

Building of a virtual paediatric cancer population for physiologically-based pharmacokinetic modelling and simulation in neonates, infants, and children



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Introduction

Determination of appropriate dosing of many anticancer agents in neonates and infants is a difficult task. Doses are routinely reduced but little pharmacokinetic data exists, especially in neonates and infants less than one year old, to act as guidance as to the magnitude of the reduction¹. Physiologically-based pharmacokinetic (PBPK) models of anticancer drug disposition allow for simulation of the effects of changes in dose and dosing interval in various age groups and therefore may assist in dose selection.

PBPK modelling and simulation in neonates and infants requires a virtual paediatric population containing information on parameters that may affect PK that are known to change with age, such as body surface area, organ volume, organ blood flow, enzyme and transporter expression, plasma protein binding concentrations, and renal function².

However, physiological changes affecting PK may occur in cancer as a result of disease and/or drug treatments, and these alterations may change typical ontogeny functions. Parameter differences seen in cancer include elevations in alpha-1 acid glycoprotein (AAG), an acute phase reactant that binds weakly basic drugs, including docetaxel, imatinib, and erlotinib, and decreases in albumin and haematocrit³. In addition, different height and weight distributions may be present in relation to age as compared with healthy children.

The aim of this ongoing work is to build a virtual paediatric cancer population for use in PBPK modelling and simulation of anticancer drug disposition, especially in neonates and infants in whom limited pharmacokinetic data exist. Here we report the initial investigations of height, weight, AAG, and GFR data in relation to age in a group of paediatric cancer patients enrolled in various pharmacokinetic trials in the UK.

Methods

- Anonymised patient data/plasma samples from 153 paediatric cancer patients who had participated in PK studies of anticancer agents (Newcastle Children’s Cancer Pharmacology Group) were used
 - Age range 1 month to 19.8 years
- AAG concentrations were measured in 120 plasma samples by ELISA (Abcam, Cambridge, UK)
- Relationships between height and age, weight and height, and AAG and age were assessed by nonlinear regression using GraphPad Prism version 6.05 for Windows, GraphPad Software, La Jolla, California, USA, www.graphpad.com
- The slope and intercept values from the height and weight curves were used to simulate height and weight values for 2,000 virtual paediatric subjects (1022 males, 978 females) within Simcyp version 14.1 (Simcyp Limited, Sheffield, UK).
- Comparison of patient ages, BSA, AAG, and corrected GFR by cancer type were performed by the Kruskal-Wallis test with Dunn’s multiple comparison’s test also using GraphPad Prism version 6.05.

Results

Table 1. Patient variables

Variable type	Variable	Number of patients			Total
		Male	Female	Not specified	
Demographic	Age (years)	75	59	19	153
	BSA (m ²)	74	59	19	152
	AAG (g/L)	34	31	55	120
Laboratory	GFR (mL/min)	29	28		57
Cancer type	Neuroblastoma	11	5	11	27
	Ependymoma			9	9
	Soft tissue sarcoma	11	6		17
	ALL	7	5		12
	Ewing’s sarcoma	14	11		25
	Rhabdomyosarcoma	14	12	1	27
	Wilm’s tumour	3	6		9
	Other*	11	14	11	36

*Includes: AML, retinoblastoma, brain tumour, germ cell tumour, PNET, yolk sac tumour, pineal gland tumour, rhabdoidtumour of kidney, paraspinal sarcoma, pulmonary blastoma, embryonal liver sarcoma, other not specified

Fig 2. Height vs. age plots for male and female paediatric cancer patients

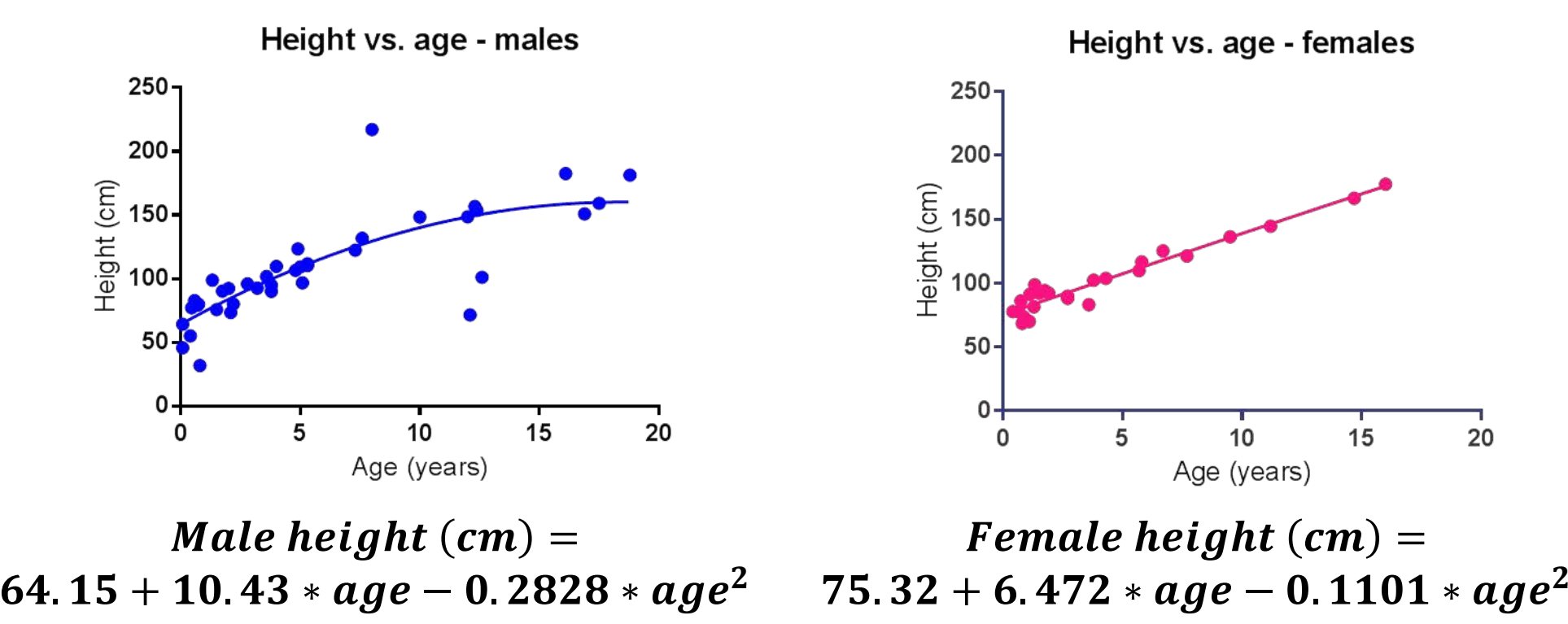


Fig 1. Patient age by cancer type

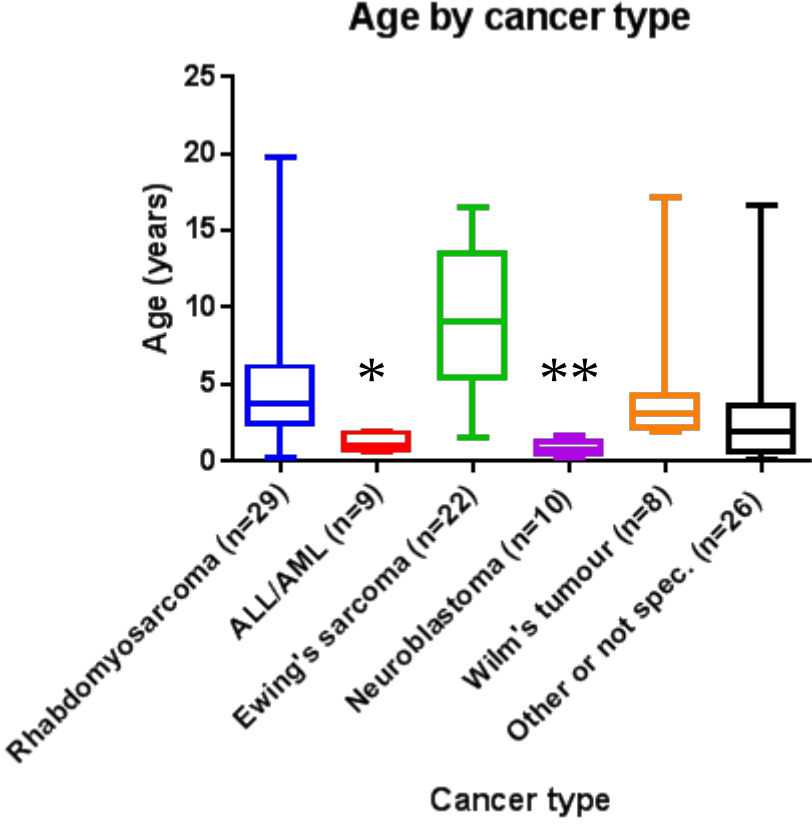
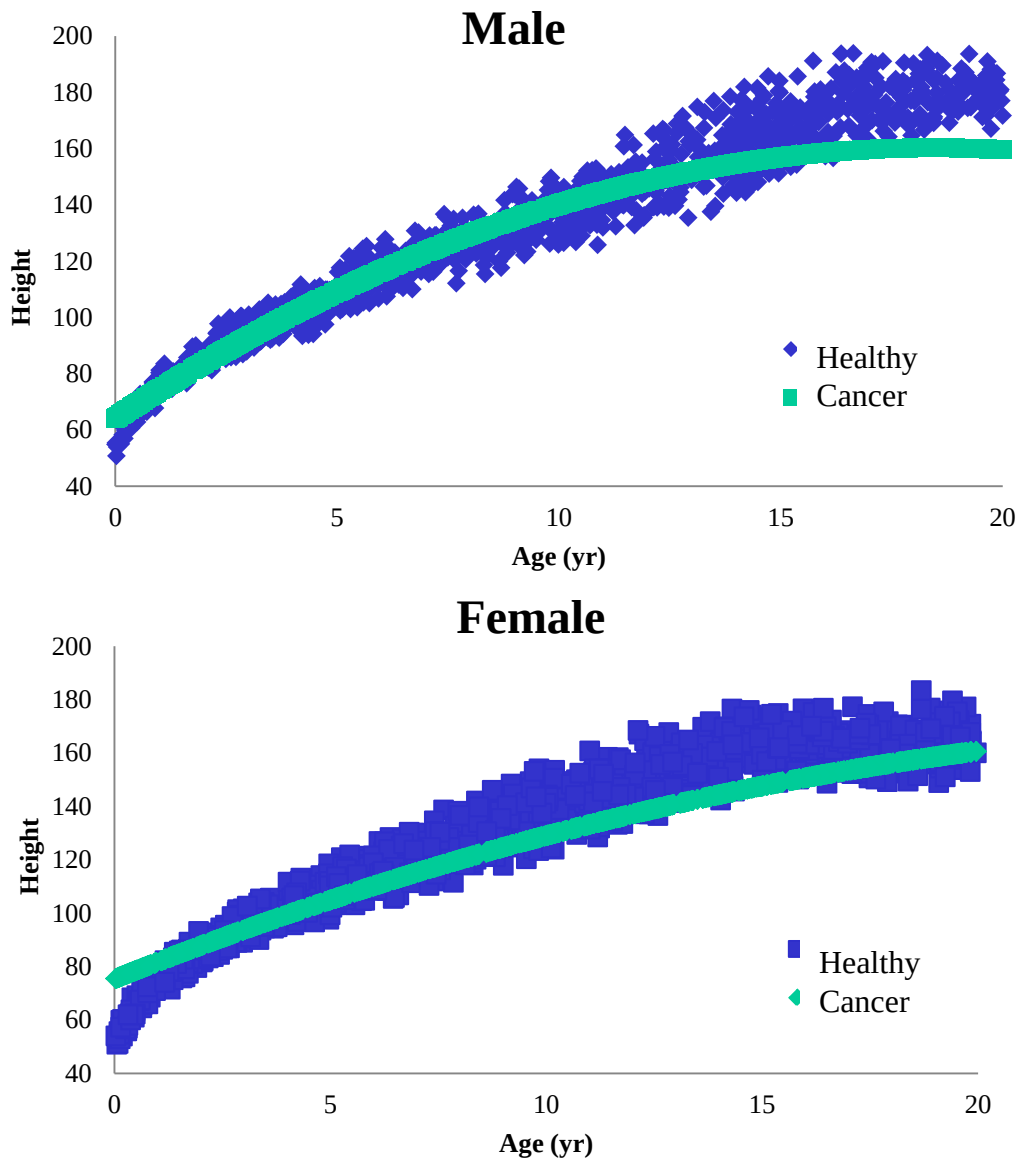


Fig 3. Simulated height vs. age for 2,000 virtual paediatric healthy and cancer patients



Results – cont’d

Fig 4. Weight vs. height for male and female paediatric cancer patients

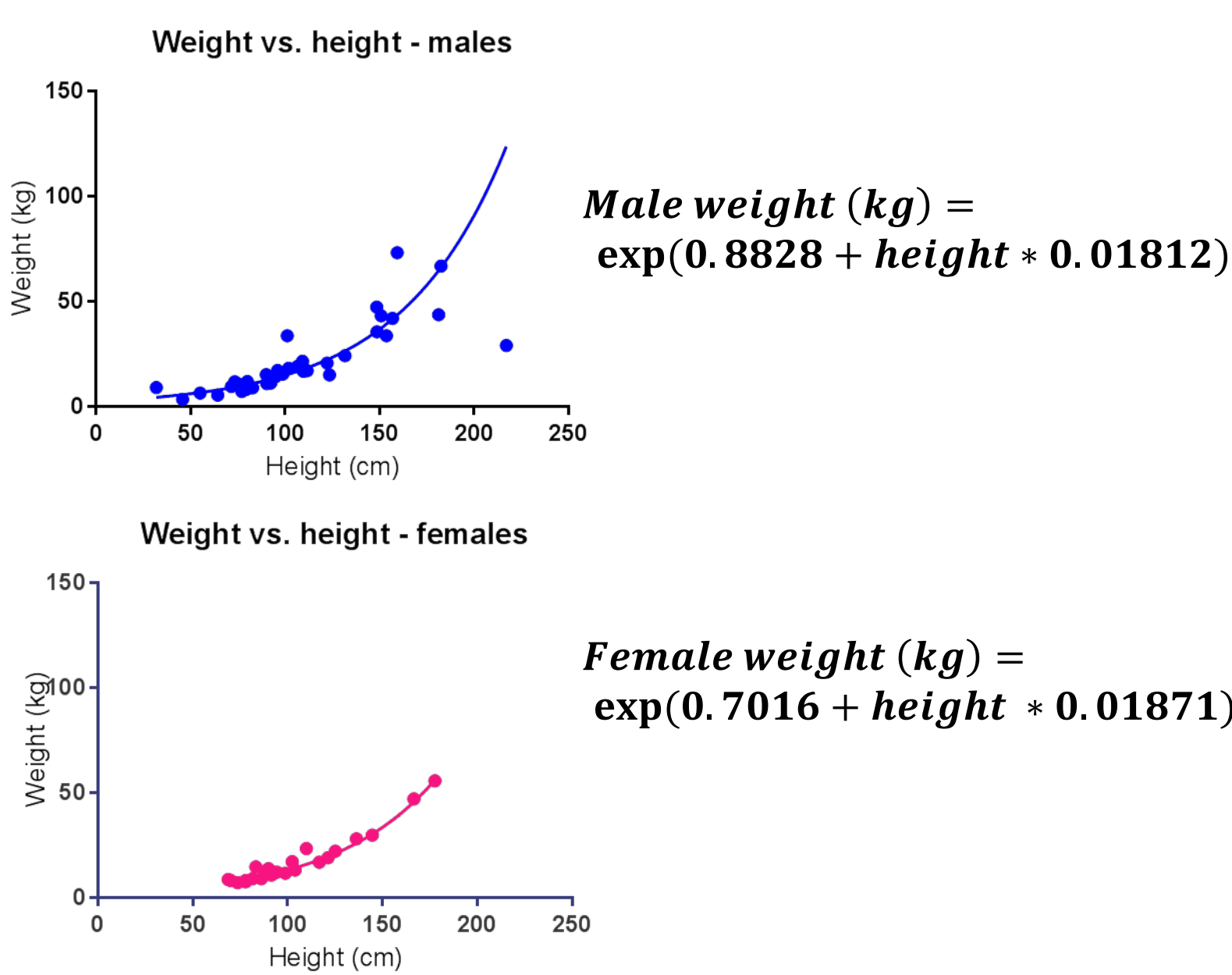


Fig 5. Simulated weight vs. height for 2,000 virtual paediatric healthy and cancer patients

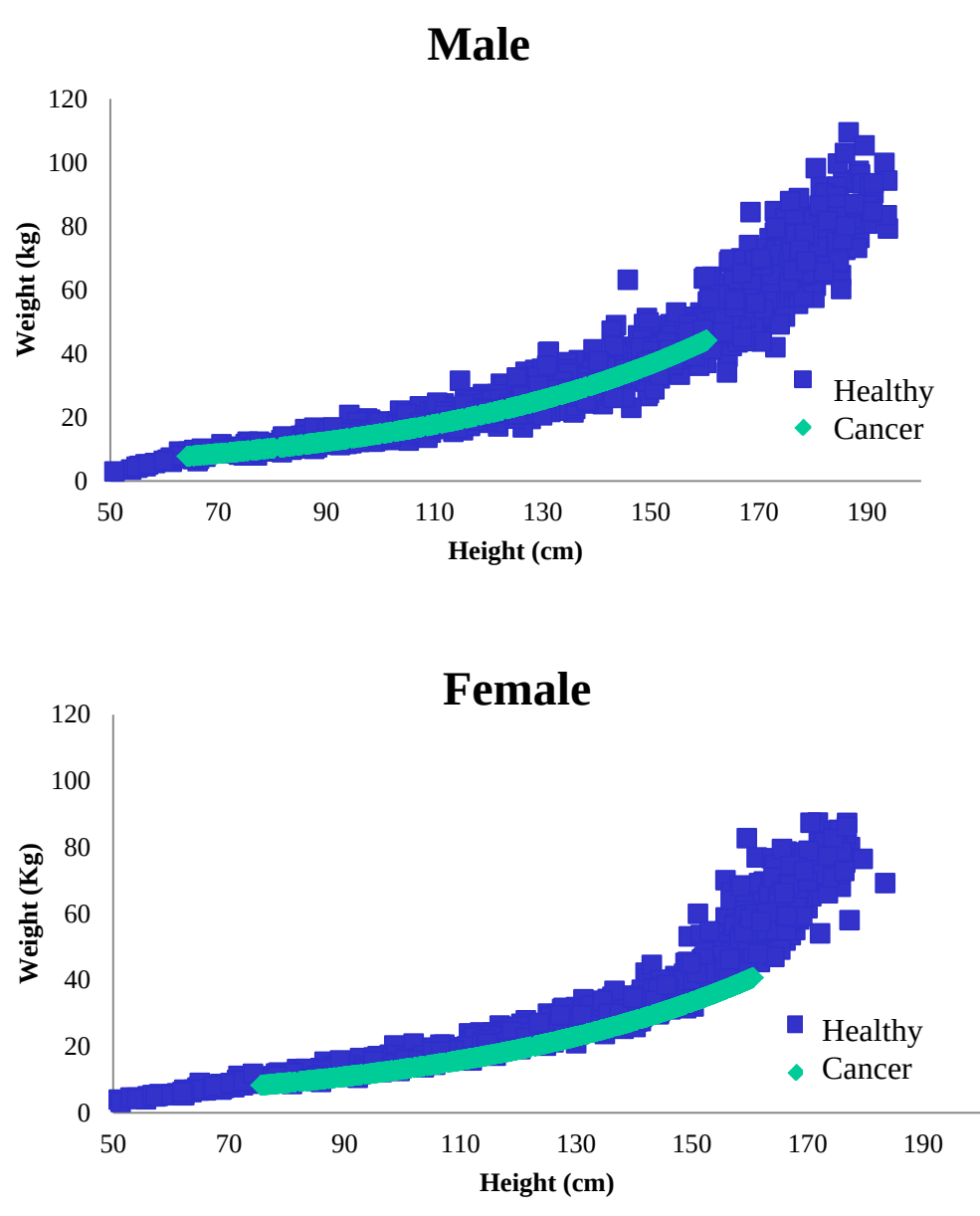
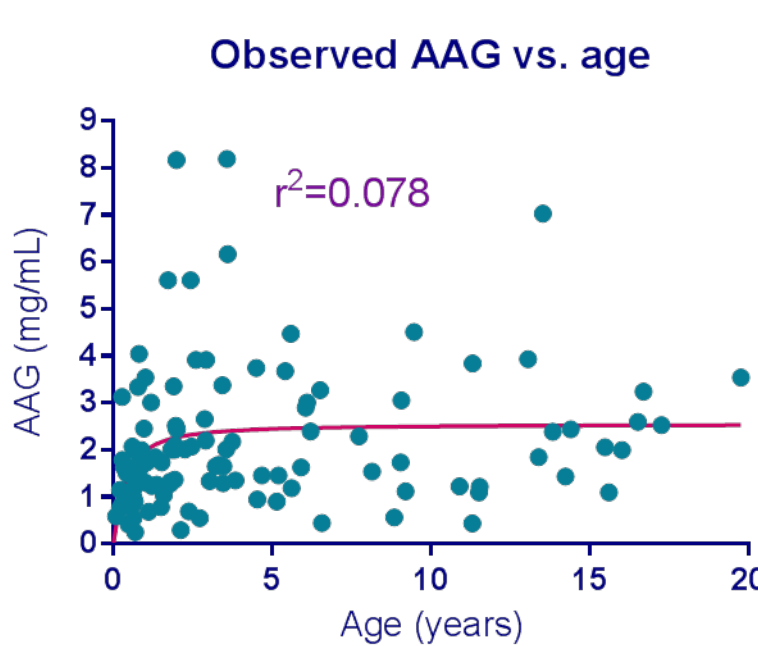


Fig 6. AAG concentrations with age – paediatric cancer patients



Mean AAG concentration, males: 2.24 mg/mL (64%CV)
Mean AAG concentration, females: 2.35 mg/mL (67%CV)
(Normal range: 0.4 – 1.1 mg/mL)

Fig 8. AAG concentration by cancer type

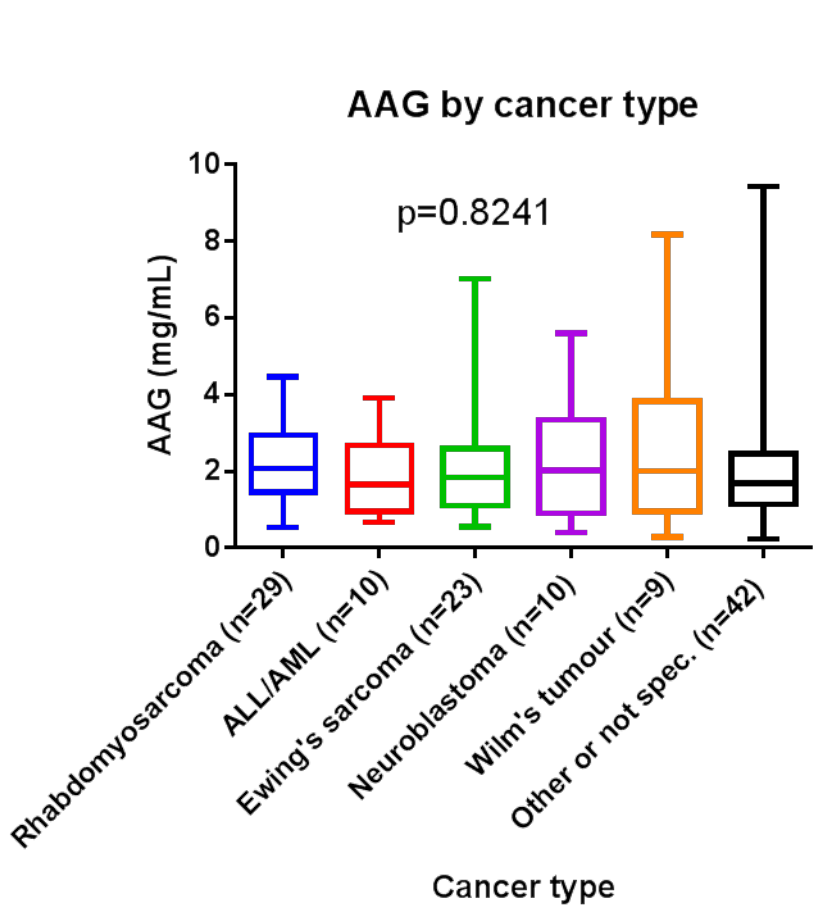
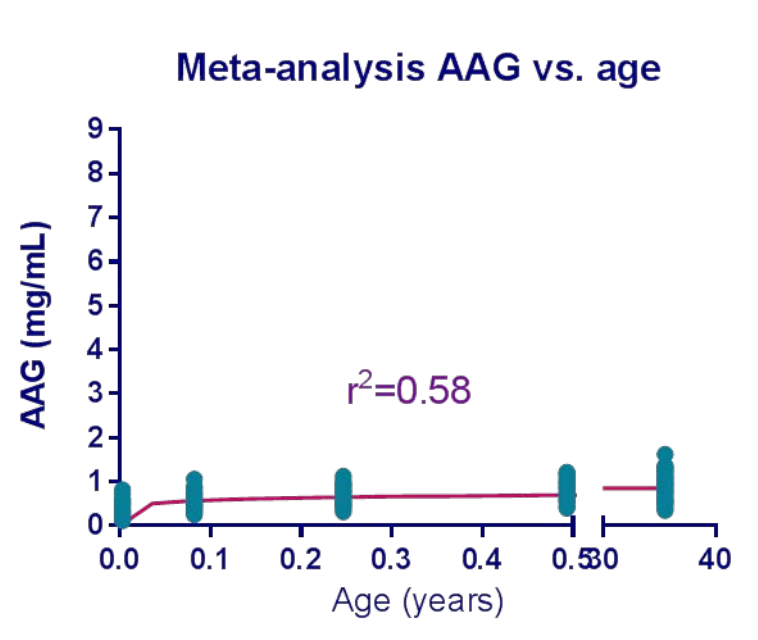
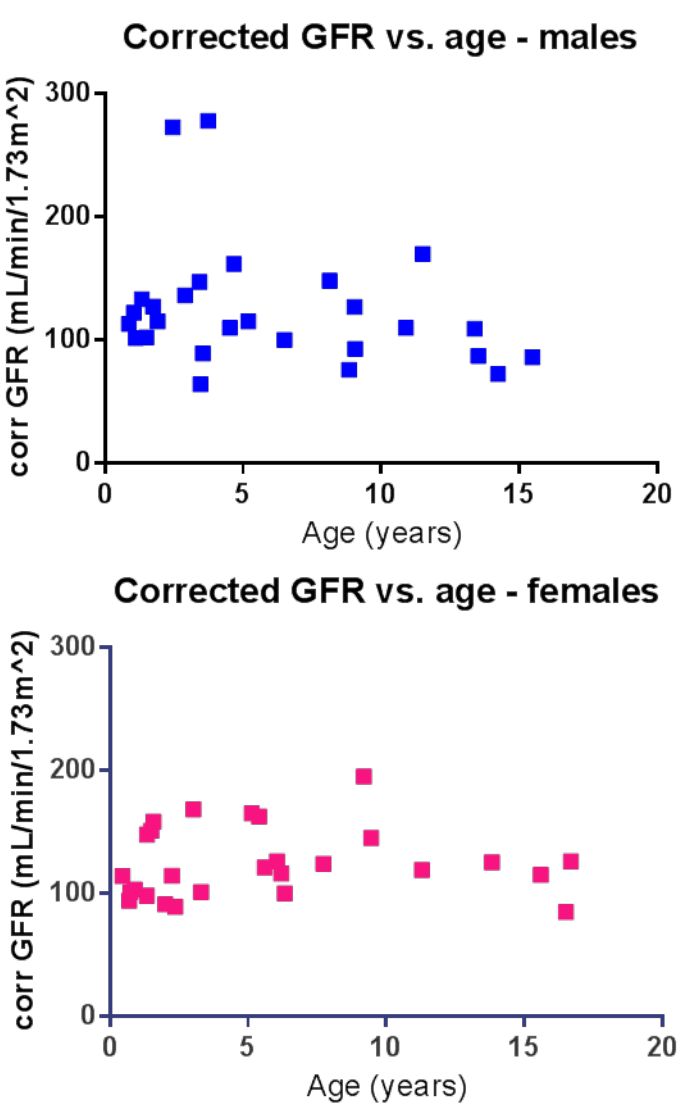


Fig 7. AAG concentrations with age – healthy subjects²



■ Plasma AAG concentrations in the paediatric cancer patients were significantly higher than the normal range and no significant correlation with age was seen as exists in healthy subjects (Figs 6 and 7).

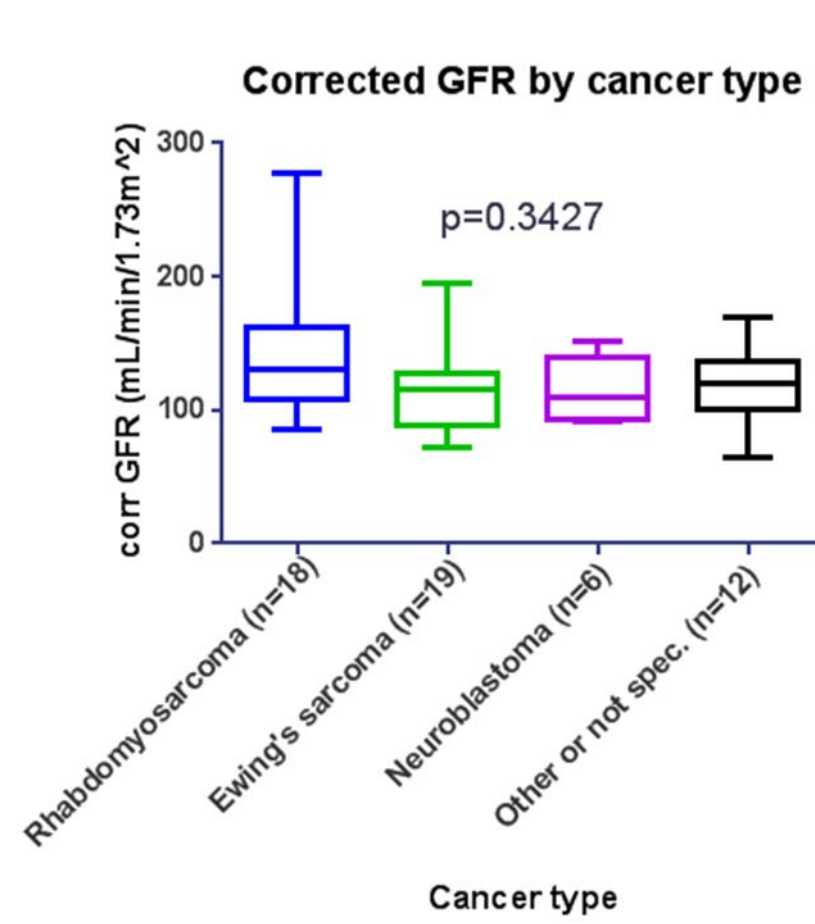
Fig 9. Corrected GFR vs. age in paediatric cancer patients



■ No correlation was observed between corrected GFR and age (Fig 9).

■ There were no significant differences in AAG concentration or GFR by type of cancer (Figs 8 and 10).

Fig 10. Corrected GFR by cancer type



Conclusions/Future directions

- These preliminary data show that:
 - Simulated individual heights and weights based on our population functions do not appear to deviate significantly from those generated by default for the healthy paediatric population within Simcyp
 - Plasma AAG values are significantly higher in paediatric cancer patients as compared with healthy children and the usual ontogeny function does not apply to the cancer population
 - AAG concentrations and GFR do not appear to differ significantly by cancer type
- Future work will include:
 - Continued gathering of height, weight, AAG, and GFR data from paediatric cancer patients with subsequent nonlinear regression analysis
 - Analysis of haematocrit and albumin values with age from paediatric cancer patients
 - Continued assessment of the effects of cancer type on patient covariates
 - Analysis of the effect of drug treatment/stage of treatment/disease stage on patient covariates
 - Creation of a paediatric cancer population file within Simcyp and validation of PBPK models of actinomycin D and 13-cis-retinoic acid in this population

References

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2. Johnson TN, Rostami-Hodjegan A, Tucker GT. Prediction of the clearance of eleven drugs and associated variability in neonates, infants and children. *Clin Pharmacokinet* 2006; 45(9):931-956.
3. Cheeti S, Budha NR, Rajan S et al. A physiologically based pharmacokinetic (PBPK) approach to evaluate pharmacokinetics in patients with cancer. *Biopharm Drug Dispos* 2013; 34:141-154.