A Model-Informed Framework for Prioritizing Drug Studies in Pregnancy

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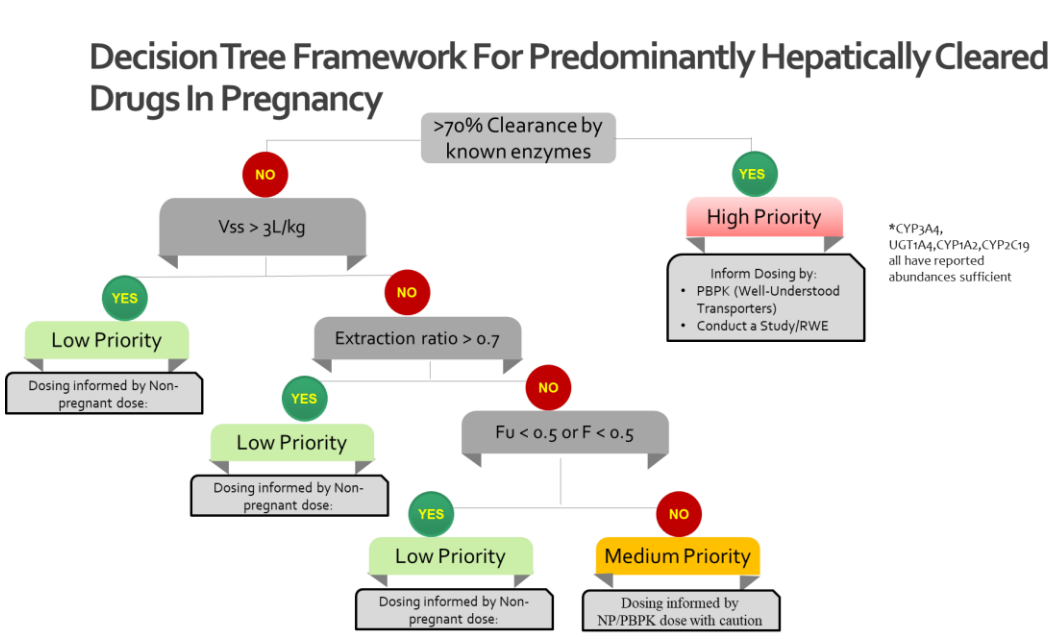
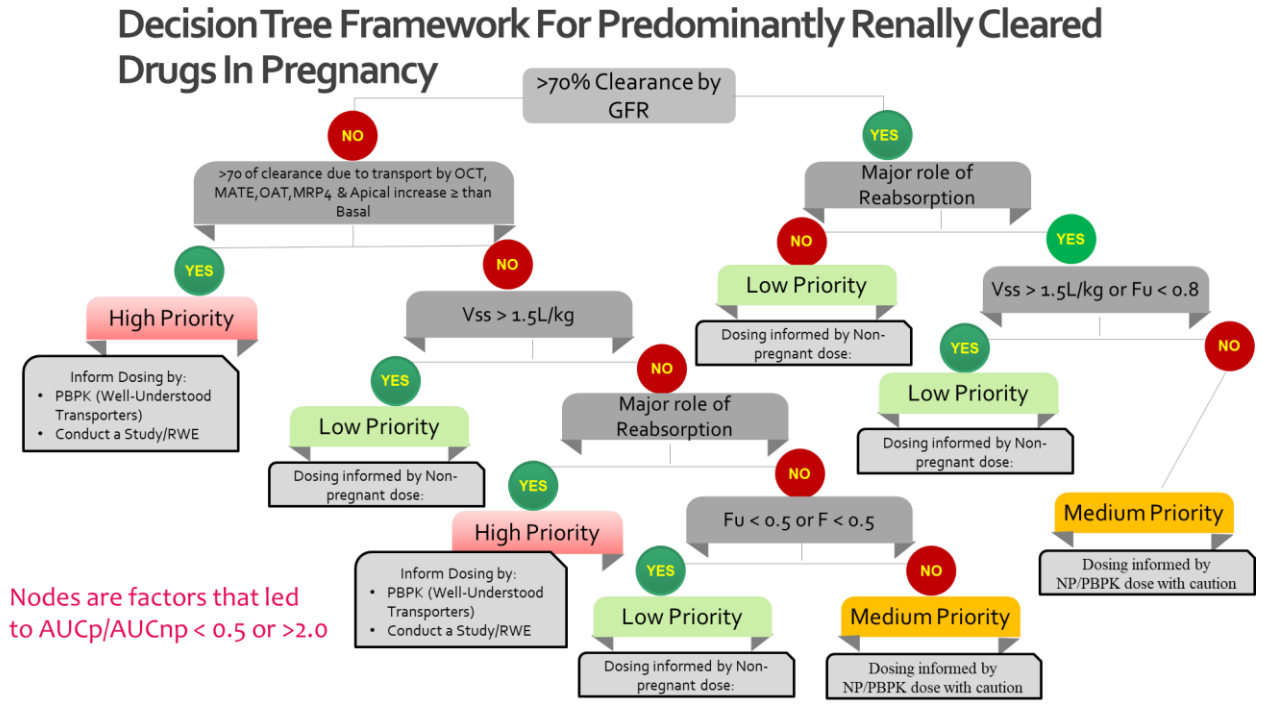
A Decision Tree Framework That Prioritizes The Drug To Be Studied In Pregnancy Is Proposed





Note: The drugs here refer to medications that are commonly prescribed to treat acute/chronic conditions during pregnancy and **does not refer** to drugs specifically used to treat pregnancy related conditions

Medication Use In Pregnancy Is Widespread & Lack Of Evidence Based Recommendations

Increasing medication use

- In the US, **9 out of 10** women take **medication** during **pregnancy**
- **80% of pregnant women take ≥ 1** medication during first trimester

Off-label use

- **90% of medications** approved do not have labeling for pregnant women

Lack of pregnancy drug trials (PDT)

- **Only 0.32%** of the active registered trials are PDT, in a 2014 global survey
- Among active PDTs, **only 4.4%** had **pharmacokinetic (PK)** evaluations
- **Only 1.3% of PK** studies included pregnant women

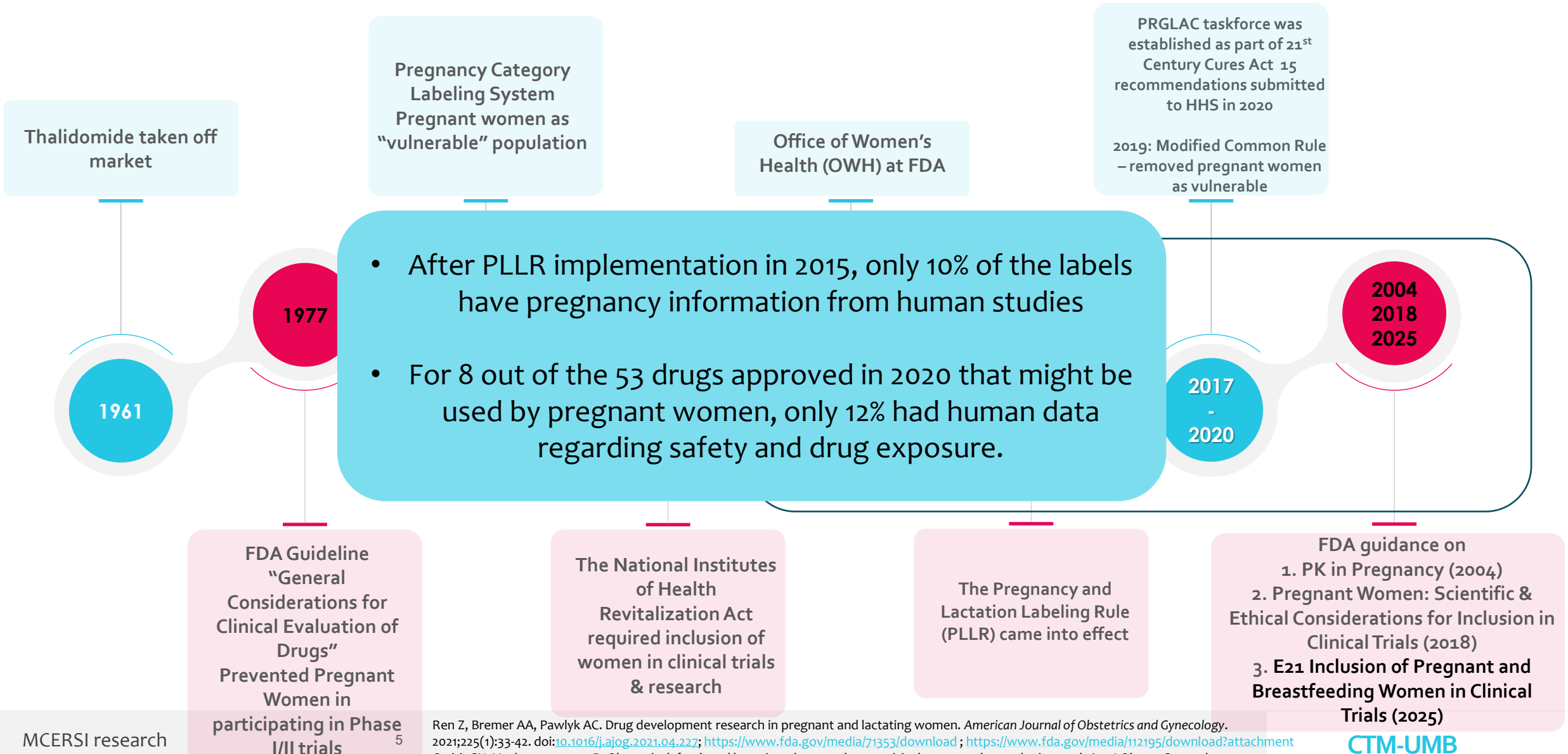
https://www.cdc.gov/pregnancy/meds/treatingfortwo/index.html

Mazer-Amirshahi M, Samiee-Zafarghandy S, Gray G, van den Anker JN. Trends in pregnancy labeling and data quality for US-approved pharmaceuticals. *American Journal of Obstetrics and Gynecology*. 2014;211(6):690.e1-690.e11.;Scaffidi J, Mol B, Keelan J. The pregnant women as a drug orphan: a global survey of registered clinical trials of pharmacological interventions in pregnancy. *BJOG: An International Journal of Obstetrics & Gynaecology*. 2017;124(1):132-140.;

Byrne JJ, Saucedo AM, Spong CY. Evaluation of Drug Labels Following the 2015 Pregnancy and Lactation Labeling Rule. *JAMA Network Open*. 2020;3(8):e2015094.

Ren Z, Bremer AA, Pawlyk AC. Drug development research in pregnant and lactating women. *American Journal of Obstetrics and Gynecology*. 2021;225(1):33-42. doi:10.1016/j.ajog.2021.04.227

Timeline Of FDA Actions Related To Inclusion Of Pregnant Women In Clinical Trials – Recent Initiatives Are Encouraging



Ren Z, Bremer AA, Pawlyk AC. Drug development research in pregnant and lactating women. *American Journal of Obstetrics and Gynecology*. 2021;225(1):33-42. doi:10.1016/j.ajog.2021.04.227; https://www.fda.gov/media/71353/download ; https://www.fda.gov/media/112195/download?attachment
Caritis SN, Venkataramanan R. Obstetrical, fetal, and lactation pharmacology-a crisis that can no longer be ignored. Am J Obstet Gynecol 2021;225:10–20.

Pregnancy Leads To Physiological Changes That May Affect Drug Exposure & Clinical Response

Cardiovascular Changes
30-50% increase in cardiac output and renal blood flow.

Body Composition
42% increase in plasma volume

Increased body water composition

Gastrointestinal Changes
30-50% delay in gastric emptying due to higher progesterone levels.

Placenta and Fetus
Acts as additional volume of distribution affecting drug accumulation.

Metabolic Changes
Altered metabolism

Plasma Proteins
Decreased albumin and α1-AGP concentrations

Renal Changes
50% increase in GFR by first trimester impacting renal clearance.

Physiological Changes During Pregnancy Can Require Changes From The Non-pregnant Dose

Indinavir

- Lower concentrations in 2nd and 3rd trimester
- **30% fell below minimum recommended AUC to manage viral load**

Lamotrigine

- Concentrations in second trimester reduced by >50%
- **Lead to a 75% increase in seizure frequency**

Sertraline

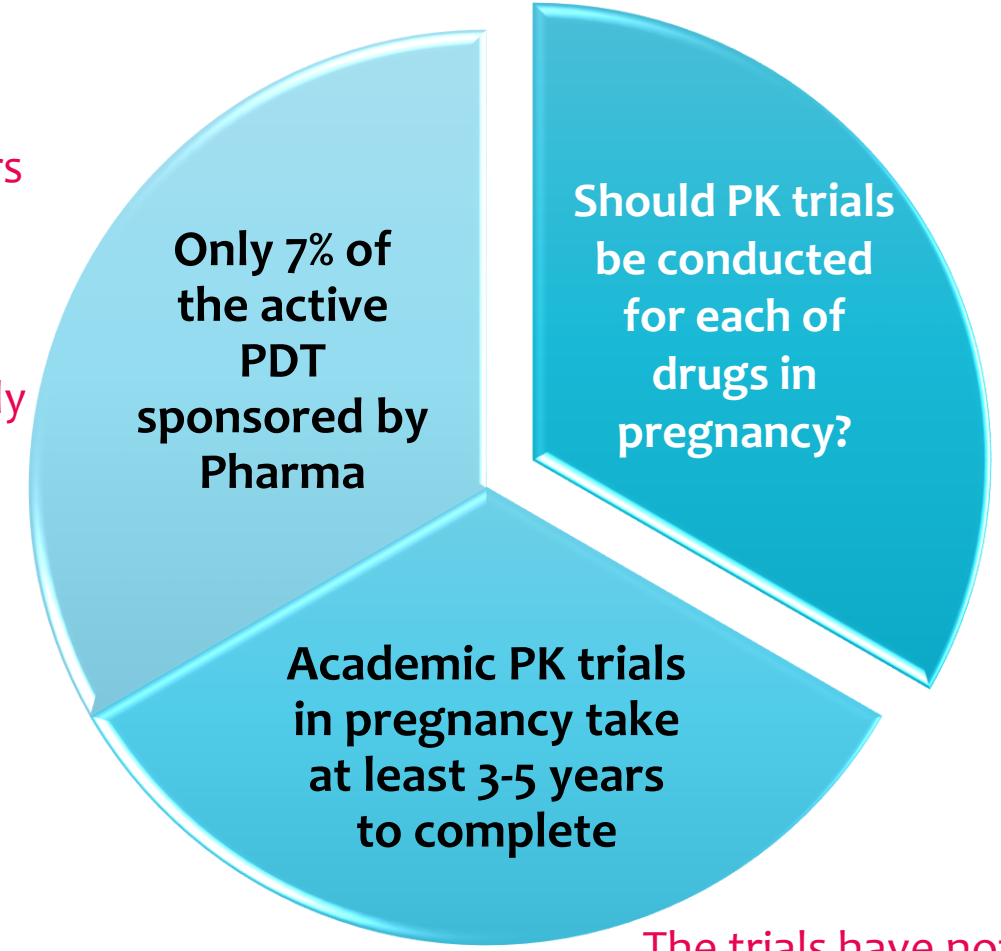
- Concentrations in second trimester significantly decreased
- **50% of subjects experienced increased recurrent depressive symptoms**

Lack of clear guidance or no information on dosing in pregnancy in drug labels

Petrenaite V, Sabers A, Hansen-Schwartz J. Individual changes in lamotrigine plasma concentrations during pregnancy. Epilepsy Research. 2005;65(3):185-188. doi:10.1016/j.eplepsyres.2005.06.0041.
Cressey TR, Best BM, Achalapong J, et al. Reduced indinavir exposure during pregnancy. British Journal of Clinical Pharmacology. 2013;76(3):475-483. doi:10.1111/bcp.120781.
Sit DK, Perel JM, Helsel JC, Wisner KL. Changes in antidepressant metabolism and dosing across pregnancy and early postpartum. J Clin Psychiatry. 2008;69(4):652-658. doi:10.4088/jcp.v69n0419

Strong Need To Address Current Lack Of Evidence Based Information For Medication Use In Pregnancy – But HOW?

- No incentive for sponsors to conduct trials in pregnancy
- No policy enforcing conduct of trials currently



Can we prioritize drugs to be studied in pregnancy?

The trials have not resulted in labeling changes for use in pregnancy

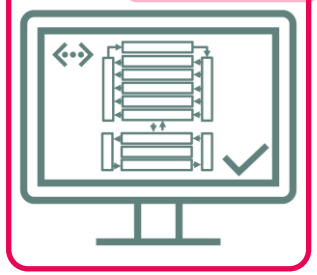
A Drug Prioritization Decision Tree Framework In Pregnancy Can Guide PK Trials

Aim 1

Identify prescription drugs commonly used in pregnant women

- Data collection from electronic health records
- Physician Expertise

Aim 2



Model-informed framework to set up the pregnancy physiological system
Develop and verify PBPK models (5 drugs)

- Literature search
- Model development and validation
  - Nonpregnant Women
  - Pregnant Women

Aim 3

Establish a drug prioritization framework

- Compare exposures across pregnant and non-pregnant women
- Develop prioritization framework

PBPK: Physiologically based pharmacokinetic

Aim 1

Electronic Medical Records (2016 – 2022) From University Of Maryland Medical System (UMMS) Informed The 50 Commonly Prescribed Drugs And Their Use Patterns In Pregnant Women

- **UMMS consists of 11 hospitals serving 25% of all hospital care in Maryland**

1,422,379 orders

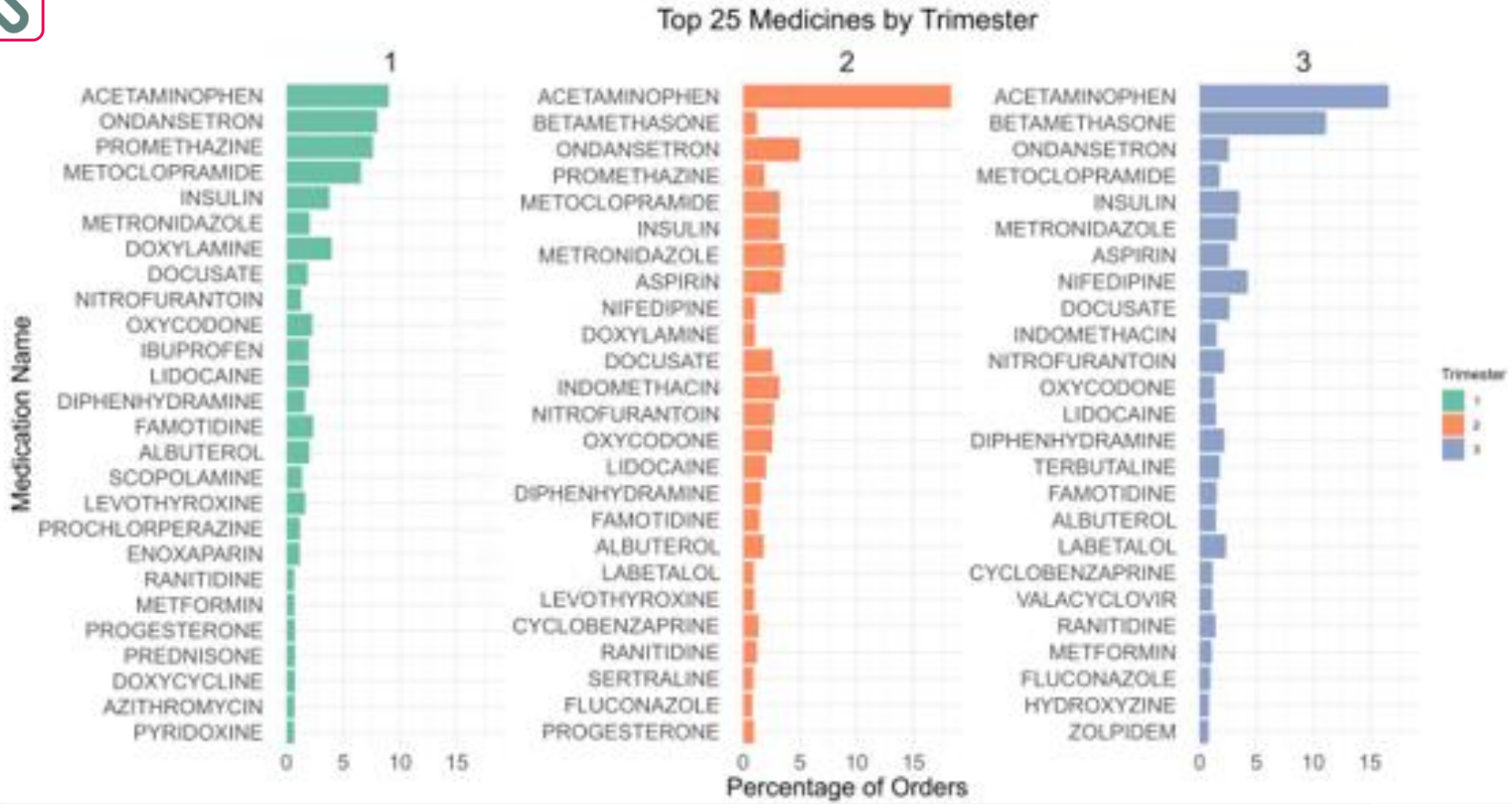
186,007 encounters

39,844 pregnant women

16 unique medication orders per woman

Aim 1

Antiemetics, Gastrointestinal Drugs More Predominant In First Trimester Vs Analgesics, Antihypertensives In The Third Trimester



Aim 1

Seven Key Medications with High Clinical Relevance in Pregnancy Demonstrated Frequent Within-patient Dose Modifications

Drug name	Therapeutic area	Women with dose change*	Women with dose change who had dose increase*	Average fold changes when increase*	Average fold change when decrease*
Nifedipine	Antihypertensive	40%	65%	2.2 x	4.2 x
Levothyroxine	Hormone	49%	71%	5.5 x	0.70 x
Levetiracetam	Anticonvulsant	41%	73%	3.0 x	0.53 x
Metformin	Anti-Diabetic	34%	76%	1.9 x	0.52 x
Methyldopa	Antihypertensive	43%	84%	2.0 x	0.50 x
Sertraline	Antidepressant	33%	67%	3.0 x	0.49 x
Prochlorperazine	Antiemetic	30%	38%	2.4 x	0.45 x

Aim 1

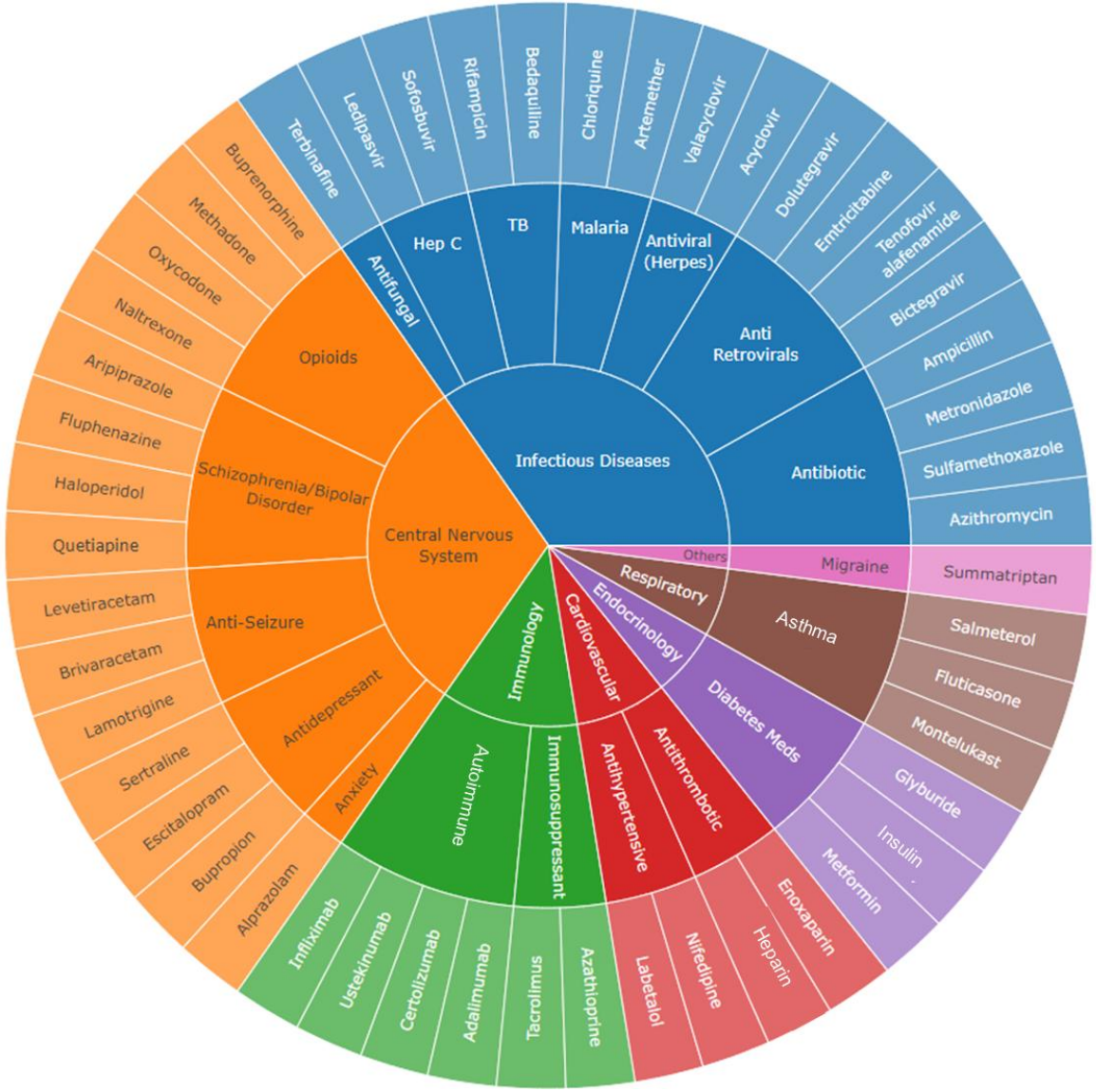
50 Drugs Encompassed Across 7 Therapeutic Areas with Varied Physico-Chemical Properties

Physicochemical Drug Properties

Molecular Weight	129 g/mol	149,000 g/mol
Log P	-3	8.8
pKa	2.6	13.9
% Protein Bound	1%	99%

Significant Transporters

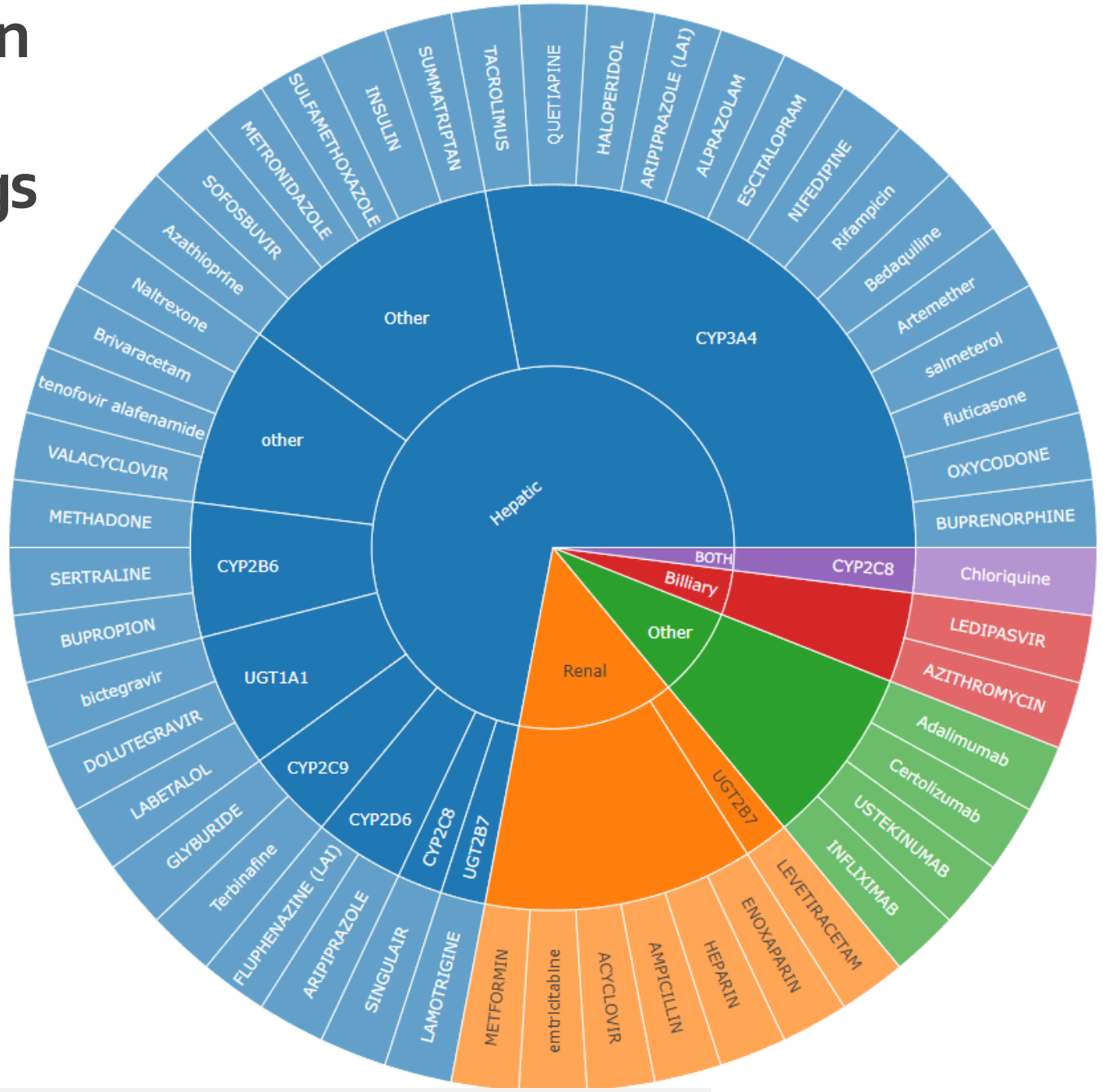
- 28% transported by P-gp
- 12% transported by OCT1
- 12% Transported by OCT2
- 6% Transported by MATE enzymes
- 8% Transported by other Proteins



Aim 1

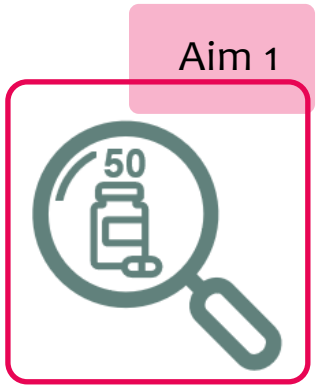
Hepatic & Renal Elimination Mechanisms were Predominant in the 50 drugs

- 4 Primary Elimination Mechanisms
- 9 primary enzymes
- Other hepatic pathways
  - Oxidation
  - Reduction
  - NAT enzymes
  - CES1
  - MAO
  - HGPRT
- >20 drugs with multiple significant elimination pathways



A Drug Prioritization Decision Tree Framework in Pregnancy Can Guide PK Trials

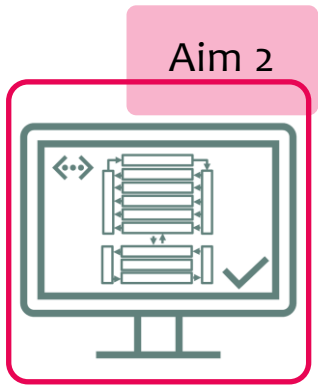
Aim 1



Identify prescription drugs commonly used in pregnant women

- 50 commonly prescribed drugs across 7 main therapeutic areas, wide range of physio-chemical properties and elimination mechanisms

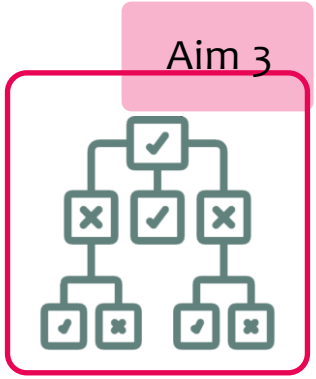
Aim 2



Model-informed framework to set up the pregnancy physiological system
Develop and verify PBPK models (5 drugs)

- Literature search
- Model development and validation
  - Nonpregnant Women
  - Pregnant Women

Aim 3

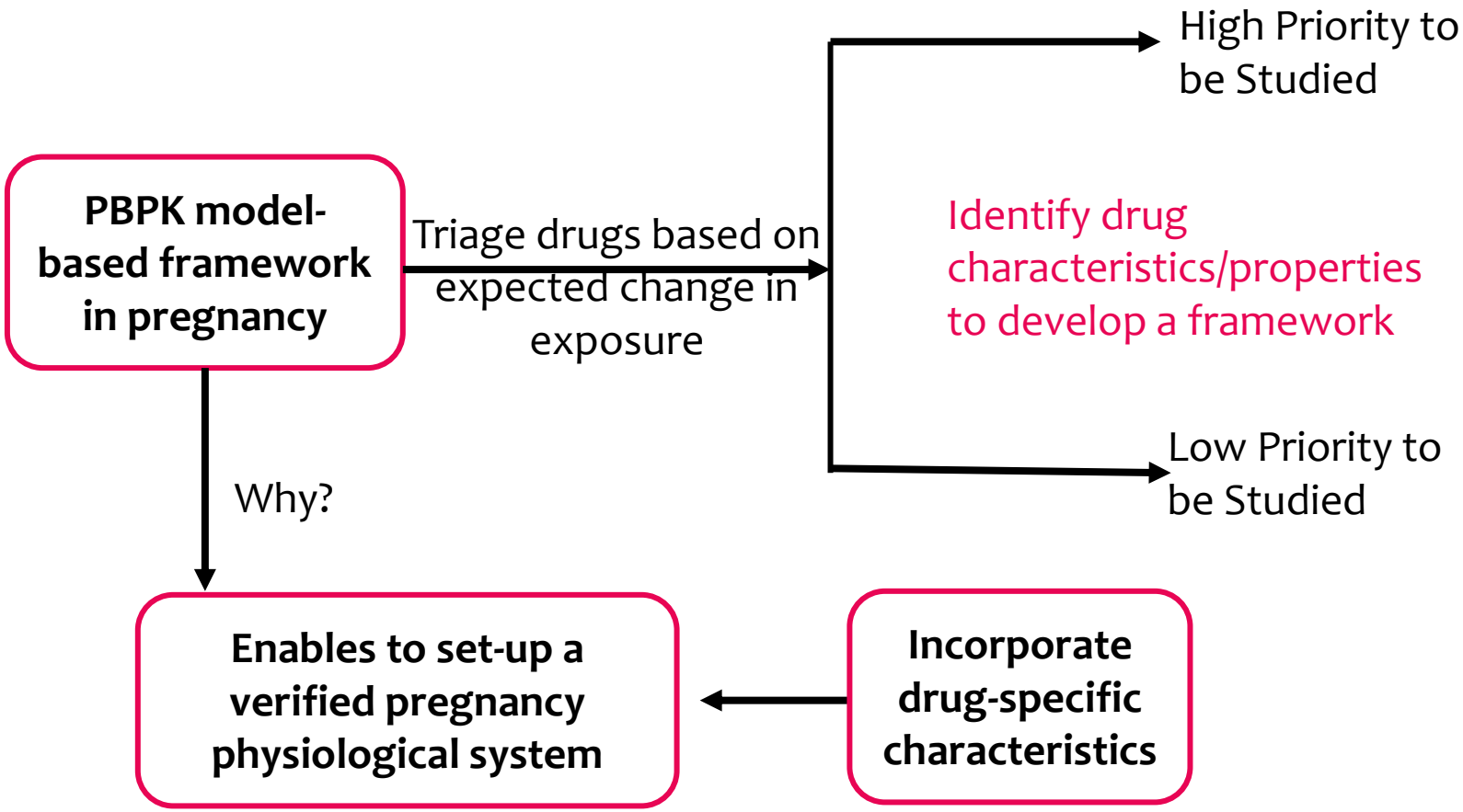


Establish a drug prioritization framework

- Compare exposures across pregnant and non-pregnant women
- Develop prioritization framework

Aim 2

Develop a Model-Informed Framework to Triage Drugs to be Studies in Pregnancy



We aimed to develop a reproducible generalizable modeling framework

Aim 2

5 Representative Drugs Based on their Frequent Prescription Patterns & Diverse Physicochemical and Therapeutic Aspects

Cefazolin
Renally cleared
Distinct transporter involved (OAT1 &3) & MRP4

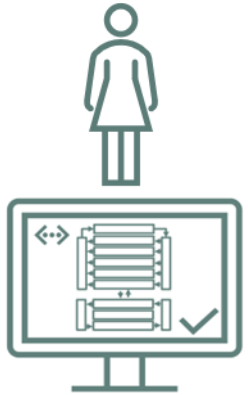
Glyburide
Hepatically cleared
CYP3A4+CYP2c19+CYP2C9

Rifampin
Hepatically cleared
AADAC

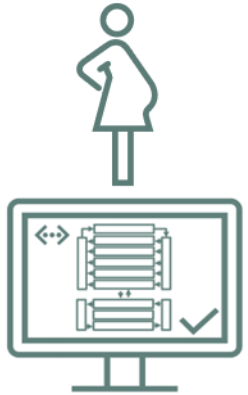
Metformin
Renally cleared
Distinct transporter involved (OCT2 , MATE)

5 representative drugs with varied physico-chemical features and mechanisms of elimination from the 50 drugs that had PK data for both pregnant and non-pregnant

Buprenorphine
Hepatically cleared
CYP3A4 + CYP2C8 + UGT1A1+UGT1A3+UGT2B7



Develop & Verify
Non-pregnant Model



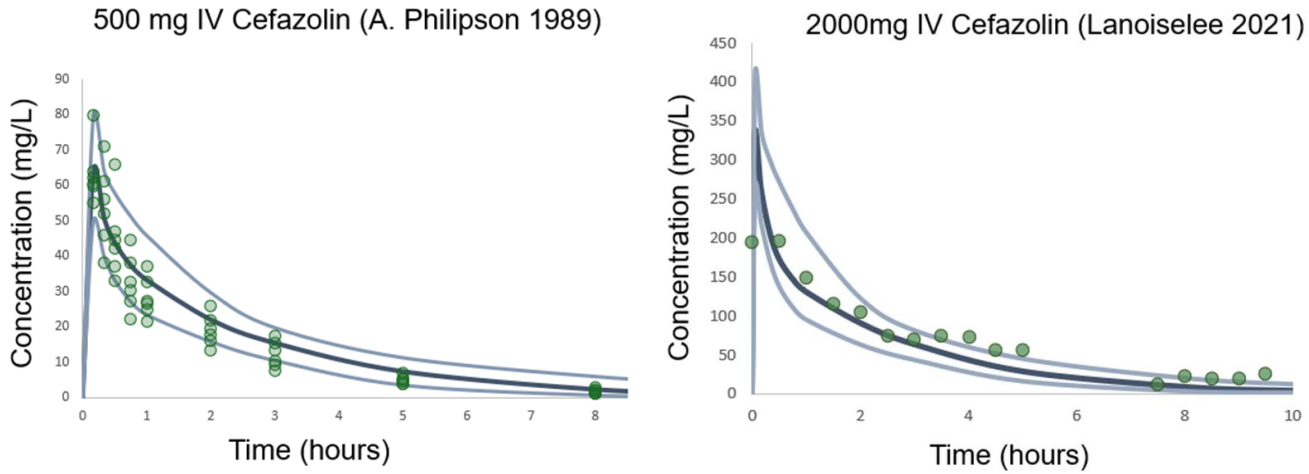
Develop & Verify
Pregnant Model

Pumas
Integrated Scientific
M&S & AI/ML Tool

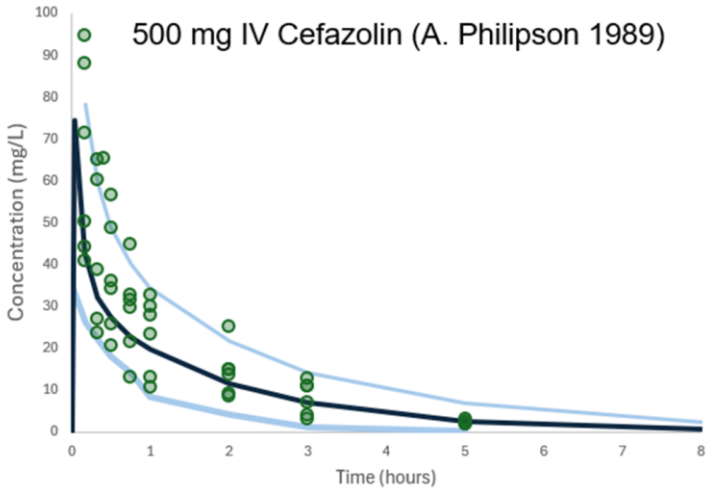
Aim 2

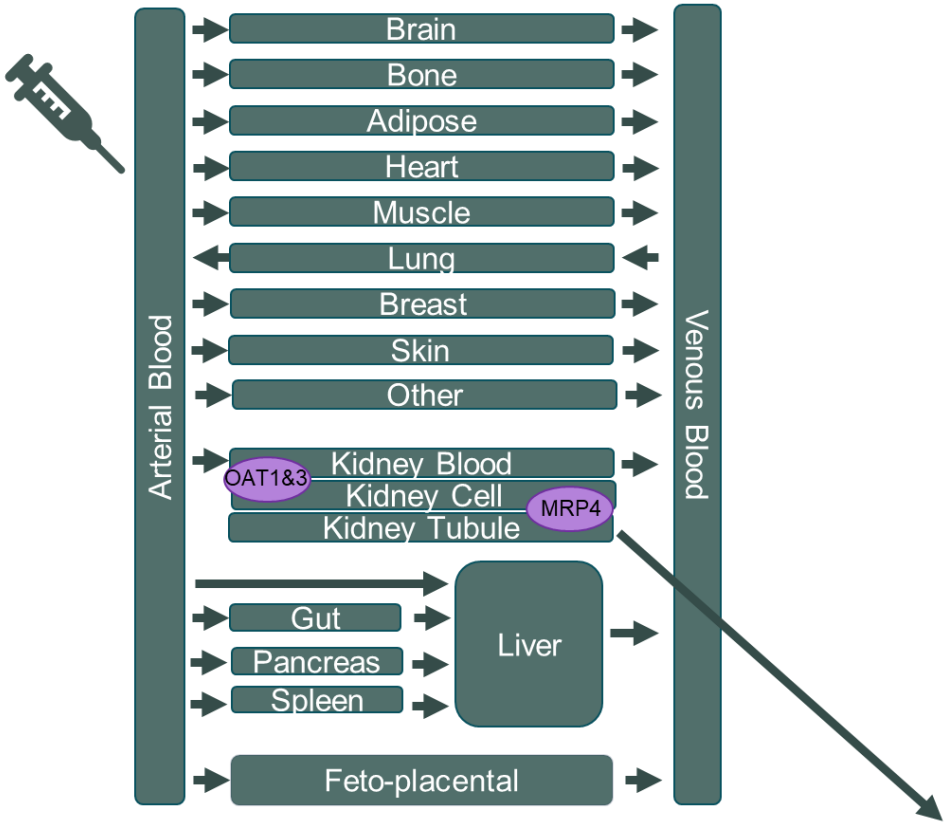
Exposures adequately captured by the PBPK model for all the 5 Drugs under Non-Pregnant & Pregnant Conditions

Cefazolin - Non-Pregnant



Cefazolin - Pregnant



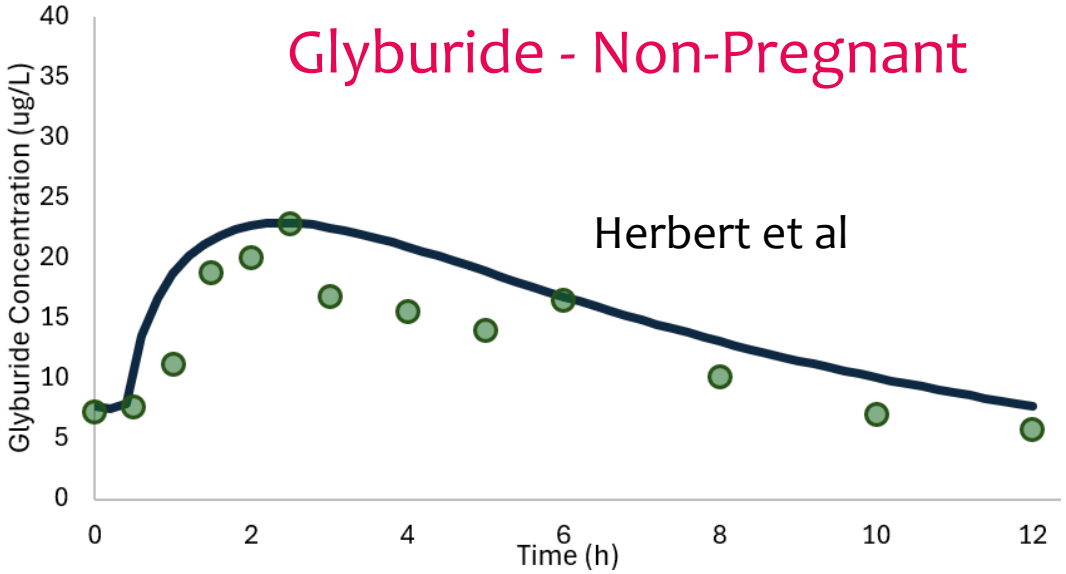


Renal OAT3 pregnancy fold Change

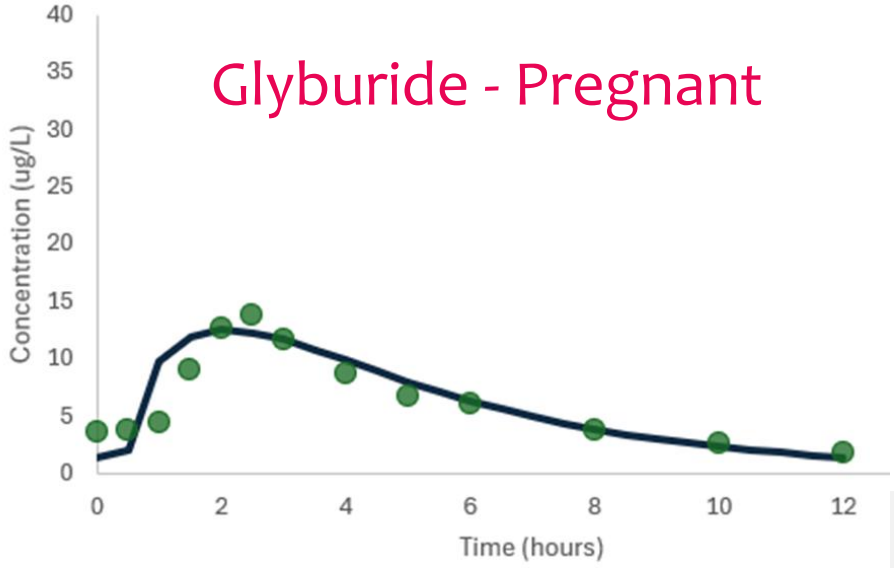
$$1 * (1 + 0.195 * GA - 0.0093 * GA^2 + 0.0001154 * GA^3$$

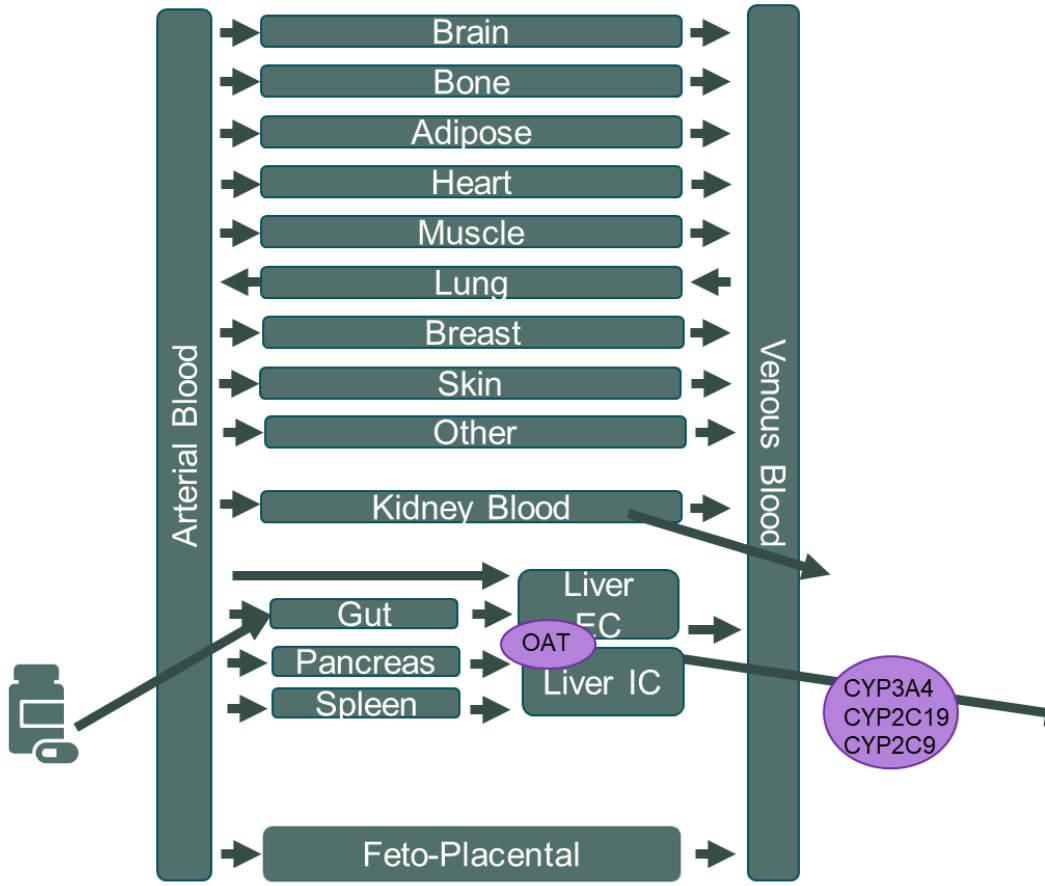
Exposures adequately captured by the PBPK model for all the 5 Drugs under Non-Pregnant & Pregnant Conditions

Glyburide - Non-Pregnant



Glyburide - Pregnant





$CL_{int,3A4\_pmol}$		T2: 2.0x NP	T3: 2.0x NP
$CL_{int,2C9\_pmol}$	T1: 1.4x NP	T2: 1.5x NP	T3: 1.6x NP
$CL_{int,2C194\_pmol}$		T2: 0.38x NP	T3: 0.32 NP

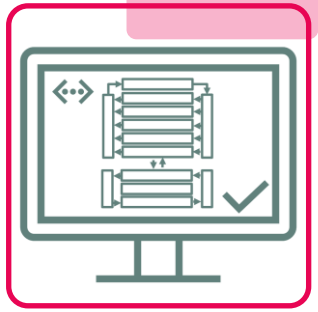
A Drug Prioritization Decision Tree Framework in Pregnancy Can Guide PK Trials

Aim 1

Identify prescription drugs commonly used in pregnant women

- 50 commonly prescribed drugs across 7 main therapeutic areas, wide range of physio-chemical properties and elimination mechanisms

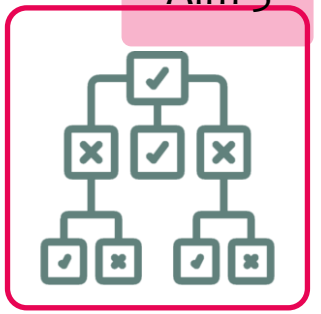
Aim 2



Model-informed framework to set up the pregnancy physiological system
Develop and verify PBPK models (5 drugs)

- A validated, reproducible pregnancy PBPK system was developed using the 5 representative drugs

Aim 3



Establish a drug prioritization framework

- Compare exposures across pregnant and non-pregnant women
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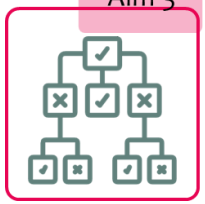
Aim 3



Drug Properties that May Impact Pregnant:Non-Pregnant Ratio

Expected Impact: High

- F_{up} : During pregnancy plasma protein levels decrease significantly.
- Degree and type of Intrinsic Hepatic Clearance: Enzymes like CYP3A4 or UGTs may be induced during pregnancy.
- Degree and type of Renal clearance: GFR is increased as is some transporter activity

Expected Impact: Medium

- logP : affects partitioning into increased fat stores
- Volume of Distribution

Expected impact: Low

- B:P : the drop in hematocrit can play a large role in highly RBC partitioned drugs
- pKa : May affect partitioning into newly forming tissues
- Molecular size: impacts placental transfer and tissue distribution

Aim 3

PBPK Model-based Simulations Performed To Establish The Decision Framework

Drug Properties

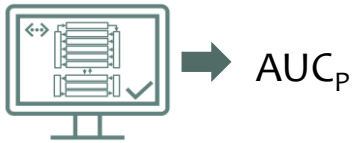
Physicochemical Drug Properties

Molecular Weight	129 g/mol	149,000 g/mol
Log P	-3	8.8
pKa	2.6	13.9
% Protein Bound	1%	>99%

Significant Transporters

- 28% transported by P-gp
- 12% transported by OCT1
- 12% Transported by OCT2
- 6% Transported by MATE enzymes
- 8% Transported by other Proteins

Simulations



AUC_P

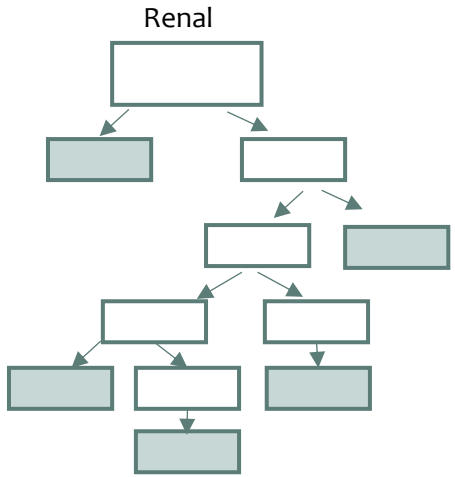
Validated P model

AUC_{NP}

Validated NP model

$$\frac{AUC_P}{AUC_{NP}} < 0.5 \;\&\; \frac{AUC_P}{AUC_{NP}} > 2.0$$

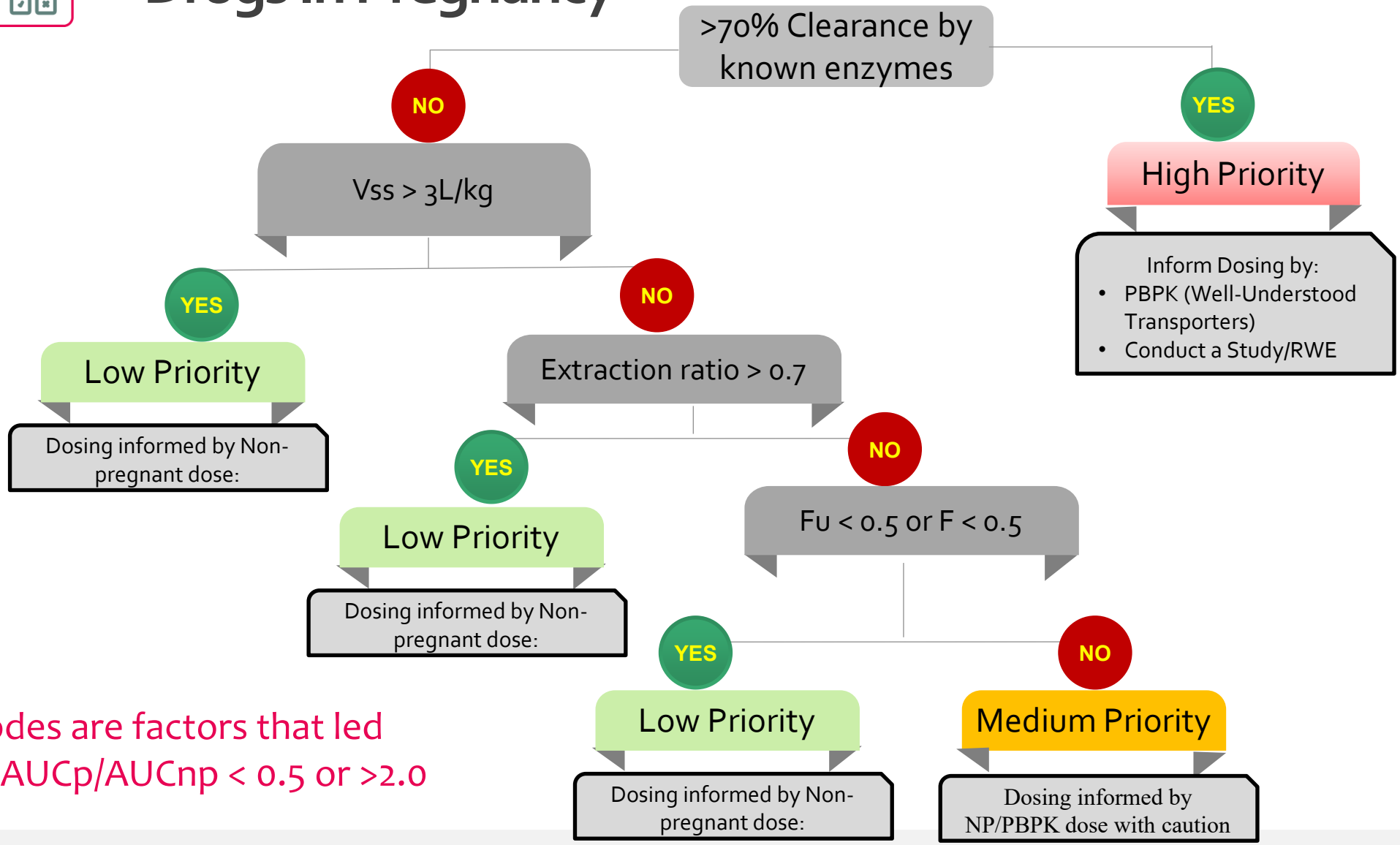
Develop Framework



Verify

Aim 3

Decision Tree Framework For Predominantly Hepatically Cleared Drugs In Pregnancy

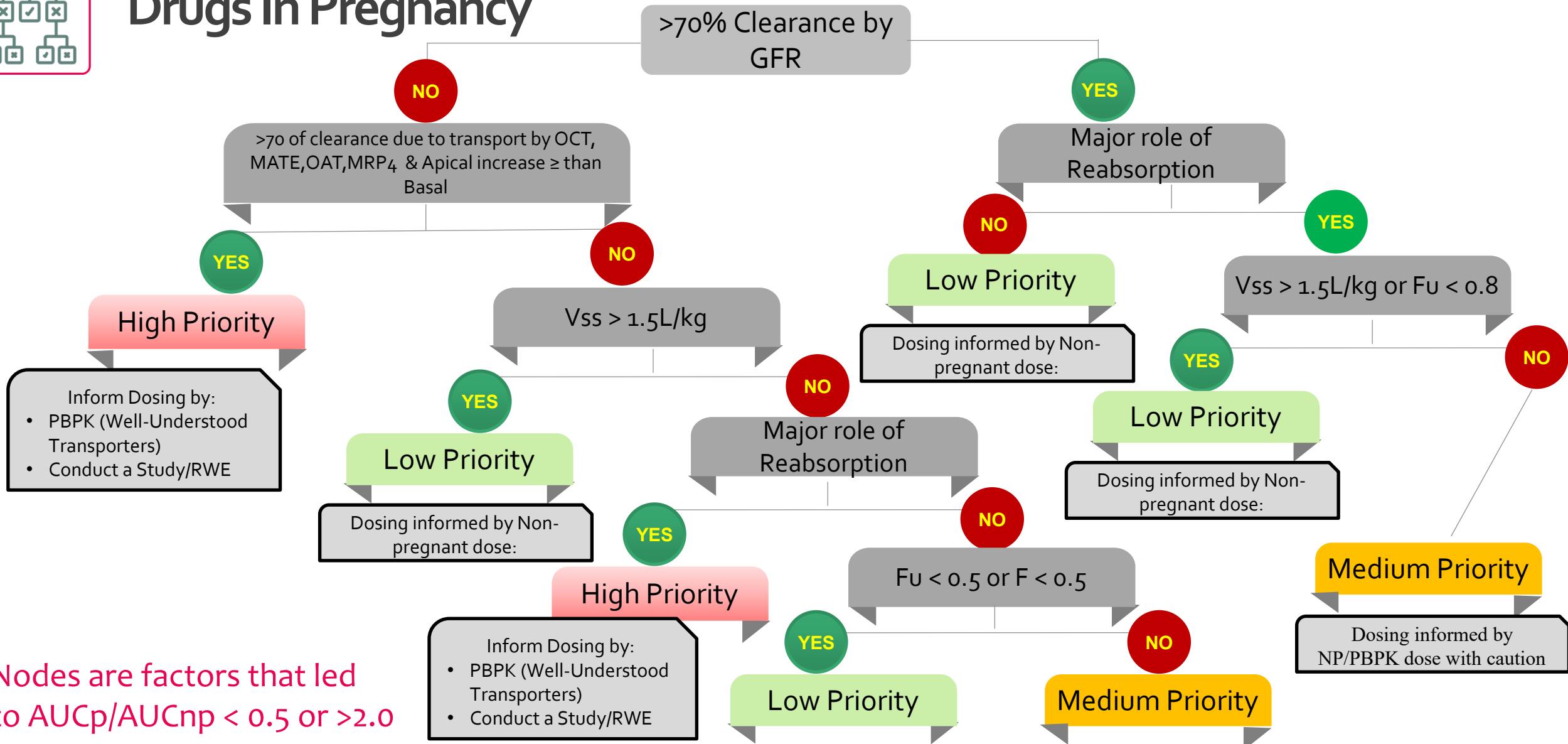


*CYP3A4, UGT1A4,CYP1A2,CYP2C19 all have reported abundances sufficient

Nodes are factors that led to AUCp/AUCnp < 0.5 or >2.0

Aim 3

Decision Tree Framework For Predominantly Renally Cleared Drugs In Pregnancy



Nodes are factors that led to AUCp/AUCnp < 0.5 or >2.0

Aim 3

Decision Tree Framework Correctly Predicted Pregnant/Non-pregnant AUC Ratios For 10 Drugs

Drug Name	Decision Tree	Decision Tree Prediction	Observed AUCp/AUCnp
Indinavir	Hepatic	High Priority	<0.5
Lamotrigine	Hepatic	High Priority	<0.5
Lithium	Renal	High Priority	<0.5
Nifedipine	Hepatic	High Priority	<0.5
Levetiracetam	Renal	Moderate Priority	0.3-0.6
Ampicillin	Renal	Moderate(IV) Low(oral)	0.66 (IV) 0.65 (Oral)
Emtricitabine	Renal	Moderate Priority	>0.5 <2.0
Gentamycin	Renal	Low Priority	>0.5 <2.0
Metronidazole	Metabolism	Moderate Priority	>0.5 <2.0
Artemether	Hepatic	High Priority	<0.5

How the Drug Prioritization Decision Tree Framework Can be Applied during Drug Development?

	Where can it help?	Benefit to sponsors
Pre-marketing	Can enable to identify compounds likely to have meaningful changes in PK exposures and support early-stage drug triaging	Sponsors can upfront plan their studies or a method to derive dosing recommendations for pregnancy
For drugs already in the market (post-marketing)	Can help prioritize drugs to be studied	Provides guidance for academic researchers to pursue research (opportunistic PK sampling)

What the decision tree does not address currently	
	• **Purely based on PK exposure changes** • **Assumes no change in exposure-response relationship during pregnancy** • **To be used with caution for narrow therapeutic index drugs** • **Fetal exposure, developmental pharmacology for the fetus not accounted**

Thank You

FDA SMEs

Dr. Qi Liu (FDA/OTS)
Dr. Yuching Yang (FDA/OCP)

UMB

Dr. Brooke Langevin
Dr. Katrina Mark
CTM members

UMB-MCERSI

Dr. Jim Polli
Ms. Dana Hammell

Compared to Literature

TABLE 1 List of medicines commonly used in pregnancy in the UK.

Anesthetics	Antidepressants (cont')	*HIV (cont')*	Diabetes medicines (cont')
Etomidate	Sertraline	Darunavir/cobicistat	Tolbutamide
Ketamine	Tranylcypromine	Darunavir/ritonavir	**Endocrine medicines**
Propofol	Trazodone	Dolutegravir	Thyroxine
Thiopentone	Trimipramine	Doravirine	**Anti-epileptics**
Antibiotics	Triptafen	Efavirenz	Brivaracetam
Amikacin	Venlafaxine	Elvitegravir/cobicistat	Buprenorphine
Amoxicillin	Vortioxetine	Emtricitabine	Carbamazepine
Ampicillin	**Anti-emetics**	Lamivudine	Clobazam
Azithromycin	Cyclizine	Nevirapine	Clonazepam
Benzylpenicillin	Doxylamine/pyridoxine	Raltegravir	Diazepam
Cefaclor	Meclozine	Rilpivirine	Eslicarbazepine
Cefadroxil	Metoclopramide	Tenofovir alafenamide	Ethosuximide
Cefalexin	Ondansetron	Tenofovir DF	Felbamate
Cefixime	Phenothiazines	Zidovudine	Gabapentin
Cefotaxime	Promethazine	*HSV*	Lacosamide
Cefradrine	**Antifungal**	Acyclovir	Lamotrigine
Ceftazidime	Amphotericin	Valiciclovir	Levetiracetam
Ceftriaxone	Clotrimazole	*Influenza*	Lorazepam
Cefuroxime	**Antihistamines**	Oseltamivir	Midazolam
Clindamycin	Cetirizine	Zanamivir	Oxcarbazepine

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Cefazolin	Metformin	Glyburide	Rifampin	Buprenorphine

Important Drug Properties
• Renally Cleared
  • GFR
  • Tubular Secretion (~50-80%)
• 77.5% Protein bound
• Monoprotic Acid
• pKa 3.6
• logP -.58
• Final Kp_scalar used = 2.2
	Important Drug Properties
	• Renally Cleared
	  • GFR
	  • Tubular Secretion
	• ~100% unbound
	• Monoprotic Base
	• pKa 11.8
	• logP -1.43
	• Final Kp_scalar used = 0.8
		Important Drug Properties
		• Metabolized
		  • CYP3A4 +CYP2C19+ CYP2C9
		• ~ 98% bound
		• Weak Monoprotic Acid/Neutral
		• pKa 5.11
		• logP 3.07
		• Final Kp_scalar used = 0.06
			Important Drug Properties
			• Metabolized by AADAC
			• 80% bound
			• Zwitter Ion
			• pKa(Acid) 1.7
			• pKa(Base) 7.9
			• logP 2.7
			• Final Kp_scalar Used = 0.094
				Important Drug Properties
				• Metabolized
				• 96% bound
				• pKa 8.31
				• logP 4.98
				• Final Kp_scalar Used = 2.8
				Overall sublingual Bioavailability 30%
				CYP3A4
				CYP2C8
				UGT1A1
				UGT1A3
				UGT2B7