Spectral-domain low coherence interferometry/optical coherence tomography system for fine needle breast biopsy guidance

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(Received 15 September 2008; accepted 8 January 2009; published online 26 February 2009)

A novel technology and instrumentation for fine needle aspiration (FNA) breast biopsy guidance is presented. This technology is based on spectral-domain low coherence interferometry (SD-LCI). The method, apparatus, and preliminary in vitro and in vivo results proving the viability of the method and apparatus are presented in detail. An advanced tissue classification algorithm, preliminarily tested on breast tissue specimens and a mouse model of breast cancer is presented as well. Over 80% sensitivity and specificity in differentiating all tissue types and 93% accuracy in differentiating fatty tissue from fibrous or tumor tissue was obtained with this technology and apparatus. These results suggest that SD-LCI could help for more precise needle placement during the FNA biopsy and therefore could substantially reduce the number of the nondiagnostic aspirates and improve the sensitivity and specificity of the FNA procedures. © 2009 American Institute of Physics.
[DOI: 10.1063/1.3076409]

I. INTRODUCTION

Breast cancer is the second leading cause of cancer deaths in women today (after lung cancer) and is the most common cancer among women, excluding nonmelanoma skin cancers.1 According to the American Cancer Society (ACS), about 1.3 × 106 women will be diagnosed with breast cancer annually worldwide and about 465 000 will die from the disease.1 However, breast cancer death rates have been dropping steadily since 1990s, according to ACS, because of earlier detection and better treatments.1 Early detection of breast cancer is the only way to effectively manage patients that suffer from this disease. Therefore, mammography screening at every 12–24 months is strongly indicated and statistical studies show that it significantly reduces mortality from breast cancer.2 When suspicious masses are found during the mammography screening, several other tests are performed to confirm and stage the disease. Among these tests, biopsy was proven to be the best way of finding out whether a suspicious area seen in an image is actually cancer.3–5

Breast biopsy represents the first surgical intervention in the treatment of breast cancer. Breast biopsies provide very useful diagnostic information and can be comfortably performed with intravenous sedation and local anesthesia. Because the majority of lesions for which women undergo biopsy prove to be benign,3 and because many women have multiple biopsies during their lifetime, less invasive techniques are desirable. Three types of biopsy are currently used on a larger scale: fine needle aspiration biopsy (FNAB), core needle biopsy (CNB), and vacuum biopsy (VB). FNAB is preferred by many patients because it is less invasive and does not produce discomfort or bleeding. However, its diagnostic yield appears to be largely dependent on the biopsy physician’s skills.6

FNAB is the most minimally invasive and best tolerated procedure, typically using a 23 gauge needle or smaller.4 The results are rapidly available for cytopathologic analysis and the patient may have a diagnosis at the time of biopsy. The number of FNAB procedure varies from one clinic to another within a range of a few hundred to thousands,7 but even for small clinics it is usually over 100 per year. Currently, most of the FNAB interventions are done without any guidance modality. However, due to the inability to identify tissue type by manual palpation and the challenges of positioning the needle tip within viable tumor which may be admixed with normal, reactive, and necrotic tissue, nondiagnostic aspirates occur in about 20% of aspirates and in 5%–15% of patients.7 Also, due to inability of the biopsy physician to always place the needle within the most representative volume of the suspicious mass, the overall diagnostic yield for FNAB ranges between 70% and 90%.8–10 Therefore, a relatively simple but efficient method for FNAB guidance would substantially increase the diagnostic yield of this simple, minimally invasive, and affordable procedure. Since FNAB samples are minute tissue specimens, any measure which could enhance biopsy yield should present an advantage.

Both CNB and VB have higher diagnostic yields than FNAB due to the relatively large volume of excised tissue. In patients with large palpable tumors, CNB and VB can diagnose the lesion in 80% to 90% of cases.11–13 However, when tumors are smaller or not palpable, the diagnostic rates are much lower. Therefore, newer techniques and instruments, including stereotactic CT and ultrasound guidance are used for the diagnosis of small nonpalpable breast tumors.14–18 Unfortunately, these technologies are usually not available in small clinics, require additional personnel, and as a result are less affordable.
In this paper we present a technology and instrumentation based on low coherence interferometry for fine needle aspiration breast biopsy guidance. Our preliminary study on breast tissue samples and a pilot validation study on a breast cancer animal model demonstrate the potential of this technology to increase the diagnostic yield of FNAB procedures.

II. MATERIALS AND METHODS

A. Breast tissue classification

Biopsy guidance requires automated tissue classification to provide the clinician with real-time feedback about the nature of the tissue present at any moment near the tip of the needle. Automated tissue classification is a very complex problem. Various optical methods have been developed over the years to automatically interpret tissue type and improve biopsy outcome. Among them, spectroscopic-based methods have shown real promise (see Alfano et al., Yang et al., Gupta, etc.) Diffuse reflectance methods have also shown potential for tissue diagnosis (see Bigio et al. and Palmer et al.). However, neither of the above-mentioned methods can probe tissue in depth and therefore their role is limited to guide the biopsy of epithelial malignancies (i.e., colon, esophagus, cervix, etc.). Another limitation of these techniques is that they cannot be performed through the lumen of very small catheters or needles. Therefore, they can only be used in combination with endoscopic instrumentation that has an instrument channel. Their use in breast biopsy or the biopsy of other organs that require the insertion of the probe through a needle has not yet been proven.

Recently, low coherence interferometry (LCI) and optical coherence tomography (OCT), which is a high resolution structural imaging technology based on LCI, have shown great promise in disease diagnosis. LCI is an optical ranging technique that is capable of measuring depth resolved (axial) tissue structure, birefringence, flow (Doppler shift), and spectra with a spatial resolution of several microns. LCI and OCT allow tissue characterization over a depth of 2–3 mm, which is almost one order of magnitude higher than the sampling depth of the spectroscopic approaches. Besides this advantage, they can be fiber optic implemented, and therefore they can use probes that can easily fit within the bore of a fine gauge needle, in both scanning and nonscanning modes, allowing diagnostic information to be obtained directly from the FNAB site.

Typical LCI profiles for adipose, fibrous, and tumor breast tissues are shown in Fig. 1. Major differences between the adipose and the other two tissue types are fairly clear: signal variations with depth are much more pronounced. However, it is more difficult to distinguish between fibrous and tumor tissue. Therefore, sophisticated algorithms are being developed by various research groups to accurately detect these differences. For example, Zysk et al. reported a method for the analysis of single axial scans within an OCT image, which is compatible with simple low coherence interferometric tissue probing. Goldberg et al. described an automated algorithm for differentiation of human breast tissue using low coherence interferometry. Schmitt et al. presented a method for the measurement of tissue optical properties based on low-coherence reflectometry. This short list of recent studies demonstrates that both LCI and OCT are being actively pursued for automated tissue differentiation.

Recently, we reported an advanced algorithm for real-time differentiation of breast tissue types. Briefly, this algorithm uses several parameters (signal slope, variance, power spectrum, mean spatial frequency of the intensity peaks, and mean peak area of the power spectrum components) derived from the LCI reflectivity profiles or A-lines from OCT images. The first step in the algorithm is to calculate the mean values of these parameters over a reasonable number of A-lines (100 or more) and group them as column vectors \( \mathbf{x}_i \). These calculations are performed for three tissue types: adipose, fibrous, and tumor. However, additional categories can be included such as fibroglandular, necrotic tissue, etc. A large number of training tissue samples that are representative for each tissue type (adipose, fibrous, and tumor: \( i = 1, 2, 3 \)), carefully selected by a highly trained pathologist, are used to build a database for these parameters. Then, covariance matrices are calculated for each tissue type accounting for all selected parameters

\[
S_i = \frac{1}{n_i} \sum_{j=1}^{n_i} (x_{ij} - \bar{x}_i)(x_{ij} - \bar{x}_i)^T,
\]

where \( n_i \) is the number of elements in each tissue class, \( T \) indicates matrix transpose, and \( j \) represents the \( j \)th training sample for each tissue class.

The covariance matrices from the training data set are used in the algorithm for the validation of tissue that is being investigated. For each sample to be diagnosed, the mean values of the same parameters used in the training set and the

![FIG. 1. Typical reflectivity profiles for adipose, fibrous, and tumor tissue.](image-url)
covariance matrices calculated for the training set are used for calculating a quadratic discrimination score: \[ d^2 = \frac{1}{2} \ln |S_i| - \frac{1}{2} (x - \bar{x})^T S_i^{-1} (x - \bar{x}), \] (2)

where \(|\cdot|\) indicates the matrix determinant, \(S_i^{-1}\) is the inverse matrix of \(S_i\), and \(x\) is the column vector made of the eight calculated parameters for that sample. At the end, three scores are obtained for each sample to be diagnosed and indicate the proximity of the sample to each of the three tissue types in a multidimensional space spanned by the eight parameters. The maximum quadratic score is selected to assign each sample to the correct tissue type.

This algorithm was preliminarily tested in an ex vivo study on breast tissue specimens and in an in vivo pilot animal study. An overall accuracy of 84% in classifying each tissue type was obtained for the ex vivo study. Details are presented in Sec. III. To our knowledge, this is the first demonstration of automated tissue differentiation with this level of accuracy by using LCI.

B. System description

We have previously reported a time-domain implementation of a LCI system for FNAB guidance of the breast procedures.\(^{34}\) However, we have recently developed an advanced SD-LCI/OCT system and probe for FNAB guidance. Compared to the previously reported approach, we have made significant improvements to system sensitivity, stability, and speed, as well as in probe technology development. The previous time-domain approach had speed and stability limitations, which could degrade the results of the in vivo measurements and impact biopsy guidance accuracy. Therefore, we decided to use a novel technology, based on the spectral-domain approach, which has proven to overcome the above-mentioned limitations.\(^{35,36}\) The new system is simpler, yet is very robust and easy to manipulate. A new probe was designed as well. This probe uses actual biopsy needles, provides good tissue suction capabilities, and superior optical performance.

A schematic of the instrument, based on the spectral-domain approach, is shown in Fig. 2. It consists of four sub-
systems: 1.3 μm light source, fiber optic interferometer, spectral detection unit, and data acquisition and processing unit. A broadband superluminescent diode with a 1310 nm central wavelength and 72 nm bandwidth and Gaussian spectrum (Denselight, CA) is used as a light source. According to Eq. (3), the theoretical axial resolution \( l_z \) provided by this source is about 10.5 μm in air and about 8 μm in tissue:

\[
l_z = 0.44\frac{\lambda_0^2}{n\Delta\lambda},
\]

where \( \lambda_0 \) is the center wavelength of the light source, \( \Delta\lambda \) is the spectral width of the light source, and \( n \) is the refractive index of the sample (~1.38 for biological tissues). An optical circulator is interposed between the light source and the fiber beamsplitter to maximize the amount of light that is transmitted to the sample arm of the interferometer and to minimize the backreflections into the light source. A fraction of the light backscattered from the sample passes back through the probe into the interferometer, where it mixes with the reference beam. An optical delay line is used to adjust the length of the interferometer’s reference arm in order to create interference fringes. The combined light beams are then sent
to a spectrometer, which consists of a collimator, a diffraction grating with 1180 lines/mm (Wassatch Photonics, Utah), a lens system, which focuses the diffracted beam onto the linear array detector, and a linear array C-link camera.

The C-link camera consists of an indium gallium arsenide (InGaAs) line detector with 512 elements (SU512LX, Sensors Unlimited Inc.), an analog board that amplifies the detected signals, a digital board that converts these signals to a camera-link format, and a digital-to-analog converter that generates frame synchronizing signals for a galvanometer pair, which is used when our system is turned into the OCT mode. Since off-the-shelf InGaAs cameras are expensive and bulky, we have decided to develop a lower cost miniaturized camera for this application. A detailed schematic of this camera is shown in Fig. 3.

The speed of the camera sets the measurement speed (A-line rate) of the system, which in our case is 5.12 klines/s. This speed is not very high compared to state of the art OCT systems, but is already two orders of magnitude higher than in the initial time-domain design and suffices for this application. However, it can be increased to about 45 kHz with the recently released 1024 element InGaAs sensor arrays from Sensors Unlimited, Inc.

The output of the camera is digitized by a camera-link board (PCI-6028, National Instruments) that resides in the computer. The sampled data is transferred continuously to computer memory. A discrete Fourier transform is performed on each set of 512 data points acquired by the camera-link card to produce an axial depth profile of the sample (A-line). A user friendly interface was developed to set the measurement mode (LCI or OCT), camera parameters (integration time, sensitivity, and sensor cooling options), sample/patient ID, measurement speed, and averaging options.

An important design parameter of the LCI/OCT system is the imaging range. As shown by Hausler, the depth range \( z \) is inversely proportional to the spectral resolution \( \Delta \lambda \).\(^{36} \)

\[
z = \frac{\lambda^2}{4 \Delta \lambda}.
\]

Therefore, we designed the spectrometer to have a spectral resolution \( \Delta \lambda \) better than 0.15 nm, which allowed us to obtain an imaging range of more than 2 mm in tissue. This spans the 1 to 2 mm typical obtainable imaging depth in tissue with a LCI system that has over 100 dB Signal-to-noise-ratio. The lens system is a crucial element for spectrometer performance. A fast well designed lens system assures a diffraction limited spot on each pixel of the linear array camera, and thus maximizes the efficiency of the spectrometer and significantly reduces the cross-talk between the individual elements of the detector array. We optimized a custom design in ZEMAX for efficient collection of light on each pixel of the detector, so that the spectral resolution is limited only by the pixel size. A schematic of the ZEMAX design is shown in Fig. 4.

Photographs of the SD-LCI/OCT system and OCT probe are shown in Fig. 5. As it can be observed, the system is fairly compact and engineered for clinical use. It weighs 35 lb and is currently enclosed within a 19 × 17 × 9 in.\(^3\) wheeled rack. It is easy to configure and very robust. No optical alignment issues or electrical problems were encountered when the system was transported to different locations (Maine and Boston) to perform the animal and the excised tissue specimen studies.

The SD-LCI/OCT system was designed to accommodate various types of probes. Since it works in both LCI and OCT modes, either scanning and nonscanning probes can be used. A benchtop OCT probe was used to test the system in the OCT imaging mode. For the ex vivo LCI experiments, a simple probe was used. It consisted of a standard 10 ml plastic syringe and a bare fiber inserted through the lumen of a 23 gauge needle. However, for the in vivo animal study a more realistic probe was developed to approximate a real biopsy procedure and test its tissue suction capability.

A photograph of the biopsy probe used for the animal study is shown in Fig. 6. This probe uses a 10 ml syringe, which was slightly modified for this application, a custom design stylet, a 23 gauge needle, and a biopsy gun. The biopsy gun is used to manually pull the plunger and produce an aspirate. The disposable parts of the probe are the biopsy needle and the stylet. The stylet consists of a 32 gauge stainless steel hypodermic tube, a single mode SM28 optical fiber, and a fiber ferrule. The hypodermic tube protects the optical

\[
\text{FIG. 7. OCT images of breast fibroadipose tissue, human finger tip, and finger nail. Scale bar: 500 \mu m.}
\]
fiber from breaking when the needle is inserted in the tissue. The fiber is polished at 12° angle at the distal end to avoid light backreflections and is glued inside the hypodermic tube with a high-temperature epoxy. The stylet ferrule is simply inserted into a custom fiber optic connector that is mounted on the plunger’s piston. A standard fiber optic connector is mounted on the other end of the plunger and is used to connect the biopsy probe to the LCI system by a regular fiber optic patch cord. Besides the stylet, the other customized part of the probe is the syringe plunger. It is designed to fit very well within the ID of the syringe and create adequate vacuum when pulled. The plunger also moves the stylet to allow enough cells to be collected within the biopsy needle and produce an aspirate that is cytopathologically interpretable, meaning that enough cells are collected to permit cytological interpretation. This probe can be modified to add a scanning option (rotation or translation) and thus to provide OCT images.

The biopsy gun, very similar to that currently used at MGH for FNAB procedures (model 391-938-E, Cameco Corp.), is used to pull the syringe plunger and produce an aspirate. The syringe can be easily pulled off from the gun to replace the disposable parts (needle and stylet) for each biopsy procedure. A glass syringe (model 10MDR-GT, SGE Analytical Science) was used in our study, but any similar syringe can be used.

The SD-LCI/OCT system was fully characterized and tested in our laboratory before performing the ex vivo/in vivo studies. It exhibits an axial resolution of 11.5 μm in air, which corresponds to approximately 8 μm in tissue (for a refractive index for tissue of ~1.38), and a sensitivity greater than 105 dB. The measured axial resolution correlates relatively well with the theoretical value of 10.5 μm. The very small discrepancy might be attributed to the shape of the spectrum, which was not purely Gaussian. The sensitivity is superior to that of time-domain system (101 dB) reported before, while the measurement speed is more than two orders of magnitude higher (5.12 kHz compared to 25 Hz). OCT images of 512 × 256 pixels are being displayed at a rate of 5 frames/s with this system. This rate is relatively low for OCT imaging, but sufficient for the LCI mode allowing for adequate averaging and elimination of tissue motion artifacts.

The benchtop OCT probe and the biopsy probe were tested as well. OCT images that were taken with the OCT probe are shown in Fig. 7. The reasonably good imaging depth (over 1.25 mm in tissue) and the high contrast and fine details shown in the OCT images demonstrate the enhanced imaging capabilities of this system. The LCI probe was used as well to collect depth reflectivity profiles from several biological samples (chicken adipose tissue, bovine muscle, pig skin, etc.). A slightly smaller penetration depth (1.15 mm) was observed compared to the OCT mode. This is explained by the fact that a simple bare fiber was used without any focusing elements. However, we recently developed a stylet probe with a GRIN fiber as a focusing element spliced to the probe’s fiber. This new design is currently being tested and shows improved depth, similar to that of the OCT probe.

### III. RESULTS AND DISCUSSIONS

The capability of our system and algorithm to differentiate tissue types was initially tested on breast tissue specimens. The breast tissue specimens were obtained from the Pathology Department at the Massachusetts General Hospital (MGH), and National Disease Research Interchange (NDRI). No information about tissue donors was provided. Tissue procurement, handling, and data collection were performed according to an MGH-approved IRB protocol (2002P000487 from 09/14/2007) and NDRI Protocol (DIFN1-001-005 from 03/05/2007).

LCI measurements were performed on 152 tissue samples. Each measurement site was marked with ink and histology was performed to correlate the LCI measurements with histologic findings. However, for 15 samples the histology reader could not find the ink marking and therefore these samples were taken out of the study. From the remaining 137 samples, 48 were assigned to a training set and 89 to a validation set. The training set allocation was based on histopathologist recommendation. These samples were selected to

**Table I. Summary of the ex vivo LCI diagnostics tissue study.**

<table>
<thead>
<tr>
<th>Histology based diagnosis results</th>
<th>Automated algorithm results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adipose</td>
</tr>
<tr>
<td>Adipose 15</td>
<td>14/TN</td>
</tr>
<tr>
<td>Normal fibrous, fibro glandular, or fibroadipose tissue 49</td>
<td>4/TN</td>
</tr>
<tr>
<td>Tumor or tumor admixed tissue 25</td>
<td>1/FN</td>
</tr>
<tr>
<td>Total samples: 89</td>
<td>54 TN; 20 TP; 10 FP; 5 FN</td>
</tr>
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best represent each of the three tissue types: adipose, fibrous, and tumor. An example of the histologic appearance of these three tissue types is shown in Fig. 8.

The algorithm was first trained on the training set and then was tested on the validation set. Histology readings were performed by a histopathologist blinded to the algorithm findings and were then correlated with the algorithm findings. Our interest in this study was to train the algorithm to distinguish between normal and abnormal tissue (tumor or tumor admixed with normal tissue), and even more importantly to preferentially recognize adipose tissue, which usually creates nondiagnostic aspirates (fatty fluid or fatty cells) that are not cytopathologically interpretable.

A correlation of over 95% between histology results and algorithm findings was obtained when the algorithm was retrospectively applied to the training set. The trained algorithm was then applied to the validation set. The classification results for this set are summarized in Table I. As shown, over 93% of the adipose samples were correctly diagnosed, while for the fibrous and tumor tissues a correlation of over 80% was found.

The sensitivity and the specificity of the algorithm findings were then calculated using the following equations:

\[
\text{sensitivity} = \frac{TP}{TP + FN};
\]

\[
\text{specificity} = \frac{TN}{TN + FP},
\]

where TP is the true positive value that was correctly attributed as positive to cancer findings, TN is the true negative value that was properly attributed to normal tissue, FN is the false negative value that was falsely ascribed as negative to cancer cites, and FP is the false positive value that was falsely assigned as positive to normal tissue samples. A sensitivity of 0.80 and a specificity of 0.84 were found. These are very good values considering the relatively small number of samples used for the training and validation sets. The algorithm can be further improved by using a larger training set and by applying a weighting function to each key parameter used in the algorithm.\(^{32}\)

After \textit{ex vivo} training of the algorithm, a pilot animal study was performed at the Jackson Laboratory, Bar Harbor, ME to test \textit{in vivo} our SD-LCI system and tissue differentiation algorithm. A Xenograft mouse model of breast cancer (MDB231) was used in this study. The main goal of the study was to develop \textit{ex vivo} LCI metrics for tissue differentiation and test them \textit{in vivo}. LCI probe integrity and suction capability were tested as well during this study. An IACUC protocol was filed for this study and approved by both Jackson Laboratory’s IACUC and PSI’s IACUC.

Four animals bearing palpable breast tumors (5–10 mm in size) were used in this study. The animals were anesthetized with 2% isoflurane in O\(_2\), 2 l/min, which was delivered by a face mask (see photograph in Fig. 9).

The study consisted of \textit{in vivo} LCI measurements, \textit{ex vivo} LCI and OCT measurements on exactly the same \textit{in vivo} locations, and histology correlation. The \textit{in vivo} nonsurgical procedures consisted of (1) skin shaving to expose the tumor area, (2) ink marking of the measurement site, and (3) minimally invasive tissue probing with a LCI probe. A special biopsy probe, described above, was used in this study. The 23 gauge needle was progressively inserted into tissue in two to four steps, depending on tumor size, in increments of 1 mm each. Measurements were performed on the tumor areas and on the adjacent healthy tissue. The measurement sites were marked with ink. At the end of the \textit{in vivo} procedure the animals were sacrificed by CO\(_3\) inhalation.

\textit{Ex vivo} measurements were performed on each animal on the ink marked locations during the \textit{in vivo} study. After the LCI measurements were performed, tissue was excised, the skin was peeled off, and OCT measurements over extended areas, around the marked locations, were performed. Typical OCT images of each tissue type are shown in Fig. 10. These measurements allowed us to examine larger areas of the tissue, determine tissue morphology, and thus have a better comparison with histology. At the end of the \textit{ex vivo} procedure each tissue sample was fixed with formalin and processed for histologic examination.

Twenty tissue samples of each three main tissue types were used for the training set. Similar to the human tissue specimens study, tissue differentiation criteria for normal adipose, normal fibrous or fibroglandular, and tumor were developed from the \textit{ex vivo} training data set. These criteria were then applied to all \textit{ex vivo} and to all \textit{in vivo} measurements. The findings of the algorithm were compared with histology results. The results of these measurements are summarized in Table II.

Good \textit{in vivo/ex vivo} correlation of the algorithm findings with histology was obtained, though better results might have been obtained with a larger number of animals. This relatively good correlation demonstrates that the \textit{ex vivo} criteria can be applied to \textit{in vivo} measurements. The implication of this finding is that our tissue differentiation criteria can be applied to the \textit{in vivo} measurements. In this way, \textit{ex vivo} metrics, which are easier to develop, can be used for \textit{in vivo} measurements.

\[\text{Fig. 9. (Color online) Photograph of the anesthetized animal during the biopsy procedure.}\]

\[\text{Fig. 10. OCT frames for typical tissue types on mice: (A) adipose; (B) fibrous; (C) tumor. Scale bar: 250 μm.}\]

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classification. Postprocessing of 100 A-lines of 256 depth points currently takes about 6 s on a laptop with a 2.0 GHz dual core processor. The majority of the processing time is due to the FFT used in the power spectrum calculation. The processing time could be significantly improved with parallel processing of A-scans, using a faster processor, and some algorithm optimization. The algorithm can also be implemented in hardware for real-time processing suitable for clinical applications.

Automated interpretation of LCI findings could have significant impact on LCI translation to clinical use. It can be also applied to real-time interpretation of OCT images. With this technology the pathologist or physician performing the biopsy will be able to guide the needle to the most representative diagnostic area of the suspicious mass and determine tissue type present at the tip of the needle before taking the biopsy sample. Having confidence that the FNA sample truly represents the investigated mass will often obviate the need for additional, more invasive, and costlier procedures, and produce important financial and emotional benefits.

ACKNOWLEDGMENTS

This research was supported in part by grants from the National Institutes of Health under Grant No. 1R41CA114896-01A1.

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