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Valuing pharmacogenetic testing services: A comparison of patients' and health care professionals' preferences

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ABSTRACT

Objective: The study compared the preferences of patients and health-care professionals for the key attributes of a pharmacogenetic testing service to identify a patient's risk of developing a side effect (neutropenia) from the immunosuppressant, azathioprine.

Methods: A discrete choice experiment was posted to a sample of patients (n=309) and health-care professionals (HCPs) (n=410), as part of the TARGET study. Five attributes, with four levels each, described the service as follows: level of information given; predictive ability of the test; how the sample is collected; turnaround time for a result; who explains the test result. Data from each sample were first analyzed separately and responses were compared by 1) identifying the impact of the scale parameter, and 2) estimating marginal rates of substitution.

Results: The final analysis included 159 patients and 138 HCPs (50% & 34% response rates). Estimated attribute coefficients from the patient and HCP sample differed in size, after taking into account the impact of the scale parameter. Patients and HCPs had similar preferences for predictive accuracy of the test and were willing to wait 2 days for a 1% improvement in test accuracy. Patients preferred to obtain more information and were willing to wait 19 days compared to 8 days for HCPs for providing higher levels of information.

Conclusions: Patients demanded accurate and timely information from health-care professionals about why it was necessary to have a pharmacogenetic test and what the test results mean. In contrast, health-care professionals appear to focus more exclusively or entirely upon the predictive accuracy and waiting time for a test result.

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Introduction

Pharmacogenetic tests rely on the premise that data on variation in specific (known) genes can provide clinicians with information about an individual's ability to absorb, distribute, metabolize, and excrete a drug, or to indicate tumor susceptibility to a particular chemotherapy. Such data can guide prescribing by providing information about the probability that an individual will have a therapeutic response, or develop side effects. In principle, pharmacogenetic testing offers potential benefits by helping clinicians to personalize prescribing so patients may benefit from improvements in health without experiencing harmful side effects. Although suggested as a technology for the future [1], there are already examples of pharmacogenetic tests being recommended and used in health-care systems [2]. Pharmacogenetic tests associated with chemotherapy are cited as the most clinically relevant examples [3], but other examples of tests being used in mainstream health care exist [4–6].

Widespread introduction of pretreatment testing will use scarce health-care resources associated with setting up and running a pharmacogenetic service. There are limited numbers of economic evaluations of pharmacogenetic tests [7] providing information on the relative costs and benefits of using technologies to generate genetic data to inform prescribing. Decision makers charged with commissioning pharmacogenetic tests will also need information on the appropriate configuration of pharmacogenetics services in mainstream health care, and associated training requirements, to meet the challenges of delivering a timely, safe, effective, and efficient service [8]. This considered approach is necessary to move from diffusion (passive spread) of an innovation to implementation (active and planned efforts to mainstream an innovation within an organization) [9].

The thiopurine methyltransferase (TPMT) test is a good example of a pharmacogenetic test currently being recommended for use in clinical practice and has been revealed to be a potentially useful means of identifying people at risk of profound neutropenia from azathioprine [10]. Azathioprine is an effective treatment used for a number of autoimmune conditions, such as rheumatoid arthritis (RA), inflammatory bowel disease (IBD), and after organ transplantation [11–14]. The effectiveness of azathioprine is limited by a number of serious side effects, including profound neutropenia, which puts patients at risk of life-threatening infections and death [9]. The primary aim of the TPMT test is to identify the activity of the TPMT enzyme, which metabolizes azathioprine to its active and inactive metabolites in the body, and indicate a person's risk of profound neutropenia. Two analytical methods of offering the TPMT test measure either enzyme activity (or phenotype) or variants in the TPMT gene of the patient (genotype). TPMT enzyme measurement is technically challenging and can be distorted following blood transfusion. Genotyping commonly involves looking for the three variant alleles, TPMT*2, TPMT*3A, and TPMT*3C, that account for 80% to 95% of intermediate or low activity cases. Genotyping for the common TPMT variants is technically straightforward but, unlike enzyme measurement, may not identify all TPMT deficient individuals. Concordance rate between TPMT genetics and phenotypes is around 98%. Genotyping and phenotyping have similar costs [15].

The TPMT test is suggested as a potentially useful test in a number of clinical guidelines in the United Kingdom [16,17], although in the UK, the enzyme-level measurement test is currently used in preference to the genotype (DNA-based) test [18,19]. Prospective trials suggest support for pretreatment TPMT testing in terms of clinical utility [20,21], defined broadly as how the results of the test can be used to inform clinical decision making [22]. Economic modeling studies suggest the TPMT test is a cost-effective use of health-care resources [23]. A robust evidence base showing clinical utility is a necessary but not sufficient prerequisite for the successful implementation of pharmacogenetics into practice. Clinicians must use such evidence and change their prescribing behavior to maximize patient benefits from pharmacogenetic testing. Health-care professionals involved with pharmacogenetic service delivery will need to understand the probabilistic nature of the information that a pharmacogenetic test will provide: when it is appropriate to test patients; how and from where should particular tests be ordered; how to engage patients in the decision about whether to test; and how much information to offer during the prescribing decision-making process. It is vital that relevant health-care professionals can interpret a pharmacogenetic test result, decide on the appropriate treatment strategy, and involve the patient in this process.

Laboratories within the British National Health Service (NHS) are providing pharmacogenetic tests [24]. A number of potential service delivery models could exist but these are yet to be described explicitly. In the UK, four priority groups have been identified who need to be prepared for moving pharmacogenetics into mainstream health care: medical practitioners, nurses, dieticians, and pharmacists [25]. However, to date, there has been no work that systematically evaluates how pharmacogenetics will be provided as part of mainstream health-care services [26]. Fargher et al. [26] explored the views of patients and health-care professionals concerning pharmacogenetic services and their future delivery. In this qualitative study, pharmacogenetics was perceived to be of benefit to both groups. Patients expressed a desire to receive timely and clear information from an educated health-care professional who explains the reason for taking the test and enabled confident interpretation of the result. None of the health-care professionals questioned expected to have responsibility for the future delivery of clinical pharmacogenetic services. Genetic specialists believed that pharmacogenetic testing should form part of mainstream health-care services rather than involving the regional specialist genetic service. In contrast, non-genetics health-care professionals did not feel they had the relevant knowledge or skills to offer advice on a pharmacogenetic test.

Stated preference methods can be usefully applied to inform the development of new models of service delivery [27]. Discrete choice experiments (DCEs) are a particularly useful form of stated preference method because they can identify the trade-offs that individuals make between the process and outcome-focused attributes of a new service [28]. Health care is characterized by asymmetry of information between clinicians, "the experts," and patients who "consume" services and

Table 1 – Attribute names and description.

Attribute name	Attribute description	Levels (coding for analysis)	Effects coding
Information	The level of information given to the patient about the test	None	Information-none (base)
		Low	Information-low
		Moderate	Information-mod
		High	Information-high
Predictive accuracy	The ability of the test to predict the risk of the side effect (neutropenia)	50% (50)	Predictive accuracy-50 (base)
		60% (60)	Predictive accuracy-60
		85% (85)	Predictive accuracy-85
		90% (90)	Predictive accuracy-90
Sample	How the sample is collected	Blood test	Sample-blood (base)
		Mouthwash	Sample-wash
		Finger prick	Sample-finger
		Mouth swab	Sample-swab
Turnaround time	How long it takes before the patient receives the result	2 days (2)	Turnaround time-2 (Base)
		7 days (7)	Turnaround time-7
		14 days (14)	Turnaround time-14
		28 days (28)	Turnaround time-28
Explanation	Who explains the result to the patient	GP	Explanation-GP (base)
		Pharmacist	Explanation-pharmacist
		Hospital doctor	Explanation-hospital doctor
		Nurse	Explanation-nurse

GP, general practitioner.

treatments to improve their health. Clinicians act as agents for their patients. This study aimed to identify and compare the preferences of patients and health-care professionals for the key attributes of an example model of a pharmacogenetic testing service. The study focused on one example of a pharmacogenetic test that is currently recommended for use in clinical practice, the pretreatment TPMT test for azathioprine; however, no standards for service delivery currently exist.

Methods

A postal DCE was designed to identify and compare the preferences of patients and health-care professionals for attributes of a pharmacogenetic testing service. The DCE used a specific case study of a pharmacogenetic test currently being used in clinical practice: the TPMT test to inform azathioprine prescribing in autoimmune conditions. Clinical guidelines and some regulatory bodies have already made strong recommendations that TPMT testing should be used prior to starting azathioprine, or other thiopurine-based, medicines. Therefore, the choice question was framed as: what are the preferred characteristics of a pharmacogenetic service? The DCE used generic attributes common to both alternatives (unlabeled design) and did not include an opt-out option. An alternative policy question would be to consider potential uptake of an intervention given the model of service delivery. This, however, assumes that patients are in the position to make a choice about whether to have a pharmacogenetic test, which is in effect, a diagnostic aid.

Establishing attributes and levels

The attributes and levels (see Table 1) were developed using three synergistic approaches. A review of the literature was conducted to understand the key outcomes important for a pharmacogenetic test. A qualitative study was then specifically designed to inform the selection and wording of attributes and levels in this DCE (see Fargher et al. [26] for the design and analysis of this study). In brief, the study used a combination of focus groups with health-care professionals (n=17) and semistructured interviews with patients (n=25) to identify the key aspects to consider when designing a pharmacogenetic service. This exercise generated 17 themes, which were independently reviewed by two members of the research team (E.F. and K.P.). Themes relevant to the framing of the choice question were considered to fall into five independent categories, which were converted into plausible attributes and levels. Finally, an expert panel comprising 10 members of the TARGET study team (three clinicians, three health economists, two health service researchers, one statistician, one pharmacist) were asked: 1) Do you agree with the selection of attributes? 2) Are there any attributes missing? 3) Do you agree with the levels? and 4) How should we phrase the attributes and levels?

The DCE included two "value" attributes, predictive accuracy and turnaround time, to allow comparison across respondent samples by calculating marginal rates of substitution. Cost had to be excluded as an attribute because of recommendations by the ethics committee. The level range for each attribute was set to represent clinically meaningful options and be sufficiently wide to encourage respondents to take account of each attribute and limit the possibility of dominant preferences. This consideration was particularly important for the two value attributes. There is little empirical evidence to support the ideal number of levels for an attribute in a choice experiment. Ratcliffe and Longworth [29] investigated the structural reliability of a DCE within health technology assessment and concluded that there was evidence to support a psychological effect of the number of attributes affecting the

relative importance that respondents place on a particular attribute. For this reason, this DCE was designed such that each attribute had the same number of levels (four), which also results in level balance.

Experimental design

Four levels for each of the five attributes result in 1024 ($=4^5$) possible scenarios, which were reduced to a manageable number of scenarios for each respondent using a fractional factorial design. The design was identified using catalogues of orthogonal arrays with 16 scenarios, five attributes, with four levels, including main effects only (see design oa.16.5.4.2) [30]. The binary choice sets were then created using Street and Burgess (2007) methods [31]. Online software was used to check that the design could estimate main-effects and compare the design efficiency with the optimal design for a choice set with two alternatives. The design was 94.5% efficient [32]. One version of the survey was created that contained 16 choice binary sets (Fig. 1).

Constructing the survey

The questionnaire was piloted on a convenience sample of 20 patients attending the clinic, while they were being recruited to the TARGET RCT, and 30 staff at the University of Manchester: to assess whether respondents could understand the task, the length and time to complete the survey, and the face validity of the attributes and level phrasing. The final design of the survey comprised five sections. To increase the chance of respondents understanding the purpose of the DCE, and decrease the chance of irrational responses, the first section of the survey provided respondents with a "training module" that contained information about the role of TPMT testing in azathioprine prescription and a description of the attributes and levels at the start of the questionnaire. In addition, a separate information sheet, which repeated the page in the survey describing attributes and levels but with a larger font size, was also inserted into the survey to allow respondents to continually refer to full definitions of each attribute and level while they completed each question in the survey [33]. The five attributes were presented in the order they would be experienced when accessing the service. This same order was used for every exercise. Section two involved a ranking exercise where respondents were asked to rank the attributes in order of preference from one to five. Section three included a question on each attribute that asked respondents to indicate their preferred level, out of the four levels defined, for each attribute. Section four contained the DCE task and section five included questions about the respondents and some background questions on whether they had been given (or used) a pharmacogenetic test, experienced a side effect from a medicine themselves, or if a family member had experienced a side effect.

Sample frame and administering the survey

The sampling frame included patients prescribed azathioprine and health-care professionals with experience of prescribing and advising on azathioprine. The DCE was conducted alongside a prospective randomized controlled trial (the TARGET study). Patients were recruited to the TARGET study (October 2005 to December 2007) from gastroenterology or rheumatology clinics at 19 participating study centers, predominantly based in the Northwest of England. Following ethical approval, the DCE was posted in January/February 2008 (with two reminders) to a sample (n=309) of patients with gastroenterology- or rheumatology-related conditions. This sample had been recruited to the TARGET study which was designed to identify the clinical utility and cost-effectiveness of the TPMT test to inform azathioprine prescribing. A DCE with the same design was posted to a sample (n=410) of

Question: Consider the following characteristics describing two tests, (Test A or Test B).

Please indicate which test you would choose.

	Test A	Test B
The level of information given to the patient about the test	low	moderate
The ability of the test to predict the risk of the side effect (neutropaenia)	85% accurate	90% accurate
How the sample is collected	mouth swab	blood test
How long it takes before the patient receives the result	2 days	7 days
Who explains the result to the patient	pharmacist	hospital doctor
Tick (✓) one box only	☐	☐

Fig. 1 – Example of a binary choice question.

health-care professionals, comprising hospital consultants, nurses, general practitioners (GP), and pharmacists, who had a role in the management of patients in the TARGET study. All questionnaires were posted after the last patient was recruited to the trial.

Data analysis

The aim of the data analysis was to identify the main effects for each attribute. The base-case analysis ran two separate models for each sample: patients and professionals. Data were analyzed using the random effects probit model to account for repeated observations from the same respondent:

$$V_{it} = \beta_0 + \beta_1 \text{info} + \beta_2 \text{pred} + \beta_3 \text{sam} + \beta_4 \text{time} + \beta_5 \text{expl} + \alpha_i + \varepsilon_{i,t}$$

V_{it} is a binary variable (choose a or b) that assumes individuals i choose the alternative for choice t that leads to higher levels of utility

β_0 is the constant term

B_x are the estimated parameters for the attributes

α_i is the error term representing between individuals, i

ε_{it} is the traditional error term unique to each observation, t within individuals, i

The qualitative data were effects coded for the analysis (see Table 1). Using effects coding means that the estimate of the omitted variable of an effects-coded attribute is equal to minus one multiplied by the sum of the estimated levels. The value attributes were included in the base-case analysis as a linear, continuous variable. A secondary analysis explored the assumption of linearity in both value attributes by 1) effects coding the value attributes and plotting the resulting size of the attributes against the level for each attribute, and 2) re-running the model including an additional quadratic term for each value attribute.

Dominant preferences

Respondents have been shown to sometimes exhibit lexicographic preferences when competing DCEs. This means the respondents make their choices by considering the attributes in a (predefined) order of priority rather than trading between the attributes. This implies non-compensatory decision making and means that the axioms of random utility theory and Lancaster's consumer theory do not hold [34]. This would mean that marginal rates of substitution between attributes have no meaning in this context [35]. Dominant preferences are one type of lexicographic preferences. The presence of dominant preferences in this study was explored using the approach taken by Scott [35]. Scott uses Lancaster's [36] definition of dominance, "A characteristic is dominant within some group of characteristics, in some set of situations, if the consumer always prefers a collection with more of the dominant characteristic, whatever the amounts of the other characteristics." This study explored dominant preferences for the quantitative attributes (predictive ability and turnaround time) and one qualitative attribute (information) where a clear direction of preferred preference could reasonably be assumed. Two approaches were used. Firstly, each of these three attributes was examined in turn, and a dominant preference was defined if the respondent always chose the scenario with the best level for that attribute, then this is a dominant preference for that attribute. Secondly, ranking data obtained from section two of the survey, which asked respondents to rank the attributes in order of preference (from 1 being most preferred to 5 being least preferred), were combined with the information on the direction of preference. The random effects probit model was then estimated using data from all respondents, including those with dominant preferences, and then re-run excluding patients who showed dominant preferences. Coefficients and 95% confidence intervals were computed for the model with and without dominant preferences and the results were compared.

Validity

The validity of the model was assessed in two ways. Face validity was identified by checking the sign of the estimated parameters accorded with a priori expectations. A positive sign would be anticipated for predictive ability, which means that respondents prefer greater predictive ability. Turnaround time for a result may be expected to have a negative sign, with respondents preferring to receive the results of the test more quickly. An explicit test for internal validity was also included in the design of the DCE, with an additional question added that held the levels of the qualitative attributes (information, sample collection, explanation) constant but showed a clear preferred direction for the two quantitative attributes with a higher level of predictive ability and shorter turnaround time. The impact of including responses from the respondents who "failed" this test for internal validity was assessed by estimating the random effects probit model including and excluding these respondents and comparing the estimated effect sizes (direction and size of the parameters).

Exploring the impact of patient and professional characteristics on preferences

The background questions, collected in section five of the survey, were used to conduct a preliminary analysis to explore whether the characteristics of the patients or health-care professionals had an impact on preferences. In the patient sample, the impact of the following characteristics on preferences was explored: presenting condition (gastroenterology or rheumatology); level of education (degree level and equivalent or above; or no degree); had a pharmacogenetic test (self-reported); reacted badly to a medicine; member of the family has reacted badly to a medicine; taken azathioprine; reacted badly to azathioprine. In the health-care professional sample, the impact of the following characteristics on preferences was explored: discipline (hospital doctor, GP, pharmacist, nurse); clinical specialty of respondent (gastroenterology, rheumatology, renal medicine, dermatology); used a pharmacogenetic test; reacted badly to a medicine; member of the family has reacted badly to a medicine. These analyses were run separately for the patient and health-care professional sample data and included covariates in the model as interaction terms of the attribute and characteristics. The goodness of fit for each model with and without these interaction terms was tested

using the likelihood ratio test with a P value threshold of statistical significance set at $P < 0.01$ to allow for multiple testing.

Comparing patients' and professionals' preferences

The preferences of patients and professionals were compared using two approaches: 1) identifying the impact of the scale parameter, and 2) estimating marginal rates of substitution with time and predictive ability as the value attributes.

Comparisons between DCEs that have been generated from two data sources, for example, a sample of patients and health-care professionals, need to take account of differences in unobserved variability between the data sources and take account of the possible effect of this scale parameter [37]. To identify the impact of the scale parameter, step one was to plot the estimated coefficients from each sample against each other on a scatter plot, to visualize whether the differences are purely due to a scaling effect. A strong linear relationship will indicate that any difference in the magnitude of the coefficients is explained by the scale parameter and differences in scale between the data from patients and health-care professionals. The Swait and Louviere [38] test was then used to formally test whether the true parameter coefficients are significantly different.

Calculating the marginal rate of substitution (MRS), using a value attribute, was used as an alternative means of overcoming the issue of the scale parameter that does not allow direct com-

Table 2 – Patient characteristics.

Characteristic		Number (%) (n=159)
Condition	Rheumatology	18 (11)
	Gastroenterology	141 (89)
Occupational status	Employed full-time	57 (36)
	Employed part-time	23 (14)
	Self-employed	11 (7)
	Unemployed	12 (8)
	Retired	39 (24)
	Homemaker	7 (4)
	Student full-time	8 (5)
	Missing data	2 (2)
Highest level of education obtained	Postgraduate	5 (3)
	Degree	34 (21)
	Diploma/NVQs, etc.	21 (13)
	A-level	13 (8)
	GCSE/O-level	49 (31)
	No formal qualifications	14 (9)
	Missing data	23 (15)
Ever had a pharmacogenetic test (self-reported)	Yes	33 (21)
	No	40 (25)
	Do not know	74 (46)
	Missing data	12 (8)
Ever reacted badly to a medicine (self-reported)	Yes	75 (47)
	No	78 (49)
	Do not know	6 (4)
	Missing data	0
Friends or family ever reacted badly to a medicine (self-reported)	Yes	27 (17)
	No	126 (79)
	Do not know	0
	Missing data	6 (4)
Ever taken azathioprine (self-reported)	Yes	148 (93)
	No	6 (4)
	Do not know	5 (3)
	Missing data	1 (1)
Side effects from azathioprine (self-reported)	Yes	81 (51)
	No	65 (41)
	Not applicable	11 (7)
	Missing data	2 (1)
Treated in hospital for side effects from azathioprine (self-reported)	Yes	9 (6)
	No	72 (46)
	Not applicable	75 (47)
	Missing data	3 (2)
Always take the dose as prescribed by your doctor (self-reported)	Yes	136 (86)
	No	6 (4)
	Not applicable	10 (7)
	Missing data	7 (4)

GCSE/O, general certificate of secondary education/ordinary level; NVQ, national vocational qualification.

parison of estimated parameters from two data sources. The scale parameter does not affect the ratio of any two coefficients. The MRS was calculated by dividing the estimated parameter coefficient for the attribute by the estimated parameter coefficient for the selected value attribute. Two value attributes were used for this analysis: 1) predictive ability, which is measuring a change of 1%, and 2) turnaround time, which is measuring a change in terms of the number of days. The MRS results were compared from the patient and professional sample. In addition, bootstrapping was used to estimate 95% confidence intervals for the MRS. This allows a direct comparison of the relative size of the MRS, but note that the absolute size of the MRS will depend on whether dummy or effects coding is used [39].

Results

The analysis included all completed questionnaires. A completed questionnaire was defined as at least 50% of the choice questions (eight questions) being completed (10 patients and 11 health-care professionals returned uncompleted questionnaires). One further questionnaire was excluded because the health-care professional answered only one choice question. The final analysis comprised 159 (18 rheumatology and 141 gastroenterology) patients and 138 health-care professionals (84 consultants, 31 GPs, 13 nurses, 10 pharmacists, and 2 clinicians with joint hospital-general practice posts who were merged with the consultant sample for the analysis). This accorded with response rates of 50% and 34%, respectively, for patients and health-care professionals. Nine (6%) of the patients and 24 (17%) of the health-care professionals did not complete all of the binary choice questions. Eight of the health-care professionals did not answer all the binary choice questions because four questions were on one page of the survey, which appeared to have been turned over in error.

Characteristics of respondents

Tables 2 and 3 summarize the characteristics of the patient and the health-care professional samples, respectively. The

Table 3 – Health care professionals characteristics.

	Hospital doctors (n=84)	GPs (n=31)	Nurse (n=13)	Pharmacist (n=10)	Total (n=138)
Years qualified*	Mean 23.1 (8 to 34)	Mean 25.6 (10 to 38)	Mean 21.3 (6 to 30)	Mean 22.7 (9 to 39)	Mean 23.2 (6 to 39)
Specialty					
Gastroenterology	41 (50%)	NA	9 (69%)	0	50 (36%)
Rheumatology	22 (27%)		2 (15%)	1 (10%)	25 (18%)
Renal medicine	1 (1%)		0	3 (30%)	4 (3%)
Dermatology	18 (22%)		0	1 (10%)	20 (14%)
Other (not named)	1 (1%)		2 (15%)	5 (50%)	8 (6%)
Ever used a pharmacogenetic test					
Yes	67 (80%)	1 (3%)	10 (77%)	0	79 (57%)
Missing data	1 (1%)	0	0	0	1 (1%)
Ever prescribed, dispensed, or educated a patient about azathioprine?					
Yes	80 (94%)	28 (90%)	10 (77%)	9 (90%)	127 (91%)
Missing data	0	1 (3%)	1 (8%)	1 (10%)	3 (2%)
Do not want to answer personal questions	13 (15%)	2 (7%)	1 (8%)	1 (10%)	17 (12%)
Have had a pharmacogenetic test (self-reported)					
Yes	0	0	0	1 (10%)	1 (1%)
No	69 (81%)	29 (94%)	12 (92%)	8 (80%)	118 (96%)
Don't know	2 (2%)	0	0	0	2 (1%)
Missing data	1 (1%)	0	0	0	1 (1%)
Ever reacted badly to a medicine (self-reported)					
Yes	18 (21%)	5 (16%)	2 (15%)	1 (10%)	26 (21%)
No	51 (60%)	24 (77%)	9 (69%)	8 (80%)	92 (75%)
Missing data	3 (4%)	2 (2%)	1 (8%)	0	6 (5%)
Friends or family ever reacted badly to a medicine (self-reported)					
Yes	12 (14%)	5 (16%)	2 (15%)	0	19 (16%)
No	58 (68%)	23 (74%)	10 (77%)	9 (90%)	100 (82%)
Missing data	1 (1%)	0	0	0	1 (1%)
Ever taken azathioprine (self-reported)					
Yes	0	0	0	0	0
No	70 (82%)	28 (90%)	12 (92%)	9 (90%)	119 (98%)
Missing data	2 (2%)	0	0	0	2 (1%)

* Missing data: n = 2 hospital doctors; n = 3 GPs; n = 1 pharmacist; n = 6 total.

Table 4 – Random effects probit regression model (time and predictive accuracy linear).

Attribute	Patient			Health care professional		
	Coefficient	Standard error	*P* value	Coefficient	Standard error	*P* value
Information-low	−0.115	0.037	0.002	0.020	0.048	0.673
Information-mod	0.183	0.037	0.000	0.044	0.046	0.342
Information-high	0.347	0.035	0.000	0.202	0.045	0.000
Predictive accuracy	0.033	0.001	0.000	0.049	0.002	0.000
Sample-wash	0.067	0.036	0.062	0.062	0.045	0.171
Sample-finger	0.019	0.036	0.607	−0.013	0.046	0.785
Sample-swab	−0.039	0.034	0.254	0.011	0.041	0.781
Turnaround time	−0.018	0.002	0.000	−0.023	0.003	0.000
Explanation-pharmacist	−0.385	0.039	0.000	−0.215	0.050	0.000
Explanation-hospital Dr.	0.264	0.040	0.000	0.299	0.048	0.000
Explanation-nurse	0.060	0.033	0.070	0.004	0.041	0.919
Constant	0.214	0.038	0.000	0.288	0.041	0.000
	Number of obs = 2521			Number of obs = 2153		
	Number of groups = 159			Number of groups = 138		
	Wald chi2(11) = 741.78			Wald chi2(11) = 649.41		
	Log likelihood = −1188.8			Log likelihood = −844.9		

mean age of the patients was 45.8 years old (range, 17–82 years old) with 90 women (56%).

The patients in the sample had a range of levels of education and employment status. The majority of the patients had gastroenterological conditions and had taken azathioprine. Some of the patients (4%) reported never taking azathioprine. Interestingly, one-fifth of the patient (21%) sample said they did know they had been given a pharmacogenetic test, even though the trial design expected patients to be "blinded" to the use of the test, but almost half of the sample were not sure. Nearly half of the patients reported having experienced a side effect to a medicine (47%) and around one-half (51%) of the patients said they had a side effect from azathioprine with 6% of patients having a serious side effect requiring hospitalization. Some patients (17%) reported that their friends or family had experienced side effects from medicines. The majority of patients (86%) still reported taking the azathioprine at the time of completing the questionnaire, in accordance with the instructions prescribed by their doctor.

The health-care professional sample was a mix of disciplines but the largest proportion were hospital-based clinicians working in gastroenterology, who had experience with pharmacogenetic testing and prescribing azathioprine (29%). This reflected the sampling frame for the study. The majority of the sample comprised health-care professionals with over 20 years of experience in practice. The health-care professionals were also asked whether they would be willing to answer questions about their personal experience of taking medicines and most (88%) agreed to answer this question. Some health-care professionals reported experience of a side effect either themselves (19%) or in their friends and family (14%). None of the health-care professionals had taken azathioprine. One pharmacist reported having had a pharmacogenetic test, but did not name which one.

Magnitude and statistical significance of attributes

Table 4 shows the estimated coefficients for the base-case analysis of the patient and health-care professional data. The estimated coefficients for the two value attributes, predictive accuracy and turnaround time, both had the expected sign and were statistically significant with patients and health-care professionals preferring a higher predictive accuracy and shorter turnaround times for the test result. Patients had strong preferences for the amount of information being given before taking the test and for who explained the test result, with statistically significant coefficients for each level of the attribute. The negative sign on the coefficient for the first information effects code suggests patients would prefer to have no information rather than low levels of information. The positive signs on the other coefficients for information provision then indicate that patients go on to prefer high compared to moderate levels of information. Two of the three estimated coefficients for information were small and failed to reach statistical significance for the health-care professional sample, which indicates this attribute was not a strong driver for their preferences, but they did prefer to give high rather than moderate levels of information. Both patients and health-care professionals indicated that they did not want a pharmacist to explain the test result but would prefer a hospital doctor. Neither patients nor health-care professionals had significant preferences for the method of how the DNA sample was collected. The constant term specified in the model was statistically significant, which indicates there was some left- or right-hand side bias in the responses, with more respondents indicating a preference for option B rather than A.

Testing for non-linear effects of the value attributes

The model estimated for the base-case analysis assumed that the two quantitative attributes were linear and continuous. This assumption was tested by specifying a random effects probit model with the two value attributes included using effects coding. Table 5 shows the results from this analysis. It can be seen that the linear assumption is reasonable for both attributes. However, the sign of moving between the lower levels of the attributes is not consistent with a priori expectations. Figures 2 and 3> show plots of the estimated coeffi-

Table 5 – Random effects probit regression model (all attributes effects coded).

Attribute	Patient			Health care professional		
	Coefficient	Standard error	*P* value	Coefficient	Standard error	*P* value
Information-low	−0.119	0.037	0.001	0.013	0.049	0.799
Information-mod	0.151	0.040	0.000	0.010	0.060	0.863
Information-high	0.353	0.037	0.000	0.213	0.055	0.000
Predictive accuracy-60	−0.293	0.038	0.000	−0.494	0.055	0.000
Predictive accuracy-85	0.373	0.035	0.000	0.705	0.046	0.000
Predictive accuracy-90	0.656	0.036	0.000	0.888	0.049	0.000
Sample-wash	0.082	0.036	0.023	0.098	0.052	0.057
Sample-finger	−0.019	0.039	0.626	−0.057	0.058	0.332
Sample-swab	−0.040	0.038	0.293	0.018	0.052	0.736
Turnaround time-7	0.114	0.037	0.002	0.129	0.050	0.010
Turnaround time-14	−0.103	0.036	0.004	−0.127	0.047	0.006
Turnaround time-28	−0.262	0.038	0.000	−0.349	0.054	0.000
Explanation-pharmacist	−0.391	0.040	0.000	−0.250	0.056	0.000
Explanation-hospital Dr.	0.282	0.041	0.000	0.340	0.060	0.000
Explanation-nurse	0.042	0.034	0.208	0.006	0.047	0.898
Constant	0.199	0.039	0.000	0.299	0.049	0.000
	Number of obs = 2521			Number of obs = 2153		
	Number of groups = 159			Number of groups = 138		
	Wald chi2(15) = 745.67			Wald chi2(15) = 614.33		
	Log likelihood = −1179.8			Log likelihood = −841.3		

cients for each attribute level for both samples. These figures also indicate that a linear assumption seems reasonable. In addition, a more formal test of linearity was conducted by adding a quadratic term into the model for predictive accuracy and turnaround time, separately in both patient and professional data sets. The quadratic term for predictive accuracy was not statistically significant ($P = 0.507$). The quadratic term for turnaround time was statistically significant for

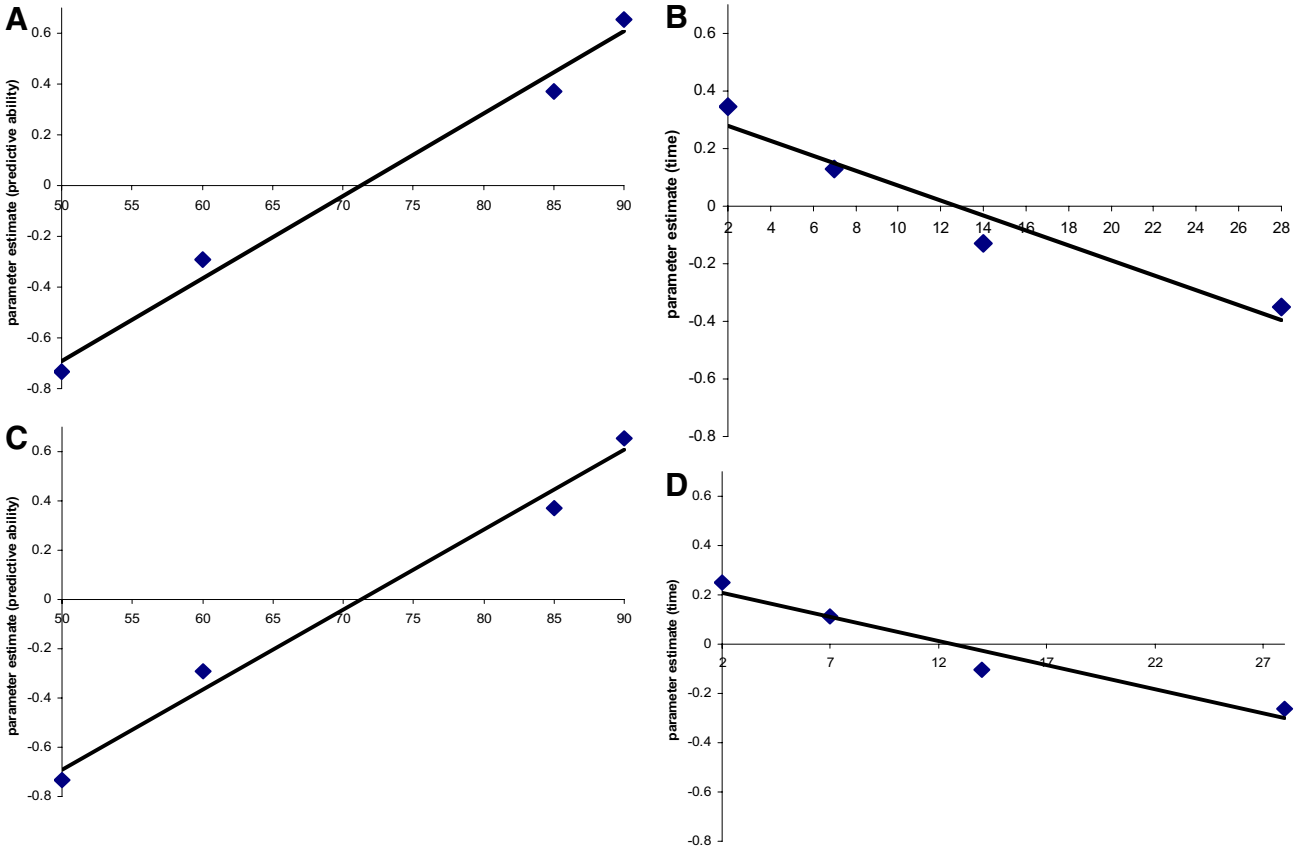

Fig. 2 – (A) Predictive ability (health-care professionals). (B) Turnaround time (health-care professionals). (C) Predictive ability (patients). (D) Turnaround time (patients).

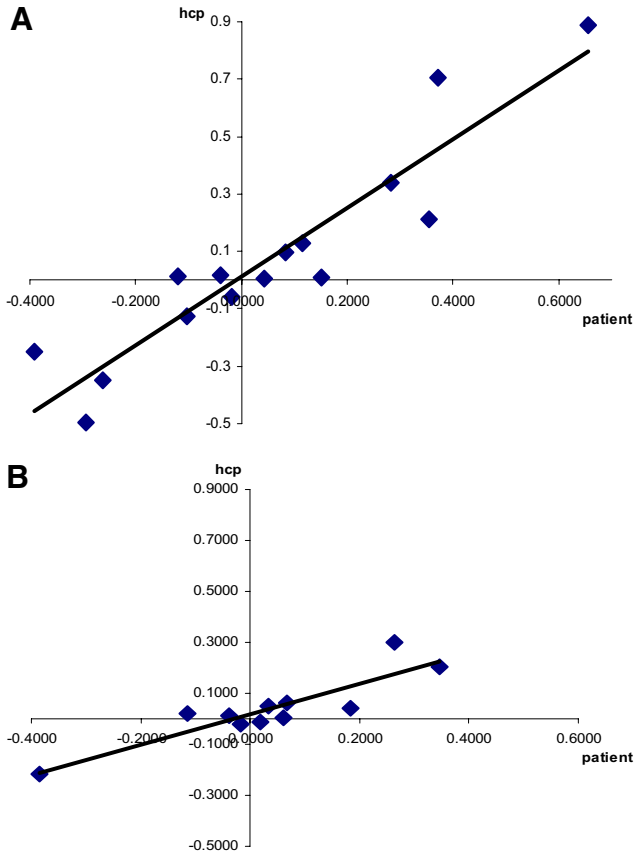

Fig. 3 – (A) Plot of patient versus health-care professionals' estimated coefficients (all effects coding). (B) Plot of patient versus health-care professionals' estimated coefficients (time and predictive accuracy linear).

both the patient ($P = 0.035$) and professional ($P = 0.033$) data, suggesting turnaround time is non-linear. However visual inspection of the data indicated that there was not a strong deviation from the linear assumption, and an average MRS computed using the linear assumption is a reasonable summary of the behavior.

Test for internal validity

Seven (4%) patients, all with gastroenterological conditions, failed the dominance check question included as a test for internal validity. One health-care professional failed the dominance check question. In addition, eight health-care professionals did not answer the dominance question because the page of the survey appeared to have been turned over in error. The impact of including the respondents who "failed" the internal validity test in the final analysis was explored by running two models with the responses included and then removed from the analysis. This analysis indicated that removing the respondents who "failed this test" did not have any impact on the analysis and so their responses were included in the final sample.

Test for dominant preferences

Three attributes were examined individually for evidence of dominant preferences in the responses. The predictive accuracy attribute showed the strongest evidence for the presence of dominant preferences in the sample, and 15 patients (9%) and 14 health-care professionals (10%) appeared to exhibit a dominant preference for "predictive accuracy". If the ranking data (from section 2 of the survey) were also used, then these figures were reduced to 13 patients and 13 health-care professionals showing dominant preferences. Three patients (2%) had a dominant preference for "information provided," which reduced to two patients if the ranking data were also considered. No patients or health-care professionals had a dominant preference for "turnaround time," The model was re-run excluding the data for dominant preferences on "predictive accuracy," but this did not appreciably affect the estimated coefficients and all data were used in the final analysis.

Comparing preferences

The Swait and Louviere [38] test confirmed that the estimated coefficients were different for patients and health-care professionals. Table 6 summarizes the estimated MRS for both samples. The marginal rates of substitution were only calculated using the results estimated for the unadjusted model, which did not include covariates representing the characteristics of the respondents and their prior experience of pharmacogenetic testing. Patients and health-care professionals had similar preferences for predictive accuracy of the test and were willing to wait 1.8 and 2.2 days, respectively, for a 1% improvement. Patients preferred to obtain more information when being told about the purpose of the pharmacogenetic test and were willing to wait 19.3 days compared to 8.9 days for health-care professionals for high levels of information provision. In general, patients had stronger preferences for whom would provide the explanation about the test results. Neither patients nor health-care professionals would want a pharmacist to explain the test result but patients showed stronger preferences by not wanting to give up 11.6% in predictive ability, or wait an extra 21.4 days for a result, compared to 4.4% and 9.5 days for the health-care professionals. Both patients and health-care professionals indicated they wanted the hospital doctor to provide the result with similar strengths (willing to give up 7.9% and 6.1% in predictive ability and wait extra 14.7 days and 13.2 days, respectively). Interestingly, patients indicated they would want the GP to provide the test result but the size of the estimated model parameter suggests, health-care professionals indicated that they would prefer them not to, but this finding was not a significant preference. Neither patients nor health-care professionals indicated strong preferences for a nurse to provide the explanation about the test results.

Influence of respondent characteristics

The potential impact of respondent characteristics on patients' and health-care professionals' preferences was explored by including interaction terms of the attribute and characteristic in the model. In the patient sample, the presenting condition of the patient had an impact on preferences for the level of information they preferred before the test ($P = 0.001$. Preferences for the predictive ability were affected by

Table 6 – Marginal rates of substitution using predictive ability and turnaround time as value attributes.

Attribute	Patients			Health care professionals		
	Coef	MRS predictive (%) [95% CI]†	MRS turnaround (days) [95% CI]†	Coef	MRS predictive (%) [95% CI]†	MRS turnaround (days) [95% CI]†
Predictive accuracy	0.033‡	—	−1.8 [−2.3 to −1.4]	0.049‡	—	−2.2 [−2.6 to −1.7]†
Turnaround time	−0.018‡	−0.5 [−0.7 to −0.4]	—	−0.023‡	−0.5 [−0.6 to −0.4]	—
Information-none*	−0.415	−12.5 [−14.6 to −10.4]	23.0 [16.0 to 30.2]	−0.266	−5.5 [−7.0 to −3.9]	11.8 [7.5 to 16.0]
Information-low	−0.115‡	−3.5 [−5.8 to −1.2]	6.4 [2.1 to 10.8]	0.020	0.4 [−1.6 to 2.4]	−0.9 [−5.2 to 3.4]
Information-mod	0.183‡	5.5 [3.4 to 7.7]	−10.2 [−14.9 to −5.5]	0.044	0.9 [−0.8 to 2.6]	−1.9 [−5.5 to 1.6]
Information-high	0.347‡	10.4 [8.3 to 12.6]	−19.3 [−24.7 to −13.9]	0.202‡	4.2 [2.4 to 5.9]	−8.9 [−12.6 to 5.3]
Sample-blood*	−0.047	−1.4 [−3.4 to 0.6]	2.6 [−1.2 to 6.4]	−0.061	−1.2 [−2.9 to 0.4]	2.7 [−1.1 to 6.4]
Sample-wash	0.067	2.0 [−0.2 to 4.2]	−3.7 [−7.8 to 0.30]	0.062	1.3 [−0.5 to 3.0]	−2.7 [−6.5 to 1.0]
Sample-finger	0.019	0.6 [−1.6 to 2.7]	−1.0 [−5.0 to 3.0]	−0.013	−0.3 [−2.1 to 1.5]	0.6 [−3.5 to 4.6]
Sample-swab	−0.039	−1.2 [−3.0 to 0.7]	2.2 [−1.4 to 5.8]	0.011	0.2 [−1.3 to 1.7]	−0.5 [−3.8 to 2.8]
Explanation-GP*	0.061	1.8 [0.0 to 3.7]	−3.4 [−6.9 to 0.0]	−0.088	−1.8 [−3.4 to −0.2]	3.9 [0.4 to 7.4]
Explanation-pharmacist	−0.385‡	−11.6 [−14.1 to −9.2]	21.4 [14.3 to 28.6]	−0.215‡	−4.4 [−6.4 to −2.4]	9.5 [4.5 to 14.5]
Explanation-hospital Dr.	0.264‡	7.9 [5.4 to 10.5]	−14.7 [−21.2 to −8.2]	0.299‡	6.1 [4.1 to 8.1]	−13.2 [−19.1 to −7.4]
Explanation-nurse	0.060	1.8 [−0.1 to 3.8]	−3.4 [−7.0 to 0.2]	0.004	0.1 [−1.5 to 1.7]	−0.2 [−3.7 to 3.3]

* Calculated by assuming estimate for effects coded omitted variable calculated by assuming = −1 ∗(sum of estimated levels).
† Confidence intervals estimated using the bootstrap method.
‡ Statistically significant at $P < 0.05$.

whether or not patients reported that they had been given a pharmacogenetic test before ($P = 0.008$) and whether they had experienced a side effect from a medicine ($P = 0.007$). Preferences for the level of information ($P = 0.001$) and predictive accuracy ($P = 0.000$) were influenced by the discipline of the health-care professional.

Discussion

This article presents the results from the first stated preference study to identify and explore the attributes of a pharmacogenetic testing service and makes a direct comparison of the preferences of a patient and health-care professional sample. The study focused on five attributes of a pharmacogenetic service: how much information should be given prior to the test; method for collecting the DNA-sample; predictive accuracy (effectiveness) of the test; waiting time for the test result; and who should explain the test result. The patients surveyed in this study had different preferences compared with the health-care professional sample, especially in terms of information provision. In particular, they placed more importance on having more information before the test and had stronger preferences for whom should provide the test result, compared with health-care professionals. In practice, specialist nurses often provide test results to patients, especially those with chronic conditions, such as rheumatoid arthritis or Crohn's disease, but this patient sample indicated that they would prefer a clinician to explain a pharmacogenetic test, ceteris paribus. Patients would be happy with a GP explaining the test result, but there was weak evidence, from the estimated model, that other health-care professionals did not agree that this was appropriate. It may seem counter intuitive for health-care professionals to not want a GP to provide test results. This may be so, but this view could also be explained that health-care professionals may be indicating concerns that GPs do not currently have sufficient knowledge and confidence to report test results back to patients and advise on how to modify their azathioprine prescription. Further research, possibly using qualitative methods to understand the reasoning behind such preferences, is required to explore this finding in more depth. Neither group would want a pharmacist to explain the test result. Patients and health-care professionals had similar preferences for predictive accuracy of the test and turnaround time.

Time and predictive accuracy proved to be key attributes in a model of a pharmacogenetic testing service and were also included as value attributes in the design of the DCE to allow for estimation of MRS and comparison between the preferences of patients and health-care professionals. The estimated MRS is the mean preferences for the study sample, and we did not account for heterogeneity in preferences in the analysis. Further work is necessary to understand if there are significantly different preferences between sub-groups of the sample — for example, between the different disciplines of health-care professionals. Using time and predictive accuracy to estimate a single MRS requires the assumption that the attribute is linear and continuous. This assumption was found to be valid for predictive accuracy, within the constraints of using a percentage as a metric. Although the analysis indicated that turnaround time was not truly linear, the amount of non-linearity was small and a single MRS is a reasonable representation over the range of values investigated.

A similar pattern in turnaround time was observed in both patient and health-care professional samples. Neither group wanted a turnaround time of 2 days, but equally would not want to wait for long turnaround times of more than 7 days. This has some practical relevance because it potentially alters the service delivery model. Both patients, with the experience of living with a chronic condition, and health-care professionals managing patients with a chronic disease, would realize that this appointment system would not work in practice.

Therefore, 1 week is a more practical and feasible turnaround time for this pharmacogenetic test for a chronic disease. However, it is likely, that a shorter turnaround time may be preferred for a pharmacogenetic test that is used to inform prescribing in acute conditions, such as testing to inform warfarin prescribing to prevent thromboembolic disease [40].

Herbild et al. [41] explored "willingness to pay" for a pharmacogenetic test using a four attribute web-based DCE to elicit preferences for the treatment of depression in terms of: changes in drug treatment, time with dosage adjustments due to adverse side effects and/or lack of effects, cost of pharmacogenetic testing, and the probability of benefits from pharmacogenetic testing. Findings suggest that if diagnosed with depression, peoples' willingness to pay for pharmacogenetic testing exceed price, as long as there is a 10% probability for improvements in treatment. This study provided useful information on the uptake of pharmacogenetic tests, but it did not indicate "how" the pharmacogenetic testing service is best provided.

This current study has provided information that is particularly pertinent in this era of demand for patient-led services and patient choice [42,43]. Patients in this study indicated that information provision is a key component of a pharmacogenetic testing service, but health-care professionals were less concerned about information provision compared to predictive test accuracy and turnaround time. Importantly, patients were clear that they would prefer to receive no information at all compared with low levels of information. Health-care professionals agreed with this which has implications for service delivery in that providing low, and potentially, insufficient levels of information is perceived to be much less useful than more detailed information. Other DCE studies in health care have highlighted the importance to patients of the provision of information in the delivery of health-care services [44,45]. A recent qualitative study also supported that patients demand educated and knowledgeable health-care professionals to explain why they should have a pharmacogenetic test and how the test results would be used; trust and familiarity were important to patients, and health-care professionals emphasized a need for an integrated service [26]. A number of commentators have questioned whether health-care professionals are ready to deliver pharmacogenetic testing services in terms of their education and current knowledge base [46,47]. Pharmacogenetic testing services are not currently established as part of mainstream health-care services, and some professional bodies [25] have started to address the core skills that would be required to safely and effectively deliver such services. This study provides further support that schools of medicine, nursing, and pharmacy need to include teaching that covers the scientific basis of using basic genetic data to inform prescribing together with the practical implications of delivering a pharmacogenetic service as a part of the core curricula for undergraduate students.

Marginal rates of substitution were calculated using predictive ability and turnaround time as the value attributes to allow direct comparison between the patient and health-care professional preferences. A cost attribute was considered, but excluded due to the objections of the ethics committee. Including a cost attribute would have allowed an estimation of marginal willingness to pay for each service attribute. It is also acknowledged that the study sample comprised NHS patients and staff who are familiar with health care that is free at the point of access. The study sample comprised patients who had been recruited to an RCT of the TPMT test and clinicians who had some role in providing the test as part of the RCT. It could be assumed that these were individuals who were familiar with the test and may have brought extra information, not included in the design in terms of attributes and levels presented, to the stated preference exercise. However, the patients were blinded to the randomization process and did not know whether they were given the TPMT test during the trial; although when questioned, one-fifth of the patients reported knowing that they had been given a pharmacogenetic test. Clinicians could be classified as being familiar with the test but the respondents were instructed to only use the attributes described to make their choices. However, there is still a possibility that the health-care professionals, in particular, were using extra information that was not controlled for in the experiment, when making their choices [25].

A higher proportion of patients compared with health-care professionals, and GPs in particular, returned completed questionnaires, which could suggest that patients were more engaged in the study as they were more willing to answer the survey questions. The response rate for the health-care professionals was disappointing and is a limitation of this study. The available sample frame and resulting sample size for this DCE meant that the design could only include main effects and did not allow estimation of two-factor interactions. The primary purpose of this DCE was to compare the preferences of patients and health-care professionals, and including main effects in the design was sufficient for this purpose. Extending the survey to a larger sample frame and size would allow the DCE design to be modified and include two-factor interactions, but this design would require more scenarios. Furthermore, Lanscar and Louviere [37] acknowledge that the true nature of the bias from using designs that do not use interactions is unknown and is a potential topic for future research.

This study included responses from the respondents who "failed" the dominance test. There were relatively few such cases and the parameter estimates were not substantially different when these respondents were excluded from the analysis. Including respondents who behave in a dominant manner can potentially lead to bias in the parameter estimates, but the dominance tests may not reliably identify these individuals. San Miguel et al. [33] suggested that failing such a test was directly related to the characteristics of the respondent and, therefore, removing them from the analysis can introduce systematic bias due to only selecting respondents who pass the dominance test [25]. Further research is necessary to understand whether it is better to accept the bias of a sample containing "irrational" respondents compared with a sample that may be prone to selection bias because of removing specific individuals.

This study focused on understanding the nature of preferences for how a pharmacogenetic testing service should be delivered rather than identifying attributes that would affect the uptake of a pharmacogenetic test. A pharmacogenetic test aims to provide quantitative information about the potential

for risk reduction by predicting which patients would experience neutropenia. This is a necessary topic of further research to understand how current and future patients value the potential risk reduction offered by pharmacogenetic testing to detect a specific side effect to a medicine.

The effect of respondent characteristics on their preferences was explored by including interaction terms in a model. This analysis identified potentially important influences of respondent characteristics on preferences such as presenting condition of the patient, whether or not patients reported that they had been given a pharmacogenetic test before, and whether they had experienced a side effect from a medicine. Preferences for the level of information and predictive accuracy were influenced by the discipline of the health-care professional. This analysis was only exploratory and starts to identify heterogeneity in preferences by looking at one potential effect of differences in preferences between individuals. A different experimental design and larger sample size for each of the discipline sub-groups would be required to further explore heterogeneity in preferences. Hole [48] appropriately suggests that individuals are likely to have different preferences (taste heterogeneity) and some of this preference heterogeneity is not related to personal characteristics of the respondents that can be observed. Therefore, alternative model specifications have been suggested as necessary to understand heterogeneity in preferences, such as the mixed logit model, which is a generalization of the multinomial logit model that accounts for two aspects 1) the panel structure of the data, and 2) allows for preference heterogeneity across individuals and allows parameters to vary randomly across individuals [49]. In a binary choice model, which is applicable for this study, random effects can be used to account for the panel structure of the data but using random effects in a probit (or logit) model does not allow you to estimate preference heterogeneity. However, there have been valid criticisms of using mixed logit to account for preference heterogeneity. Fiebig et al. [50] suggest that the generalized-multinomial logit model should be used to account for heterogeneity in preferences because, unlike the mixed logit and latent class models, the generalized-multinomial logit takes scale heterogeneity into account that can then identify "extremes" of consumers, from those who have almost lexicographic preferences to those who show very random behavior in their choices. Other methods, such as estimating individual-level models, have been suggested but these require very large data sets if the data are derived from DCE designs. Alternative experimental designs, such as best-worse scaling, are recommended as viable alternatives to look at the preferences of individual decision-makers [51].

Conclusion

This DCE determined and compared the preferences of patients and health-care professionals of TPMT testing, which is an example of a pharmacogenetic testing service providing information about azathioprine prescribing. Patients and health-care professionals had similar preferences for predictive accuracy of the test and turnaround time for the test results. There were clear differences in the patients' and health-care professionals' preferences for information provision. The findings from this study provide health-care policy makers with clear evidence that patients demand accurate and timely information about the reason to have a pharmacogenetic test, and what the test results mean, from health-care professionals. In contrast, health-care professionals appear to focus more exclusively, or entirely, on the predictive accuracy and waiting time for a test result.

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