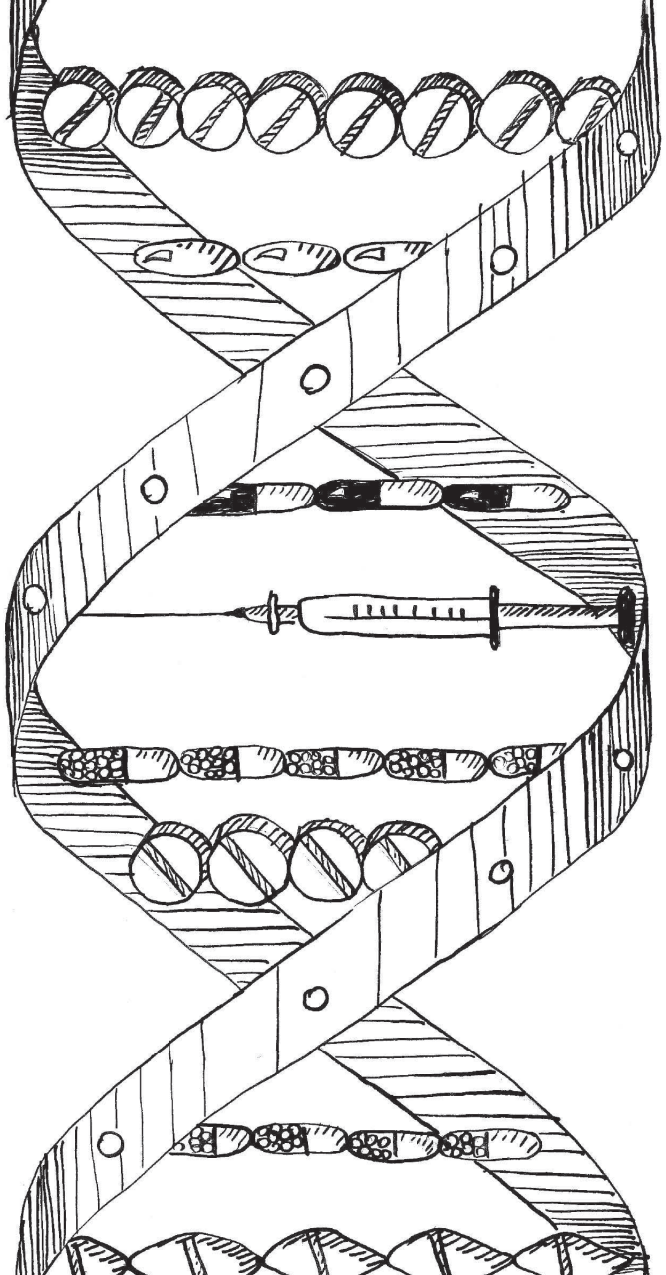
Improving acceptance of pharmacogenetic testing in patient care

Bank, P.C.D.

Part IV

Knowledge, experience and attitudes towards PGx of pharmacists and pharmacy students



Chapter 8

A nationwide survey of pharmacists' perception of pharmacogenetics in the context of a clinical decision support system containing pharmacogenetics dosing recommendations

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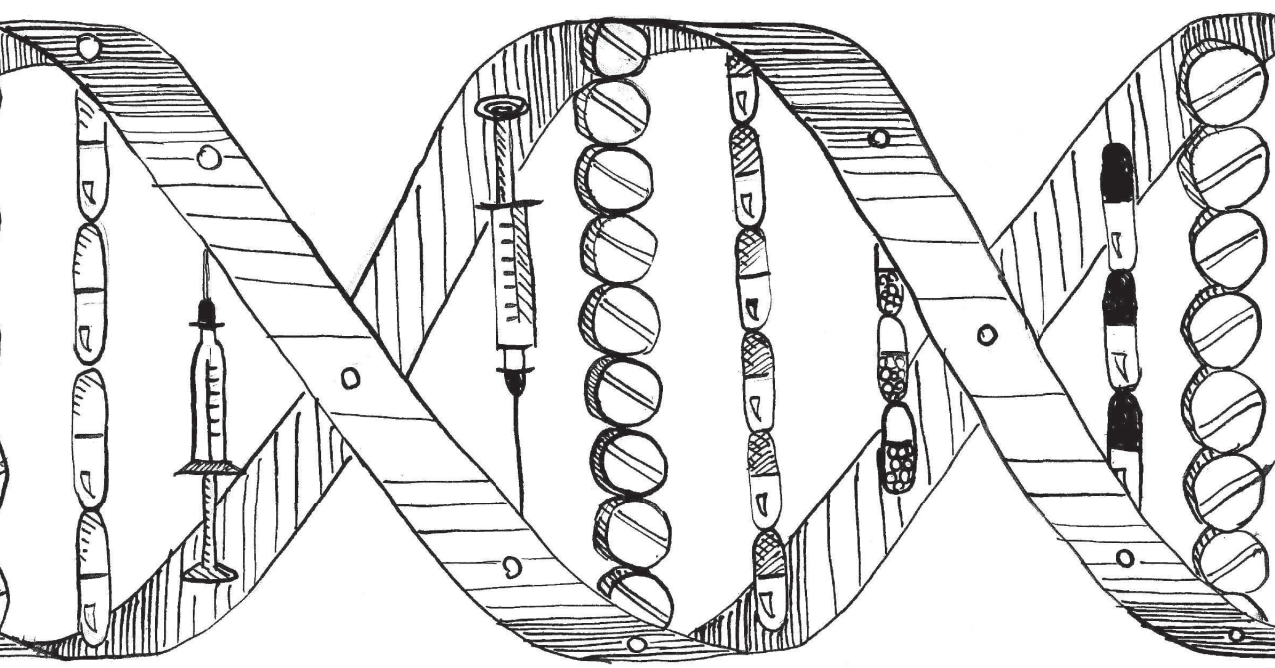

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Abstract

To benchmark Dutch pharmacists knowledge, experience, and attitudes towards PGx with a specific focus on the effects of awareness of the Dutch Pharmacogenetics Working Group guidelines. A web-based survey containing 41 questions was sent to all certified Dutch pharmacists. 667 pharmacists completed the survey (18.8%). Virtually all responders believed in the concept of PGx (99.7%). However, only 14.7% recently ordered a PGx test (≤ 6 months), 14.1% felt adequately informed and 88.8% would like to receive additional training on PGx. Being aware of the DPWG guidelines did not have any significant effect on knowledge or adoption of PGx. Dutch pharmacists are very positive towards PGx. However, test adoption is low and additional training is warranted.

Introduction

The field of pharmacogenetics (PGx) has progressed significantly with a large number of studies showing the relation between heritability and drug-response. In the United States and European Union currently 137 and 77 labels of registered drugs contain information on PGx respectively (1, 2). Moreover, initiatives by the Dutch Pharmacogenetics Working Group (DPWG) and Clinical Pharmacogenetics Implementation Consortium (CPIC) have provided guidelines containing drug/dose recommendations for a significant number of drug-gene-interactions (DGI's) (3-5).

With their knowledge on pharmacology, reputation as medication experts, and overview of drug use by their patient's, pharmacists are alleged to play a key role in the implementation of PGx into clinical care (6). However, despite their excellent position, pharmacists may not yet feel fully prepared for this task. A survey among Canadian pharmacists indicates that although they have high expectations towards PGx, only 7.7% felt comfortable interpreting and advising patients based on PGx test results (7). Similar results were found in a survey among US physicians where 10.3% of the responders felt adequately informed about PGx testing (8). Both these results stress the existence of a knowledge gap hindering the clinical uptake of PGx.

In The Netherlands, PGx guidelines developed by the DPWG providing clear cut recommendations for patients with a known genotype are available at point-of-care by incorporation into computerized systems for drug prescription, dispensing, and automated medication surveillance (Figure 8.1) (3). These computerized systems are used by all pharmacists working in a clinical setting in the Netherlands (in both primary and secondary care). The availability of DPWG guidelines in the routine workflow of healthcare professionals through interruptive clinical decision support (CDS) may reduce the perceived knowledge-gap and result in a higher clinical uptake of PGx (9, 10). The aim of this study was to benchmark Dutch pharmacists about knowledge, experience, and attitudes towards PGx. We specifically focused on investigating if the incorporation of DPWG recommendations on DGI's into CDS leads to reduction in the perceived knowledge gap, a reduction in the need of additional training on the subject and higher adoption of PGx testing.

Methods

Study design

A nationwide web-based cross-sectional survey was performed using the survey tool NetQ (11). Community, hospital and outpatient pharmacists in the Netherlands were

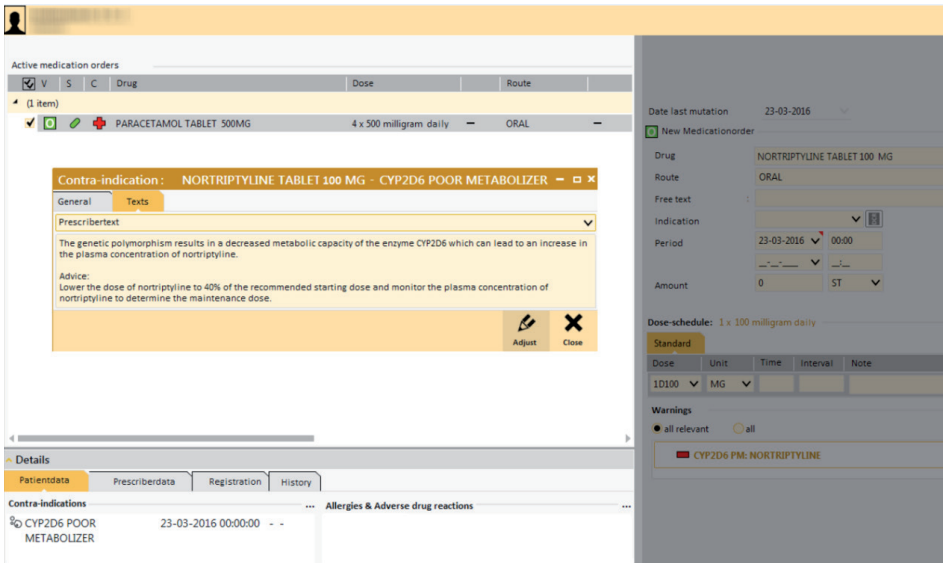

Figure 8.1: An example of an pop-up generated through clinical decision support.
A typical alert generated by automated medication surveillance after prescription of nortriptyline to a patient known to be a poor metabolizer of *CYP2D6* (condensed & translated from Dutch).

invited to participate by an email sent via their professional societies, with a reminder after two weeks. Community pharmacists were defined as pharmacists working in a primary healthcare setting outside of a hospital. Hospital pharmacists were defined as pharmacists working in a secondary healthcare setting within a hospital. Outpatient pharmacists were defined as pharmacists dispensing to outpatients from a pharmacy located in a hospital. Participants had the opportunity to complete the survey in the period from 15 November 2014 until 1st of January 2015. Responding to the invitation was completely voluntary and results were processed anonymously.

Questionnaire

A questionnaire was constructed by adapting two published surveys and translating the questions to Dutch (7, 8, 12, 13). A brief introduction explaining the terms pharmacogenetics & pharmacogenomics and the topics that would be surveyed preceded the questionnaire. The questionnaire consisted of a total of 41 questions (Supplementary Document S8.1).

Survey analysis

The survey responses of the participants were automatically tabulated and stored within NetQ [101]. Incomplete surveys were excluded from the analysis. Age was recoded into a six-level categorical variable (≤ 29, 30–39, 40–49, 50–59, and ≥ 60 years). Practice setting was recoded into a three-level variable: community pharmacy + other, outpatient pharmacy, hospital pharmacy.

Due to the low rate of responses in some answer categories the results of the questions 7–13 and 38 were condensed for the univariate and multivariate analysis into a two-level (Q 7–13) and three-level (Q38) scale respectively (8).

The univariate analyses were performed using a χ^2 test (excl. Q36). Variables that showed a significant association in the univariate analysis were included in the multivariate analyses. For the univariate and multivariate analysis of past adoption the variable future adoption was not included and for the analyses' of future adoption the group of past adopters were excluded (8). Data was analysed with SPSS version 20 (SPSS, Inc., Illinois, USA) and $p < 0.05$ was considered statistically significant.

Results

Characterization of responders

In total 3,550 pharmacists were invited to complete the questionnaire (596 hospital pharmacists, 171 outpatient, 2,780 community pharmacists and other). Of the invited pharmacists, 727 participants responded to the link and 667 (18.8%) completed the survey. Of the 667 responders 54.3% was female. Age was distributed bimodally with a median age of 41. The practice setting of the majority of the responders was community-based (69.6%), while 24.6% and 4.8% worked in a hospital or outpatient pharmacy respectively (Table 8.1). Of note, in the Netherlands pharmaceutical care in a secondary healthcare setting is delivered by hospital pharmacists. Unlike other countries, specialization does not focus on areas of medicine but on the different task within hospital pharmacy i.e. drug manufacturing, quality control, therapeutic drug monitoring, drug dispensing etc. In the primary healthcare setting drugs are dispensed to patients either by community pharmacies or outpatient pharmacies. Examples of "other" practice settings consisted of regulatory bodies, industry, and (temporarily) non-practising pharmacists.

The response rate among hospital pharmacists was significantly higher than the response rate among pharmacists working in the community + other or outpatient setting (27.5% vs. 16.9% and 18.4% respectively, $p < 0.001$). In the Netherlands all pharmacists receive

Table 8.1: Characteristics of responders

Characteristic	N	%
Gender		
Male	305	45.7
Female	362	54.3
Age		
20–29	105	15.7
30–39	209	31.3
40–49	144	21.6
50–59	158	23.7
≥ 60	51	7.6
Possession of specialty		
Yes	549	82.3
In residency	85	12.7
No	33	4.9
Practice setting		
Outpatient	32	4.8
Hospital	164	24.6
Community + other (*)	471	70.6

* For statistical purposes the group of responders working in a community setting (n = 464) and the group of responders working in a setting other than community, outpatient or hospital (n = 7) were combined.

six year university training resulting in a Pharm D degree. Afterwards pharmacists can enroll in a two or four year post-graduate specialty training to obtain a registration as community or hospital pharmacist respectively. Of the responders 12.7% were in a post-graduate residency programme to obtain a license. During their PharmD program or their postgraduate training 39.7% and 24.4% of the responders received any form of PGx training respectively (Supplementary Document S8.1, S8.2).

Belief in concept of PGx and expectations towards PGx testing

Virtually all responders (99.7%) believed that the genetic profile of a patient can influence the response to medication (Figure 8.2). To assess their expectations towards PGx testing pharmacists were asked three questions. On the question whether a PGx test could prevent their patients from taking the wrong dose or drug 80.8% of the responders answered at least 2 on a scale from 0 (no expectation) to 3 (high expectation). Using the same 4 point scale 84.9% responders answered ≥ 2 on the question whether PGx could detect which drug or dose will be more efficacious in their patient and 81.3% answered ≥ 2 on the question whether a PGx test will allow detection which drug or dose will cause less side effects (Figure 8.3 and Supplementary Document S8.1).

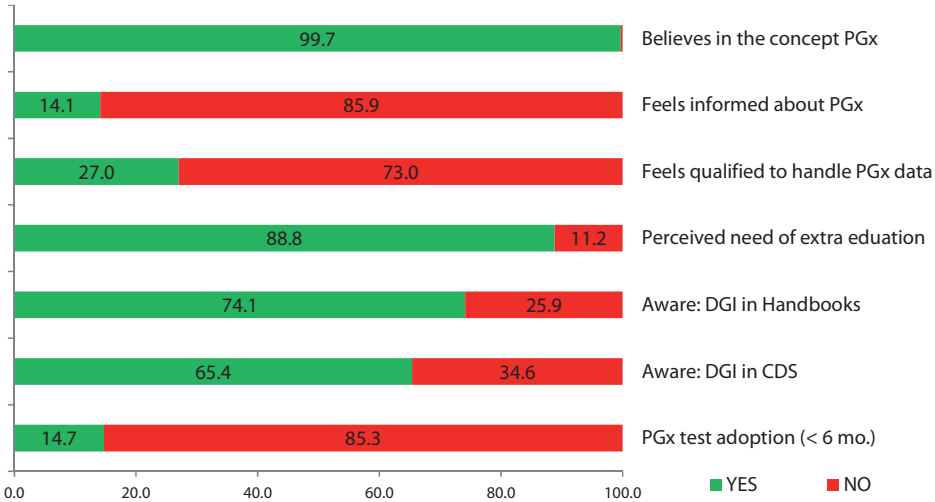

Figure 8.2: Key findings of this study to benchmark the knowledge of -, experience with - and attitude of Dutch pharmacists towards PGx testing in %.

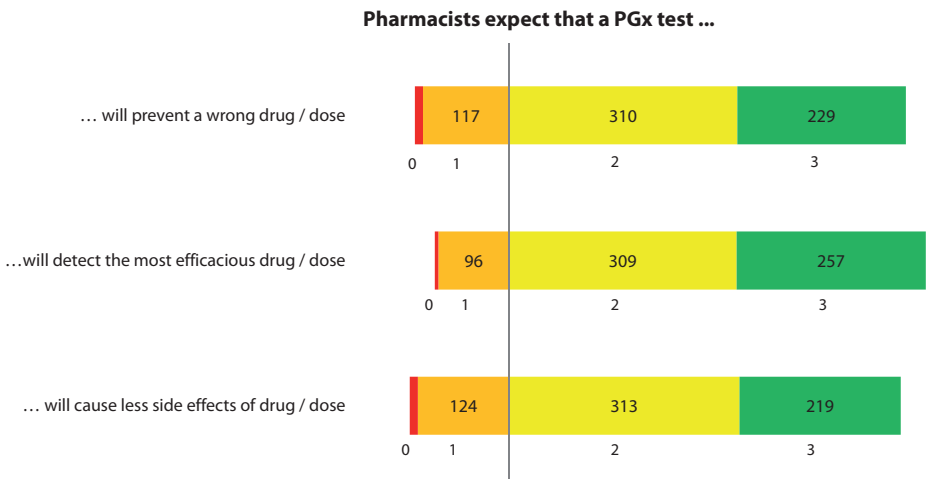

Figure 8.3: Expectations of pharmacists towards PGx testing.
Red = I have no expectations that PGx …, orange = I have low expectations that PGx …, yellow = I have high expectations that PGx …, green = I have very high expectations that PGx … (the size of the bar is proportional to the number of responders).

Adoption of PGx

In the Netherlands all pharmacists in clinical practice (community, outpatient and hospital setting) are allowed to order PGx tests directly or recommend PGx testing to the prescribing physicians. In this survey only 98 responders (14.7%) reported ordering or recommending

a PGx test in the last six months (Figure 8.2). The majority did so to improve the drug therapy of a patient (92.9%) and stated that the PGx test improved drug efficacy (52.0%), reduced toxicity (74.5%), improved the patients' understanding of their disease (18.4%), or improved the adherence of the patient to the treatment (6.1%). Of these past adopters of PGx testing 79.6% expected to order or recommend equal or more PGx test in the next six months, while 12.2% stated that they expect to order less PGx test in the near future. Of the 569 responders (85.3%) who did not order or recommend a PGx test in the last six months 71.7% stated that they did not expect to do so in the next six months. Overall, 27.1% of the surveyed pharmacists expected to order or recommend a PGx test in the next six months. Of the responders who had not adopted PGx testing or did not anticipate ordering or recommending a PGx test in the coming six months, the majority (60.3%) indicated a lack of knowledge and information on PGx testing as primary reason. Other main reasons for not ordering or recommending a PGx test consisted of "not dispensing drugs where PGx is relevant" (25.6%) or uncertainty regarding reimbursement of PGx (14.0%). From the PGx test adopters 8 stated that they did not expect to order a PGx in the next six months. Reasons given by these past adopters to not order a PGx test in the near future consisted of a lack of knowledge, resistance of patients towards PGx testing, alternate methods for monitoring of patients and limited clinical relevance.

Working in a hospital setting (OR 9.44, CI 4.13–21.57, $p < 0.001$) was the only variable independently associated with past use of PGx testing. Feeling informed about PGx testing (OR 1.99, CI 0.99–3.99, $p = 0.052$), the use of genetic laboratories as sources of information for availability of PGx tests and application in treatment (OR 2.16, CI 0.99–4.71, $p = 0.054$) and the use of other sources of information to guide drug treatment (OR 2.92, CI 0.98–8.71, $p = 0.054$) showed a trend towards significance with past adoption of PGx testing. Being aware of the existence of the DPWG guidelines (OR 1.00, CI 0.38–2.67, $p = 0.999$) and their integration in the electronic prescription and dispensing systems (OR 1.23, CI 0.57–2.69, $p = 0.596$) did not show an independent associations with past use of adoption (Supplementary Document S8.3). The multivariate analysis for future adoption indicated that working in a hospital setting (OR 5.85, CI 2.67–12.82, $p < 0.001$) or outpatient setting (OR 3.01, CI 1.05–8.57, $p = 0.039$), feeling comfortable to recommend a PGx test to a patient to predict whether a drug is effective in their case (OR 2.18, CI 1.03–4.64, $p = 0.043$), using post-academic education as source of information for availability of pharmacogenetic tests and how to apply them in pharmacotherapy (OR 2.91, CI 1.36–6.23, $p = 0.006$) and having high worries that there is no suitable drug for their patients (OR 1.31, CI 1.06–1.611, $p = 0.011$) were independently associated with future adoption of PGx testing (Supplementary Document S8.3). Differences between adopters, future adopters and non-adopters can be seen in Supplementary Document S8.4.

Attitude towards own ability to interpret PGx test results

Currently, 48.4% of the participants would feel comfortable to recommend a PGx test to predict drug efficacy. However, if the PGx test could also reveal information about disease risk only 7.8% would feel comfortable to do so. Of the surveyed pharmacists, 27.0% would feel qualified to receive PGx test results of a patient, interpret them and advise a patient or treating healthcare professional on the choice of drug or dose based on the results (Figure 8.2). Reflecting the questions informing about education and training, the majority of pharmacists (66.3%) would see themselves qualified after receiving training on the subject. Participants were also asked if they would recommend a drug treatment despite a PGx test result indicating non-response or severe side effects for their patient. Approximately half of the responders (49.0%) would not recommend the treatment, while a slightly smaller group (47.5%) would recommend the drug treatment provided it concerned a life-threatening disease. Only 3.4% would recommend the drug irrespectively of the results of the PGx test or condition of the patient.

Access to and use of PGx information

Although approximately half of the pharmacists received some sort of PGx training (see above) only 14.1% felt adequately informed about the availability of PGx tests and how to apply PGx in relation to drug therapy. Furthermore, almost all responders (88.8%) indicated they would like additional training on PGx (Figure 8.2). Responders indicated using the summary of product characteristics (SmPC), the European drug package insert (78.7%), internet (63.2%), colleagues (38.8%), post-academic courses (30.6%), genetic laboratories (24.0%) or other such as the Informatorium Medicamentorum (IM), a handbook published by the The Royal Dutch Pharmacist's Association (KNMP) containing the DPWG recommendations in addition to information on drug dosages, (contra) indications, drug-drug-interactions, (25.6%) as sources of information for availability of PGx tests and application in treatment. Concerning the evidence for adoption of PGx testing recommendation by a guideline (93.0%), scientific publication (81.3%), approval or recommendation by regulatory authorities (80.4%) were seen as high value by responders, while less responders indicated recommendation by opinion leaders as high value (46.7%).

The majority of the participants (88.0%) would use the IM to make a choice about the drug and dose in case of a patient with genotype results. Other sources indicated to guide drug treatment included the SmPC (61.0%), scientific literature (58.3%), Farmacotherapeutisch Kompas (FK), a handbook containing information on drug dosages, (contra)indications, drug-drug-interactions published by The National Health Care Institute in the Netherlands (34.2%), regulatory authorities (25.9%) or a colleague (22.9%). Only 10 pharmacists (1.5%)

had encountered a patient who had ordered a genetic test on their own account in the preceding six months (Supplementary Document S8.1).

74.1% of the responders were aware of the existence of the DPWG dosing guidelines and 65.4% was aware that these guidelines were incorporated in CDS systems (Figure 8.2). Responders who were aware of the guidelines and their integration in the CDS systems, were more likely to be early adopter ($p < 0.001$) and more likely to feel informed about PGx testing ($p < 0.001$). A subgroup analysis of pharmacy specialties showed that only hospital pharmacists were more likely to feel informed about PGx testing if they were aware of the DPWG guidelines ($p < 0.05$). In the multivariate analysis of "feeling informed about PGx testing" working in a hospital setting (OR 3.67, CI 1.57–8.55, $p = 0.003$), not being in need for additional training (OR 2.96, CI 1.38–6.33, $p = 0.005$), scoring "undecided" or "(very) important" for approval or recommendation of a PGx test by regulatory authorities (OR 42.28, CI 3.59–498.48, $p = 0.003$ and OR 14.38, CI 1.33–155.55, $p = 0.028$), still advising the only available drug to treat your patient's disease if a pharmacogenetic test revealed ineffective or leads to severe side effects (OR 8.54, CI 2.25–32.42, $p = 0.002$) and still advising the only available drug to treat your patient's life-threatening disease if a pharmacogenetic test revealed ineffective or leads to severe side effects (OR 0.46, CI 0.24–0.86, $p = 0.015$) were independently associated with feeling informed about PGx testing. No independent association between being aware of the DPWG guidelines (OR 1.36, CI 0.51–3.65, $p = 0.537$) and their incorporation in the electronic medication systems (OR 1.84, CI 0.82–4.13, $p = 0.139$) with feeling informed about PGx testing was observed (Supplementary Document S8.3).

In a similar multivariate analysis factors associated with the perceived need of extra PGx training were studied. The analysis revealed that feeling qualified to receive PGx test results of a patient, interpret them and advise upon PGx test results after training (OR 3.70, CI 1.41–9.76, $p = 0.008$) and feeling not informed about PGx testing (OR 2.40, CI 1.17–4.90, $p = 0.016$), using the SmPC as source of information to guide drug treatment (OR 1.85, CI 1.05–3.26, $p = 0.032$) were independently associated with the need for additional training on PGx related subjects. Being aware of the existence of the DPWG guidelines (OR 0.89, CI 0.41–1.95, $p = 0.770$) and the incorporation in CDS (OR 1.03, CI 0.51–2.08, $p = 0.927$) showed no significant association with a reduced need for training (Supplementary Document S8.3).

Worries related towards PGx testing, privacy and coverage

Participants were asked a total of eight questions concerning worries related to consequences of PGx test results, privacy of PGx data and coverage of PGx tests by insurance

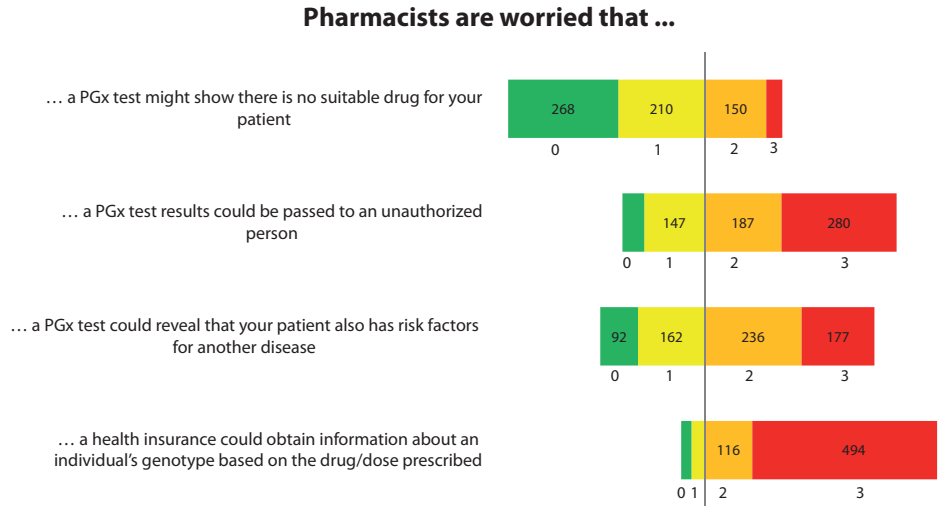

Figure 8.4: Worries of pharmacists towards PGx testing.
Green = I have no worries that …, yellow = I have low worries that …, orange = I have high worries that PGx …, red = have very high worries that PGx … (the size of the bar is proportional to the number of responders).

companies. Four questions assessed potential concerns related to PGx using a 4-point scale ranging from 0 (no worries) to 3 (very worried). To the question inquiring to whether a PGx test might reveal that there is no suitable drug available for their patients 28.3% of the participants answered that they were at least moderately worried (score ≥ 2). Of the responders 52.9% was at least moderately worried that a PGx test might reveal that a patient has risk factors for another disease. Furthermore, 70.0% of the responders was at least moderately worried that results of a PGx test could come in hands of an unauthorized individual and the majority of the responders (91.4%) was at least moderately concerned that a health-insurance company could infer a patients' genotype based on the prescribed drug or dose (Figure 8.4).

In line with the four previous questions, 76.9% of the responders are more concerned about the loss of privacy of patients' PGx test results than the results from any other laboratory or diagnostic test. With regard to privacy of the data responders agreed that the treating physician (99.3%) and the pharmacist (97.3%) should have access to the PGx test results, while nurses, psychologists and dieticians should not. The opinion whether other health-care professionals should be able to access PGx data was mixed (Supplementary Document S8.2). With regard to unfavourable results almost two-thirds of the responders (63.7%) thought that a PGx test with negative test result could have a possible adverse psychological effect on a patient and/or the patients' family. The final question of this

section related to coverage of PGx by health-insurers. Virtually all responders (99.7%) stated that health-insurance companies should provide coverage for PGx tests, however there is a mixed opinion whether PGx should always be covered (69.1%) or only in specific occasions (30.6%).

Differences between pharmacy specialties

Survey results of the different practice settings were compared and significant differences were observed between the three groups. The group of responders working in a community + other setting contained relatively more individuals of age ≥ 50 ($p = 0.003$). Hospital pharmacists had received post-graduate training on PGx during their specialization more often compared to the community + other and outpatient setting (60.4% vs. 12.7% vs. 12.5%, $p < 0.001$), were more often aware of the DPWG guidelines (91.5% vs. 67.3% vs. 84.4%, $p < 0.001$) and their integration in the CDS systems (79.9% vs. 60.3% vs. 65.6%, $p < 0.001$) compared to the other two groups. Furthermore, hospital pharmacist felt comfortable to recommend PGx testing more often (74.4% vs. 40.1% vs. 37.5%, $p < 0.001$), felt qualified to receive PGx testing results, interpret them and advise a patient based on PGx test results more often (59.1% vs. 16.3% vs. 18.8%, $p < 0.001$) and felt less need for training on the subject (24.4% vs. 7.0% vs. 6.2%, $p < 0.001$) compared to the community pharmacy + other and outpatient setting. Other differences between specialties can be seen in Supplementary Document S8.2.

Discussion

This survey shows that Dutch pharmacists are generally very positive towards PGx. Virtually all responders believe that indeed drug response can be at least partially explained by genetic variation and the majority of the participants have high expectations of PGx. We hypothesized that incorporation of the DPWG guidelines in automated CDS systems would lead to higher adoption of PGx, while simultaneously reducing the need for additional PGx training (9). However, the results from the current study show that being aware of the availability of the DPWG guidelines was not independently associated with feeling informed about PGx testing or past adoption of PGx testing. Furthermore, the percentage of PGx test adoption is comparable to the findings of a survey among physicians in the US (14.7% vs. 12.9%), where mostly information on DGI's is not readily available in CDS systems. Similar to the US, there appears to be a knowledge gap present among the Dutch pharmacists, as only 14.1% of the responders in this survey feels adequately informed about PGx testing. Similar to the association between feeling informed and adoption of PGx testing found

in the study by Stanek et al. ($p < 0.001$) our survey shows a trend towards an association between feeling informed and PGx test adoption (8). The combined data from both these studies indicate that a lack of knowledge about availability of PGx tests and their application in drug therapy is one of the remaining barriers for clinical implementation of PGx into clinical practice. The current study confirms that a large amount of responders would like additional training on the subject and that being aware of the availability of the DPWG guidelines was not associated with a reduced need for additional PGx training. A similar need for training (96.6%) is seen in a survey performed among 284 pharmacists in Canada, with a similar electronic drug prescribing and dispensing system as used in the US (7).

It appears that PGx implementation programmes should be accompanied by extensive training programmes as currently implemented in the 1200 patient project and the programmes PG4KDS, eMERGE-PGx, PREDICT and U-PGx (14-18). In all, the results from this study combined with findings from previous studies refute our hypothesis that nationwide availability of interruptive CDS containing dosing advices on DGI's leads to higher adoption of PGx and reduces the need for additional training.

Our results indicate a need of more education about PGx. Only 39.7% and 24.4% of the responders received training on PGx-related subjects in their PharmD program or their postgraduate training respectively. A stronger embedding of PGx in the curricula of pharmacists in training could be a manner to prevent a potential knowledge gap in future generations of pharmacists. An example could be by integrating PGx into courses that train PharmD students in medication surveillance as in our opinion PGx should be an integral part of this area within pharmacy practice. Post-academic education is also considered important by the responders for disseminating PGx knowledge, and was associated with adoption of PGx in the near future (OR 2.91, CI 1.36–6.23, $p = 0.006$). However an ideal setting for a PGx training for (community & outpatient) pharmacists remains to be established. Additional research in the form of targeted surveys, structured interviews and / or focus groups could further provide a more detailed answer how specific demands for PGx related information and education can be met.

The current cross-sectional study evaluated both the current attitude of Dutch pharmacists towards PGx and their own perceived abilities to interpret PGx data, as well as actual adoption of PGx testing by pharmacists. The data indicate that approximately 80% of the pharmacists are moderately hopeful that PGx could prevent patients receiving wrong drug or doses; could detect which drug or dose is the most effective for a patient and that PGx could minimize the risk of adverse advents. The survey of de Denus et al. shows similar ratings of 80.0%, 82.6% and 79.1% of Canadian pharmacists who are at least moderately hopeful on these subjects respectfully. Dutch pharmacists also have similar worries

(moderate to high) compared with their Canadian colleagues (7).

The results from this survey further show that adoption of PGx is particularly low in the community pharmacy setting, although previous research has shown that implementation of PGx in primary care is feasible (19). In the Netherlands, pharmacists working in primary care are considered the gatekeepers of patients' medication records. Prescriptions from multiple prescribers for the same patient converge in community or outpatient pharmacies. Therefore, community and outpatient pharmacists are the designated healthcare professionals to perform medication surveillance based on therapeutic recommendations from the G-standard, the nationwide electronic drug database. In our opinion PGx is an integral part of medication surveillance and therefore these pharmacists should understand a PGx test result at a phenotype level and to be able to optimize therapy based on CDS alerts. In addition, as experts in the area of pharmacology pharmacists could take a leading role in genotyped guided therapy by recommending or ordering test when this is indicated.

The low adoption might be explained by the lack of consensus on which specific patients should be tested. For several drug treatments typically applied in the hospital setting i.e. fluoropyrimidine derivatives or purine-antimetabolites, there is high quality evidence from prospective studies showing that genotyping for mutations in *DPYD* and *TPMT* improves outcome of drug treatment (20, 21). However, for many drugs frequently used in primary care such evidence is still lacking. In addition, currently available pharmacogenetic guidelines by the DPWG and the CPIC only provide recommendations for patients with a known genotype and do not indicate which patients should be genotyped. Future versions of the DPWG guidelines containing information on when genotyping is indicated in combination with clinical rules or pre-test alerts could further help with the implementation of PGx testing.

For this cross-sectional survey a voluntary basis was used introducing the potential risk of bias as strongly opinionated (both in a positive and in negative manner) or experienced individuals are more likely to respond introducing selection bias. From "The Dutch Foundation for Pharmaceutical Statistics (SFK)", an organization which gathers data from a panel which includes 95% of the community and outpatient pharmacies in the Netherlands, demographic data on pharmacists working in the community and outpatient setting was obtained. The distribution of responders to this survey working in a community or outpatient setting between the different age groups (≤ 29, 30–39, 40–49, 50–59, and ≥ 60 years) differed significantly from the distribution of all Dutch pharmacists among these age groups ($p < 0.001$). In the surveyed population a higher relative count of pharmacist was found in the combined group of 20–39 (44.0% vs. 37.8%) compared to the combined group of 40+ (56.0% vs. 62.2%) in a chi^2 analysis ($p = 0.009$). The male / female ratio and

the ratio between specialty trained and in training did not differ significantly (22). The age distribution of responders working in a hospital setting among the five age groups also differed significantly from the age distribution of the whole population of hospital pharmacists over the five age groups ($p < 0.001$). Responders were also significantly younger compared to all pharmacists working in a hospital setting when the age groups were combined in the groups 20–39 (56.2% vs. 45.1%) and 40+ (43.5% vs. 54.9%) and analysed with a chi^2 analysis ($p < 0.012$). Demographic data on the population of hospital pharmacists was obtained from the professional society of hospital pharmacists, (www.nvza.nl) (23). Likewise, no differences in gender and the ratio between specialty trained and in training were observed. Therefore, our data may not be fully applicable to the older pharmacists. The percentage of responders among the hospital pharmacists was significantly higher compared to the other two groups. In the Netherlands, several hospitals have prospective genotyping programmes for *TPMT* and *DPYD* and hospital pharmacists may therefore have more experience with PGx testing (24). As a result, our estimate of adoption of PGx among the whole population of Dutch pharmacists may be too optimistic. However, compared to the two previous surveys our study shows a higher response rate (18.8% vs. 2.59% and 6.76%) that reduces the risk of selection bias (7, 8).

Conclusion

This survey shows that adoption of PGx among Dutch pharmacists is still low and despite the nationwide availability of interruptive CDS containing the DPWG guidelines Dutch pharmacists still perceive a lack of knowledge on the subject that remains to be an important barrier for PGx test adoption.

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Supplementary Document S8.1: Questionnaire + results per question

Baseline				
			N	%
Q1: What is your gender?		☐ Male	305	45.7
		☐ Female	362	54.3
			N	%
Q2: What is your age?		☐ 20–29	105	15.7
		☐ 30–39	209	31.3
		☐ 40–49	144	21.6
		☐ 50–59	158	23.7
		☐ ≥ 60	51	7.6
			N	%
Q3: Are you in possession of a specialty or are you in training for a specialty?	☐ Yes, I am in possession of a specialty		549	82.3
	☐ Yes, I am in training for specialty		85	12.7
	☐ No, I do not possess a specialty and are not in training for a specialty		33	4.9
			N	%
Q4: What is your practice setting?		☐ Community pharmacy	464	69.6
		☐ Hospital pharmacy	164	24.6
		☐ Outpatient pharmacy	32	4.8
		☐ Other …	7	1.0
			N	%
Q5: Which department carries out the majority of the pharmacogenetic test for diagnostic purposes?	☐ Hospital pharmacy laboratory		19	11.6
	☐ Clinical chemistry laboratory		30	18.3
	☐ Human genetics laboratory		11	6.7
	☐ Samples are determined externally		87	53.0
	☐ Samples are not determined in the hospital and not determined externally		8	4.9
	☐ Other ...		4	2.4
	☐ Hospital pharmacy laboratory		5	3.0
	☐ Unknown		19	11.6
Belief and expectations towards PGx				
			N	%
Q6: Do you believe that a patient's genetic profile may influence his/her response to drug therapy?		☐ Yes	665	99.7
		☐ No	2	0.3
			N	%
Q7: Do you expect that pharmacogenetic testing will prevent your patient from taking the wrong medicine (or the wrong dose)? (0 = no expectations… / 3 = very high expectations …)		☐ 0	11	1.6
		☐ 1	117	17.5
		☐ 2	310	46.5
		☐ 3	229	34.3

Supplementary Document S8.1: ***Continued***

		N	%
Q8: Do you expect that pharmacogenetic testing will allow detecting which drug (or which dose) will be more efficacious in your patient? (0 = no expectations… / 3 = very high expectations …)	☐ 0	5	0.7
	☐ 1	96	14.4
	☐ 2	309	46.3
	☐ 3	257	38.5
		N	%
Q9: Do you expect that pharmacogenetic testing will allow detecting which drug (or which dose) will cause less side effects in your patient? (0 = no expectations… / 3 = very high expectations …)	☐ 0	11	1.6
	☐ 1	124	18.6
	☐ 2	313	46.9
	☐ 3	219	32.8
Worries toward PGx testing			
		N	%
Q10: Are you worried that a PGx test might show there is no suitable drug for your patient? (0 = not worried / 3 = very worried)?	☐ 0	268	40.2
	☐ 1	210	31.5
	☐ 2	150	22.5
	☐ 3	39	5.8
		N	%
Q11: Are you worried that a PGx test could reveal that your patient also has risk factors for another disease that he/she does not know about? (0 = not worried / 3 = very worried)?	☐ 0	92	13.8
	☐ 1	162	24.3
	☐ 2	236	35.4
	☐ 3	177	26.5
		N	%
Q12: Are you worried that a health insurance could obtain information about an individual's genotype based on the drug/dose prescribed? (0 = not worried / 3 = very worried)	☐ 0	25	3.7
	☐ 1	32	4.8
	☐ 2	116	17.4
	☐ 3	494	74.1
		N	%
Q13: Are you worried that one of your patient's PGx test results could be passed to an unauthorized person? (0 = not worried / 3 = very worried)	☐ 0	53	7.9
	☐ 1	147	22.0
	☐ 2	187	28.0
	☐ 3	280	42.0
		N	%
Q14: Do you think that your patient's unfavorable test results could have adverse psychological consequences on him and his family?	☐ Yes	425	63.7
	☐ No	105	15.7
	☐ No opinion	137	20.5
		N	%
Q15: Are you more concerned about the loss of privacy of a patient's genetic information from the results of pharmacogenetic tests than from the results of other laboratory or diagnostic tests?	☐ Yes	154	23.1
	☐ No	513	76.9

Supplementary Document S8.1: ***Continued***

		Yes		No	
		N	%	N	%
Q16: Among the following health professionals, which ones should have access to patients' pharmacogenetic information (select all that apply)	☐ Physician	662	99.3	5	0.7
	☐ Pharmacist	649	97.3	18	2.7
	☐ Genetic counsellor	517	77.5	150	22.5
	☐ Clinical chemist	319	47.8	348	52.2
	☐ Nurse practitioner	113	16.9	554	83.1
	☐ Psychologist	41	6.1	626	93.9
	☐ General nurse	13	1.9	654	98.1
	☐ Social worker	1	0.1	666	99.9
	☐ Dietician	27	4.0	640	96.0

		N	%
Q17: Do you believe that health insurers should provide full coverage for pharmacogenetic tests?	☐ Always	204	30.6
	☐ Sometimes	461	69.1
	☐ Never	2	0.3

PGx test adoption

		N	%
Q18: At any time in the past 6 months, have you ordered or recommended a pharmacogenetic test?	☐ Yes	98	14.7
	☐ No	569	85.3

		N	%
Q19: Within the past 6 months, with what average frequency have you ordered or recommended a pharmacogenetic test?	☐ 1 time /mo.	77	78.6
	☐ 2–5 times /mo.	22	22.4
	☐ >5 times /mo.	7	7.1
	☐ N/A		

		Yes		No	
		N	%	N	%
Q20: At any time in the past 6 months, have you ordered or recommended a pharmacogenetic test for … (select all that apply)	☐ A patient	91	92.9	7	7.1
	☐ Yourself	2	2.0	96	98.0
	☐ A colleague or friend	5	5.1	93	94.9
	☐ A family member?	3	3.1	95	96.9
	☐ Other	3	3.1	95	96.9
	☐ N/A				

Supplementary Document S8.1: ***Continued***

		Yes		No	
		N	%	N	%
Q21: Pharmacogenetic tests have benefited your patients by … (select all that apply)	☐ Improving drug effectiveness	51	52.0	47	48.0
	☐ Reducing drug toxicity	73	74.5	25	25.5
	☐ Increasing patients' understanding of their disease/therapy	18	18.4	80	81.6
	☐ Improving patients' adherence to therapy	6	6.1	92	93.9
	☐ No tests ordered	6	6.1	92	93.9
	☐ Patients have not benefited	11	11.2	87	88.8
	☐ Other	51	52.0	47	48.0

		N	%
Q22: Do you anticipate ordering or recommending more, less or no pharmacogenetic tests for patients within the next 6 months	☐ More PGx tests	78	79.6
	☐ Less PGx test	12	12.2
	☐ No tests	8	8.2

		N	%
Q23: Do you anticipate ordering or recommending a pharmacogenetic test for a patient within the next 6 months?	☐ Yes	181	27.1
	☐ No	486	72.9

		Yes		No	
		N	%	N	%
Q24: If you have not ordered or recommended a pharmacogenetic test in the past 6 months, or do not anticipate ordering one in the next 6 months, please indicate the main reason why (select one):	☐ Concern over privacy	10	1.7	567	98.3
	☐ Little-to-no or uncertain value in testing	8	1.4	569	98.6
	☐ Lack of insurance coverage for testing	81	14.0	496	86.0
	☐ Not enough knowledge about testing/genomic markers	348	60.3	229	39.7
	☐ Patients' resistance to genetic testing	11	1.9	566	98.1
	☐ I do not dispense drugs with PGx tests available or recommended	148	25.6	429	74.4
	☐ Other	184	31.9	393	68.1
	☐ N/A				

		N	%
Q25: Currently, various (pharmaco)genetic tests are available directly to consumers. At any time in the past 6 months, has a patient brought into your office the results of a genome-wide scan obtained on his or her own?	☐ Yes	10	1.5
	☐ No	657	98.5

Supplementary Document S8.1: ***Continued***

Education & training			
		Yes	No
		N	N
Q26: What kind of genetics test(s) had these patients performed? A "whole genome scan" is a scan of the patient's DNA that reveals markers associated with diseases and/or altered response to drug therapy	☐ A test of a single (pharmaco) gene	2	8
	☐ A test of multiple (pharmaco)genes	4	6
	☐ A "whole genome scan"	4	6

		N	%
Q27: At which University did you obtain your PharmD?	☐ University of Groningen	221	33.1
	☐ University of Leiden	38	5.7
	☐ University of Utrecht	357	53.5
	☐ University of Amsterdam	32	4.8
	☐ Other	19	2.8

		N	%
Q28: Was PGx instruction included in your graduate pharmacy education curriculum?	☐ Yes	265	39.7
	☐ No	402	60.3

		N	%
Q29: Was PGx instruction included in your postgraduate specialty training ?	☐ Yes	163	24.4
	☐ No	504	75.6

		N	%
Q30: Do you feel that you are adequately informed about the availability of genetic testing and its application in the context of drug therapy?	☐ Yes	94	14.1
	☐ No	573	85.9

		N	%
Q31: Would you like to participate in extra training on pharmacogenetics	☐ Yes	592	88.8
	☐ No	75	11.2

Attitude towards own ability to interpret PGx test results			
		N	%
Q32: Would you feel qualified to receive your patient's pharmacogenetic testing results, interpret them and advise your patient on a treatment choice?	☐ Yes	180	27.0
	☐ Yes, but after having had training on the subject	442	66.3
	☐ No, this is not my responsibility	45	6.7

Supplementary Document S8.1: ***Continued***

		N	%
Q33: Would you feel comfortable to recommend pharmacogenetic testing to your patients if those tests could predict that a specific drug could be efficacious in their case?	☐ Yes	323	48.4
	☐ No	164	24.6
	☐ Undecided	180	27.0
		N	%
Q34: If a pharmacogenetic test revealed that the only available drug to treat your patient's disease is ineffective or leads to severe side effects, would you still advise your patient to take that medicine?	☐ Yes	23	3.4
	☐ No	317	45.7
	☐ Yes, only if he/she had a life-threatening disease	327	49.0
		N	%
Q35: Would you feel comfortable to recommend genetic testing to your patients if those tests could reveal which diseases are liable to affect them in the future	☐ Yes	52	7.8
	☐ Yes, but only if that disease could be treated	84	12.6
	☐ No	339	50.8
	☐ Undecided	192	28.8

Access to and use of PGx information

		N	%
Q36: Do you obtain extra information on genetic testing and its application in the context of drug therapy? (if "No" proceed to Q38)	☐ Yes	258	38.7
	☐ No	409	61.3

		Yes		No	
		N	%	N	%
Q37: Where do you obtain information on genetic testing and its application in the context of drug therapy? (select all that apply)	☐ Drug labeling (package insert)	203	30.4	464	69.6
	☐ Internet	163	24.4	504	75.6
	☐ Genetic testing laboratory	62	9.3	605	90.7
	☐ Colleague	100	15.0	567	85.0
	☐ Post-academic education and pharmacotherapeutic meetings	79	11.8	588	88.2
	☐ Other	66	9.9	601	90.1

Supplementary Document S8.1: ***Continued***

			N	%
Q38: What level of evidence is of importance to you in consideration of ordering a pharmacogenetic test	Authority approval of recommendation	☐ Very unimportant	7	1.0
		☐ Unimportant	10	1.5
		☐ Un-decided	114	17.1
		☐ Important	310	46.5
		☐ Very important	226	33.9
	Speciality guidelines	☐ Very unimportant	4	0.6
		☐ Unimportant	3	0.4
		☐ Un-decided	40	6.0
		☐ Important	328	46.9
		☐ Very important	292	43.8
	Scientific journal	☐ Very unimportant	4	0.6
		☐ Unimportant	5	0.7
		☐ Un-decided	116	17.4
		☐ Important	374	56.1
		☐ Very important	168	25.2
	Recommendation or experience of thought leaders or respected colleagues	☐ Very unimportant	3	0.4
		☐ Unimportant	30	4.5
		☐ Un-decided	256	38.4
		☐ Important	328	49.2
		☐ Very important	50	7.5

		Yes		No	
		N	%	N	%
Q39: Where do you obtain information to make a choice about the drug and dose in case of a known genotype?	☐ Drug labeling (package insert)	407	61.0	260	39.0
	☐ Registration authority	173	25.9	494	74.1
	☐ Scientific literature	389	58.3	278	41.7
	☐ Colleague	153	22.9	514	77.1
	☐ Pharmaceutical Compass	228	34.2	439	65.8
	☐ Informatorium Medicamentorum	587	88.0	80	12.0
	☐ Other …	37	5.5	630	94.5

		N	%
Q40: Were you aware that in the Netherlands dosing guidelines are available with information on the choice and dose of drugs based on the genotype of a patient?	☐ Yes	474	74.1
	☐ No	173	25.9

		N	%
Q41: Were you aware that in the Netherlands medication surveillance based on the genotype of a patient in incorporated in the automated drug dispensing systems?	☐ Yes	436	65.4
	☐ No	231	34.6

Supplementary Document S8.2: Comparison between specialties

	Community + other		Outpatient		Hospital	
	N	%	N	%	N	%
Response	p < 0.001					
Yes	471	16.9	32	18.4	164	27.5
No	2316	83.1	142	81.6	432	72.5
	2787	100.0	174	100.0	596	100.0
Age	p = 0.003					
20–29	71	15.1	8	25.0	26	15.9
30–39	130	27.6	12	37.5	67	40.9
40–49	99	21.0	7	21.9	38	23.2
50–59	128	27.2	5	15.6	25	15.2
≥ 60	43	9.1	0	0.0	8	4.9
	471	100.0	32	100.0	164	100.0
Do you expect that…						
PGx will allow detect of which drug or dose will be more efficacious	p = 0.017					
0	2	0.4	0	0.0	3	1.8
1	57	12.1	6	18.8	33	20.1
2	225	47.8	9	28.1	75	45.7
3	187	39.7	17	53.1	53	32.3
	471	100.0	32	100.0	164	100.0
At any time in the past 6 months, have you ordered or recommended a pharmacogenetic test	p < 0.001					
No	454	96.4	30	93.8	85	51.8
Yes	17	3.6	2	6.2	79	48.2
	471	100.0	32	100.0	164	100.0
Do you anticipate ordering or recommending a pharmacogenetic test for a patient within the next 6 months	p < 0.001					
no past testing, no future testing	407	86.4	23	71.9	48	29.3
no past testing, future testing	47	10.0	7	21.9	37	22.6
past testing	17	3.6	2	6.2	79	48.2
	471	100.0	32	100.0	164	100.0

Supplementary Document S8.2: ***Continued***

	Community + other		Outpatient		Hospital	
	N	%	N	%	N	%
At which University did you obtain your PharmD	p = 0.015					
Groningen	153	32.5	8	25.0	60	36.6
Utrecht	241	51.2	22	68.8	94	57.3
Leiden	29	6.2	1	3.1	8	4.9
Amsterdam	30	6.4	0	0.0	2	1.2
Other	18	3.8	1	3.1	0	0.0
	471	100.0	32	100.0	164	100.0
Was education on PGx included in your postgraduate specialty training	p < 0.001					
No	411	87.3	28	87.5	65	39.6
Yes	60	12.7	4	12.5	99	60.4
	471	100.0	32	100.0	164	100.0
Would you like to participate in extra training on pharmacogenetics	p < 0.001					
No	33	7.0	2	6.2	40	24.4
Yes	438	93.0	30	93.8	124	75.6
	471	100.0	32	100.0	164	100.0
Would you feel qualified to receive your patient's pharmacogenetic testing results, interpret them and advise your patient on a treatment choice	p < 0.001					
No	34	7.2	2	6.2	9	5.5
Yes	77	16.3	6	18.8	97	59.1
Yes, after training	360	76.4	24	75.0	58	35.4
	471	100.0	32	100.0	164	100.0
Would you feel comfortable to recommend pharmacogenetic testing to your patients if those tests could predict that a specific drug could be efficacious in their case	p < 0.001					
No	134	28.5	11	34.4	19	11.6
Yes	189	40.1	12	37.5	122	74.4
Undecided	148	31.4	9	28.1	23	14.0
	471	100.0	32	100.0	164	100.0

Supplementary Document S8.2: ***Continued***

	Community + other		Outpatient		Hospital	
	N	%	N	%	N	%
Do you feel that you are adequately informed about the availability of genetic testing and its application in the context of drug therapy	p < 0.001					
No	444	94.3	31	96.9	98	59.8
Yes	27	5.7	1	3.1	66	40.2
	471	100.0	32	100.0	164	100.0
Where do you obtain information on genetic testing and its application in the context of drug therapy?						
Drug labelling (package insert)	p < 0.001					
No	359	76.3	23	71.9	82	50.0
Yes	112	23.7	9	28.1	82	50.0
	471	100.0	32	100.0	164	100.0
Colleague	p < 0.001					
No	429	91.1	25	78.1	113	68.9
Yes	42	8.9	7	21.9	51	31.1
	471	100.0	32	100.0	164	100.0
Internet	p < 0.001					
No	379	80.5	26	81.2	99	60.4
Yes	92	19.5	6	18.8	65	39.6
	471	100.0	32	100.0	164	100.0
Genetic testing laboratory	p < 0.001					
No	451	95.8	31	96.9	123	75.0
Yes	20	4.2	1	3.1	41	25.0
	471	100.0	32	100.0	164	100.0
Other	p < 0.001					
No	446	94.7	29	90.6	126	76.8
Yes	25	5.3	3	9.4	38	23.2
	471	100.0	32	100.0	164	100.0
What level of evidence is of importance to you in consideration of ordering a pharmacogenetic test?						
Speciality guidelines	p = 0.034					
Important/ very important	5	1.1	0	0.0	2	1.2
Undecided	37	7.9	1	3.1	2	1.2
Unimportant/ very unimportant	429	91.1	31	96.6	160	93.0
	471	100.0	32	100.0	164	100.0

Supplementary Document S8.2: ***Continued***

	Community + other		Outpatient		Hospital	
	N	%	N	%	N	%
Where do you obtain information to make a choice about the drug and dose in case of a known genotype						
Drug labelling (package insert)	p = 0.027					
No	199	42.3	10	31.2	51	39.0
Yes	272	57.7	22	68.8	113	61.0
	471	100.0	32	100.0	164	100.0
Scientific literature	p < 0.001					
No	223	47.3	16	50.0	39	23.8
Yes	248	52.7	16	50.0	125	76.2
	471	100.0	32	100.0	164	100.0
Colleague	p < 0.001					
No	396	84.1	21	65.6	97	59.1
Yes	75	15.9	11	34.4	67	40.9
	471	100.0	32	100.0	164	100.0
Pharmaceutical Compass	p < 0.001					
No	264	56.1	26	81.2	149	90.9
Yes	207	43.9	6	18.8	15	9.1
	471	100.0	32	100.0	164	100.0
Were you aware that in the Netherlands …						
dosing guidelines are available with information on the choice and dose of drugs based on the genotype of a patient?	p < 0.001					
No	154	32.7	5	15.6	14	8.5
Yes	317	67.3	27	84.4	150	91.5
	471	100.0	32	100.0	164	100.0
medication surveillance based on the genotype of a patient in incorporated in the automated drug dispensing systems?	p < 0.001					
No	187	39.7	11	34.4	33	20.1
Yes	284	60.3	21	65.6	131	79.9
	471	100.0	32	100.0	164	100.0

Supplementary Document S8.2: ***Continued***

	Community + other		Outpatient		Hospital	
	N	%	N	%	N	%
Do you think that your patient's unfavourable test results could have adverse psychological consequences on him and his family?	p = 0.002					
Yes	58	12.3	7	21.9	40	24.4
No	316	67.1	21	65.6	88	53.7
Undecided	97	20.6	4	12.5	36	22.0
	471	100.0	32	100.0	164	100.0
A PGx test might show there is no suitable drug for your patient	p < 0.001					
0	161	34.2	15	46.9	92	56.1
1	157	33.3	9	28.1	44	26.8
2	118	25.1	7	21.9	25	15.2
3	35	7.4	1	3.1	3	1.8
	471	100.0	32	100.0	164	100.0
Which of the following health professionals should have access to the patient's PGx test results						
Nurse-practitioner	p = 0.012					
No	382	81.1	24	75.0	148	90.2
Yes	89	18.9	8	25.0	16	9.8
Are you worried that …						
A health insurance could obtain information about an individual's genotype based on the drug/dose prescribed	p = 0.003					
0	16	3.4	2	6.2	7	4.3
1	21	4.5	5	15.6	6	3.7
2	68	14.4	7	21.9	41	25.0
3	366	77.7	18	56.2	110	67.1
	471	100.0	32	100.0	164	100.0

Supplementary Document S8.3: Results of the multivariate analysis

	Variables associated with past adoption (ordered or recommended a PGx test in the last six months)		Variables associated with future adoption (planned to order or recommend a PGx test in the coming six months)		Variables associated with feeling adequately informed about the availability of genetic testing and its application in the context of drug therapy		Variables associated with the need of extra training on pharmacogenetics	
	n = 667		n = 569		n = 667		n = 667	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
What is your main practice environment								
Community pharmacy + other	1.00		1.00		1.00		1.00	
Outpatient pharmacy	1.58 (0.31–8.16)	0.586	3.01 (1.05–8.57)	**0.039**	0.48 (0.05–4.21)	0.505	1.02 (0.21–4.86)	0.985
Hospital pharmacy	9.44 (4.13–21.57)	**< 0.001**	5.85 (2.67–12.82)	**< 0.001**	3.67 (1.57–8.55)	**0.003**	0.53 (0.23–1.23)	0.139
Do you feel that you are adequately informed about the availability of genetic testing and its application in the context of drug therapy								
No	1.00		1.00		Not applicable		1.00	
Yes	1.99 (0.99–3.99)	0.052	1.07 (0.47–2.47)	0.866			2.40 (1.18–4.90)	**0.016**
Was education on PGx included in your postgraduate specialty training								
No	1.00		1.00		1.00		1.00	
Yes	0.95 (0.48–1.89)	0.879	1.01 (0.50–2.01)	0.983	1.65 (0.86–3.17)	0.130	1.17 (0.59–2.33)	0.651
Would you like to participate in extra training on pharmacogenetics								
No	1.00		Variable not significant in the univariate analysis		1.00		Not applicable	
Yes	0.98 (0.43–2.25)	0.967			2.96 (1.38–6.33)	**0.005**		

Supplementary Document S8.3: ***Continued***

	Variables associated with past adoption (ordered or recommended a PGx test in the last six months)		Variables associated with future adoption (planned to order or recommend a PGx test in the coming six months)		Variables associated with feeling adequately informed about the availability of genetic testing and its application in the context of drug therapy		Variables associated with the need of extra training on pharmacogenetics	
	n = 667		n = 569		n = 667		n = 667	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Would you feel qualified to receive your patient's pharmacogenetic testing results, interpret them and advise your patient on a treatment choice								
No	1.00		1.00		1.00		1.00	
Yes	7.17 (0.76–67.85)	0.086	1.34 (0.30–5.94)	0.702	1.29 (0.32–5.17)	0.716	0.66 (0.25–1.78)	0.416
Yes, after training	2.89 (0.31–26.83)	0.351	1.41 (0.35–5.68)	0.622	0.34 (0.09–1.31)	0.117	3.71 (1.41–9.76)	**0.008**
Would you feel comfortable to recommend pharmacogenetic testing to your patients if those tests could predict that a specific drug could be efficacious in their case								
No	1.00		1.00		1.00		Variable not significant in the univariate analysis	
Yes	1.29 (0.50–3.30)	0.596	2.18 (1.03–4.64)	**0.043**	2.37 (0.88–6.42)	0.089		
Undecided	0.76 (0.25–2.30)	0.629	1.03 (0.45–2.39)	0.938	1.16 (0.38–3.51)	0.798		
If a pharmacogenetic test revealed that the only available drug to treat your patient's disease is ineffective or leads to severe side effects, would you still advise your patient to take that medicine?								
No	Variable not significant in the univariate analysis		Variable not significant in the univariate analysis		1.00		1.00	
Yes					8.54 (2.25–32.42)	**0.002**	0.51 (0.16–1.63)	0.252
Yes, only if he/she had a life-threatening disease					0.46 (0.24–0.86)	**0.015**	1.37 (0.76–2.44)	0.292

Supplementary Document S8.3: ***Continued***

	Variables associated with past adoption (ordered or recommended a PGx test in the last six months)		Variables associated with future adoption (planned to order or recommend a PGx test in the coming six months)		Variables associated with feeling adequately informed about the availability of genetic testing and its application in the context of drug therapy		Variables associated with the need of extra training on pharmacogenetics	
	n = 667		n = 569		n = 667		n = 667	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Do you think that your patient's unfavourable test results could have adverse psychological consequences on him and his family?								
No	1.00		Variable not significant in the univariate analysis		1.00		Variable not significant in the univariate analysis	
Yes	0.51 (0.25–1.07)	0.076			0.69 (0.32–1.49)	0.349		
Undecided	0.59 (0.25–1.43)	0.246			1.32 (0.54–3.18)	0.541		
Do you expect that PGx can prevent you patient from taking the wrong drug or dose								
Low expectations (0 / 1)	Variable not significant in the univariate analysis		1.00		Variable not significant in the univariate analysis		Variable not significant in the univariate analysis	
High expectations (2 / 3)			2.20 (0.98–4.92)	0.056				
Do you expect that PGx will allow detect of which drug or dose will be more efficacious								
Low expectations (0 / 1)	Variable not significant in the univariate analysis		1.00		Variable not significant in the univariate analysis		1.00	
High expectations (2 / 3)			1.51 (0.62–3.70)	0.365			0.99 (0.76–1.30)	0.957
Do you expect that PGx will allow detection of which drug or dose will cause less side effects								
Low expectations (0 / 1)	Variable not significant in the univariate analysis		1.00		Variable not significant in the univariate analysis		1.00	
High expectations (2 / 3)			1.29 (0.55–3.02)	0.557			1.20 (0.94–1.53)	0.137

Supplementary Document S8.3: ***Continued***

	Variables associated with past adoption (ordered or recommended a PGx test in the last six months)		Variables associated with future adoption (planned to order or recommend a PGx test in the coming six months)		Variables associated with feeling adequately informed about the availability of genetic testing and its application in the context of drug therapy		Variables associated with the need of extra training on pharmacogenetics	
	n = 667		n = 569		n = 667		n = 667	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Are you worried that a PGx test might show there is no suitable drug for your patient								
Low worries (0 / 1)	1.00		1.00		Variable not significant in the univariate analysis		Variable not significant in the univariate analysis	
High worries (2 / 3)	0.99 (0.46–2.13)	0.973	1.31 (1.06–1.61)	**0.011**				
What level of evidence is of importance to you in consideration of ordering a pharmacogenetic test? – Speciality guidelines								
Unimportant/ very unimportant	1.00		Variable not significant in the univariate analysis		Variable not significant in the univariate analysis		Variable not significant in the univariate analysis	
Undecided	0.89 (0.17–4.61)	0.886						
Important/ very important	1.84 (0.38–9.02)	0.451						
What level of evidence is of importance to you in consideration of ordering a pharmacogenetic test? – Authority approval or recommendation								
(very) unimportant	Variable not significant in the univariate analysis		Variable not significant in the univariate analysis		1.00		1.00	
Undecided					42.28 (3.59–498.48)	**0.003**	3.12 (0.80–12.15)	0.102
(very) important					13.38 (1.33–155.55)	**0.028**	3.28 (1.00–10.78)	0.051
Where do you obtain information on genetic testing and its application in the context of drug therapy? – Drug labelling (package insert)								
No	1.00		1.00		1.00		Variable not significant in the univariate analysis	
Yes	1.34 (0.61–2.96)	0.469	1.61 (0.72–3.59)	0.246	1.44 (0.66–3.15)	0.362		

Supplementary Document S8.3: ***Continued***

	Variables associated with past adoption (ordered or recommended a PGx test in the last six months)		Variables associated with future adoption (planned to order or recommend a PGx test in the coming six months)		Variables associated with feeling adequately informed about the availability of genetic testing and its application in the context of drug therapy		Variables associated with the need of extra training on pharmacogenetics	
	n = 667		n = 569		n = 667		n = 667	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Where do you obtain information on genetic testing and its application in the context of drug therapy? – Colleague								
No	1.00		1.00		1.00		Variable not significant in the univariate analysis	
Yes	1.73 (0.76–3.97)	0.195	1.21 (0.54–2.72)	0.650	1.08 (0.49–2.35)	0.854		
Where do you obtain information on genetic testing and its application in the context of drug therapy? – Post-academic education and pharmacotherapeutic meetings								
No	1.00		1.00		Variable not significant in the univariate analysis		Variable not significant in the univariate analysis	
Yes	1.23 (0.53–2.87)	0.631	2.91 (1.36–6.23)	**0.006**				
Where do you obtain information on genetic testing and its application in the context of drug therapy? – Internet								
No	1.00		1.00		1.00		Variable not significant in the univariate analysis	
Yes	1.44 (0.71–2.89)	0.311	1.64 (0.80–3.38)	0.176	1.05 (0.51–2.15)	0.892		
Where do you obtain information on genetic testing and its application in the context of drug therapy? – Genetic Laboratories								
No	1.00		1.00		1.00		Variable not significant in the univariate analysis	
Yes	2.16 (0.99–4.71)	0.054	1.09 (0.41–2.85)	0.867	0.57 (0.24–1.33)	0.191		
Where do you obtain information on genetic testing and its application in the context of drug therapy? – Other								
No	1.00		1.00		1.00		Variable not significant in the univariate analysis	
Yes	0.88 (0.40–1.94)	0.747	1.19 (0.52–2.76)	0.679	0.73 (0.33–1.63)	0.445		

Supplementary Document S8.3: ***Continued***

	Variables associated with past adoption (ordered or recommended a PGx test in the last six months)		Variables associated with future adoption (planned to order or recommend a PGx test in the coming six months)		Variables associated with feeling adequately informed about the availability of genetic testing and its application in the context of drug therapy		Variables associated with the need of extra training on pharmacogenetics	
	n = 667		n = 569		n = 667		n = 667	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Where do you obtain information to make a choice about the drug and dose in case of a known genotype – Drug labelling (package insert)								
No	Variable not significant in the univariate analysis		1.00		Variable not significant in the univariate analysis		1.00	
Yes			0.86 (0.46–1.61)	0.647			1.85 (1.05–3.26)	**0.032**
Where do you obtain information to make a choice about the drug and dose in case of a known genotype – Scientific literature								
No	1.00		1.00		1.00		Variable not significant in the univariate analysis	
Yes	1.50 (0.75–3.02)	0.255	1.16 (0.96–1.41)	0.132	1.41 (0.71–2.78)	0.322		
Where do you obtain information on genetic testing and its application in the context of drug therapy? – Colleague								
No	1.00		1.00		Variable not significant in the univariate analysis		Variable not significant in the univariate analysis	
Yes	0.89 (0.42–1.87)	0.759	0.99 (0.83–1.18)	0.886				
Where do you obtain information on genetic testing and its application in the context of drug therapy? – Pharmaceutical Compass								
No	1.00		1.00		1.00		1.00	
Yes	0.88 (0.38–2.07)	0.777	0.97 (0.85–1.10)	0.586	1.68 (0.77–3.65)	0.192	1.05 (0.54–2.06)	0.889
Where do you obtain information on genetic testing and its application in the context of drug therapy? – Informatorum Medicamentorum								
No	Variable not significant in the univariate analysis		Variable not significant in the univariate analysis		1.00		Variable not significant in the univariate analysis	
Yes					1.88 (0.58–6.14)	0.294		

Supplementary Document S8.3: ***Continued***

	Variables associated with past adoption (ordered or recommended a PGx test in the last six months)		Variables associated with future adoption (planned to order or recommend a PGx test in the coming six months)		Variables associated with feeling adequately informed about the availability of genetic testing and its application in the context of drug therapy		Variables associated with the need of extra training on pharmacogenetics	
	n = 667		n = 569		n = 667		n = 667	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Where do you obtain information on genetic testing and its application in the context of drug therapy? – Other								
No	1.00		Variable not significant in the univariate analysis		1.00		Variable not significant in the univariate analysis	
Yes	2.93 (0.98–8.71)	0.054			2.32 (0.77–7.05)	0.136		
Were you aware that in the Netherlands dosing guidelines are available with information on the choice and dose of drugs based on the genotype of a patient?								
No	1.00		1.00		1.00		1.00	
Yes	1.00 (0.37–2.67)	0.999	1.82 (0.79–4.22)	0.162	1.36 (0.51–3.65)	0.537	0.89 (0.41–1.95)	0.770
Were you aware that in the Netherlands medication surveillance based on the genotype of a patient in incorporated in the automated drug dispensing systems?								
No	1.00		1.00		1.00		1.00	
Yes	1.23 (0.57–2.69)	0.596	1.81 (0.93–3.53)	0.082	1.84 (0.82–4.13)	0.139	1.03 (0.51–2.08)	0.927
At any time in the past 6 months, have you ordered or recommended a pharmacogenetic test?								
No	Not applicable		Not applicable		1.00		1.00	
Yes					1.27 (0.55–2.93)	0.574	1.22 (0.56–2.67)	0.623
Do you anticipate ordering or recommending a pharmacogenetic test for a patient within the next 6 months?								
No	Not applicable		Not applicable		1.00		Variable not significant in the univariate analysis	
Yes					1.65 (0.75–3.65)	0.213		

Supplementary Document S8.4: Comparison between responders with past adoption, future adopters and non-adopters (1)

	Non-adopters		Future adopters		Past adoption	
	N	%	N	%	N	%
Specialty	p < 0.001					
Community pharmacy	407	85.1	47	51.6	17	17.3
Outpatient pharmacy	56	4.8	7	7.7	2	2.0
Hospital pharmacy	48	10.0	37	40.7	79	80.6
	478	100.0	91	100.0	98	100.0
Do you expect that…						
PGx can prevent you patient from taking the wrong drug or dose	p = 0.002					
0	8	1.7	3	3.3	0	0.0
1	97	20.3	8	8.8	12	12.2
2	229	47.9	37	40.7	44	44.9
3	144	30.1	43	47.3	42	42.9
	478	100.0	91	100.0	98	100.0
PGx will allow detection of which drug or dose will cause less side effects	p = 0.002					
0	9	1.9	2	2.2	0	0.0
1	97	20.3	11	12.1	16	16.3
2	235	49.2	31	34.1	47	48.0
3	137	28.7	47	51.6	35	35.7
	478	100.0	91	100.0	98	100.0
Was education on PGx included in your postgraduate specialty training	p < 0.001					
No	404	84.5	59	64.8	41	41.8
Yes	74	15.5	32	35.2	57	58.2
	478	100.0	91	100.0	98	100.0
Would you like to participate in extra training on pharmacogenetics	p < 0.001					
No	47	9.8	4	4.4	24	24.5
Yes	431	90.2	87	95.6	74	75.5
	478	100.0	91	100.0	98	100.0
	p < 0.001					
No	41	8.6	3	3.3	1	1.0
Yes	85	17.8	28	30.8	67	68.4
Yes, after training	352	73.6	60	65.9	30	30.6
	478	100.0	91	100.0	98	100.0

Supplementary Document S8.4: ***Continued***

	Non-adopters		Future adopters		Past adoption	
	N	%	N	%	N	%
Would you feel qualified to receive your patient's pharmacogenetic testing results, interpret them and advise your patient on a treatment choice	p < 0.001					
No	41	8.6	3	3.3	1	1.0
Yes	85	17.8	28	30.8	67	68.4
Yes, after training	352	73.6	60	65.9	30	30.6
	478	100.0	91	100.0	98	100.0
Would you feel comfortable to recommend pharmacogenetic testing to your patients if those tests could predict that a specific drug could be efficacious in their case	p < 0.001					
No	143	29.9	13	14.3	8	8.2
Yes	183	38.3	60	65.9	80	81.6
Undecided	152	31.8	18	19.8	10	10.2
	478	100.0	91	100.0	98	100.0
Do you feel that you are adequately informed about the availability of genetic testing and its application in the context of drug therapy	p < 0.001					
No	446	93.3	74	81.3	53	54.1
Yes	21	6.7	17	18.7	45	45.9
	478	100.0	91	100.0	98	100.0
Do you obtain extra information on genetic testing and its application in the context of drug therapy?	p < 0.001					
No	357	74.7	27	29.7	25	25.5
Yes	121	25.3	64	70.3	73	74.5
	478	100.0	91	100.0	98	100.0
Where do you obtain information on genetic testing and its application in the context of drug therapy?						
Drug labelling (package insert)	p < 0.001					
No	385	80.5	38	41.8	41	41.8
Yes	93	19.5	53	58.2	57	58.2
	478	100.0	91	100.0	98	100.0

Supplementary Document S8.4: ***Continued***

	Non-adopters		Future adopters		Past adoption	
	N	%	N	%	N	%
Colleague	p < 0.001					
No	439	91.8	64	70.3	64	65.3
Yes	39	8.2	27	29.7	34	34.7
	478	100.0	91	100.0	98	100.0
Post-academic education and pharmacotherapeutic meetings	p < 0.001					
No	443	92.7	66	72.5	79	80.6
Yes	35	7.3	25	27.5	19	19.4
	478	100.0	91	100.0	98	100.0
Internet	p < 0.001					
No	404	84.5	49	53.8	51	52.0
Yes	74	15.5	42	46.2	47	48.0
	478	100.0	91	100.0	98	100.0
Genetic testing laboratory	p < 0.001					
No	463	96.9	77	84.6	65	66.3
Yes	15	3.1	14	15.4	33	33.7
	478	100.0	91	100.0	98	100.0
Other	p < 0.001					
No	451	94.4	75	82.4	75	76.5
Yes	27	5.6	16	17.6	23	23.5
	478	100.0	91	100.0	98	100.0
What level of evidence is of importance to you in consideration of ordering a pharmacogenetic test?						
Speciality guidelines	p = 0.041					
Important/ very important	26	5.4	4	4.4	3	3.1
Undecided	197	41.2	33	36.3	26	26.5
Unimportant/ very unimportant	255	53.3	54	59.3	69	70.4
	478	100.0	91	100.0	98	100.0
Scientific literature	p < 0.001					
No	232	48.5	25	27.5	21	21.4
Yes	246	51.5	66	72.5	77	78.6
	478	100.0	91	100.0	98	100.0
Colleague	p = 0.001					
No	386	80.8	63	69.2	65	66.3
Yes	92	19.2	28	30.8	33	33.7
	478	100.0	91	100.0	98	100.0

Supplementary Document S8.4: ***Continued***

	Non-adopters		Future adopters		Past adoption	
	N	%	N	%	N	%
Pharmaceutical Compass	p < 0.001					
No	290	60.7	66	72.5	83	84.7
Yes	188	39.3	25	27.5	15	34.2
	478	100.0	91	100.0	98	100.0
Other	p = 0.029					
No	456	95.4	87	95.6	87	88.8
Yes	22	4.6	4	4.4	11	11.2
	478	100.0	91	100.0	98	100.0
Were you aware that in the Netherlands …						
dosing guidelines are available with information on the choice and dose of drugs based on the genotype of a patient?	p < 0.001					
No	157	32.8	9	9.9	7	7.1
Yes	321	67.2	82	90.1	91	92.9
	478	100.0	91	100.0	98	100.0
medication surveillance based on the genotype of a patient in incorporated in the automated drug dispensing systems?	p < 0.001					
No	198	41.4	18	19.8	15	15.3
Yes	280	58.6	73	80.2	83	84.7
	478	100.0	91	100.0	98	100.0
Do you think that your patient's unfavourable test results could have adverse psychological consequences on him and his family?	p = 0.002					
Yes	64	13.4	14	15.4	27	27.6
No	312	65.3	64	70.3	49	50.0
Undecided	102	21.3	13	14.3	22	22.4
	478	100.0	91	100.0	98	100.0
Are you worried that …						
A PGx test might show there is no suitable drug for your patient	p = 0.012					
0	179	37.4	34	37.4	55	56.1
1	157	32.8	28	30.8	25	25.5
2	108	22.6	25	27.5	17	17.3
3	34	7.1	4	4.4	1	1.0
	478	100.0	91	100.0	98	100.0