H3Africa Guideline for the Return of Individual Genetic Research Findings

INTRODUCTION

There is significant debate about whether and how individual genetic research findings should be returned to research participants – also known as "feedback of findings" (FoFs), and there is little guidance available for how this should be done on the African continent. There is virtually no empirical data available describing the preferences and perspectives of relevant African stakeholders including research participants, ethics committee members, researchers and research regulators on these issues. Furthermore there are contextual factors in African communities that impact on decision-making regarding the return of individual genetic results, such as familial involvement in the research process. Due to this and ongoing concerns about the position of the H3Africa Consortium concerning FoFs from genetic research, a decision was made to develop consortium-wide guidelines following a request from the Kidney Research Network in 2016. This document presents a set of key principles to inform decisions about whether to return individual genetic research findings by H3Africa Consortium members to research participants. A decision flowchart (Figure 1), which provides a logical framework to assist in planning and decision-making on whether or not to provide FoFs is also presented for further practical guidance. Considering that there is still a lot to learn about genetic variation in African populations, with a sparse evidence base about the preferences and understanding of research participants on the African continent, this document will continue to evolve and be adapted as necessary.

General consensus for FoFs

Whilst international policies for return of individual genetic research findings are still evolving, general consensus appears to be that in order to consider for feedback the following criteria need to be met.

1. Methods used to generate those findings should be able to accurately and reliably detect genetic variant(s) in the affected individual (high analytical validity).
2. Genetic variant (s) should be robustly associated with disease causation, thereby accurately and reliably predict clinical outcome (i.e. high clinical validity)
3. Findings should be able to guide therapy or prevent disease (clinical uility) AND/OR have proven therapeutic or preventive intervention (medical actionability) [1].

In addition, there should be some indication that participants wish to receive findings that fulfil these criteria, preferably following a process addressed during study consent or enrolment [2]. An important considerations is that participants should also be afforded the right not to know [3]. In summary, decisions about whether and what findings ought to be fed back need to be based on analytical and clinical validity of the results, their potential value and utility, as well as participant volition [1].

Exclusions and exceptions for FoF consideration

- This guideline expressly excludes projects that recruit participants in distant locations on a one-off basis, without any ongoing relations between the research team and the research participants.
- FoFs should be limited to the primary research study and exclude secondary use of samples and data analysis.
- In addition to revealing pertinent findings related to the condition under investigation, incidental findings may be found. At this time, it is advisable to prioritise study-related results that are pertinent to clinical diagnosis or treatment; and that only validated incidental findings be considered where appropriate (see section below).

GUIDING PRINCIPLES

In the face of uncertainty about whether and which results should be fed back, most H3Africa researchers to date have decided *not* to feedback any individual genetic research results [4][a] With evolving insight, however, H3Africa recognises that there are cases where FoFs are important for the health and wellbeing of research participants. Essentially, FoFs should be deeply considered when the associated risk for the disease is significant; there are important health implications such as premature death or substantial morbidity; there are significant reproductive implications; or proven therapeutic or preventive interventions are available [5,6]. However, a decision to feed back findings also needs to consider all of the the items as discussed below.

A. Primary conditions in deciding to feedback individual genetic results

We recommend the following key considerations when making a decision for FoFs:

Primarily feedback findings that relate to the disease being investigated in the research project.

Where researchers decide to provide FoFs, they should focus primarily on feeding back pertinent findings which are related to the disease or condition that is being investigated, and in which the research team has both clinical and analytical expertise. In that case, we assume that the research teams would be:

- in a position to review and assess the evidence base for potentially pathogenic variants in relation to the population(s) that are being investigated.
- able to assess whether the particular finding likely holds value for the individual.
- able to verify the finding(s) using an analytically validated assay and repeat the test with another sample collected from the same patient/subject and/or test in a certified diagnostic laboratory (see Section E below).
- able to ensure that patients are appropriately informed of the implications of the findings for their disease and/or treatment.
- able to advise on, and refer to, appropriate follow-up care.

Where these conditions are met in the study design, researchers should consider whether their research is likely to identify findings that should be fed back and consult with the funders and health service providers on how this could be supported. It is noted that in only a few, if any, of the H3A projects are these criteria are adequately fulfilled to consider FoFs. However, the research team should determine the minimum set of results to be fed back and the steps to be taken in consultation with Institutional Research Boards or Research Ethics Committees (IRB/RECs) and other relevant stakeholders.

Role of research ethics committees) in FoFs

We recommend that H3Africa project include provisions on feeding back findings in their consent forms and should consult with and receive approval from the local REC that approved the H3Africa project. Specifically:

- If feedback is anticipated, the plan to do so should be clearly stated in the initial protocol submission.
- Alternatively, if feedback becomes desirable subsequent to approval of the study protocol, the plan to provide feedback should be clearly stated in a supplementary protocol or study amendment.

[a] In the first round of H3Africa projects, only one of 16 genomics projects made provision for feeding back findings in both its funding structure and consent process, see Munung, N. S., et al. (2016). "Obtaining informed consent for genomics" research in Africa: analysis of H3Africa consent documents." Journal of Medical Ethics**42**(2): 132-137.

- The FoF plan should be reviewed and approved as part of the design of the research project and included in an appropriate way within the informed consent process and project proposal documents.
- In the case of children, there is an additional responsibility to ensure that experimental protocols are aligned with respective local statutes and international regulations/declarations that protect the rights of minors.

It is worth noting that most IRB/RECs in Africa (and elsewhere) may not have the requisite expertise to assess the risks and benefits of returning research results. In such cases, the responsibility of making these assessments may require ethics committees to draw upon specialised expertise comprised of medical geneticists, clinicians, genetic counsellors, ethicists, bioinformaticians and in consultation with the community advisory board where these exist [6,7]. The purpose of such a committee would be to generate guidance on what is reportable in genetic studies, provide for broad stakeholder input, allow a more consistent approach across research networks and to provide credible guidance for the researchers and IRBs [6].

Timeframe

Since research projects are time and resource limited, it may be necessary to provide a timeframe indicating how long it may be before participants can expect any individual study results to be shared. In this case, it is advisable to assess practicalities of FoFs before the start of the project in order to ensure that the time and capacity are well appropriated. For monogenic disease studies, findings with potential medically actionable findings should be provided as soon as results are validated. There are many uncertainties surrounding the appropriateness of returning individual research results in the African research context, and it may be difficult to trace individual research participants years after recruitment. Therefore, we strongly suggest that the return of study results should be limited to the primary research study and not to secondary use of samples and data.

B. Pathogenicity and clinical validity of research findings

Suggested variants that are potentially appropriate for reporting back findings should always be reviewed by investigators from individual studies for appropriateness of reporting in their study. Evidence of pathogenicity can be determined from various sources such as population genomic epidemiology data, computational predictive methods, functional studies or segregation data. Some variants may be predicted to be pathogenic but not actionable (i.e. no medical interventions exist that would avert the illness). Thefeore, regardless of the analytical methods applied, clinical validity should be ascertained whereby there is both sufficient evidence that the variant or related gene/protein results in the target phenotype or disease symptoms, and that it is relevant for the target population.

Challenges in clinical validation include phenotypic heterogeneity, pleiotropy (single genetic loci affecting multiple phenotypes), incomplete penetrance, confounding of phenotypic modifiers (e.g. environment, lifestyle), and a limited scientific evidence-base [5]. This is less problematic for monogenic disorders or where for complex traits whereby variants have large effect sizes. While most H3Africa projects work on common complex diseases with multifactorial causes, a few studies are focused on monogenic disorders. FoFs for the latter, and to some extent highly heritable complex diseases, may be easier to determine pathogenicity and clinical validity because of well-established phenotype-genotype link for known genes and in rare cases, novel genetic markers, with very strong evidence for causality. Most other complex diseases comprise weaker genetic associations spread over a large number of genomic loci [8]. Population-validated genomic risk profiles may be established based on ongoing research in Africa.

These challenges for determining pathogenicity and clinical validity are ever more pronounced in populations of African ancestry and Africa as a whole as a result of the higher levels of genetic diversity on the African continent. To strengthen this evidence base, programmes such as ClinGen plan to review clinically useful results in persons of African ancestry. H3Africa investigators may be well-placed to contribute to these initiatives and in future develop guidelines to set the evidence threshold, which can be used for determining pathogenicity and clinical validity.

C. Establishing value

One key component of discussions about feedback of findings relates to questions about whether receiving individual results is likely to be of value to the participant. There are two ways in which individual results can be of value: either because they have clinical utility and/or are medically actionable, meaning that information could be used to guide diagnosis and treatement and there is some medical intervention available that would improve outcomes for patients [2, 3]; or because they have 'personal utility', which includes considerations of how participants would use research findings confirmed in a diagnostic laboratory and may include for instance a genetic diagnosis that ends a diagnostic odyssey to understand a life-long medical condition, or reveals a carrier status that could inform reproductive decisions. This excludes cases of confirming identity and paternity and other forensic uses. Therefore, clinical utility, medical actionability and personal utility – are good reasons to feed-back individual findings in H3Africa research. Thus, **when deciding to feedback findings, researchers need to explain how results will likely be of value to individuals receiving them.**

Is there evidence of clinical utility?

When genetic testing strongly predicts an adverse clinical outcome, it is of high clinical utility, providing that there is guidance on a possible intervention. While the case for monogenic diseases is relatively more clear cut, the multifactorial nature of complex diseases means that given genetic variants that potentially contribute to the disease generally have lower predictive value and lower clinical utility as risk predictors [9, 10]. In addition, there are often no treatments or preventive measures that substantially reduce risk, therefore relevant genetic results with clinical utility in complex diseases are uncommon. Programmes such as ClinGen and ClinVar utilise combinations of evidence from clinical and public health data, basic science and in silico research to identify and curate genetic variants with clinical utility. It is important to note that clinical utility does not guarantee actionability, especially in Africa where limited access to resources could limit provision of appropriate care. However, the information may be useful in understanding diagnosis or making reproductive decisions. Although little progress has been made regarding clinical utility for complex traits, genetic markers of pharmacological response may be useful in alerting an individual of a drug toxicity risk. For diseases such as cancer, genetic risk scores and other genetic markers may be applicable for preventive, predictive and prognostic use.

Actionability: adopt one standard for the entire project

One critical feature of these discussions is that, to date, what counts as medically actionable has not taken into account the resources available in the setting where participants are based, and the treatment options available to them [11]. The challenge is that what may be actionable for a person in one country or healthcare setting, may not be actionable for someone else even if they reside in the same region or country due to socio-economic and other factors.

Emerging consensus in the H3Africa Consortium is that **it would not be appropriate to adopt different feedback policies for people in different collaborating sites in the same project**. This could be paternalistic and unfairly prevent participants from knowing something because they do not have the resources to act on the information. Also, even if a particular intervention is not available in the public healthcare system in a country, researchers are not in a position to know whether participants have recourse to other means of acting on results.[b] Thirdly, it is common for medical professionals in under-resourced healthcare settings to inform their patients of what care they can receive in the public healthcare system and what care they could receive if they could pay for it. **The implication is that where a given project decides to feedback pertinent reportable individual genetic finding(s), it should include all participants in that project, regardless of whether or not those findings are actionable in their particular contexts.** Researchers should be mindful that treatment options may change in the future, and therefore, when deciding to feedback should assess any ongoing moral obligations to reassess treatment options for participants who have received FoFs. Engagement with relevant RECs is required in order to ensure that they are familiar with the research trends and the potential benefits for participants, and guide decisions across consortia study sites.

D. Volition

Include options for feedback in the consent process

Internationally, one key criterion determining whether individual genetic research results should be fed back is the preference expressed by the participant to receive such results [1, 16]. Whilst this would normally be addressed in the informed consent document, there is ample evidence suggesting that consent processes for genomics research in Africa are already overburdened, and that participant comprehension is low in most studies [12]. Recognising this potential tension, we consider that whilst **information about each project's policy on feedback of findings policy should be mentioned in consent documents and processes, such information should be in summary form.** For instance, the consent form could state 'no individual genetic research results will be given to you', or mention the anticipatable findings that could be fed back to participants. It is important to note that volition alone is not sufficient for disclosure and that value and validity should be well articulated. It should also be made clear that participants also have a right to decline receiving their results.

Provide information about the choices people are asked to make if using tiered consent

For researchers using a broad consent model, it is important to point out that broad consent does not: prevent researchers from providing feedback; absolve researchers from their ethical obligations, nor prevent them re-contacting participants. Whilst it would be acceptable to use a tiered consent process, whereby participants are explicitly asked whether they would like to receive results and are given the possibility to opt out, there are also some risks to this approach such as difficulty in tracking the different participant consents and challenges in conducting any important research in the future, since options for 'tiered' consent may not have been exhaustive.

Most importantly, where researchers choose to ask people for their preferences, **they have to ensure that participants are appropriately informed about the potential information they may or may not receive, and how that information would impact their lives.** Where participants are not appropriately informed, the risk is that they would make decisions on the basis of partial information or misunderstanding, which could have real implications for their lives and wellbeing downstream. We recommend that engaging with participants on FoFs should start before the study commences,

[b]For instance, people may have family members abroad who could pay for interventions, or they may have access to NGOs that offer healthcare.

which is also an opportunity to explain and simplify further any difficult terminology or concept. Educational resources to support consent and feedback can be provided through community engagement activities or in conjunction with the H3Africa WG for Community Engagement.

E. If we do decide to feedback, how should it be done?

Can verification be conducted in a laboratory that is certified/accredited for diagnostic testing?

In countries where genetic testing services are established (e.g. USA, UK, South Africa), and research identifies a participant who carries a harmful and actionable mutation, the general practice is that those research results are then verified in an accredited diagnostic facility before any clinical action is taken. In the African research setting, clinical diagnostic verification of individual genetic research results in a clinical genetic diagnostic laboratory may be possible. However, one should also recognise the following challenges (i) not all tests are validated for use on the African continent, or indeed for all ethnic backgrounds, and therefore verification may require shipping samples overseas; this could prove to be prohibitively expensive and (ii) analytical validity (reproducibility) of the specific variant(s) may not yet be available and tests may still be in development. Where these challenges are faced, and validation in a clinical genetic diagnostic laboratory is not feasible**, it may be acceptable for researchers to *verify* relevant results using the resources readily available for the project. Verification could involve obtaining a second sample from the same person and re-running the genomic analysis possibly using more targeted genotyping or sequencing methods.** Researchers *should not* feedback genetic research results that have not been verified, the reason being that mistakes - such as sample mix-up or mislabelling or experimental errors- do occur when handling and processing samples, or analysing data.

The decision on which approach to follow in order to verify genetic test results should be informed by the Standard of Care, policies and laws in the relevant country or countries. In countries where there is diagnostic clinical laboratory infrastructure, researchers should adhere to the standards and policies in those countries.

Who should do the feedback?

Internationally, there is a preference for individual genetic research findings to be fed back by medical genetic health professionals, preferably genetic counsellors, or people with medical genetic training such as medical geneticists. There is a real shortage of health professionals with this kind of qualification in most African countries, meaning that they are probably not available to assist researchers in feeding back research results. H3Africa considers that the absence of genetic counsellors *per se* should not be a reason to preclude feedback of findings. Rather, the consortium should look for means to train other healthcare professionals in developing the essential skills required to communicate with participants about individual genetic research results. In the first instance, we consider it advisable that **the task of feeding back information about individual genetic research results rests with clinicians and other qualified health professionals involved in the genomic research projects**, until other staff are sufficiently trained to take over this task. Other healthcare staff that could take over these duties are, for example, psychologists, nurses, social workers or others who have been involved in the research process, and have shown aptitude for communicating with participants about the research process, and who are interested in a counselling role. It is also imperative to explore whether other methods may be appropriate for sharing results, such as telemedicine, which has shown great promise in expanding the availability of modern medical technologies to rural areas in Africa. However this method of feedback should be still be supported by a local clinician.

F. Extending feedback of genetic results/findings to families

Genetic findings have implications for family members. Yet involving families in feedback of findings could violate a participant's privacy and confidentiality. It is imperative that the privacy and confidentiality of the person enrolling in the study should be respected. In cases where there is benefit in sharing results with family members, the original participant should grant permission for them to be contacted. As with feedback to individuals, feedback should not be imposed on family members, but should be based on their voluntary consent.

G. Feedback of incidental findings

In the course of their research, H3Africa investigators may encounter incidental findings (also called secondary findings) – clinically relevant genetic information about a research participant or patient that is identified outside the scope of the original research objective or diagnostic test being performed. These could be both anticipated and unanticipated. Where this is the case, it is important for researchers to understand ethical ways of handling these incidental findings.

The current evidence base to support feedback of most incidental genomic findings for African populations is weak. This means that at the moment, there is **no sufficient evidence to support the feed-back of (most) incidental findings in H3Africa research**, although there may be exceptions, in which case further guidance will be required.[c] For example sickle cell anaemia is a common genetic disease in African populations and causes significant morbidity. Where this is common in a population, it should perhaps be raised in the consent process and followed up by skilled practitioners.

This being said, as a result of the increased use of whole genome sequencing (WGS) methods, there is more likelihood of encountering incidental findings. The American College of Medical Genetics and Genomics (ACMG) provides guidelines for feedback of incidental findings. However, as discussed above, clinical validity and relevance would still be a requirement for the target population. For H3Africa, we recommend that the research team apply the same rigorous approach as provided herein for clinically valid and actionable results, but with an additional task of determination of relevance for the target population and should only be applicable for 1 and 2 above. However, due to the potential limited skills of the research team, it would be advisable to refer the participants to their doctor and for the process to follow the standard of care in that setting. It is important to note that as knowledge increases, the listed genes or variants may change.

SUMMARY

When it comes to feedback of findings, the overall approach of the H3Africa Consortium is to proceed with caution. We recommend the following general principles:

- The current approach should be to primarily feedback findings that are pertinent to the original research project. In that case, researchers need to
    - ❖ assess evidence base for potentially pathogenic variants in relation to the population(s) that are being investigated;
    - ❖ assess whether the particular finding likely holds value for the individual;
    - ❖ ensure that patients are appropriately informed of the implications of the findings for their disease or treatment, and referred for follow-up care.

[c]One exception for instance would be finding evidence of SCD in cases where patients have not been diagnosed with SCD. Another would be findings relating to conditions that are also tested for in diagnostic genetic facilities in the country.

- Where these considerations are all fulfilled, then researchers should develop a feedback policy describing which findings they will feedback and when. The policy should be the same for the entire research project and all research sites.
- Where there is no national genetic diagnostic infrastructure, researchers must ensure that the research findings are accurate before reporting back to ensure that participants are referred to appropriate care. Verification could involve obtaining a second sample from the same person, re-running of the genomic test possibly using different methods (e.g. low throughput/single marker genotyping and Sanger sequencing). Where there is a diagnostic genetic laboratory infrastructure, then researchers need to comply with the standards and regulations in that country.
- Information about the policy for feedback of findings for any specific project should be mentioned in consent documents and processes, but this could be in summary form. Where researchers opt to specifically get consent for feedback, then they need to ensure that participants are properly informed about the questions they have been asked, and the implications of their choice.
- In the absence of genetic counsellors, and until professional staff can be trained to meaningfully feedback individual genetic research results, H3Africa considers that the task of feeding back information about individual genetic research results rests with researcher-clinicians involved in the genomic research projects.
- Although head of families and community leaders have an important influence in the decision-power over others in all aspects of their lives in Africa, and family feed back may be appropriate, the process of feeding back results should also have safeguards to ensure that the decision of the individual is met.
- In all cases, any decisions concerning the feedback of findings must be expressly approved by the research ethics board that governs the study, and comply with all local and international regulations that govern such.

Decision Tree

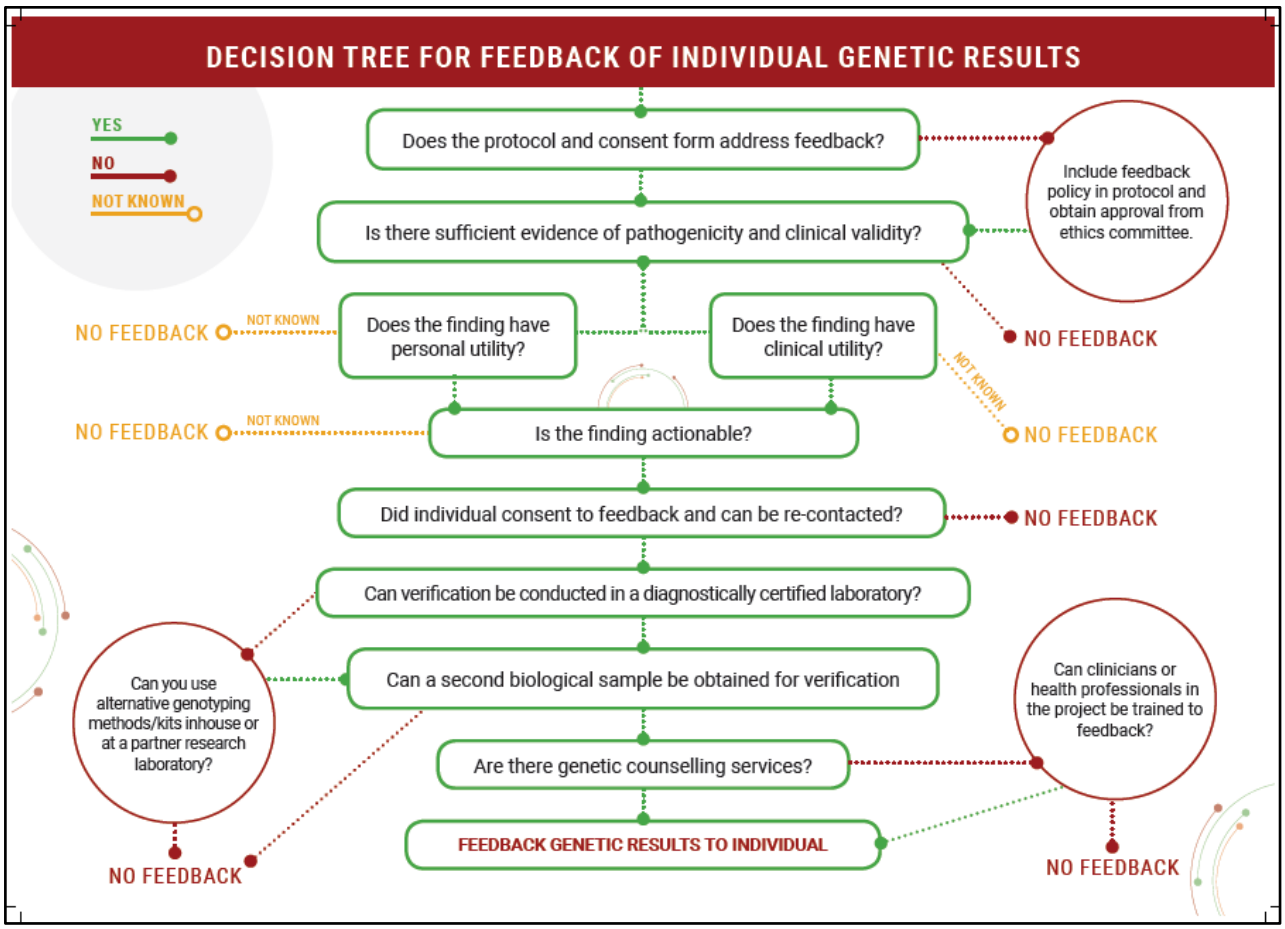

Figure 1. Decision Flowchart for Feedback of Individual Genetic Results

General points to consider for FoFs

- Develop feedback policy for project, include in ICF, obtain IRB approval. Determine feedback on a **case by case** basis for a particular genetic finding.
- Consider specific details for single marker or group of markers or classical clinical genetics setup with monogenic traits vs complex with multiple risk factors.
- Determine the nature and possibility of (i) anticipated findings pertinent to disease or research question(s) and (ii) anticipated incidental findings which have a high probability to be found due to study demographics (e.g. age, sex, disease status).
- For **medical actionability**, consider local specific issues (e.g. availability of medicines, insurance).
- Costs of feeding back, logistics and timeframe for feedback should addressed during proposal stage.
- Determine analytical validity of methods used in confirming the results i.e. accuracy and reliability in detecting genetic variant in individual.
- **Genetic counselling** should be done by a genetic counsellor or suitably qualified healthcare professional.
- Implications of findings on families - the same principles apply in evaluating value, obtaining consent and providing appropriate counselling.

Glossary

Key definitions

The following definitions are important in context of this guideline.

- **Feedback of findings** (FoFs) refers to the process of returning genetic results to individuals enrolled in a genetic/genomic research project.
- **Pathogenicity** refers to the underlying measure of the extent to which the presence of a genetic variant is related to a particular disease or condition.
- **Analytical valididity** refers to the accuracy with which a particular genetic characteristic or marker is identified in a laboratory test.
- **Clinical validity** refers to the accuracy with which a test identifies a patient's clinical status or disease condition.
- **Clinical utility** means that information from a genetic test can be used for informing effective management or prevention of a disease.
- **Personal Utility:** is the case where where receiving information about the variant is important for individuals, for instance because it ends a diagnostic odyssey, gives diagnostic closure, alerts to lifestyle-related risks or is important for reproductive health
- **Medical actionability** based on clinical validity and/or clinical utility and is defined as clinically prescribed interventions specific to the genetic disorder under consideration that are effective for prevention, delay of clinical disease or could lead to improved health outcomes. Examples include patient management (e.g., risk-reducing surgery), surveillance (e.g., colonoscopy), or specific circumstances or substances which the patient should avoid (e.g., certain types of anesthesia).
- **Monogenic disorder** is caused by a variant in a single gene or locus
- **Complex (or multifactorial) diseases** are due to effects from variations in several genes or loci and other factors such as environment and lifestyle
- **Genomic research:** H3Africa projects are applying various analytical methods including candidate gene studies whereby a set of markers or genes are investigated for association with specific disease traits. Whole genome sequencing (WGS), whole exome sequencing (WES) and genome-wide association studies (GWAS) enable interrogation of large genome regions generating large amounts of data. Analysis of these data produce findings which undergo further assessments with the aim of identification of biomarkers which are potentially useful for predicting disease risk, confirming diagnosis or guiding treatment and understanding human biology and disease mechanisms.
- **Pertinent findings**: In a research context findings are considered **pertinent** if generated or sought with the purpose of answering a particular clinical or research question either by genotyping specific areas of the genome or by specifically interrogating those areas if the whole genome has been sequenced.
  Incidental findings are additional findings concerning a patient or research participant that may, or may not, have potential health implications and clinical significance, that are discovered during the course of a research study, but are beyond the aims of the original test or investigation.

  Pathogenicity: Genotyping methods analyse known variants or candidate gene markers and significant association in a cohort is used to confirm disease link, even when the function is unknown. Sequencing has the power to detect both known and novel variants and prediction algorithms may be used to determine pathogenicity. Some of these variants could be predicted to be pathogenic, but have no clinical utility. Web-based tools and software can

be used for interpretation of sequence variants. The collaborative Clinical Genome Resource program (https://www.clinicalgenome.org) funded by the National Human Genome Research Institute, provides well-curated databases and tools useful in the interpretation of clinical relevance of genes and variants. The Clinical Genome Resource Pathogenicity Calculator applies evidence based reasoning to classify pathogenicity of sequence variants (http://calculator.clinicalgenome.org/site/cg-calculator) [13]. These tools apply standards and guidelines from the ACMG-AMP (USA) and the ACGS (UK) [14, 15, 16]. While these are more appropriate for Mendelian traits or for variants with large effects sizes, more rigorous approaches are required for most complex diseases which are highly polygenic and multifactorial, with large numbers of underlying genetic variants which individually have small effect sizes. Genetic risk scores which combine cumulative effect of multiple risk alleles to obtain a genetic risk score.

Determination of pathogenicity and clinical validity in a research context: An example of how to determine pathogenicity and clinical validity from new evidence for complex disorders, Garcia et al, 2016 [17] provide a guide that may be useful, albeit with a focus on cardiomyopathies and arrhythmias. Similar approaches may be followed for a systematic evaluation of the pathogenicity of variants identified in clinically affected individuals, supported by multidisciplinary expert teams in the disease areas particularly for complex diseases.

Annex 1: Action items for the H3Africa Consortium

Action items – validation of clinical importance

- A first necessary step is to generate an evidence base for individual genetic findings for which there currently is a sufficiently strong evidence base to support a decision to feedback in African populations. One essential component of that is to ensure that novel variations and data on variant pathogenicity for disease in African populations are submitted to reference panels that track human genetic variation, such as ENSEMBL, and databases that aggregate information on genomic variation and its relationship to human health, such as NCBI ClinVar, OMIM, GeneReviews, GeneTests. This process could be facilitated by H3ABioNet. A second component relates to building evidence on the clinical relevance of genes and variants in African populations. This could be done in collaboration with existing entities performing this task such as for instance ClinGEN in the United States;
- Another recommendation is to establish an H3Africa 'expert group' that could be consulted by individual investigators trying to decide whether to feedback certain findings or not. The NHGRI is currently in the process of establishing an expert panel to review the evidence base for reportable variants in people of African ancestry and H3Africa should explore possibilities for being involved in that endeavour so that results can be extended to African populations also.

Action item – training genetic counsellors:

- In the medium term, it will be important to develop a training platform to support effective task-shifting. These could be online modules aimed at clinicians in the first instance, and at other healthcare professionals subsequently, and that would cover topics such as how to communicate risk and uncertainty. The course could be developed with the support of the Pan-African Genomic Medicine Training Initiative, perhaps using the infrastructure deployed by the H3ABioNet for their Africa-wide bioinformatics course and other face-to-face training methods.

Action item – research:

- Consent and patient preferences - There is an urgent need to build an evidence base about how information about feedback of findings can best be integrated in the consent process and whether giving people a choice to receive results or not is meaningful and leads to informed choices.
- Understanding other factors which may determine FoFs including stakeholder views and experiences on implementation of FoFs, context, age of participants, socio-economic situation, disease conditions, demographics, funding resources and outcomes of FoFs.

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