



Implementation of Pharmacogenomics Testing in Clinical Practice in Punjab, Pakistan: A KAP Survey of Healthcare Providers

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Abstract- Pharmacogenomics (PGx) in the clinical practice help to provide personalized care, which improves clinical outcomes of treatment. The implementation of PGx among healthcare providers has not been explored yet in Pakistan. The study aims to assess the knowledge, awareness, and perception of healthcare providers toward the implementation of PGx testing in the clinical practice in the Punjab, Pakistan. A cross-sectional survey distributed to healthcare providers (Pharmacists and Physicians) from December 2019 to April 2020 at 15 government and private hospitals. Regression analyses along with some descriptive statistical measures were computed using SPSS software. Among 250 surveys, 220 participants responded with 88.1% response rate. The healthcare professionals comprised 90 physicians and 130 pharmacists with 68.18% urban participants. The results showed a fair knowledge and awareness of PGx, they preferred to learn about PGx in form of Continuous Medical Education (CME). The perception of the respondents was positive toward the implementation of PGx testing. Further, results also revealed a significant positive effect of awareness on the perceived PGx practices. Pharmacists and Physicians with high perceived knowledge and awareness were more willing to implement the PGx in their clinical practice. Recourses availability (laboratory equipment availability), high cost and lack of knowledge were the most obstacles and challenges of PGx implementation. The study provides insights of the importance of channeling resources and of continuous education regarding PGx that help to provide personalized care in medication decisions and in reducing the incidence of Adverse Drug Reactions (ADRs) in the Eastern Province hospitals.

Keywords: Pharmacogenomics; Clinical practice; Continuous Medical Education

I. INTRODUCTION

Pharmacogenomics (PGx) led to personalized medicine, explaining how the genome affects drug activity in the body, showing individuals' responses to medications, varying between efficient response, no response, or toxicity (Whirl-Carrillo, et al. (2012); Relling and Evans (2015). PGx testing implementation is the process that incorporates PGx information into the clinical practice by obtaining and interpreting genomic data. Starting with identifying the target population, determining the genetic variants to conduct genotyping and store the results (Evans and Relling, 2004). Followed by; selecting the variants to input them into electronic health records, translating the genotype to phenotype and following strong evidence recommendations regarding drug-pair interpretation. Finally, adding an alert when the medication is prescribed for a patient who has a polymorphism that affects the drug activity (Evans and McLeod, 2003). Therefore, PGx helps to provide safe, effective and personalized care by decreasing the Adverse Drug Reaction (ADRs).

American Food and Drug Administration (FDA) demonstrated the importance of PGx testing implementation as an important part of individualized medicine (Roden, et al. 2006; Nebert, et al. 2003). Clinicians can use PGx to individualize treatment and avoid undesirable serious side effects. PGx testing can predict idiosyncratic ADRs, resulting in the development of new safer medications and decrease overall costs of treatment (Lesko, et al. 2003; Frick, et al. 2018). Several studies conducted in different parts of the world to explore the knowledge, awareness and barriers of the PGx implementation in the clinical setting (Shu, et al. 2015; Williams-Jones and Ozdemir, 2009). Physicians in Quebec in Canada are willing to implement PGx in the clinical practice (Ameen et al. 2012), and they showed a positive attitude toward PGx testing but the majority did not receive any training in PGx in their undergraduate or postgraduate study (Shukla, et al. 2016). In Qatar, despite the low awareness of PGx implementation among the physicians and pharmacists; they had a positive attitude toward practicing the PGx in the clinical setting (Wyatt, et al. 2012). In Malaysia, physicians and pharmacist had a poor knowledge of PGx

implementation (Shu, et al. 2012). The limited knowledge among pharmacists was one of the obstacles toward the implementation of PGx despite of their willingness to implement it (Shukla, et al. 2016; Cavallari, 2013). In United State, a survey affiliated with American Pharmacy Services Corporation (APSC) shareholder, more than half of the respondents felt they lack the knowledge, and the majority felt they were unqualified to implement PGx testing (Frueh, et al. 2008; Nebert, et al. 2003). Most participants showed interest in providing PGx testing with lower potentiality of implementing it. Continuous education and literature were the most used sources of education as most respondents did not receive PGx education from their school curriculum and would like to attend future educational programs (Ang, et al. 2017; Thorn, et al. 2010).

In Pakistan, personalized medicine is a growing field that is contributing to crucial advancements in both diagnostics and management of diseases and although there are more than 20 certified clinical geneticists that cover the major areas of clinical genetics (Farhat, et al. 2015; Ameen, et al. 2012) the tests provided are for conditions and diseases, not for medications, the PGx tests are not available or not well-known yet (Ameen, et al. 2012). Implementation of PGx among healthcare providers has not been explored yet in Pakistan. To our knowledge up to date there are no studies in Pakistan about PGx implementation among healthcare professionals in clinical setting. Thus, this study aims to explore the knowledge, awareness and perception of healthcare providers toward the implementation of PGx testing in the clinical practice in the Punjab, Province, Pakistan. Furthermore, this study also aimed to explore the effect of awareness and knowledge on the perceived PGx implementation in the clinical practice and to highlight the barriers of implementation.

II. METHODS

2.1 Design of the Survey

A cross-sectional study design was used to perform a survey in Rawalpindi, Lahore, Faisalabad, Multan cities of Punjab. The survey was both an online version sent through e-mail and self administered to healthcare providers (pharmacists and physicians) from 16 hospitals and clinics. The survey consisted of 4 sections; demographics, knowledge, awareness and perception with a total of 27 questions (5-point scale). The survey was designed in accordance to previously published international studies (Bannur, et al., 2014; Amara, et al., 2017; Tamaoki, et al., 2007; Peterson, et al., 2017). A pilot study consisting of 30 participants of pharmacists and physicians was conducted to validate the survey by Cronbach's Alpha test.

2.2 Sampling

Sample size calculation was performed using Raosoft, with a 5% margin of error, 95% confidence interval, response rate of 88.1% and sample size consisting of Urban and Rural pharmacists and physicians working in the different cities of Punjab, 250 surveys were calculated and submitted. The population size was obtained from the Ministry of Health Punjab.

2.3 Inclusion Criteria

Pharmacists and physicians who are working in the Punjab Province of Pakistan in government or private hospitals, medical centers and clinics were included.

2.4 Exclusion Criteria:

Healthcare providers other than pharmacists and physicians were excluded.

2.5 Data Analyses

Descriptive statistics and regression analysis were conducted using a Statistical Package for Social Sciences (SPSS) version 22. The value 0.05 considered as statistically significant value of the regression model with confidence interval 95%.

III. RESULTS

3.1. Data Collection And Pilot Study

Data collection was done in a period of 4 months. A total of 250 surveys were distributed and 220 were returned. The response rate was 88.1%, none of them were incomplete. The validity of the survey was assessed by conducting a pilot study using Cronbach's Alpha test, resulting in a scores more than 0.70 for the study variables (Knowledge, Awareness and Perception).

3.2. Demographics

Total samples of 220 (165 male and 55 female) respondents are considered in this study with 82% urban and 18% rural (see Table 1). Pharmacists were 130, and 90 were physicians. The majority of the age groups are between 24 years to 39 years old (67.72%). As shown in Table 1, most of the respondents had less than four years of experiences (50%).

Table 1: Demographic Characteristics

Demographics		N	%
Gender	Male	165	75
	Female	55	25
Age	<=24	41	19
	24-29	78	35
	30-39	71	32
	40-60	15	7
	>6	5	2
Profession	Physician	90	41
	Pharmacist	130	59
Years of experience	<4 Years	110	50
	4-10 Years	75	34
	>10 Years	35	16
Region	Urban	180	82
	Rural	40	18
City	Rawalpindi	35	16
	Lahore	85	39
	Faisalabad	75	34
	Multan	20	9
	Others	5	2

3.3. Knowledge

It has been noted that about 58% (42% agreed and 16% strongly agreed) of respondents approved that PGx is important for healthcare providers, and 81% (50% agreed and 31% strongly agreed) of them approved that the response of the drugs is affected by the genetic variation. Moreover, 74% (55% agreed and 19% strongly agreed) of the participants documented that PGx is about how the drug activity is affected by specific genes, as shown in Figure 1. Therefore, the knowledge of healthcare providers in Pakistan of PGx is fair.

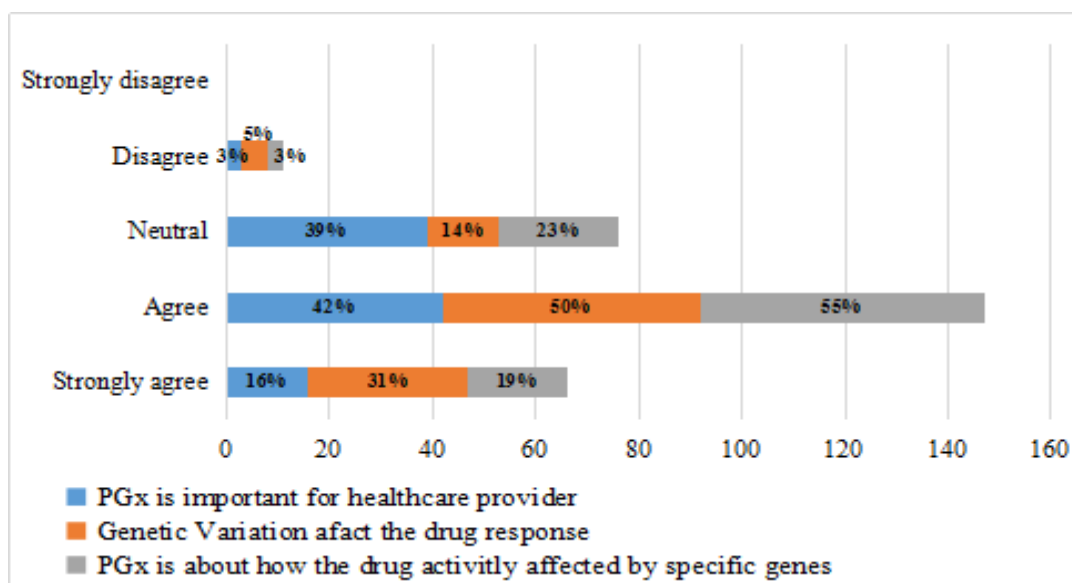


Fig. 1: Health Provider PGx Knowledge

Table 2 shows the results of independent sample t-test and ANOVA analyses. There is no significance difference of the knowledge among the respondents in term of their gender, age, nationality, city and experience. However, in terms of profession, Physicians and pharmacists had significantly different knowledge regarding the PGx with $t= 3.013$ and $p= 0.003$. Pharmacists (mean=1.962, SD=0.611) highly perceived the importance and knowledge of PGx than physicians (mean= 2.238, SD=0.598), while the lower mean refers to better knowledge (Strongly agree was coded 1).

Table 2. Independent sample t-test and ANOVA of the respondents' characteristics and PGx knowledge.

Demographics		N	Mean	S.D	t-test	p-value
Gender	Male	165	1.015	0.789	5.472	0.123
	Female	55	2.046	0.981		
Profession	Physician	90	2.238	0.598	3.013	0.003
	Pharmacist	130	1.962	0.611		
Region	Urban	180	2.680	1.251	4.63	0.113
	Rural	40	2.014	0.887		
		N	Mean	S.D	F-test	p-value
Age	<=24	41	2.051	0.398	5.61	0.0912
	24-29	78	2.143	0.987		
	30-39	71	1.584	1.247		
	40-60	15	2.039	0.398		
	>60	5	2.153	0.458		
Years of experience	<4	110	2.142	0.547	4.98	0.0641
	4-10y	75	2.930	0.357		
	>10	35	1.924	0.478		
City	Rawalpindi	35	2.042	0.698	5.07	0.716
	Lahore	85	2.031	0.887		
	Faisalabad	75	2.221	0.257		

Multan	20	2.013	0.958
Others	5	2.009	

3.4. Awareness

About 69% respondents approved (48% agreed and 21% strongly agreed) that using PGx testing can help in avoiding some adverse drug reactions. Whereas, 25% of respondents reported that they noticed PGx-warning medication label before. Moreover 72% of respondents agreed that PGx could help in decreasing health care costs, (see Figure 2). Therefore, the Awareness of healthcare providers in Pakistan of PGx is fair.

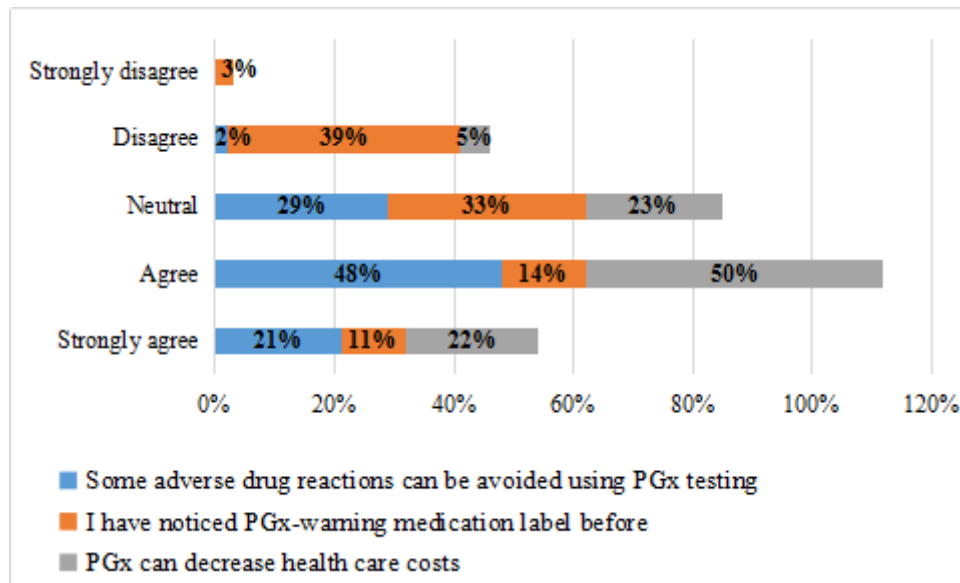


Fig. No. 2: Health care providers awareness toward PGx testing implementation

Only 5% of respondents reported that they have enrolled in a PGx course before. The courses they enrolled in were provided by their universities (Figure 3a). Thirty-one percent of respondents chose continuous medical education (CME) in form of seminars and conferences as their preferred way to be educated about PGx, online based courses came next with 47%, and 22% preferred to learn by themselves about PGx (Figure 3b).

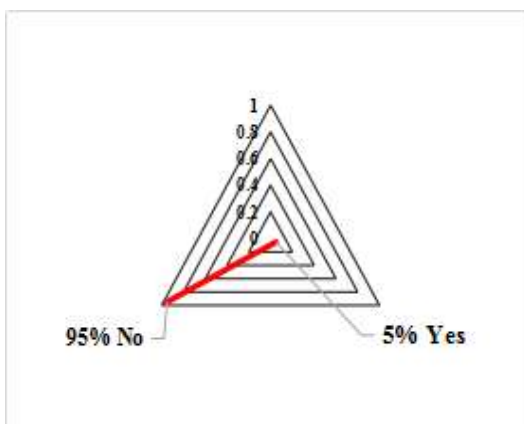


Figure 3a: Enrolled in a PGx course before

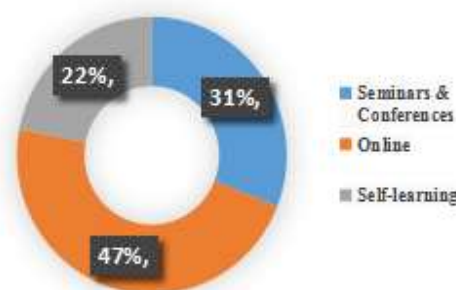


Figure 3b: Preferred type of education

Table 3 shows the results of independent sample t-test and ANOVA analyses. There is no significance difference of the awareness among the respondents in terms of their gender, age, region, city and experience. However, in terms of profession, physicians and pharmacists significantly had different awareness regarding the PGx with $t= 3.534$ and $p= 0.001$. Pharmacists (Mean=2.247, SD=0.588) had higher awareness of PGx than physicians (Mean= 2.550, SD=0.534), while the lower mean refers to better knowledge.

Table 3. Independent sample t-test and ANOVA of the respondents' characteristics and PGx awareness.

Demographics		N	Mean	S.D	t-test	p-value
Gender	Male	165	2.431	0.871	4.981	0.114
	Female	55	2.525	0.921		
Profession	Physician	90	2.550	0.534	3.534	0.001
	Pharmacist	130	2.247	0.588		
Region	Urban	180	2.413	0.887	5.011	0.0687
	Rural	40	2.413	0.810		
		N	Mean	S.D	F-test	p-value
Age	<=24	41	2.416	0.791	6.124	0.092
	24-29	78	2.460	0.678		
	30-39	71	2.271	0.698		
	40-60	15	2.315	0.715		
	>6	5	2.347	0.841		
Years of experience	<4	110	2.530	0.951	4.08	0.079
	4-10y	75	2.315	0.990		
	>10	35	2.261	0.587		
City	Rawalpindi	35	2.041	0.684	5.127	0.084
	Lahore	85	2.512	0.791		
	Faisalabad	75	2.713	0.894		
	Multan	20	2.361	0.884		
	Others	5	2.417	0.654		

3.5. Perception

Most of the respondents agreed that implementing PGx in hospitals is required and they are willing to contribute in the process of the implementation scoring 54%. About 67% of the participants are willing to request PGx testing if it was available in hospitals and two-third of the respondents are comfortable with having genetic information incorporated into deciding their patients' treatment. The majority agreed by 66% that PGx can decrease the time required to find the optimal dose. Approximately half of the respondents agreed that using PGx will result in decreasing the cost of developing new drugs and 56% agreed that PGx testing can be implemented in hospitals within 10 years in Pakistan, as shown in Figure 4.

The study participants highlighted eight factors associated with their decision toward ordering PGx test, as shown in Figure 5 (family history, Age, Gender, Ethnicity, Medications, Cost, Availability of test, Time needed to perform test). Sixty-four percent of the respondents chose family history as factor that influence their decision toward ordering PGx test representing the majority, the least selected factor was age chosen by 36% of the respondents. Time to get results and result interpretation were added by respondent as additional factors.

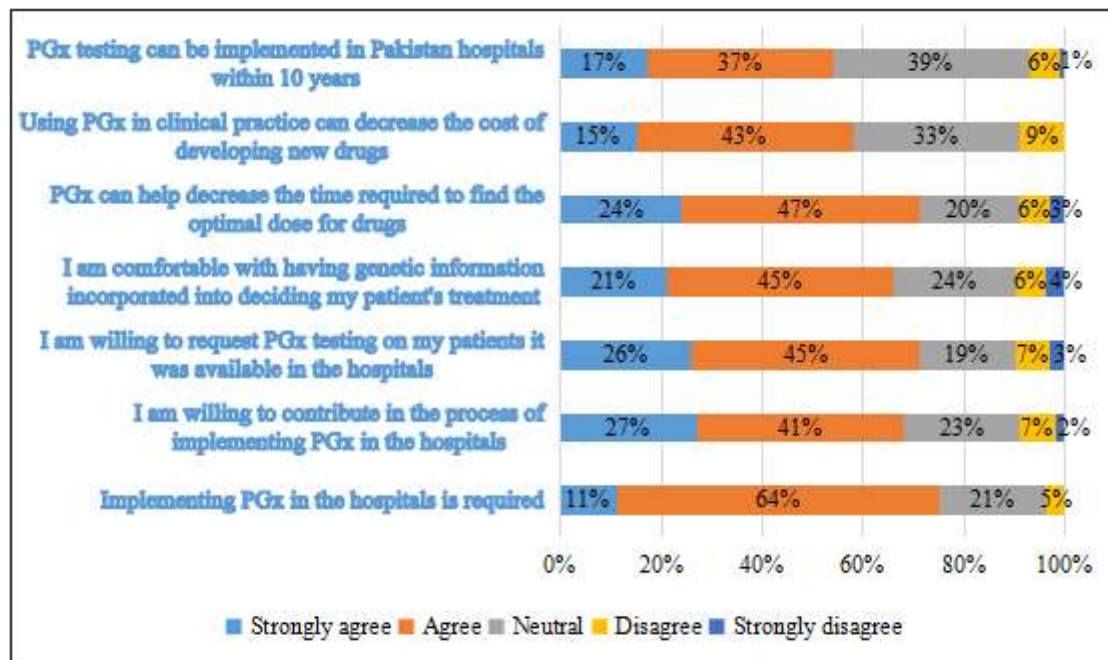


Fig. 4: Perception towards PGx testing implementation

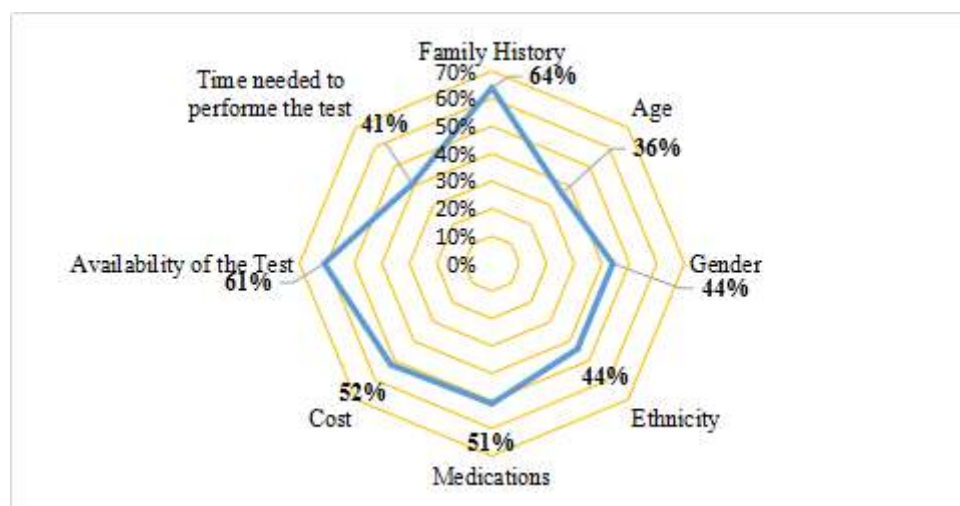


Fig. No. 5: Factors that influence decision towards ordering PGx test

The most chosen source that they will use to obtain PGx information was FDA approved drug labels by 60% of the participants, followed by guidelines with 57%, then published literature with 49% and the least chosen source was the third-party laboratory by 27% (Figure 6).

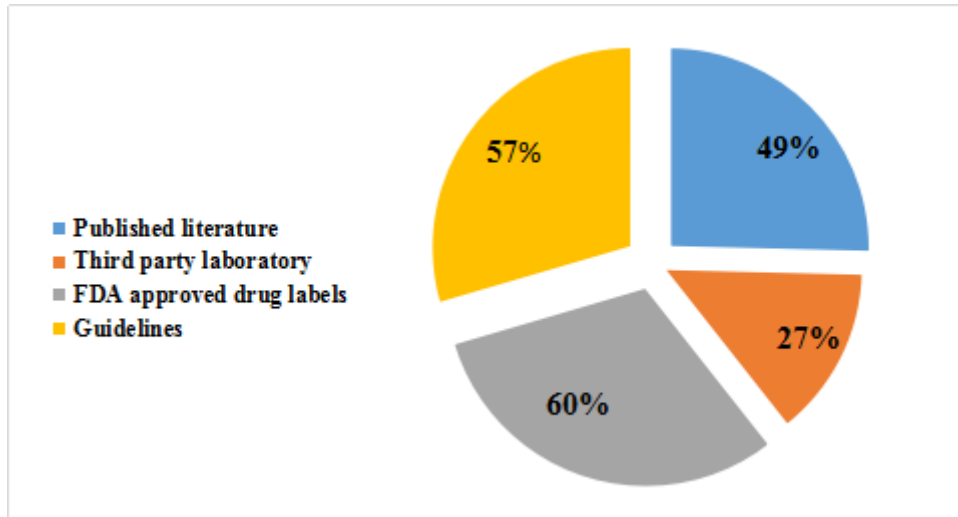


Fig No. 6: PGx Information Sources

High cost was selected by 70% of the respondents making it the most obstacles chosen that may be faced while implementing PGx, followed by laboratory equipment availability then lack knowledge. The least chosen was confidentiality by 25% respondents (Figure 7). One of the respondents added the following; Insurance acceptance, Ministry of Health permission and the Council of Cooperative Health Insurance (CCHI) regulation as additional obstacles.

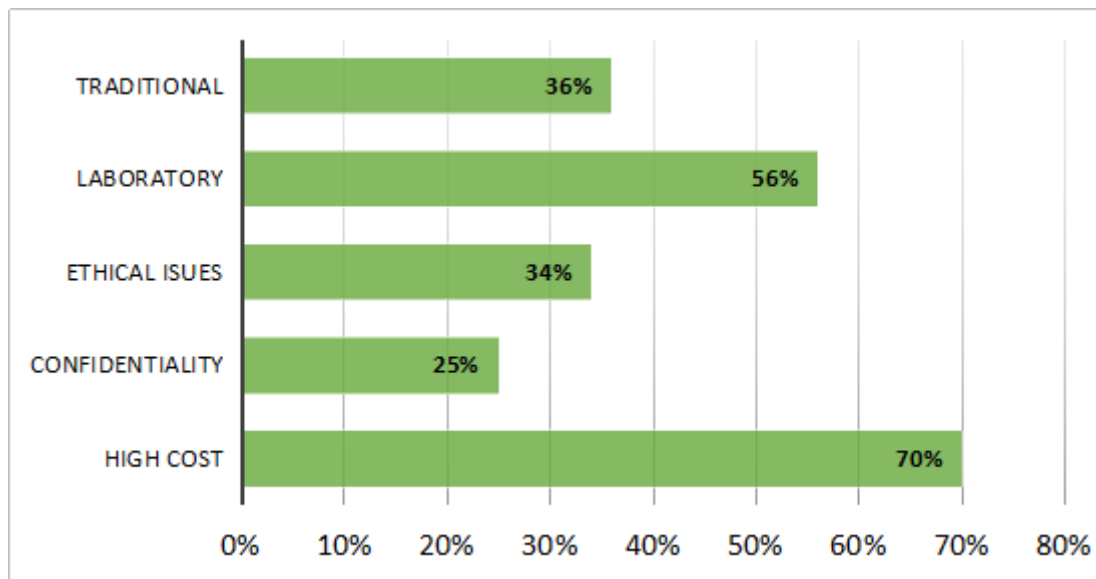


Figure No.7: Hurdles in the implementation of PGx

3.6. The effect of awareness and knowledge on the perceived PGx practices

Later on, linear regression analysis is used to identify the effect of awareness and knowledge on the perceived PGx practices. There is positive effect of both awareness ($\beta = 0.287$, $t = 3.860$, $p = 0.0001$) and knowledge ($\beta = 0.315$, $t = 4.207$, $p = 0.0001$) on the perceived PGx practices Table 4. The R^2 value indicated that the knowledge and awareness predicted 71% of variances in the perceived clinical implementation of PGx practices among healthcare provides. Pharmacists and physicians with high perceived knowledge and awareness were more willing to implement the PGx in their clinical practice. The unstandardized β coefficients indicated that one unit improve in the health care providers' knowledge and awareness led to enhance their willingness of implementing the PGx in their practice by 28.7% and 31.5% respectively.

Table 4: The Impact of Awareness and Knowledge on the perceived practices

Variable	Unstandardized Coefficients	S.D	Standardize Coefficients	t-test	p-value
Coefficient	0.610	0.162	-	6.253	0.0001
Awareness	0.287	0.048	0.310	3.860	0.0001
Knowledge	0.315	0.152	0.382	4.207	0.0001
R ²			0.71		
F			53.15		
p-value			0.0001		

IV. DISCUSSION

This study explored the knowledge, awareness and perception of pharmacists and physicians about PGx implementation in Pakistan. The majority of participants had some basic knowledge about the importance of PGx and the effects of genetic variation on drug response. This result was consistent with another study that was conducted by Bannur in Malaysia which showed fair knowledge among health care providers (Bannur, et al., 2014).

This study demonstrated that both physicians and pharmacists are keen to see PGx testing implemented as part of clinical care in Pakistan's hospitals, and that also applies for other countries. Studies have proven the importance and willingness of both physicians and pharmacists to implement PGx as part of the practice in hospitals (Yau, et al., 2015; Muzoriana, et al., 2017). In fact, participants in this study agreed that implementing PGx testing will result in avoiding ADRs scoring 69% and reducing healthcare costs scoring 58%. This study showed a positive correlation between the level of knowledge and awareness and the willingness of participants to practice PGx in their clinical setting with pharmacists having a higher levels of awareness and knowledge about PGx which is really important as the role of hospital and community pharmacists in Pakistan has changed dramatically from only medication dispensing to pharmacists that are dynamically involved in monitoring medication therapy and providing patient medication education and counseling and providing pharmaceutical care plans. It also provides an insight on the importance of PGx to be included in the curriculum of medical and pharmacy students. Training and skills should be acquired during the undergraduate study (Muzoriana, et al., 2017). Therefore, this might help to overcome the second main obstacles of PGx implementations in the clinical setting in Pakistan (The first main obstacle was the availability of resources, including; cost and availability of laboratory equipment).

Only one-third had noticed PGx warning label before. Whereas, the respondents emphasized that PGx testing will have a positive impact on controlling drug therapy costs and agreed that implementing PGx testing will result in decreasing ADRs. The minority (7%) were enrolled previously in a PGx course provided by their universities. Whereas, most of the respondents showed a great interest in learning about PGx and their most preferred type of education was CME. Therefore, we suggest providing education in the form of Continuous Medical Education (CME) including: seminars, workshops and conferences. This was supported by previous studies; healthcare providers who have learned about PGx previously were more aware and knowledgeable about PGx (McMahon, et al., 2011). This will help them provide personalized care by implementing PGx in their clinical settings.

The results showed that the participants perceived PGx implementation in a positive manner, they were willing to contribute in the process and they agreed to request PGx testing for their patients. Family history was the factor that would mostly influence the respondents' decision when ordering PGx testing. Since PGx testing is usually only ordered based on the medications prescribed. The most chosen source to obtain PGx information was FDA approved labels, in contrast with another study which showed that FDA approval labels matter the least (Bannur, et al., 2014). High cost was chosen by the majority as one of the obstacles that may be faced, followed by laboratory equipment availability then lack knowledge as expected by the authors. Many factors can affect the practitioner's decision in choosing the therapy for their patients, such as; patient's family history, age, gender, ethnic group, medications, the cost and availability of the PGx testing, and the time to perform and obtain its results. In 2016 Peterson J, et al assessed the attitude of clinicians by stating what can influence their decision wither to order PGx test for a patient or not. The results showed that "strength of evidence that genetic test results could affect the patients' drug dosing" and "absence of out-of-pocket cost to the patient" were the most influencing factors

for decision making. Also, in 2017 Moyer et al discussed the challenges facing PGx testing implementation in the clinic and stated that determining which patient required testing depended on the choice of medication to be prescribed as whether that medication selection or dosing is affected by the test result. The study also commented that with a cost ranging from hundreds to thousands of dollars to test a single gene or to get a gene panel; the implementation of PGx testing has been there for partially restrained. But with the development of technology such costs are dropping and the tests are becoming more accessible (Moyer A.; and Caraballo,2017). Compared to another study, lack of knowledge was the top perceived challenge facing PGx implementation chosen by both pharmacists and physicians followed by shortage of personnel (Kichko, et al., 2016). Therefore, this provide some insights for policy makers about the importance of channeling resources and conducting training programs covering PGx testing implementation, which will help provide a more personalized care regarding medication decisions and reduce the incidence of ADRs in Eastern Province hospitals.

4.1 Recommendations And Future Directions

This study paves the road for PGx testing implementation by assessing the knowledge and awareness of healthcare providers in the Eastern Province. Although most of the participants responded fairly; many of them lacked the actual knowledge for it, showing the need for introducing the subject into the medical education and practice, besides providing educational programs for healthcare providers. Despite some universities in Punjab still behind the developed countries and structured educational system is required. Also, structured development programs, workshops and lectures are required for healthcare professionals to provide a personalized medicine.

More than half of the participants thought that PGx testing implementation is possible within ten years in the Punjab hospitals. With the current settings, effective and feasible implementation is possible only when enough education about PGx implementation is provided alongside with the addition of resources needed for the laboratory equipment in hospitals. Therefore, as more PGx tests become available, the issue of how to implement PGx center in the Eastern hospitals must be considered. Despite the obstacle of increased cost of PGx clinical implementation, the participants agreed that using PGx will result in decreasing the cost of treatment and the cost of developing new drugs. Therefore, the policy makers need to channel resources to ensure the availability of PGx testing for optimizing the efficacy of drugs and to preventing the ADRs in hospitals. Further, future research required to conduct a cost analysis of the clinical implementation of PGx testing compared with the current usual care. This will help to provide an insight of the actual estimation of the cost saving as a result of implementing the PGx testing in the clinical setting.

4.2 Limitation

The study is a cross-sectional in one Province in Pakistan. Longitudinal study in several states in Pakistan is required to be conducted to get more insight of PGx implementation. Further, the study faced some obstacles that interfered with data collection, time being one of the notable limitations that the authors had to deal with. Also, in the future including other professionals such as the academic faculty, genetic experts will give more insight and information.

This study was limited to three variables affecting the PGx implementation. There is a need for conducting studies to indicate the best way of implementing PGx testing into the current setting, which drugs to include, the population of interest and whether the insurance can cover the cost of tests required. This might help to establish a framework of PGx implementation and the best practices in the clinical settings.

V. CONCLUSIONS

The results of the study indicated an interest in the subject of PGx amongst healthcare providers in the Punjab Province of Pakistan. The respondents in the survey showed a general willingness to contribute in implementing of PGx, and indeed, anticipated the introduction of PGx testing within 10 years. However, there is clearly a need to improve both awareness and knowledge of PGx by the addition of suitable courses into the educational curriculum, preferably through CME. The advanced statistical results revealed a significant positive effect of awareness on the perceived PGx practices pharmacists and physicians with high perceived knowledge and awareness with an advice to implement the PGx testing in their clinical practice. On the basis of results, it is recommended that similar studies should be

commenced throughout Pakistan as it is a new concept and a broader validation of this initial result will be useful.

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