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Review Article

Electrochemical paper-based devices: When the simple replacement of the support to print ecodesigned electrodes radically improves the features of the electrochemical devices

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Abstract

Paper-based electrochemical (bio)sensors have emerged as highly attractive analytical devices for their superior sustainable features, such as avoiding the use of polyester as support and the reduction of waste, being incinerated after use. However, paper-based electrochemical (bio)sensors have recently demonstrated further advantages, including the simple combination with vertical microfluidics and their use as a reservoir to deliver smart electrochemical (bio)sensors able to i) contain the reagents, ii) preconcentrate the target analyte, and iii) synthesize the nanomaterials inside the paper network. Furthermore, these devices have demonstrated their ability to overcome the limitations of the other printed electrochemical sensors in the measurement of entirely liquid samples by detecting the target analyte in the aerosol phase or solid sample, without the additional sampling system. These achievements highlight their valuable and varied advantages in the sensing sector.

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Reagent-free, Reservoir, Nanomaterial synthesis, Vertical microfluidics, Lateral flow, Office paper, Porous paper, Gas phase, Solid samples, Multiple analyses.

Introduction

Nowadays, sustainability is one of the most important concepts and it drives activities in several sectors namely environment, society, and economy [1]. Chemistry pioneered a vision of sustainability with the introduction of the 12 principles of Green Chemistry in early 1998, establishing the main benchmarks to reduce the impact on the environment [2]. However, Analytical Chemistry further follows this route with the 12 principles of Green Analytical Chemistry reported by Galuszka et al., in 2013 [3] and with the 12 principles of White Analytical Chemistry established by Nowak et al., in 2021 [4]. In this overall scenario, electrochemical sensors are well configured, being able to i) analyze the matrix on-site using low-energy equipment, ii) carry out organic-solvent-free measurements, iii) minimize the waste produced for the analyses, and iv) supply rapid, sensitive, and accurate analyses. However, to render electrochemical sensors more sustainable, scientists over the last decade have explored the use of paper to create smart and ecodesigned electrochemical (bio) sensors. Generally, paper-based electrochemical sensing tools have gained huge attention from the scientific community and industrial sectors, considering that:

1. the first paper-based electrochemical was conceived by Henry's group in 2009 and it has been highly cited with a number of citations higher than 1000 [5];
2. these devices are a close fit with the criteria of RE-ASSURED established by WHO which describe an ideal diagnostic test to be used in resource-limited settings, where RE-ASSURED means real-time, ease of specimen collection, affordable, sensitive, specific, user-friendly, rapid, equipment-free, **deliverable to those who need it** [6];
3. the increased importance of the point-of-care devices used directly at home by patients, as highlighted in 2016 by the World Economic Forum with the sentence "*Healthcare in 2030: goodbye hospital, hello home-spital*" [7];
4. the global paper diagnostic market is forecast to reach USD 10.69 billion by 2027, fueled by the increasing use of paper-based testing kits due to the ever-increasing request for low-cost and disposable quick diagnostic solutions for healthcare and environmental applications [8].

The huge interest from the scientific community has also been highlighted by an increasing number of reviews on the topic of paper-based sensors [9–24]. Furthermore, the investigation of papers on the development of sensing tools that has spread to several sectors through diverse disciplines [25–27], highlights how the use of paper is establishing itself as a benchmark in several sectors correlated to electrochemical paper-based (bio) sensors. Herein, I provide my opinion related to:

- the choice of office paper *vs* porous paper for developing electrochemical paper-based (bio)sensors;
- the selection of lateral *vs* vertical microfluidics for producing sensitive and accurate electrochemical devices for target analyte detection in the complex matrix;
- the use of paper as a reservoir to deliver smart electrochemical (bio)sensors by containing the reagents, preconcentrating the sample, and synthesizing the nanomaterials inside the paper network;
- paper-based electrochemical sensors to detect the target analyte in aerosol phase or solid sample without the additional sampling system; providing a review that compares the different uses of paper, beyond state of the art.

Office paper *vs* porous paper for developing electrochemical paper-based (bio)sensors

Compared to commercially available printed electrodes based on polyester or alumina support, paper-based electrochemical devices using chromatographic paper as support, allow for the exploitation of the porosity of the paper to manage the flow of the solution without the external pump, further avoiding the problem of the bubbles that are usually encountered using the classical microfluidic.

Beyond the easy management of the flow of the solution, the filter and chromatographic papers [28–36] are able to treat the sample, retain the particle retention, and store the reagents. However, it is important to highlight that the diffusion of the analyte is completely different compared to the analysis in drop using the office paper-based printed electrode (Figure 1a) [37], affecting the sensitivity of the analysis. Furthermore, in the case of immobilization of the immunological chain or DNA/PNA sequences onto a porous paper-based device, the incubation time for several hours of the working solution as well as the several washing steps can influence the robustness of the device. In that case, the use of office paper is to be preferred because it confers more robustness to the sensor, and to further improve it, the wax can also be printed under the electrochemical cell. Thus, the choice of the support depends on the configuration of the device, taking into account that the combination of porous paper with the filter paper is also usually employed in the case of origami paper-based electrochemical devices.

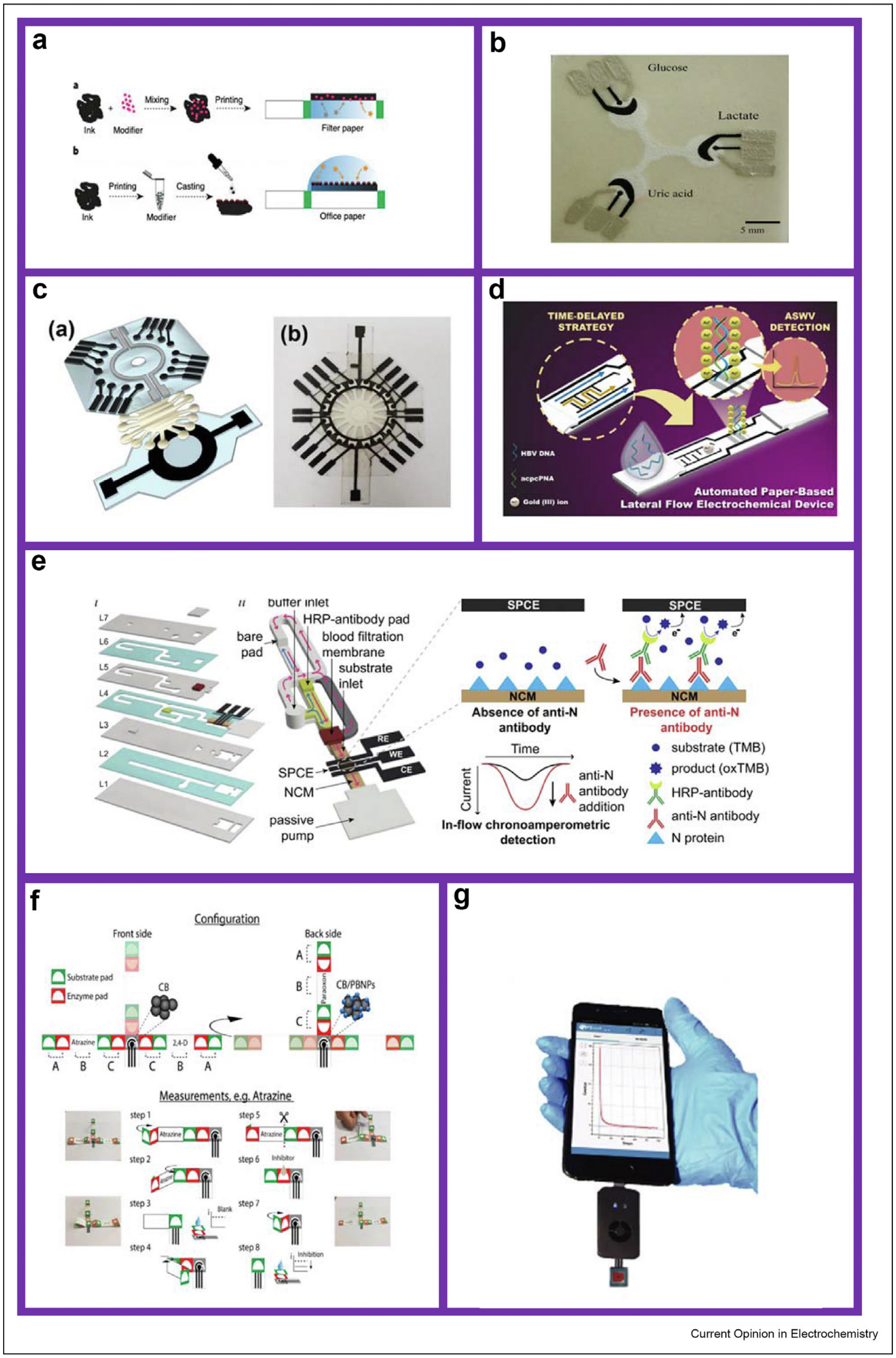
Regarding the modification of the working electrode with nanomaterials, in the case of electrodes printed onto porous paper, usually the bulk modification is to be preferred by adding the nanomaterial to the ink during the printing step, while in the case of electrodes printed on office paper, the drop approach is usually employed (Figure 1a). However, we recently demonstrated that the modification with drop-casting can also be used in the case of office paper-based electrodes, when the solvent for the dispersion is made up of dimethylformamide/water [38]. These recent results can extend the use of the drop-casting method also in the case of porous paper-based electrochemical (bio)sensors, further boosting the use of nanomaterials in the design of paper-based electrochemical sensors.

Lateral *vs* vertical microfluidics for producing sensitive and accurate electrochemical devices for multiplex/automated measurements and detection in complex matrices

The paper-based microfluidic was established by lateral flow configuration within the development of immunochromatographic devices. Lateral flow is used to manage the flow for the reaction of varying reagents including enzymes, antibodies, and DNA sequences at different times. The first paper-based electrochemical biosensor reported in the literature allowed the multi-analysis of serum sample by adding the sample in the center of the electrochemical cell, the serum moved through lateral microfluidics towards the three different biosensors, accomplishing the measurement of glucose, lactate, and uric acid (Figure 1b) [5]. To further improve the multi-analysis, the sample was loaded in the middle of electrochemical devices made up of 8–16 channels for high-throughput analysis (Figure 1c) [39]. The versatility of the paper was demonstrated by creating several different configurations to avoid any washing step, rendering the management of the multistep analyses simple. For instance, a fully-integrated device was developed for nerve agent detection by creating the device using double strips for the monitoring of enzymatic activity in the presence and the absence of the inhibitor [40]. A delayed channel was created by printing a zig-zag channel (Figure 1d) [41] to manage the flow of different reagents, avoiding the washing steps and boosting the reaction of the redox probe after the hybridization with the target analyte. Another approach relies on a hybrid system constituted of polyester-based channels with paper-based reservoirs. By using stacked layers of hydrophilic polyester and double-sided adhesive films, a passive microfluidic circuit was obtained to automate the steps for detection of anti-SARS-CoV-2 nucleocapsid protein antibodies directly in the blood (Figure 1e) [42].

The vertical microfluidic in the electrochemical paper-based devices was another choice for the development of smart electrochemical devices. One of the first interesting approaches was reported by Crooks' group

Figure 1



a) Working solution and modification procedure using paper-based electrochemical devices fabricated with porous paper or filter paper. Reproduced from Ref. [37] with permission of Springer Nature. **b)** Paper-based electrochemical biosensor for the multiple detection of glucose, lactate, and uric acid. Reproduced from Ref. [5] with permission of ACS. **c)** Multi-analysis of glucose, steps for device layer assembly and photography of the system. Reproduced from Ref. [39] with permission of Elsevier. **d)** Automated lateral flow using wax-printed barrier. Reproduced from Ref. [41] with permission of ACS. **e)** Hybrid microfluidic for the detection of antiSARS-CoV-2 nucleocapsid protein antibodies directly in the blood. Reproduced from Ref. [42] with permission of ACS. **f)** Vertical microfluidics in an origami device for pesticides quantification. Reproduced from Ref. [45] with permission of Elsevier. **g)** Vertical microfluidics in an origami device for butyrylcholinesterase activity measurement using smartphone-assisted potentiostat to customize the drug administration in Alzheimer's patient for precision medicine. Reproduced from Ref. [46] with permission of Elsevier.

developing SlipPAD [43,44]. The vertical microfluidic was also exploited for multi-analysis. For instance, an origami paper-based biosensor was developed for multiple pesticide detection by using different types of enzymes [45]. By folding the pad pre-loaded with the enzyme with another pad pre-loaded with the substrate and put together close to the electrode, it is possible to quantify the pesticides in a few minutes by wetting the origami with distilled water or water sample (Figure 1f). The vertical microfluidic has also been used in the case of whole blood analysis, for instance, combining Vivid Plasma Separation membrane to treat the whole blood sample, filter paper to load the reagents needed for the measurement, and office paper as support to print the electrode for easy measurement of butyrylcholinesterase activity using smartphone-assisted potentiostat [46] (Figure 1g) or asymmetric polysulfone plasma separation membrane, auto-injection layer, and detection layer for the measurement of C-reactive protein and prealbumin [47]. The vertical flow can have several advantages including the use of a lower volume of sample, the avoidance of the alignment of many different pads in cassettes [48], and the reduction of chemicals.

Reagent-free and pre-concentrator paper-based electrochemical (bio)sensors

The porosity of the paper to pre-load all reagents has been one of the main features exploited for the delivery of a reagent-free device. The device can be easily made by adding the proper solution to paper-based electrochemical (bio)sensors, starting from buffer to entrap salts for adjusting the pH when the sample is added [49], through the chemicals needed to carry out the measurement [50], until several different chemicals and biocomponents are loaded [51]. If paper network is largely employed to load reagents, only a few papers highlight the possibility of preconcentrating the sample by exploiting the porosity of the paper. Henry's group designed several interesting configurations allowing the drying of the solution at room temperature or using a heating system. In the case of the preconcentration at room temperature, the authors added the solution to the paper device in multiple steps and waited during the different steps for solvent evaporation for the detection of dopamine [52]. In the case of preconcentration with a heating system, they designed a paper-based device with a heating preconcentration module for lead and cadmium ion detection, observing an enhanced sensitivity (i.e. 14-fold for $Pb^{2+}$and 29-fold for Cd^{2+}).

Paper-based electrochemical sensors as reactor

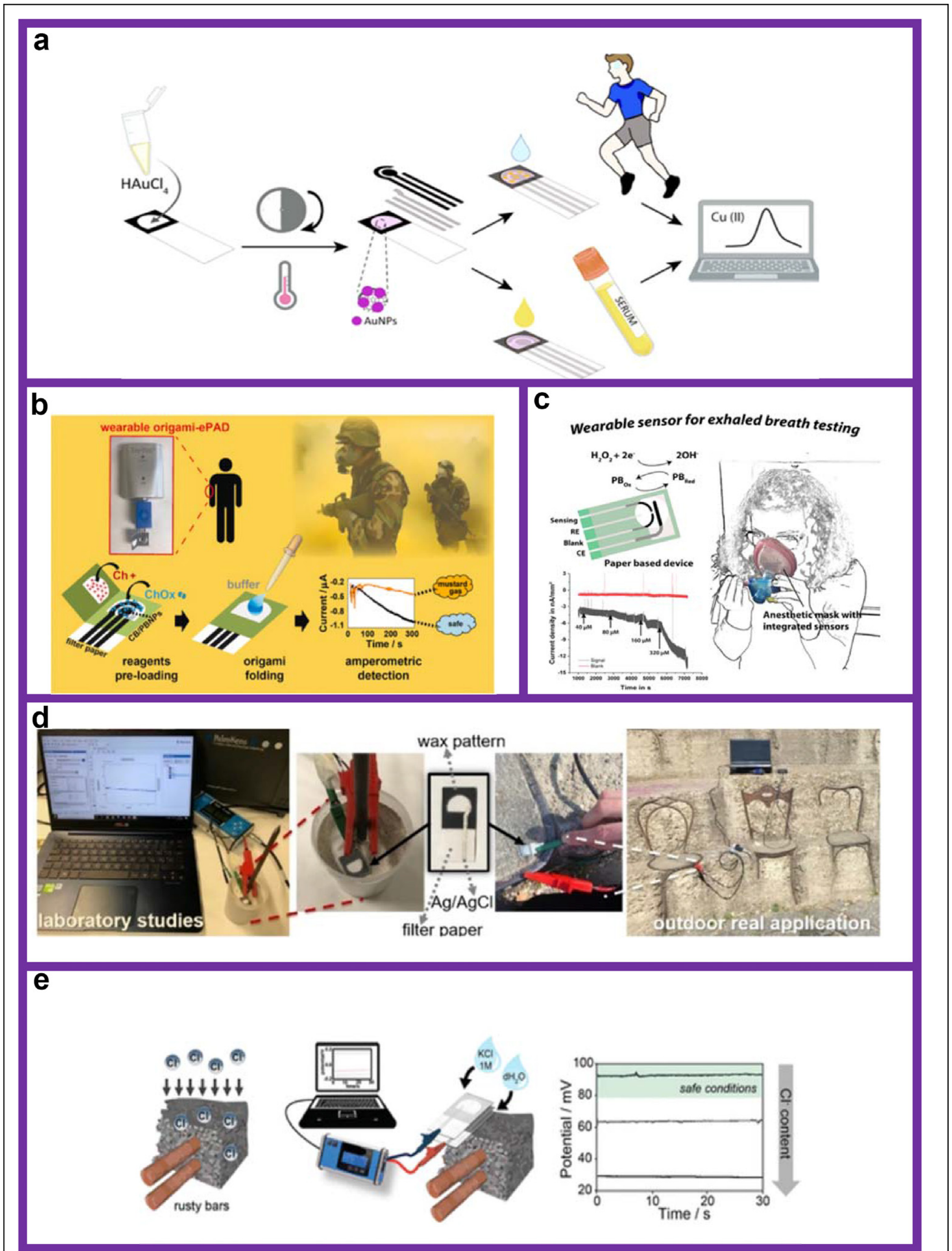
The decrease of organic solvents and any chemical for the synthesis is one of the main drivers in rendering chemical syntheses more sustainable. Regarding this vision, our group recently exploited the use of Carbon Black to tailor the dimension of Prussian Blue nanoparticles using diverse configurations, to exploit its impurities/defect sites in a variety of ways [53]. Motivated by this approach, we have used the impurities of the paper to synthesize Prussian Blue nanoparticles or gold nanoparticles within the paper, using the paper as a reactor for chemical synthesis.

In the case of the synthesis of Prussian Blue nanoparticles, a mixture of ferri/ferrocyanide/ salt is used to react together, or when used only ferri- or ferrocyanide as a precursor, acidic conditions, reductant, and voltage are required [54—56]. In this work [57], we used $K_3Fe(CN)_6$ and $FeCl_3$, prepared in water to modify filter paper and to synthesize Prussian Blue nanoparticles, producing the called "Paper Blue" used to create an electrochemical paper-based biosensor for glucose monitoring in capillary blood. In the case of paper decorated with gold nanoparticles, we used filter paper impregnated with chloroauric acid (prepared in distilled water) to synthesize gold nanoparticles on the paper; indeed, the color of the paper turned pink as a result of nanoparticles formation. Afterward, the electrochemical cell was printed and the reagents needed for measurement (i.e. solution containing hydrochloric acid) were loaded to deliver a sensor for copper detection (e.g. in sweat ready to use) [58] (Figure 2a).

Paper-based (bio)sensors for smart analysis of the target analyte in aerosol or solid surface

It is well known in the sensing field that the detection of an analyte in the gas phase is relegated to physical sensors like micro-electromechanical system (MEMS), in fact for the use of electrochemical printed (bio)sensors the liquid sample is required. To overcome this limitation, it is possible to expose the biosensor to a drop of working solution on the electrochemical cell at the gas phase to enrich the drop with the target analyte or by using a microfan able to sample the air and flow it into an electrochemical cell which contains the solution [59]. Motivated by the possibility to load the reagents on porous paper and wetting the paper with only humidity, in 2019 we developed an origami wearable electrochemical biosensor for the rapid and on-site detection of mustard agents by loading the biocomponent choline oxidase on the porous paper-based printed electrode and the enzymatic substrate choline into an additional porous paper-pad [60]. In the presence of aerosol-containing mustard agents, the humidity of the aerosol dissolves the reagents, thus the reaction starts, with a lower response in the presence of the chemical warfare agents in the gas phase (Figure 2b). In the same year, Dincer's group developed a paper-based sensor for calibration-free and real-time monitoring of hydrogen peroxide in artificial breath [61]. In this way, the breath dissolves the salts for electrochemical analysis, demonstrating the capability of the paper-based electrochemical device to

Figure 2



Current Opinion in Electrochemistry

a) Paper as reactor for synthesis of gold nanoparticles producing pink-paper used to printed the electrochemical cell and to detect copper by stripping analysis. Reproduced from Ref. [58] with permission of ACS. **b)** Paper-based electrochemical biosensor for the detection of mustard agents in gas phase. Reproduced from Ref. [60] with permission of Elsevier. **c)** Paper-based electrochemical sensor for hydrogen peroxide detection in artificial breath. Reproduced from Ref. [61] with permission of ACS. **d)** Paper-based sensor for evaluation of corrosion in concrete-based structure, by putting in contact wet paper with the concrete solid sample and metallic reinforcements usually embedded in the modern concrete constructions. Application to real outdoor artwork Music Collection Session by Arman (Milan, Italy), Reproduced from Ref. [63] with permission of Wiley. **e)** Paper-based sensor for potentiometric measurement of the chloride content in concrete-based structures using three-layer wax-modified filter paper, consisting of two Ag/AgCl screen-printed electrodes interfaced by a junction pad in a sandwich-like configuration. Reproduced from Ref. [65] with permission of ACS.

analyze the breath (Figure 2c), matching one of the Top 10 Emerging Technologies of 2021: disease-diagnosing breath sensors [62].

Having demonstrated the possibility of detecting the target analyte in the gas phase, the next step was related to understanding if the paper-based electrochemical sensors could go beyond the state of art in the case of application in the solid sample, like concrete. Taking into account that concrete works as a solid electrolyte, a wet paper was put in contact with the concrete solid sample allowing for evaluation of the corrosion level (Figure 2d) [63], pH monitoring [64], and chloride content measurement (Figure 2e) [65].

Conclusions and perspectives

Paper-based electrochemical devices have been demonstrated in the last decade to be reliable sensing tools for the detection of several analytes belonging to biomedical, agrifood, environmental, and defense fields. The variety of features of paper, namely porosity and foldability, give paper-based electrochemical devices unprecedented characteristics, allowing for reagent-free and highly sensitive analyses, thanks to the preconcentration capability. Furthermore, the porosity of the paper has been recently exploited to work as a reactor to synthesize nanomaterials, delivering decorated paper already functionalized and directly used to print the electrochemical cell. Another breakthrough regarding these devices has been their ability to overcome the limitation of detecting the target analyte only in the liquid sample. The attention on this type of device has also extended to the industrial community to develop and use plastic-free devices, decreasing environmental impact. In this direction, the reproducibility and robustness in humid conditions are key issues to be faced in the near future with the goal of market entry, supplying sustainable diagnostic devices to the community, and further boosting the multi-billion paper diagnostics market.

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.

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