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Early View

Review

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Beyond Spirometry: Understanding COPD Origins to Support a New Diagnostic Approach

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Take home message:

Spirometry detects airflow obstruction decades after COPD processes begin. Harnessing evolving mechanistic insights and novel tools is required to develop a multidimensional diagnostic approach to support early intervention and endotype-driven care.

Abstract

COPD remains a leading cause of morbidity and mortality, with outcomes stagnating relative to other long-term conditions. Current diagnostic pathways rely on spirometry, which detects airflow obstruction only after irreversible small-airway and parenchymal damage has accrued, whereas pathogenic processes begin decades earlier. This review examines how understanding early pathogenic processes could inform alternative approaches to diagnosis and treatment. We highlight the contribution of developmental and environmental exposures, genetic susceptibility, and epigenetic modification to disease initiation. We outline how these convergent mechanisms drive structural and functional abnormalities undetectable by conventional diagnostics but measurable with novel techniques. Advanced imaging—parametric response mapping, hyperpolarised gas MRI, and CT-based vascular metrics—can detect emphysema, small-airways disease, and vascular pruning before spirometric thresholds are reached. Physiological tools including forced oscillation techniques and capnography show promise for early detection in primary care and may be scalable, affordable alternatives to spirometry. Biofluid-based platforms—including exhaled breath analysis, extracellular matrix neo-epitopes, and blood-based inflammatory signatures—offer non-invasive phenotyping and risk stratification, though require validation and pathway integration. We argue for a shift from a spirometry-centric model to a multidimensional diagnostic framework integrating imaging, molecular, physiological, and biomarker data. Recent longitudinal evidence, including diagnostic schemas combining imaging with symptom burden, indicates that such approaches identify high-risk individuals missed by spirometry alone. Proactive COPD detection in its earliest stages is therefore an essential step to altering disease trajectory and improving patient outcomes and it is time our community looks beyond spirometry to deliver this.

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Introduction

Chronic Obstructive Pulmonary Disease (COPD) represents a major global health crisis. Affecting over 300 million individuals worldwide, its prevalence continues to rise, and it accounts for over half of all chronic respiratory diseases, and a majority of associated mortality with 3.3 million deaths reported in 2019(1).

COPD is a heterogenous lung condition characterised by chronic respiratory symptoms resulting from airway and alveolar abnormalities that cause persistent, often progressive airflow obstruction(2). While tobacco smoking remains the principal risk factor, fewer than half of heavy smokers develop the disease, suggesting a multifactorial aetiology involving genetic susceptibility, impaired lung development and maturation across the lifespan, infections, and other environmental exposures. Notably, pathological changes affecting the airways, parenchyma, and pulmonary vasculature can be identified well before the development of irreversible airflow limitation(3, 4).

The inadequacy of current diagnostic, categorisation and management strategies was highlighted by the recent *Lancet* COPD commission (3). Diagnosis currently focuses on detecting established disease and current therapeutic approaches largely target symptom relief, and amelioration of airflow obstruction, rather than addressing the diverse, complex disease mechanisms driving progression. There is an urgent need to broaden our understanding of COPD risk factors, endotypes and early disease mechanisms(3). The adoption of preventative and earlier intervention strategies which are standard practice in other long term conditions such as cardiovascular disease(5), rheumatoid arthritis(6) and chronic kidney disease(7) need to be developed and adopted in COPD. In this review we examine the current knowledge in these areas and highlight opportunities for novel detection strategies and consider how incorporating such approaches into clinical pathways will be key to implementation of a novel COPD management framework centred on disease risk, trajectory and prevention rather than on established disease and symptom palliation.

Limitations of current diagnostic strategies for COPD

At present, COPD is diagnosed using a post-bronchodilator FEV_1/FVC ratio <0.7 in individuals with typical risk factors or symptoms. However, this spirometric measure alone does not reliably reflect symptom burden, disease severity, or quality of life(8). Moreover, many individuals show pathological changes consistent with preclinical COPD, including small airways disease (SAD) and emphysema, yet do not meet the spirometric threshold for diagnosis, a phenomenon which is increasingly apparent with the advent of widespread use of low dose CT imaging for lung health check cancer screening (9). Consequently, alternative approaches to diagnosis are now being developed(10).

One relevant clinical signal is Preserved Ratio Impaired Spirometry (PRISm), defined as an FEV_1/FVC ≥0.7 but FEV_1 <80% predicted(11). A recent study demonstrated that individuals with PRISm experienced a slower FEV_1 decline than those with spirometry-defined COPD yet share similar exacerbation rates.(12). Findings from the three-year NOVELTY study further emphasised these diagnostic challenges but also highlights that in clinical practice treatment decisions are being made pragmatically and inhaled therapy is not infrequently started due to symptoms in the absence of airflow obstruction: about one-quarter of patients receiving treatment for COPD in routine practice did not meet GOLD diagnostic criteria, with 13% classed as “pre-COPD” (normal spirometry but a clinical diagnosis) and 14% with PRISm (13). Notably, even the “pre-COPD” group showed significant subsequent lung function decline. Similarly, many individuals presenting with relevant symptoms and radiological evidence of airway and parenchymal pathology on high-resolution computed tomography (HR-CT) lack spirometric confirmation of airflow limitation(14).

Implementation of spirometry itself poses practical challenges. There is a widespread shortage of trained healthcare professionals able to perform high-quality spirometry, particularly in primary care (15). When it is performed, due to its effort-dependent nature, suboptimal performance may result in technically invalid efforts, leading to misinterpretation and diagnostic error(16). Furthermore, prolonged waiting times and limited capacity, especially in low- and middle-income countries,

compound these challenges and contribute to diagnostic delay(17, 18). Consequently in many healthcare settings the majority of people with COPD are not diagnosed formally and so have little or no access to treatment(17, 19).

Even when spirometry is performed in a timely and technically adequate manner, it identifies disease only once pathophysiological processes are well established. It also fails to reflect the clinical and biological heterogeneity of COPD or likely disease trajectory, and it excludes many symptomatic individuals from diagnosis and treatment. It is therefore unsurprising that current therapeutic approaches are largely supportive—focused on symptom relief—rather than disease-modifying. These strategies are often initiated after irreversible structural changes such as airway remodelling, emphysema, or pulmonary vascular pathology have already occurred(3). Earlier disease processes, if adequately characterised and identified, are likely to offer greater opportunities for modification through both lifestyle interventions, use of inhaled treatments and where appropriate targeted disease modifying intervention.

The recent work from the COPDGene and CanCOLD studies has further highlighted these limitations (10). The new, proposed multidimensional diagnostic schema combines spirometry, CT-defined emphysema or bronchial wall thickening, and symptom burden. Table 1 compares this framework with that of the Lancet commission and contrasts this newly informed approach to current GOLD guidelines. In the large multicentre cohort, Bhatt et al., demonstrated that 15% percent of symptomatic individuals with imaging abnormalities but no airflow obstruction could be newly classified as having COPD as these individuals experienced significantly higher mortality, exacerbation rates, and more rapid lung function decline. Conversely, individuals with isolated airflow obstruction but no structural or symptomatic evidence had favourable outcomes.

Small airways disease and emphysema development precedes airflow obstruction

Understanding where and how the earliest origins of COPD pathology develop is absolutely key to defining new approaches to earlier disease diagnosis and characterisation. Although COPD research has centred on large airways, it is now well recognised that disease often begins in small airways (<2 mm in diameter)(20). Exposure to cigarette smoke drives remodelling of the small airway epithelium—most notably, reduced ciliated cells, increased goblet cells, and mucus plugging—leading to luminal narrowing and elevated small airway resistance (21, 22).Small airways disease (SAD) is largely missed using conventional spirometry as FEV_1 primarily reflects large airway function(23, 24). As such, reliance on spirometry alone limits the ability to identify early key pathological changes in certain COPD endotypes.

In parallel, emphysema, defined by abnormal enlargement of airspaces distal to the terminal bronchiole and destruction of alveolar walls, can develop in individuals with preserved lung function (25). Various studies have highlighted that individuals who later developed airflow obstruction already had more severe computed tomography (CT)-quantified emphysema at baseline, despite normal spirometry (26).

Similarly, analyses in the COPDGene study showed that participants with baseline SAD and/or emphysema experienced faster FEV_1 decline, and that SAD often evolved into emphysema on follow-up imaging (27). These findings underscore that both SAD and emphysema may be present in individuals with normal spirometry who are at high risk of developing COPD. As such, they highlight a critical gap in current diagnostic pathways provided by spirometry alone. While spirometry remains essential for diagnosing established airflow obstruction, it lacks sensitivity for detecting early or subclinical disease.

Improving early COPD diagnosis may require a fundamental re-evaluation of diagnostic thresholds Candidate techniques include the forced oscillation technique (FOT), which enables assessment of airway mechanics during tidal breathing(16), and advanced imaging modalities such HR-CT, which can reveal structural changes in the airways and parenchyma prior to spirometric decline(28) are explored in detail later in this review.

The need for a precision medicine approach earlier in the disease pathway

Growing evidence indicates that COPD, like asthma is highly heterogenous and comprises diverse clinical phenotypes and mechanistically relevant endotypes with differing pathophysiological drivers and clinical trajectories (29). Such heterogeneity underpins the move towards a precision medicine framework for established COPD which has been vital to the limited success to date in deploying disease modifying strategies. The recent success of dupilumab in reducing exacerbations in established COPD with a type 2 inflammatory signature illustrates the potential value of targeted treatments (30). Similarly, static lung volume measurements by body plethysmography guide selection for lung volume reduction interventions in emphysematous hyperinflation (31). The application of these principles to the understanding of treatable facets of earlier disease now needs to be considered if strategies targeting disease prevention and earlier modification are to succeed.

It is increasingly clear that COPD pathogenesis is multifactorial, with critical contributions from developmental, environmental, and behavioural factors. A wide array of early life exposures—including impaired lung growth, premature birth, and childhood respiratory illness—may set the stage for later disease(32) (Figure 1). Epigenetic changes resulting from exposures such as in utero tobacco smoke highlight the role of gene–environment interactions (33), Environmental hazards, including biomass fuel exposure and physical inactivity, further compound individual susceptibility. Mechanistic work in inflammaging, mitochondrial dysfunction, and oxidative stress offers fertile ground for innovative therapies that disrupt disease progression (34-36).

In the following sections, we consider the evolving understanding of COPD pathophysiology, with a focus on how characterisation of early disease processes could inform the development of novel diagnostic strategies and targeted therapeutic interventions which could impact not only on COPD progression but also impact of the natural history of associated morbidities.

The importance of context: understanding lung development in early life

The nine months of gestation and the first two years of life represent critical periods for lung development, during which structural and functional changes can have lifelong consequences(37). Lung development begins at 3–4 weeks of gestation and progresses through five key stages. Disruptions during this time—such as poor nutrition, maternal asthma, smoking, or early-life infections—can impair airway architecture and lead to long-term remodelling(38, 39). Maternal smoking has been linked to epigenetic alterations, such as DNA methylation, which may predispose to adult respiratory disease(40). Environmental exposures during early life, including air pollution, passive smoking, viral infections, and atopy, further influence lung growth and function(39, 41, 42).

The airway microbiome also plays a role in modulating responses to these exposures, with early microbial dysbiosis associated with increased risk of asthma and chronic lung disease(43, 44). Although the relationship between early respiratory infections and adult COPD remains under investigation, immune abnormalities at birth have been observed in infants who later develop wheezing illnesses. Collectively, childhood respiratory infections and asthma are increasingly recognised as contributors to later COPD development(45, 46). Identifying and understanding these early-life risk factors offers opportunities for targeting earlier diagnosis and preventive intervention,

Here the concept of risk scoring offers a potential route to identify individuals at risk of developing COPD and to offering pre-emptive treatment to reduce the impact of risk factors and to prevent lung

damage from developing. This concept may seem alien in the current reactive COPD treatment landscape but is of course the mainstay of intervention strategies in cardiovascular disease prevention. Here the quantifiable impact of known risk factors needs to be known and strategies to reduce their effects tested. Understanding the concept of lung health trajectories will be key to framing individual risk profiles, the seminal work by Lange et al identified that up to half of COPD patients had a low initial FEV1 and a relatively normal rate of decline(32) . Assessment of lung health like height, weight or blood pressure may need to become an everyday occurrence if we are to address the unmet clinical need driven by COPD. However, considering the global importance of the condition and the impact on health in low- and middle-income countries it is vital that new approaches are both accessible and affordable to the populations most in need.

Novel approaches to detection or preclinical disease and diagnosis of COPD

Alternative lung function measurements

In addition to spirometry, several physiological tests offer a more comprehensive assessment of lung function in COPD and may improve early detection. Techniques such as gas transfer measurements, whole-body plethysmography, and multiple breath washout (MBW)—outlined in Table 2—are commonly employed in secondary care settings to evaluate static lung volumes, gas exchange abnormalities, and ventilation inhomogeneity. While these methods are non-volitional and provide detailed physiological insights, they require specialised equipment and trained personnel, limiting their accessibility in routine clinical practice(47, 48).

There is a growing need for physiological tests that are both feasible and reliable in community settings. Such tests could facilitate earlier identification of airflow limitation or small airways disease before spirometric thresholds are met. One such method is the forced oscillation technique (FOT)—

also known as impulse oscillometry (IOS)—which assesses lung mechanics during quiet tidal breathing. FOT has been shown to detect airway abnormalities in smokers without spirometric COPD and correlates with measures of gas trapping and hyperinflation obtained via plethysmography(49, 50). Despite its potential as a simple and non-invasive diagnostic tool, clinical adoption remains limited, partly due to a lack of standardised protocols and established reference values. Capnography, or end-tidal carbon dioxide ($EtCO_2$) monitoring, is widely used in critical care and anaesthesia but its diagnostic relevance in respiratory medicine is only just emerging. Rapid capnometry devices, when combined with machine learning algorithms, have demonstrated the ability to distinguish COPD from other common differential diagnoses and to stratify disease(16, 51). These findings suggest a potential role for capnography in early COPD detection, particularly in symptomatic individuals with normal spirometry. Further research is ongoing to explore its utility in broader clinical and community-based settings. Together, these physiological tools may expand the diagnostic landscape of COPD beyond spirometry, offering earlier and more nuanced detection in at-risk populations.

Imaging modalities provides greater opportunities for personalised diagnoses

CT imaging of the lungs, enhanced by automated quantitative and functional analysis, now enables highly detailed evaluation of early structural and functional changes in COPD. Quantitative CT has long been used to assess emphysema burden and airway wall thickening, providing objective markers of disease severity and valuable prognostic information(52-55).

Novel metrics to investigate the air trapping and functional small airways disease (fSAD) that occur in early disease have recently been investigated. Parametric response mapping (PRM) is a method which pairs voxels from inspiratory and expiratory CT scans which are spatially matched, and applies density thresholds to each allowing regions of air trapping and fSAD to be differentiated from emphysematous regions(56). In early disease, regions of fSAD identified by PRM have been shown to subsequently progress to emphysema, and fSAD is associated with accelerated FEV_1 decline (57). Earlier methods—

such as the expiratory-to-inspiratory ratio of mean lung density (E/I MLD) and the percentage of lung voxels with Hounsfield units <–856 on expiratory scans—also provide estimates of air trapping but at a coarser, region-averaged resolution(58). Other quantifiable CT metrics which hold promise include total airway count (TAC), Inter-branch airway tapering (AT), standardized wall Area Fractions and quantifiable measures of mucus plugging(59, 60). Integrating these novel quantification metrics with new machine learning tools could pave the way for earlier identification of pathological processes and stratification of patients dependent on endotype and risk of progression(61). The clinical value of these imaging approaches has been substantiated by Bhatt et al., who showed that visual CT findings, specifically emphysema and bronchial wall thickening, combined with symptoms identify individuals at high risk for poor outcomes, even in the absence of spirometric obstruction(10). This supports incorporating CT-based phenotyping into diagnostic algorithms, particularly in at-risk populations with preserved spirometry.

Hyperpolarised gas magnetic resonance imaging (MRI) has also emerged as a powerful modality for detecting early parenchymal changes. This technique quantifies the apparent diffusion coefficient (ADC) of hyperpolarised gases, a measure of gas molecule displacement in airspaces. Elevated ADC values correlate with increased alveolar dimensions and show strong concordance with histological measures of alveolar destruction, such as mean linear intercept(62-64). Notably, smokers without COPD exhibit more heterogeneous ADC distributions compared to healthy controls, suggesting that alveolar disruption precedes airflow limitation(65). Molecular imaging approaches are also now being explored and could offer unique insights into both disease presence and processes *in vivo*(66). Collectively, these advanced imaging techniques offer sensitive and non-invasive means of detecting early disease processes in individuals at risk of COPD. Their application in longitudinal studies and screening programmes may enable earlier diagnosis, refined phenotyping, and improved targeting of preventive or disease-modifying therapies.

Detecting and Understanding Pulmonary vascular pathology

Remodelling of the endothelium and pulmonary vasculature is an often under-recognised component of COPD pathogenesis. Hypoxic pulmonary vasoconstriction contributes to remodelling in advanced hypoxaemic COPD and is now also thought to drive early vascular changes(67). Histological abnormalities—such as thickened arterial walls, medial hypertrophy, reduced vessel number, intimal proliferation and disorganised elastin deposition—are observed even in smokers without overt airway disease(68). Imaging studies further support early vascular pathology and CT-detected 'vascular pruning', defined as a reduction in small vessels (<5 mm^2), in both patients with COPD and smokers with preserved lung function(69). 'Vascular pruning' has been shown to correlate with histological changes, lower FEV_1, reduced 6-minute walk test distance, and higher BODE index scores in COPD(70, 71). An increased ratio of vessels with radius <0.75 mm^2 to total vascular volume also associated with accelerated FEV_1 decline in early disease in a recent study, highlighting the complexity of vascular remodelling patterns which need delineation(72)).

Inflammatory infiltrates are observed in the adventitia of pulmonary arteries, and their intensity correlates inversely with FEV_1/FVC ratio(73, 74). Pulmonary hypertension is a recognised complication of established COPD, particularly in severe disease. However, a significant proportion of patients with milder disease also exhibit pulmonary vascular changes, and even mild elevations in pulmonary arterial pressure can impact outcomes(74). Recent advances in quantifying vascular changes may suggest that preclinical signals may be detectable and may be used to inform on the risk of disease development.

Endoscopic Imaging

Novel in vivo imaging techniques, including Probe-based confocal laser endomicroscopy (pCLE), are also exciting new diagnostic modalities. pCLE allows imaging of the pulmonary tract including the alveoli during bronchoscopy and allows detection of elastin microstructure remodelling in the

submucosa of airway walls and parenchyma(75-77) . pCLE has been used to demonstrate larger alveolar diameters in COPD and to qualitatively assess ECM changes to show higher prevalence of loose fibre bronchial deposition pattern(78) . The potential utility of pCLE in detecting and tracking smoking related ECM disruption even before spirometry changes reach clinical significance deserves exploration at least for its potential to unlock new approaches for assessing disease modifying drugs which affect ECM associated pathology or the earliest genesis of emphysema.

Exhaled Breath Analysis

Exhaled breath (EB) analysis is a rapidly emerging set of techniques with potential to enable early diagnosis and phenotyping of chronic respiratory disease (CRD). EB sampling is repeatable, cost-effective, and minimally invasive, unlike sputum or bronchoalveolar lavage (79, 80). Currently, clinical application is mostly limited to fractional exhaled nitric oxide (FeNO) for managing asthma and COPD (81, 82). EB contains volatile organic compounds (VOCs) and non-volatiles (cytokines, peptides, macromolecules, and ions) reflecting oxidative stress, inflammation, and tissue damage, offering potential biomarkers for diagnosis and patient stratification (79-81, 83, 84). Aside from FeNO, three principal EB analysis methods exist: breathomics (exhaled VOCs), exhaled breath condensate (EBC), and exhaled particles (81).

Breathomics (VOCs)

Breathomics employs gas chromatography-mass spectrometry (GC-MS) or multi-array chemical sensors (electronic nose/eNose) to generate disease-specific “breath prints” (214). GC–MS has identified six VOCs distinguishing COPD from healthy controls with high sensitivity and specificity (85). More recent eNose studies differentiate COPD, healthy subjects, and asthma, and can stratify subgroups by endotype(86-92). VOC profiling has also shown promise for identifying COPD exacerbations and viral infections(88, 93, 94).

Exhaled Breath Condensate (EBC)

EBC captures airway lining fluid by condensing EB, allowing analysis of pH, oxidative markers and cytokines. Metabolomic profiling of EBC using nuclear magnetic resonance (NMR) has successfully discriminated asthma from COPD in a pilot study (95).

Exhaled particles

Exhaled particles arise from the epithelial lining fluid (ELF) of small airways and are captured using the particles in exhaled air (PeXA) device. After defined exhalation manoeuvres, non-volatile particle number and size can be measured and assessed via proteomic, lipid, and inflammatory mediator analyses(96, 97). PExA proteome studies have demonstrated clinical potential in asthma, COVID-19, and COPD, with lower particle counts and reduced surfactant protein A, correlating with COPD severity(98-100). Proteomic differences in PExA samples from current versus never-smokers suggest its capacity to detect smoking-related airway damage early(101).

EB analysis offers significant potential for early COPD detection and precision phenotyping. However, wider adoption requires standardised methods, studies including larger cohorts, and improved data integration(80, 84, 102, 103).

Other diagnostic biomarkers of risk and treatment phenotype in early disease

Genetics determinants of COPD: Creating Risk Prediction Models

COPD development is influenced by genetic predisposition, impaired lung development, and early-life exposures that shape long-term lung function trajectories. While tobacco smoking remains the principal risk factor, only a subset of smokers develop the disease, suggesting additional determinants of susceptibility. The best-characterised monogenic risk factor is alpha-1 antitrypsin deficiency, caused by mutations in the SERPINA1 gene, which predisposes to early-onset emphysema(104). Beyond this, genome-wide association studies have identified more than 80 susceptibility loci implicated in lung development, immune regulation, oxidative stress, and nicotine dependence(105, 106). Increasingly,

polygenic risk scores (PRS) are being developed that can stratify lifetime COPD risk, particularly in younger individuals and never-smokers(107).

Epigenetic modifications, such as DNA methylation and histone acetylation, may mediate these gene–environment interactions. Methylation changes in the airways of smokers and individuals with early COPD have been associated with inflammatory signalling and altered immune function, even in the absence of spirometric obstruction(108-111).

While genetic and epigenetic signatures are not yet used clinically, they hold promise as future biomarkers of early disease risk. Identification of high-risk individuals using genetic and early-life information may enable earlier intervention and redefinition of diagnostic thresholds.

Biomarkers of Key Inflammatory and Structural Disease Processes

General Considerations Blood-derived markers hold clinical appeal due to ease of sampling, reproducibility, and straightforward standardisation. However, their correlation with underlying lung pathology remains uncertain, underscoring the need to clarify lung–systemic interactions for better stratification and novel therapy development(112, 113). Various circulating biomarkers already show promise for detecting early disease mechanisms, progression risk, and distinct COPD endotypes, and there is further emerging research on cell-free DNA, lung degradation products, microRNAs, and pathogen-specific autoantibodies(111, 114, 115). A comprehensive review of blood biomarkers has previously been published (116).

ECM remodelling

The extracellular matrix (ECM) is a complex network of proteins and proteoglycans that provides structural and biochemical support to lung tissue and serves as a dynamic scaffold for respiratory function(117)). Major pulmonary ECM components—including collagens, elastic fibres, proteoglycans, fibronectin, and tenascin—interact to maintain airway architecture and function(118). Elastic fibres,

which are highly cross-linked and critical for lung recoil, are particularly vulnerable in COPD(119). Elastin degradation, typically irreversible post-adolescence, is a key feature of disease progression.

Collagen—the most abundant ECM protein—also undergoes pathological remodelling in COPD(120)(128). It provides tensile strength and resists overinflation-induced rupture(121). Human studies show increased immature, disorganised collagen alongside reduced mature collagen in COPD lungs, as visualised via second harmonic generation microscopy(122).

An illustrative example is the detection of extracellular matrix degradation products in blood(123, 124). Collagen type III (C3M), type IV (C4M, C4Ma3) and type VI (C6M) neo-epitopes have been found to be elevated in COPD patients with clinically stable disease (123). These neoepitope biomarkers may eventually aid in identifying subclinical small airways disease prior to irreversible tissue damage, however further work is required to establish their role in longitudinal studies. Early detection of ECM disruption—via combinations of molecular or imaging biomarkers may allow identification of individuals at risk. Therefore targeting ECM remodelling offers both a promising avenue for precision diagnostics and for disease-modifying interventions in early COPD.

Omics and Multiomic Approaches

Omic, multiomic and systems-based analyses are rapidly increasing in their sophistication(125-129). Harnessing these novel methodologies and integrating them with other emerging diagnostic and AI tools holds perhaps the greatest promise for an integrated approach to detecting early disease processes and identifying key therapeutic pathways. The potential of omics approaches from peripheral blood has been demonstrated in large prospective longitudinal studies, including an early example from The Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) study where they reported differential inflammasomes between smokers with preserved lung function and those with COPD(112). Application of these tools and multiomic approaches to bronchoscopic samples is also beginning to help elucidate complex pathological processes in the COPD

lung and potential novel biomarkers and therapeutic targets (126). Applying these approaches to early COPD is now essential to facilitate diagnosis when disease processes are more tractable to treatment.

Microbiota as biomarkers of risk and outcome.

The COPD lung is characterised by microbial dysbiosis, a dynamic disruption of the commensal microbial community, that facilitates chronic infection(130). Contributing factors include immune dysregulation, mucus hypersecretion, and epithelial damage, which collectively create a nutrient-rich environment conducive to bacterial proliferation(131).

Studies of microbial colonisation in early life has identified patterns of dysbiosis in infants associated with future risk of lung disease(132). Although microbial composition changes across GOLD stages 1–4, these shifts are not currently used in COPD diagnosis. No universal "core lung microbiota" has been established due to high interindividual variability; nonetheless, COPD is broadly associated with decreased diversity, notably reduced Bacteroidetes and increased Proteobacteria and Firmicutes(133, 134). Considering the potential role for dysbiosis on driving disease progression – understanding the profile in at risk patient may provide both a route to understand trajectories but also an opportunity for earlier intervention.

Microbial markers may be detectable in spontaneously-produced sputum before spirometric decline, offering a route to identify at-risk individuals(135). Such biomarkers may also help prevent exacerbation-related hospitalisations through early, tailored intervention(136)(. Promising biomarker candidates include NTHi-driven neutrophil extracellular traps(137), biofilm outer-membrane proteins(138)(75), EPS matrix components(139)(76) and bacterial outer-membrane-vesicles which confer host-immunomodulating properties(140, 141)(and antibiotic resistance(142-144).

A deeper understanding of microbial ecology in COPD could thus yield new diagnostic tools, early biomarkers, and microbiota-informed treatments, ultimately reducing exacerbation risk and disease burden through vaccination.

Direct Sampling and Detection of Epithelial changes

Disruption of the airway epithelium is a central COPD feature and represents one of the earliest sites of disease-related injury. Cigarette smoke (CS) directly damages the airway epithelium, initiating pathological changes that may precede clinical disease. Epithelial remodelling in COPD is characterised by basal and mucous cell hyperplasia, epithelial-mesenchymal transition (EMT), ciliary loss and dysfunction, and impaired barrier integrity, all of which contribute to airway obstruction and compromised mucosal defence(145, 146). Notably, many of these epithelial abnormalities are also observed in smokers with preserved lung function, suggesting that CS-induced epithelial remodelling begins prior to spirometric decline.

Transcriptomic and histological analyses of smokers without COPD reveal a shift in epithelial cell populations, including increased goblet cell numbers, reduced ciliated and basal cells, and enhanced mucus production—hallmarks of a pro-mucoid phenotype that may foreshadow disease development(147, 148). Emerging evidence suggests that the airway epithelium retains an epigenetic memory of prior CS exposure, leading to persistent alterations in barrier function, cell differentiation, cytokine release, and EMT-associated pathways(149). It is therefore enticing to hypothesize that direct sampling of the airway epithelium could reveal early signals of impending disease in a way that indirect measurements and biomarkers do not. However, the clinical and technical challenges are significant and direct sampling of the lower airway unlikely to be useful outside a research context. The nasal airway may however offer a window through which diagnostic approaches could be attempted. Boudewijn et al have reported that nasal gene expression differentiates COPD from healthy controls and recapitulates to some degree the patterns seen in the lower airway(150).

Conclusion

Current COPD diagnostic criteria remain reliant on the detection of persistent airflow limitation by a 19th century technology which occurs late in the natural history of the disease. This approach provides no insights into underlying biological processes or therapeutic targets and fails to account for early or preclinical disease when intervention will potentially have the most impact. The consequence is delayed diagnosis and uniform treatment, despite the complex differences in pathological mechanisms underpinning the disease.

This review underscores the urgent need for a paradigm shift towards early detection in lock step with precision medicine in COPD delivered at an earlier stage than currently is imagined. Identifying and characterising key early changes—such as small airways disease, immune and microbial dysregulation, epithelial remodelling, and vascular or ECM disruption—will enable the development of novel diagnostic frameworks and targeted, more impactful interventions.

Future work must prioritise longitudinal validation of trajectories of risk integrating early biomarkers, imaging, biofluid and analytical technologies, and assessment of how these tools can drive interventions to improve outcomes in diverse populations (Table 3). A new multidimensional, endotype-driven approach is essential to enable timely diagnosis, prevent irreversible damage, and deliver more effective, personalised care in COPD.

Authors' contributions:

Tom Wilkinson: Conceptualisation, Supervision, Methodology, Writing-Original Draft Preparation, Writing- Reviewing and Editing**. Tommaso Morelli**: Conceptualisation, Writing- Original Draft Preparation, Writing- Reviewing and Editing. **Karl J Staples**: Supervision, Writing- Reviewing and Editing. **C. Mirella Spalluto**: Writing- Original Draft Preparation. **Jodie Ackland**: Writing- Original Draft Preparation. **Anna Freeman**: Writing- Original Draft Preparation. **Farhan Ullah:** Writing- Original Draft Preparation. **Jake Weeks:** Writing- Original Draft Preparation. **Lee Page:** Writing- Original Draft Preparation. **Alex Kong**: Writing- Original Draft Preparation. **Benjamin Welham**: Writing- Original Draft Preparation, **Arda Tarcan**: Writing- Original Draft Preparation. **Martha Purcell:** Writing- Original Draft Preparation. **Claire Simms**: Project administration*,* Writing- Reviewing and Editing. **Alastair Watson**: Writing- Original Draft Preparation, *Writing- Reviewing and Editing,* Visualization,

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Tables

Table 1. Comparative Features of Emerging COPD Diagnostic Frameworks

Feature	GOLD 2023	Bhatt et al. (JAMA 2025)	Lancet Commission (2022)
Core diagnostic criterion	FEV1/FVC < 0.70	Spirometry + ≥1 symptom/imaging (major), or ≥3 minor criteria	Broader definition; advocates earlier detection
Structural imaging included	No	Yes – visual CT (emphysema, wall thickening)	Yes – supports CT for early pathophysiological changes
Symptom thresholds specified	Not standardised	Yes – mMRC ≥2, CAT ≥10, SGRQ ≥25	Yes – supports QOL and symptoms, no fixed cut-offs
Detects disease without obstruction	No	Yes – minor category enables diagnosis in absence of obstruction	Conceptually yes (e.g. “pre-COPD”); not operationalised
Outcome prediction validated	Partially – based on airflow stages	Yes – linked to mortality, exacerbations, FEV1 decline	Not yet validated; emphasises need for longitudinal data
Integration of biomarkers	No	No	Encouraged for future diagnostic models
Clinical feasibility	High – globally standardised	Moderate – requires CT and structured symptom assessment	Variable – setting- and resource-dependent

Table 2. Techniques for comprehensive assessment of lung function in COPD

Technique	Assessment	Parameters
Gas Transfer	Diffusion capacity Gas exchange Alveolar capillary impairment (emphysema)	Transfer factor for carbon monoxide (TLCO) Transfer coefficient (KCO), alveolar volume (VA)
Whole-body plethysmography	Static lung volumes Gas trapping and hyperinflation Airway resistance	Total lung capacity (TLC), residual volume (RV), inspiratory capacity (IC), functional residual capacity (FRC) Specific airway resistance (sRaw) and conductance (sGaw)
Multiple breath washout (MBW)	Static lung volumes Ventilation inhomogeneity and gas exchange Small airway dysfunction	As above Lung clearance index (LCI)
Oscillometry	Lung mechanics Central vs peripheral airway obstruction Airway calibre Lung compliance (elastance and inertance) Expiratory flow limitation (EFL)	Impedance (Zrs; pressure/flow) Resistance (Rrs) at 5Hz Reactance (Xrs) at 5 Hz, area of reactance (AX) Delta reactance at 5 Hz

Table 3: Research Priorities

Priority
Development, optimisation, and validation of multidimensional approaches to identify COPD and early COPD
Longitudinal studies evaluating approaches that predict risk of future COPD development
Interventional studies testing established and novel treatments in early disease
Interventional studies to mitigate risk of COPD development
Development and validation of novel biomarkers relevant to early-disease endotypes
Development of intermediate endpoints to accelerate prevention and disease-modification trials

Figure Legends

Figure 1: Laying the Foundation: Early Life and Environmental Risk Factors for COPD Development.

This figure illustrates the early life and adulthood risk factors for COPD. **(A)** key risk factors during pregnancy and early childhood, including genetic predispositions, maternal smoking, low birth weight, environmental exposures, and childhood respiratory infections. **(B)** Significant risk factors in early adulthood, namely early initiation of smoking, exposure to second-hand smoke, and occupational hazards. Created in BioRender. Purcell, M. (2025) https://BioRender.com/j8iczla

Figure 2: Bridging the Gap: From Spirometry to Advanced Detection of Early COPD in Smokers.

This figure contrasts traditional COPD detection using spirometry in already diseased lung, (**A**), with novel methods for earlier diagnosis in smokers (**B**). Spirometry, (**A**), relies on significant airflow obstruction and often detects COPD after irreversible damage has already occurred. (**B)** Promising techniques: Breathomics (breath analysis), Ultra-HRCT (structural imaging), Second Harmonic Generation/pCLE (ECM visualization), and Forced Oscillometry (small airway function). These innovations aim to identify COPD at pre-symptomatic stages, enabling earlier interventions and potentially improving outcomes. Moving beyond spirometry is crucial for timely diagnosis and management. Abbreviations: ECM, extracellular matrix; HRCT, high resolution computer tomography; pCLE, Probe-based Confocal Laser Endomicroscopy. Created in BioRender. Purcell, M. (2025) https://BioRender.com/1fxlppz

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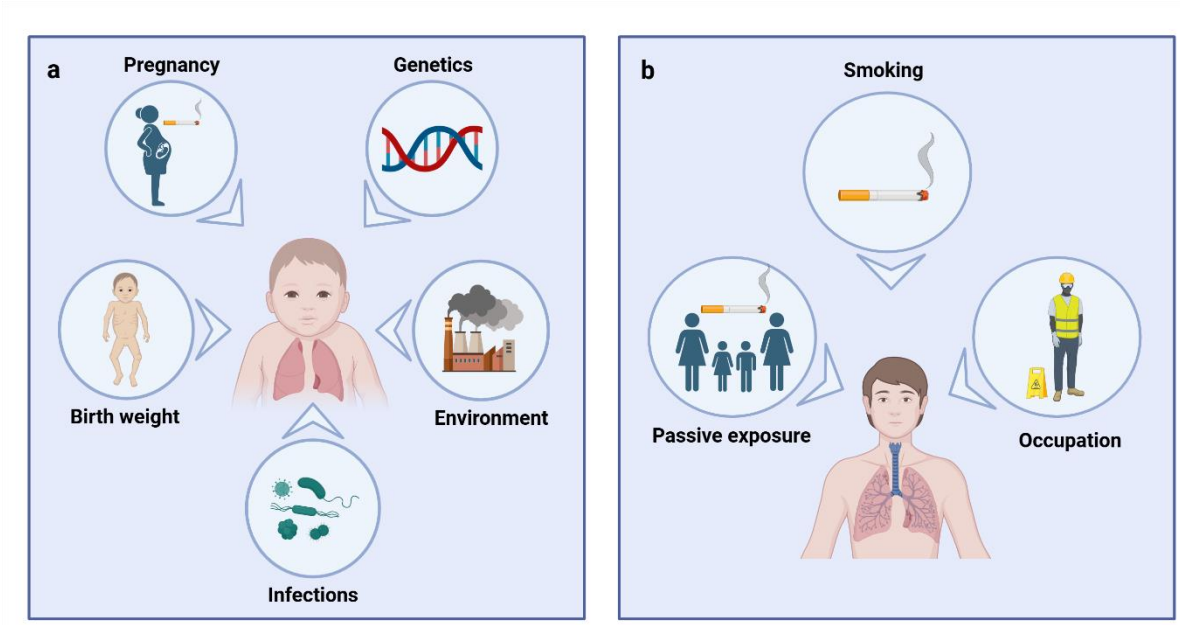

Figure 1

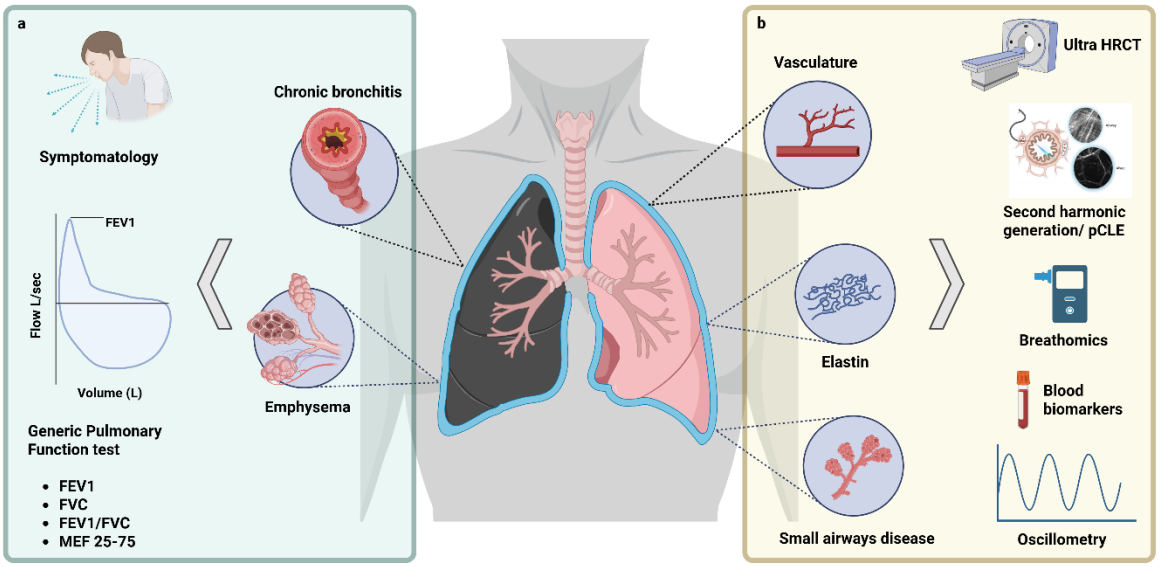

Figure 2