ΠΝΕΥΜΟΝΙΚΗ ΑΡΤΗΡΙΑΚΗ ΥΠΕΡΤΑΣΗ

ΔΙΑΓΝΩΣΤΙΚΗ ΔΙΕΡΕΥΝΗΣΗ

Άρης Μπεχλιούλης
Β΄ Καρδιολογική Κλινική
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ΟΡΙΣΜΟΣ – ΠΩΣ ΤΙΘΕΤΑΙ Η ΔΙΑΓΝΩΣΗ?

Haemodynamic definitions of pulmonary hypertension

Definition	Characteristics*	Clinical group(s)[b]
PH	PAPm ≥25 mmHg	All
Pre-capillary PH	PAPm ≥25 mmHg PAWP ≤15 mmHg	1. Pulmonary arterial hypertension 3. PH due to lung diseases 4. Chronic thromboembolic PH 5. PH with unclear and/or multifactorial mechanisms
Post-capillary PH	PAPm ≥25 mmHg PAWP >15 mmHg	2. PH due to left heart disease 5. PH with unclear and/or multifactorial mechanisms
Isolated post-capillary PH (Ipc-PH)	DPG <7 mmHg and/or PVR ≤3 WU[c]	
Combined post-capillary and pre-capillary PH (Cpc-PH)	DPG ≥7 mmHg and/or PVR >3 WU[c]	

CO = cardiac output; DPG = diastolic pressure gradient (diastolic PAP - mean PAWP); mPAP = mean pulmonary arterial pressure; PAWP = pulmonary arterial wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; WU = Wood units.

[a]All values measured at rest; see also section 7.
[b]According to Table 4.
[c]Wood Units are preferred to dynes.s.cm^{-5}.

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European Heart Journal 2016:37;67–119 -doi:10.1093/eurheartj/ehv317
European Respiratory Journal 2015 46: 903-975;

PAH Hemodynamic Definitions Have Changed Over Time

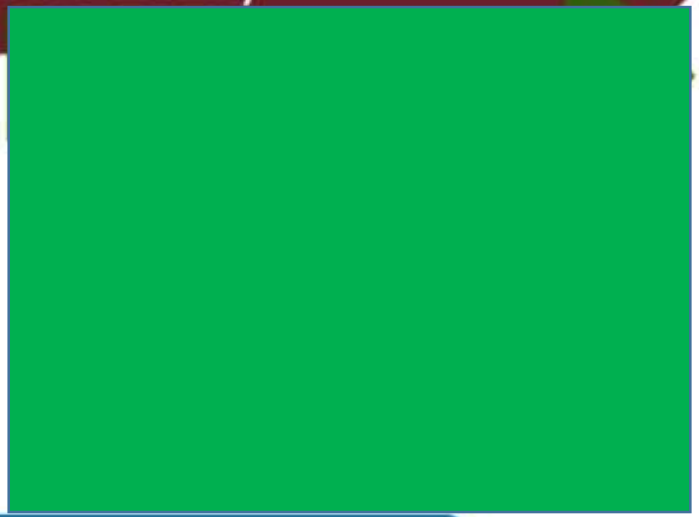
- The original definition of mPAP ≥ 25 mmHg was a conservative cut-off value that allowed physicians to discriminate severe PH from other forms of PH

Arbitrary Definition (1973)

- Mean PAP ≥ 25 mmHg at rest measured by RHC

Evolving Definition (1998-2013)

- Mean PAP ≥ 25 mmHg or > 30 mmHg during exercise
- Normal left heart filling pressure (PAWP ≤ 15 mmHg)
- PVR ≥ 3 Wood units



How to differentiate between normal and abnormal mPAP?

Simonneau G, et al. *Eur Respir J.* 2018. [Epub ahead of print]; Hoeper MM. *Eur Respir J.* 2009;34:790-791.

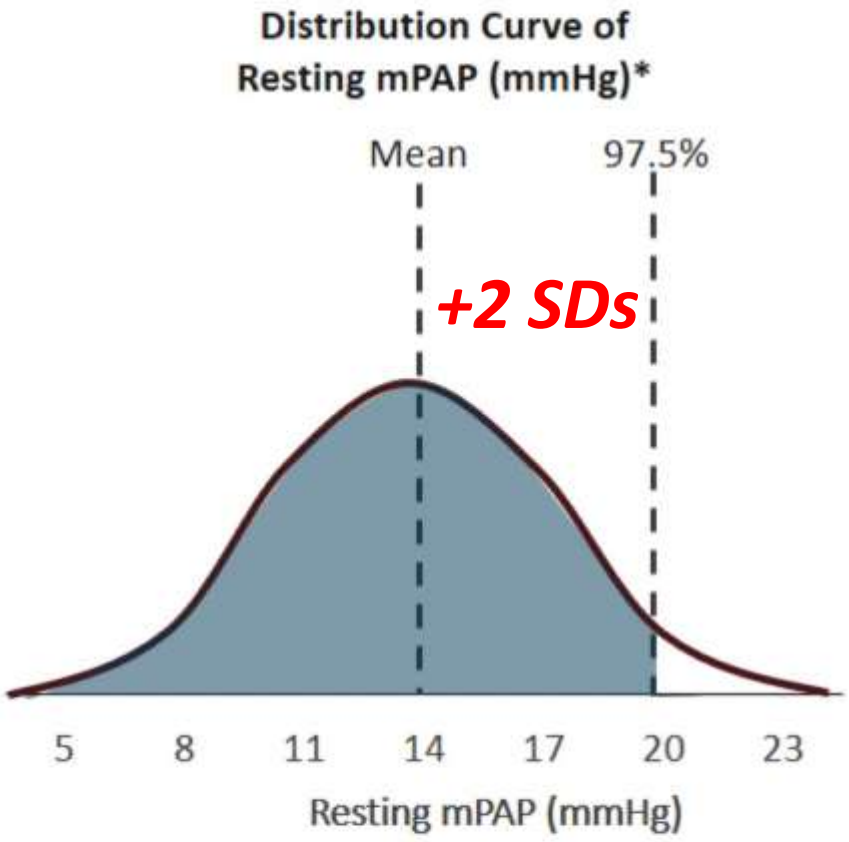
Should we redefine PH and pre-capillary PH?

Exploring the New Hemodynamic Definition

- Normal mPAP at rest:

  14.0 ± 3.3 mmHg[a]

- PAP elevation can occur due to increases[b]:
  - Cardiac output
  - PAWP in left heart disease
  - Left-to-right cardiac shunts
  - Hyperviscosity
  - PVD associated with structural changes of small pulmonary arteries



New threshold for abnormal PAP:
mPAP ≥ 20 mmHg

*For demonstration.

a. Kovacs G, et al. *Eur Respir J.* 2009;34:888-894; b. Simonneau G, et al. *Eur Respir J.* 2018. [Epub ahead of print].

Borderline mPAP (21 to 24 mmHg) is Associated With Increased Risk of PAH

Study	Results
228 patients with systemic sclerosis and baseline mPAP 21 to 24 mmHg	Patients with borderline mPAP were more likely to develop increased PVR and PAH ($P < .001$), HR 3.7
21 patients with systemic sclerosis and baseline mPAP 21 to 24 mmHg	At 3-year follow up: PVR and mPAP increased and 7 patients developed overt PH
547 patients with unexplained dyspnea or risk of PAH	Over 46 months follow up: 29% of patients died. Patients with mPAP 21 to 24 or ≥ 25 mmHg had poorer survival than mPAP ≤ 15 mmHg

mPAP ≥ 20 mmHg:
More likely to develop PAH, increased PVR, poor survival

Simonneau G, et al. *Eur Respir J.* 2018. [Epub ahead of print].

Should we redefine PH and pre-capillary PH?

- Cut-off value of PVR ⩾3 WU is also quite arbitrary
- Some recent data suggest that **PVR >2 WU** → In this sense, the use of a cut-off value of PVR ⩾3 WU is conservative, suggesting the presence of a manifest pre-capillary PH.
- ***PVR ⩾3 WU*** → clinically relevant in different clinical situations → presence of a significant PVD e.g. threshold value for which the correction of congenital systemic-to-pulmonary shunts becomes questionable, poor survival after heart transplantation

New Definitions, More Patients Will Benefit

Hemodynamic Definitions of PH	
Definitions	**Characteristics**
Pre-capillary PH	• mPAP > 20 mmHg • PAWP ≤ 15 mmHg – PVR ≥ 3 WU
IpcPH	• mPAP > 20 mmHg • PAWP > 15 mmHg – PVR < 3 WU
CpcPH	• mPAP > 20 mmHg • PAWP > 15 mmHg – PVR ≥ 3 WU

- Caveat: Data from clinical treatment trials have been studied in patients with a mPAP ≥25 mmHg
  - Data cannot be applied to patients with lower mPAP
- More patients will benefit with new criteria
  - Scleroderma patient with mPAP 20 to 25 mmHg
  - CTEPH

Simonneau G, et al. *Eur Respir J.* 2018. [Epub ahead of print].

Comprehensive clinical classification of pulmonary hypertension

1. Pulmonary arterial hypertension

1.1 Idiopathic

1.2 Heritable
- 1.2.1 BMPR2 mutation
- 1.2.2 Other mutations

1.3 Drugs and toxins induced

1.4 Associated with:
- 1.4.1 Connective tissue disease
- 1.4.2 human immunodeficiency virus (HIV) infection
- 1.4.3 Portal hypertension
- 1.4.4 Congenital heart disease (Table 5)
- 1.4.5 Schistosomiasis

1'. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

1'.1 Idiopathic

1'.2 Heritable
- 1'.2.1 EIF2AK4 mutation
- 1'.2.2 Other mutations

1'.3 Drugs, toxins and radiation induced

1'.4 Associated with:
- 1'.4.1 Connective tissue disease
- 1'.4.2 HIV infection

1''. Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension due to left heart disease

2.1 Left ventricular systolic dysfunction

2.2 Left ventricular diastolic dysfunction

2.3 Valvular disease

2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

2.5 Congenital/acquired pulmonary veins stenosis

3. Pulmonary hypertension due to lung diseases and/or hypoxia

3.1 Chronic obstructive pulmonary disease

3.2 Interstitial lung disease

3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern

3.4 Sleep-disordered breathing

3.5 Alveolar hypoventilation disorders

3.6 Chronic exposure to high altitude

3.7 Developmental lung diseases (Web Table III)

4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions

4.1 Chronic thromboembolic pulmonary hypertension

4.2 Other pulmonary artery obstructions
- 4.2.1 Angiosarcoma
- 4.2.2 Other intravascular tumors
- 4.2.3 Arteritis
- 4.2.4 Congenital pulmonary arteries stenoses
- 4.2.5 Parasites (hydatidosis)

5. Pulmonary hypertension with unclear and/or multifactorial mechanisms

5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy

5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis

5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders

5.4 Others: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

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European Heart Journal 2016:37;67–119 -doi:10.1093/eurheartj/ehv317
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Clinical classification of pulmonary arterial hypertension associated with congenital heart disease

1. Eisenmenger's syndrome

Includes all large intra- and extra-cardiac defects which begin as systemic-to-pulmonary shunts and progress with time to severe elevation of PVR and to reversal (pulmonary-to-systemic) or bidirectional shunting; cyanosis, secondary erythrocytosis, and multiple organ involvement are usually present.

2. PAH associated with prevalent systemic-to-pulmonary shunts

- Correctable[a]
- Non-correctable

Includes moderate to large defects; PVR is mildly to moderately increased, systemic-to-pulmonary shunting is still prevalent, whereas cyanosis at rest is not a feature.

3. PAH with small/coincidental[b] defects

Marked elevation in PVR in the presence of small cardiac defects (usually ventricular septal defects <1 cm and atrial septal defects <2 cm of effective diameter assessed by echo), which themselves do not account for the development of elevated PVR; the clinical picture is very similar to idiopathic PAH. Closing the defects is contra-indicated.

4. PAH after defect correction

Congenital heart disease is repaired, but PAH either persists immediately after correction or recurs/develops months or years after correction in the absence of significant postoperative haemodynamic lesions.

PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance.
[a]With surgery or intravascular percutaneous procedure.
[b]The size applies to adult patients. However, also in adults the simple diameter may be not sufficient for defining the haemodynamic relevance of the defect, and also the pressure gradient, the shunt size and direction, & the pulmonary to systemic flows ratio should be considered
(Web Table II on the web at; www.escardio.org/guidelines).

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Updated Clinical Classification of PH

1 PAH
- 1.1 Idiopathic PAH
- 1.2 Heritable PAH
- 1.3 Drug- and toxin-induced PAH
- 1.4 PAH associated with:
  - 1.4.1 Connective tissue disease
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
- 1.5 PAH long-term responders to calcium channel blockers
- 1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement
- 1.7 Persistent PH of the newborn syndrome

2 PH due to left heart disease
- 2.1 PH due to heart failure with preserved LVEF
- 2.2 PH due to heart failure with reduced LVEF
- 2.3 Valvular heart disease
- 2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH

3 PH due to lung diseases and/or hypoxia
- 3.1 Obstructive lung disease
- 3.2 Restrictive lung disease
- 3.3 Other lung disease with mixed restrictive/obstructive pattern
- 3.4 Hypoxia without lung disease
- 3.5 Developmental lung disorders

4 PH due to pulmonary artery obstructions
- 4.1 Chronic thromboembolic PH
- 4.2 Other pulmonary artery obstructions

5 PH with unclear and/or multifactorial mechanisms
- 5.1 Haematological disorders
- 5.2 Systemic and metabolic disorders
- 5.3 Others
- 5.4 Complex congenital heart disease

Group 1.3

TABLE 3 Updated classification of drugs and toxins associated with PAH

Definite	Possible
Aminorex	Cocaine
Fenfluramine	Phenylpropanolamine
Dexfenfluramine	L-tryptophan
Benfluorex	St John's wort
Methamphetamines	Amphetamines
Dasatinib	Interferon-α and -β
Toxic rapeseed oil	Alkylating agents
	Bosutinib
	Direct-acting antiviral agents against hepatitis C virus
	Leflunomide
	Indirubin (Chinese herb Qing-Dai)

Group 1.5

TABLE 4 Definitions of acute and long-term response

Acute pulmonary vasoreactivity[#] for patients with idiopathic, hereditable or drug-induced PAH	Reduction of mPAP ⩾10 mmHg to reach an absolute value of mPAP ⩽40 mmHg Increased or unchanged cardiac output
Long-term response to CCBs	New York Heart Association Functional Class I/II With sustained haemodynamic improvement (same or better than achieved in the acute test) after at least 1 year on CCBs only

PAH: pulmonary arterial hypertension; mPAP: mean pulmonary arterial pressure; CCB: calcium channel blocker. [#]: nitric oxide (10–20 ppm) is recommended for performing vasoreactivity testing, but *i.v.* epoprostenol, *i.v.* adenosine or inhaled iloprost can be used as alternatives.

Group 1.6

TABLE 5 Signs evocative of venous and capillary (pulmonary veno-occlusive disease/pulmonary capillary haemangiomatosis) involvement

Pulmonary function tests	Decreased D_{LCO} (frequently <50%) Severe hypoxaemia
Chest HRCT	Septal lines Centrilobular ground-glass opacities/nodules Mediastinal lymph node enlargement
Response to PAH therapy	Possible pulmonary oedema
Genetic background	Biallelic *EIF2AK4* mutations
Occupational exposure	Organic solvent (trichloroethylene)

- Significant pulmonary venous and/or capillary involvement has been reported in many conditions which are known causes of PAH, such as systemic sclerosis
- ***PAH and PVOD belong to a spectrum of PVDs*** rather than representing two clear-cut distinct entities

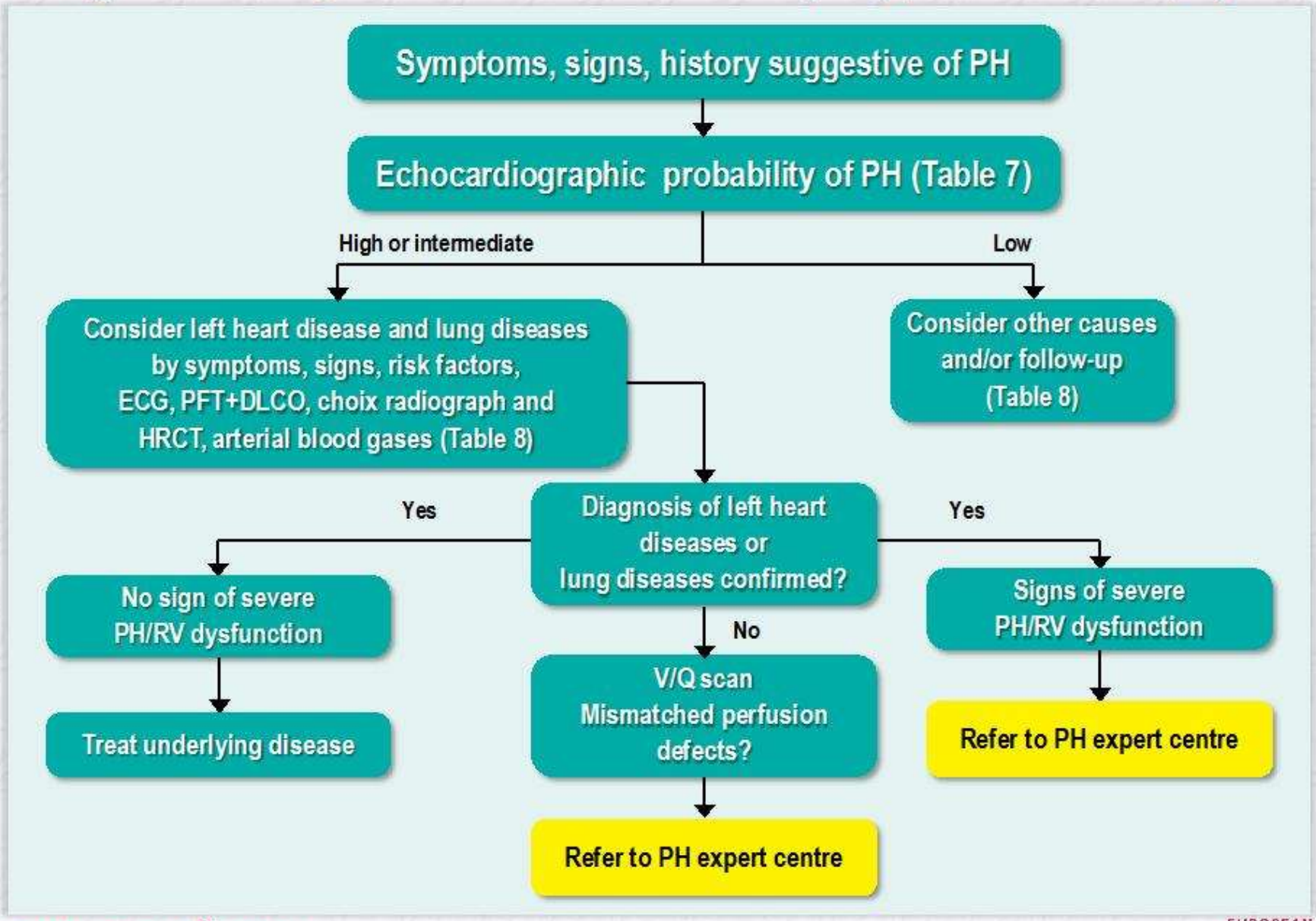
Group 5

- Chronic haemolytic anaemia is clearly associated with an increased risk of PH
- ***Sickle cell disease (SCD)*** → frequently multifactorial, including elevated CO, LHD, thromboembolic disease, altered blood viscosity and PVD due to endothelial dysfunction, mainly due to nitric oxide depletion - More recently, restrictive cardiomyopathy has been recognised
- ***β-thalassaemia*** → prevalence of PH similarly to SCD - pre-capillary PH in 2.1% of the cases, post-capillary profile in 0.3% - Older age and splenectomy were clear risk factors associated with PH

PAH – Diagnostic algorithm

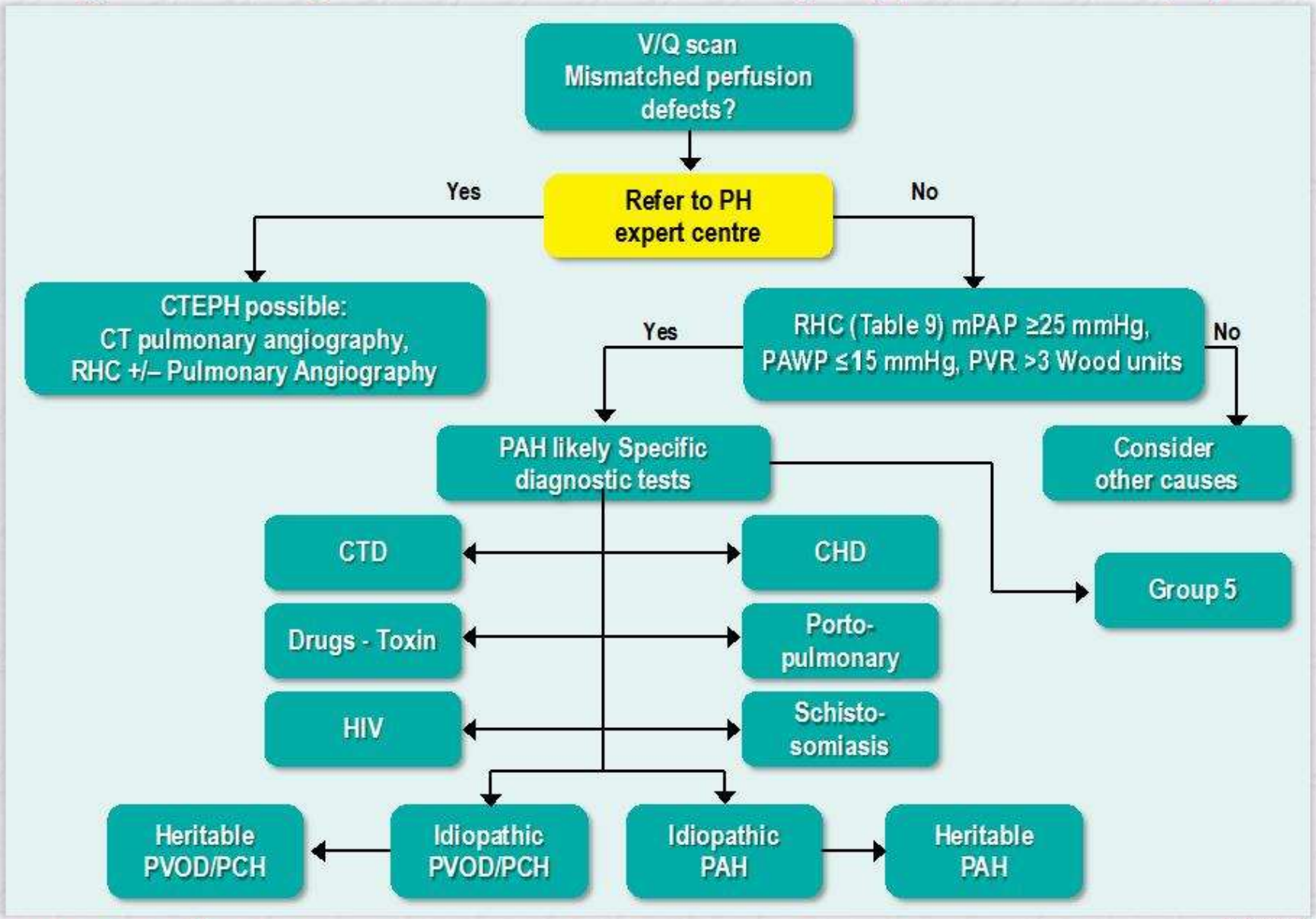
- There has been no meaningful decrease in the time from symptom onset to diagnosis of PAH in the past 20 years
- The diagnostic algorithm and guidelines for screening at-risk groups have been modified (2018), balancing the benefits of earlier diagnosis and disease recognition against the economic healthcare burden of additional screening and increased referrals to PH centres
- PH due to parenchymal, cardiac, thromboembolic and other diseases (diagnostic groups 2, 3, 4 and 5, respectively) is associated with worse outcomes and limited treatment options, resulting in referral of these patients to PH centres.

Diagnostic Algorithm for Pulmonary Hypertension (1)



European Heart Journal 2016:37;67–119 -doi:10.1093/eurheartj/ehv317
European Respiratory Journal 2015 46: 903-975;

Diagnostic Algorithm for Pulmonary Hypertension (2)



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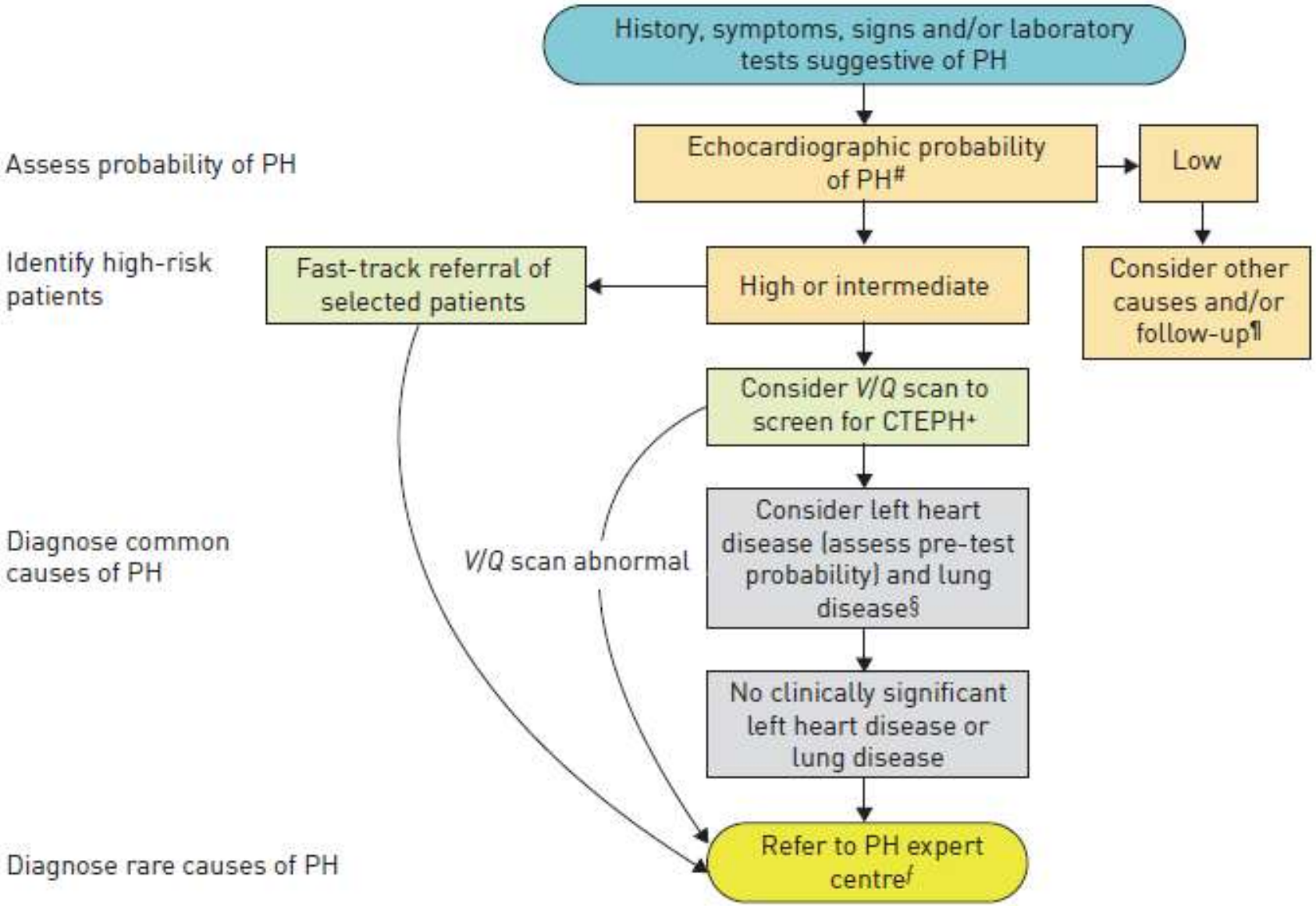
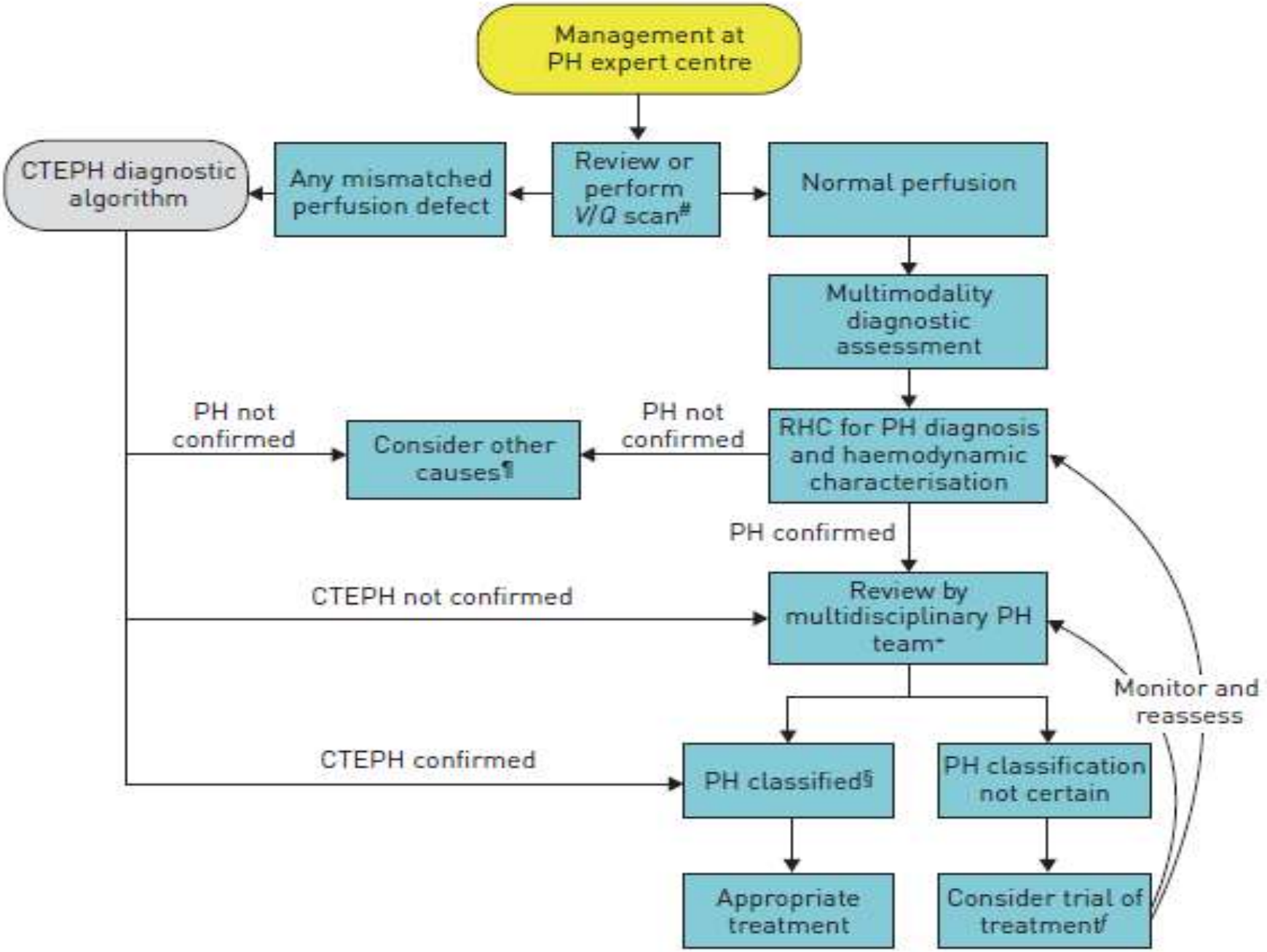

History, symptoms, signs and/or laboratory tests suggestive of PH
Assess probability of PH
Echocardiographic probability of PH#
Low
Identify high-risk patients
Fast-track referral of selected patients
High or intermediate
Consider other causes and/or follow-up¶
Consider V/Q scan to screen for CTEPH+
Diagnose common causes of PH
V/Q scan abnormal
Consider left heart disease (assess pre-test probability) and lung disease§
No clinically significant left heart disease or lung disease
Diagnose rare causes of PH
Refer to PH expert centre‡


Management at PH expert centre
Review or perform V/Q scan#
Any mismatched perfusion defect
CTEPH diagnostic algorithm
Normal perfusion
Multimodality diagnostic assessment
RHC for PH diagnosis and haemodynamic characterisation
PH not confirmed
Consider other causes¶
PH not confirmed
PH confirmed
Review by multidisciplinary PH team+
CTEPH not confirmed
CTEPH confirmed
PH classified§
PH classification not certain
Appropriate treatment
Consider trial of treatment
Monitor and reassess

PAH - Diagnosis

Clinical suspicion of PH

***Symptoms* -** Non-specific

- Exertional dyspnoea, fatigue, weakness, chest pain, light-headedness/syncope and, less frequently, cough.
- Progressive right-sided heart failure (oedema, ascites, abdominal distension) occurs in later or more accelerated disease.
- Rarely, haemoptysis, Ortner's syndrome/hoarseness (unilateral vocal chord paralysis) and arrhythmias

Physical findings

Augmented second heart sound, right ventricular lift, jugular venous distension, hepatojugular reflux, ascites, hepatomegaly and/or splenomegaly, oedema, tricuspid regurgitant or pulmonary regurgitant murmurs, and S3 gallop.

Diagnostic investigations utilised in patients with PH

- Electrocardiogram
- Chest radiograph
- Echocardiography
- Pulmonary function tests and arterial blood gases
- Ventilation/perfusion lung scan
- High-resolution computed tomography, contrast enhanced computed tomography
- Cardiac magnetic resonance imaging
- Blood tests and immunology
- Abdominal ultrasound scan
- Right heart catheterization and vasoreactivity
- Pulmonary Angiography

European Heart Journal 2016:37;67–119 -doi:10.1093/eurheartj/ehv317
European Respiratory Journal 2015 46: 903-975;

Diagnostic strategy

Recommendations	Class	Level
Echocardiography is recommended as a first-line non-invasive diagnostic investigation in case of suspicion of PH.	I	C
Ventilation/perfusion or perfusion lung scan is recommended in patients with unexplained PH to exclude CTEPH.	I	C
Contrast CT angiography of the PA is recommended in the work-up of patients with CTEPH.	I	C
Routine biochemistry, haematology, immunology, HIV testing and thyroid function tests are recommended in all patients with PAH to identify the specific associated condition.	I	C
Abdominal ultrasound is recommended for the screening of portal hypertension.	I	C
Lung function test with DLCO is recommended in the initial evaluation of patients with PH.	I	C
High-resolution CT should be considered in all patients with PH.	IIa	C
Pulmonary angiography should be considered in the work-up of patients with CTEPH.	IIa	C
Open or thoracoscopic lung biopsy is not recommended in patients with PAH.	III	C

European Heart Journal 2016:37;67–119 -doi:10.1093/eurheartj/ehv317
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Echocardiographic probability of pulmonary hypertension in symptomatic patients with a suspicion of pulmonary hypertension according with PTRV & additional signs

Peak tricuspid regurgitation velocity (m/s)	Presence of other echo "PH signs"	Echocardiographic probability of pulmonary hypertension
≤2.8 or not measurable	No	Low
≤2.8 or not measurable	Yes	Intermediate
2.9–3.4	No	
2.9–3.4	Yes	High
>3.4	Not required	

A: The ventricles	B: Pulmonary artery	C: Inferior vena cava and right atrium
Right ventricle/ left ventricle basal diameter ratio >1.0.	Right ventricular outlflow Doppler acceleration time <105 m/sec and/or midsystolic notching.	Inferior cava diameter >21 mm with decreased inspiratory collapse (<50 %with a sniff or <20 %with quiet inspiration).
Flattening of the interventricular septum (left ventricular eccentricity index >1.1 in systole and/or diastole).	Early diastolic pulmonary regurgitation velocity >2.2 m/sec.	Right atrial area (end-systole) >18 cm^2.
	PA diameter >25 mm..	

European Heart Journal 2016:37;67–119 -doi:10.1093/eurheartj/ehv317
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Diagnostic management according to echocardiographic probability of PH in patients with symptoms compatible with PH, with or without risk factors for PAH or CTEPH

Echocardiographic probability of PH	Without risk factors or associated condition for PAH or CTEPH[a]	Class	Level
Low	Allternative diagnosis should be considered	IIa	C
Intermediate	Alternative diagnosis, echo follow-up, shoud be considered	IIa	C
	Further investigation of PH may be recommended[b]	IIb	
High	Further investigation of PH (including RHC[b]) is recommended	I	C
Echocardiographic probability of PH	**With risk factors or associated conditions for PAH or CTEPH[a]**	**Class**	**Level**
Low	Echo follow-up should be considered	IIa	C
Intermediate	Further assessment of PH including RHC should be considered[a]	IIa	B
High	Further investigation of PH[b] including RHC is recommended	I	C

CTEPH = chronic thromboembolic pulmonary hypertension; Echo = echocardiographic; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; RHC = right heart catheterization.

[a]These recommendations do not apply to patients with diffuse parenchymal lung disease or left heart disease;

[b]Depending on the presence of risk factors for PH group 2, 3 or 5. Further investigation strategy may differ depending on whether risk factors/associated conditions suggest higher probability of PAH or CTEPH – see diagnostic algorithm.

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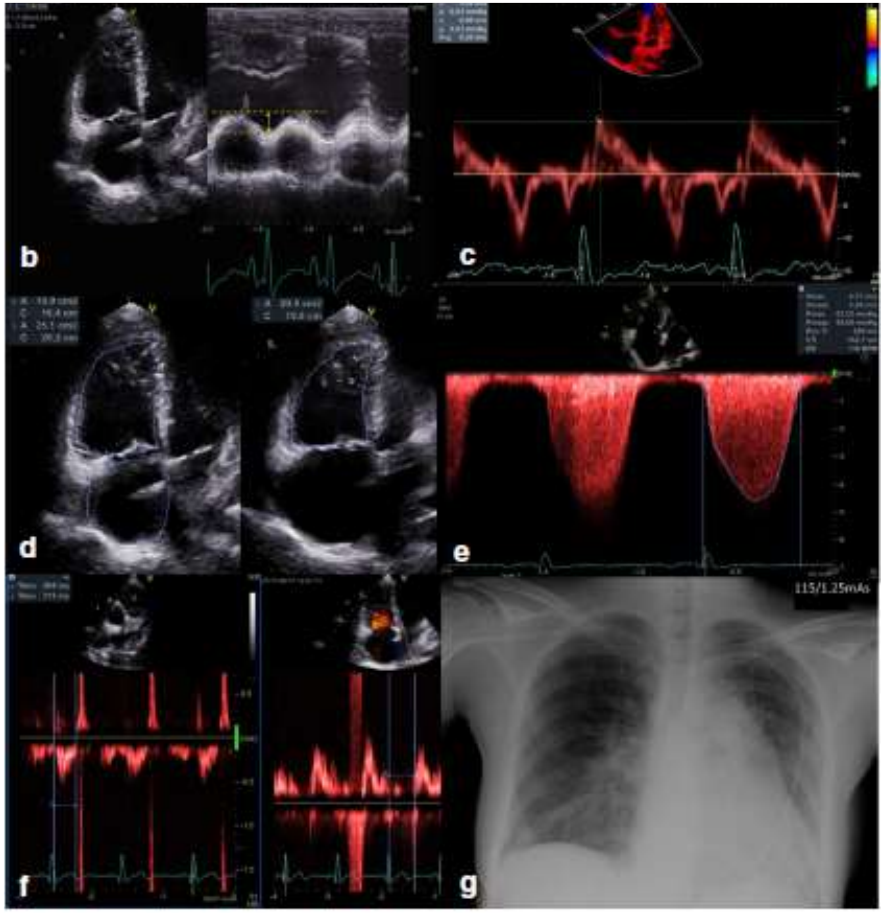
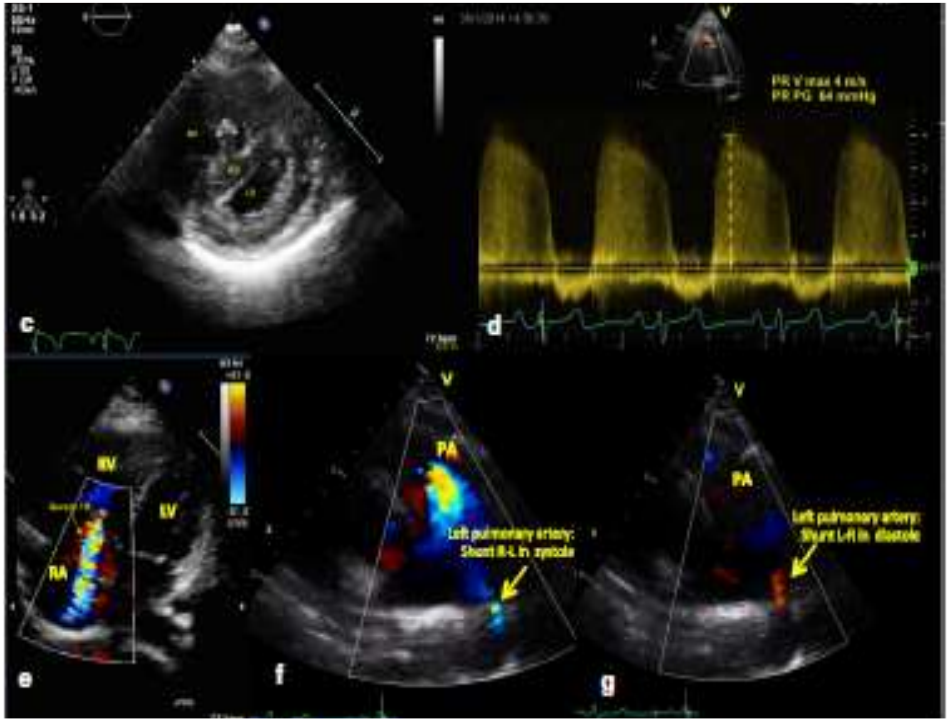
Echocardiography in Pulmonary Arterial Hypertension





PAH - Diagnosis

Electrocardiography

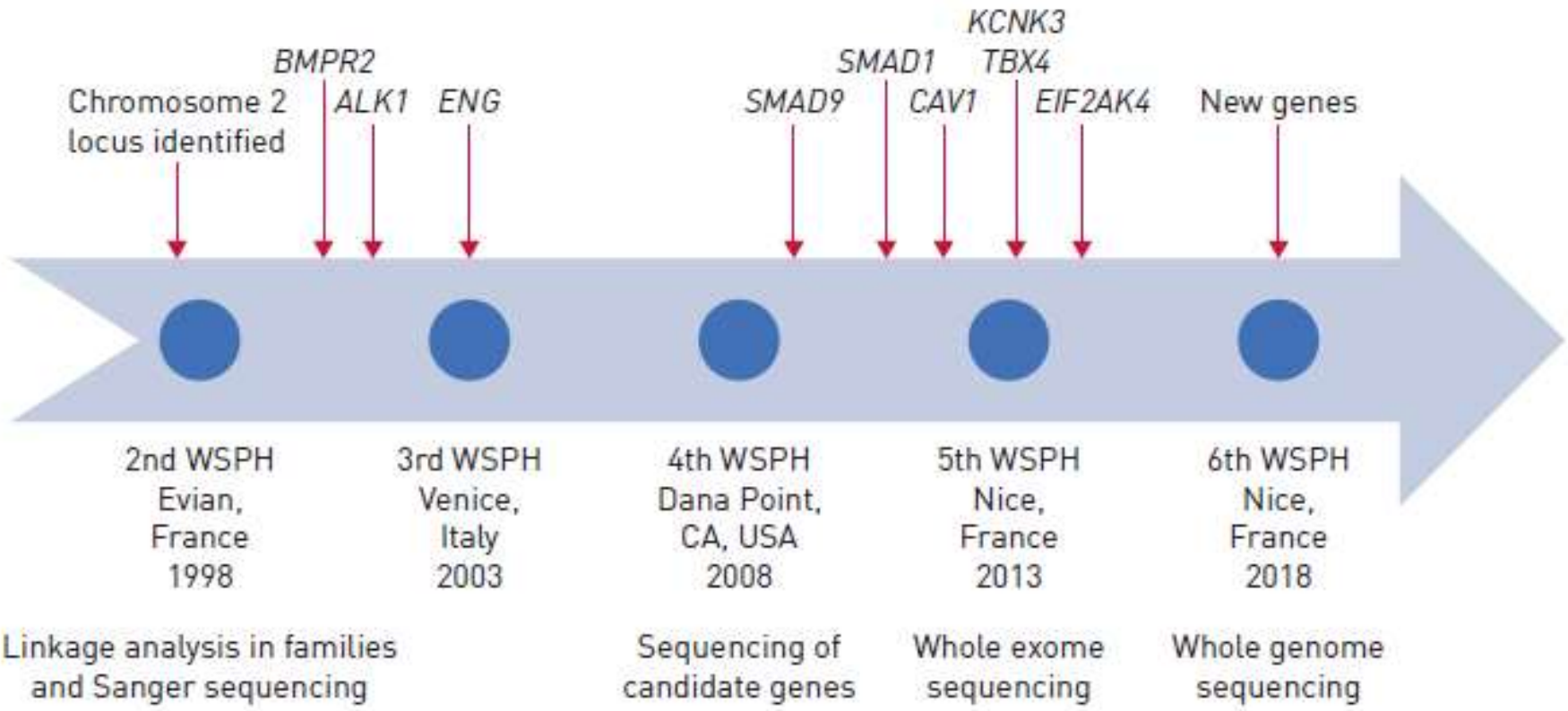
- Reliable clue to the presence of PH.
- ECG features in patients with pulmonary arterial hypertension (PAH) have been demonstrated to be associated with worse prognosis
- The utility of the ECG as a screening tool in complicated patients or those early in the course of their disease is uncertain
- A normal ECG does not exclude PH.

PAH - Diagnosis

Blood tests and immunology

- Not useful for PH diagnosis, but distinguish some forms of PH and indicate end-organ compromise.
- **Liver function** abnormalities may represent congestion, primary liver disease and/or consequences of therapy.
- **Thyroid disease** is common in PAH, may develop during the disease and should be considered in cases of abrupt deterioration
- Elevations of **natriuretic peptides** are associated with right ventricular overload, and are predictors of worse outcome.
- Routine screening for **connective tissue disease (CTD), hepatitis and HIV** is required.
- Recommended serological testing for **scleroderma** includes ANAs (⩾1:160) → high index of suspicion, consider anticentromere, antitopoisomerase, anti-RNA polymerase III, ds-DNA, anti-Ro, anti-La and U1-RNP antibodies.
- Patients with CTD and CTEPH should undergo screening for coagulopathies and **thrombophilia** → anticardiolipin antibodies, lupus anticoagulant and anti-β2-glycoprotein antibodies.

Genetics and genomics of pulmonary arterial hypertension



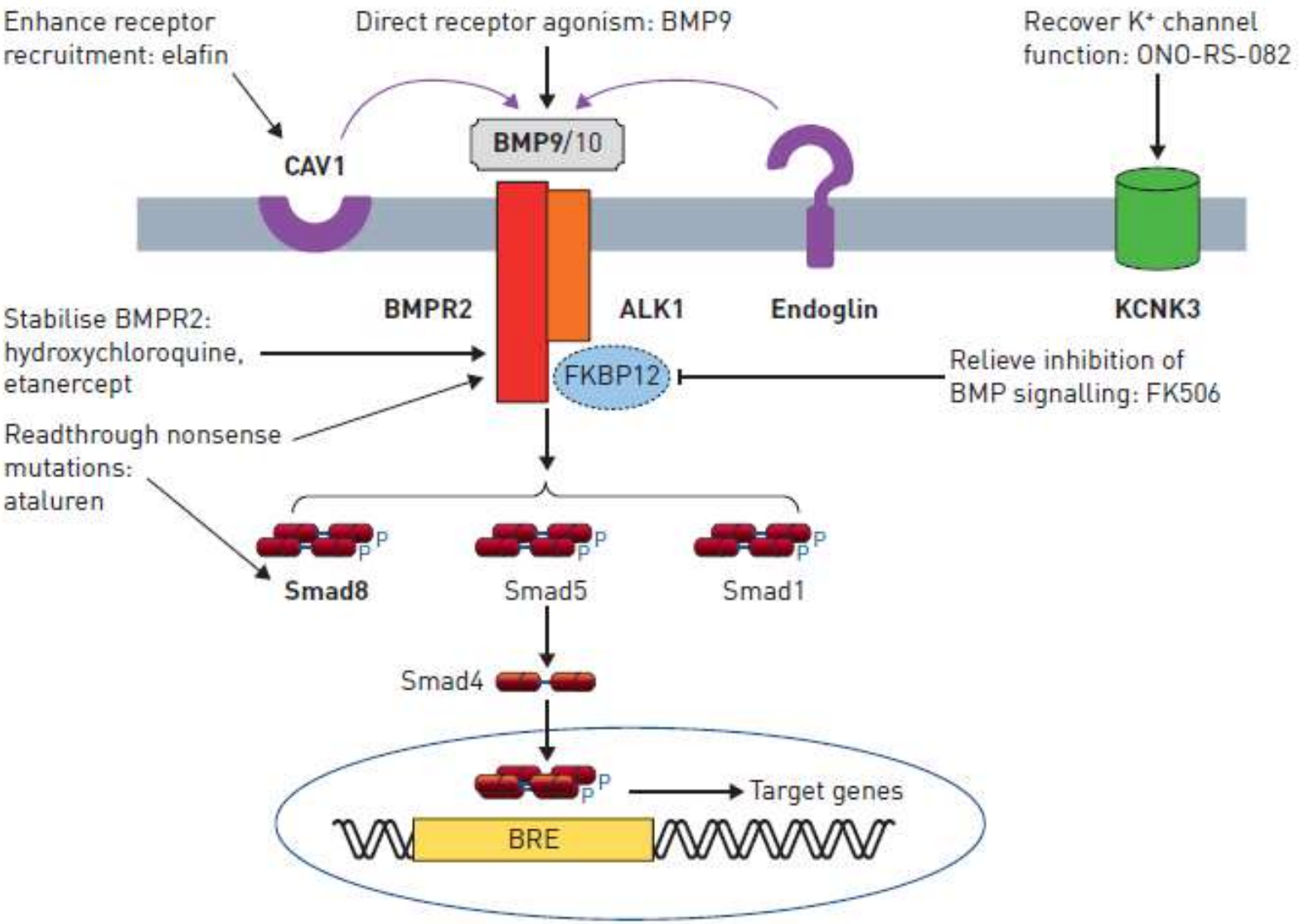
Genetics and Genomics of PAH

- The most common genetic mutations in familial PAH and IPAH are in *BMPR2* and its sequence variants (*SMAD1, SMAD4, SMAD9*)
  - Highly expressed in pulmonary vascular endothelium and forms complexes with ALK1 or ALK2 receptors
  - Female sex is an important factor in penetrance of *BMPR2* mutations
- Nearly 25% to 30% of patients diagnosed with IPAH should be re-classified as having HPAH
- Genetic testing can explain etiology and stratify risk for family members and future children

HPAH Genes Identified Through Whole Genome Sequencing	
Higher level of evidence (with causal role in disease)	*BMPR2; EIF2AK4; TBX4; ATP13A3; GDF2; SOX17; AQP1; ACVRL1; SMAD9; ENG; KCNK3; CAV1*
Lower level of evidence	*SMAD4; SMAD1; KLF2; BMPR1B; KCNA5*

Morrell NW, et al. *Eur Respir J*. 2018. [Epub ahead of print].

From genes to therapies



PAH - Diagnosis

Pulmonary function tests and arterial blood gases

- Pulmonary function tests should include total lung capacity and diffusing capacity of the lung for carbon monoxide (DLCO)
- In most patients with PAH there is a mild restrictive component.
- Marked reduction in DLCO (<60% of predicted) or severe hypoxaemia can indicate PVOD

Cardiopulmonary exercise testing

- CPET can quantify the degree of relative hypoperfusion of the lung and the systemic circulation that occurs during exercise in patients with PH, and can grade the severity of exercise limitation and assess responses to therapy.
- Abnormalities in $\dot{V}E/\dot{V}CO_2$ and end-tidal carbon dioxide tension ($PETCO_2$) obtained during CPET have been used to estimate the likelihood of PH, lower peak oxygen uptake ($\dot{V}O_2$) and/or higher $\dot{V}E/\dot{V}CO_2$ signifying an increasing likelihood of PH.
- CPET may be useful for evaluating symptomatic patients at high risk for developing PAH

PAH - Diagnosis

Ventilation/perfusion lung scanning

- A normal V/Q scan remains the preferred diagnostic tool and rules out CTEPH.
- A normal V/Q scan effectively excludes CTEPH with a sensitivity of 90–100% and a specificity of 94–100%
- Nuclear medicine societies are recommending a transition of V/Q reporting to a binary interpretation

Chest computed tomography

- Chest computed tomography (CT) demonstrating right ventricular dilation, right atrial dilation, enlarged main pulmonary artery (diameter $\geqslant$29 mm) or a main pulmonary artery/ascending aorta diameter ratio $\geqslant$1 is suggestive of PH
- High-resolution can identify parenchymal lung disease and discriminate between PH lung disease and PAH
- Newer technological advances in CT/CTPA make it equal to V/Q scan for CTEPH

Right heart catheterization in pulmonary hypertension

Recommendations	Class	Level
RHC is recommended to confirm the diagnosis of pulmonary arterial hypertension (Group 1) and to support treatment decisions.	I	C
In patients with PH, it is recommended to perform RHC in expert centres (Table 34) as it is technically demanding and may be associated with serious complications.	I	B
RHC should be considered in pulmonary arterial hypertension (Group 1) to assess the treatment effect of drugs (Table 12).	IIa	C
RHC is recommended in patients with congenital cardiac shunts to support decisions on correction (Table 23).	I	C
RHC is recommended in patients with PH due to left heart disease (Group 2) or lung disease (Group 3) if organ transplantation is considered .	I	C
When measurement of PAWP is unreliable, left heart catheterization should be considered to measure LVEDP.	IIa	C
RHC may be considered in patients with suspected PH and left heart disease or lung disease to assist in the differential diagnosis and support treatment decisions.	IIb	C
RHC is indicated in patients with Chronic Thromboembolic Pulmonary Hypertension (Group 4) to confirm the diagnosis and support treatment decisions.	I	C

European Heart Journal 2016:37;67–119 -doi:10.1093/eurheartj/ehv317
European Respiratory Journal 2015 46: 903-975;

Vasoreactivity testing

Recommendations	Class	Level
Vasoreactivity testing is indicated only in expert centres.	I	C
Vasoreactivity testing is recommended in patients with IPAH, HPAH and PAH associated with drugs use to detect patients who can be treated with high doses of a calcium channel blocker.	I	C
A positive response to vasoreactivity testing is defined as a reduction of mean PAP ≥10 mmHg to reach an absolute value of mean PAP ≤40 mmHg with an increased or unchanged cardiac output.	I	C
Nitric oxide is recommended for performing vasoreactivity testing.	I	C
Intravenous epoprostenol is considered for performing vasoreactivity testing as an alternative.	I	C
Adenosine should be considered for performing vasoreactivity testing as an alternative.	IIa	C
Inhaled iloprost may be considered for performing vasoreactivity testing as an alternative.	IIb	C
The use of oral or intravenous calcium channel blockers in acute vasoreactivity testing is not recommended.	III	C
Vasoreactivity testing to detect patients who can be safely treated with high doses of a calcium channel blocker is not recommended in patients with PAH other than IPAH, HPAH and PAH associated with drugs use, and is not recommended in pulmonary hypertension Groups 2, 3, 4 and 5.	III	C

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European Heart Journal 2016;37;67–119 -doi:10.1093/eurheartj/ehv317
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High Risk for PAH patients

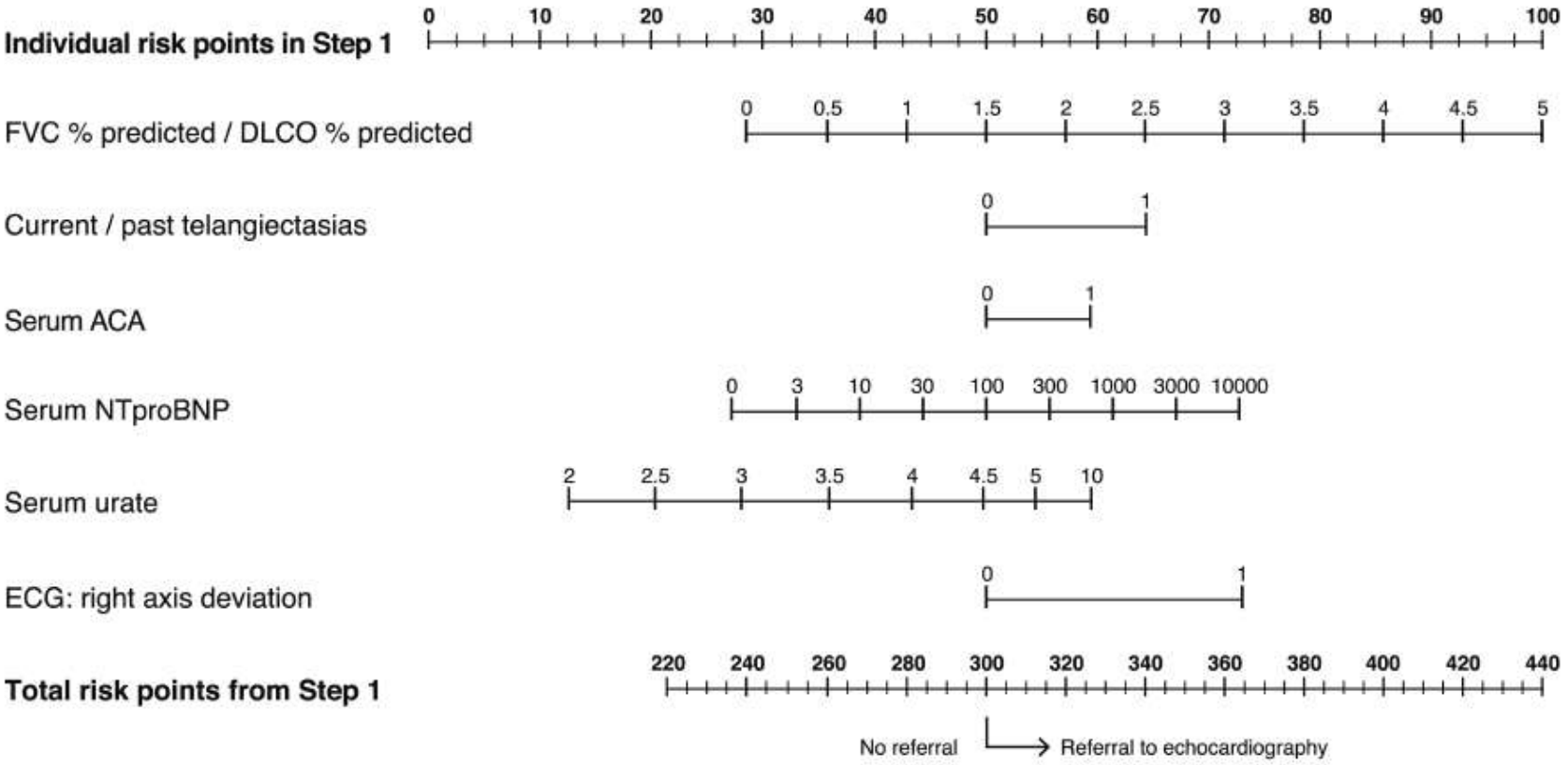
Scleroderma (systemic sclerosis) and scleroderma spectrum

Annual screening in patients with systemic sclerosis (SSc)

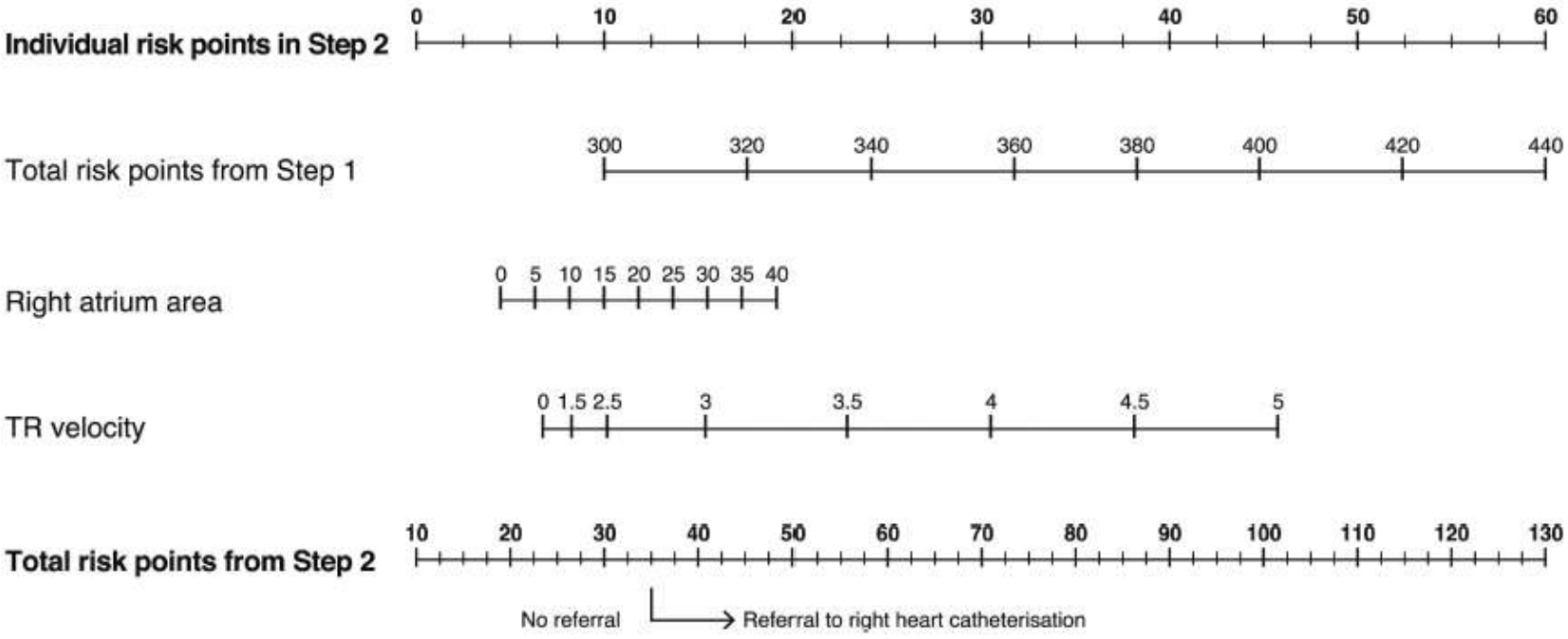
2018 Task Force recommends

- For patients with uncorrected DLCO <80% of predicted → DETECT, TTE or FVC/DLCO ratio >1.6 (assuming none-to-mild interstitial lung disease) and >2-fold upper limit of normal of NT-proBNP → If any of these screening tests are positive, these patients should be referred for RHC.
- For those with uncorrected DLCO ⩾80% of predicted screening may be considered with TTE

Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study



Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study



High Risk for PAH patients

HIV

- Incidence of PAH in HIV is low
- The large number of HIV-infected individuals worldwide makes HIV a major contributor to the worldwide incidence of PAH and a significant contributor to HIV-related death
- **Risk markers for PAH** → search for earlier diagnosis of HIV-PAH in asymptomatic patients: female sex, i.v. drug use, cocaine use, HCV infection, origin from high-prevalence country, known Nef (negative regulatory factor) or Tat HIV proteins and US African-American patients

Recommendations

• Screen for PAH in HIV patients with symptoms or with more than one risk factor for HIV-PAH

High Risk for PAH patients

Portopulmonary hypertension

- The frequency of PH in patients with liver disease varies with disease severity and duration.
- By time of liver transplantation 10.3% of patients had RHC-proven mPAP >35 mmHg
- Prevalence of PH in the portal hypertensive population has been previously estimated as 2–6%.
- Estimated median survival time was 3.75 years in this patient population.

Recommendations

• Echocardiographic screening is recommended in all patients with portal hypertension → TR jet >3.4 m·s−1 or RA/RV enlargement or dysfunction further evaluation with RHC and referral to PH expert centre is recommended

Pulmonary hypertension due to left heart disease

New proposed haemodynamic definition of PH in LHD

1) IpcPH: PAWP >15 mmHg and mPAP >20 mmHg and PVR<3 WU
2) CpcPH: PAWP >15 mmHg and mPAP >20 mmHg and PVR ⩾3 WU

Beyond a strict haemodynamic definition, other markers of disease may be taken in consideration to better determine a patient's prognosis → an additional haemodynamic marker (e.g. DPG or PAC), cardiopulmonary exercise testing (CPET) profile (level of V'E/V'CO2) slope, exercise oscillatory ventilation, end-tidal carbon dioxide tension(PETCO2), indices of RV function and RV/PA coupling (compliance and elastance) and biomarkers (Natriuretic peptides, ST2)

Pulmonary hypertension due to left heart disease

Clinical phenotype of PH due to LHD

Three main entities in group 2 PH

1) PH due to HFpEF
2) PH due to HFrEF
3) PH due to VHD

In contrast to the other aetiologies, the distinction between PH due to HFpEF, PAH and chronic thromboembolic PH (CTEPH) may be challenging.

Three-step approach to the differential diagnosis

1) identification of a ***clinical phenotype*** to establish the characteristics of group 2 PH
2) determination of a ***pre-test probability*** to identify which patients should move to an invasive evaluation
3) ***haemodynamic characterisation***, which could include provocative testing in selected cases

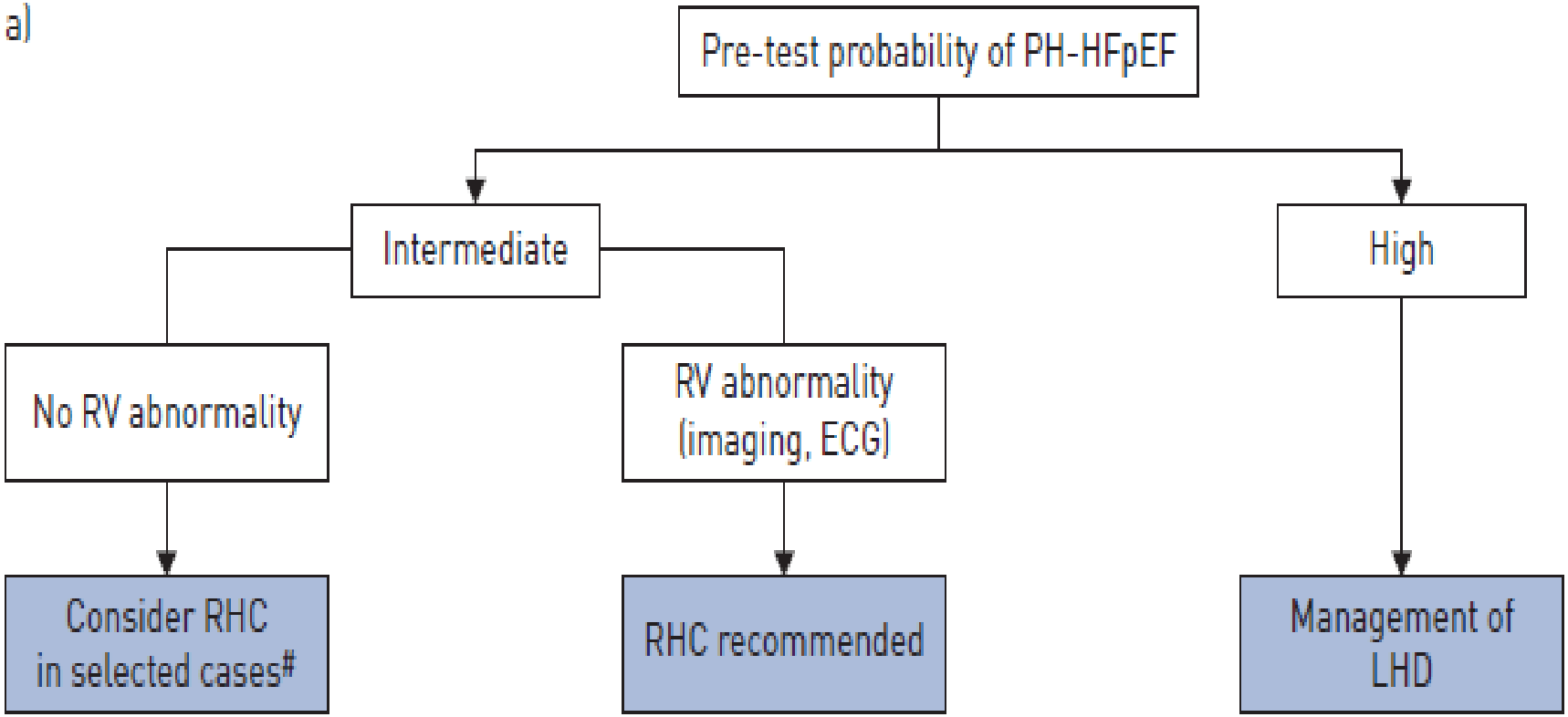
Pulmonary hypertension due to left heart disease

TABLE 1 Pre-test probability of left heart disease (LHD) phenotype

Feature	High probability	Intermediate probability	Low probability
Age	>70 years	60–70 years	<60 years
Obesity, systemic hypertension, dyslipidaemia, glucose intolerance/diabetes	>2 factors	1–2 factors	None
Previous cardiac intervention[#]	Yes	No	No
Atrial fibrillation	Current	Paroxysmal	No
Structural LHD	Present	No	No
ECG	LBBB or LVH	Mild LVH	Normal or signs of RV strain
Echocardiography	LA dilation; grade >2 mitral flow	No LA dilation; grade <2 mitral flow	No LA dilation; *E*/*e*′ <13
CPET	Mildly elevated V'_E/V'_{CO_2} slope; EOV	Elevated V'_E/V'_{CO_2} slope *or* EOV	High V'_E/V'_{CO_2} slope; no EOV
Cardiac MRI	LA strain or LA/RA >1		No left heart abnormalities

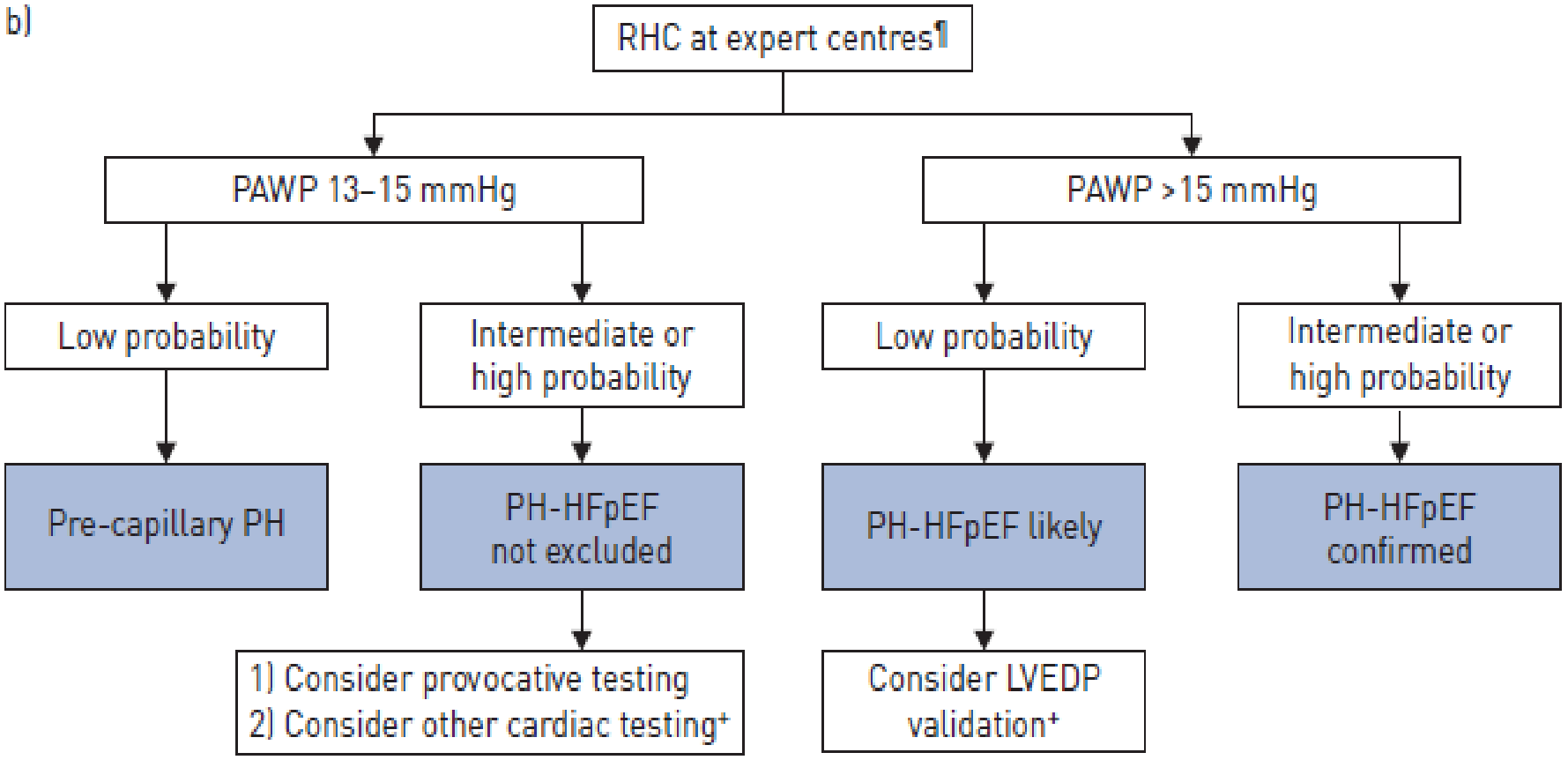
Pulmonary hypertension due to left heart disease

a)



Pulmonary hypertension due to left heart disease

b)



Pulmonary hypertension in chronic lung disease and hypoxia

COPD → The prevalence of PH is dependent on the severity of the disease

- Lung Disease stage IV → up to 90% have mPAP >20 mmHg, with most ranging between 20-35 mmHg
- Approximately 1–5% of COPD patients have mPAP >35–40 mmHg at rest

"Pulmonary vascular COPD phenotype" → less severe airflow limitation, hypoxaemia, very low diffusing capacity of the lung for carbon monoxide (DLCO), normo- or hypocapnia and a cardiovascular exercise limitation profile

- Vascular lesions in COPD-PH patients are morphologically similar to those in idiopathic PAH (IPAH).
- Presence of PH has a stronger association with mortality in COPD than FEV1 or gas exchange variables
- Enlarged PA, as detected by CT scan, predicts hospitalisation due to acute COPD exacerbation

Pulmonary hypertension in chronic lung disease and hypoxia

Idiopathic pulmonary fibrosis and other idiopathic interstitial pneumonias

- mPAP ⩾25 mmHg has been reported in 8–15% of patients upon initial work-up
- greater prevalence in advanced (30–50%) and end-stage (>60%) disease
- In most patients, PH is mild to moderate
- Limited correlation between PH severity and lung function impairment or high-resolution CT fibrosis score
- PH may also be associated with an increased risk for acute exacerbation in advanced IPF

Pulmonary hypertension in chronic lung disease and hypoxia

Combined pulmonary fibrosis and emphysema, and other lung diseases

- Patients with CPFE are particularly prone to develop PH, with estimates suggesting a prevalence of 30–50%
- Typically, normal or mildly abnormal lung volumes and the absence of airflow obstruction are accompanied by a markedly impaired diffusion capacity, significant hypoxaemia and PH.
- The PH appears to contribute to the functional limitation in CPFE and is associated with poor survival

Pulmonary hypertension in chronic lung disease and hypoxia

Sarcoidosis

- The prevalence of PH in sarcoidosis ranges from 5.7% to 74%
- Sarcoidosis-PH has a reported 5-year survival of 50–60%
- Patients with sarcoidosis-PH usually have extensive parenchymal disease
- The mechanisms underlying PH in sarcoidosis are complex, and include fibrosis-associated remodelling and obliteration of pulmonary vessels, extrinsic compression of central pulmonary vessels by lymphadenopathy or mediastinal fibrosis, pulmonary veno-occlusive-like lesions, granulomatous involvement of pulmonary vessels, left ventricular dysfunction, and portopulmonary hypertension

Pulmonary hypertension in chronic lung disease and hypoxia

When to perform RHC

- When significant PH is suspected and the patient's management will likely be influenced by RHC results (referral for transplantation, inclusion in clinical trials or registries, treatment of unmasked LV dysfunction ETC)
- Clinical worsening, progressive exercise limitation and/or gas exchange abnormalities are not deemed attributable to ventilatory impairment.

Pressure measurements during RHC

1. CLD without PH (mPAP <21 mmHg, or mPAP 21–24 mmHg with pulmonary vascular resistance (PVR) <3 Wood Units (WU)).
2. CLD with PH (mPAP 21–24 mmHg with PVR ⩾3 WU, or mPAP 25–34 mmHg) (CLD-PH).
3. CLD with severe PH (mPAP ⩾35 mmHg), or mPAP ⩾25 mmHg with low cardiac index (<2.0 L·min−1·m−2)) (CLD-severe PH).

Pulmonary hypertension in chronic lung disease and hypoxia

TABLE 1 Criteria favouring group 1 *versus* group 3 pulmonary hypertension (PH)[#]

Criteria favouring group 1 (PAH)	Testing	Criteria favouring group 3 (PH due to lung disease)
Extent of lung disease		
Normal or mildly impaired: • FEV_1 >60% pred (COPD) • FVC >70% pred (IPF) • Low diffusion capacity in relation to obstructive/restrictive changes	Pulmonary function testing	Moderate to very severely impaired: • FEV_1 <60% pred (COPD) • FVC <70% pred (IPF) • Diffusion capacity "corresponds" to obstructive/restrictive changes
Absence of or only modest airway or parenchymal abnormalities	High-resolution CT scan[¶]	Characteristic airway and/or parenchymal abnormalities
Haemodynamic profile		
Moderate-to-severe PH	Right heart catheterisation Echocardiogram	Mild-to-moderate PH
Ancillary testing		
Present	Further PAH risk factors (*e.g.* HIV, connective tissue disease, *BMPR2* mutations, *etc.*)	Absent
Features of exhausted circulatory reserve: • Preserved breathing reserve • Reduced oxygen pulse • Low $\dot{V}_E/\dot{V}O_2$ slope • Mixed venous oxygen saturation at lower limit • No change or decrease in $P_{ET}CO_2$ during exercise	Cardiopulmonary exercise test[+] ($P_{ET}CO_2$ particularly relevant in COPD)	Features of exhausted ventilatory reserve: • Reduced breathing reserve • Normal oxygen pulse • Normal $\dot{V}_E/\dot{V}O_2$ slope • Mixed venous oxygen saturation above lower limit • Increase in $P_{ET}CO_2$ during exercise
Predominant haemodynamic profile		Predominant obstructive/restrictive profile

Pulmonary hypertension in chronic lung disease and hypoxia