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Returning incidental findings in African genomics research

Ambroise Wonkam[1,2], **Jantina de Vries**[1]

[1]Department of Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa

[2]Institute of Infectious Diseases and Molecular Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa

Summary

Ancestral and geographical issues underlie the need to develop Africa-specific guidelines for the return of genomic research results in Africa. In this Commentary, we outline the challenges that will inform policies and practices moving forward.

Keywords

Genomic Research; Incidental findings; Return of genetic results; Africa

Introduction

H3Africa[1] and similar genomic research initiatives in Africa are generating a huge amount of sequencing data, including findings with personal relevance. Internationally, a thriving debate centers around what to do with individual-level results of apparent medical utility and extends to questions about whether, when and how to feedback results.[2] To date, African genomic scientists have not contributed to these discussions and there is currently scarce evidence and no agreement about which results should and could be fed back in African genomics research. This gap is rapidly becoming problematic, as projects are left to develop *ad hoc* approaches to the return of pertinent individual genetic research results, suggesting the need for a consolidated approach to the return of individual genetic research results in African genomics research.

There are two major reasons to have Africans-specific guidelines. The first of these is ancestral. Populations of African ancestry have a history of evolution spanning nearly 300,000 years. This has resulted in many more variants being present in African genomes than in any other population in the world, and this variation has not yet been fully investigated. Indeed, a recent deep-sequenced dataset of a modest sample of 910 individuals

Corresponding author: Ambroise Wonkam, MD, PhD, Division of Human Genetics, Department of Medicine, and Institute of Infectious Disease and Molecular Medicine, Faculty of Health Sciences, University of Cape Town, Anzio Road, Observatory, 7925, Cape Town, South Africa, ambroise.wonkam@uct.ac.za.

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Conflict of interest statement

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of African descent demonstrated that the African pan-genome contains ~10% more DNA (about 300 million missing variants) than the current human reference genome.[3] For monogenic conditions, there is evidence that novel variants in known genes are more likely to be found in populations of African ancestry[4], which poses a specific challenge in establishing variant deleteriousness. In addition, environmental pressure on African genomes has also impacted African genomic diversity and has increased prevalence of some variants. Obvious examples are variants associated with sickle cell disease (SCD), thalassemias and G6PD deficiency, which have become very prevalent in malaria-endemic area in Africa. The Sickle Cell – or, as we prefer, banana cell - mutation appeared in Africa about 7,000 years ago,[5] and today 80% of the 300,000 newborns affected with SCD are born in sub-Saharan Africa.[6] Similarly, under the selective pressure of exposure to trypanosome, which is the parasitic agent of sleeping sickness, protective *APOL1* variants have been selected to reach a particularly high frequency in African populations from West and Central Africa, where this parasite is endemic.[7] Unfortunately, these variants also increase susceptibility to chronic kidney disease in populations of African ancestry.[8–9] A second important reason for the development of Africa-specific guidelines is the socio-economic context of Africa, many areas of which continue to be characterized by relative poverty, under-resourced healthcare systems and an overburdened healthcare workforce, which together greatly affect access to healthcare in Africa and undermine the ability to determine contextually what is actionable, and by whom.

In this paper we discuss three major questions: **1) What results to return?** We outline unique considerations arising out of investigating African genomes and propose a process for the development of an African-specific curated list of reportable genes/variants, needed to inform the development of appropriately contextualized policies. Also, we discuss challenges in evaluating variant deleteriousness in African genomic research; **2) How to determine Actionability?** We describe how definitions of actionability should be considered in African genomics research context, owing to resource constraints and unequal access to care; **(3) Who should return results?** There is a real shortage of trained medical genetics professionals who can assist in validating genomic research results in a diagnostic environment, to assist in interpreting their significance, feeding back the appropriate information in an understandable and non-directive manner, and acting upon individual genetic research results.

What results to return?

Scientists and medical professionals in the US and Europe have made considerable headway in developing expert lists of reportable findings. For example, the American College of Medical Genetics and Genomics (ACMG) in 2013 recommended laboratory obligations to explore a minimal set of actionable genes when genomic sequencing is ordered.[10] However, there is little evidence to support the identification and proportions of pathogenic mutations in genes included in such lists in African populations.

Determining what is reportable in Africans—Early examples of variants that should be considered for inclusion in an Africans-specific priority list are Sickle Cell Disease mutations, because of the high incidence of this disease in sub-Saharan Africa and in

populations of African ancestry.[6] However, some regional nuance exists for sickle mutations within Africa, because in the past 2,000 years population migration from Central to Southern Africa - that is, out of the malaria endemic areas - has gradually reversed the high frequency of sickle cell mutations to nearly zero in South African Bantus.[11] Other mutations that should be considered for inclusion are *APOL1* risk alleles that are associated with trypanosome endemicity, and chronic kidney disease in people with West/Central African ancestry, including African Americans.[7–9] Yet then again, these *APOL1* risk alleles are rare in some populations of Eastern African regions where trypanosome is not endemic, such as Ethiopia.[7] Considering the above, we propose that there is a need for comprehensive review of evidence about variant pathogenicity resulting in the development of priority lists of actionable genes in the African research setting. We propose that the African genetic community, along with international experts, collaborates to generate the following three priority lists: 1) a list of reportable genes and mutations for African populations, for which robust evidence for pathogenicity exists across the continent; 2) a list of reportable mutations for specific regions or populations in Africa, that takes into account the considerable genetic diversity on the continent, and thus restricts itself to those areas or populations for which high prevalence and penetrance of specific genetic variants has been demonstrated; 3) a list of possible reportable genetic variants for which there is some but not sufficient evidence of pathogenicity or actionability but which may become reportable in future. For instance, Human leukocyte antigen (HLA)-B*5701 screening identifies patients at increased risk for abacavir (ABC) hypersensitivity reaction (HSR) in many populations,[12] which is important especially for countries where the HIV infection burden is high.

Determining pathogenicity in Africans' Genomes—There are also several important challenges to determining pathogenicity in African genomes. For one, African populations have been shown to be much more genetically diverse than non-African populations,[13] which may in part explain the current genomic focus on Africa. The data indicate that the current literature also identifies fewer pathogenic variants in people of African descent,[14] most likely because of the underrepresentation of participants of African ancestry in clinical and research reports and exome databases,[15] and the absence of consistent requirements for reporting pathogenic variants in African genomic research.[16] There is a risk that the under-representation of Africans in international databases that aggregate information about genetic variants of clinical significance has led to the misclassification of variants as pathogenic when they are not.[17] Moreover, the identification rate of variants in some monogenic conditions, such as hearing loss, is much lower in Africans from Nigeria and South Africa[18] and in African Americans[19] compared to Caucasian populations, indicating that a greater spectrum of novel disease genes remain to be discovered in African populations. Moreover, some identified pathogenic variants that evolved after humans moved out of Africa are very rare in Africans. For example, mutations in *GJB2* that account for nearly 50% of congenital non-syndromic hearing impairment among Europeans and Asians are nearly non-existent in childhood hearing loss in most populations of Africans Ancestry.[20] In addition, because of the under-representation of Africans in genomic databases,[21] major genetic predisposing and related polygenic risk scores for common complex conditions remain to be fully understood in Africa.[22] Indeed, there are variations that can only be found in populations of African ancestry, some of which could be disease-

related. For example, a recent genome-wide analysis on genetic susceptibility to type 2 diabetes (T2D) in sub-Saharan Africans from Nigeria, Ghana and Kenya, identified a previously-unreported genome-wide significant locus that is specific to African populations (and monomorphic in European and Asians), while the same study showed transferability of 32 established T2D loci.[23] Taken together, the underrepresentation of Africans in international genetic research and variation databases, combined with the greater genetic diversity in African populations, results in some reported variants in genes that are included on the consensus lists may not cause disease in Africans, whilst actual pathogenic variants not yet reported from African populations may not have been considered or included. Also, African genomic studies risk identifying many variants of unknown significance that will likely turn out to be benign. Finally, there may be regional variations in the identification of pathogenic mutations that should be considered for feedback.

Moreover, *in silico* tools heavily base their score on population variant frequencies, i.e. the rarer the variants, the greater the pathogenicity score – a task that is severely complicated by the scarcity of whole genome data representative of populations across the continent.[16] In order to minimize the risk of false positive/negative with *in silico* prediction tools, we propose the need for greater emphasis on the local/regional and ethnically matched control populations for genetic medicine studies in Africa. We also propose that it is important to obtain whole exome sequencing data (rather than genotyping data) for both patients and controls when studying monogenic conditions. Questions about the minimal numbers of controls required should be debated with experts to reach a consensus; it is expected that studies on conditions that are highly genetically heterogenous, such as congenital hearing loss or inherited cardiomyopathies, will require a greater number of ethnically matched controls compared to rare diseases for which the causes can be attributed to a single gene for many populations. A critical question that needs to be considered is how population-specific the data need to be – considering that many African countries contain numerous ethnic groups that are linguistically and culturally (and presumably genetically) diverse. Simulations showed that the inclusion of even small numbers of black Americans in control cohorts probably would have prevented misclassifications of benign variants as disease-causing for cardiomyopathy disease[17], further emphasizing the recommendation of using ancestry-matched controls to interpret variants in African genomic research.

How to determine Actionability in Africa?

The discussion about whether researchers have an obligation to feedback incidental or individual findings is grounded on the premise that some genetic findings have clinical relevance and there is reasonable availability of preventative measures, clinical guidance and therapeutic options. The requirement that findings need to be medically actionable means that some intervention needs to be available that would allow clinicians to act on the genomic finding, whether that be in terms of adjusting drug doses, surgery or lifestyle advice. In the African research context, we anticipate three main considerations. The first relates to returning results in the context of severely overburdened and under-resourced public healthcare systems. At a minimum, the standard for what should be considered actionable should be influenced by what is available in a particular country and not internationally. For instance, whilst preventative mastectomy can counter the effect of

pathogenic *BRCA1/2* mutations, this intervention may not be available to patients in lower- and middle-income countries. And even though certain interventions or therapies should in principle be available according to the national healthcare policy, in practice local African clinics and hospitals may not be able to afford those therapies – in fact, even the most basic drug regimens are often out of stock in rural and urban clinics. For example, in Cameroon we found that few patients have access to penicillin prophylaxis or hydroxyurea, which are the most important drugs for the management of sickle cell disease.[24] This suggests that only examining individual national healthcare policies may not be sufficient to determine actionability. What may also be a consideration is that even where an intervention is actually available, scarce resources should arguably rather be used to treat actual patients, not future possible ones, unless there is clear evidence that averting the development of certain conditions is cost-effective and thus beneficial for the healthcare system as a whole.

The second challenge in determining actionability in the African research context relates to the considerable variability in availability of interventions between participants in a research project, depending on where they are based (urban vs rural locations, for instance) and their ability to draw on transnational family networks to generate resources to act upon findings, possibly by seeking healthcare in the private setting. Actionability is further impacted upon by the large number of health-focussed NGOs operating in Africa that participants could potentially turn to for support. Researchers also have the option of providing clinical testing and counselling within the available resources and ethical approval of the research project. For example, in a rural setting in Cameroon we were investigating the impact of Fragile × syndrome in a large family in a community where the condition was particularly prevalent. Facing unexpected and pressing demands for genetic testing of at-risk individuals, we provided testing for Fragile × syndrome in an accredited laboratory in South Africa to consenting participants and referred carriers to a central Cameroonian hospital for future care. Finally, a third important question relates to whether information about homozygous sickle cell disease (SCD) status should be considered an actionable finding in countries where the burden of this disease is high and where genetic testing is not routinely available. In some of those countries, genetic testing is increasingly being recognized as important in informing marriage decisions. Therefore, actionability should extend to screening, whether this is premarital to guide individual choices, prenatal to guide reproductive option, or neonatal for anticipatory clinical guidance and care, as there is ample evidence that early detection and treatment of SCD reduce childhood mortality and improve patients' survival.

Who should return results?

In most African countries, there are insufficient numbers of healthcare professionals and institutions equipped to return individual research results and an important question is how to build and scale up the expertise of the existing workforce. General assumptions in debates around feedback of findings seem to be that research participants have access to a general physician who could receive study results on their behalf; that genetic counsellors are available to help unravel and interpret findings and to help the participant understand these; that there is an electronic records system on which findings can be marked; and that treating clinicians are available to act upon the finding. In most African countries, only one or none of these conditions may apply. For instance, very few individuals will have a designated

general physician (although many will have access to a primary care clinic where staff rotates). The absence of individual electronic health records complicates the effective recording and tracing of individual genetic predispositions. Furthermore, there is a real shortage of trained medical genetics professionals who can assist in unravelling the significance of genetic results and translating them in a meaningful and understandable way to research participants. For example, in South Africa in 2013, there were reported to be 11 registered medical geneticists, 42 medical genetic scientists and technologists and 10 genetic counsellors servicing a population of 51 million.[25] In other parts of Africa, there are far fewer and in many African countries, 'medical genetics' is not a recognized medical specialization. Other challenges are the overall shortages in health personnel and non-genetic clinician's very limited understanding of the meaning and clinical significance of genetic information. For instance, a study examining clinicians' understanding of medical genetics in Cameroon found that although they were familiar with genetics and some genetic diseases, their knowledge of the availability of molecular diagnostic tests for particular conditions was low.[26]

There are two possible ways to respond to these challenges. One would be to increase the number of medical geneticists and genetic counsellors being trained annually and build such opportunities into genomic research projects. The other would be to explore more innovative ways of ensuring that other healthcare staff, including nurses and community healthcare workers, are equipped to interpret genetic knowledge. This would involve task shifting and task sharing, and introducing concepts of genetics to healthcare staff – not unlike the way in which a study in South Africa trained healthcare workers to conduct cardiac ultrasounds, which are normally only performed by highly trained professionals.[27] The H3Africa Consortium has started offering basic genetic counselling training to nurses across the continent as one solution to the problem.

There is also a need to enhance initiatives that investigate indication of volition – or participants' expressed desire to receive results – although this position is also being challenged.[28] In the African research context, we have mounting evidence that consent processes for genomics are already overburdened and that people struggle to understand what they are being asked to sign up for.[29,30] Whilst people in urban areas may not face the same challenges,[31] and although examples of best practice are emerging,[32] integrating additional and complex information in the consent processes may not be desirable as it may fuel the misbelief that participants have expressed an informed opinion when they have hardly been given the material or time to consider their preferences. How best to go about determining what people would like to know if not in the consent process is not that clear. One suggestion could be to only add a general question about whether participants would like to be contacted if the research uncovers anything important for their health. Another, favoured in the 3rd Edition of the H3Africa Guidelines for Informed Consent (https://h3africa.org/wpcontent/uploads/) would be to simply inform participants that they will be contacted in that case.

Perspectives

Over the next years, we will systematically address some of these challenges through the Individual Findings in Genetics Research in Africa (IFGENERA), an H3Africa Collaborative ELSI Centre. The Center will pool together African and international experts in medical genetics and human genomics 1) to foster the development of priority lists of (potentially) reportable mutations in Africa; 2) to establish agreed approaches to determining variant pathogenicity across the continent; 3) to develop a more contextualized approach to determining actionability across multi-site genomic research studies and 4) to train healthcare professionals equipped to interpret and return genetic findings to individuals. Taken together, there is an urgent need to develop a progressive evidence base to inform the development of appropriate and contextualised return of results policies to guide African genomics research.

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