

DNA sampling and informed consent

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Standard consent forms for blood and tissue sampling are inadequate for DNA sampling. However, creating new and separate forms for each type of activity associated with DNA analysis (banking, linkage analysis and genetic diagnosis) tends to dissociate the participant from what is essentially a medical continuum. Furthermore, DNA sampling involves the sharing of samples and data among centres. To ensure patient control throughout this multifaceted process, we have developed an integrated approach to obtaining consent for DNA sampling at each level of participation. Movement from one level to another is reflected in the choices offered to participants. This inclusive approach is based on the underlying principle of informed consent, namely the respect for individuality, confidentiality and freedom of choice. This approach should help practitioners of medical genetics recognize the medical context of DNA sampling.

Les formulaires utilisés couramment pour le consentement aux prélèvements de sang ou de tissu ne conviennent pas à ceux qu'on fait pour l'analyse de l'ADN. Mais l'établissement d'un formulaire distinct pour chacune des facettes de celle-ci (mise en banque, étude des liaisons géniques, diagnostic génétique) donnerait au sujet l'impression qu'on le fait passer par un processus inhabituel en médecine. De plus, cette technologie comporte l'échange d'échantillons et de données d'un laboratoire à l'autre. Afin de respecter le droit du sujet de décider de toutes ces modalités, nous proposons une manière inté-

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grée d'obtenir son assentiment à chaque étape, où il soit à même d'exercer son choix quant au passage d'un stade à un autre. On croit observer ainsi le principe du consentement éclairé fondé sur le respect de l'individu, le secret et la liberté de choix et permettre au généticien de mieux replacer cette technologie dans le cadre de la pratique médicale.

On July 21, 1988, the Court of Appeal of California, regarding John Moore vs. the Regents of the University of California, concluded that "plaintiff's allegation of a property right in his own tissues is sufficient as a matter of law".¹ The majority of the judges held that a patient's "cells and genes are a part of his person".¹ With this holding began a new era of medical practice.

The Moore decision concerned the unauthorized conversion of the plaintiff's cells for commercial use, the fundamental issue being a patient's right to the control of his or her own body. This decision has become a landmark in property rights and has affected the practice of obtaining consent for the use of genetic material (such as DNA) for diagnosis and banking.

On Dec. 8, 1988, the Supreme Court of Canada, in the case of the Queen vs. Dymnt,² held that the use of a blood sample taken from an unconscious patient to provide evidence of impaired driving constituted an unlawful seizure, as postulated by section 8 of the Canadian Charter of Rights and Freedoms. The court maintained that the "use of a person's body without his consent to obtain information about him invades an area of privacy essential to the maintenance of his human dignity". This judgement is directly relevant to DNA sampling.

Recent advances in DNA technology and molecular biology have made the diagnosis of hereditary diseases possible through direct gene probing and indirect linkage analysis.³ These new approaches have opened up the possibility of individual risk prediction before any clinical mani-

festations of a disease develop, of accurate identification in paternity cases and forensic medicine, and of familial and population-based genetic epidemiology. Although direct gene identification can specifically detect the presence of a mutant gene, markers of restriction fragment length polymorphism (RFLP), found by indirect linkage analysis, can imply only the probability of such an occurrence.

Risk prediction in individual and familial studies, especially of late-onset and low-expressivity disorders, has created a particular context of participation and consent depending on the methods used, especially in the absence of specific treatment. The identification of a mutant gene, through direct or indirect means, does not imply a definitive clinical prognosis for all diseases, because phenotypic expression depends on interactions with both the genetic background and the environment. "The gene is not the disease."⁴

As probes and markers appear and as the gene map is refined, a person's status in provisional DNA banking or in initial clinical research may rapidly change from participant to potential patient.

The collaborative aspect of the search for chromosomal location and linkage groups involving rare hereditary disorders places new responsibilities on the parties involved. The isolation and characterization of markers require highly specialized laboratory resources and may sometimes result in the development of a hierarchical international system of referral of DNA samples. Within such a collaborative system responsibilities of the DNA bank, the diagnostic laboratory, the research centre, the physician and the potential patient will have to be redefined according to the principle of reciprocity. In medicine this principle upholding autonomy of the will and consensualism has always been the foundation of the physician-patient relationship.

We believe that DNA sampling is more than a technical procedure. It is primarily a medical act that involves the confidential examination of a person's genetic structure and thus the creation of a physician-patient bond, with all the obligations and protections such a bond entails. Even if the resultant information is spread, through layered collaborative research, the primary medical responsibility remains with the initial collecting centre and its representatives.

In this article we examine the current practice of obtaining consent for DNA banking, diagnostic research and services. We reaffirm the basic principle of reciprocity underlying the consent requirement and then provide a specific and integrated approach to obtaining informed consent.

Consent forms for blood and tissue sampling

The requirement of informed consent is based on respect for the inviolability and integrity of the

human being. Informed consent must be obtained before the administration of any medical treatment, except in emergencies or situations in which the patient is incapable of expression. Research projects are subject to even more stringent conditions of communication of risk.⁵ Traditionally this referred to risks of physical harm; however, today genetic research implies the possibility of psychologic and social prejudices, which might ultimately affect the rights and freedoms of the participant and his or her family.

Little attention has been paid to the innocuous consent forms for routine blood and tissue sampling commonly used in most medical centres. The wording of those forms is usually general and open, and permission is given to use, conserve and destroy samples, depending on the needs of the clinical laboratory, without patient notification. Indeed, by surveying 20 Canadian and US genetics centres we found that, unlike the consent forms for drug and product testing, transplantation and device implantation, genetic screening and testing, and clinical trials, most DNA sampling forms pay little or no attention to the specificity of consent in research into genetic risk determination. However, reflective discussions have begun, as demonstrated in the statement of the American Society of Human Genetics Ad Hoc Committee on DNA Technology.⁶

Modified consent forms have been designed that attempt to apply old approaches to new problems. From the most general and open-ended approach of clinical laboratories to the more complex, technical, legal and protectionist approaches of DNA banking, common principles concerning individual rights and familial and societal obligations are absent. Most of the forms only briefly describe the technology or the design and goals of the research project and provide little information on the phases of the study or on how the findings will be used. Rarely are subjects informed of the short-term and long-term implications of sampling. Indeed, in most cases there is no provision for mandatory notification and participation at each step of the sampling process (banking, diagnosis and research). Thus, the basic paradigm of genetic individuality is neither expressed in nor integrated into the consent forms currently used for DNA sampling.

Consent forms for DNA sampling

Basic principles

Regardless of specific disease-oriented research or clinical service, all consent forms related to genetic molecular diagnosis should respect three basic principles: individuality, confidentiality and freedom of choice. These principles constitute a solid basis for shared responsibility and patient participation in genetic medicine.

To apply these principles in research or clini-

cal situations, first a clear and simple statement should be made of the goals, objectives, accuracy (including the probability of error), significance and limits of the project as it relates to the disease and the availability of treatment if diagnosis is possible. If applicable, the statement should indicate the need for correct and exact paternity attribution, which is necessary for some molecular familial analyses. Above all the patient should be informed that gene identification is not necessarily synonymous with disease manifestation.

Second, the form must include a description of the method and the facilities used for DNA sampling, the site and the schedule for banking and testing, the minimal risks, the eventuality of repeat testing and the possibility of collaborative research.

Third, in genetic research into mendelian patterns of risk, the need to complete a questionnaire on family history must be fully explained. This does not constitute a surrogate mandate for the researcher to contact third parties named therein. Since respect for confidentiality is paramount, all contact should remain at the proband's discretion.

Fourth, the consent form should provide a specific explanation of and separate choice for participation in DNA banking or testing, communication of results to the patient (who then may authorize disclosure to others), transformation of cells and transfer of DNA to collaborative centres for research. It should be stated that counselling is available to help patients decide on these options.

Fifth, in all cases the statement must assure the patient that individual identification will remain confidential and that if there is sharing of data and samples the information will be coded.

Finally, the form should explicitly state that withdrawal from a research project or banking is possible at any time and will not affect the subject's future access to improved clinical diagnosis, new genetic information or increased benefits of treatment. However, the patient should be informed of the effect of withdrawal on the possibility of clinical diagnosis or treatment.

Application of the principles

The six basic principles of our general proposal constitute the basis of any consent form for DNA sampling. There are two possible approaches to the development of such forms. One would be individualized and fragmented according to the disease and the method of sampling; a separate form would be used for direct gene probing, RFLP marker testing, DNA banking and each disease-related research interest or possible diagnosis.

Because the form pertains to one person, whose status may change over time, our global approach would integrate all aspects of DNA sampling; the person would then be informed of the range of available techniques and their limits as well as the eventual goal of precise diagnosis of hereditary diseases. This person may be the pro-

band, a relative contacted by the proband, a patient, a carrier or a control subject. Such an all-inclusive form necessitates counselling to prevent anxiety, confusion and misunderstanding.

To illustrate how the basic principles can be applied to DNA sampling we reviewed their specificity at each of the three levels of participation before integrating the levels into one model consent form.

Direct gene probing: As of 1988 direct gene probing was available for only about 40 diseases; these included thalassemia, X-chromosome-linked muscular dystrophy, amyloidosis, chronic granulomatosis, Lesch-Nyhan syndrome and retinoblastoma. This group of diseases is expected to grow exponentially in the coming years, since the ultimate goal of clinical molecular biology is to understand the specific genic mutations responsible for a given phenotype. If such mutations could be attributed to specific ethnic or founder-effect populations, genetic screening programs might even be possible.

The status (e.g., third-party informant, carrier, patient for prenatal diagnosis and control subject) of the person giving consent in relation to the proband and to the primary disease should be clear. The consent form should describe in a concise but precise manner the primary disease for which the test is offered, the known states of prognosis, the treatments and the risks related to the phenotypes. The language should be ordinary and understandable.

The form should explain that blood (or tissue) sampling may have to be repeated for technical reasons and that the risks associated with the sampling procedure are minimal.

The person should be given the option of not being informed of the results and of refusing to allow other laboratories to use the samples. If extended family screening is being done the form should state that DNA testing may determine correct paternity either for the subject or for his or her relatives, regardless of how distant they are in the pedigree. Such information can be obtained only if relevant to the area of specified consent.

The subject should also be informed of the policy of the testing centre concerning the confidentiality of results, nominative files and information databases, and the availability of genetic counselling services.

RFLP markers: Most hereditary diseases amenable to molecular diagnosis rely on closely linked anonymous markers by means of which the risk for carrying a deleterious gene can be calculated. The long-term goal in using these markers is to sequence the gene locus and obtain a specific gene probe. The precision of the risk calculation depends on the proximity of the markers to the gene locus. Because of structural constraints on the minimum length for recombinant events in chromosomes, the presence of "flanking" markers on each side of the prospective gene may yield a highly predictive value for its presence.

In addition to the elements and choices we have described in the case of direct gene probing, the consent form should include the specific characteristics of indirect linkage analysis. This would involve stating that information will be expressed as risk, as probabilities of the presence or exclusion of the predisposition, especially in instances of late-onset and variably expressive diseases or if no treatment is available.

Over time the isolation of additional flanking markers will yield more specific information. The consent form must therefore express the probability of changes in diagnosis or exclusion. At the outset the subject could agree to the use of all markers that might become available. The discovery of such markers will reduce the probability of incorrect diagnosis inherent in linkage analysis or will lead to the development of direct gene probes. However, the person may wish to renew his or her consent each time a new set of markers is identified.

In all cases the person should be informed of the possibility of repeat sampling for technical or scientific reasons, such as an insufficient amount of DNA, unsuccessful amplification methods and unestablished lymphoblastic lines.

Unlike direct gene probing the expertise may not be centred in any one laboratory in linked RFLP analysis. Thus, DNA may have to be exchanged or transferred between centres. This possibility should be stated in the consent form, as should the option to refuse such transfer.

The discovery of the disease locus on a syntenic group (a particular chromosome) implies that the DNA deposited for research into a specific disease may be used to refine linkage maps and eventually may be in a risk relation with other diseases of which the patient has not been informed. Again, such uses and an agreement to inform the person of the results should be indicated on the form for each disease. Collaborative research centres should be notified by the principal investigator about these consents, restrictions and choices.

Risk probabilities associated with RFLP markers must be explained to the patient through available genetic counselling. In addition, this consultation helps to explain the natural history of the disease, from gene predisposition to clinical manifestation, or a diagnosis of exclusion.⁷

DNA banking: No localization on syntenic groups or linkage maps are available yet for many familial and hereditary diseases. Some of these diseases may not even be considered hereditary, but because they are occasionally encountered in a familial distribution they may be studied for major genes of susceptibility for which markers will be developed.

Laboratories involved in determining the cause of these diseases and in identifying affected people or their relatives may want to store DNA for future research or for eventual diagnosis should gene probes or RFLP markers become available.

This is especially true if patients with late-onset disease die and are thus not available when a pedigree analysis is done. People with such diseases as Huntington's chorea⁸ and Alzheimer's disease are candidates for DNA banking.

In the DNA banking contract there are reciprocal obligations on the part of both the bank and the donor. On the one hand, because DNA banking is one of the first steps toward the long-term goal of developing gene probes or markers, the bank should clearly state the conditions and the duration of maintenance (as well as any cost involved) and the eventual use of the DNA. The bank may also describe its policy of using the DNA for family studies related to the initial reason for consent if authorization is unobtainable because the donor has died or has not provided a current address. A policy of coded exchange of DNA with other laboratories for specific research or with other DNA banks for building a big enough sampling of families should be mentioned. On the other hand, the donor must inform the bank of any change of address and must accept or reject the bank's conditions.

In population genetics the determination of polymorphic frequencies of RFLP markers may occasionally result in DNA banking for reference pedigrees. Repeated sampling may be necessary if the number of markers increases or if lymphocytic samples have not been transformed. Again, it must be stated that such molecular analysis may imply testing for paternity. The measurement of such polymorphic frequencies may be useful in populations in which there is a founder effect and in which these frequencies are used as more precise measurements in mathematical calculations of risk. Although at first participation is not based on the presence of disease, the status of control subject may change to that of carrier or potential patient as more and more markers are found. In this case the bank, which is the beneficiary of the data obtained, must inform the participant of any change in status if the person so desires.

Integrated consent form for DNA sampling

We have provided an example of an integrated consent form (Fig. 1) that we hope will serve as a model for genetics centres in producing forms specific to their needs or the conditions of DNA sampling.

Conclusions

DNA sampling and banking are useful and necessary in the practice of certain aspects of genetic medicine. These procedures cannot be considered routine, because they provide the most unique identifying information about a person. Moreover, the possibility of predicting risk, especially for late-onset and low-expressivity disorders,

Patient's name: _____

Code no.: _____

Address: _____

Status (proband, relative contacted by proband [name], patient, carrier or control subject): _____

Consent to DNA sampling for (disease) (control)

This disease manifests itself in the form of (symptoms, condition of expression, phenotype, prognosis — to be completed by the genetics centre).

In relation to this particular disease and if the family structure is informative, the accuracy of the proposed test varies between ___% and ___% according to current diagnostic methods; the accuracy rate may improve over time. The test may give a definite diagnosis/risk/no diagnosis of (disease). I understand that with the use of genetic markers this test may not be informative because of the unavailability of blood/tissue from crucial family members. I do (do not) wish to renew my consent whenever more accurate markers for this disease become available.

The test is limited to studying the (disease) gene/marker or for control. Effective/palliative treatment is (is not) available at this time (to be completed by the genetics centre).

I understand that any information identifying me will be kept confidential and that any exchange of samples or information will be coded. I realize that DNA analysis may yield information on paternity status in the family study. I agree to provide a family history to the best of my knowledge. I also understand that, if necessary, contacting of informative members of my family for information/DNA sampling/DNA banking remains at my discretion. In the case of diagnosis or research I may decide on obtaining the results whether or not I agree to family members or other people, such as (physician), having access to the genetic information pertaining to me.

I, _____, do (do not) agree to give (amount) of blood/tissue for DNA extraction for the purpose of (disease) diagnosis/research/storage. I understand that the procedure involves the usual minimal risks (description of inherent risks of sampling methods [e.g., blood collection, skin biopsy, chorionic villus sampling and amniocentesis] — to be completed by the genetics centre) attributed to sampling. The procedure may have to be repeated in the absence of results or if the results are inconclusive. The test itself will take place at (location). My DNA will be stored at (location) in the form of extracted DNA or cellular lines. I understand that it will be used for family studies of (disease) (to be completed by the genetics centre). DNA analysis for individual or family studies will be done at (location). I do (do not) agree to the use of my DNA in collaborative research into this disease with other laboratories under the condition of maintaining confidentiality.

I do (do not) agree to the use of my DNA for the testing of gene probes/markers in other diseases (involving coded transfer of my DNA to other centres — to be completed by the genetics centre). In agreeing, I do (do not) want to be informed of the results of such research.

I understand that counselling is available if I request it. I also understand that I may withdraw from the study at any time without prejudice to my receiving adequate medical care and information and that I have been fully informed of the consequences.

I understand that if I have given DNA for any of the reasons stated above it is my responsibility to inform (name of centre) of any change of address. To obtain my renewed consent the centre is obliged to inform me, according to the authorization indicated, of the results, any change in my (banking/marker/gene) status, any changes in policy, the inability to maintain the quality of the sample and any possible treatment. My failure to inform the centre of any change of address means that the present informed consent and the authorizations indicated therein will remain valid and final until I indicate otherwise. In the case of DNA banking the centre must respect any time limits and fulfil conditions as herein agreed upon.

(Signature of patient or legal guardian)

(Date)

(Signature of centre's representative)

(Date)

----- Cut line -----

CHANGE OF ADDRESS FORM

Old address: _____

Address of centre: _____

New address: _____

Date blood/tissue sample received by centre for DNA sampling/banking: _____

Date of move: _____

(Signature of patient or legal guardian)

(Date)

Fig. 1 — Example of integrated consent form for DNA sampling or banking.

in individual and familial studies creates a special situation of participation and consent. We believe that DNA sampling is primarily a medical act.

Specialization and scientific accuracy require that DNA samples sometimes be analysed by different research centres over various periods. Individual choices at each step of the process are not necessarily cumbersome or a hindrance to scientific attainment; indeed, they may allow for multifaceted testing for other familial disorders or even for research in other areas, such as genomics.

Each genetics centre should modify the consent form to reflect its specific services and include information that is deemed necessary for participant understanding.

Such an integrated approach to obtaining informed consent for DNA sampling assures a solid basis for shared responsibility and patient participation in the practice of genetic medicine.

References

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2. *The Queen vs. Dymont*, SCC, Dec 8, 1988 (unpublished): 3
3. Cooper DN, Schmidtke J: Diagnosis of genetic disease using recombinant DNA. *Hum Genet [Suppl]* 1987; 77: 66-75
4. Lappé M: The limits of genetic inquiry. *Hastings Cent Rep* 1987; 17: 5-10
5. *Guidelines on Research Involving Human Subjects*, Medical Research Council of Canada, Ottawa, 1987: 21-24
6. Ad Hoc Committee on DNA Technology, American Society of Human Genetics: DNA banking and DNA analysis: points to consider. *Am J Hum Genet* 1988; 42: 781-783
7. Holtzman N: Recombinant DNA technology, genetic tests, and public policy. *Ibid*: 624-632
8. Meissen GJ, Myer RH, Mastromauro CA et al: Predictive testing for Huntington's disease with use of a linked DNA marker. *N Engl J Med* 1988; 318: 535-542

Upcoming Meetings continued from page 1022

Sept. 18, 1989: Hepatic Surgery: New Anatomy, New Techniques
Sunnybrook Medical Centre, Toronto
Continuing Medical Education, Faculty of Medicine,
Medical Sciences Building, University of Toronto,
Toronto, Ont. M5S 1A8; (416) 978-2718

Sept. 18-22, 1989: Canadian Society of Forensic Science
Annual Conference
Edmonton Inn
Canadian Society of Forensic Science, 215-2660
Southvale Cres., Ottawa, Ont. K1B 4W6;
(613) 731-2096

Sept. 20-22, 1989: National Conference on Mental
Health — Community Reinvestment: Canada's
Challenge for the 90s
Holiday Inn, City Centre Tower, London, Ont.
Kelly McKinley, conference coordinator, CMHA
London/Middlesex Branch, 355 Princess Ave.,
London, Ont. N6B 2A7; (519) 434-9178

Sept. 22-24, 1989: Pharmacy Association of Nova Scotia
and the Nova Scotia Pharmaceutical Society Annual
General Meeting and Conference
Holiday Inn Dartmouth, Dartmouth, NS
Patrick King, PO Box 3214(S), 1526 Dresden Row,
Halifax, NS B3J 3H5; (902) 422-9583

Sept. 22-25, 1989: Royal College of Physicians and
Surgeons of Canada and Canadian Society for
Clinical Investigation Annual Meeting
Edmonton Convention Centre
Mrs. Anna Lee Chabot, annual meeting coordinator,
Royal College of Physicians and Surgeons of Canada,

74 Stanley St., Ottawa, Ont. K1M 1P4;
(613) 746-8177, FAX (613) 746-8833

Oct. 11-14, 1989: 4th International Course on
Therapeutic Endoscopy
Four Seasons Hotel, Toronto
Dr. Norman E. Marcon, course director, 121 Jones Bldg.,
Wellesley Hospital, 160 Wellesley St. E, Toronto,
Ont. M4Y 1J3; (416) 926-7763

Oct. 22-25, 1989: 3rd National Palliative Care
Conference: Meeting the Challenge
Royal York Hotel, Toronto
Nancy Velluso, project coordinator, Conference and
Seminar Services, Humber College, 205 Humber
College Blvd., Etobicoke, Ont. M9W 5L7;
(416) 675-5077, FAX (416) 675-0135

Dec. 11-15, 1989: International Conference on General
Hospital Psychiatry
Hyatt Regency Cerromar Beach Resort Hotel, San Juan,
Puerto Rico
Dr. Edgardo Pérez, c/o Joan Bradden, Department of
Psychiatry, Ottawa Civic Hospital, 1053 Carling Ave.,
Ottawa, Ont. K1Y 4E9; (613) 725-4787

Feb. 4-9, 1990: Biennial Western Conference on
Anesthesiology: Clinical Update
Stouffer's Wailea Beach Resort, Maui, Hawaii
Dr. Murray G. Atnikov, M2A-601 W Broadway,
Vancouver, BC V5Z 4C2; (604) 874-5291

Sept. 22-28, 1990: 23rd International Congress on
Occupational Health: Sharing Solutions
Montreal Convention Centre
Secretariat, 23rd International Congress on Occupational
Health, 2-58 de Brésoles St., Montreal, PQ H2Y 1V5;
(514) 499-9835, FAX (514) 288-4627