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Best practices and current implementation of emerging smartphone-based (bio)sensors - Part 2: Development, validation, and social impact

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ABSTRACT

The amalgamation of computer-like capabilities and portability of modern smartphones has fuelled their implementation as detectors and interfaces in emerging smartphone-based (bio)sensors (SbSs) for e.g. healthcare, point-of-need, food safety, environmental science, and forensics systems. SbSs intrinsically carry great potential for consumer diagnostics, and future 'citizen science' approaches, which have far-reaching implications for the technological, legal, and ethical aspects associated with the research, development, and deployment of SbSs. In this review (part 2 of a pair of review papers), we evaluated the pertinent literature on issues concerning the development and validation of SbSs, and we address their potential social impact. Finally, insights gleaned are combined in a set of recommendations to guide future ethical, sustainable, and efficient research, development, and deployment of SbSs.

1. Introduction

Mobile phones were originally intended as a means of flexible telecommunication. Since then, technological advancement, the digital revolution, and constantly increasing user-demands have guided their transformation into modern smartphones. Smartphones no longer simply allow for making and receiving calls, but they also incorporate sophisticated operating systems, internal memory for data storage, global positioning systems, high-quality cameras, internet connection, and much more [1]. Given these impressive capabilities, smartphones are less like handheld and portable phones and more like convenient and compact computers [1,2]. The pervasiveness of smartphones is apparent in our daily life; their market penetration rate is constantly increasing, with the number of smartphone users forecast to reach over 6.6 billion in 2022 [3]. Beyond our everyday life, smartphones have also greatly impacted the analytical sciences by facilitating testing that would otherwise be restricted to centralized laboratories, using benchtop instrumentation, operated by trained personnel [4]. A major development has been the combination of smartphones and (bio) sensors to create smartphone-based (bio)sensors (SbSs); smartphones can acquire signals from connected (bio)sensors, process these signals into relevant results, and securely store or transmit the interpreted results to relevant parties [5,6]. As such, SbSs are highly useful for clinical analysis [7–9], food safety [10–12], environmental monitoring [13,14], and forensics [15], among other applications. Not only is this trend reflected in the scientific

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literature, but several SbSs have also been introduced to the market, demonstrating their commercial potential and the social and consumer demand for such devices [16,17]. The implementation of SbSs in the common place can be expected to contribute to the democratization of (analytical) sciences and technology, drive citizen science projects, and importantly, directly affect consumers by delivering relevant information, e.g., about their health or safety through SbS-based allergen [18] or toxins detection [19] in food commodities.

The road from SbSs research and development (R&D) to their commercialization and consumer adoption is long and ardous, with the majority of the process taking place behind the scenes, away from public scrutiny. These R&D activities are typically related to conceptualization, product and process innovation, concept adaptation to satisfy a specific application, performance assessment, upscaling, and more [20–22]. Notably, the (bio)sensing assay, including the (bio)sensing element, the transducer, and the smartphone-based detection, should all undergo extensive validation regarding the targeted application [23,24]. Additionally, all stages of SbS operation should be developed with the end-user in mind; for instance, if the device has been designed for use by a non-expert outside of a laboratory, any necessary sample preparation or collection steps should be as straightforward, fast, and as robust as possible [25]. Moreover, in establishing a novel SbS, scientific feasibility should be demonstrated while also considering the potential for social impact during deployment, as smartphones are an intrinsic part of our everyday routines [26]. Additionally, the potential of SbSs should be examined in terms of applicability in e.g., low-resource settings, to highlight their possible impact [27–29]. In literature, many reviews have been dedicated to collecting information on the technical development of SbSs, mainly focusing on electrochemical and optical SbSs [30–36]. However, the intricate relation between ethical considerations during the R&D and deployment of SbSs is rarely reported in the scientific literature. In this review, we discuss the best practices surrounding SbS R&D, the potential social impact of those devices, and to what extent such practices are currently implemented in scientific research.

The scientific publications on SbSs for analytical chemistry-related applications (and thus the general interest in SbSs development and use) show an increase over the years; the number of papers describing smartphone-based *analytical devices, optical (bio) sensors, electrochemical (bio)sensors, and mobile phone (bio)sensors* between 2016 and 2022 were plotted per year of publication (Fig. 1A). A further ranking of the SbSs-related publications based on specific terms related to the main aspects discussed in this review, i.e., the SbSs research and development, and the SbSs social impact (Fig. 1B), highlights the focus of this review. For the exact keywords searched, the inclusion and exclusion criteria and the detailed methods used to result in the number of selected publications, see the Supplementary Information. Briefly, peer-reviewed research publications were retrieved from the online databases of Web of Science, Scopus and IEEE Explore, covering the time span of 2016–2022. After discarding the duplicates, 886 articles were identified by the keyword search.

This publication is part of a pair of review papers. Part 1 [37] provided a comprehensive analysis of the technological advances in optical and electrochemical SbSs, specifically addressing the data acquisition and processing workflow. Additionally, in part 1, considerations related to privacy and data protection regulations regarding SbSs usage were reported. This review is focused on the R&D of SbSs and considers their sustainable design, development, and validation. Following this, the assessment of the wider impact of such SbSs on consumers is considered, allowing for an inclusive reflection on their implementation and potential value for society. Finally, the generated insights from this review are combined to propose best practices for future sustainable R&D of SbSs, and (assessment of) positive social impact, while minimizing potential negative impact.

2. Research, development, and validation of smartphone-based (bio)sensors

Ethical conduct in scientific work, and its applications, such as SbSs, is not a 'one-stop' box to be checked but should be interwoven in the entire process, from conceptualization to publication or commercialization. Ethical aspects concerning the R&D process can be split into relevance for the so-called internal and external domains [38]. The external domain focuses on how science impacts society, the economy, and the environment, and will be explored in more detail in Section 3. On the contrary, the internal domain focuses on scientific activities within the laboratory, including professional ethos of scientific conduct, research integrity, good research practice (GRP), research publication, education, and safety [38]. Moreover, during the R&D stage of SbS prototypes, validation

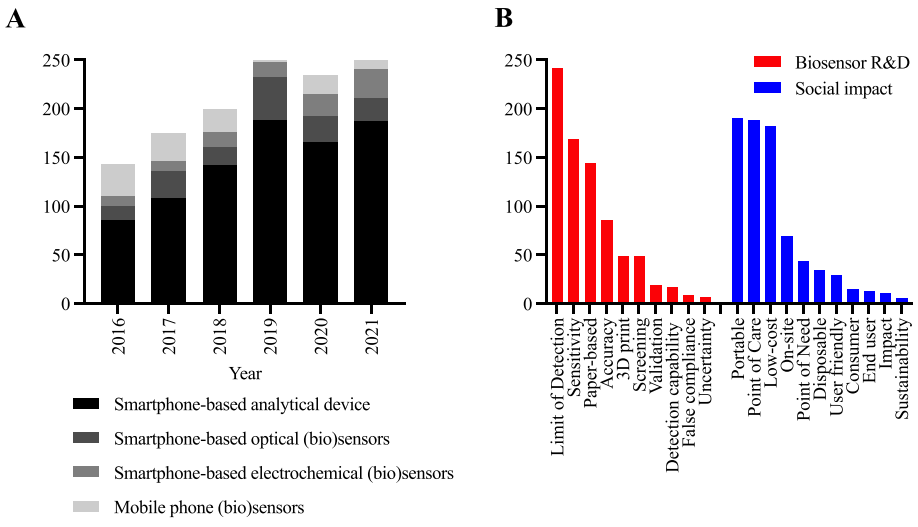

Fig. 1. Overview of the number of publications related to smartphone-based devices, (**A**) per search term, per year, and (**B**) per specific keyword related to R&D or social impact of SbSs.

studies should be carried out on developed tests in real or representative sample matrices to prove their performance and fitness-for-purpose. In addition to typical scientific R&D activities, social and ethical implications of R&D also need to be taken into consideration [38]. One crucial aspect is the sustainability of such research, which lies at the intersection between the internal and external domain.

2.1. Good research practice

Scientific research, which can be both fundamental and applicable/applied in nature, has to be conducted by upholding certain scientific, technical, and moral standards, summarized as Good Research Practice (GRP). While it is easy to agree upon the latter, it is more difficult to agree on what that means in practice. In an effort to harmonize GRP, the "European Network of Research Ethics and Research Integrity" (ENERI) (https://eneri.eu/codes-of-conduct/) [39] has collected 19 international and 28 national codes, guidelines, and recommendations related to research ethics and research integrity, thus providing a unique resource for researchers. Furthermore, the ENERI decision tree (https://eneri.eu/decision-tree/) [40] guides users to the relevant guidelines, codes, and other helpful resources, and assists researchers in contemplating ethical questions and challenges that could arise during a research project. However, harmonization efforts such as the ENERI project are not widely adopted, possibly because researchers and organizations are potentially unaware of their existence. Moreover, researchers, who are typically experiencing high work pressure to produce results, need to actively search for and implement these tools independently, further increasing the workload. The numerous codes, guidelines, and legislations pinpoint the challenges researchers and organizations face in implementing these tools; it is especially problematic for international and cross-disciplinary research projects, which might have different viewpoints or ethical standards. Additionally, ENERI lists relevant legislation related to research ethics (see Supplementary Information, Table S1). Finally, laboratories might opt for accreditation, such as ISO 17025, which aims at standardizing the processes to facilitate quality monitoring, leading to efficient research practices.

All EU-funded research projects must adhere to the European Code of Conduct (CoC) for Research Integrity [41] which describes professional, legal, and ethical responsibilities related to scientific and scholarly research. The CoC's core principles focus on GRP: reliability, honesty, respect, and accountability (see Table 1). Importantly, the CoC is regularly updated and allows for local/national implementation differences. Consequently, the descriptions of GRP are broad and open to interpretation, and there remains a risk of research misconduct and unacceptable R&D practices. The CoC describes research misconduct using the terms Fabrication, Falsification, and Plagiarism (FFP), as described in Table 1. However, when FFP occurs, individual organizations, institutions and corporations must device on how and whether they will act on research misconduct. Therefore, researchers (at an individual and institutional level) may be caught in a conflict of interest, where it could be tempting to purposefully overlook research misconduct for the sake of results and research output, project acquisition (funding), citations, H-index and/or university rankings, and career progression. As mentioned, the CoC is widely applied and accepted, but the ENERI project stresses the importance of implementing additional tools and actions at the international and national levels.

Evidently, the challenge is not to define GRP guidelines but to ensure that researchers are aware of and implement its best practices during R&D. Still, it cannot be overlooked that researchers are constrained to meet the expectations of funding bodies. These expectations are typically based on what was promised in the proposal prior to funding being granted by these organizations. Despite GRP guidelines being imposed by funding bodies, the competitive scientific funding and publishing landscape, as well as the requirements to list and meet deliverables for funding, put tremendous performance pressure on scientists. This pressure is likely to be a contributing factor to why FFP occurs in R&D. Recently, research frameworks such as Horizon 2020 and Horizon Europe (see Supplementary Information Table S1) have been actively implementing open science and FAIR data management, e.g., by requiring researchers to publish research results in open access journals. Likewise, these same funding bodies promote open science by requesting researchers to submit raw data files and codes alongside their manuscripts, to facilitate open, honest, and transparent publishing practices, and to advocate for publishing verifiable and reproducible methods/results. While this is indubitably desirable, it puts more pressure on the scientific community. While only 9/886 of the reviewed articles mentioned 'open-source', and 'open science' in the abstract or keywords, this does not provide the full picture; the reason for this is that open access articles, codes, and applications rarely mention this in their abstracts/keywords based on which the results were assessed. In reality, 226/886, i.e., approximately 25% of the reviewed articles were published as "open access". In general, an increased rate in open access publications has been observed since the beginning of the 2000s [42]. Especially in the field of biology and medicine the open access publication rate was reported to reach 50%, whereas, in engineering and computational sciences the percentage was three times lower [43]. Taking into consideration the multidisciplinary field of SbSs, a rate of 25% in open access publications, appears reasonable. Finally, it is worth mentioning that it was announced that by 2025, all USA federal funded research, must be publicly and freely available, which is expected to lead to further increase in "open access" publications [42].

2.2. Validation

The validation of screening assays is a fundamental aspect of R&D, as proper validation studies serve to enhance and support research integrity and ethics. Validation is a highly regulated methodology defined by specific, regularly updated national and international rules and guidelines. Validation is carried out to ensure that results are verifiable, reproducible, and that they adhere to the highest quality standards, one of the 'Do's' of GRP (see Table 1). However, validation is more than just a technical procedure to confirm that a method does what it claims. Scientific validation bridges the gap between science and society, as it facilitates and stimulates uptake into commercial or routine endeavours. Moreover, it fortifies trust in those methods, as this is the only evidence-based way of proving performance; from this perspective, one could argue that publishing a method without minimal validation, is to publish it without evidence. Fortunately, analytical journals increasingly insist on demonstrating the applicability of novel methods and approaches in real sample matrices, at relevant levels, benchmarked against the state-of-the-art.

While numerous validation regulations and guidelines exist, only 19 out of 886 articles mention *'validation'* in their keywords/abstracts. Of these, 11/19 focused on SbS for Point of Care (PoC) applications and 12/19 articles used an established reference method for benchmarking. Benchmarking the analytical performance of SbS against the standard methods and instrumentation they aim to replicate or improve upon during R&D, allows for meaningful comparisons between emerging and existing technologies. Different state-of-the-art technologies, such as polymerase chain reaction (PCR), chromatography, and spectrometry are typically used for benchmarking. For example, one of the reviewed

Table 1
Overview of Good Research Practice adapted from the European code of conduct for research integrity [41].

Good Research Practice				
DO's	Reliability	Honesty	Respect	Accountability
	• Reward open (e.g., open-source) and reproducible practices • Training in ethics and research integrity, ensure awareness • Seniors foster a culture of research integrity • Proper and conscientious use of funds; shared responsibility of researcher/university and funding bodies • Open, honest, transparent accurate publishing, avoid 'publication bias' • Reporting of results compatible to discipline specific standards, also verifiable and reproducible • Recognize and manage potential harms and risks • FAIR (Fair, Accessible, Interoperable, Re-useable) data management • Negative results are as valid as positive findings for publication and dissemination • Active participation in refereeing, reviewing and evaluation • Reviewers or editors with conflict of interest withdraw from involvement • Considering state-of-the-art during ideation			
DO NOTs	Fabrication	Falsification	Plagiarism	
	• Manipulating authorship or denigrating the role of other researchers • Re-publishing parts of own's previous research, including translations, without correct citation ('self-plagiarism') • Citing selectively to enhance own findings or to please others • Withholding research results • Allowing funders/sponsors to jeopardize the independence in research process, introducing bias • Unnecessarily expanding the bibliography of publication • Accusing another of misconduct maliciously • Misrepresenting research achievements, tampering with results and data • Exaggerating the importance and practical applicability of findings • (Misusing seniority to) encourage violation of research integrity • Covering up research misconduct or unacceptable practices • Supporting 'predatory journals', undermining quality of research			

studies reported the benchmarking of a SbS for the paper-based detection of COVID-19 in saliva samples against reverse transcription quantitative real-time PCR (RT-qPCR), by testing 105 saliva samples by both the SbS and by RT-qPCR, and found that the results matched in 98% of the cases [44]. On the other hand, when the target is a small chemical contaminant, the benchmark would likely be a chromatographic system, typically combined with mass spectrometry, for unequivocal identification and quantification. Below, the current implementation of validation in studies towards emerging SbSs is discussed, from the perspective of both non-medical, and medical screening SbSs.

2.2.1. Validation of non-medical screening devices

Globally, many regulatory and commercial laboratories are obliged to follow the standards for Good Laboratory Practice (GLP) which apply to non-clinical health and environmental safety studies following Directives 2004/9/EC and 2004/10/EC. From the perspective of validation of analytical procedures, an important organization upholding GLP is the Association of Official Analytical Chemists (AOAC); the AOAC is a globally acknowledged organization ensuring food safety, integrity, and public health. The AOAC brings together governments, industry, and academia to establish official standard methods of analysis focusing on the development, improvement, and validation of methods, including (binary) screening methods [45]. For a screening method to be validated under the AOAC Performance Tested Methods℠ (PTM) procedure, it must be used to test at least five different matrices spiked with at least five analyte concentrations. Moreover, an evaluation of the stability, robustness, variation, and reproducibility of the method must be carried out [46]. Scientists and companies of approved PTM test methods are licensed to use a certification mark that confirms to users that an independent assessment has verified that the test method's performance meets an appropriate standard for the claimed intended use.

In the EU, the EC sets validation regulations such as the newly adopted commission regulation 2021/808/EU [47], which replaces 2002/657/EC [48] and 98/179/EC [49] (see Supplementary Information Table S2). The 2021/808/EU [47] regulation amended sampling requirements, laboratory analysis methods, and laboratory results interpretation. The specific validation criteria for screening methods for official control purposes are outlined by Commission Regulation 2014/519/EU [50]. Both regulations 2021/808/EU [47] and 2014/519/EU [50] are relevant for SbSs, which are typically used in a screening capacity. Screening methods can be used to screen for target analytes above a particular threshold concentration, referred to as the screening target concentration (STC). The STC is typically set at or below the maximum residue limit/tolerable daily intake level for these targets [47]. This leads to a detection capability (CCβ) at which only $\leq$5% false compliant, i.e., false negative, results remain. To be considered a screening assay, a method needs to allow detection of the target analyte in the sample below the STC with a given certainty; a certainty of $\geq$95% is considered fit-for-purpose [47]. Importantly, regulation 2021/808/EU [47] mandates that only methods that have been validated in a traceable manner to have a false compliance rate of $\leq$5% (β error) can be used for screening purposes. The false negative rate can be reduced by performing the tests more than once (<0.25% in theory if the false negative is caused by random errors [51]) or by combining multiple different types of tests. A screening result is either 'negative' or 'suspect'. Whenever a sample gives a 'suspect' result, it must be re-analyzed by a confirmatory method to confirm the screening method's result [47,50]. Although confirming 'suspect' results lessens the sustainability of a method as more resources are required to re-analyze the results, it also means that false positives are not so problematic compared with false negatives, as false positives are recognized by the confirmatory method. Despite the importance of the false compliance rate (β error) for method validation, only 9/886 articles mention '*false suspect*' or '*false negative*' results. However, the search term(s) '*limit of detection*' (242/886), '*sensitivity*' (169/886), '*detection capability*' (17/886), and '*accuracy*' (86/886) were more frequently mentioned, demonstrating some effort to assess the performance of the developed

sensors.

Screening method validation is needed to demonstrate fitness-for-purpose. Briefly, the minimal requirements for validating a screening method are: (*i*) distinguishing whether the screening method is qualitative (i.e., binary - yes/no response) or semi-quantitative (multiple levels of concentration, e.g., low, medium, high), (*ii*) determining if the target analyte needs to comply with a regulatory limit and establishing the STC, (*iii*) analyzing ≥20 different blank samples and spiking these ≥20 different blanks with the target analyte at its STC (verified by confirmatory method), (*iv*) preparing a calibration curve (semi-quantitative screening methods) around the STC, (*v*) measuring the ≥20 blank and ≥20 fortified samples over different days and in random (blind) order [47,50,52].

Several screening assays have been validated according to the EU/AOAC regulations and guidelines, but these examples do not incorporate an SbS [53–59]. An example of a fully validated commercial screening assay was developed for on-site mycotoxin detection and includes a smartphone application for quantitative analysis [60]. The platform can measure at or below EU-regulated maximum levels and has been validated using certified reference material (CRM), i.e., a material/matrix previously characterized by a validated process with a specified uncertainty [61,62]. Using CRMs means that the obtained data can be directly compared with confirmatory methods through assessment of sensitivity and false compliant rate of the platform. According to the AOAC guidelines, CRMs are a requirement for the validation of screening assays, yet CRMs are unavailable for many substances, which might explain why only 3/886 articles mentioned '*certified reference materials*' or '*CRMs*' in their abstracts/keywords. Other examples of validated commercial screening assays include the gluten devices that will be discussed in more detail in the Case Study.

2.2.2. Validation of in-vitro diagnostic medical devices

In-vitro diagnostic (IVD) medical devices are used for analyzing human samples to guide clinical decision-making. The term IVD includes laboratory-developed tests, PoC devices, sample collection accessories, and assay consumables such as reagents and test kits. In the USA, the Food and Drug Administration (FDA) classifies medical devices, including IVDs into Class I, II, or III according to the level of regulatory control that is required to assure the safety and effectiveness of the device [63]. Similarly, in the EU, IVDs including PoC and self-tests, are split into risk-based classifications (Classes A-D) as defined by the 2017/746/EU *in-vitro* diagnostics regulation (IVDR), which recently replaced the IVDD directive 98/79/EC [64]. In Annex I of the IVDR, the GSPR (General Safety And Performance Requirements) describes the proof that the device is suitable for its intended purpose and risk management class, evidence of biological and electrical safety, risk reduction measures, the accuracy of the device, and instructions for intended use [65].

When searching the abstracts/keywords of the 886 unique articles, 188 articles were related to '*point of care*' or '*PoC*' testing; yet only 6 of these 188 articles mentioned '*validation*'. Additionally, among these articles, only 9/886 mentioned '*self-testing*', including '*self-monitoring*' and '*self-assessment*', categories. In both categories, glucose sensing was a popular research topic, as 53 of the 188 articles ('*PoC + self-testing*') were focused on this analyte. Interestingly, for glucose sensing devices, there is a dedicated tool available for checking the clinical accuracy of self-monitoring of blood glucose against: the gold standard Clarke Error Grid Analysis [66]. Nevertheless, only 1 of those 53 articles mentioned the use of this tool to benchmark the clinical accuracy of their biosensor in their abstracts/keywords [67].

As discussed in Section 2.2.1., currently, validation is infrequently described in the literature, and the same is true for IVDs devices. Validation proves that the developed method is performing correctly, and it is a good fit for the intended purpose. Since the implementation of the IVDR (May 26, 2022), companies commercializing IVD SbSs within the EU have to thoroughly validate their products to a high scientific standard, so it is expected that validation studies will be published more regularly in the coming years. It is still unclear whether the new IVDR will encourage researchers in academia to include more validation activities to strengthen their proof-of-concept IVDs, or whether the IVDR will broaden the gap between R&D in academia and industry.

2.2.3. Validation of smartphone-based detection

Validation procedures, both for medical and non-medical applications, are mainly focused on the biosensing part of the SbS and no guidelines exist on the validation of the smartphone-based read-out of the screening method. As stressed in a recent review on the critical assessment of trends related to screening and confirmatory analytical methods [68], the above-described minimal validation requirements should be met for SbSs to achieve acceptable analytical performance as screening assays. In addition to these requirements, when a (bio)sensor is intended to be used with a smartphone as a detector, developers should validate the (bio)sensor using different smartphone models, brands, and operating systems to ensure the total assay-smartphone system is robust and smartphone-independent. Otherwise, the SbS would be limited to a single system, which would likely become outdated [69–72]. Likewise, during their R&D, emerging optical SbSs should be validated under at least the testing conditions reported in the protocol but would benefit from testing, e.g., under different lighting, temperature, and humidity conditions [60], or with different smartphone interfaces to characterize the impact on the performance and robustness of the screening assay.

2.3. Limit of detection and (sources of) uncertainty

The keyword '*limit of detection (LoD)*' was used frequently in the pooled literature (242/886); however, the definition of this parameter varies from article-to-article. For example, in lateral flow immunoassays (LFIAs) the LoD is often estimated by visual (qualitative) observation, which differs from a (semi-quantitative) smartphone-based estimation of the LoD [73], which is typically calculated from the noise of blank measurements, or from a calibration curve [59]. According to the EU directives (2014/519/EU and 2021/808/EU) the LoD of screening methods is related to the detection capability (CCβ) of the method [47]. Here, it becomes evident that the definition and estimation of the LoD largely depend on the purpose of the analysis method. For example, in the case of screening assays, the LoD needs to be below the STC or MRL/tolerable daily intake of a certain target analyte, such as mycotoxins in food products. However, for an IVD such as the SARS-CoV-2 self-tests, the LoD needs to be as low as possible to detect the disease in the early stages of infection and minimize its spread.

Uncertainty is another key parameter used to characterize an analytical method. Despite its importance, the term '*uncertainty*' only appeared in the abstract/keywords in 3/886 of the reviewed articles [73–75]. However, this term is used interchangeably with other terms that will be discussed in this paragraph. Uncertainty provides an estimate of the range of values that a measurement result could fall within; essentially, knowledge of a measurement's uncertainty implies increased confidence in the validity of a result [76]. Several potential sources contribute to analytical uncertainty, related to (i) the equipment that is used, e.g., (uncalibrated) pipettes or balances, (ii) the samples (e.g., sampling, sample variation), and sample types (e.g., matrix effects, interference) that are tested, (iii) the environmental conditions under which the

measurements are made, and (iv) (incorrect) approximations or assumptions and other (random) variations. Moreover, uncertainty goes hand-in-hand with *'error'* which was mentioned in the abstract or keywords of 22 of the 886 articles; error can be unpredictable and uncontrollable (random error); predictable and constant (systematic error), or can arise through human mistake or instrument malfunction (gross error). The Case Study, provides an example of the implications of LoD and uncertainty for gluten screening assays.

2.3.1. Sample (handling) uncertainty - gross error

Uncertainty related to human mistake (gross error) [77] is especially problematic when sample preparation and analysis are performed by non-trained users, such as for (IVD) self-tests. For SbSs that have been designed for use by non-experts, the intended use becomes difficult to control, although incorrect use can be somewhat minimized by providing end-users with clear user instructions, as will be discussed in more detail in Section 3.4.4. Typically, devices can be developed to include some controls to at least identify incorrectly performed tests, such as the control lines used in LFIAs [77], or including an on-chip blank measurement for quality assurance [78]. Lastly, after the measurement has been made, the result interpretation can lead to increased uncertainty and decreased trust for the end-user originating from factors such as non-standardized data analysis [79]. For example, smoothing and scaling operations that are used to extract relevant information need to be consistent across measurements in order to be able to compare data from different measurements. Moreover, these operations can tamper with the data so that the results become biased [80]; but it should not be neglected that any data manipulation must be explicitly disclosed (as discussed in Part 1 of this pair of review papers [37]). Consequently, the data analysis itself can lead to variation in the results and increase uncertainty.

2.3.2. Instrumental uncertainty - systematic error

During measurements, uncertainty can also be introduced by factors such as instrument (e.g. the camera of SbSs) resolution and noise, heterogeneity of samples due to poor homogenization, a large measurement range that reduces sensitivity, and day-to-day variability, because of instrumental instability [81]. These factors relate mainly to systematic error and originate from the intrinsic properties of either the sample (e.g. material complexity), the method (e.g. replicates and measurement range), the device (e.g. resolution and noise), or all three. Even though some of these factors cannot be mitigated (e.g. the complexity of the targeted commodity), still most of these factors can be controlled or predicted during the characterization of the device to reduce uncertainty, such as minimizing the instrumental signal to noise, or optimizing the number of replicates (e.g. the amount of data the smartphone internally analyses to interpret the SbS result) and the measurement range for the specific analytical method.

2.3.3. Environmental uncertainty - random error

Uncertainty can be introduced when making measurements in non-controlled settings (random error), such as during the use of devices on-site. Here, parameters such as temperature, humidity, and contamination are more challenging to control than they are for laboratory-based tests. As a result, the day-to-day variability of the measurement is likely to increase, affecting the uncertainty and, thereby, the performance of the device. Another essential contributor to a method's uncertainty related to random error is sample variability caused by biological variation [82]. Sample variability can be especially problematic when the target analyte is a compound that is usually only present at low concentrations (e.g., a biomarker); or when interfering substances present in the sample matrix stimulate signal suppression (or enhancement), which in turn could lead to false negative or positive results. For example, clinical samples can greatly vary, since every individual has a unique physiology; likewise, agricultural samples that have been cultivated by different procedures, or food samples that have been processed under different conditions, can lead to inconsistencies in analytical measurements, due to differences in the matrix.

2.4. Sustainability during R&D

Within any field of research, the concept of sustainability can be directly linked to the 2030 Agenda for Sustainable Development (United Nations general Assembly A/RES/70/1) [83] which focuses on ensuring that present needs are met without compromising the needs of future generations. This definition is broad, but it is evident that sustainability is intertwined with social, environmental and economic aspects. The need for sustainable SbS devices has been exemplified by the unprecedented uptake in self-testing during the COVID-19 pandemic (discussed in the **Case Study** of part 1 of this pair of review papers [37]).

An important aspect related to sustainability in a R&D context is the amount of plastic that is consumed by laboratories [84–86]. Single-use plastics including pipette tips, gloves, weighing boats, tubes, flasks, and cuvettes, are indispensable to R&D laboratories. Accurate numbers on the global consumption of single-use plastics by the scientific community are unavailable. However, in one study, the amount of plastic waste from scientific laboratories was estimated to be around 5.5 million tonnes, which is equal to 83% of the plastic that was recycled worldwide in 2012 [84]. In order to tackle this issue, a Laboratory Efficiency Assessment Framework (LEAF) has been established that provides an independent standard for 'good environmental practice' in labs. Here, the three R's (Reduce, Re-use and Recycle) described in Table 1 are crucial [85]. Another current source of plastic waste/use within the scientific community can be attributed to prototyping. Considering the trend in using *'3D printing'* during the R&D process (49/886), it cannot be ignored that most ex-prototypes end up in the waste, even though the additive manufacturing process leads to little waste other than the parts themselves. Therefore, emerging SbSs could be developed by using more sustainable reusable or recyclable materials for prototyping in R&D laboratories. To make 3D printing in the lab more sustainable, researchers could move towards using filaments made from recycled materials and purchase filament recyclers that can break down ex-prototypes into reusable filaments [87], thereby fulfilling the RRR principles of LEAF.

Another consideration of the R&D of SbSs from a sustainability perspective is the use of animal materials. Directive 2010/63/EU aims to move towards animal-free testing, especially during the development of immunoassays [88]. In the EU alone, it is estimated that close to one million animals are used for antibody production each year [89,90]. Therefore, the EU Reference Laboratory for alternatives to animal testing (EURL-ECVAM) was established in 2011. In 2015–2017, the EURL-ECVAM reported a 65% increase in animals used for monoclonal antibody production [89]. This number is likely now much higher owing to the mass development of immunoassays for the detection of COVID-19 [91,92]. This increase in antibody production emphasises the demand for animal-driven affinity reagents and suggests that moving towards more ethically sound and sustainable alternatives will be challenging for the scientific community [93]. Indeed, the keywords *'immuno'* (115/886), *'antibody'* (41/886), and *'antibodies'* (32/886), appear in many abstracts/keywords of the pooled literature, suggesting that animal-derived affinity binders are frequently used in the development of SbSs.

Despite the commercial availability of non-animal derived

biorecognition elements, so far there has been very limited uptake of '*aptamers*' (4/886), '*affirmers*' (0/886), and '*molecularly imprinted polymers*' (1/886) in SbSs; this could be due to lack of (familiarity or trust in the) quality of these alternatives [89]. To promote the sustainable development of emerging SbSs, R&D scientists should consider alternative sensing substrates/materials and implement animal-free binders such as '*recombinant*' (6/886) antibodies discovered using phage display.

3. Social impact of smartphone-based (bio)sensors

SbSs could be developed to address social needs, regardless of whether this is driven by moral or economic considerations; fundamentally, all aspects of science and technology should serve society, especially when scientific research has been publicly funded. Thus, to benefit society, research should have a moral basis, and ethics in the internal and external domains should be considered. As discussed in Section 2, the internal domain focuses on the ethical aspects of SbS R&D in the laboratory. In contrast, the external domain covers ethical considerations of how the developed SbSs influence society, the economy, and the environment [38]. This section focuses on the potential social impact of SbSs and how such impact could and should be assessed.

3.1. Social impact assessment and mitigation of negative social impact

Social impact (SI) refers to any significant change that addresses a social issue. SI does not need to be positive, but can be considered negative, for instance if it is driven by ulterior motives, such as financial gain [94]. SI can be targeted at the individual or at the community level to promote cultural, health, and lifestyle changes, which can improve peoples' quality of life [95]. SI is the foundational pillar of many social enterprises and charities, whose goal is to induce positive changes in society or in the environment. An example of such is the non-profit organization "diagnostics for all," which strives for positive SI by promoting accessibility to medical diagnosis through the creation of affordable and easy-to-use PoC tests to improve the lives of people in low resource settings [96]. However, the situation for the commercial market is more complex; many manufacturers benefit from consumers' herd mentality, i.e., the desire to follow social trends or norms when purchasing popular products; therefore, a brand's SI might be (falsely) advertised to appeal to consumers' herd mentality and achieve a sales target. Such is a recent notorious example in which the public and investors were misled about the SI of novel diagnostics by false claims regarding the analytical potential, which could not be substantiated, and which has now led to criminal charges [97,98].

To prevent a negative SI, it is important that researchers and companies do not overstate the capabilities of their SbS and that they are transparent with the limitations regarding the strength and weaknesses of their inventions (see Table 1), which should come to light during R&D and proper validation studies. Additionally, social impact assessment (SIA) methodologies have been employed since the 1970s to better understand social change, which can be used at every stage of future planning, for anticipating areas of potential impact, and for implementing risk mitigation strategies to minimize negative SI [99]. To acquire large R&D grants, proposals must appeal to funders/investors. One way to do this is by presenting a SIA that focuses on the practical application of strategies striving for SI within research organizations, universities, and commercial companies [94]. Traditional examples of SIA include surveys and questionnaires, workshops, community meetings, studies, advisory committees, and checklists. Conversely, digital examples of SIA applicable during the R&D phase include online tools such as the Product Impact Tool (https://productimpacttool.org/) which guides the impact assessment of commercial and non-commercial products [100], the Constructive Technology Assessment (CTA; https://cta-toolbox.nl/) toolbox that lists different tools for technological assessment [101], and the Responsible Research and Innovation (RRI; https://rri-tools.eu/) toolkit, which assists researchers in selecting the most fit-for-purpose RRI tool to implement [102].

Misrepresentation of the science underlying diagnostic devices, in combination with malicious intent, counterfeiting, and fraud, can further lead to negative SI. In 2010, the WHO reported that 8% of all IVD medical devices in circulation are fake [95]. Examples of counterfeit diagnostic tests include reselling pregnancy tests as HIV tests or selling expired tests which can lead to devastating effects for consumers and an overall negative SI [103]. A recent study demonstrated that SbSs could be used to monitor counterfeiting of diagnostics by embedding unique optical security codes onto nitrocellulose membranes or into microfluidic devices, which can be decoded by a smartphone camera, facilitating authentication of the test [103]. Such an approach, which tracks counterfeit products through the supply chain using blockchain, undoubtedly contributes to a positive SI. Still, such security comes at a cost to the developer, so a balance should be struck between what is profitable for the company and what is helpful for society.

3.2. Impact of smartphone-based (bio)sensors

The economic, environmental, and social impact are intrinsically interlinked. In many countries, researchers are legally required to submit an environmental impact assessment (EIA) for any new projects above a certain threshold in terms of financial resources, deliverables, and duration [95]. The EIA evaluates potential human-health impacts, socio-economic impact, and sustainability of a proposed project. Moreover, while financial profit is of pivotal importance to any company, the same cannot be said for SI, as SI is neither mandatory nor directly dictated by the companies, but instead driven by morality.

3.2.1. Commercialization and impact of smartphone-based (bio) sensors

For commercial biosensors, the line between social improvement and profit is thin. One could argue that the predominant motive of emerging SbSs is financial gain because of the massive market size and financial growth for biosensors, which is predicted to reach 41.8 billion USD by 2028 [16]. However, clinical [104–106], environmental [107–109], and food-safety related SbSs [110–114], strive to solve social problems and provide people with PoC or PoN devices, leading to decentralization and democratization of healthcare systems [44], as well as of environmental, safety and security laboratories. The need for quick and personalized analysis is evident, as exemplified by the COVID-19 pandemic [44,115], but also as a response to food contamination outbreaks [116]. In such cases, it can be assumed that the SI of SbSs is positive for the overall population, even if there is a financial motivation underlying it. Still, the road from SbS development to commercialization and potential SI is arduous. As discussed in Section 2, significant effort is needed to transform a prototype SbS into a device that is ready to be scaled up for mass commercial production, and it is even more challenging to develop a SbS that is simultaneously profitable, affordable, and that has a positive SI [117]. Additionally, lack of involvement of the end-user earlier in the R&D phase can complicate a consumer-operable SbS from reaching the market. So, despite their global potential for positive SI, these challenges might explain why few SbSs have penetrated the market [5] compared to the number of proof-of-concept SbSs reported in the literature.

3.2.2. Environment and impact of smartphone-based (bio)sensors

The social impact of SbSs is associated with the environmental impact; SbSs should positively influence the environment, or else, be sustainable. One way to assess sustainability is by a life cycle assessment/analysis (LCA). The LCA model assesses the environmental impact associated with all stages of product development, from raw material acquisition, to production, packaging, usage and all the way through to disposal [118]. The disposable parts of SbSs are considered cradle-to-grave products owing to their lack of reusability; SbSs often consist of disposable, non-recyclable parts to prevent cross-contamination during analytical measurements [119]. Disposability negatively affects the sustainability and positive SI of these devices from an environmental perspective. The term 'sustainability' was mentioned in 4 out of the 886 reviewed articles, whereas 'disposable' was mentioned 34 times, indicating that for SbSs, disposability might be considered more than sustainability.

Of the four articles mentioning sustainability, three exploited 'paper-based' biosensing approaches. Paper-based (bio)sensing is convenient for on-site analysis as the paper is made of cellulose, a natural material that is recyclable, and biodegradable [120]. Therefore, SbSs using paper-based assays are typically considered more environmentally sustainable and promote a positive SI. Out of the 886 reviewed articles, 144 mentioned the term 'paper-based' in the title, abstract, or keywords showing that many SbSs use paper as a substrate. While paper might be considered a sustainable substrate, it cannot be overlooked that its production requires vast amounts of energy, contributes greatly to deforestation, and is a major cause of water and air pollution; despite being recyclable, more than 25% of landfill mass is paper [121]. Likewise, nitrocellulose, a highly flammable substrate produced by treating cellulose with a sulphuric/nitric acid mixture to substitute −OH groups with $-NO_3$ groups, is often considered sustainable and is a major component of many biosensors such as LFIAs. Yet ecotoxicological studies on the production of nitrocellulose report that discharging its delignification, bleaching, and nitration effluents into the water can be toxic for marine organisms [122]. Alternatively, textile-based and thread-based sensors have been employed the last years in various applications, often incorporating electronics and biosensing elements [123–125]. In any case, SbSs are not solely composed of paper-based materials. Typically, paper-based assays such as LFIAs or other paper-based microanalytical devices (μPADs) are contained within a plastic cassette; sometimes, the cassette has a security purpose and contains a traceable QR code that links a result to a test, or otherwise, the cassette might just offer structural support. Different types of biodegradable plastics could also replace conventional plastics, leading to a more sustainable SbSs, though, the incorporation of biodegradable plastics in end-product applications is yet to be broadly adopted [126,127]. To move away from plastic housings, alternative materials such as cardboard should be considered. In an attempt to make pregnancy testing more sustainable, one commercial company has recently launched a biodegradable pregnancy test; the assay, which is FDA approved, is flushable and fully compostable leading to an environmentally-friendly end-product (bioassay) that enables end-users to discretely manage their reproductive healthcare [128]. Examples like this indicate that sustainability is an option, especially for paper-based diagnostics, and that increased effort is needed by the scientific community to push for diagnostics with a lower environmental impact.

In addition to carrying out many similar functions compared with laptops, smartphones promote (tele)communication. Although smartphones can encourage social interaction, they are also negatively associated with lower rates of physical activity and addiction in adolescents [129]. The dramatic improvements in smartphone cameras and other features mean that consumers are increasingly dependent on their smartphones, as they are increasingly used in daily life [130]. Considering that ~90% of the global population owns or has access to a smartphone, the electronic readout for SbSs might be regarded as a sustainable detector [131]. At the same time, these continuous technological improvements result in consumers regularly upgrading their smartphone models, meaning that these devices rarely reach their lifetime limit, instead being discarded in a drawer or landfill. Smartphones are comprised of scarce earth materials (e.g., for the chips and batteries), and hazardous materials and rare and finite resources make their fabrication unsustainable [132]. From an environmental perspective, the premature disposal of smartphones is problematic and contributes to a negative social and environmental impact, because of their production practices [133]. Likewise, discarding a smartphone as soon as it becomes 'outdated' could cause issues from an SbS perspective; if an assay has been optimized and validated using a particular device, it may not be compatible with newer smartphone models. Additionally, not all smartphone brands and models will be compatible with a specific biosensor due to differences in operating systems, camera dimensions, or software updates. Still, it is unlikely that consumers would buy a smartphone only for its use as a standalone SbS, and in that sense, the combination of novel (bio)sensing approaches with products that are already in-use might be considered more sustainable than developing and producing dedicated read-out devices that can be used only for the sensing application.

3.3. Cases of social impact assessment of smartphone-based (bio) sensors

To date, no concrete "SIA" for SbSs has been reported in the abstracts/keywords of the 886 pooled articles. One interpretation of this could be that SIAs are more relevant in the long-term after the SbS has penetrated the market, often years after a scientific publication. Searching in the literature using alternative terms that might indicate some level of impact assessment, shows that scientists make use of the terms 'user-friendly', 'consumer oriented', 'improve health', 'citizen science', 'end-user', 'impact', 'questionnaire', and 'survey' for 67 out of the 886 publications. Often, publications about SbSs claim user-friendliness and affordability without any evidence that non-trained users have been involved in the development process or without having any price estimation of the developed SbS. Moreover, terms such as time-efficient and straightforward can be perceived as entirely subjective.

In a recent publication, the Industrial Buyer Innovation Adoption (IBIA) model was used to assess the market penetration of an electrochemical SbS for heavy metal detection. The IBIA model is based on the integration of business-to-business (B2B) consumer behavior theories and technology adoption models. The assessment identified several key parameters for predicting the penetration of the SbS by industrial manufacturers in Thailand. These parameters related to the potential sellers, buyers, the environment, internal organizations, internal people characteristics, and the invented technology. The study highlighted that the adoption of the SbS would be limited in this specific case, because Thai manufacturers are legally obligated to use conventional heavy metal detection strategies [134], indicating that regulators can hinder (or promote) potential SI of SbSs.

In another publication, the development of an SbS for hemoglobin detection was reported, which was deployed and tested by end-users in four in-field trials in India [135]. In this study, users recorded a smartphone image of a paper-based assay, and an on-device algorithm processed the results with no further user intervention. The field-deployment study revealed the assay to be user-friendly, enabling minimally trained frontline workers to carry out the test.

Finally, the usability of an electrochemical patch-based SbS was assessed by asking end-users to complete a survey about their expectations and requirements of such a sensor [136]. The survey revealed that users preferred recording and reporting results via a smartphone compared with traditional centralized reporting, demonstrating the public's preference towards a SbS. Furthermore, findings from the questionnaire indicated that involving the end-users in the development process could highlight new paths or confirm selected approaches [136]. While these models and strategies can help developers to assess the impact of emerging SbSs, their implementation is still completely voluntary. As a result, only an incomplete story about the actual SI in a broad context of many SbSs is obtained.

3.4. Social impact of smartphone-based (bio)sensors with respect to the ASSURED criteria

The potential SI of emerging SbSs can also be discussed in the context of the ASSURED (Affordable, Sensitive, Specific, User-friendly, Rapid and Robust, Equipment-free, and Deliverable to end-users) criteria defined by the WHO [137–139]. The ASSURED criteria can be extended to include "real-time connectivity", and "ease of specimen collection", leading to the REASSURED criteria [140]. In both cases, though, sustainability which is a key factor for a positive (environmental) impact, is notably missing. SbSs rank highly according to ASSURED criteria, which might explain their plethora of applications reported in the scientific literature [141].

3.4.1. Affordability

There are several advantages of using SbSs from an economic perspective, including affordability, portability (requiring less laboratory space), miniaturization (resulting in lower reagent consumption), and digital data storage leading to better data management (compared with data management on paper). SbSs are generally characterized by cost-effectiveness, personalized data handling, and autonomy compared to conventional laboratory equipment [142]; 182 of the 886 articles mention the keyword 'low-cost', and 20/886 'affordable' in their abstracts. A standard LFIA is estimated to cost between $0.10 and $3.00 per test, making them an excellent choice as part of SbSs for affordable diagnostics [117]. Still, while individual LFIAs can cost as little as $0.10, depending on the immunoreagents used, the overall price of the testing kit (including LFIA casing, buffers, disposable pipettes, and packaging) can be considerably higher. One example of a cost-efficient SbS was reported for an electrochemical food allergen detector; the test costs less than $4 and takes only 10 min to analyze allergens, saving money and time [143]. Yet, this is the estimated material cost, and it is possible that a commercial version of this test would cost more for the consumer. Crucially, the overall cost of SbSs is greatly increased when multiple single-use (and individually priced) capsules/tests are required to perform an analysis. Still, the affordability of emerging SbSs might be further improved by careful reflection on the cost-efficiency of these devices during the R&D stage, which could strengthen their SI.

3.4.2. Sensitivity, specificity, and robustness

Many on-site and field-deployable (bio)sensing methods are based on visual readout by the human eye. However, results based on human vision are vulnerable to incorrect user interpretation owing to perceptual differences, jeopardizing the sensitivity of the (bio)sensor [144]. As discussed in **Part 1** of this pair of review papers [37], variation in ambient lighting and other environmental conditions can be largely compensated for by using physical (light-shielding attachments) or digital (algorithms) solutions to standardize acquisition conditions. However, the subjective nature of visual detection and resulting user-to-user variability contributes to measurement uncertainty and could lead to misinterpretation of results, especially when testing a sample close to the detection limit of the biosensor [145], or when a sample is highly concentrated [119,146]. In such cases, using a smartphone for readout facilitates proper interpretation of the result [147]. In addition to the potential for (semi)quantification, SbSs have the essential advantage of recording, pinpointing, transmitting, and storing results for later re-evaluation if necessary.

The added value of using a smartphone for correct result characterization has been recently demonstrated with a commercial assay for domoic acid, where the result was more clearly read aided by a smartphone using a 3D-printed attachment and image processing with ImageJ than by simple visual interpretation of the result [148]. Similarly, as mentioned in **Part 1** [37], it has been demonstrated that using smartphones for image capture combined with artificial intelligence (AI) processing can improve result interpretation and specificity. In one example, smartphone-AI-aided App interpretation of the LFIA result was used to correctly characterize 3344 individual COVID-19 self-tests instead of using visual interpretation [149]; in addition to improving the reliability of COVID-19 self-tests from 11 different companies, by eliminating the need for human interpretation of the results, the smartphone App uses instructional videos and simplified schematics to teach the users how to perform a valid test [149]. Another benefit of using smartphone readout is the possibility to recognize and mitigate false-negative results. Testing highly contaminated samples by sandwich format LFIA can lead to the so-called 'hook-effect' [150], which cannot be reliably identified by the naked eye alone. The hook-effect can lead to false-negative results even in a laboratory [151], but it has been demonstrated in a selected number of LFIAs that this high antigen concentration effect can be identified experimentally by smartphone video processing [152,153].

Use of SbSs as screening assays shifts the responsibility of acquiring the result to the end-user, which might be considered both an advantage and a drawback [154]. On the one hand, mishandling biological material and incorrect labeling could lead to an incorrect diagnosis in a official laboratory setting, which might otherwise by avoided with a robust SbS [154]. However, as discussed earlier in Section 2.2., validating an SbS in terms of accuracy, with a strict acceptance range of ±95%, signifies a 5% uncertainty of the result in a well-performing SbS [47]. In the case of an end-user non-compliant result that falls within this 5% range, this creates doubt about who has the liability of a negative outcome (i.e., the end-user, the developer, or the authorities defining the validation rules). Therefore, it is crucial to understand and explicitly stress that SbSs are not designed to be used as confirmatory tools but rather as quick and easy screening methods, which first require confirmation before any (life-influencing) decisions are made based on their results. As mentioned in Section 2.2., another important consideration is the involvement of an end-user in SbS validation because the repeatability, selectivity, and LoD of the methods can be greatly influenced by how the test is carried out and by whom it is carried out (see also Section 3.4.4) [147].

3.4.3. Equipment-free

To meet the ASSURED criteria, tests should be 'equipment-free'. As discussed in Sections 2.4 and 3.2., many portable biosensors are composed of disposable plastic parts that are rarely recyclable after use [155]. Although these materials are unsustainable and result in a negative SI of an SbS from an environmental standpoint, these disposable parts can also promote a positive SI because their use ensures that less (laboratory) equipment is required and the potential for cross-contamination is greatly reduced.

Of course, SbSs can never be completely equipment-free

because they require a smartphone to enable data collection and for semi-quantification of results [119]. Yet, with over 6 billion active smartphone users worldwide and a global market of more than 400 billion USD in 2022, and estimated to reach over 700 billion USD [3,156,157], many people already own these devices, meaning that using a smartphone as a detector in SbSs should not introduce any additional financial or 'equipment' burden on the end-user. Despite being pocket-sized, smartphones can be used as a power source (for plug-in potentiostats), for data collection (recording photos), and for subsequent analysis (via Apps), making them a multipurpose tool in a single piece of equipment.

3.4.4. User-friendliness and delivery to end-users

SbSs are often considered user-friendly devices, especially compared to classic instrumentation used for the same analysis in a laboratory setting. So, SbSs are not only aimed at professionals in a particular field, but also at individuals, i.e., untrained laypersons [142]. Regarding use by professionals in the food safety sector, for instance, SbSs can improve food quality and safety-related needs [147] and help address the increased demand for on-site analysis [158]. However, the connection to untrained end-users is more intricate, as discussed in Section 2.2.1. and the Case Study that follows; validation regulations and guidelines assess a screening method related to analytical performance characteristics, yet these regulations do not stipulate that the envisioned end-user should be part of the validation procedure. This is remarkable since many SbS screening methods are reportedly developed for the non-trained user. Despite many articles claiming SbSs are user-friendly, there are few reported examples where end-users are actually included in testing the device during the development stage. Evidently, SbSs that are 'portable' (192/886) and 'miniaturized' (47/886) are most appropriate for user-friendly on-site applications. Moreover, portable analysis is an emerging trend and it is a positive development that there are already existing SbSs that facilitates on-site analysis by end-users. However, even commercial systems that report an "easy to use" and "on-site" nature, might still require steps, such as grinding, weighing, and pipetting manually, with laboratory equipment decreasing their actual user-friendliness [60]; the next challenge for emerging SbSs will be combining them with low-cost, miniaturized, and user-friendly sample preparation devices that simplify the total analysis workflow.

One strategy for improving the user-friendliness of SbSs is to include step-by-step instructions for how to carry out a test, and such information can be text-based, pictogram-based [78], or even video-based [149]. Providing clear instructions should ensure that the test is performed correctly but does not necessarily assist the user in interpreting the test result, which can be complicated, especially in the case of (semi)quantitative or multiplex tests. Transmitting the test results to relevant trained stakeholders for analysis minimizes the potential of misinterpretation of the result by the end-user [159], but can increase the time-to-result, which might be considered detrimental to the user-friendliness of the device. When very rapid testing and data analysis is needed, the most user-friendly approach would be to have an on-device algorithm for result interpretation. In a recent study, an application was developed using the smartphone camera and built-in image processing to accurately track haematocrit levels. The PoC system was able to accurately measure (within 1%) haematocrit in whole blood samples 20 s after application, with minimal input from the end user, facilitating rapid healthcare interventions when necessary [160]. In general, the situation is more complicated when multiple targets need to be detected within a single sample at low levels. In this case, multiplex tests can help improve user-friendliness, as the user does not need to carry out several tests for multiple analytes [161–164].

The results from emerging SbSs should be in-line with and benchmarked against those obtained by validated lab-based methods (see Section 2.2. and the Case Study). This comparison allows for proper assessment of the SbSs analytical performance and usability compared to established methods and instrumentation. Examples of benchmarking an SbS against laboratory instrumentation are the development of an SbS for detecting zearalenone, which was benchmarked against a confirmatory liquid-chromatography-tandem mass spectrometry (LC-MS/MS) method [33], or the SbS for blood cell counting, which produced results comparable to a high-end benchtop impedance spectrometer [165,166]. However, the benchmarking approach allows for performance evaluation, only involving well-trained individuals. Alternatively, user involvement during development and validation provides the most accurate interpretation of the user-friendliness of an emerging SbS. As such, researchers conducted a usability assessment on an SbS for pulse oximetry measurements. The study involved 320 patients of diverse backgrounds and evaluated the users' influence on the accuracy and precision of the obtained result [166]. While the test met FDA/ISO standards, it was found that small differences in how the user carried out the test did influence the result. For instance, a slight decrease in precision was seen when patients needed to hold their finger on the sensor for 2 min. Such findings underline the necessity of user involvement during the development, and perhaps validation stages for an SbS to ensure it is deliverable and useable by the intended end-user.

3.5. Accessibility of smartphone-based sensors

3.5.1. Potential social impact of smartphone-based (bio)sensors in developing countries

The increased use of smartphones is also evident in limited resource settings. For instance, in Sub-Saharan Africa, 55% of the population uses smartphones [164]. For this reason, SbS applications have increased potential for positive SI in low-resource or rural settings where SbSs can increase the accessibility to analysis that is otherwise restricted to centralized laboratories. 'Mobile health' or 'mHealth' (53/886) applications, are healthcare practices/applications performed by using mobile devices and are supported by the WHO. As such, mHealth applications carry a significant SI, providing access to healthcare for the least privileged through guided self-testing, long-term monitoring, and real-time reporting of results to clinicians, enabling rapid response in overwhelmed health care services [131].

SbSs provide a measurement tool for accurate and reliable diagnostics of human diseases in high-risk areas of the world, where infections such as HIV, hepatitis, malaria, and other neglected tropical diseases (NTDs) are prevalent, but access to advanced diagnostic laboratories is limited. These tools can assist individuals, clinicians, and policymakers in analyzing and tracking emerging public health issues (see **Case Study** in part 1 of this pair of review papers [37]). For instance, SbSs have been developed for the quick self-diagnosis of HIV [167,168], Dengue [169], and Zika infections [170], enabling timely interventions and prevention of disease transmission and treatment. Another example of an SbS for remote monitoring used a fluorescent microfluidic microscopic system to detect Salmonella in contaminated commodities, facilitating on-site food safety monitoring [171].

Despite smartphone coverage increasing by the year, many rural communities in remote areas still lack access to an internet network, which most SbSs require for data handling and processing. As discussed in **Part 1** of the review pair [37], SbSs that enable off-line data processing could promote accessibility. For example, in Uganda, 22% of the population live over 5 km from a medical center making centralized healthcare challenging. Moreover, 32% of

people do not have access to mobile network coverage, preventing decentralized diagnosis with SbSs using online data processing [164]. Therefore, an SbS implementing offline data handling can promote access to decentralized analysis in areas where secure internet access is not widely available.

3.5.2. Potential social impact in diagnostics for elderly individuals

Another important consideration regarding the SI of emerging SbS is accessibility and inclusivity; SbSs must be designed to be useable by as many individuals as possible. To be inclusive, SbSs should be operable by individuals regardless of age, educational background, affluence, language, or disabilities; likewise, practical barriers, such as sample preparation or data processing, should be simplified to the greatest extent possible to make these devices accessible [172].

Since the 1960s, portable electrochemical glucose meters have improved the quality of life of many people who have diabetes [173]. It has been demonstrated that regular remote reporting of results using SbSs can improve patients' outcomes [174]. Older individuals tend to use their smartphones for various social and non-social reasons, and contrary to adolescents, elders are not associated with problematic smartphone usage [175]. At the same time, elders generally suffer from more debilitating health-related problems. In this context, emerging SbSs aimed at elder individuals might improve life expectancy and quality for millions of people, and provide an alternative mechanism for the self-management of chronic disease [176], but this area has yet to be fully explored. For this reason, SbSs should always be designed considering the end-user; for example, SbSs intended to be used by the elderly population should include enlarged icons/buttons, read-aloud options for fine-print privacy policies, and step-by-step guidelines for ease of use.

4. CASE STUDY: validation and user-assessment of smartphone-based sensor for gluten

Celiac disease affects up to 1% of the global population and is characterized as a systemic autoimmune disorder triggered by ingesting foods/beverages (such as wheat, barley, and rye) containing gluten [177]. Individuals with celiac disease must stick to a strict, life-long, gluten-free diet. To protect celiac individuals, EU regulations 2013/609/EU and 2014/828/EU, and FDA regulation 78 FR 47154, stipulate that the label “gluten-free” can only be used on a food packaging/menu when the product contains less than 20 ppm gluten [178,179]. Despite the importance of labeling food commodities, it could still introduce a severe risk to consumers with celiac disease; the labeling reflects concentration, thus, the absolute ingested amount of gluten depends on the quantity of food consumed. In this context, the cumulative consumption of “gluten-free” labeled products could surpass the tolerance level of the celiac individual, thus causing severe health risks for the consumer [180]. On the other hand, the threshold of total gluten consumption per day is 10 mg for adults with celiac disease [177], so the “gluten-free” label is rather vague; two food commodities of 10 ppm and 20 ppm gluten each will be categorized both as gluten-free, but the first permits for 1 kg consumption, and the later only for 500 g. In those terms, self-testing with (semi)-quantitative SbSs, could further support the dietary requirements of celiac individuals.

Examples of AOAC validated biosensors for gluten detection include a competitive [181] and a sandwich enzyme-linked immunosorbent assay (ELISA) [46]; both tests detect gluten below the 20 ppm regulatory limit [182]. However, these validated methods are laboratory-based tests which do not use an SbS and are not designed for the consumer. In comparison, a portable smartphone-linked gluten detection device (based on proprietary antibodies) has been commercialized for gluten detection; the test is consumer-oriented and incorporates a smartphone App to allow results to be shared with other users [183]. Third parties evaluated the consumer-focused gluten detection device by testing 13 different gluten-free foods spiked on a weight-by-weight basis with six concentrations of gluten (5–100 ppm); foods were tested with the device and benchmarked against the above-mentioned AOAC validated gluten-specific ELISAs. The sensor was 100% effective at detecting gluten in samples containing 20-30 ppm gluten, 87.5% at samples containing 20 ppm, and 75.9% at samples containing 10 ppm, but below this level, the sensor became less reliable, indicating that it helps detect around the regulatory level [184]. In addition, a demonstration of the device performance assessing detection sensitivity, reproducibility, and cross-reactivity was carried out using a comprehensive list of foods [183]. Interestingly, this in-house validation dissected the errors (31 errors in 447 tests; 6.9% error) reported by the device to determine whether they were potentially avoidable. Of these, 13 errors were caused by slow strip development, ten by improper mixing, five because the extract was not adequately ejected, and three because of an inadequate volume of buffer for LFIA development. Notably, the device alerts the user to the error with a warning message on the device screen so that they know the test is unreliable and should be discarded and repeated.

Recently, the portable consumer-operable gluten sensor was subjected to a quality assessment study by end-users, namely adults, and adolescents, with celiac disease [146,185,186]. Some of the main user feedback included remarks on the device attracting unwanted attention during usage, the physical difficulty associated with using the capsules, the cost of the single-use capsules ($5), requiring multiple single-use capsules to test an entire meal, and the variability between users and sample types, leaving the user to question the test's accuracy. Despite the negative attributes, users felt more secure when consuming the gluten-free-marked foods and appreciated the compact size of the device [146,185,186]. One study concluded that the sensor had variation between different users, as well as between the sample types being tested, highlighting the necessity to improve user knowledge on the importance of sampling, the testing limitations of the device, and how to perform the test so that gluten can be reliably detected by consumers [185]. Additionally, in one study, more than half of the participants ($n = 30$) could not recall the device's testing limitations, which could lead to incorrect sampling and result interpretation [186]. Moreover, when the test gives a positive result, the consumer does not know if the food tested contains 30 or 10,000 ppm gluten. While there might be barriers for companies or researchers to subject their SbS to such extensive testing, the output is immensely valuable, as it helps to identify weaknesses and pinpoint areas for improvements, but it also stimulates user involvement and transparency, which can promote user trust in a device.

5. Perspectives & proposed best practices for the development of emerging smartphone-based (bio)sensors

The design and fabrication of SbSs is a joint effort from multiple technological and scientific disciplines. It should be ensured that SbSs intended for use by the public have a biosensor component that is actually useable by the target consumer. Usability can be aided by creating clear instructions on how to use the device in simple language/pictograms, through tutorial educational videos, and by developing robust assays that can accommodate a certain degree of user error. However, before this can be accomplished, biosensors must be meticulously validated during the R&D phase. Validation must be carried out by scientists in the laboratory to

ascertain its analytical performance characteristics. Following initial laboratory validation, the biosensor should be validated on-site/at the PoC/PoN by technicians or clinicians with some minimal training on how to perform the test. Finally, SbSs intended for consumer use should ideally be validated on-site/in-field by the target user groups to gauge if they are used correctly by these users and to identify any shortcomings that need to be overcome before a wider release. While such extensive validation and market research is essential for commercializing SbSs, especially for IVDs, it should also be implemented by researchers developing SbSs for proof-of-concept/or academic purposes. Keywords such as 'user/or consumer friendly', 'PoC' or 'PoN', 'portable', and 'on-site' are commonplace in articles about SbSs. Yet these same articles rarely report testing the developed SbS with the intended end-users or even testing the SbS outside of the laboratory - raising the question as to whether these buzzwords are being used appropriately without proof that they have been tested.

Developers of emerging SbSs should be stimulated to carry out SIAs before and after the SbSs creation to maximize their potential positive social impact, while minimizing negative impact. Much in the same way as data management plans have become the norm, these SIAs could become an important scientific contribution as part of grant applications for academic research, publications, in the early stage of a research project, or for investment pitches for commercial companies to ensure the sustainable development of SbSs and reward sustainable research practices.

It is important to promote more sustainable solutions for the future development of emerging SbSs. As such, aiming to deliver high quality results in a timely manner, in the highly competitive scientific landscape is challenging. Technologies such as additive manufacturing undoubtedly speed up the prototyping of SbSs, but it cannot be overlooked that creating several iterative prototype designs generates energy costs and plastic waste. Where possible, prototype components for SbSs should be 3D-printed using more eco-friendly and sustainable materials made from recycled, recyclable, or biodegradable materials – this is particularly important for disposables and less critical (but still desirable) for the reusable parts. Moreover, many assays, even those reported as paper-based (e.g., LFIAs/μPADs), come housed in plastic cassettes, making them less sustainable. Surely, alternatives, such as cardboard-based casing could better contribute to a positive social and environmental impact. At the same time, the sustainability of SbSs might be compromised by the need to develop new attachments for each smartphone model. Creating attachments that are universal across all major smartphone models would be beneficial in terms of sustainability, but also because a universal attachment would be easier to validate and benchmark against existing methods.

To move towards consumer operable analytical chemistry, developers of SbSs are encouraged to consider the end-user at all steps of the design and R&D process by investigating topics such as whether the SbS should work in an on-line or off-line capacity to enable consumers in remote areas; the sustainable design of the SbS (implementing GRP); how and to which standard(s) the SbS will be validated; whether the device is useable by the intended end user; what the expected SI of the SbS will be, and how it will be assessed. By reflecting on such issues early in the R&D process it is anticipated that more sustainable, intentional, and intelligent SbSs will emerge. In order to realize the full potential of SbSs, the next step is improving access to testing by moving these applications out of the lab and into the field/on-site/at the PoC/PoN by developing SbSs which are fit-for-purpose for the intended end-users, with integrated sample preparation as required. As such, emerging SbSs should be considered in the context of who their intended users are (e.g., scientists vs. consumers), where they will be used (e.g., in resource-poor vs resource-rich settings), what they will be used for (e.g., for PoC vs PoN), and how their data will be handled to customize them to meet these specific needs.

Author contributions

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Declaration of competing interest

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Data availability

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

Abbreviations

(RE)ASSURED	(Real-time connectivity, Ease of specimen collection), Affordable, Sensitive, Specific, User-friendly, Rapid and Robust, Equipment-free, and Deliverable to end-users
App	Application
AI	Artificial Intelligence
AOAC	Association of Official Analytical Chemists
B2B	Business to Business
CE	Conformitè Europëenne Mark
CRM	Certified Reference Material
CoC	Code of Conduct
EC	European Commission
EMA	European Medicines Agency
ENERI	European Network of Research Ethics and Research Integrity
EEA	European Economic Area
EU	European Union
EURL-ECVAM	European Union Reference Laboratory for alternatives to animal testing
FFP	Fabrication, Falsification and Plagiarism
FAIR	Findability, Accessibility, Interoperability and Reuse
FDA	Food & Drug Administration
GDPR	General Data Protection Regulation
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice

GRP	Good Research Practice
GSP	Good Scientific Practice
GSPR	General Safety and Performance Requirements
IVD	In-vitro diagnostic
IVDD	In-vitro diagnostics directive
IVDR	In-vitro diagnostics regulation
IBIA	Industrial Buyer Innovation Adoption
LEAF	Laboratory Efficiency Assessment Framework
LFIA	Lateral Flow Immunoassay
LCA	Life Cycle Assessments
LOD	Limit of Detection
LC-MS/MS	Liquid chromatography - tandem mass spectrometry
MRL	Maximum Residue Level
NTD	Neglected Tropical Disease
PTM	Performance Tested Methods℠
PoC	Point of Care
PoN	Point of Need
PCR	Polymerase chain reaction
QR	Quick response
R&D	Research & Development
RRI	Responsible Research & Innovation
STC	Screening Target Concentration
SbS	Smartphone-based sensor
SI	Social Impact
SIA	Social Impact Assessment
ISO	The international organization for standardization
WHO	World Health Organization

Appendix A. Supplementary data

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