REVIEW

Recent advances in nephropathy biomarker detections using paper-based analytical devices

Akhmad Sabarudin1 · Setyawan P. Sakti2 · Aulanni'am1 · Hani Susianti3 · Nur Samsu4 · Ika O. Wulandari1 · Yudit Oktanella5 · Dewi Anggraeni2

Received: 31 August 2021 / Accepted: 22 October 2021
© The Author(s), under exclusive licence to The Japan Society for Analytical Chemistry 2022

Abstract
Nephropathy or kidney disease involves the deterioration of kidney functions, causing severe diseases, such as proteinuria, chronic kidney diseases, and kidney failure. Currently, nephropathy that develops into kidney failure is increasing globally, as indicated by the increasing number of patients undergoing hemodialysis. Some developed analytical methods for nephropathy using albumin, creatinine, uric acid, and the urinary albumin-to-creatine ratio biomarkers, including spectrophotometry, turbidimetric immunoassay, and ELISA, have been reported so far, providing good accuracy and precision. However, WHO has established guidelines for developing diagnostic tools that meet several criteria: Affordable, Sensitive, Specific, User-friendly, Rapid and Robust, Equipment-free, Delivered to those who need it. This means that nephropathy detection can be carried out using a simple method compatible with point-of-care that allows independent urine analysis by patients. For this purpose, the use of paper-based analytical devices (PADs) as an alternative platform for the detection of albumin, creatinine, uric acid, and the urinary albumin-to-creatine ratio were reviewed.

Keywords Kidney disease · Point of care · Nephropathy · Diagnostic tools · Paper-based devices

Introduction
Nephropathy, also known as kidney disease, is the loss of kidney function, mainly caused by diabetes and hypertension [1]. Diabetes and hypertension often coexist and are the most well-known combination for diabetic nephropathy (DN) pathogenesis. However, the interaction mechanism of hypertension with diabetes in exacerbating nephropathy remains unclear [2]. Without early clinical detection, this disease can eventually lead to chronic kidney disease (CKD), kidney failure (KF), and even death [3–6]. Large-scale screening programs conducted in the 2000s in the USA [7], Australia [8], and Norway [9] showed that more than 10% of the adult population had markers of kidney disease. The high burden on health-care systems of this disease was also confirmed in Japan [10], Taiwan [11], China [12], India [13], African countries [14, 15], European countries [16], Brazil [17], Bangladesh [18], Indonesia [19], and several other developing countries [20]. Furthermore, Foreman et al. [21] reported that nephropathy caused 1.2 million deaths in 2017. This number is expected to increase to 2.2 million in the best-case scenario and will reach 4 million deaths in the worst-case scenario by 2040. Therefore, nephropathy can be attributed to a global health problem.

The early detection of nephropathy is of paramount importance to prevent the severity of kidney damage, which can be achieved by early clinical examination as well as good disease management. Biomarkers present...
in urine [22–26] and serum [27–30] samples are playing a significant role in this purpose. Several new markers, such as peptides [31, 32], oxidative stress [33, 34], inflammation, [35, 36], and protein-based [37–39] biomarkers, have been reported in many studies as the alternative or possible biomarkers for assessing kidney diseases. However, using these new biomarkers in clinical applications still requires further evaluation and validation to be recognized as a new diagnostic standard [6]. To date, due to extensive validations, the estimated glomerular filtration rate (eGFR) through the measurement of serum creatinine levels to assess kidney function, and the urinary albumin-creatinine ratio test (UACR, mg albumin per gram creatinine) to estimate the extent of kidney disorders, are the most commonly used clinical diagnosis of nephropathy [40, 41]. Nephropathy occurs when the urinary albumin-to-creatinine ratio (UACR) is > 30 mg g⁻¹ or microalbuminuria level in the range of 30–300 mg g⁻¹. Diabetes Mellitus (DM) patients who suffer from nephropathy for at least 3 months are referred to as chronic kidney disease (CKD) patients [42].

Because of its easiness and non-invasive collections, urine is preferable to blood/serum biological samples for the detection of nephropathy [43], and creatinine and albuminuria (expressed as UACR) detections are widely used laboratory tests to assess kidney disorders [44, 45]. The amount of creatinine excreted through the urine indicates the condition of kidneys. Urine contains proteins, end products of nucleic acid metabolism, metabolites (urea, uric acid, creatinine, ammonia, amino acids), organic and inorganic salts, electrolytes, vitamins, hormones, enzymes, and other components as end products of the body’s metabolic processes. Through quantitative and qualitative monitoring of changes in urine composition, it is possible to obtain important diagnostic information not only related to kidney and urinary tract diseases, but also pathologies of other organs, such as the cardiovascular system, endocrine system, and metabolic system [46]. Urinalysis can also provide important information on disease progression, estimation of prognosis and treatment options [47]. It should be taken into consideration that the concentration of urine components is influenced by diet, water intake, sweat, and other factors so that the quantitative composition of urine varies significantly depending on the amount of urine excreted at a certain time. As a result, measurements of a single urine component concentration, creatinine [48–51], do not provide accurate physiologic information. Furthermore, creatinine detection is considered to be less sensitive because when kidney damage reaches > 33%, the creatinine levels are just starting to rise significantly [45]. Additionally, for accurate creatinine clearance analysis, a 24-h urine collection is required for the analysis, which makes it burdensome for patients [52]. The effect of urine volume can be compensated by expressing the desired concentration of the urine component as the amount of analyte per amount of creatinine. The UACR, which is defined as mg dL⁻¹ of albumin per g dL⁻¹ of creatinine, is considered to be the best option for this purpose. Besides non-invasive sampling, the UACR examination can avoid problems caused by the volume of urine sample collection because it does not require 24-h urine collection [53], so the UACR is considered as an accurate method for screening albuminuria to indicate kidney disease [54, 55]. Other reports showed that the higher is the uric acid levels, the greater is the possibility of decreased kidney function [56–58]. This means that the presence of uric acid is linked to the development of kidney disease, confirming its possibility to be applied as a biomarker of nephropathy.

Various analytical methods have been developed for biomarker detections of kidney disease, including sequential injection analysis (SIA) [53, 54], spectrophotometry [59], turbidimetric immunoassays [60], ELISA [61], liquid extraction-chromatography [49], biosensor amperometry [50], and high-performance liquid chromatography [51]. These modern instrumentation methods provide high sensitivity and accuracy. However, relatively high-cost analysis, time-consuming analysis, complicated procedures, requires large amounts of reagents and samples, less portable, requires a well-trained operator, and expensive instrumentation, making these methods less effective, especially for patients who are far away from modern health facilities.

The World Health Organization (WHO) has set seven guidelines for developing a diagnostic tool called ASSURED (A, Affordable; S, Sensitive; S, Specific; U, User-friendly; R, Rapid and Robust; E, Equipment-free; D, Delivered to those who need it) [62]. Based on this information, it can be said that it is highly desirable to use a simple point-of-care testing (POCT) for the detection of nephropathy (kidney disease) that the general public can use. This requirement can be achieved using PADs.

PADs were first introduced by Martinez et al. [63] as analytical devices equipped with microfluidic patterns on paper as the main component. They can be considered to be an alternative tool of the previously available classical dipstick tests (CDT) [64, 65]. The philosophy behind PADs is to enable an analytical system that is inexpensive, disposable, easy-to-use. It can be applied in resource constraints, like in developing countries or at home, where technical expertise and infrastructure are limited. Under ideal conditions, PADs are considered as self-standing analysis systems equipped with all components needed to perform an analytical assay, such as sample transport systems, sample pretreatment, reagents, and detection systems. The glass or polymer materials in CDT are replaced with paper materials (PADs) to be cheap, easily available, and become disposable.
materials. Paper made from pure cellulose, such as chromatographic paper, has chemical and physical properties suitable for applying PADs [66]. Chromatographic paper does not need any additives, and almost all impurities from the raw material are removed after the bleaching process. Cellulose is the primary component of the paper material, with an abundance of hydroxyl groups (–OH) and a small amount of carboxylic acid groups (–COOH) on the surface [67]. The two groups act as a framework for immobilizing reagents on PADs. The compounds with a positive electrostatic charge will be adsorbed on the anionic surface of cellulose, while compounds with a negative charge or no electrostatic charge will not be adsorbed [68]. The essential feature of PADs is the use of a small amount of sample volume and reagents, as well as their ability to perform multitarget analysis. PADs have microfluidic channels in the form of open, porous channels with the laminar fluid flow type. Consequently, a continuous flow of solution occurs because of the wicking properties of the paper used. Thus, solution handling can be done simply without using a pump [69], but only based on the capillarity and geometry of PADs.

The PADs have been introduced as promising tools for point-of-care testing (POCT); for example, they were applied for the detection of kidney disease through the determination of blood urea nitrogen (BUN) [70], albumin [71], creatinine [72], and UACR [73] using color-based intensity/colorimetric methods [70–73]. However, these PADs rely on measuring the color intensities of the reaction between reagents and biomarkers involving the use of cameras (smartphone, CMOS) or scanners, computers, and software for color intensity analysis. Distance-based PADs make it possible to realize instrumentation-free POCT or naked-eye detection [74] without using color-to-reference comparisons (color chart), as in classical dipstick tests (CDT) [64, 65] or other tools [70–73]. The schematic illustrations for comparing colorimetric detection with flow length/distance-based detection for albumin and creatinine using PADs as well as the illustration for preparing PADs using printing method are given in Fig. 1. In this review, we focus on paper-based analytical devices as the promising POCT for detecting a single component of creatinine, albumin, uric acid, and multiple components of urinary albumin-to-creatinine ratio (UACR) using paper-based analytical devices.

**Paper-based analytical devices for determination of creatinine**

Creatinine, a biological marker in serum and urine, is commonly used in clinical applications to estimate kidney function. Regarding the POCT, some studies dealing with the determination of creatinine using a paper-based platform have been reported, as summarized in Table 1.

The enzymatic paper-based analytical device (enz-PAD) for detecting creatinine in urine samples was introduced by Talalak et al. [75] The consortium enzyme reagents (creatininase, creatinase) and detection reagents (4-aminophenazone- and 2,4,6-triiodo-3-hydroxybenzoic) were immobilized onto the PADs at two certain regions. When the device is immersed in urine samples, creatinine is converted into H₂O₂, which further reacts with the detection reagents to form a pink-red color of quinoneimine.

Sittiwong and Unob [76] used filter paper coated with 3-propylsulfonic acid trimethoxysilane for the colorimetric urinary creatinine detection. The presence of a sulfonate group allows for a cationic creatinine to bind to the paper’s surface via electrostatic interaction. Alkaline picrate reagent is employed to detect creatinine in urine samples, resulting in a yellow-orange color complex on the paper. Similar work was performed by Sununta et al. [77] using microfluidic paper-based analytical devices (µPADs) as a platform for urinary creatinine determination based on the Jaffé reaction. The resulting orange color complex, which corresponds to the creatinine concentration, is analyzed by Image J software.

Tseng et al. [72] introduced three-dimensional (3D)-PADs equipped with a portable detection system. The main components of the detection system consist of a detection box, a relay, a temperature controller, a voltage regulator module, a power source, a CMOS camera, a WiFi chip, and a smartphone. The proposed integrated system is applied to determining creatinine in human whole blood samples. The 3D-PADs include three parts as an inlet region, a separation channel, and a detection zone. The detection system is based on a Jaffé reaction where alkaline picrate is immobilized onto the detection zone. For determining creatinine, 5 µl of whole human blood is dripped onto the inlet region of the 3D-PADs, and blood plasma diffuses through the separation channel to the detection zone, which produces an orange color of the Janovsky complex as a result of the reaction between creatinine and alkaline picrate. Although the color complex, which represents the creatinine concentration, can be analyzed automatically using a portable detection system, heating the 3D-PADs at 37 °C may be a limitation of this method. Another similarly integrated system was proposed by Fu et al. [78] by combining a paper-based chip (as a reaction system) and a smartphone (as a detection system) to detect serum creatinine, according to the Jaffé reaction. A highly sensitive detection system (LOD: 0.0025 mg dL⁻¹) for creatinine determination was invented by Boobphahom et al. [79] using electrochemical paper-based analytical devices (ePADs) modified with a CuO/ionic liquid/reduced graphene oxide (CuO/IL/RGO) composite. The deposition of the composite onto the working electrode of
Fig. 1 Preparation of PADs using printing method (A), illustration colorimetric detection of albumin (ALB) and creatinine (CRE) (B) and flow length/distance-based detection of ALB-to-CRE ratio (C)

Table 1 PADs for determination of creatinine in urine and serum/blood samples

| No | Paper-based platform/structure | Working principle | Detection reagent/material used | Detection method | Sample | LOD (mg dL⁻¹) | Year | References |
|----|--------------------------------|-------------------|---------------------------------|-----------------|--------|--------------|------|------------|
| 1  | 2D                             | Enzymatic reaction using creatininase and creatinase | 4-aminophenazone, 2,4,6-triiodo-3-hydroxybenzoic acid | Colorimetry     | Urine  | 2.0          | 2015 | [75]       |
| 2  | Filter paper coated with 3-propylsulfinic acid trimethoxysilane | Jaffé reaction | Alkaline picrate | Colorimetry | Urine  | 0.42         | 2016 | [76]       |
| 3  | 2D                             | Jaffé reaction   | Alkaline picrate               | Colorimetry     | Urine  | 0.91         | 2018 | [77]       |
| 4  | 3D                             | Jaffé reaction   | Alkaline picrate               | Colorimetry     | Whole blood | 0.19     | 2018 | [72]       |
| 5  | Paper-based chip               | Jaffé reaction   | Alkaline picrate               | Colorimetry     | Serum  | 0.20         | 2018 | [78]       |
| 6  | 2D                             | Creatinine oxidation reaction | Integrated composite (CuO/IL/rGO) electrode | Amperometry     | Serum  | 0.0025       | 2019 | [79]       |
| 7  | 2D                             | Electrochemical reaction of creatinine-Fe³⁺ complex | Fe³⁺ ion | Amperometry     | Urine  | 0.95         | 2020 | [80]       |
| 8  | 2D                             | Jaffé reaction/ standard addition assay | Alkaline picrate | Colorimetry     | Urine  | 1.69         | 2020 | [81]       |
| 9  | 2D                             | Jaffé reaction   | Alkaline picrate               | Colorimetry     | Urine  | 11.88        | 2021 | [82]       |
| 10 | 2D                             | Jaffé reaction   | 3,5-dinitrobenzoate            | Colorimetry     | Urine  | 9.28         | 2021 | [82]       |

ILIonic liquid, rGO reduced graphene oxide, 2D 2 dimensional PADs, 3D 3 dimensional PADs
the PADs can improve the selectivity and sensitivity of the proposed method. Creatinine in the serum sample is then detected using amperometry at a constant potential. Fava et al. [80] has constructed ePADs with multiplexed working electrodes. In this system, urine creatinine is detected indirectly based on the electrochemical reduction of excess Fe\(^{3+}\) after forming the Fe\(^{3+}\)-creatinine complex. Therefore, the peak current intensity decreases as the creatinine concentration increases, resulting in a lower sensitivity compared with other ePAD systems [79].

PADs are generally produced by screen printing and wax/solid ink printing. Mathaweesansurn et al. [81] offer an easier, cheaper, and more practical PADs fabrication using rubber stamping to make the hydrophobic barrier pattern onto a filter paper. However, the reproducibility from device-to-device becomes a concern because it may be difficult for people to produce the reproducible PADs using this technique without being properly trained. Urine creatinine is detected by employing the Jaffé reaction, and a standard addition calibration line is applied to eliminate the matrix effect. After forming the creatinine-picrate complex, the orange color is captured, and the resulting digital image is processed using Image J software for creatinine quantification.

Two colorimetric detections, the Jaffé reaction, and 3,5-dinitrobenzoate methods were applied by Lewinska et al. [82] to determine creatinine in urine samples using PADs. As a result of the reaction between creatinine and the reagents, the color change is treated using a smartphone with a program written in-house for quantification of the analyte. It is interesting since the analytical performance obtained by an alternative 3,5-dinitrobenzoate method resulted in a slightly better sensitivity than the Jaffé reaction, as shown in Table 1.

**Paper-based analytical devices for determination of albumin**

Regardless of the clinical risk factors, urinary albumin and inflammatory markers, low serum albumin levels are strongly associated with decreased kidney function in the elderly [83]. Also, albumin derivatives have potential as a marker for the progression of kidney disease. It was found that high glycated albumin (GA) levels adversely affect patients with chronic kidney disease (CKD) [84], and cysteinyalted albumin (CA) increased with the decline of eGFR [85]. Because of being promising as tools for POCT, paper-based analytical devices were explored to detect albumin, as summarized in Table 2.

As given in Table 2, albumin determination in a biological sample using PADs is commonly performed using the dye-binding method with tetrabromophenol blue (TBPB), bromocresol green (BCG), coomassie brilliant blue (CBB), bromophenol blue (BPP), and yellow food dye based on the characteristic color change that occurs when the dye binds to proteins, called the metachromasy phenomenon. It seems that the color change of the dyes-albumin complex occurs due to the exchange of protons between the dyes and the albumin acidic or basic group.

Cassano and Fan [86] introduced a simple fabrication method of paper-based devices by craft-cutting and lamination, called laminated paper-based analytical devices (LPADs), for the determination of albumin. Synthetic urine spiked with bovine serum albumin (BSA) was dropped in the sample zone and then reacted with TBPB, resulting in a color change from yellow to greenish-blue in the detection zone. After scanning the image, the color intensity was analyzed using Image J software; the signal increased with the increasing BSA concentration. Almost similar works using similar colorimetric reagents with different PADs designs were performed by Mohammadi et al. [87] Yu et al. [89], and Xiong et al. [99].

PADs for detecting albumin in whole blood samples were reported by Boonyasit and Laiwattanapaisal [88] through the dye-binding reaction of BCG with albumin at pH 4.2 to form a blue-colored complex. To improve the accuracy of the analytical result in this work, a standard addition method was employed, while reducing the error in measuring the color intensity derived from the background of blood samples. Additionally, fructosamine was also determined as a correction for the albumin contents.

In 2015, Chen and Yang [90] used a colorimetric reagent of yellow food dye for the determination of albumin using distance-based PADs. In this work, the concentration of the albumin sample was evaluated by measuring the progression of the distance-based/flow length color change on PADs. Because of the adsorption of the albumin sample on the hydrophobic barrier, the flow length reduced as the concentration of the albumin sample increased. Other distance-based PADs for the detection of albumin using different colorimetric reagents, such as TBPB [105] and BCG [109], were also reported. As the flow length increased with increasing albumin concentration, the latter methods resulted in better sensitivity.

Although PADs provide great potential accompanied by easy-to-use, inexpensive, and portable, sensitivity and selectivity are two important points that require attention for the analysis of an analyte in complex biological samples, like urine, whole blood, and serum. By applying separation and preconcentration methods in PADs, the problems can be solved. For this purpose, ion concentration polarization (ICP) in PADs with BCG as a colorimetric reagent [91], paper-based with boronic acid-derived agarose beads [95], isoelectric focusing PADs with CBB R250 dye [96], and dynamic double gradients PADs with BPB dye [104] were...
| No | Paper-based platform/structure | Working principle | Detection reagent/material used | Detection method | Sample | LOD/mg dL$^{-1}$ | Year | References |
|----|--------------------------------|-------------------|--------------------------------|-----------------|--------|-----------------|------|------------|
| 1  | Laminated paper-based devices | Dye binding reaction | TBPB | Colorimetry | Synthetic urine | 16.61 | 2013 | [86] |
| 2  | 2D                             | Dye binding reaction | TBPB | Colorimetry | Artificial urine | 53.14 | 2015 | [87] |
| 3  | 2D                             | Dye binding reaction | BCG  | Colorimetry | Whole blood | 500  | 2015 | [88] |
| 4  | 2D                             | Dye binding reaction | TBPB | Colorimetry | BSA solution | 9.96  | 2015 | [89] |
| 5  | 2D                             | Dye binding reaction | Yellow food dye | Distance-based/flow length | BSA and HSA solution | 100  | 2015 | [90] |
| 6  | 2D                             | Ion concentration polarization/dye binding reaction | BCG | Colorimetry | BSA solution | 10  | 2016 | [91] |
| 7  | 2D                             | Dye binding reaction/ text-displaying assay | TBPB | Colorimetry | HSA-spiked urine | <30  | 2017 | [92] |
| 8  | Polyester-paper hybrid microdevices | Dye binding reaction | TBPB | Colorimetry | HSA solution | 500  | 2017 | [93] |
| 9  | Integrated paper-based chip | Dye binding reaction | BCG | Colorimetry | Whole blood | 368  | 2018 | [71] |
| 10 | Integrated paper-based chip | Dye binding reaction | BCG | Colorimetry | Patient’s HSA | 250  | 2018 | [94] |
| 11 | 2D                             | Boronic acid-derived agarose beads/Dye binding reaction | BCG | Lateral flow assay | Commercial human plasma | 470  | 2018 | [95] |
| 12 | 2D                             | Isoelectric focusing/Dye binding reaction | CBB R250 | Colorimetry | Commercial human serum | <50  | 2018 | [96] |
| 13 | 3D                             | Dye binding reaction | TBPB | Colorimetry | Human urine and serum | 23.25 | 2019 | [97] |
| 14 | Transparent PADs               | Dye binding reaction | TBPB | Light transmittance | BSA solution | 0.66 | 2019 | [98] |
| 15 | 2D                             | Dye binding reaction | TBPB | Colorimetry | Water | 0.64 | 2020 | [99] |
| 16 | 2D                             | Aggregation-induced quenching reaction | 2’-hydroxy chalcone derivatives | Ratiometric fluorescence | Whole blood | 0.12 | 2020 | [100] |
| 17 | 3D                             | Dye binding reaction | TBPB | Angular-based of discolored area | BSA solution | <30 | 2020 | [101] |
| 18 | 3D                             | Dye binding reaction | TBPB | Colorimetry | HSA-spiked serum | 100 | 2020 | [102] |
| 19 | Paper-based magnetoelastic | HSA and anti-HSA antibody binding | NiFe$_2$O$_4$ | Electro-magnetic | HSA solution | 0.043 | 2020 | [103] |
| 20 | 2D                             | Dynamic double gradients/dye binding reaction | BPB | Colorimetry | Human urine | 0.49 | 2020 | [104] |
| 21 | 2D                             | Poly-(4-styrenesulfonic acid)/dye binding reaction | TBPB | Distance-based | Artificial urine | <15 | 2021 | [105] |
| 22 | Integrated paper-based microchip | Dye binding reaction | BCG | Colorimetry | Human urine, whole blood | 50 | 2021 | [106] |
employed to improve the selectivity and sensitivity for the colorimetric determination of albumin in fluid body samples.

In 2017, text-displaying colorimetric PADs were reported by Yamada et al. [92]. The employment of a conventional colorimetric TBPB reagent and an extra inert colorant allows for a versatile text-displaying detection mechanism on PADs, making it a particularly intriguing technology for albumin detection. The analytical results of albumin in urine samples using this method were comparable with a commercially available colorimetric urine dipstick, but it should be noted that identifying a color shift on a urine dipstick might be difficult with the naked eye.

Incorporating and maintaining reagents in a stable condition while keeping low system costs is still challenging in creating PADs for fully portable and automated onsite analysis. For this purpose, Krauss et al. [93] developed field-deployable polyester-paper hybrid microfluidic devices utilizing a fabrication approach based on the print, cut, and laminate methodology that allows for easy, yet effective, dry reagent storage for improved use with centrifugal or polymeric-based devices. TBPB was used as a chemical sensing agent for the colorimetric detection of albumin. However, because the LOD was 500 mg dL\(^{-1}\), it is still very hard to be applied in real samples.

Integrating PADs with an autonomous readout system can improve the efficiency of their application. Several reports have combined colorimetric albumin analysis using PADs with portable image analysis in a unified system [71, 94, 106]. In this work, they proved the detection of albumin using BCG, resulting in the color changes dramatically from yellow to blue. The portable image analyzer system is usually a small box equipped with a program written in-house that contains a camera (CMOS camera of smartphone or CCD camera), a light guide, a lens, PADs holder, a connector, a thin, flexible heater, a WIFI module, and a battery. The utilization of temperatures above room temperature may be a constraint, despite the convenience of this integrated system.

In 2019 and 2020, three-dimensional paper-based microfluidic analytical devices (3D-PADs) were reported for the detection of albumin [97, 101, 102]. Generally, 3D-PADs are created by stacking multiple layers of patterned paper, producing sophisticated three-dimensional microfluidic networks that can improve the efficiency of analytical and bioanalytical assays. The deprotonation of TBPB as a result of the reaction between TBPB and albumin, which altered the color of the dye from yellow to blue, was used to determine the albumin concentration in biological samples in these reports. Kim et al. [101] made the design of 3D-PADs like a bow ruler, which consists of a circle sample zone and a bow-like channel, allowing for the detection of albumin-based on an angular-based measurement of the discolored area on 3D-PADs.

Zong et al. [98] created transparent PADs for the determination of albumin using BPTB as a detecting reagent. Transparent PADs are made of cellulose-based materials (paper) by eliminating the microcavities in the fiber network through the casting, filtration, and extrusion process, which creating a highly optical transmittance of the paper. Therefore, this transparent device can reduce background interferences and improve the transmittance, resulting in a highly sensitive detection of albumin by wavelength-dependent absorbance/transmittance. The principle of transparent PADs is that after the reaction of albumin with BPTB, the color changes from yellow to blue, while generating a significant shift of the transmittance on the transparent paper. The remaining light was passed through the detector to measure the absorbance, which corresponds to the albumin concentration.

A dual-state emissive chalcone probe with aggregation-induced emission integrated with PADs was produced by Luo et al. [100]. The fluorescence is first reduced because of aggregation-induced quenching, and then increased by probe molecules bound to the HSA’s hydrophobic cavity. This principle is used as the basis to determine the albumin concentration as the color change from red to green.
Currently, the application of magnetic nanomaterials in bioanalytical chemistry is growing rapidly. Guo et al. [103] developed a rapid, sensitive, and portable method for determining human serum albumin (HSA) using a paper-based magnetoelastic biosensor. In this work, NiFe2O4 was impregnated to the paper, followed by the immobilization of anti-HSA. When the sample is dropped into modified PADS, the specific binding of HSA and the anti-HSA antibody occurs, resulting in increases the compressive stress of the sensor surface and reducing the static magnetic permeability. The magnetic field strength is then measured by a Gauss meter. The higher HSA concentration, the lower is the magnetic field strength obtained. Another application of nanomaterial-modified PADS was also reported by Raj et al. [107]. The detection zone of PADS was modified with a suspension of cellulose nanocrystal (CNC) by drop-casting followed by drying for 40 min. The colorimetric reagent of TBPB was then deposited on the detection zone, while resulting in a color change from yellow to blue when albumin is dropped to the device. The image analysis was performed using Fiji software for the quantification of albumin. Pyrene carboxylic acid-modified single-walled carbon nanotubes (PCA/SNWTs) were deposited on the paper substrate and applied for a highly sensitive detection of albumin. The detection is based on the electrical resistance when the albumin sample is dropped into the detection zone. So far, this Paper-based chemiresistor biosensor provides the highest sensitivity (LOD: 1 × 10⁻⁵ mg dL⁻¹) compared to other methods for the determination of albumin. [71, 86–107, 109].

Paper-based analytical devices for determination of uric acid

Uric acid is the end product of purine degradation, and hyperuricemia occurs if the compound level is over 6.8 mg dL⁻¹. [110, 111] Several studies have reported that an increase in the amount of uric acid in biological fluids is associated with the development and progression of kidney disease [56–58, 112]. PADS that offer fast, inexpensive, portable analysis and are able to be operated by the general people without well-trained skills provide an opportunity to be used as a point-of-care testing (POCT) for uric acid detection, as summarized in Table 3.

Electrochemical detection for the determination of uric acid (UA) provides excellent detection limits. Dungchai et al. [113] constructed electrochemical paper-based analytical devices (ePADs) for uric acid determination based on the quantification of resulting peroxide during the reaction. Urate oxidase catalyzed oxidation of UA and reduction of oxygen into H₂O₂. The selectivity of this work was improved by applying Prussian Blue (PB) as a selective catalyst for H₂O₂ reduction, eliminating the potential interferences from the matrix of the biological samples. The utilization of paper-based separation devices onto a gold electrochemical microcell’s surface results in better sensitivity of ePADs toward UA analysis [115]. The utilization of nanomaterial/nanocomposite to ePADs improved the electron transfer, resulting in higher sensitivity of the electrochemical detection of UA [80, 121, 125]. The surface modification of the ePADs working electrode with nanosized carbon black (NCB) produced a seven-times higher anodic peak current than non-modified ePADs [80]. This significantly higher current signal was due to the high surface area of NCB, which strongly affects the increasing electrical conductivity. Nontawong et al. [121] prepared a nanocomposite composed of magnetic nanoparticle (Fe₃O₄), gold nanoparticle, cysteine, and polyaniline (Fe₃O₄@Au-Cys/PANI) to modify the working electrode of ePADs. The presence of gold in the nanocomposite provided a good electrical conductivity and electron transport, allowing for improved current responses. The existence of a pair of redox peaks in Fe₃O₄@Au-Cys/PANI raised this material's electroactive and conductivity properties, which means that the electrocatalytic activity and redox responsiveness are improved most in Fe₃O₄@Au-Cys/PANI. Perhaps, the use of graphene oxide in the reduced form (GO) is one of the best options for the surface modification of ePADs because it can strongly improve the electron transfer. Huang et al. [125] constructed the nanocomposite by the electrodeposition of poly (3,4-ethylenedioxythiophene) (PEDOT) and GO on disposable paper-based devices, which further integrated with the Ag/AgCl and the Pt wire to form a three-electrode system. The electrocatalytic ability of this system is much improved, resulting in the highest sensitivity among ePADs systems. The nanocomposite of PEDOT-GO provides a wide effective surface area and a highly conductive substrate that can promote electron transfer between the electrode and the UA, resulting in an improved electrocatalytic activity.

The colorimetric detection of UA using the paper-based platform was mainly based on the oxidation of dye indicators by H₂O₂ generated through the interaction of urate oxidase (UOX) with the substrate. The use of the second enzyme of horseradish peroxidase (HRP) as a catalyst potentially leads to signal amplification, and hence increased sensitivity due to the interaction of H₂O₂ with HRP. It has been reported that the sensitivity of the bi-enzyme (UOX and HRP) system was observed to be roughly 2.4-times higher than that of a single enzyme system [118]. Dungchai et al. [114] introduced μPADs with a center sample zone and multiple detection zones, and employed multiple indicators for the colorimetric detection of UA. Two kinds mixture of indicators, such as (a) 4-aminoantipyrine/AAP and 3,5-dichloro-2-hydroxybenzenesulfonic acid/DHBS, and (b) a mixture of potassium iodide, acid yellow 34, and acid black 1 were used.
Recent advances in nephropathy biomarker detections using paper-based analytical devices

Table 3 PADs for determination of uric acid (UA)

| No | Paper-based platform/structure | Working principle | Detection reagent/ Material used | Detection method | Sample | LOD (mg dL⁻¹) | Year | References |
|----|--------------------------------|-------------------|---------------------------------|------------------|--------|---------------|------|------------|
| 1  | 2D                             | Oxidation of UA and reduction of oxygen into H₂O₂ | PB/ UOx | Amperometry | Human control serum | 23.20 | 2009 | [113] |
| 2  | 2D                             | The oxidation of indicators by H₂O₂ | Multiple indicators/ UOx/HRP | Colorimetry | Human control serum and urine | 1.68 | 2010 | [114] |
| 3  | Paper-based separation device  | Oxidation of UA | Gold electrochemical microcell | Amperometry | Uric acid solution | 0.34 | 2010 | [115] |
| 4  | 2D                             | Rhodanine—H₂O₂ reaction | UOx/rhodanine derivatives | Chemiluminescence | Artificial urine | 8.74 | 2011 | [116] |
| 5  | 2D                             | Rhodanine—H₂O₂ reaction | UOx/rhodanine derivatives | Chemiluminescence | Artificial urine | 31.94 | 2011 | [117] |
| 6  | 3D                             | Oxidation of chromogenic reagents by H₂O₂ | AAP/DHBS/ Mixture of trehalose/ HRP/UOx | Colorimetry | Human serum | 0.72 | 2012 | [118] |
| 7  | Paper-based chip               | Oxidation of TMB by H₂O₂ | AuNPs/TMB | Colorimetry | Serum | 0.46 | 2016 | [119] |
| 8  | 2D                             | AgNPs formation | Ag⁺/ammonia/ PVA | Chemometric/ Colorimetry | Urine | 0.57 | 2018 | [120] |
| 9  | 3D                             | Oxidation of UA | Nanocomposite-modified electrode | Voltammetry | Urine | 0.03 | 2018 | [121] |
| 10 | 2D                             | Oxidation of chromogenic reagents by H₂O₂ | Cu²⁺-UOx-HRP/ AAP-DHBS | Colorimetry | Human whole blood | 0.42 | 2018 | [122] |
| 11 | Multilayer-modified test paper | Oxidation of TMB by H₂O₂ | Chitosan-HRP-UOx/TMB | Colorimetry | Serum | 0.05 | 2018 | [123] |
| 12 | Double-layered paper           | Oxidation of chromogenic reagents by H₂O₂ | TMB or AAP and TOPS/UOx/ HRP/ | Colorimetry | Serum | 0.08 | 2018 | [124] |
| 13 | 2D                             | Oxidation of UA | Carbon black-modified electrode | Voltammetry | Urine | 0.20 | 2019 | [80] |
| 14 | 2D                             | Oxidation of UA | Nanocomposite-modified electrode | Voltammetry | Saliva | 0.01 | 2020 | [125] |
| 15 | 2D                             | Aggregation of AuNPs | 2-thiouracil/ AuNPs | Colorimetry | Spiked goat serum | 1.19 | 2021 | [126] |

PB Prussian Blue, UOx urate oxidase, HRP horseradish peroxidase, AAP 4-amino antipyrine, DHBS 3,5-dichloro-2-hydroxy acid sodium, AuNPs gold nanoparticles, AgNPs silver nanoparticles, TOPS N-Ethyl-N-(3-sulfopropyl)-3-methyl-aniline sodium salt, TMB tetramethylbenzidine, PVA poly-(vinyl alcohol), 2D 2 dimensional PADs, 3D 3 dimensional PADs

To increase the detection accuracy by strengthening the ability to visually discriminate between different concentrations of UA. Similar principle colorimetric detections for the determination of UA using multiple indicators and dual enzyme system (UOx and HRP) were also reported by other researcher [118, 122–124].

Yu et al. [116, 117] studied the determination of UA using microfluidic paper-based chemiluminescence analytical devices (μPCADs). The principle of this method is based on the formation of H₂O₂ as the result of an enzyme–substrate reaction between UA and UOx. Then, the chemiluminescence reaction was created in the acidic medium between the generated H₂O₂ and rhodanine derivatives.

Gold nanoparticles (AuNPs) and silver nanoparticles (AgNPs) have plasmon resonance features that could be used to construct sensing alternatives to enzyme-catalyzed processes for the detection of UA. These nanoparticles act as peroxidase mimics so that the UOx and HRP enzymes are no longer required. Using this concept,
Zhao et al. [119] prepared non-enzymatic µPADs for the detection of UA using AuNPs. The basic detection of UA is as follows: the colorless tetramethylbenzidine (TMB) was oxidized to a blue color when AuNPs and a mixed solution of TMB and H2O2 were dropped on the detection zone of µPADs. The UA sample was then placed in the blue-color detection zone, reducing the blue-oxidized TMB into a colorless. The concentration of UA was calculated using the grey value of the detection zone after the image was captured by a mobile-phone camera. Another colorimetric assay for the determination of UA involving nanoparticles was also introduced by Hamedpour et al. [120]: In this case, AgNPs were formed on the µPADs under mild basic conditions through the interaction of Ag+ ions with UA, ammonia, and poly-(vinyl alcohol). The resulting yellow color AgNPs, which correspond to UA concentration, could be observed by the naked eye. In 2021, Pinheiro et al. [126] also used a non-enzymatic method for UA detection through the functionalization of AuNPs modified with 2-thiouracil (2-TU) in PADs. In this report, an interesting phenomenon remains a question; when UA at low concentration reacts with 2-TU molecules, it can promote additional aggregation of AuNPs; however, when higher concentrations of 2-TU are initially applied, UA can cause anti-aggregation of AuNPs.

**Paper-based analytical devices for determination of the urinary albumin-to-creatinine ratio**

Biological samples, for example, urine, serum, whole blood, are very complex components. The composition of these samples is influenced by food, water intake, activity, and other factors. Therefore, to improve the accuracy of the results, the detection of disease (e.g., kidney disease) cannot be estimated from a single biomarker [71, 72, 76–79, 127]. The simultaneous detection of several biomarkers, [80, 81, 128–132], although better than single component detection, cannot compensate for changes in the composition or matrix present in the sample, which is influenced by some factors mentioned above. It will be even more difficult if there is no clear correlation among the analyzed components. Measurements of the ratio between one component and another can overcome this problem, providing more accurate results. Accordingly, the detection of UACR for assessing kidney disease is the best option of choice, and is still utilized as a standard diagnosis. Furthermore, the use of random/spot urine samples, which are easy to collect and non-invasive, is another advantage.

To date, there are not many reports on concerning the detection of UACR using PADs. We searched for articles with keywords of (a) albumin-to-creatinine ratio, (b) paper-based devices via scopus.com, and only found 2 articles, entitled a novel paper-based colorimetry device for the determination of the albumin to creatinine ratio [73] and paper-based device for naked-eye urinary albumin/creatinine ratio evaluation [74].

Chaiyo et al. [73] designed simple PADs for UACR detection, as shown in Fig. 2. The pattern of PADs on Whatman chromatographic paper no.1 was printed using a solid/wax ink printer. The pattern of PADs consists of a circle with a diameter of 7 mm and a line thickness of 1.41 mm. This circle acts as the sample zone as well as the detection zone. After deposition of the reagents, the sample was dropped to the detection zone, resulting in a color change of the reagent. The colorimetric detection of albumin and creatinine (ALB + CRE) was carried out using a bromocresol green (BCG) reagent in a phosphate buffer of pH 4, which resulted in a color change from greenish-yellow to bluish-green. Creatinine (CRE) was determined based on the Jaffé reaction. Picric acid was conditioned at alkaline pH with NaOH and reacted with CRE to produce a color change from yellow to orange. PADs were placed in a light-controlled box, and the color change was captured using a digital camera. The pictures were then processed with ImageJ software to determine the average R, G, and B values at the detection zone (see Fig. 2). The albumin concentration (ALB) was calculated by subtracting the color intensity of ALB + CRE with the intensity of the CRE color. The detection limit for UACR is 7.1 mg dL−1. A commercially available dipstick test can also perform the colorimetric UACR detection. Dipstick tests are a quick and easy way for measuring UACR. However, the progression from normoalbuminuria (30 mg/g), microalbuminuria (30300 mg/g) to macroalbuminuria (> 300 mg/g) may be difficult to observe because the color shift on a dipstick might be burdensome to identify with the naked eye [64, 65, 133–135]: Perhaps, this is a limitation on all colorimetric paper- or dipstick-based devices.

PADs based on the flow length (distance-based) of the color change make it possible to realize the instrumentation-free point of care testing (POCT) without the use of a reference color chart, camera, scanner, and software for image analysis. Hiraoka et al. [74] have successfully implemented this concept by preparing a “drawing PADs” device for UACR detection. In the drawing PADs, the UACR was determined by the naked-eye detection of ALB and CRE on a single device according to the distance-based PADs approach, as shown in Fig. 3. The design of the drawing PADs is quite simple, and consists of two bars parallel with the sample inlet zone at the bottom. For the distance-based quantification of CRE, a chrome azurol S (CAS)-Pd3+ complex was deposited on the first bar (left). The ligand-exchange process occurred
Recent advances in nephropathy biomarker detections using paper-based analytical devices

from CAS to CRE when CRE react with Pd$^{2+}$, changing the color from blue CAS-Pd$^{2+}$ to yellow CAS. The higher was the concentration of CRE, the longer was the flow length (distance-based) of the color change. In the distance-based quantification of ALB, tetrabromophenol blue (TBPB) in citric acid buffer was immobilized on the second bar (right). In the presence of ALB, TBPB is protonated, resulting in a color change from yellow to blue, or greenish-blue. The flow length of the color change increased with increasing the ALB concentration. The quantitative (or semiquantitative) detection of UACR was evaluated by drawing a line/slope that connected the two top color change zones of the first bar (CRE) and the second bar (ALB), resulting in the assessment of UACR levels; normo-, micro-, and macro-albuminuria (see Fig. 3). It seems that the drawing PADs provide a high potential to be applied as a POCT for the self-screening of kidney disease, especially for people who are far from access to modern health facilities, or located in developing countries.

**Conclusion**

The paper-based device is less expensive, more portable, and easier to use because it does not require a specialized instrumentation. The main point of PADs is that they are the cheapest disposable analytical microdevices available. For the detection of nephropathy or kidney disease, the detection of single biomarkers using PADs is not recommended due to a large number of confounding factors from biological samples that cannot be compensated. Although the detection of multiple biomarkers provides better accuracy, it may not be meaningful without considering the correlation between these biomarkers. Therefore, estimating kidney disease by evaluating the ratio of one biomarker to another (i.e., UACR) is the best option, compensating...
for changes in the composition in biological samples (i.e., urine and other body fluids) and increasing the accuracy of the results. However, research on PADs for the detection of kidney disease that can be used as POCT with instrumentation-free still needs to be encouraged.

Acknowledgements The authors would like to thank the ministry of finance of the Republic of Indonesia for financial support of this work through RISPRO LPDP 2021 (PRJ-033/LPDP/2021).

References

1. W.G. Couser, G. Remuzzi, S. Mendis, M. Tonelli, Kidney Int. 80, 1258 (2011)
2. J.B. Lopes de Faria, K.C. Silva, J.M. Lopes de Faria, Hypertens. Res. 34, 413 (2011)
3. P.N. Van Buren, T. Toto, Adv. Chronic. Kidney Dis. 18, 28 (2011)
4. V. Mohart, Cor Vasa 55, e397 (2013)
5. N. Shiba, H. Shimokawa, J. Cardiol. 57, 8 (2011)
6. R.N. Kazi, J. Interve. Nephrol. 1, 15 (2018)
Recent advances in nephropathy biomarker detections using paper-based analytical devices

7. J. Coresh, B.C. Astor, T. Greene, G. Eknoyan, A.S. Levey, Am. J. Kidney Dis. 41, 1 (2003)
8. S.J. Chadban, E.M. Briganti, P.G. Kerr, D.W. Dunstan, T.A. Welnborn, P.Z. Zimmet, R.C. Atkins, J. Am. Soc. Nephrol. 14(7 suppl 2), 131 (2003)
9. S.I. Hallan, J. Coresh, B.C. Astor, A. Asberg, N.R. Powe, S. Romundstad, H.A. Hallan, S. Lydersen, J. Holmen, J. Am. Soc. Nephrol. 17, 2275 (2006)
10. E. Imai, M. Horio, T. Watanabe, K. Iseki, K. Yamagata, S. Hara, N. Ura, Y. Kiyohara, T. Moriyama, Y. Ando, T. Goto, Y. Fukuwaza, N. Seki, K. Tobe, M. Matsumoto, M. Noda, H. Unoku-kubota, Diabetes Res. Clin. Pract. 147, 37 (2019)
11. S.U. Khan, J. Lin, X. Liu, H. Li, W. Lu, Z. Zhong, H. Zhang, M. Waqas, L. Shen, BBA Proteins Proteome. 1868, 140475 (2020)
12. Y. Ogawa, T. Goto, N. Tamasawa, J. Matsui, Y. Tando, K. Sugimoto, K. Tomoda, M. Kimura, M. Yasujima, T. Suda, Diabetes Res. Clin. Pract. 79, 357 (2008)
13. A.C. Baxmann, M.S. Ahmed, N.C. Marques, V.B. Menon, G.M. Pereira, G.M. Kirsztajn, I.P. Heilig, Clin. J. Am. Soc. Nephrol. 13, 348 (2008)
14. E. Nilavan, S. Sundar, M. Shenbagamoorthy, H. Narayanan, B. Gandagopal, R. Srinivasan, Diabetes Metab. Syndr. 14, 2073 (2020)
15. G. Veiga, B. Alves, M. Perez, L.V. Alcantara, J. Raimundo, L. Zambrano, J. Encina, E.C. Pereira, M. Bacci, N. Murad, F. Fonseca, J. Clin. Pathol. 73, 713 (2020)
16. L.A. Brondoni, A.A. Soares, M. Recamonde-Mendoza, A. Dall’Agnol, J.L. Camargo, K.M. Monteiro, S.P. Silveiro, Sci. Rep. 10, 1242 (2020)
17. M. Kroghal, G. Kontostathi, P. Magalhaes, M. Makridakis, J. Klein, H. Husi, J. Leierer, G. Mayer, J.L. Bascands, C. Denis, J. Zoidakis, P. Zurbrig, C. Delles, J.P. Schanstra, H. Mishak, A. Vlahou, Sci. Rep. 7, 15160 (2017)
18. M. Serdar, E. Sertoglu, M. Uyanik, S. Tapan, K. Akin, C. Bilgi, I. Kurt, Free Radic. Res. 46, 1291 (2012)
19. D.I. Jalal, M. Chonchol, W. Chen, G. Targher, Am. J. Kidney Dis. 61, 134 (2013)
20. N.M. El-Beblawy, N.G. Andrawes, E.A. Ismail, B.E. Enany, H.S. El-Seoud, M.A. Erfan, Clin. Appl. Thromb. Hemost. 22, 718 (2016)
21. S.Y. Liu, J. Chen, Y.F. Li, J. Diabetes Invest. 9, 1182 (2018)
22. Z. Li, Y. Xu, X. Liu, Y. Nie, Z. Zhao, Nephrology (Carlton) 22, 58 (2017)
23. A. Al-Kubeaean, K. Siddiqui, M.A. Al-Ghonaib, A.M. Youssef, A.H. Al-Sharqawi, D. AlNaqeb, Sci. Rep. 7, 2684 (2017)
24. W.L. Liao, C.T. Chang, C.C. Chen, W.J. Lee, S.Y. Lin, H.Y. Liao, C.M. Wu, Y.W. Chang, C.J. Chen, F.J. Tsai, J. Clin. Med. 7, 483 (2018)
25. C.-H. Lin, Y.-C. Chang, L.-M. Chuang, World J. Diabetes 13, 1153 (2020)
26. C. García-Carro, A. Vergara, S. Bermejo, M.A. Azancot, A.I. Togtokh, S.K. Sharma, P. Koirala, S. Uprety, I. Ulasi, G. Remuzzi, Lancet Glob. Health 4, e307 (2016)
27. R.Z. Alicic, M.T. Rooney, K.R. Tuttle, Clin. J. Am. Soc. Nephrol. 12, 2032 (2017)
28. A. Krishnegowda, N. Padmarajaiah, S. Anantharaman, K. Honnur, Arab. J. Chem. 10, S2018 (2017)
29. A. Fernandes, P. de Souza, A. de Oliveira, A. Chaves, J. Braz. Chem. Soc. 29, 695 (2017)
30. A. Ramanavicius, Anal. Bioanal. Chem. 2017, 387 (1899)
31. P.S.T. Yuen, S.R. Dunn, T. Miyaji, H. Yasuda, K. Sharma, R.A. Star. Am. J. Physiol. Renal Physiol. 286, F1116 (2004)
32. A.I. Nossier, N.I. Shehata, S.M. Morisy, D.F. Saeed, N.M. Elsayed, M.F. Ismail, S. Eissa, Anal. Biochem. 609, 113967 (2020)
33. M.H.R.arker, M. Moriyma, H.U. Rashid, M.J. Chisti, M.M. Rahman, S.K. Das, A. Uddin, S.M. Saha, S.E. Ariffin, T. Ahmed, A.S.G. Faruque, Ther. Adv. Chronic Dis. 12, 1 (2021)
34. P.P. Trihono, L. Rhodia, M.R. Karyati, Acta Med. Indones. 50, 283 (2018)
35. V.R. Biljak, L. Honović, J. Matica, B. Krešić, S.S. Vojak, Biochem. Med. (Zagreb) 27, 153 (2017)
36. D.I. Jalal, M. Chonchol, W. Chen, G. Targher, Am. J. Kidney Dis. 61, 134 (2013)
37. A. Vlahou, Sci. Rep. 7, 2684 (2017)
38. C.M. Wu, Y.W. Chang, C.J. Chen, F.J. Tsai, J. Clin. Med. 7, 483 (2018)
39. A. El-Seoud, M.A. Erfan, Clin. Appl. Thromb. Hemost. 22, 718 (2016)
40. C. García-Carro, A. Vergara, S. Bermejo, M.A. Azancot, A.I. Togtokh, S.K. Sharma, P. Koirala, S. Uprety, I. Ulasi, G. Remuzzi, Lancet Glob. Health 4, e307 (2016)
41. K.J. Foreman, N. Marquez, A. Dolgert, K. Fukutaka, N. Fullmann, M. Mcguaghe, M.A. Pletcher, A.E. Smith, K. Tang, C.W. Yuan, J.C. Brown, J. Friedman, J. He, K.R. Heuton, M. Holmberg, D.J. Patel, P. Reidy, A. Carter, K. Cercy, A. Chapin, D. Douwes-Schultz, T. Frank, F. Goetsch, P.Y. Liu, V. Nanda-kumar, M.B. Reitsma, V. Reuter, N. Sadat, R.J.D. Sorensen, V. Srinivasan, R.L. Updike, H. York, A.D. Lopez, R. Lozano, S.S. Lim, A.H. Mokdad, S.E. Vollset, C.J.L. Murray, Lancet 370, 2052 (2018)
42. C.M. Wu, Y.W. Chang, C.J. Chen, F.J. Tsai, J. Clin. Med. 7, 2684 (2017)
43. V.R. Biljak, L. Honović, J. Matica, B. Krešić, S.S. Vojak, Biochem. Med. (Zagreb) 27, 153 (2017)
44. M. Baumgarten, T. Gehn, Am. Fam. Physician 84, 1138 (2011)
45. J.A. Simerville, W.C. Maxted, J.J. Pahira, Am. Fam. Physician 73, 1153 (2005)
46. V.R. Biljak, L. Honović, J. Matica, B. Krešić, S.S. Vojak, Biochem. Med. (Zagreb) 27, 153 (2017)
47. M. Baumgarten, T. Gehn, Am. Fam. Physician 84, 1138 (2011)
48. J.A. Simerville, W.C. Maxted, J.J. Pahira, Am. Fam. Physician 73, 1153 (2005)
49. U.M. Jalal, G.J. Jin, J.S. Shin, Chem. Anal. Chem. 89, 13160 (2017)
50. A. Krishnegowda, N. Padmarajaiah, S. Anantharaman, K. Honnur, Arab. J. Chem. 10, S2018 (2017)
Recent advances in nephropathy biomarker detections using paper-based analytical devices

116. J. Yu, L. Ge, J. Huang, S. Wang, S. Ge, Lab. Chip 11, 1286 (2011)
117. J. Yu, S. Wang, L. Ge, S. Ge, Biosens. Bioelectron. 26, 3284 (2011)
118. X. Chen, J. Chen, F. Wang, X. Xiang, M. Luo, X. Ji, Z. He, Biosens. Bioelectron. 35, 363 (2012)
119. T. Zhao, Y. Chen, M. Zhang, Y. Wang, H. Zhang, P. Hu, Chem. J. Chin. Univ. 37, 829 (2016)
120. V. Hamedpour, G.J. Postma, E. van den Heuvel, J.J. Jansen, K. Suzuki, D. Citterio, Anal. Bioanal. Chem. 410, 2305 (2018)
121. N. Nontawong, M. Amatatongchai, W. Wuepchaiyaphum, S. Chairam, S. Pimmongkol, S. Panich, S. Tamuang, P. Jarujamrus, Int. J. Electrochem. Sci. 13, 6940 (2018)
122. J. Huang, X.-L. Zhu, Y.-M. Wang, J.-H. Ge, J.-W. Liu, J.-H. Jiang, Analyst 143, 4422 (2018)
123. X. Wang, F. Li, Z. Cai, K. Liu, J. Li, B. Zhang, J. He, Anal. Bioanal. Chem. 410, 2647 (2018)
124. F. Li, X. Wang, J. Liu, Y. Hu, J. He, Sens. Actuators B 288, 266 (2019)
125. X. Huang, W. Shi, J. Li, N. Bao, C. Yu, H. Gu, Anal. Chim. Acta 1103, 75 (2020)
126. T. Pinheiro, A.C. Marques, P. Carvalho, R. Martins, E. Fortunato, A.C.S. Appl. Mater. Interfaces 13, 3576 (2021)
127. C.-C. Tseng, C.-H. Ko, S.-Y. Lu, C.-E. Yang, L.-M. Fu, C.-Y. Li, Anal. Chim. Acta 1146, 70 (2021)
128. C.L.S. Chagas, F.R. De Souza, T.M.G. Cardoso, R.C. Moreira, J.A.F. Da Silva, D.P. De Jesus, W.K.T. Coltro, Anal. Methods 8, 6682 (2016)
129. E.L. Rossini, M.I. Milani, E. Carrilho, L. Pezza, H.R. Pezza, Anal. Chim. Acta 997, 16 (2018)
130. F.H. Cincotto, E.L. Fava, F.C. Moraes, O. Fatibello-Filho, R.C. Faria, Talanta 195, 62 (2019)
131. K. Income, N. Ratnarathorn, N. Khamchaiyo, C. Srisuvo, L. Ruckthong, W. Dungchai, Int. J. Anal. Chem. 2019, 3457247 (2019)
132. T.-H. Chang, K.-H. Tung, P.-W. Gu, T.-H. Yen, C.-M. Cheng, Micromachines 9, 586 (2018)
133. M.P. McTaggart, C.P. Price, R.G. Pinnock, P.E. Stevens, R.G. Newall, E.J. Lamb, Am. J. Kidney Dis. 60, 787 (2012)
134. J.R. Roberts, Emerg. Med. News 37, 14 (2015)
135. S.K. Sharma, M. Bala, N. Tulsani, N. Sehgal, A. Kumar, Indian J Chem. Technol. 9, 496 (2002)

Akhmad Sabarudin is currently head of the Research Center for Advanced System and Material Technology of Brawijaya University. He received Ph.D. in Analytical Chemistry from Okayama University, Japan. He spent 2 years as JSPS postdoctoral at Nagoya University. His research interests include developing monolithic chromatography for the separation of biomolecules and enantiomers, preparation of nanomaterials for bioanalytical applications, development of solid-phase extraction, flow-based analytical methods, and rapid detection devices for analytical and bioanalytical applications.

Setyawan P. Sakti is a professor of sensors and instrumentation, Department of Physics, Faculty of Science Brawijaya University. He obtained a Ph.D. degree from the University of Magdeburg, Germany. His current research interest is dealing with the development of quartz crystal microbalance immunosensor and rapid diagnostic devices for the detection of biomolecules. He also develops a portable qRT-PCR machine, an electronic nose for detecting volatile compounds, nano-porous polymer for gas sensing, and viscosity sensing of blood serum and plasma.

Aulanni’am is a professor of biochemistry, Department of Chemistry, Faculty of Science, Brawijaya University. She received Ph.D. in Biochemistry from Airlangga University, Indonesia. Currently, she develops rapid diagnostic devices for the early detection of autoimmune thyroid diseases, diabetes mellitus, and kidney diseases. One of her research products, an early detection kit for Type 1 DM patients, is currently ready for mass production and marketing. Her research also includes the production of monoclonal antibodies for polio diseases, exploration of bioactive natural products.

Hani Susianti is a clinical pathology specialist and nephrology consultant at Saiful Anwar General Hospital and Faculty of Medicine, Brawijaya University. She obtained a Ph.D. degree from Brawijaya University. Her current research involves developing and evaluating a diagnostic test for diabetic nephropathy, lupus nephritis, heart failure, and hepatocellular carcinoma. She is also studying some biomarkers for acute kidney injury and...
urinary tract infection. In addition to articles in scientific journals, she also writes books related to kidney disease.

**Nur Samsu** is a consultant specialist in kidney disease and hypertension and a lecturer at the Kidney and Hypertension Division, Department of Internal Medicine, Faculty of Medicine, Brawijaya University. He received a Ph.D. degree from Brawijaya University. His current research deals with rosmarinic acid, telmisartan, and a combination of both in the preventing progression of diabetic nephropathy. He also studied the impact of blood flow rate and duration of dialysis sessions on nutritional status in hemodialysis patients.

**Ika O. Wulandari** is a young researcher and lecturer at the Department of Chemistry, Faculty of Science, Brawijaya University. She obtained a Ph.D. degree in chemistry from Brawijaya University. Her current research includes the development of magnetic nanomaterials for drug delivery and bioanalytical science applications. She also develops green methods by employing natural resources for the synthesis of nanoparticles. She applies the synthesized nanoparticles for antibacterial activity and colorimetric sensing of biomolecules, including nephropathy biomarkers.

**Yudit Oktanella** is a veterinarian who completed his B.S. and M.S. degrees from Airlangga University, Indonesia. She is now working as a young researcher and lecturer at the Department of Animal Reproduction, Faculty of Veterinary Medicine, Brawijaya University. Her current research interest is developing a rapid test for early detection of autoimmune thyroid disease based on thyroid peroxidase and thyroid-stimulating hormone receptors and the development of paper-based devices for early detection of kidney disease.

**Dewi Anggraeni** is a young researcher and lecturer at Instrumentation Study Program, Department of Physics, Faculty of Science, Brawijaya University. She completed her B.S. and M.S. degrees from the same university. Her current research involves the development of quartz crystal microbalance immunosensor, gas sensing by employing nanoporous polymer for detecting aromatic compounds, and paper-based devices for rapid detection of biomolecules, especially kidney disease biomarkers.