Genetic Counselling in a Pulmonary Hypertension Referral Center

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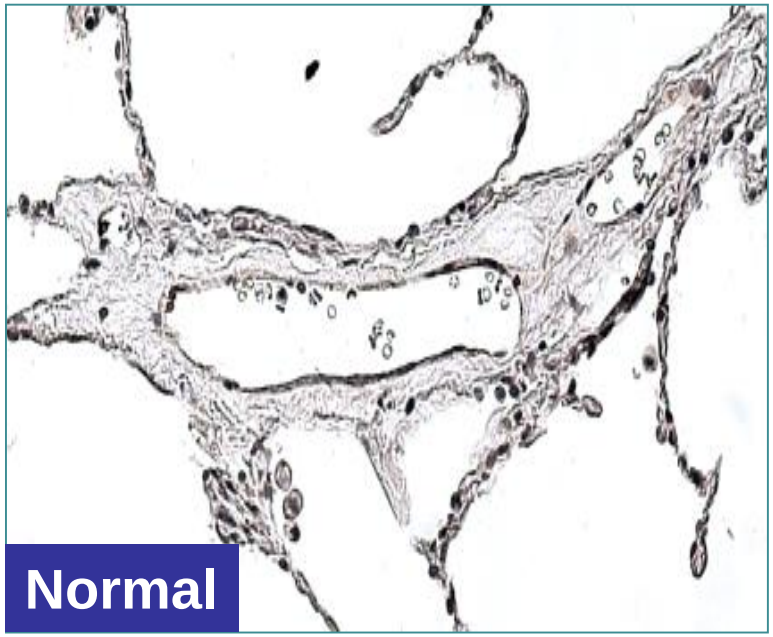
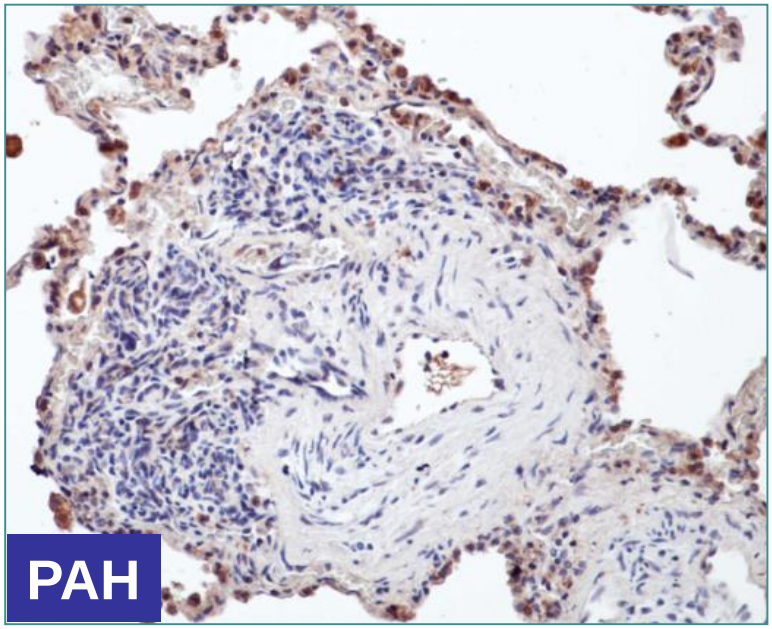
Disclosure

–**Actelion:** consultancy (current), board or advisory committee (current), speaker (current)
–**Bayer:** consultancy (current), board or advisory committee (current), speaker (current)
–**GSK:** consultancy (current), board or advisory committee (current), speaker (current), research support (current)
–**Novartis:** consultancy (current), board or advisory committee (current), speaker (current), research support (current)
–**Pfizer:** consultancy (current), board or advisory committee (current), speaker (current), research support (past)

Pulmonary arterial hypertension: A severe pulmonary vascular disease

- **Definition**: chronic pre-capillary pulmonary hypertension (PAPm ≥ 25 mmHg, PAPO ≤ 15 mmHg
- **Cause**: progressive structural remodeling of the small pulmonary arteries
- **Consequence**: right heart failure and death

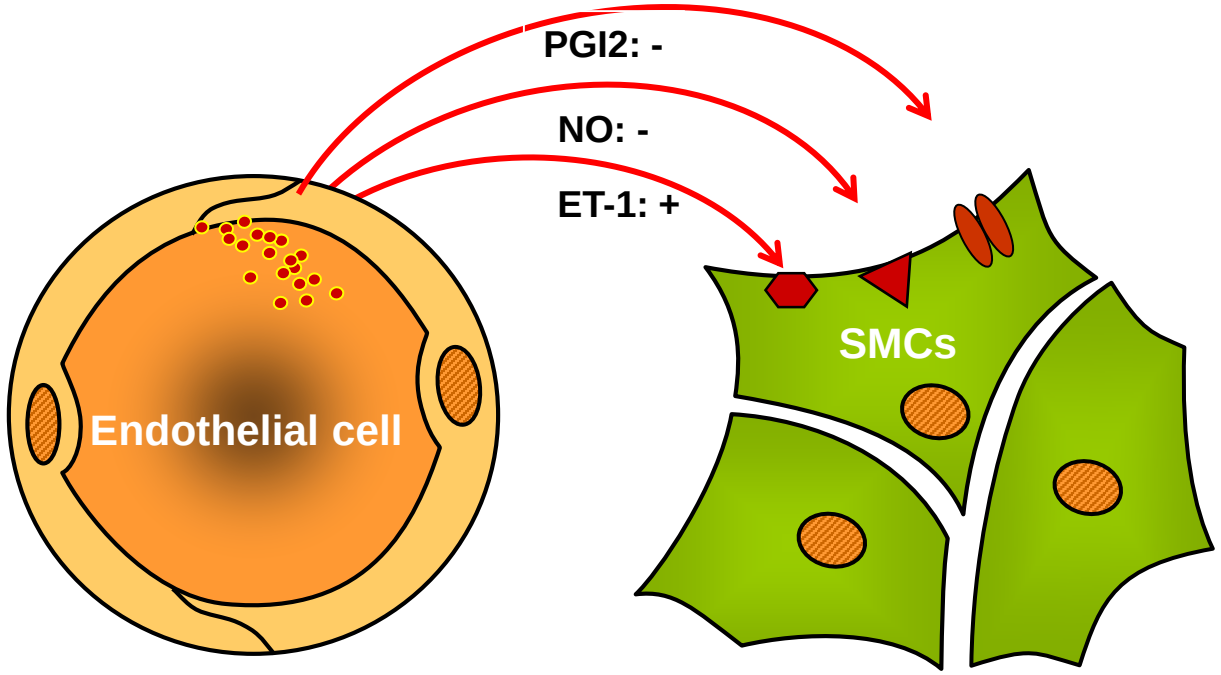




PAH, pulmonary arterial hypertension. Images are presenter's own.
Galiè N *et al. Eur Heart J* 2016;37:67–119. Galiè N *et al. Eur Respir J* 2015;46:903–75.

Pulmonary arterial hypertension: A rare, but not an orphan, disease

- **Rare**: prevalence 15–50/million (incidence 6/million/year)
- **Pathophysiology**: pulmonary artery endothelial cell dysfunction
- **Drugs**: 10 agents approved in the last 15 years (orphan drug status)
- **Lung/heart–lung transplantation**: if refractory to medical therapy



ET-1, endothelin-1; NO, nitric oxide; PGI2, prostacyclin; SMC, smooth muscle cell.
Galiè N *et al. Eur Heart J* 2016;37:67–119. Galiè N *et al. Eur Respir J* 2015;46:903–75.

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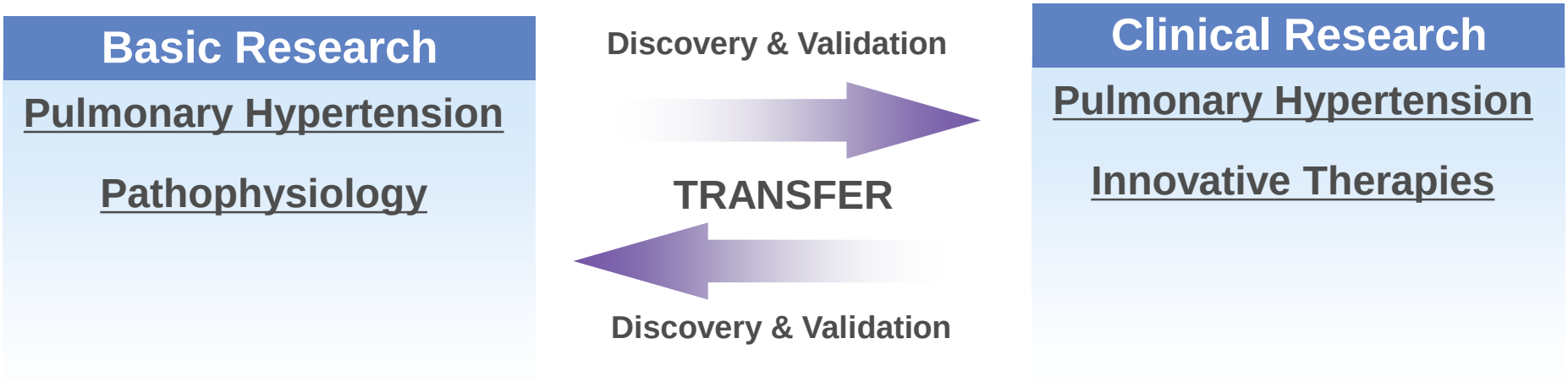

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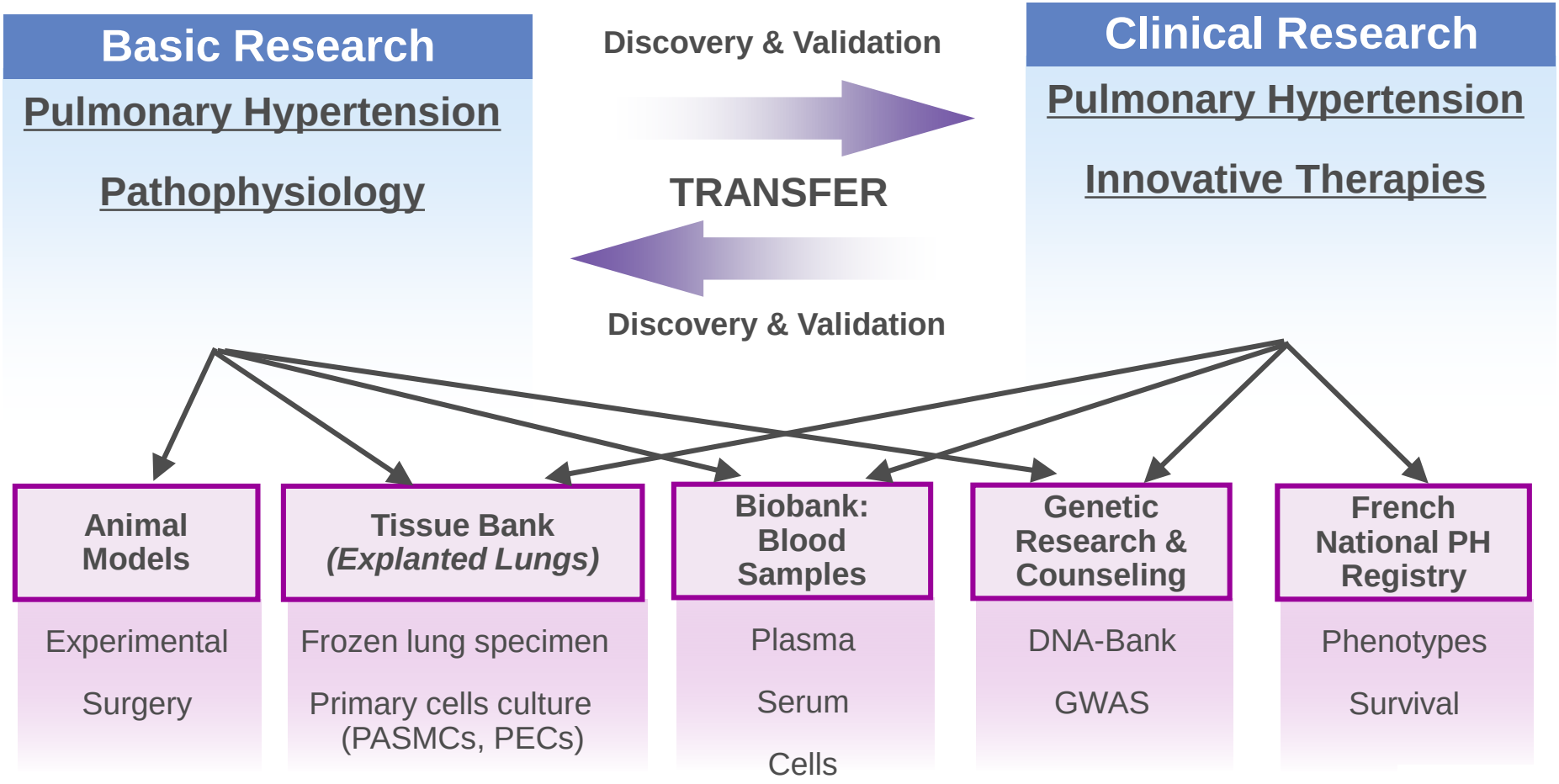

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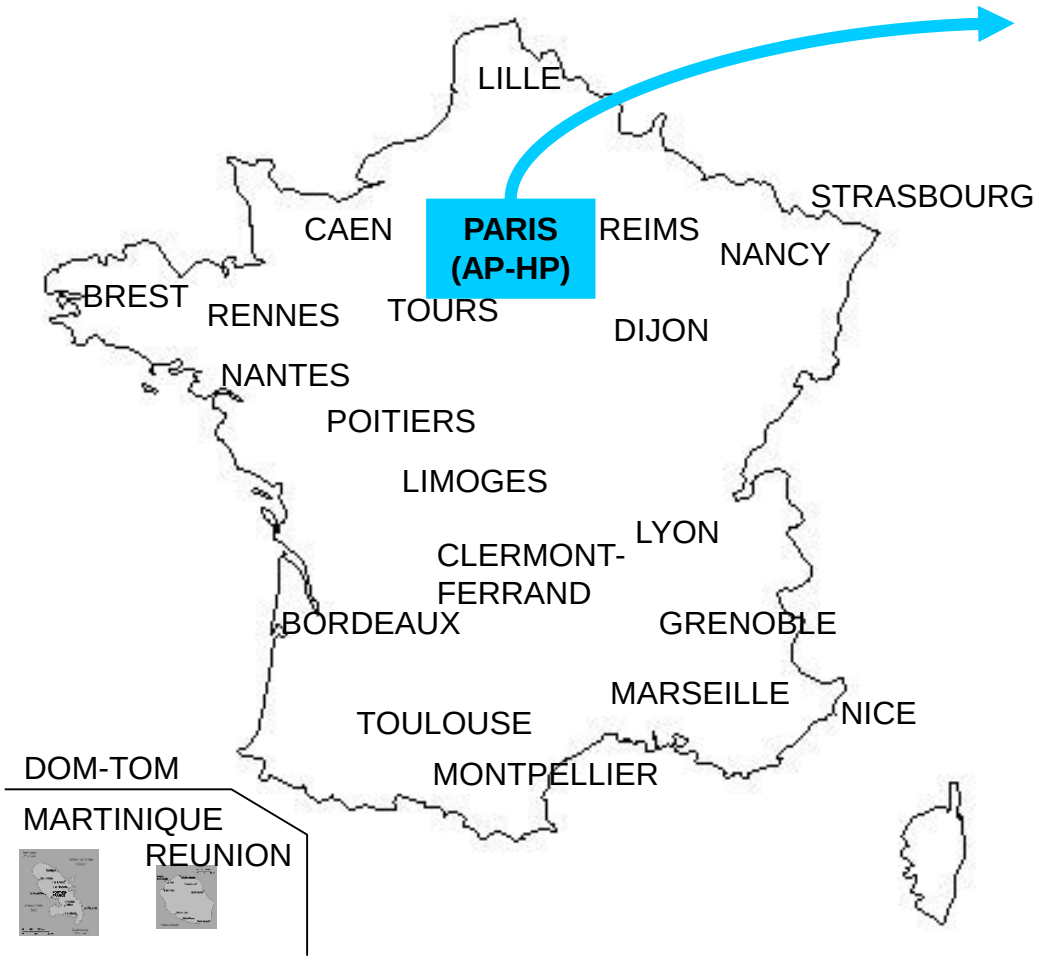
Pulmonary vascular centers in France: The French Pulmonary Hypertension Network



In Paris:
<u>National Reference Center</u>: AP-HP, Hôpitaux Universitaires Paris-Sud with 2 related centers: AP-HP, Necker (Pediatrics) and Marie Lannelongue (Thoracic Surgery & Transplantation)

Outside Paris:
<u>22 Competence Centers</u> (2 overseas)

CLASSIFICATION

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 diseases (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 EIF2AK 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

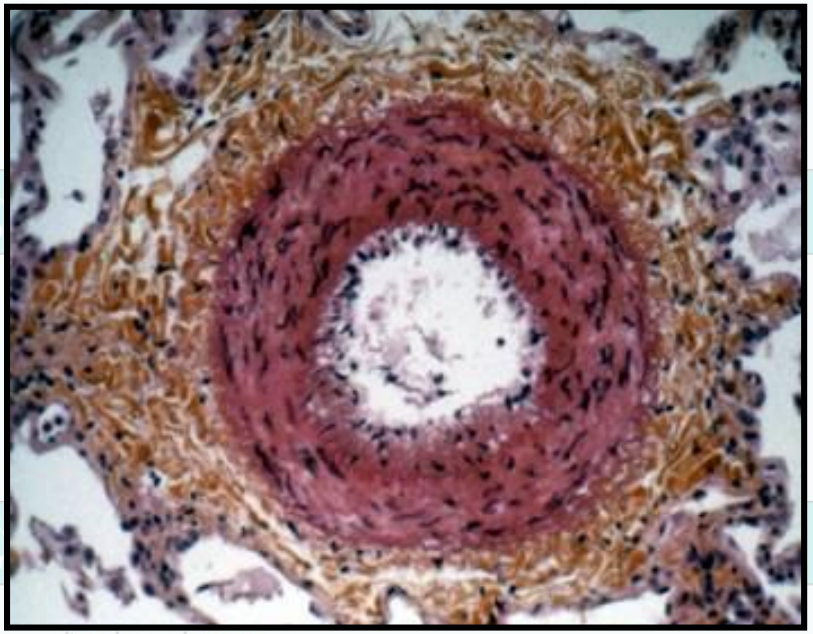
1''. Persistent pulmonary hypertension of the newborn

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



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

Eur Respir J 2015; 46: 903-75; Eur Heart J 2016; 37:67-119

BACKGROUND

2014 — **Bi-allelic mutations of *EIF2AK4*** gene involved in the development of PVOD

2013 — ***KCNK3 and TBX4*** genes involved in the development of PAH

2012 — ***Caveolin-1*** gene involved in the development of PAH

2011 — ***Smad1*** (one case) and ***Smad5*** (one case) genes involved in the development of PAH

2009 — ***Smad8*** gene involved in the development of PAH : (2 cases)

2003 — - ***Endogline*** gene involved in the development of PAH

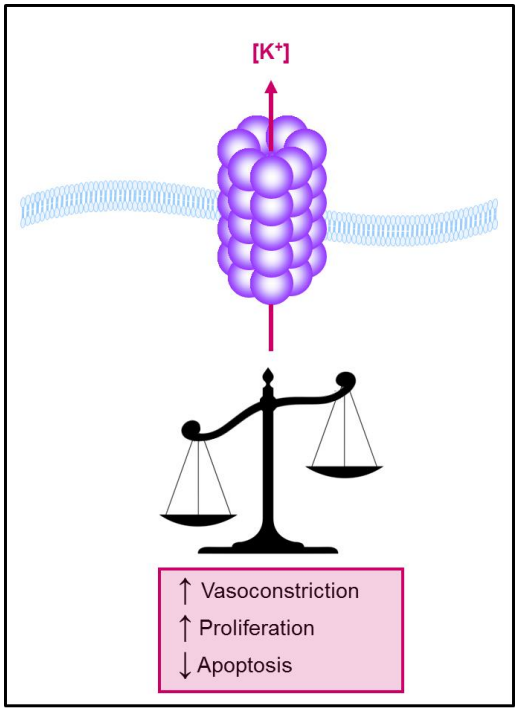
- **<u>Begining of genetic counseling in France</u>**

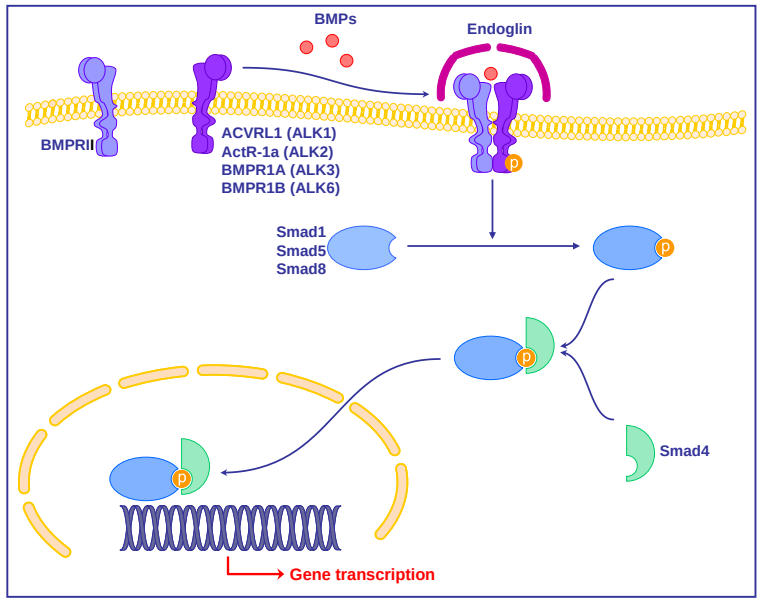
2001 — ***ALK1 (ACVRL1)*** gene involved in the development of PAH

2000 — ***BMPR2*** gene involved in the development of PAH

1997 — Locus implicated in PAH development localised on chromosome 2

1954 — First familial Pulmonary Hypertension described





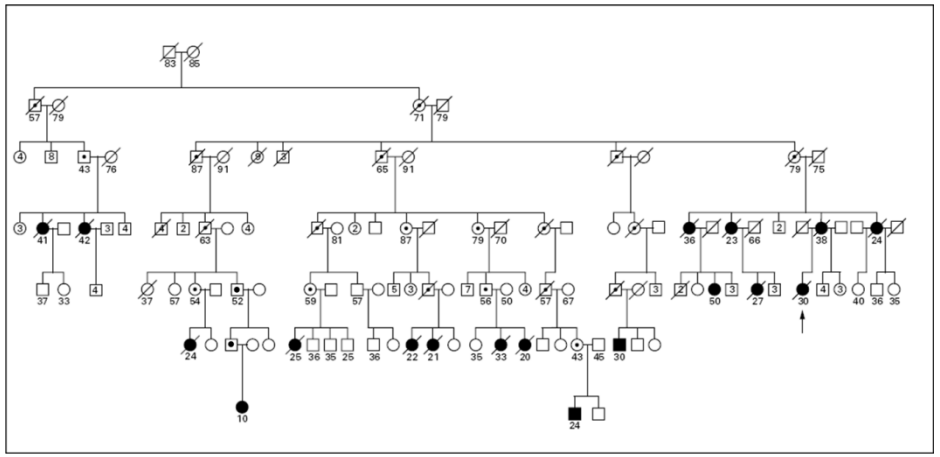
GENETIC TRANSMISSION

➢ **PAH :**

- *BMPR2, ALK1, END, KCNK3, Calveolin-1, Smad1/5/8, TBX4.*

- Autosomal dominant

- Incomplete penetrance (14% in males , 42% in females)

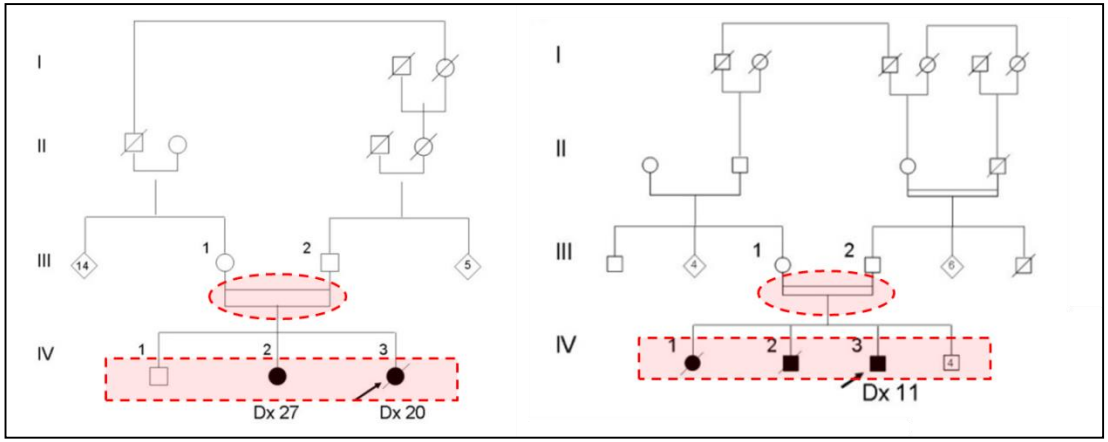


➢ **PVOD :**

- *EIF2AK4*

- Autosomal recessive

- Penetrance to be determined (#100%)



Genetic counselling in PAH and PVOD patients

ORIGINAL ARTICLE
PULMONARY VASCULAR DISEASES

Genetic counselling in a national referral centre for pulmonary hypertension

Barbara Girerd[1,2,3,6], David Montani[1,2,3,6], Xavier Jaïs[1,2,3], Mélanie Eyries[4], Azzedine Yaici[1,2,3], Benjamin Sztrymf[1,2,3], Laurent Savale[1,2,3], Florence Parent[1,2,3], Florence Coulet[4], Laurent Godinas[1,2,3], Edmund M. Lau[1,2,5], Yuichi Tamura[1,2,3], Olivier Sitbon[1,2,3], Florent Soubrier[4], Gérald Simonneau[1,2,3] and Marc Humbert[1,2,3]

Girerd B. Eur Respir J 2016

GENETIC COUNSELLING

Strategy in the French PAH network:

- Genetic couselling and testing are offered to all patients with:
  - PAH (idiopathic / familial / drug and toxin-induced)
  - PVOD (idiopathic / familial / drug and toxin-induced)

- Informed written consent is mandatory

- Genetic counselling is done in an individual consultation

- **Next generation Sequencing (NGS)**

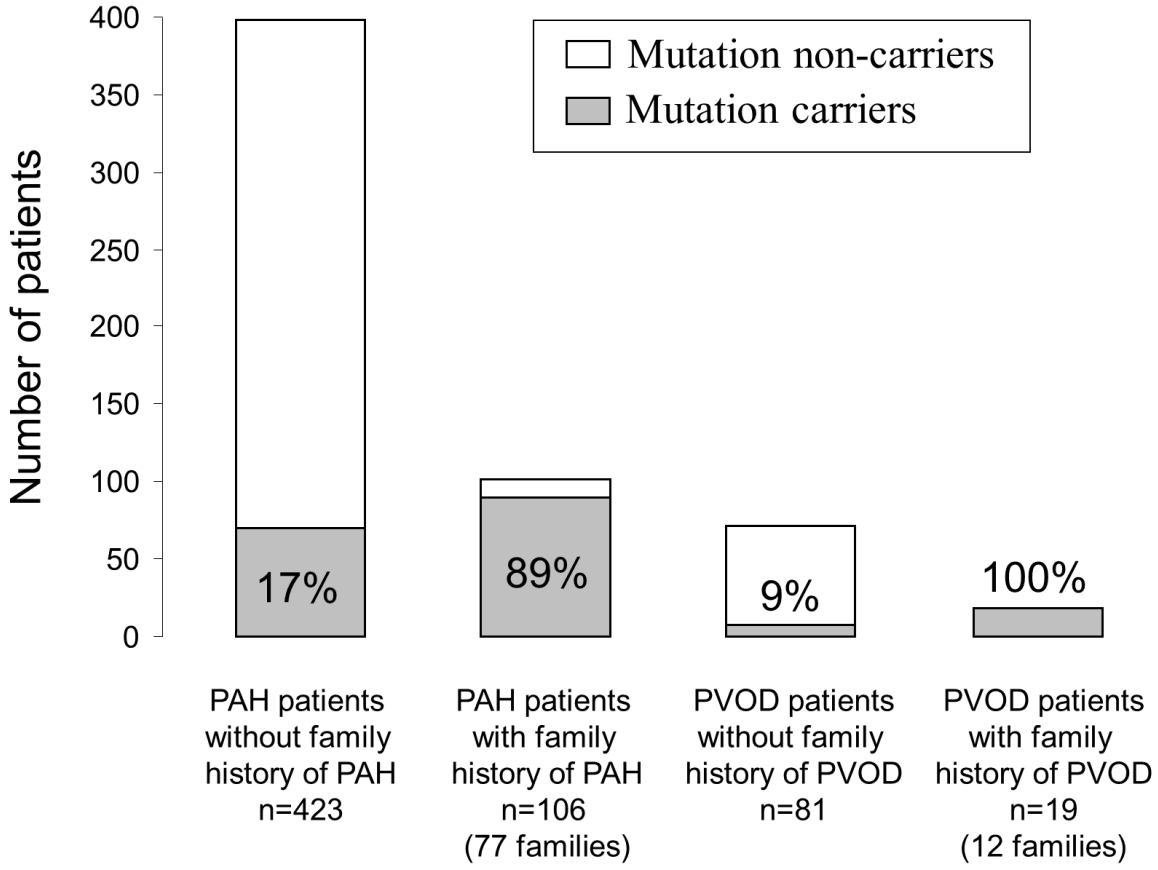
BMPR2, ACVRL1, ENG, CAV1, KCNK3, SMAD9, TBX4, SMAD4, EIF2AK4

- The prescriber informs directly the person who underwent the genetic test in an individual consultation

- A consultation with the psychologist is systematically offered because of the psychological impact of the genetic result

Girerd B. Eur Respir J 2016

MUTATIONS IDENTIFIED

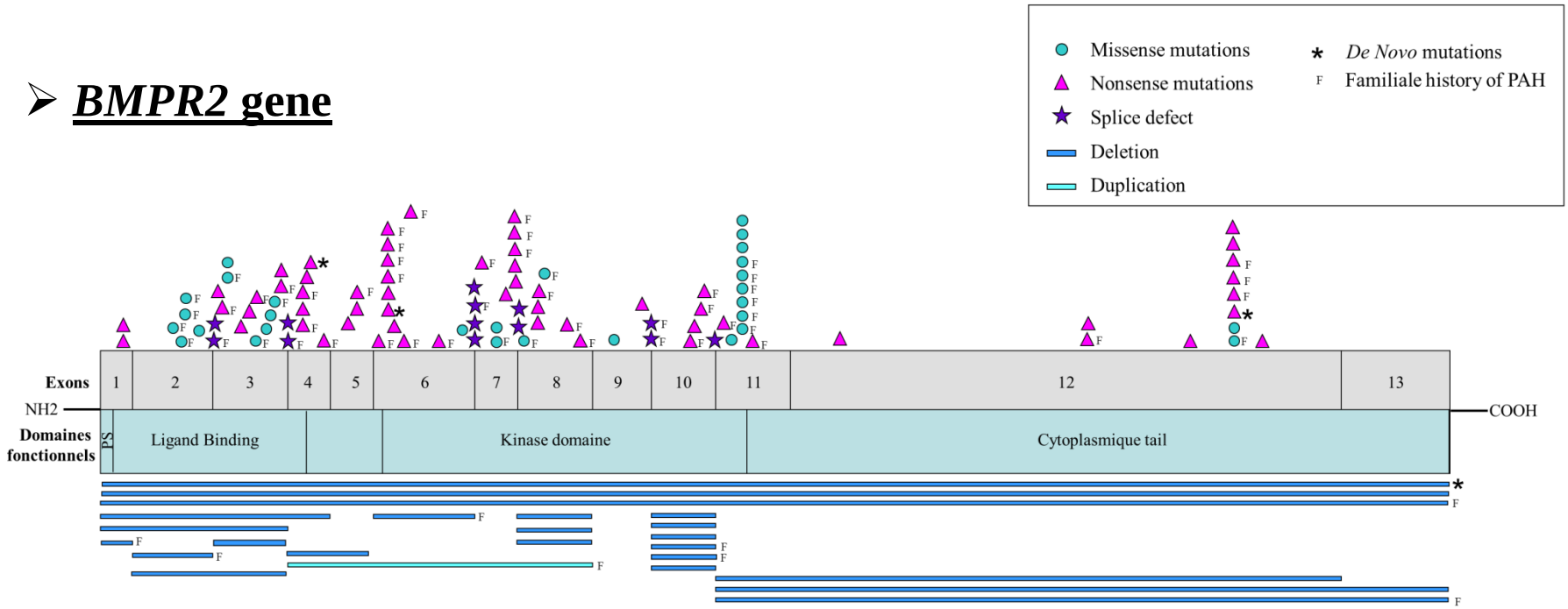


***BMPR2* mutation**	62	89 (65 families)	0	0
***ACVRL1* mutation**	9	3 (2 families)	-	0
***ENG* mutation**	1	0	-	0
***KCNK3* mutation**	-	2 (2 families)	-	-
***EIF2AK4* mutations**	-	0	7	19 (12 families)
Total mutations	72	94	7	19

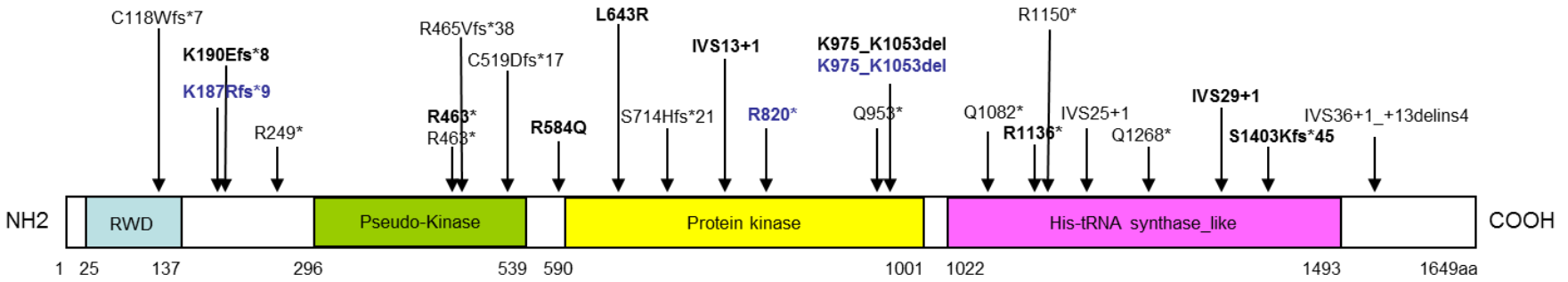
Girerd B. Eur Respir J 2016

MUTATIONS IDENTIFIED

➢ *BMPR2* gene



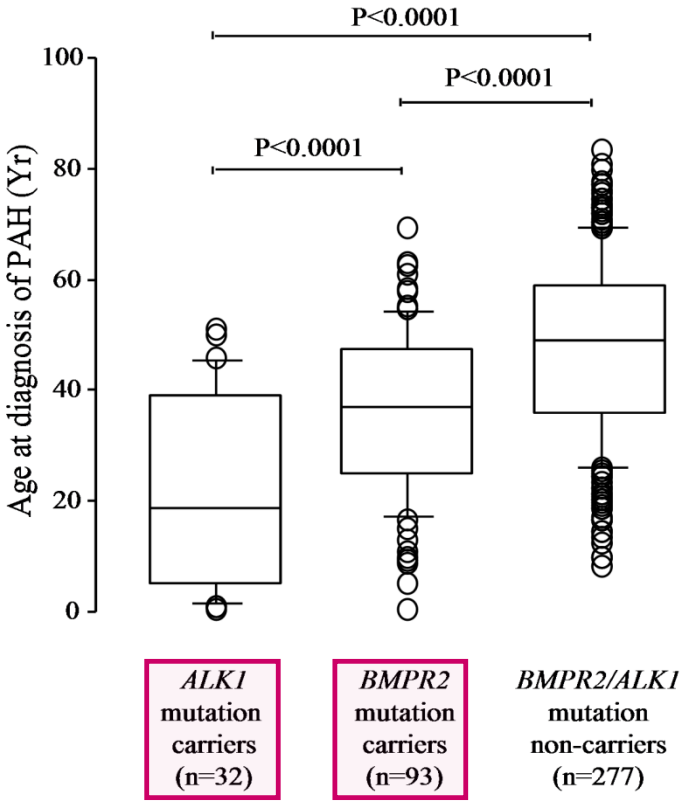
➢ *EIF2AK4* gene



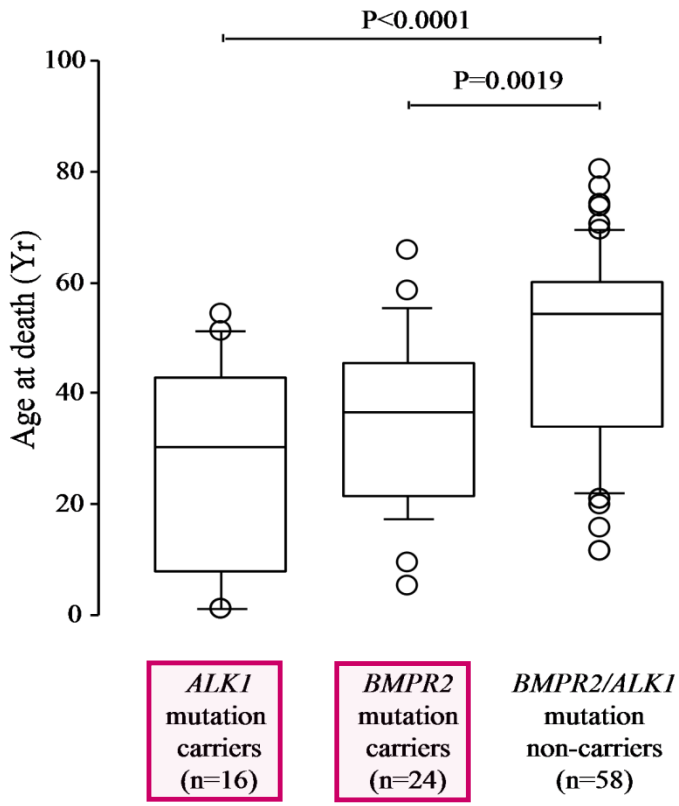
Girerd B. Eur Respir J 2016 , Eyries M, Nat Genet, 2014

PAH patients carrying *BMPR2* or *ALK1 (ACVRL1)* mutation were younger at diagnosis and at death compared to non carriers

Age at diagnosis



Age at death



Girerd, B, Am J Respir Crit Care Med 2010

BMPR2 mutations and survival in pulmonary arterial hypertension: an individual participant data meta-analysis

Jonathan D W Evans, Barbara Girerd, David Montani, Xiao-Jian Wang, Nazzareno Galiè, Eric D Austin, Greg Elliott, Koichiro Asano, Ekkehard Grünig, Yi Yan, Zhi-Cheng Jing, Alessandra Manes, Massimiliano Palazzini, Lisa A Wheeler, Ikue Nakayama, Toru Satoh, Christina Eichstaedt, Katrin Hinderhofer, Matthias Wolf, Erika B Rosenzweig, Wendy K Chung, Florent Soubrier, Gérald Simonneau, Olivier Sitbon, Stefan Gräf, Stephen Kaptoge, Emanuele Di Angelantonio, Marc Humbert*, Nicholas W Morrell**

Interpretation Patients with PAH and *BMPR2* mutations present at a younger age with more severe disease, and are at increased risk of death, and death or transplantation, compared with those without *BMPR2* mutations.

Sztrymf B, Am J Respir Crit Care Med 2008
Girerd, B, Am J Respir Crit Care Med 2010
Evans JDW, Lancet Resp Med 2016

BMPR2 mutations and survival in pulmonary arterial hypertension: an individual participant data meta-analysis

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	All patients	BMPR2 mutation status		
		Non-carriers (N=1102)	Carriers (N=448)	p value
Age at diagnosis (N=1447), years	40·1 (17·2)	42·0 (17·8)	35·4 (14·8)	<0·0001
Male sex	440/1545 (28%)	302/1097 (28%)	138/448 (31%)	0·20
Family history of PAH	202/1376 (15%)	--	202/402 (50%)	--
Body-mass index (N=1206), kg/m²	24·9 (9·1)	24·9 (10·6)	24·9 (5·9)	0·99
6-min walk distance (N=1072), m	378 (124)	374 (128)	388 (113)	0·088
NYHA functional class				0·38
I–II	423/1426 (30%)	313/1031 (30%)	110/394 (28%)	
III	896/1426 (63%)	647/1031 (63%)	249/394 (63%)	
IV	107/1426 (8%)	72/1031 (7%)	35/394 (9%)	
Mean pulmonary artery pressure (N=1503), mm Hg	57·6 (15·0)	56·4 (15·3)	60·5 (13·8)	<0·0001
Pulmonary vascular resistance (N=1300), Wood units	14·0 (8·4)	12·9 (8·3)	16·6 (8·3)	<0·0001
Right atrial pressure (N=1253), mm Hg	8·2 (5·5)	8·0 (5·7)	8·6 (5·2)	0·065
Cardiac output (N=1202), L/min	3·98 (1·44)	4·20 (1·50)	3·50 (1·17)	<0·0001
Cardiac index (N=1358), L/min per m²	2·40 (0·88)	2·51 (0·92)	2·11 (0·69)	<0·0001
Vasodilator responder	157/1287 (12%)	147/907 (16%)	10/380 (3%)	<0·0001

Evans JDW, Lancet Resp Med 2016

BMPR2 mutations and survival in pulmonary arterial hypertension: an individual participant data meta-analysis

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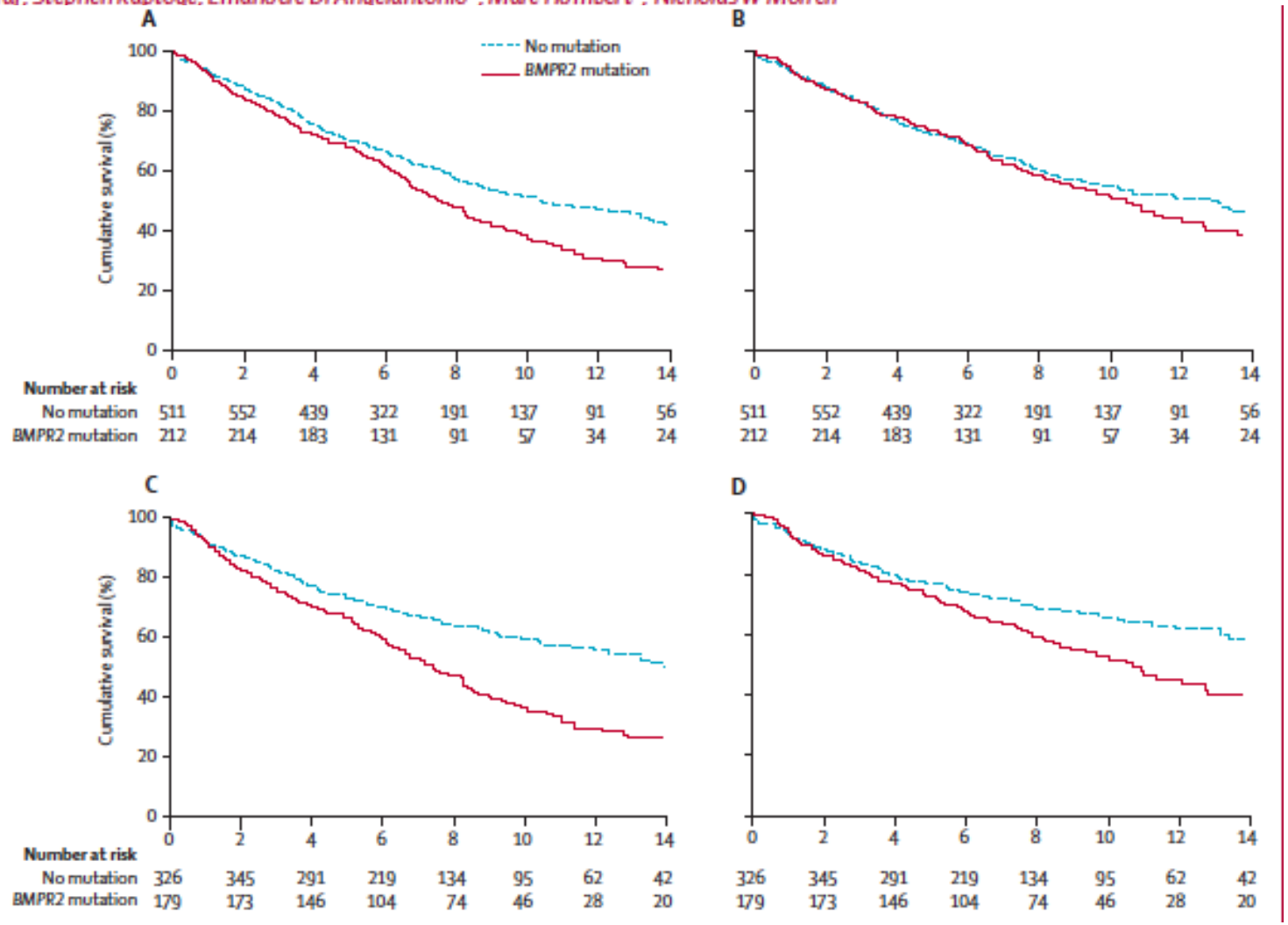


Evans JDW, Lancet Resp Med 2016

Clinical phenotypes and outcomes of heritable and sporadic pulmonary veno-occlusive disease: a population-based study

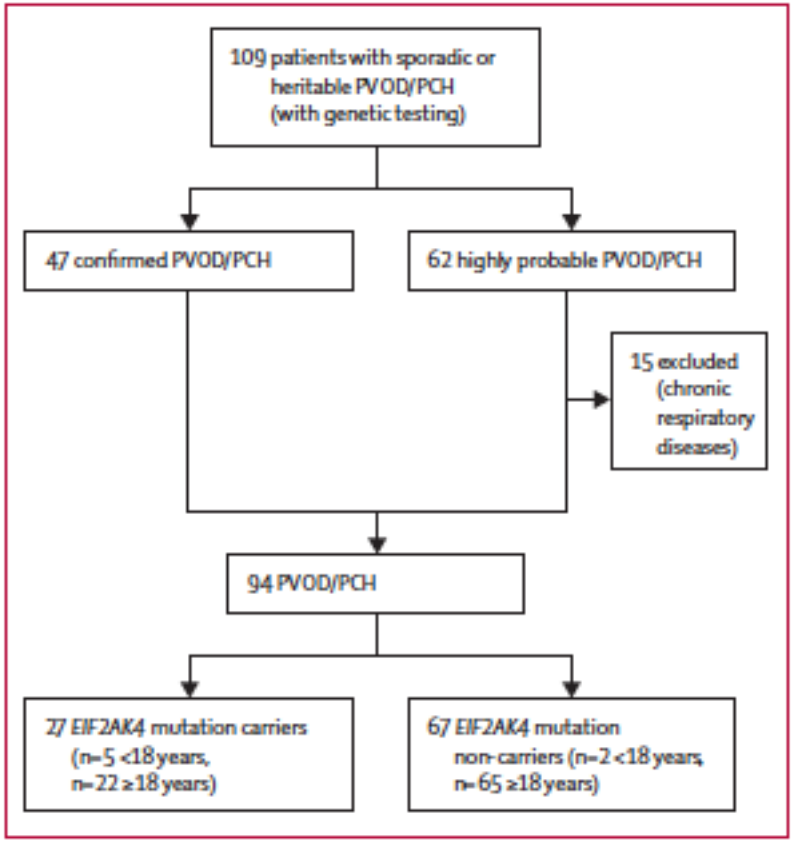
David Montani*, Barbara Girerd*, Xavier Jaïs, Marilyne Levy, David Amar, Laurent Savale, Peter Dorfmüller, Andrei Seferian, Edmund M Lau, Mélanie Eyries, Jérôme Le Pavec, Florence Parent, Damien Bonnet, Florent Soubrier, Elie Fadel, Olivier Sitbon, Gérald Simonneau, Marc Humbert

Lancet Respir Med 2017; 5: 125–34

Published Online January 10, 2017

Summary

Background Bi-allelic mutations of the *EIF2AK4* gene cause heritable pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis (PVOD/PCH). We aimed to assess the effect of *EIF2AK4* mutations on the clinical phenotypes and outcomes of PVOD/PCH.



Montani D, Lancet Resp Med 2017

PVOD patients carrying *EIF2AK4* mutations were younger at diagnosis and at death compared to non carriers

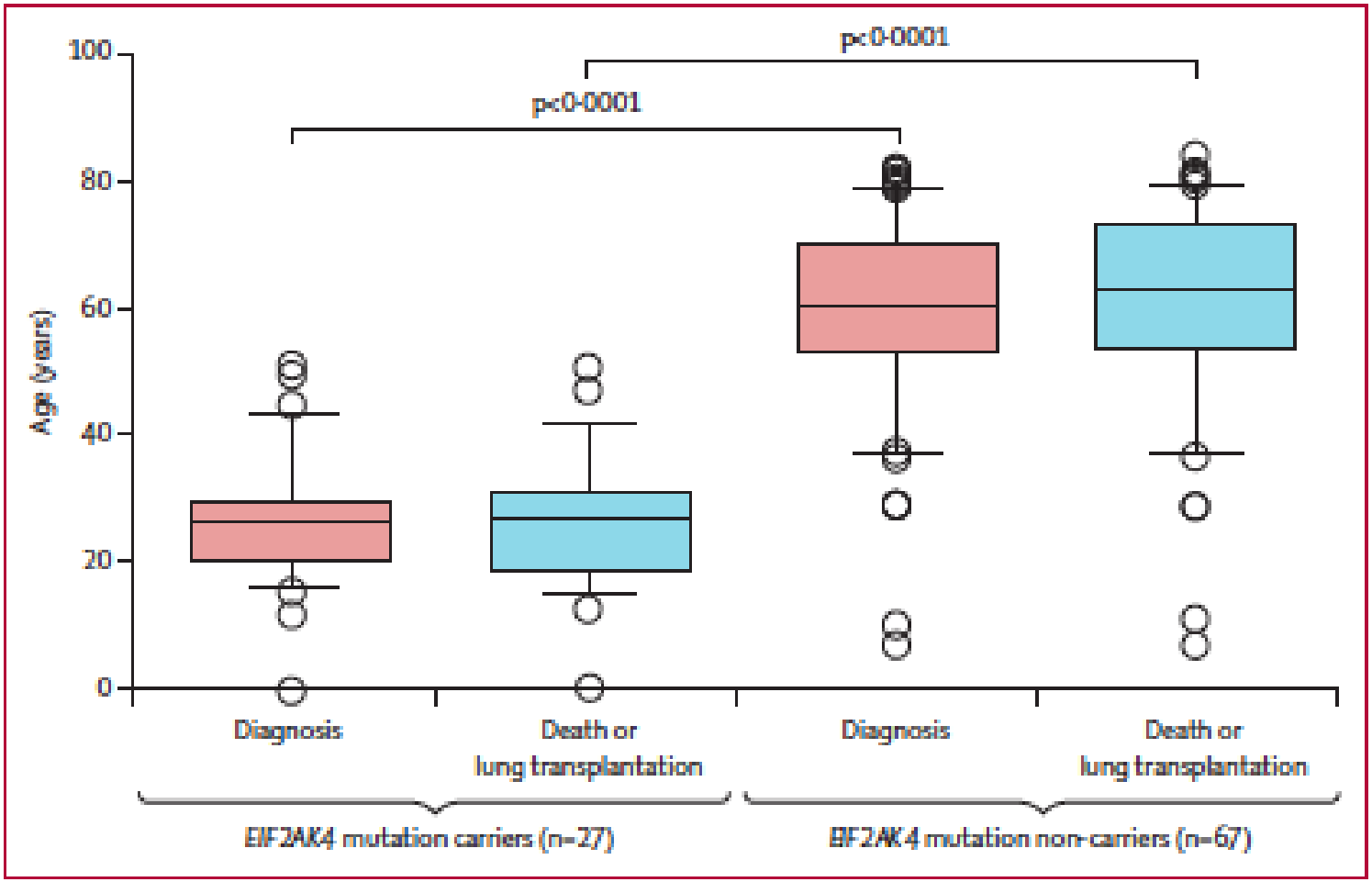


Figure 2: Age at PVOD/PCH diagnosis and age at death or lung transplantation

Montani D, Lancet Resp Med 2017

PVOD patients carrying *EIF2AK4* mutations were more likely to be transplanted as compared to noncarriers

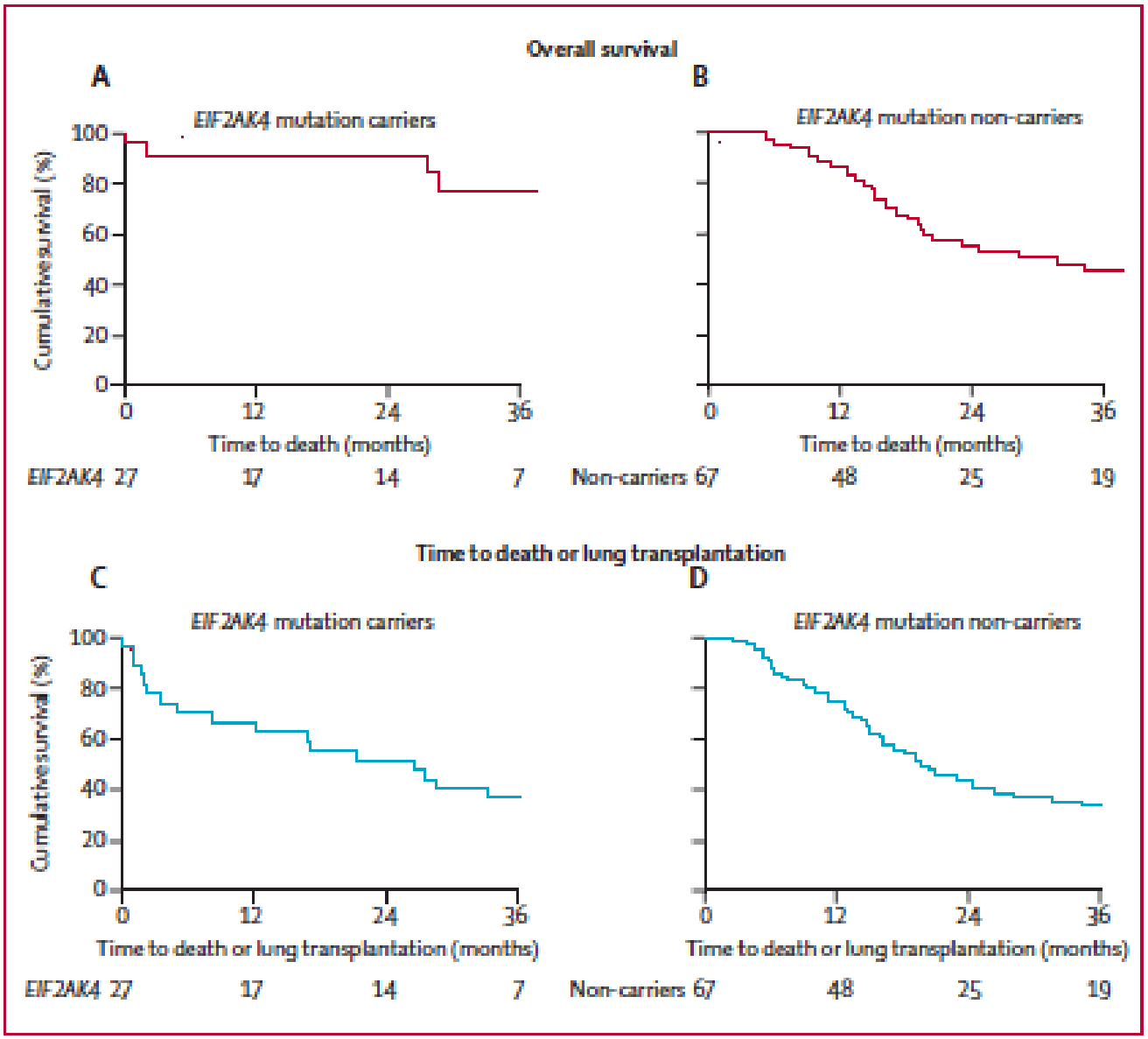


Figure 5: Overall survival and time to death or lung transplantation of *EIF2AK4* bi-allelic mutation carriers and non-carriers

Montani D, Lancet Resp Med 2017

PVOD in pediatric patients was often discovered in *EIF2AK4* mutations carriers

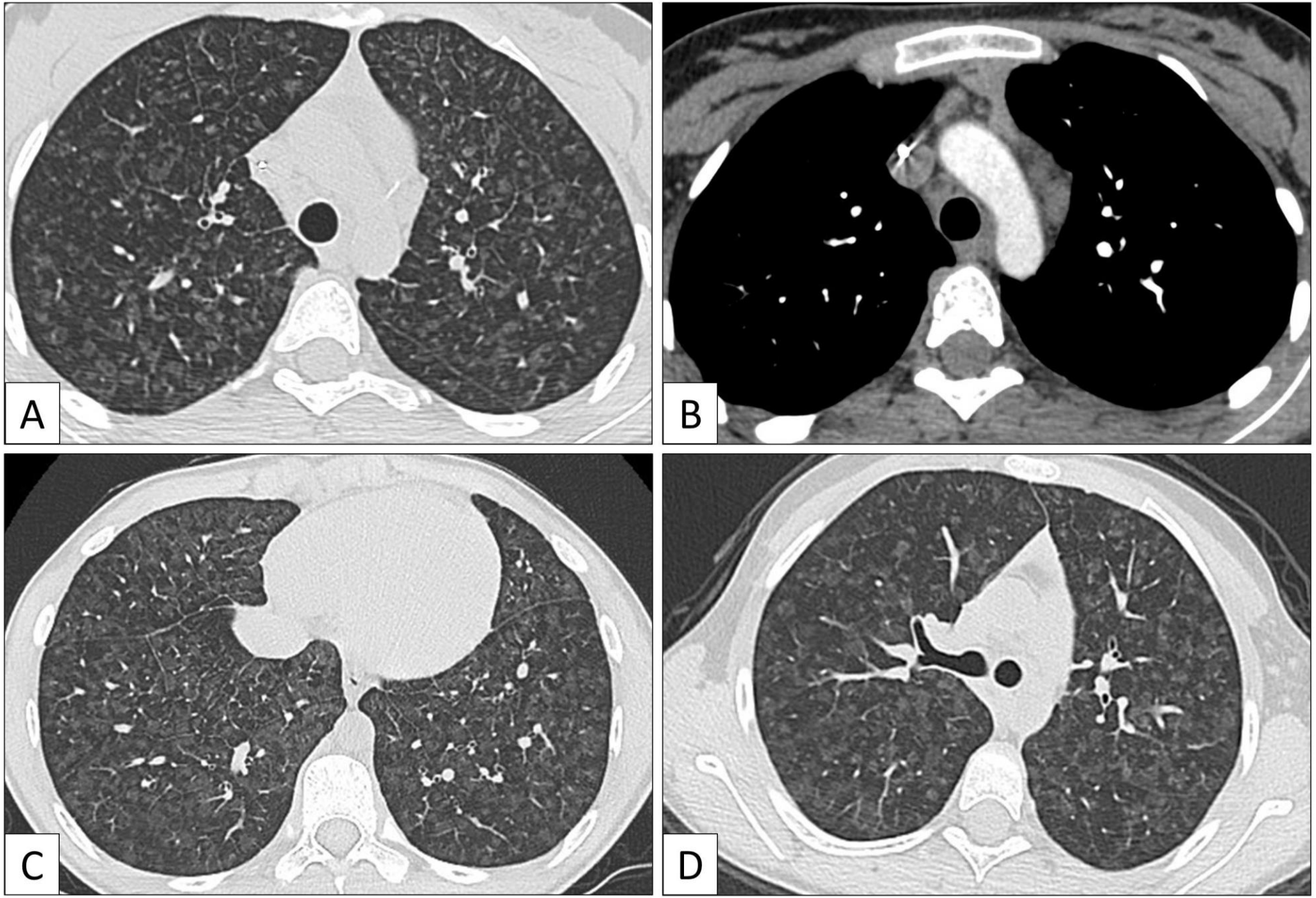
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
EIF2AK4 bi-allelic mutations	Yes	Yes	Yes	Yes	No	No	Yes
Age at diagnosis (years)	17	16	15	12	10	7	Birth
Sex	Male	Female	Female	Male	Male	Female	Male
NYHA functional class	III	III	IV	I–II	III	IV	–
mPAP (mm Hg)	75	39	54	24	49	73	–
PAWP (mm Hg)	8	8	7	11	8	5	–
Cardiac Index (L/min per m^2)	1·94	4·49	1·68	3·8	1·54	3·2	–
PVR (wood units)	24·7	4·4	18·8	2·3	26·3	21	–
High-resolution CT of the chest							
Lymph node enlargement	No	Yes	Yes	Yes	Yes	Yes	–
Centrilobular ground-glass opacities	Yes	Yes	Yes	Yes	Yes	Yes	–
Interlobular septal lines	Yes	Yes	Yes	Yes	Yes	Yes	–
Medical therapy for pulmonary arterial hypertension	ERA	ERA plus PDE5 inhibitor	Prostacyclin derivatives	ERA plus PDE5 inhibitor	ERA	PDE5 inhibitor	No
Outcome	Lung transplantation at 4 months	Lung transplantation at 21 months	Lung transplantation at 5 months	Lung transplantation at 17 months	Death at 17 months	Lung transplantation at 7 months	Death at 10 days

PVOD/PCH=pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis. NYHA=New York Heart Association. mPAP=mean pulmonary artery pressure. PAWP=pulmonary artery wedge pressure. PVR=pulmonary vascular resistance. ERA=endothelin receptor antagonist. PDE5=phosphodiesterase type 5. –=data not available.

Table 3: Clinical, functional, and haemodynamic characteristics at diagnosis, and outcomes of paediatric cases of PVOD/PCH

Montani D, Lancet Resp Med 2017

PH in patients carrying *EIF2AK4 biallelic* mutations was typical of PVOD



Montani D, Lancet Resp Med 2017

GENETIC COUNSELLING

In the presence of a mutation in PAH predisposing genes in a PAH patient:

- The patient is classified as having heritable disease.

- The patient is informed about the possible risk in their family (parents, siblings and offspring) of developing PAH

- We encourage the patient to share this genetic information with his/her relatives and to inform them about the possibility of genetic counselling and pre-symptomatic diagnosis

- Patients with PAH-causing mutations have a 50% risk of transmitting the familial mutation to their offspring.

- Discussion about the reproductive options: remain childless, adopt, have a child without genetic testing (reproductive chance), have gamete donation or undergo pre-implantation diagnosis

Girerd B. Eur Respir J 2016

GENETIC COUNSELLING

In the presence of a mutation in *EIF2AK4* genes in a PVOD patient:

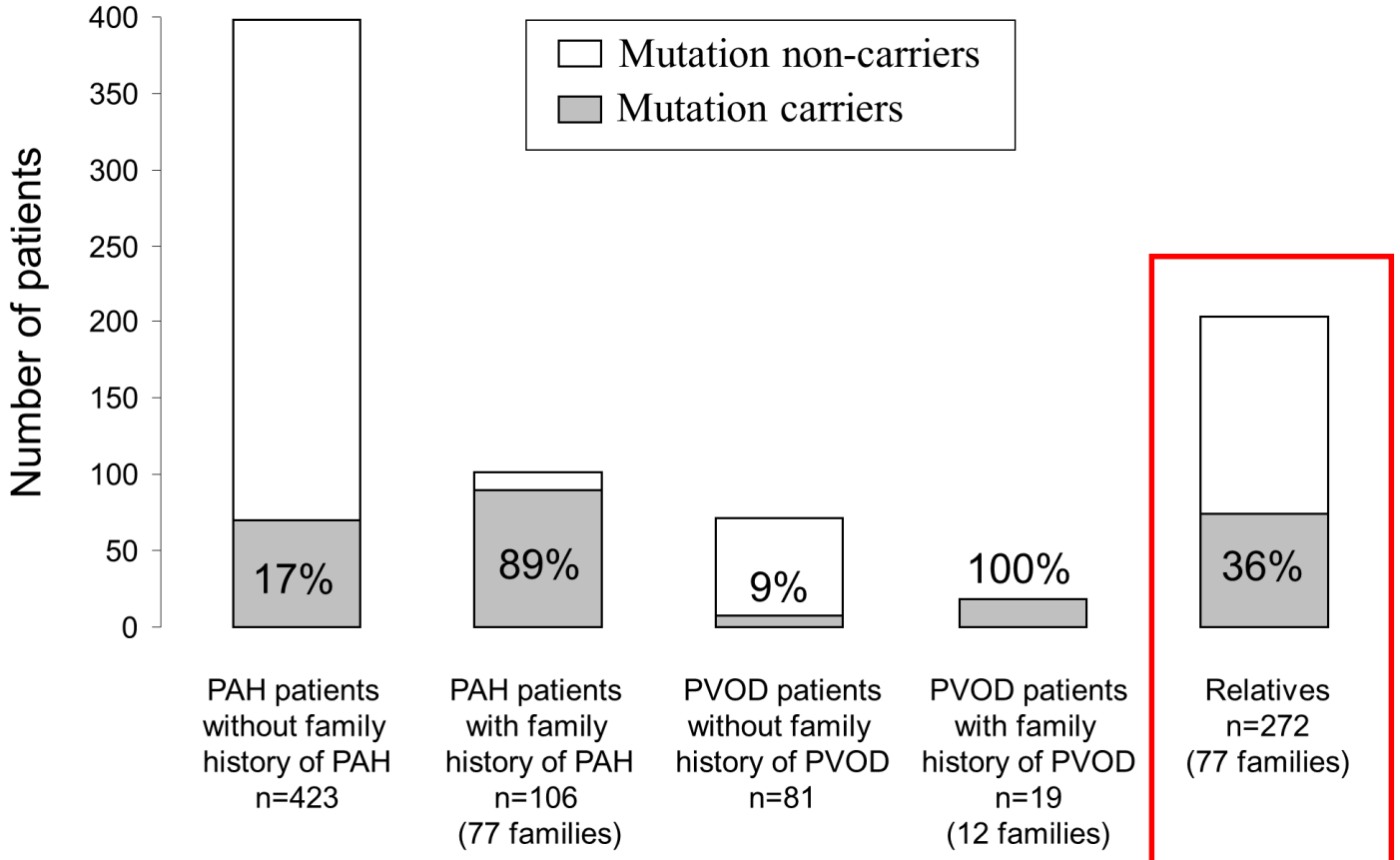
- The patient is classified as having heritable disease.

- The patient is informed about the possible risk in siblings of developing PVOD (autosomal recessive transmission)

- We recommend to share this genetic information with siblings and to inform them about the possibility of genetic counselling and pre-symptomatic diagnosis

Girerd B. Eur Respir J 2016

Genetic counselling in asymptomatic carriers



***BMPR2* mutation**	62	89 (65 families)	0	0	96
***ACVRL1* mutation**	9	3 (2 families)	-	0	1
***ENG* mutation**	1	0	-	0	-
***KCNK3* mutation**	-	2 (2 families)	-	-	2
***EIF2AK4* mutations**	-	0	7	19 (12 families)	-
Total mutations	72	94	7	19	99

Girerd B. Eur Respir J 2016

GENETIC COUNSELLING

Presymptomatic diagnosis:

- Presymptomatic diagnosis is offered to all relatives of a patient carrier of a mutation in PAH predisposing genes

- Informed written consent is mandatory

- The genetic counseling is done in an individual consultation

- Relatives are informed about their risks of carrying the familial mutation, their risk of developing the disease and the transmission of the mutation to their progeny. They also receive complete information about PAH or PVOD symptoms, disease characteristics and prognosis

- Presymptomatic diagnosis requires a multidisciplinary approach involving geneticists, pulmonologists, genetic counselors, psychologists and nurses

- The prescriber informs directly the person who underwent the genetic test in an individual consultation

- All relatives have a delay of 1 month between the first genetic consultation and the consultation for the genetic result. This delay allows relatives to change their mind and suspend their presymptomatic diagnosis temporarily or permanently

- The person can refuse to be aware about the result

Girerd B. Eur Respir J 2016

2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS)

Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT)

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Eur Respir J 2015; 46: 903-75; Eur Heart J 2016; 37:67-119

Recommendations for pulmonary arterial hypertension screening

Recommendations	Class [a]	Level [b]
Resting echocardiography is recommended as a screening test in asymptomatic patients with systemic sclerosis.	I	B
Resting echocardiography is recommended as a screening test in *BMPR2* mutation carriers or first-degree relatives of patients with HPAH and in patients with PoPH referred for liver transplantation.	I	C
A combined approach (including biomarkers, PFTs and echocardiography) should be considered to predict PH in systemic sclerosis.	IIa	B
Systemic sclerosis patients with a mean PAP ranging from 21 to 24 mmHg should be closely monitored, because of a higher risk of PAH.	IIa	B
Initial screening using the stepwise DETECT algorithm may be considered in adult systemic sclerosis patients with >3 years' disease duration and a DLCO <60% predicted.	IIb	B
Annual screening with echocardiography, PFTs and biomarkers may be considered in patients with systemic sclerosis.	IIb	B
In individuals who test positive for PAH-causing mutations and first-degree relatives of HPAH cases may be considered to have an annual screening echocardiogram.	IIb	C
Exercise echocardiography is not recommended to predict PH in high risk population.	III	C

DLCO = diffusing capacity of the lung for carbon monoxide; HPAH = heritable PAH; PAP = pulmonary arterial pressure; PAH = pulmonary arterial hypertension; PFTs = pulmonary function tests; PH = pulmonary hypertension: PoPH = portopulmonary hypertension.
[a]Class of recommendation.
[b]Level of evidence.

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RESEARCH PROGRAM : DELPHI-2

Objectives

The main objective of this study to is follow prospectively for 3 years a cohort of asymptomatic carriers of *BMPR2* mutation to

- monitor these subjects' clinical, functional, biological, echocardiographic and hemodynamic characteristics

- assess the risk of occurrence of prevalent and incident PAH

- determine predictive factors (biological, functional, radiological and hemodynamic) of development of PAH

- screen patients with PAH at an early stage of disease and offer them an early management

Inclusion completed

55 asymptomatic relatives carriers of a *BMPR2* mutation

Preliminary results

Two mild PAH screened at first evalutation in 2 *BMPR2* mutations carriers)

Three year follow-up now completed

Dépistage et **E**va**L**uation des facteurs **P**rédictifs de la survenue d'une **H**ypertension artér**I**elle pulmonaire chez les sujets asymptomatiques, porteurs de mutation *BMPR2*

Asymptomatic carriers of *BMPR2* / *KCNK3* mutation

Optional at inclusion:
Right Heart Cath
Rest / exercise

Every 12 months or symptoms

Visit
- *NYHA*
- *NT-pro BNP, CRP*
- *ECG*
- *Chest Rx*
- *Genetic counseling*

PFTs
- *VO_2 max*
- *DLCO*
- *DLNO……*

Echo cardio
- *TRJ,*
- *TAPSE,*
- *Tei…..*

Blood samples
- *Plasma/serum,*
- *Biomarkers,*
- *Fibrocytes*
- *Circulating Progenitors,*
- *PDGF, endothelin-1…*

Dyspnea or unexplained syncopa

or

Decrease in VO2 max >20% between 2 visits

or

TRJ >2.8 m/s

Right Heart Cath
Rest / exercise

No PAH

Confirmed PAH

withdrawal from the study
Management according to ERS/ESC guidelines

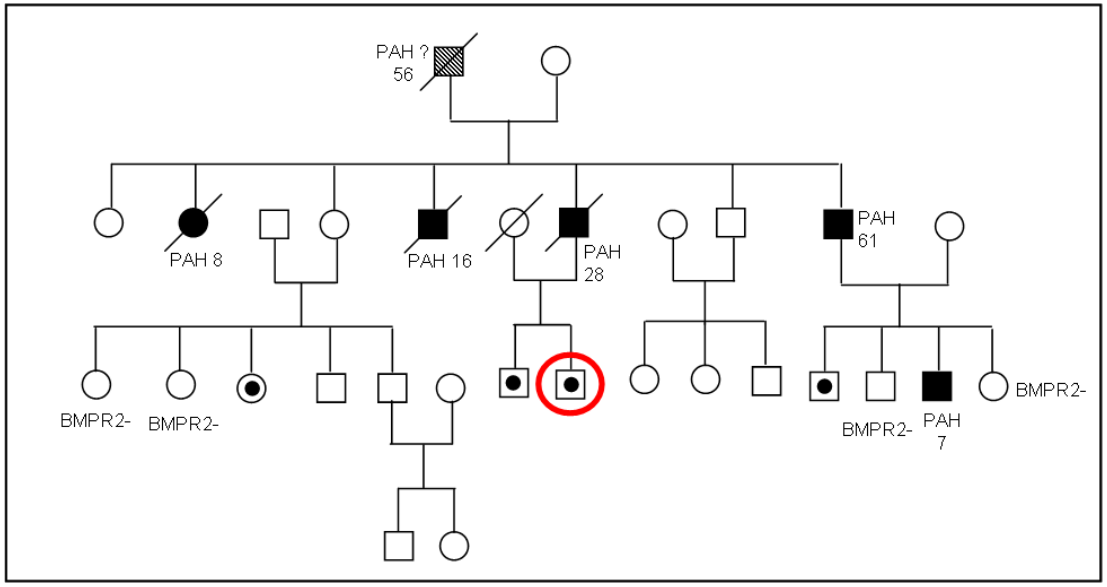
PREIMPLANTATION GENETIC DIAGNOSIS

Eur Respir J 2012; 39: 1534–1546
DOI: 10.1183/09031936.00185011

LETTERS

Pre-implantation genetic diagnosis in pulmonary arterial hypertension due to *BMPR2* mutation

➢ **Preimplantation Diagnosis (PID): in vitro fertilization with a genetic testing performed on the embryo prior to embryo transfer. Only embryos without the familial *BMPR2* mutation are implanted in the uterus**



Frydman N, Eur Respir J, 2012

Conclusions

- **Genetic testing can be proposed to patients with heritable, idiopathic, drug or toxin-induced PAH and PVOD**
- **Genetic counselling can be offered to these patients**
- **Genetic testing can be proposed to informed asymptomatic family members of patients with heritable PAH and PVOD**
- **Genetic counselling allows informed decisions in patients and family members (family planning, pre-symptomatic screening, early management…)**
- **The 2015 ESC/ERS guidelines are currently recommending genetic counselling in heritable PAH (annual screening echocardiography) (IIb-C)**
- **DELPHI-2 research program has completed its recruitment. Results will provide important informations on heritable PAH both in terms of genetic counselling and screening strategies**

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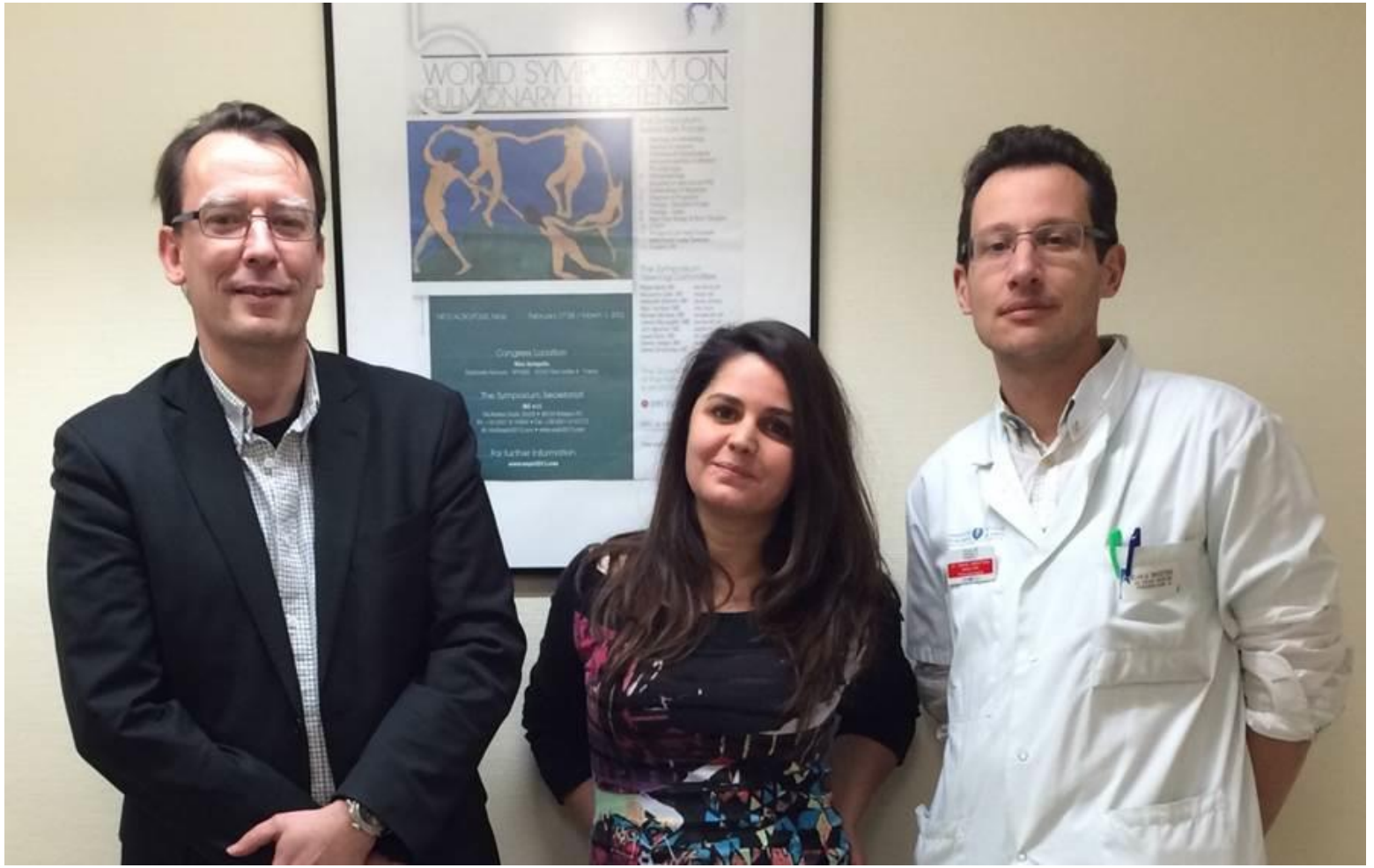

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