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Delivering Pharmacogenetic Testing in the Community Setting

The ability to individualize medication therapy for cancer patients has significantly advanced in recent years and continues to expand into new areas of practice. One of these areas is pharmacogenetic testing, which evaluates inherited genetic differences in drug metabolic pathways that can affect individual responses to drugs both in terms of therapeutic effect as well as adverse effects.[1] While more than 130 FDA-approved medications have references to pharmacogenetic testing in their package insert, until recently there has been little guidance on how to apply this information in the clinic setting.[2] The Clinical Pharmacogenetic Implementation Consortium (CPIC, cpicpgx.org) was established to provide clinical practice guidelines for meaningful prescribing decisions of specific drug/gene pairs. Since the development of the CPIC guidelines, there are currently specific dosing recommendations for 35 medications.[3] However, the majority of pharmacogenetic testing continues to be done in the academic setting—even with CPIC's supporting data, few community cancer programs are performing this form of personalized medicine.

In November 2014, St. Luke's Mountain States Tumor Institute (MSTI), Boise, Idaho, initiated a pilot program to determine the feasibility of a pharmacogenetic testing program in a community cancer program. Led by a multidisciplinary team of pharmacists, genetic counselors, and physicians, MSTI selected pharmacogenetic drug/gene pairs based on:

- Frequency of medication use
- CPIC recommendations for dosing changes
- Inclusion of genes in FDA medication labeling

For community cancer programs looking to implement or grow the use of pharmacogenetic testing, here are processes and lessons learned from MSTI's pilot pharmacogenetic testing program.

- Test cost
- Significant potential for toxicity in patients with particular genotypes.

This multidisciplinary team developed a service delivery model to facilitate the process of pharmacogenetic testing; data collection included physician acceptance to ordering tests, insurance coverage, test turn-around times, and test results.

Since the inception of the pilot program, approximately 50 percent of patients eligible to receive pharmacogenetic testing have had the test ordered, and this percentage continues to increase, with the average nearing 90 percent from February through April 2016. The current rate of DPYD (dihydropyrimidine dehydrogenase) pharmacogenetic testing insurance approval is approximately 66 percent, which has stayed fairly consistent since the beginning of the pilot. The majority of third-party payers are routinely covering DPYD and TPMT

St. Luke's Mountain States Tumor Institute, Boise, Idaho

(thiopurine s-methyltransferase) pharmacogenetic tests; however, several major payers still deny coverage. At MSTI, coverage remains a significant barrier for roughly one third of the patient population. On average, test results are received in 13.3 days for DPYD and 9 days for TPMT. Results are reported through April 2016; to date, one patient has been found to carry a variant associated with decreased DPYD activity.

For community cancer programs looking to implement or grow the use of pharmacogenetic testing, here are processes and lessons learned from MSTI's pilot pharmacogenetic testing program.

Why Test?

For cancer patients receiving chemotherapy, the development of severe toxicity as a result of genetic variations may lead to the interruption or discontinuation of potentially effective therapy, hospitalization, or fatal outcomes. One class of chemotherapy drugs, the fluoropyrimidines, are the standard of care in the treatment of colorectal cancer patients and are often associated with side effects such as diarrhea, mucositis, hand-foot syndrome, and myelosuppression. The unexpected toxicities experienced from the specific drugs in this class, 5-fluorouracil (5-FU) and capecitabine, are primarily associated with a deficiency of DPYD. This enzyme is responsible for breaking down approximately 85 percent of 5-FU to an inactive form that is eliminated from the body. However, pharmacogenetic variants of this enzyme in 3 to 5 percent of patients treated with fluoropyrimidines may lead to severe, potentially life-threatening toxicity. Published results from Adam M. Lee and colleagues, the largest study to date, demonstrate statistically significant associations between DPYD variants and the increased incidence of grade 3 or greater 5-FU adverse events.[4]

While some providers may wait to order DPYD testing until after a patient has experienced toxicity, treatment interruptions, discontinuation, or even hospitalization all significantly impact a patient's prognosis and quality of life (QOL). In addition to toxicity, a recent study from the Netherlands published in the *Journal of Clinical Oncology* demonstrated cost savings from performing upfront genotyping in patients receiving fluoropy-

Table 1. Pharmacogenetic Test Information

	DPYD [6]	TPMT [13,14]
MEDICATIONS	Fluorouracil, Capecitabine	Mercaptopurine, Thioguanine
HETEROZYGOUS VARIANT PREVALENCE	3% to 5%	3% to 14%
PHENOTYPE OF HETEROZYGOUS VARIANT	30% to 70% decreased enzyme activity	N/A
CPIC DOSING RECOMMENDATION	50% initial dose reduction	Mercaptopurine: start at 30% to 70% of the initial recommended dose
HOMOZYGOUS VARIANT PREVALENCE	0.2%	0.03 to 0.6%
PHENOTYPE OF HOMOZYGOUS VARIANT	100% decreased enzyme activity	N/A
CPIC DOSING RECOMMENDATION	Contraindicated	Start at 10% of the initial recommended dose
CPT CODE	81400	81401
COST OF TEST	approximately $210	approximately $507

rimidines.[5] The authors conclude by stating, "[prospective screening]…should therefore become standard of care in treatment with fluoropyrimidines."[5]

Multiple barriers hinder the adoption of pharmacogenetic tests into routine clinical practice, especially in the community setting, for example:

- The lack of knowledge and awareness by both patients and providers.
- The lack of a working process for performing tests in a preemptive fashion, disseminating test results, and incorporating test results into patients' medical records.
- The lack of insurance coverage.

CPIC is one of several organizations advocating for the advancement of pharmacogenetic testing.[6] CPIC's goal: to enable the translation of genetic laboratory tests into actionable prescribing decisions. CPIC conducts rigorous reviews of scientific literature when writing specific dosing recommendation guidelines. The peer-reviewed guidelines are published in the *Journal of Clinical Pharmacology and Therapeutics* with immediate online availability at PharmGKB (pharmgkb.org). The work of the consortium ultimately provides clinicians with updated pharmacogenetic testing information without the overwhelming burden of trying to gain the knowledge independently.

Utilizing CPIC recommendations, several large medical centers and academic institutions have developed their own processes for the routine ordering of pharmacogenetic tests.[7] James Hoffman, PharmD, at St. Jude's Children's Research Hospital has been a major proponent of implementing pharmacogenetic testing as a standard of care.[8,9,10] He and his colleagues have detailed their successful preemptive implementation in several publications. Their philosophy is that pharmacogenetic test results should be a part of the electronic health record (EHR) prior to drug prescribing.

Mills and Haga published an article in 2013 calling for a partnership between genetic counselors and pharmacists in the delivery of pharmacogenetic testing.[11] The authors highlight the important roles each profession contributes. Genetic counselors are well suited to provide patient education and post-test counseling, interpret pharmacogenetic variants for providers, and stay up to date on genome testing technologies. With an extensive knowledge of pharmaceuticals, pharmacists are able to make therapeutic recommendations to providers and conduct drug monitoring based on test results and other clinical factors. While this collaborative approach may seem ideal in theory, community cancer programs often lack the resources to develop infrastructure for a sustainable model.

In 2014 the American Society of Health-System Pharmacists (ASHP) released a statement on the pharmacist's role in clinical pharmacogenomics.[12] The society advocates for the profession of pharmacy to establish a leadership role in improving medication-related outcomes in the area of pharmacogenomics. ASHP asserts that this role should be shared with other hospital and health-system leaders, such as physicians, laboratory professionals, and genetic counselors. In addition, ASHP has endorsed the published CPIC guidelines in its efforts to promote safe, effective, and cost-efficient medication practices.

Genetic counselors are well suited to provide patient education and post-test counseling, interpret pharmacogenetic variants for providers, and stay up to date on genome testing technologies.

Below is a discussion of the model developed by MSTI, including its continued efforts to overcome barriers surrounding pharmacogenetic testing.

Pilot Program Methodology

St. Luke's MSTI gathered extensive background material to determine best practices for implementing a successful pharmacogenetic testing program. These preparatory activities included contacting academic institutions currently performing these services, selecting which agents and corresponding tests would be most practical for our institution, and setting up the overall process. Secondary objectives included determining to what extent insurance companies were covering pharmacogenetic testing, measuring test turn-around times from date of lab draw to receipt of test results, and application of the results.

Step 1. Selected Specific Pharmacogenetic Tests

MSTI determined the most advantageous tests for its patient population by analyzing a variety of factors, including:

- Specific dosing recommendations made by the CPIC guidelines
- The number of patients receiving the medications that would necessitate a test
- Significance of a mutation
- Incidence of genetic mutations for the test
- Cost and availability of the test from contract labs.

As discussed previously, the applicable tests identified were dihydropyrimidine dehydrogenase (DPYD), indicated for

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Figure 1. Electronic Dosing Recommendation Sheet Utilized to Disseminate Test Results to Providers

St Luke's Mountain States Tumor Institute

NAME:

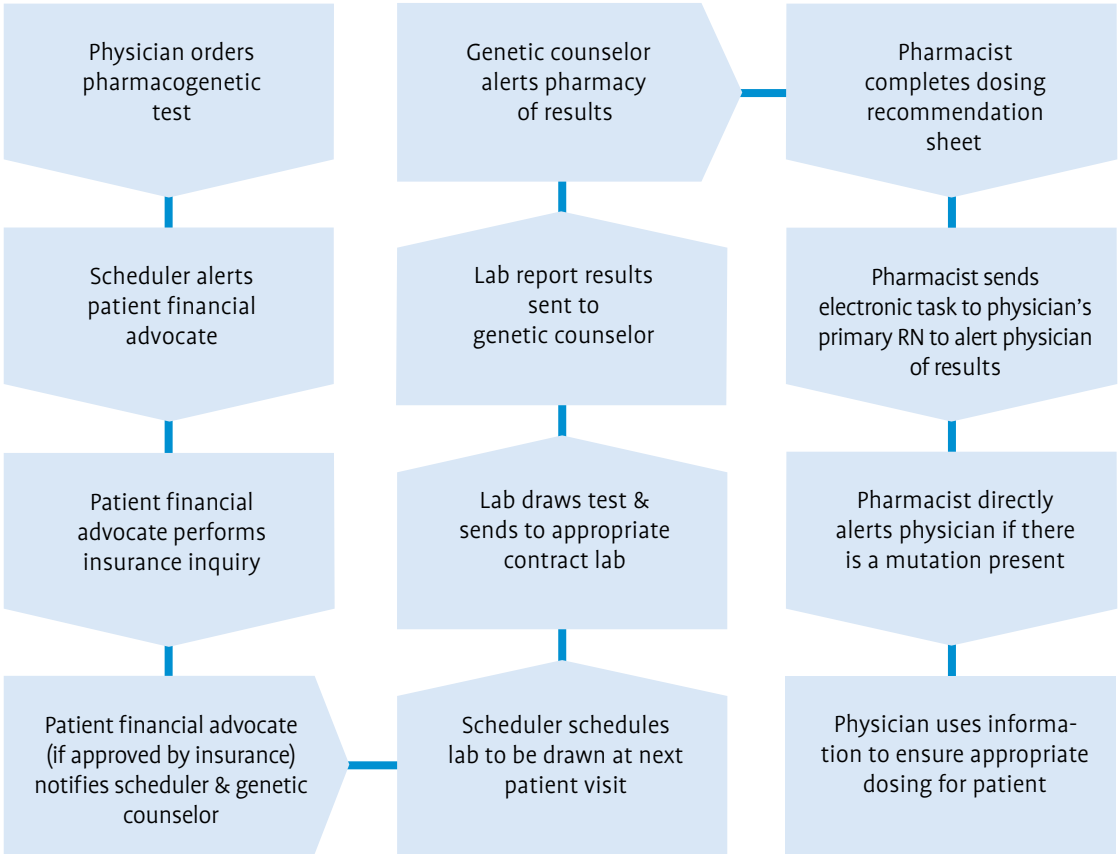
MEDICAL RECORD NUMBER:

DATE OF BIRTH:

DATE:

TEST	DRUG	RESULT	RECOMMENDATION
☐ DYPD	☐ Fluorouracil (5-FU)	☐ Homozygous Wild Type (No mutation detected)	☐ No dose adjustment
		☐ Heterozygous (One copy of the IVS14+1 G>A mutation)	☐ Start at 50% of the initial recommended dose; titrate dose based on toxicity
		☐ Homozygous Variant (Two copies of the IVS14+1 G>A mutation)	☐ CONTRAINDICATED; select alternative therapy
	☐ Capecitabine	☐ Homozygous Wild Type (No mutation detected)	☐ No dose adjustment
		☐ Heterozygous (One copy of the IVS14+1 G>A mutation)	☐ Start at 50% of the initial recommended dose; titrate dose based on toxicity
		☐ Homozygous Variant (Two copies of the IVS14+1 G>A mutation)	☐ CONTRAINDICATED; select alternative therapy
☐ TPMT	☐ Mercaptopurine (6-MP)	☐ Homozygous Wild Type (TPMT*1/TPMT*1)	☐ No dose adjustment
		☐ Heterozygous (TPMT*1/TPMT*2)	☐ Start at 30% to 70% of the initial recommended dose, allow 2 to 4 weeks to reach steady state, adjust dose based on degree of myelosuppression and disease specific guidelines
		☐ Homozygous Variant (TPMT*2/TPMT*2)	☐ Malignancy: start at 10% of the initial recommended dose and change frequency from daily to 3 days/week, allow 2 to 4 weeks to reach steady state after each dose adjustment ☐ Non-malignant condition: Consider alternative non-thiopurine immunosuppressant therapy
	☐ Thioguanine	☐ Homozygous Wild Type (TPMT*1/TPMT*1)	☐ No dose adjustment
		☐ Heterozygous (TPMT*1/TPMT*2)	☐ Start at 50% to 70% of the initial recommended dose, allow 2 to 4 weeks to reach steady state after each dose adjustment, adjust dose based on degree of myelosuppression and disease specific guidelines
		☐ Homozygous Variant (TPMT*2/TPMT*2)	☐ Start at 10% of the initial recommended dose and change frequency from daily to 3 days/week, allow 4 to 6 weeks to reach steady state after each dose adjustment, adjust dose based on degree of myelosuppression and disease-specific guidelines

Figure 2. St. Luke's Mountain States Tumor Institute's Process for Performing Pharmacogenetic Testing



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patients receiving 5-FU or capecitabine, which was comprised primarily of patients with gastrointestinal malignancies, and thiopurine methyltransferase (TPMT), indicated for patients receiving 6-mercaptopurine or thioguanine, which was comprised primarily of patients with acute lymphocytic leukemia. Genetic testing of DPYD or TPMT genes identify variants that decrease a patient's ability to metabolize the corresponding chemotherapy agents, resulting in potential increased toxicity. From analysis of the current literature, CPIC developed specific dosing guidelines that correspond with certain genetic variants to achieve appropriate therapeutic levels of each medication or to discontinue therapy. The specific testing information is summarized in Table 1, page 32.

Step 2. Determined Which Patients Should Be Tested

MSTI performed preemptive screening on all new patients, as well as current patients who were undergoing a chemotherapy regimen change. Physicians were alerted via e-mail, phone, and/or in the electronic health record.

Step 3. Established Processes & Educate Staff

In brief, here is how the process works. MSTI Pharmacy notifies the physician's primary registered nurse (RN) when patients are eligible for testing and then orders the recommended pharmacogenetic test. Once ordered, schedulers alert patient financial advocates to submit insurance prior authorization using CPT 81400 for DPYD and CPT 81401 for TPMT. If prior authorization is approved, patient financial advocates notify schedulers to add the pharmacogenetic test on the patient's next scheduled lab draw. Patient financial advocates also notify genetic counselors who track patients potentially receiving testing. Once pharmacogenetic tests are drawn and processed, they are sent out to the contracted lab: DPYD to Quest Diagnostics and TPMT to Prometheus Laboratories, Inc.

Test results are faxed directly to genetic counselors and emailed to pharmacists and scanned into the electronic health record. When results are received, pharmacists complete an electronic eScribe document in the medical record that includes:

- The test performed
- Corresponding medication(s)

Table 2. Number of Pharmacogenetic Tests Ordered on Eligible Patients
(Results from November 4, 2014 to April 1, 2016)

DRUG	# OF TESTS ORDERED	ELIGIBLE PATIENTS	PERCENT ORDERED
Fluorouracil	73	148	49.3%
Capecitabine	63	125	50.4%
Mercaptopurine	5	5	100%
Thioguanine	0	0	N/A
Total	141	278	50.7%

Table 3. Number of Pharmacogenetic Tests Ordered on Eligible Patients
(Results from February 1, 2016 to April 1, 2016)

DRUG	# OF TESTS ORDERED	ELIGIBLE PATIENTS	PERCENT ORDERED
Fluorouracil	14	17	82.4%
Capecitabine	13	14	92.9%
Mercaptopurine	1	1	100%
Thioguanine	0	0	N/A
Total	28	32	87.5%

- Test results
- Subsequent dosing recommendation from the CPIC guidelines (Figure 1, page 34).

An electronic message is sent to the physician's primary RN requesting that he or she print out the electronic document and deliver it to the physician. If the results show a variant, pharmacists call the physician directly to discuss the best therapy for the patient.

Once the pharmacogenetic testing process was established, MSTI provided education and training to all personnel that would be involved in this new process. A pharmacist provided training to schedulers, patient financial advocates, nursing, lab technicians, pharmacists, genetic counselors, and physicians through one-on-one and group meetings with oncologists, leadership, and staff. The training included MSTI's pharmacogenetic testing process—from ordering to result dissemination—which is summarized in Figure 2, page 35.

Pilot Program Results

From November 4, 2014, through April 1, 2016, 278 patients were eligible to receive pharmacogenetic testing at St. Luke's MSTI. Over the entire study period, the number of pharmacogenetic tests ordered compared to the number of patients who met eligibility for ordering was 50.7 percent (Table 2, above). However, over the last two months of the pilot program, the percentage of patients for whom testing was ordered essentially tripled, from 27 percent in the first seven months to 87.5 percent (Table 3, above).

Pharmacogenetic testing was approved by the majority of insurance companies covering our patient population. Approximately 66 percent of patients received insurance coverage for DPYD testing; 80 percent for TPMT testing. For almost all patients, Medicare has not required prior authorization for DPYD and TPMT pharmacogenetic testing. Insurance coverage without a prior authorization results in the best scenario—with minimal delay in time from when the test was ordered to when it is scheduled

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Table 4. DPYD & TPMT Pharmacogenetic Testing Insurance Coverage

INSURANCE COMPANY	DPYD	APPROVED	DENIED	TPMT	APPROVED	DENIED
AARP MEDICARE CMPLT HMO	7	7	0	-	-	-
AETNA	1	1	0	-	-	-
BLUE CROSS	22	8 (6 out-of-state)	14 (3 out-of-state)	-	-	-
BRIGHT PATH MOUNTAIN CO-OP	3	1	2	-	-	-
CIGNA	4	1	3	1	1	0
COUNTY	1	0	1	-	-	-
ODS PLUS NETWORK	1	0	1	-	-	-
HEALTH PARTNERS	1	1	0	-	-	-
IDAHO STATE CORRECTIONAL FACILITY	1	1	0	-	-	-
IPN	1	0	1	-	-	-
IPN STARMARK	1	1	0	-	-	-
KACI SMITH	1	1	0	-	-	-
MEDICAID	6	5	1	1	0	1
MEDICARE	36	35	1	1	1	0
MEDICARE ADVANTAGE	1	0	1	-	-	-
MODA	1	1	0	-	-	-
MODA MEDICARE ADVANTAGE	1	0	1	-	-	-
MOLINA	1	1	0	-	-	-
MOUNTAIN HEALTH CO-OP	1	1	0	-	-	-
PACIFIC SOURCE	5	3	2		-	-
REGENCE	9	4	3 (2 pending)	-	-	-
REGENCE MEDICARE ADVANTAGE	2	1	1	-	-	-
SELECT HEALTH	4	2	2	1	1	0
SELECT HEALTH MEDICARE ADVANTAGE	2	1	1	-	-	-
SELF-PAY	5	3 paid	2 opted out	-	-	-
SNAKE RIVER CORRECTIONAL FACILITY	1	1	0	-	-	-
TRICARE	5	1	4	-	-	-
TRUE BLUE	6	1	5	-	-	-
UNITED HEALTHCARE	6	6	0	-	-	-

TOTAL	APPROVED	DENIED	SELF-PAY
DYPD	85	44 (2 pending)	5 (3 paid, 2 opted out)
TMPT	4	1	0

Table 5. Pharmacogenetic Test Results

TEST	HOMOZYGOUS WILD TYPE	HETEROZYGOUS VARIANT	HOMOZYGOUS VARIANT
DPYD	77 (8 pending)	1	0
TPMT	5	0	0

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and drawn. The majority of commercial payers approved DPYD testing with little or no delay in time from ordering to approval. Table 4, page 37, summarizes insurance coverage by company.

St. Luke's MSTI measured the length of time from test drawn to results received from the contract lab. Turn-around time averaged 13.3 days and 9 days for DPYD and TPMT, respectively. Of the test results received (Table 5, above), one patient tested positive for a DPYD heterozygous variant; all other patients were negative for known variants. The patient with the DPYD variant was appropriately dose reduced, resulting in no significant side effects.

A Patient Case Study

Interestingly, a patient not previously tested for DPYD was transferred from an outside facility with severe capecitabine toxicity. After the patient's first cycle of treatment, the patient experienced severe myelosuppression, ultimately resulting in sepsis, hospital admission, and stays at two separate rehabilitation facilities prior to discharge. The patient then transferred care to St. Luke's MSTI.

Due to participation with this pilot program, the oncologist had greater awareness and knowledge of the impact of DPYD status on patient care, prompting the physician to order DPYD pharmacogenetic testing to determine if continued fluoropyrimidine therapy would be a viable treatment option.

The patient was found to have a heterozygous variant in the DPYD gene, indicating that the patient should have had a 50 percent dose reduction on initial treatment. If this patient had been tested prior to receiving treatment, extensive side effects, large healthcare costs, and months of hospital admissions could have been avoided. As the testing was ordered after treatment, this test result is not included in our prospective data.

Lessons Learned

The ability to perform DPYD and TPMT pharmacogenetic testing has brought St. Luke's MSTI a step forward in offering personalized medicine. The majority of St. Luke's MSTI clinics are utilizing the aforementioned pharmacogenetic testing process effectively. Expanding to outlying sites with less direct oversight created some additional challenges, but implementation was successfully achieved at all but one site. The process provides a self-sustaining program that can be applied to a variety of pharmacogenetic tests in different practice settings.

This study found 1 of 85 patients with a DPYD variant, which is similar to population prevalence. Other patients were likely missed primarily due to lack of access to pharmacogenetic testing as a result of insurance denial. However, it should be noted that current CPIC guidelines include only specific variants in DPYD, which account for approximately 50 percent of variants believed to cause decreased ability to metabolize capecitabine and fluorouracil. This implies that 50 percent of variants that increase the risk for adverse events may be missed without full sequencing of the DPYD gene. This hypothesis could explain at least one patient in our study population with no detected DPYD variants that experienced severe toxicity after receiving a first dose of fluorouracil.

At the start of this project, pharmacogenetic testing was done infrequently by a minority of physicians. Physicians questioned the clinical significance of performing this testing, which prompted MSTI to track physician ordering in an effort to measure compliance with recommendations. Through continued physician education, process improvement, and consistent patient identification, testing was readily adopted as a routine part of patient care with 88 percent of eligible patients having the DPYD test ordered. In addition, the expansion of supporting literature during this time has strengthened the evidence behind this testing.

The biggest challenge to pharmacogenetic testing in a community cancer program is the necessity for insurance coverage, which may not always be relevant in an academic setting. The majority of insurance companies are currently approving coverage; however, a few still claim that DPYD pharmacogenetic testing is experimental. Pharmacogenetic tests are considered a standard of care by several organizations and recommended in the FDA labeling of more than 130 medications. By increasing the number of requests for coverage of pharmacogenetics tests, payers may review and amend policies to follow national standards in the future. However,

the long duration of this approval and review process should be expedited as technology and knowledge are rapidly changing while patient care continues to be critically impacted.

Another barrier to this process is the delay in obtaining results once the tests are ordered. The hospital system does not perform either of these pharmacogenetic tests on site, thus requiring the use of contracted labs, which batch DPYD testing two days per week. If more tests were ordered on a regular basis, the contract lab would be able to offer the analysis more frequently. However, unlike academic centers that have on-site facilities and can report results in 24 to 48 hours, this time-frame is simply not possible for community cancer programs using a contracted lab. Further delays occur due to lack of a standardized way of ordering pharmacogenetic testing before the chemotherapy regimen is chosen and insurance coverage is verified. If the start of treatment is not delayed for results, the patient may not be prescribed the appropriate dose of chemotherapy based on their genotype.

Next Steps

Future plans are to continue to collect data and provide justification to insurance companies for coverage of these pharmacogenetic tests without a delay in therapy. Through the appeal process, one insurance company has already reversed its decision to deny insurance coverage for the DPYD pharmacogenetic testing. This change increases confidence that through continued conversations with payers, this pharmacogenetic testing program will impact coverage. In addition to collecting data, St. Luke's MSTI has initiated a subsequent project to determine if there are any differences in healthcare costs and/or additional services required for patients who receive chemotherapy in a community cancer program prior to knowing their DPYD mutation status.

While St Luke's MSTI has overcome multiple obstacles to allow patients to access pharmacogenetic testing that, until now, was only available at select academic institutions, there are still barriers to address to make this program an ideal model. The plan is to expand pharmacogenetic testing in the oncology setting, make the process more self-sufficient, and encourage pharmacogenetic testing in other disciplines throughout the St. Luke's Health System. The hope is that St. Luke's MSTI pharmacogenetic program will serve as an example to other community cancer centers of the feasibility of developing their own pharmacogenetic testing programs and help pave the way for greater application of personalized medicine. OI

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St. Luke's MSTI would like to thank the Betty Hise Foundation for Cancer Research for the generous financial support in helping to fund the development of this program.

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