The influence of genotype information on psychiatrists' treatment recommendations: more experienced clinicians know better what to ignore.

Authors: Alan J McMichael[a], Marco Boeri[b,f] Jonathan J Rolison[c], Joe Kane[d], Francis A O'Neill[a], Ric Scarpa[e], Frank Kee[a,f]

[a] Centre for Public Health, Queen's University Belfast, Royal Victoria Hospital Belfast, BT12 6BA

[b] Health Preference Assessment, RTI Health Solutions, Research Triangle Park, NC, USA and Gibson Institute, School of biological sciences, Queen's University Belfast, Belfast (UK), BT9 7BL

[c] Department of Psychology, University of Essex, CO4 3SQ, UK

[d] Institute of Neuroscience, Newcastle University, Campus of Ageing and Vitality, Newcastle Upon Tyne, NE4 5PL.

[e] Durham University Business School, Durham, DH1, University of Waikato, Hamilton, New Zealand, Universita` di Verona, Italy

[f] UKCRC Centre of Excellence for Public Health Research (NI), Queen's University Belfast, United Kingdom

Corresponding author: amcmichael01@qub.ac.uk[1]
Centre for Public Health, Queens University Belfast, Royal Victoria Hospital
Belfast, BT12 6BA
Telephone number 028 906 35020
Author's email addresses

Alan McMichael	amcmichael01@qub.ac.uk
Dr Marco Boeri	mboeri@rti.org
Dr Jonathan J Rolison	j.rolison@essex.ac.uk
Dr Joe Kane	joseph.kane@newcastle.ac.uk
Dr Francis A O'Neill	t.oneill@qub.ac.uk
Professor Frank Kee	f.Kee@qub.ac.uk
Professor Riccardo Scarpa	riccardo.scarpa@durham.ac.uk

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Abstract

Objectives: To assess if psychiatrists were influenced by a patient's genetic information, even when the patient's response to treatment was already known to them.

Methods: Sixty-seven psychiatrists were presented with patients' pre and post-treatment scores on the PANSS for two hypothetical treatments for schizophrenia. Psychiatrists were also informed whether the patient possessed a genotype linked to hyper-responsiveness to one of the treatments, and were asked to recommend one of these two treatments. Attribute non-attendance assessed whether the information on genotype influenced psychiatrists' treatment recommendations.

Results: Years of experience predicted whether psychiatrists were influenced by the genetic information. Psychiatrists with one year or less of experience had a 46% probability of considering genetic information, while psychiatrists with at least 15 years of experience had a lower probability (7%).

Conclusions: Psychiatrists and other clinicians should be cautious about allowing a patient's genetic information to carry unnecessary weight in their clinical decision making.

Introduction

Clinicians are becoming increasingly aware of how a patient's genotype can influence their response to treatment [1]. Tailoring treatments according to this anticipated response is known as stratified, or personalized, medicine [2]. In psychiatry, some genetic profiles in the population are associated with an increased risk of schizophrenia. Furthermore, some genetic profiles signal higher potential benefits of particular antipsychotic treatments [3,4], suggesting that for some patients psychiatric treatments could, in the future, be tailored to their genetic profile. However, whether or how information about a patient's genetic profile influences psychiatrists' treatment recommendations is still unclear.

Genetic information may indicate the potential benefits that a patient could receive from a treatment but is redundant when the patient's actual response to a treatment is known. Thus, in certain circumstances, genetic information about a patient could bias the psychiatrist's clinical decision making. In particular, clinicians may view treatment outcomes differently when they are aware that the patient possesses a genotype that is indicative of hyper-responsiveness to a treatment. Consequently, if aware of a patient's genetic profile, a clinician may be less or more likely to recommend or continue a treatment even though the treatment may have been shown to be effective in the patient's pre- or post-treatment scores on a given symptom report scale. The potential for genetic information to bias clinical decision making in respect of a patient's treatment is known as *pharmacogenetic exceptionalism* [5]; this may result in an inefficient allocation of resources for public health. This paper explores the topic by using a choice-format conjoint analysis (referred to as a *discrete-choice experiment* [DCE]) administered to psychiatrists in Northern Ireland, United Kingdom (UK).

In the practice of DCEs, respondents are presented with a sequence of choices for alternative options and are asked to select the one they prefer, with each alternative being described by different attributes and attribute levels [6–9]. A recent review showed a substantial increase in the application of DCEs in health economics and medical decision making and a desire to incorporate patients' and doctors' preferences in the study of effectiveness of treatments[10]. Indeed, the Food and Drug

Administration recently stated that new cancer treatments must first assess patient preferences before becoming widely available to all patients [11] The conventional underlying assumption of DCEs is that, when choosing between alternatives, respondents rationally consider all the attributes presented and select the alternative that maximizes their utility. However, research has seen an increasing focus on decision-making heuristics [12–14]. One particular type of heuristic widely explored by choice modelers in transportation [15–17] and environmental economics [18–20] is attribute nonattendance (ANA). In ANA, respondents may ignore one or more attributes that they believe are not relevant in order to simplify the process of choosing the best alternative [21]. The importance of ANA in modelling respondents' choices and preferences has been highlighted by its influence on both coefficient estimations and welfare analysis [17,22]. Recently, ANA also has been extended to health economics [14,23] where researchers warn that not accounting for ANA may lead to biased health policies [24]. However, within the context of medical decision-making research, ANA has not been widely used to assess which attributes (if any) are non-attended [23]. Researchers consider ANA a non- rational heuristic that should be included in the analysis to avoid bias but should not be included if respondents acted rationally, as assumed by the framework in which DCE operates. This study departs somewhat from this perspective, as ANA is considered the correct heuristic that a clinician should apply as the patient's response to treatment is already known, making the patient's genotype information redundant.

This article's contribution to the literature is twofold. From the methodological viewpoint, ANA is applied in a new, current and highly relevant context—stratified medicine—tackling the issues of coherence of information assessment in the psychiatrist's treatment selection. The novel methodological aspect here is the use of ANA to improve the understanding of the extent to which medical decision making incorporates irrelevant information. From a clinical perspective, the article aims to contribute to the topical issue of whether genotype information influences the treatment recommendations of psychiatrists when a patient's treatment response (in terms of symptom improvement) is already known to the psychiatrist.

Analytic framework

Analysis of DCE is based on the random utility maximization theory [25,26] where the underlying assumption is that individuals select the alternative that offers them the highest utility. In this context, it is possible to denote with *i* the treatment that psychiatrist *n* recommended when considering the vignette *t*. The utility function that psychiatrists maximize when recommending a treatment can be described by characterizing each vignette using a vector of attributes (*X)* and a vector of parameters to be estimated (β) as follows:

$$U_{nit} = \beta' X_{nit} + \varepsilon_{nit}, \qquad (1)$$

where ε represents the part of the utility function that the researcher cannot observe and is assumed to be an independent and identically Gumbel–distributed (*i.i.d.)* error term. With these definitions and assumptions, it is possible to mathematically specify the choice probability for each psychiatrist *n* selecting treatments *i* over *j* alternatives in the vignette *t*, as a multinomial logit (MNL) selection probability [26]:

$$\Pr(nit) = \frac{\exp(\beta' X_{nit})}{\sum_{j=1}^{J} \exp(\beta' X_{njt})}. \qquad (2)$$

This model is estimated as a benchmark and is the simplest starting point for behavioral analysis. Notwithstanding the importance and practicality of the MNL model results, the MNL has several restrictive assumptions. For example, preferences are homogenous across respondents and choices are independent from irrelevant alternatives. These assumptions are often considered unrealistic and are likely to bias the results [28]. The mixed logit (MXL) model relaxes the restrictive assumptions underlying the MNL model and accommodates for the possibility that respondents may have different preferences [29]. Furthermore, the model fit to observed data is typically improved when estimating MXL models [30]. The models derived under the general framework of the MXL allow for taste parameters β to vary across respondents and to account for the fact that, in the DCE, each respondent is observed across a series of *T* vignettes and therefore can be represented as a balanced longitudinal panel of responses on experimentally designed choice tasks (vignettes). If the value of β were known for each of the n^{th} respondents, the probability of a sequence of choices would be given by:

$$\Pr(y_{Tn}|\beta, X_{nit}) = \prod_{t=1}^{T} \frac{\exp(\beta' X_{nit})}{\sum_{j=1}^{J} \exp(\beta' X_{njt})}. \qquad (3)$$

Because it is impossible to know the value of β with certainty for each respondent, heterogeneity of preferences is estimated by allowing for random variation in β across respondents [31,32]. To address the research question, it is essential to understand whether psychiatrists are influenced by information about a patient's genotype in making their treatment recommendations. Therefore, we were interested in modelling ANA in this context, while addressing preference heterogeneity. In this paper, ANA was analyzed by means of behavioral latent class (LC) models, which are semiparametric variants of the MNL model. In LC models, it is assumed that each individual respondent can be implicitly sorted into a set of *C* behaviorally defined classes associated with certain estimated probabilities, with each class characterized by a unique class-specific pattern of ANA embedded in the utility parameters, β_c. With membership to class *c*, the probability of respondent *n*'s sequences of choices y_{Tn} over *T* choice occasions is:

$$\Pr(y_{Tn}|\beta_c, x_{nit}) = \prod_{t=1}^{T_n} \frac{\exp(\beta_c' X_{nit})}{\sum_{j=1}^{J} \exp(\beta_c' X_{njt})}. \qquad (4)$$

Considering that the membership probabilities π for each behavioral LC *c* are also defined according to a MNL process, we have:

$$\pi_c = \frac{\exp(\alpha_c + \gamma_c' z_n)}{\sum_{c=1}^{C} \exp(\alpha_c + \gamma_c' z_n)}, \qquad (5)$$

where z_n is a vector of covariates characterizing respondent *n*, and γ_c is the vector of associated parameters subject to estimation, while α_c is a class-specific constant. In the estimation of LC models, for identification purposes, only *C*-1 set of coefficients can be independently identified (e.g., for one arbitrary class *c*, the vector < α_c : γ_c = 0 >).

The probability of a sequence of choices is:

$$\Pr(y_{Tn}|X_{nit}) = \left(\sum_{c=1}^{C} \pi_c \prod_{t=1}^{T} \frac{\exp(\beta' x_{nit})}{\sum_{j=1}^{J} \exp(\beta' x_{njt})} \right). \qquad (6)$$

The primary hypothesis of this paper was that genotype information might influence some doctors even though this information is redundant. Therefore, this study first focused on a relatively reduced model specification where ANA affects only one attribute (genotype information). This resulted in a model with only two classes (we ignored ANA on attributes other than genotype information). Given the importance of heterogeneity, the final model accommodated for random variation of preferences across respondents by incorporating a random-parameters logit (RPL) model within each class. The final model estimated was represented as:

$$\Pr(y_{Tn}|X_{nit}) = \int \left(\pi \prod_{t=1}^{T} \frac{\exp(\text{ANA}\beta' x_{nit})}{\sum_{j=1}^{J} \exp(\text{ANA}\beta' x_{njt})} + (1-\pi) \prod_{t=1}^{T} \frac{\exp(\beta' x_{nit})}{\sum_{j=1}^{J} \exp(\beta' x_{njt})} \right) f(\beta) d\beta, \quad (7)$$

where $(\text{ANA}\beta' x)$ denotes the indirect utility of the vignette for those doctors who ignored the information on genotype while those who attended to this information have an indirect utility of $\beta' x$. The probability of nonattending to the information on genotype is represented by π (see equation 5).

Our second hypothesis was that doctors use other strategies to simplify the decision-making process (as doctors often have to make many decisions very quickly, they might use ANA to simplify their task). Therefore, we extended our behavioral investigation to explore the entire combination of ANA specifications. The combination of ANA behavior across the four attributes, each of which can be attended to or ignored, generated 2^4=16 behavioral classes (Equation 6). The models were estimated using BIOGEME 2.2 [33].

Methods

Participants

The sample comprised 67 practicing psychiatrists recruited in Northern Ireland. Respondents were tested during single-session continuous professional development meetings in three hospital trusts. Participants provided their demographic information, whether they had completed their specialist training, and, if so, years of experience in clinical practice and their subspecialty. More than half (59%) were male. Most (64%) had completed their specialist training. The average years of clinical experience in their specialty was 10 years (standard deviation, 7.19 years). Ethical permission was

granted from the Queens University Belfast Ethics Committee. Each participant also provided informed consent before completing the study.

Vignette design

Twenty-six vignettes were developed to assess the effect of each attribute on psychiatrists' treatment recommendations for patients with schizophrenia (Figure 1). Each vignette provided a hypothetical patient's pre- and post-treatment symptom scores on the positive subscale of the Positive and Negative Syndrome Scale (PANSS) for two treatments. The positive subscale of the PANSS consists of seven symptom report items, each rated on a 7-point scale, ranging from "absent" (numerical value=1) to "extreme" (numerical value=7). The scores are summed across the seven items to generate a total positive subscale score, ranging from 7 to 49, with higher scores indicative of more extreme symptoms [34]. All vignettes presented a pretreatment score of 42, indicating severe positive symptoms of schizophrenia prior to treatment [34]. Across the vignettes, the pre- post-treatment change scores ranged from 3 to 26 points.

[Figure 1 about here]

Figure 1. Example vignette. Each treatment showed the full range of scores on the PANSS with arrows showing the patient's pre- and post-treatment scores. Vignettes indicated for which treatment the patient had a hyper-responsiveness genotype. Respondents were asked to state which treatment they would be willing to recommend based on the information available.

Each vignette also identified whether the patient had a genetic biomarker for one of the treatments: participants were told that the genetic biomarker was associated with a 30% increase in the effectiveness of the corresponding treatment. The biomarker was present for only one of the two treatments in each vignette. The vignettes additionally identified two side effects associated with each treatment. One side effect referred to the number of acute treatment days spent in hospital, ranging from 17 to 45 days. A second side effect referred to the likelihood of a 10-kg weight gain over the following 6 months, ranging from 30% to 70%, a common side effect associated with antipsychotic treatment [35–37]. The attributes and levels were based on discussions with two practicing psychiatrists to ensure that the attributes and levels fell within a realistic range that might be

experienced in clinical practice. On the basis of the information provided in the vignettes, psychiatrists were asked which treatment they would recommend.

Results

As we were interested in understanding psychiatrists' preferences for different characteristics of treatments when making a recommendation, we started by modelling their choices adopting an MNL model and an RPL model to account for heterogeneity in preferences. In both models (Table 1), psychiatrists were significantly more likely to recommend treatments associated with higher posttreatment benefits. As expected, psychiatrists were also significantly less likely to recommend treatments that were associated with more days spent in hospital or a higher likelihood of a 10-kg weight gain. Interestingly, psychiatrists were less likely to recommend treatments for which the patient had a hyper-responsiveness genotype.

Table 1. Model estimations for MNL, RPL, and RPL nonattendance models.

	MNL model		**RPL model**		**RPL – ANA model**	
Variable	**Estimate**	**SE**	**Estimate**	**SE**	**Estimate**	**SE**
Change score	0.30***	0.02	0.44***	0.04	0.44***	0.04
σ Change score			0.19***	0. 03	0.20***	0.03
Genotype	-0.17**	0.09	-0.25	0.17	-2.02***	0.36
σ Genotype			1.02***	017	0.16	0.91
Days	-0.08***	0.01	-0.11***	0.01	-0.11***	0.01
σ Days			0.04***	0.02	0.04***	0.02
Weight gain	-0.08***	0.01	-0.11***	0.01	-0.10***	0.01
σ Weight gain			0.04***	0.01	0.05***	0.01
% of psychiatrists who considered patient's genotype					15.6%	
% of psychiatrists who did not considered patient's genotype					84.4%	
Variation in ANA Genotype info per year of experience					0.17***	0.06
Log-likelihood	-594.69		-533.07		-532.63	
Parameters	4		8		9	

Note. MNL (multinomial logit), RPL (random parameters logit), RPL-ANA (Random parameters – attribute non-attendance), SE (standard error)
**p<.05, ***p<.01*

Genotype and its influence on psychiatrists' treatment recommendations

To test the primary hypothesis related to psychiatrists' attending to the irrelevant information about the patient's genotype, a constrained LC model to control for ANA on only the genotype attribute (as described in equations 5 and 7) was estimated. This provided an estimated probability that psychiatrists systematically ignore the information about the patient's genotype. The results of this analysis are reported in the last two columns of Table 1 (under the heading RPL-ANA model) and suggest that the genotype information did not significantly influence most of the psychiatrists' treatment recommendations. Indeed, across the entire sample of psychiatrists, there was an 84% probability that psychiatrists' did not consider the information on patient genotype. Nonetheless, there was a small probability (approximately 16%) that psychiatrists attended to the information on genotype. Although this probability is small, it implies that, in some instances, psychiatrists considered the genotype information to be important even though the patient's treatment response on the PANSS was already known to them.

To better characterize psychiatrists who were associated with a positive probability of considering a patient's genotype information when selecting their preferred treatment, we tested the significance of various covariates likely to act as determinants of class membership probability (equation 6) and found years of clinical experience was the only significant covariate. Specifically, we found that more experienced psychiatrists were less likely to consider the information on genotype when selecting the treatment to recommend to the patients in the vignette. To be able to expand our discussion on the practical implication of this finding, we simulated posterior probabilities (based on the sequence of choices made by each physician) of being associated with one class or another conditionally to the numbers of years of experience. The result, as presented in Figure 2, suggests that psychiatrists with less than 1 year of experience had a probability close to 50% of attending to and incorporating the

genotype information in their treatment recommendations. Conversely, psychiatrists with more than 15 years of experience were not likely (with a membership probability close to zero) to consider the genotype information in their recommendations.[2]

[Figure 2 about here]

Figure 2. Psychiatrists' years of experience plotted against the probability of attending to the patient's genotype information. More experienced psychiatrists were less likely to attend to the genetic information of the patient.

Discussion

This study investigated whether psychiatrists' treatment decisions are influenced by information about a patient's genotype even when they already know the patient's actual response to treatment. We provided psychiatrists with pre- and post-treatment patient outcomes, which identify a treatment's effectiveness, and information about the patients' genotype. Our premise was that the presence of a hyper-responsive genotype should not have influenced the treatments recommended by psychiatrists. Results suggested that most psychiatrists, but not all, were not influenced by the irrelevant genetic information about the patient. Years of clinical experience strongly determined whether psychiatrists incorporated the genetic information into their recommendations. Psychiatrists with 1 year or less of clinical experience had a 46% probability of responding to the genetic information. Psychiatrists with at least 15 years of experience had a 7% probability of incorporating the same genetic information.

Why were inexperienced psychiatrists more likely to be influenced by irrelevant genetic information about a patient? One possibility is that the prescribing behaviors of psychiatrists have undergone a gradual change over time, creating generational differences in their recommendations [38]. Another

[2] To conclude the exploration of ANA in our dataset, it is possible to use the same model with additional classes. More precisely, the full model requires creation of 16 separate classes to account for all possible patterns of ANA. Estimates from this model (not included in the paper but available on request) suggest that only three classes have a membership probability significantly different from 0: full attendance (with a membership probability of 21.6%), nonattendance to genotype (60.5%), and nonattendance to both genotype and weight gain (with the lowest probability below 10% and statistically insignificant). However, the membership probability of the latter class is reduced to almost zero when the specification accounts for preference heterogeneity as in our model (RPL – ANA model) in Table 1. This makes the ANA specification proposed in Table 1 the most suitable to model the data from this study.

possibility is that, unlike more experienced practitioners, novice practitioners have been exposed to new discoveries in genetics and the potential value of patient genotype information as part of their medical training. Modern medical training has incorporated recent advances in genetics that were not known during the training of more experienced practitioners [39]. Nevertheless, current medical training may not provide adequate guidance on when genetic information about a patient should be used and how it should be incorporated into clinical recommendations and prescriptions. For instance, in 2010, only 56% of a sample of 217 chief psychiatrists in psychiatric residency programs in the United States reported receiving training on genetics during their residency, and those who did received no more than 3 hours of training [40]. Thus, although novice psychiatrists may receive training on psychiatric genomics, directing their attention to its relevance in clinical practice, they may not receive sufficient training on the appropriate use of such patient information. We tentatively recommend that researchers and policymakers investigate more closely current education practices in terms of psychiatric genomics.

Our findings resonate with recent discoveries that clinicians' treatment recommendations can be influenced by subjective factors about a patient. For example, researchers have found that clinicians are less likely to recommend amniocentesis—an invasive prenatal test for genetic and chromosomal abnormalities—when pregnancies were conceived by assisted reproductive technologies than when they were conceived spontaneously, even though the method of conception is irrelevant to the possibility of genetic or chromosomal abnormalities [41]. Our current findings reveal that genetic information about a patient may also influence psychiatrists' treatment recommendations even when a patient's actual response to treatment is known, although this is less likely among experienced psychiatrists.

Our study has some limitations. We focused on the treatment recommendations of practicing psychiatrists. Further research is essential to assess how clinicians in other medical domains may be inappropriately influenced by genetic information in their medical decision making. Additionally, we presented psychiatrists with hypothetical patient outcomes for hypothetical treatments rather than use actual patient outcomes for real treatments. We did so to control for potential redundancies between

attributes and to allow a broad range of attribute levels. Studies have validated the use of vignettes to study individual preferences [43,44]. Nevertheless, the decisions in vignette-based studies usually do not have the same financial, psychosocial, or emotional consequences of treatment decisions made in clinical practice.

Conclusions

Building on encouraging results from past research on ANA in environmental economics [21,45,46] and health [47][14], our study confirms that ANA is a valuable tool for analyzing clinical decision making. To the authors' knowledge, this study is the first to suggest that less experienced psychiatrists may be inappropriately influenced by a patient's genetic information in their clinical decision making. Several authors have warned clinicians about being unduly influenced by a patient's genetic information, and it is plausible that more experienced clinicians may be more immune to the influence of a patient's genetic profile [5,48]. The findings of this study show that less experienced psychiatrists may be more susceptible to a form of *pharmacogenetic exceptionalism*, giving undue weight to a patient's genotype when they already know the patient's actual response to treatment. As a result, it is possible that less experienced psychiatrists will be less likely to recommend effective treatments or continue with ineffective treatment plans when they are aware of a patient's genetic profile.

We believe that the results of our current study may have important implications for medical practice. With the increased knowledge and awareness of the role that genes play in a patient's potential response to treatment, it is essential that psychiatrists and other clinicians weigh this information appropriately in their clinical decision making. Understanding the role that genetics plays in treatment response could help clinicians maximize treatment response and minimize treatment side effects [42]. However, there is a risk that too much weight could be given to a patient's genotype, known as *pharmacogenetic exceptionalism* [5]. Psychiatrists and other health care professionals should be aware of the potential influence of a patient's genetic information on their clinical decision making, and this should be considered and highlighted during their education and further training.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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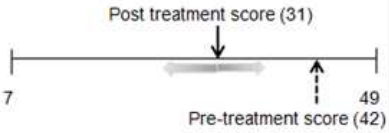
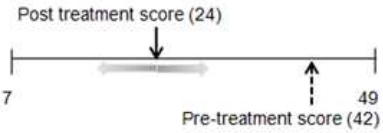
Patient Information	Treatment A	Treatment B
Displayed to the right are the patients' pre- and post-treatment scores on the positive subscale of the PANSS for Treatment A and Treatment B. The numerical values are provided in parenthesis The shaded horizontal arrows represent the 95% confidence intervals for the patients *post treatment* score		
Patient status in respect of *hyper-responsiveness* genotype to this treatment	**Yes**	**No**
Has this patient responded to treatment? (circle as appropriate)	**Yes No**	**Yes No**
How confident are you in your judgement (1=not at all confident, 7=very confident)? (circle as appropriate)	**1 2 3 4 5 6 7**	**1 2 3 4 5 6 7**
Treatment Information	**Treatment A**	**Treatment B**
The cost: acute treatment days in hospital.	**30**	**38**
The percentage probability of a 10kg weight gain in the next six months following the start of treatment	**41%**	**33%**
Based on the information above, which treatment would you recommend? (circle as appropriate)	**Treatment A**	**Treatment B**

Figure 1.

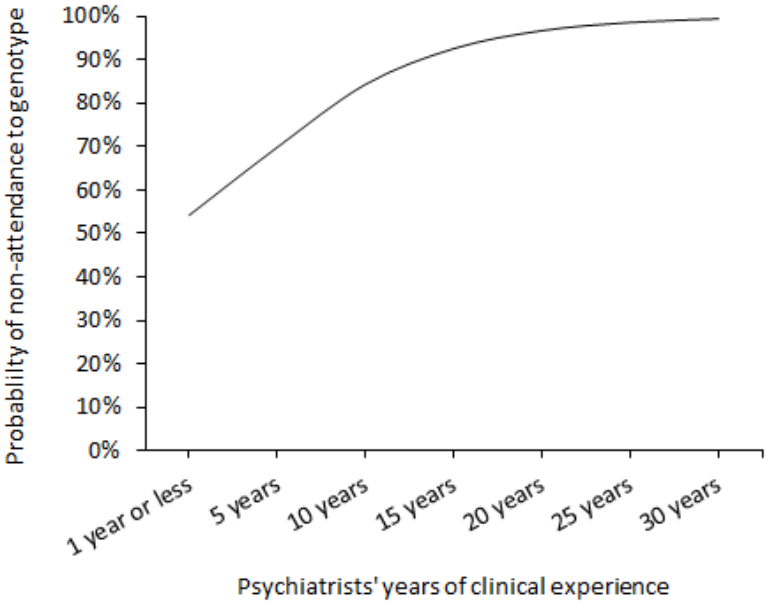

Probablilty of non-attendance to genotype
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1 year or less
5 years
10 years
15 years
20 years
25 years
30 years
Psychiatrists' years of clinical experience

Figure 2.