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The ethical use of mandatory research biopsies

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Abstract

Increasingly, clinical trials incorporate translational research questions aimed at identifying biomarkers of response or resistance to agents under investigation. Biomarker assays can require tissue samples to be collected through a research biopsy before therapy, during treatment, or at the time of tumor progression. Such biopsy samples will generally not provide a direct benefit to the patient and, given the risks associated with any surgical procedure, ethical concerns have been raised when the participant's enrollment on a clinical trial depends on their consent to undergo a research biopsy. In this Perspectives article, we present the rationale for mandatory research biopsies and offer suggestions for standardization to ensure that high-quality, patient-centered, clinical trials continue to be designed with scientific and ethical rigor.

Introduction

Cancer is a remarkably heterogeneous disease. Tumors are routinely classified into subsets defined according to their molecular profiles and tailored treatments are selected according to the biology of these different subsets. To achieve individualized therapy, innovative clinical trials are incorporating translational research questions aimed at identifying novel biomarkers of response or resistance to agents under investigation.¹⁻³ Tissue from a patient's tumor is often required for these assays. In some situations, such as to generate hypotheses, research biopsies might not be essential and hence they could be optional. However, in other settings, research biopsies must be obtained from all patients to provide sufficient statistical power for biomarker studies. Although the potential scientific knowledge gained from these studies may be of great value, important ethical concerns have been raised. Currently, there is a lack of consensus and standards surrounding the incorporation of mandatory biopsies in clinical trials. In this Perspectives article, we present the rationale for mandatory research biopsies and offer suggestions for standardization to ensure that high-quality, patient-centered clinical trials continue to be designed with scientific and ethical rigor.

What is a research biopsy?

To address the issues surrounding research biopsies, it is important to distinguish a clinical biopsy from a research biopsy. The intent of a clinical biopsy is to dictate or change a patient's course of treatment, such as diagnosing metastatic disease or delineating markers of response to targeted therapy. By contrast, the purpose of a research biopsy is to answer a

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specific, scientific question (or several questions) through the use of correlative assays.⁴ Most research biopsies will not result in a direct personal benefit to the patient, and the outcome of these tests generally will not have an impact on the clinical care of the trial participants. A notable exception is the use of research biopsies in identifying a specific molecular marker to determine eligibility for a clinical trial that is assessing a targeted agent.⁴ Tissue that is collected as part of a research protocol has great potential to advance scientific knowledge by determining how well a drug is affecting the target tissue, identifying mechanisms of drug resistance, describing a new oncologic signaling pathway, or establishing predictors of a favorable or unfavorable outcome.

Do we need research biopsies?

Identifying drugs with anticancer properties was built upon the paradigm of testing different cytotoxic chemotherapy regimens broadly across multiple tumor types. However, the most crucial treatment advances of the past decade have arisen from the recognition that tumors can often be separated into specific subtypes that are driven by targetable, molecular alterations. Effective development of the new generation of targeted therapies requires biomarkers to identify patients who are most likely to benefit from these agents. Examples of validated biomarkers that are used routinely to guide patient management include overexpression of HER2 in breast cancer,⁵ *EGFR* mutations in non-small-cell lung cancer,^{6,7} *KRAS* mutations in colorectal cancer,⁸ and *KIT* mutations for advanced gastrointestinal stromal tumors.⁹ Additionally, gene-expression profiles of tumors can also provide information regarding disease outcome and responsiveness to therapy.¹⁰ These biomarkers allow clinicians to give a drug to the patient population that is most likely to benefit from it, and illustrate the importance of analyzing tumor tissue for clinical decision-making. In the context of research biopsies, integral biomarkers are molecular characteristics that are not fully established, but are important in identifying optimal candidates for a study and for interpreting the primary end point of the trial.⁴ In the Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis (I-SPY 2) trial, patients are required to undergo a mandatory research biopsy before study enrollment.¹¹ Previous trials have required mandatory research biopsies to investigate correlative questions but many current trials—such as I-SPY 2—use the results from biomarker assays on the collected tissue to determine if a patient is eligible for the study and will exclude patients who do not meet biomarker criteria. As new treatments are developed, it is expected that tissue-based assays will become even more important as oncologists match molecular aberrations with targeted therapies.

Importantly, tumors can change their biologic profile—at least to some degree—over time. Using breast cancer as an example, recent data indicate that expression of individual biomarkers such as estrogen receptor (ER), progesterone receptor (PR), and HER2 can change from primary to metastatic diagnosis and these differences can guide clinicians to alter therapy accordingly.¹² Even though appropriate testing can often be carried out on archived tissue, such tissue may only be available from an initial biopsy sample obtained years earlier and might not accurately reflect molecular changes that may have occurred during evolution of the disease. Moreover, some biomarker analyses such as real-time PCR and microarrays may require fresh tissue.¹³ In these settings, investigators are increasingly considering the need for research biopsies.

When do we need biopsies?

Research biopsies may be collected at three time points in a prospective study: before the initiation of therapy; during—or immediately following—treatment, and after tumor progression (Table 1). Each of these settings offers the opportunity to ask a different set of

questions. In the pretreatment biopsy, tissue is obtained to describe a cancer's molecular signature before exposure to a new agent. The goal of this biopsy is to identify molecular characteristics predictive of response or primary resistance to the administered therapy. For example, in a preoperative trial of trastuzumab and vinorelbine in patients with early-stage HER2-positive breast cancer, the expression of insulin-like growth factor receptor, IGFR-1 was associated with poor outcome.¹⁴ Although this initial study was exploratory in nature, if the findings are confirmed in a larger study, they could have an impact on patient care or, at least, on the design of future trials.

For newly diagnosed patients, recently acquired tissue from a biopsy is usually available. In this scenario, a research biopsy is only required if there is an inadequate amount of tissue for additional exploratory assays or the tissue was not preserved in the appropriate manner to optimize further scientific testing. The situation is more complicated for patients with metastatic disease, particularly those who have had metastatic disease for an extended period of time. A biopsy is often not required for clinical decision-making in this setting and, although a tumor sample may be available from a previous biopsy, it may have been obtained months or years before, raising the question as to whether it mirrors the current status of the disease. If an investigator wants a current picture of the molecular characteristics of a tumor, a research biopsy is required.¹⁵

The second time point when research biopsies are collected is during treatment or immediately after therapy. By analyzing the molecular changes in tissue specimens after continued exposure to a drug, scientists can assess the *in vivo* activity of a new agent that targets a specific oncogenic pathway. In a phase I study of PI3K inhibitors across many tumor types, biomarker analysis of biopsies that were taken before treatment and during treatment provided compelling evidence of pharmacodynamic inhibition of PI3K by demonstrating downregulation of proteins downstream of PI3K.¹⁶ In a second example, response of women with early-stage breast cancer to anastrozole—an aromatase inhibitor—or tamoxifen in the preoperative setting was predicted by expression of the proliferation marker Ki67 at 2 weeks, but not at baseline.¹⁷ Therefore, the baseline tumor evaluation was not useful in predicting benefit from therapy, and the mandatory research biopsy 2 weeks into treatment was necessary to demonstrate biomarker efficacy.

Finally, research biopsies at the time of progression aim to elucidate mechanisms of acquired resistance to a new therapeutic agent, particularly in patients whose tumor initially responded to therapy. Although biopsies may not be necessary at the time of disease progression, patients may be motivated to provide research tissue to help understand why their tumor is no longer responding to therapy.¹⁸ For example, through the collection of biopsies at disease progression, resistance to the EGFR inhibitors gefitinib or erlotinib was seen in patients with lung cancer whose tumors demonstrated amplification of *MET*.¹⁹ The resistance pathways identified through this study provided an important rationale for combining EGFR and MET inhibitors in future trials.²⁰

Safety of research biopsies

The data on the safety of research biopsies are limited, and the reporting of adverse events associated with the collection of research tissue is not standardized.^{21,22} Most patients who undergo mandatory research biopsies tolerate the procedure well with anxiety reported in 30% of trial participants compared with 45% of patients undergoing a clinically indicated biopsy.²³ The potential harm to any patient undergoing a research biopsy will be proportional to the site of tissue collection. Easily accessible sites of disease (for example, skin lesions) should be preferentially targeted if they are expected to provide sufficient tissue for analysis. Tissue that has been previously irradiated can be biopsied without

significant excess risk.²¹ Intrathoracic research biopsies may be associated with a somewhat higher risk of complications. In the Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) trial, 215 patients were assessed for biomarkers with a mandatory research biopsy. Intrathoracic-core research biopsies were carried out in 55% of participants, with a resulting incidence in pneumothorax of 11.5%.²⁴ By contrast, there are less data evaluating the safety of research liver biopsies. In a carefully selected patient population, research liver biopsies in 78 participants showed no evidence of significant complications, with only 15% of patients complaining of local pain.²² Data on liver biopsies for clinical purposes show similar safety data with no major complications and a minor complication rate of 4.8%.²⁵ In an ongoing trial using trastuzumab and lapatinib in patients with metastatic HER2-positive breast cancer, there were no major complications in 85 patients who underwent a required biopsy (N. Lin, personal communication). Collection of safety data surrounding research biopsies should be reported in all trials that include these nondiagnostic procedures.

Ethical considerations

The requirement for research biopsies in the setting of a clinical trial is controversial (Table 2). Most of the oncology community accepts the practice of optional tissue donation for correlative studies. However, owing to the risks associated with any procedure, ethical concerns emerge when the enrollment of a patient on a clinical trial depends on consenting to a mandatory research biopsy.²⁶ Those who oppose mandatory research biopsies claim that these are a form of coercion,²¹ whereas supporters argue that it is unethical to avoid analysis of biomarkers that could benefit future cancer patients.²⁷ Examination of this issue requires a critical look into the motivation of the patients to enroll on a trial, the specifics of the informed consent process, and the importance of the scientific question.

Federal regulations permit an adult to accept the risks of a procedure provided the potential information gained can justify those risks.^{21,28} In one small study that required a mandatory biopsy before enrollment, 22% of the patients who considered undergoing a research biopsy were willing to accept a 5–10% risk of a major complication in order to enroll on the trial.²³ By contrast, most medical oncologists and protocol reviewers on institutional review boards are more apprehensive than the potential study population and would only accept a 1% rate of major complication before approving a study that requires a mandatory research biopsy.²³

It is the observation that patients are willing to put themselves at a risk in order to gain access to novel therapies that raises the concern of whether these patients could be subject to a form of coercion when consenting to mandatory biopsies as part of a novel therapeutic trial.²¹ When designing a new protocol, investigators must take into consideration the patient's motivation to enroll in a study. Patients with cancer can inappropriately perceive a greater chance of benefit from an experimental agent than has been proven.²⁹ The purpose of a clinical trial is to add to the scientific knowledge of a disease; however, most patients enter a study in the hope of a direct clinical benefit to themselves.^{30–32} In reality, a considerable percentage of patients will not benefit from therapy, and there are occasions when a subgroup of participants is harmed due to enrollment on a clinical trial, largely as a result of toxicity.³³ Although some patients may be motivated to enter a trial with the hope of a personal benefit and simultaneously understand the research nature of the biopsy, other participants may not have this level of comprehension. Therefore, it is the role of regulatory boards to ensure that the protocol adequately describes guidelines to minimize risk related to the collection of research specimens and that the consent forms convey the nature of the biopsy in an understandable manner.

Informed consent is key to the design of ethical protocols that include mandatory research biopsies so as to guarantee that proper information is correctly disseminated to potential trial participants. Most individuals prefer an approach that includes greater patient involvement and respect for individual autonomy. Although studies suggest that participants enrolling on a trial are generally satisfied with the informed consent process, most do not recognize the unproven nature of the investigational treatment.³⁴ Even providers at academic institutions can share the same therapeutic misconceptions as patients. In one study, fewer than half of the providers recognized that the purpose of a clinical trial is to benefit future patients.³⁴

Clinicians must provide appropriate and accurate information regarding the possibility of harm and the potential benefits of such trials to the consenting patient. The question is how do we, as investigators, achieve this goal? Interventions—such as multimedia tools using computer or video technology and enhanced consent for ms—have demonstrated disappointing results by failing to establish an improvement of patient understanding of the consenting process.³⁵ However, limited evidence suggests that direct human contact through an extra meeting with a qualified person may improve a participant's understanding.³⁵ This approach would not require additional time of the investigating physician, but would necessitate an increase in resources to provide clinics with the required additional personnel.

Some supporters of mandatory biopsies claim that investigators have a moral obligation to design clinical trials that include correlative assays that may impact clinical decisions for future patients.²⁷ These supporters argue that participants are not harmed by conditional access (on a research biopsy) to an experimental treatment as they still have access to standard therapies. Peppercorn *et al.*⁴ offer practical recommendations suggesting that mandatory biopsies should be strongly considered when an integral biomarker is needed to determine patient eligibility, guide targeted therapy, assess a primary end point of a study, or address a question that cannot be tackled with a previously acquired clinical sample.⁴ In addition, mandatory biopsies are valid to use when they evaluate the safety or efficacy of an experimental drug. However, despite their potential value, there are many additional disincentives to incorporating mandatory biopsies into clinical trials. These disincentives include the cost of tissue collection and analysis, the extra time needed to obtain appropriate informed consent, the perception that mandatory biopsies will dissuade patient enrollment, and the conflict that industry sponsors may have with trials that could ultimately restrict the use of a drug to a smaller subset of patients.²⁷

Biomarker analysis does not always require a specific research biopsy as archived tissue is already frequently obtained from clinical procedures. Certainly, correlative assays that are purely exploratory in nature and do not support a strong hypothesis, should generally be optional for patients. However, when the availability of fresh or contemporaneous tissue is essential to the study in question, optional biopsies are probably not appropriate as the scientific yield is generally not adequate. In these instances, a research biopsy should be mandatory.

Clinicians may not ask or encourage patients to undergo optional research biopsies due to concern about risks to their patients, clinical time constraints, logistical barriers in scheduling such procedures, or assumptions about patient preferences. Similarly, study participants may choose to skip a procedure that is associated with some risk, adds hassle or discomfort, or delays the start of protocol therapy. There is extreme variation in the number of patients who will choose to donate tissue on trials that use optional research biopsies, with estimates from as low as 18% (L. Carey, personal communication) to as high as 95%.³⁶ The reason for variability is unknown and requires further investigation. Incomplete sample collection can be detrimental to a study because important research questions might remain unanswered. Even more concerning is that investigators are wasting the efforts of those

patients who undergo an optional biopsy, because the obtained information is not interpretable due of lack of statistical power.⁴ In this setting, optional tissue collection would only be acceptable if the number of biopsies needed is much lower than the number of patients receiving the investigational agent and the study obtains the minimal number of samples to meet a secondary, correlative objective.²¹

Standards for including biopsies

Limited standards are available for the use of mandatory tissue collection in clinical studies, and proposed standards are listed in Table 3. Lack of consensus threatens collaboration among clinicians, clinical trialists and patients.³⁶ Mandatory research biopsies can be considered ethical if investigators uphold both scientific rigor and proper protection of trial participants. Clinicians and investigators have the responsibility to precisely inform the patients, to ensure shared decision-making.³⁷ Also, the clinician obtaining consent is required to balance the possibility of individual benefit and risk with the larger societal purpose of a clinical trial.^{30,34,38} High-quality protocol design, oversight by an institutional review board, and proper informed consent should be imperative if mandatory biopsies are requested.

The Cancer and Leukemia Group B (CALGB) Ethics Committee provided guidelines supporting the design and review of protocols that require research biopsies. These guidelines established that, for clinical trials to require mandatory biopsies, they should include: a timely scientific question that could not be answered through assays on an archival sample, adequate and thorough informed consent, and appropriate monitoring for safety.⁴ The Eastern Cooperative Oncology Group (ECOG) policy is quite different and states that any consent form requiring a research biopsy should include a separate opt-out section through which patients would be allowed to deny consent.³⁶ The widespread interest in tissue collection and research biopsies has led cooperative groups to reconsider past approaches and policies. For example, ECOG is considering permitting mandatory biopsies if there is a clear consenting process, an important scientific question is being asked, and if the eligible patient population has been offered other therapeutic options outside of the trial.³⁶ It is essential that other cooperative groups and large organizations address this issue by reviewing the available data and providing guidelines for investigators that are both ethically sound and scientifically progressive.

Future directions

It is our hope that the requirement of mandatory research biopsies—although currently necessary—will not last long. Technological advancements are allowing investigators to address questions regarding biomarkers through scientific tests that do not require additional tumor biopsies. Assays that previously required fresh-frozen tissue can be now carried out on archived, paraffin-embedded biopsy samples.³⁹ In addition, molecular imaging holds great potential as an alternative to a research biopsy,⁴⁰ and in some cases, mutations and other abnormalities in tumor tissue might be detected in peripheral blood in the near future.⁴¹ Molecular characterization of circulating tumor cells is already replacing metastatic biopsies as a diagnostic criteria for entry on selected clinical trials.^{42,43}

For the time being, tissue collection for research purposes remains central to our ability to learn how to individualize targeted therapeutics; and although less-invasive techniques are promising, their development will ultimately require a gold-standard comparison to matched-tumor tissue. As investigators, we have the responsibility to uphold both scientific integrity and work within ethical parameters when deciding to make research biopsies mandatory or optional.⁴⁴ Only through innovative protocol design and standardization

across investigational groups can patient resources be best used to answer critical scientific questions.

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Table 1

Rationale for research biopsies at different time points on a clinical trial

Biopsy time point	Reason for research biopsy
Pretreatment	Identify tumor's molecular signature before exposure to new agents. Identify predictors of response or primary resistance to new agents. Identify integral biomarkers to determine patient eligibility and define stratification before exposure to new agents.
During or immediately after treatment	Identify delivery of new agents to target tissue. Identify activity of new agents that target a specific signaling pathway.
Tumor progression	Identify mechanisms of acquired resistance to new agents.

Table 2**Ethical arguments for and against the inclusion of mandatory research biopsies in clinical trials**

For	Against
It is unethical to avoid biomarker analysis that could benefit future cancer patients. ²⁷ Participants are not harmed by making access to the experimental treatment conditional on a research biopsy, as a mandatory research biopsy does not interfere with access to standard medical care.	Mandatory biopsies can be viewed as a form of coercion when paired with access to an investigational agent. ²¹
Required biopsies are acceptable when investigators appropriately weigh the risks against the necessity of the correlative question. Required biopsies should be considered if the correlative assay has been validated, addresses a yet unknown scientific question, and has the potential to impact the clinical care of patients.	Research biopsies should be optional if the scientific value of the correlative question is not yet well established. ²⁶
Optional biopsies that are statistically underpowered to answer a scientific question can be uninterpretable. ⁴	Some authorities, such as the Eastern Cooperative Oncology Group (ECOG), still find scientific value in optional research biopsies and mandate that a separate opt-out section be included in any consent form where a research biopsy is required. ³⁶

Table 3

Standards for inclusion of mandatory research biopsies into clinical trials

loopholes in current practice	Proposed solutions
<i>Informed consent</i>	
The purpose of a clinical trial is to add to the scientific knowledge of a disease; however, most participants enter a study in hopes of a direct clinical benefit to themselves, thus making proper informed consent challenging. ^{30-32,45}	The informed consent document should: Address the unproven nature of an investigational agent. Address the purpose of a clinical trial, which is to benefit future patients. Identify the additional risks associated with a research biopsy. State clearly that the research biopsy is not associated with direct benefit to the patient. A participant's understanding of a research biopsy could potentially be improved with enhanced direct human contact with non-MD consenting personnel in addition to the standard consent procedures involving the treating investigator.
<i>Institutional review board (IRB)</i>	
Most IRBs have limited experience with protocols that include research biopsies and are not trained to perform stringent scientific reviews of correlative questions to determine if the anticipated knowledge gained is sufficient to justify the risks of the mandatory biopsy.	The IRB should: Perform a critical review of the informed consent process to maximize participant understanding. Perform a stringent review of their institutional capacity to achieve adequate participant enrollment in each clinical trial involving mandatory research biopsies. Oversee the safety measures at their local institution to ensure that research biopsy standards are equivalent to that of clinical biopsies and comparable to national standards.
<i>Reporting of safety data</i>	
The data on the safety of research biopsies are limited. Reporting of adverse events associated with the collection of research tissue is not standardized. ^{21,22}	Data collection and reporting on adverse events associated with research biopsies should be mandatory.
<i>Statistical plan</i>	
Optional research biopsies are allowed into clinical trials, however, there is extreme variation in the number of participants who will choose to donate tissue. Variability in participant donation can lead to incomplete sample collection, leaving important research questions unanswered due to a lack of statistical power. Trials with mandatory research biopsies may set unrealistic accrual goals.	Appropriate protocol design to ensure that research biopsies are associated with adequately powered correlative questions. Investigators must set realistic expectations of participant enrollment to ensure that accrual goals are achieved.