Please cite as:

Fleming J, Critchley C, Otlowski M, Stewart C, Kerridge I. Attitudes of the general public towards the disclosure of individual research results and incidental findings from biobank genomic research in Australia. Intern Med J. 2015 Sep 21. doi: 10.1111/imj.12911.

Attitudes of the general public towards the disclosure of individual research results and incidental findings from biobank genomic research in Australia

Fleming J, Critchley C, Otlowski M, Stewart C, Kerridge I. (2015)

BACKGROUND:

Recent advances in science, technology and informatics have led to a rapid expansion of genomic research worldwide. This research has yielded an unprecedented volume of data including both Individual Research Results (IRRs) - 'pertinent results from research' that may have clinical relevance for individuals and their families, and Incidental findings (IFs), which can best be understood as "unanticipated discoveries" made during the course of an investigation but are outside the scope of the research [(1)]. Over the last decade, the management of the disclosure of both IRRs and IFs in the context of genomic research has been the subject of extensive scientific, ethical and legal commentary and critique [(2, 3)] and has emerged as a major challenge for biobanks (also known as tissue banks and biorepositories)[(4-12)]. Competing views amongst scholars as to the circumstances in which disclosure should be made have been articulated in the international literature. These range from arguments for a definite duty to disclose in specified circumstances,[(3)] to more cautious and qualified stances based around principles of 'harm minimisation' [(13, 14)]. Little is known internationally however, as to how the general public, as potential donors, view the issues surrounding the return of genetic research results.

Even fewer Australian studies have directly explored the concerns of the general public and/or biobank tissue donors [(11, 15-17)]. Studies have largely mirrored those conducted in Ireland [(17)] and Sweden [(18, 19)] which found that the general public were supportive of the retention of donated tissue for future unspecified research approv and were convinced that biobanks and the linkage of biological, clinical and population data provided a vital contribution to the acquisition of new knowledge. Importantly, these initial studies also suggest that there is public support for the appropriate disclosure of IRRs and IFs from biobank related research. A preliminary study by Fleming (2007) reported that the majority of both the general public (n=464) and cancer tissue donor (n=93) respondents wished to be informed about the general results of the research (82% of the public v 62% of donors), individual results that would suggest that they may have a possible predisposition for a genetic condition (84% of public v 83% of donors) and individual results that indicated that they may have an untreatable inheritable condition (75% of public and 72% of donors) [(11)].These findings are broadly consistent with a more recent and larger study among tissue donors arising from the International Sarcoma Kindred Study that examined attitudes towards genomic research amongst

individuals diagnosed with sarcoma, their blood relatives and proband spouses [20]. This study found that all donors wanted to receive information (90-94%) about monogenic or polygenic conditions in which risk could be modified, but that for monogenic conditions that were not preventable, sarcoma probands and blood relatives were less likely to want to receive information than non-blood relative spouses (66.5% vs 76%, *p*=0.05).

AIMS:

The aim of this research was to extend our understanding of the general public's preferences for disclosure of the results of genomic research, including IRRs and IFs by surveying a nationally representative sample of Australians. Specifically, we also sought to investigate the degree of public support for different models of disclosure including; non-disclosure, mandated disclosure, or the disclosure of certain findings and not others according to their salience or to the expressed preferences of the biobank donor.

METHODS

Participants and procedure

A total of 800 Australians over the age of 18 years and who could speak English participated in a computer assisted telephone interview (CATI). The study was approved by the University of Swinburne Human Research Ethics Committee (SUHREC2013/002). Telephone numbers were randomly generated by Samplworx, and were designed to represent the proportion of residents residing in each Australian State and Territory. The response rates according to the American Association of Public Opinion Research's (2009) definitions and calculations (i.e., RR1 – RR4) (AAPOR, 2009) ranged from 12% - 17%, which is typical for Australian national surveys conducted via CATI, random digit dialling (RDD) and cold calling members of the public without introductory letters[1] Because 1000's of randomly generated numbers are used with only a small proportion resulting in contact with an eligible household or person, the response rates calculated from this internationally recognised formula are significantly underestimated. This is exacerbated by the known difficulty with estimating the proportion of potentially eligible numbers not resulting in an interview (see: http://www.aapor.org/AAPORKentico/AAPOR_Main/media/MainSiteFiles/ERATE09.pdf).

The sample was relatively representative of the Australian population in terms of the states and territory of residence, education (43.4% had a university education) and ethnicity (87.4% described their nationality as Australian). Most of the sample had children (84.0%) and were either married or in a defacto relationship (66.4%; 12.6% were single, 9.6% were separated or divorced, 10.8% were widowed). A total of 84.0% described their health as being good to excellent (19.0% excellent, 33.9% very good, and 31.1% good), with 12.0% describing their heath as fair and 3.4% as poor. In terms of spirituality, 24.5% described it as being very important to them, 21.9% as quite important, 28.0% as not very important and 23.4% as not at all important.

The sample was, however, overrepresented by older people (M = 58.17, SD = 15.53, Range = 18 - 94) and females (66.0%). The current research therefore utilised a sample weight for all analyses based on the Australian Bureau of Statistics proportions for age group and gender. Reflecting the bias in age, a total of 38.5% of the sample were retired, with 48.5% currently employed, 6.6% engaged in home duties, 2.5% were full-time students, 1.0% were on a disability pension and 5.3% were unemployed.

[1] Sending introductory letters before calling potential respondents can increase the response rate, but was not within the budget for this survey.

Measures

The questionnaire instrument from which the CATI script evolved, was adapted from a survey tool previously developed by the first author for use within the Australian context [11]. The survey was identical in content and response options to the original measure, apart from minor wording changes to ensure it was suitable for a telephone interview (i.e., to explain scoring options, e.g., "By answering yes or no….", and and lead in sentences such as "I would like to ask you about your thoughts on..."). Although a number of issues were addressed in the instrument, only those that related to the return of results are reported in this paper. Prior to these questions, respondents were informed that we were interested in "what Australians think about cancer research and tissue banks", and were asked:

I *would like to ask you about your thoughts on the use of tissue samples in cancer research. Some cancer patients allow their blood or other tissue to be removed during surgery or a medical procedure to be stored for future research after all clinical testing on the sample has been completed. This is known as "tissue banking". A cancer tissue bank is therefore a collection of biological samples taken from patients after a medical procedure. The collection is then made available for future research.*

After answering questions relating to their views on consent, storage of tissue, linkage of data, funding of biobanks, intention to participate and reasons for participation, respondents were asked, "By answering YES or NO, if you allowed your blood or tissue sample to be used for research, would you be interested in receiving the following types of research results?" The four options were randomly presented across the sample to avoid order effects, and were: general information regarding the results of the study overall, specific information obtained from your sample that may be important to your health or treatment, your own potential genetic risk of an inherited disease, and any incidental findings that weren't directly related to your (potential) diagnosed condition.

RESULTS

A latent class analysis (LCA) was tested using MPLUS version 7 to identify potential groups of respondents with distinct patterns of interest in the four types of results. Cases with unsure responses to more than 30% of the four questions (n=21) were removed from the analysis and those who remained had their unsure responses imputed using MPLUS's Bayesian analysis (Rubin, 1987) (n=779, weighted n = 706). The results clearly suggested 3 distinct groups of respondents consistent with the theoretical categorisation of Ravitsky and Wilfond, who described 3 approaches to the disclosure of IRRs and IFs: full disclosure (autonomy focussed), non-disclosure (research focussed) and contextual or specified approach to disclosure (result evaluation approach)[21]. The sample size adjusted Bayesian Information Criterion (BIC) increased in value, the Bootstrap Lo–Mendell–Rubin (LMR) test became not significant from 3 to 4 classes [22] and entropy r for the 3 class solutions was .72, indicating good homogeneity within classes [23]. The percentage of respondents indicating interest in receiving the four types of results for the total sample and the three classes is shown in Figure 1.

The results in Figure 1 suggest that amongst the total sample, the majority of respondents would like access to all types of research results arising from the use of their blood/tissue in research. Primarily this involved general information that may be important to health or treatment, followed by the general research findings, then genetic risk information and finally incidental findings. Although less people expressed a desire to receive "any IFs that were not directly related to your (potential) diagnosed condition" (73.1%), there was a suggestion that most members of the public would still like to receive IFs.

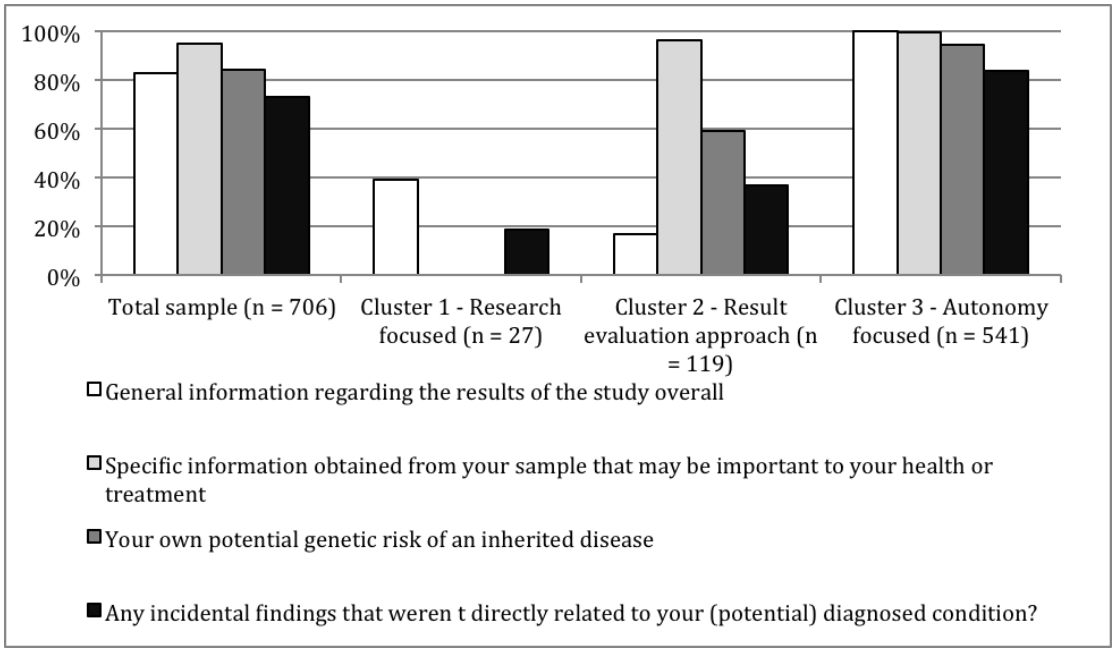

Figure 1. Percentage of 'Yes' responses to the four return of results questions. *Note.* All n's are weighted. Total unweighted n = 779.

Specifically, the majority of the sample (i.e., Class 3) displayed an "autonomy focused" perspective in that they expressed an interest in receiving all types of results, including incidental findings. A significant minority (i.e. Class 2) on the other hand tended to report a pattern more consistent with a "result evaluation" approach, with strong interest reported for receiving results that could have an impact upon health and treatment, and moderate interest in knowing their genetic risk for inherited disease, but weak interest in incidental findings and even weaker interest in general research findings. This class therefore appeared to emphasise results that were clinically valid and associated with findings that may have direct implication for their own health prevention. Although small, Class 1 displayed a pattern of findings consistent with a "research focused" approach. These respondents were generally not in favour of receiving any results, apart from the general research findings where 39.3% agreed they would be of interest. No one in this group was interested in findings that impacted on health, treatment or inherited diseases and only 18.6% reported being interested in incidental findings.

A series of Chi-Square tests computed between class membership and the demographic variables found (all were significant at $p<0.01$) that the research focused class (Class 1) tended to be more likely to be from the Northern Territory, male and retired than would be expected by chance. The autonomy focused class (Class 3) tended to be more likely to be from New South Wales, female and to have a university education, and not be retired, while the result evaluation class (Class 2) were less likely to be from NSW and to have a university education. A one-way analysis of variance (ANOVA) with Student-Newman Keuls post hoc contrasts revealed that those in the autonomy-focused class ($M = 51.16$, $SD = 17.80$) were significantly ($p<0.001$) younger than those in the research focused ($M= 60.5$, $SD = 17.82$) and result evaluation class ($M = 57.42$, $SD = 15.90$) whom were statistically similar. Although the Chi-Square tests did not reach significance for parental status, self-reported health and spiritual beliefs, the standardised adjusted residuals hinted that those in the autonomy focused class were less likely to have children ($z = 1.7$), more likely to be students ($z = 1.7$) and were more likely to report being in very good health ($z = 2.3$). There was also a suggestion that those in the result evaluation class were more likely to report that spiritual beliefs were not very important in their life ($z – 1.8$).

In summary, the research focused class (Class 1) tended to be older retired males from NT, the result evaluation class (Class 2) consisted of older people, not from NSW, with a university education and who placed low importance on spirituality, and the autonomy class (Class 3) tended to be younger people from NSW with a university degree, students and with a tendency towards very good health and not being parents. There were no significant differences across the classes in relation to marital status, and whether or not they were Australian born.

Discussion

The results of this research are broadly consistent with international data from the Scandinavia[18,19], the United Kingdom[17] and the United States[24] and suggest that the majority of the Australian public would be interested in receiving IRRs and IFs if they allowed their blood/tissue to be used in research. Specifically, 94.4% reported that they would like to receive specific information that may be important to your health or treatment, while 83.4% expressed a desire to be informed about their potential genetic risk of an inherited disease. Although less people expressed a desire to receive "any IFs that were not directly related to your (potential) diagnosed condition", most (70%) still wished to be informed about IFs.

Overall, the results of this study make clear that the majority of people want to know about most types of research results – including the overall results of the research, individual research results that may be relevant to the person's current and future health and any incidental findings arising from the research. The results also reveal that it is difficult to make broad assumptions about the public preferences for disclosure (beyond the assumption that people generally wish to be informed) as the LCA suggested people may differ in regards to what they wish to know about research results that may be less salient to them – such as the overall results of research or, to incidental findings arising from the research.

A number of limitations may restrict the generalisation of our research results and their translation into policy and practice. First, the specific results published in this paper reflect responses to only 4 specific questions regarding the return of research results (forming part of a more comprehensive survey exploring general public willingness to donate and attitudes towards ethical issues around biobank related genomic research). Undeniably, more nuanced questions and response categories would provide a deeper understanding of general public attitudes towards disclosure. All respondents were asked to indicate their willingness to take part in a brief follow up interview concerning their responses to the survey items and the majority of respondents (67%) indicating their willingness to participate in further research (findings from this qualitative study will be published in the near future).

The results from this,first national study of public attitudes and expectations to the return of research results and other ethico-legal issues relating to biobanks in Australia, nonetheless, provide a valuable account of public attitudes and a useful basis for further research. Secondly, it could be argued that the sample reflects the responses of only 800 Australians and is not representative of the general public. Further mixed-methods research would certainly establish the veracity and generalizability of our findings and we obtained the support from over 63% of respondents to participate in a brief follow up interview concerning their responses in the future. We also sought to deal with the response bias that characterizes CATI surveys by weighting the data for age and gender in line with census data. While this response rate appears relatively low, this is typical for Australian national surveys conducted via CATI, random digit dialing (RDD) and 'cold-calling' members of the Australian public without introductory letters (which range from 15-25%). Thus, while this research raises a series of further questions for study, the results presented here point to the need to think deeply about the way that we manage IRRs and IFs from biobank related genomic research in the future.

There are two major implications of this research. The first is that if people generally wish to be informed, but differ in what information they wish to know – then researchers who use biospecimens and biobank professionals need to establish policies and practices (including through information and consent forms) for establishing the information needs of tissue donors. The second is that clear strategies need to be established for determining what information derived from research, including both IRRs and IFs, may be of 'value' and how, and to whom, this information should be delivered.

CONCLUSION

The management of the results from translational genomic research in a consistent and clinically appropriate manner is already creating a practical challenge for clinical genetics services and for research biobanks around Australia and internationally. This challenge is likely to become increasingly problematic as genomic research expands, data linkage is adopted with greater enthusiasm and the amount of data generated by research increases. As more and more data is generated and interpreted to be of clinic significance, the question of defining significance and then acting upon such information in a manner expected by biobank donors, cancer patients and the community is paramount. It is crucial, therefore, that policies and processes are developed for the return of IRRs and IFs that are clinically appropriate and are consistent with the needs and expectations of biobank donors, patients and the general community.

The decisions we make about the disclosure and management of IRRs and IFs, both at a policy level and in relation to individual donors, are not however, simply a matter of science, epidemiology or medicine, as data only becomes 'evidence', or becomes important, when it is given value – irrespective of whether this value is attached by researchers, clinicians, policy-makers or patients and their families. It is vital, therefore, that policy development in this area is democratic, evidence-based and explicitly acknowledges the important ethical principles at stake, including autonomy, reciprocity and solidarity. Reassuringly, important research and policy reform is already being done in this area – with Australian oncology biobanks [20,25] recently outlining a number of models and practical strategies for managing disclosure of IRRs and IFs which aim to preserve and respect the autonomy of biobank donors while at the same time acknowledging the necessity for scientific judgements to be made about the utility and importance of research findings in different clinical and research settings. Similar research and policy development continues internationally, including by the American College of Clinical Genetics and Genomics (ACMG), the Association for Molecular Pathology (AMP), the NIH funded International Sarcoma Kindred Study group, the Presidential Commission for the Study of Bioethical Issues and the UK Biobank.

The results of this study are important because they provide data that may inform the development of practical disclosure strategies by oncology biobanks and complement recent policy responses – notably the NHMRC National Statement 2007 guidelines (sections 3. 4.10, 3.5.1 – 2 inc.) the NHMRC's *National Biobanking Strategy* and *Targeted Consultation on the Return of Results from 'Omics' based Research and Clinical Practice* (2013) developed by the Human Genetics Advisory Commission (HGAC) and the Australian Health Ethics Committee (AHEC)[26,1]. More generally, however, this research provides clear evidence that knowledge gained in the course of research is *valuable*, in different ways to different stakeholders, and that advances in genomic research will be most likely to be successfully, and to be publicly supported, when the structures that support it are scientifically robust, clinically relevant and ethically sound.

REFERENCES

1. National Health and Medical Research Council (Australia). Targeted Consultation Paper, 'Return of Results from 'Omics'-based Research and Clinical Practice' Canberra: Australian Government 2014.
2. Knoppers BM, Joly Y, Simard J, Durocher F. The Emergence of an Ethical Duty to Disclose Genetic Research Results: International Perspectives. European Journal of Human Genetics. 2006;14(1322):1170.
3. Wolf SM, Crock BN, Van Ness B, Lawrenz F, Kahn JP, Beskow LM, et al. Managing incidental findings and research results in genomic research involving biobanks and archived data sets. Genetics in medicine : official journal of the American College of Medical Genetics. 2012;14(4):361-84. Epub 2012/03/23.
4. Cambon-Thomsen A. The social and ethical issues of post-genomic human biobanks. Nature reviews Genetics. 2004;5(11):866-73. Epub 2004/11/03.
5. Cambon-Thomsen A, Rial-Sebbag E, Knoppers BM. Trends in ethical and legal frameworks for the use of human biobanks. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology. 2007;30(2):373-82. Epub 2007/08/02.
6. Hoeyer K. The ethics of research biobanking: a critical review of the literature. Biotechnology & genetic engineering reviews. 2008;25:429-52. Epub 2008/01/01.
7. Hoeyer K. Donors Perceptions of Consent to and Feedback from Biobank Research: Time to Acknowledge Diversity? Public health genomics. 2010;13(6):345.
8. Otlowski MFA. Disclosure of Genetic Information to At-Risk Relatives: Recent Amendments to the *Privacy Act 1988* (Cwth). Medical Journal of Australia. 2007;187(7):398.
9. Stranger M, Bell E, Nicol D, Otlowski M, Chalmers D. Human genetic databanks in Australia: indications of inconsistency and confusion. New Genetics and Society. 2008;27(4):311-21.
10. Catchpoole D, deFazio A, Devereux L, Fleming M, Schmidt C, al e. The importance of biorepository networks. The Australasian Biospecimens Network-Oncology. Australasian Journal of Medical Science. 2007;28:16-20.
11. Fleming J. Issues with tissues: Perspective of tissue bank donors and the public towards biobanks and related genetic research. In: Stranger ME, editor. Human biotechnology and Public Trust: Trends, Perceptions and Regulation. Hobart: Centre for Law and Genetics, Uni Tas; 2007. p. 184-201.
12. Kaye J, Boddington P, de Vries J, Hawkins N, Melham K. Ethical Implications of the Use of Whole Genome Methods in Medical Research. European Journal of Human Genetics. 2010;18:398.
13. Clayton EW, McGuire AL. The legal risks of returning results of genomics research. Genetics in medicine : official journal of the American College of Medical Genetics. 2012;14(4):473-7. Epub 2012/02/11.
14. Bledsoe MJ, Clayton EW, McGuire AL, Grizzle WE, O'Rourke PP, Zeps N. Return of research results from genomic biobanks: cost matters. Genetics in medicine : official journal of the American College of Medical Genetics. 2013;15(2):103-5. Epub 2012/09/01.
15. Critchley CR, Nicol D, Otlowski MF, Stranger M. Predicting intention to biobank: a national survey. European Journal of Public Health. 2010;Oct 5.
16. Chalmers D. Genetic Research and Biobanks. Methods in Molecular Biology2011. p. 1.

17. Cousins G, McGee H, Ring L, Conroy R, Kay EW. Public perceptions of biomedical research: A survey of the general population in Ireland. Ireland: Royal College of Surgeons in Ireland. Department of Health and Children. Health Research Board, 2005 June Report No.

18. Kettis-Lindblad A, Ring L, Viberth E, Hansson MG. Genetic Research and Donation of Tissue Samples to Biobanks. What do Potential Sample Donors in the Swedish General Public Think? European Journal of Public Health. 2005;16(4):433.

19. Kettis-Lindblad A, Ring L, Viberth E, Hansson MG. Perceptions of Potential Donors in the Swedish Public Towards Information and Consent Procedures in Relation to Use of Human Tissue Samples in Biobanks: A Population-Based Study. Scandinavian Journal of Public Health. 2007;35(2):148.

20. Young MA, Herlihy A, Mitchell G, Thomas DM, Ballinger M, Tucker K, et al. The attitudes of people with sarcoma and their family towards genomics and incidental information arising from genetic research. Clinical sarcoma research. 2013;3(1):11. Epub 2013/08/01.

21. Ravitsy V, Wilfond BS. Disclosing individual genetic results to researh participants. The American Journal of Bioethics. 2006;6(6):24-36.

22. Nylund, K.L., Asparouhov, T., & Muthén, B.O. (2007). Deciding on the number of classes in latent class analysis and growth mixture modeling: A Monte Carlo simulation study. Structural Equation Modeling, 14, 535-569.

23. Muthén, L.K. and Muthén, B.O. (2010). Mplus User's Guide. Seventh Edition.Los Angeles, CA: Muthén & Muthén

24. Haga SB, O'Daniel JM, Tindall GM et al. Public attitudes towards ancillary information revealed by pharmacogenetic testing under limited information conditions. Genetic Medicine. 2011;13(8):723-8.

25. Wakefield C.E, Thorne H, Kirk J, Niedermayr E, Doolan E.L, K. T. Improving mutation notification when new genetic information is identified in research: a trial of two strategies in familial breast cancer. Genetics in medicine : official journal of the American College of Medical Genetics. 2013;March(15(3)):187-94.

26. National Health and Medical Research Council (Australia). National Statement on Ethical Conduct in Human Research. 2007.

ACKNOWLEDGEMENTS

We wish to acknowledge that this article reports specific findings from research conducted as part of a large scale NHMRC Project Grant APP102929 (CIA Kerridge) 2012-2015: *Ensuring the utility and sustainability of tissue banks in Australia through informed regulation and community engagement*. Special thanks to Gordana Bruce and members of the CATI team at Swinburne University for ensuring the completeness of the national general public data collection.