Early detection of hereditary renal cell cancer by improved evaluation of spontaneous pneumothorax patients

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Disclosures

I have no financial or other conflicts of interest to report

Pneumothorax

"An abnormal collection of air or gas in the pleural space between the visceral and parietal pleura"

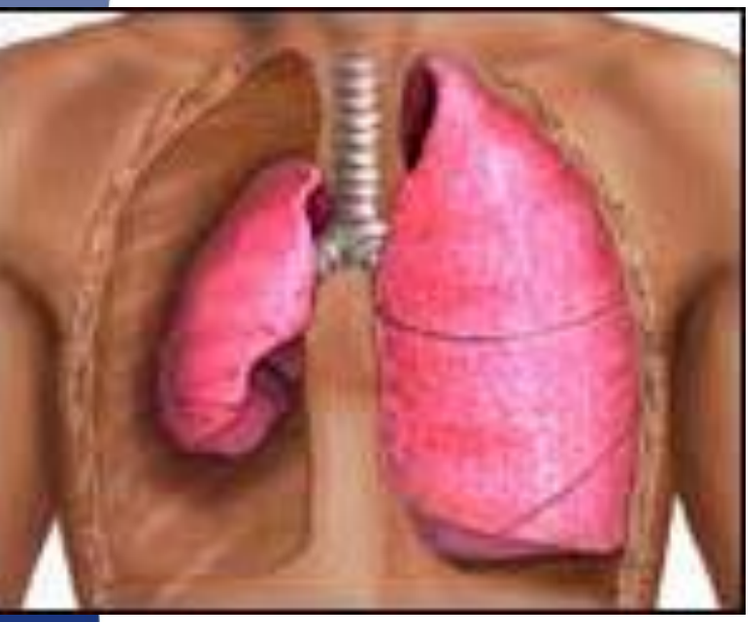
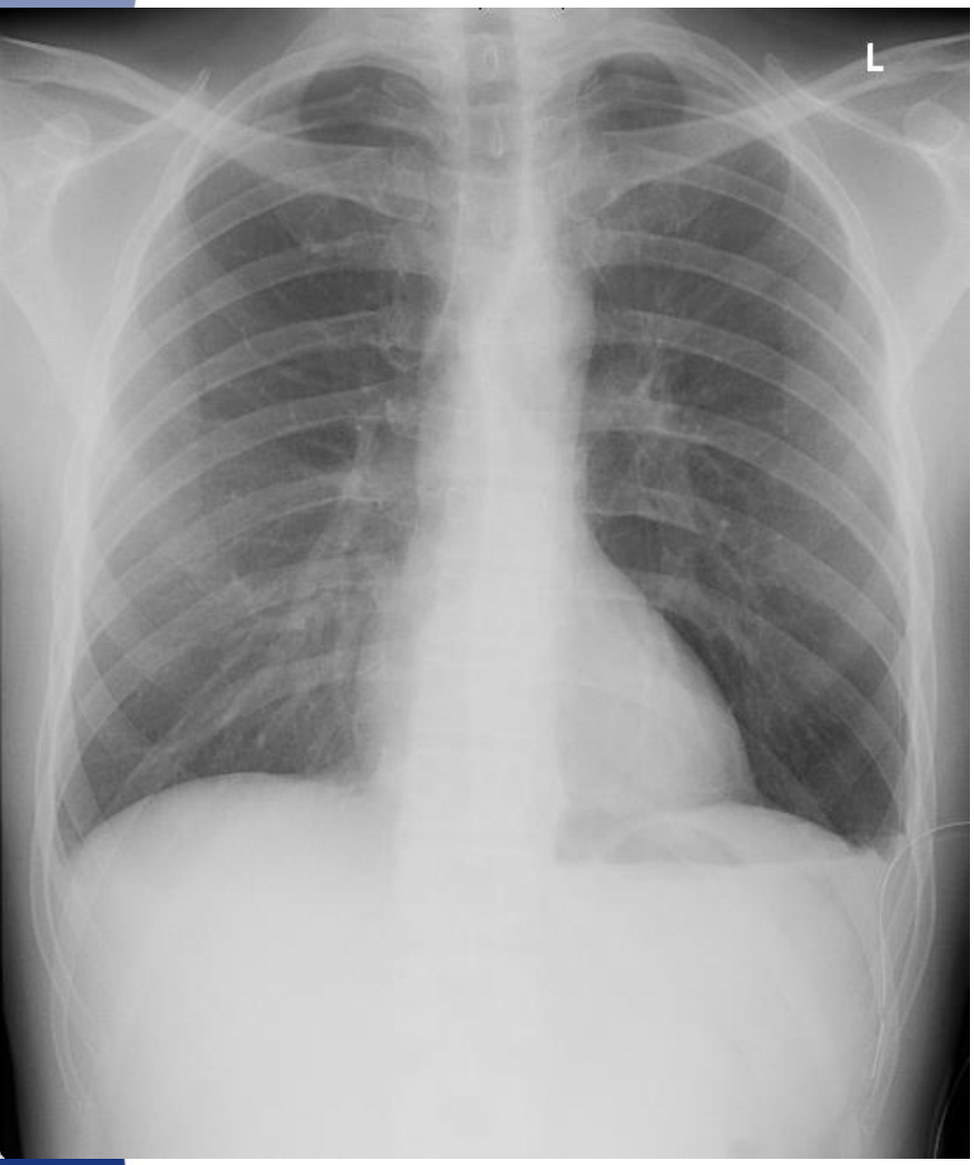


TABLE 1. CLASSIFICATION OF PNEUMOTHORAX ACCORDING TO CAUSE.

Spontaneous
Primary: no clinical lung disease
Secondary: a complication of clinically apparent lung disease
Traumatic
Due to penetrating chest injury
Due to blunt chest injury
Iatrogenic
Due to transthoracic-needle aspiration
During placement of a catheter in the subclavian vein
Due to thoracentesis and pleural biopsy
Due to barotrauma

Sahn SA, Heffner JE. *Spontaneous pneumothorax.* N Engl J Med. 2000 Mar 23;342(12):868-74.

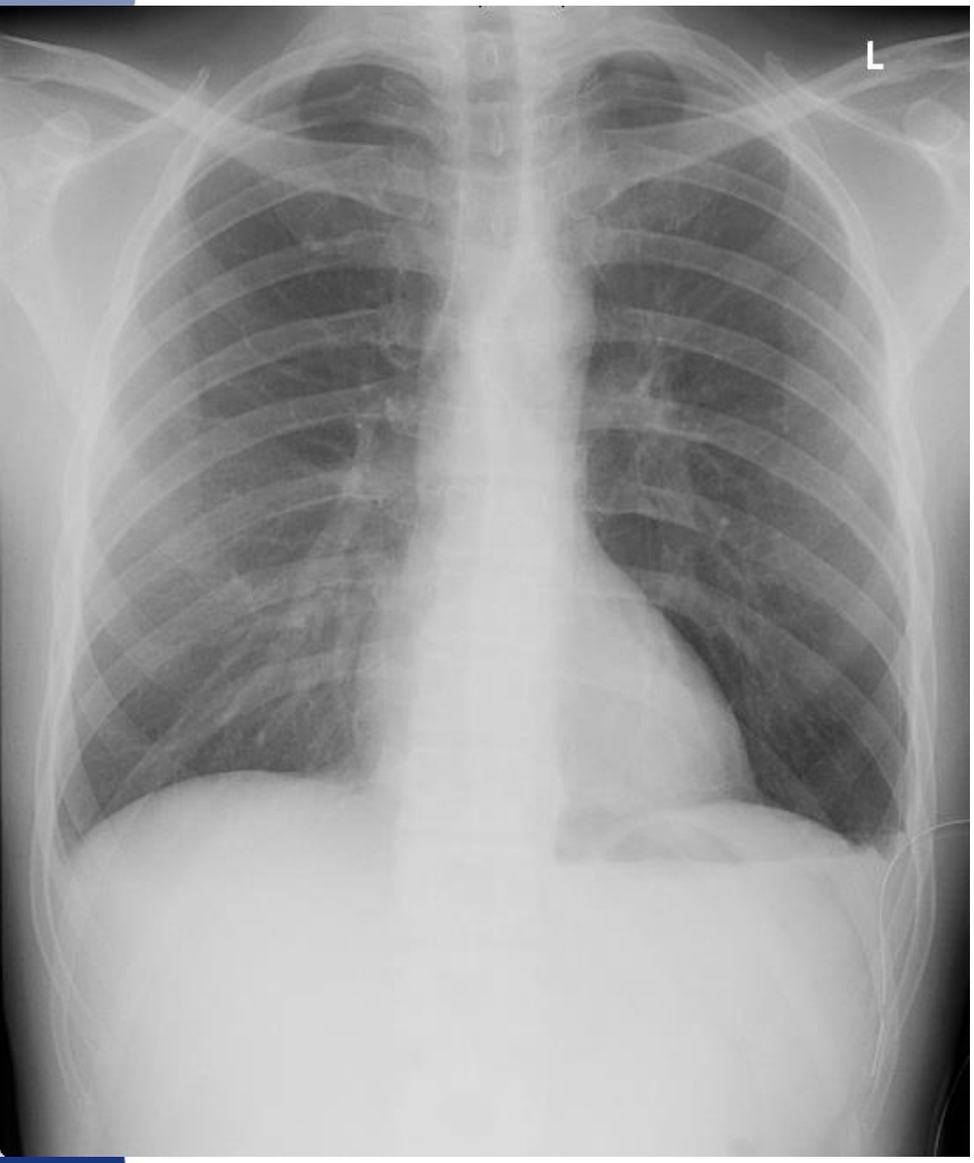
Spontaneous Pneumothorax diagnosed on chest X-ray

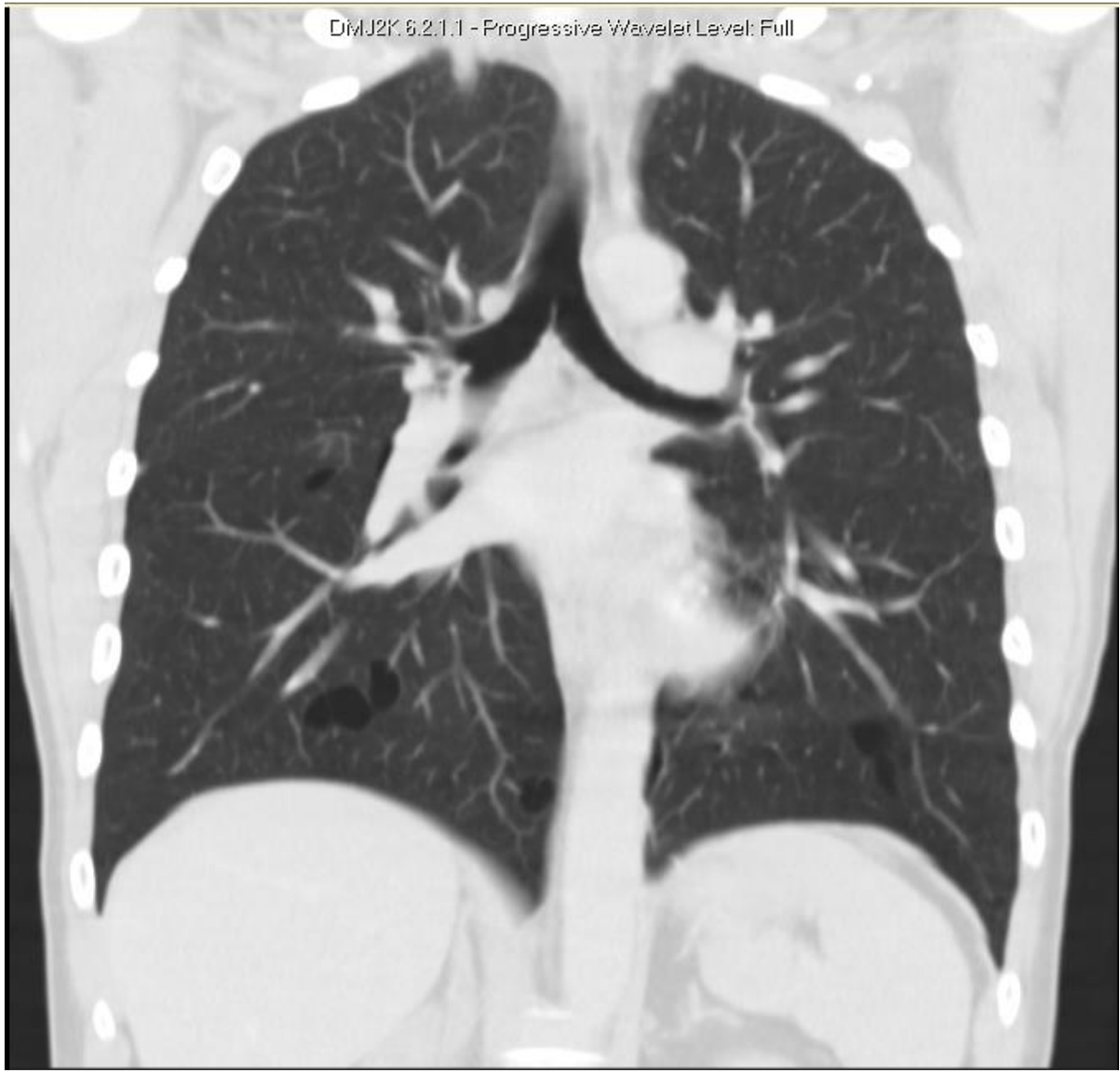


Johannesma PC, Houweling AC, Postmus PE, et al. *The pathogenesis of pneumothorax in Birt-Hogg-Dubé syndrome: a hypothesis.* Respirology (in press)

MacDuff A, Arnold A, Harvey J, et al. *Management of spontaneous pneumothorax: British Thoracic Society pleural disease guideline 2010.* Thorax 2010;65:ii18-31.

Imaging Chest X-ray versus Thoracic CT





Johannesma PC, Houweling AC, Postmus PE, et al. *The pathogenesis of pneumothorax in Birt-Hogg-Dubé syndrome: a hypothesis.* Respirology (in press)

Familial predisposition for pneumothorax

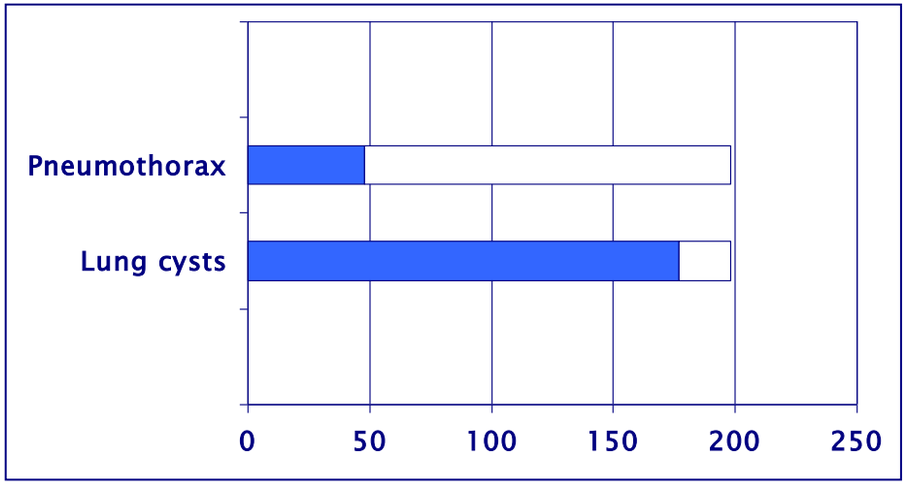
Disease	Gene(s)	Chromosomal location	Frequency Spontaneous Pneumothorax
Marfan syndrome	Fibrillin 1	15q21.1	4.4-11%
Homocystinuria	Cystathionine β-synthase	21q22.3	"minor feature"
Ehlers-Danlos syndrome	Multiple	Multiple	"rare reports"
α1-Antitrypsin deficiency	α1-Antitrypsin deficiency	14q32.1	"rare reports"
Lymphangioleiomyomatosis	TSC2	16p13	55%
Birt-Hogg-Dubé syndrome	Folliculin	17p11.2	30%

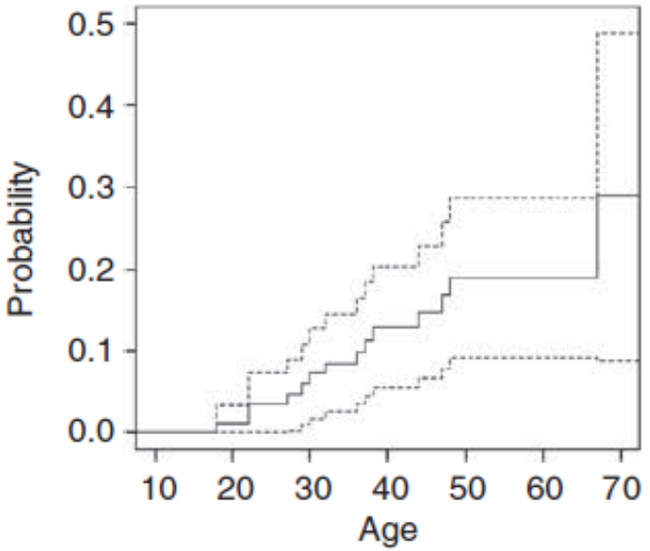
Clinical Presentation of Birt-Hogg-Dubé syndrome (BHD)

- Skin (Fibrofolliculomas)
- Lung cysts and (recurrent) spontaneous pneumothorax
- Renal cell cancer
- No geno- phenotype correlation found thus far

Pulmonary characteristics

- Lung cysts basal parts of the lung >90% of BHD patients
- Lung function unaffected
- 50-times increase in the risk of pneumothorax
- Houweling et al: Estimated pneumothorax risk: 29% age 70 (95% CI: 9-49%%)
- Median age 38
- Reports of SP in pediatric patients with BHD





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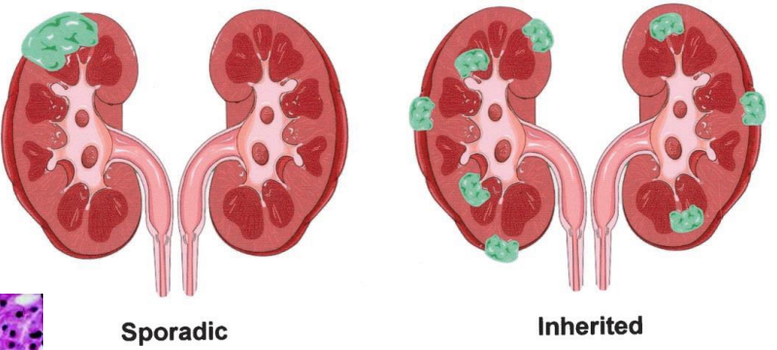
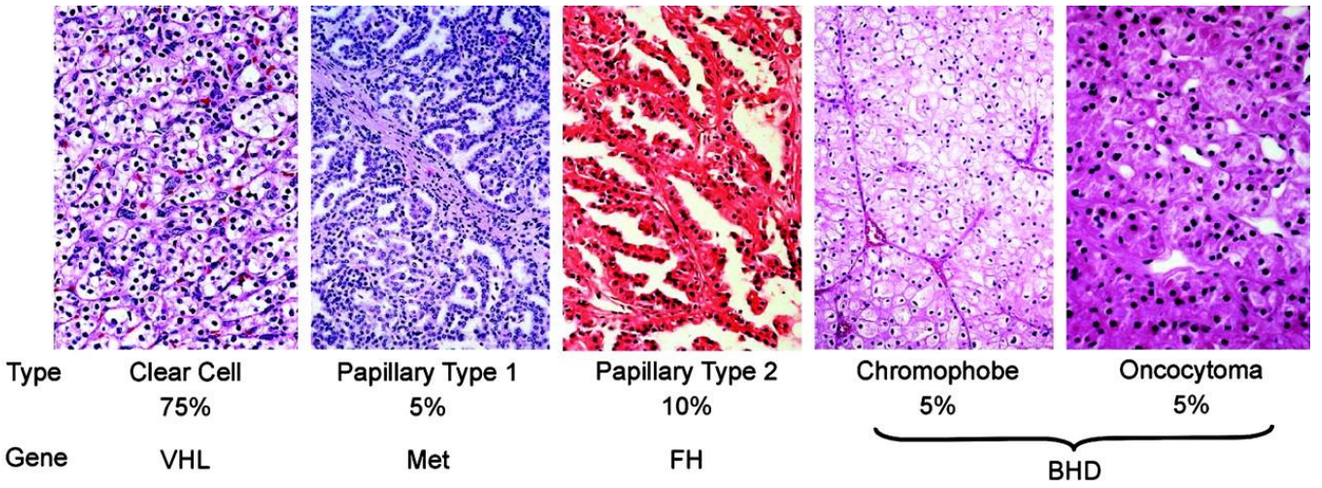
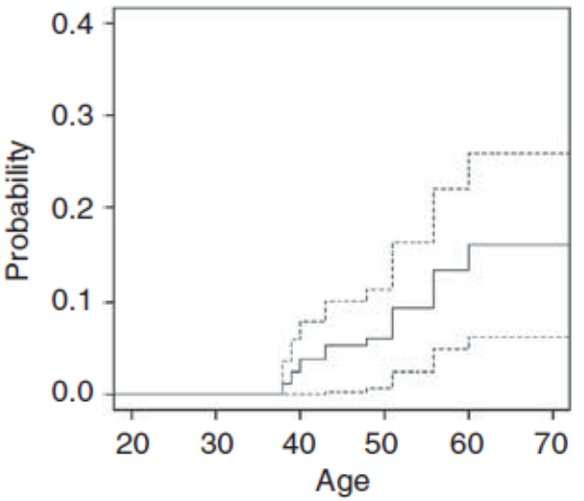
Menko FH et al. *Birt-Hogg-Dubé syndrome: diagnosis and management.* Lancet Oncol. 2009;10(12):1199-206.
Houweling AC, Gijezen LM, Jonker MA, et al. *Renal cancer and pneumothorax risk in BHD syndrome; an analysis of 115 FLCN mutation carriers.* Br J Cancer 2011;105:1912-19.
Toro JR, et al. *Lung cysts, spontaneous pneumothorax, and genetic associations in 8 families with Birt-Hogg-Dubé syndrome.* Am J Respir Crit Care Med. 2007;175(10):1044-53

Renal cell cancer risk in BHD patients







Houweling et al, 2011: Lifetime risk 16% (95% CI: 6-26%)

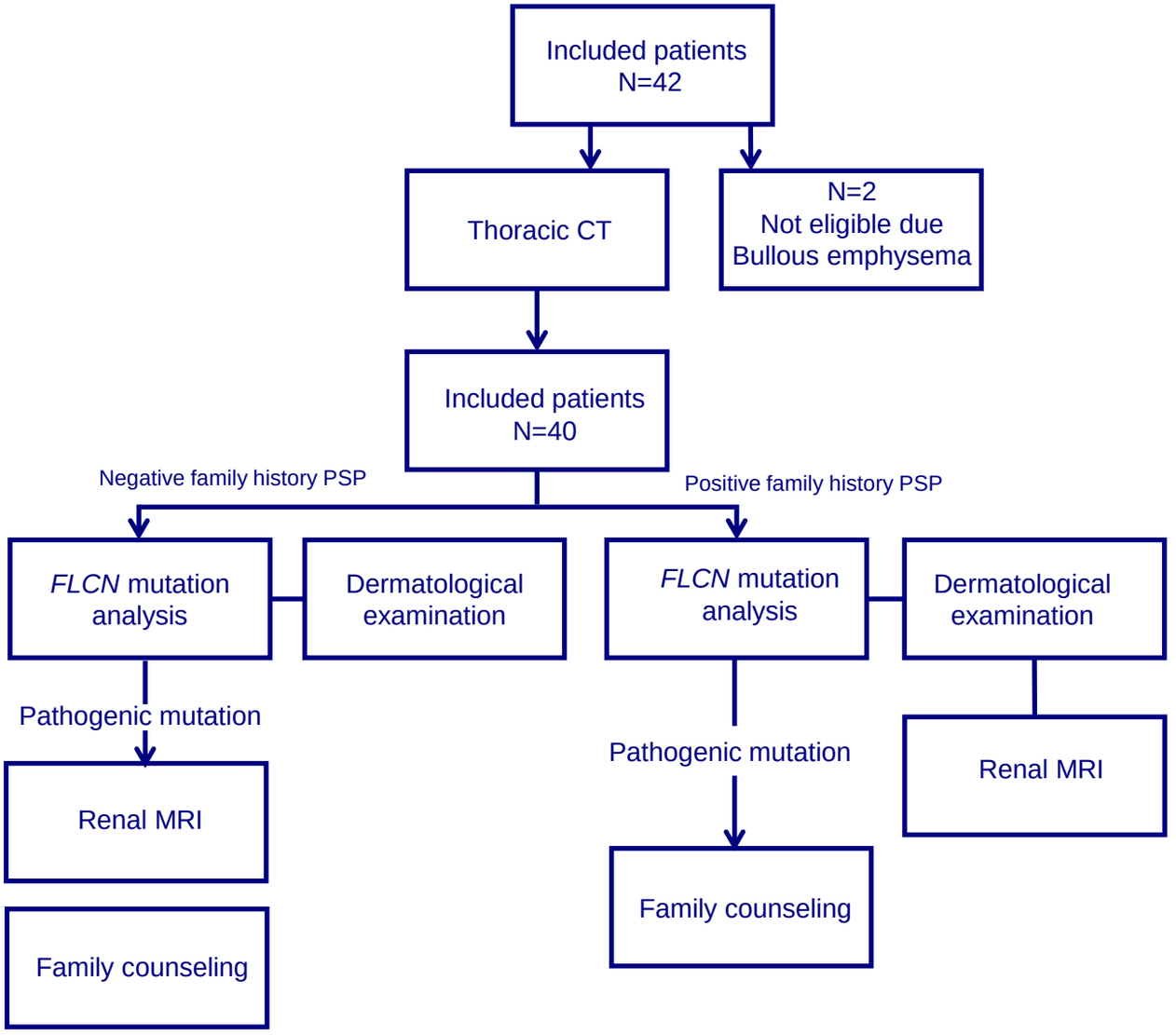
Toro et al, 2007: 34% at initial screening

Toro JR, Wei M-H, Glenn GM, et al. *BHD mutations, clinical and molecular genetic investigations of BHD syndrome… J* Med Genet 2008;45:321-331.

Linehan WM, Walther MM, Zbar B. *The genetic basis of cancer of the kidney.* J Urol 2006;170(6 Pt 1):2163-72.

Houweling AC, Gijezen LM, et al. *Renal cancer and pneumothorax risk in BHDS; an analysis of 115 FLCN mutation carriers from 35 BHD families.* Br. J. Cancer 2011; 105: 1912-1919

How frequent is BHD among patients with a primary SP?



Johannesma PC, Reinhard R, Kon Y, et al. *The prevalence of Birt-Hogg-Dubé syndrome among patients with apparently primary SP.* Respirology (in revision)

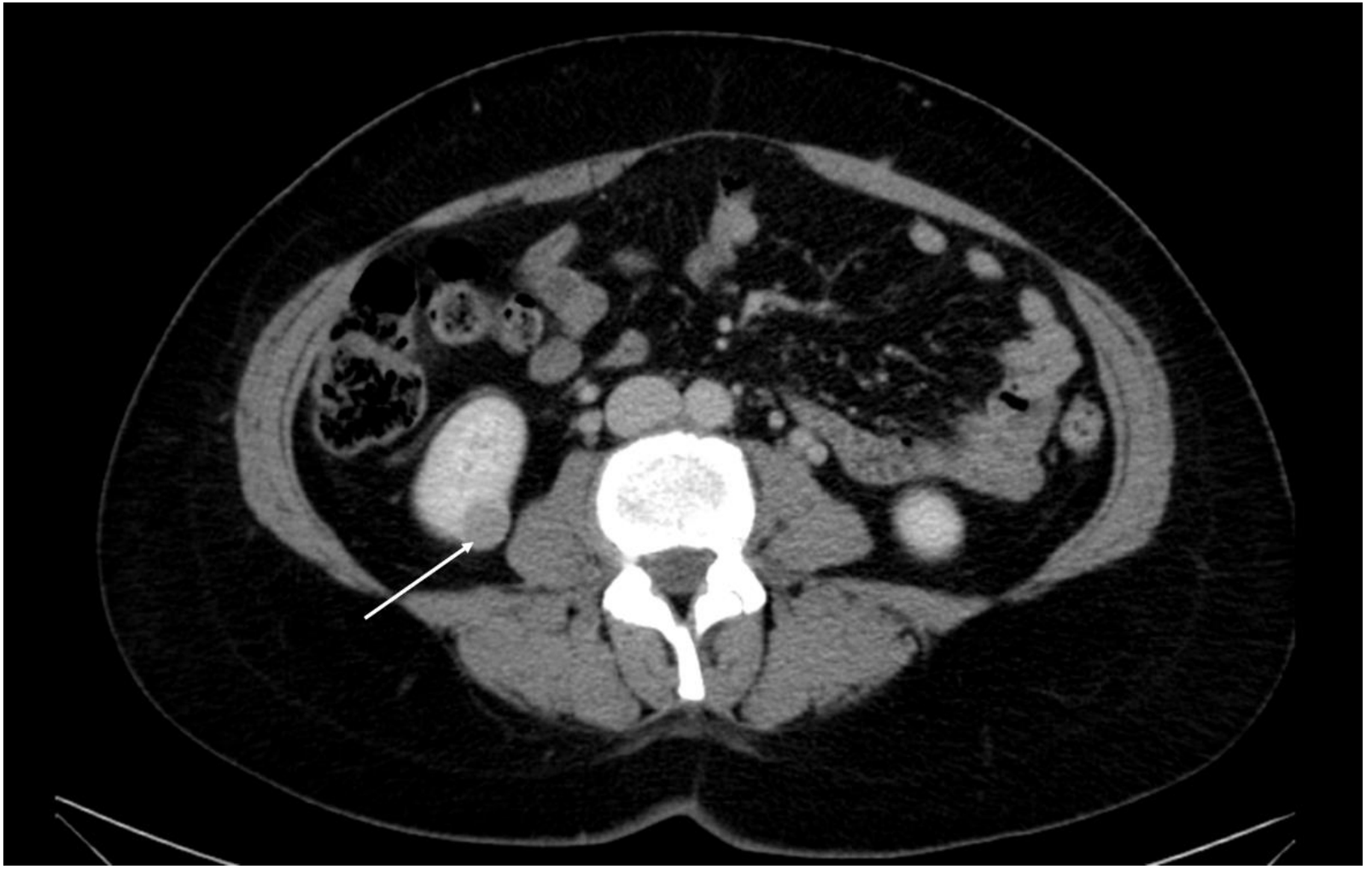
Characteristics of three spontaneous pneumothorax patients with pathogenic *FLCN* mutations

Patient (fam no.)	Gender (Age first PSP)	Delay between first symptom (PSP) and final diagnosis BHD (in months)	Recurrence of PSP	No. of recurrences PSP	Number of lung cysts	Renal tumour	FF	Smoking history	*FLCN* mutation	Counseled first degree family members	Found RCC in counseled family members
1 (84)	F (20)	243	Yes	8	13	No	Minimal	no	c.610_611delGCinsTA (p.Ala240X)	1	0
2 (85)	M (26)	153	Yes	6	140	No	Minimal	no	c.1408_1418del (p.Gly470fs)	2	0
3 (94)	M (40)	81	Yes	3	74	No	No	no	c.1539-2A>G	3	1

Comparable to study of Ren et al. (2008):
9.8% pathogenic *FLCN* mutation carriers among 102 primairy SP patients

Johannesma PC, Reinhard R, Kon Y, et al. *The prevalence of Birt-Hogg-Dubé syndrome among patients with apparently primary SP. Respirology* (in revision)

Ren HZ, Zhu CC, Yang C, et al. *Mutation analysis of the FLCN gene in Chinese patients with sporadic and familial isolated PSP.* Clin Genet 2008; **74**:178-183.

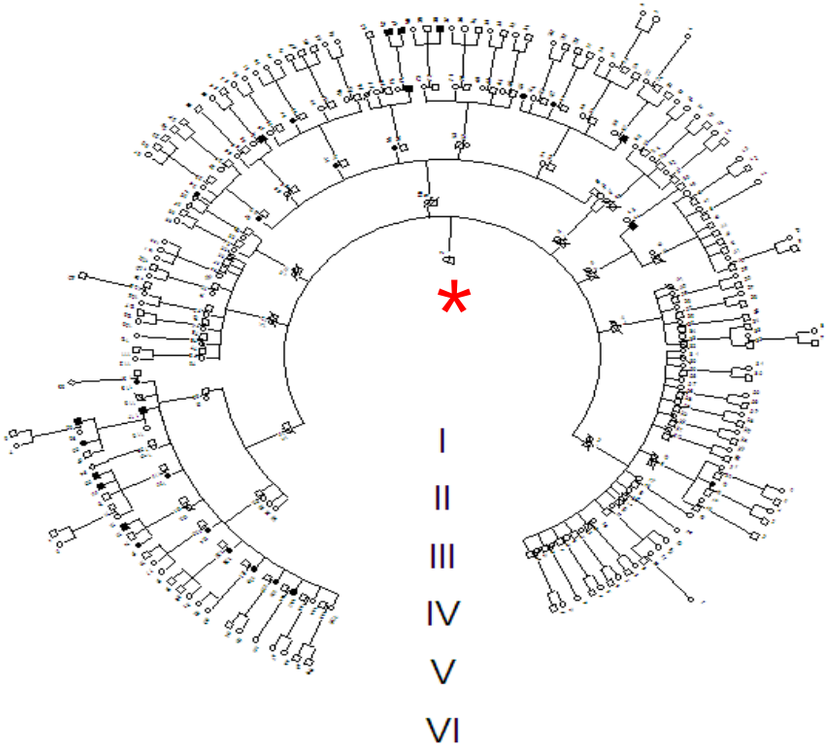


"This leads us to the question; If a thoracic CT would be performed in all SP patients and the patients with cysts in lower parts of lungs would be tested for BHD, how many RCC could then be detected?"

Johannesma PC, Reinhard R, Kon Y, et al. *The prevalence of Birt-Hogg-Dubé syndrome among patients with apparently primary SP.* Respirology (in revision)

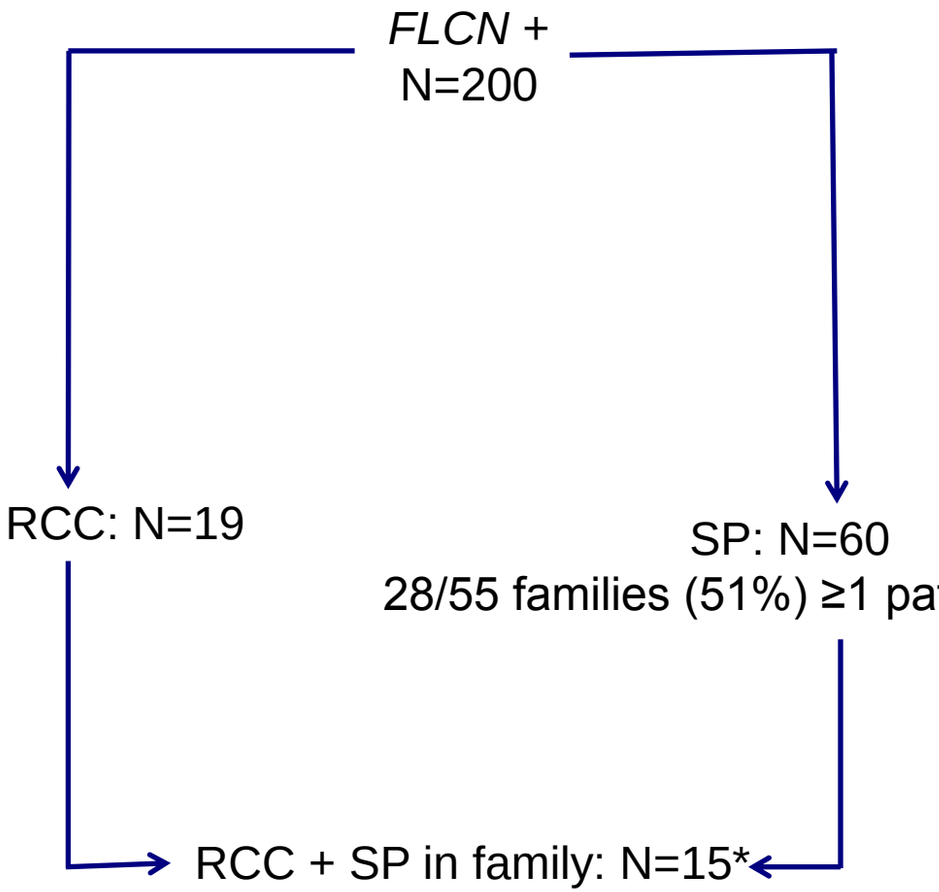
Cohort BHD patients; VU University Medical Center

- Retrospective evaluation
- 2004-2014
- 55 families
- N=200
- Mean 3.6 patients/ family (1-20)



*1872-1943 1875-1933

Evaluation of clinical and radiological characteristics among 200 *FLCN* mutation carriers in BHD 55 families.



* Including 7 patients with both RCC and SP

So far detection of BHD associated with SP revealed15 RCC patients in our cohort with mean FU of 5 years (1-10)

Current advice if BHD is detected

1. *FLCN* mutation analysis of at-risk family members
2. Surveillance of mutation carriers with renal imaging

1. 115 *FLCN* mutation carriers (Houweling AC, et al. Br. J. Cancer 2011; 105: 1912-1919)
2. Two new cases of RCC found during follow up (mean: 5 years follow up)
3. Extrapolating (2/115)x100 = 1.74 new cases per 5 years follow up
4. 0,30 new cases / 100 cases / year
5. 3 new cases of RCC /1000 cases/ year

Theoretical extrapolation current data:

1. Screening for pathogenic *FLCN* mutation of 3.6 patients per BHD family

2. Diagnosing 100 (new) families > 360 pathogenic *FLCN* mutation carriers

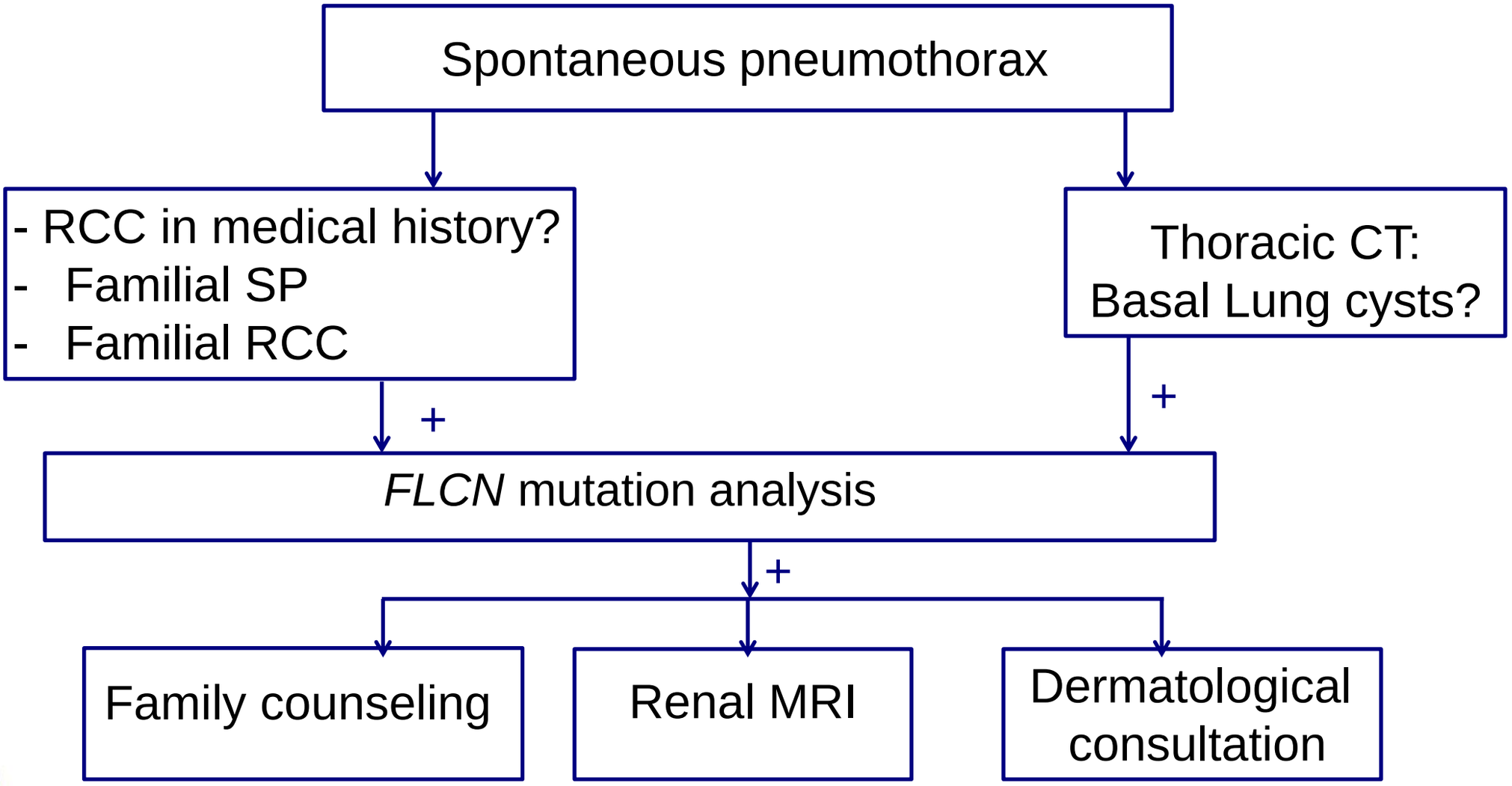
3. At age 70; 6-26%* lifetime risk to develop RCC will lead to 33-94 new RCC patients

* 95% Confidence Interval

Houweling AC, Gijezen LM, et al. *Renal cancer and pneumothorax risk in BHDS; an analysis of 115 FLCN mutation carriers from 35 BHD families.* Br. J. Cancer 2011; 105: 1912-1919

Toro JR, Pautler SE, Stewart L, et al. Lung cysts, spontaneous pneumothorax and genetic associations in 89 families with BHD. Am J Respir Crit Care Med. 2007;175:1044-53.

Flowchart for spontaneous pneumothorax



Conclusion

- In our pilot study 7.5% of all SP caused by pathogenic *FLCN* mutation
- Including (low dose) thoracic CT can lead to identification BHD families
- Annual renal imaging offered to affected relatives > detection RCC
- Limited period of observation leads to detection of RCC at early stage

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