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ABSTRACT. This article highlights major results of a study into the ethical norms and rules governing biobanks. After describing the methodology, the findings regarding four topics are presented: (1) the ownership of human biological samples held in biobanks; (2) the regulation of researchers' use of samples obtained from biobanks; (3) what constitutes "collective consent" to genetic research, and when it is needed; and (4) benefit sharing and remuneration of research participants. The paper then summarizes key lessons to be drawn from the findings and concludes by reflecting on the importance of such empirical research to inform future governance norms and practices.

Despite the rapid proliferation of genetic and genomic databases around the world, and the associated burgeoning of national and international guidance documents suggesting various ways for governing them, consensus over the most appropriate ethical norms and legal rules is still a very long way off. Partly, this is due to a lack of empirical data—especially data that capture in detail the views of experts engaged in the biobanking field on specific ethical concerns. A number of studies have been carried out to evaluate the views of patients and the public (Hoeyer et al. 2004; Pentz, Billot, and Wendler 2006). The views of experts have not been sufficiently evaluated, however, even though as members of ethics committees and advisors to research consortia they play an important role in shaping future practice.

This article discusses an international study into the ethical norms potentially applicable to genetic databases and biobanks. This multi-year

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(January 2004–June 2006), collaborative project involved several Swiss academic institutions and the Department of Ethics, Trade, Human Rights and Health Law of the World Health Organization (WHO), of which the first author was the director at the time when the project was established.[1] The study's several components include a comparative analysis of existing (and sometimes conflicting) ethical guidance documents produced by a number of organizations, as well as of relevant laws and regulations. The documents on which we drew were created by such organizations as the Human Genome Organization (HUGO) (HUGO Ethics Committee 1996; 2000; 2002), the United Nations Educational, Scientific and Cultural Organization (UNESCO) (UNESCO 1997; 2003; 2005), the Council of Europe (1994; 1997; 2006), and the National Bioethics Advisory Commission (NBAC) appointed by President Clinton (NBAC 1999). Our study focused on documents, primarily at the international level, that set forth ethical standards for the operation of genetic databases and biobanks or that address such institutions indirectly, such as through general guidelines on research with human subjects that encompass research utilizing stored human biological material. A comparison of these documents revealed certain common assumptions, numerous points of difference, and several lacunae regarding practical issues that are not fully addressed. From this exercise, we developed a set of issues that seemed likely to be salient and significant for experts concerned with biobanking around the world; as discussed later in the methodology section, these issues then provided the framework for our interview questionnaire.

In this article, we concentrate not on our analysis of the normative guidelines themselves (Knoppers and Abdul-Rahman 2008), but rather on the responses obtained from our interviews with international experts who were people knowledgeable about biobanks either because they operate, or conduct research utilizing, a biobank or because they develop policies or prepare ethical guidelines for biobanking. The paper discusses the study's methods, main results, and policy insights generated by this component of the study. We focus on the results of interviews that we conducted with 42 experts internationally. We also refer to the results of a second study involving a similar group of 45 respondents in the United States (U.S.). Following a brief description of the study's methodology, we outline our findings and analysis regarding four specific topics that present particular challenges for the international governance of genetic databases and genomic research: (1) the ownership of human biological samples held in biobanking repositories; (2) the methods that may be used

to regulate researchers' use of samples obtained from biobanks; (3) what constitutes "collective consent" to genetic research, and when it is needed; and (4) benefit sharing and remuneration of research participants. Policy insights pertaining to these four areas are then presented. In particular, we highlight that property rights in, and use of, samples ought to be governed by rules and agreements that would limit researchers' actions to the scope of the informed consent provided when samples and data are collected for a biobank. Furthermore, although collective consent is meaningful only under exceptional circumstances, group consultations may be advisable for practical purposes. Finally, monetary remuneration of individual donors usually is not acceptable, but benefits ought to be shared with the population from which the samples came, particularly when research involves vulnerable populations or individuals who are at risk of exploitation in the context of biobank research.

In what follows, the terms "biobank" and "genetic database" are used interchangeably to signify a collection of human biological samples that can be used for genetic analysis. These encompass pathology collections, repositories for specific diseases—e.g., cancer registries—and population databases created to permit longitudinal studies of multiple diseases or conditions. The term "biobank" seems to be used most commonly to signify a database that combines biological samples with the results of genetic analyses along with health or other data about the persons from whom the samples were collected (such as workplace and residential information).

SAMPLE DESCRIPTION

The 42 respondents in our international cohort were experts who worked with genetic databases or who were engaged at the level of policy making, drawn from a range of professional disciplines and institutions. The respondents were chosen on a "purposive sampling" basis—that is, they were invited because of their professional backgrounds and to achieve a varied geographical distribution, rather than being a random sample. Individuals were identified through their contributions to scientific and policy debates; subsequently, the circle of invitees was enlarged through snowball sampling. Ninety invitation letters were sent, and 42 experts agreed to participate.

The respondents' mean age was 51 years; the range was from 29 years to 77 years. Their primary affiliations (including several with two major affiliations) were as follows: 23 were employed at a university or

university hospital; 8 worked for a government agency; 3 were with non-governmental organizations; 4 were directly associated with biobanks or genetic databanks (one of which was located in the private sector); 4 were independent consultants; 3 were members of national ethics committees; and 1 worked at an international organization. The respondents came from 27 countries, from all parts of world. The Human Development Index[2] of these countries encompassed 18 High, 6 Medium, and 3 Low ranked countries. A range of expertise is represented among the respondents, with some being expert in more than one field: 17 work in the life sciences, including genetics; 18 are physicians; 7 are in bioethics and 4 in philosophy; 5 are lawyers; and 5 come from other fields such as social science and engineering. We also asked respondents about the nature of the work that they do regarding genetic databases. Twenty-nine are involved in analyzing the ethical or legal issues in biobanking; 16 are engaged in making recommendations or drafting guidelines; and 18 handle or use samples or genetic data in their work.

METHODOLOGY FOR GATHERING THE DATA

We sought the respondents' views about the alternative policy options posed in four hypothetical factual scenarios presented to them. The scenarios were constructed around the leading ethical and legal issues to have emerged in the international literature and ethical guidance documents on biobanks to date, as well as the views of a number of geneticists, bioethicists, and other experts whom we consulted. The scenarios were distributed in advance to each respondent, who was then interviewed—in most cases by telephone—by a member of the research team using an interview guide (see example in the appendix). The interviews combined open-ended questions and a semi-directive style with a few structured questions; in particular, respondents were prompted to explain the basis on which they reached conclusions. The instrument was tested through six pilot interviews; the actual interviews lasted 33 to 75 minutes, with a mean duration of 50 minutes. A majority were held in English, but, when respondents preferred, interviews were conducted in Spanish, French, and Italian. All interviews were taped, transcribed, and analyzed. In this article, we provide a brief overview of the topics that come across as key issues in the ongoing debate; the results of the qualitative analysis are presented in greater detail in a monograph (Elger et al. 2008).

FOCUSING RESPONSES THROUGH SCENARIOS

Because we were suspicious that "opinion polls" draw formulaic responses and do not permit one to get beneath the surface generalities of the existing guidelines for biobanking, we developed four hypothetical factual scenarios—several with multiple parts—to force respondents to consider the ethical and legal issues in the context of "real choices." For example, Scenario A introduced a series of questions by setting up the following situation:

> An international group of researchers has decided to establish and operate a repository in which DNA extracted from biological specimens will be stored along with related information. The purpose of the repository is to enable research on the association of certain genes with an elevated risk for developing colorectal polyps.
>
> The research is funded by the health departments of three different countries, one of which acts as the home for the repository. The project is guided by a Steering Committee consisting of the principal investigator from each of the three countries, a representative of the international association for colon cancer patients, and a member of the Medical Research Council of the home country. An independent Ethics Review Board provides ethical guidance.
>
> Local physicians will collect 3,000 biological samples from individuals diagnosed with colorectal polyps and from their blood relatives. The physicians will also fill out a health and lifestyle information sheet about every participant and send it along with the sample to the repository. This information will be periodically updated and any deaths will be reported. Informed consent will be obtained from all participants for their biological samples and associated information to be submitted to the repository. Biological samples will be stored at the repository in the form of extracted DNA.
>
> A number of policies to guide the operations of the repository are now being discussed.

The scenario then developed a number of questions for the respondents by describing various policies being considered by the Ethics Review Board and the Steering Committee. Respondents were asked not just which policy option they favored but also why they favored it. This specific scenario laid out options concerning seven key policy areas that implicate important ethical and legal issues and principles: (1) a fairly elaborate system of double-coding—as a means of protecting participants' privacy by preventing individual identification; (2) the extent to which participants should be

able to withdraw samples and associated information from the repository; (3) the use of samples for biomedical research not involving colon cancer; (4) giving notification to a participant's physician when a gene mutation believed to be linked to an elevated risk of colon cancer is discovered; (5) the obligations imposed on researchers who receive samples not to transfer these samples to persons not named in the Material Transfer Agreement (MTA)[3] and to share their research findings with the repository; (6) the closing of the repository and destruction of the samples at the end of the study; and (7) ownership of the samples and data.

To illustrate how these issues were framed, the following is the wording of the subpart of this scenario that probes the last set of issues regarding ownership:

> A member of the Steering Committee has proposed the following policy:
> 1. *Ownership of samples*. The repository is the custodian of the samples and associated information on behalf of the participants.
> 2. *Ownership of the data*. The data generated by the research will be treated as a public good and all investigators must agree to put their findings and supporting data in the public domain on a regular basis and without undue delay.[4]

The interviewer then asked whether it was preferable for the repository to be the *custodian*, as proposed, or alternatively the *owner* of the samples once they have been submitted.

DATA ANALYSIS

We carried out a modified thematic analysis of the transcribed interviews: A researcher read through the transcribed data to identify the concepts and reasons on which respondents based their viewpoints. (The accuracy of the transcription and the characterization of the response was double-checked and confirmed or corrected by another member of the team reviewing the same transcripts and checking the original tapes when necessary.) The most relevant transcribed text concerning each reason or concept was extracted; these excerpts were collated on data sheets with similar reasons given by other participants. Conceptually associated reasons described by the respondents were grouped together and labeled with "codes." Among the various types of arguments mentioned by respondents, we also identified and grouped together those that were based on similar ethical reasoning, such as consequentialist versus deontological arguments, as well as references to different ethical principles.

In this article, we provide in addition simple counts of respondents in favor or against a particular policy, following accepted methodology for providing readers with a useful summary of some aspects of the analysis (Pope, Ziebland, and Mays 2000).

FOUR KEY TOPICS OF INTEREST FOR THE GOVERNANCE OF GENETIC DATABASES

Repository Ownership vs. Custodianship of Biological Materials

Different schools of thought within property law theory vary in how they explain the nature of property rights, how they define the concept of "ownership," and how they specify the objects that property rights may legitimately encompass. No single, universally accepted theoretical account exists (Becker 1977; Harris 1996; Penner 1997; Waldron 1988). However, many property law theorists employ the term "ownership" to describe a person's control over a "thing"—that is, the ability to use, transfer, and enjoy exclusive possession of the thing, as well as to manage its use by others and to collect rents for such use. We began knowing that "ownership" is a controversial topic, but it was interesting to find what a confusing concept it is for many of our respondents, especially those who do not have a great deal to do with the law. Guidance documents that proclaim general principles about who "owns" samples and data thus not only may fail to take account of people's sense that these matters need to be resolved differently in different contexts, but also may disguise the extent to which people use the term "ownership" in very different—indeed, contradictory—ways.

Almost all responses from the international respondents to this part of Scenario A characterized the biobank as the custodian, rather than the owner, of the deposited material. Among those who explained this conclusion, most phrased their answer in terms of the participants being the owners of the samples deposited. As one respondent put it, "I own my genes, not the custodian. . . . And if I give the genes [in form of a sample] to a custodian to look after, it doesn't mean that [the custodian] owns them. I still own them, but I've given them in custody." By implication, there is no transfer of ownership simply because a sample was held in the biobank. A few respondents suggested that genetic resources are inherently collective in nature and hence are "owned" by the group of which the participant is a member, while others went still further and regarded the biobank as a custodian even though neither participants nor groups own the samples.

A small number of respondents considered the biobank the owner of the samples. The reasons given for this position included that it favors transparency or is simply best as a practical matter. Interestingly, two respondents who characterized a genetic database as an organized system that entails more than merely collecting and storing samples and information—"not only biological material but also an organized system"—concluded that this meant the biobank should be regarded as the owner of the samples it holds because the samples are part of the system as a whole, which is the creation, and hence the property, of the biobank. Several respondents insisted that ownership is not the right concept to use for such samples—"ownership is very tricky but custodianship and stewardship help to take care of your right to hold the material." Finally, one respondent said that deciding between custodianship and ownership depended on the particular circumstances.

Disparate Reasons for a Common Conclusion on Custodianship

The responses to this scenario show that many experts favored the idea of custodianship but that they based this preference on two quite different sets of belief about ownership of stored samples. (The same reasoning appeared among the respondents in the U.S. interviews.) Some expressed general dissatisfaction with the idea of anyone "owning" human samples. They described ownership as being "too strong" and "too theoretical." Further, they associated the concept of ownership with the "irreversibility" of the transfer, an issue that we had introduced earlier in the scenario, as noted previously. Others among those who regarded the repository as a custodian had no problem with the idea of people owning samples. Indeed, these respondents commonly said that a person who had contributed a sample still "owns" it even when it is stored in a biobank.

Two categories of respondents especially favored treating the repository as a custodian. The first such group comprised the organizers of biobanks (not principal investigators or comparable people on research projects who use biobanks in genetic and epidemiological studies). This group of respondents saw themselves as "mediators" between research participants and investigators, and they thought that the concept of custodianship helped them to exercise control. The second group who favored the custodianship model consisted of respondents from indigenous populations, who favored the idea of "collective ownership" residing in the group from which participants came. These respondents took a broader view of the biological material (DNA) as being part of the genealogy of the partici-

pants or as "containing [the participants'] spirit." (We return to the topic of collective action below.)

Biobanks as Owners of Biological Samples

A substantial minority of our international respondents thought that a repository owns the material deposited with it. (This view was held even more widely in our U.S. sample.) They adopted this position largely for practical reasons. First, it would help prevent abuses because a biobank is in a better position to protect and manage a collection of materials and data that belongs to it. Second, they worried that treating the repository as a mere custodian would give participants the (false) impression that they could come and take their samples out of the biobank freely and at will at any time. These respondents pointed out that participants must be told that they are surrendering ownership when they donate their samples.

Data as a Public Good

As set forth in Scenario A above, the "proposal" of the Steering Committee member presented a second issue, having to do with the policy on ownership of data generated by research projects undertaken using the repository materials. The proposal was that the data would be treated as "a public good" and that researchers would have to agree to put their findings and data into the public domain regularly and without delay. A majority of the respondents favored this requirement, even though, in the literature around biobanking, the practical implications of this view are regarded as controversial (Eisenberg 2000; Chokshi, Parker, and Kwiatkowski 2006).

Researchers' Obligations

Immediately prior to the questions regarding ownership, Scenario A presented some questions about the obligations of researchers who were given access to samples from the repository:

> The Steering Committee proposes to include the following provisions in the Material Transfer Agreement (i.e., the contract setting the terms for giving an investigator access to biological specimens and the associated information):
> 1. Investigators must not transfer the DNA and the associated information to persons not named in the Material Transfer Agreement.
> 2. Investigators are under the obligation to share all research findings and the data produced for each sample with the repository.

Duties of Nonmaleficence and Fidelity

Respondents, including those in the U.S. sample, substantially agreed about investigators' obligations to adhere to the restrictions in the MTA. Their reasoning reflected the values of nonmaleficence and fidelity. Respondents said that such restrictions would prevent abuses (material "falling into wrong hands"), would protect participants' autonomy (against secondary uses not authorized in the original informed consent document), and would honor participants' trust in the repository. Specifically, they commented that:

> [T]here is an incredible amount of secondary uses that are not authorized particularly in the informed consent.

> [Researchers] have the responsibility that the tissue is used according to agreement between the bank and the donor.

On the other hand, a small number of respondents disagreed with the proposed policy because it is often difficult to establish at the outset what all future collaborations will be, or because a narrowly drafted MTA can burden researchers excessively.

The Flip Side: Biobanks' Obligations

The chief concern expressed, however, arose from the recognition that placing restrictions on researchers carries with it the implication that biobanks are obligated to enforce rules about the use of samples by investigators who obtain access to them from the biobank. Such an obligation may prove to be complex once the samples have been placed in the hands of the initial investigator. As one interviewee stated:

> We call it "policing tissue." Because the tissue bank is custodian of the tissue and it received the permission from the donor and the next-to-kin to use the tissue, the tissue bank is also the [one] who is responsible and has the knowledge of who is using the tissue. . . . I have heard about several cases of tissue banks that gave tissue for research and the tissue ended up in the pharmaceutical company being used for something completely different. . . . We have the responsibility that the tissue is used according to agreement between the bank and the donor.

The respondents also were asked whether contractual limitations are enforceable and thus practical as a means for ensuring and monitoring compliance and to safeguard against misconduct or abuse. There was substantial agreement among interviewees, in both the international and the

U.S. samples, that contractual limitations are enforceable. Indeed, "that's taken for granted," as one respondent stated. The strategies for ensuring compliance suggested by respondents included: (1) giving investigators the minimum amounts of samples and information needed; (2) requiring investigators to return all unused material to the biobank; and (3) requiring authors to state in their publications the origins of the samples and raw data used. In addition to having explicit contracts, respondents reported that peer pressure also helps with enforcement of the limitations and requirements set down in MTAs.

Individual vs. Collective Consent

Genetic research raises the issue of "collective" or group consent for two reasons. First, some genomic research is carried out within isolated populations, which generally do not embrace Western, individualistic views. When that is the case, even matters not involving group identity may be decided through consent by group leaders rather than by the person(s) directly concerned.

Second, research findings may impose harms or burdens on a particular group. Examples of groups at risk include the relatives of a participant who provides a sample and data, the ethnic group of which a participant is a member, and other persons who share the same phenotype.[5] The interviews showed that a special issue arises when the "group" is, in effect, created by the research—that is, when the identification of a genetic susceptibility defines a group of people whose commonality lies in facing the same elevated risk of disease. In this circumstance, the utility of taking the group into account may reside less in any notion of group permission, and more in ensuring that researchers take into account the potential impact of the research on the research subjects. Such sensitivity, leading to what was seen, in the words of some respondents, as a "constructive relationship," was thought more likely to emerge from group consultation that from individual informed consent procedures.

Probing Varied Views about Appropriate Means

Commentators are divided over how to protect groups and their members adequately. Some advocate relying on collective consent (Greely 1997; North American Regional Committee of the Human Genome Diversity Project 1997), while others favor collective permission or approval as well as consent by those directly involved (Diallo et al. 2005; Reilly 1998). Still others argue that all that is needed is a formal process of group, community,

or population consultation—without actual consent or approval—or simply some form of group involvement—ranging from minimal consultation or dissemination of information to an ongoing, formal partnership (Brugge and Missaghian 2006; Foster, Eisenbraun, and Carter 1997; Foster et al. 1999; Sharp and Foster 2000).

These varied views seem to reflect a lack of clarity over the interests that are actually at stake and the objectives that should be served. Is whatever method is recommended for obtaining collective consent intended as a means of protecting individuals—for example, due to their weak bargaining position, difficulties comprehending research, and so forth? Or is it meant to provide formal recognition of the group—for example, by showing deference to its leaders? Alternatively, is a group mechanism invoked because the individual is not seen as the correct unit of decision making (because the family, village, tribe, or other such group makes comparable decisions)? Or is it because the group has interests independent of individuals' interests—and, hence, it must be consulted separately and give (or withhold) its consent or permission?

We attempted to tease out some of these differences in Scenario C:

> Biotech Incorporated proposes to collect 2,000 biological samples from the members of an indigenous population in the country where Biotech Incorporated is based. Pharma A, a publicly traded pharmaceutical company, finances Biotech Incorporated's project because it is interested in developing a genetic test to detect polymorphisms that are linked to adverse reactions to its most frequently prescribed drugs. These polymorphisms are known to occur more frequently, though not exclusively, in the studied population. Biotech Incorporated will be the owner of all intellectual property rights arising out of its research.
>
> *Scenario C.1*
> In its negotiations with the indigenous group, which is represented by a Governing Council, Biotech Incorporated has acknowledged its obligation to share the benefits of its research with the group. Biotech Incorporated is proposing various forms of benefit sharing to the Governing Council:
>
> *Option A*: Making any genetic tests resulting from the research available for free to the indigenous group for ten years.
>
> *Option B*: Making an annual donation for a period of ten years to the hospital that provides health care to the indigenous group, of a sum equivalent to 3% of the revenues generated by any intellectual property rights resulting from the research.

Option C: Donating several pieces of durable medical equipment to the hospital that provides health care to the indigenous group.

The Governing Council determines that none of the proposed forms of benefit sharing is adequate, and that an agreement can only be reached if the Governing Council owns all intellectual property rights arising out of the research (Option D).

Scenario C.2
The negotiations become difficult and eventually stop. An employee from Biotech Incorporated, who is a member of the indigenous group, believes that the Governing Council is behaving arbitrarily and is out of touch with the beliefs of the group. She suggests to the head of the company that she could approach individual members of the group and offer them a sum of US$800 (roughly equal to four weeks of the average salary for members of the group), in exchange for their participation in the research. The offer would be contingent on the participants renouncing all intellectual property claims.

Practical Aspects

In general, respondents approached the issue as an ethical matter rather than simply a practical one. Plainly, however, the scenario does present practical concerns, such as the researchers probably needing the consent of group leaders to gain access to a setting where they could speak with potential individual participants. We were told in some interviews that the scenarios therefore raised what one person called a "sneaky" choice. Going against the Governing Council would be disruptive and possibly create antagonisms among group members. In addition, as one respondent stated, "we don't want to impose values that are foreign to a society," namely, substituting individual self-choice for the authority that resides with traditional group leaders.

Respondents who were familiar with the practice of collective consent generally were more agreeable to it; these respondents came largely from countries outside the U.S. and Europe and particularly from developing countries. The major qualification raised by these respondents was to avoid concentrating excessive power in the hands of community "representatives" who lack legitimacy. Few respondents from anywhere said that collective consent "is never required." Those familiar with the practice observed that obtaining it was common in many remote areas, some-

times even a legal requirement. Some who regarded individual consent as inappropriate when it is not part of the local norms said that once the researchers have consulted the group, they must honor the choice made by the group.

Respondents were not eager to impose the requirement of consulting with every possible member or representative of any given group, as this would stifle research. They focused on the central characteristics of situations where some form of collective agreement would be required. These they identified as being: (1) where traditional systems of decision making involve collective consent; (2) where research results can affect the whole group—e.g., where the group is identifiable or faces potential discrimination; and (3) where special vulnerability exists, such as the risk of economic harm, or the burden of new knowledge on group members' lives.

Purposes Served by Group Consent or Permission

Significantly, formal "consent" was not assumed by many to be what was required. Rather, respondents first expected that group consultation would occur to ensure cultural sensitivity in the design and execution of the research. Second, respondents from places where group consent or permission is the norm regarded it as necessary to maintain group identity (expressed through the exercise of "group autonomy"). Third, they viewed it as the best means of protecting individuals: "Individuals are very vulnerable in themselves, unlike the West where historically the individual has been protected by constitutions, awareness, and culture."

In the settings under consideration, the populations are viewed as vulnerable because, for example, of poverty and a lack of education. It seemed to be assumed that group leaders would be more sophisticated and better able to act in a free and self-interested fashion than individuals.

Ethical Aspects

The concern expressed by respondents—those who favored collective consent as well as those who opposed it—was that group consent ought not to be allowed to *replace* individual consent. As one respondent noted, "It is appropriate to have collective permission, some kind of political permission for instance; it is important to have public deliberation but it doesn't replace and can never replace individual consent." Some respondents recognized that this is difficult to enforce in practice because individual refusals by members of the group may not be realistic once the group leaders have given their approval.

Respondents also mentioned the need for clarity on the source of moral authority of the "Governing Council" in the scenario—for example, is it chosen democratically, how representative is it, and will it ensure that any benefits reaped in the group's name are actually shared? In the words of a respondent familiar with the practice of collective consent: "There are governing councils in developing countries who have misrepresented, abused and exploited their own people for a long time." Some also mentioned the need to recognize group conflicts as well as affiliations. A final question asked was who would ensure that these criteria are met, and how. Is this, such respondents asked, a reasonable obligation to place on researchers?

Benefit Sharing and Remuneration

The design of Scenario C also permitted us to explore respondents' views on various types of benefit sharing arrangements. The options set forth in the scenario were shaped by combinations of three variables: (1) how closely was the benefit related to the study; (2) to whom did the benefit flow; and (3) was the benefit fixed or contingent? Although respondents generally were favorable to establishing some sort of benefit-sharing scheme, they manifested a striking lack of consensus not only in choosing the best option but also regarding the principles and arguments supporting those choices. Overall, the interviews revealed a preference toward group-based benefit sharing, that is "collective benefits" in light of the "collective" nature of the study, but many respondents were inclined to leave the choice of the best option to the community in question, especially "as an outsider," in the words of one respondent.

Challenges in Deciding What Is Owed to Participants and Communities

The difficulty in establishing a benefit-sharing scheme emerges from an examination of respondents' reasons for favoring or rejecting particular options. Some found it "inefficient" to try to tie the type or amount of benefits closely to the actual research:

> The general view is that people make a mistake in trying to link the benefits to a particular thing such as the nature of the study; it might be terribly inefficient to do so, it might be that the people could use the money [for] other things that would be of greater use . . . than just the genetic tests and that might be better for everybody.

For respondents who favored free provision of the genetic tests developed through the research (Option A), the principle of reciprocity was the predominant reason, that is, they saw this benefit as akin to the "therapeutic benefits" that are sometimes said to come to participants in clinical trials. Other respondents found this option "paltry," as one characterized it.

Sharing a percentage of profits (Option B) was in general a more favored choice, based on the principle of fairness and equity, although concerns were raised that monetary benefits could result in some form of exploitation. One respondent suggested adding developmental goals to benefit sharing: "Ideally what you would like to see is something that looks like capacity building as well as something that contributes to the health of the people."

Contingent Versus Guaranteed Benefits

Most respondents posited a distinction between sharing in the benefits produced by research and receiving a fixed compensation. They explained that a flat payment seems like direct remuneration for services, or like "purchasing your participants," which would bring into question whether the biological samples were being regarded as a commodity. By contrast, the sharing of actual benefits suggests that participants would gain in the same way as the investigators if the research succeeds. Although many liked contingency, others favored rewards that were more "here and now."

Still, most of the respondents opposed the option of fixed payments of US$800 to individuals, as described in the second part of Scenario C; once again, however, respondents' reasons for this conclusion varied markedly. Some said that people should never be paid for participation in this sort of research, some explaining that samples should always be freely donated. Others believe that people may be paid, but that US$800 was an excessive amount, smacking of over-reaching on the part of the investigators. As previously noted, some respondents thought the correct distinction was between benefits that are contingent and those that are fixed, for others the real distinction lay in appropriate benefits being those that are collective rather than individual; they rejected the US$800 payment because it was given to individuals.

The most extreme version of a contingent, collective benefit was Option D, the Governing Council's alternative—that the group should own all of the intellectual property. Through such ownership, it was assumed that the group could reap the rewards of any valuable discoveries based

on their genetic material. These respondents typically indicated that they saw the form of "benefit sharing" as less important than its goal, that is, to go beyond individuals and aim at helping the group as a whole:

> It [the precise benefit] is not relevant. What is important is that private companies share a percentage or a fixed amount with the society that has made the samples available. Whether a percentage or a fixed amount, I think it depends on the practical case and on the benefits that people expect. However, what is important and indispensable is that private companies share the benefits.

Need for a Fair Process

Many respondents also expressed the opinion that fair benefit-sharing lies not only in deciding on a specific scheme but also in deciding on its procedural aspects, such as how and with whom decisions regarding benefit-sharing should be taken:

> How do we know that this group is representative of the people who are participating in the project? On the other hand, I am also nervous about negotiating directly with individual participants because often they got cheated, they got exploited by these research teams or these biotech corporations or whatever. . . . How to make it in a way that there is fairness and justice and [there] is given [a] proper share of benefits to those who are participating in such research projects, I think it is a big ethical issue. . . . There is an ethical obligation of whoever is doing this to make sure that this is fair to the individual and not saying "you know the money, I don't care at the end who gets it."

CONCLUSIONS

This article describes the methodology and major findings from a collaborative study carried out by ethicists from WHO and the Universities of Geneva and Zurich over the past several years (Elger et al. 2008). Here, we share some results regarding four topics, relying principally on the views of the respondents in our international sample.

Several key lessons can be drawn from our findings and results. First, the interviews showed that the respondents' views on ownership of genetic samples and data are highly divergent and somewhat confused. Partly, this is due to difficulties with the concept of ownership; partly it is because of incompletely analyzed differences in the interests and objectives that "ownership" (versus "custodianship") are meant to serve. Nonetheless,

the practical consequences of the divergent and confused views is probably minimal since placing biobanks in a custodial rather than an ownership role is seen by most respondents not to produce significant practical differences, in terms of control exercised by participants once samples have been placed into a biobank and dispersed to researchers.

Second, the respondents generally regard MTAs as an effective and appropriate vehicle for ensuring responsible management of the samples and data entrusted to genetic repositories. Third, although respondents generally share a commitment to respecting group interests and abilities, this fact alone did not produce any consensus on the means to be used, such as group consultation or consent, for ensuring their respect, nor, finally, on what should be provided to the community or individuals by way of remuneration or shared benefits.

Our study was not intended to provide any normative guidance on the ethical or legal rules that should be used to govern genetic databases, whether at a national, regional, or international level. However, the findings of our study—which aims to deepen understanding of the ways in which the sometimes conflicting standards in international ethical guidelines for biobanks actually are understood by informed people around the world—generate potential implications for determining how genetic databases best may be governed in the future. In particular, we believe that our findings and analysis offer helpful insights into the following specific, key ethical issues:

(1) *Ownership of human biological samples held in biobanks*. "Classical" ownership by the biobank or by sample donors should be replaced by an umbrella concept under which the rights and obligations of the biobank, donors, researchers, and all other involved stakeholders are negotiated in the form of agreements for transfer and use of genetic material and data that take into account the differences between individual genetic data, aggregated data, and non-genomic data. The umbrella concept must include provisions under which sample donors can exercise a right to withdraw, whether this withdrawal implies destruction of samples and data or irreversible anonymization.

(2) *Regulation of researchers' use of samples obtained from biobanks*. The use of samples obtained from biobanks by third-party investigators must be regulated by agreements that confine researchers' activities within the scope of consent given by sample sources. Likewise, the range of permitted uses should reflect the degree of anonymization of samples and data that are made available to researchers. In light of the fact that

various arrangements are ethically and legally justified and that facilitating international collaboration is important, leading international organizations and research institutions not only must promulgate guidelines, but more importantly also must prepare and make available to the public model agreements that can serve as templates for collaborations between biobanks and investigators. Our study demonstrates the value that such model agreements would offer, since they could be used as a basis for institutions to improve their regulations and could contribute to the sort of international consistency that is unlikely to emerge from guidelines alone, given how differently our respondents see the relevant issues.

(3) *Collective consent*. Collective consent to genetic research can complement individual informed consent in a meaningful way if the research can be expected to have an impact not just on participating individuals but on the respective community as a whole—e.g., an ethnic group that might be stigmatized as a result of certain genetic features having been identified as widespread among this group. In other cases, although it is not a legal or ethical requirement, some form of group consultation is advisable when it offers a pragmatic advantage for researchers to get support for their study. Particular caution is required to make sure that collective consent or group consultation schemes do not pre-empt individual informed consent.

(4) *Benefit sharing and remuneration of research participants*. The requirement of benefit sharing has become widely accepted as a general idea although the means for its actual implementation has remained highly controversial. Although various options have been proposed, international collaborations may coexist with benefit sharing and remuneration arrangements that differ based on local circumstances. Benefit sharing and remuneration seem to rest on the principles of beneficence and of global justice, or some combination of the two. Thus, although few would conclude that research sponsors have a duty to provide remuneration or benefit sharing for individual participants who are "average" residents of Western, industrial democracies, both remuneration and benefit sharing should be considered when researchers use samples contributed to a biobank by participants from countries that are much less privileged than that of the research sponsor. At any rate, remuneration of individual donors should be avoided, as it may function as an undue inducement; instead, benefit-sharing arrangements should aim to help the groups that bear the burden of the research or are otherwise at risk of exploitation in the context of biobank research. Such arrangements, too, need to be scrutinized for their potential to act as inducements that might compromise leaders' commitment to protect the interests of individual study participants.

To summarize, studies such as the one reported here show the need for empirical work as a resource to assist national and international policymakers. In particular, such findings may be used to inform the framing of policies, principles, and practices applicable to biobanks; the drafting of guidelines; and the selection of measures that aim to foster greater international harmonization of legal rules, ethical norms, and technical standards.

NOTES

1. The study was organized by the Department of Ethics, Trade, Human Rights and Health Law (ETH) at the World Health Organization (WHO) headquarters in Geneva (Alexander M. Capron with Nikola Biller-Andorno, assisted by Agomoni Ganguli) and the Institute of Biomedical Ethics at the University of Geneva (Alexandre Mauron with Bernice Elger and Andrea Boggio), with support from the Geneva International Academic Network (GIAN). Subsequently, the Institute of Biomedical Ethics at the University of Zurich collaborated on completing the study when Nikola Biller-Andorno took up the ethics chair there and Agomoni Ganguli became a graduate student. The work described here is the joint product of all of these investigators, and a fuller account appears in Elger et al. (2008). The study does not aim directly to provide normative guidance on the part of WHO, and nothing in this report should be taken as representing WHO policy.
2. The Human Development Index (HDI) is the statistical measure used by the United Nations Development Program to rank UN member states in its annual Human Development Reports. Broadly speaking, the HDI measures well-being, taking into account such factors as life expectancy, literacy, education, and standard of living.
3. A MTA is a contract that may be used to govern the transfer of research materials—samples and data—between biobanks and researchers. MTAs set forth the terms for giving researchers access to biological specimens and associated information. They typically define the rights and responsibilities of both parties with respect to the materials and any derivatives.
4. This part of the scenario continued with a further elaboration, which we do not discuss here: "The representative of the colon cancer patients proposes the addition of a provision under which investigators agree not to exercise any rights they may have to patent a gene sequence." We then asked respondents what they thought of this proposal.
5. Phenotype refers to an organism's observable outward attributes, or its physical, biochemical, or physiological appearance.

APPENDIX: EXCERPT FROM THE INTERVIEW GUIDE
(FOR SCENARIO C.2, WHICH APPEARS IN THE TEXT AT P. 113)

Do you think Biotech Incorporated must first obtain permission from the Governing Council or may it approach individual members of the group directly without prior collective permission?

a. A collective permission is necessary

b. Individual consent without prior collective permission is acceptable

Why?

If the respondent answers that collective permission is NOT required, go to question 4.

If the respondent has answered that prior collective permission is required, ask questions 2–3:

Each individual's characteristics allow him/her to be placed in different groups. Do you think prior collective permission would apply to all such groups or only to groups with specific characteristics?

I will read you a list of characteristics that could require prior collective permission. Among the following, which one or ones do you feel is or are relevant, if any?

a. The members of a group that has chosen to have a formal structure, with leaders.

b. Traditionally, the group takes collective decisions on issues that affect the whole group.

c. The group is economically disadvantaged.

d. The group is identifiable and the research results may be thought to apply to the group generally.

e. The group is ethnically distinctive.

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