How to diagnose IPF

The diagnosis of idiopathic pulmonary fibrosis (IPF) requires exclusion of known causes of interstitial lung disease (ILD), plus confirmation of specific radiological and/or histological patterns.[1]

Patients with the key clinical features of IPF should be referred to a pulmonologist who will assess pulmonary function.[1-3] *If the pulmonologist suspects ILD, then a high-resolution computed tomography (HRCT) scan without contrast agent should be requested; where required, a lung biopsy may then be carried out to provide further diagnostic information.*[1]

A multidisciplinary discussion of patient cases by a pulmonologist, radiologist and pathologist with expertise in ILD has been shown to improve the accuracy of IPF diagnosis.[1,4,5]

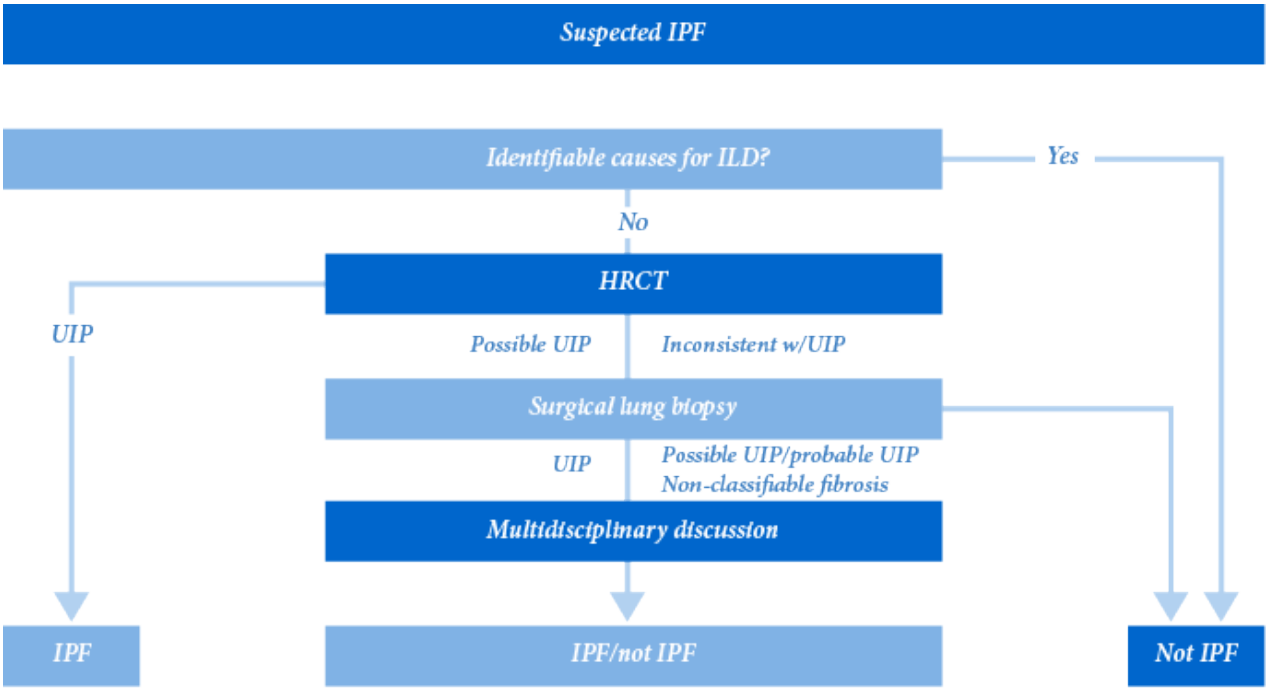
For a series of interactive educational presentations, please see 'Tips and Tricks in Diagnosis and Treatment of Idiopathic Pulmonary Fibrosis' hosted by PeerVoice

Diagnostic criteria and algorithm

Diagnosis of IPF based on the ATS/ERS/JRS/ALAT evidence-based guidelines requires[1]:

1. Exclusion of other known causes of ILD (e.g. domestic and occupational environmental exposures, connective tissue disease, drug toxicity)
2. The presence of a usual interstitial pneumonia (UIP) pattern on HRCT
3. Where a possible UIP pattern or a pattern inconsistent with UIP is found on HRCT, a biopsy should be performed and the results should be discussed by a multidisciplinary team (MDT). A diagnosis of IPF requires specific combinations of HRCT and surgical lung biopsy patterns

Diagnostic algorithm for IPF[1]



For further details on differential diagnosis of ILD see *Differential diagnosis*

HRCT

HRCT has greatly increased the accuracy of IPF diagnosis and is now an essential part of the diagnostic pathway in IPF as it is able to detect pathophysiological changes in lung tissue that cannot be seen on a standard chest X-ray.[1]
For further details on HRCT imaging, see *HRCT*

Biopsy

Surgical lung biopsy

In the absence of a definite UIP pattern on HRCT, a surgical lung biopsy should be considered.[1] With results of both an HRCT and lung biopsy, IPF can then be diagnosed by specific combinations of patterns seen across the two methods.[1]

It is also important to recognise the mortality risk associated with surgical lung biopsy and to ensure patients are carefully assessed for the procedure.[6,7]

Transbronchial cryobiopsy

Transbronchial cryobiopsy is a new bioptic approach that is being increasingly used as an alternative to surgical lung biopsy to diagnose fibrosing ILD; it involves using a cryoprobe to obtain a lung tissue sample through a bronchoscope.[8,9]

For further details on the use and safety of this technique, see *Biopsy.*

Exploratory diagnostic tests: serum and BAL markers

Other potential diagnostic measures include serum and bronchoalveolar lavage (BAL) markers, although there are limited data on their predictive value, and they are currently largely unavailable for routine clinical use.[1]

Studies have shown that elevated serum levels of KL-6,[10-12] serum CCL18[13] and surfactant protein A and D[14-16] are associated with morbidity/mortality in patients with IPF.

Studies of plasma and BAL matrix metalloproteinase (MMP) levels suggest that MMP1 and MMP7 are increased in patients with IPF; also, MMP7 levels may correlate with disease severity.[12,17] The presence of circulating fibrocytes (mesenchymal progenitor cells) has also been associated with worse short-term survival.[18]

Candidate molecular biomarkers in IPF

Potential biomarkers for IPF19

- A number of blood proteins show potential as future biomarkers in IPF

Candidate biomarker	*Proposed role*	*Comments*
SP-A, SP-D	Diagnosis, Prognosis	Increased levels predict worse survival
KL-6, MUC1	Diagnosis, Prognosis	Increased levels predict worse survival and increased risk of AEx
cCK18	Diagnosis	Higher levels in IPF; no association with IPF severity or outcome
CCL18	Prognosis	Baseline concentration >150 ng/mL associated with higher mortality
CXCL13	Prognosis	Elevated levels associated with PH, AEx and worse survival
Anti-HPS70 IgG	Prognosis	IgG positivity associated with functional decline and worse survival
Periostin	Prognosis	Higher levels in IPF and correlation with disease progression
Fibulin-1	Diagnosis, Prognosis	Elevated levels in IPF and correlation with disease progression
MMP-1, MMP-7	Diagnosis, Prognosis	Higher levels associated with disease progression and worse survival
IL-8, ICAM-1	Prognosis	High concentrations associated with worse survival
LOXL2	Prognosis	Higher levels associated with increased risk for disease progression
ECM-neoepitopes	Prognosis	Increased concentrations associated with disease progression

Diagnosis *Prognosis*

AEx, acute exacerbation; cCK18, caspase-cleaved cytokeratin-18; ECM, extracellular matrix; HSP, heat-shock protein; MMP, matrix metalloproteinase; PH, pulmonary hypertension; SP, surfactant protein.

References

1. Raghu G, et al. *Am J Respir Crit Care Med.* 2011;183:788–824. **2.** NICE Clinical Guidelines 163: Idiopathic Pulmonary Fibrosis. June 2013. **3.** NICE Clinical Pathway: Idiopathic Pulmonary Fibrosis overview. April 2015. **4.** Flaherty KR, et al. *Am J Respir Crit Care Med.* 2004;170:904–910. **5.** Cottin V, Cordier JF. *Eur Respir J.* 2012;40:519–521. **6.** Kaarteenaho R. *Respir Res.* 2013;14:43. **7.** Utz JP, et al. *Eur Respir J.* 2001;17:175–179. **8.** Poletti V, et al. *Respirology*. 2016;21:44–50. **9.** Tomassetti S, et al. *Am J Respir Crit Care Med.* 2016;193:745–752. **10.** Kohno N, et al. *Chest*. 1989;96:68–73. **11.** Yokoyama A, et al. *Respirology.* 2006;11:164–168. **12.** Hamai K, et al. *Dis Markers.* 2016;May 17:Epub. **13.** Prasse A, et al. *Am J Respir Crit Care Med*. 2009;179:717–723. **14.** Greene KE, et al. *Eur Respir J*. 2002;19:439–446. **15.** Kinder BW, et al. *Chest*. 2009;135:1557–1563. **16.** Takahashi H, et al. *Am J Respir Crit Care Med.* 2000;162:1109–1114. **17.** Rosas IO, et al. *PLoS Med.* 2008;5:e93. **18.** Moeller A, et al. *Am J Respir Crit Care Med.* 2009;170:588–594. **19.** Daccord C, et al. *F1000 Research.* 2016;5:1046.