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ORIGINAL RESEARCH ARTICLE

Patients' Preferences for Genomic Diagnostic Testing in Chronic Lymphocytic Leukaemia: A Discrete Choice Experiment

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Abstract

Background Genomic information could help to reduce the morbidity effects of inappropriate treatment decisions in many disease areas, in particular cancer. However, evidence of the benefits that patients derive from genomic testing is limited. This study evaluated patient preferences for genomic testing in the context of chronic lymphocytic leukaemia (CLL).

Methods We used a discrete choice experiment (DCE) survey to assess the preferences of CLL patients in the UK for genomic testing. The survey presented patients with 16 questions in which they had to choose between two possible test scenarios. Tests in these scenarios were specified in terms of six attributes, including test effectiveness, test reliability and time to receive results.

Results 219 patients completed the survey (response rate 20 %). Both clinical and process-related attributes were valued by respondents. Patients were willing to pay £24 for a 1 % increase in chemotherapy non-responders identified, and £27 to reduce time to receive test results by 1 day. Patients were also willing to wait an extra 29 days for test results if an additional one-third of chemotherapy non-responders could be identified, and would tolerate a genomic test being wrong 8 % of the time to receive this information.

Conclusion CLL patients value the information that could be provided by genomic tests, and prefer combinations of test characteristics that more closely reflect future genomic testing practice than current genetic testing practice. Commissioners will need to carefully consider how genomic testing is operationalised in this context if the benefits of testing are to be realised.

Key Points for Decision Makers

Both clinical and process-related outcomes are important to cancer patients when genomic tests are used to guide chemotherapy treatment decisions.

Chronic lymphocytic leukaemia patients prefer combinations of test characteristics that more closely reflect future genomic testing practice than current genetic testing practice.

1 Introduction

Genetic tests are diagnostic assays that are targeted to specific genes of interest, or can identify large chromosomal changes. These tests can inform disease diagnosis, provide prognostic information and guide treatment decisions, and are now established as routine practice in several clinical areas, such as BRCA1/2 testing in breast cancer [1]. In many of these clinical contexts attention is now turning towards genomic interventions which could

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improve disease stratification and permit the more widespread use of individually tailored therapies. These next-generation sequencing (NGS) technologies, which include targeted-, whole-exome- and whole-genome sequencing, offer genome-wide testing capability, simultaneously scrutinising multiple genes and their inter-relationships in order to identify their combined influence [2].

Although NGS technologies have shown promise in allowing disease management to be stratified, they have had a limited impact on clinical practice to date [3, 4]. In part, this is because the evidence that usually informs health technology assessment (HTA) processes around the world is lacking in genomics. Evidence of the benefits that patients derive from genomic testing is particularly limited. Measuring these benefits is difficult because genomic tests provide patients with both clinical utility (e.g. genetic information can inform treatment decisions) and personal utility (benefits or harms manifested outside medical contexts, e.g. 'the value of knowing') [5, 6]. Although these informational and process-related benefits can be valued more highly than clinical utility [7, 8], most HTA guidelines stipulate that cost-utility analyses should be conducted using metrics such as the quality-adjusted life-year (QALY). However, the estimation of QALYs is usually informed by preference scores generated by instruments which focus primarily on health outcomes (e.g. the EQ-5D – a standardised measure of health-related quality of life), rather than non-health outcomes. Ignoring these non-health outcomes can in some cases change adoption decisions [9].

An alternative approach to using QALYs is to collect information on patient preferences for genomic testing using a quantitative technique called a discrete choice experiment (DCE). Preferences are elicited in a DCE by presenting respondents with a series of choices in which at least two alternatives are specified in terms of their attributes, which can vary across a finite number of levels. Respondents complete these choice tasks in a survey and econometric techniques are used to analyse their responses and generate a model of choice behaviour. DCEs are now commonly used to quantify patient preferences for combinations of intervention attributes (including both process- and outcome-related characteristics) and provide information on trade-offs between attributes, with recent applications including the assessment of genetic counselling and genetic carrier testing [10]. The DCE approach may therefore be well placed to fill some of the evidentiary gaps in genomic HTAs by providing a more rounded summary of the true benefits of testing for patients. Furthermore, DCEs can also help to inform the design of services to deliver genomic testing and education materials for patients [11, 12].

This paper presents the results of a DCE which investigated the preferences of chronic lymphocytic leukaemia (CLL) patients for genomic testing. CLL is the most common adult leukaemia in the Western world [13], and chemotherapy is usually offered to patients with symptomatic disease. First-line treatment with fludarabine, cyclophosphamide and rituximab (FCR) combination therapy is the standard of care; however, 25 % of patients will either fail to respond to FCR or will relapse within 2 years of achieving remission [14, 15]. Genetic factors acquired during leukaemogenesis are thought to be the main factors underlying treatment resistance, in particular disruption of TP53, mutations in NOTCH1 (predictive of non-response to Rituximab) and SF3B1, and global features such as genomic complexity and clonal evolution [13, 16–22]. There is also increasing evidence that other genetic abnormalities such as sole deletions of 13q are associated with excellent long-term survival, meaning that chemo-immunotherapy may even be curative [23]. Consequently, current UK and international guidelines recommend that patients undergo pre-treatment genetic testing to detect TP53 disruption using fluorescent in situ hybridisation testing and Sanger sequencing [24–26]. This low-resolution approach can identify a third of FCR non-responders, but is unable to identify any of the other genetic abnormalities [27].

New genomic testing approaches such as targeted NGS offer a whole genome view at increased resolution, providing additional information on multiple genetic alterations with clinical utility (including several novel mutations that can only be identified at high resolution), and combinations of these alterations [15, 28, 29]. This information could further reduce unnecessary treatment and associated side effects [27, 30]. Genomic testing approaches may therefore be able to identify the remaining two-thirds of FCR non-responders, and may have additional process-related benefits (e.g. shorter time to receive test result). However, these new testing approaches are yet to be translated into clinical practice. While there is ample evidence from randomised Phase III studies that this extended genetic information is clinically useful [15–22, 28, 29], there is little information available on the costs and benefits of extensive genetic testing in this context. Furthermore, one possible consequence of a 'non-response' test result could be the use of expensive alternative therapies such as ibrutinib. As such, it is important that decision-makers are confident that the information provided by these tests will truly be valued by patients.

The DCE presented in this paper aims to fill this evidentiary gap by evaluating the preferences of CLL patients for pre-treatment genetic and genomic testing. By capturing information on both the clinical and personal utility of testing to patients we provide decision-makers with a more accurate illustration of the benefits of genomic testing in CLL. In addition, we examine whether patient preferences

vary by socio-demographic characteristics, by estimating a basic multinomial logit choice model and then relaxing the restricted assumptions underlying this model to account for preference heterogeneity using more general models [31]. Finally, given that few studies have evaluated patient preferences for genomic interventions in cancer [11], we also provide clinicians and decision-makers with more general information on which process and outcome-related characteristics of genomic testing may be important to other cancer patients.

2 Materials and Methods

This section describes the process of designing, administering and analysing the DCE survey.

2.1 Selecting a Sampling Population

The sampling population selected for this DCE was UK CLL patients as it is recommended that DCEs are undertaken in populations with experience in the area of interest [32]. To ensure that the sampling population reflected CLL patients with a range of characteristics, two populations were targeted. Population One included CLL patients attending outpatient clinics in the Oxford University Hospitals National Health Service Foundation Trust (hereafter OUH) in the UK ($n = 140$), which is one of the largest teaching trusts in the UK, providing acute care to a population of 650,000 people. All CLL patients at OUH requiring treatment can choose to participate in interventional clinical trials of CLL treatments. Population Two included all patient members of the UK CLL Support Association (CLLSA, http://www.cllsupport.org.uk/; $n = 982$), which is one of the largest patient-led charities in the UK.

2.2 Establishing Attributes and Levels

Attributes and levels (the values that an attribute could take) for the survey were developed using several approaches. First, a literature search was conducted to identify attributes used in previously published DCEs in genetics or leukaemia. Three haematologists at OUH reviewed these attributes, identifying nine that were potentially relevant: those listed in Table 1, plus 'Number of blood samples required', 'Accuracy of the diagnosis' and 'Testing location'.

Interviews were then conducted by JB with 15 randomly selected CLL patients at OUH, who were asked to rate how important each attribute would be if they were deciding whether to undergo pre-treatment testing. The six highest ranked attributes were taken forward (Supplementary Materials–Part One: Table S1), based on how many would be manageable by this population, how many would be required to enable informed choices, and which would best capture the characteristics of current and future testing practice. Four clinically-feasible levels were identified for each attribute (informed by the interviews, literature searches and test characteristics). Potential interactions were identified between the ability of the test to predict who will respond to the usual chemotherapy treatment (EFFECT) and COST, and also test reliability (REL) and COST (more expensive tests may be perceived to be better quality). Time to receive the test result (TIME), COST, EFFECT and REL were assumed to be linear and coded as continuous variables to facilitate the use of the DCE results in a future cost-benefit analysis. Length of time clinicians spend describing the test (INFO) and type of clinician who explains the test result (WHO) were effects coded. This decision was taken as the levels for these attributes may be proxies for quantity or quality of information provided, so the effect may not be linear. The use of effects coding allows coefficients to be generated for each of the attribute levels, which can then be analysed graphically to assess whether a non-linear relationship exists. Table 1 also describes the expected impact on patient utility of an increase in the level of each attribute.

2.3 Experimental Design

The chosen attributes and levels were used to design a DCE in which respondents were presented with choice sets containing two alternatives (Test A vs. Test B). An alternative design including an opt-out was considered which would have permitted the evaluation of potential test uptake. To determine whether this would add additional complexity to the experimental design for limited benefit, a pilot DCE was generated with a two-stage design (Test A vs. Test B, then Chosen test vs. No test). This was completed by a convenience sample of 14 members of the University of Oxford, and six members of the general public. 'No test' was selected in only 3.9 % of choices. Given that genetic testing is currently recommended for UK CLL patients [24] (hence their ability to choose 'no test' is limited), and general population respondents may consider an opt-out to be a more viable choice than CLL patients as they are less familiar with the consequences of not testing, this was judged to be sufficiently low that the additional complexity outweighed the information that was likely to be provided on uptake.

Respondents were asked to complete 16 choice sets. This decision was informed by studies which suggest that, below 17 choice sets, the number of choice sets does not impact on response rates [32, 33]. The two alternatives in each set were unlabelled to ensure that respondents based

Table 1 Discrete choice experiment attributes and levels

Attribute	Level 1	Level 2	Level 3	Level 4	Expected impact on utility of an increase in the level of the attribute
Time to receive the test result [TIME]	5 days	8 days	11 days	14 days	Negative
Cost of the test [COST]	£130	£260	£400	£600	Negative
Ability of the test to predict who will not respond to the usual chemotherapy treatment [EFFECT]	Test identifies 30 out of every 100 patients who will not respond to usual treatment	Test identifies 50 out of every 100 patients who will not respond to usual treatment	Test identifies 70 out of every 100 patients who will not respond to usual treatment	Test identifies 90 out of every 100 patients who will not respond to usual treatment	Positive
Test reliability [REL]	2 out of every 100 tests provide an incorrect result	4 out of every 100 tests provide an incorrect result	6 out of every 100 tests provide an incorrect result	8 out of every 100 tests provide an incorrect result	Negative
Length of time clinicians spend describing the test to you[a]	5 min [INFO0]	10 min [INFO1]	15 min [INFO2]	20 min [*base level*]	Positive[b]
Type of clinician who explains the test result to you[a]	General practitioner [WHO0]	Specialist nurse [WHO1]	Junior hospital doctor [WHO2]	Consultant hospital doctor [*base level*]	Positive?[c]

[a] Effects-coded variable

[b] Coded as categorical variable, but as levels were ordered by increasing time, a positive impact was predicted

[c] The levels for this attribute were deliberately ordered so that perceived knowledge about CLL increased from general practitioner to specialist nurse to junior hospital doctor to consultant hospital doctor. This may not necessarily translate into a positive increasing effect on utility, as other factors may also be important to patients

decisions on attribute levels, not test names. At no point were tests called 'genetic' or 'genomic'; they were only defined by attributes and levels.

A second pilot was then undertaken to generate priors to inform the main design. A fractional factorial design was produced using Ngene (ChoiceMetrics (2012) *Ngene 1.1.1 User Manual & Reference Guide*, Australia). Twelve CLL patients at OUH completed the pilot. Multinomial logit (MNL) regression was used to analyse the choice data in Stata (StataCorp. 2011. *Stata Statistical Software: Release 12*. College Station, TX, USA: StataCorp LP). These priors were incorporated into the final experimental design. This design used a model-averaging approach which allowed us to estimate a basic MNL model and then relax the assumptions underlying this model to account for preference heterogeneity using more general models (e.g. mixed logit) [34]. Full details of the experimental design are provided in Supplementary Materials–Part One: Additional Information S2.

2.4 Constructing the Survey

The final survey comprised four sections and is provided in Supplementary Materials–Part Two. Section one provided respondents with background information on genetic and genomic testing and described the attributes and levels. In section two, respondents ranked attributes in order of preference. Section three contained the DCE task, preceded by a 'rationality check' choice in which Test A contained the worst levels for each attribute and Test B contained the best. Section four collected information on respondent characteristics and clinical details. Respondents were also asked for their opinions on genetic testing, to report their current health status using the EuroQOL five dimensions survey instrument, and to rate the difficulty of the survey.

2.5 Administering the Survey

The survey was administered in two forms. Patients at OUH ($n = 140$) were asked to complete a paper survey when they attended an outpatient appointment. CLLSA patient members received either paper ($n = 148$) or electronic ($n = 834$) versions of the survey, depending on their preferred means of contact. All patients wishing to return a paper version of the survey received a prepaid envelope. All patients received two reminders. Data collection took place from July to October 2013. Ethical approval was sought from the UK National Research Ethics Service and the OUH NHS Foundation Trust R&D office. Both bodies stated that ethical approval was not required.

2.6 Data Analysis

Data analysis was undertaken using Stata. In *Model A,* the choice data was modelled using MNL regression, testing main effects and differences by study design (including sample population and completion method). This initial model assumes that preferences are homogenous across individuals. *Model B* tested the significance of attribute interactions, and considered interactions between attributes and respondent characteristics (gender, age, occupation, children, income, time since CLL diagnosis, experience of chemotherapy treatment and genetic testing, whether the respondent had favourable opinions about genetic testing, and health status). Finally, we accounted for the limitations of MNL regression [31] by fitting alternative models (including mixed logit and latent class models), which allowed for preference heterogeneity. Different specifications were compared using the Akaike, Bayesian and Consistent information criterion to identify the most appropriate specifications.

For all models the marginal rate of substitution (the ratio between cost and the other attributes) was calculated, willingness-to-pay (WTP) for testing was estimated, and ratios between attributes were calculated to understand how much of one attribute respondents were willing to give up to get more of a second attribute. We also calculated the utility associated with genetic and genomic testing in this context. To test the robustness of our results, models were estimated without patients who failed the rationality check and choices were evaluated separately for patients who stated that the survey was difficult. The presence of dominant preferences was explored by examining if respondents always chose the test with the best level for a specific attribute [35]. Again, models were run with and without these patients. Finally, the proportion of correctly predicted choices was estimated by calculating the utility associated with each choice alternative, identifying the choice alternative with the highest utility, then calculating how frequently this alternative was chosen by respondents.

3 Results

Eighty paper surveys [response rate (RR): 54 %] and 70 electronic surveys (RR: 8 %; overall RR: 15 %) were received from CLLSA members. Of 140 patients asked to complete a survey at OUH, 101 were recruited (39 already participated in study/unwilling), with 69 paper surveys returned (RR: 68 %). The overall response rate for paper surveys was 60 %. 219 CLL patients completed a DCE in total (RR: 20 %).

The age, gender distribution and employment status of respondents were typical of CLL patients (Table 2) [24]. On average, respondents were diagnosed with CLL 6 years before completing the survey, with half undergoing at least one course of chemotherapy. Of these, 44 % had at least one inpatient stay due to chemotherapy treatment, with 12 % currently undergoing chemotherapy. One in five reported undergoing genetic testing, with 96 % in favour of pre-treatment genetic or genomic tests (Supplementary Materials–Part One: Table S3). The current quality of life of respondents matched UK population norms [36, 37].

Table S4 (Supplementary Materials–Part One) presents additional demographic information for DCE respondents, broken down by type of respondent (OUH or CLLSA) and method of completion (paper or electronic). Respondent demographics were relatively consistent across these categories. In terms of type of respondent, more OUH patients had undergone chemotherapy at least once (62 vs. 38 %), whereas more CLLSA patients had undergone genetic testing (26 vs. 7 %). In terms of method of completion, respondents who completed electronic surveys were more likely to be male (66 vs. 48 %), had left full-time education at an older age (20.4 vs. 17.9 years), were less likely to have had at least one course of chemotherapy (32 vs. 52 %) but were more likely to have had an inpatient stay following chemotherapy treatment (59 vs. 39 %).

Most respondents (97 %) passed the rationality check, with 9 % rating the DCE as difficult. Prior to undertaking the DCE, the most important attribute to respondents was EFFECT and the least important was COST (Supplementary Materials–Part One: Table S5). Almost all of the patients who chose to participate in the DCE survey completed all 16 choice questions, with only 0.8 % of choice questions not answered. Missing questions were mostly consecutive (i.e. respondents likely turned over two pages at once), so were assumed to be missing at random. Ninety-six respondents (44 %) made dominant choices, although 88 (92 %) were dominant for EFFECT, which exhibited overlap in 25 % of choice sets (hence it was easier to be dominant on this attribute).

3.1 Model A

Table 3 presents the results for Model A, which tested main effects and differences by study design. Initial analyses considered the impact on model performance of excluding respondents who failed the rationality check, made dominant choices, described the DCE as difficult or missed choice tasks. The only exclusion that increased pseudo-R^2, changed at least one coefficient from insignificant to significant and retained sufficient choice data was excluding respondents who described the DCE as difficult ($n = 19$). These patients also missed out a greater proportion of the choice questions (2.0 %) compared to those who said the DCE was not difficult (0.7 %). These

Table 2 Discrete choice experiment respondent characteristics

Variable	Value	*N*
Male	117 (53 %)	219
Mean age, years (SD)	65.7 (10.2)	205
Employment status		219
Employed	67 (31 %)	
Retired	138 (63 %)	
Other	14 (6 %)	
Mean age on leaving full-time education in years (SD)	18.7 (4.5)	205
Mean household income, £	30,646	201
Mean number of people per household (SD)	2.0 (0.9)	212
Mean number of children (SD)		219
At home	0.4 (0.8)	
Away from home	1.7 (1.3)	
Mean travel time to hospital, min	35.5	217
Mode of transport used to reach hospital		215
Hospital arranged	3 (1 %)	
Public transport	34 (16 %)	
Private transport	178 (83 %)	
Mean time since diagnosis, years (SD)	6.0 (4.5)	215
Number of respondents who have undergone chemotherapy at least once	98 (45 %)	216
Average number of courses of chemotherapy in these respondents (SD)	1.3 (0.8)	93
Number of respondents who have had an inpatient stay after chemotherapy treatment	42 (44 %)	96
Number of respondents undergoing chemotherapy currently	11 (12 %)	94
Number of respondents who had undergone genetic testing previously	44 (20 %)	216
Mean EQ-5D score (SD)[a]	0.823 (0.225)	217
Mean EQ-VAS score (SD)[a]	74.2 (17)	210

SD standard deviation

[a] The EuroQOL five dimensions (EQ-5D) survey instrument is designed for self-completion by respondents and collects information on health-related quality of life in two ways. Firstly, respondents rate their health in five dimensions (Mobility, Self-care, Usual activity, Pain/discomfort, Anxiety/Depression) in terms of three levels (the EQ-5D score). Secondly, respondents record an overall assessment of their health on a visual analogue scale which runs from 0 to 100 (the EQ-VAS score)

patients—who were older (71.7 years) and left full-time education earlier (17.7 years) than respondents who did not describe the DCE as difficult—were therefore excluded from the analysis.

The TIME, COST, EFFECT (test effectiveness) and REL (test reliability) coefficients in Model A all had the expected sign: respondents prefer tests that are more effective, more reliable, cheaper and return results quickly. The signs for the INFO coefficients indicated that only a 15-min appointment with a clinician has a positive impact on utility. The signs for the WHO coefficients indicated a utility gain only when results are explained by specialist nurses or consultant hospital doctors. Figures 1 and 2 (Supplementary Materials–Part One: Figures S6) illustrate the non-linearity of the coefficients for the levels of the INFO and WHO attributes. Improvements in test effectiveness are valued, with patients willing to pay £24 for a 1 % increase in the proportion of chemotherapy non-responders identified. However, process attributes are also valued: patients are willing to pay £27 to reduce time to receive test results by 1 day. The coefficient ratios indicated that respondents would be willing to wait an extra 29 days for test results if an additional one-third of chemotherapy non-responders could be identified. Alternatively, respondents would tolerate a genomic test being wrong 8 % of the time to receive this information. Finally, receiving results from a consultant hospital doctor instead of a general practitioner is equivalent to a 15 % increase in test effectiveness.

When Model A was estimated separately for different survey formats, pseudo-R^2 was higher (0.5362 vs. 0.3335) for the model containing DCEs completed electronically (although the signs and significance of most coefficients did not change). WTP for a 1 % increase in test

Table 3 Regression results and willingness-to-pay

Attribute	Model A (main effects, MNL)		Model B (including respondent characteristics, MNL)		Model C (main effects, ML)	
	Coefficients	WTP (95 % CI)	Coefficients	WTP (95 % CI)	Coefficients	WTP (95 % CI)
Main effects[a]						
TIME	−0.0461**	−£27.19 (−£38.67 to −£15.71)	−0.1077**	−£70.66 (−£118.61 to −£22.72)	−0.0556**	−£31.05 (−£47.13 to −£14.97)
COST	−0.0017**	N/A	−0.0015**	N/A	−0.0018**	N/A
EFFECT	0.0404**	£23.79 (£16.06 to £31.51)	0.0259**	£17.03 (£6.90 to £27.15)	0.0963**	£53.79 (£32.05 to £75.54)
REL	−0.1584**	−£93.38 (−£125.79 to −£60.98)	−0.2103**	−£137.98 (−£193.11 to −£82.84)	−0.2789**	−£155.73 (−£220.09 to −£91.38)
INFO0	−0.1367*	−£80.59 (−£165.73 to £4.54)	−0.2714**	−£178.07 (−£315.02 to −£41.12)	−0.1086	−£60.66 (−£160.61 to £39.30)
INFO1	−0.0319	−£18.83 (−£81.66 to £43.99)	−0.0305	−£20.03 (−£93.91 to £53.84)	−0.0531	−£29.67 (−£117.92 to £58.58)
INFO2	0.2624**	£154.69 (£55.61 to £253.76)	0.2848**	£186.88 (£63.74 to £310.01)	0.1510	£84.31 (−£30.07 to £198.69)
INFO3[b]	−0.0937**	−£55.26	0.0171**	£11.22	0.0108**	£6.02
WHO0	−0.8399**	−£495.10 (−£646.56 to −£343.64)	−0.9531**	−£625.40 (−£856.08 to −£394.73)	−0.9739**	−£543.81 (−£753.89 to −£333.74)
WHO1	0.5071**	£298.92 (£181.14 to £416.71)	0.5416**	£355.40 (£198.52 to £512.28)	0.4756**	£265.58 (£127.83 to £403.32)
WHO2	−0.2588**	−£152.54 (−£251.26 to −£53.81)	−0.3550**	−£232.96 (−£375.84 to −£90.09)	−0.3747**	−£209.22 (−£354.08 to −£64.36)
WHO3[b]	0.5915**	£348.71	0.7665**	£502.97	0.8730**	£487.46
Interaction terms						
MALE × INFO0	–	–	0.2174*	£142.68 (£20.27 to £265.09)	–	–
MALE × WHO0	–	–	0.2177*	£142.87 (£5.02 to £280.72)	–	–
INCOME × REL	–	–	0.0798**	£52.39 (£14.80 to £89.99)	–	–
DIAGNOSIS[c] × EFFECT	–	–	0.0012**	£0.80 (£0.25 to £1.35)	–	–
CHEMO[d] × EFFECT	–	–	−0.0140**	−£9.19 (−£14.09 to −£4.28)	–	–
GENETIC TEST[e] × WHO2	–	–	0.2758**	£180.94 (£33.67 to £328.22)	–	–
EQ-5D × TIME	–	–	0.0007*	£0.48 (−£0.03 to £0.98)	–	–
EQ-5D × EFFECT	–	–	0.0002**	£0.12 (£0.02 to £0.21)	–	–
Number of choice tasks	3097	–	2818	–	3097	–
Pseudo-R^2	0.4101	–	0.4253	–	–	–

95 % CI 95 % confidence interval, *MNL* multinomial logit, *ML* mixed logit, *WTP* willingness-to-pay, *TIME* time to receive test result, *COST* cost of the test, *EFFECT* ability of the test to predict who will not respond to the usual chemotherapy treatment, *REL* test reliability, *INFO* length of time clinicians spend describing the test to you (0 = 5 min, 1 = 10 min, 2 = 15 min, 3 = 20 min), *WHO* type of clinician who explains the test result to you (0 = general practitioner, 1 = specialist nurse, 2 = junior hospital doctor, 3 = consultant hospital doctor)

* P value < 0.05

** P value < 0.01

[a] The coefficient for the alternative specific constant was not significant in the initial regressions (indicating no respondent left-right bias) so was dropped from subsequent regressions

[b] WTP 95 % CIs cannot be calculated for the base levels of the effects coded variables

[c] Time since diagnosis

[d] Ever had chemotherapy

[e] Previously undergone genetic testing

effectiveness was higher when the DCE was completed electronically (£24.33 vs. £20.92), as was WTP for a 1 % improvement in test reliability (£93.33 vs. £82.99). When Model A was estimated separately by sample population, pseudo-R^2 was higher for the model for UK CLLSA respondents (0.4510 vs. 0.2735), although the signs and significance of most coefficients again remained the same. WTP for a 1 % increase in test effectiveness was higher for CLLSA respondents (£32.21 vs. £14.07), while WTP for a 1 % improvement in test reliability was higher for OUH respondents (£121.06 vs. £58.53).

3.2 Model B

Model B evaluated interactions. Neither of the planned interactions (COST × EFFECT, COST × REL) were significant, so were excluded from the final specification. However, when significant interactions between attributes and respondent characteristics were added (Table 3), pseudo-R^2 increased and the significance of INFO0 improved. Notable interactions included MALE × INFO0 (men have a stronger preference for shorter appointments), MALE × WHO0 (men have a stronger preference for receiving results from general practitioners), and INCOME × REL (higher income patients have a weaker preference for more reliable tests).

3.3 Alternative Model Specifications

Supplementary Materials–Part One: Table S7 presents a comparison of alternative model specifications. These results confirm that Model B provides a better fit than Model A. However, alternative specifications provide a better fit than MNL for both models. For Model A the most appropriate specification is either a mixed logit or latent class approach. As limited information is available to characterise the latent classes in this main effects model, the mixed logit approach is taken forward. Coefficients and WTP values for this model (hereafter Model C) are presented in Table 3. The significance of most coefficients remains the same as in Model A, although three are no longer significant: INFO0, INFO1 and INFO2. Notable changes in WTP include EFFECT (increases from £23.79 to £53.79) and REL (decreases from −£93.38 to −£155.73). Overall, Model C correctly predicted 81 % of respondent choices.

For Model B a latent class model is the most appropriate specification. Given that a series of assumptions are required concerning respondent characteristics in order to use the results of this model to calculate WTP, these results are presented separately (Supplementary Materials–Part One: Table S8).

3.4 Utility Calculations for Genetic and Genomic Testing

The utility calculations for genetic and genomic testing are presented in Supplementary Materials–Part One: Additional Information S9. In both Model A and Model C, genomic testing is associated with higher utility: the utility gain associated with improvements in test effectiveness and reliability surpasses the utility loss associated with the higher cost of genomic testing.

4 Discussion

This paper presents the results of a DCE survey which evaluated the preferences of UK CLL patients for pre-treatment genetic and genomic testing. This survey revealed that patients prefer tests that are more effective, more reliable, cheaper and which return results quickly. Patients prefer to receive these test results in a 15-min appointment with a clinician who is perceived to be a CLL expert. Both clinical and process-related attributes are important to patients, with test effectiveness and speed of result ranked highly. Patient characteristics may modify these findings, with male patients (who account for two-thirds of CLL incidence and have worse outcomes [38]) having a stronger preference than women for shorter appointments with general practitioners (rather than with hospital-based clinicians). This supports the suggestion that health-seeking behaviour differs between men and women [39, 40].

Overall, respondents expressed a preference for combinations of attributes and attribute levels that more closely reflect genomic testing than genetic testing. Indeed, respondents were willing to make notable trade-offs for the extra information provided by genomic testing (including waiting a month longer for results if genomic testing can identify an additional one-third of chemotherapy non-responders). Furthermore, when the likely specifications of genetic and genomic testing were valued using the coefficient estimates generated in the choice models, genomic testing was always associated with higher utility than genetic testing.

These findings match those of other DCEs that have evaluated genetic and genomic tests. Regier et al. evaluated the use of genomic testing to identify the genetic causes of developmental disability, reporting that both the diagnostic rate and waiting time for test results were important to families [41, 42]. Herbild et al. evaluated WTP for pharmacogenetic testing in the treatment of depression and found that respondents placed a high value on how the intervention was delivered [43]. Finally, Najafzadeh et al.

measured the preferences of patients and the general public for genomic testing to determine drug response, finding that both clinical (e.g. test effectiveness) and process-related attributes (e.g. genetic test procedure) are important to respondents [44].

Our study has several limitations. First, a broad cross-section of patients was targeted by using two sampling populations. However, some patients may be under-represented and our sample may therefore be characterised by selective non-response. The most severely ill patients may have been unable to participate, while the healthiest OUH patients (who only have annual check-ups) may not have been sampled. Furthermore, CLLSA members differ from non-members. However, given that respondent characteristics were typical of CLL patients [24], these factors are unlikely to have affected the DCE results.

Second, the DCE response rate was low, particularly for CLLSA members who completed electronic surveys. DCE response rates have been decreasing over time [45] and low response rates are no longer unusual, particularly in elderly populations and for electronic DCE surveys [46]. Furthermore, evidence suggests that response rates are lower when more than four attributes are included in a DCE, and when there is no opt-out [45]. However, most published DCEs include between 100 and 300 respondents and our sample size of 219 respondents does fall within this range [47, 48]. It has been noted previously that response rates are positively related to the perceived benefits of completing a DCE survey [45], hence it is possible that the low response rate to our survey may have impacted on the DCE results. Specifically, if those who completed the survey were primarily patients who were more aware of the benefits of testing (e.g. patients who had previously undergone chemotherapy and were thus familiar with the consequences of treatment) this might have biased WTP estimates upwards. However, as 55 % of respondents had not undergone chemotherapy and respondent quality-of-life matched population norms, we do not believe that the low response rate impacted on our results in this manner.

Third, an opt-out design was tested in a pilot which used a convenience sample of non-CLL patients and which found that the opt-out option was rarely selected. Ideally, this pilot would have used CLL patients, but the small pool of OUH patients precluded this approach. As CLL patients are rarely able to choose 'no test' in the UK and general population respondents may consider an opt-out to be a more viable choice than CLL patients, it is likely that a pilot of the opt-out design in CLL patients would have seen even fewer respondents selecting the opt-out option, providing further justification for this design decision.

Fourth, the TIME, COST, EFFECT and REL attributes were assumed to be linear and coded as continuous attributes to permit the use of the DCE results to characterise genomic testing practice (whose attributes were unknown at that time) in future cost-benefit analyses. It is, however, possible that the relationship between these attributes and utility is not linear, hence this is a potential weakness of our study.

Finally, 19 respondents described the DCE as difficult and were excluded from the analysis, which improved model fit. These respondents were excluded because we could not be sure that they understood the choice questions. These patients also missed out a greater proportion of the choice questions compared to those who said the DCE was not difficult, hence their responses provided limited additional information on trade-offs between test attributes. This decision was considered carefully as it has been suggested that the removal of such respondents is inappropriate [32]. As few respondents were affected, this decision is unlikely to have affected the main conclusions of this study. Furthermore, by removing respondents who may not have understood the choice questions, these conclusions may also be more robust.

The results of this study have implications for decision-making in both CLL and genomics more generally. CLL patients clearly value the additional clinical information that could be provided by genomic tests; however, several process-related attributes are also important to them. This suggests that for genomic testing to be implemented successfully, commissioners will need to ensure that test results are delivered by approved CLL clinicians in an appropriate environment. Furthermore, implementation may need to be tailored to the preferences of specific patient subgroups, with gender, income and previous treatment experience all influencing preferences.

However, these results alone are not sufficient to make a case for introducing genomic testing in CLL. Future work should combine these results with information on test costs in an economic evaluation to establish whether genomic testing provides value for money in this context, i.e. do the benefits surpass the costs. One way in which this could be partially achieved is to use this behavioural information as an input into a cost-effectiveness or cost-utility analysis (e.g. accounting for potential deviations from a 100 % participation rate). However, given the importance that CLL patients attached to process-related outcomes, the most appropriate form of economic evaluation could instead be a cost-benefit analysis (CBA), in which health outcomes are expressed in monetary terms, informed by the WTP estimates generated by this DCE. However, CBAs are rarely undertaken at present as they are not valued by HTA agencies such as the National Institute for Health and Care Excellence in the UK [49]. Future work which demonstrates that CBAs are a valid approach in this context would make a notable contribution to this area.

More generally, these findings suggest that studies which use narrowly-defined outcome measures such as the QALY may not capture all the benefits of genomic testing that are important to patients. One possible consequence of ignoring process-related outcomes is that commissioners may make sub-optimal decisions concerning the provision of genomic testing services. Additional work to evaluate all the clinical and process-related outcomes of genomic testing in a variety of clinical contexts may therefore facilitate the more efficient allocation of limited healthcare resources in the future.

The key finding in this study is that both clinical and process-related outcomes are valued by patients when considering the use of genomic testing to guide CLL treatment decisions. This finding is potentially generalisable to other clinical areas in which genomic tests with similar characteristics (e.g. cost, time to receive results) can guide treatment. This includes other cancers such as colorectal cancer, in which genomic testing can guide the use of expensive targeted therapies [50], and chronic diseases such as cystic fibrosis, where genomic testing can inform the use of treatments which help patients to live a more symptom-free life [51]. Policy-makers should be aware that these genomic tests will likely need to demonstrate both effectiveness and reliability, deliver results in a timely manner, and be fully explained to patients by qualified clinicians in order for patients to participate fully in such testing programmes. If this is not achieved, the full health benefits of genomic testing are unlikely to be realised.

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Author contributions James Buchanan initiated and led the study, designed and administered the discrete choice experiment survey, conducted the analysis, interpreted the results and drafted the manuscript. Sarah Wordsworth and Anna Schuh assisted with the design of the study and the interpretation of the results, and reviewed and modified the manuscript for important intellectual content. James Buchanan acts as the overall guarantor for this work.

Compliance with Ethical Standards

Ethical approval This study has been performed in accordance with the ethical standards of the Declaration of Helsinki. Ethical approval was sought from the UK National Research Ethics Service and the Oxford University Hospitals NHS Foundation Trust R&D office. Both bodies stated that ethical approval was not required. As the researchers had no direct contact with survey respondents, the topic of research was low risk, and participation was confined to one small task, informed consent was not obtained from all individual participants in the study. As per institutional guidelines (https://www.admin.ox.ac.uk/curec/resources/informed-consent/), participants, by their actions, implied consent.

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Conflict of interest James Buchanan, Sarah Wordsworth and Anna Schuh declare that they have no conflicts of interest.

References

1. National Institute for Health and Care Excellence. Familial breast cancer: the classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care 2006. https://www.nice.org.uk/guidance/cg164.
2. Mardis ER. The impact of next-generation sequencing technology on genetics. Trends Genet. 2008;24(3):133–41. doi:10.1016/j.tig.2007.12.007.
3. Ioannidis JPA, Khoury MJ. Are randomized trials obsolete or more important than ever in the genomic era? Genome Medicine. 2013;5(4):32. doi:10.1186/Gm436.
4. Buchanan J, Wordsworth S, Schuh A. Issues surrounding the health economic evaluation of genomic technologies. Pharmacogenomics. 2013;14(15):1833–47. doi:10.2217/pgs.13.183.
5. Foster MW, Mulvihill JJ, Sharp RR. Evaluating the utility of personal genomic information. Genet Med. 2009;11(8):570–4. doi:10.1097/GIM.0b013e3181a2743e.
6. Veenstra DL, Piper M, Haddow JE, Pauker SG, Klein R, Richards CS, et al. Improving the efficiency and relevance of evidence-based recommendations in the era of whole-genome sequencing: an EGAPP methods update. Genet Med. 2013;15(1):14–24. doi:10.1038/gim.2012.106.
7. Giacomini M, Miller F, O'Brien BJ. Economic considerations for health insurance coverage of emerging genetic tests. Community Genet. 2003;6(2):61–73.
8. Grosse SD, Wordsworth S, Payne K. Economic methods for valuing the outcomes of genetic testing: beyond cost-effectiveness analysis. Genet Med. 2008;10(9):648–54. doi:10.1097/GIM.0b013e3181837217.
9. Mushlin AI, Mooney C, Holloway RG, Detsky AS, Mattson DH, Phelps CE. The cost-effectiveness of magnetic resonance imaging for patients with equivocal neurological symptoms. Int J

Technol Assess Health Care. 1997;13(01):21–34. doi:10.1017/S0266462300010205.
10. de Bekker-Grob EW, Ryan M, Gerard K. Discrete choice experiments in health economics: a review of the literature. Health Econ. 2012;21(2):145–72. doi:10.1002/hec.1697.
11. Bennette CS, Trinidad SB, Fullerton SM, Patrick D, Amendola L, Burke W, et al. Return of incidental findings in genomic medicine: measuring what patients value: development of an Instrument to Measure PReferences for Information from Next-generation Testing (IMPRINT). Genet Med. 2013. doi:10.1038/gim.2013.63.
12. Wordsworth S, Ryan M, Skåtun D, Waugh N. Women's preferences for cervical cancer screening: A study using a discrete choice experiment. Int J Technol Assess Health Care. 2006;22(03):344–50. doi:10.1017/S0266462306051245.
13. Zenz T, Kröber A, Scherer K, Häbe S, Bühler A, Benner A, et al. Monoallelic TP53 inactivation is associated with poor prognosis in chronic lymphocytic leukemia: results from a detailed genetic characterization with long-term follow-up. Blood. 2008;112(8):3322–9. doi:10.1182/blood-2008-04-154070.
14. Alsolami R, Knight SJL, Schuh A. Clinical application of targeted and genome-wide technologies: can we predict treatment responses in chronic lymphocytic leukemia? Pers Med. 2013;10(4):361–76. doi:10.2217/pme.13.33.
15. Hallek M, Fischer K, Fingerle-Rowson G, Fink AM, Busch R, Mayer J, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. Lancet. 2010;376(9747):1164–74. doi:10.1016/S0140-6736(10)61381-5.
16. Knight SJ, Yau C, Clifford R, Timbs AT, Sadighi Akha E, Dreau HM, et al. Quantification of subclonal distributions of recurrent genomic aberrations in paired pre-treatment and relapse samples from patients with B-cell chronic lymphocytic leukemia. Leukemia. 2012;26(7):1564–75. doi:10.1038/leu.2012.13.
17. Edelmann J, Holzmann K, Miller F, Winkler D, Buhler A, Zenz T, et al. High-resolution genomic profiling of chronic lymphocytic leukemia reveals new recurrent genomic alterations. Blood. 2012;120(24):4783–94. doi:10.1182/blood-2012-04-423517.
18. Malcikova J, Smardova J, Rocnova L, Tichy B, Kuglik P, Vranova V, et al. Monoallelic and biallelic inactivation of TP53 gene in chronic lymphocytic leukemia: selection, impact on survival, and response to DNA damage. Blood. 2009;114(26):5307–14. doi:10.1182/blood-2009-07-234708.
19. Ouillette P, Collins R, Shakhan S, Li J, Peres E, Kujawski L, et al. Acquired genomic copy number aberrations and survival in chronic lymphocytic leukemia. Blood. 2011;118(11):3051–61. doi:10.1182/blood-2010-12-327858.
20. Stilgenbauer S, Schnaiter A, Paschka P, Zenz T, Rossi M, Dohner K, et al. Gene mutations and treatment outcome in chronic lymphocytic leukemia: results from the CLL8 trial. Blood. 2014;123(21):3247–54. doi:10.1182/blood-2014-01-546150.
21. Zenz T, Eichhorst B, Busch R, Denzel T, Habe S, Winkler D, et al. TP53 mutation and survival in chronic lymphocytic leukemia. J Clin Oncol. 2010;28(29):4473–9. doi:10.1200/JCO.2009.27.8762.
22. Zenz T, Habe S, Denzel T, Mohr J, Winkler D, Buhler A, et al. Detailed analysis of p53 pathway defects in fludarabine-refractory chronic lymphocytic leukemia (CLL): dissecting the contribution of 17p deletion, TP53 mutation, p53-p21 dysfunction, and miR34a in a prospective clinical trial. Blood. 2009;114(13):2589–97. doi:10.1182/blood-2009-05-224071.
23. Rossi D, Rasi S, Spina V, Bruscaggin A, Monti S, Ciardullo C, et al. Integrated mutational and cytogenetic analysis identifies new prognostic subgroups in chronic lymphocytic leukemia. Blood. 2013;121(8):1403–12. doi:10.1182/blood-2012-09-458265.
24. Oscier D, Dearden C, Erem E, Fegan C, Follows G, Hillmen P, et al. Guidelines on the diagnosis, investigation and management of chronic lymphocytic leukaemia: British Committee for Standards in Haematology. 2012. http://onlinelibrary.wiley.com/doi/10.1111/bjh.12067/abstract.
25. Pospisilova S, Gonzalez D, Malcikova J, Trbusek M, Rossi D, Kater AP, et al. ERIC recommendations on TP53 mutation analysis in chronic lymphocytic leukemia. Leukemia. 2012;26(7):1458–61.
26. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Dohner H, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood. 2008;111(12):5446–56. doi:10.1182/blood-2007-06-093906.
27. Gunn SR, Mohammed MS, Gorre ME, Cotter PD, Kim J, Bahler DW, et al. Whole-genome scanning by array comparative genomic hybridization as a clinical tool for risk assessment in chronic lymphocytic leukemia. J Mol Diagn. 2008;10(5):442–51. doi:10.2353/jmoldx.2008.080033.
28. Clifford R, Louis T, Robbe P, Ackroyd S, Burns A, Timbs AT, et al. SAMHD1 is mutated recurrently in chronic lymphocytic leukemia and is involved in response to DNA damage. Blood. 2014;123(7):1021–31. doi:10.1182/blood-2013-04-490847.
29. Goede V, Fischer K, Busch R, Engelke A, Eichhorst B, Wendtner CM, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. N Engl J Med. 2014;370(12):1101–10. doi:10.1056/NEJMoa1313984.
30. Zhang L, Znoyko I, Costa LJ, Conlin LK, Daber RD, Self SE, et al. Clonal diversity analysis using SNP microarray: a new prognostic tool for chronic lymphocytic leukemia. Cancer Genet. 2011;204(12):654–65. doi:10.1016/j.cancergen.2011.10.012.
31. Ryan M, Gerard K, Amaya-Amaya M. Using discrete choice experiments to value health and health care. Springer; 2008. https://www.amazon.co.uk/Discrete-Experiments-Economics-Non-Market-Resources/dp/1402040822.
32. Lancsar E, Louviere J. Deleting 'irrational' responses from discrete choice experiments: a case of investigating or imposing preferences? Health Econ. 2006;15(8):797–811. doi:10.1002/hec.1104.
33. Bech M, Kjaer T, Lauridsen J. Does the number of choice sets matter? Results from a web survey applying a discrete choice experiment. Health Econ. 2011;20(3):273–86. doi:10.1002/hec.1587.
34. Rose J, Scarpa R, Bliemer M. Incorporating model uncertainty into the generation of efficient stated choice experiments: a model averaging approach. Working paper ITLS-WP-09-08, Institute of Transport and Logistics Studies. 2008.
35. Payne K, Fargher EA, Roberts SA, Tricker K, Elliott RA, Ratcliffe J, et al. Valuing pharmacogenetic testing services: a comparison of patients' and health care professionals' preferences. Value Health. 2011;14(1):121–34. doi:10.1016/j.jval.2010.10.007.
36. Kind P, Hardman G, Macran S. UK Population Norms for EQ-5D: University of York, Centre for Health Economics, Discussion Paper 1721999.
37. Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. Med Decis Mak. 2011;31(6):800–4. doi:10.1177/0272989X11401031.
38. Catovsky D, Wade R, Else M. The clinical significance of patients' sex in chronic lymphocytic leukemia. Haematologica. 2014;99(6):1088–94. doi:10.3324/haematol.2013.101378.
39. Galdas PM, Cheater F, Marshall P. Men and health help-seeking behaviour: literature review. J Adv Nurs. 2005;49(6):616–23. doi:10.1111/j.1365-2648.2004.03331.x.

40. Oberoi DV, Jiwa M, McManus A, Hodder R. Colorectal cancer–applying a gender lens. Qual Prim Care. 2014;22(2):71–9.
41. Regier DA, Friedman JM, Makela N, Ryan M, Marra CA. Valuing the benefit of diagnostic testing for genetic causes of idiopathic developmental disability: willingness to pay from families of affected children. Clin Genet. 2009;75(6):514–21. doi:10.1111/j.1399-0004.2009.01193.x.
42. Regier DA, Ryan M, Phimister E, Marra CA. Bayesian and classical estimation of mixed logit: an application to genetic testing. J Health Econ. 2009;28(3):598–610. doi:10.1016/j.jhealeco.2008.11.003.
43. Herbild L, Bech M, Gyrd-Hansen D. Estimating the Danish populations' preferences for pharmacogenetic testing using a discrete choice experiment. The case of treating depression. Value Health. 2009;12(4):560–7. doi:10.1111/j.1524-4733.2008.00465.x.
44. Najafzadeh M, Johnston KM, Peacock SJ, Connors JM, Marra MA, Lynd LD, et al. Genomic testing to determine drug response: measuring preferences of the public and patients using Discrete Choice Experiment (DCE). BMC Health Serv Res. 2013;13:454. doi:10.1186/1472-6963-13-454.
45. Watson V, Becker F, de Bekker-Grob EW. Discrete choice experiment response rates: a meta-analysis. Sheffield: Health Economists' Study Group meeting; 2014.
46. Bogelund M, Vilsboll T, Faber J, Henriksen JE, Gjesing RP, Lammert M. Patient preferences for diabetes management among people with type 2 diabetes in Denmark—a discrete choice experiment. Curr Med Res Opin. 2011;27(11):2175–83. doi:10.1185/03007995.2011.625404.
47. Wanders JO, Veldwijk J, de Wit GA, Hart HE, van Gils PF, Lambooij MS. The effect of out-of-pocket costs and financial rewards in a discrete choice experiment: an application to lifestyle programs. BMC Public Health. 2014;14:870. doi:10.1186/1471-2458-14-870.
48. Marshall D, Bridges JF, Hauber B, Cameron R, Donnalley L, Fyie K, et al. Conjoint analysis applications in health—how are studies being designed and reported?: an update on current practice in the published literature between 2005 and 2008. Patient. 2010;3(4):249–56. doi:10.2165/11539650-000000000-00000.
49. Buchanan J, Wordsworth S. Welfarism versus extra-welfarism: can the choice of economic evaluation approach impact on the adoption decisions recommended by economic evaluation studies? Pharmacoeconomics. 2015;33(6):571–9. doi:10.1007/s40273-015-0261-3.
50. Goldstein DA, Shaib WL, Flowers CR. Costs and effectiveness of genomic testing in the management of colorectal cancer. Oncology. 2015;29(3):175–83.
51. Whiting P, Al M, Burgers L, Westwood M, Ryder S, Hoogendoorn M, et al. Ivacaftor for the treatment of patients with cystic fibrosis and the G551D mutation: a systematic review and cost-effectiveness analysis. Health Technol Assess. 2014. doi:10.3310/hta18180.