



Idiopathic pulmonary fibrosis

The usual interstitial pneumonia pattern: mechanisms, morphology and clinical consequences

Pathogenesis • Usual interstitial pneumonia • Clinical correlation

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

- Distinguish idiopathic pulmonary fibrosis (IPF) from the histologic pattern usual interstitial pneumonia (UIP).
- Explain how epithelial vulnerability, repeated injury and fibroblast activation converge in IPF.
- Recognize spatial and temporal heterogeneity, fibroblastic foci and honeycomb fibrosis.
- Relate restrictive physiology and clinical progression to the underlying morphologic changes.

IPF: A progressive fibrosing clinicopathologic syndrome

Progressive interstitial scarring damages gas-exchanging lung and may culminate in respiratory failure.

- The disorder is idiopathic: No specific external cause is established for the individual case.
- Its diagnosis integrates clinical, radiologic and, when available, pathologic information.
- The characteristic histologic pattern is usual interstitial pneumonia (UIP).

Where IPF fits within restrictive lung disease

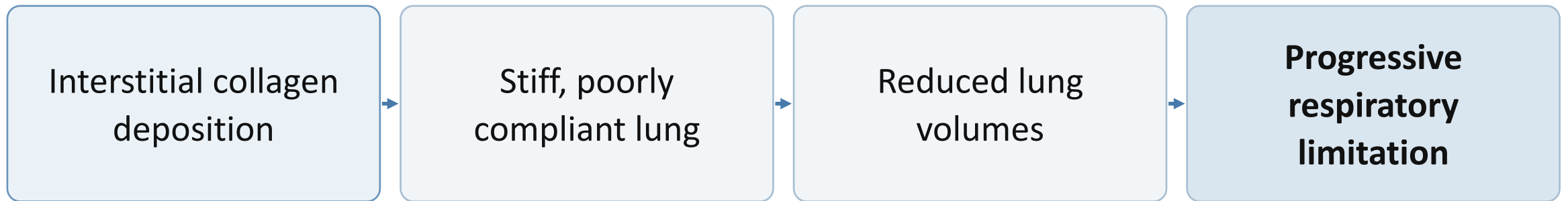
Interstitial / parenchymal restriction

- Predominantly inflammation and/or fibrosis of interstitium
- Reduced lung compliance and lung volumes
- IPF is a prototypic fibrosing example

Extraparenchymal restriction

- Mechanically limits thoracic expansion
- Examples: Obesity, pleural or neuromuscular disorders
- Does not require the UIP fibrotic lung pattern

Physiologic consequences of interstitial fibrosis



Mechanistic sequence linking microscopic scarring with restriction (schematic).

Interpretation is mechanistic and conceptual; Scale and timing are schematic.

Chronic interstitial lung diseases are heterogeneous

- Several fibrosing, granulomatous, smoking-related and other conditions can produce an interstitial syndrome.

- Imaging and pulmonary-function abnormalities overlap between entities.

- Disease identification requires clinicopathologic correlation rather than a restrictive test alone.

- The same advanced fibrotic appearance can obscure distinct early disease features.

UIP describes a pattern; IPF describes a disease

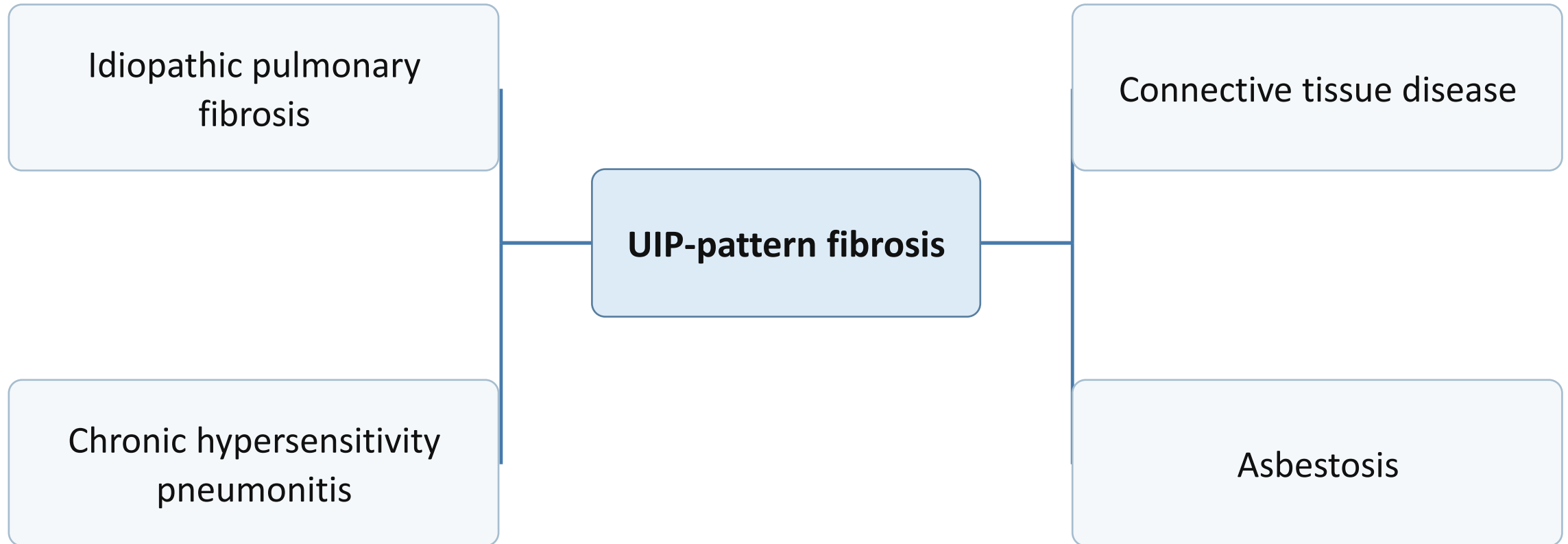
Usual interstitial pneumonia (UIP)

- Morphologic pattern of patchy interstitial scarring
- Characterized by fibroblastic foci and honeycombing
- May arise in several diseases

Idiopathic pulmonary fibrosis (IPF)

- Clinical disease with characteristic UIP phenotype
- No identified explanatory underlying disease
- Requires context and exclusion of mimics

UIP can occur outside IPF



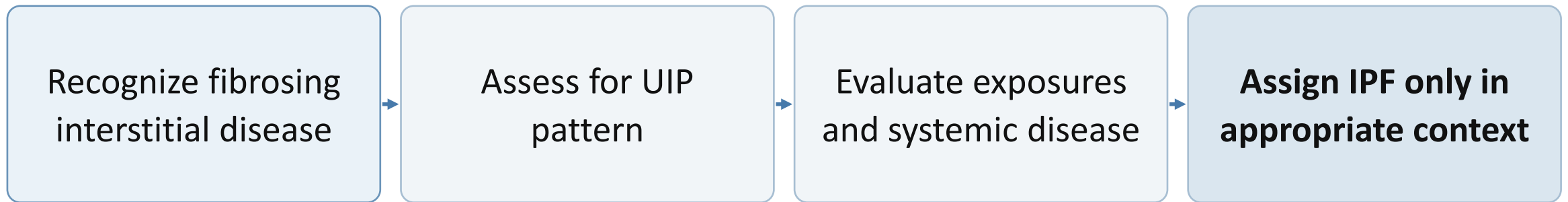
A UIP pattern is not, on its own, proof of idiopathic disease.

The diagnostic importance of computed tomography

The distinctive appearance of UIP on CT may make histologic confirmation unnecessary in appropriate clinical contexts.

- UIP as a pattern that can often be diagnosed radiologically.
- The radiologic pattern must be interpreted with clinical and exposure information.
- A CT pattern cannot independently determine whether the cause is idiopathic.

An idiopathic designation is an exclusionary judgment



Conceptual diagnostic reasoning; Not a formal guideline algorithm.

Interpretation is mechanistic and conceptual; Scale and timing are schematic.

The central pathogenic proposition

Genetic and age-related susceptibility allows recurrent alveolar epithelial injury to trigger abnormal repair rather than architectural restoration.

- Environmental factors are proposed sources of repeated epithelial damage.
- Injured epithelium and responding immune cells may release profibrotic mediators.
- Activated interstitial fibroblasts synthesize extracellular collagen.

Environmental factors associated with IPF

- Cigarette smoking is the principal environmental risk factor highlighted by Robbins.

- Air pollution, microaspiration, metal fumes and wood dust are also implicated.

- Some occupational associations include farming, hairdressing and stone polishing.

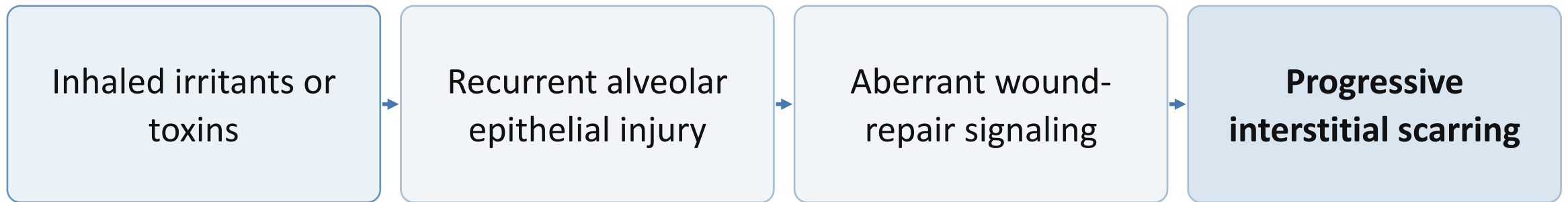
- These associations support, but do not prove, recurrent epithelial injury as a common mechanism.

Smoking is a risk amplifier, not a sufficient cause

Cigarette smoking increases IPF risk several-fold account.

- Most exposed people do not develop IPF.
- Risk therefore reflects an interaction between exposure and host susceptibility.
- Smoking is a risk association—not a unique diagnostic marker for IPF.

Inhaled irritants may repeatedly injure epithelium



Hypothesized causal chain, not an experimentally proven sequence for every exposure.

Interpretation is mechanistic and conceptual; Scale and timing are schematic.

Microaspiration is one proposed epithelial insult

Microaspiration among exposures associated with IPF.

- The proposed common consequence is recurring alveolar epithelial damage.
- Microaspiration does not by itself establish that an individual's fibrosis is idiopathic.
- The pathogenic contribution in individual patients remains incompletely resolved.

Why exposure alone cannot explain disease

Exposure is common

- Smoking and environmental irritants affect many people
- A typical exposure does not invariably lead to fibrosis
- An association does not prove a sole cause

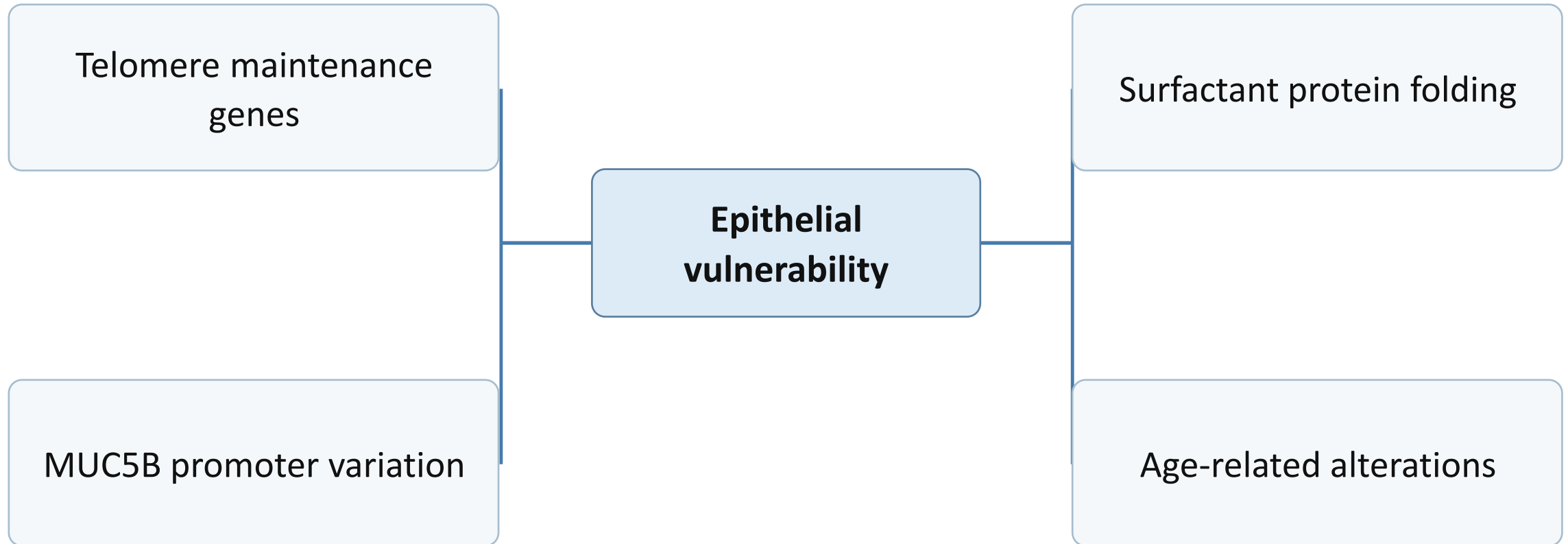
IPF is uncommon

- Inherited variation can affect cellular resilience
- Age alters vulnerability to injury
- Additional factors are necessary for disease expression

Age-related susceptibility matters

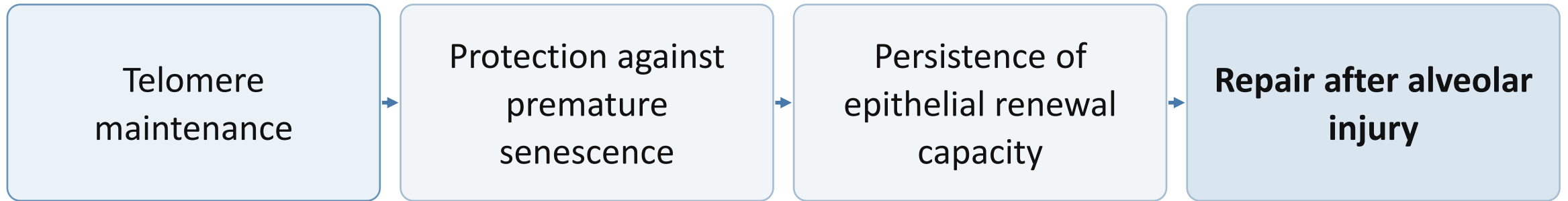
- IPF rarely presents before 50 years of age in the Robbins account.
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- Older age may reflect loss of epithelial regenerative capacity or other acquired changes.
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- Age-related telomere shortening is one candidate mechanism.
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- The exact contribution of aging-related changes remains uncertain.

Genetic susceptibility involves several pathways



Established genetic associations do not imply identical mechanisms in all cases.

Telomeres help preserve proliferative capacity



Normal-protection model; Loss of maintenance may compromise repair.

Interpretation is mechanistic and conceptual; Scale and timing are schematic.

Telomere maintenance genes linked to IPF

TERT, TERC, PARN and RTEL1 are linked to telomere maintenance and IPF risk.

- Defective maintenance can accelerate telomere shortening.
- Short telomeres predispose epithelial cells to senescence.
- A reduced capacity for epithelial replacement can increase vulnerability to repeated insults.

Familial and sporadic telomere observations

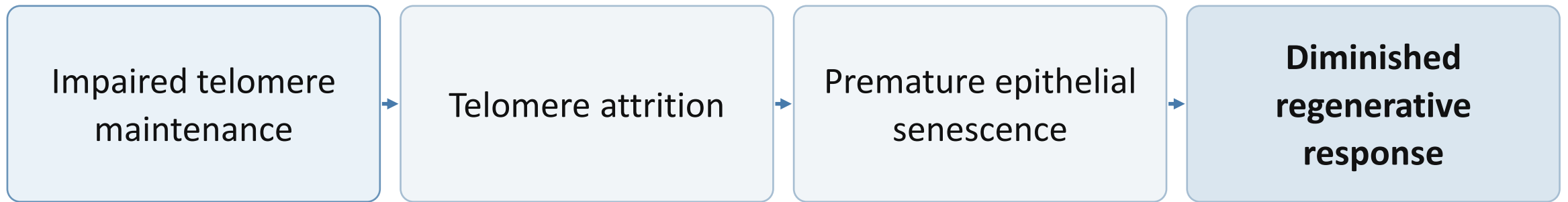
Familial IPF

- Inherited telomere gene defects are reported in up to 15% of familial cases.
- An inherited variant helps explain susceptibility.
- Not every familial case has an identified defect.

Sporadic IPF

- Abnormally short lymphocyte telomeres are reported in up to 25% of cases.
- This is an association rather than proof of causation in each patient.
- The measures and patient groups are not directly interchangeable.

Cellular senescence links telomeres to failed repair



Schematic interpretation of the telomere-senescence hypothesis.

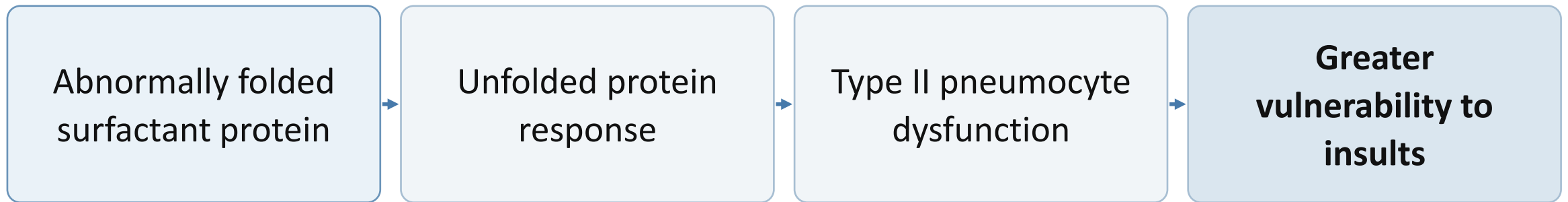
Interpretation is mechanistic and conceptual; Scale and timing are schematic.

Surfactant gene variants affect type II pneumocytes

Rare familial IPF forms involve genes encoding components of surfactant.

- Mutant surfactant proteins can fold abnormally.
- Misfolded protein burden triggers the unfolded protein response.
- The stressed type II pneumocyte becomes more sensitive to environmental injury.

Unfolded protein response: Cellular stress model



Mechanism described for certain rare inherited IPF-associated variants.

Interpretation is mechanistic and conceptual; Scale and timing are schematic.

MUC5B promoter variation is strongly associated

A promoter polymorphism affecting MUC5B is reported in roughly one-third of IPF cases.

- The variant increases production of the mucin MUC5B.
- Altered mucociliary clearance is a possible mechanistic consequence.
- Exactly how increased MUC5B influences IPF risk remains uncertain.

Genetic association does not establish mechanism

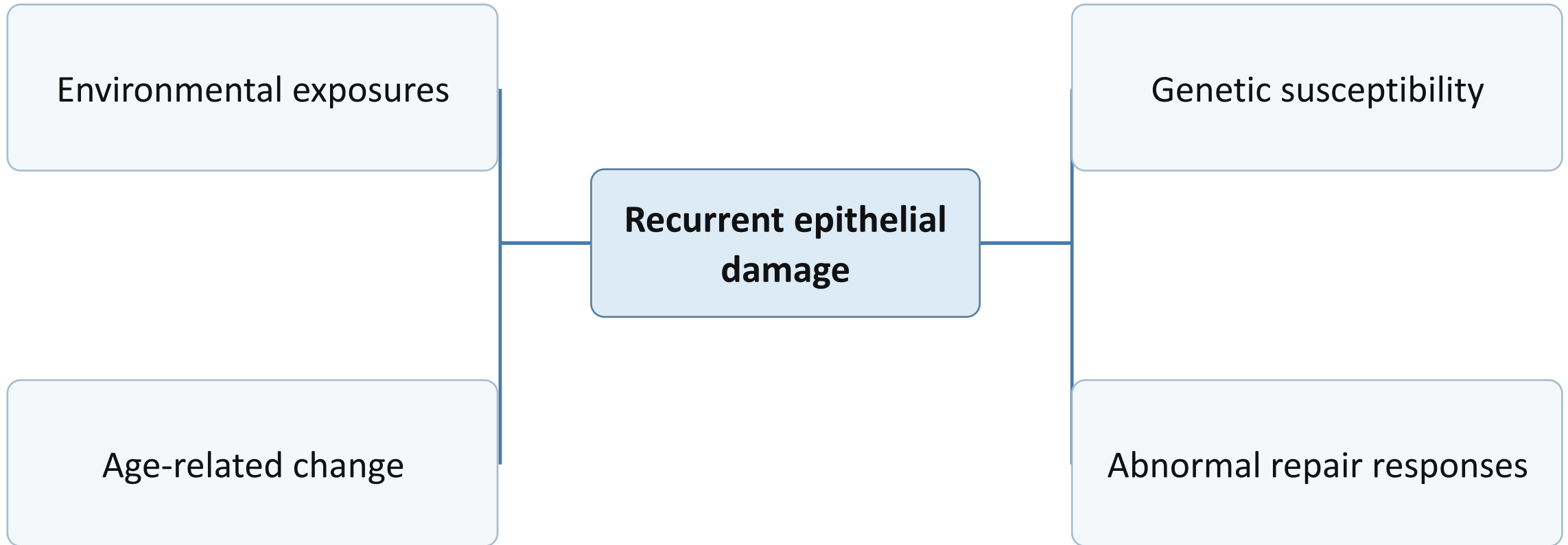
What is supported

- MUC5B promoter polymorphism associates with IPF.
- MUC5B secretion increases.
- Telomere-related defects and surfactant variants are implicated.

What remains unresolved

- Whether altered clearance mediates MUC5B-associated risk
- Precise molecular linkage from epithelial injury to fibrosis
- How different susceptibility pathways interact

A convergent model of epithelial vulnerability



Multiple inputs converge on persistent injury rather than constituting alternative diagnoses.

Injured alveolar epithelium is the proposed initiator

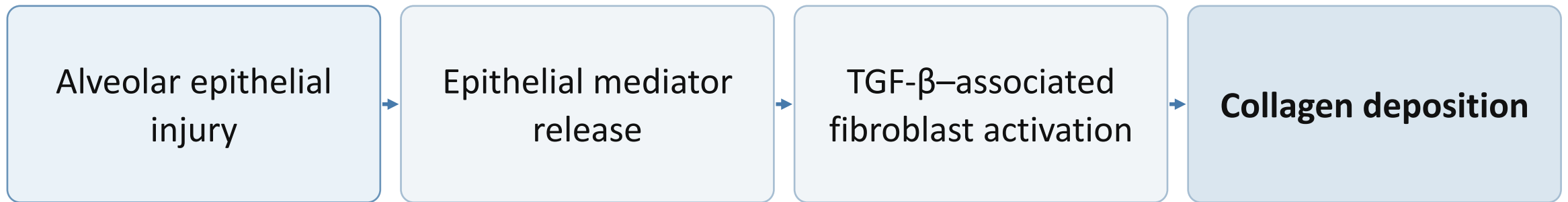
- Alveolar epithelial injury is prominent in proposed models of IPF pathogenesis.

- The initiating injury is often recurrent or persistent rather than a single discrete event.

- An abnormal healing program favors collagen deposition over restoration of thin alveolar septa.

- Precisely how epithelial injury is converted into fibrogenesis remains unknown.

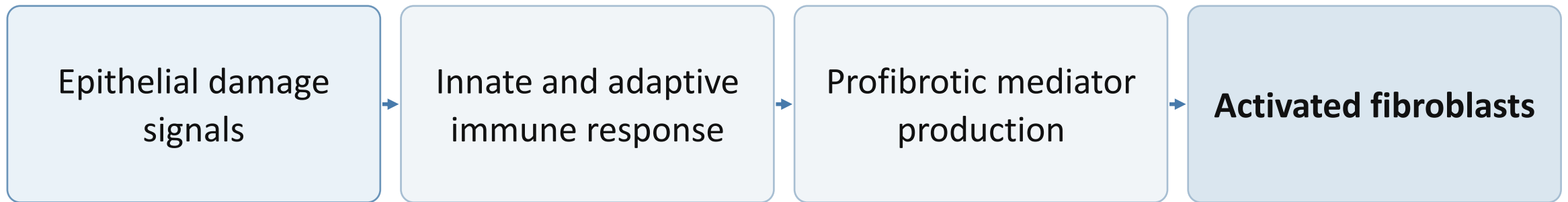
Epithelial profibrotic signaling model



One proposed mechanistic model; Mediators and relationships are not fully established.

Interpretation is mechanistic and conceptual; Scale and timing are schematic.

Immune responses may amplify fibrogenesis



Second proposed model; It is not mutually exclusive with epithelial signaling.

Interpretation is mechanistic and conceptual; Scale and timing are schematic.

The epithelial and immune models can coexist

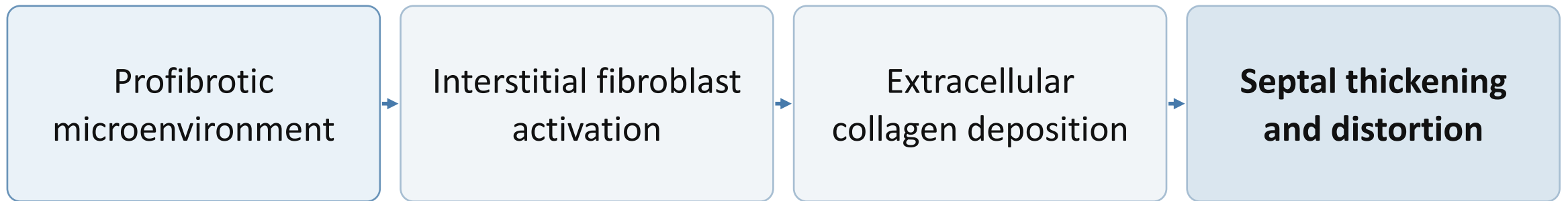
Epithelial-origin model

- Damaged epithelial cells release fibrogenic signals
- TGF- β is a candidate mediator
- Directs abnormal fibroblast activation

Immune-amplification model

- Danger signals recruit immune responses
- Immune cells may supply additional profibrotic mediators
- Amplifies and sustains local tissue repair signaling

Fibroblasts are the collagen-producing effectors



Links cellular activation to the defining scar-forming tissue response.

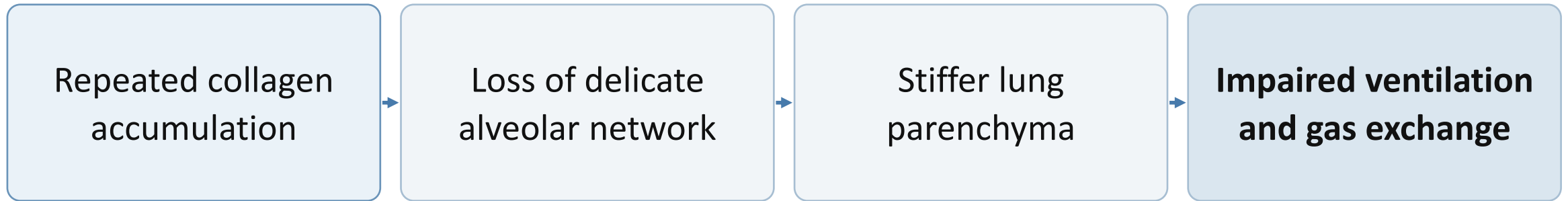
Interpretation is mechanistic and conceptual; Scale and timing are schematic.

PI3K–AKT signaling: Suggestive, not proven causal

Altered PI3 kinase signaling has been described in IPF-associated fibroblasts.

- Increased PI3K/AKT signaling is included' mechanistic model.
- Observed signaling changes may accompany aberrant fibroblast activation.
- A direct causal link between these changes and progressive fibrosis has not been established.

Fibrosis changes architecture and mechanics



Pathology-to-physiology sequence based on the described interstitial scarring.

Interpretation is mechanistic and conceptual; Scale and timing are schematic.

Mechanisms: Supported elements and open questions

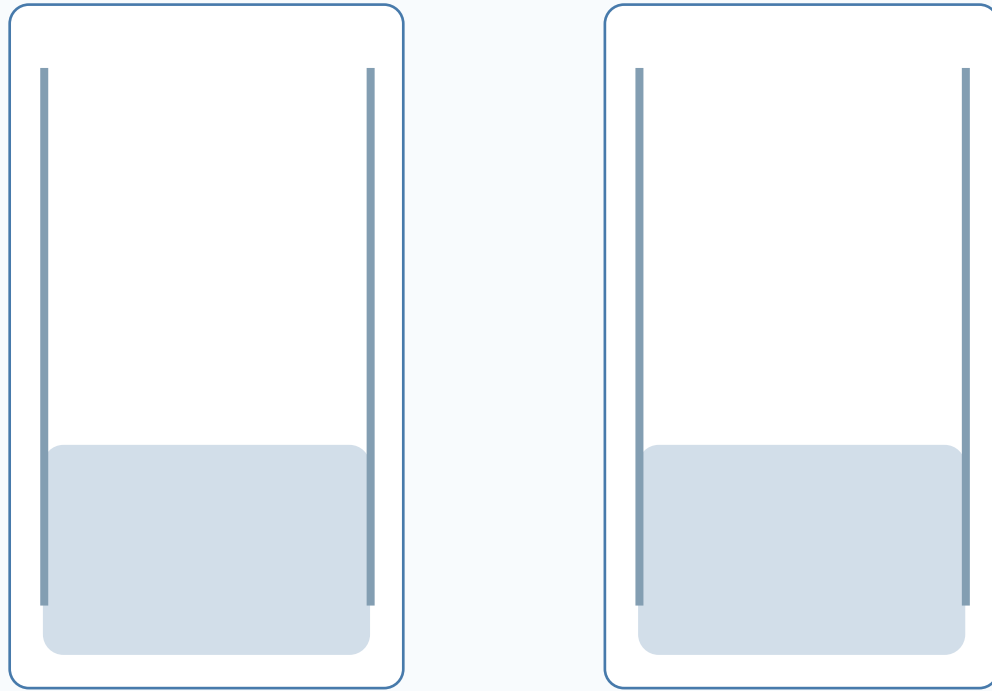
Better established

- Recurrent epithelial injury / vulnerability
- Collagen-producing activated fibroblasts
- Fibrotic architectural distortion
- Genetic risk associations

Incomplete or hypothetical

- Exact molecular initiating injury
- Dominant cellular source of profibrotic mediators
- Causal status of PI3K/AKT abnormalities
- MUC5B-to-fibrosis link

Gross disease favors peripheral and lower lung



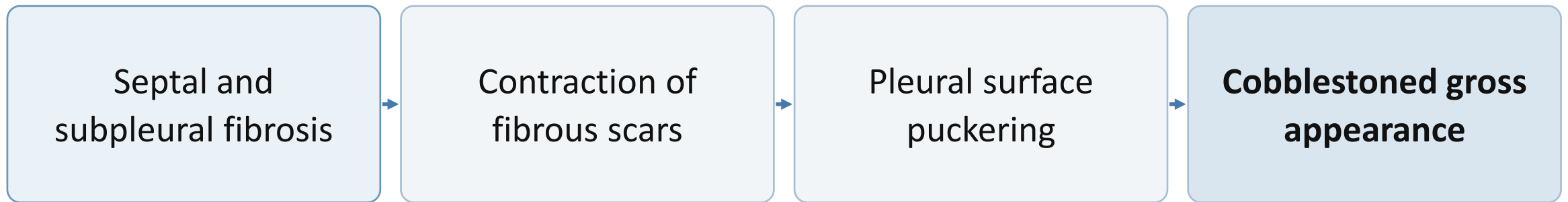
Lower-lung emphasis

Subpleural + lower-lobe predominance (schematic)

Morphologic interpretation

- Fibrosis preferentially affects lower lobes.
- Subpleural regions are emphasized.
- Scarring also tracks interlobular septa.

Pleural cobblestoning is produced by scar retraction



Anatomic mechanism of the textbook gross finding.

Interpretation is mechanistic and conceptual; Scale and timing are schematic.

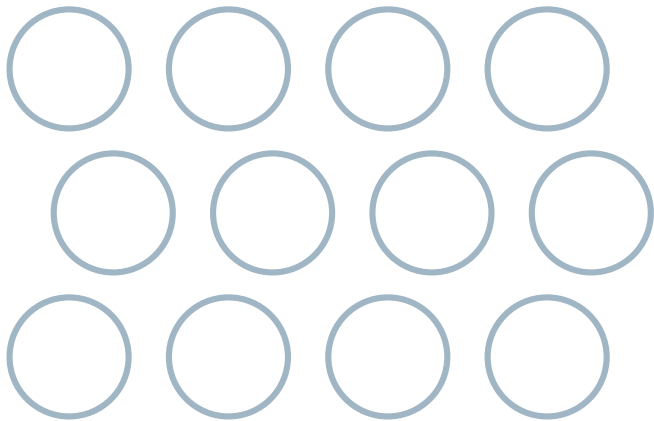
The cut lung becomes firm and rubbery

Grossly, fibrotic areas are firm, rubbery and white on the cut surface.

- Dense matrix deposition replaces normal compliant parenchyma.
- The distribution is patchy rather than entirely uniform.
- Subpleural, septal and lower-lobe accentuation is characteristic of the description.

UIP histology is defined by heterogeneity

Relatively preserved



Scarred lung



Schematic architecture — not a histology image.

Morphologic interpretation

- Normal or near-normal lung neighbors severely scarred areas.
- Lesions vary in location and severity.
- This unequal geographic distribution is spatial heterogeneity.

Spatial heterogeneity: Two regions, one specimen

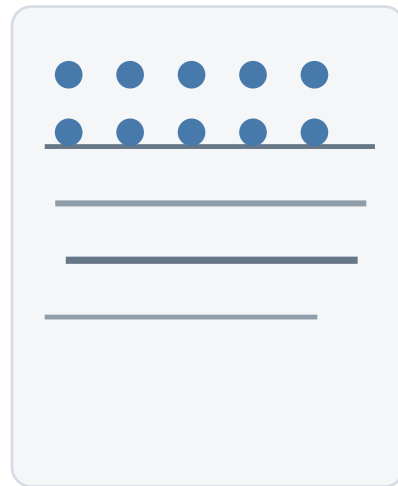
Relatively preserved region

- Open alveoli and thinner septa
- More recognizable pulmonary architecture
- Low-power comparison is essential

Advanced fibrotic region

- Loss of normal alveolar topology
- Confluent collagen deposition
- Cystic honeycomb remodeling may appear

Temporal heterogeneity reflects lesions of different ages



Cell-rich focus



Evolving scar



Dense old scar

Schematic stages coexist in UIP; Not a literal time series.

Morphologic interpretation

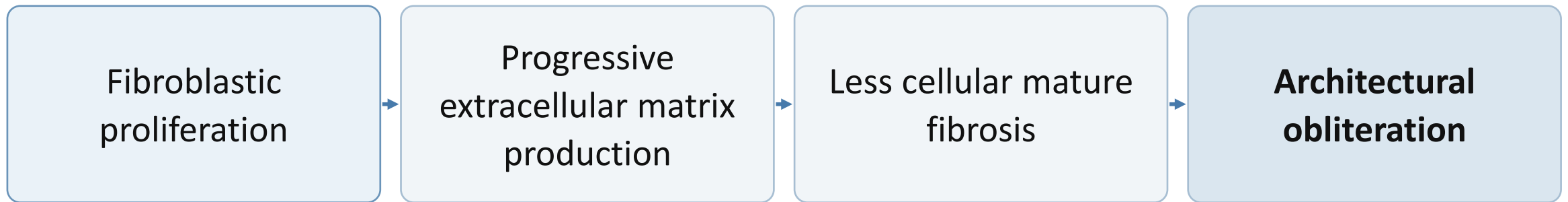
- Active fibroblastic foci coexist with older dense scars.
- Early lesions are more cellular.
- Mature lesions are increasingly fibrotic and hypocellular.

Fibroblastic foci are an early active lesion

Fibroblastic foci represent exuberant local fibroblast proliferation within the evolving lesion.

- They are characteristic components of the UIP pattern.
- They identify sites of active fibrotic remodeling.
- Their coexistence with established scar helps demonstrate temporal heterogeneity.

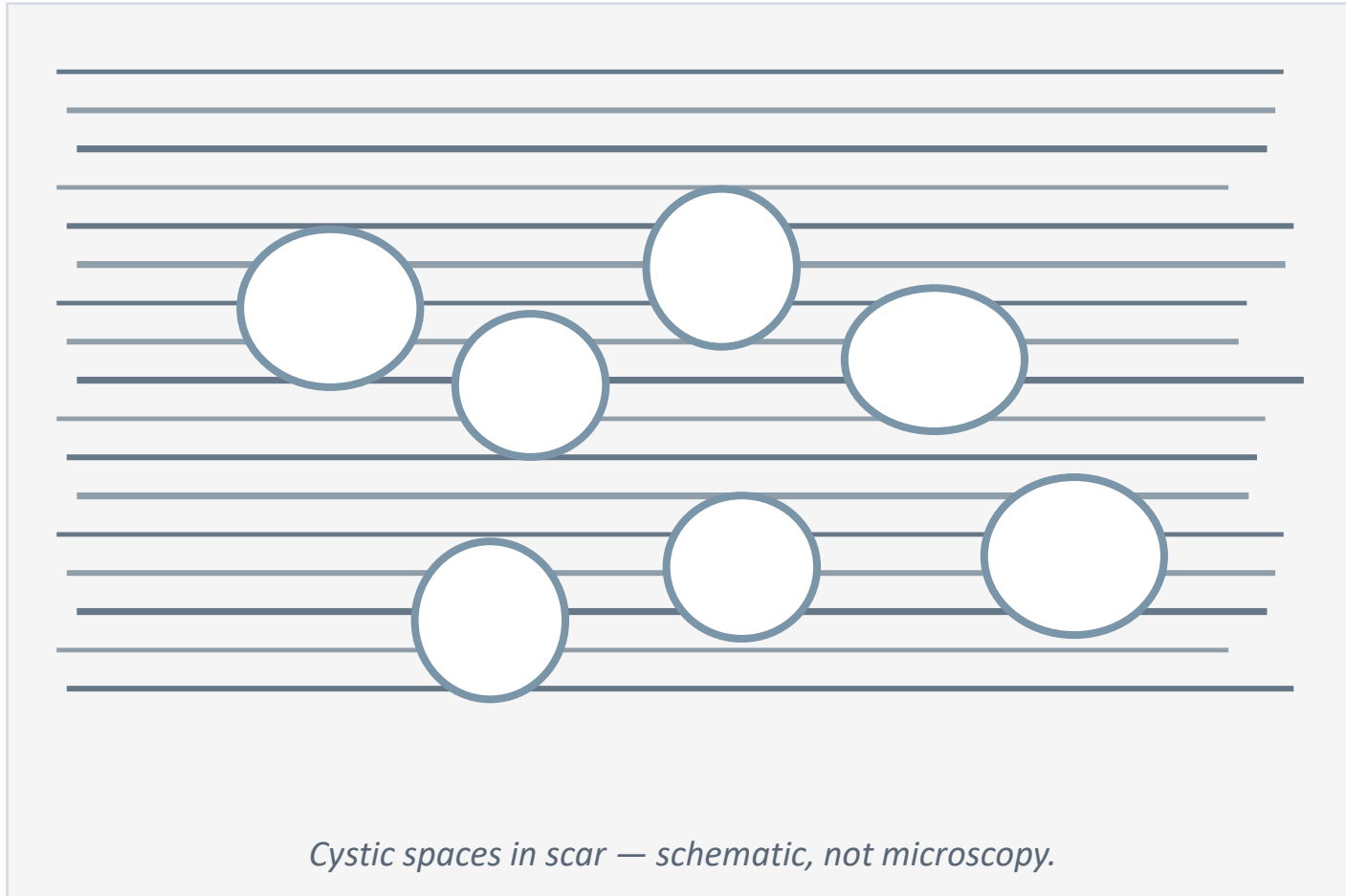
Early cellular lesion evolves toward dense scar



Simplified morphologic progression; UIP contains multiple stages simultaneously.

Interpretation is mechanistic and conceptual; Scale and timing are schematic.

Honeycomb fibrosis marks architectural destruction



Morphologic interpretation

- Dense fibrosis destroys native alveolar architecture.
- Residual cystic spaces form within remodeled fibrotic lung.
- The term refers to end-stage structural remodeling, not true normal alveoli.

Honeycomb spaces develop an epithelial lining

The cystic spaces can be lined by hyperplastic type II pneumocytes or bronchiolar epithelium.

- Epithelial lining persists despite loss of normal alveolar structure.
- Replacement-type lining differs from healthy thin gas-exchange septa.
- The surrounding collagenous scar is central to identification of honeycombing.

Inflammation is present but usually not dominant

- UIP fibrotic areas may contain mild to moderate inflammatory infiltrates.
- Lymphocytes predominate; Plasma cells and granulocytes may be admixed.
- The principal defining lesion is fibrosis, not diffuse inflammatory consolidation.
- Interpret the infiltrate in combination with spatial and temporal pattern.

Other changes may accompany UIP fibrosis

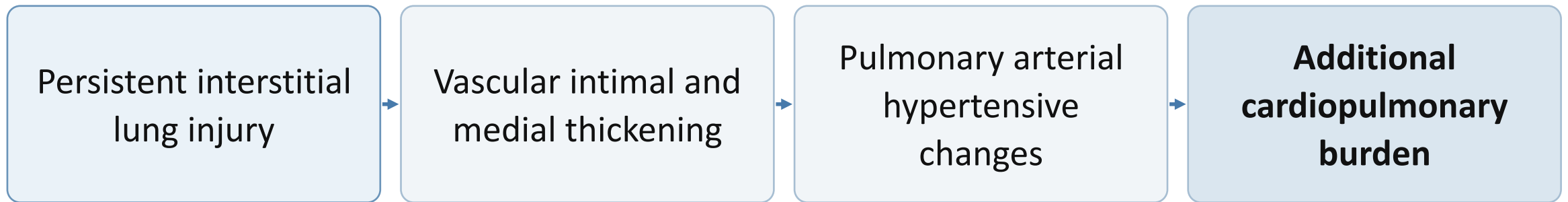
- Focal squamous metaplasia may accompany epithelial remodeling.

- Smooth-muscle hyperplasia may be encountered in fibrotic regions.

- Pulmonary vascular changes can include arterial intimal fibrosis and medial thickening.

- These are associated findings; They do not replace the core diagnostic pattern.

Pulmonary arterial remodeling accompanies advanced disease



Vascular morphology without requiring a specific hemodynamic cutoff.

Interpretation is mechanistic and conceptual; Scale and timing are schematic.

Acute exacerbation overlays an established UIP background

Underlying chronic UIP

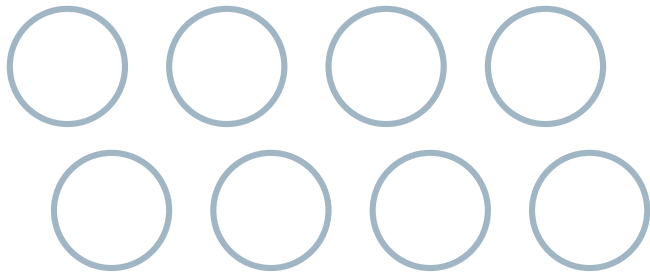
- Patchy dense fibrosis
- Fibroblastic foci and honeycombing
- Spatial and temporal heterogeneity

Superimposed acute process

- Diffuse alveolar damage (DAD)
- Abrupt additional alveolar injury
- May accompany rapid clinical deterioration

Integrated histologic recognition of UIP

Preserved lung



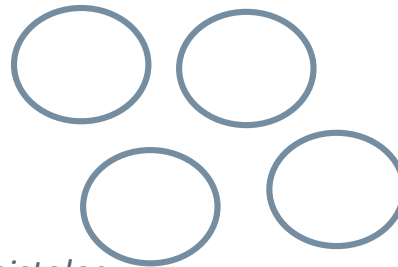
Fibroblastic focus



Dense scar



Honeycomb change



Schematic — not histology.

Morphologic interpretation

- Patchy interstitial dense fibrosis.
- Normal lung beside destroyed architecture.
- Fibroblastic foci alongside old scar.
- Honeycomb cystic spaces in advanced areas.

Adequate sampling matters in advanced fibrosis

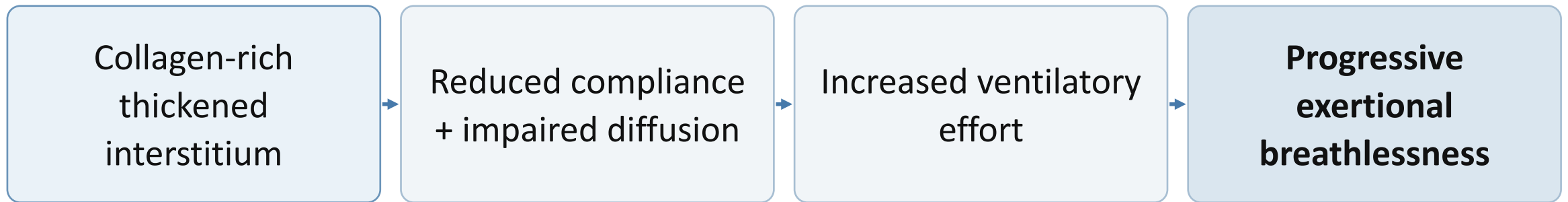
Dense fibrosis and fibroblastic foci can remain identifiable even in advanced IPF, provided sampling is adequate.

- Sampling only one fibrotic region may obscure spatial variation.
- Recognizing different lesion ages requires architectural context.
- Interpret an individual tissue sample within the overall clinical and radiologic phenotype.

Symptoms begin insidiously

- Progressive exertional dyspnea is a typical presenting complaint.
- Cough is commonly dry rather than prominently productive.
- Gradual onset is consistent with accumulating parenchymal fibrosis.
- Many patients are between 55 and 75 years at presentation account.

Stiff lung and impaired diffusion explain dyspnea



Mechanistic integration of the source pathology and restrictive physiologic pattern.

Interpretation is mechanistic and conceptual; Scale and timing are schematic.

Late clinical signs mark significant disease

- Hypoxemia may develop as gas exchange becomes compromised.

- Cyanosis and digital clubbing occur late in the described clinical course.

- End-inspiratory crackles are typical of chronic interstitial lung disease.

- Absence of wheezing helps distinguish the restrictive phenotype from classic obstruction.

Pulmonary function reflects restriction

Expected restrictive changes

- Reduced lung volumes / forced vital capacity
- Reduced lung compliance
- Reduced diffusion capacity

Relation to obstruction

- FEV₁/FVC generally remains normal in pure restriction
- The primary pathology is interstitial, not airway occlusion
- Clinical overlap still requires diagnostic assessment

Clinical progression varies between patients

More usual trajectory

- Gradually worsening exertional dyspnea
- Progressive pulmonary functional limitation
- Eventually respiratory failure

Rapid deterioration

- Acute exacerbation may occur
- Diffuse alveolar damage can be superimposed
- An individual trajectory is difficult to predict

Prognosis is serious but individually unpredictable

A median survival of approximately 3.8 years after diagnosis in its source discussion.

- This is a textbook population summary, not an individual prediction.
- A slowly progressive course and sudden acute exacerbations can both occur.
- Timing, case mix and modern management may affect estimates across cohorts.

Distinguishing UIP from nonspecific interstitial pneumonia

UIP / typical IPF pattern

- Temporal heterogeneity: Early foci + old scar
- Fibroblastic foci and honeycombing
- Typically worse prognosis

NSIP pattern

- More temporally uniform lesions
- Fibroblastic foci and honeycombing absent description
- Often a more favorable prognosis

Distinguishing UIP from organizing pneumonia

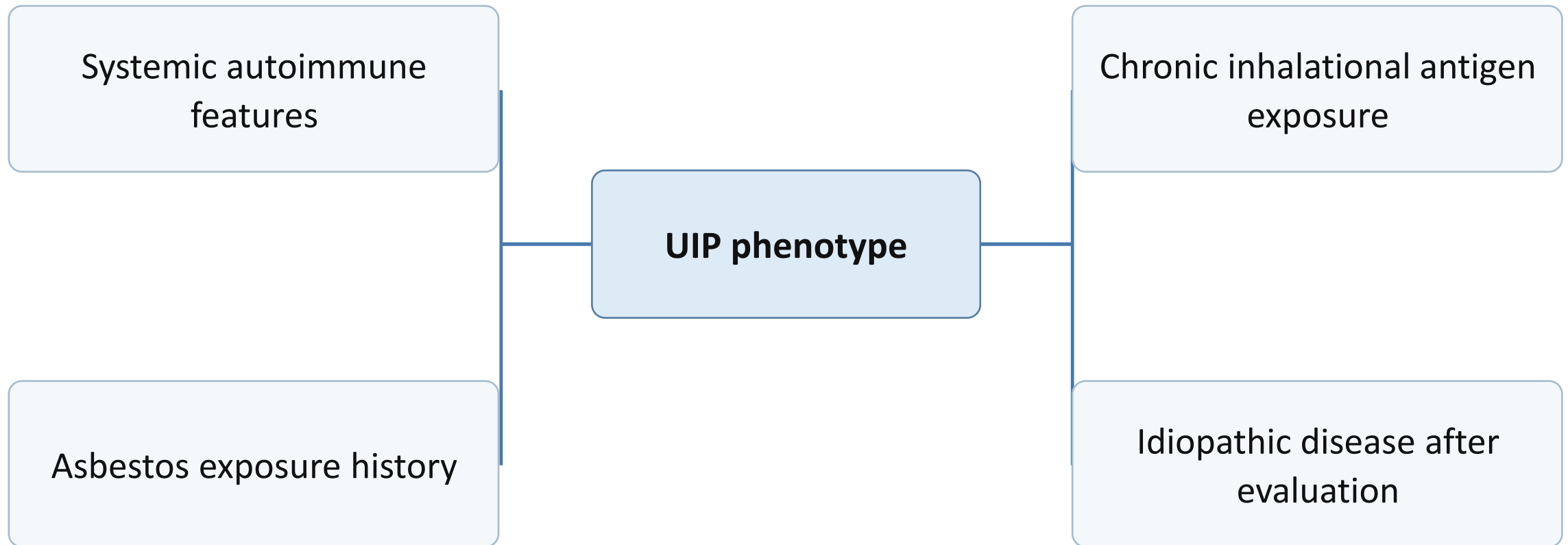
UIP pattern

- Interstitial collagenous fibrosis
- Distorted or destroyed lung architecture
- Fibroblastic foci and honeycombing

Organizing pneumonia pattern

- Loose polypoid plugs in distal airspaces (Masson bodies)
- Underlying lung architecture preserved
- Honeycombing and interstitial scar not defining features

A UIP pattern demands assessment of alternative causes



These categories must be distinguished clinically, by laboratory information and sometimes histology.

Therapeutic implications of a fibrosing disorder

Antifibrotic targeted therapy as slowing progression, rather than reversing established architectural loss.

- One reported strategy targets tyrosine kinase signaling.
- A second antifibrotic strategy is described in the source as antagonism of TGF- β signaling.
- Lung transplantation is described as the only definitive therapy.

Clinical case: Interpret the pattern

An older adult develops progressive exertional dyspnea and dry cough. A fibrotic lung sample has preserved airspaces adjacent to dense scar, fibroblastic foci and honeycomb remodeling.

What histologic pattern is being described?

Instructor answer and interpretive rationale are in speaker notes.

Clinical case: Do not equate UIP with IPF

A patient with a systemic autoimmune disease has a lung biopsy showing patchy dense fibrosis, fibroblastic foci and honeycomb cysts.

Can this be labeled IPF solely from histology?

Instructor answer and interpretive rationale are in speaker notes.

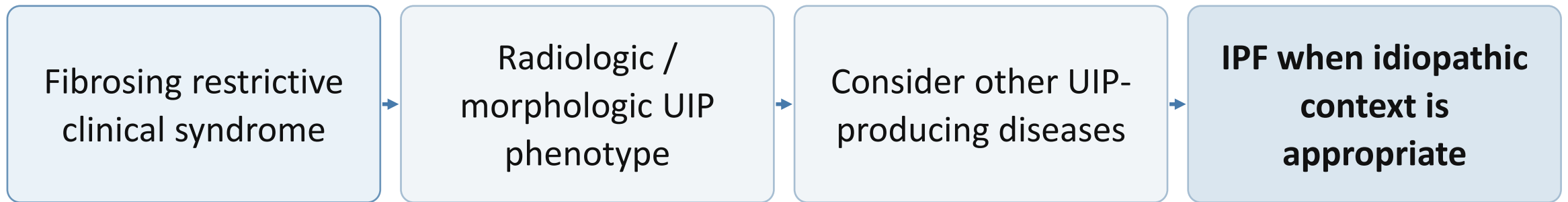
Morphology case: Spatial versus temporal heterogeneity

In one resection, a relatively normal region lies next to dense scar. Elsewhere a cellular fibroblastic focus lies alongside old acellular fibrosis.

Identify the two different heterogeneities.

Instructor answer and interpretive rationale are in speaker notes.

Integrated diagnostic reasoning



Conceptual synthesis; Not a substitute for a validated practice guideline.

Interpretation is mechanistic and conceptual; Scale and timing are schematic.

The essential morphologic signature

UIP combines a patchwork of old and active fibrosis with destruction of the normal alveolar scaffold.

- Spatial heterogeneity: Relatively preserved lung beside dense scar.
- Temporal heterogeneity: Fibroblastic foci beside mature fibrosis.
- Honeycomb fibrosis: Cystic remodeled spaces within destroyed architecture.
- These patterns require correlation before diagnosing idiopathic disease.

Five points to retain

- IPF is a progressive clinical disorder; UIP is its characteristic, nonexclusive morphologic pattern.
- Recurrent epithelial injury interacts with aging and genetic susceptibility.
- Activated fibroblasts deposit collagen; mechanistic details remain incompletely established.
- Patchy fibrosis, fibroblastic foci and honeycombing are the diagnostic morphologic triad.
- Restrictive physiology and variable progression follow architectural remodeling.