Social and Scientific Implications of Pharmacogenetic Testing

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Abstract

Advances in pharmacogenetics (PGx) provide potential for expansion of the role of pharmacists and physicians to achieve precision medicine. The objectives of the research were to: i) assess the perception of pharmacists and physicians regarding PGx testing, ii) develop, disseminate and evaluate PGx information among pharmacists and physicians, and iii) compare PGx information in official product labelling between the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for oncology drugs.

The methodology involved: i) Development, psychometric evaluation and dissemination of a self-administered questionnaire to assess awareness, attitudes, education and PGx testing in practice. The questionnaire was disseminated to pharmacists in all areas of practice and physicians practicing in oncology, cardiology, neurology, psychiatry, general and family medicine after ethics approval. Dissemination was undertaken: a) online via social media groups (pharmacists n=835, physicians n=984) and the mailing list of the Malta College of Family Doctors (n=198), b) personally by the researcher in community pharmacies, private clinics and at Mater Dei Hospital (n=135), and c) during two local medical conferences (n=60).

ii) Development and validation of a tutorial *Pharmacogenetics: A tool for precision medicine* and evaluation form. The tutorial and evaluation form were disseminated online to pharmacists (n=835) and physicians (n=984) via social media groups and delivered as a live presentation during a workshop organised by the Malta Medicines Authority.

iii) Identification of oncology drugs with PGx implications from the Government Formulary List with a 'Testing required' label annotation in Pharmacogenomics Knowledgebase and comparison of PGx information in the FDA drug label and EMA

Summary of Product Characteristics (SmPC) of the identified drugs. Descriptive statistics for the questionnaire and evaluation form were performed and mean rating scores (1-lowest to 5-highest) were calculated for Likert-type questions.

Results included: i) 292 complete responses - 179 pharmacists (64% female, 36% male) and 113 physicians (50% female, 50% male). Pharmacists (91%) and physicians (76%) were aware of the term 'PGx testing'. Physicians (3.62) agreed more than pharmacists (3.31) that PGx testing is applicable in their practice (p=0.006). Pharmacists (1.93) and physicians (1.65) perceived themselves to be insufficiently competent in PGx testing (p=0.005).

ii) The tutorial evaluation form was completed by 66 participants (57 online, 9 live presentation) - 33 pharmacists (25 female, 8 male) and 33 physicians (15 female, 18 male). Pharmacists agreed more than physicians that the material presented may help to improve the application of theory to practice (4.30/3.97, p=0.027) and enhance their skills in PGx (4.33/3.94, p=0.007). Pharmacists (4.45) are more likely to follow future tutorials on PGx than physicians (3.70) (p<0.001).

iii) Differences in the presence of PGx information between the FDA drug label and EMA SmPC were identified for anastrozole, erlotinib, lenalidomide, rasburicase, tamoxifen, trametinib, and tretinoin.

Pharmacists and physicians who participated in this study were aware of PGx, agreed that PGx is applicable in their practice and identified the need for further training. Participants recognised that PGx information presented in the tutorial has the potential to improve the clinical application of PGx. Differences in PGx information in official product labelling for oncology drugs point to the need for enhanced regulatory harmonisation.

Keywords: official product labelling; perception; pharmacists; pharmacogenetics; physicians; training

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Glossary

Actionable Pharmacogenetics

The official product label may contain information about changes in efficacy, dosage or toxicity due to the presence of gene, protein or chromosomal variants and may indicate a contraindication of the drug in a subset of patients.[1]

Allele

Alternative form of a gene at a given locus on a chromosome inherited from each parent (Chang et al, 2015)

Centralised Procedure

Procedure whereby a single marketing authorisation application is submitted to allow a marketing authorisation holder to make a medicine available to patients and healthcare professionals throughout all European Union Member States and European Economic Area countries.[2]

Clinical Pharmacogenetic Implementation Consortium (CPIC)

An international consortium that develops and curates peer-reviewed, evidence-based, detailed gene-drug clinical practice guidelines in order to facilitate the use of pharmacogenetic tests by healthcare professionals.[3]

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[1]Pharmacogenomics Knowledgebase (PharmGKB). Drug label information and legend [Internet]. USA: Stanford University, Department of Health and Human Services; 2019 [cited 2019 Jun 17]. Available from: URL: https://www.pharmgkb.org/page/drugLabelLegend

[2]European Medicines Agency (EMA). The European regulatory system for medicines-A consistent approach to medicines regulation across the European Union. EMA/716925/2016 [Internet]. UK: EMA; 2017 [cited 2019 Jun 10]. Available from: URL: https://www.ema.europa.eu/en/documents/leaflet/european-regulatory-system-medicines-european-medicines-agency-consistent-approach-medicines_en.pdf

[3]Clinical Pharmacogenetics Implementation Consortium (CPIC). What is CPIC? [Internet]. U.S. Department of Health and Human Services, 2019 [cited 2019 Jun 17]. Available from: URL: https://cpicpgx.org/

Genetic Counsellor

Professional who provides genetic information to patients and facilitates any psychosocial changes according to genetic test results (Skirton et al, 2015).

Genetics Specialist Physician

Physician with advanced training in clinical genetics and genomics, which includes clinical diagnosis, knowledge about laboratory techniques, genetic data interpretation, application of genetic test results and genetic counselling.[4]

Genotype

A specific set of alleles inherited at a locus on a given gene (Chang et al, 2015)

Informative Pharmacogenetics

The official product label mentions gene or protein involvement in metabolism or pharmacodynamics of the drug, but no information is available to suggest that the variation in the genes/proteins leads to different response.[1]

Maltese Government Formulary List

List of medicinal products, vitamins, food supplements and borderline substances enlisted without proprietary name and according to the International Non-proprietary Name available in Malta. Each product within the formulary is classified according to its indication.[5]

[1]Pharmacogenomics Knowledgebase (PharmGKB). Drug label information and legend [Internet]. USA: Stanford University, Department of Health and Human Services; 2019 [cited 2019 Jun 17]. Available from: URL: https://www.pharmgkb.org/page/drugLabelLegend

[4]European Board of Medical Genetics (EBMG). Medical genetics and genomics [Internet]. Austria: EBMG; 2019 [cited 2019 Jun 14]. Available from: URL: https://www.ebmg.eu/406.0.html

[5]Directorate of Pharmaceutical Affairs (DPA). The Government Formulary List [Internet]. Malta: Ministry of Health: DPA; 2018 [cited 2019 Jun 12]. Available from: URL: https://deputyprimeminister.gov.mt/en/pharmaceutical/Pages/formulary/formulary.aspx

National Procedure

Medicines available in the European Union with a marketing authorisation which have not gained authorisation via the centralised procedure. Reasons for this could be that the marketing-authorisation was granted prior to European Medicines Agency creation or there is no scope to gain a marketing authorisation.[2]

Pharmacogenetics

The study of interindividual variability of genes and the effect on drug metabolism and drug response (Chang et al, 2015).

Pharmacogenetic Biomarker

A measurable DNA and/or RNA characteristic that is an indicator of normal biologic processes, pathogenic processes and/or response to therapeutic or other interventions (Burt and Dhillon, 2013).

Pharmacogenomics Knowledgebase (PharmGKB)

A web-based pharmacogenomics knowledge encompassing information about dosing guidelines, drug labels, potentially clinically-actionable gene-drug associations and genotype-phenotype relationships (Whirl-Carrillo et al, 2012).

Pharmacogenetic Testing

A type of genetic test ordered to predict the likelihood of a patient to experience an adverse drug reaction or to respond to a certain drug according to genetic predisposition (Mills et al, 2013b).

[2]European Medicines Agency (EMA). The European regulatory system for medicines-A consistent approach to medicines regulation across the European Union. EMA/716925/2016 [Internet]. UK: EMA; 2017 [cited 2019 Jun 10]. Available from: URL: https://www.ema.europa.eu/en/documents/leaflet/european-regulatory-system-medicines-european-medicines-agency-consistent-approach-medicines_en.pdf

Phenotype

How the genotype presents clinically in an individual (Chang et al, 2015).

Polymorphism

Presence of two or more variants of a particular DNA sequence, present at a frequency of greater than 1% of the population (Cavallari and Lam, 2017)**.**

Precision Medicine

Medication therapeutic management designed to reach optimal therapeutic efficacy and safety for a patient by considering genetic, environmental and lifestyle factors to make decisions about a patient's therapeutic regimen (Klein et al, 2017).

Testing recommended

The official product label states or implies that gene, protein or chromosomal testing, including genetic testing, functional protein assays, or cytogenetic studies, is/are recommended or should be considered before using this drug and this recommendation may only be for a particular subset of patients.[1]

Testing required

The official product label states or implies that gene, protein or chromosomal testing, including genetic testing, functional protein assays, or cytogenetic studies, should be conducted before using this drug and this requirement may only be applicable for a subset of patients.[1]

[1]Pharmacogenomics Knowledgebase (PharmGKB). Drug label information and legend [Internet]. USA: Stanford University, Department of Health and Human Services; 2019 [cited 2019 Jun 17]. Available from: URL: https://www.pharmgkb.org/page/drugLabelLegend

List of Abbreviations

ADR	Adverse drug reaction
CDSS	Clinical decision support system
CPE	Continuing professional education
CPIC	Clinical Pharmacogenetics Implementation Consortium
DNA	Deoxyribonucleic acid
EMA	European Medicines Agency
EU	European Union
FDA	US Food and Drug Administration
GFL	Government Formulary List
HCPs	Healthcare professionals
PGx	Pharmacogenetic/s
PharmGKB	Pharmacogenomics Knowledgebase
SmPC	Summary of Product Characteristics
UK	United Kingdom
USA	United States of America

Chapter 1

Introduction

1.1 Pharmacogenetic testing and its applications

'Pharmacogenetics', a term coined by Vogel in 1959, refers to the study of interindividual variability of genes and the effect on drug metabolism and drug response (Kalow, 2006; Saini et al, 2010; Ehret, 2012; Campion and Dowell, 2019). Pharmacogenetic (PGx) testing can be applied as a tool to achieve precision medicine through optimisation of drug selection and dosing according to an individual's genetic make-up (Empey, 2016; Johnson and Weitzel, 2016; Kapoor et al, 2016; Tuteja and Limdi, 2016; Klein et al, 2017, Faruque et al, 2019). PGx tests are designed to identify PGx biomarkers to help in informing genotype-guided treatment decisions (Sadee, 2011; Wang et al, 2014; Rodríguez-Antona and Taron, 2015, Lauschke et al, 2018).

PGx biomarkers are validated based on the analytical performance of the test used to identify the biomarker, the clinical implications of the test with regards to drug response and safety, the clinical utility by having evidence on how the test result impacts on therapeutic management decisions and health outcomes, as well as ethical, legal and social implications of testing for the biomarker (Amur et al, 2015; Tonk et al, 2017; Vivot et al, 2017).

Personalisation of therapy with PGx testing has the potential to enhance treatment efficacy, improve patient safety by minimising the risk of adverse drug reactions, and decrease healthcare costs (Moaddeb and Haga, 2013; Fagerness et al, 2014; Horgan et al, 2014; Hess et al, 2015; Dong and Wiltshire, 2017; Manson et al, 2017; Klein et al, 2017; Verbelen et al, 2017; Kennedy, 2018; Faruque et al, 2019). PGx-guided therapy may be applied for a range of drugs indicated in various therapeutic areas including cardiology, oncology, neurology, psychiatry and infectious disease (Swen et al, 2011;

Martin et al, 2012; Scott et al, 2013; Caudle et al, 2014; Crews et al, 2014; Ramsey et al, 2014; Gammal et al, 2015; Hess et al, 2015; Hicks et al, 2015; Johnson et al, 2016; Patel, 2016; Hicks et al, 2017; Goetz et al, 2018).

Clopidogrel (*CYP2C19)* and warfarin (*CYP2C9, VKORC1)* are examples of cardiovascular drugs with PGx implications where evidence is available regarding the impact of PGx testing on improving the efficacy or safety of treatment with these drugs (Yang et al, 2015; Jorgensen et al, 2019). With regards to oncology drugs, clinical implementation of PGx testing has demonstrated improved treatment efficacy or safety and is advancing at an accelerated pace (Ong et al, 2012; Gillis et al, 2014; Patel, 2016; Faruque et al, 2019; Tarantino et al, 2019). PGx testing is being used routinely in oncology for drugs including dabrafenib *(BRAF),* erlotinib and gefitinib *(EGFR),* trastuzumab *(HER2/neu*), cetuximab and panitumumab *(KRAS)* (Ong et al, 2012; Patel, 2016, Hertz et al, 2018).

In neurology, PGx testing has been shown to improve safety of therapy for carbamazepine *(HLA-A)* (Yip and Pirmohamed, 2017). Amitriptyline (*CYP2C19, CYP2D6)* and fluvoxamine (*CYP2C19, CYP2D6)* are examples of drugs used in psychiatry which have PGx implications, and evidence is available regarding PGx testing and its impact on enhancing treatment outcomes (Müller et al, 2013; Ryu et al, 2017). Evidence regarding increased safety is available for abacavir *(HLA-B)* which is an example of an antiretroviral with PGx implications where PGx testing can identify a patient's risk of severe hypersensitivity reactions (Small et al, 2017).

Despite the varied clinical applications of PGx testing and reports of its clinical utility (Fagerness et al, 2014; Nussbaum et al, 2015; Yang et al, 2015; Asadov et al, 2017; Daly, 2017), the implementation of PGx testing in practice is occurring at a slow pace

(Scott, 2011; Moaddeb and Haga, 2013; Bank et al, 2014; Horgan et al, 2014; Caudle et al, 2016; Van der Wouden et al, 2016; Chan et al, 2017; Dong and Wilthshire, 2017; Just et al, 2017; Klein et al, 2017; Kennedy, 2018).

Various challenges have been reported to be associated with the limited clinical implementation of PGx testing. These challenges include; unfamiliarity and lack of proactivity by healthcare professionals (HCPs) (Gurwitz et al, 2009; Haga et al, 2012 a,c; Jamie, 2013, Horgan et al, 2014), insufficient confidence by HCPs (Mc Cullough, 2010; Haga et al, 2012a; Jamie, 2013), lack of funding (Gurwitz et al, 2009; Scott, 2011; Moaddeb and Haga, 2013; Horgan et al, 2014; Ciarleglio et al, 2017; Klein et al, 2017), inadequate harmonisation in official product labelling between regulatory bodies (Gurwitz et al, 2009; Scott, 2011; Moaddeb and Haga, 2013; Horgan et al, 2014; Klein et al, 2017), lack of patient awareness (Lam, 2013; Horgan et al, 2014), long turnaround time to obtain PGx test results (Johnson et al, 2012; Lam, 2013; Horgan et al, 2014; Kapoor et al, 2016; Klein et al, 2017), lack of prospective randomised controlled trials proving benefits of genotype-guided prescribing (Johnson et al, 2012; Lam, 2013; Patel, 2016; Klein et al, 2017) and limited availability of PGx cost-effectiveness studies (Gurwitz et al, 2009; Lam, 2013; Patel, 2016; Ciarleglio et al, 2017; Klein et al, 2017).

Ways to overcome such barriers to enhance clinical uptake of PGx include the provision of further training to HCPs, addition of more PGx modules in medicine and pharmacy curricula (Schnoll and Shields, 2011; Lam, 2013; Horgan et al, 2014; Taber and Dickinson, 2014; Ciarleglio et al, 2017 Klein et al, 2017), incorporation of PGx information in electronic medical records for application in automated clinical decision support systems (CDSS) (Schnoll and Shields, 2011; Lam, 2013; Horgan et al, 2014; Patel, 2016; Elliott et al, 2017; Klein et al, 2017; Lauschke et al, 2018; Liu et al, 2018),

development of further genotype-guided recommendations specifying clearly the therapeutic actions to be taken according to PGx test results (Horgan et al, 2014; Quinoñes et al, 2014; Klein et al, 2017), and devising frameworks indicating the responsibilities of HCPs to enhance PGx workflow (Horgan et al, 2014; Klein et al, 2017).

Barriers from a regulatory perspective should be overcome by the promotion of discussions between regulatory bodies with the aim to harmonise procedures regarding the inclusion of PGx information in official product labelling (Horgan et al, 2014; Klein et al, 2017). Pre-emptive PGx testing and advanced genotyping technologies should be developed by stakeholders to provide rapid PGx testing in order to achieve timely PGx test results (Klein et al, 2017; Van der Wouden, et al, 2019), and policies should be developed regarding effective sharing of data between institutions carrying out research about PGx testing (Horgan et al, 2014; Quinoñes et al, 2014; Klein et al, 2017).

A barrier being faced by pharmacists with the expansion of PGx in clinical practice includes unclear defined roles that the profession partakes (Jamie, 2013; Aleijalat et al, 2016; Haga et al, 2015; Kennedy et al, 2018). Since PGx is a complex discipline, specialised training and experience are required for pharmacists to be able to apply advanced PGx skills in clinical practice. (ASHP, 2015; Haga et al, 2015; Remsberg et al, 2017; Roederer et al, 2017; Kennedy et al, 2018; Dávila-Fajardo et al, 2019). The clinical implementation of PGx allows pharmacists to serve as protagonists in comprehensive medication review services, which include PGx information (Nickola et al, 2012; ASHP, 2015; Elewa et al, 2015; Haga et al, 2015; Romagnoli et al, 2016; Van der Wouden, 2019).

The roles of pharmacists in PGx may involve leading multidisciplinary efforts to educate patients and other HCPs about the principles and benefits of PGx, recommend, order, interpret and report PGx test results and use PGx information to aid decision-making towards optimal drug selection and dosing (Jamie, 2013; ASHP, 2015; Haga et al, 2015; Kisor et al, 2015; Weitzel et al, 2016; Haidar et al, 2017; Van der Wouden, 2019).

1.2 Perception of pharmacists and physicians on pharmacogenetic testing

Numerous studies which assessed the perception of pharmacists and physicians regarding PGx testing, including analysis of knowledge, attitudes and practice aspects, have been published over the past fifteen years. Most studies were carried out in the United States of America (USA) and evaluated the perception of pharmacists and physicians separately. Limited reports from Europe, Africa, Asia and Australasia, and few direct comparative studies between pharmacists and physicians have been published (Appendix 1).

Positive attitudes by pharmacists towards PGx testing regarding perceived benefits have been reported, including its application to aid drug therapy selection and dosing and improved drug expenditure (Madadi et al, 2011; Tuteja et al, 2013; Elewa et al, 2015; Aleijalat et al, 2016; Abdela et al, 2017; Bank et al, 2017). Physicians similarly perceived that implementation of PGx testing has the potential to decrease adverse drug reactions and optimise drug selection and dosing and is clinically useful (Rogausch et al, 2006; Woelderink et al, 2006; Hoop et al, 2010; Dunbar et al, 2012; Peppercorn et al, 2013; Dressler et al, 2014; Laerum et al, 2014; Thompson et al, 2015; Nishimura et al, 2016; Abdela et al, 2017; Wu et al, 2017; Owusu Obeng et al, 2018).

Limited availability of prospective randomised controlled trials on the clinical utility of PGx testing has been reported to result in reluctance by pharmacists and physicians to integrate PGx in practice (Haga et al, 2012c; Peppercorn et al, 2013; St. Sauver et al, 2016; Chan et al, 2017; Albassam et al, 2018). Cost issues are reported to be another concern by pharmacists and physicians when ordering a PGx test (Rogausch et al, 2006; Woelderink et al, 2006; Dunbar et al, 2012; Powell et al, 2015; Shishko et al, 2015; Chan et al, 2017; Wu et al, 2017). Physicians were most likely to recommend a PGx test prior to prescribing a drug with PGx implications if the test is covered by healthcare insurance (Rogausch et al, 2006). Apprehension regarding the misuse of PGx information and encroachment of an individual's privacy have also been reported (Rogausch et al, 2006; Hunt et al, 2013; Tuteja et al, 2013; Petersen et al, 2014; Muzoriana et al, 2017), which need to be addressed due to the potential ethical implications (Madadi et al, 2011; Muzoriana et al, 2017).

Physicians believe that they should be able to identify medications that require PGx testing (Elewa et al, 2015; Abdela et al, 2017; Just et al, 2017). In studies carried out in France, New Zealand and the USA, it was demonstrated that physicians believed that PGx test results should be communicated to patients by physicians (Moutel et al, 2005; Dunbar et al, 2012; Haga et al, 2012a; Selkirk et al, 2013). Pharmacists accept that they have an important role in PGx through counselling patients and providing PGx information if they are provided with the appropriate training (McCullough et al, 2011; Tuteja et al, 2013; Alexander et al, 2014; Aleijalat et al, 2016; Romagnoli et al, 2016; Muzoriana et al, 2017).

Insufficient training has been reported to be hindering confidence of HCPs in delivering PGx services (Fargher et al, 2007; Koomer et al, 2011; McCullough et al, 2011; Payne

et al, 2011; Benzeroual et al, 2012; Jamie, 2013; Selkirk et al, 2013; Alexander et al, 2014; Bannur et al, 2014; Taber and Dickinson, 2014; Kisor et al, 2015, Obara et al, 2015, Overby et al, 2015). Further training in PGx testing for pharmacists and physicians is important to improve interpretation and application of PGx test results in practice and to enhance communication of test results with patients (Moutel et al, 2005; Woelderink et al, 2006; McCullough et al, 2011; Payne et al, 2011; Haga et al, 2012a; De Denus et al, 2013; Selkirk et al, 2013; Tuteja et al, 2013; Elewa et al, 2015; Shishko et al, 2015, Abdela et al, 2017; Chan et al, 2017; Heale et al, 2017; Just et al, 2017; Vinothini et al, 2017; Arathy et al, 2019). Willingness for further training on PGx was reported by HCPs (Elewa et al, 2015, Aleijalat et al, 2016).

The benefits of PGx education for HCPs have been discussed in various publications (McCullough et al, 2011; McMahon et al, 2011; Roederer et al, 2012; Jamie, 2013; Peppercorn et al, 2013; Tuteja et al, 2013; Bannur et al, 2014; Dressler et al, 2014; Taber and Dickinson, 2014; AlEijalat et al, 2016; Luzum and Luzum, 2016; Abdela et al, 2017; Just et al, 2017; Heale et al, 2017, Vinothini et al, 2017, Kisor et al, 2019), especially if implemented as part of continuing professional education (CPE) activities (McMahon et al, 2011; Benzeroual et al, 2012; Bannur et al, 2014; Kisor et al, 2015; Kudzi et al, 2015).

1.3 Education and training on pharmacogenetic testing

Promoting the dissemination of up-to-date information on PGx testing among practicing HCPs in the precision medicine era encourages further clinical implementation (Gurwitz et al, 2005; Green et al, 2010; Lesko and Johnson, 2012; Formea et al, 2013; Kuo et al, 2013; Pisanu et al, 2014; Kisor et al, 2015; Haga et al, 2016; Weitzel et al, 2016; Haidar et al, 2017; Roederer et al, 2017; Formea et al, 2018). Training for HCPs may be undertaken by following postgraduate courses or CPE seminars via self-study or by attending live sessions (Green et al, 2010; Lesko and Johnson, 2012; Kuo et al, 2013; Haga et al, 2016; Weitzel et al, 2016; Haidar et al, 2017; Kennedy et al, 2018).

The incorporation of PGx content in education programmes for HCPs is increasing (Green et al, 2010; Di Francia et al, 2012; Nickola et al, 2012; Kisor et al, 2015; Eden et al, 2016; Weitzel et al, 2016; Frick et al, 2018). Comprehensive PGx training was included as a requirement in the professional Doctorate in Pharmacy curriculum by the Accreditation Council for Pharmacy Education in the USA in 2016, with the aim to increase PGx competence among pharmacy students (Weitzel et al, 2016; Remsberg et al, 2017; Formea et al, 2018; Kennedy et al, 2018).

Inconsistencies between pharmacy curricula in Europe and USA regarding PGx content are reported (Pisanu et al, 2014; Kisor et al, 2015; Weitzel et al, 2016; Remsberg et al, 2017; Kennedy et al, 2018). Challenges regarding the design of PGx modules include whether PGx should be taught as a stand-alone topic, integrated in other courses or as a combination of both, lack of faculty members with PGx expertise and clinical experience and inadequate time to cover comprehensive PGx discussions (Lesko and Johnson, 2012; Nickola et al, 2012; Weitzel et al, 2016; Kennedy et al, 2018).

Recommended methods for teaching PGx include didactic training, patient-centred experiential training, using web-based peer-reviewed PGx resources and via journal clubs (Nickola et al, 2012; Lesko and Johnson, 2012; Lee et al, 2015; Rao et al, 2015; Eden et al, 2016; Frick et al, 2016; Weitzel et al, 2016; Haidar et al, 2017).

1.4. Regulatory perspective of pharmacogenetic testing

At present, 310 drugs with PGx implications are listed in Pharmacogenomics Knowledgebase (PharmGKB).[6] Inclusion of PGx information in official product labelling by regulatory bodies is increasing however is reported to be insufficient and lack of harmonisation between regulatory bodies exists (Otsubo et al, 2012; Ehmann et al, 2015; Reis-Pardal et al, 2017; Dávila-Fajardo et al, 2019). The challenge of translating clinically-relevant PGx data into official product information is still being encountered by regulators (Amur et al, 2015; Reis-Pardal et al, 2017; Dávila-Fajardo et al, 2019).

The US Food and Drug Administration (FDA)-approved drug labels and the European Medicines Agency (EMA) Summary of Product Characteristics (SmPC) contain information for HCPs on the safe and effective use of an authorised medicinal product (Reis-Pardal et al, 2017). Recommendations on how PGx information should be collected and documented in official product labelling are available for both regulatory bodies (Ehmann et al, 2015; Fang et al, 2016; Reis-Pardal et al, 2017; Drozda et al, 2018).

[6]Pharmacogenomics Knowledgebase (PharmGKB). Drug label annotation [Internet]. USA: Stanford University, Department of Health and Human Services; 2019 [cited 2019 Jun 12]. Available from: URL: https://www.pharmgkb.org/labels

According to the 'Guideline on Good Pharmacogenomic Practice', EMA SmPCs should include PGx data of the medicinal product during both pre-authorisation and post-marketing phases, hence the reason for continuous updating of the SmPC to reflect additional information and facilitate the use of the medicinal product by prescribers and patients.[7] Updating drug labelling to include PGx information following approval on the market has proven to be an evident challenge since the process of revising PGx labelling relies on the quantity, quality and type of public data available. A proactive approach by the FDA has been implemented, where early collection of PGx data influencing drug efficacy and safety is encouraged during the drug development process (Drozda et al, 2018).

According to the 'Guidance for industry-clinical pharmacogenomics: Premarket evaluation in early-phase clinical studies and recommendations for labelling', the FDA drug label should include PGx information to inform prescribers about the clinical usefulness of testing for the relevant PGx biomarker. If a PGx test is available, the label should indicate whether testing is required, recommended or to be considered. PGx information in drug labels may be included under the sections; indications and usage, dosage and administration, contraindications, warnings and precautions, drug interactions, and as boxed warnings according to the level of evidence of the impact of the genetic variation on drug safety and efficacy. Detailed PGx data is usually available in the clinical pharmacology or clinical studies sections.[8]

[7]European Medicines Agency (EMA). Guideline on good pharmacogenomic practice [Internet]. UK: EMA; 2018 [cited 2019 Jun 12]. Available from: URL: https://www.ema.europa.eu/documents/scientific-guideline/guideline-good-pharmacogenomic-practice-first-version_en.pdf

[8]US Department of Health and Human Sciences. Guidance for Industry-Clinical Pharmacogenomics: Premarket evaluation in early-phase clinical studies and recommendations for labelling [Internet]. US: U.S. Food and Drug Administration; 2018 [cited 2019 Jun 12]. Available from: URL: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM337169.pdf

1.5 Rationale of the study

Few studies describing and comparing the perception of both pharmacists and physicians on PGx testing have been published (Appendix 1). A local study by Abdilla (2016), which focused mainly on ethics and social policy issues of PGx testing, assessed the perception of pharmacists and physicians regarding PGx testing as a pilot study. Response from 51 pharmacists and 28 physicians was obtained and a recommendation from this study was that further research on this topic locally is required, incorporating a larger sample size. Moreover, the need for a more comprehensive exploration of the perception of pharmacists and physicians towards PGx testing was identified, particularly regarding awareness, competence and confidence, preferred methods for further training by HCPs, cost and service provision, pre- and post-marketing concerns, patient counselling, regulatory aspects, and roles of HCPs in PGx service provision.

It has been reported, both internationally and locally, that insufficient awareness and training of pharmacists and physicians is a barrier for clinical implementation of PGx (Gurwitz et al, 2009; Haga et al, 2012a,c; Jamie, 2013, Horgan et al, 2014, Abdilla et al, 2016). Limited research about initiatives attempting to increase awareness of pharmacists (Formea et al, 2013; Formea et al, 2018) and physicians (Lee et al, 2019) about PGx testing have been published to date.

Precision medicine is reported to be at an advanced stage for oncology drugs, with drugs accounting for over 80% of PGx tests (Wu et al, 2017). Comparison of PGx information in official product labelling for oncology drugs enables the exploration of harmonisation between regulatory bodies (Otsubo et al, 2012; Ehmann et al, 2015; Reis-Pardal et al, 2017).

1.6 Aim and Objectives

The aim of this study was to analyse the social and scientific implications of PGx testing.

The primary objectives were to:

- Evaluate the perception of pharmacists and physicians on PGx testing
- Develop, disseminate and evaluate PGx information to promote awareness among pharmacists and physicians.

The secondary objectives were to:

- Compare PGx information in official product labelling between the US FDA and the EMA for oncology drugs and to analyse the present status of PGx testing in local clinical practice for drugs used in oncology.
- Collate information about the inclusion of PGx in pharmacy educational programs in Europe and the USA.

Chapter 2

Method

2.1 Methodology overview

The research study was divided into three parts:

i) Quantitative assessment of the perception of pharmacists and physicians on PGx testing using a questionnaire (Figure 2.1).

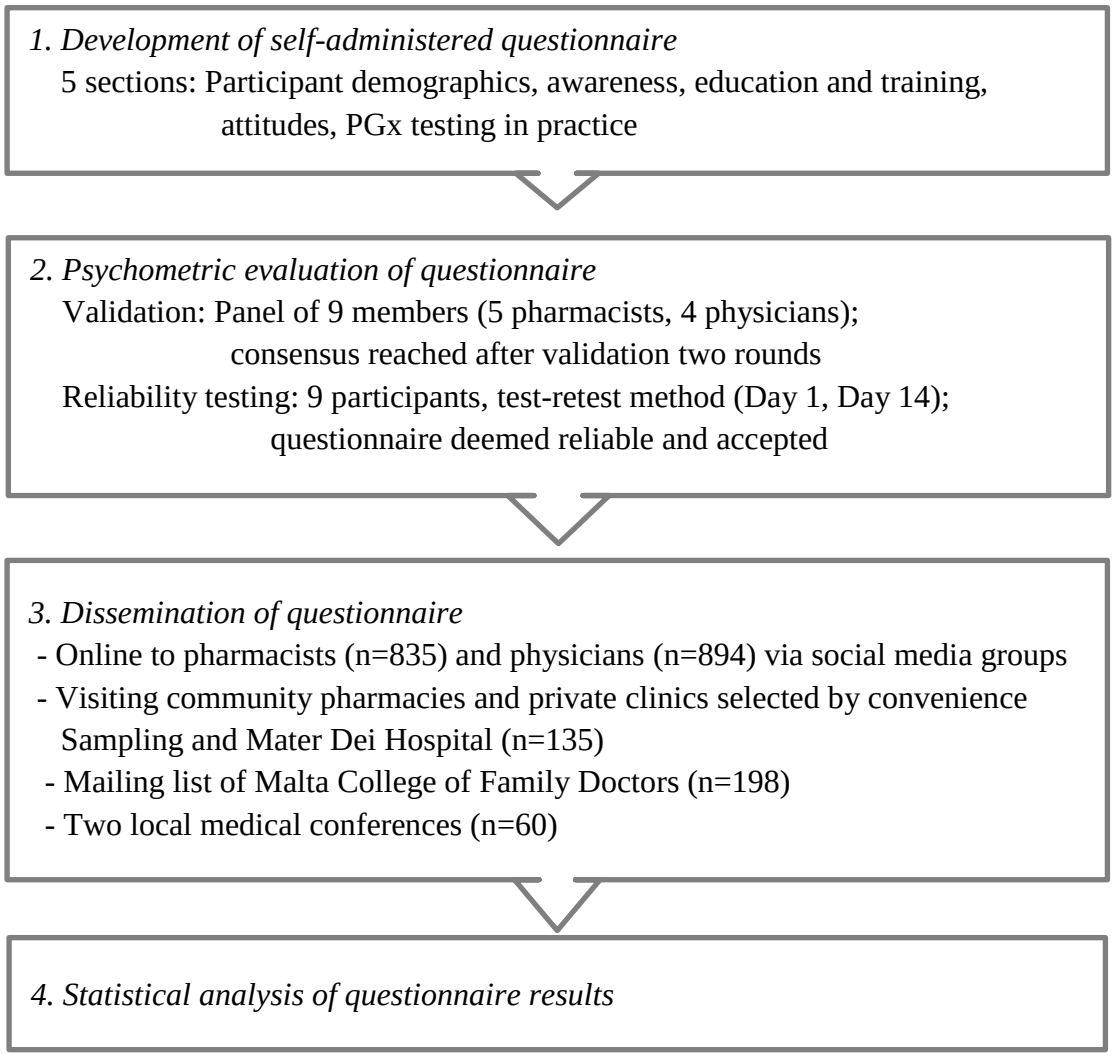


Figure 2.1 Methodology flowchart 1: Assessment of the perception of pharmacists and physicians on PGx testing

ii) Development, dissemination and evaluation of PGx information among pharmacists and physicians (Figure 2.2).

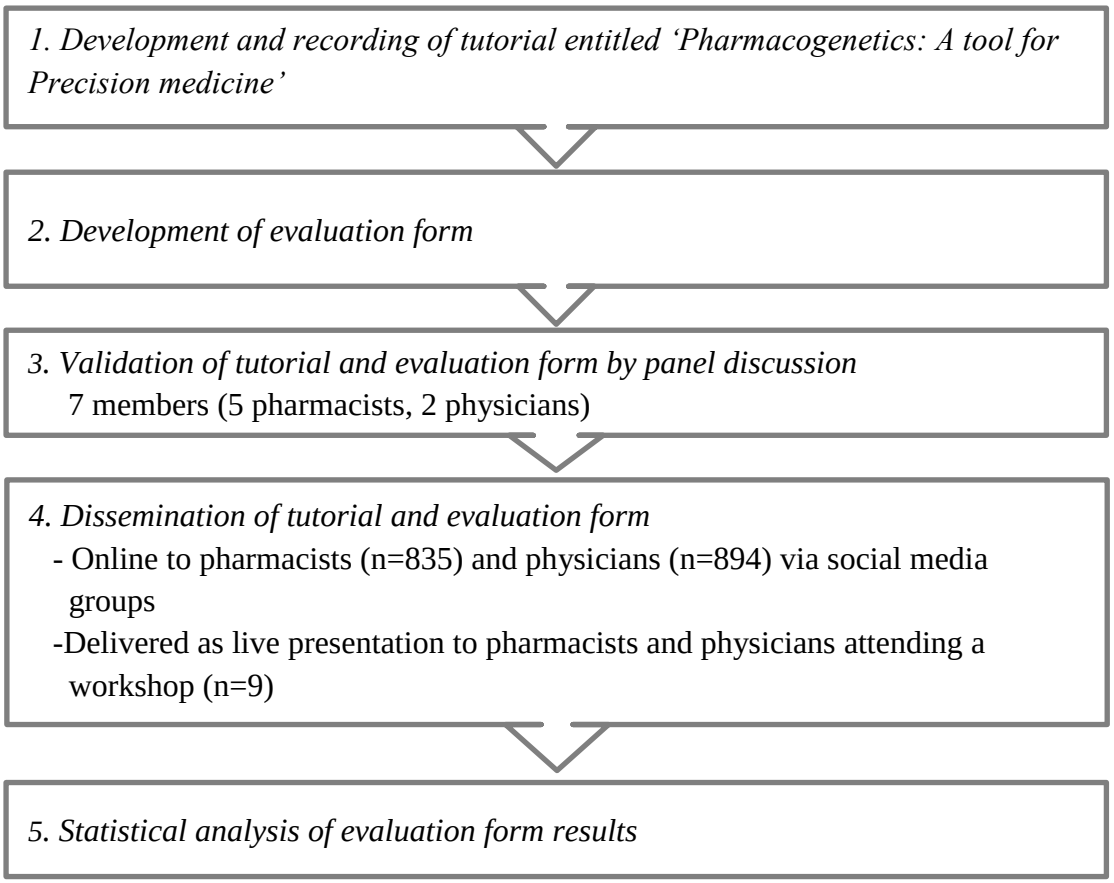


Figure 2.2 Methodology flowchart 2: Development, dissemination and evaluation of PGx information among pharmacists and physicians

iii) Comparison of PGx information in official product labelling of oncology drugs between the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) and exploring the clinical implementation of PGx testing for oncology drugs locally (Figure 2.3).

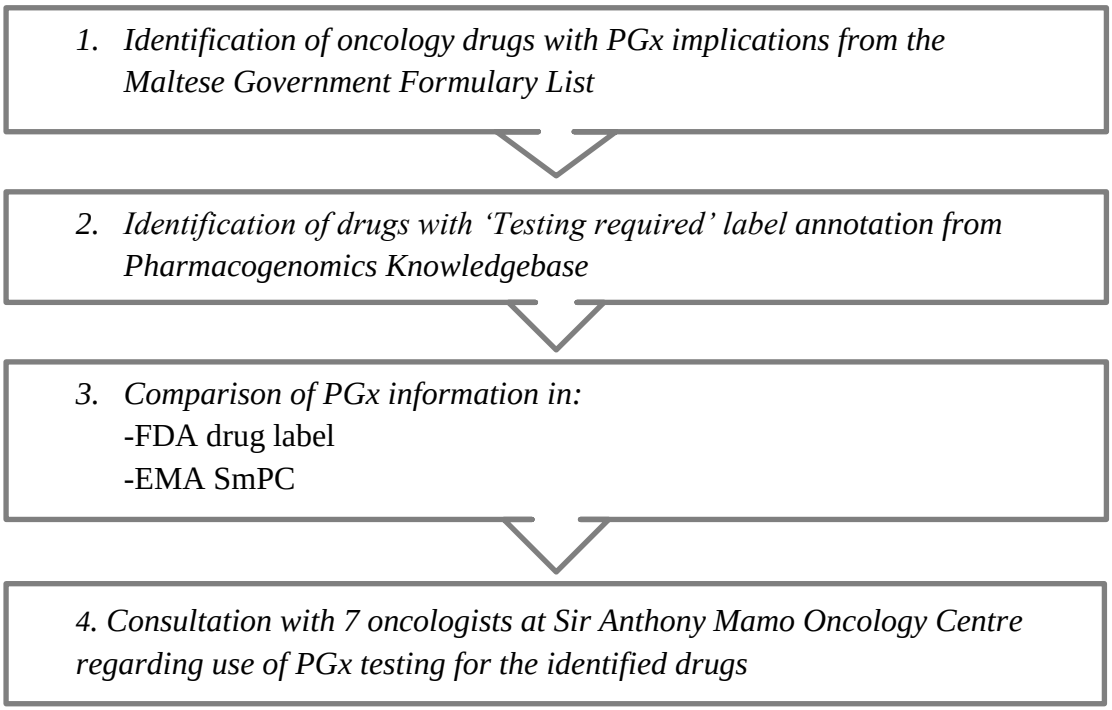


Figure 2.3 Methodology flowchart 3: Comparison of PGx information in official product labelling for oncology drugs and clinical implementation locally

2.2 Evaluating the perception of pharmacists and physicians on pharmacogenetic testing

The awareness, attitudes and practice aspects of pharmacists and physicians towards PGx testing were evaluated using a self-administered perception questionnaire.

2.2.1 Development of perception questionnaire

An anonymous self-administered questionnaire was developed following extensive literature review, highlighting topics such as ancillary findings (Henrikson et al, 2008; Haga et al, 2012c), attitudes (Laerum et al, 2014), barriers (Schnoll and Shields, 2011; Abdilla, 2016), education and knowledge of PGx testing (Higgs et al 2008; McCullough et al, 2011; Haga et al, 2012a; Formea et al, 2013; Jamie, 2013; Just et al, 2017), ethical issues (Rogausch et al, 2006), PGx testing importance for different drug classes (Heuchel et al, 2017), PGx test communication with patients (Mills et al, 2013a), and use of PGx testing in practice (Payne et al, 2011; Peterson et al, 2016). The online version of the questionnaire was created using SurveyMonkey®.[9]

2.2.2 Validation of perception questionnaire

A 9 member panel including 5 pharmacists (1 community pharmacist, 1 pharmacist in academia, 1 hospital pharmacist, 1 pharmacist practicing in industry, 1 pharmacist practicing in regulatory affairs) and 4 physicians (1 Consultant Cardiologist, 1 Resident Specialist in General Medicine -Endocrinology, 1 Basic Specialist Trainee in General Medicine -Neurology, 1 Specialist in Family Medicine) were recruited by convenience sampling for face and content validation of the questionnaire which was composed of

[9]SurveyMonkey Inc. [Internet]. USA; 2019 [cited 2019 Jun 12] Available from: URL: www.surveymonkey.com

two rounds. In round 1 of the validation exercise the panel was asked to rate each question for relevance, importance and comprehensibility and the layout of the questionnaire on a Likert-Scale of 1 to 5 (5 being the highest) using a validation tool. For questions rated 3 or less, the panel were asked to indicate reason/s and recommendation/s in the comments section. A mean rating score out of 5 was calculated for each question. The questions which; i) received recommendations for modification, or ii) obtained a mean rating score less than 4 were revised, optimised and submitted for a second validation by the same panel. New questions which were suggested by the validation panel were added and validated for relevance, importance and comprehensibility. Questions which were modified as suggested by the validation panel in round 1 were revalidated for comprehensibility. Consensus was reached after round 2 of validation since all questions obtained a mean rating score of 4 or higher, and the perception questionnaire was rendered valid (Validation tool and results in Appendix 2).

The perception questionnaire after validation consisted of 5 sections; with a total of 80 questions, including 71 ordinal scale questions, 8 nominal scale questions and 1 open-ended question (Table 2.1).

Table 2.1 Description of perception questionnaire after validation

Section	Questions	Description (Type of Question)
1: Demographics	1-5	Gender, age, profession, years of practice, academic level (all nominal)
2: Awareness	6a, b	Awareness of term PGx testing (all nominal)
	7-13	Awareness of: advantages and limitations, availability of PGx information resources, interpretation of test results, local performance of PGx testing (all ordinal)
3: Education and training	14-17	Competence, training, undergraduate curricula, postgraduate specialisation (all ordinal)
	18a-c	Mode of acquiring information on PGx, preference of learning methods, PGx topics (all nominal)
4: Attitudes	19-39	Benefits of PGx, applicability, healthcare service utility and costs, drug therapy expenditure, cost-effectiveness studies, complexity of healthcare service, PGx test results, efficacy and safety of marketed and future medications, PGx research studies, importance of PGx testing in specified drug classes (all ordinal)
5: PGx testing in Practice	40a, b, 41	Ordering of PGx test (nominal), open-ended question for which drugs PGx was done in the past, frequency of perceived need to order a PGx test (nominal)
	42-80	Availability, access, recommending, ordering, interpreting and discussing a PGx test, action taken according to test result, location and performance of PGx testing, test result storage, patient counselling, HCP responsibilities, challenges (all ordinal)

2.2.3 Reliability testing of perception questionnaire

A group of 9 professionals including 5 pharmacists (1 community pharmacist, 1 pharmacist in academia, 1 hospital pharmacist, 1 pharmacist practicing in industry, 1 pharmacist practicing in regulatory affairs) and 4 physicians (1 Consultant Oncologist, 1 Higher Specialist Trainee in Cardiology, 1 Basic Specialist Trainee in Psychiatry, 1 Specialist in Family Medicine) recruited by convenience sampling were invited to participate in the reliability testing of the perception questionnaire. The test-retest method was adopted by inviting the 9 professionals to fill in the perception questionnaire on recruitment (Day 1) and on Day 14.

The questionnaire responses were analysed using IBM® SPSS statistics version 25 software. The kappa test was used to calculate test-retest reliability for variables having a nominal scale and the Kendall-tau test was used for variables having an ordinal scale. For both tests the null hypothesis specified that there is poor test-retest reliability of the perception questionnaire and is accepted if the p-value exceeds the 0.05 level of significance. The alternative hypothesis specified that there is satisfactory test-retest reliability of the perception questionnaire and is accepted if the p-value is less than the 0.05 criterion. The threshold of reliability of kappa and kendall-tau values was set at 0.7. The perception questionnaire was rendered reliable since all kappa and kendall-tau values obtained exceeded the 0.7 threshold and a p-value less than 0.05 was obtained.

2.2.4 Determination of sample size

According to the Pharmacy Council Malta Annual Report 2016, there were 944[10] pharmacists registered with the Maltese Pharmacy Council. According to the Medical Council Malta Annual Report 2016, there were 1,993[11] physicians registered with the Maltese Medical Council, which include a total of 1,308[12] physician specialists; 519 were registered specialists in the areas of interest for the study (Section 2.2.5) and 685 physicians were registered with no specialisation. Using a 95% confidence interval and 6% margin of error, a minimum total sample size of 237 pharmacists and physicians was considered representative.

2.2.5 Ethics approval and dissemination of perception questionnaire

Following approval by the Faculty of Medicine and Surgery Research Ethics Committee (Appendix 3), the final version of the perception questionnaire (Appendix 4) was disseminated to pharmacists in different areas of practice (community, academia, hospital, industry, regulatory affairs) and to physicians in different specialities; Family Medicine, General Medicine, Cardiology, Neurology, Psychiatry, Oncology and Infectious Disease. These specialities were chosen according to the therapeutic areas

[10]Pharmacy Council Malta Annual Report 2016- obtained by personal correspondence from a Pharmacy Council member. [accessed 2018 Jan 19]

[11]Medical Council of Malta. Medical Council Malta Annual Report 2016 [Internet]. Medical Council of Malta; 2016 [cited 2019 Jun 12]. Available from: URL: https://deputyprimeminister.gov.mt/en/regcounc/medicalcouncil/Documents/MC%20Annual%20Report%202016.pdf

[12]Medical Council of Malta. Medical and dental specialists register, 2016 [Internet]. Medical Council of Malta; 2016 [cited 2019 Jun 12]. Available from: URL: https://deputyprimeminister.gov.mt/en/regcounc/medicalcouncil/Documents/registers/mcsac.pdf

with the highest number of drugs reported to have PGx implications according to Pharmacogenomics Knowledgebase (PharmGKB).[6]

Dissemination of the perception questionnaire was undertaken: a) online via the social media groups to pharmacists- 'Maltese pharmacists and pharmacy students'(n=835) and physicians-'Tobba Maltin' (n=894)and the mailing list of the Malta College of Family Doctors (n=198), b) personally by the researcher in community pharmacies, private clinics and at Mater Dei Hospital (n=135), and c) during two local medical conferences namely; the 2018 Maltese Cardiac Society Conference (n=30) and the 10th Malta Medical School Conference (n=30). The questionnaires were disseminated between 22nd September and 22nd December 2018 (3 months).

2.3 Development, dissemination and evaluation of pharmacogenetics tutorial

A PGx tutorial was developed and disseminated to pharmacists and physicians with the aim to increase awareness about PGx testing in practice. The tutorial was evaluated using an evaluation form.

2.3.1 Development of pharmacogenetics tutorial and evaluation form

A tutorial *Pharmacogenetics: A tool for precision medicine* was developed using Microsoft® Powerpoint presentation reflecting results obtained from the perception questionnaire.

[6]Pharmacogenomics Knowledgebase (PharmGKB). Drug label annotation [Internet]. USA: Stanford University, Department of Health and Human Services; 2019 [cited 2019 Jun 12]. Available from: URL: https://www.pharmgkb.org/labels

The topics chosen for discussion in the tutorial included; i) nomenclature related to PGx, ii) benefits of PGx, iii) PGx information sources, iv) clinical application of PGx using three case-studies (oncology, cardiology, infectious disease), and v) future directions of PGx testing. The three clinical cases were selected for discussion were according to the following criteria; drugs available on the Maltese Government Formulary List (GFL), confirmed to have PGx implications from PharmGKB and had a Clinical Pharmacogenetics Implementation Consortium (CPIC) genotype-guided dosing guideline available.

An evaluation form was developed to be disseminated to pharmacists and physicians to evaluate the tutorial.

2.3.2 Validation of pharmacogenetics tutorial and evaluation form

The PGx tutorial and evaluation form were validated by 7 professionals; 5 pharmacists (3 pharmacists in academia, 1 hospital pharmacist, 1 pharmacist practicing in regulatory affairs with an interest in PGx) and 2 physicians (2 specialists in Family Medicine). The PGx tutorial and evaluation form were modified according to the suggested amendments by the panel. The final versions were communicated with the panel via electronic mail and approved by all members.

2.3.3 Dissemination of pharmacogenetics tutorial and evaluation form

The PGx tutorial approved by the validation panel (Appendix 5) was recorded as a voiceover on the Microsoft® Powerpoint slide show presentation and an online version of the evaluation form (Appendix 6) was prepared using SurveyMonkey®. The PGx tutorial and evaluation form were disseminated; i) online via the social media groups to

pharmacists- ‘Maltese pharmacists and pharmacy students’(n=835) and physicians- ‘Tobba Maltin’ (n=894) and, ii) delivered as a live presentation to pharmacists and physicians in a workshop on ‘Quality in Adverse Drug Reaction Reporting’ at the Malta Medicines Authority (n=9) on the 20th March 2019. The tutorial and evaluation form responses were disseminated online between 24th March and 7th April 2019 (2 weeks).

2.4 Statistical analysis of perception questionnaire and evaluation form

The Mann-Whitney test was used to compare mean rating scores between pharmacists and physicians provided to a statement measuring ordinal variables on a Likert-Scale. All mean rating scores for Likert-Scale type questions were calculated out of 5, except for question 39 of the perception questionnaire; this question consists of the rating of drug classes for which PGx testing is perceived as important by pharmacists and physicians and that had to be rated on a Likert-Scale from 1 to 8, and questions 68-72 of the perception questionnaire consisting of the rating of HCPs responsibility in PGx healthcare service provision had to be rated on a Likert-Scale of 1 to 6 (questions 68, 71, 72) and 7 (questions 69, 70). The null hypothesis specifies that the mean rating scores provided by pharmacists and physicians vary marginally and is accepted if the p-value is greater than 0.05. If the p-value exceeds 0.05, this implies no significant difference between pharmacists and physicians. The alternative hypothesis specifies that the mean rating scores provided by pharmacists and physicians vary significantly and is accepted if p-value is less than the 0.05 criterion. If the p-value is less than 0.05, there is a significant difference between pharmacists and physicians.

The Chi-square test was used to assess the association between two categorical/nominal variables, where one of these variables describes the occupation of the participant

(pharmacist or physician), and the other variable provides a statement relating to PGx testing. The null hypothesis specifies that there is no association between the two variables and is accepted if the p-value is greater than 0.05. If the p-value is greater than 0.05, there is no significant difference between pharmacists and physicians for the statement provided. The alternative hypothesis specifies that there is a significant association between the two variables and is accepted if the p-value is less than the 0.05 criterion. If the p-value is less than 0.05, there is a significant difference between pharmacists and physicians.

2.5 Comparison of pharmacogenetics information in official product labelling for oncology drugs

PGx information in official product labelling (FDA drug label and EMA SmPC) and the clinical application of PGx information in practice for oncology drugs were analysed.

The November 2018 Maltese GFL[5] was accessed and oncology drugs listed in the 'Malignant disease and Immunosuppression' section were identified and selected for analysis. The PharmGKB[6] website was used to determine which of the drugs identified have PGx implications. The EMA and FDA label annotations assigned by PharmGKB were noted. Genotype-guided dosing guidelines were accessed using CPIC.[13]

[5]Directorate of Pharmaceutical Affairs (DPA). The Government Formulary List [Internet]. Malta: Ministry of Health: DPA; 2018 [cited 2019 Jun 12]. Available from: URL: https://deputyprimeminister.gov.mt/en/pharmaceutical/Pages/formulary/formulary.aspx

[6]Pharmacogenomics Knowledgebase (PharmGKB). Drug label annotation [Internet]. USA: Stanford University, Department of Health and Human Services; 2019 [cited 2019 Jun 12]. Available from: URL: https://www.pharmgkb.org/labels

[13]Clinical Pharmacogenetics Implementation Consortium (CPIC). Guidelines [Internet]. U.S. Department of Health and Human Services, 2019 [cited 2019 Jun 17]. Available from: URL: https://cpicpgx.org/guidelines/

The FDA drug label and EMA SmPC for drugs which had a 'Testing required' annotation reported in PharmGKB for one or both regulatory bodies were selected for comparison of PGx information (Table 2.2).

Table 2.2 PharmGKB annotations of oncology drugs found on Maltese GFL (N=14)

Drug	PharmGKB annotation	
	FDA	**EMA**
Anastrozole	Testing required	No annotation
Dabrafenib	Testing required	
Erlotinib	Testing required	
Everolimus	Testing required	
Exemestane	Testing required	No annotation
Imatinib	Testing required	
Lenalidomide	Testing required	Informative PGx
Letrozole	Testing required	No annotation
Rasburicase	Testing required	Actionable PGx
Rituximab	Informative PGx	Testing required
Tamoxifen	Testing required	No annotation
Trametinib	Testing required	
Trastuzumab	Testing required	
Tretinoin	Testing required	No annotation

The FDA drug label was retrieved from DailyMed.[14] The EMA SmPC for drugs which have gained marketing authorisation by the centralised procedure was retrieved from the EMA website[15] via the respective European Public Assessment Report. The EMA SmPC for drugs which have gained marketing authorisation via the national procedure was retrieved using the Malta Medicines Authority website.[16] The EMA SmPC for

[14]National Library of Medicine (U.S.) DailyMed. [Internet]. U.S. National Library of Medicine, National Institutes of Health, Health and Human, Services; 2018 [cited 2019 Jun 12] Available from: URL: https://dailymed.nlm.nih.gov/dailymed/

[15]European Medicines Agency (EMA). European public assessment reports [Internet]. UK: EMA; 2018 [cited 2019 Jun 12]. Available from: URL: https://www.ema.europa.eu/en/medicines

[16]Malta Medicines Authority. Medicines database [Internet]. Medicines review committee; 2018 [cited 2019 Jun 12] Available from: URL: http://www.medicinesauthority.gov.mt/medicinesdatabase

drugs which were not retrievable from the EMA website or the Malta Medicines Authority website were retrieved from the Electronic Medicines Compendium (eMC).[17] PGx information found in each section of the FDA drug label and EMA SmPC was compared.

2.6 Assessment of present status of pharmacogenetic testing locally for oncology drugs

A form consisting of the list of oncology drugs with PGx implications available on the GFL and their corresponding PGx biomarkers was completed (Appendix 7). A meeting was held with the Clinical Chairperson of the Department of Haematology and Oncology at Sir Anthony Mamo Oncology Centre to discuss the use of PGx testing for the identified drugs and form was completed. Approval was granted by the Clinical Chairperson to contact Oncology Consultants (n=6) via electronic mail to complete the form to gather information about the PGx tests being requested prior to prescribing in their practice.

2.7 Inclusion of PGx in pharmacy educational programs in Europe and USA

The inclusion of PGx in pharmacy educational programs and curricula in Europe and the USA was explored. The 82 members of the European Association of Faculties of Pharmacy[18] and the 142 members of the American Association of Colleges of Pharmacy[19] were contacted via electronic mail to provide information about inclusion of

[17]Electronic Medicines Compendium (eMC) [Internet]. UK: Datapharm Communications Ltd; 2019 [cited 2019 Jul 3]. Available from: URL: https://www.medicines.org.uk/emc/

[18]European Association of Faculties of Pharmacy (EAFP). Members and regions. [Internet]. EAFP Office, Department of Pharmacy, University of Malta; 2018 [cited 2018 Jul 20]. Available from: URL: https://eafponline.eu/regions-2/

[19]American Association of Colleges of Pharmacy (AACP). AACP Institutional Membership [Internet]. USA: AACP; 2018 [cited 2018 Jul 20]. Available from: URL: https://www.aacp.org/article/aacp-institutional-membership

PGx in the curriculum, availability of a PGx-specialised faculty member teaching the subject, number of teaching hours dedicated to PGx, overview of PGx topics discussed and method of teaching adopted (Appendix 8).

Chapter 3

Results

3.1 Results of perception questionnaire

In Section 3.1 results of the questionnaire assessing the perception of pharmacists and physicians on PGx testing are described.

3.1.1 Participant demographics

The questionnaire was completed by 292 participants; 75.3% (n=220) completed online and 24.7% (n=72) collected personally by the researcher. Participants were distributed as 61.3% (n=179) pharmacists and 38.7% (n=113) physicians. For pharmacists, 64.2% (n=115) were female, while for physicians an almost equal distribution between genders was observed (female 49.6%, n=56; male 50.4%, n=57). The highest number of participants for both pharmacists and physicians were in the 21-35 years age-group (pharmacists 63.1%, n=113; physicians 46.0%, n=52), and with more than 10 years of practice (pharmacists 38.0%, n=68; physicians 54.0%, n=61) (Table 3.1).

Table 3.1 Perception questionnaire - Participant demographics (N=292)

	Pharmacists (n=179)		**Physicians (n=113)**	
Gender	*Number*	*Percentage (%)*	*Number*	*Percentage (%)*
Male	64	35.8	57	50.4
Female	**115**	**64.2**	56	49.6
Age (Years)	*Number*	*Percentage (%)*	*Number*	*Percentage (%)*
21-35	**113**	**63.1**	**52**	**46.0**
36-45	32	17.9	21	18.6
46-55	31	17.3	20	17.7
56-69	2	1.1	17	15.0
70+	1	0.6	3	2.7
Years of Practice	*Number*	*Percentage (%)*	*Number*	*Percentage (%)*
<2	24	13.4	0	0
2-5	48	26.8	37	32.7
6-10	39	21.8	15	13.3
>10	**68**	**38.0**	**61**	**54.0**

Most pharmacists who completed the questionnaire practiced in the community pharmacy setting (43.6%, n=78) (Table 3.2).

Table 3.2 Perception questionnaire: Pharmacists' distribution by area of practice (n=179)

Area of Practice	*Number*	*Percentage (%)*
Community	**78**	**43.6**
Hospital	42	23.5
Regulatory	27	15.0
Industry	26	14.5
Academia	6	3.4

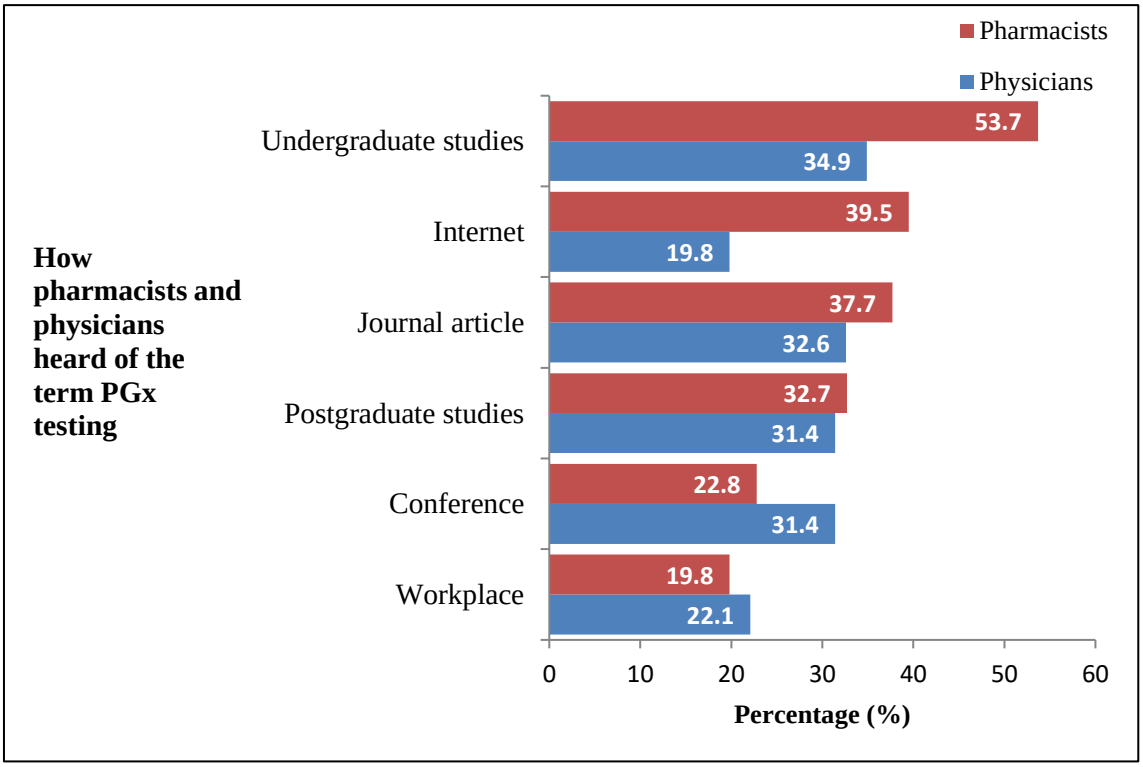
Most physicians who completed the questionnaire were practicing in Family Medicine (44.2%, n=50) (Table 3.3).

Table 3.3 Perception questionnaire: Physicians' distribution by area of specialisation (n=113)

Area of Specialisation	*Number*	*Percentage (%)*
Family Medicine	**50**	**44.2**
General Medicine	32	28.3
Cardiovascular	10	8.8
Psychiatry	8	7.1
Oncology	7	6.2
Neurology	6	5.4

3.1.2 Awareness of pharmacogenetic testing

The term *pharmacogenetic testing* was familiar to 84.9% (n=248) of participants prior to answering the questionnaire; pharmacists 90.5% (n=162); and physicians 76.1% (n=86), mostly from undergraduate studies; pharmacists 53.7%, (n=87); and physicians 34.9% (n=30) (Figure 3.1).



$X^2(5)=10.087$, p=0.073

Figure 3.1 Method of gaining awareness of the term 'pharmacogenetic testing' by pharmacists (n=162) and physicians (n=86).

Pharmacists (3.67) were significantly more aware than physicians (3.19) of the potential advantages of PGx testing (p=0.001). General lack of awareness of PGx was observed by both pharmacists and physicians since mean rating scores less than 3 were observed for the other statements. Physicians were significantly less aware than pharmacists of

drugs for which PGx testing is required or recommended (pharmacists 2.51, physicians 2.16; p=0.010), availability of PGx information sources (pharmacists 2.38, physicians 1.88; p<0.001), and when to recommend a PGx test (pharmacists 2.14, physicians 1.76; p=0.002) (Table 3.4).

Table 3.4 Awareness of PGx testing (N=292)

Statement *I am aware of:*	Mean rating score ± SD **Pharmacists** (n=179)	Mean rating score ± SD **Physicians** (n=113)	p-value
Potential advantages of PGx testing	3.67 ±1.03	3.19 ±1.20	**0.001***
Potential limitations of PGx testing	2.81 ±1.03	2.60 ±1.19	0.091
Drugs for which PGx testing is required or recommended	2.51 ±1.13	2.16 ±1.14	**0.010***
Availability of information sources regarding drugs with PGx implications	2.38 ±1.15	1.88 ±1.01	**<0.001***
When to recommend a PGx test	2.14 ±1.12	1.76 ±1.01	**0.002***
How to interpret PGx test results	1.78 ±1.06	1.76 ±1.01	0.975
Drugs for which PGx testing is performed locally	1.51 ±0.91	1.55 ±1.00	0.825

*statistically significant results p<0.05

3.1.3 Education and training on pharmacogenetic testing.

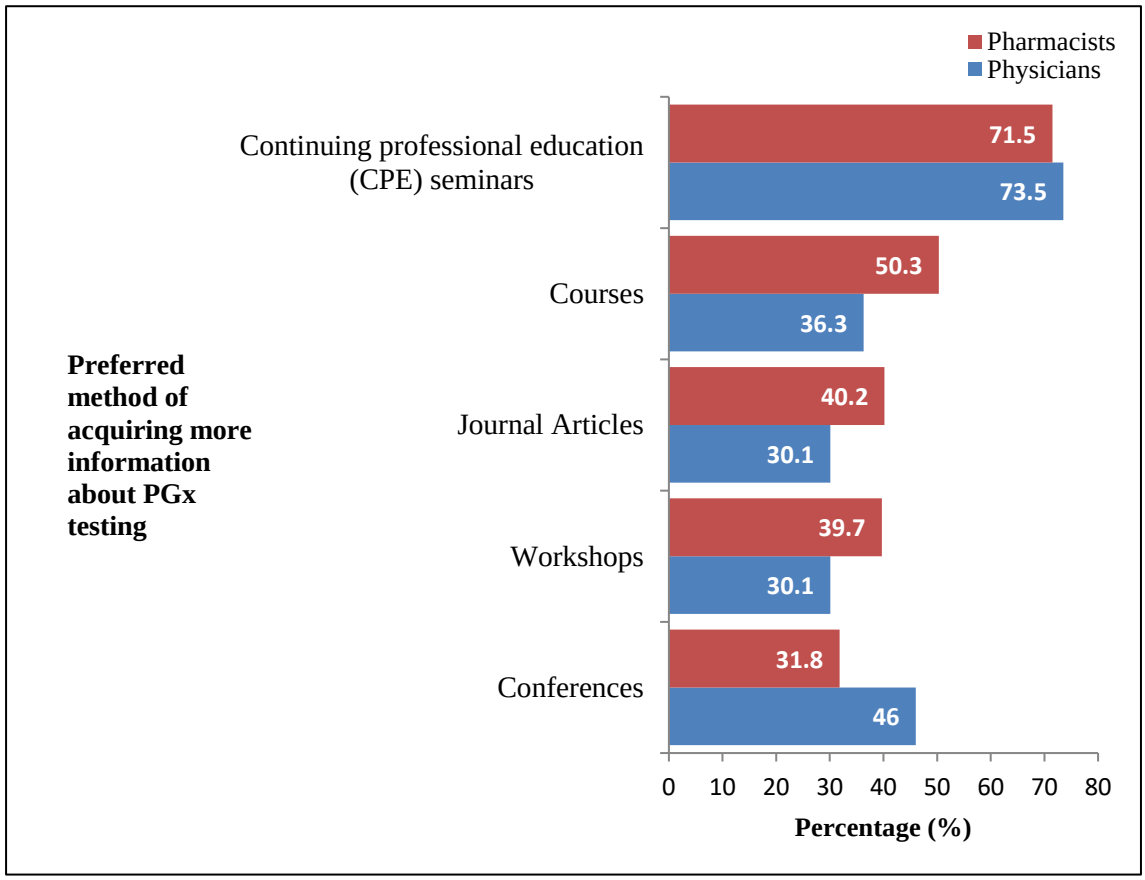
Insufficient competence in the area of PGx testing was observed by pharmacists (1.93) and physicians (1.65), since the mean rating scores were below 3, with significantly lower competence reported by physicians (p=0.005). Pharmacists significantly agreed more than physicians that PGx modules should be incorporated in undergraduate curricula and PGx training should be offered as a postgraduate specialisation (p<0.001). Pharmacists and physicians perceived the need for further training on PGx testing with high mean rating scores observed (p>0.05) (Table 3.5).

Table 3.5 Education and training on PGx testing (N=292)

Statement	Mean rating score ± SD **Pharmacists** (n=179)	Mean rating score ± SD **Physicians** (n=113)	p-value
I believe I am competent in the area of PGx testing	1.93 ±0.89	1.65 ±0.83	**0.005***
PGx modules should be incorporated in undergraduate curricula	4.13 ±0.94	3.75 ±0.79	**<0.001***
PGx should be offered as a postgraduate specialisation	4.11 ±0.92	3.81 ±0.80	**<0.001***
I require more education on PGx testing	4.43 ±0.942	4.37 ±0.847	0.194

*statistically significant results p<0.05

Pharmacists and physicians preferred continuing professional educational seminars (CPE) (pharmacists 31%, n=128; physicians 34%, n=83) for acquiring more information on PGx. The second preference for pharmacists was following courses (50.3%, n=90), while physicians preferred conferences (46%, n=52) (Figure 3.2).

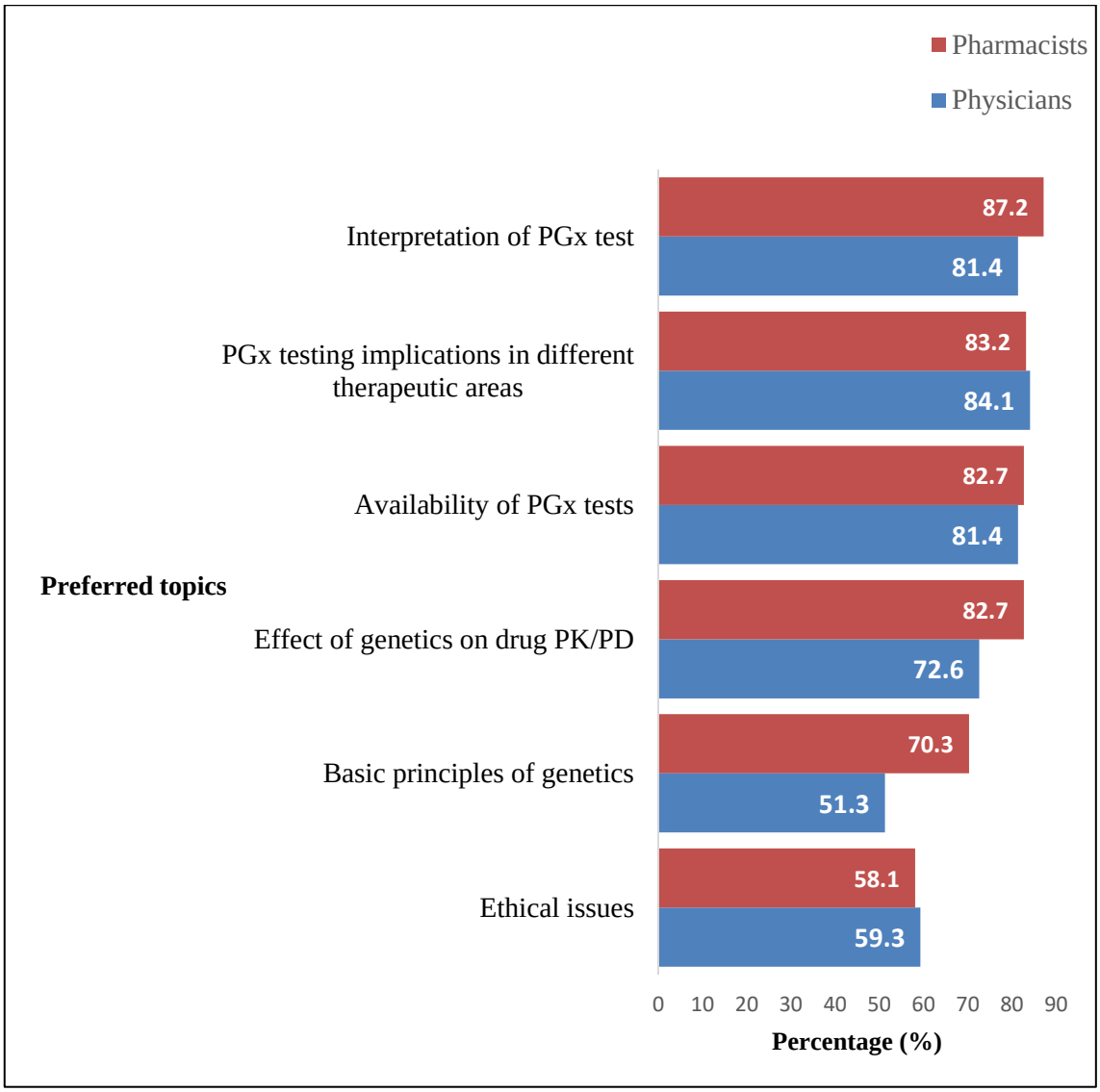


$X^2(4)=9.755$, p=0.045

Figure 3.2 Preferred method of acquiring information on PGx testing by pharmacists (n=179) and physicians (n=113)

Pharmacists (54.2%, n=97) and physicians (58.4%, n=66) preferred following the selected learning activities as a combination of attending in person and following online material.

'Interpretation of PGx test' was the topic of highest preference for pharmacists (87.2%, n=156) and physicians (81.4%, n=92). 'Ethical issues' was the topic of lowest preference by pharmacists (58.1%, n=104), while 'Basic principles of genetics' was the least preferred topic by physicians (51.3%, n=58) (Figure 3.3).



$X^2(5)=3.471$, p=0.628

Figure 3.3 Preferred PGx topics by pharmacists (n=179) and physicians (n=113)

3.1.4 Attitudes towards pharmacogenetic testing

Pharmacists significantly agreed more than physicians that PGx testing has clinical benefits, can guide individualised drug therapy selection, is useful in treatment-resistant cases, and is useful in medication-intolerance cases ($p<0.05$). Physicians significantly agreed more than pharmacists that PGx testing is applicable for use in their practice ($p= 0.006$) (Table 3.6).

Table 3.6 Attitudes towards use of PGx testing in practice (N=292)

Statement *PGx testing*:	Mean rating score ±SD **Pharmacists** (n=179)	Mean rating score ±SD **Physicians** (n=113)	p-value
Has clinical benefits	4.35 ±0.68	4.12 ±0.55	**0.001***
Guides individualised therapy selection	4.49 ±0.58	4.20 ±0.60	**<0.001***
Useful in treatment-resistant cases	4.41 ±0.69	4.22 ±0.65	**0.008***
Useful in medication-intolerance cases	4.30 ±0.70	4.09 ±0.70	**0.011***
Is applicable for use in my practice	3.31 ±1.03	3.62 ±7.36	**0.006***

*statistically significant results $p<0.05$

Pharmacists significantly agreed more than physicians that PGx testing decreases healthcare service utilisation (pharmacists 3.87, physicians 3.50; $p<0.001$) and leads to reduced healthcare costs (pharmacists 3.77, physicians 3.42; $p=0.001$). Pharmacists and physicians strongly agreed that cost-effectiveness studies are important with mean rating scores greater than 4 observed ($p>0.05$). Pharmacists and physicians agreed that PGx testing should be offered as a government-funded service rather than being paid out-of-pocket by the patient ($p>0.05$) (Table 3.7).

Table 3.7 Attitudes towards cost and service provision of PGx testing (N=292)

Statement *PGx testing*:	Mean rating score ±SD **Pharmacists** (n=179)	Mean rating score ±SD **Physicians** (n=113)	p-value
Decreases healthcare service utilisation	3.87 ±0.81	3.50 ±0.66	**<0.001***
Reduces healthcare costs	3.77 ±0.84	3.42 ±0.75	**0.001***
Cost-effectiveness studies are important	4.39 ±0.67	4.26 ±0.74	0.157
Government-funded service	3.92 ±0.83	3.82 ±0.75	0.255
Paid out-of-pocket by the patient	2.32 ±0.88	2.30 ±0.89	0.783
Guides drug therapy expenditure	3.97 ±0.73	3.82 ±0.63	0.077
Increases complexity of healthcare service provision	3.51 ±0.99	3.46 ±0.89	0.467

*statistically significant results p<0.05

More pharmacists than physicians agreed that PGx test results should be shared with family members and that potential violation of privacy may arise due to misuse of PGx test results (p<0.05) (Table 3.8).

Table 3.8 Attitudes towards ethical concerns of PGx testing results (N=292)

Statement *PGx testing results*:	Mean rating score ±SD **Pharmacists** (n=179)	Mean rating score ±SD **Physicians** (n=113)	p-value
Should be shared with family members	3.20 ±1.01	2.91 ±0.95	**0.010***
Misuse may lead to violation of privacy	4.13 ±0.88	3.96 ±0.76	**0.020***
May be misused/misinterpreted if made available to third parties	3.97 ±0.88	3.85 ±0.72	0.093

*statistically significant results p<0.05

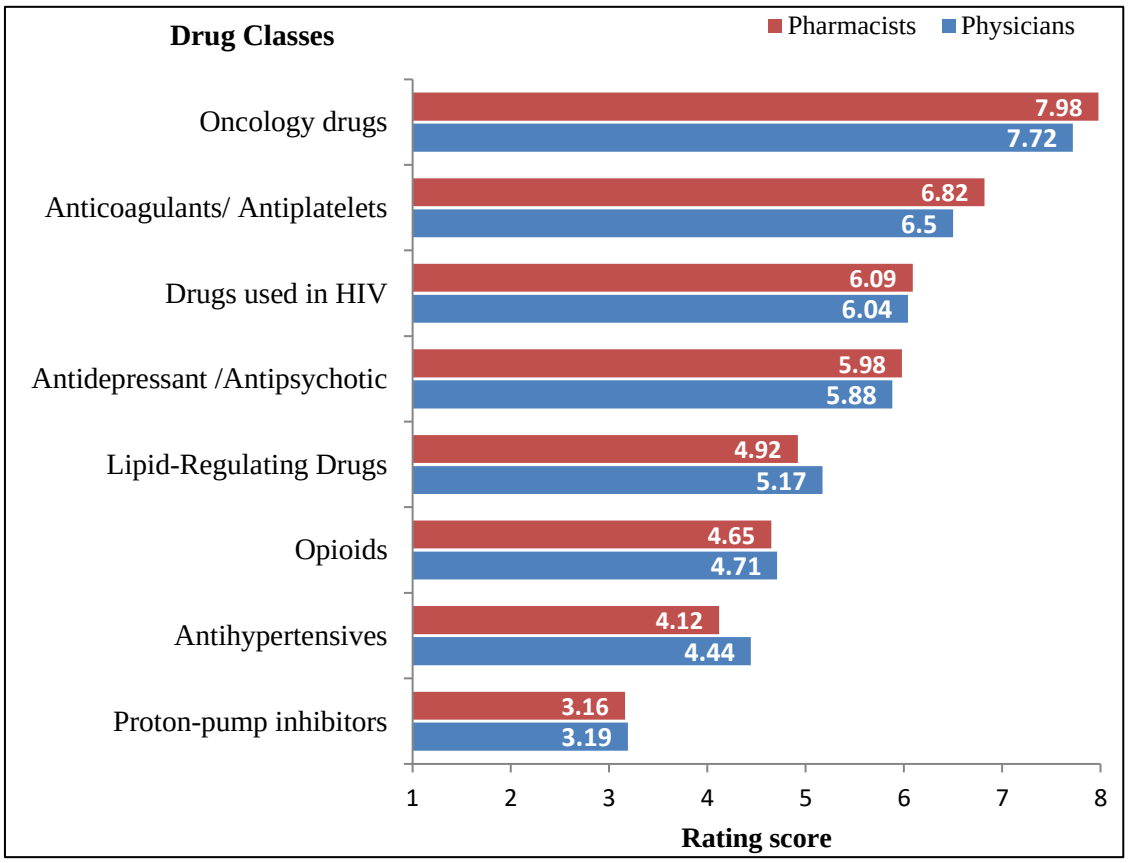
Pharmacists significantly agreed more than physicians that PGx testing improves efficacy and safety of medications on the market and of medications granted a marketing authorisation in the future, can be applied in drug development for medications used in difficult-to-treat situations. Pharmacists would be interested in PGx research studies and would recommend their patients to participate in studies if opportunities arise more than physicians ($p<0.05$) (Table 3.9).

Table 3.9 Attitudes towards pre- and post-marketing concerns of PGx testing (N=292)

Statement *PGx testing*:	Mean rating score ±SD **Pharmacists** (n=179)	Mean rating score ±SD **Physicians** (n=113)	p-value
Improves efficacy of medications on the market	4.10 ± 0.74	3.81 ± 0.63	**<0.001***
Improves safety of medications on the market	4.24 ± 0.67	3.93 ± 0.59	**<0.001***
Improves the efficacy and safety of medications granted a marketing authorisation in the future	4.15 ± 0.75	3.78 ± 0.59	**<0.001***
Can be applied in drug development for medications used in difficult-to-treat situations	4.26 ± 0.74	3.93 ± 0.64	**<0.001***
Research studies would interest you and you would recommend patients to participate in such studies if the opportunity arises	3.96 ± 0.80	3.68 ± 0.74	**0.004***

*statistically significant results $p<0.05$

Pharmacists and physicians agreed on the drug classes for which PGx testing is perceived as important (p>0.05). The top three drug classes included oncology drugs (pharmacists 7.98, physicians 7.72), antiplatelets/anticoagulants (pharmacists 6.82, physicians 6.5) and drugs used in HIV (pharmacists 6.09, physicians 6.04) (Figure. 3.4).



All comparisons between pharmacists and physicians were not statistically significant (p>0.05)

Figure 3.4 Rating of drug classes for which PGx testing is perceived as important by pharmacists (n=179) and physicians (n=113)

3.1.5 Pharmacogenetic testing in practice

Eleven physicians had previously ordered a PGx test. Examples of drugs for which a PGx test was ordered included abacavir, azathioprine and clopidogrel (Table 3.10).

Table 3.10 Drugs for which PGx testing was ordered by physicians

Examples of drugs for which PGx testing was ordered	Number of physicians
Azathioprine	4
Dabrafenib, dasatinib, erlotinib, ibrutinib, imatinib	3
Abacavir, clopidogrel	2
Co-trimoxazole, maraviroc	1

Most pharmacists (42.5%, n=76) never perceived the need to order a PGx test in their practice. Most physicians (38.9%, n=44) perceived the need to order a PGx test at least once monthly (Figure 3.5).

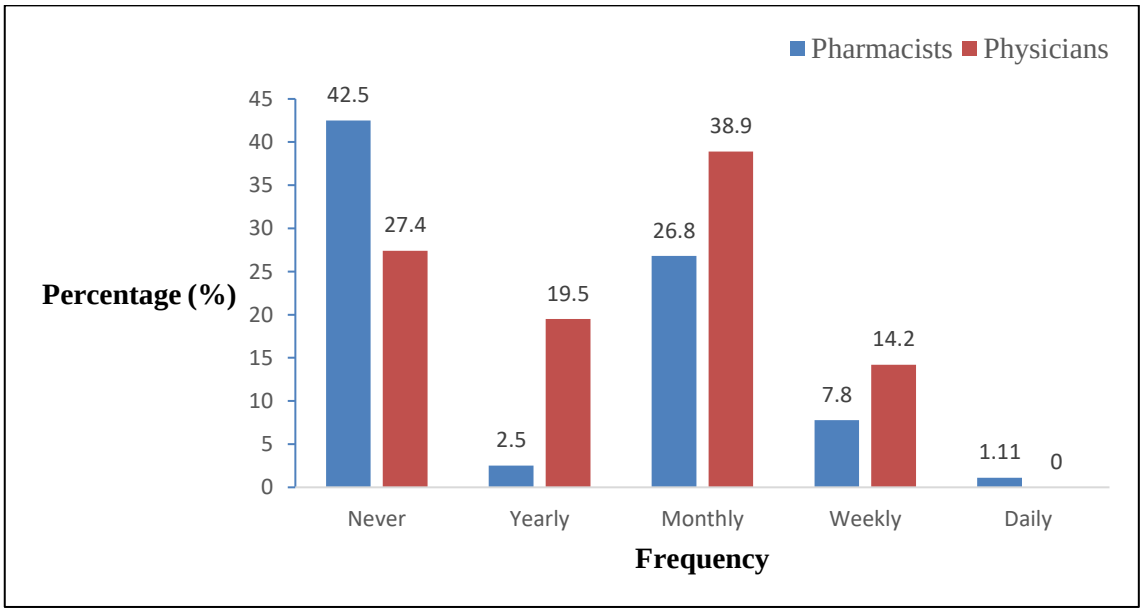


Figure 3.5 Perceived need to order a PGx test by pharmacists (n=179) and physicians (n=113)

Pharmacists (2.42) and physicians (2.10) reported limited confidence in recommending PGx testing (p=0.015). Limited confidence was reported by pharmacists and physicians in ordering PGx tests and in interpreting and discussing PGx test results (p>0.05) (Table 3.11).

Table 3.11 Confidence towards use of PGx testing in practice (N=292)

Statement *Personal degree of confidence to*:	Mean rating score ±SD **Pharmacists** (n=179)	Mean rating score ±SD **Physicians** (n=113)	p-value
Recommend PGx testing	2.42 ±1.15	2.10 ±1.09	**0.015***
Order PGx testing	2.41 ±1.18	2.25 ±1.07	0.305
Interpret PGx test results	1.98 ±1.03	2.02 ±1.04	0.751
Discuss PGx test results with patient	2.21 ±1.13	2.25 ±1.11	0.708

*statistically significant results p<0.05

Both pharmacists (4.16) and physicians (4.02) agreed, with significantly higher agreement by pharmacists, that they would take action if a PGx test result indicated the need for a change in treatment plan (p=0.042) (Table 3.12).

Table 3.12 Clinical utility of PGx testing (N=292)

Statement *I would*:	Mean rating score ±SD **Pharmacists** (n=179)	Mean rating score ±SD **Physicians** (n=113)	p-value
Take action if a PGx test result indicated need for a change in treatment plan	4.16 ±0.84	4.02 ±0.77	**0.042***
Order a PGx test to predict likelihood of an adverse effect to a drug	3.66 ±0.94	3.65 ±0.77	0.888
Order a PGx test to predict likelihood of drug efficacy	3.85 ±0.91	3.83 ±0.73	0.521
Order a PGx test to predict severity of a potential adverse effect	3.75 ±0.93	3.76 ±0.75	0.839

*statistically significant results p<0.05

Pharmacists significantly agreed more than physicians that PGx testing should be performed pre-emptively (pharmacists 3.38, physicians 3.04; p=0.002), implemented routinely with medication therapy management services (pharmacists 3.49, physicians 2.88; p<0.001), and provided as a point-of-care test in community pharmacies (pharmacists 3.18, physicians 2.82; p=0.002) (Table 3.13).

Table 3.13 Provision of PGx testing service (N=292)

Statement *PGx testing should be*:	Mean rating score ±SD **Pharmacists** (n=179)	Mean rating score ±SD **Physicians** (n=113)	p-value
Performed pre-emptively	3.38 ±0.89	3.04 ±0.84	**0.002***
Implemented routinely with medication therapy management services	3.49 ±0.97	2.88 ±0.88	**<0.001***
Provided as a point-of-care test in community pharmacies	3.18 ±1.05	2.82 ±0.90	**0.002***
Performed in hospital only	2.88 ±0.96	2.97 ±1.00	0.399
Carried out in a laboratory solely dedicated to PGx	3.35 ±0.93	3.35 ±0.95	0.859

*statistically significant results p<0.05

Pharmacists significantly agreed more than physicians that PGx test results should be available for access by all HCPs taking care of the patient (p=0.003). Physicians (3.18) significantly agreed more than pharmacists (2.49) that PGx test results should be available for access by prescribers only (p<0.001).

Pharmacists and physicians strongly agreed with mean rating scores greater than 4 that PGx test results should be stored electronically and made available in health records for clinical evaluation by the HCP (p>0.05) (Table 3.14).

Table 3.14 Storage, availability and interpretation of PGx test results (N=292)

Statement *PGx test results should be*:	Mean rating score ±SD **Pharmacists** (n=179)	Mean rating score ±SD **Physicians** (n=113)	p-value
Available for access by all HCP taking care of the patient	4.04 ±0.92	3.81 ±0.79	**0.003***
Available for access by prescribers only	2.49 ±0.98	3.18 ±0.93	**<0.001***
Stored electronically	4.16 ±0.67	4.06 ±0.62	0.213
Available in health records for clinical evaluation by HCP	4.23 ±0.73	4.17 ±0.50	0.095
Interpreted automatically by an electronic system which incorporates algorithms for treatment decisions	3.76 ±1.02	3.63 ±0.83	0.089

*statistically significant results p<0.05

Pharmacists and physicians agreed that pre- and post-test counselling should be provided, and patients should be informed about incidental/ ancillary findings from a PGx test result (p>0.05) (Table 3.15).

Table 3.15 Patient counselling and PGx testing (N=292)

Statement	Mean rating score ±SD **Pharmacists** (n=179)	Mean rating score ±SD **Physicians** (n=113)	p-value
Pre-test counselling with patient should be provided prior to PGx testing to aid in informed decision-making	4.32 ±0.63	4.27 ±0.68	0.592
Post-test counselling with patient should be provided to aid in understanding of test results	4.43 ±0.62	4.33 ±0.62	0.116
Patients should be informed about incidental/ancillary findings from a PGx test result	4.21 ±0.71	4.27 ±0.70	0.520

Pharmacists significantly agreed more than physicians that a framework should be implemented to ensure consistency of a PGx service to avoid liability issues, genetic stratification should be applied in PGx research studies to help design of drugs which target specific groups of patients, PGx testing should be included as a risk minimisation measure in the safety section of the dossier, and the SmPC should include PGx testing information when applicable ($p<0.05$) (Table 3.16).

Table 3.16 Regulatory aspects of PGx testing (N=292)

Statement:	Mean rating score ±SD **Pharmacists** (n=179)	Mean rating score ±SD **Physicians** (n=113)	p-value
Implementation of a framework to ensure consistency of procedure when ordering a PGx test to avoid liability issues	4.28 ±0.66	4.12 ±0.64	**0.028***
Genetic stratification should be applied in PGx research studies to help design drugs which target specific groups of patients. e.g non-responders	4.21 ±0.68	4.04 ±0.58	**0.010***
PGx testing should be included as a risk minimisation measure in the safety section of the dossier	4.01 ±0.76	3.87 ±0.61	**0.046***
SmPC should include PGx testing when applicable	4.30 ±0.63	4.04 ±0.61	**0.001***
Organisational infrastructures should be developed to describe the responsibilities of each HCP involved in effective provision of PGx testing services	4.13 ±0.65	4.01 ±0.59	0.073

*statistically significant results $p<0.05$

The ‘Consultant’ was ranked highest as the HCP who should be responsible to make a patient aware of PGx testing by pharmacists (5.73) and physicians (6.04) (p=0.021). Pharmacists (5.40) then considered the ‘Genetic Specialist Physician’ as the next responsible HCP while physicians (5.47) considered the ‘Physician’ as next responsible (Table 3.17).

Table 3.17 Healthcare professional responsible for patient awareness of PGx testing (N=292)

Statement **Responsibility for making patient aware of PGx testing**	Mean rating score ±SD **Pharmacists** (n=179)	Mean rating score ±SD **Physicians** (n=113)	p-value
Pharmacist	4.61 ±1.46	4.11 ±1.26	**0.003***
Physician**	5.00 ±1.29	**5.47 ±1.29**	**0.003***
Consultant	**5.73 ±1.15**	**6.04 ±1.00**	**0.021***
Genetic specialist physician	**5.40 ±1.42**	5.29 ±1.23	0.472
Genetic counsellor	4.03 ±1.44	3.92 ±1.24	0.948
Nurse	2.23 ±0.63	2.17 ±0.64	0.162

*statistically significant results p<0.05
**including: Basic Specialist Trainee, Higher Specialist Trainee, Resident Specialist, Specialist in Family Medicine

Pharmacists (5.77) ranked the 'Genetic Specialist Physician' as the HCP who should be responsible to access a patient's PGx test result, followed by the 'Consultant' (5.63). Physicians (6.02) ranked the 'Consultant' as the HCP most responsible to access a patient's PGx test result followed by the 'Physician' (5.62) (Table 3.18).

Table 3.18 Healthcare professional responsible to access PGx test result (N=292)

Statement **Responsibility for accessing a PGx test result**	Mean rating score ±SD **Pharmacists** (n=179)	Mean rating score ±SD **Physicians** (n=113)	p-value
Pharmacist	4.07 ±1.49	3.71 ±1.37	**0.036***
Physician**	4.88 ±1.33	**5.62 ±1.37**	**<0.001***
Consultant	**5.63 ±1.13**	**6.02 ±1.00**	**0.002***
Genetic specialist physician	**5.77 ±1.37**	5.28 ±1.30	**0.001***
Genetic counsellor	3.97 ±1.53	3.68 ±1.20	0.296
Biomedical Laboratory Scientist	2.16 ±1.26	2.24 ±1.05	0.116
Nurse	1.53±0.92	1.45 ±0.99	0.225

*statistically significant results $p<0.05$
**including: Basic Specialist Trainee, Higher Specialist Trainee, Resident Specialist, Specialist in Family Medicine

The ‘Genetic Specialist Physician’ was ranked highest as the HCP responsible to interpret a patient’s PGx test result by pharmacists (6.20) and physicians (5.98). The ‘Consultant’ was considered the next responsible HCP with a significantly higher ranking by physicians (5.59) compared to pharmacists (5.17) (p=0.002) (Table 3.19).

Table 3.19 Healthcare professional responsible to interpret PGx test result (N=292)

Statement **Responsibility to interpret a PGx test result**	Mean rating score ±SD **Pharmacists** (n=179)	Mean rating score ±SD **Physicians** (n=113)	p-value
Pharmacist	3.72 ±1.51	3.56 ±1.35	0.518
Physician**	4.35 ±1.19	5.00 ±1.36	**<0.001***
Consultant	**5.17 ±1.15**	**5.59 ±1.04**	**0.002***
Genetic specialist physician	**6.2 ±1.15**	**5.98 ±1.30**	0.128
Genetic counsellor	4.37 ±1.63	3.73 ±1.60	**0.001***
Biomedical Laboratory Scientist	2.95 ±1.83	2.89 ±1.40	0.291
Nurse	1.23 ±0.63	1.24 ±0.75	0.588

*statistically significant results p<0.05
**including: Basic Specialist Trainee, Higher Specialist Trainee, Resident Specialist, Specialist in Family Medicine

Pharmacists (5.74) considered the 'Genetic Specialist Physician' as the HCP who should be responsible to discuss a PGx test result with patients, while physicians (5.79) ranked the 'Consultant' as most responsible. The 'Consultant' was considered as next responsible by pharmacists (5.40) while physicians (5.71) considered the 'Genetic Specialist Physician' as next responsible. (Table 3.20)

Table 3.20 Healthcare professional responsible to discuss PGx test result with patient (N=292)

Statement **Responsibility to discuss a PGx test result**	Mean rating score ±SD **Pharmacists** (n=179)	Mean rating score ±SD **Physicians** (n=113)	p-value
Pharmacist	4.28 ±1.42	3.61 ±1.03	**<0.001***
Physician**	4.76 ±1.16	5.32 ±1.34	**0.001***
Consultant	**5.40 ±1.17**	**5.79 ±1.04**	**0.005***
Genetic specialist physician	**5.74 ±1.29**	**5.61 ±1.17**	0.183
Genetic counsellor	4.68 ±1.66	4.55 ±1.40	0.767
Nurse	2.13 ±0.56	2.13 ±0.58	0.721

*statistically significant results p<0.05

**including: Basic Specialist Trainee, Higher Specialist Trainee, Resident Specialist, Specialist in Family Medicine

The ‘Consultant’ was ranked highest as the HCP who should be responsible to take action according to PGx test result by pharmacists (6.04) and physicians (6.36), with significantly higher ranking by physicians (p=0.024). Pharmacists (5.58) then considered the ‘Genetic Specialist Physician’ as next responsible while physicians (5.84) preferred the ‘Physician’ as the next responsible HCP to take action according to PGx test result (Table 3.21).

Table 3.21 Healthcare professional responsible to take action according to PGx test result (N=292)

Statement **Responsibility to take action according to PGx test result**	Mean rating score ±SD **Pharmacists** (n=179)	Mean rating score ±SD **Physicians** (n=113)	p-value
Pharmacist	4.50 ±1.29	4.22 ±1.01	0.152
Physician**	5.19 ±1.00	**5.84 ±0.96**	**<0.001***
Consultant	**6.04 ±1.08**	**6.36 ±0.78**	**0.024***
Genetic specialist physician	**5.58 ±1.29**	5.16 ±1.12	**0.004***
Genetic counsellor	3.41 ±1.22	3.25 ±0.76	0.951
Nurse	2.27 ±0.64	2.17 ±0.61	0.057

*statistically significant results p<0.05
**including: Basic Specialist Trainee, Higher Specialist Trainee, Resident Specialist, Specialist in Family Medicine

Physicians (3.87) significantly agreed more than pharmacists (3.61) that turnaround time of test result impacts their decision to order a PGx test (p=0.023). Pharmacists and physicians agreed that the greater challenges for implementation of PGx testing are lack of HCP (pharmacists 4.33, physicians 4.27) and public awareness of PGx testing (pharmacists 4.46, physicians 4.35), and cost issues (pharmacists 4.32, physicians 4.31) (p>0.05) (Table 3.22).

Table 3.22 Challenges for implementation of PGx testing (N=292)

Statement:	Mean rating score ±SD **Pharmacists** (n=179)	Mean rating score ±SD **Physicians** (n=113)	p-value
Turnaround time of test result impacts your decision to order a PGx test	3.61 ±0.94	3.87 ±0.81	**0.023***
Lack of HCP awareness	4.33 ±0.73	4.27 ±0.67	0.331
Lack of public awareness	4.46 ±0.80	4.35 ±0.71	0.052
Cost issues	4.32 ±0.70	4.31 ±0.66	0.783
Ethical concerns	3.72 ±0.95	3.78 ±0.86	0.696
Evidence-based value of test result impacts your decision to order a PGx test	3.66 ±0.82	3.81 ±0.74	0.09
PGx testing will increase your workload in practice	3.33 ±1.04	3.47 ±1.00	0.319
PGx testing will increase waiting time for prescriber to take action on a patient's medication needs	3.74 ±0.96	3.71 ±0.95	0.704

*statistically significant results p<0.05

3.2 Results of the evaluation of the pharmacogenetics tutorial

In Section 3.2, results of the evaluation of the developed PGx tutorial disseminated to pharmacists and physicians are described.

3.2.1 Participant demographics

The evaluation form was completed by 66 participants; 57 completed online and 9 completed after the live presentation. Participants distribution was 33 pharmacists and 33 physicians. For pharmacists, 25 were female, while for physicians an almost equal distribution between genders was observed (female n=15; male n=18). The mean age for pharmacists and for physicians was 31 and 33 years respectively; the mean years of practice 7 years for pharmacists and 10 years for physicians (Table 3.23).

Table 3.23 Evaluation form - Participant demographics (N=66)

	Pharmacists (n=33)	**Physicians (n=33)**
Gender	*Number*	*Number*
Male	8	18
Female	25	15
Age (Years)	*Mean ±SD*	*Mean ±SD*
	31 ±7.56	33 ±10.44
Years of Practice	*Mean ±SD*	*Mean ±SD*
	7 ±7.02	10 ±9.89

Most pharmacists who completed the evaluation form practiced in community pharmacy (n=14) (Table 3.24).

Table 3.24 Evaluation form - Pharmacists' distribution by area of practice (n=33)

Area of Practice	*Number*
Community	**14**
Hospital	6
Regulatory	9
Research	2
Medical Representation	1
Industry	1
Academia	0

Most physicians who completed the questionnaire practiced in Family Medicine (n=8) (Table 3.25).

Table 3.25 Evaluation form- Physicians' distribution by area of specialisation (n=33)

Area of Practice	*Number*
Family Medicine	**8**
Foundation program (House Officers)	8
General Medicine	3
Emergency Medicine	2
Paediatrics	2
Surgery	2
Anaesthesia	1
Cardiology	1
ENT	1
Obstetrics and Gynaecology	1
Public Health	1
Radiology	1

3.2.2 Evaluation of pharmacogenetics tutorial

With regards to the relevance of the discussed topics in the tutorial, pharmacists and physicians perceived all the topics to be relevant and pharmacists rated all the topics with a significantly higher mean rating score than physicians ($p<0.05$) (Table 3.26)

Table 3.26 Relevance of discussion topics in PGx tutorial (N=66)

Statement **Relevance of discussion topics**	Mean rating score ±SD **Pharmacists** (n=33)	Mean rating score ±SD **Physicians** (n=33)	p-value
Nomenclature related to PGx	4.12 ±0.93	3.45 ±0.87	**0.003***
Benefits of PGx	4.45 ±0.56	3.88 ±0.74	**0.001***
PGx information resources	4.36 ±0.74	3.91 ±0.68	**0.009***
PGx clinical case 1- Oncology	4.48 ±0.62	3.97 ±0.68	**0.002***
PGx clinical case 2- Cardiology	4.48 ±0.67	3.91 ±0.84	**0.002***
PGx clinical case 3- Infectious disease	4.30 ±0.77	3.94 ±0.66	**0.034***

*statistically significant results $p<0.05$

Pharmacists significantly agreed more than physicians that the PGx tutorial may help to improve application of theory to practice (pharmacists 4.30, physicians 3.97; $p=0.027$) and skills in PGx (pharmacists 4.33, physicians 3.94; $p=0.007$). Pharmacists and physicians agreed that they are likely to follow future tutorials on PGx testing, with significantly higher agreement by pharmacists (4.45) compared to physicians (3.70) ($p<0.001$) (Table 3.27).

Table 3.27 Evaluation results of PGx tutorial (N=66)

Statement:	Mean rating score ±SD **Pharmacists** (n=33)	Mean rating score ±SD **Physicians** (n=33)	p-value
Inspired me on the subject	4.09 ±0.76	3.88 ±0.49	0.188
Reflects developments in PGx	4.24 ±0.71	4.15 ±0.36	0.343
Helped me to understand fundamental principles of PGx	4.48 ±0.57	3.88 ±0.55	**<0.001***
Sequence was appropriate	4.73 ±0.45	4.03 ±0.47	**<0.001***
Information in tutorial was clearly presented	4.58 ±0.50	3.85 ±0.57	**<0.001***
Information in tutorial was comprehensive	4.52 ±0.51	4.06 ±0.50	**0.001***
Information in tutorial was easy to understand	4.30 ±0.77	3.61 ±0.56	**<0.001***
May help to improve application of theory to practice	4.30 ±0.73	3.97 ±0.53	**0.027***
May help to improve my skills in PGx	4.33 ±0.78	3.94 ±0.43	**0.007***
Helped to identify my strengths and weaknesses regarding PGx	4.15 ±0.83	3.79 ±0.55	**0.025***
Content discussed is helpful for use in practice	4.12 ±0.86	3.70 ±0.53	**0.007***
Relevant to my practice	3.55 ±0.91	3.52 ±0.62	0.838
Met my expectations	4.39 ±0.70	3.88 ±0.49	**<0.001***
Likelihood of following future tutorials on PGx	4.45 ±0.62	3.70 ±0.59	**<0.001***

*statistically significant results $p<0.05$

3.3 Pharmacogenetics information in official product labelling for oncology drugs

Twenty-two out of the 80 drugs listed in the GFL indicated in oncology were identified to have PGx implications. Fourteen of the 22 drugs have a 'Testing required' annotation reported in PharmGKB. Comparison between the FDA drug label and EMA SmPC for the 14 drugs showed agreement for 7 drugs (dabrafenib, everolimus, exemestane, imatinib, letrozole, rituximab, trastuzumab) and differences between the regulatory bodies for another 7 drugs (anastrazole, erlotinib, lenalidomide, rasburicase, tamoxifen, trametinib, tretinoin) (Table 3.28).

Clinical Pharmacogenetics Implementation Consortium dosing guidelines are available for 7 of the 22 identified drugs, namely capecitabine, cisplatin, fluorouracil, irinotecan, mercaptopurine, rasburicase and tamoxifen.

Table 3.28 Comparison of PGx information between FDA and EMA for oncology drugs (N=14)

Drug	Month/Year of Update		Presence of PGx information in headings/sub-headings									
	FDA drug label	EMA SmPC	FDA drug label					EMA SmPC				
			BW	I	D	C	W	BW	I	D	C	W
Anastrozole	12/18	1/16	-	+	-	-	-	-	+	+	-	-
Dabrafenib	11/18	3/18	-	+	+	-	+	-	+	+	-	+
Erlotinib	10/16	3/18	-	+	+	-	-	-	+	+	-	+
Everolimus	5/14	4/18	-	+	-	-	-	-	+	-	-	-
Exemestane	7/16	5/18	-	+	-	-	-	-	+	-	-	-
Imatinib	11/17	10/17	-	+	+	-	-	-	+	+	-	-
Lenalidomide	7/18	5/18	+	+	-	-	-	-	+	-	-	-
Letrozole	11/17	10/17	-	+	-	-	-	-	+	-	-	-
Rasburicase	9/17	1/18	+	-	-	+	-	-	-	-	+	-
Rituximab	6/18	8/18	-	+	-	-	-	-	+	-	-	-
Tamoxifen	12/18	1/18	-	+	-	-	-	-	+	-	-	+
Trametinib	5/18	4/18	-	+	+	-	-	-	+	+	-	+
Trastuzumab	7/18	4/18	-	+	+	-	+	-	+	+	-	+
Tretinoin	1/18	5/17	-	+	-	-	+	-	+	-	-	-

PGx: Pharmacogenetics
BW: Boxed warning
I: Indications and usage/ Therapeutic indications
D: Dosage and administration/ Posology and method of administration
C: Contraindications
W: Warnings and precautions/ Special warnings and precautions for use
+: presence of PGx information
-: no PGx information

3.4 Implementation of pharmacogenetic testing locally for oncology drugs

The 7 Consultant Oncologists reported that PGx testing is being requested prior to prescribing for 14 drugs with a 'Testing required' annotation reported in PharmGKB (anastrozole, dabrafenib, erlotinib, everolimus, exemestane, imatinib, lenalidomide, letrozole, rasburicase, rituximab, tamoxifen, trametinib, trastuzumab, tretinoin) and for 2 drugs with an 'Actionable PGx' annotation reported in PharmGKB (busulfan and irinotecan).

3.5 PGx in pharmacy educational programs in Europe and USA

Information about PGx education programs and curricula was collated from 58 academic institutions (39 USA, 19 Europe). PGx is taught in 53 institutions, a higher number in the USA (36) than in Europe (17). Forty-two institutions had a faculty member specialised in PGx teaching the subject. The average time dedicated to PGx teaching per course is 24 hours (range 2-87 hours) in the USA and 23 hours (range 2-50 hours) in Europe. The most popular method of teaching PGx is via delivery of lectures by 48 institutions (32 USA, 16 Europe). Other teaching methods include laboratory practice (4 USA, 7 Europe), seminars (3 USA, 5 Europe), case studies (9 USA, 5 Europe) workshops (2 USA, 2 Europe), group work (5 USA, 1 Europe), debates (5 USA,1 Europe), site visits (1 Europe), journal clubs (1 Europe) and conferences (1 USA).

Topics in the curricula include basic principles of PGx (25 USA, 7 Europe), PGx testing implications in different therapeutic areas (36 USA, 12 Europe), PGx testing implications in practice (22 USA, 7 Europe), use of PGx testing guidelines (10 USA,

4 Europe), interpretation of PGx testing (8 USA, 2 Europe), and ethical, legal and social issues (11 USA, 5 Europe). Thirty-one respondents (27 USA, 4 Europe) stated that PGx should be given more importance in the curriculum whilst 20 respondents (12 USA, 8 Europe) believed that PGx is covered sufficiently in their curriculum.

Chapter 4

Discussion

4.1 The social and scientific implications of pharmacogenetic testing

Pharmacogenetics (PGx) is an advancing field in the precision medicine era and its implementation has the potential to improve patient safety and enhance efficacy of drug therapy (Klein et al, 2017). The social implications of PGx testing investigated in this study were the perception of pharmacists and physicians towards accessibility of PGx testing, the impact on the complexity of healthcare service provision, cost concerns, ethical issues, misuse or misinterpretation of PGx data by third parties, regulatory concerns and responsibilities of HCPs relating to PGx services. The scientific implications of PGx testing were explored through assessing awareness and training of pharmacists and physicians and their perception regarding benefits and challenges, inclusion of PGx information in official product labelling, and present status of PGx implementation in clinical practice.

The perception of pharmacists and physicians regarding PGx testing was analysed with respect to awareness, attitudes and practice aspects using a questionnaire developed and psychometrically evaluated in this study. Findings from this research contributed to the existing literature from other countries on the perception of PGx testing among pharmacists and physicians in Malta. Results from the questionnaire revealed the need for more information and training on PGx testing among pharmacists and physicians and a tutorial on PGx testing to promote awareness on the topic was developed, validated and evaluated.

The perception questionnaire identified oncology drugs as the drugs perceived by pharmacists and physicians to be most important for PGx testing. Moreover, in PharmGKB the highest number of drugs with PGx implications are oncology drugs

and most of these drugs have a testing required drug label annotation. Oncology drugs were selected for the comparison of PGx information in US FDA drug labels and EMA SmPCs as a means to explore harmonisation between regulatory bodies for these drugs since inadequate harmonisation between regulatory bodies is a reported challenge for the clinical uptake of PGx testing (Klein et al, 2017). The present status of the use of PGx testing for oncology drugs locally was explored in this study.

4.2 Attitudes of pharmacists and physicians towards pharmacogenetic testing

Pharmacists and physicians in this study demonstrated positive attitudes towards use of PGx testing in practice agreeing that is has potential clinical benefits in improving the efficacy and safety of drugs therapy, guiding individualised therapy, and in treatment resistant and medication intolerance cases. The perception of pharmacists was more positive compared to physicians ($p<0.05$). Studies carried out in the USA, Malaysia, Ethiopia and Kuwait have also reported similar positive attitudes by pharmacists and physicians towards PGx testing (Roederer et al, 2012; Tuteja et al, 2013; Bannur et al, 2014; Abdela et al, 2017; Albassam et al, 2018).

With regards to cost and PGx service provision pharmacists and physicians agreed that the clinical implementation of PGx testing has the potential to reduce healthcare costs and guide drug therapy expenditure. Pharmacists and physicians in this study agreed that PGx testing should not be paid-out-of-pocket by the patient and should be offered as a government-funded service. Similar findings have been reported in other studies (Koomer et al, 2011; McCullough et al,2011; Elewa et al, 2015; Albassam et al, 2018). Studies carried out in the USA and other European countries reported lack of reimbursement or health insurance coverage of the PGx test requested as reasons

for not using PGx testing routinely by pharmacists and physicians (Bank et al, 2017; Just et al, 2017; Wu et al, 2017).

When pharmacists and physicians were probed about their attitudes regarding PGx testing ethical concerns, apprehension was demonstrated regarding sharing of PGx test results with family members and misuse and misinterpretation of PGx test results if made available to third parties, such as health insurance agencies and employers. Such ethical concerns were reflected by pharmacists and physicians in other studies carried out in the Netherlands and the USA (Koomer et al, 2011; Bank et al, 2017)

4.3 Insufficient awareness of pharmacogenetic testing by pharmacists and physicians as a challenge for implementation of pharmacogenetic testing

Pharmacists and physicians in this study highlighted inadequate awareness of HCPs as a major barrier to PGx clinical implementation and concern regarding insufficient HCP awareness in PGx testing was also reported as a challenge in other studies carried out in Belgium, Germany, the Netherlands, Spain, the UK, and the USA (Gurwitz et al, 2009; Haga et al, 2012 a,c; Jamie, 2013, Horgan et al, 2014).

Lack of awareness of drugs with PGx implications by pharmacists and physicians was reported in this study, with significantly less awareness reported by physicians ($p<0.05$). This lack of awareness was observed in similar studies undertaken in other countries (Abdela et al, 2017; Just et al, 2017; Albassam et al, 2018).

Pharmacists and physicians in this study highly agreed that PGx information should be included in SmPCs. Studies have reported that pharmacists and physicians perceived the inclusion of PGx information in official product labelling as helpful in

clinical practice (Stanek et al, 2013; Romagnoli et al, 2016; Arathy et al, 2019). Pharmacists and physicians in this study were insufficiently aware of available information resources related to drugs with PGx implications, with physicians significantly less aware of PGx sources of information than pharmacists ($p<0.05$). Lack of awareness by pharmacists and physicians regarding PGx information resources was also reported in previous studies which were carried out in the USA and Kuwait (McCullough et al, 2011; Albassam et al, 2018; Owusu Obeng et al, 2018). Lack of awareness by pharmacists and physicians regarding the PGx tests currently requested locally was observed in this study, with lack of awareness similarly observed by Albassam et al (2018).

Studies which have reported lack of awareness by pharmacists and physicians towards PGx testing have suggested that there is the need for further training in order to address this challenge (Elewa et al, 2015; Obara et al, 2015; Aleijalat et al, 2016; Bank et al, 2017).

4.4 Education and training on pharmacogenetics

Klein et al (2017) identified lack of awareness by pharmacists and physicians on PGx testing as an educational barrier. Dong and Wilthshire, (2017) recommended that the lack of awareness among pharmacists and physicians should be addressed by PGx training to further improve the clinical implementation of PGx. Roederer et al (2017) suggested devising a standardised competency-based approach for PGx training of pharmacists in order to develop competences directed towards the application of PGx in clinical practice.

In this study, pharmacists significantly agreed more than physicians that PGx modules should be incorporated in undergraduate curricula and offered as a postgraduate specialisation ($p<0.05$). The incorporation of PGx training in pharmacy and medicine curricula is considered beneficial for further clinical implementation of PGx testing (Vitek et al, 2017).

Pharmacists and physicians in this study agreed that more education and training in PGx is required. Interest in further training and education in PGx is also reported in other studies (Roederer et al, 2012; Kuo et al, 2013; Alexander et al, 2014; Bannur et al, 2014; Elewa et al, 2015; Kudzi et al, 2015; Abdela et al, 2017; Bank et al, 2017; Chan et al, 2017, McCauley et al, 2017).

Pharmacists and physicians in this study preferred CPE seminars to acquire further information about PGx testing and would prefer following the seminars as a combination of attending in person and online. Preference of CPE seminars by pharmacists and physicians has similarly been reported in other studies (Roederer et al, 2012; Bannur et al, 2014), while accredited learning courses and workshops were preferred most in another study (Just et al, 2017),

The tutorial *Pharmacogenetics: A tool for precision medicine* was developed reflecting findings from the perception questionnaire, namely that pharmacists and physicians perceived the need for more information and training on PGx to increase confidence and competence and focused on the preferred topics including the application and interpretation of PGx tests. Previous studies reported similar perceptions (De Denus et al, 2013; Taber and Dickinson, 2014; Arathy et al, 2019),

hence the tutorial focused on discussion of the practical implications of PGx using clinical case studies. The case studies were selected for discussion according to the therapeutic areas which pharmacists and physicians perceived as most important for PGx testing in the perception questionnaire, namely oncology, cardiology and drugs used in HIV.

The PGx tutorial developed was well-received by pharmacists and physicians since they agreed that the PGx tutorial met their expectations and they were likely to follow future tutorials on the topic, with significantly higher agreement by pharmacists compared to physicians ($p<0.05$) Other studies reported the increased interest of pharmacists compared to physicians regarding following PGx testing tutorials (Bannur et al, 2014, Elewa et al, 2015).

The present study demonstrated agreement by pharmacists and physicians that the developed tutorial was relevant to their practice and may aid to improve skills and understanding of fundamental principles related to PGx, with significantly higher agreement by pharmacists compared to physicians for the latter. In a study by Formea et al (2018), it was agreed by pharmacists that PGx modules developed for the purpose of the study increased their confidence towards provision of therapeutic guidance about drugs with PGx implications. These results demonstrate that increased PGx training has the potential to improve awareness and support pharmacists, and also physicians in clinical decision-making incorporating PGx information (Horgan et al, 2014; Klein et al, 2017).

4.5 The way forward for further pharmacogenetics implementation in practice

The present study indicates that the clinical implementation of PGx locally is promising since positive attitudes by pharmacists and physicians were demonstrated. PGx testing was reported by physicians to be more applicable for use in their practice compared to pharmacists ($p<0.05$). Conversely in other studies, it was reported that pharmacists perceived PGx testing as more applicable in their practice compared to physicians (Abdela et al, 2017; Albassam et al, 2018). Kudzi et al (2015) demonstrated that there was high agreement towards relevance of PGx testing in practice by both pharmacists and physicians.

However, to enhance implementation of PGx in practice, various challenges need to be addressed and overcome. Some of these challenges, including insufficient competence, cost issues and long turnaround time for tests results, were identified by pharmacists and physicians in the perception questionnaire.

Insufficient competence in the area of PGx testing and lack of confidence by pharmacists and physicians with regards to recommending and ordering a PGx test, interpreting a PGx test result, and discussing a PGx test result was observed in this study. The lack of confidence and insufficient competence by pharmacists and physicians regarding PGx service provision was also reported in other studies carried out in the USA, Singapore, Kuwait (Koomer et al, 2011; McCullough et al, 2011; Chan et al, 2017; Albassam et al, 2018). Insufficient competence and confidence by pharmacists and physicians was reported as a potential barrier for the clinical implementation of PGx testing, possibly reflecting low adoption rate in practice (Klein et al, 2017; Vitek et al 2017).

A low adoption rate of PGx testing locally was observed in this study, since in the questionnaire only 11 physicians stated that they had ever ordered a PGx test. These physicians were practicing in Oncology (5), General Medicine (4) and Cardiology (2). Low adoption rates of routine PGx testing by physicians has also been reported in studies carried out in other countries (Stanek et al, 2013; Bannur et al, 2014; Taber and Dickinson, 2014; Bank et al, 2017; Just et al, 2017; Albassam et al, 2018; Arathy et al, 2019). Oncology is the therapeutic area where PGx testing is being practiced most locally as evidenced by the discussions with the Consultant Oncologists in the present study.

In PharmGKB the majority of oncology drugs have a 'Testing required' or Testing recommended' drug label annotation. These annotations reflect PGx information from official product labelling by the regulatory bodies. Differences in PGx information between FDA drug labels and EMA SmPCs for drugs used in malignancy were identified in this study. Inadequate harmonisation between regulatory bodies is a challenge for the clinical implementation of PGx and these findings point to the need for further discussion between regulatory bodies for continued regulatory harmonisation of the presence and quality of PGx information in official product labelling (Tan-Koi et al, 2018).

In this study, pharmacists more than physicians significantly agreed that PGx testing should be performed pre-emptively and should be implemented routinely in medication therapy management services to optimise clinical decision making ($p<0.05$). A pilot study where pre-emptive PGx testing, showed that pharmacists and physicians were able to document PGx test results and apply PGx information in practice to optimise clinical decision making (Van der Wouden et al, 2019).

Pharmacists and physicians participating in the study identified cost issues as a potential challenge for implementation of PGx testing, as was reported in numerous other studies (Rogausch et al, 2006; Woelderink et al, 2006; Dunbar et al, 2012; Powell et al, 2015; Shishko et al, 2015; Chan et al, 2017; Wu et al, 2017). Lack of PGx cost-effectiveness studies are also reported as a barrier in PGx implementation (Klein et al, 2017). In this study, pharmacists and physicians perceived cost-effectiveness studies relating to PGx testing as important, and this finding was also demonstrated in other studies (Dunbar et al, 2012; Chan et al, 2017).

With respect to ordering a PGx test, physicians in this study showed concern regarding the long turnaround time of obtaining a PGx test result which was also observed in other studies (Wu et al, 2017; Dong and Wiltshire 2017). Ways to overcome the barrier of lengthy turnaround time of PGx testing include the development of pre-emptive PGx testing programs including screening of a panel of gene variants which are kept in a patient's health record and are accessible to prescribers and through the use of and further development of rapid, point of care assays (Dunnenberger et al, 2015; Wirth et al, 2016; Klein et al, 2017).

The development of a guided-framework for pharmacists and physicians to overcome the lack of clear guidelines in PGx healthcare service provision has been suggested in various studies (McMahon et al, 2011; Haga et al, 2012b; Haga et al, 2012c; Tuteja et al, 2013; Peterson et al, 2016; St. Sauver, 2016; Van der Wouden et al, 2017; Wu et al, 2017). In this study, pharmacists and physicians agreed that a guided-framework should be devised to ensure consistency of procedures when ordering a PGx test to avoid liability issues, with significantly higher agreement by pharmacists compared to

physicians ($p<0.05$). This guided-framework would reflect whether the PGx service provision would be provided from community or a hospital-based entity.

HCP responsibilities in PGx testing service as perceived by pharmacists and physicians has been reported to be unclear (Fargher et al, 2007). Results from the perception questionnaire showed that pharmacists and physicians perceived the Consultant Physician, and the Genetic Specialist Physician among the higher ranked HCPs who should be responsible in different roles within PGx testing service provision. Such responsibilities include making a patient aware of PGx testing, accessing and interpreting PGx test results, discussing PGx test results with patients and taking action according to a PGx test result. Elewa et al (2015) reported that pharmacists significantly perceived themselves to be more appropriately responsible than physicians to apply PGx testing in drug therapy selection and dosing and should make the patients aware of relevant PGx testing according to drugs being prescribed.

Pharmacists and physicians in this study agreed that PGx test results should be available in health records for clinical evaluation by HCPs and were receptive towards electronic storage of PGx test results and automated interpretations of PGx test results using an electronic system. This finding has also been reported in various studies (Schnoll and Shields, 2011; Lam, 2013; Horgan et al, 2014; Elewa et al, 2015; Patel, 2016; Elliott et al, 2017; Klein et al, 2017; Lauschke et al, 2018; Liu et al, 2018). For successful implementation of PGx testing in the healthcare service, access to PGx test results by both the community and hospital HCPs should be granted. Automated systems will potentially facilitate PGx test result interpretation and actioning and would help to diminish HCPs concerns that PGx might increase complexity of healthcare delivery (Laerum et al, 2014; Overby et al, 2015; Nishimura et al, 2016).

4.6 Limitations of the study

Dissemination of the perception questionnaire, PGx tutorial and evaluation form mainly carried out through the respective social media groups. The response rate in this study was relatively low (14%), however low response rates (10-34%) have also been reported in other studies assessing perception of HCPs towards PGx testing out in other countries (Bannur et al, 2014; Petersen et al, 2014; Elewa et al, 2015; Nishimura et al, 2016; Bank et al, 2017; McCauley et al, 2017). This low response rate could be attributed to the reluctance of the HCPs to complete a questionnaire about an innovative and advancing topic without appropriate training and awareness of PGx.

The recorded PGx tutorial was not made available to all pharmacists and physicians since only the respective social media groups were used for dissemination.

Pharmacists and physicians in this study were asked to rate their own awareness and competence in PGx testing rather than carrying out a knowledge assessment test. This may have led to over or underestimation of the participants' awareness and competencies related to PGx resulting in self-reported bias. Use of Likert-scale questions in the questionnaire is another limitation as intervals between points on the scale do not present equal changes in attitude for all individuals.

Selection of individuals for the validation and reliability testing exercises by convenience sampling is another possible limitation.

4.7 Recommendations for further study

The data collected from the perception questionnaire could be developed as a discussion paper to be reviewed and discussed by stakeholders in a focus group and presented in the form of a white paper to devise a national multidisciplinary framework and guidelines for PGx clinical implementation. Data collected from the perception questionnaire should be supported by a review of the present status regarding PGx implementation in practice from international healthcare institutions.

An extensive review of the present status of PGx training in international curricula is recommended and followed-up by a study assessing the local perception of academic staff, students and HCPs regarding the preferred methods of teaching PGx and on the preferred topics to be integrated in undergraduate and postgraduate curricula.

The positive feedback obtained from the PGx tutorial, which was a pilot study, could serve as a stimulus for further study by disseminating PGx information and obtaining feedback from a larger sample size of pharmacists and physicians and using different methods. The impact of the suggested study can be measured by pre- and post-evaluation of the educational intervention implemented to assess improvement in knowledge and skills acquired by the participants and the impact of the intervention. Offering some form of certification or accreditation for attendance to such educational sessions is an initiative which may increase uptake.

Further study on methods to provide continued regular updates of PGx information to HCPs is recommended, including regarding the optimal interface preferred by HCPs, for example through developing an easily accessible and user-friendly application using digital devices.

The comparison of PGx information in FDA drug labels and EMA SmPCs and the present status of PGx testing in practice is recommended for other therapeutic areas and drug classes following differences observed between regulatory bodies for oncology drugs.

4.8 Conclusion

Findings from the perception questionnaire demonstrated that pharmacists and physicians in this study were aware of the term PGx testing, showed positive attitudes towards PGx testing and perceived PGx testing to be applicable to their practice. Insufficient competence was reported as a significant challenge and the need for further training on the topic was identified by the participants.

A PGx tutorial, reflecting findings from the perception questionnaire and including practical clinical case studies, was developed as an initiative to disseminate information on PGx to pharmacists and physicians locally as a contribution towards increasing awareness and to promote the clinical implementation of PGx. The tutorial was well-received since pharmacists and physicians agreed that the tutorial has potential to improve application of PGx theory to practice and enhance skills in PGx.

Differences in PGx information in official product labelling for oncology drugs points to the need for continued harmonisation in PGx information between the FDA and EMA for this class of drugs to improve PGx implementation.

Dissemination of study findings

Xuereb AM, Wirth F, Mifsud Buhagiar L, Serracino-Inglott A. Pharmacogenetic testing for drugs used in malignancy. Malta Medical Journal 2018;30(Suppl):129. (Discussed Poster Presentation, 10th Malta Medical School Conference, 29 November – 1 December 2018, Malta).

Xuereb AM, Wirth F, Serracino-Inglott A. Perception of hospital pharmacists towards pharmacogenetic testing. EJHP. 2019;26(Suppl1):A290. (Poster Presentation, 24th Congress of the European Association of Hospital Pharmacy, 27-29 March 2019, Barcelona, Spain).

Xuereb AM, Mifsud-Buhagiar L, Wirth F, Serracino-Inglott A. Awareness and attitudes of pharmacist and physicians towards pharmacogenetic testing. (Poster Presentation, 79th FIP World Congress of Pharmacy and Pharmaceutical Sciences 2019, 22-26 September 2019, Abu Dhabi, United Arab Emirates).

Xuereb AM, Mifsud-Buhagiar L, Wirth F, Serracino-Inglott A. An online approach to enhance awareness on pharmacogenetics among pharmacists and physicians. (Poster Presentation, ESCP International Symposium, 23-25 October 2019, Ljubljana, Slovenia).

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Appendices

Appendix 1: Studies which assessed the perception of pharmacists and physicians towards PGx testing

This appendix includes a compilation of 57 studies (2005-2019) which assessed perception of pharmacists and/or physicians on PGx testing. Most studies were carried out in the USA (n=29), followed by Europe (n=11), Asia (n=9), Africa (n=4), Australasia (n=2), and Canada (n=1), and one study included countries from multiple regions.

Table A1.1 Studies which assessed perception of PHARMACISTS towards PGx testing (n=18)

Reference (Country)	Number of pharmacists [% response rate]	Method of data collection	Outcome/s Measured	Key Findings
Koomer et al, 2011 (USA)	32 pharmacists [67%]	Online questionnaire	Perception of use of PGx information based on their practice setting. Education and training needs in PGx.	Confidence was low for hospital and non-hospital pharmacists. Hospital pharmacists were more informed about PGx compared to non-hospital pharmacists. Pharmacists indicated a low confidence rating which warrants need for more informative education and training in this field.
Madadi et al, 2011 (Nigeria)	5 pharmacists	Face-to-face interview using questionnaire	Knowledge and experience with PGx. Expectations about how a PGx testing service should be used. Capacity building for PGx service delivery.	Pharmacists aware of benefits of PGx. Cited hurdles to overcome before this field can become a routine part of patient care in their communities which included possible encroachment into individual's privacy need to be addressed because of its potential ethical implications

Reference (Country)	Number of pharmacists [% response rate]	Method of data collection	Outcome/s Measured	Key Findings
McCullough et al, 2011 (USA)	303 pharmacists [64%]	Online questionnaire	Perception of knowledge and confidence of inpatient and outpatient pharmacists	Pharmacists perceived the importance of PGx knowledge to the profession, but lack of knowledge and self-confidence to act on the PGx test results was reported.
McMahon et al, 2011 (Australia)	291 pharmacists [36%]	Mail questionnaire	Perception of the pharmacists' understanding of PGx, their capacity of patient counselling, their belief of impact on the profession and preference of education about PGx	Further research across the pharmacy profession on the issue of preparedness for the implementation of PGx into the healthcare system and everyday practice is needed. Participants suggested that PGx education should be delivered during tertiary studies, as seminars and workshops forming part of their CPE.
Benzeroual et al, 2012 (USA)	102 pharmacists [32%]	Mail questionnaire	Assessment of knowledge and confidence in PGx concepts	Development of an educational program CPE or certificate is needed for the improvement of pharmacists' education and training, confidence in PGx testing.

Reference (Country)	Number of pharmacists [% response rate]	Method of data collection	Outcome/s Measured	Key Findings
De Denus et al, 2013 (Canada)	284 pharmacists	Online questionnaire	Perception of PGx (opinions, expectations, concerns)	Pharmacists were hopeful towards PGx testing, willing to integrate the tests in clinical practice and required further education to ensure optimal patient care
Jamie, 2013 (UK)	39 pharmacists	Face- to-face and telephone interviews	Educational challenges around implementing PGx into pharmacy education	A knowledge gap was identified between newly graduated pharmacists who were literate in genetics and more experienced pharmacists who have decreased genetics training in professional development. The difference in knowledge between generations could have an impact on the quality and consistency of patient advice. Pharmacists have a major role in the PGx testing service delivery in the future.
Tuteja et al, 2013 (USA)	580 pharmacists [10.3%]	Online questionnaire	Attitudes towards PGx testing including clinical utility, ethical, social, legal, practical implications.	Positive attitudes towards PGx was shown by the pharmacists, 87% perceived that it would decrease ADR and optimize drug dosing. 57% of participants perceived that it was their role for patient counselling regarding PGx information. 65% believed that PGx test results may be misused to have effect on health insurance coverage hence pharmacist education about legal protections is needed.

Reference (Country)	Number of pharmacists [% response rate]	Method of data collection	Outcome/s Measured	Key Findings
Alexander et al, 2014 (USA)	101 pharmacists [24.3%]	Questionnaire (fax-based or online-depending on availability of email)	Perception of pharmacists implementing personalised medicine services, perceived readiness to provide service and barrier to implementation	Interest in incorporating personalised medicine services into the community pharmacy practice but require further education. Initiatives should focus on development of comprehensive education programs to further train pharmacists for provision of personalised medicine services.
Kisor et al, 2015 (USA)	20 pharmacists	Pre- and post-program questionnaire	Evaluation of PGx certificate training program relative to competencies in basic genetic concepts, genetics and disease, PGx and ethical/legal and social implications	Increased self-understanding of defined PGx competencies was achieved following self-study and a live, interactive component in the certificate training program. Electronic-based platforms may serve to increase pharmacists PGx education hence increase the uptake of PGx in clinical practice.
Obara et al, 2015 (Japan)	268 pharmacists [72%]	Mail questionnaire	Awareness of PGx in general	16.8% were aware of the clinical application of PGx tests in Japan. <1% of pharmacists indicated ability to query regarding prescriptions based on patients' PGx information. 61.2% of participants indicated that PGx tests were preferred to predict efficacy or ADR of a drug. Action is needed to improve pharmacists' awareness of PGx and ensure pharmacists' ability to provide appropriate PGx service provision
Shishko et al, 2015 (Abu Dhabi, Canada, Indonesia, Singapore, USA)	91 pharmacists (psychiatric pharmacists) [0.09%]	Online questionnaire	Evaluation of psychiatric pharmacists' use, knowledge, perception of effectiveness of PGx testing	The use of PGx is underappreciated due to lack of availability and understanding of PGx testing among psychiatric pharmacists. Greatest limiting factors for using PGx testing includes that lack of education about its use practice and concerns were raised about potential cost of testing considering the lack of allocated funding to PGx

Reference (Country)	Number of pharmacists [% response rate]	Method of data collection	Outcome/s Measured	Key Findings
Aleijalat et al, 2016 (Jordan)	128 pharmacists	Face-to-face questionnaire	Assessment of knowledge, opinions, expectations and concerns toward PGx among pharmacists	Positive attitudes of pharmacists toward PGx, but general knowledge was relatively low. Updated educational system is needed
Romagnoli et al, 2016 (USA)	14 pharmacists	Interview and observations of pharmacists in their working environment	The PGx information needs and resource requirements of pharmacists.	Pharmacists anticipate an emerging role for PGx application in their practice. The participants reflected about the challenge of finding PGx information quickly in FDA product labels and value information on the drug label to be trustworthy. It was observed that information is needed about clinically relevant guidelines, genotype-specific dosing.
Bank et al, 2017 (Netherlands)	667 pharmacists [18.8%]	Online questionnaire	Perception of PGx with a focus on the effects of awareness of the Dutch PGx Working Group (DPWG) guidelines	99.7% of pharmacists believed in the concept of PGx. 14.7% of participants only had ordered a PGx test in the previous 6 months. Only 14.1% of participants felt adequately informed and 88.8% would like to receive further training on PGx. It was observed that being aware of the DPWG had no significant effect on knowledge or adoption of PGx
Muzoriana et al, 2017 (Zimbabwe)	86 Pharmacists	Questionnaire disseminated at continuing education meeting and online questionnaire.	Knowledge, attitude, perceptions about PGx	Positive attitudes towards PGx was reported and would support PGx application to improve treatments. Concerns about privacy and discrimination by respondents when data is misused by those who have a lack of understanding of the subject. Respondents agreed that they would play a leading role in PGx testing if provided with appropriate training.

Reference (Country)	Number of pharmacists [% response rate]	Method of data collection	Outcome/s Measured	Key Findings
Perwitasari et al, 2017 (Indonesia)	118 pharmacists (84 hospital pharmacists and 24 community pharmacists)	Face-to-face Interview using a questionnaire	Knowledge, awareness, attitudes of pharmacists practicing in hospital and community settings	Knowledge and awareness of pharmacists towards PGx are good. Attitude towards PGx testing between community and hospital pharmacists were significantly different. Score for knowledge, awareness and attitude in community setting are higher than the score of those in hospital settings

Table A1.2: Studies which assessed perception of PHYSICIANS towards PGx testing (n=29)

Reference (Country)	Number of physicians [% response rate]	Method of data collection	Outcome/s Measured	Key Findings
Moutel et al, 2005 (France)	11 physicians	Face-to-face interviews	Perception in relation to PGx testing for HIV-treated patients	Test results need to be communicated to patients by physicians with knowledge of how to interpret the results and how to explain the significance of the results on clinical care. More training for physicians to deliver genetic results to patients is required.
Rogausch et al, 2006 (Germany)	106 physicians (general practitioners) [28%]	Telephone Interviews using a questionnaire	Perception of PGx testing in asthma	PGx testing facilitates choice of drug in asthma patients. PGx test would be recommended by GPs prior to prescription of drug if cost of testing is covered by health insurance. Patients might be disadvantaged if PGx information is used by employers or insurance agencies. GPs in agreement to recommend patients to participate in PGx research studies.
Woelderink et al, 2006 (Germany, UK, Netherlands, Ireland)	111 physicians [27%]	Online questionnaire	Practice of PGx testing in TPMT and HER2	Respondents reported that communication with laboratory and the capacity of the testing laboratory are not always sufficient leading to problems in testing when sending samples. Cost of test are perceived to be high. The participants perceived the clinical utility of the tests as high, particularly for HER2. Lack of specialised education of the physicians could be interfering with the clinical use of PGx.

Reference (Country)	Number of physicians [% response rate]	Method of data collection	Outcome/s Measured	Key Findings
Hoop et al, 2010 (USA)	75 physicians (psychiatrists) [37%]	Online questionnaire	Attitudes and practice of psychiatrists where PGx testing is clinically available	Endorsement of the clinical utility of PGx testing but lack of consensus was shown on safeguards other than the patients' and risks
Dunbar et al, 2012 (New Zealand)	33 physicians	Face-to-face interview or telephone interview using questionnaire	Clinician experiences of employing the AmpliChip® CYP450 test in psychiatric practice	PGx testing supported drug dosing decisions. PGx testing and PGx test results were perceived as potentially useful in developing relationships with patients. Reported limitations include potential over-reliance at the expense of clinical expertise, cost, challenges inherent in introduction of a new clinical procedure into routine practice. Psychiatric physicians were willing to employ PGx testing as a clinical decision aid if its implementation is justified economically.
Haga et al, 2012a (USA)	597 physicians (Primary care physicians) [15%]	Mail questionnaire	Knowledge, attitudes, familiarity toward PGx testing in order to identify barriers	PCPs envisioned a major role for themselves in PGx testing service provision. The lack of adequate knowledge and experience is recognised by the PCPs.
Haga et al, 2012b (USA)	222 physicians (clinical geneticists) [30%]	Online questionnaire, Mail questionnaire, Fax questionnaire	Attitudes, preparedness, perception of role of clinical geneticists in PGx testing	Almost all respondents had some education on PGx, 58% indicated that they felt well informed about PGx testing. 46% felt they would play 'some' role in PGx service provision. The role of clinical geneticists is unclear; however, their experience may aid in preparation of PGx testing and informing service delivery strategies into clinical practice

Reference (Country)	Number of physicians [% response rate]	Method of data collection	Outcome/s Measured	Key Findings
Haga et al, 2012c (USA)	12 physicians (4 family medicine, 5 internal medicine, 3 medical geneticists)	Focus group	Perception of PGx testing and management of ancillary findings	Interest in use of PGx testing was reported however concerns were raised about the lack of evidence of clinical utility and the physicians' ability to interpret and communicate information about risk of ancillary disease. The appropriate use of PGx testing would be facilitated by availability of educational resources, access to genetic specialists and clear guidelines about the use of PGx testing.
Hunt et al, 2013 (USA)	58 physicians (primary care physicians)	Face-to-face Interview	Practice of PGx concepts in primary care	Innovation in PGx has not led to personalised treatment but rather the use of essentialized/racial ethnic identity as a proxy for genetic heritage was encouraged. Concern was raised on how PGx innovations will affect diverse populations.
Peppercorn et al, 2013 (USA)	201 physicians (oncologists) [44%]	Mail questionnaire	Knowledge, attitudes, practice of PGx testing of CYP2D6 of tamoxifen in breast cancer	A minority of oncologists reported the routine use of CYP2D6 and were willing to change treatment based on PGx test results. The clinicians and public need to be educated about the uncertainty of benefits from commercially available genetic tests in clinical practice when there is still emerging evidence from ongoing trials.
Selkirk et al, 2013 (USA)	260 physicians [13%]	Online questionnaire	Preparedness for incorporation of PGx testing into practice by determining knowledge, experience, comfort level, barriers, practice expectations and educational needs	Physicians were underprepared for the clinical application of PGx since they perceive insufficient knowledge and confidence. Physicians expected their role in PGx to develop. The importance of enhancing policies and initiatives to increase physician knowledge and comfort level in PGx was reported.

Reference (Country)	Number of physicians [% response rate]	Method of data collection	Outcome/s Measured	Key Findings
Stanek et al, 2013 (USA)	10,303 [3%] physicians	Fax-based questionnaire	Proportion of US-based physicians who obtain PGx testing information from drug labelling Knowledge, attitudes, practice of PGx	39% of respondents obtained PGx information from drug labelling especially if respondents have postgraduate instruction, make use of other information sources, regulatory approval/ recommendation of PGx testing, reliance on labelling for information and perception that patients have benefited from testing. Physicians used PGx testing information from drug labelling, highlighting importance of labelling information that is conducive to practice application
Dressler et al, 2014 (USA)	94 physicians (oncologists)	Mail Questionnaire	Physician experience and factors influencing adoption of cancer PGx testing	98% of participants perceived good promise in using PGx in their practice, 33% were comfortable with their knowledge, 37% were comfortable to interpret test results. Interest in additional PGx education is reported. Accurate and updated cancer PGx information needs to be disseminated.
Laerum et al, 2014 (Norway)	9 physicians	Online questionnaire, Non-structured interview	Attitudes towards prototype of automated interpretation of PGx test for immunosuppressive treatment during kidney transplantation	Participants were positive about PGx testing and incorporation to their clinical practice. With respect to the interpretive algorithm prototype for PGx test results it was preferred by the participants to see the results and recommendations first, then the explanations and references.
Petersen et al, 2014 (USA)	104 physicians [9.7%]	Online Questionnaire	Key elements/tools and potential barriers to personalised medicine in connections with their perceptions of the availability of the latter across subpopulations	Differing views of physicians about PGx availability and implementation. Complex relationships between race/ethnicity and personalised medicine were established leading to serious implications affecting its clinical success.

Reference (Country)	Number of physicians [% response rate]	Method of data collection	Outcome/s Measured	Key Findings
Taber and Dickinson, 2014 (USA)	300 physicians (PCPs, cardiologists, psychiatrists)	Online Questionnaire	Knowledge deficit and educational resource needs of PGx	Physicians demonstrate PGx knowledge gaps, and uncertainty about application of PGx testing in clinical practice is reported. Clinically oriented PGx related information resources which are easily accessible are preferred by physicians, and may best support appropriate clinical implementation of PGx
Overby et al, 2015 (USA)	22 physicians	Pre- experiment questionnaire, Experimental questionnaire instruments, post-experiment questionnaire	Communication effectiveness and clinical impact of using a prototype clinical decision support system (CDSS) embedded in an electronic health record to deliver PGx information to physicians	83% of physicians saw relative advantage to using PGx CDSS at the initiation of the study compared to 94% at conclusion of study. Semi-active alerts were used 74-88% of the time. No association was noted between previous experience with, awareness of and belief in relative advantage of using PGx CDSS and improved uptake. The prototype needs to be improved such that the PGx CDSS content is more useful and shown in a way that physicians' confidence in prescribing decisions is improved.
Powell et al, 2015 (UK)	83 physicians (neurologists)	Online questionnaire	Preferences of clinicians to inform carbamazepine PGx services.	Less expensive PGx tests were given preference, but decreased turnaround time did not have significant influence on the probability of requesting a PGx test.
Thompson et al, 2015 (USA)	113 physicians (psychiatrists)	Online and paper questionnaire	Attitudes of psychiatrists, on the benefit of PGx data, direct to consumer genetic testing and genetic counselling	94.6% of participants indicated the usefulness of genetic data to make pharmaceutical decisions and 86% perceived that that PGx testing would be used as a standard. 55.8% respondents would refer patient to direct to consumer genetic testing. 72.6% perceive the inclusion of genetic counsellors in psychiatric patient care to be beneficial.

Reference (Country)	Number of physicians [% response rate]	Method of data collection	Outcome/s Measured	Key Findings
Peterson et al, 2016 (USA)	80 Physicians (cardiologists, endocrinologists) [52%]	Online questionnaire	Attitudes towards large-scale PGx implementation program	99% agreed that PGx variants influence patients' response to drug therapy. 92% favoured immediate active notification if a significant interaction was present. Clinicians perceptions were divided on which HCP is responsible for acting on a result when a prescription change was indicated and whether patients should be directly notified of a significant result.
Nishimura et al, 2016 (USA)	52 Physicians [11%]	Online simulation and questionnaire	Attitudes towards usefulness of clinical decision support alerts for PGx drug gene interactions	PGx alerts would be accepted by participants, if built using minimalistic design and placed at the end of the prescribing process. Careful selection of educational resources present in the alert and written concisely due to limited time during prescribing.
St. Sauver et al, 2016 (USA)	90 physicians [57%]	Online questionnaire	Perception on the implementation and use of PGx testing in clinical practice	Physicians reported lack of confidence with PGx data being integrated into primary care. Clinician satisfaction may be improved by refining electronic PGx Clinical Decision Support alerts to ensure usefulness and friendliness of using system
Heale et al, 2017 (USA)	6 physicians	Pre-study questionnaire, observation, post-study questionnaire, post-study interview	Information needs and information-seeking behaviour, in order to guide the design of PGx information resources	Dispersion of content to support information needs makes it uneasy to come across. Information needs included: description of test interpretations which are clinically relevant, molecular description for the clinical effect of drug variation, information on the logistics of carrying out a PGx test (cost, availability, turn-around time, insurance coverage, accessibility of expert support

Reference (Country)	Number of physicians [% response rate]	Method of data collection	Outcome/s Measured	Key Findings
McCauley et al, 2017 (USA)	155 physicians [1%]	Online questionnaire, follow-up telephone interview	Knowledge, experience, attitudes and perceptions of PGx testing.	PGx testing is becoming part of personalised medical care however educational gaps and understanding is present. Further studies should be done to examine ways on how this could be improved especially with primary care providers.
Vinothini et al, 2017 (India)	Physicians	Questionnaire	Knowledge, attitude and practice of PGx among clinicians	Wide gap between knowledge and practice which highlighted the perceived need to include PGx in the medical curriculum
Wu et al, 2017 (USA)	10 Physicians (Oncologists)	Telephone interview with predesigned questions	Experiences and views of PGx test access and strategies used for test access in oncology.	Accessibility of test is made challenging by the process of ordering PGx test which is time consuming. Affordability was perceived as a barrier to some patients who noted that the cost of PGx tests and medications is high. Acceptability of test was high as providers since they are viewed positively
Owusu Obeng et al, 2018 (USA)	285 physicians	Administered in person or online questionnaire	Perceptions towards clinical utility of data and their preparedness to integrate it in practice	Physicians perceived themselves to be unprepared to use PGx information in their practice and development of effective PGx clinical tools and training strategies should be considered
Arathy et al, 2019 (India)	100 physicians	Self-administered questionnaire	Knowledge of PGx, test ordering, current and ideal PGx source	Use of PGx testing in practice is low. There is need for improved electronic resource material to increase clinical application.

Table A1.3: Studies which assessed perception of PHARMACISTS and PHYSICIANS towards PGx testing (n=10)

Reference (Country)	Number of pharmacists/ physicians [% response rate]	Method of data collection	Outcome/s Measured	Key Findings
Fargher et al, 2007 (UK)	17 pharmacists and physicians	Focus group	Attitudes towards PGx testing services and their future development	Observations of lack of knowledge and reluctance for delivery of PGx services. The need for improved education and training of pharmacists and physicians in PGx is highlighted.
Payne et al, 2011 (UK)	125 physicians (84 hospital doctors, 31 general practitioners), 10 pharmacists	Mail questionnaire	Preferences of key attributes of a PGx testing service in use of Azathioprine	Concern that general practitioners have insufficient knowledge and confidence to explain PGx test results to patients and give advice on modification of azathioprine dose. Participants were willing to wait 2.2 days for a PGx test result for a 1% improvement in test predictive accuracy.
Bannur et al, 2014 (Malaysia)	324 pharmacists 179 physicians [33.5%]	Online questionnaire	Attitude, knowledge, adoption of PGx in practice.	Low clinical application of PGx in practice was reported but high future adoption is envisaged. HCPs reported benefits of using PGx in the clinical scenario. Poor to fair knowledge on PGx was observed. There is increased interest in education and CPE programs are preferred.
Elewa et al, 2015 (Qatar)	202 pharmacists and physicians (108 pharmacists, 94 physicians) [20%]	Online-based questionnaire	Awareness and attitudes of pharmacists compared with doctors towards PGx and its implications	Despite low awareness of PGx, positive attitudes were observed by both pharmacists and physicians towards the clinical implications of PGx. Motivation to learn about PGx and willingness to take initiatives in its clinical application and patient education was observed more by pharmacists.
Kudzi et al, 2015 (Ghana)	29 pharmacists, 42 physicians	Face-to-face interview using questionnaire	Assessment of PGx knowledge	60% of HCPs rated their knowledge of PGx as good. The need for CPE on PGx and development of competency standards for all HCPs in Ghana was observed.

Reference (Country)	Number of pharmacists/ physicians [% response rate]	Method of data collection	Outcome/s Measured	Key Findings
Abdilla, 2016 (Malta)	28 physicians, 51 pharmacists	Online questionnaire	Familiarity, views, knowledge and attitudes toward PGx testing	66% of respondents were aware of PGx. Only 10% of respondents knew about patients who have undergone a PGx test of which only 4% of respondents being directly involved in the management of such treatment.
Abdela et al, 2017 (Ethiopia)	72 physicians, 70 pharmacists	Face-to-face interview using questionnaire	Knowledge, attitudes, interests towards PGx	Participants showed limited knowledge and had positive attitude towards PGx. The needed for educational programs focusing on PGx testing and its clinical application
Chan et al, 2017 (Singapore)	167 Physicians [48%], 27 pharmacists [69%] (both physicians and pharmacists practicing in psychiatry)	Online questionnaire	Perception of PGx use in psychiatry.	81% of participants believed that PGx testing would be useful for identifying optimal drug therapy, while 71% believed that it would be useful for medication intolerance. 46.4% of respondents felt competent to order PGx tests, concern about cost was raised by 94.3% of respondents, concern was raised by 84.5% of respondents about the unavailability of clear guidelines, 98.5% of respondents were keen on training about the applicability of PGx, 44.5% of respondents preferred further education in the format of a lecture.
Just et al, 2017 (Austria, Great Britain, Greece, Italy, Netherlands, Slovenia, Spain)	53 Physicians, 11 pharmacists	Online Questionnaire	Current educational background in the context of the European PGx implementation project	General positive attitudes and interest towards PGx testing. Grade of own experience and knowledge about application and interpretation of PGx caused uncertainty. Education and training programmes may be helpful for implementation of PGx at a homogenous level within Europe.

Reference (Country)	Number of pharmacists/ physicians [% response rate]	Method of data collection	Outcome/s Measured	Key Findings
Albassam et al, 2018 (Kuwait)	238 pharmacists, 379 physicians [98.1%]	Self-administered questionnaire	Knowledge, perceptions and confidence, preferred learning format for their future education and identify the barriers to its application in practice settings	Low mean knowledge score and low confidence in clinical application of PGx was observed. Positive perception was reported more common in pharmacists than physicians. Barriers to implementation included lack of education and training in PGx, lack of PGx clinical guidelines.

Appendix 2: Validation tool and validation results of perception questionnaire

Questionnaire Validation

Introduction and Instructions

You are invited to participate in the **validation** of a questionnaire titled **'Social and Scientific Implications of Pharmacogenetic Testing'** developed as part of a research project being undertaken by Doctorate in Pharmacy student Althea Marie Xuereb.

You are requested to:
Complete the following **validation tool** to rate the **relevance**, **importance** and **comprehensibility** of each question and the **layout** of the questionnaire, on a Likert scale of 1 to 5.
Your feedback will be considered to revise the questionnaire.

QUESTION NUMBER	RELEVANCE	IMPORTANCE	COMPREHENSIBILITY
	Rate each question from 1 to 5, 5 corresponds to 'very relevant'	*Rate each question from 1 to 5, 5 corresponds to 'very important'*	*Rate each question from 1 to 5, 5 corresponds to 'very comprehensible'*
Part A			
1			
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3			
4			
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6a			
6b			
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15			
16a			
16b			
17			
18			
19			

QUESTION NUMBER	RELEVANCE	IMPORTANCE	COMPREHENSIBILITY
	Rate each question from 1 to 5, 5 corresponds to 'very relevant'	*Rate each question from 1 to 5, 5 corresponds to 'very important'*	*Rate each question from 1 to 5, 5 corresponds to 'very comprehensible'*
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QUESTION NUMBER	RELEVANCE	IMPORTANCE	COMPREHENSIBILITY
	Rate each question from 1 to 5, 5 corresponds to 'very relevant'	*Rate each question from 1 to 5, 5 corresponds to 'very important'*	*Rate each question from 1 to 5, 5 corresponds to 'very comprehensible'*
56			
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58			
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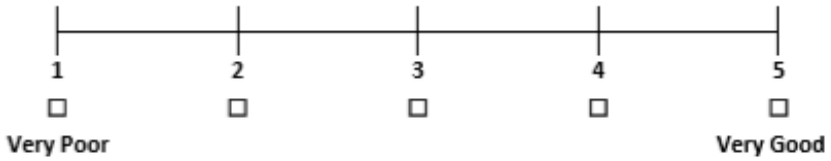
For questions rated as 3 or less, kindly indicate reason/s and recommendation/s in the comments section on page 4 of this validation tool.

Rate the LAYOUT of the questionnaire:



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Comments and recommendations (particularly for questions rated as 3 or less):

Question No.	Comments/recommendations

Thank you

Table A2.1 Validation of perception questionnaire results -Round 1

	Mean rating score (out of 5)		
Question Number	**Relevance**	**Importance**	**Comprehensibility**
1	4.00	**3.89**	4.89
2	4.56	4.44	4.89
3	4.78	4.67	4.78
4	4.67	4.56	4.89
5	**3.78**	**3.67**	4.78
6a	4.33	4.67	5.00
6b	4.56	4.67	4.89
7	4.67	4.56	4.67
8	4.67	4.56	4.67
9	4.78	4.67	4.67
10	4.67	4.56	4.67
11	4.78	4.44	4.78
12	4.67	4.44	4.89
13	4.78	4.78	4.89
14	4.89	4.67	4.89
15	5.00	4.67	4.89
16a	4.67	4.56	4.78
16b	4.67	4.44	4.67
17	4.67	4.67	4.89
18	4.67	4.67	4.78
19	4.78	4.78	4.89
20	4.67	4.67	4.78
21	4.67	4.67	4.78
22	4.56	4.56	4.78
23	4.67	4.67	4.67
24	4.78	4.67	4.56
25	4.56	4.67	4.67
26	4.44	4.56	4.56
28	4.67	4.78	4.78
29	4.56	4.44	4.56
30	4.00	4.22	4.33
31	4.56	4.67	4.78
32	4.67	4.78	4.78
33	4.67	4.78	4.78
34	4.67	4.78	4.78
35	4.67	4.78	4.78
36	4.67	4.78	4.78
37	4.67	4.78	4.78
38a	4.78	4.56	4.89
38b	4.71	4.71	4.86
39	4.22	4.22	4.56

	Mean rating score (out of 5)		
Question Number	**Relevance**	**Importance**	**Comprehensibility**
40	4.67	4.67	4.89
41	4.67	4.67	4.89
42	4.67	4.67	4.67
43	4.67	4.67	4.78
44	4.67	4.78	4.67
45	4.78	4.78	4.78
46	4.78	4.78	4.67
47	4.78	4.78	4.78
48	4.44	4.56	4.44
49	4.78	4.78	4.56
50	4.56	4.56	4.78
51	4.67	4.44	4.78
52	4.67	4.67	4.78
53	4.67	4.56	4.78
54	4.78	4.78	4.78
55	4.56	4.44	4.78
56	4.67	4.67	4.78
57	4.44	4.67	4.78
58	4.67	4.67	4.78
59	4.67	4.67	4.78
60	4.78	4.78	4.67
61	4.67	4.56	4.78
62	4.78	4.67	4.78
63	4.56	4.56	4.22
64	4.44	4.67	4.56
65	4.44	4.67	4.44
66	4.44	4.67	4.56
67	4.56	4.78	4.67
68	4.44	4.67	4.44
69	5.00	4.89	4.89
70	5.00	4.78	4.89
71	5.00	4.78	4.89
72	5.00	4.78	4.89
73	4.89	4.78	4.56
74	4.89	4.78	4.89
75	5.00	4.89	4.89
76	5.00	4.89	4.78

Layout of questionnaire mean rating score =4.56

Table A2.2 Suggested modifications by validation panel in round 1 of validation and action taken

Question Number	Original question/statement	Action taken
5	'Location of practice' (district area of practice) was deemed irrelevant for purpose of this study	The question was removed from the questionnaire as was suggested by the panel; question was replaced with a new question (refer to 'new questions' below)
6a	'Have you heard of the term *pharmacogenetic testing* prior to **working** on this questionnaire?'	Modified wording to: 'Have you heard of the term *pharmacogenetic testing* prior to **answering** this questionnaire?'
9	'I am aware of **medications with pharmacogenetic implications**'	Modified wording to: 'I am aware of **drugs for which pharmacogenetic testing is required or recommended**'
11	'**I know** when to recommend pharmacogenetic testing **to patients**'	Modified wording to: '**I am aware of when to recommend a pharmacogenetic test when indicated'**
12	'**I know** how to interpret pharmacogenetic test results'	Modified wording to: '**I am aware of** how to interpret pharmacogenetic test results'
15	'I require ***(more)*** education on pharmacogenetic testing'	Modified to: 'I require *more* education on pharmacogenetic testing'
18b	'**Preference for following** the selected learning activities in question 18a:'	'**How would you prefer to follow** the selected learning activities in question 18a:'

Question Number	Original question/statement	Action taken
31	'Pharmacogenetic testing results **should be accessible and** shared with family members'	Modified wording to: 'Pharmacogenetic testing results **should be** shared with family members'
39	Drug class description: 'Nucleoside reverse transcriptase inhibitors'	Modified wording to: 'Drugs used in HIV'
66	'Genetic stratification should be applied in pharmacogenetic research studies to help design **therapeutic agents targeting** specific groups of patients e.g. non-responders to treatment'	Modified wording to: 'Genetic stratification should be applied in pharmacogenetic research studies to help design **drugs which target** specific group of patients e.g. non-responders to treatment'
69-73	'Please answer the following questions by marking the respective healthcare professionals in order of **importance; 1 (most important) up to 7 (least important), the same number may be repeated if of equal importance.'**	Modified wording to: 'Please answer the following questions by marking the respective healthcare professionals in order of **who should be responsible; 1 (least responsible) up to 7 (most responsible)**
	Healthcare professional label: i) 'Physician' ii) 'Clinical Geneticist' iii) 'Other'	Modified wording to: i)'Physician***'-'*-including: Basic Specialist Trainee, Higher Specialist Trainee, Resident Specialist, Specialist in Family Medicine** – *added * to heading which lead to a description below the table to be more specific of what is meant by 'physician'* ii) '**Genetics Specialist Physician'** iii) '**Nurse'**-*heading was changed to be more specific and preferred over 'other'*

Table A2.3 New questions suggested by the validation panel in round 1 of validation.

Question Number	New questions included for round 2 of validation
5	‘Highest academic level’ □ Undergraduate □ Postgraduate (□ Master □ Doctorate)
13	‘I am aware of drugs for which pharmacogenetic testing is performed locally’ – to be rated on a Likert-scale of 1 (not at all aware) to 5 (extremely aware)
14	‘I believe I am competent in the area of pharmacogenetic testing’- to be rated on a Likert-scale of 1 (strongly disagree) to 5 (strongly agree)
18c	‘Which topic/s would you like to follow during the selected learning activities in 18a? *(You may select* more than one *option)* □ Basic principles of genetics □ Effects of genetics on drug pharmacokinetics/pharmacodynamics □ Pharmacogenetic testing implications in different therapeutic areas □ Availability of pharmacogenetic tests □ Interpretation of a pharmacogenetic test □ Ethical issues □ Other (please specify_____)
67	‘Pharmacogenetic testing should be included as a risk minimisation measure in the safety section of the dossier i.e. in post-authorisation safety/efficacy studies
68	The Summary of Product Characteristics should include pharmacogenetic testing when applicable

Table A2.4 Validation of perception questionnaire results -Round 2

New questions:

	Mean rating score (out of 5)		
Question Number	**Relevance**	**Importance**	**Comprehensibility**
5	4.56	4.56	4.44
13	4.78	4.78	4.78
14	4.78	4.89	4.67
18c	4.89	4.78	4.78
67	4.78	4.67	4.56
68	4.67	4.78	4.67

Modified questions:

Question Number	**Comprehensibility** mean score (out of 5)
6a	4.89
7	4.89
8	4.78
9	4.89
10	4.67
11	4.33
12	4.78
15	4.89
18b	4.89
31	4.56
39	4.67
66	4.67
69	4.67
70	4.78
71	4.78
72	4.78
73	4.78

Appendix 3: Ethics approval

L-Università ta' Malta

Faculty of
Medicine & Surgery
University of Malta
Msida MSD 2080, Malta

Tel: +356 2340 1879/1891/1167
umms@um.edu.mt

www.um.edu.mt/ms

Ref No: **FRECMDS_1718_066**

Monday 27th July 2018

Ms. Althea Marie Xuereb
96, Kavatina
Triq l-Imriekeb
M'Scala MSK3534

Dear Ms. Xuereb

Please refer to your application submitted to the Research Ethics Committee in connection with your research entitled:

Social and scientific implications of Pharmacogenetic testing

The Faculty Research Ethics Committee granted ethical approval for the above mentioned protocol.

Yours sincerely,

Dr. Mario Vassallo
Chairman
Research Ethics Committee

Appendix 4: Final version of perception questionnaire

Social and Scientific Implications of Pharmacogenetic Testing

Althea Marie Xuereb

Pharm D Student

Department of Pharmacy, University of Malta

Introduction and Instructions

Dear Participant,

You are invited to participate in a research project entitled 'Social and Scientific Implications of Pharmacogenetic Testing'. This research is being conducted by Althea Marie Xuereb as part of the Doctorate in Pharmacy at the Department of Pharmacy, University of Malta, under the supervision of Professor Anthony Serracino-Inglott and Dr Francesca Wirth.

The questionnaire developed aims to assess awareness, education aspects, attitudes and practice of pharmacogenetic testing among physicians and pharmacists in Malta.

ALL pharmacists are eligible to participate.

Physicians eligible to participate include those practicing in: FAMILY MEDICINE, GENERAL MEDICINE, ONCOLOGY, CARDIOVASCULAR, NEUROLOGY, PSYCHIATRY and INFECTIOUS DISEASE.

You are invited to complete the attached anonymous, self-administered questionnaire. Questionnaire responses will only be accessed by research team members. The questionnaire should be completed without resorting to reference material.Participation is voluntary and the estimated time of completion is 25 minutes.

Should you have any queries kindly contact the researcher Althea Marie Xuereb:
Email: althea.m.xuereb.11@um.edu.mt
Contact number: 79920801

Thank you very much for your participation

1

'Pharmacogenetics' is the study of how genetic variation can influence a patient's response to a drug with respect to therapeutic and adverse effects.

'Pharmacogenetic testing' refers to a type of laboratory investigation of a patient's genetic make-up to predict risk of experiencing an adverse effect to a drug and/or likelihood to respond to a given drug, hence informing individualised drug selection and dosing.

For each question please select one option unless you are instructed that you may select more than one option.

SECTION 1: PARTICIPANT DEMOGRAPHICS

1. **Gender** ☐ Male ☐ Female ☐ Other
2. **Age** (years) ☐ 21-35 ☐ 36-45 ☐ 46-55 ☐ 56-69 ☐ 70+
3. **Profession**

☐ **Pharmacist** Area of Practice ☐ Community ☐ Academia ☐ Hospital ☐ Industry ☐ Regulatory ☐ Other (*Please specify* _____)
☐ **Basic Specialist Trainee** Area of Specialisation (*Please specify* _____)
☐ **Higher Specialist Trainee/ Resident Specialist** Area of Specialisation (*Please specify* _____)
☐ **Consultant** Area of Specialisation (*Please specify* _____)
☐ **Specialist in Family Medicine**

4. **Years of practice** ☐ <2 ☐ 2-5 ☐ 6-10 ☐ > 10
5. **Highest academic level**

☐ **Undergraduate** (*Please specify* _____)
☐ **Postgraduate** ☐ Master (Please specify_____) ☐ Doctorate (Please specify_____)

SECTION 2: AWARENESS OF PHARMACOGENETIC TESTING

6. **a) Have you heard of the term 'pharmacogenetic testing' prior to answering this questionnaire?**

☐ Yes *(Go to question 6b)* ☐ No *(Go to question 7)*

b) If Yes, where did you hear it from?

(You may select **more than one** *option)*

☐ Undergraduate studies ☐ Journal Article

☐ Postgraduate studies ☐ Workplace

☐ Conference ☐ Internet

☐ Other (*please specify*:_____)

On a Likert scale of 1 *(not at all aware)* to 5 *(extremely aware)*, rate each of the following statements by marking with an 'X' in the appropriate box.

No.	Statement	1 not at all aware	2 slightly aware	3 somewhat aware	4 moderately aware	5 extremely aware
Awareness *I am aware of…*						
7.	potential advantages of pharmacogenetic testing					
8.	potential limitations of pharmacogenetic testing					
9.	drugs for which pharmacogenetic testing is required or recommended					
10.	availability of information sources regarding drugs with pharmacogenetic implications					
11.	when to recommend a pharmacogenetic test when indicated					
12.	how to interpret pharmacogenetic test results					
13.	drugs for which pharmacogenetic testing is performed locally					

SECTION 3: EDUCATION AND TRAINING ON PHARMACOGENETIC TESTING

On a Likert scale of 1 *(strongly disagree)* to 5 *(strongly agree)*, rate each of the following statements by marking with an 'X' in the appropriate box.

No.	Statement	1 strongly disagree	2 disagree	3 neutral	4 agree	5 strongly agree
Education and Training						
14.	I believe I am competent in the area of pharmacogenetic testing					
15.	I require more education on pharmacogenetic testing					
16.	Pharmacogenetics modules should be incorporated in undergraduate curricula					
17.	Pharmacogenetics should be offered as a postgraduate specialisation					

18. a) Which mode of acquiring information on pharmacogenetic testing do you prefer?
(You may select **more than one** *option)*

- ☐ Continuing professional education seminars
- ☐ Courses
- ☐ Conferences
- ☐ Workshops
- ☐ Journal articles
- ☐ Other (please specify: _____)

b) How would you prefer to follow the selected learning activities in question 18a?

- ☐ Attending in person
- ☐ Following online material
- ☐ A combination of both

c) Which topic/s would you like to follow during the selected learning activities in 18a?
(You may select **more than one** *option)*

- ☐ Basic principles of genetics
- ☐ Effect of genetics on drug pharmacokinetics/pharmacodynamics
- ☐ Pharmacogenetic testing implications in different therapeutic areas
- ☐ Availability of pharmacogenetic tests
- ☐ Interpretation of a pharmacogenetic test
- ☐ Ethical issues
- ☐ Other (please specify: _____)

Other comments/recommendations:

_____

_____

_____

SECTION 4: ATTITUDES TOWARDS PHARMACOGENETIC TESTING

On a Likert scale of 1 *(strongly disagree)* to 5 *(strongly agree)*, rate each of the following statements by marking with an 'X' in the appropriate box.

No.	Statement	1 strongly disagree	2 disagree	3 neutral	4 agree	5 strongly agree
Use in practice *Pharmacogenetic testing…*						
19.	has clinical benefits					
20.	can guide individualised therapy selection					
21.	can be used in treatment-resistant cases					
22.	can be used in medication intolerance cases					
23.	is applicable for use in my practice					
Costs and Service Provision *Pharmacogenetic testing…*						
24.	decreases healthcare service utilisation e.g. readmissions and duration of inpatient stay					
25.	leads to reduced healthcare costs					
26.	guides drug therapy expenditure					
27.	should be a government-funded service					
28.	should be paid out-of-pocket by the patient					
29.	cost-effectiveness studies are important					
30.	increases complexity of healthcare service provision					
Ethical Concerns *Pharmacogenetic testing results:*						
31.	should be shared with family members					
32.	may be misused or misinterpreted if made available to third parties e.g. health insurance/employers/family members					
33.	misuse may lead to violation of privacy					

No.	Statement	1 strongly disagree	2 disagree	3 neutral	4 agree	5 strongly agree
Pre and Post- Marketing Concerns *Pharmacogenetic testing:*						
34.	improves efficacy of medications on the market					
35.	improves safety of medications on the market					
36.	improves the efficacy and safety of future medications granted a marketing authorisation					
37.	can be applied in drug development for medications used in difficult-to-treat situations e.g. orphan medicines, treatment resistance					
38.	research studies would interest you and you would recommend patients to participate in such studies if the opportunity arises					

Other comments/recommendations :

_____

_____

_____

39. Rate the following drug classes for which you think pharmacogenetic testing is important

(Please rate as 1 (least important) to 8 (most important). You may also specify other drug classes in the Others section.

Drug Classes	Order of Importance (1-8)
Anticoagulants/ Antiplatelets (e.g. warfarin, clopidogrel)	
Lipid -regulating drugs (e.g. simvastatin)	
Antidepressants/ Antipsychotics (e.g. paroxetine, aripiprazole)	
Opioids (e.g. codeine)	
Antihypertensives (e.g. perindopril)	
Proton-pump inhibitors (e.g. omeprazole)	
Oncology drugs (e.g. capecitabine, imatinib, trastuzumab)	
Drug used in HIV (e.g. abacavir)	
Others (*please specify)*	

SECTION 5: PHARMACOGENETIC TESTING IN PRACTICE

40. a) Have you ever ordered a pharmacogenetic test?

☐ Yes *(continue to question 40b)* ☐ No (*continue to question 41)*

b) If YES, for which drug/s? (*Please specify:* _____)

41. How often do you perceive the need to order a pharmacogenetic test in your practice?

☐ Never ☐ Daily ☐ Weekly ☐ Monthly ☐ Yearly

On a Likert scale of 1 *(not confident at all)* to 5 *(very confident)*, rate each of the following statements, which capture your current or future practice of pharmacogenetic testing by marking with an 'X' in the appropriate box

No.	Statement	1 not confident at all	2 not confident	3 neutral	4 confident	5 very confident
Personal degree of confidence to...						
42.	recommend pharmacogenetic testing when indicated					
43.	order a pharmacogenetic test when indicated					
44.	interpret pharmacogenetic test results					
45.	discuss pharmacogenetic test result with patient					

On a Likert scale of 1 *(strongly disagree)* to 5 *(strongly agree)*, rate each of the following statements, which capture your current or future practice of pharmacogenetic testing by marking with an 'X' in the appropriate box

No.	Statement	1 strongly disagree	2 disagree	3 neutral	4 agree	5 strongly agree
Clinical Utility						
46.	I would order a pharmacogenetic test to predict likelihood of an adverse effect to a drug					
47.	I would order a pharmacogenetic test to predict likelihood of drug efficacy					
48.	I would order a pharmacogenetic test to predict severity of a potential adverse effect					
49.	I would take action if a pharmacogenetic test result indicated need for a change in treatment plan					
Pharmacogenetic testing...						
50.	should be performed pre-emptively					
51.	should be implemented routinely with medication therapy management services					
52.	should be performed in hospital only					
53.	should be carried out in a laboratory solely dedicated to pharmacogenetics					
54.	should be provided as a point-of-care test in community pharmacies					

No.	Statement	1 strongly disagree	2 disagree	3 neutral	4 agree	5 strongly agree
Pharmacogenetic test results…						
55.	should be stored electronically					
56.	should be available in health records for clinical evaluation by healthcare professionals					
57.	should be available for access by all healthcare professionals taking care of the patient					
58.	should be available for access by prescribers only					
59.	should be interpreted automatically by an electronic system which incorporates algorithms for treatment decisions					
Patient Counselling						
60.	Pre-test counselling with the patient should be provided prior to pharmacogenetic testing to aid in informed decision-making and patient understanding of procedure					
61.	Post-test counselling with the patient should be provided to aid in understanding test results					
62.	Patients should be informed about incidental/ancillary findings from a pharmacogenetic test result					
Regulatory aspects						
63.	Organisational infrastructures should be developed to describe the responsibilities of each healthcare professional involved in effective provision of pharmacogenetic testing services					
64.	A framework should be in place to ensure consistency of procedure when ordering a pharmacogenetic test to avoid liability issues					
65.	Genetic stratification should be applied in pharmacogenetic research studies to help design drugs which target specific groups of patients e.g. non-responders to treatment					
66.	Pharmacogenetic testing should be included as a risk minimisation measure in the safety section of the dossier i.e. in post-authorisation safety/efficacy studies					
67.	The Summary of Product Characteristics should include pharmacogenetic testing when applicable					

Please answer the following questions by marking the respective healthcare professionals in order of who should be responsible; 1 (least responsible) to 7 (most responsible).

No.	Question	Pharmacist	Physician*	Consultant	Genetics Specialist Physician	Genetic Counsellor	Biomedical Laboratory Scientist	Nurse
68.	Who should be responsible for making a patient **aware** of pharmacogenetic testing for drug/s with pharmacogenetic implications that the patient is taking or being considered?							
69.	Who should be responsible to **access** a patient's pharmacogenetic test result?							
70.	Who should be responsible to **interpret** a patient's pharmacogenetic test result?							
71.	Who should be responsible to **discuss** a pharmacogenetic test result with a patient?							
72.	Who should be responsible to take **action** according to the pharmacogenetic test result? E.g. change of drug, dose adjustment							

**including Basic specialist trainee, Higher specialist trainee, Resident specialist, Specialist in Family Medicine*

On a Likert scale of 1 *(strongly disagree)* to 5 *(strongly agree)*, rate each of the following statements by marking with an 'X' in the appropriate box.

No.	Statement	1 strongly disagree	2 disagree	3 neutral	4 agree	5 strongly agree
	Challenges for implementation of pharmacogenetic testing					
73.	Lack of healthcare professional awareness					
74.	Lack of public awareness					
75.	Cost issues					
76.	Ethical concerns					
77.	Turnaround time of test result impacts your decision to order a pharmacogenetic test					
78.	Evidence-based value of test result impacts your decision to order a pharmacogenetic test					
79.	Pharmacogenetic testing will increase your workload in practice					
80.	Pharmacogenetic testing will increase waiting time for prescriber to take action on a patient's medication needs					

Other comments/ recommendations :

_____

_____

_____

Thank you for your participation!

Appendix 5: Tutorial slides- ***Pharmacogenetics: A tool for precision medicine***

1

PHARMACOGENETICS:

A TOOL FOR PRECISION MEDICINE

Althea Marie Xuereb

Doctorate in Pharmacy Candidate 2019

February 2019

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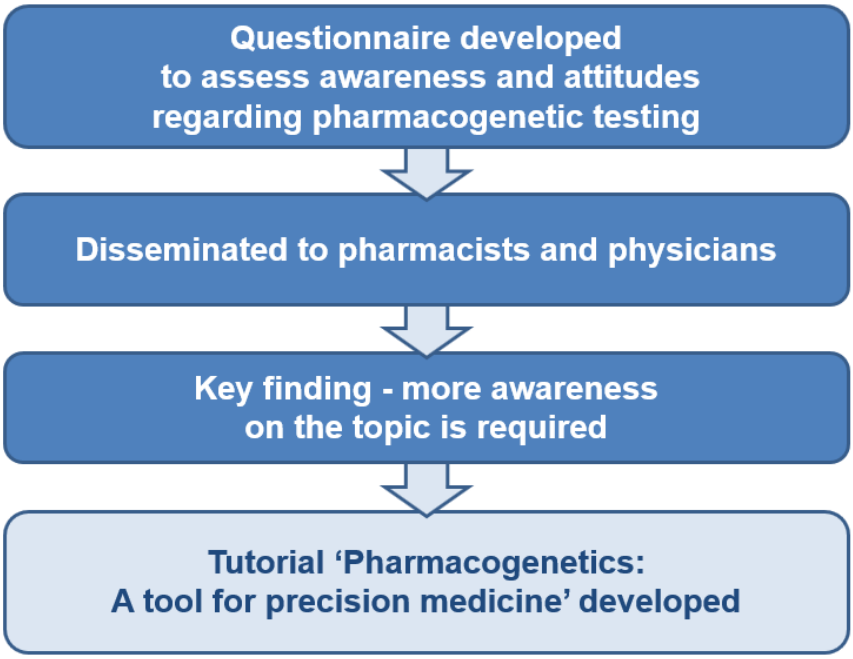
Disclaimer:

This tutorial is not meant to be used for clinical purposes or clinical judgement, it should only serve as an academic exercise. The material stated is my own personal interpretation and responsibility and the Department of Pharmacy and any reference to any third party are not in any way responsible for any data presented.

Any queries should be addressed solely to the researcher, who has taken full responsibility of the material as part of her studies.



Overview

General information about Pharmacogenetics (PGx)

Application of PGx in practice using case studies

What is pharmacogenetics?

Study of the interindividual variability of genes and its effect on drug metabolism and response

NOMENCLATURE

Allele

Alternative form of a gene at a given locus on a chromosome inherited from each parent

E.g. *CYP2C19* gene

- ***1* - wild-type, normal function allele**
- ***2* - loss-of-function allele**
- ***17* - gain-of-function allele**

Pharmacogenetic Polymorphisms

Presence of 2 or more variant alleles for a particular gene

Type of genetic polymorphisms	Examples of drugs affected
Drug metabolising enzyme	amitriptyline, clopidogrel, azathioprine
Drug transporter gene	simvastatin
Drug target gene	warfarin

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Pharmacogenetic Biomarker

Measurable DNA/RNA characteristic indicating a biologic process and/or response to therapeutic interventions

Examples of PGx biomarkers	Examples of drugs
CYP2D6	tamoxifen, codeine, TCAs, SSRIs
HER-2	trastuzumab
VKORC1	warfarin
*HLA-B*5701*	abacavir

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Genotype

Specific set of alleles inherited at a locus on a given gene

e.g. CYP2C19 gene		
Genotype	**Examples of alleles making up the genotype**	**Prevalence (%)**
Homozygous wild-type	*1/*1	35-50
Heterozygous	*1/*2	18-45
Homozygous variant	*2/*2	2-15

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Phenotype

Clinical presentation of an individual with a particular genotype

e.g. CYP450 metaboliser status

Phenotype - Metaboliser status
Poor Metaboliser (PM)
Intermediate Metaboliser (IM)
Normal Metaboliser (NM)
Rapid Metaboliser (RM)
Ultra-rapid Metaboliser (UM)

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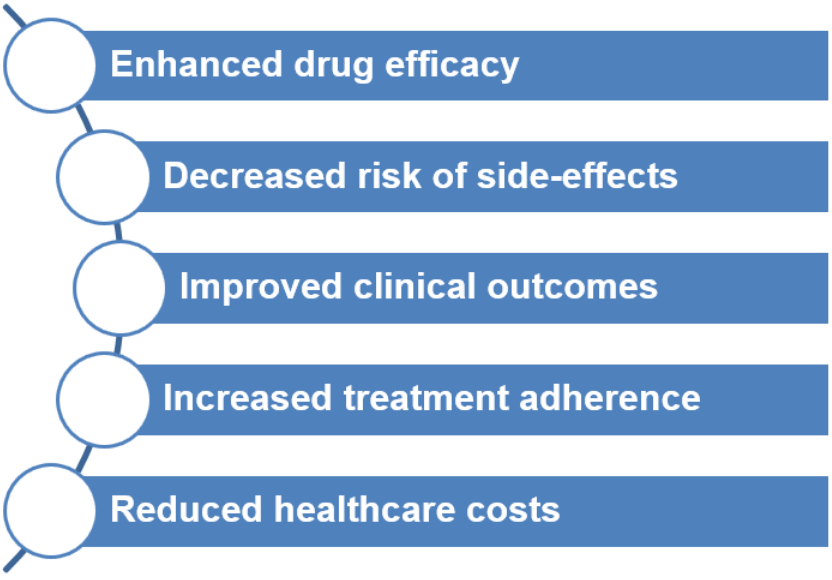
Benefits of pharmacogenetics



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Challenges of pharmacogenetics

- Inadequate healthcare professional awareness and confidence
- Limited evidence from RCTs; cost-effectiveness studies
- Testing availability and accessibility; minimal rapid, on-demand testing platforms
- Lack of harmonised regulatory frameworks
- Ethical issues

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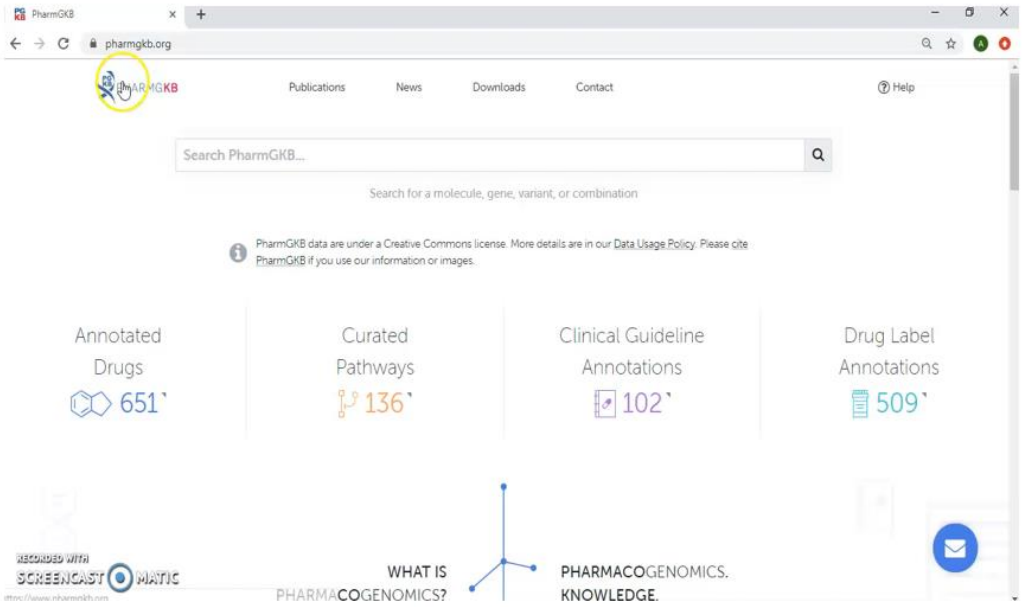
PHARMACOGENETICS-RELATED INFORMATION RESOURCES

Pharmacogenomics Knowledgebase
https://www.pharmgkb.org/



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Pharmacogenomics Knowledgebase
https://www.pharmgkb.org/

Drug label annotations	Examples of drugs
Testing required	abacavir
Testing recommended	azathioprine
Actionable PGx	clopidogrel
Informative PGx	simvastatin

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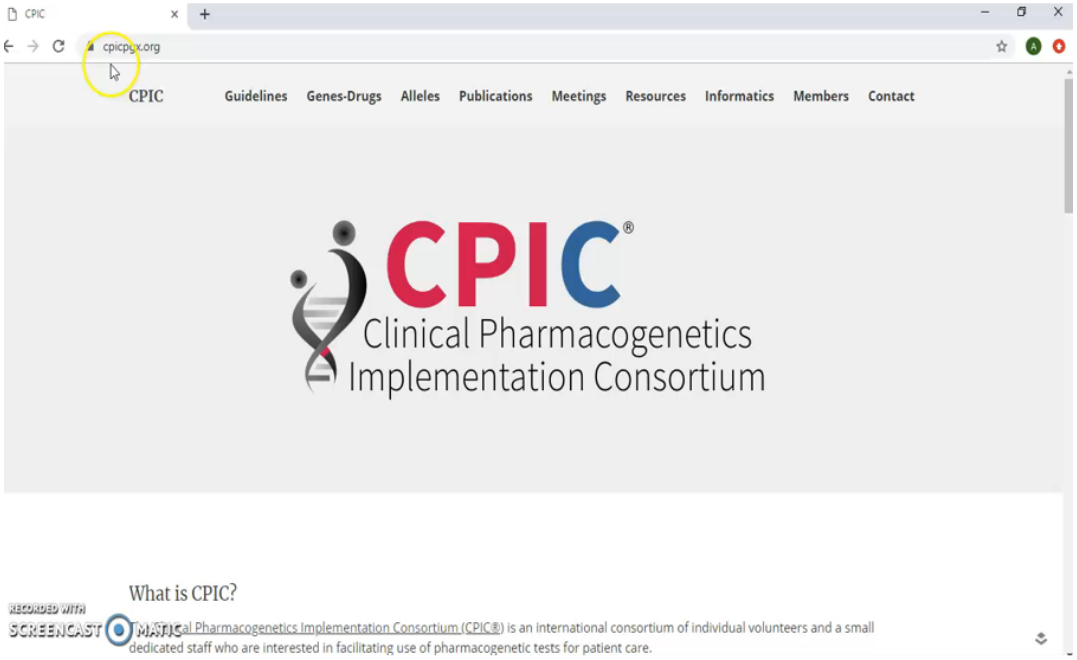
Clinical Pharmacogenetics Implementation Consortium
https://cpicpgx.org/



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Other resources:

Resource	Reference
Dutch Pharmacogenetics Working Group (DPWG)	Swen JJ, Nijenhuis M, de Boer A, Grandia L, Maitland-van der Zee AH, Mulder H et al. Pharmacogenetics: from bench to byte- an update of guidelines. Clin Pharmacol Ther. 2011; 89(5):662-73
US Food and Drug Administration (FDA) drug label	*DAILYMED* *https://dailymed.nlm.nih.gov/dailymed/*
Summary of Product Characteristics (SmPC)	*European Medicines Agency* https://www.ema.europa.eu/en/medicines *Malta Medicines Authority* *http://medicinesauthority.gov.mt/maltamedicineslist*

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CLINICAL APPLICATIONS OF PHARMACOGENETICS

1) Oncology
2) Cardiology
3) Infectious Disease

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Clinical Case 1- Oncology

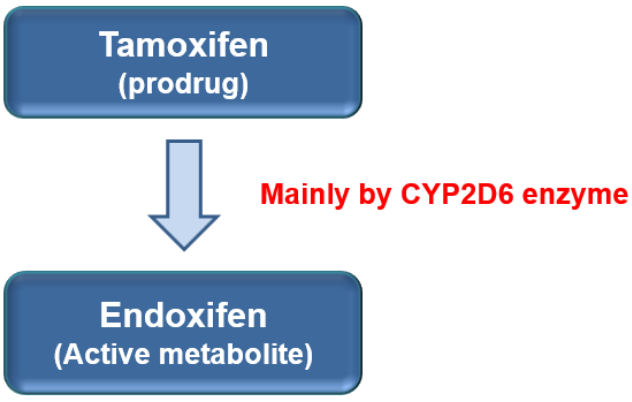
- 55-year old female
- Post-menopausal
- Diagnosed with oestrogen receptor positive breast cancer
- Breast surgery and irradiation performed
- *CYP2D6* status unknown
- Tamoxifen 20mg daily prescribed

Pharmacogenetic information - Tamoxifen

Pharmacogenetic Biomarker	*CYP2D6*	
		Year of update
FDA drug label (Testing required)	Indications and Usage Precautions Adverse Reactions Clinical Studies	2017
SmPC	Special warnings and precautions for use Pharmacodynamic properties Pharmacokinetic properties	2018
Genotype-guided dosing recommendations	CPIC	2018

Tamoxifen Pharmacokinetics

Metabolism



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Pharmacogenetic biomarker - *CYP2D6*

Function	Examples of alleles
Normal	**1, *2*
Decreased	**9, *10, *17, *41*
No function	**3,*4, *5, *6*

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CYP2D6 Phenotype, Implications and Relevance

Phenotype	Implications	Clinical Relevance
Ultra-rapid metaboliser (UM)	*Therapeutic* endoxifen concentration	No ↑ risk of recurrence and complication development
Normal metaboliser (NM)		
Intermediate metaboliser (IM)	*Lower* endoxifen concentration compared to NM	↑ risk of recurrence and complication development
Poor metaboliser (PM)		

Tamoxifen Therapeutic Recommendations

Phenotype	Therapeutic Recommendation	Classification of recommendation
UM, NM	20mg tamoxifen daily	Strong
IM	Postmenopausal - alternative hormonal therapy e.g. aromatase inhibitors (AIs)	Moderate
PM	Premenopausal - AIs and ovarian function suppression 40mg tamoxifen daily considered if AIs contraindicated	Strong

Clinical Case 2- Cardiology

- 60-year old male
- STEMI
- Dual antiplatelet therapy for 12 months post-PCI
  - Aspirin 75mg OD
  - Clopidogrel 75mg OD
- *CYP2C19* metaboliser status unknown
- No history of stroke or transient ischaemic attack
- No hepatic impairment

Pharmacogenetic information-Clopidogrel

Pharmacogenetic Biomarker	*CYP2C19*	
		Year of update
FDA drug label (Actionable PGx)	Boxed Warning Warnings and Precautions Clinical Pharmacology	2018
SmPC (Actionable PGx)	Special warnings and precautions for use Pharmacodynamic properties Pharmacokinetic properties	2018
Genotype-guided dosing recommendations	CPIC DPWG	2013 2011

Clopidogrel Pharmacokinetics

Prodrug

Clopidogrel metabolised to 2-oxo-clopidogrel [intermediate metabolite]

Mainly by CYP2C19 enzyme

2-oxo-clopidogrel metabolised to thiol derivative of clopidogrel [active metabolite]

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Pharmacogenetic Biomarker- *CYP2C19*

Functional Groups	Examples of Alleles
Normal function	**1*
Gain-of-function	**17*
Loss-of-function	**2, *3, *4, *5, *6, *7, *8*

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CYP2C19 phenotype, implications and recommendations

Phenotype	Implications		Therapeutic recommendations (Classification of recommendation)
	Platelet aggregation	Risk of adverse CV events	
UM	Decreased	No increased risk	Guideline recommended dosage and administration (Strong)
NM	No increased risk		
IM, PM	Increased	Increased	Alternative antiplatelet if no contraindications e.g. prasugrel (IM - Moderate, PM - Strong)

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Clinical Case 3 - Infectious disease

- 29-year old male
- Newly diagnosed with HIV
- *HLA-B*5701* status unknown
- Prescribed abacavir 600mg and lamivudine 300mg OD, efavirenz 600mg OD

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Pharmacogenetic information - Abacavir

Pharmacogenetic Biomarker	*HLA-B*5701*	
		Year of update
FDA drug label (Testing required)	Boxed Warning Dosage and Administration Contraindications Warning and Precautions	2018
SmPC (Testing required)	Therapeutic Indications Special Warnings and Precautions for Use Pharmacodynamic properties	2018
Genotype-guided dosing recommendations	CPIC DPWG	2012 2011

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HLA-B Phenotype and Implications

Phenotype	Implications
Non-carrier (absence of **5701* allele)	Very low risk of developing hypersensitivity reaction
Carrier (presence of at least 1 **5701* allele)	Very high risk of developing hypersensitivity reaction

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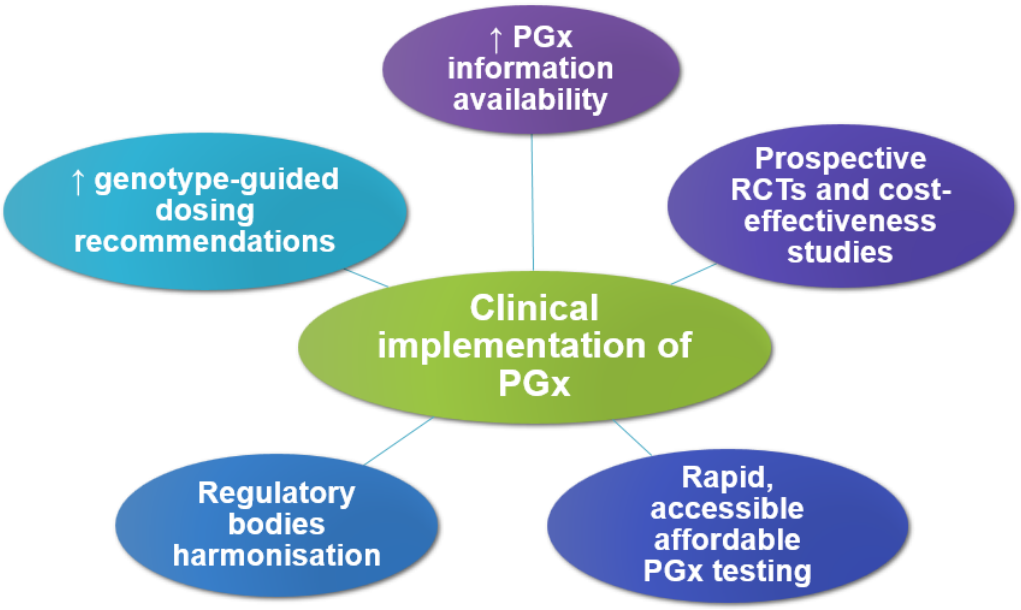
Therapeutic Recommendations

Phenotype	Therapeutic Recommendation	Classification of recommendation
Non-Carrier *HLA-B*5701*	Use of abacavir according to standard dosing guidelines	Strong
Carrier *HLA-B*5701*	Abacavir NOT recommended	Strong

Alternative drug to abacavir is recommended in *HLA-B*5701* positive patients

Future directions



Appendix 6: Evaluation form of pharmacogenetics tutorial

Evaluation of tutorial - Pharmacogenetics: A tool for Precision Medicine

Althea Marie Xuereb, Pharm D Student

Introduction and Instructions

Dear Participant,

The tutorial entitled 'Pharmacogenetics: A Tool for Precision Medicine' is being conducted as part of my Doctorate in Pharmacy research at the Department of Pharmacy, University of Malta, under the supervision of Professor Anthony Serracino-Inglott and Dr Francesca Wirth. Kindly complete the evaluation questionnaire after following the tutorial. Responses will only be accessed by research team members.

ALL pharmacists and physicians are eligible to participate.

Thank you very much for your participation

Section 1: Demographics

1. **Gender** ☐ Male ☐ Female ☐ Other
2. **Age** (years) _____
3. **Profession**

☐ **Pharmacist**

Area of Practice ☐ Community ☐ Academia
☐ Hospital ☐ Industry
☐ Regulatory ☐ Other (*Please specify* _____)

☐ **Physician**

Area of Specialisation (*Please specify* _____)

4. **Years of Practice** _____
5. **Highest Academic level** _____

Section 2: Evaluation of Tutorial

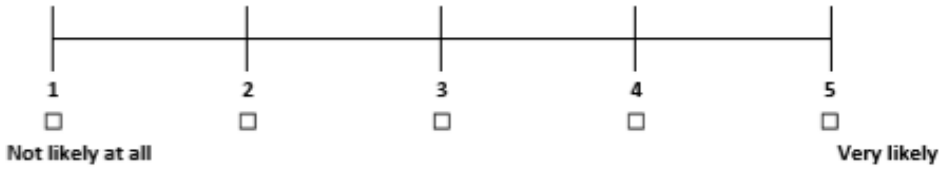
6. On a Likert scale of 1 to 5, (1 corresponds to 'least relevant'; 5 corresponds to 'very relevant') rate each of the following discussion topics by marking with an 'X' in the appropriate box.

	Discussion Topic	RELEVANCE TO PRACTICE →				
		1	2	3	4	5
A	Nomenclature related to pharmacogenetics					
B	Benefits and challenges of pharmacogenetics					
C	Pharmacogenetics-related information resources					
D	Pharmacogenetics related clinical case study- Case 1- Oncology					
E	Pharmacogenetics related clinical case study- Case 2- Cardiology					
F	Pharmacogenetics related clinical case study- Case 3- Infectious disease					

On a Likert-scale of 1 *(strongly disagree)* to 5 *(strongly agree)*, rate each of the following statements by marking with an 'X' in the appropriate box.

No.	Statement	1 strongly disagree	2 disagree	3 neutral	4 agree	5 strongly agree
7.	Tutorial is relevant to my practice					
8.	Tutorial reflects the latest developments in pharmacogenetics					
8.	Tutorial helped me to understand fundamental principles of pharmacogenetics					
9.	Tutorial sequence was appropriate					
10.	Information in tutorial was clearly presented					
11.	Information in tutorial was comprehensive					
12.	Information in tutorial was easy to understand					
13.	Tutorial will help to improve application of theory to practice					
14.	Tutorial will help to improve my skills in pharmacogenetics					
15.	Tutorial helped to identify my strengths and weaknesses regarding the topic					
16.	Content discussed is helpful for use in practice					
17.	Tutorial inspired me to read more about the subject					
18.	Tutorial met my expectations					

19. On a Likert Scale of 1 to 5, (1 corresponds to 'not likely at all'; 5 corresponds to 'very likely') rate the likelihood of following future tutorials on the topic.



20. Any additional feedback or suggestions related to the educational seminar may be included below.

Thank you

Appendix 7: List of oncology drugs for discussion with Consultant Oncologists

Status of pharmacogenetic testing in oncology drugs

List of drugs with pharmacogenetic (PGx) implications and their respective drug label annotations[1] found on the Maltese Government Formulary List[2].

Kindly indicate with an 'x' for each respective drug whether the indicated PGx biomarker is being requested prior to prescribing.

Active ingredient	EMA	FDA	PGx Biomarker	Request of PGx test prior to prescribing	
				Yes	No
anastrazole	-	1	Hormone receptor +ve		
busulfan	-	3	Philadelphia Chromosome (Ph1)		
capecitabine	3	3	Dihydropyrimidine dehydrogenase (DPD) activity		
cisplatin	-	4	Thiopurine S-methyltransferase (TPMT) activity		
dabrafenib	1	1	BRAF V600 mutation		
enzalutamide	-	4	CYP 3A4, 2C9, 2C19, 2C8		
erlotinib	1	1	EGFR mutations		
everolimus	1	1	Hormone receptor +ve, HER2/neu		
exemestane	-	1	Oestrogen receptor +ve		
fluorouracil	-	3	DPD activity		
imatinib	1	1	BCR-ABL, PH+, Kit (CD 117), PDGFR		
irinotecan	-	3	UGT1A1*28 variant		
lenalidomide	4	1	Deletion 5q abnormality		
letrozole	-	1	Hormone receptor +ve		
mercaptopurine	3	2	TPMT activity		
rasburicase	3	4	G6PD deficiency		
rituximab	4	4	CD20		
sunitinib	4	-	CYP3A4		
tamoxifen	-	1	CYP2D6, hormone receptor +ve		
trametenib	1	1	BRAFV600		
trastuzumab	1	1	HER2 +ve		
tretinoin	-	1	t(15;17) gene		

1- **Testing required**-The label states or implies that some sort of gene, protein or chromosomal testing, including genetic testing, functional protein assays, cytogenetic studies, etc., should be conducted before using this drug. This requirement may only be for a particular subset of patients. PharmGKB considers labels that state the variant is an indication for the drug, as implying a test requirement. If the label states a test "should be" performed, this is also interpreted as a requirement.

2- **Testing recommended**-The label states or implies that some sort of gene, protein or chromosomal testing, including genetic testing, functional protein assays, cytogenetic studies, etc., is recommended before using this drug. This recommendation may only be for a particular subset of

patients. PharmGKB considers labels that say testing "should be considered" to be recommending testing.

3- **Actionable PGx**-The label does not discuss genetic or other testing for gene/protein/chromosomal variants, but does contain information about changes in efficacy, dosage or toxicity due to such variants. The label may mention contraindication of the drug in a particular subset of patients but does not require or recommend gene, protein or chromosomal testing.
4- **Informative PGx**-The label mentions a gene or protein is involved in the metabolism or pharmacodynamics of the drug, but there is no information to suggest that variation in these genes/proteins leads to different response.

References:

1- Pharmacogenomics Knowledgebase- PharmGKB [Internet]. Stanford University: Department of Health and Human Services: c2001 [cited 2018 Jul. 15]. Available from: URL: https://www.pharmgkb.org/labels
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Appendix 8: List of academic institutions who participated in preliminary study regarding inclusion of PGx in pharmacy education programs

The data collated from the academic institutions regarding inclusion of PGx in pharmacy curricula was collected between July and September 2018.

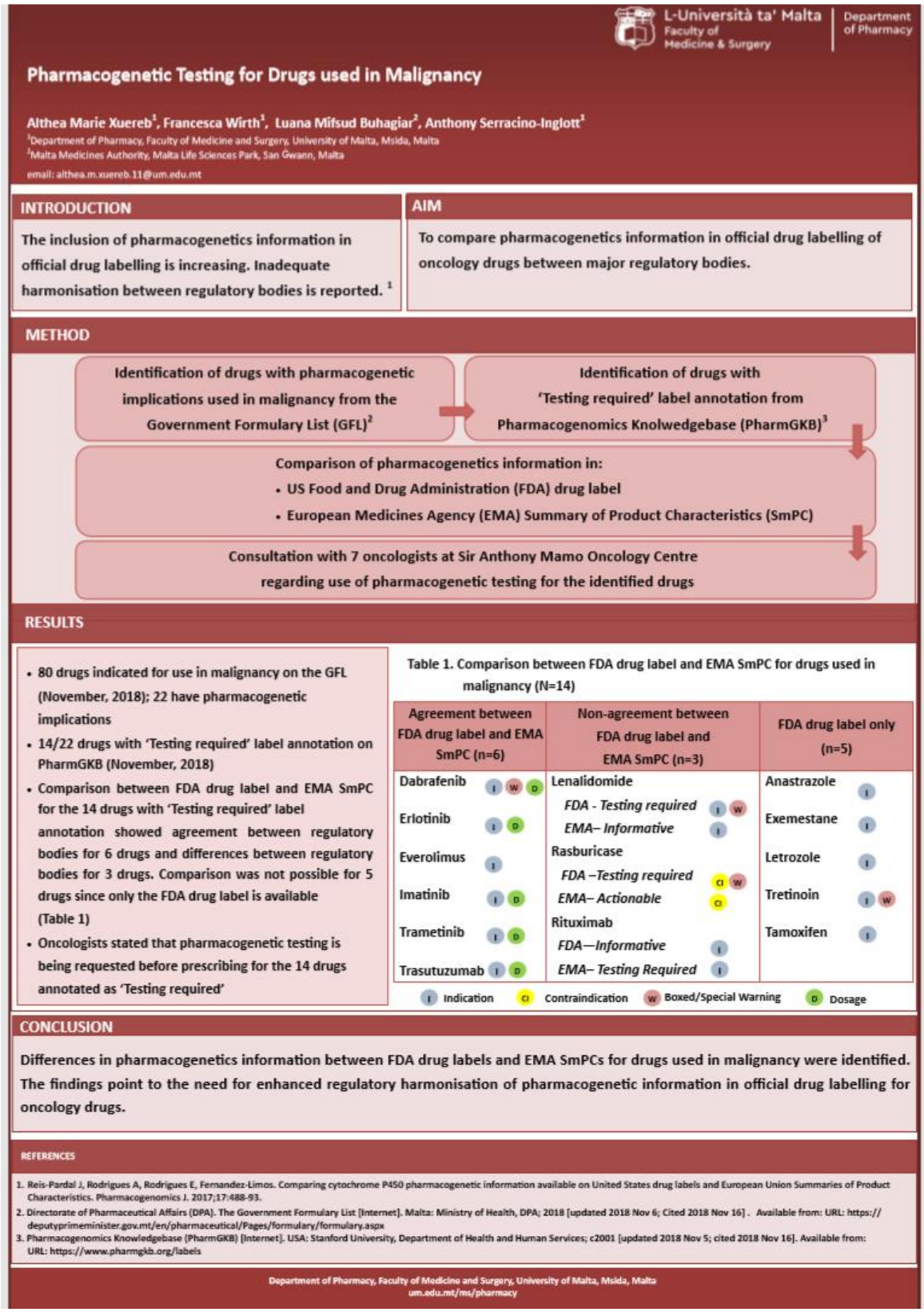
Europe
Antwerp Universiteit, Antwerpen Departement Farmaceutische Wetenschappen, **Belgium**
Brussels, Vrije Universiteit Brussel, Faculteit Geneeskunde en Farmacie, **Belgium**
Plovdiv Medical University of Plovdiv, Faculty of Pharmacy, **Bulgaria**
Sofia Medical University of Sofia, Faculty of Pharmacy, **Bulgaria**
Varna Medical University, Varna Faculty of Pharmacy, **Bulgaria**
Nicosia, Near-Eastern University, Faculty of Pharmacy, **Cyprus**
Nicosia, University of Nicosia, Department of Life and Health Sciences, **Cyprus**
Brno University of Veterinary and Pharmaceutical Sciences, Faculty of Pharmacy, **Czech Republic**
Kuopio University of Eastern Finland, School of Pharmacy, **Finland**
Reykjavik, University of Iceland, Faculty of Pharmaceutical Sciences, **Iceland**
Groningen Rijksuniversiteit Groningen, Groningen Research Institute of Pharmacy, GRIP, **Netherlands**
Utrecht Universiteit, Utrecht Department of Pharmaceutical Sciences, **Netherlands**
Oslo, University of Oslo, School of Pharmacy, **Norway**
Tromsø, Arctic University of Norway, Department of Pharmacy, **Norway**
Alcalá de Henares, Universidad de Alcalá, Facultad de Farmacia, **Spain**
Universidad de Salamanca, Facultad de Farmacia, **Spain**
Ankara, Ankara University, Faculty of Pharmacy, **Turkey**
Kharkov National University of Pharmacy, **Ukraine**
University of Nottingham, School of Pharmacy, **United Kingdom**

USA
Chapman University, School of Pharmacy, **California**
Keck Graduate Institute, School of Pharmacy, **California**
University of California San Diego, Skaggs School of Pharmacy and Pharmaceutical Sciences, **California**
West Coast University, School of Pharmacy, **California**
University of Saint Joseph, School of Pharmacy, **Connecticut**
Nova Southeastern University, College of Pharmacy, **Florida**
University of Florida, College of Pharmacy, **Florida**
Mercer University, College of Pharmacy, **Georgia**
University of Illinois at Chicago, College of Pharmacy, **Illinois**
Manchester University, College of Pharmacy, **Indiana**
Drake University, College of Pharmacy and Health Sciences, **Iowa**
University of Kentucky, College of Pharmacy, **Kentucky**
The University of Louisiana at Monroe, School of Pharmacy, **Louisiana**
MCPHS University, School of Pharmacy (Worcester/Manchester), **Massachusetts**
Ferris State University, College of Pharmacy, **Michigan**
University of Michigan, College of Pharmacy, **Michigan**
Wayne State University, Eugene Applebaum College of Pharmacy and Health Sciences, **Michigan**
University of Minnesota, College of Pharmacy, **Minnesota**
University of Missouri-Kansas City, School of Pharmacy, **Missouri**
The University of Montana, Skaggs School of Pharmacy, **Montana**
Creighton University School of Pharmacy and Health Professions, **Nebraska**
University of Nebraska, Medical Center College of Pharmacy, **Nebraska**
The University of New Mexico, College of Pharmacy, **New Mexico**
Albany College of Pharmacy and Health Sciences, **New York**
Binghamton University, the State University of New York School of Pharmacy and Pharmaceutical Sciences, **New York**
St John Fisher College-Wegmans School of Pharmacy, **New York**
High Point University, Fred Wilson School of Pharmacy, **North Carolina**
North Dakota University, College of Health, **North Dakota**
Cedarville University school of Pharmacy, **Ohio**
Northeast Ohio Medical University, College of Pharmacy, **Ohio**

USA (continued)
The Ohio State University College of Pharmacy, **Ohio**
Temple University, School of Pharmacy, **Pennsylvania**
Presbyterian College, School of Pharmacy, **South Carolina**
University of South Carolina, College of Pharmacy, **South Carolina**
The University of Texas at El Paso, School of Pharmacy, **Texas**
University of North Texas, Health Science Center, College of Pharmacy, **Texas**
Marshall University, School of Pharmacy, **West Virginia**
Virginia Commonwealth University, School of Pharmacy, **Virginia**
Medical College of Wisconsin, School of Pharmacy, **Wisconsin**

Appendix 9: Dissemination of study findings

Discussed poster presentation, 10th Malta Medical School Conference



L-Università ta' Malta | Faculty of Medicine & Surgery | Department of Pharmacy

Pharmacogenetic Testing for Drugs used in Malignancy

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INTRODUCTION

The inclusion of pharmacogenetics information in official drug labelling is increasing. Inadequate harmonisation between regulatory bodies is reported. [1]

AIM

To compare pharmacogenetics information in official drug labelling of oncology drugs between major regulatory bodies.

METHOD

Identification of drugs with pharmacogenetic implications used in malignancy from the Government Formulary List (GFL)[2]

→ Identification of drugs with 'Testing required' label annotation from Pharmacogenomics Knolwedgebase (PharmGKB)[3]

Comparison of pharmacogenetics information in:
- US Food and Drug Administration (FDA) drug label
- European Medicines Agency (EMA) Summary of Product Characteristics (SmPC)

Consultation with 7 oncologists at Sir Anthony Mamo Oncology Centre regarding use of pharmacogenetic testing for the identified drugs

RESULTS

- 80 drugs indicated for use in malignancy on the GFL (November, 2018); 22 have pharmacogenetic implications
- 14/22 drugs with 'Testing required' label annotation on PharmGKB (November, 2018)
- Comparison between FDA drug label and EMA SmPC for the 14 drugs with 'Testing required' label annotation showed agreement between regulatory bodies for 6 drugs and differences between regulatory bodies for 3 drugs. Comparison was not possible for 5 drugs since only the FDA drug label is available (Table 1)
- Oncologists stated that pharmacogenetic testing is being requested before prescribing for the 14 drugs annotated as 'Testing required'

Table 1. Comparison between FDA drug label and EMA SmPC for drugs used in malignancy (N=14)

Agreement between FDA drug label and EMA SmPC (n=6)	Non-agreement between FDA drug label and EMA SmPC (n=3)	FDA drug label only (n=5)
Dabrafenib (I, W, D)	Lenalidomide	Anastrazole (I)
Erlotinib (I, D)	*FDA - Testing required* (I, W)	Exemestane (I)
Everolimus (I)	*EMA– Informative* (I)	Letrozole (I)
Imatinib (I, D)	Rasburicase	Tretinoin (I, W)
Trametinib (I, D)	*FDA –Testing required* (CI, W)	Tamoxifen (I)
Trasutuzumab (I, D)	*EMA– Actionable* (CI)	
	Rituximab	
	FDA—Informative (I)	
	EMA– Testing Required (I)	

I Indication · CI Contraindication · W Boxed/Special Warning · D Dosage

CONCLUSION

Differences in pharmacogenetics information between FDA drug labels and EMA SmPCs for drugs used in malignancy were identified. The findings point to the need for enhanced regulatory harmonisation of pharmacogenetic information in official drug labelling for oncology drugs.

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2. Directorate of Pharmaceutical Affairs (DPA). The Government Formulary List [Internet]. Malta: Ministry of Health, DPA; 2018 [updated 2018 Nov 6; Cited 2018 Nov 16] . Available from: URL: https://deputyprimeminister.gov.mt/en/pharmaceutical/Pages/formulary/formulary.aspx
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Poster Presentation, 24th Congress of the European Association of Hospital Pharmacy

L-Università ta' Malta | Department of Pharmacy
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PERCEPTION OF HOSPITAL PHARMACISTS TOWARDS PHARMACOGENETIC TESTING

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INTRODUCTION

Pharmacogenetic (PGx) testing can be used as a tool in personalised medicine. PGx has potential to improve drug efficacy, patient safety and clinical outcomes and decrease healthcare costs.[1] Advances in PGx may provide for the expansion of the role of hospital pharmacists in precision pharmacotherapy.

AIMS

To assess awareness, attitudes and confidence of hospital pharmacists regarding PGx testing.

METHOD

1. *Development of self-administered questionnaire*
   5 sections: Participant demographics, Awareness, Education and Training, Attitudes, PGx Testing in Practice
2. *Psychometric evaluation of questionnaire*
   Validation: Panel of 9 members (5 pharmacists, 4 physicians); Consensus reached after two rounds.
   Reliability testing: 9 participants, Test-retest method (Day 1, Day 14); Questionnaire deemed reliable and accepted.
3. *Dissemination of questionnaire*
   Questionnaire was disseminated to 70 hospital pharmacists practicing in 4 hospitals (3 public, 1 private) after ethics approval.
   Descriptive statistics were calculated.

RESULTS

- Forty-two pharmacists answered the questionnaire; 24 female, 18 male (18 practicing for more than 10 years).
- Forty-one pharmacists were aware of the term 'PGx testing'. Awareness and attitudes of the pharmacists in relation to PGx testing are shown in Table 1 and 2.
- Seventeen pharmacists perceived the need to order a PGx test at least once monthly. The greatest challenges for PGx testing implementation were cost issues (n=41) and lack of healthcare professional awareness (n=39).
- Lack of confidence was expressed in recommending (n=31) a test, in interpreting test results (n=35) and discussing test results with patients (n=31). Thirty-eight pharmacists believe that they require education and training to increase competency and confidence in PGx testing. Seminars (n=29) and courses (n=24) were the preferred approaches for acquiring further education on PGx testing.

Table 1. Awareness of PGx testing (N=42)

Pharmacists were 'moderately' and 'extremely' aware of:	Number of pharmacists
Advanages of PGx testing	27
Limitations of PGx testing	11
Drugs for which PGx is required/recommended	13
Availability of PGx information resources	12
Drugs for which PGx testing is performed locally	5

Table 2. Attitudes towards PGx testing (N=42)

Pharmacists 'strongly agreed' and 'agreed' that PGx testing:	Number of pharmacists
Guides individualised therapy selection and dosing	41
Should be a government-funded service	30
Leads to reduced healthcare costs	24
Is applicable for use in their practice	21
Should be routinely implemented in practice	25

CONCLUSION

PGx is considered to be a measure to achieve personalised medicine by pharmacists and is applicable for use in their practice, however lack of confidence and the need of further training is expressed[2]; these findings have also been reflected by participants in this study. Increased training to improve competency in PGx testing and the designing of a standardised framework with regards to application of PGx testing in practice will have an effect on the role of the hospital pharmacist in precision medicine.

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[1]Klein ME, Parvez MM, Shin JG. Clinical implementation of pharmacogenomics for personalised precision medicine: Barriers and solutions. J Pharm Sci. 2017;106:2368-79.
[2]Kennedy MJ. Personalized medicines-are pharmacists ready for the challenge? Integr Pharm Res Pract. 2018;7:113-23.

Poster Presentation: 79th FIP World Congress of Pharmacy and Pharmaceutical Sciences, Abu Dhabi, United Arab Emirates

L-Università ta' Malta | Faculty of Medicine & Surgery | Department of Pharmacy

Awareness and Attitudes of Pharmacists and Physicians towards Pharmacogenetic Testing

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INTRODUCTION

Increased awareness of pharmacogenetic (PGx) testing by healthcare professionals paves the way towards its clinical implementation[1].

AIMS

To assess awareness and attitudes of pharmacists and physicians regarding PGx testing.

METHOD

Development of self-administered questionnaire

5 sections: Participant demographics, Awareness, Education and Training, Attitudes, PGx Testing in Practice

Psychometric evaluation of questionnaire

Validation: Panel of 9 members (5 pharmacists, 4 physicians); Consensus reached after two rounds.

Reliability testing: 9 participants, Test-retest method (Day 1, Day 14)

Dissemination of questionnaire following ethics approval

i) Online to pharmacists (n=835) and physicians (n=984) via social media groups, ii) online via mailing list of the Malta College of Family Doctors (n=198), iii) visiting community pharmacies and private clinics selected by convenience sampling and an acute general hospital (n=135), and iv) attending two local medical conferences (n=60).

Statistical analysis of questionnaire results

Descriptive statistics were calculated as mean rating scores (1-lowest to 5-highest) for Likert-type questions.

RESULTS

- The questionnaire was completed by 292 participants, 179 pharmacists (64% female, 36% male, 38% practicing >10 years) and 113 physicians (50% female, 50% male, 54% practicing >10 years).
- Participants (91% pharmacists, 76% physicians) were aware of the term 'PGx testing' prior to answering the questionnaire. Awareness and attitudes of pharmacists and physicians in relation to PGx testing are shown in Table 1 and 2.

Table 1. Awareness of PGx testing (N=292)

	Mean rating scores	
I am aware of:	Pharmacists (n=179)	Physicians (n=113)
Advantages of PGx testing	3.7	3.2
Limitations of PGx testing	2.8	2.6
Drugs with PGx testing required	2.5	2.2
PGx information resources	2.4	1.9
Drugs for which PGx testing is performed locally	1.5	1.6

Table 2. Attitudes towards PGx testing (N=292)

	Mean rating scores	
PGx testing:	Pharmacists (n=179)	Physicians (n=113)
Guides individualised therapy selection	4.5	4.2
Should be a government-funded service	3.9	3.8
Leads to reduced healthcare costs	3.8	3.4
Is applicable for use in their practice	3.3	3.6
Should be routinely implemented in practice	3.5	2.9

- Fourty-two percent of pharmacists and 27% of physicians never perceived the need to order a PGx test in their practice. Thirty-nine percent of physicians and 27% of pharmacists perceive the need to order a PGx test in their practice on a monthly basis.
- Competence in PGx testing was perceived to be insufficient (1.93 pharmacists, physicians 1.65) and participants agreed that further training is required (4.43 pharmacists, 4.43 physicians).

CONCLUSION

Pharmacists and physicians in this study showed positive attitudes towards PGx testing. Pharmacists and physicians agreed that further PGx training is required to increase competence and improve awareness to facilitate the clinical implementation of PGx.

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Poster Presentation: ESCP International Symposium, Ljubljana, Slovenia

L-Università ta' Malta | Faculty of Medicine & Surgery | Department of Pharmacy

An Online approach to enhance Awareness on Pharmacogenetics among Pharmacists and Physicians

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INTRODUCTION

Clinical implementation of pharmacogenetics (PGx) may be encouraged through increased awareness among healthcare professionals[1]. Online-based learning methods provide improved access to information for healthcare professionals[2].

AIMS

To develop, disseminate and evaluate PGx-related information to promote awareness among pharmacists and physicians.

METHOD

Development of tutorial and evaluation form

A fifteen-minute video 'Pharmacogenetics: A tool for precision medicine' was developed and recorded.

Topics included: Nomenclature, benefits of PGx, PGx-related information resources, clinical application of PGx using three case studies (Oncology, cardiology, infectious disease) and future directions.

A questionnaire to evaluated the video 'Pharmacogenetics: A tool for precision medicine' was developed.

Content validation of PGx video and evaluation questionnaire

The PGx video and evaluation questionnaire were validated by 7 professionals; 5 pharmacists and 2 physicians.

Modifications to the PGx video and evaluation questionnaire were done according to the suggested amendments by the panel

Dissemination of evaluation form

i) Online to pharmacists (n=835) and physicians (n=984) via social media groups

ii) Live presentation to pharmacists and physicians attending a workshop

Statistical analysis of evaluation questionnaire results

Descriptive statistics were calculated as mean rating scores (1-lowest to 5-highest) for Likert-type questions.

RESULTS

- The evaluation questionnaire was completed by 66 participants (57 online, 9 live presentation). Thirty-three participants were pharmacists (25 female, 8 male, mean age 30 years) and 33 were physicians (15 female, 18 male, mean age 33 years).
- Fifty-six participants were willing to follow future online-based learning related to PGx. Participants' agreement towards relevance of discussion topics and information presented in PGx video are shown in Table 1 and Table 2.

Table 1. Relevance of discussion topics (N=66)

Relevance of discussion topics:	Mean rating scores	
	Pharmacists (n=33)	Physicians (n=33)
Nomenclature related to PGx	4.1	3.5
Benefits of PGx	4.5	3.9
PGx information resources	4.4	3.9
PGx clinical case 1 (Oncology)	4.5	4.0
PGx clinical case 2 (Cardiology)	4.5	3.9
PGx clinical case 3 (Infectious disease)	4.3	3.9

Table 2. Evaluation of results of information presented (N=66)

Participants agreed that the information presented in PGx video:	Mean rating scores	
	Pharmacists (n=33)	Physicians (n=33)
Was up-to-date	4.2	4.2
May help to improve application of theory to practice	4.3	4.0
Inspired them on the topic	4.1	3.9
Helped them identify their strengths and weaknesses in PGx	4.2	3.8
Is helpful for use in their practice	4.1	3.7

CONCLUSION

Participants in this study recognised the relevance of the discussed topics and considered the acquired PGx-related information to be applicable in their practice. Both healthcare professionals were receptive towards following future online-based learning on PGx.

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