1+MG Incidental Findings Policy - Summary and Recommendations

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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 organizations 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 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 organized 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.[1] 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:

a. developing a plan outlining what kinds of IF will be returned and how,
b. informing data subjects about the plan and seeking their consent to receive IFs,
c. establishing processes to assess IF validity and utility,

[1] Additional considerations apply to minors, addressed as part of best practices.

d. providing feedback through a medically, legally, and ethically appropriate channel,
e. 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 analyze 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 analyze 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[2] 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.[3] 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

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.

[2] This policy equally covers other forms of next-generation sequencing depending on the final scope of the 1+MG (e.g., whole exome sequence data, genome-wide array data).

[3] Please note that in the background section, the guidelines reviewed mainly focused on IFs. When collecting genomic data for a specific study with a specific study question, there is a clear difference between individual research results (IRRs) and IFs, because researchers can more easily inform the data subject about the former. In a large-scale data sharing project such as 1+MG however, data subjects are not necessarily informed beforehand about the specific research questions that the project will try to answer using data derived from them. From the data subject's perspective there is thus no notable difference between IRRs, in which the findings are related to the (research) aims, and IFs, in which the findings are unrelated to the (research) aims.

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).[4] This policy excludes handling of diagnostic findings from rare disease matchmaking.[5]

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.

[4] We assume all WGS data submitted to 1+MG has undergone a primary analysis. There is no indication as of yet that 1+MG would involve cases where a data holder generates raw data for direct deposit within 1+MG for further research and healthcare uses without an initial analysis.

[5] Rare disease matchmaking is where a health care provider makes data about an undiagnosed, still active patient available through a database with the aim of matching with another patient with similar genetic variants and phenotypes, which may provide support for a diagnosis. In this case, the health care providers who exchange data with each other will handle and communicate any diagnostic information to their active patient according to the applicable standard of care. It is currently unclear to our Working Group if this use case is supported by 1+MG.

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 standardization 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 organizational 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 organization 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 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:

1. **Common Requirement for Users to Feedback (Only) Serious, Clinically Actionable IFs(*recommended*)**
2. National Node/Country Tags Data with Local Feedback Requirement (Flexible)
3. "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

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 organizations 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 organizations 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 individualized 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 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

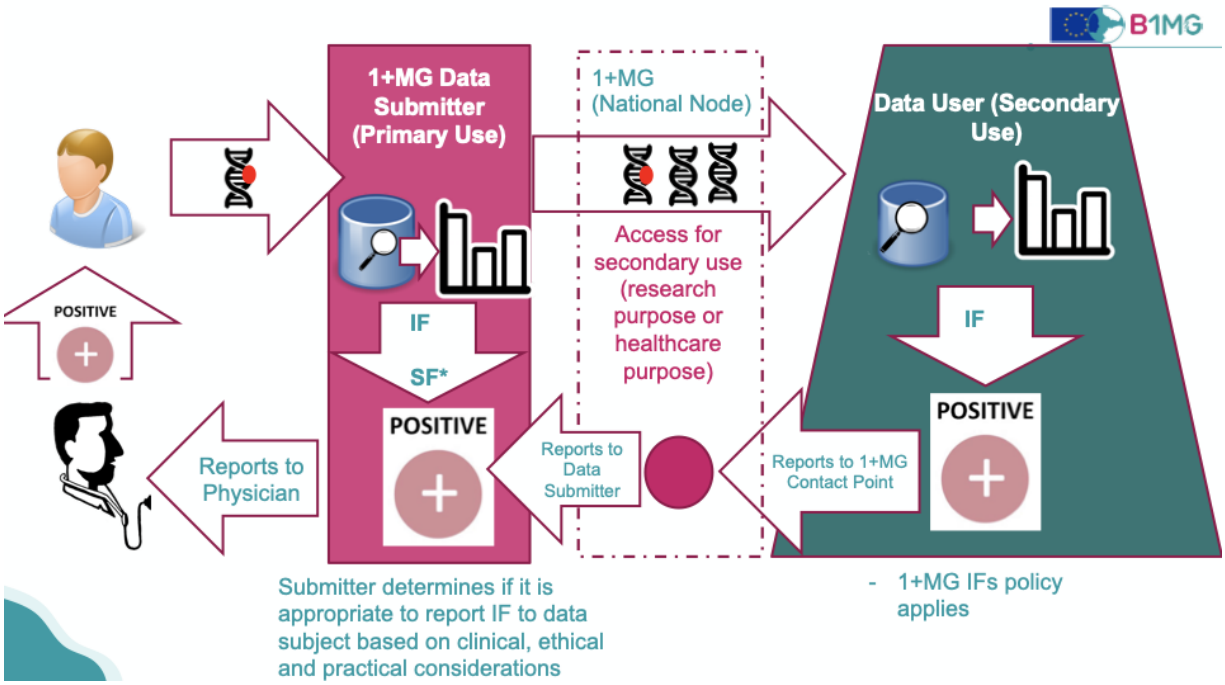
1+MG does not permit any feedback of IFs from secondary use to the national node.

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.

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 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.
- 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[6] (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).

[6] In cases where patients receive a test result (e.g. genetic diagnosis) as part of their primary healthcare workup, that test result may change in a clinically relevant way over time, for example because of advances in general knowledge about the medical significance of genetic variants.

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.
- 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 fulfill 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 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.