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A Point-of-Care Measurement of NT-proBNP for Heart Failure Patients

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ABSTRACT Heart Failure (HF) diagnosis, subsequent admissions, and possible readmissions present challenges for health systems worldwide. An increasing number of patients within an ageing population are surviving cardiac conditions which can leave them with residual heart function impairment. Follow-up visits of either confirmed HF sufferers or HF high-risk patients could be reduced through the implementation of Point-of-Care (PoC) measurement of N-terminal pro-B-type natriuretic peptide (NT-proBNP), an inactive signal portion of the active hormone BNP that is released in response to cardiac wall stretch. Serial measurements of NT-proBNP concentration may serve to indicate progress/deterioration of HF sufferers which in turn indicates the quality of the interventions designed to treat HF. We present an integrated PoC solution that involves the user-friendly, low volume sampling of blood directly into a single-use sampling key with an integral NT-proBNP biomarker detection strip operating on a lateral flow immunoassay principle. When inserted into a corresponding portable electronic reader it forms an integrated detection and measurement platform that wirelessly communicates measurements (Wi-Fi) for cloud-based reporting, trending and data analysis. The system provides a practical, inexpensive support tool for HF management by informing those involved in clinical decision-making with necessary biomarker data. The PoC NT-proBNP measurement compares well against alternative technologies based on image analysis.

INDEX TERMS Heart failure interventions, lateral flow immunoassay, low volume blood sampling, NT-proBNP, point-of-care.

I. INTRODUCTION

Heart failure (HF) refers to the heart failing to pump enough blood around the body at the right pressure. HF usually occurs because the heart muscle has become too weak or stiff to work properly as a consequence of different cardiac conditions. HF is a global problem affecting at least 26 million people worldwide and is increasing in prevalence [1].

Initial insights about HF, and corresponding readmissions, point to a number of key interventions during follow-ups. According to the literature [2], [3], the number of HF readmissions depends directly on the quality of interventions (or patient management) after the patient is released from the hospital for primary care. The quality refers to the "how", "when", "how often", "type of contact" provided to the patient during the follow-up. These interventions generally look to ensure the patient is following the treatment, appropriately taking medication, making the necessary changes in lifestyle to keep HF as a chronic illness at bay. Monitoring, education and training are key practices for the interventions.

Integrated healthcare systems for home-based, point-of-care (PoC) for monitoring heart failure are recognised as having a significant future role in the interventions of heart failure for being cost-effective and reducing patient readmissions [4]. Currently in the literature, there are many examples of IoT frameworks and, separately, systems for integrating information into databases, and also many PoC diagnostic tools. For example, Spanakis *et al.* [5] produced an IoT integrated disease management system, utilising an alarm based on heart-rate monitoring and blood pressure using external sensors whilst Jin *et al.* [6] produced a neural network-based approach for predicting heart failure

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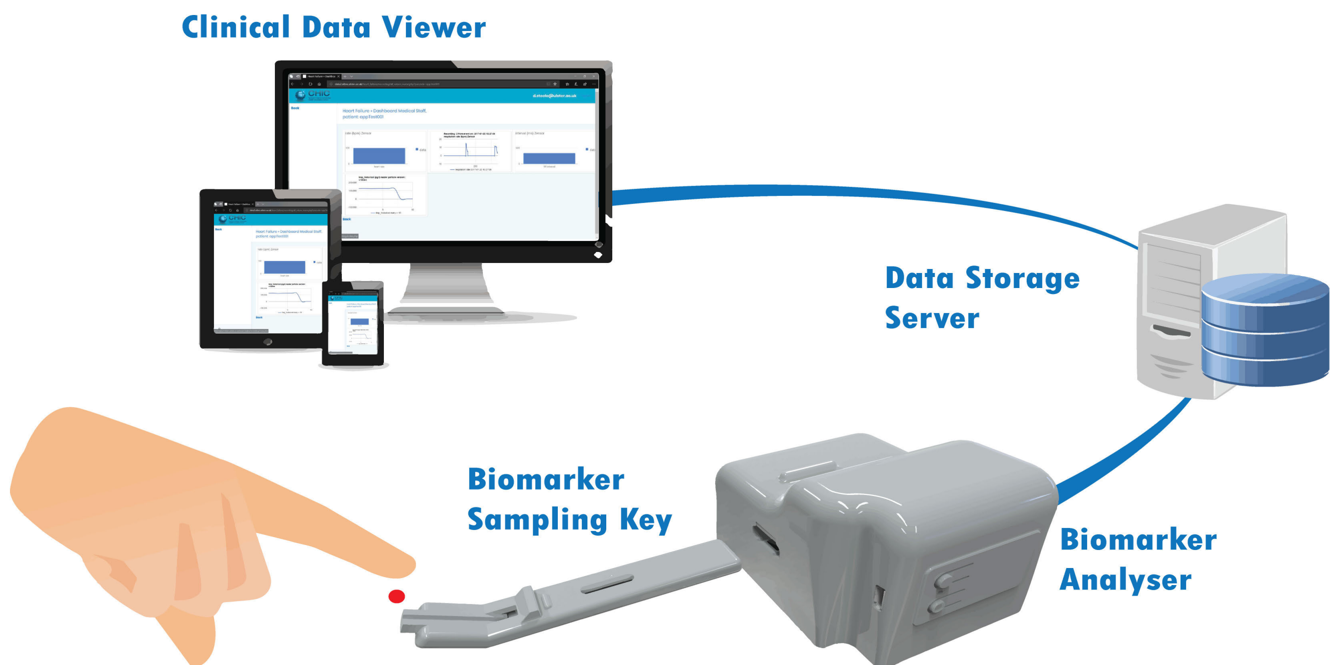

FIGURE 1. **Components for the proposed PoC solution for home monitoring Heart Failure patients: Lateral flow PoC system for measuring NT-proBNP that transmit values to a server for data storage and data viewer. The server can also send alerts to the physician in charge in order to adjust treatment or recommend re-admission.**

from existing electronic health records taking advantage of the possibility of analysing time series. In terms of PoC diagnostic systems of blood-based biomarkers, B-type natriuretic peptide (BNP) and NT-proBNP have been identified as key biomarkers for Heart Failure sufferers [7]–[9]. Both peptides have an excellent ability to distinguish HF from non-HF subjects, however some studies have reported that NT-proBNP may be more useful, owing to a longer half-life [10]. These biomarkers are released in response to cardiac wall stretch or pressure overload conditions and shown to be increased in patients with HF. They are increased in patients with HF and provide an indication for risk stratification in HF, which may then be confirmed by echocardiography. If the level of the biomarker is normal it generally rules out HF since it exhibits a high negative predictive value of around 99% [9].

There are many examples of PoC sensing systems designed for home use, for example DeGregory *et al.* [11] produced a rapid PoC diagnostic system for monitoring N-terminal pro-B-type natriuretic peptide (NT-proBNP) using a low-cost electrochemical assay, though the dynamic range of their assay is low compared with the clinically relevant range (0 to thousands of pg/ml). Further PoC assays exist for NT-proBNP, based on optical and electrochemical sensors [12]–[15]. Other methods of assessing heart failure include monitoring the cardiac pulmonary edema [16] and heart rate variability [17]. New developments attempt to incorporate more sensors and new techniques for processing the information. Gjoreski *et al.* [18] present a method for HF detection based on heart sounds. They combine classic Machine-Learning and end-to-end Deep Learning applied to the recorded signals in order to distinguish between healthy subjects and patients and for the detection of different HF phases. However at present the currently available devices in the literature lack integration between the IoT e-health systems and PoC diagnostics and thus there is a requirement for a holistic, IoT ''patient-to-cloud'' based framework.

The PoC approach presented in this paper allows quantitative measurement of NT-proBNP during a home visit or self-test in contrast to the use of a laboratory by hospital request. The approach lends itself to being used to obtain serial measurements of NT-proBNP, with the cloud-based clinical data viewer enabling the visualisation of an individual's biomarker trend over time. We present a home-based PoC solution for measurement of NT-proBNP, as a part of follow-up home visits of HF high-risk patients or for confirmed HF sufferers. The measurements allow for patient monitoring and trending of NT-proBNP values over time, and could form an evidence-base for the selection of appropriate therapeutic interventions. We aim to keep the advantages of a PoC solution for home use and the possibility of analysing serial measurements of NT-proBNP. The cost and assay time of the proposed solution are similar to the one reported by DeGregory *et al.* [11] but with an extended range and accuracy.

The components of the proposed PoC solution for measuring NT-proBNP for HF are shown in figure 1. The solution uses a novel, single-use holder containing a blood sampling port in fluidic connection with an enclosed bespoke

NT-proBNP lateral flow immunoassay (LFIA) strip. Together these form the biomarker sampling key. A single analysis requires that this be inserted into the inexpensive Wi-Fi enabled electronic 'biomarker analyser'. The sample required is about one drop (25μL) of finger-prick blood, and its collection can be performed in a simple fashion, similar to a standard diabetes-style personal test kit, either individually by the patient or during a home-care visit. Placement of an appropriate quantity of blood onto the blood sampling port initiates NT-proBNP analysis via passive capillary flow during which the biomarker analyser takes a reading and securely transmits this to the data storage server via Wi-Fi. The entire follow-up can be monitored via a web-based data viewer or mobile app.

In the subsequent sections of this paper we explain in detail the components of our solution that includes, a system for simplified blood sampling, encased lateral flow strips, the electronic reader, the data storage and display.

II. MATERIALS AND METHODS

A. NATRIURETIC PEPTIDES

BNP and its amino-terminal cleavage fragment, NT-proBNP are cardiac peptides that have been described as an "emergency-rescue" cardiac hormone against ventricular overload [19]. The peptides are released (typically in a 1:1 ratio) [20] into plasma in response to excessive stretching of cardiomyocytes in the ventricular wall. BNP, the active form of the peptide, acts through the natriuretic peptide receptor type A causing peripheral vasodilation and a decrease in blood pressure. While the concentration of each peptide corresponds to the degree of ventricular stretching, it has been shown that the NT-proBNP form exhibits a $\sim 6\times$ longer plasma half-life and so measured levels may appear to be higher [21].

On an individual basis, measured levels of NT-ProBNP/BNP vary each day suggesting that the peptides function as continuous and sensitive markers of ventricular stress. Several drugs used to treat heart failure (i.e. angiotensin converting enzyme -ACE- inhibitors, angiotensin receptor blockers, aldosterone antagonists, beta-blockers) have been shown to decrease circulating concentrations of natriuretic peptides including NT-proBNP [22], with lower peptide levels corresponding to an improved prognostic outcome. Furthermore, in some cases, it has been shown that peptide levels precede felt symptoms of worsening pulmonary congestion, such as breathlessness and weight gain. It has therefore been proposed that BNP levels can be used to guide treatment of heart failure [9].

Maisel *et al.* [8] have proposed thresholds in the level of NT-proBNP for ruling-in and ruling-out patients with suspected heart failure. For patients aged $<$50, the cut-off point is 450 pg/ml, for those aged 50 to 75, the cut-off is 900 pg/ml, and is 1800 pg/ml for those aged $>$75. We stress that for an initial heart failure diagnosis, this primary rule-in or rule-out needs to be performed in a clinical setting, along with other measurements (for example if injection fraction measured using echocardiography is below 40% [23], body measurements, etc). Our home-based PoC system is intended as a tool for further regular monitoring of NT-proBNP values, and trending over time, in order to guide treatment and recovery.

B. PREPARATION OF CARBON-BASED NT-proBNP DETECTION CONJUGATES

1) PRINCIPLE OF LATERAL FLOW SENSING

Here we present the design and implementation of our LFIA for NT-proBNP sensing. Lateral flow immunoassays have a number of advantages over laboratory assays for use at point-of-care. They are inexpensive, have a long shelf life and have a simple operational procedure when compared to typical biomarker measurement tests such as the enzyme-linked immunosorbent assay (ELISA). The principle of LFIAs has been well reviewed by Koczula *et al.* [24], thus we present only a brief overview here. Initially, biomarkers in fluid form (in our case: blood, which flows directly from the capillary channel of the biomarker sampling key, but this can be also plasma, serum, urine, etc.) are introduced into the absorbent pad. The pads are all porous and hydrophilic, and thus liquids are passively 'pumped' through the strip by capillary flow. The applied fluid will flow into the conjugation pad, where biomarkers can interact with conjugate labels, in our case these are amorphous carbon nanoparticles (AC-NPs). The liquid then flows into a nitrocellulose reaction membrane, in which there is a 'test line' printed. The test line is printed with antibodies which are reactive to the AC-NP-labelled antigens. As the number of AC-NPs which react, and bind, to the antibody test line is a function of the concentration of biomarkers in the blood, the optical intensity of this line may be used to transduce the biomarker concentration.

2) REAGENTS / AB / CONJUGATION PROTOCOL

The detection of NT-proBNP in blood samples was achieved using a bespoke LFIA developed for use with our biomarker analyser. The LFIA employs AC-NPs that act as high-contrast optical detection labels via a functionalisation step involving their conjugation to an NT-proBNP specific detection antibody. The capillary flow of fluid samples over time causes the accumulation of functionalised detection labels on the test line zone of the lateral flow membrane. The accumulation of functionalised AC-NPs varies with the concentration of NT-proBNP in the sample. This has been optimised for the clinically-relevant range of 30-1360 pg/ml of NT-proBNP. The integration of the LFIA with the housing permits direct connection of LFIA with the blood sampling capillary, as well as mechanical alignment with the optical detection portion of the biomarker analyser. The biomarker analyser measures the increase in light absorption caused by accumulating carbon labels.

3) CARBON NANOPARTICLE TO ANTIBODY CONJUGATION

Conjugation of antibody to carbon was achieved via a modification of a previously described physical adsorption technique [25]. Briefly; 1ml of 5mM Borate buffer (pH 8.8), containing 140 μg of 15F11 Anti-proBNP antibody (Abcam, Cambridge, UK) was added to 2mg of Carbon black nanoparticles (Alfa Aesar, Lancashire, UK) with sonication for a total of 60 seconds (Branson Sonifier 250). Sonication was maintained over an ice bath at a maximum of 50 W power to avoid thermally induced damage to the antibody conjugate. A deep black suspension of colloidal carbon moderately stabilized by the adsorbed antibodies is formed. The suspension was then incubated with gentle agitation at 4°C for a further 18-hour period.

The conjugate was then centrifuged at 16000g for 15 minutes. After removal of the supernatant, the pellet was resuspended in 1ml of a wash buffer comprising 5mM Borate buffer (pH 8.8), containing 0.5% BSA (w/v). Further 1-hour incubation with gentle agitation (4°C) was used to complete blocking of any remaining adsorption sites on the AC-NPs. Centrifugation was repeated twice more, and the resulting stably passivated colloidal carbon conjugate suspended in a storage buffer comprising 100 mM Borate (pH 8.8) and 0.5% (w/v) BSA. This was stored at 4°C.

4) ASSEMBLY AND CALIBRATION OF 24E11-CNP LATERAL FLOW TEST STRIP

The XYZ3060 Dispense Platform (Biodot Ltd) was used to quantitatively dispense the NT-proBNP detection conjugate (1:30 dilution at 10μl/cm) onto the Ahlstrom 6613H conjugate release pad material. Similarly, a 0.5 mm wide test line of 24E11 anti-NT-proBNP antibody was deposited (1μl/cm at 0.5mg/ml) onto Sartorius UniSart CN95 cellulose nitrate membrane at an optimal width for alignment with the optical detector in the biomarker analyser. Dispensed reagents were dried at 37°C for 2 hours, prior to immediate assembly into 300mm wide "panels" with the addition of sample and absorbent pad materials. Panels comprised a backing substrate bearing a pressure-sensitive adhesive to which the conjugate pad (Ahlstrom 6613H), cellulose nitrate membrane (Sartorius UniSart CN95) and absorbent pad (Ahlstrom 222) were fixed in the overlapping arrangement common to LFIA strips [26]. This arrangement enables the sequential transfer of applied biosample by capillary action through the various zones of the test strip. Individual strips (4 mm wide) were cut from panels using a guillotine (Rexel ClassicCut CL410) and immediately transferred into prepared strip holders. Such populated strip holders were then sealed into foil pouches with desiccant to maintain humidity below 10% during storage. For low volume sampling, the channel, sampling pad and conjugate pad of each strip were then etched to a width of 1.5 mm using a CO_2 laser (Universal VLS 230) [27].

We calibrated the NT-proBNP test strips using a dilution series of NT-proBNP in negative control serum to establish a calibration curve from a range of 30 to 1360 pg/ml. We note that the clinical range of NT-proBNP extends beyond this range [23] however, at present we have been limited by the maximum level of NT-proBNP patient sample available to us. Given the lack of an accepted NT-proBNP reference standard [28] we elected to produce an internal standard containing native human NT-proBNP in a serum matrix. The use of several samples in a pool increases the potential representation of multiple uncharacterized NT-proBNP proforms and glycosylation states [29]. Patient samples containing NT-proBNP >1000 pg/ml (via Roche Cobas e411 analysis) were mixed in equal proportion to form a pooled sample (average 1360pg/ml NT-proBNP). This was used to create calibration standards by dilution of the pooled sample into a pooled 'normal human' control serum (NT-proBNP < 50 pg/ml).

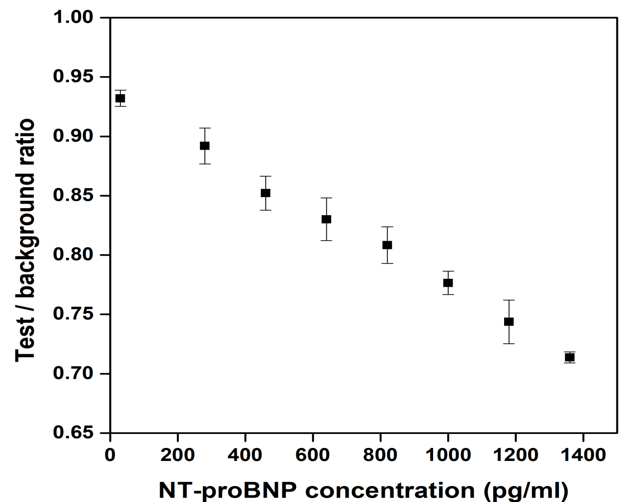

FIGURE 2. The calibration curve of negative control serum spiked with human NT-proBNP in the range of 30 to 1360 pg/ml.

We measure the absorbance of the test strip in two locations, (i) at the test line and (ii) the background (blank area) of the test strip using the biomarker analyser, as explained in greater detail in the hardware section II-D1. We then use the ratio of the optical absorbance of the test line and background, which helps to overcome any heterogeneity in the test strip background [30]. The calibration curve, test/background ratio R against NT-proBNP concentration C, with a goodness of fit (R^2) equals 0.9966 as is shown in figure 2. The calibration curve was modelled as a linear fit as equation (1):

$$C = 6174R + 5775.2 \tag{1}$$

The average coefficient of variation (CV) of the calibration curve is 1.6% which compares favourably to similar LFIA NT-proBNP tests [31]. The combination of low CV and linear response of the sensor in the tested range (30 to 1360 pg/ml) demonstrate a clear ability to accurately detect NT-proBNP for HF patients.

C. LOW VOLUME BLOOD SAMPLING

Here we present the design and fabrication of our biomarker sampling key, used for obtaining and transferring a blood sample for use in the biomarker analyser. This section details how blood samples will be taken in future medical trials and by patients at home, we stress that our present work uses human clinical plasma samples. The intended use of the biomarker sampling key is a simple, inexpensive tool for collecting a finger-prick blood sample, without training or the need of a healthcare worker. For a PoC system, the preferred source of patient's blood is finger-prick blood, since venous-draw blood needs to be collected by a nurse or phlebotomist, which can be a source of distress [32]. Our previous experience in using PoC diagnostics for measurement of blood-based biomarkers (particularly in the global diagnostic Qualcomm Tricorder XPRIZE competition [33]) demonstrated that the user experience must be improved if PoC diagnostics are to find widespread use, especially for more elderly patients. Our design has the following features:

(i) the patient should be able to use the system, alone, without the need of a healthcare worker, and by using a standard commercial blood collecting lancet.

(ii) the required blood volume is low (<25μL), as this is the average amount of blood that can be comfortably obtained [34].

(iii) external pipettes and capillary tubes (especially those requiring the use of one hand to extract blood from the other) require a high level of dexterity and need not be used. Blood is introduced directly from one finger into the device.

(iv) sampling is rapid thereby reducing discomfort.

1) POLYMER HOUSING FOR THE LATERAL-FLOW ASSAY

The basic design of the biomarker sampling key is of a polymer housing which includes a 25μL capillary channel, in fluidic connection with an enclosed LFIA test strip. This 'single-use' assembly must be placed directly into the biomarker analyser, ready for the addition of a blood sample and subsequent analysis. The key is constructed from two polymer pieces as shown in figure 3(a) and has a hydrophilic cover tape (ARCARE 93049 hydrophilic pressure-sensitive adhesive), over the channel to aid wicking. The principle is that, initially, a blood drop is obtained on the finger, using a standard lancet and then rapidly wicked from the patient's finger, directly into the capillary channel, figure 3(b-c). Secondly, when the required volume is full; the entire blood volume drains into the NT-proBNP LFIA. The channel outlet is in direct physical contact with the LFIA sample pad as shown in figure 3(d). This can be performed in one drop or in several small drops according to which is easier for the patient. The test is then completed and a measurement is obtained by the biomarker analyser. The main design features of the device are described in the following paragraphs.

The required volume of blood required in most of the available PoC NT-proBNP test kits varies from 70 to 150μL [35].

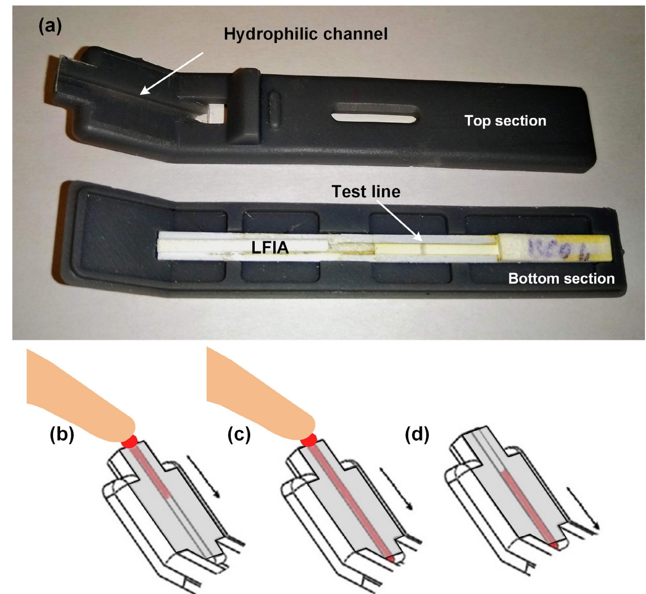

FIGURE 3. (a) photograph of the biomarker sampling key with top, bottom pieces and LFIA, (b) patient starts to sample blood (c) blood is rapidly wicked into the channel (d) when full, the blood rapidly drains into the LFIA for measurement.

We have reduced the required volume in our LFIA by minimising the physical width of the test strip. The typical width of a commercial lateral flow assay is between 4 to 5 mm which is needed to help facilitate reading by eye. We have, however, designed our strips as 1.5 mm wide, for opto-electronic measurement which can be successfully performed with 25μL of whole blood. Minimising the time taken to introduce the blood sample into the test, through the use of highly 'wicking' capillary action helps to reduce the likelihood of blood spills. To draw blood by capillary action the capillary channel must have both a capillary length below that of blood, and a positive surface energy force. This has been achieved by ensuring that the diameter of the blood collection channel is below the capillary length λ_c [36] of blood calculated as:

$$\lambda_c = \sqrt{\gamma/(\rho g)} \tag{2}$$

where γ is the surface tension of blood ($\sim 55.9\, mNm^{-1}$) [37], ρ is the density of blood (1060kg m^{-3}) [38] and g is the acceleration due to gravity; thus the capillary length is ~2.3 mm and the channel height is set as 1.5mm. The capillary force is calculated as [36]:

$$F_\gamma = w\gamma(\cos\theta_2 + \cos\theta_1) + 2h\gamma(\cos\theta_1) \tag{3}$$

where θ_1 is the contact angle between blood and the three 3D-printed walls, θ_2 is the contact angle between blood and the top surface, w is the channel width and h is the channel height. The value of θ_1 is $\sim 69°$ (measured using KSV Instruments LTD Cam200 contact angle meter) and by using a hydrophilic, biologically compatible adhesive tape, the contact angle of the top surface, θ_2 is much lower at $\sim 25°$. The surface energy force is thus highly positive and provides

rapid wicking. After the channel is filled, the blood quickly and fully drains into the sampling pad of the LFIA which will reach completion without further user intervention by relying on passive capillary flow. The result is a test line of variable density which is measured by the biomarker analyser.

D. BIOMARKER ANALYSER

1) HARDWARE

The principle of the biomarker analyser is to measure the optical absorbance of the LFIA at the test line and divide this value by the optical absorbance at the LFIA background. Our embedded system consists of a microcontroller, light emitting diodes, optical sensors, and a Wi-Fi module for data transmission. We used two small PCBs, the first includes 2 LEDs (LED PCB) for illuminating the LFIA and the second includes 2 ambient light sensors (ALS PCB) for measuring absorbance, as shown in figure 4(a) which shows the optical layout of the lateral flow strip reader used to quantify the NT-proBNP concentration in the blood sample. In the biomarker analyser, two green (525nm) LEDs (Würth Elektronik) have been used as optical illuminating sources. One LED is positioned directly above the test line and the second LED is used to illuminate a blank, 'background' section of the LFIA.

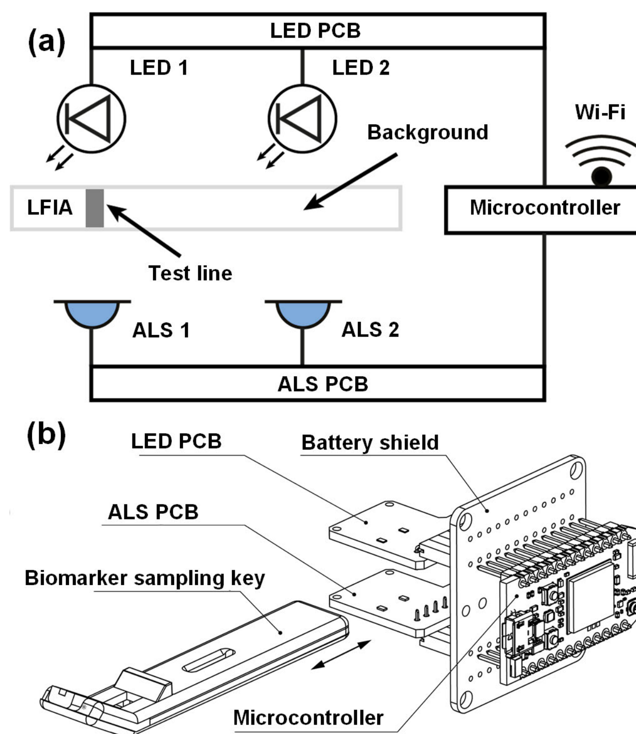

FIGURE 4. (a) Block diagram of the electronic circuit. (b) Optical layout of the strip reader. Two LEDs are used to illuminate the control and test line with an ALS under each line to measure the optical intensity after passing through the biomarker sampling key.

In our system, 2 ambient light APDS 9301 sensors (Avago Technologies) were used for light detection. This ALS contains two integrating analog-to-digital converters (ADC) that digitise and integrate the currents from two photodiodes. Two integrating ADCs convert the photodiode currents to a digital output that represents the irradiance measured on each channel. The light intensity to digital signal output capable of direct I2C interface. This digital input is used in a microcontroller to calculate the NT-proBNP concentration in the sample using equation (1). Two ALS have been placed on the ALS PCB and aligned to the two LEDs on the LED PCB, as shown in figure 4(b). The biomarker analyser microcontroller is a Particle Photon board (Wurth Elektronik) that combines an ARM Cortex M3 microcontroller with a Broadcom Wi-Fi chip. A lithium-ion battery, which may be charged using the battery shield, enables the biomarker analyser to be used portably.

ALS 1 is located directly below the test line (7 mm separation) and measures the intensity at the carbon line illuminated by the corresponding LED. The separation between the LED and the test line is 3 mm. The LED illuminates the line and the AC-NP absorbs the photons and subsequently reduces the intensity measured by the ALS. The AC-NP that binds at the test line results in a darker line, with increased optical absorbance. Since the density of the test line is related to the number of AC-NP attached to the NT-proBNP, the optical intensity is used to measure the quantity of the NT-proBNP present in the sample.

ALS 2 is used to measure the absorption of the LED light through the LFIA and it is used as a background measurement for the ratio of test line divided by background measurement.

2) FIRMWARE

The firmware was uploaded to the Particle Photon board via the Wi-Fi network. The Particle Photon board enables updates to the firmware via a Wi-Fi network.

The firmware tasks can be broken into:

1) Control the illumination of the two LEDs
2) Control the gain and integration time of the sensors
3) Collect the digitised sensor measurements
4) Transmit the measurements to the web-based dashboard

The input voltage used to turn the LEDs on and off is supplied by the Particle board which in turn collects the sensor measurements every 5s. Each sensor measurements extracted from the I2C communication line is transmitted via Wi-Fi to the private server for viewing and analysis.

E. WEB-BASED DASHBOARD FOR MONITORING

Initial insights about HF point to key interventions during follow-ups to provide better care and for avoiding re-admissions. We have adopted and extended a data model initially developed for an outpatient clinic for heart failure patients at the Academic Medical Center (AMC) in Amsterdam, The Netherlands [39] to capture the different practices, medications, and data in general about Heart Failure and the key interventions. We extended the model in order to capture data from the proposed PoC solution.

The solution presented in this paper focuses on interventions where a PoC device is used during a medical visit to the patient's home, or for self-use. NT-proBNP is measured and monitored through consecutive visits. The progression of NT-proBNP serves as an indication of patient response to the treatment and also serves as a deciding factor for considering readmission.

Measured values of NT-proBNP are sent via Wi-Fi to the data storage server and they can be viewed in the web-based data viewer or mobile app. Figure 5(a) shows a screen in the web-based system for monitoring NT-proBNP. The system also is capable of sending alarms for risk analysis based on the proposed algorithm based on changes in consecutive concentrations of NT-proBNP 5(b).

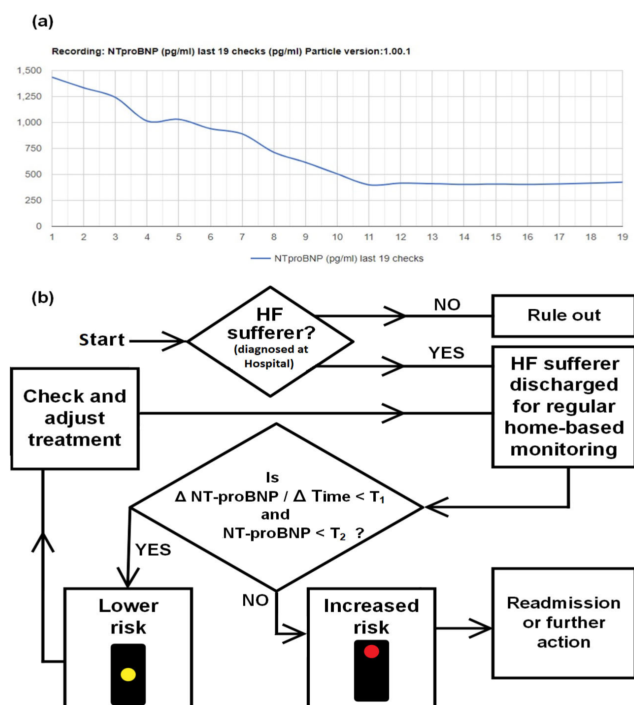

FIGURE 5. **(a) Screen from a web-based system to monitor the progression of NT-proBNP during a hypothetical patient's follow-up. (b) An algorithm for home monitoring of NT-proBNP on discharged HF sufferers. T_1 and T_2 are thresholds for relative and absolute changes on the biomarker.**

III. RESULTS

A. COMPARISON OF THE MEASUREMENTS

To compare the result of the ALS to a standard method of measuring LFIA test results, we used a flatbed scanner (HP OFFICEJET PRO 8600, 1200 DPI) to image the test strips (which had been removed from the biomarker key).

We used ImageJ [40] for analysing scanned images of the test strips. For each LFIA test strip, a selection box of defined size was manually centered over the LFIA membrane corresponding to the test line region. The 'Profile-plot' tool was used to measure the peak amplitude of the test line in greyscale values with reference to the background greyscale value of the non-test line region of the membrane.

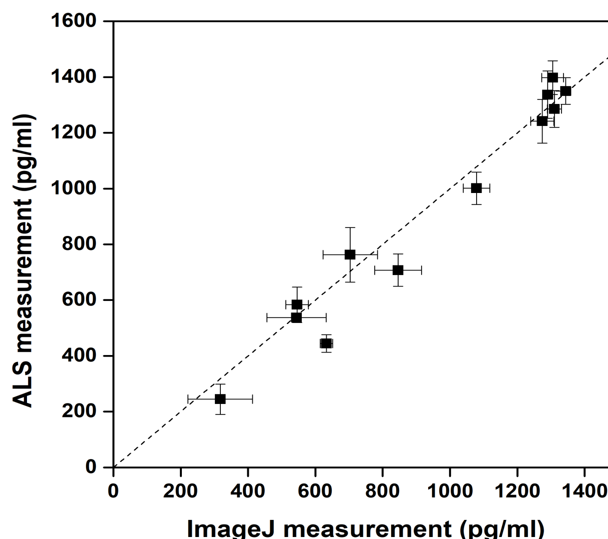

FIGURE 6. **Comparison curve between the measured values of 12 LFIA patient samples, as measured using ImageJ image analysis from a scanned image, and the biomarker analyser ALS-based measured value.**

This is an established method for deriving a quantitative output from LFIA test strips [41]–[43]. Its previous and common usage makes it useful as a 'reference' measurement method to which we can compare results from the biomarker analyser.

Image analysis using ImageJ is a technical procedure that requires some level of training and skill. Meanwhile, the biomarker analyser is designed and programmed for home-based use with minimal training; such that patient need only (i) insert biomarker sampling key and (ii) provide a blood sample.

A plot of the measurement of 12 patient samples obtained from both the Image analysis and the biomarker analyser is shown in figure 6. The results show a close trend, with the accuracy of each measurement system of a similar order: the average coefficient of variation (CV) of results (triplicate sets of LFIA tested at each concentration for the biomarker analyser is 7.8% versus 7.3% for ImageJ. Some of the heterogeneity in measurement derives from defects in the optical quality of the test line (for example, variation caused by unequal fluid flow [44]). It should be also noted that our conjugate antibody was the '24E11' antibody which recognises a.a. 61-76 of NT-proBNP and the test line antibody was the 15F11 which recognises a.a. 13-27 of NT-proBNP. Neither of these regions appears to be affected by glycosylation [45], [46] whereas the Roche assay does appear to be affected by the glycosylation status of the particular patient sample [47]. Thus in future testing our PoC assay will be cross-correlated against further commercial NT-proBNP assays.

The same 12 patients NT-proBNP plasma samples ($\tilde{x}_i \;\; i = 1..12$) were measured using LFIA test strips used with the biomarker sampling key and biomarker analyser PoC device and were compared with their corresponding reference values extracted from the image analysis ($x_i \;\; i = 1..12$)

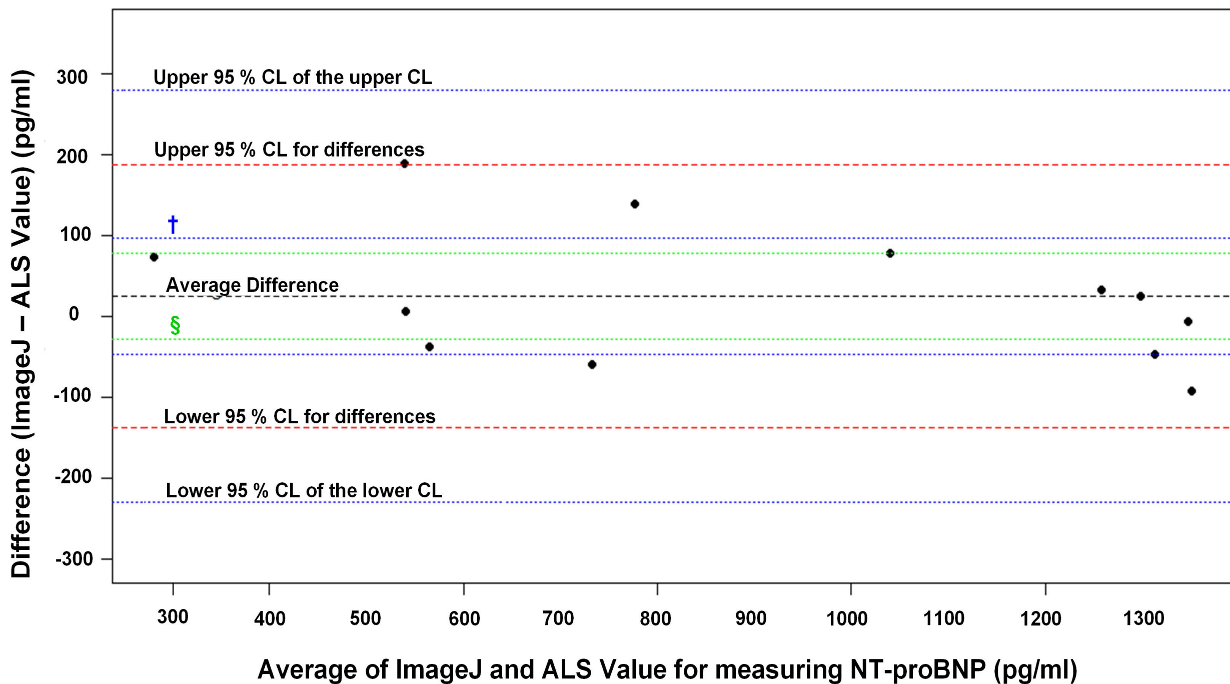

FIGURE 7. Bland-Altman plot for 12 pairs of measurements of NT-proBNP. The reference values from Image J analysis are compared to the PoC solution reported in this paper. The average difference $\bar{d}$ is 24.58 pg/ml, the lower and upper limit of the confidence interval at 95% for the differences are −138.42 and 187.58 pg/ml respectively which are delimited by the dotted red lines. These limits also define the Limits of Agreement (LoA) and the seen differences are expected to be confined to them and not to exceed the maximum allowed clinical deviation. However, the differences could be inside the envelope provided by the outmost limits given by the confidence intervals of the LoA plotted in blue. Additionally, the confidence interval at 95% for the mean difference is indicated in green lines; † for the upper limit and § for the lower limit.

independently performed on the scanned image of the LFIA. A Bland-Altman plot [48] was generated using the 12 pairs of measurements and it is shown in figure 7. The range of values covers values from HF sufferers and normal individuals. Each point in the plot has coordinates (a_i, d_i) where the average of the two measurements $(a_i = (x_i + \tilde{x}_i)/2)$ goes in the horizontal axis and the difference $(d_i = x_i - \tilde{x}_i)$ is located in the vertical axis. For the analysed data, the average of the differences $\bar{d} = \sum_{i=1}^{12} d_i/12$ is 24.58 meaning that the PoC values $(\tilde{x}_i)$ are in general 24.58 pg/ml below the reference value (x_i). This offset could be corrected by just adding 24.58 to the PoC values. The standard deviation of the differences (according to $sd = \sqrt{\sum_{i=1}^{12}(d_i - \bar{d})^2/11}$) is 83.16. The confidence interval at 95% for the differences $(\bar{d} \pm 1.96sd)$ is used as a tool for verifying agreement between the measurements. It is, however, important to additionally check for any obvious skew and ultimately to demonstrate clinical agreement. At this time, a true estimation of limit of detection or quantification has not been made as we have focused on the trending performance for patients who are clearly suffering from heart failure and have significantly elevated levels of NT-proBNP.

IV. DISCUSSION

In this paper, we have aimed to present a PoC solution that can aid in the treatment and care of HF patients through the use of a novel diagnostic system based on NT-proBNP LFIA. A key driving force in this work has been to produce a reliable system that can be used without supervision, and with minimal discomfort. Commercial portable PoC systems are available, for example, the Roche cobas h 232 POC system but this is intended for pre-hospital and emergency room, rather than home-based settings. For example, the most widely used home-based diagnostic kits worldwide are blood-based glucose testing for diabetes patients [49]. The success of diabetes testing is that is simple and relatively pain-free, and the volume of blood need not be tightly measured by the user. The level of discomfort is minimised by enabling testing with one drop of blood. In contrast, lateral flow immunoassay-based testing typically requires several blood drops which is very off-putting for the patient. This system tries to address this issue of usability by reducing the blood volume down to a minimum and by automatically measuring blood volume by means of filling a capillary channel.

We present results of the concentration of NT-proBNP measured by our PoC solution compared to the ImageJ method. The two methods do not replace the validated Roche analyser (or similar lab-based analysers) for NT-proBNP currently used in many hospital labs. However, the biomarker analyser is a simplification of a quantitative method offered by image analysis aimed for home use. It can give an account of changes on the concentration of NT-proBNP that can be an indication of adherence to the treatment or could raise a flag for a possible readmission if required. For example,

a 2015 study on the serial measurement of NT-proBNP in patients with stable coronary heart disease showed that, after 12 months, an increase in NT-proBNP levels was associated with increased risk of subsequent cardiovascular event [50]. Furthermore, Masson *et al.* [51] showed that NT-proBNP levels measured at time periods of 4-month intervals enabled greater risk stratification for HF patients, whilst Pascual-Figal *et al.* [23] showed that changes in NT-proBNP level were predictive of subsequent cardiovascular events in HF patients after a period of 2 weeks to 6 months. NT-proBNP levels need to be carefully interpreted in elderly patients with comorbidities, who may have elevated NT-proBNP levels without having HF [52]. We emphasise that this is an additional tool for HF monitoring, on a case-by-case basis, and not intended for diagnosis of HF.

It can be observed that the 12 points of the Bland-Altman plot in figure 7 are well contained within the confidence interval at 95% (LoA) for the differences and the points uniformly spread up and down from the horizontal line defined by the average of differences $\bar{d}$ along with the range of values. No systematic skew is seen and the possible offset can be removed to bring the mean difference to zero. Guidelines suggest that, in serial measurements, a practical threshold of a 30% variation in the measured value of NT-proBNP over time is indicative of a clinically relevant change [53]. Thus, for a patient with elevated (above 450 pg/ml [8]), the sensitivity of our PoC system suggests that this could become a clinically useful tool, though we stress the need for further testing with patients. We present the framework in figure 5(b) for serial monitoring of NT-proBNP levels over time, and how increased values of the biomarker may be used as an alarm to readmit patients to hospitals or to readjust the treatment. The low CV and linearity of the LFIA test (as shown in figure 2) and the linear response of the biomarker analyser relative to the standard ImageJ analysis, figure 6, show that clinically relevant changes in NT-proBNP measurements would be detectable with our system.

It is understood that the system is intended mainly for already diagnosed HF-sufferers and the algorithm as presented in figure 5(b) serves as an example for the aim and it would require data collected and validated to tune the thresholds and parameters involved. The framework proposes two thresholds: T_1, for the rate of change of NT-proBNP with time, and T_2 for the absolute value of NT-proBNP, as proposed by Maisel *et al.* [8]. When both T_1 and T_2 fall below the threshold levels, this would be indicative of patient improvement whilst values further increasing above these thresholds would indicate deterioration and may signify the requirement for further treatment. This paper has set out the framework for how our PoC will be used. Future ongoing work will aim to show the system in a clinical setting.

V. CONCLUSION

The presented PoC solution has shown promise in being adopted for routine follow-up medical visits for HF sufferers and for HF high-risk patients.

The home-based biomarker analyser and blood sampling key enable the measurement and monitoring of a patient's progress and may help in the decision for readmission, or changes in treatment. Early warnings in non-adherence with the treatment reflected by significant increases of the biomarker, may improve patient management and consequently reduce hospital readmissions.

The low-cost solution is relatively easy to operate after minimal training and requires no specialist equipment.

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REFERENCES

[1] G. Savarese and L. H. Lund, "Global public health burden of heart failure," *Cardiac Failure Rev.*, vol. 3, no. 1, pp. 7–11, Apr. 2017.

[2] J. McMurray, S. Adamopoulos, and S. Anker, "ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012," *Eur. Heart J.*, vol. 33, pp. 1787–1847, May 2012.

[3] C. W. Yancy, M. Jessup, B. Bozkurt, J. Butler, D. E. Casey, Jr., M. H. Drazner, "2013 ACCF/AHA guideline for the management of heart failure," *Circulation*, vol. 128, no. 16, pp. e240–e327, 2013.

[4] C. Bugge, E. M. Sether, A. Pahle, S. Halvorsen, and I. S. Kristiansen, "Diagnosing heart failure with NT-proBNP point-of-care testing: Lower costs and better outcomes. A decision analytic study," *BJGP Open*, vol. 2, no. 3, pp. 1–9, Oct. 2018.

[5] E. G. Spanakis, M. Psaraki, and V. Sakkalis, "Congestive heart failure risk assessment monitoring through Internet of Things and mobile personal health systems," in *Proc. 40th Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. (EMBC)*, Jul. 2018, pp. 2925–2928.

[6] B. Jin, C. Che, Z. Liu, S. Zhang, X. Yin, and X. Wei, "Predicting the risk of heart failure with EHR sequential data modeling," *IEEE Access*, vol. 6, pp. 9256–9261, Jan. 2018.

[7] R. L. Fitzgerald, R. Cremo, N. Gardetto, A. Chiu, P. Clopton, V. Bhalla, and A. S. Maisel, "Effect of nesiritide in combination with standard therapy on serum concentrations of natriuretic peptides in patients admitted for decompensated congestive heart failure," *Amer. Heart J.*, vol. 150, no. 3, pp. 471–477, Sep. 2005.

[8] A. Maisel *et al.*, "State of the art: Using natriuretic peptide levels in clinical practice," *Eur. J. Heart Fail*, vol. 10, no. 9, pp. 824–839, Sep. 2008.

[9] A. Maisel, D. Barnard, B. Jaski, G. Frivold, J. Marais, M. Azer, M. I. Miyamoto, D. Lombardo, D. Kelsay, K. Borden, N. Iqbal, P. R. Taub, K. Kupfer, P. Clopton, and B. Greenberg, "Primary results of the HABIT trial (heart failure assessment with BNP in the home)," *J. Amer. College Cardiol.*, vol. 61, no. 16, pp. 1726–1735, Apr. 2013.

[10] A. Clerico, M. Fontana, L. Zyw, C. Passino, and M. Emdin, "Comparison of the diagnostic accuracy of brain natriuretic peptide (BNP) and the N-terminal part of the propeptide of BNP immunoassays in chronic and acute heart failure: A systematic review," *Clin. Chem.*, vol. 53, no. 5, pp. 813–822, May 2007.

[11] P. R. Degregory, J. Tapia, T. Wong, J. Villa, I. Richards, and R. M. Crooks, "Managing heart failure at home with point-of-care diagnostics," *IEEE J. Transl. Eng. Health Med.*, vol. 5, Sep. 2017, Art. no. 2800206.

[12] M. D. Wilkins, B. L. Turner, K. R. Rivera, S. Menegatti, and M. Daniele, "Quantum dot enabled lateral flow immunoassay for detection of cardiac biomarker NT-proBNP," *Sens. Bio-Sens. Res.*, vol. 21, pp. 46–53, Nov. 2018.

[13] Y. Liu, H. Wang, C. Xiong, Y. Chai, and R. Yuan, "An ultrasensitive electrochemiluminescence immunosensor for NT-proBNP based on self-catalyzed luminescence emitter coupled with PdCucarbon nanohorn hybrid," *Biosensors Bioelectron.*, vol. 87, pp. 779–785, Jan. 2017.

[14] A. Panneer Selvam and S. Prasad, "Nanosensor electrical immunoassay for quantitative detection of NT-pro brain natriuretic peptide," *Future Cardiol.*, vol. 9, no. 1, pp. 137–147, Jan. 2013.

[15] I. Sarangadharan, S.-W. Huang, W.-C. Kuo, P.-H. Chen, and Y.-L. Wang, ''Rapid detection of NT-proBNP from whole blood using FET based biosensors for homecare,'' *Sens. Actuators B, Chem.*, vol. 285, pp. 209–215, Apr. 2019.
[16] S. A. Rezaeieh, K. S. Bialkowski, and A. M. Abbosh, ''Microwave system for the early stage detection of congestive heart failure,'' *IEEE Access*, vol. 2, pp. 921–929, Aug. 2014.
[17] W. Pan, A. He, K. Feng, Y. Li, D. Wu, and G. Liu, ''Multi-frequency components entropy as novel heart rate variability indices in congestive heart failure assessment,'' *IEEE Access*, vol. 7, pp. 37708–37717, Feb. 2019.
[18] M. Gjoreski, A. Gradišek, B. Budna, M. Gams, and G. Poglajen, ''Machine learning and end-to-end deep learning for the detection of chronic heart failure from heart sounds,'' *IEEE Access*, vol. 8, pp. 20313–20324, 2020.
[19] O. Nakagawa, Y. Ogawa, H. Itoh, S. Suga, Y. Komatsu, I. Kishimoto, K. Nishino, T. Yoshimasa, and K. Nakao, ''Rapid transcriptional activation and early mRNA turnover of brain natriuretic peptide in cardiocyte hypertrophy. Evidence for brain natriuretic peptide as an 'emergency' cardiac hormone against ventricular overload,'' *J. Clin. Invest*, vol. 96, no. 3, pp. 1280–1287, Sep. 1995.
[20] H.-N. Kim and J. L. Januzzi, ''Natriuretic peptide testing in heart failure,'' *Circulation*, vol. 123, no. 18, pp. 2015–2019, May 2011.
[21] M. Weber, V. Mitrovic, and C. Hamm, ''B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide—Diagnostic role in stable coronary artery disease,'' *Exp. Clin. Cardiol.*, vol. 11, no. 2, pp. 99–101, 2006.
[22] N. Li and J.-A. Wang, ''Brain natriuretic peptide and optimal management of heart failure,'' *J. Zhejiang Univ. Sci.*, vol. 6B, no. 9, pp. 877–884, 2005.
[23] D. A. Pascual-Figal, M. Domingo, T. Casas, I. Gich, J. Ordoñez-Llanos, P. Martínez, J. Cinca, M. Valdés, J. L. Januzzi, and A. Bayes-Genis, ''Usefulness of clinical and NT-proBNP monitoring for prognostic guidance in destabilized heart failure outpatients,'' *Eur. Heart J.*, vol. 29, no. 8, pp. 1011–1018, Feb. 2008.
[24] K. M. Koczula and A. Gallotta, ''Lateral flow assays,'' *Essays Biochemistry*, vol. 60, no. 1, pp. 111–120, Jun. 2016.
[25] M. O'Keeffe, P. Crabbe, M. Salden, J. Wichers, C. Van Peteghem, F. Kohen, G. Pieraccini, and G. Moneti, ''Preliminary evaluation of a lateral flow immunoassay device for screening urine samples for the presence of sulphamethazine,'' *J. Immunological Methods*, vol. 278, nos. 1–2, pp. 117–126, Jul. 2003.
[26] E. B. Bahadir and M. K. Sezgintürk, ''Lateral flow assays: Principles, designs and labels,'' *TrAC Trends Anal. Chem.*, vol. 82, pp. 286–306, Sep. 2016.
[27] P. Spicar-Mihalic, B. Toley, J. Houghtaling, T. Liang, P. Yager, and E. Fu, ''CO_2 laser cutting and ablative etching for the fabrication of paper-based devices,'' *J. Micromech. Microeng.*, vol. 23, no. 6, May 2013, Art. no. 067003.
[28] A. Larsson, ''Specificity of b-type natriuretic peptide assays: Knockin' on the assay door,'' *J. Lab. Precis. Med.*, vol. 2, no. 1, pp. 2–4, Jan. 2017.
[29] A. G. Semenov and E. E. Feygina, ''Standardization of BNP and NT-proBNP immunoassays in light of the diverse and complex nature of circulating BNP-related peptides,'' *Adv. Clin. Chem.*, vol. 85, pp. 1–30, Mar. 2018.
[30] C. Li, W. Luo, H. Xu, Q. Zhang, H. Xu, Z. P. Aguilar, W. Lai, H. Wei, and Y. Xiong, ''Development of an immunochromatographic assay for rapid and quantitative detection of clenbuterol in swine urine,'' *Food Control*, vol. 34, no. 2, pp. 725–732, Dec. 2013.
[31] K.-S. Song, S. Nimse, M. Sonawane, S. Warkad, and T. Kim, ''Ultra-sensitive NT-proBNP quantification for early detection of risk factors leading to heart failure,'' *Sensors*, vol. 17, no. 9, p. 2116, Sep. 2017.
[32] B. Deacon and J. Abramowitz, ''Fear of needles and vasovagal reactions among phlebotomy patients,'' *J. Anxiety Disorders*, vol. 20, no. 7, pp. 946–960, Jan. 2006.
[33] Connected Healh and Innovation Centre (CHIC) Northern Ireland and Intelesens/Scanadu. (2016). *Qualcomm Tricorder Xprize Finalist*. Accessed: Jun. 23, 2020. [Online]. Available: https://tricorder.xprize.org/prizes/tricorder/teams/intelesens_scanadu
[34] H. R. Peck, D. M. Timko, J. D. Landmark, and D. F. Stickle, ''A survey of apparent blood volumes and sample geometries among filter paper bloodspot samples submitted for lead screening,'' *Clinica Chim. Acta*, vol. 400, nos. 1–2, pp. 103–106, Feb. 2009.
[35] C. Gils, R. Ramanathan, T. Breindahl, M. Brokner, A. L. Christiansen, Ø. Eng, I. J. Hammer, C. B. Herrera, A. Jansen, E. C. Langsjøen, E. S. Løkkebo, T. Osestad, A. D. Schrøder, and L. Walther, ''NT-proBNP on cobas h 232 in point-of-care testing: Performance in the primary health care versus in the hospital laboratory,'' *Scandin. J. Clin. Lab. Invest.*, vol. 75, no. 7, pp. 602–609, Aug. 2015.
[36] F. Brochard-Wyart, ''Droplets: Capillarity and wetting,'' in *Soft Matter Physics*, M. Daoud and C. Williams, Eds. Berlin, Germany: Springer, 1999.
[37] E. Hrncír and J. Rosina, ''Surface tension of blood,'' *Physiol. Res.*, vol. 46, no. 4, pp. 319–321, 1997.
[38] S. Tripathi, Y. V. B. V. Kumar, A. Prabhakar, S. S. Joshi, and A. Agrawal, ''Passive blood plasma separation at the microscale: A review of design principles and microdevices,'' *J. Micromech. Microeng.*, vol. 25, no. 8, Aug. 2015, Art. no. 083001.
[39] J. E. Bosmans, M. H. Baljon, W. R. M. Dassen, E. T. van der Velde, and O. Labots, ''Evaluating connectivity for a heart failure database,'' in *Proc. Comput. Cardiol.*, 2002, pp. 373–375.
[40] C. A. Schneider, W. S. Rasband, and K. W. Eliceiri, ''NIH image to ImageJ: 25 years of image analysis,'' *Nature Methods*, vol. 9, no. 7, pp. 671–675, Jun. 2012.
[41] L. Lee, E. Nordman, M. Johnson, and M. Oldham, ''A low-cost, high-performance system for fluorescence lateral flow assays,'' *Biosensors*, vol. 3, no. 4, pp. 360–373, Oct. 2013.
[42] X. Zhu, P. Shah, and C. Li, ''Paper-based immunosensor for oxidative DNA damage biomarker detection,'' in *Proc. 29th Southern Biomed. Eng. Conf.*, May 2013, pp. 125–126.
[43] J. Park, ''An optimized colorimetric readout method for lateral flow immunoassays,'' *Sensors*, vol. 18, no. 12, p. 4084, Nov. 2018.
[44] A. I. Barbosa, J. H. Wichers, A. van Amerongen, and N. M. Reis, ''Towards one-step quantitation of prostate-specific antigen (PSA) in microfluidic devices: Feasibility of optical detection with nanoparticle labels,'' *BioNanoScience*, vol. 7, no. 4, pp. 718–726, Dec. 2017.
[45] K. R. Seferian, N. N. Tamm, A. G. Semenov, A. A. Tolstaya, E. V. Koshkina, M. I. Krasnoselsky, A. B. Postnikov, D. V. Serebryanaya, F. S. Apple, M. M. Murakami, and A. G. Katrukha, ''Immunodetection of glycosylated NT-proBNP circulating in human blood,'' *Clin. Chem.*, vol. 54, no. 5, pp. 866–873, May 2008, doi: 10.1373/clinchem.2007.100040.
[46] S. Fu, P. Ping, Q. Zhu, P. Ye, and L. Luo, ''Brain natriuretic peptide and its biochemical, analytical, and clinical issues in heart failure: A narrative review,'' *Frontiers Physiol.*, vol. 9, p. 692, Jun. 2018.
[47] A. G. Semenov and A. G. Katrukha, ''Analytical issues with natriuretic peptides—Has this been overly simplified?'' *EJIFCC*, vol. 27, no. 3, pp. 189–207, Aug. 2016.
[48] J. M. Bland and D. Altman, ''Statistical methods for assessing agreement between two methods of clinical measurement,'' *Lancet*, vol. 327, no. 8476, pp. 307–310, Feb. 1986. [Online]. Available: http://www.sciencedirect.com/science/article/pii/S0140673686908378
[49] A. S. John and C. P. Price, ''Existing and emerging technologies for point-of-care testing,'' *Clin. Biochem. Rev.*, vol. 35, no. 3, pp. 155–167, Aug. 2014.
[50] D. Dallmeier, M. J. Pencina, I. Rajman, W. Koenig, D. Rothenbacher, and H. Brenner, ''Serial measurements of N-terminal pro-brain natriuretic peptide in patients with coronary heart disease,'' *PLoS ONE*, vol. 10, no. 1, pp. 1–13, Jan. 2015. [Online]. Available: https://doi.org/10.1371/journal.pone.0117143
[51] S. Masson, R. Latini, I. S. Anand, S. Barlera, L. Angelici, T. Vago, G. Tognoni, and J. N. Cohn, ''Prognostic value of changes in N-terminal pro-brain natriuretic peptide in val-HeFT (Valsartan heart failure trial),'' *J. Amer. College Cardiol.*, vol. 52, no. 12, pp. 997–1003, Sep. 2008.
[52] F. Fabbian, A. De Giorgi, M. Pala, R. Tiseo, and F. Portaluppi, ''Elevated NT-proBNP levels should be interpreted in elderly patients presenting with dyspnea,'' *Eur. J. Internal Med.*, vol. 22, no. 1, pp. 108–111, Feb. 2011.
[53] K. Thygesen, J. Mair, C. Mueller, K. Huber, M. Weber, M. Plebani, Y. Hasin, L. M. Biasucci, E. Giannitsis, B. Lindahl, W. Koenig, M. Tubaro, P. Collinson, H. Katus, M. Galvani, P. Venge, J. S. Alpert, C. Hamm, and A. S. Jaffe, ''Recommendations for the use of natriuretic peptides in acute cardiac care: A position statement from the study group on biomarkers in cardiology of the ESC working group on acute cardiac care,'' *Eur. Heart J.*, vol. 33, no. 16, pp. 2001–2006, Feb. 2011, doi: 10.1093/eurheartj/ehq509.

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