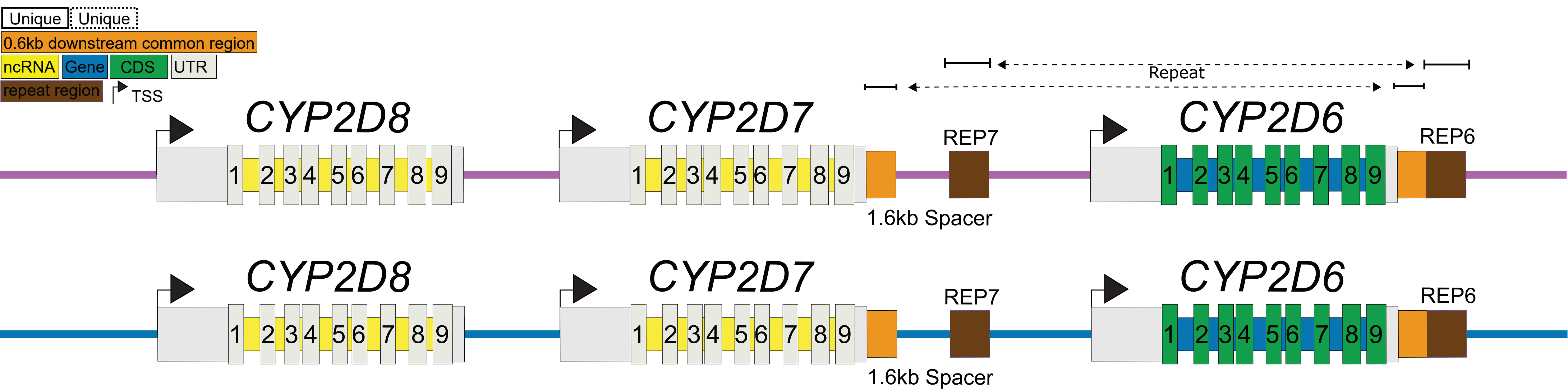


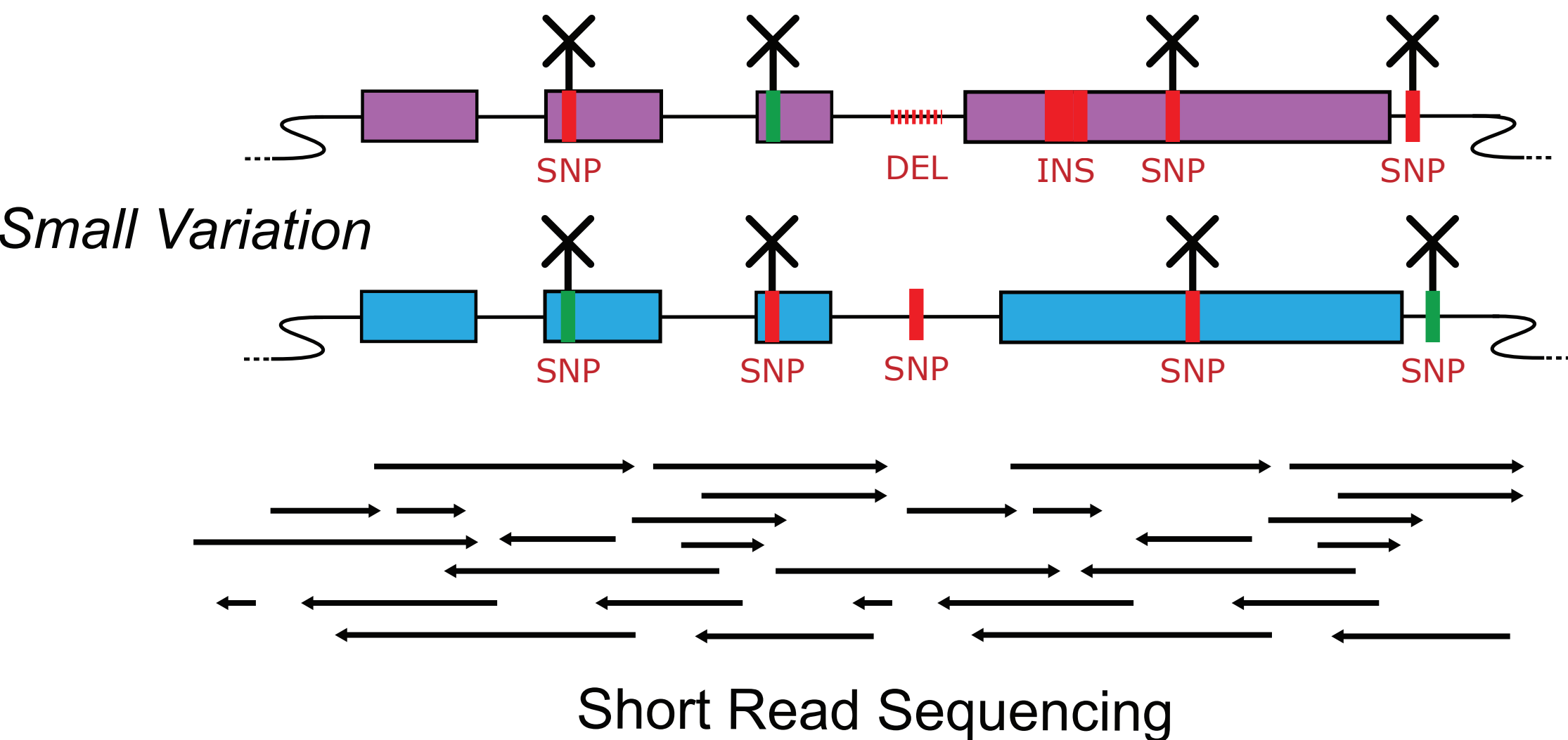
Abstract

Breast cancer treatment, particularly for estrogen receptor-positive (ER+) tumors, often relies on tamoxifen, a drug whose efficacy is significantly influenced by the CYP2D6 gene and its variants. However, conventional pharmacogenomic tests frequently fail to detect complex structural variations in CYP2D6, leading to discrepancies in predicting patient outcomes. This project aims to address these challenges by utilizing long-read sequencing, guided by CRISPR/Cas9 technology, to accurately detect structural variations and novel genetic variants in the CYP2D6 gene. In collaboration with the National Cancer Centre Singapore (NCCS), we will investigate the relationship between these variants and the pharmacometabolic profiles of tamoxifen-treated breast cancer patients. This approach enables the identification of variants missed by short-read sequencing and offers more precise pharmacogenomic predictions. By correlating genetic data with patient outcomes, this research will improve the accuracy of personalized treatment strategies, particularly for Asian populations, where genetic diversity plays a key role in drug metabolism. Ultimately, the project aims to enhance tamoxifen therapy and inform broader pharmacogenomic applications.

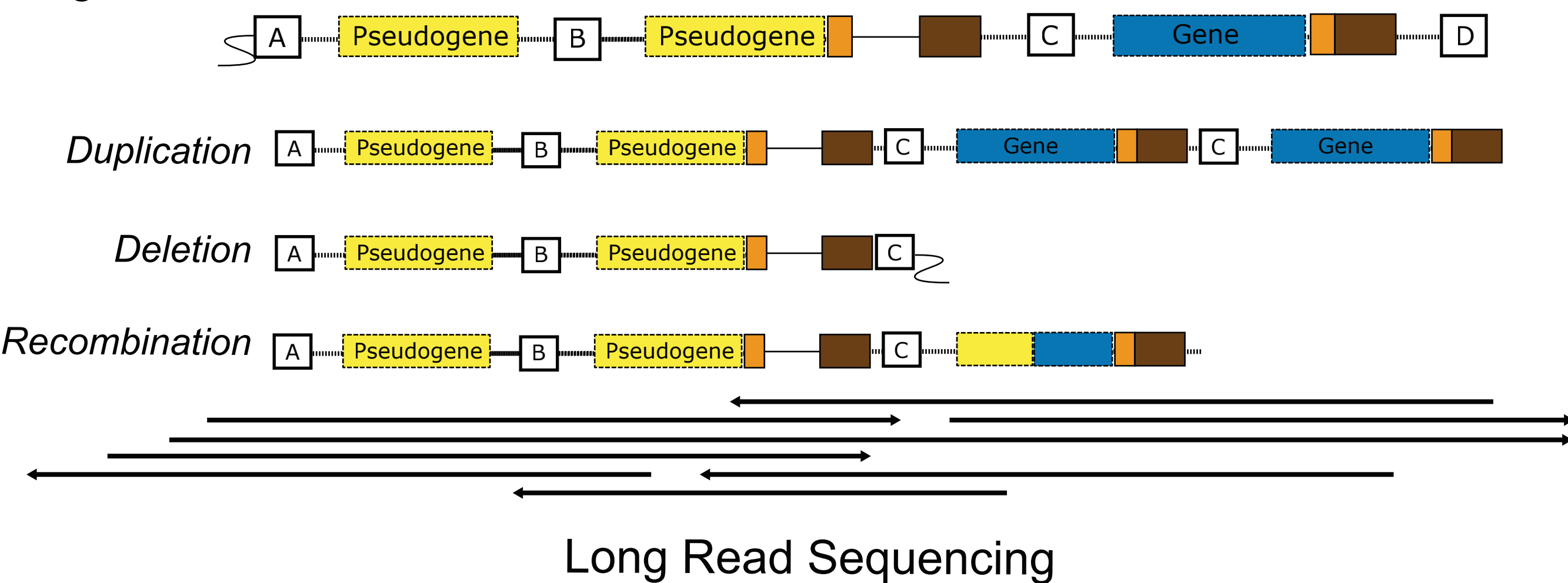
CYP2D6 Pharmacogene Locus



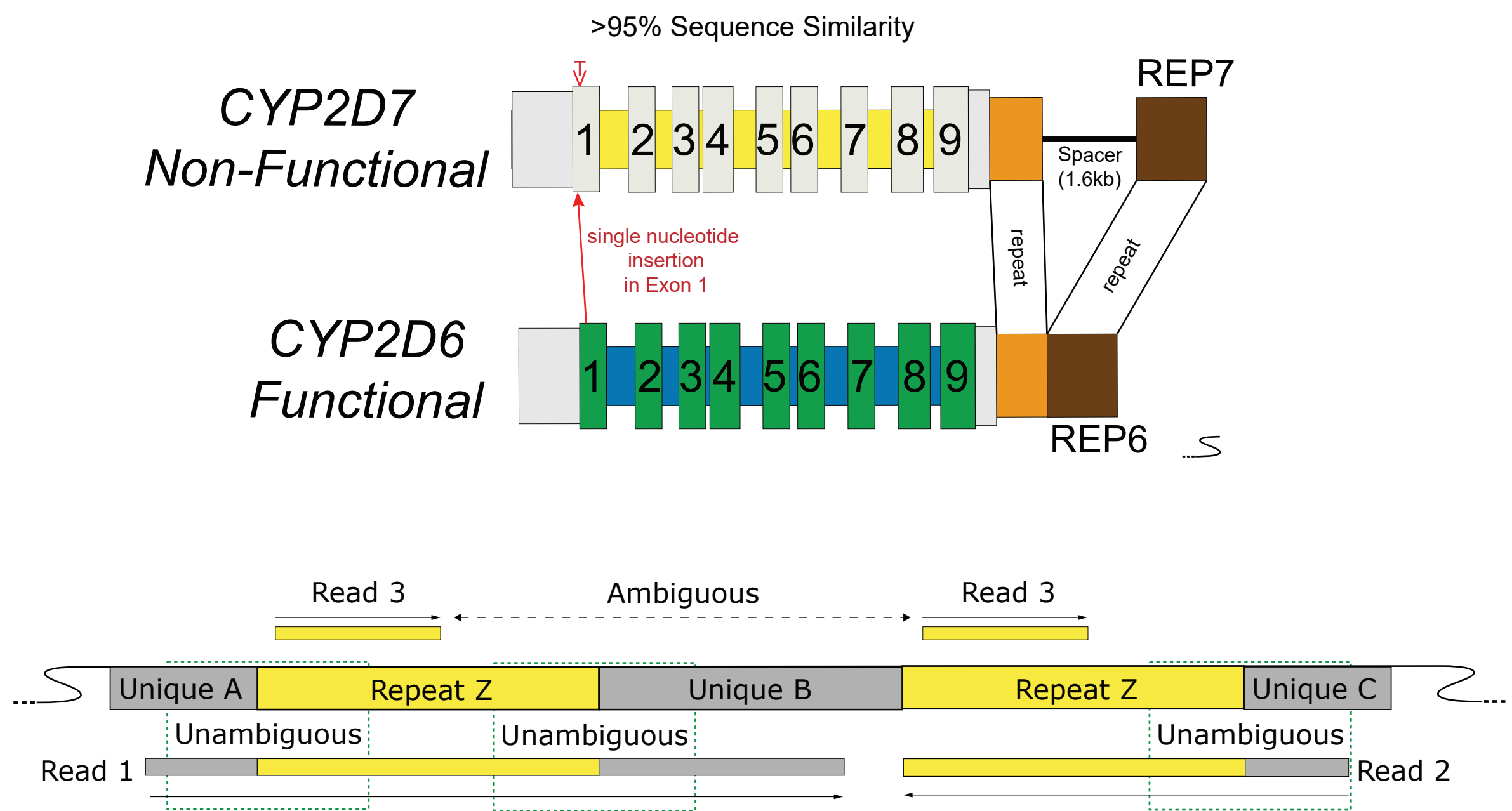
Pharmacogenetic Variation Detection



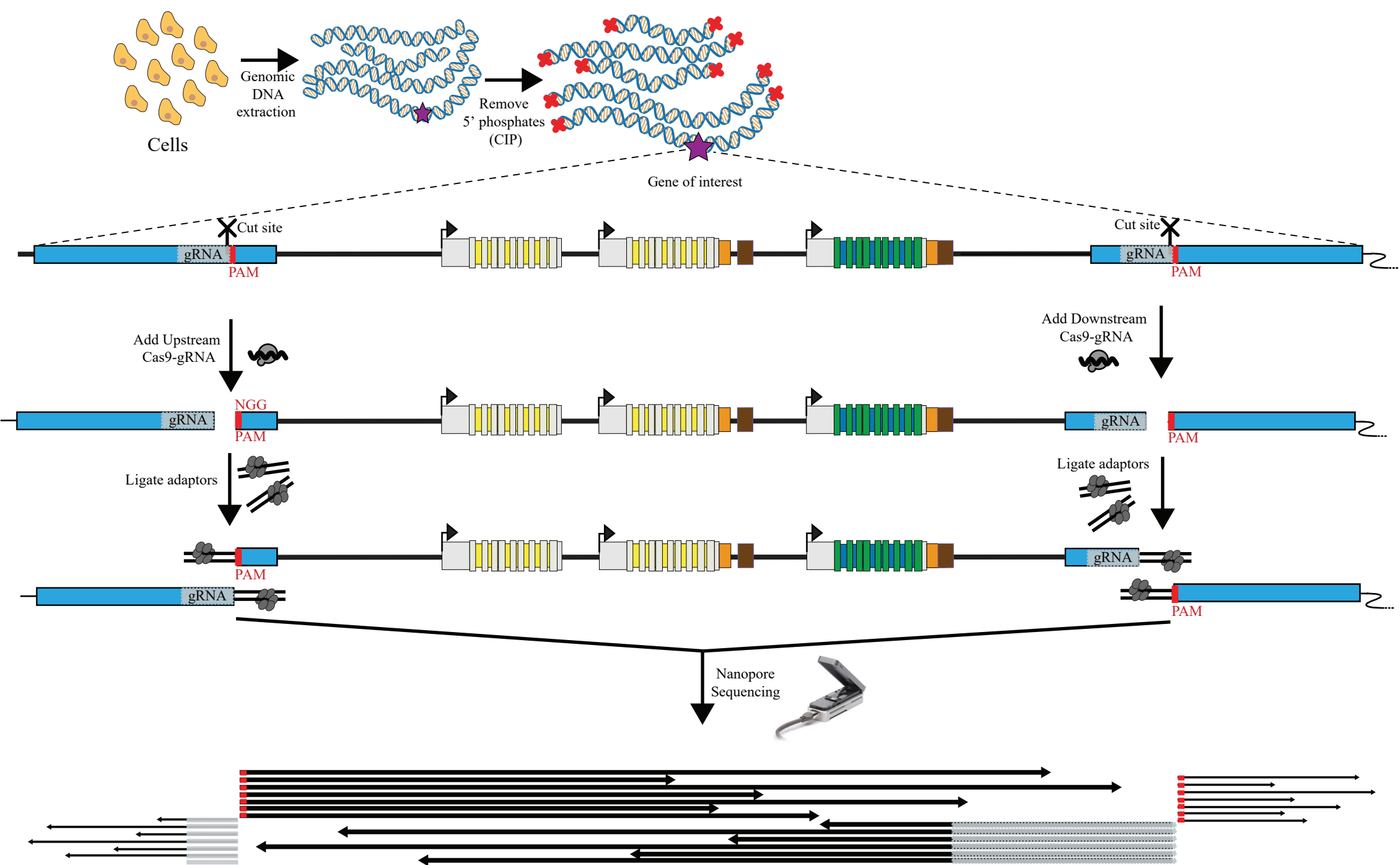
Large Variation



Structural Variation causes Mappability Issues



Cas9-guided PGx Assay



Project Design

This project leverages CRISPR/Cas9-guided long-read sequencing to target and sequence the entire CYP2D6 region, allowing for the identification of structural variants and novel mutations that are typically missed by short-read sequencing methods. By focusing on 75 breast cancer patients from NCCS, who have already undergone pharmacometabolic profiling, the project aims to correlate genetic variations in CYP2D6 with tamoxifen metabolism and clinical outcomes, providing a clearer understanding of how these variants affect drug response. A significant innovation in this study is the use of machine learning models to improve the accuracy of variant detection and quality score validation, incorporating plasmid-based sequencing standards to ensure high precision. The ability to resolve complex regions of the CYP2D6 gene will allow for more reliable pharmacogenomic predictions and the development of personalized treatment strategies that account for individual genetic profiles. Beyond breast cancer treatment, this study has the potential to impact the broader field of pharmacogenomics by improving the understanding of drugs metabolized through the CYP2D6 pathway, such as antidepressants and opioids. The insights gained from this project will set new standards for pharmacogenomic testing, particularly in diverse populations, and could lead to enhanced therapeutic outcomes in various clinical settings. This research not only aims to improve the accuracy of tamoxifen therapy for breast cancer patients but also to establish a robust framework for integrating long-read sequencing into clinical practice, paving the way for more personalized and effective treatments across a variety of conditions.