Project Roadmap
2010 - 2012

PD01-2010

making the vision a reality

12 April 2010
Status of this Document

This document has been prepared by the Genomic Disorders Research Centre in its capacity as the Coordinating Office of the Human Variome Project. It has been adopted as an official policy of the Human Variome Project by the International Planning Group.

This document serves multiple purposes. It:

- clarifies the definition of the Human Variome Project;
- outlines an overarching strategic vision for the Human Variome Project;
- documents the new internal structure for the Human Variome Project Consortium; and
- outlines several internal processes for the creation and adoption of Standards, Guidelines and affiliated projects.

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Executive Summary

Worldwide acclaim met the complete sequencing of the human genome; not only because a significant mountain had been climbed but because we now possessed the potential to simplify the analysis of both common and inherited disease. The next frontier is the discovery and documentation of all variations present in human genes so that the results of the Human Genome can be put to practical use treating disease. The Human Variome Project can make this happen. It has the potential to be the single most effective means of eradicating human suffering in the 21st Century.

Vision

The vision of the Human Variome Project is to be a catalyst for reduction in human disease in the 21st century by facilitating the establishment and maintenance of standards, systems and infrastructure for the worldwide collection and sharing of all genetic variations effecting human disease.

The Human Variome Project is an international consortium committed to reducing the burden of genetic disease on the world’s population. We believe that the collection of information on every instance of a genetic variation and its affect on human health is the only way that our vision can be achieved. The sharing of information on genetic variation and its consequences allows existing treatments to be delivered more effectively to patients and new treatments and cures to be developed.

Strategy

To ensure the complete capture of all human genetic variation, the Human Variome Project is focussed on collecting information through two separate, yet complementary, channels: country specific collection and gene/disease specific collection.

Through a network of HVP Country Nodes, created in partnership with Human Genetics Societies in individual countries across the globe, the Human Variome Project is not only ensuring the comprehensive capture of data directly from diagnostic testing laboratories in a manner that is compliant with each country’s existing ethical and legal requirements, but is also creating a vital resource for medical research and healthcare provisioning within each country. HVP Country Nodes are data repositories that are run, managed and funded within each country, so control of the data contained within them maintained at the local level. Yet through a system of data sharing agreements negotiated within the Human Variome Project context, core elements of those data are shared with other repositories, ensuring open and equitable access to potentially life-saving information.

The second channel of data collection the Human Variome Project is supporting is via the many existing gene/disease specific databases. These databases gather and, most importantly, expertly review data from numerous sources, including the published scientific literature, diagnostic and research
laboratories and also via direct submission by interested members of the scientific community. Gene/disease specific database provide an invaluable step in the data lifecycle, providing expert review and curation of data.

The Journey from Here

The needs of the Human Variome Project, in terms of structure and governance are evolving and the existing committee structure is reaching the end of its useful life. To meet the challenges of the next few years, and to enable the Human Variome Project to achieve its lofty goals, a new internal structure is required.

The Human Variome Project will become an incorporated entity with an international Board of Directors that is charged with setting the strategic direction of the Project and ensuring that it remains in a position to reach its full potential. An international Scientific Advisory Committee will be formed, ensuring that the views and expertise of the scientific community are represented. This Scientific Advisory Committee will in turn be advised by two Advisory Councils, each representing one of the two areas of focus of the Human Variome Projects: country specific collection and gene/disease specific collection.

Human Variome Project International Limited, an Australian public company limited by guarantee (a not-for-profit company with no shareholders) will be incorporated immediately prior to the 3rd Human Variome Project Meeting in May, 2010. This company will be managed by an interim Board of Directors appointed at the time of incorporation. At the 3rd Human Variome Project Meeting, an interim Scientific Advisory Committee will be elected to effect the implementation of the Human Variome Project Consortium’s internal structure and activity process.

In parallel to these efforts, the work of the Human Variome Project will continue unabated. The Coordinating Office and the HVP Working Groups will continue to facilitate the creation of HVP Country Nodes and gene/disease databases, as well as develop and expand existing databases. Data sharing plans between gene/disease specific databases and the central data repositories will continue to be developed.

By the end of 2012, the Human Variome Project will have facilitated the establishment of country-specific collection systems in five countries around the world and will have shared information on 100,000 individual cases of inherited disease. By the end of 2015, the number of countries will have risen to twenty, with information on over a million cases of genetic disease shared.
The Human Variome Project

What is the Human Variome Project?

The Human Variome Project is the natural successor to the Human Genome Project.

The Human Genome Project provided the world with the complete genetic sequence of an average individual through a co-ordinated global effort involving thousands of researchers and billions of dollars over a period of almost 15 years.

For over a decade, the complete sequence of the human genome has been freely available to every biomedical researcher with access to the internet. For over a decade, the complete sequence of the human genome has been analysed, scrutinised and tested. And for over a decade, we have been told that it is the sequence of the human genome that will provide the answers to curing all genetic illness.

However, the Human Genome Project has only provided us with some of the answers. While we may know the complete sequence of a handful of individuals, the myriad of small and large differences between individuals have not been reliably described, and with many severe and debilitating diseases, including some cancers, caused by a single change to an individual’s sequence, we are a long way from providing useful benefits for real people using the data from the Human Genome Project alone.

The Human Variome Project is an international consortium of scientists, doctors, informaticists and diagnostic laboratory specialists working towards the complete capture and sharing of information on all genetic variation effecting human disease. Access to this information will mean a faster diagnosis and more accurate prognosis for patients with inherited diseases by making the interpretation of variations discovered in the clinic easier, as well as providing a platform for basic medical research and the delivery of “personalised medicine.”

The Human Variome Project is working closely with all members of the genetic variation community, including established central databases, gene and disease specific databases, and the publishers of scientific journals to facilitate the establishment and maintenance of standards, systems and infrastructure that will ensure the transmission of genetic variation data from the source through to ultimate deposition in existing and new central databases. The work of the Human Variome Project is initially focussed on inherited variations that directly cause disease.

Why the Human Variome Project is important

Changes in our genes, both small and large, are a fact of life. They drive evolution, constantly introducing phenotypic variability into the population, ensuring that we, as a species, can adapt to changing environments. However, this same process can also cause disease and illness; in the most
obvious instances, and the most devastating, these diseases are diseases of childhood: cystic fibrosis, muscular dystrophy, Tay-Sachs disease, to name a few.

The statistics are overwhelming: 60% of all humans will be affected by a mutation in their lifetime\(^1\); 71% of admissions to a major US paediatric hospital have an underlying genetic basis\(^2\); 50% at the Royal Children’s’ Hospital in Melbourne. This, together with the fact that the incidence of diagnosis of genetic disorders at birth is 1% per annum, is clear evidence that genetic disease is a major health problem.

In the past decade, we have made great strides in improving the technical side of managing genetic health. Where once it took a global consortium of thousands, close to fifteen years, and several billion dollars to sequence the human genome, that same work can now be completed on the lab benchtop in a few days for a fraction of the cost. Diagnostic tests now exist for many genetic disorders, many targeting specific mutations in the genes responsible. In an increasing number of cases, mutation specific therapies are being developed to manage and treat the symptoms of some genetic conditions, for example: cystic fibrosis\(^3\). But technical advancement only supports one side of this complex problem and unfortunately the other side, the basic information side, is lagging disastrously behind.

**A real life problem**

_The Australian population is multicultural with more residents born outside than inside the country. Ethnic groups are diverse, and countries of origin even more diverse. Frequently, in our familial cancer clinic, we are faced with branches of families where the informative genetic information is located overseas. Australian data is patently inadequate to manage these families, as key genetic information resides in repositories and registers overseas, or has not yet been brought to the attention of genetic services in the country of origin. If there has been work done on a variant found in such families overseas, it remains largely invisible, and inaccessible to us and other emigrant countries._

— Professor Finlay Macrae  
Head of Colorectal Medicine and Genetics  
Royal Melbourne Hospital

Unfortunately this story is far too common. Not enough information on genetic variations and their effects is making its way out of labs and clinics and being shared, within countries and internationally. Too often there is no available information, or even worse, incorrect information, because there is no system in place to collect all of this vital knowledge and make it accessible to the world.

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\(^3\) Kerem, E. (2006). Mutation specific therapy in CF. Paediatric Respiratory Reviews, 7:S166–S169
Vision for the Human Variome Project

Our Vision is to be one of the world’s most significant catalysts for the reduction in human disease in the 21st century by:

- facilitating the establishment and maintenance of standards;
- systems; and
- infrastructure

for the worldwide collection and sharing of all genetic variations effecting human disease.

The Human Variome Project Consortium envisions a world where the availability of and access to genetic variation information is not an impediment to diagnosis and treatment; where the burden of genetic disease on the human population is significantly decreased; and where the sharing of genetic variation information is standard clinical practice.

The Consortium also envisions a future where thousands of individuals and groups across the world are working together to ensure universal access to all genetic variations effecting human disease.

If that envisioned future was today – that is, if all the current global data on genetic variations effecting human disease was able to be collected and shared immediately, then many, many millions of the world’s people and their families would benefit from the faster diagnosis and the more accurate prognosis of their disease and the better treatments this information can be used to create.

That envisioned future is not today, but by working together towards this Vision, it can become a reality much sooner than we think.

Our Core Purpose

Our Core Purpose is to alleviate needless human suffering for many millions of the world’s people by collecting, organising and sharing data on genetic variation.

If diagnosis is much slower than otherwise possible and worse still, if prognosis is inaccurate, then millions of people will suffer needlessly. They will not only suffer from the physical effects of disease, but they and their families will also suffer from the significant psychological, emotional and economic effects.

The Human Variome Project Consortium is motivated by the knowledge that by working together, we will be able to significantly reduce such needless physical, psychological, emotional and economic suffering for millions of people.
Our Core Values

The following Core Values will guide and direct all our actions and behaviours and be embedded in our systems and processes, the way we make decisions and the way we deal with each other, be they Consortium members, other stakeholders and the global community. Our Core Values are as follows:

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<tr>
<th>Collaboration</th>
<th>we recognise that success will come by acting together with the widest possible stakeholder group. We will work hard to understand, respect and take account of the differing needs of each.</th>
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<td>Celebration</td>
<td>we will give credit and acknowledge all contributions made, celebrate key milestones, including all diseases that are diagnosed, treated and prevented, as a result of the sharing of data.</td>
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<tr>
<td>Respect</td>
<td>we will work hard to understand and respect the varying needs of all stakeholders. We will have the utmost respect for the privacy and confidentiality of patient information and will be serious about relevant ethical, legal, political and social issues.</td>
</tr>
<tr>
<td>Inclusion</td>
<td>we will include all countries, all peoples and all disciplines without discrimination.</td>
</tr>
<tr>
<td>Service</td>
<td>we exist to serve each other, the Consortium as a whole, its members, the community and in particular, to serve those now and in the future with a disease that can be more easily diagnosed, treated and prevented as a result of the sharing of data.</td>
</tr>
<tr>
<td>Professionalism</td>
<td>we will adopt the highest standards in all we do. Data accuracy and operational excellence will be paramount.</td>
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The Vision and the Core Purpose of the Human Variome Project will only be fully achieved if we remain true to our Core Values. This will require collaboration on an unprecedented scale, the utmost respect for all stakeholders and all our collective actions being undertaken in a true spirit of service. We will also continue to be motivated by our Vision and Core Purpose.
**Our Mantra/Tagline**

Our Mantra and our Tagline for our logo will simply be *sharing data • reducing disease.*

Our Mantra will inform our numerous stakeholders why we exist and continue to reinforce our primary focus in a simple way.

Put simply, our aim is the sharing of data which will result in reducing disease.

**Our Golden Goal**

Our Golden Goal is to have facilitated the sharing of data on over 1,000,000 cases of genetic disease by December, 2015.

We will seek to add urgency to our efforts by setting aspirational goals three to five years in the future. We will stretch ourselves and our stakeholders to come up with new plans and ways of sharing more data and therefore reducing more disease.

**The Project & the Consortium**

In 2006, at the inaugural Human Variome Project Meeting, the delegates, representing a wide gamut of researchers, clinicians and laboratory specialists working with inherited disease, initiated the Human Variome Project to ensure that one day there would be universal access to all human genetic variation data. The work that has been done, is being done, and the vast amount of work that lies ahead, is the work of many individuals across the globe. It is this work that makes up the Human Variome Project.

The individuals performing the work, as well as relevant academic institutions, government agencies, not-for-profit companies, corporations and funding bodies comprise the membership of the Human Variome Project Consortium. These two terms—Project and Consortium—are often used interchangeably, to refer to both the work, and the people. However it should be understood that when, in this document, references are made to concepts such as internal structures, strategic objectives and published standards, guidelines and recommendations, these references are made in the context of the Human Variome Project Consortium.
One Project-Two Channels-Multiple Locations

The central task of the Human Variome Project Consortium is to establish and maintain standards, systems and infrastructure for the collection and sharing of data on all genetic variations effecting human disease. The Human Variome Project Consortium envisions a world where a newly discovered genetic variant in a patient in Australia will lead to the diagnosis, prognosis, treatment and cure of patients in Germany, Peru and Tonga, and vice-versa. Achieving this vision will require an unprecedented scale of cooperation among the healthcare systems of the world’s countries, but the benefits, in concrete terms of decreased morbidity and mortality, increased diagnosis and treatment rates, lower costs of healthcare delivery, higher quality of life, make the effort required seem trivial.

The global nature of the Human Variome Project, combined with the sensitive nature of genetic information, presents a unique set of challenges for our goal of universal collection. A centrally mandated, “one-size-fits-all” approach is unfeasible, as it would be subject to the ethical and legal requirements of all participating nations, as well as needing to be sensitive to various cultural differences relating to genetic health. For this reason, the Human Variome Project has developed its One Project—Two Channels—Multiple Locations strategy: a strategy designed to ensure complete collection of all genetic variation data and its accurate and timely expert curation.

Country Specific Collection

The diverse legal and ethical landscape of the world’s nations makes the sharing of information on genetic variation between countries a difficult undertaking. Even within countries, different legal structures can be imposed at the state, provincial and local government levels. It is the considered opinion of the Human Variome Project Consortium that the best people to navigate these legal and ethical questions and facilitate the collection of genetic variation within individual countries are the members of the Project already resident within those countries.

Working closely with human genetics societies within individual countries, the Human Variome Project Consortium is building a network of national genetic information repositories. These repositories, or HVP Country Nodes, are built, managed and resourced by individual countries to meet the requirements of those individual countries. The Human Variome Project Consortium facilitates their
construction and operation via the creation of standards and systems, examples of which include: nomenclature standards, data visualisation tools and database software.

The HVP Australian Node is already well underway. Operated by the Genomic Disorders Research Centre, in collaboration with the Victorian Partnership for Advanced Computing, BioGrid Australia and the Victorian e-Research Strategic Initiative, the HVP Australian Node is a national repository of genetic test results and corresponding clinical information, as reported by pathology labs conducting genetic testing within Australia. By sharing data among themselves, Australian pathology labs will draw on the collective experience of the country’s experts when making determinations on the significance of variants.

The HVP Country Node model provides a level of flexibility and modularisation that would not be available in a centrally mandated system. As each individual country is responsible for the funding, collection and storage of the data generated by their own country, they can ensure that it is handled according to their own nation’s laws and in an ethical and culturally sensitive manner. Benefits local to those nations hosting HVP Country Nodes include an increase in the consistency of the interpretation of genetic variations and the provision of a rich dataset to aid in national health policy planning.

Internationally, the real benefit becomes apparent when considering how to transfer these data to a global gene or disease specific repository (LSDB). Such data transfers, without the intervening step of a locally managed, country specific repository, would necessitate each separate data generating institution within each and every country forming a collaborative agreement with each LSDB. Utilising the HVP Country Node model, the LSDBs need only collaborate with the individual nodes, and each node is able to determine for itself, if, when and how much data it releases to the global LSDB community.

**Gene/Disease Specific Collection**

The HVP Country Node model is designed to provide a mechanism for the bulk transfer of large amounts of data from the data generators to the HVP Country Nodes. The Human Variome Project aims to develop a network of such nodes to become the primary source of genetic variation information for gene or disease specific databases (LSDBs).

However, the Human Variome Project recognises that this network of country specific nodes alone will not provide complete capture of the world’s genetic variation information. Other sources of data include: the published scientific literature, collaborations between LSDB curators and individual researchers and clinicians, and diagnostic and pathology labs in countries that are yet to develop an
HVP Country Node. The Human Variome Project Consortium is actively supporting LSDB curators in facilitating collection from these sources in a timely, accurate and ethically responsible manner.

In addition to ensuring complete capture of genetic variation data, the gene and disease specific databases provide another important function. It is the firm belief of the Human Variome Project Consortium that curation of genetic data by experts in specific genes is the best way to ensure the accuracy and quality of that data. Gene and disease specific databases currently provide this function, and the Human Variome Project is dedicated to developing systems and standards to help LSDB curators improve their databases and curatorial practices. Where necessary, the Human Variome Project Consortium is facilitating the creation of new LSDBs and disease specific consortia, to ensure the entire human genome is covered.

**Ultimate Deposition of Data**

The deposition of all genetic variation data in central databases such as Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim/), the Human Gene Mutation Database (http://www.hgmd.cf.ac.uk/), the UCSC Genome Browser (http://genome.ucsc.edu/), and those at the National Centre for Biotechnology Information (http://www.ncbi.nlm.nih.gov/) and the European Bioinformatics Institute (http://www.ebi.ac.uk/) is the ultimate goal of the Human Variome Project. By ensuring that data first undergoes a period of expert curation in an LSDB will improve the quality and accuracy of these important resources.

This integrated system of collection will give clinicians, researchers and therapists access to all examples of all variations in every country. We believe the Human Variome Project can be “dovetailed” into any existing facility wishing to collect, store or use the data, above and beyond those mentioned above. Already data from several LSDBs have been loaded on to NCBI databases and the UCSC Genome Browser. It is a goal of the Human Variome Project Consortium to provide this data free of charge to any repository wishing to host it. Plans are currently being developed to address the issues surrounding the costs of curation.
Consortium Membership

The Human Variome Project is an international consortium of scientists, doctors, informaticists and diagnostic laboratory specialists working towards the complete capture and sharing of information on all genetic variation affecting human disease. Our members come from across the globe, from a range of disciplines and backgrounds. Our members are individuals, institutions, corporations and funding bodies, who share the vision of alleviating human suffering through the open sharing of genetic variation data.

Individual Members

Individuals are contributing to the Human Variome Project in two ways: as members of the wider community of interested parties, or as active members of the Human Variome Project.

Wider Community

The number of individuals that are working towards the vision of the Human Variome Project is extensive, and not all of them will, through choice or circumstance, be active participants in the Human Variome Project Consortium. Despite this, the Human Variome Project Consortium is committed to supporting their work to ensure the complete collection of all genetic variation information.

Consortium Members

Consortium Members are those individuals in the wider community who register their details formally with the Human Variome Project Consortium via the Human Variome Project website (http://www.humanvariomeproject.org/). In addition to actively working towards the vision of the Human Variome Project, Consortium Members periodically:

- attend the Human Variome Project biennial meeting;
- attend HVP Fora;
- participate in HVP Working Groups;
- participate in HVP Country Nodes or Gene/Disease Specific Databases; or
- serve on the Human Variome Project Scientific Advisory Committee or either of the Advisory Councils.

Institutional Members

Academic, government and non-profit institutions whose work and values align with those of the Human Variome Project can elect to become Institutional Members of the Human Variome Project Consortium. Institutional Members are recognised as official partners in the fight against genetic disease. In addition, relevant projects of Institutional Members can apply to be recognised as Affiliated
Initiatives of the Human Variome Project, under the procedures outlined on page 28, Affiliated Initiatives.

**Corporate Members**

Companies in the for-profit sector, who share similar values to those of our Institutional Members can elect to become Corporate Members of the Human Variome Project Consortium. Likewise, relevant projects of Corporate Members can also apply to be recognised as a Human Variome Project Affiliated Initiative.

**Funding Partners**

National and International funding bodies and agencies that financially support the core activities of the Human Variome Project are recognised as Funding Partners.

**Countries & Databases**

Countries and databases wishing to be associated with the Human Variome Project can do so under the processes outlined on page 28, Partner Initiatives.
Consortium Structure

Current Structure

Currently, the activities of the Human Variome Project are coordinated in a loose and *ad-hoc* manner by the Genomic Disorders Research Centre, which was appointed the Human Variome Project Coordinating Office at the inaugural Human Variome Project Meeting in 2006. The Genomic Disorders Research Centre is advised by the Human Variome Project Planning Group, a collection of influential scientists and clinicians put in place to oversee the initiation of the Human Variome Project. Changes to policy and strategic direction are proposed by the Coordinating Office and approved by the Planning Group.

The actual work of the Human Variome Project is carried out by 12 general Working Groups, covering:

- Data Collection From Clinics;
- Data Collection From Labs;
- Overall Data Integration And Access;
- Databases, Data Transfer And Curation;
- Country Specific Collection;
- Funding And Sustainability;
- Nomenclature And Standards;
- Ethics;
- Education;
- Publication, Credit And Incentives;
- Translation to Healthcare; and
- Pathogenicity.

The Need for a New Structure

While the current *ad-hoc* structure of the Human Variome Project has served the Project well during the initiating and planning phases, the time has come for a more representative, formal structure. As the Project moves in to the implementation and integration phase, mechanisms for the proposal, development and adoption of standards, systems and infrastructure are required, and the internal structure of the Consortium needs to suit these mechanisms.

The ultimate structure of the Human Variome Project is outlined below. The shift to this new structure will not be immediate: a period of transition will be overseen by an interim Board of Directors and Scientific Advisory Council. The timetable for the transition period is laid out on page 31, Moving Towards the Vision.
In the proposed ultimate structure, the existing role of the Coordinating Office is maintained, although its scope and activities are explicitly described and some degree of its autonomy is curtailed. The Planning Group concept is evolved to that of a Scientific Advisory Committee, while two new Advisory Councils are created to manage the two separate areas of collection outlined in the One Project–Two Channels–Multiple Locations strategy. Most importantly, the concept of the HVP Working Groups is re-examined, with the outcome being the Advisory Councils should have the power to charter specific Working Groups to address specific problems, rather than relying on a fixed number of general groups.

Additionally, to secure the long term viability of the Human Variome Project, a legally constituted entity will be created to oversee the governance aspects of the Human Variome Project. Human Variome Project International Limited will be an Australian public company limited by guarantee, a company with no shareholders, tax-free status, and a Board of Directors with an independent Chair.
Proposed Structure

In line with the One Project–Two Channels–Multiple Locations strategy, the scientific activities of the Human Variome Project are balanced between two areas of expertise: country specific collection and gene/disease specific collection. This strategy allows a level of redundancy in the collection of genetic variation data, ensuring complete coverage. The activities of each of these areas are overseen by an Advisory Council, whose membership is made up of a representative nominated by each participating country or gene/disease LSDB. The Coordinating Office facilitates, manages and coordinated communication between these Advisory Councils and the Board of Directors and its Scientific Advisory Council. The actual work of the Project, in terms of formulating recommendations, developing software and systems, and creating educational materials, is performed by one or more HVP Working Groups, formed from time to time for a specific purpose under the auspices of one or both Advisory Councils. The governance and business aspects of the Human Variome Project are overseen by the Board of Directors of Human Variome Project International Limited, a not-for-profit public company limited by guarantee registered in Australia.

![Diagram of Proposed Structure]

Figure 4: Human Variome Project Structure

Board of Directors

The Board of Directors of Human Variome Project International Limited is responsible for the governance, policy development, strategic planning and financial sustainability of the Human Variome Project. The Board consists of six directors and an independent Chair, each serving a three year term, with two seats being vacated each year. The membership of the Board of Directors is open to prominent
members of the scientific community, major funders of the Human Variome Project and appropriate interested persons. Three members of the Board are appointed by the Scientific Advisory Committee from amongst their members, and three are elected by the members of the Human Variome Project International Limited (as distinct from the members of the Human Variome Project Consortium). The Chair is appointed by the Board of Directors.

**Scientific Advisory Committee**

The Board of Directors is advised by the Scientific Advisory Committee in matters of strategic scientific direction for current and future projects. The Scientific Advisory Committee has the delegated authority of the Board of Directors on the publication of all HVP Standards and Guidelines, and the arbitration of any dispute resolution processes in the generation of HVP Standards and Guidelines.

The Scientific Advisory Committee consists of twelve members including one Chair. The Scientific Advisory Committee members are elected by the two Advisory Councils every two years, with half the positions on the Committee becoming vacant every two years. The Chair of the Scientific Advisory Committee is appointed by the Coordinating Office from among the members of the Scientific Advisory Committee. Membership of the board, in an *ex-officio* capacity, is also extended to:

- the Scientific Director of the Human Variome Project Coordinating Office;
- the President of the Human Genome Variation Society;
- the President of the International Federation of Human Genetics Societies; and
- a representative from the central genetic databases, chosen from amongst themselves.

Any Individual Member of the Human Variome Project Consortium is eligible to stand for election to the Scientific Advisory Committee. Candidates must be nominated and seconded by a member of either of the Advisory Councils.

The Scientific Advisory Committee meets on a face–to–face basis once per year, usually in conjunction with the HVP Fora series. The Scientific Advisory Committee also regularly meets via telephone/video–conference.

**Coordinating Office**

The Coordinating Office manages the day–to–day operations of the Human Variome Project.

The Coordinating Office is responsible for:

- facilitating, managing and coordinating communication between the various HVP Working Groups, the Advisory Councils and Scientific Advisory Committee;
- tracking the progress of the Human Variome Project;
• facilitating the elections of the Scientific Advisory Committee and Councils;
• disseminating standards and guidelines developed by the HVP Working Groups;
• providing administrative support to the Board of Directors;
• providing administrative support to the Scientific Advisory Committee and Councils;
• assisting the Working Groups to achieve their goals;
• educating the field on resources (tools, websites, data bases, funding sources) available;
• communicating progress to both the scientific and lay communities;
• organising the Human Variome Project biennial meetings and Fora series; and
• educating the public on the importance of understanding genetic variation.

Advisory Councils

The Advisory Councils of the Human Variome Project are directly responsible for overseeing and directing the work of the various HVP Working Groups that are formed from time to time under the auspices of either or both Advisory Councils.

The Advisory Councils, with the assistance of the Coordinating Office, also manage the Human Variome Project’s Activity Process (see page 27). Specifically, the Advisory Councils solicit proposals for new Activity Areas from the Human Variome Project Consortium membership, charter HVP Working Groups to perform work in those Action Areas, which will usually include drafting new, or modifying existing HVP Standards and Guidelines, and finally recommend the release for publication and implementation of the outcomes of those Action Areas by the Scientific Advisory Committee.

International Confederation of Countries Advisory Council

The International Confederation of Countries Advisory Council is composed of one representative from each of the HVP Country Nodes. Representatives are appointed by their respective Nodes; the Chair is elected by the membership of the Human Variome Project Consortium present at the HVP biennial meetings.

Gene/Disease Specific Database Advisory Council

The Gene/Disease Specific Database Advisory Council is composed of a representative from each gene/disease specific database recognised by the Human Variome Project. Representatives are appointed by the management of their respective databases; the Chair is elected by the membership of the Human Variome Project Consortium present at the HVP biennial meetings.
Activity Process

The Human Variome Project Consortium both supports and directs the work of its individual members by developing and publishing standards and guidelines for the collection and sharing of genetic variation data. These standards and guidelines are produced by HVP Working Groups in a deliberative and consultative fashion, following the Human Variome Project’s Activity Process.

Standards and Guidelines

The Human Variome Project produces two categories of recommendations: HVP Standards and HVP Guidelines. HVP Standards are those systems, procedures and technologies that the Human Variome Project Consortium has determined should be used by the community. These carry more weight than the less prescriptive HVP Guidelines, which cover those systems, procedures and technologies that the Human Variome Project Consortium has determined would be beneficial for the community to adopt.

HVP Standards and Guidelines are central to supporting the work of the Human Variome Project Consortium and cover a wide range of fields and disciplines, from ethics to nomenclature, data transfer protocols to collection protocols from clinics. They can be thought of as both technical manuals and scientific documents, and while the impact of HVP Standards and Guidelines differ, they are both generated in a similar fashion.

Process

1. A member of the Human Variome Project Consortium submits an Activity Proposal to the relevant Advisory Council via the Coordinating Office. This proposal should outline:
   a. the need the proposed activity is attempting to address;
   b. the scope of the proposed activity;
   c. short and long term objectives;
   d. a plan of action for addressing the activity;
   e. any resources required;
   f. the expected deliverables of the project; and
   g. the Working Group the activity would fall under, if one exists.
2. The Advisory Council invites the Coordinating Office to comment on the Activity Proposal, with a particular view to identifying potential collaborators and the capacity of the Human Variome Project to help secure the required resources.
3. The Advisory Council determines whether or not to accept the proposal.
4. Once accepted, the Advisory Council either:
   a. charters a new HVP Working Group to oversee the Activity; or
   b. modifies the charter of an existing HVP Working Group.
5. The HVP Working Group produces a working draft of an HVP Standard or Guideline.
6. The Advisory Council calls for comments on the working draft from the community.
   a. Steps 4 and 5 continue in an iterative fashion until the HVP Working Group submits the
      working draft as a Draft HVP Standard or Guideline to the appropriate Advisory Council.
7. The Advisory Council recommends the Draft HVP Standard or Guideline to the Scientific
   Advisory Committee for publication, or refers it back to the Working Group for further work.
8. The Scientific Advisory Committee signs off on the Draft HVP Standard or Guideline and
   publishes it via the Human Project Variome website.

**Systems and Infrastructure**

The capacity exists for the Human Variome Project Consortium to recommend the use of specific
systems and infrastructure without publishing such a recommendation as an HVP Standard or
Guideline. The developers of such systems can apply to the appropriate Advisory Council through the
Coordinating Office for a Warrant of Recommendation, and upon the completion of a review by the
Advisory Council, the Scientific Advisory Committee shall decide if such a warrant is to be issued.

The Scientific Advisory Committee is the arbiter of the conditions that systems must meet in order to
qualify for a Warrant of Recommendation. However, in broad terms, systems must be:

- free to the academic community;
- comply with all HVP Standards and Guidelines;
- be open-source where applicable; and
- be compatible with similar systems already recommended by the Human Variome Project
  Consortium.

**Affiliated Initiatives**

The Scientific Advisory Committee, acting upon the recommendation of one or both of the Advisory
Councils, may decide to issue a Warrant of Affiliation to specific relevant projects. Projects may be
offered affiliated status in recognition of their impact and relevance to the overall vision and objectives
of the Human Variome Project. Affiliated Projects receive no special treatment or favour from the
Consortium above the publishing of their status on the Human Variome Project website.

**Partner Initiatives**

Country consortiums that have successfully applied to become an HVP Country Node and gene/disease
specific databases recognised by the Human Variome Project shall be issued a Warrant of Partnership
by the Scientific Advisory Committee.
Consortium Policies

The Coordinating Office of the Human Variome Project shall from time to time prepare documents outlining the policies and procedures of the Human Variome Project Consortium. These documents will be prepared with the advice and consent of the Scientific Advisory Committee and Councils. Upon formal adoption by the Scientific Advisory Committee, they shall become official policy of the Human Variome Project.

Table 1: Types of document produced and published by the Human Variome Project Consortium

<table>
<thead>
<tr>
<th>Document Types</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>HVP Standard</td>
<td>ST</td>
</tr>
<tr>
<td>HVP Guideline</td>
<td>GL</td>
</tr>
<tr>
<td>Warrant of Recommendation</td>
<td>WR</td>
</tr>
<tr>
<td>Warrant of Affiliation</td>
<td>WA</td>
</tr>
<tr>
<td>Warrant of Partnership – Country</td>
<td>WA-C</td>
</tr>
<tr>
<td>Warrant of Partnership – Database</td>
<td>WA-D</td>
</tr>
<tr>
<td>Consortium Policy Document</td>
<td>PD</td>
</tr>
</tbody>
</table>
Moving Towards the Vision


Implement Structure

Currently the Human Variome Project is directed by the Convenor, Professor Richard Cotton and overseen by a Planning Committee. It is not an incorporated entity under any jurisdiction. While this ad-hoc, flexible structure was convenient during the initiation and planning phases of the Human Variome Project, the future of the Project calls for a more defined structure.

The first step in the future of the Human Variome Project is the implementation of the structure outlined above. The Coordinating Office will create a new legal structure, Human Variome Project International Limited, an Australian public company limited by guarantee, to oversee the business activities of the Human Variome Project. Human Variome Project Limited will be a not-for-profit company with tax-exempt status under Australian law.

A company limited by guarantee

- This is the most common form of entity for “not for profit” organisations within Australia.
- They are public companies and thus provide to parties dealing with them the comfort that the entity must comply with the public company requirements of the Corporations Act (auditors, annual lodged accounts etc) and that the officeholders are similarly bound.
- These entities do not have shareholders, but company members, who “guarantee” the payment of the debts of the company in case of a deficiency on wind-up for a nominal sum, say $20.00 or $100.00, thus limiting any liabilities.
- The company members are distinct from the members of the Human Variome Project Consortium.
- This structure allows for obtaining Income Tax Exempt status and Deductible Gift Recipient status within Australia.
- A company limited by guarantee can have as few as one company member.

This company will be governed by an interim Board of Directors for the initial three year term, with members of the interim Board being gradually replaced to avoid a loss of institutional memory.

At HVP3, the 2010 biennial meeting, an interim Scientific Advisory Committee will be elected to oversee the implementation of the Project’s organisational structure. This interim Scientific Advisory Committee will be similar in structure to that described above, but will be chartered for a single two-year term and will be elected by the Consortium Membership present at HVP3, rather than the Advisory Councils. The interim Scientific Advisory Committee’s mandate will be to oversee the creation of the Project’s Advisory Councils.

Prior to HVP3, the Coordinating Office will create an online form on the Human Variome Project website to allow interested individuals to declare their membership of the Human Variome Project Consortium.

**Funding**

Funds to cover the costs of creating Human Variome Project International Limited will be sourced from the operating budget of the Coordinating Office. Administrative support for the Board of Directors, Scientific Advisory Committee and Advisory Councils will be provided by the Coordinating Office.

**Monitoring & Evaluation**

The Board of Directors will monitor the progress of the Scientific Advisory Committee’s implementation of the proposed structure to ensure that it occurs in a timely and legally compliant manner.

### Implement Structure

<table>
<thead>
<tr>
<th>Phase</th>
<th>Title</th>
<th>Duration</th>
<th>Responsible Entity</th>
</tr>
</thead>
<tbody>
<tr>
<td>A001</td>
<td>Incorporate Human Variome Project International Limited</td>
<td>February 2010 - April 2010</td>
<td>Coordinating Office</td>
</tr>
<tr>
<td>A002</td>
<td>Elect Interim Scientific Advisory Committee</td>
<td>May 2010 - May 2010</td>
<td>Coordinating Office</td>
</tr>
<tr>
<td>A003</td>
<td>Implement Advisory Council structure</td>
<td>June 2010 - October 2010</td>
<td>Scientific Advisory Committee</td>
</tr>
<tr>
<td>A004</td>
<td>Consortium membership declaration mechanism</td>
<td>March 2010 - May 2010</td>
<td>Coordinating Office</td>
</tr>
</tbody>
</table>

**Establish HVP Country Nodes**

During the next five years, the Human Variome Project will continue with the *One Project–Two Channels–Multiple Locations* strategy. Accordingly, The Human Variome Project, led by the Coordinating Office, will continue to facilitate the establishment of HVP Country Nodes in countries around the world.

This phase has already commenced, albeit at a very preliminary stage. Over the past year, the Coordinating Office has contacted the heads of the national genetic societies sanctioned by the
International Federation of Human Genetics, introduced the concept of HVP Country Nodes and encouraged them to begin the process of implementing such a concept in their countries. The Australian Node of the Human Variome Project has obtained funding from the Australian Federal Government for the creation of software and systems which are capable of being used as models in other countries.

A comprehensive policy governing the activities and responsibilities of HVP Country Nodes will be developed by the International Confederation of Countries Advisory Council, in consultation with the Coordinating Office and the wider Human Variome Project Consortium membership. Once in place, those countries (e.g. Saudi Arabia, Korea, China) who have agreed in principle to become HVP Country Nodes will be formally accepted, and new applications sought.

**Funding**

Administrative and communications support will be provided to the International Confederation of Countries Advisory Council by the Coordinating Office.

**Monitoring & Evaluation**

The Board of Directors will monitor the activities of the International Confederation of Countries Advisory Council through regular written reports.

<table>
<thead>
<tr>
<th>Establish HVP Country Nodes</th>
<th>Phase</th>
<th>Title</th>
<th>Duration</th>
<th>Responsible Entity</th>
</tr>
</thead>
<tbody>
<tr>
<td>B001</td>
<td>Continue contacting genetic societies</td>
<td>February 2010 to December 2010</td>
<td>Coordinating Office</td>
<td></td>
</tr>
<tr>
<td>B002</td>
<td>Develop HVP Country Node Policy</td>
<td>November 2010 to April 2011</td>
<td>ICC Advisory Council</td>
<td></td>
</tr>
<tr>
<td>B003</td>
<td>Facilitate Country Node creation</td>
<td>January 2011 to December 2011</td>
<td>Coordinating Office</td>
<td></td>
</tr>
</tbody>
</table>

**Support Gene/Disease Specific Databases**

The second channel in the *One Project–Two Channels–Multiple Locations* strategy concerns gene/disease specific databases. While many of these databases currently exist and are performing a vital function within the overall genetic information collection scheme, many more databases need to be created. The Human Variome Project believes that the societies and support groups based around particular diseases have an important role to play here. As such, the Human Variome Project, via the Coordinating office has been reaching out to these societies, encouraging them to create new databases to fill in the gaps within the current database landscape.

An early adopter of this scheme is the InSiGHT Group: the International Society for Gastrointestinal Hereditary Tumours. InSiGHT has been involved in the Human Variome Project since its inception in 2006, and has already begun an aggressive process of combining and consolidating the disparate databases for the mismatch repair genes associated with colorectal cancer.
Simultaneously with the formation of new databases, the Human Variome Project will be working hard to support the work of existing databases, through research into, and the developments of standards, tools and structures for performing the vital curatorial work performed by these databases. This work will be administered by the collection of HVP Working Groups auspiced by the Gene/Disease Specific Database Advisory Council.

**Funding**

Administrative and communications support will be provided to the HVP Working Groups by the Coordinating Office. In addition, the Coordinating Office will provide assistance to the HVP Working Groups in sourcing and applying for appropriate grants and other funding opportunities.

**Monitoring & Evaluation**

The appropriate Advisory Council will be responsible for monitoring the progress of each HVP Working Group and ensuring that their work outputs are progressing according to their charters.

<table>
<thead>
<tr>
<th>Support Gene/Disease Specific Databases</th>
<th>Phase</th>
<th>Title</th>
<th>Duration</th>
<th>Responsible Entity</th>
</tr>
</thead>
<tbody>
<tr>
<td>C001</td>
<td></td>
<td>Continue contacting genetic societies</td>
<td>February 2010</td>
<td>Coordinating Office</td>
</tr>
<tr>
<td>C002</td>
<td></td>
<td>Develop standards, systems &amp; infrastructure</td>
<td>June 2010</td>
<td>HVP Working Groups</td>
</tr>
</tbody>
</table>

**Facilitate Deposition**

Once genetic variation information has been collected in a country and curated by a gene/disease specific database, that information must be stored in a manner that allows the greatest possible use. The Human Variome Project believes that the ultimate deposition of all genetic variation information should occur in at least one, and preferably all, of the existing central databases.

Negotiate a coordinated system of data sharing between gene/disease specific databases and internationally recognized genetic data collection centres such as NCBI (USA), EBI (UK), the Human Gene Mutation Database (UK), and the UCSC Genome browser (USA).

Such a coordinated system will need to be mindful of the various ethical and legal issues surrounding the collection, storage and transmission of genetic data, as well as provide a suitable mechanism for the attribution of providence of genetic data, to ensure that credit for the collection and curation work is properly assigned.

**Funding**

Administrative and communications support will be provided to the HVP Working Groups by the Coordinating Office. In addition, the Coordinating Office will provide assistance to the HVP Working Groups in sourcing and applying for appropriate grants and other funding opportunities.
**Monitoring & Evaluation**

The appropriate Advisory Council will be responsible for monitoring the progress of each HVP Working Group and ensuring that their work outputs are progressing according to their charters.

The Gene/Disease Specific Database Advisory Group will be responsible for measuring the impact of Human Variome Project submissions to Central Repositories and communicating that information to the Scientific Advisory Committee.

<table>
<thead>
<tr>
<th>Phase</th>
<th>Title</th>
<th>Duration</th>
<th>Responsible Entity</th>
</tr>
</thead>
<tbody>
<tr>
<td>D001</td>
<td>Develop data sharing plan &amp; policy</td>
<td>June 2011 - December 2011</td>
<td>HVP Working Groups</td>
</tr>
<tr>
<td>D002</td>
<td>Deposition of data</td>
<td>January 2012 - Ongoing</td>
<td>HVP Members</td>
</tr>
</tbody>
</table>
Long Term Viability

The long term viability of the Human Variome Project is an important consideration. While it is conceivable that the Human Variome Project can be supported by scientific grants and similar funding opportunities in the short term, looking further into the future, alternative sources of funding will need to be identified.

The operations of the Human Variome Project are structured in such a way as to allow for each avenue of collection, as well as the core activities of the Human Variome Project, to be funded independently, and thus the inability of one aspect of the Human Variome Project to attract funding does not adversely impact the other aspects.

HVP Country Nodes

The responsibility for sourcing and maintaining funding to continue the operation of an individual node rests with that node alone. Support, in terms of administrative services and lobbying, can be provided by the Coordinating Office.

HVP Country Nodes, as well as providing a reliable means of collection for the global Human Variome Project, also possess many benefits for the countries that host them. A comprehensive picture of the extent and severity of the genetic disease burden affecting the population of a country, combined with rich datasets to coordinate diagnostic testing policy and healthcare planning, can lead to significant savings to national governments. These savings will be significantly higher than the cost of developing and maintaining an HVP Country Node system. It should not prove difficult to convince national governments to provide financial support to a system with such benefits to the economy and the health of its citizens.

Additional funding could also be sourced for HVP Country Nodes by making the data contained in the nodes available to private sector industry on a subscription basis. Obviously such a scheme would have to operate in a manner that was compliant with all relevant national and local laws and ethical requirements, and would be made by the governing body of each individual node.

Gene/Disease Specific Collection

The major expense in running such a collection is far and above the human effort required to curate and manage these collections. As the majority of gene/disease specific databases are run as an adjunct to the research effort of professional academics, the technical expenses, in terms of hardware and web-hosting, are usually defrayed through the curator’s institution. Additionally, much of the software required to run such a collection can be acquired free-of-charge by making use of Open Source Software products, such as the Leiden Open Variation Database (http://www.lovd.nl/).
To cover the cost of curation, the Human Variome Project has developed the Adopt-a-Gene™ scheme. Adopt-a-Gene™ partners gene/disease specific databases with interested private sector companies, non-governmental organisations and public associations, such as patient support groups. In exchange for financial support for the curation activities of the database, the sponsor receives recognition as a valued supporter on the database and on Human Variome Project website.

In addition, the Human Variome Project is investing heavily in initiatives that will decrease the costs required to curate gene/disease specific databases, including developing curation methodologies and automated curation tools.

**Coordinating Office**

The Coordinating Office of the Human Variome Project, currently the Genomic Disorders Research Centre, is the administrative hub of the Human Variome Project Consortium and a necessary overhead to ensure that the vision of the Human Variome Project is achieved. There are a number of suitable incomes sources that form the basis for future financial sustainability:

- **General sponsorship**
  Government and commercial strategic and supporting partners will be expected to contribute annual funds towards the operation of the Coordinating Office to cover salaries & wages, office, administration and infrastructure costs.

- **Events and conferences**
  A nominal income can be earned for well attended events and conferences.

- **Advertising**
  The website of the Human Variome Project, operated by the Coordinating Office, is an attractive target for advertising, especially to the Corporate Members of the Human Variome Project Consortium.

- **Philanthropic support**
  A limited amount of support can be expected to be sourced from individuals and philanthropic institutions who share the vision of the Human Variome Project.

The Human Variome Project Consortium is a finite entity. It exists to establish and put in place maintenance structures for systems that will capture global genetic variation data. The key aspect of these maintenance structures will be the integration of the collection systems into standard clinical practice. Once this has been achieved, the need for the Human Variome Consortium, and as such, the need for continued funding will be diminished.