PedNet Haemophilia Registry

Focus on immunogenicity of FVIII and FIX products and general reflections on registries

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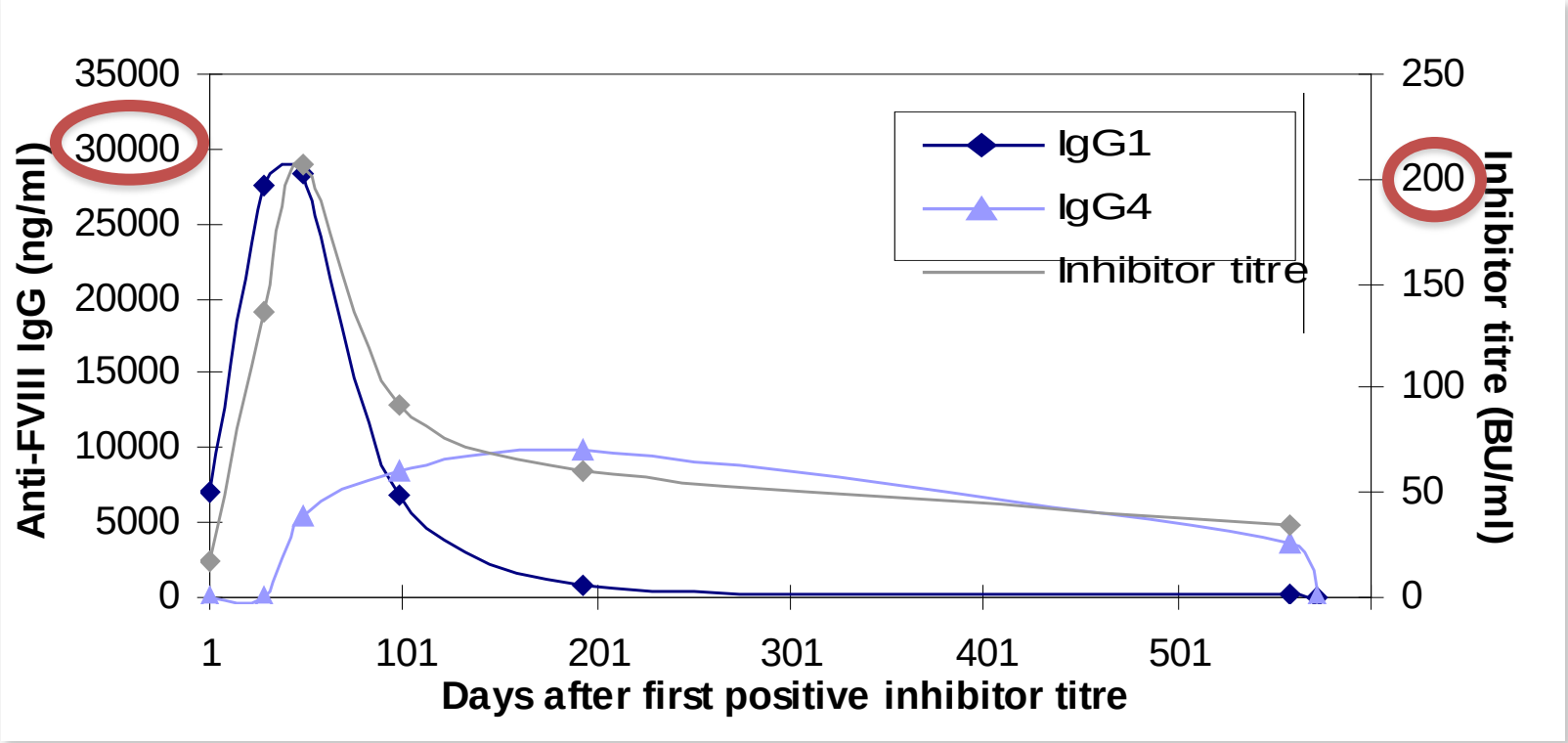
Workshop on registries CHMP/BPWP/EMA - 01-02/07/15

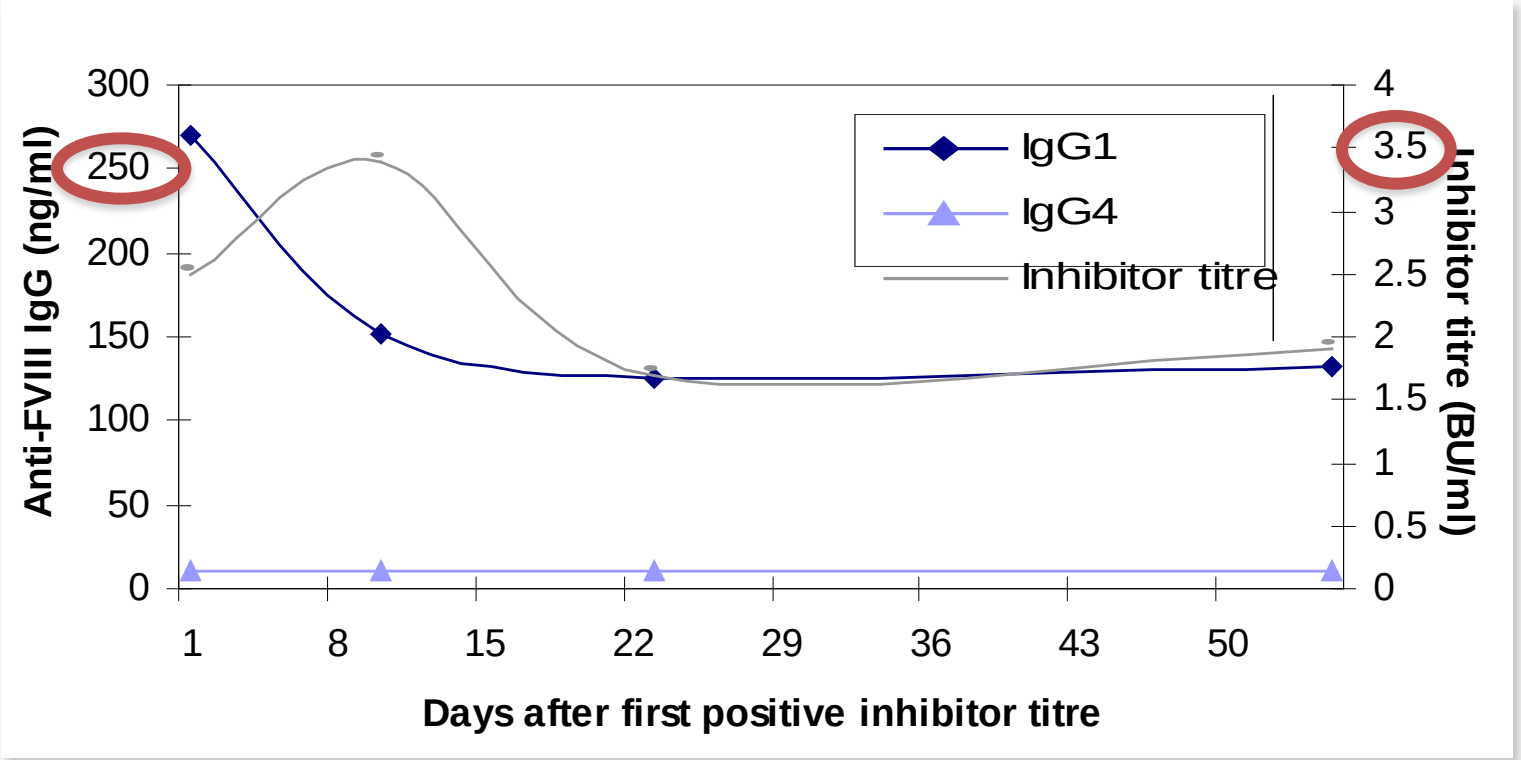
Let's start with the patient

- Monozygotic twins
- Factor VIII gene defect
  - Inversion
- Both treated with *Advate*
- Patient A developed high-titre inhibitor after ICH and intensive treatment
  - >250 BU/ml during 24 months
- Patient B had low-titre inhibitor
  - 3.5 BU/ml during 4 weeks

Patient A: high-titre inhibitor after treatment for ICH



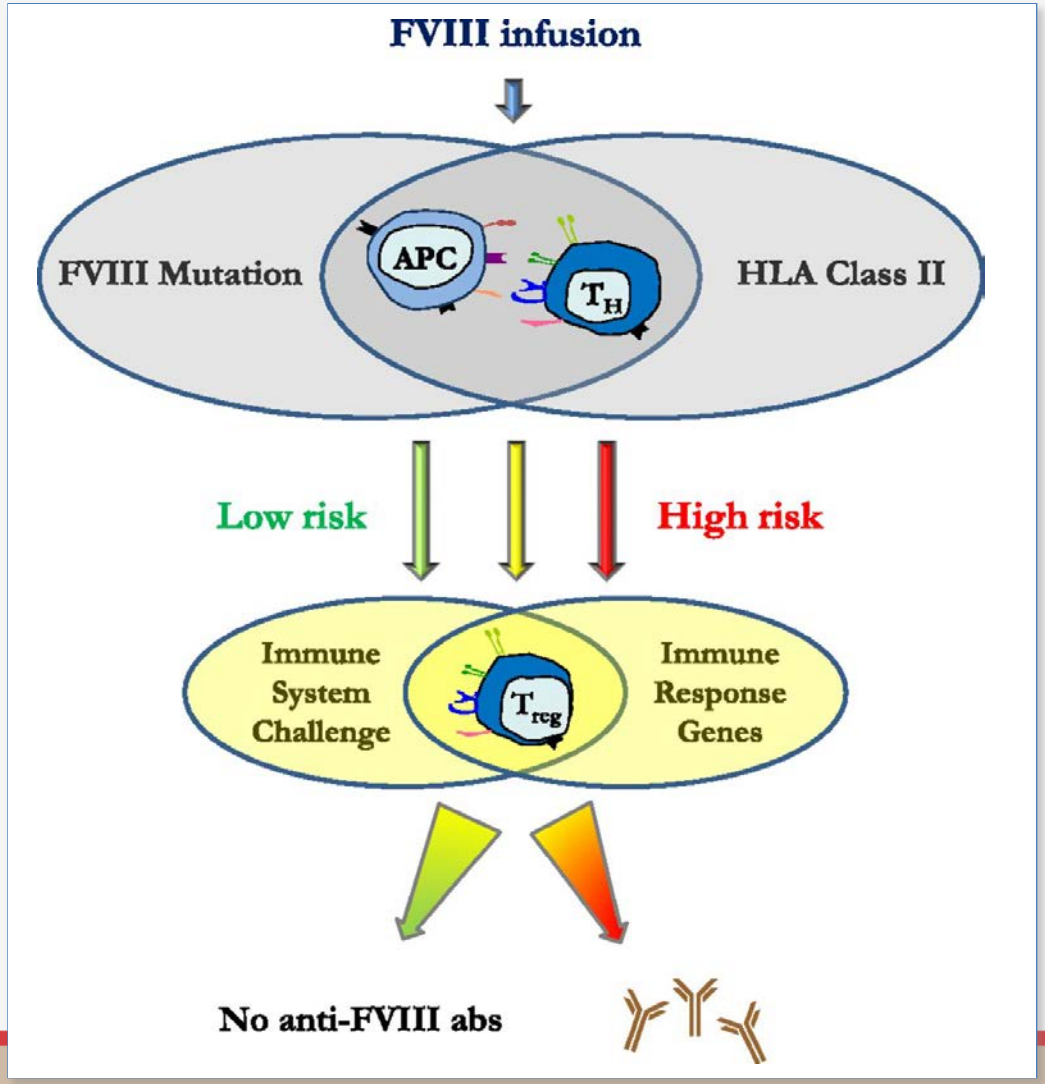
Patient B: low-titre inhibitor disappearing on ‘prophylaxis’



Patients A and B: summary

- Monozygotic twins, same gene defect, same product, same environmental factors
- Differing in
  - Age at start treatment
  - Intensivity of treatment (dose, time period)
  - Low-titre versus high-titre inhibitor
  - No ITI versus high-dose ITI

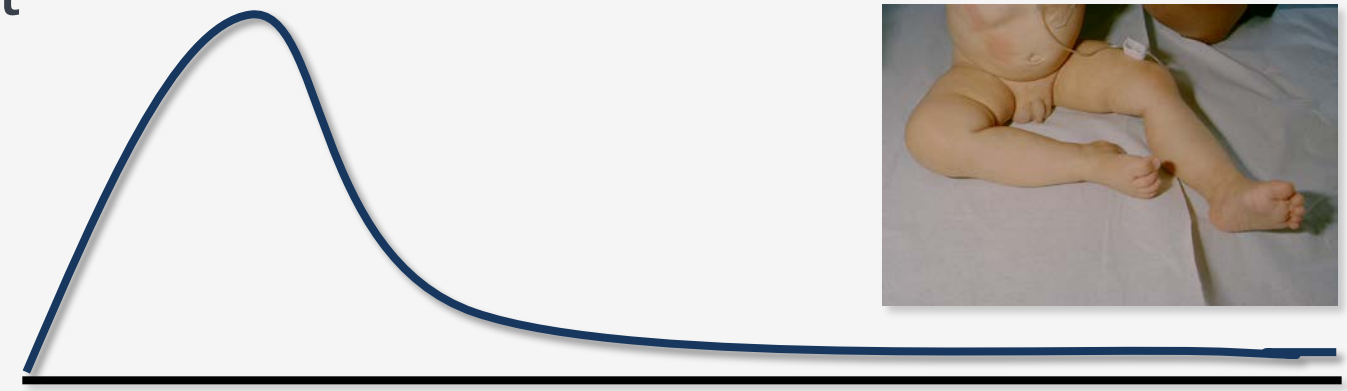
Inhibitor development

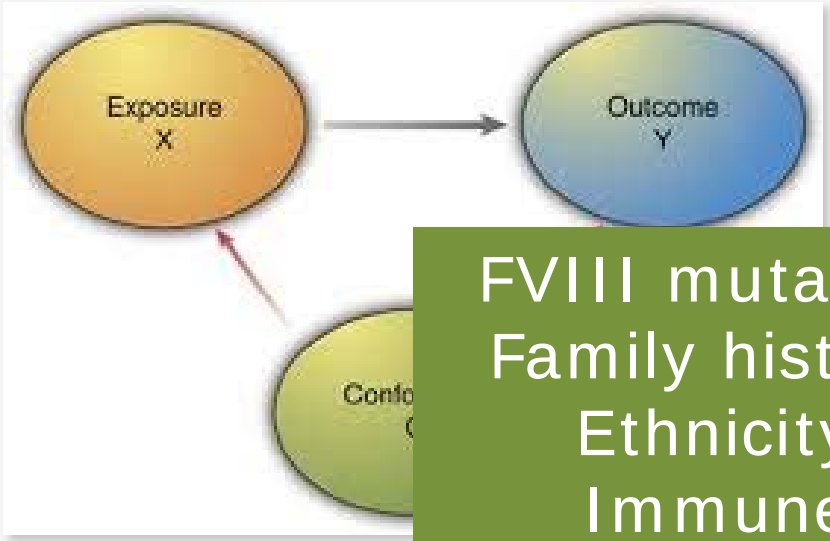


- Fixed factors
  - –Genetic, HLA, ethnicity, immune regulatory genes
- Time-dependent
  - –Intensive treatment, dose, products, surgery, bleeding

How to define inhibitors

- Major side effect is development of inhibitors
- Inhibitors are allo-antibodies that block the binding sites for factor VIII and IX
- Inhibitors occur very early after the start of treatment





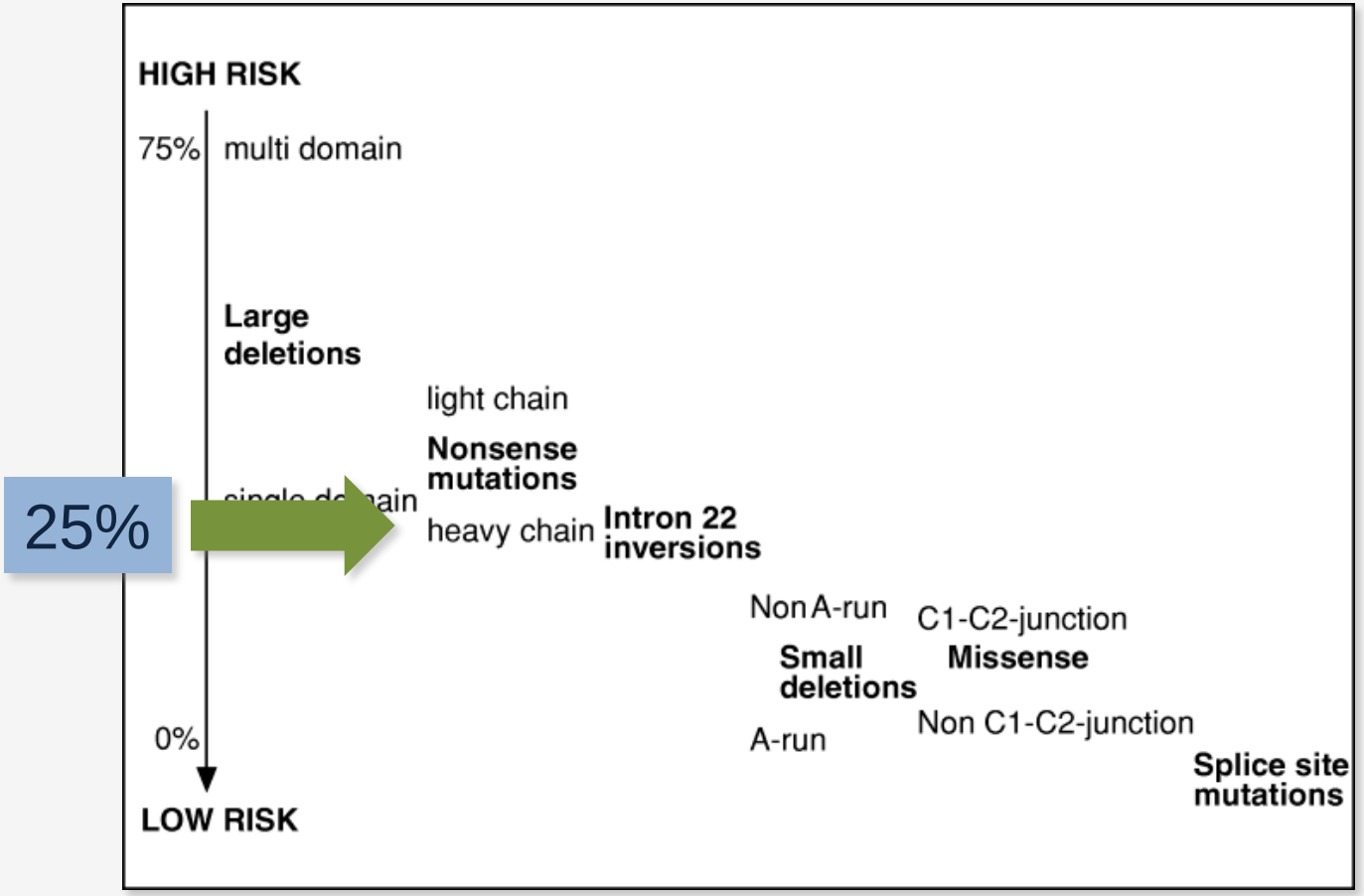
FVIII mutation
Family history
Ethnicity
Immune regulatory genes

Test method
Confirmation of test
Frequency of testing

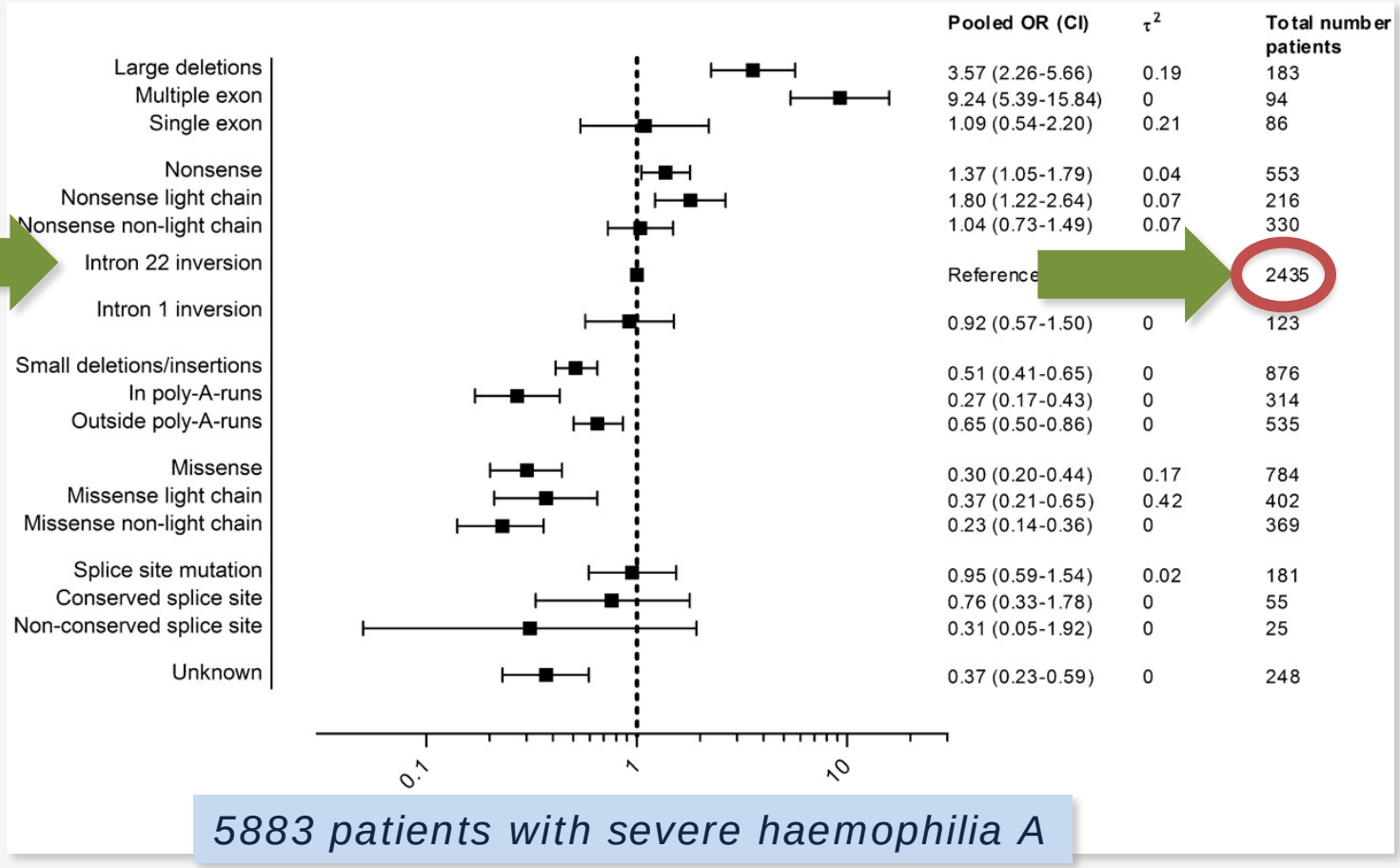
Dose
Peak treatment
Intensive treatment
Products

Inhibitors

Inhibitor development versus FVIII genotype

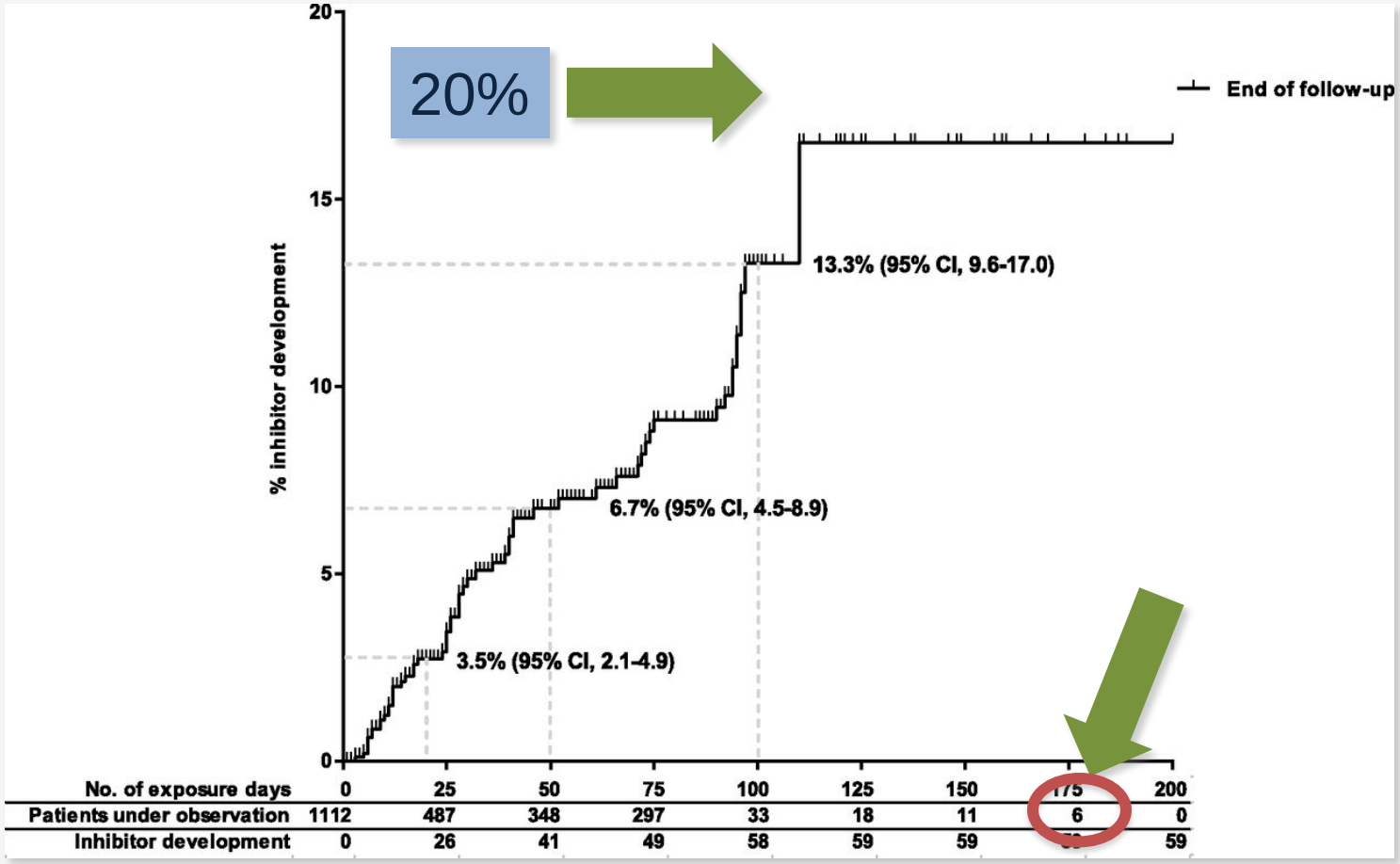


Inhibitor development versus FVIII genotype



5883 patients with severe haemophilia A

Inhibitor risk in mild hemophilia: *Insight* study

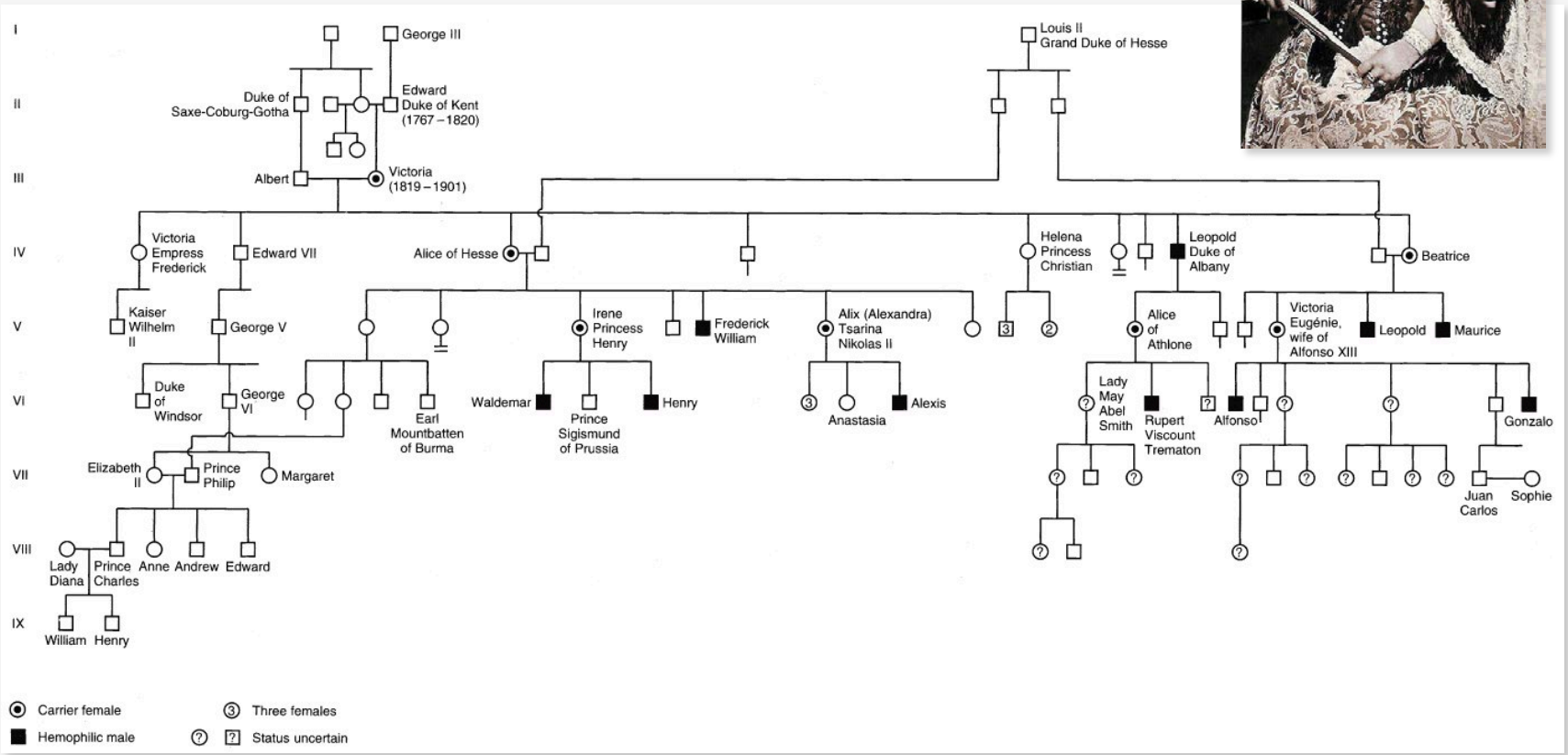


Genetic factors: conclusion

- Genetic factors
  - Can not be changed in a given patient
- Patients with severe haemophilia
  - 60% have high-risk mutations
  - While 25% develop an inhibitor
  - Impact of immune regulatory genes*
- Non-genetic factors
  - Are important
  - Can be influenced

*Astermark J. Blood 2015;125:2045

Impact of family history on age of diagnosis



Griffiths AJF, et al. Introduction to genetic analysis. 10th ed., 2012

Impact of family history on age of diagnosis

← Large family

Small family ↓

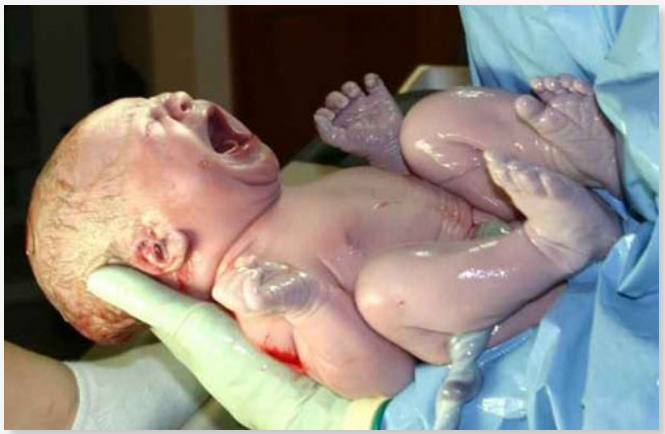
Impact of family history on age of diagnosis

- According to the literature, 70% of patients would have a positive family history at diagnosis
- But prospective data show that presently over 55% have a negative family history*

*Chambost H, et al. J Pediatr 2002;141:548 - Gouw SC, et al. Blood 2013;121:4046

Haemophilia patient without family history

- Negative family history for haemophilia
- No suspicion of haemophilia at delivery
- Intracerebral haemorrhage as a neonate
- Diagnosis outside of haemophilia treatment centre
- No prospective collection of clinical data
- Mostly excluded from trials



Results from the PedNet registry

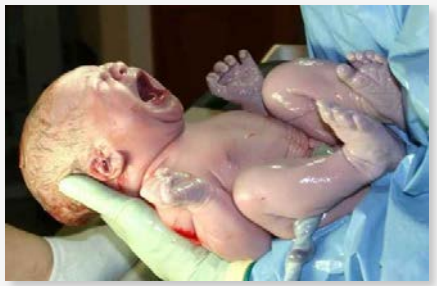
- Data May 2013
- Cohort born 2000-2009
- In total 622 children with severe haemophilia A
- At the first exposure day, 25% had to be treated for at least 3 days
- 9 children had an intracerebral haemorrhage
  - 8 of them (42%) developed an inhibitor

Patient according to the Handbook

- Positive family history
- Gene defect available
- Diagnosis known at delivery
- Diagnosed and treated in a haemophilia centre
- Choice of product
- Clinical data prospectively collected
- Mostly included in trials

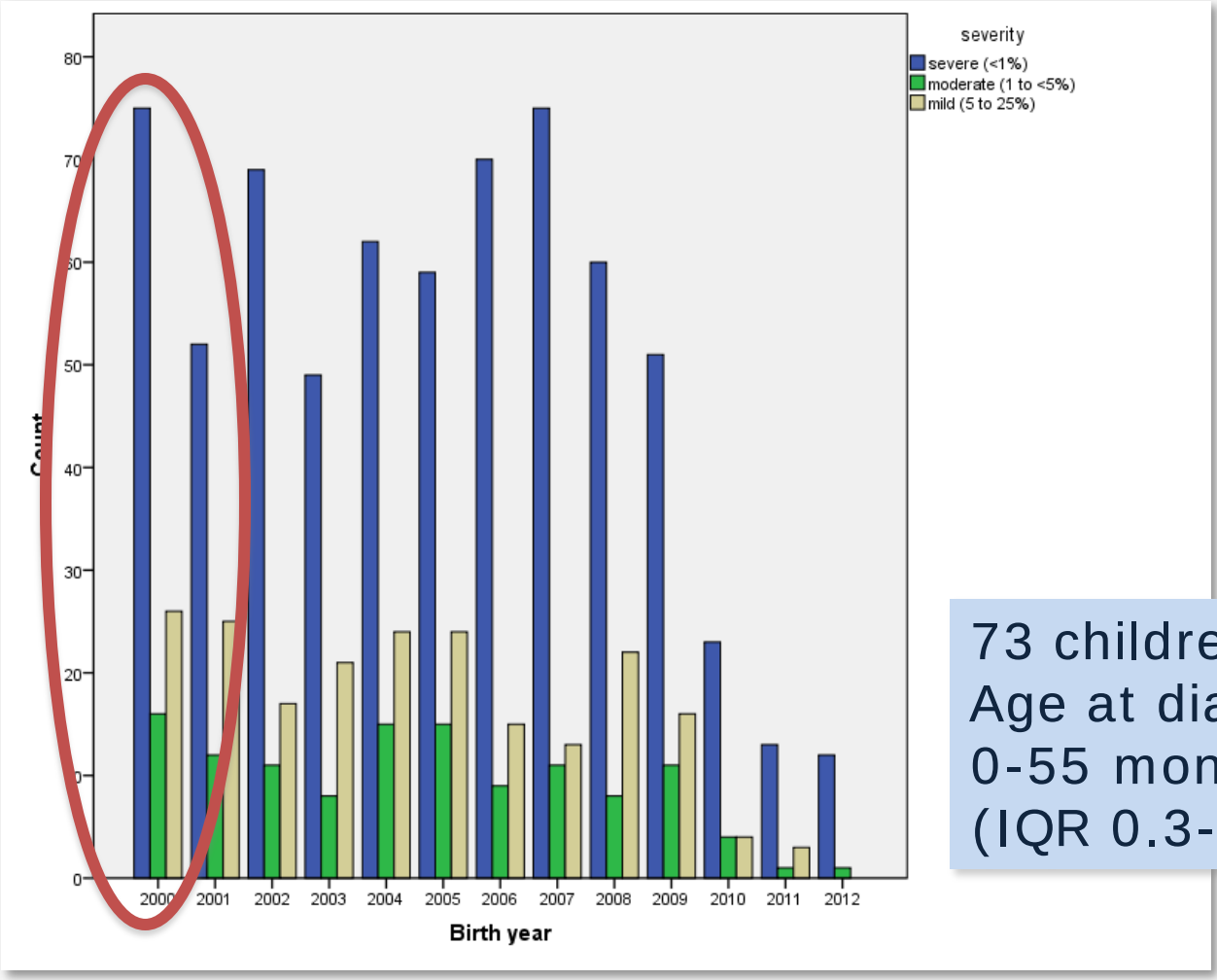
Studies of severe haemophilia: Factors to consider when

- At diagnosis, over 55% of all newly diagnosed children with severe haemophilia have a negative family history
  - Will be diagnosed through bleeding
  - Mostly outside of haemophilia centre



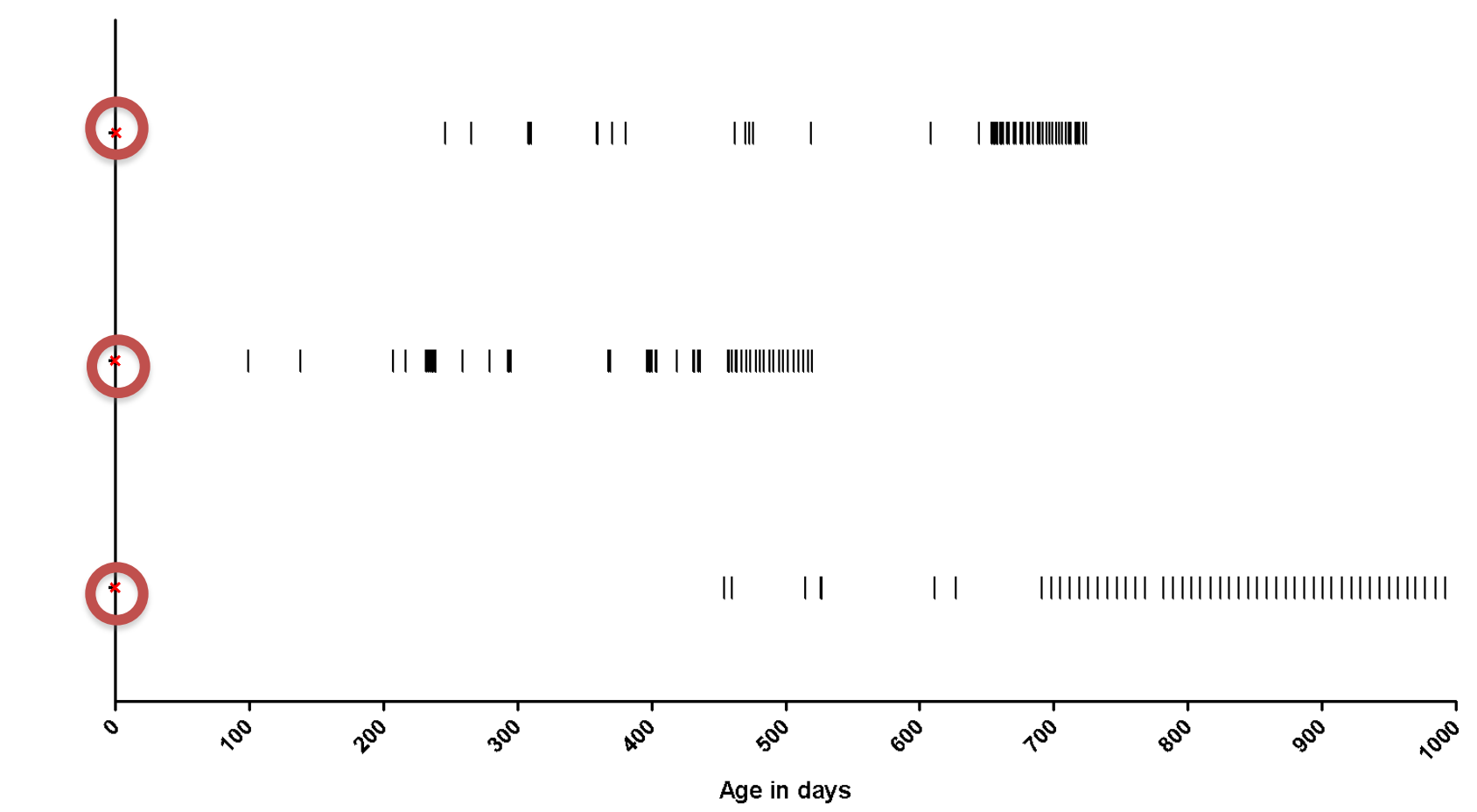
- Not included in studies → Selection bias

Data from PedNet registry

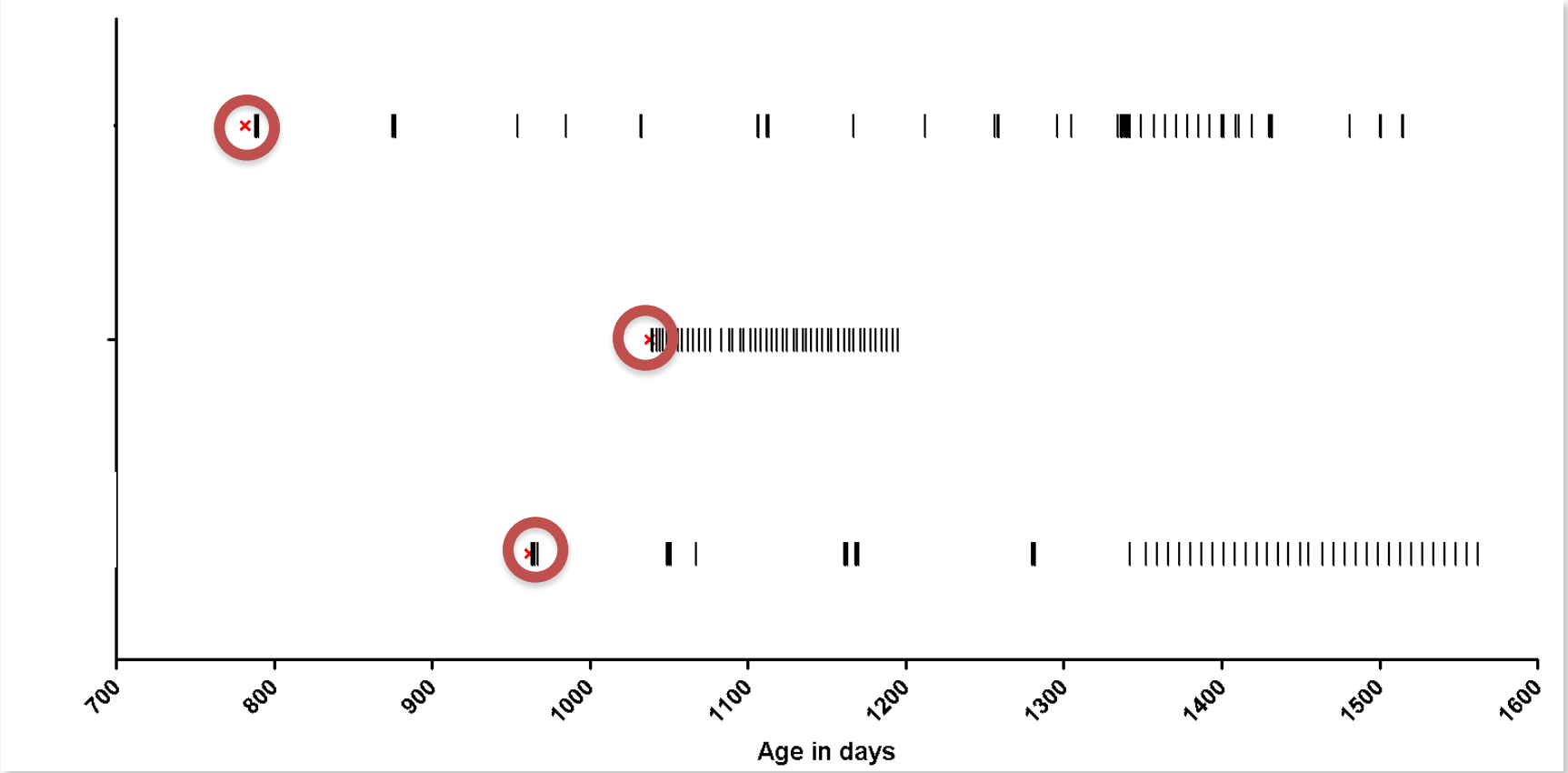


73 children
Age at diagnosis
0-55 months
(IQR 0.3-11 months)

Early diagnosis
Positive familiy history



Late diagnosis (>2 year)
Negative family history



Changing practice in inhibitor diagnosis

- Before 1990, inhibitors were suspected when the patient did not respond to treatment
- After outbreak inhibitor on plasma products, awareness increased
- Screening for inhibitors with frequency of testing up to every 5 exposure days

Changing practice in inhibitor diagnosis

- Modification of Bethesda assay
- Cut-off value for positivity was decreased by the Nijmegen modification
- Further standardization did not improve the large interlaboratory variation
- Advice: confirm a positive sample

Faveloro et al. Semin Thromb Hemost 2014

Definition of inhibitor (ISTH-SSC)

- Clinically relevant inhibitor development
  - 2 or more positive titers
  - In combination with decreased FVIII recovery
- High-titer inhibitor development
  - Clinically relevant inhibitor with peak titer ≥5 BU/ml

Conclusions I

- Inhibitor development is influenced by many genetic and non-gentic factors
- High dosing increases the risk up to 3 times
- For the study of the impact of combined risk factors, data of large, similarly defined patients populations are essential
- 55% of patients with severe Haemophilia A are diagnosed after bleeding

Conclusions II

- Differences in assays and in testing frequency have an impact on the numbers of patients diagnosed with inhibitors (low titre inhibitors)
- Variances in outcome can be limited by the definition of clinically important inhibitors
- Comparison of only high-titre inhibitor incidence will make studies more comparable