

INVESTIGATOR PROTOCOL TEMPLATE FOR MEDICAL STUDIES

Revised: Sept. 11, 2017

1) Abstract of the study

The project is a collaboration between Dr. Chang-Hee Won of department of electrical and computer engineering, Dr. Dina Caroline of radiology and Dr. Kathleen Reilly of surgery. Dr. Won and his colleagues have developed a tactile imaging sensor designed to display and quantify the touch sensation to discriminate between normal and abnormal tissues. Breast tumor detection is the first application for which the sensor will be tested. The goal is to develop a simple, inexpensive tool ideally to be used as an aid to diagnostic device in underserved communities.

2) Protocol Title

Tactile Breast Imaging Sensor

3) IRB Review History

This protocol has been reviewed once by the Temple IRB and modifications were required.

4) Investigator

Dina Caroline, MD, PhD

5) Objectives

The main objective of this study is to image the known tumor and compare the results with mammography or ultrasound.

6) Background

Compression-induced tactile images represent a relatively new and untapped resource in cancer imaging. The technology may be utilized to provide comprehensive mechanical and spectral information about a lesion or a tumor. This information can be used to develop algorithms to discriminate between malignant and benign lesions. Separately, elasticity imaging (Krouskop 1998; Hall 2003; Regini 2010) is actively being researched for breast cancer applications. However, a compression-induced tactile imaging sensor that addresses mechanical signatures has not yet been fully investigated. Compression of the tissues from the surface by an imaging probe may change certain properties of a lesion such as size and shape; and this information as well as data regarding other mechanical properties including elasticity will be collected and analyzed. Spot compression will be used to significantly increase the depth of interrogation. All these mechanical properties of the tumor will be analyzed and correlated with results from histopathological exams. We propose to develop Tactile Breast Imaging Sensor to characterize mechanical properties of spontaneous canine mammary tumors.

Preliminary Data: We have already developed a prototype tactile sensor for tumor detection (Lee 2011c, Won 2011). The phantom study indicates that we can detect embedded inclusion size with 4.09% error, depth with 7.55% error (Lee Won 2010), and elasticity with 5.38% error (Lee Won 2011b, Lee 2011c, Lee Won 2013).

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4. Lee, Jong-Ha and **C.-H. Won**, (2011b) "Topology Preserving Relaxation Labeling for Non-rigid Point Matching," *IEEE Transactions on Pattern Analysis and Machine Intelligence*, Vol. 33, No. 2, February 2011, pp.427-432.
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6. Lee, J.-H., Chang-Hee Won. (2013). "Tactile Sensation Imaging System for Embedded Lesion Characterization," *IEEE Journal of Biomedical and Health Informatics*, Vol. 17, No. 2, ISSN 2168-2194, pp. 452-458.
7. Regini, E., Bagnera S., Tota D., Capanino P., Luparia A., Barisone F., Durando M., Mariscotti G., Gandini G., (2010) "Role of sonoelastography in characterizing breast nodules. Preliminary experience with 120 lesions," *Radiol. Med. (La Radiologia Medica)*. Springer. February 22, 2010.

Description of the Device

The Tactile Breast Imaging Sensor operates on the principle of total internal reflection of light inside the soft and transparent silicone waveguide. Fig. 1(a) shows the conceptual diagram of the light scattering and the schematics of the system design. Fig. 1(b) shows the design of the current sensor.

The sensor prototype utilizes one layer of polydimethyl siloxane (PDMS) optical waveguide with dimensions of $20\text{ mm} \times 23\text{ mm} \times 14\text{ mm}$ and stiffness of $27.16 \pm 0.57\text{ kPa}$. We use CCD camera (Guppy F-038, Allied Vision Technologies, Exton, PA) with pixel size of $8.4\text{ }\mu\text{m} \times 9.8\text{ }\mu\text{m}$. The tactile image resolution is $768\text{ pixels} \times 492\text{ pixels}$. We attach the external force gauge (Mark-10 Series 3, Mark-10, Long Island, NY) on the top of device to measure the applied force and to ensure the accurateness of the tactile algorithm calculations. The range of the possibly measured force is from 0 to 50 N with the resolution of $1.0 \times 10^{-3}\text{ N}$. The current sensor prototype has the $1\text{ k}\Omega$ potentiometer with a digital-turning knob to control brightness of the four LEDs ($4 \times 1500\text{ mcd}$). These are commercially available LEDs, which are known to have no harmful effect on humans. The output is a JPEG digital image. The tactile images are typical JPEG images, which we analyze using a commercial software such as MATLAB.

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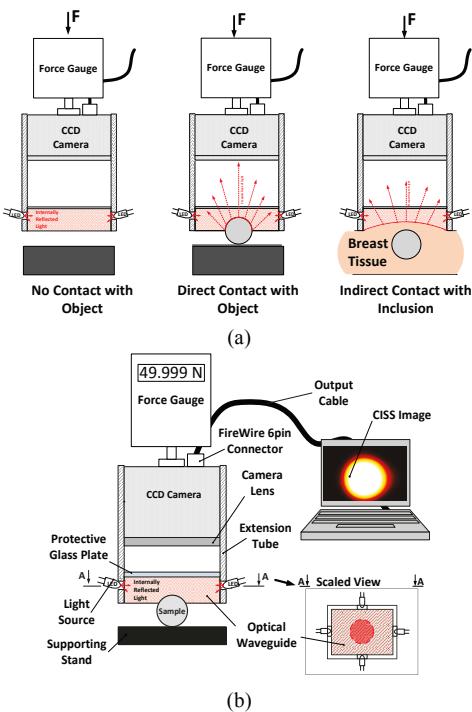


Figure 1. (a) The sensing principle is based on total internal reflection. (b) The schematic of the tactile breast imaging sensor. The output is an image as shown on the laptop screen.

7) Setting of the Human Research

The research will recruit and perform procedures at Temple University Hospital. We do not have a community advisory board. No research procedure will be performed outside of Temple University Hospital.

8) Resources Available to Conduct the Human Research

Temple University Hospital conducts over 100 breast biopsies each year. We will recruit less than 20 of those patients over a period of one year. Approximately 5% of the investigator's time will be required to recruit and enroll subjects into the study, and conduct the study procedure. All study personnel have been trained on and passed the protection of human subjects certification required by Temple University. The investigator has experience in conduct of clinical trials and have over twenty years of treating patients at Temple University Hospital.

The facilities are located at 3401 N. Broad Street Philadelphia PA 19140. The procedure is noninvasive and it will be conducted in one visit.

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Medical doctor will perform the procedure at the Temple University Hospital. If any medical assistance is needed, the medical doctor will be available.

9) Prior Approvals

No other approvals are necessary. This is a non-invasive, minimal risk procedure that can be performed in one visit.

10) Study Design

a) Recruitment Methods

Subjects will be recruited from the breast surgery clinic on a weekly basis until the required number of subjects has been enrolled. We will provide the consent form to the patient. No advertised will be used. No payment will be made to the subject.

b) Inclusion and Exclusion Criteria

Inclusion Criteria:

- Women who had mammogram and/or ultrasound Birads (category IV or V)
- Women ages between 30 and 80.
- Women who have been scheduled for biopsy from the Temple breast surgery clinic
- Women who have been scheduled for biopsy by Dr. Kathleen Reilly.
- Women, who speak and understand English.

Exclusion Criteria:

- Women who do not meet the criteria requiring biopsy.
- Women who have allergic reaction to silicone.
- Women who cannot speak or understand English.
- Women who are pregnant.
- Women, younger than 30 years old, and older than 80 years old.

c) Local Number of Subjects

Less than 20 subjects will be enrolled.

d) Study-Wide Number of Subjects

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NA

e) Study Timelines

The subject will participate during one visit before biopsy. The study will remain open for one year. The preliminary analysis will be completed by December of 2016.

f) Study Endpoints

The study will end in one year. There are no secondary study endpoints.

g) Procedures Involved in the Human Research

Procedure:

The patient should have had mammography or ultrasound by the time of this procedure. Once the doctor decides to perform biopsy, the tactile imaging will be planned. The breast scan, mammography, ultrasound, and biopsy are standard of care. The consent will be obtained before the biopsy. One of the investigators (Dr. Caroline or Dr. Reilly) will obtain the consent. Before the biopsy, the doctor will identify the mass(es) using other modalities such as an ultrasound. The tactile imaging sensor operator will obtain the tactile images. Then the biopsy will be performed. Radiology doctor, resident, and radiology technologist are always present during the procedure. In addition a professional assistant from the engineering group will operate the tactile imaging sensor. That person will not have any physical contact with the patient. The procedure will be very similar to the ultrasound device and it will be as follows:

- The patients will be lying on their back.
- The doctor will locate the mass using other modality (ultrasound or mammogram)
- The tactile imaging sensor will press the part of the breast where mass are located.
- An assistant will sketch the locations of the masses with the mass number.
- An assistant will operate the laptop to take image of the mass.
- The mass number will be noted with the images.
- The tactile imaging sensor will manually compress the mass with different force gently.
- The image will be taken and the mass number will be recorded.
- This procedure will be repeated until all the masses are imaged.
- This will take less than three minutes per mass.

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- After the tactile images are taken the doctor will perform the biopsy of the masses.
- The assistant will note the mass number and the order of the biopsy.
- The patient will receive standard biopsy results and a letter from the doctor.

Only one visit will be required for this study.

NOTE:

- None of the procedures done for research purposes involve radiation.
- The use or disclosure of protected health information involves no more than a minimal risk to the privacy of individuals. A unique subject identifier will be assigned to each subject. The subjects name and date of birth will be associated with the identifier and will be kept on a list and stored electronically in a secure password protected computer under the control of the Principal Investigator.
- Data will be kept on a password-protected computer; data is only recorded electronically. Data will be saved on a secure server.
- Once the data is recorded and verified for accuracy and completeness the link to the patient identifier will be destroyed.

h) Data and Specimen Banking

No specimens will be bank for this study.

i) Data Management

In this project we will collect the tactile data of the tumors

Standards that Would Be Applied for Format and Metadata Content:

We will use standard formats to the data that are being stored. Tactile spectral data will be stored in Excel “.xls” or “.xlsx” formats. Matlab source codes will be stored in “.m” or “.c/cpp” formats. Computer algorithm results will be stored in “.dat” or “.fig” formats. Technical report and papers will be either in Word format.

Provisions for Keeping Data Secure:

Experimental data, algorithm results, source codes, reports, and paper will be kept on a server in the CSNAP laboratory in the electrical and computer engineering department at Temple University. The data will be encrypted and password protected. All the patient identifiers will be removed from the spreadsheets.

Data will be stored locally for no less than 6 years or as required by law.

j) Confidentiality

Data will be stored in a secure and password protected computer. Only study team members, the Temple University IRB, the FDA or their designated representatives will have access to the data. The study

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investigators or team members will receive/transmit the data via secure computer system used by the university. No specimens will be transported.

k) Provisions to Monitor the Data to Ensure the Safety of subjects

NA.

l) Withdrawal of Subjects

NA

11) Risks to Subjects

The device is not a significant risk because the device involves optical means and:

- The device is NOT intended as an implant that presents a potential for serious risk to the health, safety, or welfare of a subject
- The device is NOT purported or represented to be for a use in supporting or sustaining human life that presents a potential for serious risk to the health, safety, or welfare of a subject
- The device is NOT for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health that presents a potential for serious risk to the health, safety, or welfare of a subject
- The device does NOT otherwise present a potential for serious risk to the health, safety, or welfare of a subject (Required for abbreviated IDE determination.)

Risks and Discomforts:

The sensor device uses an LED light source (similar to a LED flashlight). The sensing probe part is made out of silicone gel. There may be minor discomfort resulting from the sensor pressing on breast tissues. An allergic reaction to the silicone, which is the part that will be touching the tissues, is possible but uncommon. Currently, we are not aware of any side effects of this device.

The tactile imaging sensor will not affect patient management. It will take less than three minutes to image each mass. There are no risks beyond usual activities of daily living. However, we will label all devices with the prominent sticker stating the following: “CAUTION-Investigational device. Limited by Federal law to investigational use.”

The investigator will comply with the requirements of 21 CFR §812.46 with respect to monitoring investigations.

- Securing compliance. If the investigator discovers that a co-investigator is not

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complying with the signed agreement, the investigational plan, the requirements of this part or other applicable FDA regulations, or any conditions of approval imposed by the reviewing IRB or FDA will promptly either secure compliance, or discontinue use of the device by the co-investigator and terminate the co-investigator's participation in the investigation. The investigator will also require such a co-investigator to dispose of or return the device, unless this action would jeopardize the rights, safety, or welfare of a subject.

- Unanticipated adverse device effects.
- The investigator will immediately conduct an evaluation of any unanticipated adverse device effect.
- If the investigator determines that an unanticipated adverse device effect presents an unreasonable risk to subjects, the investigator will terminate all investigations or parts of investigations presenting that risk as soon as possible. Termination shall occur not later than 5 working days after the investigator makes this determination and not later than 15 working days after the investigator first received notice of the effect.
- The investigator may not resume a terminated investigation without IRB approval.

The investigator will maintain the following records required under 21 CFR §812.140:

- Records of each subject's case history and exposure to the device. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. Such records shall include documents evidencing informed consent and, for any use of a device by the investigator without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent. The case history for each individual shall document that informed consent was obtained prior to participation in the study.
- The protocol, with documents showing the dates of and reasons for each deviation from the protocol. . (Required for abbreviated IDE determination.)

The investigator will make the following reports required under 21 CFR §812.150:

- Unanticipated adverse device effects. The investigator will submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than

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- 10 working days after the investigator first learns of the effect.
- Withdrawal of IRB approval. The investigator will report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.
- Withdrawal of FDA approval. The investigator will notify the IRB and participating investigators of any withdrawal of FDA approval of the investigation, and shall do so within 5 working days after receipt of notice of the withdrawal of approval.
- Informed consent. If an investigator uses a device without obtaining informed consent, the investigator will report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs. (Required for abbreviated IDE determination.)
- Progress reports. At regular intervals, and at least yearly, The investigator will submit progress reports to the IRB.
- Recall and device disposition. The investigator will notify FDA and all reviewing IRB's of any request that an investigator return, repair, or otherwise dispose of any units of a device. Such notice will occur within 30 working days after the request is made and shall state why the request was made.
- Final report. The investigator will submit a final report to the IRB within 6 months after termination or completion. (Required for abbreviated IDE determination.)

The investigator will not:

- Promote or test market the device, until after FDA has approved the device for commercial distribution.
- Commercialize the device by charging the subjects or investigators for a device a price larger than that necessary to recover costs of manufacture, research, development, and handling.
- Unduly prolong the investigation.
- Represent that the device is safe or effective for the purposes for which it is being investigated. (Required for abbreviated IDE determination.)

The device will not be used for diagnosis or treatment.

The data will be periodically monitored by the investigator to ensure that there are no new risks.

12) Potential Benefits to Subjects

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No direct benefit.

13) Privacy and Confidentiality

Subjects name will not be used.

14) Compensation for Research-Related Injury

The research involves no more than minimal risk to subjects, and there is no compensation available.

15) Economic Burden to Subjects

All research procedures will be done free of charge to the patients.

16) Consent Process

After patient received mammography or ultrasound, once the doctor decides to perform biopsy, the tactile imaging will be planned. The consent will be obtained before the biopsy. One of the investigators (Dr. Caroline) will obtain the consent. The consent will take place at the Temple University Hospital. This process may take about 10 minutes. The patient will have an option not to participate in the study.

“HRP-090 SOP: Informed Consent Process for Research” will be followed to obtain informed consent.

Non-English Speaking Subjects

No none-English speaking patients will be recruited into the study.
The subjects must understand English.

Subjects who are not yet adults (infants, children, teenagers)

No infants, children, or teenagers will be recruited into the study.

Cognitively Impaired Adults

No Cognitively Impaired Adults will be recruited into the study.

Adults Unable to Consent

No Adults unable to consent will be recruited into the study.

17) Special considerations when obtaining consent for genetic studies

No genetic studies will be conducted during this study

18) Process to Document Consent in Writing

All subjects will sign a written informed consent document. A signed and dated copy of the consent form will be given to each subject enrolled into the study.

“HRP-091 SOP: Written Documentation of Informed Consent” will be followed to document informed consent in writing.

19) Vulnerable Populations

None of the populations listed below will be recruited into the study

- Adults unable to consent
- Individuals who are not yet adults (infants, children, teenagers)
- Pregnant women
- Prisoners

20) Drugs or Devices

Only authorized investigators associated with the study will use the imaging sensor. When not in use, the sensor and associated equipment will be stored in a secure lock area in the Investigators office.

21) Multi-Site Human Research

This is a single-site study

Results of the study will not be shared with the subjects.

22) Statistical Data Analysis Plan

We will obtain 20 tactile image data sets from the breast tumor patients. The tactile images will be converted to size and deformation index. Then these two parameters will be converted to risk score, which is compared against pathology results. This is a small number of patients for statistically significance study. Therefore, we plan to use the Leave-One-Out-Cross-Validation (LOOCV) technique to validate the human test results to determine the performance of the device.

We obtain the Risk Score. Risk Score is a unit less numerical value, which can be used as a scale to classify the tumor as malignant and benign. Based on the calculated size of the tumor and measured deformation index, the breast tumors are classified as benign and malignant using scoring method. The risk score will range

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from 0 to 5, where 0 represents the benign and 5 represents the malignant tumor. A marginal threshold value was set, where any risk score below threshold is considered benign. The calculated risk score is based on the below equation,

$$RiskScore = \left[\left(\frac{W_1 \times S}{S_{max}} - \frac{W_2 \times DI}{DI_{max}} \right) \right] R,$$

where, W_1 and W_2 are the two weights used for size and deformation index respectively, S represents the estimated size value, S_{max} is the maximum estimated size value, DI is the calculated deformation index, DI_{max} is the maximum calculated deformation index. R is the range of risk score used.

Comparing the Risk Score and the Pathology reports we obtain the following measures. The sensitivity, specificity and accuracy of the system have to be measured to know the reliability of the device. These system performance parameters helps to evaluate the performance of device, which is calculated based on the Risk Score using the below equations,

$$Sensitivity_{CISS} = \frac{TP}{TP + FN} (\%),$$

$$Specificity_{CISS} = \frac{TN}{TN + FP} (\%),$$

$$Accuracy_{CISS} = \frac{TN + TP}{TN + FP + TP + FN} (\%).$$

The positive result shows the presence of malignant tumor whereas the negative result implies the presence of benign tumor. TP , TN , FP , and FN represent true positive, true negative, false positive and false negative cases respectively. False positive is considered to be a case where benign masses are classified as malignant, whereas false negative are cases where malignant masses are classified as benign. True positives are the correctly classified malignant cases. True negatives are the correctly classified as benign cases.