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Editorial

Journals are more than mere vehicles for dissemination. They are likely to have an impact on the fields they represent and on the forms of research they make accessible. The GSP will, I suspect, be no exception to this rule. It is likely to have a significance beyond the simple objective of providing authors with an effective channel for scholarly communication. What will the impact of GSP be, or rather, what would we like it to be? As Ruth Chadwick pointed out in the editorial to the first issue of our journal, we encourage submissions that address issues at an early stage, in a responsive and anticipatory manner. This will allow us to do away with the prejudice (unfortunately widespread) that ethical and social reflection on scientific innovation is by definition "behind schedule", commenting on what is actually a "fait accompli". And there are some other misunderstandings that we would like to challenge. First of all, there is the widespread idea that ethics is by definition about "ethical problems", that is: inflictions of harm or violations of informed consent. The scope of ethics is, of course, much broader. Ethical assessments of scientific fields entail a comprehensive analysis that should also address the broader societal impact, the social and economical benefits and risks, the way we understand ourselves, our world, our future.

There is, however, another impact I hope this journal will have, and that is interdisciplinary research. During the past few years we already made some progress in challenging the long-standing dichotomy between facts (to be studied by social scientists) and values (to be analyzed by ethicists). Interdisciplinary collaboration should not only involve collaborations of scientists with either ethicists or social researchers. Rather, it must become a triangular affair. In recent years, social scientists increasingly managed to overcome their ethics phobia, their allergy to opening-up normative perspectives. They have learned that an assessment of normative dimensions, as well as the ways in which they are addressed, is not something that can be delegated to others, but rather an inherent part of relevant research. Likewise, ethicists increasingly became aware of the importance of facts, trends and social data. They learned to appreciate and use the tools developed by social scientists to study them in a professional and reliable manner. These developments have led to an "empirical turn" in ethics and a "normative turn" in social research. It greatly encourages the development of innovative methods and approaches. The GSP I hope will stimulate these innovative forms of collaborations between empirical researchers and philosophers (moral or other), as an important dimension of interdisciplinary research.

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Blood, Sweat and Grants
'Honest Jim' and the European database-right

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Abstract

Access to detailed, up-to-date and available bioinformatics databases has been identified by the Commission of the European Union as a pillar for the harvesting of the potential of life-sciences and biotechnology. Unconditional access to research data, however, is squarely at odds with the primary interest of every scientist to be the first to make a discovery. This classical dilemma is specifically pressing in the data-driven field of biomedical research, where data-quantity has become a quality on its own, where speed matters and patients can't wait. The dilemma urges a consideration of the principle, the practice and the law regarding access for academic researchers to unpublished research data. The consideration will include the presentation of the outcome of a global and a national survey among biomedical researchers on the accessibility of 'their' research data. The principled arguments pro unconditional access and the laws and practical considerations contra unconditional access offer conflicting perspectives and the resulting situation is compounded by the uncertainty created by the European database-right as to who holds legal title to the databases. Therefore, it is explored whether the two opposing concerns – unconditional access vs. legitimate restrictions – can be accommodated by the adoption and implementation of a general policy for access to biomedical data that greases the wheels of (European) research.

Prologue

In 1953 Watson and Crick won the race to discover the molecular structure of DNA. They described the double helix in an article in *Nature*. The second last sentence of the article reads:

> *We have also been stimulated by a knowledge of the general nature of the unpublished experimental results and ideas of Dr. M.H.F. Wilkins and Dr. R. E. Franklin and their co-workers at King's College London.*[1]

How appropriate this gesture was, appears from a paragraph in *The Double Helix*, the personal account of the race to discover the DNA-structure, published fifteen years later by 'Honest Jim' Watson:

> *Rosy [Franklin], of course, did not directly give us her data. For that matter no one at King's realized they were in our hands.*[2]

Watson and Crick had come upon Franklin's data via Max Perutz, the leader of their unit, to whom the data had been reported as a member on a committee appointed by the Medical Research Council to look into the research activities of Wilkins' lab. Confronted with this alleged breach of faith on his part, Perutz later replied that the incident inaccurately pictured Wilkins and Franklin as jealously trying to keep their

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data secret and Watson and Crick as getting hold of crucial data in an underhand way. Perutz pointed out that, first, the remit of the committee on which he had served was not to look into the research activities of Wilkins but to establish contact between the groups of people working for the MRC; second, that the MRC report was not confidential and, third, that the one important piece of information it contained might have been known by Crick a year earlier if Watson had taken notes at the seminar where Franklin had presented the data.[3]

Introduction

Watson's revelations illustrate the dilemma of every scientist: the race to be the first *versus* the need to stand on the shoulders of colleagues and competitors. Fifty years after the description of the double helix, this dilemma is more urgent than ever before, especially in the area of biomedical research. The principle is simple: both verification of scientific findings and the public nature of its funding demand unconditional access to research data. In real life, things ain't that simple. After Internet and the ICT-revolution, GRIDS are increasingly providing a new research tool. GRIDS make possible a whole new type of experiments and enable researchers to work jointly and simultaneously on the same datasets. As a result, biomedical research is more 'data-driven' than ever before and 'unique datasets' have become a researcher's 'life-line'. Which data can he claim as his own? Is he under an obligation to give access to his unpublished data? Why? Which data? To anybody? For what purpose? With or without conditions attached?

Over these complex questions hangs, as from March 11, 1996, as a *deus ex machina*, the sword of the European database-right.[4] This novel, *sui generis* right aims to protect the blood, sweat and tears that go into producing a database, against unauthorised use by third parties. To that end, it provides for an exclusive right to use and and re-utilize databases that demonstrate a substantial investment. *Prima facie* this right is at odds with the scientific imperative of the *free flow of information*. However, depending on who actually owns the right, it is a double-edged sword that could cut either way. In the hands of a public funding body, it is an instrument to secure academic scientists access to the research data produced by their colleagues. In the hands of a scientist it may be used as a weapon to legitimise and enforce data-exclusivity.

A recent and urgent case study to analyse the above issues is presented by the Netherlands National Genomics Strategy.[5] This strategy is built on the premise that the Netherlands have a number of unique biomedical databases and population cohorts, which may yield a competitive edge globally. Part of this strategy is to open up these databases for further, large-scale research into the 'nature and nurture' of common complex diseases. For this strategy to succeed, however, the scientists that build these collections must be willing to give access to their data, and, if not, such access should be legally enforceable. As we will see, this discussion is inextricably interwoven with and has implications for similar issues at the European level, where similar initiatives exist such as COGENE and the GenomEUtwin project. In fact, the European Commission has identified 'access to detailed, up-to-date and available bioinformatics databases and open access to knowledge' as two of the three pillars for the harvesting of the potential of life-sciences and biotechnology.[6]

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This Article discusses the 'essential tension' between the need for academic researchers to have unconditional access to unpublished research data and the exclusive database-right. The sharing ethos in academia is paradigm, as is the assertion that the European database-right constitutes a violation of that ethos. However, for these issues too, 'context is King'. To do justice to this context, I took the following approach. Part I sets forth the *Principle* underlying access to data: *Communism*. Revisiting the Four Commandments for scientific behaviour postulated by Robert K. Merton, this Article will argue that there is a need to formulate a Fifth Commandment: unconditional access to unpublished research data. Part II will examine the current *Practice* governing access to research data in biomedical academia: *Capitalism*. It will first present and discuss the outcome of two surveys into the actual willingness of biomedical researchers to grant access to 'their' research data. One survey was held among human geneticists worldwide; the second survey was held among all principal investigators in the area of specific biomedical research in the Netherlands. Second, Part II will review a variety of reasons why, in practice, access may be denied or subjected to specific conditions. We will see that the principled arguments *pro* unconditional access (Part I) and the laws and practical considerations *contra* (unconditional) access (Part II) offer divergent if not downright conflicting perspectives. Therefore, Part III will analyse whether this Gordian knot can be cut by operation of the *Law*, *i.e*. by analysing who *owns* scientific research data. As the European database-right seems the most obvious avenue for this legal analysis, we will apply the European database-right to a concrete biomedical database, which has both a Dutch and a European dimension: the Netherlands Twin Registry that forms part of the GenomEU-Twin project. Finally, Part IV will discuss *Policy*: how can the *principle*, the *practice* and the *law* pertaining to access to unpublished research data be converted into an effective data-access policy designed to grease the wheels of publicly funded biomedical research.

I. In principle: Communism

I.1 Merton's Four Commandments

The goal of science. The scientific *mores* have been formulated by science sociologist Robert K. Merton.[7] Merton first determines the institutional goal of science as the 'extension of certified knowledge.'[8] The technical method employed toward this end is empirical research. The scientific *mores* both derive from and serve the goal and method of science: universalism, communism, disinterestedness and organised skepticism.[9]

Universalism. This imperative aims to guarantee that 'truth-claims are to be subjected to *pre-established impersonal criteria*'. What works in a Tokyo laboratory must also work in a laboratory in Leiden. Thus, universalism enables scientists from diverse backgrounds and personal beliefs to contribute to the universal tree of knowledge.

Communism. '*Communism*' is meant by Merton as the communal ownership of 'intellectual goods'. 'Secrecy is the anti-thesis of this norm: full and open communication its enactment'. The communal nature of science is incompatible with exclusive (intellectual) property rights.[10] Scientific findings constitute a '*common heritage'* in which 'the equity of the individual producer is limited'. It follows from

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the institutional goal and method of science that the scientist's sole property right in 'his' findings is that of recognition and esteem. This emphasis on recognition forces a scientist to be the first to make a scientific discovery. According to Merton this results in a system of 'competitive co-operation'.[11] The products of this competition are communized, with the original contributor being rewarded only with recognition and eternal fame.[12] Merton emphasises that this competitive co-operation cannot prejudice the status of scientific knowledge as common good. The communist nature of science is also illuminated and reinforced by the *mos* to acknowledge in publications that the individual contribution of the author to the tree of knowledge was made possible by the contributions of many others.[13]

Disinterestedness and organised skepticism. The imperative of disinterestedness means that the pursuit of scientific truth should always prevail over the pursuit of the scientists' personal interests. In particular, scientists should not serve political interests.[14] The norm of *'organised skepticism'*, means that the scientific community should subject any findings of its members to empirical and logical testing before accepting them as true.[15]

The reward structure of science. In addition to formulating the Four Commandments of science, Merton also elucidated how these norms are reinforced by the reward system of science.[16] Scientific communism is rewarded by recognition.[17] Recognition takes many forms: eponymy, - Pythagoras' axiom, Kepler's laws, Huntington's disease, Factor V Leiden; prizes and premiums, – the Nobelprize, the Spinoza prize, and membership of academies – the Royal Society, the Royal Netherlands Academy of Sciences.[18] Recognition of course requires publication and here the goal, method and reward system interrelate. Publication serves the norms of universalism and disinterestedness and enables independent replication and thus verification of truth claims. Publication of original findings also serves the institutional goal of science: the extension of certified knowledge.

I.2 The Fifth Commandment: unconditional access to research data

Merton's communism demands and implies that researchers have access to each other's publications. The question, however, is whether access to published findings is sufficient. 'Honest Jim's account of the race to discover the structure of DNA illustrates the importance of access to the '*unpublished experimental results and ideas'*. Following is an inventory of arguments to formulate a Fifth Commandment: unconditional access to unpublished research data.

I.2.1 Unconditional access is necessary for scientific revolutions. The primary goal of unconditional access is to enable verification of scientific findings by others. Thus, this imperative helps create a barrier against 'fraud, theft and self-deception'.[19] However, verification also serves a more remote goal. While Merton and later on Popper assume that scientists are continuously engaged in improving respectively falsifying each other's findings, Kuhn has pointed at the confirmatory behaviour of scientists.[20] Scientists are inclined to mainly confirm and refine established theories or 'paradigms'.[21] Kuhn has named that process 'normal science'. He compares 'normal science' to solving puzzles, in that both are not aimed at producing major novelties, neither conceptual nor phenomenal.[22] The solution of a puzzle is anticipated and not intrinsically interesting or important; the challenge is to find a new

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way to achieve that solution.[23] Inadvertently, Watson aptly illustrates this point in his description of Sir Lawrence Bragg, then director of the Cavendish laboratory where Watson and Crick did their work on DNA:

> *For almost forty years Bragg, a Nobel Prize winner and one of the founders of christallography, had been watching X-ray diffraction methods solve structures of ever-increasing difficulty. The more complex the molecule, the happier Bragg became when a new method allowed its elucidation.*[24]

In contrast, Kuhn points out that the 'really pressing problems, *e.g.* a cure for cancer (..) are often not puzzles at all, largely because they have no solution.'[25] Kuhn emphasises, however, that paradigms are necessary for the conduct of 'normal science'. Paradigms indicate which data to select, which experiments should be done and which refinements are necessary to perfect a theory.[26] However, if scientists spend more time to adjust facts to theory rather than the other way around,[27] a crisis will emerge in case too many facts no longer fit the paradigm. Such a period of crisis may lead to the formulation of new theories, the so-called paradigm shift or 'scientific revolution'.[28] In a revolution those who challenge the scientific establishment will scrutinize existing paradigms by:

> *handling the same bundle of data as before, but placing them in a new system of relations with one another by giving them a different framework.*[29]

However, the revolution will not take place or be delayed, unless there is unconditional access to the data. It is precisely in a period of crisis that such access is crucial. If Kuhn is right, his theory provides a powerful argument for unconditional access to research data. If scientists are in a position to deny access to their research data, they will be inclined to grant access exclusively to scientists who adhere to the same paradigms. [30] This inclination may be reinforced by the existence of symbiotic, informal networks of like-minded scientists.[31]

I.2.2 Unconditional access is necessary for the 'Invisible Hand of Research'. Related to the paradigm issue, is the importance of individualism and independence in science.[32] Traditional academic freedom entails that scientists are free to choose their research objectives and method. This freedom will be curtailed if science is centrally co-ordinated, whether by non-scientists or by scientific peers. Co-ordination seems a logical and necessary instrument to avoid duplication of efforts and a waste of resources. However, co-ordination can be fatal to individual initiatives. In *The Republic of Science*, Michael Polyani has argued that independent initiatives, undertaken by competing scientists, are the most efficient way to organise scientific research.[33] As long as a scientist keeps an eye on the work of the others, he will take their efforts into account when formulating his own research questions.[34] Polyani has labelled this system a system of self 'co-ordination by way of mutual adjustments of independent initiatives.[35] This co-ordination should not be centralised, but rather be guided by an 'invisible hand'. Just as the 'invisible hand' in a free market-economy helps producers and consumers make supply meet demand and thus achieve maximum welfare, the 'invisible hand of research' will guide scientists to achieve maximum progress of science.[36]

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The Jigsaw puzzle. Polyani illustrates his point using the metaphor of the 'Jigsaw puzzle', a fitting metaphor in view of Kuhn's description of 'normal science' as puzzle-solving. Solving a Jigsaw-puzzle requires, just as solving complex scientific problems, the contributions of multiple persons.[37] Each person will, watched by the others, focus on a particular section of the puzzle and make use of the insights which develop successively as other sections are being solved. The effectiveness of the group will exceed that of its isolated members 'to the extent to which some member of the group will always discover a new chance for adding a piece to the puzzle more quickly than any one isolated person could have done by himself.'[38] Now imagine, Polanyi argues, that the activities of the group are co-ordinated by a single authority. That would reduce the joint effectiveness of the group as a whole to the effectiveness and insights of this co-ordinator. In the alternative model, the 'Invisible Hand' will prevent this from happening.

Polanyi's model however, requires that each scientist knows what the other puzzle-solvers are doing. For the 'Invisible Hand' to succeed, every helper also needs access to all pieces of the puzzle. According to Polanyi, mutual adjustment of independent initiatives will take place by scientists' taking note of the published results of other scientists. Publications thus play the role in science, which the prices of goods and services play in the economy, as a means to 'make supply meet demand'.[39] However, Polanyi fails to complete his analogy with Adam Smith's 'Invisible Hand'. He fails to mention that the 'Invisible Hand' cannot operate, if the market forces do not have complete information or if one party has a monopoly.[40] A similar market-failure is likely to paralyse the operation of the 'Invisible Hand' of research, if a scientist has no knowledge of, or no access to, unpublished research data. In other words, if Polanyi is right, his model of the 'Invisible Hand' is also a powerful argument for unconditional access to research data.

I.2.3 Unconditional access is necessary to enable new research. This argument has a financial and a scientific component. First of all, unconditional access will save costs. Absent exclusive rights on data, other researchers need not negotiate terms of access and save both transaction costs and real costs, such as royalties and other forms of compensation. Thus, the original data-producers subsidize 'second comers'.[41] Though this may look like a 'free ride' for the second comer on the blood, sweat and tears of the original researcher, the system has an element of 'distributive justice'. Most likely, the original researcher has had the benefits of the efforts put in by his predecessors. And the system works two ways, of course. The potential 'free ride' may be offset by reciprocal access or access to data elsewhere. The scientific component of this argument cannot be better formulated than by Newton's aphorism: If I have seen farther, it is by standing on the shoulders of giants.

I.2.4 Unconditional access is required because of public funding. Another argument is the fact that the research has been paid for out of public means. In this view, the government should not fund the same research twice, since that would be a waste of taxpayer's money. On closer investigation, however, this position may be too simple. As Merton made clear, duplication of effort does not always amount to a waste of resources.[42] First, the replication of research, for purposes of validating or falsifying truth claims, is an essential element of the scientific method. Second, as Polanyi made clear, chances are that a particular problem is solved more quickly if worked upon by

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multiple researchers. Third, if multiple researchers reach the same conclusions, the results are more likely to be accepted. Fourth, multiple researchers may have diverse approaches, give diverse interpretations and see diverse implications for subsequent research. A fifth, more prosaic consideration is that the data are not always fit for use by others. To that end, they must be made accessible and stored, which may require an *extra* investment. This extra investment is typically not funded by the funding bodies, since they typically only fund the original research. In this view, a researcher may legitimately reject a request for access to 'his' data on the ground that such access requires an investment which has not been publicly funded.

I.2.5 Unconditional access is necessary because research is 'data-driven'. Since Merton formulated his Four Commandments, a number of developments have heightened the need of access to data.[43] Most recently, after Internet and the ICT-revolution, scientists increasingly make use of GRIDS. GRIDS are operating systems for virtual networks of computers which enable the bundling of hardware and information – such as computational power, data-storage and measurements devices.[44] GRIDS enable a quintessentially novel type of experiments and enable scientists to work on the same data simultaneously. The 'permanent data-revolution' has created 'oceans of data' in biomedical research, such as the sequence of the human genome, a database of three billion base-pairs.[45] The sequence illustrates how the boundaries between 'data' and research results have become blurred. The sequence is both milestone and a starting point for further research.[46]

One of the consequences of the data-explosion is that contemporary biomedical research has become *data-driven* rather than *hypothesis-driven*. One of the challenges in the post-genomic era, for example is the research into the "nature and nurture" of common complex disorders.[47] This research involves the correlation of millions of data-points by correlating molecular measurements of thousands of genes, proteins and metabolites with all sorts of clinical data (such as blood pressure, cholesterol, diabetes and MRI-scans). Subsequently or sometimes initially, these data are aggregated with data from databases resulting from comparable research data stored in other databases.[48] Any identified patterns and correlations can be used to formulate new hypotheses. This type of research may be aided by the creation of bio-banks, large-scale collections of "nature and nurture" information in the form of human biological material and associated health information. Such a bio-bank can be constructed by linking pre-existing molecular and clinical databases.[49] As we saw in the Introduction, the opening up of existing collections is part of the Netherlands National Genomics Strategy and one of the pillars of the EU for the harvesting of the potential of life-sciences and biotechnology. Obviously, this type of research and this strategy is to a large extent dependent on unconditional access to appropriate datasets.

I.2.6 Unconditional access is necessary as science is used for policy-making: policy-embedded research. In Science and the Social Order, Merton mentions a dinner for scientists in Cambridge. The scientists are said to toast:

> *[t]o pure mathematics and may it never be of use to anyone!*

Science however, has come to be used as both an impetus and a justification for most, if not all kinds of far-reaching policy-making. As to public health policy, virtually all decision-making and priority setting nowadays must be 'evidence-based', meaning

based on scientific evidence. For example, as part of its 6th Framework Programme for research and development, the EU has established a special programme to enhance research for policy support in the area of public health, with an indicative budget of EUR 590 million. As 'policy-enhancing' instruments, scientific 'truth-claims' have assumed an impact that goes far beyond the traditional goal of extending certified knowledge for its own sake. This impact provides an extra argument for the replication of the scientific evidence that is used to justify a specific policy. The recent controversy over climate change and global warming illustrates this point. The Kyoto protocol aimed to address the environmental concerns has been ratified, without any replication of the original research findings underlying its policies. It was not until a couple of researchers undertook to replicate this research, that it became clear that it might be seriously flawed[50]. Obviously, replication of 'policy supporting' science requires unconditional access to research data.

I.2.7 Unconditional access is necessary because speed matters and patients can't wait. A final argument does, strictly speaking, not derive from the institutional goal or method of science, but is no less principled. It concerns the actual object of biomedical research: the patient. Ultimately, it is his problem science is trying to solve. Scientists however, are inclined to appropriate problems. Watson and Crick's decision to devote themselves to the discovery of the molecular structure of DNA, was against the academic etiquette. DNA was Wilkins' problem, not to be touched by others. As Watson put it:

> *At this time molecular work on DNA in England was, for all practical purposes, the personal property (sic) of Maurice Wilkins, a bachelor who worked in London at King's College'. It would have looked very bad if Francis (Crick) had jumped in on a problem that Maurice had worked over for several years.'*[51]

Wilkins, in turn, was having difficulties with Rosalind Franklin, his assistant, who claimed DNA as *her* problem.[52] Such an appropriation of problems is undesirable in biomedical research, at least to the extent the interests of patients are at stake. Unlike, let's say, the fruit fly, the object of this type of research, the patient, has a stake in the outcome. Even more so, the outcome may not only be vital for himself, but also for his family, his progeny, an entire population and, where globally spread diseases such as AIDS and SARS are concerned, the global community. Should researchers nevertheless refrain from '*jumping in*' on their colleagues' problems, patients and their relatives will stand up to enforce unconditional access and sharing. For them 'speed matters'; they cannot and will not wait until the researcher who claims *their* problem as *his* problem, has actually solved the problem. Recent examples are patient initiatives in the United Sates to bundle forces, collect material and data of their peers worldwide and make these available for the research community.[53] A group of parents of autistic children, for example, has, frustrated by the unwillingness of the researchers to share their data, created their own database, the Autism Genetic Resource Exchange. This database is accessible for every researcher and has so far yielded some 18 publications.[54] As a related, additional benefit, unconditional access obviates the need for a researcher to re-contact a patient or volunteer and subject him to repeat investigations.

Conclusion Part I. In addition to Merton's Four Commandments, scientific revolutions, the 'Invisible Hand of Research', public funding, the data-driven nature

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of research and the interests of patients and the public at large, jointly and separately provide powerful arguments to postulate a Fifth Commandment: unconditional access to unpublished research data. The next part will examine the current *Practice* governing access to research data in biomedical academia.

II In practice: Capitalism

II. 1 'Honest Jim'

As was to be expected, neither Merton's communist ideal nor the ideal of unconditional access are standard practice in the real life of science. In *The Double Helix* Watson reveals a number of incidents of 'capitalist' behaviour.[55] The quote in the Introduction already revealed that Watson and Crick had been 'stimulated by a general knowledge of the unpublished experiments and results' of Wilkins and Franklin, unbeknownst to the latter. Also, Wilkins, who was to share the Nobelprize with Watson and Crick, was said to have rejected a request by his competitor Linus Pauling for a copy of Wilkins' X-ray photos of DNA. Watson asserts that Wilkins wanted to study the data in more detail before releasing them.[56] And when Watson and Crick find out that Pauling made a mistake in his published description of the structure of DNA, they go to the pub to toast to the 'Pauling failure'.[57]

Watson's revelations struck the scientific community like a bombshell.[58] That was, however, not because of the departures from Merton's Four Commandments, but because Watson had violated the community's *omerta*. Violations of the sharing ethos were known to occur, but, whereof one cannot speak, thereof one must be silent. Since the publication of *The Double Helix*, however, a number of commentators have pointed at the fact that Merton's science ethos is not always adhered to.[59] In his review of *The Double Helix*, Merton asserted that, historically, Watson's competitive behaviour was not unique and a necessary corollary of the institutional emphasis on scientific priority.[60] Merton could not resist noting the intense and successful co-operation of Watson and Crick with other scientists. Thus, he managed to squeeze Honest Jim's behaviour within the 'competitive cooperation', he had described in his Four Commandments.

II.2 Data-access in Biomedical Academia

II.2.1 The Bermuda Principles. The evidence presented in *The Double Helix* is, obviously, anecdotal. In contrast, a number of recent large-scale 'community resource projects' have achieved their objective of pre-publication release of the raw data they produced, suggesting adherence by the scientific community to the Five Commandments. Namely, the 1996 Bermuda principles, encouraging producers of large scale DNA sequencing assemblies to release prior to publication their data immediately for free and unrestricted use by the scientific community[61], have been reinforced by various funding agencies, including the US National Human Genome Research Institute (NHGRI). To date, these policies have secured open access to at least 548[62] public genetic databases worldwide, available on the internet, including the large international nucleotide databases (EMBL and GenBank).[63] In 2003, the attendees of a meeting organized by the Wellcome Trust, reaffirmed the Bermuda principles of pre-publication release and recommended their extension to other existing and future 'community resource projects', such as the SNP-consortium and

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the International HapMap Project[64]. However, the meeting also considered that beyond those large-scale 'community resource projects', many valuable small-scale data sets could come from other sources. Since those resources emerge from research efforts whose primary goal is not resource generation, the meeting considered that the contribution of these data to the public domain is more a voluntary matter. That raises the question to which extent such contributions are standard practice.[65]

II.2.2 Global survey. With the assistance of the Human Genome Organisation, the American Society of Human Genetics and the European Society of Human Genetics, I conducted a global survey among their members in the fourth quarter of 2003. The web-survey was completed by a total of 118 human geneticists.[66] While this was only a fraction of the sample taken and therefore not representative, the responses offer an interesting peek in the practice of data-access in academic genetics in a range of countries (over 15 different countries) and at a diversity of institutions (universities, hospitals and research institutes). A majority of 51% of the respondents responded that they did not grant access to their own databases to non-commercial institutions. Notably, in view of the predominantly public funding of the databases, only one third (35%) of the respondents reported to grant access to their databases to non-commercial institutions for free. These percentages were only slightly different for those databases that were labelled 'unique' or single-source.

II.2.3 United States survey. In the US, Campbell et al. conducted the first national survey on data-withholding among American geneticists. Their study yielded, *inter alia*, the following results.[67] In a 3 year period, 47% of the respondents had had denied at least one request for additional information, data or material concerning published results. Most denials concerned requests for biomaterial (35%), sequence information (28%), applicable findings (25%), phenotype information (22%) and additional information concerning laboratory techniques. Due to these denials, 28% was unable to verify published findings.

II.2.4 The Netherlands survey. In a 2004 websurvey, Dutch biomedical researchers were asked whether they granted access to 'their' data to other scientists. This and related questions formed part of a survey I conducted as part of a survey of Dutch population-cohorts and patient-databases, conducted by the Royal Netherlands Academy of Sciences.[68] Its specific purpose was 'to investigate whether the opening up of the banked material and the linking of existing datasets is possible', which might help erect another pillar supporting the Netherlands National Genomics Strategy.[69] The survey was held among all principal investigators in the Netherlands in the area of general practitioner's medicine and epidemiology, as well as the principal investigators in the area of asthma, Alzheimer's disease, breast cancer, lymfome cancer, reumatoid artritis and multiple sclerose. The response rate was 60%. Asked whether they granted access to 'their' research data, the respondents answered as follows. 15% did not grant access, 9,3 % granted access on demand, without conditions, 1,5% made their data publicly available (anonimised) and 73,3% only gave access on special terms and conditions.[70] Admittedly, this type of survey has many limitations and additional empirical data is to be gathered before any definitive conclusions can be drawn. Nevertheless, the responses clearly suggest that a large majority does not grant unconditional access to their research data. Their attitude is at odds with the Fifth Commandment, postulated in Part I. As a result, it may deter or delay scientific revolutions, paralyse the 'Invisible Hand', delay patient cure and care,

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result in suboptimal use of 'unique datasets' for the Netherlands National Genomics Strategy and undermine two of the three European pillars for the harvesting of the potential of the life sciences and biotechnology.

II.3 Reasons for 'capitalist' behaviour

II.3.1. Reasons for data withholding. The respondents in the global and Netherlands surveys have not been asked to state the reasons for denying or imposing conditions on access. However, the Netherlands survey was designed so as to preclude a number of reasons that are typically advanced to justify the withholding of data, *i.e.* privacy[71], technical inaccessibility of the data and/or its limited potential of the collection for 'secondary use'. Specifically, 79% of the respondents confirmed that, assuming compliance with privacy rules, 'their' database could be used for research other than the research for which the data had originally been collected. And 76% indicated that, assuming again privacy-compliance, their database was technically (in terms of hard- and software) accessible for additional research by others.

In general, a variety of reasons could be advanced to explain why scientists depart from the sharing ethos: personal motives, financial interests, legal constraints, institutional incentives and uncertainty as to which data should be accessible.

II.3.2 Personal motives, financial interests and informal networks

The Nobelprize. Watson was rather blunt about his motives; honour, the desire to accomplish something to brag about against friends and, especially, girlfriends, the desire to defeat giants like Linus Pauling and, ultimately, to win the Nobelprize. As we have seen above, these competitive notions form part, to a certain extent, of Merton's normative structure.

Blood, sweat and subsidies. The American survey revealed as an important motive for data-withholding the time and costs involved in meeting the requests. Another major motive was the desire to use the data for new research.[72] Having to share data may also lead to a drop in 'authorships', another yardstick for government and public funding bodies to assess and reward productivity. Apart from being a resource for new research and new publications, the data can also be a potential source for new patent applications and a new round of public (or private) funding, as illustrated by the Netherlands National Genomics Strategy. The Dutch government acknowledges the unique character of certain Dutch datasets and takes that into consideration when deciding on grant proposals. If the primary data-producers would be under an obligation to grant unconditional access to 'their' datasets, their opportunities to capitalize on their resource would be diluted to the extent other scientist would have a 'free ride' on their original efforts.[73]. Such a 'free ride' might also prove a disincentive to start producing such databases in the first place.[74]

Access by whom and for whom? Informal networks. Proponents of unconditional access typically assume the standard situation: a secondary researcher requests access to a primary researcher's data. In complex research, however, this situation will be a rarity. Hilgartner and Rauf have pointed out that researchers, both data-requesters and data-producers, form part of research-networks.[75] The decision whether or not to grant access is not made by a single scientist, but by multiple parties: the research

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team, representing various departments or universities and public and private funding bodies[76]. And increasingly, as we saw above, patients have come to claim a say on access issues as well, patients being both data-suppliers and stakeholders. The parties requesting access to data could be competing research groups, complementary research groups, public and private funding bodies[77] and, again, patient interest groups. Factors to consider when deciding on a request for access will include the likelihood of future reciprocity,[78] recognition,[79] the proposed use of the data,[80] potential abuse of the data, loss of control over the data for future own use[81] and the quality of the researcher or research team making the request. Some data-collections have built a reputation which may suffer from publications of inferior research. And finally, the decision may be affected by the existence of symbiotic and informal networks between like-minded scientists.

II.3.3 Legal constraints

II. 3.3.1 Privacy. To the extent biomedical research data contains personal data, the access to such data is subject to an array of intersecting privacy laws. In the UK for example, a Wellcome Trust report has identified the following current and proposed legislation governing public health researchers accessing existing collections of research data and biological samples:

- the Data Protection Act 1998;
- the common law of confidentiality;
- the Human Tissue Act;
- the Human Rights Act;
- the stance of local ethics committees;
- the application of Section 60 of the Health and Social Care Act 2001;
- the requirements of clinicians' regulatory bodies regarding patient confidentiality; and
- the Medicines for Human Use (Clinical Trials) Regulations 2003[82] .

As the resulting situation is awfully complicated, only a few basics will be discussed here.[83] Implementing the EU Data Protection Directive, the Dutch Data Protection Act[84] provides that personal data may be processed for research purposes, provided that the processor has taken appropriate security measures so as to ensure that processing is limited to this specific purpose.[85] Processing personal *health* data however, without that person's consent, is prohibited. Yet, this prohibition does not apply to processing for research purposes, provided that the research serves a public interest, the processing is necessary for the research concerned, asking explicit consent is either impossible or requires a disproportionate effort and the research provides for guarantees so as to minimise potential harm to the data-subject's privacy.[86]

II.3.3.2 Informed consent for research. A related legal impediment that may provide a legitimate reason to withhold access is the requirement of informed consent. For example, to the extent research data contains patient-data, the Dutch Act on the physician patient relationship provides that a physician may only grant access to patient data for scientific research in the limited events set forth in the Act and provided that the statutory conditions be met.[87] In all other events, any processing of

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personal health data requires the patient's prior informed consent. A controversial issue in this respect is whether researchers are required to obtain specific re-consent for each new research project. While this is the case under the current construction of the informed consent requirement, there is a trend towards acceptance of simplifying existing specific informed consent requirements for previously unanticipated research use, which would obviate the need for *re*-consent for each new research project.[88] Notably, the global survey mentioned above revealed that most respondents (81%) indicated that they asked their patients or research subjects for their consent to use their data and material not only for the initial diagnosis, treatment or research, but also for future, unspecified research purposes. The Dutch survey revealed that 54% of the respondents asked consent for a specific research question, while 34% asked consent for research in general.[89]

II.3.3.3 Quality, liability and a wrongful life. Another legal constraint concerns the quality of biomedical data and the related potential for their producers to incur liabilities for the publication of inaccurate or incomplete data. For example, for a couple of decades now, geneticists have been collecting so-called mutations, changes in DNA comprising just one base-pair. A mutation can cause an inheritable disease or cancer. A major number of mutations has been discovered, described and included in the so-called 'Locus Specific Databases' ('LSDB's'). Prior to inclusion in the LSDB, the data have been verified by a curator. The trouble is that the data in these databases is not only used for fundamental research, but also for clinical applications, such as diagnosis. Obviously, it is vital that the mutations data are accurate and complete. In spite of a number of built-in safeguards and quality-controls, 100% accuracy and completeness can never be guaranteed. As a result, a mutation may wrongfully be held as harmful and thus give ground for, for example, an abortion or prophylactic surgery, or *vice versa*.[90] Depending on the circumstances, the original data-producer may be liable for any resulting damages, which liability may even extend, as per a recent Dutch Supreme Court ruling, to liability for a wrongful life. To limit his potential exposure, a researcher or his institution, may want, in addition to a proper disclaimer[91], to impose conditions for access to the data, or only supply the data for a specific purpose or only grant class access, *i.e.* for accredited academics only.

II.3.3.4 Proprietary claims and commercialisation of research. Finally, access may be limited by proprietary claims, as is often, but not necessarily, the case for drug research sponsored by industry. Industry normally allows publication of the research results, subject to a right to comment and a sixty-day waiting period to allow for patent applications.[92] However, industry is likely to make a proprietary claim to the underlying research data as such, if only to satisfy the requirements for obtaining a market authorisation for the product concerned. In addition to proprietary claims by industry, academia itself is also increasingly staking its own proprietary claims. Researchers are being pushed, if not obligated under the terms of their grant, to commercialise the results of their research. Part of the 'mission' imposed by the Netherlands National Genomics Strategy is to have grantees "sell genomics-knowledge to the business community". [93] Given the ever increasing value of biomedical data, this mission is likely to extend to not only the filing of patent applications but also the exploitation of datasets, as they are a major source of patentable inventions. Arguably, the exploitation of these databases requires the licensing of exclusive rights to the data concerned, which, in turn, is likely to

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compromise unconditional access by other academic researchers, who are likely to be equally pressed to capitalise on the results of their own publicly funded research.

II.3.4 Which data, actually?

II. 3.4.1 Typology of data. Another reason that might explain data-withholding is the issue *which data* ought to be accessible. Proponents of unconditional access base their claim on the traditional model: a scientist produces 'data' (output), disseminates these data by means of a publication, which publication makes the published findings available for other scientists as 'input' for further research. In practice, however, things are not that simple.[94] First, a lot of data cannot be used by third parties without a proper explanation by the original data-producer, if only an explanation of the inclusion criteria used to determine the research sample. Second, as part of the scientific process, scientists record a host of divergent data: lab notebooks, raw data, derived variables, preliminary analyses, draft articles, grant applications etc.[95] And if the research involves human subjects, the Good Clinical Practice guidelines prescribe[96] a research protocol[97], an Investigator's brochure[98], source documents[99], 'case-report forms'[100] and a clinical research report.[101] Should all these data be accessible? Or, for example, only the clinical research report?

II. 3.4.2 Data-units or data-streams? A more fundamental question is whether 'data' as such actually exist. According to Hilgartner and Rauf[102] there are only data-streams, heterogeneous collections of data, assembled in various formats. They give protein-christallography as an example. Protein-chrystallography comprises many forms of data, including 'clones' for the production of protein samples, protein christallisation techniques, atomic models, algorithms to construct these models, atomic co-ordinates and computer generated images of molecular structures.[103] What data streams really are about, are the complex connections between these forms, the so-called 'assemblages'. A second characteristic of data-streams is the heterogeneity of their factual status. The meaning and usefulness of some data are beyond reasonable doubt, while the meaning and usefulness of other data are so uncertain that they are even questioned by the data-producers themselves. Many data are on a gliding scale somewhere in between those two extremes. Their status also changes during the research process. Scientists are continuously analysing and interpreting data and that may explain their reluctance to release them too early.[104] This may explain, for example, Wilkins' refusal to send his DNA photos to Pauling. In addition, data are constantly being processed. X-ray photos are converted into numbers, numbers into tables, graphics, models and images which may finally be published. This processing may change content, format and usefulness of the data.[105]

In brief, data are no pre-packaged units, capable of being shared or published. On the contrary, there is a continuous stream, which can be split, shared and published at a number of points and intervals, depending on the conventions of the specific research discipline concerned, according to Hilgartner and Rauf.[106] Their concept of data-streams applies *a fortiori* to contemporary biomedical research. As we have seen in Part I, this research involves the correlation of millions of data-points by relating molecular measurements concerning thousands of genes, proteins, metabolites with all sorts of clinical data (such as blood pressure, cholesterol, diabetes and MRI-scans).[107] This research is not about data-streams; it is about waves of data.

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Conclusion Part II. With the notable exceptions of the publicly available raw data produced by a number of recent large-scale community resource projects, such as the HGP, the ideal world of unconditional access is not always the real world. This may be due to personal interests, scientific interests, financial interests, legal constraints such as privacy-concerns, informed consent requirements, quality issues, potential exposure to liability, proprietary claims, and conceptual doubt as to what research data exactly are. The principled arguments *pro* unconditional access (Part I) and the personal, institutional and legal arguments *contra* (unconditional) access (Part II) provide divergent, if not mutually exclusive and potentially conflicting perspectives. Part III will analyse whether this Gordian knot can be cut by operation of the law, in particular the double-edged sword of the European database-right. This right should provide an answer to the question who actually owns the research data.

III The Law: who owns the research data?

III.1 The European database right.

III.1.1 Introduction. The question who owns the research data will be analysed on the basis of the EU database-right. This right was introduced in 1996 by the European Union and entered into force in the Netherlands in 1999. The right vests an exclusive right in the producer of a database to grant permission to extract and re-utilize the contents of the database.[108] If owned by the government it could be used as an instrument to enforce access; if owned by a researcher it could be used as an instrument to legitimise and enforce data-exclusivity. This Part first examines to which extent the database right applies to research databases and flags a number of complications. It then discusses the issue of allocation: who actually owns the database right in a research database.

III.1.2 Case study: the Netherlands Twin Registry. Due to the potentially unlimited diversity of biomedical research databases, any analysis of the above issues '*in abstracto*' may get lost in assumptions. To move beyond assumptions and generalities, the application of the database-right to research data will be analysed using a concrete example: the Netherlands Twin Registry ("NTR"). In many ways, the NTR is representative for the databases that are the object of the Netherlands National Genomics Strategy. As part of the European GenomEUtwin program, it may also be representative for the databases that are part of the European biomedical research infrastructure. The NTR was incorporated at the Amsterdam Free University, for purposes of scientific research aimed at elucidating to which extent differences between individuals are determined by heritable and environmental factors.[109] The NTR comprises a large number of families having twins and contains *inter alia* data on birth weight, pregnancy, physical abnormalities, health and behaviour as well as physiological data, as blood pressure and cholesterol level.[110] The NTR also contains blood samples from which genetic data can be derived.

III.2 The database-right and research data

III.2.1 Database-right and research data. The database-right aims to protect collections of data which meet the statutory definition of a database. The definition reads as follows:

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> *A compilation of works, data or other elements, systematically or methodically arranged and independently accessible by electronic means or otherwise and of which the creation, control or presentation of the contents demonstrates in quantitative or qualitative respects a substantial investment.*[111]

Prima facie this right is squarely at odds with Merton's communism and the Fifth Commandment of unconditional access to research data. Because of its adverse implications for science, the right has been criticised by many observers of scientific research.[112] Indeed, the theoretical justification of the introduction of this novel right was clearly not the advancement of science. Rather, the database-right has been created with the explicit goal to promote the (European) database-*industry*. This triggers the question whether the database-right actually applies to scientific research databases. Neither the Dutch law, nor the European Directive, nor their respective legislative histories, however, provide for a ground to exempt research databases from the application of the database-right. On the contrary, the research exemption and the definition of research data in the preamble to the Directive[113] imply that this right does also apply to collections of scientific research data.[114] So far, the issue has not provoked any lawsuits before the Dutch, German or French courts. Notably, critics in the science community have not questioned its applicability and simply assume that it does apply to research databases. The *communis opinio* of legal commentators on the database-right in general is that the statutory definition of a database practically encompasses all types of data imaginable.[115] It is to be assumed therefore, that the database right could extend to collections of research data.

III.2.2 Independent data. The next element of the definition is that the data be 'independent', *i.e.* they must have a meaning of their own, regardless of the rest of the contents of the database. Whether that is the case, will vary from database to database. Conceptually, it is possible to have a database of which the individual data only have meaning when taken together, just as the various chapters making up a novel only make sense when read as a whole. In fact, the very goal of any research on the data will be to gain insight in the relationships between the individual data. The concept of data-streams even suggests that independent data never have a meaning of their own. Rather, there are many forms of data, which are constantly processed and their meaning may vary from experimental (*e.g.* Rosy's data) to paradigm. This conceptual approach however, cannot take away from the fact that usually subsets of a database can be independently studied for separate research questions, suggesting that the individual data in the database have independent significance. The NTR data, for example, are frequently used to create small subsets to allow more specific research.

III.2.3 Systematically arranged and separately accessible. This requirement holds that the database must have a search function allowing for direct retrieval of specific data.[116] It is generally held that digitally stored data will, by definition, meet this requirement.[117] Thus, even a collection of unstructured (clinical) data could qualify, as long as the collection is searchable for specific items, without the user having to scroll over all the data.[118] Obviously, the NTR satisfies this requirement and it seems safe to assume that most other biomedical research databases do so as well. 76% of the respondents in the KNAW-survey confirmed that their databases were accessible (qua hard- and software) for additional research by other researchers.

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III.2.4 Substantial investment. The goal of the database-right is to promote investment in database-production. Only those database are eligible for protection that demonstrate a *substantial* investment. It is held that it is not necessary that the database has been produced for exploitation purposes. Databases produced for internal purposes or produced by volunteers are said to demonstrate substantial investment.[119] An investment may take the form of monetary investment, time, effort and energy, or 'blood, sweat and tears'. Both the Directive and Netherlands law are silent as to when an investment qualifies as substantial. This will require a case-by-case analysis. Given the amount of time and money required to build the NTR, this database most likely demonstrates a substantial investment.

III.3 Complications of the database-right

III.3.1 Complications. While many research databases will satisfy the various elements of the statutory definition, the application of the database-right to research databases nevertheless gives rise to three complicated questions. First, is a database eligible for protection, even if it is a mere 'spin off' from another investment. Second, does the database-right create a monopoly on 'unique data'? Third, how does the right relate to the public domain?

III.3.1.1 Complication 1: the 'spin off'-theory. As we have seen, the goal of the database-right is to promote investment in (European) database-production. Given this goal, it has been argued that those databases which are not a direct product of a specific investment but rather a spin-off from an investment that was made in another activity, do not qualify for protection.[120] This question was raised during the debate in the Dutch Parliament over the implementation of the database-right into Dutch law, when members of Parliament asked the following question. 'The discovery of a new solar system requires a substantial investment in a telescope or a journey into space. Among other things, it will result in obtaining a collection of stars with names attached to them. Is such a collection a protected database?'[121]

In response to this question, the Dutch Minister replied that this collection does not satisfy the statutory definition of a database, because the investment was not *aimed* at obtaining the list of stars but concerned research by way of a telescope or a journey into space.[122] Commentators by and large concur, be it that some have argued that this could be different if observations and measurements are made for the specific purpose of creating a catalogue of stars.'[123] While the Dutch lower courts and even the Dutch Supreme Court seem split on the issue, the 'spin off-theory' has recently been adopted by the European Court of Justice.[124] The ECJ construed the statutory requirement of an investment in obtaining the *contents* of a database as to require an investment made to *obtain* the existing elements *and* to put them in a specific database. For purposes of assessing whether a database demonstrates a substantial investment, investments that were made to merely create the elements that form the contents of a database do not suffice.[125]

The ECJ-cases concerned databases which had been produced by the commercial sports industry and subsequently used in the gambling-industry. It remains open to question therefore, whether the 'spin off'-theory also applies to public investments in scientific research. On the one hand, no single public investment in science is, strictly speaking, *aimed* at creating a database. As we have seen in Part I, the institutional

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goal of science is 'the extension of certified knowledge'. The goal of the NTR, for example is not to create a twin registry, but to extend the knowledge concerning the nature and nurture of differences between individuals. As a matter of principle, given academic freedom, it is even questionable whether a public funding body can impose that its funding be applied for a specific research goal, such as building a database. And as a practical matter, we saw in Part I that the public funding of research in many cases does not include the costs of creating and maintaining accessible databases.

On the other hand, as Kuhn made clear, most research methods consist to a large extent of collecting, verifying and presenting data, incidentally the terms used in the Dutch statutory definition of a database. The explicit goal of the Human Genome Project, for example, was to create a database containing the fully annotated sequence of human DNA. The effort has produced a (downloadable) public database which constitutes both an 'extension of certified knowledge' *and* a database for future research. And for contemporary *data-driven* biomedical research, creating databases is a crucial element. If we were to adopt this approach, any investment in research amounts to an investment to *obtain* existing elements *and* to collect these in a database, and thus such investment would meet the spin-off criterion as adopted by the ECJ.

III.3.1.2 Complication 2: unique data. The application of the EU database-right is further compounded by the phenomenon of 'unique data'. The preamble to the EU database-right Directive explicitly provides that the database-right may not give rise to the creation of a new right on data proper.[126] A database-right is only an exclusive right in the database as such. It does not pre-empt anyone from collecting the same data to create his own database. However, this framework does not apply in the event the collected data are one of a kind or 'unique'. For example, a specific twin's weight or length at a specific age can be measured only once. Conceptually, then, as a corollary of the preamble to the Directive, the database-right should simply not apply to databases containing unique data. The Directive, however, does not provide for such a ban, but purports to offer alternative solutions to secure access to unique data.

First, if unique data make up only an *in*substantial part of the database, they can be extracted and re-utilized without the consent of the owner of the database-right.[127] Second, the Directive provides that the exercise of a database right is at all times subject to the competition laws. Under these laws, a data-monopolist abusing his monopoly can be forced to grant access to the data on the terms of a compulsory license. In practice, this is not a viable option for most scientists since competition proceedings are a costly and time-consuming affair that public funding bodies are unlikely to fund. Third, the database-right provides for a 'research exemption', which allows the lawful user to use the database for research purposes, without the consent of the owner of the database. This solution too, however, is rather limited.[128] It requires a 'lawful user', *i.e.* a user who has legitimate access to the database, *e.g.* under the terms of a license. Also, the exemption only applies if the database has been made available, one way or the other, to the public. This latter requirement may be satisfied once a researcher has published his findings, as most journal policies demand that authors make the data underlying their published findings available to others for purposes of verification.[129] The research exemption is also limited in that it is not compulsory; it can be excluded in the license of a lawful user. And the exemption only covers the use and not the re-utilisation of the database, although this restriction

is not necessarily an impediment to research, as research typically only requires the right to use the data and not the right to make the data available to the public.[130] Furthermore, the exemption limits access to the extent justified by the non–commercial purpose, a line which, in contemporary, 'profit driven' academia, will be hard to draw. Finally, the exemption as provided in the Directive was optional. The review of the implementation of the Directive in the Member States revealed that France and Italy had not implemented the research exemption.[131]

III.3.1.3 Complication 3: public databases and the public domain. A third complication, at least under Dutch law, is that the database-right does not apply to databases which have been produced by the 'public authority', unless the database-right has been reserved either by statute, regulation or decree, or in a specific case by means of an explicit notice attached to the database itself or an explicit reservation when the database was made available to the public.[132] This provision is based on article 13 of the Directive which provides that the database-right does not prejudice existing rights to access public documents. The rationale behind this provision is that public works, produced by the public authorities should in principle be part of the public domain.[133] 'Public authorities' include public institutions, to the extent they are operating within the scope of their public remit and/or within their public competences.[134] Obviously, public research funding bodies will usually satisfy this criterion. The resulting situation is rather awkward. While these bodies are likely to qualify as the producers of the database (as we will discuss next), the database-right does not apply, except if it has been reserved. Whether it has been reserved is to be judged on a case-by-case basis, as the database may be funded by a variety of public funding bodies. The terms and conditions of the Netherlands Organisation for Research Funding (NWO), for example, provide that its grants *may* be subject to specific conditions concerning ownership rights in respect of the databases that are produced in the course of the funded research.[135] In the event NWO elects not to reserve its database-right, the databases generated by the funded research seem to form part of the public domain. While that outcome may be intuitively appealing, whether it is desirable for scientific research-databases, is open for debate. Apart from privacy concerns, a number of legitimate concerns presented in Part II argue for placing limitations on unconditional access. It is unclear which party is in a position to impose such limitations if the database forms part of the public domain.

III.4 Who actually owns the database-right?

III.4.1 The producer: the funding body or the researcher? The database-right vests in the producer of the database. The producer is the person who bears the *risk* of the investment in the database. An investment may comprise a financial or a professional investment.[136] However, for purposes of determining who bears the risk, only financial risks will be taken into account.[137] Employees and contractors[138] who do not bear a financial risk, cannot be the owners of the database-right.[139] Departing from the Directive, the Dutch legislator considers it also irrelevant who took the *initiative* to create the database.[140] As long as the initiative and the funding are provided by one and the same person or entity, this should not be a problem. However, in the case of publicly funded research, the initiative and the responsibility for the database will typically vest in the researcher, whereas the funding body bears the financial risk. In that event, it is unclear which person qualifies as the producer,[141] although the financial component is probably decisive. On the one hand, this seems a desirable

outcome: the sword of the database-right would thus provide an instrument for public funding bodies to secure all scientists access to the data produced by their peers. This outcome would also underpin the pillars for the harvesting of European life sciences and biotechnology research. On the other hand, being a producer may have undesirable implications for a public funding body. As the owner of the database-right, it will have to handle requests for access and impose conditions to meet the legitimate objections against unconditional access advanced in Part II. This will require expert knowledge of the area of research in question which the body may not have and/or a balancing of interests the body may not be capable of handling.

III.4.2 Multiple funding bodies: co-producers. The previous analysis was based on the rather hypothetical assumption that a research database is funded by a single funding body. In practice, this is unlikely to be the case. The NTR, for example, is only partly funded out of the so-called primary funding, a lump sum amount allocated by the government to the Netherlands universities for further distribution among their departments.[142] Additional funding is provided by the European Union which funds the GenomeEUtwin project of which NTR and a group of European and Australian twin registries form part.[143].[144] The GenomeEUtwin project, in turn, forms part of the international consortium 'P3G', which has been awarded Canadian and, recently, EU funding.[145] In addition, the NTR forms part of the Centre for Medical Systems Biology ("CMSB"), a consortium of Netherlands research institutes, funded by NWO, as part of the National Genomics Strategy, the so-called secundary funding. And as a condition for this secundary funding, the amounts involved may have been 'matched' by the Free University of Amsterdam, so that the Free University could also qualify as a producer. The situation gets even more complicated if these investments took place successively, and each investment has resulted in amendments and modifications of the NTR. Successive investments in an existing database create new database-rights in the databases that have resulted from these investments.[146] The answer, then, to the question who actually owns the database-right in the NTR is that multiple funding bodies are likely to qualify as 'co-producers', collectively owning the database,[147] assuming the bodies have reserved the database-right and absent contractual provisions to the contrary.

Conclusion Part III. While the database-right does apply to research databases, this application is complicated by the 'spin off-theory', unique data monopolies and the requisite reservation by the public authorities. The right belongs to the producer, being the person who bears the risks of the financial investments in the database. To the extent biomedical databases are funded by multiple funding bodies, the respective producers are jointly entitled to the database-rights in the database. The European database-right is an inevitable but awkward fit for databases comprising scientific research data. Apart from the fact that its provisions do not readily apply to the specific contexts of this type of databases, its most striking feature is that it fails to acknowledge the 'investment' made by a researcher or his institution in the production of such databases. In conclusion, the European database-right does not seem to be the sharp sword to cut the Gordian knot in which the issue of access to research databases is tied up.

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IV. Policy: Greasing the Wheels of Research

IV. 1 Policy or No Policy? If there is no reason to develop policy, then that is a good reason not to develop policy. Existing co-operation between academic research institutes and a number of widely used data-collections suggest that either data-access was no issue to these co-operations or that the data-producers involved were able to strike a deal on the terms of access. However, the principled arguments *pro* unconditional access (Part I) and the laws and practical considerations *contra* (unconditional) access (Part II) offer conflicting perspectives. The resulting situation is compounded by the uncertainty created by the database-right as to who holds legal title to the databases. This lends urgency to the formulation of at least a number of principles and recommendations. Therefore, this final Part will explore whether the two opposing concerns – unconditional access vs. legitimate restrictions – can be accommodated by the adoption and implementation of a general policy for access to biomedical data. As an additional benefit, a well designed policy could remedy the adverse implications of the database-rights, by allocating certain rights to the scientist or his institution or by other means granting appropriate credit. This could also help alleviate the plight of funding bodies that may be surprised to find themselves as the owners of the databases they have funded. The above applies in particular to large, *data-driven* research projects in biomedical research. As we saw in the Introduction, two pillars for the harvesting of the potential of life-sciences and biotechnology are access to detailed, up-to-date and available bioinformatics databases and open access to knowledge. The more access becomes vital for research, the better it may be to have a clear set of rules and principles to guide access decisions. A clear policy could help avoid costly and time-consuming negotiations and prevent stalemates, in an era where speed matters and patients can't wait. This way an access policy could actually grease the wheels of research. A final reason for adopting a policy is the fact that funding agencies in other countries have recently established data-sharing policies, which may extend to forms of multinational research. Most notably, the US NIH adopted in 2003 its Data-Sharing policy, which requires grant applicants to include a plan for sharing final research data.[148]

IV.2 Accessibility: compulsory or voluntary? Any policy is eventually dependent on political and scientific choices. The most fundamental choice to be made is whether the leading principle should be that access should be always be voluntary or that access should be compulsory, subject to a predefined set of conditions. The conclusions concerning the database-right indicate that the bodies funding the research own the resulting data and thus they are the entities that ultimately make this decision.

IV.3 General requirements. A policy should in any event meet the following requirements:

- Be transparent, flexible and doing justice to the context of specific research, the status of the (unique) data involved and the legitimate interests of both researchers and patients;
- Be compliant with applicable legislation, in particular the privacy rules;
- Be in line with data-sharing policies of national and international journals;

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- Be in line with grant-policies; references to the database in publications should be a factor to consider in grant applications and a factor in the performance assessment of the institutions concerned;
- Be enforceable; including extra grants to make and maintain data available;

IV.4 Policy issues. The issues set forth below reflect and seek to accommodate the concerns for and against accessibility of research data set forth in Part I and Part II. Some issues draw on the issues listed in the NIH Data Sharing Policy. A policy should in any event address the following issues:

- Definition of the data that should be made accessible, taking into account the concept of data-streams, in particular as regards the type and the status of (unique) data;
- Quality control and peer review;
- The right of the maker of the database to be the first to publish; the moment third parties should get access;
- Mode of accessibility, which may be dependent on the type of data, number of expected requests, sensibility of data etc. The NIH-data sharing policy, for example, mentions the following forms:
    - Publications;
    - Data-archives;
    - 'Data-enclaves';
    - Any combination of the above
- Mode of recognition by the requesting party in publications and grant applications, based on the database;
- The grounds on which access may be denied, deferred or subjected to a predefined set of conditions, such as the goal and the quality of the research proposal, and/or the quality of the requesting researcher,[149] approval by medical-ethics committee, reasonable doubt as to status of the data;
- The conditions to which access may/may not be subjected;
- Reimbursement of costs;
- Transfer of data to third parties;
- Allocation of IP rights to the results of the research;
- Liabilities and disclaimers;
- Enforcement and mechanisms for conflict resolution;

Conclusion

Access to detailed, up-to-date and available bioinformatics databases is identified by the European Commission as a pillar for the harvesting of the potential of life-sciences and biotechnology. Unconditional access to research data, however, is at odds with the primary interest of every scientist to be the first to make a discovery. This classical dilemma forces us to consider the *principle*, the *practice* and the *law* regarding access for academic researchers to unpublished research data. As to *principle*, it is argued that, in addition to the *Communism* postulated in Merton's Four Commandments for the conduct of science, scientific revolutions, the 'Invisible Hand of Research', public funding, the data-driven nature of biomedical research and the interests of patients and the public at large, provide powerful arguments to postulate a Fifth Commandment: unconditional access to unpublished research data. However, in

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practice, access to research data is governed by *Capitalism*, due to the egos of scientists, the financial interests of their institutions, public privacy-concerns, proprietary claims and conceptual doubt as to what data exactly are. The *Law*, in the form of the European database-right, potentially addresses the conflicting perspectives on access to data offered by communism and capitalism. However, the European database-right is an awkward fit for databases comprising scientific research data and does not provide a straight answer to the question who owns the database. It thus fails to provide a sharp sword to cut the Gordian knot of principled arguments *pro* unconditional access and the laws and practical objections *contra* (unconditional) access. As a matter of *Policy*, then, at least a number of principles and recommendations should be formulated, if only to create legal certainty. In addition this policy should seek to remedy the failure of the Law to acknowledge the 'investment' made by a researcher or his institution in the production of databases, either by allocating certain rights to the scientist or his institution or by other means granting appropriate credit. That could also help alleviate the plight of funding bodies that may be surprised to find themselves as the joint legal owners of the databases produced by the research projects they have funded.

Epilogue

The Bermuda Principles. Apart from guidance provided by existing policies regarding specific issues and existing repositories (*e.g.* pathology archives), guidance may be found in examples and experiences, such as the NIH Data-Sharing policy. A major source of inspiration ought to be, *mutatis mutandis*, the Bermuda principles adopted by the Human Genome Project (HGP). Fifty years after the discovery of the molecular structure of DNA, the HGP completed the assembly of the human DNA sequence. After it had abandoned, at the urge of Watson, its initial drive to patent the cDNA sequences it was producing, the HGP adopted the Bermuda principles to secure rapid and unconditional access to the sequence data. Under these principles all participating scientists were required to release their unpublished DNA-sequence data in public databases.[150] The first director of the HGP was 'Honest Jim' Watson.

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Benefit-sharing: an inquiry regarding the meaning and limits of the concept in human genetic research

KADRI SIMM

Abstract

The Human Genome Project and the related research and development activities have raised heated discussions around some very basic ethical and social issues. A much debated concern is that of justice in human genetic research and in possible applications, especially pertaining to questions of just benefit-sharing - who and based on what sort of argumentation has the right to require benefits arising from research and discoveries, and what can even be considered as benefits? In what follows I will be examining and clarifying the notion of benefit-sharing by focusing on its justifications. I will argue for certain qualifications and limitations in using this concept in specific and universal contexts.

The idea of benefit-sharing

Social justice has been first and foremost discussed as distributive justice or the sharing of benefits and burdens of social cooperation. Some objects of distribution (goods, services, duties) aspire to universal status, some are particular to a specific cultural, geographic, religious or other context, ultimately leaving the society or community handling the distribution as the measure by which certain goods become valued. It has generally been agreed that some goods or benefits like food and shelter are valued in all societies but the list is almost endless, including rights and liberties, money and commodities, jobs and opportunities, medical care, education, honours and prizes, personal security, special privileges, resources and so on.

How does research in human genetics link up with the discussions of benefit-sharing and justice? It has been suggested that the potential harm of the genetic revolution may rather lie in the ability of technology to distribute the available resources even more unequally than is currently the case, and in that way enforce and strengthen the existing disparities and inequity.[1] On the other hand it is suggested that genetics might have enormous potential in levelling the existing inequalities and providing for a more just and equitable existence. Few would dispute that the impact the application of genetics might have in specific societies, as well as in a global context, owes much to the way its fruits, as well as its burdens, will be distributed. Hence the rise of the benefit-sharing concept, as most would agree that the potential for both greater good and greater harm is there.

There are also views that dispute the application of a benefit-sharing framework within genetics, and these are mostly related to a perception that discussions of benefit-sharing actually legitimate the attempts to commercialize and profit from (human) genome. This approach could be based on an understanding that genetic research is part of a larger humanistic project of medicine, where financial or other incentives should recede before important values like human health and quality of life. If human genetic research is about locating genes, understanding their functions and

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possibly attempting to modify these with the aim of treating or preventing the occurrence of the gene-related disease,[2] it might seem curious why there are such heated debates on benefit-sharing.[3] After all, so far, the understanding has been that the results of scientific inquiries suffice as the benefits are then available to the public. What has become of the concept of altruism in medical research? Why shouldn't we nowadays continue this honourable tradition of volunteering to help science to progress, so that future generations may have a life of less pain and illness? Indeed, some might feel offended when their honest altruistic participation is answered with the promise of a benefit. "That it not why I am doing it", people would say.

I think we can distinguish several counterarguments against this reasoning. Firstly, discussions of benefit-sharing are necessary even if one disagrees with the underlying trends of commercialising the genome, as closing ones eyes to a certain existing and increasingly powerful "evil" does not make it disappear. Also, non-engagement with the issue is an option that only some can afford, and not so for populations or communities already in the midst of genetic mining. Thirdly, we should also consider seriously the possibility that medical research itself has changed considerably and is consequently not an arena of altruism it perhaps used to be.

Defining benefits or sharing what, exactly?

Benefit-sharing is not a concept that has been invented for the explicit use in human genetic research (or genetics) and the origins of the discussion can be traced in various international documents:

- UN International Convention on Economic, Social and Cultural Rights (Article 15,1b): *"The States Parties to the present Covenant recognize the right of everyone to enjoy the benefits of scientific progress and its applications"*;

- UN Convention on Biological Diversity (Article 17,7): "*Each Contracting Party shall take legislative, administrative or policy measures /…/ with the aim of sharing in a fair and equitable way the results of research and development and the benefits arising from the commercial and other utilization of genetic resources /…/*";

- UNESCO Declaration on the Human Genome (Article 12a): *"Benefits from advances in biology, genetics and medicine, concerning the human genome, shall be made available to all, with due regard for the dignity and human rights of each individual"*; (Article 19a,iii): *"In the framework of international co-operation with developing countries, States should seek to encourage measures enabling: countries to benefit from the achievements of scientific and technological research so that their use in favour of economic and social progress can be to the benefit of all"*.

The HUGO ethics committee expressed in its statement on benefit-sharing the following: "*A benefit is a good that contributes to the well-being of an individual and/or a given community (e.g. by region, tribe, disease-group...). Benefits transcend avoidance of harm (non-maleficence) in so far as they promote the welfare of an*

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individual and/or of a community. Thus, a benefit is not identical with profit in the monetary or economic sense. Determining a benefit depends on needs, values, priorities and cultural expectations." Firstly, benefit is clearly a positive change for the recipient(s) and should not be defined as simply providing a neutral result, with the insistence that potential burden was avoided. Secondly, and more importantly, the definition recognizes that benefits or *goods* cannot be established as neutral or objective facts but are inherently value-laden.

This is to say that behind the possibilities that are suggested as benefits (or burdens), lay understandings about why these things would be beneficial (or burdensome). And they are beneficial of course because they are valued as such, accepted by specific people, communities, societies. There are values that are shared by many, and then there are ones that test the limits of cultural relativism. All decisions, principles, perspectives within assessing the benefits and burdens are dependent on where one is looking from, and the values and benefit-sharing principles themselves can be traced to various understandings of justice – be it liberal, communitarian, utilitarian, egalitarian, libertarian etc. These perceptions include both political bias and moral judgement, and thus even the most general benefit-for-all is essentially value-based (as it values giving the benefit to all, and not only to the needy, for example).

The rhetoric, the media hype, the trusted position of scientists and researchers construct an arrangement that values and disvalues certain aspects of social life. Probably the most popular and popularised example of a benefit arising from human genetic research concerns health, be it individual (personalised medicine, pharmacogenomics) or public health related (preventive medicine, genetic screenings of embryos etc). Health is seemingly a non-controversial good that we all would be happy to have, or at least to improve on. Thus, generally speaking, within genetic research it is assumed that health is one such benefit accepted by certain, or even most, societies. But how are we then to assess the case from Finland where 10% of the young men attending their compulsory national service were found to have problematic dental health (large number of cavities)? [4] This is in a country where free dental care had been available to all and I do not believe we are dealing with extreme forms of cultural specificity, as Finland surely qualifies as a democratic country, with general values at least shared with other Western countries.

It has been argued, that "the choice of risks and the choice of how we live are taken together",[5] and I believe the same is true of hoped-for benefits. Similarly to the ways people choose to selectively pay attention to risks, they are also selective in defining benefits. Perhaps not surprisingly, those with dental problems came from the lower socio-economic strata of the society, and researchers attributed their disregard towards dental care to the values and lack of motivation of their strata. There is of course the slogan of "educating" them to the benefits of good dental health, but at the same time it is obvious that the problem was really not in education but rather, in the fact that they did not value free dental care enough to take advantage of it.[6] Thus in our assessment of potential benefits and burdens, it is essential to realize that these conceptions are not a matter of education, as if the providing of "sufficient" information would guarantee the commonality of argument and perception. I think this sort of cautious attitude is especially important to keep in mind as regards the many potential "genetic" products that have been speculated about in the media,

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especially pertaining to different lifestyle, feel-good-smart-beautiful drugs and therapies.

The discussion above is not meant to attack genetics as irrelevant or unable to provide "real" benefits, but it does point to an important detail that should be accounted for in the benefit-sharing discussion. The example above also points to an important conclusion that 90% of the Finnish population do value dental health and thus insists that values, while different, can still be and are shared. The difficult aim of the just benefit-sharing would then be to take into account the diversity without ignoring the shared values. Secondly, careful attention needs to be paid to the question of who is defining and deciding upon specific benefits to be shared, but this is a point I will be unable to elaborate on presently.

Benefits put forward by the scientists, as well as the pharma industry, patients, investors and public health officials span a wide array of potential valued "goods", starting from improved health and scientific knowledge to financial gains and wider social benefits. What is behind the notions of benefits of genetic research that are utilized in various discussions? The HUGO definition is rather vague and I think intended to be such, but below I sketch an outline of issues that have been named as benefits by various actors internationally. This overview is by no means exhaustive but rather illustrative.

<table>
<tr><th></th><th>Health</th><th>Commercial</th><th>Scientific</th></tr>
<tr><td>Individual level</td><td>Designer drugs and other individual aspects of "personalised medicine"</td><td rowspan="2">Profits to the investors</td><td rowspan="4">Non-instrumental knowledge: development of science and knowledge as a value in itself, regardless of the fact whether it is useful to humans</td></tr>
<tr><td>Communal level</td><td>Relief to disease-related populations etc</td></tr>
<tr><td>National, state level</td><td>Efficient health care services, policy planning etc</td><td>Development of biotech and related sectors, new jobs etc</td></tr>
<tr><td>Global level</td><td>Eradication of diseases etc</td><td></td></tr>
</table>

The table demonstrates the all-encompassing scope of the hopes and dreams we have with respect to developments in genetic research. The question now is, what would be the basis or rationale for the sharing of these benefits? And here various, even competing justifications can be distinguished.

Sharing on what basis?

From the abovementioned international documents as well as from various other sources, I have sketched below some relevant strands of reasoning that the calls for benefit-sharing could be based on:

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1) Benefit-sharing as **compensation for risk(s) taken**. This aspect is currently clearly more relevant in clinical trials where risks can be rather direct and serious, especially as new medical interventions are tried out and evaluated. Human genetic research currently involves mostly giving of various samples, and risks have so far been more theoretical - discrimination based on one's genetic makeup, concerns of privacy and of psychological stress when genetic tests reveal a potential disease without the possibility for cure. Benefit-sharing in this instance would be a compensatory activity geared towards those who have taken risks that are necessary for research to take place and to possibly succeed. (Besides health risks, for example, the financial risks of investors can also be considered under this reasoning).

2) Benefit-sharing discussions in the context of genetic research are characterized by another aspect that focuses on **compensatory arguments based on the notion of property**. The world's agricultural sector has had the earliest experiences with this aspect of benefit-sharing. There exist numerous examples of cases where the results of the research and developing activities accomplished throughout the centuries by local communities are seized by big industry (as a rule originating from the industrialized country), and the latter has the available resources to allow it to 'cross the finish line' and capitalize alone on a certain product through patenting.[7] Once the patent has been granted, the local community from a developing country has no means or resources to challenge the situation. Thus the goods are extracted from poorer countries, labelled as someone's property and often very little or nothing goes back to the communities that have originally contributed. Bioprospecting or perhaps biopiracy? Therefore one of the arguments behind benefit-sharing refers to the past and present inequalities of power and resources in the world, that are capitalized upon by big international corporations, creating and enforcing further injustice between the developing and industrialized countries. Benefit-sharing here is an attempt to change or at least alleviate this situation by putting forward essentially rectifying arguments that are based on some sort of notion of property and the utilization of that property.

The subject matter of human genetic material as property is a much debated one. This is either conceptualized as a shared property in human genome, or alternatively, as property in one's own personal genome. The UNESCO declaration on the Human Genome and Human Rights established genome as a heritage of humanity in a *symbolic sense*, such wording specifically not being capable of supporting legal action. In reality, the abovementioned declaration, as well as others that stress the need for benefit-sharing, (e.g. the HUGO Statement on the Principled Conduct of Genetic Research), exist side by side with others that directly contradict the ideas and principles embedded in the former (like the WTO's Trade Related Aspects of International Property Rights, the TRIPs agreement). Thus while the notion of shared property in human genome has been established symbolically, the parallel conventions detail out the private ownership rights and duties in utmost practicality, with pharmaceutical companies owning patents on human genes and cell lines.

However, private ownership does not seem to imply personal ownership. The first infamous legal case in establishing a property right in one's bodily material concluded that even if one would own the specific cells in one's body, this did not mean that the cell lines derived from it would also be owned.[8] The owner(s) of the genetic data have

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not done anything to make their property valuable and therefore, at least in terms of patenting, should not have similar rights as researchers who have added value to it[9] - a sort of Lockean understanding of mixing one's labour with natural resources.[10] David Townend has concluded that the only function that the property right in one's own genetic information can have, is that of a shield.[11] That is, property right in this case allows for protection only, and not for exploitation, selling or buying. The ongoing patenting of human gene sequences allows for the property argument but mostly not on behalf of individuals or communities.

3) **Compensation for fairness** as a basis for benefit-sharing refers to a realization that increasingly some aspects of medicine are not as altruistic as they used to be. Certainly not all medicine can straightforwardly be equated with business but the developments in genetics have brought this characteristic to the forefront, and gradually our hopes and dreams in medicine are linked up with the rather expensive promises of genetics. The medical industry has become big business - the pharmaceutical trade sector, for example, has for a while been the most profitable in the world.[12] Perhaps benefit-sharing has become such an issue because people have realized that their volunteering is not matched with altruism from the other side, and consequently compensation for fairness is required? If big profits are made, then a feeling of fairness would ask for a sharing with participants.

Historically, rewards or incentives for research participation were outlawed in order to ensure that no coercion or pressure was put on the volunteers. Much of the benefit-sharing discussion, with the exception of the HUGO statement, has so far mostly been silent on that aspect, although it is clear that the promised benefits might have direct relevance to the participation decision. Presently, compensation for fairness as a moral argument seems to be the strongest basis for benefit-sharing and thus supported by various international documents. Compensation for fairness usually includes various international and social justice concerns, and here the justification for benefit-sharing is a moral one - those who have the power and are able to act in alleviating suffering have the moral obligation of doing so, based on concepts of solidarity and justice.[13] But the question of who exactly is responsible for such activities is unclear. More specific examples of moral duties that are relevant here include:

- *Duty not to exploit the vulnerable* (Nuffield Council) [14] refers to the duty to abstain from taking advantage of the unequal circumstances of power, resources and opportunities in this world, a negative duty to refrain.

- *Duty to alleviate suffering* (Nuffield Council) points to the necessity of providing benefits to those in need, a sort of positive requirement for those who have the power to act.

- *Special moral obligations of medical enterprises.* Human health is a fundamental value, a base upon which much else in life can be built. This is an idea that the HUGO ethics committee referred to when suggesting, in its statement on benefit-sharing, that companies involved in health care and medicine might have special moral obligations that other enterprises do not have. Genetic research and its applications were initially clearly situated in the sphere of medicine, suggesting that benefits should be allocated based on

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need. However, for the past decade, the investments into biomedical research have increasingly been originating from private enterprises, and the distributive principles of the business-world (like desert and merit) are increasingly influential within genetic research. From a justice point of view there is a conflict between health care and business in terms of their distributive principles.[15] As in genetic research the spheres of health care and business overlap, the principles of need and desert create conflicts with both sides utilizing the arguments of justice for their own cause.

So should participants refer to charity and benevolence when discussing benefit-sharing or should they feel entitled to a profit based on ownership rights and justice concerns? Whether it is compensation for risks taken, for fairness' sake or for having contributed their property for the research, entitlement to some benefits can in principle be justified. When genetic research is viewed as a for-profit activity then certainly business relationships can be applied. True, it is a special kind of business, having to do with human life and death issues. It is the very sensitivity of this particular area that causes difficulties for benefit-sharing discussions.

Sharing with whom?

An understanding that benefit-sharing can be justified through different arguments does not say much about how this framework should be applied. Traditionally, in a medical context, benefit-sharing has centred on research participants, be it individuals, families or (increasingly) communities. How is that focus on research participants justified in genetic research? The intergenerational nature of genetic information also engages other people besides those directly participating. If taking risks has been an appropriate argument for benefit-sharing among those directly involved, then genetic research might also create risks for those people who have not been participating. The content of the notion of risk is increasingly difficult to pin down where genetic information is concerned, which suggests that while risk-taking was useful for regulating benefit-sharing within traditional medical research, it might not be a suitable justification in many instances of genetic research.

The property argument for benefit-sharing has been most successfully applied in cases of communities and nations (usually having to do with non-human genetic resources). Possibly some specific cases of monogenetic diseases can also rely on this argument, at least implicitly. For example, disease-advocacy groups in the US have in some instances been successful in negotiating for direct benefits, as their contributions are easier to prove.[16] But their argument for sharing can also be based on the notion of fairness.

Fairness and various justice-related concepts are notoriously difficult to agree on, and the complex nature of genetic information hampers the successful application of this concept in benefit-sharing further. Whose concerns are to be taken as relevant? In small-scale clinical drug trials this is easier to assess compared to large population-based genetic databases, where significant social concerns might arise.[17] Subsequently I would draw attention to a very close dependency between how we justify benefit-sharing and who those are to be shared with. This works both ways – whether we start with abstract justification that will determine the circle of those to

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whom it applies; or whether we are concerned with certain individuals, communities, peoples etc., and therefore argue for a benefit-sharing principle that would take their interests into account. For example, when we consider the genome to be a common property of humanity, the sharing should clearly be done among all human beings. An understanding that these aspects of benefit-sharing are closely linked is important to keep in mind. Some of the uncertainties and doubts that have accompanied the benefit-sharing discussion in human genetic research might have to do with the fact that some justificatory arguments are not efficient in including the interests of relevant populations. For example, benefit-sharing arguments based on international injustice might not fit so well with the public concerns regarding research conducted in industrialized countries.

By drawing on parallels with clinical research I have so far focused mostly on benefit-sharing among research participants, but other possibilities have been argued for. In recent years, the discussions regarding benefit-sharing in human genetic research have increasingly stressed that everyone should benefit, and that the entire humankind should be involved in the sharing.[18] Here the concept is employed to fight the activities of patenting and commercialization that monopolize and limit access to the results of genetic research. The right to benefit from genetic research would then be based on a fact that humans share 99% of the genome. To quote Ortúzar: " *there is no reason to confer benefit exclusively on the population which is the subject of the research /…/ all benefit derived from genetic research on populations should be available to anyone in need of the health improvement offered by it*."[19] Indeed, benefits to participants can be seen as unfair from the point of view of universal benefit-sharing.

I believe it is necessary to distinguish two different aspects in the benefit-sharing framework. At least a differentiation needs to be made between the *universal* list of benefits mentioned in the table above - that describes the entire positive potential of the genetic enterprise - and a *specific* benefit-sharing framework directed towards those who directly participate in research. I believe these two issues need to be kept separately if we still want to make use of the sharing framework. By differentiating between universal and specific sharing, much confusion is avoided because many benefit-sharing arguments function only in specific context, whereas others have relevance in universal context.

Limitations of universal benefit-sharing framework

Calls for universal benefit-sharing have been based on concerns for justice in an international genetic research situation. The agricultural background to benefit-sharing can possibly explain some tendencies that have characterized this discussion within human genetics. Namely, the presupposition that in genetic research (in parallel with agriculture, and say, mining) there exist certain clear-cut and tangible benefits and/or resources that can be easily assessed, accessed and distributed. The assumption that benefits are out there, almost graspable, disregards the social context of human genetics and the controversial nature, as well as the mere potentiality, of many benefits. Because of the amount of hype that has surrounded human genetics (in comparison to plant and animal genetics), many overoptimistic visions as well as nightmares have become regarded as rather realistic benefits and burdens.

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Benefit-sharing seems to be on the one hand fuelled by feelings of injustice emerging from the inequalities of power between the global medical and pharmaceutical industry and the resource-rich less developed countries; on the other hand the scene has been much influenced by the often over-hyped visions of grand future developments. I think that benefit-sharing discussion in genetics would not have gained such prominent status if it was not for the previously existing global injustices that are not directly linked to genetic research. I refer to a larger background of current world inequalities in terms of opportunities and resources that stem from various sources, be it inherited from colonization experience or the international establishment of market-oriented liberal capitalism that favours certain prominent players and regulations in the ordering of our world. The dissatisfaction that forms the basis for a universal benefit-sharing requirement is larger than only genetic research allows for. It is clear that benefit-sharing is hoped somewhat to address this dissatisfaction, despite the fact that much of it stems from areas not connected to genetic research. To my mind the problem is that a benefit-sharing framework is not able to respond adequately to those concerns that surface from this larger background of injustice issues. Genetics is not only a health issue, and even health itself does not contain the various aspects of human existence that are relevant from the justice point of view.

Different political and economic instruments can be and should be utilized once there is political will to seriously deal with existing injustices and inequalities in the world. But I fear that benefit-sharing as a framework originating from research lacks coherent strength, and might be simply inadequate for enforcing the claims that are currently made within it to alleviate the widening gap between the industrialized and developing countries. If the patenting system is unfair, then benefit-sharing is not able to challenge that unfairness sufficiently, but rather, policy changes are required. Benefit-sharing should be used to its maximum potential, including, if possible, the sharing of benefits to those not directly involved, but that will not even be a remotely adequate solution for the international justice predicament. Below I have attempted to draw out some concerns that ground my scepticism regarding the inadequacy of a benefit-sharing framework in this universal-benefit-for-humanity context.

Benefits from genetic research, despite being potentially very widely applicable and relevant to human health, will only be capable of addressing a limited cluster of health care issues. Applications based on traditional (meaning non-genetic) medicine, improvements in hygiene and nutrition are still more useful in helping the populations of developing countries to achieve better health and quality of life. Currently, around 800 million people, or 18% of the world's population go hungry every day and suffer the related consequences to their health; 1.1 billion do not have access to safe water.[20] Thus, even very generous redistributive actions resulting from genetic research or new medical research will not have the effects that are sorely needed and hoped for in the international situation. It is the fair provision of most basic medicine that would benefit the populations of developing countries. This of course raises the question whether shared benefits would necessarily have to be related to, or result from, genetic research. Possibly benefit-sharing in genetic research could allow for anything to be shared, as long as it is defined as a benefit by a substantial amount of stakeholders. On the other hand, this only illustrates the concern I alluded to above – namely that benefits distributed via genetic research (whether they themselves are

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"genetic" or not) are not in any way a sufficient measure to alleviate the problems where genetic research forms only a minor part, or indeed, is only a symptom and not a cause. And it should not be forgotten that many of these hoped-for benefits currently constitute little more than heavily hyped visions of the contingent human enterprise of science.

Secondly, much of the discussion in benefit-sharing discourse is ambiguous and incoherent, as it utilizes several arguments that exclude each other. Thus it can be easily dismissed or 'dealt with' through dispersing with a few coloured ribbons and glass-beads, so to speak. After all, fairness and justice are very difficult to pin down and agree on. Many would refer to a certain 'gut-feeling' that in principle benefits are due in return for a contribution, but in the complexities of genetic research these are in many cases very hard to establish. Monogenetic diseases (where contributions would perhaps be easier to distinguish) are very rare, and most of the genetics-related expectations are linked to discoveries in the common complex diseases. Research on these diseases, especially because they are strongly linked to environmental factors, will necessarily involve very many participants and samples. Involvement of hundreds and thousands would be needed even to start contemplating any relations between a disease outbreak, DNA and environmental factors. This also means that tracking someone's individual contribution would be unthinkable. The quality here really comes with quantity.

It is difficult to fathom that universal benefit-sharing based on the universal property argument is realizable. Presently the symbolic heritage of humanity is privatized with increasing speed to companies, research agencies and others. Even if appropriate laws were changed, it is open to discussion what entitlements this would create as regards benefits. It could be argued that no-one can be excluded from enjoying benefits (and this is already demanded now - see the quotes from the beginning of the article), but it is much more complicated to argue for anything more substantial, at least based on the notion of property. The notion of global public goods or the human rights discourse has a better chance in distributing the needed resources. Compensation for risk cannot be highly relevant in universal sharing, as risks in medical projects traditionally involve limited number of participants. Even if communities or populations are engaged (for example in setting up population based genetic databases), universal sharing is still not relevant within this risk-based reasoning. Compensation for fairness is too vague, at least within genetic research, as its potential is bound by the specific research protocols and by particular issues under investigation. It lacks coherence and complexity to be successful outside of these limits to tackle the real causes for rallying behind benefit-sharing.[21]

My final reason for scepticism regarding the universal applicability of benefit-sharing framework in genetics is a pragmatic one. If the currently most powerful universal discourse – that of human rights - is only slowly improving the international situation regarding human health and quality of life satisfactorily, then the rather specific line of benefit-sharing thought originating from the uneasy mixture of research and business activities, does not look very promising. However, this is a conclusion regarding universal benefit-sharing and not the framework for specific research projects.

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Ted Schrecker has insisted that any "responsible ethical analysis must not regard crucial background elements of the social and economic context /…/ as too big to change" and has urged the linking of benefit-sharing discussion with the critique of "market fundamentalism".[22] What I hope to have done is precisely the investigation of this link. My conclusions however state the theoretical and practical inadequacy of the benefit-sharing concept to deal with these large scale issues.

This does not mean that the battle for a more just world is lost - it simply needs more suitable and more powerful "weapons". Unfailing and consistent political pressure on the enforcement of so-called second generation or socio-economic rights is important in the context of health care. On the other hand, the implementation of these rights is very much dependent on the available resources of countries. Therefore simply pressure on rights discourse is inadequate without the inclusion of more systematic critical approaches to tackling the global structural inequalities. For example, the way international copyright and trade regulations function in reproducing and enforcing the age old disparities between the industrialized and developing countries should be challenged. These rules are by no means neutral or even fair.[23] I believe that these approaches are better equipped to address the concerns that have been behind much of the engagement for benefit-sharing of the technological and biomedical developments on a more universal level. It is the investigation and application of these frameworks that have a better chance in dealing with global inequalities, both because they are better grounded theoretically and because their implications are much wider than the limited areas of benefit-sharing of genetic or even biomedical research results. This research promises, and hopefully will deliver, a lot, but the improvement in the health and condition of humankind cannot be achieved with the focus on a rather ambiguous concept of universal benefit-sharing.

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[1] P. A. King. 1992. The Past as Prologue: Race, Class, and Gene Discrimination. In Gene Mapping. Using Law and Ethics as Guides, G. J. Annas and S. Elias, eds. New York. Oxford University Press :95.; World Health Organization. 2002. "Genomics and World Health". Geneva.

[2] This definition and my entire article has its main focus on human genetic research, leaving aside agriculture, forestry, animal husbandry and many other areas where genetic research is ongoing.

[3] As a side-remark, I'd like to note that benefit-sharing discussion in genetics is such a prominent topic first and foremost because the potential benefits are envisioned rather significant and pretentious in both financial and scientific terms, and also that many of the risks or burdens taken are rather serious as

well. Most likely, more altruistic approaches and less benefit calculating characterize co-operations of less extravagant promises.

[4] T. Airaksinen. Why Do Inequalities in Health Exist? Acta Philosophica Fennica. Justice, Charity, and the Welfare State: Moral and Social Dimensions 2001; 68.

[5] M. Douglas, A. Wildavsky 1982. Risk and Culture. An Essay on the Selection of Technical and Environmental Dangers. Berkeley, CA. Univerisity of California Press. P.8.

[6] I do not attempt to clarify this situation in terms of possible causes for such behaviour, I have simply used it here to illustrate the point about the existence of various understandings of 'benefits' regardless of how we can or cannot explain them.

[7] Some classic examples from agriculture are presented by David Magnus. International Agricultural Perspectives. Conference „Toward an understanding of benefit-sharing", Philadelphia, March 3, 2003. http://www.bioethics.upenn.edu/prog/benefit/pdf/Magnus_David.pdf (accessed 24.05.2005)

[8] On *Moore v. Regents of University of California* see C. A.Erin. 1994. Who Owns Mo? Using historical entitlement theory to decide the ownership of human derived cell lines. In Ethics and Biotechnology, A. Dyson and J. Harris, eds. London, Routledge.

[9] R. Chadwick, K. Berg. Solidarity and equity: new ethical frameworks for genetic databases. Nature Review Genetics 2001; 2: 320.

[10] Locke of course had an important clause to the property-creation process, namely this was only allowed when „there was still enough and as good left" („An Essay", ch.5, paragraph 33). It is questionable whether patenting gene functions and sequences does leave enough for others.

[11] D. Townend. 2003.Who owns genetic information? In Society and Genetic Information, Codes and Laws in the Genetic Era, J. Sandor ,ed.Budapest-NY. Central European University Press: 142.

[12] HUGO Ethics Committee. Genetic Benefit-sharing. Science 2000; 290: 49.

[13] See for example Chadwick,Berg, op.cit.note 10.

[14] Nuffield Council on Bioethics. 2002. The ethics of research related to healthcare in developing countries. Available at http://www.nuffieldbioethics.org/publications/pp_0000000013.asp (accessed 24.05.2005).

[15] R. Chadwick, A. Hedgecoe. 1998. Commercialisation of the human genome. In A Companion to Genethics , J. Burley, J. Harris, eds. Oxford. Blackwell.

[16] Some of the best known examples are PXE International and Alpha-One Foundation.

[17] For some such concerns raised by the Estonian Genome Project see M.Sutrop, K.Simm. The Estonian health care system and the genetic database project: from limited resources to big hopes. Cambridge Quarterly on Health Care Ethics 2004; 13, 3: 254-262.

[18] See for example, L. Mansur. Gene Discovery, Ownership and Access for Developing Countries in the Era of Molecular Genetics. Electronic Journal of Biotechnology 2002; 5, 1. (http://www.ejbiotechnology.info/content/vol5/issue1/issues/05/); M. G. de Ortúzar. 2003. Towards a Universal Definition of 'Benefit-Sharing. In Populations and Genetics: Legal and Socio-Ethical Perspectives, B.M.Knoppers, ed. Leiden. Martinus Nijhoff. ; Ted Schrecker. 2003. Benefit-Sharing in the New Genomic Marketplace: Expanding the Ethical Frame of Reference. In B.M.Knoppers, ed.

[19] Ortúzar op.cit.note 18, p.478.

[20] United Nations Human Development Report. 2003. http://www.undp.org/hdr2003/

[21] On the limited global relevance of some genetic benefits see for example R. Chadwick, S. Wilson. Genomic Databases as Global Public Goods. Res Publica 2004; 10.. P.123-134.

[22] Schrecker, op.cit.note 18, pp.406-407.

[23] See for example T. Pogge. 2002. World Poverty and Human Rights. Cambridge.Polity Press.

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Charitable Trusts and Human Research Genetic Databases: The Way Forward?*

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Abstract

Human genetic research databases cast a new light on the controversial issue of which uses of the human body are morally permissible. More specifically, banking human tissue raises issues relating to the ownership of the samples that the participants have donated, to the ownership of the data that are derived through processing the donated samples, and to the management arrangements that better balance the interest of genetic research with the protection of participants' rights. Winickoff & Winickoff suggest that the charitable-trust model is a superior legal arrangement for biobanking compared with private biobanking. This paper critically assesses Winickoff & Winickoff's claim by highlighting some areas of implementation where such a model could be problematic. The charitable trust is certainly an advantageous arrangement because (1) it favors the separation between control and use of the samples, (2) it provides a procedural mechanism that facilitates the participation donor groups in the biobank management and (3) it mediates the different interests that are affected. On the other hand, the charitable-trust model leaves unresolved several issues—among them the ownership of the sample, the right of withdrawal, access and funding mechanism. I conclude that further theoretical and empirical analysis is required in the area.

1 The Challenges of Genomic Biobanking

Large collections of human tissues cast a new light on the controversial issue of which uses of the human body are morally permissible. The technical possibilities of automatized data analysis of large collections of DNA samples and their bioinformatics processing have developed dramatically over the last few years and are constantly being improved. The protection of genetic data that is collected in human genetic research databases has consequently emerged as a highly complex ethical issue that urgently needs to be addressed. In its summary of the most pressing issues raised by advances in genetic research, the 2002 Report of WHO's Advisory Committee on Health Research on Genomics and World Health points out that "[t]he planned development of large-scale genetic . . . databases offers a series of hazards and ethical issues which have not been encountered before", and it then outlines, as possible hazards, the "many ambiguities regarding access and control . . . the potential harm to individuals, groups and communities . . . risks . . . arising from access to genetic information, both by individuals themselves and by third parties." [1] Furthermore, the Report lists access by "health insurance companies, government bodies, or the legal profession and police" as well as "the effect of stigmatizing entire countries or particular groups of individuals, and there are concerns about commercial exploitation without adequate compensation" as pressing ethical issues.[2] Ethical issues become even more acute when genetic data are combined with information on individuals' health, lifestyle or genealogy. Furthermore, human genetic research databases raise specific issues of ownership of samples that the participants have

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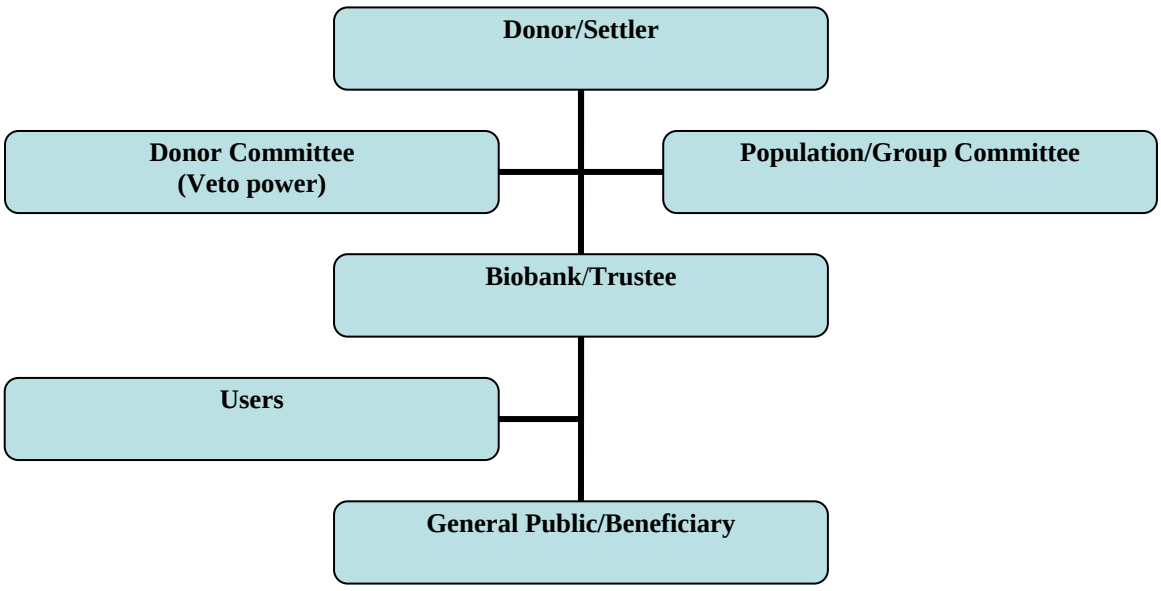
donated, ownership of the data that are derived through processing the donated samples, and of management arrangements that better balance the interest of genetic research with the protection of participants' rights.

In recent years, per-profit companies have been increasingly involved in genetic research and in the creation of large genetic databases. However, commercial biobanking has raised even more substantial questions about the conditions under which genetic databases can be established, kept, and made use of in an ethically acceptable way. To address some of the growing concerns, scholars have proposed arrangements that are alternative to commercial biobanking. In a 2003 paper, David and Richard Winickoff proposed the charitable trust as a model for genomic biobanks superior to commercial biobanking.[3] This paper critically analyzes Winickoff & Winickoff's article, concluding that the charitable trust model in itself does not solve many of the open questions. My basic argument is that the charitable trust model provides an interesting governance model, but many of the issues can only be solved at level of rules that are governing the trust rather than in the model itself. The following sections lay out my critique of Winickoff & Winickoff first by describing their proposal (Section 2) and then by critically assessing and illustrating the critical aspects of their proposal (Section 3). Finally, I present my conclusion and provide some indication for further policy research of biobanks (Section 4).

2 The Charitable Trust Model

A biobank organized as a charitable trust would be created by a trust agreement under which the participant in the research project (or settler), "formally expresses a wish to transfer his or her property interest in the tissue to the trust."[4] By donating the tissue samples to the biobank, the donor contextually appoints the recipient as trustee of the property, who has legal fiduciary duties to keep or use the property for the benefit of the beneficiary. Winickoff & Winickoff suggest that in genetic biobanking the general public acts as the beneficiary of the charitable trust.[5]

Figure 1 - The Charitable Trust Model



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To provide a more viable arrangement, the authors add a few features to the model. First, the trust shall collect samples only if each donor gives "permission" to collect and store the sample. The authors are thus avoiding the traps of the informed consent terminology by using the terminology that was first proposed by Henry Greely. In fact, talking about informed consent would be inappropriate in genomic biobanking, Professor Greely argues. When dealing with large collections of biological samples, participants are not asked to consent to a particular research protocol with specific risks and benefits. In fact, all the uses that investigators will make of the samples are often not foreseeable at the time of the collection. Their samples are therefore more likely becoming part of a research resource, usable for many different protocols, concerning many different medical conditions. "Without knowing what research will be done, one can only speculate on the risks and benefits. For this reason, it might be better in this context to talk about 'permission' for research uses of patient data."[6]

Second, an institutional review board (IRB) shall approve any subsequent research. Therefore, although the donors have given permission to an open list of researchers, the collected samples can only by used in new research if the IRB approves it. Third, participants should be granted an absolute right of withdrawal. Whenever settlers/donors are no longer interested in being part of the biobank, they should be able to withdraw their permission, and to prevent the biobank from using the samples in future research studies. Furthermore, permission for future research projects would not be required providing that participants are periodically updated on the different protocols that have been approved, and that they retain a right of opting-out whenever dissatisfied with the medical research that is carried out. Finally, Winickoff & Winickoff envisage other features as essential components of a biobank: the full disclosure of commercial arrangements and the protection of the participants' confidentiality by encrypting all identifying information.

Winickoff & Winickoff argue that the charitable trust presents three clear advantages, namely the protection of the participants' rights, the propensity to build participants' trust, and the protection and maximization of the scientific value of the biological collection. I shall briefly discuss these arguments. First, the charitable trust protects the rights of the participants in at least two ways: a) the trusted collection shall serve exclusively the interests of the beneficiary – the "general public" –, and the participants are within the general public; b) by having a donors committee and a group or population committee, the interests of the participants are directly taken into consideration in managing the collection. Second, by not being geared toward the maximization of profits but rather toward the maximization of the utility for the beneficiary of the trust, the charitable trust engages in a trust-building relationship with the potential participants. Third, by serving the "general public," the scientific value of the collected samples is maximized. On the other hand, a commercial biobank might have an interest in restricting the access to samples by other research groups.

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3 Assessing the charitable trust model

In assessing the advantages and disadvantages of the charitable trust model, I shall begin by outlining the advantages that, in my opinion, the model presents. I will then discuss my perplexities of the Winickoff & Winickoff's proposal.

3.1 Three advantages of the charitable trust model

The charitable trust model presents at least three advantages if compared to a model based purely on contractual relationships. First, the charitable trust model favors the separation between control and use of the collected samples. Large collections of human tissue are often being developed as resources that enable future research projects rather than as tools to enhance pre-existing genetic investigations. Therefore, who stores samples and data is often not the user of the same because he/she is not carrying out genetic research directly. In other words, in the real world storage of material and use of the same are often separate, and having an institutional framework—such as the charitable trust model—that builds upon this distinction is a clear advantage.

This dichotomy also (1) reduces the possibilities of conflict of interest between having custody of samples and using them especially in making prioritization decisions, (2) enhances the possibility to perform ethics review of the genetic research, and (3) favors the participation of different interest groups in deciding the fate of stored tissue. First, who manages a collection of human material in the public interest faces prioritization decisions regarding the use of the samples—who should access the database? For what purposes? In which country? Under which conditions? Therefore, if the manager of the collection is himself/herself one of the potential users of the material, he/she faces a constant conflict of interest in making decisions about the use of the collection. In fact, he/she may be inclined to favor a project where he/she has a personal stake over one where he/she has no bearing, without focusing exclusively on the public interest—that's human nature. By having an institutional framework based on the separation between storage and use, the conflict of interest in making prioritization decisions would certainly be reduced.

First, as a practical matter, transparency and opportunity for ethics review are enhanced if storage and use are separate. In this scenario, third-party researchers interested in accessing the samples would always be required to file a request to access the samples—or the genetic data that are derived from the samples. By filing such requests, external researchers would make explicit the circumstances and the intended purpose of their access. This practice would certainly favor a transparent access to databases and accountability of the both the third parties towards the trustees and of the trustees towards the "general public."

Second, the charitable trust model provides a governance framework that facilitates the participation of donor groups in the management of the database. In fact, procedural mechanisms are built in the model so that one or more committees that represent the donor group, or other groups that have an interest in the management of the database, must be established. In the end, this requirement favors participation in the management of the biobank, its transparency, and eventually societal trust.

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Third, the charitable trust model facilitates balancing the different interests that are affected in large-scale DNA collections. The trusted biological samples can only by used to serve the interest of the beneficiary. Thus, each request for access shall be balanced against the interest of the "general public". However, the "general public" can be construed as a complex entity. As the French *Comité Consultatif National d'Ethique pour les sciences de la vie et de la santé* points out, the "curator [of a database] is at the center of a network of rights and obligations that need to be managed."[7] It is certainly wider than the totality of the participants and it probably includes all the different communities that are affected by the genetic research that is conducted by using the database. However, the charitable trust presents the advantage of establishing a procedural mechanism that mediates between the different interests that come into play in genetic research.

3.2 Unresolved issues

If the charitable trust model provides the advantages described in the paragraph above, it also fails to solve many controversial issues that biobank raise and its implementation may be practically problematic. In particular, the charitable trust model fails to address controversial issues relating to the ownership of the genetic database and its data and its samples, the right of withdrawal, third-party access, and funding. In the remains of the paper, I illustrate my critique of the model by analyzing issues from these four controversial areas. The conclusion I draw from my analysis is that, although the charitable trust provides an interesting governance model, many of the controversial issues are left open and can only be resolved at the level of the rules that are governing the trust.

3.2.1. Ownership of samples

The charitable trust model fails to fully address the ownership issue that genetic databases raise. In today's debate, thinking of a database in terms of ownership is inescapable. In fact, policymakers and courts have thoroughly discussed the donation of human body parts from a property perspective. The charitable trust model partially addresses the issues, because—as ordinarily happen with trusts—the ownership of the samples goes to the trustee. In fact, under the trust agreement, participants formally express their wish to transfer his or her interest in the tissue to the trust. However, many important questions concerning the ownership of the tissue samples, the derived data, and the database in itself are unanswered.

First of all, Winickoff & Winickoff's model assigns the samples' property to the trust, thus contemplating that owning human material is legally admissible. However, the ethical admissibility of property in the body is controversial. Moreover, from a legal standpoint, "[b]oth the common law and the views of many developing countries' people agree that there is no such thing as property in the body."[8] As a consequence, the charitable trust model might not be compatible with many legal systems to the extent that it requires a formal recognition of property in the body. Alternatively, in order to avoid the intricate question of whether donated tissue becomes the property of the recipient or the participant in biomedical research, commentators and policymakers have proposed the less drastic arrangement of "custodianship" or "stewardship." For instance, the 2005 Draft of the UK BioBank "*Policy and Intellectual Property and Access*" provides that "UK Biobank Limited [is] the steward

of [samples and data]".[9] On the other hand, even this second model leaves open many important questions that are intimately connected with the storage and use of human tissue. In fact, being the steward or the custodian of samples assigns you the right to court of law to seek the restitution of stolen samples or the right to pass them out under certain circumstances—all "traditional incidents of property."[10] In the end, the question that first needs to be addressed is whether a formal recognition of property in the body is the best way to reason about collections of human tissue. To put it in Alexandra George's words: When dealing with banking of human tissues, "[i]s 'property' necessary?"[11]

The model based on ownership to the trust is also in conflict with those policies that provide that the donation of a tissue sample does not transfer its property to the recipient. Thus the Icelandic Act on Biobanks explicitly provides that the biobanker is not to be considered the owner of the biological samples that are donated to the bank.[12] Moreover, the non-binding WHO Regional Office report on genetic databases provides that participants in biomedical research should have the "primary control [of] samples or the information generated from them", and that their legal interest "is *akin* to a property right" (emphasis added).[13]

3.2.2 Right of withdrawal: How to implement it?

The controversial aspects of property and biobanks do not end by qualifying the biobanker as trustee of the donated samples. Although the trust as proposed by Winickoff & Winickoff becomes formally the owner of the donated tissue, the availability of the right of withdrawal challenges the notion that donors are giving up their property interests in the sample. Winickoff & Winickoff propose that donors shall have an "absolute right" to withdraw the permission to use the samples.[14] First of all, Winickoff & Winickoff seems to propose a form of revocable trust—a trust that may be changed or cancelled by its settler/donor or by another person— with an unusual twist: the settler/donor is also a member of the beneficiary group (the public). However, technically it is not a "revocable" trust because, in this case, the withdrawal of biological material of a single settler/donor does not revoke the whole trust. This ambiguity, which derives from the double hat of grantors and beneficiaries that donors wear, may in fact create conflicts between the interest of the participant as a donor and the interest of the participant as a beneficiary. In fact, if a participant exercises his/her right of withdrawal, the charitable trust has to comply even if the withdrawal is against the "interest of the general public"—the genetic make-up of the withdrawing participant could be unusually interesting to researchers. As a consequence, Winickoff & Winickoff's model leaves open several questions: may the trustee refuse to comply with the request for withdrawal if against the interest of the beneficiaries, thus including the withdrawing participant in the category? What if, after the participant dies, the request comes from a participants' family member or his/her legal representative? Therefore, the property-based model, in which the general public acts as the beneficiary, is somehow in contrast with the idea of granting an absolute right of withdrawal to participants.

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Second, the model does not address the issue of what is the best mechanism to implement the withdrawal of samples and data. The policy options offered by the available policies are several: withdrawal could substantiate in returning samples to the participants, in destroying the samples, in destroying the link between the identity of the donor and the sample (anonymization), in removing the identifying information from the database, in destroying the genetic data derived from the sample, or in "no longer" using them.[15] However, the charitable trust in itself cannot answer the question of which mechanism is ethically permissible and better protects the interest of both genetic research and research participants.

3.2.3 Access

Winickoff & Winickoff propose the charitable trust model as sharing information and favoring an open-access model.[16] Indeed, wide access is arguably the best avenue to realize the potentialities of a genetic database. However, the charitable trust model in itself does not answer some questions that access implies. First, the framework does not address the issue of whether external research groups may access the samples—by having the samples shipped to their labs—or simply the genetic data that have been derived by processing the samples. Second, the charitable trust does not answer the question of who may access the samples and whether the public interest that the trust serves implies some prioritization mechanism. Winickoff & Winickoff suggest that commercial companies may have access to the database.[17] However, the model does not solve the problem of whether commercial entities that access the databases become owners of the data that are derived from the access, or even may retain (and own) the specimen to whom the trust has granted access. Furthermore, the charitable trust model fails to address the issue of whether donors, health care providers and family doctors may access the database. Shall participants be only given information about the aggregate results of genetic research undertaken using the donated samples or shall they be individually informed if the research findings affect their future care? Finally the model does not solve the issue of whether external researchers and private corporations may access sensitive data that have been collected along with the samples.

Arguably, if broad access is granted, benefits for the "general public" will be greater. However, the notion of "general public" as beneficiary is too vague to provide practical guidelines without further specifications. One can argue that providing genetic counselling to the participants is serving the "general public." At the same time, one can argue that granting exclusive access to one pharmaceutical company is the best way to serve the "general public." In the end, the trustees will be asked to make these sorts of judgements in adopting the policies that regulate third-party access. Most of the answers will only lie in those rules governing the biobank and its contractual relations with external actors rather than in the governance framework.

The 2005 Draft of the UK BioBank "*Policy and Intellectual Property and Access*" provides a clear illustration that a governance framework in itself does not address the most pressing issues that biobanking activities raise.[18] In fact, although the UK BioBank has a well-defined governance structure based on the principles of stewardship of the samples, open-access of data and serving the public interest, the overall framework leaves unresolved many issues that must be addressed by specific rules. In particular, the 2005 Draft regulates a wide variety of issues such as

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intellectual property rights, the access to human material and data, the re-contacting of participants, the terms of access, and the dissemination of research results.

Finally, Winickoff & Winickoff argue that the charitable trust model is the best way to ensure that the scientific value of the collected samples is maximized.[19] It follows that commercial entities would be less willing to maximize the potentialities of the samples, if in charge of the same collection. With its governance structure, the charitable trust model is arguably able to retain the sort of identifiers that are usually stripped in the commercial context—in fact, at least the United States, commercial companies have tighter restraints that non-profit entities performing medical research.[20] Therefore, maintaining the longitudinal and epidemiological component of the genomics cohort study would be enabled and facilitated, which would consequently lead to maximizing the "scientific value" of the collection. However, one could argue that accountability to the shareholders provides stronger incentives to the managing board than accountability to the "general public" and that corporate law requires the disclosure of enough information to ensure public oversight of the operations of the company. Because of the differences in the legal regimes of commercial companies and of non-profit companies, one can argue that the charitable trust model is superior. However, this argument opens the door for debating whether the legal disadvantages of commercial corporations are reasonable. Also, the argument is based on an empirical claim that ought to be demonstrated before accounting maximization of scientific value among the benefits of the charitable trust model. In my opinion, the empirical claim ought to be demonstrated and the policy merits of different regimes for different actors ought to debated before accounting maximization of scientific value among the benefits of the charitable trust model.

3.2.4 Funding

The key benefit of the charitable trust is that the collection serves the "general public." An ideal corollary to this premise is that public money entirely funds the trust. However, a charitable trust is likely to need some private funding to reach its goals. It follows that charitable trusts are likely to transact with per-profit companies, for instance by paying a fee-based access. In a stronger scenario, charitable trusts would also have to form partnerships with per-profit companies that operate in the market. At least that is what Winickoff & Winickoff envision: "biotechnology and pharmaceutical companies that want tissue bank or data . . . could be partners with the tissue bank in order to help fund it."[21] However, in the end, the Winickoff & Winickoff model insufficiently details how it could balance openness and public-benefit with commercial collaboration.

4. Conclusions

The charitable trust model provides an interesting governance model that is fertile of practical applications. It certainly offers a procedural mechanism to mediate the different interests that come into play, and to balance them. However, many of the issues can only be solved at level of rules that govern the trust—or more generally any biobank, whether public or private. Thus the charitable trust model does not fully solve issues of ownership of the samples—especially if combined with an absolute right of withdrawal—of access to the samples and the data, and of the residual role of

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commercial entities in population genetics. Further theoretical and empirical analysis of the permissible actions that biobankers can take with regard to the collections that they manage is needed to develop the intellectual capacity that is necessary to cope with the pressing challenges of genetic databases.

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[20] I am indebted for this point to one of the anonymous referees, whose words are almost entirely reflected in the last two sentences.
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Bioethics and large-scale biobanking: individualistic ethics and collective projects*

GARRATH WILLIAMS

Abstract

Like most bioethical discussion, examination of human biobanks has been largely framed in terms of research subjects' rights, principally informed consent, with some gestures toward public benefits. However, informed consent is for the competent, rights-bearing individual: focussing on the individual, it thus neglects social, economic and even political matters; focussing on the competent rights-bearer, it does not serve situations where consent is plainly inappropriate (eg, the young child) or where coercion can obviously be justified (the criminal).

Using the British experience of large-scale biobanking, I argue that the focus on consenting individuals distorts our ways of thinking about biobanks and has serious practical ramifications. This becomes clear if we contrast the case of adult biobanks intended for medical research with two other forms of biobanking. Thus child cohort studies – vital for sound scientific investigation of the interplay of genetics and environment in health – have been very badly funded next to adult studies. On the other hand, forensic databases have attracted massive investment, but little debate – partly owing to a sense that here, at least, is a case where consent is not relevant.

Contrasting these central types of biobanking, I will suggest that there are powerful factors at work in limiting 'ethics' to individual rights. Projects of this size should direct our attention to more overtly political questions concerning priority setting and organisation of medical research.

Introduction

In this paper I wish to cast a critical eye at the way in which we – meaning both bioethicists and practitioners – frame ethical and bioethical discussion. A slow swell of protest has been gathering, from many directions, against the idea that protection of individual rights should be the central focus of bioethical concern.[1] Nonetheless, standard assumptions, and powerful institutions, continue to equate (bio)ethics with the protection of individual patients or research subjects – protections most often framed in terms of confidentiality and informed consent.[2]

My discussion will be particularly concerned with large-scale biobanks, and the difficulties that we have experienced in deciding – or discovering – the principles by which they might be regulated and governed. Part of our difficulty has come from the fact that biobanking is in fact highly variegated in form: many different sorts of biobank exist, but those that have attracted the most attention are as yet more intent than reality. Especially in the UK, but also beyond, debate has centred around two examples of large-scale biobanking for medical research which are either – in the case of UK Biobank – still being planned, or – the Icelandic database – only partly realised. One difficulty, then, is that we have spoken more about intended projects –

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and not exploited the experience we do have with biobanking. The second is that public and policy discourse, and to some extent bioethical reflection, has taken its orientation from now conventional moral categories of medical research ethics. So we have heard a great deal more about principles focussing on individual rights and protections – informed consent and confidentiality – than other principles or ethical frameworks. This is surely very odd, given the necessarily collective nature of these projects.[3]

This suggests two routes toward greater clarity about the legitimating principles for human biobanking. First, that we ask whether our dominant focus on individual rights, so clearly ill-suited to reflecting on large-scale collaborative research, might serve other purposes beyond the protection of individual rights. Second, that we give attention to the already existing, and in some cases highly successful, examples of biobanking, and how far individual rights provide a framework for ethical reflection on these.

I begin by examining how it may be that we have come to identify ethics with a focus on individual rights, above all informed consent, and the different purposes and interests this focus may serve. I then describe some notable examples of large-scale biobanks, and examine how a focus on individual rights hinders us in appreciating the ethical issues that they raise. I conclude with the contention that, although some organised interests may be motivated to separate (bio)ethics from questions of undoubted political significance, a concern with ethics must point us in exactly the opposite direction. To focus on individual rights may actually undermine individual rights and interests, in ways that benefit some organised interests, because important social, political and scientific questions are left out of consideration.[4]

Individual rights and informed consent

The main planks of medical research ethics after the second world war are well-known, first and foremost in the form of the World Medical Association's Declaration of Helsinki (1962). Against the horrifying abuses of individuals that were perpetrated in Nazi Germany and Japan, and against increasing awareness of serious on-going abuses within democracies such as the USA or even Sweden, two ideas were made central to medical research ethics. The first was the free and voluntary consent of the individual research subject. This coincided, of course, with Western societies' increasing emphasis upon the informed consent of patients to any medical interventions they might undergo. The second measure was ethical review of research trials via 'research ethics committees' or 'institutional review boards.' Of course, it was not only that 'experiments' were done that no-one in their right mind would consent to, but – and this fact gets forgotten when we focus on informed consent alone – the research (or so-called research) should never have been conceived of in the first place. To these two key planks of research ethics we should also add confidentiality, carried over from conventional medical ethics.

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The individual rights, to confidentiality but above all to informed consent, have come to dominate ethical thought about medical research. This may be an unfair generalisation so far as academic bioethical reflection is concerned, long since advanced beyond its 'four principles' stages. But so far as a generalisation can be fair, I suggest this reasonably applies to the teaching of bioethics, to common perceptions of (bio)ethics, and to the avowedly 'ethical' components of policy thinking. Simply and crudely: when most people, and most organisations, think of ethics they think of ethical safeguards for individuals. The background assumption is that research is a good, if not a good in itself; and therefore all that ethics need do is ensure that the rights of participants are respected: consent and confidentiality. While research ethics committees continue to scrutinise research proposals from the point of view of scientific soundness and not just individual rights, we still find a natural and unfortunate division between 'good science' and 'good conduct.' More than this, these standard mechanisms to protect rights and to ensure that research is well-conceived do not answer as to which research is pursued, which avenues ignored, and how research is organised. Not all research, after all, is equally desirable.

It is a difficult question, why we should have come to think that the ethics of medical research can be decided in terms of safeguards for individual rights, above all informed consent. I would like to suggest that a diverse range of factors has been at work. Some of these undoubtedly reflect good and valid reasons for insisting on the importance of consent to medical research (although my own view is that consent should not be necessary for every sort of research[5]). But there are other factors at work here, that suggest that our focus on consent is a little too convenient: that it may fit too neatly with some common habits of Western thought, that such a focus may in fact serve organised interests which can work against the public good and even the good of individual research subjects. We can view informed consent as a powerful case study of how any principle – however valid it may be – is always more complicated and ambivalent in its practice than we might like to think.

The difficulty of this question – why we should so often focus on informed consent – is only enhanced when we remember some obvious and well-known difficulties that attend it. Allow me to mention only a few.[6]

- As study upon study has shown, the 'informed' aspect of informed consent proves to be rather fleeting. People persistently ignore, forget, misunderstand the information that researchers provide them with; quite often they forget that they have consented to a research project at all. There is the further question as to whether the promises and information that potential research subjects are given are actually accurate, which points us to the need for institutional oversight of this, and other, aspects of how any research project is conducted. It seems, indeed, that many research ethics committees have come to see their most substantive 'ethical' task as ensuring the accuracy of informed consent *forms*.

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- Informed consent is irrelevant to many groups of (potential) research subjects. It is impossible with infants and problematic with older children. It is also pretty much useless for the retarded, the senile, the demented and for some types of mental illness.[7] Indeed, as evidence for my claim that informed consent tends to orient our thinking and practice, sometimes harmfully, we might recall the well-known problem of *non*-research that arises here. The effects of many drugs on children are simply not researched or documented, vastly increasing the risk when they are thought necessary to treat a child. Instead of organised research, then, we have a plethora of unorganised, unreported and unsynthesised experiments on people who are incompetent to consent.

- When we focus upon individual consent to research, we also neglect the importance of statutory research, that poses few risks to individuals but is essential to the running and improvement of collective health provision. Examples include: audits of medical practitioners, teams and organisations; monitoring for cost-effectiveness; research concerning public health and epidemiology; follow-up of medical interventions for side-effects and efficacy; monitoring of notifiable diseases; and the keeping of disease registers. These have usually not been subject to informed consent and their value would be undermined if they were, in terms of not only incompleteness but also probable selectivity in opting out.[8] One way such research has been defended from the requirement of informed consent is by the anonymisation of subjects' samples and/or information; but this is not always possible or desirable.

- Informed consent is about individuals, and one of its purposes is to empower individuals against organised and expert researchers. However, it can actually obscure this power relationship. Requiring consent will not, by itself, alter the fact that uncoordinated individuals are always subject to the power of organised groups or institutions. This fact may not be problematic so long as we can reasonably take the benefits and organisation of research for granted. But for many reasons this is not something we should do. One important advance in the organisation of medical research occurred with the advent of HIV/AIDS. As we know, this disease was very badly researched to begin with, largely because of prejudice against the groups who were worst affected. One response was political organisation among some of those groups, to lobby for and even fund the necessary research. As became clear, not all the institutions involved in medical research are operating in the public interest; indeed, we should be well aware that no organisation can be trusted reliably to serve that interest without active public scrutiny.

All these well-known difficulties only sharpen the question: why should informed consent have become so definitive of medical and research ethics – not just in (philosophical) bioethics but above all in how ethics is understood by practitioners, policy-makers and their institutions?

In the philosophical context, consent has a natural fit with certain framing assumption of much ethical theory. Key among these is our customary focus on individual duties,

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individual rights, and respect for the choosing subject via the elusive, multivalent notion of autonomy. This relates to a tendency to focus on the competent, rights-bearing adult, wrongly seen as independent rather than *inter*dependent. Furthermore, it is connected with a view of ethics that is separated from politics by a focus on individual decision-making – and exhibits a corresponding tendency to ignore how contexts of choice are formed, especially how institutions structure, enable and disable our choices. That is to say, some framing assumptions of philosophical ethics fit rather neatly – too neatly – with a focus on consent and other individual rights such as confidentiality. To put the point mildly, this makes it more difficult to frame discussion of issues that arise in collective action and decision-making – not least, in my context here, how medical research is organised and prioritised. However – this point is essentially to do with academic theorising, and has less explanatory power when it comes to practitioners' and policy discourse, not to mention that of lay people.

So far as lay people are concerned: None of my contentions here are meant to dispute how important are the protections and guarantees that informed consent provides to the subject of both treatment and research. The openness and choice signalled by informed consent procedures provide some protection for the subject's basic interests, and perhaps some opportunity to choose in the light of h/er own values. For parents, proxy consent provides a means to protect their child(ren) in the face of organisations that are not always trusted. The provision of information makes for openness, which is at least a precondition in ensuring fairness as well as protection of interests.

Some have argued that there is more to the story that this, and here we enter more ambiguous territory. One can see the practical emphasis on informed consent as fitting with a certain sort of self-conception. Investigation of what research subjects say – and of what people who refuse to participate in research also say – suggests that informed consent supports an image of the 'responsible subject.'[9] That is, it enables people to see themselves as moral and responsible, choosing in the light of a moral imperative to participate in research. This is true even of those who refuse to participate: it is only that they find that possible risks weigh more heavily than the duty to assist research. In short, informed consent fits well with our ideas of what it is to be a responsible person – and who does not want to see h/erself as responsible?

This suggests that informed consent is serving, not the interests, but rather the self-image of actual and potential research subjects. In itself, this may not sound particularly sinister. Protecting autonomy is protecting the right to choose in the light of one's values; and we have good reason to hope that people will number social responsibility amongst those values. If mechanisms of informed consent encourage this, then this is only a sign that our 'autonomy' is necessarily limited by the institutions in which we act and think – and rightly so, insofar as those institutions are just.

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This raises the question, of course, as to how just those institutions and their divisions of responsibility may be. Part of seeing oneself as responsible is accepting responsibility; and it may be that subjects of research are finding themselves accepting more responsibility than they ought. Many have noticed that informed consent procedures can involve an *imposition* of responsibility upon the subject, as co-decider, co-responsible for the project – someone who becomes 'concerned' in both senses, participating *and* anxious. Neo-Foucauldians such as Nikolas Rose have analysed modern Western societies in terms of 'responsibilisation.' Thus Rose claims, 'individuals are not merely "free to choose," but *obliged to be free*, to understand and enact their lives in terms of choice.'[10] As a simple example, we might notice how many Western governments have preferred to target health interventions at individuals, rather than regulating the activities of commercial organisations. In the UK, childhood obesity has become a source of great concern, not to say moral panic. Thus far the response has been to emphasise parental responsibilities, and not (for example) to regulate the marketing of energy-dense foods by private enterprise.

In the context of genetics, an emphasis on individual responsibility has often been seen as a guarantee against the bad old eugenics. This has been very clear in the case of genetic counselling, for instance, in advising couples concerning the possible transmission of genetic disorders to any children they may have. The professional ethos of genetic counselling has centred on non-directiveness – a purported refusal to impose medical or state values upon the subject (in direct contrast not only to eugenics but also to the conventional value-laden-ness of medical care).[11] But this distancing of the state – or rather, of health care practitioners who may be funded by the state – from individual choice has a potentially invidious aspect. It can be, indeed sometimes is, experienced as a handing-over of responsibility to the parents, constituting a refusal to help, to share responsibility for what can be immensely difficult decisions.[12]

Returning to the context of medical research, this immediately suggests one reason why many subjects show so little recall of information about the project, and indeed may show very little interest in even "reading the form." What you don't know about can't be an object of your responsibility – or so we commonly tell ourselves. Not knowing can operate as a way of refusing a (dimly perceived) imposition of responsibility.

Consent procedures not only impose responsibility, for better or for worse. They can and do impose risks and costs on subjects.[13] Informed consent procedures usually make clear that research subjects will not share in any profits or gains that stem from the research. Whatever its motivation, this clarification effectively functions as a renunciation of any possible entitlement to a share in profits or benefits. Thus informed consent forms become a contract clarifying future rights – or lack thereof. Sometimes consent forms will even disavow the researcher's liability should certain risks to the subject materialise – a provision that is certainly against the subject's interest and unquestionably to the benefit of the researcher's host institution. In either case, as one writer puts it, 'the consent becomes a waiver'[14] – with regard to future risks to the subject, and future benefits to the researching institution.

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These darker aspects of informed consent are increasingly well-recognised, in the bioethical literature at least. Another problem is simpler, cruder and larger than all of the above. A focus on informed consent is also highly convenient for researchers and their institutions, and above all commercial enterprises. The reason is simple: insofar as individual rights delimit the domain of ethics, they shield other substantive issues from critical scrutiny. Not the least of these is the most important factor distorting priorities for medical research in the world today: the transnational pharmaceutical industry, operating in a context of gross global injustice and often in the context of inadequate or ill-conceived national health care frameworks. Pursuing a pill for every lucrative ill, this is an industry more concerned with marketing than research, more concerned with markets than needs, more concerned to market treatments than to prevent ill-health. The industry naturally promotes a reductive, individualistic and remedial approach to health, one that governments, researchers and health organisations have too often fallen in with. In the face of this enormous problem, informed consent, or other individual rights, are no answer at all – worse, such a focus constitutes an obstacle to perceiving the problem at all. Too often, it seems that to talk about such large and overwhelming factors is to stop talking ethics and to start talking something less respectable – that is, politics, something which (it may be implied) neither researchers or bioethicists should concern themselves with.

A second problem is related. If ethics is about consent or confidentiality, then ethics is no longer concerned with the scientific validity of research, gauging the likely benefits of research, and establishing priorities among well-grounded research possibilities. Evidently research ethics committees play an important role in addressing such issues at the micro level. Apart from the signal fact that this still leaves the macro level unaddressed, there remains the problem that 'science' and 'ethics' can too easily come apart. If such committees see their ethical task as protecting individual rights, and their scientific task as scrutinising the validity and workability of proposals, then at least two results ensue. The fact that scientific validity is a *moral* demand tends to drop from sight: yet validity matters so much because we want *effective* health interventions. Second, the extent to which a research proposal is worthwhile comes back to the narrower question of whether it should be able to properly investigate its leading hypothesis. The narrowing of ethics to individual rights can thus operate to support technocracy,[15] distancing assessment and decision-making from the perspectives and concerns of non-experts, and leaving 'ethics' unable to challenge commercialism or other distorting factors in priority-setting for medical research. The questions of whose health and whose interests will be served by research are too rarely asked, and need not be answered.

In short, while there are certainly good reasons for valuing informed consent, there are also several bad reasons why we may be led to over-emphasise it – reasons that have nothing to do with protecting research subjects and which divert our attention from the plain collective duty to choose our research priorities wisely.

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Biobanking as a case study

I turn now to the case of large-scale biobanking. Biobanking involves the storage of (i) tissue samples and/or genetic information *and* (ii) personal information, such as health care data (disease histories, treatments received), lifestyle information (nutrition, exercise, wealth, family background) and sometimes genealogy, or certain other sorts of identifying data.

Biobanking is not a new phenomenon, but it has taken on a much greater significance with the emergence of research into genetics and the first practical applications of genetic knowledge. In fact, two of the most important applications of genetic knowledge have not been medical at all. As we know, we are still a very long way from decoding all but the most simple health information from a person's genetic make-up (that is, chromosomal abnormalities and single gene disorders). What we can do is to use genetic samples to identify individuals and to identify basic genealogical linkages. At present, then, the most significant uses of genetic information are forensic investigation and paternity (or maternity) testing. Biobanking can then take two main forms: either to exploit these existing abilities, or as a basis for research to increase our understanding of the human genome and how its tiny variations between individuals might affect our bodily make-up and our health.

Exploiting existing abilities, and correspondingly the most well-established of biobanks, are forensic biobanks. The UK's National DNA Database is the largest in the world, with genetic profiles from just over three million people[16] – it has doubled in size since 2002 and we are told to expect a similar rate of increase for the foreseeable future. When DNA samples can be extracted from traces left at crime scenes, they can be processed and the resulting 'profile' compared with the millions on record. Sometimes a match will occur, which can be invaluable in linking different crimes or in identifying a culprit. Sometimes too a sample can be taken from a suspect and shown not to match DNA that can be reliably identified with the crime: so suspects can be shown to be innocent, not just guilty. The UK also has a large database for paternity testing, so that financial responsibilities for childcare can be allocated to the biological father, where partnerships have broken up. This is much smaller, and I will leave it aside here.

Of course, these sorts of biobank can also be used for various forms of research, however unclear the ethics of this might be. The greatest interest here has naturally been in deriving phenotypic information from a genetic sample, so as to aid identification of the person who has left traces at a crime scene – thus information about quantitative traits such as height; hair, skin and eye colour; or even facial characteristics. This research is still in its infancy, and other possible discoveries such as correlations between genetic make-up and behavioural traits (the 'criminal gene'?) are, for the moment, no more than science-fiction.

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The other forms of biobanking are principally concerned to increase our knowledge of how genetic variation influences body and health. One older form of biobanking, which I will not be concerned with here, is simply the storage of human tissues from people suffering from particular disorders. This has been going on for a long time, because there are many properties of tissues that are more immediately and obviously relevant to health than DNA. These banks tend to be relatively small, spread out across the health service and private companies, and are often not documented, many being built up by individual researchers in the course of their careers. These disease-specific banks, apart from not being principally concerned with genetic research, are also close to conventional medical research in that it is samples and data from the unwell that are used. Often the data will be gathered post-mortem, which also means it can effectively be anonymised and does not raise so many issues of individual rights. (However, it can raise profound concerns about parental rights, as we saw in the UK's Alder Hey scandal, when organs from dead children were taken for research without parents' understanding.)

Neither the involvement of the unwell, nor even the deceased, apply to the two forms of biobanking which I would like to consider alongside the forensic case. In these cases, samples and information are taken from many people, most of whom are not suffering any particular disease or disorder. The information, and perhaps samples too, are taken on an on-going basis.

The examples that have attracted the most attention, perhaps because of their sheer scale and novelty, are the large-scale biobanks for *adult* medical research. The most well-known, and the furthest along the path to being realised, is the Icelandic genetic database. This is a complicated arrangement, which was originally supposed to be made up of three different databases, and has several distinctive features:

- Samples and genetic information, and genealogical information are being entered onto two separate but linked databases. Originally a further database of health care data was conceived, the Health Sector Database, but it now appears unlikely that this will be created.

- The whole population is included in the genealogical database (around 290,000 people in 2004); consent is not involved as this uses existing public data. The database of genetic samples is gathered on the basis of informed consent. The Health Sector Database was enormously controversial because it presumed consent – that is, health data was to be gathered automatically, *except* from those who specifically opted out.[17]

- The resulting database is under exclusive licence to a commercial enterprise, deCode genetics.

These last two aspects have made the Icelandic database especially controversial, in that informed consent was to have been waived for health data collection, and that the research agenda is being shaped by a private company – which is, of course, hoping to profit from any findings.

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Almost as well-known is UK Biobank, a major initiative currently in its pilot stages.[18] This is supported by the UK government, the Medical Research Council, and the Wellcome Trust (the world's largest medical research charity) at a projected cost of £60 million (and many suggest this will represent only the initial costs). It will gather samples and data from half-a-million people, aged 40-69 – most of whom will be healthy but many of whom will develop some of the major diseases of Western societies – heart disease, cancer and so on – in the next decades. Consent will be asked, and there will be no exclusive licence to a commercial enterprise, though private companies will have access to the biobank, on terms yet to be established.

Finally, I want to mention a third type of research biobank, smaller and better established than the large-scale adult databases just mentioned. Various child-cohort studies exist around the world. The UK has two important examples. In Bristol, there is the Avon Longitudinal Study of Parents and Children, ALSPAC, otherwise known as the 'Children of the 90s' study. This includes information about 14,000 children born in the early nineties, as well as their mothers and fathers. Biological samples, medical information and lifestyle information are gathered on a regular basis from all the children. By stark contrast with UK Biobank, this project has been funded on a shoe-string, by small, discontinuous grants from the various UK funding bodies. There is also the North Cumbria Community Genetics Project, which is more narrowly directed toward genetic studies, with samples from about 5,000 children and their mothers.

The scale of the Iceland database and UK Biobank can only partly explain the attention they have received. After all, the UK's National DNA Database is far larger than both combined, and much longer established; this is true of forensic biobanks in other countries too.[19] The child cohort studies are also much better established, having been up and working for over a decade. I would like to suggest that the greater attention devoted to these new, largely speculative projects has arisen not only because of their scale but because they are more congenial to our framing assumptions about ethics. Although the large adult biobanks unquestionably pose difficulties for our established ethical framework for medical research, they are by no means as problematic as the forensic and child cohort cases, because informed consent remains an important and relevant issue.[20] (So too confidentiality, but this is a concern for all my examples.) Nonetheless, consent serves us badly as a point of orientation for the adult medical banks, as well as being nigh-on useless in the child and forensic cases. The larger, better-established forensic databases can help us meet this difficulty, because in these cases it is self-evident that not consent but public policy principles (such as institutional oversight) and competing political priorities (eg, crime detection, limiting state surveillance) must provide the framework for our thinking. Here we can no longer maintain artificial divides between the ethical and the political, between individual rights and public goods

Why are individual rights, to consent or confidentiality, inadequate to the new large-scale research biobanks, like Iceland's or UK Biobank? I suggest the answer is relatively straightforward. They transcend our usual examples of medical research in three important respects: (1) These projects are prospective and open-ended by their very nature, and necessarily are very broad and indeterminate in their research purposes; (2) Most of the research subjects will not be ill; in many respects, moreover,

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it would be better to begin with children rather than adults; (3) Their sheer scale means that they evade our standard mechanism for ensuring that individuals participate in well-designed research, the research ethics committee. I will comment on the first and second points in turn; the question of how well-conceived the research biobanks arises as an important issue for both.

With regard to the prospective nature of the studies: The biobanks require an *on-going* contribution from the research subject. If not samples, then at least health information and possibly lifestyle data should be entered into the bank over an indefinite period of time – ideally, until death, or, rather, post-mortem. This has, in turn, two important implications. First, complete anonymisation of data is impossible, as this would prevent new data being linked to the old, and to the tissue sample or genetic information. The best we can do is to code data, and entrust linkages to a secure bureau or trustee. (As the forensic databases remind us, genetic information is in principle never securely anonymous.) This means that there are always risks to subjects in terms of breaches of confidentiality, and there are many interested parties such as insurance companies, employers and even state agencies who might use such information against subjects' interests. Of course, these risks are likely to increase over time, to the extent that we become better able to interpret individual genetic variations.

Second, and more important from the point of view of consent: it is necessarily impossible to inform research subjects about the nature of the research that will be conducted with the biobank. As our knowledge increases, we can hope to investigate much more with the information banked, but what that 'much more' will be no one can say. However – and this point is by no means incidental – this is not just a problem of inevitable ignorance on the part of scientists and subjects. (After all, there will always be ignorance about the future outcome of any meaningful research study.) It also relates to an on-going problem of overstatement regarding the projected uses and findings of the biobanks. We are being promised all sorts of knowledge and benefits, yet these promises are often vaguely articulated and, on examination, frankly implausible.

This implausibility begins with the major practical issue for any study of such a scale: how to obtain and process sufficiently detailed and accurate information concerning the lives, health and changes in physical condition of the research subjects. Though some lifestyle and environmental factors, such as smoking, are fairly easy to record, others, such as diet, alcohol intake and physical activity are more complex and problematic (self-reporting is notoriously unreliable), so too psychosocial variables. Similarly, medical information is extremely difficult to gather and codify except in categories that will often be too wide for meaningful comparison. Measurements of simple physical variables such as blood pressure need to be repeated if research subjects are to be compared informatively, while repeated measurements of more complex variables – anything from glucose levels to cholesterol to blood cell counts – will be extremely costly on such a scale. Thus greater understanding of the connections between genetic variations and disease susceptibility is only likely to arrive in the most crude and unhelpful forms. Smokers with these genetics variants and a diet including meat (Which meats? Eaten how often? And with what?) have – on average – an *x*% higher risk of heart disease.

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At least some of these issues can be overcome with sufficient resources. Behind them, however, stands the well-known yet neglected fact that the diseases most often mentioned in connection with the medical biobanks are diseases of Western societies – that is, diseases whose causation can only have a slight basis in genetic variations, and are overwhelmingly related to socio-economic, environmental and lifestyle factors.[21]

These obvious scientific difficulties have not discouraged highly speculative suggestions about the findings and technologies that might result from biobank research. Two in particular recur in the literature. We are promised pharmacogenomics – drugs 'tailored to each individual's genetic constitution' – and population genetic screening – the possibility of screening for susceptibility to various diseases, with the promise that preventative measures can then be tailored to individuals. Both seem unlikely to materialise and unlikely to generate significant benefits if they do. Consider population screening: we may find out that some individuals have a higher risk of some sort of heart disease should they fail to exercise regularly as compared to others. The obvious preventative measure is regular exercise – something which we should all undertake anyhow. More speculative measures include drugs that will have a prophylactic effect – 'pills for the healthy ill,' as they have been ironically christened – with the attendant costs of testing and the risks of any pharmaceutical intervention. None of this looks likely to represent good value for money from a public health perspective.[22]

So far as pharmacogenomics is concerned: there may be some basis for expecting some useful tests for some particular (classes of) drug, but the overall benefits are likely to be relatively slight. So far as the cost-benefit ratio of any test that does emerge is concerned, the issues here are twofold. First, most adverse drug reactions arise from dosage problems, interactions with other drugs or environmental factors, or physiological problems such as impaired liver or kidney function. Second, many problems of intolerance or non-response to drugs will therefore not be predicted by genetic tests, which in any case are likely to yield only probabilistic information, so that the need for careful monitoring of a patient's drug response will not be diminished. Both of these difficulties would apply even if it proved relatively straightforward to identify pertinent genetic variations and turn them into a cheap, reliable test.[23]

Clearly much more might be said with regard to these difficulties, but the broad problems with both sets of promises are easy to see. I mention them here for two reasons. First, as regards the 'informed' part of consent, they suggest that subjects are liable to be misled about the broad terms of the biobanks they join.[24] Second, they point us to issues that go much beyond those individuals – above all, to the question of whether these projects are scientifically well-justified and reasonable value for money, as against the many other ways we might invest in health and health research. It is interesting, moreover, that the biobanks' ambitions are notably congenial to pharmaceutical companies (in terms of markets for genetic tests and prophylactic and remedial drugs), despite the fact that most large-scale medical biobanks are heavily reliant on public funding. It seems that a reductive, individualistic and medicalised approach to health is dominating our thinking about genetic research – despite the fact

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that this research is essentially collective in nature, despite the fact that genetics might just as well remind us how much human beings have in common and how greatly variations between people must be attributed to *non*-genetic factors.

To turn, now, to a second important respect in which large-scale medical biobanking differs from conventional medical research: Most of the participants will not be suffering any particular illness. This is advantageous from the point of view of consent, both so far as adult subjects and parents of child subjects are concerned: not experiencing the strain of illness and not needing to be grateful for present health care, people are more able to attend to the research proposal and less likely to feel pressured into participating. The disadvantage of this, however, is that research subjects are much less likely to take an active interest in the research being done – that is, to feel responsible for ensuring research is done that reflects their interests. Over the past two decades, we have increasingly seen patient groups forming (albeit sometimes with the connivance of pharmaceutical companies), who have lobbied for research into their conditions: I have already mentioned the crucial role of patient activism, and more broadly gay activism, in HIV/AIDS research. We surely cannot expect participants in UK Biobank to take to the streets to ensure that this resource is used for the public interest; at most, there may be a tendency for subjects to withdraw their participation if it becomes clear that a biobank is not being used for ends they can endorse.[25]

In addition to being mostly well, there is a case for thinking children would make more suitable subjects, so long as we want to give due weight to environmental factors. In particular, if we want to know about the explosion of allergies, asthma and food intolerances, or about conditions that promise premature death such as diabetes and obesity, then we need to know an awful lot about the details of childhood development, including development during pregnancy.[26] As with the common causes of mortality mentioned in connection with the adult biobanks, these are obviously *not* disorders with a substantial genetic basis. Furthermore, the findings of such studies are unlikely to point to pharmaceutical interventions. Most probably such interventions will consist in broad public health measures, likely to be lower in risk, cheaper per person and more beneficial to everyone – apart, one is tempted to add, from those with an interest in selling more medical drugs or tests.

It is quite clear that informed consent is barely relevant to justifying child-cohort studies, and it is at least arguable that our preoccupation with consent has undermined them – making child research appear much more problematic than need be. (I have already mentioned how badly funded such projects have tended to be; the disparity in funding between these and UK Biobank is especially notable.) If such projects are to be justified, consent must of course play a role – to start with, parental consent, and later and increasingly, the children's consent. Here consent is operating not so much to protect children's interests, which must be an important duty on the part of those designing and managing the study, but rather to ensure trust and to promote fuller participation. (The sort of detailed information required about subjects cannot, after all, be discovered without the willing involvement of parent as well as child.) But beyond consent, and still more important, is scrutiny of the research undertaken using the data – whether it is well-conceived and likely to yield meaningful knowledge and benefits. The crucial question must be the soundness of the project *in toto* – whether it

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really brings together data of the detail and quality needed to investigate lifestyle-environment-health interactions (with the possibility of investigating genetic factors where this seems likely to be fruitful), whether it is really likely to yield cost-effective measures to improve health.

It is useful, too, to remember the forensic databases, where genetic knowledge is being exploited for non-health purposes. Here, no one talks about consent, which would render the collections barely useful; samples are usually taken on a statutory basis. What has been important in justifying such databases is not individual rights but the public interest in detecting the culprits of violent crimes. Especially the association of DNA samples with sexual offences has made this justification overwhelmingly persuasive to the public. This does not mean that many critical points should not be made about forensic databases.[27] Here we lack not only the limited protections afforded by consent procedures but also the other well-developed checks of medical and research ethics – above all concerning confidentiality, scrutiny of research proposals and institutional oversight. These databases represent a huge growth in potential state power. Costs (as benefits) to individuals can be very severe, and abuses or infringements of individual rights are easy to imagine. Here, again, one may fear that a seductive 'genetic fix' is at work: some worry that genetics is diverting attention from careful forensic work; in any case, such a database is hardly preventative of crime and its overwhelmingly social causes (although we might hope that the databases will develop some deterrent effects).

Nonetheless, there is widespread recognition that we should think about forensic databases in political terms such as the public interest, the extent of state power, and checks and balances such as (presently lacking) institutional oversight mechanisms to regulate access and usage. Much less is said about the forensic banks: this is partly because it is much more difficult to investigate their workings, and partly because they fall less than squarely within the conventional domain of bioethics. But I have also pointed to a less welcome explanation: might this neglect not also reflect the indubitable fact that they raise significant *political* questions – questions which expose the narrowness of 'ethics' as it is commonly understood? So long as we do pay attention to the forensic banks, however, we will have no doubt that large-scale biobanking raises important policy and political issues, issues which cannot be dealt with by focussing on individual rights. Not the least of these – as in the forensic case, as in the justification of studies on children who cannot meaningfully consent – will be whether the banks represent a worthwhile priority, liable to generate knowledge and benefits on a scale commensurate with the investment they demand.

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Conclusion

Most bioethical writing on biobanking recognises some of the limitations of a framework based on individual rights, and there have been repeated calls for other principles to frame the issues. Some candidates that have been offered include solidarity, altruism (the 'gift relationship'), benefit-sharing and 'governance.' These concepts have made some impact on public and policy discourse, but have often been taken up in a frankly instrumental way – 'gift' being a well-documented example, whereby subjects get moral credit and *nothing else* in return for their participation.[28]

The first part of my discussion argued that informed consent is an ideal whose practice has turned out to be more complicated and ambivalent than one would wish. This is no more than one might expect when an ideal is pulled into practice: situated amid competing interests and diverse institutional imperatives, deployed in contexts which were quite unthought of when it was originally coined. We might suspect that other general principles are liable to meet similar fates: a duty to participate in collective research, a notion of altruistic donation, the imperative for just sharing of benefits, and the importance of institutional regulatory mechanisms – these are all ideas with clear validity, but their limits are not difficult to see. Moreover, none of them really highlight the central questions that biobanks pose: How well-conceived is this line of research? What will its benefits be? Why this research and not something else? How are we organising and funding research? Nor do they help us uncover the presuppositions we may be making about the nature of health and ill-health: I have only alluded to a few of the problems involved in conceiving of health in individual, genetic, and medicalised terms. No one can believe that this is anything like the whole story about health, but as an unexamined assumption it is surely a powerful factor in keeping (bio)ethics away from political and economic factors.

Be that as it may, the more immediate motivation for my argument here has been the fear that the new large-scale medical biobanks will prove wrong-headed ventures, which will generate relatively little basic knowledge and few useful applications. Certainly, they seem unlikely to take us much closer to key sources of chronic ill-health, nor to generate population-wide measures that tackle common causes of premature death. We may end up thinking of UK Biobank as the Millennium Dome of British medical research, a glamorous white elephant, expensive but of little use. However much UK Biobank may not infringe individual rights, it has been too large to be caught by less commonly mentioned research safeguards such as scientific peer review. This assessment may be overly pessimistic. But I think my central argument will still stand: that 'ethics' must engage important questions about what is being researched and why, about our priorities for publicly funded research, about how research is organised and funded. Informed consent is much too close up for us, or research subjects, to see this question: its limitations should remind us of the huge power differentials between individual research subject and researching organisations. Likewise, the net of research ethics committees and scientific peer review is also too close to catch such issues, which concern the aggregate picture. Yet the worse reasons for the enduring popularity of informed consent may remind us that there are powerful factors at work in keeping 'ethics' away from these questions.

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[1] Summarised usefully by B. Knoppers and R. Chadwick. Human genetic research: emerging trends in ethics. *Nature Reviews: Genetics* 2005; 6: 75-79.

[2] In making this case, I shall most be concerned with Anglo-American discussions of these questions. Some may wish to argue that other Western countries, having different legal and philosophical backgrounds, tend to frame the issues differently. However, European statements on biobanking also tend to focus very narrowly on individual rights. See: Nationaler Ethikrat [German National Ethics Advisory Board]. 2004. *Biobanken für die Forschung: Stellungnahme* [Statement on research biobanks]. Berlin. Nationaler Ethikrat; Comité Consultatif National d'Éthique [National Consultative Bioethics Committee]. 2003. *Ethical issues raised by collections of biological material and associated information data: "biobanks," "biolibraries"*. Paris; and European Society of Human Genetics. [Recommendations on] Data Storage and DNA Banking for Biomedical Research: Technical, Social and Ethical Issues. *European Journal of Human Genetics* 2003; 11: 8-10.

[3] For similar criticisms see: Ted Schrecker. 2003. Benefit-Sharing in the New Genomic Marketplace: Expanding the Ethical Frame of Reference. In *Populations and Genetics: Legal and Socio-Ethical Perspectives*. Bartha Knoppers, ed. Martinus Nijhoff. Leiden: 405-411; and Chris MacDonald. 2003. Patents and Benefit-Sharing as a Challenge for Corporate Ethics. Also in Knoppers, op cit: 505-523.

[4] Contrast Anne Kerr's argument, using the examples of gene patenting and stem cell research: Governing genetics: reifying choice and progress. *New Genetics and Society* 2003; 22: 111-126.

[5] See also O. O'Neill. Informed consent and public health. *Philosophical Transactions of the Royal Society: Biological Sciences* 2004. 359: 1133-1136.

[6] Another difficulty is whether the choice offered is Hobson's choice, that is, not a real choice for subjects at all: an issue for those with serious conditions who have few options left for treatment. An interesting issue, just coming into sight, is the question of what information should be provided to subjects about the progress and interim findings of their studies.

[7] Different problems arise with regard to the position of criminals and soldiers, who (are judged to) have forfeited certain rights. While there has been widespread recognition that trials should not be conducted on prisoners, the position of soldiers has remained deeply problematic.

[8] This is not to deny that statistical methods will sometimes be able to compensate for incomplete samples or bias in selection, depending on the investigators' purpose, situation and possession of relevant background knowledge.

[9] See: E. Haimes and M. Whong-Barr. 2004. Levels and Styles of Participation in Genetic Databases: A Case Study of the North Cumbria Genetics Project. In *Genetic Databases: Socio-ethical issues in the Collection and Use of DNA*. O. Corrigan and R. Tutton, eds. London. Routledge: 57-77; H. Busby. 2004. Blood donation for genetic research: what can we learn from donors' narratives? In Corrigan and Tutton, op. cit: 39-56.

[10] N. Rose. 1999. *Powers of Freedom: Reframing Political Thought*. Cambridge. Cambridge University Press: 87; quoted in A. Petersen and R. Bunton. 2002. *The New Genetics and the Public's Health*. London. Routledge: 183.

[11] Cf A. Petersen and R. Bunton, op cit: 193f, who highlight the prominence of 'freedom of choice' and 'informed consent' in many support groups' aims and discourse.

[12] This is to leave aside the argument that there is nonetheless a certain loading of the issues in making 'information' available via such counselling, leading some disability rights writers to refer to present practice as 'weak eugenics': thus T. Shakespeare. Eugenics, Genetics and Disability Equality. *Disability and Society* 1998; 5: 665-681, 669.

[13] G. Annas. Reforming informed consent for genetic research. *JAMA* 2001; 286: 2326-2328; G. Porter. 2004. The wolf in sheep's clothing: informed consent forms as commercial contracts. In G. Árnason, S. Nordal & V. Árnason, eds. *Blood and data: ethical, legal and social aspects of human genetic databases*. Reykjavik. University of Iceland Press: 85-93.

[14] B. Hofman. 2004. Do biobanks promote paternalism? On the loss of autonomy in the quest for individual independence. In Árnason et al, eds, op cit: 237-242, 241.

[15] On technocracy, see S. Weldon. 'Public Consent' or 'Scientific Citizenship'? What Counts as Public Participation in Population Based DNA Collections? In Corrigan and Tutton, op cit (n. 9): 172. Particularly notable in our context is the regulatory framework for UK Biobank, where the Ethics and Governance Council and Science Committee form two quite separate entities, with different forms of 'expertise' being deemed appropriate to each.

[16] NDNAD's Fact Sheet of March 2005 claims 'NDNAD now holds around 2.9 million DNA profiles from individuals and 237,500 profiles from crime scenes' (at www.forensic.gov.uk).

[17] As an aside, it may be worth noting that this opt-out provision would undermine the statutory health care research that the health sector database would also have been used for. An opt-out rate of around 10% was expected, one that would probably be much greater in specific sub-groups such as the mentally ill. Thus research on the functioning of the health service as a whole would be compromised by introducing this malnourished cousin of informed consent.

[18] See www.ukbiobank.ac.uk. For a more detailed critique of the project, see A. Petersen. Securing our genetic health: engendering trust in UK Biobank. *Sociology of Health & Illness* 2005; 27: 271- 292.

[19] For an early alarm call on the US situation, see Pamela Sankar. The Proliferation and Risks of Government DNA Databases. *American Journal of Public Health* 1997; 87, 336-337.

[20] There are many discussions of the limitations of, and possible modifications that might be made to, informed consent procedures here. See *inter alia*: G. Annas. Reforming informed consent for genetic research. *JAMA* 2001. 286: 2326-2328; T. Caulfield, E.G.U. Ross and A. Daar. DNA databanks and consent: a suggested policy option involving an authorisation model. *BMC Medical Ethics* 2003. 4; D. Schroeder and G. Williams. Human genetic banking: altruism, benefit and consent. *New Genetics and Society* 2004. 23: 89-103

[21] It might still be argued that knowledge of the (many) relevant genes might improve our understanding of the pathways of such diseases. Yet the sheer statistical difficulty of tracking multiple gene associations should caution us against this claim.

[22] See P. Vineis, P. Schulte and A. McMichael. Misconceptions about the use of genetic tests in populations. *Lancet* 2001; 357: 709-12; GeneWatch. 2002. *Genetics and predictive medicine: selling pills, ignoring causes*. Briefing paper 18; GeneWatch. 2004. *Bar-coding babies: good for health?* Briefing paper 27. Both at www.genewatch.org.

[23] For overview and references, see GeneWatch. 2003. *Pharmacogenomics: Better, safer medicines?* Briefing paper 23, as well as their 2001 paper: *Human bio-collections: who benefits from gene banking?*. Briefing paper 14. Both at www.genewatch.org.

[24] UK Biobank's website promises that the project will 'improve our understanding of the biology of disease and develop improved diagnostic tools, prevention strategies and tailor made treatments for disorders that appear in later life' (www.ukbiobank.ac.uk).

[25] There may be some basis for optimism here. Some have suggested that the prospective and collective nature of biobanks might allow us to think of them, not like conventional research projects where control must reside with the researcher, but rather on the model of 'subscription clubs,' where subjects retain an on-going stake in the project. It is difficult to see how this might work in practice (and there is little sign that UK Biobank is thinking in these terms) but we can certainly conceive of mechanisms that would permit subjects to be not just informed about, but involved or represented in, establishing the uses made of the biobank.

[26] Likewise, if we want to understand the glaring relation between health and socio-economic class – patently far more important to variations in health than genetic make-up – then we need to be tracking health and physical development against environment, nutrition, familial background, and so on.

[27] See: GeneWatch. 2005. *The Police National DNA Database: human rights and privacy*. Briefing paper 31. At www.genewatch.org; R. Williams, P. Johnson and P. Martin. 2004. *Genetic Information and Crime Investigation*. At www.dur.ac.uk/p.j.johnson.

[28] R. Tutton. 2004. Person, property and gift: exploring languages of tissue donation to biomedical research. In Corrigan and Tutton, op cit (n. 9): 19-38.

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2005, Vol.1, No.2, pp.67–79.

Cost-effectiveness of predictive genetic tests for familial breast and ovarian cancer

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Abstract

Aim: To examine the relative cost-effectiveness of predictive genetic tests for familial breast and ovarian cancer provided by Genetic Services of Western Australia.

Methods: The relative cost-effectiveness was assessed using a decision analytic model.

Results: The cost and outcomes of genetic testing was compared in first-degree relatives of known BRCA1/2 mutation-carriers who have a 50% risk of carrying the mutated gene (intervention group) to individuals with the same a priori risk but who do not undergo a genetic test (control subjects).

Since genetic testing enables the restriction of intensive surveillance to individuals with an identified BRCA1/2 gene mutation, net savings in the period observed (age 25-70) were $980-$1008 per woman in the ovarian intervention group and $1681-$1795 per woman in the breast intervention group, and delayed the onset of breast cancer (6mths BRCA1, 3mths BRCA2).

Compared to control subjects undergoing population surveillance, it was estimated the onset of breast cancer could be delayed at a total net cost of $3055 (5.1yrs) to $3389 (3.2yrs) for women in the breast intervention group with BRCA1/2 mutations. Since population surveillance is not currently recommended for ovarian cancer, control subjects undergoing no surveillance were compared with the intervention group. The onset of ovarian cancer was delayed at a net cost of $1630 (3.5yrs) to $2509 (1.2years) for women with BRCA1/2 mutations.

Conclusions: Testing allows targeted high-level surveillance for gene mutation carriers, which ensures the cost-effective use of resources and reduces cancer-related morbidity if clinical recommendations for intervention are adopted.

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Introduction

Inherited predisposition to cancer is thought to account for 5-10% of all cancer incidence[1]. Advances in genetic testing technology have many promising applications in health including improved diagnosis of disease and the earlier detection of genetic predisposition to adult-onset conditions, such as familial cancer. This will have important implications for resource allocation given the capacity to compare costs with associated benefits. Economic evaluation helps determine the relative value of new technology and enables better planning for the provision of future cancer genetic services.

In order to understand the relative cost-effectiveness of genetic testing the prevalence and penetrance of the gene mutation must be considered as well as the uptake and efficacy of available interventions to prevent or detect cancer early[2]. Reported benefits resulting from increased surveillance in women with a mutated BRCA gene have included earlier detection of breast cancer and an expected mortality reduction in women less than 50 years of age[3,4]. There is also evidence that prophylactic intervention, such as bilateral mastectomy, has been associated with a reduction in the incidence of breast cancer of at least 90%[5]. Though there is evidence to suggest oophrectomy reduces risk of breast cancer, it is not within the scope of this study.

The absence of reliable surveillance methods for the early detection of ovarian cancer, and the poor prognosis following symptomatic presentation, have prompted many oncologists to recommend bilateral prophylactic salpingo-oophorectomy after childbearing[6,7]. Furthermore, studies have validated the prophylactic role of surgical intervention and provided a convincing rationale for genetic testing in women with a strong family history[8,9].

This study aimed to evaluate the relative costs and outcomes of genetic testing for familial breast and ovarian cancer through Genetic Services of Western Australia (GSWA). The investigation included familial breast and ovarian cancers suitable for predictive DNA based testing on the basis of inherited BRCA 1/2 mutations. The theoretical cohorts simulated asymptomatic first-degree relatives of individuals with a known BRCA1/2 mutation, who had a 50% chance of inheriting the cancer-predisposing gene mutation.

Since reliable age and gene-specific cancer mortality data were not available at the time of modelling for relevant population subgroups, the impact of genetic testing and increased surveillance on mortality was not explored in this study. Instead the study focus was confined to the impact of genetic testing and increased surveillance on reduced cancer morbidity and, accordingly ‘cancer-free years’ was the most appropriate method to measure and report reduced cancer morbidity.

Methods

Models

Economic decision modelling software (TreeAge Data™ version 4.0) was used to develop a decision-analysis model, which mimicked the course of testing and treatment for women entering the Familial Cancer Program at GSWA. The attendance of women at high-risk of inherited breast or ovarian cancer in the program was

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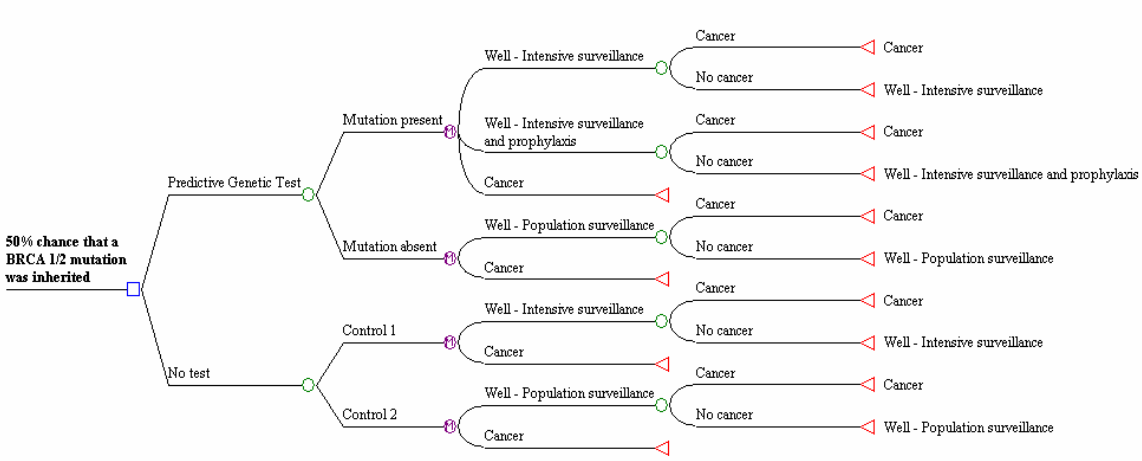
adequate to warrant this study. Previous studies from which much of the data is derived also indicated women in this risk group merited further study.

Internet based searches were conducted using PubMed, Medline and Ovid on the cost-effectiveness of genetic testing, cancer surveillance and surgical intervention to reduce cancer morbidity.

Markov models were used to predict the age of breast and ovarian cancer onset and costs of surveillance for carriers of a mutated BRCA1/2 cancer gene compared with non-mutation carriers and control subjects.

Each Markov cycle represented one year. The age and penetrance (or likelihood a person will develop cancer) relating to each cycle governed what proportion of women stayed in the 'well' state or shifted into the 'cancer' state. See Figure 1.

Figure 1: Predictive genetic testing decision model for persons at high risk of familial breast cancer



Surveillance strategies modelled in this study (See Table 2) were based on the National Health and Medical Research Council (NHMRC) clinical practice guidelines for the detection and treatment of familial cancer[10,11] and corroborated by Western Australian (WA) surgeons and oncologists working in the area. Accordingly, the models cover the period from age 25 to 70.

All women in the intervention group had predictive genetic testing to determine their mutation status. Inherited cancer segregates as an autosomal dominant trait, thus the offspring of a BRCA1/2 gene mutation carrier have a 1 in 2 chance of inheriting their cancer-predisposing mutation. Hence, half the women in the intervention group were deemed to be mutation positive and underwent intensive surveillance and prophylaxis as recommended. The other half were identified as mutation negative and only had population surveillance.

Control Groups

Despite their high-risk family history, since control subjects did not undergo predictive genetic testing, their mutation status was unknown.

Women may or may not have increased their surveillance based on family history alone (perceived breast or ovarian cancer risk) so dichotomous scenarios were reviewed corresponding to surveillance extremes. For example, the intervention group (known mutation status) was compared with control subjects (unknown mutation status) having either intensive surveillance and prophylaxis, or population surveillance.

As a baseline for comparison we examined two scenarios corresponding to each extreme. The intervention group was first compared to control subjects (unknown mutation status) who adhered to clinical recommendations for increased surveillance based on their family history alone (control group 1). The intervention group was then compared with control subjects who have population or no surveillance, despite their high-risk family history (control group 2). The actual surveillance behaviour of control subjects was expected to be a mid-point between population surveillance or intensive surveillance and prophylaxis.

Costs

All costs are provided in Australian dollars and standardised to 2001-2002 prices using health index deflators[12]. Future costs were discounted at a rate of 5% per annum. Counselling, genetic testing, surveillance, surgery and treatment costs were based on patterns of care in WA and are consistent with NHMRC clinical practice guidelines for familial cancer[13]. Lifetime cancer treatment costs were taken from the Australian Institute of Health and Welfare[14]. Mean ages for surgery and cancer diagnosis were used to estimate years of discounting[15,16,17,18].

Counselling costs were estimated in accord with GSWA and based on the average session time of Familial Cancer Program patients. Hourly costs were assigned based on staff and office requirements. Since diagnostic tests are required to confirm an index case before cascade testing is possible, a diagnostic cost component was also included.

Genetic testing costs were provided by the Molecular Genetic Laboratory, Princess Margaret Hospital. Cancer prevention and prophylaxis costs were provided by costing centres in Perth's major teaching hospitals based on a breakdown (pathology, medical, nursing, allied health and other) of surgical procedures in 2001-2002 and averaged to provide an estimate. Though capital expenditure was not assessed, a review of total WA health expenditure in 1999-2000 indicates this component would be less than 5%[19].

Indirect costs were not included.

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Outcome data

Outcomes on the effectiveness of cancer screening and interventions on cancer incidence in these high risk individuals were derived from the published literature. Age-related 'population risk' of breast cancer represented national rates in 2000[20]. To enable comparisons between the simulated cohorts breast and ovarian cancer were examined separately and the risks of developing the two cancers were assumed to be independent.

Cumulative age-related cancer incidence in mutation carriers, with and without the recommended clinical intervention, were gathered from previous studies and factored for attrition, and hence took account of all-cause mortality. The age-specific 'inherited risk' of breast cancer in BRCA1/2 mutation-carriers was based on 65% or 45% penetrance respectively by age 70 consistent with studies by Antoniou et al[21]. The age-specific 'inherited risk' of ovarian cancer in mutation-carriers was based on 39% or 11% penetrance for BRCA1/2 respectively by age 70, as previously reported[22].

The simulated population represented offspring of known mutation-carriers (at 50% risk of inheriting the gene mutation) and assumed full compliance with NHMRC clinical recommendations for intervention[23].

Interventions modelled on behalf of population or intensive surveillance and prophylaxis are listed in Table 1. For each intervention the optimal age, required frequency of an event and the non-discounted cost is reported.

Based on trends in WA, it was assumed that around 30%[24] of the breast intervention group would elect prophylactic bilateral mastectomy at a mean age of 38 years, with a lifetime reduction in breast cancer risk of 90%[25,26] since many women elect surveillance but no surgery, this option was examined within the model. Mammographic screening of women between 50-69 years has been shown to reduce their lifetime risk of breast cancer by 35%[27]. Previous studies indicated that the younger age of cancer diagnosis in women with BRCA mutations justified screening from an earlier age[28,29,30,31,32]. On this basis it was presumed that mutation carriers aged 35 to 49 would also reduce their lifetime risk of breast cancer by 35% though mammographic screening and clinical breast examination.

The available screening measures for ovarian cancer, such as transvaginal ultrasound and serum CA-125, have limited sensitivity and specificity and may not reduce ovarian cancer mortality[33]. For this reason it was assumed that all women in the intervention group would undergo the recommended prophylactic salpingo-oophorectomy at age 40 and achieve a lifetime reduction in ovarian cancer risk of 96% as previously reported[34,35]. Sensitivity analysis was used to test the effects of varying these outcomes.

Complications from medical intervention, intangible costs and benefits were not incorporated.

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Results

Costs associated with genetic testing, surveillance, prophylaxis and cancer treatment are listed in Table 1. Estimated total surveillance costs are listed in Table 2.

Table 1: Intervention costs at 2001-2002 prices

Intervention	Age of intervention (yrs)	Frequency of event	Cost per event (undiscounted)
Genetic counselling + test, carrier		once only	$1,012
Ovarian Cancer Intensive Surveillance & Prophylaxis			
Transvaginal ultrasound	35*-40	12mths	$129
CA125	35-40	12mths	$24
Prophylactic salpingo-oophorectomy	40	once only	$7,216
Breast Cancer Intensive Surveillance & Prophylaxis			
Clinical breast examination	25-37	4mths	$65
Mammogram	35*-37	12mths	$163
Prophylactic bilateral mastectomy	38	once only	$11,547
CT chest scan post surgery	39	once only	$175
Clinical ex. of chest wall and lymph nodes	39-70	6mths	$65
Breast Cancer Intensive Surveillance only			
Clinical breast examination	25-70	4mths	$65
Mammogram	35*-70	12mths	$163
Population Surveillance (breast cancer only)			
Mammogram	50-69	24mths	$163
Ovarian cancer treatment (life)		once only	$19,735
Breast cancer treatment (life)		once only	$11,616

**Or 5yrs before youngest affected family member*

Table 2: Total surveillance costs

Intervention	*No Discount*	*5% Discount*
Breast Cancer		
Intensive surveillance and prophylaxis	$18,906	$9,785
Intensive surveillance only	$14,838	$6,493
Population surveillance	$1,630	$315
Ovarian Cancer		
Intensive surveillance and prophylaxis	$7,981	$3,381
Population surveillance	n/a	n/a

Results of the cost-effectiveness analysis of genetic testing for familial breast cancer are shown in Figure 2. The intervention group was compared to control subjects for the period modelled (age 25-70). Costs incurred in the future have been discounted.

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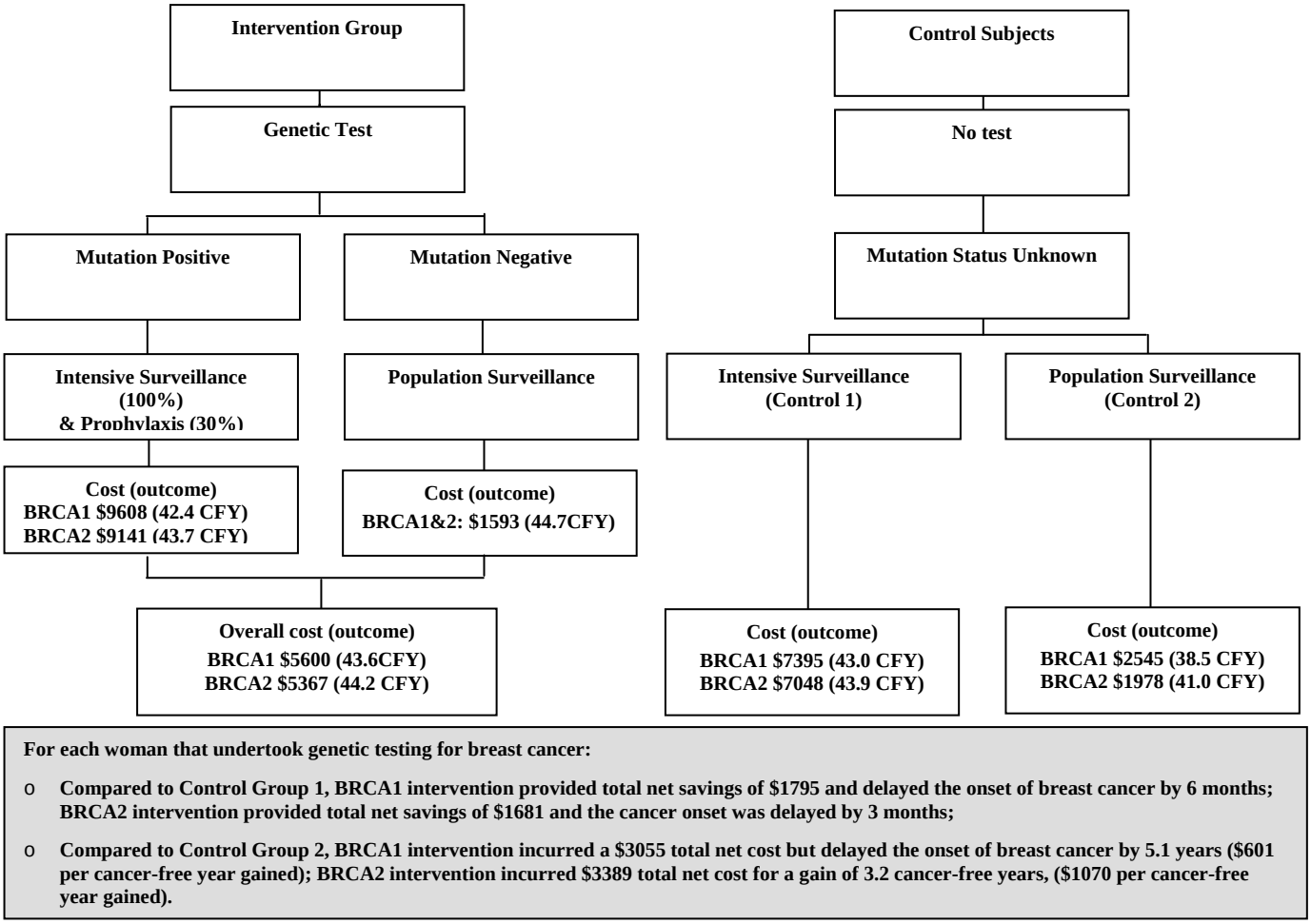
Intervention effectiveness was measured by the number of years that the onset of cancer is delayed.

Figure 2: Cost-effectiveness of genetic testing for familial breast cancer (BRCA1-BRCA2)



Compared to control subjects undergoing high-level surveillance since their mutation status is unknown, targeted BRCA1 intervention provided total net savings of $1795 per woman and delayed the onset of breast cancer by 6 months. Likewise, BRCA2 intervention provided total net savings of $1681 and delayed cancer by 3 months.

Compared to control subjects having population surveillance, BRCA1 intervention incurred a total net cost of $3055 per woman but improved her outcome by 5.1 cancer-free years which is $601 per cancer-free year gained. Similarly, BRCA2 intervention delayed the onset of breast cancer by 3.2 years, at a total net cost of $3389 or, $1070 for each cancer-free year gained.

The cost-effectiveness analysis of genetic testing for familial ovarian cancer is shown in Figure 3.

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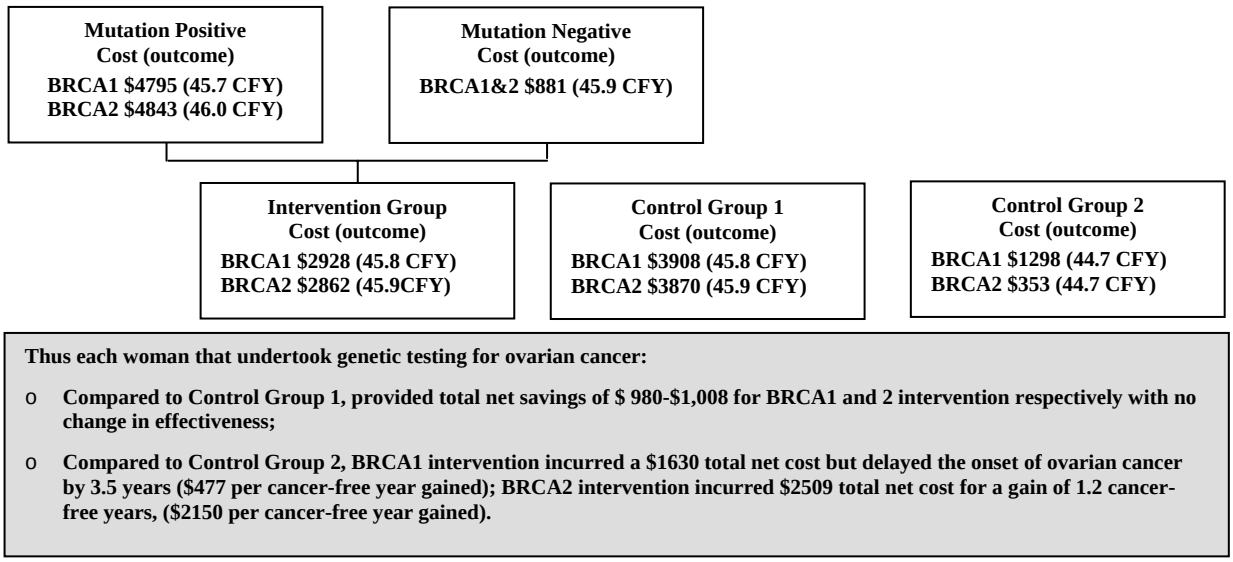
Figure 3. Cost-effectiveness of genetic testing for familial ovarian cancer



Thus each woman that undertook genetic testing for ovarian cancer:

- **Compared to Control Group 1, provided total net savings of $ 980-$1,008 for BRCA1 and 2 intervention respectively with no change in effectiveness;**
- **Compared to Control Group 2, BRCA1 intervention incurred a $1630 total net cost but delayed the onset of ovarian cancer by 3.5 years ($477 per cancer-free year gained); BRCA2 intervention incurred $2509 total net cost for a gain of 1.2 cancer-free years, ($2150 per cancer-free year gained).**

Compared to control subjects undergoing no surveillance, BRCA1 intervention incurred a $1630 total net cost but delayed the onset of ovarian cancer by 3.5 years ($477 per cancer-free year gained); BRCA2 intervention incurred $2509 total net cost for a gain of 1.2 cancer-free years, ($2150 per cancer-free year gained).

Sensitivity Analysis

One-way sensitivity analysis was utilised to check the stability of the outcome given uncertainty in some variables, specifically the penetrance of BRCA mutations. Since this varied widely in the published literature[36] cumulative cancer incidence by age 70 was explored using reported confidence intervals[37]. The results shown in Table 3 indicated that a higher level of penetrance would provide the intervention group with increased effectiveness (cancer-free years gained) for a lower net cost or greater net savings compared to no genetic testing.

Table 3: Impact of adjusted mutation penetrance on cost-effectiveness

Cancer type		Penetrance	Cumulative incidence	Net Saving[1]	Net Cost[2]
Breast:	BRCA1	Low	44%	$1687 (3mths)	$3581 (3.2yrs)
		High	78%	$1900 (7mths)	$2656 (6.6yrs)
	BRCA2	Low	31%	$1642 (2mths)	$3865 (2.3yrs)
		High	56%	$1719 (4mths)	$3403 (3.9yrs)
Ovarian:	BRCA1	Low	18%	$1011 (0mths)	$2289 (1.8yrs)
		High	54%	$1002 (1mth)	$1056 (5.0yrs)
	BRCA2	Low	2.4%	$993 (1mth)	$2765 (6mths)
		High	19%	$1011 (0mths)	$2265 (1.8yrs)

[1] Compared to control subjects having intensive surveillance
[2] Compared to control subjects having population or no surveillance

The estimated number of women that elect prophylactic bilateral mastectomy to prevent breast cancer in Western Australia (30%) is low compared to the uptake in The Netherlands (51%)[38]. The impact on cost-effectiveness of higher uptake was examined in the breast models (see Table 4). A greater uptake of prophylactic mastectomy in high-risk women compared to surveillance alone was found to increase the cost-effectiveness of genetic testing.

Table 4: Impact of prophylactic bilateral mastectomy uptake on cost-effectiveness

	Prophylactic uptake	Net Saving[1]	Net Cost[2]
BRCA1	0%	$2125 (1mth)	$2725 (4.6yrs)
	30%	$1795 (6mths)	$3055 (5.1yrs)
	50%	$1574 (9mths)	$3276 (5.4yrs)
BRCA2	0%	$2081 (0mths)	$3179 (2.9yrs)
	30%	$1691 (3mths)	$3569 (3.2yrs)
	50%	$1432 (5mths)	$3828 (3.4yrs)

The impact of various discount rates (0, 3%, 5% and 7%) on the net cost or saving in the breast (BRCA1) intervention group was examined in Table 5.

Table 5: Discount rate effect on net cost or savings in the breast-BRCA1 intervention group

Discount rate	Net Saving[1]	Net Cost[2]
No discount	$5028	$5012
Discount 3%	$2687	$3550
Discount 5%	$1795	$3055
Discount 7%	$1232	$2724

The application of a 3% discount rate instead of the 5% rate utilised would increase per person net savings by $892 or, increase the per person net cost by $495 for the period observed, depending on the surveillance undertaken by control subjects. Findings were similar for the ovarian intervention group when the discount rate was adjusted (not shown).

Discussion

Early detection and intervention strategies resulting from predictive genetic testing for BRCA1/2 mutations in Western Australia has been demonstrated to be a cost-effective use of resources under a range of scenarios.

Genetic testing enables the restriction of intensive surveillance to individuals with an identified BRCA1/2 gene mutation, leading to large net savings for the period observed (age 25-70). Compared with control subjects undergoing intensive surveillance and prophylaxis, the ovarian intervention group provided total net savings of $980-$1008 per woman. The breast intervention group provided total net

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savings of $1681-$1795 per woman and delayed the onset of breast cancer (6mths BRCA1, 3mths BRCA2).

Compared to control subjects undergoing only population surveillance, it was predicted the onset of cancer could be delayed in the genetic testing intervention group. For example, breast cancer could be delayed at a total net cost of $3055 (5.1yrs) to $3389 (3.2yrs) for women with identified BRCA1/2 mutations. This is a cost of $601 or $1070 per cancer-free year gained. Since population surveillance is not currently recommended for ovarian cancer, control subjects undergoing no surveillance were compared with women in the intervention group who were expected to delay the onset of ovarian cancer at a net cost of $1630 (3.5yrs) to $2509 (1.2years) for women with BRCA1/2 mutations. This is a cost of $477 or $2150 per cancer-free year gained.

These findings are consistent with a study by Tengs and Berry[39] which found BRCA testing of high-risk women to be cost-effective, with estimated savings of $3400-$4700 per quality-adjusted life-year gained in a 30-year-old woman. Grann et al[40] also found genetic screening women to be cost-effective in Ashkenazi Jewish, but only if known mutation-carriers underwent the recommended prophylaxis. In the current study, genetic testing for BRCA mutations was found to be cost-effective even if women elected increased surveillance but declined surgery.

In addition to the reduction of cancer morbidity, benefits of predictive genetic testing include reduced anxiety from an unknown genetic background and the ability to make proactive decisions regarding medical and lifestyle options to prevent or minimise the risk of breast or ovarian cancer. The confirmation of risk status may also have important implications for family planning.

Although intangible costs and benefits were not explored in this study, aspects such as the psychological impact of extreme surgery, particularly bilateral mastectomy, on body image and sexuality warrants concern. However, a study by Hatcher et al found bilateral prophylactic mastectomy in women with high familial risk reduced psychological morbidity and anxiety and did not have a detrimental impact on women's body image or sexual functioning. They noted that women who chose such surgery had undergone more investigative tests than women who declined and had a higher, often inaccurate, perception of their risk of developing breast cancer[41]. Given the complexity of genetic risk communication this finding was not unexpected since confirmation as a BRCA mutation-carrier provides no certainty when, or if, cancer will occur in an individual, nor can a negative BRCA mutation result guarantee an individual will not develop cancer.

For clarity and comparison purposes the models were cancer and mutation specific. This represented a limitation of the study since some women may develop both breast and ovarian cancer and rarely carry both BRCA1 and BRCA2 mutations. We also assumed high-level patient compliance with clinical recommendations for intervention since the cost-effectiveness of genetic testing depends on compliance.

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The value of regular surveillance in women with a genetic or familial predisposition to breast cancer is uncertain[42] although many studies have indicated a potential benefit for young women with a family history of cancer[43,44,45,46]. Other research suggested screening may be less effective since women with these mutations were more likely to develop cancer before menopause when breast tissue was dense, making it difficult to detect tumours on a mammogram[47]. Additionally the rate of growth of breast cancer is often faster in younger women, which can also decrease the effectiveness of screening at regular intervals[48].

Findings by Kreige et al[49] indicated magnetic resonance imaging was more sensitive than mammography for detecting beast cancers in women at increased risk because of inherited susceptibility. It is hoped that future research will provide clarity on the efficacy of intensive breast or ovarian cancer surveillance in known mutation-carriers.

The success of a genetic screening program however is dependent largely upon the compliance of clients with clinical recommendations for surveillance and the disclosure of mutation status by the proband to genetic relatives. In addition, the uptake of prophylactic surgery varies greatly between nations. In the Netherlands 51% of asymptomatic mutation carriers opted for bilateral mastectomy and 64% for oophorectomy[50] while the proportion of mutation-carriers that elect prophylaxis in Western Australia is around 30%[51].

According to Grann et al[52] screening for BRCA mutations in the Ashkenazi Jewish population is only cost-effective if all women who tested positive underwent prophylactic surgery. However, this approach is complicated by prophylactic mastectomy not being totally protective, since breast cancer has been documented in women following prophylactic surgery[53,54] and evidence that genetic information may even reduce motivation to change health behaviour[55]. Scheuer[56] found that genetic counselling and testing increased compliance with surveillance and led to risk-reducing operations and diagnosis of early-stage tumours in patients with BRCA1/2 mutations.

Investigation into the uptake of prophylactic surgery in Australia, the impact of cultural differences and support in the medical sector for such interventions may provide insight into levels of patient compliance with clinical recommendations and help shape future intervention protocols.

Early detection and intervention through predictive genetic testing for BRCA mutations in Western Australia has been demonstrated to be a relatively cost-effective use of resources under a range of scenarios, though further studies are needed to verify the results of long-term gains and, or costs from genetic testing. Additional research into compliance with clinical recommendations for surveillance, the disclosure of risk information to relatives and the degree of community support for such programs is required, since the cost-effectiveness of genetic testing will depend on the value of this information to patients and society.

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What Should Scientists Do Outside the Laboratory? Lessons on Science Communication from the Japanese Genome Research Project

MACHIKO ITOH & KAZUTO KATO

Abstract

It is essential for scientists to introduce their research in a comprehensible manner and to communicate with colleagues in the same/different fields and with the public. As genome research requires the massive expenditure of public funds, and raises ethical, legal, and social issues, genome scientists have communicated extensively with the public. In addition, they have established interdisciplinary collaborations that resulted in the creation of a new research field known as bioinformatics.

We examined the history of communication activities involving Japanese genome scientists between 1989 and 2005 using extensive literature surveys and interviews. We found that genome researchers went through much trial and error, particularly with respect to collaborative interdisciplinary efforts, and although they early on recognized the necessity of communicating with colleagues in different fields, it was not until the introduction of a large governmental research budget, the Millennium Project (2000 – 2004), that individual researchers began to be actively engaged in communication activities. In conclusion, to facilitate the participation of scientists in communication activities, researchers who are acquainted with different research fields, community, and society should proactively function as coordinators of interdisciplinary programs or mediators of collaborative research. It is also of primal importance to present to scientists the advantage of dialogue with society scientifically and to design effective communication programs that provide researchers with such opportunities.

1. Introduction

In the past, scientists could follow their intellectual curiosity much as artists followed their muse. Pure scientific research had relatively little impact on society and its cost was much less than it is today. This condition has changed drastically. In the life sciences, for example, the sequencing of the human genome has led to new insights[1], and the expenditures required for research continue to increase. As it is now possible to buy genetically modified foods and to clone one's pet[2], an average citizen is alert to the possible effects of science on everyday life and monitors the use of research funds more keenly than in the past. Consequently, scientists must disclose their activities and are no longer able to devote their entire effort exclusively to a narrow field of research.

Modern scientific research raises ethical, legal, and social issues (ELSI). Although ELSI has been addressed primarily by sociologists, ethicists, and legal experts, as research budgets mount and the results of research exert a direct impact on society, it has become incumbent on scientists to be mindful of ELSI. This concept is acknowledged in the ‘Declaration on Science and the Use of Scientific Knowledge’

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adopted by the 1999 UNESCO-sponsored World Conference on Science.[3] The declaration confirms that 1) scientific knowledge should be shared, 2) cooperation is needed among governments, civil society, business sectors, and scientists, and 3) scientists must adhere to ethical standards. In the United Kingdom, scientists and government lost public trust over their handling of the outbreak of Bovine Spongiform Encephalopathy (BSE). To restore public faith, the House of Lords Science and Technology Committee recommended a direct dialogue with the public. Their 3rd report influenced the policies promulgated by organizations such as the British Association for the Advancement of Science, and the Royal Institution.[4,5] An editorial in the journal Nature suggested that the public should be consulted on how government research funds are to be spent.[6]

Thus, scientists are expected to present their research endeavours in a manner comprehensible to the public,[7] to understand the social implications of their research and its results, and to advance the dialogue with society.[8] This goal is not easy to achieve. Most researchers do not expect non-researchers to interfere in their research, and do not know effective ways of communicating their research to the public. In fact, this gap itself is an issue to be resolved through dialogue with society. However, is the communication with the public a burden for researchers? For scientists to succeed in their endeavours, they must acquire interdisciplinary knowledge and the ability to publicize their results in a fashion accessible to a wide range of audiences. To develop effective research strategies, they must recognize the relative position of their area of research in a global scientific context as well as the context of societal goals and apprehensions.

Although modern science is highly specialized, seminal work, irrespective of the research area, is related with other fields of science.[9] It is difficult to keep abreast of detailed developments in multiple fields, but scientists must possess a broad perspective and must understand trends not only in their field but also in a global context of society as a whole to be able to pose fundamental questions and to publish in highly respected journals. The internet provides wide and easy access to research and academic papers (Google scholar: http://scholar.google.com/) and the ISI journal impact factor has been proposed as a quantitative measure of scientific research and its global impact (http://www.isiwebofknowledge.com/). Moreover, the increasingly competitive funding environment makes it necessary for individual scientists to present their research goals clearly. To obtain funding, they must take into account underlying fundamental, and often social, problems and must be able to streamline their research plan and to present their goals and results skillfully.

Here we present the history of the Japanese Genome Research Project (1989 - 2005). We focus on its communication activities including its trial-and-error experience and self-evaluation. Genome scientists have been engaged in wide communications with different research fields and the public, partly because genome science has flourished by cooperating with different research fields, and partly because progress in genome science involves ELSI. This report is a summary of our extensive literature surveys and of interviews with five leading Japanese genome scientists and one ethicist (Figure 1).

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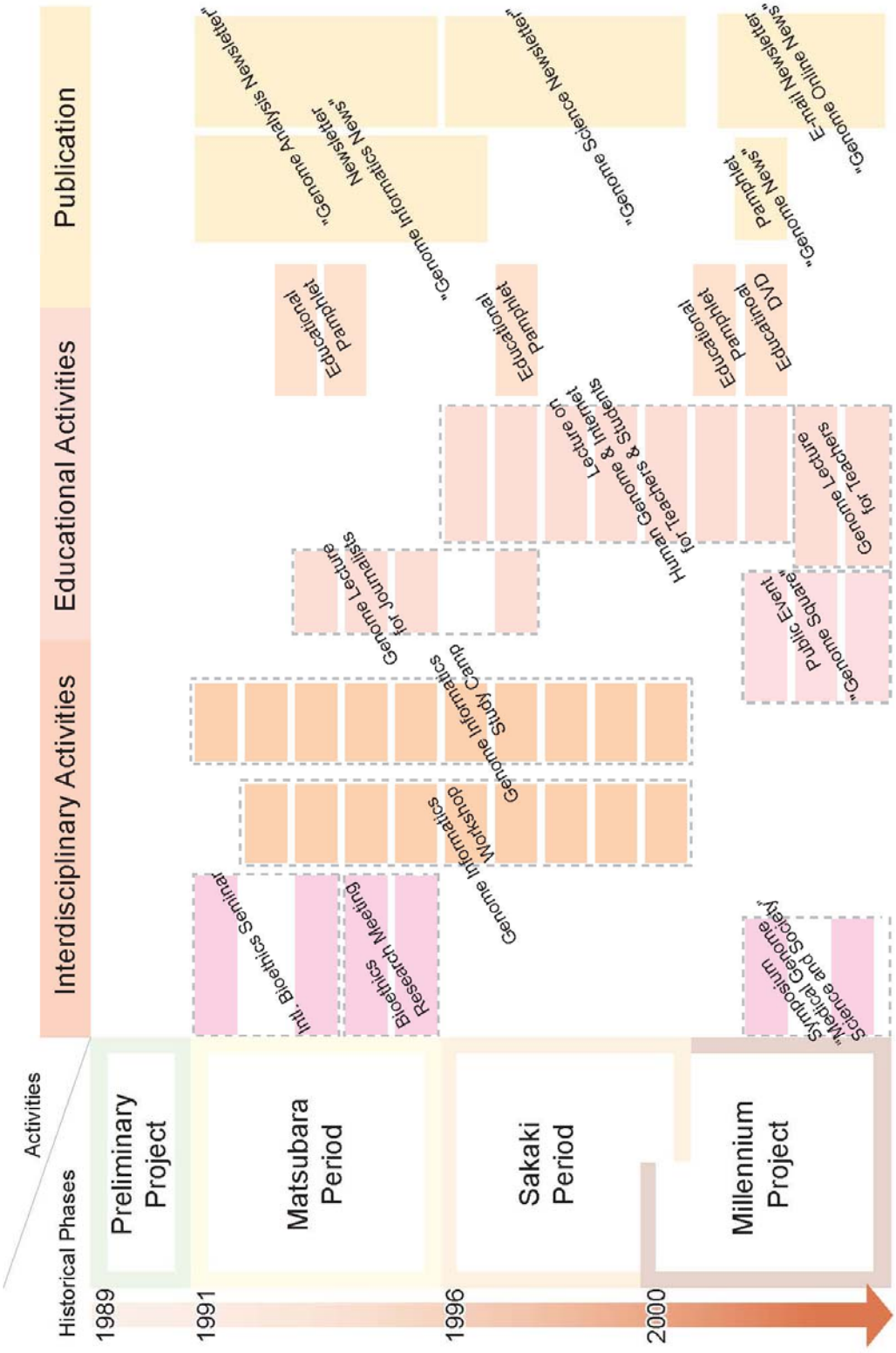
Figure 1



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2. Brief outline of Japanese genome research projects

Most genome research in Japan has been funded by three ministries, the Ministry of Education, Culture, Sports, Science and Technology (MEXT), the Ministry of Health, Labor and Welfare (MHLW), and the Ministry of Agriculture, Forestry and Fisheries. The latter two primarily support medical and agricultural genomics, respectively, whereas MEXT funds multiple groups to establish interdisciplinary genome sciences.

The Science and Technology Agency (STA), which was merged into MEXT in 2001, took a leading role in the International Consortium for Human Genome Sequencing. It allocated ca. 1 billion yen (or 10 million dollars) per year to the sequencing project from 1995 to 2000 and in 1998 established the Riken Genomic Sciences Center (Riken GSC) in Yokohama as the primary institution for large-scale DNA sequencing and protein structure determination.

Research grants from MEXT are unique in that they encourage academic researchers from different fields to come together to establish interdisciplinary genome sciences. The funded groups include almost all eminent Japanese genome researchers who together as a group led Japanese genome sciences. Currently, approximately 200 laboratories participate in the genome research projects supported by Grants-in-Aid for Scientific Research on Priority Areas from MEXT. Their projects cover medical research, genomics, comparative genomics, and bioinformatics of model organisms. We refer to the genome research projects supported by MEXT as the 'Genome Project' (GP).

Table 1 shows a brief history of the GP. Although there were several independent sub-projects conducted in parallel, the effort can be regarded as that of a single community. The GP involved four consecutive periods: the Preliminary Project, the Matsubara Period, the Sakaki Period, and the Millennium Project.

Table 1: Brief History of the GP

	Fiscal Year	Director	Number of Principal Investigators	Total Amount of Research Budget (million yen)
The Preliminary Project	1989-1990	Kenichi Matsubara	-	570
The Matsubara Period	1991-1995	Kenichi Matsubara Minoru Kanehisa	100	2,490 N/A
The Sakaki Period	1996-2000	Yoshiyuki Sakaki	90	3,000
The Millennium Project	2000-2004	Yuji Kohara	430	20,000

The Preliminary Project (1989 – 1990)

The goal of the Preliminary Project was to formulate genome research in Japan. Members of the Project performed a survey of possible research topics and studied the requirements for driving future genome science in Japan. In its final report, it recommended that the domestic plans for genome research be scheduled as five-year projects to perform full-fledged research.[10] It also stressed the necessity to form interdisciplinary research groups for the Project, i.e., the research community for bioinformatics and for ELSI.

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The Matsubara Period (1991 – 1995)

In the subsequent Matsubara Period, basic research started according to recommendations promulgated by members of the Preliminary Project. Two research groups, the biology group and the informatics group, were established and approximately 100 principal investigators were involved (Table 2).[11] Of these, approximately 10% participated in both groups.

The biology group constructed genetic maps and cDNA libraries of human (Homo sapiens), worm (Caenorhabditis elegans), and unicellular microorganisms. Experimental techniques such as rapid DNA sequencing and Fluorescent In Situ Hybridization (FISH) were established. The informatics group constructed the wide-area network 'GenomeNet' and databases for biological information (http://www.genome.ad.jp/). It also developed tools for genomic data mining. Both groups held annual research conferences and study camps (tutorials) to encourage the participation of computer scientists in genome science.

Table 2: Research Activities in the Three Periods

	Director	Research group	Major research activities and achievements
The Matsubara Period (1991-1995)	Kenichi Matsubara	Human Genome Analysis Group	Genetic maps and cDNA libraries of human, worm, and single-cell microorganisms, High-throughput sequencing and FISH techniques
	Minoru Kanehisa	Large-scale information Processing Group	Wide-area network 'GenomeNet', Databases and tools for data mining
The Sakaki Period (1996 - 2000)	Yoshiyuki Sakaki	Genome Science	Precise map of human chromosomes, Functional analysis, Techniques for gene expression profiling, Databases and tools for data mining
The Millennium Project (2000 - 2004)	Yuji Kohara	Genome Science	Genome-wide functional analysis, Comparative genomic analysis, Sociological research
	Sumio Sugano	Medical Genome Science	Identification of genes responsible for lifestyle diseases, Research on personalized medication
	Naotake Ogasawara	Genome Biology	Experimental analysis of unicellular organisms and their genetic networks
	Toshihisa Takagi	Genome Information Science	Analysis of protein structures and their dynamics, Metabolic and signaling networks, Simulations

The Sakaki Period (1996 – 2000)

During this period, the human genome was sequenced and the complete genomic sequence of several species was released.[12] Three research subgroups were formed,[13] the Group for Structure Analysis of the Human Genome prepared a precise genetic map of the human chromosomes and identified some disease-related genes. The Group for Genome Functional Analysis conducted functional analysis of important genes in model organisms and developed experimental techniques for gene expression

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profiling. The Group for Genome Informatics developed algorithms and software programs for data-mining and constructed and maintained databases.

The Millennium Project (2000 – 2004)

During this post-sequencing era, four research groups were formed, the Genome Science-, Medical Genome Science-, Genome Biology-, and Genome Information Science Group.[14]

The Genome Science Group conducted genome-wide functional and comparative genomic analysis, targeting not only model organisms but also different species. It also included sociological themes such as 'intellectual property' for the first time in GP history. The Medical Genome Science Group employed genotyping to identify genes responsible for diseases and conducted research on personalized medication. The Genome Biology Group was responsible for the experimental analysis of unicellular organisms and their genetic networks. The Genome Information Science Group conducted research on protein structures and their dynamics, metabolic and signaling networks, and simulations.

3. Results

In this section we focus on the efforts undertaken to establish new, interdisciplinary areas and to address ELSI in each period (Table 3). We performed extensive literature searches and conducted interviews totaling more than fifteen hours with five leading Japanese genome scientists (Shigeki Mitaku, Asao Fujiyama, Yoshiyuki Sakaki, Sumio Sugano, and Toshihisa Takagi) and one ethicist (Darryl Macer).

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Table 3: Communication Activities in the Three Periods

a. The Matsubara Period

Activity	Title	Introduction of research	ELSI	Educational activity	Dialogue	Venue	Date (Year-Month)	Frequency	Number of implementation
Publication of newsletters	Genome Informatics Newsletter					-	91-04 - 93-03	2	5
Publication of newsletters	Genome Informatics News	N/A	N/A	N/A		-	93-10 - 96-10	4	11
Publication of newsletters	Genome Analysis Newsletter	yes				-	91-10 - 96-02	3	over 13
Intl. Bioethics Seminar		yes	yes			Fukui	92-03, 93-11	1	2
Publication of pamphlet	Human Genome Project			yes		-	93-01,	-	1
Publication of pamphlet	The Human Genome - Toward Understanding Ourselves (both in Japanese & English)	yes		yes		-	93-07,	-	1
Genome Lecture for Journalists				yes	yes	Tokyo	93-09, 94-12, 96-01	1	3
Publication of ELSI research papers			yes			Kyoto	95-03, 96-03	1	2
Workshop	Genome Informatics Workshop	yes			yes	Tokyo, Yokohama	Dec 1990-1995	1	6
Study camp	Genome Informatics Tutorial	yes			yes	Kyoto, Osaka, Fukuoka, Toyama, Kobe	Jul 1991-1995	1	5

b. The Sakaki Period

Activity	Title	Introduction of research	ELSI	Educational activity	Dialogue	Venue	Date (Year-Month)	Frequency	Number of implementation
Lecture for teachers and students	Human genome project and internet			yes	yes	Tokyo	Jul/Aug 1996-2000	1	5
Publication of newsletters	Genome Science Newsletter	yes				-	96-10 - 01-??	3	over 12
Publication of pamphlet	Genome Science	yes		yes		-	97-05,	-	1
Genome Lecture for Journalists				yes	yes	Tokyo	97-06,	-	1
Workshop	Genome Informatics Workshop	yes			yes	Tokyo	Dec 1996-2000	1	5
Study camp	Genome Informatics Tutorial	yes			yes	Toyama, Shizuoka, Oita, Hokkaido	Jul/Aug 1996-1999	1	4

c. The Millennium Project

Activity	Title	Introduction of research	ELSI	Educational activity	Dialogue	Venue	Date (Year-Month)	Frequency	Number of implementation
Publication of pamphlet	What is life?	yes		yes			2001?	-	1
Publication of e-mail newsletters	Genome online news	yes				-	01-12 - 05-04	12	41
Production of educational DVD	Genome Science	yes		yes		-	02-??	-	1
Publication of pamphlet	Genome News	yes				-	02-02 - 03-01	4	5
Lecture and panel discussion	Medical genome science and society	yes	yes		yes	Tokyo, Osaka	02-04, 02-11, 04-01, 04-	2	4
Exhibition, lecture and panel discussion	Genome Square	yes		yes	yes	Tokyo, Fukuoka, Kyoto	02-11, 03-11, 04-08	2 or 3	8
Lecture for teachers and students	Human genome project and internet			yes	yes	Tokyo	2001-2002	1	2
Lecture for high school teachers	Summer/Autumn school of bioinformatics, Invitation to Genome Square			yes	yes	Fukuoka, Kyoto	03-10, 04-06	1 or 2	3

All of these activities above were done using Japanese language except international seminars.
Usual symposia are not listed.

The Preliminary Project (1989 – 1990)

In their final report, members of the Preliminary Project recommended that future genome research projects should include the participation of computer scientists and that a research community of ELSI should be organized to stimulate discussion [10]. The report also advised that the GP should contain five groups; of these, three were to be involved with experimental biology and two were to be responsible for bioinformatics and ELSI research. Thus, the Preliminary Project membership recognized the importance of science communication and ELSI research to render GP truly interdisciplinary. However, this forward-looking perspective was not fully realized as we describe below.

The Matsubara Period (1991 - 1995)

In response to the recommendations of the Preliminary Project, participants in the Matsubara Period organized annual Genome Informatics Workshops and Genome Informatics Tutorials (study camps). On average, there were 290 participants in the Workshops and 120 in the Tutorials. Other events were also organized such as the publication of newsletters and lectures for journalists. In addition, seminars on international bioethics were held twice during that period.

One percent of the budget was spent for ELSI research, basically 5 million yen per year. The ELSI research community was led sequentially by three researchers in bioethics. Although no records are available regarding the activities of the first leader, he was succeeded in March 1991 by Norio Fujiki who participated in the Organizing Committee of the second and third International Bioethics Seminar in Fukui Prefecture. In the second seminar, 10 out of a total of 30 speakers were GP scientists. According to the Proceedings of the second International Bioethics Seminar,[15] most speakers from the GP left immediately after giving their talks and did not participate in subsequent ELSI discussions. Darryl Macer, an ethicist, also reported that many scientists could not well communicate with the audience, and their 'highly technical talks' went over the heads of the audience.[16] The cooperation between the GP, Fujiki, and the International Seminar ended in 1993, although the Seminar itself was continued thereafter with other scientists in genome sciences who worked on the development of the Universal Declaration on the Human Genome and Human Rights (1995-1997).

The third leader was a philosopher, Hisatake Kato, who joined the GP in 1994. He organized meetings on bioethics and philosophy, and published two meeting reports;[17] 26 and 45 contributors submitted papers to the first and second report, respectively. Only one contributor, Keiko Nakamura, was a member of the GP, all others were philosophers or ethicists. Although Nakamura assessed and advised the genome research community in Japan, she was not directly involved in genome research. We can conclude, therefore, that no genome scientists participated directly in this research on ethical issues, and their activities were less effective compared with those by Fujiki, the previous leader.

After this slow beginning, in their proposal to the next GP, genome scientists recommended that ELSI be handled by an advisory board of the GP rather than invited researchers.[18] In other words, they did not pursue cooperative endeavors with

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philosophers or ethicists to establish a new, interdisciplinary research community.

Newsletters published throughout the period were distributed to GP members and subscribers. One researcher from each group served as editor of the newsletters which included the opinions and impressions of GP members of academic meetings outside the GP. The newsletters also provided space for communication among GP members. In the next period, one editor, Asao Fujiyama, continued to publish the newsletters; the main role of the other editor, Shigeki Mitaku, was in educational outreach activities. They also published pamphlets introducing GP research activities to the wider public.

The Sakaki Period (1996 - 2000)

This period overlapped with the international competitive human genome sequencing project, and the amount of sequences to be analyzed was drastically increased (http://www.ncbi.nlm.nih.gov/Genbank/genbankstats.html). Scientists were under pressure to speed up their work, and except for educational outreach, ELSI activities and efforts to continue with the establishment of interdisciplinary science faltered during this period; communication activities were continued by a few, highly motivated individuals. The significance of this lack of organization in the GP will be discussed in the next section.

The annual Genome Informatics Tutorials were discontinued at the end of this period. It was thought that the Tutorials had fulfilled their mission, the induction of computer scientists into the GP, based on the observation that the number of newly participating computer scientists had decreased compared to the previous period. Later, however, a similar activity was resumed as a summer school project offered by the Japanese Society for Bioinformatics, a research community that included major members of the GP.

The Millennium Project (2000 - 2004)

With fiscal year 2000, significant research funding under the designation The Millennium Project was launched.[19] A large goal of this project was to address lifestyle-related diseases. The funds for life science from MEXT amounted to approximately 10 billion yen per year; 5 billion were allotted to cancer research, 4 billion to genome science, and 1 billion to brain science.[20] The fund for genome science was increased prominently, reflecting the completion of the Human Genome Project. The number of new GP members grew more than four-fold compared to the preceding Sakaki Period, and approximately 87% of the members were newcomers. The attitude toward ELSI research began to change due to rapidly increasing research funding for medical applications of genomics. The directors of the four research groups in the GP were conscious of their accountability and they joined the Committee on ELSI and on Public Relations, which until then contained only a few GP participants. The new committee organized the Task Force on Ethical Issues in Medical Genome Research and invited Kazuto Kato, whose background was developmental biology, to join the committee. Kato, who had been engaged in science outreach activities such as the interpretation of current biological research for the public, organized the ‘Genome Square’ events we describe below.

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In cooperation with eight academic societies including The Japan Society of Human Genetics, the Task Force on Ethical Issues in Medical Genome Research formulated guidelines for genetic testing.[21] GP members were provided with information regarding prescribed procedures applicable to medical genome research, for example, a procedure for the protection of personal genetic information.

In the course of 2002 - 2004, two-day Genome Square events (http://hiroba.genome.ad.jp/; in Japanese only) were held eight times in three cities (Tokyo, Kyoto, Fukuoka).[22] The participants from the GP and visitors numbered approximately 1300 and 9700, respectively. This was the first activity that elicited the participation of a large number of GP members. The event featured exhibitions from approximately 30 GP laboratories, seminars, and panel discussions. Staff members and graduate students from each laboratory were presenters at the exhibitions. The Genome Square events provided researchers with the opportunity to communicate with lay persons from different generations and with different perspectives. Among participants who replied a questionnaire (80% of total), about half answered "yes" to the question “I have reexamined the purpose and meaning of my research through discussions with non-researchers” and “The members of my laboratory were educated and motivated by their participation in this event".[22]

Starting with this period, the office work and public relations component of the GP was handed over to a commercial enterprise which published a monthly e-mail newsletter as well as the pamphlet ‘Genome News’. The pamphlet was later discontinued and the e-mail newsletter was reduced to short announcements and a listing of the latest publications.

4. Discussion

4.1 Establishment of an interdisciplinary research community

In this section we review the activities of the GP as it attempted to establish an interdisciplinary research community that included ELSI and bioinformatics components.

The ELSI perspective

Despite the initial intent to organize an interdisciplinary ELSI research contingent, GP scientists ceased cooperating with philosophers and ethicists at the start of the Sakaki Period. Why did the cooperative efforts fail? According to Sakaki, the ethicists' perspective did not have a sufficiently strong connection with actual genome research.[23] He also explained that the focus was shifted from ELSI to the public understanding of genome science as a whole, because ELSI should be treated by MHLW, not MEXT. Fujiyama, on the other hand, contended that bioethics in Japan at that time tended to be impractical because most concepts were directly imported from overseas.[24] He also pointed out that the lack of suitable researchers to cooperate on ELSI led to the passive decision, at the start of the Sakaki Period, to assign responsibility for ELSI to a GP advisory board. During the Sakaki Period, 2 senior advisors were assigned responsibility for ELSI, however, no activity records are available. The failure to appoint a coordinator conversant with multiple research cultures and to induct appropriate researchers into the GP, aborted the birth of a truly

interdisciplinary research community. This situation was also pointed out by Darryl Macer already in 1992:[25] "(Natural) scientists in Japan who do see the relevance of ethical studies do not think they should be the responsibility of natural scientists, but of social scientists or lawyers. But even if social scientists start such research, they may still be unable and/or unwilling to challenge the views of biologists or policymakers". He also remarked in his interview that "I think non-scientists in Japan could engage scientists, but generally do not have the attitude to do so effectively. Often they like to confront scientists. Prof. Fujiki was a medical doctor, and the GP has come back to working with a natural scientist, Dr. Kazuto Kato, to work on social issues and communication. To make the situation better, improve the attitude of all to be multidisciplinary and not threatening each other with a critical attitude".[26]

The GP has now entered the Takagi Period (2005- 2009) in which four principal investigators address ELSI; they are Kazuto Kato and three medical scientists. Their successful collaboration with researchers knowledgeable in the fields of sociology and the humanities may constitute the first step by the GP towards a truly interdisciplinary research.

The bioinformatics perspective

With the active pursuit of computer scientists by the GP, the scientific community in the Matsubara Period began to establish interdisciplinary bioinformatics research. Indeed, many of the attendees of the Tutorials and Workshops held during the Initial Period now constitute the core of the GP. After the initial influx, however, the number of newcomers from computer science decreased and this was, at least in part, the reason for discontinuing the Tutorials.

According to Toshihisa Takagi, it is difficult for computer scientists to participate in the biological aspects of research because they need to learn the requisite biology background and are still expected to output discoveries in the context of their original area of expertise.[27] He estimated that 5 years are required for a computer scientist to publish a first bioinformatics paper; this may explain the reluctance to dive into a new research field. The establishment of more academic departments for bioinformatics could improve this situation, but the creation of new disciplines at Japanese universities is difficult.[28] For this reason, Takagi confessed, the Bioinformatics Group in the Millennium Project could not be evaluated by the traditional measure of its biological achievements. Newcomers from areas outside biology were given preferential treatment in terms of affirmative programs to encourage their participation in the GP.

The heated competition among sequencing centers during the Sakaki Period may constitute another reason for the discontinuation of interdisciplinary GP activities: scientists had little time to cultivate new areas of research, and this attitude was carried over into the Millennium Project. Under these circumstances, the Genome Square events provided a unique opportunity for graduate students to survey a wide range of genome research and to communicate with researchers in different fields. Although the Genome Square events were initially intended to offer researchers and the general public an opportunity for exchanges in a social setting, they also served as an introduction to interdisciplinary education for young scientists.[22]

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In the Takagi Period, scientists from the field of biology and informatics joined a single group known as “Biological Systems Informatics”. According to Takagi, the formation of this group constitutes the end of the affirmative program and, simultaneously, a step toward establishing a truly integrated science.

4.2 Communication successes and failures of the Millennium Project

With the almost seven-fold increase in research funding, leading scientists in the Millennium Project became highly conscious of the social implications of their work. A cumulative total of 1300 scientists participated in the Genome Square events and communicated with the public.

Concurrently, GP scientists stepped up their participation in ELSI activities. In the Matsubara Period, the Committee on ELSI and Public Relations consisted of only two advisory researchers and invited ethicists. Only invited researchers conducted ELSI activities and the participation of genome scientists was lacking. In the Sakaki period, the Committee consisted of only two advisory researchers and no ELSI activities were pursued. On the other hand, in the Millennium Project, the Committee is comprised of one advisory scientist, the directors of the four research groups, Kazuto Kato, one legal expert, and one medical researcher who serves as director on ethical issues in medical genome research. The Committee organized the Genome Square events and symposia on social issues in medical genome science (“genome ikagaku to shakai”) and more GP members than ever participated in these events.

According to Sumio Sugano, however, the main reason for the shift in the attitude of genome scientists toward social activities was increasing outside pressure for the GP to justify its huge budget requests [20]. While some scientists had long been cognizant of their responsibility toward society as a whole, some participants in the Genome Square events continued to regard their participation in these activities as an unwelcome burden (personal communication). There were additional failures. In the Matsubara and Sakaki Period, educational outreach activities and the publication of newsletters involved a few individual scientists who labored on a volunteer basis. In the Millennium Project, the production of newsletters was placed into the hands of a professional office. Consequently, the newsletters became reminiscent of official reports rather than the more satisfying lively exchange of letters among GP participants. Moreover, the pamphlet ‘Genome News’ was suddenly discontinued when the office was succeeded by a different company.

4.3 The attitude toward society

We have seen that only after the Millennium Project started, many researchers began to participate in the ELSI activity. Before then, how had the communication between the research community and society been recognized by the organizers of the GP? In the Matsubara Period, social activities meant the research on bioethics and the education of journalists. For the Sakaki Period, let us quote the Sakaki’s own remark in his interview: "We tried to emphasize educational activities, basically because we were engaged in basic science (and we needed public understanding). So I personally showed up in many TV programs and public lectures. It is my contribution that the public came to be familiar with the word 'genome'." (Parenthesized part is by the

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authors.) In the Sakaki Period, a few highly motivated GP researchers organized and participated in the outreach activities: one lecture course for journalists and five for (junior) high school teachers and pupils. The remark of the principal organizer of the high school lecture courses, Shigeki Mitaku, is noteworthy: "Answering to the questions from the public is rewarding for both researchers and the public, because we always face fundamental, top-down questions in the process. We start to see our research from the viewpoint of the public. The important point is the motivation for the good of the society".[29] In the Millennium Project, the symposia "Medical genome science and society" and the event "Genome Square" were conducted in addition to educational activities. These activities were intended as a dialogue with the society, in parallel with the international movement as described in Introduction.

4.4 Conclusions

Although the establishment of an interdisciplinary research community was recognized as an important issue even in the Preliminary Project, this goal has not been fully realized yet. GP scientists failed to identify appropriate collaborators to address ELSI from ethical perspective and the establishment of the interdisciplinary bioinformatics community encountered similar difficulties. The number of participating computer scientists declined as the GP progressed, presumably because of a lack of academic departments and bioinformatics positions. To facilitate researchers' participation in interdisciplinary programs, therefore, researchers who are acquainted with different research fields, community, and society should proactively function as coordinators of interdisciplinary programs or mediators of collaborative research.

As for the dialogue with society, researchers began to recognize its importance in their research. Indeed, GP researchers' attitude toward society has changed from one-way education to dialogue in the Millennium Project. Many researchers participated in the social events such as Genome Squares and experienced dialogue with society. Therefore, it is of primal importance to present to scientists the advantage of dialogue with society scientifically and to design effective communication programs that provide researchers with such opportunities.

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Book Review

Genetically Modified Athletes: Biomedical Ethics, Gene Doping and Sport. By Andy Miah. London: Routledge, 2004

ANTHONY MARK CUTTER

As new technologies are developed and applied in a sporting context we ask the questions: What is good sport? What is cheating? What technologies should athletes use? In pursuit of the answer to these and other questions, the author indulges his, self confessed, fascination with post-human and trans-human technologies as a tool for presenting a detailed discussion of the issues that the possibility and reality of genetic modification poses for athletes. In so doing he contemplates the nature of human enhancement in a context that makes the major issues clear, whilst avoiding the negativity associated with the term eugenics.

Structured around four distinct but inter-related sections headed *Anti-doping and Performance Enhancers; Conceptualising Genetics in Sport; The Ethical Status of Genetic Modification in Sport* and *Genetically Modified Athletes* the book reveals from the outset the authors positive stance on the development and use of enhancement technologies in sport. However, the discussion is for the most part balanced posing questions and explaining positions, before drawing conclusions apparently in favour of genetic enhancement.

In the first part, the author discusses *Anti-doping and Performance Enhancers* by posing two questions *why genetics now?* and *why not dope*? His response to the first of these questions recognises the fast pace of technological developments and the fact that "for many the prospect of *genetically modified athletes* conjures up highly dystopian ideals, which the sporting examples ground in potential and detailed contexts. The use of performance enhancement in sport brings into question a curiosity for testing humanity in a manner comparable to, say, life extension" (pg.11). Thus we see the beginnings of the parallels the author seeks to develop between the applications of new technologies in sport and their use in other areas of human life. To answer the question *why not dope?*, there is first a review of the attitudes that exist within the sporting community towards doping (initially referring to the use of performance enhancing drugs, developing later to the book's broader theme of the use of performance enhancing genetic technologies). Drawing on literature discussing "the harms" of drug doping, a framework for understanding the related social and ethical concerns is developed. The concepts of doping as harm to the athlete and harm to the sport help to frame the key debates of *genetically modified athletes* in relation to athletes' health and the concept of cheating and unfairness, providing the bedrock for the author's later bioethical analysis. These two ideas appear to develop throughout the book, building around notions of the altering of the nature of the athlete and the nature of sport.

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The second part, *Conceptualising Genetics in Sport*, discusses the nature of genetic technologies such as they might be developed to promote or enhance athletes and athletic performance. Noting the wide and varied nature of genetic and genomic technologies, the author articulates the suggestion that, though varied in their nature, the potential applications of these technologies give rise to relatively similar ethical problems. The author identifies those technologies characterised in terms of genomics, somantic cell modification and/or genetic selection as being those most likely to be of use for developing the genetically modified athlete. He then observes that "while modest expectations are sensible in relation to genetically modifying athletes, there is a growing expectation that science will soon make possible such alterations" (pg.50). Having identified some specific technologies and studies that may lead to the advent of the genetically modified athlete – discussing in particular studies of "growth factors" and their impact potential impact on sport – the author then provides a brief review of the wide range of "concerned voices" that have spoken against the notion of the genetically modified athlete or gene-doping. Among these "concerned voices" we hear at first from many athletes who speak against the potential uses of genetic technologies in a sporting context, a view that is then supported by many scientists who debunk the usefulness of any actual technology that might be developed, and by policy making bodies who express a desire to "stay ahead of the cheaters". In contrast to these views it is suggested that the genuine reaction of sporting professionals remains uncertain, pointing to the desirability of selecting the best possible members for a sporting team as an indicator of the "ambiguous ethical status" of the technologies in question. By highlighting the disparate views within both the scientific and sporting communities, the author also highlights the general interest of the world media in portraying a sensationalised image of "superhumans" in sport. It is through placing the discussions of gene-doping and the genetic medication of athletes in a socio-political and socio-legal context that the author's own trans-humanist sympathies become abundantly clear. However, he articulates a clear response to criticisms of enhancement technologies, and strives to place the discussion in a clear conceptual framework to provide the opportunity for genuine ethical discussion.

Thus the subsequent discussion, in part three, of what is termed *The Ethical Status of Genetic Modification in Sport* deals with a broad range of ethical issues, under the chapter headings: *humanness, dignity, and autonomy*; *personhood, identity and the ethics of authenticity*; *viruses, disease, illness, health, well-being and enhancement* and *unfair advantages and other harms.* Throughout this discussion the author draws on the critical mass of philosophical and sociological literature around questions of both human enhancement and sport to review in detail the nature of the academic debate, and to develop a synergy between bioethics and sports ethics.

The final section draws together the key points from the earlier three sections to discuss the nature of *Genetically Modified Athletes.* Asking the important question: is genetic modification a method of *enhancing, altering, or manipulating people?* and arguing that *Sport Needs GM* the author charges that "there has not been a sufficient level of analysis within sports ethics and policy making to derive a *conceptual framework for performance enhancement*" (pg.175) and criticises policy makers for

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being overly concerned with performance enhancing drugs as opposed to other technologies with similar effects. He theorises the end of the "anti-doping" mentality in sport, and calls for a policy to engage with the uses of genetic modification in sport suggesting the possibility of the creation "of distinct, genetically enhanced competitions". The utopia or dystopia of sport that this would create remains to be seen, but as the author notes in conclusion "the ramifications for competitive sport would be immense".

It would be a mistake to categorise this book as either a discussion of sports ethics or bioethics, rather it develops an integrative approach to the discussion of sporting activities and human enhancement drawing on an interdisciplinary body of literature. The discussion of human enhancement in the recognisable, everyday, setting of sport provides a solid framework that avoids an overly abstract analysis. With a definite pro-enhancement theme throughout, the author carefully considers the current world attitudes towards sports and sportsmen, and the current policies of key policy making bodies in the world of sport. Whether the notion of genetically modified athletes (or genetically modified humans in general) fills the reader with utopian joy or dystopian dread the book is of interest to a range of disciplines, uniting sports studies with interdisciplinary bioethics and policy discussions.

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