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Barcode-Like Paper Sensor for Smartphone Diagnostics: An Application of Blood Typing

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Supporting Information

ABSTRACT: This study introduced a barcode-like design into a paper-based blood typing device by integrating with smartphone-based technology. The concept of presenting a paper-based blood typing assay in a barcode-like pattern significantly enhanced the adaptability of the assay to the smartphone technology. The fabrication of this device involved the use of a printing technique to define hydrophilic bar channels which were, respectively, treated with Anti-A, -B, and -D antibodies. These channels were then used to perform blood typing assays by introducing a blood sample. Blood type can be visually identified from eluting lengths in bar channels. A smartphone-based analytical application was designed to read the bar channels, analogous to scanning a barcode, interpret this information, and then report results to users. The proposed paper-based blood typing device is rapidly read by smartphones and easy for the user to operate. We envisage that the adaptation of paper-based devices to the widely accepted smartphone technology will increase the capability of paper-based diagnostics with rapid assay result interpretation, data storage, and transmission.

Paper-based analytical devices (PADs) have generated great interest in the field of medical diagnostics in recent years because they demonstrate great potential to develop affordable, rapid, and practical diagnostic sensors for resource-limited areas.[1−5] Numerous research works have been reported, covering methods of paper sensor fabrication,[6,7] analyte-specific assays,[8] and various result-reporting ideas, including colorimetric,[9] fluorescent,[10] electroluminescent,[11] and electrochemical,[12] as well as text-reporting.[13] Among the analyte-specific assays, PADs were demonstrated to be able to provide semiquantitative to quantitative analysis.[14−16] Recently, PADs, investigated as a class of field-based, equipment-free blood typing devices, have achieved the same accuracy but have been proven to be much more rapid than the mainstream blood typing technologies.[13,17] These developments show that current research has produced a wide range of new concepts for making paper-based devices a new platform that does not require hospital and laboratory support. Among these concepts, several have been extensively developed and have almost reached commercialization.[18,19]

Most PADs research focuses on the development of stand-alone devices that function under nonlaboratory conditions.[20−22] While in this direction many innovative ideas have been explored and reported, it should be noted that PADs will be more successful if they can be adapted to existing technologies that are ubiquitous in modern society. From the early days of PADs research, it was proposed that camera phones can significantly enhance low-cost diagnostics by connecting the users who perform the tests with professionals who receive the results and provide medical instructions.[23,24] The extremely high acceptance of smartphone technology by the human population in both developed and developing countries makes this technology a valuable infrastructure for any other technology to build upon.[25] The adaptation of PADs to smartphone technology, particularly through software innovation, will significantly enhance the power of PADs as a platform technology for diagnostic applications through providing simple analytical tools, increasing coverage and connection between users and professionals, and allowing data sorting, storage, and management for local and temporary medical facilities in remote medical emergencies and disaster response missions.

In this study, we applied a barcode reading concept to adapt paper-based blood typing assays to smartphone technology. Blood typing is a routine clinical assay in surgical procedures, medical emergencies, and blood transfusions, as well as in blood banking.[26] Our group has reported a series of studies on the fabrication of new types of PADs and thread-based analytical devices for blood typing.[27−29] These studies have demonstrated new stand-alone blood typing devices that can be operated by users without the need of any supporting instrument. While the stand-alone devices promise a superior platform to the mainstream hospital-based technologies in

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providing health care to home-based users and users living in impoverished areas, adaptation to smartphones through software innovation will provide further advantages to paper-based blood typing technology in digital data sorting, storage, and transmission. It is anticipated that the use of software will be an effective means of reducing human error in data sorting and storage. In this work, we developed a simple software for smartphones and used it for paper-based blood typing assays.

EXPERIMENTAL SECTION

Reagents and Apparatus. Antibodies against RBC antigens approved for human blood grouping were obtained from the Commonwealth Serum Laboratory (CSL), Australia. They were IgM antibodies commercialized under the names of Epiclone Anti-A, Anti-B, and Anti-D (IgM) FFMU Concentrate. All of them are transparent solutions. Phosphate-buffered physiological salt solution (PBS, pH 7.4), sourced from Sigma-Aldrich, Australia, was used as the diluent for all antibody solutions. Alginic acid sodium salt (NaAlg) was acquired from Sigma-Aldrich, Australia. Anti-A and Anti-B were diluted to 1/5 with PBS solution for use in our study. All antibodies were stored at 4 °C.

Blood samples acquired from adult volunteers of a known blood group were provided by Red Cross, Australia. Samples were stored in Vacutainer tubes containing heparin, citrate, and EDTA and refrigerated at 4 °C; they were used within 10 days of collection. Reagent red blood cells Revercell (15% A1, 15% B red blood cells) and Abtectcell III (3% R1R1, 3% R2R2, and 3% rr red blood cells) were purchased from CSL Limited, Australia, stored at 4 °C and used within 30 days of delivery. All blood samples, including reagent blood cells, were diluted to 15% with PBS for performing blood typing assays in our printed barcode paper devices. Ultrapure water (≥18.2 MΩ) purified by a Milli-Q System (Millipore, Bedford, MA, USA) was used for the preparation of all solutions. Kleenex paper towels (Kimbly-Clark, Australia) with a basis weight of 34 g/m^2 and an apparent thickness of 140 μm were purchased from a local supermarket.

Bar Pattern Design for Blood Typing. Alkyl ketene dimer (Precis900, Hercules Australia Pty Ltd.) was used as the cellulose hydrophobization reagent. Analytical-grade *n*-heptane (Sigma-Aldrich, Australia) was used as the solvent for the dimers. The Kleenex paper, cut into A4 size, was selected as the substrate to fabricate the bar pattern paper-based blood typing devices. The fabrication procedure involves using a reconstructed commercial desktop ink jet printer (Canon Pixma ip4500) to print computer-generated patterns onto the paper with an ink solution of alkyl ketene dimer−heptane (3%, v/v) according to previous works.[30] The printed paper was heat-treated in an oven at 105 °C for 1 h to allow the hydrophobicity of the printed area on paper to fully develop. In this work, the device was fabricated with three separate channel patterns, which were labeled with the printed letters "A", "B", and "D". Each pattern consisted of a bar channel (0.3 cm × 5 cm), a buffer rinsing zone (r = 0.2 cm), and a bridging channel linking these two (Figure 1). The channel patterns were hydrophilic and used for the assaying application.

Preparation of Antibody-Loaded Bar Channels. Before loading antibodies, the bar channels were treated with NaAlg for the purpose of enhancing antibody loading efficiency. NaAlg solutions with concentrations of 0%, 0.01%, 0.05%, and 0.1% (w/v) were prepared using Millipore-purified water. The patterned paper devices were divided into four groups; the

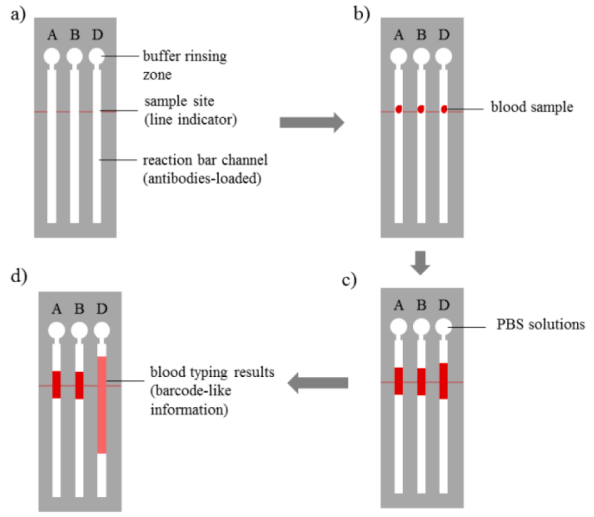

Figure 1. Schematic diagram of the barcode-like blood typing device. (a) Anti-A, Anti-B, and Anti-D antibodies were introduced into the reaction bar channels. (b) 3 μL of blood samples was introduced in the sample sites for the blood typing test and allowed to wick and react for 30 s. (c) 10 μL of PBS solutions was added as eluting buffer for 1 min of elution. (d) Reading the blood typing test results.

channels of each group were treated with 10 μL of each of the four NaAlg solutions, respectively. All the papers modified with NaAlg solutions were dried for 30 min at room temperature.

All channels marked with "A" (channel "A") in all four groups of NaAlg-treated papers were treated with Anti-A; 10 μL of diluted Anti-A antibodies were uniformly deposited into the entire channel length. Likewise, for channels "B" and "D", 10 μL of Anti-B and 10 μL of Anti-D antibodies were deposited into the "B" and "D" channels of all papers, respectively. All the paper devices were dried for 1 h at room temperature.

Covalent antibody immobilization involves two steps: activating the NaAlg-modified paper surface using EDC-NHS chemistry and then conjugating it with the antibody molecules. In the paper surface activation step, 20 μL of an equal-volume mixture of 20 mg/mL EDC and 12 mg/mL NHS solutions was uniformly deposited into each channel and the activation reaction was allowed 30 min for completion in an environment with a controlled high humidity. After activation, each channel was rinsed with 60 μL of H_2O three times. For the conjugation of antibodies, all of the "A" bar channels were uniformly deposited with 10 μL of diluted Anti-A antibodies and allowed 1 h for conjugation at 50% humidity. Similarly, bar channels "B" and "D" of all groups were deposited with 10 μL of Anti-B and 10 μL of Anti-D, respectively, under the same conditions, for conjugation reactions. At the end of the conjugation reactions, each channel was rinsed three times using 60 μL of PBS and then allowed to dry for 1 h at room temperature.

Water Drop Penetration Time (WDPT) Measurement. To evaluate the influence of paper surface modification on paper wettability, a water drop penetration time test was adopted. The untreated and antibody-conjugated Kleenex paper towel was cut into 1 cm × 1 cm squares for water penetration time testing. A contact angle instrument (Data-physics OCA230, Germany) was used to take video of the water drop penetration process. The experimental procedure was as follows: a piece of a paper square was horizontally fixed to the measurement platform; a 3 μL water droplet was delivered onto the paper surface by a syringe; the drop landing

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and penetration processes were recorded at a frame speed of 56 frames/s; the final penetration time was calculated by the system software from the video data. Three measurements were taken for each paper sample.

Blood Typing Using the Barcode-Like Paper Device. A volume of 3 μL of prediluted 15% blood samples was introduced into each channel via its sampling site indicated by the red line (Figure 1); red blood cells were permitted to react with the antibody in the channel for 30 s. Then, a volume of 10 μL of PBS buffer solution was introduced onto the rinsing zone and allowed to elute through the channel by capillary wicking for 1 min. The testing assay was then scanned and interpreted by smartphone-based technology.

Smartphone-Based Analysis Design. The mobile software designed for carrying out the preset analytical procedures (app) was developed on the Android platform. The software was coded with Java using ADT (Android development tools), and the functions of the smartphone were controlled through APIs (application programming interfaces). The app can be supported by Android version 2.2 and above. The app was designed to read the information in each bar channel along its length, since the blood penetration along the channel gives the most distinguishable difference between a positive and negative result. In this study, a Google Nexus 5 smartphone (Google Android version 4.4) was used to read the final blood typing results.

RESULTS AND DISCUSSION

The Sensor Design Concept. Paper-based analytical devices have been designed for ABO/RhD blood grouping based on the principle of hemagglutination reaction between RBCs and antibodies.[31] When a blood sample wicks into the fiber network of paper treated with the corresponding antibody, hemagglutination will occur within the fiber network which will lead to the formation of large lumps that lock inside the fiber network and cannot be eluted out. Therefore, when hemagglutination occurs in the bar channels of our blood typing device (Figure 1), buffer elution will not elute the agglutinated RBC lumps along the channel, leaving a short bar of blood stain with a strong color. The deep red color came from the aggregated red blood cells. In contrast to this, when RBCs contact a noncorresponding antibody inside the fiber network, no hemagglutination will occur. Free RBCs can be eluted along the channel by PBS solution, forming a diluted bar of much greater length along the channel (Figure 1). For the purpose of interpreting an assay result, if we can distinguish a "short" bar from a "long" bar in a channel, it will be possible to identify whether hemagglutination has occurred in this channel or not. Therefore, making sure the "short" and "long" information are distinguishable is an important consideration when designing this sensor.

However, the length difference between agglutinated (positive, "P") and nonagglutinated (negative, "N") RBCs was not significant enough to be clearly identified (Figure S-1a, Supporting Information), since the limited volume of blood samples cannot provide enough driving force for non-agglutinated RBCs to continue penetrating forward. Therefore, we introduced PBS buffer solutions as eluting buffer into channels to supply a driving force for free RBCs to continue to move forward. The RBCs eluting length difference between positive and negative tests was distinct: agglutinated RBCs formed a short eluting length in the bar channel, while nonagglutinated RBCs led to a much longer eluting length (Figure S-1b, Supporting Information). Such difference makes this sensor viable for accurate identification by smartphone-based analysis. In the final design of this blood typing assay (Figure 1), three separate patterns labeled with "A", "B", and "D" were designed for the identification of A, B, and D antigens, respectively, to determine ABO and RhD blood types.

Sensor Development. On the basis of the above sensor design concept, a smartphone-based app was designed to read the RBC elution length in a channel. To ensure unambiguous results identification using this design idea, different physicochemical channel modifications have been considered. Emphasis is given to the design of the bar channels to provide the negative and positive tests with a significant sample eluting length difference for easy and fast identification by the software. This relies on detailed consideration of channel surface treatment to enhance the antibody sorption and wetting ability of paper. For this reason, different paper surface modification methods have been investigated to obtain the maximum eluting length difference between positive and negative tests.

Physical or Chemical Immobilization. Physical and chemical methods for antibody immobilization were investigated so that the method capable of producing a larger difference between the positive and negative assays could be selected. The chemistry applied here is the EDC/NHS activating agent pair which is commonly used for the coupling of primary amines with carboxyl groups to yield amide bonds. Since there are sparse carboxyl groups on the paper, NaAlg was used to increase carboxyl groups on paper because of its great biocompatibility and the retention of NaAlg has been proven to be satisfactory.[32] However, the antibody-treated channels with chemical coupling have failed to retain a sufficient amount of antibody on the paper surface for performing a blood typing assay. Also, this approach causes a decrease of paper wettability as shown by the water drop penetration test (WDPT) (Table S-1, Supporting Information). These undesirable outcomes make the chemical coupling approach unsuitable, since poor paper wettability prevents the blood sample from wicking into the fiber network and contacting antibody molecules. In contrast to this, antibodies physically immobilized on paper can be freely released from the fiber matrix into the blood samples to effectively collide and react with RBCs to allow hemagglutination reactions to occur.

NaAlg Concentration. Among the systems that were considered above, physical immobilization was judged to be the only appropriate method to provide a suitable surface modification for the sensor design. To optimize the physical immobilization of NaAlg, the bar channels were first modified with 0% (w/v) NaAlg (Figure S-2,1, Supporting Information), 0.01% (w/v) NaAlg (Figure S-2,2, Supporting Information), 0.05% (w/v) NaAlg (Figure S-2,3, Supporting Information), and 0.1% (w/v) NaAlg (Figure S-2,4, Supporting Information), followed by treatment with Anti-A antibodies (Figure S-2a, Supporting Information), Anti-B antibodies (Figure S-2b, Supporting Information), and Anti-D antibodies (Figure S-2c, Supporting Information). Both positive (Figure S-2, "P", Supporting Information) and negative (Figure S-2, "N", Supporting Information) assays were performed by, respectively, introducing antigen-positive and -negative RBCs in bar channels modified with different concentrations of NaAlg and the corresponding antibodies. As shown in Figure S-2, Supporting Information, all positive assays had shorter bar lengths than the negative reactions. Although antigen-positive and -negative blood samples could be distinguished among all

the NaAlg modified channels, the modification that led to the greatest difference was selected for more accurate identification. Therefore, 0.05% NaAlg was chosen for the final sensor design since the length difference was the greatest with this concentration (Figure 2).

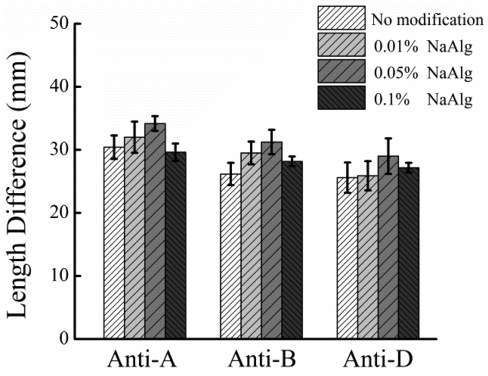

Figure 2. Eluting length difference in "A", "B", and "D" reaction bar channels modified with different concentrations of NaAlg. Bar channels based on untreated paper were used as controls (No modification by NaAlg). "A", "B", and "D" channels were, respectively, loaded with Anti-A, Anti-B, and Anti-D antibodies. The error bars represent the standard deviation of five tests.

Sensor Validation. The final paper-based blood typing device was designed under optimum conditions based on the above results. Figure 3 shows a photo of the actual tests of all

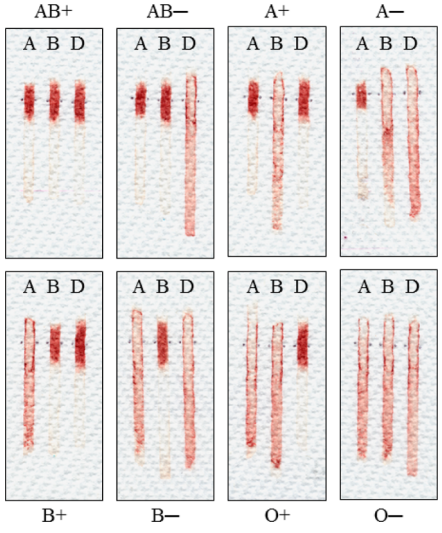

Figure 3. Actual assays of all eight ABO/RhD blood types by the optimized barcode-like paper-based blood typing device.

eight ABO/RhD blood types by our blood typing device. Figure 4 shows the average eluting lengths of positive and negative assays in A, B, and D channels. The measured bar lengths for the positive assays were: A, 9.9 ± 1.2 mm; B, 12 ± 1.6 mm; D, 13.4 ± 1 mm. By comparison, the bar lengths for the negative assays were: A, 42.6 ± 1.6 mm; B, 42.2 ± 1.3 mm; D, 42.5 ± 1.7 mm. The distinct length difference between positive and negative assays makes this device possible for easy result interpretation by smartphone-based analysis.

Smartphone-Based Analysis. To rapidly identify the eluting length information resulting from a blood type assay,

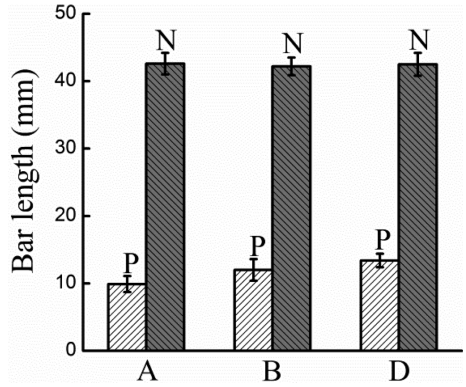

Figure 4. Average eluting lengths for positive (P) and negative (N) reactions in "A", "B" and "D" channels.

smartphone-based analysis software (app) was developed. The basic principle of the identification process is as follows: If a short RBC eluting length appears in one channel, it will be encoded as "1" by the app; on the contrary, if a long eluting length occurs in the channel, it will be encoded as "0". On the basis of this design, all eight blood types are encoded as "AB +"/"1 1 1", "AB−"/"1 1 0", "A+"/"1 0 1", "A−"/"1 0 0", "B +"/"0 1 1", "B−"/"0 1 0", "O+"/"0 0 1", and "O−"/"0 0 0". The code messages will be presented from the "A", "B", and then "D" channel for further interpretation. Therefore, for instance, when acquiring code message "1 1 0", the app will interpret it as blood type "AB−".

To quantitatively assess whether one channel message is "1" or "0", references with eluting lengths of positive and negative assays of this channel will be required for comparison purposes. The app designed in this study has preloaded references which were obtained from statistical analyses based on a large amount of known blood samples; therefore, after acquiring the eluting lengths of the target blood assay, the app will compare the lengths with the references, transfer the length data to code messages, and then interpret the code messages into the corresponding blood type.

The basic statistical analysis principles used to obtain references are described as follows: (1) assume both the eluting length values of negative (L_n) and positive (L_p) reactions in one channel, respectively, follow normal distributions: $L_n \sim N_0(\mu_0, \sigma_0^2)$ with unknown mean μ_0 and unknown variance σ_0^2 and $L_p \sim N_1(\mu_1, \sigma_1^2)$ with unknown mean μ_1 and unknown variance σ_1^2; (2) on the basis of data measured from negative reactions (sample size is Q) in this channel, get the sample mean $\overline{L_n}$ and sample standard deviation s_n. Since the true value of standard deviation σ_0 is unknown, the distribution of the sample mean $\overline{L_n}$ follows the t distribution (t_n) with mean μ_0 and standard deviation ($s_n/(Q)^{1/2}$); (3) on the basis of data measured from positive reactions (sample size is Q) in this channel, get the sample mean $\overline{L_p}$ and sample standard deviation s_p. Similarly, since the true value of standard deviation σ_1 is unknown, the distribution of the sample mean $\overline{L_p}$ follows the t distribution (t_p) with mean μ_1 and standard deviation ($s_p/(Q)^{1/2}$); (4) two t distributions (t_n and t_p) obtained from step (2) and step (3) are taken as the references for testing whether the length value is "0" or "1". For instance, two basic steps will be run by this app for determining the code message of the "A" channel: (1) Get the average value of eluting length in the "A" channel of target sample; (2) At a significance level of 0.01, if

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the value only falls into the confidence intervals for the mean μ_0 based on t_n distribution of "A" channels, get message "0"; if the value merely falls into the confidence intervals for the mean μ_1 based on t_p distribution of "A" channels, get message "1"; if the value fall into the confidence intervals of both t_n and t_p distribution, the one whose sample mean value is closer to the tested value will be chosen; otherwise, do not report the result.

This app was tested on a Google Nexus 5 smartphone for identifying blood assays (Figure 5) in this study. The blood

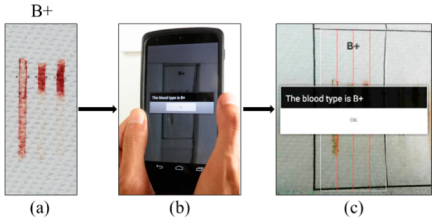

Figure 5. Testing results based on smartphone-based analysis. (a) Blood typing test result (B+) is shown in bar channels, (b) reading the result using the Android app, and (c) obtaining the blood result with text on the screen.

type of the target assays will be displayed and reported with text on the smartphone screen. For simple operation of this app, three scanning channels, which were indicated by three red solid lines, have been designed for, respectively, scanning "A", "B", and "D" channels. One simple instruction to operate this app is to use the camera of the smartphone to make sure the three indicating red lines of the app match with the "A", "B", and "D" bar reaction channels of the paper-based device. Figure 6 shows that the snapshots of all eight ABO/RhD blood group

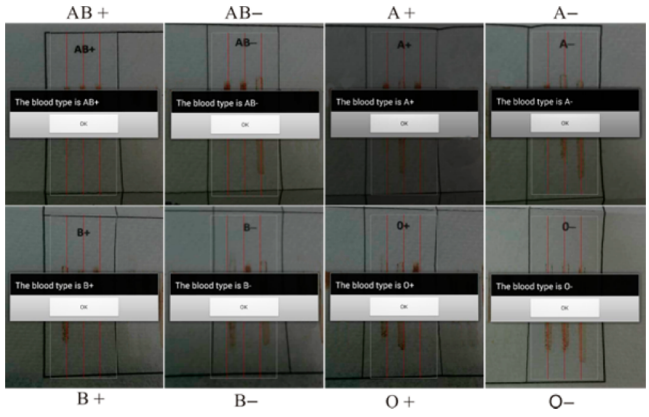

Figure 6. All eight ABO/RhD blood types were reported by the Android system-based smartphone app.

types were successfully text-reported by this Android app. This barcode-like design makes smartphone-based analysis easier and more reliable through reading the length information, which is less affected by environmental factors (such as light source, temperature, etc.) compared to other forms of signals such as colorimetric and electric.

Validation for Blood Typing. A total of 98 blood samples were assayed using this barcode-like blood typing device. All samples were also assayed in the pathological laboratory of Red Cross Australia using the mainstream blood typing technologies. These samples contain all the 8 blood types in the ABO blood typing system. All results agree with those reported by the Red Cross Australia. All results are shown in Table S-2, Supporting Information.

CONCLUSIONS

In this study, a barcode reading concept has been applied for the first time in designing paper-based devices by adapting to smartphone-based technology. This sensor design has been used for the application of blood typing. Users can obtain all eight ABO/RhD blood types as text messages on the screen of the smartphone, without the need of further interpretation. The specific barcode-like design of the paper-based device makes smartphone-based analysis more reliable by reading the bar length information. In addition, by utilizing smartphone technology, test results from paper sensors can be automatically saved in e-form and transferred conveniently between users and professionals. It is expected that paper-based technology with smartphone diagnostics will be greatly expanded and applied as a diagnostic platform for medical and environmental applications.

ASSOCIATED CONTENT

Supporting Information

Additional figures and tables. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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