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Is it research or is it clinical? Revisiting an old frontier through the lens of next-generation sequencing technologies

Gabrielle Bertier[a,b,*], Anne Cambon-Thomsen[b], Yann Joly[a]

[a] Centre of Genomics and Policy, McGill University Department of Human Genetics, Faculty of Medicine, 740 Dr. Penfield Avenue, Montreal, Quebec, H3A 0G1, Canada
[b] Université Toulouse III Paul Sabatier and Inserm UMR 1027, 37 allées Jules Guesde, Toulouse, F-31000, France

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ABSTRACT

As next-generation sequencing technologies (NGS) are increasingly used in the clinic, one issue often pointed out in the literature is the fact that their implementation "blurs the line" between research and healthcare. Indeed, NGS data obtained through research study may have clinical significance, and patients may consent that their data is shared in international databases used in research. This blurred line may increase the risk of therapeutic misconception, or that of over-reporting incidental findings. The law has been used to impose a distinction between the two contexts, but this distinction may not always be as clear in the practice of clinical genomics. To illustrate this, we reviewed the legal frameworks in France and Quebec on the matter, and asked the opinion of stakeholders who use NGS to help cancer and rare disease patients in practice.

We found that while there are clear legal distinctions between research and clinical care, bridges between the two contexts exist, and the law focuses on providing appropriate protections to persons, whether they are patients or research participants. The technology users we interviewed expressed that their use of NGS was designed to help patients, but harbored elements pertaining to research as well as care. We hence saw that NGS technologies are often used with a double objective, both individual care and the creation of collective knowledge. Our results highlight the importance of moving towards research-based care, where clinical information can be progressively enriched with evolutive research results. We also found that there can be a misalignment between scientific experts' views and legal norms of what constitutes research or care, which should be addressed. Our method allowed us to shed light on a grey zone at the edge between research and care, where the full benefits of NGS can be yielded. We believe that this and other evidence from the realities of clinical research practice can be used to design more stable and responsible personalized medicine policies.

1. Introduction

As next-generation sequencing technologies (NGS) are increasingly used in patient care, one issue often pointed out in the literature is the fact that their implementation "blurs the line" between research and healthcare (Botkin et al., 2015; Lyon and Segal, 2013; Matthijs et al., 2016; Nguyen and Charlebois, 2015; Nicol et al., 2016; Shkedi-Rafid et al., 2014; Vrijenhoek et al., 2015). This issue is not new in genetics (Pullman and Hodgkinson, 2006; Samuels et al., 2008), nor is it exclusive to this field, as its importance was first recognised as early as 1979 in the Belmont report (Department of Health Education and Welfare, 1979). But the difficulty to distinguish research from care may be exacerbated through the growing use of NGS to help patients that are running out of possible diagnostic (rare diseases) or therapeutic (oncology) options. Indeed, research participants who have had access to whole-genome sequencing (WGS) or whole-exome sequencing (WES) through a research project may consent to be informed of results that are clinically relevant to them or their families. In addition, patients who have benefited from the use of these technologies as part of their care are often asked to consent that their data be anonymized and shared with the research community to advance knowledge on their and other diseases. If the test result is inconclusive, they may also consent that their data be regularly re-analysed in light of evolving research findings in order to improve their medical prevention and care. Hence, NGS data obtained through a research study may be used for patient care, and a research project can bring new clinical significance to an inconclusive clinical test. This blurred boundary issue stands at the heart of a number of scientific, ethical, legal and administrative considerations. It is indeed linked to the questions of free and informed consent, its content, design and its mode of collection (Nicol

* Corresponding author. Centre of Genomics and Policy, McGill University Department of Human Genetics, Faculty of Medicine, 740 Dr. Penfield Avenue, Montreal, Quebec, H3A 0G1, Canada.
E-mail addresses: gabrielle.bertier@mail.mcgill.ca (G. Bertier), anne.cambon-thomsen@univ-tlse3.fr (A. Cambon-Thomsen), yann.joly@mcgill.ca (Y. Joly).

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Table 1
Study participants.
Participants' answers to the question: "Could you describe your current position?".

		France	Quebec
Cancer	Principal Investigator	Medical doctor and group leader in pediatric clinical research	Senior researcher, professor in the department of pediatrics
	Clinician	Onco-geneticist in charge of recruiting patients to the WES study	Medical resident in pediatric hemato-oncology in charge of recruiting patients to the WES study
	Bioinformatician	Bioinformatician working on institution's bioinformatics platform	Bioinformatician working in the research laboratory
	Head of biochemistry lab	Head of biochemistry lab, responsible for molecular analysis in clinical and research project	**NA**
Rare Diseases	Principal Investigator	Professor in genetics practices clinical genetics	Professor in the pediatric department, research director
	Clinician	University hospital lecturer in clinical genetics participates to clinical and research activities in the team	Medical geneticist, associate professor of medicine
	Clinical Researcher	**NA**	PhD, clinical specialist in medical biology
	Bioinformatician	Research engineer in bioinformatics	Bioinformatician

et al., 2016; Ponder et al., 2008; Rahimzadeh et al., 2015; Rigter et al., 2013). Since NGS can yield results which are not linked to the specific disease concerned, this also involves the right of patients to know or not to know (Dheensa et al., 2016; Vears et al., 2017; Vrijenhoek et al., 2015) about incidental or secondary findings, and particularly the thorny issue of informing children or their parents of incurable or adult-onset conditions (Botkin et al., 2015; Dheensa et al., 2016; Jarvik et al., 2014; Mitchell et al., 2017; Rahimzadeh et al., 2015; Shkedi-Rafid et al., 2014). Importantly, the blurred line between research and clinical care poses a number of risks for patients. It may indeed increase the risk of over-reporting non relevant variants (Rosenblatt, 2013), and of therapeutic misconception (Burke et al., 2014; Mitchell et al., 2017; Rahimzadeh et al., 2015; Shkedi-Rafid et al., 2014), where patients confuse participation in a research project with undergoing a test required for their medical care. The law has been used to impose a distinction between the contexts of clinical care and research. However, this distinction may not always be as clear in the practice of clinical genomics. To illustrate this, we review the relevant legal provisions of two comparable systems, France and Quebec on the matter, and report views of stakeholders who use NGS to help patients in practice. We chose to study these two jurisdictions because while these technologies are in transition towards meeting clinical standards, they still have an ambiguous regulatory status.

2. Methods

First, we conducted an analysis of French and Quebec legal frameworks applicable to the context of medical care and medical research. This analysis aimed at replying to the three following research questions: What norms are applicable to research with human subjects in France and Quebec? What norms apply to the delivery of care? Is there overlap between the two sets of norms, and if so, how can it be described? Three main databases were used to collect relevant legal documents; namely: Legisquebec[1] for Quebec norms, Legifrance[2] for French norms, and the HumGen database[3] for legal and ethical norms applied to genomics in both jurisdictions. We also consulted the academic literature on the topic. To do so, we used permutations of the terms "research", "clinical use", "clinical", "medical", "healthcare" AND "genomics", "next-generation sequencing", "whole-exome sequencing, "whole-genome sequencing" in three academic databases: Google Scholar,[4] Pubmed[5] and Scopus.[6] Keywords were also entered in French, in order to identify publications in the official language shared by the two jurisdictions.

Second, we interrogated technology users on their views and perspectives on the distinction between research and care. Within a larger observational study conducted between 2015 and 2017 on the clinical use of genomics in France and in Quebec, we identified teams who use next-NGS technologies in order to inform patient care. This was done though consultation of the academic literature, and by discussing with genomics experts in France and Quebec. We identified four teams, two in France and two in Quebec, who had implemented the clinical use of these technologies within the context of comparable projects. The small number of teams identified is an indicator of how novel the technologies were in 2015. The technology used in all four projects was WES, therefore we will refer to its clinical use as clinical exome sequencing (CES). Two of these teams use CES to uncover the genetic basis of rare diseases (RD), and two others use it in the context of pediatric oncology. We approached the four team leaders, and all accepted to participate in our study. We obtained ethics approval both in France and Quebec to conduct interviews with professionals from these four teams. In each of the four teams, after obtaining consent,[7] we interviewed three types of personnel involved in CES projects: (1) Bioinformaticians in charge of designing and updating the software pipeline used by the team to analyse WES data. (2) Group leaders (or Principal Investigators, PIs) who direct the research teams. (3) Clinicians trained in clinical genetics, and who are in charge of collecting patients' consent for the test, and give results back to patients. For a full description of all interviewees, see Table 1: Study Participants. We conducted fourteen 1-h semi-directed interviews, which included questions on a range of aspects of participants' use of NGS technologies, including projects organization, data trajectory, applicable regulatory frameworks, and opinions on the future of these technologies. Interviews were recorded and transcribed verbatim. Interview data was analysed using NVivo. Themes were drawn from interview data using an inductive methodology, and the final thematic tree was validated by two researchers independent from the study. One interview was also co-coded in full to obtain inter-rater validity. The data presented here was extracted from two main sources: First, we present interviewees' response to the two first questions asked, namely "what is your position?" and "in your institution would you say that WES is used in the context of research or in the context of care?". Second, one of the theme extracted from interviews' inductive analysis was that of the research/clinic boundary. Indeed, this theme was discussed by interviewees throughout the interviews. Here, we present a narrative review of how interviewees discussed this theme.

[1] http://legisquebec.gouv.qc.ca/ (accessed 26 April 2018).
[2] https://www.legifrance.gouv.fr/(accessed 26 April 2018).
[3] http://www.humgen.org/database-laws-policies#box-A-C (accessed 26 April 2018).
[4] https://scholar.google.com/(accessed 14 April 2018).
[5] https://www.ncbi.nlm.nih.gov/pubmed (accessed 26 April 2018).
[6] https://www.scopus.com/ (accessed 26 April 2018).

[7] Following recommendations from the ethics boards, oral consent was obtained for participants in France, and written consent in Quebec.