BMJ Open

Heath policy guiding the identification, analysis and management of secondary findings for individuals undergoing genomic sequencing: a systematic review protocol

Safa Majeed,[1,2] Chloe Mighton,[3,4] David Malkin,[1,2,5,6] Yvonne Bombard [3,4]

To cite: Majeed S, Mighton C, Malkin D, *et al*. Heath policy guiding the identification, analysis and management of secondary findings for individuals undergoing genomic sequencing: a systematic review protocol. *BMJ Open* 2022;**12**:e065496. doi:10.1136/bmjopen-2022-065496

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-065496).

Received 09 June 2022
Accepted 14 December 2022

For numbered affiliations see end of article.

Correspondence to
Dr Yvonne Bombard;
yvonne.bombard@utoronto.ca

ABSTRACT

Introduction Genomic sequencing is increasingly enabling precision care across medical specialties; however, the discovery of genomic 'secondary findings' (SFs) unrelated to the patient's primary indication remains a profuse, unintended consequence. Existing practices within the continuum of SF identification, analysis and management are numerous, inconsistent and sometimes contradictory across health conditions and regions. Final decisions are often at the discretion of the genomic sequencing laboratory, bioinformatician or treating physician. This difference in healthcare delivery causes inconsistent information, disclosure and downstream impacts required to manage SFs and patient outcomes. Improving our understanding of the SF health policy landscape can determine components of the SF policy continuum spanning generation through to management that are in conflict, limitations of current guidance and existing needs across clinical settings.

Methods and analysis We will carry out a systematic review to catalogue and appraise current guidance directing the identification, analysis and management of SFs for participants receiving genomic sequencing globally. We will conduct a comprehensive search of Medline (Medline R, Medline Epub Ahead of Print and Medline-In-Process & In-Data-Review Citations), Embase and Cochrane databases (n=5, inception to Feb 2022) and a grey literature search of international genomics websites (n=64; inception to May 2022). Key inclusion criteria include: guidance produced by health organisations, bioethics committees and professional associations, outlining recommendations for: (1) SF identification, (2) SF analysis or (3) SF management. Non-English language articles and conference abstracts will be excluded. Guidance will be critically appraised with the Appraisal of Guidelines for Research & Evaluation Instrument (AGREE) II tool. We will interpret our findings by process and across populations using a qualitative descriptive approach.

Ethics and dissemination Our systematic review evaluates published data and does not require ethics review. Our findings will be disseminated through peer-reviewed publications, conference presentations and workshops with precision medicine stakeholders.

PROSPERO registration number CRD42022316079.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This systematic review will offer the highest level of rigorous, evidence synthesis of the most comprehensive set of international guidance for the identification, analysis and management of secondary findings (SF).
⇒ This systematic review will only consider English-language articles, introducing a potential language bias that may result in missing relevant SF health policy from non-English-speaking countries and international organisations.
⇒ This systematic review will critically appraise the quality and rigour underlying global SF guidance in clinical practice, for the first time, to inform future policy development for the identification, analysis and management of SF.

INTRODUCTION

Over the last decade, the widespread integration of genomic profiling across medical disciplines through programmes like the 100 000 genomes project[1] has dramatically improved our understanding of how to diagnose, manage and treat disease, heralding a new era for precision medicine globally.[2–4] This vast expansion of next-generation sequencing (genome, exome and large targeted panel sequencing) has consequently led to the incidental and sometimes opportunistic discovery of 'secondary findings' (SFs), genomic variants thought to be unrelated to a patient's presenting clinical condition. Current guidance relating to (a) the identification of such SFs (ie, which SF genes should actively be interrogated), (b) SF analysis methods including bioinformatic standard practices and (c) downstream SF clinical management (ie, disclosure, screening, surveillance, etc) is incongruous.

Legal, ethical and social implications brought about by SF interrogation have led to

numerous SF policies that fluctuate in their recommendations across patients, health conditions and geographic regions globally.[5–9] For instance, the European Society of Human Genetics has taken a cautious approach to SF analysis, similar to that of the Canadian College of Medical Geneticists,[10] whereby the active interrogation or clinical return of SFs is not recommended.[9 11 12] This is contradictory to parallel recommendations released by the American College of Medical Genetics and Genomes (ACMG) guidelines in 2013[13] (and subsequently updated to recommend a minimum list of 73 SF gene–disease pairs,[14] which represented the first tangible gene list published to direct the identification and analysis of genomic SFs. Furthermore, institutional SF practices within countries are variable and often left to the discretion of the genomic sequencing laboratory, bioinformatician or treating physician. This variation leads to differences in healthcare delivery across patients, which can cause inconsistent information, disclosure and downstream impacts required to manage SFs and outcomes for patients.

There are a myriad of SFs which can be categorised into the following 'bins': medically actionable genes and pharmacogenomic variants, common disease risk variants, Mendelian disease genes, early onset neurodegenerative disorder genes and carrier status results.[15] However, even genes within these SF categories may differ in their prevalence and impact across patient populations (ie, prenatal, neonatal, paediatric, adult, etc), and these differences should be accounted for by recommended bioinformatic SF analysis pipelines and clinical practice guidelines.

Moreover, significant research efforts to better understand SF analysis and disclosure preferences among patients, clinicians and other healthcare professionals internationally have been conducted; most studies concluded that all three parties favour the analysis and disclosure of clinically relevant findings.[16–19] Parallel research efforts to synthesise evidence surrounding clinical SF disclosure practices and management[5 6] have been unremunerated due to the widespread practice variation and disparate reporting across studies that limit study generalisability and comparison. Although key policies such as the ACMG V.3.0 guidelines identify a subset of SFs for investigation and report some recommendations for SF disclosure, gaps in guidance remain across the continuum of SF identification, analysis and management, and with respect to how these processes link together. An improved understanding of the landscape of SF health policy is necessary to identify existing gaps and inconsistences and to inform future policy work.

To address this unmet need, we propose a systematic review of the literature that synthesises current international guidance directing healthcare providers on the identification, analysis and management of SFs. Our systematic review addresses the following question: What are the current health policies guiding the identification, analysis and management of SFs for individuals undergoing genomic sequencing, and how do they vary internationally?

METHODS AND ANALYSIS

Design and registration

This systematic review will follow the 2020 Preferred Reporting Items in Systematic Reviews and Meta-Analyses (PRISMA) guidelines[20 21] and the protocol adheres to the PRISMA-Protocols guidelines.[22 23] The systematic review protocol was registered in the International Prospective Register of Systematic Reviews database on 10 March 2022. Any revisions to the systematic review protocol will be reported in the primary review publication. The PRISMA-P checklist and locations for their corresponding application to this protocol are found in online supplemental appendix.

Eligibility criteria

A complete outline of the PICOS eligibility criteria is found in table 1.

Population

We will include articles that report policy for human participants receiving genomic sequencing. Participants can be healthy or disease-affected individuals or mixed cohorts and can include adult, paediatric, neonatal, prenatal or mixed populations.

Intervention

Only articles which reference (whole) exome-wide, targeted and/or genome-wide sequencing or profiling will be included. Articles do not need to evaluate a comparator group. Included articles must also discuss genomic secondary findings from genomic sequencing, defined as genomic findings to secondary to the primary clinical indication for testing including secondary incidental, additional, unsolicited or unexpected, findings, variants or results. However, articles evaluating policy surrounding the incidental discovery of parental consanguinity through genomic sequencing are beyond the scope of this review and will be excluded.

Outcomes

Articles included must also encompass written guidance (guidelines, policy or statements) produced by international, national and regional governmental and non-governmental health organisations, bioethics committees or professional associations, societies or colleges. Articles which evaluate or build on guidance or policy previously published can be included. Three primary processes will be evaluated. These include written guidance regarding the (a) identification (ie, classes of SFs recommended for evaluation), (b) analysis pipeline for genomic secondary findings (such as bioinformatic pipelines used, filtering and masking procedures, etc) and (c) policy regarding their return and management to individuals or families undergoing genomic sequencing. Secondary processes considered include age-specific distinctions in policy

Majeed S, *et al*. *BMJ Open* 2022;**12**:e065496. doi:10.1136/bmjopen-2022-065496

Table 1 Eligibility criteria for the systematic review of heath policy guiding the investigation and disclosure of genomic secondary findings

	Inclusion	Exclusion
Population	Individuals of all ages and disease indications (including healthy populations) receiving genomic sequencing.	Articles that do not focus on humans (eg, animal, model organism, in vitro studies).
Intervention	Identification of secondary findings through genomic sequencing (next-generation sequencing such as genome, exome, or targeted genomic sequencing). Secondary findings are defined as secondary incidental, additional, unsolicited, or unexpected, findings, variants or results.	Article populations that do not receive exome or genome sequencing or profiling (eg, articles that only involve analysis such as chromosomal microarray (CMA), genotyping, single-gene testing, karyotyping). Exclude articles in which secondary findings are not referenced (eg, studies that reference guidance of only primary genomic results/analysis). Articles regarding the incidental discovery of parental consanguinity through genomic sequencing.
Comparator	No comparator groups.	
Outcomes	Written guidance (guidelines or statements) produced by international, national, and regional governmental and non-governmental health organisations, bioethics committees or professional associations relating to the A. identification, B. analyses and/or C. disclosure of secondary findings to individuals/families undergoing genomic sequencing. Evidence that reports one or more of these processes will be included.	Articles that do not encompass written guidance (guidelines, policy, or statements) produced by international, national, and regional governmental and non-governmental health organisations, bioethics committees or professional associations, societies or colleges. Articles that do not reference the identification, analyses or return of genomic secondary findings.
Study design	All articles (empirical and non-empirical evidence) that address documentation comprising guidelines (such as clinical practice guidelines, reporting guidelines), legislation, position papers, consensus statements and other reports. Review articles (eg, scoping, systematic, etc.), editorials, commentaries whereby one of the aims of the study was to develop relevant guidelines. English language and full-text articles.	Review articles, editorials, commentaries whereby none of the study aims are to develop the relevant guidelines. However, reference lists of relevant excluded articles will be reviewed for any references missed by the search strategy. Non-English language articles. Conference abstracts.

across population groups. Evidence that reports one or more of these processes can be included.

Study design

All articles (empirical and non-empirical evidence) that address documentation comprising guidelines (such as clinical practice guidelines, reporting guidelines), legislation, position papers, consensus statements and other reports will be included. Review articles (eg, scoping, systematic, etc), editorials, commentaries will be excluded unless one of the aims of the study was to develop the aforementioned guidelines. However, their reference lists will be reviewed for any references missed by the search strategy. Only English-language and full text-articles will be included.

Information sources

A professional librarian will run an extensive search in the following databases (n=5; from inception to February 2022): Medical Literature Analysis and Retrieval System Online (MEDLINE; including R, Epub Ahead of Print, In-Process & Other Non-Indexed Citations), Excerpta Medical dataBASE (EMBASE; OvidSP) and Cochrane (Wiley). We will also run a grey literature search of International Federation of Human Genetics Societies (IFHGS) member websites (n=64; from inception to May 2022).

Search strategy

The electronic database search strategy proposed was developed by a professional librarian in MEDLINE and adapted for each of the other databases as needed. Both subject headings and text-word terms for "Gene sequencing" AND "incidental findings" AND "policy" were used. For grey literature searching, terms related to 'genetic testing', 'secondary findings', 'analysis', 'disclosure' and 'management' will be used to search for records on the search box of all IFHGS member websites. We will include all languages and years covered in the databases but excluded conference abstracts. All references will be saved in an EndNote library used to identify duplicates. The remaining unique references will be reviewed against our inclusion criteria. The references of included articles will be hand-searched for relevant publications that were not identified in the search. Preliminary searches and strategies across all databases, conducted in February 2022, are found in online supplemental appendix table S1–S5.

Data management

All search results will be saved and deduplicated in an EndNote 20.3 library. Records will be transferred to Covidence (www.covidence.org) where record management, screening and data extraction will be conducted.

Screening and data extraction

Each article will be screened independently by two members of the review team (n=6) at each stage (title/abstract, followed by full-text screening) based on the predefined inclusion/exclusion criteria. Conflicts will be resolved through discussion, leading to consensus opinion, and subsequent inclusion of a third reviewer where needed. Reasons for exclusion will only be recorded at the full-text screening phase. The Cohen's

Kappa metric will be calculated to capture inter-rater reliability during screening phases.

Next, two reviewers will independently extract data for each article that is included after full-text screening. Data for extraction include: (a) bibliographic information (publication title, authors, affiliations, date, country of origin in addition to other countries referenced by the article), (b) participant population described (age, sex/gender, race/ethnicity/ancestry, disease phenotype for primary indication), (c) genomic sequencing indicated (type of sequencing such as genome or exome, etc) and (d) processes which include guidance about SF identification and analysis methods (variant analysis and interpretation methods and pipelines, SF categorisation or classification methods, etc), and policy surrounding SF management and disclosure to individuals/families undergoing genomic sequencing (time of disclosure, participants involved, settings, etc).

Risk of bias

Each of the included policies will subsequently undergo critical appraisal. Thus, we will use the Appraisal of Guidelines for Research & Evaluation Instrument (AGREE) II tool, an international tool to assess the quality and reporting of practice guidelines, to identify areas of strength and weakness across the guidance we identify. The AGREE-II tool will evaluate the guidance development processes and the rigour with which each guidance was developed.[24 25] Specifically, the AGREE tool evaluates six distinct domains: scope and purpose—overall aim of the guideline, stakeholder involvement—role and expectations of stakeholders, rigour of development—gathering and summarising the evidence, clarity of presentation—technical guidance, applicability—barriers and facilitators to implementation, editorial independence—identifying potential biases. Each domain includes items that are scaled from 1 to 7[25]. A quality score is calculated for each of the domains, with an overall score calculated by summing all the domains. Two members of the study team will independently appraise each study. Conflicts will be resolved through discussion and inclusion of a third reviewer if needed.

Evidence synthesis

A qualitative descriptive[26–28] approach will be used to synthesise and summarise core elements identified across SF guidance. Guidance will be synthesised across target populations and key stakeholders involved in SF genomic sequencing. The recommendations will be coded using an inductive approach to first understand the topics covered within the guidance. Next, key themes underlying these topics will be summarised. Finally, we will compare our themes across populations and stakeholder subgroups (healthcare providers, laboratories, regulatory bodies, researchers, etc) to identify commonalities and differences. The qualitative synthesis from our review will enable us to understand the core elements defined across policy for the identification, analysis and management of SFs and pertaining to various stakeholders and patient populations. We will also describe the topics of guidance that are most debated within the field, presenting all views and policy characteristics (demographics, date of publication, etc) and participant populations referenced. Written guidance pertaining to each of the primary processes will be compared and represented to depict the landscape of SF health policy internationally and across age groups. Overall quality of the included studies from the critical appraisal process will be summarised and used inform final conclusions drawn regarding SF investigation, analysis and management guidance identified internationally.

Patient and public involvement

None.

Ethics and dissemination

The proposed study is a planned systematic review of published data and thus does not contain clinical studies or patient data. There are no ethical or safety concerns. The study findings will be disseminated in a peer-reviewed journal article and conference presentations.

DISCUSSION

The proposed systematic review will report the most comprehensive and up-to-date synthesis of guidance across the entire continuum of SF generation through to management. It will be the only existing review to characterise the quality of guidance produced by organising and regulatory institutions and identify gaps for future iterations of SF health policy. Our review will search several existing databases in addition to website of international human genetics associations to capture the global health policy landscape for SFs. Existing heterogeneity across SF health policy in genomic precision medicine demonstrates that a singular SF policy cannot sufficiently address all of the components in the SF policy continuum (from identification through to management) and for all patient groups; therefore, we will integrate a qualitative descriptive perspective to interpret and contextualise the results to understand core elements and areas of debate defined across policy for the identification, analysis and management of SFs.

Although our systematic review aims to capture and integrate global perspectives, it will only consider English-language articles. This limitation is particularly relevant for human genetic association websites that are not written in English or house English language articles, as they will not be adequately searched or included. Notwithstanding, we will make note of the non-English websites and articles encountered to better understand how significantly our results are limited and to ensure any conclusions specifically state and adequately represent the countries and perspectives reported.

Author affiliations
[1]Medical Biophysics, University of Toronto, Toronto, Ontario, Canada

[2]Genetics & Genome Biology, The Hospital for Sick Children, Toronto, Ontario, Canada
[3]Genomics Health Services Research Program, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada
[4]Institute of Health Policy, Management, and Evaluation, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada
[5]Division of Hematology/Oncology, The Hospital for Sick Children, Toronto, Ontario, Canada
[6]Department of Pediatrics, University of Toronto, Toronto, Ontario, Canada

Contributors SM and CM contributed to the design and draft of this systematic review protocol. YB and DM contributed to protocol design and revisions. The final manuscript was approved and edited by all authors.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD
Yvonne Bombard http://orcid.org/0000-0002-9516-4539

REFERENCES

1 Turnbull C, Scott RH, Thomas E, *et al*. The 100 000 Genomes Project: bringing whole genome sequencing to the NHS. *BMJ* 2018;361:k1687.
2 Ginsburg GS, Phillips KA. Precision medicine: from science to value. *Health Aff* 2018;37:694–701.
3 Nakagawa H, Fujita M. Whole genome sequencing analysis for cancer genomics and precision medicine. *Cancer Sci* 2018;109:513–22.
4 Sabbagh R, Van den Veyver IB. The current and future impact of genome-wide sequencing on fetal precision medicine. *Hum Genet* 2020;139:1121–30.
5 Sapp JC, Facio FM, Cooper D, *et al*. A systematic literature review of disclosure practices and reported outcomes for medically actionable genomic secondary findings. *Genetics in Medicine* 2021;23:2260–9.
6 Knoppers BM, Zawati Ma'n H, Sénécal K. Return of genetic testing results in the era of whole-genome sequencing. *Nat Rev Genet* 2015;16:553–9.
7 Kalia SS, Adelman K, Bale SJ, *et al*. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of medical genetics and genomics. *Genet Med* 2017;19:249–55.
8 Pujol P, Vande Perre P, Faivre L, *et al*. Guidelines for reporting secondary findings of genome sequencing in cancer genes: the SFMPP recommendations. *Eur J Hum Genet* 2018;26:1732–42.
9 van El CG, Cornel MC, Borry P, *et al*. Whole-Genome sequencing in health care: recommendations of the European Society of human genetics. *Eur J Hum Genet* 2013;21:580–4.
10 Boycott K, Hartley T, Adam S, *et al*. The clinical application of genome-wide sequencing for monogenic diseases in Canada: position statement of the Canadian College of medical geneticists. *J Med Genet* 2015;52:431–7.
11 de Wert G, Dondorp W, Clarke A, *et al*. Opportunistic genomic screening. recommendations of the European Society of human genetics. *Eur J Hum Genet* 2021;29:365–77.
12 Hehir-Kwa JY, Claustres M, Hastings RJ, *et al*. Towards a European consensus for reporting incidental findings during clinical NGS testing. *Eur J Hum Genet* 2015;23:1601–6.
13 Green RC, Berg JS, Grody WW, *et al*. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet Med* 2013;15:565–74.
14 Miller DT, Lee K, Chung WK, *et al*. ACMG SF v3.0 list for reporting of secondary findings in clinical exome and genome sequencing: a policy statement of the American College of medical genetics and genomics (ACMG). *Genet Med* 2021;23:1381–90.
15 Reble E, Gutierrez Salazar M, Zakoor K-R, *et al*. Beyond medically actionable results: an analytical pipeline for decreasing the burden of returning all clinically significant secondary findings. *Hum Genet* 2021;140:493–504.
16 JE C*et al*. Whether, when, how, and how much? General public's and cancer patients' views about the disclosure of genomic secondary findings. *BMC Med Genomics* 2021;14.
17 Mackley MP, Fletcher B, Parker M, *et al*. Stakeholder views on secondary findings in whole-genome and whole-exome sequencing: a systematic review of quantitative and qualitative studies. *Genet Med* 2017;19:283–93.
18 Delanne J, Nambot S, Chassagne A, *et al*. Secondary findings from whole-exome/genome sequencing evaluating stakeholder perspectives. A review of the literature. *Eur J Med Genet* 2019;62:103529.
19 Horiuchi Y, Matsubayashi H, Kiyozumi Y, *et al*. Disclosure of secondary findings in exome sequencing of 2480 Japanese cancer patients. *Hum Genet* 2021;140:321–31.
20 Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
21 Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535–336.
22 Moher D*et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2016;20:148–60.
23 Shamseer L, Moher D, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;349:g7647.
24 Dans AL, Dans LF. Appraising a tool for guideline appraisal (the agree II instrument). *J Clin Epidemiol* 2010;63:1281–2.
25 Brouwers MC, Kho ME, Browman GP, *et al*. Agree II: advancing Guideline development, reporting and evaluation in health care. *Can Med Assoc J* 2010;182:E839–42.
26 Sandelowski M. What's in a name? qualitative description revisited. *Res Nurs Health* 2010;33:77–84.
27 Colorafi KJ, Evans B. Qualitative descriptive methods in health science research. *HERD* 2016;9:16–25.
28 Sandelowski M. Whatever happened to qualitative description? *Res Nurs Health* 2000;23:334–40.