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Opportunities for Personalizing Colorectal Cancer Care: An Analysis of SEER-Medicare Data

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Abstract

United States clinical practice guidelines for metastatic colorectal cancer recommend use of medications impacted by genetic variants but do not recommend testing. We analyzed real-world treatment using a cancer registry and claims dataset to explore pharmacogenomic (PGx) medication treatment patterns and characterize exposure. In a cohort of 6 957 patients, most (86.9%) were exposed to at least one chemotherapy medication with PGx guidelines. In a cohort of 2 223 patients with retail pharmacy claims available, most (79.2%) were treated with at least one non-chemotherapy (79.2%) medication with PGx guidelines. PGx-associated chemotherapy exposure was associated with age, race/ethnicity, educational attainment, and rurality. PGx-associated non-chemotherapy exposure was associated with medication use and comorbidities. The potential impact of PGx testing is large and policies aimed at increasing PGx testing at diagnosis may impact treatment decisions for patients with metastatic colorectal

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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.

Conflict of Interests

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cancer as most patients are exposed to medications with pharmacogenomics implications during treatment.

Introduction

In 2021, 150 000 Americans are projected to receive a diagnosis of colorectal cancer and 22% of those 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) Additionally, 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. Other objectives included an exploration of pre-treatment patient, disease, and environmental characteristics that impacted exposure to PGx at-risk medication in this population, as well as the insurance-reimbursed use of PGx testing in this population.

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 diagnosed 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 any colorectal cancer specific chemotherapy in the 3 months following the month of diagnosis. (Figure 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) Figure 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-chemotherapy. PGx at-risk chemotherapy exposure occurred when a claim was identified for a fluoropyrimidine or an irinotecan-containing medication. Non-chemotherapy exposure occurred when a claim was identified for a 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 (RUCC) 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 (RUCC 1–3), urban (RUCC 4–6), and rural (RUCC 7–9), with individuals of an unknown rurality (RUCC 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 4: 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 4)

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, 1 628 (73.2%) were exposed to at least one, while 671 (30.1%) were exposed to two or more. In the therapeutic class analysis, 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 3) Incident exposure 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. (Figure 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 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 socio-economic 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% to 3.1% are classified as poor metabolizers.(41, 42) Ultra-rapid

metabolizers are less likely to respond to ondansetron, increasing the odds of nausea and vomiting, while both ultrarapid and poor metabolizers are likely to either not respond or experience significant toxicity when treated with codeine or tramadol.(43, 44)

A similar approach can be taken with the PGx at-risk chemotherapy agents. Decreased function variants for *DPYD* 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*, *DPYD*, 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 prescriptions 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 *SLCO1B1* 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 prescriptions 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% to 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.

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 that this dataset did not capture. The Medicare population may not be generalizable to other populations with mCRC, especially the growing early onset mCRC population.(50) Previous work using this dataset has demonstrated that identifying capecitabine exposure can be challenging due to complex reimbursement systems.(51) Thus, our data may underestimate the exposure to fluoropyrimidines in this population.

This project serves as a springboard for additional exploration of the role of personalized medicine in oncology care. These results should inform clinical trial design to further characterize the impact of PGx-guided dosing and medication selection in the population of mCRC, by highlighting genes of interest to include on pre-emptive panel testing. Additionally, these results provide a springboard for a cost-effectiveness analysis to explore the likely financial and clinical outcomes observed with PGx testing. The research framework illustrated here, using claims data to identify opportunities for PGx-informed treatment can be translated to other disease states. Pancreatic cancer is treated with similar chemotherapy regimens, and fluoropyrimidines are used in the management of breast cancer, as well as tamoxifen, another agent with PGx guidelines.(52, 53) This approach should also be applied to commercial claims data, to explore treatment opportunities in the rising population of young adults diagnosed with mCRC.(50)

Our analysis demonstrates that most patients over the age of 65 treated with chemotherapy for mCRC are exposed to multiple PGx at-risk medications, and that this exposure is relatively constant across the population. PGx testing at or around the time of diagnosis has a significant opportunity to identify patients at risk of treatment-related morbidity and mortality and preemptively modify therapies which may reduce healthcare costs and improve quality of life.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement

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/seermedicare/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, Butterly LF, Anderson JC, et al. Colorectal cancer statistics, 2020. CA: a cancer journal for clinicians. 2020;70(3):145–64. [PubMed: 32133645]
2. National Comprehensive Cancer Network. Rectal Cancer (2021.1) 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. Upjohn Company. Camptosar [package insert]. Package Insert. New York, New York.; 2020.
6. Freseneius 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 Oncology Practice. 2020;16(12):793–8. [PubMed: 33197222]
8. Amstutz U, Henricks LM, Offer SM, Barbarino J, Schellens JHM, Swen JJ, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 Update. Clin Pharmacol Ther. 2018;103(2):210–6. [PubMed: 29152729]
9. Takano M, Sugiyama T. UGT1A1 polymorphisms in cancer: impact on irinotecan treatment. Pharmacogenomics and personalized medicine. 2017;10:61–8. [PubMed: 28280378]
10. Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Annals of oncology : official journal of the European Society for Medical Oncology. 2016;27(8):1386–422. [PubMed: 27380959]
11. Lunenburg C, van der Wouden CH, Nijenhuis M, Crommentuijn-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(4):508–17. [PubMed: 31745289]
12. European Medical Association. EMA recommendations on DPD testing prior to treatment with fluorouracil, capecitabine, tegafur and flucytosine 2020 [Available from: https://www.ema.europa.eu/en/documents/referral/fluorouracil-fluorouracil-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: https://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(9):2368–79. [PubMed: 28619604]
19. Tuteja S, Haynes K, Zayac C, Sprague JE, Bernhardt B, Pyeritz R. Community pharmacists' attitudes towards clinical utility and ethical implications of pharmacogenetic testing. Personalized medicine. 2013;10(8):793–800. [PubMed: 24409195]
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 Pharmacol Ther. 2012;91(3):450–8. [PubMed: 22278335]
21. Zgheib NK, Arawi T, Mahfouz RA, Sabra R. Attitudes of health care professionals toward pharmacogenetic testing. Molecular diagnosis & therapy. 2011;15(2):115–22. [PubMed: 21623646]
22. Lau-Min KS, Varughese 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(1):47. [PubMed: 34996412]
23. National Cancer Institute. Surveillance, Epidemiology, and End Results 2021 [Available from: seer.cancer.gov.
24. Enewold L, Parsons H, Zhao L, Bott D, Rivera DR, Barrett MJ, et al. Updated Overview of the SEER-Medicare Data: Enhanced Content and Applications. J National Cancer Inst Monogr. 2019;2020(55):3–13.
25. National Cancer Insititue, Division of Cancer Control Population Sciences. Cancer Medications Enquiry Database(CanMED) 2021 [Available from: https://seer.cancer.gov/oncologytoolbox/canmed/.
26. Hefti E, Blanco JG. Documenting Pharmacogenomic Testing with CPT Codes. J AHIMA. 2016;87(1):56–9.
27. Warren JL, Harlan LC, Fahey A, Virnig BA, Freeman JL, Klabunde CN, et al. Utility of the SEER-Medicare data to identify chemotherapy use. Med Care. 2002;40(8 Suppl):IV-55–61.
28. Andersen RM. National health surveys and the Behavioral Model of Health Services Use. Medical Care. 2008;46(7):647–53. [PubMed: 18580382]
29. Davidoff AJ, Rapp T, Onukwugha E, Zuckerman IH, Hanna N, Pandya N, et al. Trends in disparities in receipt of adjuvant therapy for elderly stage III colon cancer patients: the role of the medical oncologist evaluation. Med Care. 2009;47(12):1229–36. [PubMed: 19786906]
30. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. Journal of clinical epidemiology. 1994;47(11):1245–51. [PubMed: 7722560]
31. Klabunde CN, Potosky AL, Legler JM, Warren JL. Development of a comorbidity index using physician claims data. Journal of clinical epidemiology. 2000;53(12):1258–67. [PubMed: 11146273]
32. Deyo RA, Cherkin DC, Ciol MA. Adapting a Clinical Comorbidity Index for Use with Icd-9-Cm Administrative Databases. Journal of clinical epidemiology. 1992;45(6):613–9. [PubMed: 1607900]
33. Jones CP. Invited commentary: "race," racism, and the practice of epidemiology. Am J Epidemiol. 2001;154(4):299–304; discussion 5–6. [PubMed: 11495851]
34. Abdel-Rahman O Outcomes of non-metastatic colon cancer patients in relationship to socioeconomic status: an analysis of SEER census tract-level socioeconomic database. Int J Clin Oncol. 2019;24(12):1582–7. [PubMed: 31240498]
35. Gomez SL, O'Malley CD, Stroup A, Shema SJ, Satariano 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(1):193. [PubMed: 17939875]

36. Le H, Ziogas 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(8):1950–62.
37. Ohri A, Robinson A, Liu B, Bhuket T, Wong R. Updated Assessment of Colorectal Cancer Incidence in the U.S. by Age, Sex, and Race/Ethnicity. Digestive diseases and sciences. 2020;65(6):1838–49. [PubMed: 31701261]
38. Carethers JM. Clinical and Genetic Factors to Inform Reducing Colorectal Cancer Disparitites in African Americans. Front Oncol. 2018;8:531. [PubMed: 30524961]
39. Dimou A, Syrigos KN, Saif MW. Disparities in colorectal cancer in African-Americans vs Whites: before and after diagnosis. World J Gastroenterol. 2009;15(30):3734–43. [PubMed: 19673013]
40. Rutter CM, Knudsen AB, Lin JS, Bouskill KE. Black 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(1):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 Pharmacol Ther. 2012;92(4):414–7. [PubMed: 22992668]
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. Clinical Pharmacology & Therapeutics. 2017;102(2):213–8. [PubMed: 28002639]
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.
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-Coffinier 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(6):e195345. [PubMed: 31173123]
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(12):e2029411. [PubMed: 33315113]
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 Pharmacol Ther. 2021;110(1):179–88. [PubMed: 33428770]
49. Anderson HD, Crooks KR, Kao DP, Aquilante CL. The landscape of pharmacogenetic testing in a US managed care population. Genetics in medicine : official journal of the American College of Medical Genetics. 2020;22(7):1247–53. [PubMed: 32291400]
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(6):1695–8.
51. Lund JL, Sturmer T, Harlan LC, Sanoff HK, Sandler RS, Brookhart MA, et al. Identifying specific chemotherapeutic agents in Medicare data: a validation study. Med Care. 2013;51(5):e27–34. [PubMed: 22080337]
52. National Comprehensive Cancer Network. Breast Cancer (2021.5) 2021 [Available from: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.

53. Tempero MA. NCCN Guidelines Updates: Pancreatic Cancer. J Natl Compr Canc Netw. 2019;17(5.5):603–5. [PubMed: 31117041]

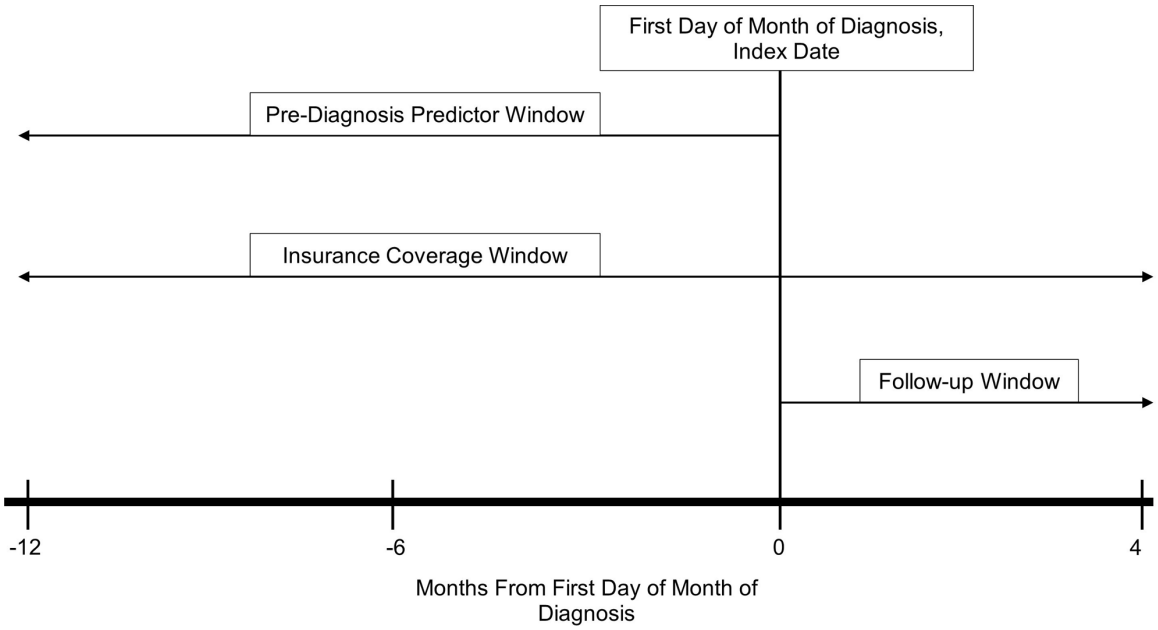

Figure 1:
Study Design Diagram
None

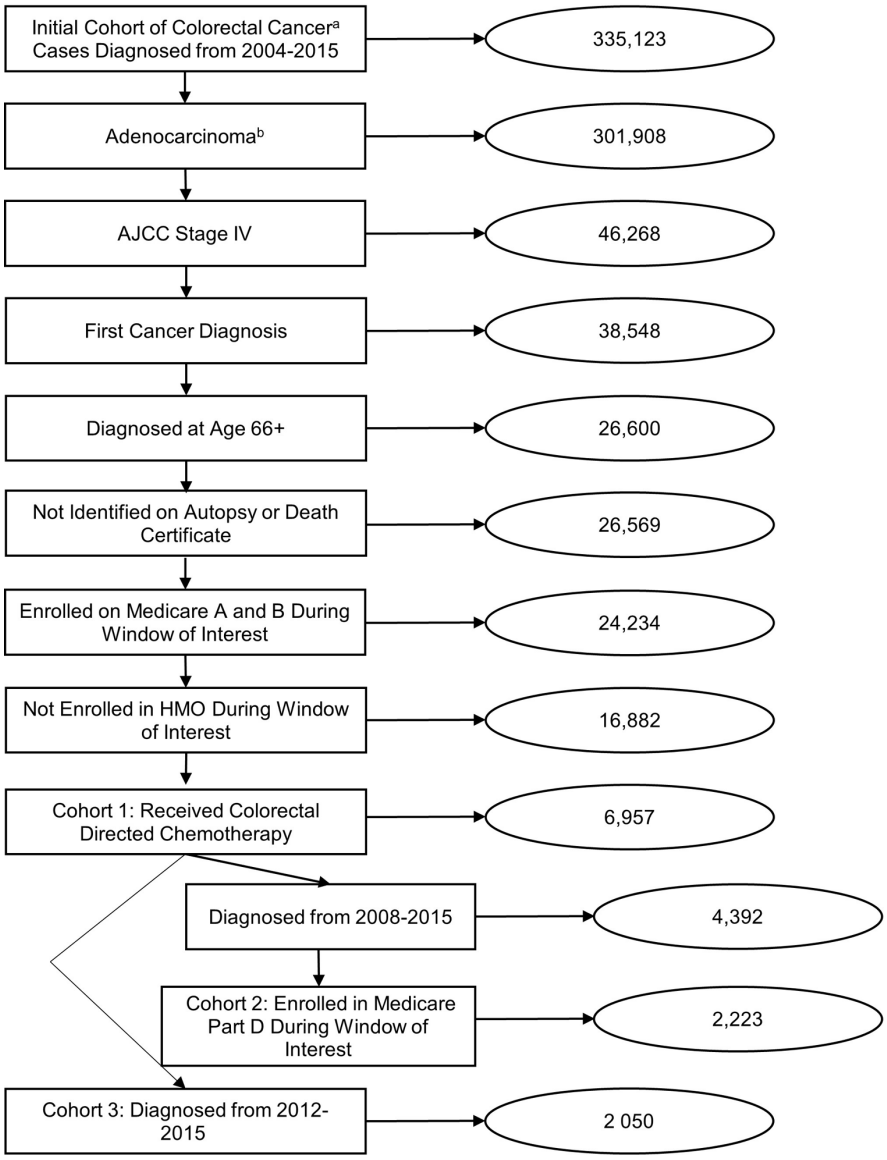

Figure 2:

Cohort Identification

[a] ICD-O codes used: C18.0, C18.2, C18.3, C18.4, C18.5, C18.6, C18.7, C18.8, C18.9, C19.9, C20.9, C26.0

[b] Histology codes used: 814, 821, 822, 826, 848, 857

AJCC: American Joint Committee on Cancer, HMO: Health Maintenance Organization

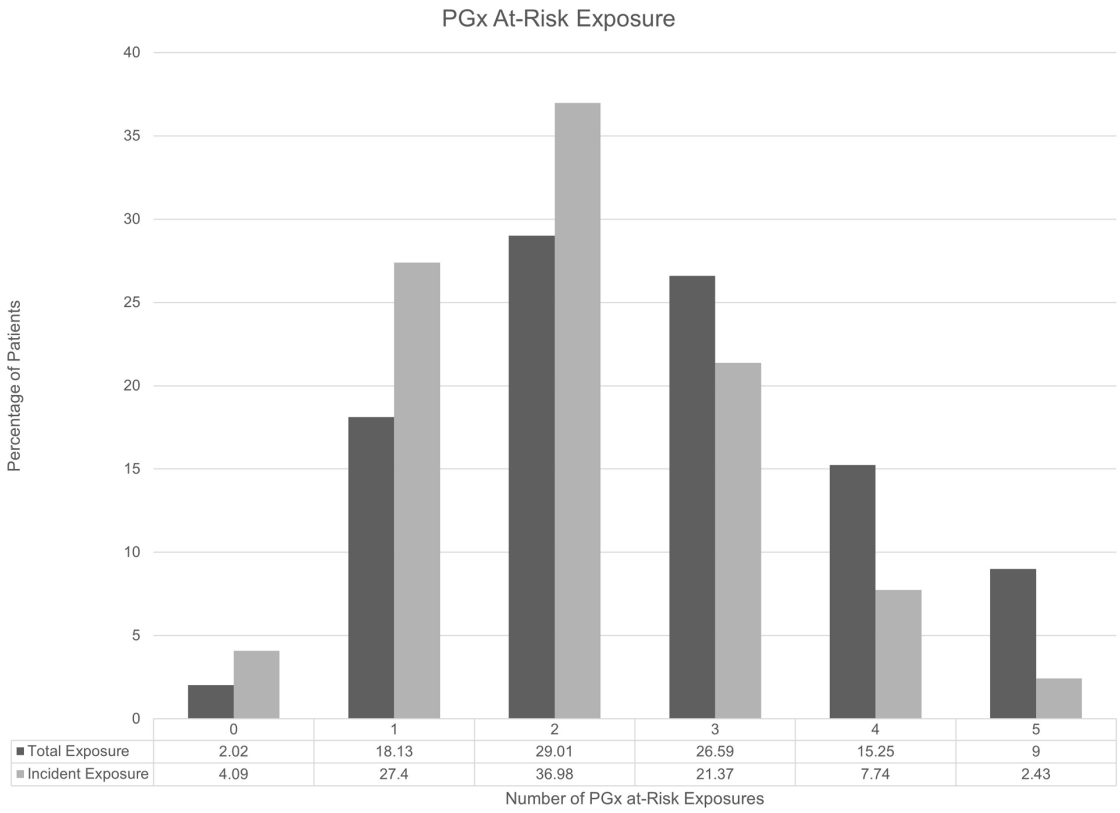

Figure 3:
Combined Chemotherapy and Non-Chemotherapy PGx at-Risk Exposure

None

Table 1:

Predictor Variable Distributions

		Cohort 1: Chemotherapy Analysis (%)	Cohort 2: Non-Chemotherapy Analysis (%)	Cohort 3: Testing Analysis (%)
	Total Patients	6 957	2 223	2 050
Variable	Level			
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%)

		Cohort 1: Chemotherapy Analysis (%)	Cohort 2: Non-Chemotherapy Analysis (%)	Cohort 3: Testing Analysis (%)
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	1091 (15.7%)	468 (21.1%)	391 (19.1%)
Pre-Diagnosis Prescription Count	0 to 3	-	573 (25.8%)	-
	4 to 6	-	534 (24%)	-
	7 to 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%)
Rurality	Metropolitan/Unknown	5 783 (83.1%)	1 805 (81.2%)	1 688 (82.3%)
	Urban	770 (11.1%)	276 (12.4%)	238 (11.6%)
	Rural	404 (5.8%)	142 (6.4%)	124 (6.1%)
Census Region	Midwest	919 (13.2%)	290 (13%)	262 (12.8%)
	Northeast	1 606 (23.1%)	519 (23.3%)	478 (13.3%)
	West	2 618 (37.6%)	840 (37.8%)	749 (36.5%)
	South	1 814 (26.1%)	574 (25.8%)	561 (27.4%)
Race, Ethnicity, and Age Matched Education	At Least 4 Years of College	2 178 (31.3%)	729 (32.8%)	670 (32.7%)
	Some College	1 707 (24.5%)	520 (23.4%)	506 (24.7%)
	High School	2 438 (35%)	783 (35.2%)	724 (35.3%)
	No High School Diploma	467 (6.7%)	146 (6.6%)	105 (5.1%)
	Missing	167 (2.4%)	45 (2.0%)	45 (2.2%)
Race, Ethnicity, and Age Matched Poverty	Less than 20% inviduals below Poverty Line	6 310 (90.7%)	1 993 (89.7%)	1 856 (90.5%)
	At least 20% of individuals below Poverty Line	647 (9.3%)	230 (10.3%)	194 (9.5%)

NOS: Not otherwise specified

SUP: Value suppressed due to data use agreement to protect patient confidentiality.

Pre-Diagnosis Prescription Count not calculated for cohorts 1 and 3 as Medicare part D coverage was not an inclusion criterion.

Table 2:

PGx at-Risk Exposure

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)

No Legend

Table 3:

Medication and Test Exposure

Cohort	Outcome Category	Outcome	Post-Diagnosis Exposure (%)	Incident Exposure (%)
Cohort 1	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)
		UGT1A1	845 (12.2)	845 (12.2)
Cohort 2	Non-Chemotherapy	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 Gastrointestinal **	**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 Pain ***	**701 (31.5)**	**568 (25.6)**
		Any PGx at-Risk ****	**1 871 (84.6)**	**1 631 (73.4)**
	Genes	CYP2C8	91 (4.1)	48 (2.2)

Cohort	Outcome Category	Outcome	Post-Diagnosis Exposure (%)	Incident Exposure (%)
		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	CYP2C9	SUP (<0.5)	SUP (<0.5)
		CYP2C19	SUP (<0.5)	SUP (<0.5)
		CYP2D6	SUP (<0.5)	SUP (<0.5)
		G6PD	SUP (<0.5)	SUP (<0.5)
		HLA-B	SUP (<0.5)	SUP (<0.5)
		UGT1A1	SUP (<0.5)	SUP (<0.5)
		VKORC1	SUP (<0.5)	SUP (<0.5)
		Any PGx Test	**12 (0.6)**	**13 (0.6)**

Bold text indicates an aggregate outcome.

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

**Includes ondansetron, dexlansoprazole, lansoprazole, omeprazole, and pantoprazole.

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

****Includes all medications listed above, as well as ivacaftor, efavirenz, voriconazole, fosphenytoin, phenytoin, atomoxetine, tamoxifen, tacrolimus, rasburicase, carbamazepine, oxcarbazepine, abacavir, allopurinol, peginterferon alfa-2a, peginterferon alfa-2b, ribavirin, desflurane, enflurane, halothane, isoflurane, methoxyflurane, sevoflurane, succinylcholine, azathioprine, mercaptopurine, thioguanine, atazanavir.

CYP: Cytochrome P-450, G6PD: Glucose-6-phosphate dehydrogenase, HLA: Human Leukocyte Antigen, PGx: Pharmacogenomic, SLCO1B1: Solute carrier organic anion transporter family member 1b1, UGT1A1: Uridine diphospho-glucuronosyltransferase Family 1 Member A1, VKORC1: Vitamin K epoxide reductase complex subunit 1.

Table 4:

Predictors of PGx at-Risk Chemotherapy Exposure

			Unadjusted		Adjusted	
Variable	**Level**	**N (% with exposure)**	**Odds Ratio (95% CI)**	**P-Value**	**Odds Ratio (95% CI)**	**P-Value**
Year	2004	626 (92.1%)				
	2005	606 (89.1%)	0.71 (0.49–1.02)	0.0640	0.69 (0.47–1.01)	0.056
	2006	529 (86.0%)	0.53 (0.37–0.76)	<0.001	0.52 (0.36–0.76)	<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%)	0.55 (0.38–0.78)	0.0010	0.6 (0.41–0.88)	0.008
	2009	501 (85.2%)	0.5 (0.35–0.71)	<0.001	0.52 (0.36–0.76)	<0.001
	2010	514 (86.0%)	0.53 (0.37–0.76)	<0.001	0.54 (0.37–0.79)	0.001
	2011	479 (86.3%)	0.54 (0.38–0.79)	0.0010	0.54 (0.37–0.80)	0.002
	2012	442 (86.5%)	0.55 (0.38–0.81)	0.0020	0.6 (0.40–0.89)	0.011
	2013	459 (84.8%)	0.48 (0.34–0.69)	<0.001	0.49 (0.33–0.72)	<0.001
	2014	470 (88.0%)	0.63 (0.43–0.93)	0.0190	0.62 (0.42–0.93)	0.02
	2015	401 (86.4%)	0.55 (0.37–0.81)	0.0020	0.61 (0.40–0.91)	0.017
Registry-Defined Sex	Female	2 853 (86.1%)				
	Male	3 189 (87.5%)	1.14 (0.99–1.3)	0.0740	1.13 (0.97–1.32)	0.108
Age at Diagnosis	66–69	1 625 (89.4%)				
	70–74	1 853 (89.3%)	0.98 (0.8–1.2)	0.8600	0.98 (0.79–1.21)	0.837
	75–79	1 450 (86.6%)	0.76 (0.62–0.94)	0.0110	0.74 (0.60–0.91)	0.005
	80–84	832 (83.0%)	0.57 (0.46–0.72)	<0.001	0.54 (0.43–0.69)	<0.001
	85+	282 (72.9%)	0.32 (0.24–0.42)	<0.001	0.3 (0.22–0.39)	<0.001
Marital Status	Partnered	3 512 (87.5%)				
	Single, Never Partnered	502 (86.1%)	0.89 (0.69–1.14)	0.3550	0.87 (0.67–1.14)	0.311
	Single, Previously Partnered	1 815 (85.8%)	0.86 (0.74–1.01)	0.0610	0.98 (0.83–1.17)	0.848
	Other/Unknown	213 (87.7%)	1.02 (0.69–1.51)	0.9340	0.95 (0.63–1.43)	0.812
Race/Ethnicity	Non-Hispanic White	4 790 (87.6%)				
	Non-Hispanic Black	610 (88.8%)	1.13 (0.88–1.45)	0.3520	0.88 (0.66–1.17)	0.379
	Hispanic	363 (81.8%)	0.64 (0.49–0.82)	<0.001	0.74 (0.55–0.98)	0.037
	American Indian or Alaskan Native	SUP (<0.5%)	0.6 (0.22–1.59)	0.3020	0.7 (0.25–1.93)	0.489
	Asian or Pacific Islander	252 (78.3%)	0.51 (0.39–0.67)	<0.001	0.7 (0.52–0.95)	0.02
	Other/Unknown	SUP (<0.5%)	0.85 (0.1–7.1)	0.8830	0.86 (0.10–7.41)	0.888
Claims-Based Performance Status	0	5 047 (87.0%)				
	1	924 (86.3%)	0.94 (0.77–1.13)	0.4910	1 (0.81–1.24)	0.988
	2 or 3	71 (80.7%)	0.62 (0.36–1.06)	0.0810	0.73 (0.41–1.31)	0.291
Charlson Score	0	3 867 (87.2%)				
	1	1 237 (86.6%)	0.95 (0.8–1.13)	0.5640	1.01 (0.83–1.21)	0.958

			Unadjusted		Adjusted	
Variable	**Level**	**N (% with exposure)**	**Odds Ratio (95% CI)**	**P-Value**	**Odds Ratio (95% CI)**	**P-Value**
	2 or Higher	938 (86.0%)	0.9 (0.75–1.1)	0.3020	1.01 (0.81–1.26)	0.929
Radiation	No	5 440 (86.8%)				
	Yes	602 (87.1%)	1.03 (0.81–1.3)	0.8250	1.01 (0.77–1.32)	0.954
Primary Surgery	No	2 424 (86.7%)				
	Yes	3 618 (86.9%)	1.02 (0.88–1.17)	0.8060	0.94 (0.79–1.13)	0.534
Other Surgery	No	5 052 (86.6%)				
	Yes	990 (88.4%)	1.18 (0.97–1.44)	0.0950	1.08 (0.87–1.33)	0.495
Tumor Grade	Well Differentiated	271 (86.9%)				
	Moderately differentiated	3 212 (86.9%)	1 (0.71–1.41)	1.0000	0.97 (0.68–1.40)	0.884
	Poorly or Undifferentiated	1 390 (86.7%)	0.99 (0.69–1.41)	0.9440	1 (0.68–1.46)	0.998
	Other/Unknown	1 169 (87.0%)	1.01 (0.7–1.46)	0.9550	0.97 (0.65–1.45)	0.893
Side of Body	Left	2 637 (86.5%)				
	Right	2 089 (87.1%)	1.06 (0.9–1.24)	0.5040	0.95 (0.80–1.12)	0.534
	Rectum	965 (87.6%)	1.1 (0.9–1.36)	0.3520	1.08 (0.84–1.38)	0.538
	Large Intestine, NOS	351 (86.5%)	1 (0.74–1.35)	0.9970	1.01 (0.72–1.40)	0.972
Rurality	Metropolitan/Unknown	5 024 (86.9%)				
	Urban	659 (85.6%)	0.9 (0.72–1.11)	0.3220	0.69 (0.54–0.87)	0.002
	Rural	359 (88.9%)	1.21 (0.88–1.66)	0.2520	0.8 (0.57–1.13)	0.205
Census Region	Midwest	847 (92.2%)				
	Northeast	1 432 (89.2%)	0.7 (0.52–0.93)	0.0150	0.75 (0.55–1.02)	0.064
	West	2 152 (82.2%)	0.39 (0.3–0.51)	<0.001	0.39 (0.29–0.53)	<0.001
	South	1 611 (88.8%)	0.67 (0.51–0.89)	0.0060	0.71 (0.53–0.95)	0.02
Race, Ethnicity, and Age Matched Education	At Least 4 Years of College	1 839 (84.4%)				
	Some College	1 480 (86.7%)	1.2 (1–1.44)	0.0470	1.41 (1.15–1.73)	0.001
	High School	2 182 (89.5%)	1.57 (1.32–1.87)	<0.001	1.19 (0.97–1.46)	0.1
	No High School Diploma	399 (85.4%)	1.08 (0.82–1.43)	0.5850	1.27 (0.92–1.73)	0.142
Race, Ethnicity, and Age Matched Poverty	Less than 20% inviduals below Poverty Line	5 482 (86.9%)				
	At least 20% of individuals below Poverty Line	560 (86.6%)	0.97 (0.77–1.23)	0.8140	1.02 (0.77–1.34)	0.893

NOS: Not Otherwise Specified

SUP: Value suppressed due to data use agreement to protect patient confidentiality.

Blank cells represent the reference case.

Table 5:

Predictors of PGx at-Risk non-Chemotherapy Exposure

			Total Exposure			Incident Exposure		
Therapeutic Class	**Predictor Variables**	**Level**	**N (%)**	**OR (95% CI)**	**P-Value**	**N (%)**	**OR (95% CI)**	**P-Value**
Antidepressant	Charlson Score	0	108 (8.7%)			49 (4.0%)		
		1	67 (12.9%)	1.55 (1.12–2.14)	0.01	33 (6.4%)	1.64 (1.05–2.59)	0.032
		2 or Higher	69 (14.7%	1.81 (1.31–2.49)	<0.001	22 (4.7%)	1.19 (0.71–2.00)	0.5
	Pre-Diagnosis Prescription Count	0 to 3	15 (2.6%)			13 (2.3%)		
		4 to 6	42 (7.9%)	3.18 (1.74–5.80)	<0.001	21 (3.9%)	1.76 (0.87–3.56)	0.113
		7 to 10	70 (13%)	5.54 (3.13–9.81)	<0.001	36 (6.7%)	3.08 (1.61–5.87)	<0.001
		11 or more	117 (20.3%)	9.48 (5.46–16.46)	<0.001	34 (5.9%)	2.70 (1.41–5.17)	0.003
Cardiovascular	Charlson Score	0	221 (17.9%)			56 (4.5%)		
		1	169 (32.6%)	2.22 (1.75–2.80)	<0.001	30 (5.8%)	1.29 (0.82–2.04)	0.27
		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 to 3	57 (9.9%)			30 (5.2%		
		4 to 6	124 (23.2%)	2.74 (1.95–3.84)	<0.001	25 (4.7%)	0.89 (0.52–1.53)	0.672
		7 to 10	168 (31.1%)	4.09 (2.94–5.68)	<0.001	23 (4.3%)	0.81 (0.46–1.40)	0.446
		11 or more	221 (38.4%)	5.63 (4.09–7.76)	<0.001	35 (6.1%)	1.14 (0.71–1.93)	0.537
Gastrointestinal	Charlson Score	0	845 (69.1%)			784 (63.4%)		
		1	371 (71.5%)	1.12 (0.89–1.40)	0.32	329 (63.4%)	1.00 (0.81–1.24)	0.99
		2 or Higher	333 (71.2%)	1.10 (0.87–1.39)	0.41	280 (59.8%)	0.86 (0.69–1.07)	0.17
	Pre-Diagnosis Prescription Count	0 to 3	367 (64%)			355 (62%)		
		4 to 6	367 (68.7%)	1.23 (0.96–1.58)	0.1	342 (64%)	1.09 (0.86–1.40)	0.472
		7 to 10	383 (70.9%)	1.37 (1.06–1.76)	0.02	342 (63.3%)	1.06 (0.83–1.35)	0.635

			Total Exposure			Incident Exposure		
Therapeutic Class	**Predictor Variables**	**Level**	**N (%)**	**OR (95% CI)**	**P-Value**	**N (%)**	**OR (95% CI)**	**P-Value**
		11 or more	441 (76.6%)	1.83 (1.42–2.37)	<0.001	354 (61.5%)	0.98 (0.77–1.24)	0.863
Pain	Charlson Score	0	389 (31.5%)			333 (26.9%)		
		1	165 (31.8%)	1.01 (0.81–1.27)	0.9	132 (25.4%)	0.92 (0.73–1.17)	0.51
		2 or Higher	147 (31.4%)	1.00 (0.79–1.25)	0.98	103 (22%)	0.77 (0.59–0.98	0.038
	Pre-Diagnosis Prescription Count	0 to 3	158 (27.6)			152 (26.5%)		
		4 to 6	151 (28.3%)	1.04 (0.80–1.35)	0.79	136 (25.5%)	0.95 (0.72–1.24)	0.688
		7 to 10	178 (33%)	1.29 (1.00–1.67)	0.05	140 (25.9%)	0.97 (0.74–1.27)	0.82
		11 or more	214 (37.2%)	1.55 (1.21–1.99)	<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