Tacrolimus (TAC) is an immunosuppressant with a narrow therapeutic index and high pharmacokinetic variability leading to uncertainty in blood concentrations. TAC is dependent on CYP3A4/5 enzymes for metabolism. The CYP3A4/5 genes are highly polymorphic and variants significantly influence the metabolism of TAC. The CYP3A4*1, *6, *7, are important variants in African Americans (AA) whereas CYP3A5*3 and CYP3A5*22 variants are common and important variants influencing pharmacokinetics in European American (EA) subjects. These variants in combination with clinical factors account for 30%-50% of variability in TAC trough concentrations. Little is known about important genetic variants in other populations. We performed a targeted genome-wide association study (GWAS) to identify variants that may be associated with TAC troughs in other populations. Defining variants for all populations will improve precision medicine approaches to genotype-guided dosing.

OBJECTIVES
To define the differences in TAC daily doses requirements and troughs in EA, AA, His/Nat and AsA tx recipients. To evaluate the association of well-known variants (CYP3A4*3, 6, 7 and CYP3A5*22) towards TAC troughs in four populations. To identify new and novel genetic variants associated with TAC troughs in tx recipients of Asian and Hispanic/Native American ancestry.

METHODS
Study Design
- A genomic association analysis of log dose-normalized TAC troughs was conducted in patients enrolled in the DeKAF Genomics study and GEN03 studies. These are multicenter, observational studies which prospectively followed kidney tx recipients from 2005 to 2016 at 7 study sites in the United States and Canada. Registered at www.clinicaltrials.gov (NCT00270712). Tx recipients were selected for this study if they received TAC as maintenance immunosuppression, had TAC trough concentrations measured and GWAS data available.

TAC Troughs
- TAC troughs and corresponding doses in the first 6 months posttx were obtained as part of routine clinical care and taken from the medical record for analysis. Two TAC troughs were obtained per week in the first 8 weeks and two troughs were obtained per month in months 3, 4, 5 and 6 for a maximum of 24 troughs per patient.
- Generally, the target trough concentrations were 8 to 12 ng/mL in the first 3 months, then 6 to 10 ng/mL for 3 to 6 months post-transplant.

Genotyping and Genetic Association Analysis
- Genotyping was conducted on an exome-plus Affymetrix Tx Array chip with ~800,000 high quality SNP markers after QC and >34M markers after imputation using the 1000 Genomes phase 3 and Genome of the Netherlands v5. Both cohorts were genotyped on this array. Approximately, 45,000 SNPs from the CYP3A4 and CY3AS genes were taken from the chip and analyzed.
- Race was determined in each cohort using principal components with ancestry informative markers from the GWAS panel. Patients identified as Hispanics/Native Americans (His/Nat), Asian Americans (AsA), EA or AA were selected for the analysis.
- We tested the associations between CYP3A4 and 5 gene variants and log dose-normalized TAC troughs in tx recipients of the four populations. Longitudinal Mixed Effect models for known and top identified variants were constructed adjusting for center, age and gender for all populations. For the CYP3A4 and 5 gene wide association analysis a p-value of <1.1e-6 was considered significant after adjusting for multiple testing.

RESULTS
TAC troughs, dose-normalized troughs and daily doses by population are shown in Table 1. His/Nat received the lowest TAC daily dose (5 mg) and the AA received the highest dose (8 mg). His/Nat also had the highest dose normalized TAC trough and the AA the lowest levels (P <0.001, ANOVA).

Objective
- Objective of this study was to define the differences in TAC daily doses requirements and troughs in EA, AA, His/Nat and AsA tx recipients. To evaluate the association of well-known variants (CYP3A4*3, 6, 7 and CYP3A5*22) towards TAC troughs in four populations. To identify new and novel genetic variants associated with TAC troughs in tx recipients of Asian and Hispanic/Native American ancestry.