

Diagnostic Criteria

Early diagnosis of BHD is critical to minimise the risk of kidney cancer through regular kidney scans to monitor any tumour growth. However, the rarity and broad spectrum of clinical manifestations of BHD can make it difficult to diagnose and is likely underdiagnosed.

Diagnosis of BHD relies on a combination of clinical evaluation, family history and genetic testing. Genetic testing for mutations in the gene *folliculin* (*FLCN*) should be performed where possible and can confirm over 90% of cases that fulfil the diagnostic criteria for BHD. However, it should be noted that a negative *FLCN* gene test does not necessarily exclude the diagnosis of BHD, depending on the criteria used. For more information on genetic testing please see [here](#) or [email us](#) and we can assist you in locating centres for genetic testing.

Although multiple diagnostic criteria have been proposed there are currently no official guidelines. To date, 3 different diagnostic criteria have been proposed in the literature. The first criteria, proposed by Menko *et al.*, in 2009 includes major and minor criteria (1). Patients need to fulfil one major criteria, or two minor criteria for diagnosis. The criteria are as follows:

Diagnostic Criteria proposed by Menko *et al.*, 2009

Major Criteria

- At least five fibrofolliculomas or trichodiscomas, at least one histologically confirmed, of adult onset.
- Pathogenic *FLCN* germline mutation.

Minor Criteria

- Multiple lung cysts: bilateral basally located lung cysts with no other apparent cause, with or without spontaneous primary pneumothorax.
- Renal cancer: early onset (age <50 years) or multifocal or bilateral renal cancer, or renal cancer of mixed chromophobe and oncocytic histology.
- A first-degree relative with BHD.

A second criteria was proposed in 2013 by Gupta *et al.*, focusing more on the pulmonary manifestations of BHD and involves high resolution CT imaging (HRCT) as a diagnostic tool (2):

Diagnostic Criteria proposed by Gupta *et al.*, 2013

Definite Pulmonary BHD

- Characteristic* or compatible† lung HRCT and skin biopsy positive for fibrofolliculoma or trichodiscoma.
- Characteristic or compatible lung HRCT and confirmed family history of BHD in first- or second-degree family member.
- Characteristic or compatible HRCT and tissue confirmation of renal chromophobe adenoma or oncocytoma.
- Characteristic or compatible HRCT and tissue confirmation of genetic testing positive for BHD.

Probably Pulmonary BHD

- Characteristic HRCT, exclusion of TSC and LAM, and personal or family history of pneumothorax.
- Compatible HRCT, exclusion of TSC and LAM, and any of the following:
 - Family or personal history of renal tumors.
 - Skin angiofibroma
 - Renal angiomyolipoma

Possible Pulmonary BHD

- Compatible or characteristic HRCT.

*Characteristic lung HRCT findings: Multiple thin-walled round, elliptical or lentiform well-defined air-filled cysts, without internal structure, in a basilar, medial and subpleural predominant distribution, with preserved or increased lung volume, and no other significant pulmonary involvement (specifically no interstitial lung disease).

†Compatible HRCT findings: Thin-walled cysts without the more typical elliptical shape or subpleural distribution.

Although it is interesting to include CT imaging in the diagnosis of BHD, not everyone who has BHD will have features of the lung cysts described and

so the diagnostic criteria here are not fully inclusive of the BHD community. However, it is important to raise awareness of the strong link between familial spontaneous pneumothorax and BHD, which these guidelines do promote, by emphasising that CT imaging alone should be enough to warrant further investigation into a possible BHD diagnosis. Indeed, it has been suggested previously that radiologists should be able to suggest BHD based on CT imaging, particularly when there is patient or family history of pneumothorax (3–5).

The third diagnostic guidelines were proposed in 2015 by Schmidt and Linehan, and are broadly similar to those proposed by Menko *et al.* with the main difference being that a germline *FLCN* mutation is required for a diagnosis of BHD (6). They propose that the following diagnostic criteria are suggestive of BHD syndrome:

Diagnostic Criteria proposed by Schmidt and Linehan, 2015

- At least 2 cutaneous papules clinically consistent with fibrofolliculoma/ trichodiscoma and at least 1 histologically confirmed fibrofolliculoma.
- Multiple bilateral pulmonary cysts located mainly in the basilar regions of the lung with or without a history of spontaneous pneumothorax that develops prior to age 40, but especially with a family history of these pulmonary manifestations.
- Bilateral, multifocal chromophobe renal carcinomas or hybrid oncocytic tumors especially with a family history of renal tumors or diagnosed at an age <50 years.
- A combination of these cutaneous, pulmonary or renal manifestations presenting in the patient or members of their family.

Sources

1. Menko FH, van Steensel MA, Giraud S, Friis-Hansen L, Richard S, Ungari S, et al. Birt-Hogg-Dubé syndrome: diagnosis and management [Internet]. Vol. 10, The Lancet Oncology. Lancet Oncol; 2009 [cited 2021 May 20]. p. 1199–206. Available from: <https://pubmed.ncbi.nlm.nih.gov/19959076/>
2. N G, K S, FX M. Pulmonary manifestations of Birt-Hogg-Dubé syndrome. Fam Cancer [Internet]. 2013 Sep [cited 2021 Jul 20];12(3):387–96. Available from: <https://pubmed.ncbi.nlm.nih.gov/23715758/>

3. Lee E, Sayyoub M, Haggerty JE, Kazerooni E, Agarwal PP. Role of Radiologists in the Diagnosis of Unsuspected Birt-Hogg-Dubé Syndrome in a Tertiary Clinical Practice. <https://doi.org/10.2214/AJR.19.21176> [Internet]. 2019 May 23 [cited 2021 Jul 20];213(4):792–7. Available from: www.ajronline.org
4. Torricelli E, Occhipinti M, Cavigli E, Tancredi G, Rosi E, Rossi C, et al. The Relevance of Family History Taking in the Detection and Management of Birt-Hogg-Dubé Syndrome. *Respiration* [Internet]. 2019 Aug 1 [cited 2021 Jul 20];98(2):125–32. Available from: <https://www.karger.com/Article/FullText/498973>
5. K M, D L, PD P, ER M, SJ M. A systematic review assessing the existence of pneumothorax-only variants of FLCN. Implications for lifelong surveillance of renal tumours. *Eur J Hum Genet* [Internet]. 2021 Jul 15 [cited 2021 Jul 20]; Available from: <https://pubmed.ncbi.nlm.nih.gov/34267338/>
6. Schmidt LS, Linehan WM. Molecular Genetics and Clinical Features of Birt-Hogg-Dubé-Syndrome. *Nat Rev Urol* [Internet]. 2015 Oct 1 [cited 2021 Jul 20];12(10):558. Available from: [/pmc/articles/PMC5119524/](http://pmc/articles/PMC5119524/)

Last Updated: July 2021

Review date: July 2024