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Learning Health Systems

RESEARCH REPORT

Informed consent within a learning health system: A scoping review

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Abstract

Introduction: A major consideration for the implementation of a learning health system (LHS) is consent from participants to the use of their data for research purposes. The main objective of this paper was to identify in the literature which types of consent have been proposed for participation in research observational activities in a LHS. We were particularly interested in understanding which approaches were seen as most feasible and acceptable and in which context, in order to inform the development of a Quebec-based LHS.

Methods: Using a scoping review methodology, we searched scientific and legal databases as well as the gray literature using specific terms. Full-text articles were reviewed independently by two authors on the basis of the following concepts: (a) LHS and (b) approach to consent. The selected papers were imported in NVivo software for analysis in the light of a conceptual framework that distinguishes various, largely independent dimensions of consent.

Results: A total of 93 publications were analysed for this review. Several studies reach opposing conclusions concerning the best approach to consent within a LHS. However, in the light of the conceptual framework we developed, we found that many of these results are distorted by the conflation between various characteristics of consent. Thus, when these characteristics are distinguished, the results mainly suggest the prime importance of the communication process, by contrast to the scope of consent or the kind of action required by participants (opt-in/opt-out). We identified two models of consent that were especially relevant for our purpose: metaconsent and dynamic consent.

Conclusions: Our review shows the importance of distinguishing carefully the various features of the consent process. It also suggests that the metaconsent model is a valuable model within a LHS, as it addresses many of the issues raised with regards

to feasibility and acceptability. We propose to complement this model by adding the modalities of the information process to the dimensions relevant in the metaconsent process.

KEYWORDS

approaches to consent, health data research, learning health system, metaconsent

1 | INTRODUCTION

A learning health system (LHS) is a system in which research and clinical activities are intertwined. It involves—but is not limited to—the secondary use of clinical data for different activities including research (eg, retrospective studies and pragmatic, registry-based trials) and knowledge transfer (eg, audit, feedback, and decision support systems).[1] A LHS would be an important step for providing cost-effective, evidence-based, up-to-date health care.[2]

It is however not clear how patients should give consent for the secondary use of their clinical data for research. Various research activities in an LHS might require various kinds of consent. Indeed, different learning activities might imply different clinical benefits and risks for the participant and operate under different modalities.[3] For example, Lee et al[4] note that retrospective research, contrarily to prospective randomization of approved medical practices, "does not invol[ve] deviating from the care that patients would normally receive."

We conducted a scoping review to identify, in the literature, which types of consent have been proposed for participation in research activities in a LHS. This review was conducted with the purpose of informing key stakeholders on how best to implement a consent process in a LHS that will be developed in Quebec, Canada, named the "Learning Health and Social Services Research Platform" ("*Plateforme apprenante pour la recherche en santé et services sociaux au Québec*" in French, abbreviated "PARS[3]"[5]). The platform aims at supporting the development and execution of research and knowledge transfer projects. To achieve this, the platform relies on a clinical ontological model supporting semantic interoperability across various data systems.

We analysed the literature through a unified conceptual framework that distinguishes the characteristics of the consent process that are proposed for different types of research activities in the relevant literature. Indeed, several terms are used for similar but not identical concepts, depending on the context. For example, do the terms "broad consent," "blanket consent," and "open consent" refer to the same construct? Can both opt-in and opt-out be combined with specific or broad consent, and do they imply a specific way to inform the participants? Clarifications in terminology are crucial for the understanding and development of a shared perspective on consent within a LHS. They would also enable to determine better which aspect of the consent process is responsible for variation in acceptability.

2 | METHODS

We addressed our research objectives by performing a scoping review, following the methodology framework in the five stages proposed by Arksey and O'Malley.[6] Our aim was to obtain a large spectrum of articles, from original research to opinion papers as well as law articles and workshop reports. The research question was convened within a team composed by an expert in LHS (J.F.E.), a stakeholder in research ethics (A.C.), an expert in ethics and philosophy of science (A.B.), and an independent methodology expert. Our research questions were the following: what are the important characteristics of the informed consent process for participation to research activities in a LHS? Which of those approaches are considered as ethically acceptable according to the literature, for which LHS research activities and in which context? To answer this, we had to define first "research activities" in a LHS and to decide on a search strategy.

Research in a LHS can include both observational (record-based) studies and interventional studies such as the so-called "pragmatic" clinical trials or cluster randomization studies (in which sites, such as hospitals or services, may be randomized to two acceptable and currently used clinical interventions).* However, we limited our scoping review to observational studies since the first application of the Quebec LHS will concern such studies. We also do not distinguish between "research" and "quality improvement" (QI).

An extensive literature search was performed in May 2017 in several databases: Medline (through PubMed), Scopus, PsycINFO, HeinOnline, and in the gray literature (Google Scholar). The search strategy was developed with the assistance of a university librarian and was adapted to each database. The search terms in PubMed were: ((("Informed Consent"[Mesh] OR consent* OR ethic*) AND ("Research"[Mesh] OR research OR trial*) AND ("learning health system" OR "learning healthcare system" OR "learning health care system" OR "learning healthcare project" OR "learning health care project" OR "learning health" OR "learning healthcare" OR "learning health care" OR "big data research" OR "big data healthcare")). We did not have to limit the time span, as the concept of LHS only emerged in the literature in the last two decades.

*Note also that a same research activity can be decomposed into several, more basic research activities that might each require consent. For example, several health care centers could be engaged together in a cluster randomization of treatment conditions, in which the patients' data generated during their treatment would be used for research; here, two kinds of consent could be requested (or waived): the consent to be treated in this system based on cluster randomization, and the consent for one's data generated during this process to be used for research or QI.

Two reviewers (R.D. and R.J.) independently screened the full-text of all articles identified by the search strategy. To be included, an article had to (a) mention "consent" or synonyms, (b) mention "Learning Health System" or an analog system, and (c) detail a specific approach or type of consent portrayed (thus, we excluded articles that only mention consent without detailing it or discussing it). In order to perform an in-depth and broad research, no article was excluded on the basis of its year, type, or place of publication. Every discrepancy between reviewers was discussed to obtain a consensus. If a consensus could not be reached, a third reviewer (A.C.) was consulted. A manual search of references was performed to identify further relevant articles.

The selected articles were imported into the NVivo software. This program was used to code the relevant sequences of the included articles according to the themes consistent with the research question and to the most recurrent themes as sorted by NVivo. One reviewer (R.J.) coded all articles, a process that was subsequently validated by a second author (A.C.). The coding was performed in an iterative manner to permit the emergence of themes, which were organized manually in a tree of nodes within NVivo. The information was subsequently analysed to examine which model of consent were proposed for various research activities. We also aimed at identifying topics that were not addressed in the literature in order to address them in future work.

3 | RESULTS

The initial literature search yielded a total of 495 citations. After examination, 86 were removed because of duplication, incomplete text, or publication in a language other than French and English, leaving 404 citations for full-text review. Using the criteria mentioned above, 68 relevant articles were identified. The manual examination of the references of these articles led to the inclusion of 25 additional publications. Thus, a total of 93 articles were analysed (see Data S1 for the exhaustive list). We then concentrated on relevant findings and assertions dealing with observational studies and summarized them in this scoping review (50 publications cited). Our analysis led to two results helping to meet our objective of determining how to best implement consent in a LHS model for Quebec. First, we developed a conceptual framework to distinguish carefully the characteristics of various informed consent processes. Second, we classified the views from various stakeholders towards according to this conceptual framework.

3.1 | Conceptual framework

To overcome the difficulty arising from overlapping definitions and polysemy, we developed a conceptual framework to distinguish relevant characteristics of the informed consent process, building on prior work.[7]

We will call in the following "enrollment process" the process of an individual being considered for enrollment into some research activities. Enrollment processes can be classified across several dimensions (Figure 1). First, they can be characterized depending on whether individual consent is waived or not (cf characteristics 1 and 2 in Figure 1): in the latter case, the enrollment process will include a consent process, but not in the former. Then, in both cases, the enrollment process may include an information process (characteristics A), and the scope of research activities concerned might be specific or broad (characteristics B). Additionally, if the enrollment process includes a consent process, the consent process can be characterized by the action the participant needs to perform to give consent (characteristics C).

The information provided to the participant might be verbal, written, or electronic (characteristic A.α); and it can be communicated directly to each participant, or indirectly by simply being available to all the participants (characteristic A.β). For example, information given by the doctor to the patient during a consultation would be verbal and direct; whereas a poster in a hospital disclosing to the patients that their data is used for specific research projects would constitute

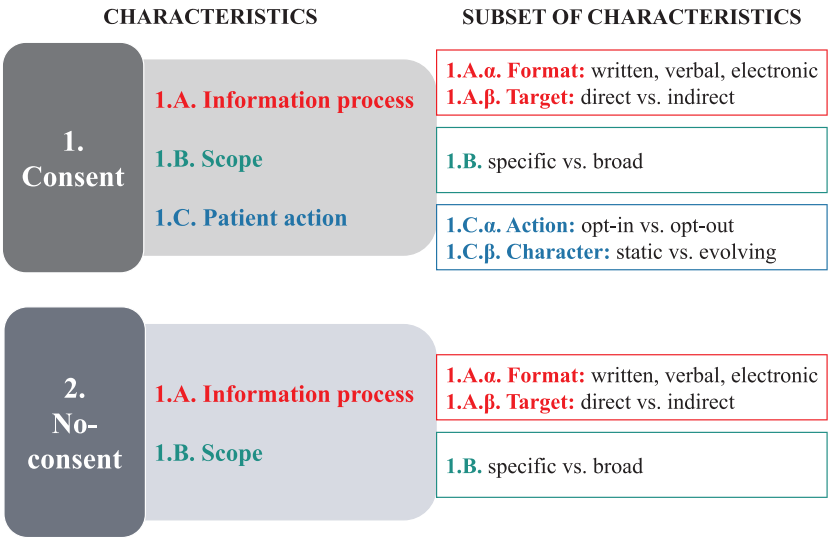

FIGURE 1 A framework to separate different characteristics of the enrollment process

a written and indirect information process. Information can be provided in both a system involving consenting (eg, explaining how it will be obtained) or waiving consent (eg, explaining the reasons why it is waived).

The characteristic B concerns the scope of the required or waived consent, which can be specific or broad. In the former case, a single research activity is concerned—eg, a specific comparative effectiveness research study about anti-acid drugs. In the latter case, a range of research activities is concerned—eg, all observational studies in cardiology that will be performed in a given hospital or all research activities that are approved by some governance body such as a Research Ethics Board (REB). Blanket consent is a very broad consent that is "open-ended and unspecified".[8]

The characteristic C only appears in case of informed consent: it concerns the action of a patient to provide or refuse his consent, and also encompasses two subsets of characteristics. The first subset (characteristic C.α) describes the kind of action required to obtain consent: consent may be obtained by opt-in, that is by the patient approving his participation; or by opt-out, that is by the patient not opposing his participation. The second subset (characteristic C.β) is the static vs evolving character of the consent process. A static consent process has a limited time extension and does not offer to the participants the possibility to change their decision over time; on the other hand, an evolving consent process is more extended in time and offers to the participants the possibility to alter their choices about consent.

The characteristics and subsets of characteristics are largely independent from each other. Any combination of characteristics could theoretically be proposed. For instance, the terms "dynamic consent" generally refers to what we would describe an evolving consent with electronic, direct communication.[9] However, as clarified by Williams et al,[9] dynamic consent should not be opposed to broad consent: a person can give his consent for a broad range of activities in a dynamic fashion, and later narrow or widen those consented research activities. In addition, it is important not to confuse opt-in broad consent with several opt-out specific consents for various research activities. In the former case, the participant can actively choose to participate to a broad range of research activities as a whole. In the latter, the participant is by default considered to consent to all those research activities, but can then opt-out of any—or even all—of them, with more opportunities to personalize his choices.

3.2 | Waiving consent

3.2.1 | Origin of informed consent

A first question is whether informed consent is a sound requirement for research activities in an LHS. The importance of informed consent was declared successively by the Nuremberg Code (1946-1947), the Declaration of Helsinki (1964), and the Belmont Report (1979). The Declaration of Helsinki and the Belmont Report do not apply to de-identified medical data, although the declaration recognizes that there may be situations where consent would be impossible or impractical to obtain—in which case, the approval of a REB is required. Therefore, it is important to dissociate interventional studies from record-based studies using electronic health records (EHR) data (and further dissociate the use of de-identified data and identified data) when considering whether a no-consent model would be acceptable. As explained earlier, we will concentrate this paper on the latter. We will consider in succession the legal, ethicists', and participants' views on such matters.

3.2.2 | Legal views

In the United States, the Health Insurance Portability and Accountability Act (HIPAA) of 1996 permits a waiver of consent for secondary use of EHR data without approval by a REB when data has been de-identified according to the Safe Harbor and Limited Dataset policies[10]—that is, when a set of 18 identifiers are removed. These identifiers include names and a variety of identification numbers, geographic subdivisions smaller than a state, and elements of date (except year) directly related to an individual.[11-14] Exceptions exist for research use of health data: "limited data sets," which include all elements of dates and zip codes, may be disclosed without patient consent if the recipient signs a data use agreement that prohibits re-identification of the data. Of note, waivers of consent do not meet legal standards in some jurisdictions, even for de-identified record-based data[15] (for considerations on the similarities with the European system, see Kaplan, Meystre et al, and Rumbold & Pierscionek[16-18] as well as the European Commission website[19]).

3.2.3 | Views from some ethicists and official bodies

Faden et al[3] have built an ethical framework for LHS defined by seven moral obligations. These include respect of patients' rights, respect for clinician's judgment, providing optimal care to each patient, avoiding the burden of nonclinical risks, addressing health inequalities, conducting continuous learning activities to improve quality of care, and contribution to the common purpose of improving health systems. In a separate article, Faden et al[20] propose that a range of observational studies could be conducted without informed consent, and with only oral disclosure, when they involve only small additional burdens for the patients. Rodwin[21] has suggested that after records are fully de-identified, they should be made available to the public, possibly for a fee. In 2015, the Institute of Medicine (IOM),[22] now named the National Academy of Medicine, recommended granting waivers of informed consent for identifiable data when approved by a REB with relevant expertise, taking into account measures to safeguard data security, possible harms to which inappropriate disclosure would expose subjects, and potential benefits of the study. However, the IOM did not recommend REB review for studies in which no direct identifiers would be available to investigators.

Transparency (as defined as the sharing of information regarding the research activities) and the risk of re-identification are seen as major factors limiting the application of a waiver of consent or withdrawal of REB oversight.[16] This is particularly true of genetic data since most genome data is uniquely identifiable.[23] Because of this risk of re-identification, Hoffman and Podgurski[24] propose that all record-based studies—even involving de-identified data—should be reviewed and monitored by a REB with expertise in records-based research. In situations where researchers must obtain directly identifiable data, REBs could require patient consent if deemed necessary; and in case involving data de-identified in accordance with the HIPAA Safe Harbor procedures, the approval process by the REB could be streamlined.

3.2.4 | Participants' views

Patients tend to value the use of health data for research.[11-14] Despite this, they seem to have mixed opinions concerning waiving consent. In a British study by Campbell,[25] a majority of patients were willing to share their de-identified data without being asked for consent. On the other hand, in a Canadian study by Willison et al,[14] 60% of respondents felt that their permission should be obtained for access to their health data, even when de-identified. In another study, participants would accept alternative models to consent if written permission impacted on research.[11]

It is not clear whether participants think that identifiable and de-identified data should be treated differently with regards to waiving consent. On one hand, a study by Hull et al[26] showed that patients made no distinction between identifiable and de-identified data for their consent or information requirements; and according to an IOM report,[27] public opinion polls show that "a significant portion of the public would like to control all access to their medical records for research via an individual informed consent mechanism." On the other hand, in Willison et al,[14] more than twice more people were comfortable with the use of information without permission or notification in the case of de-identified data than in the case of identifiable data (27% vs 12%). There might be intercultural variations concerning the use of de-identified data for research.[28] And, as suggested by Hoffman and Podgurski,[24] such differences might also be explained by different wordings of the question in different studies and may show some ambivalence of participants towards such issues.

3.2.5 | Balancing welfare and autonomy: comparing ethicists' and participants' views

Waiving consent in the context of observational studies has been defended by several ethicists on the basis that an important gain in common good could compensate for a possible small decrease in personal autonomy, provided that important safeguards are put into place.[24] This weighting of values is shared to some extent by the population. In Willison et al,[14] 68% agreed to some degree with the statement "Research that could be beneficial to people's health is more important than protecting people's privacy." Similarly, 50.8% of participants strongly agreed or somewhat agreed with the statement that "societal benefit was more important than privacy," although a majority valued individual control over societal benefit.[29]

3.3 | Specific vs broad consent

We will now review stakeholders' views on the question of the scope of consent: specific or broad.

3.3.1 | Specific individual consent

Views from some ethicists

Specific individual consent with opt-in is described by several researchers and ethicists as impractical as it would be too time-consuming and expensive to ask consent from every patient for every research project.[20,24,30] Having participants understand the difference between clinical care and research also takes time.[31] Moreover, recontacting patients is sometimes impossible and usually resource intensive. Overall, few seem to believe that this approach to consent would fit well the needs of a LHS.

Participants' views

Various studies have shown that at first glance, participants seem to favor an "ask each time" model in research.[12,30,32-37] Those findings are inconsistent with the results of two studies exploring public attitudes toward consent in biobanking, both indicating that a broad one-time opt-in is preferred by the public in general.[7,38] In addition, the results of the survey by Nayak et al[34] were criticized by Kraybill et al,[13] who argue that the trade-offs involved in specific consent were not disclosed to the participants of the survey. When the trade-offs are better understood by participants, it appears that what matters more to the public may be being informed directly[11,14] and some degree of decision-making control (for instance an initial broad consent) rather than intrusive, resource-costly, recurrent, study-specific consent.[7,36,39] In addition, perceptions of patients may depend on other factors such as the user and the intended use. In a recent survey among patients with cancer, only a third thought it was necessary to obtain consent for each secondary use of their data for research.[40]

3.3.2 | Broad consent

Views from some ethicists

Broad consent was discussed in several different contexts ranging from biobanking,[39,41,42] research on medical practice[4] to secondary use of health information.[14,43-45] Zook et al.[45] proposes broad consent as an ethically acceptable approach to data sharing, as long as researchers and REBs keep in mind the best interests of the patients with regards to breeches in confidentiality and the risk of

reidentification. Kupersmith[46] sees broad consent as a realistic approach that respects patients' autonomy better than an approach based on waiving consent. Some authors emphasize the importance of allowing withdrawal of consent in all forms of broad consent.[18] Others raise recurrent concerns regarding whether broad consent is truly informed,[47-49] and about a possible selection bias.[50]

Participants' views

A sample of Canadian adults perceived broad consent as an adequate compromise between specific consent and waiving consent for the secondary use of their health information.[14] In this study, acceptance of broad consent was highest for academically based research performed by trained research personnel. This confirms that providing adequate information or the opportunity for periodic re-consent to participants is a key asset for acceptance.[14,41]

3.4 | Modalities of communication

We will now turn to the modalities of the communication process to the patients who participate to research activities in a LHS: why should we communicate about this? What should be communicated, by whom, how, and when?

3.4.1 | Why communicate?

Some systems do not require active consent from participants, such as consent waiving or opt-out. In those systems, communication with participants might seem useless to some LHS leaders for certain research activities such as QI, which many participants may assume are already occurring.[51] However, there are good reasons to communicate about all research activities.

A first reason is that the ability to opt-out loses its meaning when participants are not aware that they are participating to research activities and that they can opt-out. This was clear in Thiel et al,[39] which showed a lack of public awareness about a program named "BioTrust"; the public seemed not satisfied with the lack of information when implementing the opt-out model.

A second reason is building trust. Past examples of deficient communication may have been based on concerns that providing information on research might lead to patients opting-out. However, Staa et al[52] suggest that sharing information with patients regarding research projects would increase trust and therefore reduce opting-out. Trust in the physician and transparency about the research projects seems to be a major factor in the willingness to participate in research in a LHS.[12] Participants seem to value a discussion about the general use of their data, especially with their physician. The level of trust patients have in their physician and health system seems to be an important contributor of their acceptance of an opt-out system for research activities involving randomization of participants.[13] Communication may actually matter more to patients than the act of consent itself. The physician-patient relationship is thus an important factor to consider in a LHS. For example, some participants in a study by Kass et al[33] explained that when they trust their doctor, they are more willing to accept a model where study-specific consent is replaced by providing general information. In fact, participants seem less concerned about the model of consent and the means to disclose information than with the context and the relationship with the person seeking consent.[12]

Faden et al[20] argue that as long as people are informed of the trials implemented in a LHS and the results, it would be ethical to conduct some research activities without asking for consent in a LHS framework. They also argue that randomization without consent is acceptable as long as people are informed that it is a current practice in the institution. In a study by Lee et al,[4] REB members disagreed on whether consent was required for various LHS activities including randomization or data use, but most of them felt that transparency was important, and that studies involving participant randomization should be fully disclosed to participants, even in the absence of a formal consent process. This is in line with Kelley et al,[12] who conclude that patients care most about how risks and consent are managed and communicated within a trustful physician-patient relationship.

Conversely, as patients may expect to be informed,[39] a deficient communication can have devastative effects on trust. In the context of the care.data project (a central database of primary care medical records in England), many Tweeter users expressed a lack of trust arising from a perceived lack of transparency, which some interpreted as dishonesty or incompetence; this lack of trust led to a massive opt-out.[53] In view of this failure, Rumbold and Pierscionek[18] have emphasized the importance of "continuing public engagement."

3.4.2 | What should be communicated?

The object of communication may range from a statement on the existence of a LHS and its various research activities to the precise mechanics of the consent process, such as how to opt-out. In addition, some patients not only expect to be informed about the research that is going to be pursued, but also to be returned research results.[12] In the LHS model proposed by Faden et al,[54] patients would have the possibility to obtain more information about the governance structure.

3.4.3 | Who should communicate?

According to Faden et al,[3] the health provider has an important role to play in informing the patient population of the research activities carried out in their institution. In a study on oncologists' perception of the learning system CancerLinq,[55] some think that the doctor should explain the system to the patients, whereas others think that it should be delegated to a staff member who is not a health care professional. Patients' perceptions seem to vary to a lesser extent. In a study on adult patients and parents of pediatric patients,[12] participants strongly prefer a notification or consent process led by their physician rather than by

researchers or other clinical staff. Indeed, patients consider that physicians know the participant's medical profile and are able to judge the pertinent risks associated with the project. Here, again, trust is central. Similarly, 84.5% of participants in Cho et al[11] preferred that they be asked permission to participate in the medical records review study by their physician, rather than by a researcher or research nurse not involved in their care. Kelley et al[12] also conclude that a conversation between patients and their physician would improve both the rate of consent to research and the patient-physician relationship.

This preference for communication by the physician is not universal though. In a study by Kass et al,[33] some patients thought that a discussion about research project was a waste of time and that physicians should instead give more time to care activity for the patient. Similarly, several Twitter users questioned for the same reasons that general practitioners were ultimately responsible for informing patients about the program care.data.[53] However, Faden et[54] think that an integrated model, where verbal consent is given during a conversation with the physician, could result in a minimal excess burden for the clinician.

3.4.4 | How to communicate?

There does not seem to be a consensus concerning the format of the conveyed information. Indirect communication might not reach its audience: Tweets analysis suggested that many households either did not receive the leaflet about the program care.data or did not notice it[53]; some criticized it as insufficient and wasteful. In the CancerLinq study,[55] some oncologists emphasize the need to provide patients with a written notice; however, Kelley et al[12] suggested that participants were happy with a verbal notification.

3.4.5 | When to communicate?

The timing of communication is also important for participants: in the CancerLinq study, several oncologists thought that patients receive too much information during their first visit, which can cause them distress[55]; however, most agreed that patients should be notified with repeated messaging through multiple channels.

3.4.6 | Summary

The following conclusions about the information process can be drawn from the literature. The information process is important to build trust; it is necessary in an opt-out system; and it could make some waiving consent approaches ethically acceptable. Participants may want to know about the existence of a LHS, the research activities involved, the mechanism of the consent process, the research results returned, and the governance structure. There is a preference—though not universal—for the physician being the person who would communicate such information. Finally, the information should be communicated in a way that is sure to reach its audience at multiple times.

3.5 | Patient action

We will now consider the patient action (or absence of action) required for expressing consent. A classical distinction is made between opt-in (no consent is presumed by default) and opt-out (consent is presumed by default).

3.5.1 | Opt-in and opt-out

Opt-out is a kind of nudge, namely, an intervention that aims to influence people to make better decisions while leaving intact their freedom of choice.[56] In the present case, the decisions favored by the opt-out mechanism are supposedly better for society as they facilitate medical research – and thus will hopefully improve care for future patients: opt-out in this context is thus a "prosocial" nudge.[57,58] Opting in and opting out are options that are each compatible with specific, broad, or dynamic approaches.

Views from some ethicists and official bodies

To optimize the outcomes of observational research and avoid what has been called "selection bias", one will want to include the most representative population. When compared with a waiving consent system, both opt-in and opt-out can lead to selection bias—albeit less in the case of an opt-out model.[12,13,24,33] Some communities tend to opt-in less or opt-out more, leading to less representative data and decreasing the external validity of researchs results.[9,50,55,59] The concern of how patient authorization impacts the validity of research outcomes has been raised by several authors and official bodies such as the Institute of Medicine in the United States of America (now known as the National Institutes of Health).[24] Consequently, some stakeholders think that even opting-out should not be an option.[9,55,60] To prevent problems resulting from mass opt-out, Hoffman and Podgurski[50] suggest that the opt-out mechanism should not be too easy, so that only the participants really wanting to opt-out would follow through. This position might not be considered as ethically acceptable to all; there is a balance to find between considerations of scientific validity leading to an increase in population's well-being and considerations of autonomy.

Participants' views

Several studies seem to suggest that participants favor opt-in over opt-out,[29,61-64] with opt-in reinforcing their feeling of control of their data.[65] This preference for opt-in might be stronger though in case of surrogate consent. In Thiel et al,[39] about half the people wanted to choose by opt-in the possibility to have their baby's blood stored for use in research.

However, participants' preferences may be revised when facing technical difficulties for conducting research. In a study by Cho et al,[11] despite originally preferring a written opt-in system, most participants said they would accept an oral opt-in system, or even general notification†, if obtaining written permission would make the research too difficult to conduct. This capacity to make trade-offs is also apparent in the study by Kim et al[29] in which 66% of participants would accept access to their data without agreement in case of emergency, despite an initial preference for opt-in.

3.5.2 | The importance of information

In many cases, opt-in vs opt-out might not be the most important criterion for participants. Kraybill et al[13] found that some patients are satisfied to simply keep a right to opt-out from an intervention as long as they are well-informed about underlying motivations and risks.

Communication and its characteristics (direct or indirect) remain key to understanding the stakeholders' perspective. Study-specific disclosure with an explicit option to opt-out was deemed an acceptable alternative to opt-in specific consent for minimal-risk comparative effectiveness research trials.[37] This study presented to different stakeholders (researchers, REB members, and patients) different scenarios based on opt-in or opt-out with direct or indirect information. The authors conclude that a combination of opt-out and direct verbal information from the doctor enhances transparency, trust, respect, and autonomy relatively to opt-in, while facilitating recruitment for research and not burdening patients with information.

Kass et al[33] found no statistical difference between the rates of approval for either opt-in or opt-out model, as long as it is accompanied by a discussion with a professional about the intended research: thus, what seems to matter is being adequately informed.[13] This is corroborated by a study of Twitter users about care.data[53]; although some users argued that the opt-out system in care.data was unethical, the problem seemed to be above all the patients' lack of awareness of the care.data system and of the possibility to opt-out. Indeed, an opt-out system with inadequate information is arguably dysfunctional, as explained earlier.

3.6 | OTHER CONSIDERATIONS

We will briefly discuss a few additional considerations that emanated from the review of the literature.

3.6.1 | Privacy

The literature on LHS reveals a clear concern raised by many members of the population about the use of their data, especially when their consent is not obtained. However, in one study, almost no patients spontaneously offered their perspectives on data collection and privacy.[13] What may matter most to patients is who has secondary access to the data. In one study, a minority expressed concern about motivations behind research, such as the promotion of interests of insurance companies or other financial drivers of care.[53] Participants accept that researchers and hospitals (for most uses) would access their data, but would be nervous at the idea that drug companies or insurance companies would have access to "even some of those data".[55] Patients may fear their data could be used for wrongful reasons. For example, they may fear the insurance companies could have access to medical data and deny coverage on this basis.[55] This fear could decrease population's consent to a general use of their data for all research purposes. Privacy concerns are even greater when patients do not know what their data are used for, and in particular for genetic data.[16,17] Lack of information may lead to a magnification of such concerns. The likelihood of consent to share information varied based on the organization conducting the research, with the highest likelihood associated with a hospital or university, followed by doctors and government agencies, and the lowest likelihood associated with biotechnology, pharmaceutical, and insurance companies.[29]

3.6.2 | Data characteristics

Genetic data

The secondary use of genetic information for research purposes poses special challenges. Gene sequencing technologies are more and more efficient and affordable, leading to an increasing presence of genomic data in medical files. Zook et al.[45] were concerned that even when broad consent has been given for use of participants' genomic data, researchers should pay a particular attention to the best interests of the participants, given the risk of re-identification. Opt-in may have an important role for such data as it permits to share more intensive information while confirming patients' comprehension of the unpredictable nature of the risks to which the patients might be exposed in the future. For example, a system named "open consent" has been proposed in the context of the Personal Genome project[66]: it consists in opt-in broad consent for sharing of genetic data, with no assurance that the data will never be re-identified. It was proposed by researchers who believe that due to the identifiability of genomic data, a promise of research privacy might not be fulfilled.

De-identified data

There is no clear consensus concerning the use of de-identified data in a LHS. It seems to increase patients' acceptance, but it has a negative impact on the scope and scientific validity of the research. Drawbacks in using de-identified data include their unsuitability to answer all research questions as they do not permit the research team to follow up with the participants were it necessary.[67]

Although de-identified data are generally thought to present less risk, one should consider the risk of re-identification.[68] This may occur by using information obtained illegally or legally – such as information

†It is not clear to us whether "general notification" in Cho et al[11] also involved the possibility to opt-out or referred to a system of waiver of consent.

about patients' purchases or voter registration records. Members of a citizens' Council[59] go as far as to argue that data can never be truly anonymised. Recent models estimate that the risk of re-identification for incomplete datasets can reach nearly 100% in the presence of 15 demographic attributes.[69] Critical attention should therefore be given to which data are present in the dataset.

3.6.3 | Population characteristics

The type of population targeted by the research may also influence people's perception of the best approach to consent.

The pediatric population and the need for re-consent

For some, pediatric data are viewed as especially sensitive. Some suggest that consent should be required even for de-identified pediatric data.[70] Marsolo et al.[71] argue for the need of re-consent‡ once the participant turns 18 years old, implemented by a computer application that would alert the researchers when the participant turns 18 years old. However, participants who become adult may not always perceive this request for re-consent favorably if they learn that their data has been used for a number of years without their own specific consent.

Other vulnerable populations

Patients with cognitive decline and other vulnerable populations may have a lower understanding of technology and its implications. Members of a citizens' Council[59] argues that elderly patients may be more vulnerable to wrongful use of data because of limited informatics skill. They might also be less susceptible of giving a truly informed consent for lack of access to complete information. Furthermore, the authors raise concerns around the capacity to fully understand the opt-out process.

Terminally-ill patients are another type of vulnerable populations: their consent may not be truly free as they may accept to participate in research that they would not have done if they had not been in such a serious state; in these cases, an evaluation by a second physician is proposed to ensure respect of the patient's autonomy and dignity.[73] This approach could be used in a LHS to ensure the participation of vulnerable populations in research: their participation is indeed essential in order to help populations with similar characteristics.

Other demographic factors

Demographic factors can also influence participants' views on consent. Kim et al.[28] suggested that the white population in the United States tends to consent more to data sharing than any other ethnicity; and that lower education is associated with a lower willingness to share medical data. In addition, Bakken et al.[74] reported that ethnic minorities seem to have a lower level of trust in the use of their data in research, have smaller participation rate in research, and appear to use less health technologies. Participants older than 60 years tend to favor opt-in over opt-out in comparison with younger participants.[33] Another study by Sugarman[75] did not show any demographic difference in attitude towards consent but revealed that people with fewer experiences in the LHS were more willing to waive their consent.

‡Note that "re-consent" can take different meanings in the literature: for example, Ali et al.[72] use "re-consent" to refer to the consent, by individuals who have already consented to some data uses, to new data uses. Here, this refers to a consent by the individuals themselves, in case surrogate consent concerning their data had been given earlier.

3.7 | Dynamic consent

3.7.1 | The use of an informatic platform

Alternate approaches to specific consent are often based on the use of technology, such as some forms of dynamic consent, in which consent choices can evolve over time.[42,76-78] This makes particular sense in the context of a LHS.[71] For example, Shelton[78] proposes an Internet-based program for people to share their information with the researchers whose field of study interest them. Web infrastructures can also be used to give information to the patients about the ongoing research projects, so that their consent can be fully informed.[3]

3.7.2 | Dynamic nature of consent

The dynamic consent approach gives the patient an active role within the consent framework.[42,67] It is considered practical, respectful, and supportive of participant autonomy.[9,78,79] Rumbold and Pierscionek[18] have emphasized that "a one-off process of obtaining consent can no longer be considered sufficient in all circumstances, especially with long-term ongoing Big Data projects." Dynamic consent appears to promote participation to research by informed and scientifically literate participants.[80] It increases participant trust in comparison with a broad opt-out approach.[9,52] It does not require for participants to predict all future uses for their data.[66] It can be implemented through a computer platform to manage consent, helping the patient to express his preferences; however, a technologic infrastructure might exclude some populations and therefore bias the research.[9]

Dynamic consent does not exclude the addition of verbal/written information processes: Gray and Thorpe[67] propose a system that generates a form with a common consent and elements that are adapted to the information present in the patient's medical record. This dynamic form is shared at the time of a clinical encounter with the physician and could increase consent for data sharing.

3.8 | Meta-consent

Ploug and Holm[8] propose a model named "meta-consent," in which people are asked how and when they would like to be presented with requests for consent to the use of their personal health data and biological material. Their proposal stems from the risk of routinization in providing or refusing consent: given the frequency of consent requests, and the abundant information material, there is a risk that the provision or refusal of consent would become a

matter of nondeliberative habit. Meta-consent avoids this risk of routinization by enabling participant to decide exactly how little or how much they want to be asked for consent; for example, participants can chose broad consent for some types of data or contexts of research, avoiding being asked for consent too often. A meta-consent model enables preferences that are more informed and deliberated, as well as more consistent, than alternative models of consent.

This model shares some similarities with dynamic consent, in that both rely on a bio-informatic technology and support individual stating their preferences concerning the future use of their health data, and enable those preferences to be communicated to researchers. However, meta-consent goes further insofar as it incorporates this "meta" aspect of designing how they would like in the future to provide consent to the use of their personal health data.

4 | DISCUSSION

Our scoping review presents a number of opinion papers, reviews, and studies that focus on aspects pertaining to consent in a LHS. Overall, LHS are generally seen as an acceptable means to better link patient care and research. Our review enabled the development of a conceptual framework that permits a finer analysis of stakeholder perceptions on different consent models by distinguishing the distinct characteristics. Our review also led us to alternative models of consent that can guide our implementation of a LHS.

4.1 | Conceptual framework

This framework can help to better characterize the various kind of consents considered in the literature. For example, what is called "universal consent" by Fiscella et al[60] would be better characterized as a form of limited opt-out, in which patients, if they want to refuse participating to QI (or QI research), have to receive care at other organizations. This taxonomy can also help to identify the relevant characteristics when comparing different enrollment systems. For example, Kass et al[33] compare what they call a "general approval" (waiver of consent) system with a so-called "opt-out" system and an "opt-in" system, and conclude that participants favor opt-in or opt-out with respect to a waiver of consent. However, their general approval system involves indirect written information, whereas both their opt-out and opt-in systems involve direct verbal information and additional written information in the opt-in model. So it might be that what participants actually favor in their study is direct information over indirect information, or verbal over written information, rather than opt-in or opt-out over waiver of consent. This framework may help others in interpreting conflicting points of view in the literature of consent to participating in a research project.

4.2 | Meta-consent in a LHS

Information and trust are central to all models of consent. The information about research needs to be clear, shared by a trusted health professional and delivered in a timely manner (which may mean repeated in time). Consent need not be obtained for each research activity, as it may be acceptable to balance feasibility with patient autonomy. Our review brought forward two complementary models whose characteristics fit particularly well with our objective of implementing consent to research within a LHS: dynamic consent and meta-consent.

Dynamic consent is a model that can be applied to the context of a LHS. This model provides information and a personalized approach to consent that engages individuals in an active conversation with research platforms about their choices and decisions with regards to different research activities in a LHS. In addition, this approach to consent can be managed by an electronic platform that supports sharing of information and active engagement in decision making. As explained by Williams et al,[9] a dynamic consent platform could be implemented to provide all the information to the participant so that he can fully consent or withdraw and know about the use of its data.

When further taking into account perceptions from stakeholders and each characteristic of the framework, Ploug and Holm's model of meta-consent becomes of even greater interest.[8] It permits separation of the information and consent process and the use of a broad consent to categories of research. Meta-consent can be accompanied by regular information including updates on how the data was used in research and the subsequent positive fallouts. This model fosters autonomy while supporting research. Patients may select how and when they will be informed about and give consent to the use of their data, ongoing research activities, and research results, depending on the research sponsor and research characteristics.[81]

4.3 | Study limitations

An important limitation relates to the different settings in which the opinions were collected and the different populations surveyed. While a scoping review enables to gather the opinions of different kinds of stakeholders, it is hard to extrapolate results from these articles into a universal proposal because a lot of factors can influence the perception of consent in each setting. For example, it is hard to compare the opinions given by two groups of physicians when one group is working in the context of a LHS-inspired system and the other group is not. The same problem exists with regards to the answers from patients who have prior research or health care experience versus those who have not. In addition, one must be careful to balance the differences in opinions expressed between uninformed citizens and informed citizens.

As explained in Section 1, our study concerns only observational studies, but not interventional studies. It would also be important to analyze consent in interventional studies and contrast it with consent

in observational studies. As a matter of fact, Cho et al[11] revealed a higher perceived risk and a lower willingness to participate to activities involving randomization than to purely observational medical record review.

Our research keywords emphasized LHS or closely synonymous, as this was our focus point. However, some other keywords might have been relevant, such as "research on medical practice." Note also that our goal here was mainly descriptive, namely, identifying the relevant characteristics of the consent process and the opinions of various stakeholders about them. In this context, we do not bring answers to important question such as how to gain and maintain trust; how to ensure autonomy within the consent system, considering the fact that many people may not engage or respond to information; and how to ensure that people with low technical literacy would still have research conducted on their needs, in an informatics-based consent system. We did not include aspects pertaining to community engagement. Community engagement defined as "a process that establishes an interaction between a researcher and a community with regards to a research process" is an interesting perspective relevant to particular communities where different cultural expectations around research exist.[82] This form of engagement could therefore have relevance for special populations partaking in a LHS. Further work could help to establish the role of community engagement in the information process and trust building in a LHS.

Another important consideration is the relevance of a vast body of literature around electronic health records, personalized medicine, big data, and health informatics. Although some of this literature served as a basis for discussion within the framework of a LHS, we did not systematically review all these connected domains. Because we are aiming to implement a LHS in Quebec, we focused our question on LHS models. The literature around biobanking also has some relevance to this question. We did not review this domain systematically but our review found some examples relevant to our question.

Our scoping review permitted us to highlight a few aspects not yet addressed by the current literature on the subject. For example, while several consent models rest on the use of technology, only few studies analyze the benefits of electronic consent in a LHS. Given the informatic nature of a LHS, there is an opportunity to better define the use and role of technology in the consent process. Can tools be developed that will not only inform patients of all ages but also assist in obtaining a truly active participation in the process of consent and engagement in research activities of a LHS regardless of the patient's literacy level? Another blind spot relates to the frequency for optimal reconfirmation of consent. With regards to a broad consent, there are not a lot of references that specify the frequency of reiterating a consent process in order to update patient preferences. If we apply a broad consent model, what would be the delay after which the consent would need to be validated again? It will be necessary to address those questions in order to implement a consent process in a LHS.

5 | CONCLUSION

Our scoping review exposed the variety of positions from different stakeholders in the literature as to what would be the best approach to consent for different research activities in a LHS. Combining the mixed results on people's perception on waiving consent and the declared importance of health research for participants, more education and explanation of the value of record-based research might lead people to be more willing to share de-identified data without consent. Otherwise, some models of consent seem to be more accepted by the public (a model based on opting in or out rather than no consent), whereas models that best promote research, namely, waiver of consent or broad consent, raise other concerns. Divergent opinions also exist among experts with regards to the merits and shortcomings of opting out as a nudge strategy. In the future, ethical investigations about nudging need to be applied to the specific situation of opt-out consent.

Communication will be a key factor in ensuring the successful development of a LHS. The importance of information, trust, and autonomy are underlined in a number of articles. We found several examples of how an information deficit associated with broad consent approaches can lead to negative perceptions of research. When communication is lacking, trust is undermined, and so is the process of informed decision making. This explains why some patients fear the broad consent model. Specific measures should be taken to provide a significant degree of information on the different research projects.[41] A discussion regarding research with a trusted health professional will improve and facilitate the consent process in a LHS and mitigate concerns around privacy and security. The involvement of a health professional seems also to make some approaches to consent, such as broad consent, more acceptable. Participants who do not trust their doctor or have few links with health care professionals may favor models where they have more control.[33]

Finally, regardless of which model is implemented, we posit that the conversation between health care professionals and patients should continue to play a central role: the consent platform can be seen as a tool to improve understanding and communication, foster discussion, support decision making, and promote health literacy.

The results of this scoping review were used to design a series of discussion groups concerning the future Quebec LHS, which were performed from May to June 2019. On the basis of the lessons abovementioned from the scoping review, the discussion groups were based on the following points: (a) proposing a system inspired by meta-consent and dynamic consent, providing to participants the possibility to personalize how fine or broad, should be the consent that they may consider giving in the future; (b) investigating the degree of opting out and waiving out what are deemed acceptable by patients; (c) discussing how and by whom the participants want to be informed about the future LHS and how to provide or refuse consent for one's own data use in this LHS; (d) discussing the possibility to personalize consent depending on whether the data is de-identified or genetic, depending on the persons or organizations that request access to it;

(e) integrating into the design process of the future consent platform more vulnerable populations by recruiting, for half of the discussion group, participants with low literacy. The results of those discussions groups will be presented in a future article.

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CONFLICT OF INTEREST

Jean-François Ethier is an associate editor of the *Learning Health Systems* journal.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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