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Research paper

Cost-effectiveness of genetic and clinical predictors for choosing combined psychotherapy and pharmacotherapy in major depression

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ABSTRACT

Background: : Predictors of treatment outcome in major depressive disorder (MDD) could contribute to evidence-based therapeutic choices. Combined pharmacotherapy and psychotherapy show increased efficacy but higher cost compared with antidepressant pharmacotherapy; baseline predictors of pharmacotherapy resistance could be used to identify patients more likely to benefit from combined treatment.

Methods: : We performed a proof-of-principle study of the cost-effectiveness of using previously identified pharmacogenetic and clinical risk factors (PGx-CL-R) of antidepressant resistance or clinical risk factors alone (CL-R) to guide the prescription of combined pharmacotherapy and psychotherapy vs pharmacotherapy. The cost-effectiveness of these two strategies was compared with standard care (ST, pharmacotherapy to all subjects) using a three-year Markov model. Model parameters were literature-based estimates of response to pharmacotherapy and combined treatment, costs (UK National Health System) and benefits (quality-adjusted life years [QALYs], one QALY=one year lived in perfect health).

Results: : CL-R was more cost-effective than PGx-CL-R: the cost of one-QALY improvement was £2341 for CL-R and £3937 for PGx-CL-R compared to ST. PGx-CL-R had similar or better cost-effectiveness compared to CL-R when 1) the cost of genotyping was £100 per subject or less or 2) the PGx-CL-R test had sensitivity $\geq$ 0.90 and specificity $\geq$ 0.85. The cost of one-QALY improvement for CL-R was £3664 and of £4110 in two independent samples.

Limitations: **:** lack of validation in large samples from the general population.

Conclusions: : Using clinical risk factors to predict pharmacotherapy resistance and guide the prescription of pharmacotherapy combined with psychotherapy could be a cost-effective strategy.

1. Introduction

Major depressive disorder (MDD) is the fourth-leading cause of disability worldwide (GBD 2015 Disease and Injury Incidence and Prevalence Collaborators, 2016). Overcoming the trial and error principle in treating MDD has been the object of multiple research efforts, but the heterogeneity of the disorder makes it challenging to identify reliable response predictors (Fried and Nesse, 2015; Kraus et al., 2019).

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Pharmacogenetic biomarkers are a potential strategy, but only pharmacokinetic variants are endorsed by guidelines so far (Fabbri et al., 2018), while genetic variants involved in drug pharmacodynamics have an unclear role, probably because of their multiplicity and complex interactions. Pharmacokinetic variants alone explain only a limited part of inter-individual variability in treatment clinical outcomes and, despite there is no definitive evidence, genotyping may be most beneficial in those who have experienced an adverse drug reaction or inadequate response to at least one previous antidepressant trial (International Society of Psychiatric Genetics, 2019; Greden et al., 2019). Another issue is the lack of definitive evidence on the cost-effectiveness of pharmacogenetic testing. Previous studies evaluated the cost-effectiveness of testing individual genetic variants in candidate genes, such as cytochrome 2D6 and 2C19 (*CYP2C19* and *CYP2D6*) genes and the serotonin transporter (*SLC6A4*) (Olgiati et al., 2012; Perlis et al., 2009; Maciel et al., 2018; Groessl et al., 2018; Hornberger et al., 2015). These studies showed that pharmacogenetic testing may be cost-effective compared to standard care, but results were heterogeneous, mostly because of the different effect size of the considered genetic variant(s) on clinical outcomes to different drugs. Further, none of the previous studies selected the candidate genes using genome-wide or sequencing data, and none of them compared pharmacogenetics-guided treatment with treatment guided by clinical risk factors, which is a cheaper option with broader availability since no genotyping is needed but only a clinical interview. To the best of our knowledge, the cost-effectiveness of using clinical predictors of pharmacotherapy response to guide treatment prescription in MDD has not been tested in previous studies, despite a number of clinical predictors have been identified (De Carlo et al., 2016).

Markov models were the most commonly used method to estimate cost-effectiveness in previous studies; they simulate a cohort of patients moving between health states (e.g. from depression to remission) over time based on a matrix of transition probabilities that depend on treatment effects (Pierucci and Zarca, 2019). Each health state has a different level of well-being, defined as utility and measured as quality-adjusted life years (QALYs), each QALY representing a year lived in perfect health, and different costs associated with it. Utilities and costs are compared between an experimental intervention or treatment strategy and standard care. The experimental treatment strategy is considered as cost-effective vs standard care when it is more effective at an extra-cost that the society is willing to pay. There is no univocal value defining the willingness-to-pay threshold, the National Institute for Health and Care Excellence (NICE) provides a threshold of £20,000 per each QALY gained as a very general indication to evaluate cost-effectiveness of new interventions, but other thresholds have been suggested and the disability associated with a specific disease is an important factor to consider (National Institute for Health and Care Excellence, 2015).

This study aimed to provide a proof-of-principle on the cost-effectiveness of different strategies to guide treatment choice in patients with MDD. We investigated the cost-effectiveness of genetic and clinical risk factors of pharmacotherapy resistance (PGx-CL-R model) and clinical risk factors alone (CL-R model) in guiding the identification of MDD patients more likely to benefit from an alternative treatment strategy compared to standard pharmacotherapy. The predictors used in the PGx-CL-R and CL-R models were developed to estimate the risk of pharmacotherapy resistance using a machine learning approach on whole exome sequence and genome-wide data in a previous work (Fabbri et al., 2020). We chose pharmacotherapy combined with psychotherapy (cognitive behavioural therapy [CBT] or interpersonal therapy [IPT]) as alternative to standard care (pharmacotherapy alone) because: 1) it has evidence of increased efficacy with the same risk of side effects compared to pharmacotherapy alone, but higher cost and therefore limited availability (Cuijpers et al., 2014; Ijaz et al., 2018); 2) there is no convincing evidence supporting the choice of a particular antidepressant based on the genetic profile of a patient (Food and Drug Administration, 2019).

2. Methods

2.1. Predictive models and target patients

The predictive models of TRD (treatment-resistant depression) used in this study were developed in a previous work (Fabbri et al., 2020). In this previous study, TRD was defined as lack of response to least two adequate antidepressant drugs during the current depressive episode in patients with MDD according to DSM-IV criteria. The study was cross-sectional and each antidepressant trial during the current episode was considered as adequate if the duration was at least four weeks and the dose was at least the minimum therapeutic dose reported in the drug labeling. The study was approved by local ethical committees of all participating centers and all patients signed an informed consent.

Predictive models were developed in a training set of patients treated with serotonergic antidepressants, according to the pharmacology domain reported in the Neuroscience-based Nomenclature (Wilson, 2018) (n=269); the corresponding receiver operating characteristic (ROC) curves were obtained by testing the models in an independent testing sample treated with serotonergic antidepressants (n=118) (ROC curves are in Supplementary Figure 1; the description of the clinical-demographic features of the samples is in Supplementary Table 1). The choice to use models developed in patients treated with serotonergic drugs aimed to reflect the characteristics of patients who would be treated with pharmacotherapy in primary care, having non-severe MDD and seeking treatment for the first time. This group was indeed the target of the present study since they are expected to benefit more from a baseline prediction of their risk to progress towards TRD (alternative treatment strategies can be implemented).

The clinical risk-guided (CL-R) model included five clinical risk factors independently associated with TRD in the training sample (chronic depression, number of depressive episodes > 3, suicidal ideation, Montgomery and Asberg Depression Rating Scale (MADRS) interest-activity score ≥ 13 and MADRS pessimism score ≥ 7). These two MADRS subscales were determined according to previous studies (Uher et al., 2012). The pharmacogenetic + clinical risk-guided (PGx-CL-R) model included the same clinical risk factors and the burden of rare variants (from whole-exome sequencing data) combined with common genetic variants (from genome-wide data) in 83 genes (Supplementary Table 2) selected in the training sample based on their Correlation-Adjusted T score and Local False Discovery Rate (a process that reduced dimensionality and selected variables with higher probability of being informative, Supplementary Methods). Both models were trained using a gradient-boosting classifier. Further details are reported in Supplementary Methods and in a previous paper (Fabbri et al., 2020). Compared to other studies of antidepressant response, the described data have the advantage of availability of both common and rare variants. Rare variants were indeed demonstrated to add significant information to common variants when studying the genetics of complex disorders (Flannick et al., 2019). In addition, sequencing is becoming more and more feasible in large samples (e.g. biobanks including hundreds of thousands participants) thanks to a more than exponential drop in costs in the last 10 years (National Human Genome Research Institute, 2018).

We did not include *CYP2C19* and *CYP2D6* genes because:

1) "Clinical trials to date have suggested testing might be most beneficial for individuals who have experienced an adverse drug reaction or inadequate response to a previous antidepressant trial" (International Society of Psychiatric Genetics, 2019; Greden et al., 2019), while our study aims to guide treatment choice in patients seeking treatment for the first time to maximise potential benefits;
2) *CYP2C19* and *CYP2D6* testing is useful to select which drug and dose to prescribe (PharmGKB, 2020), but it does not provide an overall estimate of the risk of treatment-resistance to pharmacotherapy, which was the aim of our predictive models, and therefore it does not

seem applicable to guide the prescription of combined pharmacotherapy and psychotherapy vs pharmacotherapy. Therefore, the design of a study to evaluate the cost-effectiveness of *CYP2C19* and *CYP2D6* genotyping should have been different (e.g. based on the concordance between prescribed drug and predicted activity of the enzyme responsible for the metabolism of the drug);

3) structural variants in *CYP2D6* would have required a different genotyping approach to be accurately detected (Nofziger and Paulmichl, 2018);
4) *CYP2C19* and *CYP2D6* should be analysed according to a phenotypic classification based on haplotypes (PharmGKB, 2020), not using the variant burden score that we applied (Supplementary Methods).

2.2. Cost and utility estimation

We took as reference the costs within the National Health System (NHS) of the United Kingdom (UK). The considered costs included outpatient visits, hospitalizations, liaison mental health service in case of emergency room access and brief psychotherapy (16 sessions) based on data available on the Personal Social Services Research Unit (PSSRU) website for the year 2018 (Personal Social Services Research Unit (PSSRU), 2018a) (Personal Social Services Research Unit (PSSRU), 2018b), while medication costs were based on NHS prices (as of April 2019) (REGIONAL DRUG AND THERAPEUTICS CENTRE, 2019) in GBP. Psychotherapy was assumed to be CBT or ITP, 16 sessions per cycle, as these were the most common types of psychotherapies in the meta-analysis used to estimate the effects of combined treatment and the greatest part of the included studies had a number of sessions between 10 and 20 (Cuijpers et al., 2014). CBT or ITP are also the types of psychotherapy suggested in patients with depression by the NICE guidelines (NICE, 2018).

The cost of whole-exome sequencing and genome-wide genotyping were based on commercial prices in 2019 in US dollars (Suwinski et al., 2019) and converted in GBP using purchasing power parity (ppp) exchange rates in 2018 (OECD, 2018). Cost units for visits, psychotherapy and days spent in hospital were inflated by 2.1% yearly, based on the mean inflation rate in the United Kingdom (UK) in 2018-2020 (Statista portal, 2019). Indirect costs related to productivity were not included, because they are likely to be captured by the utility weights (QALYs) (Olgiati et al., 2012).

The probability of hospitalization, emergency room access and mean hospitalization duration during a depressive episode were based on hospital episode statistics reported by the NHS for the period 2017-2018 (NHS digital, 2018) and the literature (Citrome et al., 2019). The frequency of visits in each health state was based on the NICE guidelines and the literature (NICE, 2018; Judd et al., 2016; Simon, 2000). An overview of the considered costs is reported in Supplementary Table 3.

Utilities (health quality) were measured as QALYs (varying between 1, that represents perfect health, and 0, that represents death). The assigned values were 0.40, 0.67, 0.88 and 0 for the health states of depression, response, remission and death, respectively (Olgiati et al., 2012; Hornberger et al., 2015). A value of 0.88 and not 1 was considered for remission because of a negative utility associated with treatment (side effects) (Olgiati et al., 2012).

2.3. Statistical analyses

2.3.1. Creation of the Markov model

A Markov model was created using the R package "heemod" (Pierucci and Zarca, 2019). The time horizon was three years and each cycle lasted 12 weeks which reflects the duration of most clinical trials of antidepressant response in MDD (Jakobsen et al., 2017), including each treatment level of STAR*D which was used to estimate the reduction in response and remission probability after the first cycle (Supplementary Methods). Markov models estimate the cost-effectiveness of alternative treatment strategies to standard care based on the probability of transition of simulated individuals between health states having different costs and QALYs. A new intervention or treatment strategy is expected to have increased costs compared to standard care, but to improve health outcomes (QALYs), and Markov models estimate the ratio between costs and health benefits to evaluate if the additional costs are worth paying based on the expected benefits.

Four health states were considered: depression, response, remission and death by suicide; the costs and QALYs associated with each of these health states were different and based on the existing literature and publicly available databases (paragraph 2.2). For example, the number of outpatient visits and the risk of hospitalization were different among the considered health states; the costs of psychotherapy were a major contributor to the costs in the PGx-CL-R and CL-R groups (Supplementary Table 3).

At the beginning of the simulation, 1,000 depressed patients were included in each strategy arm (Figure 1). After the first cycle (12 weeks) and each following cycle (until the 12th, i.e. 3 years), transition to another state was regulated by the probabilities described in Supplementary Table 4, which were also dependent on the time spent in a certain health state (Figure 2, which is based on the results of previous studies and meta-analyses (Cuijpers et al., 2014; Jakobsen et al., 2017; de Maat et al., 2007; Sinyor et al., 2010)). Transition probabilities for each treatment group (pharmacotherapy and pharmacotherapy combined with psychotherapy) were estimated based on the existing literature, data from the STAR*D trial (Cuijpers et al., 2014; Jakobsen et al., 2017; de Maat et al., 2007; Sinyor et al., 2010) and sensitivity/specificity of the predictive models (Supplementary Methods, Supplementary Tables 4 and 5). Whenever available, we used the results of meta-analyses (Cuijpers et al., 2014; Jakobsen et al., 2017; de Maat et al., 2007) rather than individual studies, since the reliability of the Markov model depends on the validity of the estimations provided by the studies used to calculate the model parameters.

The two experimental groups were compared to standard care (ST, pharmacotherapy only). In the PGx-CL-R group, subjects at risk of TRD according to the corresponding predictive model were treated with pharmacotherapy combined with 16 sessions of psychotherapy per cycle until response or remission; subjects predicted to be non-TRD were assigned to pharmacotherapy. In the CL-R group, clinical risk factors only were used to assign patients to the combined treatment strategy or pharmacotherapy. In both PGx-CL-R and CL-R, transition probabilities were dependent on the sensitivity and specificity of the used predictive models of TRD. For example, response and remission rates reported in the literature for combined psychotherapy and pharmacotherapy (Cuijpers et al., 2014) were applied for patients correctly classified as TRD according to the used predictive models (true positives), since the effect size of this treatment was shown to not be different between general MDD samples and TRD samples (Ijaz et al., 2018). Response and remission to pharmacotherapy were also based on previous studies (Jakobsen et al., 2017; de Maat et al., 2007; Sinyor et al., 2010) and applied to our study design: response and remission probabilities took into account that patients with TRD not correctly classified (false negatives) had nearly zero probability of response to standard pharmacotherapy. For a complete description of the approach see Supplementary Methods.

Transitions were possible between all states, while death was modelled as an absorbing health state (i.e. subjects entering in this group could not move to other health states and their QALYs as well as the costs for their health care remained zero after that point to the end of the last cycle) (Figure 1). Only death by suicide was considered because other causes of death were expected to have a negligible effect in a time period of three years in an adult population in the UK. We did not consider dropouts because: 1) many are expected to re-enter the health care system seeking treatment if their depressive symptoms did not remit and this appears to be very likely in a time horizon of three years; 2) no literature data are available to model the probability of dropout and return into the health care system in the considered time frame; 3)

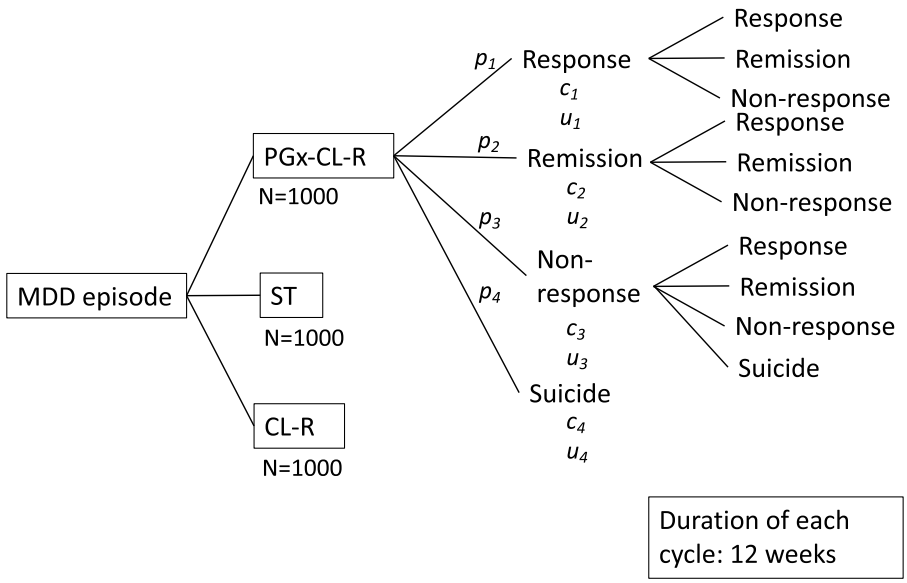

Figure 1. : Markov model representation. Each transition is associated with a probability (*p1…pn*) and each health state with a utility (*u1…un*), measured in QALYs, and cost (*c1…cn*) .

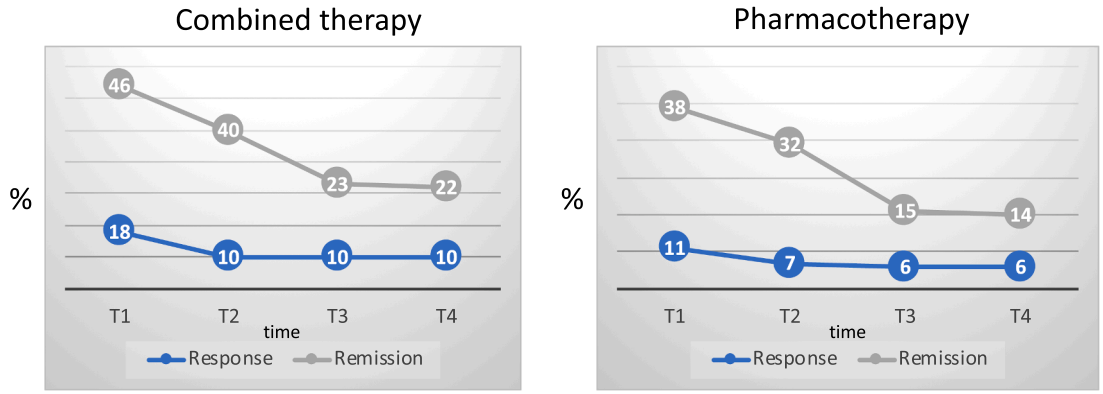

Figure 2. : transition probabilities from depression to response and remission in the combined treatment group and pharmacotherapy group. Details on the estimation of these probabilities are reported as Supplementary Methods. T1, T2, T3 and T4: weeks 12, 24, 36, 48.

no difference in dropout rates was reported between combined psychotherapy and pharmacotherapy vs pharmacotherapy, therefore the inclusion of dropouts would not affect the difference in cost-effectiveness of the considered interventions (Cuijpers et al., 2014).

Pharmacotherapy included only antidepressants for those who responded or remitted in the first two cycles, while in those who did not remit or respond in the first two cycles the cost of first-line pharmacological treatments for TRD, according to the Maudsley Prescribing Guidelines in Psychiatry (Taylor et al., 2018), was added. All pharmacological treatments were hypothesized to be continued for the whole duration of the simulation.

For each strategy alternative to ST, we calculated the incremental cost-effectiveness ratio (ICER). ICER is the ratio between the difference in costs and difference in effect (QALYs) of an alternative treatment strategy (*C1* and *E1*) compared to the reference strategy (*C0* and *E0*), and it expresses the cost of one QALY improvement in the alternative strategy group compared to standard care:

$$ICER = \frac{(C1 - C0)}{(E1 - E0)}$$

2.3.2. Sensitivity analyses

A probabilistic sensitivity analysis was used to simulate 10,000 cases in each strategy arm for each model parameter (each model parameter could vary based on its mean and standard deviation; Supplementary Table 6). This generated a probability distribution of ICERs and cost-effectiveness acceptability curves (CEAC) for each treatment strategy.

We also studied the effect of changing key parameters in our model: sensitivity and specificity of the predictive models used in the PGx-CL-R and CL-R groups (Supplementary Figure 1) and costs of sequencing/genotyping. Different combinations of sensitivity and specificity of the PGx-CL-R predictive model were also evaluated to estimate the extent to which hypothetical improvements in the test would change the results.

2.3.3. Replication

The cost-effectiveness of the CL-R strategy was tested in two independent samples, GENDEP and TRD2 (clinical-demographic characteristics are in Supplementary Table 1), but we could not test PGx-CL-R, because of the unavailability of whole exome sequence data. Indeed, in our previous study we showed that genome-wide array data provided poor coverage of coding regions (exons) which were particularly relevant for the replication of the results (Fabbri et al., 2020). Based on sensitivity and specificity of the CL-R predictive model in these samples, we calculated the transition probabilities between the considered health states (Supplementary Table 7). GENDEP was a 12-week partially randomized open-label pharmacogenetic study with two active treatments

(nortriptyline and escitalopram). 867 patients with MDD (ICD-10 or DSM-IV criteria) were included and severity of depressive symptoms was assessed at baseline and weekly by scales including the MADRS (Uher et al., 2010). TRD and response were defined according to a previous study (Iniesta et al., 2016). TRD2 included 417 MDD patients (DSM-IV criteria) who had failed to respond to a previous retrospectively assessed antidepressant and were entered into an open two-phase naturalistic trial: in the first phase patients received a 6-week venlafaxine treatment; then those who failed to respond to venlafaxine were treated for a further 6-week period with escitalopram. Depressive symptoms were assessed every two weeks using the MADRS (Souery et al., 2015).

TRD2 and GENDEP studies were approved by the ethical committees of all participating centers and all patients signed an informed consent.

3. Results

Our analysis suggested that PGx-CL-R is not cost-effective compared to the other treatment strategies, since it showed an ICER of £3937 per QALY when compared to ST, while CL-R had an ICER of £2341 compared to ST (Table 1; number of subjects in each group during the three-years simulation: Supplementary Figure 2).

In our sensitivity analyses, PGx-CL-R would have an ICER comparable to CL-R if:1) the cost of sequencing/genotyping is £100 or less (ICER would be £2343); or 2) the PGx-CL-R test had sensitivity $\geq$ 0.90 and specificity $\geq$ 0.85 (Figure 3). The CEAC showed that if the willingness-to-pay threshold is £3923 or higher, CL-R has higher chances of being cost-effective compared to the other treatment strategies (Figure 4A). The ICER for CL-R and PGx-CL-R vs. ST were similar when a different threshold was used to distinguish TRD from non-TRD, aiming to maximize specificity (Supplementary Figure 1; Table 1) and we confirmed that CL-R was the most probable cost-effective strategy when the willingness-to-pay threshold was £3769 (Figure 4B).

In GENDEP, the CL-R model had a sensitivity of 0.34 and a specificity of 0.76 and the area under the ROC curve was 0.61 (95% CI 0.55-0.67). The ICER of CL-R compared to ST was £3664. According to the CEAC, CL-R had a higher chance of being cost-effective compared to ST when the willingness-to-pay threshold was £5389 or higher (Supplementary Figure 3A).

In TRD2, the CL-R model had a sensitivity of 0.30 and a specificity of 0.76. The area under the ROC curve was 0.56 (95% CI 0.51-0.62). The ICER of CL-R compared to ST was £4110. According to the CEAC, if the willingness-to-pay threshold was £5942 or higher, CL-R had higher chances to be cost-effective compared to ST (Supplementary Figure 3B).

Table 1
Incremental cost-effectiveness ratio (ICER) for the different treatment strategies tested. Effect difference was measures in QALYs (quality-adjusted life years). All results refer to a three-years simulation. The reference treatment is standard care in all cases. PGx-CL-R=pharmacogenetics and clinical risk guided group. CL-R=clinical risk-guided group.

Treatment strategy	Sample	Cost difference £	Effect difference (QALYs)	ICER (£ per QALY)
PGx-CL-R	Main sample	1594	0.405	3937
	Main sample, sensitivity analysis[†]	1353	0.266	5083
CL-R	Main sample	941	0.401	2341
	Main sample, sensitivity analysis[†]	671	0.291	2311
	GENDEP	861	0.235	3664
	TRD2	864	0.210	4110

[†] this is the sensitivity analysis performed by changing the threshold for distinguishing TRD and non-TRD patients, see Supplementary Figure 1

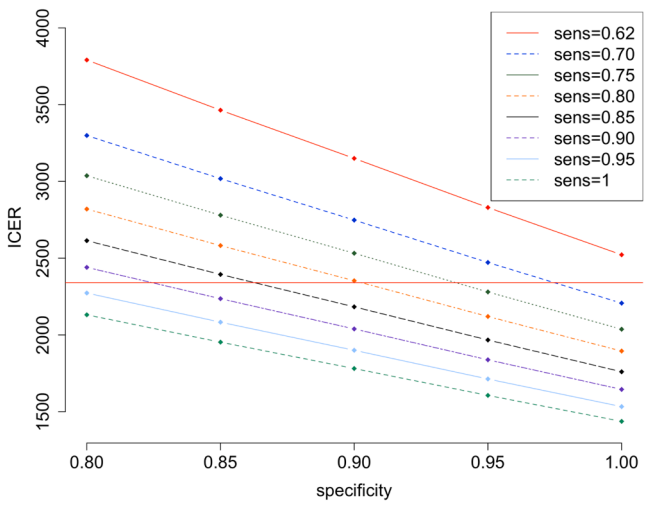

Figure 3. : ICER values (British pound sterling or GBP) in the PGx-CL-R group for different combinations of sensitivity and specificity of the predictive test. The ICER of the CL-R group is marked by a red horizontal line for comparison.

4. Discussion

4.1. Main findings

Our results suggest that the PGx-CL-R treatment strategy is not cost-effective compared to CL-R, since it provided a specificity only 7-10% higher, at a high cost of exome sequencing/genotyping, which had a major impact on the ICER. According to our findings, there are two key scenarios which would make the ICER of PGx-CL-R analogous or better than the ICER of CL-R: 1) cost of genotyping of £100 or less; or 2) sensitivity of the test of at least 0.90 and specificity of at least 0.85 (Figure 3).

Our CL-R model was based on only five variables, in order to make the assessment as easy as possible, and we included only variables generalizable to most MDD samples. The clinical score showed a fair performance in the testing sample, in which it was estimated to improve the detection of TRD cases of 22% compared to assigning the combined treatment randomly to the same proportion of subjects (62% vs. 40% in 1000 simulations). In the two replication samples, the predictive performance was weaker, and the proportion of TRD cases that can be identified was 7% higher (GENDEP) and 4% higher (TRD2) than what would be expected if combined treatment was assigned randomly to the same proportion of subjects, probably as a consequence of different clinical characteristics of the replication samples. It should also be noted that these estimates depend on the prevalence of TRD, which was assumed to be 31% in this study (Supplementary Methods). The proportion of TRD patients identified by our predictive models compared to chance would improve in samples with lower prevalence of TRD. For example, if the prevalence of TRD is 20%, the clinical model would improve the detection of TRD cases by 31%, 8% and 5% in the main testing sample, GENDEP and TRD2, respectively. The reported increase in TRD identification may be seen as a marginal benefit, but the corresponding ICER are good compared to the standard for new interventions (National Institute for Health and Care Excellence, 2015) and MDD is the fourth-leading cause of disability worldwide (GBD 2015 Disease and Injury Incidence and Prevalence Collaborators, 2016), justifying the investment of resources in its treatment. The relatively low sensitivity of the clinical predictive model may not be a major issue, as long as the specificity is quite good, because the intervention is relatively expensive compared to standard care, and as long as there is an increase in the number of subjects who will develop TRD who are correctly identified and assigned to combined treatment compared to random allocation, with an acceptable risk of false positives, there is a potential benefit.

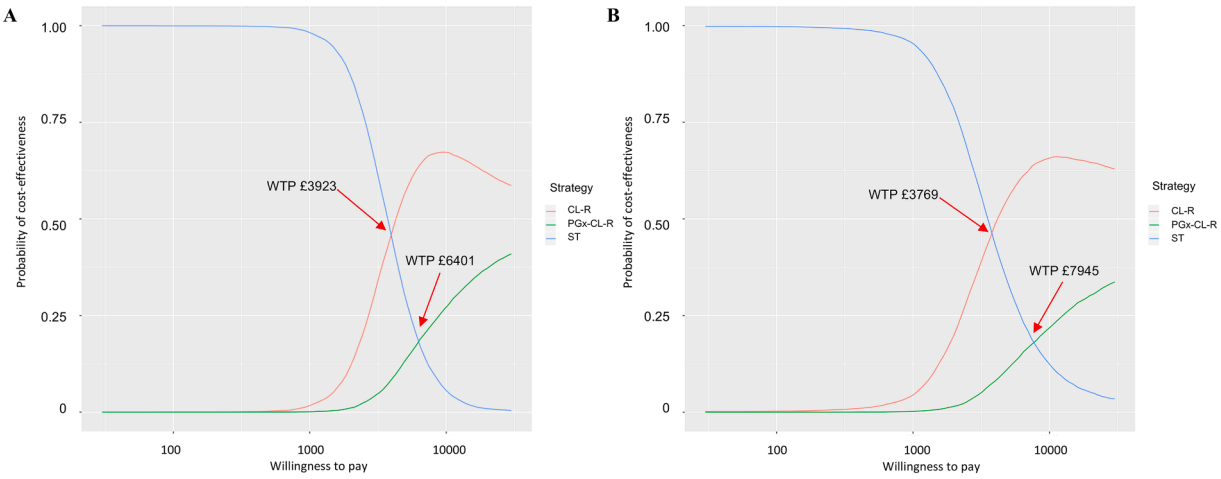

Figure 4. : cost-effectiveness acceptability curve (CEAC) for the main analysis (**A**) and in the sensitivity analysis (**B**) maximizing the specificity of the predictive model in the experimental treatment groups (PGx-CL-R and CL-R). ST=standard care. PGx-CL-R=pharmacogenetics and clinical risk guided group. CL-R=clinical risk guided group. WTP=willingness to pay measured in British pound sterling (£).

Furthermore, our study made a step further compared to previous research that was limited to the evaluation of clinical variables associated with TRD without replication of their predictive performance in independent samples or estimation of their cost-effectiveness for guiding clinical decisions (Iniesta et al., 2016; Kautzky et al., 2018).

Our results are in line with a previous clinical trial that assessed the cost-effectiveness of combined psychotherapy and pharmacotherapy vs pharmacotherapy in patients with MDD who did not respond to at least one previous pharmacotherapy. This study found that the ICER was £5374 for combined treatment vs pharmacotherapy after 3.3 years (Wiles et al., 2016). After three years, we showed similar ICER values in the probabilistic sensitivity analyses, but these were obtained by assigning the treatment group based on a clinical risk score at baseline, therefore saving the time and costs of the first treatment phase.

4.2. Limitations

The PGx-CL-R model validity could not be tested in other samples, because of the lack of comparable genetic data (whole-exome sequencing). However, the rapid growth of sequence data in large cohorts such as biobanks, as well as the rapid drop in the costs of sequencing, will facilitate the replication and development of pharmacogenetic models with improved predictive performance, affordable costs and broad availability. The CL-R model showed weak predictive performance in two of the three testing samples, which could have in part been due to the partial comparability of the main clinical characteristics of these samples (Supplementary Methods; Supplementary Table 1). This study provides a proof-of-principle approach to be refined in primary care samples rather than a definitive method ready to be applied in the clinical practice. The generalizability of the CL-R model is an important step before application to guide treatment choice in clinical trials; testing the model in larger samples, possibly reflecting the characteristics of primary care patients, would be an important validation. Large population-based samples from biobanks and national registries can be used for this purpose. After this step, cost-effectiveness could be measured in a randomized controlled trial (RCT) rather than using a Markov simulation. It should be noted that there could be other scenarios in which genetic testing could be cost-effective vs other treatment strategies (e.g. we did not test the cost-effectiveness of *CYP2D6/CYP2C19* genotyping, which can be performed for prices around £100 (e.g. $149 (MyDNA, 2020), or of commercial pharmacogenetic tests which currently have a median cost of CA$499 (range from CA$199 to CA$2310) (Maruf et al., 2020) and may be used to guide drug choice).

Another issue related to the use of estimates from the literature was that response and remission to combined pharmacotherapy and psychotherapy were based on a meta-analysis of RCTs, which were single-blind in ~1/3 of cases (the assessors were blind to treatment, but of course the patients were not) (Cuijpers et al., 2014). Besides, we used cost data referred to the UK NHS which could vary in other countries.

A treatment strategy that our study did not explore was the use of pharmacological augmentation to antidepressants, which would likely be a cheaper option compared to augmentation with psychotherapy. However, there is no meta-analysis estimating the effect size of pharmacological augmentation vs antidepressant monotherapy as first-line treatment in MDD; in TRD the effect size of this treatment on symptom improvement is similar to that reported for augmentation with psychotherapy (Cuijpers et al., 2014; Ijaz et al., 2018; Zhou et al., 2015; Strawbridge et al., 2019). However, the main issue would be the increased risk of side effects associated with combined pharmacotherapy (our models have 10-20% of false positives who would receive combined pharmacotherapy with increased side effects but no benefits).

4.3. Conclusions

Our results suggest that a clinical risk score of pharmacotherapy resistance may be a cost-effective strategy to guide the prescription of combined psychotherapy and pharmacotherapy vs pharmacotherapy at the baseline assessment of patients with MDD. Despite this is likely the most cost-effective strategy to optimize the prescription of combined psychotherapy and pharmacotherapy at present, in the future the drop of genotyping/sequencing costs and availability of genetic data in large population-based samples could lead to the development of cost-effective genetic predictors.

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Contributors

CF designed the study, performed the statistical analyses and wrote the first draft of the manuscript. CML and AS supervised the analyses. The other authors contributed to the collection of the sample used for creating the predictive models and TRD2 and/or contributed to the design of the study and revision of the manuscript.

Declaration of Competing Interest

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None

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.10.049.

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