Journal of Contemporary Studies in Epidemiology and Public Health
2026, 7(1), ep26018
e-ISSN: 2634-8543
https://www.jconseph.com

MODESTUM

Review Article

OPEN ACCESS

Omics technologies for diagnosis of infectious diseases: A review

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Citation: Delegkou M, Spyridakis E, Zoumi C, Galanis A, Panagopoulou A, Karamalis C. Omics technologies for diagnosis of infectious diseases: A review. J CONTEMP STUD EPIDEMIOL PUBLIC HEALTH. 2026;7(1):ep26018. https://doi.org/10.29333/jconseph/18118

ARTICLE INFO

Received: 11 Dec. 2025

Accepted: 13 Feb. 2026

ABSTRACT

Infectious diseases remain a leading cause of global morbidity and mortality, underscoring the need for rapid, accurate, and comprehensive diagnostic approaches. Advances in omics technologies have evolved our ability to detect, characterize, and monitor pathogens. Together, these technologies offer a systems-level perspective that enhances diagnostic accuracy which can be applied both in clinical and public health laboratories, in order to ameliorate infectious diseases policies and strategies. Despite significant progress, challenges remain in terms of cost, data integration, standardization, and clinical translation. Future directions include the development of multi-omics platforms, real-time sequencing technologies, and robust bioinformatics pipelines to accelerate implementation in routine clinical practice. This review highlights the current landscape, key applications, and future potential of omics-based diagnostics in combating infectious diseases.

Keywords: infectious diseases, diagnosis, omics technologies, biotechnology, public health

INTRODUCTION

Infectious diseases pose a major issue on a global scale as they are responsible for the significant morbidity and mortality rates worldwide affecting global economy and trade, over pressuring health systems and negatively impacting quality of life. The impact of such diseases can be quantified in disability-adjusted life years (DALYs) which express healthy life years lost to premature death and disability [1, 2]. In 2021, infectious diseases were responsible for an estimated 2.88 billion DALYs worldwide, 52% of which were concentrated in Asia. As far as socioeconomic factors go, the largest shares of DALYs were observed in low-middle and upper-middle income countries with 44.7% and 29%, respectively [3]. In a study conducted in 2025 it was revealed that the COVID-19 pandemic caused a shift in DALYs worldwide with low-income, low-middle income and high-income countries accounting for almost 56%, 39% and 10%, respectively, of communicable, maternal, neonatal, and nutritional diseases in 2021 [4].

Moreover, climate change substantially exacerbates the global burden of infectious diseases through its effect on key environmental factors including air quality, water contamination, hygiene and extreme temperature exposure. Due to the increasing global temperature vectors, like mosquitos, can migrate to new areas carrying non-native diseases causing problems for native populations that lack defense mechanisms and herd immunity. Also, extreme temperatures increase host susceptibility leading to increased transmission of diseases across the population. Additionally, poor air quality compromises respiratory health and immune function amplifying the intensity and occurrence of respiratory tract infections while disruptions in water supply and safety, aggravated by droughts, floods and climate induced infrastructure stress, increase the burden of enteric infections, especially in kids under the age of five [5, 6]. Lastly, it is important to note that due to the migration of vectors to new environments, viruses, which were previously geographically isolated, interact with each other through cross species infections resulting in viral recombination. This leads to the creation of new highly infectious and deadly strains that affect humans [7].

These findings emphasize the global demand for the development of novel, accurate, rapid and accessible disease diagnostics that will add extra diagnostic value in the current field of diagnostics. Conventional diagnostic methods, although known for their timeless reliability, often require highly trained personnel and consist of lengthy protocols, in other cases, culture based methods, hemagglutination inhibition tests and enzyme-linked immunosorbent assays rely solely on the antigenic characteristics of pathogenic organisms resulting in poor specificity and sensitivity [8].

Diagnostic techniques based on the aforementioned conventional methods need to be replaced by more modern, high-throughput and sensitive methods like PCR, biosensors and next-generation sequencing (NGS) which can be used for a variety of cases, from the detection of pathogens to the identification of genes related to antimicrobial resistance [9, 10]. A major contribution to the development and implementation of these methods will be the use of multi-omics data. This data could be retrieved from omics-fields such as genomics, proteomics and metabolomics, shedding light on

Table 1. Examples of omics technologies applied in infectious disease diagnosis

Omics field	Infectious disease	Application in diagnosis	Outcome	Reference
Genomics	Tuberculosis, COVID-19, and bacterial meningitis	WGS and nanopore sequencing for outbreak tracking, detection of antimicrobial resistance genes, and precise species identification	Real-time pathogen surveillance, detection of resistance determinants, and discrimination between closely related strains	[14-16]
Metagenomics	CNS infections, sepsis, respiratory infections	Detection of bacteria, viruses, fungi, and parasites directly from clinical samples	Broader pathogen detection including unculturable and unexpected microbes; enhanced sensitivity in culture-negative infections	[17-20]
Transcriptomics	COVID- 19	Use of RNA-seq for host immune profiling	Identification of novel biomarkers	[21-23]
Proteomics	COVID-19, tuberculosis	Host-pathogen profiling and biomarker discovery	Identification of protein signatures distinguishing disease stages and pathogen types; improved diagnostic specificity and monitoring	[24-26]
Metabolomics	AIDS, hepatitis (HBV/HCV), COVID-19, tuberculosis, malaria	Profiling of host metabolites to identify infection-specific patterns	Discovery of metabolic biomarkers differentiating pathogens and distinguishing infection from inflammation	[27-29]

molecular pathways involved in infectious diseases and uncover useful biomarkers leading to the development of more accurate tests that will allow the detection of diseases at an early stage. However, the integration of multi-omics data necessitates sophisticated bioinformatic approaches, the use of artificial intelligence, deep learning technologies and systems biology methods due to the significant complexity and volume of raw data which comes as a result of this multi-source approach [11, 12].

Even with major advances in diagnostics, current methods still fail to address the challenges posed by infectious diseases. Traditional microbiological tests remain dependable but are often time consuming. Similarly, serological assays can confirm that someone has been exposed to a pathogen, but they cannot reliably show whether the infection is active or past. However, human immunodeficiency virus (HIV) is an exception since its occurrence can be estimated by measuring IgG antibodies quantitatively and qualitatively. This method is based on the lower levels of IgG antibodies, their decreased avidity with antigens and the lack of HIV-specific IgG antibodies, all of which are present in early HIV infection (post-seroconversion period) [13]. These gaps underline the need for new diagnostic tools, more rapid, more accurate, and able to provide deeper biological insights. Omics technologies offer a way forward by allowing systematic study of the genome, transcriptome, proteome, and metabolome. These techniques provide a more holistic approach to both pathogens and host responses. This review summarizes recent advances in omics technologies for infectious disease diagnostics, considers their benefits and limitations, and highlights their potential to reshape diagnostic strategies worldwide.

Table 1 shows the examples of omics technologies applied in infectious disease diagnosis.

GENOMICS

Genomics assists in the identification and description of genes, and their respective functional elements, as this facilitates the research on organism's metabolism, development and behavior [30].

Genomics utilize whole-genome sequencing (WGS), shotgun metagenomics and NGS to reveal the sequence of an organism's genetic material leading to the identification of pathogens [14, 31]. Applications of WGS are being used in public health, enhancing laboratory surveillance in outbreaks but also with the detection of multi-drug-resistant pathogens [14]. A major example of genomics application in pathogen identification are host gene expression arrays that work by quantifying a host's gene expression, when infected by a pathogen, and using that expression pattern as a molecular signature to identify the responsible pathogen and choose suitable treatment methods [32]. Moreover, in the context of outbreak tracking, genomic sequencing enables the examination of pathogens isolated from different patients. This facilitates the construction of phylogenetic trees, which help in the identification of closely related infections as well as with sporadic cases lacking clear transmission relations [33]. Additionally, genomic techniques, such as nanopore sequencing, have proven to be advantageous when tasked with reading sequences rich in gas chromatography (GC) nucleotides whereas alternative methods struggle significantly [15].

On the other hand, genomic approaches have some drawbacks as they show decreased sensitivity in samples with high background noise whether it is of human origin (e.g., tissue biopsies) or the microbiome (e.g., stool) and pathogens may go unnoticed. Furthermore, NGS analysis requires highly trained personnel and extreme care in sample preparation and handling to avoid errors or cross-contamination as even miniscule amounts of exogenous genetic material will result in a detectable signal misguiding scientists or practitioners. Finally, user-friendly bioinformatics software has yet to be developed requiring highly qualified programming staff to develop, validate and maintain the pipeline for clinical purposes [34].

Thankfully, *16S rRNA* sequencing (small subunit sequencing [SSU]) can be employed as an alternative to WGS as it offers great accuracy, versatility and simplicity that can be used for every kind of pathogen. Specifically, this sequence is present in all bacterial DNA, and it has regions which have been conserved throughout the evolution of bacterial species. These conserved regions offer a countless advantage over other genes such as *rpoA, rpoB, rpoC* or *rpoD* in discrimination among bacteria [35, 36]. The SSU sequencing utilizes *16S rRNA* gene responsible for the encoding of the ribosomal RNA which acts as a building block for the small 30S subunit of the ribosome. Its versatility stems from the fact that since the gene is responsible for protein production its sequence is highly conserved as most deviations from the original gene may halt

protein resulting in the cell's death. According to the recent literature, the use of *16S rRNA* sequence as an identification tool offer significant advantages concerning accurate identification compared to other genes, used for the same purpose [36]. A recent study evaluating conventional techniques alongside molecular methods, including PCR and SSU, demonstrated that while traditional culture detected numerous pathogens, the combination of 16S amplicon sequencing and molecular culture identified a greater number of organisms, such as anaerobes that were not detected by conventional culture. This finding highlighted that culture based methods may miss anaerobic or hard-to-detect organisms, while *16S rRNA* sequencing identifies a wider range of bacteria, including those that cannot be cultured [37]. Additionally, a recent study examining the use of SSU in culture-negative infections among children found that applying *16S rRNA* testing identified nearly half of the cases that were previously misdiagnosed. These misdiagnoses were likely due to slow-growing bacteria or samples taken from patients who had already received antibiotic treatment [38].

Although culture-based methods are a gold standard in diagnosis, they are prone to contamination and often lack accuracy, particularly when it comes to closely related species. On the other hand, genomic approaches provide greater accuracy and can detect organisms that are not cultivable; however, they tend to be more costly. A notable example of misidentification using culture-based techniques is the differentiation between *Streptococcus pneumoniae* and *Streptococcus* spp. belonging to mitis group (MG), such as *S. mitis, S. oralis, S. pseudopneumoniae*, etc. Furthermore, certain *Streptococcus* spp. of the MG may acquire phenotypic characteristics of their closely relate specie *S. pneumoniae*, due to the same colonization point and may be challenging to identify [16, 39]. In clinical cases where culture-confirmed samples are unavailable, or when prior antibiotic treatment has been administered, the use of *16S rRNA* PCR and sequencing may offer valuable diagnostic information [14, 15].

However, the introduction of new technologies in the fields of genomics poses major risks and economic complications that influence their long-term implementation and sustainability. One of the major risks lies in the ethical domain as mass-sequencing of newborns' genome underlines the need for strict frameworks that ensure the privacy and consent of participants , as to avoid future discrimination or any other consequences that may arise from genomic data leakage [40]. Additionally, there is a substantial cost for the adequate training of healthcare staff, system wide changes to support protocols as well as quick and accurate results and the creation of guidelines, regulations and standards [41]. Finally, the lack of knowledge present in medical professionals acts as a barrier to the implementation of genomics and highlights the need for proper education through seminars, case reviews and peer-to-peer learning [42].

METAGENOMICS

Metagenomics are based on the sequencing of all nucleic acids in a sample without the need for prior culturing of known species. The aforementioned technologies enable an unbiased assessment of microbial composition in both clinical and environmental samples, such as blood and tissues, without the need for traditional culturing methods. Therefore, this approach is applied in the diagnosis of infectious diseases, besides ecological and biotechnological uses, overcoming the limitations of traditional diagnostic methods, culture, microscopy and targeted PCR methods. Two types of metagenomics next-generation sequencing (mNGS) are mostly utilised, targeted sequencing amplicon metagenomics and whole-genome shotgun metagenomics, the latter being the most applied as a diagnostic method [43-45].

The development of mNGS incites the partial replacing of conventional diagnostics. Specifically, shotgun metagenomics have been used to detect unculturable organisms, diagnose viral infections, identify rare infections and contribute to investigations of outbreaks [17, 46]. Host depletion and the enrichment of pathogen nucleic sequences by exhausting host DNA and RNA, applying mechanical, chemical and enzymatic methods, can increase mNGS sensitivity. The selection of sequencing platforms depends on several factors, such as laboratory needs and priorities, pathogen load and sample type. Also, it is suggested utilizing bioinformatics computational pipelines to filter host and low-quality genomic reads and compare the rest to viral reference databases [18].

A variety of applications and combinations of these steps in different studies have shown the clinical utility of shotgun metagenomics in cases where pathogens are unknown or culture negative. A seven-year performance of mNGS testing was able to identify a broad array of pathogens including novel, emerging, and unexpected microorganisms by utilizing a workflow consisted of nucleic acid extraction and microbial enrichment using antibody-based removal of methylated host DNA (for DNA libraries) and DNase treatment (for RNA libraries), library preparation and pooling in equimolar concentrations, sequencing on Illumina NextSeq 550 instruments [17].

Metagenomic next-generation sequencing (mNGS) can be employed in a variety of clinical samples to identify microorganisms such as bacteria, viruses, fungi and parasites. Research of mNGS in sepsis of immunocompromised patients discovered the increased sensitivity of the method compared to the culture method in samples of blood, bronchoalveolar lavage fluid, cerebrospinal fluid and sputum. The aforementioned workflow consisted of nucleic acid extraction, nucleic acid fragmentation, end repair, end adenylation, primer ligation, and purification to form a sequencing library, real-time PCR for library assessment, sequencing on Illumina NextSeq 550 instrument and bioinformatics analysis aligning sequence data to a microbial database comparable to the NCBI [20] (**Figure 1**). An assay for the detection of respiratory viral pathogens from upper respiratory swab and bronchoalveolar lavage samples demonstrated the increased performance of mNGS compared to the RT-PCR method by utilizing a workflow consisted of nucleic acid extraction, reverse transcription of purified RNA, ribosomal RNA (rRNA) depletion, second strand cDNA synthesis and cDNA purification, sequencing on Illumina NextSeq 550 and MiniSeq instruments and a SURPI+ bioinformatics analysis pipeline [18] (**Figure 1**).

The emerging technology of metagenomics appears to surpass traditional diagnostic methods' efficiency in infectious disease diagnosis. The application of mNGS offers an unbiased, broad detection of bacteria, DNA and RNA viruses, fungi and parasites, revealing unusual, unexpected, and novel pathogens [17, 44]. Furthermore, this technique can be applied when results from culture-based methods and PCR are negative or insufficient [44]. Moreover, mNGS is suitable to detect co-infections, providing genomic information about different

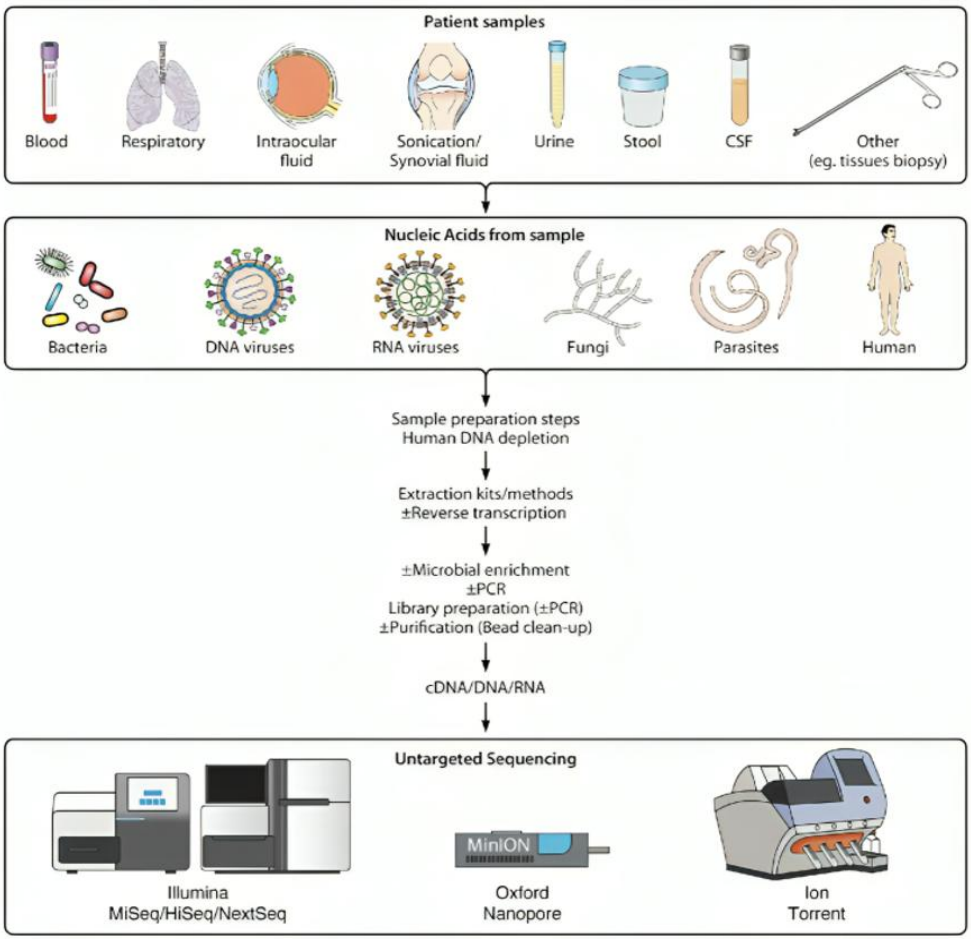

Figure 1. Demonstration of mNGS (https://eor.bioscientifica.com/view/journals/eor/8/4/EOR-22-0136.xml)

types of pathogens simultaneously [17, 18, 44]. Additionally, infections such as bone and joint infections, central nervous system infections, and infections in immunocompromised patients can also be detected [47]. According to recent studies, applications of mNGS find place in the identification of unexpected pathogens in central nervous system infections [17], enhancing pathogen identification in sepsis cases among immunocompromised individuals [20], and enabling the simultaneous recognition of multiple viral infections in respiratory samples [18].

However, the use of mNGS has limitations so conventional diagnostic methods should not be abandoned. Sensitivity can be impacted negatively by the background reads of host nucleic acids in a sample if they are not depleted successfully [44]. Results depend on pipelines, reference databases, and filtering rules, therefore possible poor pipelines, incomplete databases and misclassification will produce false results [44]. Also, contaminations and false-positive (FP) results complicate clinical interpretation, which is already hard because not all microbial nucleic acids belong to pathogens [48]. Therefore, considering the advantages and disadvantages of mNGS, studies focusing on diagnosing infectious diseases could be more complete if they include both metagenomics and traditional diagnosis methods. A primary limitation of mNGS is the microbial load present within the specimen. Specifically, when analyzing samples from sterile sites, human DNA is often detected, resulting in microbial reads representing less than 1% of total sequences [49]. According to recent studies, the size of human DNA is approximately 1,000 times greater than that of bacterial DNA. These proportions substantially reduce analytical sensitivity and increase costs due to the need for deeper sequencing to identify pathogens [49, 50]. Moreover, mNGS can detect almost anything within the range of sequencing, including commensal microorganisms and also contaminants from reagents or the environment, which makes interpretation challenging [51]. Determining whether findings represent true infection, contamination, or harmless colonization is still a major issue. For instance, identifying non-pathogenic or commensal microbes in ocular fluid, mNGS can make clinical interpretation more complex. Additionally, misclassification caused by incomplete reference databases or inadequate bioinformatics pipelines adds to these difficulties [52, 53].

TRANSCRIPTOMICS

Transcriptomics assesses messenger RNA expression profiles for genes within cells or tissues. The primary objectives of transcriptomic analysis include the evaluation of gene activity and regulation, distinguishing between infectious and non-infectious inflammatory processes, and identifying pathogenetic mechanisms and predictive parameters for clinical outcomes [54]. Gene expression studies are commonly used to examine human host responses to infection and changes in immune function. The development of omics technologies based on gene expression has offered a great opportunity in gene expression alterations in cells and tissues to evaluate the host's response to vaccines or infections (**Figure 2**) [55].

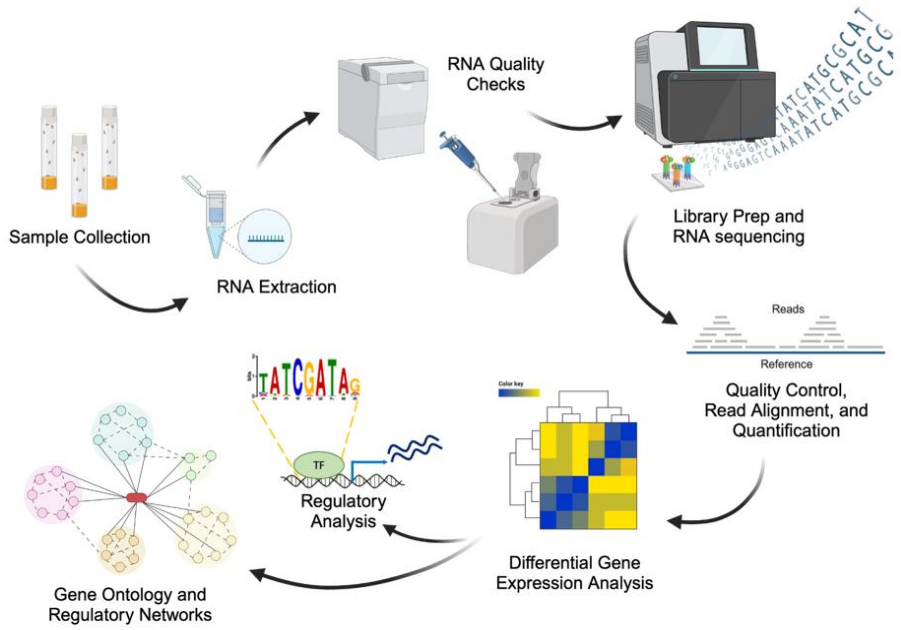

Figure 2. A scheme representing the step-by-step analysis using transcriptomics (https://biotech.ncsu.edu/2024/10/28/what-is-transcriptomics-and-why-is-it-important-heres-what-dr-cartwright-has-to-say/)

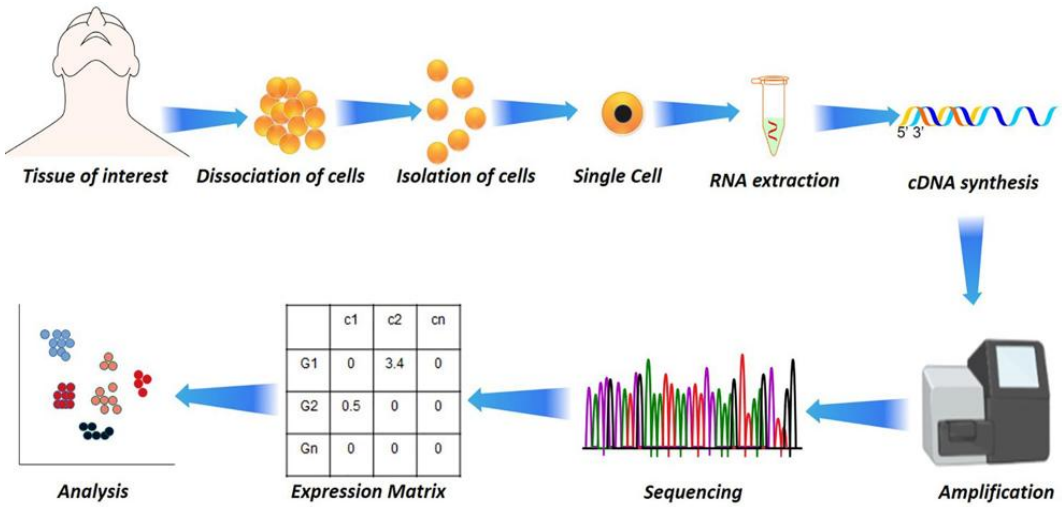

Figure 3. Demonstration of single-cell RNA sequencing (scRNA-seq) assay (https://www.frontiersin.org/journals/neuroscience/articles/10.3389/fnins.2021.591122/full)

Transcriptomics involve techniques with high levels of sensitivity. One of these methods can detect the hybridization of fluorescently labeled mRNA transcripts to specific nucleotide probes immobilized on a bead chip (microarrays), while the most common method is a sequencing- based assay applied on individual transcripts and aligning them to a reference genome (RNA-seq) [55]. Microarrays use short nucleotide probes fixed on a solid surface to measure transcript abundance. Fluorescently labelled transcripts bind to these probes, and fluorescence intensity reflects the amount of each transcript. However, designing microarrays requires prior information about the organism, such as an annotated genome for probe generation [56]. RNA-seq uses high-throughput sequencing and computational analysis to identify and measure RNA transcripts by deeply sampling the transcriptome and assembling short sequence reads into full transcripts using a reference genome or de novo methods. Applications of RNA- seq include gene identification within a genome, as well as determining gene activity at specific times [56]. Nowadays, RNA-seq are widely used in antimicrobial and antiviral immune response due to its competence to identify non- coding RNAs. However, recent studies mention that RNA-seq assays could be employed as biomarkers too [55]. In addition to RNA-seq, single-cell RNA sequencing (scRNA-seq) has emerged as a transformative tool, enabling transcriptome profiling at single-cell resolution (**Figure 3**).

This approach uncovers immune heterogeneity, distinguishes infected from bystander cells, and identifies rare immune subsets contributing to disease progression [57, 58]. As a next step in transcriptomics technologies, spatial transcriptomics allows measurement of gene expression while preserving the spatial context within tissues. This approach has been used to study SARS-CoV-2 infection in lung tissue, where viral RNA was co-localized with inflammatory host signatures, and in fungal infections to map immune-pathogen interactions *in situ* [59].

Through transcriptomics it is possible to correlate alterations in gene expression with other clinical aspects such as C-reactive protein (CRP) [55]. Furthermore, it was used transcriptomics to reveal the linkage between COVID-19 disease severity and gene expression [55]. The application of RNA-seq to whole blood from patients with the disease demonstrated that the levels of CRP were found meaningfully raised, corresponding transcriptomic groups associated with immune dysregulation. As a conclusion, it could be affirmed that a raised CRP, indicating a relationship between transcriptomic signatures and systemic inflammation [21]. Moreover, it is found that the application of transcriptomics on blood samples can facilitate the distinguish between bacterial and viral infections, as well as the comparison of genomes among pathogens [22, 23]. More specifically, during COVID-19 pandemic blood transcriptomics were used in order to detect interferons and alterations on gene expression of SARS-CoV-2 [22]. Additionally, identifying transcriptomic markers linked to immunogenicity and protection may help develop more effective vaccines against diverse pathogens. These signatures could also serve as non-serological biomarkers for predicting vaccine-induced protection [55].

PROTEOMICS

Proteomics refers to the comprehensive study of proteins concerning their expression, modifications, and interactions in organisms. Proteins have a role as priceless markers that not only show the presence of pathogens but also display the immunological response from the host in infections. Through recent technologies such as MALDI-TOF MS, LC-MS/MS, and selective platforms such as Olink PEA, it's now feasible to generate comprehensive diagnostic profiles. With the ability to test both pathogen and host simultaneously, proteomics offers knowledge often not achievable through standard diagnosis tests [24].

MALDI-TOF MS has become a standard instrument in clinical laboratories for the rapid identification of bacteria and fungi from colonies. Although it is highly precise for common pathogens it is, however, limited in use when it involves detecting rare or fastidious organisms because it requires prior culture. LC-MS/MS methodologies enable protein examination directly from clinical specimens without culture requirement, although such methodologies are largely experimental at this point. Such methodologies have been utilized in tuberculosis- and COVID-19-related research for typing strains, monitoring outbursts, and determining antimicrobial resistance, thus aiding both clinical diagnosis and public health surveillance [60].

During infection, the expression of hosts' proteins is altered dramatically. Cytokines, acute-phase proteins, and complement proteins are key diagnostic markers indicating the intensity of inflammation and immunoresponse. In infection due to SARS-CoV-2, plasma proteomic panels have been successful in distinguishing between severe and mild disease and distinguishing from bacterial sepsis and therefore yield critical directions for clinical intervention [26]. Moreover, in tuberculosis, protein signatures in plasma and urine serve to differentiate between active and latent disease, and measurement over time of these markers can reflect drug response and disease dynamics [25]. Utilization of multi-protein panels greatly enhances both precision and reproducibility, especially across variable patient populations.

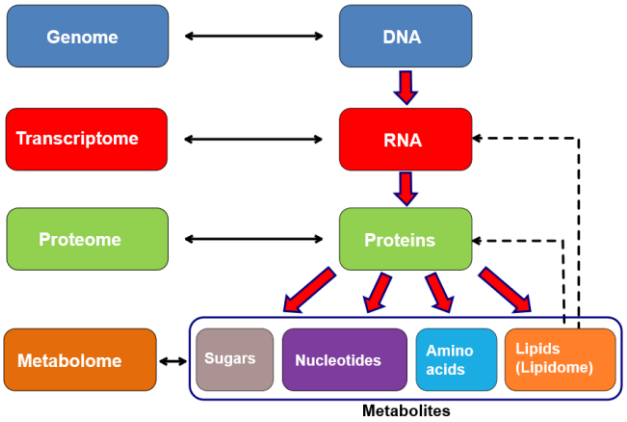

Figure 4. General diagram showing the relationships between genome, transcriptome, proteome, and metabolome (lipidome and glycome) (https://commons.wikimedia.org/wiki/File:Metabolomics_schema.png)

Findings from recent studies have demonstrated that multi-protein panels be more specific and sensitive than conventional methods such as cultures or in some cases multi-protein panels are used instead of molecular methods (e.g., PCR). For the disease COVID-19, plasma protein profiles have been utilized for prediction of disease severity and discrimination between viral infections and infections caused by sepsis-induced bacteria. Correspondingly, for tuberculosis, plasma, and urine protein measurement in conjunction enables differentiation from pneumonia and demonstrates the practical significance of proteomic markers for diagnosis of infectious diseases and monitoring patients [25, 26]. However, although proteomic assays have elevated specificity and sensitivity levels, it has been shown that in identification of close genetic microorganisms in species level such as *Streptococcus spp.* and *Neisseria spp.*, application of MALDI-TOF could lead in misidentification [16, 61].

Proteomics allows for simultaneous identification of several biomarkers, identification of novel proteins, and rapid identification of pathogens. Challenges are complex data analysis, high costs and standardization needs [24]. Furthermore, in order to enhance diagnostic accuracy, the combination of proteomics with other "omics" technologies and artificial intelligence, assists in recognition patterns in large datasets, unlocking opportunities for personalization in diagnosis. Future advances will encompass portable proteomic devices, standard panels of biomarkers, and cross-verification across large population databases, thereby paving the way for broader clinical implementation [60].

METABOLOMICS

Metabolomics is an important and arising tool in the field of "-omics" alongside with genomics, transcriptomics and proteomics that surpasses the limitations of conventional methods. The main aim of metabolomics is to study metabolites, small molecules produced by cells [62]. It is a holistic approach most closely related to phenotype as it reflects the direct signature of biochemical activity of the cell (**Figure 4**) [27, 63]. Furthermore, metabolomics offers the ability of simultaneous identification and quantification of low

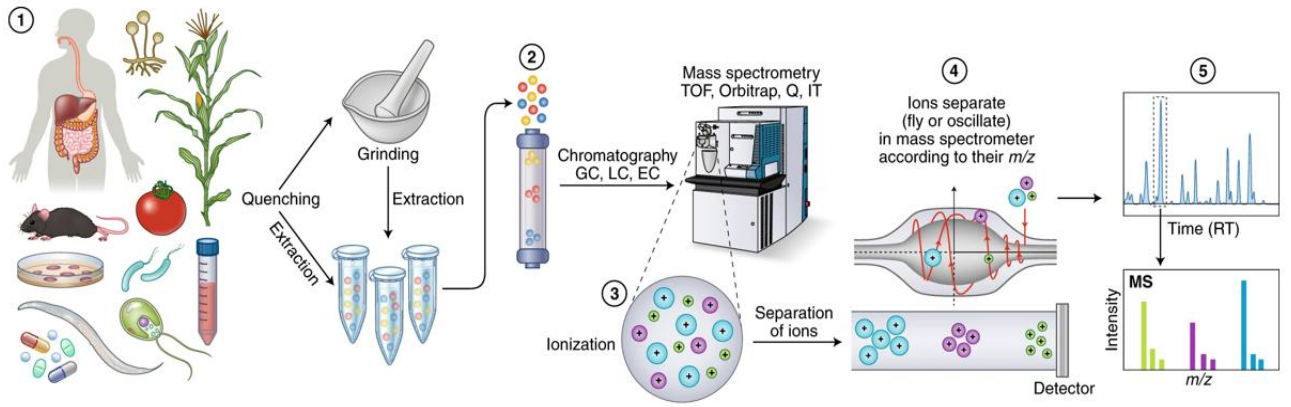

Figure 5. General workflow of metabolomics (sample preparation and extraction, chromatographic separation [GC, LC, and EC], ionization, mass analysis based on mass-to-charge [m/z] ratio, and detection; metabolite identification relies on retention time and MS signature; & common mass analyzers include TOF, quadrupole, and ion trap) (https://www.nature.com/articles/s41592-021-01197-1)

molecular weight metabolites that can be endogenous or exogenous to the organism [63].

Approaches that are used in metabolomics can be divided into two categories, targeted and untargeted [28, 64]. The targeted methods examine a predefined total of metabolites that are suspected whereas the untargeted ones examine the whole metabolome for differences from the normal [28, 64]. The most common analytical techniques employed to study the metabolome are nuclear magnetic resonance spectrometry, liquid chromatography, GC, capillary electrophoresis, and mass spectrometry (**Figure 5**) [28, 63, 65].

Nowadays, significant progress has been made in metabolomics through the integration of new and advanced analytical technologies, including high-resolution mass spectrometry (HRMS). HRMS has enhanced the sensitivity and accuracy of metabolite detection, while imaging mass spectrometry has enabled spatially resolved analyses, providing insights into tissue- and cell-specific metabolic distributions. In addition, stable isotope-based metabolite flux analysis has expanded the field beyond static metabolite profiling, allowing the dynamic characterization of metabolic pathway activity [66]. Collectively, these innovations have transformed metabolomics from a primarily descriptive approach into a powerful tool for mapping and understanding metabolic dynamics in health and disease.

Metabolomics have an extensive application in both infectious and non-infectious diseases, such as cancer, cardiovascular diseases, neurodegenerative diseases and metabolomic syndromes [29]. In the field of infectious diseases, technologies based on metabolites gained ground, as metabolomic profiling facilitates the discovery of diagnostic biomarkers that distinguish the different kind of pathogens (virus, bacteria, parasite) and provides information for the host-pathogen interactions [27, 28, 67]. These approaches can also discriminate inflammation from infection states and can thereby enhance the specificity and sensitivity of the diagnostic assays [67]. Extensive research on metabolites, has been on the line, to develop novel diagnostic assays for several infections, among which are HIV, hepatitis B, and hepatitis C virus (HBV and HCV, respectively), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), *Clostridium difficile*, tuberculosis and malaria [28].

Despite the widespread clinical implementation of biomarkers like metabolites, this approach faces challenges such as the need for standardized sampling protocol, the additional influence of microbiome variability and environmental factors. Moreover, it should be enhanced with a large-scale multicenter validation trial. Overall, metabolomics offers a powerful complimentary technique for more fast, sensitive, and specific diagnosis of infectious diseases. Omics-based assays offer significant advantages over traditional diagnostic methods like culture, microscopy, and serology by being faster, more sensitive, and capable of detecting a wider range of pathogens. For instance, techniques such as WGS and mNGS can detect pathogens that can't be cultured or are present in mixed infections directly from clinical samples, whereas conventional culture methods may require several days and sometimes produce false negatives [17, 20]. Proteomic and metabolomic panels have enhanced specificity relative to serological assays for both tuberculosis and COVID-19, thereby enabling earlier and more precise disease classification [25, 60]. Nevertheless, conventional methods continue to play a critical role in phenotypic antimicrobial-susceptibility testing and confirmatory analyses. The integration of traditional approaches with omics-based diagnostics offers a more robust and comprehensive diagnostic strategy.

CONCLUSIONS

Omics technologies have redefined the diagnostic landscape of infectious diseases by enabling high-resolution detection, comprehensive pathogen characterization, and deeper understanding of host-pathogen interactions. Collectively, genomics, transcriptomics, proteomics, metabolomics, and metagenomics provide perspectives that enhance diagnostic accuracy.

Despite these advances, several challenges remain, including high costs, limited accessibility in low-resource settings, and the need for rapid, clinically validated workflows. Data analysis and interpretation also represent critical points, as large-scale omics datasets require advanced bioinformatics tools, standardized pipelines, and robust reference databases to ensure accuracy and reproducibility.

Looking ahead, the integration of multi-omics approaches promises to deliver a holistic view of infectious disease dynamics, enabling the identification of novel biomarkers, and improving outbreak surveillance. Emerging trends such as real-time nanopore sequencing, AI-driven data analytics, and portable point-of-care platforms may further accelerate translation into routine clinical practice. Continued collaboration between researchers, clinicians, and policymakers will be essential to overcome existing limitations and fully harness the transformative potential of omics technologies in infectious disease diagnostics.

Apart from the advantages of the implementation of omics technologies in clinical microbiology, there are numerous limitations concerning their practicality and sustainability. Firstly, during all analytical procedures, there is a high risk of FP results due to contamination. Furthermore, a significant limitation which could function as an impediment from various laboratories is the cost of both the equipment and data analysis. however, the standardization of pipelines, the external quality assessments, and training of bioinformatics staff are necessary prerequisites for a sustainable implementation.

To conclude, future diagnostic workflows are expected to merge rapid sequencing with portable bioinformatics platforms, connecting laboratory practice and public-health surveillance in real time.

Author contributions: MD, ES, CZ, AG, AP, & CK: data curation, investigation, visualization, writing – original draft; **ES:** project administration, writing – review & editing; **CK:** conceptualization, methodology, project administration, supervision, writing – review & editing. All authors agreed with the results and conclusions.

Funding: No funding source is reported for this study.

Ethical statement: The authors stated that the study does not require any ethical approval. It is a review study, and no human or animal experiment was conducted

AI statement: The authors stated that they used a generative AI tool (ChatGPT, OpenAI) solely for language editing and improvement of clarity in selected sections of the manuscript. The authors carefully reviewed, edited, and verified all content and take full responsibility for the final version of the manuscript.

Declaration of interest: No conflict of interest is declared by the authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

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