

# **Global Alliance for Genomics and Health:**

## **2021 Policy on Clinically Actionable Genomic Research Results**

### **I. Context**

#### **1. Background**

The Global Alliance for Genomics and Health (GA4GH) is a policy-framing and technical standards-setting organization seeking to enable responsible genomic data sharing within a human rights framework.<sup>1</sup> Its *Framework for Responsible Sharing of Genomic and Health-Related Data* is founded on the universal human right to benefit from science and its applications.<sup>2</sup> Responsible disclosure of clinically actionable genomic findings from research studies to those research participants who elect to receive them could advance data sharing and benefit the research participants themselves.

When data is shared, the knowledge that the initial researchers responsibly addressed the return of results can reassure data repositories aggregating those data and researchers conducting secondary research with those data that obligations to return results have been seriously considered and addressed with research participants. Data repositories and researchers conducting secondary research may have their own duties with regards to addressing the return of results,<sup>3</sup> but as a starting point establishing the minimum core obligations for the original researchers is important. This is particularly pertinent in cases in which data is shared across jurisdictional boundaries, because of the existence of multiple legal and ethical frameworks, requiring adherence to different rules and principles. Ensuring that the wellbeing and the rights of sequenced individuals have been appropriately addressed facilitates international data sharing, the core purpose of the GA4GH. The need to achieve transparency at all stages of data sharing and for all the relevant parties — namely the data controllers, processors, recipients and users, including the secondary users of data — helps motivate the move towards a clear minimum global standard with regards to the return of results.

#### **2. Purpose**

The focus of this policy is on clinically actionable genomic results, that is, results that indicate risk for or the presence of a condition for which prevention or treatment is available. We restrict ourselves to such results because, as outlined below, the vast majority of the ethical and legal arguments that favor the return of results in genomic research studies are focused on such information. However, there is a large literature debating the ethically appropriate definition of “clinically actionable.” We include not only

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results for which clinicians can provide prevention or treatment, but also results that allow a participant to take steps (such as change in diet or health surveillance) that can prevent or ameliorate a genetically based disease or disability. Moreover, clinical actionability can differ between jurisdictions, where prevailing opinions on appropriate treatment, and available resources to act on these opinions, may differ. We note that a significant part of the literature would go further, contemplating the return of results valued by participants, even if no effective action is currently available.<sup>4</sup> However, in keeping with the goal of this document to set minimum standards, we focus here on clinically actionable results.

This document uses “return of results” to include return of results sought by the research, incidental findings that are not sought but are discovered in the course of research, and secondary findings that are not the focus of the research but are deliberately sought.

The following GA4GH Policy on Clinically Actionable Genomic Research Results aims to provide a reference point for managing the return of such results that recognizes the importance of the accountability and transparency of genomic researchers towards participants. It also acknowledges the differing levels of evidence behind the clinical utility of such information, and the complexities involved in returning it to individuals in an ethically and legally appropriate manner. The Policy aims to identify common ground while also allowing for appropriate customization by locale and by research project. The GA4GH recognizes the evolving thinking and research around the return of genomic research results and will revisit and update this Policy as required.

## II. Policy

1. **A clear protocol that is adhered to.** Every research study generating clinically actionable genomic research results should have a specific protocol regarding the return of such results. Such a protocol should be devised before the start of the study, should be approved by the relevant research oversight body, and be revisited periodically throughout the duration of the study. Researchers should be held accountable by their participants, funders, and ethics committees to meet the standards they define in this protocol.
2. **Upfront resourcing.** Where return of clinically actionable genomic results is intended, resourcing should include funding for the full process of returning results to participants, as well as ensuring the availability of appropriately trained personnel.
3. **Link to clinical standards.** In deciding the parameters for return of clinically actionable genomic results, researchers should be guided by current practice regarding the clinical standard of care within their jurisdictions.
4. **Community engagement.** Which genomic research results should be returned and how they are returned will be project and community specific, and depending on the nature of the research should be guided by community involvement.

5. **Sharing of resources.** Whenever feasible, medical, behavioral and economic tools and outcomes associated with the return of clinically actionable genomic research results should be documented and shared to continue to lower the barriers to responsible return.
6. **Funders urged to support the return of results.** Funders should set aside resources to support the return of results in those projects that plan to do so.

### III. Discussion

We note a combination of four trends that support the return of clinically actionable results to research participants.

#### 1. Emerging Ethical and Legal Consensus in Support of the Return of Results

There is an emerging ethical and legal consensus in support of the return of results. Many international bodies and countries have guidance, legislation, and regulations in place that support a robust return of results, i.e. mandate that certain results should or must be returned. These are summarized in Table 1 of a 2019 overview of the relevant international legal landscape.<sup>5</sup> Some of these regulations are genomics specific and others are broader in scope. This legislative landscape reflects growing agreement throughout the world that if clinically actionable results are found during the course of a research study, they should be returned to those participants who wish to receive them. Specifically, in the context of genetics research, the Council for International Organizations of Medical Sciences (CIOMS), in collaboration with the World Health Organization (WHO), stated in their 2016 report: "There is an emerging consensus that at least some findings in genetic research must be returned to individual donors if they wish" and that "life-saving information and data of immediate clinical utility involving a significant health problem must be offered for disclosure."<sup>6</sup>

This consensus is grounded in an extensive patchwork of ethical reasoning.<sup>7</sup> Most laws and policies, where they give reasoning, refer to rights of participants: the right to access (e.g. in the EU's General Data Protection Regulation), the right to be informed (e.g. in Spain's Law on Biomedical Research)<sup>8</sup>, and the right not to know (e.g. in the UNESCO Universal Declaration on the Human Genome and Human Rights, 1997).<sup>9</sup> Many bioethicists have also focused on the duties of researchers, such as the duty of care<sup>10-12</sup> (a duty also enshrined in the Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research),<sup>13</sup> the duty to warn,<sup>14</sup> the duty of rescue,<sup>15</sup> and the duty of reciprocity.<sup>16</sup>

Many of these duties rest on a beneficence argument, which is supported by the strengthening data on the clinical benefit of individuals receiving certain genomic results.<sup>17</sup> An appeal to beneficence rests on a favorable overall benefit-to-risk tradeoff. Systematic review of the literature suggests that where genomic research results have been returned, they have been well received without demonstrated physical or psychological harm (*forthcoming from Vears et al*). Other types of potential harm, however, such as

insurance reimbursement or payment denial (e.g. life, disability, or long-term care insurance payments) have not been evidenced adequately in the relevant literature. Despite these remaining evidence gaps, systematic review of the literature suggests that researchers and members of ethics review committees are supportive of returning results that are sufficiently reliable and clinically actionable. An important caveat is that much of the existing data is US focused.

## **2. The Evolving Research Enterprise Supports the Return of Results**

The nature of the research enterprise is changing in a way that supports the return of results. There is a broad international trend in research towards respect for research participants as partners in the research process, and more participant engagement in how research is carried out, including what results will be offered to participants. The return of results is becoming an increasingly important part of the research process because it is part of this move towards participants becoming more involved in the research process.<sup>14</sup>

## **3. The Public Supports the Return of Results**

Related to the previous point, systematic review of the published literature suggests that participants and members of the public highly desire the return of results. Return of results may also motivate some individuals to donate their data to research (in general, motivations for participating in genetics research are complex).<sup>18,19</sup> Evidence from the ‘Your DNA Your Say’ survey suggests that this is variable based on country: across the 22 countries surveyed, the proportion of people responding that they would be influenced to participate in genetics research by receiving results vary from below 50% (Spain, Portugal, Brazil, Argentina, UK, Sweden) to 70% and upwards (Russia, USA, China, India) (*publication forthcoming*).

## **4. There are Fewer Barriers for the Return of Results**

There are now widely available tools and resources which reduce the barriers to enacting the return of results, and hence enhance the benefits-to-cost tradeoff inherent in returning results. For example, a large component of returning results is identifying whether a given result is indeed likely to be clinically actionable.<sup>20</sup> To aid in this, ClinGen curates disease-gene associations, and publishes their full methodology and findings.<sup>21</sup> ClinVar is a freely available repository of variant classifications, including those from expert panels that can form the basis for more automated filtration and reporting of well-established clinically actionable variants.<sup>22</sup> (Though we note that current data biases in ClinVar lead to higher Variant of Uncertain Significance rates outside of predominantly European ancestry populations).<sup>23,24</sup>

We now elaborate on each policy point.

### **1. A clear protocol which is then adhered to**

A clear protocol that specifies whether and how a study intends to return results is a prerequisite for informed consent. The informed consent process — and hence the protocol — needs to cover *what* types

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of information will be returned and how judgment will be made on whether a variant qualifies for return. Additionally, it needs to specify *how* that information will be returned, focusing on ensuring this is done responsibly. If a study adopts a protocol to not return clinically actionable results, this should be clearly stated in the consent process. Depending on the nature of the study, a protocol may or may not allow participants to opt out of receiving results. Prospective participants should be able to exercise their right not to know genetic information about themselves,<sup>9</sup> which can involve not participating in a study.<sup>25</sup> (We note that there is some debate about whether there should be an absolute right not to know if an individual has had a result generated about them,<sup>26</sup> and that in some jurisdictions limitations are put on this right.<sup>5</sup>)

For informed consent to be meaningful, this protocol must then be adhered to. There is a danger that consent for return of results may be viewed by researchers more loosely as permission to return clinically actionable results, rather than as a more strict commitment. Ethics review committees and funders should hold researchers to account for adhering to the policy that they outline. Participants can also have a role in this.

### 2. Upfront resourcing

The return of genomic results is a resource-intensive process. The identification of what needs to be returned is only one part of the whole process which connects a patient to downstream resources. An additional component piece is the potential need to validate results, for example the need for a CLIA'88 (US) or ISO15189 (international) confirmation of the findings before these are used to change clinical management. An additional major consideration is the availability of appropriately trained clinical staff to communicate the significance of a genetic result. In some countries, there is a lack of appropriately trained personnel, potentially necessitating the training of healthcare professionals supported by clinical point-of-care tools<sup>27</sup> to be able to manage these results. Within this context, the return of research results requires careful budgeting and resource planning from the outset of project conceptualization. This also allows the benefit-to-cost tradeoff of the return of results to be estimated as accurately as possible at study inception, in turn helping to frame a study's chosen protocol. Such resourcing considerations mirror the move in the last decade by funders to require data sharing plans and budgets in funding applications.

### 3. Link to clinical standards

Clinical standards include identifying which variants are deemed clinically actionable, standards for analytical validity, and processes that ensure results are returned with appropriate counseling and/or clinical guidance. There are three main considerations that justify the relevance of clinical standards to the return of clinically actionable results in research. The first is that ultimately it is the prospect of a clinical action that motivates such return. It is to support such action that standards in the clinical setting have been adopted in the first place. Second, relevant clinical standards will be appropriately sensitive to the health system context (including its cost structure), legal system, and additional constraints of the location of the participants. For example, as noted above, perspectives on clinical actionability can differ by country (see the differences in approaches to secondary findings between the American College of Medical Genetics and Genomics on the one hand and the European Society for Human Genetics and

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Canadian College of Medical Genetics on the other).<sup>28-31</sup> The link to relevant clinical standards helps ensure that the return of results will be appropriately tailored to the whole context in which those results are received. Third, the blurring of the research/clinical divide<sup>32</sup> suggests harmonization could lead to consistency across the continuum that encompasses clinical care, clinical trials, research studies embedded in health systems, other research studies, and population biobanks. Despite the relevance of clinical standards in this context, there are key differences between the research and clinical endeavours. Particularly relevant in this instance is that the duties of researchers do not extend beyond the duration of their research projects.<sup>33</sup>

### **4. Community engagement**

Consultation with the communities to be approached as research participants is important in order to address local concerns. The GA4GH's *Framework For Involving And Engaging Participants, Patients And Publics In Genomics Research And Health Implementation*, outlines why and how engaging with people can best address the concerns of those who give their genomic data, or who are otherwise impacted by genomics research. Members of the community, or communities, who are the intended participants should have a say in the content and mechanisms for return of genomic results. For example, the costs, including opportunity costs, of return of results will be context specific and relevant to decisions about scarce resources across a population. The protections against genetic discrimination in a particular jurisdiction will also have an impact. These considerations are key for ensuring that a return of results policy is suitably informed by the principles of justice and beneficence. Community engagement can also help determine the level of support that participants will require on result return to ensure adequate understanding. Community engagement hence not only helps with the instrumental ends of a research project, such as the recruitment and the retention of participants, but is also part of ethical good practice.<sup>34</sup> For certain communities, there are specific guidelines already in place for community involvement.<sup>35</sup>

### **5. Sharing resources**

A time-consuming aspect of implementing the return of results is the development of resources that enable this process, such as informed consent documents and tools, detailed protocols, and budgets. If researchers share these resources with other projects, the barriers to the return of results are lowered, enhancing the benefit-to-cost ratio of the return of results. GA4GH projects can contribute to these evolving resources. For example, the H3Africa's Guideline for the Return of Individual Genetic Research Findings could be useful in settings where there are limited resources, expertise, and data, and where there are particular sociocultural issues around consent.<sup>36</sup>

### **6. Funders urged to support the return of results**

The reasoning outlined at the beginning of this Discussion supports studies opting to return results to participants. Evidence suggests the existence of a large gap between what researchers would consider best practice for returning results and what is currently being implemented.<sup>37</sup> This motivates our appeal to funders. Additionally, this appeal is motivated by the debates over the risk-benefit trade-offs in returning



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genomic results. These debates, which cover both the research and clinical settings, suggest the need for more research, from multiple countries. Return of results as part of this research not only directly benefits participants, but — when suitably coupled with data gathering strategies — allows for the assessment of impact and overall cost effectiveness of return of genomic results in general. The gathering of this evidence supports the human right of everyone to benefit from science and its applications.<sup>2</sup> A number of observational and randomized studies with limited sample size have suggested that returning selected research results has been useful and cost-effective in participants' clinical care.<sup>38–41</sup> Larger projects returning clinically actionable research findings to participants and, to various degrees, tracking outcomes and cost-effectiveness, are underway. These include: the Project Baseline by Verily, the Framingham/Jackson Return of Results Study (both in the US), the 100,000 Genomes Project (UK), Australian Genomics, Melbourne Genomics, a program through the Institute of Precision Medicine, Singapore,<sup>23</sup> the Incidental Genomics Trial in Canada,<sup>42</sup> and the All of Us Research Program in the US.<sup>43</sup> Future research needs to cover the global breadth of settings, including sociocultural perspectives, in which individuals may receive genomic results.

### IV. Acknowledgements

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### **Policy Revision History**

<b>Policy Number/Version</b>	<b>Date Effective</b>	<b>Summary of Revisions</b>
v1.0	June 24 2021	n/a