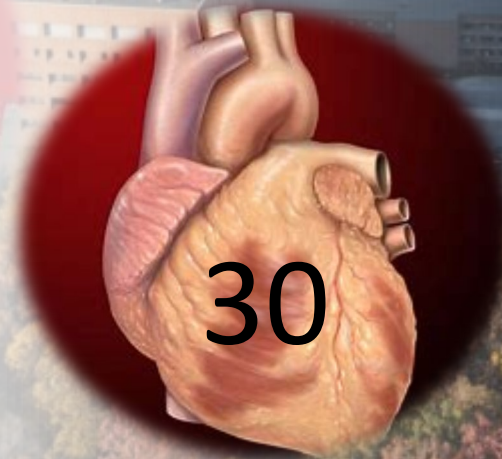
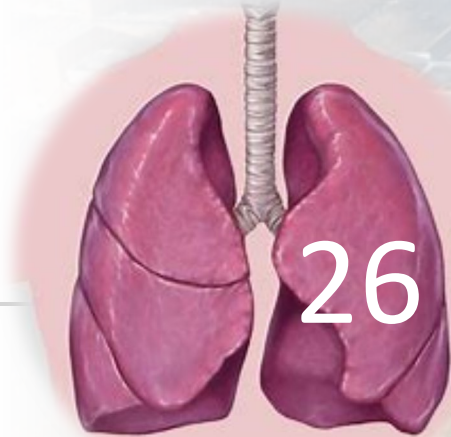
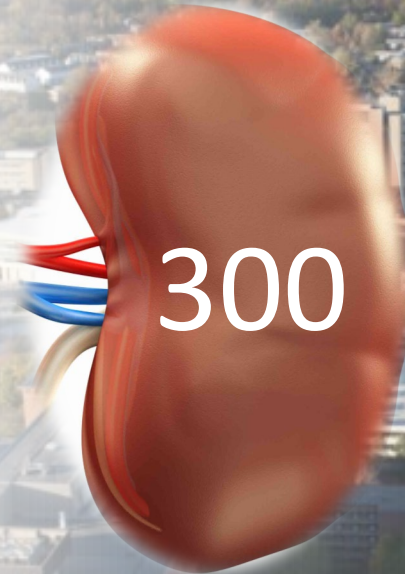
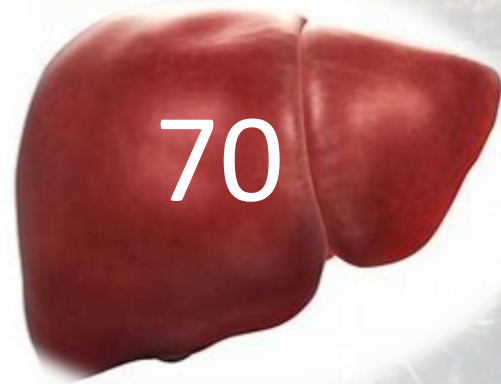




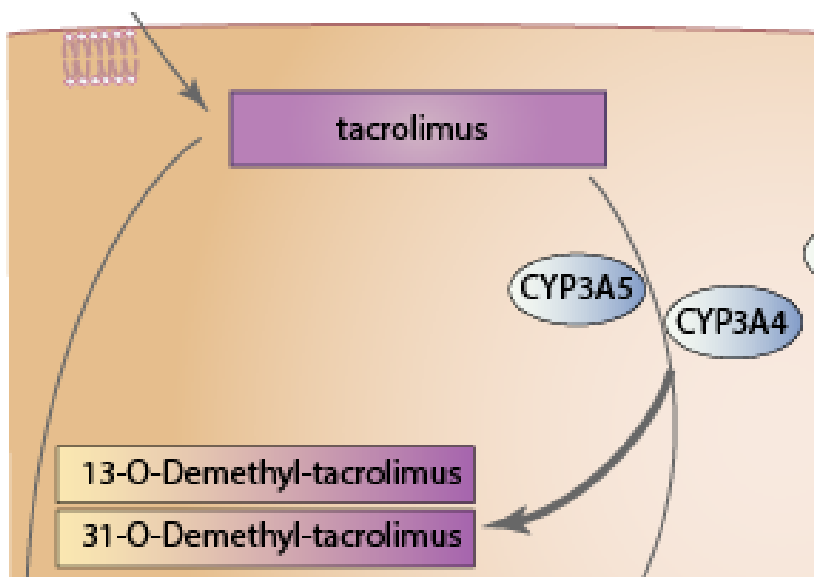
# Implementing *CYP3A5* and Tacrolimus

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ClinPGx 2024

# University of Michigan Health



# CYP3A5 and Tacrolimus



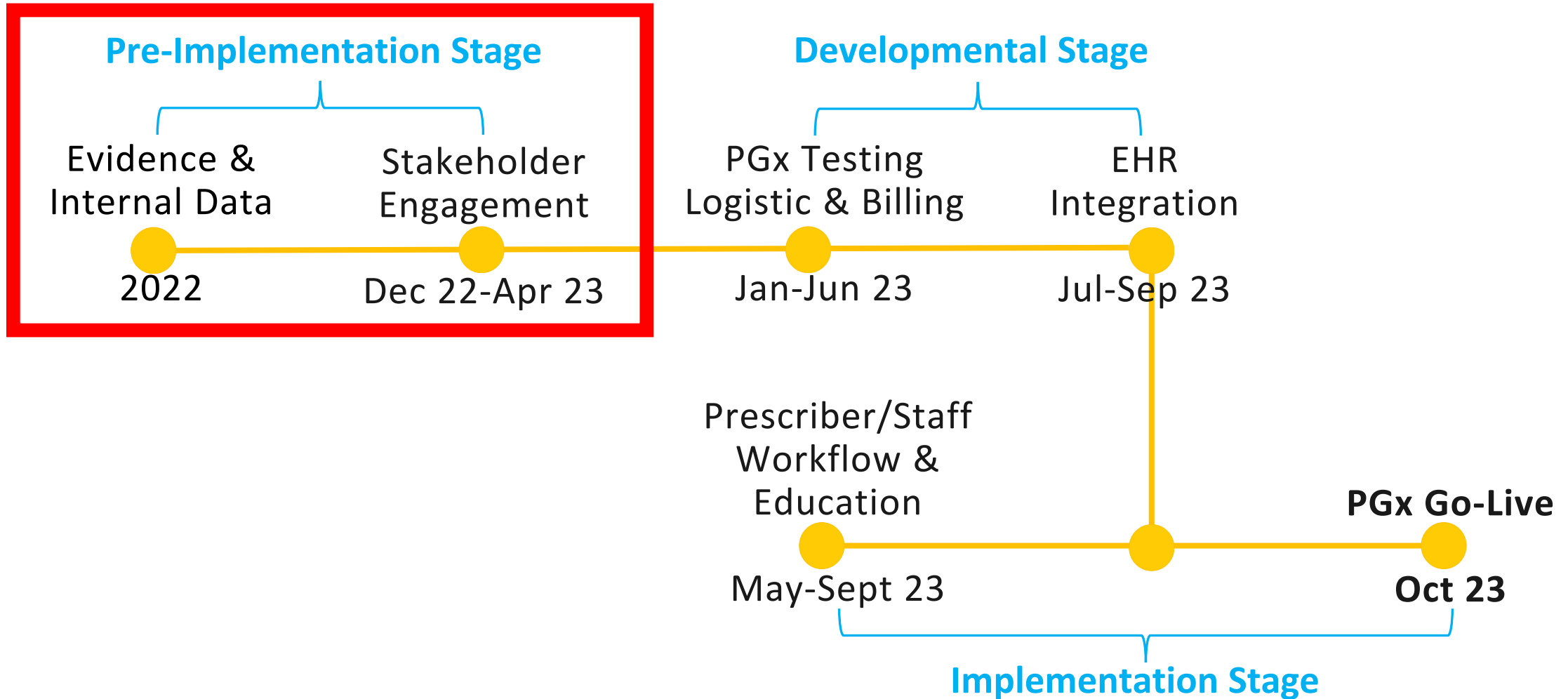
## CPIC Recommendation CYP3A5 and Tacrolimus Guideline

CYP3A5 Genotype	CYP3A5 Phenotype	Tacrolimus Dosing
One or two normal function alleles (*1/*1, *1/*3, *1/*6, *1/*7)	CYP3A5 <b>expresser</b> (Normal & Intermediate metabolizer)	1.5 – 2x standard dose (Max 0.3 mg/kg/day)
Two no function alleles (*3/*3, *6/*6, *7/*7, *3/*6, *3/*7, *6/*7)	CYP3A5 <b>nonexpresser</b> (Poor metabolizer)	Standard dose

## RCT of Genotype-guided Tacrolimus in adult kidney transplant recipients

Study	Group	First trough at goal		Median [IQR] days to achieve goal trough		# of dose adjustments		
		%	P	Control	PGx	Control	PGx	
<b>Thervet (2010)</b>	Control	29.1%	P=0.030	7 [3-25]		420	P=0.004	
	PGx	43.1%		6 [3-8]				281
<b>Shuker (2016)</b>	Control	37.4%	P=0.79	6 [3-17]		156	P=0.30	
	PGx	47.0%		6 [3-28]				129
<b>Anutrakulchai (2019)</b>	Control	23.8%	P=0.048	*1/*1	10 [2-29]	P=0.06	--	
				*1/*3	2 [1-7]			4 [2-7]
				*3/*3	4 [3-5]			3 [2-4]

# Steps for PGx Implementation



# Considerations for selecting a population

- Tacrolimus formulation
  - Intravenous
  - Sublingual
- Drug-drug interactions
- Donor genotype

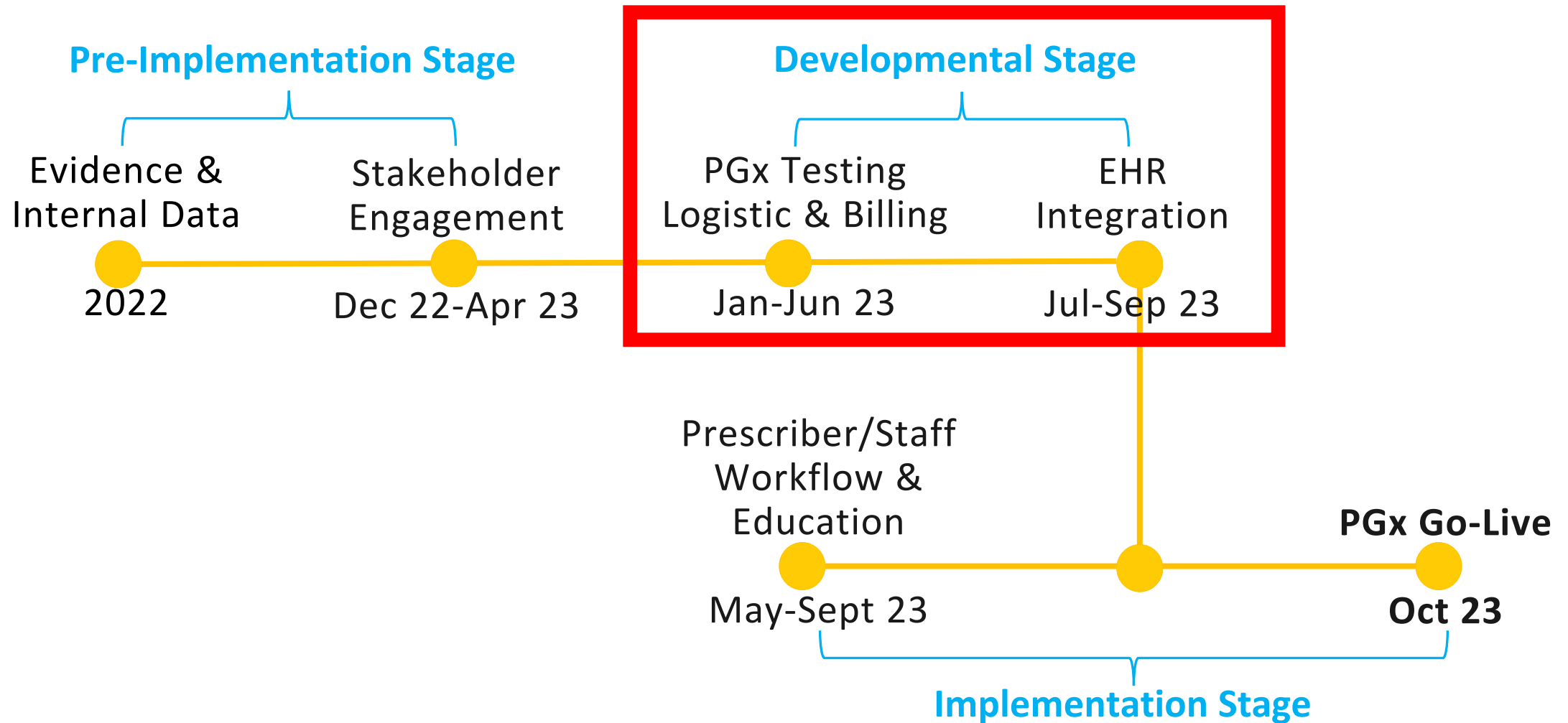
# Considerations for selecting a population

Internal evidence- 160 adult kidney transplant recipients with Michigan Genomics Initiative research genotypes

		CYP3A5 expressers		CYP3A5 nonexpressers
		Normal metabolizers (n=5)	Intermediate metabolizers (n=19)	Poor metabolizers (n=136)
Initial tacrolimus trough	Subtherapeutic (<8 ng/mL)	5 (100%)	15 (79%)	34 (25%)
	Therapeutic (8-12 ng/mL)	0	4 (21%)	47 (35%)
	Supratherapeutic (>12 ng/mL)	0	0	55 (40%)
Time to first steady-state therapeutic trough (days)		44 [26.5-63.8]	19.5 [8.3-26.5]	13 [5-27]
Tacrolimus dose at therapeutic steady-state trough (mg/kg/day)		0.31 [0.17-0.38]	0.21 [0.19-0.25]	0.13 [0.09-0.16]



# Steps for PGx Implementation



# CYP3A5 testing process and cost

- Result needed prior to transplant

Living Donor	New Listing	Waitlist
On-site collection at H&P for scheduled transplant	On-site sample collection at transplant listing visit	On-site collection for in person annual follow up visit  Mailed collection kits for virtual annual follow up visit

- Cost of testing included in pre-transplant cost report
  - Rationale: Resources saved (e.g., nurse efforts for patient education, billing issues, tacrolimus monitoring and dose adjustments) may justify the lab costs





# Tacrolimus dose recommendations

## Adult Kidney Transplant Immunosuppression Protocol

- Historical initial dose: IR tacrolimus 0.075 mg/kg po q12h (0.15 mg/kg/day)

	Tacrolimus IR dose
CYP3A5 Normal Metabolizer	0.15 mg/kg/dose
CYP3A5 Intermediate Metabolizer	0.1 mg/kg/dose
CYP3A5 Poor Metabolizer OR No <i>CYP3A5</i> Genotype	0.075 mg/kg/dose

### **Patient's Excluded from Genotype-guided dosing:**

- Previous liver transplant recipients
- Multi-organ transplant recipients including kidney/pancreas
- Patients who are currently taking tacrolimus
- Patients who are taking CYP3A4/5 inhibitors or inducers



# Clinical Decision Support

- Upon genotype result return the corresponding CYP3A5 phenotype is added to the patient Genomic Indicators section of the EMR
- Automatically modify initial tacrolimus dose in Post-Op Kidney Transplant order set

▼ Tacrolimus (PROGRAF OR ENVARUSUS)

 Tacrolimus (PROGRAF OR ENVARUSUS)

This patient has CYP3A5 Intermediate Metabolizer genomic indicator. Dosing below has been defaulted accordingly to transplant specific protocol. Rounded to the nearest mg.

Please select one:

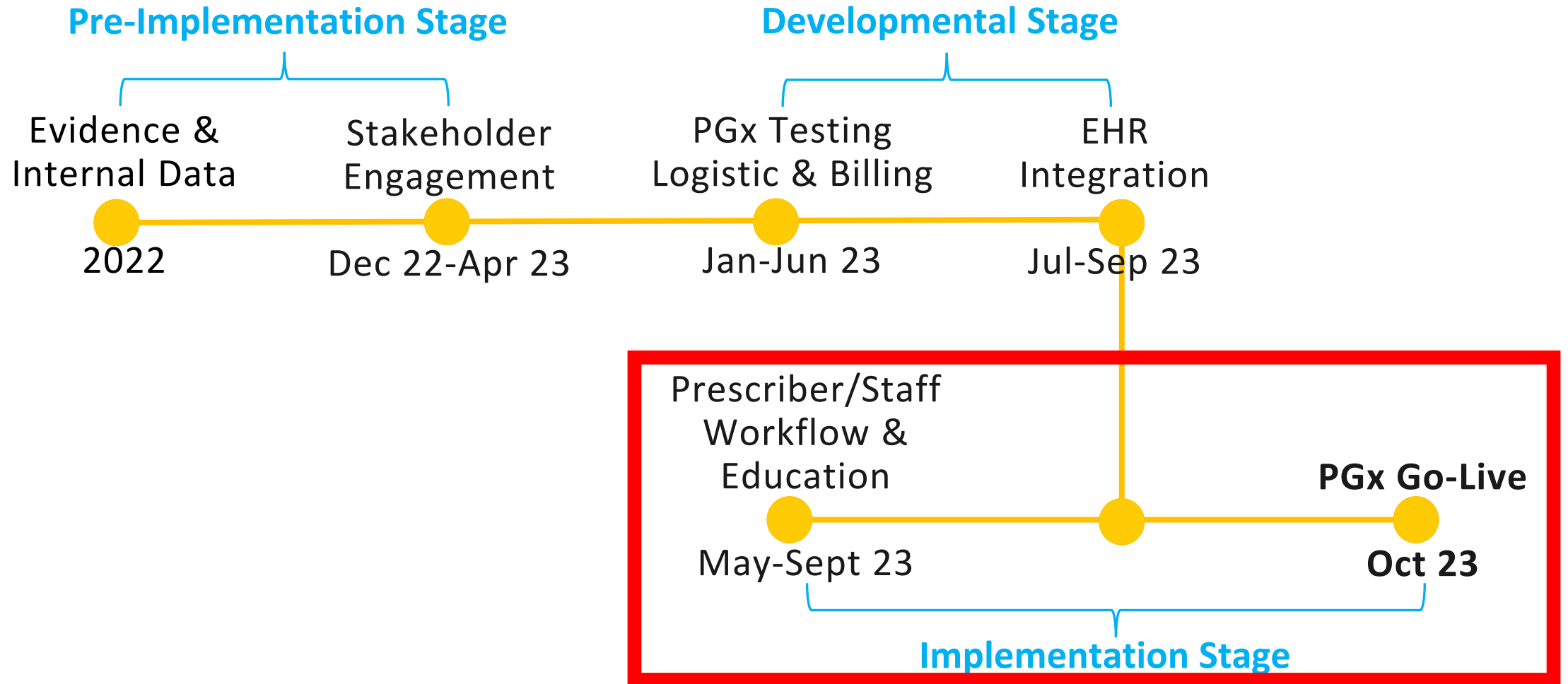
tacrolimus (PROGRAF) capsule

0.1 mg/kg per DOSE, Oral, EVERY 12 HOURS SCHEDULED, Start on POD 0, Initial dose for kidney transplant recipients is determined based on CYP3A genotype. See adult kidney transplant immunosuppression protocol, Starting 11/30/23

Embedding CDS in the post-op order set, instead of traditional BPA

- ✓ Eliminate reliance on prescribers
- ✓ Avoid alert fatigue
- ✓ Apply to target population and initial dose only
- ✓ Avoid medication errors

# Steps for PGx Implementation



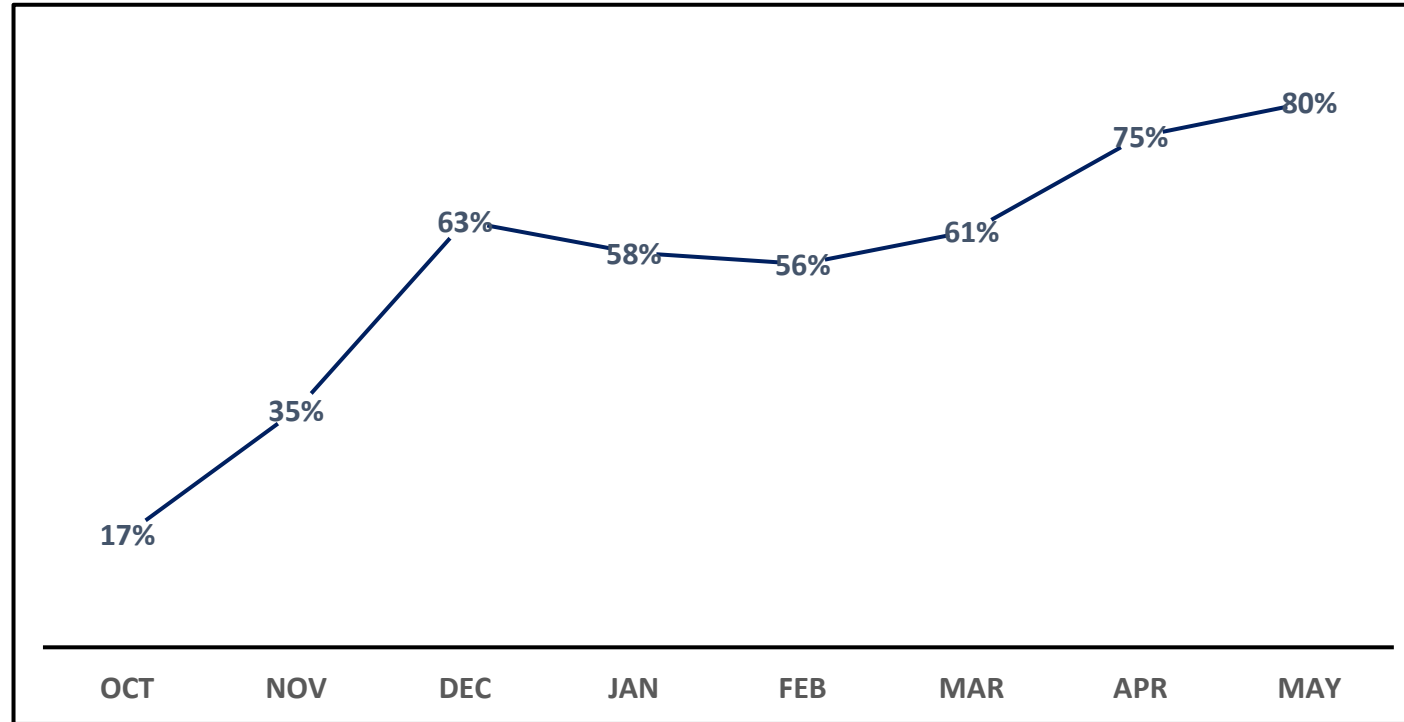
# Provider education

- Pre-transplant nurses
  - Testing purpose and ordering workflow
  - Mailing kit instructions
  - Patient education
  - Clinical decision support
- Surgical team and Nephrology
  - Immunosuppression protocol updates
  - Clinical decision support



# Preliminary Program Outcomes

Percent of recipients with *CYP3A5* genotype at transplant

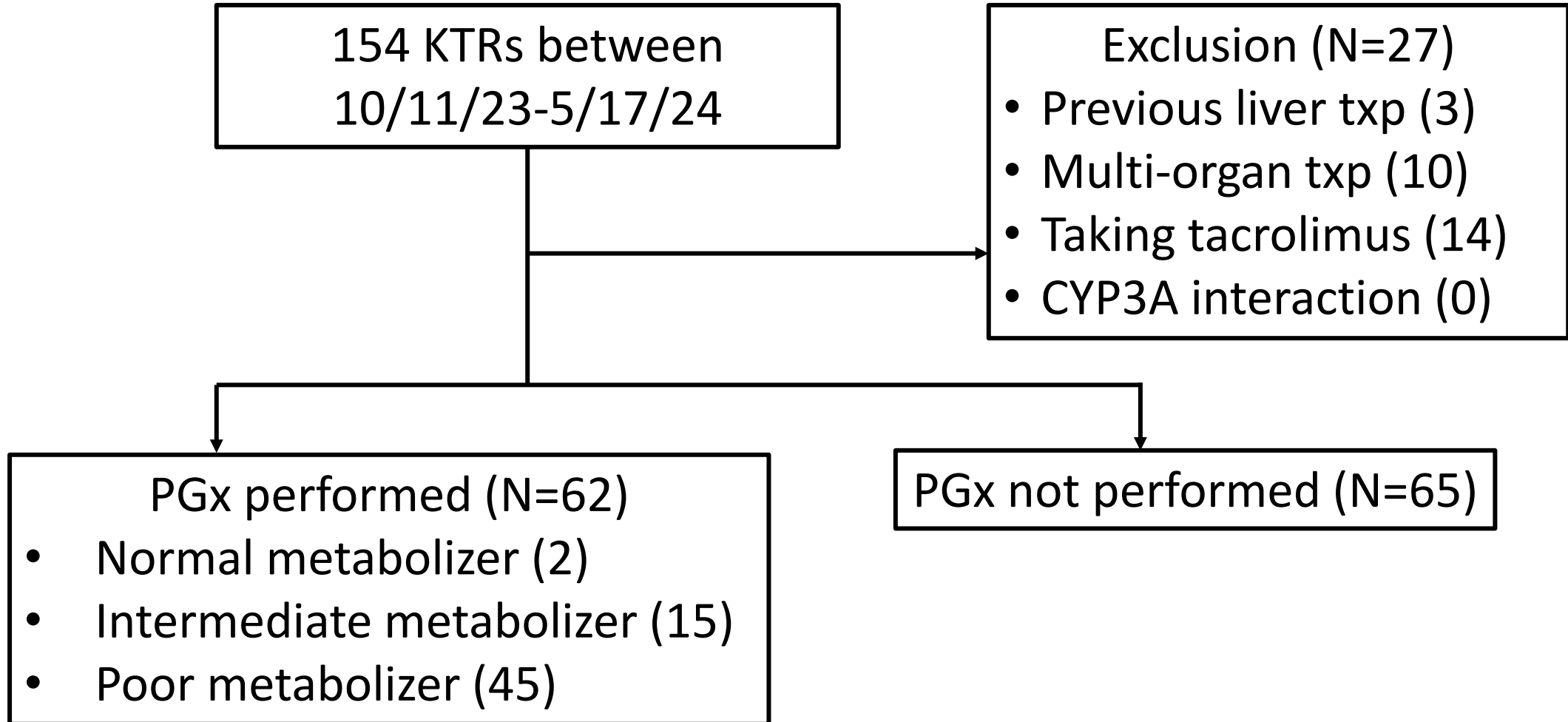


On-site collection at listing, annual evaluation & living-donor txp H&P

+ Mailing kits for waitlisted patients



# Preliminary Program Outcomes



# Thank you

- Jamie Park, PharmD, MS, BCTXP
- UM Precision Health Initiative
- Pre-transplant clinic nurses
- Transplant surgery team
- Nephrology team
- Lab formulary Committee
- Clinical Decision Support Committee

