Primary Care Clinicians Attitudes and Knowledge of Pharmacogenetics in a Large, Multi-state, Healthcare System

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Abstract

Background: *Considerable progress has been made in the way of pharmacogenetic research and the development of clinical recommendations; however, its implementation into clinical practice has been slower than anticipated. We sought to better understand its lack of clinical uptake within primary care.* ***Aim:*** *The primary objective of this survey was to ascertain primary care clinicians' perceptions of pharmacogenetic use and implementation in an integrated health system of metropolitan and rural settings across several states.* ***Methods:*** *Primary care clinicians (including MDs, DOs, NPs, and PAs) were invited to participate in a survey via email. Questions about pharmacogenetics knowledge and perceptions were presented to assess current understanding and usage of pharmacogenetics in practice.* ***Results:*** *The rate of response for the survey was 17%. Of the 90 respondents, 58% were female, 69% were MDs/DOs, 20% were NPs, and 11% were PAs. Fifty-eight percent of respondents received their clinical degree in or after 2000. Ninety percent of respondents noted that they were uncomfortable ordering a pharmacogenetics test, with 76% stating they were uncomfortable applying the results of a pharmacogenetic test. Notably, 78% of respondents were interested in having pharmacogenetic testing available through Medication Therapy Management (MTM) services, although PAs were significantly less interested as compared to NPs and MD/DOs. Ninety-five percent of respondents were interested in a clinical decision support tool relevant to pharmacogenetic results.* ***Conclusions:*** *As a whole, prescribing clinicians in primary care clinics are uncomfortable in the ordering, interpreting, and applying pharmacogenetic results to individual patients. However, favorable attitudes towards providing pharmacogenetic testing through existing MTM clinics provides the opportunity for pharmacists to advance existing practices.*

Keywords: pharmacogenetics, provider survey

Introduction

Over the past two decades pharmacogenetics has seen considerable growth in both research and clinical applications. Pharmacogenetics is the study of how pharmacokinetic and pharmacodynamic genes impact an individual's ability to metabolize and/or respond to specific medications, and thus allows clinicians an additional tool when prescribing medications by increasing the likelihood of clinical response while also reducing the risk of an adverse drug event in the individual patient.[1] In the United States alone, nearly 1 in 5 medications dispensed have actionable recommendations found within the package insert.[2]

Several surveys have assessed clinician's knowledge, perceptions, and attitudes towards pharmacogenetics;[3] however, few have included rural and non-metropolitan areas. While the majority of physicians agree that a patient's genetic profile may influence their response to drug therapy, early adopters of pharmacogenetic testing are limited.[4] This slow adoption of pharmacogenetic testing may be due to limited educational opportunities for prescribing clinicians, as a 2012 study showed that only 14.7% of physicians received instruction on pharmacogenetics during medical school, while only 23% reported pharmacogenetic training during postgraduate medical training.[4] Surveys of predominantly urban hospitals and clinics have also shown that most clinicians in the United States do not feel comfortable ordering, interpreting, or applying pharmacogenetic test results in their patients.[5]

In rural and metropolitan areas there are known differences in population health, such as mortality rates, number of individuals insured, death by motor vehicle accident, and patient reported health status.[6,7] Additionally, there are substantial differences in health outcomes based on levels of urbanization, especially with cerebrovascular disease.[6] According to the County Health Rankings of Minnesota, rural areas of the state have the lowest health outcomes, including the lowest frequency of diabetes monitoring, highest frequency of preventable hospital stays, lowest access to mental health providers, and highest smoking rates. Precluding these areas from pharmacogenetic testing may worsen already existing health disparities. Many pharmacists are trained in these disciplines, and may have the opportunity to play a greater role in patient health outcomes in rural areas by providing individualized precision care to patients.

Currently, widespread pharmacogenetic testing is limited to large healthcare institutions; however, pharmacists are well positioned to take the lead on implementation and application within their respective practice setting. The American Society of Health System Pharmacists recently released a statement

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advocating for pharmacists to take the lead on the clinical application of pharmacogenetics.[8]

The primary objective of this survey was to compare attitudes and perceptions of prescribing clinicians between metropolitan and non-metropolitan practice settings. Secondary objectives included comparing responses between types of clinicians (i.e. Medical Doctors (MDs)/Doctors of Osteopathy (DOs) as compared to Physician Assistants (PAs) or Nurse Practitioners (NPs)) and year of graduation.

Methods

Development of survey

Questions were developed independently by the study team with the goal of describing prescribing clinician's knowledge, comfort, and attitudes of pharmacogenetics in clinical practice. The survey consisted of questions related to demographics and pharmacogenetics knowledge as presented in Table 1. A full version of the survey can be found as a part of the supplemental materials. Demographics of gender, clinical degree, specialty, year of graduation with clinical degree, and current practice site were self-reported.

Sampling methods

The survey was approved by the local Institutional Review Board (EIRH-17-1614) and sent to 520 primary care providers in the Essentia Health system that included primary care physicians (MDs and DOs) and advanced practitioners (NPs and PAs). E-mail addresses were confirmed by the study coordinator. An email was sent to primary care providers by the director of primary care describing the survey's purpose and providing a link to access the survey questions through REDCap. Completion of the survey was voluntary with no compensation. Participants could choose to skip questions or stop the survey at any time. Two reminder emails were sent out to those who did not complete the survey. REDCap generated a participant ID for each respondent in order to keep responses anonymous.

This survey was conducted through Essentia Health, which is an integrated, not for profit, 501(c)(3) integrated healthcare delivery system with facilities in 4 states: Minnesota, Wisconsin, North Dakota and Idaho. Essentia has 15 hospitals, 75 clinics, and more than 1,900 physicians and credentialed practitioners that provide more than 1.6 million patient encounters annually. The Essentia service area includes 63 counties covering over 61,000 sq. miles with over 1 million residents. Over 80% of Essentia's geographical service area is rural and the majority of outpatient clinics (66%) are located in small towns and rural communities. Essentia Health cares for more than 400,000 individuals seeking primary care services (Family Medicine, Internal Medicine and Pediatrics).

Data analysis

Based on census data from 2010, clinics were stratified based on Rural Urban Commuting Area (RUCA) codes for the clinic zip codes. The Federal Financial Institutions Examination Council Geocoding and Mapping system from the WWAMI Rural Research Center was used to determine the State-County-Tract FIPS Code for each clinic. A database then associated each State-County-Tract code with a RUCA code. The definitions of each are as follows:

1: Metropolitan area core: primary flow within an urbanized area (UA)
2: Metropolitan area high commuting: primary flow 30% or more to a UA
3: Metropolitan area low commuting: primary flow 10% to 30% to a UA
4: Micropolitan area core: primary flow within an Urban Cluster of 10,000 to 49,999 (large UC)
5: Micropolitan high commuting: primary flow 30% or more to a large UC
6: Micropolitan low commuting: primary flow 10% to 30% to a large UC
7: Small town core: primary flow within an Urban Cluster of 2,500 to 9,999 (small UC)
8: Small town high commuting: primary flow 30% or more to a small UC
9: Small town low commuting: primary flow 10% to 30% to a small UC
10: Rural areas: primary flow to a tract outside a UA or US

Primary RUCA codes were used to determine if the clinic was in a metropolitan area (code 1-3), micropolitan area (codes 4-6), small town (codes 7-9), or rural area (code 10).

Statistical Analysis

Response frequencies were calculated for all variables of the survey. Responses were omitted if less than 50% of the questionnaire was completed. Analysis was completed using chi-squared tests to look at differences in groups categorized by RUCA scores and clinical degree. Statistical significance was evaluated using 95% confidence intervals with significance defined as p-values <0.05. Statistical analyses were performed using JMP Pro 13 (SAS Institute, Cary, NC).

Results

A total of 520 eligible clinicians were surveyed, with 90 responses received (17% response rate). Fifty percent of the respondents were female, 59% were MDs, and 27% completed their clinical degree in or after 2010. Of the practice sites surveyed, 41% were in a metropolitan area, 19% in a micropolitan area, 24% from a small town, and 16% from a rural

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area (Table 2). Figure 1 shows the geographic distribution of clinic responses based on RUCA score of the clinic zip code.

Response rates to the knowledge based and perception based questions are listed in Table 3. Regarding the use of pharmacogenetic resources, 59% of respondents would look at 3 or more sources, 15% at 2 sources, and 26% at a single source. Thirty-five percent believe that pharmacogenetic testing should be implemented in current practice, while 63% of respondents agreed that pharmacogenetic testing will soon become a valuable tool to predict the risk of adverse events and the likelihood of effectiveness with commonly used medications. Most providers stated that they were uncomfortable ordering (82%) and applying (71%) pharmacogenetic test results.

Results were stratified based on RUCA scores of metropolitan versus non-metropolitan (micropolitan, small town, and rural), clinical degree, and year of graduation. No significant differences were found between year of graduation and survey responses. When comparing metropolitan clinic sites to non-metropolitan sites, metropolitan sites were significantly more comfortable ordering pharmacogenetic tests (p=0.045). When examining interest in a clinical decision support (CDS) tool, there were significant differences between MD, NP, and PA, with PAs expressing the lowest interest (p=0.01). There was also a significant difference (p=0.03) between clinical degree and interest in pharmacogenetics being housed in medication therapy management (MTM), where again PAs were the least interested and NPs were the most interested in pharmacogenetics being a part of MTM services (Table 3).
Open ended responses from providers were predominantly related to concerns around cost/insurance coverage, evidence and benefits of the testing, improvement upon current guidelines, and additional education related to pharmacogenetics.

Discussion

This survey of primary care clinicians in a large, multi-state health care system showed support for the use of pharmacogenetics in practice while revealing concerns related to cost and insurance coverage, evidence and benefits of the tests, and a lack of general knowledge of pharmacogenetics. Most notable was the enthusiastic support of incorporating pharmacogenetic testing into existing MTM practices in addition to a CDS tool.

Other than a greater level of comfort ordering pharmacogenetic tests in rural clinics, results from this survey did not show notably different attitudes surrounding pharmacogenetics between rural and metropolitan areas. Similar to our results, a previous survey of healthcare providers in rural Montana revealed optimism for pharmacogenetic testing, but also noted concerns related to the turnaround time of genetic tests, availability of a genetics specialist, and acceptability of genetic tests in rural populations.[3] Essentia Health is well positioned to provide pharmacogenetic services to rural areas given their broad rural network and availability of MTM pharmacists in these locations.

Currently, MTM practices have allowed pharmacists to assume a more active role within primary care.[9] Pharmacists meet one-on-one with patients for a consult on their medication experience to optimize drug therapy and improve outcomes for patients. Nearly 75% of respondents of this survey indicated they would like to see pharmacogenetic testing made available within MTM services. Essentia Health has 17 clinic sites in Minnesota that offer MTM as a complement to other primary care services, therefore it may be a reasonable place for pharmacogenetic testing and counseling to take place. Notably, rural pharmacies have a higher rate of MTM services than metropolitan areas, which may provide an ideal framework into which pharmacogenetics could be implemented.[10]

CDS tools and best practice alerts within the electronic medical record could also help implement pharmacogenetic testing across a large healthcare system. As shown by Caraballo *et al*, these tools can be extremely useful in preventing adverse drug reactions related to pharmacogenetics.[11] Nearly 90% of clinicians supported having a CDS tool to alert them to potential drug-gene interactions, considerably greater than a previous study where just 40% said being prompted by an alert within the EMR was of major importance.[5] CDS tools may also be useful in discerning when to order pharmacogenetic testing and how to interpret and apply those results.[12] Given the overwhelmingly low levels of comfort around ordering and interpreting pharmacogenetic tests within this survey, guidance from pharmacists and CDS tools could improve these aspects for clinicians.

In order to effectively deliver pharmacogenetic information, an integrated healthcare team is needed. Pharmacists are the experts in medication management and those with an understanding of how genetic differences impact therapeutic outcomes are well positioned to recommend and interpret pharmacogenetic testing. Additionally, since 2016 the Accreditation Council for Pharmacy Education has required pharmacogenetics as part of the standard didactic curriculum,[13] uniquely positioning pharmacists within the healthcare team to take the lead on such efforts. Based on the survey results, about 1 in 5 clinicians would contact genetic counseling for interpretation of pharmacogenetic test results, 11% would contact pharmacy, and only 1% would contact both. This presents an interprofessional opportunity for pharmacists to work with genetic counselors who are skilled in discussing the genetic basis of disease and how results are best shared with individuals and family members.[14] Lack of agreement between clinicians on who should interpret and communicate pharmacogenetic test results may lead to some patient's needs

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going unmet.[5] Increased clarity of the expertise that each individual on the healthcare team has with pharmacogenetics and who will provide interpretation of results is needed. Establishing pharmacists as the primary clinician ordering, interpreting, and applying pharmacogenetic results would standardize the process and could result in improved patient care.

Physicians and advanced practitioners had some differing views on the implementation of pharmacogenetic testing, most notably the resistance seen with PAs. The reason for this resistance is not clear but it could stem from a lack of understanding of the role pharmacists can play in supporting the implementation of pharmacogenetic testing and the role of pharmacists on the health care team. The lack of interest observed may be similar in nature to the working relationship between pharmacists and physicians, where recent studies have shown that some physicians lack a clear understanding of pharmacists roles in primary health care and their training received in school.[15] While the same may be true for PAs, midlevel practitioners have positive attitudes towards pharmacists in discussing adverse drug reactions and risk benefit information. Additionally, both physicians and midlevel practitioners had positive responses for pharmacists being consulted on decision making processes for optimizing a patient's drug therapy.[16] Future studies are needed to fully understand why all clinicians do not have the same positive view on pharmacogenetic testing but utilize pharmacists in other ways.

Implementing pharmacogenetics into clinical practice presents specific challenges. Most notably these include the availability of tests, timeliness of test results, integrating results into the electronic medical record, and standardizing how pharmacogenetic results are applied in practice. Since there is not currently a standardized return of results, multiple tests from different commercial companies may be completed on the same individual with differing recommendations.[17] Additionally, there is limited availability of evidence for cost effectiveness of pharmacogenetic testing, making reimbursement variable and slowing implementation.[18] More research into cost effectiveness of pharmacogenetic testing could lead to widespread implementation within hospital systems as they would be preventing unneeded hospital stays, clinic visits, and drug costs.

This study has several limitations. First, the relatively low response rate may have affected the results due to response bias. Second, the majority of respondents were from a metropolitan area, and not all clinics in the health care system are represented. Lastly, while this was a multi-state survey it was limited to a single health system with ingrained pharmacy services readily available, and thus may be limited in its comparability to other health systems.

This survey shows that although prescribing clinicians are interested in pharmacogenetic testing, additional education is needed prior to widespread implementation. Importantly for pharmacists, widespread agreement for pharmacogenetics to be made available within existing MTM practices in addition to a CDS tool provides great opportunity to advance the overall practice of pharmacy by providing individualized precision care to patients.

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Treatment of Human Subjects: IRB determined project was non-HSR

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Table 1. Provider Survey Questions

General Knowledge Questions

At their annual physical, a patient brings a copy of their results from a direct-to-consumer pharmacogenetic testing service and asks you to help them understand the results.

1. Which course of action describes what you would do? (select all that apply)
   - Provide an interpretation based on your knowledge of certain genetic risks
   - Refer the patient to genetics counseling
   - Contact pharmacy for interpretation
   - Other (please specify)

2. Which sources would you consult when interpreting the results? (please select all that apply)
   - Scientific literature
   - Medical association meetings/guidelines/recommendations
   - Drug resources (e.g. Lexi-comp, Micromedex, etc.)
   - Internet (e.g. MayoClinic, WebMD, PharmGKB, etc.)
   - Drug labeling/ FDA website
   - Pharmacy
   - Colleague
   - Other (Please specify)

3. How would you document their test result information? (all that apply)
   - Enter notes into the EHR
   - Scan document into medical records
   - Unsure what to do with the results
   - Other (please specify)

Pharmacogenetic Perception Based Questions

4. Pharmacogenetics testing will soon become a valuable tool to predict the risk of adverse events and the likelihood of effectiveness with commonly used medications.
   - Agree
   - Somewhat agree
   - Somewhat disagree
   - Disagree
   - Depends on the evidence-based protocol of each drug

5. Do you think pharmacogenetic testing should be implemented in current practices?
   - Yes
   - No
   - Need more information

6. What additional information would be most valuable to you?

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7. How comfortable are you ordering pharmacogenetic testing for your patients?
   - Very comfortable
   - somewhat comfortable
   - somewhat uncomfortable
   - Very uncomfortable
   - Not applicable

8. How comfortable are you applying pharmacogenetic testing for your patients?
   - Very comfortable
   - somewhat comfortable
   - somewhat uncomfortable
   - Very uncomfortable
   - Not applicable

9. Essentia Health offers Medication Therapy Management (MTM) services to all patients. How interested are you in making pharmacogenetic testing available through Essentia's current MTM program?
   - Very interested
   - Somewhat interested
   - Somewhat not interested
   - Not interested
   - Not applicable

10. Would you want a decision support tool to alert you to potential drug-gene interactions in patients with pharmacogenetic results?
   - Very interested
   - Somewhat interested
   - Somewhat not interested
   - Not interested

11. Is there anything else you'd like us to know about this topic?

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Table 2. Demographics of Survey Respondents	
Categories	**N (%)**
Gender	
Female	45 (58)
Male	31 (34)
Other	2 (2)
No response	12 (13)
Clinical Degree	
Medical Doctor (MD)	52 (58)
Doctor of Osteopathic Medicine (DO)	5 (6)
Physician Assistant (PA-C)	9 (1)
Nurse Practitioner (NP/CNP)	17 (19)
No response	7 (8)
Year of Graduation with Clinical Degree	
2010-2016	24 (27)
2000-2009	18 (20)
1990-1999	13 (14)
1980-1989	8 (9)
Before 1980	10 (11)
No response	17 (19)
Current Practice Site RUCA score	
Metropolitan (1-3)	31 (34)
Micropolitan (4-6)	14 (16)
Small town (7-9)	18 (20)
Rural (10)	12 (13)
No response	15 (17)

Table 3. Summary of Responses to General Knowledge and Perception Based Questions	
General Knowledge Questions (select all that apply)	**N (%)**
At their annual physical, a patient brings a copy of their results from a direct-to-consumer pharmacogenetic testing service and asks you to help them understand the results.	
1. Which course of action describes what you would do? (select all that apply)*	
• Provide an interpretation based on knowledge of certain genetic risks	52 (45)
• Refer the patient to genetic counseling	36 (31)
• Contact pharmacy for interpretation	18 (16)
• Other	9 (8)
2. Which sources would you consult when interpreting the results? (select all that apply)*	
• Scientific Literature	58 (22)
• Medical association meetings/guidelines/recommendations	43 (16)
• Drug resources (e.g. Lexi-comp, Micromedex, etc.)	39 (15)
• Internet (e.g. MayoClinic, WebMD, PharmGKB, etc.)	39 (15)
• Drug labeling/ FDA website	11 (4)
• Pharmacy	36 (13)
• Colleague	38 14)
• Other (Please specify)	3 (1)
3. How would you document their test result information? (select all that apply)*	
• Enter notes into Electronic Health Record	46 (34)
• Scan document into medical records	77 (56)
• Unsure what to do with results	12 (9)
• Other	2 (1)
Pharmacogenetic Perception Based Questions	**N (%)**
4. Pharmacogenetic testing will soon become a valuable tool to predict the risk of adverse events and the likelihood of effectiveness with commonly used medications.	
• Agree	27 (30)

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• Somewhat agree	30 (33)
• Somewhat disagree	6 (7)
• Disagree	0 (0)
• Depends on the evidence-based protocol of each drug	20 (22)
• No response	7 (8)
5. Do you think pharmacogenetics testing should be implemented in current practices?	
• Yes	32 (35)
• No	2 (2)
• Need more information	49 (54)
• No response	7 (8)
6. How comfortable are you ordering pharmacogenetic testing for your patients?	
• Very comfortable	1 (1)
• Somewhat comfortable	7 (8)
• Somewhat uncomfortable	22 (24)
• Very uncomfortable	52 (58)
• No response	8 (9)
7. How comfortable are you applying pharmacogenetic testing for your patients?	
• Very comfortable	2 (2)
• Somewhat comfortable	17 (18)
• Somewhat uncomfortable	31 (34)
• Very uncomfortable	33 (37)
• No response	7 (8)
8. Essentia Health offers Medication Therapy Management (MTM) services to all patients. How interested are you in making pharmacogenetic testing available through Essentia's current MTM program?	
• Very interested	24 (27)
• Somewhat interested	41 (46)

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• Somewhat uninterested	13 (14)
• Not interested	6 (7)
9. Would you want a decision support tool to alert you to potential drug-gene interactions in patients with pharmacogenetic results	
• Very interested	44 (49)
• Somewhat interested	35 (39)
• Somewhat uninterested	4 (4)
• Not interested	0 (0)
• No response	7 (8)

*These categories are not mutually exclusive.

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Figure 1. Multi-state Practice Sites Coded Based on the RUCA Score of their Zip Code.