but also the costs of transportation and refrigeration. Therefore, it is critical to explore methods that can use the samples directly without processing. (2) The proposed system should be able to detect multiple analytes simultaneously, especially for diagnosing serious diseases, because selection of only one analyte as the indicator of diagnosis is not effective enough in modern medicine. For example, the concentration of Na^+ is a key indicator in the diagnosis and monitoring of cystic fibrosis, but the concentrations of Cl^- and K^+ ions as well as pH may also be significant. Meanwhile, multiple tests can avoid misdiagnosis; (3) The quality of the App has become the standard to judge the proposed system because all smartphone-based POCTs systems need a custom-built App. For users, the App should be simple and easy to operate. For developers, the App should meet the commercial and technological standards for ease of functional expansions and upgrades in the future. In addition, if an App can upload patient information (age, sex, location information, etc.) to a server or a cloud, it would help a health department make rapid and accurate

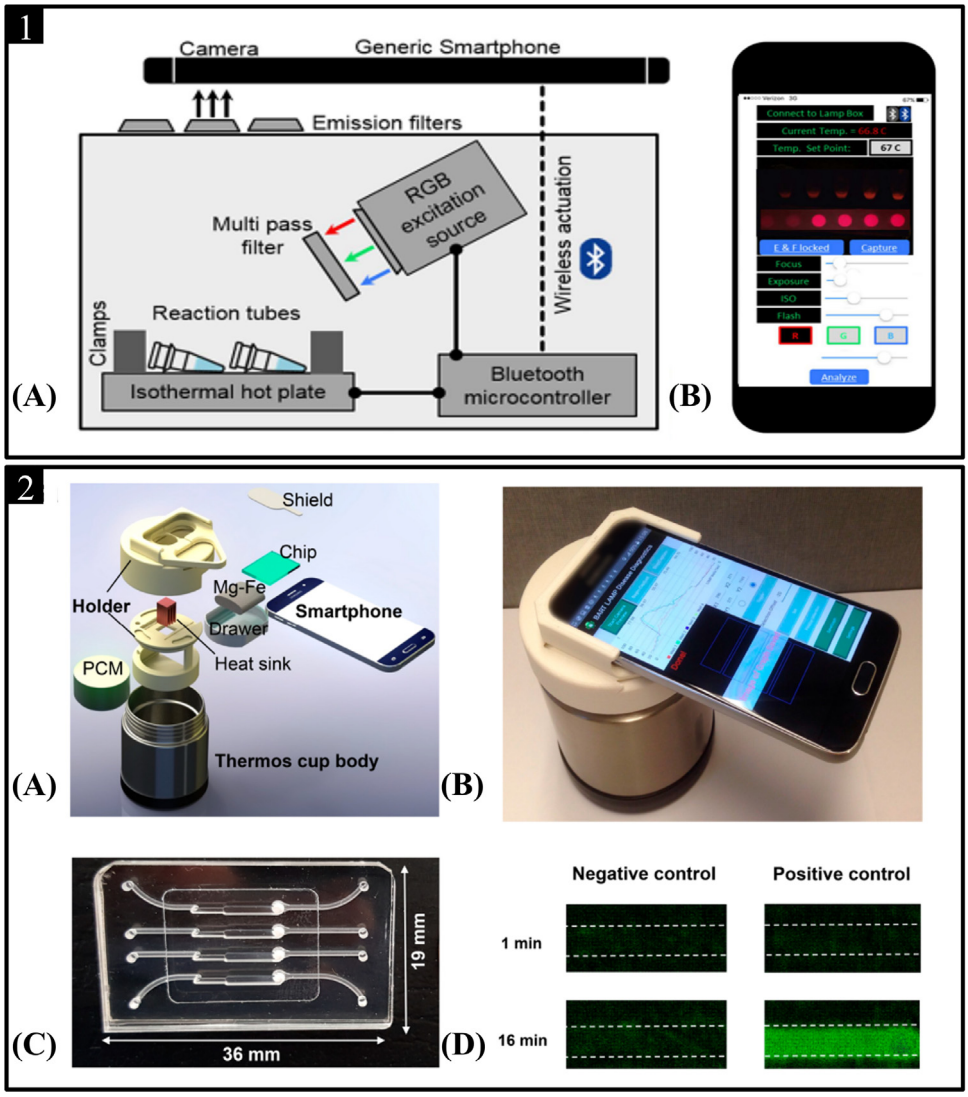

Fig. 12. The device using fluorescence method for POCT in saliva samples. Panel 1: (A) Schematic of the Zika detection device, including a isothermal heater with reaction tubes, LEDs, and a Bluetooth microcontroller; **(B)** The screenshot of custom-built App. Reproduced from Priye et al. (2017). **Panel 2: (A)** and **(B)** Exploded view of SCC and a photograph of the whole system; **(C)** A photograph of MIAR chip with four reactors; **(D)** Bioluminescence emission images (left: negative control; right: positive control). Reproduced from Song et al. (2018).

decisions about outbreaks of infectious diseases; (4) Both testing techniques and samples of smartphone-based POCT should be more diversified. Currently, blood test is still the mainstream liquid biopsy method, and the number of blood-based POCT devices far exceeds that of devices based on other samples, although the invasive feature of blood test causes inconvenience in some situations. Saliva, urine, sweat and tears are ideal supplements because of the massive same biomarkers as those for blood. However, there are only a few test methods available for sweat, urine and tears. Because of the difficulties in collecting sweat samples, electrochemical-based flexible electronics is expected to be an important alternative. Presently, colorimetry continues to be the dominating theory for urine testing. Smartphone POCT based on tears sample mainly depends on paper/cloth sensors. Thus, it is essential that researchers explore possible ways to expand the detection methods of these supplements include multifarious biomarkers. (5) POCT should be a rapid test, which can ensure the patient to receive follow-up treatment directly after the test. Smartphone-based multichannel technology may be able to meet this requirement. Recently, for example, a multichannel smartphone optical spectrometer was firstly proposed (L.-J. Wang et al., 2017b). This device can once handle 96 samples. Therefore, efficiency of POCT has been greatly improved via multichannel method. (6) New powering methods, including wireless energy transfer, portable biofuel cells, body energy harvesters and piezoelectric materials, can overcome the rapid energy consumption. Meanwhile, self-powered POCT maybe an important development direction (Zarei, 2017). Furthermore, powering of flexible sensors should be considered separately. Current energy-storage devices, such as lithium-ion batteries and supercapacitors, are not matching the particular requirements of flexible electronics due to heavy, rigid and bulky (Wang et al., 2014). Therefore, to develop flexible energy-storage device or chip such as flexible lithium-ion batteries, flexible supercapacitors and thin-film solar cells etc. is necessary. (7) The application scope of POCT will be further expanded. In addition to clinical application, POCT will be widely used in environmental safety, food safety, biochemical technology and other aspects. (8) Miniaturization and integration will be a fast-developing field. They continuously accelerate the practical applications of POCT diagnostic device.

Current smartphone-based POCT should combine numerous promising technologies such as paper-based sensors, flexible sensors, and microfluidics. Paper-based sensor is widely used in many research fields because of its low cost, biodegradability, easiness of preparation and modification (Yang et al., 2017). However, due to the accuracy, service

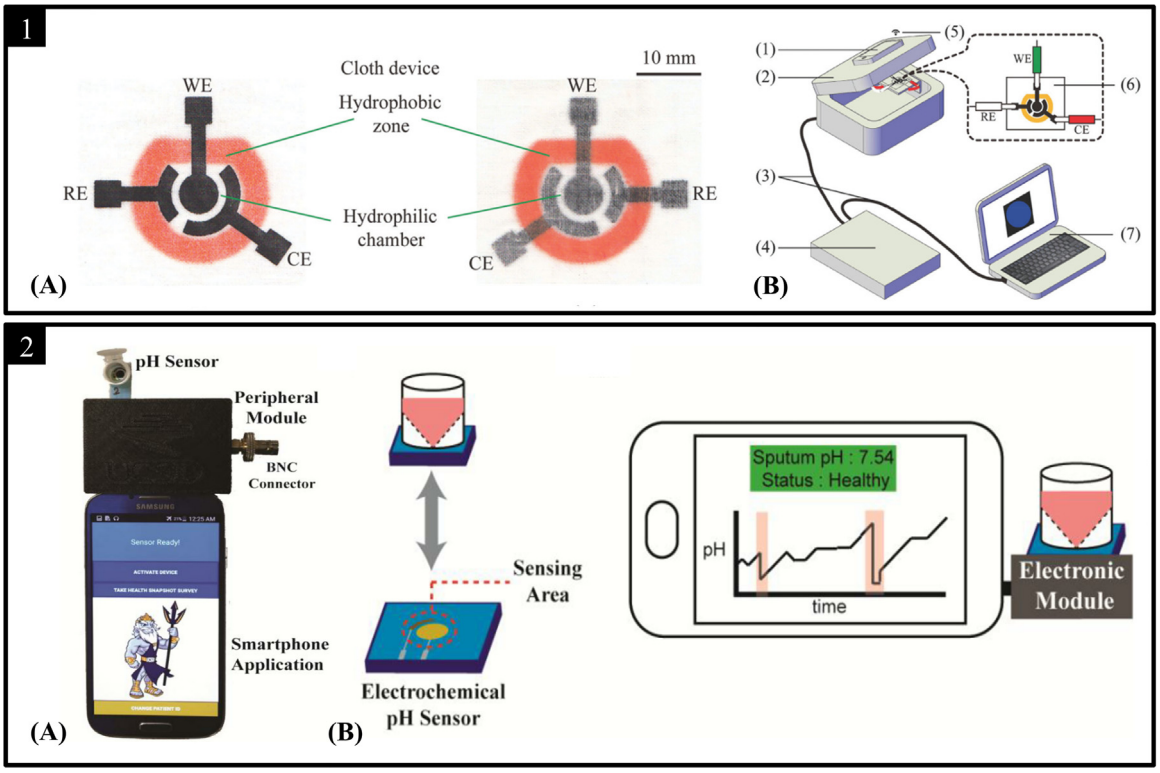

Fig. 13. The device using electrochemical method for POCT in saliva samples. Panel 1: (A) Cloth-based three-electrode system for electrochemiluminescence (left: front view, right: back view); **(B)** Schematic of the system for detecting lactate. (1) smartphone, (2) instrument container, (3) cables, (4) potentiostat, (5) wireless transmission of electrochemiluminescence signal, (6) electrode, (7) computer. Reproduced from Yao et al. (2017). **Panel 2: (A)** A photograph of the whole system; **(B)** The workflow of smartphone-based detection of cystic fibrosis equipment, sputum collection via a sample holder, the bottom of which is a reusable electrochemical pH sensor. Reproduced from Sun et al. (2017).

life and stability of biological components, no large number of paper-based products appeared on the markets. Presently, researchers have achieved many meaningful results for overcoming these difficulties. The problem of insufficient accuracy for smartphone-based paper sensors is being solved by improving algorithms (Yetisen et al., 2014) and materials (Wang et al., 2018). Additionally, flexible electronics is a rapidly developing field in recent years. It can be seamlessly integrated onto any surface to provides users more improved spaces due to light weight, thinness, and robustness, which is difficult to realize in conventional electromechanical sensors (Han et al., 2017). Therefore, flexible sensors integrated in wearable devices are widely used in sweat-based smartphone POCT. The sensing element of most current sweat-based smartphone POCTs is on the plastic substrates. However, poor stability, complex interconnects and integration, and limited surface area are their inherent defects (Y. Zhang et al., 2018b). Paper-based sensors are also making progress in wearable technology. Nevertheless, one of the major drawbacks of paper-based sensors is interference from humidity. If plastic and paper-based biosensors are combined together, the active components on the paper substrate were encapsulated by plastic films, satisfactory performance will be obtained in sweat-based POCT. In addition, POCT should integrated with microfluidic technology, which has a potential to accomplish complex diagnostic assays, as a sample to answer format for POCT by integrating all the functional modules into smartphone or attachment.

Both the opportunities and challenges of smartphone-based POCT are enormous. Researchers must improve the accuracy of a smartphone-based POCT system and the sensitivity of the biosensor. It is evident that machine learning has been rapidly progressing in recent years and has brought about beneficial changes in a number of fields including the field of POCT. Machine learning has been widely implemented in several applications such as medical image diagnosis, treatment queries and advice, disease prevention and intervention, in addition to smartphone-based colorimetric detection of pH values (Mutlu et al., 2017), ELISA (Nath et al., 2018), cell counting (Huang et al., 2016), and detection of parasites (Koydemir et al., 2015). Nevertheless, it is rather difficult to utilize a single smartphone-based liquid biopsy performed by using machine learning algorithms. Therefore, the direction for future developments in smartphone-based liquid biopsy lies in the

Table 6
The information of tears sample POCT device.

Theory	Detect Target	Accessory	Time	LOD	Disease	Ref
Fluorescence	Na^{+}, K^{+}, Ca^{2+}, pH	3D-printed case, wide-angle lens, optical filter, LED, battery, switch	3 min	50–200 mmol/L(Na^{+}), 20–80 mmol/L(K^{+}), 0.5–2.0 mmol/L(Cl^{-}) 7–9 (pH)	Dry eye	(Yetisen et al., 2017)
Colorimetric	Uric acid, glucose	LED, test paper	10 min	0.003 mM (uric acid), 0.014 mM (glucose)	Gout, Rheumatology, Hyperuricaemia, Diabetes	(Wang et al., 2018)
Colorimetric	Ascorbic acid	The custom-built color rings	5–30 min	50 μM	Full-thickness injuries to the ocular surface	(Misra et al., 2018)

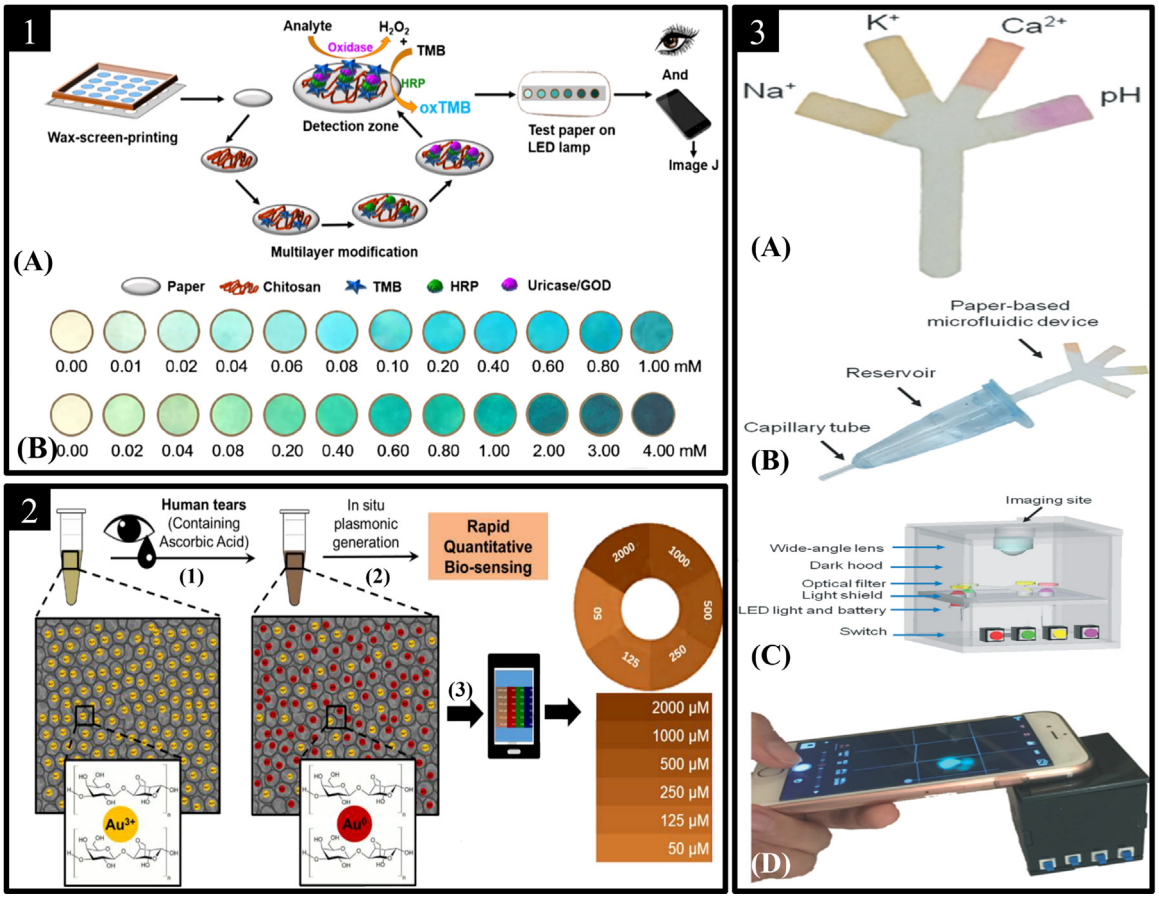

Fig. 14. The device using colorimetric and fluorescence method for POCT in tears samples. Panel 1: (A) Schematic illustration for detecting uric acid and glucose via the paper-based colorimetric assay; **(B)** Photograph of the test papers under different concentrations of uric acid (Top) and glucose (Bottom). Reproduced from Wang et al. (2018). **Panel 2:** Schematic for describing relationship of colorimetric changes of the test paper and ascorbic acid concentration. Reproduced from Misra et al., 2018). **Panel 3: (A)** Photograph of the test paper; **(B)** Sample collection device; **(C)** Sectional view of the portable readout device; **(D)** Photograph of the whole system. Reproduced from Yetisen et al. (2017).

successful integration of machine learning algorithms (including big data and cloud computing et.) into smartphone Apps, coupled with paper-based sensor, flexible electronic and microfluidic chip.

CRediT authorship contribution statement

Junjie Liu: Investigation, Writing - original draft. **Zhaoxin Geng:** Conceptualization, Writing - review & editing, Supervision, Resources, Project administration, Funding acquisition. **Zhiyuan Fan:** Data curation. **Jian Liu:** Formal analysis. **Hongda Chen:** Methodology.

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Declaration of interest statement

None.

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