European Haemophilia Consortium
Round Table of Stakeholders

Women and Rare Bleeding Disorders

Access to- and inequalities in treatment

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Women with bleeding disorders (WBD): Agenda

- What?
  - Main symptoms
- Who?
  - Types of diseases and numbers
- Needs? Example chosen: carriers of haemophilia
  - How many?
  - Diagnosis delay (both for genetic and bleeding risk)
  - Paediatric focus
- How to improve access to care for WBD?

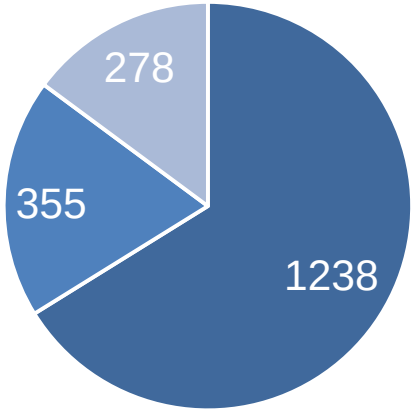
Women with bleeding disorders (WBD) : main symptoms

- All severities +++
  - Post-surgical bleeding
  - Bleeding after tooth extractions
  - Mucosal, haematomas
  - More rarely haemarthrosis, gastrointestinal and intracranial bleeds

- Women specific
  - **Heavy menstrual bleeding +++**
    - Anemia, iron deficiency,
    - Days off school/work
    - Pain
    - Decreased quality of life
  - Challenge **every month**
  - **Post partum bleeding**

Distribution of women by type of congenital bleeding disorder included in FranceCoag

- Women = 1,870 (18%)
- Men = 8,298



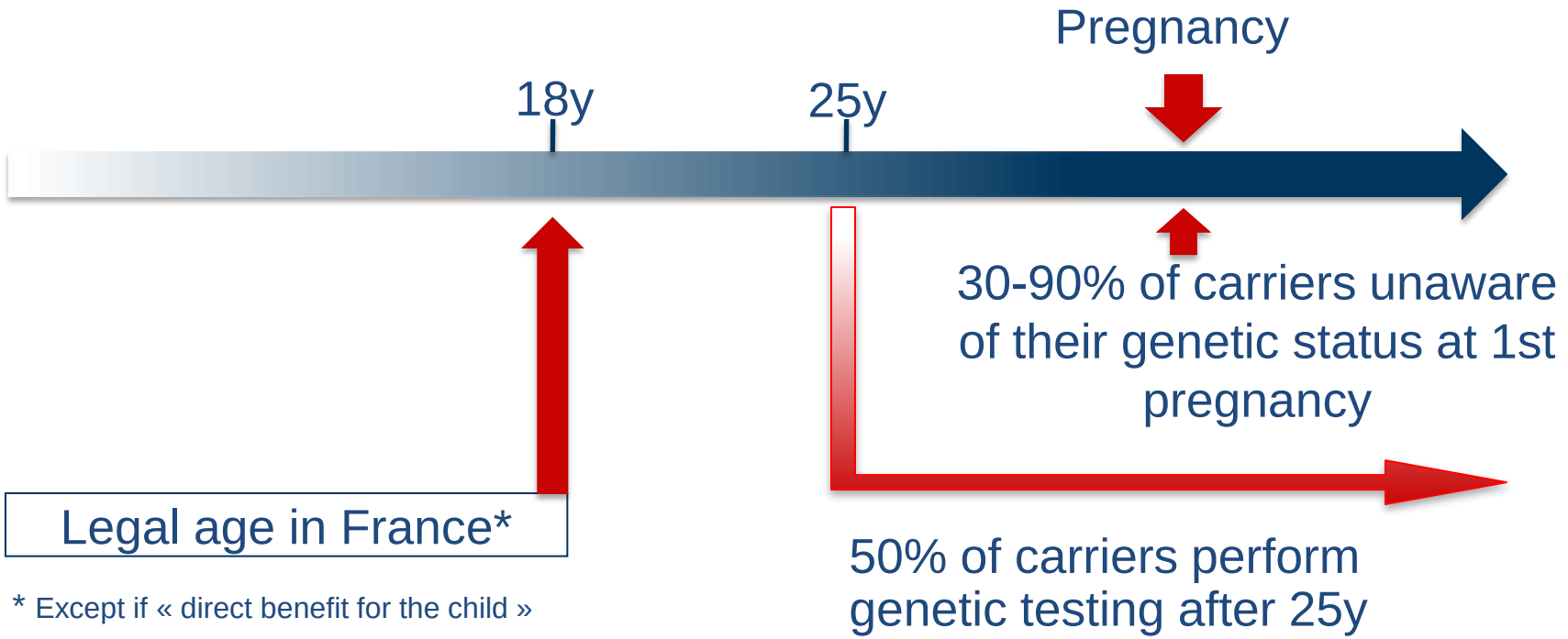
Total (men+women)= 10,168
Platelets disorders not included

Inclusion criteria for carriers: FVIII or FIX < 40 IU/dL
www.francecoag.org (accessed June 2018)

Carriers of haemophilia

Genetic diagnosis

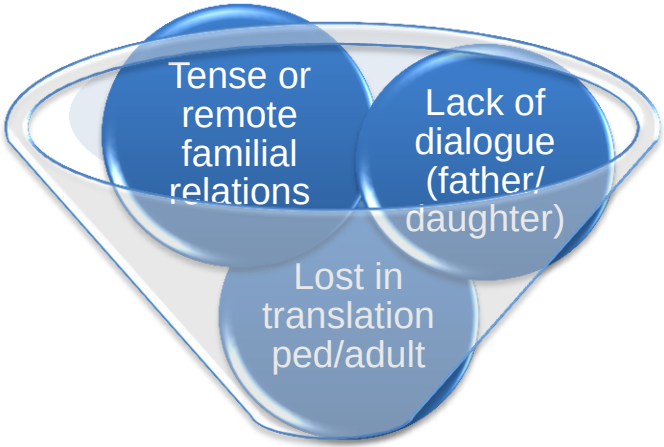
Genetic diagnosis of carrier status: when?



* Except if « direct benefit for the child »

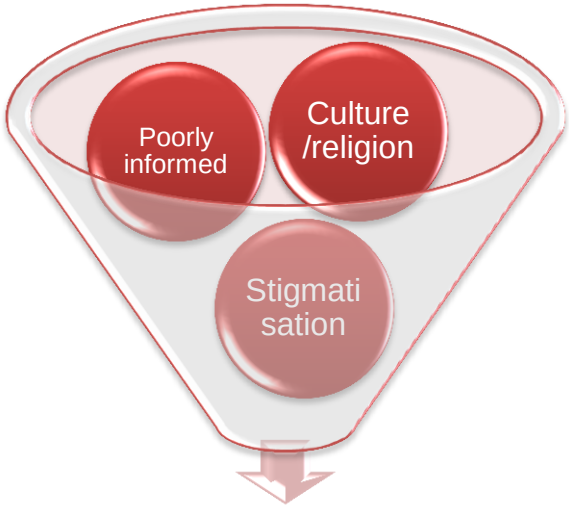
MacLean et al. Haemophilia 2004;10(5):560-4; Dunn et al. Haemophilia 2008;14(3):584-92; Kessler, Haemophilia 2014, Nov;20(6):e384-91; Knol et al, Haemophilia 2011;17(2):233-6

Reasons for delayed genetic diagnosis of carrier



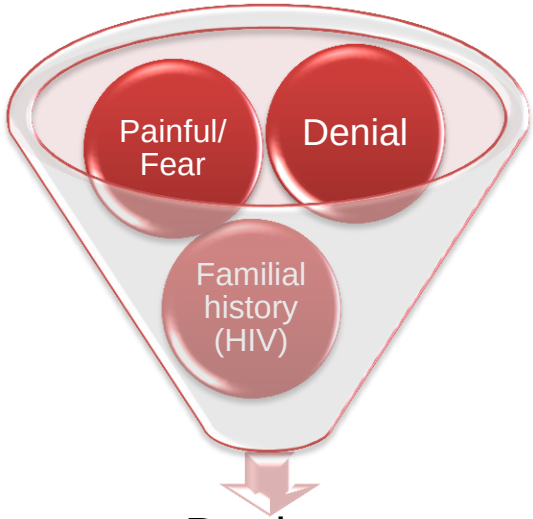
Ignorance

Not aware about the risk of being a carrier



Benefits and Risks unknown

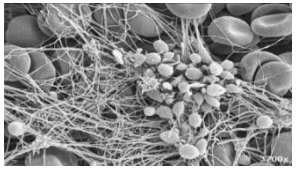
Aware about risk of being a carrier but
Unaware of advantages to be diagnosed
and of risks if not diagnosed



Barriers

Aware about risk of being a carrier
and advantages to be diagnosed
But too difficult to face

Delay



Carriers of haemophilia

Bleeding risk diagnosis (low factor level)

Women and haemophilia: 2 issues

Transmission

?

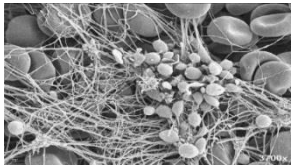
Bleeding risk

Genetic tests

(DNA)

Coagulation tests

(FVIII/FIX)



Non carrier

Carrier

Carrier With hemophilia

Carrier Without hemophilia

FVIII: Factor VIII; FIX: Factor IX

APPROXIMATELY

1/3

CARRIERS

OF HAEMOPHILIA

BLEED

How many carriers of haemophilia?
How many women with haemophilia (low factor levels)?

- ± 30% of carriers with FVIII or FIX* < 40 IU/dL[3-4]
- For one male with hemophilia[1-2]
  - 2.7 to 5 women potential carriers
  - 1.5 women actual somatic carrier
  - So, expected :

    ± 0.5 carrier with low FVIII or FIX

Women with haemophilia are not rare

- Women with hemophilia still infrequently included in national databases

*Normal factor levels: 60-120%

1. Kasper personal communication & Kasper et al. Haemophilia 2007;13(1):90-2; 2. Plug et al. Blood 2006;108:52-56; 3.Kadir et al. BJOG 1997;104:803-810;
4. Mauser-Bunschoten, WFH Monograph 2008

Distribution of haemophilia by gender in national and international databases: women rarely included

	WFH 2014	France FranceCoag 2014	USA UDC 2011	Canada CHR 2014	UK UKHCDO 2014
Inclusion criteria (FVIII or FIX IU/dL)	Country specific	<40	<50	≤ 40	<40 / <50
Total males with hemophilia	144,772	6,090	18,056	3,345	6,891
Total females with hemophilia	3,388	203	582	355	609 / 955
% females/total	2.5	3.2	3.1	9.6	7.0 / 10.9

WFH: World Federation of Hemophilia; UDC: Universal Data Collection CHR: Canadian Hemophilia Registry; UKHCDO: UK Haemophilia Centre Doctors' Organisation

Factor levels are mainly assessed during adulthood in carriers of haemophilia in most publications

- Age of carriers included in cohorts reported in 10 studies*:
  - **Median 18 - 40y** (ranges 8 - 82y)
- Likely due to factor levels testing performed at the same period as the genetic testing (frequently at the time of first pregnancy)

→ Extremely limited data in girls/adolescents

- Gynaecologists but also paediatricians and general practitioners are unaware that carriers may have low levels of factor VIII or IX
- Consequently, anticipation of menarche is difficult +++

*Plug et al. Blood 2006;108:52-56; Sharathkumar et al. Haemophilia 2009;15(1):91-100; Ay et al. Haemophilia 2010;16(1):111-7; Miesbach et al. 2011;17(2):246-51; Van Herrenwengen et al. Haemophilia 2012;18(suppl 3):13; Ollson et al, Blood Coagul Fibrinolysis. 2014 Jul;25(5):471-5; Paroskie et al, Br J Haematol. 2015; 170(2): 223-8

Diagnosis of **severe/moderate** haemophilia is delayed in girls versus boys in USA

- In girls, diagnosis of haemophilia is delayed compared to boys
  - 6.5 months for severe
  - 39 months for moderate

	US Females		US Males	
	Severe	Moderate	Severe	Moderate
Total subject, *n*	14	8	7,578	3,475
Haemophilia A	13	4	6,384	2,256
Haemophilia B	1	4	1194	1,219
Age at diagnosis Median, months (range)	8.5 (3–72)	48 (14–312)	2 (0–660)	9 (0–816)

- Discrepancy in age for diagnosis expected to be even more important in mild forms

HA: Haemophilia A; HB: Haemophilia B;

Di Michele et al. Haemophilia 2014;20(2):e136-43

Facts for Women with Bleeding Disorders

- High **discrepancy in diagnosis** of congenital bleeding disorder between women and men
- When diagnosis is done, it is done **later**
- **Girls/adolescents frequently neglected** until adulthood
  - Diagnosis unfrequently done in girls/adolescents before menarche
- **Insufficient number of centres with dedicated clinics** for women and girls WBD
- **Lack of knowledge and awareness**
  - Non specialists health care professionals, general practitioners, gynecologists
  - Families
  - Even in HTC
- **Research limited**

Non-recognition of «female with haemophilia»: Consequences

http://www.hemaware.org[3]

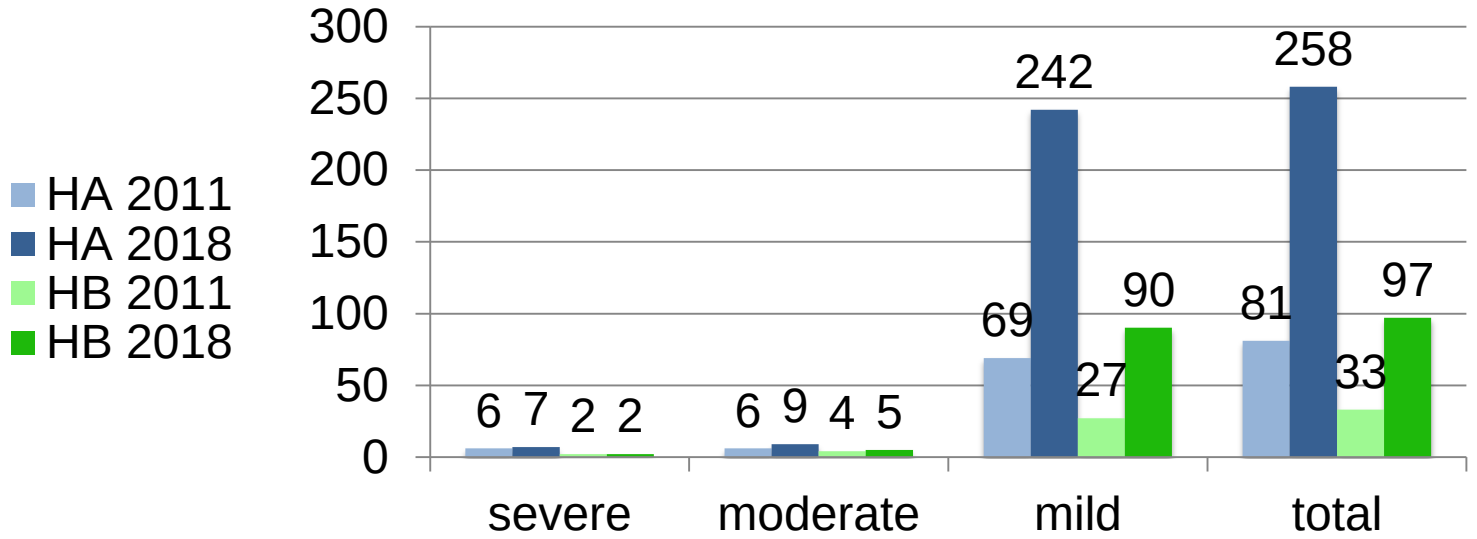
- Delay and loss of opportunity for diagnosis and treatment of bleeding episodes
- Lower chance to test girls at young age regarding bleeding risk
- Delayed diagnosis of infectious complications (HCV, HIV)[1]
- “Hemophilia” Treatment Centre not enough recognised as the suitable place for care (“I am only a carrier”)
- Denial of insurance coverage
- Exclusion from clinical studies (even after diagnosis)
- Relatives rather than patients : Genetic designation (“carriers with low factor levels”) at the expense of a clinical bleeding disorder
- Negative emotional and behavioural responses to medical experiences (even in HTC)[2]

HTC: Haemophilia treatment centre

1. Peynet et al for France Coag, WFH 2012;
2. 2. Renault et al. Haemophilia 2011;17(2):237-45;
3. 3.Aldridge, HemAware, NHF 2012

Evolution of number of females with haemophilia included in FranceCoag: 3-fold increase in 7 years

- Impact of outreach programs launched in 2011 with French Patient Organization (AFH): Awareness is increasing

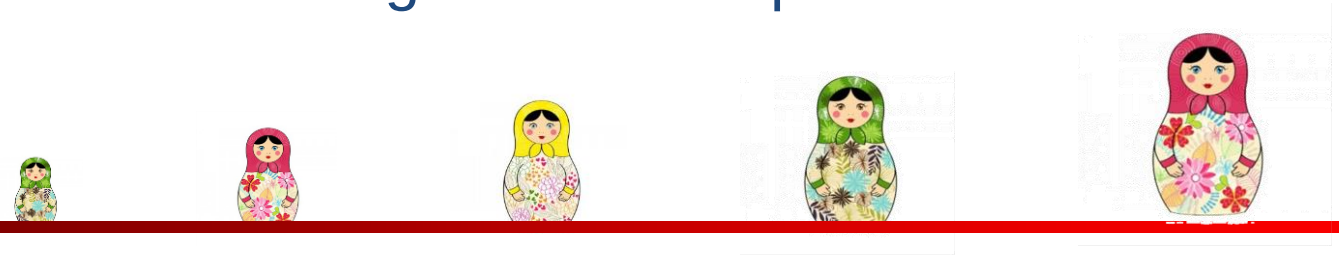


Criteria of inclusion : FVIII ou FIX < 40%;www.francecoag.org (accessed June 2018); AFH: Association Française des Hémophiles; HA : haemophilia A, HB: haemophilia B

Conclusion: How to improved care for WBD?

Mixed efforts to improve awareness and education	• Multidisciplinary team, Health Care Professionals • Families/Patient, Patient Organizations, • Agencies and authorities
Organization of care	• Network of professionals, • Centres for Rare Bleeding Disorders • Dedicated clinics, including for young girls
Multiply actions and information	• Booklets • Websites • Outreach programs and campaigns
Develop research	• Develop registries • Unexpected favourable effects+++
Regular basis	• Checking understanding, Update family tree, • Special care at each age • Gain-framed rather than loss-framed messages

Women and Bleeding disorders: special care at each age



- Early childhood
  - Assess the bleeding risk (several assays), long-term follow up if low levels
- Pre-adolescence
  - Anticipate menarche, follow-up of menstruations, information
- Adolescence / young adult
  - Prepare, support and perform genetic carrier testing
- Young adult ± partner:
  - Counselling, PND, PGD, multidisciplinary protocol for pregnancy and delivery
- Ageing women with bleeding disorders
  - Premenopausal period, surgeries, co-morbidities

PND: Prenatal diagnosis; PGD: Preimplantation genetic diagnosis

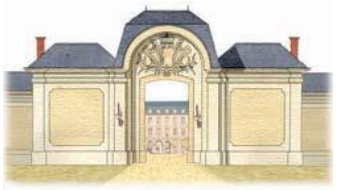
Thank you for your attention, time and welcome in European Parliament

Parlement européen

Bicêtre

Haemophilia Centre (HTC)

Thierry Lambert
Anne Rafowicz
Patricia Lezeau



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Women and men from families with bleeding disorders

from Bicêtre HTC

EHC

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Association française des hémophiles (AFH)

Women's committee
Yannick Collé
Maryse Dien

"Commission Femmes"