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D1.4 Report on External ELSI Developments

WP1 – Scientific Coordination

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Authors (Partner)	Cambon-Thomsen Anne, Pigeon Anna (INSERM)		
Responsible Author	Cambon-Thomsen Anne	Email	cambon@cict.fr
	Partner	INSERM	Phone

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Definitions

- Partners of the GEN2PHEN Consortium are referred to herein according to the following codes:

ULEIC – University of Leicester (UK) – Coordinator

EMBL – European Molecular Biology Laboratory (Germany) – Beneficiary

FIMIM – Fundació IMIM (Spain) – Beneficiary

LUMC – Leiden University Medical Center (Netherlands) – Beneficiary

INSERM – Institut National de la Santé et de la Recherche Médicale (France) – Beneficiary

KI – Karolinska Institutet (Sweden) – Beneficiary

FORTH – Foundation for Research and Technology Hellas (Greece) – Beneficiary

CEA – Commissariat à l’Energie Atomique (France) – Beneficiary

EMC – Erasmus Universitair Medisch Centrum Rotterdam (Netherlands) – Beneficiary

UH.FGC – Helsingin Yliopisto (Finland) – Beneficiary

UAVR – Universidade de Aveiro (Portugal) – Beneficiary

UWC – University of the Western Cape (South Africa) – Beneficiary

CSIR – Council of Scientific and Industrial Research (India) – Beneficiary

SIB – Swiss Institute of Bioinformatics (Switzerland) – Beneficiary

UNIMAN – The University of Manchester (UK) – Beneficiary


BIOBASE – BioBase GmbH. (Germany) – Beneficiary

deCODE – Islensk Erfoagreining EH (Iceland) – Beneficiary

PHENO – Phenosystems S.A. (Belgium) – Beneficiary

BCP – Biocomputing Platforms Ltd. Oy (Finland) – Beneficiary

- Grant Agreement:** The agreement signed between the beneficiaries and the European Commission for the undertaking of the GEN2PHEN project (HEALTH-200754).
- Project:** The sum of all activities carried out in the framework of the Grant Agreement by the Consortium.
- Work plan:** Schedule of tasks, deliverables, efforts, dates and responsibilities corresponding to the work to be carried out for the GEN2PHEN project, as specified in Annex I to the Grant Agreement.
- Consortium:** The GEN2PHEN Consortium, conformed by the above-mentioned legal entities.
- Consortium agreement:** agreement concluded amongst GEN2PHEN participants for the implementation of the Grant Agreement. Such an agreement shall not affect the parties’ obligations to the Community and/or to one another arising from the Grant Agreement.

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1. INTRODUCTION

This deliverable under the responsibility of Inserm U558, Toulouse aims to give an overview of ethical developments outside GEN2PHEN, complementary to what was developed in D1.3 (on the General Ethical Issues in G2P Databases Work) and that could shed light on the ethics awareness or ethics policy of the project.

2. PROJECT SUMMARY

The GEN2PHEN project aims to unify human and model organism genetic variation databases towards increasingly holistic views into Genotype-To-Phenotype (G2P) data, and to link this system into other biomedical knowledge sources via genome browser functionality.

It will establish the technological building-blocks needed for the evolution of today's diverse G2P databases into a future seamless G2P biomedical knowledge environment, by the projects end. This will consist of a European-centred but globally-networked hierarchy of bioinformatics GRID-linked databases, tools and standards, all tied into the Ensembl genome browser.

The Project involves a pool of European research groups and companies from Belgium, Finland, France, Germany, Greece, the Netherlands, Portugal, Spain, Sweden, and the United Kingdom. Non-EU participants, i.e. Iceland, India, South Africa and Switzerland have been included to bring extra capabilities to the initiative of the G2P databasing challenges.


Answering to the need of European G2P research and biotech industries in terms of database technologies and data integration systems will contribute to permit our societies to better benefit from the current exponentially increasing rate of genetic data generation in disease research and clinical settings.

The Project focuses on three essential components of a functioning G2P database system:

- Getting data in
- Data storage & infrastructure
- Getting data out

In this context, the Project addresses 9 specific strategic objectives:

- 1- To analyse the G2P field and investigate current needs and practices
- 2- To develop key standards for the G2P field
- 3- To create generic database components, services, and integration infrastructures for the G2P domain
- 4- To create a data search and presentation solutions for G2P knowledge
- 5- To facilitate the populating of research and diagnostic G2P databases
- 6- To build a major G2P internet portal
- 7- To develop GEN2PHEN solutions to the community

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- 8- To address system durability and long-term financing
- 9- To undertake a system utility and validation pilot study.

More than merely devising potentially useful technologies, the Project is building a tool that tangibly benefits to the community putting it to use to show that it truly works.

3. PLACE OF THE WP1 IN THE GENERAL WORK PLAN


The implementation plan of this programme is built on technical aspects to be achieved:

- The creation of standards: data models, nomenclatures and ways to use ontologies, with specific versions for use when constructing different types of databases, and a generic version for integration-level activities.
- The database construction work based on these standards
- The development of technologies for integration and for holistic searching to operate above the database layer
- Steadily feeding the emerging system with data from various sources
- The development of the “GEN2PHEN Knowledge Centre” (internet portal)

These various technical aspects are complemented and influenced by complementary activities: community consultation, quality insurance, ethics analysis, societal perspectives, internal and external training activities. **This deliverable D1.4 relates to ethics analysis and societal perspective.**

The Programme is planned according to the following “workpackages”:

- WP1: SCIENTIFIC COORDINATION
*(Gathering and reacting to new scientific ideas, optimising the use made of the project committees, supervising work package leaders, and **providing ethical oversight of the whole project**)*
- WP2: DOMAIN ANALYSIS AND COMMUNITY RELATIONS
(Formal “requirements analysis”: identification of database users and actors and their current and future needs in the G2P field)
- WP3: STANDARD DATA MODELS AND TERMINOLOGIES
(Creation of reference data models as basis for the database development work)
- WP4: GENETICS G2P DATABASES & WP5: GENOMICS G2P DATABASES
(Creation of modular and generic G2P database components to construct major demonstration databases)
- WP6: INTEGRATION AND DATA ACCESS TECHNOLOGIES
(Enabling processes of data exchange between databases, data integration and synchronisation within central databases or warehouses, and holistic searching across databases)
- WP7: DATA FLOWS
(Gathering of data to populate the databases constructed by the GEN2PHEN project)

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- WP8: GEN2PHEN KNOWLEDGE CENTRE
(*Creation of a strategic internet portal for maximal visibility and added-value utility*)
- WP9: DISSEMINATION, USE AND FUTURE SUSTAINABILITY
(*“Dissemination” and “exploitation” tasks*)
- WP10: MANAGEMENT
(*Overall scientific, legal and financial management and coordination*)

The overall objective of GEN2PHEN is to help create a functioning first version of a hierarchical network of G2P databases, to provide comprehensive access to the rapidly growing corpus of new knowledge pertaining to G2P relationships in humans and model-organisms.

WP 1 is contributing to this objective through the optimization of the overall scientific direction and progress of the project. It also addresses any ethical concerns that might arise during the project by establishing a system to provide expert analysis and guidance for the workers concerned.

This version 1.2 concerns Deliverable “D1.4: Report on External ELSI Developments” and will also include the revised version of the project ethics policy.

4. PROJECT OBJECTIVES FOR THE DELIVERABLE D 1.4


This report will summarise ethics developments that emerge from activities outside GEN2PHEN but which could impact the project. It is also useful to remind the tentative proposal for GEN2PHEN ethics policy construction basis in order to analyse only the relevant external ethical legal and societal issues developments that are closely related to this policy. The deliverable D1.3 together with the deliverable D1.4 allow to propose an ethics policy that can be now validated by the Consortium and proposed to the external advisors for the mid-term project review.

4.1. Proposal for a GEN2PHEN ethics policy construction basis

4.1.1. Basis for an ethics policy

Although much discussion is necessary a tentative proposal of the basis for an ethics policy has been made following completion of D1.3 in order to start a debate on the topic rather than already setting the rule. This proposal of an ethics policy was a point on the agenda for the M18 general assembly (GAM4) in EBI, June 2009, and discussion groups occurred which allowed to refine it.

- A preliminary chapter with **definitions** of the data considered in GEN2PHEN, the aims of the tools and the ultimate benefits expected for different stakeholders should be written. If several categories of data in terms of possible identification co-exist state the policy for each category. When various definitions exist in the literature, choose one and give reasons and reference.
- A second part should recall the **most relevant reference texts and main principles considered**, with a preference when such texts exist to international and European regulations, giving

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information on their binding or non binding characteristics and taking into account what the EU commission is asking at the time of ethical reviews of projects (for example compliance with Oviedo Convention even if the country has not ratified it).


- A third part should give a policy for the 4 levels identified:

- 1. Getting data in:** giving the conditions to be checked before data can come into the system (original consent checked for mention of international data sharing, further uses of data, preferably by a local/institutional committee, and specific provisions for data from minors or persons unable to consent). In case a local relevant committee is not available GEN2PHEN should set up a policy to address this question (if a GEN2PHEN ethics oversight committee is composed members and mandate should be made public). Options of providing more information on the documents provided to participants or consent forms templates themselves may be open but not mandatory. Specific provisions must be made for non anonymised samples in case this situation occurs. Also the policy will make clear what is also needed in terms of data authority approval.
- 2. Database and infrastructure:** a clear identification of data owners, database/tools intellectual property management must be described. The possible involvement of stakeholders in the definitions of the various regrouping that will be made available could be considered. The responsibilities distribution between actors should be made explicit.
- 3. Getting data out and using them:** the divide between completely open access data and those with controlled access will have to be done with explicit rules; for controlled access the way to assess the “bona fide” scientists and institutional responsibility engagement will have to be also explicit. In parallel with the policy on use of data, a policy of reporting results (general level) in order that they can be communicated and made available for data providers and possibly other stakeholders is needed.
4. Finally the **process for checking the tools** for “ethics policy compliance” will have to be clearly established.

The last part will include the **statements that will appear on the web site** on those issues, visible to anyone.

Each of these points has been the topic of a part of a workshop discussion with the most relevant WP and at the general assembly. This was the first step of the ethics policy decision process. Now that this discussion took place, a summary and an assessment of the results of the discussion have been done, and the ethics policy completed.

Many of the points identified and discussed have also been extensively examined in a larger cooperation to prepare together with the Human Variome Project a set of guidelines regarding ethics, aimed at helping taking into account ethical aspects in the curation of human locus-specific variation databases (LSDBs), domain highly relevant for GEN2PHEN. ULEIC, LUMC and EMC have especially participated in this last work in addition to INSERM, (see manuscript in Annex). The results of all these works are included in this Deliverable D1.4 at M24 as planned, and the paragraph below presents the ethics policy agreed upon.

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Following the same logic as the project in general and as it was done in the previous “ethics” deliverable 1.3, the new draft of the ethical policy is presented according to issues encountered in the general 3 steps of the technical developments of the tools alongside the project.

4.1.2. Finalisation of the GEN2PHEN project ethics policy

As was done in the previous deliverable D1.3, the new draft of the ethics policy is presented through issues prospectively envisaged in each of the three technical development of the tools.

4.1.2.1 As regard to the getting data in part:

Three sets of ethical keys issues have been identified:

1. The data definition issue.

At the GAM4 meeting it became obvious that several kinds of data are going to be processed:

- Diagnostic labs data,
- LSDBs,
- Whole genome information in a context of research.
- The possibility of dealing with individual data has also been confirmed.
- Both data from published literature and quality assessed but non published data will be considered.


2. The data protection issue

Data may come from various types of individuals, identifiable or not, thus to protect the rights of persons in the utilisation of their data, ethical issues were identified the respect of autonomy thanks to informed consent and the confidentiality.

The data protection already cited in the deliverable 1.3, (Directive 95/46/EC of the European Parliament and the Council of October 1995 on the protection of individuals with regard to the processing of personal data¹ on the free movement of such data) provides an adequate framework for many of the issues regarding confidentiality issues. All European countries have a data protection authority and have transposed the Directive 95/46/EC regarding personal data, which applies to genetic data.

Other ethical and legal references are available on the previous deliverable 1.3 if needed, or in annexe III of this report, related to ethical and legal framework related to GEN2PHEN and references.

¹ The directive in its article 2 contains a broad definition of personal data: “personal data shall mean any information relating to an identified or identifiable natural person, an identifiable person is one who can be identified, directly or indirectly, in particular by reference to an identification number or to one or more factors specific to his physical, physiological, mental economic cultural or social identity.” The definition related to coded or anonymised could also be related to the definition in Article 2 “personal data” and “identifiable person”

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On the one hand GEN2PHEN consortium had to decide if it has to systemically make sure that an initial informed consent² has been collected and how. It has been decided that it is completely necessary.

Furthermore, it has been decided that the original consent should mention at least the international data sharing, further uses of data, and must contain specific dispositions for data coming from minors if relevant. As data coming from minors present specific issues, and the literature, particularly that presented underneath, debated recently a lot on this issue, it has become necessary to decide a clear policy on this issue. Indeed the informed consent must be clear on the consent and assent aspect, the re-contacting issue and the moment or criteria allowing assessing that a minor is old enough to understand and when he or she is capable of discernment.

On the other hand an accepted definition of confidentiality and appropriate way of guarantee had to be worked out, as guarantees must be offered to the participants that their data are actually protected.

Regarding the definition of confidentiality, in agreement with the answer of GEN2PHEN members to the previous questionnaire the following framework has been considered: “Any information of a personal nature collected during biomedical research shall be considered as confidential and treated according to the rules relating to the protection of private life”.

As regards to the data protection of the participants, in principle, biomedical data are originally collected in a context of trust and it is standard practice to protect confidential health and research data. GEN2PHEN consortium agreed on the fact that anonymised data is the best way to ensure confidentiality. And so the policy proposes that the data must be collected in an anonymised form and shared in the same way. Nevertheless as anonymisation can be a fiction. Indeed the article of Homer et al. (PLOS Genetics, 2008) showed that re-identification of individuals from pooled data is possible.


Given this, coded data may allow further data to be gathered, thus enriching the resource, while permitting the participants to withdraw their consent and their data and consequently, allowing GEN2PHEN to be in compliance with the rights of the participants.

In case where the solution of coded data would be retained by GEN2PHEN consortium, serious independence guarantee must be established regarding the owner of the code in order to secure the data.

3. The role of GEN2PHEN in managing issue

In order to make the protection of the rights of person effective, the GEN2PHEN consortium had to ensure that an appropriate consent has been obtained for the envisaged use of data prior to anonymisation or coded data whether what is going to be decided by GEN2PHEN consortium.

² According to the directive 95/46/EC, the data subject “consent” shall mean any freely given specific and informed indication of his wishes by which the data subject signifies his agreement to personal data relating to him being processed.

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After observing the activities of the project it has been decided to draw a distinction between two situations.

In the case where GEN2PHEN is gathering data in its own initiative, the consent has to be verified, the ethical committee must approve the transfer stating that the data could be transferred having considered the original protocol and aim of GEN2PHEN. To achieve this goal GEN2PHEN must provide to the local ethical committee or the institutional authorised person all the information about the aim and the goal of GEN2PHEN. Then the local ethics committee or the institutional authorised person must provide an attestation certifying that informed consent containing at least the prerequisites we saw above are fulfilled for each participant for the envisaged use. So it might be a solution to rely on local ethics committee or institutional approval but with a specific statement that they have considered the dimension that GEN2PHEN is giving in terms of access to data and that it fits with the provisions described to the research participant or equivalent procedures.

In the case where data providers were willing to put the data into the system and make their data available through GEN2PHEN, they have to provide the appropriate informed consent in itself or the institutional certificate or the agreement of the local ethics committee.


In both cases a problem occurs when it is impossible to obtain this informed consent sheet or institutional certificate, or local ethical committee approval.

The question is: must GEN2PHEN accept data when the consent cannot be verified. In this situation the most protective solution for participants and also in conformity with ethical and legal requirements is that the GEN2PHEN consortium doesn't accept any data where the consent cannot be verified. One of the envisaged solutions for data considered as scientifically especially relevant, was that an internal committee with all the independence requirements could take this decision and whether refuses the data to come in or guarantee at least some degree of oversight as an alternative solution.

As regards to the constitution of the GEN2PHEN ethics oversight board, it has to be independent.

The European Union addressed this issue in the Newsletter, Ethically speaking n°12 of august 2009. Indeed, a chapter was dedicated to the conditions for the proper working of national and international ethics committees. The establishment of an internal GEN2PHEN ethics committee, its organisation and abilities could be inspired by the features described. In this letter the most important features are transparency, time tolerance, explicitness, independence and interdisciplinary nature. The first one is transparency, about composition, methods of selecting members and chairpersons and the term of reference of the committee. Who decides what the committee discusses, its working methods and the rules of procedure of the group, including the possibility to express and record dissent, and so forth...

What is also important to highlight and must be respected is integrity in the GEN2PHEN internal ethics committee which means that personal interests and prestige, religious persuasions, and economic and political interests should not be allowed to interfere with this process, particularly when it comes to testing hypotheses, interpreting and drawing conclusions from the results of the

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research – or deciding whether the data can come in the system or not and if the results should be published.

The oversight ethics board must also be independent. It ranges from economic independence (the committee is able to decide for itself about how to use its funds) to independence in terms of deciding which topics to work on, deciding which experts to invite, the decisions the committee will take.

Eventually, interdisciplinary composition of the committee is essential to ensuring that relevant background information and perspectives are not missed; one solution for GEN2PHEN could be that each work package be represented, and if it is not possible that one member could be requisitioned on specific topics, and that 2-3 people external to the project and with expertise in ethics and data protection are included, as well as one representative of patients association.

Interaction with the general public is also important. Translated to GEN2PHEN project it would be interaction with the participants, data providers, donor's, scientific community, users... So in addition to the ethics oversight board, an active process of transparent information has to be set up (newsletter with a language accessible to all, catalogue of data and their sources, publically available ethics policy, public access to questions asked and their answers...)

4.1.2.2 As regards to the data storage and infrastructure part

The data storage and infrastructure is the construction of the GEN2PHEN database tools based upon data models, nomenclature and technology standards and built on generic database components and a deeply networked infrastructure.

Two main ethical issues were identified, the data ownership issue (to whom do the data gathered belong) and the database ownership issue.


1. Data ownership issue

This issue is related to the responsibilities linked to the property of those data.

Data belonging to an institution refer to a framework that can guarantee a certain procedure for protection of data and an institution being legally responsible towards the research participants as the promoter of a research; data belonging to a PI (an individual who then would be responsible for any misuse or further use) underlines the intellectual property rights over a use, rather than responsibility towards research participants; data belonging to research participants indicate that they should keep a control over the uses of data, which is different from an ownership.

2. Database ownership issue

The majority of participants considered that consortium agreement was the best way to address this issue, but this call for a different system in the long run when federated databases will include databases from groups outside the GEN2PHEN consortium.

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The Directive on the Legal Protection of Databases adopted by the EU's Council of Ministers on 26 February 2006, creates an exclusive 'sui generis' right for database creators, valid for 15 years, to protect their investment of time, money and effort, irrespective of whether the database is in itself innovative. The Directive also harmonises copyright law applicable to the structure of databases. On the basis of the Directive, manufacturers of databases will be in a position to prohibit the extraction and/or reutilisation of the entirety or substantial parts of the database by third parties. However, this new form of protection should not affect the rights of traditional right holders, in particular of creators of works incorporated in the contents of a database. The scope of application for the directive is


1. This Directive concerns the legal protection of databases in any form.
2. For the purposes of this Directive, 'database' shall mean a collection of independent works, data or other materials arranged in a systematic or methodical way and individually accessible by electronic or other means.
3. Protection under this Directive shall not apply to computer programs used in the making or operation of databases accessible by electronic means.

The Directive strikes a balance between the interests of the manufacturers of databases and the legitimate interests of their users. Particular account has been taken of situations in which the extraction of contents of databases is required for teaching purposes as well as for scientific research. Indeed in the article 9 indicates that there is an exception to the Sui generis right, in the case of extraction for the purposes of illustration for teaching or scientific research, as long as the source is indicated and to the extent justified by the non-commercial purpose to be achieved.

Otherwise the article 7 says that "Member States shall provide for a right for the maker of a database which shows that there has been qualitatively and/or quantitatively a substantial investment in either the obtaining, verification or presentation of the contents to prevent extraction and/or re-utilization of the whole or of a substantial part, evaluated qualitatively and/or quantitatively, of the contents of that database".

So we can highlight that GEN2PHEN database is protected by the sui generis right of the directive without prejudice of any intellectual property rights which can be discussed in the GEN2PHEN consortium. For tools not pertaining to the database as open source is the philosophy of the project no specific issue has been considered.

Regarding the question related to discrimination, although a majority of GEN2PHEN members considers that constructing group on the basis of ethnic information would raise ethical questions and that grouping on the basis of genetic elements is less often raising ethical questions, the issue had to be considered. Consideration has been given to the proposals made by GEN2PHEN members such as having a representative of ethnic group involved in setting up provisions regarding data in relation to ethnic group. This could be a member added to the ethics oversight board when the issue occurs, but the feasibility and the representativity is questioned. An easier way may be to ensure that when using data from sensitive groups, the ethics committee that gave the approval has included a sentence addressing the issue and to include a box to tick regarding engagement not to use data in a discriminative way for future users.

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As regards to minors, the literature debated this issue a lot, lately. Reference can be done to an article “Biological sample collections from minors for genetic research: the call for a reflection on policy and ethical issues» which assess international European and national instruments dealing with this question.

The proposals made by GEN2PHEN members related to that subject are in compliance with those instruments, such as having parents or authorised person to sign the consent, having a consent that specify what will be done when the minor becomes adult , and verify that there is a procedure that inform the minor, in order to be in full compliance with the United Nations Convention on the Rights of the Child, that asserts that children have a right to say what they think should happen when adults make decisions that affect them (Article 12) and have the right to get and share information (Article 13). As this is a legally binding document for most countries, it makes sense that for GEN2PHEN, children are also given appropriate information and their opinions are taken into account.

4.1.2.3 As regards to the getting data out part

The issues considered here are those associated with the use of the data once they have been included in the GEN2PHEN federated database and can be queried by users using GEN2PHEN tools.

Two ethical issues were identified, access and commercialisation issue and the protection of the persons from whom the data are processed.


1. Access and commercialisation

This issue is related to the accessibility of the data and results, and to the sustainability of the project. The divide between completely open access and those with controlled access have to be done with explicit rules and an explanation must be given whether certain data or combinations of data will not be made available and for which reasons.

For controlled access, the way to assess the bona fide scientists and institutional responsibility engagement will have to be also explicit. It will imply a level of personal engagement (ticking boxes regarding uses and liability, and providing an institutional authorisation. Different ways could be combined: data access could be restricted via fees, legal threats, technological censoring e.g. GPS and encryption algorithms, and study design in eliminating useless data linkages for instance.

2. The protection of individuals from whom the data are processed

.Question of anonymisation: GEN2PHEN consortium should consider the extent to which the genetic data held or inter-related might allow the identification of participants, either alone or in combination with other available data and reference samples. The data may be assessed to one of three categories :

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- Known as possibly indentifying (coded) and the keys are never available through GEN2PHEN; only anonymised information is provided
- With incidental technical possibility of indirect re-identification that may occur over time; a policy has to be put in place to address this issue. First a systematic follow up of relevant literature and technical tools as an identified tasks; second a technical way of assessing the data publically available for this issue; third a procedure to efficiently change the status of relevant data from “publically accessible” to “controlled access”
- Data with no possibility of identification or re-identification, the criteria for this being publically available; these may be publically available, without external controlled access, but all data accessed should be preceded by an engagement on their use in a way that respect fundamental rights ticked by the users.

. Question of withdrawal where the data are anonymised: the impossibility to withdraw anonymised data has to be clearly indicated.

. In terms of incentives a problem is perceived because, contrary to the research community the data providers are most of the time not considered to benefit from the data sharing. Institutions have to push to data sharing as institutional policies. Reference to institutions policies aiming at data sharing could be indicated as reference on the website and this in itself would work as an incentive. Duty to optimise the use of data towards participants hopes and expectations must be underlined.

. Determination of the best level at which feedback information on results generated thanks to GEN2PHEN should be done. The proposal is to present regularly new insights thanks to data sharing and developing of tools and to make this actively available (alert) to data providers with an encouragement to inform their participants about these developments, by an appropriate way in their context.

For LSDBs the guidelines proposed in the article in Annex that has been approved by an international advisor (Bartha M Knoppers) and has been submitted for endorsement to the HUGO ethics committee will be followed by GEN2PHEN.

This policy has already benefited of the current developments outside GEN2PHEN.


4.2. Methodology

The aim of this deliverable and so this report is to summarise ethics developments that emerge from activities outside GEN2PHEN and which could impact the project and its ethics policy.

In order to address the question of the external ELSI developments it has been decided to divide the analysis in three parts.

The first one assesses the activities and news in the relevant legal and ethical framework at an International, European, and National level.

The second part summarise the ethical, legal and social issues developments that occurred in GEN2PHEN related fields, that is to say projects presenting common points of interest with GEN2PHEN project.

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In the third part the scope of the analysis performed to GEN2PHEN closely related fields with a focus on specific ethical points of interest which are particularly relevant for GEN2PHEN and where the literature pointed out valuable developments.

Those focus points are Data on children, Publishing, locating and accessing research data, Biobanks, Direct to consumer genetic testing, What is new ELSI in genomics and possible relevant recent events.

On each of those issues the summary is only oriented towards GEN2PHEN relevant points of interests.

5. External ELSI Developments

5.1. News regarding the relevant ethical and legal framework

5.1.1. *International bioethical framework*

- ❖ Non binding international framework
 - WHO and WMA, the worldwide instruments

WHO: [First international standard for common genetic test, 2004.](#)


WHO: The World Health Organization published documents of interest for [guiding ethics committees](#) in analysing biomedical research projects as well as [guidelines for research](#).

WMA: The World Medical Association (WMA) has developed the [Declaration of Helsinki](#) 1964, amended in 2000, clarification notes 2002, 2004 and the last revision in October 2008 (Seoul). The World Medical Association [Declaration on Ethical Considerations Regarding Health Databases](#), Seoul, October 6th 2008.

This declaration proscribes the inhumane exploitation of individuals in research and protects autonomy through the process of obtaining consent. The principle of informed consent is largely recognised and considered a pillar in the practice of bioethics. Although it does not in itself protect a person, informed consent allows individuals to exercise their fundamental right to decide whether and how their body, body parts and associated data will be used in research.

The Declaration of Helsinki also applies to elements of the body (separated from the person). This Declaration is the first text that introduced the generally accepted notion of an external independent ethics committee to give an opinion about each biomedical research project prior to its start.

- OECD published in October 2009 its Recommendation on Human Biobanks and Genetic Research Databases, which aims to provide guidance for the establishment, governance,

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management, operation, access, use and discontinuation of human biobanks and genetic research databases. www.oecd.org/sti/biotechnology/hbgrd

This OECD Recommendation on Human Biobanks and Genetic Research Databases (“Recommendation”) aims to provide guidance for the establishment, governance, management, operation, access, use and discontinuation of human biobanks and genetic research databases (“HBGRD”), which are structured resources that can be used for the purpose of genetic research and which include: (a) human biological materials and/or information generated from the analysis of the same; and (b) extensive associated information. It is intended that this Recommendation be applied as broadly as possible.

This recommendation which is a non binding instrument is nevertheless fully relevant for the creation of the GEN2PHEN ethical and legal policy.

It is important to precise that this Recommendation, and the Guidelines (“Guidelines”) that it sets out, are intended to be evolutionary in nature and should be reviewed in light of relevant scientific and societal developments. Thus, there will be a need for the Recommendation and its Guidelines to be assessed, five years after adoption at the latest, and periodically thereafter, in order to ensure that it is fostering the desired objectives.

Those guidelines are constituted with 10 recommendations, starting with general elements and ending with discontinuation of the HBGRD and disposal of materials and data.

In this summary, the focus is on the elements directly relevant for the GEN2PHEN policy. Nevertheless, the website is indicated above in case of need of additional information.


As regards to general principles, it is important to highlight among other recommendations, that *the operators and users* of the HBGRD, should respect human rights and freedom and secure the protection of participants’ privacy and the confidentiality of data and information.

As regards to best practices, the operators should make available information on the scientific rationale underlying the HBGRD, and on the scientific and business uncertainties and risks associated with the establishment, operation and use of the HBGRD.

The establishment, governance, management, operation, access to, and use of the HBGRD and its protocols and processes for research activities, should be approved or reviewed, as applicable, by an independent research ethics committee. We find here again the duty to create an independent ethics oversight committee for GEN2PHEN, which will be competent for every stage of the project, getting data in, data storage and infrastructure and getting data out. It has to be decisional and not only consultative and supervise all the relevant activities that are taking place in the project. It is also important to emphasize the independent nature of the committee, when this committee will be created.

The operators of the HBGRD should take reasonable measures to avoid discrimination against or stigmatisation of a person, family or group, whether or not they have contributed to the HBGRD.

As regards to the establishment of HBGRDs, the operators of the HBGRD should make information publicly available in easily accessible form detailing its background, purpose, scope,

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ethical and governance framework, name(s) of senior management, answers to frequently asked questions (FAQs) as well as contact information of a representative who will answer questions from the public. This recommendation joins the proposal made in GEN2PHEN policy, regarding the fact that the ethics policy framework which will include statement must appear on the web site, visible to anyone.

It is also important to note that the guidelines envisage that where the operators of the HBGRD foresee attracting private investment or entering in commercial collaborations, this should be clearly articulated and communicated before such collaborations have been established, especially to participants.

This must also be clear in the GEN2PHEN policy.

Regarding the governance, management and oversight, and in the principles it is reminded that the governance structure should be designed to ensure that the rights and well-being of the participants prevail over the research interests of the operators and users of the HBGRD.

Also, the operators of the HBGRD should have in place oversight mechanisms to ensure that the governance, management, operation, access to, use of and discontinuation of the HBGRD comply with legal requirements and ethical principles. This is going to be in the hand of the GEN2PHEN oversight ethics committee as we have developed it in the policy. In the best practices part, it is specified that this control procedure must be especially done in the case where human biological materials or data are to be used in a manner not anticipated in the original informed consent process including:

for previously collected human biological materials or data where the use might deviate from the original consent;

for cases where informed consent may not have been obtained at the time of collection;


for determining when to seek re-consent;

for use of human biological materials or data where consent was obtained using a broader or layered format for uses unspecified at the time of collection, especially in the case of large-scale genetic epidemiology studies.

As regards to the terms of participation, in the 4.B paragraph it is recommended that prior, free and informed consent should be obtained from each participant. The HBGRD may provide for obtaining consent/authorisation from an appropriate substitute decision-maker, or for obtaining waiver of consent from a research ethics committee or an appropriate authority, in accordance with applicable law and ethical principles pertaining to the protection of human subjects. This recommendation is already what has been envisaged in the GEN2PHEN ethical policy and so the policy is in compliance with the guidelines. The issue of vulnerable participants is treated in the same terms than the GEN2PHEN policy as it refers to authorisations and protection in accordance with law and ethical principles. As regards to minors, the operators of HBGRDs involving participants who are minors should have a clearly articulated policy on whether, when and how the minor's assent will be obtained, in accordance with applicable law and ethical principles.

Law and ethical principles have been discussed in the literature seen above.

As regard to re-contact, it is recommended to envisage a clear articulated policy.

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The best practices that follow describe all the information that have to be delivered to the participants and contained in the information sheet prior obtaining consent.

As regard to the content of the HGBRDs, it can be highlighted that the recommendation states that the operators of the HBGRD should have a clearly articulated policy of whether data will be accessed from health or other records, and/or be independently assembled, and whether or not these data will be linked with or stored in the HBGRD. GEN2PHEN must define a clear policy if it is gathering information coming from health or other records at the “getting data in” stage.


The best practices part indicates among other best practices that it must happen through a participant’s information.

Regarding the protection of human biological material and data, GEN2PHEN has already approached those enounced principles and is in compliance with it, except the question of the duration of the duration of storage of data. This guideline recommends that the operators of the HBGRD should have a clearly articulated policy on the duration of storage of human biological materials and data. It has to be done for GEN2PHEN.

Regarding access, the principle enounces that access to human biological materials and data should be based on objective and clearly articulated criteria, and should be consistent with the participants’ informed consent. This statement joins the GEN2PHEN ethics policy where it is stated that the divide between completely open access data and those with controlled access will have to be done with explicit rules. And as the GEN2PHEN ethical policy envisaged it, researchers should only have access to data that are coded or anonymised, in such a way that the participant cannot be identified, and researchers should be required to not attempt to re-identify participants. However, under exceptional conditions, researchers may be provided with access to human biological materials or data that are not coded or anonymised. In the best practices it is indicated that the terms of access for researchers to the whole or a part of the database(s) of the HBGRD should be set out in an access agreement. Users of data should sign confidentiality agreements when access pertains to data that are not publicly available. This statement could be taken and use for GEN2PHEN.

Regarding Custodianship, benefit sharing and intellectual property, this part refers to the database and infrastructure part in GEN2PHEN. As it is said in these guidelines, a database tool intellectual property management must be described, as well as a clear policy on benefit sharing. In the best practices part it is said that this policy should address, inter alia, whether tests or products arising from research using its resources might be shared with the community and/or the general population, and how such sharing will be effected. This OECD guidelines also refers to the fact that a summary results arising from research conducted using the HBGRD’s resources should be made available in easily accessible forms, such as through a newsletter or website. We can highlight here that the important part is to give back information the way this is achieved remains in the hand of each project. And so it is to the GEN2PHEN consortium to decide which way is the most appropriate to give feedback.

Regarding Discontinuation of the HBGRD and disposal of materials and data, it is necessary that GEN2PHEN also define a policy related to that issue. It could be inspired by those

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principles, the operators of the HBGRD should plan for its possible discontinuation and should have a suitably detailed policy setting out the manner in which the human biological materials and data that it holds will be dealt with in the event of its discontinuation.

Where an HBGRD of scientific value can no longer be supported by its current operators, efforts should be made to transfer the human biological materials and data to another HBGRD or another entity.

Once an HBGRD is no longer required or is no longer of scientific value and it has been determined that it will be discontinued, the human biological materials should be disposed of in an appropriate manner, consistent with the principles of consent, privacy and confidentiality.

Also it is appropriate to remind the OECD recommendations already existing and relevant for the GEN2PHEN project.

OECD recommendations on quality assurance in Molecular genetic testing, adopted by the OECD council in 2007, sets out inter alia, a number of principles and best practices for governments, professionals bodies, and providers of molecular genetic testing.

OECD recommendations on the Licensing of genetic inventions, adopted by the OECD Council in 2006, provides guidance on licensing, transferring agreements, and joint developments activities in regards to genetic inventions.

OECD Best Practice Guidelines for Biological Resource Centres set out further complementary quality assurance and technical aspects for the acquisition, maintenance and provision of high quality biological materials and associated data in a secure manner.


5.1.2. European Bioethical framework

- ❖ European Union News
 - Conference on ethics, biometry politics, and international data sharing, 4 and 5, of January 2010, Hong Kong, China. Organised by RISE Project («Rising pan-European and international awareness of biometrics and security ethics») funded by the European Union and gathering nine European institutions, United States, China and India.

This conference is on research, ethics, biometry politics, and data sharing. Biometry uses are well extended and concerns raises in terms of ethics, private life, and political implications of biometry.

- Newsletter, Ethically speaking n°12, august 2009-12-03

This newsletter is providing information on the activities on the National Ethics Committees compiled by the European group on Ethics of Science and New technologies secretariat and relevant services to the European Commission. A chapter was dedicated to the conditions for the proper working of national and international ethics committees. The establishment of a GEN2PHEN oversight ethics committee, its organisation and abilities could be inspired by the features described. Indeed people having served on regional, national, and international ethics committees over a long period of time have realized that these committees have a number of

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general features in common which are important in terms of their ability to function properly. According to this article function properly means describing the problems/issues described concisely and clearly, providing relevant scientific, legal, and social information in an unbiased and fair way, and proposing recommendations supported by sound arguments, while at the same time maintaining credibility, being open about dissent, and differences of views in the committee and avoiding being manipulated or used for political ends. The article adds that needless to say that, the list below makes no claim to completeness, and the emphasis placed on some of the factors may vary according to the types of ethics committees.

The first one is **transparency**, about composition, methods of selecting members and chairpersons and the term of reference of the committee. Who decides what the committee discusses, its working methods and the rules of procedure of the group, including the possibility to express and record dissent, and so forth...

Time for deliberation is essential. The state of the art in the relevant sciences must be described, the legal background clarified, and the relevant value premises identified. If there are dissenting views within the group, it is essential to allow time to clarify the reasons for the dissent.

Tolerance for different views and mutual respect are two other important features of ethics committees.

Explicitness, The knowledge basis has to be explicit and unambiguous, and this also holds true for information about the legal and social background, where relevant. It is very important that uncertainties, knowledge gaps and value instability are not covered up or swept under the carpet.


Integrity, it refers to the idea that scientific work should be carried out according to its own logic and methodological rules.

Personal interests and prestige, religious persuasions, and economic and political interests should not be allowed to interfere with this process, particularly when it comes to testing hypotheses, interpreting and drawing conclusions from the results of the research – or deciding whether or not the results should be published. Similar concerns about integrity are relevant when it comes to the work of ethics committees

Independence. It ranges from economic independence (the committee is able to decide for itself about how to use its funds) to independence in terms of deciding which topics to work on, choosing between alternative working methods and rules of procedure, deciding which experts to invite, and in particular – this goes without saying – adopting its conclusions.

Interdisciplinary nature. This is essential in order to avoid a one-sided perspective or the risk of overlooking important aspects of the problem. Interdisciplinary composition of the committee is essential to ensuring that relevant background information and perspectives are not missed. Different scientific, legal and cultural backgrounds are vital in this context, including as a way to avoid the predominance of particular scientific views in the work of the committee.

The experiences of several professions, genders and age groups are vital too. Obviously, if the size of the committee is to be manageable, not all disciplines and experiences can be represented.

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However, the committee's remit should be wide enough for it to be able to recognize when it needs to invite additional experts.

Interaction with the general public is also important. Translated to GEN2PHEN project it would be interaction with the participants, data providers, donor's, scientific community, users...

- ❖ Council of Europe, Steering committee on bioethics (CDBI), News

The CDBI is preparing a reconsideration of the recommendation on use of biological samples for research and biological samples in biobanks.

- Bioethics division of the Council of Europe is celebrating this year the 10th anniversary of the OVIEDO Convention (Convention on human rights and biomedicine).

Related to that, the council of Europe organised one regional conference on the impact of the Oviedo convention in central and eastern European countries and a one day workshop in Athens on the occasion of the 10th anniversary of the Oviedo Convention.


On May 2009, the Council of Europe also organised a debate on the ethical issues raised by genetic testing with young people. It had been told that development in biology and medicine raise concerns with regard to the protection of human dignity and fundamental rights and freedom. To that end through the steering committee on bioethics (CDBI) the council of Europe works at defining principles and establishing legal standards which would be applicable in its member states. A substantial set of legal instruments has already been adopted and serves as a reference point in the field of bioethics at international level. The Convention on Human Rights and Biomedicine (the Oviedo Convention), the first international legally binding instrument in that field, provides a framework for the protection of human rights and human dignity by establishing fundamental principles applicable to daily medicine as well as to new technologies in the fields of biology and medicine. Additional protocols to the Convention develop these principles in greater detail in specific fields such as cloning, transplantation of organs and tissues of human origin, biomedical research and genetic testing for health purposes.

The CDBI is currently focusing its work on predictivity and genetic testing in the field of insurance with a view to elaborating a new legal instrument. Furthermore, in the field of biomedical research, a group of specialists is preparing a guide intended to members of research ethics committees. This tool will aim at explaining in practical terms the principles laid down in the relevant European legal instruments and will offer methods for their implementation.

- Educational tool on bioethical issues: an initiative of the Council of Europe

The Council of Europe – an organisation composed of 47 European states has been studying ethical problems raised by the developments in biology and medicine for a number of years. In developing an educational tool, the Council of Europe aims at providing support to teachers and professors wishing to address and discuss with their students (from 10th to 12th grade) bioethical questions.

- ❖ European Group on Ethics in Science and New Technologies (EGE) News

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The Group is a neutral, independent, pluralist and multidisciplinary body, composed of fifteen experts appointed by the Commission for their expertise and personal qualities. It will be re-appointed in 2010.

On November 17, 2009 the European Group on Ethics of science and new technologies (EGE) adopted their Opinion n° 25 on the ethics of synthetic biology.


Synthetic biology is a new research field within which scientists and engineers seek to modify existing organisms by designing and synthesising artificial genes or proteins, metabolic or developmental pathways and complete biological systems in order to understand the basic molecular mechanisms of biological organisms and to perform new and useful functions. Synthetic biology might have an impact on the following sectors: biofuels, antipollutants, textiles, cosmetics, diagnostic and therapeutic tools, vaccines, drugs food and feed ingredients.

In its Opinion the EGE identifies and addresses ethical concerns particularly but not exclusively from the point of view of safety and security. Beyond this, the ethical reflection addresses justice, governance, science and society dialogue, intellectual property and concepts of life. As for other new technologies, synthetic biology must respect the international framework on ethics and human rights and in particular the respect for human dignity, which is conceived as not only a fundamental right in itself but ‘the real basis of fundamental rights’. Other ethics principles that have to also be taken into account include, inter alia, the principles of safety; sustainability, justice, precaution, freedom of research and proportionality.

5.1.3. National Bioethical Framework

- Belgium has adopted its Law on the Procurement and Use of Human Bodily Material for Human Medical Applications or for Scientific Research.
- The Swiss federal authorities recently published a Draft Law Pertaining to Research on Human Subjects.
- In Germany there was no law regulating genetic testing. After 10 years of debate the German parliament has passed a strict law aimed at preventing misuse of genetic tests. [EuroGentest](#) has recently posted an unofficial English translation of the recently passed and soon to be enacted German legislation, the *Human genetic examination act (Genetic diagnosis act - GenDG)* [[PDF - 162 KB](#)]. The new law addresses genetic examinations (including consent, duty to inform, counselling, and disclosure), genetic testing and insurance contracts, workplace issues (including discrimination), and criminal penalties (prison time, in some circumstances, and fines of up to EURO 300,000).
- In France, Ministère de la Santé et des sports: Arrêté du 23 juin 2009 fixant les règles de bonnes pratiques en matière de dépistage et de diagnostic prénatals avec utilisation des marqueurs sériques maternels de la trisomie 21 Paris - June 23, 2009.
- Review of the Bioethics law for 2010 in France.

Since September 2008 lots of debates and consultation took place in France in order to prepare the 2004 Bioethics Law revision for 2010.

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What is relevant for GEN2PHEN is the regulation related to the utilisation of human biological samples and in a context of a biobank and inter alia genetic testing regulation that is part of this law. The corresponding parliamentary commission has performed numerous expert consultations on this topic in the second part of 2009 (all interviews are publicly available on the internet).

The debate concerns further uses of human body product for clinical or research purposes different from the originally collected aim. The bioethical law of 2004 requires a non- opposition procedure.

However this is not applicable for genetic testing where an enlightened consent is required. The French parliamentary office requires a clarification of this disposition and tends to admit a consent presumption, or ask authorisation via delegation questions. This question is still controversial.

As regards to genetic characteristic examination a debate exists on the forensic utilisations but it is not relevant for GEN2PHEN. Regarding the uses of genetic data in the clinical frame, and specifically in case of serious genetic disease the way information of the relatives is done and the responsibility of patients and doctors still controversial.

5.2. Relevant ELSI developments in other projects


5.2.1. *The Public Population Project: P3G*

The Public Population Project in Genomics (P³G) is a not-for-profit international consortium that provides the international population genomics community with easy access to the expertise, resources, innovative tools and most up-to-date information from all areas of public population genomics.

The Public Population Project in Genomics (P³G) is an international consortium dedicated to the development and management of a multi-disciplinary infrastructure that can compare and merge results from population-based genomic studies conducted around the world. Through its tools, support and network, P³G can help the international research community to consider more effective health care strategies aimed at disease prevention, and tailoring medicines and other treatment regimens for individuals, families and communities. A formal MOU between GEN2PHEN and P3G has been acted.

- P3G, BBMRI and PHOEBE combined efforts and resources to create a major event in the field of biobanking entitled “Harmonised Biobank Research: Maximising value Maximising Use” in Brussel, March 25-27, 2009, Chaired by Jennifer Harris.

The event brought together 250 key experts from the international biobanking community and demonstrated the benefits of combining efforts and leadership in the field of population-based biobanks. Lots of debate took place around the data-sharing issue. Indeed with the advent of increasingly powerful data collection tools, analytic techniques and results, the research is forced to reconsider the ethical and legal boundaries drawn from an earlier era that could not have anticipated the issues of today. The report of this conference is available on the PHOEBE

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website

(http://www.populationbiobanks.org/eway/default.aspx?pid=271&trg=Content:_5687&Content:_5687=5717:17383::0:5697:1:::0:0) .

- P3G annual meeting will be led in Montreal on April 26-27 2010
- Genome Canada International Conference, April 28-30, 2010.
- P3G –Wellcome Trust Biobank Summer School. Took place in July, 1-5th, 2009. This summer school was set up to address in practical terms the scientific, legal and ethical challenges in setting up and maintaining a biobank and the tool available to meet those challenges.

A project on data sharing in genomics (ELSI issues), (financed by the Core Financing program of P3G) is ongoing and mostly investigated by Dr. Jane Kaye, Wellcome trust research fellow, who recently set up a new centre in University of Oxford (HeLEX - Centre for Health, Law and Emerging Technologies at Oxford).

The project explores the ethical legal and social issues surrounding data sharing between biobanks. Their particular interest is the use of GWAS and moving to next generation sequencing, and the twist that the use of those methodologies gives to perennial issues such as feedbacks.

The issues they will explore are among others consent for data sharing, whether to give feedbacks on incidental findings, the tension between data sharing and IP protection and how we develop appropriate structures and partnerships for translation.

They will organize an international conference in Oxford in June 2010 which will focus on Data Sharing in Genomics.


It might be interesting for GEN2PHEN consortium to continue thinking about this very important and evolving issue and to decide whether the data coming into the project and generated through it will be publicly shared and under which conditions. If data sharing is envisaged by the funders, there is a need to consider ethical tools to guarantee the rights of participants and data providers, participants in terms of fundamental rights (autonomy, privacy...) and data providers in terms of intellectual property rights. Participation to this Conference from the project members might be appropriate.

5.2.2. Report on UK National DNA database from the Human Genetics Commission

The independent UK government advisory body the [Human Genetics Commission \(HGC\)](#) has released a new report on the controversial National DNA database in 2009-12-15.

The idea is to set out proposals for tighter regulation and oversight for the forensic national DNA database.

Although it relies on general principles, this report is not completely relevant for GEN2PHEN in its details, as it refers to forensic database.

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5.2.3. *The UK biobank cancer facility onCore Uk is to cease active biobanking.*

In a public statement explaining the decision, onCore biobank explained that “ a standardised national approach has been difficult to achieve” for biosamples collections and that the “needs for biobanking can be effectively fulfilled by local biobank activity”.

5.3. Relevant ELSI developments in the literature:

In this part the scope of the analysis was extended to GEN2PHEN closely related fields and focused on specific ethical points of interest which are particularly relevant for GEN2PHEN and where the literature pointed out valuable developments.

On each of those issues the summary is only oriented towards GEN2PHEN relevant points of interests.

5.3.1. *Data on children.*

The main issues raised by research on data from minors are related to consent and confidentiality and to follow up over time. Indeed some of the data coming into the GEN2PHEN project can originally be collected on minors.


- “Biological sample collections from minors for genetic research: the call for a reflection on policy and ethical issues” 2009, 08

[Hens K, Nys H, Cassiman JJ, Dierickx K.](#), Am J Med Genet A. 2009 Oct;149A(10):2346-58; see also Eur J Hum Genet. 2009 Aug;17(8):979-90.;

http://www.ncbi.nlm.nih.gov/sites/entrez?cmd=Retrieve&db=%20pubmed&dopt=AbstractPlus&list_uids=19223929

Genetic research on biological material from minors can yield valuable information on the development and genesis of early-onset genetic disorders and the early interaction of environmental and genetic factors. Stored tissue samples are an important resource for epidemiological genetic research. However, the use of such tissue raises some specific ethical and governance questions, which are not completely covered by the discussion on biological materials from adults. The authors of an article appeared in the /European Journal of Human Genetics/ gathered 29 guidelines and position papers pertaining to the storage and use of biological tissue samples for genetic research, originating from 27 different organisations. Five of these documents have an international scope, three have a European scope and 21 have a national scope. Eleven of the documents did not contain a section on biological materials from minors. The content of the remaining 18 documents was categorised according to four themes: consent, principles of non-therapeutic research on vulnerable populations, ethics committee approval and difference between anonymous and identifiable samples.

While these themes are not consistently mentioned in each document, those papers that do discuss the same themes were mostly in agreement in their recommendations. However, the

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authors conclude that a systematic reflection on the ethical and policy issues arising from the participation of minors in biobank research is lacking.”

In this article the issues are mainly directed to biobanks but a transposition to GEN2PHEN issues is relevant. This article is wondering about, who should give consent and is the general requirement that non-therapeutic research can only be done with children if it involves no more than minimal risk applicable to biobank research?

As regard to consent:

Who should give consent? Most of the time in guidelines and opinion which are non binding it is the legal representative or parents, UNESCO in 2003 states the legal representative should have regard to the best interest of the person concerned. Some guidelines also discuss the issue of child’s assent (permission) or dissent (refusal), and the article mention that most of documents agreed that when appropriate the child should be consulted and their agreement should be obtained, CIOM’s makes a distinction between the deliberate objection of an older child and the behaviour of an infant who is likely to cry or withdraw in response to any stimulus”.


When the minor should be re-contacted to give full consent? Two guidelines mention when they are old enough to understand or comprehend, or when they are capable of discernment CIOM’s mention that research subject become capable of giving independent informed consent during the research, their consent to continue participation should be obtained”. They do not specify whether they mean a legal age or a level of maturity.

It is fruitful to look at the United Nations Convention on the Rights of the Child, that asserts that children have a right to say what they think should happen when adults make decisions that affect them (Article 12) and have the right to get and share information (Article 13). As this is a legally binding document for most countries, it makes sense that in longitudinal genetic research, small children are also given appropriate information and their opinions are taken into account.

Another aspect of the scope of consent is the question of content of the consent. Are parents allowed to consent to any future genetic research on their children’s DNA? This is called broad consent. Or can they only give specific consent to research on specific genes and diseases? Most biobanks have as an aim the accommodation of future research, the nature of which is undetermined at the moment of storage. Hansson has argued that broad consent at the time of storage is sufficient to keep the data available for research for a long period of time. In the case of children, however, it is not the donor self who has consented and it may seem fair to restrict proxy consent only to specific research protocols or research on certain genes or diseases.”

- Regulating trust in pediatric clinical trials. [Pinxten W](#), [Nys H](#), [Dierickx K](#). Med Health Care Philos. 2008 Dec;11(4):439-44; see also Eur J Pediatr. 2009 Oct;168(10):1225-34 and Am J Bioeth. 2009 Jan;9(1):21-3

In this article, the same questions of parent permission and child assent are studied.

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It is interesting because it specifies that assent from the child can only be sought after obtaining parental permission and must be obtained before the child's enrolment into the study.

Here again the article mention that there is a considerable debate about the minimum age at which assent should be sought from a child: When does a child knows what it means to be part of research? Is the child aware of the right to withdraw? Is the child able to understand the described study?


The American Academy of Pediatrics ([American Academy of Pediatrics, Committee on Drugs, 1995](#)) suggests that children with an intellectual age of 7 years or older are competent to understand research participation. Although some IRBs require assent of children 10 years and older, the AAP states that children 7 years of age or older should be given the opportunity to refuse participation in research and that their refusal should be respected ([Burns, 2003](#) and [Lewin & Dale, 2003](#)). However, it is not surprising that children's understanding of what research involvement really means increases dramatically after the age of 11 years ([Tait, Voepel-Lewis, & Malviya, 2003](#)).

- Children and population biobanks. David Gurwitz, Isabel Fortier, Jeantine E. Lunshof, Bartha Maria Knoppers. Science, 14 august 2009 Vol. 325. no. 5942, pp. 818 - 819 <http://www.sciencemag.org.gate2.inist.fr/cgi/content/full/325/5942/818> and Comment in:
 - [Science. 2009 Nov 6;326\(5954\):797; author reply 799.](#)
 - [Science. 2009 Nov 6;326\(5954\):798-9; author reply 799.](#)
 - [Science. 2009 Nov 6;326\(5954\):798; author reply 799.](#)

This article in proposing solutions for data coming from minors has been the object of lots of debates.

First the authors remind the state of the art, saying that population biobanks, which store and distribute human DNA, cell lines and tissue samples collected from large cohorts are being established and are growing in size, and that many of these biobanks collect samples and data from children, often along with their parents. Then this article highlights that children are vulnerable research population in the sense that they lack the capacity to consenting for their participation. They are different from the other vulnerable population, as their vulnerability is temporary and does not arise from a disorder. The controversial point arises with the proposals.

This article makes a distinction between disease specific biobank and population biobank as the balancing of potential harm and benefits is fundamentally different from disease specific biobank to voluntary participation in population research. They propose that for disease specific biobank, one should continue to collect and share children DNA samples and data within the limits authorised by parents, and that ideally the affected children themselves should be recontacted once they reach the age of consent or maturity to allow continued research on their samples and data. They propose a revision on the policies related to population biobank. Indeed, they propose that population biobank continue to collect, store, analyse children's DNA and phenotypic data with the appropriate authorisation by parents or guardians, but that they may not make these

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DNA samples accessible outside the biobank until donors are recontacted as adults and give their own informed consent. Paediatric population biobanks could publish and give access to aggregated phenotypic data and results, including from genetic studies, in order to advance paediatric research. Individual DNA sequence should not be released. The authors recognise that their proposal are provocative but they base their opinion on the long term benefit of maintaining public trust in biomedical research by waiting for participating children to consent as adults and justifying extra governance efforts and added costs.

- Ethical principles and legal requirements for pediatric research in the EU: an analysis of the European normative and legal framework surrounding pediatric clinical trials. [Pinxten W, Dierickx K, Nys H](#). Eur J Pediatr. 2009, Oct
- European survey on ethical and legal framework of clinical trials in paediatrics: results and perspectives. [Altavilla A, Giaquinto C, Ceci A](#).

Given this important literature and interrogations, a clear statement on how to deal with children data must be include in GEN2PHEN ethics policy.

5.3.2. Publishing, locating and accessing research data

- To share or not to share publishing research data: Report from the RIN. 2008.

The Research Information Network (www.rin.ac.uk) was set up in 2005 and is funded by a consortium made up of the four UK Funding Councils, the seven Research Councils and the three National Libraries. Its fundamental role is to undertake evidence-based research into information and data issues that relate to professional researchers – and particularly academic researchers – and to develop policy, guidance and advocacy on that basis. The report is available at www.rin.ac.uk/our-work/data-management-and-curation/share-or-not-share-r...


This report can be used as an introduction to the issues related to the sharing of published research data. This issue is relevant for GEN2PHEN as it has to decide how the information will be shared and disseminated.

The constraints are as significant as the opportunities when it comes to publishing, locating and accessing research data, according to a new report from the RIN.

- Public access to genome-wide data: five views on balancing research with privacy and protection. [P3G Consortium, Church G, Heeney C, Hawkins N, de Vries J, Boddington P, Kaye J, Bobrow M, Weir B](#). PLoS Genet. 2009 Oct;5(10):e1000665. Epub 2009 Oct 2

This article deals with public access to genome wide data. As regard to this concern five viewpoints are presented.

The public population genomics(P3G) is calling for a universal researcher ID with an access permit mechanism for bona fide researchers, as it is also an issue developed in GEN2PHEN (see

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the specific forum discussion and GEN2PHEN meeting report on the knowledge center, of the Meeting held also in Toronto in May 2009 on Research ID).

The contribution by Catherine Heeney and others outlines some of the concerns over possible misuse of individual identification in conjunction with medical and family history data, and points out that if geneticists mishandle public trust, it will backfire on their ability to conduct further research. Georges Church poses that actions directed toward restricting data access are likely to exclude researchers who might provide the most novel insights into the data and instead makes the argument that full disclosure and consent to the release of genomic information should be sought from study participants, rather than making difficult to guarantee promises of anonymity. Martin Brobow weighs the risk and benefits and proposes four steps that represent a middle ground: retain restricted access for now, makes malicious de-identification practices illegal, increase public awareness of this issue, and encourage recognition that scientists have a special professional relationship of trust with study participants. Finally Bruce Wair, provides a commentary on the contribution of the two research articles from Braun et Al. and Vissher and Hill.

To conclude this article presents that what is essential is to get to the balance of privacy protection and open, honest, and uniform consent right, and they hope that this short article will encourage greater participation in the debate and education surrounding the issues.


- Prepublication data sharing, Nature. 2009 Sep 10;461(7261):168-70.

This article deals with the rapid release of prepublication data which has served the field of genomics well and conducted the Genome Canada and others funding agencies including the European Commission, to set up a data release workshop in Toronto, May 2009. This workshop aimed to reaffirm and refine, where needed, the policies related to the early release of genomic data (based on the HGP meeting held in Bermuda in 1996) and to extend, if possible, similar data release policies to other types of large biological data sets, whether from proteomics, biobanking or metabolite research.

New issues that were addressed include the importance of simultaneously releasing meta data that will enable users to fully exploit the data, as well as the complexities associated with clinical data, because of concerns about privacy and confidentiality.

At a practical level, The Toronto Meeting developed a set of suggested best practices for funding agencies, for scientists in their different roles (whether as data producers, data analysts/users, and manuscripts reviewers) and for Journal editors.

We can highlight that in the Toronto Statement, it is established that the data producer must ensure that research participants are informed that their data will be shared with other scientists in the research community. As regards to data users, data producers had to inform them about the data being generated, data standards and quality, planned analyses, timelines, and relevant contact information, ideally through publication of a citable marker paper near the start of the project or by provision of a citable URL project or funding agency website.

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As regards recommendations to data analysts and users, the statement says that they have to ensure that use of data does not harm research participants and is in conformity with ethical approvals.

- Post publication sharing of data and tools. Nature 2009, September,10

This article reports the efforts of one such community to address issues of particular relevance to the free sharing of data and resources for mouse biology, genetics, and functional genomics. The main issues are the barriers created by material transfer agreements and the underutilization of public mouse repositories.

A meeting of mouse researchers in Rome proposes ways to promote a culture of sharing. The Rome agenda described and summarized in this article represents a challenge to stakeholders to coordinate their efforts to facilitate the ready exchange of data and resources and to share good practices already implemented by some organizations and journals.

Five issues have been studied and recommendations established: access to data and materials, licensing and patenting, data and resource-sharing infrastructure, standards and tool development, attribution and reward.


The Rome meeting strongly encourages sharing behaviours that promote a research commons which is when academic research is not impeded by restrictions on use and access to data and materials, in line with the principles of the Creative Commons.

- Data sharing in genomics re-shaping scientific practice. Nat Rev Genet. 2009 May;10(5):331-5.

This article is highly relevant for GEN2PHEN issues concerning data sharing and the protection of the participants to research.

Indeed, This paper discusses four areas, the difficulties of acknowledging individual contributions; the generation of data and the way these data sharing structures change the responsibilities of researchers towards participants; the implication that these policies have for maintaining public trust; and the new mechanisms that that have been developed to oversight of access of data.

Open access to data is believed to accelerate advances in science, by making data freely available to all while ensuring the expedient use of existing resources that have been funded by public funds. The main point of interest regarding ethical and legal issues is the one of responsibilities towards study participants. Indeed this paper highlights that in the original context where the samples and data are collected there are expectations from both researchers and participants that often extend beyond the original terms of consent. This responsibility may not be felt by the secondary researchers who have no connection with the research participants and see themselves as only dealing with data. Although secondary researchers have an obligation to use the data in a scientifically sound, ethical and lawful manner, these obligations are not the same as for the researchers enrolling patients in a study. Researchers have a responsibility for their samples and

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feel a legal and moral responsibility towards research participants that often extends informed consent forms which try to be succinct, may not embody all of the expectations that are associated with enrolment in a study and an ongoing clinical relationship, and may leave room for differing interpretations of the scope of consent.

It is also very important to say that the mechanisms that have traditionally been used to protect research participants are informed consent and anonymization of data sets. However, the sharing of data from genomic studies challenges the effectiveness of these standards mechanisms of privacy protection. Thus, The Wellcome trust and the NIH decided in the fall of 2008 to remove SNP data from publicly accessible databases, following the above cited paper by Homer et al.

To conclude this paper says that in this new context of global data sharing, better methods of informing participants about the use of their personal information for different research purposes need to be developed.

5.3.3. *Biobanks*


- The CDBI agreed to organise a Seminar on Biobanks in 2011 with a view of re-examination of the Recommendation (2006) 4 on research use of biological materials of human origin.
- OECD published in October its Recommendation on Human Biobanks and Genetic Research Databases, which aims to provide guidance for the establishment, governance, management, operation, access, use and discontinuation of human biobanks and genetic research databases. www.oecd.org/sti/biotechnology/hbgrd (see above)
- European Symposium on Biobanks: From Biobanks to Experts Centres, December 16th 2009, Paris.

The topics discussed were perspective for biobanking, experience and unmet needs of industry partners, experience and unmet needs of academic partners, scientific and technical expertise required for the future, intellectual property and ethical and regulatory issues and eventually panel discussion: perimeter of expert centres, facilities and expertises they could provide.

5.3.4. *Direct to consumer genetic testing*

As already underlined in the deliverable D1.3, the latest developments within Europe is the Additional Protocol on Genetic Testing for health purposes, where some principles could be applicable to research, which has been passed by the Council of ministers of the Council of Europe. It will be the first European legal instruments in this area and had been open for signature in November 2008. At the present time only 4 members signed but it wasn't followed by ratification. Slovenia is the only country which has ratified this protocol.

It will apply to all genetic tests whether they are provided publicly or privately and it requires that the clinical utility of genetic test must be determined before deciding to offer this test to a person or a group of persons and that all genetic testing must be accompanied by genetic counselling that is appropriate to the individual.

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- Problems in the Regulation of Genetic Tests in Japan: What Can We Learn from Direct-to-Consumer Genetic Tests? Watanabe M, Ohata T, Muto K, Takada F. Public health genomics, 2009

The key issue is how to regulate the quality of genetic testing. Indeed, genetic testing can be provided without supervision of medical professionals. While medical geneticists have publicly criticized DTC genetic testing, a group of industries have established self regulatory guidelines on the quality control of genetic analyses, based on OCDE guidelines.

- The regulation of direct-to-consumer genetic tests. Jane Kaye. Human molecular genetics. Hum Mol Genet. 2008 Oct 15;17(R2):R180-3. Review.

This article deals with issues related to the emergence of several companies offering tests using genome wide technology direct to consumers over the internet.

On the basis of published research findings of GWAS and other studies, these companies will calculate an individual's risk to a number of common diseases, outside the health system and the results are provided without involving a visit to a practitioner.

One of the significant challenges of direct to consumer genetic testing is that it shifts the control of genetic testing from the clinical domain and medical professionals into the hands of consumers. Direct to consumer testing challenges many of the assumptions that underpin current practice surrounding genetic tests while at the same time exposing the current regulatory frameworks to regulate this area.


Jane Kaye highlights that the reason why such companies can market genetic tests in such a way is that there are only few regulatory controls in place at national, European or global levels to first assess the clinical validity of tests before they get to market or secondly to control marketing to the public.

- A common framework of principles for direct-to-consumer genetic testing services. Principles and Consultation question. Human Genetics Commission (HGC)

In this study, HGC is seeking views on a common framework of principles for direct-to-consumer genetic testing services which will promote high standards and consistency in the provision of direct-to-consumer genetic tests amongst commercial providers at an international and national level in order to protect the interests of people seeking genetic test and their families.

This principles covers all aspects all genetic tests, including the marketing and advertising of services, the collection, analysis and storage of biological samples the interpretation of results and the provision of results to the consumer.

The HGC is not a regulatory body. It hopes that these Principles will lead to the development of codes of practice that take account of existing regulatory structures where the need for additional regulation or legislation is revealed to be necessary. These Principles are intended to cover all

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situations in which it is possible for a private consumer to purchase a genetic test without prescription by a qualified medical professional subject to statutory regulation.

Those principles apply for marketing and advertising and recommends that the test provider should comply with any legislation or voluntary codes for advertising medical tests including genetic tests. Those recommendations also deals with regulatory information and information for prospective consumers, indeed the test provider should supply easily understood, accurate, appropriate and adequate information to consumers before obtaining consent for a genetic test. Eleven precisions explain in detail the level of information.

Regarding consent the report recommends that the test provider should give consideration, not only to the nature of the test and the information that it generates, but also to the personal and familial circumstances of the consumer. A genetic test should only be carried out after the person concerned has given free and informed consent.

Informed consent can only be provided when a consumer has received sufficient relevant information about the genetic test to enable them to understand the risks, benefits, limitations and implications of the genetic test.

There is also a disposition about data protection. Indeed genetic information is sensitive personal data and requires the highest level of security and confidentiality.

The test provider and laboratories should not release biological samples or records containing personal data and genetic information that can be linked to an identifiable person to any third party without the prior consent of the person to whom they relate.

Eventually the report considers samples handling, laboratory processes, interpretation of test results (which should be carried out under the responsibility of an appropriately qualified professional), and provision of results, continuing support, and complaints.


- The Icelandic company deCODE has filed for bankruptcy.

It raises questions about ownership of their genetic databases.

The deCODE database is a highly valued resource amongst researchers, since it is unique in the extent of its coverage of a highly genetically homogenous population; the resource is thought to include the anonymised DNA samples and linked medical records of around 140,000 of Iceland's total population of 320,000...

deCODE reportedly plans to sell most of its assets to the US venture capitalists Saga Investments; the data and samples in the database will not be included in the sale

However, as the bioethics website [Genomics Law Report](#) points out in its [analysis](#) of the case, whoever the new management of the database is, they will presumably aim to do all they can to maximise profits from the resource, and “*within the range of allowable uses... deCODE's new owner may choose to change or even expand its use of that information*”. The precise range of what those uses are could well end up being decided in court.

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5.3.5. What is new ELSI in genomics

- What is new ELSI in genomics is a law report, fall 2009.

From October 5 to December 8, 2009, the Genomics Law Report featured a series of thirty-six guest commentaries by industry, academic and thought leaders in the fields of genomics and personalized medicine. Entitled What ELSI is New?, the series asked each contributor to briefly respond to the following question: “What do you believe is the most important ethical, legal or social issue (ELSI) that must be addressed by the fields of genomics and/or personalized medicine?”

The methodology adopted here is to present ELSI that are the most relevant for GEN2PHEN. Nevertheless you may find further information on: <http://www.genomicslawreport.com/wp-content/uploads/2009/12/ELSI-eBook.pdf>

We can also highlight that most of the ELSI developed in this text are dealing with the rapid release of genetic information and the concerns often center around topics such as privacy, access to genetic information and re-contacting, uses of this information.

The first ELSI is: To Share or not to Share, that is the question and it was contributed by Catherine A. McCarty, Marshfield Clinic Research Foundation.

According to her the most important ELSI is return of genetics results to research participants. Indeed the era of candidate gene and early genome-wide association studies and the genotyping cost decrease, researchers will find that they have clinically relevant data for research subjects who were initially consented under the assumption that genetic results would not be returned to them. Researchers will then need to consider the ethics of withholding information known to be clinically relevant versus the fact that some subjects may have initially chosen to participate because they would not have information returned to them.


In addition to these basic ethical questions, the issue about how to adequately inform subjects about the meaning of the genetic results must be considered.

One other ELSI is open access for genomic research. The question is the discussion of open-access vs. research-only models for genomic research.

One other ELSI is privacy and ownership of an individual’s personal genetic information, contributed by Jennifer Sweeney.

As personal genetic information becomes increasingly accessible and affordable, the ownership and privacy of such data will emerge as a central issue in genomics.

As yet, industry and regulators have placed little focus on ownership and privacy concerns. GINA addresses discrimination once an employer or insurer already has access but is silent on who actually owns the genetic information. For the most part HIPAA’s privacy protections do not apply because DTC genomics companies are not “covered entities” under the privacy rule. Corporations, namely DTC genomics companies, have become the default guardian of personal genetic information.

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5.3.6. Last events

- HUGO Symposium on Genomics and Ethics, Law and Society
Organized by: The Human Genome Organisation
Date: November 1-3, 2009
Location: Geneva, Switzerland
Information: <http://www.hugoevents.org/gels/index.php>
 - The Convention on Human Rights and Biomedicine: 10 years later Organized by: Council of Europe
Date: November 3, 2009
Location: Strasbourg, France
Information: [http://www.coe.int/t/dg3/healthbioethic/activities/10th anniversary/default_FR.asp?](http://www.coe.int/t/dg3/healthbioethic/activities/10th anniversary/default_FR.asp?URL_ID=12662&URL_DO=DO_TOPIC&URL_SECTION=201.html)
 - Sixteenth Session of the International Bioethics Committee (IBC)
Organized by: UNESCO - International Bioethics Committee (IBC) Date: November 23-25, 2009
Location: Mexico City, Mexico
Information: http://portal.unesco.org/shs/en/ev.php-URL_ID=12662&URL_DO=DO_TOPIC&URL_SECTION=201.html
 - The Eur Soc Human Genetics is currently finalising a background document and recommendations on genetic testing and common disorders. The documents are a co-production of PPC of ESHG with EUROAGENTEST and IPTS, Seville, Spain. It will be made available on the ESHG website.
 - The French society of human genetics has launched a working group on “Pangenomics and society” that is going to produce two statements, one a genetic tests for ancestry available on internet and one on predictive medicine and pan genomics.
 - The “genetics and society” platform in Toulouse, France (<http://societal.genotoul.fr/>) has hold annual open workshops with 3 ½ day sessions since several years. In 2008 and 2009 the themes were
 - o 2008: Ethical aspects of genetic testing: from exception to routine. [session 1: genetic testing and health, session 2: genetic testing and market; session 3: genetic testing and regulation]
 - o 2009: Is human genetic information special? [[session 1: genetic information available for all, session 2: the status of genetic information in society; session 3: use of genetic information in administrative and judicial contexts]
- The syntheses of these workshops have been made available (in French) by November 2009 at: <http://societal.genotoul.fr/>
- o 2010 workshop will be organised on the topic : use, protection and circulation of genetic information in 3 sessions on March 11, April 8 and June 24 in Toulouse.


6. NEXT STEPS

The follow up of external developments will be continued and an update if relevant will be done yearly

Regarding the GEN2PHEN governance for the ethics policy:

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- Get comments on the policy and practical aspects (all; synthesis by Inserm, A. Cambon-Thomsen)
- Set up ethics oversight committee and its mandate (Inserm, Coordinator + WP leaders)
- Contact by Inserm group with each WP for practical application (what it means in practice for each tool, LSDB etc.)
- Write summary chart of principles and summary policy for website (Inserm plus coordinator and communication manager)
- Prepare information for data providers/ local ethics committees on GEN2PHEN (Coordinator)
- Send the ethics policy to external advisor J Taupitz (include him in Ethics oversight Committee)
- Calendar for these actions: before project review in May 2010
- Write an article on the construction of this policy: A. Cambon-Thomsen and colleagues, with co-authors from GEN2PHEN as relevant, for an ethics or genetics international Journal.

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ANNEXES

Annex I – Publication related to ethical guidelines for curators of LSDBs

Manuscript to be submitted shortly to Human mutation on ethical guidelines for curators of LSDBs prepared together with the Human Variome Project

This document is still confidential at the moment of this Deliverable D1.4 and might be further modified

Practical guidelines addressing ethical issues pertaining to the curation of human locus-specific variation databases (LSDBs).

Sue Povey¹, Aida I. Al Aqeel², Anne Cambon-Thomsen³, Raymond Dalglish⁴, Johan T. den Dunnen⁵, Helen V. Firth⁶, Marc Greenblatt⁷, Carol Isaacson Barash⁸, Michael Parker⁹, George P. Patrinos^{10,11}, Judith Savige¹², Maria-Jesus Sobrido^{13,14}, Ingrid Winship¹⁵ and Richard G. H. Cotton^{15,16}

¹Dept of Genetics, Evolution and Environment, University College London, Wolfson House, 4 Stephenson Way, London, NW1 2HE, UK

²Dept of Paediatrics, Riyadh Military Hospital, Department of Genetics and Stem Cell Therapy Program, King Faisal Specialist Hospital and Research Centre, Kingdom of Saudi Arabia

³UMR Inserm, Université Paul Sabatier - Toulouse III, U 558 Epidémiologie et analyses en santé publique : Département d'épidémiologie et de santé publique Faculté de Médecine, 37 allées Jules Guesde, F-31073 Toulouse, France

⁴Dept of Genetics, University of Leicester, University Road, Leicester, LE1 7RH, UK

⁵Human and Clinical Genetics, Leiden University Medical Centre, Leiden, The Netherlands

⁶Dept of Medical Genetics, Addenbrooke's Hospital, Cambridge, CB2 2QQ, UK

⁷College of Medicine, Burlington, Vermont, USA

⁸Genetics, Ethics & Policy Consulting, 317 Lamartine Street, Suite 200, Boston, MA 02130, USA

⁹Ethox Centre, Department of Public Health and Primary Health Care, University of Oxford, Badenoch Building, Old Road Campus, Headington, Oxford, OX3 7LF, UK

¹⁰**University of Patras, School of Health Sciences, Department of Pharmacy, Patras, Greece**

¹¹Erasmus University Medical Center, School of Medicine and Health Sciences, Department of Bioinformatics, Rotterdam, The Netherlands


¹²Dept of Medicine, University of Melbourne, Epping, Australia

¹³Fundacion Publica Galega de Medicina Xenomica, Santiago de Compostela. Spain,

¹⁴Center for Network Biomedical Research on Rare Diseases, Institute of Health Carlos III, Madrid, Spain

¹⁵Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne, Royal Melbourne Hospital, Parkville VIC 3010, Australia.

¹⁶Genomic Disorders Research Centre, Howard Florey Institute, Carlton South VIC 3053, Australia

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Definition

For this purpose, a locus-specific variation database (LSBD) is defined as a listing of known sequence variants in a specific human gene together with some assessment of the effects of these variants on the phenotype. It may also highlight the frequency of both common and rare variants (*e.g.* single nucleotide polymorphisms) prevalent in particular populations groups.

Introduction

This document was designed to assist a curator who intends to provide access to the information via a web interface, usually to everyone but occasionally to selected professional groups. The need for such guidelines has been highlighted by the recognition by initiators of the Human Variome Project (HVP) of the immense unpublished and inaccessible resource of information existing in diagnostic laboratories and the significant clinical need to have access to this information (Cotton, et al., 2007; Kaput, et al., 2009).


These guidelines are largely an expansion in detail of the guidelines proposed by Cotton and co-authors in 2005 (Cotton, et al., 2005) which were rooted in the principles described by Knoppers and Laberge in 2000 (Knoppers and Laberge, 2000). They were discussed and modified as a result of the international HVP planning meeting in Spain May 2008 attended by participants from a wide range of developed and emerging countries (Kaput, et al., 2009). Details of this can be found in the published meeting report and its supplementary information (Kaput, et al., 2009). The order of headings has been altered from that of Cotton and co-authors 2005 and some new ones added.

Background: Develop a common ethical framework

The goal of all such databases is the sharing of genomic and phenotypic information for the benefit of humanity. This requires the protection of privacy, which in this context is the right of the individual and members of their family to be protected against intrusion into their personal information and further intrusions ensuing from access to this, by publication of information. The balance between the public's interest in the value of the shared information and its interest in the strict protection of privacy has been widely discussed,(see footnote)³ This balance will be viewed differently in different cultures (Al Aqeel, 2007) and so international input into detailed guidelines is essential to ensure collective agreement which is requisite to effective collaboration. Harmonisation of standards will be a challenge. While the development of a common ethical framework must be nurtured by culture and country-specific input, the converse also holds true: the guidelines will serve as reference for the developers of national laws and local ethics committees.

For many of the genes and for most of the issues dealt with below it seems likely that an independent group of well-informed individuals to oversee specific LSDBs not only at their initiation but on an ongoing basis will be essential. This general need is underlined by the 2008 revision of the Declaration of Helsinki <http://www.wma.net/e/policy/b3.htm> which states that monitoring of ongoing studies must be put in place in addition to the initial approval by an ethics committee. Governance is thus necessary as new issues may appear in the course of a project or activity.

³ for example in the UK by the Academy of Medical Sciences (report in (2006b)); adverse comment in (Matthews, 2007) recent report from UK government (Lords, 2009), in a commentary from an Islamic perspective (Al Aqeel, 2007), from the USA (Taylor, 2008) and from the French National Bioethics advisory Committee (CCNE) (2003).

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Inevitably in these guidelines there is a strong emphasis on the validity and complexities of consent and the increasing difficulty of guaranteeing privacy in an era of electronic publishing and growing internet use. The authors would not wish to discourage the curation of LSDBs on this account! In practice, the great majority of patients and research participants are happy to share their data and so far curators have been as likely to receive complaints about the omission of a personal unique variant from the relevant database as its unexpected inclusion.

The guidelines are presented in approximately the order in which the issues are encountered by the prospective curator:-

1. Clarify the main purpose of the particular database, recognising that this may change over time. Who does the curator expect will use this LSDB and why?

This will allow evaluation of the exact information required or desirable and whether compliance with the remaining guidelines will be possible with a database open to the public or whether at least part of the information should be restricted to identified persons. (For discussion of robust methods for validation of identities of enquirers see the GEN2PHEN Knowledge Centre (2009)). It will also allow the generation of a list of ethical requirements which any submitter must fulfil. Examples of questions which should be answered at this stage include:-

Will it be used as a tool by diagnostic laboratories assessing the likelihood that the DNA change that they have found is the necessary and sufficient cause of a serious disease and can be used to inform treatment and/or prevention, including preimplantation and prenatal diagnosis and neonatal screening?

How much detailed clinical data will be needed and will this be in the form of a link to another database?

Will there be any family information, for example, the use of familial and *de novo* variants and combinations of these to support conclusions drawn on potentially associated pathogenicity?

Will an attempt be made to record every apparently unrelated case with the same mutation?

What ethnic and geographic origin data will be needed?

Will an attempt be made to record all known ‘neutral’ (‘normal’) variation?

Is it intended to assist in the evaluation of the contribution of common variants to common diseases?


Is the goal to inform basic research into the mechanism of disease, identification of modifier genes or variation in response to therapy according to genetic variation in different populations?

Will the LSDB collect results of *in vitro* functional analysis? Will this include results from a cell or tissue culture of patient/ participant material?

Will the database be used to assemble volunteers for new therapies such as mutation-specific strategies?

Is the interest mainly from an evolutionary perspective?

Both those LSDBs which catalogue very rare or even unique changes relating to serious disease and those which deal with common variants of small individual effect should adhere to stringent rules of data standardization, validation, quantification, and transparency of sources, as described by participants at the HVP planning meeting (Kaput et al 2009)

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These aims should be clarified and explained in terms understandable by non specialists on the public part of the LSDB website.

2. Define database policy with respect to sources of data. There are distinctions between the handling of prospective and that of archived data.


In **future research projects**, consent forms should specifically indicate what data will be included in a publicly available database and describe their possible intended uses. It may be appropriate to include agreement about the need for re-contact or delegation of decision-making to an ethical committee for future unforeseen uses.

Usually, information which is **already published and available electronically** can be used in the LSDB even though the person giving the consent for the research and publication may not have foreseen the full implications of web-based sharing of information. The main obligation on the curator is to check its scientific accuracy as far as possible, including writing to authors when necessary. Curators should keep in mind that integration of published data may on occasion give rise to conclusions with serious implications for individuals or groups. Similar concerns have been discussed previously, for example, relating to accumulated data on CGH microarrays (Tabor and Cho, 2007). Occasionally discussion with the oversight group might be needed before full public release of the integrated data.

The **data currently being generated in diagnostic laboratories** are more problematic, both because of limited clinical data but also because current practice does not usually ensure that those consenting to genetic testing have given permission for sharing (including scientific publication) of these data beyond the laboratory and clinical team undertaking the analysis. LSDBs must be cautious in accepting unpublished data from any investigators or from accredited diagnostic laboratories, and consider issues that could limit the clinical accuracy of unpublished submissions, including standardization of clinical language, source of data, individual identification and consent. In many cases patients/families report the data themselves (often with a copy of the lab result they obtained) and this can be encouraged with appropriate further information requested if needed. LSDBs should then have a consent form that should be signed by the self-submitter and by all relatives whose results the submitter forwards to the LSDB.

With regard to consent, we would strongly recommend that **informing donors of the possibility of transmission of data to an LSDB** should in the future be part of the consent form for all genetic testing, together with an explanation of why this is useful, and how their privacy will be secured. Refusal to include data in an LSDB should not affect genetic testing since this would contravene the traditional commitment of medicine ‘Make the care of your patient your first concern’ (2006a) and this should be made clear on the consent form. However, although this must be done in a non-compulsory way in order to preserve the freedom of the consent, the information provided to the patients /research participants should clearly explain the value of gathering such data and mention that in the long term, if data cannot be collected, interpretation of testing results may be less reliable or even impossible and development of future possibilities for treatment might be compromised. Although the curator should require a statement that the submitter has obtained appropriate consent in whatever way is acceptable in the country of origin of the data, the primary responsibility is that of the submitter. The curator should supply to the testing laboratory a clear explanation about the LSDB on an information sheet that the laboratory can provide to clinicians and patients.

A suggested form of wording as an addition to the consent for diagnostic testing (and which may also be appropriate for testing as part of a research project) is as follows:

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- i. I understand that the interpretation of DNA test results, including my own is based mainly on publicly available data from other who have been tested before me.
- ii. I agree that the results of my DNA test and clinical examination may be added to these public data sets, in the accepted manner which does not disclose my personal identity and which is in agreement with data protection law in my country.
- iii. This information will then be available to help the diagnosis of others, and to further understanding about the disease. Improved understanding of the molecular mechanisms of disease may be important in developing new treatments and/or prevention.
- iv. Any information which could identify me or members of my family may only be stored when a high standard of privacy and confidentiality (as defined and in accordance with national standards for health data) is maintained. However, unintentional third party cross examination of stored non-identified data, might indicate, but not prove, identity. Should this happen, users of the database will undertake not to explore this information further or to contact me
- v. I understand that I will not receive any payment for this.


This wording may need modification in certain circumstances and if any part of the interpretation of the result to be shown on the database depends on family history or testing of other members of the family, this should be considered and consent sought if appropriate.

Available but unpublished diagnostic data are a major problem. It is suggested that where it is not feasible to obtain explicit consent, the decisions about which data should be uploaded and also which should be publicly displayed, or protected by controlled access, should be made by the independent LSDB ethical oversight committee (see point 5). This committee must also be sensitive to different cultural views. In many cases it may be appropriate for these data to be anonymized, *i.e.* made ‘not identifiable’ (see point 6 for explanation of ICH sample coding terminology (2007)). Note that the current version of LSDB software LOVD (Fokkema, et al., 2005) has the option to store data that are not public but that can be queried. The result of a query hitting non-public data is a notification that there is such information in the database but that the curator needs to be contacted to get more information.

3. Take Specific communities/cultures into account. Identifiable groups such as Ashkenazi Jews or Roma (Gypsies) may be particularly affected by a specific disease and thence become a major part of the relevant LSDB. Following consultation with the community, every effort must be made to take this into account and to provide privacy protection and respect cultural sensitivity ensuring that high ethical standards are maintained. A small specialised database gives the greatest chance of the unintended identifiability of one of the subjects. It may occasionally be necessary to store data only at summary level to preserve anonymity, as has been done in the Israeli National/Ethnic Mutation Database (NEMDB) (Patrinos, 2006; Zlotogora, et al., 2007). The cultural sensitivity of particular groups such as the Maori of New Zealand will need a step of local consultation before any sharing of DNA data, even for disorders not especially prevalent in that group.

4. Take vulnerable persons into account. Persons who do not have the capacity to consent either because of disability or young age are especially vulnerable. In some disorders, this will apply to many of the patients/ participants and regular external review of procedures for obtaining consent from appropriate relatives/ representatives or other suitable authority should be in place.

5. Create an ethics oversight committee. A variation database which accepts genotype and phenotype data not already in the public domain (or that are in the public domain but whose combination and

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integration are foreseen to change the degree of identifiability of persons) and makes them widely available, should have an independent and well-informed oversight group drawn from several disciplines and from relevant society stakeholders, including patient groups, to review the particular ethical issues arising in relation to that LSDB. They should recommend constraints needed in uploading and displaying data and decide on any requirement for control of access or for anonymization. The delegation of such decisions to committee with a long term remit will balance the difficulty of having truly informed consent in such a fast moving field. The decisions of this committee may require formal ethical approval either from their own institution or a national body.


A database which only accepts publicly available data would still benefit from some independent ethical review, perhaps from an international HGVS or HVP group who could advise a number of databases.

6. **Remove identifying information before submission to database.** Every effort must be made to ensure that the individuals whose DNA variation is displayed in an LSDB are not individually identifiable. With increasing availability of total genomic sequence and the enormous amount of personal information retrievable from websites, absolute certainty of non identifiability is no longer guaranteed (Barash, 2007; Homer, et al., 2008; Lowrance and Collins, 2007; Walter, 2007). However, with care, the risk of identification from an LSDB will be very low in almost every case, particularly if data from genome-wide analyses such as SNP genotyping data are not associated with the mutation. (see point 7 for possible exceptions such as unique variants). There is now a set of definitions including sample coding terminology agreed internationally and recognised by all constituents of the International Conference on Harmonisation (ICH) that has become official in 2008 (2007). These definitions will be used here and are explained below:-

Decide whether data should be **‘coded’** (also called **‘re-identifiable’**) or **‘anonymized’** (also called **‘de-identified’**). For the purposes of these guidelines, ‘coded’ is taken to mean removal of all existing identifiers as far as is compatible with usefulness of the data and substitution by proxy identifiers which are used in the database. The link between the existing identifier and the proxy identifier could be maintained either by the submitter acting as the ‘honest broker’ between the hospital records and the LSDB or within a securely non-public area of the LSDB. It would be desirable that each proxy identifier is unique and generated by a standard coding mechanism, perhaps by some national or international body. This would avoid inadvertent duplication of identifiers that might arise if the process was left to individual LSDB curators. For published data, and especially for recent publications, many cases are already coded and then classified as ‘re-identifiable’ specifically for publication. These codes might be acceptable if not recorded in hospital notes. However, new coding for the database would be safer. Unpublished data, unless anonymized, should always be re-coded to make them re-identifiable and not directly identifiable.

Anonymized (or ‘de-identified’) here means that identifiers and any information which might be used as clues to identity through other links are permanently removed and the link to the ID used by the submitter is **destroyed**. This would limit the usefulness of the data, particularly with regard to long term phenotype follow-up data and any late correction of wrong information but also possibly in ways that cannot currently be predicted. It also makes withdrawal of consent impossible and is not the approach of choice.

If the decision is to proceed with **coded** or in other words **‘re-identifiable’** data, although the original identifier is replaced by a code, many other pieces of information give possible clues to identity and will need to be removed to avoid unauthorised re-identification and, in many countries, to obey


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privacy laws. In most published cases, all data given in the publication would be acceptable to include in the database, including geographical location and ethnic group of individuals studied (both for cases and for population controls) and clinical details of patients. Limited family details present in the original report which help in the interpretation of the mutation may also be included. A link to the original publication is acceptable and useful. Note that data on frequency and population/ethnicity can be very helpful in the design of cost-effective targeted diagnostics and/or treatment protocols.

For unpublished data, the specific nature of the LSDB will be considered by the ethical oversight committee in recommending which data can be collected and displayed. Coding the identity of submitters of unpublished data may be required to safeguard privacy of donors.

Special consideration should be given to rare mutations, (see point 7).

7. **Add further protection of confidentiality if needed.** This may be necessary in the case of rare or unique mutations in rare diseases, unique combinations of clinical features or where higher protection is required for some other reason. The oversight committee will be valuable here. The database will have limited usefulness if important genotype phenotype data cannot be released because this information alone might allow identification of the individual. In diseases where very detailed clinical data have been collected (especially clinical photographs or detailed pedigrees) access to these data may have to be restricted by appropriate registration and approval for access. Even in databases where clinical data are minimal and there are no identifiers, the combination of a rare mutation and the identity of the submitter may allow re-identification of the individual at least by the family concerned. Here the submitter could be coded and the submission date left imprecise. A possible solution here which could also be applied to any unpublished data for which explicit consent is not certain would be to display the mutation in the database with no other data at all. Someone with a genuine reason for wanting to know if this mutation causes disease could then click on a tool which would send an email to the curator and thence either to the submitter or to a member of the oversight committee who could use professional judgement in their response. There are several variations to this approach and this one is least error-prone in making the request. As mentioned in point 2, one of us (JdD) has already provided a similar facility for LOVD databases (Fokkema, et al., 2005).
8. **Allow no disclosure without consent.** Requests made to clinician submitters for information beyond what is publicly viewable in the database should be considered using professional judgement and this will usually require seeking further explicit consent from the patient. The independent oversight committee might be consulted.
9. **Provide provision for removal of data from database.** Those who have given consent for their own or a child's or incompetent adult's information to be included in the LSDB should be made aware of their right to withdraw this information at any time (unless data are truly not identifiable). The LSDB should make available information in order to facilitate this task. If a child has an age (usually 16 or whatever is usual in the country) and has reached a stage of development where he or she is capable of making a decision, those who previously authorised data sharing should ensure that he/she is aware of his/her LSDB entry and has the right to withdraw it. However, it should be made clear that whilst it will be possible to eradicate information which was originally displayed from the database, it may not be

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possible to eradicate it from other sources which have used this information for example in an overview publication.

10. **Be cautious in response to requests to an LSDB curator for a private opinion** on whether a particular variant is pathogenic, especially if any of the information used is not published. Add a disclaimer about responsibility for the clinical use of the opinion and be cautious of a ‘virtual medical advisor relationship’. From the medico-legal point of view, it is safest to obtain clinical interpretation from published data. If unpublished information is used, a careful record should be kept. Recommendations of the IARC Working Group on Unclassified Genetic Variants encourage that classification of pathogenicity be carried out not by individuals but by teams of experts that can carefully evaluate all lines of evidence (Greenblatt, et al., 2008; Tavtigian, et al., 2008).
11. **Limit links to other LSDBs.** If mutations in more than one gene are relevant to a particular disease, it may be useful to record the variation of both genes in the same individual and link the entries so that the fact that it is one person is recorded. This facility is already available on at least one LSDB platform (LOVD) and can be of great value in the interpretation of results. However, logically it may eventually extend to enough genes to allow identification of the individual. At this point, the considerations of the ethics of large scale resequencing will be relevant (see (2006a)). For example, a recent investigation into DNA variants causing X-linked mental retardation included substantial amounts of sequence information on the coding regions of X-linked genes (Tarpey, et al., 2009). These data were regarded as too sensitive for the full set of variants for each patient to be entered onto the LSDBs in the most informative way. See <http://www.LOVD.nl/MR> for the summary data submitted.
12. **Consider carefully the transfer of publicly available data from LSDBs to genome browsers.** This does not raise entirely new ethical issues except in the need for adequate recognition of the work of the LSDB curator. It makes the misuse of data for re-identification slightly more likely and may also increase the chance of a mistake being widely disseminated in a short time. There is a case for recommending that clinical data linked to a particular entry, even if available publicly via the LSDB, should be displayed as a link rather than held by the browser. This will encourage rapid correction of errors and ensure some recognition for the LSDB. Further discussion of the sharing of data with genome browsers can be found elsewhere (den Dunnen, et al., 2009).

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Annex II – Summary of GEN2PHEN ethics policy

GEN2PHEN Ethics policy as presented in GAM5 (Aveiro, Portugal, January 11-12 2010)

Annex II Summary of the ethics policy proposed to GEN2PHEN GAM5 for endorsement in order to start further steps

The **ethics policy of the GEN2PHEN** project has been constructed based on:

- Reference texts and existing guidelines review
- Internal consortium questionnaire survey of opinions and discussion in general assembly
- Discussion with other relevant EU and international projects: especially PRIVILEGED, BBMRI, P3G and HVP
- Review of recent literature on relevant ethical and societal issues.

It has been proposed for validation at M 24 of the GEN2PHEN project, at the 5th general assembly (January 2010).

It is presented according to the main structure of the project:

Issues related to:


- Getting data in
- Database and infrastructure
- Getting data out and using them.

Data in

Scope: Which data? Several kinds of data are going to be processed

- from different sort of sources (diagnostic laboratories, various databases including LSDBs = Locus specific databases, published and quality validated but non published data),
- with different contents (clinical information, molecular information, ethnic information, whole genome information...),
- summary or pooled data, metadata but also possibly individual data
- data from patients and healthy people, data from minors.

The ethics policy takes into account the differences between these kinds of data, based on the following guiding principles and best practices: transparency on sources of data, any information of a personal nature collected considered as confidential and consequently treat them according to the rules relating to the protection of private life; anonymised data preferred, coded data accepted if scientific/medical justification exists but key only available at the local site in legally compliant form and never communicated directly through GEN2PHEN, no access to any known identifier through GEN2PHEN; in case of possibly indirectly identifying data, indication of their existence and set up procedure so that they can only be accessed through specific controlled

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access [to be documented] or by direct contact with the original data provider [outside responsibility of GEN2PHEN, disclaimer].

The practical measures for incoming data have been developed according to 2 situations:

GEN2PHEN is gathering data in its own initiative, the consent has to be verified, an ethical committee must approve the transfer stating that the data could be transferred having considered the original protocol/context of obtaining the data and the aim of GEN2PHEN and containing at least the following items: international data sharing (in non identifying format), further uses of data, and specific dispositions for data coming from minors if relevant. To achieve this goal GEN2PHEN must provide to the local ethics committee or the institutionally authorised person, through the contact person for the data considered, all necessary information about the aim and the goal of GEN2PHEN. Then the local ethics committee or the institutional authorised person must provide an attestation certifying that informed consent containing at least the information indicated above has been obtained for each participant for the envisaged use. So the procedure is to rely on local ethics committee or institutional approval but with a specific statement that they have considered the dimension that GEN2PHEN is giving in terms of access to data and that it fits with the provisions described to the patient or research participant or lawful equivalent procedures.

Data providers are willing to put the data themselves into the system and make their data available through GEN2PHEN, they have to provide the appropriate informed consent in itself or the institutional certificate or the agreement of their local ethics committee, as above prior to be technically allowed to provide their data.


In both cases a problem occurs when it is impossible to obtain this informed consent or institutional certificate, or local ethical committee approval. In that case, either refuse data (informed consent being part of the quality of the data) or if of specific interest, submit the case to a GEN2PHEN ethics oversight board, that has to be put in place.

The GEN2PHEN ethics oversight board: independent (autonomous decisions), the various competencies of the project represented (1 per WP), some external experts [proposal is 3, various disciplines, plus patient association representative], possibility to ask for other expert opinion or other party representation [e.g. ethnic group representative] as needed, a written mandate.

So main features of Data in ethics policy:

- Clear indication of the source of data (responsibility of GEN2PHEN) [with provisions to protect confidentiality of patients if necessary, see LSDB guidelines]
- Check that an initial informed consent has been obtained including the international data sharing, (in non identifying format), further uses of data, and specific dispositions for data coming from minors if relevant, (responsibility of the data provider to do it locally and to provide a relevant ethics committee/institutional approval, but responsibility of GEN2PHEN to ask this question)
- In case of incidental technical possibility of re-identification that may occur over time, indicate that a policy is in place to address this issue (see “accessing data and data out”⁴)

⁴ Make a link in order that access to this policy indication is possible easily at this point without browsing the full document

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- If information on consent and international access not available, inform the data provider about his responsibility to check, and provide information about GEN2PHEN (scientific aim, context and ethics policy) for data providers and for their local ethics committee (responsibility of GEN2PHEN).
- If documented impossibility to check for consent and international access permission persists, do not consider these data as suitable for GEN2PHEN or if particularly scientifically important, consult a project oversight ethics board (responsibility of GEN2PHEN to set up such a board).


Data storage and infrastructure

3. *Data ownership issue*: on the basis of transparency, the following situations will be clarified

- Data belonging to an institution refer to a framework that can guarantee a certain procedure for protection of data and an institution being legally responsible towards the research participants as the promoter of a research
- Data belonging to a PI (an individual who then would be responsible for any misuse or further use) underlines the intellectual property rights over a use, rather than responsibility towards research participants
- Data belonging to research participants indicate that they should keep a control over the uses of data, which is different from an ownership
 - *Database ownership issue*: refer to consortium agreement and to Directive on the Legal Protection of Databases adopted by the EU's Council of Ministers on 26 February 2006.
- It creates an exclusive 'sui generis' right for database creators, valid for 15 years, to protect their investment of time, money and effort, irrespective of whether the database is in itself innovative. The Directive also harmonises copyright law applicable to the structure of databases. On the basis of the Directive, manufacturers of databases will be in a position to prohibit the extraction and/or re-use of the entirety or substantial parts of the database by third parties. However, this protection should not affect the rights of traditional right holders, in particular of creators of works incorporated in the contents of a database.
- The scope of application for the directive is:
 1. This Directive concerns the legal protection of databases in any form.
 2. For the purposes of this Directive, 'database' shall mean a collection of independent works, data or other materials arranged in a systematic or methodical way and individually accessible by electronic or other means.
 3. Protection under this Directive shall not apply to computer programs used in the making or operation of databases accessible by electronic means.
- There is an exception to the Sui generis right, in the case of extraction for the purposes of illustration for teaching or scientific research, as long as the source is indicated and to the extent justified by the non-commercial purpose to be achieved.
- Responsibility of GEN2PHEN is to indicate this in a visible form adapted to the project so that users are aware of what it means for their possible use, and data providers are aware of their own protection.

For tools not pertaining to the database as open source is the philosophy of the project no specific issue has been considered. Specific provision for certain pieces of software if necessary will have to be individually worked out, not as a general project policy.

- Discrimination risk (by grouping on the basis of genetics and/or ethnicity)

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- Ensure that for using data from sensitive groups, the ethics committee that gave the approval has included a sentence addressing the issue
- In doubt, ask the GEN2PHEN ethics oversight committee (that can solicit external relevant expertise)
- Include a box to tick regarding engagement not to use data in a discriminative way for future users.
 - Children

Ensure that parents or authorised person sign the consent, that the consent specifies what will be done when the minor becomes adult, and verify that there is a procedure that informs the minor, in order to be in full compliance with the United Nations Convention on the Rights of the Child, that asserts that children have a right to say what they think should happen when adults make decisions that affect them (Article 12) and have the right to get and share information (Article 13). Responsibility of GEN2PHEN: ask data providers for such elements in original consent.

Data out and use


- Access and commercialisation
- Explicit rules for the divide between completely open access and those with controlled access
- Explanation given whether certain data or combinations of data will not be made available and for which reasons
- For controlled access, the way to assess the bona fide scientists and institutional responsibility engagement made explicit. It will imply a level of personal engagement (ticking boxes regarding uses and liability), and providing an institutional authorisation. Different ways could be combined: data access could be restricted via fees, legal threats, technological censoring e.g. GPS and encryption algorithms, and study design in eliminating useless data linkages for instance.
 - Protection of individuals from whom the data are processed

Three categories :


- Known as possibly indentifying (coded) and the keys are never available through GEN2PHEN; only anonymised information is provided
- With incidental technical possibility of indirect re-identification that may occur over time; a policy has to be put in place to address this issue:
 - First a systematic follow up of relevant literature and technical tools as an identified tasks;
 - Second a technical way of assessing the data publically available for this issue;
 - Third a procedure to efficiently change the status of relevant data from “publically accessible” to “controlled access”
- Data with no possibility of identification or re-identification, the criteria for this being publically available must be indicated; these may be publically available, without external controlled access, but all data accessed should be preceded by an engagement on their use in a way that respect fundamental rights ticked by the users. This question has been debated, but the discussion shoed that there was some confusion between “data published” and data free to be used without control. As a matter of fact it is not, for example, because data are published that the conditions indicate in the consent and that restrict their use do not apply anymore for further uses or that obligation of information on the various uses if this has been indicated in the consent do not apply.

Question of withdrawal when data are anonymised: impossibility to withdraw anonymised data to be indicated.

- Incentives
- Reference to institutions policies aiming at data sharing could be indicated as reference on the website

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- Underline duty to optimise the use of data towards participants hopes and expectations
- Underline the rights of data providers
- - Feedback information
- present regularly new insights thanks to data sharing and developing of tools
- make this actively available (alert) to data providers
- encourage them to inform their participants about these developments, by an appropriate way in their context
 - For **LSDBs curation** the guidelines proposed in an article submitted, that has been approved by an international advisor and has been submitted for endorsement to the HUGO ethics committee will be followed by GEN2PHEN.

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Annex III– Ethical and legal framework related to GEN2PHEN and References

I. Ethical and Legal framework related to GEN2PHEN

1.1 The United Nations

Universal Declaration on Fundamental Human Rights (1948)
International Covenant on Civil and Political Rights (1966)
UNESCO Declaration on the Human Genome and Human Rights (1997)
UNESCO International Declaration on Human Genetic Data (2003).

WHO (1998) Proposed International Guidelines on Ethical Issues in Medical Genetics and Genetic Services (WHO/HGN/GL/ETH/98.1)

WHO: First international standard for common genetic test, 2004.

WHO: The World Health Organization published documents of interest for guiding ethics committees in analysing biomedical research projects as well as guidelines for research.

1.2 The European Union

Consolidated EC Treaty, Official Journal of the European Union C 321 E/39, 29.12.2006

Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data


Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions

Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells

European Medicines Agency (EMA) ICH Topic E15 Definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding categories. Note for Guidance on Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories, EMA/CHMP/ICH/437986/2006.

Article 29 Data Protection Working Party, Working Document on Genetic Data adopted in March 2004, 12178/03/EN WP 91

Article 29 Data Protection Working Party Opinion 4/2007 on the concept of personal data, 01248/07/EN WP 136.

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European Group on Ethics in Science and New Technologies (EGE)

Opinion n° 3 - 30/09/1993 - Opinion on ethical questions arising from the Commission proposal for a Council directive for legal protection of biotechnological inventions

Opinion n° 8 - 25/09/1996 - Ethical aspects of patenting inventions involving elements of human origin

Opinion n° 11 - 21/07/1998 - Ethical aspects of human tissue banking,

Opinion n° 19 - 16/03/2004 - Ethical aspects of umbilical cord blood banking

Opinion n° 22 - 13/07/2007 - The ethics review of hESC FP7 research projects

Opinion n° 16 - 07/05/2002 - Ethical aspects of patenting inventions involving human stem cells.

1.3 The Council of Europe

European Convention for the Protection of Human Rights and Fundamental Freedoms (1950, ETS no. 005).

Convention for the Protection of Individuals with regard to Automatic Processing of Personal Data (1981, ETS no. 108)

Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine, known as Oviedo Convention (1997, ETS no. 164)

Explanatory Report to the Convention on Human Rights and Biomedicine, 1996

Additional Protocol to the on Human Rights and Biomedicine, concerning Biomedical Research (2005, ETS no.195)

Recommendation R (79) 5 of the Committee of Ministers to member States concerning international exchange and transportation of human substances


Recommendation R (90) 13 of the Committee of Ministers to member States on prenatal genetic screening, prenatal genetic diagnosis and associated genetic counselling

Recommendation R (92) 1 of the Committee of Ministers to member States on the use of analysis of deoxyribonucleic acid (DNA) within the framework of the criminal justice system

Recommendation R (92) 3 of the Committee of Ministers to member States on genetic testing and screening for health care purposes

Recommendation R (94) 1 of the Committee of Ministers to member States on human tissue banks

Recommendation (97) 5 of the Committee of Ministers to Member States on the protection of medical data

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Recommendation Rec (2006) 4 of the Committee of Ministers to member states on research on biological materials of human origin

1.4 The OECD

OECD 2008 Guidelines for Human Biobanks and Genetic Research Databases.

OECD recommendations on quality assurance in Molecular genetic testing, adopted by the OECD council in 2007, sets out inter alia, a number of principles and best practices for governments, professionals bodies, and providers of molecular genetic testing.

OECD recommendations on the Licensing of genetic inventions, adopted by the OECD Council in 2006, provides guidance on licensing, transferring agreements, and joint developments activities in regards to genetic inventions.

OECD Best Practice Guidelines for Biological Resource Centres set out further complementary quality assurance and technical aspects for the acquisition, maintenance and provision of high quality biological materials and associated data in a secure manner.

1.5 The WMA

WMA: The World Medical Association (WMA) has developed the [Declaration of Helsinki](#) 1964, amended in 2000, clarification notes 2002, 2004 and the last revision in October 2008 (Seoul).

WMA: The World Medical Association [Declaration on Ethical Considerations Regarding Health Databases](#), Seoul, October 6th 2008.

1.6 Professionals and scientific Organisations

European Society of Human Genetics

Population genetic screening programmes: technical, social and ethical issues”

Genetic services in Europe”

Patenting and licensing”

European Journal of Human Genetics 11: 2003 (a special issue)

HUGO Ethics Committee

Statement on Human Genomic Databases”, 2002

Statement on The Principled Conduct Of Genetics Research”, 1996


Statement on Patenting of DNA sequences”, 1995

Statement on Benefit Sharing”, 2000

Statement on Pharmacogenomics (PGx): Solidarity, Equity and Governance”, 2007

1.7 Advises from Ethics groups and Committees at the European level

Expert group, 25 recommendations on ethical, legal and social aspects of genetic testing,

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European Commission Research DG, ‘Contribution to the analysis of the positions of trade unions and employers regarding genetic pre-employment tests’, EUR 18497 EN, Luxembourg, 1999

European Commission, European Group on Ethics in Science and New Technologies, ‘Genetic Testing in the Workplace - Proceedings of the Round Table Debate’ at the Centre Borchette, Brussels, ISBN 92-894-0017-X March 2000

European Commission, DG RTD, Quality of Life and Management of Living Resources, ‘Genetic Testing: Patient’s rights, insurance and employment - A survey of regulations in the European Union’, EUR 20446, 2002

European Commission, European Group on Ethics in Science and New Technologies, ‘Statement on advertising genetic tests via the Internet,’ February.2003

European Group on Ethics of Sciences and new technologies Opinion n°18 - 28/07/2003 - Ethical aspects of genetic testing in the workplace

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http://www.ncbi.nlm.nih.gov/sites/entrez?cmd=Retrieve&db=%20pubmed&dopt=AbstractPlus&list_uids=19223929

Regulating trust in pediatric clinical trials. [Pinxten W, Nys H, Dierickx K.](#) Med Health Care Philos. 2008 Dec; 11(4):439-44; see also Eur J Pediatr. 2009 Oct; 168(10):1225-34 and Am J Bioeth. 2009 Jan; 9(1):21-3


Children and population biobanks. David Gurwitz, Isabel Fortier, Jeantine E. Lunshof, Bartha Maria Knoppers. Science, 14 august 2009 Vol. 325. no. 5942, pp. 818 - 819

<http://www.sciencemag.org.gate2.inist.fr/cgi/content/full/325/5942/818> and Comment in: [Science. 2009 Nov 6;326\(5954\):797; author reply 799.](#)

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Ethical principles and legal requirements for pediatric research in the EU: an analysis of the European normative and legal framework surrounding pediatric clinical trials. [Pinxten W, Dierickx K, Nys H.](#) Eur J Pediatr. 2009, Oct

European survey on ethical and legal framework of clinical trials in paediatrics: results and perspectives. [Altavilla A, Giaquinto C, Ceci A.](#) J Int Bioethique. 2008 Sep;19(3):17-48, 121-2.

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Public access to genome-wide data: five views on balancing research with privacy and protection. [P3G Consortium](#), [Church G](#), [Heeney C](#), [Hawkins N](#), [de Vries J](#), [Boddington P](#), [Kaye J](#), [Bobrow M](#), [Weir B](#). PLoS Genet. 2009 Oct;5(10):e1000665. Epub 2009 Oct 2

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The regulation of direct-to-consumer genetic tests. Jane Kaye. Human molecular genetics. Hum Mol Genet. 2008 Oct 15;17(R2):R180-3. Review.

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