Attitudes among South African university staff and students towards disclosing secondary genetic findings

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Abstract

The present study represents an initial step in understanding diverse academic perspectives on the disclosure of secondary findings (SFs) from genetic research conducted in Africa. Using an online survey completed by 674 university students and academic staff in South Africa, we elicited attitudes towards the return of SFs. Latent class analysis (LCA) was performed to classify sub-groups of participants according to their overall attitudes to returning SFs. We did not find substantial differences in attitudes towards the return of findings between staff and students. Overall, respondents were in favour of the return of SFs in genetics research, depending on the type. The majority of survey respondents (80%) indicated that research participants should be given the option of deciding whether to have genetic SFs returned. LCA revealed that the largest group (53%) comprised individuals with more favourable attitudes to the return of SFs in genetics research. Those with less favourable attitudes comprised only 4% of the sample. This study provides important insights that may, together with further empirical evidence, inform the development of research guidelines and policy to assist healthcare professionals and researchers.

Keywords Secondary findings · Return of results · Genetics · South Africa

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Introduction

The widespread integration of genomic methods and approaches across the life sciences and, increasingly, into medicine and society are evident (Green et al. 2020). Technological advances have resulted in the identification of thousands of genetic variants associated with both common and rare diseases in genomic studies and have led to an increase in the number of genetic tests available in both research and clinical practice (Dawkins et al. 2018; Jackson et al. 2018). However, there is still much uncertainty about how to implement genetic testing in clinical settings and more robust research is needed to evaluate the analytic and clinical validity, and clinical utility, of genetic tests (Khoury 2017).

Genome-wide association studies (GWAS) and whole genome/exome sequencing (WGES) are widely used approaches for research projects and diagnostic purposes (White et al. 2019). A study by the Wellcome Trust Case Control Consortium (WTCCC) analysed genetic variants in 14,000 people and revealed associations between 24 diseases

and specific single-nucleotide polymorphisms (SNPs) for use by the scientific community. This study encouraged advances in the field and set the standard for GWAS (Manolio 2017). Valuable advances in genotype calling were made; the study developed and disseminated methods for imputing non-genotyped variants, demonstrated the advantage of including larger sample sizes, and helped propel data distribution (Manolio 2017). This was one of the first GWAS that provided information about the individual genotypes of each participant and associated traits (Manolio 2017).

GWAS and WGES are emerging population genetic study designs that generate vast amounts of data outside the scope of an original investigation (Buck and Lieb 2004; Stadler et al. 2010; Jackson et al. 2012) and yield findings that may not be directly related to a participant's primary symptoms. These secondary findings (SFs), which are unanticipated discoveries, may have potential health or reproductive implications for research participants (Wolf et al. 2008) who can be treated but may also indicate conditions for which treatments are not currently available. This has stirred up debate on how researchers should deal with secondary genetic results generated in the process of performing genome-wide analyses. Key questions that arise are how to interpret these SFs and how to communicate them to primary care physicians and patients (Ewuoso 2016; Middleton et al. 2016; Mackley and Capps 2017; Thorogood et al. 2019).

Studies in different research and clinical settings empirically investigating the disclosure or non-disclosure of genetic SFs have found that if there is perceived clinical utility and the possibility of prevention or treatment, most researchers and health care professionals working in the genomics field are in favour of disclosing SFs (Jackson et al. 2012; Christenhusz et al. 2013a). In a recent systematic review, the majority of participants in 19 included studies, mostly from the USA, believed that there was an obligation to disclose SFs to research participants. Study participants included researchers, IRB chairs and members, geneticists/genetics specialists, patients and the public (Ewuoso 2016). In another study that assessed a discrete patient sample who underwent genome-wide sequencing, most participants preferred their SFs returned to them, regardless of potential harm, insurance bias, psychosocial impact or stigma (Bishop et al. 2016).

In order to ethically guide decisions around which SFs should be returned to patients and which should not, the development of various taxonomic systems have emerged (Boardman and Hale 2018). The data supporting these taxonomies has largely been generated by clinicians and professional bodies, with far less data from patients and the general public (Boardman and Hale 2018). Whilst there is variation between studies regarding the categories used, generally the taxonomies merge around the following components: the relevance of the SF beyond the index case, the strength of the

genotype/phenotype correlation and the impact, severity and treatability of the associated genetic disease(s) (Boardman and Hale 2018).

Despite the rapid progress globally, African populations have long been underrepresented in genomics research (Tucci and Akey 2019). African genomes contain more genetic variation than those from any other continent, yet only a fraction of the genetic diversity among African individuals has been surveyed (Nielsen et al. 2017). A recent study uncovered more than 3 million previously undescribed variants (Choudhury et al. 2020). A systematic review of 19 studies on the management of SFs in genomic research showed that the majority of studies include the views of Northern Americans, with critical contributions of Africans, Asians and Europeans lacking (Ewuoso 2016). Conducting genomics research in diverse populations is important in ensuring that the revolution in, and proliferation of studies, in the field does not exacerbate health disparities by facilitating discoveries that will disproportionately benefit well-represented populations (Bentley et al. 2017). In order to address this, the Wellcome Trust (UK) and the National Institutes of Health (NIH, USA) launched the H3Africa Initiative in 2010. This initiative supports the development of skills and infrastructure required for genomics research in Africa and ensures sequencing of numerous African genomes and exomes, given the declining cost of next generation sequencing (Wright et al. 2013). In South Africa, centres (equipped with the latest technology) have been launched to facilitate conducting large-scale studies on whole genome sequencing. These initiatives will realise the potential for localised cutting-edge genomic research and generation of new knowledge on the African population genome. Genomics research in Africa presents a unique set of ethical, scientific, legal and practical challenges with regard to dealing with SFs. There is very little guidance available at governmental, professional or academic level. Furthermore, there are many factors, including ethical, practical and technical factors and logistical aspects of disclosure that contribute to the decisions in whether or not to disclose a SF (Klitzman et al. 2013). For these reasons, guidelines for disclosing SFs that can flexibly be applied across diverse medical contexts need to be developed. Many factors could influence whether to disclose/reveal the SFs to the participant. For example, the finding may or may not be very significant, that is it may be a minor condition or there may not be anything that can be done about the finding (i.e. it is not clinically actionable); or it may be that something can be done about the finding (i.e. it is clinically actionable). The age of the research participant is also a factor that should be considered. Some diseases may only develop in adulthood (adult onset), whilst others can already develop in childhood (childhood onset). Given the dearth of studies on secondary genetic findings in Africa and virtually no empirical data available describing the preferences and perspectives of relevant African

stakeholders, it is important to explore these perspectives to inform future studies and policy recommendations. Our study aims to fill this gap and represents an initial step in understanding perspectives on SFs in Africa.

Materials and methods

Survey instrument

A cross-sectional online electronic survey in English and Afrikaans was administered to staff and students at the following tertiary institutions in South Africa: (1) Faculty of Medicine and Health Sciences, Stellenbosch University, (2) Faculty of Health Sciences, University of Cape Town and (3) the Division of Human Genetics, the University of the Witwatersrand, Johannesburg, the three largest institutions involved in genomics research. The survey was also distributed to the members of the Southern African Society for Human Genetics (SASHG; <http://sashg.org/>), which included responses from other universities. The development of the survey was informed by previous studies (Christenhusz et al. 2013a, b; Lemke et al. 2013; Appelbaum et al. 2014; Strong et al. 2014). The questionnaire was piloted and changes were made to the framing of some questions based on the feedback received from respondents. Respondents ($n = 10$) were researchers, clinicians, postgraduate students in genetics and mental health. Potential participants were emailed the final survey using the universities' mailing lists and existing email distribution lists. Participants were required to consent to the survey via an informed consent form on the first online page that preceded the survey. Although there are 11 languages spoken in South Africa, English and Afrikaans were chosen as these are the most universal languages spoken in South Africa and most university staff and students would speak and understand one of these languages. An anonymous online questionnaire that took approximately 20 minutes to complete was used as the data collection tool to assess study participants' attitudes and reasoning for returning SFs, factors affecting the disclosure of SFs, types of SFs that should or should not be returned and who should return the SFs. Study participants were emailed information about the study and the link to the online survey. Two email reminders, a week apart, were sent to potential participants after the initial invitation. The e-survey was conducted through Research Electronic Data Capture (REDCap), a secure online program for creating and managing e-surveys and databases (<https://projectredcap.org/software/>). The term incidental findings (IFs) was used in the survey. The term IFs was changed by the American College of Medical Genetics and Genomics (ACMG) to SFs in 2016, after we conducted the survey. A copy of the survey and information leaflet is provided in the Supplement.

Data analysis

Data were analysed using Statistica version 13 (Dell Software). Data were summarised using descriptive statistics. Latent class analysis (LCA) was performed in order to identify sub-groups (or classes) of participants with different overall attitudes to returning SFs in genetics research (Formann and Kohlmann 1996; Lanza and Rhoades 2013). Models postulating different numbers of classes were fitted and the best-fitting model identified by information criteria (Akaike information criterion, AIC) was included in further analyses. Posterior probabilities were derived to determine the probability of an observation classified in a given class. Analysis of variance (ANOVA) or chi-square tests were used to examine whether latent group membership differed by demographic characteristics (age, gender, ethnicity, highest level of education, home language, years of experience, university, experience in genetics research and whether the respondents had any children).

Ethical considerations

Ethical approval for the study was obtained prior to data collection from the Health Research Ethics Committees of Stellenbosch University (reference no.: N14/07/081), University of Cape Town (reference no.: 760/2014), and the University of the Witwatersrand (reference no.: M150981). All participants provided informed consent, which was required at the commencement of the anonymous on-line e-survey. Once all data had been collected, all completed surveys were entered into a lucky draw with one participant winning R1500 (\$99).

Results

Participant characteristics

A total of 674 individuals completed the survey and 518 partially completed surveys were excluded. Of the survey respondents, 63.3% were between the ages of 18 and 30 years, 60% were students, 50% listed English and 35% listed Afrikaans as their home language and 31% were males. The majority of participants self-identified as white women with no genetic research experience (Table 1).

Attitudes and guidelines

A total of 524 respondents (80%) indicated that research participants should be given the option of deciding whether to have genetic SFs returned. In contrast to the 27.9% who felt that researchers from low-income countries might not have the resources to deal with SFs and should therefore have different guidelines to high-income countries for disclosing SFs, 34.1%

Table 1 Demographic information on 674 survey participants

Variable	Data available <i>n</i>	Responses	
		<i>n</i>	%
Sex	671		
Male		206	31
Self-identified race	656		
African/Black		109	16.6
Asian/Indian		50	7.6
Caucasian/White		391	59.6
Coloured (mixed race)		106	16.2
Age	619		
18–30 years		392	63.3
30–50 years		188	30.4
50–70 years		36	5.8
> 70 years		3	0.4
Home language	670		
English		332	50
Afrikaans		237	35
isiXhosa		20	3
isiZulu		15	2.2
Sesotho		6	0.9
Setswana		8	1.2
Sepedi		3	0.4
Siswati		3	0.4
Tshivenda		2	0.3
Xitsonga		2	0.3
isiNdebele		4	0.6
Other		38	5.7
Highest education level	674		
No formal schooling		0	0
Grades 1–6		0	0
Grades 7–12		170	25.2
Post-school diploma		31	4.6
Bachelor's degree		90	13.4
MS or doctoral degree		240	35.7
Other		141	21
Employment status	670		
University employee		135	20.1
University student		405	60.3
Government employee		60	8.9
Non-government employee		43	6.4
Self-employed		21	3.1
Unpaid, homemaker, retired or unemployed		6	0.8
Do you have children?	674		
Yes		153	23
Experience in genetic research (yes)	671		
< 1 year		24	23.3
1–5 years		36	35
6–10 years		25	24.3

Table 1 (continued)

Variable	Data available <i>n</i>	Responses	
		<i>n</i>	%
11–20 years		14	13.6
>20 years		4	3.9
Has generated IF	103		
Yes		17	16.5
Has returned IF	103		
Yes		11	10.7
Participated in genetic research	661		
Yes		92	13.9
Willing to participate in genetic research	566		
Yes		493	87.1

felt that researchers from all countries should follow the same guidelines for the purpose of standardisation and uniformity. Given that the genetic variants are heritable, 59.2% indicated that a research participant is responsible for informing their family members of any SFs (Table 2).

Disclosing specific types of SFs

Of the total group of respondents, 89% indicated they would want to know about a SF that indicates a genetic association with an adult-onset disease that is clinically actionable (i.e. unanticipated diagnosis that can be treated or prevented), 59% for a disease that is not clinically actionable (i.e. a diagnosis that cannot be treated or prevented) and 68% for a disease with uncertain clinical significance. Of all respondents, 92% indicated they would want to know about a SF for their child that indicates a clinically actionable childhood-onset disease and 71% for a childhood-onset disease that is not clinically actionable. Moreover, 88% indicated they would want to know about a SF for their child that indicates a genetic association with an adult-onset disease that is clinically actionable, 67% for a disease that is not clinically actionable and 68% for a disease with uncertain clinical significance (Table 3).

Reasons for returning SFs

The majority of respondents indicated that the most important reasons for or benefits of returning SFs in genetics research were that (i) they could be life-saving (75%), (ii) a treatable disorder might be identified (71%) and (iii) participants have a right to that information (65%). Respondents indicated that the most important factors that result in researchers not disclosing SFs, were (i) lack of expertise to interpret and return results (32%); (ii) a possible need for further testing, counselling and follow-up (26%); (iii) unavailability of funds from the study to pay for disclosure (26%); (iv) the risk of stigma/

Table 2 Summary of responses to general survey questions about Secondary findings (SFs)

Statement in the survey	Data available <i>n</i>	Responses	
		<i>n</i>	%
Attitude towards returning SFs. Research participants should:	657		
Be given the option of deciding whether to have genetic SFs returned		524	79.9
Probably have the option of deciding whether to have genetic SFs returned		116	17.7
Not have the option of deciding whether to have genetic SFs returned		17	2.6
Should low-income countries (LICs) have different guidelines to high-income countries (HICs) for disclosing SFs?	659		
Yes, because researchers from LICs might not have the resources to deal with SFs.		184	27.9
Yes, because research participants from LICs might not be able to afford treatment.		142	21.5
No, because countries that cannot deal with SFs should not start studies.		71	10.8
No, because research participants from countries that do not have the resources to deal with SFs should not participate in studies.		52	7.9
Other		210	31.9
Should South Africa have unique guidelines for returning SFs?	660		
Yes, because South Africa does not have the same resources for dealing with SFs as other countries, therefore different guidelines are needed.		207	31.4
Yes, because there are many different types of people and cultures in South Africa, therefore unique guidelines are needed.		144	21.8
No, researchers from all countries should follow the same guidelines so that there is standardization and uniformity.		230	34.8
No, research should not be allowed to be conducted if the resources for dealing with SFs are not in place.		41	6.2
Other		38	5.8
SFs in genetic research may be inheritable. This could mean that the participant's family members are also affected by the finding.	669		
The participant is responsible for informing his family.		396	59.2
It is the researchers' responsibility to ensure the participant's family is informed.		138	20.6
It is not feasible for researchers to inform participants' families of SFs.		135	20.2

Table 3 Summary of responses to survey questions dealing with specific Secondary findings (SFs) and their return

Statement in the survey	Data available, <i>n</i>	Responses, <i>n</i> (%)					
		Strongly disagree	Disagree	Strongly disagree and disagree	Neutral	Agree	Strongly agree
I would want to know about a SF that indicates a genetic association with adult onset disease							
That is clinically actionable	668	22 (3.3)	7 (1)	29 (4.3)	43 (6.4)	160 (24)	436 (65)
That is NOT clinically actionable	668	54 (8.1)	74 (11)	128 (19.1)	147 (22)	165 (25)	228 (34)
With uncertain clinical significance	661	30 (4.5)	48 (7.3)	78 (11.8)	154 (23)	207 (31)	222 (34)
I would want to know about a SF about my child that indicates a genetic association with							
Childhood onset disease that is clinically actionable	665	22 (3.3)	6 (0.9)	28 (4.2)	25 (3.8)	144 (22)	468 (70)
Childhood onset disease that is NOT clinically actionable	664	47 (7.1)	45 (6.8)	92 (13.9)	97 (15)	188 (28)	287 (43)
Adult onset disease that is clinically actionable	663	25 (3.8)	16 (2.4)	41 (6.2)	40 (6)	140 (21)	442 (67)
Adult onset disease that is NOT clinically actionable	662	50 (7.6)	62 (9.4)	112 (17)	110 (17)	171 (26)	269 (41)
Disease with uncertain clinical significance	666	33 (5)	45 (6.8)	78 (11.8)	137 (21)	190 (29)	261 (39)

discrimination (e.g. in insurance) if information about their tests became known (25%); (v) the interpretation and clinical significance of SFs may vary in the future as more knowledge is acquired (18%); (vi) participants might not want this information (24%); and (vii) the possible negative psychological responses (22%) (Table 4).

Who should return a genetic SF to the participant?

Genetic counsellors were ranked as being the most responsible individuals for returning genetic SFs (51%), whereas 60% felt that family members were the least responsible for returning genetic SFs (Table 5).

Overall attitudes to returning SFs in genetics research

Using AIC in LCA, three latent classes were selected and included in further analyses (Fig. 1). The largest subgroup was latent class 3, making up 53% of the sample and the smallest subgroup was latent class 2, making up 4% of the sample. The second and smallest latent class (group 2) scored lowest on questions pertaining to reasons/benefits for returning SFs in genetics research. This group was less homogeneous, with a wider spread of scores. Class members in this group have high probabilities of responding negatively to the questions, and can be labelled as having less favourable attitudes to return of SFs in genetics research. Thus, members in this class were more likely to have a consistently negative response across a range of genomic results returning scenarios (Fig. 1). Group 1, consisting of 43% of participants, scored highest on questions pertaining to the reasons/benefits for return of SFs in genetics research. In this group, class members have low probabilities of responding negatively to the questions, and can be labelled as having more favourable attitudes to the return of SFs in genetics research. The third and largest latent class (group 3) was also characterised by a low probability of responding negatively to receiving SFs, although class members may have indicated attitudes that were more neutral. This group was homogeneous, with scores closer together (Fig. 2). The opposite was true for questions pertaining to barriers causing researchers not to disclose SFs in genetics research. The second latent class (group 2) scored highest on these questions and the third latent class (group 3) scored lowest on these questions (Figs. 3, 4, and 5). In all three latent classes, the majority of members were university students (62%; 58%; 63%).

Additional analyses revealed that for responses relating to the benefits of returning SFs, the groups did not differ by age, years of experience or highest level of education ($p > 0.05$). Although participants belonging to the latent class 1 were more educated than participants in the other two latent classes, this difference was not statistically significant ($p = 0.08$; ANOVA). The classes did not differ by home language,

Table 4 Summary of responses to survey questions dealing with reasons for returning Secondary findings (SFs)

Question	Data available <i>n</i>	Responses, <i>n</i> (%)				
		Completely unimportant	Unimportant	Neutral	Important	Very important
How important are each of the following reasons/benefits for returning SFs in genetics research						
It would encourage participation in research	667	18 (2.7)	72 (11)	160 (24)	268 (40)	149 (22)
Participants have a right to the information	668	6 (0.9)	4 (0.6)	36 (5.4)	190 (28)	432 (65)
It could be life-saving; there's a moral obligation to return life-saving information	666	6 (0.9)	1 (0.2)	28 (4.2)	132 (20)	499 (75)
Other disciplines return SFs	667	53 (7.9)	98 (15)	279 (42)	165 (25)	72 (11)
Concern over legal ramifications over adverse outcome	668	22 (3.3)	73 (11)	212 (32)	257 (39)	104 (16)
A treatable disorder might be identified	665	5 (0.8)	2 (0.3)	20 (3)	163 (25)	475 (71)
Modern reproductive techniques may allow carriers to have children with minimal risk of the specific disorder	666	15 (2.3)	26 (3.9)	103 (16)	230 (35)	292 (44)
Knowing one's propensity for developing particular conditions can help with life planning	667	6 (0.9)	10 (1.5)	48 (7.2)	220 (33)	383 (57)
Knowing whether or not they carry a disease mutation can relieve anxiety for some people	668	12 (1.8)	34 (5.1)	91 (14)	252 (38)	279 (42)
How important are these factors when causing researchers NOT to disclose SFs						
Insufficient staff to disclose large numbers of SFs	665	103 (16)	163 (25)	145 (22)	198 (30)	56 (8.4)
Lack of expertise to interpret and return results	667	31 (4.6)	54 (8.1)	76 (11)	294 (44)	212 (32)
Many SFs are of uncertain clinical significance	666	49 (7.4)	96 (14)	181 (27)	227 (34)	113 (17)
Burden and distraction from primary research	667	136 (20)	212 (32)	135 (20)	136 (20)	48 (7.2)
Participants might expect to receive medical care from the researchers	665	82 (12)	145 (22)	145 (22)	203 (31)	90 (14)
Participants might not want this information	667	28 (4.2)	65 (9.7)	156 (23)	257 (39)	161 (24)
Participants can get this information from their doctors	663	107 (16)	223 (34)	188 (28)	106 (16)	39 (5.9)
Possible negative psychological responses	665	24 (3.6)	69 (10)	117 (18)	310 (47)	145 (22)
The participant may be confused by the ambiguous nature of the SFs	668	26 (3.9)	77 (12)	146 (22)	286 (43)	133 (20)
The interpretation and clinical significance of the SFs may vary in the future as more knowledge is acquired	665	26 (3.9)	108 (16)	145 (22)	266 (40)	120 (18)
The risk of stigma/discrimination (e.g. in insurance) if information about their test results becomes known	667	31 (4.6)	88 (13)	103 (15)	281 (42)	164 (25)
Possible need for further testing, counselling and follow-up and the unavailability of funds from the study to pay for it	666	49 (7.4)	94 (14)	90 (14)	260 (39)	173 (26)

Table 5 Who should return a genetic secondary findings (SFs) to the participant?

Person returning IF	Data available <i>n</i>	Responses to each scale component, <i>n</i> (%)				
		1	2	3	4	5
Primary researcher of the study	593	151 (26)	127 (21)	126 (21)	112 (19)	77 (13)
Nurse	574	10 (1.7)	84 (15)	154 (27)	246 (43)	80 (14)
Genetic counsellor	597	307 (51)	143 (24)	62 (10)	40 (6.7)	45 (7.5)
Family member	619	68 (11)	24 (3.9)	49 (7.9)	108 (17)	370 (60)
Medical doctor	637	104 (16)	229 (36)	198 (31)	69 (11)	37 (5.8)

Participants were asked to rank a person for their role in returning SFs using a scale of 1 to 5 (1 representing the most responsible person and 5 the least responsible person)

university, employment status or whether they had any children ($p > 0.05$; chi-square test). There were, however, differences in gender, with more women than men in all three latent classes ($p = 0.04$), ethnicity, with more respondents who identified themselves as white in all three latent classes ($p < 0.01$), and by genetic research experience, with more respondents indicating they had no genetic research experience in all three groups ($p = 0.01$). For responses underpinning the barriers to disclosing SFs, the groups did not differ by gender, age, ethnicity, years of experience, home language, whether they had any children, employment status, highest level of education or genetic research experience ($p > 0.05$).

Discussion

We investigated the attitudes and expectations of South African university students and staff surrounding the return of SFs in genetics research. We did not find substantial

differences in attitudes towards the return of findings between these groups. Overall, we found that responses were in favour of the return of SFs in genetics research. The degree to which participants favoured the return of findings varied depending on the type of SF (e.g. actionable vs. not actionable) and whether the finding was for the participant themselves or their child—all which represent key factors that would be relevant for policymaking. The majority of survey respondents indicated that research participants should be given the option of deciding whether to have genetic SFs returned. The majority also indicated they would want to have SFs disclosed to them for a disease that is clinically actionable (i.e. treatable or preventable). We found that a greater number of respondents would prefer to receive variants of uncertain significance (VUS) than results that are not clinically actionable. Pathogenicity is an important consideration and is widely debated (Saelaert et al. 2019). Disclosure of VUSs might have a significant psychological impact or, as a consequence of unnecessary interventions, medically harmful consequences.

Fig. 1 Selection of clusters using latent class analysis (LCA). Altogether, eight classes were identified. The first three were selected for further analyses. AIC = Akaike information criterion

Fig. 2 Principle component (PC) analysis. Biplot showing scores for PC1 and PC3 on items pertaining to benefits for returning SFs in genetics research using LCA. Alpha ellipses show the position and direction of classes. For the original survey questions, see Supplement. Table 4 lists the statements used in the survey for this analysis. Red, blue and black ellipses refer to the three LCA groups identified in Fig. 1. BQ = knowing whether or not they carry a disease mutation can relieve anxiety for some

people; BJ = participants have a right to the information; BP = knowing one's propensity for developing particular conditions can help with life planning; BK = it could be life-saving; there's a moral obligation to return lifesaving information; BN = a treatable disorder might be identified; BO = modern reproductive techniques may allow carriers to have children with minimal risk of the specific disorder; BM = concern over legal ramifications over adverse outcomes

Fig. 3 Principle component (PC) analysis. Biplot showing scores for PC1 and PC2 on items regarding barriers to disclosing SFs in genetics research using LCA. Alpha ellipses show the position and direction of classes. For the original survey questions, see Supplement. Table 4 lists the statements used in the survey for this analysis. Red, blue and black ellipses refer to the three LCA groups identified in Fig. 1. BU = burden and distraction from primary research; BR = insufficient staff to disclose large numbers of SFs; BT = many SFs are of uncertain clinical significance; BV = participants might expect to receive medical care from the researchers; CC = possible

need for further testing, counselling and follow-up, and the unavailability of funds from the study to pay for it; CA = the interpretation and clinical significance of the SFs may vary in the future as more knowledge is acquired; CB = the risk of stigma/discrimination (e.g. insurance) if information about their test results becomes known; BZ = the participant may be confused by the ambiguous nature of the IF; BY = possible negative psychological responses; BW = participants might not want this information

They could result in unnecessary interventions or harm and a false sense of security (Saelaert et al. 2019). This opportunistic screening has been criticised and the American Presidential Commission for the Study of Bioethical Issues (Bioethics Commission) notes how it might entail additional health risks, overwhelm patients with (ambivalent) information and stimulate a trend of medicalisation (Weiner 2014). A recent systematic review on the disclosure of SFs included four studies that were methodologically diverse with contrasting aims (Jackson et al. 2012). Given these disparities and limitations of the individual studies, conclusions were difficult to draw. Moreover, none of these studies were conducted in Africa (Jackson et al. 2012). Another systematic review including 19 studies on the management of SFs in genomic research confirmed majority support for the return of clinically actionable findings; however, once again, the support represents views of only North Americans (Ewuoso 2016). A large international study including 4961 members of the public, 533 genetic health professionals, 843 non-genetic health professionals and 607 genomic researchers found that the four relevant stakeholder groups considered treatability and perceived utility of SFs important, with the majority of stakeholders (98%) indicating interest in learning about life-threatening conditions that are preventable (Middleton et al. 2016). However, compared with other stakeholder groups, health professionals in genetics had significantly less favourable views. This demonstrates a division between the views of

those participating in the research and those handling research findings (Middleton et al. 2016). Health professionals in genetics were five times more likely to disagree that SFs should be returned and three times more likely to disagree that genomic researchers should actively search for SFs irrelevant to their research (Middleton et al. 2016). In our sample, the majority of survey respondents indicated that they had no genetics research experience, potentially explaining the more favourable attitudes towards the return of genetic SFs. Future studies should include more geneticists to elucidate whether the support for the return of SFs is shared among all relevant stakeholders. However, it should be highlighted that there are multiple variables, outside of the area of speciality, that could explain the differences in attitudes observed (e.g. education level, setting). Future studies involving more diverse groups of stakeholders whose views need to be accounted for in policymaking (e.g. geneticists, patients and general public) should be conducted.

Using LCA to compare attitudes of staff and students on issues relevant to the return of SFs from genetics research, three distinct classes of responders were revealed. We found a cluster of responders scoring lowest on questions pertaining to the benefits of returning SFs. In other words, responses among class members to key questions on the benefits of returning SFs leaned more towards the ‘unimportant’ or ‘completely unimportant’ response options, suggesting less favourable attitudes towards the return of SFs in genetics

Fig. 4 Benefits for returning SFs by latent class: weighted means plot using item-response probabilities. Classes 1–3 (blue, red and green lines) refer to the classes identified in LCA in Fig. 1. Y-axis response options: 1 = completely unimportant; 2 = unimportant; 3 = neutral; 4 = important; 5 = very important. X-axis survey statements: BI = it would encourage participation in research; BJ = participants have a right to the information; BK = it could be life-saving; there’s a moral obligation to return lifesaving

information; BL = other disciplines return SFs; BM = concern over legal ramifications over adverse outcomes; BN = a treatable disorder might be identified; BO = modern reproductive techniques may allow carriers to have children with minimal risk of the specific disorder; BP = knowing one’s propensity for developing particular conditions can help with life planning; BQ = knowing whether or not they carry a disease mutation can relieve anxiety for some people

research. This class was the smallest group. The second cluster of responders scored highest on questions pertaining to the benefits for returning SFs in genetics research. In other words, responses among class members to key questions on the benefits of returning SFs in genetics research leaned more towards the ‘important’ or ‘very important’ response options, suggesting more favourable attitudes. Class members in this group were more educated than the other two latent classes; however, this difference was not statistically significant. The remainder of the sample fell in the third group, also characterised by a low probability of responding negatively to receiving SFs, although class members may have indicated attitudes that are more neutral. This class was the largest group. Very similar findings were reported in the study by Middleton and colleagues, with the largest group in their study also showing more favourable attitudes to the return of results and very low probabilities of responding negatively to questions (Middleton et al. 2016). Our findings revealed that the three classes significantly differed by gender, ethnicity (more respondents self-classified themselves as ‘white’) and genetic research experience (more respondents indicating they had no genetic research experience) in all three latent classes. Future studies should include more men and individuals of other ethnicities and more genetic health professionals to elucidate whether the support for the return of SFs is shared among all relevant stakeholder groups.

Although this study provides valuable evidence about the attitudes towards the hypothetical return of SFs, what stakeholders (i.e. researchers and clinicians) do in a real situation may vary. Until genetic SFs are returned and the experience of this is measured, it is impossible to know how closely these positive hypothetical attitudes are aligned with reality. Although robust empirical evidence should inform the development of policy on SFs, the question of what to do in individual cases will need to account for the beliefs and preferences of individual research participants (Middleton et al. 2014). Furthermore, although the majority of respondents in this study have positive attitudes regarding the feedback of genetic SFs, this does not mean that this is the most appropriate policy to currently adopt in South Africa. Other considerations such as the appropriate use of limited health care or research resources and difficulties in data interpretation may result in a different conclusion being drawn, the latter being a pertinent consideration in African contexts.

Whilst various policy documents have been published regarding SFs in the USA, Europe and Canada (van El et al. 2013; Boycott et al. 2015; Matthijs et al. 2016; Kalia et al. 2017; Vears et al. 2018), these documents differ on fundamental issues and none of them is accepted as the general standard. Unresolved issues include a practice of unintentional incidental versus actively pursued SFs, patient opt-out possibilities and the spectrum of reportable findings (Gourna et al. 2016;

Fig. 5 Barriers to disclosing SFs by latent class: weighted means plot using item-response probabilities. Classes 1–3 (blue, red and green lines) refer to the classes identified in LCA in Fig. 1. Y-axis response options: 1 = completely unimportant; 2 = unimportant; 3 = neutral; 4 = important; 5 = very important. X-axis survey statements: BR = insufficient staff to disclose large numbers of SFs; BS = lack of expertise to interpret and return results; BT = many SFs are of uncertain clinical significance; BU = burden and distraction from primary research; BV = participants might expect to receive medical care from the researchers; BW = participants

might not want this information; BX = participants can get this information from their doctors; BY = possible negative psychological responses; BZ = the participant may be confused by the ambiguous nature of the IF; CA = the interpretation and clinical significance of the SFs may vary in the future as more knowledge is acquired; CB = the risk of stigma/discrimination (e.g. insurance) if information about their test results becomes known; CC = possible need for further testing, counselling and follow-up, and the unavailability of funds from the study to pay for it

Mackley et al. 2017; Ormond et al. 2019). Another important policy consideration is the return of SFs on the African continent. In our study, when asked whether low-income countries (LICs) should have different guidelines to high-income countries (HICs), the majority of participants indicated that they should not have different guidelines because research participants from countries that do not have the resources to deal with SFs should not be asked to participate in studies. The second most frequent response was that LICs and HICs should have different guidelines because researchers from LICs might not have the resources to deal with SFs and research participants from LICs might not be able to afford treatment. Many agreed that because there are many different types of people and cultures in South Africa, unique guidelines are needed. A very small percentage of respondents agreed that researchers from all countries should follow the same guidelines so as to ensure standardization and uniformity. The H3Africa guideline for the return of individual genetic research findings (H3Africa 2018) aims to provide consortium-wide guidelines about whether and how individual genetic research findings should be returned to research participants, given the current dearth in guidelines for countries on the African continent (H3Africa 2018). Contextual factors in African communities may impact on decision-making regarding the return of individual genetic results, such as family involvement in the research process. Some of the key principles to inform decisions about whether to return individual genetic research findings include whether a second biological sample can be obtained for verification and whether verification can be conducted in a diagnostically certified laboratory. Additional considerations are whether genetic counselling services available in the country and whether staff (clinicians or health professionals) on the project can be trained to give feedback to participants (H3Africa 2018). These are important considerations and may differ from those implemented in Western countries. Future empirical research should aim to gain perspectives of relevant African stakeholders including research participants, ethics committee members, researchers and research regulators on these issues to inform these policy debates (H3Africa 2018).

The present study has several limitations. Over 500 participants did not complete the survey, which may in part be due to the survey being too long/time consuming, and the study did not assess whether this group differed from the group of participants that completed the survey. Their attitudes towards genetic SFs may have differed and led to different results, interpretations and conclusions. Future studies should aim to investigate these possible differences. Additionally, the survey was sent through email list serves, and participants could have forwarded the survey to other individuals. Therefore, the authors do not know how many individuals received the survey, or opened the survey—just those who completed part or all of it. Findings may not be representative of the attitudes of

staff and students at all universities in the country. The survey was sent out to thousands of students and staff at three different institutions in South Africa but we only received 674 complete responses, as such the poor response rate and possibility of response bias may have influenced findings. Moreover, this study comprised an e-survey to elicit attitudes towards the return of SFs. A more nuanced understanding of this topic in the future could be obtained using a mixed-methods design. A further limitation of the design of our online survey is that we were not able to capture details on the non-response rate. Our sampling approach likely resulted in bias, through the inclusion of a highly selective sample of participants who were more likely educated about genomics and SFs. The socio-demographic characteristics of our sample were likely not representative of the general South African population to which these results would typically be inferred. This study provides the view of students and staff within academic (medical) settings. Therefore, results are likely not representative of patients nor the general public in South Africa—two stakeholder populations whose views need to be accounted for in policymaking. The target group was chosen as they were easily accessible, with university-linked email accounts, making it possible to carry out the online survey anonymously. Whilst the general perspectives of these groups do not fully inform policy development, these data provide important insights that may, together with further studies in more specific stakeholder groups, inform the development of policy on the future use of genomics in research and clinical practice. The perspectives of a wide range of stakeholder groups such as patients, health professionals, researchers and ethics committees are needed. This study is a valuable contribution to the global knowledge around disclosure of genetic SFs and especially valuable as research studies, policies and education programs are designed for genomic medicine in Africa.

Conclusion

There is a lack of primary research on genetic SFs, particularly in Africa, highlighting the urgent need for context-appropriate evidence. As a result, some healthcare professionals and researchers may be hampered to varying degrees by the lack of coherent guidelines and are unsure of their obligations in relation to clinical and ethical practice. Whilst the issue of genetic SFs has been widely discussed in the ethical literature, there is a paucity of primary research data pertaining to the views of the most interested stakeholders. The views of patients, health professionals, researchers and ethics committees need further investigation with a view to establishing a robust ethical framework and guidelines for good practice. To our knowledge, this is the first study of its kind in Africa and provides important insights that may, together with further empirical evidence, inform the development of policy on the

future use of genomics in research and clinical practice. The majority of survey respondents in this study indicated that research participants should be given the option of deciding whether to have genetic SFs returned. However, the degree to which participants favoured the return of findings varied depending on the type of SF (e.g. actionable vs. not actionable) and whether the finding was for the participant themselves or their child. The majority of participants indicated that they would want to have SFs disclosed to them regarding both themselves and their child for a disease that is clinically actionable (i.e., treatable or preventable). These insights underscore the key factors that would be relevant for consideration in policymaking going forward.

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Authors' contributions Soraya Seedat and The SHARED ROOTS Group contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Jolynne Mokaya, Jacqui Steadman, Nicole Schuitmaker, Martin Kidd, Sian Hemmings, Helena Kuivaniemi and Georgina Spies. The manuscript was written by Georgina Spies and all authors commented on previous versions of the manuscript. All co-authors (Jolynne Mokaya, Jacqui Steadman, Nicole Schuitmaker, Martin Kidd, Sian Hemmings, Jonathan Carr, Helena Kuivaniemi, and Soraya Seedat read and approved the final manuscript.

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Data availability The datasets generated during and/or analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Compliance with ethical standards

Competing interests GS, JM, JS, NS, MK, SH, JC and HK have no competing interests to declare. SS has received pharmaceutical sponsorship from Pfizer, Astra Zeneca, Servier and Dr. Reddy's, speaker's honoraria from Pfizer and Lundbeck, and honoraria from the Discovery Foundation and Cambridge University Press. She has also received research funding from the National Institutes of Health and the National Research Foundation (<https://www.nrf.ac.za/>).

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to participate Informed consent was obtained from all individual human research participants included in the study.

Consent for publication The authors affirm that in the informed consent process (consent landing page of the online survey), research participants were informed that the results may be used for publication in the future.

Code availability Not applicable.

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