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Current smartphone-assisted point-of-care cancer detection: Towards supporting personalized cancer monitoring

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ABSTRACT

With the rising incidence of cancer-related mortality, new enabling technologies are necessary to offer comprehensive molecular profiles of patients in order to assist clinicians to establish an early presumptive diagnosis. Biosensors that are technically comparable to conventional laboratory diagnostics have been developed. However, because the manufacture and operation processes of these biosensors were not well adjusted for end-users as patients, the approach is not optimized in these newly built platforms. Hence, smartphone-assisted biosensors have been developed for point-of-care utilization. They are faster, simpler, and more affordable than standard examinations and first-generation biosensors, however, they raise numerous concerns regarding their applicability for early cancer detection. Therefore, this review focuses primarily on cutting edge developments in smartphone-assisted biosensing platforms that are most relevant to early cancer diagnosis, including optical and electrochemical biosensors, and cancer imaging. What is needed to bring this important technology to realization as early cancer diagnosis tool is discussed.

1. Introduction

Cancer is a complex disease characterized by abnormal cell development caused by multiple epigenetic changes, resulting in uncontrolled proliferation, differentiation, and invasion of neighboring tissues. When-cancerous cells metastasize to various sites or organs of the body, this may result in severe morbidity and lead to mortality [1,2]. Cancer is currently the second leading cause of human deaths worldwide, accounting for 7.6 million deaths per year and 13% of all fatalities [3]. Cancer incidence is anticipated to continue increasing, with cancer-related deaths projected to exceed 16.1 million by 2030 [3]. Notably, most malignancies have a significantly higher five-year survival rate if they are detected earlier rather than later, indicating that early identification of various types of cancer improves survival rates

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[4–6]. For instance, colorectal and lung cancers have one-year survival rates of 97.7% and 87.3% if identified at stage 1, but only 43.9% and 18.7% if detected at stage 4, respectively [4]. This statistical database emphasizes the crucial importance of cancer detection at an early stage.

In light of the increasing frequency of cancer-related deaths, approaches to provide detailed molecular profiles of patients to assist medical professionals in making accurate diagnoses are required. In order to detect early cancer biomarkers, besides performing traditional techniques such as standard physical examination and imaging tests, highly accurate and informative multiple diagnostics were applied simultaneously, including biopsy and pathology-based tests [7–9]. However, these methods have met with critical concerns for both clinicians and patients, such as time spent, facilities required, financial burden and need for skilled specialist healthcare professionals; discontinuously; contains high risk of infection and inappropriate to investigate tumor heterogeneity [10,11]. Thus, the requirement for diagnostic methods that are simpler to carry out, less resource-consuming and less invasive, as well as being performed in real time and appropriate to replace conventional techniques, has been raised in recent years to overcome these difficulties, thereby driving the establishment of biosensors in the field of medical diagnostics [12]. Although these biosensors have proved comparable to laboratory-based diagnostic tests in regard to limit of detection (LOD) and ease of sample processing, these platforms still encounter difficulties, such as cost-effectiveness and complexity of the manufacturing process [12,13]. These challenges create significant obstacles to the successful development of biosensors for point-of-care (POC) testing for clinical assessment.

With several advantages over first generation biosensors, the introduction of smartphones as reading devices, actuators, image processors, or cloud connections holds great promise for smartphone-assisted biosensors, providing user-friendly, compact and informative POCT products [14]. In fact, these novel biosensing platforms have been manufactured for a range of diverse purposes, such as food safety surveillance, biosecurity, medical diagnostics, and environmental monitoring [15–17]. The recognized potential from initial trials has prompted further research and development to optimize smartphone-assisted biosensors for early cancer screening and detection. This has led to improvements on previous biosensors, such as through simpler fabrication, lower cost, real-time readout, and feasibility of data processing and management [18].

The suitability of smartphone-assisted biosensors should be considered carefully in seeking to commercialize this novel platform as a helpful and valuable POCT device for early cancer diagnosis as an approach to precise and personalized medicine. Here, we discuss current prospects for cancer diagnosis using approaches based on detection of molecular cancer biomarkers including DNA, miRNA, protein, exosome, cancer cell, metabolites (Fig. 1). The most relevant smartphone-assisted cancer detection platforms, including optical- and electrochemical-based biosensors and bioimaging, are categorized and assessed in terms of their benefits and drawbacks. These are explored in depth to provide an informed perspective on the feasibility of producing and ease of applying these unique technologies for early and accurate cancer diagnosis.

2. Current approaches to cancer diagnosis

2.1. History-taking and physical examination

Cancer diagnosis and treatment require intensive history-taking and a thorough physical examination by a qualified healthcare professional. Inheritable cancer susceptibility genes are observed in 5–10% of tumors. Therefore, family history is critical in identifying individuals who have an inherited cancer predisposition syndrome and are at increased risk for other primary cancers. This affords preliminary determination of the risk of a familial predisposition and thus development of a preliminary management plan for each patient [19]. A complete physical exam is performed to look for lumps or anomalies in or on the body, such as organ enlargement or changes in skin color, that may suggest the presence of cancer. The test offers dynamic information regarding the progression of cancer at no additional cost, which supports interpretation of other findings from different tests such as computed tomography (CT) or magnetic resonance imaging (MRI). Furthermore, physical examination allows clinicians to quickly determine a patient's general medical status, enabling more efficient use of medical resources by appropriately selecting subsequent testing methods and avoiding unnecessary procedures [20,21]. History-taking and physical examination also play an important role in providing patients with a sense of comfort and trust, allowing clinicians to build trust with each of a patient's successive responses, stimulating further probing and the formation of diagnostic hypotheses, on which clinicians can help their patients to make better-informed decisions. However, history-taking and physical examination require substantial training of medical and nursing practitioners. Premature judgment or the failure to examine feasible alternatives following an initial diagnosis might result in an erroneous diagnosis [22,

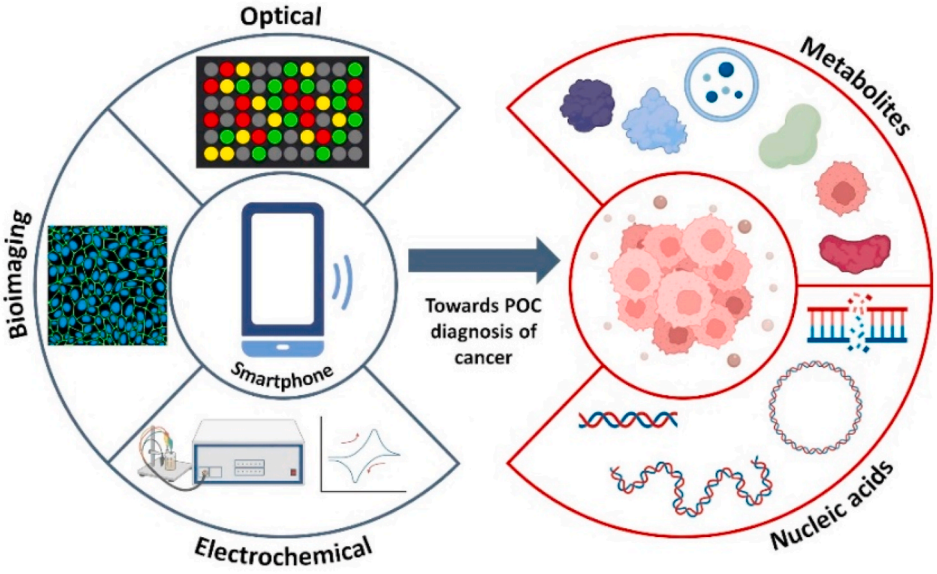

Fig. 1. Smartphone-assisted cancer diagnosis by optical and electrochemical biosensors and imaging of nucleic acid-based and metabolite-based biomarkers.

23]. While historical clues can raise or lower probabilities, they may not be preserved over time, leaving insufficient relevant information on which to make valid conclusions.

2.2. Imaging tests

Biomedical imaging is one of the primary pillars of comprehensive cancer care. This creates images of cross-sections within the body such as of bones or internal organs in order to monitor tumors, show the extent of disease, and aid in determining the efficacy of treatment. Imaging tests have numerous advantages, including capacity for real-time monitoring, accessibility without tissue destruction, minimal or no invasiveness, and the ability to function across a wide variety of time and size scales involved in biological and pathological processes [24].

2.2.1. X-ray

Traditional X-rays are utilized as a first-line screening method for primary or secondary (metastatic) lung and bone cancers. Breast cancer is identified by digital mammography, which employs static low dose-amplitude X-rays or digital breast tomosynthesis, generating three-dimensional tomographic images using X-rays with a limited rotation angle. Digital fluoroscopy, consisting of an X-ray source and a fluorescence detection system linked to an image digitization and recording device, is frequently used to obtain real-time moving images of internal structures [25]. Due to cumulative radiation exposure, X-rays also pose a threat of the risk of cancer, which increases with the total number of doses throughout an individual's lifetime [26].

2.2.2. Computed tomography (CT)

CT imaging generates a three-dimensional visualization of the scanned area by using multi-positional X-ray imaging for tomographic reconstruction, which provides precise anatomical information about the imaged patient [27,28]. The tumor vasculature and perfusion can also be scanned by CT imaging using contrast agents. However, because of the cumulative risk of exposure to ionizing radiation, the frequency of repetitive CT imaging must be considered from both clinical evaluation and investigation perspectives [29].

2.2.3. Magnetic resonance imaging (MRI)

MRI is utilized for cancer detection, staging, therapy response monitoring, biopsy guiding, and minimally invasive therapy guidance. This technique is based on nuclear magnetic resonance (NMR), a physical phenomenon of atomic nuclei that measures changes in nuclear spin in response to a strong external magnetic field, resulting in signal detection following nuclear spin relaxation [30,31]. Observing metabolic changes in malignant and normal tissues with magnetic resonance spectroscopy provides information on biochemical changes in response to tumor growth and helps to distinguish different metabolic tumor phenotypes [32].

2.2.4. Nuclear medicine scanning

Nuclear medicine imaging has made substantial contributions to cancer diagnosis, treatment planning, and evaluating a patient's responsiveness to treatment. Nuclear scans, unlike other imaging procedures that generate pictures of physical shapes and forms, create images based on the body's chemistry (such as metabolism) by employing liquids containing radionuclides (also known as tracers or radiopharmaceuticals) that emit low levels of radiation. Therefore, nuclear medicine scanning is beneficial in detecting cancers and monitoring metastatic progression [33].

2.2.5. Positron emission tomography (PET)

PET imaging is a commonly used imaging method in both clinical and fundamental research settings that analyzes physiological functions by examining blood flow, metabolism, neurotransmitters, and radiolabeled drugs [28]. PET imaging works by detecting gamma rays emitted by positron-emitting radionuclides (radioactive tracers) injected into a peripheral vein and labeled with oxygen-15, fluorine-18, carbon-11, or nitrogen-13 isotopes [34]. PET provides qualitative data, allowing for the monitoring of relative changes over time as a disease process evolves or in response to a specific stimulus.

2.2.6. Ultrasound

One of the most commonly used diagnostic imaging modalities, ultrasound provides good resolution of human soft tissue, particularly in diagnosing minute lesions of biological tissue via volume ultrasound. Images can be produced without staining and are used to diagnose a variety of cancers. A transducer, which can both emit and detect ultrasound echoes, generates ultrasonic waves. When these echoes hit the transducer, they generate electrical signals that are transmitted to the ultrasound scanner, which calculates the distance between the transducer and the tissue boundary to provide two-dimensional images of tissues and organs. Ultrasound is also very useful for guiding biopsies [35,36].

2.3. Biopsy

In most cases, a biopsy is the only approach to definitively diagnose an ambiguous mass based only on history, physical, laboratory, and imaging examinations. A biopsy involves the removal of a sample of abnormal tissue in order for its microscopical examination and to perform histological tests. The goal of a biopsy is to obtain diagnostic tissue while minimizing morbidity, limiting tumor spread, and preventing complications with future therapy. Pathology data from a biopsy can also help show what therapy options might work for that patient [37]. Several techniques that have arisen to meet the goals of biopsy including open surgical biopsy, core biopsy, and fine-needle aspiration [38]. However, they are associated with hematoma, tumor spread, and wound problems that may interfere with adjuvant therapy [39]. Therefore, such complications have driven advancements in less intrusive procedures, such as liquid biopsy.

2.3.1. Tissue biopsy

Tissue biopsies are the gold standard for diagnosing cancer. This procedure entails extracting biological samples from a suspicious mass in order to examine its composition, which will inform a diagnosis, and to proceed with potential therapy options [40]. Despite their unparalleled significance in cancer care, tissue biopsies continue to pose challenges in terms of both practice and ethics. Tissue biopsy is typically performed once the mass is evident using imaging modalities, which may delay diagnosis and have a detrimental impact on treatment outcome. As it is an invasive technique, tissue biopsy may cause stress, pain, and discomfort for the patient, and it cannot be repeated to monitor disease progression and therapy response [41,42]. The procedure remains difficult for tumors in sites that are extremely difficult to reach. Typically, a sample of just a portion of the tumor is obtained, including only a fraction of tumor heterogeneity, resulting in incomplete information on the levels of genetic and epigenetic variability of a patient's cancers. Failure to visualize the tumor's heterogeneity creates substantial obstacles to determining an effective treatment strategy [43].

2.3.2. Liquid biopsy

In order to overcome the limitations of tissue biopsies, liquid biopsy has been introduced as a modern diagnostic and prognostic tool in precision oncology, which includes the non-invasive clinical evaluation of ctDNA and circulating tumor cells, as well as other biomarkers such as microRNAs (miRNAs), exosomes, or platelets, by utilizing a variety of bodily fluids such as blood, plasma, serum, saliva, urine, and gastric fluid [44–46]. Serial liquid biopsy has proved to be a better strategy for monitoring the complete population of tumor cells, which ensures tumor heterogeneity longitudinally, leading to successive profiling of a tumor's

genetics [47]. Unlike tissue biopsies, liquid biopsy enables tumor detection at an early stage, which not only significantly lessens the risk of cancer mortality but also reduces morbidity and expenses.

2.4. Laboratory tests

Biomedical laboratory tests detect changes in certain components in the body by using biological fluids such as blood, urine, and sputum to assist clinicians in making diagnoses. Biochemical, microbiological and other laboratory tests, in conjunction with biopsies and imaging, provide information regarding cancer progression [48]. Data are frequently displayed as a range, with lower and upper limits based on test results from large numbers of persons who have previously been tested. Due to variances in age, gender, race, medical history, and overall health, laboratory findings for healthy people can vary [49]. As a result, it is possible to have "normal" findings for many tests even if the patient has cancer, while having test results outside the normal range does not by itself establish that the patient is unwell [50–52].

2.4.1. Blood tests

A blood test typically entails a phlebotomist taking blood from a blood vessel in the arm for hematological testing at a biomedical laboratory. Blood tests are commonly utilized in primary care, serving vital diagnostic, prognostic, and therapeutic objectives, as well as providing patients with reassurance and validation [53]. The complete blood count (erythrocytes, leucocytes of various subtypes, and platelets, usually measured per cubic mm) is one of the most commonly ordered laboratory tests in medicine [54]. Tumor marker tests evaluate biochemicals associated with malignancy. Cell surface antigens, cell surface receptors, cytoplasmic proteins, enzymes, hormones, oncofetal antigens, and oncogenes and their products are all examples of tumor indicators [55], which are either derived from tumor cells (tumor-derived) or made by the body in reaction to tumor cells (tumor-associated). If they are released into the circulation, levels can be measured in the blood and urine [56]. Currently, tumor markers are only utilized as a laboratory test to support a diagnosis, not as the primary means of confirming the presence of cancer [57].

2.4.2. Urinalysis

Urine is a potential specimen for extensive health monitoring [58]. Urinalysis is the process of testing urine for physical characteristics, solutes, cells, casts, crystals, microorganisms, or particle materials. Urinalysis is simple, inexpensive, effective, and always considered as part of the initial examination of all patients, and which should be repeated as clinically warranted [59]. Urine collection is painless, non-invasive, and causes no physical discomfort due to the fact there is no contact with the body [60]. Urine has enormous diagnostic potential since cancer cells shed components directly into the urine [61], resulting in an abundance of urine-based biomarkers for specific conditions, particularly cancer [62]. Urinalysis has been used to detect several forms of cancer, such as that of the bladder, kidney, and prostate [63–65]. Urine cytology provides reasonable sensitivity for advanced tumors based on the visual identification of abnormal cells in urine sediment, but sensitivity lowers to only 33% for early or low-grade cancer [66].

2.4.3. Sputum cytology

Sputum is a collection of mucoid material consisting of cells from the buccal cavity, pharynx, larynx, and trachea, as well as inflammatory cells, microorganisms, and so on. Sputum cytology is a type of exfoliative cytology that relies on the spontaneous shedding of cells from an organ's lining into a cavity where they can be collected using a non-invasive approach [67]. This test is straightforward, accurate, reliable, cost-effective, and non-invasive for assessing respiratory disorders such as pre-invasive and invasive pulmonary malignancies [68]. Multiple sputum samples detect central tumors more clearly, whereas bronchial washings and fine needle aspirations detect the remaining ones, which are mainly subpleural lesions [69].

2.4.4. Other biosample-based tests

Tumors shed cells and cell products, such as nucleic acids, proteins, metabolites, and extracellular vesicles containing various analytes, into body fluids such as blood, urine, cerebrospinal fluid, sputum, and saliva, depending on entity and location (Fig. 2) [70]. Although the potential utilization of body fluids in cancer diagnostics has long been recognized, applications have been limited due to a lack of techniques with sufficient sensitivity and specificity. Testing using body fluids other than blood and urine has not been standardized, including every pre-analytical process for all key analytes, emphasizing the importance of developing true multiomics protocols.

3. Cancer biomarkers in early diagnosis

Knowledge of cancer biomarkers has improved considerably in recent years, opening up enormous opportunities for enhancing cancer patient care by increasing diagnosis efficiency and treatment efficacy. Recent technological advances have enabled the analysis of a large number of potential biomarkers, as well as fostering a renewed interest in developing novel biomarkers. Building on the landmark discovery of cancer hallmarks [2,71,72], further novel cancer biomarkers have been identified through research on sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis [72]. It is established that early cancer identification can significantly reduce cancer mortality. Consequently, substantial effort has gone into researching novel technologies for detecting early indicators of the disease. Cancer biomarkers include nucleic acids, proteins, carbohydrates, minor metabolites, cytogenetic and cytokinetic characteristics, as well as complete tumor cells detected in physiological fluid [73]. They can be used to assess risk, facilitate diagnosis, aid prognosis, and predict therapy effectiveness, toxicity, and recurrence [74]. Cancer biomarkers are categorized into numerous functional categories, including diagnostic, prognostic and predictive biomarkers [75]. In this context, the primary focus of this review is diagnostic markers for risk assessment and early-stage disease based on molecular types, including metabolites and nucleic acids.

3.1. Metabolite-based biomarkers

A characteristic of cancer cells is metabolic alteration, which is essential for the initiation and progression of aberrant growth and

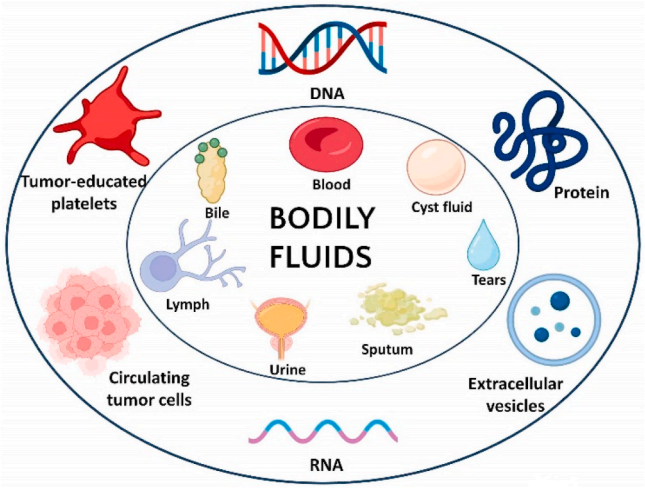

Fig. 2. Example of body fluids and analytes that may be used in cancer diagnostics.

division. This interchange leads to the abnormal production of metabolic and post-transcriptional products termed as oncometabolites, including proteins, enzymes and chemicals, that are produced by tumor cells [76]. Hence, detecting these biomarkers could hold a key to precise and early diagnosis of cancer. In the clinical laboratory, the identification of multiple proteins has been verified to classify tumor samples and thereby to assist early diagnosis [77]. For example, tyrosine kinase receptor proteins that regulate cell growth, such as human epidermal growth factor receptor 2 (HER2) and epidermal growth factor receptor (EGFR), are considered as biomarkers for a variety of cancer types including breast, lung and gastric cancers [78–80]. In addition, specific antigens are considered as selective biomarkers for early diagnosis of cancer, such as carcinoembryonic antigen (CEA) in many types of cancer [81,82], or prostate-specific antigen (PSA) in prostate cancer [83]. Moreover, since cellular activities like signaling transduction, post-transcriptional modifications and epigenetic alterations are impacted by chemical oncometabolites, it is considered to be an important factor for early diagnosis of cancer [84]. For instance, the presence of a high level of D-2-hydroxyglutarate is a distinguishing characteristic in isocitrate dehydrogenase -mutated tumors that has been harnessed for molecular diagnostics and imaging techniques [85]. Furthermore, abnormal metabolism typically harms the reducing equivalent in cancer cells, including reduced versions of coenzymes including NADH, NADPH, and flavin adenine dinucleotide (FADH2), which are considered as metabolite-related cancer biomarkers [86]. Notably, exosomes, vesicles involved in cell-to-cell communication and cell signaling transportation that carry nucleic acids, proteins, lipids and metabolites, are considered as promoters of tumor progression. Hence, novel methods for early cancer diagnosis have focused on seeking exosomes as possible cancer biomarkers [87–90].

3.2. Nucleic acid-based biomarkers

In cancerous patients, levels of nucleic acid (DNA, mRNA, and miRNA) in the blood reflect pathological processes such as malignant and benign lesions, inflammatory disorders, stroke, trauma, and sepsis, leading to apoptotic and necrotic cells releasing nucleic acids into the peripheral circulation [91]. Cancer-related genetic and epigenetic modifications in circulating DNA are crucial to cancer genesis, progression, and resistance to treatment [91,92]. Loss of heterozygosity and mutations in tumor suppressor genes such as TP53 and oncogenes like KRAS and BRAF are examples of these changes [93–97]. In addition, the integrity of non-coding genomic DNA repeat sequences (such as ALU and LINE1) is another genetic change observed in circulating DNA and utilized as a biomarker in cancer [98–101]. In circulating DNA of cancer patients, epigenetic alterations in genes such as glutathione S-transferase P1, septin 9 and adenomatous polyposis coli that are relevant to tumorigenesis and the progression of solid tumors have been detected. Moreover, their potential clinical utility is indicated by of the detection of each underpinning a commercial cancer screening test [102–104]. On the other hand, dying tumor cells also release miRNAs, which circulate in the blood indefinitely. For example, miR-21 and miR-155 are overexpressed in many malignancies [105]. Furthermore, miRNAs such as miR-10b and miR-655 have a role in metastasis, influencing the tumor microenvironment through immune cell modulation or angiogenesis [106]. The key roles of miRNAs in cancer genesis and progression may explain the hopeful outcomes of pilot studies on cancer patients that employ miRNA blood tests for tumor identification and prognosis [107, 108].

3.3. Current status of biomarkers in POC cancer diagnostics

Tests that measure biomarkers in biofluids such as blood or urine are highly desirable since they fulfill an important objective of clinical practice: gathering diagnostic data with minimal discomfort and invasiveness for patients [109]. In recent years there has been a rapid proliferation of techniques for detecting and identifying new markers. As technology advances, utilizing tumor markers has become a major trend in clinical oncology [110]. Tumor markers have many advantages in cancer screening and early detection, monitoring therapy responses, assessing disease progression, and indicating relapse during follow-up periods [111]. They can also be the target for POCTs [112,113]. Typically, these are administered during a clinical visit and produce immediate findings without the need for samples to be sent to a biomedical laboratory. This could provide alternatives to standard laboratory testing in primary care, with the potential to preserve or improve patient convenience, satisfaction, and health outcomes, while saving both time and cost [114,115]. Along with conventional cancer biomarkers, endosomal-derived exosomes and plasma membrane-derived microvesicles or ectosomes are the two main subsets of extracellular vesicles that have been emerged as innovative and useful cancer biomarkers. These subsets have been discovered to be applied recently to several significant cancers including pancreatic, lung, breast, prostate cancers. The capability of detecting and monitoring circulating tumor cells, cell-free DNA, and extracellular vesicles makes liquid biopsy as a revolutionary approach to cancer diagnosis [116,117].

On a cautionary note, the indiscriminate use of tumor markers raises the risk and consequences of inappropriate therapy (either under- or over-treatment). Only a few tumor markers that have been identified, reported, and intensively researched are utilized in routine clinical practice; each of which has established consensus standards for implementation in day-to-day patient care [110]. While formal cancer diagnosis frequently occurs in secondary care, the first suspicion of cancer is generally established in primary care. Despite the expansion of cancer biomarker research in secondary care, relevant primary care studies remain scarce [118]. Cancer markers applied in hospital settings have low positive predictive values and high false positive rates when used on low-risk primary care patients. Identifying patients with non-specific symptoms who may be suffering from cancer rather than a benign disease is therefore an ongoing challenge for primary care practitioners [119]. While numerous cancer biomarkers are under investigation, particularly for “hard to diagnose” tumors such as those located in the pancreas or ovary, or for early detection of malignancy recurrences, it is anticipated that only a few will undergo clinical trial [120]. Thus, the process of biomarker discovery, development of POC tools, and testing in clinical trials should be accelerated to bring POC cancer diagnostics to routine clinical practices.

4. Trends in smartphone-assisted early diagnosis of cancer

4.1. Smartphone-assisted optical biosensors

Optical biosensors, one of the most common types of biosensors, exhibit excellent advantages in biomarker and biochemical analysis when compared to other approaches, including increased sensitivity, high specificity, and real-time results in a short performance time [12]. Typically, an optical biosensor comprises two main components: an optical transducer system that generates a signal corresponding to the analyte concentration, and a biorecognition-sensing element based on simple biological reactions such as DNA hybridization, immunoassay interaction or biochemical aggregation [121]. The straightforward components of optical biosensors reduce the complexity of both manufacturing and using the measurement device. Recent developments and modifications of these biosensors have demonstrated that with the assistance of integrating POC platforms, such as smartphones, these analytical devices can be reduced in size, complexity, and cost while remaining effective. These advances can bring opportunities for detecting cancer biomarkers in early stages with more approachable sampling and reduced expense, hence lowering mortality rates for patients [4,12]. Table 1 summarizes recent achievements in the development of smartphone-based optical biosensors for cancer biomarkers.

Table 1
Summary of smartphone-based optical biosensors of cancer biomarkers.

Method	Technique	Platform	Reaction type	Biomarker	Biosample	Reaction time	Sensitivity	Stability	Ref.
Colorimetry	Imaging	Fe_3O_4@SiO_2-prNH_2-Au@$Pd_{0.30}$NPs-*anti*-IgG	Immunoassay	anti-p53a Ab	Human serum	-	3.1 pg/mL	-	[122]
Colorimetry	Imaging	d-AuNPs-acpcDNA, PBS, $MgCl_2$	DNA hybridization	HPV DNA 16	SiHa and CaSki cell lines	30 min	1 μg/mL	7 days, 4 °C	[123]
Colorimetry	Imaging + Machine learning	Cyst/AuNPs	Aptasensor	APC	Blood sample	30 min	3 nM	-	[124]
Colorimetry	Paper-based immunoassay + imaging	Chitosan-$C_5H_8O_2$@Ab-BSA@HRP Ab, TMB	Immunoassay	CEA	-	48 min	0.015 ng/mL	-	[125]
Colorimetry	Paper-based immunoassay + imaging	AuNPs@aHIgG-biotin-DNA-streptavidin-HRP	Immunoassay	KLK3	Diluted human serum	15 min	10 pg/mL	14 days, 4 °C	[126]
Colorimetry	Paper-based immunoassay + imaging	$Co_2(OH)_2CO_3$–CeO_2-Ab2, TMB, H_2O_2	Immunoassay	CEA	-	60 min	0.51 pg/mL	30 days, 4 °C	[127]
Colorimetry	Colorimetric assay + imaging	T1-T2 aptamer, H1–H2 hairpin – Hemin, ABTS – H_2O_2	Aptasensor	Met-Met dimers in MKN-45 cell	Peripheral blood	120 min	1 cell	-	[128]
Colorimetry	Colorimetric assay + imaging	AuNP-Cys@anti-AFP AuNP-Cys@anti-MUC16	Immunoassay	AFP MUC-16	-	30 min	1.054 ng/mL 0.413 ng/mL	4 days	[129]
Colorimetry	LAMP + imaging	non-buffered LAMP solution, HNB–Mg^{2+}	DNA amplification	HPV DNA 16, 18, 31	Clinical cervical swab and saliva sample	85 min	50 copies	21 days, RT, daylight exposure	[130]
Fluorescence	Imaging	SiO2@QDs-TAC	Immunoassay	HER2	-	2 days	0.3 nM	-	[131]
Fluorescence	Imaging	NS-CDs/ENF	-	DOX	Human serum	10 min	5.4 nM	-	[132]
Fluorescence	Imaging	Hydrogel NPs-biotin aptamer-SA-PE	DNA hybridization	miR-21 let-7a	-	120 min	100 fM 100 fM	7 days, 4 °C	[133]
Fluorescence	Imaging	PcAb-Eu_2O_3@PAA NCs	Immunoassay	CEA	Human saliva	10 min	1.47 pg/mL	-	[134]
Fluorescence	LFIA + imaging	Fe_3O_4@PEI@QDs MQBs-Abs	Immunoassay	f-PSA c-PSA	Human serum	60 min 60 min	0.009 ng/mL 0.087 ng/mL	-	[135]
Fluorescence	LFIA + imaging	NPs-Ab1-Ab2	Immunoassay	CEA	-	-	0.037 ng/mL	-	[136]
Fluorescence	Immunoassay + imaging	f-MNPs-Abs	Immunoassay	PSA	-	1 min	100 pg/mL	-	[137]
Fluorescence	dPCR + imaging	d-PCR mixture	Amplification	CD47	-	-	10 copies/μL	-	[138]
Fluorescence	FRET	NH2–Cu-MOFs, PPi	Reduction	ALP	Human serum	60 min	0.078 mU/mL	-	[139]
Fluorescence	FRET	DNA origami book - ddUTP-Cy3, ddUTP-Cy5	Aptasensor	miR-21 let-7a	MCF-7 cells	10 min	10 pM	-	[140]
Fluorescence	LRET	UCNPs-CEA Ab1, AuNPs-CEA Ab2	Immunoassay	CEA	Human serum	30 min	0.36 ng/mL	28 days, 4 °C, dry environment	[141]
Reflectance	DRS + imaging	Fiber-optic endoscope, proflavine	-	N/C of epithelial tissues	Human epithelial tissue	-	~3.5 μm	-	[142]
Surface plasmon resonance	PIA + imaging	Biotin-PEG-1000-SH@NeutrAvidin@Biotin-Abs	Immunoassay	exosomal EGFR	A549 NSCLC cells	20 min	9.72×10^9 exosomes/mL	-	[143]
Photothermal imaging	RCA + imaging	Cu_xS-DNA-Ab1	Immunoassay	PSA	PSA-spiked solution	8 min	0.2 ng/mL	-	[144]

Abbreviations: LAMP, Loop-mediated isothermal amplification; LFIA, Lateral flow immunoassay; dPCR, Digital polymerase chain reaction; HSFM, handheld smartphone fluorescence microscope; FRET, Fluorescence resonance energy transfer; PQF, Plasmon-quenched fluorescence; LRET, Luminescence resonance energy transfer; DSR, Diffuse reflectance spectroscopy; PIA, Plasmon-induced absorption; RCA: Rolling-circle amplification.

4.1.1. Colorimetric biosensors

Among optical-based detection techniques, those using colorimetry are considered as potential on-site testing platforms due to their visual simplicity, ease of use, affordability, and high compatibility with simple platforms such as paper-based analytical devices (PADs), lateral flow immunoassays (LFIAs), as well as being easily compliant with smartphones for data processing purposes [122–130]. Fig. 3 shows representative colorimetric platforms successfully applied to smartphone-assisted optical-based cancer biosensors.

Recently, a colorimetric assay has been developed using functional nanomaterials to detect the antigen kallikrein-3 (KLK3) that is specific for prostate cancer (Fig. 3A). The detection mechanism was based on a simple antigen-antibody reaction with anti-human IgG (HIgG) in an affordable PAD. For favorable binding sites and enhanced signal, this complex was attached to modified functional gold nanoparticles (AuNPs) fused with streptavidin-horseradish peroxidase (HRP) bound to biotinylated poly(A) DNA sequences. By using a smartphone camera to analyze blue/red ratio changes in the PAD under artificial white light

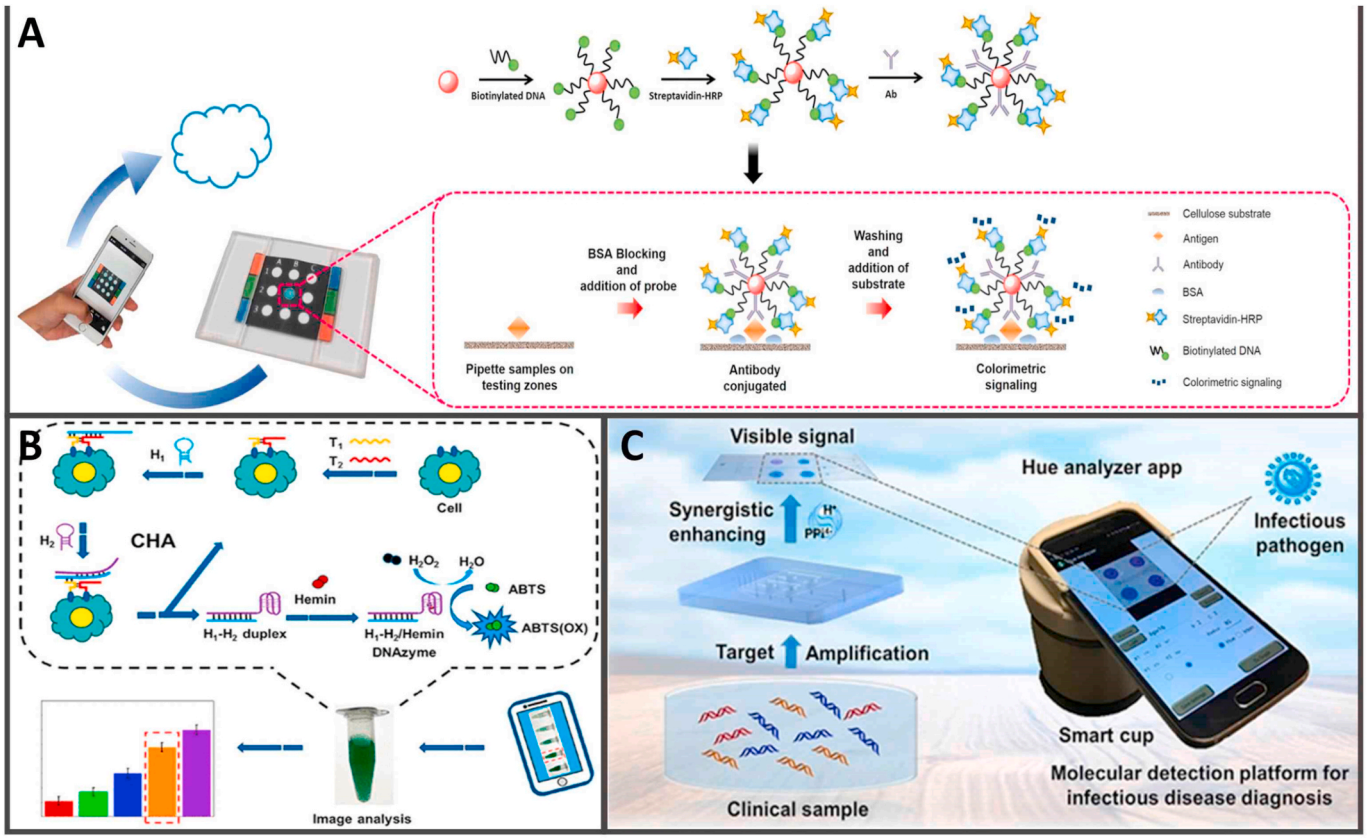

Fig. 3. Smartphone-based colorimetric biosensors of different cancer biomarkers; A) P-ELISA Test with KLK3 antigen for prostate cancer using functionalized DNA-AuNP nanoconjugation. Adapted with permission from Ref. [126]. B) Recognition of membrane protein dimerization in MKN-45 cells of gastric cancer by catalytic hairpin assembly (CHA) reaction-based colorimetric assay. Adapted with permission from Ref. [128]. C) Hue-based colorimetric detection platform for HPV DNA 16, 18 and 31. Adapted with permission from Ref. [130].

only, quantitative data were preset using an in-house developed application (app) and reached a LOD for this antigen of 10 pg/mL within 15 min [126]. This demonstrates the high potential of the smartphone-integrated PAD platform for rapid simultaneous analysis with minimal sample and cost consumption.

Membrane protein dimerization, a significant sign of cancer development [95,145,146], is readily detected by an aptasensor-based colorimetric assay in the case of MKN-45 cells in gastric cancer (Fig. 3B). Living cells from human peripheral blood with native Met-Met dimers were used as the target for a proximity-ligation-assisted catalytic hairpin assembly (CHA) reaction with multiple sets of single-stranded DNA, resulting in the formation of G-quadruplex (G4) fragments. In addition, this duplex cooperated with DNAzyme and hemin to utilize peroxidase activity, leading to a visible dark green solution in samples containing Met-Met dimers. This color differentiation was investigated by a smartphone by image-taking, image acquisition and processing. The platform achieved an impressive LOD of 1 cell per test, and also supported tracking the Met-HGF signaling pathway in viable cells [128], a key point in for developing malignancies [147]. This demonstration shows that POC smartphone-assisted biosensors have strong potential to simplify proof-of-concept research beyond purely diagnostics.

Interestingly, DNA amplification methods such as loop-mediated isothermal amplification (LAMP), which previously required complex and large-scale devices, can now be downsized to a microfluidic chip base and be integrated into smartphone analyzers for colorimetric assays. These can be used to detect nucleic acid biomarkers in cancers, such as human papillomavirus (HPV) DNA types 16, 18 and 31 for cervical cancer (Fig. 3C). PPi^{4-} and H^{+} ions are byproducts of the LAMP reaction using target HPV DNA collected from saliva and clinical swab samples. These combine with HNB color indicator and Mg^{2+} to produce a marked change in transparency from fuchsia to blue. This reaction is performed in a 36 mm × 21 mm x 3.50 mm microfluidic chip with the support of a smart cup to supply heat for isothermal amplification reaction. A smartphone is used for image collecting and further analysis by the Hue Analyzer app. The hue value was developed to have a lower susceptibility to picture noise than saturation and intensity, leading to reliable outputs. The platform exhibits a LOD of 50 copies per test with a total performance time of 85 min. In addition, the assay has a preservation time of up to 21 days at room temperature and daylight exposure conditions [130]. Each test costs approximately US $2, making it an effective and affordable POC diagnostic tool for HPV-associated cancer screening.

4.1.2. *Fluorescence biosensors*

Fluorescence-based approaches are also widely employed in downsizing for smartphone-based platforms due to the simplicity in compacting analysis components and high-sensitivity fluorescence detection [12], which is very effective for early stage cancer diagnosis. The approaches used in building smartphone-assisted fluorescence biosensors for cancer biomarkers range from visualizing fluorescence intensity by simple imaging to microscopy or are combined with LFIAs. Each offers considerable potential to be combined with more complicated laboratory-based techniques such as fluorescence resonance energy transfer (FRET) [131–141].

The fabrication of novel quantum dots (QDs) has supported the development of optical, especially fluorescence based POC biosensors. Specifically, colloidal semiconductor QDs were combined with silica nanoparticles to detect the HER2 antigen, a widely acknowledged biomarker of various cancers (Fig. 4A). Based on immunoconjugation, a tetrameric antibody complex (TAC) including anti-dextran and anti-

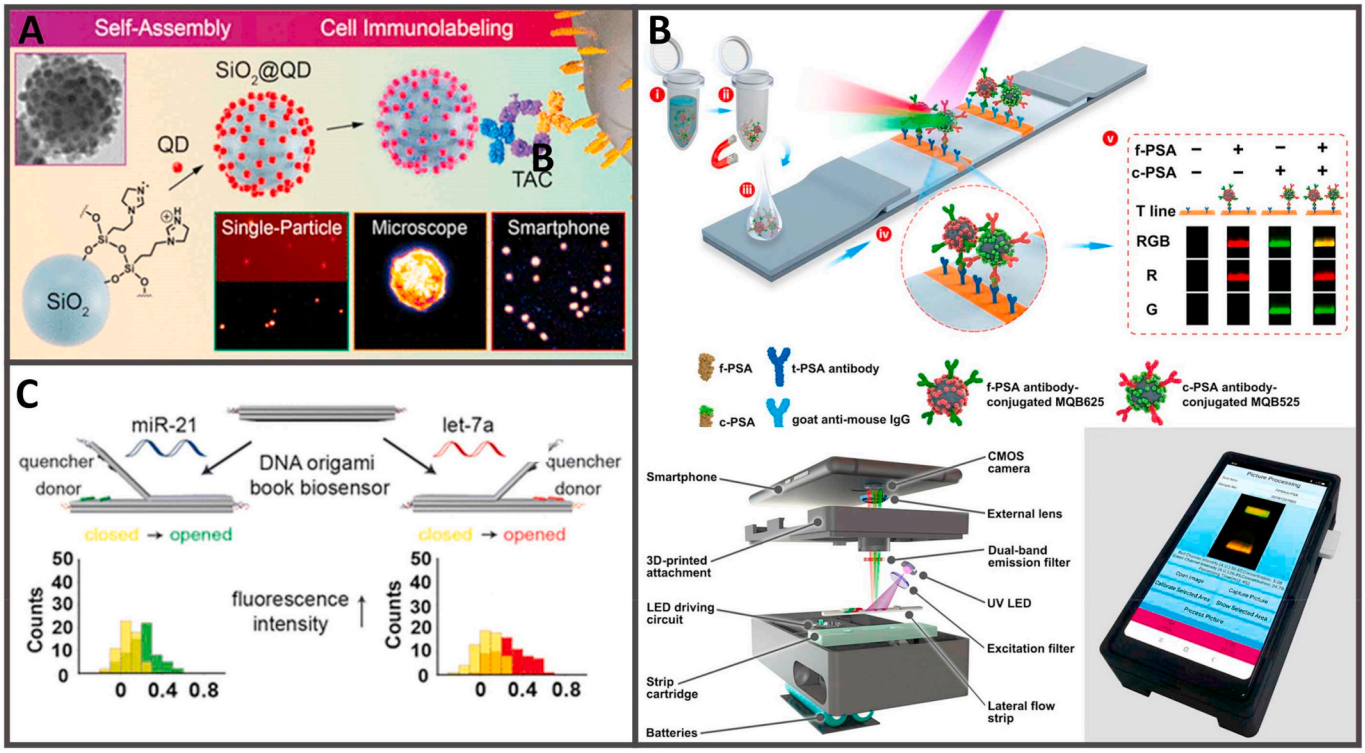

Fig. 4. Smartphone-based fluorescence biosensors of different cancer biomarkers; A) Imidazole-functionalized silica nanoparticles with quantum dots (SiO_2@QD), and tetrameric antibody complexes (TACs) in fluorescence imaging of HER2 in cancer cells. Adapted with permission from Ref. [131]. B) LFIA with luminescence magnetic nanobeads (MBs) for prostate cancer antigens detection. Adapted with permission from Ref. [135]. C) DNA origami book biosensor based on FRET and fluorescence quenching for miR-21 and let-7a detection with high potential for application on a POC smartphone-based platform. Adapted with permission from Ref. [140].

HER2 was used to search for the presence of HER2 in the SK-BR3human breast cancer cell line. In order for this complex to be photoluminescent in fluorescence imaging, TACs were fused with SiO_2@QDs to enhance photoluminescence and lower background noise. The excitation light source was collected directly from the smartphone camera flash and an in-house reflector to provide blue excitation light. The image that was captured by the smartphone camera lens with excitation and emission filters was analyzed based on RGB values and performed on the.DNG format. The allowance cell concentration for good quality imaging is 0.3 nM, with total performance time for both cell culture and image analysis of around 2 days [131]. Hence, this platform proves the utility of QD technology in high-sensitivity, smartphone-based POC cancer diagnostics.

Magnetic nanobeads (MBs) are also used for detecting cancerous antigens in smartphone-based LFIA platforms. For example, high-luminescence MBs were designed to conjugate with antibodies to PSA, enabling visualization of f-PSA and c-PSA in test strips via a smartphone imaging and analysis system (Fig. 4B). The antibodies were conjugated with superior magnetic, dual-color fluorescent MQB625 and MQB525, then electrostatically attached to the nitrocellulose test strip. To observe the presence of PSA in LFIA strips, a smartphone readout device was developed using a three-dimensional-printed optomechanical attachment with an ultraviolet light-emitting diode (LED) driven by a constant current circuit and filtered by a 365 nm band-pass filter. Fluorescence signals were collected using a dual-band emission filter and an external plano-convex lens. Subsequent image recording and data analysis via red and green channel readout values were performed by Android Studio on a Xiaomi smartphone. This platform was claimed to simultaneously detect f-PSA and c-PSA with LODs of 9 pg/mL and 87 pg/mL within 60 min, respectively [135], leading to the potential development of rapid and accurate fluorescence LFIA using a smartphone.

To the best of our knowledge, although the FRET-based technique is proposed for a variety of biosensors to detect cancer biomarkers [148], application of these platforms to smartphone-based cancer diagnostics has not been widely suggested. Recent research has presented potential platforms to combine with a smartphone; for example, DNA nanostructures with the ability to generate precise fluorophore networks for strong optical signals, enabling FRET effects in specific oligonucleotide targets, were applied in a FRET-based DNA origami book for the detection of two micro-RNA cancer biomarkers, miR-21 and let-7a (Fig. 4C). The DNA origami book consists of three layers of DNA helices packed on a square lattice, its partially hybridized locks keeping the layers closed while prompting their opening when the oligonucleotide target appears due to electrostatic repulsion and device entropy. As a result, the distance between donor and receptor fluorophores increases, energy transfer decreases, and the fluorescence signal increases. Through examining the fluorescence quenching properties by wide-field fluorescence microscopy, the DNA nanostructure was reported to detect miR-21 and let-7a from MCF-7 cell extraction at a concentration of 10 pM, with fluorescence intensities of dye quencher pairs increasing to 10% in 10 min [140]. This platform is expected to convert to closed-circuit microfluidic chips with smartphone-based microscopy for recording the change in fluorescence intensity, thus helping to bring FRET-based detecting techniques to the design of POC diagnostic devices.

4.1.3. Other optical biosensors

Several other methods in traditional optical biosensors are utilized to build smartphone-based POCT platforms. However, currently they are limited due to technical complexity, analytical software that is not fully developed commercially, and integrating sensing components being sensitive to ambient and light exposure conditions [121]. Recent discoveries and improvements are addressing these challenges by employing more diverse optical approaches to boost specificity of cancer

biomarker identification [142–144].

Spectroscopy and smartphone imaging are actively combined to detect for the presence of aberrant nuclei in malignant cells, specifically the observation of epithelial tissues using a smartphone-based dual modality fiber-optic micro-endoscope (Fig. 5A). In studies, three types of epithelial tissues were selected: labial mucosa, gingival tissue, and tongue dorsum tissue. These cells were dyed with proflavine and observed under the SmartME smartphone-based spectroscopy system. This consists of a smartphone, a fiber-optic endoscope, a phone attachment, an app, and two functional LED channels. The FLI channel uses a blue LED, condenser lens, and short pass excitation filter for fluorescence excitation. The DRS channel uses a 20-mW white LED, which is delivered to the tissue through two 200/220 μm multimode fibers. The diffuse reflectance is collected by a single detection fiber, narrowed down by a 100 μm slit, and passed through a collimating lens. The smartphone app uses SmartME Uploader custom software to ensure a smooth connection between the SmartME and the server. This allows users to set camera parameters, initiate measurements, store images, perform simple analysis, send raw data to the server, and to receive and display analyzed results. The entire process takes a few seconds, with a limit for cell visibility of ~3.5 μm, and the total cost for whole system is less than US $2500 [142]. Integrating optical imaging technologies in smartphones can reduce cost, weight, and size, thus making this system affordable in low- and middle-income countries (LMIC). Hence, it could provide an attractive option for cost-effective pre-cancerous screening for cervical and oral cancer in resource-limited settings.

A whole smartphone-based plasmonic interferometer array (PIA) sensor was developed for early detection of EGFR in non-small cell lung cancer (NSCLC) cells. The exosomal EGFR is captured by an immunoassay with PEG200-SH, biotin-PEG-1000-SH, and biotinylated anti-EGFR antibodies on a biochip. The PIA biochip is built from nanogroove rings, enabling surface plasmon waves to interfere with free-space light. This causes intensity interference in the presence of target exosomal EGFR, with real-time recordings of intensity changes enabling real-time detection of EGFR in test samples. In trials, a 1 mm plano-concave lens was embedded in a phone case and aligned with a Nokia Lumia 1020 smartphone camera. The built-in CMOS camera detected light transmitted through loaded samples via a 6x6 PIA chip, which provided a sensing resolution of 9.72×10^9 exosomes/mL in A549 lung cancer cells [143]. When compared to traditional prism-based surface plasmon resonance systems, this downsized, compact PIA platform does not require angular adjustable prism-coupling devices. This permits a significant reduction in both device cost and instrument complexity, which thus shows enormous promise for label-free sensing with significant implications for POC diagnostics.

A novel smartphone-based photothermal immune-imager combining Cu_xS nanocrystals with a smartphone-based infrared thermal imaging processor has been described for the visual, quantitative detection of prostate cancer biomarkers (Fig. 5B). PSA was identified by antibody and attached to an aptamer in the sandwich assembly, giving a specific primer sequence for the subsequent rolling-circle amplification (RCA) reaction. The final RCA copies complementary for Cu_xS-DNA binding are converted by PSA-aptamer recognition into amplifiable photothermal output signals under infrared light stimulation. Cu_xS turns the excitation energy of infrared light into thermal energy, which is displayed as thermal imaging and a temperature reading using the smartphone-based infrared imager. The LOD of the test was 0.2 ng/mL, with a total reaction time of about 10 min, which is comparable to traditional immune-imaging assays [144]. This approach to early cancer diagnosis substitutes complex devices with cost-effective and versatile testing apparatus. Another benefit of the technique is the impressive photothermal conversion efficiency and high stability of Cu_xS NCs, which ensure the sensitivity and reproducibility of the results.

4.2. Smartphone-assisted electrochemical biosensors

Electrochemistry has a wide use in biochemical analysis by detecting important analytes such as proteins, RNA and volatile organic compounds (VOCs) that are potential biomarkers for cancer diagnosis. Although numerous different approaches for such biomarker diagnostics have been published, an electrochemical method is favored due to its low cost, fast response, ease of operation, easy quantifiability, miniaturization potential, and high sensitivity and selectivity with a lower LOD [149]. Typically, electrochemical biosensors comprise three components; a biorecognition element (antibody, enzyme, and nucleic acid), a signal transducer (converts the molecular recognition of the target analyte into an electrical signal), and a three electrode-based electrochemical system. In such biosensors, the selective binding affinity, alongside the catalytic activity between an analyte and a fixed or immobilized bioreceptor, causes an electrochemical reaction at the electrode surface. In turn, this leads to a change in electrical signal for monitoring and recording [150].

Potentiometric, amperometric, conductometric, impedimetric, and voltametric techniques are the main electrochemical methods used for constructing, adjusting, and optimizing electrochemical sensors and biosensors [151]. A potentiometric biosensor integrates a biological sensing element with an electrochemical transducer (the working electrode) to generate a difference in the electrical potential by using ion-sensitive field-effect transistors, or ion-specific electrodes. An amperometric biosensor drives a faradaic current occasioned by any redox reaction(s) that might occur at the surface of the working electrode at a fixed voltage. The value of the generated redox current is dependent on the concentration of the analyte that is presented in a supporting electrolyte. A conductometric biosensor can detect any electrochemical reactive change occurring in a solution, which includes the ionic composition of the tested sample, due to chemical and biochemical reactions. An impedimetric biosensor, such as an electrochemical impedance spectroscopy (EIS) analyzer, records the electrical impedance created at the interface of a solid electrode surface when a small AC potential is applied. The detected changes in resistance are measured as a function of frequency. A voltametric biosensor analyzes the target concentration by determining the generated faradaic current through the variation in electrical potential caused by oxidation or reduction of the electroactive analyte at the working electrode surface. The peak position at a certain potential value is used for identification (analyte character cathodic/anodic peak potentials), while the concentration of the corresponding species is reflected by the intensity of the peak (Faradaic) current. Several chemical modification approaches have been used on the electrode to improve signal transduction efficiency. Proper immobilization should result in high-performance, low-cost detection systems, which are often achieved by using appropriate functional materials for the electrode. The latest developments in smartphone-based electrochemical sensing systems for biochemical analysis (summarized in Table 2) have provided powerful detection and analysis tools for early diagnosis of cancer through the quantification of low-abundance cancer biomarkers.

Recently, a novel smartphone-based electrochemical immunochromatography (EIC) system for rapid detection of serum PSA has been developed to diagnose prostate cancer [150]. This is composed of two parts: the smartphone-based electrochemical detector and the EIC biosensor chip. The biosensor is constructed from screen-printed carbon electrodes (SPCE), which include a carbon gold nanoflowers (AuNFs) modified-working electrode, an Ag/AgCl reference electrode, and a carbon counter electrode (Fig. 6A). The EIC structure is formed by a sample pad (with HRP-labeled PSA monoclonal antibody, mAb, on the front and the SPCE/AuNFs/PSA mAb chip in the upper part), nitrocellulose film and adsorbent pad with a card case that has a sample hole and a detection hole installed outside. The sample is added to the sample well and combined with PSA mAb-HRP to form a PSA mAb–HRP/PSA complex, which is chromatographically directed to the SPCE/Au

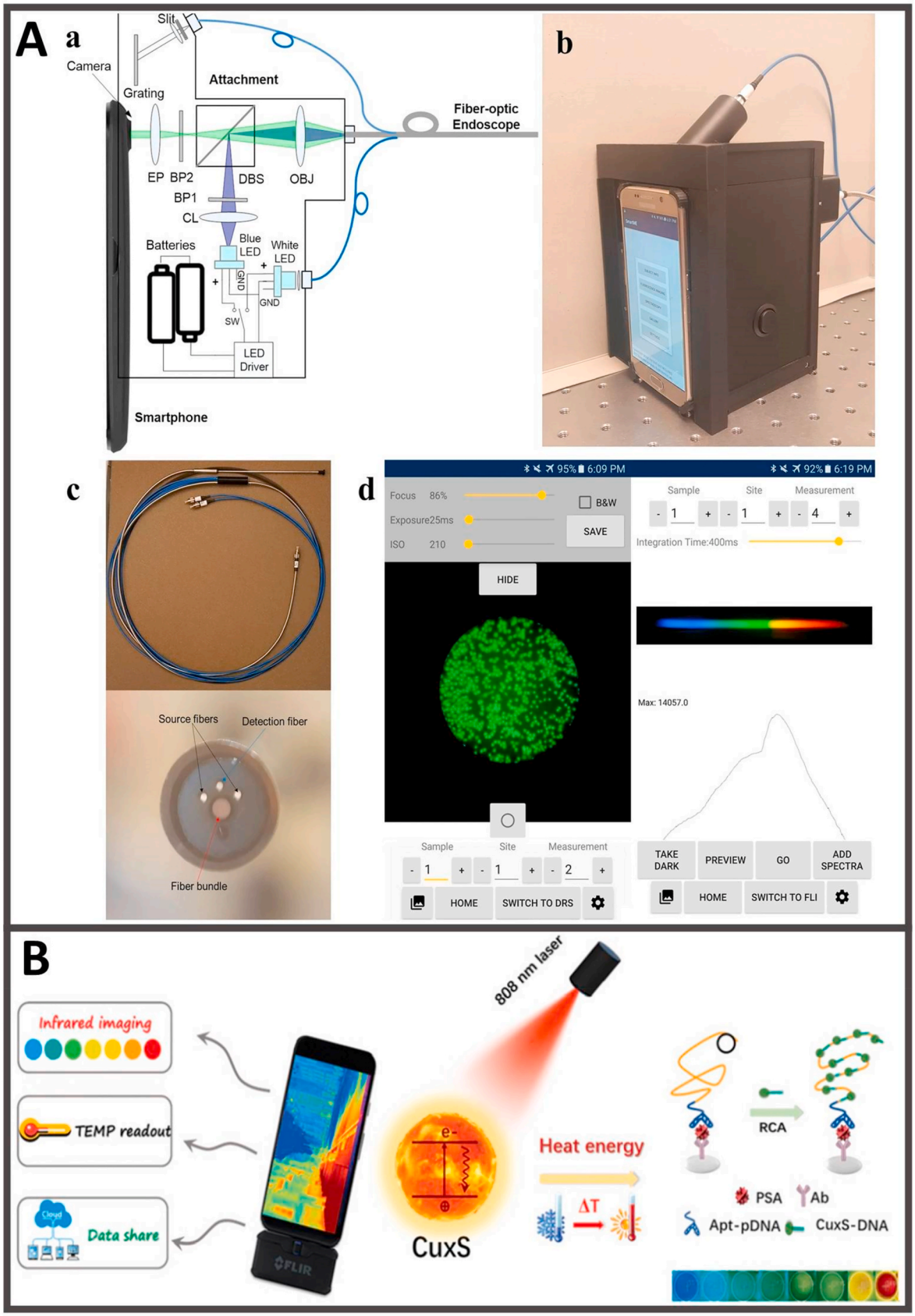

Fig. 5. Smartphone-based optical biosensors of biomarkers using a variety of methods. A) Smartphone-assisted immunoassay-LRET based biosensor with UCNPs for carcinoembryonic (CEA) detection. Adapted with permission from Ref. [141] B) CuxS nanocrystal-based photothermal immune-imaging asssay of prostate-specific antigen (PSA) on a smartphone. Adapted with permission from Ref. [144].

Table 2
Summary of smartphone-based electrochemical biosensors of cancer biomarkers.

Detection Technique	Platform	Reaction type	Biomarker	Biosamples	Reaction time	Sensitivity	Stability	Ref.
Amperometry	Anti-PSA@SPCE/Au NFs	Immunosensor	PSA	Blood	15 min	0.28 ng/mL	-	[152]
CV and amperometry	Anti-CD63@SPCE, SA-polyHRP	Immunosensor	CD-63 expressing Exosomes	Human Serum and PC-3 cell culture	120 min	1.446 ng/μL	-	[90]
CV	Anti-PSA@C-MEMS-derived Glassy Carbon	Immunosensor	PSA	Human serum	-	1 pg/ml	-	[153]
DPV	Anti-NSE@NH_2-G/Thi/AuNPs-modified μPADs	Immunosensor	NSE	Quality-control serum	18 min	10 pg/ml	-	[154]
DPV	Anti-CA_{125}@MWCNTs/Thi/AuNPs@SPE	Immunosensor	CA125	Human serum	20 min	2 mU/mL	-	[155]
DPV	ssDNA@rGO/Au/SPE	ssDNA - miRNA interaction	miR-21	Saliva	60 min	1 pM	7 days	[156]
CV and DPV	ssDNA@GoQdots/SPE	ssDNA - miRNA interaction	miR141	miR141-spiked solution (saline sodium citrate)	120 min	0.091 pM	-	[157]
CV and DPV	AuNFs/PNA modified CFME	PNA - CircRNA interaction	CircRNA	Human serum	180 min	3.29 fM	Up to 24 days	[158]
CV, EIS and DPV	Fc-PNA@SPCE with magnetic nanoparticles	PNA - DNA methylation interaction	methylation level of mSEPT9 gene	Blood	85 min	0.37%	-	[159]
CV and EIS	LSG-AuNS aptasensor	Aptasensor	HER2	Serum	15 min	0.008 ng/mL	-	[160]
EIS	PD/MnO_2	-	ALP	Cell (MDCK and MDAMB)	~1 day	3.98 cells/ml	-	[161]
EIS	Enzyme-responsive CD (HA)/TiO_2/Cu^{2+}	-	ALP	Cell (HeLa and MDCK)	15 h	2.31 cells/mL	-	[162]
PEC	Anti-HER2@Co_9S_8@$ZnIn_2S_4$/SPE	Immunosensor	HER-2	Serum	300 min	3.5 pg/mL	-	[163]
Chemiresistor sensor	ZnO nanosheet@GE	Gas sensor	VOC: Diethyl ketone Acetone Isopropanol	Gas	20 s	0.9 ppb 4.5 ppb 11 ppb	3 months	[164]
EIS	ZnO/graphene@IE	Gas sensor	VOC: Acetone	-	220 s	1.56 ppm	-	[165]

Abbreviations: CV, Cyclic Voltammetry; DPV, Differential pulse voltammetry; EIS, Electrochemical impedance spectroscopy.

NFs/PSA mAb capture layer, finally forming PSA mAb/PSA/PSA mAb–HRP double-body sandwich complexes on the surface of SPCE/AuNFs. The smartphone acts as a data receiver from the integrating device that is used to monitor the reduction in current signal. This correlates with the concentration of PSA measured by the electrochemical detector after adding the chromogenic substrate TMB to the detection well. With the assistance of a smartphone-integrated platform, in trials the system achieved an excellent linear range from 0 to 100 ng/mL within 20 min, with an LOD of 0.28 ng/mL, successfully discriminating prostate cancer patients from healthy controls [152].

Exosomes are another potential biomarker for early diagnosis and prognostic prediction of cancer-related diseases [166]. A sensitive and portable electrochemical biosensor can be used in conjunction with smartphones to quantify exosomes using an enhanced double-antibody sandwich method-based poly-enzyme signal amplification (Fig. 6B). After sample incubation and exosome capture by immobilized antibodies on SPCEs, biotin-modified antibodies are added to form a "sandwich"-type complex with exosomes, followed by the addition of streptavidin polyhorseradish peroxidase (SA-polyHRP) that binds to biotin to provide an output signal. The SPCE is inserted into the USB port of the portable EC detector, which communicates with the smartphone via Wi-Fi or Bluetooth to process electrochemical signals. The smartphone-based system can detect as low as 7.23 ng of CD63-positive exosomes in 5 μL of serum within 2 h [90].

A biosensing system has been developed for electrochemical detection of circulating microRNA-21 (miR-21) in human saliva that is upregulated in a variety of cancers [156,167]. The system is constructed of a reduced graphene oxide/gold (rGO/Au) modified screen-printed biosensor, a detection circuit board and a Bluetooth-enabled smartphone equipped with a specially designed app. Hybridization between the miR-21 target and ssDNA probe on the rGO/Au-modified electrode leads to a decrease in peak current due to increased negatively charged phosphoric acid groups that interfere with the electron transfer process, which is correlated with the rise in miR-21 concentration. The system displays good linearity for detection of miR-21 in the concentration range of 1×10^{-4} M to 1×10^{-12} M ($R^2 = 0.99$). Using a specialized app, the smartphone is connected with the circuit board to perform and manage differential pulse voltammetry (DPV) analysis. The current response is maintained at 95.5% of its initial level after storing at 4 °C for 7 days, indicating good stability of the electrode. The smartphone-based device is simple, portable, and cost-effective, and can be utilized in resource-limited and non-clinical settings, opening up new avenues for the rapid and non-invasive detection of circulating miRNA biomarkers in POCTs [156].

A wireless hybrid electrochemical-fluorescence biosensor that utilizes the overexpression of extracellular alkaline phosphatases (ALP) for cancer diagnosis has been developed based on polymer dot-manganese dioxide complexes (PD/MnO_2) (Fig. 7A). After complexation, MnO_2 nanosheets exhibit the ability to not only quench the fluorescence of PDs but also increase their conductivity. The PD/MnO_2 complex cleaved by ascorbic acid (AA) as the product of 2-phospho-L-ascorbic acid (AAP) hydrolysis in the presence of extracellular ALP is secreted by cancer cells, recovering the PD fluorescence and biosensor resistance. The PD/MnO_2-coated substrate containing the cells is connected to the wireless device, which consists of a microcontroller (Arduino Uno) and a Bluetooth module (AppGosu) to send the results directly to a smartphone as a resistance graph for real-time data monitoring. In tests, the electrochemical PD/MnO_2 biosensors exhibited excellent LOD values (3.98 cells/mL), compared to those using the fluorescence approach (1995 cells/mL) [161].

A portable smartphone-based photoelectrochemical (PEC) immunoassay that was designed for the on-site detection of the breast cancer

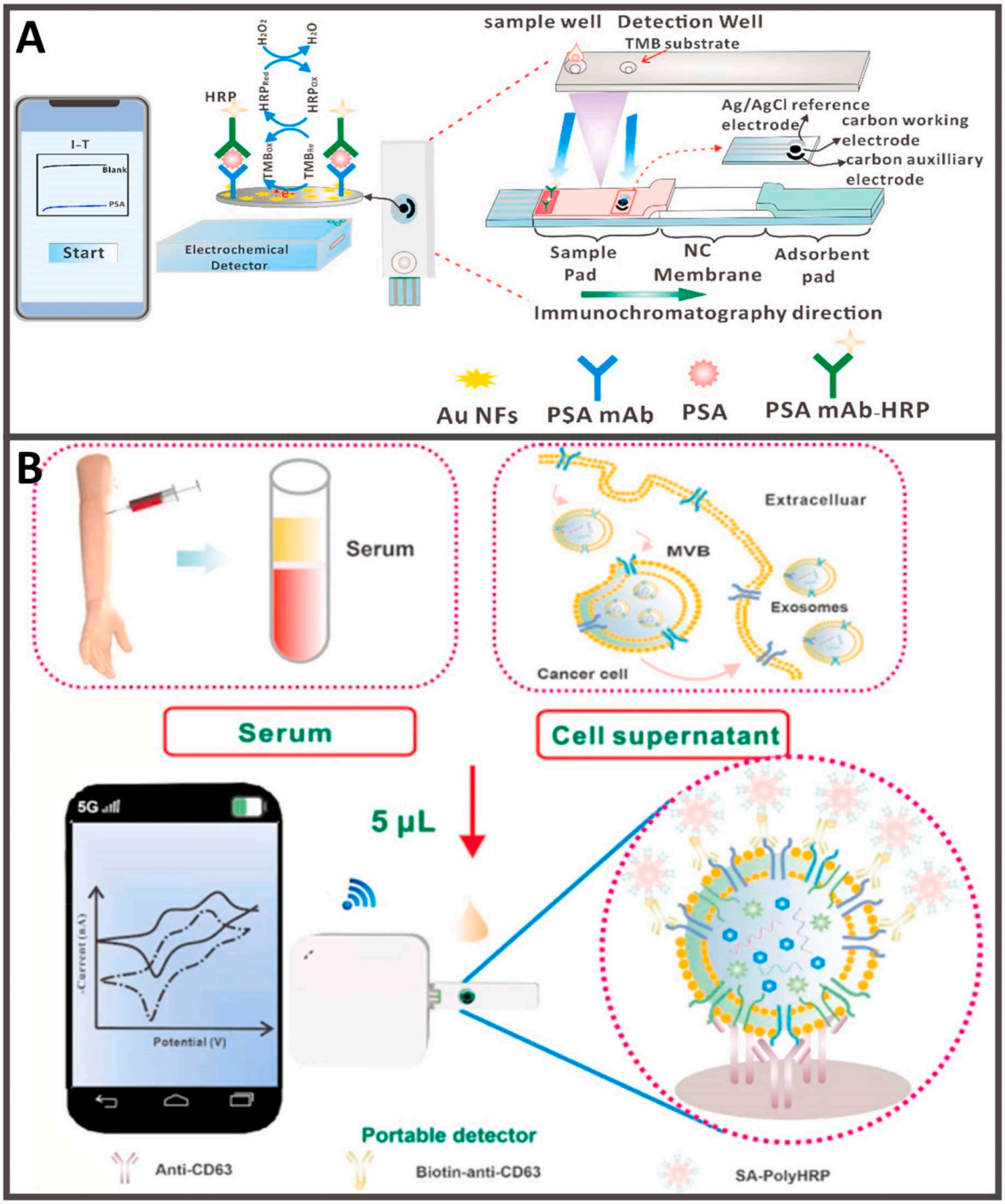

Fig. 6. Smartphone-based electrochemical cancer diagnosis systems. A. PSA detection with EIC detection chip for prostate cancer using double antibody-complexes (PSA mAb-PSA-PSA mAb-HRP) on the working electrode with the i-t measurement of the reduction current signal generated by HRP-catalyzed TMB substrate, which positively correlates with the concentration of PSA. Adapted with permission from Ref. [152]; B. Smartphone-based biosensor for detection and monitoring of serum-derived exosomes through a portable detector via wireless connection. Adapted with permission from Ref. [90].

biomarker HER2 consists of a split-type immunoassay mode, a hierarchical Co_9S_8@$ZnIn_2S_4$ heterostructure-coated SPE, an integrated circuit board, and a Bluetooth smartphone equipped with a specially designed app (Fig. 7B). Co_9S_8@$ZnIn_2S_4$ modification of SPE acts as a photoactive material for realizing photoelectric conversion to improve PEC performance with good photocurrent response. Following the addition of AA2P, the corresponding ALP of HER2 antigen in the antibody-antigen reaction catalyzes the production of AA, which effectively traps holes and inhibits electron hole recombination, thereby triggering photocurrent amplification of Co_9S_8@$ZnIn_2S_4$. Using the portable miniature circuit board relayed over Bluetooth to the smartphone, the specialized app can measure the real-time photocurrent, estimate the concentration of HER2 in the sample using a linear equation and share diagnostic results easily to specific data platforms. In trials, the detected concentration of HERS2 ranged from 0.01 ng/mL to 10 ng/mL, with a LOD of 3.5 pg/mL, which is well below the clinical threshold [163].

Produced and emitted through the metabolism of cancer cells or the body's immune system, VOCs are considered novel lung cancer biomarkers for diagnostic purposes [168]. A smartphone-based lung cancer-related disease detection system has been developed that detects VOCs using rapid synthesis of ZnO nanosheets. The chemiresistive sensor is made of a ZnO-coated alumina (Al_2O_3) ceramic tube with two

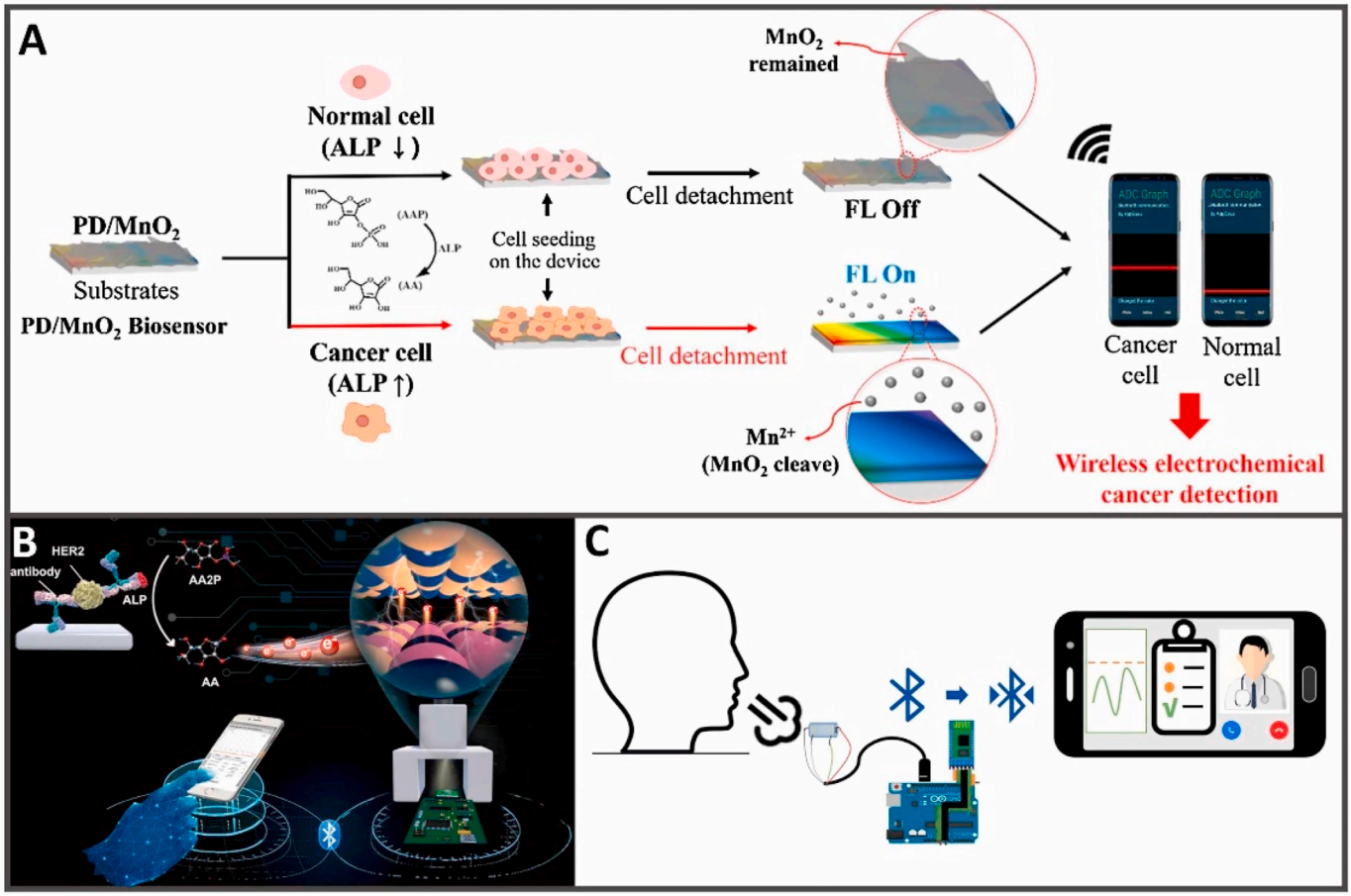

Fig. 7. Smartphone-based electrochemical cancer diagnosis systems. A. Wireless cancer detection by using a hybrid electrochemical-fluorescent PD/MnO_2 biosensor which shows increased conductivity with fluorescence recovery due to decomposition of MnO_2 in the presence of cancer cells that generate wireless electrochemical signals for recording on a smartphone. Adapted with permission from Ref. [161]; B. Smartphone-based photoelectrochemical immunoassay for the detection of HER2 for breast cancer diagnosis. Adapted with permission from Ref. [163]; C. Detection of VOCs using a smartphone-based biosensing system consisting of a glass gas chamber with chemiresistor sensor, and an Arduino Uno-based device wirelessly connected to a smartphone for displaying the measurement of VOCs in real-time. Adapted with permission from Ref. [164].

gold electrode wires installed at each end and a heating wire passed through to control the operating temperature (Fig. 7C). The gas sensor is placed inside the sealed glass chamber equipped with a septum for injection of sample and appropriate inlets and outlets to purge the chamber. The gas sensor can measure the differential resistance of the sensor and send data to a smartphone for monitoring in real-time by connecting with the Bluetooth module-integrating Arduino UNO board. The smartphone-based system provides excellent performance for the detection of VOCs, the sensor reaching an absolute stable state in 20 s after sample injection and with lower LODs of 0.9, 4.5, and 11 ppb, respectively, for diethyl ketone, acetone, and isopropanol, proving the high sensitivity of the sensor for measurement of these VOCs. Testing of the long-term stability of the sensor showed that even after three months, sensor sensitivity is similar to the first day's use [164].

4.3. Smartphone-assisted imaging

Smartphones have evolved into sophisticated portable devices with tremendous computing power, physical sensors, and networking capability. This enables the current generation to provide versatile platforms for a variety of biomedical applications, including cancer diagnosis. Smartphone-based imaging devices utilize image sensors within the smartphone's camera module that are sufficiently sensitive to support a wide range of diagnostic applications, especially in locations where staffing is limited and a rapid diagnosis is urgently needed. Add-on attachments or modifications of the built-in camera set-up can further enhance the image quality for diagnosis confirmation and rapid data sharing. This makes the whole diagnostic system attractive, affordable and beneficial to a large section of the population. Table 3 summarizes recent developments of smartphone-based imaging devices in cancer diagnosis.

There are multiple types of cancer that can be detected through images captured by smartphone. For example, oral cancer is a malignant neoplasia arising on the lips or in the mouth and which is one of the most common cancers in the world that lack a specific biomarker [181]. Non-melanoma skin cancer (NMSC) occurs mainly on sun-exposed sites of the body, is the most common malignancy among Caucasians, and its incidence continues to rise annually [182]. Cervical carcinoma, which can be noticeably visible in the cervical region, remains the second most common cancer in females worldwide, with an especially high incidence in LMIC [183]. The mortality rate from breast cancer in less developed countries in South America, Africa, and Asia is still increasing, partly due to a lack of access to state-of the-art diagnosis and therapy [184]. Thus, it is important to develop a simple, fast and reliable approach to cancer detection that can be applied worldwide. Hence, smartphone-integrated imaging systems are highly sought due to their effectiveness in primary cancer detection.

By implementing autofluorescence imaging (AFI) and white light imaging (WLI) on a smartphone platform, a dual-modality, dual-view, point-of-care oral cancer screening device was developed for high-risk

Table 3
Recent developments of smartphone-based imaging devices in cancer diagnosis.

Analytical Program	Special Lighting Condition	Reagent	Specimen	Accuracy	Sensitivity	Specificity	Ref
HRNet			Oral lesion	84.30%	83.00%	96.60%	[169]
NIH ImageJ, Python	X[ab]	5-aminolevulinic acid (ALA)-induced protoporphyrin IX (PpIX) fluorescence	Oral cancer lesion	-	~75%–100%	~75%–100%	[170]
Convolutional neural network (CNN)	X[ab]		Oral lesion	86.88%	85%	88.75%	[171]
Skin detection, Hierarchical lesion segmentation			Skin lesion	80.09%	89.09%	≥90%	[172]
Custom 3-layer CNN			Skin lesion	71.17%	67.67%	72.76%	[173]
VGG-16 CNN				76.67%	78.00%	75.97%	
Google Inception V3				81.00%	84.33%	79.06%	
Image processing, Synthetic Minority Over-sampling Technique (SMOTE) and without SMOTE			Skin lesion	SMOTE: 88% Without SMOTE:90%	SMOTE: 80% Without SMOTE: 55%	SMOTE: 90% Without SMOTE: 95%	[174]
CNN (for raw images) and CNN (for audio - sonification)			Skin lesion	DI: 87.8% SI: 74.8%	DI: 95.5% SI: 75.3%	DI: 57.6% SI: 71.4%	[175]
Matlab R2015a			Skin lesion	-	78.60%	84.60%	[176]
"Exam" app		Acetic acid (VIA) and Lugol's iodine	Cervical cancer	93.30%	-	-	[177]
RetinaNet		Acetic acid	Cervical cancer	94%	-	94%	[178]
VGG				92%		86%	
Inception-based models				91%		86%	
KNN		Acetic acid	Cervical cancer	78.3%	75.0%	80.3%	[179]
SVM				75.8%	63.6%	82.9%	
DT				74.2%	72.7%	75.0%	
Inception V3	X[c]		Breast cancer	98.104%	-	-	[180]
Inception V4				99.712%			
Modified inception MV4				99.748%			

Abbreviations.
[a] Fluorescent.
[b] White lighting.
[c] Thermal.

populations in remote regions with limited infrastructure, enabling early detection of pre-cancerous and cancerous lesions in the oral cavity (Fig. 8A). The images captured for AFI and WLI are synchronized with external LED illumination using a custom smartphone app. They are then uploaded to a cloud server for diagnosis by a remotely located clinician after viewing via a web-based app, and triage instructions are transmitted back to the device and passed to the patient. After training, validation accuracy of the network was 86.88%, with sensitivity and specificity values of 85% and 88.75% respectively, when compared to the gold standard of an on-site clinical diagnosis by an oral oncology specialist [171]. This smartphone-based system is a promising advancement for low-cost, portable, and easy-to-use autofluorescence imaging for oral cancer diagnosis, which can be improved with further images and device hardware improvements.

In order to determine whether artificial intelligence can close the gap in diagnostic accuracy of NMSC detection, a dual convolutional neural network (CNN) performance metrics analysis compared dermoscopic (DI) versus smartphone-captured images (SI). A unified malignancy classifier was built by combining a CNN for receiving raw images and predicting malignancy with a second CNN for processing sonification (image-to-sound mapping) of the original images (Fig. 8B). Images acquired by DI were compared to SI using the unified malignancy classifier, resulting in higher accuracy and sensitivity but not specificity. This indicates that CNN assessment of dermoscopic images improves NMSC diagnostics when compared to smartphone imaging, emphasizing the current advantage of dermoscopy over smartphone image-based telemedicine. CNN analyses do not reduce the previously reported difference in face-to-face diagnosis accuracy between dermoscopy and smartphone photographs, which appears to be inherent to the skin layer studied by the classifiers. When diagnosing with non-standardized smartphone teledermatology, clinicians and through them, patients, should be informed of a possible loss in sensitivity [175].

Visual inspection after application of acetic acid (VIA) and Lugol's iodine (VILI) is a cervical cancer screening approach that has recently been adopted in LMIC. However, this method remains subjective as its quality is affected by intrapersonal variants such as the depth of training and level of experience of the examiner, as well as external factors including the lighting conditions and the woman's cervical anatomy. Therefore, development of a smartphone-based imaging system could assist clinicians in the diagnosis of cervical pre-cancer. Biopsies of human papillomavirus-positive women's cervix were taken for VIA/VILI assessment using a smartphone with an app called "Exam", which was designed to obtain high-quality images and to classify them in the following sequence: native, VIA, VILI and post-treatment. The quality of the photographs was judged as adequate for diagnosis in 93.3% of cases by experts in coloscopy [177]. Hence, it provides good quality images for VIA/VILI diagnosis followed by classification in a patient database, which facilitates continuous clinical education and making them accessible to on- and off-site experts also. Therefore, this smartphone app may offer an alternative to coloscopy for cervical cancer screening in LMIC.

A new tool has been developed that is based on thermal imaging, deep CNNs (include modified model Inception V4-MV4), health apps on smartphones, and cloud computing for early detection of breast cancer with the use of Mastology Research with the infrared image DMR-IR database [178]. This was designed in a graphical user interface that links with the app to send thermal images from the smartphone to the cloud and to retrieve the suggestive diagnostic result from the cloud server (Fig. 8C). Different effects on the thermal images (blur, shaken, tilted, and flipping) were added to verify detection accuracy. After repeated experiments, the classification results of early detection of breast cancer, generated from the MV4, illustrated high accuracy performance of 99.748% [180]. It only takes 6 s to receive responses after successfully transferring diagnostic findings from the smartphone to the cloud and back to the smartphone using an AirDroid application. This smartphone-based system improves the efficiency of initial

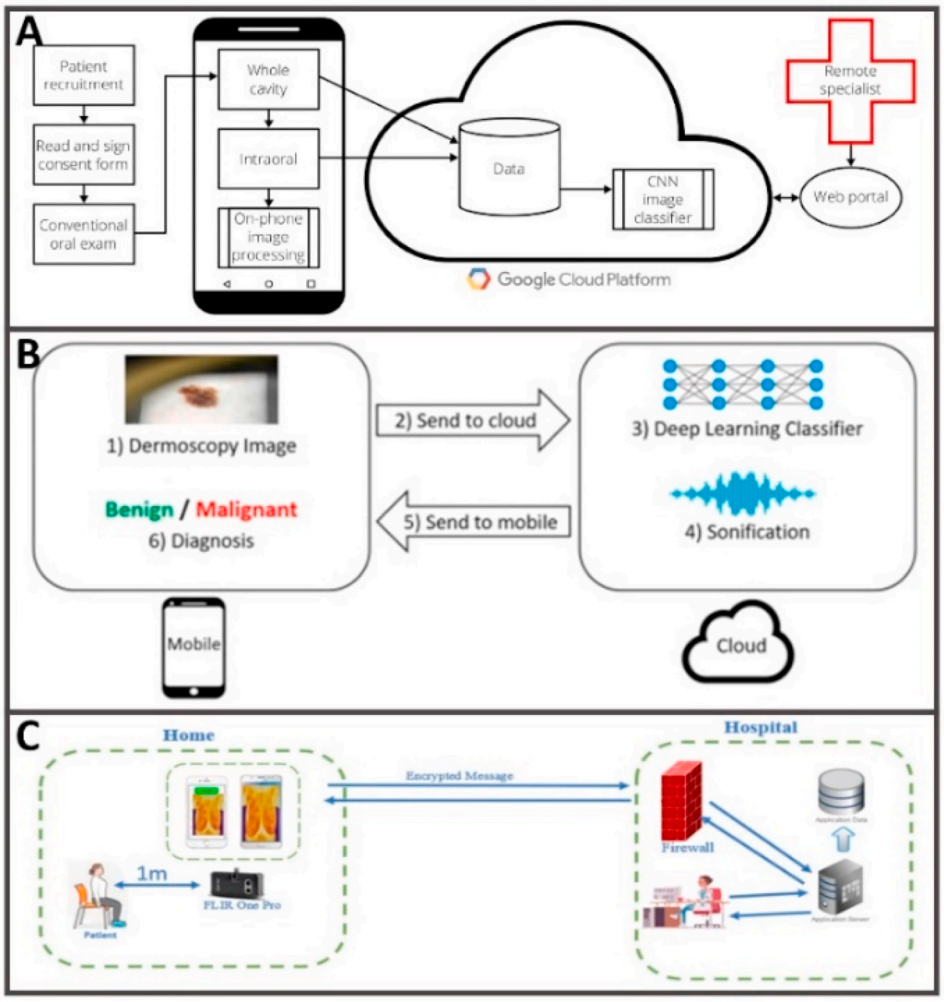

Fig. 8. Smartphone-based cancer imaging systems. A. Field testing workflow for smartphone-based oral cancer screening. Adapted with permission from Ref. [171]; B. Flowchart prediction process for non-melanoma skin cancer detection: a dermoscopy image is acquired by a smartphone and conveyed to cloud computing by a dedicated application. Pre-trained deep-learning and audio classifiers are combined to predict output findings. The final diagnosis is conveyed to the user as either a malignant or benign lesion diagnosis. Adapted with permission from Ref. [175]; C. Flowchart of self-detection of breast cancer based on a smartphone application with infrared camera. Adapted with permission from Ref. [180].

self-diagnosis, especially for remote areas and by immobile elderly patients, in addition to providing features related to health education, rapid response, and periodic follow-up for patients.

5. Perspectives

The most recent innovations in smartphone-based biosensing systems hold great promise for cancer diagnosis due to several pivotal benefits (summarized in Table 4). In comparison to laboratory-based analytical technologies, they are simple, portable, and cost-effective. These advances together offer enormous potential for improving cancer diagnosis and treatment, particularly in resource-limited areas. As a commercialized product, smartphones have a variety of valuable features, including a user-friendly operation interface, high-resolution image acquisition, data-processing capabilities, large internal memory, wireless connectivity, and excellent data transfer capability, which can be integrated in a POC test for mobile diagnostics outside of the laboratory. Smartphone-based mobile POCT applications will play a significant role in personalized healthcare, especially when fully integrated with information technology such as cloud computing, artificial intelligence, and machine learning.

In smartphone-based biosensing systems, smartphones currently perform key functions in optical imaging, such as image acquisition,

Table 4
A comparison of various smartphone-based sensing technologies for cancer diagnostics.

Method	Description	Advantage	Disadvantage
Fluorescence	Detects changes in fluorescence emission by an excited substance	High sensitivity, high specificity	Expensive fluorimeters, background interference, low stability
Colorimetry	Detects a change in light absorbance or reflectance	Simple process, rapid response	Poor accuracy, clear samples required, low stability
Electrochemistry	Detects a change in electron transfer during an electrochemical reaction	High sensitivity, high specificity, rapid response	Power supply required, environmentally sensitive
Imaging	Detects abnormal changes in different areas of the body through images	Simple process, rapid response	Requires trained personnel to interpret the results, background interference, latent diagnosis

data transfer, and data post-processing. However, the detection technique for optical-based biosensors is limited mainly to fluorescence and colorimetric because these platforms require a simpler process and are easy to downsize with acceptable sensitivity and rapid response. Yet, they are easily interfered with by different factors such as sensing materials and sample characteristics, leading to unexpected consequences such as low stability, background interference, or high costs. Hence, there is a need to develop more optical-based biosensors with diverse techniques for overcoming these difficulties.

External accessories have been utilized to increase the image quality for optical smartphone-based detection. However, further research is required to develop easy-to-use, lightweight, cost-effective, and even standardized or universal accessories. Using sophisticated image processing techniques, such as machine learning and artificial intelligence on smartphones with expanded computational capabilities, can enhance the accuracy and resolution of quantitative images, leading to improved biosensing sensitivity. Thus, artificial intelligence technology in smartphone software should be created and unified in order to operate as a universal app to analyze images and deliver data immediately. Bidirectional data transfer between the smartphone and the electrochemical analyzer can be accomplished through wired or wireless methods. To date, this frequently involves intricate circuit design for electrochemical biosensors, resulting in the smartphone serving only as a data receiver and analyst in electrochemical systems. Although electrochemical assays are favored for tumor marker identification at low LODs, only a few smartphone-based electrochemical sensing systems have been created, necessitating the thorough integration of smartphones into electrochemical systems.

Each year, much research is published about various technologies coupled with smartphones. However, these novel findings are yet to be translated into a commercial product because most clinical tests coupled with smartphone-based systems are still laboratory-centralized with multiple time-consuming steps. This raise concerns that smartphone-based technologies do not add significant diagnostic or scientific value but rather their potential is overestimated. Current smartphones are not built with health monitoring in mind. Consequently, they have limited functions in clinical practice due to a lack of attention to health monitoring. In order to improve the health sensing power of smartphones, scientists and manufacturers must collaborate to develop a set of "dedicated health sensors" that push the limits of existing sensors. This will necessitate working with dedicated hardware and then identifying the minimum requirements required to support the app. Due to smartphone heterogeneity, the different smartphone environments present a challenge to designing a universal health sensing system. An app that relies on built-in sensors of whichever smartphone model scientists chose for prototyping may not work on other smartphone models or software operating systems. Therefore, constructing transfer functions based on sensor specifications between different smartphone models may provide a solution.

Visiting the healthcare clinic ensures quality control of a patient's sample collection processes under the supervision of a professional practitioner, which is unavailable in a remote setting where a smartphone is used to collect information. Environmental conditions and the user's technical abilities can affect the sample, resulting in illogical results that are not indicative of their health. Hence, it is required to design automatic checks to analyze the ambient environment prior to data collection, as well as a classifier that determines if data is "valid" before passing it to the primary analysis component. Furthermore, real-time visualizations can be created to educate users on how to enhance data quality.

Clinical test results are typically difficult to understand for users without training. Results that are not within the normal range may not always indicate a health problem, but they may serve as a warning to be cautious. Furthermore, false positives and false negatives can have serious consequences for the patient, such as unnecessary stress or a missed diagnosis. All models have uncertainty limitations that impede decision-making. If smartphone-based health sensing apps are to be widely distributed rather than prescribed and supervised by expert clinicians, the process of generating a post-test probability should be as automated as possible. Based on risk factor data, apps should be able to calculate a pre-test likelihood. Machine learning models that "learn" how clinical parameters change over time can assist clinicians to identify high-risk patients.

6. Conclusions

With the advancement of the fields of computer technology and bioengineering, smartphones-based biosensors and imaging will become powerful and affordable diagnostic tools, facilitating comprehensive, daily health monitoring. Smartphone-assisted cancer diagnostics are an intriguing and growing topic for research and development. Such systems offer significant potential for achieving rapid, accurate, and cost-effective cancer diagnosis in resource-limited settings. Although it is envisaged that in the near future smartphone-based POCTs will improve personal healthcare, particularly cancer diagnosis, they are still too early in development to replace current methodologies for patient diagnosis. Nevertheless, with continuing improvement, the deep integration of smartphones in cancer diagnostic systems promises to be important for accurately and affordably diagnosing cancer, especially in remote areas, thereby promoting personalized cancer monitoring.

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CRediT authorship contribution statement

Linh Thi Phuong Le: Conceptualization, Writing – original draft. **Anh Hoang Quan Nguyen:** Conceptualization, Writing – original draft. **Le Minh Tu Phan:** Conceptualization, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing. **Hien Thi Thanh Ngo:** Writing – original draft. **Xing Wang:** Conceptualization, Writing – original draft. **Brian Cunningham:** Conceptualization, Writing – original draft. **Enrique Valera:** Conceptualization, Writing – original draft. **Rashid Bashir:** Conceptualization, Writing – original draft. **Andrew W. Taylor-Robinson:** Writing – original draft, Writing – review & editing. **Cuong Danh Do:** Conceptualization, Project administration, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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