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Review Article

Point-of-Care Diagnoses and Assays Based on Lateral Flow Test

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Analytical devices for point-of-care diagnoses are highly desired and would improve quality of life when first diagnoses are made early and pathologies are recognized soon. Lateral flow tests (LFTs) are such tools that can be easily performed without specific equipment, skills, or experiences. This review is focused on the use of LFT in point-of-care diagnoses. The principle of the assay is explained, and new materials like nanoparticles for labeling, new recognition molecules for interaction with an analyte, and new additional instrumentation like signal scaling by a smartphone camera are described and discussed. Advantages of the LFT devices as well as their limitations are described and discussed here considering actual papers that are properly cited.

1. Introduction

There are standard laboratory methods (chromatographic, mass, immunochemical, genetical, etc.) suitable for the analysis of various compounds and substances. Although the aforementioned laboratory methods exert superior features, they are quite expensive for both purchasing and cost per one assay. Moreover, education related to the type of analysis or experiences at least are required for staff controlling the instruments.

In the bioanalytical approaches, there is a little different situation to the standard analytical methods in the central laboratories. While the dominant part of analyses is expected to be made in clinical laboratories, it is also necessary to perform some analyses outside. The term point-of-care testing has emerged in current medicine. It can be explained as a simple test suitable to be finished including data evaluation in the home conditions by a patient or by a caregiver with no education in the bioanalyses or similar disciplines. Disposable urine test strips for multiple biochemical parameters and glucose biosensors for a fast glycemia assay can be mentioned as the standard commercial devices. Research on diagnostical biosensors is ongoing, and a number of new biosensor devices suitable for point-of-care testing have been investigated [1–5]. Other types of point-of-care tests like the colorimetric one based on a digital camera are developed [6–9].

The current review is focused on lateral flow immunochromatographic assays also known as lateral flow tests (LFTs) and their use in point-of-care. The LFT has started quite a long ago, and many analytical and diagnostical methods have been developed on the platform. In recent time, further improvement was achieved due to the use of advanced materials like colored nanoparticles. The recent progress in the field of LFT is surveyed here, and the progress is analyzed and discussed. The actual literature on LFT is summarized here.

2. LFT Development as a Standard Platform

Various paper tests for measuring a wide scale of parameters like pH or thin-layer chromatography assay have been extensively researched since the beginning of modern chemistry. Chromatography as a general method is connected with the work of Russian scientist Mikhail Tsvet in the early 1900s, and thin-layer chromatography was first reported by Russian scientists Izmailov and Shreiber in 1938 [10]. Further research on immunoassays including the latex fixation test provided a simple analytical tool significantly

improving and simplifying the previous methods [11, 12]. The first LFT devices were developed as an outcome of knowledge from previous methods and a series of patents applied in the 1980s. LFTs for proving pregnancy by the assay of human chorionic gonadotropin in urine were the first commercial tests working on the lateral flow principle and using specific antibodies against the hormone [13].

The original types of LFT were based on the recognition capacity of antibodies that served as a recognition part of the assay. The general principle is shown in Figure 1 and can be described as follows: the assay is performed on a sheet-shaped matrix from paper, cellulose, etc., that contains freely adsorbed antibodies labeled by color or fluorescent mark and specific against the analyte on the first end. The matrix also contains two zones with immobilized antibodies on the second end: the first zone contains antibodies specific to the analyte, and the second zone immobilized antibodies specific against free-labeled antibodies. A liquid sample is applied on the first end and the analyte presented in the sample interacting with the labeled antibodies. The complex analyte-labeled antibody and the unreacted antibodies are carried by the lateral flow on and in the hydrophilic matrix. The complex analyte-labeled antibody is captured on the first zone forming a colored spot visible by a naked eye. The unreacted labeled antibodies interact with the second zone and form a visible spot as well. The coloration caused by an analyte is frequently called the test line, while the spot by unreacted antibodies is frequently called the control line.

As seen from the principle of the LFT, it is a simple method suitable for simple assay relying on a naked eye, no specific instrumentation is necessary, and even liquid sample can be measured directly without further treatment. It is typically suitable for field applications [14]. Though LFT can be called by a synonym lateral flow immunochromatographic assay and antibodies are relevant and are also the most traditional recognition part in them, other recognition molecules fully replacing the antibodies can be also embedded. Aptamers can be exampled [15].

Gravidity tests for semiquantitative determination of human chorionic gonadotropin in urine are well known and are mass-produced types of LFT [16]. However, other types of LFT are currently available in the market, and many of them serve for the purpose of point-of-care diagnosis. The LFT kits for the detection of lipoarabinomannan in urine as a marker of *Mycobacterium tuberculosis* and diagnosis of tuberculosis disease [17, 18], detection of antibodies responsible for allergic reactions like the antibodies causing allergic bronchopulmonary aspergillosis [19, 20], detection of allergenic substances like peanut and hazelnut in food products [21], diagnosis of coronavirus disease 2019 (COVID-19) including antigens and specific antibodies [22–25], detection of antibodies against *Brucella* sp. to diagnose brucellosis [26], peste des petits ruminants virus disease diagnosis by antigen detection in fecal and nasal swab samples [27], measuring of C reactive protein in the blood, blood plasma, and serum [28], and assay of biological warfare agents and toxins like *Bacillus anthracis*, *Escherichia coli* O157:H7, staphylococcal enterotoxin B, ricin, botulinum toxin, *Francisella tularensis,* and *Yersinia pestis* [29–32] can be mentioned as examples of commercially available devices. The appearance of a commercially available LFT is depicted in Figure 2.

The standard methods have a lack in the inability to measure the exact concentration of the analyte, and the assays can be performed as a semiquantitative test only. The spots formed on the LFT matrix are typically narrow which is optimal for coloration scaling by a naked eye but not an ideal solution for colorimetry. Digital cameras including the cameras integrated into smartphones are considered as the future tool for coloration scaling in various analytical protocols [8, 33–36]. The assays can be also improved by spot design or by manufacturing more positive spots with an unequal affinity toward analyte placing in the LFT strip, so the concentration of analyte would be better estimated by a naked eye. The next evolution of LFT should be made with regard to the measuring platforms making the formerly qualitative or semiquantitative tests to be the quantitative ones.

2.1. Current Trends in LFT Construction in Point-of-Care Diagnosis. Though the original LFT devices from the 1980s are the functional ones, further improvement is desired to improve their analytical specifications and reduce costs. Comparing to the original devices from the 1980s, the currently researched and developed LFT contains typically alterations in selected recognition molecule and substance responsible for the visualization of the interaction with the analyte. Evolution of materials for matrix manufacturing, overall design resolving problems with manipulation by an unskilled worker, and improving LFT package to make it have long-term stability can be mentioned as the other areas of improvement. The evolution of LFTs is not of course related to devices for diagnosis only because the platform gained overall popularity in analytical chemistry and various applications are known for this moment.

The immunoassay-based point-of-care diagnostic tool was, for instance, described for COVID-19. The researchers investigated seroprevalence for COVID-19 using standard enzyme-linked immunosorbent assay (ELISA) and compared it with a standard LFT based on antibodies labeled by colloidal gold [37]. The LFT and ELISA mutually correlated and the authors concluded their work by a recommendation that LFT is suitable for point-of-care in the healthcare setting and COVID-19 monitoring. In another study on COVID-19, an LFT device for immunoglobulins (Ig) M and G in blood was constructed using selenium nanoparticles labeled SARS-CoV-2 nucleoproteins causing interaction with IgM and IgG antibodies [38]. The assay exerted a limit of detection of 20 ng/ml for IgM and 5 ng/ml for IgG in a 10-minute lasting assay. Other types of nanoparticles can be also used for an LFT immunoassay. For instance, LFT based on carbon nanoparticles conjugated with p48 protein was developed for the diagnosis of mycoplasma caused by *Mycoplasma bovis* [39]. The assay exerted 100% specificity and no cross-reactivity with antibodies to other bovine pathogens. A full correlation with ELISA was also reached. An LFT test using monoclonal antibodies labeled by gold nanoparticles

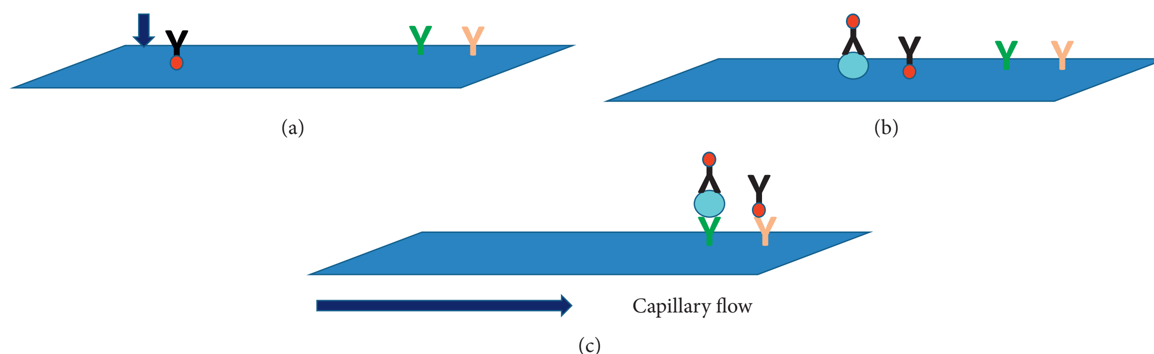

Figure 1: General principle of an LFT immunoassay. (a) Sample with an analyte (circle) is added to the pad where a labeled antibody (Y shaped) already exists. (b) Analyte and a labeled antibody are carried by a lateral flow (arrow) and they can mutually interact. (c) Complex of analyte-labeled antibody and the labeled antibody are captured on test spot (analyte) or control spot (unreacted antibody) forming colored lines.

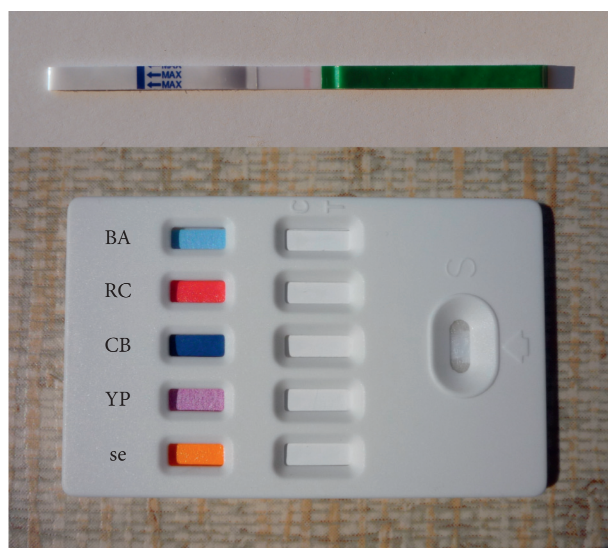

Figure 2: Appearance of commercial LFT devices. In the upper part, there is LFT for human chorionic gonadotropin; in the down part, there is a photograph of LFT for the contemporary determination of five biological warfare agents *Bacillus anthracis*, ricin, *Clostridium botulinum*/botulinum toxin, *Yersinia pestis*, and staphylococcal enterotoxin B by Pro Strips (Advnt Biotechnologies, Phoenix, AZ, USA).

was developed by Liu and coworkers for assay of dinitolmide in chicken tissue [40]. The researchers reported a limit of detection of 2.5 μg/kg for chicken tissue containing dinitolmide, and the assay was fully comparable to liquid chromatography and ELISA. Gold nanoparticles (gold spheres with size 30 and 100 nm or gold-silica shells with size 150 nm) and antibody-based detection were also used in the development of an LFT for the human immunodeficiency virus [41]. The gold nanoparticles were covered by a monoclonal antibody against protein p24 of the human immunodeficiency virus, and the whole assay was made in a standard manner. Signal was recorded by thermal contrast reading using an IR camera and laser. The assay was highly sensitive as a limit of detection of 8 pg/ml of p24 was achieved.

The relevance of LFT can be largely perceived in the recent events when a fast test for the diagnosis of COVID-19 was demanded. The standard diagnosis of COVID-19 was based on the polymerase chain reaction (presence of pathogen) and ELISA (prove of antibodies), but the tests have to be performed in specialized laboratories, and they require a quite long time to be finished. LFTs were successfully introduced as an alternative to the polymerase chain reaction and ELISA, and they were proved to be suitable for routine diagnosis based on the detection of COVID-19 antigen. Though they are not a replacement of polymerase chain reaction and ELISA, they were proved to be a suitable tool to be developed in a short period and used wherever necessary.

Concurrently, the recognition capability of antibodies suitable for antigens measuring respective antigens when antibodies are assayed is frequently replaced by the use of aptamers by many assays. Extensive progress in aptamer preparation has been reached in recent years, and the aptamers typically comprise ribonucleic acid (RNA), deoxyribonucleic acid (DNA), peptides, or proteins [42–48]. Their potency for LFT development was recognized as well [49]. Aptamers found their way to the construction of LFT, and they have become a relevant recognition molecule in LFT devices' development. In a work by Tripathi and coworkers, the LFT test was constructed for the point-of-care cancer diagnosis by the measurement of marker CA125 level [50]. The researchers used aptamer linked with gold nanoparticles serving as peroxidase mimetic and optimized the assay for the detection of CA125 in human serum. The assay had a limit of detection of 3.71 U/ml and correlated with ELISA. A DNA aptamer for residual penicillin antibiotic ampicillin was prepared by Lin and coworkers [51]. The researchers used hexachlorofluorescein for oligonucleotide labeling and were able to detect ampicillin in a range of 10 to 200 ng/l and a limit of quantification of 2.71 ng/l when water sample was analyzed. DNA aptamer was also used for the detection of dopamine in urine [52]. In this study, dopamine duplex DNA aptamers were conjugated to 40 nm gold nanoparticles, and LFT was performed in a standard manner resulting in a limit of detection of 50 ng/ml. Protein

osteopontin representing a new marker for cancer was detected by a biotinylated aptamer and then streptavidin modified gold nanoparticles served for the visualization purpose [53]. The assay had a limit of detection of 0.1 ng/ml with dynamic detection of osteopontin in a range from 10 to 500 ng/ml for a measuring time of 5 minutes. Aptamer-based LFT was chosen by Ali and coworkers for the early diagnosis of type-2 diabetes by assay of protein vaspin using fluorescent upconverting nanoparticles [54]. Vaspin was recognized in a range of 0.1–55 ng/ml with a limit of detection of 39 pg/ml. LFT does not have to be targeted on defined molecules only. In a work by Yu and coworkers, LFT was developed for tumor-derived exosomes for rapid diagnosis of lung cell cancer [55]. Aptamer specific to CD63 on exosome surface and gold nanoparticles giving good visualization and observability of the assay by a naked eye were used for the LFT construction. The assay was proved on exosomes isolated from human lung carcinoma cells in a dilution of 6.4×10^9 particles/ml. Quantum dots are another material that can serve for the purpose of reaction visualization and macromolecules labeling [56–59]. An LFT method based on CdTe quantum dots was, for instance, constructed by Lu and coworkers in order to detect Shiga toxin type II [60]. The authors also worked with gold nanoparticles as a material for labeling antibodies. While labeling by quantum dots provided a limit of detection of 25 ng/ml, the LFT based on CdTe quantum dots had a five times lower limit of detection: 5 ng/ml. The LFT tests can be improved by connecting with other techniques improving samples and sensitivity increased. For instance, detection of *Escherichia coli* O157:H7 was performed in two steps: the first step was based on bacterium captured by immunomagnetic nanoparticles and monoclonal antibody conjugate with beta-lactamase and gold nanoparticles; the second step contained penicillin solution application and hydrolysis by the beta-lactamase [61]. The final test containing LFT consisted of an ultrasensitive penicillin immunochromatographic test strip. The assay had a limit of detection of 137 CFU/ml. Further investigation is also focused on other types of recognition parts and labels like molecularly imprinted polymers [62] and the use of liposome enhanced signal amplification [63]. Highly fluorescent europium chelate loaded silica nanoparticles can be mentioned as another type of label [64]. Research on matrix composition is also demanded, and it can improve analytical properties. Nitrocellulose or nitrocellulose coated with nanocolloids appears to be promising [40, 65]. An overview of the aforementioned LFTs is given in Table 1.

Considering the current trends, it is clear that the new directions in LFT research are focused on two major areas. Firstly, new recognition elements are researched. Secondly, new types of nanoparticles are used for LFT construction. All the new materials can improve the final analytical parameters of a final LFT, but the suitability of the particular materials will depend on the type of assay and other conditions. There probably will never be an ideal recognition element or a label for any assay scenarios. Molecularly imprinted polymers and aptamers can be prospective recognition elements, but antibodies will probably remain an irreplaceable part of many commercial LFTs. Standard chemical labels like fluorescein will also remain a part of standard LFTs though nanoparticles like the gold one or quantum dots will probably represent a better alternative gaining higher popularity in the future praxis.

Considering the current options in analytical chemistry, LFT remains probably the major tool for point-of-care specific diagnosis of various pathologies besides the devices like Clark glucose biosensor and simple urine colorimetric test strips. Compared to the other tests, LFT has quite high versatility for the diagnosis of good presumptions to be used under point-of-care conditions; on the other hand, LFT has a limitation on the molecular weight of analyte because the assay is on an affinity principle. Analytes with low molecular weight are not suitable for a standard immunoassay, and a competitive format is the only possibility of how to use an immunoassay for the analysis of a small compound. However, the new types of recognition elements like aptamers bring improvement and even LFT for small molecules like dinitolmide, ampicillin, and dopamine can be seen in the examples of new research on LFT.

2.2. Instrumentation of LFT for Point-of-Care Diagnosis. LFT methods are typically intended to be either qualitative or semiquantitative, and the coloration is determined by a naked eye. If the assay is performed as a semiquantitative, the found range of value is highly inaccurate. The overall simplicity of the method and no necessity to use an analytical device, electricity, or elaborative sample manipulation are the major advantages of LFT. On the other hand, there are disadvantages as well. The scaling of coloration by a naked eye is highly subjective and also depends on ambient light conditions. The subjective perception of color may be a problem when the point-of-care diagnosis is performed by elderly or disabled people. Development of coloration readers suitable for standard LFT is a way of how to improve the assay. The reader devices are especially desired in point-of-care testing [66]. The improved LFT assays are quantitative or at least semiquantitative with acceptable accuracy of concentration range determination.

In the current time, broad attention is given to digital photography because of the good availability of cameras and their integration into smartphones. Standard cameras integrated into smartphones are able to provide at least 8-bit digital photography in a format like jpg and have information about color depth for the 8-bit photography equal to 256 variables for each channel. Better cameras giving figures in 12, 14, 16, and more bits and providing raw data from the digital sensor are also widely available in the market. Digital photography is highly suitable for colorimetry by color depth analysis and colorimetric tests performed on a thin-layer-like paper-based assays and detector strips like the pH and others can be recorded this way, and the digital photography-assisted assay is well suitable for point-of-care testing [7, 36, 67–69]. Digital photography has also its limitations making the assay inaccurate under some conditions. In the first point, the light source has to be mentioned. The light conditions are crucial when a sensor is photographed; integrated light-emitting diodes can have problems with the light temperature setting. There can be

Table 1: Overview of LFT in point-of-care diagnosis.

Assay/diagnosis of a pathology	Type of recognition part	Type of label attached to the recognition part	Analytical specifications	Reference
COVID-19	Antibody	Colloidal gold	Full correlation with ELISA for clinical samples testing	[37]
COVID-19-specific antibodies recognition	SARS-CoV-2 nucleoproteins	Selenium nanoparticles	20 ng/ml for IgM and 5 ng/ml for IgG in 10 minutes	[38]
Mycoplasma	p48 protein	Carbon nanoparticles	100% specificity, no cross-reactivity, full correlation with ELISA	[39]
Dinitolmide in tissue	Monoclonal antibody	Gold nanoparticles	Limit of detection of 2.5 μg/kg for chicken tissue containing dinitolmide	[40]
Protein p24 of human immunodeficiency virus	Monoclonal antibody	Gold nanoparticles	Limit of detection of 8 pg/ml	[41]
Diagnosis of cancer by CA125 assay	Aptamer	Gold nanoparticles	Limit of detection of 3.71 U/ml	[50]
Ampicillin in water	DNA aptamer	Hexachlorofluorescein	Limit of quantification of 2.71 ng/l	[51]
Dopamine in urine	DNA aptamer	Gold nanoparticles	Limit of detection of 50 ng/ml	[52]
Cancer marker osteopontin	Biotinylated aptamer	Conjugate streptavidin-gold nanoparticles	Limit of detection 0.1 ng/ml, with a dynamic range of 10 to 500 ng/ml, time per assay 5 minutes	[53]
Assay of vaspin as an early marker of type-2 diabetes	Aptamer	Fluorescent upconverting nanoparticles	Limit of detection for vaspin of 39 pg/ml	[54]
Exosomes for rapid diagnosis of lung cell cancer	Aptamer specific to CD63 on exosomes surface	Gold nanoparticles	Detection of 6.4×10^9 exosomes/ml	[55]
Shiga toxin type II	Antibodies	Gold nanoparticles and CdSe quantum dots	25 ng/ml (labeling by gold nanoparticles), 5 ng/ml (labeling by quantum dots)	[60]

also problems with the setting of white balance and color temperature in the camera. Problems with lens quality can also play a role when a cheap camera is used for point-of-care testing. Nevertheless, the use of digital cameras in personal diagnosis is considered as the next direction of research and application into praxis [70–75].

Instrumental analysis of spots formed in LFT was introduced in several applications. In the aforementioned study by Zhan and coworkers, detection of p24 protein of the human immunodeficiency virus was made using thermal contrast reading [41]. The spot on LFT was formed by a complex of gold nanoparticle conjugate with p24 from a sample and capturing zone on the LFT pad. The spot was focused by laser with wavelength 532 or 800 nm with power adjusted in the range from 10 to 500 mW. The alighted spot was recorded, and temperature measured by an IR camera and digital data for further processing and signal scaling were recorded. Digital camera containing complementary metal-oxide-semiconductor (CMOS) chip served for the spot color recording in the study by Jahanpeyma and coworkers [76]. The researchers tested their LFT device for the hybridization of DNA, and visualization was made by the application of a biotinylated detector probe in the presence of peroxidase-streptavidin conjugate. Just the peroxidase was responsible for the chemiluminescence reaction recorded by a camera. The assay was tested for proving the 16S rRNA gene from *Escherichia coli*, and the lowest reached limit of detection was equal to 1.5 pmol/l. The use of peroxidase-catalyzed reaction in an LFT was also described in a paper by Mirasoli and coworkers [77]. They adopted their method for the detection of fumonisin in food samples, and the mycotoxin was detected in a range of 2.5–500 μg/l with a limit of detection of 2.5 μg/l for an assay lasting for 25 minutes. The detection signal was evaluated by a charge-couple device (CCD) camera. The authors stated that the peroxidase reaction generating chemiluminescence products is more suitable for quantitative LFT assay than an assay where colloidal gold is used instead of peroxidase. The digital scaling of coloration can be even made by simpler devices than cameras. Digital scanner was selected as an analytical tool in the work by Posthuma-Trumpie and coworkers [78]. The authors successfully performed a standard LFT test for progesterone assay using antibodies and carbon colloid as a label and the LFT strips scanned and analyzed digitally. Spots on an LFT test can be evaluated, and coloration was determined by a smartphone camera which makes the assays more available to most people. A smartphone camera assay based on an LFT was investigated for the detection of mercury [79]. The assay comprised of the use of streptavidin-biotinylated DNA probes modified with gold nanoparticles and adsorbing mercury was proved with a limit of detection of 2.53 nmol/l. In another smartphone application, uricemia (uric acid content in the blood) was measured by a combination of an LFT where coloration was initiated Prussian blue nanoparticles as artificial nanozymes and standard smartphone for spots characterization [80]. The assay

Table 2: LFT signal recording by an analytical instrument.

Type of assay	Type of instrumentation	Physical principle of the instrumental assay	Reference
LFT for p24 protein from human immunodeficiency virus, gold nanoparticles conjugated with a monoclonal antibody against p24 were used	Laser alighting specific spots, IR camera visually recording temperature	Thermal contrast reading	[41]
Detection of 16S rRNA gene from *Escherichia coli* by hybridization and use of biotinylated probe and peroxidase conjugated with streptavidin, peroxidase was responsible for the chemiluminescent reaction	Digital camera with CMOS chip	Digital camera recorded chemiluminescence provided by peroxidase	[76]
Detection of fumonisin, labeling of antibodies by peroxidase allows performing chemiluminescent chemical reaction that is instrumentally measured	Digital camera with CCD chip	Digital camera recorded chemiluminescence provided by peroxidase	[77]
LFT immunoassay of progesterone based on labeling by carbon colloid	Digital scanner	Strips were scanned and digital data analyzed	[78]
The LFT assay comprised of the use of streptavidin-biotinylated DNA probes modified with gold nanoparticles	Smartphone camera	Detected spots were photographed by a smartphone camera, and coloration was measured	[79]
LFT where coloration was initiated Prussian blue nanoparticles as artificial nanozymes	Smartphone camera	Detected spots were photographed by a smartphone camera, and coloration was measured	[80]

exerted a linear range of 1.5–8.5 mg/dl for uric acid. An overview of the types of instrumentation applicable for an LFT assay is shown in Table 2.

3. Conclusions

LFT devices and kits can be found in the current market as standard devices, and new improved types are researched. Three major directions of improvement can be observed when the current research is compared with the traditional LFT devices on immunoassay principle: (1) new labels and materials including nanoparticles providing contrast coloration, (2) new recognition molecules selectively interacting with analytes, and (3) types of instrumentation making the LFT-based assays quantitative from the originally qualitative one. All the facts make the LFT a significant tool in point-of-care diagnostic where it can be performed for multiple diagnoses or analyses of harmful substances or microorganisms. Overall simplicity and growing sensitivity allow making LFT a tool for a wide number of markers. Though the traditional analytes in an LFT assay were molecules with higher molecular weight, it is expected that the LFT will become a universal tool even for analytes with lower molecular weight and make the assay more universal. The relevance of LFT was also evident during the COVID-19 crisis when the tests COVID antibodies and antigens were urgently developed and marketed in a quite short time.

Data Availability

No data were used to support this study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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