

Multi-omics: the future of asthma research

MULTIOMIKA – ASTMOS TYRIMŲ ATEITIS

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Summary. Multi-omics technologies are transforming the understanding and treatment of asthma, a complex and heterogeneous chronic respiratory condition. The integration of genomics, transcriptomics, epigenomics, proteomics, metabolomics, microbiomics, and exposomics enables an in-depth analysis of asthma phenotypes, paving the way for more accurate diagnosis, risk assessment, and personalised therapy. Modern challenges in asthma management, including treatment resistance and the unpredictability of drug effects, highlight the need for precise molecular insight. Advanced tools, such as machine learning, artificial intelligence, and systems biology, offer the capacity to decode intricate biological networks and identify key biomarkers across patient subgroups. Large-scale multi-omics initiatives like Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes (U-BIOPRED), AsthmaMap, and Severe Asthma Research Program (SARP) demonstrate the potential to uncover previously unrecognized disease mechanisms and define endotype-specific therapeutic targets. Although clinical application is still developing, progress in high-throughput technologies and data integration continues to narrow the gap between research and real-world practice. Comprehensive profiling across multiple molecular layers reveals how asthma develops and progresses, offering a path toward truly personalized medicine. Asthma care's future increasingly lies in combining biological, environmental, and clinical data into cohesive strategies for prevention, monitoring, and treatment.

Keywords: asthma, multi-omics, omics analysis, genomics, transcriptomics, multi-omics integration.

Santrauka. Multiomikos technologijos vis labiau keičia astmos – sudėtingos ir heterogeninės lėtinės kvėpavimo takų ligos – supratimą ir gydymo būdus. Genomikos, transkriptomikos, epigenomikos, proteomikos, metabolomikos, mikrobiomikos ir ekspozomikos duomenų integracija leidžia giliau analizuoti astmos fenotipus, prisidedant prie tikslesnės diagnostikos, rizikos vertinimo ir individualizuoto gydymo pasirinkimo. Šiuolaikiniai astmos gydymo iššūkiai, tokie kaip atsparumas vaistams ir prognozavimo neapibrėžtumas, rodo būtinybę naudoti tikslus molekulinis duomenis. Dirbtinis intelektas, automatizuotas mokymasis ir sistemų biologija padeda atskleisti sudėtingus biologinius tinklus ir identifikuoti svarbius skirtingų pacientų biožymenis. Didelės apimties multiomikos projektai, tokie kaip „Nešališki biomarkeriai kvėpavimo takų ligų baigčių prognozavimui“ (U-BIOPRED), „Astmos žemėlapis“ ir „Sunkios astmos tyrimų programa“ (SARP), atskleidė naujus ligos mechanizmus ir galimus terapinius taikinius specifiniams astmos endotipams. Nors klinikinis šių tyrimų pritaikymas dar nėra pakankamai išvystytas, spartus aukštos raiškos technologijų ir didžiųjų duomenų analizės progresavimas leidžia tikėtis artimos integracijos į kasdienę praktiką. Molekuliinių sluoksnių sąveikų analizė padeda geriau suprasti astmos patogenezę ir eigą, o tai suteikia pagrindą individualizuotai medicinai. Astmos gydymo ateitis vis labiau grindžiama gebėjimu integruoti biologinius, aplinkos ir klinikinius duomenis į veiksmingas prevencijos, stebėsenos ir gydymo strategijas.

Reikšminiai žodžiai: astma, multiomika, omikos analizė, transkriptomika, multiomikos integracija.

DOI: <https://doi.org/10.37499/PIA.1697>

INTRODUCTION

Asthma is a chronic inflammatory disease of the airways that affects over 300 million individuals worldwide, posing a major global health burden. Characterized by airflow obstruction, airway hyperresponsiveness, and episodic respiratory symptoms, asthma varies significantly in its clinical presentation and response to treatment [1]. This heterogeneity complicates accurate diagnosis, patient classification, and the selection of effective therapeutic strategies. For some patients, especially those with severe asthma, conventional treatments, such as inhaled corticosteroids, are often insufficient, leading to persistent symptoms and a re-

duced quality of life [2]. Recent advances in molecular biology and high-throughput technologies have introduced a new paradigm in disease research through the omics sciences. These include genomics, epigenomics, transcriptomics, proteomics, metabolomics, microbiomics, and exposomics, each providing unique insight into different biological layers [3]. Rather than analyzing these components in isolation, multi-omics integrates data from multiple levels, enabling a more comprehensive understanding of disease mechanisms.

Applying multi-omics in asthma research offers the potential to identify distinct endotypes, biologically defined subtypes of the disease that can be linked to

specific biomarkers and treatment responses [4]. The growing ability to capture detailed molecular profiles using omics tools allows for the development of precision medicine approaches tailored to individual patients. When combined with clinical, phenotypic, and environmental data, multi-omics offers a powerful strategy to uncover the complex interplay between genes, environmental exposures, and immune responses in asthma pathogenesis [5]. This approach is especially important in an era where traditional one-size-fits-all treatments are being replaced by more personalised therapies. Multi-omics not only deepens biological understanding but also brings researchers closer to identifying predictive markers, optimizing treatment decisions, and ultimately improving patient outcomes in asthma care.

METHODS

The scientific review draws on information from freely available foreign scientific periodicals indexed in the Clarivate Analytics Web of Science, Scopus, and SpringerLink databases. The information was collected using the National Center for Biotechnology Information (NCBI), PubMed and PMC, Google Scholar, and the Wiley Online Library search systems. The following keywords were used in the search process: asthma, multi-omics, omics analysis, genomics, transcriptomics, and multi-omics integration. The exclusion criteria applied during the selection of sources included non-peer-reviewed materials, non-English articles, irrelevant subject matter, and publications with low citation impact.

CHALLENGES FACED IN FINDING NEW TREATMENT SOLUTIONS

The drug titration paradox

The identification of new therapeutic targets and tools is essential for improving patient care, as it enables the development of more precise, effective, and personalised treatments. Each year, regulatory agencies approve between 40 and 60 new medications, marking significant progress in the field of medicine [6]. However, discovering and developing these drugs remains an incredibly complex and challenging undertaking. This process is hindered by high costs, lengthy development timelines, low success rates in clinical trials, and the need to understand intricate disease mechanisms at the molecular level. Additionally, issues such as drug resistance and the emergence of rare or poorly understood diseases further emphasize the urgent need for innovative therapeutic approaches.

As scientific knowledge advances, technologies like multi-omics analysis, artificial intelligence, and bioinformatics are becoming indispensable in addressing these challenges. These tools hold the potential to

accelerate the development of novel treatments and improve outcomes for patients. A fundamental principle of pharmacology is that increasing a drug's dose typically results in a stronger therapeutic effect. This concept underlies the practice of anaesthetic titration, where the dosage is adjusted, upward or downward, based on the desired level of drug effect. However, in titration settings, an unexpected inverse relationship between dose and effect is sometimes observed: as the dose increases, the effect diminishes. This phenomenon is known as the drug titration paradox [7].

One explanation for this paradox may lie in individual variability in drug sensitivity. If the observed inverse relationship is merely a result of aggregating data across multiple individuals, then using a mixed-effects analysis should correct the apparent anomaly and reveal the expected positive dose-response relationship. This highlights why, although controlled experimental conditions can clarify the relationship between drug dose and effect, in routine clinical practice, where patient conditions vary and dosages are frequently adjusted to achieve specific responses, it becomes exceedingly difficult to draw definitive conclusions about this relationship.

The "black box" problem

The management of asthma is a complex process. In science, computing, and engineering, a "black box" refers to a device, system, or object that provides useful output without disclosing how it works internally. Its inner processes remain hidden or "black", making its reasoning opaque. When we view the human body as a "black box", it means that each treatment we administer travels through an incredibly complex network of organs, tissues, and biochemical pathways whose interactions and feedback loops are not fully understood (Fig. 1). As a result, although we aim to address a primary issue, the treatment can trigger additional, sometimes unexpected, effects throughout the body.

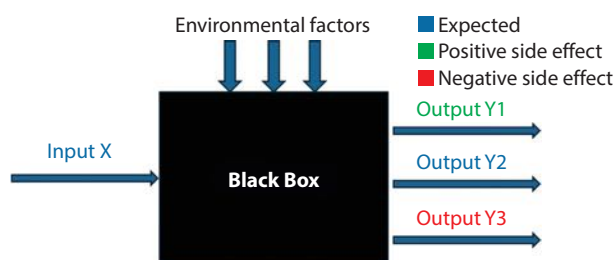


Fig. 1. The "black box" problem

The diagram illustrates the concept of the "black box" problem in complex systems. It shows how a single input (labelled Input X) enters a black box, which represents a system with unknown or poorly understood internal mechanisms. Additionally, environmental factors, depicted as multiple downward-pointing arrows, also influence the "black box", further complicating its internal processing. The system then produces multiple outputs, which may include the expected or intended outcome, a positive side effect, or a negative side effect. Original figure by the author.

These effects might be beneficial or problematic, appearing as side effects, drug interactions, or unforeseen long-term impacts. The challenge is that every person's physiology and genetic makeup vary, so even the same drug dose can produce different outcomes. Ultimately, this view of the body as a "black box" highlights the importance of careful monitoring and individualized approaches: while medical science can predict many patterns of response, it can't always foresee every subtle ripple a treatment might set off in the body's vast, interlinked systems [8].

Scientific research often focuses on exploring the behaviour of complex systems, such as living organisms. To accurately assess how a particular variable influences such systems, especially when using data generated by omics technologies, it is crucial to have a solid understanding of the underlying system. Without this understanding, data interpretation can be prone to error due to the abundance of potential correlations. One proposed explanation for these phenomena is that it represents a case of Simpson's paradox, a statistical illusion that arises when a third variable, correlated with both dose and effect, distorts the apparent relationship. In this instance, patient sensitivity to the drug acted as a confounding factor, leading to the observed paradox. More broadly, hidden group heterogeneity can generate similar misleading results [8, 9].

The next era of disease understanding with multi-omics

Multi-omics refers to the integrated use of various high-throughput screening technologies, such as genomics, epigenomics, transcriptomics, proteomics, metabolomics, lipidomics, microbiomics, and exposomics, to advance the study of human diseases. In addition to these main technologies, new approaches of radiomics, spatial transcriptomics, single-cell omics, phenomics, ionomics, pangenomics, mutagenomics, immunomics, and more are also being integrated. As medical technologies continue to advance rapidly, there is an increasing need for researchers to conduct in-depth analyses of disease pathogenesis. Omics technologies offer powerful, high-throughput screening methods that enable the efficient and comprehensive exploration of the biological underpinnings of human diseases. Each omics layer provides distinct insights, often identifying disease-associated molecules with differential expression that can serve as biomarkers and reveal altered biological pathways or processes between diseased and healthy states (Fig. 2) [10].

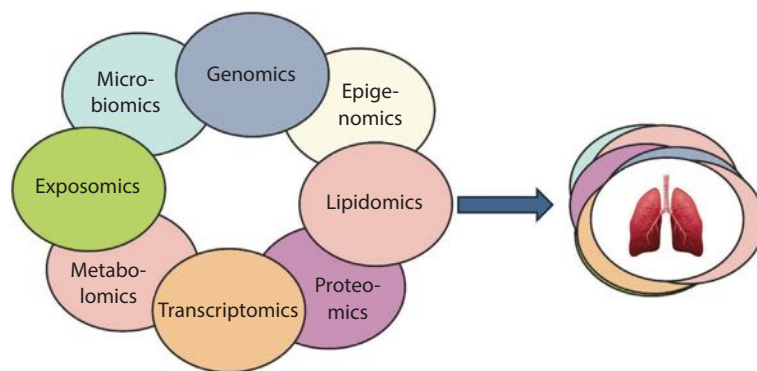


Fig. 2. Integration of multi-omics approaches in lung research

The integration of various omics disciplines in the study of lung biology and disease offers a comprehensive view of biological processes by capturing information at different molecular levels. Original figure by the author.

However, relying on a single omics approach is often insufficient to fully capture the complexity of disease mechanisms. For instance, DNA mutations can affect protein expression and function, potentially resulting in biological dysfunction, yet the degree of functional impairment cannot be determined from genomic data alone. Gene expression levels and the quantity of proteins produced are also closely linked to disease states. Moreover, disease development may be influenced not only by genetic mutations but also by errors in transcription, translation, or other molecular processes [11]. In practice, single-omics studies primarily establish associations with disease phenotypes, reflecting changes that occur during disease progression without necessarily elucidating the underlying causal mechanisms.

Genomics

Genomics is a foundational branch of omics that involves the comprehensive study of an organism's entire genome, aiming to identify, characterise, and understand the function, structure, and interactions of all its genes. It includes high-throughput sequencing, genome assembly, and annotation, and has been widely applied in medicine, most notably through initiatives, such as the Human Genome Project [12]. A major application of genomics is the Genome-Wide Association Study (GWAS), which identifies genetic variants, such as single-nucleotide polymorphisms (SNPs), associated with specific diseases or traits. Despite the utility of GWAS in uncovering novel susceptibility genes and biological pathways, many identified variants lack direct functional relevance. Structural genomics focuses on sequence polymorphisms and chromosomal architecture, allowing the construction of genetic and physical maps to identify traits of interest. Functional genomics, on the other hand, explores gene function and regulation concerning those traits. Other specialised branches of genomics have also emerged [13].

Epigenomics

Epigenomics explores reversible chemical modifications to DNA or histone proteins that influence gene expression without altering the underlying DNA sequence. Key modifications include DNA methylation and various forms of histone modification, both of which play crucial roles in regulating gene activity and fundamental cellular processes, such as development and differentiation [14]. These epigenetic changes can be triggered by environmental or genetic factors and may be stable or even heritable across generations. A growing body of research has linked epigenetic alterations to a range of diseases, including type 2 diabetes, cardiovascular disease, and cancer. Importantly, epigenetic marks are often tissue-specific, adding complexity to their study. Large-scale initiatives, such as the Reference Epigenome Mapping Centres, aim to catalogue these modifications across various tissues and conditions [15].

Transcriptomics

Transcriptomics is the comprehensive study of all RNA transcripts produced by the genome of a cell or tissue under specific conditions. It offers a global view of gene expression dynamics, capturing molecular changes in response to environmental stimuli, pathogenic agents, or developmental signals. The transcriptome includes a wide variety of RNA species, such as protein-coding messenger RNAs (mRNAs) and numerous noncoding RNAs, including long noncoding RNAs (lncRNAs), microRNAs (miRNAs), small interfering RNAs (siRNAs), small nuclear RNAs (snRNAs), piwi-interacting RNAs (piRNAs), enhancer RNAs, and circular RNAs [16].

Although mRNAs represent only a small fraction (1–4%) of total RNA, growing evidence suggests that non-coding RNAs play vital roles in gene regulation and are strongly associated with human diseases, such as diabetes, cancer, cardiovascular disease, and neurological disorders. Among these, circular RNAs have been specifically linked to cardiovascular and central nervous system diseases [17].

RNA sequencing (RNA-seq) has become the primary technology for transcriptomics, enabling high-throughput, quantitative analysis of RNA transcripts, even from small sample sizes. The field has advanced further with the rise of single-cell transcriptomics (scRNA-seq), allowing researchers to resolve gene expression at the level of individual cell types. This is particularly valuable for dissecting heterogeneous tissues in complex diseases like cancer and Alzheimer's disease. Overall, transcriptomics serves as a critical bridge between genomic information and functional gene regulation, with impactful applications in biomedical research.

Proteomics

Proteomics is the large-scale study of the entire set of proteins, collectively known as the proteome, expressed by a cell, tissue, or organism at a given time. Unlike transcriptomics, which measures RNA levels, proteomics provides a more direct and functional snapshot of cellular activity, as protein expression is often regulated by post-transcriptional and post-translational modifications, which may not correlate with RNA levels. This makes proteomics an essential tool for understanding how environmental changes, stressors, or diseases affect cellular functions [18].

Proteomics is typically divided into four major branches:

- Sequence proteomics, which identifies the amino acid sequences of proteins, often using techniques, such as high-performance liquid chromatography.
- Structural proteomics, which investigates the three-dimensional structures of proteins to infer function, using methods including X-ray crystallography, nuclear magnetic resonance, and electron microscopy.
- Functional proteomics, which studies protein activity and interactions, often using yeast hybrid systems or protein microarrays.
- Expression proteomics, which quantifies protein levels to identify expression changes across different conditions [19].

Importantly, proteins often undergo post-translational modifications, including phosphorylation, glycosylation, ubiquitination, acetylation, and nitrosylation, that regulate key processes, such as signal transduction, enzymatic activity, and protein transport. Specialized fields, such as phosphoproteomics, focus on these modifications and have revealed critical insights into various diseases. Overall, proteomics serves as a powerful tool in both biomedical and biological research, enabling the discovery of disease mechanisms, biomarkers, and therapeutic targets through a comprehensive understanding of protein function and regulation [20].

Metabolomics and lipidomics

Metabolomics is the comprehensive study of small-molecule metabolites that are produced through cellular metabolic processes. These metabolites, which include carbohydrates, fatty acids, amino acids, and other intermediates or end products, reflect the biochemical state of cells and tissues, offering a direct readout of physiological and pathological changes [21]. Lipidomics is a rapidly growing field at the intersection of lipid biology, analytical technology, and medicine. Its primary goal is to create a comprehensive map of the lipidome – the complete set of lipids within a cell,

tissue, or organism. Owing to their structural complexity, functional diversity, and high abundance of lipids in biological systems, lipidomics has evolved from a sub-discipline of metabolomics into a distinct area of study [22]. Metabolomics mainly focuses on the hydrophilic classes, while lipidomics has emerged as an independent omics field owing to the complexities of the organismal lipidomes. Metabolomics is typically categorized into untargeted (broad profiling) and targeted (specific compound quantification) approaches.

In human health research, metabolomics has proven valuable in identifying biomarkers and unravelling mechanisms underlying disease progression. For example, altered metabolite levels or ratios have been linked to metabolic disorders and chronic conditions. Moreover, metabolomics can be integrated with other omics data to reveal system-wide interactions: mRNA levels may predict metabolite concentrations, gut microbiota have been linked to altered amino acid profiles in fibromyalgia patients, and mitochondrial protein expression has been correlated with acylcarnitine and acetyl-CoA levels in hypertrophic cardiomyopathy. Metabolomics serves as a vital link between genotype and phenotype, offering rich insights into the molecular basis of health, disease, and environmental adaptation. Its integration with other omics layers continues to enhance our understanding of complex biological systems across medical research domains. Metabolomics and lipidomics have become essential tools for investigating fundamental biological processes and uncovering the molecular mechanisms underlying human diseases. Distinct metabolites and lipids possess unique functional characteristics and play critical roles in regulating a wide range of cellular activities, including proliferation, metabolism, organelle function, endocytosis, autophagy, stress responses, apoptosis, signal transduction, and ageing [23].

Microbiomics

Microbiomics is a scientific field dedicated to the comprehensive study of microbial communities, known as microbiomes, that inhabit various ecosystems, including those on and within plants, animals, and humans. These communities, which consist of bacteria, archaea, protozoa, fungi, and viruses, play essential roles in maintaining ecosystem function, influencing everything from nutrient cycling and climate regulation to plant, animal, and human health [24]. In humans, the gut microbiome is of particular interest due to its significant variability among individuals, largely shaped by environmental factors rather than genetics. As a result, the microbiome often provides a more accurate explanation for differences in clinical phenotypes under specific conditions than genetic factors alone. This has led to the discovery of links

between gut microbiota and various diseases, including neurological disorders, renal failure, and cancer.

Microbiomics employs a combination of DNA- and RNA-based methods, such as metagenomics and metatranscriptomics, alongside biochemical and bioinformatics tools, to analyse the composition, functional capabilities, and dynamic changes of microbial communities over time and space. Among these, 16S rRNA gene sequencing remains one of the most widely used techniques for assessing microbial diversity [25]. As the field advances, microbiomics continues to transform our understanding of ecosystem functioning and offers promising approaches to the restoration and management of degraded environments.

Exposomics

Exposomics is the study of the environmental exposure throughout a person's life and its influence on health and disease. This involves several exposures, such as lifestyle factors (diet, smoking, etc.), air pollution, chemical exposures, and many others. The environment to which a person is exposed (the exposome) constantly influences the development and progression of asthma. This ongoing interaction between environmental factors and individual biology adds complexity to understanding asthma's pathophysiology and evolution. As awareness grows among healthcare providers, there is increasing recognition of how environmental exposures contribute to asthma's onset, symptom severity, long-term outcomes, and overall disease course [26, 27].

The exposome concept takes into account all exposures a person experiences throughout their lifetime and how these exposures affect health. Within this context, some associations between environmental factors and asthma are well-established, while others remain less clear or demonstrate varied effects depending on a person's age, genetic background, and the duration or intensity of exposure. Continued research is essential to unravel these complexities, enabling more targeted, personalised approaches to treatment and a deeper understanding of how environmental factors affect both individuals and broader at-risk populations.

INTEGRATION OF MULTI-OMICS DATA

Integrating multi-omics data requires various approaches depending on study design. Common methods include simple correlations and combined mapping, where shared drivers or regulatory influences cause elements across omics layers to correlate. More advanced techniques, like mediation analysis, assess causal relationships, for example, testing if gene expression mediates the effect of a single-nucleotide polymorphism on disease. Similar strategies have been applied across other omics layers. Network-based modelling is

another powerful framework, where multi-omics data are represented as nodes and edges within biological networks. These can be data-driven or informed by existing molecular interactions, such as metabolic pathways, protein-protein interactions, or genomic structures. A key challenge in multi-omics studies is aligning identifiers across datasets, often resolved using databases like Kyoto Encyclopedia of Genes and Genomes (KEGG). Ideally, multi-omics data are collected from the same samples, but in practice, datasets like genome-wide association studies (GWAS) and transcriptomics are often derived from different cohorts. In such cases, tools like expression quantitative trait loci mapping can bridge the gap. However, assumptions, such as RNA abundance reflecting protein levels, are not always true. While some proteins show strong RNA-protein correlation, most exhibit modest or inconsistent relationships due to regulatory processes like translation control and protein turnover. Understanding these discrepancies is essential for accurate interpretation, especially in disease contexts. Co-expression networks, built from control and disease-specific gene expression data, help identify modules and key drivers linked to pathology. While many networks are undirected, integrating genetic data can infer causality and highlight disease-relevant pathways [3].

Omics for the future in asthma

Asthma is a prevalent and complex disease with multiple distinct phenotypes, each potentially responsive to different targeted therapies. Better characterisation of these phenotypes and a deeper understanding of their biological foundations are essential for implementing precision medicine approaches. Advances in various omics technologies, including (epi)genomics, transcriptomics, proteomics, metabolomics, microbiomics, and exposomics, have enabled researchers to examine asthma from multiple biological perspectives. With technological progress, the use of omics in asthma research has expanded significantly, narrowing the gap between laboratory discoveries and clinical application. However, several design and methodological challenges must still be addressed before omics can be fully integrated into routine asthma care. Collaborative efforts within harmonised frameworks, such as international consortia using standardised methodologies, are critical to overcoming these barriers.

Over the past two decades, numerous large-scale international collaborations have been launched to deepen our understanding of asthma. Multi-omics projects, in particular, are the result of long-term, intensive efforts by multidisciplinary research teams. One notable example is the Severe Asthma Research Program (SARP) in the United States, a multicentre initiative focused on exploring severe asthma in both adults and children by integrating clinical and cellular data. In Europe, the U-Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes (U-BIOPRED) project has taken a similar approach, aiming to uncover insights into severe asthma across age groups by combining data from multiple omics layers. Another broad initiative, Mechanisms of the Development of Allergy (MeDALL), investigated the molecular mechanisms behind allergic diseases, including asthma, using multi-omics strategies [28, 29].

Integrative omics in asthma

Integrating multi-omics profiling offers a powerful avenue for comprehensively characterising the molecular and biological landscape of asthma. Theoretical applications of machine learning have enabled the combination of data from genomics, transcriptomics, epigenomics, proteomics, metabolomics, and microbiomics. This integrated approach is key to developing models that identify diagnostic and predictive markers

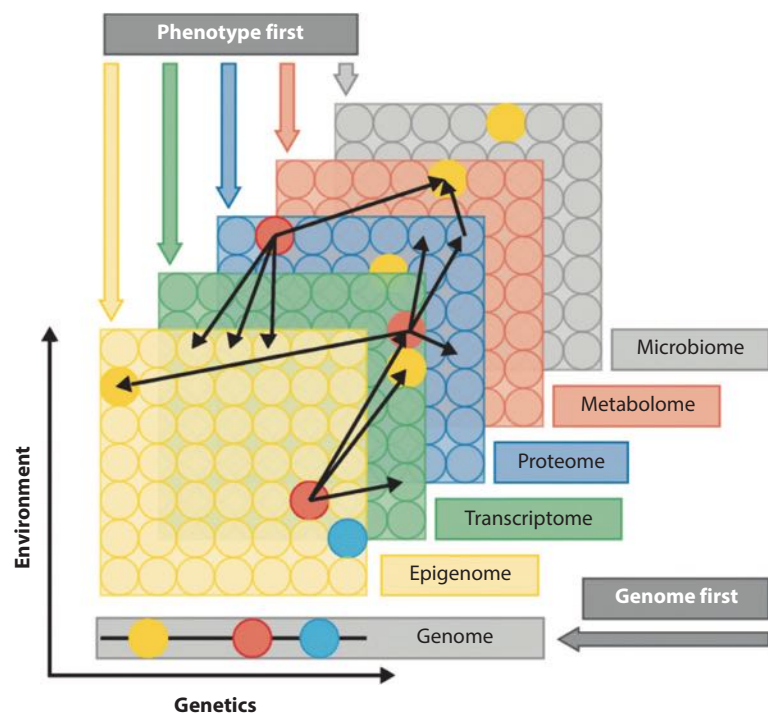


Fig. 3. Various omics data types and research approaches used to study disease

Each layer represents a distinct type of omics data, capturing comprehensive information about a specific class of molecules, illustrated as circles. With the exception of the genome, all other layers are influenced by both genetic regulation and environmental factors, which may affect each molecule to varying degrees [3]

across different patient populations and varying degrees of asthma severity. Machine learning also plays a critical role in defining asthma endotypes and forecasting the effectiveness of endotype-specific therapies, thus supporting personalised precision medicine. Commonly used techniques for patient stratification include unsupervised methods, such as K-means clustering, as well as supervised approaches such as random forests, decision trees, logistic regression, and feature selection. These methods help uncover patterns and correlations within high-dimensional omics datasets [30]. Despite its potential, multi-omics integration in asthma research is still at an early stage. Many of the biomarkers and risk factors identified through these analyses require further validation through experimental studies and clinical trials. To generate robust and clinically meaningful evidence, larger sample sizes and advancements in computational methodologies are essential [31].

Integrative omics, or multi-omics, in asthma involves combining data from multiple molecular layers to better understand disease mechanisms. Most studies have focused on pairing two layers (e.g., eQTL studies), while fewer have explored more comprehensive integration. Merging three or more omics layers, especially those with complementary information, can enhance biological insight and reduce noise, leading to more meaningful discoveries. It is also believed that integrating more omics layers can reduce the required sample size, as shown in a study where combining 5–7 layers achieved perfect COPD classification with as few as six subjects [32]. That study also used permutation and cross-validation to prevent overfitting, an important consideration when predictors outnumber samples.

Several supervised and unsupervised methods have been developed for multi-omics analysis. Supervised approaches (e.g. machine learning) use predefined labels, while unsupervised methods, such as Similarity Network Fusion, iClusterPlus, PINSPPlus, and Spectrum [33, 34], cluster data based on internal similarities. There is currently no gold standard method, and the choice of technique should depend on the dataset's features. Unsupervised techniques are especially useful in early, exploratory phases due to their unbiased nature.

Traditionally, these approaches have analysed bulk tissue, but emerging single-cell omics now allow molecular profiling at the individual cell level. Single-cell multi-omics enables detailed investigation of the (epi) genome, transcriptome, proteome, and metabolome within a single cell [35, 36]. In asthma, single-cell transcriptomics has already revealed novel cell types and altered cellular states, offering fresh insights into disease pathogenesis.

Benefits of omics analysis in asthma research

Omics research enables comprehensive molecular profiling of asthma patients, allowing for the identification of biomarkers linked to specific endotypes and the discovery of novel mechanisms involving genes, proteins, metabolites, and microbiota that contribute to asthma progression. This, in turn, supports the development of more targeted therapies. Integrating multi-omics and non-omics data through statistical methods enhances precision medicine in asthma by informing diagnosis, risk stratification, and personalised treatment strategies [37].

Advancements in omics have significantly deepened our understanding of asthma's molecular underpinnings. For instance, GWAS have uncovered numerous genetic loci associated with asthma susceptibility across various populations. Similarly, epigenome-wide association studies have identified distinctive DNA methylation patterns linked to the disease. Protein levels related to inflammation, apoptosis, and cell proliferation also fluctuate during asthma, and proteomic analysis of these changes offers further insight into the pathophysiology of bronchial asthma [38]. The U-BIOPRED project exemplifies the application of transcriptomics, proteomics, lipidomics, metabolomics, and clinical phenotyping to define multiple asthma endotypes and identify genes involved in inflammatory pathways. Overall, omics approaches offer unprecedented opportunities to identify asthma endotypes and biomarkers, which is particularly critical in managing the disease [39].

The future of omics in asthma

Asthma is a complex, dynamic condition influenced by interactions among diverse molecular and cellular pathways. Instead of viewing it as a single disease, it is more accurately understood as a system of interrelated endotypes and phenotypes shaped by genomic, epigenomic, proteomic, metabolomic, and environmental factors.

The rise of cost-effective omics technologies has enabled their routine use in asthma research, providing deep molecular insights [40]. The integration of multiple omics layers, combining genomics, transcriptomics, proteomics, metabolomics, microbiomics, and exposomics, has enhanced our understanding of asthma pathogenesis, subtypes, and progression. Projects, such as AsthmaMap and U-BIOPRED demonstrate how this approach can reveal underlying mechanisms and identify novel biomarkers and therapeutic targets. Systems biology, which contextualizes these omics layers within biological networks, offers a holistic view of asthma's molecular landscape. When applied longitudinally, it can uncover dynamic changes over time, linking molecular signatures with clinical outcomes. Tools

such as genome-wide and epigenome-wide association studies (GWASs, EWASs), breath-based metabolomics (e. g. eNoses), pharmacogenomics, and microbiome profiling hold promise for real-time, non-invasive, and personalised asthma care [41, 42]

However, translating these findings into clinical practice requires overcoming several challenges: standardising omics analysis techniques, identifying minimal yet informative biomarker sets, validating clinical relevance beyond statistical significance, and ensuring cost-effectiveness. Current advances in portable sequencing and tailored genetic chips may support future clinical implementation. Ultimately, integrating multi-omics data with clinical, environmental, and digital health records in diverse populations will be key to advancing precision medicine in asthma. This approach may enable more accurate diagnosis, better risk stratification, and targeted treatment strategies, paving the way for personalised, effective, and equitable asthma care.

CONCLUSIONS

Understanding of asthma, a highly complex and prevalent disease, has been greatly enhanced through omics techniques examining the genome, transcriptome, and epigenome. The integration of multiple omics layers, particularly when combined with clinical features, environmental data, and machine learning, provides a powerful framework to identify asthma endotypes, understand pathophysiological mechanisms, and discover novel therapeutic targets. Initiatives such as the U-BIOPRED and AsthmaMap projects exemplify how omics data can reveal biologically distinct subtypes and guide more precise, individualised treatments. Furthermore, advanced technologies like scRNA-seq, portable genetic sequencers, and breath-based metabolomics are beginning to show promise for future clinical applicability.

Despite these advances, the full clinical translation of omics in asthma remains in its early stages. Key challenges include the need for standardised protocols, reproducibility across cohorts, tissue-specific sampling, and the development of cost-effective and scalable tools for real-world use. Multidisciplinary collaboration, high computational capacity, and well-characterized, multi-ethnic longitudinal cohorts will be essential to address these challenges and validate the clinical utility of omics-guided strategies. Integrating multi-omics data within a systems biology framework offers a transformative path toward precision medicine in asthma. With continued investment in technology, data integration, and rigorous study design, this approach holds significant potential to revolutionize asthma care by enabling more accurate diagnosis, improved disease monitoring, and targeted therapeutic interventions tailored to individual patient profiles.

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