Personalized medicine: A novel approach to chronic obstructive pulmonary disease treatment

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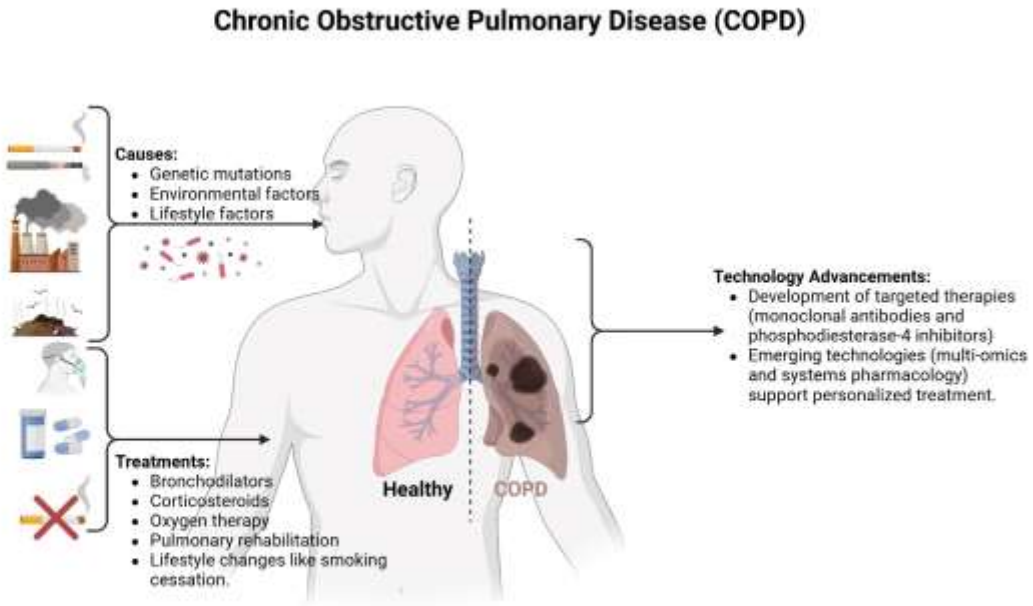
Abstract:

COPD is a long-standing and multifactorial respiratory disease brought on mainly by chronic bronchitis and emphysema and constitutes a substantial global burden of morbidity and mortality, especially in LMICs (low- and middle-income countries). Advances in research have revealed the multifactorial nature of COPD, driven by genetic predisposition, environmental exposures, and lifestyle factors. Key molecular biomarkers, including C-reactive protein and malondialdehyde, have improved diagnostic and prognostic capabilities. Genetic insights, such as SERPINA1 mutations and telomerase deficiencies, have deepened the understanding of its pathogenesis, highlighting the potential of precision medicine. Innovations in imaging techniques like computed tomography and quantitative imaging have facilitated the classification of COPD subtypes, enabling the development of targeted therapies such as monoclonal antibodies and phosphodiesterase-4 inhibitors. However, challenges like disease heterogeneity, limited pharmacogenomic applications, and insufficient clinical trial models persist. Emerging technologies, including multi-omics and systems pharmacology, offer promising pathways for personalized treatment. Future studies focus on incorporating these innovations into clinical settings and overcoming current challenges to ensure holistic COPD management and better patient outcomes. Collaboration between researchers and healthcare professionals will play a crucial role in developing advanced treatments and enhancing the quality of life for those living with COPD.

Key word: SERPINA1, Smoking, Chronic bronchitis, Biomarkers, COPD, personalized medicines etc

GRAPHICAL ABSTRACT:



1. INTRODUCTION:

Chronic Obstructive Pulmonary Disease (COPD) encompasses a group of disorders that impair breathing and is a chronic, irreversible condition. It is primarily caused by emphysema and chronic bronchitis, with severity ranging from mild to severe. In 2019, COPD ranked as the third most common cause of death, impacting 3.2 million individuals and contributing to approximately 80% of loss of life in developing and financially constrained nations. COPD mortality rates have increased from 44.5 million in 1990 to 75.1 million in 2010 in Southeast Asian nations [1].COPD was previously referred to as irreversible airway limitation. Still, the variation in disease pathways, diagnostic imaging, frequency of exacerbations, and associated mortality, headway in, modest treatment development, has required a re-examination of this disease [2] [3]. The Lancet has recently convened a task force on the future trajectory of COPD this task force proposed that COPD be reconceptualised dramatically genetically: formative year circumstances, infections, smoking, and other ecological agents [4]. Patients with normal FEV1/FVC ratio but impaired spirometry [5], [6] this group of patients, identified to be at risk for chronic airflow obstruction by the GOLD and ATS/ERS pulmonary function testing guidelines, is at great risk of chronic airflow obstruction [7]. The increased involution of COPD affects diagnosis, prognosis, and treatment nowadays. Recent studies have focused on groups of people with shared mutual features, and further subtypes and other developments have been made in the study of COPD, which has helped a lot in the identification of the disease and its subtypes. Technologies like Computed Tomography (CT Scan) and Quantitative Imaging have helped a lot in the illustration of blockage of the airway of the lungs, asthma, COPD, and its subtypes [8], [9].

Several subtypes of CT imaging associated with pulmonary vasculature [10] and mucus build-up [11] has also been found to be linked to poor outcomes related to COPD. Other clinically significant subgroups that could affect therapy choices include eosinophilic COPD and asthma–COPD overlap [12]. As COPD is evolving gradually with variable severity and extensive subtyping research the line of treatment and drug therapies till date remain the same. As COPD is much largely diversified disease in this condition, the targeted medicine is the necessity of the date. One of the con of targeted/precision medicine is tailoring medicine according to the individual's risk, pathobiology and his/her psychosocial status, and environmental conditions. Genetics, omics, and other biomarkers can easily be identified if the link between two individuals is interconnected and pathophysiological signs and symptoms with other clinical features or their end typing are similar. For the management of COPD with "precise medicine" it is very crucial to consider the genotyping of the patient.

2. CLASSIFICATION OF COPD:

COPD can be categorized according to the degree of airflow obstruction, the presence of symptoms, or a combination of both (Table 1). The predicted post-bronchodilator FEV1 percent, which is the ratio of volume exhaled in the first second, shows how bad the obstruction is. We calculate the expected value using reference equations, accounting for factors like age, gender, race, and height [13]. In addition to assessing the degree of airflow limitation through spirometric classification, the 2022 Global Strategy for the Diagnosis, Management, and Prevention of COPD by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) emphasizes evaluating patient symptoms using standardized tools such as the Modified British Medical Research Council (mMRC) questionnaire or the COPD Assessment Test (CAT) [14].

Table 1:- Classification of COPD According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines.

	COPD Classification	**Definition**
Airflow limitation classification (post-bronchodilator FEV1). [15]	Gentle GOLD Stage I	FEV_1 ≥80% predicted
	Average GOLD Stage II	FEV1 between 50% and 80% of the predicted value.
	Acute GOLD Stage III	FEV1 ranging from 30% to less than 50% of the predicted value.
	Extremely severe GOLD Stage IV	FEV1 below 30% of the predicted value.

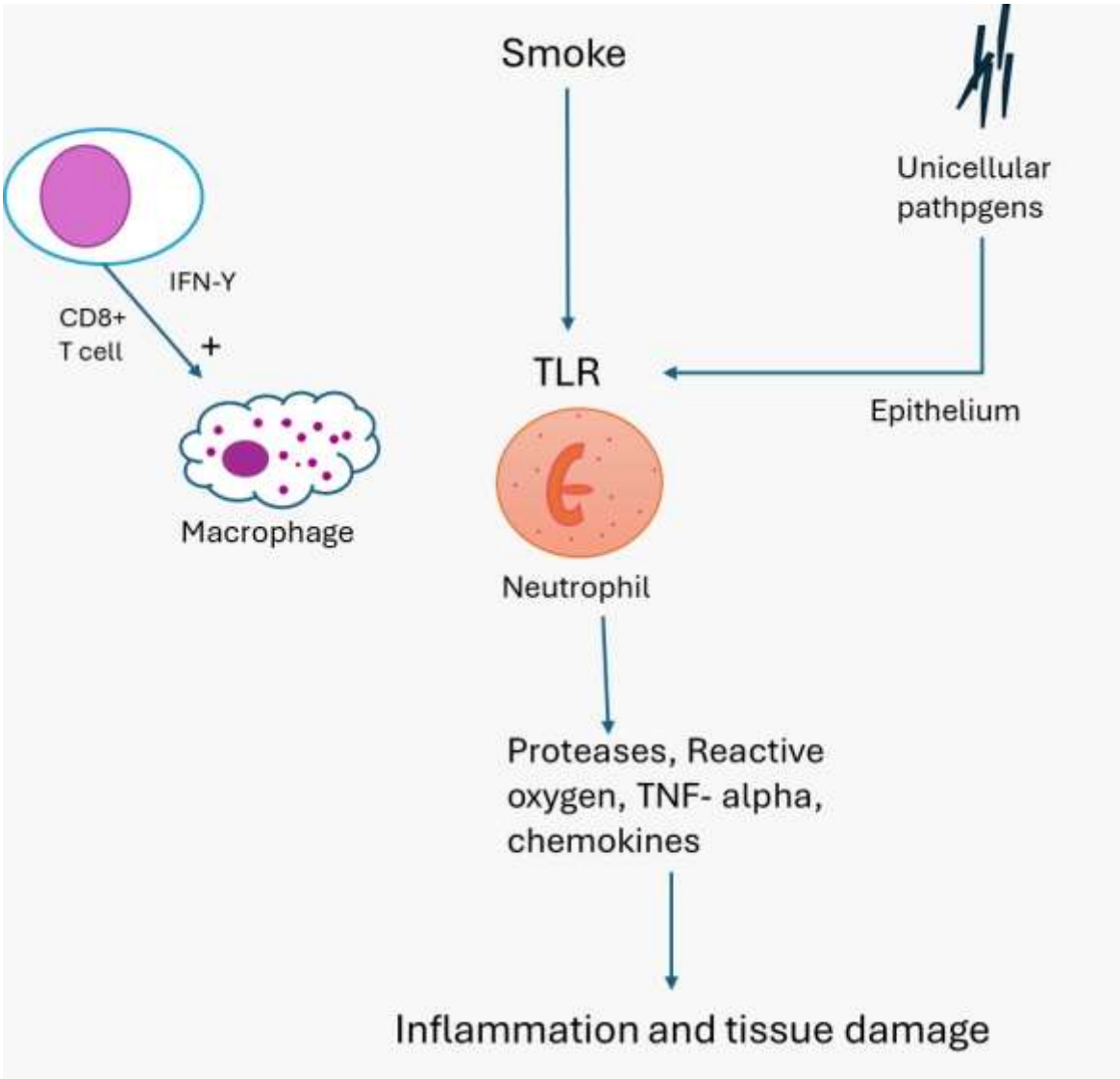
Symptom classification and exacerbation risk assessment.	GOLD group A	mMRC 0–1 or CAT score under 10 (minimal symptoms) No more than 1 moderate exacerbation without hospital admission history.
	GOLD group B	mMRC ≥ 2 or CAT ≥ 10 (significant symptoms) Up to 1 moderate exacerbation with no hospitalizations.
	GOLD group C	mMRC 0–1 or CAT < 10 (low symptom levels) History of 2 or more moderate/severe exacerbations or at least 1 hospitalization due to exacerbation.
	GOLD group D	mMRC ≥ 2 or CAT ≥ 10 (high symptom burden) History of 2 or more moderate/severe exacerbations or at least 1 exacerbation requiring hospitalization.

3. PATHOGENESIS OF COPD

Emphysema and chronic bronchitis are the two types characteristic features of COPD. Chronic bronchitis is a condition in which the chronic inflammation of bronchial tubes occurs and the production of excess mucus with the obstruction of airways. Emphysema is characterized by the destruction of alveoli, leading to minimal surface area for gaseous exchange. The advancement of the disease is because of the interaction of the complex molecules of the disease. To treat COPD with personalized medicines, it is necessary to understand these processes [16].

An essential component of the pathophysiology of COPD is inflammation of the airways of the lungs, which creates a series of immunological reactions in the respiratory system. Macrophages, neutrophils, and dendritic cells are innate immune cells activated by prolonged exposure to dangerous particles like air pollution and tobacco smoke [17]. Interleukin 6 (IL-6), and Interleukin 8 (IL-8), mainly the tumor necrosis factor-alpha (TNF-α), pro-inflammatory cytokines are released by these immune cells, making both pain and tissue damage chronic. The 'activation' of T-cells aggravates the inflammation process in the lungs, airway remodelling, and lung function inhibitor [18]. Another factor that was found to be a part of COPD is oxidative stress, which is described as an increase in the generation of ROS and a concomitant decline in the ability to scavenge ROS [19]. Tobacco smoking, which is the primary cause of COPD, gives rise to oxidative stress that results in cellular injury impacting the airway epithelial cells and the pulmonary macrophages [20]. Since oxidative DNA damage, proteins, and lipids, with the help of ROS, increases inflammation, impairs mucociliary clearance, and hampers repair of the lung parenchyma, it plays a major role in the pathogenesis of COPD [21]. Oxidative stress further aggravates the protease-antiprotease imbalance by activating matrix metalloproteinases (MMPs) and suppressing tissue inhibitors of metalloproteinases (TIMPs), leading to increased extracellular matrix breakdown and contributing to emphysematous changes in the lungs. [22].

FIG:1 This pathway highlights how pathogenesis factors like smoking and infections interact with immune cells, causing inflammation and ultimately contributing to tissue damage and airflow limitation in COPD.



4. MOLECUIAR BIOMARKER IN COPD

COPD's diagnosis, prognosis, and monitoring can easily be made with the help of molecular biomarkers. The biomarkers include a distinct array of molecules like proteins, metabolites, and nucleic acids, which can be detected in various biological samples, including blood, sputum, and through imaging techniques. The utilization of molecular biomarkers holds the potential to improve the accuracy of COPD diagnosis, categorize the austerity of the disease, forecast exacerbations, and guide treatment strategies [23].

4.1 BIOMARKERS BASED ON BLOOD

Blood Testing is one of the best methods for the disease's confirmation and diagnosis. It is a minimally invasive technique in which blood is drawn from the body. Blood testing as a biomarker helps identify the oxidative stress, systemic inflammation, and molecular signatures associated with COPD [24]. For the confirmation of the inflammation, it is necessary to take into account the testing of the fibrinogen, WBC count (White Blood Cell count), and C-reactive protein (CRP), [25]. The confirmatory test for oxidative stress can be confirmed with the oxidized DNA/RNA and malondialdehyde MDA which delves deeper into the methodical redox reactions in COPD [26].

Table.2:- Biomarkers in COPD: Functions and Clinical Significance.

COPD biomarker	Function	Clinical Significance	References
MMPs	Proteins associated with tissue	Remodeling of the extracellular matrix and pulmonary function	[27]
C-reactive protein	Systemic inflammation indicator	Associated with risk of aggravation and severity of disease	[28]
Fibrinogen	Function in the cascade of coagulation	Connected to comorbidities of the cardiovascular system	[29]
White blood cells	Indication of immune response	Represents the degree of inflammation and the course of the disease.	[30]
Malondialdehyde	Indicator of oxidative stress	Indicates systemic redox abnormalities in COPD	[31]

4.2 BIOMARKERS FROM THE SPUTUM IN COPD

COPD is characterized primarily by inflammation of airways and cells; hence, the sputum test is by far the most natural test to see this condition [32]. Induced sputum can obviate the requirement for invasive procedures and provide quantitative data on both inflammatory cells (neutrophils, eosinophils), mediators (cytokines, chemokines) and protease activity (neutrophil elastase) within the airway microenvironment. [33]. The sputum test explains the high level of eosinophils, which is the sign of a high risk of corticosteroids in COPD patients and fosters the treatment therapy. The metabolomic profiling and sputum proteomics assist in determining the new biomarkers of concern to COPD phenotypes and response to therapy [34].

5. CAUSE OF COPD:

COPD is generally not hereditary, it is usually caused by environmental factors like pollution, and smoking, and is also termed an occupational disease. However, smoking individuals are less susceptible to COPD unless hereditary.

5.1 GENETIC CAUSES OF COPD:

A highly potent serine protease inhibitor which is Alpha-1 antitrypsin (AAT), that is encoded by SERPINA1 [35]. The increased risk of emphysema is due to the inheritance of two SERPINA1 alleles leading to the inequality of neutrophil elastase and AAT leading to AAT deficiency (AATD). SERPINA1 Z alleles promote polymerisation of AAT molecules, intracellular deposition that poses a risk of liver disease since the liver secretes it [36]. The confirmation that the individual is a true phenotypic patient is made through the phenotyping of proteins and/or molecular genotyping; the diagnosis of the disorder, on the other hand, is made through the levels of serum proteins amounting to below 11 μmol/L. Refinement of genotyping/phenotyping of the protein is therefore required in order to achieve accurate diagnostic results of the disease. As far as diagnostic significance is concerned, today most of the heterozygotes who transport one SERPINA1 allele are attrs: [37]. Conventional/standard medicine as a treatment for COPD is fine, although there has been a recent increase in the accurate medicine for AATD COPD. This is referred to as augmentation therapy, and as earlier highlighted, it has little impact on the management of emphysema progression; therefore, much more research has to be carried out more often to enhance the standard of the same [38][39]. Telomerase is the enzyme of telomerase catalytic unit; it synthesizes telomeres at the ends of chromosomes. The communication of cellular senescence and apoptosis is associated with telomere shortening. Early greying, osteoporosis, cirrhosis, bone marrow failure and pulmonary fibrosis diseases are associated with telomerase mutations. [40], [41]. A research conducted in which the mice were reported to be suffering from emphysema were directly linked to cigarette smoking and were vulnerable to telomerase deficiencies [42]. Recent investigations on familial history of telomerase mutations indicate that non-smokers are more predisposed to pulmonary fibrosis, whereas smokers are more vulnerable to emphysema and mixed pulmonary fibrosis-emphysema [43]. Telomerase insufficiency and short telomere-related COPD represent a potentially identifiable subgroup, as it is associated with the female sex, a preference for upper lobe emphysema, lung fibrosis, and an elevated risk of pneumothorax, in contrast to AATD. [44]. No specific treatments for COPD are associated with telomerase mutations or shortened telomeres. Telomere length has not been associated with markers of COPD progression, rendering it an unreliable biomarker at this time, despite COPD patients exhibiting shorter telomeres than smokers._At present, investigations are probably underpowered to identify these clinical outcomes. Patients with loose skin condition, a rare genetic disorder Cutis laxa, are more likely to be affected by pulmonary emphysema [45].Cutis laxa is an autosomal dominant disorder that occurs when there's a mutation in the elastin gene (ELN), during research on mice they developed emphysema-like lesions with $Eln^{-/-}$ gene expression. [46].Severe COPD patients showed enhanced alveolar *ELN* expression, [47]these patients have a higher mortality rate due degradation of elastin and its products [48].When there's an early

onset of COPD, it is because of the mutation of Gly677Asp, other nonsynonymous variants of *the ELN* gene are usually not responsible for the same. [49] [50].

A rare autosomal dominant connective tissue illness known as Marfan syndrome is defined by a mutation in fibrillin-1 (encoded by FBN1) [51] It's an inherited disorder that usually affects connective tissue, skeletal tissue, and ocular health. Regardless, emphysema and pneumothoraces are related to the mutations of the FBN1 gene [52] In the pathogenesis of emphysema, Fibrillin1 plays a major role as it is an important extracellular matrix component.

5.2 ENVIROMENTAL AND LIFESTYLE RISK FACTORS COPD:

5.2.1 Tobacco use:

Smoking is the primary etiological factor for COPD and is estimated to be accountable for around 90% of cases globally. The deleterious substances in tobacco smoke, such as tar, carbon monoxide, and formaldehyde, cause significant harm to the respiratory tract and pulmonary lining [53]. Extended exposure to these substances results in chronic inflammation, heightened mucus production, and lung tissue destruction, which are characteristic features of COPD. Smoking diminishes the lungs' capacity to eliminate debris and combat infections, worsening respiratory ailments. Ceasing smoking is the most efficacious strategy to impede the advancement of COPD, facilitating partial restoration of pulmonary function and diminishing the likelihood of additional harm. Exposure to secondhand smoke, or passive smoking, has been linked to an increased risk of COPD, especially in those who experience prolonged exposure in confined spaces.This underscores the extensive public health ramifications of smoking and the significance of smoke-free settings.

5.2.2 Occupational Exposure to Aerosols and Particulates:

Prolonged exposure to specific dusts, fumes, and chemicals in occupational environments is a notable risk factor for COPD. Cadmium coal dust, welding fumes, dust and fumes,isocyanates, grain and flour dust, and silica dust are known to be harmful to lung tissue and can negatively affect respiratory function. These particles may induce inflammation and fibrosis in the airways, resulting in persistent respiratory complications. The risk is significantly heightened when occupational exposure is coupled with smoking, as this combination has a synergistic effect that exacerbates lung damage [54]. Employees in sectors such as construction, mining, and manufacturing are especially susceptible, and the implementation of safety protocols, including sufficient ventilation, protective gear, and routine health assessments, can alleviate these hazards [55] . The Health and Safety Executive offers essential guidelines for mitigating occupational hazards associated with COPD.

5.2.3 Atmospheric Contamination:

Extended exposure to air pollution is a significant factor that can negatively impact lung health and potentially elevate the risk of developing COPD. Particulate matter having pollutants (PM2.5 and PM10), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2) are recognized for their detrimental effect lungs in long run,

particularly urban regions characterized by elevated vehicular and industrial emissions [56]. Studies indicate that residents in regions with elevated air pollution may suffer a more significant deterioration in lung function and an increased susceptibility to respiratory ailments, such as COPD. Nonetheless, the direct causal link air pollution and COPD is still being examined, yielding inconclusive results to date. Initiatives to mitigate air pollution via stringent environmental regulations, the promotion of cleaner energy sources, and the improvement of urban planning may contribute to a reduction in COPD prevalence among impacted populations.

Comprehending and mitigating these environmental and lifestyle factors is essential for alleviating the global burden of COPD. Preventive strategies, such as smoking cessation, occupational safety protocols, and initiatives to reduce air pollution, are crucial for alleviating risks and enhancing respiratory health worldwide.

6. PHARMACOGENETICS, PHARMACOGENOMICS AND GENOME-WIDE ASSOCIATION ANALYSES INCOPD:

6.1 Pharmacogenetics and Pharmacogenomics in COPD:

Action and toxicities of the drug on an individual's genetic variant are studied under pharmacogenetics while pharmacogenomics inscribes the problems of genome sequence on a wide scale. In the treatment of COPD, studies have been extensively focused on the *ADRB2*, which is responsible for the encoding of the β2-adrenergic receptor, while studies have not yet been conducted on the bronchodilator responsiveness [57]. A genome-wide association study (GWAS) with over 5,000 smokers discovered two genetic variations in the CDH13 gene associated with bronchodilator responsiveness in African American persons [58]. A GWAS performed in a paediatric asthma cohort found the rs591118 mutation (minor allele frequency 0.44) in the PDGFD gene as a risk factor for adrenal suppression linked to inhaled corticosteroid usage. This discovery was additionally corroborated in an adult COPD cohort [59]. As of now, no genome-wide significant variations have been identified that correlate with the response to combination therapy involving long-acting beta-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs), or with triple therapy that includes inhaled corticosteroids [60].

Pharmacogenomics can be verified with the help of omics data, which can further elucidate the mechanistic under planning of the genome-wide associations and drug- induced effects. For instance , research was conducted on white people treated with Long Term Oxygen Treatment Trial which showed drastic results, and 97 SNPs were identified in 15 loci which confirms the gene treatment effects [61]. Blood expression quantitative trait loci (eQTLs) are constituted of SNPs of *ARSB* which is a mitochondrial gene. It is unclear whether *ARSB* has effects on the lungs. COPD pharmacogenomics has been limited due to the small sample size, inability to collect samples from the lungs, heterogeneity, its subtypes/endotypes, and insufficient replication cohorts, while pharmacogenomics has been of much useful in the field of oncology. To address this situation it is need of the hour that larger lung multi-omics studies need to be conducted.

6.2 Genome-wide Association Analyses:

Since most cases of COPD are not caused by rare inherited syndromes, it is necessary to study genetic risk factors throughout the genome, to gain a complete understanding of what causes the disease and how it develops. GWAS identifies common genetic variants and their links with specific traits. To date, the largest GWAS on COPD has identified 82 loci that are linked with the condition [62] and 1,020 loci with spirometry [63]. COPD GWAS loci that are frequently replicated include AGER, FAM13A, HHIP, and SFTPD. The AGER gene encodes the soluble receptor for advanced glycation end products (sRAGE), a well-established protein biomarker associated with emphysema [64]. Hhip +/- mice exposed to prolonged smoking exhibit more severe emphysema compared to wild-type controls [65]. They exhibit enhanced airway remodelling, marked by diminished glycolysis in airway smooth muscle and heightened hyperplasia [66]. Fam13a was readily obliterated when the mice were subjected to continuous smoking and elevated Wnt/β-catenin signalling, which protected it from emphysema [67]. A distinctive FAM13A single nucleotide polymorphism (SNP), rs2013701, was identified as a human functional variation influencing FAM13A expression and cellular proliferation by massively parallel reporter assays. Identifying the locations of GWAS genes that are repeatable at an accelerated rate is really tough. A further analysis employing ATAC-Seq, which examines open chromatin regions, prioritised 22 of these COPD GWAS SNPs for further validation [68]. A study examining nonsynonymous exonic variants, which are notably overrepresented among genome-wide significant variants, failed to identify new genetic loci for COPD. This indicates that genetic risk for COPD may not be entirely attributed to alterations in protein structure or function, highlighting the need to explore other potential mechanisms [69]. For example, studies on GWAS variants located upstream of the HHIP gene have demonstrated that SNPs can exert long-range regulatory influences. Zhou et al. utilized chromosome conformation capture to show that the COPD-interconnected allele of rs1542725, situated approx 85 kb before HHIP, lowers HHIP manifestation by interfering with Sp3 transcription factor binding [70].

7. TREATMENT TARGETS AND TAILORED APPROACHES IN COPD MANAGEMENT:

A paradigm change in the management of COPD is being noticed through molecularly targeted medicines and precision medicine approaches. They accommodate tailored medication techniques aligned with unique patient characteristics. Focusing on these particular pathways related to COPD pathogenesis aids in altering disease development, reducing exacerbation incidents, improving respiratory conditions, and enhancing quality of life [71].

Table.3:- Molecularly Targeted Therapies and Their Clinical Impact in COPD Management.

Clinical Aim	Procedure	Expected Medical Significance	Reference
PDE4 inhibitors	Inflammation reducing agent	Decreased exacerbation rates and enhanced pulmonary function.	[72]
IL-5 monoclonal antibodies	Focusing eosinophilic inflammation	Decreased exacerbation frequency and improved pulmonary function	[73]
M3 receptor antagonists	Enhanced bronchodilation	Demonstrates potency and safety profiles superior to those of conventional therapy.	[74]
Biologic agents targeting IL-17 pathway	Regulating immune responses	Possesses potential for addressing neutrophilic inflammation.	[75]
Beta-2 adrenergic receptor	Enhanced bronchodilation	A well-established, symptom-focused, and effective therapeutic target.	[76]

7.1 Therapies With Molecularly Targeted :

Beyond the traditional anti-inflammatory and bronchodilator drugs used to treat COPD, molecularly targeted therapies target the molecular mechanisms that lead to disease progression. PDE4 inhibitors, such as roflumilast, prevent the degradation of cAMP in inflammatory cells, functioning as anti-inflammatory agents. Roflumilast has shown reduced exacerbation rates and improved lung function in patients with severe COPD and chronic bronchitis [77]. Treatment for COPD demonstrates potential in pathways such as IL-5, which is crucial in eosinophilic inflammation and alterations in the airways. Monoclonal antibodies directed against IL-5, including mepolizumab and benralizumab, have diminished exacerbations and enhanced pulmonary function in individuals with eosinophilic COPD. In cases of neutrophilic inflammation and airway alterations, the utilisation of monoclonal antibodies such as secukinumab to target IL-17 demonstrates prospective advantages [78]. Advancements in bronchodilators targeting specific muscarinic receptor subtypes, particularly M3 receptor antagonists, have been noted, in conjunction with β2-adrenergic receptor agonists exhibiting extended efficacy, as demonstrated by ultra-LABAs. These are considered formidable competitors, with effectiveness and safety profiles that may surpass those of conventional bronchodilator therapy [79].

7.2 Personalized Medicine Strategies.:

Precision medicine focuses on identifying specific COPD subtypes and endotypes based on genetic causes, clinical symptoms, and biomarker profiles. This assists physicians in delivering customized therapeutic approaches for specific patients. COPD categorization may be based on the inflammatory phenotype, revealing distinct therapeutic responses in eosinophilic and neutrophilic subtypes [80]. Therapeutic procedures may be directed by a biomarker-centric therapy algorithm, such as the blood eosinophil count, to identify individuals likely to benefit from specific medications, like inhaled corticosteroids (ICSs) or biologic agents targeting eosinophilic inflammation. Moreover, the incorporation of genetic data, namely alpha-1 antitrypsin (AAT) deficiency status, in therapeutic strategies enables a customised strategy to managing COPD, including enhanced treatment with AAT modification for individuals with AAT deficiency [81]. Novel "omics" technologies, including as genomics, transcriptomics, and metabolomics, offer opportunities for the identification of molecular markers relevant to therapeutic response and the progression of COPD. The utilisation of multi-omics data allows researchers to identify novel therapeutic targets and create predictive models for customising treatment according to individual patient requirements and conditions [82].

8. FUTURE PERSPECTIVES: FROM OMICS TO MECHANISMS AND TREATMENT:

The efficacy of genetically informed medication development has been demonstrated in a variety of ailments, which has been correlated with a double transformation increase in the speed of progress in the second and third phases of drug testing when pharmacological objectives are supported by Mendelian syndromes or GWAS data [83]. However, notable advancements in COPD pharmacotherapy must be acknowledged. Azithromycin and dupilumab represent efficacious agents for drug repurposing. Diverse pharmaceutical repurposing techniques, including simvastatin [86], zileuton [87], and angiotensin-regulating agents [88], demonstrated potential in disease-pattern investigations but failed in clinical trials for COPD. The factors contributing to this stagnation include disease heterogeneity, inadequate tissue bioavailability, lung cellular diversity, challenges in subject selection for trials and lung tissue acquisition, lack of consensus on treatment outcomes and targets, and insufficient in vitro and animal models, among emerging challenges.

Systems pharmacology is an emerging field that employs computational biology techniques to elucidate pharmacological therapies and their adverse consequences. Systems pharmacology grounded in molecular biology has highlighted the complexity of pharmacotherapy. IL-18 treatment increased the vulnerability of ovarian tumour cells to the cytotoxic effects of conventional chemotherapeutic agents when supplied within a designated temporal window [89].Network-based systems pharmacology techniques can aid in finding opportunities for medication repositioning, anticipating off-target adverse effects, distinguishing beneficial and harmful drug combinations, and improving trials for drug responders [90].They identified carbamazepine as a risk-modifying drug for coronary artery disease. The researchers assessed their findings utilising Medicare claims data, contrasting individuals administered carbamazepine with those receiving levetiracetam, another principal anticonvulsant medicine. Their findings indicated that carbamazepine was associated with an increased risk of coronary artery disease [91]; this revelation exemplifies how network methodologies can identify medications that influence disease risk.

Genes identified in COPD GWAS were associated with the human protein network, and candidates for medication repurposing were selected based on the quantity of edges affecting risk genes. The composer identified an antioxidant and a tetracycline antibiotic as suitable options for adaptation [92], however replication and further confirmation are necessary. These approaches demonstrate potential for correlating biological data with pharmaceutical interventions in particular patients.

9. CONCLUSION:

Chronic Obstructive Pulmonary Disease (COPD) continues to pose a considerable worldwide health challenge, influenced by an interplay of genetic, environmental, and lifestyle determinants. Progress in comprehending its complex aetiology, encompassing the involvement of inflammation, oxidative stress, and genetic predispositions, has yielded significant insights into disease mechanisms. Biomarkers and advanced imaging techniques have enhanced diagnosis and allowed for the identification of subtypes, facilitating more accurate and personalised treatment strategies. Notwithstanding these gains, obstacles include illness heterogeneity, restricted pharmacogenomic applicability, and inadequate replication in clinical trials impede development. Innovative technologies, like as multi-omics, genome-wide association studies, and systems pharmacology, offer potential solutions to these restrictions and could transform COPD care. Advancing the incorporation of these innovative methods into standard clinical practice, coupled with improved preventive interventions, provides a means to better the quality of life and outcomes for COPD patients. Cooperative initiatives among research, healthcare, and policy will be essential in attaining these objectives.

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