

1 **CLINICAL OPPORTUNITIES FOR GERMLINE PHARMACOGENETICS AND**
2 **MANAGEMENT OF DRUG-DRUG INTERACTIONS IN PATIENTS WITH**
3 **ADVANCED SOLID CANCERS**

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47 **ABSTRACT**

48 **PURPOSE:** Precision medicine approaches, including germline pharmacogenetics (PGx) and
49 management of drug-drug interactions (DDIs), are likely to benefit advanced cancer patients who
50 are frequently prescribed multiple concomitant medications to treat cancer and associated
51 conditions. Our objective was to assess the potential opportunities for PGx and DDI management
52 within a cohort of adults with advanced cancer.

53 **PATIENTS AND METHODS:** Medication data were collected from the electronic health
54 records (EHRs) for 481 subjects since their first cancer diagnosis. All subjects were genotyped
55 for variants with clinically actionable recommendations in Clinical Pharmacogenetics
56 Implementation Consortium (CPIC) guidelines for 13 pharmacogenes. DDIs were defined as
57 concomitant prescription of strong inhibitors or inducers with sensitive substrates of the same
58 drug-metabolizing enzyme and were assessed for six major cytochrome P450 (CYP) enzymes.

59 **RESULTS:** Approximately 60% of subjects were prescribed at least one medication with CPIC
60 recommendations, and ~14% of subjects had an instance for actionable PGx, defined as
61 prescription of a drug in a subject with an actionable genotype. The overall subject-level
62 prevalence of DDIs and serious DDIs were 50.3% and 34.8%, respectively. Serious DDIs were
63 most common for CYP3A, CYP2D6, and CYP2C19, occurring in 24.9%, 16.8%, and 11.7% of
64 subjects, respectively. When assessing PGx and DDIs together, ~40% of subjects had at least one
65 opportunity for a precision medicine-based intervention and ~98% of subjects had an actionable
66 phenotype for at least one CYP enzyme.

67 **CONCLUSION:** Our findings demonstrate numerous clinical opportunities for germline PGx
68 and DDI management in adults with advanced cancer.

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70

71 INTRODUCTION

72 Pharmacogenetics (PGx) and management of drug-drug interactions (DDIs) are two
73 aspects of precision medicine that have the potential to optimize medication therapy in oncology
74 and other therapeutic disciplines. PGx-guided approaches have been shown to enhance drug
75 efficacy and safety, including results from prospective clinical trials that have demonstrated the
76 potential for PGx to improve drug safety.¹⁻³ Accordingly, the U.S. Food and Drug
77 Administration (FDA) currently includes PGx information within the labels for nearly 300
78 medications.⁴ Moreover, clinical practice guidelines that include PGx-guided recommendations
79 have been published by the Clinical Pharmacogenetics Implementation Consortium (CPIC) and
80 prominent discipline-specific professional organizations (e.g., the National Comprehensive
81 Cancer Network) for over 100 medications.^{5,6} Similarly, DDIs are known to contribute to
82 adverse drug events,^{7,8} and strategies to manage DDIs have been shown to improve patient
83 outcomes.⁹ Given their important clinical implications, DDIs constitute a major consideration
84 both during drug development and in clinical medicine, and recommendations to manage DDIs
85 are therefore included both in FDA drug development guidance to industry¹⁰ and in numerous
86 clinical practice guidelines.^{11,12}

87 The clinical utility of precision medicine is expected to be especially high for patients
88 with advanced cancer given that drug therapy is commonly used not only to treat cancer, but also
89 to manage both cancer treatment-related adverse events (e.g., nausea and vomiting) and
90 comorbid conditions associated with cancer (e.g., psychiatric conditions and pain syndromes).
91 As a result, polypharmacy, typically defined as the concomitant use of 5 or more drugs, is
92 exceedingly common in advanced cancer patients.¹³ Polypharmacy carries an increased risk for
93 DDIs,¹⁴ and, predictably, multiple investigations¹⁴ have identified serious DDIs in advanced
94 cancer that impact patient outcomes.¹⁵ PGx-guided approaches also offer the ability to optimize

95 therapy for numerous anticancer medications based on somatic and germline genetic biomarkers.
96 While molecular tumor boards have effectively harnessed somatic genome-guided treatment
97 approaches to improve patient outcomes,¹⁶ germline PGx biomarkers can enhance medication
98 safety with agents such as fluoropyrimidine and thiopurine chemotherapies.^{17,18} Additionally,
99 PGx-guided approaches have been shown to enhance both efficacy and safety of selective
100 serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), and opioid analgesics
101 that are often prescribed for comorbid conditions prevalent in cancer.¹⁹⁻²¹ Given these abundant
102 PGx opportunities in cancer patients, it has been suggested that preemptive testing for PGx
103 variants at first cancer diagnosis may be an effective clinical strategy to optimize patient
104 outcomes.²² Furthermore, recent advancements in bioinformatics technology have enhanced the
105 feasibility of PGx approaches in cancer through the creation of methods to extract PGx
106 information from existing germline sequencing data generated during the clinical workflow of
107 molecular tumor boards.^{23,24}

108 Although past studies have characterized opportunities for DDI management and PGx-
109 guided approaches in patients with advanced cancer, we are not aware of any work that has
110 simultaneously investigated both approaches to provide a comprehensive assessment of the
111 potential for precision medicine. Therefore, the objective of this study was to determine
112 composite opportunities for precision medicine, incorporating both PGx-guided and DDI
113 management strategies, within a cohort of adults with advanced solid cancers. By analyzing the
114 potential for PGx-guided interventions since each subject's respective date of first cancer
115 diagnosis, we also directly investigate the potential clinical utility of preemptively obtaining PGx
116 information when patients are first diagnosed with cancer.

117

118 **METHODS**

119 **Subject Enrollment and Eligibility**

120 This study was a retrospective electronic health record (EHR) review and prospective
121 genotyping of eligible patients with solid cancers at Indiana University Health in Indianapolis,
122 Indiana, USA. Subjects were eligible to participate in the study if they 1) had been seen in the
123 Indiana University Health Precision Genomics clinic and enrolled in the accompanying Indiana
124 University Total Cancer Care Protocol (part of the larger Oncology Research Information
125 Exchange Network-wide Total Cancer Care initiative [<https://www.oriencancer.org/>]) and 2)
126 agreed to submit a blood sample for genotyping. Subjects were enrolled into the study at clinic
127 visits from February 2015 to February 2018. This research protocol, as well as the parent Total
128 Cancer Care Protocol, were approved by Indiana University's Institutional Review Board. All
129 subjects provided written informed consent.

130

131 **Study Design and Data Collection**

132 The purpose of this study was to investigate potential opportunities for precision
133 medicine interventions, including PGx and management of DDIs, within a cohort of 481 adults
134 seen at our institutional precision oncology clinic and associated solid tumor board.
135 Demographic and clinical data, including medication prescriptions, were collected from the
136 EHRs of all institutions participating in the Indiana Health Information Exchange, a statewide
137 EHR data repository that includes 38 healthcare systems. Demographic data included age, sex,
138 and race. Clinical data included first oncologic diagnosis and all inpatient and outpatient
139 prescriptions. Genotyping for major pharmacogenes was performed at the College of American
140 Pathologists-accredited Indiana University Pharmacogenomics Laboratory using a laboratory-
141 developed assay based on the OpenArray[®] Platform (ThermoFisher; Waltham, MA). The genes

142 included on the genotyping platform, along with the number of variants tested for each gene,
143 were as follows: *CYP2B6* (2), *CYP2C19* (6), *CYP2C9* (6), *CYP2D6* (11, including copy number
144 targeting exon 9), *CYP3A4* (2), *CYP3A5* (3), *CYP4F2* (1), *DPYD* (2), *G6PD* (2), *IFNL3* (1),
145 *SLCO1B1* (2), *TPMT* (2), and *VKORC1* (1). Detailed genotyping methods are provided in the
146 **Supplemental Methods**, and a complete list of tested variants is shown in **Table S1**.

147

148 **Medication Inclusion into Precision Medicine Analyses**

149 The PGx analysis included 46 medications with published guidelines as of 09/25/20 by
150 CPIC (full list available in **Table S2** and online).⁵ Drugs were considered for inclusion in the
151 DDI analysis if they were listed as substrates, inhibitors, or inducers of *CYP2B6*, *CYP2C19*,
152 *CYP2C8*, *CYP2C9*, *CYP2D6*, or *CYP3A* within 1) the “Clinical substrates,” “Clinical
153 inhibitors,” or “Clinical inducers” tables of the current version (as of 09/25/20) of the U.S. Food
154 and Drug Administration’s “Drug Development and Drug Interactions: Table of Substrates,
155 Inhibitors and Inducers”²⁵ or 2) the Indiana University School of Medicine’s Drug Interactions
156 Flockhart Table™.²⁶ Medications contained in these resources were reviewed for inclusion into
157 DDI analyses based on the expertise of the study team. The final list of included substrates,
158 inhibitors, and inducers are displayed in **Table S2**. Medications included in the DDI analysis
159 between tyrosine kinase inhibitors (TKIs) and acid reducers are also listed in **Table S2**. Within
160 our analyses, acid reducers included antacids, histamine-2 receptor antagonists (H2RAs), proton
161 pump inhibitors (PPIs), and sucralfate.

162

163 **PGx Analyses**

164 Within our analyses, PGx recommendations for drug-gene pairs were classified by
165 genotype-predicted phenotype (e.g., metabolizer status) based on annotations from the
166 Pharmacogenomics Knowledge Base (PharmGKB). Phenotypes were considered actionable if
167 CPIC guidelines recommended a clinical action to manage the drug-gene interaction (see **File S1**
168 for actionability determinations). Specific clinical actions included adjustment of initial or
169 maintenance dosing, selection of alternative therapy, or performing additional tests to determine
170 enzyme activity.

171 Using these determinations, we considered genotype-predicted phenotypes as actionable
172 within our phenotype distribution (**Table 2**) if CPIC guidelines for one or more drug-gene pairs
173 recommended clinical action based on the specified phenotype. For our analyses characterizing
174 the prevalence of actionable PGx opportunities, we only included instances where a medication
175 was prescribed to a subject with a CPIC-defined actionable genotype-predicted phenotype for
176 that same medication (e.g., prescription of clopidogrel in a CYP2C19 poor metabolizer).

178 **DDI Analyses**

179 DDIs involving CYP enzymes were defined as concomitant prescription of an inhibitor or
180 inducer with a sensitive substrate of the same drug-metabolizing enzyme. To account for
181 temporal delays in CYP induction and de-induction following the onset and offset of CYP
182 inducers, the window for DDIs with co-administered CYP substrates was defined as starting 7
183 days after initiation of inducer therapy and lasting 7 days after termination of inducer therapy.
184 DDIs involving CYP enzymes were analyzed for CYP2B6, CYP2C19, CYP2C8, CYP2C9,
185 CYP2D6, and CYP3A for each patient from their date of first cancer diagnosis until the last date

186 of data collection (04/20/20). DDIs were also assessed for concomitant prescription of drug-drug
187 pairs that included TKIs and medications known to reduce gastrointestinal acidity.

188 Extracted medication data contained the date, time, and location (i.e., whether
189 administered in a medical setting, including outpatient clinics, or whether dispensed from a
190 pharmacy) for each prescription. The days supply for each prescription was conservatively
191 estimated using the following assumptions. For prescriptions administered in a medical setting,
192 the days supply was assumed to be one. For prescriptions dispensed from a pharmacy, the days
193 supply was assumed based on the shortest days supply for indications for which the drug is
194 typically prescribed (see **Table S3** for a complete list of assumed durations for all prescriptions
195 dispensed from a pharmacy). An exception to this method was made for prescriptions dispensed
196 from a pharmacy that were 1) dispensed for at least three consecutive regular intervals (e.g.,
197 every 30 days, every 90 days) and 2) written for medications that are commonly used as
198 maintenance therapy for chronic medical conditions (e.g., antihypertensives). For these
199 prescriptions, the patient was assumed to be taking the medication for the entire interval between
200 consecutive prescriptions.

201 Instances of autoinhibition and autoinduction (i.e., a medication altering its own
202 metabolism upon chronic administration) were not considered as DDIs in our analyses. In
203 addition, DDIs involving common chemotherapy regimens (e.g., prednisone and docetaxel) were
204 not included in our analyses. Instances of co-administration of multiple proton pump inhibitors
205 were also not considered as DDIs.

206 We defined “serious DDIs” as DDI pairs with sensitive substrate drugs that have one or
207 more of the following: 1) a narrow therapeutic index, 2) indications as cancer treatments, or 3) an
208 association with significant adverse drug reactions (see bolded drugs in **Table S2**).

209

210 **Composite Precision Medicine Analyses**

211 The prevalence of CYP inhibitor-mediated phenoconversion was assessed for CYP2B6,
212 CYP2C19, CYP2C9, CYP2D6, and CYP3A4. Within our analyses, we coded subjects as
213 positive for CYP inhibitor-mediated phenoconversion if they were (1) genotype-predicted
214 ultrarapid, rapid, normal, or intermediate metabolizers and (2) prescribed a relevant strong CYP
215 inhibitor at any time after first cancer diagnosis.

216

217 **Statistical Analyses**

218 Data for the PGx and DDI analyses were analyzed using descriptive statistics (counts and
219 percentages) using JMP Pro v.15.0.0.

220

221 **RESULTS**

222 **Subject Demographic, Clinical, and Medication Data**

223 Demographic and clinical characteristics of the 481 study subjects with advanced cancer
224 included are shown in **Table 1**. Our cohort was a median of 57 ± 16.6 (median \pm interquartile
225 range [IQR]) years old, and most subjects were white (87.9%) and female (53.2%). The most
226 common types of cancer at first diagnosis included breast (12.7%), pancreatic (10.8%), and
227 colorectal (9.6%). The median duration of follow-up, defined as the time between the date of
228 first cancer diagnosis and the date of last prescription, was 2.9 ± 4.9 (median \pm IQR) years.

229 Extracted medication data contained ≥ 1 prescription for 469 out of 481 (97.5%) subjects.
230 Filtering to include only prescriptions since each subject's respective date of first cancer
231 diagnosis yielded 158,188 unique prescriptions that were assessed within our precision medicine

232 analyses (schematic of filtering results shown in **Figure S1**). Since first cancer diagnosis, our
233 cohort had 1) a total of 7,074 unique prescriptions for medications contained within a CPIC
234 guideline (herein called “PGx medications”) and 2) a total of 22,642 unique prescriptions for
235 medications that were defined as inducers, inhibitors, or sensitive substrates of CYP2B6,
236 CYP2C19, CYP2C8, CYP2C9, CYP2D6, and/or CYP3A, acid reducers, or TKIs (herein called
237 “DDI medications”).

238

239 **PGx Analyses**

240 The distribution of genotype-predicted phenotypes within our cohort for all
241 pharmacogenes is displayed in **Table 2**. When defining actionable phenotypes as those with
242 clinically actionable recommendations within CPIC guidelines for at least one medication, the
243 rates of actionable phenotypes were highest for CYP2C19 (59.5%) and VKORC1 (52.4%) and
244 lowest for TPMT (7.3%), G6PD (1.5%), and DPYD (1.0%).

245 Of 469 analyzed subjects, 282 (60.1%) were prescribed at least one PGx medication.
246 These included a total of 1,045 unique PGx medications (i.e., prescription of a unique PGx
247 medication for a unique subject), with an average of 2.2 ± 2.4 (mean \pm standard deviation) PGx
248 medications/subject and a maximum of 12 PGx medications in one subject. When considering
249 both prescribed medications and genotype-predicted phenotypes, we identified a total of 81
250 unique opportunities for “actionable PGx,” defined as an instance where a PGx medication was
251 prescribed to a subject with an actionable phenotype based on CPIC recommendations. Instances
252 of actionable PGx occurred for 67 subjects (14.3%), with 56 subjects having instances of
253 actionable PGx involving 1 medication, 8 subjects having actionable PGx involving 2
254 medications, and 3 subjects having actionable PGx involving 3 medications.

255 The prevalence of instances of actionable PGx, when stratified by the drug-gene pairs
256 involved, are shown in **Table 3**. For PGx medications prescribed in at least five subjects, the
257 rates of actionable PGx were highest for warfarin (87.5%), amitriptyline (58.3%), and
258 clopidogrel (42.9%). Conversely, capecitabine, 5-fluorouracil, sertraline, and celecoxib had no
259 instances for actionable PGx. For warfarin, subjects had actionable PGx recommendations based
260 on *CYP2C9*, *CYP4F2*, and *VKORC1* genotype-based phenotypes in 20.8%, 58.3%, and 50.0% of
261 cases, respectively. For amitriptyline, subjects had actionable PGx recommendations based on
262 *CYP2C19* and *CYP2D6* genotype-based phenotypes in 16.7% and 50.0% of cases, respectively.

263

264 **DDI Analyses**

265 Of 469 analyzed subjects, the prevalence of ≥ 1 prescription for an inducer, inhibitor, or
266 substrate of any CYP enzyme was 49.0%, 58.0%, and 64.0%, respectively. **Figure S2** displays
267 the prevalence of subjects with prescriptions for inducers, inhibitors, and substrates across the six
268 enzyme systems that were assessed. Prescriptions for CYP inducers were most common for
269 *CYP2C19*, *CYP2C9*, and *CYP3A*, occurring in 49.0% of subjects. Prescriptions for inhibitors
270 were most common for *CYP2D6* (occurring in 53.3% of subjects), *CYP2C9* (35.0%), *CYP3A*
271 (33.9%), and *CYP2C19* (31.8%), while prescriptions for sensitive substrates were most common
272 for *CYP3A*, *CYP2D6*, and *CYP2C19* (prescribed in 60.3%, 59.9%, and 48.2% of subjects,
273 respectively).

274 When assessing concomitant prescription of both a relevant perpetrator (inducer or
275 inhibitor) and victim (sensitive substrate) drug, 236 subjects (50.3%) had a DDI affecting at least
276 one CYP enzyme system. Given the frequent use of corticosteroids to treat and manage
277 treatment-related complications for many types of cancer,²⁷ we also performed DDI analyses

278 excluding corticosteroids, which are potent inducers of CYP2C19, CYP2C9, and CYP3A; 225
279 subjects (48.0%) had a DDI affecting at least one major CYP enzyme when excluding
280 corticosteroids. As shown in **Table 4**, the prevalence of DDIs in our cohort was highest for
281 CYP2D6 (affecting 45.2% of subjects; average of 1.5 DDIs/subject), followed by CYP3A
282 (29.9%; 0.8 DDIs/subject), CYP2C19 (23.9%; 0.5 DDIs/subject), CYP2C9 (11.7%; 0.2
283 DDIs/subject), CYP2B6 (0.2%), and CYP2C8 (0%). When excluding corticosteroids, the
284 prevalence of DDIs for CYP2C19, CYP2C9, and CYP3A was reduced to 10.2%, 7.0%, and
285 20.3%, respectively (**Table 4**). The most common drug-drug pairs contained within observed
286 DDIs, stratified by enzyme, are shown in **Table S4**. The subject-level prevalence for serious
287 DDIs, which were classified by the substrates involved, was 34.8% for any CYP enzyme when
288 including corticosteroids and 29.4% when excluding corticosteroids (**Table 4**). Serious DDIs
289 were most common for CYP3A, occurring in 24.9% of subjects and including sensitive
290 substrates like fentanyl, midazolam, and tramadol. In contrast, serious DDIs were less common
291 for CYP2C19 (11.7% of subjects; sensitive substrates included escitalopram, sertraline, and
292 citalopram), CYP2C9 (4.7% of subject; substrates included warfarin, dronabinol, and phenytoin),
293 and CYP2D6 (16.8% of subject; substrates included tramadol, sertraline, and mirtazapine).
294 When adjusting the prevalence of CYP enzyme-mediated DDIs based on subject genotype (i.e.,
295 excluding DDIs involving inducer or inhibitor drugs in subjects who are genotype-predicted poor
296 metabolizers), the subject-level prevalence is as follows: CYP2B6: 0.2%; CYP2C19: 23.9%;
297 CYP2C8: 0%; CYP2C9: 11.7%; CYP2D6: 44.1%; and CYP3A: 29.6% (adjusted based on
298 *CYP3A4* genotype).

299 TKIs have emerged as first-line treatment options for a variety of cancers. However,
300 multiple investigations have described the potential for significant DDIs involving orally-

301 administered TKIs and acid reducing agents, including antacids, H2RAs, and PPIs, that reduce
302 TKI bioavailability and impact treatment outcomes.²⁸⁻³¹ Accordingly, we characterized the
303 prevalence of DDIs involving TKIs and acid reducers in our study population. Within our cohort,
304 68 subjects (14.5%) were prescribed at least one TKI, with pazopanib (prescribed in 17 subjects),
305 sunitinib (10), and crizotinib (9) being the most commonly prescribed. Of the 68 subjects
306 prescribed a TKI, 33 (48.5%) had a concomitant prescription of at least one acid reducer. Within
307 our population, the most common acid reducer classes involved in DDIs were PPIs (perpetrator
308 drug in 34 DDIs), followed by H2RAs (10) and antacids (6).

309

310 **Composite Precision Medicine Analyses**

311 To assess the prevalence of composite opportunities for precision medicine interventions,
312 we aggregated findings from our actionable PGx, serious CYP-mediated DDI, and acid reducer-
313 TKI DDI analyses at the subject level. As shown in **Figure 1**, 186 subjects (39.7%) had at least
314 one opportunity for a precision medicine intervention. 68 subjects (14.5%) had opportunities for
315 more than one type of precision medicine intervention, with 9 of these subjects (1.9%) having
316 opportunities for PGx and management of both CYP-mediated and acid reducer-TKI DDIs.

317 Finally, we assessed the prevalence of CYP inhibitor-mediated phenoconversion, the
318 process by which co-administration of a strong inhibitor functionally converts those with any
319 genotype to a poor metabolizer phenotype, for CYP2B6, CYP2C19, CYP2C9, CYP2D6, and
320 CYP3A4. As shown in **Figure 2**, CYP inhibitor-mediated phenoconversion enhanced the
321 number of subjects with actionable phenotypes for CYP2C19, CYP2C9, and CYP2D6, and
322 CYP3A4, increasing the prevalence from 59.5% to 72.8%, 33.3% to 55.9%, 44.7% to 76.3%,
323 and 8.9% to 38.9%, respectively. In contrast, CYP inhibitor-mediated phenoconversion only

324 slightly changed the number of actionable phenotypes for CYP2B6 (prevalence increased from
325 48.4% to 49.1%) due to the low prevalence of prescription of CYP2B6 inhibitors within our
326 cohort. When considering all five investigated CYPs together, nearly every subject in our cohort
327 (98.3%) had an actionable phenotype (either genotype-predicted or from CYP inhibitor-mediated
328 phenoconversion) for at least one CYP since their date of first cancer diagnosis. Also, 47
329 subjects (9.8%) had genotype-predicted or phenoconverted actionable phenotypes for all five
330 CYP enzymes.

331

332 **DISCUSSION**

333 In this investigation, we provide quantitative evidence to support the immense clinical
334 opportunities for precision medicine approaches, including germline PGx and management of
335 DDIs, in a cohort of patients with advanced cancer. Our findings indicate that ~14% of subjects
336 had opportunities for actionable PGx (i.e., prescription of a PGx medication to a subject with a
337 CPIC guideline-defined actionable genotype) and that ~35% and ~7% of subjects had a serious
338 DDI involving major CYP enzymes and acid reducers co-prescribed with TKIs, respectively.
339 When incorporating both PGx and DDIs, we found that ~40% of subjects had at least one
340 opportunity for a precision medicine-based intervention and nearly all subjects (~98%) had an
341 actionable phenotype (genetically-predicted or drug-induced) for ≥ 1 CYP enzyme. Based on our
342 findings, implementation of precision medicine approaches at first cancer diagnosis is likely to
343 provide clinical benefit to a significant proportion of patients. Although a limited number of
344 other studies have addressed similar topics, our investigation has significant methodological
345 advantages, including 1) a larger cohort (n=481), 2) a broader PGx analysis consisting of 13

346 CPIC-actionable pharmacogenes, and 3) utilization of a statewide data repository to enable more
347 comprehensive collection of medication data.

348 Previous investigations have demonstrated the potential clinical impact of PGx
349 approaches in patients with advanced cancer. Nichols, et al. catalogued medications in a cohort
350 of 193 patients with advanced cancer, demonstrating that 65% of patients were taking at least
351 one PGx medication (i.e., those with a CPIC guideline).³² Using population estimates of allele
352 frequencies, the authors predicted that 7.1% of patients in their cohort could benefit from at least
353 one PGx intervention involving medications associated with nine major pharmacogenes:
354 *CYP2C19, CYP2C9, CYP2D6, CYP3A5, CYP4F2, DPYD, HLA-B, SLCO1B1, VKORC1*.
355 Similarly, Hertz, et al. found that 2.6% of 115 adult and pediatric patients with cancer could have
356 benefitted from a PGx intervention involving substrates of their analyzed drug-metabolizing
357 enzymes, which included CYP2C19, DPYD, and TPMT.³³ An investigation by Kasi, et al. also
358 predicted abundant opportunities for PGx interventions within their cohort of 155 patients with
359 advanced cancer based on patient genotypes for major CYP450 enzymes, though they did not
360 specifically collect and analyze medication data.³⁴ Many of our findings are similar to those
361 reported in past investigations. For instance, our findings related to the prevalence of prescription
362 of PGx medications are remarkably similar to results from Nichols, et al. when considering both
363 prescription of any PGx medication (~60% in our analysis vs. 65% in their study) and
364 prescription of specific PGx drugs such as ondansetron, capecitabine, and simvastatin.³² Our
365 findings related to the distribution of actionable phenotypes are also consistent with those from
366 past investigations^{32,34} as well as those predicted from large analyses of population allele
367 frequencies.³⁵ In contrast, our finding for the prevalence of subjects with potential PGx
368 interventions (14.3%) is higher than those reported by Nichols, et al. (7.1%) or Hertz, et al.

369 (2.6%).^{32,33} These differences are likely attributable to the facts that we (1) investigated the
370 potential for PGx interventions across a wider array of pharmacogenes and (2) that we utilized a
371 statewide repository with prescription data from 38 health systems to enhance the richness of our
372 collected medication data.

373 Multiple investigations have also characterized the clinical potential of DDI management
374 strategies in adult patients with advanced cancer. A 2009 review by Riechelmann, et al.
375 summarized the prevalence of potential DDIs from six studies, finding rates between 27% and
376 72%.³⁶ The high variability they observed among studies is likely attributable to differences in
377 employed methodologies (e.g., utilizing patient-verified medication lists versus all drugs listed in
378 EHRs, focusing on all potential drug interactions versus only those involving cancer
379 medications). More recently, investigations within the U.S. and abroad have characterized the
380 prevalence of potential DDIs in cancer patients, finding rates of 40-78%.³⁷⁻⁴¹ Again, it appears
381 that observed differences in potential DDI prevalence are due to methodological differences
382 among the studies. For instance, we found that studies that included DDIs based on both
383 pharmacokinetic (i.e., concomitant administration of an inhibitor or inducer of a drug-
384 metabolizing enzyme along with a sensitive substrate of that enzyme) and pharmacodynamic
385 (i.e., concomitant administration of two or more drugs with the same adverse event profile)
386 mechanisms had higher rates of potential DDIs.^{38,39} Similarly, studies that utilized medication
387 lists taken from the EHR (rather than those verified by patients during medication reconciliation)
388 had higher potential DDI prevalence.^{38,39} The overall DDI prevalence of ~52% in our study falls
389 in the middle of those reported by past investigations. In terms of methodology, extracting
390 medication data from the EHR likely resulted in a higher DDI prevalence in our study relative to
391 those that used patient-verified medications. We attempted to control for this by utilizing

392 prescription dates to only identify potential DDIs when there was temporal overlap in the
393 prescription (and presumed coadministration) of perpetrator and victim drugs for the same CYP
394 enzyme. Relative to other studies, our DDI prevalence was likely more conservative based on
395 other elements in our methodology, including (1) that we excluded DDIs with pharmacodynamic
396 mechanisms and (2) that we excluded DDIs involving drugs commonly co-administered as
397 cancer treatment regimens (e.g., corticosteroids co-administered with docetaxel or vincristine).
398 Our rationale for excluding these DDIs was that, in the case of pharmacodynamic DDIs, co-
399 administration of drugs with similar adverse event profiles is often clinically indicated (e.g., dual
400 antiplatelet therapy) and, in the case of DDIs within established cancer regimens, treating
401 clinicians are familiar with these DDIs and have likely already determined a favorable risk-
402 benefit ratio for the patient before prescribing. Therefore, based on these methodological
403 elements, we believe our findings represent a conservative estimate of the prevalence of potential
404 DDIs in advanced cancer patients involving major CYP enzymes. Additionally, our study
405 expands on past investigations assessing potential DDI prevalence in a few significant ways.
406 First, our results stratified DDI prevalence by the CYP enzymes involved, which could aid
407 clinicians in selecting drugs with metabolic pathways less likely to be associated with DDIs.
408 Next, we specifically investigated the prevalence of DDIs for acid reducing agents and TKIs,
409 which has emerged as an important consideration in cancer precision medicine.⁴² Finally, we
410 performed both a composite subject-level analysis and CYP inhibitor-mediated phenoconversion
411 analysis to elucidate the net prevalence of precision medicine opportunities in our study cohort
412 that incorporate both PGx and DDI management approaches.

413 Our findings are impactful since they demonstrate the abundant clinical opportunities for
414 precision medicine approaches to optimize medication therapy in patients with advanced cancer.

415 Specifically, we found that ~60% of subjects in our cohort were prescribed at least one PGx
416 medication and that approximately 1 in 7 subjects had an opportunity for actionable PGx since
417 their date of first cancer diagnosis. These findings directly support the clinical utility of PGx
418 approaches in patients with cancer, including the suggestion of preemptive genotyping at first
419 cancer diagnosis.²² Advances in technology have also improved the feasibility of PGx
420 approaches by reducing the costs associated with obtaining genetic information and enabling
421 repurposing of genetic information obtained from molecular tumor boards.²⁴ In addition,
422 economic analyses have demonstrated cost savings due to toxicity sparing for both *DPYD* and
423 *TPMT* testing.^{43,44} As a result, there is clinical momentum for standardized testing of PGx
424 markers associated with fluoropyrimidine and thiopurine chemotherapies.^{45,46} Our findings also
425 corroborate those from other studies^{32,34} in identifying significant opportunities for PGx to
426 optimize supportive care therapies in patients with cancer, including SSRIs, TCAs, opioids, and
427 commonly used antiemetics (e.g., ondansetron), based on CPIC guidelines.^{19-21,47}

428 Related to the clinical opportunities for DDI management strategies, we found that
429 slightly over half of our study subjects had a DDI affecting at least one major CYP enzyme since
430 first cancer diagnosis. This finding is important given that DDIs have been associated with poor
431 clinical outcomes and increased adverse drug events in cancer patients. For instance, CYP-
432 mediated DDIs have been shown to increase the rates of adverse events attributable to both
433 cancer therapies (e.g., increased paclitaxel-induced peripheral neuropathy during co-treatment
434 with clopidogrel)⁴⁸ and concomitant medications (e.g., increased warfarin-induced bleeding
435 during co-treatment with capecitabine)⁴⁹ in patients with cancer. Additionally, several studies
436 have investigated the potential for DDIs between acid reducing agents and TKIs, demonstrating
437 reduced progression-free and overall survival during concomitant therapy attributed to reduced

438 TKI systemic absorption.²⁸⁻³⁰ Our findings support the potential for clinically significant DDIs
439 between acid reducers and TKIs since we observed that these DDIs occurred in nearly half of
440 subjects that were prescribed a TKI. However, it is possible that the providers told the patient to
441 discontinue the acid reducers while taking the TKI's. Nonetheless, our findings support the
442 clinical potential of DDI management strategies, which have been shown to improve outcomes in
443 other populations,⁹ in patients with advanced cancer. Finally, our work serves as one of the first
444 investigations to assess the prevalence of potential drug-drug-gene interactions (DDGIs) (i.e.,
445 CYP inhibitor-mediated phenoconversion) within a clinical cohort. While the strategies to
446 manage DDGIs borrow from both PGx and DDI management approaches, consideration of
447 DDGIs may provide critical information that modifies the risk of adverse drug events predicted
448 from consideration of either approach in isolation.⁵⁰ As demonstrated by our composite study
449 findings that ~40% of subjects had at least one opportunity for precision medicine intervention
450 and ~98% of subjects had an actionable phenotype for ≥ 1 CYP enzymes, PGx information and
451 concomitant drug lists should be used in tandem to most accurately inform approaches to
452 optimize medication therapy. Given the complexities of DDGIs, including concepts like
453 phenoconversion and interplay of multiple drug biotransformation pathways, expert guidance
454 that includes perspectives from both clinical pharmacologists and clinicians is needed to inform
455 actionable clinical management strategies.

456 We acknowledge several limitations of our study. First, our extracted medication data did
457 not include a way to conclusively ascertain days supply in order to assess temporal overlap
458 between perpetrator and victim drugs within our DDI analyses. To compensate for this
459 limitation, we used conservative methods in our DDI analyses to estimate days supply for each
460 prescription, as described in the methods. While this limitation may have influenced our findings

461 related to the prevalence of DDIs, it did not impact results from our PGx analyses. Our extracted
462 medication data also did not consistently contain information about the medication dose. As a
463 result, our analysis may have overestimated the prevalence of instances for actionable PGx with
464 amitriptyline since current CPIC guidelines do not recommend clinical action at daily doses
465 under 50 mg.¹⁹ Also, our panel-based genotyping method only tested for relatively common
466 functional variants in the assessed genes within our primary ethnic and racial populations,
467 potentially excluding rare functional variants that alter drug response. While we do not expect
468 that this approach significantly impacted our findings, it is important to note that utilizing panel-
469 based genotyping (as opposed to a more complete approach like whole genome sequencing) may
470 have caused us to underestimate the actual clinical opportunities for actionable PGx in our
471 cohort. Additionally, advances in knowledge since study initiation limited our ability to assess
472 variants with newly established relevance to pharmacotherapy (e.g., HapB3 in *DPYD*). Our
473 genotyping panel also did not assess every pharmacogene included within a CPIC guideline.
474 However, the pharmacogenes covered in our panel serve as the genetic basis for over 80% of the
475 PGx recommendations contained within current CPIC guidelines.⁵

476 In conclusion, our work provides quantitative evidence of the vast clinical opportunities
477 for precision medicine approaches in patients with advanced cancer, demonstrating the clinical
478 utility of both germline PGx and DDI management strategies. Given their established clinical
479 benefits and the abundant opportunities for their use demonstrated by our results, precision
480 medicine approaches are likely to improve medication outcomes in cancer patients and may
481 provide clinical benefit if incorporated into the workflow of molecular tumor boards. In order to
482 facilitate widespread adoption of precision medicine approaches in this high-value patient
483 population, future research is needed to (1) prospectively demonstrate the clinical benefit of

484 precision medicine approaches on patient outcomes and to (2) identify effective strategies for
485 clinical implementation of precision medicine approaches.

486

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619 **FIGURE LEGENDS**

620 Figure 1. Subject-level prevalence for composite precision medicine opportunities, including
621 actionable PGx, management of serious CYP-mediated DDIs, and management of DDIs
622 including acid reducers and TKIs.

623
624 Figure 2. Subject-level prevalence of clinically actionable phenotypes for major CYP enzymes
625 based on genotype and due to CYP inhibitor-mediated phenoconversion.

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642 **TABLES**

643 **Table 1. Demographic and clinical characteristics of study cohort with advanced cancer.**

Variable	Value in Full Cohort (n=481)
Age in years at first cancer diagnosis (median [IQR])	57.4 (16.6)
Sex_(Count [Percent])	
Female	256 (53.2%)
Male	225 (46.8%)
Race (Count [Percent])	
White	423 (87.9%)
Black	38 (7.9%)
Asian	8 (1.7%)
Other*	3 (0.4%)
Unknown	9 (1.9%)
Cancer type at first diagnosis (Count [Percent])	
Breast	61 (12.7%)
Pancreatic	52 (10.8%)
Colorectal	46 (9.6%)
Prostate	40 (8.3%)
Soft-tissue sarcoma	36 (7.5%)
Ovarian	26 (5.4%)
Non-small cell lung	23 (4.8%)
Renal	18 (3.7%)
Thymic	13 (2.7%)
Cholangiocarcinoma	12 (2.5%)
Head and neck	11 (2.3%)
Bladder	10 (2.1%)
Unknown primary	13 (2.7%)
Duration of follow-up in years ⁺ (median [IQR])	2.9 (4.9)

644 *One individual who reported a race of “other” reported Hispanic ethnicity.

645 ⁺Defined as the time elapsed between the date of first cancer diagnosis and date of most recent
646 prescription

Table 2. Distribution of genotype-predicted phenotypes within study cohort for major pharmacogenes.

Gene	Ultrarapid Metabolizer	Normal Metabolizer	Intermediate Metabolizer	Poor Metabolizer	Indeterminate	Actionable
<i>CYP2B6</i>		248 (51.6%)	199 (41.4%)	34 (7.1%)		233 (48.4%)
<i>CYP2C19</i>	153 (31.8%)*	189 (39.3%)	124 (25.8%)	9 (1.9%)	6 (1.2%)	286 (59.5%)
<i>CYP2C9</i>		321 (66.7%)	146 (30.4%)	14 (2.9%)		160 (33.3%)
<i>CYP2D6</i>	9 (1.9%)	254 (52.8%)	182 (37.8%)	24 (5.0%)	12 (2.5%)	215 (44.7%)
<i>CYP3A4</i>		437 (90.9%)	41 (8.5%)	2 (0.4%)	1 (0.2%)	43 (8.9%)[‡]
<i>CYP3A5</i>		17 (3.5%)	71 (14.8%)	391 (81.3%)	2 (0.4%)	88 (18.3%)
<i>CYP4F2</i>		265 (55.1%)	175 (36.4%)	41 (8.5%)		216 (44.9%)
<i>DPYD</i>		476 (99.0%)	5 (1.0%)	0 (0%)		5 (1.0%)
<i>G6PD</i> ⁺		474 (98.5%)	4 (0.8%)	3 (0.6%)		7 (1.5%)
<i>IFNL3 (IL28B)</i> ⁺		204 (42.4%)	220 (45.7%)	57 (11.9%)		0 (0%)
<i>SLCO1B1</i> ⁺		333 (69.2%)	107 (22.2%)	11 (2.3%)	30 (6.2%)	118 (24.5%)
<i>TPMT</i>		440 (91.5%)	35 (7.3%)	0 (0%)	6 (1.2%)	35 (7.3%)
<i>VKORC1</i> ⁺		229 (47.6%)	199 (41.4%)	53 (11.0%)		252 (52.4%)

*For CYP2C19, count in ultrarapid metabolizer column includes counts of both ultrarapid metabolizers (n=20) and rapid metabolizers (n=133).

⁺For designated genes, “normal metabolizer,” “intermediate metabolizer,” and “poor metabolizer” designations refer to subjects who are non-carriers, heterozygous, and homozygous for CPIC-defined actionable variants, respectively.

[‡]While CPIC does not make *CYP3A4* genetic-guided recommendations for any drugs, we classify subjects with one or two copies of the *CYP3A4**22 loss-of-function allele as intermediate and poor metabolizers, respectively, and consider these phenotypes to be actionable since they are used at our institution to guide tacrolimus dosing in *CYP3A5* non-expressers.

Table 3. Prevalence of PGx medications prescribed in subjects with clinically actionable genotype-predicted phenotypes based on CPIC recommendations.

Drug-Gene Pair	# Prescribed Drug	% with Actionable PGx
Ondansetron- <i>CYP2D6</i>	256	0.8%
Pantoprazole- <i>CYP2C19</i>	171	4.7%
Omeprazole- <i>CYP2C19</i>	99	2.0%
Ibuprofen- <i>CYP2C9</i>	93	5.4%
Tramadol- <i>CYP2D6</i>	81	6.2%
Capecitabine- <i>DPYD</i>	62	0%
5-Fluorouracil- <i>DPYD</i>	40	0%
Sertraline- <i>CYP2C19</i>	28	0%
Escitalopram- <i>CYP2C19</i>	25	12.0%
Lansoprazole- <i>CYP2C19</i>	24	4.2%
Warfarin- <i>CYP2C9/CYP4F2/VKORC1</i>	24	87.5%
Citalopram- <i>CYP2C19</i>	21	23.8%
Simvastatin- <i>SLCO1B1</i>	21	23.8%
Meloxicam- <i>CYP2C9</i>	16	12.5%
Celecoxib- <i>CYP2C9</i>	15	0%
Amitriptyline- <i>CYP2C19/CYP2D6</i>	12	58.3%
Nortriptyline- <i>CYP2D6</i>	9	11.1%
Dexlansoprazole- <i>CYP2C19</i>	8	12.5%
Clopidogrel- <i>CYP2C19</i>	7	42.9%
Codeine- <i>CYP2D6</i>	7	14.3%
Paroxetine- <i>CYP2D6</i>	6	16.7%
Tamoxifen- <i>CYP2D6</i>	6	33.3%
Doxepin- <i>CYP2C19/CYP2D6</i>	3	100%
Voriconazole- <i>CYP2C19</i>	3	66.7%
Rasburicase- <i>G6PD</i>	2	0%
Atomoxetine- <i>CYP2D6</i>	1	0%
Azathioprine- <i>TPMT</i>	1	0%
Imipramine- <i>CYP2C19/CYP2D6</i>	1	100%
Phenytoin- <i>CYP2C9</i>	1	0%
Ribavirin- <i>IFNL3</i>	1	0%
Tacrolimus- <i>CYP3A5</i>	1	0%
Total	1045	

The “number prescribed drug” indicates the number of subjects within our cohort that were prescribed the corresponding drug. The “percent with actionable PGx,” which was calculated at the subject-level, indicates the percent of subjects prescribed the corresponding drug that had genotypes for which current CPIC guidelines recommend actionable clinical management strategies.

Table 4. Number and prevalence of unique DDIs (i.e., unique co-prescription of a relevant drug-drug pair in a unique subject) by enzyme involved in n=469 subjects prescribed ≥ 1 medication, including (left) and excluding (right) DDIs involving corticosteroids.

Enzyme	DDIs Including Corticosteroids				DDIs Excluding Corticosteroids			
	Total DDIs	DDIs/Subject (Mean)	DDI Prevalence (%)	Serious DDI Prevalence (%)	Total DDIs	DDIs/Subject (Mean)	DDI Prevalence (%)	Serious DDI Prevalence (%)
CYP2B6	1	0.00	0.2%	0.2%	1	0.00	0.2%	0.2%
CYP2C19	237	0.51	23.9%	11.7%	89	0.19	10.2%	5.8%
CYP2C8	0	0	0%	0%	0	0	0%	0%
CYP2C9	76	0.16	11.7%	4.7%	39	0.08	7.0%	2.3%
CYP2D6	695	1.48	45.2%	16.8%	695	1.48	45.2%	16.8%
CYP3A	392	0.84	29.9%	24.9%	217	0.46	20.3%	18.6%
Any DDI	1401	2.99	50.3%	34.8%	1041	2.22	48.0%	29.4%

Note: All DDI prevalence calculations are at the subject level.

FIGURES

Figure 1.

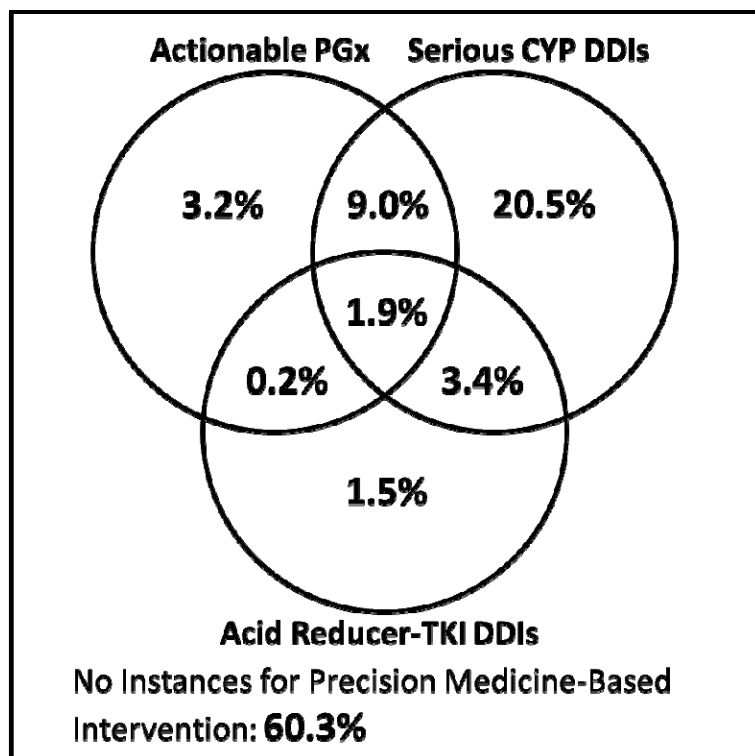


Figure 2.

