



Coordinating Office Position Paper

Themes and Issues To Be Discussed When Preparing the Next Project Roadmap

AUGUST 16, 2011

Human Variome Project International Ltd.
Level 2, 161 Barry St
Carlton South VIC 3053
AUSTRALIA

Prepared by:
Timothy D. Smith

Contact:
Timothy D. Smith
Level 2, 161 Barry Street
Carlton South VIC 3053
AUSTRALIA
+61 (0)3 8344 2096
tim@variome.org

Authorisation:

This Position Paper has been prepared by Timothy D. Smith and represents the official position of the Human Variome Project Coordinating Office only. It does not represent an official position of the Human Variome Project, its Consortium, Advisory Councils or International Scientific Advisory Committee.

-s-

Prof. Richard Cotton
Scientific Director

I Background

As detailed in our previous Position Paper on this issue,¹ the next iteration of the *Project Roadmap* is due to be authored. The current timetable requires that a Discussion Paper on the themes and issues to be addressed in the *Project Roadmap* be released for public consultation by the Coordinating Office on 1 August, 2011. This document is intended to present to the International Scientific Advisory Committee a brief overview of what the Coordinating Office feels those themes and issues should be.

The *Project Roadmap* is an important document. It sets the strategic scientific direction of the Human Variome Project and articulates the processes and procedures through which the goals of the Project will be obtained. Additionally, it plays an important role in setting the objectives and measures by which the success of the Human Variome Project will be judged. As such, considerable care and thought must be taken in the construction of this document, as well as ample consultation undertaken with the people that will be affected: the Human Variome Project Consortium.

We have prepared this Position Paper for the Project's International Scientific Advisory Committee so that they can provide much needed input as to the direction of the Roadmap at an early stage of the authoring process. It outlines the themes and issues that the Coordinating Office feel require discussion amongst the Consortium and, as such, should be included within the forthcoming Discussion Paper. We are seeking the Committee's input into the list of themes and issues enumerated below.

II Broad Themes

The core purpose of the Human Variome Project is to alleviate needless human suffering for many millions of the world's people by collecting, organising and sharing data on genetic variation. The purpose of the *Project Roadmap* is to outline the strategies that the Consortium shall employ during the life of the document to fulfill that purpose. As such, the themes presented within the *Project Roadmap*, and thus put up for discussion during the authoring process, should be constructed with the scope of the ultimate document in mind.

The Coordinating Office feels that the following list encapsulates the themes that should be present within the next *Project Roadmap*.

1. principles and ideals of the Human Variome Project and its Consortium;
2. overall collection strategy;
3. overall sharing strategy;
4. education of the field and the public;
5. facilitating collaborations and partnerships; and
6. work methods.

III Specific Issues

Comprising each of these themes is a suite of specific issues that merit discussion amongst the Consortium prior to the new *Roadmap* being prepared. The following, while not an exhaustive list of those issues, presents those issues the Coordinating Office needs guidance from the Consortium on.

¹ *Preparing the next Project Roadmap*, June 17, 2011

Principles and Ideals

No Defined Principles

The Project currently has no single statement on what its overarching principles and ideals are. The current *Roadmap* lists a set of core values, but does not cover ideals such as free and open access to data, etc.

Clarify Purpose

As stated above, the core purpose of the Human Variome Project is to alleviate needless human suffering for many millions of the world's people by collecting, organising and sharing data on genetic variation. This is a noble purpose and in very broad terms describes what the Human Variome Project is seeking to achieve. However, it may be too broad and can lead to confusion. The Project's purpose should be clarified, in line with the definition of its principles and ideals. Possibilities include:

- definition of standards;
- promotion of standards and tools;
- be an advocate for the field;
- be a forum for collaboration; and
- educate the field and the public.

Scope of the Project

There currently exists a deal of confusion around the anticipated scope of work for the Human Variome Project. Our purpose is to collect and share information on genetic variations, but how are we defining variations? Should the Human Variome Project be interested only in those variations causing Mendelian disease, or should the scope of the Project be broader than this? Should we capture all variations, even those associated with but not directly causative of disease, and if so, does this include somatic mutations?

Intellectual Property

The Human Variome Project Consortium must develop a position on how the intellectual property generated by Consortium Members during the course of Project Activities should be managed, protected and exploited. There are several different classes of IP that must be considered:

1. IP generated by Consortium Members during their everyday activities that contributes to the vision of the Human Variome Project;
2. IP generated by Consortium Members during the course of activities that is initiated, sponsored or paid for by the International Scientific Advisory Council, an Advisory Council or the Coordinating Office; and
3. IP generated directly by the Coordinating Office.

The developed positions must respect the rights of the individuals involved in the development of the intellectual property and existing agreements they may have with their employers, but at the same time must ensure that the protection or exploitation of the intellectual property does not compromise the principles and ideals of the Human Variome Project.

Overall Collection Strategy

Next Generation Sequencing

The advent of next generation sequencing has the potential to radically impact the way gene/disease specific databases collect, store and present data. How should the Human Variome Project be preparing itself to meet these new challenges. Is it simply a matter of improving data models for gene/disease specific databases or are the days of gene-centric databases numbered and should we be looking at a new databasing paradigm?

How is the Gene/Disease Specific Database Advisory Council going to work?

The current structure of the Human Variome Project calls for a single Advisory Council to be formed to represent gene/disease specific databases and generate standards and guidelines for their operation. Each gene/disease specific database is entitled to appoint a representative to this council. There are currently some 1800 databases in existence. Even allowing for some redundancy in the genes and diseases covered, a committee formed by representatives for each of the unique databases would be too unwieldy to operate effectively. How can we make the operations of this Advisory Council more efficient without losing the representative nature that the Advisory Councils require?

The Role of Patient Registries

Gene/disease specific databases and patient registries share many similarities, both in purpose and underlying technical infrastructure. Some within the Human Variome Project Consortium have advocated previously for existing gene/disease specific databases to develop into patient registries. Obviously, the legal and ethical challenges that would need to be overcome in order to do this are not trivial. Do the expected benefits of co-locating variant databases with patient registries outweigh these challenges. What stakeholders outside the Human Variome Project Consortium would need to be engaged to proceed with this initiative?

Overall Sharing Strategy

The Data Aggregator

As can be seen in Figure 1, the *HVP Data Aggregator* has been proposed previously as a concept. It acts as a transport mechanism for data that are collected by HVP Country Nodes so that they can be submitted to gene/disease specific databases. It is not designed to store data, merely move it around. Without such a tool, each HVP Country Node would be responsible for forming a data link between itself and each and every gene/disease specific database. With the Aggregator, a Node need only form one such link, with the Aggregator itself. Likewise, each gene/disease specific database could form one link to the Aggregator and immediately begin receiving country node data.

Such a proposal is not novel. *The Waystation* (<http://www.centralmutations.org>) had similar goals but has not been actively developed for some time. *Cafe Variome* from the Gen2Phen Consortium is also concerned with making the sharing of variant data easier. How should the Human Variome Project go about developing the Aggregator functionality? Is there an existing service that could be utilised 'off-the-shelf' or with modification, or does a new service have to be developed? How would such a service operate?

Extending Clinical Utility

Sharing of variant data is paramount to the Human Variome Project's purpose. Part of sharing data effectively is making sure that data is useful to the people who will be using it. Are the existing gene/disease

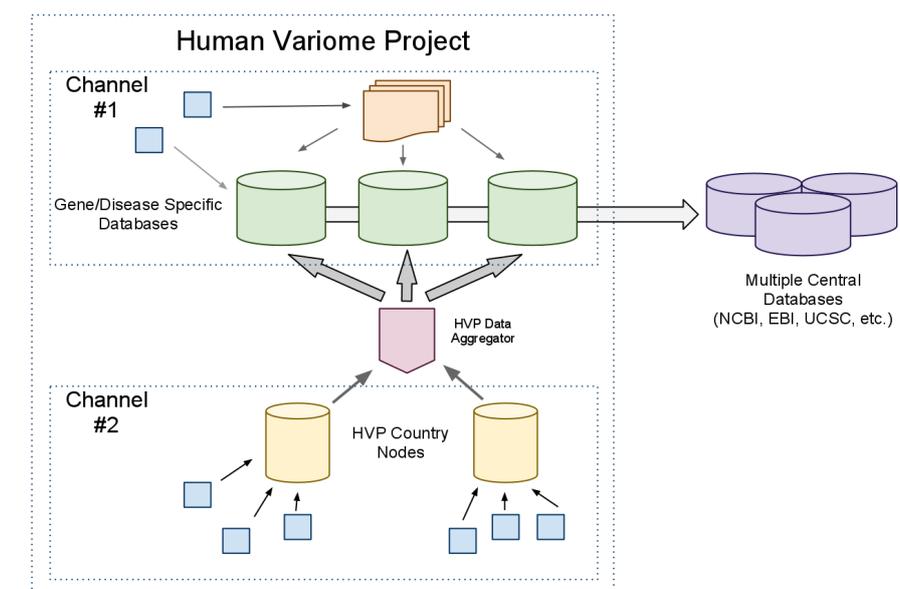


Figure 1: Data Sharing Strategy

specific database data models extensive enough to be useful in an everyday clinical setting? Can we expand the coverage of the data model, especially around the strength of pathogenicity determination, to make them more useful? Should this be a goal of the Human Variome Project, to directly support clinical decision making, or should the focus be on supporting research that will in turn lead to new knowledge for clinicians to implement? IN either event, how can clinical data be more readily collected?

Database Accreditation

The Human Variome Project's Gene/Disease Specific Database Advisory Council (G/DSDAC) will produce standards and guidelines for the operation of gene/disease specific databases. Members of this Council will be representatives appointed by databases that have been deemed to comply with HVP Standards and Guidelines. At a very basic level, this is a form of database accreditation: the Human Variome Project is judging these databases as meeting a certain level of quality.

It has been suggested that a more comprehensive accreditation scheme be developed for these databases. How would such a system work: an expert review of all databases, or a self-assessment process with random compliance testing? On what criteria would accreditation be based? Accreditation would need to be at least moderately achievable for most current databases, at least in the first instance, to ensure the program does not fail at the first hurdle.

Education

Management of Education Activities

A heavy focus was placed on education of both the field and the general public, particularly in low- and middle-income countries (LMICs), in recent submissions to the World Health Organisation by the Coordinating Office. The Human Variome Project has always devoted time in its meetings to both education and LMICs; each topic has had specific working groups formed. However, with the progression to the new Activity Process² for the Human Variome Project, wherein Working Groups are no longer enduring entities formed around broad topics, but rather expert groups with a finite lifespan formed to work on a specific topic or document, how should the education activities of the Human Variome

²as outlined in *Project Roadmap 2010-2012*

Project be managed? Should a new Education Advisory Council be formed on par with the existing two Advisory Councils and how would such a Council operate? Or should the International Scientific Advisory Council form an extraordinary working group that would work on education activities in an enduring fashion? How should Human Variome Project activities interface with the extensive genetic education activities already extant?

Collaborations and Partnerships

Dealings with Commercial Entities

The Human Variome Project Consortium is primarily designed to be a collection of individuals working towards a common goal. The previous *Roadmap* left open the possibility that institutions and companies could join the Consortium if they so wished. Is this still an option that should be maintained? If so, how do we balance the concerns of the World Health Organisation around commercial involvement in the Project?

IV Next Steps

The Coordinating Office would appreciate any thoughts the International Scientific Advisory Committee have on the themes and issues outlined above. We are also seeking suggestions for additional issues facing the Human Variome Project that merit discussion prior to authoring the next *Roadmap*. We would appreciate a single formal response to this Position Paper from the Committee by the 8th of July. The Coordinating Office will prepare a Discussion Paper around these issues by 1 August.