Opportunities for personalizing colorectal cancer care: an analysis of SEER-medicare data

Zachary T. Rivers, Helen M. Parsons, Pamala A. Jacobson, Karen M. Kuntz, Joel F. Farley and David J. Stenehjem

© The Author(s), under exclusive licence to Springer Nature Limited 2022

The Pharmacogenomics Journal (2022) 22:198–209; https://doi.org/10.1038/s41397-022-00276-6

INTRODUCTION
In 2021, 150,000 Americans are projected to receive a diagnosis of colorectal cancer and 22% of these are expected to be diagnosed with distant or metastatic disease [1]. Treatment options for metastatic colorectal cancer (mCRC) are focused on extending overall survival and improving quality of life, rather than a cure. First-line treatment generally consists of multiagent chemotherapy, with a fluoropyrimidine being combined with either irinotecan or oxaliplatin [2, 3]. These treatments come with significant side effects, including nausea, vomiting, diarrhea, and neutropenia, resulting in treatment associated morbidity and mortality [4–6]. Treatment with 5-fluorouracil alone is associated with 0.5%–1% mortality [7]. Advances in supportive care medicine have reduced, but not eliminated, these toxicities.

Pharmacogenomics (PGx), or the use of genetic variants to predict medication toxicity and response, has been proposed as an approach to reduce treatment-related toxicities in mCRC. The toxicities associated with irinotecan and the fluoropyrimidines have a known genetic component and use of PGx-guided dosing may be beneficial in patients with mCRC [8, 9]. This approach is not currently endorsed by the National Comprehensive Cancer Network (NCCN), though the European Society of Medical Oncology now recommends testing for variants in dihydropyrimidine dehydrogenase (DPYD) prior to treatment with fluoropyrimidines [7, 10]. In addition, the Dutch PGx Working Group and the European Medical Association recommend testing DPYD prior to fluoropyrimidine treatment [11, 12].

Genetic variants also impact outcomes with non-chemotherapy medications, including those recommended by NCCN supportive care guidelines such as ondansetron, selective serotonin reuptake inhibitors, and selected opioids [13–16]. The Clinical Pharmacogenetics Implementation Consortium (CPIC) curates PGx implementation guidelines, with 26 published as of October 2021 [17]. While these guidelines are not recommendations for testing, they highlight the impact that testing would have on a diverse group of medications. Implementing these guidelines into clinical practice has been limited by questions around cost of testing, magnitude of impact, insurance reimbursement, and unclear clinical actionability [18–22].

Claims and cancer registry data provides an opportunity to address questions about the potential opportunities for PGx to positively impact the lives of patients with mCRC. Understanding how many and to what extent patients with mCRC are exposed to medications with known PGx variants that impact treatment outcomes, defined here as PGx at-risk medications, will allow patients and their clinicians to make informed decisions about testing. This project, using the Surveillance, Epidemiology, and End Results Program linked to Medicare claims data (SEER-Medicare), explores the hypothesis that patients with mCRC are routinely exposed to new PGx at-risk medications after their diagnosis, and that individual and contextual characteristics impact the odds of being exposed to these medications. The primary objective of this project was to characterize the use of PGx at-risk medication utilization in the United States Medicare population receiving chemotherapy for newly diagnosed mCRC.

1Department of Pharmaceutical Care and Health Systems, University of Minnesota College of Pharmacy, Minneapolis, MN, USA. 2Hutchinson Institute for Cancer Outcomes Research, Fred Hutchinson Cancer Research Center, Seattle, WA, USA. 3Division of Health Policy and Management, University of Minnesota School of Public Health, Minneapolis, MN, USA. 4Masonic Cancer Center, University of Minnesota, Minneapolis, MN, USA. 5Department of Experimental and Clinical Pharmacology, University of Minnesota College of Pharmacy, Minneapolis, MN, USA. 6Department of Pharmacy Practice and Pharmaceutical Sciences, University of Minnesota College of Pharmacy, Duluth, MN, USA. 7email: zrivers@fredhutch.org

Received: 15 November 2021 Revised: 4 March 2022 Accepted: 17 March 2022 Published online: 31 March 2022
METHODS

We conducted a retrospective cohort study characterizing treatment patterns and medication utilization with a focus on PGx at-risk medications, for patients over the age of 65 with newly diagnosed mCRC. Patient-level data for this analysis were obtained from the SEER-Medicare data linkage spanning 2004-2015, integrating data of cancer cases from 18 registries, covering roughly 28% of the US population [23, 24]. Chemotherapy and supportive care medications were identified using the NCCN clinical practice guidelines [2, 3, 13–16]. Pharmacogenomically at-risk medications were identified from the CPIC guidelines published on or before April 1, 2021, with the exception of irinotecan, which was identified from the FDA package labeling [5, 17]. This analysis was determined as exempt from IRB review by the University of Minnesota IRB under study number STUDY00006832.

The first analytic cohort for this analysis comprised all individuals in the SEER registry with American Joint Committee on Cancer stage IV disease with a primary location in the colon or rectum identified via ICD code with adenocarcinoma histology. Patients with prior cancer diagnoses were excluded. Patients identified on autopsy or death were excluded as this analysis was interested in treatment patterns. Patients enrolled on Medicare for reasons other than age were excluded. Patients without Medicare A and B coverage for 12 months prior to diagnosis through three months after month of diagnosis were excluded, as were those who were enrolled in a health management organization (HMO). Finally, patients were eligible for analysis if they received an irinotecan cancer specific chemotherapy in the 3 months following the month of diagnosis. (Fig. 1: Study Design Diagram) This window was used to ensure at least three months of follow-up as SEER does not report the exact date of diagnosis. This was identified using the National Cancer Institute’s Cancer Medicine Enquiry Database [25]. Fig. 2: Cohort Identification demonstrates how the cohort was formed.

The second analytic cohort comprised all individuals in the initial cohort with additional exclusion criteria to identify patients with retail prescription claims data. Patients were excluded from this cohort if they were diagnosed prior to January 1st, 2008, or if they did not have Medicare part D enrollment for the 12 months prior to diagnosis, the month of diagnosis, and the three months following. The third cohort was comprised of individuals from the initial cohort who diagnosed on or after January 1st, 2012, when CPT codes were assigned to PGx tests, to identify patients who may have received PGx testing [26].

Chemotherapy medications were identified in claims data using National Drug Codes (NDC) and Health Care Common Procedure Coding System (HCPCS) codes. (Supplemental Table 1: Chemotherapy Identification Codes) Chemotherapy exposure was identified in hospitalization data using diagnosis codes, and from institutional outpatient claims and provider-based claims. A single claim was considered indicative of exposure to a given medication. If a patient had a claim for leucovorin or levoleucovorin, without exposure to a fluoropyrimidine, it was assumed that the claim for the fluoropyrimidine was missing in the data, given the lack of other clinical rationale for use of these agents, and the patient was coded as receiving 5-fluorouracil. Inpatient claims for chemotherapy in patients with colorectal cancer are nearly always 5-fluorouracil; so patients receiving chemotherapy in this setting were assumed to receive 5-fluorouracil [27]. The window for PGx at-risk exposure to occur was defined as the first day of the month of diagnosis to the last day of the third month following the month of diagnosis. This window was selected to account for the lack of specific diagnosis day in SEER data.

PGx at-risk medication exposure was characterized as either chemotherapy or non-chemistry. PGx at-risk chemotherapy exposure occurred when a claim was identified for a fluoropyrimidine or an irinotecan-containing medication. Non-chemotherapy medication exposure occurred when a claim was identified for the non-chemotherapy medication with dosing or alternative medications recommendations from the CPIC guidelines [17]. Medications were identified using the generic name field in the claims data. Non-chemotherapy PGx at-risk medication exposure was further categorized by therapeutic class. Therapeutic classes used for this analysis include gastrointestinal, pain, cardiology, and psychiatry. PGx test exposure was identified using Common Procedure Terminology (CPT) codes. A single code for any of the medications or tests was considered exposure. A full list of CPT codes can be found in Supplemental Table 2: PGx Test Identification.

Predictor variables for receiving a PGx at risk medication were selected using Andersen’s Behavioral Model of Health Services Use [28]. Individual characteristics selected were patient demographics, tumor characteristics, non-pharmacologic treatment approaches, pre-diagnosis comorbidities, and a claims-based measure of performance status [29]. Contextual characteristics included rurality, defined using the Rural-Urban Continuum Codes (RUC) classification in SEER, and zip-code level age and race matched income and educational attainment. Zip-code level variables were assigned by identifying the highest percentage of residents within a zip code that matched an individual’s race/ethnicity and age range. Rurality was defined as metropolitan (RUC 1–3), urban (RUC 4–6), and rural (RUC 7–9), with individuals of an unknown rurality (RUC 88 or 99) included in metropolitan. Comorbidities were identified using the Charlson Comorbidity Index with metastatic cancer removed as a predictor per the National Cancer Institute’s recommendation [30–32]. Prescription medication exposure and comorbidities 12 months prior to cancer diagnosis were considered as predictors of post-diagnosis non-chemotherapy medication exposure variable.

Descriptive statistics were used to characterize patient exposure to PGx at-risk chemotherapy, non-chemotherapy, and PGx testing. Univariate and multivariate logistic regression models were used to explore the impact of individual and contextual characteristics on PGx at-risk chemotherapy exposure. All predictors identified using Andersen’s model were retained for the multivariate analysis. Patients with missing covariates were dropped from the multivariate analysis. Univariate logistic regression models were constructed to understand the impact of pre-diagnosis comorbidities and pre-diagnosis prescription medication exposure. No models were fit for PGx testing exposure due to small sample size. Data points with fewer than 11 individuals are suppressed and reported as “SUP” in this analysis to protect patient anonymity. All analysis was conducted in SAS version 9.4.

RESULTS

There were 6,957 patients available for analysis in the cohort who received chemotherapy for mCRC. (Table 1: Predictor Variable Distributions) Of these, 6,042 (86.9%) were exposed to at least one PGx at-risk chemotherapy medication in the three months following the month of diagnosis. Most patients (5,931, 85.3%) were exposed to 5-FU or capecitabine (metabolized by DPYD), while 845 (12.2%) patients were exposed to irinotecan (a medication metabolized by UGT1A1). (Table 2: PGx At-Risk Exposure) There were 735 (10.6%) patients treated with both irinotecan and a fluoropyrimidine during the observation period. Comparing patient characteristics to examine potential differences between patients at risk for receiving PGx at-risk chemotherapy medications to those not at risk, we found a number of interesting observations in our univariate analysis. The individual characteristics that impacted the odds of a PGx at-risk chemotherapy exposure included age (85+: Odds Ratio 0.32, 95% Confidence Interval (CI) (0.24–0.42); 80-84: 0.57, (0.46–0.72); 75-79: 0.76, (0.62–0.94) compared to 66–69) and race/ethnicity (Hispanic: 0.64, (0.49–0.82); Asian or Pacific Islander: 0.51, (0.39–0.67)
compared to non-Hispanic White). (Table 3: Predictors of PGx at-Risk Chemotherapy Exposure) Contextual characteristics for PGx at-risk chemotherapy exposure included census region (Northeast: 0.7, (0.52–0.93); West: 0.39, (0.3–0.51); South: 0.67, (0.51–0.89) compared to Midwest) and race, ethnicity, and age-matched zip-code level of educational attainment (some college: 1.2, (1–1.44); high school: 1.57, (1.32–1.87) compared to completed college).

In the multivariate analysis for PGx at-risk chemotherapy exposure, there were 167 patients with missing education variables and they were excluded. In this multivariate analysis, the same individual characteristics (age: 85+: 0.3, (0.22–0.39); 80–84: 0.54, (0.43–0.69); 75–79: 0.74, (0.60–0.91) compared to 66-69, and race/ethnicity: Hispanic: 0.74, (0.55–0.98); Asian or Pacific Islander: 0.7, (0.52–0.95), compared to non-Hispanic White) and contextual characteristics (education: some college: 1.41, (1.15–1.73) compared to completed college, and census region: West: 0.39, (0.29–0.53); and South: 0.71, (0.53–0.95) compared to Midwest) impacted PGx at-risk chemotherapy exposure when compared to the univariate analysis. Rurality was an additional contextual characteristic found to impact exposure in the multivariate model (urban: 0.69, (0.54–0.87) compared to metropolitan). (Table 3)

The second cohort included 2,223 patients treated with chemotherapy for mCRC with Part D claims data available, 1,873 (84.3%) who were exposed to one or more PGx at-risk non-chemotherapy medications after diagnosis. (Table 2: PGx at-Risk Exposure) When considering incident exposure, 1,393 (62.7%) patients experienced an incident exposure to medications in the gastrointestinal class, 568 (25.6%) experienced an incident exposure to a pain medication, 113 (5.1%) were treated with a new cardiovascular medication, and 104 (4.68%) had an incident treatment with an anti-depressant (Table 4).
Table 1. Predictor Variable Distributions.

| Variable                     | Cohort 1: Chemotherapy Analysis (%) | Cohort 2: Non-Chemotherapy Analysis (%) | Cohort 3: Testing Analysis (%) |
|------------------------------|-------------------------------------|----------------------------------------|-------------------------------|
| Total Patients               | 6,957                               | 2,223                                  | 2,050                         |
| Year                         |                                     |                                        |                               |
| 2004                         | 680 (9.8%)                          | –                                      | –                             |
| 2005                         | 680 (9.8%)                          | –                                      | –                             |
| 2006                         | 615 (8.8%)                          | –                                      | –                             |
| 2007                         | 590 (8.5%)                          | –                                      | –                             |
| 2008                         | 601 (8.6%)                          | 263 (11.8%)                            | –                             |
| 2009                         | 588 (8.5%)                          | 251 (11.3%)                            | –                             |
| 2010                         | 598 (8.6%)                          | 279 (12.6%)                            | –                             |
| 2011                         | 555 (8%)                            | 272 (12.2%)                            | –                             |
| 2012                         | 511 (7.3%)                          | 260 (11.7%)                            | 511 (25.0%)                   |
| 2013                         | 541 (7.8%)                          | 303 (13.6%)                            | 541 (26.4%)                   |
| 2014                         | 534 (7.7%)                          | 316 (14.2%)                            | 534 (26.0%)                   |
| 2015                         | 464 (6.7%)                          | 279 (12.6%)                            | 464 (22.6%)                   |
| RegistrY-DEFINED SEX         |                                     |                                        |                               |
| Female                       | 3,314 (47.6%)                       | 1,136 (51.1%)                          | 972 (47.4%)                   |
| Male                         | 3,643 (52.4%)                       | 1,087 (48.9%)                          | 1,078 (52.6%)                 |
| Age at diagnosis             |                                     |                                        |                               |
| 66-69                        | 1,817 (26.1%)                       | 554 (24.9%)                            | 543 (26.5)                    |
| 70-74                        | 2,076 (29.8%)                       | 654 (29.4%)                            | 620 (30.2)                    |
| 75-79                        | 1,674 (24.1%)                       | 540 (24.3%)                            | 460 (22.4)                    |
| 80-84                        | 1,003 (14.4%)                       | 343 (15.4%)                            | 304 (14.8%)                   |
| 85+                          | 387 (5.6%)                          | 132 (5.9%)                             | 123 (6%)                      |
| Marital status               |                                     |                                        |                               |
| Partnered                    | 4,015 (57.7%)                       | 1,184 (53.3%)                          | 1,142 (55.7%)                 |
| Single, Never Partnered      | 583 (8.4%)                          | 228 (10.3%)                            | 205 (10%)                     |
| Single, Previously Partnered | 2,116 (30.4%)                       | 718 (32.3%)                            | 610 (29.8%)                   |
| Other/Unknown                | 243 (3.5%)                          | 93 (4.2%)                              | 93 (4.5%)                     |
| Race/Ethnicity               |                                     |                                        |                               |
| Non-Hispanic White           | 5,471 (78.6%)                       | 1,679 (75.5%)                          | 1,555 (75.9%)                 |
| Non-Hispanic Black           | 687 (9.9%)                          | 225 (10.1%)                            | 228 (11.1%)                   |
| Hispanic                     | 444 (6.4%)                          | 172 (7.7%)                             | 157 (7.7%)                    |
| American Indian or Alaskan Native | SUP        | SUP                                    | SUP                           |
| Asian or Pacific Islander    | 322 (4.6%)                          | 135 (6.1%)                             | 95 (4.6%)                     |
| Other/Unknown                | SUP                                  | SUP                                    | SUP                           |
| Claims-based performance status |                                     |                                        |                               |
| 0                            | 5,798 (83.3%)                       | 1,823 (82%)                            | 1,721 (84%)                   |
| 1                            | 1,071 (15.4%)                       | 371 (16.7%)                            | 313 (15.3%)                   |
| 2 or 3                       | 88 (1.3%)                           | 29 (1.3%)                              | 16 (0.8%)                     |
| Charlson score               |                                     |                                        |                               |
| 0                            | 4,437 (63.8%)                       | 1,236 (55.6%)                          | 1,235 (60.2%)                 |
| 1                            | 1,429 (20.5%)                       | 519 (23.3%)                            | 424 (20.7%)                   |
| 2 or Higher                  | 1,091 (15.7%)                       | 468 (21.1%)                            | 391 (19.1%)                   |
| Pre-diagnosis prescription count |                                     |                                        |                               |
| 0–3                          | –                                    | 573 (25.8%)                            | –                             |
| 4–6                          | –                                    | 534 (24%)                              | –                             |
| 7–10                         | –                                    | 540 (24.3%)                            | –                             |
| 11 or more                   | –                                    | 576 (25.9%)                            | –                             |
| Other Treatments             |                                     |                                        |                               |
| Radiation                    | 691 (9.9%)                          | 210 (9.4%)                             | 170 (8.3%)                    |
| Primary site surgery         | 4,162 (59.8%)                       | 1,175 (52.9%)                          | 1,016 (49.6%)                 |
| Other surgery                | 1,120 (16.1%)                       | 343 (15.4%)                            | 306 (14.9%)                   |
| Tumor Grade                  |                                     |                                        |                               |
| Well differentiated           | 312 (4.5%)                          | 86 (3.9%)                              | 86 (4.2%)                     |
| Moderately differentiated    | 3,698 (53.2%)                       | 1,151 (51.8%)                          | 1,058 (51.6%)                 |
| Poorly or undifferentiated   | 1,603 (23%)                         | 481 (21.6%)                            | 389 (19%)                     |
| Other/unknown                | 1,344 (19.3%)                       | 505 (22.7%)                            | 517 (25.2%)                   |
| Side of Body                 |                                     |                                        |                               |
| Left                         | 3,050 (43.8%)                       | 957 (43%)                              | 884 (43.12%)                  |
| Right                        | 2,399 (34.5%)                       | 746 (33.6%)                            | 690 (33.7%)                   |
| Rectum                       | 1,102 (15.8%)                       | 358 (16.1%)                            | 344 (16.8%)                   |
| Large Intestine, NOS         | 406 (5.8%)                          | 144 (6.5%)                             | 132 (6.4%)                    |
was most frequent with medications metabolized by CYP2C19 (472, 21.2%) and CYP2D6 (1,466, 66%). When considering both chemotherapy and non-chemotherapy PGx at-risk exposure, most patients experienced two or more incident (1,524, 68.5%) and total (1,775, 79.8%) PGx at-risk exposures. (Fig. 3: Combined Chemotherapy and Non-Chemotherapy PGx at-Risk Exposure)

Next, we examined differences between patients receiving and not receiving non-chemotherapy PGx at-risk medications. The number of prescription medications that a patient was treated with prior to their diagnosis with mCRC had a significant impact on the odds of their incident and post-diagnosis exposure to a PGx at-risk non-chemotherapy medication. Pre-diagnosis prescription use increased the odds of incident exposure to PGx at-risk medications in the antidepressant therapeutic class (11+ prescriptions: 2.70, (1.41–5.17); 7–10 prescriptions: 3.08, (1.61–5.87), compared to 0–3 prescriptions). (Table 5: Predictors of PGx at-Risk non-Chemotherapy Exposure) Pre-diagnosis outpatient prescription use increased the odds of any exposure to a PGx at-risk antidepressant (4–6 prescriptions: 3.18, (1.74–5.80); 7–10 prescriptions: 5.54, (3.13–9.81); 11+ prescriptions: 9.48, (5.46–16.46)), cardiovascular (4–6: 2.74, (1.95–3.84); 7–10: 4.09, (2.94–5.68); 11+: 5.63 (4.09–7.76)), gastrointestinal (7–10: 1.37, (1.06–1.76); 11+: 1.83, (1.42–2.37)), and pain medications (11+: 1.55, (1.21–1.99)) compared to individuals with three or fewer pre-diagnosis prescriptions. Patient comorbidities increased the odds that an individual would be exposed to an incident prescription of a PGx

| Exposure | Total or incident | Number of exposures | Cohort 1: chemotherapy analysis (%) | Cohort 2: non-chemotherapy analysis (%) |
|----------|------------------|---------------------|-------------------------------------|----------------------------------------|
| PGx at-risk chemotherapy exposure | Total post-diagnosis | 0 | 915 (13.2) | 323 (14.5) |
| | 1 | 5307 (76.3) | 1692 (76.11) | |
| | 2 | 735 (10.6) | 208 (9.36) | |
| PGx at-risk non-chemotherapy exposure | Total post-diagnosis | 0 | – | 350 (15.74) |
| | 1 | – | 719 (32.34) | |
| | 2 | – | 630 (28.34) | |
| | 3 | – | 337 (15.16) | |
| | 4 | – | 140 (6.3) | |
| | 5 | – | 34 (1.53) | |
| | 6 or more | – | 13 (0.85) | |
| Incident post-diagnosis | 0 | – | 595 (26.77) | |
| | 1 | – | 957 (43.05) | |
| | 2 | – | 478 (21.5) | |
| | 3 | – | 155 (6.97) | |
| | 4 or more | – | 38 (1.6) | |
Table 3. Predictors of PGx at-Risk Chemotherapy Exposure.

| Variable                              | Level                        | N (% with exposure) | Unadjusted | Adjusted   |
|---------------------------------------|------------------------------|---------------------|------------|------------|
|                                       |                              |                     | Odds ratio (95% CI) | P Value   | Odds ratio (95% CI) | P Value   |
|                                       |                              |                     | P Value |                | P Value |                |
| Year                                  | 2004                         | 626 (92.1%)         | 0.71 (0.49–1.02) | 0.0640 | 0.69 (0.47–1.01) | 0.056    |
|                                       | 2005                         | 606 (89.1%)         | 0.46 (0.32–0.65) | <0.001 | 0.45 (0.31–0.66) | <0.001   |
|                                       | 2006                         | 529 (86.0%)         | 0.46 (0.32–0.65) | <0.001 | 0.45 (0.31–0.66) | <0.001   |
|                                       | 2007                         | 496 (84.1%)         | 0.46 (0.32–0.65) | <0.001 | 0.45 (0.31–0.66) | <0.001   |
|                                       | 2008                         | 519 (86.4%)         | 0.46 (0.32–0.65) | <0.001 | 0.45 (0.31–0.66) | <0.001   |
|                                       | 2009                         | 501 (85.2%)         | 0.46 (0.32–0.65) | <0.001 | 0.45 (0.31–0.66) | <0.001   |
|                                       | 2010                         | 514 (86.0%)         | 0.46 (0.32–0.65) | <0.001 | 0.45 (0.31–0.66) | <0.001   |
|                                       | 2011                         | 479 (86.3%)         | 0.46 (0.32–0.65) | <0.001 | 0.45 (0.31–0.66) | <0.001   |
|                                       | 2012                         | 442 (86.5%)         | 0.46 (0.32–0.65) | <0.001 | 0.45 (0.31–0.66) | <0.001   |
|                                       | 2013                         | 459 (84.8%)         | 0.46 (0.32–0.65) | <0.001 | 0.45 (0.31–0.66) | <0.001   |
|                                       | 2014                         | 470 (88.0%)         | 0.46 (0.32–0.65) | <0.001 | 0.45 (0.31–0.66) | <0.001   |
|                                       | 2015                         | 401 (86.4%)         | 0.46 (0.32–0.65) | <0.001 | 0.45 (0.31–0.66) | <0.001   |
| Registry-defined sex                  | Female                       | 2,853 (86.1%)       | 0.87 (0.79–1.21) | 0.379   |
|                                       | Male                         | 3,189 (87.5%)       | 0.87 (0.79–1.21) | 0.379   |
| Age at diagnosis                      | 66–69                        | 1,625 (89.4%)       | 0.87 (0.79–1.21) | 0.379   |
|                                       | 70–74                        | 1,853 (89.3%)       | 0.87 (0.79–1.21) | 0.379   |
|                                       | 75–79                        | 1,450 (86.6%)       | 0.87 (0.79–1.21) | 0.379   |
|                                       | 80–84                        | 832 (83.0%)         | 0.87 (0.79–1.21) | 0.379   |
|                                       | 85+                          | 282 (72.9%)         | 0.87 (0.79–1.21) | 0.379   |
| Marital status                        | Partnered                    | 3,512 (87.5%)       | 0.87 (0.79–1.21) | 0.379   |
|                                       | Single, never partnered      | 502 (86.1%)         | 0.87 (0.79–1.21) | 0.379   |
|                                       | Single, previously partnered | 1,815 (85.8%)       | 0.87 (0.79–1.21) | 0.379   |
|                                       | Other/Unknown                | 213 (87.7%)         | 0.87 (0.79–1.21) | 0.379   |
| Race/Ethnicity                        | Non-Hispanic White           | 4,790 (87.6%)       | 0.87 (0.79–1.21) | 0.379   |
|                                       | Non-Hispanic Black           | 610 (88.8%)         | 0.87 (0.79–1.21) | 0.379   |
|                                       | Hispanic                     | 363 (81.8%)         | 0.87 (0.79–1.21) | 0.379   |
|                                       | American Indian or Alaskan Native | SUP (<0.5%) | 0.87 (0.79–1.21) | 0.379   |
|                                       | Asian or Pacific Islander    | 252 (73.8%)         | 0.87 (0.79–1.21) | 0.379   |
|                                       | Other/Unknown                | 213 (87.7%)         | 0.87 (0.79–1.21) | 0.379   |
| Claims-based performance status       | 0                            | 5,047 (87.0%)       | 0.87 (0.79–1.21) | 0.379   |
|                                       | 1                            | 924 (86.3%)         | 0.87 (0.79–1.21) | 0.379   |
|                                       | 2 or 3                       | 71 (80.7%)          | 0.87 (0.79–1.21) | 0.379   |
| Charlson score                        | 0                            | 3,867 (87.2%)       | 0.87 (0.79–1.21) | 0.379   |
|                                       | 1                            | 1,237 (86.6%)       | 0.87 (0.79–1.21) | 0.379   |
|                                       | 2 or Higher                  | 938 (86.0%)         | 0.87 (0.79–1.21) | 0.379   |
| Radiation                             | No                           | 5,440 (86.8%)       | 0.87 (0.79–1.21) | 0.379   |
|                                       | Yes                          | 602 (87.1%)         | 0.87 (0.79–1.21) | 0.379   |
| Primary surgery                       | No                           | 2,424 (86.7%)       | 0.87 (0.79–1.21) | 0.379   |
|                                       | Yes                          | 3,618 (86.9%)       | 0.87 (0.79–1.21) | 0.379   |
| Other surgery                         | No                           | 5,052 (86.6%)       | 0.87 (0.79–1.21) | 0.379   |
|                                       | Yes                          | 990 (88.4%)         | 0.87 (0.79–1.21) | 0.379   |
| Tumor grade                           | Well differentiated          | 271 (86.9%)         | 0.87 (0.79–1.21) | 0.379   |
|                                       | Moderately differentiated    | 3,212 (86.9%)       | 0.87 (0.79–1.21) | 0.379   |
|                                       | Poorly or undifferentiated   | 1,390 (86.7%)       | 0.87 (0.79–1.21) | 0.379   |
|                                       | Other/Unknown                | 1,169 (87.0%)       | 0.87 (0.79–1.21) | 0.379   |
| Side of body                          | Left                         | 2,637 (86.5%)       | 0.87 (0.79–1.21) | 0.379   |
|                                       | Right                        | 2,089 (87.1%)       | 0.87 (0.79–1.21) | 0.379   |
|                                       | Rectum                       | 965 (87.6%)         | 0.87 (0.79–1.21) | 0.379   |
|                                       | Large intestine, NOS         | 351 (86.5%)         | 0.87 (0.79–1.21) | 0.379   |
| Rurality                              | Metropolitan/Unknown         | 5,024 (86.9%)       | 0.87 (0.79–1.21) | 0.379   |
|                                       | Urban                        | 659 (85.6%)         | 0.87 (0.79–1.21) | 0.379   |
|                                       | Rural                        | 359 (88.9%)         | 0.87 (0.79–1.21) | 0.379   |
| Census region                         | Midwest                      | 847 (92.2%)         | 0.87 (0.79–1.21) | 0.379   |
at-risk antidepressant (Charlson score of one: 1.64, (1.05–2.59)), while they decreased the odds that a patient would be exposed to an incident PGx at-risk pain medication (Charlson score of two or more: 0.77, (0.59–0.98)) compared to patients with a Charlson score of zero. Comorbidities increased the odds of total post-diagnosis PGx at-risk exposure to antidepressants (Charlson score of one: 1.55, (1.12–2.14); Charlson score of two or more: 1.81, (1.31–2.49)), and cardiovascular medications (Charlson score of one: 2.22, (1.75–2.80) Charlson score of two or more: 2.87, (2.27–3.64)) compared to patients with a Charlson score of zero. The third analytic cohort was comprised of 2,050 patients who were diagnosed on or after January 1st, 2012. In the year prior to diagnosis 12 (0.6%) patients had any claims for PGx testing. These 12 patients had claims for testing for variants in CYP2C9, CYP2C19, CYP2D6, VKORC1, HLA-B, or G6PD. No patients were tested for variants in UGT1A1. (Table 2: PGx at-Risk Exposure). In the timeframe after diagnosis, 13 (0.6%) patients had claims for any PGx testing, covering CYP2C9, CYP2C19, CYP2D6, VKORC1, UGT1A1, and G6PD. No patients were tested for variants in HLA-B. Fewer than 11 patients had claims for testing for any one of these genes.

**DISCUSSION**

This analysis found that 6,042 (86.9%) of patients treated with chemotherapy for mCRC are exposed to at least one PGx at-risk chemotherapy medication following diagnosis. Non-chemotherapy PGx at-risk exposure occurred in 1,628 (73.2%) of mCRC patients. These findings demonstrate that most patients with mCRC are newly exposed to at least two medications with known genetic variants that can result in treatment failure, significant adverse events, or death.

The NCCN clinical practice guidelines recommend treatment with a fluoropyrimidine for patients with mCRC and several recommend regimens in the first and subsequent line setting include irinotecan [2, 3]. This project represents a novel analysis of mCRC treatment patterns as we considered exposure to PGx at-risk medications as a whole, rather than distinct treatment regimens. Among the predictors explored in this analysis, age and race/ethnicity impacted PGx at-risk chemotherapy exposure, with older patients, as well as Hispanic or Asian or Pacific Islander patients, less likely to be exposed. Given that 89.6% of patients with a mCRC diagnosis treated with chemotherapy are exposed to a PGx at-risk chemotherapy, the clinical utility of these predictors in informing testing decisions is likely to be small. The reduced PGx at-risk chemotherapy exposure in older populations is potentially informed by the more common use of monoclonal antibodies in the 85+ year old population over cytotoxic chemotherapy, as monoclonal antibodies were classified as chemotherapy treatment in this analysis.

It is important to consider the findings around race and ethnicity as measurements of the impact of social constructs, rather than a biological hypothesis [33]. Multiple analyses have shown that the use of race and ethnicity in analyses of SEER and SEER-Medicare highlights the impact of uncontrollable socioeconomic factors and unmeasured social determinants of health [29, 34–38]. A review of screening, diagnosis, treatment, and outcome patterns across race and ethnicity identified that socioeconomic status and access to care drove racial differences in colon cancer care, not underlying biology [39]. A more recent review of screening and screening outcomes supports this finding [40]. In this light, our findings that Hispanic or Asian or Pacific Islander patients are less likely to be exposed to PGx at-risk chemotherapy should not be used to restrict PGx testing in this population. We demonstrate that the majority of patients that self-identify as Hispanic (81.8%) and Asian or Pacific Islander (78.3%) are still exposed to PGx at-risk chemotherapy.

The genes associated with the highest frequency of incident non-chemotherapy PGx at-risk medications were CYP2D6 (1,466, 66%) and CYP2C19 (472, 21.2%). Variants in these genes are included in CPIC guidelines for opioid pain medications, antidepressants, proton pump inhibitors, and ondansetron. These medications are recommended in the NCCN clinical practice guidelines for supportive care, but the only mention of PGx testing is found in the pain guidelines, where reactive testing is mentioned if toxicity or lack of efficacy has occurred [13–16]. It would be reasonable to not test for PGx variants if variant rates were low and the variants had low clinical impact. The drug-gene pairs considered in this analysis have strong or moderate levels of evidence supporting their use with clinical PGx guidelines and would support more widespread testing given the levels of exposure identified in this study and the corresponding potential clinical impact. This study establishes that patients with newly diagnosed mCRC are frequently exposed to medications impacted by variants in these genes, and the literature demonstrates these variants occur frequently and may have significant impact on quality of life. For example, between 4.4% and 5.5% of Americans are expected to carry variants in CYP2D6 resulting in an ultra-rapid metabolizer designation, while an additional 2.1–3.1% are classified as poor metabolizers [41, 42]. Ultra-rapid metabolizers are less likely to respond to ondansetron, increasing the odds of
Table 4. Medication and Test Exposure.

| Cohort 1 | Outcome category | Outcome       | Post-diagnosis exposure (%) | Incident exposure (%) |
|----------|------------------|---------------|-----------------------------|-----------------------|
| Chemotherapy | 5-Fluorouracil  | 5,910 (85)    | 5,910 (85)                  |
| Capecitabine | 22 (0.3)       | 22 (0.3)      |
| Any fluoropyrimidine | 5,931 (85.3)   | 5,931 (85.3)  |
| Irinotecan | 845 (12.2)     | 845 (12.2)    |
| Any PGx at-risk | 6,042 (86.9)   | 6,042 (86.9)  |
| Oxaliplatin | 4,803 (69.1)   | 4,803 (69.1)  |
| Bevacizumab | 3,403 (49)     | 3,403 (49)    |
| Cetuximab | 211 (3)        | 211 (3)       |
| Panitumumab | 47 (0.7)       | 47 (0.7)      |
| Genes     | DPYD            | 5,931 (85.3)  | 5,931 (85.3)                |
| UG1A1     | 845 (12.2)     | 845 (12.2)    |

| Cohort 2 | Non-chemotherapy | Outcome       | Post-diagnosis exposure (%) | Incident exposure (%) |
|----------|-------------------|---------------|-----------------------------|-----------------------|
| Amitriptyline | 28 (1.3)       | SUP (<0.5)    |
| Citalopram | 121 (5.44)      | 56 (2.5)      |
| Escitalopram | 67 (3.01)      | 32 (1.4)      |
| Nortriptyline | SUP (<0.5)   | SUP (<0.5)    |
| Paroxetine | 35 (1.6)        | 15 (0.6)      |
| Sertraline | 65 (2.9)        | 28 (1.26)     |
| Any antidepressant* | 244 (11)   | 104 (4.68)    |
| Clopidogrel | 141 (6.34)    | 13 (0.6)      |
| Simvastatin | 359 (16.15)   | 20 (0.9)      |
| Warfarin | 143 (6.43)     | 83 (3.7)      |
| Any cardiovascular | 570 (25.6)  | 113 (5.1)     |
| Lansoprazole | 46 (2.1)      | 25 (1.1)      |
| Omeprazole | 433 (19.5)     | 242 (10.9)    |
| Ondansetron | 1,333 (60)    | 1,238 (55.7)  |
| Pantoprazole | 169 (7.6)     | 137 (6.2)     |
| Any gastrointestinalb | 1,558 (70.1) | 1,393 (62.7)  |
| Celecoxib | 25 (1.1)       | SUP (<0.5)    |
| Codeine | 93 (4.18)       | 69 (3.1)      |
| Hydrocodone | 474 (21.3)    | 397 (17.9)    |
| Ibuprofen | 40 (1.8)        | 30 (1.35)     |
| Meloxicam | 24 (1.08)       | SUP (<0.5)    |
| Tramadol | 140 (6.3)       | 94 (6.3)      |
| Any painc | 701 (31.5)     | 568 (25.6)    |
| Genes     | CYP2C8          | 91 (4.1)      | 48 (2.2)                    |
| CYP2C9    | 242 (10.9)     | 132 (5.9)     |
| CYP2C19   | 846 (38.1)     | 472 (21.2)    |
| CYP2D6   | 1,608 (72.3)   | 1,466 (66)    |
| CYP4F2   | 143 (6.4)      | 83 (3.7)      |
| HLA-B    | 81 (3.6)       | 18 (0.8)      |
| SLCO1B1  | 359 (16.2)     | 20 (0.9)      |
| VKORC1   | 143 (6.4)      | 83 (3.7)      |

| Cohort 3 | Tests | Outcome       | Post-diagnosis exposure (%) | Incident exposure (%) |
|----------|-------|---------------|-----------------------------|-----------------------|
| CYP2C9 | SUP (<0.5) | SUP (<0.5) | SUP (<0.5) |
| CYP2C19 | SUP (<0.5) | SUP (<0.5) | SUP (<0.5) |
| CYP2D6 | SUP (<0.5) | SUP (<0.5) | SUP (<0.5) |
| G6PD   | SUP (<0.5) | SUP (<0.5) | SUP (<0.5) |
| HLA-B  | SUP (<0.5) | SUP (<0.5) | SUP (<0.5) |
| UG1A1  | SUP (<0.5) | SUP (<0.5) | SUP (<0.5) |
| VKORC1 | SUP (<0.5) | SUP (<0.5) | SUP (<0.5) |
| Any PGx test | 12 (0.6)   | 13 (0.6)    | 13 (0.6) |

Bold text indicates an aggregate outcome.

CYP Cytochrome P-450, G6PD Glucose-6-phosphate dehydrogenase, HLA Human Leukocyte Antigen, PGx Pharmacogenomic, SLCO1B1 Solute carrier organic anion transporter family member 1b1, UG1A1 Uridine diphospho-glucuronosyltransferase Family 1 Member A1, VKORC1 Vitamin K epoxide reductase complex subunit 1.

*Includes citalopram, escitalopram, fluvoxamine, paroxetine, sertraline, amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, and trimipramine.

bIncludes ondansetron, dexlansoprazole, Lansoprazole, omeprazole, and pantoprazole.

cIncludes celecoxib, flurbiprofen, ibuprofen, lornoxicam, meloxicam, naproxen, piroxicam, tenoxicam, codeine, hydrocodone, and tramadol.

dIncludes all medications listed above, as well as ifavaclof, efavirenz, voriconazole, fosphenytoin, phenytoin, atomoxetine, tamsulosin, rasburicase, carbamazepine, oxcarbazepine, abacavir, allopurinol, peginterferon alfa-2a, peginterferon alfa-2b, ribavirin, desflurane, enflurane, halothane, isoflurane, methoxyflurane, sevoflurane, succinylcholine, azathioprine, mercaptopurine, thioguanine, and azanavar.
In this analysis, 54.8% of patients had exposure to at least one prescription between 2011 and 2017 because it did not assess for the appropriate variants, negating any benefits of testing. A similar approach can be taken with the PGx at-risk chemotherapy agents. Decreased function variants for DPD occur in ~7% of patients of a European ancestry, and in 3-5% of patients of African ancestry [8]. With conservative estimates, this means that there were 178 individuals (3% of 5,931) treated with a fluoropyrimidine that likely experienced significant treatment-related toxicities that would have been reduced or prevented had they been genotyped prior to treatment. Approximately 10% of North Americans are likely to be homozygous for UGT1A1*28, the most common loss of function variant for this gene [45]. With 845 patients treated with irinotecan in this analysis, that represents a further 85 (10% of 845) individuals who were at increased risk of febrile neutropenia or death. Pre-treatment genetic testing would have likely prevented these events.

These findings also highlight which genes clinicians should consider when ordering PGx testing. A PGx panel that genotypes variants in CYP2D6, CYP2C19, DPD, and UGT1A1 represents the minimum set of genes that should be included on a panel for mCRC patients. However, clinicians should consider comorbidities, prior medication exposures, and potential future therapies and order a comprehensive panel if appropriate. In many cases the cost of single gene testing is similar to the cost of a comprehensive panel. Importantly, the variants screened for within each gene should also be considered, as not all panels screen for the same variants. This can impact outcomes in genes with multiple impactful variants, such as CYP2D6. There are 147 variants known to impact function in this gene [41, 42]. A panel without robust testing may misclassify a patient as not at risk because it did not assess for the appropriate variants, negating any benefit of testing.

Other large datasets have been used to explore the potential impact of implementing PGx testing in a variety of populations. The US Veterans Health Administration dataset was used to understand exposure to CPIC level A medications among veterans who received at least one prescription between 2011 and 2017 [46]. In this analysis, 54.8% of patients had exposure to at least one CPIC Level A medication. Simvastatin drove this finding, with SLC01B1 being the gene associated with the greatest number of prescriptions. The lower exposure rates found in this dataset are likely due to the study approach, where individuals were included when they filled a prescription of any sort, while our study identified individuals upon diagnosis with a specific disease.

Researchers within the Implementing GeNomics in practice (IGNITE) working groups have explored the prevalence of CPIC level A medications among pediatric and adult health systems [47]. In the analysis of 16 pediatric sites, medications metabolized by CYP2D6 and CYP2C19 were most frequently prescribed among all CPIC level A medications. This was driven by use of ondansetron and the opioid analgesics. A similar analysis of 11 adult health systems identified that medications metabolized by CYP2D6 and CYP2C19 were again most frequently prescribed [48]. These findings are in line with our findings, where we identified that CYP2D6 and CYP2C19 were the genes associated with the greatest number of PGx at-risk non-chemotherapy exposures. While neither of these analyses were able to separate incident from prevalent exposures, they found that between 15.7% and 17.6% of adult and 7.9–10.6% of pediatric patients treated in a given year at the included health systems were exposed to a CPIC level A medication [47, 48]. Given our finding that 97.9% (2,178 out of 2,223) of patients treated for mCRC are exposed to a PGx at-risk medication, this suggests that disease-focused PGx testing would identify more patients exposed to PGx at-risk medications than health-system level testing.

Patient privacy considerations prevent a direct report of the analysis of PGx testing in this study population. When using SEER data, patient counts of less than 11 cannot be reported directly. We showed that 0.63% of patients received testing. This is similar to the findings by Anderson et al., who found that 0.12% of the general population in the IQVIA claims registry received testing [49]. These claims estimates may underestimate the total number individuals who received testing by not including those who paid without insurance coverage. Likely representing a higher out-of-pocket burden to those that do receive testing without insurance coverage and acting as a deterrent for those who did not receive testing.
| Therapeutic class | Predictor variables | Total exposure | Incident exposure |
|-------------------|---------------------|----------------|-----------------|
|                   | Level               | N (%)          | OR (95% CI)     | P Value | N (%)          | OR (95% CI)     | P Value |
| Antidepressant    | Charlson score      |                |                |         |                |                |         |
|                   | 0                   | 108 (8.7%)     | 1.55 (1.12–2.14)| 0.01    | 49 (4.0%)      | 1.64 (1.05–2.59)| 0.032   |
|                   | 1                   | 67 (12.9%)     | 1.81 (1.31–2.49)| <0.001  | 22 (4.7%)      | 1.19 (0.71–2.00)| 0.5     |
|                   | 2 or Higher         | 69 (14.7%)     | 1.55 (1.12–2.14)| 0.01    | 13 (2.6%)      | 1.29 (0.82–2.04)| 0.27    |
|                   | Pre-diagnosis       |                |                |         |                |                |         |
|                   | prescription count  | 0–3            | 15 (2.6%)      | 1.55 (1.12–2.14)| 0.01    | 13 (2.6%)      | 1.29 (0.82–2.04)| 0.27    |
|                   |                     | 4–6            | 42 (7.9%)      | 1.81 (1.31–2.49)| <0.001  | 21 (3.9%)      | 1.76 (1.07–2.56)| 0.113   |
|                   |                     | 7–10           | 70 (13%)       | 2.87 (2.27–3.64)| <0.001  | 36 (6.7%)      | 3.08 (1.61–5.87)| <0.001  |
|                   |                     | 11 or more     | 117 (20.3%)    | 5.63 (4.09–7.76)| <0.001  | 34 (5.9%)      | 2.70 (1.41–5.17)| 0.003   |
| Cardiovascular    | Charlson score      |                |                |         |                |                |         |
|                   | 0                   | 221 (17.9%)    | 1.55 (1.12–2.14)| 0.01    | 56 (4.5%)      | 1.29 (0.82–2.04)| 0.27    |
|                   | 1                   | 169 (32.6%)    | 1.81 (1.31–2.49)| <0.001  | 30 (5.8%)      | 1.29 (0.80–2.07)| 0.29    |
|                   | 2 or Higher         | 180 (38.5%)    | 2.87 (2.27–3.64)| <0.001  | 27 (5.8%)      | 1.29 (0.80–2.07)| 0.29    |
|                   | Pre-diagnosis       |                |                |         |                |                |         |
|                   | prescription count  | 0–3            | 57 (9.9%)      | 1.55 (1.12–2.14)| 0.01    | 13 (2.6%)      | 1.29 (0.82–2.04)| 0.27    |
|                   |                     | 4–6            | 124 (23.2%)    | 1.81 (1.31–2.49)| <0.001  | 25 (4.7%)      | 1.29 (0.80–2.07)| 0.29    |
|                   |                     | 7–10           | 168 (31.1%)    | 5.63 (4.09–7.76)| <0.001  | 35 (6.1%)      | 1.14 (0.71–1.93)| 0.537   |
|                   |                     | 11 or more     | 221 (38.4%)    | 5.63 (4.09–7.76)| <0.001  | 34 (5.9%)      | 2.70 (1.41–5.17)| 0.003   |
| Gastrointestinal  | Charlson score      |                |                |         |                |                |         |
|                   | 0                   | 845 (69.1%)    | 1.55 (1.12–2.14)| 0.01    | 784 (63.4%)    | 1.00 (0.81–1.24)| 0.99    |
|                   | 1                   | 371 (37.1%)    | 1.81 (1.31–2.49)| <0.001  | 329 (63.4%)    | 1.00 (0.81–1.24)| 0.99    |
|                   | 2 or Higher         | 333 (71.2%)    | 2.87 (2.27–3.64)| <0.001  | 280 (59.8%)    | 0.86 (0.69–1.07)| 0.17    |
|                   | Pre-diagnosis       |                |                |         |                |                |         |
|                   | prescription count  | 0–3            | 367 (64%)      | 1.55 (1.12–2.14)| 0.01    | 35 (62%)       | 1.09 (0.86–1.40)| 0.472   |
|                   |                     | 4–6            | 367 (68.7%)    | 1.81 (1.31–2.49)| <0.001  | 342 (63.4%)    | 1.06 (0.83–1.35)| 0.635   |
|                   |                     | 7–10           | 383 (70.9%)    | 5.63 (4.09–7.76)| <0.001  | 354 (61.5%)    | 0.98 (0.77–1.24)| 0.863   |
|                   |                     | 11 or more     | 441 (76.6%)    | 5.63 (4.09–7.76)| <0.001  | 354 (61.5%)    | 0.98 (0.77–1.24)| 0.863   |
| Pain              | Charlson score      |                |                |         |                |                |         |
|                   | 0                   | 389 (31.5%)    | 1.55 (1.12–2.14)| 0.01    | 333 (26.9%)    | 1.00 (0.79–1.25)| 0.038   |
|                   | 1                   | 165 (31.8%)    | 1.81 (1.31–2.49)| 0.01    | 132 (25.4%)    | 0.92 (0.73–1.17)| 0.51    |
|                   | 2 or Higher         | 147 (31.4%)    | 2.87 (2.27–3.64)| <0.001  | 103 (22%)      | 0.77 (0.59–0.98)| 0.038   |
|                   | Pre-diagnosis       |                |                |         |                |                |         |
|                   | prescription count  | 0–3            | 158 (27.6)     | 1.55 (1.12–2.14)| 0.01    | 152 (26.5%)    | 1.00 (0.79–1.25)| 0.038   |
|                   |                     | 4–6            | 151 (28.3%)    | 1.81 (1.31–2.49)| <0.001  | 136 (25.5%)    | 0.95 (0.72–1.24)| 0.688   |
|                   |                     | 7–10           | 178 (33%)      | 2.87 (2.27–3.64)| <0.001  | 140 (25.9%)    | 0.97 (0.74–1.27)| 0.82    |
|                   |                     | 11 or more     | 214 (37.2%)    | 5.63 (4.09–7.76)| <0.001  | 140 (24.3%)    | 0.89 (0.68–1.16)| 0.387   |

Charlson Score was calculated without awarding points for metastatic cancer, as this was an inclusion criterion.
Blank cells represent the reference case.
There are several limitations associated with this analysis. Retrospective claims data only captures the treatments submitted and reimbursed by insurance companies, so patients may have received treatments with mCRC that this dataset did not capture. The Medicare population may not be generalizable to other populations with mCRC, especially the growing early onset mCRC Medicare population may not be generalizable to other populations. The findings of this study are available from The National Cancer Institute Division of Cancer Control and Population Sciences. (https://healthcaredelivery.cancer.gov/seemedicare/obtain/) Restrictions apply to the availability of these data, which were used under license for this study. The data that support the findings of this study are available from The National Cancer Institute Division of Cancer Control and Population Sciences. (https://healthcaredelivery.cancer.gov/seemedicare/obtain/) Restrictions apply to the availability of these data, which were used under license for this study.

REFERENCES

1. Siegel RL, Miller KD, Goding Sauer A, Fedewa SA, Butterfly LD, Anderson JC, et al. Colorectal cancer statistics, 2020. CA: a cancer J clinicians. 2020;70:145–64.
2. National Comprehensive Cancer Network. Rectal Cancer (2021.11) 2021 [Available from: https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf]
3. National Comprehensive Cancer Network. Colon Cancer (Version 2021.2) 2021 [Available from: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf]
4. Genentech. Xeloda [package insert]. Package Insert. South San Francisco, CA: 2020.
5. UppJohn Company. Camptosar [package insert]. Package Insert. New York, New York; 2020.
6. Fresenius Kabi U S, A LLC. Fluorouracil [package insert]. Package Insert. Lake Zurich, IL; 2017.
7. Innocenti F, Mills SC, Sanoff H, Ciccolini J, Lenz HJ, Milano G. All you need to know about DPYD genetic testing for patients treated with fluorouracil and capecitabine: a practitioner-friendly guide. Jco Oncol Pract. 2020;16:793–8.
8. Amstutz U, Henricks LM, Offer SM, Barbarino J, Schellens JHM, Sven JJ, et al. Clinical pharmacogenetics implementation consortium (CPIC) guideline for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing: 2017 update. Clin Pharm Ther. 2018;103:210–6.
9. Takano M, Sugiyama T. UGT1A1 polymorphisms in cancer: impact on irinotecan treatment. Pharmacogenomics personalized Med. 2017;10:61–8.
10. Van Cutsen E, Cervantes A, Adam R, Sobrojo A, Van Kireken JH, Aderka D, et al. ESOMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol: Off J Eur Soc Med Oncol. 2016;27:1386–422.
11. Lunenburg C, van der Wouden CH, Nijenhuis M, Cmuentunij-van Rhenen MH, de Boer-Veger NJ, Buunk AM, et al. Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction of DPYD and fluoropyrimidines. Eur J Hum Genet. 2020;28:508–17.
12. European Medications Agency. EMA recommendations on DPD testing prior to treatment with fluorouracil, capecitabine, tegafur and fluotyocine 2020 [Available from: https://www.ema.europa.eu/en/documents/referral/fluorouracil-capecitabine-fluotyocine-related-substances-article-31-referral-ema-recommendations-dpd-testing_en.pdf]
13. National Comprehensive Cancer Network. Distress Management (2021.1) 2021 [Available from: https://www.nccn.org/professionals/physician_gls/pdf/distress.pdf]
14. National Comprehensive Cancer Network. Cancer-Associated Venous Thromboembolic Disease (2021.1) 2021 [Available from: https://www.nccn.org/professionals/physician_gls/pdf/vte.pdf]
15. National Comprehensive Cancer Network. Antiemesis (2021.1) 2021 [Available from: https://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf]
16. National Comprehensive Cancer Network. Adult Cancer Pain (2021.1) 2021 [Available from: https://www.nccn.org/professionals/physician_gls/pdf/pain.pdf]
17. Clinical Pharmacogenomics Implementation Consortium [Available from: http://cpicpgx.org/]
18. Klein ME, Parvez MM, Shin JG. Clinical implementation of pharmacogenomics for personalized precision medicine: barriers and solutions. J Pharm Sci. 2017;106:2368–79.
19. Tuteja S, Haynes K, Zayac C, Sprague JE, Bernhardt B, Pyeitz R. Community pharmacists’ attitudes towards clinical utility and ethical implications of pharmacogenetic testing. Personalized Med. 2013;10:793–800.
20. Stanek EJ, Sanders CL, Taber KA, Khalid M, Patel A, Verbrugge RR, et al. Adoption of pharmacogenomic testing by US physicians: results of a nationwide survey. Clin Pharm Ther. 2012;91:450–8.
21. Zgeibh N, Arai T, Mahfouz SR, Sabra R. Attitudes of health care professionals toward pharmacogenetic testing. Mol Diag Ther. 2011;15:115–22.
22. Lau-Min KS, Varugheese LA, Nelson MN, Cambareri C, Reddy NJ, Oyer RA, et al. Preemptive pharmacogenetic testing to guide chemotherapy dosing in patients with gastrointestinal malignancies: a qualitative study of barriers to implementation. BMC Cancer. 2022;22:47.
23. National Cancer Institute. Surveillance, Epidemiology, and End Results 2021 [Available from: seer.cancer.gov]
24. En et al. Evaluation of the SEER-Medicare data: enhanced content and applications. J Natl Cancer Inst Monogr. 2019;2020:13–13.
25. National Cancer Institute, Division of Cancer Control Prevention. Cancer Medications Enquiry Database(CanMED) 2021 [Available from: https://seer.cancer.gov/oncologytoolbox/canmed/]
26. Hefi E, Blanco JG. Documenting pharmacogenomic testing with CPT codes. J AHIMA. 2016;87:56–9.
27. Andersen RM. National health surveys and the behavioral model of health services use. Med Care. 2008;46:647–53.
28. Charison M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol. 1994;47:1245–51.
29. Klubunde CN, Potosky AL, Legler JM, Warren JL. Development of a comorbidity index using physician claims data. J Clin Epidemiol. 2006;59:1238–67.
30. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol. 1992;45:633–9.
31. Jones CP. Invited commentary: “race,” racism, and the practice of epidemiology. Am J Epidemiol. 2001;154:299–304.
32. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol. 1992;45:633–9.
33. Jones CP. Invited commentary: “race,” racism, and the practice of epidemiology. Am J Epidemiol. 2001;154:299–304.
34. Abdel-Rahman O. Outcomes of non-metastatic colon cancer patients in relation to socioeconomic status: an analysis of SEER census tract-level socioeconomic database. Int J Clin Oncol. 2019;24:1582–7.
35. Gomez SL, O’Malley CD, Group A, Shema SJ, Sataniaro WA. Longitudinal, population-based study of racial/ethnic differences in colorectal cancer survival: impact of neighborhood socioeconomic status, treatment and comorbidity. BMC Cancer. 2007;7:193.
36. Le H, Zoigas A, Lipkin SM, Zell JA. Effects of socioeconomic status and treatment disparities in colorectal cancer survival. Cancer epidemiology, biomarkers & prevention. A publication of the American Association for Cancer Research cosponsored by the American Society of Preventive. Oncology 2008;17:1590–62.
37. Ohri A, Robinson A, Li B, Bhuket T, Wong R. Updated assessment of colorectal cancer incidence in the U.S. by Age, Sex, and Race/Ethnicity. Digestive Dis Sci. 2020;65:1838–49.
38. Carethers JM. Clinical and genetic factors to inform reducing colorectal cancer disparities in African Americans. Front Oncol. 2018;8:531.
39. Dimou A, Syrigos KN, Salf MW. Disparities in colorectal cancer in African-Americans vs Whites: before and after diagnosis. World J Gastroenterol. 2009;15:3734–43.

40. Rutter CM, Knudsen AB, Lin JS, Bouskill KBlack. and White Differences in Colorectal Cancer Screening and Screening Outcomes: A Narrative Review. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive. Oncology 2021;30:3–12.

41. PharmGkb. Gene-specific Information Tables for CYP2D6.

42. Whirl-Carrillo M, McDonagh EM, Hebert JM, Gong L, Sangkuhl K, Thorn CF, et al. Pharmacogenomics knowledge for personalized medicine. Clin Pharm Ther. 2012;92:414–7.

43. Bell GC, Caudle KE, Whirl-Carrillo M, Gordon RJ, Hikino K, Prows CA, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 Genotype and Use of Ondansetron and Tropisetron. Clin Pharmacol Therapeutics. 2017;102:213–8.

44. Crews KR, Monte AA, Huddart R, Caudle KE, Kharasch ED, Gaedigk A, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6, OPRM1, and COMT Genotypes and Select Opioid Therapy. Clin Pharmacol Ther. 2021;110:888–96.

45. Dean L Irinotecan Therapy and UGT1A1 Genotype Introduction. In: Victoria M Pratt SASMPBEMSKBLKaAJM, editor. Medical Genetics Summaries. Bethesda, Maryland: National Center for Biotechnology Information; 2015.

46. Chanfreau-Coffnier C, Hull LE, Lynch JA, DuVall SL, Damrauer SM, Cunningham FE, et al. Projected prevalence of actionable pharmacogenetic variants and level A Drugs prescribed among US veterans health administration pharmacy users. JAMA Netw Open. 2019;2:e195345.

47. Ramsey LB, Ong HH, Schildcrout JS, Shi Y, Tang LA, Hicks JK, et al. Prescribing prevalence of medications with potential genotype-guided dosing in pediatric patients. JAMA Netw Open. 2020;3:e2029411.

48. Hicks JK, El Rouby N, Ong HH, Schildcrout JS, Ramsey LB, Shi Y, et al. Opportunity for genotype-guided prescribing among adult patients in 11 US health systems. Clin Pharm Ther. 2021;110:179–88.

49. Anderson HD, Crooks KR, Kao DP, Aquilante CL. The landscape of pharmacogenetic testing in a US managed care population. Genet Med: Off J Am Coll Med Genet. 2020;22:1247–53.

50. Siegel RL, Jemal A, Ward EM. Increase in incidence of colorectal cancer among young men and women in the United States. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive. Oncology 2009;18:1695–8.

ACKNOWLEDGEMENTS

We would like to acknowledge the two anonymous reviewers for their thoughtful feedback and constructive criticism.

AUTHOR CONTRIBUTIONS

ZTR was responsible for designing the research proposal, conducting data analysis, interpreting the results, and drafting and revising this report. DJS contributed to conceiving this work, interpreting the results, and revising this report. JFF, KMK, and PAJ contributed to interpreting the results and revising this report. HMP acquired data for this project, contributed to conceiving this work, interpreting results, and revising this report.

COMPETING INTERESTS

ZTR received support through National Institutes of Health’s National Center for Advancing Translational Sciences, grants TL1R002493 and UL1TR002494 for his work on this project. JFF, KMK, and PAJ contributed to interpreting the results and revising this report. HMP acquired data for this project, contributed to conceiving this work, interpreting results, and revising this report.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41397-022-00276-6.

Correspondence and requests for materials should be addressed to Zachary T. Rivers.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.