# Implications of Research Biopsies in Clinical Trials

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**Introduction**

Biospecimens are invaluable lynchpins in translational oncology, both to engender new discoveries and to assess the efficacy of new treatment paradigms. The collection and use of such specimens relies upon the patients and subjects who entrust clinicians with their bodies. This is especially true for research biopsies that are solely performed to enhance scientific understanding and may not offer any benefit to the individual patient or subject.

An ethical framework was recently developed by the American Society for Clinical Oncology (ASCO) to improve and inform the procurement of research biopsies in clinical trials. By considering their potential to increase scientific knowledge, the inherent risk of their collection, and whether they are required for clinical management, these guidelines assign weighted utility to biopsies.[1] While the ASCO guidelines serve as an excellent model for researchers and clinicians alike, how they will be implemented in practice remains uncertain. It is thus critical to understand the guidelines, as well as to identify barriers to their utilization, especially as research biopsies become an increasingly common component of clinical trials.

In this issue of *The Oncologist*, Olympios *et al.* examine requests and consent for research biopsies in a series of clinical trials designed prior to the publication of the ASCO Ethical Framework. Notably, only 39% of clinical trials requiring mandatory biopsies would have been compliant with the subsequently published framework. The authors assessed several study attributes to determine compliance with the ASCO framework, including the potential utility of the biopsy, the risk for patients, and the mandatory or optional request for biopsy. Informed consent forms were analyzed for thoroughness regarding biopsy

risk and explanation of the scientific rationale. Multiple studies requested biopsy for exploratory objectives. Other reasons for lack of compliance included inadequate statistical analyses or disproportionate risk. Olympios *et al.* also report that the amount of risk of research biopsies was often inadequately described in informed consent documents. This study highlights the need for critical reappraisal of current practices, and how we can best respect and serve of our existing patients while advancing the science necessary to improve the care of future patients like them.

With the growing impetus to identify predictive biomarkers in the era of precision medicine, it is essential to critically assess the implications of research biopsies in clinical trials. We offer a discussion on the risk-benefit analysis of inclusion of research biopsies in clinical trials, the inherent tensions for dual clinician-researchers, and questions for an age of increasing commercialization of patient information.

**Risk-benefit Analysis**

When would a patient be willing to accept the associated risks of a biopsy outside of the context of their current medical needs? Research biopsies may ask participants to assume incremental risk beyond the experimental therapeutic intervention itself –in some cases to assess the response to treatment, and others for unrelated correlative study. As noted by Olympios *et al.*, many studies lack a clearly stated scientific rationale for the biopsy, which poses a challenge when assessing the risk benefit ratio to the patient-participant. Plus, the risk of obtaining specimens is quite variable. For example, a blood draw is different from a skin biopsy, which are both very different from procuring tissue from the liver or lung. Several factors contribute to risk associated with research biopsies, including the way tissue is obtained, the

timing of biopsy, and the proficiency of the provider performing the biopsy.[1] As anticipated, there is augmented risk to participants when a research biopsy is obtained in a separate procedure distinct from a clinically indicated intervention.[2-4] This added hazard poses a challenge when balancing the risk-benefit ratio of a clinical trial. While a research biopsy does not benefit the individual study subject, findings derived from these biopsies have the potential to benefit the scientific community and future patients. Scientific rationale for biopsy, and possibility of future contributions from tissue analysis, must be rigorously assessed to justify the added risk endured by study subjects.

As illustrated in a study at MD Anderson, there is a substantial difference in the willingness of patients to undergo research biopsies when the procedure is mandatory for enrollment in a clinical trial versus optional.[5] Often, patients who are enrolled in early phase clinical trials have few other treatment options available. If an invasive biopsy is a requirement for determining eligibility, patients may be more willing to accept the associated risk since refusal may preclude study enrollment. In addition, the magnitude of risk may be couched in the language of the informed consent process. There is no standardization of reporting adverse events associated with research biopsies, and this void of data poses a challenge when contextualizing risk for individual participants. While Olympios *et al*. analyzed the written informed consent forms of included trials, the authors were not present at bedside to witness these encounters. Intangible elements of the consent process, including as patient-researcher dialogues and assessment of patient understanding, cannot be captured through review of documents. Open and honest communication between providers and participants is paramount when discussing the role of research biopsies.

Another component of the risk-benefit analysis within the ASCO framework is the magnitude of potential discovery, which is also quite subjective and frequently unknowable. It is difficult to ascertain which biologic advancements might impact patient outcomes. The revolution in precision medicine has allowed for identification of biomarkers that may predict response or resistance to therapy. For example, predictive biomarkers identified from research biopsies have been transformative in the field of immunotherapy.[6,7] The age of immunotherapy offers an environment ripe for discovery of novel predictive biomarkers that may influence patient care, but as with a great deal of experiments, many will have negative results. As such, the unknown potential for clinical advancement may challenge researchers, clinicians, and patients to weigh the proportionality of risk-benefit when making individual decisions as part of translational research.

**Dual Role of Clinician Researchers**

The dual role of the clinician researcher creates a tension when enrolling patients in clinical trials. The dichotomy between the individuality of the physician-patient relationship and the more utilitarian view of clinical research must be considered when transitioning from bench to bedside and back as a clinician researcher. When considering patient motivation to consent to research biopsies and clinical trials, clinicians and researchers must consider the inherently vulnerable state of the patient. Studies have illustrated that most patients who choose to enroll in clinical trials are motivated by optimism rather than altruism.[8,9] While the purpose of clinical research is to gain generalizable knowledge for the general population, this concept is often challenging for patients to comprehend.[10] In another study, observed

informed consent conversations did not clearly distinguish between biopsies performed for clinical care versus research.

When a patient or research subject fails to understand the distinction between the goals of clinical research and standard of care treatment, a therapeutic misconception occurs as the patient may erroneously attribute therapeutic intent to interventions designed for research purposes.[11] Despite clinicians' best efforts to convey the purpose and possible risks of research biopsies, patients may still presume personal benefit as a possible outcome – especially when their doctor is part of the enrollment process.

**Commercial interests**

The future success of garnering clinically useful data from research biopsies relies on patient and participants' willingness to provide biospecimens for analysis and research. This poses myriad issues of specimen and data property, privacy, and access. With the rapidly evolving landscape of health technology and the pharmaceutical marketplace, it is important to scrutinize guidelines and patient perceptions regarding use of their biospecimens.

The cost of translational research can be prohibitory to academic medical centers, causing many to rely on commercialization of patient-derived materials to fund scientific endeavors. Selling biospecimens or data to a company for profit introduces a layer of conflict of interest for researchers and clinicians. A large national survey of the US population found that the majority of people agree that clear notification of

potential data commercialization is warranted, and few are comfortable with such use.[12] But in a series of focused interviews with clinicians and their head and neck cancer patients, it was clinicians who reported less comfort with data commercialization than the patients themselves.[13] The partnership between a medical center and industry in a research protocol adds another element to the physician-patient relationship and may engender distrust or skepticism for patients and providers, especially for the potentially risky procurement of research biospecimens that are not clinically necessary.

**Future Directions**

With the rapid progression of novel therapeutics and personalized medicine, there has been an increased interest in non-invasive testing to monitor response to treatment, estimate tumor burden, and predict disease recurrence. An avenue for further study involves the use of lower-risk research specimens. The advent of liquid biopsies such as blood, saliva, and urine may obviate many of the risks of invasive biopsies in some settings.[14,15] While the risk of liquid biopsy collection is negligible, this adds new dimensions to privacy and risk. For example, if DNA can be readily and routinely extracted and sequenced from bodily fluids, what restrictions will guide the dissemination and use of this data?

The advancing field of precision medicine and the increasing requests for research biopsies in clinical trials pose ever-evolving challenges for patients and providers. Further studies analyzing clinical trials after publication of the ASCO guidelines must elucidate their dissemination and compliance. Funding agencies should be urged to judiciously assess clinical trial protocols based on ASCO recommendations.

The ASCO Ethical Framework serves as an excellent model for the scientific community – yet it is our responsibility to ensure that these guidelines are followed for the good of both our existing and future patients.

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