



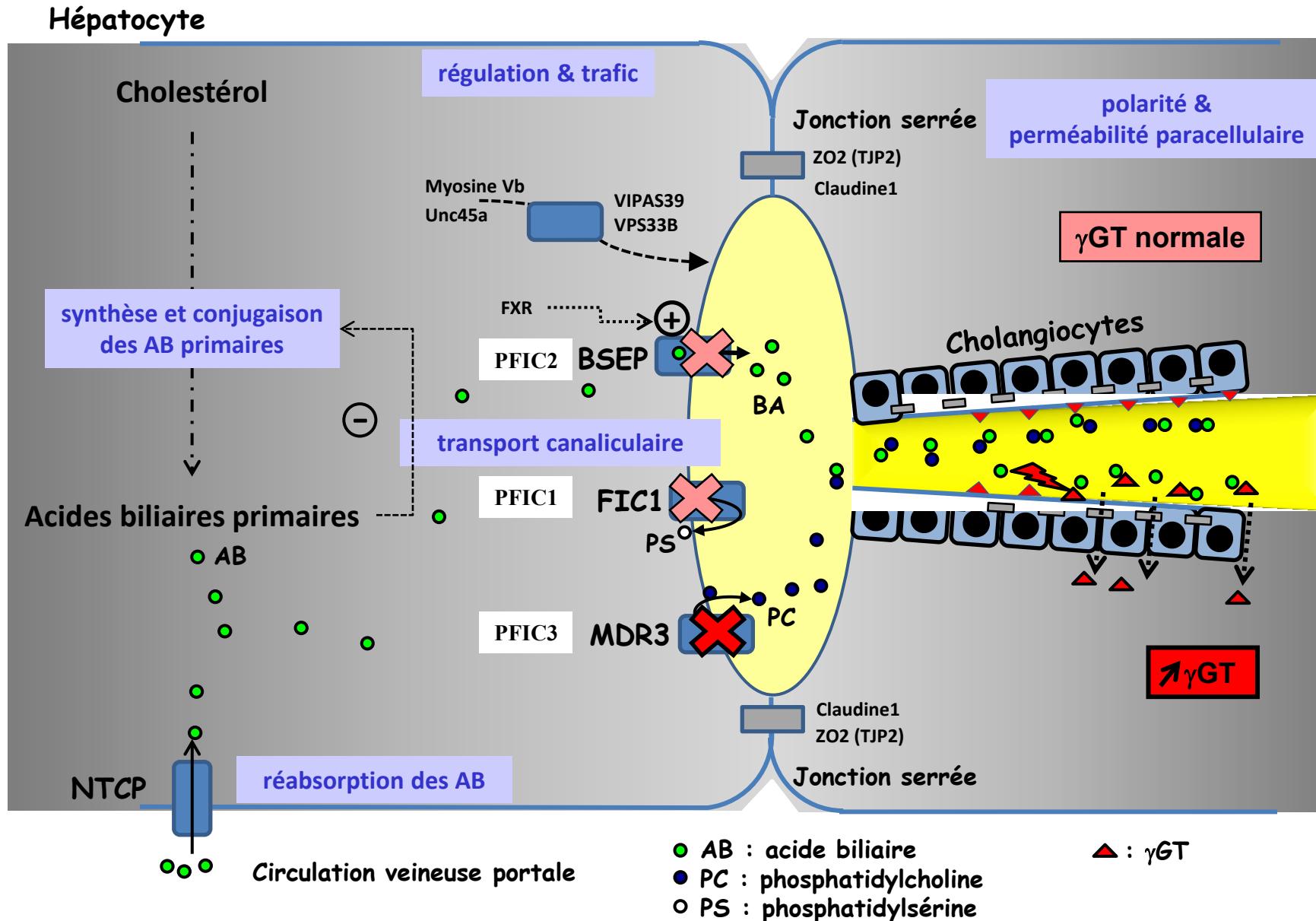
FILFOIE

Filière de Santé Maladies Rares du Foie de l'Adulte et de l'Enfant

**Données du registre international NAPPED
NAatural course and Prognosis of PFIC and Effect of biliary Diversion**

E Gonzales

Déficits en transporteur canalicular



Variabilité phénotypique des anomalies des transporteurs canaliculaires

BRIC1-3 → **PFIC1-3**

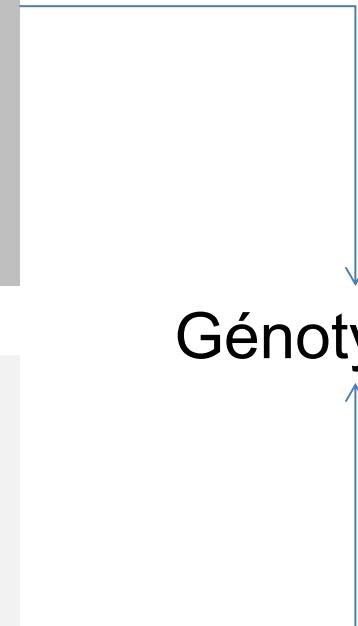
2 allèles mutés

Second événement?

Formes intermédiaires

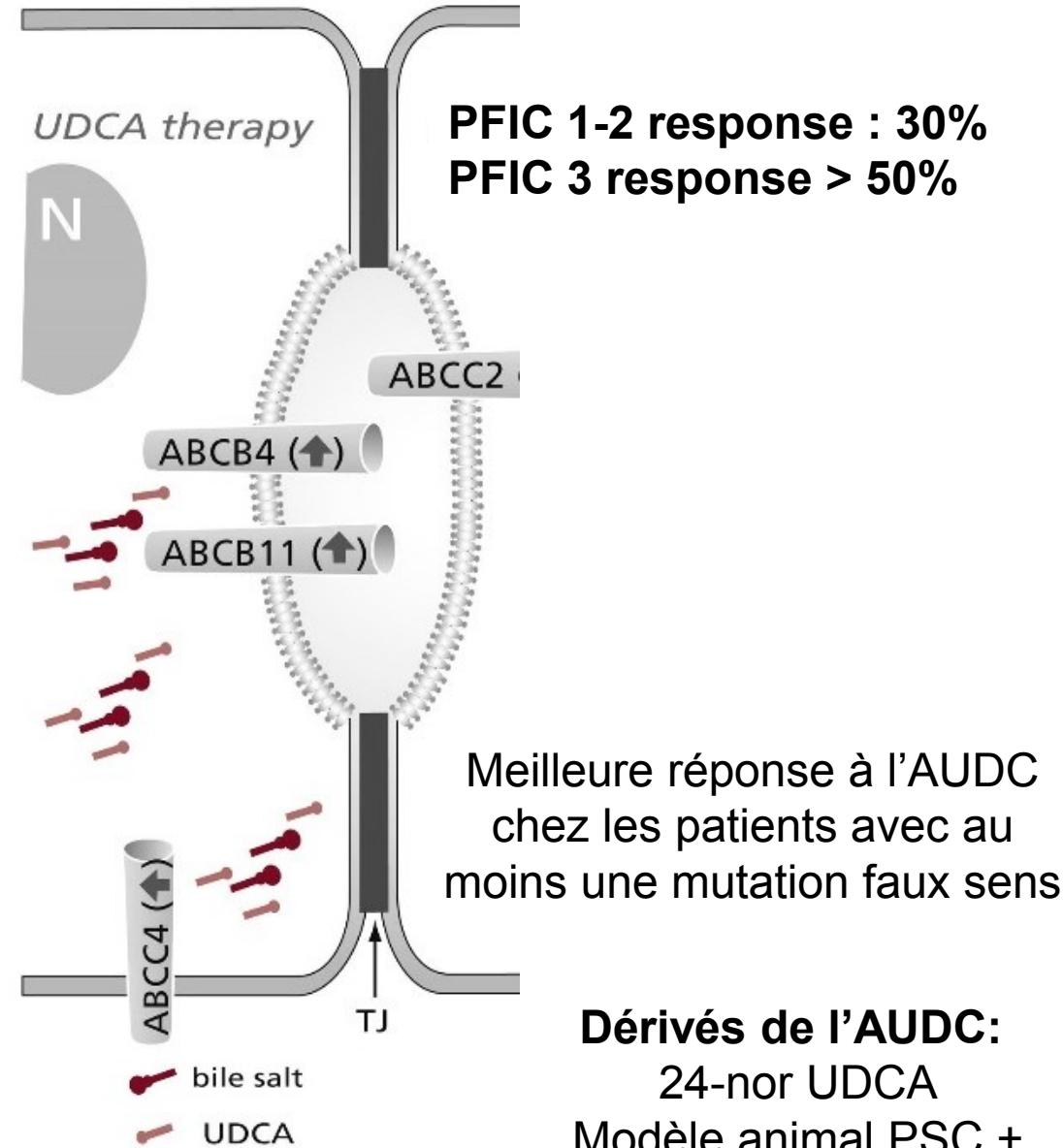
1 allèle muté

- Cholestase gravidique (ICP1-3)
- Cholestase médicamenteuse (DIC1-3)
- Cholestase néonatale transitoire (TNC1-3)
- Lithiase biliaire (syndrome LPAC)
- Cancer du foie ou des voies biliaires



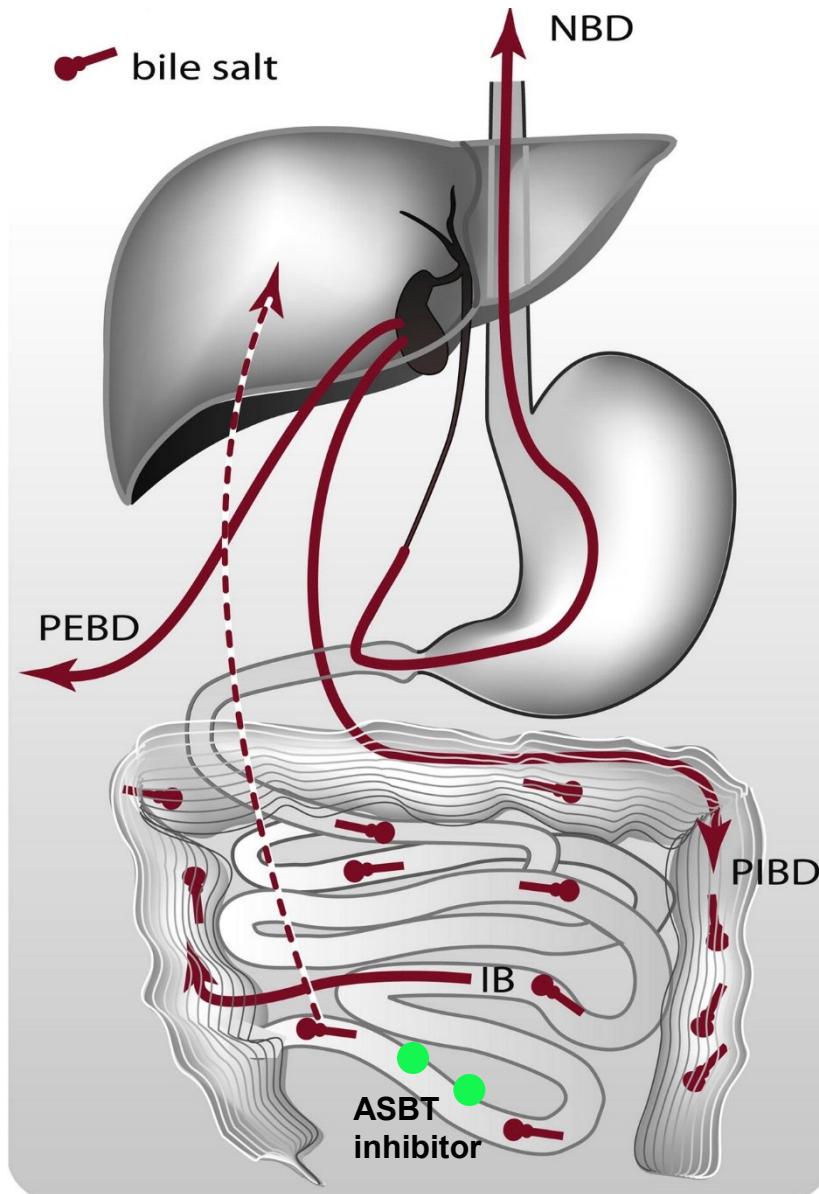
Traitements des PFIC : l'AUDC

- protection des hépatocytes et cholangiocytés par remplacement des AB endogènes toxiques (cytoprotection et antiapoptose)
- Augmente l'expression canaliculaire de transporteurs fonctionnels: effet transcriptionnel (BSEP, MRP2) et post-transcriptionnel (BSEP)
- Hypercholérétique, par shunt choléhépatique et augmentation de la sécrétion de HCO₃⁻ (AE2)
- Effet immunomodulateur



Jacquemin et al. Hepatology 1997
Jacquemin Gastroenterology 2001
Stapelbroek et al. J Hepatol 2010
Spraul Hepatology 2010
Pawlakowska J Hepatol 2010

Dérivation biliaire et PFIC1-2



- Dérivation biliaire partielle externe**

Bénéfice chez certains patients
PFIC1 et PFIC2 (mutation non sévère?)

Dérivation biliaire partielle interne

Ileal bypass

- Inhibiteurs d'ASBT: « dérivation chimique »**

Whitington PF et al., *Gastroenterology* 1988
Balistreri W et al. *Hepatology* 2005
Stapelbroek et al. *J Hepatol* 2010



NAPPED:

NAtural course and **P**rognosis of **P**FIC and **E**ffect of biliary **D**iversion

Endorsements : ESPGHAN, ERN RARE-LIVER

The Natural Course of BSEP-deficiency

Results from the global NAPPED-consortium

Daan van Wessel¹

Richard Thompson, Tassos Grammatikopoulos, Agustina Kadaristiana, Irena Jankowska Patryk Lipiński, Piotr Czubkowski, Emmanuel Gonzales, Emmanuel Jacquemin, Anne Spraul, Etienne Sokal, Mohammad Shagrani, Dieter Broering, Talal Algoufi, Nejat Mazhar, Emanuele Nicastro, Deirdre Kelly, Gabriella Nebbia, Henrik Arnell, Björn Fishler, Jan Hulscher, Daniele Serranti, Cigdem Arikan, Esra Polat, Dominique Debray, Florence Lacaille, Cristina Goncalves, Loreto Hierro, Gema Muñoz Bartolo, Yael Mozer- Glassberg, Amer Azaz, Jernej Breclj, Antal Dezsőfi, Pier Luigi Calvo, Enke Grabhorn, Ekkehard Sturm, Wendy van der Woerd, Bettina Hansen², Henkjan J. Verkade¹

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Natural course and prognosis of PFIC and effect of biliary diversion

Aims of NAPPED

- To characterize the natural course of disease in FIC1-deficiency (PFIC1) and in BSEP-deficiency (PFIC2)
- To determine associations between genotype and phenotype
- To assess effects of surgical biliary diversion on native liver survival

Patients & Methods

- 22 centers from around the globe

- Retrospective collection of clinical data

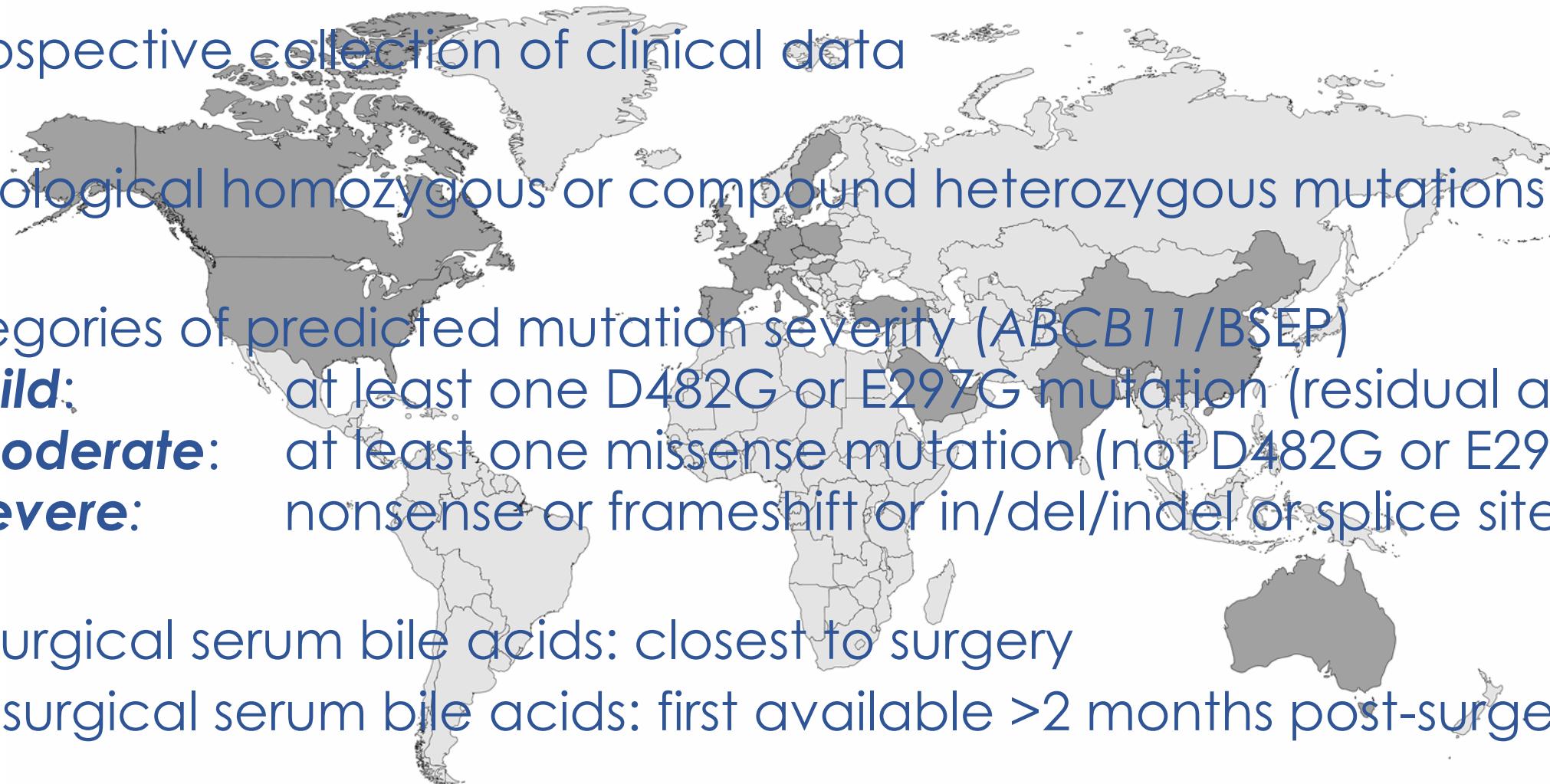
- Pathological homozygous or compound heterozygous mutations

- Categories of predicted mutation severity (ABCB11/BSEP)

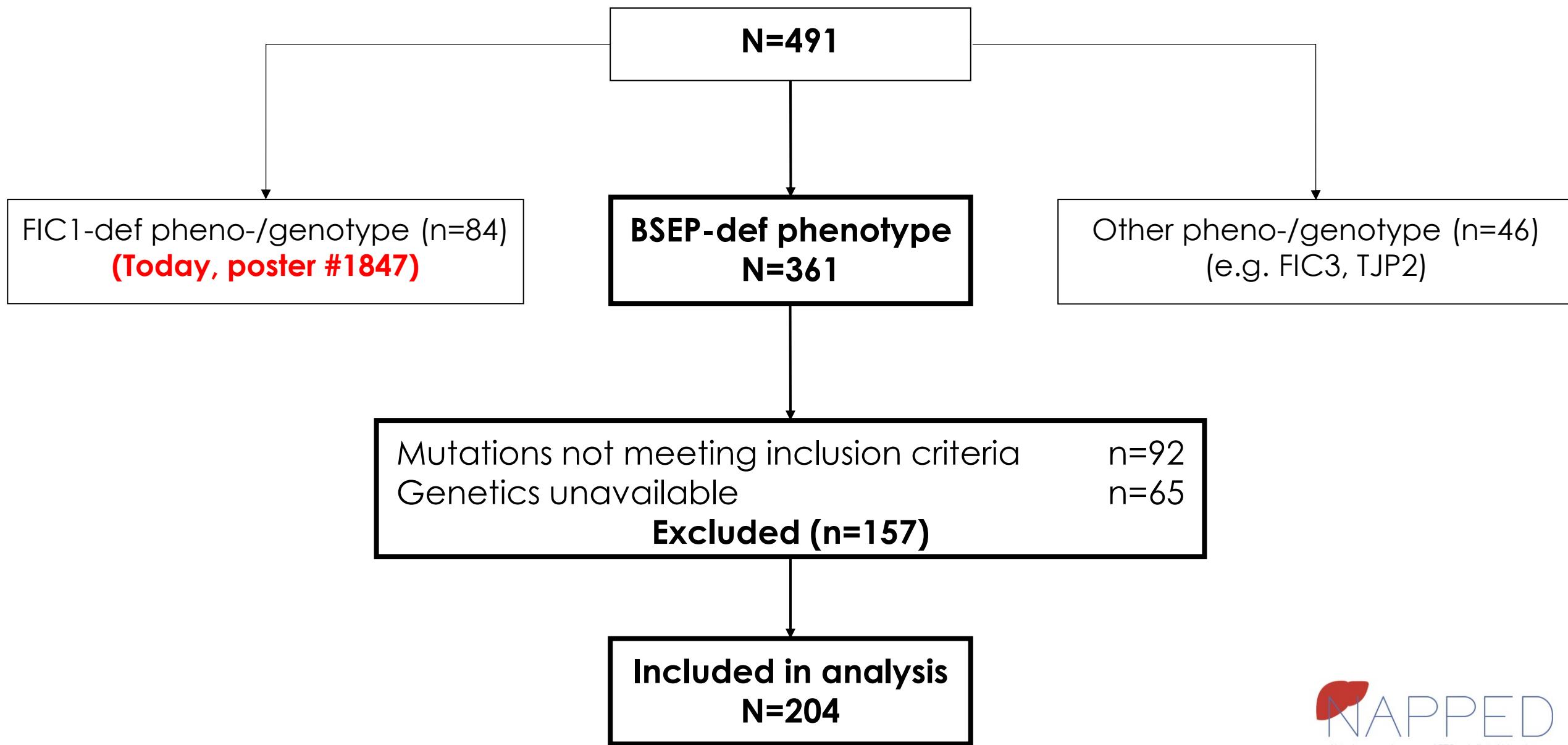
- **Mild:** at least one D482G or E297G mutation (residual activity)
- **Moderate:** at least one missense mutation (not D482G or E297G)
- **Severe:** nonsense or frameshift or in/del/indel or splice site

- Pre-surgical serum bile acids: closest to surgery

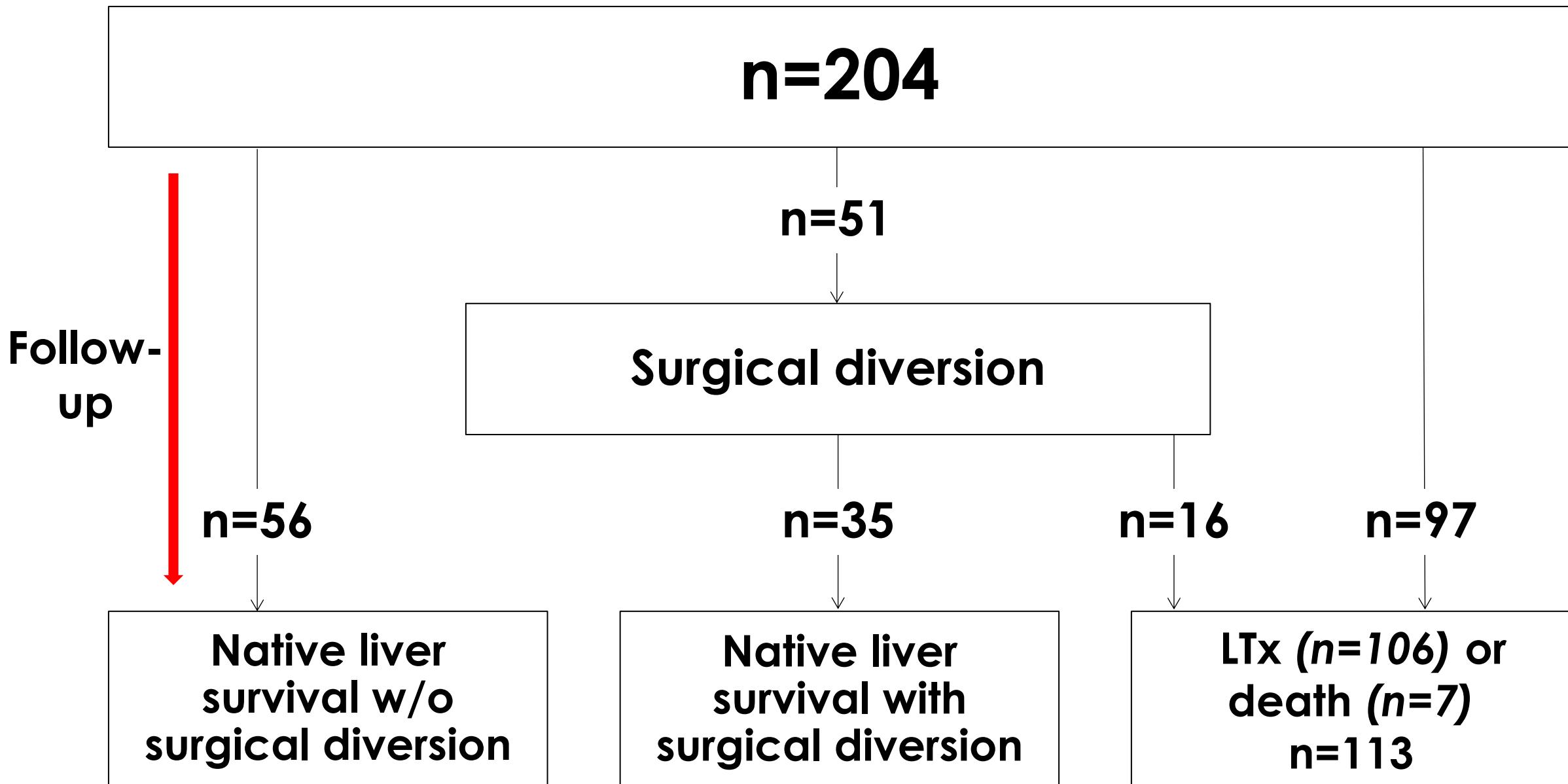
- Post-surgical serum bile acids: first available >2 months post-surgery



NAPPED database per May 2018



Endpoints of BSEP-deficiency patients



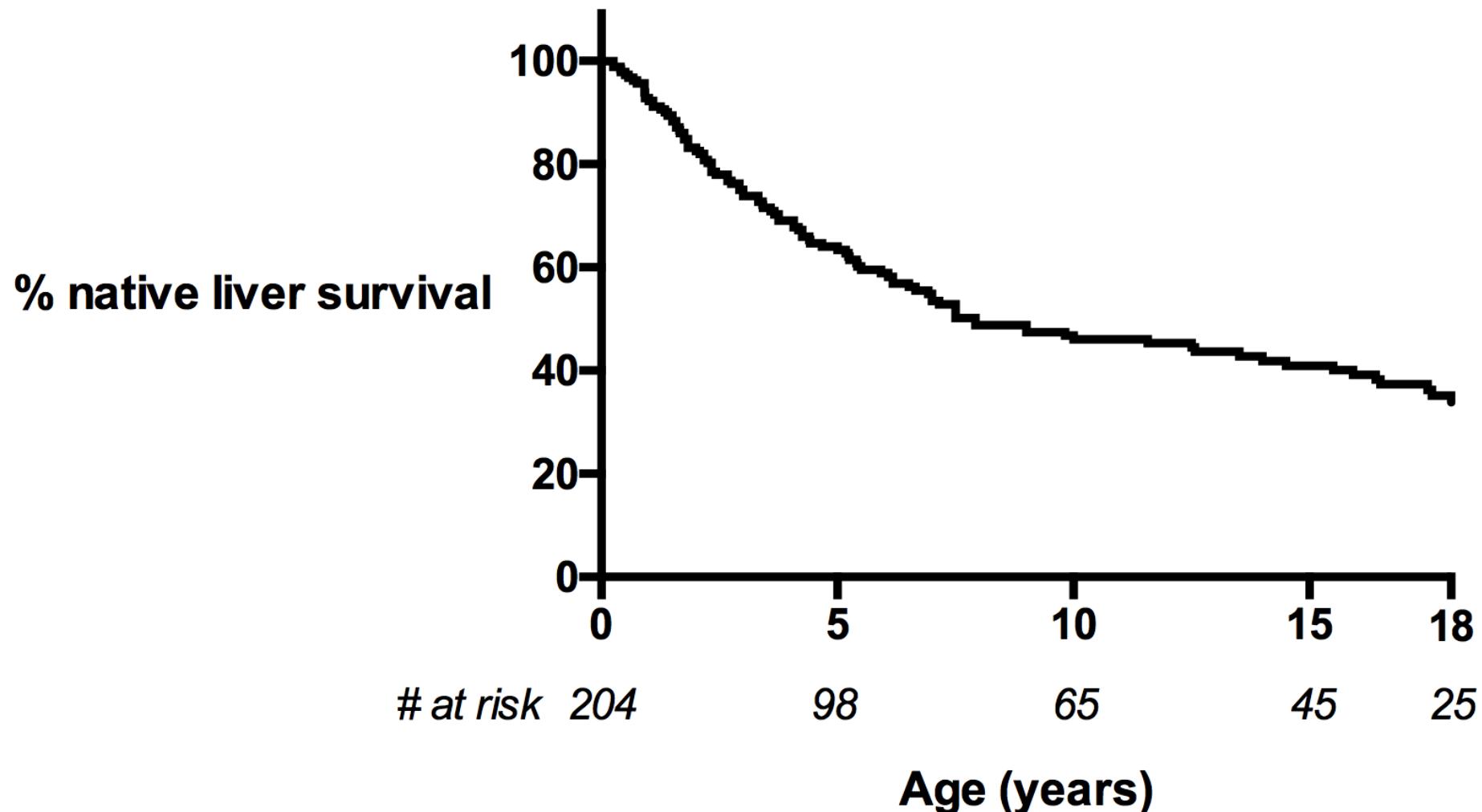
Patient characteristics BSEP-deficiency

n=204

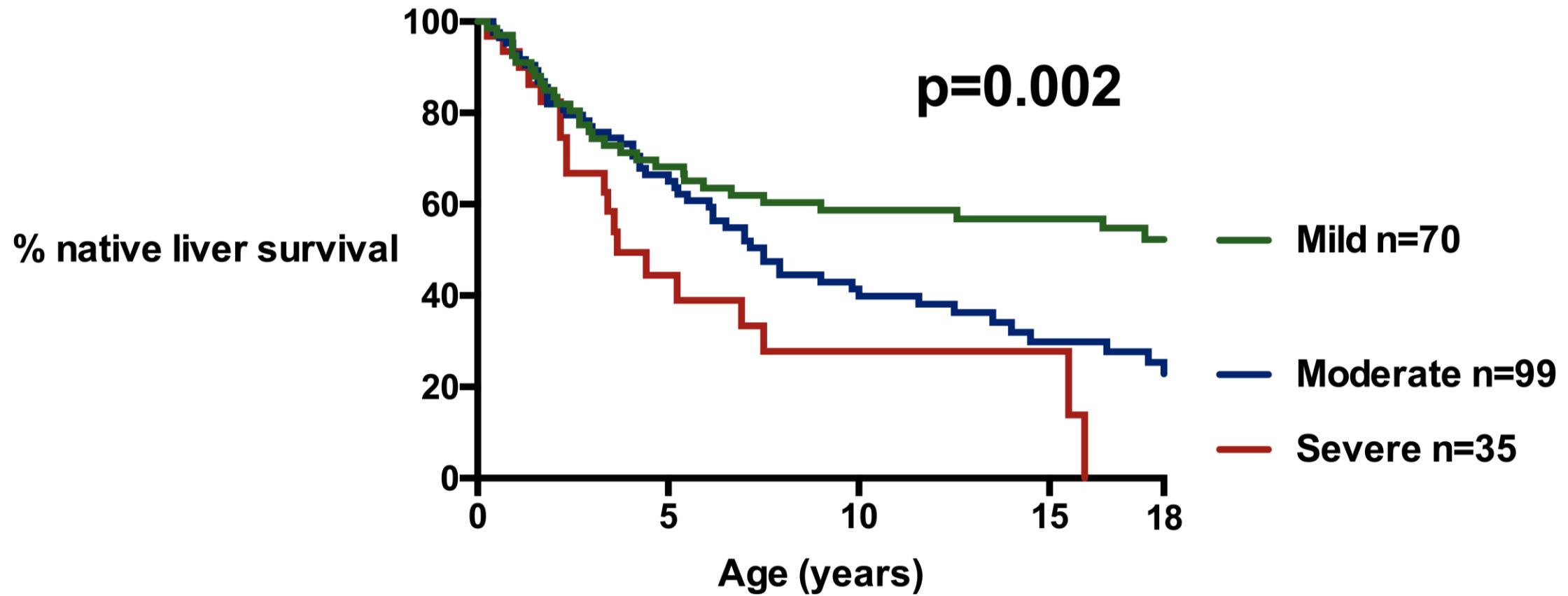
Males	53%
Age first visit	0.8 [0.3-2.4] years
Duration of follow-up	3.7 [0.8-10.1] years
Pre-transplant mortality	7 (3%)

Medians and IQR

A third of all BSEP-deficiency patients reach adulthood with their native liver

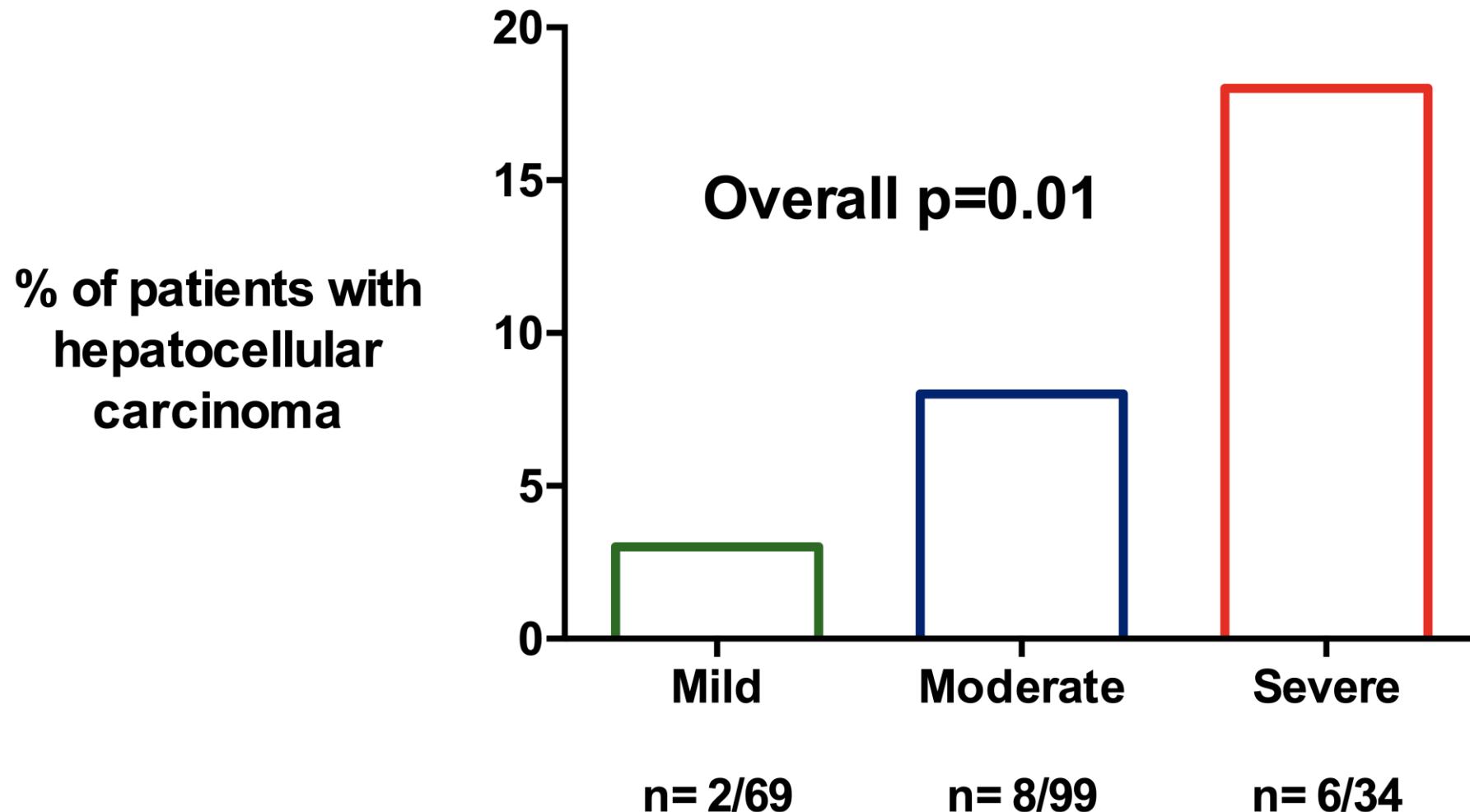


Native liver survival is associated with the severity of mutation

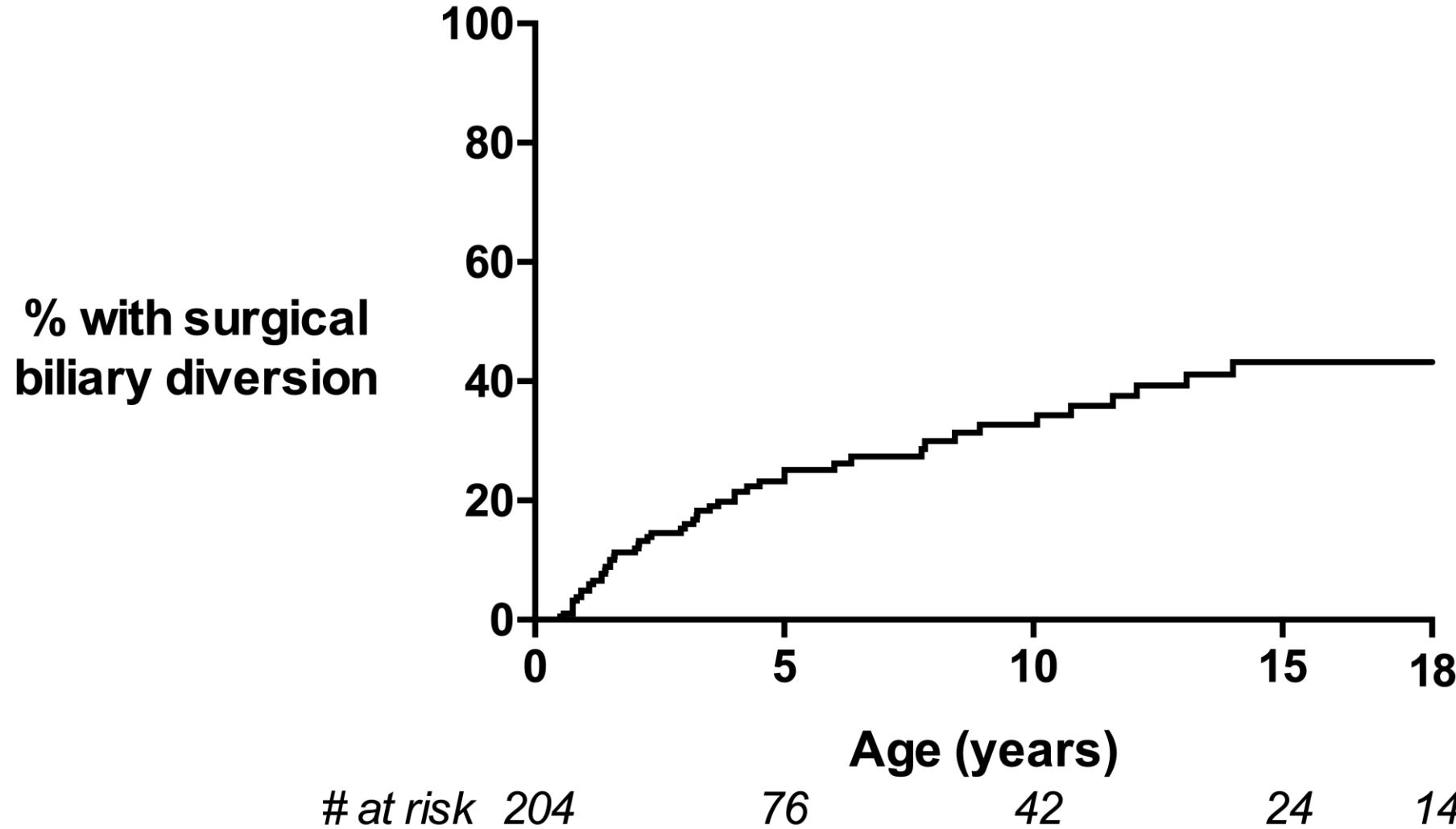


# at risk	Mild	70	44	35	29	16
	Moderate	99	47	26	15	10
	Severe	35	8	5	2	0

Hepatocellular carcinoma incidence is associated with severity of mutation



Almost half of patients with BSEP-deficiency undergo surgical biliary diversion before adulthood



at risk 204

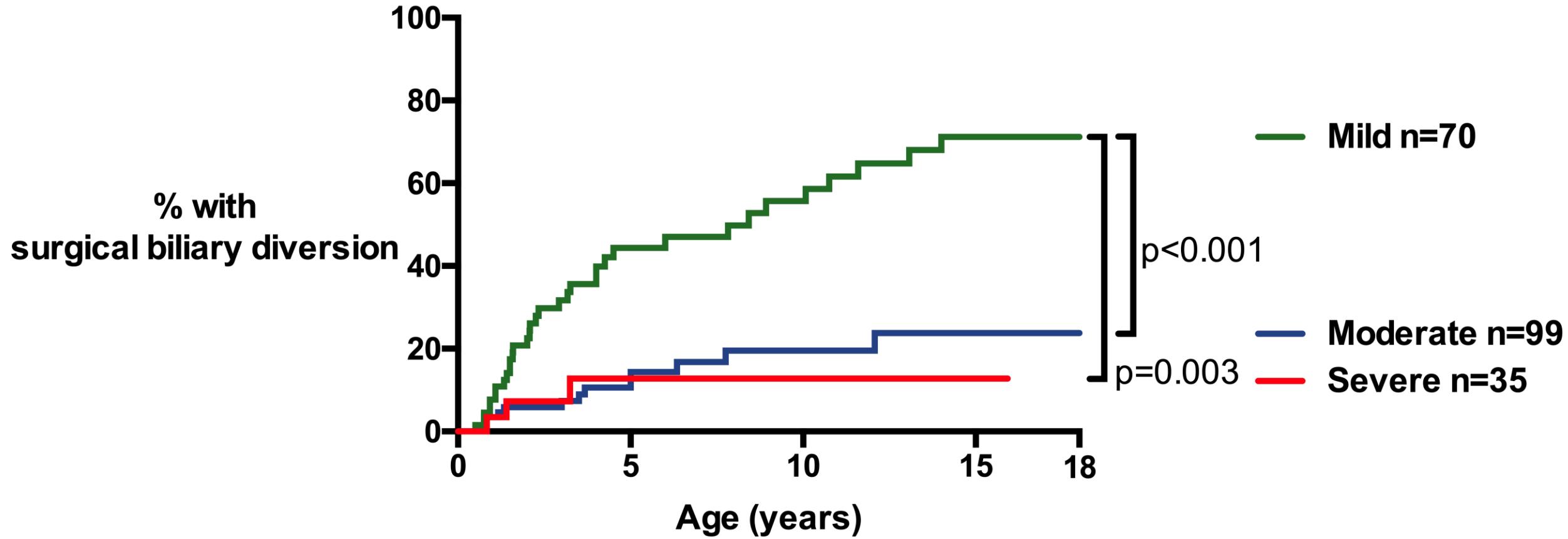
76

42

24

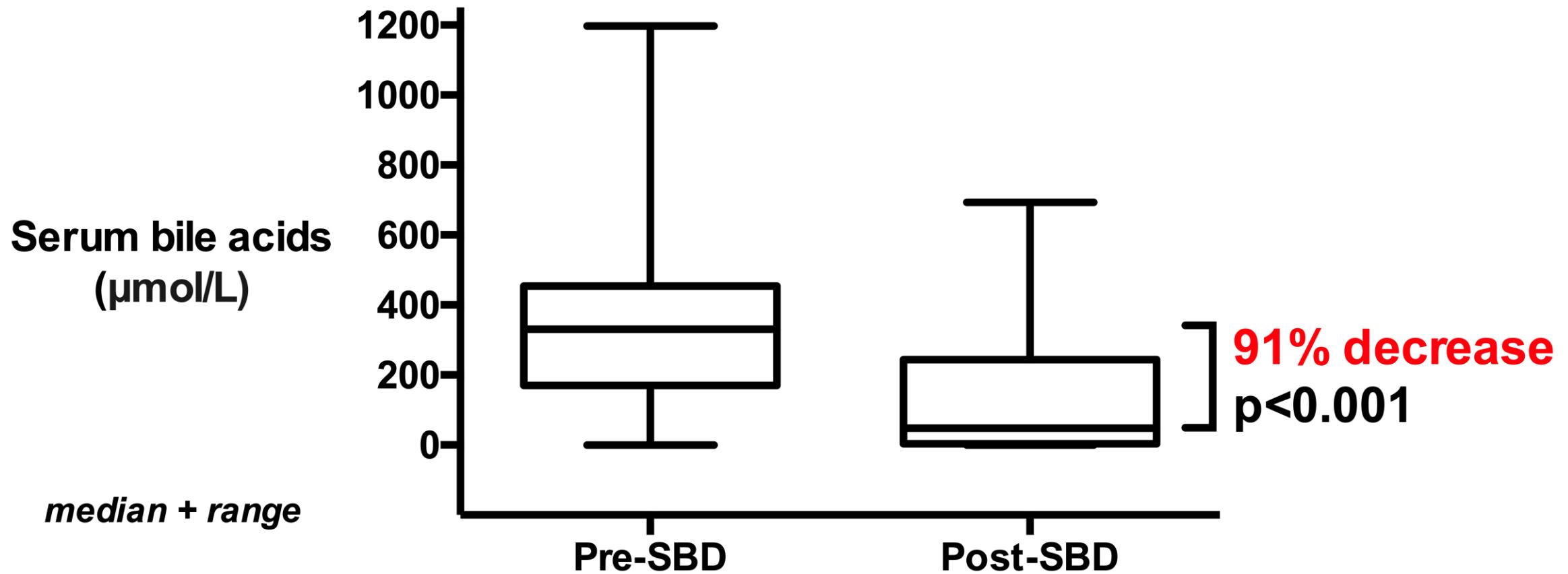
14

More *mild* patients undergo surgical biliary diversion than *moderate* or *severe* patients

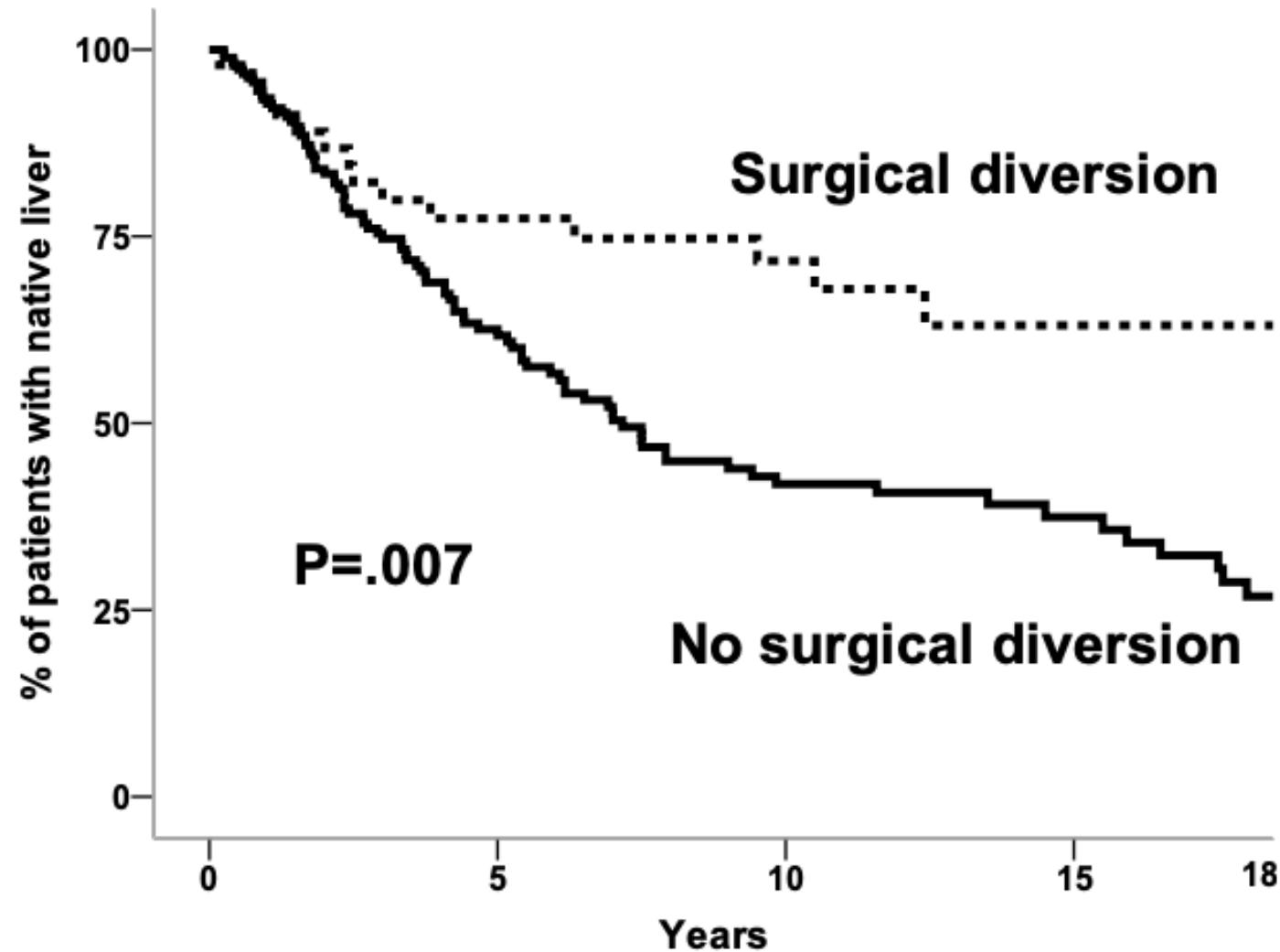


# at risk	Mild	Moderate	Severe
0	70	99	35
2	57	84	28
4	45	64	19
6	38	54	10
8	32	44	5
10	26	34	2
12	20	24	0
14	14	14	0
16	9	10	0
18	5	10	0

Surgical biliary diversion associated with decrease in serum bile acids

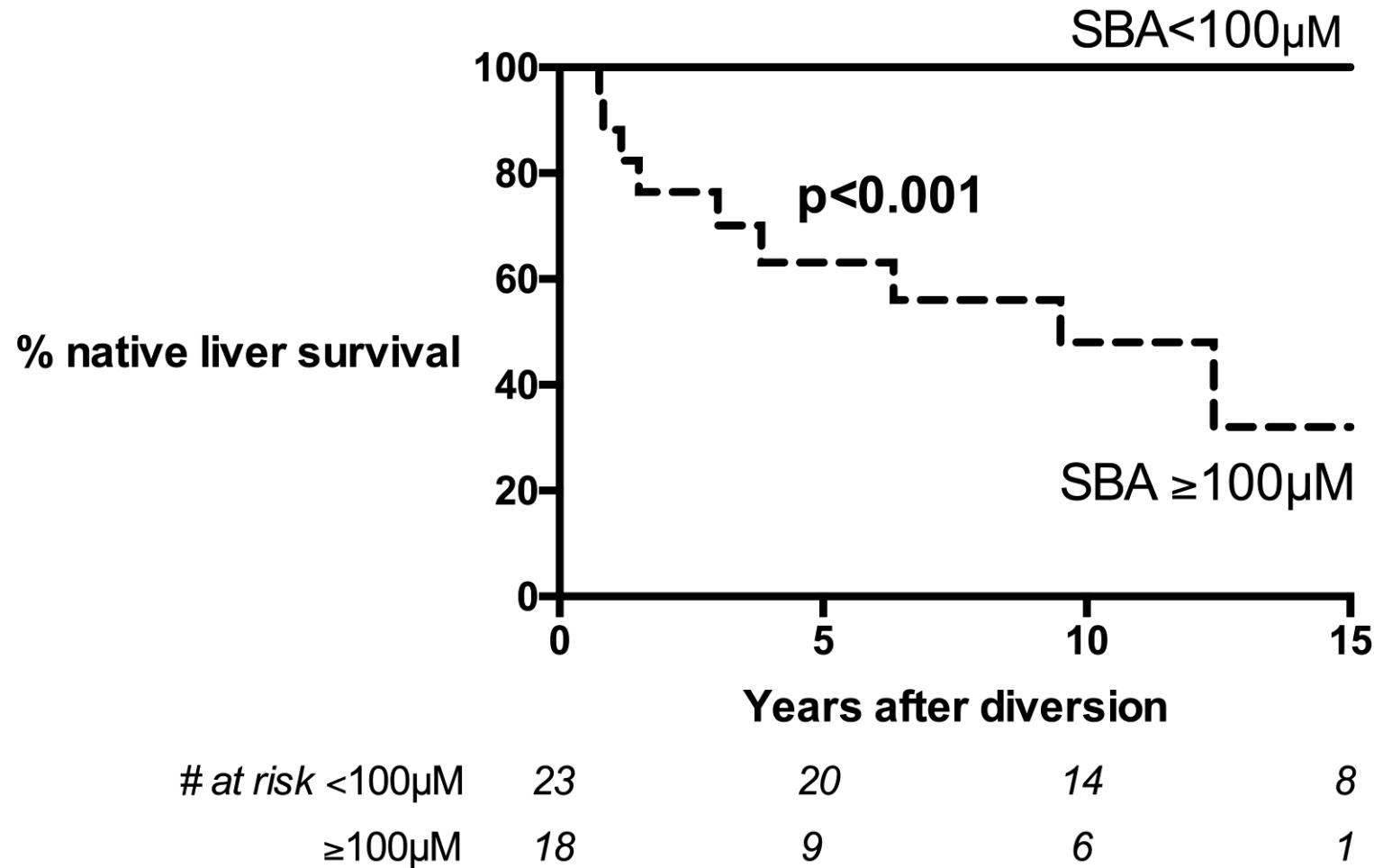


Surgical biliary diversion is significantly associated with improved native liver survival



- Subgroups: mild and moderate
- Cox regression, time-dependent covariate
- Corrected: sex, birthyear, severity mutation
- $HR=0.44$; $95\%CI 0.23-0.88$

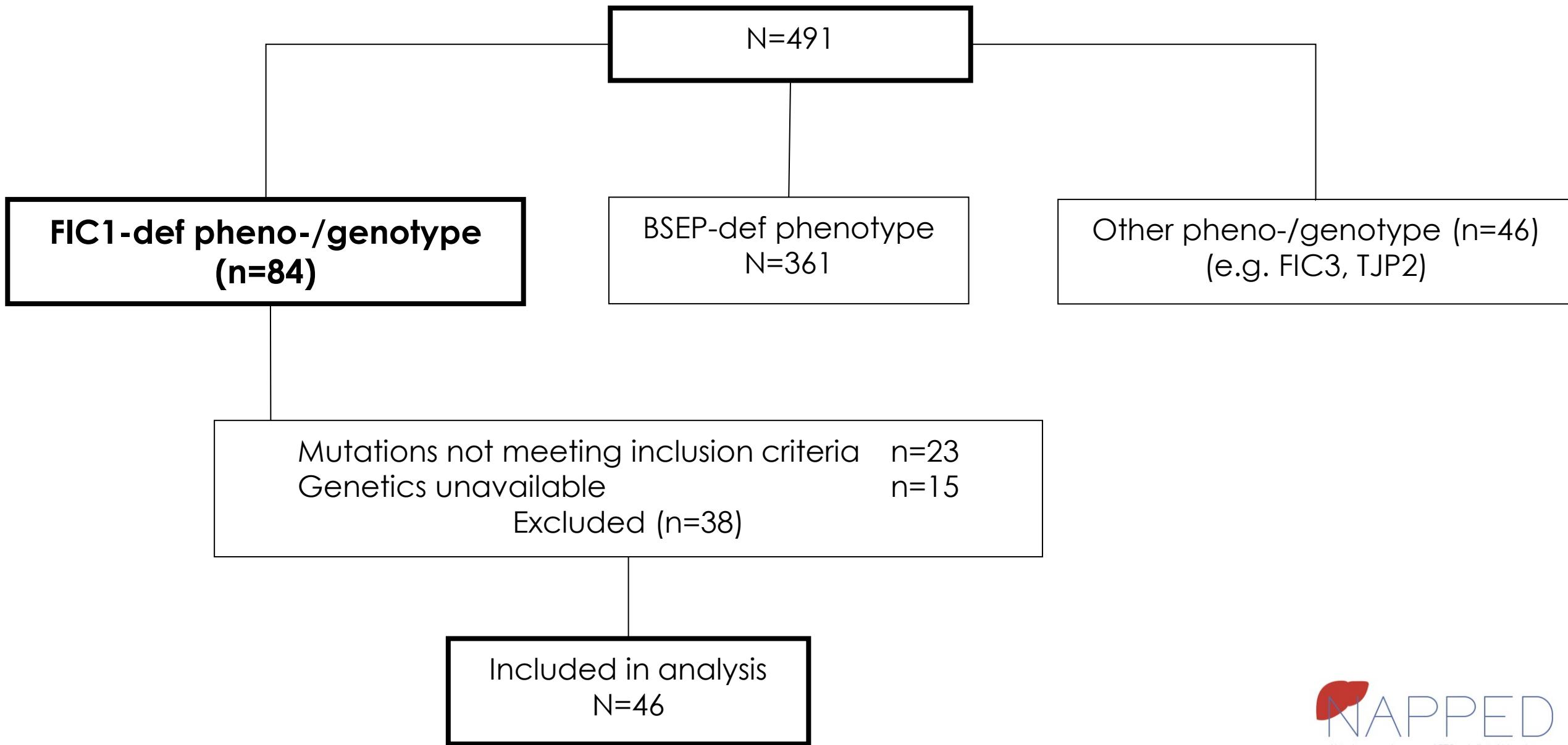
Serum bile acid level after diversion associated with native liver survival



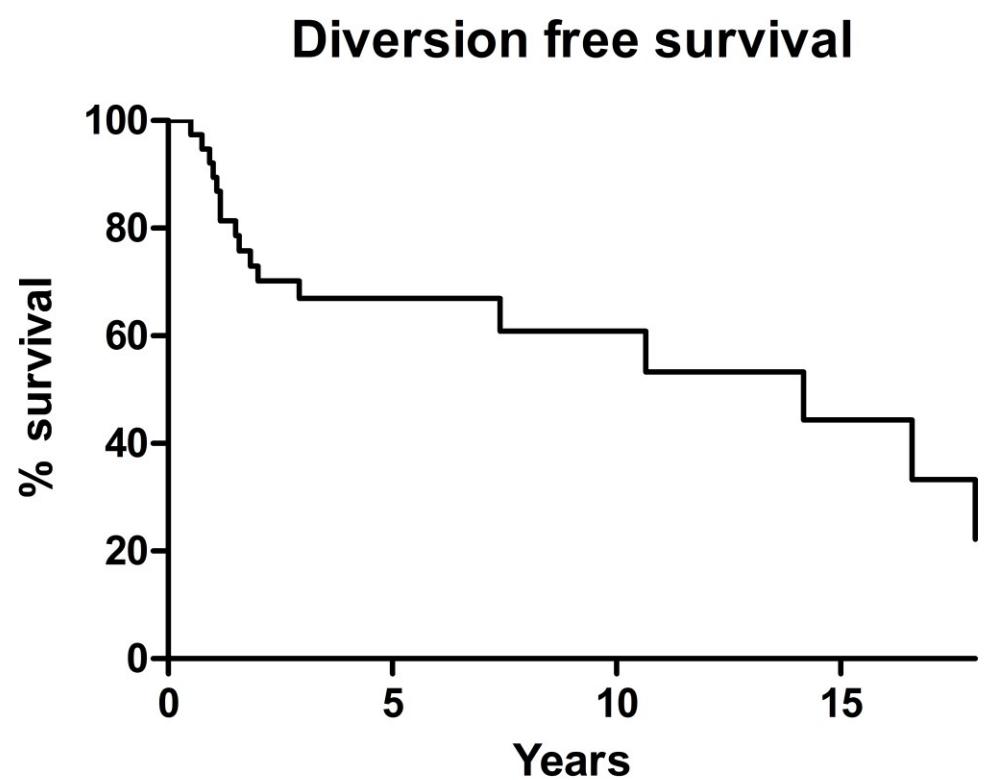
Conclusions on BSEP-deficiency

- A third of patients reach adulthood with native liver
- Native liver survival and incidence of hepatocellular carcinoma are associated with severity of mutation
- Surgical biliary diversion is associated with increased native liver survival in mild and moderate mutations
- Post-surgical serum bile acid levels are associated with native liver survival

NAPPED database per May 2018



During childhood, 70% of FIC1-def patients receive a surgical diversion and 54% need a liver transplant



- Surgical diversion not correlated with native liver survival
- Genotype not associated with diversion-free or native liver survival

Acknowledgements

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