Pulmonary Arterial Hypertension

when to suspect, when to refer

Dr. Kristina Kemp

Disclosure: Conflict of interest

- I have a relationship with a for-profit and/or a not-for-profit organization over the previous 2 years including
- Direct financial payments including receipt of honoraria/membership on advisory boards or speakers' bureaus: Astra-Zeneca, Boehringer Ingelheim, Covis, GSK, Janssen
- Employed by Horizon Health Authority

What is pulmonary hypertension?

- Pulmonary hypertension is a **clinical-physiologic syndrome** characterized by elevated mean pulmonary artery pressure (PAP) and the consequent symptoms including dyspnea, fatigue, exercise intolerance, chest pain, and syncopal episodes
- PH may involve multiple clinical conditions and **can complicate the majority of cardiovascular and respiratory diseases**

What is pulmonary hypertension?

- Mean pulmonary arterial pressure (PAP): **>20 mm Hg**
- Elevated PAP burdens normally thin-walled right ventricle
- Without treatment, right heart dysfunction = progressive symptoms, often eventually death

- PH classified into **5 categories**, each with a different…
  - Mechanism for the elevated PAP
  - Natural history
  - Approach to treatment

Clinical Classification of Pulmonary Hypertension

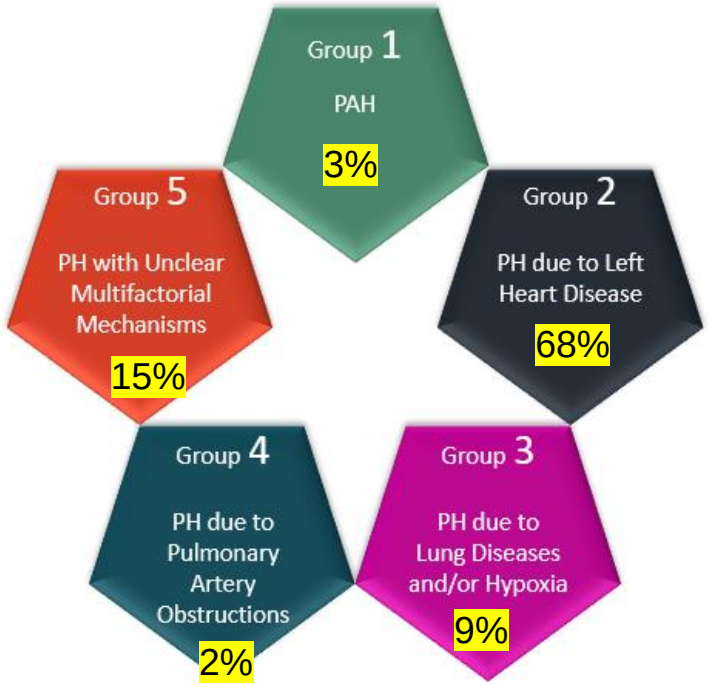

TABLE 2 Updated clinical classification of pulmonary hypertension (PH)

1 PAH
- 1.1 Idiopathic PAH
- 1.2 Heritable PAH
- 1.3 Drug- and toxin-induced PAH (table 3)
- 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 (table 4)
- 1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement (table 5)
- 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 (table 6)
- 4.1 Chronic thromboembolic PH
- 4.2 Other pulmonary artery obstructions

5 PH with unclear and/or multifactorial mechanisms (table 7)
- 5.1 Haematological disorders
- 5.2 Systemic and metabolic disorders
- 5.3 Others
- 5.4 Complex congenital heart disease

Simonneau G, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019; 53: 1801913
Strange G, et al. Heart . 2012;98(24):1805-11

PAH Definition

- The term PAH describes a group of PH patients characterized hemodynamically by the presence of **pre-capillary PH**:
- Pulmonary artery wedge pressure ≤15 mmHg
- Pulmonary vascular resistance >3 Wood units (240dynes)

- The absence of other causes of precapillary PH such as PH due to lung diseases, CTEPH or other rare diseases (**diagnosis of exclusion**)
- Pre-capillary PH includes different forms that share a similar clinical picture and virtually identical pathological changes of the lung microcirculation

Simonneau G, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019; 53: 1801913

Hemodynamic definitions for classification of pulmonary hypertension at right heart catheterization

Definitions	Characteristics	Clinical groups[#]
Pre-capillary PH	mPAP >20 mmHg PAWP ⩽15 mmHg PVR ⩾3 WU	1, 3, 4 and 5
Isolated post-capillary PH (IpcPH)	mPAP >20 mmHg PAWP >15 mmHg PVR <3 WU	2 and 5
Combined pre- and post-capillary PH (CpcPH)	mPAP >20 mmHg PAWP >15 mmHg PVR ⩾3 WU	2 and 5

mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; WU: Wood Units. [#]: group 1: PAH; group 2: PH due to left heart disease; group 3: PH due to lung diseases and/or hypoxia; group 4: PH due to pulmonary artery obstructions; group 5: PH with unclear and/or multifactorial mechanisms.

Pre-capillary PH

1. Pulmonary arterial hypertension
3. PH due to lung diseases
4. Chronic thromboembolic PH
5. PH with unclear and/or multifactorial mechanisms

Isolated post-capillary PH
Combined pre- and post-capillary PH

2. PH due to left heart disease
5. PH with unclear and/or multifactorial mechanisms

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When to suspect

Initial symptoms are typically induced by exertion	**Shortness of breath, fatigue, weakness, angina and syncope**	**Symptoms at rest occur only in advanced cases**	**Abdominal distension and ankle edema will develop with progressing RV failure**

** The presentation of PAH may be modified by diseases that cause or are ** associated with PAH as well as other concurrent diseases

Diseases Most Commonly Associated with PAH

- HIV infection
- Connective tissue diseases (CTD)
  - Scleroderma (SSc)
  - Systemic lupus erythematosus (SLE)
  - Mixed connective tissue disease (MCTD)
- Portal hypertension
- Congenital heart diseases (CHD)
  - ASD/VSD/PDA
  - Reversed shunt: Eisenmenger's syndrome

When to suspect

- First degree family member with PAH
- Established diagnosis of a diseases associated with PAH (CHD, CTD, HIV and POPH)
- Echocardiogram findings with no alternative explanation
- Exposure history of toxins:

Definite	Possible	Likely	Unlikely
Aminorex	Cocaine	Amphetamines	Oral contraceptives
Fenfluramine	Phenylpropanolamine	L-Tryptophan	Estrogen
Dexfenfluramine	St. John's wort	Methamphetamines	Cigarette smoking
Toxic rapeseed oil	Chemotherapeutic agents	Dasatanib	
Benfluorex	Interferon-α and -β		
SSRIs	Amphetamine-like drugs		

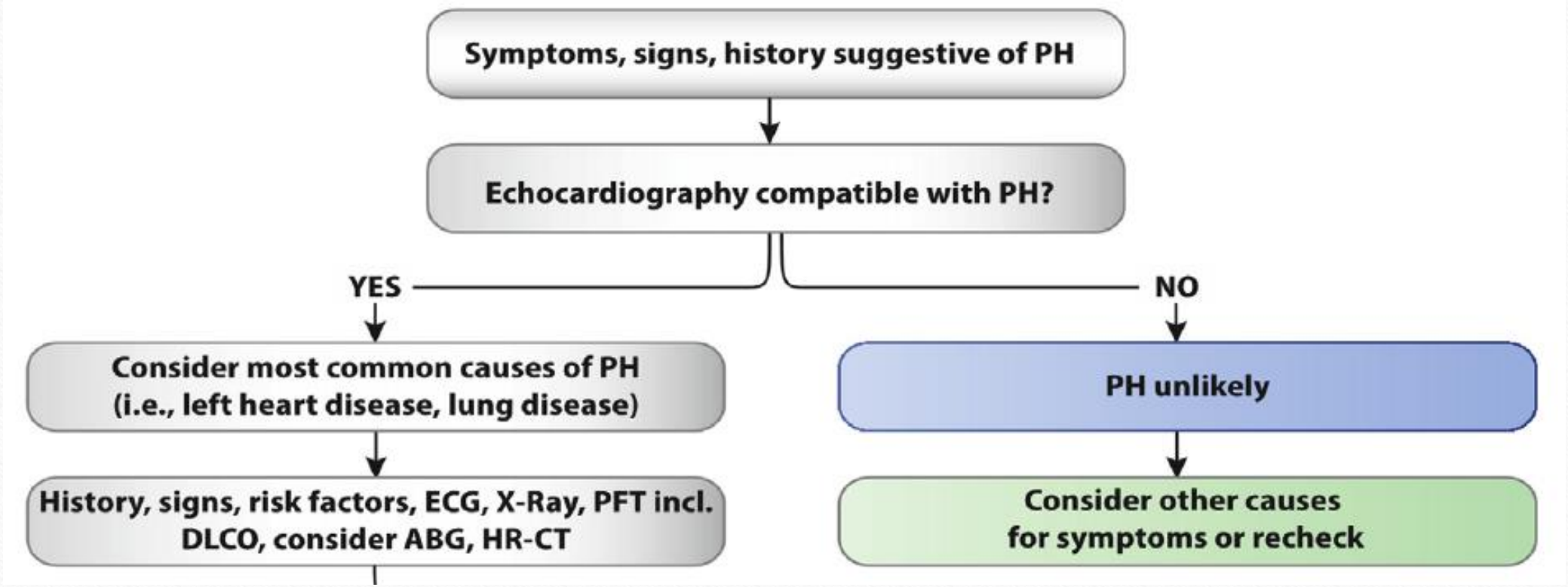
SSRI, selective serotonin reuptake inhibitors.

Orcholski M et al. Drug-induced pulmonary arterial hypertension: a primer for clinicians and scientists. Am J Physiol Lung Cell Mol Physiol. 2018 Jun 1; 314(6): L967–L983

PAH physical exam

- Cardiac findings:
  - Left parasternal lift
  - Accentuated pulmonary component of the 2nd heart sound
  - RV 3rd heart sound
  - Pansystolic murmur of tricuspid regurgitation and a diastolic murmur of pulmonary regurgitation
  - Elevated JVP, hepatomegaly, ascites, peripheral edema and cool extremities characterize patients with advanced disease
- Wheeze and crackles are usually absent
- Clinical examination may suggest an underlying cause of PH:
  - Telangiectasia, digital ulceration and sclerodactyly are seen in scleroderma
  - Inspiratory crackles may point towards interstitial lung disease
  - Spider nevi, testicular atrophy, and palmar erythema suggest liver disease

When to suspect



Hirani N, et al . Canadian Cardiovascular Society/Canadian Thoracic Society Position Statement on Pulmonary Hypertension. Canadian Journal of Cardiology 36 (2020) 977-992

Investigations

ECG

- An abnormal ECG is more likely in severe rather than mild PH
- ECG abnormalities may include P pulmonale, right axis deviation, RV hypertrophy, RV strain, right bundle branch block, and QTc prolongation
- A normal ECG does not exclude the diagnosis

CXR

- Central pulmonary arterial dilatation
- Pruning of the peripheral blood vessels
- RA and RV enlargement (more advanced cases)
- CXR may show signs suggesting lung disease or pulmonary venous congestion due to LHD
- The degree of PH in any given patient does not correlate with the extent of radiographic abnormalities
- A normal chest radiograph does not exclude PH

Investigations: Echocardiogram evaluation

- When PH is suspected, transthoracic echocardiography is suggested
- Conclusions derived from an echocardiographic examination should aim to assign a level of probability of PH

TABLE 1 Echocardiographic probability of pulmonary hypertension (PH) in symptomatic patients with a suspicion of PH

Peak tricuspid regurgitation velocity m·s^{-1}	Presence of other echocardiographic "PH signs"#	Echocardiographic probability of PH
≤2.8 or not measurable	No	Low
≤2.8 or not measurable 2.9–3.4	Yes No	Intermediate
2.9–3.4 >3.4	Yes Not required	High

TABLE 2 Echocardiographic signs suggesting pulmonary hypertension (PH) used to assess the probability of PH in addition to tricuspid regurgitation velocity measurement in table 1

A: The ventricles	B: Pulmonary artery	C: Inferior vena cava and right atrium
Right ventricle/left ventricle basal diameter ratio >1.0	Right ventricular outflow Doppler acceleration time <105 ms and/or mid-systolic 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·s^{-1}	Right atrial area (end-systole) >18 cm^2
	Pulmonary artery diameter >25 mm	

Echocardiographic signs from at least two different categories (A/B/C) from the list should be present to alter the level of echocardiographic probability of PH. Reproduced and modified from [24] with permission.

Diagnosis of pulmonary hypertension. Frost A, Badesch D, Gibbs JSR, et al. Eur Resp J 2019; 53: 1801904

Investigations

PFT/ABG

- Patients with PAH have usually mild to moderate reduction of lung volumes related to disease severity
- Most PAH patients have decreased lung diffusion capacity (DLCO)
- ABG tends to exhibit alveolar hyperventilation at rest, PaO_2 remains normal or is lower than normal and $PaCO_2$ is decreased

Sleep Evaluation

- The prevalence of nocturnal hypoxemia and central sleep apneas are high in PAH (70–80%)
- Overnight oximetry or polysomnography should be performed where obstructive sleep apnea syndrome or hypoventilation are considered

Investigations

V/Q lung scan

- Ventilation/perfusion lung scan (V/Q) should be performed in patients with PH to look for chronic thromboembolic pulmonary hypertension (CTEPH)
- V/Q scan is the screening method of choice for CTEPH because of its higher sensitivity compared with CT pulmonary angiogram
- A normal- or low-probability V/Q scan effectively excludes CTEPH with a sensitivity of 90–100% and a specificity of 94–100%

CT chest

- Suggest the diagnosis of PH (PA or RV enlargement)
- Identify a cause of PH such as CTEPH or lung disease, provide clues as to the form of PAH (esophageal dilation in SSc or congenital cardiac defects)
- High-resolution CT provides detailed views of the lung parenchyma and facilitates the diagnosis of interstitial lung disease and emphysema
- Contrast CT angiography of the PA is helpful in determining whether there is evidence of surgically accessible CTEPH

Investigations

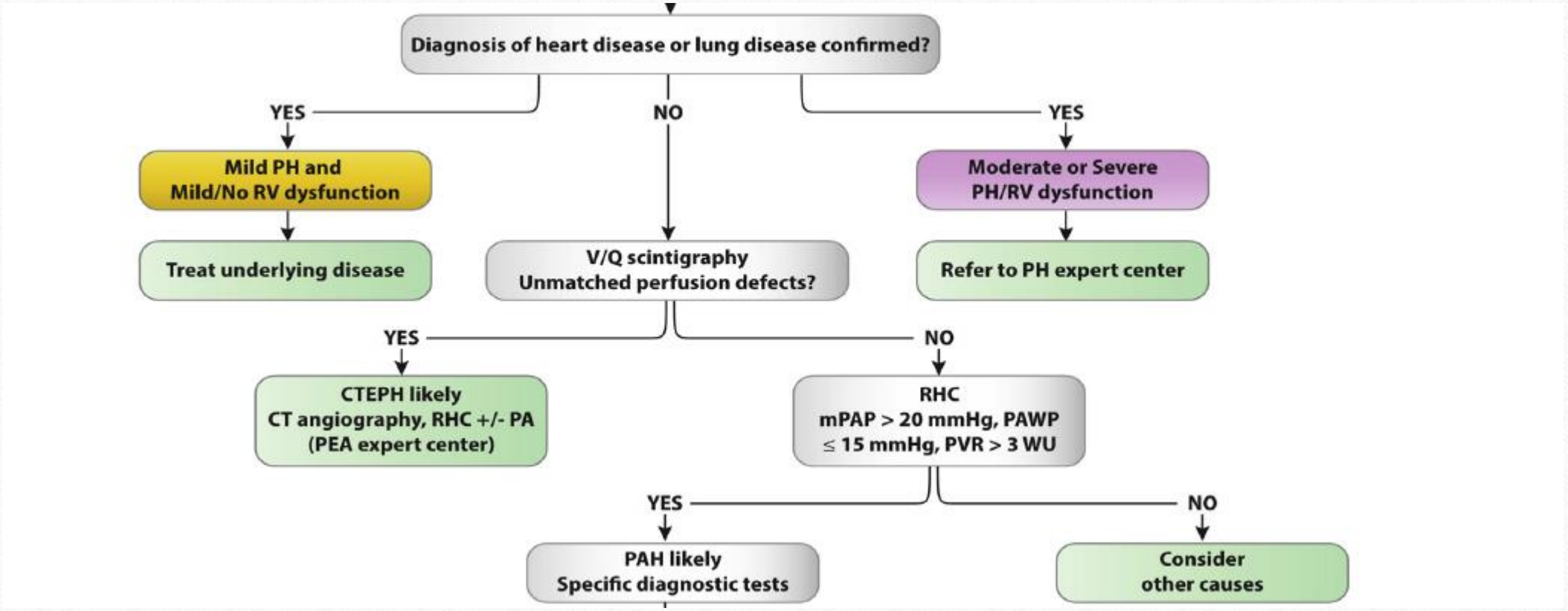
Labs

- Helpful to identify the etiology of some forms of PH as well as end organ damage
  - Routine biochemistry, hematology and thyroid function tests
  - Liver function tests may be abnormal because of high hepatic venous pressure, liver disease
  - Hepatitis serology should be performed if clinical abnormalities are noted
  - Serological testing is required to detect underlying CTD, hepatitis and HIV
- NT-proBNP may be elevated in patients with PAH and is an independent risk predictor

Cardiac Investigations

- Depending on cardiac risk factors and clinical history, further testing may be helpful
  - Exercise stress testing
  - Myoview stress testing
  - Stress Echocardiogram

When to suspect



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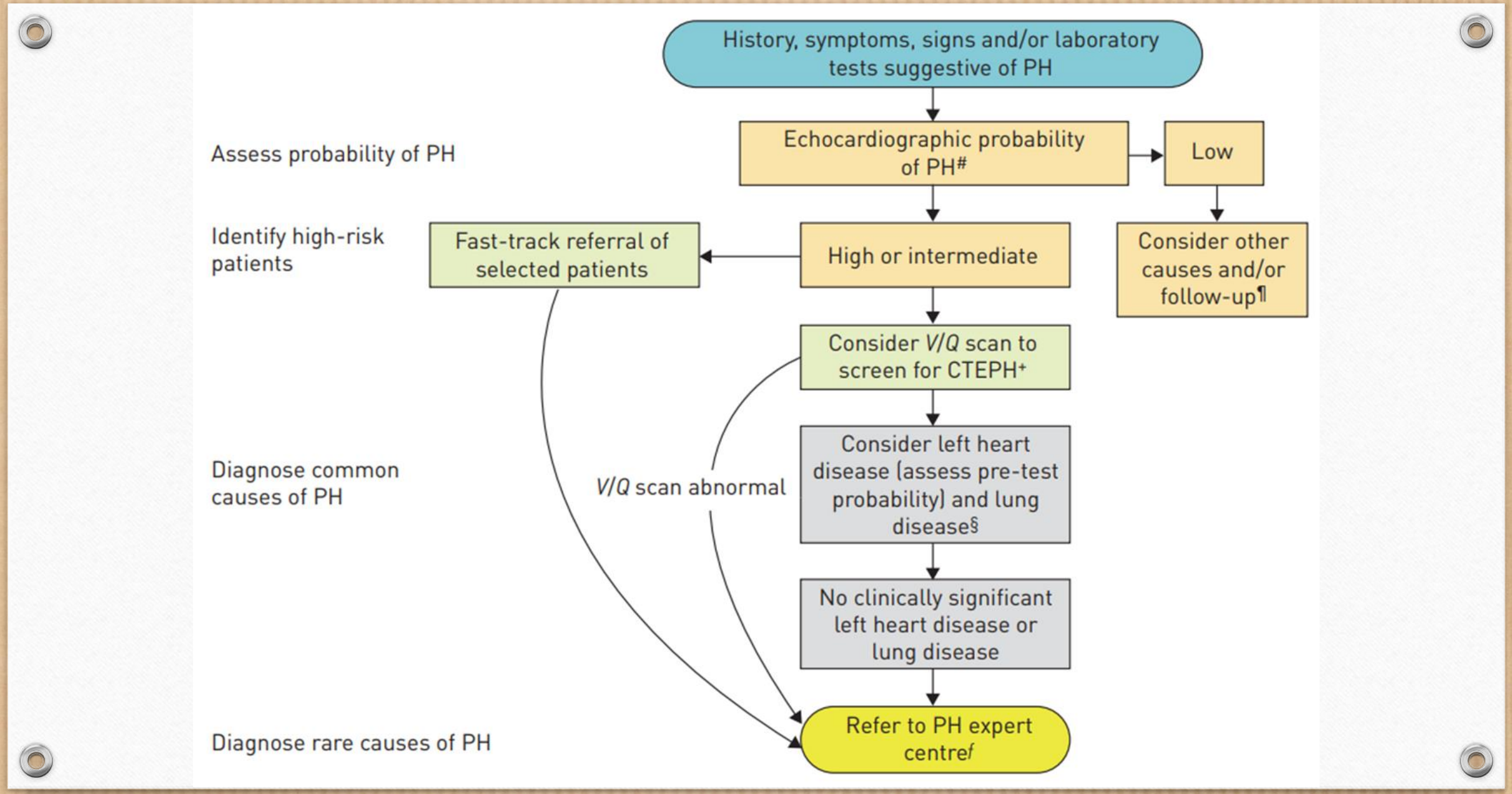
When to refer

- Patients with suspected PAH (or CTEPH)
- Patients with significantly disproportionate PH out of keeping with underlying secondary cause (left heart disease, lung disease) or diagnostic uncertainty



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Take home points

- Pulmonary hypertension is a clinical-physiologic syndrome which may complicate the majority of cardiovascular and respiratory diseases
- PAH is defined by a pre-capillary hemodynamic profile and the exclusion of significant lung and cardiac conditions
- Algorithms are directive in the investigation of this rare condition
- PH expert centers are a resource for help in challenging cases and for definitive diagnosis and treatment of the diesease

Questions?

Thanks for your attention

Please contact me if you want more information on how to refer a patient

Dr.Kristina.kemp@horizonnb.ca