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Does Pharmacogenetic Testing for CYP450 2D6 and 2C19 Among Patients with Diagnoses within the Schizophrenic Spectrum Reduce Treatment Costs?

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Abstract: The effect of pharmacogenetic testing for CYP450 2D6 and 2C19 on treatment costs have not yet been documented. This study used Danish patient registers to calculate healthcare costs of treating patients with diagnoses within the schizophrenic spectrum for 1 year with or without pharmacogenetic testing for polymorphisms in the genes for the CYP2D6 and CYP2C19 enzymes. In a randomized, controlled trial, stratified with respect to metabolizer genotype, 104 patients were assigned to treatment based on pharmacogenetic testing and 103 patients to treatment as usual. Random exclusion of extensive and intermediate metabolizers was used to increase the frequency of extreme metabolizers (poor metabolizers and ultrarapid metabolizers for CYP2D6) to 20% in both groups. Cost differences were analysed at several levels including (i) overall healthcare expenditure, (ii) psychiatric hospital cost (iii) nonpsychiatric hospital cost, (iv) primary care spending and (v) pharmaceuticals. Statistically significant differences in costs of psychiatric care dependent on metabolizer status were found between intervention groups. Pharmacogenetic testing significantly reduced costs among the extreme metabolizers (poor metabolizers and ultrarapid metabolizers) to 28%. Use of primary care services and pharmaceuticals was also affected by the intervention.This study confirms earlier findings that extreme metabolizers (poor and ultrarapid metabolizers) incur higher costs than similar patients with a normal metabolizer genotype. However, this study shows that these excess costs can be reduced by pharmacogenetic testing. Pharmacogenetic testing for CYP2D6 and CYP2C19 could thus be considered as a means of curtailing high psychiatric treatment costs among extreme metabolizers.

Limited healthcare budgets and cost-containment challenge payers and providers of health care worldwide. New technologies and treatments are compared with existing ones to maximize health gain. Pharmacogenetic testing (PGx) is one among these new technologies. In psychiatry, several attempts have been made to estimate whether PGx for polymorphisms (genetic changes) in different genes provides a cost-effective alternative to treatment based on clinical dose titration or therapeutic [1–5].

Psychiatric treatment is characterized by problems of adverse drug reactions and lack of effect. This leads to compliance problems, frequent shifts in medicine and high costs [6–8]. PGx was expected to ease some of these problems. The fundamental hypothesis being that knowledge regarding patients' genotype could guide the treating clinician in the choice of pharmaceutical and/or dosage. This could potentially individualize treatment and reduce the time from initiation of pharmaceutical therapy until an acceptable medical response occurs, thus leading to improved patient treatment, care and outcome.

Pharmacogenetic testing for changes in the CYP2D6 and CYP2C19 enzymes is one candidate for the use of PGx in psychiatry. Numerous antipsychotics and antidepressants are metabolized by the CYP2D6 and CYP2C19 enzymes. The genes of which are rich on functional polymorphisms [9] allowing for four functionally different groups of metabolizers to be predicted, dependent on the number of functional copies of each CYP gene: poor metabolizers(PM), intermediate metabolizers(IM), extensive metabolizers(EM) or ultrarapid metabolizers(UM) [10]. PMs' ability to metabolize a number of antidepressants and antipsychotic drugs is reduced, whereas UMs require increased dosages of these drugs to obtain plasma concentration levels within the desirable margin [11,12]. However, far from all antipsychotic drugs are metabolized by CYP2D6 or CYP2C19 and other variables such as age, gender, diet, smoking and comedication, etc. affect metabolism. Patients' genotype is thus only one piece in a larger puzzle.

In a Danish population, the frequency of PMs owing to CYP2D6 polymorphisms is 8.4% and 3.1% for UMs [13]. Both groups have an altered capacity to metabolize some antipsychotics and could thus potentially benefit from genotyping for CYP2D6 when treated with any of these antipsychotics. The CYP2D6 IMs constitute 36%, but these patients' potential to benefit from genotyping for CYP2D6 is less clear. The remaining 52.4% make up those with the ordinary extensive metabolic capacity with respect to the CYP2D6 enzyme.

The polymorphisms in the CYP2C19 gene do not include a duplication (leading to UM phenotype); however, a promoter polymorphism exists, which appears to increase the rate of

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metabolism of CYPC19-dependent drugs. However, so far the clinical relevance of this polymorphism is uncertain [14]. The prevalence of PMs is reported to be 5% in Caucasians [10].

Studies of treatment response of antidepressants show higher proportions of PMs among patients with adverse events as well as more shifts in medicine among PMs [15–17].Treatment costs have also been found to be higher among the PMs and UMs relative to EMs [1]. Identifying the UMs and PMs and taking their baseline metabolic capacity into account when prescribing has been suggested to relieve problems of frequent changes in psychopharmacological treatment as well as adverse events in the treatment with antidepressants as well as antipsychotics. However, the evidence on the actual benefit in clinical practice has been disappointing so far [18,19].

This study reports the health economic results from a study involved in a Danish health technology assessment of which the results have not yet been published in the international literature. In this study, information was gathered through the Danish patient registers alongside a randomized, controlled trial that assessed the dependence of treatment outcome on metabolic status determined by pharmacogenetic analyses of CYP2D6 and CYP2C19. These registry data were used to calculate the costs of treating the patients depending on knowledge of metabolic status. The study shows that pharmacogenetic testing does reduce excess psychiatric treatment costs among patients with an extreme metabolic capacity (i.e. among poor metabolizers and ultrarapid metabolizers).

Materials and Methods

The randomized, controlled trial. Three hundred and eleven patients were recruited between February 2008 and October 2009 and randomized to one of three different treatment strategies, including (i) treatment after the results of genotyping for CYP2D6 and CYP2C19 (PGx group), (ii) extensive clinical monitoring of adverse side effects or (iii) treatment as usual (i.e. control group) (fig. 1). Informed consent was obtained from all patients, and the protocol was approved by required ethical committees and regulatory bodies (further information on the study design is available at ClinicalTrials.gov: NCT00707382). Blood samples were collected from all patients and pharmacogenetic testing conducted. Tests were made for allelic changes in the CYP2D6 *3, *4 and *5 (deletion) as well as duplication/multiplication. For CYP2C19 *2 and *3 were tested for.

Patients were categorized according to the number of functional alleles into the following metabolizer groups: PMs (no functional alleles), IMs (one functional allele), EMs (two functional alleles), UMs (three or more functional alleles). Subsequently, PMs and UMs were categorized as extreme metabolizers.

Patients were stratified according to genotype thus ensuring an equal number of extreme (PMs and UMs) and extensive metabolizers in the treatment arms. During recruitment, a number of patients with extensive-metabolizer and intermediate-metabolizer genotype were randomly excluded to increase the frequency of extreme metabolizers (i.e. PMs and UMs) artificially to 20%.

Only data from the 209 patients included in treatment groups 1 and 3 (i.e. genotyping group and control) were analysed, as cost estimation on the intervention in the second group could not be conducted. Patients were not incident cases and some had thus been diagnosed for years.

Only those psychiatrists who were treating patients assigned to the PGx group were informed about the genotype of the patient. Depending on a patient's genotype, the treating psychiatrist was recommended to follow a specific treatment approach outlined in a set of clinical guidelines. The psychiatrists treating patients in the intervention group were also asked to actively acknowledge and sign for the receipt of test results. Psychiatrists treating patients enrolled in the trial were not urged to use specific antipsychotics nor limited. The intervention thus only consists of the additional information regarding the genotype of the patient and recommendations to adjust the pharmacological treatment accordingly.

Psychiatric health care in Denmark. Psychiatric health care in Denmark is provided by general practitioners (GPs), specialists in psychiatry in private clinics, outpatient clinics at psychiatric hospitals as well as district centres and inpatient wards at psychiatric hospitals. All services are covered by national health insurance, except from limited copayments for pharmaceuticals, dental services and a small number of other services such as physiotherapy.

Pharmacological treatment for patients with diagnoses within the schizophrenic spectrum is usually initialized alongside inpatient stays. Follow-up is situated at the outpatient settings at psychiatric hospitals and district centres. Eventually, responsibility for the pharmacological treatment can be shifted to patients' GP or a psychiatric specialist at private clinics.

Costs of public health care. All Danes have a unique personal identification number, called the CPR number. Whenever a person receives public health care, the CPR number is used for registration of the services provided. The primary care clinic or hospital is remunerated based on the services registered.

In the psychiatric hospital system, remuneration is based on fees (number of outpatient visits, emergency visits or inpatient days), whereas DRGs and DAGS (diagnose-related-groupings for inpatients and outpatients) are used in the nonpsychiatric hospital system. Primary care physicians are primarily paid by fee-for-service. With regards to pharmaceuticals, the CPR number is used to keep track of the patients' out-of-pocket payments to increase public coverage for those with high spending. Only pharmaceuticals collected at pharmacies are registered, thus excluding pharmaceuticals handed out at outpatient clinics or given at inpatient wards (as these are free of charge for the patient and covered by the DRG/DAGS or psychiatric inpatient/outpatient fee).

The extensive registration of services makes it possible to trace individual patients based on their CPR number. For this study, information on the incurred costs was drawn from a number of different Danish patient registers. Total costs of treating each patient were calculated for a period of 365 days after inclusion in the study. Costs calculated in this study cover primary care services (general practitioners, specialist services, including psychologists and psychiatrists, dental care and physiotherapy), secondary care (hospital services, inpatient, outpatient and emergency services), psychiatric hospital care (inpatient, outpatient and emergency services) [20] and pharmaceuticals (only those registered as paid for at Danish pharmacies). Costs are in 2010 prices.

Costs of pharmacogenetic testing. The analysis of the blood samples for the pharmacogenetic testing was conducted at the Research Institute of Biological Psychiatry at Sct. Hans psychiatric hospital [21]. The price of the laboratory tests was DKK 1000 (US$179). In addition to the price of the test, PGx was also assumed to involve additional time for the treating psychiatrist informing the patient of the test and the results. Based on a questionnaire among participating psychiatrists, PGx was assumed to require additional 15 min. of patient-related time. Additional time related to taking the blood

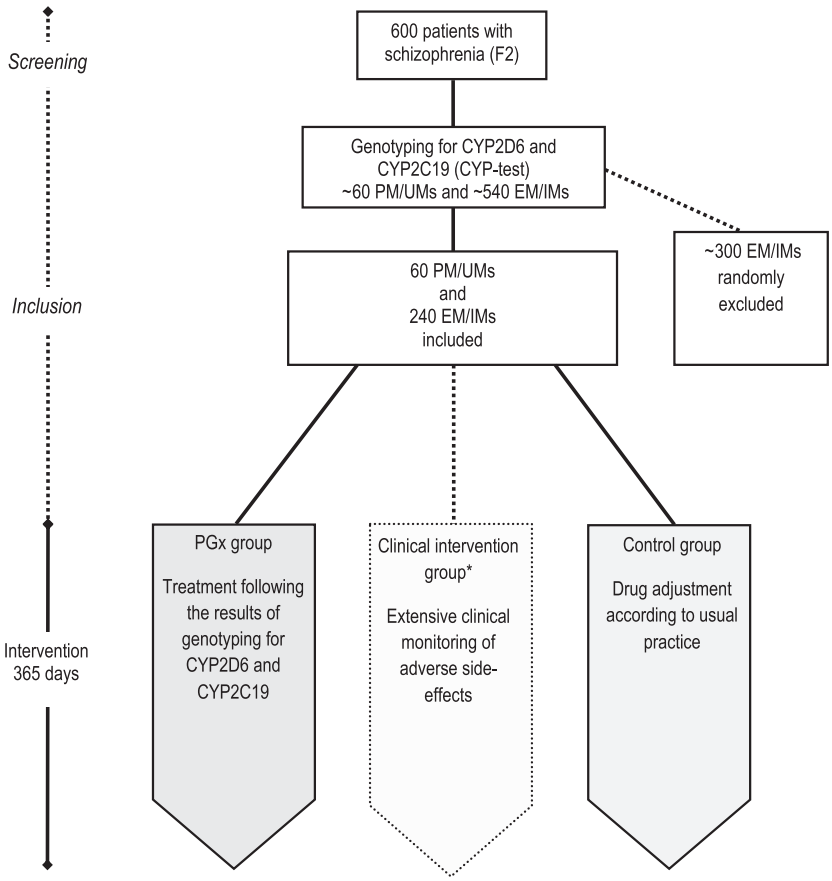

Fig. 1. Study design of the randomized clinical trial. *This group was not included in the economic analysis.

sample was assumed also to require 15 min. on average from a medical laboratory assistant. For some medical laboratory assistants, this would include some travel time.

Sensitivity analysis was used to test the assumptions regarding additional patient-related time. In addition to the base case, a minimal-cost-scenario and a maximum-cost scenario were analysed. In the minimal-cost-scenario, PGx was assumed only to enquire additional costs attributable to the laboratory testing [i.e. DKK 1000 (US$179)], whereas the maximum-cost-scenario was specified with additional labour costs of ½ hr for both the treating psychiatrist as well as the medical laboratory assistant. The price of the laboratory analysis in this upper-level scenario was DKK 2,285 (US$410).This equals the laboratory price at another laboratory in Denmark where testing is conducted for an increased number of allelic variants of the CYP2D6 gene (*1,*2,*3,*4, *5,*6,*9,*10,*13,*16,*17,*41) [22]. In the base-case analysis, the total costs of the PGx were assumed to be DKK 1,195 (US$214). For the sensitivity analyses, costs of pharmacogenetic testing were thus DKK 1000 (US$179) for the lower level and DKK 2674 (US$480) for the upper level. Sunk costs associated with psychiatrists' one-off information meeting regarding the use of PGx were not included.

Econometric model for the analysis of costs. Two different generalized linear models were fitted to the data. In the first model (Model 1), costs were assumed to depend upon: gender, age, treatment site, diagnosis (limited to three groups), whether the patient was included in the first half or second half of the study period, and whether the patient was treated according to the results of PGx (i.e. in the intervention group). Results from this model should be interpreted as the overall effect of introducing PGx for CYP2D6 and CYP2C19 *on healthcare budgets*.

In the second model (Model 2), two additional dummy variables were included identifying the extreme metabolizers (i.e. the PMs and the UMs) as well as an interaction term between the extreme metabolizers and PGx. The last term allows for a separate effect of PGx to be identified among the extreme metabolizers. In this model, results reflect the effect of PGx for CYP2D6 and CYP2C19 *on the treatment costs between patient genotypes*.

The variable on whether the patient was included in the first or the second half of the study period was included due to a hypothesis that learning might take place during the study period. Using the PGx results might raise awareness among co-working psychiatrists with regards to the importance of drug interaction, metabolism and adverse side effects with spill-over effects on patients in the control group. Knowledge regarding these patients has been suggested to be better incorporated into practice, the longer the study had been going on.

As costs were highly skewed, a generalized linear model with log-link function was used, specified with a gamma distribution for the relationship between the variance and the conditional mean ($E[y|x] = \exp(x'\beta)$, $\mathrm{var}[y|x] \approx (E[y|x])^2$).

Analyses were conducted separately on (i) the total costs of treatment within the healthcare system and (ii) costs of psychiatric treatment, defined as psychiatric outpatient visits, psychiatric admissions and psychiatric emergency visits. In addition, three-two-stage models were used to analyse costs of primary care, secondary nonpsychiatric treatments and pharmaceuticals. The two-stage models were necessary due to a number of patients with zero expenditure within primary care, secondary nonpsychiatric care as well as zero spending on prescription pharmaceuticals. A probit model was used for the first stage, modelling the probability of having nonzero costs. For the second stage, a generalized linear model identical to the one used for analysing the total costs was

used. Statistical software included SAS 9.2 (SAS Institute Inc, Cary, NC, USA) for handling the substantial amount of data and STATA 12.0 (StataCorp LP, College Station, TX, USA) for conducting cost estimation.

Results

One hundred and three patients were treated on the basis of pharmacogenetic testing (PGx), whereas 106 had ordinary standard treatment. Information on two patients in the control group was lacking from psychiatric registers; these two patients were excluded from the analysis. Characteristics of the patient sample are shown in table 1. In both groups, 21 patients (20%) were characterized as extreme metabolizers, that is, with genotypes corresponding to either PMs or UMs. This high frequency was deliberate and part of the sampling strategy.

Total costs in the healthcare system and costs of psychiatric care. Mean total costs of treatment within the healthcare sector were DKK 131,141 (US$23,361) in the intervention group, ranging from DKK 1,702 (US$303) to DKK 1,189,742 (US$211,774). In the control group, mean total costs were DKK 153,536 (US$27,350), ranging from DKK 12,032 (US $2142) to DKK 1,052,956 (US$187,426). Both means were affected by few patients with very high healthcare costs (median costs were DKK 86,388 (US$15,389) and DKK 105,392 (US$18,774), respectively).

Most of the total costs could be attributed to services in the psychiatric hospital sector, with mean costs of psychiatric care being DKK 100,433 (US$17,891) in the intervention group [ranging from DKK 1642–1189,742 (US$292–211,774)] and DKK 121,648 (US$21,670) in the control group [ranging from DKK 1,642-1,030,560 (US$292–183,440)]. Costs of psychiatric care were also highly influenced by a minority of patients with extremely high expenditure (median costs in the two groups were DKK 47,618 (US$8482) and DKK 76,348 (US$13,600) in the intervention group and control group, respectively).

Table 1.
Characteristics of the patient sample by intervention group.

	Intervention group n (%)	Control group n (%)	Total n
n	103	104	207
Diagnose groupings (ICD10)			
F20 – schizophrenia	74	71	145
F21 – schizotypal disorders	24	21	45
Other disorders[1]	5	12	17
Inclusion in the study			
First half of the study period	57 (55)	63 (61)	120
Last part of the study period	46 (45)	41 (39)	87
Share of men	55%	56%	
Age			
Mean age at inclusion	41 years	42 years	–
Youngest/oldest patient	19/68 years	20/73 years	–
Psychiatric district center			
Copenhagen district	63 (61)	65(63)	128
Hvidovre district	11 (11)	7 (7)	18
Frederiksberg district	18 (17)	16 (15)	34
Amager district	11 (11)	16 (15)	27

[1]Other diagnoses: F22.8 (n = 1), F22.9 (n = 5), F25.0 (n = 3), F25.1 (n = 4), F25.2 (n = 1), F25.9 (n = 5), F28.9 (n = 1), F29.9 (n = 1), one patient was registered without specific diagnosis.

Table 2 shows the results of the generalized linear models of the total costs as well as the costs of psychiatric care. Coefficients should be interpreted as percentages. The reference is a female patient included from the Copenhagen psychiatric district center in the first half of the study period diagnosed with other delusional, schizoaffective or psychotic disorders.

The second column in table 2 shows the result from Model 1 (representing the effects of the intervention *on healthcare budgets*). In the intervention group, total costs of treatment are 76% of those in the control group, however, not statistically significant ($p>|z| = 0.072$). When the two additional variables (identifying the extreme metabolizers and the effect of the intervention among these) are included (Model 2), the effect of the intervention only persists among the extreme metabolizers (PMs and UMs), as would be expected. Total costs among all extreme metabolizers are 177% higher than among the 'normal' (EM) metabolizers (95% C.I.: 0.96; 3.25). This difference is, however, reduced by 48% among extreme metabolizers in the intervention group (95% C.I.: 0.22; 1.02). Neither of the results are statistically significant at the 5% level, however, close ($p>|z| = 0.066$ and 0.058).

The results of the analysis of costs of psychiatric care (disregarding primary care, nonpsychiatric hospital care and pharmaceuticals) are shown in table 2, columns 4 and 5.

Again, the use of PGx for CYP2D6 and CYP2C19 appears to reduce costs in the intervention group to 77%, although the difference does not reach statistical significance (95% C.I.: 0.53; 1.13). However, among the extreme metabolizers (PMs and UMs), the excess costs amount to 239% (95% C.I.: 1.29; 4.40), reducible by 28% by the intervention (95% C.I.: 0.12; 0.67). This equals costs of approximately DKK 373,682 (US $67,064) among the extreme metabolizers, which are reduced to DKK 114,403 (US$20,532) by pharmacogenetic testing; differences which are highly statistically significant.

Changing the price of PGx in the sensitivity analyses does not alter the magnitude of the estimated coefficients. The statistical significance levels improve slightly with higher costs of testing. This makes the effect of PGx among the extreme metabolizers on total costs approach statistical significance ($p>|z| = 0.054$).

Costs of primary care, secondary nonpsychiatric care and pharmaceuticals. Ninety patients in the PGx group and 96 in the control group used primary care services within the 365 days follow-up. Costs were relatively modest with mean costs of DKK 1,899 (US$338) in the PGx group and DKK 2408 (US$429) in the control group. Median values in the two groups correspond to DKK 1165 (US$208) and DKK 1546 (US$275), respectively.

With regards to the nonpsychiatric hospital visits, only 40 patients in the PGx group and 45 in the control group used these services within follow-up. Mean costs in the two groups were DKK 7101 (US$1265) and DKK 6936 (US$1236) for

Table 2.
Models of total costs within the healthcare system and costs of psychiatric care.

	Total costs of health care[1]		Costs of psychiatric care[2]	
	Model 1 Exp(β) ($p>\|z\|$)	Model 2 Exp(β) ($p>\|z\|$)	Model 1 Exp(β) ($p>\|z\|$)	Model 2 Exp(β) ($p>\|z\|$)
Intervention (PGx)	*0.760 (0.072)	0.942 (0.721)	0.774 (0.189)	1.078 (0.712)
Extreme metabolizer[3]	–	1.769 (0.066)*	–	2.385 (0.005)**
Extreme metabolizer in intervention group[4]	–	0.477 (0.058)*	–	0.284 (0.004)**
Gender (male)	1.213 (0.214)	1.192 (0.230)	1.170 (0.449)	1.200 (0.332)
Age	1.018 (0.018)**	1.016 (0.044)**	1.010 (0.309)	1.008 (0.357)
Inclusion time[5]	0.998 (0.990)	0.895 (0.526)	0.959 (0.860)	0.837 (0.421)
Diagnose: group F20	0.639 (0.200)	0.545 (0.085)*	0.574 (0.154)	0.480 (0.037)**
Diagnose: group F21	0.456 (0.022)**	0.442 (0.018)**	0.412 (0.024)**	0.391 (0.010)**
Amager district	0.700 (0.130)	0.836 (0.450)	0.755 (0.408)	0.953 (0.881)
Frederiksberg district	0.823 (0.289)	0.859 (0.387)	0.730 (0.227)	0.793 (0.337)
Hvidovre district	2.121 (0.038)**	2.012 (0.035)**	2.056 (0.091)*	2.188 (0.042)**
_constant[6]	114 157 (0.000)**	134 529 (0.000)**	145 307 (0.000)**	156 680 (0.000)**

[1]Includes the total costs of healthcare services for the period of 365 days including costs of pharmacogenetic testing in the intervention group.
[2]Includes costs of treatment in the psychiatric hospital system including admissions, outpatient visits and psychiatric emergency visits as well as costs of pharmacogenetic testing in the intervention group.
[3]Extreme metabolizers with either a reduced or a absent capacity to metabolize some pharmaceuticals (PMs) and ultrarapid metabolizers with increased and fast metabolism of some pharmaceuticals (UMs).
[4]Interaction term representing the effect on costs of being an extreme metabolizer in the intervention group.
[5]Patients included in the last half of the study period for whom there might have been spill-over effects of the intervention, regardless of being in the intervention or control group.
[6]The reference is female, included in the first half of the study period from Copenhagen psychiatric district center.
*Statistically border significant at a 10% level.
**Statistically significant at a 5% level.

the PGx and control group, respectively. Median costs were zero in both groups.

The analysis of pharmaceutical spending should be interpreted as a point-of-collection perspective and not as representative of the use of pharmaceuticals *per se* (i.e. patients could have collected medicine without taking it or collected it at outpatient clinics). Ninety-five and 98 patients were registered with pharmaceutical expenditure in the PGx and control group, respectively, with mean costs of DKK 21,709 (US$3867) and DKK 22,544 (US$4016). Median values correspond to DKK 17,018 (USS$3032) and DKK 16,527 (US$2944).

The results of the two-stage analyses are shown in table 3. The top rows of the table show the effect of the three variables of interest on the probability of using primary care services, nonpsychiatric hospital services or picking up pharmaceuticals from a pharmacy within follow-up. Only the coefficients of interest are shown, that is, the additional explanatory variables from the model (age, gender etc.) are not. Only the probability of using primary care services is affected by being an extreme metabolizer (i.e. PMs and UMs). In accordance with expectations, the probability of using primary care services is thus significantly higher relative to the 'normal' (EM) metabolizers ($p>|z| = 0.000$) among extreme metabolizers (i.e. PMs and UMs).

The bottom rows of table 3 show the effect of the three explanatory variables of interest on the costs of primary care services, costs of nonpsychiatric hospital services and pharmaceutical expenditure given that the individual had a nonzero level of consumption. Only pharmaceutical spending appears to be affected by the intervention and by whether the individual is an extreme metabolizer or not. Extreme metabolizers thus have reduced costs of pharmaceuticals of 53% compared with nonextreme metabolizers. Being in the intervention group, however, increases the costs of pharmaceuticals by 259%. Both results are statistically significant ($p>|z| = 0.014$ and 0.022).

Discussion and Conclusion

This study confirms earlier findings that extreme metabolizers (PMs and UMs) in a real-life setting incur substantially higher costs than similar patients with a normal metabolizer genotype [1]. However, our study also shows that these excess costs can be reduced by pharmacogenetic testing for CYP2D6 and CYP2C19 polymorphisms.

However, the percentage of extreme metabolizers analysed in this study is higher than would be expected from the general patient population [13]. The greater the percentage of extreme metabolizers, the greater the overall benefits of PGx. A consequence of the sampling strategy, increasing the percentage of extreme metabolizers, would be that the effects of PGx on costs would be easier to detect.

However, in spite of the artificially high number of extreme metabolizers, due to the sampling strategy, our study was not able to detect statistically significant differences in costs between intervention groups when metabolic capacity was disregarded. Thus, the variation in costs across all patients remains too great and the sample size too small to confirm statistically significantly different costs across groups when intervention groups are compared.

Table 3.
Results from two-stage models of costs of primary care, nonpsychiatric hospital care and costs of pharmaceuticals.

	Primary healthcare costs		Nonpsychiatric hospital care costs		Pharmaceutical expenditure	
	Coefficient	Z ($p>\|z\|$)	Coefficient	Z ($p>\|z\|$)	Coefficient	Z ($p>\|z\|$)
Probability of nonzero costs[1]						
Intervention PGx	−0.026	−1.29 (0.198)	−0.030	−0.39 (0.700)	−0.004	−0.12 (0.902)
Extreme metabolizer	**0.229***	**10.25 (0.000) ***	0.002	0.02 (0.986)	−0.001	−0.02 (0.984)
Intervention and extreme metabolizer	−0.980		−0.124	−0.74 (0.462)	−0.036	−0.47 (0.641)
Cost differences (percentages)[2]					NB![3]	NB![3]
Intervention PGx	0.869	−0.83 (0.404)	0.878	−0.34 (0.735)	0.869	−1.01 (0.311)
Extreme metabolizer	0.736	−1.24 (0.216)	0.754	−0.48 (0.631)	**0.530***	**−2.46 (0.014) ***
Intervention and extreme metabolizer	1.122	0.32 (0.749)	1.488	0.46 (0.649)	**2.589***	**2.29 (0.022)***

[1]Results from probit model of having nonzero cost. The coefficient gives the percentage difference in probability of having costs. Only the three variables of primary interest are shown. The variables equal those of Model 2.
[2]Results from a generalized linear model with a log link and a gamma family. Coefficients display the percentage difference in costs among those with nonzero costs. The complete model is specified as Model 2. Only the variables of primary interest are shown here.
[3]The generalized linear model for pharmaceutical expenditure did not pass the Park test for the specification of the variance with a gamma family. However, with a poisson specification, the Link test of the link between the dependent and independent variables does not pass (_hat $p>|0.072|$ og _hatsq $p>|0.053|$ – both should be insignificant). Coefficients reported in the table are those from the model with the gamma variance with robust S.E. Using the poisson specification gives highly statistically significant differences on all coefficients ($p>|z| = 0.000$).
*Results are statistically significant ($p>|z| \leq 0.05$).

However, the relatively high number of extreme metabolizers does not affect the conclusion that identification and awareness of extreme metabolizers reduces treatment costs among these patients, possibly reflecting better treatment, care and outcome.

Pharmaceutical spending appears to be affected by the intervention and by metabolizer status. Costs of pharmaceuticals collected at pharmacists are only 53% among extreme metabolizers of those among nonextreme metabolizers. Being in the intervention group, however, increases the costs. This could be explained by earlier discharges and better compliance allowing for patients to pickup their medication from public pharmacies instead of receiving them in a controlled environment at hospital clinics. A cost shift from the psychiatric hospital sector to increased pharmaceutical expenditure thus seems to be a plausible consequence of the use of PGx for CYP2D6 and CYP2C19.

The largest drawback in the study is the lack of information on accurate resource use in the psychiatric hospital system. Costs are based on average fees for outpatient visits, inpatient stays as well as fees for emergency visits. These fees are calculated at the national level across all psychiatric patient groups, thus disregarding differences due to particular difficulty of treatment of extreme metabolizing patients, severity of disease, diagnosis, timing, etc. However, it is very likely that resource use per inpatient day differs among patients. Important possible reasons for cost differences are as follows: whether it is the first or second admission, whether it is the first or second week of admission, whether the patient suffers from anxiety, depression or schizophrenia, etc., is a debutant or not. In case the national fees underestimate the true resource use among the schizophrenic patients in our study, the cost reductions are likely to be underestimated as well. If the opposite is true, the results are likely to be biased in favour of the intervention. Unfortunately, we do not have any way of controlling the validity of the fees or adjusting them appropriately. With regards to the validity of the other sources for the calculation of resource use, these are of high quality and are expected to represent the actual resource consumption incurred.

Information on two patients was lacking from psychiatric registers, giving the impression of no psychiatric admissions, no outpatient visits and no psychiatric emergency visits. However, all patients in the study were recruited from psychiatric treatment sites, implying that the visits of these two patients had either not been registered or were lost from the national database. As there is no way of estimating their use of health care services, these two patients were excluded from the analysis. Both were in the control group.

Few patients were not registered as having bought pharmaceuticals within the follow-up period. These patients had either had very long admissions or received their medication at the hospital outpatient clinic for free, which is not uncommon.

This study did not include other costs than those of the healthcare system. Community services (in terms of psychiatric residences and other supportive and precautionary arrangements) as well as costs associated with productivity losses, due to inability to work, might further have established the benefits of PGx. Healthcare costs usually only constitute a fraction of the total cost-of-illness when it comes to psychiatric diseases [23]. It is, however, doubtful whether the 1-year time horizon of this study would have been able to capture benefits on employment rates in this group of patients. Also, with a long follow-up period, after, for example, 5 or 10 years, it would have been possible to establish whether PGx is preventive of relapses as well of capable of reducing the costs associated with these.

This study is concerned with the economics of care. Patient perspectives are important as well, in particular within this patient group, as well as how to implement this kind of testing in real life to maximize gains. The study is part of a Danish

health technology assessment, from which further results are not yet available. Ultimately, the success of pharmacogenetic testing depends upon the uptake of the test among practitioners. Long-term benefits of the once-in-a-life-time test do rely on the search for test results in the often very extensive hospital records and the incorporation of information in the treatment decisions made by the prescribing doctor. Previous studies on pharmacogenetic testing for CYP2D6 and CYP2C19 in a Danish context, describe problems of unawareness of test results or no effect of test results on clinical decision-making [5,24]. Despite these problems, this study shows a potential economic gain, demonstrating that the full clinical potential of genetic testing for CYP2D6 and CYP2C19 polymorphisms is not yet fully understood.

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Statement of Conflict of Interest

The authors have no conflict of interest.

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