Beyond One Million Genomes

D2.2

Policy document for a genome data sharing initiative

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19/05/2023	0v1	Susanne Rebers (BBMRI-NL)	Initial draft circulated to WP participants for feedback
01/06/2023	0v2	Susanne Rebers (BBMRI-NL)	WP comments addressed.
11/07/2023	0v2	Nikki Coutts (ELIXIR Hub)	Version circulated to B1MG-OG, B1MG-GB and Stakeholders for feedback
21/07/2023	0v3	Susanne Rebers (BBMRI-NL)	Comments addressed.
31/07/2023	1v0	Nikki Coutts (ELIXIR Hub)	Version uploaded to the EC Portal

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1. Executive Summary

In task 2.2, three policy recommendations were developed, based on existing literature, policy documents and guidelines. Care was taken to develop recommendations specifically for use in a large-scale pan-European research infrastructure. Three policy recommendations were developed:

1: minimal standards for inclusion of special groups of data subjects such as minors, persons not able to consent, vulnerable population groups, minorities, and deceased persons;

2: minimal standards for feedback provision to data subjects;

3: minimal standards on how to deal with incidental findings.

The fourth planned policy recommendation, minimal standards and best practice guidelines for consent forms to allow the use of genomic data in a pan-European genome initiative, was built on ethical best practice and subsequently transferred and combined for the deliverable 2.4, because the recommendations needed to be integrated in the GDPR requirements for a final recommendation on transparency and consent that meets both ethical and data protection best practice.

Below the main recommendations of the policies are described. Full recommendations, including the precise scope, background, considerations, and other relevant aspects, can be found further in this document.

Minimal standards for inclusion of special groups of data subjects

Before including data of persons, who had been considered vulnerable during the initial collection of data and biological samples, for secondary use in the 1+MG initiative, researchers and/or respective RECs must re-examine the content of the informed consent given during the initial collection of data and samples to ensure that the scope of the consent covers activities planned in 1+MG initiative and the way of communicating the information clearly delivers a message that the data may be used in an initiative, like 1+MG.

National 1+MG nodes, researchers and RECs should recognize that vulnerability impacts not only the informed consent process, but also different aspects of the ongoing participation in 1+MG initiative, such as withdrawing consent, relationships with researchers, participation in public/patient involvement activities, dealing with incidental findings etc. These aspects should be discussed in detail among the stakeholders before including data for secondary use in 1+MG initiative.

National 1+MG nodes, researchers and RECs should recognize that including the data for secondary use in 1+MG initiative may enable new types of vulnerability applying to already vulnerable groups, vulnerable persons, or groups that were not considered vulnerable at the time of primary collection of data and samples. Ongoing reflection on such possible new types of

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vulnerability emerging from, e.g., application of new analytical techniques, artificial intelligence or prediction tools should be pursued.

If an ethnic or cultural group (including ethnic and cultural groups from third countries) is to be the subject of including their data for secondary use in 1+MG initiative, additional consent may be required "*at a group level through its cultural appropriate authorities*" (ESHG, 2003). The respective REC has to decide whether additional group level consent is needed, taking into account cultural differences, potential of discrimination and stigmatisation, and respecting rights of minorities within the group. (Kowal, 2015; Rotimi & Marshall, 2010) The rights and interests of the group should be protected, especially "*in terms of benefit sharing*". (WMA, 2016)

In line with the "1+MG Incidental Findings Policy" including specific points-to-consider for research involving minors, return of clinically actionable findings in minors might be even more pressing than in less vulnerable groups. In general, if 1+MG incidental findings reveal conditions in minors that are clinically actionable during childhood through early life intervention, they should be communicated as considered to be in the best interests of the child. The communication must involve professional support to explain the research findings and to deal with the psychological and emotional impacts of information.

Considerations for inclusion of specific special groups can be found in the full policy below.

Minimal standards for feedback provision to data subjects

This policy recommendation covers general feedback of the general results of research studies conducted with data provided through 1+MG to data subjects. The 1+MG policy only applies to analyses conducted in the context of 1+MG data sharing. Data uses addressed in the primary data collection context should be covered by local policies.

In an analysis of current guidelines and best practices, we identified four important principles to provide feedback of general research results to data subjects: transparency, accountability, privacy, and the fair distribution of benefits. Based on these four principles, a recommendation to provide feedback of general research results to data subjects is set up. Other considerations are taken into account when determining how to provide this feedback. In the 1+MG federated infrastructure, the responsibility to engage with data subjects lies with the signatories. It is therefore presumed that feedback is organised by the national nodes. Practical issues, such as restricted time and expertise available to develop information that is clear to data subjects, are taken into account. The summarised recommendations are as follows:

1: Provide a complete list of scientific publications using the 1+MG infrastructure online. In order to facilitate the completion of this list, it is recommended to require data users to acknowledge 1+MG in the acknowledgements of each scientific publication, and requiring them to use a standardised sentence and/or a 1+MG study number. This requirement should be agreed upon in the Data Transfer Agreement. 1+MG personnel can then easily search catalogues of scientific publications (e.g. Pubmed.gov) for papers using the 1+MG infrastructure. It may be decided that

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the central 1+MG organisation takes over this search to increase efficiency to the benefit of all national nodes.

2: Provide examples of completed studies and their research results on the 1+MG website. A science communication expert should be involved in the development of the examples and provide advice on the best format to provide each example (e.g. written text, movies, animations, etc.) to ensure the examples will be understandable for most data subjects. If a participant panel is available, it could provide valuable input. If the studied population is expected to have special communication needs (e.g. a visual or mental impairedness), these should be taken into account. Examples should be offered in at least the official language of the member state from which data subjects were included in the study (i.e. the national node).

We also recommend 1+MG to follow as many of the best practices outlined below as feasible:

- 1+MG may allow data subjects or other interested people (general public) to subscribe to a yearly newsletter. This (e-mail) newsletter, offered in all official EU languages, could contain a hyperlink to the list of publications, the examples of completed research studies, and potentially also request for (further) participation in 1+MG.
- If 1+MG decides to set up a participant panel, 1+MG may request this participant panel to offer (binding) advice about which research studies should be converted into an example on the website. The participant panel may be asked to ensure all relevant types and the whole width of research studies are covered.
- 1+MG may use social media (e.g. Facebook, Instagram or Twitter) to inform the public about new examples of completed research studies on the website. When determining which social media should be used, available resources and the target audience(s) should be taken into account.
- Use best practice examples, such as the Cochrane plain language summaries guidance[1] or other guidelines, to write clear text about examples of studies.

Minimal standards on how to deal with incidental findings

The 1+MG ethical and legal data governance framework will need to adopt policies and agreements addressing the handling of IFs emerging from secondary use of 1+MG data. Unless otherwise indicated, the policy options below apply regardless of the initial sequencing context (e.g., research or healthcare), and regardless of the use case (e.g., research secondary use or healthcare secondary use).

Any return of IFs through 1+MG requires coordination between several actors. First, a data user (researcher or healthcare provider) would identify a potential IF, and report it - possibly through a contact point at the national node - to the original data holder. The data holder would make the final determination if reporting the IF to the data subject is possible, feasible and appropriate, according to local IF policy incorporating clinical, ethical, and practical considerations, including the data subject's consent. Recognizing not all data holders will have

[1] https://training.cochrane.org/handbook/current/chapter-iii#section-iii-4

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the same maturity of policies and processes, we encourage voluntary best practices and points-to-consider below ("Handling IFs - Best Practices and Points-to-Consider for Data Submitters").

This recommendation focuses on the IF policy applying to 1+MG data users (researchers or healthcare providers accessing 1+MG data). It presents policy options, including a recommended option, and discusses pros and cons of each.

The policy options only address if and when a 1+MG user flags a potential IF to the national node/data holder. Under all policy options, we recommend that the **data holder (ideally in collaboration with the data subject's physician) makes the final decision whether or not, and how, to feedback IFs to data subjects and their family members. This ensures respect for the original IF policy and local legal and ethical requirements**. Furthermore, the data holder is best positioned to check whether the IF is relevant (and new). The user and 1+MG would have no more responsibility. To assist data holders, we outline best practices for handling IFs below.

Option 1. Common Requirement for Users to Feedback (Only) Valid and Clinically Actionable IFs (*recommended*)

- 1+MG requires users to report IFs if the following reporting criteria are met:
- Analytic validity - the sequencing assay reliably detects the variant.
- Clinical validity - the variant confers a significant degree of risk of the condition to the data subject or his/her family members.
- Excludes variants of unknown significance.
- Clinically actionable - reporting of information provides an opportunity to improve the clinical care of the data subject or his/her family members.
- Findings relate to a condition that is sufficiently serious or severe enough to merit clinical intervention.
- There is a standard clinical intervention available to treat (or in some cases prevent) the condition.

The exact definitions and thresholds for these criteria would need to be agreed upon by the 1+MG community.

This obligation would apply to 1+MG data users regardless of the secondary use case (research or healthcare use), and regardless of the initial sequencing country or context (research or healthcare). The obligation would be made binding on users through the 1+MG data access agreements or a similar mechanism. These general criteria trigger an initial reporting of an IF back to the 1+MG data holder. The data holder then follows local IF policy to confirm the finding is truly an IF that should be reported back to the data subject or family member (where appropriate and legally permissible). If for example the data holder knows data are low quality, or that the IF has already been reported to the data subject or family member, then the data holder may opt not to return the finding. A geneticist or designated physician may be involved in

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the assessment of the IF to determine if it is relevant (and new) in the data subject's particular health context, as well as in the communication.

We recommend only clinically actionable IFs be reported through 1+MG. Recall that this policy does not stand alone or replace local IF policies. It applies as a **complementary reporting mechanism**, in addition to any local IF policies and processes applying in primary sequencing contexts (healthcare, research, and biobanking). Local IF policy may cover a broader set of findings. The 1+MG can only increase (and will never decrease) the probability that an IF is reported back. Given this complementary quality, it is not necessary for all stakeholders to agree on the exact meaning of the criteria.

We recommend this option because it provides meaningful consideration for the welfare of data subjects, while providing clear and manageable obligations for 1+MG data users, while also leaving the ultimate decision with data holders.

Option 2. Data Submitter Tags Data with Local Feedback Requirement

1+MG allows data holders to establish their own local policy/criteria for reporting IFs, to apply to secondary use of their own data, subject to the data holder's ability to demonstrate capacity to ensure the appropriate handling of IFs.

Under this option, data holders could be permitted to impose different feedback policies on 1+MG users for research-generated data and healthcare-generated data.

We discourage this option because it is likely to lead to complex and hard to understand obligations for 1+MG and data users.

Option 3. "No Feedback" Policy for Users

1+MG does not permit any feedback of IFs from secondary use to the national node.

We discourage this option because it risks failing to demonstrate adequate concern for the welfare of 1+MG data subjects and their families.

2. Contribution towards project objectives

With this deliverable, the project has reached or the deliverable has contributed to the following objectives/key results:

[Select 'Yes' (at least one) if the deliverable contributed to the key result, otherwise select 'No'.]

	Key Result No and description	Contributed
Objective 1 Engage local, regional, national and European stakeholders to	**1.** B1MG assembles key local, national, European and global actors in the field of Personalised Medicine within a B1MG Stakeholder Coordination Group (WP1) by M6.	No
	2. B1MG drives broad engagement around European access to personalised medicine data via the B1MG Stakeholder	No

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define the requirements for cross-border access to genomics and personalised medicine data	Coordination Portal (WP1) following the B1MG Communication Strategy (WP6) by M12.	
	3. B1MG establishes awareness and dialogue with a broad set of societal actors via a continuously monitored and refined communications strategy (WP1, WP6) by M12, M18, M24 & M30.	No
	4. The open B1MG Summit (M18) engages and ensures that the views of all relevant stakeholders are captured in B1MG requirements and guidelines (WP1, WP6).	No
Objective 2 Translate requirements for data quality, standards, technical infrastructure, and ELSI into technical specifications and implementation guidelines that captures European best practice	**Legal & Ethical Key Results**	
	1. Establish relevant best practice in ethics of cross-border access to genome and phenotypic data (WP2) by M36	Yes
	2. Analysis of legal framework and development of common minimum standard (WP2) by M36.	No
	3. Cross-border Data Access and Use Governance Toolkit Framework (WP2) by M36.	Yes
	Technical Key Results	
	4. Quality metrics for sequencing (WP3) by M12.	No
	5. Best practices for Next Generation Sequencing (WP3) by M24.	No
	6. Phenotypic and clinical metadata framework (WP3) by M12, M24 & M36.	No
	7. Best practices in sharing and linking phenotypic and genetic data (WP3) by M12 & M24.	Yes/No
	8. Data analysis challenge (WP3) by M36.	Yes/No
	Infrastructure Key Results	
	9. Secure cross-border data access roadmap (WP4) by M12 & M36.	Yes/No
	10. Secure cross-border data access demonstrator (WP4) by M24.	Yes/No
Objective 3 Drive adoption and support long-term operation by organisations at local, regional, national and European level by providing guidance on phased development (via the B1MG maturity level model), and a methodology for economic evaluation	**1.** The B1MG maturity level model (WP5) by M24.	No
	2. Roadmap and guidance tools for countries for effective implementation of Personalised Medicine (WP5) by M36.	No
	3. Economic evaluation models for Personalised Medicine and case studies (WP5) by M30.	No
	4. Guidance principles for national mirror groups and cross-border Personalised Medicine governance (WP6) by M30.	No
	5. Long-term sustainability design and funding routes for cross-border Personalised Medicine delivery (WP6) by M34.	No

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3. Methods

All policy recommendations were conceived by combining existing knowledge and expert opinions, which were then used to set up the recommendations for a large-scale genome data sharing initiative. First, the recommendations started by collecting and studying existing knowledge through literature, existing guidelines, recommendations, and policy documents. Early versions of the recommendations were then refined by involving the ELSI Working Group as a sounding board, through a workshop with a larger B1MG community, the B1MG stakeholder meeting, and finally the B1MG special group. Final versions were approved by the ELSI Working Group. The B1MG special group provisionally adopted all recommendations. They were subsequently feeding into the data governance that is developed by task 2.4 of the B1MG project.

Importantly, task 2.2.4, minimal standards and best practice guidelines for consent forms to allow the use of genomics data in a pan-European genome initiative, was transferred to deliverable 2.4, because further discussion revealed that these minimal standards needed to be integrated in the GDPR requirements. The policy was integrated with the requirements from a data protection point of view. Subsequently, the integrated policy was transferred into a 'Transparency and Consent Guidance'.

4. Next steps

All policy recommendations based on tasks 2.2.1, 2.2.2 and 2.2.3 are provisionally accepted by the B1MG special group. The Transparency and Consent Guidance is now further pursued by Task 2.4 and is currently being tested for its suitability to establish information and consent sheets.

Building on the 1+MG initiative and the B1MG work, the Genomic Data Infrastructure (GDI) project was launched in Brussels in November 2022. The aim of the GDI project is to realise the 1+MG initiative's data infrastructure that will enable secure access to genomics and corresponding clinical data across Europe. Policy recommendations will be used to ensure the responsible implementation of the data infrastructure. They will be discussed with governmental representatives as part of the data governance proposed by task 2.4.

5. B1MG WP2 Recommendations for a 1+MG Minimal Standards for Inclusion of Special Subjects

VERSION 2.0 (March 2022)

Leader: Signe Mezinska

Contributors and reviewers: Regina Becker, Mihaela Matei, Susanne Rebers, Adrian Thorogood

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Scope

Recommendations for the responsible inclusion of special groups of data subjects in 1+MG such as minors, persons not able to consent, minorities, vulnerable persons and groups, and deceased persons. The recommendations are directed towards researchers, research ethics committees (RECs), and 1+MG data centres and oversight bodies.

Objectives

To identify existing approaches and best practices for inclusion of special groups.

To develop 1+MG minimal requirements for inclusion of special subjects.

Background

The term 'special subjects' in the context of 1+MG project applies to a diverse set of potential research subjects: minors, persons with diminished capacity to consent, persons not able to consent, other vulnerable groups, deceased persons etc. These special subjects in at least some respects are incapable of deliberating or acting based on their own plans or are controlled by others. To respect a person representing a special group means to protect him/her to ensure that the person is not subjected to abuse, exploitation, or discrimination.

Usually, definitions of vulnerability combine two aspects: (1) lack of ability, capacity, means and/or willingness to protect one's own interests, and (2) exposure to the possibility of being harmed, especially through exploitation. As outlined in the Declaration of Helsinki, vulnerable groups and individuals "*may have an increased likelihood of being wronged or of incurring additional harm*" (WMA, 2013), including physical, psychological, social and other types of harm, e.g., harm resulting from the withholding of access to standard of care. In case of involving vulnerable persons and groups in research "*specific protections should be provided for vulnerable subjects and vulnerable populations, based on the general principle of acting in their best interest*" (ESHG, 2003).

There is ongoing discussion in the field of research ethics regarding the usefulness of the concept of vulnerable groups. CIOMS Guidelines advise to "*avoid considering members of entire classes of individuals as vulnerable*" (CIOMS, 2016) and instead suggest looking at specific characteristics and situations that may render persons vulnerable, as this can "*aid in identifying the special protections needed*" (CIOMS, 2016). CIOMS Guidelines also remind us that different characteristics and situations generating vulnerability may co-exist, making some individuals more vulnerable than others. Evaluating vulnerability of research subjects or groups before involving them in research is a duty of researchers and respective research ethics committees (RECs). For initial identification of vulnerability, a useful tool is Kipnis's taxonomy of vulnerability in research (see Table 1).

Table 1. Taxonomy of vulnerability in research (Kipnis, 2001)

Cognitive	Does the person have the capacity to deliberate about and decide whether or not to participate in the study?
Juridic	Is the person liable to the authority of others who may have an independent interest in that participation?

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Deferential	Is the person given to patterns of deferential behaviour that may mask an underlying unwillingness to participate?
Medical	Has the person been selected, in part, because he or she has a serious health-related condition for which there are no satisfactory remedies?
Allocational	Is the person seriously lacking in important social goods that will be provided as a consequence of his or her participation in research?
Infrastructural	Does the political, organisational, economic, and social context of the research setting possess the integrity and resources needed to manage the study?

When planning involvement of vulnerable subjects in research, it is also important to consider differences regarding capacity of these persons: many of them are autonomous persons, some are not yet fully autonomous (minors), some have fluctuating autonomy, some are persons of diminished autonomy, and others are permanently non-autonomous.

Researchers implementing primary collection of data and biological samples from vulnerable subjects for inclusion in 1+MG initiative must impose protective conditions, including providing appropriate information and seeking consent or assent, in accordance with applicable international and national law and ethical principles.

Minimal standards

Primary collection and storage of data and samples

Before recruiting subjects for primary collection of data and samples, researchers and RECs must first determine whether vulnerable individuals and/or groups are involved and to ensure the well-being and rights of vulnerable research subjects.

The research planned in the framework of the 1+MG initiative has no potential to produce direct benefit to a person's health; at the same time, it is likely to entail only minimal risk and minimal burden (assuming appropriate safeguards are in place). Data from minors, persons not able to consent, patients in emergency clinical situations and persons deprived of liberty may be involved for secondary use in the 1+MG initiative if (1) research of comparable effectiveness cannot be carried out without the participation of these groups of persons; (2) the research has the aim of contributing to the ultimate attainment of results capable of conferring benefit to these groups of persons. (CoE, 2005a)

Vulnerable persons and/or groups should not be unnecessarily excluded from research participation, and in turn the benefits of scientific progress. Resources should be provided to ensure their responsible inclusion in research.

Many vulnerable persons (e.g., many persons with psychiatric diagnosis) have normal cognitive function, are able to evaluate risks and benefits of research, and are able to give informed consent. Regarding persons with limited capacity to give consent or where the capacity to give consent is in doubt, "*arrangements shall be in place to verify whether or not the person has such capacity*" (CoE, 2005a). RECs and researchers must ensure that procedures for assessment of capacity are in place in accordance with applicable international and national law and ethical principles.

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If vulnerable persons have the capacity to consent and are able to consent, informed consent must be obtained from the individuals themselves for storage and research use of their data and biological samples.

In case of non-autonomous persons, in addition to the consent of a legal representatives, the assent of the person must generally be sought, meaning that the person "*is meaningfully engaged in the research discussion in accordance with his or her capacities*" (CIOMS, 2016). Assent is a process, not "*merely the absence of dissent*" (CIOMS, 2016). The person must receive information, be engaged in the conversation at the level of his/her capacity to understand, and be given an opportunity to agree to or to decline participation.

Researchers and RECs must plan in detail the content, form, and most effective way of communication of information to vulnerable subjects, bearing in mind the specific type of vulnerability. It is highly advisable to involve persons with respective types of vulnerability, or appropriate representatives, in this planning process. (Diez-Domingo, 2021; Rotimi & Marshall, 2010)

Researchers and RECs must ensure that no undue influence is exerted on vulnerable persons to participate in research or donate samples and data to a biobank. (CoE, 2005a) It should be taken into account that undue influence may take different forms, e.g., pressure, misuse of power, undue inducement or presence of therapeutic misconception. If necessary, RECs and researchers should consider incorporation of voluntariness assessment into the consent process by using appropriate voluntariness assessment instruments. (Mamotte & Wassenaar, 2015)

Vulnerable persons or their legal representatives, as any other research subject, generally have the right to withdraw their consent or assent to research participation at any time and to ask for their identifiable data and samples to be withdrawn from the research project or a biobank (i.e., anonymised, no longer used in future research, or destroyed).

Refusal to give consent or assent or the withdrawal of consent or assent to participate in research or donate data and biological samples to a biobank shall not lead to any form of discrimination of vulnerable persons or groups, as any other research subject.

Minors

Researchers must specifically plan the informed consent/assent process for collection of data and biological samples from children or adolescents to adjust to their developing capacity and maturity. It is advisable to prepare age-appropriate information and supplement it with visual information, as well as to involve children and adolescents in this planning process, e.g., by testing the perception and understandability of informative materials. (Nuffield Council on Bioethics, 2015)

The conditions (e.g., risk/benefit ratio, level of risk, safeguards, requirements for consent/assent procedures) that govern the participation of the minor in research are subject to applicable national law and vary from jurisdiction to jurisdiction. The legal age of consent to research and details of assent procedure are established by the national law. (Lepola et al., 2016)

Researchers should seek REC advice about all aspects of informed consent/assent process and ensure that specific protections are in place to safeguard the best interests, rights, and welfare of minors.

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Usually, informed consent for collection of data and biological samples from children or adolescents must be obtained from at least one parent or guardian; however, some national legislations may establish that the permission of both parents is required. (Lepola et al., 2016)

Researchers must actively involve children and adolescents in the informed consent/assent process, taking into consideration their age and maturity. The assent should be documented, and in case it is not possible to seek assent from the minor the reasons should be explained.

The opinion of the child or adolescent must be taken into consideration as an increasingly determining factor in proportion to his/her age and degree of maturity. "*The potential subject's dissent should be respected*." (WMA, 2013) In the case of infants or very young children, it is necessary to evaluate their attitude, taking account of their age and considering both verbal and non-verbal resistance. Researchers and parents/guardians should discuss beforehand whether and when resistance will be considered a reason to stop research participation.

Researchers should involve the child or adolescent in the actual decision-making process and to provide information which is adjusted to the different levels of child's or adolescent's maturity and to the individual needs of the minor (e.g., psychological maturity, intellectual capabilities, cultural background, family situation). (Nuffield Council on Bioethics, 2015)

If during the implementation of research a minor reaches the legal age of majority, at a minimum an opt-out policy should be introduced, but preferably his/her written informed consent should be sought for continued storage and research use of their data and biological samples. (Giesbertz et al., 2016)

Adult persons not able to consent

Researchers and RECs must specifically plan the informed consent/assent process for collection of data and biological samples from adult persons not able to consent, as well as the process for withdrawal of consent.

For collection of data and biological samples from an adult person not able to consent, the informed consent of his/her legal representative must be obtained according to the procedures established by national law.

The adult person not able to consent must give assent, unless he/she is "not in a state to receive the information" (CoE, 2005b). For this, researchers must involve the person in the actual decision-making process and to provide information which is adjusted to the actual level of person's cognitive capacities and to the individual needs of the person.

It is not acceptable to force a person who is not able to consent to donate data and biological samples against his/her will. The research subject has the right to object and to withdraw assent at any time.

The relevant REC should advise researchers about all aspects of informed consent/assent process and ensure that specific protections, such as adjusted information, are in place to safeguard the best interest, rights, and welfare of persons not able to consent.

If there is reason to believe that the person not able to consent will attain or regain the capacity to consent, reasonable efforts should be made to seek the consent of this person for continued storage and research use of their data and biological samples after he/she attains or regains the capacity to consent.

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The instructions and wishes made by capable adults concerning a willingness or refusal to share and re-use of their samples and data, as well as their values and beliefs, must be considered by researchers and legal representatives in circumstances where they experience a diminishment of capacity. The initial consent should, however, clearly address that samples and data may continue to be used following a loss of capacity or death. (Thorogood et al., 2015)

Collecting and/or using data from deceased persons

The data and samples of deceased persons should generally be treated with respect and care, like data and samples of living ones, with appropriate modifications for the fact that deceased persons cannot actively participate in the governance of their data and samples. "*Concerning postmortem uses of samples, a policy of unrestricted access cannot be justified on the grounds that the risk or harm for the subject are no more an issue."* (ESHG, 2003)

For collecting and/or using data and biological samples from deceased persons, the researchers and RECs must follow to rules and procedures established by national law (e.g., requirements for consent from next of kin; consent waiver; data subject rights persisting (or not) after death).The person's consent to share data, restrictions to use of their samples and data, as well as persons' wishes regarding data sharing should be generally respected after their death. *"If individuals restrict use of their sample when they are still alive, those restrictions apply after their death*." (ESHG, 2003)

Inclusion in a 1+MG data repository, access, and secondary use of data in 1+MG initiative

Before including data of persons, who had been considered vulnerable during the initial collection of data and biological samples, for secondary use in the 1+MG initiative, researchers and/or respective RECs must re-examine the content of the informed consent given during the initial collection of data and samples to ensure that the scope of the consent covers activities planned in 1+MG initiative and the way of communicating the information clearly delivers a message that the data may be used in an initiative, like 1+MG.

National 1+MG nodes, researchers and RECs should recognize that vulnerability impacts not only the informed consent process, but also different aspects of the ongoing participation in 1+MG initiative, such as withdrawing consent, relationships with researchers, participation in public/patient involvement activities, dealing with incidental findings etc. These aspects should be discussed in detail among the stakeholders before including data for secondary use in 1+MG initiative.

National 1+MG nodes, researchers and RECs should recognize that including the data for secondary use in 1+MG initiative may enable new types of vulnerability applying to already vulnerable groups, vulnerable persons, or groups that were not considered vulnerable at the time of primary collection of data and samples. Ongoing reflection on such possible new types of vulnerability emerging from, e.g., application of new analytical techniques, artificial intelligence or prediction tools should be pursued.

If an ethnic or cultural group (including ethnic and cultural groups from third countries) is to be the subject of including their data for secondary use in 1+MG initiative, additional consent may be required "*at a group level through its cultural appropriate authorities*" (ESHG, 2003). The respective REC has to decide whether additional group level consent is needed, taking into account cultural differences, potential of discrimination and stigmatisation, and respecting rights

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of minorities within the group. (Kowal, 2015; Rotimi & Marshall, 2010) The rights and interests of the group should be protected, especially "*in terms of benefit sharing*". (WMA, 2016)

In line with the "1+MG Incidental Findings Policy" including specific points-to-consider for research involving minors, return of clinically actionable findings in minors might be even more pressing than in less vulnerable groups. In general, if 1+MG incidental findings reveal conditions in minors that are clinically actionable during childhood through early life intervention, they should be communicated as considered to be in the best interests of the child. The communication must involve professional support to explain the research findings and to deal with the psychological and emotional impacts of information.

6. B1MG WP2 - Recommendation of minimal standards for feedback provision of general results of research studies conducted with data provided through 1+MG to data subjects

VERSION 2.0 (February 2022)

Susanne Rebers on behalf of B1MG WP2

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Executive summary

This policy recommendation covers general feedback of the general results of research studies conducted with data provided through 1+MG to data subjects.

The 1+MG policy covers:

- what information should and should not (necessarily) be shared with data subjects (and potentially other people interested in 1+MG, i.e. the general public);
- how this information should be shared (e.g. through which medium and in which language(s)).

The 1+MG policy only applies to analyses conducted in the context of 1+MG data sharing. Data uses addressed in the primary data collection context should be covered by local policies.

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In an analysis of current guidelines and best practices, we identified four important principles to provide feedback of general research results to data subjects: transparency, accountability, privacy, and the fair distribution of benefits. Providing feedback towards data subjects about general research results contributes to transparency, and as a result, accountability, about conducted studies with health data. Factors that contribute to the need for transparency and accountability, both towards data subjects and the general public, are the use of public funding to set up the infrastructure, collect the data, and conduct the studies. Moreover, it is often difficult in observational research to provide a detailed account of the exact studies that will be conducted with the data at the moment the data subject is informed about participation. In the long run, providing feedback may add to the (prolonged) trust of data subjects and the broader society in 1+MG and health research in general. Importantly, providing feedback towards data subjects about general research results should adhere to the principle of privacy. First, the contents of the general research results should be anonymous. Second, data subjects should only be actively informed about these general research results if they indicate that their communication data (e.g. e-mail address) can be used for this purpose. The fourth principle, fair distribution of benefits from the data infrastructure, should not only be seen as the fair distribution of the resulting clinical progress, but also as the fair distribution of knowledge gained from the use of data. Sharing general research results adds to this knowledge sharing.

Based on these four principles, a recommendation to provide feedback of general research results to data subjects is set up. Other considerations are taken into account when determining how to provide this feedback. In the 1+MG federated infrastructure, the responsibility to engage with data subjects lies with the signatories. It is therefore presumed that feedback is organised by the national nodes. Practical issues, such as restricted time and expertise available to develop information that is clear to data subjects, are taken into account. Below we summarise the recommendations and provide a short list of best practices.

Recommendations (summarised)

1: Provide a complete list of scientific publications using the 1+MG infrastructure online. In order to facilitate the completion of this list, it is recommended to require data users to acknowledge 1+MG in the acknowledgements of each scientific publication, and requiring them to use a standardised sentence and/or a 1+MG study number. This requirement should be agreed upon in the Data Transfer Agreement. 1+MG personnel can then easily search catalogues of scientific publications (e.g. Pubmed.gov) for papers using the 1+MG infrastructure. It may be decided that the central 1+MG organisation takes over this search to increase efficiency to the benefit of all national nodes.

2: Provide examples of completed studies and their research results on the 1+MG website. A science communication expert should be involved in the development of the examples and provide advice on the best format to provide each example (e.g. written text, movies, animations, etc.) to ensure the examples will be understandable for most data subjects. If a participant panel is available, it could provide valuable input. If the studied population is expected to have special communication needs (e.g. a visual or mental impairedness), these should be taken into account. Examples should be offered in at least the official language of the member state from which data subjects were included in the study (i.e. the national node).

We also recommend 1+MG to follow as many of the best practices outlined below as feasible:

- 1+MG may allow data subjects or other interested people (general public) to subscribe to a yearly newsletter. This (e-mail) newsletter, offered in all official EU languages, could

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contain a hyperlink to the list of publications, the examples of completed research studies, and potentially also request for (further) participation in 1+MG.

- If 1+MG decides to set up a participant panel, 1+MG may request this participant panel to offer (binding) advice about which research studies should be converted into an example on the website. The participant panel may be asked to ensure all relevant types and the whole width of research studies are covered.

- 1+MG may use social media (e.g. Facebook, Instagram or Twitter) to inform the public about new examples of completed research studies on the website. When determining which social media should be used, available resources and the target audience(s) should be taken into account.

- Use best practice examples, such as the Cochrane plain language summaries guidance[2] or other guidelines, to write clear text about examples of studies.

Scope

The B1MG ELSI WG makes the following recommendations with regard to the scope of the 1+MG Policy.

The policy recommendation covers general feedback of the results of research studies conducted with data provided through 1+MG to data subjects.

The 1+MG policy should cover:

- what information should and should not (necessarily) be shared with data subjects (and potentially other people interested in 1+MG);

- how this information should be shared (e.g. through which medium and in which language(s)).

The 1+MG policy should only apply to analyses conducted in the context of 1+MG data sharing. Data uses addressed in the primary data collection context should be covered by local policies.

Other forms of transparency not covered by this policy recommendation

Besides the reporting of general research results to data subjects, other forms or types of transparency are common when conducting scientific research. These are not covered by this policy recommendation. These excluded types of transparency include:

- Any potential periodical communication about the data subject's continued (passive) participation in 1+MG.

- Any potential periodical communication about the data subject's continued active participation in 1+MG, e.g. in the form of 'dynamic consent'.

- Legal requirements on transparency and communication, based in the GDPR articles 13, 14, and 15. These describe the exercise of individual rights to access (health) information. Individual access rights are addressed in other deliverables as part of the 1+MG ethical and legal data governance framework.

[2] https://training.cochrane.org/handbook/current/chapter-iii#section-iii-4

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- Communication towards data providers, e.g. to enrich the original database with additional analyses results.
- Publication requirements (most notably scientific publications in peer-reviewed, scientific (open access) journals) that might be part of the requirements for researchers to access data from 1+MG.

Important to mention here, is that although it is out of scope of this policy recommendation, all researchers submitting a data access request are required to provide a summary for the lay public of the proposed research study and its intended outcomes. The summaries of accepted projects will be shared online. This guarantees that some information about all research studies will be available to data subjects.

Transparency on health care use of 1+MG data

Data within 1+MG may also be used for health care purposes. For example, the data may be used to guide understanding of an unknown syndrome a yet undiagnosed patient may have. We considered whether results of such health care use should be part of this recommendation. Many of the principles underlying the argument for feedback of research results may also be applied to an argument for feedback of the results of health care use of data retrieved from 1+MG. However, there are two reasons why health care use is taken out of the scope of this policy recommendation. First of all, it is not reasonable to request data users for health care, who usually only request the data of one data subject or a small set of data subjects, usually for an exploratory examination, to spend the time needed to e.g. write a clear abstract of their data use for laymen. Secondly, and perhaps more importantly, since data use in health care will be focused on very small groups of data subjects, or even individual data subjects, the chance that an individual will be identified through open communication about data use is high. To prevent individual data subjects from being recognized, it is recommended that requesting feedback to data subjects about the results of data use in health care is generally prevented. This of course does not preclude providing a few examples of healthcare data uses, for instance in the form of an article or interview with a physician, provided the data subjects provided informed consent for this.

Context

Transparency and accountability

Feedback of general research results contributes to transparency and accountability (see background). Data subjects value this feedback as a form of reciprocity for their contribution. Moreover, data subjects may have an interest in learning more about conducted research studies, and their general results. From the point of view of the general population, transparency, accountability, and reciprocity might also play a role. These norms are for these stakeholders however not relevant based on their data contribution, but on the contribution of public resources on the 1+MG infrastructure and publicly funded studies using this infrastructure.

Feedback of general research results may also increase the trust of data subjects and potential future data subjects in 1+MG. It may contribute to the continued participation of data subjects, especially when they are requested to provide longitudinal data. It may also contribute to the future participation of newly recruited data subjects.

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How to provide feedback

The background review highlights several potential media to provide data subjects with general research results:

- Online list of all publications based on the infrastructure;
- More extensive descriptions of a selection of studies in a clear language. Sometimes includes an interview with a researcher or a data subject;
- Overview of current studies including a short abstract;
- Newsletter;
- Press statements;
- Social media news items;
- Participant events for a selection of data subjects. Videos of presentations may be shared online afterwards.

In choosing the right medium (or media) to inform data subjects about general research results, accessibility should be an important starting point. Most of the media summed above can be accessible in principle, with an important exception being the online list of all publications. While a list of all publications may be the easiest way to provide a complete overview of conducted research, scientific publications are not written in an understandable way for most data subjects. They are full of jargon and technical terms, and are written for a public with a specific professional background. Yet, for part of the data subjects, scientific publications may provide an added value.

Many media are internet-based. The large majority of households in the EU has an internet connection[3]. When choosing an internet-based medium for the feedback of general research results, it should be taken into account however that the feedback might not be accessible to a small part of data subjects.

The EU has 24 official languages. When providing feedback of general research results, given the same amount of resources, the most optimal trade-off between the amount of studies data subjects are informed about and the number of people that can understand the information should be chosen.

The provided options through which general research results can be fed back differ in whether they are offered directly to the data subject upon request (e.g. a newsletter) or whether the data subject should take action in order to see whether new information is available (e.g. website). If offering directly to the data subject is feasible, this might offer heightened transparency.

The options also differ with respect to whether data subjects actively look for general research results (e.g. on a website), or whether a national node actively sends information to the data subject (e.g. newsletter or participant event). In case of the national node taking the initiative, the right to privacy of the data subject should be taken into account. When choosing such an option, data subjects should always make an active decision to receive this information, or to be invited for participant events.

[3] Digital economy and society statistics - households and individuals - Statistics Explained (europa.eu)

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Who should provide the feedback?

Researchers can be expected to contribute to the provision of general research results. They are the experts on the conducted studies. Therefore, even if they are not requested to e.g. write an abstract for laymen, they should at least check the information for accuracy.

It is important to realise that writing information suitable for laymen is a more difficult task than it appears at first glance. Although researchers are experts in their field and most knowledgeable about the conducted research project, this does not necessarily mean that they are best able to communicate the general research results to data subjects. A science communication expert might find the words and means to communicate complex research results more easily than a scientist. If 1+MG decides to set up a participant panel, this panel may also provide guidance to a communication expert or the national node.

How much to communicate?

Transparency and accountability are two important norms to determine the importance of providing feedback of general research results. In order to be fully transparent, it could be argued that all completed studies should provide research results to data subjects. However, it is most likely that resources prohibit turning all studies' results into accessible formats.

Offering the research results of a selection of the completed studies might be less transparent about the extent of all research studies, but might be equally transparent about the types and width of research studies conducted using the 1+MG infrastructure as providing a complete overview. Care should be taken to ensure that the breadth of research topics and techniques is covered, to ensure data subjects know the types of studies that are (potentially) conducted with their data. If 1+MG will set up a participant panel, this panel might play a role in determining whether all relevant types and the whole width of research studies are covered.

An advantage of offering feedback of research results of only a selection of research studies is that the studies that will be discussed can be offered in more detail, potentially also using media that are more labour intensive to develop (e.g. movies or animations), but that offer more clear information to more data subjects.

Who should be responsible?

In the 1+MG federated infrastructure, the responsibility to engage with data subjects lies with the signatories. Feedback of general research results should therefore be organised by the national nodes. An additional advantage of organising feedback on this level, is that specific viewpoints of each country of what information is necessary or essential to share can be taken into account.

To ensure the most efficient use of public funds, national nodes might of course decide to cooperate in sharing general research results.

Policy recommendations for 1+MG

We recommend 1+MG to adopt the following minimal requirements regarding feedback of general research results to data subjects:

1: Provide a complete list of scientific publications using the 1+MG infrastructure online. In order to facilitate the completion of this list, it is recommended to require data users to acknowledge 1+MG in the acknowledgements of each scientific publication, and requiring them to use a

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standardised sentence and/or a 1+MG study number. This requirement should be agreed upon in the Data Transfer Agreement. 1+MG personnel can then easily search catalogues of scientific publications (e.g. Pubmed.gov) for papers using the 1+MG infrastructure. It may be decided that the central 1+MG organisation takes over this search to increase efficiency to the benefit of all national nodes.

Advantages: 1+MG offers full transparency of all conducted studies using the 1+MG infrastructure to its data subjects with minimal efforts. This list may provide further benefits if it can be linked with data subject identifiers and used to facilitate data subjects' right to be informed about the use of their data.

Disadvantages: Scientific publications may only be understood by a selection of data subjects.

2: Provide examples of completed studies and their research results on the 1+MG website. A science communication expert should be involved in the development of the examples and provide advice on the best format to provide each example (e.g. written text, movies, animations, etc.) to ensure the examples will be understandable for most data subjects. If a participant panel is available, it could provide valuable input. If the studied population is expected to have special communication needs (e.g. a visual or mental impairedness), these should be taken into account. Examples should be offered in at least the official language of the member state from which data subjects were included in the study (i.e. the national node).

Advantages: Offering these examples provides optimal transparency and accountability towards data subjects and takes into account their communication needs.

Disadvantages: The proposed minimal requirement is labour intensive, both because of the extensive process to develop the right text and format, and because each national node will be responsible to provide feedback about general research results to their data subjects and/or citizens. National nodes may decide to cooperate to increase efficiency.

Of course, national nodes have the opportunity, where feasible, to provide more general research results than these minimal requirements prescribe. National nodes may for instance request (or write) lay summaries from all studies using data from data subjects from their jurisdiction, or may organise participant events.

We also recommend 1+MG to follow as many of the best practices outlined below as feasible:

- 1+MG may allow data subjects or other interested people (general public) to subscribe to a yearly newsletter. This (e-mail) newsletter, offered in all official EU languages, could contain a hyperlink to the list of publications, the examples of completed research studies, and potentially also request for (further) participation in 1+MG.
- If 1+MG decides to set up a participant panel, 1+MG may request this participant panel to offer (binding) advice about which research studies should be converted into an example on the website. The participant panel may be asked to ensure all relevant types and the whole width of research studies are covered.
- 1+MG may use social media (e.g. Facebook, Instagram or Twitter) to inform the public about new examples of completed research studies on the website. When determining which social media should be used, available resources and the target audience(s) should be taken into account.

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- Use best practice examples, such as the Cochrane plain language summaries guidance[4] or other guidelines, to write clear text about examples of studies.

Background

Methods

WP2 of B1MG has developed and maintains a living inventory[5] of existing guidelines relevant for the ethical and legal governance of a data sharing initiative. The guidelines in the inventory were reviewed to identify recommendations concerning the feedback of general research results. The inventory includes guidelines, policies, recommendations, including those published in academic journals. Existing policies were reviewed and interpreted for application in a large-scale pan-European genomic data sharing initiative.

Further, the websites of a random selection of larger current biobanks and research databases were searched for examples of feedback of general research results in practice.

Results

Recommendations from existing guidelines can be separated into two categories: general principles, norms and values that are related to the feedback of results to data subjects, and direct recommendations about feedback of results to data subjects.

General principles

Many guidelines indicate the norms or core principles on which their recommendations are based. Identified principles that are related to the issue of feedback to data subjects are transparency, accountability, privacy, and the fair sharing or distribution of benefits.

Many guidelines and recommendations, even if they don't specifically mention whether or how to give feedback about general research results to data subjects, argue that genomics research should always be conducted transparently (WMA 2002, revision 2016, Ministers. 2006, GA4GH 2014, BBMRI-ERIC 2015, Alliance 2019), either towards data subjects or towards 'the public' as a whole. The OECD refers to 'openness' as an important principle, and as a prerequisite for participation (OECD 2013). Importantly, the OECD here refers to several different types of transparency, most of which are meant to provide information before a data subject provides informed consent. However, especially for data subjects who sign informed consent after the first research results of 1+MG have been published, might get an indication of the type of research conducted using data from 1+MG. Most guidelines implicitly take privacy into account, stating that general research results should never provide personal information about the data subjects involved in the study.

Another core element mentioned by more than one guideline is accountability (Ministers. 2006, Alliance 2019). Sharing information about conducted research with data subjects and/or the public can add to the accountability of 1+MG to EU citizens, which is especially relevant in initiatives funded by public means.

The third principle is the fair distribution of benefits. This was for instance a foundational principle of the Australian Genomics Health Alliance (2019). Additionally, the Human Genome Organization (HUGO) International stresses that '*Human genomic databases are a public resource*'

[4] https://training.cochrane.org/handbook/current/chapter-iii#section-iii-4
[5]

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and therefore, that *'All humans should share in and have access to the benefits of databases'* (Organization 2002) . This benefit sharing is also stressed in the Universal Declaration on Bioethics and Human Rights by UNESCO (UNESCO 2005). This Declaration makes it clear that by 'benefits' one should not only think about access to care (e.g. new diagnostic tools or treatments), but also '*access to scientific and technological knowledge'*. This benefit sharing is probably related to another aim of the Australian Genomics Health Alliance (2019), which is the aims to foster trust, integrity and reciprocity. BBMRI-ERIC (BBMRI-ERIC 2015) also stresses the importance of reciprocity: *'Stewardship also implies giving something back*'.

All in all, these principles set a stage in which transparency, openness, privacy and accountability are highly valued. Moreover, value is seen in returning some of the benefits, including gained knowledge, of a genomic database to either data subjects and/or a broader population.

Direct recommendations

Besides relevant principles, many guidelines give direct recommendations on giving feedback about conducted research to data subjects.

Guidelines consistently recommend to provide feedback of research results to data subjects (Committee 2000, Europe 2005, Ministers. 2006, BBMRI-ERIC 2015), while one provides such feedback as an option (OECD 2009).

The guidelines also offer some guidance on how to offer this feedback. Importantly, only generalised results should be offered, data subjects should never be identifiable in this type of feedback (Ministers. 2006). None of the guidelines indicate feedback should be given actively, i.e. by actively approaching data subjects. Rather, information should be given on request (Europe 2005). The form in which the information is presented should be easily accessible. Examples given are newsletters (Ministers. 2006, OECD 2009) or websites (OECD 2009). However, sometimes specific groups might require other means, such as paper or video (OECD 2009). Personal contact is seen as either impractical (Ministers. 2006) or even potentially '*unduly burdensome*' (OECD 2009). When providing feedback, language issues or data subjects should be taken into account. The language should be understandable (Committee 2000), and sometimes translation in another language or for instance Braille for the visually impaired should be considered (OECD 2009).

Examples / best practices

Current biobanks and research databases with health data provide some examples of how feedback on research results can be given to data subjects. A random selection of mostly larger research infrastructures provides a multitude of possible methods. An online list of all publications is published by Finngen[6], Lifelines[7], the Cancer Genome Atlas Program (TCGA)[8], the Dutch Twin Registry[9], and the Canadian Partnership for Tomorrow's Health (CanPath)[10]. A selection of finished studies and their results, written in clear language that is suitable for a broader audience, is given by Finngen, Hebon[11], the Dutch Twin Registry, and Lifelines. In some cases e.g. interviews with the researcher(s) are included. Biobank Graz[12] provides an overview of current (COVID-19) studies, including a short abstract. Lifelines provides an overview of all

[6] www.finngen.fi
[7] www.lifelines.nl
[8] https://www.cancer.gov/about-nci/organization/ccg/research/structural-genomics/tcga
[9] www.tweelingenregister.vu.nl
[10] www.canpath.ca, only offers part of the publications using their data on their website
[11] www.hebon.nl
[12] www.biobank.medunigraz.at

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studies, both aimed at informing the participants and providing researchers the possibility to search for studies with an overlap in aims with their own study. The UK Biobank[13], Hebon, and Lifelines provide participants the opportunity to subscribe to a newsletter, which is sent regularly to inform interested data subjects. The Dutch Twin Registry sends an online magazine through email to subscribers. Lifelines sometimes shares research results through press statements or social media. The UK Biobank moreover offers two ways to interact with their data subjects. They invite participants to 'participant events' regularly. These are meant for a selection of participants, but videos of some of the presentations are offered on YouTube as well. Further, they communicate with participants (and potentially a broader audience) through Twitter.

Sharing of research results by researchers is sometimes, for instance in Lifelines, agreed upon by the researchers through the MDTA.

7. B1MG WP2 Incidental findings policy

22 March 2022

Susanne Rebers and Adrian Thorogood on behalf of B1MG WP2

Executive Summary

Context

Analysis of whole genome sequence data can reveal information of clinical relevance to data subjects and their family members (incidental findings (IFs), broadly defined here to include any individual finding of clinical relevance, whether related or unrelated to the aims of secondary use (e.g. research project or healthcare diagnosis). Clinicians and researchers have legal and ethical obligations to appropriately handle IFs in a manner that shows due concern for the welfare of data subjects and their family members. The likelihood of IFs in healthcare and research contexts, as well as the benefits, risks, and costs of reporting them, are not fully understood. European healthcare and research organisations tend to handle IFs cautiously.

1+MG aims to facilitate the secondary use of pseudonymised genomic and related-health data for the purposes of research, health-care and policy-making. The scope of this policy therefore focuses on genomic IFs revealed in secondary use contexts. The uncertainties surrounding IFs are greater still in secondary use contexts compared to (both clinical and research) primary contexts. Secondary use contexts may be very distant from a patient care context. This makes it unclear if distant 1+MG data users, especially researchers, have legal and ethical duties of care towards data subjects. Practically speaking, it is also difficult for 1+MG data users to assess if a potential IF is (still) clinically actionable. Secondary use may occur many years after sequencing. The health and familial situation of a 1+MG data subject are not fully known to the data user, and become more uncertain with the passage of time. 1+MG minimum data standards ensure sufficient data quality to enable secondary use, but the data may not be suitable for informing diagnosis of the original data subjects or their family members. A key practical difficulty in cross-border, secondary use contexts is that the data user does not know what IF policy applied in the initial healthcare or research context. Efforts to communicate an IF from secondary use

[13] www.ukbiobank.ac.uk

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may be undermined if the IF has already been returned to the data subject or family members. Another practical difficulty in cross-border secondary use contexts is that reporting IFs requires dedicated coordination and collaboration between data users, 1+MG coordinating bodies, data holders, and (designated) healthcare professionals. Because of this context, reporting of IFs should be handled cautiously.

Recommendations

Our recommendations are organised under the following five principles:

Autonomy. 1+MG should respect the autonomy of Member States, data holders, and data subjects. 1+MG data users should never communicate directly with the data subjects or their families. However, IFs encountered by 1+MG data users should be communicated through the 1+MG back to the data holder. Below we propose a technical solution to filter out the IFs of datasets with a no return policy or of data subjects who opted out of receiving IFs. The data holder maintains the link back to the data subject's identity; understands the data subject's health, familial context, and consent choices; and knows what IFs have already been analysed and reported. The data holder should make the ultimate decision whether or not to return the IF to the data subject or a family member, respecting consent, and in collaboration with an appropriate healthcare professional. Decisions to report findings will always be made according to the local IF policy, ensuring respect for local legal, ethical, clinical and feasibility considerations.

Clarity. 1+MG data users should have clear obligations with regards to handling IFs. We recommend that 1+MG establish a common, minimum obligation for 1+MG data users to report (only) IFs that are valid and clinically actionable for 1+MG data subjects or their family members. IFs meeting these criteria have the strongest ethical justification in the context of 1+MG's purposes, balancing potential benefits with competing costs and risks. Data holders have the final say over how the IF is handled, according to consent and local policy. Data subject's wishes are an essential part of this decision. Note that the 1+MG IF policy for secondary use is a complement to local IF policies applying in the primary analysis context, which are free to be more expansive or limited. We recommend this option over alternatives (discussed below) as it balances respect for individual welfare, clarity for data users, and autonomy for data holders.

Evidence. Any 1+MG policy should be initially launched as a pilot project to generate evidence to show the benefits of requiring the reporting of IFs through 1+MG outweigh the costs and risks. A pilot project would involve a small number of parties, with clearly defined performance indicators.

Capacity Building and Support. We recommend that 1+MG should not impose any minimum requirements for how data holders handle any IFs reported through 1+MG. Instead, 1+MG should promote responsible handling of IFs by outlining voluntary best practices, including:

developing a plan outlining what kinds of IF will be returned and how,

informing data subjects about the plan and seeking their consent to receive IFs,

establishing processes to assess IF validity and utility,

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providing feedback through a medically, legally, and ethically appropriate channel,

taking into account special points-to-consider for minors.

1+MG central or national nodes could also potentially provide support and expertise to 1+MG actors with assessment and validation of analytic validity, clinical validity, and clinical actionability.

Scope. A practical issue for handling IFs in secondary use contexts is uncertainty over what IF policy was applied in the initial sequencing context. In theory, this could be addressed by requiring all data holders to analyse a standard list of "secondary findings" before submission. Imposing such a requirement at this time, however, would unduly interfere with local policies and practices applying in primary sequencing contexts, which are diverse and rapidly evolving. Such a requirement could also discourage data submission. The 1+MG policy should be limited in scope to handling genomic IFs from secondary use. Data submitters should not be obliged to analyse a standard list of secondary findings before submission to 1+MG. In the longer run, 1+MG could establish a forum to develop and promote a common, regularly updated, list of secondary findings to be analysed in European clinical sequencing contexts.

Recommendations

Background and References are available in an accompanying document.

The 1+MG enables cross border access to whole genome sequence and health-related data for secondary use (research, healthcare and policy making purposes). Analysis of 1+MG data during secondary use may reveal genomic findings with health relevance for 1+MG data subjects and their family members. The 1+MG must establish a policy defining common criteria for incidental findings, and describing how they will be handled and communicated within 1+MG.

Question: When should IFs revealed by genomic analyses as part of secondary use enabled through 1+MG be reported back to data subjects and their family members?

Incidental Findings (IFs) are findings with health relevance for 1+MG data subjects (or their families), revealed through the analysis of genomic and health related data made available through 1+MG. We use this term broadly to include individual findings both related and unrelated to the (research) aims of secondary use. This means that IFs in this definition are not necessarily incidental (unintended, accidental) in the literal sense, but may also be 'intended', in the sense that they may be expected to be encountered based on the aims of a research project or diagnostic process. We exclude "secondary findings" from the scope of this term, and address them separately.

Scope of the Policy

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The B1MG ELSI WG makes the following recommendations with regard to the scope of the 1+MG Policy.

The 1+MG policy **should only apply to genomic IFs**, as the 1+MG is focused on providing cross-border access to whole genome sequence data and a limited clinical dataset. The policy does not cover other types of IFs assumed to be addressed in the primary data collection context (e.g., blood pressure; laboratory readings, medical imaging, or environmental findings). These other types of IFs should, however, still be addressed by national and local policies applying in the primary sequencing context.

The policy **should only apply to IFs revealed through *secondary use* by an external user**, i.e., IFs revealed from research or healthcare analyses by a 1+MG user of data made available through 1+MG. Local policies will already apply to IFs revealed during the initial healthcare or research analysis, or any further processing in that context (e.g., re-analysis or re-interpretation). This policy excludes handling of diagnostic findings from rare disease matchmaking.

IFs are identified by 1+MG users according to common criteria (e.g., analytic/clinical validity and clinical utility). Secondary findings are predefined lists of genes/variants deliberately searched for when analysing genomic data, unrelated to the primary indication for sequencing, with the aim of informing the data subject. These lists are usually defined by an expert body or consensus of practitioners, such as the American College of Medical Genetics and Genomics (ACMG) (Miller et al., 2021) or the French Society of Predictive and Personalized Medicine (Pujol et al., 2018). Secondary findings are excluded for the following reasons:

European professional guidelines recommend a cautious approach to analysing and reporting secondary findings, particularly for minors, even in clinical contexts (De Wert et al. 2020)

It is uncommon in Europe to analyse secondary findings in research or biobanking contexts.

Secondary findings, where applicable, would normally be analysed during primary use, before submission to 1+MG.

There is currently no European consensus on what secondary findings to report in what contexts, though 1+MG could provide a mechanism for driving such a consensus, as a complementary strategy. Any such attempts should be part of a pilot study to establish clinical utility and consider data subjects' perspectives.

This policy should not apply to the exercise of individual rights to access (health) information. It focuses on obligations to "push" findings to data subjects agreeing to receive them, not requests from data subjects to "pull" information from 1+MG. The policy does not cover reporting of general research results to data subjects. Individual access rights and general research results will be addressed in subsequent deliverables as part of the 1+MG ethical and legal data governance framework.

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Context

These recommendations are developed in a period in which there are some knowns, but also many unknowns regarding the feedback of incidental findings, especially incidental findings in the context of a large-scale genomic data sharing initiative. It is known that when analysing whole genome sequences, clinically relevant findings will consistently be found in a percentage of individuals. It is estimated that when an individual's genome is sequenced (WGS), the chance of finding a pathogenic genetic variant lies around 3% (Ding et al. 2015). It is also known that the majority of data subjects wish to receive IFs when offered a choice (e.g. Vermeulen et al. 2018). Yet, to our knowledge, it is unknown whether secondary use of data accessed through 1+MG will reveal a significant number of IFs. In general, the beneficial impact of returning IFs in primary sequencing contexts (research and healthcare), remains poorly understood given the complexity of interpretation, the lack of interventions for many genetic conditions, and the challenges of hand-off to healthcare systems. This explains in part the lack of standardisation for handling IFs across countries and contexts in Europe. Uncertainty over the benefit of reporting IFs is even greater in secondary use contexts, given the distance of the data in purpose, time and space from the patient context. When a user decides to feedback an IF, it will generally not be fully known if the data holder has a means to re-identify and recontact the data subject, or to know what findings have already been reported to the data subject. The organisational costs of identifying, communicating, interpreting and feeding back findings across a complex infrastructure, as well as the resulting impact on national health systems after hand-off are also poorly understood. It is also less clear if data subjects feel a large-scale data sharing initiative such as 1+MG is obligated to return incidental findings. and the complex and possibly costly organisation of returning them. However, in 1+MG, it is unknown how often an incidental finding, found during secondary use, is already known by the data subject and/or their treating physician, because the variant has already been found during diagnosis or primary use. It is therefore unclear how much clinical benefit data subjects will actually have from returning IFs revealed by secondary use in 1+MG. This uncertainty is a key consideration in the recommendations that follow, in particular the recommendation that any 1+MG policy be piloted before being generally adopted.

Policy options for 1+MG

The 1+MG ethical and legal data governance framework will need to adopt policies and agreements addressing the handling of IFs emerging from secondary use of 1+MG data. Unless otherwise indicated, the policy options below apply regardless of the initial sequencing context (e.g., research or healthcare), and regardless of the use case (e.g., research secondary use or healthcare secondary use).

Any return of IFs through 1+MG requires coordination between several actors (see Figure 1). First, a data user (researcher or healthcare provider) would identify a potential IF, and report it - possibly through a contact point at the national node - to the original data holder. The data holder would make the final determination if reporting the IF to the data subject is possible, feasible and appropriate, according to local IF policy incorporating clinical, ethical, and practical considerations, including the data subject's consent. Recognizing not all data holders will have the same maturity of policies and processes, we encourage voluntary best practices and

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points-to-consider below ("Handling IFs - Best Practices and Points-to-Consider for Data Submitters").

This document focuses on the IF policy applying to 1+MG data users (researchers or healthcare providers accessing 1+MG data). It presents policy options, including a recommended option, and discusses pros and cons of each. The policy options include:

Common Requirement for Users to Feedback (Only) Serious, Clinically Actionable IFs(*recommended*)

National Node/Country Tags Data with Local Feedback Requirement (Flexible)

"No Feedback" Policy for Users

The policy options only address if and when a 1+MG user flags a potential IF to the national node/data holder. Under all policy options, we recommend that the **data holder (ideally in collaboration with the data subject's physician) makes the final decision whether or not, and how, to feedback IFs to data subjects and their family members. This ensures respect for the original IF policy and local legal and ethical requirements**. Furthermore, the data holder is best positioned to check whether the IF is relevant (and new). The user and 1+MG would have no more responsibility. To assist data holders, we outline best practices for handling IFs below.

Option 1. Common Requirement for Users to Feedback (Only) Valid and Clinically Actionable IFs (*recommended*)

1+MG requires users to report IFs if the following reporting criteria are met:

Analytic validity - the sequencing assay reliably detects the variant.

Clinical validity - the variant confers a significant degree of risk of the condition to the data subject or his/her family members

Excludes variants of unknown significance.

Clinically actionable - reporting of information provides an opportunity to improve the clinical care of the data subject or his/her family members.

Findings relate to a condition that is sufficiently serious or severe enough to merit clinical intervention

There is a standard clinical intervention available to treat (or in some cases prevent) the condition

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The exact definitions and thresholds for these criteria would need to be agreed upon by the 1+MG community.

This obligation would apply to 1+MG data users regardless of the secondary use case (research or healthcare use), and regardless of the initial sequencing country or context (research or healthcare). The obligation would be made binding on users through the 1+MG data access agreements or a similar mechanism. These general criteria trigger an initial reporting of an IF back to the 1+MG data holder. The data holder then follows local IF policy to confirm the finding is truly an IF that should be reported back to the data subject or family member (where appropriate and legally permissible). If for example the data holder knows data are low quality, or that the IF has already been reported to the data subject or family member, then the data holder may opt not to return the finding. A geneticist or designated physician may be involved in the assessment of the IF to determine if it is relevant (and new) in the data subject's particular health context, as well as in the communication.

We recommend only clinically actionable IFs be reported through 1+MG. Recall that this policy does not stand alone or replace local IF policies. It applies as a **complementary reporting mechanism**, in addition to any local IF policies and processes applying in primary sequencing contexts (healthcare, research, and biobanking). Local IF policy may cover a broader set of findings. The 1+MG can only increase (and will never decrease) the probability that an IF is reported back. Given this complementary quality, it is not necessary for all stakeholders to agree on the exact meaning of the criteria.

We do not recommend further limiting the 1+MG criteria, e.g., to "life threatening" conditions that pose a clear and present danger to data subjects or their family members. Genomic IFs, the sole focus of this policy, are generally probabilistic and rarely if ever meet this criteria. We also do not recommend expanding the criteria to a wider set of conditions at this time, such as findings with personal, predictive, or reproductive importance (e.g. carrier status). The recommended set of IF criteria follows current best practices (see background below) and evidence. Returning serious, clinically actionable IFs promises to provide significant benefit to data subjects and their families, and thus offers the strongest ethical justification balanced against the purpose of 1+MG to advance precision medicine, not to provide consumer testing; the significant financial resources and time required of 1+MG organisations for interpretation, communication, and follow-up; and the potential anxiety caused to recipients of IFs. However, these recommended criteria are not set in stone. Evidence should be systematically gathered in a pilot project to determine the effectiveness of the current policy, which may inform subsequent modifications. Once the benefit of returning these IFs is demonstrated in a pilot project, the criteria could potentially be expanded through subsequent pilot projects.

Advantages: this option is a simple and relatively clear standard for data users, data submitting organisations and data subjects. A common policy applies to users across 1+MG regardless of source country or context. The relatively strict criteria bounds the obligations of data users and 1+MG to implement handling and communication procedures. The kinds of IFs reported would be those most likely to benefit data subjects and/or their family members clinically.

Disadvantages: data subjects and their families would only receive individualised feedback about their genome from 1+MG in limited circumstances. 1+MG stakeholders would need to reach a rough consensus on the criteria for reporting IFs.The policy may not align with national/local IF policies, which require the reporting of a broader or narrower range of IFs (though the data holder makes the final decision). Data submitters requiring external users to feed back a broader

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set of IFs may not be able to submit to 1+MG. Efforts of data users and 1+MG to communicate findings to the data holder may be ineffective if the data holder does not have the capacity to carry through with feedback to the relevant data subject or family member, if the individual has already received the IF, or if the reporting of a narrower range of IFs has been agreed upon with the data subject.

We recommend this option because it provides meaningful consideration for the welfare of data subjects, while providing clear and manageable obligations for 1+MG data users, while also leaving the ultimate decision with data holders.

Option 2. Data Submitter Tags Data with Local Feedback Requirement

1+MG allows data holders to establish their own local policy/criteria for reporting IFs, to apply to secondary use of their own data, subject to the data holder's ability to demonstrate capacity to ensure the appropriate handling of IFs.

Under this option, data holders could be permitted to impose different feedback policies on 1+MG users for research-generated data and healthcare-generated data.

Advantages: This option would not require agreement on terms, criteria, and responsibilities by 1+MG stakeholders. Data submitters set their own policy, so there is no barrier to submitting to 1+MG. It is also more likely that the data holder will be able to follow through with feedback to the data subject.

Disadvantages: This option involves complex tracking and communication of many different policies that differ depending on source (country/context). 1+MG may still need to establish a common menu of terms, criteria etc. to ensure clear communication between submitters and users. Data integration would mean multiple different policies could apply to a secondary use, posing a significant burden on data users.

We discourage this option because it is likely to lead to complex and hard to understand obligations for 1+MG and data users.

Option 3. "No Feedback" Policy for Users

1+MG does not permit any feedback of IFs from secondary use to the national node.

Advantages: The policy is simple and clear for data users, data holders and data subjects. There is no burden on data users, data holders, or 1+MG to implement handling and communication procedures. There is no burden for 1+MG Member States to agree on common terms and criteria.

Disadvantages: 1+MG would not offer data subjects or their family members clinical benefits to data subjects or their families. Data submitters may require reporting of IFs from secondary use, presenting a barrier to data submission. The policy may conflict with the norms or professional responsibilities applying to some data users, presenting a barrier to secondary use of 1+MG data.

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We discourage this option because it risks failing to demonstrate adequate concern for the welfare of 1+MG data subjects and their families.

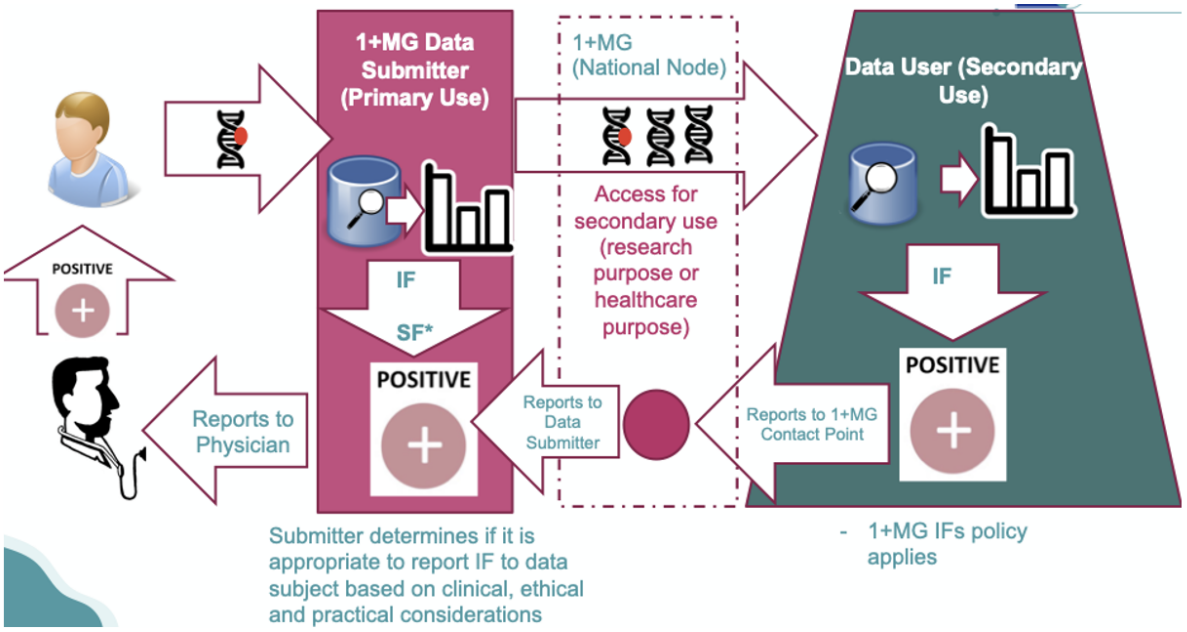

Figure 1: Return of Individual Findings Through 1+MG

Pilot phase

Because of the many uncertainties around the return of IFs in 1+MG (see also context section above), 1+MG should implement a pilot phase for any IF policy. During this phase, details of the frequency and types of IFs that are reported by data users to national nodes or data holders should be recorded, for instance by appointing a designated pilot project leader. Main outcomes of the pilot project could be the frequency and types of incidental findings reported back to the data holder, the frequency and types of IFs actually reported by the data holder to the data subject and/or treating physician, the percentage of IFs already known to the data subject, the costs of incidental findings reporting (including the costs for the national nodes, data holders, and potential costs of sample re-analyses), and the extent of the beneficial and negative impact on patient outcomes and, where relevant, on their family members. Secondary outcomes may be the experiences and wishes of data users, national nodes, and data subjects. Before the start of the pilot project, 1+MG may wish to decide on the minimal ratio between costs and other disadvantages and the welfare of data subjects that will warrant the continued reporting of IFs through 1+MG, or a modification to the criteria defining what IFs should be reported.

Handling IFs - Best Practices, Points-to-Consider, and 1+MG Support

If data holders are not in a position to follow up with the data subject or their family members, IFs reported by 1+MG users will not reach the concerned individuals. Reasons for this may for example be lack of resources to handle this follow up responsibly. There is therefore a risk of misalignment between the obligations of the data user, and the capacity of the data holder to

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follow-up. Reporting may therefore be limited and uneven across 1+MG. There are different ways to deal with this misalignment:

- Accept the misalignment and promote the development of local best practices over time.
- Establish standards for data holders relating to handling IFs. Where these are not met, the particular dataset would be tagged with a "no return" policy. However this does not address the issue of uneven follow-up within different data countries/subjects.
- Establish minimum requirements for data holders for handling IFs. However this may excessively restrict inclusion of data in 1+MG.

If data holders do not have best practices for handling IFs in place, it is unlikely that they will be in a position to follow up with the data subject. Based on common ethical and legal principles, our Working Group has identified the following examples of best practices and points to consider for data holders for the effective and responsible handling of IFs in European contexts.

- A local policy is in place for handling IFs - defining what types of findings will be returned and how.
- Local policies should take into account the most optimal timing of returning IFs, e.g. as soon as responsibly possible after establishing the validity of the IF and within the time frame in which data subjects may expect or appreciate the return of an IF.
- IFs should generally only be reported to the data subject or family member if the individual has provided informed consent to receive IFs (e.g., opted-in or did not opt-out). Exceptionally, there may be overriding legal professional obligations to report where a finding is life threatening if no action is taken.
- Original data submitted to 1+MG meets diagnostic quality standards.
- Resources (i.e., funding) have been allocated to confirm the analytic validity of the IF, where necessary, through follow-up testing. Funders have an important role here to provide appropriate support to researchers to handle IFs (GA4GH, 2021).
- Experts are available to confirm the clinical validity/utility of the result, e.g., by an expert clinical committee.
- There are clear contact points at the national node and data holder.
- The submitter has the ability to re-identify participants (identifiers maintained), check whether they opted in (or did not opt-out) to the return of IFs, and contact the data subject (up to date contact information is maintained).
- Feedback to the data subject is done through a legally and ethically appropriate channel, such as a medical geneticist, family physician, and/or genetic counsellor. Disclosure of this confidential information to a health professional must be consented or otherwise lawful. The professionals and associated resources should be designated, or at least informed, in advance of their potential role.

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- Appropriate information and/or disclaimers should be provided during communication to the data subject concerning the quality and accuracy of the IF. This includes clearly describing the implications of the IF and underlying uncertainty, and resources available for follow-up (US National Academies of Science, 2018).
- Clinical utility of the IF should be evaluated in the context of the data subject's or family member's particular health and familial context (e.g., the data subject is still alive).
- Appropriate follow-up care for the data subject can be ensured through the national healthcare system.
- Because 1+MG makes clinical test results available for secondary health-care use, IFs revealed through 1+MG might also include clinical test re-interpretations (Carrieri et al, 2019).
    - Ideally clinical data holders would have policies in place clarifying if and when to recontact patients if test results change over time
    - The possibility that results may change over time and the recontact policy should be described in the informed consent process.
    - Criteria should be established to define "material" re-interpretations that should be reported, such as those with clear clinical utility, but also considering impact on the health system.
- Community engagement about the content and mechanisms of IF policies, can help to improve acceptability, effectiveness and positive impact (GA4GH, 2021).

Additional Points-to-consider for minors

Given the complexity and diverse views in this area, we provide points-to-consider rather than best practices.

- Assessment of clinical utility should be guided by the principle of the best interests of the child. Only IFs clinically actionable (i.e., treatable) during childhood should generally be returned, to respect the child's future autonomy. The relevance of the findings for parents, as well as the parents' rights to know/not to know, should also be considered.
- Parents should not be permitted to opt-out of receiving IFs about their children that are clinically actionable during childhood. This restriction should be made clear in the informed consent.
- Results that are not actionable during childhood should not be reported to children, to preserve their future autonomy, unless there are overriding considerations in their best interests (e.g., clear future benefit during adulthood, or benefit to a family member).
- Return of IFs should be addressed in age-appropriate assent processes.

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- Results should be reported to both parents and to the sequenced minor where age-appropriate.
- Where consent to processing is required to be renewed at the age of majority, this re-consent should also address return of incidental findings.

How can 1+MG Support the Responsible Handling of IFs?

1+MG could also potentially provide central services to assist countries to fulfil these best practices. For example, 1+MG could play a role in ensuring or confirming analytic validity. Clinical validity and utility need to be confirmed by a clinically expert body. This body need not be established by each data holder. It could also be provided as a service by the 1+MG national node, or as a central 1+MG service.

A Consensus List of Secondary Findings for Europe?

Another important interdependency between users and submitter policies and practices is that the benefits of users reporting IFs is reduced or negated if the submitter has already analysed and reported the finding before submitting to 1+MG. It is difficult to know what findings have already been analysed before submission. Submitters across different contexts and countries have different policies and processes for analysing and reporting secondary findings before submission to 1+MG.

There are three ways for 1+MG to deal with this.

- If 1+MG selects Policy Option 2 above, data submitters could consider any completed analyses of secondary findings when they establish their own IF policy for users of their data.
- A communication mechanism could be developed to clarify when secondary findings have already been returned. I.e., data would be tagged with a description of already-analysed secondary findings.
- 1+MG could develop a common list of secondary findings, and recommend these findings be analysed and reported to data subjects during certain primary use contexts, where appropriate in light of national health policy and legislation and individual consent, before data are submitted to 1+MG.

Developing a European secondary findings standard would be a challenging, long-term effort. One advantage is that any individual sequenced in Europe (at least in clinical contexts) would be checked for the same genes/variants. Also, if secondary findings are reliably addressed before submission, this may reduce or negate the need to impose IF reporting obligations on 1+MG users. However, establishing such a policy would require significant consensus building, and subsequent modifications to local policies and processes. Moreover, ethical and legal considerations may hinder or prohibit the deliberate search for secondary findings when there is no clear clinical indication in specific EU countries. If eventually a European secondary findings

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standard would be developed, it could be promoted as a best practice for data submitting countries, who could adopt this European list where suitable considering national health policy and individual consent. National nodes could support data submitters with assessment and feedback.

8. B1MG WP2 Incidental findings policy Background

10 September 2021
Susanne Rebers and Adrian Thorogood on behalf of B1MG WP2

Background

This background document supports the 1+MG Incidental Findings Policy - Summary and Recommendations.

The task described in the grant proposal was to develop recommendations for minimal standards for 1+MG on how to deal with incidental findings (IFs). The recommendations are based on a review of current best practices and guidelines, summarised below.

Methods

The review included guidelines addressing IFs in both research and healthcare contexts. Existing policies were reviewed and interpreted for application in a large-scale pan-European genomic data sharing initiative.

WP2 of B1MG has developed and maintains a living inventory[14] of existing guidelines relevant for the ethical and legal governance of a data sharing initiative. The guidelines in the inventory were reviewed to identify recommendations concerning the handling of IFs. The inventory includes guidelines, policies, recommendations, including those published in academic journals. We extended research beyond the inventory by also reviewing relevant ELSI literature. In terms of legal aspects relating to IFs, this background relies on a legal taxonomy of different national legislations developed as part of WP2. This research was also informed by discussion in healthcare and research use case workshops, which addressed questions of the types of potential IFs that could emerge through secondary use for research and healthcare purposes, and expectations of how they should be handled.

The territorial scope of the guidelines focused on the European context. However, we also included some important guidelines from international bodies and other jurisdictions, including the United States and Canada. Our focus on the European context is justified by the fact that differences in health care systems, societal norms and legal regulations have important implications for policies of IFs, leading to potential divergence between Europe and non-European countries. For example, it is more common in the US than in Europe to search for secondary findings or to return variants of unknown significance to sequenced individuals.

[14] https://docs.google.com/spreadsheets/d/1_8uA-xPaFmKK8Fe2z1iLb6g016gUWOHY/edit#gid=2009336217

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Categories of genomic findings of individual health relevance

Genomic findings of individual health relevance may be categorised in different ways, including the following definitions relevant to be used in a large European data-sharing initiative:

- **Incidental Findings (IFs)** - a finding concerning an individual research participant or patient that has health [or reproductive] importance for the individual or his/her relatives. This term is sometimes used specifically for findings discovered in the course of research or healthcare, which are beyond the study or clinical aims.
- **Individual Research Results (IRRs)** - a finding concerning an individual research participant that has potential health [or reproductive] importance for the individual or his/her relatives and is discovered in the course of research in relation to the study aims.
- **Secondary Findings (SFs) -** a finding that is not the primary target of a test, but is an additional result deliberately analysed by the practitioner, usually based on a recommended list developed by an expert body or by a consensus of practitioners.
- **Genomic Test Re-interpretation** - where a patient receives a test result (e.g. genetic diagnosis) as part of his or her primary healthcare workup, the test result may change over time in a clinically relevant way, for example because of advances in general knowledge about the medical significance of genetic variants.

The discussion below explores the circumstances under which there is an ethical and/or legal obligation to report these findings to data subjects, out of respect for their welfare.

Legal considerations

There is a concern that a failure to return an IF could breach a healthcare professional's legal duties towards a patient. A failure to return might lead to liability under the theory of negligence or civil responsibility. Healthcare professionals have fiduciary duties towards patients; whether or not their legal duties extended to seeking for or reporting IFs would be determined according to the prevailing standard of care. Health researchers primarily aim to generate generalizable knowledge, though they have a duty of care towards participants.

Another theoretical basis for a legal duty to report IFs in genomic research or medicine is the duty to warn (common law) or the duty to rescue individuals in imminent danger (civil law). In the case of family members, this duty may be in tension with obligations of confidentiality towards the sequenced individual. Under Spain's biomedical research law, researchers have an obligation to return information to the participant's relatives to avoid serious harm, even where this conflicts with the participant's preferences.

More generally, European human rights documents highlight a "right to know" information of health relevance, potentially underpinning an obligation to report IFs (e.g., European

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Commission, *European Convention on Human Rights and Biomedicine*, 1997). These documents also recognize a competing right not to know, which is also enshrined in a number of national laws (Thorogood et al., 2019), including Estonia's biobank law, Latvia's genomic research law, Italy's genetic data privacy law, and Germany's diagnostic act (clinical contexts only). This right not to know is typically implemented by seeking consent or offering an opt-out to receive incidental findings. The right may be overridden by a competing legal duty to inform, e.g., where there is a risk of serious harm, such as in the example of the Spanish law above.

Sequencing in research context

The guidelines below were written for biobanks and/or research databases that were meant to serve multiple research projects. None of the guidelines specifically cover the 1+MG situation in which data are collected and stored in several countries (or EU member states), all with different national legislations.

Developing an incidental findings policy

Before the start of a research project, an IFs policy should be set up. Such a policy, which can be part of the study protocol, should include for instance whether IFs are returned, and how (ISBER 2012, Aarts et al. 2017, Bovenberg et al. 2009, Lewis et al. 2021). The *Guide to the detection, management and communication of incidental findings for biobanks in BBMRI-NL* provides an extensive overview of how to set up an IFs policy and what considerations should be taken into account (Aarts et al. 2017). It is recommended that such a policy is discussed and approved by a research ethics committee (NIH, ISBER 2012, Bovenberg et al. 2009), and that the reporting preferences of the most important stakeholders are taken into account (Bovenberg et al. 2009). The Global Alliance for Genomics and Health (GA4GH), *2021 Policy on Clinically Actionable Genomic Research Results* echoes these recommendations, additionally highlighting that the policy be revisited periodically, and that researchers should be held to account by other stakeholders for compliance with the policy (GA4GH, 2021, Lewis et al. 2021).

The policy should also indicate how IFs should be returned to research participants or their families. It is recommended that the IF is communicated promptly by a physician or researcher who understands the IF and its possible clinical significance, and who has good communication skills (Aarts et al. 2017). Importantly, the communication should not be handled by an external researcher who has received access to samples or data (Bovenberg et al. 2009). But before any return can take place, the finding should be discussed with clinical experts. Main topics of discussion should be what the clinical significance of the finding is, and whether feedback is warranted. If an IF was not anticipated beforehand (see below on how it is determined which findings should be communicated), a multidisciplinary team should discuss the finding (Aarts et al. 2017). The policy should also contain emergency procedures to inform both participants and non-participants (Bovenberg et al. 2009).

The policy should describe several procedural aspects that should be dealt with before the start of the study, including:

- Setting up a committee or multidisciplinary team in case IFs occur that were not anticipated (Aarts et al. 2017, Bovenberg et al. 2009);

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- Making arrangements with experts and/or laboratories for consultation and/or follow-up tests to confirm IFs (Aarts et al. 2017). If necessary, tests should be repeated under good laboratory practices by a certified diagnostic lab (NIH, Aarts et al. 2017);
- Instructing researchers and other relevant personnel on the protocol to follow when IFs are detected (Aarts et al. 2017);
- Coordinating with clinical specialists for prompt follow-up when necessary (Aarts et al. 2017)

Further, any policy should be realistic and only spell out obligations that can actually be met (Bovenberg et al. 2009). This includes funding and appropriately trained personnel (GA4GH 2021, Lewis et al. 2021). It should take into account potential future findings that may be found due to technological or scientific advancements. It should also describe what the termination of the research study or biobank means for the handling of IFs (Bovenberg et al. 2009).

Patient/participant consent and information

Current guidelines strongly recommend that IFs policies should be reflected in the patient/participant information (NIH, WMA 2002, revision 2016, ISBER 2012, Aarts et al. 2017, Fellmann, Rial-Sebbag et al. 2020, Bovenberg et al. 2009). This includes circumstances under which IFs would and would not be disclosed to participants (NIH) or to family members (NIH), also after the participant or patient is deceased (Fellmann, Rial-Sebbag et al. 2020). It should include what types of IFs may be returned (NIH, Fellmann, Rial-Sebbag et al. 2020), when (NIH), and how (NIH, Aarts et al. 2017), and whether or not participation may lead to any benefits (Bovenberg et al. 2009). Patients or participants should be informed that IFs may be returned by secondary investigators if data are shared through a data repository (NIH).

NIH specifies several other items that are specific for genetic IFs that should be specified in the informed consent process. Many of these items should be seen in light of an IFs policy that has a low threshold for reporting:

- That the clinical significance of some results may be unknown;
- That the absence of a result does not equate with absent or reduced disease risk;
- That future research may change the clinical significance attributed to results at the time of the investigation;
- Whether the study team will be responsible for providing updates to participants regarding the significance of individual results;
- Whether return of results is dependent on the age of the participants and whether participants will be given the opportunity to provide consent for return of results when they reach the age of majority;
- The relevance to reproductive planning of any results that are to be returned (for men and women of reproductive age and for women known to be pregnant at the time of enrollment) (NIH).

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The BBMRI-NL guidelines recommend giving research participants the option of opting out of receiving information about IFs. However, in situations when serious harm could be inflicted on the participant or their relatives, this opt-out might be overruled by the researcher, after consulting an expert (Aarts et al. 2017). Asking participants about their individual reporting preferences is also part of the recommendations by Bovenberg et al. (2009). If a participant indicated not wanting to know (certain) IFs, not including them in a specific research study could be considered (Bovenberg et al. 2009).

Which IFs should be returned?

None of the guidelines give a specific list of genetic variants that should always be disclosed. Some guidelines however, outline criteria or processes to guide decisions on whether or not an IF should be returned.

The guideline of BBMRI-NL gives the following recommendations on how to determine which of the potential IFs should be reported to research participants:

- Consult the literature, best practices and/or a multidisciplinary team;
- Draw up a list of anticipated IFs in consultation with a multidisciplinary team, and decide together whether these need to be reported;
- When deciding this, consider the following criteria:
    - Is there a real risk of a serious disorder?
    - Is there a realistic management option that can be offered? (Aarts et al. 2017).

Additionally, benefits to the data subject should be weighed against any disadvantages (Bovenberg et al. 2009). These guidelines are based on the Dutch practice to use a cautious approach to the return of IFs, in which only high risks of a serious disorder that is uncertain to be incorporated in the donor's current treatment, and for which a realistic management option can be offered.

As a starting point, the guideline recommends to consult the literature, best practices and experts, including the list of variants that warrant return of results by the American College of Medical Geneticists (Dorschner, Amendola et al. 2013; Miller et al. 2021). The GA4GH Policy recommends researchers to let themselves be guided by current clinical standards of care and by community involvement (GA4GH 2021, Lewis et al. 2021). The list of IFs that should be returned should be checked and updated regularly (Aarts et al. 2017).

The US-based NIH offers a broader list of types of IFs that could be considered in setting up an IFs policy:

- Medically preventable conditions;
- Medically relevant results with unclear treatment implications;
- Results of uncertain significance;
- Results with clinical implications for the individual, but which may be useful for reproductive planning (e.g., carrier status);

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- Adult-onset disorders to children or their parents (NIH).

Other guidelines are less specific about how to determine which IFs should be returned. However, in many cases they implicitly imply that IFs of a severe and high-risk nature should be returned, for instance when referring to '*serious and significant findings (either within the scope of the research project or outside of its scope) that have serious and significant health implications for the participant or their genetic relatives*' (ISBER 2012). Bovenberg et al. explicitly refer to returning IFs that relate to a serious health condition and where the possibility of an individual health benefit is realistic: '*The basic factors guiding disclosure and non-disclosure decisions should be: nature and size of the health risk, validity of the research finding, clinical utility for the participant, feasibility of feedback and integrity of the research and the meaning and 'non'-meaning of findings for different groups.'* (2009). Findings with high clinical importance should be reported to the data subject, even if that means overriding the wish of the data subject not to be informed. For other findings with potential health implications, data subjects may be informed that they can access relevant information if they want to (Bovenberg et al. 2009).

Most guidelines do not specify between findings that may be relevant for the data subject or that may have implications for family members. Bovenberg et al. (2009) indicate that in general, biobanks should only return IFs to data subjects. Where relevant, data subjects are then responsible to communicate the finding to family members for whom the finding might be of relevance. However, after a data subject has deceased, and a finding of high clinical relevance has been found, reasonable efforts should be made by the biobank to return the finding to them.

Practical Considerations and Building an Evidence Base

The potential benefits, risks, and costs of feedback of IFs in research are not clearly understood. It is important to identify these, and to develop an evidence base over time in order to refine policy over time. There are a number of analytic challenges to identify an IF, including uncertainty and change with updated bioinformatics pipelines, re-interpretation based on the clinical presentation of the individual, and mosaicism requiring alternative DNA samples (Kochan et al., 2020).

There are challenges in participant contact, including non-responders, decedents, and situations where the result was already known by the participant (Kochan et al., 2020).

Another key challenge that remains poorly understood is the hand-off of the IF to the healthcare system.

Sequencing in health care context

In summary, the following recommendations can be seen as the best practice in Europe in dealing with IFs in the health care setting (Matthijs et al. 2016; Van El et al. 2013; Vears et al. 2018):

- A protocol/policy on how to deal with IFs in the health care setting should be set up and followed;

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- Patients should be informed about this policy, including:
    - The chance of IFs
    - A question whether the patient wants IFs to be returned, either through an opt-in or opt-out procedure
- When a patient does not consent to the return of IFs, this should be respected. However, this 'right not to know' may sometimes be overridden by professional responsibilities for life-threatening IFs
- Genetic variants that are beyond the aim of the clinical question, but are indicative of a serious health problem for the person tested or close relatives, should be reported. When a genetic variant has no health implications for the person tested or their family, they should not be reported;
- When there is insufficient evidence of the pathogenicity of a genetic variant (VUS; Variants of Unknown/Uncertain Significance), this variant should not be reported;
- Clinicians should explain the potential crossover with research to patients
- The EuroGentest guidelines recommend laboratories to confirm IFs before informing patients (Matthijs et al. 2016).

Recontacting When Test Results Change Over Time

Recontacting is the Establishment of a new contact—initiated by either former patient or clinician – with former patients, seen in the past, discharged from care, and no longer in an ongoing relationship with the specific healthcare professional involved (Carrieri et al. 2019).

Most often, recontacting concerns a contact established to communicate a re-interpretation of a genetic variant that was interpreted in the past. Although such a situation does not cover the definition of IFs as defined above, since the re-interpretation usually concerns a finding within the aims of the previous analysis. However, the recommendations about recontacting might be informative for the discussion on IFs, because as in IFs, it is about findings that usually occur a certain period of time after the data were collected and after a patient is still under treatment of its treating physician. The ESHG recommends the following:

If possible, recontact should take place for findings with clinical or established personal utility, even though currently there is no duty to do so (recommendation 1);

- The decision to recontact should be based on the best interests of the patient/family (recommendation 2);
- Recontacting should be sustainable for the healthcare system and its workforce (recommendation 3);
- The allocation of dedicated resources for activities on recontacting should be considered (recommendation 4);
- Recontacting should strive to be equitable for patients from all socioeconomic backgrounds and contexts (recommendation 5);

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- There is a need for professional consensus about what constitutes good practice regarding consent for recontacting (recommendation 6);
- Recontacting should be a shared responsibility with patients (recommendation 7);
- Recontacting should be a shared responsibility with the genetic laboratories (recommendation 8);
- Data sharing should be promoted (recommendation 9);
- Other stakeholders should also share responsibility for recontacting (recommendation 10);
- Do the best you can with limited resources (recommendation 11);
- Each country should define its own organisational policy on the recontact process (recommendation 12);
- More research is needed to inform responsible recontacting processes (recommendation 13) (Carrieri et al. 2019).

There is discussion on whether laboratories should reanalyze data to generate new findings. Both the guidelines from EuroGentest and the 'points to consider' based on expert opinions indicate that there is no obligation for laboratories to routinely reanalyze data systematically for novel findings (Matthijs et al. 2016, Vears et al. 2018). The latter however, indicates that if a laboratory learns that a specific variant is reclassified, it is 'good clinical practice' to identify patients and inform their clinicians.

Considerations for Minors

The UN Convention on the Rights of the Child, 1989 highlights that children have the right to their interests being a primary consideration in all decisions concerning their well-being. They have the right to be heard and the right to the highest attainable standard of health. Whole genome sequencing in paediatric contexts raises a number of challenges in relation to these rights, which will be addressed in a complementary task of WP2. This section reviews issues specific to the handling of IFs in paediatric contexts, which a focus on ensuring policy supports the best interests of the child.

General questions of when and what IFs to report apply equally in paediatric contexts. One potential conflict that may arise is between the welfare of the child and the autonomy interests of the parent. Should feedback of IFs in paediatrics that are actionable (i.e., preventable or treatable) during childhood be mandatory, regardless of the wishes of the parents? Mandatory reporting of such IFs to parents is recommended by the Canadian College of Medical Genetics (CCMG) (Boycott et al, 2015).

Another tension arises between the child's welfare in adulthood, and the child's right to know or not to know about health information in adulthood. Should feedback of IFs about adult-onset conditions be restricted? Or should parents be given discretion over such findings? (Vears, 2021)

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This may depend on whether or not the findings are actionable or not during adulthood. Restricting return can preserve the child's right to an open future, the right to decide whether or not to be tested once he or she reaches the age of majority. But the feedback may also have implications for the health of the child's parents, which is tied to the child's own best interests. There is a chance that the child does not have another opportunity to be sequenced or informed of an adult onset condition. Canada's CCMG recommends not returning actionable, adult-onset IFs unless the parents' request this, and the disclosure would be actionable for the parent or another family member. (Boycott et al, 2015) The US ACMG recommends a list of secondary findings be reported from clinical sequencing, regardless of the age of the patient, but suggests patients (or their parents may opt-out). However, there is also advocacy for mandatory reporting of serious, medically actionable, childhood-onset findings. (ACMG, 2015) The US ASHG recommends in research contexts (?) that parents should generally be able to opt out of receiving IFs, "...in general, parents should be able to decline to receive secondary findings in advance of genetic testing." (Botkin et al. 2015) However, the ASHG recommends that reporting of serious, medically actionable, child onset IFs should be mandatory. The ESHG states that certain IFs should generally be reported. In paediatric contexts, "In case of testing minors, guidelines need to be established as to what unsolicited information should be disclosed to balance the autonomy and interests of the child and the parental rights and needs (not) to receive information that may be in the interest of their (future) family." (van El et al. 2013)

Other considerations relate to the involvement of the child in consent and feedback processes in an age-appropriate manner. Decisions about sequencing and IFs, and associated communications, should be made by the appropriate parent(s) or legal guardian, unless the patient has reached legal maturity. Consent/assent should inform the parent/child if IFs may or may not be returned and under what conditions. "the pre-test counselling session with parents is an opportunity for health professionals to explore parents' wishes and ensure they have a good understanding of the information and its implications for both the child and the broader family." (Vears, 2021) Choices may be offered where appropriate. Some recommended consent clauses include the following: medically actionable during childhood will be returned; parents may choose to receive (or not) IFs actionable during adulthood or for family members; non-actionable adult-onset will not be returned. (GA4GH, 2021) Reporting of findings should consider appropriate ways to communicate the information to the child, and involving the child in subsequent healthcare decisions (Vears, 2021).

Common Principles / Variation in Europe (Return of IFs)

From the above review, we can ascertain some general principles applicable for handling IFs in the European context:

- Beneficence: information with a high clinical relevance may be returned to the benefit of the data subject or his/her relatives. Yet, duties in research differ from those in health care, though these fields can be blurred.
- Importance of the Right not to Know in Europe and Purpose Limitation Principle under Data Protection. This is typically operationalized by requiring (separate) consent to feedback of individual genomic findings.

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- High consent requirements (e.g., pre-test genetic counselling) before predictive genetic testing or carrier screening (generally excluding the return of these findings as IFs).
- Cautious approach in Europe to actively seeking out Secondary Findings in healthcare contexts (and by extension also research contexts), given uncertain and unproven benefit-risk balance of "opportunistic screening". (e.g., De Wert et al. 2020)
- Professional obligation (duty to warn/rescue) in some countries/contexts for reporting life-saving information to the patient.
- Cautious approach to return 'non-actionable' findings.
- Common legal or ethical obligation to return serious, analytically/clinically valid, and clinically actionable IRRs and IFs to sequenced individuals from research contexts.
- Importance of having a plan for handling, assessing, and communicating individual genomic findings.
- The decision to participate in research should be based on solidarity. This means that having more access to health information than those who do not participate should not be assumed when participating. This argument of equality is also used in for instance the conservative European approach towards opportunistic screening: opportunistic screening would lead to differential access to health information based on availability instead of needs.
- Balance between benefits to data subject and burden (resources) on infrastructure and healthcare systems (distributive justice).

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