Attributes of Exemplary Research

Cancer Genomics: Conducting Exemplary Trials With Biospecimen and Biomarker Components

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The National Cancer Institute has articulated a goal to translate what we learn about genomic changes associated with cancer into novel preventive, diagnostic, and therapeutic interventions for patients with cancer.¹ Achieving this strategic goal requires increased collection and analysis of biospecimens and biomarkers in cancer clinical trials. Because of the magnitude of this topic, two articles in the Attributes of Exemplary Research series will be dedicated to this subject.² The first article, presented here, focuses on procedural requirements of clinical trials with biospecimen and biomarker components. The next article in the series will focus on ethical and legal concerns and share practical tips for talking with patients about participation. Both articles incorporate advice from experts and present resources helpful to sites that conduct clinical research.

Cancer trials incorporating biospecimen and biomarker components allow researchers to integrate knowledge about cancer cell biology and its impact on treatment options and patient prognosis. Through this new understanding, novel treatment options may be developed to target specific pathways that are dysregulated in cancer cells. Additionally, biomarker tests may help identify patients with specific mutations or abnormal protein expression in certain cell pathways, allowing individualization of therapies addressing specific abnormalities. Outcomes from these clinical trials continue to advance oncology care and predict which treatments will provide the greatest disease response and least toxicity for patients.

Participation in these clinical trials helps physicians gain a professional advantage by contributing to the discovery of emerging treatments and gaining experience using predictive indicators long before they become standard care. Experience gained through these research studies prepares physician researchers for the future of cancer care and enables them to provide patients with the best possible treatment options.

Background

Biomarkers are measurable traits used to determine a specific clinical process. They can include DNA mutations, overexpression of certain cell proteins or receptors, drug levels, radiologic imaging traits, and even adverse effects of therapy, such as skin toxicity with epidermal growth factor receptor (EGFR) inhibitors. Biomarkers can be used to predict the likelihood of toxicity or treatment response to a certain regimen. Biomarkers can

either be prognostic, suggesting a clinical outcome regardless of therapy, or predictive, measuring a characteristic that indicates the likelihood of therapeutic response to treatment. Many practice-changing clinical trials have used biomarkers to determine prognostic and predictive indicators. For example, a study of pure and mixed anaplastic oligodendroglioma found that regardless of the treatment used, patients with tumors missing chromosomal arms 1p and 19q had a better survival prognosis than patients with tumors not possessing the missing alleles.³ Another study demonstrated that for patients with metastatic colorectal cancer, the presence of a *KRAS* mutation predicted that patients would have no benefit from treatment with EGFR inhibitors.⁴

Predictive biomarkers can also be positive or negative indicators. Positive biomarkers indicate a desired outcome (ie, human epidermal growth factor receptor 2 positivity predicts an increased chance of response to trastuzumab [Herceptin; Genentech, South San Francisco, CA]).⁵ On the contrary, negative biomarkers indicate a detrimental effect (ie, patients with metastatic colorectal cancer expressing the *KRAS* wild-type mutant biomarker do not benefit from anti-EGFR therapies such as cetuximab [Erbix; ImClone Systems, New York, NY; Bristol-Myers Squibb, Princeton, NJ] or panitumumab [Vectibix; Amgen, Thousand Oaks, CA]).

Biospecimens are biologic products such as tissue, blood, urine, skin, and hair from a person that can be used to predict, diagnose, and monitor disease and treatment effect. Biospecimens are essential for researchers to identify biomarkers that can be validated for clinical use. Biospecimen collection and processing procedures for clinical research often vary greatly between clinical trials and are stated explicitly in research protocols. The accuracy of testing conducted on biospecimens is largely dependent on proper collection and processing, increasing the need for quality and consistency at the site level. Testing completed on biospecimens can lead to greater understanding of disease processes and how or whether treatment is working. The role of researchers in the process cannot be overstated; without careful procedures, clinical trial results can lead to incorrect conclusions that might affect thousands of patients.

Conducting Biospecimen Clinical Trials

The first step toward participating in clinical trials that use biospecimen and/or biomarker components is evaluating the

capabilities of the research site. These capabilities influence what trials the site is able to conduct. Does the site have the necessary technology to process samples in the manner specified in the protocol? Do staff have the manpower and capability to coordinate the trial and collect specimens? If not, what modifications can be made to better prepare the site? Frequently evaluating site capabilities and investing in personnel and equipment will assure that the site remains prepared to conduct scientifically compelling trials.

Research staff are a vital component of the success of a site and should be incorporated into every aspect of the trial, including initial selection. When initially selecting trials, a research nurse or clinical research associate can help predict the likelihood that the site can realistically complete all clinical trial components for every patient enrolled. If the site identifies protocol components that cannot be completed, a discussion of these concerns with the clinical trial sponsor to find a mutually agreeable solution should be considered. For example, if the protocol requires refrigerated centrifugation of a specimen, but the site does not have the necessary equipment, the sponsor may agree to room-temperature centrifugation followed by immediate freezing. Such modifications must first be discussed with the sponsor, because only the sponsor can decide acceptable deviations.

Strict adherence to the study calendar and protocol details is vitally important. To ensure biospecimens are collected uniformly, all staff involved in specimen collection should review the study protocol and use collection kits provided by the sponsor. The research nurse or laboratory technician can usually collect specimens such as blood and urine, but coordination with nonresearch staff may be necessary to collect other specimen types. For example, if a bone marrow biopsy is needed, coordination with the physician, nurse practitioner, or physician assistant to perform the biopsy is necessary. The practitioner needs to be aware of any special requirements indicated in the protocol, such as the amount of aspirate needed and the medium in which to place the specimen. The same is true of surgical tissue biopsies. In advance of clinical trial implementation, the research site must establish a relationship with a surgeon and/or interventional radiologist committed to meeting the protocol requirements, which involves adherence to specific timelines and collection specifications established in the protocol. Because trial requirements necessitate extra effort from the clinician, the principal investigator may need to take an active role in maintaining open communication and rapport with these nonresearch staff. The research site must also have the capability of contracting with clinicians and their offices to perform protocol-specific procedures. After the specimen is collected, a trained technician familiar with the protocol should be available to receive specimens and immediately begin protocol-specific processing, which requires advanced coordination with the operating room or procedure staff and the pathology department.

Processing biospecimens also requires care and coordination. Dedicated laboratory staff are needed to process specimens exactly as required by the clinical trial, which may differ from

standard procedures at each site. Research protocols are usually explicit regarding processing requirements (ie, temperature requirements, centrifuge time, and the manner in which the specimen should be processed and shipped). Many sites meet this challenge by developing standard operating procedures specific to each trial that guide laboratory technicians through the processing requirements. For example, careful foresight is needed when dry ice is required, so the laboratory is adequately prepared before receipt of a specimen. Research staff must know in advance if items such as dry ice are to be ordered through a vendor or provided by the sponsor. There should also be appropriate storage space, in temperature-specified freezers, if needed, for the specimens. Resources for sites, such as guidance documents to assist with the development of standard operating procedures, are discussed later in this article.

Shipment of specimens must also be appropriately coordinated. It is imperative that staff know exactly where and how specimens are to be shipped. A central laboratory is generally used, but sometimes, a sponsor will require that tissue and blood specimens be sent to different laboratories, an important detail that must be verified. Staff should also consider the type of specimen being shipped. For example, if the specimen is being sent on dry ice, then staff must verify that someone at the central laboratory will be available to receive it, which is usually not the case on holidays and weekends. Small matters like this have great implications, because they restrict the days of the week in which specimens can be collected, ultimately influencing scheduling for patients and health care providers. Costs need to be addressed in the study budget, and staff should verify whether there is a specific courier or shipping company used by the sponsor. Clarification is also needed regarding whether samples must be shipped immediately or can be stored at the site and sent as a batch shipment. Coordination of specimen pickup is also necessary; staff must learn whether carriers should be called for pickup or whether study site staff should drop off the specimens at an appropriate facility. For instance, biospecimens usually need to be dropped at a manned facility.

ASCO Statement on Minimum Standards and Exemplary Attributes of Clinical Trial Sites

The ASCO statement addresses the minimum requirements for sites conducting quality clinical trials as well as the attributes of exemplary sites. Both minimum requirements and exemplary attributes are based on a review of the literature, current regulatory requirements, and consensus among community and academic clinical researchers. To conduct quality clinical research, sites should meet the minimum requirements. However, it should be noted that the exemplary attributes are voluntary and suggested as goals, not requirements. Not all attributes will apply to all clinical trial sites, and many sites may be able to conduct high-quality clinical trials without accomplishing all attributes.

Additional Considerations

As clinical trials become more complex, so do the concerns researchers must address. Original correlative trials have now led to a new generation of clinical trials, some of which exclude patients who do not possess the specific biomarker being studied. When these biomarker tests must be completed before enrollment onto a clinical trial, it is important that the study budget provide reimbursement for testing of individuals who are afterward deemed ineligible. Additionally, because biomarker testing is generally completed at a central laboratory designated by the sponsor, it is important that physicians know how long it will take to receive the results. If the turnaround time is 3 to 4 weeks, it should be considered whether patients will agree

to wait that long to begin treatment, especially if they may ultimately be excluded from the clinical trial on the basis of the test results. Considerations such as these should be discussed in advance with the sponsor, so efforts can be made to expedite testing. The research site should also be aware of all options that can be provided to patients who are excluded from the clinical trial. Sometimes sponsors will offer an expanded access option or suggest alternative trials using the medication, important factors when enrollment onto the clinical trial is the only remaining treatment option for a patient.

An additional challenge includes clinical trials requiring specimens that are collected before the patient enrolls onto the trial, such as when slides from a diagnostic biopsy are necessary. Researchers should verify with the study protocol what exactly is needed (ie, tumor block, unstained slide, and so on). Part of determining eligibility for the patient involves checking to see that these specimens are available and exist in the proper format. Usually these specimens are fixed and do not require the same shipping concerns as fresh samples. Obtaining the specimens, however, may present an entirely different set of challenges, especially when a specimen is stored at an offsite laboratory. Research staff must first confirm that the patient completes all appropriate forms to permit release of the specimen and its use for research purposes. Research staff then need to work with the laboratory to ensure the specimen is released in an acceptable period of time, which may require frequent follow-up. If the specimen is required to verify inclusion criteria, delays may postpone the patient's enrollment onto the clinical trial, which is why research sites need to designate committed staff to oversee the process.

Resources

Numerous resources are available to assist sites in streamlining trial requirements. The Office of Biorepositories and Biospeci-

Figure 1. Best practices for biospecimen resources. Data adapted.⁷

Biospecimen Checklist			
1) Do I have personnel who can be dedicated to coordinate biospecimens in clinical trials? 2) Do I have the proper equipment, space, and trained personnel to assure proper processing, storage, and shipping? 3) Do I have relationships (support of the protocol and biospecimen acquisition procedure, appointment coordinating ability, contracting ability) with outside personnel who need to participate in the biospecimen acquisition (surgeon, interventional radiologist, radiologist)?			
Management 1) Have contracting/budgeting been completed? 2) Have all IRB requirements been met? 3) Are source documents available to record procedures?	Personnel 1) Are dedicated personnel trained? 2) Have relationships been established with surgeon/interventional radiologist? 3) Has reimbursement for required procedures been contracted with external practice/department?	Specimen Collection 1) Are the study kits on site? 2) Have SOPs been developed to guide staff through collection and processing procedures?	Shipment 1) Are shipping labels/kits on site? 2) Is dry ice needed; is it on site? 3) Is carrier pickup coordinated?

Figure 2. Biospecimen checklist. IRB, institutional review board; SOP, standard of practice.

men Research (OBBR), a division of the National Cancer Institute, is dedicated to researching the impact of biospecimen processing studies, developing and distributing guidelines for biospecimen research, and developing new technology and standards for biorepositories.⁶ Numerous resources are available to researchers through the OBBR, including the Biospecimens Resource Network and voluntary guidelines called the “National Cancer Institute Best Practice for Biospecimen Resources.”⁷ The best practices are available free online and provide an outline of how to incorporate these practices into the internal procedures of a site. The guidelines are divided into two broad areas, including “Technical and Operational Best Practices” and “Ethical, Legal, and Policy Best Practices.” The technical guidelines are most applicable to this article and provide a comprehensive review of operational procedures that should be in place at research sites (Fig 1). The next article in this series will relate to additional topics covered in the guideline document.

Another helpful resource offered through the OBBR Web site is a searchable database of scientific literature addressing how procedural variables affect biomarkers and gene expression patterns.⁸ There are several mechanisms in place to search the database, enabling researchers to efficiently access all available literature on their chosen topics. For example, a researcher can enter a specific biospecimen type and immediately gain access to literature regarding preservation mechanisms that are least likely to affect specimen quality. In addition, researchers may also submit literature to be included in the database. This expansive database is free to use and is a joint effort between the Biospecimen Research Network, RAND Corporation, and National Cancer Institute Center for Bioinformatics.

A research site that successfully conducts biospecimen clinical trials must have dedicated personnel, interdepartmental collaboration, and operating procedures regarding specimen collection and processing. Using a checklist is a helpful way for a site to determine whether it is prepared to implement such clinical trials (Fig 2). With organization and commitment, sites can conduct exemplary biospecimen trials and offer patients cutting-edge treatment options.

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Upcoming Events

ASCO plans to offer online educational opportunities in which content providers to the series will discuss these topics in more detail. Visit the ASCO Web site at www.asco.org/ClinicalTrialResources for more information, and access the entire Attributes of Exemplary Research series at <http://jop.ascopubs.org>. The next article in this series, focusing on legal and ethical concerns regarding biospecimens and biomarker trials, will be published in an upcoming issue of *Journal of Oncology Practice*.

Feedback Request

Suggest future topic ideas for the series and provide your feedback by sending an e-mail to researchresources@asco.org.

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