


Feasibility of Integrating Panel-Based Pharmacogenomics Testing for Chemotherapy and Supportive Care in Patients With Colorectal Cancer

Technology in Cancer Research & Treatment
Volume 18: 1-6
© The Author(s) 2019
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/1533033819873924
journals.sagepub.com/home/tct


Pashtoon Murtaza Kasi, MD, MS¹, Tyler Koep, PhD², Erica Schnettler, PhD², Faisal Shahjehan, MD³ , Vaishnavi Kamatham, MD⁴, Candice Baldeo, MD⁴, and Caren L. Hughes, PharmD, RPh⁴

Abstract

Introduction: Pharmacogenomics is about selecting the “right drug in the right amount for the right patient.” In metastatic colorectal cancer, germline pharmacogenomics testing presents a unique opportunity to improve outcomes, since the genes dihydropyrimidine dehydrogenase and UDP-glucuronosyltransferase metabolizing the chemotherapy drugs, 5-fluorouracil, and irinotecan are already well known. In a retrospective analysis of the landmark TRIBE clinical trial [(TRIBE - TRIpIet plus BEvacizumab multicenter, phase III trial by the Italian Cooperative GONO (Gruppo Oncologico Nord Ovest) group (NCT00719797)], the proportion of patients with serious adverse events was higher in those with dihydropyrimidine dehydrogenase/UDP-glucuronosyltransferase aberrations and was dose dependent. We aimed to report on the feasibility and the results of incorporating pharmacogenomics testing into clinical practice. **Methods:** As a quality improvement initiative and a center of individualized medicine grant, we integrated the use of OneOme RightMed comprehensive test, which reports on 27 genes related to pharmacogenomics and over 300 medications of interest. We limited initial testing to patients with colorectal cancer. Pharmacists provided dosage recommendations based on test results in real-time. **Results:** At our cancer center, 155 patients underwent pharmacogenomics testing from November 2017 to January 2019. Results were available within 3 to 5 days of testing for most patients and were integrated into treatment decision-making. Of 155 sampled participants, a total of 89 (57.4%) participants had an *UGT1A1* variant genotype, NM_000463.2: c.-53_-52[8] *1/*28, n = 74 (47.7%); *28/*28, n = 15 (9.7%). Additionally, 4 (2.6%) participants were heterozygous for dihydropyrimidine dehydrogenase. Two (1.3%) individuals were heterozygous for both UDP-glucuronosyltransferase and dihydropyrimidine dehydrogenase genes. All (100%) the patients had at least 1 actionable aberration related to supportive care medications (*CYP*-family) of all the possible medications listed on their pharmacogenomics report. **Conclusion:** Preemptive comprehensive pharmacogenomics testing can be integrated into clinical practice in real-time for patients with cancer given faster turnaround and low cost. Pharmacist-driven, patient-specific medication management consults add further value given the number of genes/drugs. This sets the stage for a prospective randomized clinical trial to demonstrate the amount of benefit this can result in these patients.

Keywords

pharmacogenomics, colorectal cancer, CRC, chemotherapy, supportive care, DPYD, UGT1A1, irinotecan, 5-fluorouracil

¹ Division of Hematology, Oncology and Blood & Bone Marrow Transplantation, Department of Internal Medicine, University of Iowa, Iowa City, IA, USA

² OneOme, LLC, Minneapolis, MN, USA

³ Conemaugh Memorial Medical Center, Johnstown, PA, USA

⁴ Mayo Clinic Florida, Jacksonville, FL, USA

Corresponding Author:

Pashtoon Murtaza Kasi, Division of Hematology, Oncology and Blood & Bone Marrow Transplantation, Department of Internal Medicine, University of Iowa, 200 Hawkins Dr, Iowa City, IA 52242, USA.
Email: pashtoon-kasi@uiowa.edu



Abbreviations

CI, confidence interval; CPIC, Clinical Pharmacogenetics Implementation Consortium; CRC, colorectal cancer; *DPYD*, dihydropyrimidine dehydrogenase; 5-FU, 5-fluorouracil; OR, odds ratio; PGx, pharmacogenomics; PM, poor metabolizers; SAEs, serious adverse events; *UGT1A1*, UDP-glucuronosyltransferase; UM, ultrarapid metabolizers

Received: April 22, 2019; Revised: July 21, 2019; Accepted: August 13, 2019.

Background

Patients with cancer oftentimes experience debilitating serious adverse events (SAEs) from chemotherapy drugs as well as supportive care medications. These patients can experience various side effects including ongoing nausea, mouth sores, diarrhea, severe anxiety, and low white blood cell count leading to infections, extreme fatigue, and so on, which can tremendously reduce the quality of life. Supportive care medications are often introduced to help relieve cancer treatment-related SAEs. However, like many medications, the drugs used to relieve those side effects sometimes have side effects of their own, and response can vary significantly among individuals. Pharmacogenomics (PGx) is the study of how person's genes influence their response to medications. The rationale of PGx testing is to identify the appropriate dose of chemotherapeutic agent and supportive care medication to help prevent these adverse effects.¹⁻³ The integration of preemptive PGx testing at the time when the patient is diagnosed with colorectal cancer (CRC) can significantly improve the quality of life of these patients.^{4,5}

Preemptive PGx testing may have a clinical value in the management of CRC. Mostly patients with CRC are treated with combination chemotherapy regimens. The aberrations in the encoding genes for the metabolizing enzymes of the drugs result in the building up of the drug concentration in the blood.^{6,7} Hence, the poor metabolizers (PMs), with the decreased activity of drug metabolizing enzyme, are more likely to experience SAEs from the medications.

The role of the 2 encoding genes, that is, dihydropyrimidine dehydrogenase (*DPYD*) and UDP-glucuronosyltransferase (*UGT1A1*), for metabolizing enzymes of the 2 common CRC chemotherapy drugs, that is, 5-fluorouracil (5-FU) and irinotecan, has been previously investigated.^{8,9} In the multicenter, phase III TRIBE study [(TRIBE - TRIPlet plus BEvacizumab multicenter, phase III trial by the Italian Cooperative Gruppo Oncologico Nord Ovest (GONO) group (NCT00719797)], the FOLFOXIRI plus bevacizumab group was extensively associated with an increased incidence of grade ≥ 3 neutropenia (50% vs 23%), diarrhea (18% vs 12%), and stomatitis (9% vs 5%) when compared to the FOLFIRI plus bevacizumab group; retrospective pharmacogenomics analyses confirmed that the proportion of patients with serious adverse events was higher in those with dihydropyrimidine dehydrogenase/UDP-glucuronosyltransferase aberrations and was dose dependent.¹⁰ The previous studies have demonstrated that patients having an aberration or/and decreased expression of the encoding genes are associated with higher incidence of side effects.¹¹⁻¹⁴

Pharmacogenomics testing, despite its significance and utility, has not yet been included as a standard of care in the management of patients with CRC.

As part of a quality improvement project and center of individualized medicine grant at Mayo Clinic, we aimed at assessing the feasibility of integrating the use of PGx OneOme RightMed comprehensive test in the management of every patient who presented with metastatic CRC at our center. Our goal was to gather an estimate of the potential number of patients who may have aberrations in the *DPYD/UGT1A1* genes, as well as explore the *CYP*-family of genes that may potentially affect choice of supportive care and other concurrent medications that a patient with cancer may need.

Materials and Methods

Study Design and Participants

This retrospective analysis evaluated findings from a pilot clinical implementation project within the Department of Hematology and Oncology at Mayo Clinic, Florida. Patient care involved a multidisciplinary team including a Mayo Clinic gastrointestinal oncologist, pharmacist, disease specialist, and allied health staff. Primary outcomes included estimates of genotype frequencies among the sample population and the number of potential major and moderate gene-drug interactions identified at baseline.

Pharmacogenomics Testing and Interpretation

Patient DNA was collected at point of care through a buccal swab by a Mayo Clinic health professional and shipped to OneOme, LLC (Minneapolis, Minnesota) for genotyping. OneOme's laboratory is accredited by the College of American Pathologists and certified by the Clinical Laboratory Improvement Amendments. The OneOme RightMed comprehensive test uses TaqMan single-nucleotide polymorphisms genotyping and copy number variation assays run on an IntelliQube qPCR Platform (Douglas Scientific, Alexandria, Minnesota). At the time of this feasibility pilot, the RightMed test included 27 genes (Supplementary Figure 1). The RightMed test is an end-to-end solution that analyzes both pharmacodynamic and pharmacokinetic genes (eg, *CYP2D6*, *CYP2C19*, *UGT1A1*, *DPYD*, and *TMPT*) and applies a proprietary haplotyping algorithm to convert patient genotypes into diplotype calls. Phenotype determinations (eg, "PM") were based on allelic-driven activity scores, rigorous curation of the published literature by OneOme scientists and pharmacists, and recommendations from expert clinical bodies

such as the Clinical Pharmacogenetics Implementation Consortium (CPIC).¹⁵ The RightMed interpretive report further makes recommendations that pair individual medications and multi-gene determinations of metabolism to create drug-by-drug risk classifications. Medications are stratified into red, yellow, and green risk categories, corresponding to major, moderate, and minimal gene–drug interactions, respectively. Furthermore, the current implementation project led to the creation of the RightMed Oncology Specialty Report that subselects medications from the RightMed comprehensive report to provide the most relevant chemotherapy and supportive care information to providers. Iterative feedback, provided by the Mayo Clinic team, contributed to the content and design of the medication list. A sample of the RightMed Oncology Specialty Report is included in Supplemental Figure 2.

In parallel with the aid of a pharmacist at the cancer center, PGx-guided dosing was provided to the care team and included in the electronic medical record of the patient for future use. The reports were also shared with the patient to be shared with all their care providers if needed for future use. The whole process went through several iterations based on the “Plan, Do, Study, Act” model of care.¹⁶ Reference to suggested modifications were based on CPIC guidelines.

Supportive Care Opportunity

In addition to presenting genotype and phenotype information, the RightMed test also provides a comprehensive medication-oriented view of gene–drug interaction risks to providers. Aside from chemotherapy medications, the RightMed Oncology Specialty Report identifies nearly 100 supportive care medications of particular relevance to oncology health-care professionals, across cancer types.

The report again through collaboration with the Mayo Clinic investigators underwent iterations and rationale for grouping the patient results into the following led to the development of the oncology specialty report: (1) gastrointestinal (nausea/vomiting, appetite, gastritis, and gastroesophageal reflux disease), (2) pain, (3) neuropathy and nonopioid pain, (4) mental health, (5) neuropsychiatry (sleep medicine, anticonvulsant, and smoking cessation), (6) antimicrobial, (7) anticoagulant and cardiovascular, and (8) other. In order to estimate the opportunity of preemptive PGx testing to identify drug therapy problems within a population with cancer, potential medication issues at baseline were aggregated from individual RightMed generated reports. Initial summary statistics are intended to represent the potential cumulative risk to patients based on all possible supportive care medications included on each report, not actual medication regimens.

Clinical Workflow

Medical oncologist explained to the patient that PGx testing would be performed. RightMed test results were returned in 3 to 5 days (mean = 3.19 ± 1.69 days) and were primarily interpreted by Mayo Clinic pharmacists. Patients were also

provided with a copy of their results. Pharmacists then generated patient-specific medication management recommendations and delivered electronic consults to physicians coordinating the patient’s care, across a variety of specialties. Chemotherapeutic agent modifications and dose adjustments were the responsibility of the treating medical oncologist/care team. Medical oncologist used the Food and Drug Administration label for dosing guidance. Supportive care medication changes were handled separately by Mayo Clinic specialists or in consult with supportive care physicians and pharmacists.

Results

Participant Characteristics

Overall, 155 patients received the RightMed comprehensive test between November 2017 and January 2019. Study participants had a median age of 56 years (range: 24–78 years), with 59% males and 41% females, reflective of demographic trends in CRC diagnosis rates within the US population. Most (80%) of the patients were white.

Chemotherapy Genes of Interest

Both *UGT1A1* and *DPYD* genes are commonly tested single genes for the CRC therapies irinotecan (*UGT1A1*) and fluorouracil (*DPYD*). Of 155 sampled participants, a total of 89 (57.4%) participants had a *UGT1A1* variant genotype, NM_000463.2: c.-53_-52[8] *1/*28, n = 74 (47.7%); *28/*28, n = 15 (9.7%). Additionally, 4 (2.6%) participants were heterozygous for *DPYD* (2.6%), and 2 (1.3%) individuals were heterozygous for both *UGT1A1* and *DPYD* genes.

Supportive Care Medication Burden

Supportive care medications are largely metabolized by the *CYP450* enzyme family. Examples include *CYP2D6* testing for codeine, tramadol, and ondansetron and *CYP2C19* testing for pantoprazole and citalopram.⁸ In this study, genotype and phenotype frequencies for *CYP450* enzymes were representative of the demographic profile of the Mayo Clinic (Jacksonville, Florida) patient population (Table 1). Of particular interest, 4.0% of patients were categorized as *CYP2D6* PM, 8.0% were poor to intermediate, and 2.6% were ultrarapid metabolizers (UM). For *CYP2C19*, 25.8% were identified as rapid metabolizers, 6.5% were UMs, and 4.0% were PMs. Phenotype rates for all *CYP450* enzymes were comparable to known population frequencies.¹⁷

For the primary outcome, the average patient in this pilot had 34 (40%) of 86 possible supportive care medication bin yellow or red (34% yellow, 6% red) on their reports. The number of yellow/red medications per person was normally distributed across the sample ($P = .27$). Furthermore, yellow/red medications were not isolated to a single medication class or supportive care area. Of the 8 supportive care areas on the report, 94% of patients had at least 1 yellow/red medication in 5 or more therapeutic areas; 60% of patients had at least 1 in 7 or 8 categories. For many first-line supportive care

Table 1. The Proportion of the CYP450 Phenotypes and UGT1A1/DPYD Aberrations in the Cohort.^a

| Gene | PM and IM-PM | IM and NM-IM | NM | RM | UM |
|---------|--------------------------|--------------|--|-------|----------------------------|
| CYP2D6 | 11% | 57.4% | 29% | N/A | 2.6% |
| CYP2C19 | 3.9% | 24.5% | 39.4% | 25.8% | 6.5% |
| CYP2C9 | 1.9% | 32.9% | 65.1% | N/A | N/A |
| CYP2B6 | 14.2% | 38% | 43.9% | 3.9% | N/A |
| CYP1A2 | 0% | 0.6% | 9% | 90.3% | N/A |
| CYP3A4 | 0% | 8.4% | 91.6% | N/A | N/A |
| CYP3A5 | 79.4% | 14.8% | 5.8% | N/A | N/A |
| | Normal | Intermediate | | Poor | |
| UGT1A1 | Wild-type (*1/*1), 42.6% | | Heterozygous (*1/*28), 47.7% | | Homozygous (*28/*28), 9.7% |
| DPYD | Wild-type (*1/*1), 97.4% | | Heterozygous (*1/*n ^b), 2.6% | | |

Abbreviations: *DPYD*, dihydropyrimidine dehydrogenase; IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer; RM, rapid metabolizer; UGT1A1, UDP-glucuronosyltransferase; UM, ultrarapid metabolizer.

^a[Symbol] In the case of CYP1A2, rapid metabolizer refers to inducible phenotypes.

^bThe RightMed test detects rs3918290 (*2A), rs55886062 (*13), and rs67376798.

medications, a greater percentage of patients binned as yellow/red than did green. For example, for oxycodone which is primarily metabolized by the CYP3A4 and CYP2D6,¹⁸ 67% of patients binned yellow/red, while 33% binned green. Similarly, pantoprazole, which is metabolized by CYP2C19,¹⁹ had a comparable profile to oxycodone, despite having entirely different genes driving binning status—59% of patients binned yellow/red, 49% and 10%, respectively, while 41% binned green.

The average number of medications for each supportive care area (eg, pain, mental health, etc) that were binned as yellow, red, or green across the population was estimated. Neuropathy (63.7%), cardiology (63.8%), and gastrointestinal (56.7%) indications had the highest proportion of yellow/red medications. Cardiology also had the highest proportion of major drug–gene interactions, with 46.3% of all medications binning as red across the sample. Clopidogrel was largely responsible for this trend, as 22% of individuals had a red bin status. Consistently, each supportive area had a roughly similar number of yellow/red medications as green alternatives. On the RightMed Oncology Specialty Report, the average supportive care category has approximately 10.8 listed medications. Among our sample, the mean number of yellow/red and green medications per category was 4.4 and 6.4, respectively. Only the antimicrobial/infection and urology categories had less than 25% of medications in their respective class flagged as yellow/red, potentially indicating a lower chance of prescribing a drug with moderate and major drug–gene interactions through trial-and-error prescribing than other categories.

Discussion

Growing evidence about the importance of PGx testing suggests that the individuals having *DPYD* and *UGT1A1* aberrations are more likely to experience fluoropyrimidine- and irinotecan-related side effects.^{7,20} Furthermore, it has also been reported that a considerable proportion of individuals carry aberrations in the aforementioned genes.¹⁰ This,

however, is often underestimated, since these genes are often examined and discussed in isolation of each other. This also implies that these are the potential candidates who are expected to benefit the most by dose modifications per the results of PGx testing.⁹ Nonetheless, the role of PGx testing in the management of gastrointestinal cancers, especially CRC, has remained debatable and not integrated into guidelines. This is probably partly due to lack of prospective studies highlighting the value of PGx testing and showing how impactful this could be in the management of CRC in terms of improving quality of life, decreasing health-care costs, and lowering emergency department visits.^{21–23}

This study spotlights several intriguing facts. First, we found that the majority (57.4%) of our patient population had an aberration in either *DPYD* and/or *UGT1A1* genes which were identified on preemptive PGx testing. Second, this study looked at genes beyond just chemotherapy. In our cohort of patients, there was at least 1 potentially actionable aberration among the 27 genes related to over 300 medications that a patient with cancer may receive pertinent to the cancer diagnosis, for example, pain control or be on them already, for example, a proton pump inhibitor. The faster turnaround and low cost overcome the other historical barriers to PGx testing.^{21–24} Third, our results demonstrated that 47.7% of the sampled participants had UGT1A1*28 NM_000463.2: c.-53_-52[8] genotype which matches the published allele frequency for Caucasians.²⁵

Pharmacogenomics testing and its application into clinical practice have been investigated in the past few years. However, its feasibility has always been questioned and could not reach a consensus. Hence, it has not yet been incorporated into CRC management guidelines. Research has shown that the individuals having gene variants of different chemotherapy and supportive care medications including *DPYD* and *UGT1A1* are more prone to experience drug-related toxicities.^{13,14} According to one estimate, about 2% to 8% of the individuals having *DPYD* deficiency can develop toxic SAEs to fluoropyrimidines.²⁶

Lee *et al* did a randomized controlled trial by enrolling patients with stage III CRC (n = 2886) and investigated the association between *DPYD* variants and the incidence of drug-related SAEs. The researchers reported that among the individuals having *DPYD**2A, I560S, and D949V variants, the incidence of grade ≥ 3 adverse events secondary to 5-FU were 88%, 50%, and 81.5%, respectively.¹¹ Their results further indicated that the individuals carrying *DPYD**2A (odds ratio [OR] = 15.21; 95% confidence interval [CI]: 4.54-50.96) and D949V (OR = 9.10; 95% CI: 3.43-24.10) variants were at an increased risk of developing grade ≥ 3 fluoropyrimidines-related adverse reactions.¹¹ Another study of 67 patients with gastrointestinal cancer reported that 25% of the patients were found to have *DPYD* variants.²⁷ A prospective study conducted on 1181 patients with cancer in 17 hospitals in the Netherlands reported the finding of heterozygous *DPYD* variant in 8% of their cohort. Their results also indicated that the greater proportion of patients with *DPYD* variants (39%) had fluoropyrimidine-related SAEs than those with wild-type *DPYD* (23%).²⁸

One major challenge to the implementation of PGx testing into clinical practice has been the unavailability of clinical guidelines and the required expertise to adjust medication dosage based on genetic results.²⁹ The CPIC is an international association, consisting of a panel of PGx experts, which provides the guidelines to help physicians and pharmacists to translate the genetic test results into medication dosage modification.^{30,31} The CPIC has published peer-reviewed guidelines for several chemotherapy and supportive care medications based on their respective genetic results.³²⁻⁴¹ Again, more research is needed to demonstrate the applicability to clinical practice, but at least with our study, feasibility was shown. The pharmacists also need to play a leadership role in advancing the field of PGx and making it a part of the clinical practice.⁴² Our own experience in this study indicated that the whole process of successfully integrating PGx testing into clinical practice requires close collaborations among all the health-care team members including the clinicians, pharmacists, geneticists, and investigators. With advancing technology, electronic health record also remains one of the cornerstone prerequisites for the implementation of PGx testing.^{43,44}

In summary, our study suggests that genotype-driven dosing of chemotherapy and supportive care medications for CRC is a feasible approach to avoid drug-related adverse events and improve quality of life. The preemptive PGx testing for patients with CRC could be integrated into regular clinical practice based on its clinical utility.

Due to the lack of funding and support, we did not have the capacity to prospectively capture data in terms of serial quality-of-life assessments and assessment of adverse events in this cohort, which indeed is a limitation of our study. This sets the stage for prospective studies and potentially randomized controlled trials showing its true value to help incorporate it into guidelines.


Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: PGx testing was provided through a Center of Individualized Medicine (CIM) grant at Mayo Clinic to the investigator PMK.

ORCID iD

Faisal Shahjehan  <https://orcid.org/0000-0001-7384-2960>

Supplemental Material

Supplemental material for this article is available online.

References

1. Aneesh TP, Sonal Sekhar M, Jose A, Chandran L, Zachariah SM. Pharmacogenomics: the right drug to the right person. *J Clin Med Res.* 2009;1(4):191-194.
2. Zhang Y, Somtakoune SD, Cheung C, Listiawan M, Feng X. Therapeutic application of pharmacogenomics in oncology. *AAPS J.* 2016;18(4):819-829.
3. Andersen RL, Johnson DJ, Patel JN. Personalizing supportive care in oncology patients using pharmacogenetic-driven treatment pathways. *Pharmacogenomics.* 2016;17(4):417-434.
4. Cecchin E, De Mattia E, Ecça F, Toffoli G. Host genetic profiling to increase drug safety in colorectal cancer from discovery to implementation. *Drug Resist Updat.* 2018;39:18-40.
5. Patel JN, Fong MK, Jagosky M. Colorectal cancer biomarkers in the era of personalized medicine. *J Pers Med.* 2019;9(1):E3.
6. Toffoli G, Cecchin E, Corona G, et al. The role of UGT1A1*28 polymorphism in the pharmacodynamics and pharmacokinetics of irinotecan in patients with metastatic colorectal cancer. *J Clin Oncol.* 2006;24(19):3061-3068.
7. Meulendijks D, Henricks LM, Sonke GS, et al. Clinical relevance of *DPYD* variants c.1679T>G, c.1236G>A/HapB3, and c.1601G>A as predictors of severe fluoropyrimidine-associated toxicity: a systematic review and meta-analysis of individual patient data. *Lancet Oncol.* 2015;16(16):1639-1650.
8. Patel JN, Wiebe LA, Dunnenberger HM, McLeod HL. Value of supportive care pharmacogenomics in oncology practice. *Oncologist.* 2018;23(8):956-964.
9. Henricks LM, Opdam FL, Beijnen JH, Cats A, Schellens JHM. *DPYD* genotype-guided dose individualization to improve patient safety of fluoropyrimidine therapy: call for a drug label update. *Ann Oncol.* 2017;28(12):2915-2922.
10. Cremolini C, Del Re M, Antoniotti C, et al. *DPYD* and UGT1A1 genotyping to predict adverse events during first-line FOLFIRI or FOLFOXIRI plus bevacizumab in metastatic colorectal cancer. *Oncotarget.* 2018;9(8):7859-7866.
11. Lee AM, Shi Q, Pavey E, et al. *DPYD* variants as predictors of 5-fluorouracil toxicity in adjuvant colon cancer treatment (NCCTG N0147). *J Natl Cancer Inst.* 2014;106(12).
12. Liu X, Cheng D, Kuang Q, Liu G, Xu W. Association of UGT1A1*28 polymorphisms with irinotecan-induced toxicities in colorectal cancer: a meta-analysis in Caucasians. *Pharmacogenomics J.* 2014;14(2):120-129.
13. Leung HW, Chan AL. Association and prediction of severe 5-fluorouracil toxicity with dihydropyrimidine dehydrogenase gene

- polymorphisms: a meta-analysis. *Biomed Rep.* 2015;3(6):879-883.
14. Li Q, Liu Y, Zhang HM, et al. Influence of DPYD genetic polymorphisms on 5-fluorouracil toxicities in patients with colorectal cancer: a meta-analysis. *Gastroenterol Res Pract.* 2014;2014:827989.
 15. Clinical Pharmacogenetics Implementation Consortium (CPIC®). <https://cpicpgx.org/>. Accessed 29 August 2019.
 16. Donnelly P, Kirk P. Use the PDSA model for effective change management. *Educ Prim Care.* 2015;26(4):279-281.
 17. Zhou Y, Ingelman-Sundberg M, Lauschke VM. Worldwide distribution of cytochrome P450 alleles: a meta-analysis of population-scale sequencing projects. *Clin Pharmacol Ther.* 2017;102(4):688-700.
 18. Smith HS. Opioid metabolism. *Mayo Clin Proc.* 2009;84(7):613-624.
 19. Meyer UA. Interaction of proton pump inhibitors with cytochromes P450: consequences for drug interactions. *Yale J Biol Med.* 1996;69(3):203-209.
 20. Campbell JM, Stephenson MD, Bateman E, Peters MD, Keefe DM, Bowen JM. Irinotecan-induced toxicity pharmacogenetics: an umbrella review of systematic reviews and meta-analyses. *Pharmacogenomics J.* 2017;17(1):21-28.
 21. Henricks LM, Lunenburg CATC, de Man FM, et al. A cost analysis of upfront DPYD genotype-guided dose individualisation in fluoropyrimidine-based anticancer therapy. *Eur J Cancer.* 2019;107:60-67.
 22. Plumpton CO, Roberts D, Pirmohamed M, Hughes DA. A systematic review of economic evaluations of pharmacogenetic testing for prevention of adverse drug reactions. *Pharmacoeconomics.* 2016;34(8):771-793.
 23. Roncato R, Cecchin E, Montico M, et al. Cost evaluation of irinotecan-related toxicities associated with the UGT1A1*28 patient genotype. *Clin Pharmacol Ther.* 2017;102(1):123-130.
 24. Johnson JA, Bootman JL. Drug-related morbidity and mortality. a cost-of-illness model. *Arch Intern Med.* 1995;155(18):1949-1956.
 25. Liu JY, Qu K, Sferruzza AD, Bender RA. Distribution of the UGT1A1*28 polymorphism in Caucasian and Asian populations in the US: a genomic analysis of 138 healthy individuals. *Anticancer Drugs.* 2007;18(6):693-696.
 26. Dihydropyrimidine Dehydrogenase Deficiency. 2019. <https://ghr.nlm.nih.gov/condition/dihydropyrimidine-dehydrogenase-deficiency#statistics>. Accessed 29 August 2019.
 27. Khushman M, Patel GK, Hosein PJ, et al. Germline pharmacogenomics of DPYD*9A (c.85T>C) variant in patients with gastrointestinal malignancies treated with fluoropyrimidines. *J Gastrointest Oncol.* 2018;9(3):416-424.
 28. Henricks LM, Lunenburg CATC, de Man FM, et al. DPYD genotype-guided dose individualisation of fluoropyrimidine therapy in patients with cancer: a prospective safety analysis. *Lancet Oncol.* 2018;19(11):1459-1467.
 29. Klein ME, Parvez MM, Shin JG. Clinical implementation of pharmacogenomics for personalized precision medicine: barriers and solutions. *J Pharm Sci.* 2017;106(9):2368-2379.
 30. Caudle KE, Klein TE, Hoffman JM, et al. Incorporation of pharmacogenomics into routine clinical practice: the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline development process. *Curr Drug Metab.* 2014;15(2):209-217.
 31. Caudle KE, Dunnenberger HM, Freimuth RR, et al. Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC). *Genet Med.* 2017;19(2):215-223.
 32. Caudle KE, Thorn CF, Klein TE, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing. *Clin Pharmacol Ther.* 2013;94(6):640-645.
 33. Amstutz U, Henricks LM, Offer SM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing: 2017 update. *Clin Pharmacol Ther.* 2018;103(2):210-216.
 34. Hicks JK, Swen JJ, Thorn CF, et al. Clinical pharmacogenetics implementation consortium guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. *Clin Pharmacol Ther.* 2013;93(5):402-408.
 35. Hicks JK, Sangkuhl K, Swen JJ, et al. Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. *Clin Pharmacol Ther.* 2017;102(1):37-44.
 36. Hicks JK, Bishop JR, Sangkuhl K, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and dosing of selective serotonin reuptake inhibitors. *Clin Pharmacol Ther.* 2015;98(2):127-134.
 37. Crews KR, Gaedigk A, Dunnenberger HM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for codeine therapy in the context of cytochrome P450 2D6 (CYP2D6) genotype. *Clin Pharmacol Ther.* 2012;91(2):321-326.
 38. Crews KR, Gaedigk A, Dunnenberger HM, et al. Clinical pharmacogenetics implementation consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. *Clin Pharmacol Ther.* 2014;95(4):76-82.
 39. Bell GC, Caudle KE, Whirl-Carrillo M, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 genotype and use of ondansetron and tropisetron. *Clin Pharmacol Ther.* 2017;102(2):213-218.
 40. Wilke RA, Ramsey LB, Johnson SG, et al. The Clinical Pharmacogenomics Implementation Consortium: CPIC guideline for SLCO1B1 and simvastatin-induced myopathy. *Clin Pharmacol Ther.* 2012;92(1):112-117.
 41. Ramsey LB, Johnson SG, Caudle KE, et al. The clinical pharmacogenetics implementation consortium guideline for SLCO1B1 and simvastatin-induced myopathy: 2014 update. *Clin Pharmacol Ther.* 2014;96(4):423-428.
 42. Crews KR, Cross SJ, McCormick JN, et al. Development and implementation of a pharmacist-managed clinical pharmacogenetics service. *Am J Health Syst Pharm.* 2011;68(2):143-150.
 43. Wilke RA, Xu H, Denny JC, et al. The emerging role of electronic medical records in pharmacogenomics. *Clin Pharmacol Ther.* 2011;89(3):379-386.
 44. Stocco G, Franca R, Londero M, Decorti G. Processes for incorporation of pharmacogenetic tests and interpretations in medical records for clinical practice. *Pharmacogenomics.* 2013;14(3):236-237.