

A model-informed framework for prioritizing pharmacogenomic drug-gene interactions in an Asian context for chemotherapy

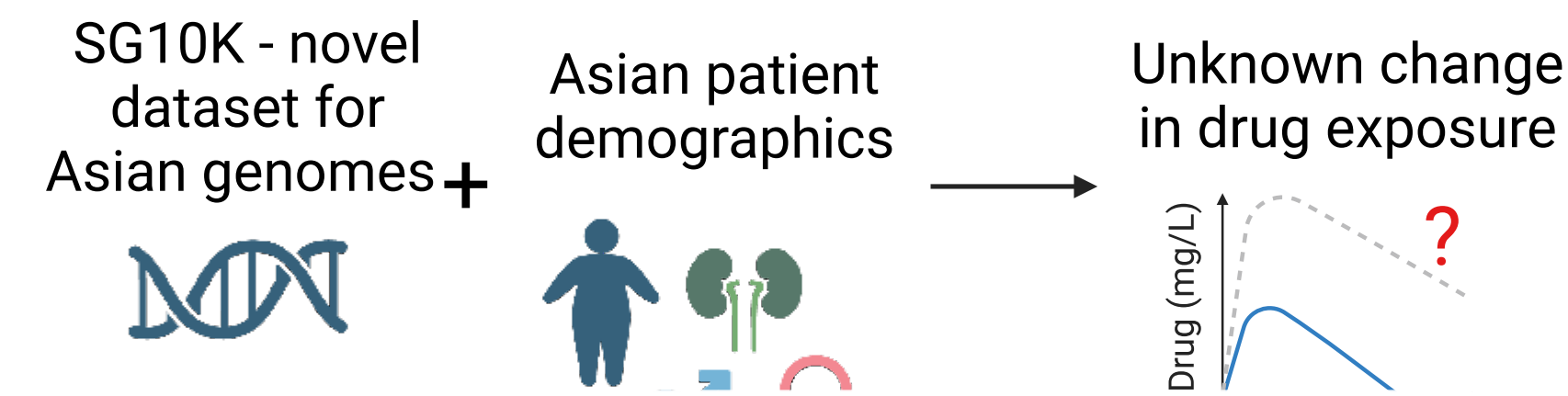


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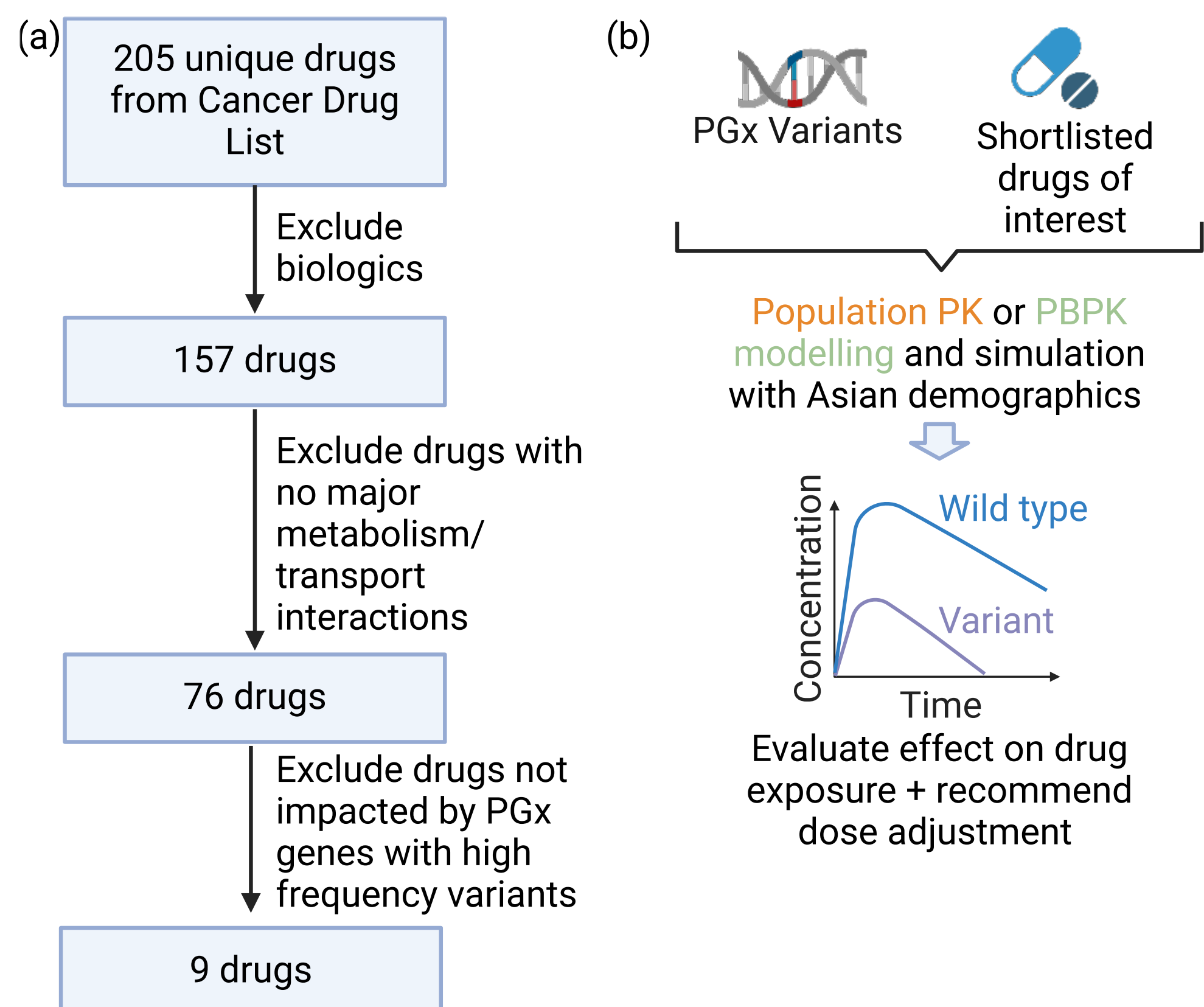
INTRODUCTION

No systematic methods for prioritizing drug-gene interactions of clinical importance currently exist for Asians



- Asian genomes are under characterized
- SG10K (a large scale whole genome sequencing) describes pharmacogenomic (PGx) polymorphisms that are enriched in Asia.¹
- Clear guidance for dose adjustments in Asians with PGx polymorphisms has yet to be developed. A framework for prioritizing drug-gene interactions to develop Asian specific guidance for drug dosing in the context of pharmacogenomics is thus needed.
- We focused on prioritizing chemotherapy drugs, the majority of which have a narrow therapeutic window, that were likely to be impacted by pharmacogenomic variants in the Singaporean population

METHODS



(a) A framework for prioritizing drug-gene interactions

- Essential chemotherapeutics were identified from the Cancer Drug List
- Information on drug-drug interactions was added to elucidate major metabolism/transport interactions.² PGx variants can similar alter these pathways.
- Additionally, the criteria for an important PGx gene in our population was set using a cut off of 10% or more of the population with PGx variants with significant predicted change in function.

(b) Evaluating drug-gene interaction impact

- Using drug-gene sets that were deemed important, we did a literature search for popPK models with both patient demographics and PGx variants as covariates.
- Simulations using Singaporean demographics were then carried out to evaluate the impact of PGx variants on drug exposure.
- A change in AUC >30% was considered to be significant, warranting a dose adjustment or change in therapy.
- For tamoxifen, a population PK model referenced from Mueller-Schoell, A. *et al* 2020 was used for simulation of both tamoxifen and its active metabolite endoxifen

RESULTS

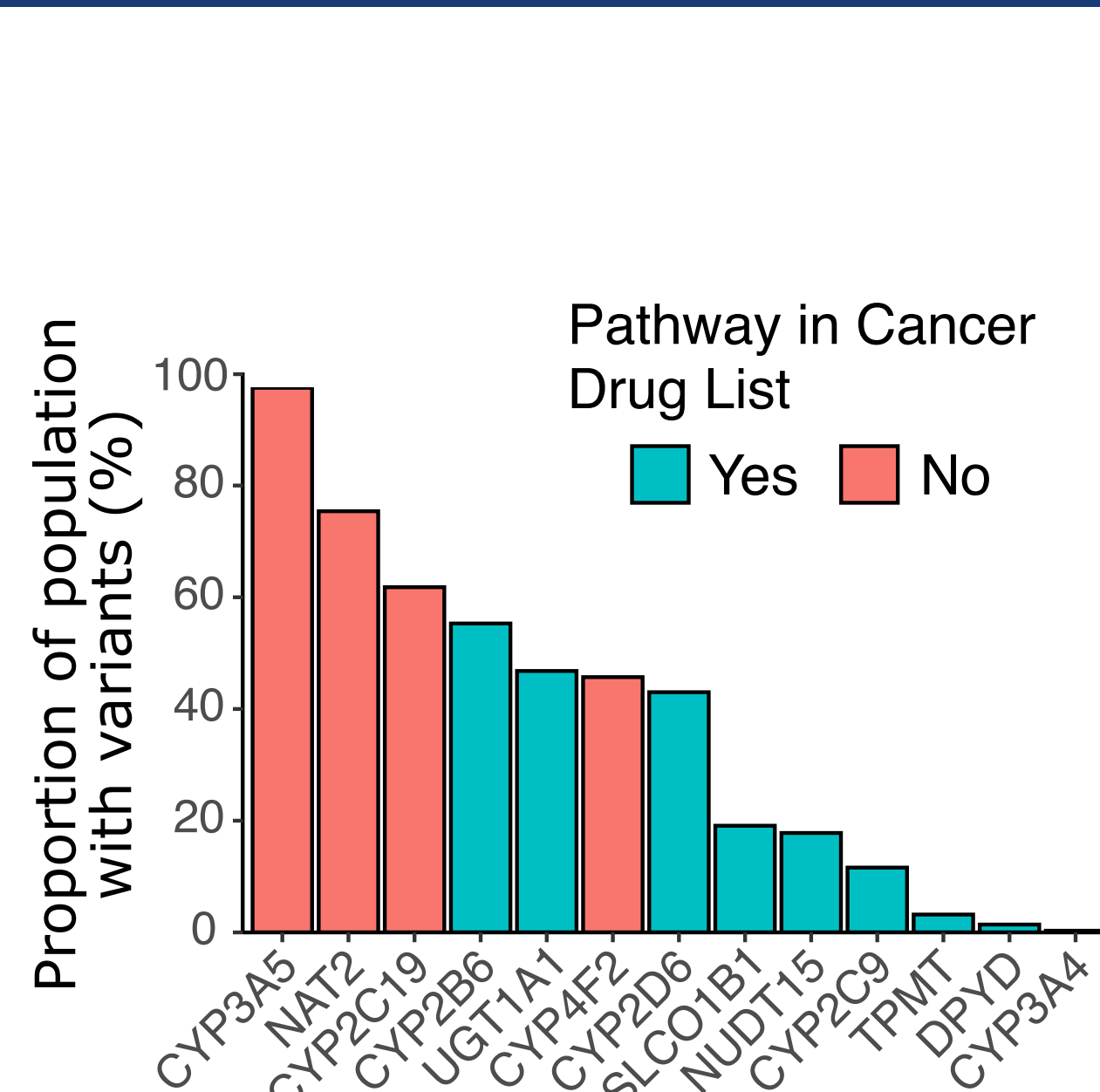


Figure 1. SG10K highlights PGx genes with frequently occurring variants implicated in chemotherapy drug clearance.

- CYP2C19, CYP2B6, UGT1A1, CYP2D6, SLC01B1 and NUDT15 had >10% of the population with variants and were also found to impact chemotherapy drug clearance.

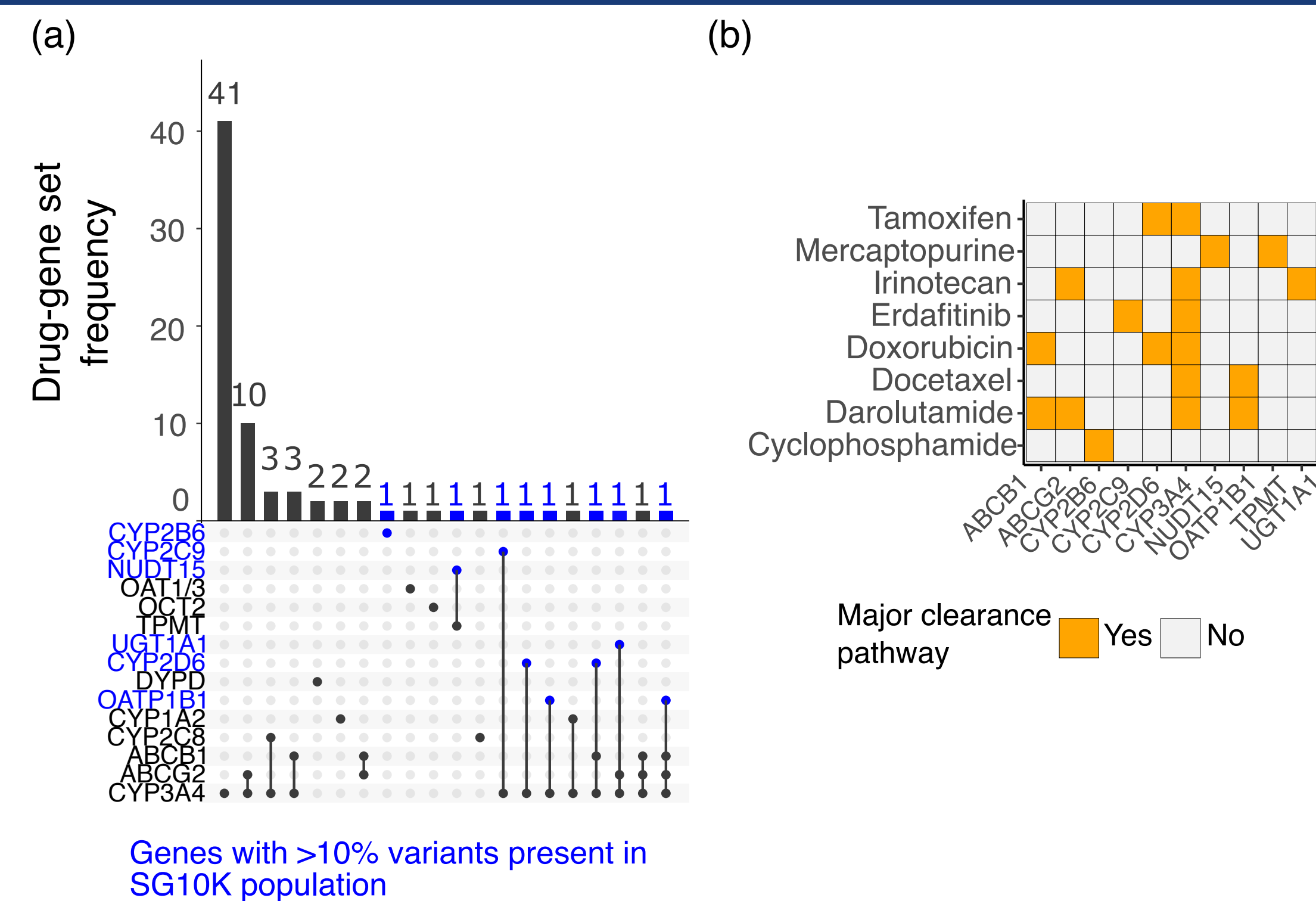
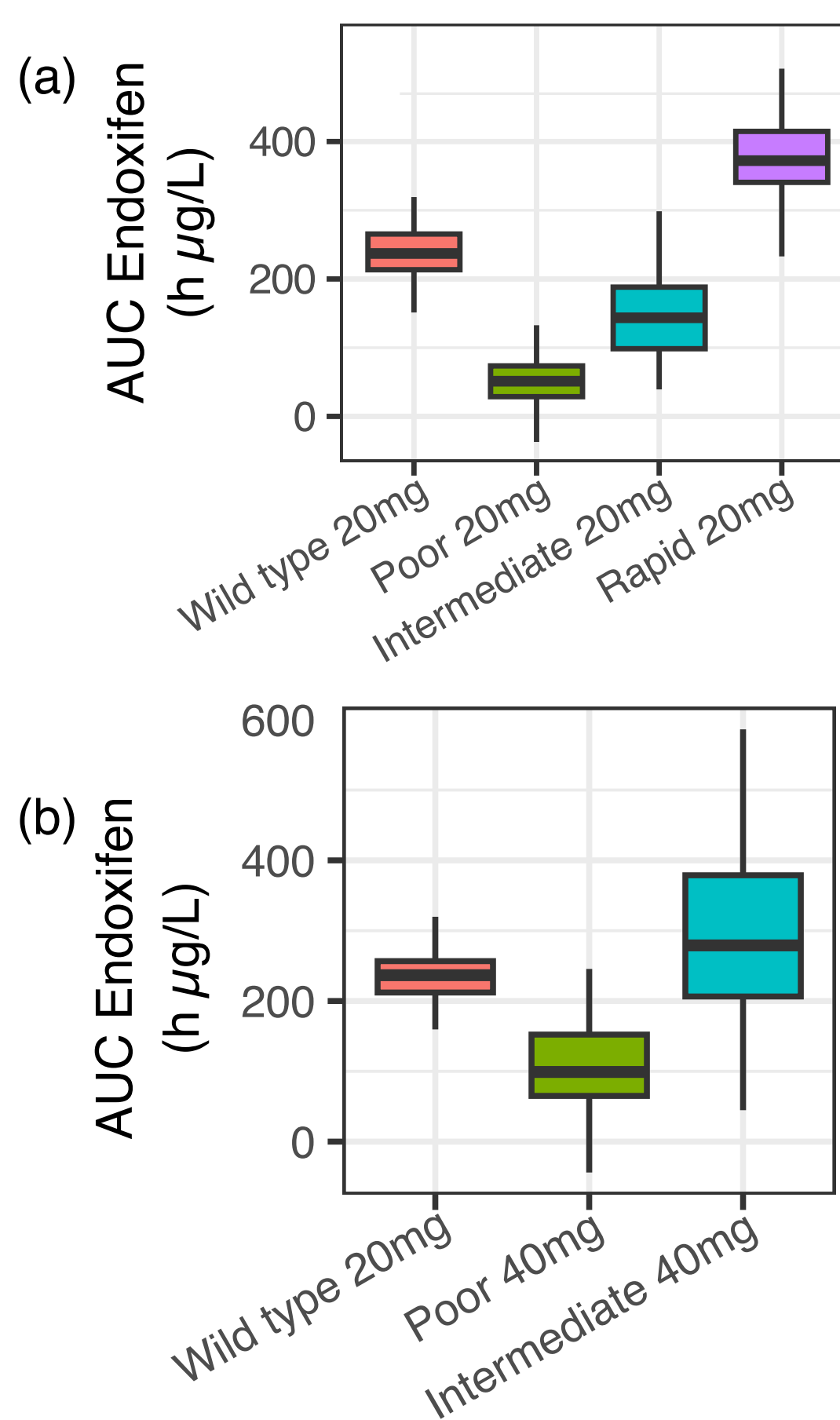


Figure 2. Chemotherapy drug-gene sets present in SG10K (a) Frequency of drug gene set interactions (b) Drug-gene sets identified to be of clinical importance and breakdown by major clearance pathways

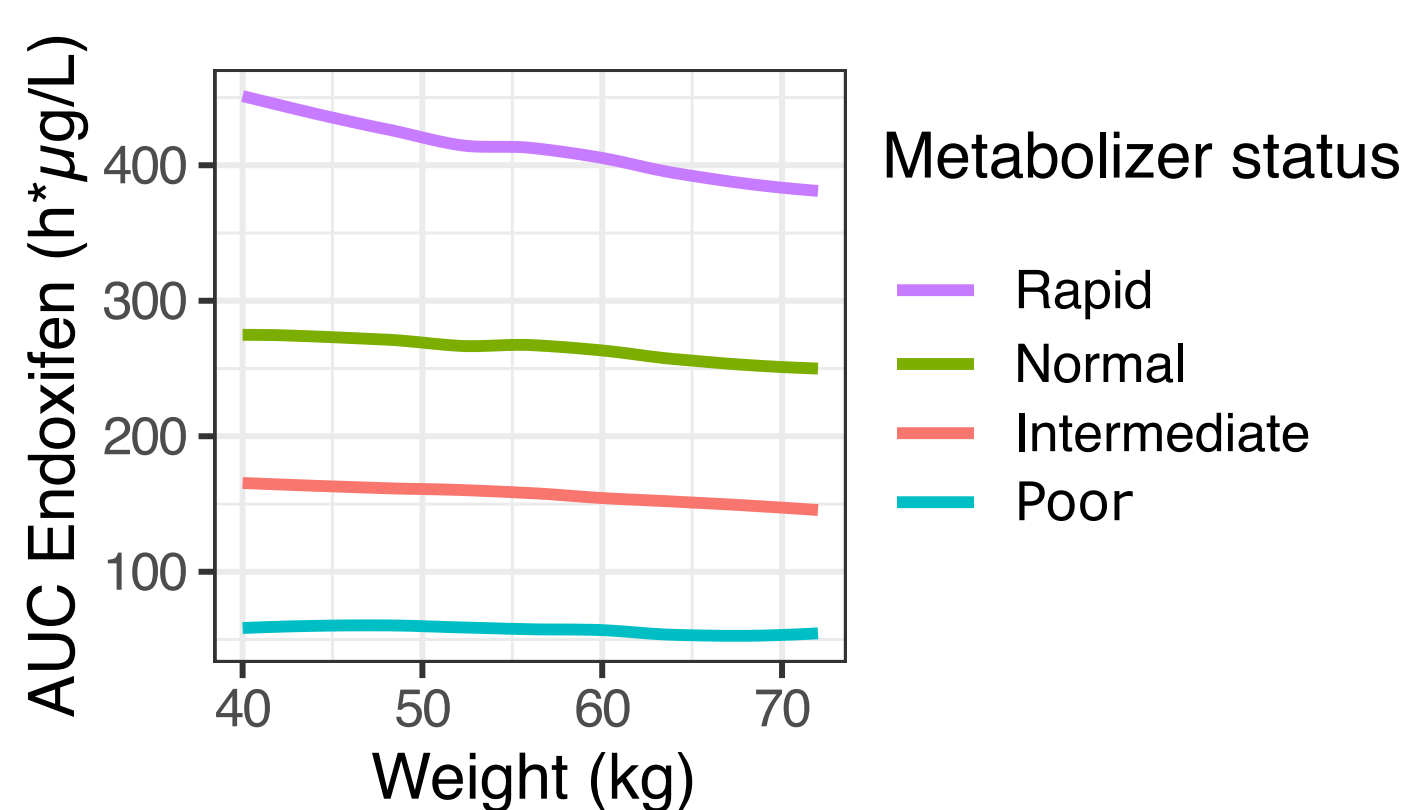
- Among genes with high amounts of PGx variants, 8 unique drug-gene sets were identified
- Only cyclophosphamide was impacted by a single pathway
- With tamoxifen, CYP3A4 did not have a high variant proportion. Hence a popPK model with just CYP2D6 variants was sufficient.

Figure 3. Simulation of endoxifen drug exposure population pharmacokinetics using SG10K demographics (a) using regular flat dose of tamoxifen 20mg (b) using adjusted dosing of 40mg in poor and intermediate metabolizers



- Tamoxifen is a prodrug with active metabolite endoxifen
- CYP2D6 poor and intermediate metabolizers have a decrease in median endoxifen AUC by 4.62 and 1.65 fold respectively, indicating tamoxifen-CYP2D6 was an important drug-gene pair
- 37.8% of the SG10K population are reported to be intermediate metabolizers
- A dose adjustment in poor and intermediate metabolizers of 40mg show intermediate metabolizers can achieve similar AUC to wild type metabolizers, while poor metabolizers should have a change in therapy

Figure 4. Simulated median endoxifen AUC by weight at median age of 55 years old⁴



- CYP2D6 metabolizer status impacted endoxifen AUC more significantly than weight.
- Weight marginally changed endoxifen AUC within the average weight range of Singaporean females 56.8kg +/- 7.2kg (sd).⁵
- This suggests that despite smaller Asian body build, we do not need to adjust for body weight for tamoxifen.

CONCLUSION

- Using a list of 205 chemotherapy drugs, their metabolizer-transporter interactions, and variant frequency in SG10K, we have identified 8 drug-gene sets of potential clinical importance.
- In our example study using tamoxifen, we show that an increased dose of 40mg can be beneficial for intermediate CYP2D6 metabolizers which is present in 37.8% of the population.
- This framework describes a systematic method of evaluating clinically important drug-gene interactions, and highlights the utility of using population PK models to evaluate these interactions and recommend appropriate dose adjustments, before conducting actual clinical studies.

1) Chan, S.H., Bylstra, Y., Teo, J.X. et al. Analysis of clinically relevant variants from ancestrally diverse Asian genomes. Nat Commun 13, 6694 (2022). <https://doi.org/10.1038/s41467-022-34116-9>

2) UpToDate Lexidrug. UpToDate Lexidrug app. UpToDate Inc. Version 8.2.0. Accessed March 28, 2024.

3) Mueller-Schoell, A. et al. Obesity Alters Endoxifen Plasma Levels in Young Breast Cancer Patients: A Pharmacometric Simulation Approach. Clin. Pharmacol. Ther. 108, 661–670 (2020).

4) Ho P.J., Yeoh Y.S., Miao H., Lim S.H., Tan E.Y., Tan B.K.T., Tan V.K.M., Tan S.M., Yong W.S., Wong F.Y., Madhukumar P., Chan C.W., Iau P.T.C., Lee S.C., Putti T., Buhari S.A., Lee J.Y., Lim G.H., Woo E., Yan Z., Chan P.M.Y., Chen J.J.C., Lu S.Q., Dent R., Lee W.P., Mok C.W., Seah J.C.M., Sim X., van Dam R.M., Chia K.S., Li J., Hartman M. Cohort profile: The Singapore Breast Cancer Cohort (SGBCC), a multi-center breast cancer cohort for evaluation of phenotypic risk factors and genetic markers. PLoS One. 2021 Apr 26;16(4):e0250102. doi: 10.1371/journal.pone.0250102. PMID: 33901219; PMCID: PMC8075208.

5) Lee, Y.C., Chen, C.H., Khoo, L.P. (2018). A Pilot Study of Gender Differences on Anthropometric Measurements in Singapore Population. In: Goonetilleke, R., Karwowski, W. (eds) Advances in Physical Ergonomics and Human Factors. AHFE 2017. Advances in Intelligent Systems and Computing, vol 602. Springer, Cham. https://doi.org/10.1007/978-3-319-60825-9_5