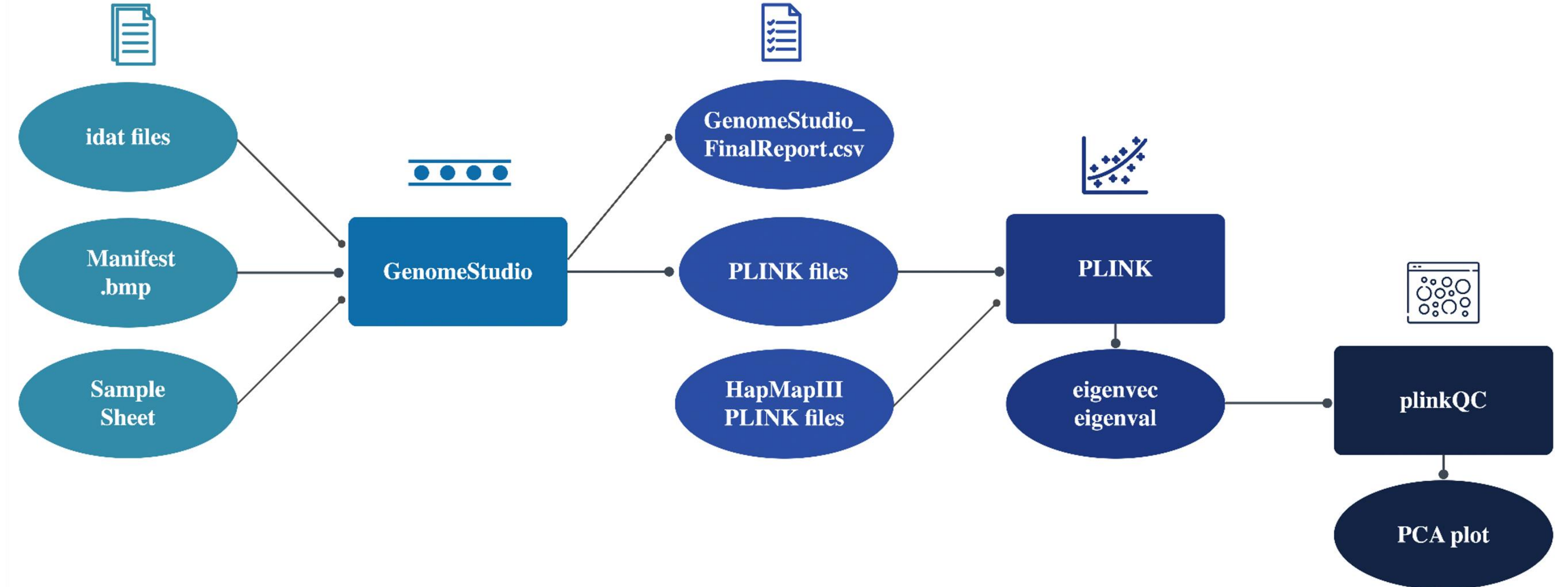


BACKGROUND

- As declared by the Centers for Disease Control and Prevention (CDC), the United States is in the midst of an opioid epidemic. There remains a paucity of research regarding how one’s individual genetic composition may affect opioid consumption patterns.
- This study aims to further the field of personalized medicine by analyzing pharmacogenomics to predict patient’s drug response in opioid consumption patterns post ACL reconstruction surgery.
- Oxycodone is metabolized by CYP2D6, CYP3A4, and CYP3A5, primarily.¹
- We are interested in why some people take more opioids post-surgery than others
- We are incorporating ancestry information, age, sex, previous drug use, and many other covariables to reduce confounding bias

MATERIALS AND METHODS



- Multinomial logistic regression is used to model categorical outcome variables. The log odds of the outcomes are modeled as a linear combination of the given predictor variables. It is an extension of normal logistic regression that allows us to have a response variable with more than just two categories.
- Interpretation of model coefficients: Multinomial model coefficients are given initially as log-odds ratios. These model coefficients can be converted to the ratio of the probability of choosing one outcome category over the reference category by taking the exponentiated value of the original coefficient. This exponentiated value is often referred to as relative risk.
- Generalized Linear Modeling (GLM) uses the response variable as the continuous tablets outcomes and determines whether allele categorization had a significant effect on tablet consumption.
- Prior to modeling, the data is checking for outliers, defined as more than 3 standard deviations away from the other sample principal component values along a given axis, using Principal Component Analysis (PCA).

RESULTS

Tablets	0	1	2	3	4	5	6	7	8	9	10	12	15
Normal	19	4	2	2	2	4	1	2	1	2	1	1	5
Int-Normal	2	0	0	0	0	0	0	0	0	0	0	0	0

- Table 1. TABLETS ~ CYP3A4 + SEX + AGE + PCI + PC3 GENERALIZED LINEAR MODEL.**
- Due to the lack of samples in group Int-Normal, we get an extremely significant ($P < 0.05$) coefficient for TABLETS. Looking at the distribution of TABLETS across the Normal group when compared to the Int-Normal group, this is expected as both Int- Normal samples are listed with a TABLET value of 0.
 - No coefficients were found to have a significant effect the response variable tablets.
 - PC2 removed due to singularity (it has a near perfect linear relationship with another PC.)
 - Patient IDs 13 and 55, which separate in distinct ways from the rest of the samples based on the model graphs, are shown to be the 15 tablet patients who still classify as ‘Normal’.

Tablets	0	1	2	3	4	5	6	7	8	9	10	12	15
Poor	16	4	1	1	2	4	1	2	1	1	1	1	4
Intermediate	4	0	1	1	0	0	0	0	0	1	0	0	1

- Table 2. CYP3A5 ~ TABLETS + SEX + AGE + PCI + PC2 + PC3 MULTINOMIAL MODEL (BASELINE: POOR).**
- Normal group not considered in model. The effect of TABLETS was not a statistically significant ($P < 0.05$) contributor to the classification of CYP3A5. No coefficients were found to be significant in the outcome of this model.
 - No coefficients were found to have a significant effect the response variable tablets.
 - PC2 removed due to singularity (it has a near perfect linear relationship with another PC)
 - Patient IDs 13 and 55, which separate in distinct ways from the rest of the samples based on the model graphs, are shown to be the 15 tablet patients who classify differently

Tablets	0	1	2	3	4	5	6	7	8	9	10	12	15
Normal	11	2	1	1	0	3	0	1	1	1	0	1	2
Int-Nml	1	1	1	0	0	0	0	1	0	0	0	0	1
Intermediate	6	0	0	1	2	0	0	0	0	1	1	0	1
Poor	0	0	0	0	0	1	1	0	0	0	0	0	1

Tablets	0	1	2	3	4	5	6	7	8	9	10	12	15
High	8	3	0	2	1	1	0	0	0	0	0	3	0
Intermediate	10	1	1	0	1	1	1	2	1	1	0	1	3
Low	3	0	1	0	0	2	0	0	0	1	1	0	2

- Table 3. COMT ~ TABLETS + SEX + AGE + PCI + PC2 + PC3 MULTINOMIAL MODEL (BASELINE: LOW)**
- The coefficient tablets was not found to be a statistically significant contributor ($p < 0.05$) to the classification of COMT when the reference group was set as ‘Low’.
 - The COMT classification difference of “High” to “Low” was found to have a significant effect on the response variable “Tablets.”
 - PC2 was removed from the model due to singularity (it has a near perfect linear relationship with another PC.)

Tablets	0	1	2	3	4	5	6	7	8	9	10	12	15
Asn/Asn	13	3	2	2	1	3	0	1	1	1	0	1	3
Asn/Asp	7	1	0	0	1	1	1	1	0	1	1	0	2
Asp/Asp	1	0	0	0	0	0	0	0	0	0	0	0	0

- Table 4. OPRMI ~ TABLETS + SEX + AGE + PCI + PC2 + PC3 MULTINOMIAL MODEL (BASELINE: ASN/ASP)**
- The coefficient tablets was not found to be a statistically significant contributor ($p < 0.05$) to the classification of OPRMI when the reference group was set as ‘Asn/Asp’.
 - No coefficients were found to have a significant effect on a one unit increase of tablets.

- Table 5. CYP2D6 ~ TABLETS + SEX + AGE + PCI + PC2 + PC3 MULTINOMIAL MODEL (BASELINE: NORMAL)**
- The coefficient TABLETS was found to be a statistically significant ($p < 0.05$ contributing factor in the classification of the group ‘Poor’ when ‘Normal’ is used as the reference group. The relative risk ratio for a one unit increase of the variable TABLETS is $\exp(0.4696) = 1.599$.
 - No coefficients were found to have a significant effect the response variable tablets.
 - Patient IDs 68 and 55, which separate in distinct ways from the rest of the samples based on the model graphs, are shown to be the patients who classify the same with very different tablet outcomes.

CONCLUSIONS

- For CYP2D6, The coefficient TABLETS was found to be a statistically significant ($P < 0.05$) contributing factor in the classification of the group ‘Poor’ when ‘Normal’ is used as the reference group. The relative risk ratio for a one unit increase of the variable TABLETS is $\exp(0.4696) = 1.599$.
- The COMT classification difference of “High” to “Low” was found to have a significant effect on the response variable “Tablets.”
- The CYP3A4, CYP3A5, and OPRMI classifications did not have a significant effect on the response variable “Tablets”