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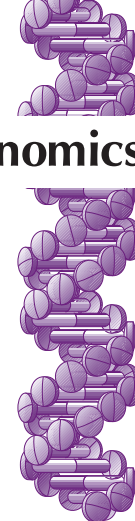
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# Availability of *CYP2D6* genotyping results in general practitioner and community pharmacy medical records

**Aim:** To investigate the availability of *CYP450-2D6* (*CYP2D6*) genotyping results in general practitioner (GP) and/or community pharmacy records, and the influence thereof on psychotropic *CYP2D6* substrate dosing. **Materials & methods:** Primary outcome was the percentage of patients genotyped for *CYP2D6* with their genotype/phenotype registered in GP and/or pharmacy records. Secondary outcome was the number of defined daily doses of psychotropic *CYP2D6* substrates prescribed after genotyping. **Results:** For 216 out of 1307 eligible patients, medication overviews could be obtained. Genotyping results were available at GPs for 3.1% and at pharmacies for 5.9%. The average psychotropic *CYP2D6* substrate dose was not different between any non-extensive metabolizer group and extensive metabolizer group (all  $p \geq 0.486$ ). **Conclusion:** Valuable information for individualizing psychiatric pharmacotherapy is lost on a large scale.

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**Keywords:** clinical practice • communication • *CYP450-2D6* • gene polymorphisms • medication safety • personalized medicine • psychiatry

*CYP450-2D6* (*CYP2D6*) genotyping is probably the most widely accepted application of genotyping in psychiatric practice [1,2]. Approximately 5–10% of the Caucasian population can be classified as poor metabolizer (PM) by lacking *CYP2D6* activity and 1–10% as ultrarapid metabolizer (UM) by gene duplication resulting in high enzyme activity. Furthermore, 30–35% of Caucasians are classified as intermediate metabolizer (IM) [3]. IMs have a metabolic capacity in between a PM and an extensive metabolizer (EM) with two active alleles [3]. A previous study has shown that 52% of psychiatric patients use at least one drug that is metabolized by *CYP2D6* [4]. Out of the drugs metabolized by *CYP2D6*, 62% were classified as an antidepressant or antipsychotic [4]. These figures implicate that a substantial proportion of psychiatric patients are at risk of unsatisfactory response to psychotropic

drugs due to polymorphisms in *CYP2D6*. The resulting number of patients needed to genotype (to find one additional psychiatric patient with compromised *CYP2D6* metabolism [PM, IM and UM] treated with at least one drug metabolized by *CYP2D6*) is four [4].

In The Netherlands, recommendations are available for the choice of drug and dose based on the *CYP2D6* phenotype, written by the Pharmacogenetics' Working Group of the Royal Dutch Association for the Advancement of Pharmacy (WINAp/KNMP) guidelines [5,6]. The recommendations are incorporated in the Dutch computerized medication surveillance systems for physicians, and as such reach general practitioners (GPs), psychiatrists and pharmacists. These recommendations include guidelines for the application of *CYP2D6* genotyping for appropriate drugs and potentially are a major step

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forward in the implementation of pharmacogenetic testing in daily clinical practice. However, in order to optimize the use of genotyping results, an important precondition is the adequate documentation of the *CYP2D6* genotyping results in the medical records of the patient and communication to all healthcare providers involved with the individual patient.

The genetic laboratory of the Wilhelmina Hospital in Assen is one of the centers in The Netherlands that offer genotyping services. This laboratory performs about 350 *CYP2D6* genotyping per year, predominantly ordered by physicians in mental healthcare institutions. Recent research of our group showed that there are clinically relevant shortcomings in the availability of the actual medication use in the medical records of psychiatric patients [7]. Given the potential lifetime benefits of a *CYP2D6* genotyping and the absence of previous literature, we decided to quantify – for the first time – how genotyping results are communicated to other healthcare providers like the GP and/or community pharmacies, who have a central role in the delivery of care in The Netherlands.

### Aim of the study

The primary objective of this study is to quantify the availability of *CYP2D6* genotyping results in the medical records of the GP and/or community pharmacy. The secondary objective is to determine whether registration of the *CYP2D6* genotyping result in the medical records influences the dosing of psychotropic drugs metabolized by *CYP2D6* as suggested in the Dutch/International guidelines.

### Material & methods

#### Design & setting

We cross-sectionally assessed the percentage of patients genotyped for *CYP2D6* for whom the genotyping result was available in the medical record of their GP and/or community pharmacy. The extent to which the registration of the *CYP2D6* genotyping result in the medical records influenced the dosing of psychotropic drugs metabolized by *CYP2D6* was examined in a retrospective survey.

*CYP2D6* genotypings were performed by the genetic laboratory of the hospital pharmacy of the Wilhelmina Hospital Assen (WHA), The Netherlands. The hospital pharmacy delivers pharmaceutical care to – among others – a large secondary mental healthcare institution. The hospital pharmacy is specialized in psychopharmacology and in the implementation of pharmacogenetics in patients with psychiatric disorders [8–10]. The genetic laboratory of the WHA is one of a few that perform pharmacogenetic tests. In The Netherlands, physicians and nursing specialists from any (mental)

healthcare institution can order pharmacogenetic tests, including *CYP2D6* from the WHA genetic laboratory. The *CYP2D6* phenotype is determined on the basis of genotyping of *CYP2D6* \*3, \*4, \*5, \*6, \*10, \*17 and \*41, performed as described previously [11]. Approximately 90% of all *CYP2D6* genotyping requests are ordered by psychiatrists treating patients in mental healthcare institutions, either directly or through a laboratory. Genotyping results, including the genotype and phenotype, are communicated on paper with the healthcare provider that requested the test. By Dutch law, the laboratory is not allowed to transfer this information to the medical records of the requestor or any other healthcare provider.

### Study population

Patients were eligible if they were 18 years or older, and their *CYP2D6* genotype was determined by genetic laboratory of the WHA between 1 February 2010 and 1 May 2015. The starting date was chosen 1 February 2010 because therapeutic recommendations based on the *CYP2D6* phenotype were available for all psychotropic drugs metabolized by *CYP2D6* from that date onward. Patients genotyped for *CYP2D6* solely for (genetic) research purposes were excluded. Patients with both the IM phenotype and duplications in the *CYP2D6* gene were also excluded, because their metabolic capacity cannot be predicted accurately.

As mentioned before, approximately 90% of all *CYP2D6* genotyping requests come from psychiatrists working in mental healthcare institutions. With these requests, the names of the GP and pharmacy are not regularly provided. In order to trace the GP and community pharmacy for genotyped patients, we screened two databases (the WHA medical records and the National First-line Healthcare shared database). Furthermore, we asked the retrieved healthcare providers for additional names of GPs and community pharmacies of their patients.

Patients were included in the study if they were genotyped by the laboratory of the WHA and an actual medication record was available from their GP and/or their community pharmacy. If, in addition, the medication history was available at the community pharmacy only, patients were included for analysis of the secondary objective. We were logistically unable to collect information on the race or ethnicity of the patients, which appears irrelevant for our research aims.

The independent medical ethics committee in Leeuwarden, The Netherlands (fTPO Leeuwarden), waived formal review of the study protocol since participants were not subject to procedures, nor were they required to follow any rules of behavior. As this study was a

critical evaluation of the process around genotyping at the genetic laboratory of the WHA, no informed consent from patients was needed by the Dutch law, as confirmed in writing by the legal expert of the rTPO Leeuwarden.

### Primary outcome

The primary outcome was the percentage of patients genotyped for *CYP2D6* for whom genotyping results were available at their GP, community pharmacy, GP or community pharmacy, and GP and community pharmacy. Availability of the genotyping results in the medical health records at these healthcare providers was assessed by requesting an actual medication overview (which, by definition, includes contraindications such as the *CYP2D6* genotyping result) and checking if the *CYP2D6* genotype or phenotype was present on it. We hypothesized that genotyping results indicating a non-EM phenotype would be communicated to other healthcare providers more often than genotyping results indicating an EM phenotype. Therefore, we also compared the availability of test results between patients with EM and non-EM phenotypes.

### Secondary outcome

The secondary outcome was the average number of defined daily doses (DDDs) per patient year of use of psychotropic drugs metabolized by *CYP2D6* by each patient in the period between the date of the genotyping and 1 May 2015 (or date of death, whichever occurred first; the observation period; DDDs per patient year). A *CYP2D6* substrate psychotropic drug was defined as any oral, rectal or parenteral drug approved by the Dutch Medicines Evaluation Board or the European Medicines' Evaluation Authority with the anatomical therapeutic chemical (ATC) code starting with N05 or N06, which is metabolized by *CYP2D6*, and as such is mentioned in the WINAp/KNMP guidelines with the necessity to perform a therapeutic intervention in case of an aberrant *CYP2D6* phenotype (e.g., choose another drug or adjust dose). These criteria apply to 13 drugs: amitriptyline, aripiprazole, atomoxetine, clomipramine, doxepin, haloperidol, imipramine, nortriptyline, paroxetine, pimozone, risperidone, venlafaxine and zuclopenthixol. We investigated the difference in DDDs per patient year between groups of patients for whom the genotyping result was, or was not, registered in the medical records at the GP and/or community pharmacy. In addition, we investigated data for potential effect modification by the *CYP2D6* phenotype, using the 'availability of the genotyping result\*phenotype' interaction term.

### Statistical analysis

We performed descriptive and statistical analyses using Excel 2013 (Microsoft, WA, USA) and IBM SPSS (version 24 for Windows; IBM Corp., NY, USA). For comparison of differences in categorical variables, we used  $\chi^2$  tests or Fisher's exact tests as appropriate, and for comparison of differences in continuous variables we used *t*-tests or linear regression techniques in case multivariate analysis was appropriate. We report medians (range) when distributions are not distributed normally. In all analyses, differences were considered statistically significant for the two-tailed test if  $p < 0.05$ .

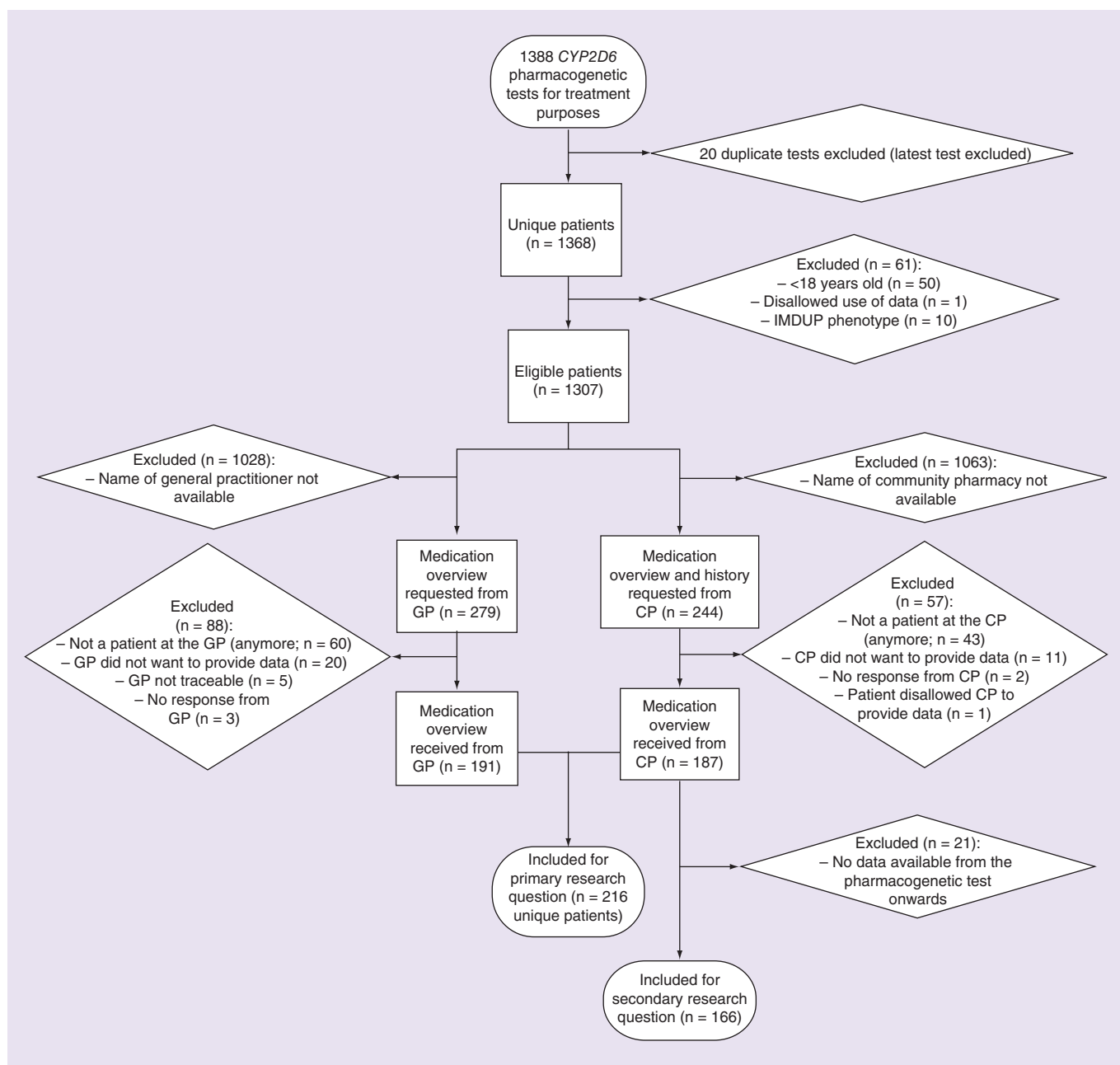
In order to investigate the association between the *CYP2D6* phenotype (categorized as EM and non-EM phenotypes) and the availability of the *CYP2D6* genotyping results in the medical records at the GP and community pharmacy, we used logistic regression analysis. As genotyping information may be lost over time - for example when a patient switches from GP and/or community pharmacy -, the chance that a genotyping result is still adequately registered in the medical records shortly after the genotyping is higher than a few years later. In order to avoid inflation of our regression analysis results by this bias, we wanted to correct for the time between the date of the genotyping and the date of extraction of the actual medication overview in these models.

We investigated the association between the availability of the genotyping results in the medical records at the GP and/or community pharmacy and the number of DDDs per patient year of use across all prescribed psychotropic *CYP2D6* substrates under study, by using a linear regression model. In order to prevent bias by higher DDDs with shorter duration of follow-up because of less time for trial and error, in case the WINAp/KNMP guidelines are not followed, we corrected for the length of the observation period. In addition, we investigated potential effect modification by the *CYP2D6* phenotype using the 'availability of the genotyping result\*phenotype' interaction term in this model.

## Results

### Study population

Figure 1 shows the flow chart for patient eligibility and inclusion. Between 1 February 2010 and 1 May 2015, the genetic laboratory of the WHA had performed 1388 *CYP2D6* genotyping procedures, including 20 duplicate tests, for 1307 unique, eligible patients. Of all eligible patients, we were able to retrieve contact details and requested data from a GP for 279 patients and from a community pharmacy for 244 patients. Included and excluded patients were not different regarding age ( $p = 0.881$ ), phenotype ( $p = 0.693$ ) or year of genotyping ( $p = 0.596$ ). We were unable to test directly whether



**Figure 1. Flowchart of patient inclusion and data collection.**

CP: Community pharmacy; CYP2D6: CYP450–2D6; GP: General practitioner; IMDUP: Intermediate metabolizer with duplications of the CYP2D6 gene.

they differed in their requesting (mental) healthcare institution as more than half of all genotypings (51.6%) were requested indirectly through a laboratory, and we could not logistically verify the original requesting institutions. For 216 unique patients, we received up-to-date medication overviews from the GP and/or community pharmacy. The most important reasons for not including otherwise eligible patients were unavailability of or incorrect name of the GP and/or community pharmacy or the healthcare provider refusing to provide data for

privacy reasons (despite approval of the study and waiver of informed consent).

Characteristics of the included patients are summarized in Table 1. Directly addressed genotyping requests (35/216, 16.2%) came from 13 different (mental) healthcare institutions throughout The Netherlands. For 166 patients we could retrieve the medication history from the community pharmacy for the period from the genotyping to 1 May 2015, for answering our secondary research question.

### Primary outcome

Genotyping results were registered in the medical records at the GP for six of 191 patients (3.1%), and at the community pharmacy for 11 of 187 (5.9%; Table 2). In six of 162 patients (3.7%), the genotyping result was available at both the GP and the community pharmacy. Because none of the test results indicating EM were available at a GP or community pharmacy and the number of subjects with transferred phenotype (PM, IM and UM) results were low, we were restricted to  $\chi^2$  tests instead of logistic regression analysis. Therefore, we could not correct for potential bias by increasing time between the date of the genotyping and the date of extraction of the actual medication overview. Non-EM phenotypes (PM, IM and UM taken together) were communicated more often to GPs and to community pharmacies than EM phenotypes (both  $p < 0.010$ ; Table 2). Of note, only IM and PM phenotypes were communicated, while none of the EM and UM phenotypes were available at GPs or community pharmacies.

### Secondary outcome

The phenotypic distribution of the patients for whom we could retrieve the medication history ( $n = 166$ ) was similar to the total sample ( $n = 216$ ). Half of these patients (87/166; 52.4%) had used no psychotropic CYP2D6 substrates for which an intervention is advised in the WINAp/KNMP guidelines during the observation period. Risperidone was used by 24 patients (14.5%), nortriptyline by 21 patients (12.7%), venlafaxine by 18 patients (10.8%) and both aripiprazole and haloperidol were used by 12 patients (7.2%). Amitriptyline, atomoxetine, clomipramine, doxepin, imipramine, paroxetine, pimozone and zuclopentixol were used by eight patients or fewer ( $\leq 4.8\%$ ).

The median duration of follow-up was 862 days (range: 3–1884 days). Patients for whom the test results were still available at the GP and/or community pharmacy had been prescribed on average 133.27 DDDs of psychotropic CYP2D6 substrates per patient year less than patients for whom the result was not available. This difference was corrected for the duration of follow-up and was not statistically significant ( $p = 0.341$ ). Since none of the EM and UM phenotypes were available at GPs or community pharmacies, we could not investigate potential effect modification by the CYP2D6 phenotype using the ‘availability of the genotyping result\*phenotype’ interaction term, due to collinearity issues. We therefore used a linear regression model to investigate whether the psychotropic CYP2D6 substrate dose (in DDDs per patient year) was different between any of the non-EM phenotype groups compared with the

EM phenotype, still correcting for the duration of follow-up, but irrespective of the availability in the medical records at the GP and/or community pharmacy. The average psychotropic CYP2D6 substrate dose was 183.8 corrected DDDs per patient year (95% CI: 57.4–310.3). This dose decreased with increasing CYP2D6 metabolic activity according to phenotype with 253.3 (95% CI: -97.9 to 604.5) DDDs per patient year for PMs and 111.7 (95% CI: -443.0 to 666.4) DDDs per patient year for UMs. However, there was no linear relationship ( $p = 0.514$ ) and the differences were not significant between any of the non-EM phenotype groups compared with the EM phenotype group (all three values of  $p \geq 0.486$ ).

### Discussion

To take full advantage of the lifelong benefits of genotyping results in psychiatric patients, it is critical to communicate genotyping results to other healthcare providers. To our knowledge, this is the first study that investigated the extent to which genotyping results were communicated with other healthcare providers. We found that the transfer of CYP2D6 genotyping results from the requesting physician to GPs and community pharmacies is poor. CYP2D6 genotyping results were adequately registered in the medical records for only 3.1 and 5.9% of patients genotyped for CYP2D6 at the GP and community pharmacy, respectively. All cases of

Table 1. Characteristics of the study population ( $n = 216$ ).

Characteristic	Value
Gender: female, n (%)	91 (42.1%)
Age (years $\pm$ standard deviation)	41.8 $\pm$ 13.8
Year of (first) CYP2D6 pharmacogenetic test, n (%):	
– 2010 (from 1 February onward)	33 (15.3%)
– 2011	41 (19.0%)
– 2012	46 (21.3%)
– 2013	49 (22.7%)
– 2014	32 (14.8%)
– 2015 (until 1 May)	15 (6.9%)
CYP2D6 phenotype, n (%):	
– Poor metabolizer	19 (8.8%)
– Intermediate metabolizer	77 (35.6%)
– Extensive metabolizer	114 (52.8%)
– Ultrarapid metabolizer	6 (2.8%)
CYP2D6: CYP450–2D6.	

Table 2. Availability of pharmacogenetic test results at general practitioners' practices and community pharmacies.

Test results still available?	General practitioner		Community pharmacy		General practitioner or community pharmacy, number (%)	General practitioner and community pharmacy, number (%)
	Number (%)	p-value <sup>†</sup>	Number (%)	p-value <sup>†</sup>		
EM	0/101 (0.0)	0.010*	0/95 (0.0)	0.001*	0/82 (0.0)	0/82 (0.0)
Non-EM	6/90 (6.7)		11/92 (12.0)		3/80 (3.8)	6/74 (7.5)
Total	6/191 (3.1%)		11/187 (5.9%)		3/162 (1.9%)	6/162 (3.7%)

<sup>†</sup>Compared to non-EM; p < 0.05 is considered significant. From Pearson  $\chi^2$  or Fisher's exact test – whichever was appropriate. EM: Extensive metabolizer.

registered test results concerned CYP2D6 IM or PM phenotypes, which were present in 35.6 and 8.8% of the study population, respectively. This is indicative of a large loss of important information. We could not detect any significant differences between the phenotype groups in dosing of psychotropic CYP2D6 substrate drugs, suggesting that no adjustment of pharmacotherapy had been performed after genotyping, despite recommendations thereof in the WINAp/KNMP guidelines.

### Strengths & limitations

The strength of this study is the large population obtained from different (mental) healthcare institutions nationwide. We believe that our results can therefore be extrapolated to The Netherlands and, given our high standard of care, presumably also to other countries with similar healthcare systems. However, a few limitations apply. First, many eligible patients could not be included, and for some included patients, there were missing data for one of both healthcare providers. The main reason for these exclusions and missings was the absent, incorrect or not up-to-date name of the GP and/or community pharmacy. However, we were able to show that included and excluded patients were not different regarding age ( $p = 0.881$ ), phenotype ( $p = 0.693$ ) or year of genotyping ( $p = 0.596$ ). In addition, any potential selection bias seems unlikely to be based on the institution which requested the genotyping, as the communication of *CYP2D6* genotyping results did not differ between patients for whom the genotyping was requested directly by their institution ( $p = 0.189$ ) or between those patients and patients for whom the laboratory requested the genotyping ( $p = 0.417$ ). We were able to include patients from at least 13 different (mental) healthcare institutions. Nevertheless, any bias because of missing data would probably result in an underestimation of the percentage of available *CYP2D6* genotyping results in our study because the records for patients without a name of a GP and/or community pharmacy may be poorly filled and updated for *CYP2D6* genotyping

results as well. Still, exclusion of subjects reduced the power of our analysis and may affect the robustness of the findings. In addition, the low numbers of patients in specifically the PM and UM phenotype groups and the fact that none of the UM and EM patients had a registered genotyping result at their GP and/or community pharmacy, hampered our original plans for analyses. Nevertheless, in our alternative analysis without correction for time since the genotyping, we showed significant differences in reporting the CYP2D6 phenotype. Furthermore, we found no differences between the dosages of psychotropic CYP2D6 substrate drugs for the various phenotypes (irrespective of the registration of the genotyping results at the GP and/or pharmacy). Concomitant use of CYP2D6 inhibiting drugs may be a partial explanation for a lack of difference in dosing of psychotropic CYP2D6 substrate drugs. In a posthoc analysis, after we excluded all non-PM patients who used psychotropic CYP2D6 substrate drugs and at least one strong nonparoxetine CYP2D6 inhibitor (according to the Dutch Health Base Foundation classification  $\geq +++$  [12]: bupropion, cinacalcet, fluoxetine, kinidine, mirabegron, ritonavir and terbinafine;  $n = 5$ ) concomitantly, we still found no differences in psychotropic CYP2D6 substrate dosing between the phenotype groups ( $p \geq 0.454$ ) or a linear association ( $p = 0.479$ ). We excluded paroxetine because this is both a CYP2D6 substrate and an inhibitor, and this is already taken into account in the phenotype-based dosing recommendations. Therapeutic drug monitoring is another way to adjust the CYP2D6 substrate drug dose to the CYP2D6 metabolic capacity without the knowledge of the *CYP2D6* genotype or phenotype. In another posthoc analysis, after we excluded drugs for which regular therapeutic drug monitoring is advised (amitriptyline, clomipramine, imipramine and norriptyline), we again found no differences between the dosages of psychotropic CYP2D6 substrate drugs for the various phenotypes ( $p > 0.888$ ) or a linear association ( $p = 0.866$ ). So we feel quite convinced that in this sample, no CYP2D6 phenotype-based adjustment of pharmacotherapy has

been performed in regular clinical practice. Because of the abovementioned limitation, we cannot adequately evaluate the influence of the correct or absent registration of the genotyping result at the GP and/or pharmacist on dosing of psychotropic *CYP2D6* substrate drugs, nor assess the extent to which specific recommendations in the WINAp/KNMP guidelines in clinical practice have been followed.

Second, our study concerned prescribed dosages of psychotropic *CYP2D6* substrate drugs and expectations about effects of nonadjusted doses following the WINAp/KNMP guidelines, while we were unable to collect data about more direct results of different *CYP2D6* phenotypes: adverse effects or treatment failures.

Finally, we could not distinguish between reasons for the poor availability of genotyping results in the medical records at GPs and community pharmacies. One reason could be noncommunication of the test results by the physician who ordered the genotyping; another reason could be that the GP/pharmacist did not enter the communicated test results in the patient's electronic medical records as a contraindication that is taken into account by the medication surveillance system.

#### Registration of *CYP2D6* genotyping results in perspective of previous literature

To the best of our knowledge, we are the first to investigate the availability of *CYP2D6* genotyping results in the medical records at the GP and the community pharmacy, who are – at least in The Netherlands – the ultimate first-line, and often lifelong, healthcare providers for every patient. One previous study described the extent of registration and translation of *CYP2D6* and *CYP2C19* genotyping results in daily clinical routine based on medical records within a psychiatric center [13]. In 53 out of 101 cases, their PM or/and UM status for *CYP2D6* and/or *CYP2C19* was mentioned in the medical record; in 33% of the cases, the deviant genotyping result was mentioned in the discharge letter; and in 4% of the cases, it was noted in the observations space [13]. Compared with this study within a center, we found even worse availability of genotyping results in the medical records of first-line healthcare providers. The lack of communication regarding genotyping results prevents healthcare providers to use the opportunities of personalized healthcare at a large scale and ignores a very favorable number needed to genotype [4]. This should be improved in order to fully utilize the information from the genotyping procedure, to optimize personalized medicine and to prevent duplicate tests (as we found for 19 patients).

#### Implications for clinical practice

In a recent meta-analysis of three prospective clinical trials, integrated pharmacogenetic testing guiding psychiatric treatment has been shown to increase the odds of a clinical response to antidepressant treatment 2.3-fold, with a number needed to treat of six for one clinical response compared with treatment as usual [14]. Although this suggests a large potential for *CYP2D6* genotyping for increasing treatment effectiveness by individualizing antidepressant treatment, we point to the fact that the transfer of such genotyping results to other relevant healthcare professionals can be improved substantially. Good communication and storage is a crucial precondition in order to cost-effectively implement *CYP2D6* genotyping in daily clinical practice. This appears particularly important for (psychiatric) patients treated by different healthcare providers and in patients admitted to different institutions on a regular basis. Psychiatric patients are vulnerable and at risk for the lack of communication between healthcare providers, as found in this study. Furthermore, *CYP2D6* genotyping results can also be applied to somatic drugs like metoprolol and tramadol as prescribed by the GP. The lack of communication of the *CYP2D6* genotyping result to the GP puts the patient at risk, unnecessarily, for adverse events for somatic drugs as well.

Several opportunities to improve communication of genotyping results exist. First, the best solution probably is a direct, digital communication of the test results from the laboratory to the electronic medical records of the GP and community pharmacy, in addition to the report sent to the requestor. However, in The Netherlands, privacy legislation has so far hampered the implementation of such a direct communication. Second, it is important to clarify and subsequently decrease barriers for communication of genotyping results to, and registration by, GPs and pharmacists. Third, improvement of knowledge about application of the results will reinforce the way this information is appreciated and used. Previous research indeed showed the necessity for more effective physician education on the clinical value, the importance of communicating the genotyping results, the interpretation and the application of the results with respect to drug choices and dosing strategies [15]. Fourth, the genotyping and result as well as the implications for dosing of pharmacotherapy should be discussed with the patient [16]. Patients appear to be interested in the background and consequences of the genotyping, and want to receive the results [17–20], which may even improve medication adherence [21]. Still, about a third of patients may wish to withhold these results from their physicians because they feel that their doctors are too busy, not interested or incompetent [17]. To our opinion, informing patients



about their test results cannot, therefore, replace communication of patient information between healthcare providers. In addition, a genetic passport could be handed out by every genetic laboratory that lists a person's pharmacogenetic profile [22]. This passport might be useful to transfer the genotyping results to first-line healthcare providers and avoids privacy legislation problems. Also, it may contain machine-readable data for use in clinical decision support systems used by GPs and pharmacists [22].

### Conclusion

In conclusion, we demonstrate that communication of genotyping results to other healthcare professionals like GPs and pharmacies needs improvement, in order to utilize the clinical benefits of *CYP2D6* (and other) genotypings. This will provide valuable information for individualizing pharmacotherapy and prevents the large-scale loss of information about (psychiatric) patients.

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No writing assistance was utilized in the production of this manuscript.

### Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations.

### Summary points

- Although highly relevant for clinical decisions on dosing, *CYP450-2D6* (*CYP2D6*) genotyping results are poorly transferred from requesting (mental) healthcare institutions to general practitioners (GPs) and community pharmacy medical records: <10% of the genotyping results were adequately registered.
- Nonextensive metabolizer phenotypes (poor metabolizer, intermediate metabolizer and ultrarapid metabolizer taken together) were communicated more often to GPs and to pharmacies than extensive metabolizer phenotypes (both  $p < 0.010$ ).
- We could not detect any significant differences between *CYP2D6* phenotype groups in dosing of psychotropic *CYP2D6* substrates, indicating that no phenotype-based adjustments of pharmacotherapy had been performed, despite recommendations in Dutch/International guidelines.
- Due to missing data, many eligible patients could not be included, which hampered our primary and secondary objectives.
- This study used prescription records of GPs and community pharmacies. Therefore, we were unable to investigate whether the availability of genotyping results was associated with adverse events or treatment failures.
- Communication of genotyping results to other healthcare professionals like GPs and pharmacies needs to be improved, in order to prevent valuable information for individualizing pharmacotherapy of psychiatric patients from being lost on a large scale.
- Probably the best way to improve communication of genotyping results is a direct, digital communication of the test results from the laboratory to the electronic medical records of the GP and pharmacy in addition to the report sent to the requestor. However, in The Netherlands, privacy legislation has so far hampered the implementation of such a direct communication.
- More effective physician education on the clinical value, the importance of communicating the genotyping results, the interpretation and the application of the results with respect to drug choices and dosing strategies may result in optimized utilization of the potential lifetime clinical benefits of *CYP2D6* (and other) genotypings.

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