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The lung as an autoimmune organ: From mucosal tolerance breach to AI-enabled interception

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ABSTRACT

Autoimmune diseases have traditionally been conceptualized as systemic disorders that secondarily involve the lung. This roadmap review proposes a complementary framework in which the lung is considered an autoimmune organ: a mucosal site where tolerance may be breached, a vulnerable target of systemic autoimmunity, and a sentinel from which future disease trajectories can be inferred. Across connective tissue diseases, the lung is also a major determinant of prognosis through airway disease, interstitial lung disease, progressive fibrosis, pulmonary vascular involvement and acute alveolar injury. A compelling human model for lung-first autoimmunity is rheumatoid arthritis, in which inhaled exposures, airway inflammation, citrullination, neutrophil extracellular traps, mucosal immunoglobulin A responses and anti-citrullinated protein antibodies may precede clinically apparent synovitis. We integrate these observations into a lung autoimmune continuum linking inhaled exposome, epigenetic remodeling, microbiota-redox imbalance, mitochondrial dysfunction, alarmins, local autoantibody generation, systemic immune spread and target-organ injury. We then outline a forward-looking model in which artificial intelligence supports prevention, risk prediction, treatable-trait classification, therapy-response prediction and closed-loop monitoring. Multimodal models integrating high-resolution computed tomography, pulmonary function tests, autoantibodies, omics, electronic health records, exposome data and patient-generated data may enable earlier interception of autoimmune lung trajectories. Clinical implementation will require prospective utility studies, external validation, calibration, explainability, fairness assessment, data governance and human oversight. Reframing the lung as an autoimmune organ could shift the next decade from reactive recognition of irreversible pulmonary damage to personalized interception before fibrosis, vascular remodeling or acute injury become clinically fixed.

Abbreviations: ACPA, anti-citrullinated protein antibodies; AI, artificial intelligence; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; APS, antiphospholipid syndrome; CTD, connective tissue disease; CTD-ILD, connective tissue disease-associated interstitial lung disease; DLCO, diffusing capacity of the lung for carbon monoxide; EHR, electronic health record; FAIR, findable, accessible, interoperable and reusable; FVC, forced vital capacity; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; IIM, idiopathic inflammatory myopathy; IVIg, intravenous immunoglobulin; MCTD, mixed connective tissue disease; NET, neutrophil extracellular trap; PAH, pulmonary arterial hypertension; PFT, pulmonary function test; PPF, progressive pulmonary fibrosis; RA, rheumatoid arthritis; RF, rheumatoid factor; RP-ILD, rapidly progressive interstitial lung disease; SARD, systemic autoimmune rheumatic disease; SjD, Sjögren disease; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

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1. Introduction: Why the lung should be reframed in autoimmunity

The lung is the largest exposed mucosal surface of the body, a site of constant antigenic sampling, epithelial stress, microbial contact, vascular-immune exchange and inducible lymphoid organization. For the purposes of this roadmap, 'lung' is used broadly to encompass the entire lower respiratory tract mucosal-vascular unit: the conducting airways (trachea to terminal bronchioles), the alveolar-capillary interface, the pulmonary vasculature and lymphatics, and associated lymphoid structures (BALT). We do not include the oral cavity or upper respiratory tract in this definition; however, we acknowledge that periodontal disease and oral mucosal dysbiosis, particularly *P. gingivalis*-driven citrullination, are proposed upstream contributors to the same mucosal-origin hypothesis in RA and represent a distinct, complementary mucosal site outside the scope of the present lung-centred roadmap.

Accordingly, the lung commonly enters in autoimmune nosology through complications such as interstitial lung disease (ILD) in systemic sclerosis (SSc), rheumatoid arthritis (RA) or inflammatory myopathies (IIM); pulmonary arterial hypertension in SSc or mixed connective tissue disease (MCTD); diffuse alveolar hemorrhage in systemic lupus erythematosus (SLE) or anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV); and airway disease in RA or Sjögren disease (SjD). However, it is inappropriate to merely look to the lung as a victim of systemic autoimmunity; rather it represents a potential site of immune education and dysregulation.

This review proposes the concept of the lung as an autoimmune organ, although in not absolute manner since current evidence does not prove that the lung initiates all autoimmune diseases. Rather, the lung may act in three interlinked roles: as an initiating mucosal site in selected diseases, especially RA; as a secondary target and amplifier of systemic autoimmune injury across connective tissue diseases and vasculitides; and as a measurable sentinel organ whose imaging, physiology and molecular signals can be used to predict future trajectories [1,2]. This organ-centered framework is timely because screening and treatment recommendations for systemic autoimmune rheumatic disease-associated ILD have rapidly matured [3–5], while digital medicine and artificial intelligence (AI) are beginning to transform pulmonary imaging, multimodal prediction and longitudinal monitoring [6–10].

The central thesis is that the next decade should not be limited to earlier diagnosis of autoimmune lung involvement. The goal should be interception: identifying individuals and patients who are moving along an autoimmune lung trajectory before irreversible fibrosis, vascular remodeling, airway destruction or acute alveolar injury become fixed. This requires integration of mechanisms, clinical phenotypes, treatable traits and computational prediction. It also requires a cautious distinction between plausible biology and clinically actionable evidence.

A further reason to adopt an organ-centered framework is that pulmonary autoimmunity often becomes visible before it is irreversible, but only if clinicians know where to look. High-Resolution Computed Tomography (HRCT) can show subclinical interstitial abnormalities, small-airway changes or vascular clues; pulmonary function tests (PFTs) can detect disproportionate Diffusing Capacity of the Lung for Carbon Monoxide (DLCO) reduction; serology can identify patients with autoantibody-defined risk (such as anti-MDA5); and exposure history can reveal preventable drivers. The lung is therefore both a biological interface and a clinical observation window. This dual identity makes it unusually suited for a roadmap that links pathogenesis, prevention and digital prediction.

2. Search strategy and reference verification

This roadmap review was developed from a targeted PubMed/MEDLINE search through July 2026 using combinations of the following terms: autoimmune disease, lung, mucosal origin, RA, anti-citrullinated protein antibodies, connective tissue disease, interstitial lung disease, systemic sclerosis, inflammatory myopathy, anti-MDA5, Sjögren disease, systemic lupus erythematosus, vasculitis, exposome, epigenetics, oxidative stress, mitochondrial dysfunction, microbiota, alarmins, artificial intelligence, machine learning, radiomics, prediction, treatment response, prevention and interception. Priority was assigned to PubMed-indexed articles with verifiable DOI, international guidelines, randomized trials, systematic reviews, meta-analyses and mechanistic studies. References in the working bibliography are reported with DOI.

3. The lung autoimmune continuum

The proposed lung autoimmune continuum contains five stages. First, the susceptible lung is shaped by host factors and inhaled exposures. Genetic risk, gender, age, smoking, silica, particulate matter, occupational inhalants, respiratory infections and airway or gut dysbiosis interact at a mucosal interface. Second, a breach of local tolerance occurs when epithelial damage, oxidative stress, mitochondrial dysfunction, alarmins, neutrophil extracellular traps, citrullination, carbamylation, and altered microbial signals activate dendritic cells, macrophages, B cells and T cells. Third, local immune activation may expand into systemic autoimmunity through mucosal IgA and IgG responses, autoantibody maturation and epitope spreading. Fourth, the lung becomes a target organ through airway disease, inflammatory ILD, progressive fibrosis, vascular involvement and acute alveolar injury. Fifth, the same organ can be monitored by HRCT, pulmonary function, autoantibodies, omics, electronic records and home-based data to predict future disease trajectories.

This continuum should be read as a clinical-biological map, not as a linear inevitability. Some individuals may have airway autoimmunity without joint disease; some patients with systemic autoimmune disease may never develop pulmonary disease; and some connective tissue disease-associated interstitial lung disease (CTD-ILD) phenotypes may be dominated by fibrotic or vascular pathways rather than active mucosal autoimmunity. Nevertheless, the framework has practical value because it links prevention and therapy. It allows the same patient to be described by disease label, organ phenotype, molecular trait, risk trajectory, and potential therapeutic window.

RA is used here as the most extensively studied example of a lung-first autoimmune trajectory, given the depth of mechanistic and longitudinal data linking airway autoimmunity to systemic disease. This does not imply that other diseases – including diffuse cutaneous systemic sclerosis or idiopathic pulmonary fibrosis-adjacent immune phenotypes - could not represent equally compelling, if less extensively characterized, starting points for this roadmap. RA provides a particularly compelling and well-studied example of possible lung first autoimmunity. The classic gene-environment model links smoking and HLA-DRB1 shared epitope alleles with seropositive RA and immune responses to citrullinated antigens [11,12]. Subsequent studies identified autoantibodies in sputum such as anti-citrullinated protein antibodies (ACPA), ACPA-related neutrophil extracellular trap signatures, structural airway abnormalities in at-risk individuals, and inducible bronchus-associated lymphoid tissue in rheumatoid lung disease [13–18]. These data do not prove a single obligatory origin, but they support a mucosal model in which airway injury, local post-translational modification and local antibody generation may precede or accompany the systemic phase [1,2,19].

The same mechanistic vocabulary is relevant to other autoimmune lung phenotypes. Neutrophil extracellular traps (NETs), first described as antimicrobial chromatin structures, may expose modified autoantigens and amplify type I interferon (IFN) or inflammatory loops [20,21]. Carbamylated proteins expand the universe of modified antigens beyond citrullination [22]. In SSc, IIM, SjD, and SLE, the initiating events may differ, but epithelial-endothelial stress, altered innate sensing, dysregulated repair and immune-fibrotic crosstalk remain central. Fig. 1 illustrates this continuum from inhaled and host

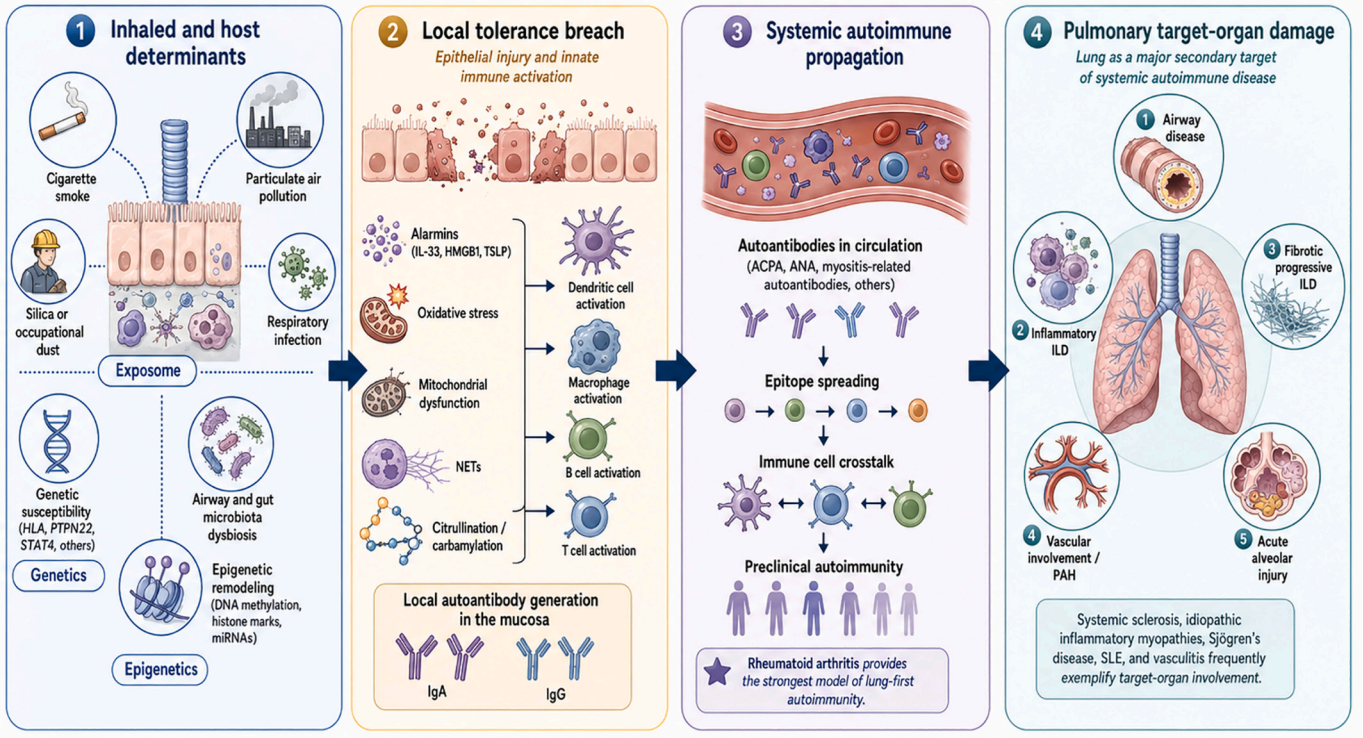


Fig. 1. Mechanistic architecture of the lung autoimmune continuum. Inhaled and host determinants converge on the airway mucosal interface, generating epithelial injury, danger signals, oxidative and mitochondrial stress, neutrophil extracellular traps (NETs), post-translational modification, local autoantibody production and systemic immune propagation. These mechanisms connect possible lung initiation with target-organ damage.

determinants to target-organ damage.

The continuum also accommodates bidirectionality. Once systemic autoimmunity is established, pulmonary inflammation may feed back into systemic disease by sustaining antigen release, B-cell activation, cytokine production, and vascular injury. In a patient with RA and bronchiectasis, for example, chronic airway infection and inflammation may perpetuate systemic immune activation. In SSc, recurrent epithelial injury and aberrant repair may reinforce fibroblast activation. In myositis, antiviral-like IFN programs may connect skin, muscle, and lung. A roadmap for the lung as an autoimmune organ should therefore consider not only where autoimmunity begins, but how pulmonary disease becomes a chronic amplifier of systemic immune dysregulation.

4. Lung as an initiating mucosal site: Rheumatoid arthritis as the paradigm

The lung-first hypothesis in RA should be interpreted as probabilistic and testable, rather than as a demonstrated obligatory causal pathway. Current support derives from converging lines of evidence: smoking and occupational inhalants interact with genetic susceptibility to increase the risk of seropositive RA; airway inflammation may promote citrullination, carbamylation and NET-related autoantigen exposure [3,4,20–22]; ACPA, RF and IgA-enriched autoantibody responses have been detected in sputum or respiratory compartments [13–15]; anti-CCP-positive individuals without clinical arthritis may present with lung disease [16]; and ACPA-positive subjects can show structural lung abnormalities and antibody enrichment before clinically apparent synovitis [17]. Inducible BALT in rheumatoid lung disease provides an anatomic substrate for local antigen presentation, B-cell activation, and class switching [18]. These findings support the concept that, in selected individuals, the lung may participate in early tolerance breach and autoimmune amplification. However, definitive causality will require prospective cohorts integrating exposure history, sputum or BAL immune profiling where appropriate, serial serology, pulmonary imaging, joint imaging and long-term clinical outcomes. Sputum sampling is proposed as the primary, non-invasive, repeatable matrix for serial monitoring in at-risk or preclinical cohorts, whereas BAL, being invasive, should be reserved for clinically indicated diagnostic evaluations (e.g., suspected infection, atypical presentation) rather than for routine longitudinal biobanking. Cytokine and autoantibody signatures derived from both matrices are not directly interchangeable and should be validated separately. Recent expert algorithms for RA-ILD/SSc-ILD/PM-DM-ILD and emerging data on lung ultrasound may help define safer monitoring strategies, but they should be considered implementation tools rather than proof of lung-first causation [23,24].

The future implication is prevention. Recent preclinical RA trials demonstrate that interception is now possible as a clinical research field. Abatacept reduced inflammation and/or delayed RA development in high-risk individuals in APIPPRA and ARIAA, rituximab delayed arthritis in seropositive at-risk subjects in PRAIRI, whereas hydroxychloroquine did not show a sufficiently convincing preventive effect in STOP-RA [25–28]. These mixed results are informative. They show that autoimmunity can be modified before full-blown onset of the disease, but they also expose the danger of treating too broadly. Future prevention trials should not rely only on serum ACPA/RF and articular symptoms. They should test whether lung or mucosal signatures - sputum IgA ACPA, airway inflammation, quantitative HRCT, exposome history or local immune markers - improve enrichment of individuals who are truly on a rheumatoid trajectory.

A practical implication is the possible development of “preclinical autoimmune lung clinics” embedded within early arthritis and high-risk autoimmunity programs. These clinics would not perform indiscriminate CT screening. Instead, they would select individuals with convergent risk: family history, inflammatory arthralgia, respiratory signs and symptoms, high-titer or expanding ACPA/RF, sputum/airway inflammatory markers, reduced DLCO, bronchiectasis, smoking or silica exposure. Such programs would need conservative thresholds, shared decision-making and careful avoidance of overmedicalization.

5. Lung as target organ and amplifier of systemic autoimmunity

In most systemic autoimmune diseases, the lung is encountered clinically as a target organ. This target-organ view remains essential because pulmonary involvement drives treatment intensity, disability, and mortality. ILD occurs across several CTDs, with disease-specific differences in prevalence, imaging pattern and progression risk [29,30]. In RA, ILD is strongly influenced by male sex, older age, seropositivity, smoking, and genetic factors such as the *MUC5B* promoter variant [31].

Recent guidelines have transformed the field (Table 1). The ACR/CHEST guidance supports risk-based screening and monitoring with pulmonary function tests and HRCT in systemic autoimmune rheumatic diseases, while discouraging less informative approaches such as routine chest radiography for screening [3]. The companion treatment guideline provides a framework for immunosuppressive and antifibrotic decisions across SARD-ILD [4]. ERS/EULAR guidelines now offer multidisciplinary recommendations for screening, diagnosis, monitoring and treatment across systemic rheumatic autoimmune diseases, and explicitly identify gaps where evidence remains insufficient [5]. These documents reinforce the need for shared rheumatology-pulmonology pathways.

A roadmap should move beyond disease-by-disease catalogues. The clinically useful unit is increasingly the pulmonary phenotype. Airway-predominant diseases include bronchiolitis, bronchiectasis and small-airways disease, particularly in RA and SjD. Inflammatory ILD includes organizing pneumonia and cellular Nonspecific Interstitial Pneumonia (NSIP)-like patterns, which are often seen in myositis-spectrum disease. Fibrotic progressive ILD includes usual interstitial pneumonia-like RA-ILD, fibrotic SSc-ILD and other progressive pulmonary fibrosis phenotypes addressed by contemporary PPF concepts [32]. Vascular/endothelial involvement includes pulmonary arterial hypertension, disproportionate DLCO reduction and thrombo-inflammatory disease, especially in SSc, MCTD, SLE, and antiphospholipid syndrome. Acute alveolar injury includes rapidly progressive anti-MDA5 dermatomyositis ILD, diffuse alveolar hemorrhage in SLE and capillaritis in ANCA-associated vasculitis [33–44].

SSc illustrates the target organ paradigm with particular clarity. In SSc, ILD is one of the major causes of disease-related mortality and has become the reference model for randomized therapeutic trials [45–48]. ILD can appear early, may be clinically silent at onset, and often progresses most rapidly in the first years of disease. The risk is not captured by symptoms alone. Skin subset, disease duration, autoantibody profile, pulmonary function (FVC, DLCO), baseline HRCT involvement, and disease trajectory each contribute to risk stratification and disease management. The future standard should be not only baseline screening, but early identification of progression risk and the therapeutic window. For some patients, immunosuppression may be sufficient; for others, early combination with antifibrotic therapy may be justified when fibrotic progression dominates [45].

Inflammatory myopathies represent a different problem: heterogeneity and urgency. Anti-synthetase syndrome can show relapsing ILD, arthritis, mechanic's hands and myositis, whereas anti-MDA5 dermatomyositis may cause rapidly progressive ILD with high early mortality. In this setting, the lung is not merely an organ to be monitored; it is the organ that often determines survival. Treatment escalation pathways and predictive models should incorporate ferritin levels, anti-MDA5 titer, anti-Ro52 co-positivity, HRCT extent, oxygenation status, and early response to therapy [33–37].

Sjögren disease highlights the central role of the airway-B-cell interface in pulmonary disease pathogenesis. The dynamic interaction between airway epithelial cells and B cells promotes local autoimmunity, perpetuates local inflammation, and may represent an interesting target for biomarker development and B-cell targeted therapies. Chronic cough, small-airway disease, bronchiectasis, cystic lung disease and lymphoproliferative complications complicate the distinction between inflammatory, infectious, and lymphoid phenotypes [38–40].

SLE and ANCA-associated vasculitis, in contrast, remind us that autoimmune lung disease can be acute and catastrophic. Diffuse alveolar hemorrhage requires rapid differentiation from infection, drug toxicity and pulmonary edema, while pulmonary-renal syndromes require coordinated emergency treatment [41–44].

Therapeutic evidence reflects this phenotypic shift. Cyclophosphamide and mycophenolate established immunosuppression as a foundation in scleroderma lung disease [47,48]. Nintedanib slowed FVC decline in SSc-associated ILD and in progressive fibrosing ILDs, supporting an antifibrotic strategy when progression dominates [49,50]. RECITAL demonstrated that rituximab was not superior to cyclophosphamide for FVC change in severe or progressive CTD-ILD, but both groups improved and toxicity profiles differed [51]. Tocilizumab preserved lung function in early inflammatory SSc with elevated acute-phase reactants [52]. These trials support a strategy based on combination therapies and tailored treatment sequencing rather than a single universal algorithm.

Another mechanistically distinct example of the lung as a predominantly pulmonary autoimmune target is autoimmune pulmonary alveolar proteinosis (aPAP), in which pathogenic IgG autoantibodies against GM-CSF impair alveolar macrophage function and surfactant clearance, resulting in a purely pulmonary autoimmune disease without an obligatory systemic autoimmune syndrome. Unlike RA-ILD or SSc-ILD, aPAP shows that the lung can be the primary and sole target of a well-defined autoantibody-mediated mechanism, reinforcing the organ-centred

Table 1
The lung as initiator, target and sentinel across systemic rheumatic autoimmune diseases.

Disease area	Lung as initiator	Main pulmonary target patterns	Sentinel value	Next-generation action
Rheumatoid arthritis	Most extensively studied evidence forlung/ mucosal contribution in selected patients	Airway disease, bronchiectasis, RA-ILD, UIP-like fibrosis	Preclinical autoimmunity, ILD progression	Add lung/mucosal signatures to at-risk RA cohorts
Systemic sclerosis	Not established as primary initiator	SSc-ILD, PAH, vascular-endothelial disease	Mortality, progression, therapy escalation	Quantitative HRCT and progression-guided combination therapy
Inflammatory myopathies	Possible viral/mucosal amplification in subgroups	NSIP, OP, anti-synthetase ILD, anti-MDA5 RP-ILD	Early mortality in RP-ILD	Risk models at diagnosis; early escalation
Sjögren disease	Mucosal and B-cell biology relevant but lung-first evidence limited	Airway disease, bronchiectasis, cystic lung disease, ILD	B-cell/airway phenotype	Joint airway, microbiome and lymphoproliferation surveillance
SLE	Systemic immune-complex disease rather than lung-first	Pleuritis, DAH, rare ILD, infection-mimics	Acute injury and flare risk	Rapid differentiation of DAH, infection and drug toxicity
ANCA-associated vasculitis	Airway/ENT mucosal triggers plausible in some phenotypes	DAH, nodules, capillaritis, airway stenosis	Relapse and life-threatening pulmonary injury	Integrated pulmonary-renal risk and rapid treatment pathways
APS/MCTD	No primary lung-first model	PAH, thromboembolic disease, CTD-ILD	Vascular trajectory	Combine vascular, thrombotic and autoimmune monitoring

Abbreviations: ANCA, Anti-neutro APS, Antiphospholipid syndrome; DAH; HRCT, High-resolution computed tomography; ILD, interstitial lung disease; MCTD, Mixed Connective Tissue Disease; NSIP, Nonspecific Interstitial Pneumonia; OP, Organizing Pneumonia; PAH,; RA, Rheumatoid arthritis; RP-ILD, Rapid Progressing Interstitial Lung Disease; SLE, Systemic Lupus Erythematosus; UIP, Usual Interstitial Pneumonia.

framework proposed here [53].

6. Mechanistic bridge: Exposome, epigenetics, microbiota-redox imbalance and mitochondria

The lung sits at the intersection of exposome and immune tolerance. Inhaled smoke, silica, particulate pollution, occupational dusts and infections can injure epithelium, alter macrophage and neutrophil programs, and expose modified self. Beyond these established triggers, a broader environmental framework recognises air pollution, dietary and lifestyle factors, endocrine disruptors, and climate change-related exposures as contributors to the rising incidence of autoimmune disease. Within this framework, amphibole asbestos exposure – distinct from chrysotile - has been specifically linked to systemic autoimmune disease, including autoantibody production and ILD, via both occupational and environmental (non-occupational) pathways, providing a well-characterized example of how a defined inhaled exposure can drive a durable mucosal risk state [54,55]. Epigenetic remodeling provides a mechanistic layer through which transient exposures may create persistent immune memory in airway epithelial cells (airway epithelial innate immunity memory or epigenetic memory), dendritic cells, macrophages, fibroblasts or lymphocytes. This concept aligns with previous work emphasizing the exposome-epigenetics axis in autoimmune diseases [56]. In the pulmonary context, the key unresolved question is not simply whether exposures increase autoimmune risk, but which exposure combinations generate a durable mucosal risk state.

Microbiota-redox interactions represent a second bridge. The airway is not sterile, and the gut-lung axis can shape systemic and pulmonary immune responses balance. Dysbiosis may modify mucosal metabolites, epithelial barrier responses and innate immune thresholds. Oxidative stress, mitochondrial dysfunction, and respiratory chain defects can amplify danger signaling, alter antigen processing, and promote inflammatory or fibrotic repair programs. These mechanisms are relevant to SLE, inflammatory myopathies, and autoimmune lung disease, and build on prior work linking microbiota, oxidative stress and intravenous immunoglobulin (IVIg) in SLE, and oxidative stress and mitochondrial dysfunction in IIM [57,58].

Alarmins and damage-associated molecular patterns are a third bridge. Molecules such as HMGB1, IL-33 and TSLP, extracellular DNA and RNA, ATP and S100 proteins may convert epithelial stress into immune activation. In the lung, this is particularly important because sterile injury and microbial danger often coexist. Repeated epithelial damage may initiate a loop in which innate sensing, NETs, modified proteins, and local lymphoid organization create permissive conditions for autoantibody development or for chronic inflammatory-fibrotic remodeling [14–16].

Mechanotransduction represents an additional, underexplored bridge. The mechanosensitive ion channel Piezo1, expressed in airway and alveolar epithelium, fibroblasts, and innate lymphoid cells, converts mechanical stretch (physiological breathing, ventilator-induced strain, or fibrotic stiffening of the extracellular matrix) into calcium influx and downstream fibrogenic and inflammatory signaling. Piezo1 activation has been shown to drive epithelial-mesenchymal transition and fibrosis after mechanical ventilation and irradiation, and to regulate group 2 innate lymphoid cell-driven type 2 inflammation in preclinical models. This mechanosensitive pathway may be particularly relevant to autoimmune ILD, in which chronic inflammation stiffens the extracellular matrix, potentially creating a feed-forward loop between fibrotic remodeling and Piezo1-dependent immune activation. Whether Piezo modulation represents a viable therapeutic target in autoimmune lung disease remains an hypothetical, open, testable question for future mechanistic work [59].

These pathways also suggest why prevention may need to be environmental, metabolic, and immunologic at the same time. Smoking cessation, occupational exposure mitigation, vaccination, infection control, reflux management, and treatment of bronchiectasis are not peripheral measures; they may modify the inflammatory ecology in which autoimmunity is sustained. In the future, exposome assessment should move from being a checkbox in an individual's history to becoming a structured variable in risk models. A patient with anti-citrullinated protein antibody (ACPA) positivity and continued silica exposure is not biologically equivalent to an ACPA-positive patient without airway injury.

Single-cell and spatial biology are now redefining these pathways. Fibrotic lung disease is not a uniform accumulation of scar but a multicellular process involving epithelial transitional states, macrophage subsets, fibroblast and myofibroblast activation, endothelial dysfunction, and immune-stromal niches [60–65]. In SSc-associated ILD, single-cell and molecular studies have identified altered macrophage, fibroblast, and epithelial signatures, while the Human Lung Cell Atlas provides a reference for mapping disease-specific cell states [60–63]. Spatial multiomics extends this approach by preserving tissue architecture and may help clarify why some autoimmune inflammatory lesions resolve, whereas others progress to fibrosis [64,65]. The future challenge is to translate these discoveries into clinically measurable biomarkers.Two examples illustrate this translational path. First, single-cell profiling in anti-MDA5-positive dermatomyositis identified a circulating ISG15+ CD8+ T-cell population reflecting interferon-driven pathogenic signaling; its baseline frequency was associated with one-year survival, providing a candidate prognostic biomarker for rapidly progressive ILD [66]. Second, more clinically tractable serum panels, including KL-6, ferritin, IL-6 and soluble mesothelin-related peptide, have shown diagnostic value in distinguishing SARD-ILD from idiopathic ILD in large clinical cohorts [67]. These examples illustrate two complementary routes: discovery-level immune profiling and near-term standardized assays. Bridging these levels will require staged validation, including discovery, technical validation, clinical validation, assessment of clinical utility and evaluation of how biomarker-guided decisions improve patient outcomes.

7. Treatable traits and precision therapy

Disease classifications remain essential for diagnosis, trial eligibility, and regulatory decisions, but they are insufficient for personalized care. Two patients with the same diagnostic category, such as RA-associated ILD or SSc-associated ILD, may differ in some conditions such as inflammatory airway, fibrotic burden, pulmonary vascular disease, and rate of progression. The treatable-traits approach proposes that therapy should target the dominant biology at the right time.

The most clinically actionable traits include B-cell/autoantibody-driven disease, T-cell co-stimulation and preclinical immune activation, type I interferon or antiviral-like inflammation, progressive fibrosis. B-cell-dominant traits may support rituximab, belimumab in specific lupus contexts, or IVIg in selected immune-mediated phenotypes. The therapeutic rationale for IVIg should be cautious and phenotype-specific, not generalized to all autoimmune lung diseases. Prior work on IVIg as a therapy for autoimmune conditions, and machine-learning models for IVIg/SCIg response in inflammatory myopathies, provides a relevant platform for future response-prediction studies [68–70].

Fibrotic progression is another trait that transcends disease categories. A patient with SSc-associated ILD, RA-associated UIP-like ILD or myositis-associated fibrotic ILD may share a trajectory of persistent symptoms, declining FVC, and increasing reticulation or traction bronchiectasis despite immunomodulation. Nintedanib and the concept of Progressive Pulmonary Fibrosis (PPF) have already moved the field toward decisions based on disease progression [32,45,49,50]. Conversely, patients with inflammatory organizing pneumonia, a cellular NSIP pattern, anti-synthetase syndrome, or early anti-MDA5 disease may require rapid escalation of immunomodulatory therapy rather than a delayed antifibrotic approach [33–37].

Fig. 2 summarizes a practical treatable-traits framework. It links clinical phenotypes with relevant readouts – including autoantibodies,

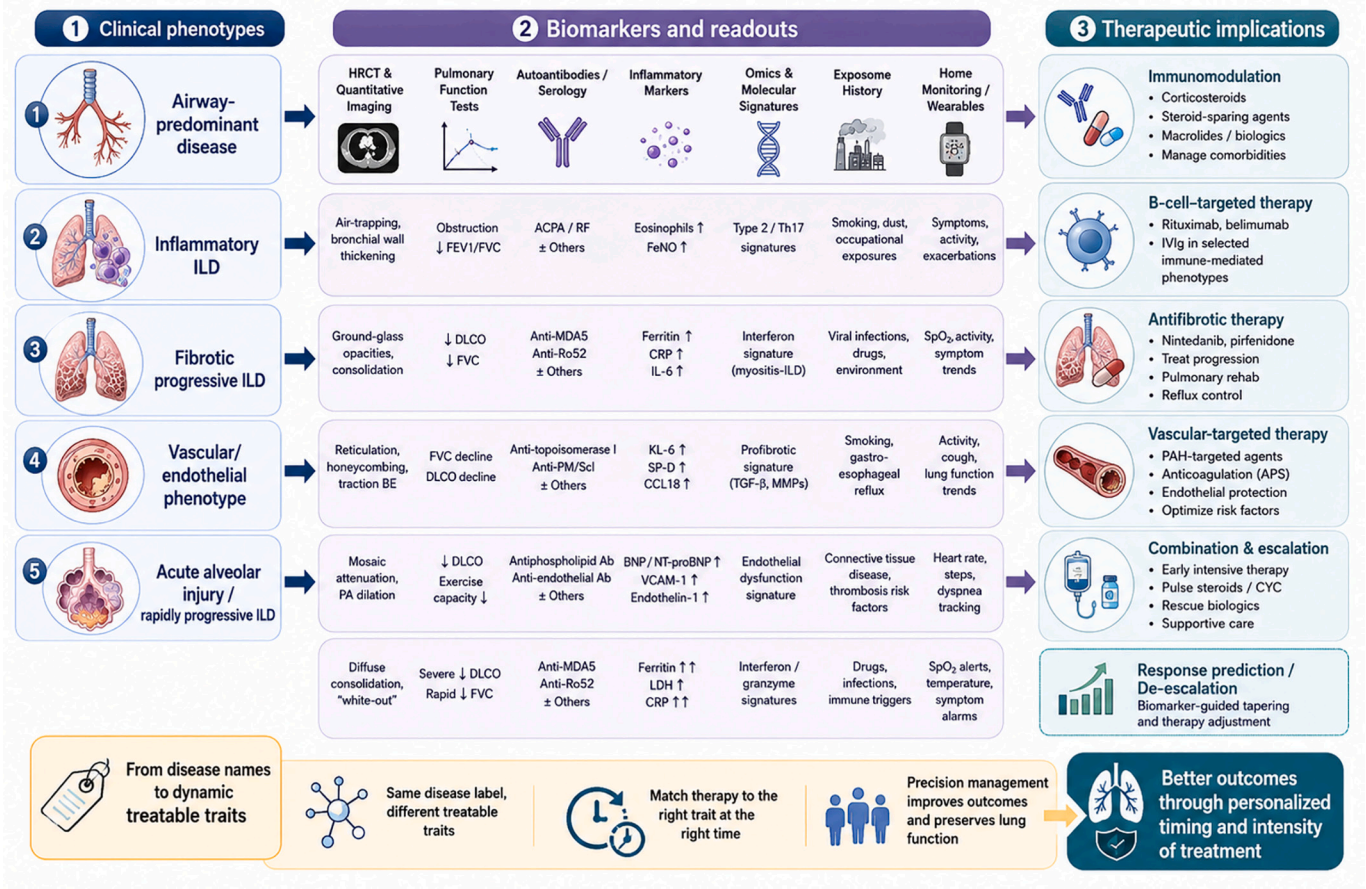


Fig. 2. Treatable traits and precision management in autoimmune lung disease. Clinical phenotypes should be linked to measurable readouts and actionable therapy choices. Disease labels remain important, but dynamic treatable traits may better define timing, intensity, escalation and de-escalation.

selected biomarkers PFTs, HRCT, quantitative imaging, and home monitoring - and with corresponding therapeutic implications. The most important message is dynamic timing. The same patient can move from inflammatory to fibrotic dominance, or from stable disease to accelerated decline. Precision medicine in autoimmune lung disease will therefore depend less on one-time classification and more on repeated reassessment of risk, dominant trait, and therapeutic window.

This approach also changes how treatment response should be measured. A binary responder/non-responder classification at a single time point is too simplistic for chronic autoimmune lung disease. Clinically meaningful response may include improved dyspnea, preserved exercise capacity, reduced inflammatory biomarkers, stabilization of FVC, slower quantitative HRCT progression, reduced steroid burden, fewer flares, or avoidance of hospitalization. Conversely, apparent stability may represent undertreated disease if the patient is losing activity and quality of life. Future response-prediction models should therefore incorporate multidimensional outcomes, including toxicity, infection, and comorbidity as competing dimensions of treatment benefit.

8. AI-enabled prevention, risk prediction and longitudinal monitoring

Artificial intelligence should not be viewed solely as a radiology tool. In autoimmune lung medicine, its most valuable role will be multimodal and longitudinal. The key clinical questions are: who is at risk of developing autoimmune disease or lung involvement; which phenotypes or endotypes are associated with disease progression; which patients are likely to progress over the next 6, 12 or 24 months; which treatment is most appropriate; and when should monitoring or treatment be intensified, maintained or de-escalated?

Although deep-learning and multimodal models in ILD have shown promising performance, their clinical utility depends on transportability across scanners, reconstruction protocols, disease prevalence, annotation strategies, populations and care settings [6–9]. In fibrotic ILD, algorithmic HRCT classification has been evaluated against expert thoracic radiologists, and deep-learning-derived imaging probabilities have shown prognostic value in progressive fibrotic lung disease. However, performance obtained in curated cohorts should not be assumed to generalize to autoimmune lung disease, where CTD-ILD, RA-ILD, SSc-ILD, IIM-ILD and anti-MDA5-associated rapidly progressive ILD differ in prevalence, imaging pattern, treatment exposure, competing diagnoses and outcome trajectories. Deep learning models applied to HRCT have demonstrated strong performance in classifying fibrotic lung disease, predicting clinical outcomes and mortality, and integrating longitudinal clinical data for diagnostic and prognostic refinement [6–9]. Furthermore, machine learning based on plasma proteomics can differentiate CTD-ILD from idiopathic pulmonary fibrosis, highlighting the potential of molecular data to complement imaging modalities [10]. Finally, machine learning algorithms have been successfully applied to predict disease progression in anti-MDA5– and inflammatory myopathies–associated ILD [36,37].

The next frontier in this field will require moving beyond isolated algorithms toward integrated, structured data hubs. In practice, an autoimmune-lung data hub should be developed as a stepwise, federated infrastructure rather than as a single unstructured repository [71,72]. First, participating centres should agree on a minimum common dataset including disease classification, disease duration, exposure history, autoantibody profile, PFTs, HRCT acquisition and reconstruction metadata, visual and quantitative CT scores, treatment exposure, adverse events, comorbidities and longitudinal outcomes. Second, structured

clinical data should be mapped to an interoperable common data model, such as OMOP/OHDSI, while imaging data should retain DICOM provenance and be linked through imaging-specific CDM extensions and/or FHIR ImagingStudy resources. Third, harmonized vocabularies, missing-data definitions, quality-control rules and versioned annotation protocols should be used across centres. Fourth, governance should define data minimization, pseudonymization, access control, audit trails and explicit consent for individual care versus secondary AI model training. Federated or privacy-preserving learning may reduce the need to centralize sensitive patient-level data, but it does not remove the need to evaluate performance, fairness, security and model drift. Finally, every model update should trigger validation against a locked external test set, calibration assessment, subgroup fairness analysis and documentation of model drift before clinical redeployment. Adherence to FAIR data principles, implementation of common ontologies, and long-term longitudinal follow-up are essential to develop models that maintain validity as they are iteratively updated. Fig. 3 illustrates an AI-enabled framework encompassing data ingestion, multimodal modeling, validation, governance, clinical deployment, and continuous learning.

Consequently, clinical AI models must be tailored to specific tasks. For instance, a screening model for SSc–associated ILD should emphasize sensitivity and well-calibrated negative predictive value; a model for rapidly progressive anti-MDA5 ILD must prioritize early identification of patients requiring aggressive intervention; a treatment-response model should quantify prediction uncertainty and potential toxicity; and a monitoring model needs to distinguish true clinically meaningful changes from noise. A single algorithmic architecture cannot serve all these distinct tasks. Furthermore, endpoints must directly align with decision-making: parameters such as dyspnea, oxygen requirements, FVC or DLCO decline, HRCT extent, cumulative steroid exposure, drug toxicity, hospitalization rates, patient-reported quality of life, and mortality may each carry varying relevance depending on the specific clinical context.

Future models should therefore report discrimination, calibration, sensitivity and specificity at pre-specified clinically meaningful thresholds, decision-curve analysis or net benefit, missing-data handling, uncertainty estimates, and subgroup performance. External validation should be multicentre and, ideally, multinational; subgroup analyses should address sex, age, ancestry, smoking and occupational exposure history, disease phenotype, scanner/reconstruction protocol and care setting. Before deployment, models should be assessed using TRIPOD+AI, PROBAST+AI, CLAIM and FUTURE-AI principles, and after deployment they should undergo drift surveillance, periodic recalibration, audit of false-positive and false-negative consequences, predefined human override procedures and prospective clinical-utility studies [73–76]. Risk-of-bias appraisals should incorporate PROBAST alongside emerging AI-specific extensions, complemented by domain-specific checklists for medical imaging [77–80].

The most ambitious frontier is fully integrated, closed-loop care. In this paradigm, management of complex diseases—such as SSc, RA, or anti-synthetase syndrome—shifts away from static, semi-annual or annual reviews. Instead, a continuous, multi-source data stream (integrating patient-reported symptoms, cough tracking, oxygenation, home spirometry, PFTs, HRCT scans, wearable telemetry, and longitudinal biomarkers) dynamically refines a personalized trajectory. Automated alerts do not replace physician judgment; rather, they identify meaningful changes in risk status that warrant timely clinical reassessment. Ultimately, digital-twin architectures may simulate patient outcomes

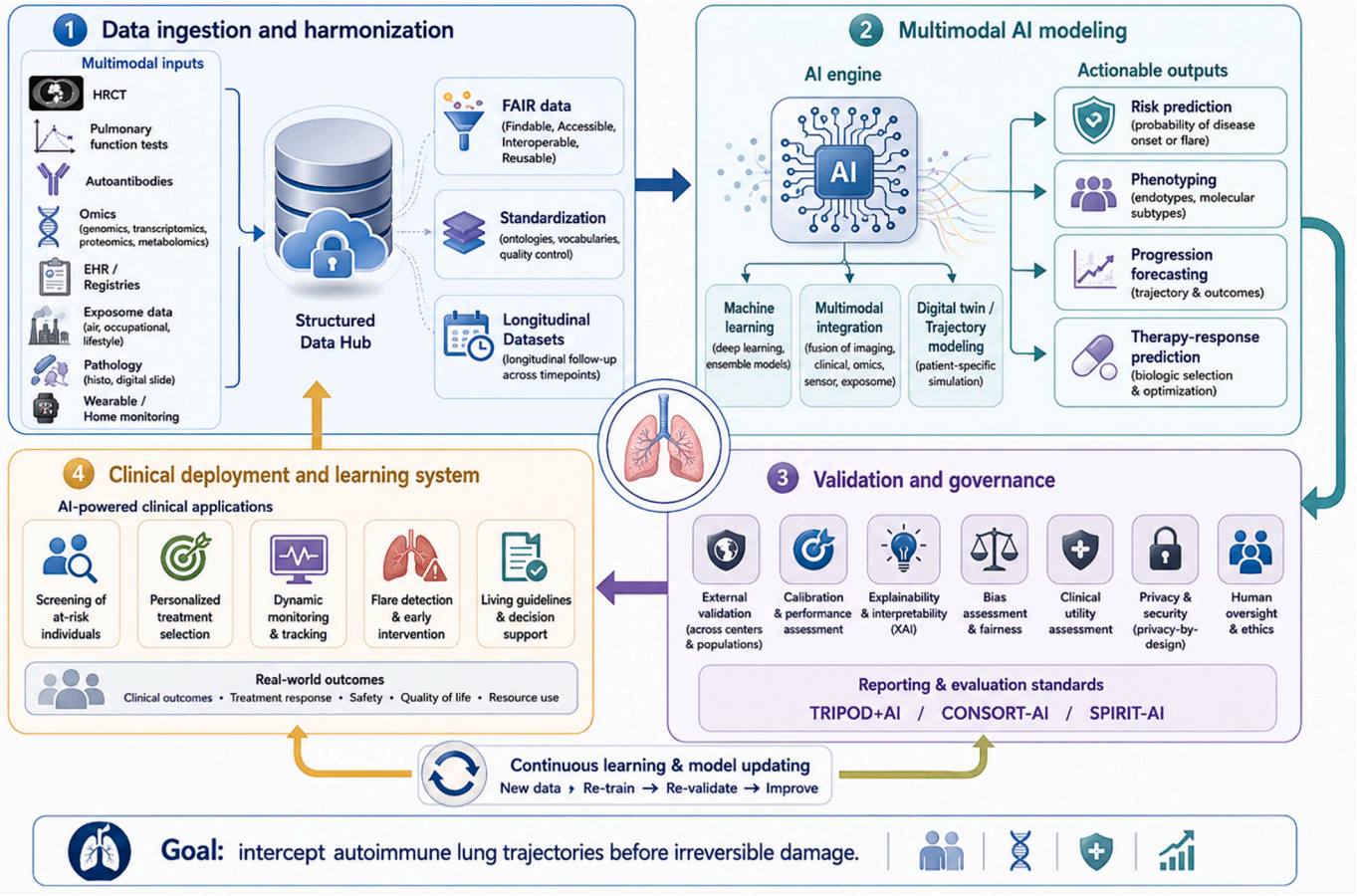


Fig. 3. AI-enabled roadmap for autoimmune lung medicine. Multimodal data ingestion, harmonization, modeling, validation, governance and deployment form a continuous learning system. The goal is to intercept autoimmune lung trajectories before irreversible damage.

across different therapeutic strategies, but their use should remain strictly hypothesis-generating until validated through prospective clinical trials.

The greatest opportunity may lie in transforming clinical trials. Autoimmune lung diseases are individually heterogeneous and often rare within each phenotype. Multimodal AI could enrich trials with patients at high risk of progression, reduce sample-size requirements, identify early response signals and support adaptive randomization. Federated learning could allow centers to collaborate without centralizing sensitive data, although privacy-preserving methods must still be assessed for performance, fairness and security. Ultimately, the best AI tools will be those that improve decisions clinicians already face: when to scan, when to treat, when to intensify, when to taper and when to suspect a competing diagnosis.

9. Roadmap for the future

We propose a forward-future roadmap (Tables 2, 3). The first priority should be the implementation of guideline-based multidisciplinary pathways. Rheumatology and pulmonology clinics should harmonize exposure history, autoantibody testing, baseline PFTs, HRCT, and follow-up intervals, with special attention to high-risk SSc, RA, myositis and Sjögren disease populations [3–5]. In the following step quantitative HRCT and AI-assisted imaging should move from research to validated second-reader use, with human supervision and prospective utility studies. Quantitative and AI-assisted HRCT will inevitably increase the detection of subclinical or indeterminate abnormalities, such as minimal ground-glass change, limited reticulation or isolated interlobular septal thickening, whose natural history may be uncertain. To avoid overdiagnosis and overtreatment, clinical significance should be defined by converging criteria rather than by imaging alone: reproducibility of the abnormality, radiological progression on serial imaging, functional decline, new or worsening respiratory symptoms, high-risk autoimmune phenotype or autoantibody profile, and multidisciplinary adjudication after exclusion of alternative explanations such as infection, pulmonary edema, drug toxicity, smoking-related disease or thromboembolism. Isolated, non-progressive subclinical findings in an asymptomatic and functionally stable patient should prompt structured monitoring rather than treatment initiation or escalation, in line with existing concepts of ILD/PPF progression. Next, lung and mucosal signatures should be incorporated into studies of preclinical RA and at-risk individuals with autoimmunity.

In future studies platform and adaptive trials should stratify and enrich patient populations according to treatable traits rather than by diagnosis alone. Trial arms could be built around inflammatory, fibrotic, vascular, B-cell-dominant, interferon-dominant or acute injury phenotypes, with shared endpoints including FVC, DLCO, quantitative HRCT, patient-reported outcomes and steroid-sparing success. In future research, closed-loop monitoring should be evaluated in pragmatic care pathways, integrating home-based data with scheduled clinical assessment. Looking further ahead, the field should aim for true autoimmune lung interception: preventing RA in selected at-risk individuals and preventing irreversible ILD in systemic autoimmune diseases before established fibrosis develops.

This roadmap will require a different culture of collaboration. Pulmonologists, rheumatologists, radiologists, immunologists, occupational physicians, data scientists, patients and trialists should define shared datasets and clinically meaningful thresholds together. The lung can then become a bridge between mechanistic science and bedside decision-making, rather than a late complication managed after systemic disease has already declared itself.

Table 2
A proposed roadmap for autoimmune lung medicine.

Main objective	Required infrastructure	Expected output
Implement of CTD-ILD guidelines	Multidisciplinary rheumatology-pulmonology pathways	Standardized HRCT/PFTs/autoantibody follow-up
Validate quantitative HRCT and AI second readers	Multicenter imaging and clinical datasets	Progression and outcome prediction tools
Introduce of lung/mucosal signatures in at-risk cohorts	Sputum, BAL (when clinically indicated), serum, exposome and imaging biobanks	Preclinical autoimmune lung risk scores
Design treatable-trait trials	Adaptive/platform trial networks	Therapy based on inflammatory, fibrotic, vascular and B-cell traits
Test closed-loop monitoring	Home spirometry, wearables, EHR integration	Dynamic risk reclassification and early alerts
Interception before irreversible damage	Validated AI, ethical prevention frameworks	Prevention of RA onset and CTD-ILD progression in selected patients

Abbreviations: AI, Artificial Intelligence; CTD-ILD, Connective tissue disease-associated interstitial lung disease; BAL, Bronchoalveolar lavage, HER, Electronic health record; HRCT, High-resolution computed tomography; PFTs, Pulmonary function tests.

10. Implementation challenges and governance

Several challenges must be anticipated. Predictive screening of asymptomatic at-risk individuals raises three specific ethical concerns that should be addressed prospectively. First, overmedicalization: a positive risk score should not automatically trigger treatment unless an actionable and clinically validated threshold has been defined. Risk communication should clearly distinguish “eligible for closer monitoring” from “eligible for preventive intervention.” Second, informed consent: individuals undergoing predictive testing, including genetic, serological, imaging-based or AI-assisted assessment, should be informed about predictive uncertainty, possible psychological consequences of risk labelling, incidental findings and their right not to know. Third, data privacy and secondary use: multimodal datasets should adhere to data minimization principles, distinguish consent for individual care from consent for AI model training, and include safeguards against inappropriate downstream use, including insurance or employment discrimination, in line with applicable regulatory frameworks such as GDPR and emerging AI-specific regulation. Governance structures, ideally including patient representatives, should define these boundaries before predictive tools are deployed in at-risk autoimmune populations [81].

11. Conclusions

The role of lung in autoimmunity should be reconsidered. It may be an initiating mucosal site in selected diseases, especially RA; a major target organ in systemic autoimmune disease; and a sentinel for future disease trajectories. The proposed lung autoimmune continuum connects inhaled exposome, epigenetics, microbiota-redox imbalance, mitochondrial dysfunction, alarmins, autoantibodies, systemic immune spread, tissue injury and clinical phenotypes. The future of autoimmune lung medicine will not be defined only by earlier detection of ILD. It will be defined by the ability to predict who is at risk, identify the dominant treatable trait, select therapy at the right time, monitor trajectory dynamically and prevent irreversible damage. The most important future study will not be a single biomarker or a single algorithm, but a prospective, multicenter, longitudinal program that follows at-risk individuals and autoimmune patients from exposure and early immune activation through lung phenotype, treatment and long-term outcome. The next decade should move from describing pulmonary involvement to intercepting autoimmune lung trajectories.

The most important future study will not be a single biomarker or a single algorithm, but a prospective, multicenter, longitudinal program that follows at-risk individuals and autoimmune patients from exposure

Table 3
AI applications and validation requirements in autoimmune lung disease.

AI application	Inputs	Output	Clinical use	Validation requirement
Risk prediction	Autoantibodies, exposome, genetics, EHR, HRCT	Probability of RA or CTD-ILD onset	Targeted screening	External validation, calibration, decision-curve analysis
Phenotyping	HRCT, PFTs, serology, omics	Inflammatory, fibrotic, vascular or airway trait	Treatment selection	Independent cohorts and expert adjudication
Progression forecasting	Longitudinal FVC, DLCO, HRCT, symptoms	6–24-month trajectory	Escalation/de-escalation	Prospective utility studies
Therapy-response prediction	Baseline phenotype, biomarkers, prior drugs	Probability of benefit/toxicity	Personalized therapy	Randomized or target-trial emulation evidence
Closed-loop monitoring	Home spirometry, wearable, EHR, patient reports	Change alerts	Earlier reassessment	Safety monitoring, model-drift surveillance, human oversight

Abbreviations: AI, Artificial Intelligence; CTD-ILD, Connective tissue disease-associated interstitial lung disease; DLCO, Diffusing Capacity of the Lungs for Carbon Monoxide; FVC, Forced vital capacity; HER, Electronic health record; HRCT, High-resolution computed tomography; PFTs, Pulmonary function tests; RA, Rheumatoid arthritis.

and early immune activation through lung phenotype, treatment and long-term outcome. The future should move beyond describing pulmonary involvement toward intercepting autoimmune lung trajectories.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Ethical approval

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Declaration of generative AI use in the manuscript preparation process

ChatGPT 5.6 (OpenAI) was used to assist with structuring the framework and organizing the references. All reference information was reviewed, verified, and edited by the authors, who take full responsibility for the content, accuracy, and integrity of the published article.

Declaration of competing interest

The authors declare that they have no affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

Data availability

Data will be made available on request.

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