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Decoding the Complexity of COPD, Multi – Omics approaches to Diagnosis and Treatment

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Abstract

COPD represents a heterogeneous, progressive respiratory disease pathology which is uniquely associated with the persistent presence of airflow restriction, high morbidity and mortality, as well as a wide heterogeneity of underlying molecular and clinical phenotype. The standard diagnostic platforms, such as spirometry, imaging, and symptoms-based assessment, do not often reveal the underlying molecular heterogeneity and early disease pathways which can be targeted in precision interventions. The most recent innovations in the field of multi-omics techniques, such as genomics, epigenomics, transcriptomics, proteomics, metabolomics, metagenomics and other pie-

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omics layers have been utilized to separate the complicated pathobiology of COPD, to reveal new biomarkers, to characterize mechanistic sub-phenotypes, and to inform personalized therapeutic approaches. This review represents a synthesis of all current knowledge on multi-omics in COPD to question the major findings, technology, strategy of data-integration, underlying difficulties as well as future opportunities. The review highlights: (i) the biological heterogeneity of COPD; (ii) progress in individual omics layers, taking a COPD diagnosis and treatment; (iii) integration approaches and multi-omics research studies which have refined the molecular subtypes and the identification of therapeutic targets; (iv) translational possibilities and limitations; and (v) outlooks on research, such as the application of precision medicine to COPD. Two tables that outline the main omics modalities and exemplary biomarker/target results are presented, and a conceptual framework is suggested to demonstrate how multi-omics has the potential to transform clinical COPD management.

Keywords

COPD, multi-omics, biomarkers, molecular subtypes, precision medicine, integrative analysis.

1. Introduction

COPD is a major health problem facing the world. Estimates by the World Health Organization indicate that COPD in the near future is expected to be ranked among the three major causes of death in the world [1]. The disorder can be characterized by accumulated airflow restriction that is progressive and irreversible due to chronic inflammation, small-airway remodelling, and parenchymal destruction (emphysema) and chronic bronchitis phenotypes [2]. Although the standard paradigm considers risk determinants as tobacco consumption, environmental exposures and aging, it is becoming clear that COPD is highly heterogeneous when it comes to its underlying mechanisms, clinical presentation, disease progression and response to treatment [3].

There are significant drawbacks to the existing diagnostic and treatment models. Spirometry measures only at a relatively late point in the disease how much of its functions have been impaired; imaging modalities find structural damage only once a large amount of lung tissue is

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lost; and the clinical phenotypes (such as frequent exacerbator, emphysema, chronic bronchitis, or chronic bronchodiliger-leen) are not always very much aligned with the molecular heterogeneity. Thus, the rate of innovation in therapy in COPD has been slower than in other chronic disease fields like oncology and cardiovascular medicine [4].

Here, the combination of multi-omics data opens a decent prospect of paradigm shift. Muilti-simultaneously recording and merging a variety of layers of biological data genomics, epigenomics, transcriptomics, proteomics, metabolomics and microbiome profiles, researchers can reveal early indicators of disease, define molecular endotypes, predictive biomarkers of therapeutic reaction, and the new therapeutic targets [5]. The aim of the review is to explain the complexity of COPD by applying a multi-omics approach and summarize the emerging evidence in terms of diagnosis and treatment [6].

2. Pathobiology and Heterogeneity of COPD

Chronic obstructive pulmonary disease is not a singular entity of existence and more so an umbrella term that includes a continuum of pathophysiological processes [7]. Key features include: Airways, pulmonary, and vascular chronic inflammation [8]. Small airways restructuring which leads to luminal constriction and blocking. Standards of damage include: alveolar destruction (emphysema) with loss of gas -exchange surface area and loss of elastic recoil [9]. Mucus hypersecretion, dysfunctional mucociliary clearance and frequent infections or exacerbations, One of them is skeletal-muscle wasting and cardiovascular comorbidities that are systemic. Other significant factors which serve as sources of heterogeneity [10]. it include Difference in risk factors: although the main risk continues to be smoking, there are also major roles of exposure to biomass fuels, work in chemical makeup, air pollution, and early pulmonary insults in infancy [11]. Molecular and developmental factors: such as low maximum lung capacity in young adulthood increases the risk of COPD at later stages of life [12].

Phenotypic diversity: patients can have emphysema -dominant, chronic bronchitis -dominant, frequent-exacerbator, airways -dominant or vascular/cardiac-associated phenotypes [13]. The following are the

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findings of molecules heterogeneity: immune / inflammatory cell profiles, protease/antiprotease imbalances, oxidative stress, extra-cellular-matrix remodelling and changes in the microbiome have been established [14]. With this stratification of heterogeneity, an ultimate call has to be made to go beyond the one-size-fits-all approaches to management of COPD. A multi-omics strategy can provide a potential solution to unravelling this complexity [15].

3. Overview of Omics Modalities in COPD

This section is an overview of the key omics layers utilized in COPD studies, their area of measurement, key findings, and the limitations (**Table 1**).

Table 1. Major Omics Modalities and their Application in COPD

Sr No.	Omics Layer	Applications in COPD	Biological Information Captured	Key Limitations	References
1.	Genomics	Identifies genetic risk factors and susceptibility genes	DNA sequence, gene variants	Complex analysis, limited functional correlation	[16]
2.	Transcriptomics	Reveals dysregulated genes and inflammatory pathways	mRNA expression patterns	Tissue-dependent, RNA instability	[17]
3.	Proteomics	Identifies protein biomarkers for diagnosis and disease severity	Protein levels and post-translational modifications	Protein instability, costly analytical methods	[18]
4.	Metabolomics	Highlights metabolic alterations and oxidative stress	Metabolite concentrations and metabolic pathways	Influenced by diet and environmental factors	[19]
5.	Epigenomics	Explains smoking-related gene regulation changes	DNA methylation, histone modifications	Complex interpretation, tissue-specific effects	[20]

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6.	Microbiomics	Examines microbiome dysbiosis and immune response	Lung and gut microbial composition	Sampling challenges, high individual variability	[21]

The table presented above gives a brief description of the discrete domains of omics. Though both domains have brought forth illuminating insights on chronic obstructive pulmonary disease, both also have a certain limitation when taken separately. The ability of the multi-omics methods to combine these disparate data layers is what gives them the strength to provide a more comprehensive view of the molecular perspective.

4. Key Findings in COPD via Omics Approaches

In this section, we review representative findings in each omics area as applied to COPD.

4.1 Genomics and Epigenomics in COPD.

Chronic obstructive pulmonary disease (COPD) is a multifactorial, multifaceted respiratory disease that is regulated by interactions of genetic inclinations as well as environmental exposures [22]. Genomic studies have delivered significant information about COPD susceptibility, pulmonary functioning, and heterogeneity found in clinical phenotypes [23]. Various genome-wide association studies (GWAS) have identified a great number of loci associated with major indices of lung functioning, such as forced expiratory volume in one second (FEV1) and the forced expiratory volume divided by forced vital capacity (FVC) be linked with lung functioning and 55 of these are already known to be used in therapy. These findings highlight the potential of the use of genetic findings in speeding up the adoption of precision medicine in COPD [24].

In addition to inherent risk, the processes of epigenomics play an extremely important role in balancing the expression of genes without changing their DNA structure. However, epigenetic modification especially DNA methylation has been widely studied in COPD using blood and

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lung tissue samples [25]. The patterns of differential methylation have been associated with the severity of the disease, inflammatory condition as well as environmental exposures including cigarette smoke- the greatest risk factor of COPD [26]. Particular examples are CpG methylation at ALOX5AP gene, which has been linked with the response to corticosteroid therapy in acute episodes of COPD (AECOPD) [27]. Taken together, the genomic and epigenomic studies have contributed to our understanding of pathophysiology of COPD demonstrating both genetic predisposition and regulatory dysregulation. However, these aspects of molecular aspects, studied separately, are still insufficient to outline clinical phenotypes and guide personalized treatment plans [28].

4.2 Transcriptomics

Profiling Transcriptome profiling, which involves the examination of mRNA, microRNA and lncRNA, performed on lung tissue, bronchial biopsies, induced sputum, or peripheral blood has produced useful gene-expression signatures that predict COPD severity, emphysema, recurrent exacerbations and lung-function deterioration [29]. Such patterns of transcriptomics can be used to explain disease pathophysiology and define possible treatment goals; a 2016 review has combined transcriptomic, proteomic, and metabolomic data, emphasizing its use as a biomarker in the early diagnosis and prognosis of COPD [30]. This finding supports the use of multi -omics methods in understanding the intricate nature of the molecular interactions that lead to the development of COPD pathologies as well as providing personalized, mechanism-based clinical care [31].

4.3 Proteomics

Proteomics analyses of blood plasma, serum, bronchoalveolar lavage fluid (BALF) or lung tissue in COPD have identified protein panels associated with disease severity, progression or phenotypes. For instance, a study reported that 377 plasma proteins were common between early COPD individuals and controls, and identified 15 validated proteins associated with early COPD [32].

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4.4 Metabolomics/lipidomic

Metabolomic and lipidomic profiling has clarified unique small-molecule changes in chronic obstructive pulmonary disease (COPD) and thus defining key pathological pathways such as oxidative stress, extra-cellular remodelling, energy and lipid metabolism discharge, and engagement with microbial metabolites [33]. These changes of the molecules provide useful information on the progression of the disease and systemic consequences that go beyond pulmonary pathology. More specifically, high levels of homocysteine, changes in sphingolipid metabolism and deregulation of fatty-acid metabolites have been linked to COPD severity and exacerbation [34]. These metabolomic and lipidomic signatures therefore have future potential as biomarkers of disease stratification, therapeutic surveillance and explaining of new pathways of metabolism which lead to the pathogenesis of COPD [35].

4.5 Microbiome/Metagenomics

Lung and airway microbiome has become an essential point in the pathophysiology of chronic obstructive pulmonary disease (COPD). When airway microbiome data were thoroughly meta-analyzed, regular changes in microbial genera structure, and inferred metabolite-host gene interaction which is related to COPD were identified. In a multi-omics study in 99 COPD patients and 36 controls, tryptophan metabolism was dysregulated by airway Lactobacilli that led to reduced concentrations of indole-3- acetic acid (IAA) [36]. Such a decrease was associated with the impaired interleukin-22-signaling and aggravated epithelial apoptosis. It is against this background that the importance of hostmicrobiome-metabolites interactions cannot be understated in regulating the effects of inflammation, tissue remodeling, and disease pathophysiology in COPD [37].

5. Multi-Omics in Diagnosis and Prognosis of COPD

Multi-omics technologies, involving genomics, transcriptomics, proteomics, metabolomics, and epigenomics, offer an overview of the underlying molecular details of chronic obstructive pulmonary disease [38] (**Figure 1)**. Multi-omics can be used to discover new biomarkers and

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molecular signatures that are correlated with the emergence, advancement, and reactivity to therapy by merging datasets obtained on various biological layers. Genomic profiling determines locations of the predisposition, but transcriptomic and proteomic studies determine the alternate dysregulated pathways involved in the inflammation and tissue reorganization [39]. Metabolomic profiling also explains metabolic disruptions that indicate the presence of oxidative stress and energy imbalance. Systems-biology and integrative bioinformatics aid in better stratification of patients, which translate into precision medicine in COPD management [40]. Finally, multi-omics is promising a lot in terms of enhancing diagnostic precision, prognostic analysis, as well as the creation of personalized treatment, depending on the particular molecular endotypes [41].

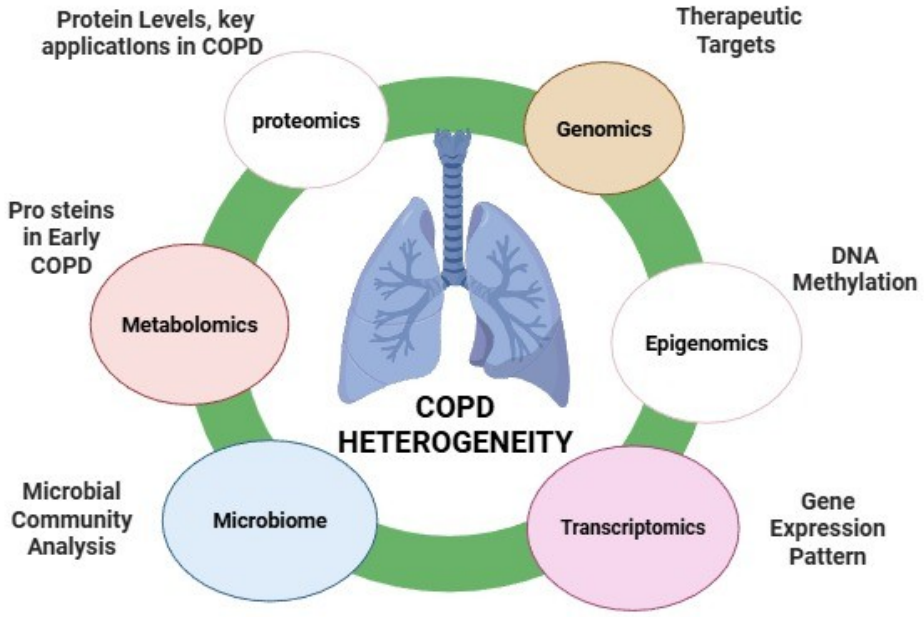

Figure 1: multi – omics modalities in COPD Research.

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This figure highlights how different multi-omics approaches ranging from genetic and epigenetic analyses to protein, metabolism and microbiome profiling that works together to provide clear and more comprehensive understanding of COPD'S biological complexity.

5.1 Early Detection and Risk Stratification

The traditional method of diagnosing chronic obstructive pulmonary disease (COPD) is based on the spirometric evaluation, where the ratio of forced expiratory volume in one second to forced vital capacity (FEV1/FVC) is less than 0.70, or the lower normative value, and the airflow is considered to be limited [42]. However, the spirometric analysis detects pulmonary dysfunction only after the development of significant, structural and molecular deformations in the respiratory parenchyma [43]. Multi-omics approaches provide the promise of predicting the pre-clinical or early-stage illness by identifying molecular disruptions that go ahead to cause observable changes in spirometerics parameters. In one such study, a proteomic and metabolomic study was done on 176 Chinese adults (88 healthy and 88 with early COPD) found 248 proteins and 137 metabolites that were significantly correlated with early COPD [44].

5.2 Molecular Sub-phenotyping

Molecular sub-phenotyping identifies clinical and biological heterogeneity in patients having chronic obstructive lung disease (COPD), who might have strong variability in the course of the disease, the frequency of exacerbation, therapeutic responsiveness, and comorbidity patterns [45]. Multi-omics sub-typing enables categorizing people into molecular endotypes, groups that have different biological processes but are not limited to the classical clinical phenotypes [46]. This molecular stratification forms a basis of personalised therapy where specific therapy may be given to specific underlying pathology including choice of anti-inflammatory therapy to patients with immune-dominant endotypes and choice of matrix-remodeling therapy to patients with prominent tissue remodelling [47]. Molecular sub-phenotyping, therefore, represents the potential of going beyond empiric, one-size-fits-all approaches in favor of precision medicine that maximizes clinical outcomes of individual COPD patients [48].

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5.3 Biomarker Panels for Prognosis

In addition to diagnostic use, biomarkers derived through omics are also being explored in terms of their prognostic use in chronic obstructive pulmonary disease (COPD) [49]. These molecular signatures have the potential to forecast disease progression, frequency of exacerbation, and risk of mortality and, therefore, support early and tailored intervention plans [50]. Much genetic research, including epigenomic studies, has found evidence of DNA methylation of the ALOX5AP gene CpG sites associated with corticosteroid responsiveness in acute exacerbation. Proteomic and metabolomic analyses have also identified promising sets of biomarker candidates which mirror inflammatory and oxidative stress and metabolic derangements [51].

Though most of these panels are still at the research and validation stage, they are good tools that can be used in clinical practice in the future, to help in the stratification of risks, optimization of treatment, and monitoring of therapeutic outcomes in the treatment of COPD [52].

5.4 Therapeutic Target Identification

Integration of multi-omics provides a powerful system of therapeutic targets recognition and repurposing of available pharmacological drugs in chronic obstructive pulmonary disease (COPD) [53]. Computational pipelines by testing and ranking molecular networks that mediate disease pathogenesis can be compiled by merging genomic, transcriptomic, proteomic and metabolomic data [54]. As an illustration, specific integrative analysis outlined 70 druggable genes that were involved in COPD thus creating a baseline of targeted pharmacological intervention and rational drug development. In addition to the genomic determinants, host microbiome-metabolites interactions have also opened up exclusive treatment prospects [55]. A good example relates to the disturbed metabolism of tryptophan that is caused by airway Lactobacilli and results in a reduction in the concentration of indole 3 acetic acid (IAA) and the subsequent disruption of interleukin 22 signalling and epithelial integrity [56]. Regulation of these microbial or metabolic pathways can be a novel therapy. Altogether, the multi-omics-inspired target discovery can bridge the gap between the molecular pathophysiology and

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translatable therapies, thus supporting the creation of precision therapies to address the unique COPD endotypes (**Table 2**) [57].

Table 2. Representative Omics-Derived Biomarkers/Targets in COPD

Sr. No.	Omics modality	Representative biomarker / target	Context / use	Reference no.
1.	Proteomics	15 plasma proteins (early Chinese cohort)	Early detection	[58]
2.	Metabolomics	Altered metabolites: palmitate, homocysteine	Severity stratification	[59]
3.	Microbiome–metabolite	Low indole-3-acetic acid (IAA) from airway *Lactobacilli*	Host–microbiome link, therapeutic potential	[60]
4.	Integrative target identification	Signature genes: SPP1, APOA1, CTSD, TIMP1, RXFP1, SMAD3	Therapeutic repurposing	[61]
5.	Multi-omics classification	5–7 omics integration showing 100% accuracy in a small cohort	Molecular sub-phenotyping	[62]

6. How Multi-Omics Works:

6.1 integration techniques in COPD

Multi-omics investigation into chronic obstructive pulmonary disease (COPD) requires careful planning of data collection, data integration, computational analysis, and biological interpretation

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in order to have meaningful results [63]. An adequate selection of a suitable cohort is a critical first step, where either homogenous or heterogeneous groups of participants are outlined according to the goals of the study, and the phenotyping is performed in detail using pulmonary function testing, imaging, exacerbation history, and biomarker profile [64]. The selection of the biological tissue or source is also the most important; invasive lung tissue provides the most disease-specific data, but less invasive specimens, like airway brushings, sputum, bronchoalveolar lavage fluid, and peripheral blood, can also be used to be considered valuable biological endotypes [65]. The choice of omics platform should be in line with the research question, and it will include transcriptomics (RNA sequencing), proteomics (mass spectrometry), metabolomics, and microbiome analysis using 16S rRNA or shotgun sequencing [66]. Temporal research design, cross-sectional and longitudinal sampling, helps to capture the dynamics, progression, and changes related to exacerbations of a disease over time. Lastly, to guarantee the data integration and sound interpretation of multi-omics findings in COPD, the confounding factors including smoking status, age, sex, comorbidities, and the use of medications should be strictly controlled to ensure unbiased and accurate data integration [67].

6.2 Data Pre-processing & Quality Control

Standardization of the procedures of sample making, handling and processing needs be uniform to curb technical variability across experimental cohorts. The use of batch-effect correction procedures also ensures that datasets obtained on different platforms or even across an extended period can be compared [68]. Normalization of data, filling of missing values and leaving outlies all enhance better analysis accuracy and reliability. The thorough annotation of genetics, proteins, metabolites, and microbial taxa contribute to and support powerful pathway analysis and integrative interpretation when considering the research of chronic obstructive pulmonary disease [69].

6.3 Integration Techniques

There are a number of computational approaches to the integration of multi-omics data: Early integration is a

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technique that involves a concatenation of raw or processed features of all omics layers into one or more matrices before statistical modeling, which allows joint analysis processes such as clustering or predictive modeling after suitable normalization and scaling [70]. Intermediate integration**,**This approach entails individually integrating every omics layer, e.g., using autoencoders, and then aggregating the latent representations to do downstream clustering or prediction, e.g. in COPD Gene sub-typing studies [71]. Late integration**,** Individual predictive models are built on each omics layer and the relevant predictions or learned features are assembled to get a unified result [72]. Network-based integration**.** Multi-layered biological networks (gene-protein-metabolite-microbe) are built to gauge network topology, identify modules and hubs, and take advantage of relational data of the omics modalities [73]. similarity-network fusion. It involves combining various blocks of omics through merging similarity networks of subjects, which has been used in COPD multi-omics classification [74].

6.4 Interpretation & Validation

Pathway and enrichment: mapping identified set of features into established biological pathways, e.g. immune modulation, extracellular-matrix remodelling, and metabolic regulation [75]. Molecular sub-typing: Unsupervised clustering algorithm has been used to define endotypes and then the result has been correlated with clinical outcomes [76]. Biomarker validation and target validation: validation in non-target (independent cohort based) validation and validation in both in-vitro and in-vivo functional assays, equivalent validation in other centres [77]. Translational linkage: linking molecular signatures and clinical phenotype (e.g., exacerbation, loss of lung function, response to therapy, etc) [78].

6.5 Challenges in Integration

Data heterogeneity: the heterogeneity of the omics platforms and the existence of the missing data across layers makes integration difficult [79]. Sample size vs feature number: given that omics data involve high dimensionality, the sample size needs to be large, or regularisation methods powerful enough must be used [80]. The batch and technical effects: the confounding variables will have

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to be strictly managed in order to avoid spurious relationships [81]. Interpretability: the identification of the candidate features by more complex models can be done, but the biological plausibility of the results must be scrutinized [82]. Cost and logistics: multi-omics data is resource-intensive to produce and the human lung tissue is especially difficult to acquire [83]. Ethics, privacy, and data-sharing implications: the large-scale integrative research frequently requires significant cooperation and implementation of the open-data policies [84].

7. Multi-Omics Approaches to Treatment and Drug Discovery in COPD

The conceptual approach to therapeutic development in chronic obstructive pulmonary disease (COPD) has been fundamentally changed by the multi-omics methodology, which has allowed development of a comprehensive systems-level description of the molecular architecture of COPD [85]. The combination of genomic, transcriptomic, proteomic, metabolomic and epigenomic streams of data, together, enable researchers to identify key molecular drivers and therapeutic targets that help in airway inflammation, structural remodeling and immune dysregulation in a systematic way [86]. It is these types of integrative analyses that can be used to identify new pharmacology candidates and to repurpose currently available agents by using advanced pathway and network-based interrogation approaches [87]. The further application of high-throughput proteomic and metabolomic profiling can be used to determine the efficacy of the drug and predict the toxicological profile, and the basis of the pharmacogenomic knowledge helps to create an individualized treatment regimen depending on the genetic variability. Besides, computational modeling and machine-learning algorithms on multi-omics datasets are used to expedite biomarker validation and therapeutic target prioritization and, therefore, is a promising direction in the field of precision medicine and improved patient outcome in COPD [88].

7.1 Drug Repurposing + Target Discovery.

Recently, Wang and Barrero (2024) used a multi-omics pipeline based on the combination of genomic, transcriptomic, proteomic and metabolomic data to define COPD-related gene signatures and to identify the drugable targets, including SPP1, APOA1, CTSD, TIMP1, RXFP1, and SMAD3. This

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research was published by MDPI and shows that the plan simplifies drug discovery by using already FDA-approved drugs in COPD repurposing in accordance with the substantial cost of de novo drug-development [89].

7.2 Host-Microbiome-Metabolite Interventions.

The microbiome–host metabolite interaction study (such as indole -acetic acid produced by Lactobacilli that restores IL-22 signalling) is an indication of a new treatment paradigm: microbial metabolism manipulation to regulate host immune and epithelial pathways in chronic obstructive pulmonary disease. This practice provides new opportunities of probiotic/biotherapeutic or metabolite-supplementation interventions [90].

7.3 Stratification of Therapy by Biomarkers.

Recent developments in multi-omics profiling have enabled the finer stratification of patients with chronic obstructive pulmonary disease (COPD) based on different molecular endotypes, which contributes the application of personalized therapeutic plans. Biomarker driven classification can be used to predict responsiveness to anti-inflammatory, anti-fibrotic, anti-oxidative or matrix repair, thus excluding individuals who are unlikely to respond, like those with non-eosinophilic inflammation [91].

7.4 Precision Medicine and Real-World Implementation.

Use of omics-based biomarkers in design of clinical trials and in everyday clinical practice assists in adaptive trial designs, biomarker-driven therapeutic distribution and the optimization of outcome assessment models. As an example, the methylation signatures, including the CpG sites of the ALOX5AP gene locus, have been examined as possible predictors of corticosteroid therapy responsiveness [92].

7.5 Challenges in Translating to Treatment

The difficulties of translation to treatment entail challenges in translating to cure and additional challenges in translating to treatment. The stringent authentication of therapeutic targets using

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lung-relevant in vitro and in vivo models [93]. Assessment of safety profile and intervention specificity especially if acting at immune or metabolic level. Managing regulatory and reimbursement policies as applicable to molecular diagnostics [94]. Smooth integration with existing clinical processes and affordability at the same time [95].

8. Current Gaps and Future Directions

Multi-omics technologies have significantly improved our understanding of chronic obstructive pulmonary disease (COPD) however, there are a number of crucial weaknesses that still exist, thereby hindering translational developments [96]. One of the key issues is the need to have larger longitudinal cohorts that would allow the detection of the inter-individual variability and the development of the disease in the long term. The available studies are often limited by small sample sizes and cross-sectional study designs that reduce the capability to describe causal biological pathways as well as to find predictive biomarkers [97].

The issue with tissue specificity and accessibility is still a major obstacle. Invasive sampling of the lung tissue is unattractive and frequently infeasible, forcing the use of peripheral samples including blood or sputum, which are less likely to be effective at capturing the changes in the molecular perturbation of the pulmonary microenvironment. This gap could be overcome by the emergence of minimally invasive procedures combined with spatially resolved omics technologies, which would make the process more representative [98].

Additionally, more layers of omics that encompass lipidomics, metabolomics, microbiomics, and epigenomics should also be improved to achieve a systems- level portrait of COPD pathogenesis [99]. Nevertheless, the current absence of standardized procedures in the data acquisition, preprocessing, and data sharing makes a significant impediment. Comparability and reproducibility of cross-study would be significantly enhanced when there are harmonized structures and open repositories [100].

9. Conceptual Framework: From Multi-Omics to Precision COPD Care

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Multi-omics integration of chronic obstructive pulmonary disease (COPD) management is a paradigm shift in managing this disease to precision medicine [101]. This conceptual framework is associated with stages that are interlinked with one another and which are combined to aid in individualized diagnosis and prognosis as well as therapy. Baseline risk stratification involves the use of genomic, epigenomic, exposomic and clinical information to define the people who are at risk of developing COPD in order to facilitate preventive measures before a person actually develops the symptomatic disease [102]. Early detection is a predictive method that uses predictive molecular biomarkers and machine learning algorithms to detect subtle changes in the body to enable early clinical evaluation and specific management [103].

Molecular sub-phenotyping is a redefinition of COPD heterogeneity, in that patients are categorized by unique molecular and cellular processes, instead of being classified by clinical phenotypes (e.g., emphysema or chronic bronchitis). This sophisticated categorization assists in biomarker-based selection of therapies where therapies are based on molecular pathways that are unique to the disease in a certain patient [104]. Response prediction and therapeutic monitoring combine longitudinal multi-omics profiles to assess the real-time treatment responses, optimize pharmacological therapy, and provide therapeutic outcomes (**Figure 2**). Also, omics-based network analyses are used in drug discovery and repurposing efforts to discover new therapeutic targets and identify currently available compounds with the potential to be effective across COPD subtypes [105].

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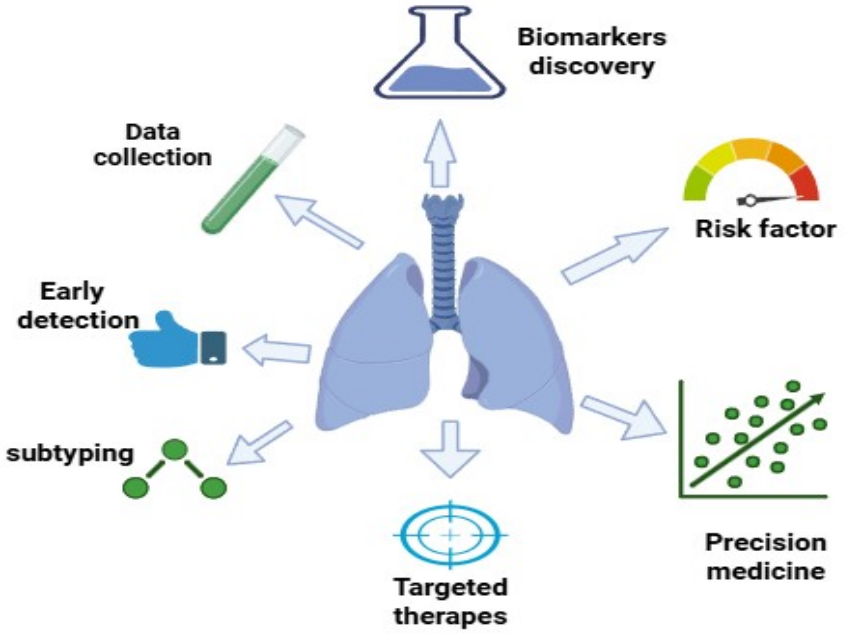

Figure 2: multi-omics to precision COPD care

This figure shows how combining different types of molecular data can guide more precise COPD care, helping identify biomarkers, assess risk, detect disease earlier. Classify patient sub type and tailor treatment to individual needs.

10. Practical Recommendations for Researchers and Clinicians

When applying multi-omics methods in the study of chronic obstructive pulmonary disease (COPD), a large and well-characterized cohort of participants should be the primary goal of the study design, with sufficient sample size as an indicator of sufficient statistical power and model stability. Biological accuracy is ensured by rigorous phenotyping, such as spirometry-based categorization based on GOLD stages 2 4 and the exclusion of ambiguous cases. Combining various layers of omics, which include genomics, transcriptomics, proteomics, and metabolomics using a system, like the Similarity Network Fusion, or graph neural networks enhances the delineation of a subgroup and prediction of outcomes. Longitudinal sampling is highly essential in tracking of the molecular trends which reflect disease progression. The protocols of sample

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collection and processing should as much as possible reduce the effect of batch and degradation to maintain cross-omics comparability [106].

Clinicians have to be updated on accepted omics biomarkers that characterize COPD heterogeneity. The following directions would be achieved by engaging in precision-medicine programs that enable the clinical translation of these insights, especially when the plasma and airway proteomic programs are more and more aligned to the molecular endotypes and the paths of inflammation [107]. When the diagnostic or prognostic utility of a diagnostic method is proven, introduction of molecular phenotyping into the standard practice is justified to support individualized treatment plans. Also, methodological rigour and reproducibility is important to editors and reviewers of SCOPUS index journals [108].

11. Conclusion

COPD is a complex and heterogeneous pathology with significant shortages in the accuracy of diagnosis at the early stage, molecular subtyping, and accurate treatment methods. Multi-omics technologies have transformative capability, having exhaustive molecular information that optimizes clinical phenotypes, identifies new biomarkers, and exposes therapeutic targets. These integrative studies, which include proteomics, metabolomics, genomics, and transcriptomics, would help differentiate the COPD subgroups with diverse inflammatory and vascular signatures, thus improving the diagnostic accuracy and risk stratification even in the initial stages of the disease. Despite the difficulty of integration of complicated data, large amounts of financial resources, and limited access to tissues, early multi-omics studies show promising possibilities to predict pulmonary performance and successfully rank patients. The future course of COPD management is based on the strategic use of multi-omics frameworks to allow the detection of the disease at an earlier stage, a more precise prognostication, and personal and stratified treatment that will result in better patient outcomes. With the help of artificial intelligence and machine-learned algorithms, the synthesis of complex data streams to be used in clinical practice will be supported, which will transform the paradigm of precision medicine to the model of an active, focused intervention. To overcome these cross-disciplinary challenges

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and achieve this vision, there should be multidisciplinary interactions among the investigators, clinicians, data scientists, regulatory agencies, and industry stakeholders to overcome the barriers of translation, establish clinically actionable assays, assure adherence to regulations, and integrate cost-efficiency analysis.

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