Economic and practical considerations in implementing novel diagnostics

Naiera M. Helmy

Microbial Biotechnology Department, Biotechnology Research Institute, National Research Center, Giza, 12622, Egypt

**ABSTRACT**

The application of novel diagnostic strategies has vital economic and practical considerations. This book chapter demonstrates the cost-benefit inquiry of different advanced diagnostic approaches until reaching the machine learning approach. Also, includes illustration of the resource-limited settings including the challenges and adaption for the new diagnostic techniques. In addition to discussion of some strategies for implementation of advanced diagnostics in healthcare systems. At last, casing some application including case studies to explain the cost effectiveness approach in clinical microbial diagnosis.

**Keywords:** Clinical, Diagnosis, Microbiology, Cost-effectiveness, Challenges.

1. **INTRODUCTION**

The laboratory diagnosis is one of the same contributor’s to the success of health care system. The reduction of stresses on the laboratory's delivery of results is relied on adjustment and development of molecular technologies to run short duration’s turnaround times and provide upper quality of diagnosis [1]. During this era, the biotechnology field integrated the applied bio-scientific and bioengineering disciplines into the industrial processing of materials through biological agents. The base of using the fundamentals to deliver valuable products, which could be designed for diagnostic purposes [2].

The purpose of diagnostic tests mission is vital to the judgement of the consumer on how of important a process such as two measures to the output of diagnosis [3]. The division of any population has been characterised on two group’s one indicative with the presence of a particular disease or condition, and the other lack this character. The use of diagnosis involves the process of performing tests to divide the population into these category groups. The threshold value is used in diagnostic tests through a diagnostic variable for distinguishing between individuals as disease-positive or disease-negative cases. The economic value of information (voi) methods have considered the costs and outcome of testing [4] . The importance of microbiology laboratory as the first line of defence against pathogens is characteristic to the economic importance of applying advanced diagnosis methods [5].

1. **COST-BENEFIT ANALYSIS OF ADVANCED DIAGNOSTIC METHODS**

In past, the majority of clinical microbiology laboratory diagnostics were not automated and required extensive practice to yield accurate, clinically significant results [6]. The accurate identification of the aetiological agents has been loaded with cost concerns and sufficient communication between clinician and microbiologists in laboratory [7].

The clinical diagnosis of common bacterial organisms related with diarrheal disease comprising the stool specimen’s collection, transport of samples, and processing, and use test methods required for identification of these bacterial isolates in addition to antimicrobial susceptibility testing[8]. The recent technological advances in microbial molecular diagnostics, digital microbiology and mass spectrometry techniques resulted in more time management diagnosis thus effective treatments [9]. The introduction of omics machineries (proteomics, culturomics, genomics, transcriptomics and metabolomics) diminished the limitation of time consuming of results from blood cultures in the emergency room, provided the availability of identification and antibiotic-susceptibility testing within the next 72 hours after sampling. Early patient management according with rapid diagnostic speed is advantages to use of omics techniques [10].

Developments in whole genome sequencing (WGS) have caused in a reduced cost in the full economic sequencing of a bacterial genome. In addition, the increased speed of sequencing resulted in less time-consumed process of sequencing a microbial genome to be within several days or weeks to few hours. Thus, combining the economic balance between low cost and rapid turnaround interval[11]. Microarrays application in clinical microbiology either quantitative based (gene expression) or qualitative (diagnostic) data has become routinely applied and continued to expand rapidly [12].

The matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS), which aims to provide proteomic profile for microbial isolates has been widely used in the clinical microbiology laboratory. The fast and exact identification of MALDI-TOF MS has been used in determination of epidemic relation and antibiotic resistance in microbial isolates [13]. MALDI-TOF MS displayed a high reliability, less time taken and effectivity in the identification of bacteria and fungi. MALDI-TOF MS represented a proper tool in direct detection of pathogens through the clinical samples. The application of positive blood cultures in identification of microorganisms in addition to detection of antimicrobial resistance is one of the valuable applications. The rapid, accurate, and low prices of reagents and consumables of MALDI-TOF MS has been useful to diverse fields in clinical microbiology diagnosis [14]. Other whole-genome sequencing (WGS), and acquirement of [microbiota](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/microflora) data through next-generation sequencing developed the rapid and accurate clinical microbiology diagnostic tools[15].

The progress of Machine learning (ML) in analysis of complex and large data is additional in improvement of clinical microbiology laboratory diagnostics. The main gap in current ML systems is the evaluation and application processes signified by focusing on their interpretability and prospective integration into the settings of real world. The ML systems used 73% data from high-income countries and 37% data from low and middle-income countries [15].

Cost-effectiveness analyses (CEAs) is one of the most important considerations, which could be applied to determine the value of diagnostics in clinical practice. Improvement and feasibility CEAs performance have been recognized due to the provided clinical data from new diagnostics [16]. The equation of cost effectiveness applied in accurate determination of infection causes according to microbial diagnosis for the suitable therapy instead of prescribing great amounts of unnecessary antibiotics. As example, at least one out of 19 different antimicrobial agents as cure for acute nasopharyngitis (the common cold) was given to about 60% of over 2000 patients and less than 2% of their infection was accompanied with bacterial sinusitis or otitis. As the cause for their symptoms were viral infections, prescription of antibiotics was not useful. In addition, the treatment of chronic cough using antimicrobial agents despite the cause of about 90% due to smoking, gastroesophageal reflux, postnasal drip, asthma, and chronic bronchitis[17].

Point-of-care (POC) tests compromise actual significant paybacks to the management of infectious diseases. The main conception of this test is short duration of result and test availability either bedside or at distant care centres. The wide availability of commercial POC tests covers the diagnosis of both bacterial and [viral infections](https://www.sciencedirect.com/topics/immunology-and-microbiology/viral-disease) in addition to [parasitic diseases](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/parasitosis). The indications and limitations of rapid tests should be taking in consideration from both infectious diseases specialists and clinical microbiologists for appropriate and accurate result’s interpretation [18].

1. **RESOURCE-LIMITED SETTINGS: CHALLENGES AND ADAPTATIONS FOR NEW DIAGNOSTICS**

Infectious diseases diagnostic methods should be characterized with fastness, accuracy, simplicity and reasonable prices. As administration of proper antibiotics is the critical step in healing of the infected patient, the speed of diagnosis will block the progress of infections. The high risk of serious infections initiated with multidrug resistant bacterial infections could be more effectively treated if rapid diagnosis is applied [9]. Research significances is based on three parameters human interests as well as both theoretical tractability and centrality [19]. The discovering of correlation between two non-related parameters is defined to be not useless but less helpful [19].

The molecular techniques is most preferred diagnostic methods for the recognition of acute respiratory viruses. The advantages is automation accessibility, high-throughput workflows, and testing nearby patient. The high quality programs is required to avoid laboratory contamination in additional to accurate pre-analytical screening methods for appropriate to utilization of laboratory resources appropriately. The high speed of results achievement will help in deification of viruses thus blocking the transition of infections [20].

The high sensitivity and specificity, low risk of contamination, and speed has made the technology of real-time PCR an attractive alternative to the culture- or immunoassay-based testing techniques in infectious diseases diagnosis [21].The cheaper and faster results from rapid antigen tests provides quick positive cases isolation [13]. Despite enzyme immunoassays being rapid and easy when compared to time-consuming reference standards methods, they have been described to be sensitivity-limited and/or low specific tests. Thus many diverse testing protocols has been developed comprising the submission of multiple sample or several testing of samples using different methods [22].

The development of clinical laboratory through covering large geographical regions is important in representing the application of efficient in addition to cost-effective novel laboratory technologies[23]. On the other side, the improvement of clinical microbiology diagnosis in developing countries was blocked through the poor laboratory application for defined diagnosis of infections [24].

The problem of low microbiological testing in outpatient settings explains the large amounts of prescribed antibiotics which comes in accordance with resistant pathogens in the community-acquired infections and the absence of the data about various of these pathogens [25].

1. **STRATEGIES FOR IMPLEMENTATION IN DIVERSE HEALTHCARE SETTINGS**

Factors affecting effective clinical diagnosis based firstly on the clinical microbiologist’s awareness of clinical practice guideline. Secondly, the determination of the best practice by the clinical microbiologist when conflicting guidelines rises. Thirdly, the specificity of guideline depending on data rather than primarily expert opinion. Lastly, the availability of necessary resources including technology or staffing in according with guideline [26].

The occurrence of common ocular infections in developed nations in addition to neglected ocular infections in developing nations provided the need for pre-analytic, analytic, and post-analytic features of deep exploration of laboratory diagnosis as well as antimicrobial susceptibility testing [27].

The appropriate use might be assessed though parameters of test performance, test cost, or the available alternative test procedures.  The appropriate use from third-party payer’s view is defined with minimization of health care costs. The appropriate use from public health official’s view is distinct with screening patient populations for public health interest diseases. The appropriate laboratory use from regulatory bodies view is well-defined with the medical necessity’s principle. The incompatibility of these definitions with one another provides the reason for applying the appropriate laboratory test use in addition to efforts to set the definition for appropriate use, frequently results in inconsistency or conflicts of data[28].

The rise of informatics tools application in microbiology testing leads to increase in the accuracy and decrease in time and laboratory workload thus optimization of laboratory workflow and reduction in costs[29].

The integration of the [whole genome sequencing](https://www.sciencedirect.com/topics/immunology-and-microbiology/whole-genome-sequencing) (WGS) in the routine clinical microbiology laboratory workflow. The progress in workflow for WGS is directed to reduce the [turnaround time](https://www.sciencedirect.com/topics/immunology-and-microbiology/turnaround-time), decrease in costs, in addition to streamline downstream data analyses. Due to this progress, the WGS usage is for routine patient managing and feasibility and implemented into infection control management. Thus, [clinical microbiology](https://www.sciencedirect.com/topics/immunology-and-microbiology/clinical-microbiology) transformed to be based on genome and personalized diagnostic approach [30].

The advances in microbiology technologies changes the diagnostic ability of infections, improves the patient care and enhances the clinical workflow. These tools acts on influencing three parameters the breadth, depth, and speed of diagnostic data generated from each patient. Also, the close movement of testing to the patient using the rapid diagnostic tools comprising point-of-care (POC) technologies [31].

The increased cost of 24-h clinical microbiology laboratory is services’ costs divided into the staffing cost, which considered the highest cost and the technology and consumables cost. As reported the hours of operation didn’t caused an increase in the number of submitted specimens but resulted in alteration of specimen receiving thus impacting the workflow [32].

Artificial intelligence’s (AI) application in clinical microbiology could be the best route in efficiency, accuracy, and leading to new conclusions from the laboratory- generated data [33].

In Vitro Diagnostic Regulation (IVDR) involved in application of verification and validation is one of the main objectives in clinical microbiology diagnosis. Verification aiming to verify the performance characteristics of test’s before usage. Validation targeting the demonstration of test’s accurate performance and reliability[34].

The administration of patients with infectious diseases based on informative techniques of bacterial pathogens and their antimicrobial susceptibility. The introduction of MALDI-ToF and rapid molecular tests into routine diagnostics improved the identification of particular species in addition the reduction of time-to-result approach. Furthermore, phenotypic susceptibility testing new methods supports the clinical decision-making during the early stages [35].

The implementation of Next-generation sequencing (NGS) into the routine clinical microbiology diagnostic procedures is one of the most significant approaches. The first is whole-genome sequencing, the second is targeted next-generation sequencing and the third is metagenomics next-generation sequencing [36].

Industrial factors has a great contribution in cost-effectiveness equation including taking in consideration the utility, accuracy, potential of timesaving’s, associated instrumentation and reagent’s cost, and prospective for diverse applications in applying new technologies in clinical laboratory diagnosis [37].

1. **CASE STUDIES INDICATING THE COST-EFFECTIVENESS OF CLINICAL MICROBIAL DIAGNOSTICS**

The diagnostic procedures is important in controlling the Invasive fungal infections (IFIs) rapid diagnosis and optimum management to diminish the caused high rate of morbidity and mortality resulted from infections. There are also high economic problem due to long duration of hospitalization, necessary intensive support care, in addition to need for costly novel antifungal agents [38].

An example is cost- effectiveness is the improved the diagnosis of Clostridium difficile infection (CDI) through evaluation of the enzyme immunoassays (EIAs) identifying toxins A and B as a commercial laboratory test in comparison to nucleic acid amplification as a reference test and the results included in a meta-data analysis. The results indicated that only one commercial test was inadequate as individual diagnostic test with positive predictive values at prevalence of low CDI. Thus, a two-step algorithm is required [39]. Another approach of cost-effectiveness is the microbiological laboratory diagnostic of *Candida auris* as a transmissible and nosocomial pathogenic infection. The advances in diagnosis developed beyond culture-based techniques to comprise PCR and WGS. Also, MALDI-TOF MS could be used for the early echinocandin antifungal susceptibility testing (AST).The progress of the informative WGS methods could be used for assessment of phylogenetic relationships and development of drug resistance [40]. Microbial clinical laboratory diagnosis contributes to improvement of patient outcomes such as the reduced mortality in addition to administrative outcomes such as reduced length of stay, hospital costs, few adverse actions such as *C. difficile* infections (CDIs) and drug reactions [41].

In case of typical and multidrug resistance, particularly extended-spectrum beta-lactamase- (ESBL-) producing bacteria (ESBL) and carbapenemase expressing Enterobacteriaceae, it is problematic to accomplish therapeutic achievement through the calculated antibiotic therapy. Thus, the rapid antibiotic resistance testing is necessary. Several molecular and mass spectrometry-based methods have been presented in clinical microbiology diagnosis to speed up the results of reliable resistance data [42].

The improved standardization of testing and more adaptability to act according with different threats after infectious microorganisms including causes of bioterrorism and developing pathogens [43]. The essential support of clinical microbiology laboratory capacity in the low-resource settings has become more critical than ever after worldwide health crisis of COVID-19 and the rise of antimicrobial resistance[44].

1. **CONCLUSION**

The development of advanced clinical microbial diagnosis is important in fighting against the progress of infectious diseases. Application of cost effectiveness standards is indicative to the effect of application of advanced clinical microbial diagnosis. This includes the recent advances in microbial molecular diagnostics technologies, digital microbiology and mass spectrometry techniques. Also, The introduction of omics machineries, whole genome sequencing (WGS), full Microarrays, matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) in addition to Machine learning (ML) in diagnosis methods. The balance between accuracy and time to introduce the optimization of laboratory workflow and saving in costs is the most vital request in the future of clinical microbial diagnostics.

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