

Your Biobank, Your Doctor?

The right to full disclosure of population biobank findings

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"To wrest from nature the secrets which have perplexed philosophers in all ages, to track to their sources the causes of disease, to correlate the vast stores of knowledge, that they are quickly available for the prevention and cure of disease -- these are our ambitions." - Sir William Osler, 1906

Abstract

The advent of personal genomics companies offering direct translation of scientific data into personal health information, calls into question traditional policies to refuse disclosure of such scientific data to research participants. This seems especially true for population biobanks, as they collect not only genotype information but also associated phenotype information, and thus may be in a unique position to translate their scientific findings into personal health information for their participants. Disclosure of such information seems mandated by the expectations raised by biobanks ('to help bring about the era of personalized medicine') and their participants' rights to know health information, to know clinical research results, to life and health and particularly their right to benefit. Refusals to disclose such information can be grounded in the lack of analytical validity and/or clinical utility of most findings, the need to avoid the therapeutic misconception, the complexity and costs involved in translation and disclosure and the disproportionate burden resulting from the obligation to respect participants' right not to know before any disclosure can be made. Currently, any demands by participants in population biobanks for full disclosure of all pertinent personal health information potentially resulting from the biobank's scientific findings are unlikely to be granted by a Dutch court under Dutch and international law. As the law stands now, a population biobank is neither a doctor nor a personal genomics company. However, in view of the rapid scientific, medical, technological, commercial and social developments, population biobanks must prepare to take more care of their participants' legitimate interest in receiving as much validated personal health information as reasonably possible, in a timely fashion, by developing appropriate translation and disclosure mechanisms. This paper examines whether population biobank participants have the right, under Dutch civil law and international law, to full disclosure, i.e. to all information generated by the biobank that is pertinent to their present and future health. It pioneers the format of a hypothetical court case to elucidate the legal and policy arguments for and against full disclosure.

Introduction

If you provide your DNA to deCodeme, you will be provided, within 2- 4 weeks, with information on your genetic risk for a series of diseases, based on the relation of your genetic scan measurements to relevant scientific literature regarding genetic risks. If you provide your DNA to a population biobank, you will not be provided with any information, genetic or otherwise. True, a population biobank is not a commercial personal genomics company and the utility of “direct-to-consumer” susceptibility testing has been questioned. Nevertheless, the ability of companies like deCodeme to translate scientific findings into personal health information for their customers, in a matter of weeks, does raise the question why population biobanks decline any translation of their findings into personal health information for their participants. The question is even more pertinent given that a population biobank has all the data necessary for a proper translation that commercial providers have not: the phenotype measurements, the medical record, the family history and the life-style data of the individual participant, all regularly updated and accessible in standardized format.

The rationale for non-disclosure is that most research findings are aggregate findings of an exploratory nature, lacking analytical validity or clinical utility for the individual concerned. However, both the nature of population biobank studies and recent developments in technology, medicine and ethics seem to provide support for calls for more or even full disclosure to individual participants. In addition, international legal instruments increasingly recognize a right to feedback of research results in general. It has been argued, convincingly, that under common law a biobank might owe its participants a legal duty to feed back in the, admittedly rare, situation where biobank research reveals that an individual is at imminent risk of a serious yet treatable condition.² That argument, however, begs some questions. What, exactly, is a ‘serious condition’? What, exactly, is ‘treatable’? And, more fundamentally, why should such a duty be limited to imminent risks, to serious conditions and conditions that are treatable?

This paper examines whether population biobank participants have the right, under Dutch civil law and international law, to full disclosure, i.e. to all information generated by the biobank that is pertinent to their present and future health. It pioneers the format of a hypothetical court case to elucidate the legal and policy arguments pro and con full disclosure and to illustrate how a Dutch civil law court might arrive at its verdict. While fictitious, the case draws on a number of existing population biobank studies. The presentation of the facts of the case will be followed by the briefs of both parties, the considerations of the hypothetical court and the verdict.

Case study

The invitation. A healthy 45-year-old woman (X) receives an invitation letter from her family doctor (GP) to participate in a major study called the “Biobank”. Her GP explains to X that the study aims ‘to track to their sources the causes’ of common complex disorders, such as diabetes, cancer and Alzheimer’s. These disorders are

thought to be caused by a large number of small, often additive effects, representing the outcome of the interplay, at various levels, of genes, lifestyle and the environment.^{3, 4, 5, 6} To reveal these complex interactions, the Biobank will collect and study genetic, clinical, biological, and molecular information and corresponding blood and urine samples from 150,000 participants (patients and healthy persons) and their family members for 30 years. The samples and data collection will be a resource for multiple researchers to '*correlate the vast stores of knowledge*' for multiple studies of a host of common complex disorders. Eventually, the researchers hope to find out what determines the effect of a universal risk factor for a given disorder in a particular individual, such as X.

Joining the biobank. X decides to join the study. At an appointment at the assessment centre, a nurse practitioner measures her height, weight, BMI, pulmonary function, bone density and blood pressure. A specially trained staff member collects three tablespoons of her blood for future DNA-analysis and she provides a urine sample. She fills in a questionnaire, answering detailed questions about her education, employment, physical activity, nutrition habits, general health condition, smoking and alcohol consumption, hospitalisations, diseases suffered, medicaments used, hormonal contraceptive preparations and menopause medicaments, and pregnancies. There are also questions about her nationality and native language, as well as detailed questions relating to her parents, grandparents and great-grandparents. X signs a consent form allowing the Biobank to re-contact her and to follow her health for the term of her participation, directly through her medical record and through other records that may be related to her health (e.g. occupational or residential information). She goes home with a print-out of her measurements. Every other year, she shows up at the appointment centre to provide fresh samples and updates to the questionnaires.

Demanding disclosure. Halfway into the study, X develops diabetes and suffers a heart attack. As cardiovascular diseases run in the family she is fearful of an imminent stroke. Her daughter has just been recruited into the study and was informed that both her cholesterol level and her blood pressure were abnormally high. Fearing that this may all be related and 'genetic', X contacts the Biobank. For some years now, the Biobank's newsletters have alerted her to a series of scientific publications pertaining to these disorders, all based on research on the Biobank. She reminds the Biobank of its stated ambition that research findings should be '*quickly available for the prevention and cure of disease*'. Arguing that the Biobank is in a perfect position to translate its findings to her individual situation, she demands disclosure of all genetic and non-genetic risk information pertaining to her present and future health, regardless of whether the risks indicated by the findings are imminently life-threatening, high, moderate or low risk, regardless of whether the findings concern a condition that is treatable, actionable, have reproductive importance or are merely recreational, and regardless of whether the findings relate to conditions that are late or early onset.

The lawsuit. The Biobank denies her request, referring to the Participant Information Brochure, which reads as follows:

Participants will NOT be provided with information (genetic or otherwise) about their own individual results or incidental findings derived from or made in the course of examination of the database or samples by research undertaken after enrolment.

X initiates legal proceedings, challenging the Biobank's non-disclosure policy. She posts her complaint on the Biobank webforum, which in no time is filled with expressions of support from thousands of other participants, who are willing to join the lawsuit.

The Tuskegee Experiment. In 1932 the US Public Health Service (PHS), with the approval of Tuskegee Institute and the local health department, initiated in Macon County, Alabama, an observational study to determine the natural course of untreated, latent syphilis in black males.⁷ The study comprised 410 Negro men with untreated syphilis and a comparable group of 201 uninfected Negro men.⁸ The syphilites were recruited under the impression that they were being treated for their ‘bad blood’, a local idiom that encompassed syphilis as well as some anemias.⁹ They were enticed with offers of free medical examinations and special free treatments.¹⁰ Although data from the Study were reported in medical journals, neither the general public nor, with the exception of a few local doctors and administrators and officials of the Tuskegee Institute, the public in Macon County had any knowledge of the study until it was exposed by the Associated Press in 1972.^{11, 12} After a 1973 government report concluded that the study, in retrospect, was ethically unjustified and that penicillin should have been made available to the participants in the study not later than 1953, the study was halted.¹³

The lawsuit. Surviving participants filed a lawsuit against the US federal government, Casper Weinberger as Secretary of the Department of Health, Education and Welfare, the Public Health Service, the State of Alabama, the Milbank Fund and a number of individuals connected with the study, seeking \$1.8 billion in damages for the surviving participants and the heirs of those who had died (*Pollard v. United States of America*).¹⁴ Alleging that the Public Health officials purposely did not inform the participants when they were found to have syphilis, that they intentionally withheld this information from participants, that the participants were never advised that any of them had syphilis, and were never treated for syphilis, the participants’ attorney claimed that the government had violated their civil rights guaranteed under the Fifth, Ninth, Thirteenth and Fourteenth Amendments to the Constitution of the United States and Article I, section VI of the Alabama Constitution of 1901.¹⁵

X’s Brief

Theory of X’s case

Legal arguments. To support her claims, X advances a variety of legal arguments under Dutch civil law and international law. First, she invokes the terms of her participation in the Biobank which are set forth in the consent form (A. Contract). Second, she maintains that the Biobank’s non-disclosure policy has become obsolete, in view of scientific, technological and societal developments (B. Invalidity of Non-Disclosure). Third, she invokes a number of statutory, constitutional and international human rights and professional norms to support her action for negligence (C. Negligence).

A. Contract

A. 1 Consent and Patient Information Brochure. X’s relationship with the Biobank is, primarily, governed by contract. She participates in the Biobank on the basis of her

informed consent. Her consent is based upon the information she has received from the Biobank: the Participant Information Brochure (PIB). Collectively, the consent document signed by X and the PIB set forth the contractual terms and conditions of her participation. A core provision of the contract is X's right to discontinue her participation and to withdraw her consent. X admits that she has the right to withdraw at any time. But her point is that her right to withdraw entails the right to be informed on any relevant personal findings so she can make an informed decision whether she has reason to withdraw. Her willingness to continue to participate might be affected by significant new findings developed during the course of the research. The implications of these findings for an individual, no matter how qualified and limited in terms of analytical validity and clinical utility, may lead her to reconsider her initial consent and to withdraw from the study.^{16, 17} She can only effectively use her right to withdraw if she receives disclosure of the Biobank's findings.

A.2 Raised expectations. X also claims that the Biobank raised her expectation that she would receive information pertaining to her personal health. According to the PIB, the study aims to link abstract genomic data with concrete patient medical records, to generate large amounts of data to accurately describe patients and to bring about the era of personalised medicine. These objectives were a major incentive for X to participate in the study and part of the contract. As the Biobank could have known that a primary reason for participants to participate in genetic studies is their wish to find out about their own health, not disclosing pertinent health information amounts to a breach of contract.

B. Invalidity of Non-Disclosure policy

B.1 Non-disclosure policy obsolete. The traditional policy of non-disclosure rests on a number of considerations, which include, but are not limited to, (i) the fact that most research findings in epidemiology or cohort studies are aggregate findings of an exploratory nature, with little or no analytical validity or clinical utility for the individual concerned, (ii) the costs, competence and complexity involved in proper reporting to individuals and (iii) the fact that these findings ordinarily cannot be linked to identifiable participants.¹⁸ Also, the policy is based on the traditional concept of hypothesis-driven research. For this type of research, the chances of making incidental findings, i.e. findings discovered in the course of conducting the research but *beyond* the aims of the study, were considered to be minimal. Traditional disclosure policies are based on the recommendation that the research must be designed so as to *minimize* the chances of an incidental finding.¹⁹ X argues that the above rationale has become obsolete, in view of the nature of Biobank research developments in technology, medicine and society.

B.1.1 Nature of Biobank research. Unlike most traditional studies, the Biobank is designed to form a *resource* that will enable the conduct of not just one, but hundreds of different research projects into all kinds of diseases, some of which have yet to be formulated, by a host of multidisciplinary research teams, rather than focusing on a

specific disease.²⁰ It is expected to identify risk factors related to more than one disease and the occurrence of various diseases within one individual.²¹ The Biobank is set up to facilitate large-scale genomic epidemiology pursued as “discovery research”. In such research any genomic pattern correlating with pathology may be captured and studied.²² Finally, the Biobank researchers have the ability to link research findings to individual research participants and, in many cases, to participants’ blood relatives.²³

B.1.2 Technological and scientific developments. X further points to a number of new high-throughput technologies used by the Biobank which are capable of generating large amounts of information at low cost and high speed.²⁴ In addition, Genome Wide Association Studies (GWAS)²⁵ permit interrogation of the entire human genome at levels of resolution previously unattainable, in thousands of unrelated individuals, unconstrained by prior hypotheses regarding genetic associations with disease.^{26, 27} Even if their purpose is not to provide results about individual participants, the work may generate such results, ranging on a continuum from clinically significant information to information relevant to ancestry and genealogy, to information that is merely of recreational interest.²⁸ Every time a GWAS is conducted, the researcher has the opportunity to look in each individual’s DNA, not only for data that correlates with the disorder being studied, but also for other data that have been identified with other disorders.²⁹

B.1.3 ‘Translational’ developments. One of the rationales of traditional non-disclosure policies is that the interpretation and application of scientific findings in the clinic requires a chain of evidence, the goal being to translate findings from “PubMed to patient”. It involves replication, randomized clinical trials, professional consensus building, the adoption of protocols, and the establishment of analytical validity and clinical utility. The ultimate use of the information in the clinic is controlled and limited by the physician as the traditional gatekeeper of the healthcare infrastructure. This traditional chain of translation has been challenged by the emergence of personal genomics services. Personal genomics companies^{30, 31, 32} claim to be able to bridge the gap between peer-reviewed and published findings on the one hand and the individual, or at least, his genotype, on the other.^{33, 34} Using scientific, published knowledge, they analyze samples collected at home, to discover individual predispositions for a variety of common conditions.^{35, 36, 37} X argues that if these companies can translate the scientific literature into personal health information in a matter of weeks, then the Biobank could do the same for her, and more. After all, it is the Biobank that is the primary producer of such findings. On top of that, the Biobank has superior, long-term access to all relevant phenotype data, stored in a standardized way, to help translate its findings into personal health information for the individual participant.

C. Negligence

The third argument advanced by X is an action for negligence. For a negligence lawsuit to succeed under Dutch civil law, X must establish that the refusal by the Biobank to feed back findings, intended or incidental, to X either infringes upon her personal rights (*C.1 Personal rights*), or breaches a statutory obligation (*C.2 Statutory obligation*), or violates a generally accepted standard of care (*C.3 Standard of care*).

C.1 Non-disclosure infringes personal rights. X claims the following personal rights: the right to know health information; the right to know research results; the right to benefit; the right to life; and the right to health.

C.1.1 Right to know health information. X asserts that she has a right to know health information. She refers to the Convention of the Council of Europe for the Protection of Human Rights and Dignity of the Human Being with regard to the application of Biology and Medicine.³⁸ This convention covers all medical and biological applications concerning human beings, including research applications.³⁹ Pursuant to article 10 everyone is entitled to “know” any information collected about his or her health. According to the Explanatory Report, a person's "right to know" encompasses all information collected about his or her health, whether it be a diagnosis, prognosis or “any other relevant fact”.⁴⁰ In addition, Article 13 of the Additional Protocol to the Convention on Human Rights and Biomedicine provides that, before being asked to consent to participate in a research project, “the persons concerned shall be specifically informed, according to the nature and purpose of the research, of arrangements for access to information relevant to the participant arising from the research and to its overall results”. The protocol further provides that research participants shall be entitled to know “any information collected on their health” in conformity with the provisions of Article 10 of the Convention. If research gives rise to “information of relevance” to the current or future health or quality of life of research participants, this information must be offered to them. That is to be done within a framework of health care or counselling. As to the availability of results, Article 28 of the Additional Protocol provides that the conclusions of the research shall be made available to participants in reasonable time, on request. Notably, this right is limited neither to information on “real and immediate risks” to her life, nor to information on risks which are treatable or actionable.

C.1.2 Right to benefit. X refers to a series of international instruments in the area of biomedical research that all call for benefit sharing. For example, the International Declaration on Human Genetic Data,⁴¹ which specifically applies to biobanking, requires that the benefits resulting from the research on the data be shared with society as a whole. And Article 3 of the Universal Declaration on Bioethics and Human Rights⁴² provides that, in advancing scientific knowledge, direct and indirect benefits to patients, research participants and other affected individuals should be maximized. In giving effect to the principle of benefit-sharing, benefits may take the form of special assistance to the persons participating in the research, provision of new diagnostics stemming from research, or access to scientific knowledge. X argues

that her participation in the Biobank amounts to a significant contribution. In addition to providing, biennially, blood and urine samples, she frequently fills in questionnaires, answers detailed questions about her education, employment, physical activity, nutrition habits, general health condition etc. She has also allowed the Biobank access to her health records and other records that may be related to her health. X maintains that, in exchange, the Biobank owes her a benefit in the form of full disclosure of any findings pertinent to her health.⁴³

C.1. 3 Right to life. X also invokes her right to life, laid down in Article 2 of the European Convention on Human Rights (ECHR).⁴⁴ As well as a negative obligation not to take anyone's life, this right imposes a positive obligation on the state and public authorities to protect the right to life.⁴⁵ Applying the Convention to the non-disclosure policy of UK Biobank, Johnson and Kaye have argued that Article 2 of the ECHR could impose a positive obligation on UK Biobank to put in place measures to avoid a risk to the lives of the participants.⁴⁶ More specifically, citing the Osman case⁴⁷ they argue that this positive obligation entails the provision of feedback of risk of a serious genetic disease, if this is revealed during the course of the research project.⁴⁸ In Osman, the ECHR noted that Article 2 of the Convention might, in well-defined circumstances, imply a positive obligation on the authorities to take preventive measures to protect an individual whose life is at risk from the criminal acts of another individual. X takes this a step further and asserts that she can reasonably expect the Biobank to take measures to avoid any risk, not just genetic risks, as the Biobank has or ought to have superior knowledge and access to all relevant records.

C.1. 4 Right to health. Next, X invokes her right to health. Failure to protect a person's health may amount to a breach of the right to respect for one's private life, set forth in Article 8 of the ECHR.⁴⁹ 'Private life' includes not merely a right to control personal information, but also protection of privacy interests in physical and moral integrity.^{50, 51} The right imposes both negative and positive obligations on the state, including a right to have assistance in the fulfilment and enjoyment of one's private life.⁵² X argues that Article 8 also applies to the Biobank as a semi-public institution, so that failure by the Biobank to disclose "essential information that would enable her to assess the risks she and her family might run" constitutes a violation of her right to health.⁵³

C.2 Non-disclosure violates statutory obligations

X maintains that the Biobank's refusal to feed back pertinent health data violates a number of statutory obligations.

C.2.1 Clinical trials. X analogizes her situation with that of human subjects in clinical trials, who are protected by the Dutch Act on Medical Scientific Research involving Human Subjects. The Act provides that participants in clinical research enjoy certain

information rights during the trial. Specifically, in the event the trial has serious events that turn out to be more adverse than foreseen in the research protocol, the investigator must immediately notify the trial subject. In addition, Article 10 of the Act provides that the investigator is responsible for informing the subject about “the course of the trial”.

C.2.2 Right to know medical record. As a patient, X has a statutory right to know all the health information kept by her treating physician in her medical record. That would include information about diagnosis, test results, prognosis, risks and treatment.⁵⁴ According to X, this right should be extended to health information generated in the context of the Biobank for the following reasons. First, the Biobank has been established by and forms an integral part of a series of academic hospitals. From X’s perspective, the Biobank is an extension of the healthcare infrastructure. Second, X’s donations of blood and urine and physical examinations qualify as medical examinations. Third, the Biobank research on her samples and data is not an isolated and incidental affair, performed in a remote university lab. Rather, all measurements and findings have added to an integrated and comprehensive dataset that the Biobank can combine with access to her health records, family history and life-style data. X argues, therefore, that the Biobank setting crosses the line between research and care.

C.3 Negligence: Breach of generally accepted standard of care

It has been argued that researchers have a duty of ancillary care to subjects of research, based on the principle that, by participating in (clinical) research, participants entrust their health to the researchers.⁵⁵ In the context of the Biobank, this duty encompasses the duty to feed back findings to individual participants. In support of this claim, X cites the International Guidelines for Ethical Review of Epidemiological Studies issued by the Council for International Organizations of Medical Sciences (CIOMS)⁵⁶ and international precedent.

C.3.1 CIOMS Guidelines. The CIOMS Guidelines apply to epidemiological studies. They are based on the four basic ethical principles governing all research involving human subjects: *respect for persons*, *beneficence*, *non-maleficence*, and *justice*.⁵⁷ Respect for persons incorporates *autonomy*, which requires that those who are capable of deliberation about their personal goals should be treated with respect for their capacity for self-determination. *Beneficence* is the ethical obligation to maximize possible benefits and to minimize possible harms and wrongs.⁵⁸ *Non-maleficence* (“Do no harm”) holds a central position in the tradition of medical ethics, and guards against avoidable harm to research subjects. The principle of *justice* is mainly concerned with the rules of *distributive justice*: the class of persons bearing the burden should receive an appropriate benefit. The preamble to the CIOMS Guidelines provides that part of the benefit that communities, groups and individuals may reasonably expect from participating in studies is that they will be told of

findings that pertain to their health.⁵⁹ In informing individuals of the findings and their pertinence to health, their level of literacy and comprehension must be considered. Research protocols should include provision for communicating such information to communities and individuals.⁶⁰ In addition, research findings and advice to communities should be publicized by whatever suitable means are available. This may entail that, where feasible, specific testing and individual counselling ought to be available.⁶¹ And when findings indicate a need for health care, those concerned should be advised of means of obtaining personal diagnosis and advice.

C.3.2 Disclosure of findings is supported by international precedent. X refers to the Estonian Genebank, a project similar to the Biobank. The Estonian Genebank is a national Gene Bank consisting of tissue samples, descriptions of DNA, descriptions of state of health and genealogies of the Estonian population. The objective of the Estonian Genebank is twofold: to enable gene and health research to find genes that influence the development of illnesses and to provide a gene donor with an opportunity to assess his or her health risks and diagnose illnesses more precisely, prevent illness and receive more effective treatment in the future.⁶² Gene donors participating in Estonian Gene Bank have the right to access personally their data stored in the Gene Bank, except for their genealogies, for free. In addition, the Estonian gene donors have the right to genetic counselling upon accessing their data.⁶³

The Framingham Heart Study. In 1948, at a time that the administrators in the Tuskegee study should have realized that an effective medicine had become available for their subjects, the US Public Health Service initiated what is considered the ‘mother of all biobanks’, the Framingham Heart Study.⁶⁴ The study was to look for the root causes of cardiovascular diseases (CVD), which had become an American epidemic.⁶⁵ The project was designed to study the expression of coronary artery disease in a “normal” or unselected population and to determine the factors predisposing to the development of the disease through clinical and laboratory examinations and long-term follow-up of such a group.⁶⁶ The researchers recruited 5,209 men and women between the ages of 30 and 62 from the town of Framingham, Massachusetts. With time, they found suggestive links between high blood pressure and heart disease, between tobacco use and heart disease, and between elevated levels of blood cholesterol and heart disease.⁶⁷ The researchers wanted everyone to have the information they had on the risk factors for heart disease. Reportedly, at times they wanted to shout from the rooftops: “*Quit smoking*”, or “*Lose weight*”. But all they would say was “*See your physician*”.⁶⁸ This policy of non-disclosure rested on two premises. First, the objective of the study was to be a long-term observational study of healthy people, not to be a public health program. Before the physicians could *do* anything about heart disease, they had to wait for others to transform the Study’s findings into treatments and preventive measures.⁶⁹ Second, the local doctors of Framingham were worried that the Heart Study was the first step toward federal

intrusion into their practice - they wanted to be sure that they would not lose their patients to the Study's doctors. To maintain the trust of local physicians, the Study's researchers would not treat or even offer advice to the participants they were seeing. The only way to let the volunteers' physicians, and all physicians, know what advice to give was to publish the results of their years of observation. These publications had a powerful effect and laid the groundwork for translating medical research from the observations to real changes in the way doctors practice medicine.⁷⁰ Over the years, careful monitoring of the Framingham Study population has led to the identification of the major CVD risk factors - high blood pressure, high blood cholesterol, smoking, obesity, diabetes, and physical inactivity.⁷¹ The accomplishments have been listed among cardiology's 10 greatest achievements of the twentieth century.⁷²

The Biobank's brief

The Biobank advances a number of legal defences. It claims that its contractual non-disclosure policy is clear (*A. Clear contract*) and its underlying rationale still valid (*B. Rational policy*). Next, it argues that the personal rights invoked by X do not apply (*C. No negligence*). Finally, the Biobank counters that an obligation to (offer to) disclose its findings would be at odds with a series of law and policy considerations (*D. Statutory, medical and practical justifications for non-disclosure*).

A. Clear contract

The Biobank maintains that the PIB contains a clear explanation of the Biobank's disclosure policy. By signing the consent form X has agreed to this policy, the terms of which are crystal clear and not in need of further interpretation. The references in the PIB to personalised medicine are generic descriptions of the ultimate goal of the bank. They cannot reasonably be construed so as to confer on participants an enforceable right to receive personalised feedback on Biobank findings. Similar limitations on the disclosure of findings have been upheld by the courts in the context of population screening, when population screening administrators and radiologists were sued for not reporting findings or reporting findings as 'not suspect', which later turned out to be malign and fatal.

B. Rational Policy

The rationale for the non-disclosure policy is still valid. Statutory standards of clinical care would require any feedback to be analytically valid, clinically valid and have clinical utility.^{73 74} The assessment of analytical validity would require the performance of independent confirmatory testing. Clinical validity refers to the quality and quantity of empirical evidence regarding the association between a genotype and a particular clinical outcome.⁷⁵ The interpretation of associations reported by research on the Biobank requires a chain of evidence substantiating the validity of the association found in a single initial study.^{76 77 78} Results that do not

meet this basic prerequisite simply do not constitute “information” and the Biobank cannot reasonably be held to an obligation to provide “non-information”.

C. No negligence

C.1 No breach of personal rights.

C.1.1 International declarations are not binding. The international declarations invoked by X are either non-binding or non-enforceable, as they have not been ratified in the Netherlands. They are directed at Member States. Absent implementation at the national level, the instruments cannot be used to construe enforceable obligations on the part of the Biobank in a private cause of action.

C.1.2 International declarations do not apply to observational research. Most international instruments invoked by X do not apply to the Biobank anyway, as they apply to interventional or clinical research rather than the observational research pursued by the Biobank. Admittedly, the Council of Europe Recommendation (2006) on research on biological materials of human origin does apply to research using biological materials kept in population biobanks. However, it does not contain a provision on disclosure of the results from this type of research. The Recommendation even puts severe limitations on the type of screening to be done in such biobanks. It stipulates that screening for serious late-onset diseases for which there is no treatment should remain exceptional, even when screening is related to scientific research, as it would put too much strain on the free participation and on the privacy of individuals.⁷⁹

C.1.3 International guidelines limit reporting obligations. The international instruments and declarations invoked by X do not provide for an unconditional obligation on the part of scientists to feed back findings to individual participants. Article 10 of the International Declaration on Human Genetic Data explicitly provides that it does not apply to research on data for which links to identifiable persons are irretrievably broken or to data that do not lead to individual findings concerning the persons who have participated in such a research. The CIOMS Guidelines allow that an ethics committee may approve the non-disclosure of the data for a stated reason that will, itself, be given to the participant. Such reasons could include: lack of relevance of data, limitations of predictive capability of research data, concerns of misinterpretation by the participant, absence of ‘good clinical practices’ standards in exploratory research or lack of feasibility (e.g., data are anonymised). Also, the duty to inform research subjects of any finding that relates to their particular ‘health status’ at the end of the study is open to wide interpretation – it is not clear that it would include most polygenic determinants of disease susceptibility, even if they had been validated.⁸⁰ The CIOMS Guidelines provide that subjects of epidemiological studies

should be advised that it may not be possible to inform them about findings that pertain to their health, but that they should not take this to mean that they are free of the disease or condition under study.

C.1.4 No violation of the right to life and health. The European Convention on Human Rights is directed at states. It does not impose positive or negative obligations on “non-state” entities such as the Biobank. In the *Osman* case cited by X, the European Court of Human Rights made it clear that any positive obligations for the State (to safeguard lives or to protect private and family life) must be interpreted in a manner that does not pose an impossible or disproportionate burden, bearing in mind the difficulties involved in policing modern societies, the unpredictability of human conduct and the operational choices which must be made in terms of priorities and resources. For the Court not every claimed risk to life could entail for the national authorities a Convention requirement to take operational measures to prevent that risk from materializing.⁸¹ *Osman*, furthermore, is clearly distinguishable from the Biobank scenario at hand. Unlike *Osman*, which involved specific, acquainted individuals involved in a series of (alleged) criminal confrontations over a couple of years, the Biobank cannot reasonably know, without extensive translation, decoding and interpretation of a given finding, whether a specific individual is at a particular risk.

C.2 No violation of statutory rights

C.2.1 No right to know research results. No such right exists, the Biobank claims, as regards the outcome of scientific, non-interventionist studies. In fact, such a right does not even exist as regards the outcome of interventional research, i.e. clinical trials. The Dutch Medical Research on Human Subjects Act,⁸² which implements the EC Directive on Clinical Trials, does not contain an obligation to inform subjects of trial data of any nature. Notably, neither the EC Clinical Trial Directive, nor the International Conference on Harmonisation of Good Clinical Practices (ICH-GCP) nor even the Declaration of Helsinki contains an obligation to inform subjects of trial data. Indeed, Renegar et al have concluded that there appears to be no definitive requirement in relevant laws and regulations in the US or the EU that research results have to be, in all circumstances, returned to study participants.⁸³

C.2.2 Right to know medical record does not apply. The Biobank operates a resource for scientific research. It is not a healthcare provider and its participants are not its patients. Hence, the statutory right of a patient to know his medical records and any corresponding obligations for healthcare providers, such as the duty to disclose to patients all health information collected in the course of diagnosis, prognosis and therapy, do not apply to the Biobank setting.

C.3 No violation of standard of care

C.3.1. No conflation of care and research. X wrongly implies that standards for clinical practice and clinical research can be extended to observational research. The goal of clinical practice is improvement of the individual health of patients. In contrast, the goal of research is development of generalizable knowledge for the benefit of society and future patients.⁸⁴ Much effort has been spent in making a clear delineation between the role of the researcher and the role of the treating physician, because of the conflict of interest that the dual roles present.⁸⁵ Imposing an obligation on the Biobank to (offer to) feed back findings to individuals would reinforce the ‘therapeutic misconception’ held by participants and sometimes also by researchers. Some have even proposed a *per se* ban for treating physicians to do research on their patients.⁸⁶ From the researcher perspective too, blurring the lines between clinical research and research obligations should be undertaken only for compelling reasons, based on accurate information and clear informed consent.⁸⁷

C.3.1.2 Ancillary care and bailment analogy does not apply. The Biobank further argues that no duty of ancillary care can be based on the theory of ‘entrustment’. Such a duty is grounded in the vulnerability and dependency of participants.⁸⁸ However, participation in the Biobank does not render the participants ‘vulnerable’. Most of them are not patients, but healthy volunteers. And if they become patients during the course of their participation, they will be treated outside the Biobank setting, in an ordinary clinical care setting. Likewise, the participants in the Biobank are not dependent on the Biobank. They can withdraw from the Biobank at any time. The Biobank does not offer them anything they need to maintain their health, to cure their disease or to take informed reproductive decisions. To fulfill these needs, they are dependent on their GP or specialist healthcare professional, not on the Biobank. Likewise, the legal theory described in the law concerning bailment does not hold in the context of the Biobank. The Biobank is not a bailee. It is not offering a service of any kind. It is not a depository where people can store their samples and data and have them returned or fixed. The Biobank has not undertaken to heal, cure or care for any participant. It is a research facility where people can donate samples and data for future research. Another vital element belying the classification of the relationship between participants and the Biobank as entrustment or bailment is the fact that the participants are not being charged. If the Biobank were to be seen as a professional bailee of some sort, with ancillary duties on top of its obligations as a bailee, then, under Dutch law, it would have a statutory right to compensation for its services.⁸⁹

C.3.1.3 Case law on standard of care. It follows from a number of Dutch court cases that clinicians performing population screening are not held to a standard of clinical care, but to a standard akin to that applied to reasonably acting and reasonably competent “screening” radiologists in “similar circumstances”.⁹⁰ Whether the standard has been breached has to be determined by an expert witness, taking into account the population screening in its original context. Applying this standard to the Biobank situation, it is clear that the Biobank will not be held to the standard of an individual medical professional acting in a clinical setting. Instead, it will be held to

the standard of a reasonably acting researcher, in similar circumstances. This standard is even lower than the standard for population screening, as the Biobank is not intended to find high or low classes of at-risk individuals, but to carry out research, and as the researchers are not clinicians.

C.3.2 Foreign examples. The Biobank's policy of non-disclosure is further supported by a number of similar policies of similar biobanks in other countries. In the Singapore Tissue Network, neither donor nor doctor will receive the results of research carried out using donated samples.⁹¹ The UK Biobank will not provide individual feedback to participants of results obtained through the research process for any reason.⁹² Participants in the Canadian biobank CartaGene will not receive any individual research results, unless they have opted to receive a document containing the measurements taken during the enrolment visit.⁹³ Generation Scotland will give participants health information on some important clinical measurements such as blood pressure, cholesterol and kidney function, but no personal genetic information.⁹⁴ The current consent form for the Framingham Heart Study provides that participants will not be informed of the results of the research performed upon their genetic blood sample, although genetic tests may be developed as a result of the combined analysis of samples in the Framingham Heart Study.⁹⁵

D. Statutory, medical and practical justifications for non disclosure

D.1 Statutory justifications for non-disclosure

D.1.1 Compliance with domestic law. Any offer to disclose any findings must be compliant with domestic law. This truism was reiterated by the European Court of Human Rights in *Osman*, where the Court considered as a relevant factor the need to ensure that the police exercised their powers to control and prevent crime in a manner which fully respected the due process and other "guarantees which legitimately placed restraints on the scope of their action" to investigate crime and bring offenders to justice. Applied to biobanks, any obligation to feed back results and findings, indeed any obligation to warn, is always subject to statutory, legitimately placed restraints.

D.1.2. Protection of the public against false alarm/assurances. According to the Biobank, meeting X's request for health information in compliance with these statutory restraints is not feasible. The provision of medical or health information by public- and private-sector parties to populations, subpopulations and individuals, both healthy and affected, is governed by a host of sometimes conflicting statutes and EC directives. The thrust of these consumer and patient protection regulations is to protect the general public against "false alarms", "non-actionable alarms" and "false reassurances". To that end, these regulations prohibit or condition the generation and provision of health information. The thrust of these conditions is that both the information and the way it is offered and presented must meet certain standards. These standards range from technical requirements for the devices used in generating the information⁹⁶ to a prior demonstration of a positive outcome of a cost-benefit

assessment of the offer of the information.⁹⁷ There is no reason why such protection would not extend to the information generated in the Biobank context. The Biobank cannot be obliged to provide or to offer to provide information that otherwise would not pass statutory standards in similar or analogous settings. A substantial part of the information generated by the research on the Biobank's data is unlikely to meet these standards. Put briefly, as national and international regulators step up efforts to curtail the offer of health risk information,⁹⁸ the Biobank cannot be obliged to lower the bar.

D.2 Medical and practical justifications for non disclosure

Pursuant to the Dutch Civil Code no act or omission is wrongful in the event of 'force majeure', i.e. circumstances which justify an otherwise actionable act or failure to act. The Biobank advances the following justifications: complexity, costs and consent to know.

D.2.1 Complexity and (in)competence. The broad array of new genome-scale tests has led to the discovery of multiple abnormal or 'unexpected findings', analogous to the 'incidentalomas' that are often discovered in radiological studies.⁹⁹ The application of comprehensive genotype and functional genomic measurements across the general population is likely to yield incidental findings for nearly everyone. Any large-scale genomic panel is therefore likely routinely to report false-positive results. Even if genomic tests were to achieve 100% sensitivity and a false-positive rate of 0, the risks of the incidentalome remain and will lead to iatrogenic pathology, i.e. aggressive diagnostic and therapeutic investigations in an otherwise healthy individual.¹⁰⁰ The consequences of an incidentalome for Biobank researchers are obvious. To oblige them to look beyond the variables under study to findings of potential clinical significance for individual participants would place on them a disproportionate burden. Lacking clinical competence¹⁰¹ and professional clinical qualifications¹⁰², Biobank researchers would be overwhelmed by the complexity of pursuing all sorts of genomic measures. As even regular healthcare providers lack training and expertise in the interpretation of genetic research results,¹⁰³ X might be subjected to unnecessary follow-up tests.¹⁰⁴

D.2.2 Costs. Even the most ardent proponent of a reporting obligation has acknowledged that the disclosure of results has economic implications for researchers in planning their budgets and for funding agencies in determining an appropriate level an duration of funding.¹⁰⁵ Or, as another 'full disclosure' proponent put it: "The problem, of course, is money".¹⁰⁶ The consequence of requiring researchers to budget for managing incidental findings is "in the present financial climate ...that half as much research gets done, and that has, in my mind, a much greater impact on society than the very, very low incidence of incidental findings which are actually correct and an even lower incidence where there is something you could have done".¹⁰⁷ The setting in which Biobank results are generated typically lacks the resources for additional research, replication of results and clinical counselling and follow-up of

individual participants. Costs will be increased by the requirement that the disclosure of genetic and predictive health information must be “subject to appropriate genetic counselling”.¹⁰⁸ Notably, Article 7.1 of the recent Additional Protocol to the Convention on Human Rights and Biomedicine provides that ‘a genetic test for health purposes may only be performed under individualized medical supervision’.¹⁰⁹ According to the explanatory report, ‘a precise evaluation of the situation of the person concerned, involving direct contact with a medical doctor with him or her, is a determining element in that respect. A mere telephone conversation with a medical doctor, for example, does not allow for such evaluation’. This requirement of ‘live’ and individualized medical supervision is likely to impose a disproportionate burden on the Biobank, in view of the volume of findings and participants.

D.2.3 Consent to know. All international legal instruments relied upon by X provide that the participants’ right not to know should always be respected. However, participants’ desire to know or not to know cannot be fixed at the outset, but will vary according to their age, sex, offspring, education level, employment status, ethnicity, religion, health status and other factors. Their wishes will also vary according to the disease concerned, probability of onset, and the (im)possibility of an intervention. Their wishes may also change over time, as participants grow sadder and wiser or as therapeutic or life-style modifications become possible. The wealth of findings and the infinite variety of participants’ desires to know or not to know these findings would make it practically unfeasible for the Biobank to meet the requirement of obtaining participants’ prior informed consent to know. The Framingham Heart Study, for example, has produced more than 1000 scientific papers since its inception or some 20 papers per annum.¹¹⁰ If the Biobank reporting obligation were to be limited to published findings (disclosure proponents claim it could also cover unpublished findings),¹¹¹ then the Biobank would have to go back to 150,000 individuals (or their GPs) 20 times per year to ask them whether or not they want to be informed on the individual implications (positive or negative) of the finding concerned.

Considerations of the court

The outcome of the case is hard to predict. The above discussion has been limited to the threshold legal issue of whether participants have the right to receive (full) disclosure of pertinent health information. In practice, any liability of the Biobank in this respect will depend on the circumstances of the case, procedural issues, statute of limitations, burden of proof, damages (loss of chance), and causation. Much will also depend on the actual configuration of the Biobank, which involves a heterogeneous set of stakeholders, including not only the Biobank itself, but also third-party researchers (academic and from industry). The Biobank is not necessarily in a position to secure relevant disclosures from these third parties. Subject to these limitations, a Dutch civil law court might consider as follows.

In essence, this case pitches an intuitively appealing claim of lifelong participants in a population biobank for disclosure of pertinent health information against the logically appealing notion that this biobank is not their doctor. The fate of the participants in the Tuskegee Experiment (a public health observational study of the natural course of untreated syphilis) reminds us of the imperative to inform research participants that (i) they are the subjects of an investigation, (ii) whether or not they actually suffer from the disease under investigation and (iii) whether an evidence-based intervention is available to cure or prevent such disease. On the other hand, the successes of another public health observational study, the Framingham Heart Study, are a reminder that observational research should focus on observation, validation and publication rather than direct translation into clinical application.

The arguments to be made on either side can be summarized as follows.

According to X the following arguments support her claim for full disclosure of pertinent health information: the (contractual) terms of her participation; the characteristics of the Biobank research; its stated purpose of linking abstract genomic data and concrete patients records; the expectations it raised of delivering personalised medicine; the embedding of the Biobank research in an academic-clinical setting which blurs the line between research and care; developments in technology, science and society; her (international human) rights to know health information, the right to know clinical research results, her right to life and to health; and, last but not least, her significant, lifetime contribution to the Biobank of a wealth of detailed and sensitive samples and data (right to benefit).

According to the Biobank the following arguments speak against (full) disclosure: the unambiguous language of its policy of non-disclosure and the rationale behind it; the lack of analytical validity and/or clinical utility of most findings; the need to avoid conflation of research and care; the inappropriateness of applying standards developed for clinical research to observational research; the Biobank's lack of (statutory) competence to provide health information to individuals; the complexity and costs associated with reporting a potentially endless number of sometimes conflicting findings; and the disproportionate burden resulting from the need to respect the right not to know before any disclosure can be made.

It goes without saying that the legal duty to warn of imminent dangers implies that the more the requested data pose a real, imminent and actionable risk to X, the more likely it is that a reporting obligation on the part of the Biobank will be found. Also, the more the Biobank has raised the level of feedback expectations, the more likely it is that it will be required to meet those expectations. However, the terms of the non-disclosure policy at hand are indeed unambiguous. The Biobank may have raised some expectations, but the references to personalised medicine are too global to uphold a claim for disclosure of findings at the individual participant level. Case law in the analogous area of population screening suggests that a proper 'non-disclosure

policy' will be upheld. The case law also suggests that the Biobank is unlikely to be held to a clinical standard of care or even a standard of 'semi-clinical' care. Participants in the Biobank should and could have realized that the Biobank is not and cannot be their (collective) doctor. Rather, the standard of care of the Biobank must be determined in the proper context, i.e. the research context, taking into account all relevant circumstances.

As evidence of the predictive value of genetic variants accrues, investigators may face growing pressure to report findings that have an influence on risk.^{112 113} Some commentaries maintain that participants are even entitled to receive provisional results, with an explanation of the limitations of the data.¹¹⁴ Concurrently, a trend in international legal instruments towards the recognition of a right to feedback of research results has been reported in ethical and legal commentaries. These soft law instruments and opinions could be taken into account when assessing the proper standard of care in a tort action for negligence. Closer examination of these instruments, however, reveals that, assuming they are binding and enforceable in a private cause of action, most of them relate to clinical research, not to non-interventional research. Contrary to the situation in a clinical trial, X is neither vulnerable nor dependent on the Biobank. She can go to see her doctor at will. Unlike the Biobank, a doctor would be qualified and competent to make a diagnosis and to offer or refer to evidence-based interventions. This is also true for information bearing on reproductive choices, for which X could turn to regular counsellors. In addition, X could enrol in validated population screening programmes, which typically will be initiated or informed by validated findings of studies like the Biobank.

The features of the observational Biobank findings further caution against the extension of these standards to population biobank research without appropriate adjustments: the sheer number of participants, the number of findings and the nature of these findings, which are likely to include both 'good news' and 'bad news'. Notably, the CIOMS Guidelines, one of the few instruments which does apply to observational research, allows for an ethical review committee to approve temporary or permanent non-disclosure of data in view of the scale of a particular study. In addition, the 2009 OECD Draft Guidelines on Human Biobanks and Genetic Research Databases (which recommend that biobanks should elaborate an adequate feedback policy) provide that, as a general rule, non-validated results from scientific research using a biobank's materials and data should not be reported back to the participants and that this should be explained to participants during the consent process.

Under the present circumstances and based on the above considerations, we are reluctant to honour X's demand to be offered full disclosure of the Biobank's findings pertaining to her individual health. However, that is not to hold that the Biobank is not under an obligation to use best efforts to inform its participants, at the

*appropriate community or sub-community level, of its findings and their implications for individual participants. Indeed, providing as much validated personal health information to participants as is reasonably possible might also benefit the Biobank. It has even been suggested that disclosing to participants their own genotype would give them a personal stake in the ongoing research effort and could persuade them to (continue to) participate in longitudinal research.*¹¹⁵

*As the Biobank acquires, over time, an increasingly enriched 'picture' of its participants, it would breach its duty of care owed to its participants if it failed to develop appropriate mechanisms to disclose pertinent health information to the appropriate community of participants. There is no reason to limit this feedback to genetic information regarding rare disorders that are life-threatening and for which clinical treatments exist. Any such mechanism should fit the type, the urgency, the context, the limitations and the validity and utility of the information to be so provided. Such mechanisms could include a website, a participants' forum, regular meetings and newsletters updating and summarizing recent findings, accessible bibliographies of completed studies, a register of ongoing studies, webcasts, regular updates of FAQs, and webchat sessions with designated investigators. In due course, the Biobank should consider the provision to participants of a web-based, personally controlled health record empowering them to access and use any data generated by the Biobank.*¹¹⁶

In brief, as the Biobank seeks "to track to their sources the causes of disease", it should take note of its own stated ambition that research findings should be "quickly available for the prevention and cure of disease". The Biobank is neither X's doctor nor her personal genomics company. However, as a collaborative research enterprise the bank must take care of her participants' legitimate interest in receiving validated personal health information in a timely and appropriate manner.

Acknowledgments

This publication is one of the results of a research project by the authors in cooperation with the Dutch Centre for Society and Genomics (CSG) and funded by the Netherlands National Genomics Initiative. The project generated another legal publication proposing Guidelines for Biobank Feedback [Bovenberg, Meulenkamp, Smets and Gevers, Biobank research: reporting results to individual participants, *European Journal of Health Law*, 16 (2009) 229-247]. The project has benefited from comments made by Prof B. Wolffenbuttel, University of Groningen, Prof D. Postma, University of Groningen, Dr M. Boeckhout, University of Amsterdam, Dr M. Boenink, Center for the Philosophy of Technology and Science, University of Twente, Dr G. Fobelets, Centre for Biomedical Ethics and Law, Katholieke Universiteit Leuven, Prof J.C.J.M. de Haes, Academic Medical Centre/ University of Amsterdam, Dr A.C.J.W. Janssens, Department of Epidemiology and Biostatistics, Erasmus MC, Prof L.P. ten Kate, VUMC, Prof D.A. Legemate, Academic Medical Centre/ University

of Amsterdam, Prof N.J. Leschot, Academic Medical Centre/ University of Amsterdam, Dr J.G. Loeber, National Institute for Public Health and the Environment (RIVM), Prof Dr G.J. B. van Ommen, Center for Human and Clinical Genetics, Leiden University Medical Center, Dr G.J. Olthof Ministerie van VWS, Dr C. Oosterwijk, Dutch Genetic Alliance/Verenigde Samenwerkende Ouder- en Patiëntenorganisaties (VSOP), Dr E.B. van Veen, MedLawconsult, Mevr. M. Verduyn Astma Fonds, Prof T. Caulfield, University of Alberta, Canada, and Prof B.M. Knoppers, McGill University, Montreal, Canada.

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² C. Johnston and J. Kaye. Does the UK Biobank have an obligation to feedback individual findings to participants? *Medical Law Review* 2004; 12: 239-67.

³ J. Kaiser. Biobanks. Population databases boom, from Iceland to the U.S. *Science* 2002; 298: 1158-1161.

⁴ A. Bouchie. Coming soon: a global grid for cancer research. *Nature Biotechnology* 2004; 22: 1071-1073.

⁵ H.E. Hagen et al. Building global networks for human diseases: genes and populations. *Natural Medicine* 2004; 10: 665-667.

⁶ T.A. Manolio et al. Genes, environment and the value of prospective cohort studies. *Nature Reviews Genetics* 2006; 7: 812-820.

⁷ J. Jones. 1981. *Bad Blood: The Tuskegee Syphilis Experiment*, New York: Free Press. M. Solomon. The Rhetoric of dehumanization, an analysis of medical reports of the Tuskegee Syphilis Project, Experiment, reprinted in S.M. Reverby (ed.) *Tuskegee's Truths*, University of North Carolina Press, 2000, originally published in *Western Journal of Speech Communication* 1985; 49: 233-47. A.M. Brandt. Racism and research, The case of the Tuskegee Syphilis Experiment, reprinted in S.M. Reverby (ed.) 2000. *Tuskegee's Truths*, Chapel Hill: University of North Carolina Press, originally published in *The Hastings Center Report* December 1978; 8: 21-29. S.M. Reverby. Introduction: More than a metaphor, an overview of the scholarship of the study. In Reverby, 2000, op. cit.: 1-11.

⁸ J.R. Heller et al. Untreated Syphilis in the Male Negro, Mortality during 12 years of observation. *Journal of Venereal Disease Information* 1946; 27: 34-38.

⁹ Reverby, op. cit. note 6.

¹⁰ Brandt, op. cit. note 6.

¹¹ F.D. Gray. 1998. *The Tuskegee Syphilis Study, an insider's account of the shocking medical experiment conducted by government doctors against African American men*, Montgomery: NewSouthBooks, Montgomery.

¹² J. Heller. Syphilis victims in US study went untreated for 40 years, AP, *New York Times*, July 26, 1972.

¹³ US Department of Health, Education and Welfare. 1973. Selections from the Final Report of the Ad Hoc Tuskegee Syphilis Study Panel, reprinted in Reverby, 2000, op. cit.

¹⁴ Gray, op. cit. note 10.

¹⁵ Gray, op. cit. note 10.

¹⁶ G. Renegar et al. Returning genetic research results to individuals: points-to-consider. *Bioethics* 2006; 20(1): 24-36.

¹⁷ C.V. Fernandez et al. Informing study participants of research results: an ethical imperative. *IRB* 2003; 25(3): 12-19.

¹⁸ L.M. Beskow et al. Informed consent for population-based research involving genetics. *JAMA* 2001; 286: 2315-2321. B.M. Knoppers et al. The emergence of an ethical duty to disclose genetic research results: international perspectives. *European Journal of Human Genetics* 2006; 14: 1170-1178. A. Boggio. 2008. Informing Participants about Research Results. In B. Elger, N. Biller-Andorno, A. Mauron, A. Capron (eds.), *Ethical Issues in Governing Biobanks: Global Perspectives*, Ashgate.

-
- ¹⁹ The Federation of Dutch Medical Scientific Societies (FDMSS). 2001. Code of Conduct: Proper Secondary Use of Human Tissue.
- ²⁰ C. Sallée and B.M. Knoppers in *Creation and Governance of Human Genetic Research Databases.*, Organisation for Economic Co-operation and Development (OECD), Directorate for Science, p.35 ISBN 92-64-02852-8, available on line via www.sourceoecd.org/scienceIT/9264028528.
- ²¹ KNAW, Verkenningcommissie Multi-factoriële Aandoeningen. 2006. *Multifactoriële aandoeningen in het genomics tijdperk*. Amsterdam.
- ²² S.M. Wolf et al. The law of incidental findings in human subjects research: establishing researchers' duties. *J Law Med Ethics* 2008; 36 (2): 361-83, 214.
- ²³ Boggio, op. cit.
- ²⁴ Nature Biotechnology, October 2008. Focus on next generation sequencing 26 (10).
- ²⁵ National Institutes of Health. Policy for sharing of data obtained in NIH supported or conducted genome-wide association studies (GWAS). Federal Register 2007; 72(166): 49290-49297.
- ²⁶ J.N. Hirschhorn et al. Genome-wide association studies for common diseases and complex traits. *Nature Reviews Genetics* 2005; 6 (2): 95-108.
- ²⁷ Th. A. Pierson. How to interpret a genome-wide association study. *JAMA* 2008; 299: 11.
- ²⁸ T. Caulfield et al. Research ethics recommendations for whole-genome research: consensus statement. *PLoS Biol* 2008; 6 (3): e73.
- ²⁹ S.M. Wolf, op.cit. note 22.
- ³⁰ Navigenics, website of Navigenics: <http://www.navigenics.com/> [Accessed October 8, 2008].
- ³¹ deCodeme, website of deCodeme: <http://www.decodeme.com/> [Accessed October 9, 2008].
- ³² 23andMe, website of 23andMe: <https://www.23andme.com/> [Accessed October 9, 2008].
- ³³ Navigenics, op. cit. note 30.
- ³⁴ 23andMe op. cit. note 32.
- ³⁵ Navigenics, op. cit. note 30.
- ³⁶ deCodeMe, op. cit. note 31.
- ³⁷ 23andMe, op. cit. note 32.
- ³⁸ Council of Europe, 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*, Oviedo, 4.IV.1997.
- ³⁹ Council of Europe, Explanatory Report to the 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*, Oviedo, 4.IV.1997.
- ⁴⁰ Ibid.
- ⁴¹ UNESCO. 2003. International Bioethics Committee (IBC): *International declaration on human genetic data*. Paris: UNESCO, International Bioethics Committee.
- ⁴² UNESCO, 2005, the Universal Declaration on Bioethics and Human Rights, adopted by acclamation the General Conference, at its 33rd session, on 19 October 2005
- ⁴³ Wolfe, op. cit. note 22.
- ⁴⁴ Council of Europe. Convention for the Protection of Human Rights and Fundamental Freedoms. 1950.
- ⁴⁵ Johnston and Kaye, op. cit. note 2.
- ⁴⁶ Ibid.
- ⁴⁷ *Osman v. the UK*, European Court of Justice, 1997.
- ⁴⁸ Ibid.
- ⁴⁹ Johnston and Kaye, op. cit. note 2.
- ⁵⁰ *X and Y v. the Netherlands*, European Court of Justice, 1985 Series A.; 91.
- ⁵¹ G. Laurie. 2003. *Genetic Privacy, A Challenge to Medico-legal Norms*. Cambridge University Press.

-
- ⁵² *López Ostra v. Spain* 16798/90 (1994) ECHR 46 (9 December 1994).
- ⁵³ *Guerra and Others v. Italy* 116/1996/735/932 (1998), ECHR (19 February 1998).
- ⁵⁴ Medical Treatment Contracts Act, Wet Geneeskundige Behandelingsovereenkomst (WGBO).
- ⁵⁵ P.B. Miller and C. Weijer. Fiduciary obligation in clinical research. *Journal of Law, Medicine & Ethics* 2006; 424-440. H.S. Richardson and L. Belsky. The ancillary-care responsibilities of medical researchers. *The Hastings Center Report* 2004; 25-33.
- ⁵⁶ CIOMS 1991 International Ethical Guidelines for Epidemiological Studies Prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO).
- ⁵⁷ Ibid.
- ⁵⁸ Ibid.
- ⁵⁹ Ibid.
- ⁶⁰ Ibid.
- ⁶¹ Ibid.
- ⁶² Website of Estonian Gene Bank: <http://www.geenivaramu.ee/>
- ⁶³ Human Genes Research Act: <http://www.geenivaramu.ee/>
- ⁶⁴ Framingham Heart Study, A Project of the National Heart, Lung and Blood Institute and Boston University, website: <http://www.framinghamheartstudy.org/about/background.html>, [Accessed July 15, 2009].
- ⁶⁵ T.R. Dawber, G.F. Meadors and F.E. Moore. Epidemiological approaches to heart disease: The Framingham study. *American Journal of Public Health* 1951; 41: 279-286.
- ⁶⁶ D. Levy and S. Brink. 2005. *A Change of Heart*, New York: Alfred A. Knopf: p60.
- ⁶⁷ Ibid. pp 3-10.
- ⁶⁸ Ibid. pp. 99-100.
- ⁶⁹ Ibid. pp. 62-63.
- ⁷⁰ Ibid. pp. 62 and 100.
- ⁷¹ Ibid.
- ⁷² Framingham Heart Study, op. cit. note 64.
- ⁷³ V. Ravitsky et al. Disclosing individual genetic results to research participants. *American Journal of Bioethics* 2006; 6(6): 8-17.
- ⁷⁴ Beskow, op. cit. note 18.
- ⁷⁵ Ravitsky op. cit. note 73.
- ⁷⁶ Ibid.
- ⁷⁷ Beskow, op. cit. note 188.
- ⁷⁸ The Federation of Dutch Medical Scientific Societies (FDMSS). Code of Conduct: Proper Secondary Use of Human Tissue. Explanatory report; 2001.
- ⁷⁹ Council of Europe, Committee of Ministers. Recommendation Rec (2006) 4 of the Committee of Ministers to member states on research on biological materials of human origin. http://www.coe.int/t/e/legal_affairs/legal_co-operation/bioethics/texts_and_documents/Rec_2006_4.pdf.
- ⁸⁰ Renegar, op. cit. note 16.
- ⁸¹ *Osman v. the UK*, op. cit. note 47.
- ⁸² Medical Research (Human Subjects) Act, Wet medisch-wetenschappelijk onderzoek met mensen (WMO).
- ⁸³ Renegar, op. cit. note 16.
- ⁸⁴ Ibid.
- ⁸⁵ M.Cho in Wolf et al, op.cit. note 22.
- ⁸⁶ D. Lenrow. The Treating Physician as Researcher: Is assuming this dual role a violation of the Nuremberg Code? 25 *Temp. J. Sci. Tech & Envtl. Law* 2006; 15.
- ⁸⁷ Wolf, op. cit. note 22.

-
- ⁸⁸ Richardson, op. cit. note 55.
- ⁸⁹ Article 601, Book 7, Dutch Civil Code.
- ⁹⁰ District Court Amsterdam, LJN: AT7785, Rechtbank Amsterdam, 274686, 04-02-2004.
- ⁹¹ Website of The Singapore Tissue Network (STN): <http://www.stn.org.sg/> [Accessed October 9, 2008].
- ⁹² UK Biobank Ethics and Governance Framework, Version 2.0, July 2006: http://www.ukbiobank.ac.uk/docs/EGF_Version2_July%2006%20most%20uptodate.pdf
- ⁹³ Website of CARTaGENE: http://www.cartagene.qc.ca/index.php?option=com_content&task=view&id=1&Itemid=5 [Accessed October 9, 2008].
- ⁹⁴ Website of Generation Scotland: www.generationscotland.org [Accessed October 9, 2008].
- ⁹⁵ Framingham Consent Form, Generation III Exam 1, Res. v. 1, Last Amendment: 7/6/2007, Research consent form Generation III Exam 1 H-22762- The Framingham Heart Study N01-HC-25195 1910G.
- ⁹⁶ EU Directive nr 98/79EC of October 27, 1998 on *in vitro* diagnostic medical devices, OJ of the European Communities, L331/1.
- ⁹⁷ Dutch Act on Population Screening, Stb. 1992, 611.
- ⁹⁸ C. Schmidt. Regulators weigh risks of consumer genetic tests. *Nature Biotechnology* 2008; 26 (2): 145-6.
- ⁹⁹ I.S. Kohane et al. The Incidentalome: a threat to genomic medicine. *JAMA* 2006; 296 (2): 212-215.
- ¹⁰⁰ Ibid.
- ¹⁰¹ Individual Health Care Professions Act, Wet op de beroepen in de individuele gezondheidszorg (Wet BIG).
- ¹⁰² Special Medical Procedures Act, Wet op Bijzondere Medische Verrichtingen (WBMV)
- ¹⁰³ E.B. Bookman et al. Reporting genetic results in research studies: summary and recommendations of an NHLBI working group. *American Journal of Medical Genetics Part A* 2006; 140: 1033-1040.
- ¹⁰⁴ Ibid.
- ¹⁰⁵ C.V. Fernandez, op. cit. note 17.
- ¹⁰⁶ Wolf, op. cit. note 22.
- ¹⁰⁷ K. Ross. When volunteers are not healthy. *EMBO reports* 2005; 6 (12): 1116-1119 at 1118: <http://www.pubmedcentral.nih.gov> (quoting Alan Evena, neuroimaging researcher from McGill University, Montreal, Canada, quoted by Alan C. Mistein in Wolf, op. cit. at note 22).
- ¹⁰⁸ Council of Europe, op. cit. note 38.
- ¹⁰⁹ Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, Strasbourg, 25.I.2005.
- ¹¹⁰ Farmingham, op. cit. note 64.
- ¹¹¹ Fernandez, op. cit. note 17.
- ¹¹² Bookman op. cit. at note 103.
- ¹¹³ V. Ravitsky op. cit. at note 73.
- ¹¹⁴ E. Wright Clayton, Incidental Findings in Genetics Research using Archived DNA, in Wolf et al. Challenge of incidental findings, *Journal of Law, Medicine and Ethics* 2008; p. 288.
- ¹¹⁵ Positively Disruptive (Editorial). *Nature Genetics* 2008; 40 (2): 119.
- ¹¹⁶ I.S. Kohane. Reestablishing the Researcher-Patient Compact. *Science* 2007; 216: 836-837.