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Evaluating the return of additional findings from the 100,000 Genomes Project: A mixed methods study exploring participant experiences of receiving secondary findings from genomic sequencing

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Abstract

Purpose: 100,000 Genomes Project participants could consent to receive additional findings (AFs) for variants associated with susceptibility to cancer and familial hypercholesterolemia (FH). Here we evaluate stakeholder experiences to inform clinical practice.

Methods: Mixed-methods study conducted at 18 sites across England that comprised a cross-sectional survey and interviews with participants who received a positive AF (PAF), and interviews with participants who had no AFs (NAF).

Results: There were 146 surveys followed by 35 interviews with PAF participants, and 29 interviews with NAF participants. Surveys found that PAF results were seen as useful and would influence health management (82%). Most (90%) had shared their result with family members. Experiences differed by PAF type; cancer PAF participants were often initially shocked and anxious, and found telling family members challenging compared to participants with an FH PAF. Whilst most experiences of NAF results were positive, some misunderstandings were identified. Participants supported returning AFs when offering genome sequencing.

Conclusion: Patient experiences of receiving AFs were primarily positive and there is support for offering AFs routinely. Considerations for offering AFs in clinical practice include adapting approaches tailored to individual conditions and greater support for people with a NAF result.

Keywords

Genome sequencing, additional findings, secondary findings, experiences, psychosocial

Introduction

The use of genome sequencing (GS) continues to expand in both research and clinical settings, affording patients with rare disease and cancer the opportunity to find a diagnosis for their condition. GS also has the potential to identify variants associated with an increased risk of conditions unrelated to the initial reason for GS. If the variant is actively looked for, these findings are referred to as "secondary" or "additional" findings. It has been estimated that ~1-2% of people in the general population will have a secondary finding.[1-4] Identifying and disclosing secondary findings allows the recipient to seek advice and follow guidance to reduce the risks associated with the condition and share the information with family members. Recent reviews of patient experiences of receiving secondary findings indicate that patients value the information and there was no evidence of negative psychological impacts.[5, 6] There are, however, gaps in our understanding, for example few studies have looked at the process or impact of returning a no findings result,[7-9] despite no findings making up the vast majority of results returned. Moreover, the reported approaches for returning secondary findings results vary widely[6] and further research is required to guide best practice.

In England, GS is offered in clinical practice through the National Health Service (NHS) Genomic Medicine Service,[10] but secondary findings are not routinely offered alongside GS. The NHS Genomic Medicine Service was partly informed by the 100,000 Genomes Project (100kGP), a hybrid research and clinical project offering GS to patients and their relatives with cancer or rare disease. Potential participants were identified by NHS clinical care teams and consent was obtained by professionals from a range of backgrounds, including genetic counsellors and research nurses, following 100kGP consent training.[11] Between 2015 and

2018, around 85,000 adults and children were consented to receive main findings relating to their cancer or rare disease. More than 90% also consented to receive clinically actionable secondary findings, referred to as additional findings (AFs) for the 100kGP. The same AFs were offered to every participant in the 100kGP, regardless of their reason for joining the study. AFs for adults were 13 genes associated with an increased risk of some cancers (*MLH1, MSH2, MSH6, MUTYH, APC, BRCA1, BRCA2, VHL, MEN1, RET*) or familial hypercholesterolaemia (FH) (*LDLR, APOB, PCSK9*).[12] AFs for children (*MUTYH, APC, VHL, MEN1, RET, LDLR, APOB, PCSK9*) excluded genes for adult onset conditions. These AFs have screening, management, and treatment options to enable proactive personalised healthcare for the associated condition.

Between August 2021 and March 2022, more than 700 positive AF (PAF) and 80,000 no AF (NAF) results were returned across England through NHS clinical pathways. Previous research considering the return of AFs from the 100kGP has focused on patients with a PAF from one region in England.[13, 14] Here we describe a mixed-methods study exploring the short-term experiences of patients across England who received either a PAF or NAF result. This research is part of a broader study examining the clinical, behavioural, psychological, and economic impacts of returning AFs to 100kGP participants. Longer term impacts on participants, experiences of health professionals[15] and costs[16] are reported separately.

Methods

Design

A convergent mixed methods design with data collection conducted in parallel[17, 18] was used to allow the researchers to develop a comprehensive understanding of participant

experiences of receiving an AF result from the 100kGP. Our study comprised a cross-sectional survey followed by qualitative interviews with participants who received a PAF and interviews only with participants who received an NAF. The quantitative survey data and the two qualitative interview data sets were each analysed separately prior to being merged for analysis and comparison.[17, 18] Ethical approval was obtained from the NHS Research Ethics Committee West Midlands (15/WM/0258).

Setting

The setting is the return of AFs from the 100kGP through NHS clinical care pathways. The return of AFs was undertaken separately from main findings as a unified national process. Guidance and template letters were shared, but local teams could make adaptations to care pathways.[19] During our study period, AF results were released by Genomics England to regional coordinators in five batches several weeks apart. Patients with a PAF result were initially contacted by phone or letter and then had a clinical appointment within a suggested timeframe of six weeks. Cancer PAFs were returned through genetic services or, occasionally, by oncology services. FH PAFs were returned through lipid clinics or genetic services. Ongoing care followed standard NHS pathways, including recommendations for risk management and cascade testing. All NAF results were shared by letter.

Participants and Recruitment

100kGP participants who had received an AF, were over 18 years old and, for the survey only, could read and understand English were eligible for the study. At 18 NHS hospitals across England, 100kGP participants with a PAF result were invited to take part following their clinical appointment, with no restrictions on the length of time after their appointment. They

were given a paper survey, a pre-paid envelope and a link to the online survey (hosted on RedCap) after their clinical appointment or via mail. All survey participants from 14 hospitals who indicated they were willing to be interviewed were invited for interviews via post. Survey respondents from the remaining four hospitals were not invited for interviews due to overlap with another interview study.[14] At five hospitals, 100kGP participants with an NAF result were invited to take part in an interview via post. Potential participants were selected to include a range of ages, ethnic backgrounds and genders. If there was no response to study invitations after two weeks, a reminder phone call was made. All participating hospitals completed a recruitment log to enable response rate calculations. Participants were sent a gift voucher: £15 for surveys and £10 for interviews.

Data collection

Quantitative: Survey development and the final surveys are included in the Supplementary Materials. Survey questions assessed: 1) experience of receiving AF results; 2) communication of AF results with others; 3) potential impact, perceived value and understanding of results; 4) decisional regret; 5) psychological impact and adaptation to receiving AF results; 6) impact on healthcare, lifestyle and behaviour; 7) financial costs and 8) demographics. There were two versions of the survey, with section 3 and 6 modified to be relevant for PAF type (cancer or FH). Findings from 1-5 and 8 are described here and findings from 6-7 will be reported separately as the focus here is patient experiences of receiving results.

Items seeking information about the experience of receiving AFs results (1) were informed by the national guidance for returning AFs.[19] Items assessing communication of results (2) were adapted from Charles et al., (2006).[20] Items assessing perceived value and understanding or

results (3) were adapted from Zoltick et al., (2009).[21] Decisional regret (DR) (4) was measured using the Decisional Regret Scale (DRS).[22] DRS scores range from 0 (no regret) to 100 (high regret). For this sample, Cronbach's alpha revealed good internal consistency (α=0.89). Psychological impact (5) was measured using an adapted version of the Multidimensional Impact of Cancer Risk Assessment (MICRA).[23] Twenty-three items were taken from the original 25-item MICRA and comprise three subscales: Distress, Uncertainty, and Positive Experiences. Scores range from 0 (no impact) to 95 (high impact). Cronbach's alpha revealed good internal consistency across the whole scale (α=0.88) and for both the Distress (α=0.84) and Uncertainty subscale (α=0.84). Internal consistency was poor for the Positive Experiences subscale (α=0.58).

Qualitative: The semi-structured interview topic guides were developed by qualitative researchers (MP, MH, BSS, JG) with input from a clinical expert in genomics (LSC). Topic guides were informed by national guidance on returning AFs,[19] survey content and existing literature, including previous qualitative studies exploring experiences of the 100kGP.[24, 25] Final versions are included in the Supplementary Materials. Topic guides included: motivations, decision-making, experience of receiving results, and understanding and impact of results and family communication. Interviews were conducted by four researchers (BSS, JG, MD, MP) by telephone and videocall. Interviews were audio recorded, professionally transcribed verbatim and de-identified prior to analysis. Recruitment continued for the PAF cohort until all eligible survey participants had been invited. For the NAF cohort, recruitment ceased when sufficient data was available to address the research questions and no new codes or patterns were being identified.

Data analysis

Quantitative: Descriptive statistics using frequencies and percentages were reported. Where relevant, comparative analyses were conducted to identify relationships between outcome variables and demographic variables (Education and Age) and between outcome variables and PAF type (cancer or FH). Chi-squared tests of independence, Fisher's exact test, and two-proportion *z*-tests were used to assess differences between categorical variables. Independent *t*-tests were used to compare continuous data. $p \leq 0.05$ was considered statistically significant. DRS scores were classified into three categories as previously described,[26] where 0 = no regret; 5-25 = mild regret; and ≥ 30 = high regret. For MICRA scores (residuals were approximately normally distributed), multiple regression with bootstrapped simulations (R=1000) was performed and 95% confidence intervals and *p* values for model estimates were obtained. All analyses were conducted using R 4.0.2.[27]

Qualitative: A team-based codebook approach to thematic analysis was used.[28, 29] Separate codebooks were developed for the PAF and NAF interview data sets. Whilst a "deductive-leading" approach was used for codebook development, the researchers remained open to the inclusion of inductive codes.[30, 31] Draft codebooks were informed by the aims of the study, the topic guides and survey content (deductive codes). The draft codebooks were revised by three researchers (BSS, MD, MH) who each read and independently coded the same three-four transcripts and added additional codes (inductive codes). The revised codebooks were discussed and agreed. Each transcript was then coded by one researcher (PAF: AGA, BL, MD, BSS / NAF: MD, BSS). When coding was complete, three researchers (BSS, MD, MH) synthesised the codes into potential themes that were reviewed and revised during

the process of integrating the qualitative and quantitative data.[17, 31] NVivo 13 (QSR International, Australia) was used to facilitate coding and analysis.

Co-authors include clinicians and clinical scientists involved in the returning AFs from the 100kGP. The researchers undertaking data collection and analysis were female with previous experience in genomics research (MP, MH, BSS, JG, MD, BL, AGA). Two are genetic counsellors (BSS, JG) and two are genomics associates (BL, AGA). All recognise and have reflected on the impact of their personal and professional experiences on data interpretation. The guiding epistemological framework for the study was pragmatism.[32]

Integration: A narrative integration of the data was conducted by weaving the quantitative and qualitative findings together on a concept-by-concept basis.[17] Data integration was undertaken by four researchers (MH, MP, BSS and MD) who developed the narrative with consideration for any areas of convergence or divergence between the different data sets. The findings were then shared with the wider team for feedback and discussion.

Results

Between November 2021 and May 2023 survey invitations were shared with 322 100kGP participants with a PAF (cancer PAF: 199, FH PAF: 123). Of 147 completed surveys (46% response rate), 92 (63%) had a cancer PAF and 55 (37%) had an FH PAF. Of 67 survey respondents invited to participate in an interview, 35 agreed (response rate 52%): 24 (69%) had a cancer PAF and 11 (31%) had an FH PAF. Interviews were conducted between February 2022 and April 2023 and lasted between 18 and 88 minutes (median=34 minutes). Of 139 100kGP participants with an NAF result invited to participate, 29 agreed (response rate 21%).

Interviews were conducted between December 2021 and December 2022 and lasted between 14 and 57 minutes (median=25 minutes). One interview was conducted via an interpreter.

Participant characteristics

Participant characteristics are presented in Table 1. For survey participants, only age differed significantly by PAF type: respondents with an FH PAF were older ($t(104.93)=-2.20$, $p=0.03$). Clinical appointment dates were available for 116 survey participants and 30 interview participants. The median time between appointment and survey completion was 3 months (range 0 – 16 months); 80% completed the survey within six months. The median time between appointment and interview completion was 6 months (range 2 – 14 months). Dates that NAF results letters were sent were not available.

Motivations

For both PAF and NAF interview participants, the most commonly cited motivations for choosing to receive AFs were: wanting to find out actionable information about their own health because *"the more information the better"* and *"knowledge is power"*, wanting to help with research, and hoping for an explanation of their family history of cancer or heart disease (Table 2: Q1). Several also noted that being offered AFs as part of the 100kGP was a *"fantastic opportunity"* or a *"privilege"* they wanted to take advantage of.

Experiences of receiving PAF results

Most survey respondents reported being notified about their PAF result by either letter (*n*=92; 64%) or phone call (*n*=36; 25%) (Table 3). Around half (n=67; 47%) reported that the

condition was named in the notification. This occurred more frequently for FH PAFs than cancer PAFs ($p<0.001$). When surveyed about their appointment, most agreed / strongly agreed that the explanation of their result was clear ($n=130$; 96%), the language used was easy to understand ($n=129$; 96%), and the clinician explained what would happen next ($n=127$; 95%) (Supplemental Table 1). Most felt the clinician had lessened their worries ($n=107$; 82%); this differed according to age, with older respondents more likely to report that their worries had been alleviated ($p=.016$). Some survey participants reported that the clinician had increased their anxiety ($n=21$; 16%), most had a cancer PAF (19/21).

Interview participants reported that their PAF notification had come *"out of the blue"* and could not recall the details of the consent conversation. Almost all (33/35) reported they had not been told the condition name in the notification and described waiting for the appointment as a time of *"worry"* or *"anxiety and concern"*. Some participants could call and speak to a clinician, others recalled having their appointment booked between one and four weeks after the notification. Two participants, both with a cancer PAF, reported being told the condition before their clinical appointment. Both spoke to a clinician within a few days and felt knowing the condition made it helpful to *"prepare"* for the appointment. One participant further described being grateful for a short wait for the appointment after learning the condition (Table 2: Q2). Four interview participants reported that family members received their notifications at different times which led to anxious waiting for one participant (Table 2: Q3).

Many interview participants with a cancer PAF (16/24), reported feeling *"shocked"* or *"overwhelmed"* when the PAF result was disclosed, especially when there was no family history of cancer.

"I thought I was going to get a positive DNA thing that I was going to carry the heart condition gene that my dad had. That's what I had in my mind. I had no idea that it was going to be anything else… I was in so much shock. I literally just cried." (P_044, female cancer PAF)

Other participants with a cancer PAF (6/24) noted that the result was *"certainly not a surprise"* given their personal or family history of cancer.

In contrast, no interview participants with FH PAFs described feeling distressed upon learning their result. Most (9/11) reported that the FH result was not a surprise as they or a family member had high cholesterol or had previously received an FH diagnosis via another pathway. For the two participants where the FH finding was wholly unexpected, the result was described as a *"surprise" or "shock",* but not distressing as the condition was perceived as manageable.

"I suppose it did shock me a little bit but not massively… It's more of a get-up and go sort of feeling rather than being upset about it." (P_042, female, FH PAF)

Four participants noted feeling *"relieved"* that it was FH and not a cancer PAF that had been picked up.

Regardless of PAF type, interview participants were generally positive about their clinical appointment, with content described as *"clear"* and *"comprehensive"*. Several participants with a cancer PAF described finding it difficult to take in the information when first told their result.

"I think my brain stopped after the BRCA2 bit." (P_033, female, cancer PAF)

Accordingly, follow-up appointments were valued to allow time to regroup and *"do a little bit of research and then come armed with what my questions are*" (P_041, female, cancer PAF).

Experiences of receiving NAF results

Like those who received a PAF, NAF participants also reported that the letter describing their result was unexpected and that they had forgotten the details of consenting as *"it was years ago"* (N_06, male, NAF). Most (21/29) felt the letter communicated their results effectively. Some did, however, comment that the letter was *"too long"* or that they were confused by the information. For example, one participant was uncertain whether the result was *"good news or not good news"* (N_09, female, NAF) and one participant was initially unsure if the letter related to them or their child who had a rare condition, noting "*I thought everything is all regarding my son's condition, but now I know that there are findings about myself*" (N_05, male, NAF). Whilst some participants demonstrated good understanding of their NAF results (Table 2: Q4), there were also misunderstandings about how AFs differed from main findings, what conditions were included, and the limitations of the results. For example, one participant was unsure of the scope of the test, noting *"rightly or wrongly I sort of assumed that anything big genetically, I haven't got"* (N_04, female, NAF). Several participants said that

in addition to the letter, they wanted to speak to a clinician who could explain the result in more detail and answer questions (Table 2: Q5).

Potential impact, perceived value and understanding of results

Survey respondents were asked to rate out of ten how useful their AF results were to them. The mean rating across all respondents (*n*=144) was 8.84 (*SD*=1.92, range=0-10, median=10) for utility of results now, and 8.97 (*n*=143; *SD*=1.77, range=0-10, median=10) for utility of results in the future (Supplemental Table 2). Three quarters of respondents (cancer PAF: *n*=67; 74%, FH PAF: *n*=40; 75%) reported that their healthcare provider had made suggestions to lower their risks. The majority (cancer PAF: *n*=75; 85%, FH PAF: *n*=46; 94%) stated they would follow these recommendations (Supplemental Table 3). Most respondents were confident they understood their results (*n*=135; 92%) and most stated that they could explain the meaning of their result to others (*n*=127; 88%). No differences in understanding across AF type were observed, and there were no associations between understanding and education or age.

When asked whether their result would influence their health management, 87% (*n*=123) agreed / strongly agreed that it would and 80% (*n*=113) stated that their PAF result helped them to get a better perspective on their health. Fewer people felt that knowing their AF would reduce their chances of getting sick (*n*=95; 67%). No differences were observed across PAF type (Supplemental Table 4).

Interview participants with a cancer PAF valued their result and risk reducing options such as earlier and more frequent monitoring, preventative surgery and/or lifestyle changes. Initial

decisions about next steps varied, influenced by the type of cancer, risk perception, family history of the condition, family responsibilities or having a child with a rare condition.

"With the breasts, obviously surgery and you can have annual mammograms… I feel that it's all or nothing. For me, even though I have a choice, I don't feel I have a choice because I have a family and I have [adult child with rare condition] to consider and look after." (P_039, female, cancer PAF)

Participants with FH PAFs also valued their result and reported being willing to take steps to reduce risks, with referrals to specialists, changes in medication, more frequent monitoring and alterations to diet and exercise highlighted.

"It's been good for me, it's been really positive… the call I had with the nurse was really helpful… she felt [my treatment plan] would benefit from a consultant's view so that is really good." (P_102, female FH PAF)

Whilst participants with an NAF felt their result would have little impact on their health management, most valued having the information for themselves and other family members.

"I'm definitely pleased that I did it. It gave me that peace of mind and also, I think being able to communicate that to my siblings was helpful as well." (N_16, female, NAF)

Decisional regret (DR)

Across all survey participants (*n*=139) overall DR was low. The mean DR score was 13.2 (*SD*=19.29, range=0-100) and the median score was 5 (IQ1=0, IQ3=20). No differences across PAF type were observed (*p*=.068). Viewing the data in discrete categories showed that some people (*n*=24; 17%) had high levels of regret (Figure 1). Chi-squared tests revealed no association between DR and PAF type [χ^2 (2)=2.34, *p*=.311].

None of the interview participants who scored as having high DR (cancer: *n*=4, FH: *n*=1) or mild DR (cancer: *n*=6, FH *n*=7) expressed ongoing regret. The median time between survey and interviews for these participants was 3 months (range 2-10 months).

"*When I first found out I regretted it massively. Massively. But thinking about it from like a sensible point of view and obviously, it could save my life, and also maybe possibly my family. So, I think no I don't regret it now, but my first thought I did.*" (P_002, female, cancer PAF)

No participants with an NAF result expressed regret in their interviews.

Emotional impact and adaptation

Interview participants with a PAF described a range of emotional trajectories. Participants with an FH PAF generally saw their AF as "*a positive*" from the point of first learning their result: *"the finding is helpful. It's giving you the opportunity to make changes to your life now to protect your future"* (P_042, female FH PAF). One participant felt "*lucky*" to have the information as her cholesterol had been low and FH *"wouldn't have been picked up if it hadn't have been for this study"* (P_020, female, FH PAF).

Many participants with a cancer PAF described being initially *"scared"* or *"stunned"* and highlighted that the information often took *time to "sink in"*.

"I just felt like a ticking time bomb… the 'what if' was very daunting for me. Very frightening, especially because my kids are young… it's definitely been an emotional few months for me. I think I've got my head around it a lot better now than I did." (P_070, female, cancer PAF)

Implications for family members could impact responses. Participants with a cancer PAF were sometimes concerned that the condition had been passed on, which added to worries about their own health (Table 2: Q6). Three male participants with a cancer PAF of *BRCA1* felt *"shock"* at the result; their main concerns were not for themselves, but for female relatives (Table 2: Q7).

Over time, as interview participants with a cancer PAF *"adjusted"* or *"learned to live with it"* many described feeling *"grateful"* or *"lucky"* (Table 2: Q8). Taking steps to reduce risks and feeling supported by their clinical team helped participants with a cancer PAF feel more in control. For example, one participant noted, *"I didn't know what to do next or who to speak to, I think was my biggest stress... Yeah I am more in control now. I feel, I have a plan"* (P_076 female, cancer PAF). Delays in actively taking next steps, such as long waiting times for specialist appointments, screening or surgery could, however, prolong anxiety.

The emotional impact of receiving an NAF result was commonly described as providing "*a sense of relief*". Negative emotional impacts were rare, although some were disappointed that the AF result did not explain their original health issues.

"I will always be disappointed until I know what's wrong with me" N_26, female, NAF

Psychological impact of receiving a PAF result

In the survey, the MICRA was used to assess psychological impacts of receiving results (Table 4). Across all participants (n=147), the mean score (collapsed across subscales) was 28.54 (SD=17.68, range=0-79) and the median was 24 (IQ1=15.5, IQ3=39.5), indicating mild negative psychological impact. To examine differences by PAF type, a multiple regression was performed for the overall scale and each of the subscales. Scale score was included as the outcome variable and PAF type (cancer or FH) as the independent variable. Overall MICRA scores were higher for those with a cancer PAF (β=3.28, [0.54, 5.88], SE=1.36, p=.016). Those with a cancer PAF also reported higher levels of distress (β=2.03, [0.77, 3.23], SE=0.63, p<.001). Uncertainty, however, did not differ between those with a cancer PAF and an FH PAF (β=1.43, [-0.19, 3.02], SE=0.82, p=.081), nor did positive experiences (β=0.02, [-0.75, 0.84], SE=0.41, p=.955).

Sharing AF results with others

Most survey respondents had shared their result with family (cancer PAF: n=90 (98%), FH PAF: n=53 (96%) (Supplemental File - Figure 1). All interview participants with a PAF had shared their results with some family members, often with support from clinical teams who provided a letter to share with family. Around half of interview participants with a cancer PAF (13/24) did not raise any issues with sharing findings or described conversations that went well (Table 2: Q9). Others with a cancer PAF initially *"struggled"* with sharing their result because of the implications for their family and feelings of *"guilt"* for passing on the

condition or because they were upset themselves and uncertain how others would respond (Table 2: Q10). Sharing results with family prompted others to be tested and some participants described a worrying wait to find out family members' test results.

"So, it is a worrying time, and you have to tell relatives and then obviously they tell their relatives and they're still waiting to find out if they've actually got the gene." (P_017, female, cancer PAF)

Participants with an FH PAF generally reported that sharing results had been straightforward, particularly when high cholesterol was common in the family (Table 2: Q11). Many NAF interview participants viewed the information as good news to share with family, for example one participant noted, *"I immediately shared it with my family 'cause … my sister has a daughter. So, yeah, everyone was relieved"* (N_21, female NAF). Others chose not to share their results as they did not feel it impacted their own or their family's health. For example, one participant commented that there was *"no information, so there's not really anything to share."* (N_23, male NAF)

Views on offering AFs routinely

All interviewees (PAF and NAF participants) supported offering AFs routinely, holding the view that people were *"better off knowing"* and that the *"positives outweigh the negatives"*. Positive views were linked to conditions being medically actionable with opportunities for early intervention.

"It could prevent a heart attack; it could prevent a stroke… Definitely, it's got to be beneficial to the patient, the family but also to the NHS as well." (P_042, female FH PAF)

Concerns were primarily linked to the potential to cause anxiety and the importance of only offering actionable AFs; *"if you can't do anything about it, it could just cause worry without any benefit"* (P_102, female FH PAF). Several participants also emphasised that offering AFs should be a choice as some people will not want to know. The importance of clear communication and appropriate support was described (Table 2: Q12).

Discussion

An exploration of patient experiences receiving both PAFs and NAFs from the 100kGP is extremely timely as access to GS is rapidly expanding worldwide and a growing number of patients and research participants could be offered AFs. Participants largely valued the information their AF result afforded. Those with an NAF were relieved and reassured, while those with a PAF were grateful for the opportunity to be proactive with their health and reported that they would follow healthcare and lifestyle recommendations. In addition, for participants with a PAF, decisional regret was low overall and MICRA scores indicated few negative psychosocial impacts. Participants supported offering AFs routinely if conditions were medically actionable and testing was optional. Overall, these findings align with recent reviews showing that patients who receive PAFs value receiving these results with no evidence of negative psychological impacts.[5, 6] It is important to note, however, that participants reported that the results came "out of the blue" and many with a cancer PAF reported initial overwhelm or distress, and took time to adjust to their result.

Participants with an NAF had initial misunderstandings about their result, including what conditions had been ruled out and how the result related to their original indication for GS. Previous research considering the experiences of patients who receive an NAF result is limited, however, research from the US[7-9] is consistent with our findings. For example, misunderstandings were also seen by Sapp et al.,[7] who reported a "surprising degree of confusion" regarding the distinction between main findings and AFs. Our findings support suggestions that additional information and support strategies are needed for patients receiving NAF results to reduce misunderstandings.[8] Support could include a website with additional information or a contact point for questions, as highlighted by our participants.

Participant experiences of PAF results could differ depending on the type of PAF (cancer or FH), whether there was a relevant family history or family circumstances, such as having a child with a rare condition. For example, we found that participants with cancer PAFs were more likely to be distressed, took more time to adjust to their results and found them harder to share with family than those with FH PAFs. The potential for differing responses to cancer and cardiac AFs has been raised in previous research.[33] Participants from the general public in Finland who reviewed hypothetical vignettes perceived cancer PAFs as more threatening than cardiac AFs.[33] Further, in a qualitative study with 100kGP participants with a PAF, younger women with a cancer PAF of *BRCA* in particular found it difficult to make sense of their disease risk and decide on next steps.[14] Overall, these findings highlight that individualised support following results disclosure is crucial.[5, 14, 34, 35] This may be facilitated by condition specific pathways and support structures when returning PAFs.

Notably, almost a quarter of survey participants (22%) with a PAF reported that their healthcare provider had not made any recommendations to lower the risk associated with their PAF. In addition, one third reported that their PAF would not help to reduce their chances of getting sick. This may be because they didn't recall the suggestions made to reduce risks, the symptoms associated with the condition were already being managed or that the clinician had felt that the person did not currently require clinical or lifestyle changes to lower their risk. Further research is needed to explore how participants interpret their PAF results and ensure that they understand the steps needed to reduce their risks.

The time period of several years between consent and return of AF results meant that participants had limited recall of consent and that results largely came "out of the blue". These experiences align with what has been described as "genome first" care where research participants are only referred to clinical services after GS results are available.[36, 37] The value of timely and efficient access to clinical services to manage participant distress and promote adaptation to results in genome-first care has been highlighted.[5, 35] In the 100kGP PAF results disclosure and support for next steps was delivered by NHS clinical care teams trained to share and manage genomic results in both genetics services and lipid clinics. Participants with a PAF had professional support to understand the implications of their findings, to put treatment and management plans in place and to share findings with family members. Future research should consider approaches to consent and ongoing contact to redress issues resulting from lengthy gaps between consent and results. Given the anxiety associated with waiting for a clinical appointment after the initial notification of a PAF result, future studies should explore the most appropriate approach for notifying participants and minimising waiting times, with consideration for the type of condition.

Limitations

Limitations of our study include enrolment of self-selected participants, who may have been more interested in genetic information or hold strong views on the topic of AFs, and the response rate, which was around 50% for surveys and interviews. A further limitation is that not all survey participants were eligible for interviews as we did not contact survey participants from one region of England due to their possible involvement in another interview study. Consequently, we were less likely to be able to capture in our interviews the full range of experiences of receiving a PAF reported in the survey. Our sample primarily included people who identified as white, female and as having a degree or higher education which does not reflect the wider population. In addition, non-English speakers were excluded from the survey. The time between receiving AF results and completing a survey or interview varied between participants and may have influenced responses. In this study the experiences of participants who received a NAF were assessed through qualitative interviews only, future research should consider using a survey to understand experiences from a broader cross-section of people.

Conclusion

Patient experiences when receiving AFs from the 100kGP provide valuable evidence for offering AFs in both research and clinical settings. By incorporating patient perspectives into the design and implementation of future pathways, we can promote patient autonomy, emotional well-being, and enable proactive and personalised healthcare. The vast majority of people offered AFs will have a NAF, and more research is needed to develop and evaluate approaches with clear information materials and options to resolve queries. In turn, patients

receiving unexpected PAFs will benefit from timely access to tailored support from experienced clinical care teams. Going forward it will be important to look at the longer-term impacts for patients receiving PAFs, therefore we are now conducting surveys and interviews with participants 12-months after receiving their AF results.

Data Availability

The data that support the findings of this study are available from the corresponding author (MH) upon request and where participant consent has been given.

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Conceptualization: LSC, MH, SM; Data curation: MP, BSS, MD, RB, LG, JG; Formal analysis: MP, BSS, MD, BL, AG-A, MH; Funding acquisition: LSC, MH, SM; Investigation: MP, BSS, MD, MH, LSC; Methodology: MH, MP, BSS, JG, MD, SM, ES, SHE, LSC; Project administration: MD, BSS, LG, BG, BP, MH; Resources: XB-M, MB, LB, PB, RC, VC, PC, BDS, LD, AG, EG, RH, LH, SEH, AJ, EAJ, AK, DH, MM, SS, AT, VT; Writing-original draft: MP, BSS, MD, MH; Writing-review and editing: MP, BSS, MD, MH, LSC, ES, BL, AG-A, BP, LG, RB, MB, LB, PB, RC, VC, PC, BDS, LD, AG, EG, LH, SEH, EAJ, AK, DH, MM, SS, AT, VT.

Ethics Declaration

Ethical approval was obtained from the NHS Research Ethics Committee West Midlands (15/WM/0258). Participants provided informed consent.

Conflict of interest

The authors declare no conflicts of interest.

Supplemental Files

Supplemental Materials

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Figure Legend

Figure 1: Levels of decisional regret by additional finding type. Decisional regret scores, which can range from 0 (no regret) to 100 (high regret), were classified into three categories: 0 = no regret; 5-25 = mild regret; and ≥ 30 = high regret.

Table 1. Participant characteristics

	Survey participants [n (%)]			Interview participants [n (%)]	
	Overall	**Cancer**	**FH**	**Positive AF**	**No AF**
	n = 147	**n = 92**	**n = 55**	**n = 35**	**n = 29**
Gender					
Female	83 (60)	52 (59)	31 (61)	21 (61)	21 (72)
Male	56 (40)	36 (41)	20 (39)	14 (39)	8 (28)
Age, years					
Mean (*SD*), range	51.6 (13.6), 21-83	49.7 (13.7), 21-83	54.9 (12.9), 30-79	51.1 (12.2), 32-79	55.6 (13.), 25-75
Education					
Degree and above	75 (53)	47 (55)	28 (51)	21 (64)	11 (46)
Below degree	66 (47)	39 (45)	27 (49)	12 (36)	13 (54)
Ethnicity					
White/White British	127 (91)	81 (92)	46 (90)	31 (89)	25 (89)
Asian/Asian British	4 (3)	3 (3)	1 (2)	1 (3)	1 (4)
Black/Black British	3 (2)	1 (1)	2 (4)	2 (6)	0 (0)
Mixed ethnicity	1 (1)	0 (0)	1 (2)	0 (0)	1 (4)
Other ethnicity	4 (3)	3 (3)	1 (2)	1 (3)	1 (4)
Language					
English	133 (96)	83 (94)	50 (98)	32 (91)	22 (88)
Other	6 (4)	5 (6)	1 (2)	3 (9)	3 (12)
Children					
Median, IQR	2, 1-3	2, 1-3	2, 1-3	2, 1-2	2, 1-3
Religion					
Christian	64 (46)	37 (43)	27 (53)	7 (22)	12 (50)
None	64 (46)	41 (47)	23 (45)	24 (75)	11 (46)

Jewish	3 (2)	3 (3)	0 (0)	1 (3)	0 (0)
Muslim	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Hindu	1 (1)	0 (0)	1 (2)	0 (0)	1 (4)
Sikh	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Other	4 (3)	4 (5)	0 (0)	0 (0)	0 (0)
Religiosity					
Very	18 (13)	9 (10)	9 (18)		
Somewhat	36 (26)	24 (28)	12 (24)		
Not at all	84 (61)	54 (62)	30 (59)		
Employment					
Full-time	45 (32)	25 (28)	20 (28)		
Part-time	19 (14)	17 (20)	2 (4)		
Retired	34 (25)	19 (22)	10 (9)		
Disabled	14 (10)	7 (8)	15 (29)		
Self-employed	12 (9)	9 (10)	3 (6)		
Looking after family	12 (9)	8 (9)	4 (8)		
Student	2 (1)	2 (2)	0 (0)		
Leave	1 (1)	1 (1)	0 (0)		
100kGP Proband					
Self				16 (46)	17 (59)
Child				16 (46)	12 (41)
Self and child				1 (3)	0 (0)
Relative				2 (6)	0 (0)

Note: Some categories do not reflect the total number of respondents since provision of this information was optional; percentages are calculated over known information.

Key: FH = Familial hypocholesterolaemia; AF = additional finding; SD = standard deviation; IQR = Interquartile range

Table 2: Illustrative quotes from the interviews with 100kGP participants

Quote number	Illustrative quote
Q1	*"Yeah, just the more information the better. I'm not one to, I mean my mum's had a couple of bouts of bowel cancer. My dad's obviously had various heart conditions, so I knew there was something going to come up, somewhere along the lines."* P_034, male, FH PAF
Q2	*"[The letter with the gene name] was like three days or two days before my appointment… so it gave me the weekend to sort of prepare some questions to take with me… I didn't have to wait two weeks knowing I'd got this thing, not really knowing what it was or what it could do. It wasn't long enough for me to worry about it."* P_070, female, cancer PAF
Q3	*"I panicked because [my family member's AF results] had come back and I still hadn't had mine… and then all of a sudden I did get a letter saying that they'd found additional findings but didn't tell me what it was"* P_017, female, cancer PAF
Q4	*"I didn't have a disposition to certain diseases, but not that I could never get them". N_08, female, NAF*
Q5	*"I was just a bit confused by the wording. I mean I had got a lot going on so I was probably rushing reading it, but it would have been nice to have a follow up call for someone to just explain this a bit to me."* N_18, female, NAF
Q6	*"You know I am worried for my daughter. Again it's knowing that she's going to have to have the test and the implications for that so you have a negative/positive… I hope I haven't passed it on but I suppose positive in that if I have, then at least we can do something about it."* P_033, female, cancer PAF
Q7	*"And the saddest thing of all is that it didn't relate to me, but it did relate to my children. So it was, yeah, so it was a bit of a shock."* P_071, male, cancer AF
Q8	*"I was shocked to find out the information, but I am grateful now I know as it means I can get the screening I need and surgery I need. Lifestyle changes are already made."* P_076, female, cancer PAF
Q9	*"And then I told [my parents] I had the appointment, told them what the additional findings were. And then I told them or asked them would they be willing to have blood tests done as part of this. And they said "Of course, yes. Get us referred, however you need to do it and we'll get blood tests done".* P_033, female, cancer PAF
Q10	*"First of all it was quite a shock and trying to process it yourself and then you can't process it yourself because you're worrying yourself sick about your other family members and how they're going to react"* P_051, female, cancer PAF
Q11	*[Sharing the finding with family has gone] "very straightforwardly because they were all aware of what we've got. And they all have high cholesterol apart from my oldest daughter."* P_028, female, FH PAF
Q12	*"I think it is a benefit for people to know, but I think you have to be very careful about the way it's communicated."* P_063, male, cancer PAF

Table 3. Delivery of PAF results by additional finding type.

	Overall	**Cancer**	**FH**	***p*-value†**
	n (%)	**n (%)**	**n (%)**	
How were you told about your AF?				< .001
Letter; AF named	39 (27)	9 (10)	30 (60)	
Letter; AF unnamed	53 (37)	42 (46)	11 (22)	
Phone; AF named	28 (19)	24 (26)	5 (10)	
Phone; AF unnamed	8 (6)	5 (5)	1 (2)	
Other	16 (11)	11 (12)	3 (6)	
Had an appointment with a specialist clinician?				.024
Face-to-face	44 (30)	26 (29)	18 (33)	
Phone	57 (39)	34 (37)	23 (43)	
Video	33 (23)	25 (27)	8 (15)	
No	5 (3)	5 (5)	0 (0)	
Other	6 (4)	1 (1)	5 (9)	
Who was your discussion with?				
Genetic counsellor	-	44 (52)	8 (16)	
Geneticist	-	20 (24)	6 (12)	
Cancer specialist	-	4 (4)	0 (0)	
Consultant physician	-	0 (0)	14 (27)	
Nurse	-	2 (2)	18 (35)	
Not sure	-	8 (10)	4 (8)	
Other	-	6 (7)	1 (2)	

Key: † = Fisher's exact test

Table 4. Descriptive statistics for MICRA scores by additional finding type

	Overall (n = 147)	**Cancer (n = 91)**	**FH (n = 55)**	***p*-value†**
Overall scale (possible scores range from 0-95)				
Mean	28.54	30.99	24.44	0.016
95% CI	(25.7-31.4)	(27.3-34.7)	(19.9-20.0)	
SD	17.68	17.84	16.78	
Range	0-79	0-79	0-71	
Q1	15.5	19	12	
Median	24	29	20	
Q3	39.5	42	35.5	
Distress (possible scores range from 0-30)				
Mean	8.38	9.91	5.85	< 0.001
95% CI	(7.1-9.7)	(8.2-11.6)	(4.0-7.7)	
SD	7.99	8.30	6.79	
Range	0-30	0-30	0-28	
Q1	1	3	0	
Median	6	9	3	
Q3	12.75	15.5	10	
Uncertainty (possible scores range from 0-45)				
Mean	12.03	13.10	10.25	0.081
95% CI	(10.5-13.6)	(11.1-15.1)	(7.8-12.7)	
SD	9.54	9.67	9.13	
Range	0-40.5	0-39	0-40.5	
Q1	5	5	3	
Median	10.25	12	8	
Q3	17.75	20	15	
Positive experiences (possible scores range from 0-20)				
Mean	8.3	8.32	8.27	0.955
95% CI	(7.5-9.1)	(7.3-9.3)	(7.0-9.5)	
SD	4.70	4.75	4.66	
Range	0-20	0-20	0-18	
Q1	6	5.5	6	
Median	8	8	8	
Q3	12	11	12	

Key: CI = confidence interval; *SD* = standard deviation; Q1 = first quartile; Q3 = third quartile; † = multiple regression with bootstrap simulations