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Consent for Nondiagnostic Research Biopsies: A Pilot Study of Participant Recall and Therapeutic Orientation

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A growing number of clinical trials incorporate invasive procedures like nondiagnostic tumor biopsies for biomarker or pharmacodynamic analysis.[1] Such invasive research procedures are ethically contentious. Tumor biopsies involve pain and complication risk,[2] and at least one procedure-related death has been reported.[3] However, nondiagnostic tumor biopsies obtained in the research context generally have no value for managing the participant's medical condition. Some commentators therefore argue that research biopsies "take" from participants without "giving in return."[4]

Because such procedures are conducted contrary to research participants' medical interests, an ethical framework for enrolling patients in studies that include a research biopsy rides heavily on informed consent. In particular, study participants should understand that research biopsies are nontherapeutic and burdensome and that participation is discretionary in studies involving them. Yet little is known about whether decisions to enroll in a study that involves a research biopsy, including those that permit participants to opt out of the procedure, meet thresholds of consent validity, in other words, whether individuals sufficiently understand and appreciate the consequences of their decision and whether they are not unduly influenced.[5] Some studies about research biopsies suggest that individuals often misconstrue nondiagnostic biopsies as therapeutic;[6] others suggest the contrary.[7] Interpreting these findings is further complicated by the fact that because participants were often enrolled in clinical drug trials, they might have legitimately imputed therapeutic value to research biopsies when receiving access to investigational drugs was conditioned on providing a biopsy for research.[8]

There are at least three reasons that clinical trials that include research biopsies might present challenges for consent validity. First, because procedures are burdensome, individuals who enroll in these trials might do so under the mistaken belief that the biopsies provide a therapeutic benefit to them. Second, biopsies are often conducted proximate to therapeutic encounters, where patients undergoing a biopsy might be focused on a recent diagnosis and on management options, not on their role as a research participant. Last, some argue that because research participants often conflate research with clinical care,[9] they might fail to appreciate the nontherapeutic nature of a research biopsy. To investigate these issues, we used semistructured interviews to probe recalled perceptions, motivations, and consent quality for research participants in a cancer biomarker study involving nondiagnostic biopsies.

Study Methods

Our primary goal was to describe the extent to which research participants with confirmed breast cancer diagnoses ascribed therapeutic orientation to nondiagnostic tumor biopsies in biomarker studies (hereinafter "parent studies") in which they had previously participated. Our study was conducted at a major cancer research and treatment hospital in metropolitan Montreal.

Prospective participants for the biomarker studies arrived at the research site—a breast cancer clinic—on referral after a positive mammogram. In the first appointment, these patients were informed of the need for a diagnostic biopsy and approached about enrolling in three studies involving nondiagnostic breast tumor biopsies. Consent for research biopsies was

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Table 1.
Demographics of Patient-Respondents

Individual	*Age (yrs)*	*Race/Ethnicity*	*Highest Educational Level*	*Date of First Diagnosis*
N01	34	White	Bachelor's degree	January 2011
N02	84	White/Italian	Fifth grade	1990
N03	60	White	Bachelor's degree	September 2010
N04	47	White/Middle Eastern	Bachelor's degree	March 2011
N05	43	White	High school graduate	2010
N06	62	Asian/Pakistani	High school graduate	January 2011
N07	47	White/Mohawk	High school graduate	December 2010
N08	42	White/Middle Eastern	Master's degree	November 2011
N09	67	White/Portuguese	Fifth grade	1998
N10	48	White/Ashkenazi	Bachelor's degree	2009

sought during the patients' initial visits by the head nurse (responsible for intake of patients at the clinic, discussing diagnostic biopsies, and overseeing research), and research biopsies were obtained by a radiologist (not the principal investigator or care surgeon) in the same session during which clinically indicated biopsies were collected (except in one case, where a participant received diagnostic and research biopsies on a return visit). Research biopsies required additional needle trajectories; three were sought from each patient, and a research nurse was present during the procedures. Biopsies were performed either during the first meeting or a few days later. All women received standard of care for their cancer, and none were participating in drug trials. The benefits section of the consent documents stated, "There will be no direct benefit to you by taking part in this research . . . . While not directly offering you a specific therapeutic benefit, the careful follow-up may well represent a degree of improved quality of care for you." As a condition of granting us access to participants in the parent studies, the biomarker research team required that we interview women after the last follow-up session for the parent studies.

■ *Semistructured Interviews.* The theory guiding our interview template is described elsewhere.[10] Briefly, we designed a 30-minute interview template probing three domains: motivation for enrollment, comprehension, and voluntariness. Participants in the parent studies were approached to participate in our interview study after their last research follow-up—typically six months after undergoing the research biopsies. We also conducted 20-minute interviews with the principal investigator (a surgeon-oncologist) of the parent studies and the head nurse to assess their perception of informed consent quality; interviews were recorded and transcribed.

Interviews were conducted in English by Roberto Abadie, between December 2011 and April 2012, recorded, and transcribed. Coding was performed independently by Roberto Abadie and Jonathan Kimmelman, using an iterative process. Interviews were interpreted using grounded theory.[11] This facilitated development of analytically meaningful coding schemes and attachment of codes to text segments. We measured the frequency with which codes appeared. Codings were compared until a consensus was reached on categories and definitions. Following Miles and Huberman,[12] we targeted inter-rater agreement of 80%. Analysis ended once all transcripts had been coded and saturation obtained (a list of codes is available from the

authors). The study was approved by the institutional review board (IRB) at the hospital hosting the parent study, and all participants provided written informed consent.

Study Results

All of the individuals approached (10 in total) agreed to participate in our interview study. We were unable to interview patients declining research biopsies, primarily because refusal was rare. Table 1 shows the demographics of participants we interviewed. Most of the participants were Caucasian, though the sample was diverse in terms of age, socioeconomic status, and length of time since initial diagnosis. Two patients entered the parent study after relapse (patients N02 and N09). The mean time between biopsy and interview was 14.18 months (range: 2-30 months).

■ *Motivation for Enrolling in Biopsy Study.* We began the interview by asking why each woman had agreed to undergo research biopsies. Without exception, respondents offered reasons rooted in altruism, for instance: "If we can help another patient in the future, by all means, let's help" (N02). And as described below, some responses were tinged with expressions of reciprocity toward previous study subjects or the study team.

Respondents often appealed to their identification with other members of society in explaining their motivations. One respondent said, for example,

> I am like you, and you are like me, and I am like my family, like my neighbor, your mother, your sister. We are all people on this planet, and I feel like they all are like me. And if they can benefit from what I do in the future, then it is good. My daughter, maybe 20, 30 years from now might be diagnosed. (N07)

Consistent with previous studies of nontherapeutic research,[13] responses often evoked benefits flowing to family members. In no instance did respondents describe primary motivators as therapeutic or diagnostic access or collateral benefits like extra contact with the study team.

■ *Comprehension of Benefits and Purpose.* When asked about direct benefits of participation, all respondents accurately stated that there were none: "[I]mmediate expectations from this would be nil," one stated. I never expected that" (N02). We probed with slightly different wording for confirmation. In every case, respondents accurately stated that there were no direct benefits from the research biopsies. The investigators of the parent study correctly predicted this nontherapeutic orientation. Nevertheless, we occasionally heard a response that attributed indirect benefits to participation, including the prospect that discoveries might be relevant to participants, as well as increased monitoring. For instance, once respondent noted that "anytime that I had a question, if I felt funny, or if it was something new because I am very vigilant of anything that happens to me, I call my nurse, I call Dr. X's secretary, and if needed, I can be at the hospital if not the same day, the day after" (N01).

Most respondents were also able to accurately state that they had participated in a research study. However, two harbored misunderstandings. In one case, a respondent (the one who described "helping other women" as her primary motivation for enrollment) believed that the biomarker study involved a "phase IV" drug trial (N10). Another respondent seemed unable to recall she had undergone a research biopsy: "I don't think we really were asked to do anything extra. I don't think they told us, we are doing this because of the research only." (N02)

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Despite emphatically altruistic motivations for enrolling in the parent studies, respondents were disengaged from the substance of the research. The consent form stated,

> The purpose of this study is to understand why tumors become resistant to anticancer treatment. To understand clinical resistance, we need to obtain small pieces of tumor (biopsies) from your primary breast lesions . . . we hope to understand resistance to the particular anticancer treatment that you are receiving . . . we want to find markers that are associated with resistance to the anticancer treatment. Markers are proteins found in tumor tissue . . . that are resistant to treatment.

However, none of the respondents could state the study's purpose. One respondent's answer was, "I don't know. I was under the impression that they were taking samples and then researchers would do research using my tissue" (N07). And another respondent said, "Why

is he doing this? I guess it is because he has a research clinic and he wants further improvement for breast cancer in women" (N03). The medical team accurately surmised that participants in their study would be disengaged with the research objectives. As one principal investigator predicted, "They wouldn't know that we are sequencing the tumor . . . but they might know that we are doing research to understand how the tumors work."

Few of the respondents reported contemplating future impacts of research findings, though according to one respondent, "You hope [advances] are possible, but I don't think about that" (N05). Most were unable to estimate the probability that the studies would produce a major medical advance. One respondent said, "I'll say 50/50; I don't have a clue, no clue" (N04), and another said, "I have no knowledge of research" (N06). When pressed, many respondents offered expectations exceeding historic odds of medical breakthroughs. When asked whether long odds of a breakthrough might have deterred their enrollment, one respondent's resolve to participate seemed to intensify: "We need even more because if you have a smaller rate of success, you need more people and everything to make progress" (N05).

■ ***Recall and Perception of Risk.*** Breast tumor biopsies are associated with discomfort and complication risk. We probed the extent to which respondents understood risk and drew on this knowledge in their decision-making about enrolling in the biopsy study. Even after having participated in the parent study, many participants were unable to recall any risks, and some reported being indifferent to burdens at the time of deciding whether to enroll. According to one respondent, "[The biopsy] didn't seem like a big deal because it didn't take very long and it is not that invasive" (N01). The following dialogue captures the spirit of many responses:

> **Interviewer:** [W]hen you do the biopsy for diagnosis, you have two tissue samples, and then if you do the research biopsy, you undergo three more additional extractions.
>
> **N06:** [*Smiles.*] [O]ne time, two times, three times, four times. It doesn't matter!
>
> **Interviewer:** You were not worried about the pain or the bleeding?
>
> **N06:** No. I wanted to help other people, and also some pain and bleeding are to be expected.

When asked to recall the biopsy, most respondents described burdens as modest to minor. Said one respondent, "I had a little bit of bruising after the biopsy, but it was not a concern. It didn't scare me, and it didn't concern me" (N05). Yet when asked to rate the pain on a scale from 1 to 10 (with 10 being the highest), respondents generally scored pain at 5 or 6. Some noted that, in contrast with those associated with chemotherapy, biopsy burdens were transient and did not threaten physical identity, by, for instance, rendering a patient publicly ill the way hair loss can. However, two respondents considered burdens significant and described them as equal to or greater than chemotherapy. One respondent applied a score of 9 to the biopsy, describing it as "very painful" (N06). Another respondent emphasized experiential aspects of the procedure: "[I]t is very invasive. The needle is big, but that doesn't bother me. What bothers me, it's the click; it is like a point that comes and grabs the tissue . . . . I remember myself thinking, I wish it's a good one, I don't want them to take more, make it a good one" (N07). No respondents reported being surprised about the level of burden.

■ ***Voluntariness.*** Along with capacity and comprehension, freedom from undue influence is an essential element of valid consent.[14] We asked a series of questions about perceptible factors that might have adversely affected voluntary decision-making.

Respondents did not report any pressure to enroll in the parent study and reportedly perceived ample opportunity to query investigators and to decline to participate. When asked whether declining might have adversely affected their medical care, respondents generally replied in the negative: "I don't think that Dr. X would treat me any different if I agree to participate or not to participate" (N08). Yet, two participants suggested that this was a possibility: "That's a good question," one replied (N01), and another said, "I think being part of the study, the treatment . . . I was better treated, I think . . . better supported . . . better followed . . . . Maybe they were more 'there' because they needed certain things or they needed to know more or how I felt or what I did" (N04).

■ ***Decision-Making Process.*** To better understand why many respondents seemed unperturbed by research burdens, we asked a series of questions about the decision-making process. Many respondents said enrolling in the parent study was an easy decision to make. One replied, for example, "To be honest, didn't give it a lot of thought" (N02). Another said, "I wanted to sign it the same day, but the oncology nurse was

not there anymore so I think that it was a week after" (N10). Three respondents recalled asking questions about the research, and enrolling in the parent study gave one respondent pause. "[I]initially," she explained, "we didn't know how much tissue he was going to remove and . . . we were a little bit concerned that because of this study he was going to remove some nodes no matter what, but then he told us that he was going to remove them anyway. So I didn't see any harm in participating" (N01). Most respondents recalled that the research decision-making context was distracting and overwhelming. In some cases, this led to indifference. As one respondent said,

> We have so many things in our minds, [research] is the least of our concerns [*laughs*] . . . . [I] think that [subjects] are probably not well informed but not because the information isn't there. It is just that the concerns they are dealing with, whether they are going to go through or not, that's their main concern. I mean, clearly, that's the priority for them. (N02)

Yet some respondents said they were overwhelmed, with one explaining,

> [I]t is so much information, getting all the documents, absorbing all the information is hard. . . . I couldn't process all the information; even after, I would ask, What did he say? We are relatively educated people and can ask questions, so I can imagine how other people that might be older or with fewer resources, or another language might have more difficulty understanding. (N01)

Another respondent described the consent process as follows: "They tell you okay, we are going to do this and this and this. You are not mentally there; you are in shock" (N05).

■ ***Additional Themes.*** Our interviews uncovered several additional themes. First, though some respondents expressed skepticism about medicine or research, all showed unswerving confidence in both the institution and study team. As one stated, "I don't expect the research performed at [institution] to be harmful" (N01). Respondents also deferred all aspects of moral decision-making or science to the institution or researchers. For instance, some said they were comfortable knowing little if anything about the research. "I don't need to know everything," one respondent said. "I don't want him to waste time, so I said, Where do I sign? As I said before, I really trust them" (N05). And another said, "I am sure that there are people [at the hospital] that struggle with [the risk or benefit]" (N01).

Even in this unusual research setting where research procedures occurred outside of a trial where drugs were being administered, another theme emerged from accounts of research intertwined with those of care. In particular, beliefs and convictions arising out of care shaped the research encounter. The following quotation, prompted by a question about concerns on entering the parent study, illustrates the way trust, built in the care setting, grounded confidence in the research: "I put my trust in [the physician-investigator] and in God. First God [*laughs*]. The first time I met [the physician-investigator]—he is such a sweet person. I was scared; I was discouraged; I asked [him], 'Do you believe in God?' He said, 'Yes.' I said, 'Me too, let's work at this together!'" (N03)

Finally, the theme of reciprocity also emerged. Some respondents regarded participation as an act of care for the investigators: "It's me almost saying, 'What can I do to help you?'" one said (N05), and another explained, "Sometimes I would ask Dr. X, 'So, was I a good patient for you, a good subject?'" (N02)

Interview responses from our study paint a reassuring picture about informed consent for research biopsies—respondents recruited from a parent study did not demonstrate a propensity to view an invasive nondiagnostic biopsy as therapeutic.

Discussion

The interview responses from our study paint a reassuring picture about informed consent for research biopsies, at least for the parent studies from which our respondents were recruited. Respondents did not demonstrate a propensity to view an invasive nondiagnostic biopsy as therapeutic. This was in spite of a somewhat suggestive phrase in the consent form describing potential benefits due to "careful follow-up." Instead, they consistently recalled altruism as their primary if not exclusive motivation to enroll in the parent study, understood they had participated in research, and perceived the research biopsies correctly as nontherapeutic. They further recalled comprehending risk and expressed no surprise at the level of burden experienced. None of the respondents perceived pressure to enroll in the parent study, and several cited the consent process as evidence of voluntary decision-making. These find-

ings are inconsistent with some studies suggesting that research participants occasionally view research biopsies as therapeutic.[15] These differences may reflect our particular research site. They may also reflect the fact that respondents in our study were not participating in drug trials involving experimental treatments. Given the fluidity with which respondents transitioned from discussing treatment to research, differences may also reflect our sustained and careful probing of therapeutic perceptions.

Notwithstanding altruistic motivation for enrolling in the parent study, the answers respondents gave to our questions suggest they were preoccupied with their diagnosis and treatment during the consent process for the parent study. Most recalled being disengaged in the research itself, as indicated by rapid decision-making, scarce questioning, poor recollection of objectives, and little contemplation of research benefits. Instead, decision-making about the parent study was embedded within a network of trust relations toward the investigators, institutions, and the research enterprise.[16] That is, respondents generally entrusted moral and scientific matters relating to how the study was carried out to the research team and research systems. Disclosure elements during the consent process did not appear to play a direct role in decision-making, though the enactment of consent seemed to engender perceptions of researcher and institutional trustworthiness. These findings underline the point that informed consent is no substitute for independent risk and benefit review. They also make clear that informed consent and IRB review of protocols—in addition to serving substantive ethical ends—help sustain relationships that make burdensome research possible.[17]

Findings from our pilot study also leave many unanswered questions. To what extent are responses at this research site representative of other sites? Would perceptions about therapeutic orientation differ if the parent study had been an investigational drug trial? Where does the trust that underlies altruistic motivations originate, how is it sustained, and how resilient is it? And above all, are perceptions reported here a reliable proxy for perceptions of research participants during the informed consent process itself?

Our findings are subject to several limitations. First, our sample was small and limited to one site. Though interviews converged on key themes, our findings should be replicated before drawing conclusions about consent validity for studies that include a research biopsy. Second, interviews were conducted months, and in some cases years, after the biopsies were conducted, as we were unable to obtain permission from study investigators to interview patients during or immediately after the consent process for the parent studies. Recall of a consent process and of the information conveyed is an imperfect representation of the actual process and decision-making at that time, and respondents likely came to understand the research they were in and their relationship with the study team better after having participated in it. Third, the biopsy study team's knowledge that we were studying their consent process may have induced more scrupulous conduct. We consider this unlikely, however, as biopsies had been collected from most of our respondents before we initiated our research. Fourth, our research was partially funded by the team that conducted the biopsies. Maintaining critical distance from funders and parent-study investigators is always a methodological challenge; we leave it to others to decide whether we effectively navigated this relationship.

Disclosure

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