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Low-Cost Molecular Diagnostics for Clinical Microbiology

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Introduction

Within the scopes of the newly launched journal "Advanced Techniques in Clinical Microbiology" is the continuous discussion among the scientists on the field of the current advancements in clinical techniques that will facilitate "the understanding of the challenges that humans encounter when coming into contact with microbes and how to mitigate them successfully". The publication of newly developed diagnostics or bioanalysis devices and concepts would be essential for attainment of that specific aim, since successful diagnosis is essentially the backbone of clinical microbiology.

Sensitive, accurate and rapid detection of a pathogenic microbe is of great importance either for treatment of an individual patient or to decide the appropriate response to an epidemic, in national or international level. Even though, diagnostic technologies are rapidly advancing, these innovations are still far from adaptation in the patient level. In most cases, suspected infections caused by bacteria, viruses, fungi, mycobacteria or parasites, are treated with broad-spectrum antibiotics instead of pathogen-specific antimicrobial therapy. Moreover, most clinical laboratories continue to rely heavily on traditional analysis methods, including culture, phenotypic, and biochemical tests, to identify microorganisms present in clinical specimens. However, traditional microbiology methods are usually laborious, time-consuming and present moderate sensitivity. For that reason, many research and diagnostic laboratories have shifted their interest to molecular methods which are more sensitive, specific, exhibit reduced turnaround times (TATs) and lower costs per sample. As an example of the anticipated benefits, a study indicated that use of molecular methods instead of traditional culturing resulted in reduction of hospital costs by >$21,000 [1].

A turning point for wide adaptation of molecular diagnostics was the introduction of polymerase chain reaction (PCR) for nucleic acids amplification, a method which remains largely unchanged as it forms the backbone of molecular diagnostics in clinical microbiology laboratories today. However, the nucleic acid amplification tests (NAATs) are largely considered as "high-complexity" tests and are limited to molecular laboratories with skilled technologists [1]. The majority of NAAT assays are based on sample pre-treatment, i.e., offline nucleic acid extraction, subsequent performance of PCR amplification and a separate step of product detection, and results assessment. The multi-step protocols are making the analysis time-consuming, laborious and prone to contamination at several points. Efforts to overcome these drawbacks include the introduction of real-time quantitative PCRs (qPCRs), and automated protocols in the form of sample-to-result instrumentation. Digital PCR, microarrays and next-generation sequencing (NGS) allow analysis of complex samples with multiple microbes and high sensitivity. All of these methods, however, have high costs in terms of reagents, equipment and result analysis, making their wide adaptation difficult.

Low-cost diagnostics are quite attractive for use in microbiological laboratories. Several steps have been made towards the development of these types of assays and are mostly based on integration of the NAAT steps (e.g. extraction-amplification-detection), with simple formats. The extraction step is the most difficult to eliminate, even though research is currently focused on the use of special filter papers. The amplification step is the most critical since the methods' sensitivity and specificity is heavily based on that. A variety of isothermal amplification methodologies have been developed, including loop-mediated isothermal amplification (LAMP), rolling circle amplification (RCA), nicking enzyme amplification reaction, recombinase polymerase amplification, helicase-dependent amplification and others. Among them, LAMP is very attractive since it is rapid, simple, sensitive and its products can be easily detected. Isothermal methods are gaining more interest because they eliminate the need for expensive thermocyclers and allow the test to be performed outside of a molecular laboratory, closer to a patient bedside or point-of-care (POC).

An advantage of the isothermal amplification methods is that the amplification products can be easily labelled during the reactions and their detection can be achieved by applying them directly to lateral flow biosensors (LFBs) or immunochromatographic strips. Paper LFBs are POC devices optimal for accurate, rapid and sensitive analysis. In general, they are prefabricated strips of materials containing dry reagents that are activated by applying a fluid sample. They are designed for disposable single use, for applications where an on/off signal is sufficient. The most popular LFB is the widely used home pregnancy test. LFBs are considered one of the most promising technologies owing to their simplicity, rapid analysis, low cost, high sensitivity and specificity, and no need for specialized

personnel to run the tests. Several lateral flow biosensors have been developed to detect many analytes such as DNA, mRNA, miRNA, proteins, biological agents and chemical contaminants [2]. It should be noted that use of paper substrates for LFBs lowers the cost for sensors manufacturing, and dehydrated reagents can withstand warm temperatures preserving their long term stability; therefore no refrigeration or electricity is necessary, facilitating storage and transportation. In clinical practice, point-of-care testing devices have already been used for urinalysis, blood glucose testing and monitoring, blood gas and electrolyte testing, coagulation (INR), blood chemistries including enzymes and lipids, drugs of abuse, pregnancy testing, cardiac markers, hemoglobin and hematocrit, as well as several infectious disease [3].

It is anticipated that combination of isothermal amplification methods and lateral flow biosensors, as point of care devices will be beneficial in advanced and medium size (i.e., doctors office) healthcare systems with time and cost-related advantages. Apart of using this technology in well-equipped facilities, it is very important that they are ideal for use in resource-limited settings where infrastructure is underdeveloped and underfunded. In that case, POC molecular diagnostics can help increase access to health care and timely treatment of infectious diseases. Concluding, it should be noted that the molecular diagnostics are able to reduce the turnaround time for obtaining reliable results, increase assays' specificity and sensitivity, and provide more accurate diagnosis with lower cost than the traditional methods, enhancing thus the clinical microbiology benefits.

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