Image-Guided Biopsy in the Era of Personalized Cancer Care: Proceedings from the Society of Interventional Radiology Research Consensus Panel

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BACKGROUND

Image-guided percutaneous biopsy is a common procedure in oncology that is integral in confirming the diagnosis of cancer, staging the disease, and determining tumor histology. However, in the era of personalized medicine, in which advances in knowledge of specific cellular pathways and characterization of tissue at molecular and genetic levels has resulted in an increase in targeted therapies, the role of the image-guided percutaneous biopsy is evolving (1). Biopsy samples are required for more than just histologic diagnosis, as biomarker status now guides standard-of-care therapy in a growing number of solid tumors including melanoma, breast, colon, and lung cancers. In addition, biopsies are no longer being performed only at the time of initial diagnosis, but are being performed at multiple time points to detect progression, predict prognosis, and guide next-line therapy (1). Image-guided biopsies are also playing an increasing role in oncologic clinical trials (2,3), as the US Food and Drug Administration (FDA) has mandated that targeted therapies be accompanied by a companion diagnostic test for appropriate patient selection (4). The research biopsy is so critical to clinical trial design that many stakeholders share the sentiment that the absence of high-quality biologic specimens is one of the most significant roadblocks to developing and validating biomarkers for their intended use (5,6). Finally, prioritizing the actualization of personalized cancer care in the United States was brought to the forefront by President Obama in his 2015 State of
the Union address, in which he announced the Precision Medicine Initiative, which should “bring us closer to curing diseases like cancer.”

Because biologic specimens acquired from biopsies will continue to play an important role in this era of cancer medicine, and the majority of biopsies are now being performed by radiologists with the use of image guidance (7), the Society of Interventional Radiology (SIR) Foundation gathered a multidisciplinary group of experts to form a research consensus panel (RCP) to explore how image-guided biopsy should evolve to meet the future needs of patients.

METHODS

Panel Membership

On June 1, 2015, the SIR Foundation assembled an RCP meeting for the development of a research agenda on image-guided biopsy in the era of personalized medicine. The panel membership included (i) a multidisciplinary group of expert panelists, (ii) representatives from governmental agencies, and (iii) representatives from industry. There were 11 expert panelists, including three interventional radiologists, one medical oncologist, one molecular pathologist, four biomedical and/or mechanical engineers, one chemical engineer, and the executive director of clinical research for cancer medicine at a National Cancer Institute designated cancer center. Representatives from the FDA Laboratory of Cardiovascular and Interventional Therapeutics and the Molecular Pathology and Cytology Branch were also present. Industry representatives came from major pharmaceutical companies, medical device companies, and manufacturers of medical imaging equipment. A member from the SIR Comparative Effectiveness Committee was also present.

Agenda Methodology

The goals of the RCP were to (i) provide a summary of the key aspects of the existing knowledge base, (ii) identify gaps in current knowledge, and (iii) provide and prioritize research recommendations. In addition, the panelists were asked to identify critical alliances that should be developed to advance the prioritized research and determine how the SIR Foundation could support these initiatives.

Ten panelists were asked to give a focused (10-minute) presentation in his or her area of expertise. Specifically, panelists were asked to (i) define the most important clinical questions that could realistically be answered through pivotal multiinstitutional clinical trials or registries, (ii) describe the most promising future directions that merit preclinical or early clinical exploration, and (iii) outline how SIR investigators could engage in these initiatives. The critical question was how to obtain high-quality biopsy tissue samples that could be processed for a number of pathologic assessments from a percutaneous image-guided approach. As such, the topics for the RCP largely revolved around the current status and potential future directions for target identification, localization, and verification.

Following the presentations, a round-robin discussion was held to identify gaps in knowledge, examine important research questions, explore potential opportunities for future research studies, and consolidate similar ideas into a short list of potential research topics. Thereafter, comments were invited from the audience. Finally, the preclinical and clinical research ideas were prioritized.

RESULTS

The panel produced 10 presentations, the results of which are summarized as follows.

Why Biopsies Are Critical

Carcinogenesis is an immensely complex process, such that, even within a histologic cancer subtype—for example, adenocarcinoma of the lung or breast—there is significant variability in cancer behavior and response to therapy. The identification of an oncogene, or other specific products required by the tumor cells for sustained growth, followed by administration of a specific inhibitor to the target, are the basis of personalized cancer treatment. Frequently, multiple different signaling pathways are involved in disease growth and progression. The pathways involved can change over the course of the disease, creating mutational heterogeneity and resulting in significant challenges for therapy. Intratumoral heterogeneity occurs when the dominant cellular composition and/or gene expression varies within the tumor at a specific site of disease within one person. In a study by Gerlinger et al (8), multiple biopsy samples were taken from patients with metastatic renal-cell carcinoma for the purposes of whole-exome sequencing as part of a predictive clinical trial with everolimus. Significant variations of gene expression and prognostic signatures were found within biopsy samples within the same tumor (8). Temporal tumoral heterogeneity can also result in genomic variations within the same and/or metastatic tumors over time. For example, it is known that breast cancer biomarkers, such as estrogen, progesterone, and HER2 receptors, vary by 32.4% when biopsies of the primary tissue are compared with biopsies of relapsed metastatic tissue (9). Therefore, biopsies of biologically relevant tissue, adequate for the evaluation of the genetic signature encoded in DNA and RNA, are essential for the analyses needed to determine and develop future treatments.

Currently, the method of acquisition of tissue can be variable and lacks standardization, ranging from different sampling techniques [fine needle aspiration (FNA) vs core biopsy] to different sampling sites (primary vs
metastatic). Given the heterogeneous nature of cancer, the quality of the biopsy can significantly affect the downstream genomic analysis, and therefore the ability to direct therapy to the appropriate oncologic pathway (10–14). As novel therapeutic agents begin to be routinely introduced with companion biomarkers, it is expected that molecular biomarker testing will become the standard of care. Therefore, cancer centers should prepare for this change in treatment algorithms.

**Pathology Implications on Molecular Testing Using Next-Generation Molecular Sequencing**

Molecular testing should be performed in the tumor tissue specimen at the time of pathologic diagnosis and when tumors exhibit resistance to chemotherapy or targeted therapy to determine changes that have occurred in molecular markers associated with treatment resistance. Although tissue specimens are preferable, tissue (ie, biopsy) and cell (ie, cytology) specimens are suitable for molecular testing. The critical requirements are appropriate sample processing and the presence of adequate amount of viable tumor cells. During tissue sampling, as much tissue as possible should be obtained to avoid insufficient samples for molecular testing. In several clinical research protocols in lung cancer at M.D. Anderson Cancer Center (eg, Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination [BATTLE] program), as many as five core needle biopsy (CNB) specimens were obtained in addition to an FNA specimen (12). The biopsy and cell samples available for molecular testing in advanced metastatic tumors are likely to be small specimens, including CNB and/or FNA biopsy specimens, which may limit molecular and genomic analysis with currently available methodologies and technologies.

The ideal specimens for molecular testing are tumor tissues obtained fresh, followed by immediate snap-freezing. However, these samples are usually available only for research purposes in academic centers and used for discovery purposes. In most pathology laboratories, diagnostic clinical tumor tissue specimens (eg, CNB, endoscopy samples, surgical resections) are fixed in formalin and embedded in paraffin for histologic processing, which can compromise the integrity of protein and nucleic acids (ie, RNA, DNA) for molecular testing, particularly when the specimens are fixed in formalin for more than 24 hours. The cytology specimens (eg, brushes, lavages, pleural and peritoneal fluids, and FNA biopsy specimens) are fixed in alcohol, which is optimal for preservation of nucleic acids, and, if there is sufficient specimen, the sample also can be fixed in formalin and processed as a tissue specimen (ie, cell block) to obtain histologic sections (15).

The requirement of malignant cell content for adequacy for molecular testing varies between laboratories and testing platforms; however, a minimum of 50 viable cells per tissue section is required for fluorescence in situ hybridization testing, and at least 500 cells per histology section are needed for DNA extraction (∼200 ng of DNA) for genotyping analysis (16). However, recently developed genotyping methodologies applying next-generation sequencing (NGS) can be performed in samples with as few as 10 ng of DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tissue samples, as well as cytology specimens (17). For DNA extraction for mutation analysis, at least 10% malignant cell content is needed for proper identification of mutations.

The need for analysis of multiple molecular and genetic changes in small biopsy and cytology specimens is driving the development of multiplexed approaches for molecular testing to maximize the use of small tumors samples. These multiplexed assays can simultaneously determine mutation, amplifications, and translocation status of many genes. Currently, direct nucleic acid sequencing using polymerase chain reaction amplification of extracted DNA is the most common technique for gene mutation analysis. There are several sequencing methods available for mutation analysis applied to DNA extracted from tumor tissue and cell specimens, especially for FFPE samples. The current polymerase chain reaction-based sequencing mutation analysis methods can be divided into uniplex (eg, Sanger sequencing and pyrosequencing) and multiplex (eg, matrix-assisted laser desorption ionization time-of-flight mass spectrometry, primer extension assay, and NGS) methodologies. Although only one hot-spot sequence is examined at a time in the uniplex methods, multiple hot-spot mutations are examined simultaneously with the use of multiplex techniques. Multiplex methodologies, including NGS platforms, are available in several testing laboratories capable of high-throughput molecular analysis, including the ability to fully sequence large numbers of genes in a single test while simultaneously detecting deletions, insertions, copy number alterations, translocations, and exome-wide base substitutions (including known hot-spot mutations) in all known cancer-related genes (14,18). Currently, NGS platforms, including whole-genome, whole-exome, and targeted gene sequencing, represent emerging diagnostic methodologies for the detection of oncogene fusions and mutations in tumor tissue specimens, including FFPE samples.

Handling of biopsy and cytology specimens for histologic and subsequent molecular testing requires thoughtful prioritization. Use of the sample for less important analysis can limit the ability to perform molecular testing required for therapy selection. It is crucial that the pathologist determine if the specimen is adequate for nucleic acid extraction and histology section-based molecular testing such as fluorescence in situ hybridization if necessary. In addition, the advent of immunotherapies, particularly those targeting immune checkpoint molecules (eg, CTLA-4, PD-1/PDL-1), will require the analysis of additional predictive
molecular markers in cancer tissue specimens (19). For adequate prioritization of tissue use, there is a need for effective communication between the pathologist, molecular diagnostic laboratory, interventional radiologist, endoscopist, surgical oncologist, and oncologist treating the patient.

TARGET IDENTIFICATION AND LOCALIZATION

Molecular Imaging Current Status and Future Directions

The standard diagnostic [18F]fluorodeoxyglucose (FDG) positron emission tomography (PET) fused with computed tomography (CT) imaging has been integrated into the biopsy process for target identification because it is particularly useful in determining the hypermetabolic portion within a large morphologically abnormal lesion or in determining the most metabolically active portion of a tumor in a morphologically normal-appearing lesion. However, for the majority of radiologists who do not perform PET/CT–guided biopsies, the major limitation of molecular imaging and intra procedural tissue biopsy is the lack of “real-time” multimodality imaging during the time of tissue sampling, as the metabolically active (ie, FDG-avid) portion of a tumor for targeted for biopsy, as detected on a previously obtained PET/CT scan, has to be correlated with an intra procedural view of the lesion based on the radiologist’s judgment (20). Fusion technologies attempt to overcome this lack of real-time multimodality imaging by marrying the molecular image, which identifies the information-rich portion of the tumor, with the intra procedural anatomic image during biopsy. The incorporation of fusing PET imaging with intraoperative CT or ultrasound (US) can presumably lead to higher-quality biopsy samples (21). However, real-time fusion imaging platforms are often bulky and used more frequently at specialized centers, rendering them less generalizable to allow for molecular imaging guidance during biopsy.

Another approach is to develop biopsy devices capable of detecting molecular tracers in the tumor tissue, allowing for more accurate intra procedural tissue sampling (22,23). For example, a biopsy device that incorporates a needle γ-detector allows for real-time intra procedural detection of a molecular tracer (ie, FDG) during the biopsy (22). These tools can be applied to existing molecular tracers that can detect key molecular events such as metabolism (ie, FDG), neovascularity (ie, arginine-glycine-aspartic peptides), and proliferation (deoxyfluorothymidine).

Other emerging technologies that warrant further investigation include microbubble and intraluminal molecular tracers. The intradermal injection of microbubble molecular tracers results in localization of the contrast agent into the sentinel lymph node of a patient with breast cancer and can be used to direct US-guided biopsies of the sentinel lymph nodes to the enhancing portions (24). This type of technology may be translatable to other tissues such as liver in the near future. Intraluminal molecular tracers, including surface-enhanced Raman scattering nanoparticles (25), can be visualized and used to detect various molecular events within hollow organs such as the gastrointestinal tract (25). These functionalized nanoparticles, with the capacity for intraluminal imaging, may provide an interesting avenue toward molecular targeting and tissue sampling of intrabiliary masses, for which current biopsy techniques (biliary brush or clamp biopsies) are historically of low yield.

Ultimately, the limiting factors for exploring molecular image-guided identification of biopsy targets are not related to the capacity of functionalized probes. Rather, the success of using molecular imaging to optimize the targeting of biologically relevant tissue is related to how well molecular information can be incorporated into the procedure.

Radiogenomics

Radiogenomics, the systematic extraction of phenotypic data from clinical imaging modalities and integration with large-scale biologic data, provides a unique opportunity for bringing molecular diagnosis to the clinic. By leveraging (i) new knowledge extractable from existing diagnostic imaging tools, (ii) rapidly expanding computational power, and (iii) improved understanding of disease biology, it is becoming increasingly feasible to extract spatially and temporally resolved, clinically meaningful large-scale molecular detail of a given disease from existing CT, magnetic resonance (MR), and PET imaging scans by using radiogenomics (26–29). In the realm of personalized medicine and molecular diagnostics, data suggest that radiogenomics can play an important role by identifying the best biologic targets in which to perform biopsy and thereby increase informational yield. Indeed, published data suggest that radiogenomics can be used to (i) augment targeted biopsy by identifying specific lesions likely to harbor specific tumor molecular phenotypes of interest, (ii) guide regional biopsy by identifying within a specific lesion where specific molecular alterations of interest are likely to be harbored, and (iii) replace biopsy altogether in instances in which radiogenomic phenotypes are able to capture global phenotypic information that cannot be adequately or reliably captured by spatially localized biopsy (ie, “the sum is greater than the parts”; 30–36).

Navigational Tools

A variety of navigation systems have been developed to improve target visibility and access for these complex cases. Current navigation systems include two major
components: (i) registration, whereby the current imaging dataset is matched to a reference dataset; and (ii) tracking, whereby the position of a device is displayed on the current imaging dataset in real time (37,38). Registration involves fusing two or more disparate imaging datasets on one display and spatially aligning these datasets together. Fusion display techniques have been in widespread use in the clinical setting with diagnostic imaging as in PET/CT, but have only recently been employed for interventional procedures. The spatial alignment between the two datasets may be “rigid,” allowing only rotation or translation of the datasets, or “elastic,” allowing local stretching to accommodate local deformities of the tissue. Tracking involves real-time localization of the instrument, displaying its relationship to the target lesion. There are three major categories of tracking systems. First, electromagnetic (EM) tracking involves a sensor coil mounted on the instrument within a differential magnetic field positioned over the procedure area (39). The pitfall of EM tracking is that adjacent metallic structures may distort the tracking. Second, optical tracking uses light-emitting diodes to report the location of the instrument but requires an uninterrupted “line of sight” between the instrument and camera. Therefore, optical tracking techniques are limited because they can track only the handle of the instrument and not the tip. Last, medical imaging–based tracking with cone-beam CT–based navigation uses real-time fluoroscopic guidance of the instrument for tracking, which is fused to the cone-beam CT three-dimensional data set (or any other cross-sectional imaging). This tracking modality is most often used in vascular interventions but can also be used for positioning of needles in biopsy and ablation procedures.

Multiple studies have been published supporting the role of navigation systems for image-guided intervention with quantifiable goals such as accuracy, decreased radiation exposure, or decreased overall procedure time (40,41). However, few randomized controlled studies have been performed. In a phantom study, Applebaum et al (40) were able to demonstrate statistically significant improvement in accuracy (decreased number of passes) and reduced time to reach the target with the use of EM navigation compared with conventional CT-guided technique for biopsy of small lesions. Penzkofer et al (41) were able to demonstrate a statistically significantly reduced radiation dose compared with conventional CT-guided biopsy. Interestingly, a prospective, randomized trial (42) comparing CT fluoroscopy versus CT fluoroscopy with EM navigation in percutaneous lung biopsies did not demonstrate improvement in radiation dose, number of needle repositions, or diagnostic yield, and even demonstrated increased procedure time in the EM navigation group. The limited level I data demonstrating the clinical utility of navigation systems may be related in part to the fact that prospective, randomized controlled trials are more difficult to design for lesions with limited visibility, which are also the lesions whose treatment will likely derive the greatest benefit from the use of navigation systems. In addition, part of the difficulty in demonstrating improved efficacy is that current biopsy techniques are already successful. Additionally, there are technical aspects of navigation systems, specifically related to compensating for respiratory motion during registration and tracking, that still need to be improved.

**Optical Imaging**

An “optical biopsy” refers to the different novel imaging methods that use the properties of light to acquire microscopic images to characterize tissue in vivo, enabling an operator to make a real-time diagnosis that was previously possible only by using histologic or cytologic analysis. Optical imaging techniques can provide improved image resolution, contrast, tissue penetration, and biochemical and molecular information about mucosal or tissue surface disease. With its high degree of sensitivity, high spatial resolution, real-time image display, and three-dimensional imaging, the addition of optical imaging to biopsy procedures has the potential to improve image guidance and decrease the risk of sampling error. However, any optical biopsy system would need to be compatible with the existing clinical armamentarium of needles, sheaths, and catheters (23).

Contrast-based and label-free techniques are used for real-time in vivo optical imaging. Contrast-based techniques can be divided into those that measure contrast in different tissues or are target-specific. The contrast agents that are used for imaging are considered drugs and subject to Investigational New Drug approval by the FDA. Optical molecular imaging of exogenously administered indocyanine green, a clinically approved agent that fluoresces in the near-infrared range and localizes to hepatocellular carcinoma, has been evaluated in an initial clinical trial (43). Photoacoustic imaging is a hybrid technique that uses optical absorption and ultrasonic wave propagation. It has been used to detect the presence of microcalcifications during breast biopsy (44). Probe-based confocal laser endomicroscopy is a technique that has been integrated into gastrointestinal and pulmonary interventional procedures whereby a low-power laser illuminates the tissue with subsequent detection of the fluorescence of light reflected in the tissue through a pinhole at a resolution of 1 μm (45).

Label-free techniques often involve the use of lasers that pulse in the near-infrared range of the spectrum to measure intrinsic tissue optical properties such as absorption, scattering, autofluorescence, second harmonic generation, and Raman or polarization response. These techniques provide direct nondestructive in situ assessment of biochemical, structural, and functional changes in tissues and cells. They are considered as
medical devices and are subject to Investigational Device Exemption approval by the FDA. Label-free methods have several advantages over contrast-based methods: they have broader clinical implications, cost less, and have the potential for more universal adoption. Near-infrared spectroscopy can be used in the diagnosis of cancers in which tumor blood flow, oxygenation, and oxygen metabolism (ie, tumor metabolic rate of O₂) vary. A dynamic technique of near-infrared diffuse correlation spectroscopy was used to assess the blood flow in tumor versus normal breast tissue, with tumor tissue exhibiting decreased blood flow (46). Endoscopists have used elastic scattering spectroscopy, whereby tissue pathologic conditions are detected and diagnosed by using spectral measurements of the elastic-scattered light in a manner that evaluates tissue scattering and absorption properties over a wide range of wavelengths to assess for Barrett esophagus and colon cancer (47,48). Raman-based spectroscopy and imaging techniques measure molecular vibration that is based on the inelastic scattering of monochromatic light from a laser in the visible, near-infrared, or near-ultraviolet range. Raman spectroscopy captures intrinsic chemical changes within tissues and uses these signatures to identify disease states (49), and has been shown to have a sensitivity of 94%, specificity of 96%, and overall accuracy of 86% in the identification of cancer (50). However, it is limited by its long acquisition time (> 1 s per pixel). Coherent anti-Stokes Raman scattering microscopy has been developed as a label-free imaging tool with subwavelength spatial resolution. The coherent anti-Stokes Raman scattering signal is several orders of magnitude stronger than the conventional Raman sign, and imaging is faster. This imaging modality has been used in the evaluation of prostate, lung, and breast cancer (49–52).

Given the use of ultrafast lasers in powering some of these optical imaging modalities, it is conceivable that we will be able to extend real-time optical imaging for high-precision intervention or therapy. With the advantages of better pinpoint sampling locations and better ability to assess tumor margins and characterize tumors, optical molecular imaging techniques are well positioned to support locoregional drug delivery and integrate with genetics and nonthermal microsurgery to support precision medicine.

TISSUE ACQUISITION
Developments in Needle Design
Biopsy techniques, which are all experience-based without rigorous validation, vary among physicians trained at different institutions. A biopsy is a tissue cutting process in which the tissue can be at different disease states and can vary in hardness, toughness, and texture. Modifications to biopsy needle design that enhance tissue acquisition are topics of engineering research. The rake and inclination angle are two key parameters that define the geometry and orientation of the cutting edge (53), and can also affect the needle insertion force (54). By using a mathematical model to predict the needle insertion force (55), an optimization algorithm can be applied to vary the parameters that define the tip geometry of a needle. Results demonstrate that needles with a large bevel surface have the lowest insertion force (55). A low needle insertion force is advantageous because it reduces tissue and organ deformation and deflection for better guidance to a targeted site and enables more efficient tissue cutting for longer tissue lengths in CNB (55) or better acquisition of cells in FNA biopsy. Other modifications that have been shown to increase the length of the core biopsy specimen include the creation of a vacuum inside an 18-gauge needle to consistently acquire 40–60-mm-long cores and the use of a magnetic abrasive powder to polish the inner needle surface to reduce frictional forces with the tissue (Shih A, oral communication, June 1, 2015). Finally, for FNA, high-frequency oscillations (0.83 Hz) with suction have been shown to yield samples with better cellularity than samples obtained with the use of low-frequency (0.47 Hz) oscillations (personal communication, Albert Shih).

The consistency, homogeneity, and texture of soft tissues are issues that affect the study of needle biopsies with quantitative, repeatable outcomes. Physical clinical simulators with anatomically accurate geometries made of tissue-mimicking phantom materials (gellan gum [56], silicone [57], polyvinyl chloride) with proper mechanical (needle insertion, hardness, and viscoelasticity) and imaging (x-ray, MR imaging, US) properties have aided in the performance evaluation of biopsy devices and may serve as training tools for interventional radiologists to learn biopsy skills.

Emerging Steerable Needle Technologies
A number of novel steerable needle technologies have emerged recently, making it possible to steer flexible needles from outside the body to reach specified anatomical targets not accessible using traditional needle insertion methods (58,59). Steering techniques can be grouped into four categories: (i) tissue manipulation, (ii) lateral needle manipulation, (iii) tip-based steering, and (iv) “shaft-based” steering (60,61). Tissue manipulation techniques involve applying forces to tissue (eg, with one’s hand or a robotic system with a closed-loop control [62]) to intentionally deform tissue and thereby move the tumor into the path of the needle as the needle is inserted. Lateral needle manipulation techniques involve the application of forces and torques to the end of the needle outside the patient to intentionally bend the needle and deform tissue (63,64). One limitation of this technique is that, although it works well near the surface, the deeper the needle is inserted, the more...
challenging it is to significantly affect the needle’s path because more tissue must be deformed. In contrast, tip-based steering techniques have equal steerability regardless of depth within tissue \((58–60)\). The most widely used approach is to harness the asymmetry of a bevel tip to intentionally deflect the needle, an effect typically amplified by making the shaft of the needle flexible (eg, making it from nitinol) \((65)\). Robotic systems have been developed in recent years that use models of needle–tissue interaction to automatically control the axial rotation of the needle to aim the bevel so that the needle steers toward the desired physician-specified target. Recent advancements include a flexure tip design \((66)\) that provides a high degree of curvature without the additional tissue damage exhibited by earlier highly steerable tip designs, as well as closed-loop control techniques that can deliver the needle tip to the desired spatial target \((67)\). Another category of steerable needle is shaft-based steering, which involves the use of precurved, telescoping, concentric tubes. These devices are typically made from nitinol, and can be used as needles or manipulators. An advantage of the shaft-based technique is that the magnitude of steering is not sensitive to tissue properties, but a disadvantage is that there is less flexibility in the shapes that can be achieved, as the curvature of each tube must be selected a priori. However, tubes can be manufactured to almost any desired curve, so the possibility exists for personalized sets of tubes for each patient. These robots have been suggested for, or specifically adapted to, the requirements of interventions in the brain, throat, lung, stomach, heart, sinuses, prostate, liver, and eye \((61)\). Despite the fact that it remains future work, we note that, in principle, it is possible for many of the designs discussed here to be implemented in handheld forms \((68–71)\).

Clinical Applications of Robotically Assisted MR-Guided Interventions

MR imaging has an unmatched potential for guiding, monitoring, and controlling therapy. In needle biopsies, the high sensitivity of MR imaging in the detection of lesions allows excellent visualization of the pathologic process, and the high tissue contrast helps to avoid critical structures along the needle trajectory. However, in the current standard of care, MR imaging is used primarily for preprocedural planning, and the potential for intraoperatively updated MR imaging is rarely leveraged during the procedure itself. To best take advantage of interactively updated MR imaging, the use of robotic assistants for image-guided manipulation of the surgical tools proves promising, as it allows for continuous monitoring and control of the instrument motion. Although there is the potential for significant benefits of intraoperative MR imaging coupled with robotic assistants, the ability to create and deploy a device capable of operating within the scanner bore is still hampered by the high-strength magnetic fields, extreme sensitivity to EM interference, and mechanical constraints of operating inside the bore of the scanner. To leverage the existing base of imaging systems and avoid the need for specialized interventional suites, it is important to develop platforms capable of operating within the bore of readily available diagnostic high-field MR scanners.

To date, a few research teams have developed clinically viable systems for intraoperative MR imaging-guided interventional procedures in the fields of neurosurgery \((72)\), prostate interventions \((73,74)\), and percutaneous interventions \((75)\) with varying levels of complexity and integration into the workflow. Several of these systems have undergone clinical trials. Krieger et al \((76)\) developed a remotely actuated manipulator for access to prostate tissue under MR guidance in a closed-bore diagnostic scanner that was demonstrated in clinical trials; the system was later improved with robotic motion control \((77)\). Su et al \((78)\) developed a piezoelectrically actuated system capable of robotic assistance during live MR imaging for image-guided prostate interventions, which has also been adapted for neurosurgical interventions inside the MR scanner bore \((79)\). Stoianovici et al \((80)\) tried to improve the accuracy problems of pneumatic actuation by developing a robotic assistant for MR image-guided percutaneous prostate interventions based on novel pneumatic stepping motors; this system is now in clinical trials. Although most systems to date are focused on image-guided percutaneous interventions within the bore of the scanner, Sutherland et al \((81)\) developed a dexterous robot to perform neurosurgery beside the bore of the scanner with a system that is now being commercialized.

COMPETING TECHNOLOGIES

Liquid Biopsy

Liquid biopsy solutions are emerging as potential alternatives to traditional biopsies. A liquid biopsy offers a noninvasive method to access the tumor and involves the analysis of blood or other body fluids to detect tumor-originated cells or fragments of DNA, micro-RNA, or exosomes. There are three main biomarkers that can be accessed through liquid biopsy: circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), and exosomes containing micro-RNA. The advantages of liquid biopsy over tissue biopsy include \((i)\) noninvasive methodology, \((ii)\) ease of obtaining serial samples, \((iii)\) lower risk, \((iv)\) lower cost, and \((v)\) less pain. Moreover, liquid biopsy may reflect the spectrum of heterogeneity present in the tumor \((82,83)\), a distinction compared with traditional biopsy, as a tissue sample may not represent the tumor molecular profile in its entirety.

Although ctDNA is an attractive option for the detection of disease burden, it does not allow for
functional assays like CTC assessments (84). In addition, ctDNA seems to be sensitive in patients with high tumor burden but remains to be assessed in localized disease. On the contrary, the coming of age of more sensitive and reproducible techniques for detection, capture, and isolation of CTCs has led to the emergence of these rare, blood-borne cells as potential biomarkers in the prognosis and treatment of many solid tumors, including breast, prostate, lung, pancreatic, and colon cancers (85–87), and as a potential tool in the diagnosis of cancer and metastasis (88). The relative number of CTCs in the blood is an independent predictor of progression in several types of cancer (89). In fact, CTCs have now been proposed as surrogate biomarkers in more than 270 clinical trials (90). The aims of research on CTCs include (i) estimation of the risk of metastatic relapse or metastatic progression (prognostic information), (ii) stratification and real-time monitoring of therapies, (iii) identification of therapeutic targets and resistance mechanisms, and (iv) understanding of metastasis development in patients with cancer.

Despite these developments, the integration of liquid biopsies into routine clinical practice remains challenging for several reasons. A vast number of methods have been described for the potential detection of circulating biomarkers, without a consensus on the ideal technical approach. There are a multiplicity of potential biomarkers for evaluation, and it remains unknown which one, CTCs or ctDNA, may prove to be the better marker. There is also difficulty in controlling the preanalytical phase to obtain robust and reproducible results. Currently, only a limited number of technologies are available and distributed widely. The emerging technologies that are more sensitive for detection have yet to be approved by the FDA and integrated into clinical care. The available techniques are not cost-effective, which limits accessibility for patients. Finally, the lengthy turnaround time for analysis is incompatible with the urgent need for actionable results in clinical care.

In summary, liquid biopsy provides new opportunities for management of patients with cancer, adding a new useful tool for diagnosis, staging, and prognosis. Development of standardized methodologies for analysis and validation in large prospective clinical trials is needed for the implementation of the liquid biopsy approach in the clinical management of patients with cancer.

### PANEL DISCUSSION

Following the presentations, the panelists identified gaps in knowledge (Table 1). Subsequently, a list of possible basic science research and clinical trial ideas (Tables 2, 3) was proposed and the ideas were ranked. Organizational support initiatives (Table 4) were also developed, as the panelists recognized the need for a multidisciplinary approach to evolving the image-guided biopsy to meet emerging standard-of-care and clinical trial needs.

<table>
<thead>
<tr>
<th>Table 1. Gaps in Knowledge Identified by the RCP</th>
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<tr>
<td><strong>How to determine a biologically relevant lesion in which to perform biopsy.</strong></td>
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<tr>
<td><strong>Where is the best place to get samples based on microenvironment?</strong></td>
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<td><strong>Is there a sentinel metastatic implant that needs to be sampled?</strong></td>
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<tr>
<td><strong>Verification of sample: does the quantity of the biopsy sample matter? How can we improve the yield of the biopsy specimen?</strong></td>
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<td><strong>Does the size of the tumor matter for successful biopsy?</strong></td>
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<td><strong>When using needles that can navigate, how to image the needle tip?</strong></td>
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<td><strong>Does imaging heterogeneity correlate with genetic heterogeneity?</strong></td>
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<td><strong>Need to use tumor and temporal heterogeneity to guide therapies.</strong></td>
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<td><strong>Need for centralized database and standardization among sites, techniques, and metrics to qualify procedures, genetic profiling.</strong></td>
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<td><strong>Tumor mapping using optical imaging.</strong></td>
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<td><strong>Need for better man–machine interfaces.</strong></td>
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<td><strong>Possibility of continuous monitoring to be able to recognize resistance to therapy earlier.</strong></td>
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<tr>
<td><strong>Liquid tumors: would site-selective acquisition of blood (ie, hepatic vein for liver tumors) be beneficial?</strong></td>
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RCP = research consensus panel.

Quality-improvement guidelines for image-guided biopsy have defined acceptable diagnostic yield rates for the establishment of a histologic diagnosis (91); however, achieving these success rates, which often exceed 90%, is less certain when biomarker testing needs to be incorporated (92). Several factors make research on image-guided biopsies challenging: pathology techniques for sample evaluation are constantly evolving, and none have been established as a gold standard; technical aspects of the biopsy procedure, such as the device used to acquire the sample, number of samples acquired, and how to determine which lesion should be sampled, vary among practitioners and are not based on objective data; and how inherent tumor tissue characteristics and history of previous treatment influence yield is also unknown. Finally, there are neither registry data nor an attempt to collect or analyze large amounts of biopsy data from a radiologic perspective. Despite the lack of objective data, there is a clear expectation for the image-guided biopsy to meet the diagnostic and clinical trial needs for personalized cancer medicine. Considering all these challenges, the panel used this opportunity to develop clinical and basic research priorities that could generate high-level data for the optimization of image-guided biopsy.

The primary clinical gap in knowledge was the issue of biologic relevance, or, in other words, selecting an
appropriate lesion to yield tissue that reflects temporal heterogeneity and adequately represents the state of disease at the time of the treatment decision. If personalized cancer care is to be a reality, the goal should be to improve the biopsy yield for molecular testing, as 10%–15% of patients currently do not have sufficient material for next-generation molecular testing (93). So how can we ensure that a patient undergoing an image-guided biopsy will have sufficient and representative material for genomic analysis? These are two multifaceted issues that are distinct and related. It is clear from the gaps in knowledge identified that emerging developments in biomedical engineering, radiogenomics, and molecular imaging all have the potential to contribute significantly to how biopsies are performed. However, until these technologies are ready for widespread use, there remains a need for a reliable way to identify a suitable lesion for biopsy. The RCP proposes that a clinical trial be designed to develop an objective and predictive classification scheme that could be used for lesion selection for the purpose of molecular diagnostic testing. This would likely require the aggregation of radiologic and pathologic data from multiple institutions to establish and validate the imaging and technical factors influencing yield.

In terms of preclinical research, the potential to develop new biopsy tools beyond the devices that have been traditionally used for FNA and cutting core biopsy is immense. The developments in biomechanical engineering include optical or genomic sensory capability in the needle tip and the integration of handheld robotic

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**Table 2. Basic Science Research Themes**

1. Need for smarter needle with sensory component (optical vs genomic); optical spectroscopy to determine histology or genomics
2. Explore needle design: tendon operated needles, concentric tube devices, flexure-tip needle
3. High-precision label-free single-cell imaging for biopsy
4. Magnetic gripper installation to increase biopsy yield
5. Insert a smart chip to get continuous information from tumor

**Recommendation:** Optimizing needle design for biopsy was consistently ranked by the panel as an important research theme. However, the group was split in terms of prioritizing between supporting a research initiative that could integrate current developments in needle design engineering or supporting efforts to develop a “smart” needle armed with sensory capabilities.

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**Table 3. Clinical Research Themes**

1. Develop objective classification scheme for lesion assessment correlated to yield (biologic relevance)
2. Correlate biopsy samples with liquid biopsies to determine pathways to metastases (development of a tumor behavior map to study development/temporal heterogeneity)
3. Compare real-time imaging vs static imaging with or without navigation systems
4. Reinvestigate imaging fusion systems to target biopsy for specific sites
5. QI initiative to optimize existing biopsy techniques
6. Higher level modeling of imaging phenotypes of tumors
7. Correlation of findings from different sources of samples: CTC, ctDNA, image-guided biopsy; include CTC markers in clinical trials; liquid biopsies from different sources (peripheral blood vs local blood samples)
8. Standardize technologies; improve biopsy size
9. Role of 3D printing: education, planning biopsies, comparison of biopsies/thermal ablation with or without 3D modeling for planning

**Recommendation:** Proposals addressing the question of how to determine biological relevance and improve biopsy yield were ranked highest by the panel. A secondary area of interest involved exploring ways of correlating the liquid biopsy with the image-guided biopsy. 3D printing as a tool to make patient specific needle guides or patient specific training phantoms also garnered interest.

Studying the utility of real-time imaging vs. static imaging vs. image fusion vs. imaging navigation was also favored.

CTC = circulating tumor cell; ctDNA = circulating tumor DNA; QI = quality improvement; 3D = three-dimensional.

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**Table 4. Organizational Support Initiatives**

1. Need for better dialogue between clinicians and basic research scientists
2. Develop a multidisciplinary focus group to advance biopsy knowledge—could be organized as a forum during a national meeting (ie, ASCO, ASCO Gastrointestinal Cancers Symposium)
3. Need to increase awareness of the importance of image-guided biopsy through public relations and education

**Recommendation:** Members of the panel and the audience unanimously thought these proposals should be pursued.

ASCO = American Society of Clinical Oncology.
devices that allow for sampling within multiple sites in a lesion, addressing the issue of tumoral heterogeneity. The panel also recognized the importance of a multi-disciplinary cooperative approach and the need for early engagement of the FDA to bring these devices successfully from the bench to bedside.

Finally, the panel acknowledged the need to increase the awareness of the importance of image-guided biopsy and the role that it plays in personalized cancer medicine. Stakeholders, including radiologists who perform the procedures, oncologists who treat patients and design trials, pathologists, basic scientists, engineers, and pharmaceutical and medical device companies, need to understand the challenges and collectively be engaged to advance the biopsy procedure. Historically, radiologists, the physician specialists who most commonly perform image-guided biopsies, have largely been left out of clinical trial designs and national discussions regarding the use of biomarkers and biologic specimens. For example, the American Association for Cancer Research, FDA, and National Cancer Institute convened a consensus panel and issued a report on the use of biomarkers in cancer drug development in 2010 (6). Of the 122 members of the multidisciplinary panel, which included 27 physicians, only one had a background in radiology, and he was a nuclear medicine physician (6). It is important that SIR makes the image-guided biopsy an organizational priority for research and explores ways to become more integrated into the national discussion on biologic specimen acquisition and use in the age of personalized medicine.

REFERENCES

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