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ARTICLE

Decision-making, attitudes, and understanding among patients and relatives invited to undergo genome sequencing in the 100,000 Genomes Project: A multisite survey study

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ABSTRACT

Purpose: The purpose of this study was to assess decisions, attitudes, and understanding of participants (patients, parents, relatives) having genome sequencing for rare disease diagnosis.
Methods: This study involved a cross-sectional observational survey with participants in the 100,000 Genomes Project.
Results: Survey response rate was 51% (504/978). Most participants self-reported that they had decided to undergo genome sequencing (94%) and that this was an informed decision (84%) with low decisional conflict (95%). Most self-reported that they had chosen to receive additional findings (88%) and that this was an informed decision (89%) with low decisional conflict (95%). Participants were motivated more by the desire to help others via research than by the belief it would help them obtain a diagnosis ($Z = 14.23$, $P = 5.75 \times 10^{-46}$), although both motivations were high. Concerns were relatively few but, where expressed, were more about the potential psychological impact of results than data sharing/access ($Z = 9.61$, $P = 7.65 \times 10^{-22}$). Concerns were higher among male, Asian or Asian British, and more religious participants. General and context-specific understanding of genome sequencing were both moderately high (means 5.2/9.0 and 22.5/28.0, respectively).
Conclusion: These findings are useful to inform consent guidelines and clinical implementation of genome sequencing.
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Introduction

In the United Kingdom, over 70,000 patients with rare diseases and their relatives had their genomes sequenced via the 100,000 Genomes Project (100kGP).[1] Following this, the United Kingdom National Health Service (NHS) Genomic Medicine Service was introduced, offering patients genome sequencing in the clinical setting for genetic diagnosis.[2]

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Integration of genome sequencing into health care raises many ethical and psychosocial challenges, one of the most immediate being informed consent and decision-making.[3] As with other medical tests, patients have the right to consent or not on the basis of communication of understandable and adequate information.[4] With increasing clinical implementation, there is a need to know whether patients are making informed decisions about genome sequencing. A widely used definition is that a person is deemed to have made an informed decision if they have adequate knowledge and make a decision that is consistent with their attitudes or values.[5] However, measures of informed decision-making composed of attitudes and knowledge measures, which can be used as indications of whether an informed decision about genome sequencing has been made, are currently lacking.

Several qualitative studies have explored genome sequencing decisions, attitudes, and knowledge among parents and patients with rare diseases taking part in the 100kGP.[6-11] Dheensa et al[6] found that patients and their families' decisions to participate in the Project were based on interpersonal trust in the NHS and on an investment in improving care for the future. Participants' concerns about data security, privacy, and access regulations reported by Dheensa et al[6] were also reported in studies by Mackley et al[7] and Lewis et al.[10] In these 2 later studies, patients with rare disease and their families demonstrated high levels of understanding of genomic sequencing, including the potential benefits (a diagnosis) and the limitations of the technology.[7,10] In contrast, Ballard et al[11] reported that a proportion of study participants did not appear to understand the complexities of the project and what types of results they might receive. Greater genomic knowledge has been associated with lower test-related distress and greater perceived understanding of genome sequencing in a longitudinal quantitative study in the United States looking at genomic knowledge among participants undergoing diagnostic exome sequencing.[12]

Our aim in this study was to conduct a large-scale survey to quantitatively assess decision-making around main and additional findings, including calculating informed choice, among individuals who had been invited to consent to undergo genome sequencing through the 100kGP. The findings from this work will inform development of standards for consent processes during clinical implementation.

Materials and Methods

Ethics statement

This study was reviewed by NHS Research Ethics Committee West Midlands, 15/WM/0258. All participants received a Participant Information Sheet alongside the questionnaire, and returning a completed survey was taken as implied consent to participate. All personal data, including participants' contact details, were kept on a separate log that could only be accessed by the research team and was password protected.

Study design

This was a multisite cross-sectional observational survey study. The study was overseen by an advisory board composed of research scientists, a genetic counselor, a geneticist, representatives from the patient groups Genetic Alliance UK and Unique, and a patient taking part in the 100kGP.

Participants and recruitment

Participants of the study reported here were a subset of individuals recruited to the 100kGP between 2017 and 2018. Recruitment occurred across England through 13 NHS Genomic Medicine Centres that were established to support delivery of the project, each composed of a number of hospitals to cover the whole of England. Participants included patients with rare diseases and their relevant family members and patients with cancer.[13] The rare disease inclusion criteria included anyone with a rare disease meeting certain phenotypic criterion and no molecular diagnosis as well as those with undiagnosed dysmorphic conditions.[13] No method of sampling stratification was applied to recruitment for the 100kGP.

Participants for this study were recruited from 6 London hospitals across 2 Genomic Medicine Centres from July 1, 2017 to September 30, 2018. Participants included (1) adult patients with rare diseases ("patients"), (2) parents of children with rare diseases (unrelated to the adult patients in the study) ("parents"), and (3) adult relatives of adult patients or children with rare diseases ("relatives"). Individuals invited to the rare disease arm of the 100kGP at these sites during this time period were eligible for this study if they were over 18 years old and could read and understand English. Patients recruited into the cancer arm of the 100kGP were excluded. Multiple participants from single families were eligible; however, all of the adult patients were unrelated to the parents in this study. The invitation to participate was given to consecutive potential participants, after they had decided whether or not to consent to the 100kGP but before receiving results. No method of stratification or oversampling was applied to recruitment for this study. At each site, participants were recruited by health professionals (consenters) who were consenting individuals into the 100kGP. The consenters gave eligible individuals a pack containing a Participant Information Sheet, the questionnaire, and a stamped addressed envelope. Participants could either complete the questionnaire immediately and return it to the health professional in a sealed envelope, take the questionnaire home and return it by post, or complete it online. Packs were given to those who consented to undergo genome sequencing as well as those who declined. The

consenters completed a recruitment log of each participant approached to record acceptance rates and contact details so that nonresponders could be contacted after 4 weeks to offer the opportunity to conduct the questionnaire over the telephone and also to send a second questionnaire 1 year later to explore longer-term impact. Participants who returned a completed questionnaire were sent a £10 gift voucher as a token of appreciation for their time.

Measures

The full questionnaire is available online (see Supplemental Material and Methods). Three versions of the questionnaire were developed so that the wording reflected whether the participant was a patient, parent, or relative.

Sociodemographic and individual characteristics

Sociodemographic characteristics were assessed with standard items (Table 1). Perceived severity of the rare condition was assessed with 2 items adapted from the Revised Illness Perceptions Questionnaire.[14] Resilience was assessed with the 6-item Brief Resilience Scale.[15] Information-seeking personality style was assessed with 2 items adapted from a previously published measure.[16]

Decisions and decisional conflict

Participants were first asked whether or not they had chosen to take part in the 100kGP. To measure self-reported informed decision-making, they were asked whether they thought they had enough information and discussion with doctors or other health care providers to make an informed choice about undergoing genome sequencing. To assess decisional conflict about their decision, participants were asked to complete the decisional conflict scale.[17]

To assess participants' decisions about additional findings, participants were asked whether they chose to receive additional findings related to their health. They were then asked whether they had enough information to make an informed choice about whether to receive additional findings. To assess decisional conflict about additional findings, participants were asked to complete the decisional conflict scale.[17]

Specific attitudes toward genome sequencing (perceived benefits and concerns)

A total of 14 new attitudes scale items were developed specifically for this study by reviewing the existing literature, drawing on a previous survey of biobank participants,[18] and conducting qualitative interviews with 20 participants in the 100kGP,[10] with input from the advisory board.

General attitudes toward genome sequencing

We assessed general attitudes toward genome sequencing with 4 items adapted from previous research.[19,20]

Context-specific knowledge about genome sequencing

To assess context-specific knowledge about genome sequencing for this study, we developed a new measure. This involved 2 stages.

Stage 1: Selection of knowledge domains

We reviewed selected professional guidelines and recommendations, patient information materials, and an existing measure of more general knowledge[21]; conducted 2 focus groups at 2 sites with 9 health professionals; and had input from our advisory board. The 8 draft domains produced at the end of this stage of the process were (1) what is involved in having genome sequencing done, (2) the purpose, (3) the benefits, (4) the risks, (5) the limitations and uncertainties, (6) how the samples and data will be stored and who will have access, (7) how additional findings will be managed, and (8) that having genome sequencing is voluntary.

Stage 2: Item development

A large pool of over 70 candidate items was then developed to cover each draft domain using 3 approaches: (1) review of items included in published measures, (2) the 100kGP patient information sheet and consent documents, and (3) items suggested from in-depth qualitative interviews with 20 patients taking part in the 100kGP.[10] We then conducted an iterative process whereby we reduced the items down to a final set of 28 covering the 8 knowledge domains described earlier.

General knowledge of genome sequencing

In addition to the new context-specific knowledge items, we administered the previously published 9-item Knowledge of Genome Sequencing (KOGS) questionnaire.[22] A conceptual framework illustrating the context-specific understanding and attitude domains can be seen in Supplemental Figure 1.

Pilot testing the survey instrument

Cognitive interviews to assess wording and comprehension were conducted with patients ($n = 4$) participating in the 100kGP and health care professionals consenting to the Project ($n = 4$). After feedback, minor revisions to wording were made before conducting a pilot feasibility and acceptability study, where the full questionnaire was posted to 100 participants in the 100kGP at 4 sites. A total of 52 questionnaires (52%) were returned. Final revisions to the processes, procedures, and questionnaire content were made in light of this pilot testing.

Sample size

We aimed to recruit a minimum of 500 participants for the T1 survey. This would allow the percentage of participants making an informed choice to be estimated within at least ±4.5% with 95% confidence. This precision is obtained if

Table 1 Participant characteristics

Characteristic	Response Options	*n* (%)
Participant type	Patient	229 (45.4)
	Parent	237 (47.0)
	Other relative	38 (7.5)
Sex	Female	308 (61.1)
	Male	195 (38.7)
	Missing	1 (0.2)
Age, y	Mean (SD), range	45.4 (14.0), 16-82
Currently employed	Yes	308 (61.1)
	No	179 (35.5)
	Do not wish to answer	13 (2.6)
	Missing	4 (0.8)
Education	No qualification	30 (6.0)
	GCSE or O level	94 (18.7)
	GCE, A-level, or similar	45 (8.9)
	Vocational, eg, BTEC	117 (23.2)
	Bachelor's degree	136 (27.0)
	Master's degree	58 (11.5)
	PhD, MD, JD	18 (3.6)
	Missing	6 (1.2)
Ethnicity	White or White British	424 (84.1)
	Asian or Asian British	37 (7.3)
	Black or Black British	11 (2.2)
	Mixed	14 (2.8)
	Other ethnic group	17 (3.4)
	Missing	1 (0.2)
Religious faith	None	182 (36.1)
	Christian	250 (49.6)
	Muslim	25 (5.0)
	Hindu	10 (2.0)
	Jewish	3 (0.6)
	Buddhist	2 (0.4)
	Sikh	3 (0.6)
	Other	23 (4.6)
	Missing	6 (1.2)
Religiosity (How religious are you?)	Not at all	252 (50.0)
	Somewhat	193 (38.3)
	Very	52 (10.3)
	Missing	7 (1.4)
No. of children (range 0-9)	0	118 (23.4)
	1	86 (17.1)
	2	173 (34.3)
	3	72 (14.3)
	≥ 4	46 (9.2)
	Missing	9 (1.8)
Age of child/relative patient, y	Mean (SD), range	12.64 (12.44), 0-74
Perceived severity of rare condition (2 items, possible range 1-5)	Median, Mean (SD), range	4.0, 3.75 (1.06), 1.0-5.0
Resilience (possible range 1-5)	Median, Mean (SD), range	3.50, 3.49 (0.74), 1.0-5.0
Information-seeking style (2 items, possible range 1-5)	Median, Mean (SD), range	4.0, 4.21 (0.67), 1.0-5.0

BTEC, Business and Technology Education Council; *GCE*, General Certificate of Education; *GCSE*, General Certificate of Secondary Education.

half actually do make an informed choice and improves if the percentage is other than 50%, eg, if 85% of participants make an informed choice, then this will be estimated to be within ±3.2% with a sample of 500. Assuming a 50% response rate based on our pilot data, we therefore aimed to administer 1000 surveys with a view to obtaining a final size of 500 participants.

Statistical analyses

Sociodemographic variables, single-item measures, knowledge, and attitude outcomes were assessed and reported using frequencies, means, and SDs. Decisional conflict was calculated by summing the total of the 15 items, in accordance with published scoring guidance.[23] The reliability of

Table 2 Decisions, self-reported informed choice, decisional conflict, attitudes, and understanding: Summary scale scores compared between patients and parents

Variable	Total, including 38 relatives, $n = 504$	Patients $n = 229$	Parents $n = 237$	Sig
1. Decision about genome sequencing				
1.1. Decision about GS[a]				
Decided to take part in 100kGP and have GS (1 item), *n* (%)				
Yes	490 (97.2)	227 (99.1)	225 (94.9)	$\chi^2(1) = 7.02$, $P = .008$
No	3 (0.6)	1 (0.4)	2 (0.8)	
Did not answer	11 (2.2)	1 (0.4)	10 (4.2)	
1.2. Self-reported informed decision about GS[a]				
Had enough information and discussion with doctors/HCPs to make informed choice about GS (1 item), *n* (%)				
Yes	453 (89.9)	201 (87.8)	222 (93.7)	$\chi^2(1) = 4.84$, $P = .028$
Partly	38 (7.5)	22 (9.6)	12 (5.1)	
No	6 (1.2)	3 (1.3)	3 (1.3)	
There was no choice	0 (0)	0 (0)	0 (0)	
Not sure	6 (1.2)	2 (0.9)	0 (0)	
Did not answer	1 (0.2)	1 (0.4)	0 (0)	
1.3. Decisional conflict about GS[b]				
Total DCS score (23 items); median, mean (SD), range	18.75, 16.54 (14.79), 0-98	17.19, 16.25 (15.09)	17.19, 16.09 (14.74)	$Z = 0.07$, $P = .94$
2. Decision about additional findings				
2.1. Decision about additional findings[a]				
Decided to receive additional findings (1 item), *n* (%)				
Yes	441 (87.5)	201 (87.8)	209 (88.2)	$\chi^2(1) = 0.02$, $P = .89$
No	23 (4.6)	8 (3.5)	11 (4.6)	
Cannot remember	13 (2.6)	8 (3.5)	4 (1.7)	
Did not answer	27 (5.4)	12 (5.2)	13 (5.5)	
2.2. Self-reported informed decision about additional findings[a]				
Had enough info/ discussion with doctors/HCPs to make informed choice about AFs (1 item), *n* (%)				
Yes	449 (89.1)	194 (84.7)	222 (93.7)	$\chi^2(1) = 6.13$, $P = .013$
Partly	30 (6.0)	20 (8.7)	7 (3.0)	
No	9 (1.8)	4 (1.7)	5 (2.1)	
There was no choice	0 (0)	0 (0)	0 (0)	

(continued)

Table 2 Continued

Variable		Total, including 38 relatives, $n = 504$	Patients $n = 229$	Parents $n = 237$	Sig
Not sure		8 (1.6)	4 (1.7)	2 (0.8)	
Not applicable		1 (0.2)	0 (0)	1 (0.4)	
Did not answer		8 (1.6)	7 (3.1)	0 (0)	
2.3. Decisional conflict about additional findings[b]					
Total DCS score (23 items); median, mean (SD), range		20.31, 16.53 (15.26), 0-100	18.75, 16.89 (16.92), (0-98.4)	20.31, 15.69 (14.07), (0-95.3)	Z = 0.51, $P = .96$
3. Attitudes and knowledge					
3.1. Positive attitudes[b]					
Scale score (7 items), 0-7; median, mean (SD), range		7.0, 6.16 (1.08), 2-7	7.0, 6.10 (1.13), 3-7	7.0, 6.21 (1.03), 2-7	Z = 0.66, $P = .51$
3.2. Negative attitudes[b]					
Scale score (7 items), 0-7; median, mean (SD), range		1.0, 1.20 (1.71), 0-7	1.0, 1.05 (1.54), 0-7	1.0, 1.35 (1.85), 0-7	Z = 1.2, $P = .23$
3.3. Understanding					
General[c]					
KOGS generic knowledge scale score (9 items), 0-9; median, mean (SD), range	Median, Mean (SD), range	5.0, 5.21 (2.35), 0-9	5.0, 5.22 (2.37)	5.0, 5.24 (2.33)	F(464) = 0.09, $P = .76$
Specific[b]					
Total context-specific knowledge scale score (28 items), 0-28; median, mean (SD), range		23.5, 22.5 (4.0), 0-28	23.0, 22.4 (4.0), 0-28	24.0, 22.7 (4.0), 0-28	Z = 1.02, $P = .31$

100kGP, 100,000 Genomes Project; *AF*, additional finding; *DCS*, decisional conflict scale; *GS*, genome sequencing; *HCP*, healthcare professional; *info*, information; *KOGS*, Knowledge of Genome Sequencing; *sig*, significance.

[a]Comparison between patients and parents using Chi-square test.

[b]Comparison between patients and parents using Wilcoxon signed-rank test.

[c]Comparison between patients and parents using analysis of variance.

the knowledge and attitudes measures was assessed using Cronbach alpha coefficients. To reduce our correlated observed variables on the attitudes scales to a smaller set of important independent composite variables, we conducted principal component analysis. Varimax rotation was used, eigen values >1 were extracted, and items were interpreted as loading on to a given factor if they had a value of 0.4 or greater. Knowledge measures scores were calculated by summing the number of correct items. We conducted correlations and *t* tests (normally distributed variables) or Spearman's rank correlations (non-normally distributed variables) to examine bivariate associations between the primary dependent variables (attitudes and knowledge scales) and participant characteristics (sex, age, employment, education, ethnicity, religiosity, children, participant type [patient, parent], child/relative age, perceived severity, information-seeking style, and resilience); variables associated with dependent variables in the bivariate analyses were entered into multivariable analysis of covariance. We ran a series of analyses to compare the primary dependent variables (attitudes and knowledge scales) between parents and patients (participant type) to check for differences between these 2 subsets. First, an analysis of variance was conducted to compare parents' and patients' mean general KOGS score. Next, Wilcoxon signed-rank tests were used to compare scores between participant types where the data diverged from normality (positive attitude scale, negative attitude scale, and context-specific KOGS scores) and to compare scores across participant type. Because there were few differences (see Table 2), all subsequent analyses were conducted combining the 2 participant types. $P < .05$ was considered significant. All analyses were conducted with

statistical software package IBM SPSS Statistics for Windows v22 (Armonk, NY: IBM Corp).

Informed choice calculation

Consistent with the Multidimensional Measure of Informed Choice developed by Marteau et al,[5] an informed choice was defined as one where the participant had good knowledge and either had a positive attitude and consented to genome sequencing (main findings) or had a negative attitude and declined genome sequencing (main findings). There are no agreed criteria for what constitutes good or poor knowledge, although cutoffs between 60% and 80% have been used in previous studies using an adapted Multidimensional Measure of Informed Choice.[20,24,25] We therefore presented rates of informed choice using a range of cutoffs for what constitutes good knowledge in our informed choice calculation (60%, 70%, 75%, and 80%; see Table 3). In addition, we assessed knowledge as the combined scores from the general knowledge (KOGS) and context-specific knowledge items ($n = 37$), as well as the context-specific knowledge questions alone ($n = 28$). The rationale for this was that the context-specific items relate to the 100kGP specifically and therefore test participants' understanding of what it means to take part in the project. We used the general attitudes scale to calculate positive or negative attitudes toward genome sequencing. In line with previous research, we categorized attitudes into 3 equal categories (positive, negative, and neutral) and removed people with a neutral attitude from the informed choice calculation.[20,24]

Table 3 Informed choice calculations

Cutoff, %	Actual Threshold for Knowledge Score	Rounded Threshold for Knowledge Score: Poor Knowledge	Rounded Threshold for Knowledge Score: Good Knowledge	Knowledge Scale	Knowledge and Attitude Level, *n* (%): Good Knowledge/Positive Attitude	Good Knowledge/Negative Attitude	Poor Knowledge/Positive Attitude	Poor Knowledge/Negative Attitude
60	22.2	<22	≥22	General + specific knowledge	383 (83.8)	0 (0)	72 (15.8)	2 (0.4)
	16.8	<17	≥17	Specific knowledge	412 (90.2)	0 (0)	43 (9.4)	2 (0.4)
70	25.9	<26	≥26	General + specific knowledge	300 (65.6)	0 (0)	155 (33.9)	2 (0.4)
	19.6	<20	≥20	Specific knowledge	347 (75.9)	0 (0)	108 (23.6)	2 (0.4)
75	27.8	<28	≥28	General + specific knowledge	231 (50.5)	0 (0)	224 (49.0)	2 (0.4)
	21.0	<21	≥21	Specific knowledge	318 (69.6)	0 (0)	137 (30.0)	2 (0.4)
80	29.6	<30	≥30	General + specific knowledge	149 (32.6)	0 (0)	306 (67.0)	2 (0.4)
	22.4	<22	≥22	Specific knowledge	270 (59.1)	0 (0)	185 (40.5)	2 (0.4)

Content analysis of decliner responses

Recruitment to the survey was done by invitation to individuals attending consent appointments for genome sequencing in the 100kGP. Because most of these individuals agreed to take part, the views of individuals who declined genome sequencing were underrepresented in our survey. To gain insight into the views of individuals who declined to undergo genome sequencing in the 100kGP ("decliners"), we reviewed the routinely collected records of the reasons given for declining by individuals at one of our participating hospital sites. This included individuals contacted by phone to discuss the study and offer appointments as well as those attending in person. Reasons for declining were coded independently by 2 researchers and grouped into broad categories using an inductive content analysis approach.[26] These were then compared, and any disagreement was checked, discussed, and resolved with a third researcher (S.C.S.).

Results

Sociodemographic characteristics of participants

Of 978 questionnaires sent out, 506 (51.7%) completed questionnaires were returned. Of these, 1 respondent was

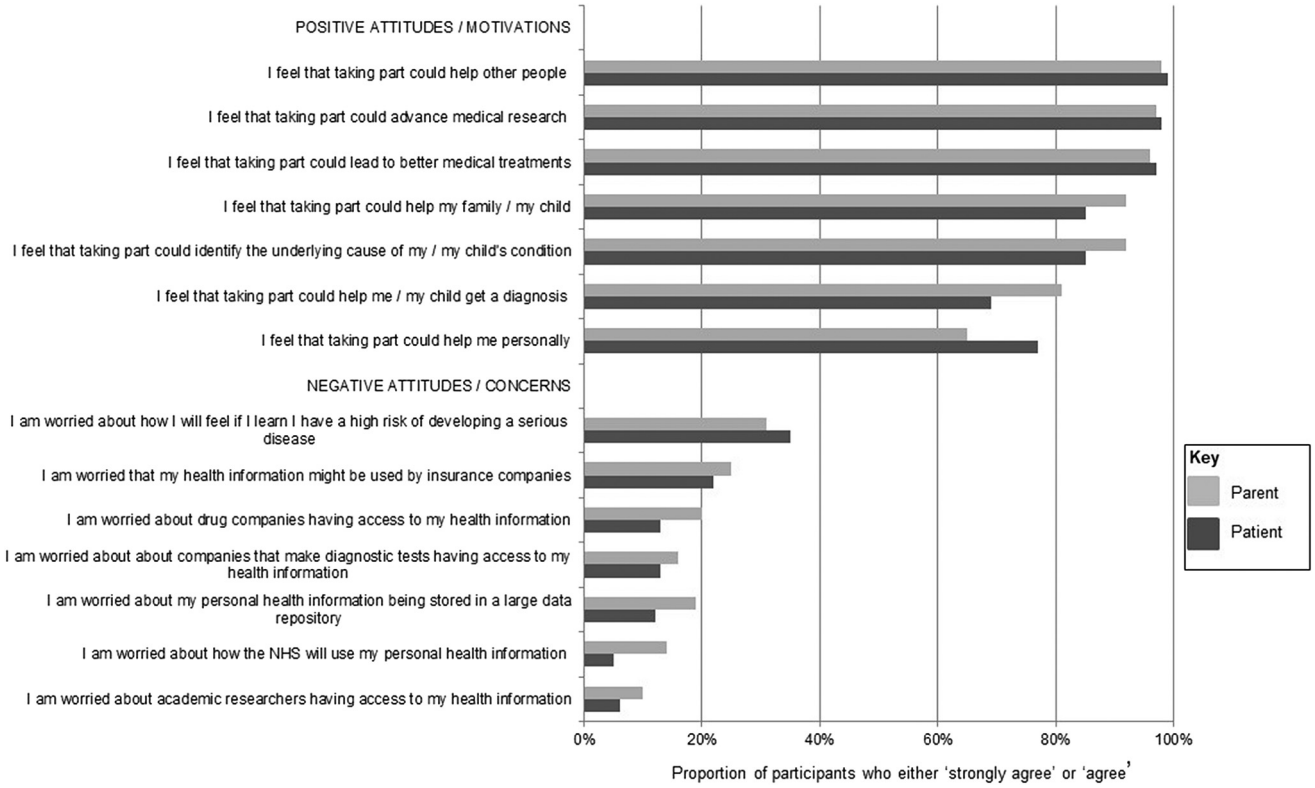

Figure 1 Attitudes towards genome sequencing: individual items compared between parents and patients.

excluded because they reported an age of 12 years and 1 because they straight-lined their answers (where the respondent clicked on the same response every time). Of the remaining 504 eligible respondents (51.5% response rate), 229 were adult patients, 237 parents (all unrelated to the adult patients), and 38 other relatives. The mean scores for perceived severity, resilience, and information-seeking style were 4.0, 3.5, and 4.0 respectively. Demographic details are given in Table 1.

Decisions and decisional conflict

Most participants (97%) reported they had chosen to take part in the 100kGP and undergo genome sequencing; most (84%) also felt they had made an informed decision. In total, 491 participants (97%) had completed the multi-item decisional conflict scale for genome sequencing (DCS-GS). The mean DCS-GS score was 16.51, indicating low decisional conflict overall. A total of 25 participants (5.0%) were categorized as experiencing some decisional conflict, using the DCS-GS cutoff score of 37.5.

Most participants (88%) reported that they had opted to receive additional findings and most (89%) self-reported that they had made an informed decision. Overall, 488 completed the decisional conflict scale for additional findings. The mean decisional conflict scale for additional findings score was 16.53, indicating low decisional conflict overall; 27 participants (5.4%) were experiencing some decisional conflict about additional findings (using the 37.5 cutoff) (Supplemental Table 1).

Perceived benefits/motivations

When factor analysis was conducted on the perceived benefits/motivations items, 2 clear factors emerged. The first was composed of 4 items and was subsequently labeled "Perceived benefits for self/family." The second was composed of 3 items and was labeled "Perceived benefits for others." Cronbach alpha coefficients were 0.72 and 0.71, respectively.

Perceived benefits for self/family

On the 4 individual items, 89% felt that taking part in the 100kGP could identify the underlying cause of the condition, 89% felt that it could help their family/child/relative, 74% felt that it could help them/their child/relative get a diagnosis, and 71% felt that it could help them personally. The overall mean score on the perceived benefits for self/family subscale was 4.15 (median 4.00, mode 5.00) (Supplemental Table 2, Figure 1). In multivariable analyses, perceived benefit for self/family was associated with lower educational attainment ($t = -4.44$, $P = 1.1 \times 10^{-5}$), perceived severity of the condition ($t = 3.16$, $P = .002$), and higher information-seeking style ($t = 4.49$, $P = 9.0 \times 10^{-5}$).

Perceived benefits for others

On the 3 individual items, 98% of participants felt that taking part in the 100kGP could help other people, 98% felt that it could advance medical research, and 97% felt that it could lead to better medical treatments. The mean score on

the perceived benefits for others subscale was 4.59 (median 4.67, mode 5.00) (Supplemental Table 2, Figure 1). In multivariable analysis, perceived benefit for others was only associated with higher information-seeking style ($t = 4.16$, $P = 3.8 \times 10^{-5}$). A Wilcoxon signed-rank test was conducted to compare mean scores on the 2 benefits subscales; this indicated that perceived benefit for others was significantly higher than perceived benefit for self/family (median scores 4.67 vs 4.00, respectively; $Z = 14.23$, $P = 5.75 \times 10^{-46}$).

Concerns

In factor analysis comprising all the concerns items, 2 factors emerged. The first factor was composed of the 6 items that were about data sharing and access (Cronbach alpha coefficient was 0.91). The second was composed of the single item assessing concern about psychological impact of results.

Concerns about data sharing

On the 6 individual items, 23% of participants were worried their health information might be used by insurance companies; 8% selected "strongly disagree" for all data sharing concerns, ie, they did not have any data sharing concerns; and 13% selected "disagree." Overall, the mean (SD) data sharing concern subscale score (range 1-5) was 2.38 (median 2.25, mode 2.00) (Supplemental Table 2, Figure 1). In multivariable analysis, concern about data sharing was higher among participants who self-identified as male ($t = 2.05$, $P = .041$), Asian or Asian British ($t = 2.35$, $P = .019$), and more religious ($t = 2.03$, $P = .043$); reported higher perceived severity of the rare condition in their family ($t = 2.69$, $P = 7.4 \times 10^{-3}$); and reported lower resilience ($t = -3.35$, $P = 8.6 \times 10^{-4}$). When general knowledge (KOGS) was entered into the model, there was no association between KOGS and concern about data sharing; similarly, when context-specific knowledge was entered, there was no association between context-specific knowledge and concern about data sharing.

Concern about psychological impact

Overall, 32% of participants reported feeling worried about how they would feel if they learned they had a high risk of developing a serious disease (ie, concern about the potential psychological impact). The mean (SD) psychological impact concern score (range 1-5) was 2.96 (median 3.00, mode 3.00) (Supplemental Table 2, Figure 1). In multivariable analysis, this concern was higher among participants who were younger ($t = -2.17$, $P = .003$) and had lower resilience ($t = -4.74$, $P = 3.0 \times 10^{-6}$). Using a Wilcoxon signed-rank test, we compared mean scores on the 2 concerns subscales and showed that concern about psychological impact was significantly higher than concern about data sharing/access (median scores 3.00 vs 2.25, respectively; $Z = 9.61$, $P = 7.65 \times 10^{-22}$).

General attitudes

Factor analysis revealed that all 4 of the general attitudes items loaded onto a single factor (all values over 0.7), and the Cronbach alpha coefficient was 0.87. The mean general attitudes scale score was 18.4, where score 5 was considered to be low and score 20 to be high (Supplemental Table 2).

Knowledge

Context-specific knowledge about genome sequencing in the 100kGP

The Cronbach alpha coefficient for context-specific knowledge was 0.81. The mean context-specific knowledge scale score was 22.5, where score 0 was considered to be low and score 28 to be high. In bivariate analyses, context-specific knowledge was associated with being a female ($F = 8.47$, $P = .004$), being employed ($F = 5.62$, $P = .004$), having higher educational attainment ($F = 11.40$, $P = 3.07 \times 10^{-7}$), ethnicity ($F = 3.06$, $P = .017$), having lower religiosity ($F = 9.66$, $P = 8.0 \times 10^{-5}$), having higher psychological resilience ($r = 0.13$, $P = .003$), and having higher information-seeking style ($r = 0.16$, $P = 2.1 \times 10^{-4}$). In multivariable analysis, context-specific knowledge remained significantly associated with being a female ($t = 4.20$, $P = 3.2 \times 10^{-5}$), being employed ($t = -2.07$, $P = .039$), having higher educational attainment ($t = 5.21$, $P = 2.80 \times 10^{-7}$), having lower religiosity ($t = -4.16$, $P = 3.7 \times 10^{-5}$), and having higher information-seeking style ($t = 2.68$, $P = .008$). On the individual items, 97% correctly responded "true" to the statement that "One purpose of sequencing your/your child's genome is to benefit research." Only 34% knew that the statement "Commercial organisations (such as drug companies or companies making diagnostic tests) will not be allowed access to your/your child's data" was false; people who answered this question correctly had slightly lower concerns about data sharing/access ($F = 6.06$, $P = .014$). See Figure 2 for further details.

General KOGS

The Cronbach alpha coefficient for supports early-career researchers in developing their identity as authors and reviewers was 0.60. The mean KOGS score was 5.21, where score 0 was considered to be low and score 9 to be high general understanding of genome sequencing. Examination of specific KOGS items suggested that most participants understood broadly what a genome is; eg, in response to the statement, "A person's genome is their body's 'instruction manual' containing the information needed to make them, run them and repair them," 85% correctly stated this was true. A few participants exhibited advanced genomics knowledge; eg, 30% correctly stated that the statement "A person's genome is the 1% of their DNA that makes proteins" was false. In bivariate analyses, KOGS scores were

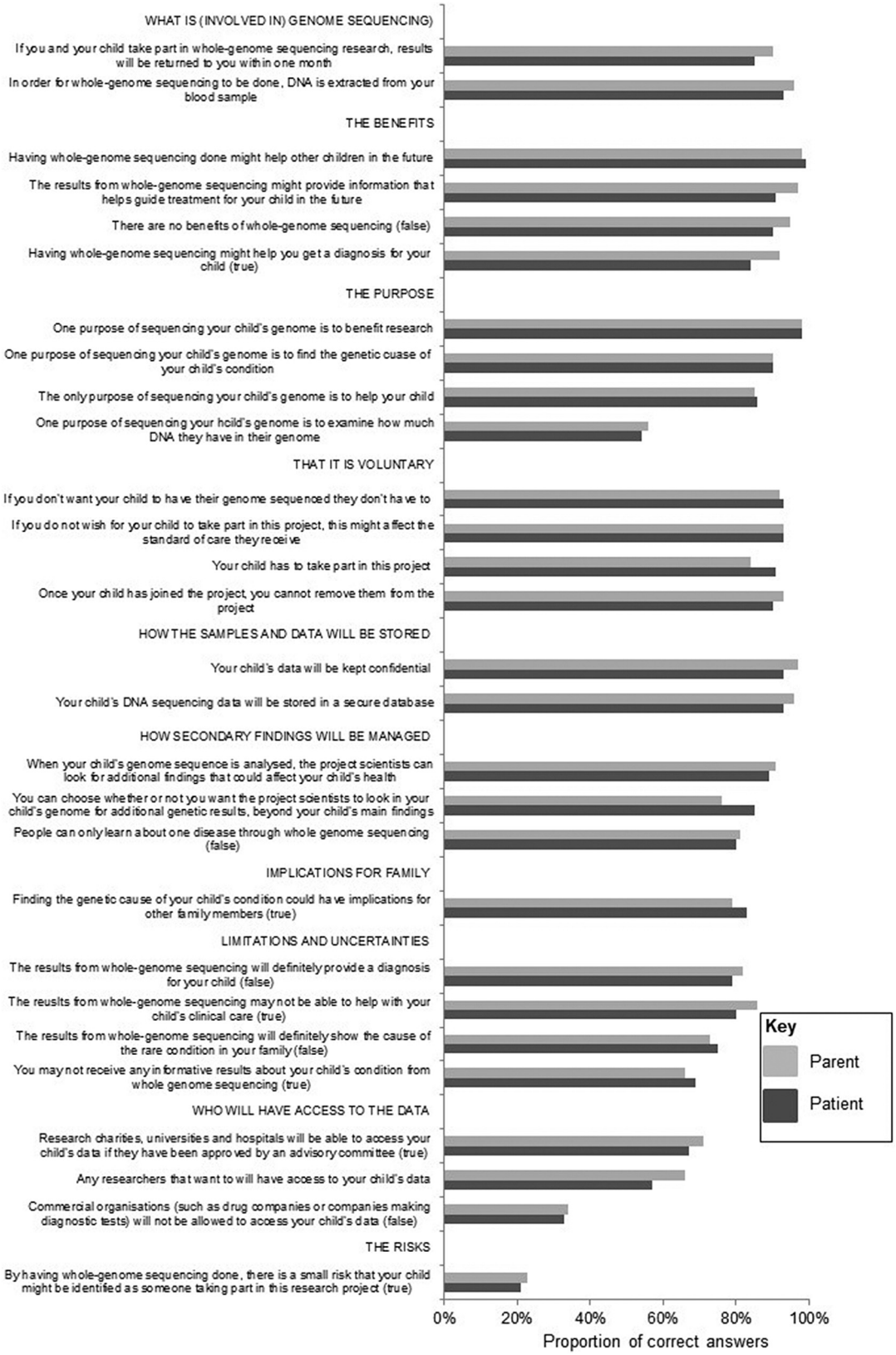

Figure 2 **Context-specific understanding of genome sequencing: individual items compared between parents and patients.**

higher among people who were female (F = 5.93, P = .015), had higher educational attainment (F = 13.40, $P = 2.03 \times 10^{-8}$), were Asian or Asian British or another ethnic group (F = 2.78, P = .026), were less religious (F = 7.64, P = .001), had higher resilience (r = 0.12, P = .008), and had higher information-seeking style (r = 0.17, $P = 9.3 \times 10^{-5}$). In multivariable analysis, KOGS scores remained significantly associated with higher educational attainment (t = 6.45, $P = 2.72 \times 10^{-10}$), lower religiosity (t = −3.81, $P = 1.59 \times 10^{-4}$), and higher information-seeking style (t = 3.38, $P = 8.0 \times 10^{-4}$).

Informed choice

Overall, 455 participants (90.3%) were categorized as having a positive attitude and 2 (0.4%) were categorized as having a negative attitude. The 47 participants (9.3%) categorized as having a neutral attitude were excluded from the informed choice calculation. When informed choice was calculated using both the general and context-specific knowledge items, scores ranged from to 32.6% (80% cutoff) to 83.8% (60% cutoff). When informed choice was calculated using only the context-specific knowledge items, scores ranged from 59.1% (80% cutoff) to 90.2% (60% cutoff) (Table 3). All participants who had made an informed choice had good knowledge and a positive attitude and had accepted genome sequencing. On the basis of this analysis, none of the participants who completed the questionnaire and who had declined genome sequencing (n = 3) had made an informed choice; they all had a positive attitude but declined genome sequencing.

100kGP decliners

Of 153 decliner records reviewed, 66 stated simply "unknown," and so our analysis of the records was based on 87 cases. Responses ranged from 4 words (eg, "too busy right now") to longer responses of up to 4 sentences. Nine major overarching categories emerged. These were "too much else going on," eg, personal life and school/university (26 cases); "process," eg, blood test and length of time for results (23 cases); "parent reluctance," eg, child has already had numerous investigations (21 cases); "lack of benefit to patient," eg, unlikely to affect medical care and do not need diagnosis (21 cases); "not interested" (17 cases); "personal data," eg, data access (5 cases), sharing data with commercial companies (4 cases), insurance (2 cases), and concerns over viruses or hacking (1 case) (12 cases in total); "practical," eg, distance and travel (10 cases); "proband declined" (6 cases); and "psychological," eg, anxious and worried (3 cases).

Discussion

This large empirical study conducted with patients, parents, and relatives undergoing genome sequencing in a clinical research context shows that the majority self-reported making an informed decision about undergoing genome sequencing. When measured objectively, rates of informed choice varied considerably depending on where the cutoff for what constitutes good knowledge was placed, and whether knowledge scores were derived from general plus context-specific knowledge or context-specific knowledge alone. This raises important questions about what it means to make an informed choice about genomic testing, and how important knowledge of the technical aspects of genome sequencing are (eg, what is a genome and what is involved in genome sequencing) when making decisions about testing. Nevertheless, given that at most knowledge cutoffs informed choice was lower when measured using the knowledge and attitude scale than when self-reported, this finding potentially suggests a mismatch between participants believing they are informed and what might be judged objectively as an informed decision in the context of genomic testing.

Genome sequencing, with the potential to identify additional findings as well as variants of uncertain significance, is by its very nature complex. A recent study by Vears et al[27] highlighted the tension that exists for health professionals between providing sufficient information but potentially overwhelming patients and providing less information and risking uninformed decision-making. It is questionable whether patients making a decision about genome sequencing for diagnostic purposes require an understanding of the technical aspects of genome sequencing. In fact, when we removed the general knowledge questions from the measure, between 59% and 90% were judged to have made an informed choice. At the very least, patients should understand that they might not get a diagnostic result, that they might receive an uncertain result, that they might receive an additional finding unrelated to the original reason for testing (if this is offered), the timeframes for receiving results, how their data will be used, how their data will be stored and protected, and that the results may have implications for other family members. Face-to-face or other types of pretest counseling should also be accompanied by supportive materials such as written or online information to enhance the decision-making process and provide the opportunity for a more detailed understanding for those that want it.[28]

A very low proportion of participants were found to have decisional conflict, and we found that overall, the perceived benefits of genome sequencing outweighed concerns. These results provide some tentative evidence for the effectiveness of the consent procedures for genome sequencing in the rare disease cohort arm of the 100kGP, which included one-to-one consent appointments, participant information sheets, and requirement to sign consent forms. However, it is important to note that our study and others have highlighted misunderstandings around topics such as additional findings and data sharing.[10,11] Largely positive attitudes toward genome sequencing in the 100kGP may also be partly attributed to trust in the health professional consenting them and/or the project itself.[11]

We found that participants were motivated as much, if not more, by a desire to help others via contributing to research than to obtain a diagnosis for their own families and that participants' perceived benefits of genome sequencing outweighed their concerns. These findings were consistent with previous smaller scale qualitative studies.[6,8,9] Although the themes of concern about emotional impact and concerns about data sharing/access have been raised previously,[6,7] our survey study adds to this by demonstrating that participants were measurably more concerned about the potential psychological impact of genomic findings than about data sharing or data access. However, although this may reflect the nature of the consent conversations, because only 34% of respondents answered the question about data access correctly, we need to interpret this with caution.

We found that there were important differences between sociodemographic groups that could have implications for clinical implementation of genome sequencing in the United Kingdom and elsewhere. For example, concerns about data sharing and access were higher among participants who self-identified as being male, Asian or Asian British, and/or more religious. In addition, we found that participants who were younger and reported lower psychological resilience had greater worry about how they would feel if they learned that they had a high risk of developing a serious disease. These findings need to be considered when designing genomic medicine services and communication materials for different patient groups going forward. Our study adds significantly to the existing literature on this topic, most of which has been much smaller qualitative interview single-site studies.

Strengths and limitations

Our sample was broadly representative of the total rare disease cohort in the 100kGP; 45.4% of our participants were probands (compared with 46.8% of participants in the 100kGP), 61.1% were female (compared with 52.3%), 84.1% self-reported White ethnicity (compared with 67.4%), and 7.3% self-reported Asian ethnicity (compared with 9.3%) (data taken from Genomics England research embassy; December 03, 2019). A strength of this study is that we developed a rigorous new measure of knowledge (the KOGS) as part of this work, which has been used as part of a formal assessment of informed choice. Arguably, a weakness is that we did not do the same for the context-specific knowledge or attitude measures. However, all of these new items and scales should still be useful for other researchers to use and build on. We do not have any data on participants who declined to respond to the survey and so are unclear whether those that did respond are truly representative of the overall sample. Participants in the 100kGP who declined to take part in the survey may have lower levels of informed decision-making than those that did respond, as might those who declined to take part in the 100kGP itself. Obtaining insights from decliners is notoriously difficult in health research. However, ideally, future studies would measure informed choice among individuals from all these groups, potentially using a reduced set of questions from the measure to compare across groups. When offered in a purely clinical context with more rapid turnaround for results, some of the reasons given for declining, eg, the long wait for results, may no longer be relevant. Non-English speakers were excluded from the study and our response rate was only 51.7%; this may limit the generalizability of the study findings. Finally, our attitude question focusing on concerns around the psychological impact was intended to assess attitudes around additional findings (not main findings). However, we acknowledge that this was not made explicit. Future use of this question should clarify this.

In summary, after a detailed consent appointment, individuals undergoing genome sequencing felt that they were generally well informed, wanted to receive additional findings results, and did not have significant concerns about data security or participating in research, which they largely saw as a potential benefit to others. Nevertheless, rates of informed choice were lower when measured using the knowledge and attitudes scales developed for this study, and we are unable to comment on levels of informed choice among those participants who declined to take part in this survey study. Our findings act as a catalyst for further exploration of the nature and requirements of consent in the context of genome sequencing that is informed by professionals, patients, and researchers.

Here, we have developed new measures of genome sequencing knowledge and attitudes that may be valuable to other researchers and health care practitioners. Researchers using these measures in the future will need to consider whether to use the context-specific knowledge questions and/or general knowledge questions, and this will likely depend on their particular research question and research context. Future research to examine informed decision-making with patients offered genome sequencing in the NHS Genomic Medicine Service would be of value to ensure that the consent process is working effectively. Future research might also valuably explore the impact of family dynamics on responses to the offer of genome sequencing. Finally, further research to explore the clinical, psychological, behavioral, and social outcomes from getting a negative, diagnostic, or inconclusive result from genome sequencing is also required.

Data Availability

The de-identified data set is available on request to the corresponding author.

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Ethics Declaration

This study was reviewed by National Health Service Research Ethics Committee West Midlands, 15/WM/0258. All participants received a Participant Information Sheet alongside the questionnaire, and returning a completed survey was taken as implied consent to participate.

Conflict of Interest

Christine Patch has been on a secondment with Genomics England as Clinical Lead for Genetic Counselling since October 2016. Meriel McEntagart has been seconded to Genomics England 1 day a week since September 2019. All other authors declare no conflicts of interest.

Additional Information

The online version of this article (https://doi.org/10.1016/j.gim.2021.08.010) contains supplementary material, which is available to authorized users.

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