

Return of Clinically Actionable Pharmacogenetic Results From Molecular Tumor Board DNA Sequencing Data: Workflow and Estimated Costs

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Pharmacogenetic testing can prevent severe toxicities from several oncology drug therapies; it also has the potential to improve the outcomes from supportive care drugs. Paired tumor and germline sequencing is increasingly common in oncology practice; these include sequencing of pharmacogenes, but the germline pharmacogenetic variants are rarely included in the clinical reports, despite many being clinically actionable. We established an informatics workflow to evaluate the clinical sequencing results for pharmacogenetic variants. We used the Aldy computational tool, which we have previously shown to determine the variant alleles in 14 pharmacogenes in clinical sequencing data with >99% accuracy, to identify pharmacogenetic variants in the clinical whole exome sequencing from our molecular tumor board. Patients with genetic variants that are clinically actionable for their individual therapy programs, including both treatment and supportive care, are referred to a clinical pharmacogenetics testing laboratory for confirmation. Through an evaluation of our weekly informatics workflow, we determined it took approximately 3.25 hours to complete the analysis of the sequencing data from approximately 20 patients. Using a United States pharmacist's median salary, we estimated the incremental added cost of the process to be only ~\$15 per patient. This adds only a minor increase to the patient's cost of testing and has the potential to improve the safety and efficacy of their treatment.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Molecular tumor boards (MTBs) with DNA sequencing have become an essential part of state-of-the-art oncology care that can improve clinical outcomes. Germline pharmacogenetic (PGx) information can provide clinical opportunities to improve the safety and effectiveness of cancer treatments.

WHAT QUESTION DID THIS STUDY ADDRESS?

What tasks are required to extract clinically actionable PGx variants from the whole genome or exome sequencing data obtained by MTBs and what is the time and cost generally needed to obtain the PGx results from the DNA sequencing data?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This study estimated the real-world costs and time required to identify PGx variants in the DNA sequencing conducted in

the MTBs. Additionally, to support the implementation of PGx allele determination, we have described the necessary steps used to extract the germline PGx alleles in our MTB.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

By describing an exemplary workflow used to extract the germline PGx alleles from our MTB DNA sequencing data, and the relatively low estimated assay costs, these results should help other MTBs add value to their MTBs by implementing the extraction of clinically actionable PGx alleles from the routine DNA sequencing data. Ultimately, this should help improve the safety and efficacy of drug therapies used for both cancer treatment and supportive care.

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Molecular tumor boards (MTBs) are commonly used among many healthcare systems. They include multidisciplinary teams that interpret and discuss the genetic and molecular information of tumors to optimize cancer treatment. Although most MTB discussions focus on the selection of anticancer medicines tailored to target the somatic mutations in the tumors,¹ germline sequencing from blood cells is increasingly also being utilized by MTBs to identify targetable variants specifically expressed in the somatic genome (i.e., germline subtraction) and to identify variants predicting increased risk of heritable cancers.¹ The germline sequencing data also covers pharmacogenetic (PGx) variants that can be accurately extracted from DNA sequencing data,^{2,3} but they are rarely reported on clinical reports from the sequencing vendors.

Nearly all individuals have at least one clinically actionable PGx variant.⁴ Furthermore, cancer patients commonly use many drugs either to treat their cancer or for supportive care, which creates a great opportunity to optimize drug regimens through pharmacogenetic testing.⁴ Since many drugs have published clinical implementation guidelines or warning information or prescription their drug labels, reporting these genetic variants from routine clinical sequencing would likely be clinically meaningful for patients.⁴ For example, the US Food and Drug Administration (FDA) lists PGx information in the labels of over 380 medicines as of July 2024.⁵ Moreover, consortium networks like the Clinical Pharmacogenetics Implementation Consortium (CPIC), the Dutch Pharmacogenetics Working Group, and the Canadian Pharmacogenomics Network for Drug Safety have published pharmacogenetic implementation guidelines for over 100 medicines.^{6–8} Thus, utilizing the PGx information in clinical sequencing has the potential to help healthcare providers personalize therapies that have the potential to enhance therapeutic effectiveness and reduce adverse drug events.⁹

Since DNA sequencing is already being done for the cancer diagnosis and therapy selection, we hypothesized that the additional costs of extracting the PGx variants would be minimal. However, little information is available on the real-world cost of extracting the PGx information. Thus, we conducted a thorough investigation into each detailed step of preparation and the time spent on each task, to analyze the overall time commitment and cost of extracting the PGx information from the DNA sequencing and reporting it to the providers at the tumor board. By documenting the time and resources required to extract and report this information,

we aim to provide a roadmap for other institutions looking to adopt similar practices. Ultimately, we expect this implementation will enhance the efficacy and safety of cancer and supportive care drug therapies, which should reduce the costs of their care and likely improve the overall patient outcomes and satisfaction.

MATERIALS AND METHODS

As part of the routine care for the patients seen in the MTB for our Health Precision Genomics Program, tissue and blood for sequencing are obtained at initial patient visits and sent to a commercial laboratory for sequencing. Binary alignment map (BAM) files are returned to the Precision Health Cloud database (LifeOmic, Inc., Indianapolis, IN). Patient consents for sequencing and treatment indicate that the results may provide information about other health problems; this includes PGx, such as drug metabolism.

The PGx analysis was run once per week for the patients being seen at that week's MTB. The workflow begins by identifying new patients each week who have paired germline and somatic whole exome sequencing. The PGx variants from those patients' germline BAM files are then extracted using Aldy^{2,3,10} run in a Jupyter Notebook in the LifeOmic Precision Health Cloud environment. Aldy returns the star allele haplotypes for *CYP2B6*, *CYP2C8*, *CYP2C9*, *CYP2C19*, *CYP2D6*, *CYP3A4*, *CYP3A5*, *CYP4F2*, *DPYD*, *G6PD*, *NUDT15*, *SLCO1B1*, *TPMT*, and *UGT1A1*. PGx experts evaluate the results for clinically actionable variants. Any potentially actionable results are reported at the MTB discussion. Since the bioinformatics analysis of the PGx results is not part of a CLIA (Clinical Laboratory Improvement Amendments) approved process, any variants that may impact clinical care are recommended to be confirmed by additional testing in a CLIA-certified laboratory.

The volume of cases analyzed by MTB was collected from our Precision Genomics Program from January 1, 2023, to December 31, 2023. Salaries for pharmacists in the United States were obtained from the Occupational Employment and Wage Statistics, 2023, by the US Bureau of Labor Statistics.¹¹ The times for the PGx processing were estimated by an external observer who timed the process and also had follow-up discussions with the PGx team.

RESULTS

An overview of the main steps to extract the PGx information from the sequencing data is illustrated in **Figure 1**. The entire hands-on processing time was approximately 3 hours and 15 minutes. (**Section S1**) Patients with sequencing data were identified from the standard clinical workflow from our Precision Genomics Program clinic. Names and medical record numbers were used to identify patient BAM sequencing files in the Precision Health

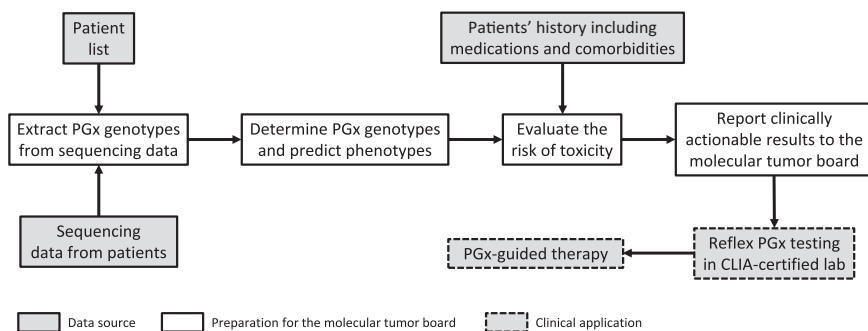


Figure 1 Overview of the workflow for extracting the pharmacogenomic information. Data sources include electronic health records and DNA sequencing data. Clinical applications are carried out by other physicians or staff following the discussion at the molecular tumor board. PGx, pharmacogenomics; CLIA, clinical laboratory improvement amendments.

Cloud, and those BAM files were downloaded into the Jupyter Notebook computing environment. Initial time to get the patient information and locate the sequencing data was approximately 1 hour; this step included identifying patient BAM files and initializing the Jupyter environment to download BAMs. Downloading BAM files took approximately 2 hours, depending on the number of patients; however, this did not require human labor. After the download was complete, the running time for Aldy to extract the PGx diplotypes was approximately 45 minutes. Although the number of patients varied by week, that variability had little impact on the hands-on time due to the automation. Assessment of the actionability of the PGx variants for all the patients took approximately 30 minutes. Participation in the weekly MTB, where the results were presented, took approximately 1 hour. Therefore, the overall time required for all preparation steps to extract PGx information for the weekly MTBs and report the clinically actionable results was approximately 3 hours and 15 minutes.

On average in 2023, there were approximately 20.6 patients per week analyzed by the tumor board. To estimate the costs related to these practices above, we assumed that all tasks were performed by a clinical pharmacist. The median annual base salary of a pharmacist in the United States in 2023 was \$134,665.¹¹ We added an additional 40% to account for benefits. In addition, the incremental computing cost (over the required infrastructure for receiving, storing, and accessing the BAM files) for extracting PGx diplotypes within the LifeOmic Precision Health Cloud environment was approximately \$20 per week. It was estimated based on the computing cost of the cloud computing services for using Jupyter Notebooks in the LifeOmic Precision Health Cloud environment. Collectively, the final estimated cost for extracting PGx information and reporting the clinically actionable results to the tumor board in the United States was \$15.27 on average per patient.

DISCUSSION

In this report, we describe our process for extracting PGx information from germline whole exome sequencing that is being done as part of our Precision Genomics Program. Since we don't control the entire informatics pipeline at the commercial sequencing laboratory, it should be emphasized that this does not replace CLIA-approved PGx reporting. Rather our program explores the value of testing patients with complicated medical profiles, who could benefit from more expensive PGx testing with its potential to reduce drug complications. With hands-on time of only 3–4 hours per week (~20 patients per week), our estimates of cost to screen for those patients likely to have actionable variants were approximately \$15 per patient. The pharmacist's time required could vary depending on the pharmacist's expertise in pharmacogenetics. These calculations are based on adding the PGx analysis superimposed on an existing informatics platform that stores and provides access to the BAM files and has the capability to run Aldy within the environment; it also requires that the germline sequencing BAM files from the sequencing lab are already received into the platform. Since we have shown that extracting these results from clinical sequencing is accurate,^{2,3} this process provides a strategy to focus the more expensive CLIA-based genotyping on those that are likely to carry clinically actionable

variants for their current medications. This practice is likely to enhance the cost-effectiveness of PGx testing, which is an established barrier to PGx adoption.^{12–14} According to our cost estimation, conducting confirmatory PGx testing for patients having clinically actionable variants would be more cost-effective than testing every patient (Sections S2 and S3). Our \$15 per patient calculations do not include the costs of the confirmatory testing of those actionable results, which would increase the cost primarily for those who have actionable variants and would benefit from the testing; however, the variable confirmatory testing is included in the supplementary materials. According to previous research, patients' willingness to pay for PGx testing is typically not more than \$100.¹⁵ This is lower than most clinical laboratories charge for the testing; however, the amount they are willing to pay may be different if they knew they were highly likely to carry variants that would impact their care. Further research would be needed to understand the patients' willingness to pay if they were given this additional information.

A previous investigation reported using research-grade genotyping array data from a biobank to trigger alerts for *DPYD* testing when patients were to receive a fluoropyrimidine therapy.¹⁶ Their oncologists avoided a normal dose of a fluoropyrimidine therapy in a patient who carried a *DPYD* variant that would likely have caused severe toxicity. Our genotype extraction procedure builds upon this practice to allow return of extracted PGx results for 14 PGx genes with clinically actionable recommendations in clinical practice guidelines or drug labels. In addition, incidental cancer risk genetic variants are occasionally identified in the sequencing of MTBs.^{17,18} Similar to our process, those are also confirmed by genetic testing in clinical laboratories. Thus, with the appropriate patient consent, this efficient and cost-effective method to identify patients likely to benefit from confirmatory clinical genotyping may mitigate hesitation to implement genetic testing in at least some patients. It is important to recognize that this should not replace clinical genetic testing; PGx genotypes extracted by Aldy, in the absence of a CLIA-approved workflow, should be considered preliminary, since false negatives would put patients at risk of extreme toxicities. So, this should be implemented in clinics where routine PGx testing is not yet implemented.

This research has several limitations. First, to run this analysis, a substantial amount of infrastructure must already be in place to receive, store, and have the computing environment to run the Aldy analysis. It also requires the agreements with the laboratory to send the BAM files. The cost estimate does not include the cost of setting up that infrastructure, the agreements, or transferring the sequencing files. Second, many clinics sequence DNA only from the tumors but not from matched normal tissues or cells. Since previous results from tumor sequencing have shown that pharmacogenes occasionally undergo genetic changes in the tumors,¹⁹ using sequencing data from tumors would need to be interpreted with caution. Third, if the weekly patient volume increases significantly, there would be a proportional increase in the hands-on time required for the PGx evaluation, the computation time, and the MTB discussion. Last, we did not account for the cost of educating the pharmacists and pharmacist salaries are likely to vary depending on geographic location, hospital size and type, and other

factors not considered in this report. The salaries used included all types of pharmacist positions in the United States; however, the impact of the variable salaries across disciplines on the local cost is likely to have little impact since the final cost for extracting PGx information is low. Since we provided the details of each of the inputs used in the calculation, others could use their local salary and benefit values to calculate their local costs. Future studies are needed to optimize the inclusion of this PGx data extraction into the CLIA-approved laboratory process and enhance the accuracy of the PGx data extracted from the tumor DNA sequencing.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

Steven M. Bray is employed at LifeOmic, Inc. All other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

H.K. and T.C.S. wrote the manuscript. H.K., T.B.S., J.T.C., W.O., S.M.B., E.M.T., M.T.T., C.A.F., B.P.S., T.S., and T.C.S. designed and performed the research, and analyzed the data.

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