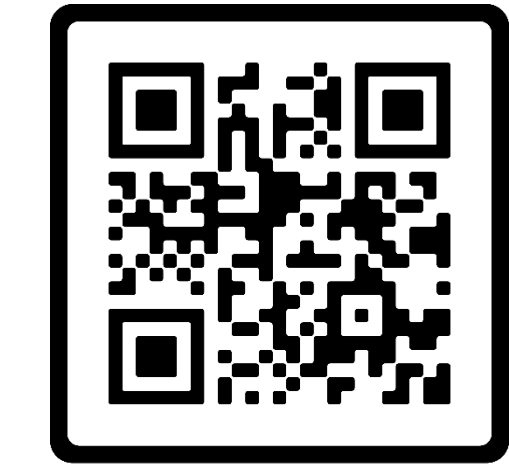




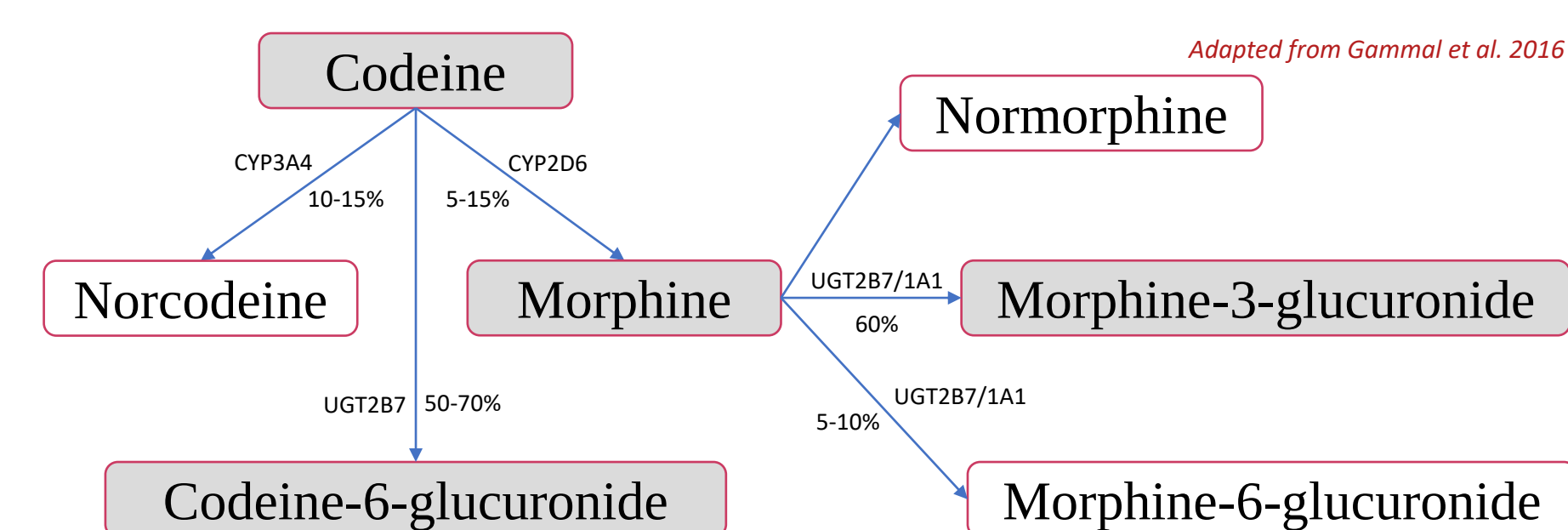
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Introduction

- No less than 30% of day-case surgical patients suffer from severe or moderate pain at 24 hours after surgery^{1,2}, while multimodal analgesia with codeine, paracetamol and non-steroidal analgesic agents is proven effective for treatment

- Codeine is a prodrug, activated to morphine via CYP2D6,
 - Genetic polymorphism plays a vital role in morphine exposure³, and may lead to therapeutic failure (low to none CYP expression) or morphine toxicity



- CYP2D6 expression has been quantified categorically using four subclasses, i.e., Poor (PM), Intermediate (IM), Normal (NM), or Extensive (EM) metaboliser depending on CYP2D6 activity

- Recent guidelines from Clinical Pharmacogenetics Implementation Consortium (CPIC®)⁴ and Dutch Pharmacogenetics Working Group (DPWG) devise a numerical system based on quantitative increments for each gene in a diplotype
 - Activity score (AS) for CYP2D6 expression can be implemented as a covariate in population model

- In vivo CYP2D6 activity of different allele variants and genotypes has **not** been precisely quantified during codeine therapy

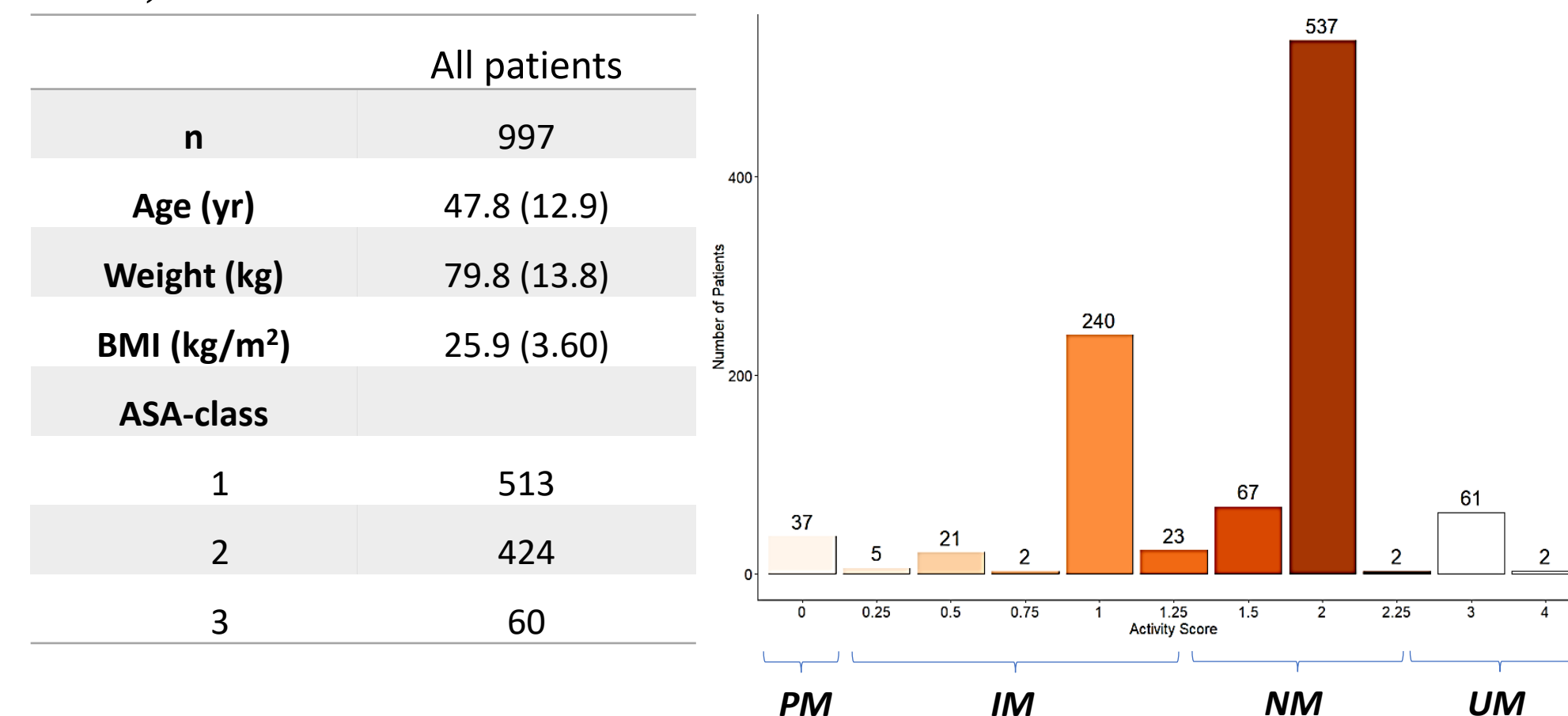
- Previous studies are retrospective and have evaluated pooled data from several small studies with limited number of CYP2D6 allele variants

Study protocol/data

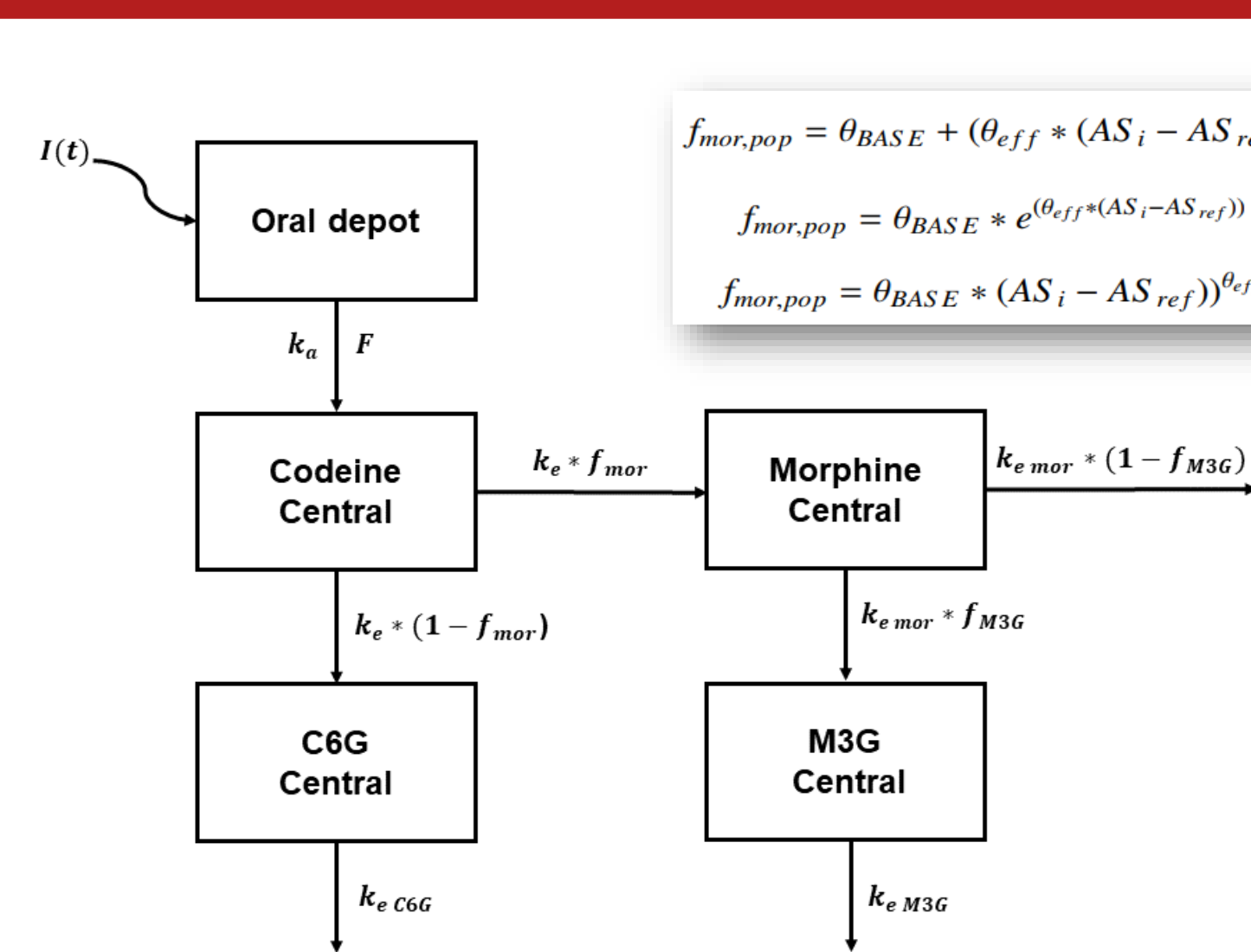
- Prospective exploratory clinical trial was conducted at the **day surgery unit of Jorvi Hospital in Espoo, Finland**
 - N = **1000** ambulatory surgery patients, **997** individuals were modelled for a lack of CYP2D6 genetic profile for 3 study subjects
- Study was registered with **EudraCT** (number: 2015-005561-23)
 - Approved by the Coordinating Ethics Committee of the **Helsinki and Uusimaa Hospital District** (3/2016) and by the **Finnish National Agency for Medicines** (KL no 4/2016)

- Oral premedication with 60mg codeine and 1000mg paracetamol for prophylactic preoperative analgesia

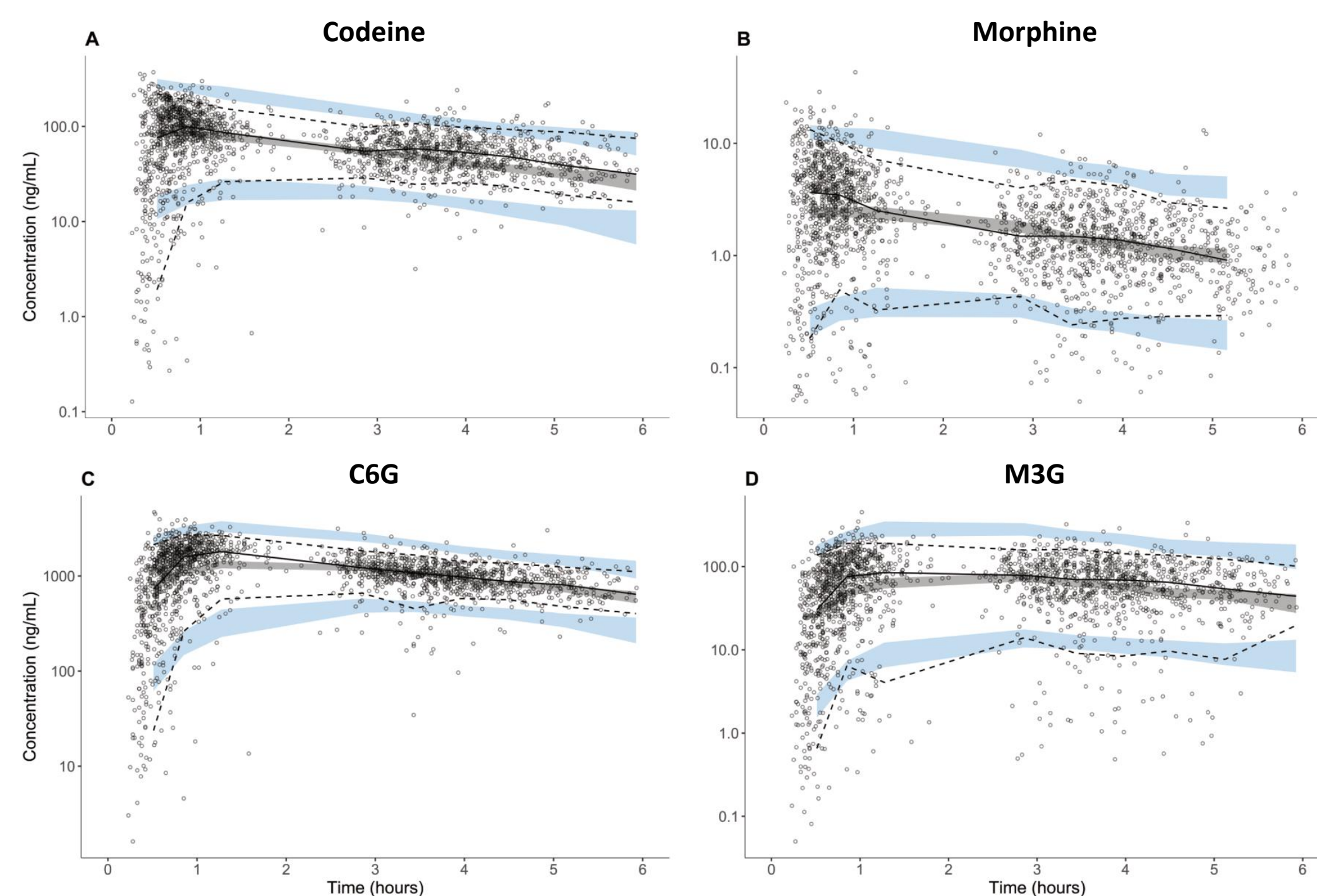
- Drug concentrations (i.e., codeine, morphine, C6G and M3G) were analysed using LC-MS system (Sciex, Toronto, Ontario, Canada), while CYP2D6 genotyping and CNV was carried out using TaqManR genotyping assays (Thermo Fisher Scientific, Waltham, MA)



Results



Parameter	Parameter estimate	SIR results
	Median	Median
k _{a,cod}	8.74	8.81
CL _{cod}	110	108.9
V _{c,cod}	427.5	414.1
F _{cod}	0.84	0.83
CL _{mor}	357.5	353.7
V _{c,mor}	22.8	22.5
F _{mor}	0.16	0.16
GEN _{eff}	1.00	1.00
CL _{C6G}	7.96	7.89
V _{c,C6G}	5.36	5.36
CL _{M3G}	9.45	9.41
V _{c,M3G}	8.47	8.43
η _{k_{a,cod}}	3.75	3.78
η _{V_{c,cod}}	0.181	0.181
η _{F_{cod}}	0.024	0.024
η _{CL_{mor}}	0.062	0.061
η _{R_{mor}}	0.334	0.334
ε _{cod}	0.259	0.259
ε _{mor}	0.149	0.149
ε _{C6G}	0.103	0.103
ε _{M3G}	0.096	0.096



Category	CYP2D6 activity	Predicted AUC _{cod} (SD) µg.h/L	Predicted AUC _{mor} (SD) µg.h/L
POOR	0.55	209 (120)	0.98 (1.3)
INTERMEDIATE	6.82	215 (125)	3.7 (3.4)
NORMAL	13.8	210.4 (121)	8.7 (7.3)
ULTRARAPID	19.9	206 (121)	19 (14)

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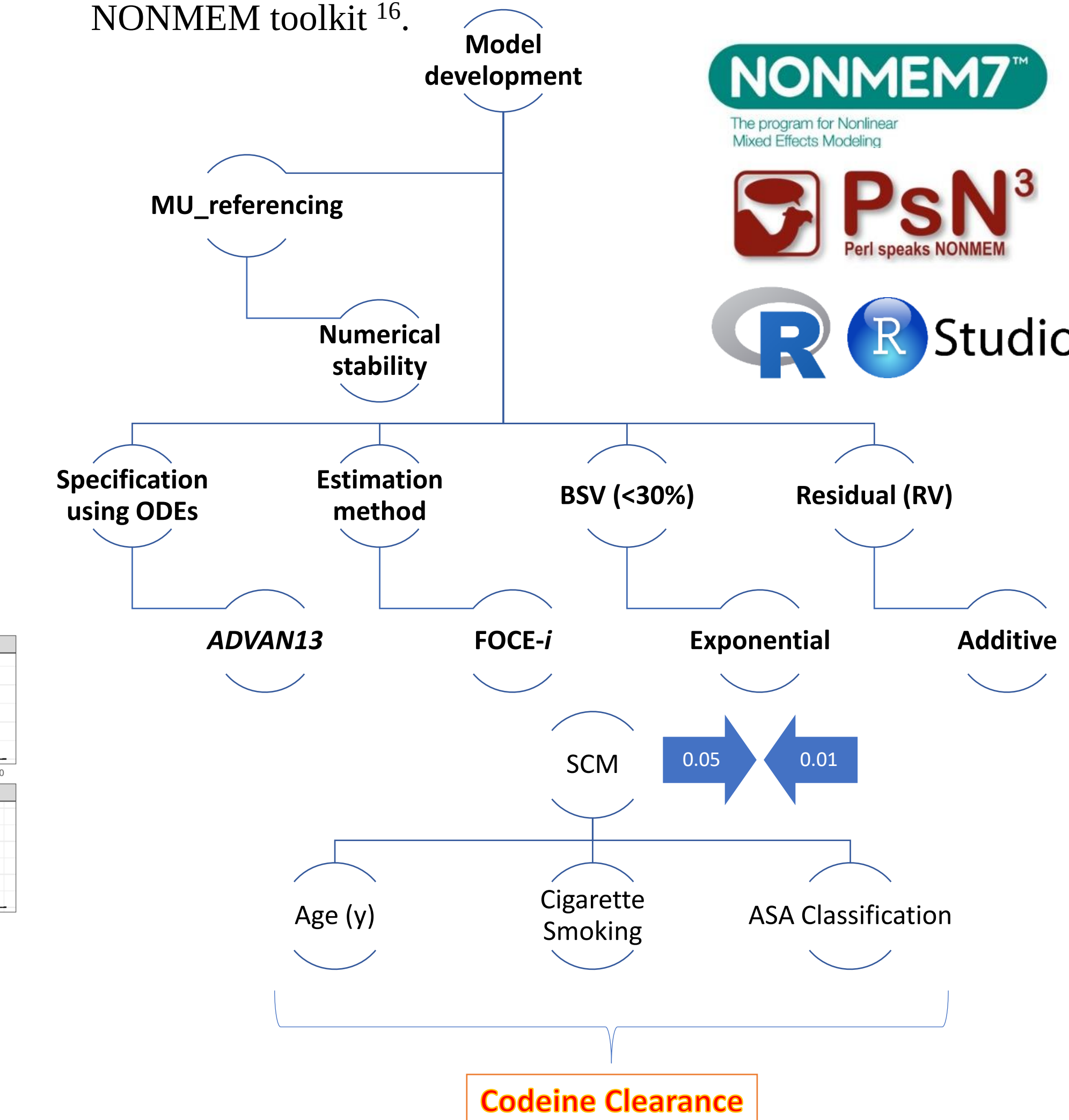
Aim and methodology

Aims:

- popPK modelling for codeine and its metabolites in ambulatory surgery patients
- CYP2D6 genetics-based covariate model for prediction of codeine metabolism
- Identifying the role of each gene in the diplotype towards morphine exposure
- Involvement of other patient covariates in complex codeine pharmacokinetics
- Model simulations for quantifying morphine exposure based on CYP2D6 genetics

Methodology:

- Non-linear mixed effects modelling was conducted with NONMEM® (version 7.4.3 or above) (ICON Development Solutions, Ellicott city, MD, USA)¹⁵, assisted by the Perl-Speaks-NONMEM toolkit¹⁶.



Discussion

- 58-83% reduction of the apparent CYP2D6 activity from NM
- CYP2D6*10 decreased function alleles showed higher apparent CYP2D6 activity compared with genotypes with CYP2D6*41 allele
- Unexplained variability in f_{mor,pop} could be reduced from 52% to 30% with covariate model (still high!)
- Codeine to morphine metabolism ranges from approx. 0% to more than 30% for PM and UM respectively (20 folds higher AUC!)
- For AS 3 and 4, simulations show normal dosing regimens can cross the EC50^{5,6} for respiratory depression for morphine concentrations

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