

Ethical Issues in Whole-Genome/Genetic Studies

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This document is meant to guide researchers and members of USM Research Ethics Committee for Human Studies for preparing and reviewing studies on human genetics. This should be considered as complementary to the existing Guidelines issued by Malaysian Ministry of Health (2007).

No.	Issues	Practical Implications
<i>General Issue in Genetic Research</i>		
1.	<p>Human genetic research is not conducted with the aim of providing research participants with specific information about their genetic status or health. However, if there is a possibility that the research may yield individual data of clinical significance, the research participant should be informed of this possibility and whether he or she would receive such information if so desired, prior to participation in the research. (BAC Singapore, 2005)</p> <p>It is ethically imperative that when genetic testing that may have significant implications for a person's health is being considered, genetic counselling should be made available in an appropriate manner. Genetic counselling should be non-directive, culturally adapted and consistent with the best interest of the person concerned. (UNESCO, 2003)</p>	<ol style="list-style-type: none"> 1. Researchers are required to provide genetic counseling based on the signed informed consent with regards to disclosure of research results and incidental findings. 2. Whenever applicable, genetic counseling should be incorporated into the research methodology and budget for as far as any cost concerned. 3. Involvement of genetic counselors should be highlighted within the research team OR as part of professional services 4. Refer to Genetic Counseling section in MOH "Guidelines on Ethical Issues in Medical Genetics..." (April 2007)
2.	<p>Researchers have an obligation to protect the privacy of research participants and their family members, and to ensure confidentiality of all genetic information derived from the research, including information about the participant's relatives, who may not be part of the research project (BAC Singapore, 2005)</p>	<ol style="list-style-type: none"> 1. Researchers are required to keep all samples and data, pertaining to identifying particular individual, confidential. 2. Researchers are required to inform participants about how their sample and data are kept (whether their sample and data will be anonymous and how). 3. Researchers are required to inform participants that their genetic data may also concern other family members as well as their community, as far as shared genetic materials exist. 4. Researchers are required to inform participants about limitation in confidentiality efforts as well as situations of reportable conditions

		(such as HIV status) and risks associated with possible loss of privacy.
3.	Research considerations should not compromise or prejudice the clinical purpose of genetic testing where such testing is also providing information for research (BAC Singapore, 2005)	1. In the events where research and clinical services concur, all aspects pertaining to clinical services must be prioritized.
4.	When human genetic data, human proteomic data or biological samples are collected for medical and scientific research purposes, the information provided at the time of consent should indicate that the person concerned has the right to decide whether or not to be informed of the results. This does not apply to research on data irretrievably unlinked to identifiable persons or to data that do not lead to individual findings concerning the persons who have participated in such a research. Where appropriate, the right not to be informed should be extended to identified relatives who may be affected by the results. (UNESCO, 2003)	<ol style="list-style-type: none"> 1. Researchers are required to determine if certain research results are clinically meaningful for the participants' and related family members' health and well being and if such results are worthy of disclosure. 2. Researchers are required to provide options to participants on whether to be informed about the research results or not 3. Even in the case where researchers determined un-worthiness of disclosure, participants retain the utmost rights to retrieve their data. In this case, the researchers must provide enough information with regards to un-worthiness of the data disclosure.
5.	The persons and entities responsible for the processing of human genetic data, human proteomic data and biological samples should take the necessary measures to ensure the accuracy, reliability, quality and security of these data and the processing of biological samples. They should exercise rigour, caution, honesty and integrity in the processing and interpretation of human genetic data, human proteomic data or biological samples, in view of their ethical, legal and social implications. (UNESCO, 2003)	<ol style="list-style-type: none"> 1. Research methodology is of utmost importance in the context of ethical conduct of research. 2. Researchers are required to ensure the accuracy, reliability, quality and security of the data and processing of biological samples. 3. Ethics Committee reserves the rights and responsibilities to assess study viability and provide recommendation pertaining to it.
Context of Whole-Genome Research (Kaye et al., 2010)		
1.	Variable Usage of Data. Whole-Genome methods are being used alongside the increasing accumulation of samples and information, which are held by projects, large international consortia, or within biobanks. Such resources can then be used for a number of different research projects as the information is compared, used, and exchanged between researchers who come together to address specific research questions. These data and sample storage infrastructures meet the scientific need for very large sample sizes to understand the complexity of genotypic, phenotypic, and environmental interactions. Example: the Human Genome Project, the HapMap project, the 1000 Genomes project and the Human Variome Project.	
2.	Wide-Scale Data Sharing. Data sharing is becoming a crucial element of scientific policy with the development of more open access guidelines. Funders are encouraging researchers to deposit data created in newly-funded projects to be shared with others, and increasingly the presumption is that the data	

	<p>should be shared. Funders have also been active in financing and supporting the establishment of data-generating projects, especially for the creation of sequence data using GWAS methods. Examples : Wellcome Trust Case Control Consortium (WTCCC) and MalariaGEN in the United Kingdom and the Genetic Association Information Network (GAIN) in the United States. The data created by these projects can be a valuable resource for potentially many different research projects and purposes. This raises a number of ethical issues as many of the principles and procedures in medical research are not designed for wide-scale data sharing.</p>	
3.	<p>Personal-Familial-Community Genome. These genomic methods are used in a social context where privacy concerns about the loss and unauthorized use of digital information have come to take a prominent place, and where the democratization of biological technologies means that individuals have greater access to their own genomes through direct-to-consumer genetic testing companies as well as genealogical registries and ancestry tracing companies. These events outside of medical research cannot be ignored, as there is the potential for these to have an effect on the medical research context, which in the case of an unfavourable event could undermine the public trust and support that is necessary for medical research to continue and to thrive.</p>	
<p><i>Issues on Consent</i></p>		
6.	<p>Prior to participation in a whole-genome project, participants should be asked to provide consent for future use that includes as much detail as possible, including information about the sampling and sequencing process, associated commercialization activities, possible risks, and the nature of likely future research initiatives. The consent process should also include information about data security and the governance structure and, in particular, the mechanism for considering future research protocols. When deemed appropriate by the governance scheme, re-consent for specific research projects may be required (e.g., when the proposal deviates significantly from what was stated in the initial consent) (Caulfield et al., 2008).</p>	<ol style="list-style-type: none"> 1. Informed consent must be signed by prospective participants prior to enrollment into the study. 2. Informed consent form must include (but not limited to) information topic of research, names of researchers involved, study procedure, purpose of the study, risks, possible benefits, incidental findings, disclosure of research results, questions, confidentiality, nature of likely future research activities, withdrawal from the study and signature pages. 3. Whenever applicable, information on associated commercialization activities should also be included. 4. Scope of the consent must be well understood by researchers, research participants and ethics review committee. 5. As both participants data and samples are retained by the researchers, consent process should take into account governance structure and mechanism for considering future research protocol (Figure 1). 6. One ethical clearance is valid only for one research study for which ethical approval has been granted. Shall researchers need to use the same data and sample for different study, a fresh ethical approval must be obtained. Whenever deemed necessary by the ethics committee, re-consent may be requested (e.g., when the proposal

deviates significantly from what was stated in the initial consent).

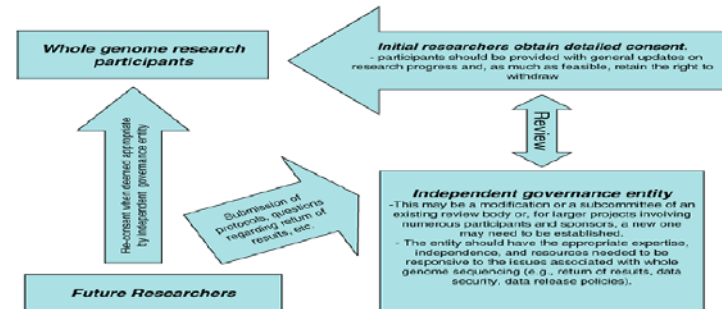


Figure 1. Example Governance Structure
 The following governance structure is similar to other policies [22]. It is only an example and should be modified to meet the needs and scope of each research initiative. The mandate and scope of the entity's responsibilities, obligations, and powers should be clear and should be reconciled with roles and requirements of existing ethics review committees. The membership of the entity, their criteria and process for making decisions, and the review and appeal system should be publicly available in order to ensure transparency and accountability.

Issues on Sample/Data Storage and Withdrawal from Research

7.	<p>The right to withdraw consent, including the destruction of tissue samples and written information, must, so far as possible, be respected and be part of the whole-genome research ethics process. In addition, the fact that this right may be severely limited once data are disseminated must be clearly communicated as part of the initial informed consent process. (Caulfield et al., 2008)</p>	<ol style="list-style-type: none"> 1. Participant's biological sample and data will be kept by the researchers for the duration specific in the informed consent. Upon indicated participants' consent, however, researchers may keep the sample and data for a longer duration. Researchers are responsible for adequate storage system to ensure privacy protection. 2. Withdrawal from genetic/whole-genome studies is enabled by sample destruction and data elimination for as much as possible effort. 3. Researchers are required to inform participants of their rights on
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8.	<p>The design of personal genome projects and ethics review should explicitly consider how the ability to withdraw from subsequent use is enhanced or diminished by how data and samples are collected, stored, and disseminated. The appropriate balance will need to be considered for each project on a case-by-case basis. (Caulfield et al., 2008)</p>	<p>withdrawal from research as well as limitations in data elimination effort.</p> <ol style="list-style-type: none"> 4. Researchers are required to inform participants on the mechanism of withdrawal. 5. If participants would like to withdraw, they can do so by contacting the Principal Investigator. 6. Although sole responsibility of withdrawal lies with the researcher concerned, the ethics committee reserves the rights and responsibilities in overseeing the process. 7. Subsequent to sample destruction and data elimination, researchers must officially declare as such to both the participants and the ethics committee.
<i>Issues on Return of Results</i>		
9.	<p>Personal genome research projects should have an established process, approved by a research ethics review entity, for evaluating whether findings (incidental or otherwise) meet criteria for offering to individual participants (Figure 1). This process should be highlighted in the initial consent and should acknowledge the participants' right not to know certain results. (Caulfield et al., 2008)</p>	<ol style="list-style-type: none"> 1. Researchers are required to determine if study results (incidental or otherwise) meet criteria for offering to individual participants. This should be subject of approval by the ethics committee. 2. In the case that the researchers decide to return the study results to the participants, researchers must state in the informed consent the time frame of such results return. 3. The process of identifying and disclosing research results should involve professionals with the appropriate expertise required to provide the participant with sufficient interpretive information. (In general, the results offered should be scientifically valid, confirmed, and should have significant implications for the subject's health and well-being).
10.	<p>The process of identifying and disclosing research results should involve professionals with the appropriate expertise required to provide the participant with sufficient interpretive information. In general, the results offered should be scientifically valid, confirmed, and should have significant implications for the subject's health and well-being. Plans to return other forms of data— such as significant non-health-related data—should be built into the study design and governance structure.</p>	<ol style="list-style-type: none"> 4. Whenever applicable, this should be incorporated into the research methodology and budget for as far as any cost concerned. 5. Involvement of related professionals for this purpose should be highlighted within the research team OR as part of professional services.

(Caulfield et al., 2008)

6. Researchers are required to provide options to participants if they are willing to be informed of study results (incidental or otherwise), where such knowledge are currently available.
7. Researchers are required to provide options to participants if they are willing to be re-contacted of study results (incidental or otherwise), where such knowledge are currently unavailable but may be available in the future.
8. Whenever applicable, plans to return or not to return other significant non-health related data (such as incidental findings of non-paternity) should be shown in study design and stated in the informed consent.
9. Return of results should be implemented in accordance with genetic counseling processes and principles.

Issues on Public Data Release

<p>11.</p>	<p>Data release policies must be designed to appropriately balance the benefits and requirements of access against the privacy interests of research participants. The rationale for the proposed data release policy needs to be clearly explained, justified as necessary for the goals of research, and deemed acceptable by the relevant ethics review entity (Caulfield et al., 2008)</p>	<ol style="list-style-type: none"> 1. Use of public funds, resources and samples for research necessitates return of the benefit to the society at large, where public data release of the research results may serve. 2. Researchers are required to provide public data release policy within their study design/research methodology. <p>Example language <i>[whenever applicable]</i>: <i>As a community resource project, the 1000 Genomes Project publicly releases data on a regular basis [or specify if the data will be stored in a database, specify what database]. The database is freely available to the public, thus enabling retrieval of the data by anyone [specify if the database only allows paid access]. However, there will be no personal identifiers submitted to the database. Once we submitted the data to the database, it will not be possible to retract the data in case withdrawal ensues.</i></p> <p><i>The sequencing centers release the raw reads to the Sequence Read Archive (SRA). The Data Processing Group, Analysis Group, and Data Coordinating Center (DCC) release alignments, re-calibrated error rates, and SNP calls on individual samples. Data that passed quality filters are the most visible, but data that did not pass quality filters are also available. When the Structural Variation Group has developed its methods, the structural variant calls on individual samples will be released. Eventually the Project will release haplotypes and imputed variant calls. Data formats and analysis software developed by the Project are also made publicly available.</i></p> <ol style="list-style-type: none"> 3. Data release policy must include (but not limited to) rationale and justification for the proposed data release policy, what database to channel the data release, public coverage of the database, implications to withdrawal, and types and nature of data to be released. 4. Informed consent must particularly disclose implications of public data release to research participants, which include issues associated with family members and relevant groups/population, discussion of likely finality of the release process and the implications that this may have on privacy and the future right to withdraw.
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12.	The implications of data release must be adequately disclosed to the potential participants in the consent process. This disclosure should include a discussion of the likely finality of the release process and the implications that this may have on privacy and the future right to withdraw (Caulfield et al., 2008)	<p>5. Public Data Release policy is subject of approval by the ethics committee.</p> <p>6. Researchers are required to oblige to the provision stated in DNA Act 2009 and inform the participants on the risk that in case the participant become crime suspect, the police may collect their data from the researchers.</p>
13	Malaysian DNA Act 2009 stated that in the case of crime investigation, the police reserve the authority to collect DNA information of crime suspects.	
14.	As part of the consent and ethics review process, the issues associated with family members and relevant groups and populations should be considered (this may, for example, involve encouraging/requiring discussions with family members) (Caulfield et al., 2008)	

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