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ARTICLE

Patient/family views on data sharing in rare diseases: study in the European LeukoTreat project

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The purpose of this study was to explore patient and family views on the sharing of their medical data in the context of compiling a European leukodystrophies database. A survey questionnaire was delivered with help from referral centers and the European Leukodystrophies Association, and the questionnaires returned were both quantitatively and qualitatively analyzed. This study found that patients/families were strongly in favor of participating. Patients/families hold great hope and trust in the development of this type of research. They have a strong need for information and transparency on database governance, the conditions framing access to data, all research conducted, partnerships with the pharmaceutical industry, and they also need access to results. Our findings bring ethics-driven arguments for a process combining initial broad consent with ongoing information. On both, we propose key item-deliverables to database participants.
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INTRODUCTION

There is growing recognition of the value of collecting and sharing data on a globalized scale, particularly in the context of rare diseases where research on health records from the largest number of patients is crucial. The European Commission has recommended gathering national expertise predicated on the strategic importance of patients' registries in the field of rare diseases.[1,2] One of the objectives of the EU LeukoTreat program (2010–2014) was to gather clinical and biological data on patients with leukodystrophies (LDs). LDs are a group of rare genetically inherited neurodegenerative diseases of the white matter and its main component, myelin. More than 20 different types of LDs have been identified which can be inherited in a recessive, dominant, or X-linked manner, depending on the type, gene involved, and mutation. LDs predominantly affect young children but can also hit adults, causing cognitive deficits and potential loss of autonomy. Prevalence is approximately 1 in 10 000 of the population, with around 1000 new cases reported every year in Europe. Despite great strides in terms of advances in each individual LD, there is currently still no curative therapy.[3,4]

The aim of the LeukoDataBase is to foster epidemiological research, help develop therapeutic approaches, and facilitate recruitment in clinical trials. The referring clinical centers gather socio-demographic and medical data extracted from patient records, including biological, genetic analyses, and cognitive evaluations. The use of personal health information in research changes the perception of ethical regulations to protect human subjects. Here, the integrity of the body is less a concern than in clinical trials, but the concept of protection of human subjects has to factor in issues such as privacy, conditions of access to the data, consent, and information.[5] In 1995, the EU Data Protection Directive restricted access to data unless consent had been obtained from the subject, with exceptions made in cases of health-related research in the public interest.[6] At international level, ethical frameworks need to be established across national borders to allow large-scale data sharing, particularly in rare diseases where data need to be collected from patients in different countries. In 2012, the EU proposed a legal framework on the protection of personal data[7] to strengthen individual rights in a wider context of rapid technological progress and globalization. Experts are also working to establish general principles and tools to reach a consensus on promoting ethical regulation at international level.[8–10] The principles of information and initial consent have gained consensus, but there is ongoing debate over the information content.[11] The challenge is to determine what kind of consent would cover future research and what changes in research orientations would require fresh consent.

The aim of this study was to optimize the information and consent process to meet participants' expectations against the background of the LeukoTreat project database. A survey questionnaire was used to explore patient/family motivations and reluctances to share health data at European level. This approach was carried out in synergy with ethical management of the project[12] to better integrate the wishes of patients, particularly in terms of information and conditions of participation.

MATERIALS AND METHODS

Survey design

Given the characteristics of LDs, the questionnaire was issued to patients and their close relatives. It was built by a panel of experts from medical pediatric genetics, psychology, medical ethics, and patient associations. The questionnaire

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was composed of close-ended questions, most of which included the options for adding comments. The questionnaire was first tested during the European Leukodystrophies Association (ELA) Families/Scientists meeting in Paris in 2011. Analysis of the 55 questionnaires returned guided the construction of the final revised version, which was translated (by A-T-T, Clermont-Ferrand, France) into English, Spanish, Italian, and German.

An information document inviting persons to participate in the study described (i) the goal of the research, (ii) the LeukoTreat partners in charge of the survey, (iii) the way participants can gain access to results, and (iv) the fact that the survey is completely anonymous. None of the questions led to potentially identifying elements in responses. Questionnaire, information document, and survey delivery process were all validated by the Ethics Committee in charge of the project.

Survey distribution and delivery

Information document and questionnaire were distributed in the different countries *via* two vectors:

- *Via* the ELA network: in France, directly to patient and relatives during the ELA Families/Scientists annual meeting in 2012; outside France, *via* referral partners met or contacted by mail to explain the objectives of the survey and facilitate survey distribution and delivery.
- *Via* referral clinical centers in France and in countries of LeukoTreat partners. A contact person was identified in each center.

The number of questionnaires to be distributed was evaluated with input from ELA and clinical-center contact persons, and that number was then sent out to them (with pre-paid return envelopes) for distribution. A total 250 questionnaires were delivered in France, 100 in Germany and Italy, and 50 in Belgium and Spain.

Survey analysis

Survey data were entered into an Excel spreadsheet. Results were expressed in percentages. All participant comments were listed; here, we cite the most representative ones to better specify the answers given and the arguments for and against.

RESULTS

In total, 195 questionnaires were returned: 149 from relatives (96 mothers, 43 fathers, 10 close relatives) and 46 from patients. Despite a significant difference in the number of answers from these two groups, the choice was made to analyze them separately. In contrast, the significant difference in numbers of answers from each country (130 from France (23 patients) *vs* 24 from Italy (2 patients), 9 from Belgium (2 patients), 6 from Spain (1 patient), 26 from Germany (18 patients)) ruled out per-country analysis.

Profile of respondents

The majority of respondents are in the 40–64 years age bracket (90/149 relatives and 31/46 patients) and have been aware of the diagnosed disease for over 5 years (83/149 relatives and 41/46 patients). Genetic diagnosis has been established in most cases (102/149 relatives and 45/46 patients). A majority of respondents belong to one or more patient organizations (98/149 relatives and 32/46 patients). In total, 66% of respondents all countries combined and 73% of respondents in France are members of a patient organization.

Table 1 Would you agree to participate in any research that collect data for leukodystrophies?

	Relatives n = *149 (%)*	*Patients* n = *46 (%)*
Yes	83.9	89.1
No	1.3	
Don't know	14.8	10.9

Participation in the database

As shown in Table 1, a majority of respondents would agree to participate in research that collects data for LDs. Nearly all spontaneous comments highlight that the main reason is to promote the advancement of research with the objectives to find a treatment, cure the disease, halt its progression, and advance its diagnosis. The importance of providing data for researchers is widely recognized: '*leukodystrophies are little-known diseases. Patients are key to advancing research by providing data to researchers*', '*the more information collected, the more it will promote advancement of research*', '*in a rare disease like this, maximum participation is required for effective research*'. The possibility to access clinical trials is occasionally mentioned.

Limits to participation include concerns over patient wellbeing and a desire to avoid practical disability-related difficulties: '*may tire the patient*', '*could lead to unnecessary further testing, sample-taking and painful examinations*', '*risk of distressing displacement linked to travel (more difficult if the disease progresses)*', '*to advance medical research provided it does not put added constraints on our son*', '*loss of precious time devoted to my child*'. Two parents expressed the fear that use of the data may be diverted from the primary objective. As shown in Table 2, seven out of the eight motivations proposed appear particularly important: for relatives it is 'to face up to the disease'; for patients it is a 'better understanding of how the disease progresses'.

Conditions of access for research purposes

Data security and confidentiality is an essential prerequisite to participation for 75.4% of respondents (107 relatives and 40 patients) (data not shown).

Access for researchers outside the project. A large majority of patients and relatives are in favor of opening access to the database to researchers not involved in the LeukoTreat project, whether for research on LDs or on other diseases (Table 3). Respondents highlight the following points: '*no objection if researchers pledge to respect a good practice charter*', '*sharing data with a lot of researchers in different countries is a plus to improve research*', '*the effort to combat the disease must be global, it will be stronger*', '*the disease has no frontier*', '*it is necessary to multiply, federate and pool research*'. Some express reservations: '*ensure confidentiality of international exchanges*', '*everything depends on the political orientations of the nations*', '*the rights of individuals should be respected*', and '*be attentive to financial issues*'.

Access for the pharmaceutical industry. A majority of respondents are in favor, a minority are against (Table 4). Those in unconditional favor point out that '*collaboration is necessary for the development of treatments*' and '*the only important thing is progress and hope for a better future*', but most respondents express reservations: '*on condition that, if treatment innovations are achieved through use of patient data, then the treatments will be accessible at affordable prices to all patients*', '*if anonymity is preserved*', '*if transparency is ensured*', '*if I am informed about the objectives and the results*', '*if the partnership is not driven by profit incentives only*', and '*the database should not become owned by the pharmaceutical industry*'. One respondent expressed strong opposition: '*If there is such a partnership, I refuse to participate in the database. The pharma industry orients research in their own interests, not in the interests of patients*'.

Conditions governing access by health professionals, patients, and relatives

A vast majority of relatives (95.9%) and patients (91.3%) are unconditionally in favor of opening access to their specialist physician

(data not shown)—the very few exceptions revealed bad patient–physician relationships. Opening access to the family doctor received a less favorable response rate (relatives 75.8%, patients 71.7%) (data not shown). Reasons cited by those in favor included '*for them to better understand the disease*', '*important for follow-up*', '*he/she assists the patient in everyday life, so it is essential*', and '*he/she can help us understand the scientific terms*'. Those expressing reservations state the lack of expertise on rare diseases or that '*when it comes to specific points, my doctor does not feel particularly concerned*'.

A majority (87%) of patients wish to have unconditional access to their own data (data not shown). Reasons cited include 'I am the one most involved', 'I have the right to know and to be informed about the evolution of the disease in order to organize my future', 'nothing must be hidden from the patient'. Those who express reservations (10.9%) set out the need for a psychological and educational approach (struggle to understand the data or to face up to it alone): 'depends on the nature of the data', 'who delivers it', or 'data are too complex, a health professional needs to give explanations'.

Length of data conservation

Most respondents think it justifiable to continue the storage and use of data after the patient's death (Table 5). Comments include '*very important for next generations*', '*data is precious as it is complicated to collect*', '*important not to destroy it*'. For several relatives, the use of data for science helps make sense of the patient's death. They state that '*the research timeframe is often longer than the life of a patient*', '*research must not stop*', '*destruction of the data would be a loss for research and we would be failing the deceased*', '*my child has died, I'll be happy to know that his data is a useful legacy for scientific advancement*', and '*destroy what was collected is very selfish*'. Some express conditions: '*that confidentiality is respected*', '*if my son has not objected previously*', '*if this question has been previously discussed*', '*if I gave prior consent*', '*illegitimate if the family has not been informed*'. One relative was opposed: '*I will struggle to deal with the fact that there are still things of my child that I do not control*'.

Patient involvement in data processing

Most participants would agree to enrich the database by self-entering data on daily life and follow-up parameters (Table 6), but a large proportion would prefer to do it with the help of a professional. More than 88% of relatives and 85% of patients would agree to enter the following types of data (data not shown): evolution of the disease, physical/psychological/behavioral changes, learning disabilities, feeding difficulties, treatment compliance and side effects, changes in pain, and quality of life. Motivations are: '*to support research*', '*to optimize knowledge of the day-to-day impact of the disease*', '*to enable studies of quality of life and to enrich the database*', '*to improve the quality of medical care*', '*because I know my child better than anyone*', '*inform about things that researchers would not have thought*', '*help collect daily data*'. Many underline the importance of participating in a collective

Table 2 Scores of the reasons for participating according to how important you rate the following items?

Important-Very important	*Relatives* n = *149 (%)*	*Patients* n = *46 (%)*
A better understanding of how the disease progresses (prognostic markers)	89.3	97.8
A better understanding of the disease causes	89.9	89.1
Access to clinical trials	82.6	78.3
Discoveries with therapeutic impact for you/your relative	91.3	91.3
Discoveries with no therapeutic impact for you/your relative	82.6	78.3
More efficient diagnostic tests (diagnostic markers)	91.3	82.6
To belong to a community	70.5	54.3
To face up to the disease	90.6	89.1

Table 3 Under certain conditions, researchers outside LeukoTreat may be able to access the database at their request. How do you feel about giving database access to outside researchers?

	Leukodystrophies		*Others diseases*	
For research on:	*Relatives* n = *149 (%)*	*Patients* n = *46 (%)*	*Relatives* n = *149 (%)*	*Patients* n = *46 (%)*
Without reservations	89.9	76.1	76.1	64.1
With reservations	5.4	10.9	10.9	10.9
Opposed	0.7	10.9	2.2	7.6

Table 4 Pharmaceutical industry partnership may develop diagnostic or therapeutic innovation and/or contribute to research funding. Would you agree to the use of your own, or your relative's data in such partnership?

	Relatives n = *149 (%)*	*Patients* n = *46 (%)*
Yes	61.1	65.2
No	6.7	13
Don't know	27.5	21.7

Table 5 The storage of data after patient death is controversial; in your opinion, the continued storage and use of the data and biological samples in this case is:

	Relatives n = *149 (%)*	*Patients* n = *46 (%)*
Justifiable	82.6	69.6
Wrong	2	2.2
Don't know	11.4	28.3

Table 6 Would you agree to enter your own data (or your relative's)?

	Relatives **n**=*149 (%)*	*Patients* **n**=*46 (%)*
Yes	94	91.3
No	2	2.2
Don't know	0.7	0
If yes	Relatives (%)	Patients (%)
On my own	55.7	43.5
With the health professional	35.6	47.8

approach '*to feel more of an actor in a human chain of solidarity*'. A few reservations emerged: '*if I am confident in the system collecting the data*', '*if my child agrees*' and '*depends what kind of data*'.

Database as a bridge to clinical trials

A strong motivation to participate in the database is access to clinical trials (see Table 2). In response to the question '*There are eligibility and ineligibility criteria governing participation in clinical trials; were you aware of this?*', 53% of relatives and 43.5% of patients said yes (data not shown). Answers to an open-ended question investigating the information they would like to receive about a clinical trial clearly show the desire to receive as much information as possible: '*to know everything in detail*', '*information throughout the trial*', '*to be informed about all the benefits and risks*', and the '*side effects and long-term effects*', '*to know the impact for health*'. They also want be informed about the organizational conditions: '*constraints*', '*conduct of the trial*'.

Asked whether patient organizations should have a role in the drafting and design of clinical trials (Table 7), 48.3% of relatives and 26.1% of patients answered yes. The comments partly explain the observed differences between relatives and patients' numbers of positive responses. Relatives see patient organizations in a support role: '*to ensure patient safety*', '*to ensure maximum transparency*', '*to help make information more understandable*', '*to provide elements that researchers do not necessarily think of*', '*to better account for the social and financial consequences of the trial*', '*to help with practical organization of the trial*', and '*to help embed the prerequisite condition of patient access to research results*'. Patients show more trust in research professionals because of their competence: '*it is important to clearly identify and segregate roles and responsibilities*', '*this is the work of medical scientists*', '*information is confidential and only concerns the medical profession and the patient, not the associations. Everyone in their place*'.

The research program included an Ethics Committee. What do you expect from it?

This open-ended question elicited a response from 122 respondents, and all emphasized its importance. For them, the role of such an ethics committee is to protect '*patients' rights over time and privacy*', '*ensure respect of confidentiality and secrecy*', '*ensure compliance with commitments*', '*respect for the Charter framing the database*', '*respect for the dignity and wishes of patients*', '*transparency on the use of data*'. Furthermore, it should '*avoid financial drift*'. At the same time, they insisted on the importance of '*not blocking the advancement of research*', and some expressed that the committee '*should listen to the problems and expectations of families*'.

Table 7 In your opinion, should patients' organizations have a role in the drafting and design of a clinical trial protocol?

	Relatives n = *149 (%)*	*Patients* n = *46 (%)*
Yes	48.3	26.1
No	17.4	30.4
Don't know	28.2	37

Table 8 What information would you like to receive from the Leukodatabase? (Several possible answers)

Expectation in terms of information	*Relatives* n = *149 (%)*	*Patients* n = *46 (%)*
On the possible evolution of the disease	87.2	93.5
On new research directions	73.8	67.4
On research results	89.9	93.5
On scientific publications related to research	66.4	58.7
On general information from the database (number of patients included, changes, etc.)	57.1	63

Need for information

Most respondents want information on research results and on the possible evolution of the disease (Table 8). To a lesser degree, they also want information on new research directions and general feedback on how the database is evolving and the scientific publications produced. Comments specify that they expect information on '*how the data are used*', '*what type of research stems from the database we are contributing to*', '*causes of the disease for undetermined leukodystrophies*', '*progression of the disease and impact for the future (potential deficits)*', '*links between leukodystrophies and other diseases*', '*existence of clinical trials and the type of leukodystrophy concerned*', '*advancement of therapeutic solutions*'.

DISCUSSION

This study explores the views of patients and their families affected by leukodystrophies in the setting of a European database.

Strong adhesion

A major result is that patients/families are strongly driven to participate in any research that collects data. Patient registries and databases are widely recognized as highly vital in the context of rare diseases, and health data collection is often an integrated functional process in centers of expertise where clinical care and research are intimately linked.[2,13] For patient organizations, the development of international databases and registries is a political priority.[14] Indeed, patients are aware that data sharing by the largest number at global level is the way to better understand their diseases and accelerate the research and development process. They are on the frontline in terms of facing up to the disease and the deficit of curative treatments. Motivation is also reflected by the fact that nearly all respondents would be willing to participate by self-populating the database with data on their daily life and evolution of their disease. They consider this type of data as highly relevant and complementary to data collected by doctors and researchers.

Their comments show the wish to be engaged in a collective struggle against the disease with an altruistic dimension of helping other patients, as already observed in other studies: participants know they are contributing to an enterprise that aims to improve the wider human condition rather than benefit individually.[15–17] For the

respondents in our study, participating in a database helps belong to a community. Being a subject of interest for researchers is also essential given the difficulties involved in access to care and the feeling of exclusion associated with a rare disease. All these points are felt even more sharply in the context of rare diseases.[18–20]

Data access: between trust and control

Respondents have a high level of trust in the constitution and use of the database by researchers. They trust professionals who jointly provide care and research missions, especially in the context of LDs where there is no real frontier between care and research.[12] However, respondents are vigilant over the conditions framing the constitution and use of the database. This is consistent with other studies showing that, for the general population, the existence of ethical principles and rules accompanying data sharing is recognized as indispensable.[20–23] Communication and transparency on the conditions governing data usage are key to effective collaboration and trust.[17,24]

Survey respondents want to be assured of compliance with initial commitments through the consent and information they receive. Every professional involved in the project is expected to adhere to the ethical principles accepted by all partners. Moreover, the respondents are sensitive to monitoring by an ethics committee, the existence of which appears essential. In LeukoTreat, all these points are developed in a dedicated ethical charter[12] signed by all partners. Any new research team wishing to access the database has to propose a scientific project to be evaluated by the program follow-up committee and commit to uphold the rules described in the charter. This principle was set in agreement with the ELA patient association. The alternative, if any, would be to request a specific patient consent—an approach that in practice would prove impossible at operational level. This information should be given to the patient at initial consent.

Regarding potential partnership with the pharmaceutical industry for access to the database, respondents tend to be more reserved or without opinion. Although they recognize that such a partnership is valuable for therapeutic advance, they demand guarantees and want to be informed of the scientific and medical purposes as well as the results of the research. They express major concerns over the issue of profit that would not benefit the patients. Indeed, it has been shown that the fact that biobanks or registries are run publicly is an important factor for trust, and that commercialization, private interests, and ownership issues can affect people's perceptions and willingness to participate.[6,25] In any such partnership, participants' rights and expectations must be properly integrated as conditions governing contract collaborations.[23] Patients and patient organizations should thus be given some kind of control over the partnership-framework conditions governing patient data management and access in rare diseases.[26]

Transparency on data storage and the length of data accessibility is also an issue. Most respondents agree on no time limitation, as they feel that the data are precious, especially in their context of rare disease. Storage even after a patient's death is viewed as legitimate as it contributes to the collective interest. This is in line with a recommendation from a European Commission expert group emphasizing that '*in the case of the overriding interest, even in the absence of consent given before death, their use could be legitimate: absence of consent should not be considered as equivalent to non-consent*'.[27] For greater transparency, we believe participants should be informed on this point at the time of initial consent in order to clarify the situation while empowering participants who are opposed to opt out. This procedure would allow participants to give consent specifically on this point (as wished by some respondents in this study).

Toward a broad and ongoing consent process?

In registries and databases, consent is always a challenging issue. As they are designed for the long term, governance elements and associated research projects may evolve over time. Various approaches to database consent have been discussed, and the question raised is how to conciliate respect for autonomy, particularly the right to withdraw at any time, with the impracticalities of repeatedly asking for fresh consent on each new research orientation. This approach is always complex, sometimes impossible, and potentially detrimental to rare disease patient and research communities.[28,29]

The traditional strictly specific consent used for medical research is designed for a specific study, for a clear period of time, and for defined investigators. This type of consent appears ill-suited to registries and has been hotly debated in biobank research.

The principle of blanket consent (ie, consent with no restrictions on future research) has been discussed in clinical practice[30] and in biobanking,[31] but some consider it hard to accept in terms of patient information, validity of consent over time, and the possibility to exercise the right to withdraw.[21,32]

An alternative is broad consent,[33] which makes it possible to promote the development of research in a large and pre-defined field, avoiding the need to re-consent. This model has been adopted by many current biobank projects. However, Master *et al*[34] reviewed the literature on populations' preferences for different types of consent to biobanking, and found very diverse patterns of consent between countries, prompting a call for vigilance as consent practices are part and parcel of participant trust. Broad consent needs to be devised to always consider borderline situations, which should require re-consent if necessary.[35,36] The question then becomes who is in charge of deciding whether or not participants need to be re-contacted for fresh consent? Hanson[24] and Steinbeck *et al*[35] tackled this issue by proposing to set up an independent ethics steering committee. On the basis of the patient expectations collected here, we advocate this procedure as it provides an independent decisional framework that can account for the views and standpoints of researchers, promoters, and patients' representatives alike. Finally, post-inclusion information is a major concern for patients and families, proving just as important as initial consent. Indeed, there is a growing body of evidence to show that participants want to be kept informed over time.[37]

In the ethical management of LeukoTreat, we propose to optimize broad consent with ongoing information and oversight by an ethics steering committee (Table 9). This process appears optimal for promoting research that respects participant choices and the ethical validity of consent over the longer term.

Table 9 Key information factors for database participants

Initial information for broad consent	*Ongoing information*
Nature of data collected and purposes of the database	Growth of the database
Data security and confidentiality	New research orientations
Length of storage with/without limit	Setting up clinical trials
Database ownership and governance	Research results
Conditions governing academic and pharma-industry partnerships	New partnerships (academic and/or pharma-industry)
Commitment to give ongoing information	Change in database ownership and governance
Existence of an ethics steering committee	

Limits of the study

The lack of enough respondents to establish sub-groups limited the study of potential differences between patients/families from different countries or the effects of factors that could influence point of view such as form, evolution and seriousness of the disease or socio-economic factors.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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