Integrating Somatic and Germline Pharmacogenomics for Therapeutic Decisions in Precision Oncology

Vai S. Pathak, MS[1,2]; Courtney E. Hershberger, PhD[1,2]; Suneel Kamath, MD[3]; Porscha Johnson Williams, PharmD[4]; Terence D. Rhodes, MD, PhD[5]; Howard L. McLeod, PharmD[6]; and Daniel M. Rotroff, PhD[1,2,7]

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ABSTRACT

PURPOSE Clinical genomic profiling of tumors identifies therapeutic targets, while germline pharmacogenomics (PGx) guides drug dosing and toxicity avoidance. However, the combined clinical landscape of both somatic and germline actionable variants across cancers has not been comprehensively defined.

METHODS Tumor and matched germline whole-exome sequencing data were analyzed for 10,302 patients in The Cancer Genome Atlas. Somatic mutations with therapeutic relevance were mapped to US Food and Drug Administration (FDA)–approved targeted drugs using the Oncology Knowledge Base database (levels 1-4). Germline PGx variants were identified using PyPGx and cross-referenced with drug-gene interactions in PharmGKB (levels of clinical annotation 1-2). This enabled construction of an integrated germline-somatic PGx profile per patient.

RESULTS All 10,302 patients (100%) harbored at least one actionable germline PGx variant (median = 3; range = 1-9), including 7,520 (73%) with variants relevant to chemotherapy toxicity or supportive care medications (*DPYD*, *UGT1A1*, *CYP2C9*, and *CYP2C19*). Somatic profiling revealed 4,312 patients (42%) with at least one actionable mutation matched to an FDA-approved targeted therapy (eg, *PIK3CA*, *KRAS*). Across the cohort, 5,275 (51%) patients had more actionable germline variants than somatic mutations, whereas 1,988 (19%) had more actionable somatic mutations.

CONCLUSION Integrating germline PGx with somatic profiling reveals that actionable germline variants are nearly universal among patients with cancer in our cohort, extending beyond tumor-specific therapy to encompass toxicity and supportive care management. Routine implementation of combined germline and somatic sequencing in oncology could enhance therapeutic precision, minimize adverse effects, and inform individualized treatment decisions.

ACCOMPANYING CONTENT

Data Sharing Statement

Data Supplement

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INTRODUCTION

Next-generation sequencing (NGS) has revolutionized targeted cancer therapeutics by improving patient outcomes and reducing adverse effects and health care costs.[1] This technology facilitates selection of precise treatments tailored to a patient's tumor-specific genetic profile from over 100 US Food and Drug Administration (FDA)–approved treatment options. Despite its demonstrated utility, NGS adoption for somatic screening remains sparse, and interpretation of the findings can be challenging.[2-5] Accumulating evidence supports early and consistent implementation of NGS for cancer treatment to improve patient survival and value-based care.[6,7] A recent study of 510 patients with metastatic non–small cell lung cancer assessed the impact of waiting for NGS results before prescribing molecular-guided therapy, initiating clinician choice of therapy then adjusting treatment based on subsequently returned NGS results, or initiating clinician choice of therapy without regard to subsequent NGS results.[8] Waiting for NGS results before initiating therapy caused a 14-day delay but led to superior survival compared with either alternative option.[8]

In addition to identifying potential targeted therapies through somatic tumor NGS, germline DNA analysis can help to predict response and/or extreme toxicity risk of cancer therapy or the many concomitant supportive care medications commonly used during cancer treatment.[9,10] Recently, the FDA reinforced testing for all patients receiving chemotherapy sensitive to metabolism dependent on the *DPYD* gene, since certain variants can increase risk for severe toxicity or mortality due to slower metabolism of chemotherapy drugs,

CONTEXT

Key Objective

To our knowledge, this is the first analysis of the landscape of individual genome-mediated treatment benefit and risk to guide therapeutic decision making for patients with cancer.

Knowledge Generated

The assessment of somatic tumor driver mutations is associated with improved clinical outcomes. In addition, the contribution of germline variants to altered efficacy or severe toxicity of certain treatments is also recognized. This analysis directly defines the patient-level impact of combined pharmacogenomics (PGx) and somatic mutation analysis to offer valuable guidance for therapeutic decision making in oncology.

Relevance

Combined germline and somatic genomic profiling could enhance precision oncology by expanding actionable insights beyond antineoplastic activity to include drug dosing and toxicity management.

thereby causing toxic buildup in a patient.[11,12] In addition, patients undergoing cancer treatment are commonly prescribed supportive care medications to ameliorate pain, depression, anxiety, nausea and vomiting, and other comorbidities, and their efficacy can be affected by genetic variation.[13] A population study of Danish patients with cancer found that of the 24,808 individuals included, 35% were prescribed ≥5 medications.[14] Assessment of genomic data from 487,409 participants in the UK Biobank found that 99.5% had pharmacogenomic (PGx) markers associated with atypical response to at least one drug, while the average risk burden was 10 drugs.[15] Another study examined a large, multicenter health system and found that nearly half of the patients with cancer received a supportive care medicine that was influenced by PGx, most commonly for pain control and prevention of nausea and vomiting.[16]

Individual patient data can guide the selection of tumor treatment while mitigating toxicity risks, providing an opportunity for a more comprehensive precision medicine strategy. However, there is a paucity of data on the landscape for both risk and benefit genomics in patients with cancer. These data are critical as the field matures from a simplistic one-gene-one-drug approach to a population precision health strategy.

METHODS

NGS results from 10,302 patients across 98 cancer types from The Cancer Genome Atlas (TCGA) were used to construct a cohort of matched germline and somatic samples.[17] The cohort included 5,324 females and 4,978 males with a median age of 60 years (Table 1). Somatic and germline genomic data were retrieved as variant call format (VCF) and annotated using *bcftools* v1.16.[18] Sequencing results from germline and somatic exomes were processed and analyzed separately, as explained below. Actionable germline variants were defined as diplotypes known to affect drug absorption, dispersion, metabolism, or excretion—as defined by the Clinical Pharmacogenetics Implementation Consortium (CPIC)[19] and PharmGKB.[20,21] Only drug interactions with PharmGKB levels of evidence were considered: Level 1A—describes variant-drug combinations that have variant-specific prescribing guidance available in a current clinical guideline annotation or an FDA-approved drug label annotation; Level 1B—has drug-variant combinations with a high level of evidence supporting the association but no variant-specific prescribing guidance in an annotated clinical guideline or FDA drug label; and Level 2A—variants are in known pharmacogenes (found in PharmGKB Very Important Pharmacogenes), implying causation of drug phenotypes is more likely, with a moderate level of evidence supporting the association.[20,21]

Actionable somatic mutations were defined as alterations in genes with therapeutic relevance according to Memorial Sloan Kettering's Precision Oncology Knowledge Base (OncoKB).[22] Only mutations following therapeutic levels defined in OncoKB were considered: Level 1—FDA-recognized biomarker predictive of a response to an FDA-approved drug; Level 2—standard care biomarker predictive of a response to an FDA-approved drug; Level 3A/3B—having compelling clinical evidence or standard care supporting a biomarker having a predictive response to an FDA-approved drug or investigational drug; Level 4—having compelling biological evidence for a biomarker as having a predictive response to a drug; Level R1/R2—standard care or compelling clinical evidence of a biomarker being resistant to a drug.[23]

Germline Variant Analysis—Phasing and PGx Assessment

Germline VCF files were processed using the PyPGx NGSpipeline v0.23.0,[24-26] which facilitates pharmacogenetic genotype classification by (1) phasing the raw VCF file using Beagle v5.2[27] and (2) calling diplotypes for 59

TABLE 1. Clinical and Demographic Cohort Characteristics by Sex

Characteristic	Female (n = 5,324), No. (%)	Male (n = 4,978), No. (%)	Total (N = 10,302), No. (%)
Age at index, years			
Median	60	61	60
Range	15.00-90.00	14.00-90.00	14.00-90.00
Race			
American Indian or Alaska Native	18 (0.3)	9 (0.2)	27 (0.3)
Asian	290 (5.4)	369 (7.4)	659 (6.4)
Black or African American	597 (11.2)	349 (7.0)	946 (9.2)
Native Hawaiian or Other Pacific Islander	10 (0.2)	1 (0.0)	11 (0.1)
White	3,946 (74.1)	3,827 (76.9)	7,773 (75.5)
Not reported	463 (8.7)	423 (8.5)	886 (8.6)
Ethnicity			
Hispanic or Latino	197 (3.7)	155 (3.1)	352 (3.4)
Not Hispanic or Latino	3,987 (74.9)	3,838 (77.1)	7,825 (76)
Not reported	1,140 (21.4)	985 (19.8)	2,125 (20.6)
Primary diagnosis[a]			
Adenocarcinoma, NOS	486 (9.1)	1,064 (21.4)	1,550 (15.0)
Squamous cell carcinoma, NOS	427 (8.0)	729 (14.6)	1,156 (11.2)
Infiltrating duct carcinoma, NOS	792 (14.9)	98 (2.0)	890 (8.6)
Papillary adenocarcinoma, NOS	346 (6.5)	322 (6.5)	668 (6.5)
Serous cystadenocarcinoma, NOS	528 (9.9)	0 (0.0)	528 (5.1)
Malignant melanoma, NOS	169 (3.2)	252 (5.1)	421 (4.1)
Endometrioid adenocarcinoma, NOS	400 (7.5)	0 (0.0)	400 (3.9)
Glioblastoma	144 (2.7)	249 (5.0)	393 (3.8)
Clear cell adenocarcinoma, NOS	135 (2.5)	235 (4.7)	370 (3.6)
Hepatocellular carcinoma, NOS	114 (2.1)	245 (4.9)	359 (3.5)
Transitional cell carcinoma	93 (1.7)	250 (5.0)	343 (3.3)
Lobular carcinoma, NOS	196 (3.7)	0 (0.0)	196 (1.9)
Acute myeloid leukemia, NOS	65 (1.2)	77 (1.5)	142 (1.4)
Mixed glioma	58 (1.1)	73 (1.5)	131 (1.3)
Astrocytoma, anaplastic	59 (1.1)	71 (1.4)	130 (1.3)
Mucinous adenocarcinoma	63 (1.2)	63 (1.3)	126 (1.2)
Adenocarcinoma with mixed subtypes	56 (1.1)	60 (1.2)	116 (1.1)
Pheochromocytoma, NOS	65 (1.2)	45 (0.9)	110 (1.1)
Papillary carcinoma, follicular variant	78 (1.5)	27 (0.5)	105 (1.0)
Squamous cell carcinoma, keratinizing, NOS	47 (0.9)	55 (1.1)	102 (1.0)
Leiomyosarcoma, NOS	67 (1.3)	34 (0.7)	101 (1.0)

Abbreviations: NOS, not otherwise specified; TCGA, The Cancer Genome Atlas.
[a]Selected the 21 most common cancers out of 98 in the TCGA cohort. Primary Diagnoses were limited in specificity based on available information in TCGA.

pharmacogenes. Our analysis focused on 13 established pharmacogenes based on their clinical relevance to patients with cancer and molecular phenotypic information: *CACNA1S*, *CYP2B6*, *CYP2C9*, *CYP2C19*, *CYP2D6*, *CYP3A5*, *DPYD*, *F5*, *NUDT15*, *RYR1*, *SLCO1B1*, *TPMT*, and *UGT1A1*.[9] Diplotypes with an uncertain, unknown, or indeterminate phenotype were excluded, while those with known functional impacts were considered clinically actionable. Among these genes, *DPYD*, *UGT1A1*, *CYP2D6*, and *CYP2C19* were designated as toxicity management and supportive care PGx genes, with known drug interactions for medications commonly used in the clinical management of patients with cancer.[28] Table 2 provides a summary of each of the 13 pharmacogenes and the distribution of samples with actionable variants.

Somatic Mutation Analysis—Genomic Assessment for Therapeutic Implications

Somatic VCF files from TCGA were annotated using Ensembl's Variant Effect Predictor (VEP) v110.1.[29] VEP

TABLE 2. Frequency of Patients With Actionable PGx Variation

Germline			
PGx Gene/Metabolizer Status	Patients With an Actionable Genotype	Patients Without an Actionable Genotype	Percentage (%)
CYP2B6 total[a]	4,952	5,022	
Normal		5,022	48.74
Intermediate	3,857		37.43
Rapid/ultrarapid	288		2.80
Poor	807		7.83
UGT1A1[b] total	4,300	5,985	
Normal		5,985	58.10
Intermediate	3,829		37.20
Poor	471		4.57
CYP2C9 total[a]	3,362	6,929	
Normal		6,929	67.3
Intermediate	3,166		30.70
Poor	196		1.90
CYP2C19[b] total[a]	3,276	6,988	
Normal		6,988	67.80
Likely intermediate	24		0.23
Likely poor/poor	341		3.31
Rapid/ultrarapid	23		0.22
SLCO1B1 total[a]	3,267	6,739	
Normal		6,739	65.40
Decreased/possibly decreased	2,644		25.67
Poor	265		2.57
Increased	358		3.48
CYP2D6[b] total[a]	3,144	6,909	
Normal		6,909	67.10
Intermediate	2,789		27.10
Poor	355		3.45
TPMT total[a]	852	9,340	
Normal		9,340	90.70
Intermediate/possibly intermediate	834		8.10
Poor	18		0.17
F5 total[a]	456	9,846	
Favorable		9,846	95.6
Unfavorable	456		4.43
DPYD[b] total[a]	244	10,058	
Normal		10,058	97.60
Intermediate	244		2.37
Poor	0		0
NUDT15 total[a]	206	10,070	
Normal		10,070	97.70
Intermediate/possibly intermediate	200		1.94
Poor	6		0.06
CYP3A5 total[a,c]	110	10,191	
Normal	110		1.07
Intermediate		303	2.94
Poor		9,888	96.00
RYR1 total[a]	11	10,291	
Uncertain susceptibility		10,291	99.90
Malignant hyperthermia susceptibility	11		0.11

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TABLE 2. Frequency of Patients With Actionable PGx Variation (continued)

Germline			
PGx Gene/Metabolizer Status	Patients With an Actionable Genotype	Patients Without an Actionable Genotype	Percentage (%)
CACNA1S total[a]	1	10,301	
Uncertain susceptibility		10,301	99.99
Malignant hyperthermia susceptibility	1		0.01

Abbreviation: PGx, pharmacogenomics.
[a]Counts and percentages include actionable genotypes only. Genotypes with indeterminate phenotypes were excluded.
[b]Genes included as part of our toxicity management and supportive care PGx assessment.
[c]*CYP3A5* is a PGx variant where a normal metabolizer is considered an actionable variant.

annotated functional impacts of single-nucleotide polymorphisms, insertions and deletions, copy-number variants, and structural variants. VEP also provided information regarding the type of alteration such as stop-gained, stop-lost, missense, and frameshift mutations. To link these somatic alterations with potential therapeutic options, we subsequently converted the VCF files to Mutation Annotation Format (MAF) using VCF2MAF v1.6.2[30] and performed annotation with the OncoKB annotator v3.3.2.[31] The OncoKB annotator assigned clinical actionability levels to mutations based on drug responsiveness or resistance.[31] This information enabled each mutation to be associated with targeted drugs and corresponding therapeutic levels (Table 3).

RESULTS

A total of 10,302 matched germline and somatic tumor samples were available from TCGA.[17] The cohort was 52% female and included the following racial categories: White (75.5%), Black or African American (9.2%), not reported (8.6%), Asian (6.4%), American Indian or Alaska Native (0.3%), and Native Hawaiian or Pacific Islander (0.1%). Patients with an actionable somatic mutation spanned 98 of the 132 TCGA reported cancer categories. Table 1 presents a subset of the most frequent cancers appearing in the cohort.

Actionable Germline Variation

After calling diplotypes across 13 PGx genes using the PyPGx pipeline, all patients harbored at least one actionable germline variant (Table 2) and are depicted in the Data Supplement (Figs S1-S13). Genes with the highest frequency of actionable variants were *CYP2B6* (48%), *UGT1A1* (42%), *CYP2C9* (33%), and *CYP2C19* (32%; Table 2). Actionable PGx variants per patient with cancer ranged from 1 to 9 (median = 3). The number of at-risk medications—drugs significantly influenced by genetic variation and known to pose a higher risk of adverse drug reactions—per patient ranged from 1 to 46 (median = 16). The number of at-risk medications per patient with cancer for toxicity management and supportive care genes (*DPYD*, *UGT1A1*, *CYP2D6*, and *CYP2C19*) ranged from 1 to 36 (median = 10). Seventy-three percent of patients in the cohort had at least one actionable toxicity management and supportive care PGx variant.

Actionable Somatic Mutations

Among the 10,302 individuals, 4,312 (42%) had at least one actionable mutation matched to a therapy in OncoKB. In total, 7,035 actionable somatic mutations were identified across these individuals, with many patients having multiple actionable mutations. Of these 4,312 patients, 2,723 had one mutation, while 1,589 had two or more mutations. Actionable mutations per patient ranged from 1 to 19 (median = 1). The most frequently altered genes with therapeutic relevance across all cancer types were *PIK3CA* (1,359), *KRAS* (800), and *PTEN* (750; Data Supplement, Fig S15). The highest therapeutic level for each case was tabulated across the 10,302 individuals—29% of actionable mutations were classified as OncoKB Therapeutic Level 1, 16% Level 2, 4% Level 3A, and 19% Level 4 (Fig 1). However, 5,990 patients did not have an actionable mutation characterized within a therapeutic level. Among patients who did have an actionable mutation (n = 4,312)—43% were classified as OncoKB Therapeutic Level 1, 23% Level 2, 5% Level 3A, and 28% Level 4 (Fig 1). Additionally, 1,085 patients had mutations associated with drug resistance levels R1/R2 in OncoKB.

Combined Germline Variants and Somatic Mutations

We combined counts for therapeutically actionable somatic mutations and PGx germline variants for all 10,302 patients. Overall, 62% of patients had equal to or fewer than the median number of actionable somatic mutations (median = 1) and actionable germline variants (median = 3), whereas 4% exceeded both medians (Fig 2A). When restricting analysis to toxicity management and supportive care genes, 12.2% of patients had greater than one germline variant (median = 1) and at least one somatic mutation (median = 0; Fig 2A). Figure 2B depicts the distribution of both somatic actionable mutations and PGx gene variants for toxicity management and supportive care. Notably, 30.4% of patients in the cohort contained an actionable somatic mutation and an actionable germline variant in a toxicity management and supportive care gene (Fig 2C). Finally, the per-patient distribution of actionable variants was calculated by taking the difference between the number of actionable somatic mutations and germline variants in each patient (Fig 2D), highlighting the heterogeneity in PGx

TABLE 3. Frequency of Drug/Gene Interactions Across All Cancers

HUGO Gene Symbol	Drugs for Therapeutic Implications Only	No. of Cases (N = 10,302)
PIK3CA	Alpelisib	1,197
KRAS	Adagrasib, cetuximab, cobimetinib, panitumumab, sotorasib, trametinib, trastuzumab, tucatinib	761
IDH1	Ivosidenib, olutasidenib	467
ARID1A	Tazemetostat	348
NF1	Cobimetinib, selumetinib, trametinib	301
ATM	Olaparib	239
KDM6A	Tazemetostat	134
ERBB2	Ado-trastuzumab emtansine, lapatinib, margetuximab, neratinib, pembrolizumab, pertuzumab, trastuzumab, trastuzumab deruxtecan, tucatinib, zanidatamab, zongertinib	128
BRCA2	Niraparib, olaparib, rucaparib, talazoparib	101
STK11	Bemcentinib, pembrolizumab	93
FGFR2	Erdafitinib, futibatinib, infigratinib, pemigatinib	88
ERCC2	Cisplatin	70
MTOR	Everolimus, temsirolimus	69
BRCA1	Niraparib, olaparib, rucaparib, talazoparib	68
TSC2	Everolimus	68
EGFR	Afatinib, amivantamab, lazertinib, dacomitinib, erlotinib, gefitinib, lapatinib, mobocertinib, osimertinib, patritumab deruxtecan, poziotinib	63
TSC1	Everolimus	62
PTCH1	Sonidegib, vismodegib	54
BRIP1	Olaparib	51
MAP2K1	Cobimetinib, trametinib	49
CDK12	Cemiplimab, nivolumab, olaparib, pembrolizumab	45
KIT	Avapritinib, imatinib, nilotinib, pazopanib, regorafenib, ripretinib, sorafenib, sunitinib	44
EZH2	Tazemetostat	35
IDH2	Enasidenib	34

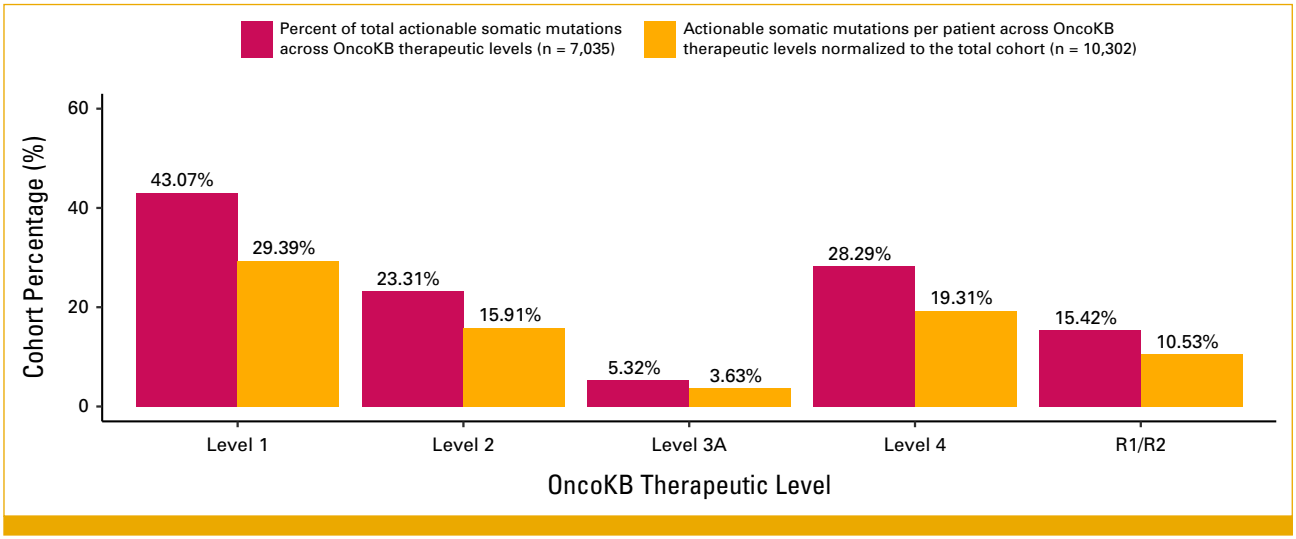

FIG 1. Distribution of somatic alterations by OncoKB therapeutic level. Pink bars represent the percentage of total actionable somatic mutation across the OncoKB therapeutic levels of evidence (n = 7,030). Yellow bars represent the percentage of patients out of the total cohort (N = 10,302). Levels 1-4 are reported as the highest therapeutic level achieved according to OncoKB. All patients harboring somatic mutations associated with drug resistance (Levels R1 and R2) were included as these categories were not assigned a hierarchical therapeutic level within OncoKB. OncoKB, Oncology Knowledge Base.

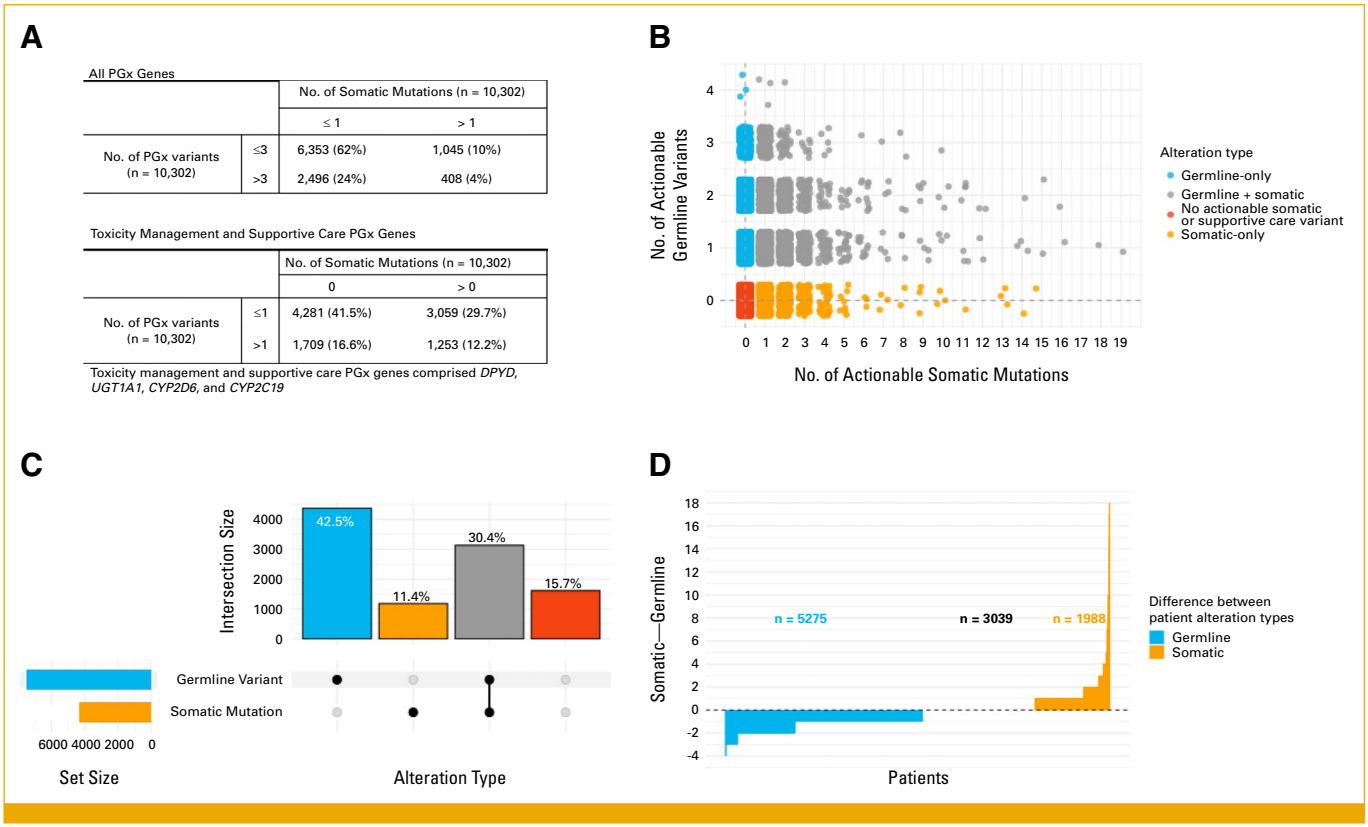

FIG 2. Integrated visualization of somatic mutations and germline variants in toxicity management and supportive care genes. (A) Table summarizing patient-level distributions of actionable somatic mutations and germline PGx variants. The upper table displays counts of patients stratified by median values for both somatic and PGx for the entire cancer cohort (median values for mutations/variants were used for categorization). The lower table stratifies patients by the median values of harboring actionable somatic mutations and variants in toxicity management and supportive care genes (median values for mutations/values were used for categorization). (B) Quadrant plot showing the distribution of patients by number of actionable somatic mutations and germline variants. Patients are color-coded by alteration type: somatic-only (gold), germline-only (blue), both (gray), or neither having germline or somatic alterations in toxicity management and supportive care genes (red). (C) UpSet plot illustrating the quantitative intersection sizes of patients with somatic mutations, germline variants in a toxicity management and supportive care gene, both, or neither. (D) Patients are stratified by the net difference (somatic—germline). Blue bars represent patients with more toxicity management and supportive care germline variants, gold bars indicate more somatic mutations, and black bars reflect an equal number of both. PGx, pharmacogenomics.

profiles across the cohort. Notably, 5,275 patients (51%) harbored more actionable germline variants than somatic mutations, emphasizing the substantial potential for germline-guided therapeutic decision making. Conversely, 1,988 patients (19%) exhibited a predominance of actionable somatic mutations, while 3,039 patients (30%) had an equal number of actionable alterations from both sources. This finding demonstrates that a majority of patients with cancer could benefit from a dual consideration of both somatic and germline alterations when determining personalized treatment strategies, rather than relying solely on somatic mutation data, as is commonly practiced.

DISCUSSION

Looking across a diverse landscape of 10,302 patients spanning nearly 100 cancer types, every individual harbored at least one therapeutically actionable variant with potential to guide clinical care. Although the incidence of therapeutically actionable somatic and PGx alterations has been previously explored,[32] to our knowledge, this study represents the first large-scale analysis to define their combined landscape of clinical actionability. Much attention has focused on somatic sequencing to objectively select therapy with a higher probability of disease control. Indeed, significant impacts on objective response, progression-free survival, and overall survival have been observed with targeted therapy directed by somatic sequencing results. Interpatient analysis demonstrated that 42% of patients in this cohort had at least one actionable somatic mutation. Characterizing the value of germline PGx analysis as part of routine care of patients with cancer is an existing gap.

Although germline PGx has limited direct relevance to anticancer drug selection, its major clinical utility lies in toxicity management and supportive care. All patients in this cohort harbored at least one actionable PGx variant, consistent with findings by McInnes et al[15] conducted in the UK Biobank across all individuals in the general biorepository population (mostly patients without cancer). A recent

analysis by Leong et al[33] reported that 62.7% of the 76,805 patients in the cohort carried actionable PGx variants affecting chemotherapy dosing, toxicity risk, and supportive care management, comparable with the 73% observed here for supportive care PGx genes. Although a prior review by Tremmel et al emphasized the conceptual need to integrate germline PGx with somatic profiling,[34] to our knowledge, this is the first large-scale study to evaluate germline PGx variants in the context of therapeutically actionable somatic mutations. The opportunity here is to understand that both germline and somatic sequencing help make objective clinical decisions. The past focus on one or the other has resulted in a lack of consideration for the need to use both benefit and risk biomarkers to manage a patient's care.

Importantly, some patients without therapy-matched somatic alterations nonetheless harbored genotypes conferring substantial risk for severe drug toxicity. For example, 8% of patients carried *TPMT* genotypes associated with thiopurine toxicity,[35] and 42% harbored *UGT1A1* variants linked to irinotecan-related adverse affects, resulting in increased toxicity due to modified glucuronidation.[36] Although irinotecan is commonly used in colorectal and pancreatic cancers, guidance around irinotecan use based on *UGT1A1* is not yet included in the CPIC guidelines. However, we chose to include it in this analysis based on high-level clinical evidence from PharmGKB (Levels 1-2) and FDA labeling, which recognizes *UGT1A1**28 and related variants as modifiers of irinotecan toxicity risk. Moreover, modified *CYP2C9* metabolism is expected in 33% of our patient cohort—*CYP2C9* mutations are clinically relevant for many commonly used drugs, including nonsteroidal anti-inflammatory drugs such as ibuprofen, celecoxib, flurbiprofen, and meloxicam, where poor metabolizers have increased drug exposure and risk of adverse effects.[37,38] Variants in *CYP2C9* are also known to modify risk of adverse effects to erdafitinib, an FGFR inhibitor, approved for the treatment of urothelial cancer.[39] Variants in *CYP2D6* were detected in 31% of patients and are known to affect metabolism of commonly prescribed medications in oncology. For example, the CPIC guideline for 5-HT_3 receptor antagonists (ondansetron and palonosetron) shows that ultrarapid metabolizers may have reduced efficacy due to faster clearance.[40-42] Hydrocodone is metabolized by *CYP2D6* to its active metabolite hydromorphone; poor or intermediate metabolizers may have reduced analgesic response.[43] *CYP2D6* is also known to play a role in modifying efficacy of anti-anxiety medications, such as duloxetine.[44] Finally, we identified 144 patients (1.4%) with variations in the *DPYD* gene, which have been shown to increase the risk of treatment-related death for standard fluoropyrimidine chemotherapies because of the inability to rapidly clear toxic metabolites.[45]

When restricting to PGx genes relevant to toxicity management and supportive care of patients with cancer, 30.4% of patients had an actionable finding in both germline variants and somatic mutations (Fig 2A). The per-patient analysis of actionable variants (Fig 2C) reinforces the critical need to integrate germline PGx testing alongside somatic tumor profiling. Despite the current paradigm of prioritizing somatic alterations in oncology, our data demonstrate that more than half of the patients possess a greater burden of actionable germline variants. Ignoring germline PGx thus risks overlooking clinically actionable information that could guide both cancer-directed and supportive care therapy. Personalizing treatment plans in anticipation of polypharmacy or targeted cancer therapeutics is needed to improve outcomes and minimize adverse events. Several studies have pointed to the clinical utility of universal germline or somatic genetic testing for patients with cancer.[8,46-48] Each of these studies compounds evidence that universally sequencing both germline variants and somatic mutations will provide clinical benefits for patients and opportunities to elucidate disease biology. Our analysis further supports this premise by showing the expected number of patients who would be harboring either an actionable somatic mutation, or germline variant, or in some cases, both—which could potentially lead to beneficial targeted therapeutic treatments.

Although this paper focused on pharmacologically actionable germline variants, an additional clinical benefit of performing paired tumor-normal sequencing is the potential identification of germline mutations associated with hereditary cancer syndromes, such as *BRCA*-associated hereditary breast and ovarian cancer syndrome,[49] Lynch syndrome,[50] Cowden syndrome,[51] or Li-Fraumeni syndrome,[52] which presents an important complementary clinical application.

There remains a substantial knowledge gap regarding the real-world clinical impact of universal germline and somatic NGS testing in patients with cancer. Although uptake of NGS by clinical oncologists is increasing for guiding treatment decisions, reasons for usage is varied—where 34% of oncologists used NGS to guide treatment decisions, 29.1% determined eligibility for clinical trials, and 17.5% to decide on the use of off-label drugs approved by the FDA.[53] Further research is essential to assess the direct clinical benefits and utility of these applications. We suggest that improved access to precision medicine experts, who can assist with therapeutic decision making in the targeted treatment options, is crucial to ensure that patients receive the appropriate therapy at the right time.

Our analysis was limited to the TCGA database, which may not fully represent the spectrum or population-level frequencies of cancer types in the general population. For example, the TCGA cohort is predominantly composed of individuals of European ancestry, potentially limiting generalization of PGx variant frequencies to more diverse populations; future studies in ancestrally diverse cohorts are therefore needed. Because germline assessment was based on whole-exome sequencing (WES), PGx variants outside of exonic regions were not captured, likely underestimating the overall impact of PGx. For this analysis, only variant-level information from WES VCF files was available, limiting our

ability to detect structural variants, such as gene duplications and deletions of *CYPD6*. Deletions that would affect the metabolizer status, such as *CYP2D6**5, could not be called; therefore, the number of patients with modified metabolism of those drugs affeted by *CYP2D6* may be underrepresented in this analysis. Future studies are needed to determine the impact that structural variation may have on therapeutic decision making in patients with cancer. Furthermore, actionable biomarkers derived from RNA expression, immunohistochemistry, tumor mutational burden, or microsatellite instability were not included. Our analysis was restricted to genes annotated within OncoKB and CPIC, and thus, actionable variants outside these resources were not considered. As a result, some clinically relevant gene-drug interactions may not be represented, particularly where FDA-approved therapies are tumor-type–specific despite evidence of biological actionability, for example, alpelisib with OncoKB Level 3B evidence within colon cancer. Finally, although established PGx phenotype classifications were applied, not all gene-drug interactions confer equivalent clinical risk, and future studies incorporating quantitative risk modeling may further refine individualized treatment decisions.

In conclusion, although precision oncology has important focus on somatic drivers to maximize tumor control benefit, there are also opportunities to incorporate markers to inform toxicity minimization, pain control, nausea/vomiting control, anticoagulation/antiplatelets, and antifungal prophylaxis. The best patient care for patients will prioritize the latest approaches to precision medicine, and ensure clinicians have the best information available to provide their patients with the right drug and at the right dose.

AFFILIATIONS

[1]Department of Quantitative Health Sciences, Cleveland Clinic Research, Cleveland Clinic, Cleveland, OH
[2]Center for Quantitative Metabolic Research, Cleveland Clinic, Cleveland, OH
[3]Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH
[4]Northside Hospital Cancer Institute, Atlanta, GA
[5]Intermountain Health, St George, UT
[6]Center for Precision Medicine and Functional Genomics, Utah Tech University, St George, UT
[7]Endocrinology and Metabolism Department, Cleveland Clinic, Cleveland, OH

CORRESPONDING AUTHOR

Daniel M. Rotroff, PhD; e-mail: rotrofd@ccf.org.

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AUTHOR CONTRIBUTIONS

Conception and design: Howard L. McLeod, Daniel M. Rotroff
Provision of study materials or patients: Daniel M. Rotroff
Collection and assembly of data: Vai S. Pathak, Howard L. McLeod, Daniel M. Rotroff
Data analysis and interpretation: All authors
Manuscript writing: All authors
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Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Courtney E. Hershberger
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Suneel Kamath
Honoraria: Jazz Pharmaceuticals, AstraZeneca
Consulting or Advisory Role: Exelixis, BeiGene, Jazz Pharmaceuticals, Takeda, Sirtex Medical, Amgen
Speakers' Bureau: Takeda, Pfizer, AstraZeneca, BeiGene
Open Payments Link: https://openpaymentsdata.cms.gov/physician/711572

Porscha Johnson Williams
Employment: Johnson & Johnson/Janssen
Stock and Other Ownership Interests: Johnson & Johnson/Janssen
Honoraria: Hematology/Oncology Pharmacy Association, GenomeWeb, Clarified Precision Medicine, Advancing Precision Medicine, Atlanta Academy of Institutional Pharmacy
Consulting or Advisory Role: Clarified Precision Medicine, GenomeWeb, PJW Clinical Pharmacy Consulting, LLC, Johnson & Johnson/Janssen, CommGeniX
Speakers' Bureau: Mirati Therapeutics
Travel, Accommodations, Expenses: Hematology/Oncology Pharmacy Association, GenomeWeb, Advancing Precision Medicine

Howard L. McLeod
Employment: GenDx
Leadership: Cancer Genetics, Vyant Bio
Stock and Other Ownership Interests: Cancer Genetics, Interpares Biomedicine, Pharmazam, Total Dx Connect, Vyant Bio, PGx Accelerator, Genovation Health, Clarified Precision Medicine, XYGene, LLC, Cofactor Genomics
Honoraria: Genentech/Roche, Illumina
Consulting or Advisory Role: Gentris, Cancer Genetics, Saladax Biomedical, NIH/NCI, Admera Health, eviCore healthcare, Pharmazam, Total Dx Connect, VieCure, Illumina, Intermountain Precision Genomics, DoseMe, Cofactor Genomics
Speakers' Bureau: Genentech
Other Relationship: Northwestern University, Xiangya Hospital, Kansas University Medical Center, AGBT Precision Health, Southern California University of the Health Sciences

Daniel M. Rotroff
Employment: Cleveland Clinic
Leadership: Cleveland Clinic, Genovation Health, Clarified Precision Medicine
Stock and Other Ownership Interests: Clarified Precision Medicine, Genovation Health
Consulting or Advisory Role: Clarified Precision Medicine, Genovation Health
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