J Community Genet (2017) 8:311–318
DOI 10.1007/s12687-017-0327-3

ORIGINAL ARTICLE

Increasing the involvement of diverse populations in genomics-based health care—lessons from haemoglobinopathies

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Received: 13 May 2017 / Accepted: 23 August 2017 / Published online: 6 September 2017

Abstract Integrating genomic medicine into health care delivery poses significant challenges to health professionals. To draw clinical benefit from genomic information, there is a need to build an evidence-based relationship between genotype and the physical expression of that genomic information. The work presented here uses preliminary work in the field of haemoglobinopathies to address two important challenges: to ensure that health care professionals in low- and middle-income countries are actively involved in the processes that will support genomic medicine, and that equity and diversity concerns are met so that clinical services can have relevance across all population and sub-population groups. Haemoglobinopathies provide an opportunity for gaining a better understanding of how long-standing genetic knowledge can be leveraged to determine if genomic-based services can be beneficial in low-resource settings. The Global Globin 2020 Challenge (GG2020) is an international initiative that uses haemoglobinopathies as an entry point to achieving growth in the quality and quantity of curated inputs into internationally recognised databases, harmonising the sharing of variant information within and between countries for better health care delivery and ensuring that storing, curation and sharing of variant information become an integral part of health care. Early findings from GG2020 indicate that paying attention to population diversity is an integral part of prevention and control of haemoglobinopathies.

This article is part of the Topical Collection on *Inclusion of Diverse Populations In Genomics Research and Health Services: A Scientific and Health Equity Imperative*.

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Keywords Variant information · Diverse sub-populations · Curation · Haemoglobinopathies

Introduction

The need to integrate advances in genetics and genomics into health systems and health service delivery—often given the name 'Genomic Medicine'—is much discussed. How to do this is in a beneficial manner is occupying the minds of many health professionals. Sadly, the issue of equity of access is not often raised, let alone addressed. The need to ensure that underserved populations can benefit from the advances in genetics and genomics, and that any new approaches in both research and service delivery do not increase the so-called 'genomic divide' that is perceived to exist between countries in different parts of the world, is important.

To draw clinical benefit from any genomic information that it generated by testing, there needs to be a relationship between the specific number of genes that are related to a particular trait and the physical expression of that genomic information. This information needs to be stored and shared using some form of shared annotation if it is to contribute to the prevention and control of disease. Many clinicians and researchers are looking for databases that store genotype and phenotype information that is generated in individual countries that is standardised in some way to form the basis to improved service delivery to patients. In an environment where the costs of many types of genomic testing continues to fall and direct-to-consumer testing is becoming more wide spread, pressure to better manage efforts in this area is growing.

This paper will highlight one initiative currently seeking to focus on gaining a better understanding of the practical steps that need to be taken if patients in low- and middle-income

countries are to have better access to developments in genomics.

The initiative focuses on haemoglobinopathies and is called the Global Globin 2020 Challenge (GG2020). GG2020 is project-wide initiative of the Human Variome Project (HVP)—refer to Box 1 The Human Variome Project (HVP). GG2020 use haemoglobinopathies as an entry point for developing a better knowledge of how best to provide the structural underpinnings of genomic medicine, including the following:

- Oversee data sharing—including developing practical solutions for storage, sharing, retrieving and archiving of the genetic/genomic data produced in diagnostic laboratories for clinical and research access
- Link up genotype-phenotype information generated in countries within these databases so that clinical-grade, properly annotated genomic and phenomic data can be accessed
- Ensuring that these systems and standards allow for every specific variant to be given the same definition, and same medical interpretation and
- Ensuring that this is comprehensive and mirrors the diversity of populations and sub-populations in countries

BOX 1 The Human Variome Project (HVP)

GG2020 Challenge is an initiative of the Human Variome Project (HVP).

HVP is an international, not-for-profit, non-governmental organisation that aims to increase the amount of information about clinically validated and classified genomic variants available in open, curated databases so that all people can benefit from advances in genomic medicine. It does this by means of cooperation at the individual, organisational, national, regional and international levels

HVP focusses on increasing the quality and quantity of genomic data that is collected, curated, interpreted and shared for clinical practice. It does this by supporting the building of capacity in the practice of responsible genomics. To ensure that this contributes to improving global health outcomes, it focusses on increasing both the quality and quantity of genomic knowledge that is collected, curated, interpreted and shared for clinical practice.

HVP acts as an umbrella organisation across multiple countries, institutions and initiatives to establish collaboration around its central vision—the responsible, free and open online publishing of the international consensus on genomic variant pathogenicity.

Unique genetic variants are uncovered every day in diagnostic labs, clinical centres and research institutions around the world. The HVP recognises the importance of sharing high-quality genetic variation data to expedite the diagnosis and treatment of patients with genetic diseases worldwide.

Currently, the HVP Consortium includes over 1200 individual researchers, healthcare professionals, policy makers and organisations from 81 countries that collaborate to develop and maintain the necessary standards, systems and infrastructure to support global-scale genomic knowledge sharing.

HVP uses two main mechanisms to achieve growth in the responsible, free and open online publishing of the international consensus on genomic variant pathogenicity One is to support individual countries to develop their own capacity to generate and contribute their own variant information. The other is to support international groups formed around specific genes or diseases to do the same.

HVP is an NGO with operational status with UNESCO and has an MOU with the World Health Organization (WHO).

Refer: www.humanvariomeproject.org

Why haemoglobinopathies?

Haemoglobinopathies and haemolytic anaemias are genetic diseases leading to deficiencies in the structure and functioning of haemoglobin that can cause in the most severe cases early death but more often lead to ill health and disability. Thalassaemias, sickle cell diseases and glucose-6-phosphate dehydrogenase (G6PD) deficiency are among the key causes of concern. It is beyond the scope of this paper to define the genomic complexities of haemoglobinopathies in various world populations. But it is known that haemoglobinopathies, collectively, are cause for significant morbidity and mortality, especially in parts of the world where health systems are weak. Children are the most severely affected.

Despite much of the genetics and biology of haemoglobinopathies being known for some time, and that this information is being used successfully in some countries to systematically reduce burden of disease, many low- and medium-income countries remain practically untouched by this knowledge and these innovations. GG2020 seeks to apply recent developments in human genomics involving the systematic collection and sharing of variation data to fighting haemoglobinopathies (notably thalassaemias and sickle cell disease) in low- and middle-income countries where the burden of disease and carrier status is the highest. G6PD deficiency is also addressed as proof of principle that additional health services can cheaply be added to a knowledge base and infrastructures established for haemoglobinopathies.

Commitment to systematic variant data collection for the purposes of delivering health care is increasing, but this is occurring mostly in high-income countries where much of the diagnosis and testing takes place. There is a risk that countries where the burden of these diseases is highest—low- and middle-income countries—are being left behind in a form of ‘genomic divide’. Capacity to generate quality data on variants, to store it so that it can be shared internationally, needs to be built in these countries. This genomic capacity will enable the following:

- Building the genetic evidence base for better management of delivery of local treatment, care and eventually even cure
- Forming a foundation for genomic medicine by working with national, regional and local health care professionals

to raise public awareness of the genetic basis of haemoglobinopathies as an important part of their improved management.

According to Modell and Darlison (2008), haemoglobin disorders present a significant health problem in more than two thirds of the 229 countries they investigated. Globally, they suggest, an estimated 7% of pregnant women carry one of the known forms of inherited haemoglobin disorders, and over 1% of couples are at risk. These figures underestimate the overall disease burden, because these disorders affect broader families, not just individuals as a result of carrier status.

The prevalence of haemoglobinopathies is expected to increase in coming years for two main reasons: the conditions remain unmanaged in most parts of the world; and increased migration of people particularly from developing to developed parts of the world will cause greater spread, thus exposing health systems in many more countries. Recent literature attests to the challenges of fully understanding the impact of haemoglobinopathies on global health (Piel 2016), suggesting that the burden is increasing largely as a result of poor management of these conditions. It is also noted that there is an inverse relationship between the absolute carrier frequency in a given country and the availability of knowledge and resources to provide public health care. Despite recent efforts (McGann et al. 2015), much of the data used to model the disease burden in haemoglobinopathies in various parts of the world is based on outmoded and inconsistent methods and sporadic data sources. Without a more comprehensive and systematic approach to measurement, haemoglobinopathies are unlikely to attract the investment necessary to address them effectively.

In 2011, Giardine et al. reported a total of 1941 unique genetic variants in 37 genes being recorded and detailed the benefits of sharing data collected systematically in describing this genetic variation to provide insights into understanding both disease-related and healthy states. Further, a recent study of EU countries (Haemoglobinopathies on the Move: is Europe ready? 2013) found that even in the 12 countries studied in the EU, haemoglobinopathies are underdiagnosed and that health systems are not sufficiently responsive to health care needs necessary for these conditions. Poorly coordinated efforts between countries and lack of relevant infrastructure (including electronic databases) were identified as being major factors contributing to this situation.

To date, the impact of haemoglobinopathies on health outcomes in LMICs has not been a high priority for many in the global health community partly because their burden is not well understood and also because of the mismatch between the location of much of the expertise and resources available to provide care, and the frequency of carriers. GG2020 seeks to address situation by using a systematic methodology to capture the distribution and determinants of these conditions as a contribution to the debate on increasing the investment in their prevention by applying genomic approaches.

GG2020 Challenge goals

Goals of the project are the following:

1. To see growth in the quality and quantity of curated inputs into internationally recognised genetic databases from low- and middle-income countries participating in the project. Tackling haemoglobinopathies is an ideal entry point for these countries to develop the necessary infrastructure and expertise that can expand into other areas of health service delivery
2. To harmonise the sharing of all relevant variant data between countries in accordance with international best practice that integrates all the relevant ethical and regulatory frameworks and policies required to serve and protect patients at the same time that the biotechnical systems and procedures are developed
3. To ensure that the storage, curation and sharing of the relevant DNA variation information is sustainable in the medium and longer term by expanding and strengthening the international network of professionals, including curators, researchers, clinicians, bioinformaticians, counsellors, patient groups and health professionals

Pursuit of these goals will raise the profile of genomic medicine in low- and middle-income countries among health professionals in national, regional and international health organisations. It will also develop the capability of those required for diagnosing, treating and counselling carriers in low- and middle-income countries, thus giving them a greater voice and profile among genomic researchers and clinicians globally, so they can actively participate in regional and international partnerships related to genomic medicine research and innovative health service delivery in low-resource settings.

The problems that GG2020 seeks to tackle include the following:

1. Promoting the use of genomic techniques in national health systems to support more effective diagnosis, treatment and prevention
2. Promoting standardisation both within and between countries to establish common criteria for best practice and to harmonise diagnosis, treatment and prevention
3. Promoting collaboration within and between countries to support a better understanding of the factors underlying these conditions and to guide resource-efficient research into haemoglobinopathies, especially in diverse, multiethnic populations

4. Providing a platform and sustainable infrastructure for effective knowledge sharing between professionals using genomic techniques in all parts of the world

Assessing the current situation in various regions of the world

The early work of GG2020 has focussed on bringing together current knowledge and information concerning various haemoglobinopathies in as many regions of the world as possible. Participation began with national networks of geneticists with an interest in open and transparent variant information sharing that are called HVP Country Nodes—refer Box 2 HVP Country Nodes, who then reached out to colleagues working in haemoglobinopathies in their country. They were asked to review the situation in their country by completing and sharing a self-reporting tool (refer Annexure A GG2020 Country Checklist).

BOX 2 HVP Country Nodes—at a glance

The Human Variome Project (HVP) uses two main mechanisms to achieve growth in the responsible, free and open online publishing of the international consensus on genomic variant pathogenicity. One is to support countries to develop their own capacity to generate and contribute their own variant information: these are called Country Nodes. The other is to support international groups formed around specific genes or diseases to do generate, curate and support interpretation of relevant variant information.

HVP Country Nodes: a definition

Recognising that data collection and sharing is almost always subject to laws, regulations and best practice guidelines operating at national and subnational levels, the HVP Global Collection Architecture proposes that much of the routine data collection will be done through HVP Country Nodes. Country Nodes are a vital component for finally achieving improved health outcomes for people both within the country and around the world.

An HVP Country Node is defined as having three components:

I. A repository, or linked network of databases, that collects and stores information on variation in the human genome that has been generated within each country to enable the sharing of that information both nationally and internationally;

II. A governance structure that ensures that the work of the Node is both sustainable in the long term and is consistent with all relevant national and international standards including ethical, legal and social requirements; and

III. A set of policies and procedures—a data model—that ensures that the repository is operated and maintained in a responsible, accountable and sustainable manner that is consistent with national and international standards, and when and where these are not available, with HVP standards.

1. HVP Country Nodes: what do they do?

The three components above enable HVP Country Nodes to carry out specific roles both within their country and internationally. These include the following:

1. Taking an active role in ensuring that data on variation is easily shared among research institutes, projects, diagnostic laboratories and clinics and determining the conditions under which information can be accessed and by whom;
2. Contributing to building the capacity for storing and sharing data responsibly;
3. Monitoring and reporting on activities that will contribute to better targeting of healthcare planning and policy development; and
4. Sharing data between other HVP Country Nodes and international Gene/Disease Specific Databases in the HVP Consortium.

Exactly, how each HVP Country Node fulfils these roles is determined by each country and is based on their unique mix of needs and capabilities.

HVP Country Nodes should progressively increase their activities by seeking to expand and improve the quality of their data collection activities within the country and their networks with other researchers, clinicians, diagnosticians, counsellors, patient groups, and relevant government officials at the national level and in other countries. Ultimately, the data that is collected, stored and shared should be of a quality appropriate for use in clinical settings.

Because HVP Country Node repositories contain information on patients and subjects, every care must be taken to ensure that the data is collected and stored in a responsible manner. Countries vary in their cultural, religious and ethnic backgrounds; they also have different legislative and regulatory environments. HVP Country Nodes must conduct all their activities openly and transparently, and within all the relevant national requirements.

HVP Country Nodes must have an appropriate form of governance and decision-making capacity to develop the policies and procedures for sustainable activities. Policies determining how data is collected, stored and shared must be developed and implemented. These practices should be reviewed and updated on a regular basis. The quality of the data that is collected, stored and shared must be transparently assessed and reported.

HVP Country Nodes do not operate in isolation. As part of an international consortium, they are active in HVP activities, participating in the development of HVP Standards and Guidelines and sharing their knowledge and experience with other HVP Country Nodes. Continuing membership of the Consortium and recognition as an HVP Country Node is at all times subject to the Human Variome Project Code of Conduct.

Work to date across the global network suggests that there is considerable information available, and many individuals and teams are devoting their efforts to researching and treating individual patients and families, but these efforts are not always well coordinated.

It is also clear that there are ‘two worlds’ in relation to the diagnosis and treatment of these conditions: one that exists in well-resourced health systems in developed countries where the disease burden is relatively small and localised, but growing; and the other, in parts of the world where health systems are under-resourced and these conditions are vastly more common.

Since its establishment in 2014, GG2020 has expanded its members to include a multidisciplinary mix of experts in database curation and in haemoglobinopathies. There are now more than 40 countries actively involved, including more than half from LMICs, with members from each region of the world.

Preliminary results

Preliminary results from the work so far can be grouped into four main areas. These are addressed in turn below.

1. A review of the situation in various parts of the world—we are we now?

   The general picture with regard to the use of genomic techniques for diagnosis and to guide treatment of these conditions is also uneven across GG2020 partners. What emerges is an apparent need to pool knowledge globally, utilise resources synergistically and integrate advanced diagnostic techniques in health systems to allow fact-guided implementation of disease management and prevention programmes. These measures are required to achieve better and more uniform results, especially in the face of the growing numbers of cases likely to occur in coming decades.

   There was also preliminary consensus regarding the following:

- Currently, in most parts of the world, the resources put into research and treatment of these conditions are both insufficient and poorly distributed, leading to inability to manage and control these the conditions effectively, which in turn causes unnecessary suffering of extant patients and a likely increase in the number of new cases, respectively.
- As many national information systems keep poor records on cases and trends in haemoglobinopathies in their population, information used to determine the prevalence of the relevant variants in most national and regional populations is often based on out-dated or unreliable estimates, leading to potentially suboptimal allocation of resources and faulty cost-benefit analyses. Likewise, little information is systematically available for specific communities and ethnic groups in diverse societies. Improving data systems therefore needs to be considered as a key priority action for national health systems.
- A better understanding at bio-molecular level can greatly assist in identifying individuals at risk and in realistic projections for measures and outcomes. Systematic screening programmes therefore may have much to offer for cost-effective prevention, treatment and management of these conditions at the level of the individual as they have at the population level.
- A better coordinated and more efficiently targeted international research agenda for identifying predictive markers would assist both global and national efforts and would directly benefit those affected or at risk (towards genotype-phenotype correlation, genetic counselling and personalised disease management).
- Haemoglobinopathies have severe and well-characterised pathophysiologies, but are an increasing global health challenge given that

  – The single SCD mutation and the numerous thalassaemia mutations produce extreme variability in clinical presentation, which is hard to predict given current knowledge of molecular biomarkers;
  – Through long-running but currently extreme levels of global migration, haemoglobinopathies are posing an increasing health burden on northern and southern, and on affluent and poor societies alike;
  – Haemoglobinopathies need to be understood and managed in almost every national health system, a development that would greatly benefit from a truly global understanding of prevailing mutations, cross-border information interchange and harmonisation of methods.

  Also, as a result of conducting their local situational analysis, country groups were asked to categorise themselves according to one of four possible groups. These groups are defined in Table 1 Country groupings based on prevention and control of haemoglobin disorders below. This informal categorisation was undertaken for several reasons:

1. To serve as a baseline for evaluating progress over time
2. For identifying areas of local priority and determining the potential key stakeholders and collaborators
3. Grouping various country-based groups with similar needs and priorities for knowledge sharing and collaboration

This review of the situation with regard to haemoglobinopathies in various regions of the world confirmed the need for GG2020 to focus on the following priorities:

1. Raise the profile of hereditary haemoglobin disorders on the agenda of Ministries of Health, particularly those in low- and middle-income countries
2. Ensure that advances in human genomics, including simple molecular technologies for disease control, are integrated into new innovative models for primary health care and service delivery
3. Apply these new techniques to strengthen prevention and establish cost-effective service delivery
4. Achieve this through inter-country co-operations and knowledge sharing—south-south and south-north
5. See approaches to addressing haemoglobinopathies as a means of addressing broader issues of integrating genomics into health care

Table 1 Country groupings based on prevention and control of haemoglobin disorders

A	Countries where services are well established with a national system for prevention and control
B	Countries where some elements of a national control programme exist but it is not available to all; more effort is needed in areas like the following:
	i. Improving access to services
	ii. Raising awareness among families and patients, health professionals and community in general
	iii. Establishing national centres of excellence/expertise to provide advice, measure progress
	iv. Ensuring that savings from disease prevention are returned back to expand and improve services
C	Countries where expertise in diagnosis, treatment, management and prevention exist but is not part of a sustainable national control programme
D	Countries where services are limited or not available

With regard to the use of genomic techniques for diagnosis, this was found to be somewhat unevenly applied. With the emphasis on diagnosis being increasingly offered in the context of health service delivery, there is an increasing amount of variant information being produced in many parts of the world. This was creating a steady supply of variant information that could be captured into variant databases and be used more effectively for both research and public health purposes if made available in a more systematic and harmonised way. Creation of national data-sharing facilities for improving clinical testing services and to support public health research, in particular, was affirmed as a high priority for the GG2020 Challenge.

The review also suggested that two different levels of action were potentially simultaneously required to bring about progress. Identification of actions that could only be taken at the local or country level as a result of the key players and their sphere of influence being contained within the framework of national regulations, for example, are different from actions that could be taken at an international or global level. Table 2, below, sets out a preliminary framework for defining the differences between these two spheres of action.

2. Better understanding of the disease burden

A second outcome from the preliminary assessment of the global situation was the confirmation that biomolecular techniques would greatly assist in the process of determining more accurately carrier status both across populations, and within sub-populations. In particular, there was an apparent absence of any extensive data from various minority communities.

Information suggested that, at the local level, prevalence may not be well aligned with global estimates of the burden of haemoglobinopathies. Despite recent efforts (McGann et al. 2015, for example), much of the data used to model the disease burden in haemoglobinopathies in various parts of the world is based on outmoded models and produced via inconsistent methods and sporadic data sources, or that possibly, information held at the local level was not contributing to a broader understanding of the situation. Without a more comprehensive and systematic approach to measurement, haemoglobinopathies are unlikely to attract the investment necessary to address them effectively.

3. Selecting an international database

The question of where to house variant information so that it can easily contribute to knowledge sharing across countries is key. The answer is an important animator of the international collaboration of GG2020. Given the aims of GG2020, the community needed to address the issue of determining an international variant database to host data and information. The third outcome of the preliminary work of GG2020 has been a review of existing databases was conducted using a set of criteria developed for the purpose. These criteria are set out in brief form in Table 3 Criteria for assessing database suitability below.

As a result of reviewing all known existing databases GG2020 is now linked to ITHANET Portal (www.ithanet.eu) hosted and managed by the Cyprus Institute of Neurology and Genetics, through their Molecular Genetics Thalassaemia Department and Cyprus School of Molecular Medicine. This was agreed at the GG2020 meeting held at UNESCO Headquarters in May 2016. One country which stands out as an exemplar of tackling these problems effectively is Cyprus. For the past 30 years, Cyprus has developed a national public health response to managing a carrier population estimated to be about 15%. At the core of this response is the central database of the national screening programme that stores and shares population-wide genetic variant data internationally.

The partnership with ITHANET Portal has been instrumental in advancing the work of GG2020 in two important ways:

1. Members in each country are able to make their own individual relationships at the national level based on their own needs and priorities; each country is able to determine their own strategies and policies to oversee

Table 2 Two levels of action

At national/country level	At international/regional level
Identify who is working in the field—researchers, diagnosticians, clinicians	Identify 'safe havens' for data = recognised curated databases
Identify who is generating data and variant information on haemoglobinopathies—who keeps this data now?	Participate in the development, review and application of internationally agreed nomenclature, data standards, file formats etc
Determine who will use the data for clinical or research purposes	Link with international user groups, collaborators, researchers etc
Create a national network—formal or informal—involving all partners—patient groups, counsellors, public health officials	Review existing data access models to determine suitability
Develop a data model—format of data, who will have access to it, to do what?	Contribute to interpretation of pathogenicity; genotype/phenotype alignment
Ethics, conflict of interest—identify local regulations and requirements—privacy, consent for example	Harmonise with already agreed international frameworks that cover access to data (privacy, consent processes)
Determine level of interest at local and national government level—Ministry of Health/WHO	Contribute to global epidemiological surveys and other knowledge
And ….	And ….

how national data sources are identified, how access to the data will happen both nationally and internationally, determining how compliance with their own regulatory frameworks will be undertaken, and how to harmonise these national concerns with the international database and the requirements for international data sharing.

2. It has been fundamental to the progress of GG2020, for example, it is the basis for the application to ClinGen/ClinVar based in the USA, to become an international Expert Panel for Haemoglobinopathies.

4. Preliminary implications for population diversity and beyond

The work shared here is of a preliminary nature; there is still much to be done. However, these preliminary outcomes do suggest some issues that could be used as the basis for future discussion.

a) One issue that has arisen from this recent work is how to address the need to map variants against the many characteristics required for ensuring the meaning of the information for both research and clinical use. This issue needs further attention and is it not easy to resolve. For reasons of public health utility, research and clinical service delivery, information on ethnicity is very important. In reviewing the nature and type of information that may be collected on individual cases/records, a system for recording ethnic background needs to be developed. It was thought that many countries may already have systems in place for recording this information for other health-related purposes. This will need to be systematically reviewed, country by country, so that knowledge can be shared. Ethnically diverse countries will have a lot to teach us; knowledge about the variants prevalent in

Table 3 Criteria for assessing database suitability

Assessment criteria
1. Comprehensiveness of existing material—that the database itself was both user friendly and of good quality; that it was being used regularly by large numbers of users
2. Current and future funding needs—that the database itself and the team supporting it was sustainable
3. Quality of technical tools used—that the technical tools in current use were able to be used in all parts of the world
4. Availability of graphic tools for presentation and display of information in useable formats
5. Epidemiological data—ability to house and grow this type of data
6. Future developments—that the current practice and management of the database would integrate well into both present and future needs

individual ethnic groups will help streamline diagnostic procedures and make disease prevention and health planning more cost-effective. But it also begs the question of how to do this in a manner that supports international comparisons, while avoiding any stigmatisation.

b) Importance of partnerships being part of an international community where others are doing similar thing knowledge sharing

c) Needs of low-resource settings need to be taken into account when developing the necessary infrastructure and technological assistance to integrate genomic techniques into health care delivery; with increasing cost pressures on health systems in all countries, opportunities to share, collaborate variant information will help prevention efforts.

What is the way ahead?

Much work remains to be done and only preliminary findings are reported here. That said, there is evidence to assist in setting priorities for continued work, and more importantly, for a broader more inclusive discussion of the implications of what has been learned so far.

GG2020 focuses in haemoglobinopathies as an entry point to genomic medicine in low-resource settings and as a proof of concept for the case of international sharing of variant information. While it is early days, it has found enthusiastic communities in parts of the world where these health conditions are commonly found. It has also identified a collaborative network of experts willing to be involved in the various aspects of variant sharing between countries and who are sensitive to meeting the needs of diverse populations.

It cannot be underestimated how better information on variants and their occurrence in the population will also assist in furthering genome-phemone research.

As is often the case with innovations of the type of biomolecular genomic analysis, there is the potential for a growing divide between those who have and those who do not—those with weaker health systems fear falling farther behind as their health systems struggle to add this to their already crowded global health agenda. To date, the impact of haemoglobinopathies on health outcomes in low- and middle-income countries has not been a high priority for many in the global health community partly because their burden is not well understood, and also because of the mis-match between the location of much of the expertise and resources available to provide care, and the frequency of carriers, particularly those in marginalised communities.

If this is going to be addressed, discussions about the integration of genomics into health care delivery need to be broadened:

- to encompass the needs of those countries with weaker health systems
- to acknowledge the challenges faced by those in low-resource settings
- more evidence needs to be sought in order to gain better understanding of barriers and opportunities to this integration of genomic techniques into LMICs.

The discussion of how to establish variant databases needs to include more stake holders, particularly health professionals and health policy makers from low- and middle-income countries, together with researchers, clinicians, patients and their families. With a growing acceptance of the right for all to benefit from advances in science and research, there is a need to think about how international standards and harmonised approaches might be developed in an open and transparent manner. History tells us that these things tend not to happen without some form of deliberate intervention to include diverse groups.

Raising and shaping of issues for open discussion is an important aim of GG2020, and hopefully, this presentation of a work in progress might assist in stimulating some more inclusive action.

Funding This study was not funded by a grant.
The author has received funding from HVP to conduct this work.

Compliance with ethical standards This article does contain any studies with human participants or animals performed by any of the authors.

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