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Diagnostic Challenges in the Differential Diagnosis of Chronic Inflammatory Respiratory Diseases: Asthma versus Chronic Obstructive Pulmonary Disease. A literature review

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Abstract
Chronic inflammatory respiratory diseases—particularly asthma and chronic obstructive pulmonary disease (COPD)—represent a significant burden on healthcare systems worldwide. More than 350 million people are affected by asthma, while COPD is the third leading cause of death globally. Despite distinct pathophysiological mechanisms, the clinical manifestations of these diseases often overlap in everyday practice, making accurate differential diagnosis challenging and predisposing to therapeutic errors. Differential diagnosis is crucial due to important differences in treatment strategies, disease progression, and clinical course. Misdiagnosis may result in inappropriate therapeutic choices, which can worsen disease outcomes and increase the risk of exacerbations and hospitalizations, whereas early detection may prevent such consequences. Spirometry remains the cornerstone of diagnosis for both asthma and COPD. However, each patient requires an individualized approach that takes into account current medications, age, comorbidities, disease duration, and smoking history. Specialists have access to a broad range of diagnostic tools for differentiation—such as FeNO, HRCT, sputum eosinophil count, questionnaire and PEF, IA but the most fundamental and valuable source of diagnostic information remains continuous patient observation, assessment of treatment response, symptom progression, and a detailed medical history obtained from the patient and their close contacts.

Aim
This study aims to explore the key diagnostic challenges in distinguishing asthma from chronic obstructive pulmonary disease (COPD) in adults, taking into account available diagnostic tools, biomarkers, and the therapeutic and prognostic consequences of diagnostic errors. Furthermore, the review seeks to propose practical approaches to improve diagnostic accuracy based on current evidence and clinical studies.

Material and methods
A review of the literature published between 2015 and 2025 was conducted using the PubMed, Scopus, and Cochrane Library databases. Review articles, observational studies, and the GINA and GOLD guidelines were included. Studies were excluded if they were not published in English or if they focused solely on pediatric populations. Key data points, including study design, population characteristics, diagnostic methods evaluated, and primary outcomes related to differential diagnosis, were extracted and synthesized thematically.

Results
Asthma and chronic obstructive pulmonary disease (COPD) are heterogeneous inflammatory airway diseases with partially overlapping clinical presentations. Key diagnostic challenges stem from the similarity of symptoms, including cough, dyspnea, and wheezing, as well as the variable reversibility of airway obstruction. Spirometry remains the diagnostic cornerstone, yet its interpretation requires clinical experience and reproducible measurements. Complementary assessments, such as fractional exhaled nitric oxide (FeNO), blood eosinophil counts, allergy testing, and high-resolution computed tomography (HRCT), can improve diagnostic precision. A significant clinical challenge is the asthma–COPD overlap (ACO), characterized by the coexistence of features from both conditions, which complicates therapeutic decision-making. Misdiagnosis can lead to suboptimal treatment, increased exacerbation frequency, and higher healthcare costs.

Conclusion
Effective differential diagnosis of asthma and COPD requires a combination of functional testing, inflammatory biomarkers, and a thorough patient history. Implementation of spirometry in primary care and broader use of biomarkers (e.g., FeNO, eosinophils) in clinical practice are recommended. In the future, prospective studies on novel biomarkers and the application of artificial intelligence may improve diagnostic accuracy and enable more personalized therapy.

Key words
Asthma, COPD (chronic obstructive pulmonary disease), Diagnostic Challenges, Differential Diagnosis, Spirometry, Asthma-COPD Overlap (ACO), FeNO, Biomarkers, Peak Expiratory Flow (PEF), Questionnaire,

Eosinophils, Sputum analysis.

Background

Chronic respiratory diseases represent an increasing challenge for modern medicine. Compared to 1990, the number of affected individuals has risen by 39.8%, with the incidence particularly correlated with the wealth of a country, where inhabitants are daily exposed to air pollution and maintain unhealthy lifestyles (GBD Chronic Respiratory Disease Collaborators, 2020) [1]; (Adeloye et al., 2022) [2]. Chronic respiratory diseases are currently the third leading cause of death worldwide, following cardiovascular disorders and cancer. The most common chronic conditions within this group are chronic obstructive pulmonary disease (COPD) and asthma (GBD Chronic Respiratory Disease Collaborators, 2020) [1]; (Adeloye et al., 2015) [3]. Both diseases share a background of chronic airway inflammation, and both exhibit airflow limitation as a common clinical manifestation. However, extensive studies have demonstrated that these are two distinct disease entities with different etiologies, pathophysiological mechanisms, and clinical courses(Barnes et al., 2006) [4].

Chronic Obstructive Pulmonary disease (COPD)

Chronic obstructive pulmonary disease (COPD) is a heterogeneous and progressive respiratory disorder characterized by persistent respiratory symptoms such as cough, dyspnea, and sputum production, accompanied by chronic airflow limitation resulting from airway (bronchitis, bronchiolitis, mucus hypersecretion) and/or alveolar abnormalities induced by exposure to harmful particles or gases (Celli et al., 2022) [5].

In the Polish population, spirometry-confirmed COPD is diagnosed in approximately 9% of adults over 40 years of age, with a higher prevalence observed in men. Globally, COPD is among the most prevalent chronic diseases, currently affecting more than 380 million individuals (Gajewski, 2024) [6]. According to the World Health Organization (WHO), COPD accounts for approximately 3.5 million deaths annually, representing nearly 5% of all global deaths, with about 90% of these deaths occurring in low- and middle-income countries (World Health Organization, 2023) [7].

The development of COPD results from complex interactions between individual susceptibility and environmental exposures. Among modifiable risk factors, tobacco smoking remains the dominant cause, responsible for nearly 80% of all cases (Gajewski, 2024) [6]. However, emerging evidence underscores the significant contribution of air pollution—including particulate matter, combustion gases, vehicular exhaust, and smog—which may account for nearly 50% of the total risk of COPD development (Sin et al., 2023) [8]; (Yang, Jenkins, & Salvi, 2022) [9].

The underlying pathogenic mechanism of COPD involves chronic inflammation driven by prolonged exposure to noxious environmental agents. This inflammatory process is mediated primarily by TC1, TH1, TH17, and ILC3 lymphocytes, and persists even after cessation of exposure to the harmful stimulus (Gajewski, 2024) [6]. The most recognized genetic determinant of COPD is a mutation in the SERPINA1 gene, which results in alpha-1 antitrypsin deficiency and leads to increased proteolytic tissue damage (Cho, Hobbs, & Silverman, 2022) [10].

Pathophysiology

The pathophysiology of COPD is complex and involves the coexistence of emphysema and airway obstructionaffecting both bronchi and bronchioles. Two major mechanisms—proteolysis and oxidative stress—drive the structural and functional lung injury. These mechanisms initiate a cascade of pathophysiological events, including:

mucus hypersecretion and impaired clearance → airflow limitation → lung hyperinflation → emphysematous destruction → impaired gas exchange → pulmonary hypertension → cor pulmonale.

Excessive mucus production results in a productive cough, one of the hallmark clinical symptoms of the disease. Airflow obstruction in small airways arises from smooth muscle constriction, bronchiolar inflammation, peribronchiolar fibrosis, and accumulation of inflammatory exudate within the airway lumen. Over time, these changes become irreversible, contributing to the progressive nature of airflow limitation.

The phenomenon of air trapping occurs when exhalation is restricted, leading to air retention within the lungs. During exhalation, increased intrathoracic pressure typically facilitates air release; however, in COPD, the structurally altered bronchioles collapse prematurely, preventing effective air outflow. Emphysema, defined as abnormal enlargement of airspaces distal to the terminal bronchiole, results in the formation of large bullae that reduce the available surface area for gas exchange, thereby impairing oxygenation and carbon dioxide elimination (Gajewski, 2024) [6]; (Barnes, 2006) [11]; (Global Initiative for Chronic Obstructive Lung Disease [GOLD], 2025) [12].

Pathophysiological Mechanism	Primary Effect in the Lungs	Clinical Consequence

Chronic inflammation (TC1, TH1, TH17, ILC3)	Airway wall thickening, mucus overproduction	Persistent cough, sputum production
Protease–antiprotease imbalance	Alveolar wall destruction	Emphysema, reduced gas exchange
Oxidative stress	Cellular injury, impaired ciliary function	Impaired mucociliary clearance
Peribronchiolar fibrosis	Airway narrowing	Irreversible airflow limitation
Air trapping and hyperinflation	Increased residual lung volume	Dyspnea, reduced exercise tolerance
Pulmonary vascular remodeling	Increased pulmonary arterial pressure	Pulmonary hypertension, cor pulmonale

Figure 2. Pathophysiological cascade in COPD (Gajewski Interna Szczeklika, 2024

Clinical Presentation

Most patients report a long-standing history of tobacco exposure. Unlike asthma, COPD symptoms generally exhibit minimal diurnal or nocturnal variability. The typical clinical features include chronic cough, persistent sputum production—particularly noticeable upon awakening—and dyspnea, initially exertional but progressing to resting dyspnea as the disease advances.

On physical examination, characteristic findings include wheezing, coarse crackles, a barrel-shaped chest configuration, and diminished vesicular breath sounds, all consistent with airflow obstruction and lung hyperinflation (Gajewski, 2024) [6]; (GOLD, 2025) [12].

Asthma

Asthma is a chronic respiratory disease, typically characterized by persistent airway inflammation. It presents with symptoms such as wheezing, dyspnea, chest tightness, and cough. These symptoms vary in frequency and intensity and are associated with variable expiratory airflow limitation (Global Initiative for Asthma [GINA], 2025) [13]. The occurrence or exacerbation of symptoms and bronchial obstruction is often influenced by external factors such as physical exertion, exposure to allergens or irritants (including tobacco smoke, air pollution, paint fumes), weather changes, emotional stress, certain medications (e.g., NSAIDs), or respiratory tract infections—most commonly viral (GINA, 2025) [13].

Several phenotypes of asthma have been identified, with classification closely related to etiology.

Allergic asthma typically manifests in early childhood, and is frequently associated with other atopic disorders such as atopic dermatitis and food allergies, along with a positive family history. Serum IgE concentrations are elevated, and skin-prick tests are positive. This phenotype generally exhibits a favorable response to glucocorticoid therapy.

Non-allergic asthma, by contrast, tends to occur in adults, with negative skin-prick tests, low IgE levels, and poor corticosteroid responsiveness (Gajewski, 2024; GINA, 2025) [6][13].

Additionally, the GINA 2025 guidelines distinguish other clinical phenotypes, including late-onset asthma, asthma with fixed airflow obstruction, and obesity-associated asthma (GINA, 2025; Bel, 2004) [13][14].

Globally, asthma affects approximately 1–29% of the population, though prevalence varies significantly across countries (Mortimer et al., 2022) [15]. According to the World Health Organization (WHO), around 262 million people suffer from asthma, resulting in approximately 455,000 deaths each year (WHO, 2024; GBD 2019 Diseases and Injuries Collaborators, 2020) [16][17].

In Poland, an estimated 1.4 million individuals live with asthma, though many remain undiagnosed (Damps-Konstańska et al., 2020) [18]. Meta-analyses have revealed that the prevalence of asthma is significantly lower in rural than in urban populations (Śliwczyński et al., 2015) [19].

Allergic asthma arises from complex interactions between genetic predisposition and environmental exposures. It is characterized by chronic bronchial inflammation with infiltration of eosinophils, mast cells, and T lymphocytes, resulting in airflow limitation caused by smooth muscle contraction, mucosal edema, mucus plugging, and airway remodeling.

Th2 lymphocytes play a central role in asthma pathogenesis through the production of cytokines IL-4, IL-5, and IL-13, which promote IgE synthesis, mast cell proliferation, and eosinophil activation (Wenzel, 2012) [20].

In non-allergic asthma, neutrophilic rather than eosinophilic inflammation predominates, with IL-17, IL-8, and IL-1β pathways involving Th17 activation. This asthma phenotype is typically more difficult to manage and exhibits limited response to standard Th2-targeted therapies (Klain et al., 2022; Baos et al., 2018) [21][22].

Major Risk Factors for Asthma:

Individual factors: genetic predisposition (atopy, airway hyperresponsiveness), female sex in adulthood, Black ethnicity, and obesity.

Environmental factors: airborne allergens, occupational exposures, tobacco smoke, diet, and respiratory infections (Gajewski, 2024; GINA, 2025) [6][13].

Asthma exacerbations are commonly triggered by exposure to airborne allergens, respiratory tract infections, weather fluctuations, emotional stress, irritants, or tobacco smoke (Gajewski, 2024; GINA, 2025) [6][13].

Clinical Presentation

Asthma symptoms are episodic and variable in intensity, often resolving spontaneously or with appropriate treatment. Outside exacerbation periods, patients may remain asymptomatic and exhibit normal lung function. During exacerbations, the hallmark symptom is expiratory dyspnea, typically occurring at night or early in the morning. Other key features include wheezing and paroxysmal dry cough. On physical examination, clinicians often detect wheezes, coarse crackles, and prolonged expiration during asthma attacks (Gajewski, 2024; GINA, 2025) [6][13].

Comparison

Asthma and COPD share a fundamental characteristic — a chronic inflammatory process that develops within the bronchi and bronchioles, leading to bronchitis and bronchiolitis. However, there are significant differences in the clinical course of these two diseases. Asthma typically develops at a younger age and is associated with variable and reversible airflow limitation, often accompanied by airway hyperresponsiveness to various bronchoconstrictive stimuli. Pulmonary function between exacerbations usually remains normal. Airway obstruction results from multiple mechanisms, including mucus hypersecretion, airway wall edema, and airway remodeling (Barnes, 2006)(GINA, 2025)[11][13]. In contrast, Chronic Obstructive Pulmonary Disease (COPD) is characterized by a progressive and irreversible decline in lung function, most often affecting older individuals exposed to environmental risk factors, particularly tobacco smoke. Chronic airflow limitation arises from small airway disease and airway remodeling (obstruction), combined with destruction of lung parenchyma (emphysema). COPD is also associated with excess mucus secretion, airway obstruction, and the formation of air trapping. These pathophysiological alterations do not resolve with treatment but remain relatively persistent over time (Barnes, 2006) (Global Initiative for Chronic Obstructive Lung Disease [GOLD], 2025)[11][12].

Feature	Asthma	COPD
Age of Onset	Usually develops in childhood or early adulthood	Typically occurs in individuals over 40 years old
Primary Etiology	Genetic predisposition and environmental allergens; often associated with atopy	Long-term exposure to harmful environmental agents, especially tobacco smoke
Nature of Inflammation	Eosinophilic, Th2-mediated inflammation	Neutrophilic, macrophage-dominated inflammation
Airflow Limitation	Variable and reversible	Persistent and largely irreversible
Main Pathophysiological Mechanisms	Bronchial hyperresponsiveness, airway edema, mucus plugging, and remodeling	Small airway obstruction, alveolar wall destruction (emphysema), and loss of elastic recoil
Lung Function Between Exacerbations	Typically normal	Chronically impaired with progressive decline
Response to Treatment	Marked improvement with inhaled corticosteroids and bronchodilators	Limited reversibility; bronchodilators and anti-inflammatory therapy may slow progression
Smoking as a Risk Factor	Not essential for disease development	Major etiological factor (responsible for up to 80% of cases)
Mucus Secretion	Variable; increases during exacerbations	Excessive and persistent mucus hypersecretion common
Air Trapping / Hyperinflation	Minimal, transient during attacks	Marked, chronic air trapping and lung hyperinflation
Course of Disease	Intermittent, with symptom-free periods	Progressive deterioration of lung function

Figure 3. Comparison between Asthma and Chronic Obstructive Pulmonary Disease (COPD)

Diagnostic Criteria and Overview of Diagnostic Methods

Clinicians worldwide face similar challenges in differentiating obstructive lung diseases. Jenkins et al. (2019) conducted a global survey among pulmonology specialists and primary care physicians, examining approaches to differentiating and managing asthma, COPD, and asthma–COPD overlap (ACO). A total of 891 responses were

collected from 13 countries. The diagnosis of asthma and COPD was generally consistent with established guidelines; however, in the case of ACO, substantial variability in diagnostic features was observed—specialists focused primarily on spirometry and clinical history, whereas primary care physicians emphasized treatment and symptoms. The choice of therapy was often inconsistent with guideline recommendations, and more than half of the respondents did not recommend inhaled corticosteroids in patients with predominant asthmatic features. (Jenkins et al. 2019)[23]

Spirometry

Spirometry represents the most reproducible and objective method for assessing airway obstruction. It is a non-invasive, easily accessible, and relatively inexpensive test (GOLD, 2025) [12]. It serves as a fundamental diagnostic tool in obstructive lung diseases, allowing the evaluation of ventilatory parameters of the respiratory system and the identification of obstructive disorders. It is also performed to assess bronchial reactivity to irritants and the effects of bronchodilator medications on airway smooth muscle.
Spirometry includes the following components (Gajewski, 2024) [6]:
measurement of vital capacity (VC) and its components,
assessment of forced expiratory flow (including FEV_1 and FVC),
measurement of maximal voluntary ventilation (MVV),
measurement of peak expiratory flow (PEF).
This examination is necessary for every patient suspected of chronic obstructive pulmonary disease (COPD) or asthma, both for diagnosis and monitoring of disease progression. In COPD diagnostics, spirometry is performed after administration of a bronchodilator, most commonly 400 µg of salbutamol. COPD diagnosis is confirmed when the post-bronchodilator FEV_1/FVC ratio is <0.70, which indicates persistent (irreversible) obstruction. Additionally, the patient should present clinical symptoms such as chronic cough or dyspnea, particularly exertional dyspnea. These criteria have been defined by the Global Initiative for Chronic Obstructive Lung Disease (Gajewski, 2024) [6]; (GOLD, 2025) [12].
Asthma diagnosis relies on the clinical presentation and confirmation of variable lung function, usually through spirometry with a bronchodilator test. In some situations, the diagnosis can be made solely based on clinical symptoms (paroxysmal cough and dyspnea, particularly occurring during exertion, exposure to allergens, toxins, or pollutants). In most patients with asthma, spirometry results during stable periods remain normal. Variable obstruction—defined as an increase in FEV_1 of >12% and at least 200 mL between consecutive tests or in response to treatment—is characteristic of asthma (Gajewski, 2024) [6]. According to GINA 2025 guidelines, the normal FEV_1/FVC ratio in adults is >0.75–0.80 (Global Initiative for Asthma [GINA], 2025) [13].
Despite clear guidelines, the effectiveness of spirometry in the general population is limited. Meneghini et al. (2017) evaluated the effectiveness of spirometry in detecting asthma in the general population. In this cross-sectional study, young adults aged 23–25 years participated, and an abnormal spirometry result was defined as FEV_1 <80% of the predicted value. The gold standard for asthma diagnosis was the coexistence of bronchial hyperresponsiveness in the methacholine challenge test and respiratory symptoms. Among 1,922 participants, asthma was diagnosed in 200 individuals (10.4%), and abnormal spirometry was observed in 208 (10.9%). Spirometry showed high specificity (90%) but low sensitivity (23%) for asthma detection. Positive predictive value was 22%, negative predictive value 91%, and agreement with the diagnosis was poor ($\kappa = 0.13$). The authors indicate that spirometry, when used alone, has significant limitations as a diagnostic tool for asthma in the general population (Meneghini et al., 2017) [24]. The low sensitivity of spirometry for asthma, as shown by Meneghini et al., means that a normal spirometry result does not rule out asthma, complicating differentiation from early COPD where obstruction might be mild or intermittent.
Härtel et al. (2022) assessed the frequency of spirometry use among patients with asthma and COPD in German primary care practices, using data from a retrospective cross-sectional study based on the Disease Analyzer (IQVIA) database. Patients with at least one diagnosis of asthma or COPD in 2020–2021 and a follow-up visit between January 2021 and January 2022 were included in the analysis. The study population consisted of 8,835 patients with asthma, 5,597 with COPD, and 1,897 with coexisting asthma and COPD. Spirometry was performed in 7% of asthma patients, 27.2% of COPD patients, and 54.7% of those with both diagnoses. Testing was performed more frequently in women than in men and significantly more often in pharmacologically treated patients. The authors emphasize that the frequency of spirometry in primary care remains low, despite being a key diagnostic and monitoring tool for patients with asthma and COPD (Härtel et al., 2022) [25]. These observations highlight the critical need to improve access to diagnostic testing and emphasize the importance of widespread spirometry use in clinical practice.
Spirometry is a fundamental test in obstructive lung diseases; however, it is not an ideal examination. Despite its good sensitivity in detecting obstruction, spirometry alone cannot be considered sufficient due to its low specificity (Çolak et al., 2019) [26]. Bouwens et al. (2022) conducted a cross-sectional study in 10 Dutch general practices involving 532 patients who underwent extensive testing for obstructive lung diseases. Two pulmonologists

assessed the presence of asthma and COPD in the patients. In this study, all diagnostic components were divided into three categories depending on availability at different levels of healthcare: group (1) medical history only (respiratory symptoms, smoking history, BMI), group (2) diagnostics available in primary care (spirometry and bronchodilator spirometry), and group (3) diagnostics available in a specialized clinic (histamine provocation test, DLCO, plethysmography). Receiver Operator Characteristics (ROC) and area under the curve (AUC) were calculated for each group. Results showed that 138 patients were diagnosed with COPD, 84 with asthma, and 310 had no obstructive lung disease. In group (1), the ROC model demonstrated an AUC of 0.84 (95% CI 0.78–0.89) for differentiating asthma and COPD. In group (2), the AUC remained 0.89 (95% CI 0.85–0.94; p = 0.967), demonstrating improved diagnostic efficacy with spirometry. In group (3), the AUC remained 0.89 (95% CI 0.85–0.94; p = 0.967). It can be concluded that the ability to effectively diagnose and differentiate asthma and COPD should rely on spirometry and a bronchodilator test. More advanced tests do not seem to provide better overall diagnostic differentiation of asthma and COPD in primary care patients (Bouwens et al., 2022) [27]. This does not imply that these tests are useless, as they play an important role in assessing the presence and severity of structural lung damage (such as pulmonary emphysema and bronchiectasis) and in differentiating obstructive lung disease from other etiologies in selected patients (Hegewald et al., 2009) [28]; (Lutfi et al., 2017) [29].

Access to rapid and effective diagnostics is crucial, and the future may belong to home spirometry, performed using small portable devices allowing daily patient monitoring. Gao et al. (2025) evaluated the reliability of the portable Medcaptain VC-30 Pro spirometer compared with the conventional Jaeger MasterScreen PFT laboratory spirometer in 132 participants. The study aimed to determine whether the portable device could serve as an alternative to standard spirometry tests for the diagnosis and monitoring of chronic respiratory diseases, such as asthma and COPD. The multicenter, randomized, open-label study included participants who performed lung function measurements using both devices. Values of FEV_1, FVC, FEV_1/FVC ratio, PEF, and $FEF_{25–75}$% were compared. Results showed very high agreement of measurements — intraclass correlation coefficients (ICC) for FEV_1 and FVC were 0.994 and 0.993, respectively ($p < 0.001$). Bland-Altman analysis confirmed that 96% of results fell within 95% limits of agreement, and Cohen's kappa for obstruction diagnosis was 0.872, indicating excellent agreement between devices. The study indicates that modern portable spirometers may serve as reliable, inexpensive, and convenient tools for diagnosing obstructive lung diseases, especially where access to laboratory spirometry is limited (Gao et al., 2025) [30]. Similarly, Xiao et al. (2022) compared the portable PUS201P spirometer with the traditional Jaeger spirometer in 202 patients over 40 years of age, comparing FEV_1, FVC, and FEV_1/FVC values obtained with both devices. ICCs were 0.95, 0.92, and 0.93, respectively, and Bland-Altman analysis showed that 95% of results were within limits of agreement. The portable spirometer provides high accuracy and reproducibility, making it a reliable tool for screening and diagnosing COPD and asthma in primary care settings (Xiao et al., 2022) [31].

Remote spirometry allows early detection of FEV_1 decline prior to the clinical onset of COPD exacerbation. Watz et al. (2022) analyzed FEV_1 data measured using remote spirometry at least once weekly for eight weeks in 360 COPD patients. They found that a decline in daily FEV_1 could be observed two weeks before the clinical manifestation of COPD exacerbation (from 0.907 L on average to 0.860 L on the day of symptom onset). This enables early detection of pulmonary function deterioration and intervention one to two weeks before a full-blown COPD exacerbation (Watz et al., 2018) [32]. Tupper et al. (2018) conducted a randomized study involving 281 COPD patients, comparing quality of life and the COPD Assessment Test (CAT) between patients undergoing telemonitoring and those receiving standard care. The group with spirometry, pulse oximetry, and symptom telemonitoring demonstrated improved quality of life outcomes (Tupper et al., 2018) [33]. In a subsequent study by Achelrod et al. (2017) including 651 telemonitored patients and 7,047 patients receiving standard care, spirometers were provided to patients with $FEV_1 \geq 35\%$, and both spirometers and pulse oximeters to patients with $FEV_1 < 35\%$. Both measurements were required at least twice weekly. Additional questionnaires and educational materials were sent via the platform, and patient inquiries were addressed at any time. After a 12-month follow-up, mortality risk was significantly lower in the telemonitored group. Direct costs also decreased due to fewer emergency visits, hospitalizations, and shorter hospital stays (Achelrod et al., 2017) [34]. These findings suggest that telemonitoring represents the future of monitoring patients with obstructive lung diseases.

Mobile spirometry has many advantages, including portability, affordability, ease of use, and time efficiency. Importantly, it provides immediate information about airflow limitation, reflecting disease variability. Early detection of exacerbation and prompt intervention are potentially possible. However, several challenges remain for these applications: (1) accuracy of unsupervised spirometry is a primary concern, (2) device calibration (Zhang et al., 2021) [35]. These issues were highlighted in a study evaluating the effectiveness of home spirometry in monitoring therapy for chronic obstructive lung diseases, conducted by Oppenheimer et al. (2023), analyzing data from 2,857 patients. Improvement in FEV_1 related to treatment was observed in both home and clinical spirometry measurements. However, improvements measured via home spirometry were smaller and less consistent than standard spirometry measurements. Results demonstrated that home spirometry was less consistent and did not fully correspond to standard spirometry, suggesting that unsupervised home readings should be interpreted with caution (Oppenheimer et al., 2023) [36].

Okazawa et al. conducted a study to evaluate the added value of the maximal inspiration maneuver to standard spirometry in differentiating chronic obstructive pulmonary disease and bronchial asthma. The study included 285 patients (143 with COPD and 142 with asthma), in whom maximal inspiratory and expiratory flows were measured. ROC analysis and logistic regression showed that an FEV_1/FVC ratio <62.4% was the single best predictor of COPD, while combining this parameter with a PIF/MEF_{50} ratio >3.06 significantly improved diagnostic accuracy (probability of COPD diagnosis increased to 82%). Among patients with asthma and a history of smoking, threshold values of FEV_1/FVC <63.4% and PIF/MEF_{50} >3.29 allowed prediction of COPD with a probability of 94.4%. The authors emphasize that incorporating the maximal inspiration maneuver into routine pulmonary function tests can be a simple and effective method for differentiating asthma and COPD in ambulatory settings, particularly in older smoking individuals (Okazawa et al., 2020) [37].

Peak Expiratory Flow (PEF)

Peak expiratory flow (PEF) is the highest velocity of airflow achieved during a maximal exhalation (GINA, 2025) [13]. The value of this parameter depends on lung capacity, respiratory muscle strength, and the caliber of the bronchi. Since an individual's lung capacity changes only slightly over time, the degree of airway narrowing plays the primary role in daily PEF measurements. Bronchial narrowing or bronchoconstriction represents a key mechanism leading to symptoms of asthma and COPD (Gajewski, 2024; GINA, 2025) [6]. Patients are not always able to adequately assess the severity of their symptoms, and mild obstruction may remain asymptomatic, particularly at rest. Therefore, regular PEF measurement serves as an objective tool for daily monitoring of lung function. Nevertheless, it should be noted that PEF is less precise than spirometry and cannot replace it (NICE Guideline, 2024) [38].

In the context of potential screening applications of PEF, Mahboub et al. (2014) conducted a cross-sectional study in a population aged 40–80 years in Dubai, United Arab Emirates, evaluating the utility of PEF as a tool for preliminary detection of COPD. Among 525 participants who underwent both PEF and spirometry, obstruction consistent with COPD was identified in 12.9% of individuals. PEF measurements independently allowed identification of 141 participants potentially affected by obstruction, achieving a specificity of 80% and a sensitivity of 73.5%. The authors emphasize that PEF may serve as a simple, inexpensive, and objective tool supporting the early detection of COPD, particularly in settings with limited access to spirometry, enabling faster referral of patients for further testing (Mahboub B et al., 2014) [39].

With the development of simple screening tools, the combination of clinical questionnaires with PEF measurements has gained importance. Martinez FJ et al. (2017) evaluated the effectiveness of the CAPTURE tool, augmented with PEF, in identifying undiagnosed COPD in primary care. Comparing patients with clinically significant obstruction (FEV_1 <60% predicted or ≥1 exacerbation/year) with individuals without COPD or with mild COPD, they demonstrated that the short, five-question CAPTURE questionnaire exhibited very high sensitivity. The addition of PEF significantly improved the specificity of the tool, and the combination of both methods achieved an optimal balance of test parameters (sensitivity approximately 90%, specificity >90%), making CAPTURE+PEF a practical screening tool feasible for implementation in routine primary care practice (Martinez FJ et al., 2017) [40].

Simultaneously, there is growing interest in the use of PEF not only for detecting obstruction but also as an alternative endpoint in clinical trials. Halpin DMG et al. (2019) assessed the utility of peak expiratory flow (PEF) as an alternative primary endpoint in asthma clinical trials, which traditionally rely on FEV_1 measurements. They demonstrated that changes in FEV_1 and PEF, measured under supervised clinical conditions, were strongly correlated. Importantly, the correlation between measurements performed independently at home and supervised clinical measurements was markedly stronger for PEF than for FEV_1. The authors suggest that home PEF measurements may serve as a reliable endpoint in asthma clinical trials, while simultaneously simplifying study conduct and increasing accessibility for patients (Halpin DMG et al., 2019) [41].

Given its simplicity and affordability, PEF, particularly when combined with symptom questionnaires, offers a pragmatic first-line screening tool in primary care to identify individuals requiring formal spirometry for definitive differential diagnosis.

Questionnaire

Asthma and COPD belong to obstructive lung diseases, with obstruction resulting from distinct pathophysiological mechanisms, as described in detail in the earlier section of this review. Although the clinical presentation of both conditions may be similar, there are significant differences between them that can be leveraged in the diagnostic process. One practical tool supporting the identification and differentiation of obstructive diseases is clinical questionnaires, based on patient-reported symptoms and medical history. The following studies illustrate how various questionnaire-based tools can assist in the diagnosis of asthma and COPD.

The use of clinical questionnaires for identifying and differentiating patients with COPD and asthma to guide further diagnostics has proven to be an effective strategy. Lozano-Forero et al. (2025) developed a new instrument – the COPD and Asthma Differentiation Questionnaire (CAD-Q). The researchers conducted cross-sectional

studies with diagnostic test analysis. The CAD-Q questionnaire was compared with other questionnaires (LFQ; CDQ, PUMA), considering sensitivity, specificity, predictive values, likelihood ratios, and ROC curve analysis. The study included 444 patients. Among them, 235 were diagnosed with COPD, and 209 with asthma. A score ≥20 on the CAD-Q questionnaire yielded an ROC curve of 70% (95% CI: 65–75; $p < 0.001$) with a sensitivity of 83.8% (95% CI: 81.1–86.6) and specificity of 47.8% (95% CI: 44.1–51.6). Compared with other questionnaires differentiating COPD and asthma, CAD-Q exhibited the highest sensitivity (83.8%), the highest negative predictive value (88.7%), and the highest ROC curve (70%). One conclusion from these studies is that the CAD-Q questionnaire is a more effective tool for differentiating COPD and asthma, outperforming previous instruments (Lozano-Forero et al., 2025) [42]. The high sensitivity of CAD-Q suggests its utility as a rule-out tool for one condition over the other, while tools with higher specificity might be better for confirming a suspected diagnosis.
Subsequent studies confirm the usefulness of questionnaires but also highlight their limitations compared with objective methods. Schnieders et al. (2021) conducted a systematic review and meta-analysis assessing alternative diagnostic tools for COPD in primary care settings where access to spirometry is limited. Twenty-four studies involving 14,635 participants were analyzed. Microspirometers demonstrated higher diagnostic accuracy (AUC 0.84) than COPD-PS questionnaires (AUC 0.77) and CDQ (AUC 0.72), with the difference being statistically significant only compared with CDQ. The results suggest that microspirometers outperform questionnaires in detecting COPD, although combining both methods could improve diagnostic efficiency (Schnieders et al., 2021) [43].
In the context of diagnostic strategies, combining survey-based tools with simple functional tests is also of significant importance, as illustrated by another study. Another promising approach for differentiating asthma from COPD involves the use of a peak flow meter combined with a questionnaire and a mini-spirometer. The combination of these two tools may help distinguish asthma from chronic obstructive pulmonary disease. Thorat YT et al. (2017) conducted a study including 189 patients with various respiratory complaints. Participants completed a short questionnaire and underwent measurements of peak expiratory flow (PEF), standard spirometry using a Koko spirometer, and mini-spirometry (POChP-6). Asthma was diagnosed in 115 patients, COPD in 33, and other diseases in 41. The most significant items for detecting obstructive lung disease were "dyspnea lasting >6 months" and "cough lasting >6 months." The item "symptom-free period >2 weeks" exhibited the highest sensitivity and specificity in differentiating asthma from COPD. PEF <80% of predicted value was the most effective cut-off for detecting obstruction. The presence of respiratory symptoms combined with PEF <80% of predicted value yielded a sensitivity of 84% and specificity of 93% for diagnosing COPD and asthma. PEF measurements, complemented by a brief symptom history, may serve as a useful tool for the objective identification of asthma and COPD in settings with limited access to full spirometry. Mini-spirometers are effective in identifying obstruction, although the obtained FEV_1 values have limited accuracy (Thorat YT et al., 2017) [44].
Simultaneously, new screening questionnaires are being developed, primarily aimed at identifying undiagnosed COPD. Martinez FJ et al. (2023) conducted a multicenter cross-sectional study to evaluate the effectiveness of the CAPTURE tool (COPD Assessment in Primary Care to Identify Undiagnosed Respiratory Disease and Exacerbation Risk) in detecting undiagnosed COPD in primary care settings in the USA. The study included 4,325 patients aged 45–80 years without a prior COPD diagnosis. CAPTURE questionnaire results, peak expiratory flow (PEF), and spirometry outcomes were assessed. Among participants, 2.5% (n = 110) met the criteria for clinically significant, previously undiagnosed COPD. The CAPTURE tool achieved a sensitivity of 48.2%, specificity of 88.6%, and an AUC of 0.81, indicating moderate diagnostic accuracy. The authors emphasize that while CAPTURE demonstrates high specificity, further optimization is required to increase its sensitivity and effectiveness in identifying patients requiring spirometric evaluation (Martinez et al., 2023) [45].
The latest study demonstrates that the development of questionnaires can be integrated with advanced analytical technologies. In the study by Kocks et al. (2023), the diagnostic performance of the Asthma/COPD Differentiation Classification (AC/DC) tool, based on machine learning algorithms, was evaluated for differentiating asthma, COPD, and asthma-COPD overlap syndrome (ACO) in patients aged ≥35 years. The tool utilizes 12 parameters derived from electronic patient records, including clinical data, disease history, pulmonary function test results, and treatment information. For validation, 119 patient cases from a prospective observational study were used, of which 116 had diagnoses confirmed by an expert panel (53 asthma, 43 COPD, 7 ACO, 13 other). These cases were subsequently evaluated by 180 primary care physicians and 180 pulmonologists from nine countries, and results were compared with expert panel diagnoses. The mean diagnostic accuracy of the AC/DC tool was 73%, exceeding that of primary care physicians (50%) and pulmonologists (61%). The study indicates that the AC/DC tool can significantly support clinicians in accurately differentiating asthma and COPD in clinical practice, which is crucial for appropriate treatment, minimizing the risk of complications, and reducing the frequency of inappropriate therapy (Kocks et al., 2023) [46].

Fractional Exhaled Nitric Oxide (FENO)

FENO is a non-invasive, portable, and convenient method, widely used in the diagnosis and monitoring of asthma treatment (Dey S et al., 2021) [47]. The concentration of nitric oxide in exhaled air, measured at different expiratory flow rates, reflects inflammation in airways of various diameters. Fractional exhaled nitric oxide measured at 50

mL/s ($FENO_{50}$) is one of the most commonly used biomarkers of airway inflammation, primarily reflecting inflammation in the large, central airways, yet it remains relatively insensitive to inflammatory changes in the peripheral airways. In recent years, the biomarker concentration of nitric oxide in the alveoli (CANO) has gained considerable attention as an indicator of small airway inflammation, offering diagnostic advantages over $FENO_{50}$ in assessing lung function (Zeng GS et al., 2021) [48]; (Högman M et al., 2022) [49].

In this context, the findings of Zeng G et al. (2024) are particularly relevant. They assessed the clinical significance of exhaled nitric oxide concentration measured at a flow rate of 200 mL/s (FENO200) and alveolar nitric oxide concentration (CANO) in patients with asthma, COPD, and asthma–COPD overlap (ACO). The study included 178 patients, analyzing demographic, spirometric, and NO parameters. In the asthma group, FENO200 showed a negative correlation with selected ventilatory indices, whereas CANO did not correlate significantly with lung function. In COPD, both FENO200 and CANO were associated with impaired respiratory function. In ACO, the associations differed: FENO200 did not correlate with parameters, whereas CANO showed significant correlations with several spirometric indices. Discriminative analysis indicated that the most effective parameters for differentiating asthma, COPD, and ACO were sex, age, MEF75, and FENO50. The authors concluded that FENO200 and CANO reflect distinct pathological mechanisms in each disease entity, with FENO50 potentially being the more useful parameter for differentiation (Zeng G et al., 2024) [50].

Additional studies extend the application of FENO to patients with COPD, emphasizing that this parameter may be relevant beyond asthma. Högman M et al. (2024), in a literature review, highlighted the role of fractional exhaled nitric oxide (FeNO) measurement in COPD. Although this disease is traditionally associated with a Th1-type inflammatory response, a subset of patients exhibits Th2-type inflammation, similar to asthma, justifying the use of FeNO as a biomarker. Studies indicate that FeNO levels increase during COPD exacerbations regardless of baseline values; however, no established diagnostic threshold exists for this disease. The authors suggest that individualized determination of baseline FeNO during stable disease may allow for personalized monitoring and early detection of exacerbations (Högman et al., 2024) [51].

Clinical studies further indicate that FENO may reflect inflammatory phenotypes in patients with COPD. Gao J et al. (2017), in a study including 163 patients with COPD exacerbations, demonstrated that FeNO levels and the blood eosinophil percentage were higher in patients with sputum eosinophilia. A moderate correlation was observed between sputum eosinophil percentage and FeNO ($\rho = 0.221$) and with blood eosinophils ($\rho = 0.399$), whereas FeNO did not directly correlate with blood eosinophils. Predictive analysis showed that blood eosinophil percentage and FeNO could predict the presence of sputum eosinophilia, albeit with moderate sensitivity and specificity. The results suggest that FeNO, sputum eosinophil percentage, and blood eosinophil counts may serve as non-invasive biomarkers of eosinophilic COPD, although further studies are needed to establish optimal diagnostic thresholds (Gao J et al., 2017) [52].

Tang B et al. (2020) provided additional confirmation of these observations. They analyzed 247 patients with acute exacerbations of COPD (AECOPD), dividing them into an eosinophilic group (≥2%, n = 97) and a non-eosinophilic group (<2%, n = 150). In the eosinophilic group, higher FeNO values ($p = 0.005$), FEV_1 (% predicted, $p = 0.043$; absolute volume in 1 s, $p < 0.001$), and FVC ($p = 0.011$) were observed compared with the non-eosinophilic group. The eosinophil count correlated positively with FeNO ($p = 0.004$) and spirometric parameters (FEV_1 % predicted, $p = 0.003$; FEV_1, $p < 0.001$; FVC, $p < 0.001$). A FeNO level of 22.5 ppb best predicted the presence of eosinophilia. The findings indicate that blood eosinophil count is a reliable biomarker of inflammation and respiratory function in patients with AECOPD (Tang B et al., 2020) [53].

While elevated FeNO is strongly indicative of Type 2 inflammation prevalent in asthma, its presence in a subset of COPD patients (eosinophilic COPD) complicates its standalone use for differentiation. However, persistently high FeNO in a younger patient without significant smoking history strongly favors asthma, whereas transient elevations in a smoker might suggest eosinophilic COPD.

Sputum analysis

The differential diagnosis of asthma and chronic obstructive pulmonary disease (COPD) remains a clinical challenge, particularly in the context of overlapping features in asthma–COPD overlap (ACO). Differences in the underlying inflammatory profile and airway remodeling directly influence treatment response, making precise classification of the inflammatory phenotype therapeutically crucial. In this context, the analysis of induced sputum provides significant information regarding airway inflammation.(Huang X et al., 2019)[54]

In the study by Correnti et al. (2024), an integrated metabolomic and lipidomic analysis of induced sputum from patients with asthma and COPD was performed using UHPLC-MS/UHPLC-MS-MS and PLS-DA modeling. A clear separation of metabolic profiles between the two diseases was observed. Twenty-two differentiating molecules were identified, of which 18 were decreased and 4 increased in patients with COPD. The most significant biomarker was putrescine, while higher concentrations of phosphatidylethanolamine (PE 34:1), phosphatidylglycerol (PG 18:1;18:2), and spermine were observed in asthma. These results highlight the key role of polyamines, glycerophospholipid metabolism, and amino acid and energy pathways in distinguishing disease phenotypes. The authors propose a panel of biomarkers in induced sputum as a potential diagnostic tool, warranting further validation in larger cohorts (Correnti et al., 2024) [55].

Similarly, Gao et al. (2017) analyzed the value of differentiating inflammatory phenotypes in induced sputum among patients with asthma, COPD, and ACO. The analysis included 374 patients who underwent pulmonary function tests, bronchial reactivity testing, and sputum induction on a single day. Significant differences in sputum cellular composition were observed between groups: patients with COPD had a lower proportion of eosinophils than those with asthma and ACO, whereas the proportion of neutrophils and macrophages differed across all groups. No differences in eosinophil levels were noted between asthma and ACO. The findings suggest that sputum cytology may serve as a useful biomarker of airway inflammation in patients with asthma, COPD, and ACO (Gao et al., 2017) [56].

Vanetti M et al. (2025) describe a COPD subtype characterized by eosinophilic inflammation, present in 20–40% of patients, which influences disease course, exacerbation frequency, and treatment response. Blood and sputum eosinophils may serve as biomarkers, and the eosinophilic phenotype represents a "treatable trait," showing a favorable response to biologic therapy (Vanetti M et al., 2025) [57].

In the SPIROMICS study, Hastie AT et al. (2017) demonstrated that a high proportion of eosinophils in sputum, rather than peripheral blood, is a better indicator of a more severe COPD phenotype, including more frequent exacerbations, greater emphysema, and airflow limitation (lower FEV_1). Although elevated blood eosinophil counts correlated weakly with sputum eosinophils, they were not a reliable biomarker of disease severity or exacerbation risk. These findings suggest that sputum eosinophilia should be considered in clinical trials investigating therapies targeting eosinophilic inflammation in COPD (Hastie AT et al., 2017) [58].

Babu A et al. (2023) assessed the role of neutrophil gelatinase-associated lipocalin (NGAL) in sputum as a potential biomarker for ACO. The study included 180 participants divided into four groups of 45: asthma, COPD, ACO, and healthy non-smokers. Sputum differential cell counts and NGAL concentrations were analyzed. Patients with ACO had the highest sputum NGAL levels, significantly higher than those with asthma, COPD, or healthy controls. ROC curve analysis demonstrated that NGAL had the highest diagnostic value in identifying ACO patients compared with other groups, with an optimal cutoff of 2473 pg/mL, yielding 80% sensitivity and 50% specificity. Elevated NGAL levels correlated with the severity of airway inflammation and may reflect both neutrophilic and eosinophilic components in ACO. These results suggest that measuring NGAL in sputum could serve as a useful tool for differentiating ACO from asthma and COPD, which is clinically relevant given the higher exacerbation frequency, faster progression of obstruction, and increased hospitalization risk in this patient group (Babu A et al., 2023) [59].

Regarding the role of the airway microbiome, Tanabe N et al. (2024) analyzed airway mucus plugging in patients with asthma, COPD, and ACO in the context of the airway microbiome and eosinophilic inflammation severity. The study included 91 patients (ACO: 56, asthma: 10, COPD: 25). In ACO, higher mucus plugging scores correlated with greater relative abundance of Proteobacteria and Haemophilus, independent of smoking status, degree of obstruction, or emphysema severity. In COPD, higher mucus plugging was associated with a greater presence of Actinobacteria. Among patients with high sputum eosinophil counts (n = 22), mucus plugging correlated with Streptococcus, whereas in those with moderate eosinophil counts (n = 26), it correlated with Haemophilus. These findings suggest that in ACO, the microbiome—particularly Proteobacteria and Haemophilus—may play a key role in mucus plugging, differing from mechanisms observed in asthma and COPD (Tanabe N et al., 2024) [60].

Despite its diagnostic power, the invasiveness and logistical challenges of induced sputum collection and analysis limit its widespread use in routine primary care, often reserving it for specialist centers.

Blood Eosinophil Count

Eosinophils are multifunctional leukocytes involved in the initiation and maintenance of inflammatory responses as well as in the modulation of adaptive immunity (Hogan SP et al., 2008) [61]. In recent years, it has been demonstrated that, in addition to their pro-inflammatory functions, eosinophils also play significant physiological roles—they participate in intestinal immune responses (production of IgA and mucus) (Sugawara et al., 2016) [62], in the regulation of adipose tissue metabolism, and in insulin sensitivity. Eosinophils are important for maintaining metabolic homeostasis and proper organ function (Marichal et al., 2017) [63]. Their highest accumulation is observed in the gastrointestinal tract, whereas the presence of eosinophils in the lungs usually reflects a pathological inflammatory response. These cells are relevant in many respiratory diseases, such as asthma, eosinophilic pneumonia, or chronic rhinosinusitis with nasal polyps, although their role in the pathogenesis of chronic obstructive pulmonary disease (COPD) remains unclear (Celli BR et al., 2019) [64].

In asthma, elevated blood eosinophil counts are associated with more severe disease and constitute an important marker for differentiating endotypes. Biologic therapy targeting cytokines such as IL-5, IL-4, or IL-13 has been shown to reduce exacerbation frequency, improve lung function, and enhance symptom control (FitzGerald et al., 2016) [65] (GINA, 2025) [13]. In COPD, the relationship between eosinophil counts and therapeutic efficacy is more complex—counts above 300 cells/μL predict a better response to inhaled corticosteroids, whereas values below 100 cells/μL are associated with limited efficacy of this therapy (Lipson et al., 2020) [66] (GOLD, 2025) [12]. While high blood eosinophil counts (>300 cells/μL) are more commonly associated with asthma, their presence in COPD patients necessitates careful clinical correlation, as they can indicate an eosinophilic COPD

phenotype that may respond to ICS, rather than unequivocally pointing to asthma.

Cabrera López et al. (2023) investigated differences in eosinophil subtypes in patients with asthma and COPD using flow cytometry and confocal microscopy. The study included patients with asthma, COPD, smokers without COPD, and healthy volunteers, with asthma and COPD patients matched for age, sex, and FEV_1% predicted. Patients with asthma had a higher proportion of inflammatory eosinophils (iEos, 25 ± 15%) compared to COPD patients (0.5 ± 1%) and control groups. In asthma, iEos exhibited higher IL-5 receptor expression than resident eosinophils, independent of total eosinophil count. In COPD, no relationship was found between iEos counts and inhaled corticosteroid use, disease severity, or exacerbation frequency. These results suggest significant differences in circulating eosinophil subtypes between asthma and COPD, which may have clinical implications for interpreting eosinophil roles and guiding therapy in these patients (Cabrera López et al., 2023) [67].

Yang et al. analyzed eosinophil activation as a potential biomarker for acute exacerbations of COPD (AECOPD), including cases complicated by pulmonary embolism. Levels of four eosinophil-derived proteins (ECP, EDN, EPX, MBP) were measured in patients with AECOPD, AECOPD with concomitant pulmonary embolism, and a control group. All markers were significantly elevated in patients compared to healthy individuals, while no differences were observed between groups with or without pulmonary embolism. The most promising biomarker was eosinophil cationic protein (ECP), which best distinguished patients from healthy individuals. No correlation was observed between the markers and age, sex, or disease severity. These findings indicate that eosinophil activation proteins, particularly ECP, may have diagnostic relevance in identifying AECOPD (Yang et al., 2017) [68].

Makiya et al. (2014) developed a multiplex immunoassay enabling simultaneous measurement of four key eosinophil granule proteins: MBP, ECP, EDN, and EPO. The study confirmed high reproducibility and concordance of the multiplex assay with conventional ELISA tests, while substantially reducing the required sample volume (up to 500-fold less serum). Significant correlations were observed between MBP, EDN, and EPO levels and eosinophil counts, as well as their activation marker expression (CD69). Notably, patients with eosinophilic gastrointestinal diseases exhibited elevated levels of all tested proteins despite normal peripheral blood eosinophil counts. The authors suggest that multiplex measurement of granule proteins constitutes a rapid, sensitive, and clinically useful tool for assessing eosinophil activity and degranulation processes in patients with eosinophilic diseases (Makiya et al., 2014) [69].

Computed Tomography; Low-Dose CT

In recent years, computed tomography (CT) has become a key tool for the non-invasive assessment of airway morphology, significantly expanding the capabilities for structural characterization of the airways in various phenotypes of obstructive diseases. Despite the increasing number of studies, available data regarding airway wall parameters in populations of healthy individuals, smokers, and patients with asthma and COPD remain inconsistent. A systematic review by Dudurych et al.(2022), including 169 studies (66 of which were included in a meta-analysis), demonstrated significant heterogeneity in measurement methods, including differences in segmentation, algorithms, and choice of airway generation—most commonly analyzing third-generation bronchi in the upper and lower lobes. The highest values of wall area percentage (WA%) were observed in COPD patients (mean 62.9 ± 7.4%), whereas the highest Pi10 was reported in asthma (4.03 ± 0.27 mm). The normalized airway lumen area (Ai/BSA) was largest in the never-smoking population (12.46 ± 4 mm^2). Although significant differences were observed between groups, the range of values often overlapped, limiting the potential for establishing definitive diagnostic thresholds. An additional limitation was the small number of never-smokers in the analyzed studies, complicating the interpretation of the impact of individual factors on measured parameters. The authors emphasize the need for standardization of CT measurement techniques and broader inclusion of control groups to enhance the utility of airway wall parameters as biomarkers of obstructive diseases (Dudurych et al., 2022) [70].

Complementary data were provided by the recent population-based study by Dudurych et al. (2024), which represents an important reference for interpreting airway parameters. Analysis of over 8,800 healthy individuals (mean age 60.9 ± 10.4 years; 54.6% women), without respiratory disease and with normal spirometry, allowed the establishment of reference values for Pi10, lumen cross-sectional area (LA), wall thickness (WT), and wall area percentage based on automated airway segmentation in low-dose CT. Significant sex-related differences were observed—men exhibited higher values for most parameters, while Pi10, LA, and WT gradually increased with age. Smoking status also emerged as an important factor: never-smokers had the lowest Pi10 (3.62 ± 0.13 mm), whereas higher values were observed in former and current smokers ($P < 0.001$). Demographic factors and lifestyle explained up to 46% of the variability in measurements. These findings highlight that CT interpretation of the airways must account for anthropometric characteristics and smoking status, and that population-based reference values should serve as the basis for clinical comparisons in studies of asthma and COPD (Dudurych et al., 2024) [71].

In the search for more precise diagnostic tools, advanced imaging analysis supported by artificial intelligence is increasingly utilized. For example, Moslemi et al. (2022) evaluated the potential for differentiating COPD and asthma using CT parameters and machine learning techniques. The study included 95 patients (48 with COPD and 47 with asthma), matched for age and FEV_1. Ninety-three CT parameters were analyzed, including LAA950, low attenuation clusters (LAC), airway wall thickness (Pi10), and total airway count (TAC). An SVM model based on

the full dataset achieved 80% accuracy (F1 = 81%). The most important features were LAA950, outer and inner airway perimeters, TAC, RB1 cross-sectional area, and LAC total hole count. In a model limited to airway features only, accuracy decreased to 66% (F1 = 68%). Ultimately, the authors concluded that just seven appropriately selected CT parameters are sufficient for effective differentiation of asthma and COPD, highlighting the potential of advanced imaging and AI algorithms in the diagnosis of obstructive diseases (Moslemi et al., 2022) [72].
The importance of precise airway structural assessment is further supported by studies of the asthma–COPD overlap (ACO) syndrome. Liang et al. investigated airway changes, emphysema extent, and air trapping in 113 patients, comparing ACO with mild-to-moderate COPD and non-severe asthma. Patients with ACO were older, more frequently male, and had greater exposure to tobacco smoke. Functional parameters, including FEV_1, FEV_1/FVC, MMEF, and PEF, were significantly worse in ACO. CT analysis revealed greater wall thickening (WA%) and higher Pi10 compared to COPD, whereas these values did not differ from those observed in asthma. Conversely, emphysema extent and air trapping were significantly higher in ACO than in asthma. The authors concluded that ACO is characterized by pronounced structural changes and more severe airway obstruction, representing an intermediate phenotype with greater clinical complexity than mild-to-moderate COPD (Liang J et al., 2024) [73].
An important addition to the understanding of structural indicators of obstructive diseases comes from the study by Kirby et al. (2018), which highlighted total airway count (TAC) as a potential biomarker of early airway destruction. In the CanCOLD cohort, comprising 1,184 participants (ranging from never-smokers to patients with GOLD I and II COPD), TAC was significantly reduced—by approximately 19%—even in early-stage COPD, independent of emphysema severity. Notably, TAC correlated most strongly with lung function parameters and bronchodilator response, and emerged as an independent predictor of disease progression. These results suggest that TAC reduction may reflect airway damage in the so-called “silent zone” and serve as a readily accessible marker of COPD progression, assessable with standard CT software (Kirby et al., 2018) [74].
Despite its diagnostic power, the cost and radiation exposure associated with CT scans mean it is not a first-line diagnostic tool for differential diagnosis but is reserved for cases with diagnostic uncertainty, suspected structural lung disease, or to characterize specific phenotypes like emphysema or bronchiectasis.

Artificial Intelligence

Artificial intelligence (AI) is playing an increasingly important role in medicine, particularly in areas requiring the analysis of large datasets and pattern recognition. Kaplan et al. (2021) indicate that AI has been successfully applied in the classification of skin lesions, the assessment of diabetic retinopathy, and the detection of brain tumors, and in pulmonology, in the analysis of lung cancer imaging, recognition of interstitial lung diseases, and—in more recent applications—in the interpretation of pulmonary function tests and the differentiation of obstructive and restrictive lung diseases. Effective implementation of AI, however, requires large, well-structured datasets and algorithms robust to variable data quality. The authors emphasize that in heterogeneous diseases such as asthma and COPD, it is essential to understand the limitations and clinical context of algorithmic outputs and to ensure patient safety. Currently, AI primarily serves as a decision-support tool, and its full integration requires further validation, physician education, and confidence in its reliability. In the coming years, this technology has the potential to become a routine component of respiratory disease diagnosis and monitoring, offering tangible benefits for both clinicians and patients (Kaplan et al., 2021) [75].
The evolving capabilities of AI algorithms have also been applied to more complex areas, such as differentiating phenotypes of obstructive diseases. In this context, the findings of Joumaa et al. (2022) are particularly relevant, demonstrating the practical use of AI in population-level analyses of large datasets. Studies show the effectiveness of AI algorithms in distinguishing asthma, COPD, and the ACO phenotype within databases lacking clinical diagnoses. The analysis included data from 178,962 patients treated with R03 drugs between 2016 and 2018, with clinical diagnoses serving as the gold standard. Three approaches were applied: polynomial regression, gradient boosting, and recurrent neural network (RNN) models. The highest performance was achieved with boosting and RNN, reaching approximately 68% classification accuracy, with models better identifying asthma than COPD. Using the best-performing model on the large LRx claims database, it was estimated that approximately 3.7 million patients with asthma and 1.2 million with COPD are treated in France. Asthma patients were younger (mean age 49.9 years vs. 72.1 years), whereas COPD more frequently affected men (68% vs. 33%). These results indicate that AI, including deep learning models, may be useful for epidemiological identification of obstructive diseases in administrative databases, although current accuracy remains moderate and requires further optimization (Joumaa et al., 2022) [76].
Further research expands the perspective of AI utilization from disease classification to integrating continuously and remotely acquired data. In this context, the study by Chen et al. (2025) provides significant insights into AI in COPD from the perspective of real-world patient monitoring. Chronic Obstructive Pulmonary Disease (COPD) remains a major global health problem, imposing substantial burdens on healthcare systems. Digital health technologies (DHT) and AI algorithms are increasingly important for early detection, risk assessment, and patient monitoring. In a systematic review of 41 studies published up to December 2024, Chen et al. (2025) analyzed the

application of AI in the context of data obtained from DHT, including clinical data, environmental information, and patient-reported outcomes. Machine learning algorithms (34 studies) and deep learning approaches (16 studies), including SVM, boosting, deep neural networks (DNN), and convolutional neural networks (CNN), were most frequently employed. Three main areas of AI application in COPD were identified: diagnosis and screening, exacerbation prediction, and remote monitoring. The most frequently studied topic was disease progression and exacerbation prediction, with promising model accuracy results. The authors emphasize that further development requires improved interpretability of algorithms, assessment of cost-effectiveness, and clinical validation before implementation into routine practice (Chen et al., 2025) [77].
While promising, the current integration of AI tools for direct differential diagnosis in routine clinical workflows is limited, primarily due to the need for extensive validation, regulatory approval, and the development of user-friendly interfaces for clinicians.

Biomarkers
While fascinating, the clinical utility of specific metabolomic profiles, VEGF, or microRNAs for routine differential diagnosis of asthma versus COPD is still largely in the research phase and not yet integrated into standard clinical practice.
Metabolomics and lipidomics constitute key pillars of modern precision medicine, enabling in-depth phenotypic characterization of chronic diseases such as asthma and COPD. As highlighted by Heiles (2021), the rapid development of mass spectrometry technologies, particularly advanced tandem MS methods, allows for more accurate mapping and structural annotation of metabolites and lipids than previously possible. The application of alternative ionization techniques—based on electrons, photons, or ion/ion reactions—has significantly expanded the potential for identifying bioactive compounds that may serve as diagnostic and prognostic biomarkers. Consequently, metabolomics and lipidomics are transitioning from purely exploratory tools to integral components of translational biological and clinical research, with the potential to fundamentally transform the diagnosis and monitoring of respiratory diseases in the future (Heiles, 2021) [78].
In the context of identifying biomarkers important for differentiating and monitoring asthma and COPD, factors related to vascular remodeling also play a crucial role. Bakakos et al. (2016) described the role of vascular remodeling in asthma and COPD, emphasizing its significance in disease progression. In asthma, angiogenesis predominates, whereas in COPD, vasodilation is more prominent, with vascular leakage occurring in both conditions. VEGF is a key regulator of vascular growth, particularly in asthma, where it promotes endothelial cell proliferation, vascular permeability, and enhancement of Th2 responses. Dysregulation of VEGF signaling has also been associated with emphysema development. Anti-asthmatic drugs exert effects on the vascular component of airway remodeling, while data regarding COPD remain limited (Bakakos et al., 2016) [58]. Therapies targeting VEGF or its receptors may represent promising approaches for controlling chronic inflammation and vascular remodeling in asthma, offering a potential novel strategy for treating inflammatory airway diseases (Meyer N et al., 2013) [79].
The significance of VEGF as a biomarker is also supported by studies examining its serum concentration. Farid Hosseini et al. (2013) demonstrated that serum VEGF levels are significantly elevated in COPD patients compared to healthy controls, as confirmed by ELISA. The mean VEGF concentration in the patient group was 189.9 pg/mL, compared with 16.4 pg/mL in the control group ($p < 0.001$). An association was also observed between increased VEGF levels and disease severity, independent of smoking status. In patients with the emphysematous phenotype, the difference was not statistically significant. The authors suggest that VEGF may serve as a sensitive biomarker of COPD activity and progression, as well as a potential prognostic indicator (Farid Hosseini et al., 2013) [80].
The role of VEGF extends beyond vascular processes, also influencing airway remodeling. Lv et al. (2023) focused on the role of VEGF in airway remodeling, particularly regarding airway smooth muscle cell (ASMC) migration. Remodeling, resulting from increased ASMC mass, correlates with reduced lung function in asthma patients. The authors demonstrated that VEGF significantly enhances ASMC migration without affecting their proliferation. Mechanistically, VEGF activated the RhoA/ROCK pathway, induced F-actin reorganization, and increased phosphorylation of MYPT1 and MLC, thereby promoting cell migration. Inhibition of ROCK kinase substantially attenuated these effects. These findings suggest that modulation of the RhoA/ROCK pathway may represent a potential therapeutic target to limit airway remodeling in asthma (Lv et al., 2023) [81].
Molecular factors modulating ASMC proliferation and function are increasingly recognized in airway remodeling studies. Hu et al. (2023) investigated the pathogenesis and inhibition of airway remodeling in asthma, highlighting the key role of the RAS signaling pathway in regulating ASMC proliferation. Baicalin, a compound with potent anti-inflammatory and antiproliferative properties, shows therapeutic potential in respiratory diseases. In an OVA-induced asthma mouse model, baicalin significantly reduced inflammatory cell infiltration, airway resistance, and remodeling-associated cytokine levels, including IL-13, VEGF, TGF-β1, MMP9, and TIMP1. Analysis of RAS pathway proteins revealed that baicalin treatment inhibited the activation of cascade elements, including PKC-α, A-RAF, MEK2, ERK, MNK1, and ELK1. These results suggest that baicalin limits airway remodeling and ASMC proliferation by inhibiting the RAS pathway, supporting its potential as a novel targeted adjunctive therapy in

asthma patients (Hu et al., 2023) [82].
MicroRNAs (miRNAs) are also emerging as significant molecular regulators of airway remodeling, with an intensively studied role in asthma pathology. Wang H. (2018) demonstrated that microRNA-638 (miR-638), despite its high expression in ASMCs, plays a critical role in bronchial smooth muscle remodeling in asthma. The study showed that under mitogenic stimulation (PDGF-BB, TGF-β1, FBS), miR-638 expression is significantly reduced in proliferating ASMCs. Experimental inhibition or overexpression of miR-638 confirmed its function: overexpression suppressed ASMC proliferation and migration, while inhibition enhanced these processes. Mechanistically, miR-638 downregulated key regulators of the cell cycle and migration, including cyclin D1 and NOR1. The authors emphasize that miR-638 acts as an anti-proliferative and anti-migratory factor, and its modulation may represent a potential therapeutic target for preventing smooth muscle hypertrophy in asthma (Wang H. et al., 2018) [83].

Discussion

Differentiating asthma from chronic obstructive pulmonary disease (COPD) remains a significant clinical challenge due to overlapping clinical presentations, variable airflow obstruction, and shared inflammatory mechanisms. Our literature review demonstrates that no single diagnostic tool provides sufficient sensitivity and specificity for all patients, highlighting the need for a multimodal approach.
Spirometry remains the cornerstone of differential diagnosis, providing objective measurements of airway obstruction. However, studies consistently show that its sensitivity for detecting asthma is limited, particularly in mild or intermittent cases, whereas post-bronchodilator testing reliably identifies persistent obstruction characteristic of COPD (Meneghini et al., 2017; Bouwens et al., 2022).[24][27] Despite clear guideline recommendations, spirometry is underutilized in primary care settings, which may contribute to delayed or inaccurate diagnoses (Härtel et al., 2022)[25]. Emerging technologies, including portable and home-based spirometry, offer opportunities for earlier detection, frequent monitoring, and timely intervention, although unsupervised measurements require cautious interpretation (Gao et al., 2025; Oppenheimer et al., 2023)[30][36].
Complementary diagnostic tools such as peak expiratory flow (PEF) measurements, clinical questionnaires, and mini-spirometry may improve early screening and support decision-making in resource-limited settings. Integrating symptom-based questionnaires with PEF or mini-spirometry achieves high sensitivity and specificity, particularly when distinguishing COPD from asthma in primary care (Thorat et al., 2017; Martinez et al., 2017)[44][40]. Novel machine learning–based classification tools further enhance diagnostic accuracy and provide decision support to clinicians, outperforming conventional approaches in differentiating asthma, COPD, and asthma–COPD overlap (AC/DC tool) (Kocks et al., 2023)[46].
Biomarkers, including fractional exhaled nitric oxide (FeNO), blood and sputum eosinophil counts, and sputum metabolites, provide valuable insights into underlying airway inflammation and may guide individualized therapy. However, the overlap of inflammatory phenotypes, particularly in eosinophilic COPD and asthma–COPD overlap (ACO), limits their standalone diagnostic utility (Gao et al., 2017; Zeng et al., 2024)[52][50]. Similarly, advanced imaging techniques, such as CT and AI-assisted analysis of airway structures, improve phenotypic characterization but are not feasible for routine first-line diagnosis due to cost and radiation exposure (Moslemi et al., 2022; Dudurych et al., 2024)[72][71].
Emerging molecular biomarkers, including VEGF, microRNAs, and metabolomic profiles, hold potential for precision medicine approaches in obstructive lung diseases. These markers may inform future diagnostic algorithms and targeted therapies, though they remain primarily in the research domain and require validation in larger clinical cohorts (Heiles, 2021; Lv et al., 2023; Wang H., 2018)[71][81][83].
Overall, the reviewed evidence underscores the complexity of differentiating asthma and COPD, emphasizing the importance of a comprehensive, individualized diagnostic approach. Combining clinical assessment, functional testing, biomarkers, and imaging—potentially augmented by AI-driven tools—offers the most promising pathway for improving diagnostic accuracy, reducing misdiagnosis, and guiding optimal treatment strategies.

Conclusions

Our review suggests that while no single test definitively differentiates asthma from COPD, a multi-modal approach combining detailed clinical history (as highlighted by questionnaire studies), spirometry with bronchodilator response, and inflammatory biomarkers such as FeNO and blood eosinophil counts provides the most robust diagnostic framework. Advanced imaging and AI hold future promise but require further validation and accessibility improvements.
1. Multimodal approach is essential: No single test reliably distinguishes asthma from COPD. A combination of spirometry, bronchodilator testing, clinical questionnaires, and selective biomarkers enhances diagnostic accuracy.
The most important conclusions from the scientific work:
2. Spirometry remains fundamental: Despite limitations in sensitivity for asthma, post-bronchodilator spirometry is critical for identifying persistent obstruction in COPD and for longitudinal monitoring. Home-based and portable spirometers show promise in increasing accessibility and early detection.
3. Biomarkers provide complementary insights: FeNO, eosinophil counts, and sputum analysis support

differentiation and may guide personalized therapy, particularly in eosinophilic phenotypes and asthma–COPD overlap, but should not be interpreted in isolation.
4. Advanced imaging and AI have potential: CT-based structural assessment and AI-assisted diagnostic algorithms can improve phenotypic differentiation and risk stratification, but are currently adjuncts to clinical assessment rather than primary diagnostic tools.
5. Future directions: Integrating functional, molecular, and computational diagnostics—supported by telemonitoring and AI—represents the future of precision diagnosis in chronic obstructive airway diseases, aiming to reduce misdiagnosis, optimize treatment, and improve patient outcomes.

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