JEFF WOODHEAD, SIMULATIONSPLUS

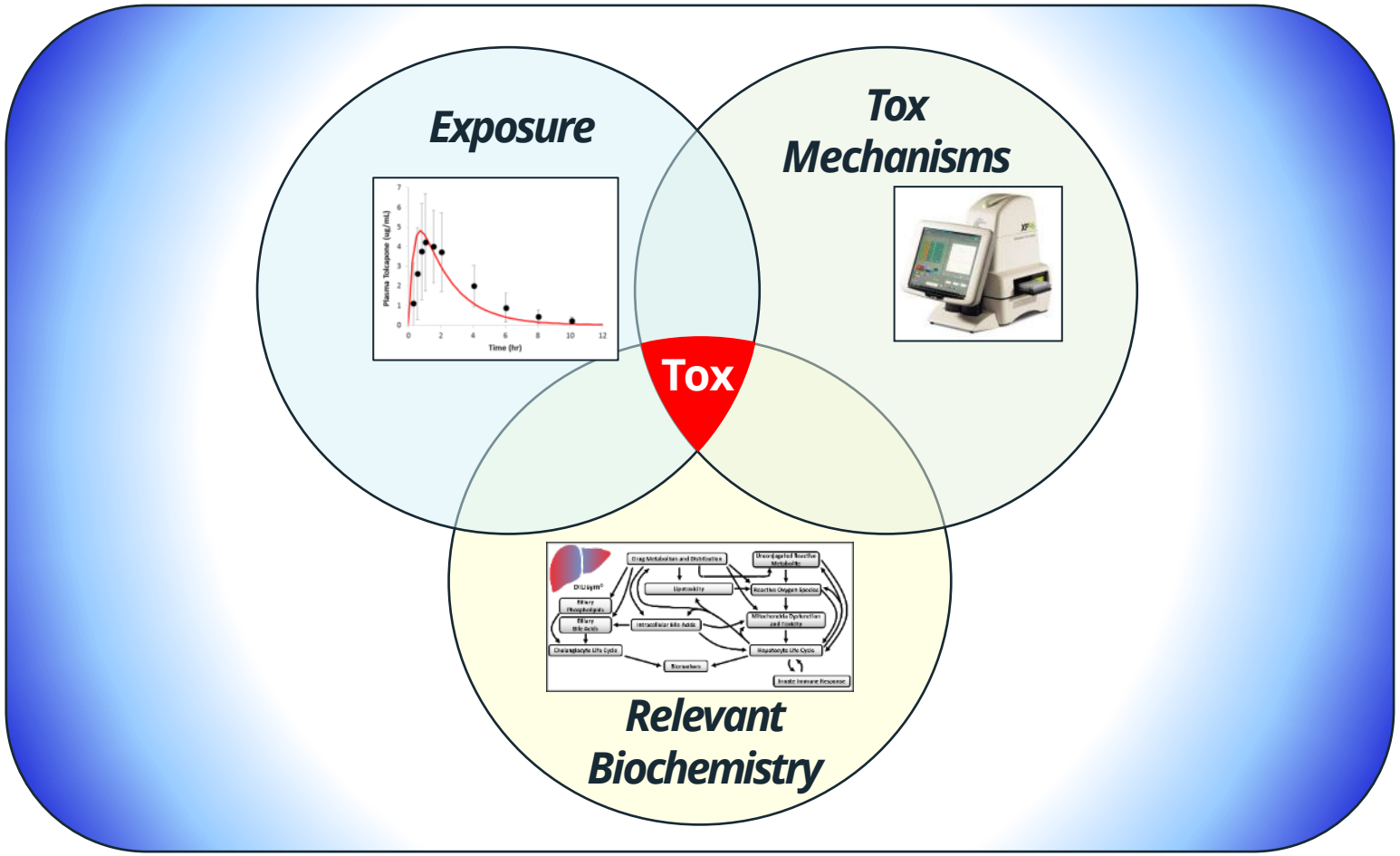
Construction of a Simulated Population of Post-Menopausal Women for the Prediction of Drug-Induced Liver Injury (DILI)

ASCPT 2024 ANNUAL MEETING

POST-MENOPAUSAL WOMEN CONSTITUTE A KEY PORTION OF MOST THERAPEUTIC POPULATIONS

- Post-menopausal women are about one-eighth of the total population worldwide (according to the WHO)
  - Likely represent a higher proportion of individuals on chronic medication
- Normal healthy volunteer (NHV) population skews young and male
  - 77% male, 15% over 50 according to Kalbaugh 2021
- Pharmacokinetics and pharmacodynamics/toxicodynamics can vary due to sex and age
- Models constructed largely on NHV data will miss some of the variability introduced by inclusion of this population in Phase 2/3 clinical trials and broader population
  - Some drugs are targeted specifically at older female patients

QST PREDICTS TOX VIA THE INTERSECTION BETWEEN EXPOSURE, MECHANISMS, AND INTER-PATIENT VARIABILITY



POSTMENOPAUSAL WOMEN (PMW) SIMPOPS CONSTRUCTED USING LITERATURE DATA ON COMMON DILI MECHANISMS

- Data differentiating postmenopausal women from other healthy individuals are available for two of the three main toxicity mechanisms in DILIsym, a QST model of drug-induced liver injury (DILI)
  - Bile acid transport
  - Oxidative stress
- Data are not available for mitochondrial dysfunction mechanism, but qualitative expectations exist
- Basic demographic data (body mass, BMI) are well characterized
  - Healthy weight and obese women are included in SimPops

Category	SimPops Data Availability
Bile acid transport	Some data available
Oxidative stress	All necessary data available
Mitochondrial dysfunction	Qualitative data only
Demographic data	All necessary data available

BLENDED PMW SIMPOPS HAS APPROPRIATE BMI DISTRIBUTION

- BMI distribution of PMW driven by literature for healthy and obese PMW

TABLE 1
Output for cross-sectional studies

Fat mass measure	Studies, n (samples)	Total sample size, n		Mean age, y (standard deviation)[a]			Mean fat mass, •••• (standard deviation)[a]		Unstandardized estimate, •••• (95% confidence interval)[b]	*P* value
		Premenopausal	Postmenopausal	Premenopausal	Postmenopausal	Age difference	Premenopausal	Postmenopausal		
Body mass index	171 (181)	453,036	523,796	41.96 (3.69)	59.42 (3.06)	14.82 (5.36)	24.75 (1.60)	26.64 (1.25)	1.14 (0.95–1.32)	<.0001
Bodyweight	109 (122)	113,603	204,845	43.36 (4.71)	59.55 (3.27)	15.00 (5.37)	64.82 (7.91)	66.12 (9.17)	1.00 (0.44–1.57)	.0005
Waist circumference	70 (72)	214,712	326,639	42.28 (3.65)	59.07 (1.91)	16.23 (4.24)	78.58 (4.24)	83.61 (3.19)	4.63 (3.90–5.35)	<.0001
Waist-to-hip ratio	47 (50)	199,140	309,797	42.39 (3.44)	59.09 (1.42)	16.17 (3.20)	0.78 (0.03)	0.81 (0.03)	0.04 (0.03–0.05)	<.0001
Body fat percentage	46 (52)	58,605	113,226	43.81 (4.67)	59.55 (3.81)	14.83 (6.56)	32.44 (3.47)	35.69 (3.84)	2.88 (2.13–3.63)	<.0001
Hip circumference	25 (25)	185,885	297,189	42.48 (3.08)	59.15 (0.95)	16.22 (2.61)	100.30 (2.66)	102.73 (2.25)	2.01 (1.36–2.65)	<.0001
Subcutaneous abdominal fat	10 (10)	696	833	41.01 (6.96)	57.48 (5.36)	15.00 (10.70)	194.05 (23.65)	221.21 (32.09)	28.73 (8.56–48.91)	.0053
Visceral fat	10 (10)	696	833	41.01 (6.96)	57.48 (5.36)	15.00 (10.70)	69.22 (15.75)	104.36 (13.92)	26.90 (13.12–40.68)	.0001

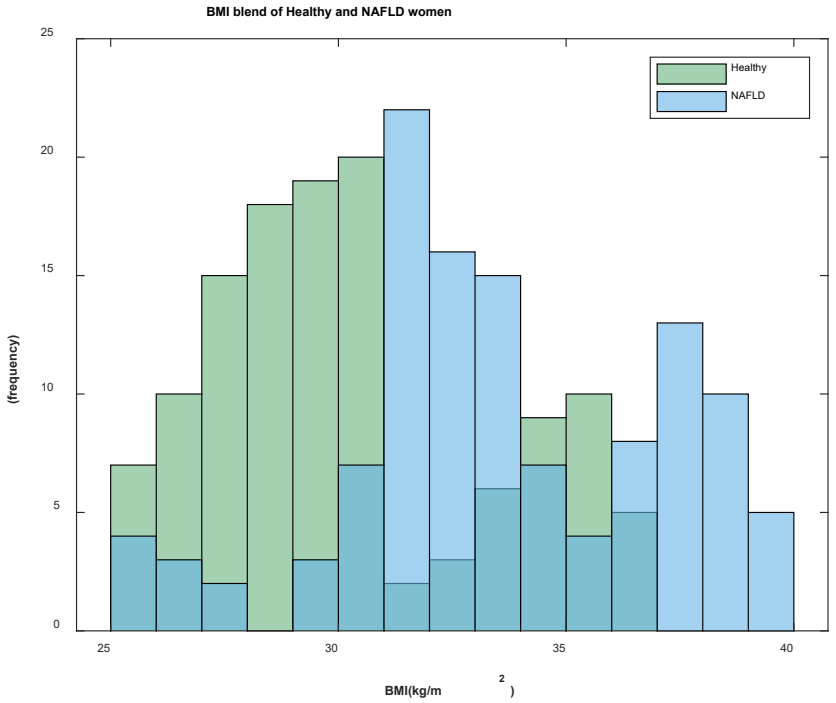
Ambikairajah 2019

Obese PMW

Table 1 Baseline physical and metabolic characteristics of the 132 participants

Variables	Mean ± SD	Range
Age (years)	57.2 ± 4.7	46.0–69.3
Body mass index (kg/m^2)	35.0 ± 3.7	30.0–48.5
Lean body mass (%)	49.1 ± 4.0	39.7–59.8
% Body fat	48.0 ± 4.0	37.6–57.9
Body adiposity index (%)	41.2 ± 4.9	32.0–61.3
Waist circumference (cm)	101 ± 8.2	85.5–117
Hip circumference (cm)	121.1 ± 9.4	105.5–166.5
Visceral fat (cm^2)	206 ± 51	104–346

Elisha 2012



Cohort composition

124 healthy + 120 NAFLD = 244 total

OXIDATIVE STRESS AND ANTIOXIDANT STATUS DIFFERENCES IN POST-MENOPAUSAL WOMEN

- Antioxidants are generally mildly reduced in post-menopausal women compared to pre-menopausal women

Table 1: Serum γ-glutamyltransferase, glutathione and malondialdehyde levels in the pre- and postmenopausal women.

Serum Level	Premenopausal group (n=17)	Postmenopausal group (n=16)	*p* value
GGT (U/L)	5.96±2.99	9.44±2.89	0.025
GSH (mmole/L)	0.62±0.17	0.47±0.11	0.008
MDA (µmole/L)	1.04±0.06	1.32±0.05	0.035

Abdul-Rasheed 2010

Table 2. Status of antioxidant enzymes in pre- and postmenopausal women

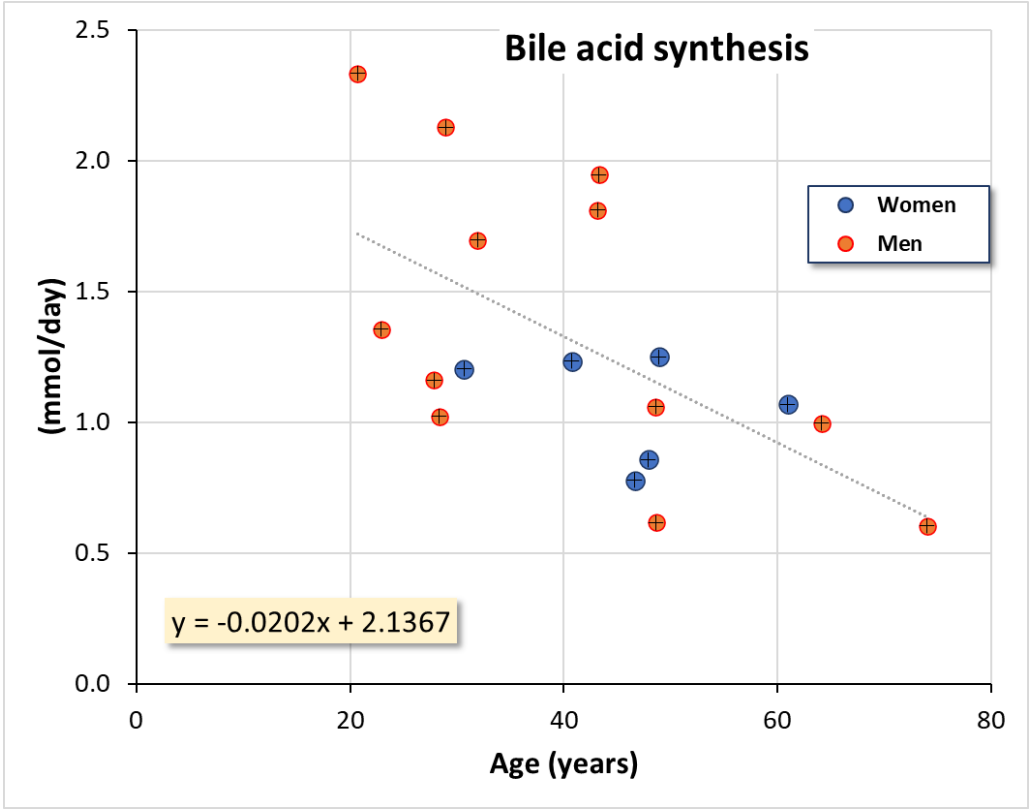
Parameters	Subject	
	Premenopausal (Control group)	Postmenopausal (Study group)
	N=50	N=50
SOD (IU/mg prot)	11.12 ± 2.89	7.15 ± 2.31**
CAT (IU/mg prot)	7.31 ± 1.16	5.12 ± 1.13**
GP_x (nmol/mg prot)	12.15 ± 1.23	8.89 ± 1.81**
Vitamin C (mg/dl)	2.51 ± 0.32	1.21 ± 0.08*
Vitamin E (mg/dl)	2.11 ± 0.91	1. 99 ± 0.34

*P<0.05 (significant) and **P<0.001 (highly significant).

Ansar 2015

BILE ACID SYNTHESIS REDUCES WITH AGE

- Synthesis of both primary bile acids (cholic and chenodeoxycholic acids) decreases with age; as the postmenopausal women population is older, this will need to be accounted for
- Bile acid transporter variability reconstructed in order to meet desired bile acid profile
  - Minimal differences in profile between post-menopausal and pre-menopausal women



Einarsson 1985

TOXICITY-RELATED SIMPOPS PARAMETERS ADJUSTED TO FIT PMW PHENOTYPE

- Literature-informed parameter adjustments were made to the healthy population in order to represent the post-menopausal population
  - Mitochondrial electron transport chain (ETC) flux based on qualitative data suggesting weaker mitochondrial health with age and BMI increase rather than quantitative data
- Biochemical variability was superimposed upon demographic variability in order to generate the post-menopausal women SimPops

SimPops Parameter	BMI < 35	BMI >= 35
Liver RNS/ROS clearance scale (Vmax)	Reduce by **10%**	Reduce by **10%**
Bulk bile acid (i.e. CA) synthesis rate*	Reduce by **40%***	Reduce by **40%***
CDCA baseline synthesis rate*	Reduce by **40%***	Reduce by **40%***
Basal value of mitochondrial ETC flux	Reduce by **12%**	Reduce by **20%**

PMW SimPops Simulated with APAP Shows Expected Liver Signals

- PMW SimPops were simulated with Acetaminophen (APAP) at a dose of 1g, 4 times daily, for 2 weeks
  - As expected, ALT levels mildly increase for many individuals (16.5% in PMW SimPops)

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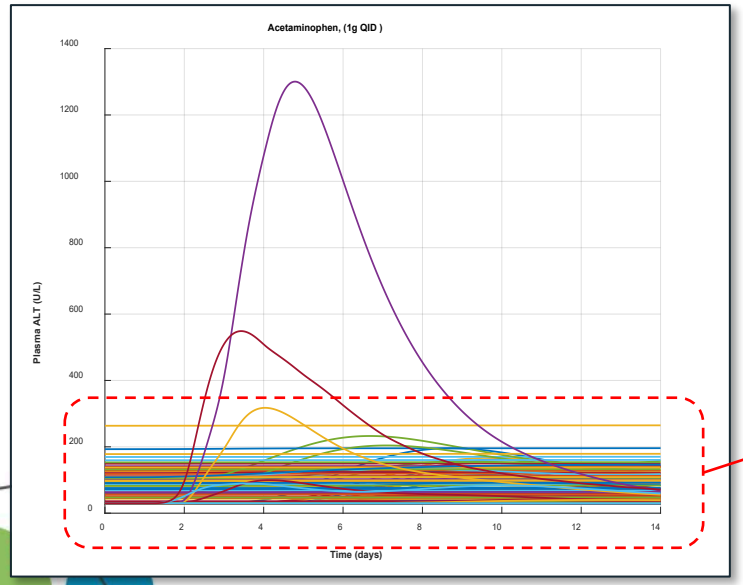

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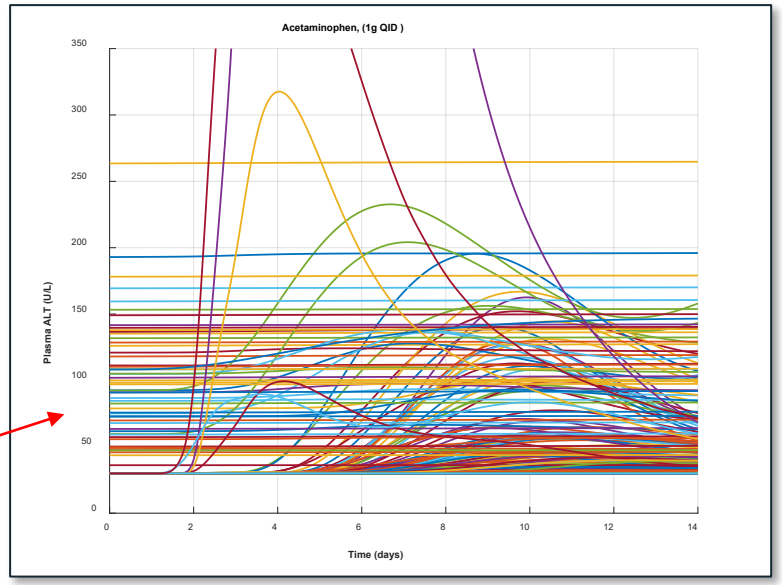

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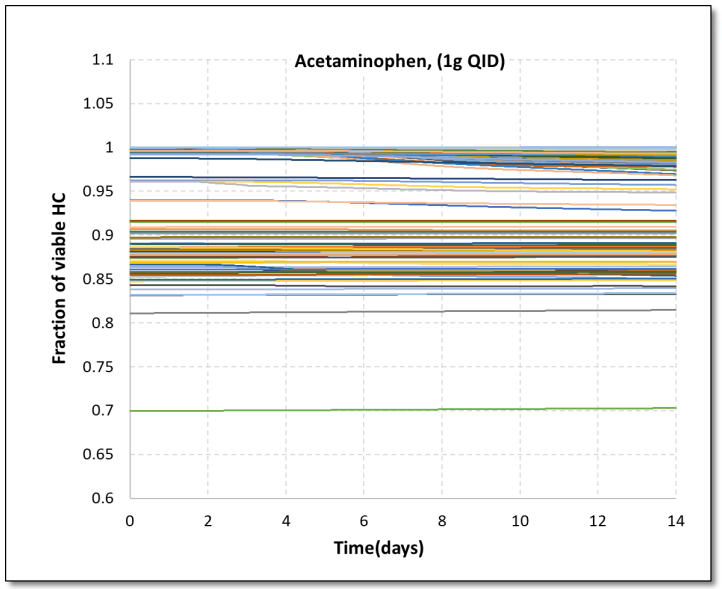

PMW SIMPOPS PREDICTS MILD ALT ELEVATIONS WITH TAMOXIFEN

- Clinical data suggests potential for mild ALT elevations in post-menopausal women taking tamoxifen
- Tamoxifen treatment simulated with PMW SimPops; mild ALT elevations predicted
- No signals predicted in NHV SimPops
- Demonstrates validity of PMW SimPops

Treatment	ALT ≥ 3x ULN
Placebo	(7.4%) 17/229
20 mg BID Tamoxifen for 5 weeks	(15.7%) 36

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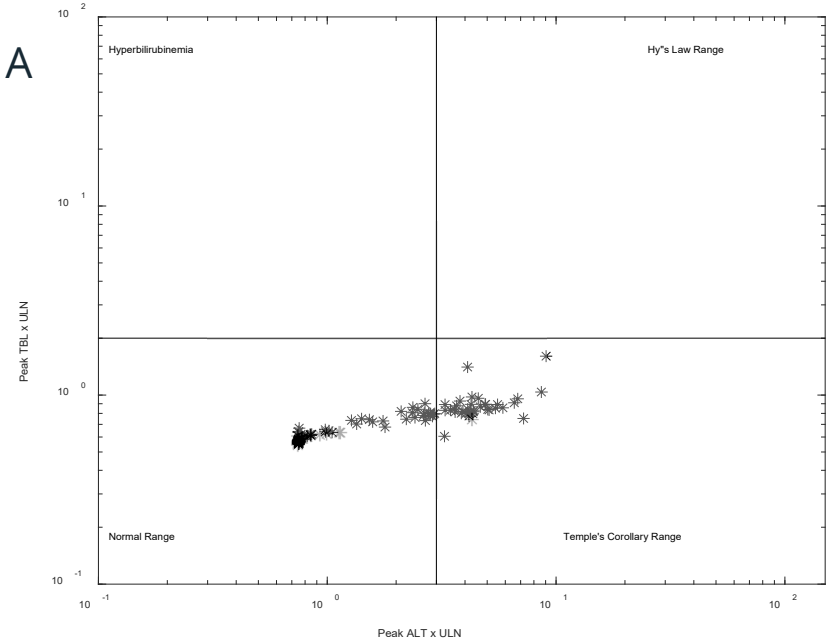

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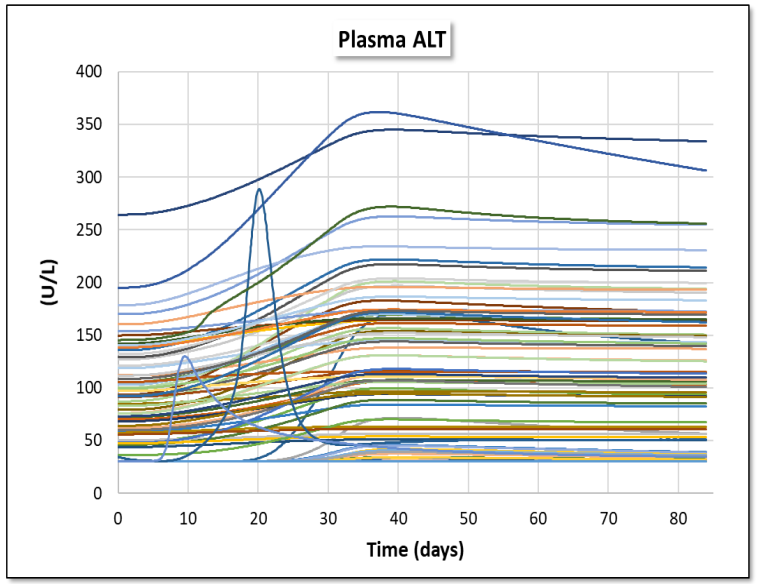

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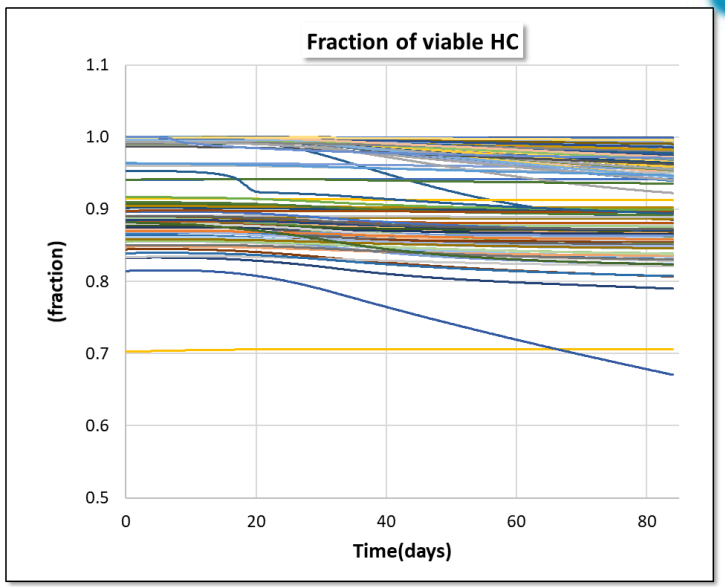

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CONCLUSIONS

- Post-menopausal women (PMW) SimPops accurately predicts differential risk of tamoxifen ALT elevations between normal healthy volunteer (NHV) and PMW populations
- Representation of individuals outside of the NHV population can aid in the prediction of drug-induced liver injury in broader populations
  - Liver injury liability can differ with age, sex, and underlying disease state
- Representation of non-NHV populations is limited by the amount of literature data available
  - More research on broader populations and on specific sub-populations can help inform construction of more predictive population-based models

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