Final Progress Report for Research Projects Funded by Health Research Grants

Instructions: Please complete all of the items as instructed. Do not delete instructions. Do not leave any items blank; responses must be provided for all items. If your response to an item is "None", please specify "None" as your response. "Not applicable" is not an acceptable response for any of the items. There is no limit to the length of your response to any question. Responses should be single-spaced, no smaller than 12-point type. The report **must be completed using MS Word**. Submitted reports must be Word documents; they should not be converted to pdf format. Questions? Contact Health Research Program staff at 717-231-2825.

1. **Grantee Institution:** UE LifeSciences, Inc.

2. **Reporting Period (start and end date of grant award period):** 6/1/2012 - 2/25/2015

3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** Mihir Shah, BS

4. **Grant Contact Person's Telephone Number:** 267-342-3303

5. **Grant SAP Number:** 4100059198

6. **Project Number and Title of Research Project:** 1 - *Commercial Prototype Development and Clinical Validation of Low-Cost Hand-Held Breast Scanner*

7. **Start and End Date of Research Project:** 6/1/2012 - 2/25/2015

8. **Name of Principal Investigator for the Research Project:** Mihir Shah

9. **Research Project Expenses**.

   9(A) Please provide the total amount of health research grant funds spent on this project for the entire duration of the grant, including indirect costs and any interest earned that was spent:

   $ 883,050.65

   9(B) Provide the last names (include first initial if multiple individuals with the same last name are listed) of **all** persons who worked on this research project and were supported with health research funds. Include position titles (Principal Investigator, Graduate Assistant, Post-doctoral Fellow, etc.), percent of effort on project and total health research funds expended for the position. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project	Cost
SHAH, MIHIR	Chief Executive Officer, UE LifeSciences Inc.	55%	$191,125
CAMPISI, MATTHEW	Chief Technology Officer, UE LifeSciences Inc.	52%	$166,260
YEGINGIL, HAKKI	Materials Scientist, UE LifeSciences Inc.	46%	$111,150
WHITE, IAN	President, DesignDesign Inc.	5%	$26,000
JOHNSON, ANDREW	Senior Industrial Designer, DesignDesign Inc.	5%	$26,000
BROOKS, ARI	Professor of Surgery, Penn Medicine	2% Yr1, 5% Yr2	$16,000
ENGLANDER, BRIAN	Clinical Assistant and Prof of Radiology, Penn Medicine	0% Yr1, 11% Yr2	$29,554
BROACH, ROBYN	Clinical Research Coordinator, Penn Medicine	0% Yr1, 33% Yr2	$33,000
MALONE, EVAN	President, NextFab Studio	2%	$7,500
WARAKSA, ADAM	Machinist, NextFab Studio	5%	$7,500

9(C) Provide the names of **all** persons who worked on this research project, but who *were not* supported with health research funds. Include position titles (Research Assistant, Administrative Assistant, etc.) and percent of effort on project. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project
Parekh, Chinmai	Biomedical Engineering Intern	0% Yr1, 10% Yr2
Gutta, Sirisha	Biomedical Engineering Intern	0% Yr1, 10% Yr2
Thrash, Holly	iBreastExam Clinic Operator	0% Yr1, 25% Yr2

9(D) Provide a list of **all** scientific equipment purchased as part of this research grant, a short description of the value (benefit) derived by the institution from this equipment, and the cost of the equipment.

Type of Scientific Equipment	Value Derived	Cost
None		

10. Co-funding of Research Project during Health Research Grant Award Period. Did this research project receive funding from any other source during the project period when it was supported by the health research grant?

Yes_____ No___X_____

If yes, please indicate the source and amount of other funds:

11. Leveraging of Additional Funds

11(A) As a result of the health research funds provided for this research project, were you able to apply for and/or obtain funding from other sources to continue or expand the research?

Yes__X_____ No_____

If yes, please list the applications submitted (column A), the funding agency (National Institutes of Health—NIH, or other source in column B), the month and year when the application was submitted (column C), and the amount of funds requested (column D). If you have received a notice that the grant will be funded, please indicate the amount of funds to be awarded (column E). If the grant was not funded, insert "not funded" in column E.

Do not include funding from your own institution or from CURE (tobacco settlement funds). Do not include grants submitted prior to the start date of the grant as shown in Question 2. If you list grants submitted within 1-6 months of the start date of this grant, add a statement below the table indicating how the data/results from this project were used to secure that grant.

A. Title of research project on grant application	B. Funding agency (check those that apply)	C. Month and Year Submitted	D. Amount of funds requested:	E. Amount of funds awarded:
Lab Testing and Validation for US FDA Submission and Clinical Evaluation in Developing Countries	☐NIH ☐ Other federal (specify:___) ☒ Nonfederal source (specify: University City Science Center Digital Health Accelerator Grant)	April 2014	$50,000	$50,000
Technology Transfer and Clinical Validation in India	☐NIH ☐ Other federal (specify:_____) ☒ Nonfederal source (specify: Units Seed Fund's StartHealth Grant)	April 2015	$80,000	$80,000
Development and clinical validation of a low-cost, hand-held device (iBreastExam or iBE) that can be used	☒NIH ☐ Other federal (specify:_____) ☐ Nonfederal source (specify:_)	Jan 2014	$3,400,000	$0

by healthcare workers in LMICs				

11(B) Are you planning to apply for additional funding in the future to continue or expand the research?

Yes____X_____ No_____

If yes, please describe your plans:

UE LifeSciences (UELS) will continue to find suitable grant funding opportunities in the areas of affordable healthcare, innovations for low- and-middle income countries, technology commercialization grants and other similar funding prospects. In July 2015, UELS will be applying to the United States–India Science & Technology Endowment Fund (USISTEF) under the "Healthy Individual" program, which aims to support the development of affordable biomedical devices, diagnostic, preventive and/or curative measures, or food and nutrition products to improve health. UELS wishes to further expand the capabilities of various sensor technologies to aid and assist the commercialization of innovative, easy-to-use tools for early stage cancer detection.

12. Future of Research Project. What are the future plans for this research project?

This research project is resulting in a commercial grade medical device that will enable thousands of health workers globally to help detect breast lesions at an early stage and thereby help save lives of many women being affected by breast cancer.

As a follow-up to this research project, UELS was able to apply for additional funds that helped cover the cost of lab testing and preparation of US FDA submission for iBreastExam. As a result, on April 23rd 2015, iBreastExam received US FDA 510(k) clearance as a "breast lesion documentation system."

UELS now plans to commercialize iBreastExam in developing countries where breast cancer rates are rising faster than in developed countries and where mechanisms such as mammography are difficult to implement. With strong clinical validation, UELS plans to convince clinicians, health authorities and insurance agencies in developed countries regarding the clinical utility of iBreastExam as an adjunctive breast cancer screening tool for women with dense breasts, women younger than 40 years of age and women at high-risk for breast cancer.

13. New Investigator Training and Development. Did students participate in project supported internships or graduate or post-graduate training for at least one semester or one summer?

Yes___X_____ No_____

If yes, how many students? Please specify in the tables below:

	Undergraduate	Masters	Pre-doc	Post-doc
Male		1		
Female		1		
Unknown				
Total		**2**		

	Undergraduate	Masters	Pre-doc	Post-doc
Hispanic				
Non-Hispanic		2		
Unknown				
Total		**2**		

	Undergraduate	Masters	Pre-doc	Post-doc
White				
Black				
Asian				
Other		2		
Unknown				
Total		**2**		

14. Recruitment of Out-of–State Researchers. Did you bring researchers into Pennsylvania to carry out this research project?

Yes_____ No__X_____

If yes, please list the name and degree of each researcher and his/her previous affiliation:

15. Impact on Research Capacity and Quality. Did the health research project enhance the quality and/or capacity of research at your institution?

Yes___X_____ No_____

If yes, describe how improvements in infrastructure, the addition of new investigators, and other resources have led to more and better research.

This health research project has greatly enhanced the quality of research at UE LifeSciences (UELS). As a healthcare industry start-up, we've been able to organize our approach to innovation under this research project. Working through each engineering challenge, we were able to organize our collective experience, talent and the team was able to leverage a

number of translational research activities with an intent and focus to commercialize each step into a production-level capability.
This project had concurrent inputs from clinicians, industrial designers, software developers as well as electronics, ergonomics and computer human interaction experts. We were able to build a 'product' from the ground up, holistically. We created and implemented an iterative design-bench-lab-clinic-resign loop that enabled us to quantify the measure of success while making innovative progress concurrently.

16. Collaboration, business and community involvement.

16(A) Did the health research funds lead to collaboration with research partners outside of your institution (e.g., entire university, entire hospital system)?

Yes___X_____ No_____

Health research funds have led to a close collaboration with University of Pennsylvania's Abramson Cancer Center, Women's Imaging Center and thought leaders in breast cancer imaging and treatment. In January 2014, UELS filed an application for NIH's RFA-CA-13-015 grant opportunity for Cancer Detection, Diagnosis, and Treatment Technologies for Global Health in collaboration with University of Pennsylvania as a key partner. The proposal aims to finalize the development and clinical validation of a low-cost, hand-held device (iBreastExam) for community healthcare workers (CHWs) to administer breast exams in settings with limited medical infrastructure such as low- and middle-income countries (LMICs).

This health research project has also enabled UELS to make plans to collaborate with international centers of excellence in cancer research and treatment. The Barretos Cancer Hospital (BCH) in Brazil and the Apollo Health Education and Research Foundation (AHERF) in India are supporting UELS' research & development efforts and have signed a Collaborative Research Agreement with UELS to conduct clinical studies involving iBreastExam. Located 300 miles from the city of São Paulo, BCH exclusively serves rural populations to provide cancer care. BCH has a well-established breast cancer prevention and treatment program with several mobile mammography units and three fixed sites. BCH provides healthcare services at no charge to its patients and is recognized by the National Cancer Institute's US Latin-America Cancer Research Network as a leading research center. The Apollo Group of Hospitals (AGH) is one of the largest private healthcare networks in India with 40 hospitals and 100+ primary care clinics. Integrated with AGH's healthcare network is the Apollo Health Education and Research Foundation (AHERF), a dedicated clinical research institution with experience of over 650 clinical studies, 8 clinical sites and a dedicated staff of over 100 investigators and researchers.

UELS has received follow-on grant funding ($80,000) from the StartHealth program of Unitus Seed Fund along with Pfizer Pharmaceuticals (a leading pharmaceuticals manufacturer), PATH (a leader in global health innovation), Narayana Health and Manipal

Hospitals (Private healthcare systems in India). StartHealth funding will help commercialize iBreastExam in India with support from above stated partners.

16(B) Did the research project result in commercial development of any research products?

Yes___X_____ No_____

If yes, please describe commercial development activities that resulted from the research project:

With the engineering progress under this research project, we were able to design, develop and build a manufacture-ready product for commercial sales and marketing.

The research project, essentially enabled scientific research to be translated into a product that can be used in a clinic. In early 2014, UE LifeSciences was able to apply for follow-on funding to the University City Science Center's Digital Health Accelerator program, with the progress made with the commercial-prototype that was made ready under this research project. The UCSC DHA grant award ($50,000) offered access to additional lab space, ability to hire intern-staff and paid for all the lab testing that was required to apply for US FDA 510(k) clearance.

As a result, in April 2015, UELS received US FDA 510(k) clearance for iBreastExam as a "breast lesion documentation system" and is now legally and commercially marketable in the United States. With globally acceptable lab-test reports and US FDA clearance, UELS is now ready to make regulatory applications in several other countries in Asia, Latin America and the Middle East.

16(C) Did the research lead to new involvement with the community?

Yes___X_____ No_____

If yes, please describe involvement with community groups that resulted from the research project:

With progress made under this research project, UELS has initiated a global campaign (www.WeMustTry.com) to offer 25,000 free breast exams in 5 LMICs including India, Brazil, Panama, Mexico and Egypt in an effort to deliver tools developed by UELS to women who otherwise have no access to secondary prevention mechanisms. UELS is working with several non-profits focused on breast cancer awareness by hosting screening camps in LMICs.

Panama based FundAyuda (www.fundayudapanama.org), the country's leading breast cancer awareness agency is working with UELS to help women residing in rural areas of Panama.

In collaboration with India based Aastha Breast Cancer Support Group (www.abcsgp.org) UELS has conducted a clinical study that has enrolled 1,300 women in Pune, India and neighboring rural-areas. The iBE device was operated by breast cancer survivors and community health workers appointed by Aastha. In this study, three breast cancer lesions were detected primarily by the iBreastExam device.

With support from Mumbai city's Municipal Corporation Health Chairwoman (Ms. Geeta Gawli), UELS organized Breast Cancer screening camps for the city's municipal employees. Now, Ms. Gawli is planning to scale the plan to 6,000 city residents. UELS recently partnered with Karunakare Foundation (www.canceraid.org) and 15 sister NGOs, to provide breast cancer awareness, education and screening services to housing communities and corporate employers in India. These events and activities are all raising awareness of UELS' potential in LMICs.

UELS plans to work towards publishing a white paper on iBreastExam's usability as an "affordable, point-of-care technology in a community outreach program" in collaboration with Prashanti Cancer Care Mission (www.prashanticancercare.org), a non-profit organization focused to provide information and counseling on various cancers, their causes, underlying risk factors, life style, issues, prevention and early detection options, symptoms, latest diagnostics and treatments available, dealing with life after cancer and rehabilitation to organized groups in urban and rural communities.. This project will be a 6 month exercise with 5-7 health workers from Prashanti using iBreastExam on a daily basis and travel to sub-rural and rural areas to perform breast exams. Women who show signs of concern on iBreastExam, can be offered targeted breast ultrasound or mammogram as the next step of intervention. The objective is to demonstrate how existing healthcare resources can be greatly enhanced to make an impactful intervention.

17. Progress in Achieving Research Goals, Objectives and Aims.

List the project goals, objectives and specific aims (as contained in the grant agreement). Summarize the progress made in achieving these goals, objectives and aims <u>for the period that the project was funded (i.e., from project start date through end date).</u> Indicate whether or not each goal/objective/aim was achieved; if something was not achieved, note the reasons why. Describe the methods used. If changes were made to the research goals/objectives/aims, methods, design or timeline since the original grant application was submitted, please describe the changes. <u>Provide detailed results of the project.</u> Include evidence of the data that was generated and analyzed, and provide tables, graphs, and figures of the data. List published abstracts, poster presentations and scientific meeting presentations at the end of the summary of progress; peer-reviewed publications should be listed under item 20.

This response should be a <u>DETAILED</u> report of the methods and findings. It is not sufficient to state that the work was completed. Insufficient information may result in an unfavorable performance review, which may jeopardize future funding. If research findings are pending publication you must still include enough detail for the expert peer reviewers to evaluate the progress during the course of the project.

Health research grants funded under the Tobacco Settlement Act will be evaluated via a performance review by an expert panel of researchers and clinicians who will assess project work using this Final Progress Report, all project Annual Reports and the project's strategic plan. After the final performance review of each project is complete, approximately 12-16 months after the end of the grant, this Final Progress Report, as well as the Final Performance Review Report containing the comments of the expert review panel, and the grantee's written response to the Final Performance Review Report, will be posted on the CURE Web site.

There is no limit to the length of your response. Responses must be single-spaced below, no smaller than 12-point type. If you cut and paste text from a publication, be sure symbols print properly, e.g., the Greek symbol for alpha (α) and beta (ß) should not print as boxes (□) and include the appropriate citation(s). DO NOT DELETE THESE INSTRUCTIONS.

Clinical Research Objective: To further develop and clinically validate Piezoelectric Finger Sensor (PEFS) based mobile breast scanner.

Specific Aim 1: To develop a low-cost, accurate and easy-to-use hand-held breast scanner for commercial application:

Sub-Aim 1a: To develop software and signal processing algorithms.
Sub-Aim 1b: To reduce the overall procedure duration.
Sub-Aim 1c: To integrate low-power electronics within the PEFS sensor.
Sub-Aim 1d: To develop connectivity with various mobile operating system environments.

Specific Aim 2: To clinically validate the effectiveness of PEFS breast scanner:

Sub-Aim 2a: To correlate PEFS findings with conventional exams for tumor *identification*, in-vivo.
Sub-Aim 2b: To correlate PEFS findings with conventional exams for tumor *classification*, in-vivo.
Sub-Aim 2c: To compare the efficacy of PEFS against hand-palpation using gelatin breast phantoms.

Methods for achieving the above objectives and aims:

Sub Aim 1a: Apply image processing and frequency analysis techniques to earlier raw PEF data to extract physical features, use MatLab and Simulink to implement filters and digital signal processing algorithms. The tuning of the analysis will be based on a 'metaheuristic' optimization approach.
Sub Aim 1b: Build multiple array (4x4) PEFS sensor, positioning by optical sensor or gyroscope integration.

Sub Aim 1c: Redesign the controller board circuitry for miniaturization to 3"x3".

Sub Aim 1d: Application Programming Interface (API) enables building native mobile

application.

Sub Aim 2a, 2b: Under an IRB-approved clinical study, consenting women meeting the study criteria will be enrolled in the study. Asymptomatic women presenting to the clinic for routine breast exam and symptomatic women scheduled to undergo pathological exam will be examined by a trained technician using PEFS but blinded to mammogram/pathology results. Results will be documented and analyzed for efficacy metrics.

Sub Aim 2c: General population women will be requested to palpate a mechanical gelatin breast phantom to detect embedded 'tumor-like' lumps first by using the PEFS device and then by using bare hands. The same test will be repeated by clinicians/technicians skilled in performing Clinical Breast Exam (CBE). Results will be compared.

Progress with Sub-Aim 1a: To develop software and signal processing algorithms.

Sub-aim 1a was successfully completed.
Sub-aim 1a Progress during Phase 1 Required DC voltage amplitudes and number of DC voltage steps were analyzed to obtain the balance between the best data accuracy and least amount of time required during data collection. Analog to digital conversion (ADC) was sampled at 2 kHz, followed by data interpolation, up sampling and digital bandpass filtering. These signal filtering systems have been applied, as well as the electronics have been fine-tuned (as described in Sub-Aim 1c), which minimized the generated induced voltage signal peak time to less than 250 ms per channel (i.e. per PEF sensor). Since the peak amplitude values are monitored during data acquisition, the fine-tuning has allowed quicker acquisition of data (2.5 seconds per 8 PEF sensors) and enabled the system to be ready in shorter time for the next data acquisition. Functionality of the iBE unit requires accurate analog peak detection on each channel. Based on the impulse response, frequency response, and additional *a priori* information, interpolation routines to accurately detect the peaks in the digital domain were developed. In addition, proprietary noise filtering was incorporated to eliminate the effects of thermal and electromechanical noise induced by the piezoelectric material. To facilitate clinical testing a software package was created to analyze the data stored on the SD Card of the device. The software package imports the entire measurement database from the device and instantaneously provides custom statistical information such as mean, standard deviation and variance. This information is essential during the quality control of the iBE device, data reproducibility, and also the accuracy during data collection, most importantly during clinical trials. The tool is designed to provide an efficient method of analyzing the performance of the device, both physically and clinically. Statistical data points (mean, standard deviation and variance) essential for the newly developed software package were not available from the original single PEF system with which the past clinical data (71 ex-vivo and 40 in-vivo cases) was generated. As a result, efforts were focused on analyzing the new clinical data. Testing and analysis of software

and signal processing algorithms created with the new clinical data (Aim 2) and newly engineered iBE unit were successfully expedited. Thus far, 22 cases have been completed as reported in Table 1 (pg 22).

Sub-aim 1a Progress during Phase 2

New signal processing algorithms were developed to reduce quantization noise introduced by the limited spatial resolution of the 16 sensors. Creating a smooth contiguous spatial data matrix required unique interpolation schemes to develop an aesthetically pleasing image that accentuates the clinical findings (Fig. 1 below). The output frames are now capable of characterizing the lesion for size, location, stiffness and shape information.

Noise reduction algorithms were revised and applied to the spatial data to avoid misrepresentation of artifacts as clinical findings. Certain clinical conditions such as anatomy (example: ribs of a thin individual) often appears as artifacts on the iBE. Separation of these artifacts from true lesions was addressed using artificial intelligence and feature extraction algorithms. Artifacts were further addressed by declassifying lesions that appeared distributed as opposed to centralized. Bilinear and bi-cubic interpolation further refined the data to create smooth image visualization, removing the "blocky" nature of the piezoelectric sensor geometry. Additionally, anti-aliasing blurring was implemented, resulting in smooth topological mapping of the discrete data.

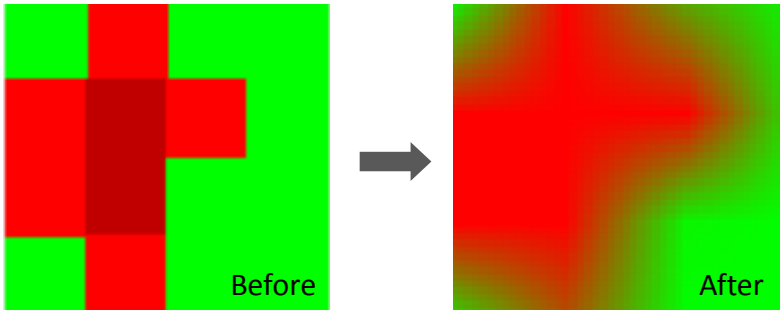

Fig.1 - Bilinear, bicubic interpolation and anti-aliasing blurring techniques create smooth, contiguous frames

Sub-aim 1a Progress during Final Phase

iBE's detection accuracy is a direct function of the integrity of the data collected on the induced voltage in the sensing piezoelectric layer. The induced voltage is a response to the driving step function, which is created by converting an electrical step function to a mechanical step function. When the step function is applied to the driving piezoelectric layer, the resulting induced voltage on the sensing piezoelectric layer includes thermal and mechanical noise, as illustrated in Fig. 2 (below) Denoising is a common signal processing technique to increase the stability and repeatability of data measurements. The current iBE prototype now utilizes a basic denoising technique (3rd order blurring filter) to remove majority of the noise on the induced voltage (Fig 2(b)). However, this basic approach, while

appropriate for early prototype development, still permitted errors in identifying the induced voltage peak value, as seen in Fig 2(d) resulting in false positive measurements. We designed and tested filters that could better estimate the desired deterministic response (Fig. 2(c)). The new filter design uses advanced higher order filters (based on the desired response) after basic denoising to eliminate the thermal and mechanical noise elements without introducing significant delay. In order to specify the optimal filter, cutoff frequency, Gibbs phenomena (ripple) and transition bandwidth characteristics were determined. Lastly, the step response was curve fitted to the desired deterministic response seen in Fig 2(c). The known desired step response follows a standard resistor-capacitor transient response with decay factor τ=RC, where τ is the decay factor, R and C are the equivalent resistance and capacitance values, respectively, and the induced voltage,

$$v(t) = v_f + (v_u - v_f)e^{-\frac{t}{\tau}}$$

Where t and $v(t)$ are time and the induced voltage at a specific time, respectively and v_f, v_u are constants. The optimum values of v_f, v_u and τ will be determined using least squares optimization. These values correlate with the piezoelectric sensor array tip deflection characteristics that relate to tissue elasticity measurements.

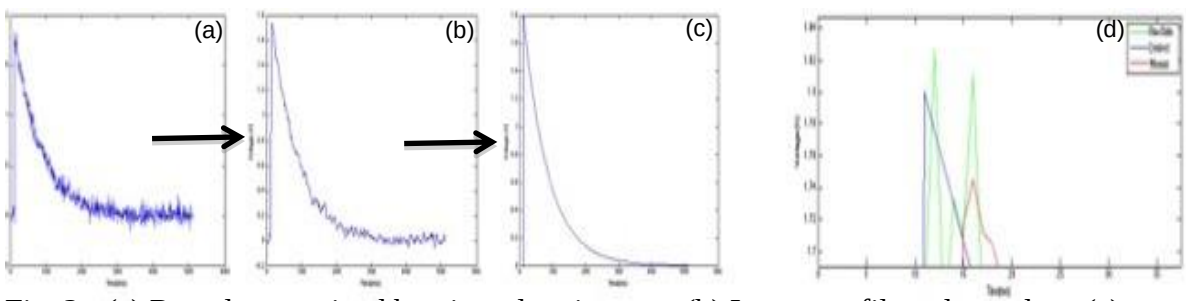

Fig. 2 - (a) Raw data received by piezoelectric array, (b) Low pass filtered raw data, (c) Desired response curve fitted, (d) Peak characteristics of (a), (b), and (c). Note the difference in peak detection (value and delay) for the different stages of processing.

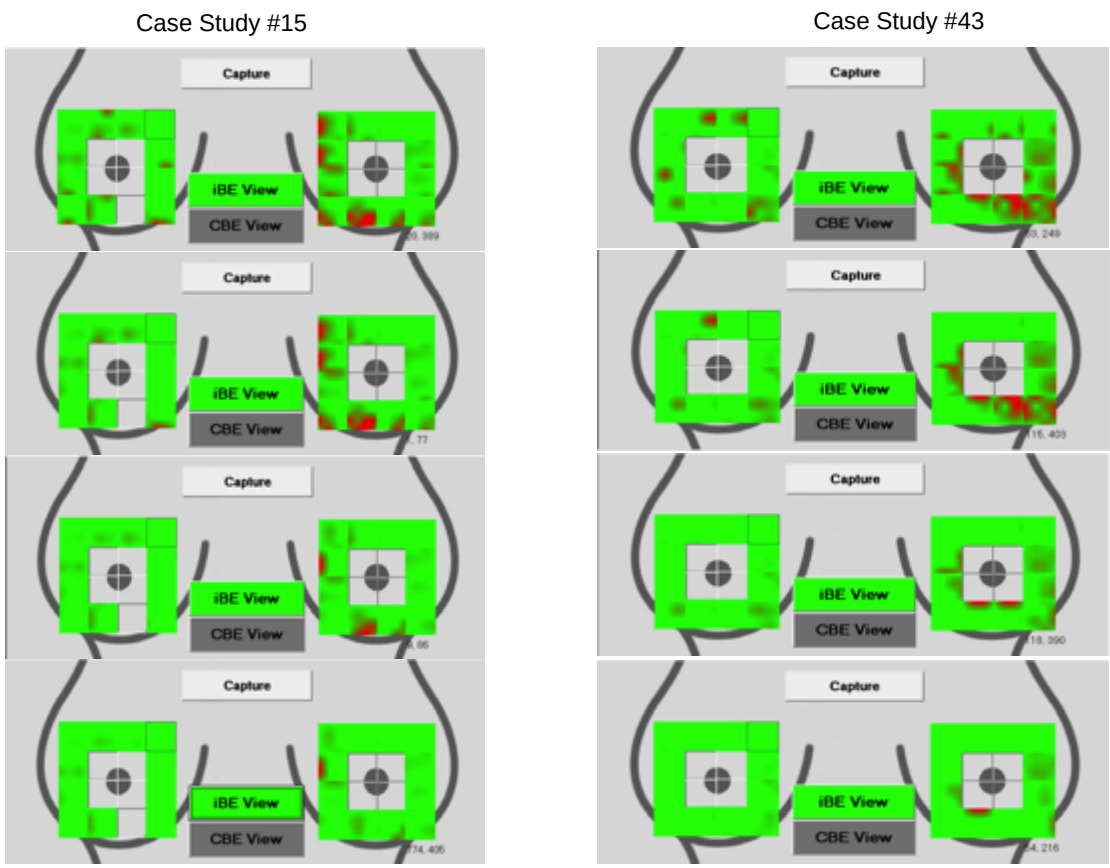

Figure 2.1 - Examples of improvements in specificity; from (a) to (d), noise/artifacts were removed using signal-processing techniques.

Progress with Sub-Aim 1b: To reduce the overall procedure duration.

Sub-aim 1b was successfully completed.
Sub-aim 1b Progress during Phase 1 The overall procedure duration is now reduced from 20 minutes to 3 minutes per breast by designing and testing 4 x 4 PEFS array (Fig 5a,b) that is reliable and easy to install and maintain. A 35 mm^2 area can now be examined (including data capture and analysis) in 5 seconds. Initial design was a 2 x 4 PEFS array, which mirrored the 1 x 4 PEFS array, doubling the device footprint (as shown in Figure 3(a)). The purpose of the 2 x 4 PEFS array was to resolve the mechanical-cross talk amongst neighboring PEFS by driving the PEFS in two separate groups where a zig-zag driving pattern was implemented. Also, a 2 x 4 PEFS array provided a good platform to assess the challenges with driving a large group of PEFS and also the algorithm required to analyze the induced voltages generated in the least amount of time. A proprietary design and fabrication process was developed to manufacture a composite 1 x 4

PEFS array structure in such a manner that the footprint of the device would be minimal (less than 3 x 3 in^2). A stepladder type sub-structure was designed to support each 1 x 4 PEFS array and also provide DC voltage to the common driving PZT layer (top PZT layer). A smart clamp design was chosen, where the required driving DC voltage and sensing electrode leads to the PEFS array was also incorporated into the clamp, as shown in Figure 5a. An iterative design process has been implemented, where the design was built around the PEFS sensor. Also, to further eliminate the cross-talk, on top of the implemented PEFS driving pattern, a grid design was developed.

Several positioning systems were evaluated, such as gyroscope, accelerometers, and optical sensors (laser, functional near-infrared). None of these systems were satisfactory in conveniently and reliably recording iBE unit's position as required during routine monitoring and screening applications. While essential for the commercial use of iBE technology during routine breast monitoring at the consumer level, the positioning feature has not impeded the progress of clinical evaluations, as summarized under Aim 2. Currently, the position of the iBE unit during clinical trials is being manually recorded the way Clinical Breast Exam is performed (i.e. superimposing a clock face on the breast and measuring the distance of the lesion from the nipple).

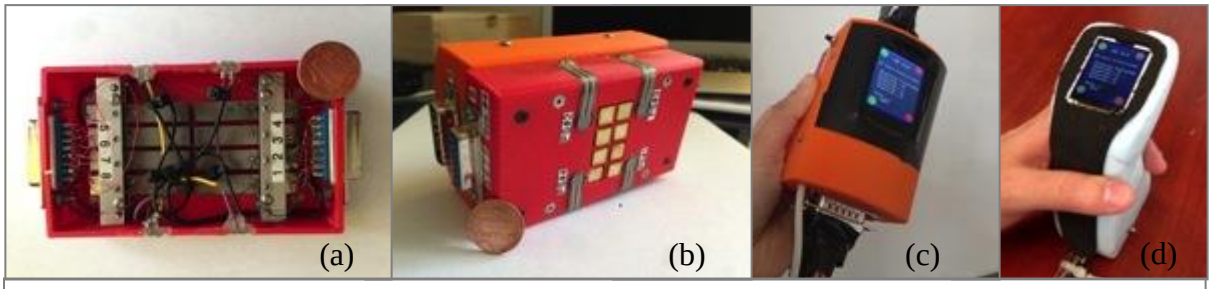

Figure 3: Iterative design steps; (a) preliminary 2x4 PEF sensor array in housing, (b) Grid system that eliminates mechanical cross-talk and pressure sensors, (c) On sensor display shows test results, device pressure, (d) Alternative ergonomic design.

Sub-aim 1b Progress during Phase 2

iBE system is dependent on transient voltage responses and hence the scanning time has a practical lower limit. Testing and evaluation verified that this limit was not optimized. We further modified the circuitry to increase the decay rates, thereby reducing the single scan time to 250ms per 16 PEF scan. This resulted in a 15-fold improvement over the previous iBE system. iBE system now provides a continuous data stream as opposed to single snapshot, per scan.

Software assisted positioning is developed and tested. The user is now guided through a breast examination to perform routine screening in a pre-determined sequence (Fig.4). The breast tissue is divided into adjoining segments spanning the entire breast area. The software then informs the user where specifically to place the iBE sensor. The software assisted positioning conserves battery power since there are no active sensors employed for positioning. Based on

the feedback from the clinicians, software assisted positioning is user-friendly and requires minimal training. It also eliminates the need for expensive sophisticated positioning hardware that is not likely to have the spatial resolution necessary to be effective.

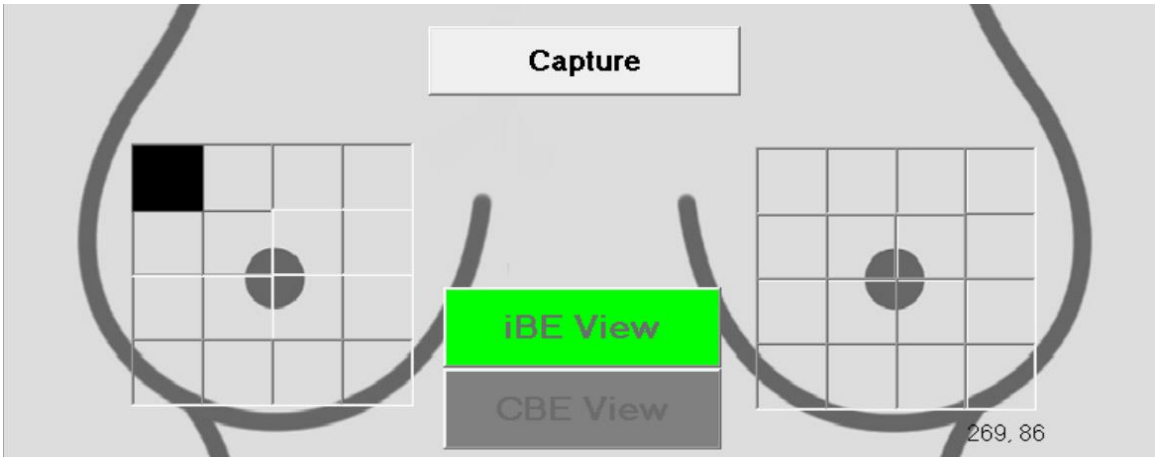

Fig. 4 Software assisted positioning

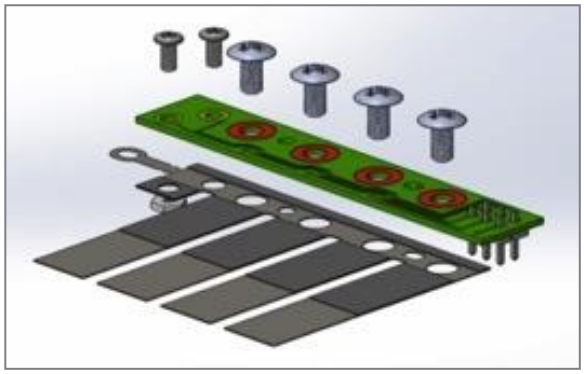

Figure 5(a): manufacture ready sensor design and assembly process.

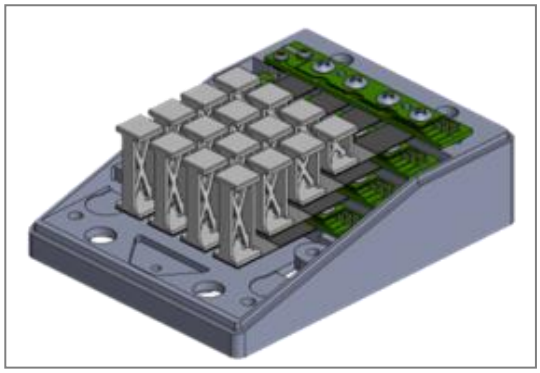

Figure 5 (b): 4x4 PEF sensor array in compact 2”x3” housing. This housing also embeds circuitry as shown in Fig 6 with Power supply, PZT driver and reader, Lithium Polymer battery, wireless communications and Pressure sensor monitoring.

Progress with Sub-Aim 1c: To integrate low-power electronics within the PEFS sensor.

Sub-aim 1c was successfully completed.

Sub-aim 1c Progress during Phase 1

This sub-aim was accomplished in three iterations. The first iteration of the electronics reduced the size of the original electronics printed circuit board by 75% and integrated 8 Analog to Digital Converter (ADC) devices to acquire data from 8 individual PEF sensors simultaneously. This eliminated the need for a large manual multiplexor board. A 2 x 16 text display for basic user interface and an on-board SD Card reader for local data storage were incorporated. In addition, this eliminated the requirement for manual recording of PEF sensor data. The resulting electronics were housed in an enclosure and tethered to the PEFS array enclosure that contained 2 x 4 PEFS array, as shown in Figure 3(b).

The second iteration further miniaturized the system by replacing the large electromechanical relays with a custom designed solid-state board providing driving voltage to the PEF sensors. This step reduced the size of the electronics package by an additional 50%. Also, during the redesign procedure of the solid-state board, additional input/output (I/O) ports were made available. The additional I/O ports enabled solid-state multiplexing of the PEF sensors, essentially doubling the capacity of the 8 ADCs to drive and sense 16 PEF sensors in a single measurement. As an integrated circuit, the total scan time was brought down to less than 4 seconds per measurement. A TFT active matrix 1.8inch screen was added to provide an enhanced user interface.

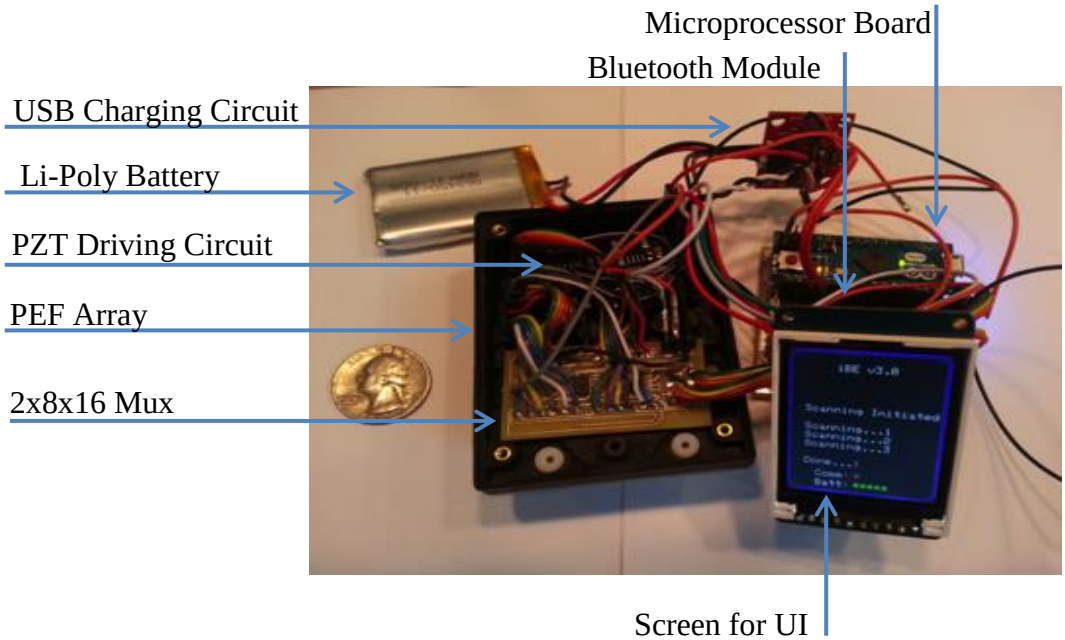

Figure 6. iBE prototype with system components

In the third iteration, a comprehensive power budget analysis was performed and it was determined that 1000 mAh energy was required to power the device during routine use. Therefore, a small lithium-polymer battery (1000 mAh capacity) was incorporated to power

the electronics of the second iteration. The major change on the second iteration was the addition of a voltage up-converter and regulator to be able to operate the system using a 3.7 V voltage supply. A supporting micro-USB charging circuitry was also developed and incorporated. Lastly, Bluetooth wireless communication interface was incorporated to transmit PEF sensor data in real-time to a remote host for data acquisition and analysis (currently supported only on Windows PC platforms). This advancement eliminated the requirement for local storage (SD card reader) and TFT screen. The entire electronics package including the electronics board, solid-state relay board, battery, wireless interface and supporting circuitry are now contained within a single enclosure of the iBE unit. This enclosure also contains the 4 x 4 PEF sensor array as well. Therefore, the entire iBE device is now tether-free, self-sufficient and is the size of a computer mouse. The components comprising the current generation iBE unit is shown in Figure 6.

Sub-aim 1c Progress during Phase 2

The new electronics are now capable of measuring 16 analog inputs (16 PEF fingers) through 8 ADCs though a high speed/low noise multiplexor. Protection Zener diodes were added to protect these ADC inputs and new circuitry was implemented to monitor the health of the PEF fingers and driving circuitry. This information is made available on the electronics through LED indicators and is available through the API interface in the software. Battery monitoring hardware was implement to provide battery statistics through the software interface. Industrial design of the iBE enclosure is completed with the support of DesignDesign Inc. (Fig.7) and commercial-grade components are made using vacuum casting process. The new industrial design houses all the components including the electronics and is also designed to be ergonomic, easy-to-use and ready for compliance testing (required to obtain US FDA clearance) procedures.

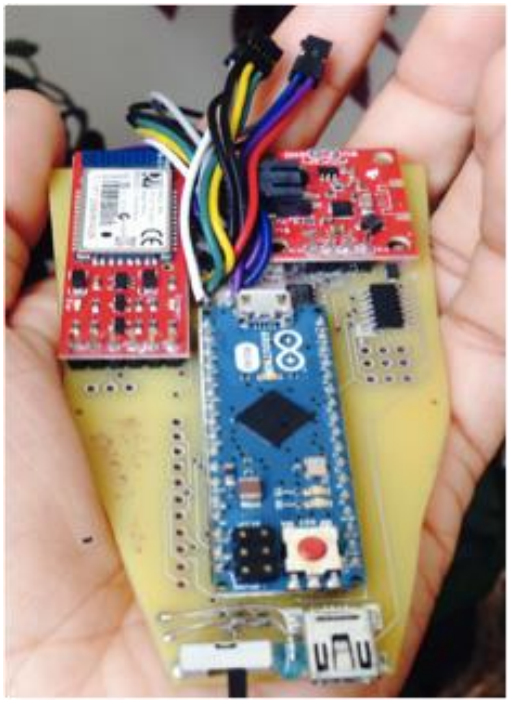

Fig. 7 iBE electronics

Form factor of the electronics board was modified to accommodate inside the new, iBE commercial grade prototype enclosure design (Fig.8). We had 20 of the newly designed boards fabricated and populated at NextFab Studio, using industry standard electronics fabrication techniques, maximizing quality assurance and minimizing probability of faulty manufacturing. All boards were tested prior to integration into the iBE enclosure.

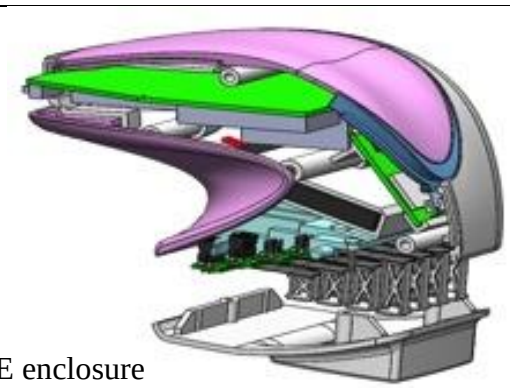

Fig. 8 iBE enclosure

Progress with Sub-Aim 1d: To develop connectivity with various mobile operating system environments.

Sub-aim 1d was successfully completed.

Sub-aim 1d Progress during Phase 1

The development of the smartphone application with graphical user interface (GUI) design has been initiated for iOS devices. As shown in Fig. 9, using this application the operator will have access to all iBE functionalities and also the collected data.

Fig. 9 iBE Mobile App User Interface

Sub-aim 1d Progress during Phase 2

A software package called “iBEConnect” was initiated and the current version is 3.0. It is developed for the Windows 8 platform and is designed for tablet (touch enhanced) operation. iBEConnect now implements user management, patient management, reporting and settings related capabilities. It also performs maintenance, calibration, and iBE-sensor health assessment. Battery statistics are provided as well. A new database structure is implemented using MySQL, which handles data management and statistical data analysis. Fig.10 provides system screen-shots.

The entire software is hosted in the cloud environment (DropBox), offering the ability to remotely update new versions and collect scan data from multiple locations, simultaneously and in near-real time. The software is able to record the entire iBE scan procedure, event-by-event along with the voice of the operator/physician, allowing the development team to experience the procedure in playback mode. Currently the software is compatible with tablet form factor and the graphical user interface (GUI) is completed for the mobile-phone environment.

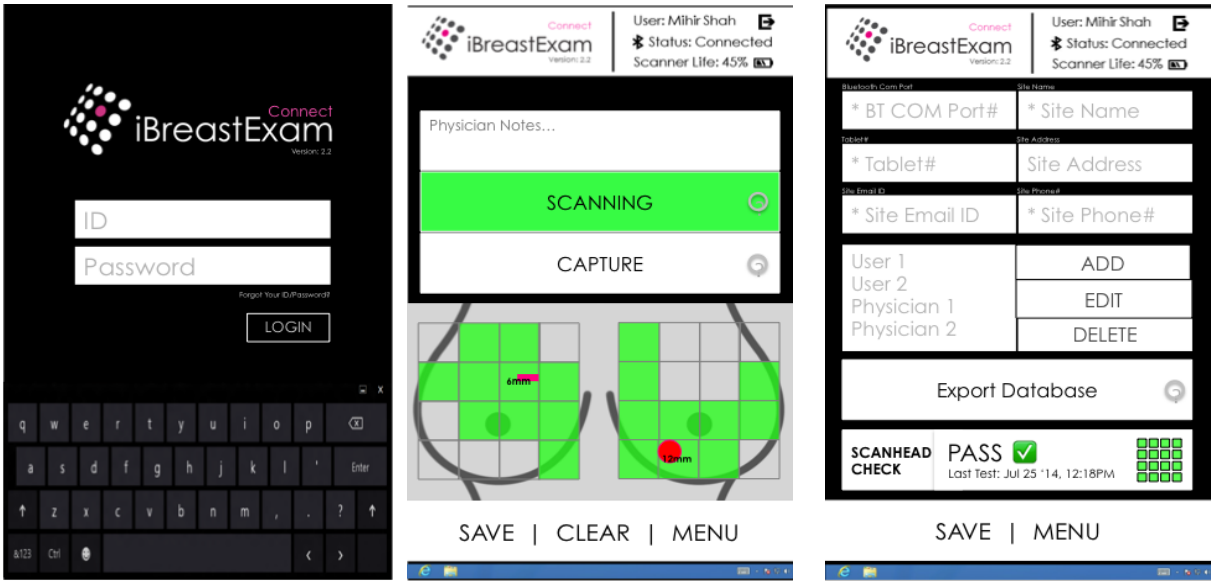

Fig. 10 “iBE Connect” Windows Software Screen Shots

Sub-aim 1d Progress during Final Phase

Software package “iBEConnect” mobile application was developed for android and iOS mobile platforms. Functionalities from tablet software application suite were ported with the addition of report printing and emailing features added in the Mobile App.

Progress with Sub-Aim 2a: To correlate PEFS findings with conventional exams for tumor *identification*, in-vivo.

Sub-aim 2a was completed partially.

At the start of this research project, we had IRB approval from Hahnemann Hospital, however a new IRB application had to be filed at Pennsylvania Hospital since Dr. Ari Brooks (Clinical PI) moved his practice there in September 2013. Due to the delay related to the review and approval of this new IRB approval process and related recommendations made by Abramson Cancer Center of the University of Pennsylvania, we were able to only partially complete the clinical validation as planned under this phase.

Sub-aim 2a Progress during Phase 1

Our Iterative hardware and software design strategy was being constantly evaluated with actual *in-vivo* studies performed at the clinic. 22 patients were recruited at various stages of development during this period of the project. Since the iBE system's hardware, software and algorithms were constantly improved as necessitated by each clinical trial, the clinical trial enrollment was maintained at a limited pace in this period. A tumor detection criterion was established to ensure each case was subjected to the same criterion during data analysis. The established criterion is based on two aspects; 1) The internal calibration of each PEF sensor to ensure accurate tissue elasticity measurement, and 2) The contrast of elasticity between each PEF sensor in the system to locate the tumor accurately. The 1st criterion is based on comparing the magnitude of the contrast of each PEF sensor's tissue induced voltage reading to no sample induced voltage reading. The 2nd criterion is based on establishing a baseline contrast when scanning the healthy tissue with no tumor underneath and when the sensor is above an abnormal region within the PEFS array. For a single PEF sensor, since the abnormal region is expected to have higher effective elastic modulus values compared to the healthy tissue, the abnormal region's induced voltage contrast will be higher compared to that of the healthy tissue induced voltage contrast. When an array of PEFS is considered, the baseline effective elastic moduli is established for the healthy tissue and a higher measured effective elastic moduli would be an indication of an abnormality.

A set of data for a single PEF sensor in a PEFS array during an *in-vivo* breast tumor detection experiment is shown in Figure 11. The data shows that when the PEF sensor was placed on the abnormal region, the scan separated itself from the normal region's contrast showing a clear sign of abnormality. In this specific case, the separation is greater than 100 mV for each applied DC driving voltage, while the standard deviation of induced voltage is less than 10 mV. As the tumors get smaller or deeper, the separation will be less and the accuracy in detection will be diminished when the separation becomes less than the standard deviation. As summarized in Table 1, the results show that iBE unit provided 16 True Positive (TP), 3 True Negative (TN), 1 False Positive (FP) and 2 False Negative (FN) results (Table 1).

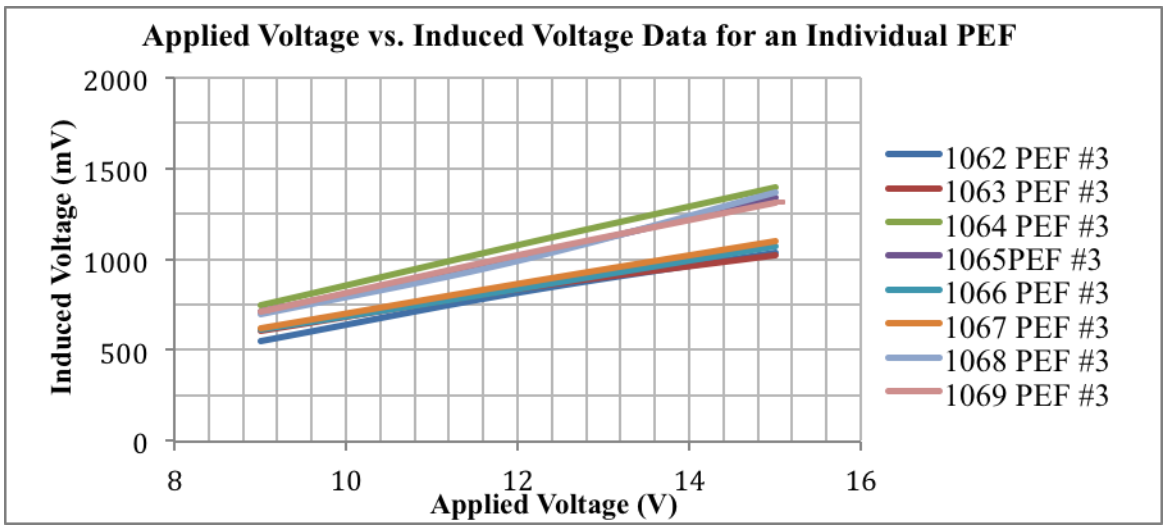

Figure 11: Representative data showing the scanning of the in-vivo breast cancer. The data belongs to one of the sensors on the iBE unit in different locations of the same patient.

		Comparison to Clinical Findings	
Patient No	iBE Unit Detection Results	True Positive (TN) OR True Negative (TN)	False Positive (FP) or False Negative (FN)
1	Yes	TP	-
2	Yes	TP	
3	Yes	TP	-
4	Yes	TP	-
5	No	-	FN
6	No	TN	-
7	Yes	TP	-
8	Yes	TP	-
9	Yes	TP	-
10	Yes	TP	-
11	No	-	FN
12	Yes	TP	-
13	Yes	TP	-
14	Yes	TP	-
15	Yes	TP	-
16	No	TN	-
17	Yes	TP	-
18	No	TN	-
19	Yes	-	FP
20	Yes	TP	-
21	Yes	TP	-
22	Yes	TP	-

Table 1: Results summarizing the 22 clinical trials performed using the iBE prototype

Sub-aim 2a Progress during Phase 2 and Final Phase

At the start of this research project, we had IRB approval from Hahnemann Hospital, however a new IRB application had to be filed at Pennsylvania Hospital since Dr. Ari Brooks (Clinical PI) moved his practice there in September 2013. Due to the delay related to the review and approval of this new IRB approval process and related recommendations made by Abramson Cancer Center of the University of Pennsylvania, we were able to only partially complete the clinical validation as planned under this phase.

The IRB filed at Pennsylvania Hospital required review and subsequent approval from the Abramson Cancer Center of the University of Pennsylvania. After several reviews and discussions, Abramson Cancer Center IRB committee advised that we divide the clinical validation in two parts; first a smaller population 'pilot study' was to be performed in <80 women and a follow-up phase 2 trial to be conducted in 1000 women (a number larger than

originally planned). The preliminary pilot study was completed at Pennsylvania Hospital and based on the satisfactory results; the phase 2 study has commenced and is currently enrolling.

77 subjects were consented and enrolled in an IRB approved pilot study at the Women's Imaging Center, Pennsylvania Hospital to receive iBE breast exam prospectively. The average age of the enrolled population was 42 (range 21-79), including one male, with the racial breakdown as 40 Caucasian, 26 African American, 2 Asian, 4 Hispanic and 5 unknown. The suspicious lesions identified by mammography or ultrasound were classified into BIRADs categories (see Table 1). Breast biopsies were performed on 39 of the 77 subjects. Suspicious lesions identified by Mammography, Ultrasound, or clinical breast exam were assigned a breast quadrant and identified as positive studies. Non-suspicious quadrants provided the normal population of negative studies. Results from these studies are summarized in Table 2.

BIRADs Categories	Classification by Mammography or Ultrasound Results	
	Numbers	Percentage
1	3	3.9%
2	26	33.8%
3	5	6.5%
4A	18	23.3%
4B/4C	20	26.0%
5	4	5.2%
6	1	1.3%

Table 2: Classification of Clinical Results

Positive iBE	66	28	94
Negative iBE	11	237	248
Total	77	265	342
Sensitivity = 86%, Specificity = 89%, PPV = 70%, NPV 95.5%			

Table 3: Summary of Results

Progress with Sub-Aim 2b: To correlate PEFS findings with conventional exams for tumor *classification*, in-vivo.

Sub-aim 2b was completed partially.

At the start of this research project, we had IRB approval from Hahnemann Hospital, however a new IRB application had to be filed at Pennsylvania Hospital since Dr. Ari Brooks (Clinical PI) moved his practice there in September 2013. Due to the delay related to the review and approval of this new IRB approval process and related recommendations made by Abramson Cancer Center of the University of Pennsylvania, we were able to only partially

complete the clinical validation as planned under this phase.

Sub-aim 2b Progress during Phase 1

The iterative design approach on the compression aspect of the iBE system resulted in major improvements in the tumor detection algorithm, as well as improving and optimizing the PEFS compression array design and clamping mechanisms for accurate data collection in the shortest amount of time. Unlike the PEFS compression array, PEFS shear array data does not provide conclusive data on its own and needs to be paired with PEFS compression array data; shear (G) over elastic (E) modulus (G/E) data provides information regarding tumor differentiation. Since the PEFS compression array was constantly being improved and redesigned, the PEFS shear array progress was limited until a satisfactory PEFS compression array system has been established.

Sub-aim 2b Progress during Phase 2

The progress made on the PEFS compression array system regarding the sensor design, electronics and software algorithm has been transferred to PEFS shear array system for tumor classification. Prototype design of the PEFS shear array system is shown in Fig.12. Single PEFS shear array has been used to collect data from model breast tumors with inclusions embedded inside. Elastic and shear moduli data have been derived from the induced voltage data collected on the breast models and it has been shown that shear to elastic moduli ratio is equal to ~0.3 (G/E ≅ 0.3), which is the expected value to be obtained from model tissue with no inclusion and also containing inclusions with smooth surfaces. Upon further verification of the shear array system, it will be applied for use in *in-vivo* tumor classification.

Fig. 12 Pictures of Shear Array

Sub-aim 2b Progress during Final Phase

The knowledge and experience gained from the iBE compression array has been transformed to the iBE shear array to establish the shear (G) over elastic (E) modulus (G/E) data information. iBE shear array box was further developed using only one iBE sensor (1x4) and the iBE compression box electronics with a modified algorithm for induced voltage timing. Model tissues have been studied with the iBE shear array box, where iBE was able to differentiate between inclusion with smooth and corrugated surface when buried in the silicone model tissue. To assess the G/E ratio variation with respect to the corrugation of the inclusion, spherical inclusions with speculation (meaning with spikes or points on the surface) lengths varying from 1mm to 3mm were prepared and compared to that of the inclusions with smooth surfaces. For this experiment, the depth of the inclusions were kept at 5mm and the surface on top of the inclusions were scanned with both compression and

shear box sensors. The G/E results have shown that for the inclusion with a smooth surface, G/E ratio is approximately 0.33, while as the speculation length of the inclusion increased from 1mm to 3mm, and the G/E ratio gradually increased to >0.7. This means that the Shear sensor has the ability to not only potentially differentiate between benign and malignant masses but the G/E ratio may also indicate the type of malignancy.

Reproducibility and Repeatability (R&R) studies were performed with the iBE shear box on the model tissue with tumors of varying depths. For this experiment, two inclusions, one with a smooth surface and one with the spiculation length of 3 mm length were chosen. The depth of the inclusions varied from 2mm to 20mm, gradually, with 2mm increments to assess the depth sensitivity using shear moduli measurements, as well as its effect on the G/E ratio. For the current shear sensor with 7mm tip width, the shear depth sensitivity is established at around 14 mm (twice the width of the sensor). It has also been shown that G/E ratio is equal to ~0.33 for the smooth surface inclusion and is steady beyond 14mm. It has been shown that the G/E ratio is greater than 0.7 for the inclusion with spiculations and gradually decreases to appx. 0.33 beyond the shear sensor depth sensitivity limit of 14mm for this specific sensor with a width of 7mm.

Progress with Sub-Aim 2c: To compare the efficacy of PEFS against hand-palpation using gelatin breast phantoms.

Sub-aim 2c was successfully completed.

Sub-aim 2c Progress during Phase 1

During each development stage, the redesigned iBE unit was vigorously tested on model tissues to ensure the accuracy of data collection. For this purpose, model tissues have been prepared from silicone samples with shore hardness of 00-10 (Ecoflex Supersoft 0010, Smooth-On). Various sized inclusions were embedded inside the prepared model silicone tissue. The first model consisted of breast shaped silicone samples with 6 mm diameter spherical inclusions embedded inside the silicone at depths up to 15 mm from the surface of the silicone. These inclusions were scanned using a 2 x 4 PEFS array and the experiments were repeated by different operators to obtain statistically significant data, while including the operator variability. The results showed that iBE unit was able to accurately detect 6 mm diameter spherical inclusions consistently at depths up to 15 mm. Experiments regarding the accuracy of latest generation iBE unit on detecting inclusions smaller than 4 mm in size and deeper than 15 mm in depth are ongoing.

The second tissue model was a two-layered silicone model where the first layer had a thickness of 10 mm and the second layer had a thickness of 20 mm. In this model, the layers could be separated from each other allowing placement of inclusions in between each layer. Cylindrical inclusions that were 1.5 mm in height and with diameters varying from 5 mm to 25 mm were placed in between the two layers to analyze the accuracy of inclusion detection of the developed iBE prototypes with varying inclusion width. Repetitive experiments were performed with different operators and inclusions were placed at random locations in

between the two silicone layers to obtain statistically significant data. The results showed that 2 x 4 iBE array was able to successfully detect the inclusions underneath the 10 mm thick silicone layer varying from 5 mm to 25 mm in size. It should also be noted that in both model tissue studies, the experimental results were similar when tested by different operators. This proves that iBE system results on the aforementioned model tissue experiments were operator-independent.

Sub-aim 2c Progress during Phase 2

Palpation of each lesion was documented with a binary yes/no result depending on if the subject could feel the lesion or not. The subjects were instructed to place the iBE unit on the lesion to perform a scan. If there was an iBE finding at that location, as determined by the subject after adequate training, the data was tagged as a true positive, otherwise, the data was tagged as a false negative. A summary of the results is shown in Table 5. Different operators and inclusions were placed at random locations in between the two silicone layers to obtain statistically significant data. The results showed that 2x4 iBE array was able to successfully detect the inclusions underneath the 10 mm thick silicone layer varying from 5 mm to 25 mm in size. It should also be noted that in both model tissue studies, the experimental results were similar when tested by different operators. This proves that iBE system results on the aforementioned model tissue experiments were operator-independent.

	Accuracy	Description
Intra-operator Repeatability	98%	Single user to scan lesions repeatedly with same results
Inter-operator Repeatability	96%	Multiple users to scan lesions repeatedly with same results
Inter-device Repeatability	100%	Single user to scan lesions with 2 different devices with same results
Size Evaluation (8mm, 1.3cm)	98%	Ability to detect the size of a lesion with ± 5mm accuracy
Stiffness (relative)	97%	Ability to classify stiffness using three discrete stiffness levels
Shape	100%	Ability to classify Circular vs. Tubular

Table 4: Intra-Operator, Inter-Operator and Inter-Device Repeatability Estimation Results

Lesion	Lesion Coordinate	Correlation Accuracy
A (8mm spherical, 1cm deep)	3cm, 4cm	96%
B (1.3cm spherical, 1cm deep	5cm, 2cm	100%
C (1.3cmm spherical, 2cm deep)	4cm, 4cm	94%

Table 5: Lesion Localization Results

(clock-wise from top left) – Complete iBreastExam System, iBreastExam Sensor Enclosure, iBreastExam In Use, iBreastExam CAD Rendered Graphic, iBreastExam Software Screen Shots

To date, as a direct impact of this research project, UELS has been able to achieve the following milestones:

- Two grant awards
  - University City Science Center's Digital Health Accelerator Award ($50,000) with lab and office space for one year.
  - Unitus Seed Fund's StartHealth Award ($80,000) with support from Pfizer Pharmaceuticals, PATH Foundation, Narayana Health System and Manipal Hospitals System.

- Follow-on investment capital
  - $500,000 convertible note investment
  - $3,000,000 in equity investment (term-sheet signed)

- Successful completion of several lab tests per US FDA's consensus standards. These lab tests results and reports are usable for most regulatory agencies worldwide.

- US FDA 510(k) clearance as "breast lesion documentation system"

- Clinical study of 1,300 women in rural parts of India. Of 150 women flagged by iBreastExam, 3 were diagnosed with breast cancer. (Supported by sources other than CURE funds.)

- Feasibility study in Fiji Islands where access to expert medical care is highly limited. 160 women participated in health camps to get checked for breast lesions for the first time in their lives. (Supported by sources other than CURE funds.)

- Collaborations with several research, non-profit and business entities as well as clinicians from around the world to globally commercialize this Pennsylvania born innovation.

18. Extent of Clinical Activities Initiated and Completed. Items 18(A) and 18(B) should be completed for all research projects. If the project was restricted to secondary analysis of clinical data or data analysis of clinical research, then responses to 18(A) and 18(B) should be "No."

18(A) Did you initiate a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

__X___Yes
_____No

18(B) Did you complete a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

_____Yes
___X__No

If "Yes" to either 18(A) or 18(B), items 18(C) – (F) must also be completed. (Do NOT complete 18(C-F) if 18(A) and 18(B) are both "No.")

18(C) How many hospital and health care professionals were involved in the research project?

__5___Number of hospital and health care professionals involved in the research project

18(D) How many subjects were included in the study compared to targeted goals?

_570__Number of subjects originally targeted to be included in the study
__77__Number of subjects enrolled in the study

Note: Studies that fall dramatically short on recruitment are encouraged to provide the details of their recruitment efforts in Item 17, Progress in Achieving Research Goals, Objectives and Aims. For example, the number of eligible subjects approached, the number that refused to participate and the reasons for refusal. Without this information it is difficult to discern whether eligibility criteria were too restrictive or the study simply did not appeal to subjects.

18(E) How many subjects were enrolled in the study by gender, ethnicity and race?

Gender:
__1___Males
__76__Females
_____Unknown

Ethnicity:
__4___Latinos or Hispanics
__73__Not Latinos or Hispanics
_____Unknown

Race:
_____American Indian or Alaska Native
__2___Asian
__26__Blacks or African American
_____Native Hawaiian or Other Pacific Islander
__40_ White
_____Other, specify:_____
__5___Unknown

18(F) Where was the research study conducted? (List the county where the research study was conducted. If the treatment, prevention and diagnostic tests were offered in more than one county, list all of the counties where the research study was conducted.)

The study was conducted in Philadelphia county.

19. Human Embryonic Stem Cell Research. Item 19(A) should be completed for all research projects. If the research project involved human embryonic stem cells, items 19(B) and 19(C) must also be completed.

19(A) Did this project involve, in any capacity, human embryonic stem cells?
_____Yes
___X__ No

19(B) Were these stem cell lines NIH-approved lines that were derived outside of Pennsylvania?
_____Yes
_____ No

19(C) Please describe how this project involved human embryonic stem cells:

20. Articles Submitted to Peer-Reviewed Publications.

20(A) Identify all publications that resulted from the research performed during the funding period and that have been submitted to peer-reviewed publications. Do not list journal abstracts or presentations at professional meetings; abstract and meeting presentations should be listed at the end of item 17. **Include only those publications that acknowledge the Pennsylvania Department of Health as a funding source** (as required in the grant agreement). List the title of the journal article, the authors, the name of the peer-reviewed publication, the month and year when it was submitted, and the status of publication (submitted for publication, accepted for publication or published.). Submit an electronic copy of each publication or paper submitted for publication, listed in the table, in a PDF version 5.0.5 (or greater) format, 1,200 dpi. Filenames for each publication should include the number of the research project, the last name of the PI, and an abbreviated title of the publication. For example, if you submit two publications for Smith (PI for Project 01), one publication for Zhang (PI for Project 03), and one publication for Bates (PI for Project 04), the filenames would be:

Project 01 – Smith – Three cases of isolated
Project 01 – Smith – Investigation of NEB1 deletions
Project 03 – Zhang – Molecular profiling of aromatase
Project 04 – Bates – Neonatal intensive care

If the publication is not available electronically, provide 5 paper copies of the publication.

Note: The grant agreement requires that recipients acknowledge the Pennsylvania Department of Health funding in all publications. Please ensure that all publications listed acknowledge the Department of Health funding. If a publication does not acknowledge the funding from the Commonwealth, do not list the publication.

Title of Journal Article:	Authors:	Name of Peer-reviewed Publication:	Month and Year Submitted:	Publication Status (check appropriate box below):
1. None				☐Submitted ☐Accepted ☐Published

20(B) Based on this project, are you planning to submit articles to peer-reviewed publications in the future?

Yes___X_____ No_____

If yes, please describe your plans:

Based on this project, two articles are being planned for submission to peer-reviewed publications in the near future.

21. Changes in Outcome, Impact and Effectiveness Attributable to the Research Project. Describe the outcome, impact, and effectiveness of the research project by summarizing its impact on the incidence of disease, death from disease, stage of disease at time of diagnosis, or other relevant measures of outcome, impact or effectiveness of the research project. If there were no changes, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

The American Joint Committee on Cancer (AJCC) staging system indicates prognosis based on the size of the tumor at detection viz. stage of breast cancer. Identifying tumors at earlier stages (down-staging) can improve survival, assuming high-quality treatment is accessible. In the U.S., approximately 40 million women receive mammograms annually and roughly 232,000 new cases are identified; vast majority are detected at stage Tis and T1, for whom the 5-year survival is near 100%. In the context of LMICs, where up to two-thirds of breast cancer cases present at late stages, systematic down-staging is required, such that majority of the cases would be identified at Stage II or earlier, where survival can be 93% or better; again, with the assumption that treatment options are available.

(In pilot studies) iBreastExam has shown that it is capable of detecting non-palpable breast lesions in areas where mammography is either inaccessible or unadoptable. In addition, the pilot study under this research project found that iBreastExam can identify breast lesions with 86% Sensitivity, 89% Specificity, Negative Predictive Value of 95.5% and Positive Predictive Value of 70%.

22. Major Discoveries, New Drugs, and New Approaches for Prevention Diagnosis and Treatment. Describe major discoveries, new drugs, and new approaches for prevention,

diagnosis and treatment that are attributable to the completed research project. If there were no major discoveries, drugs or approaches, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

In LMICs, community health workers (CHWs) often represent an affordable resource for the education and provision of preventive, primary and promotive healthcare. Low-cost, user-friendly technology can help equip minimally trained CHWs to administer standardized breast exams without any special infrastructure, with the goal to down-stage breast cancer (Stage II or earlier). The low-cost technology must perform with better detection sensitivity than CBE (higher than 50%) and equally high specificity as CBE (94%) to accurately and effectively identify breast lumps in need of further diagnostic follow-up (diagnostic ultrasound, breast biopsy) without clogging the under-resourced infrastructure with false positives due to typical benign breast features (tissue variability, lumpiness and nodularity).

As a complete medical device that is clinically validated and cleared by the regulatory agencies, iBreastExam offers a totally new approach to secondary prevention in these parts of the world. In addition, iBreastExam may be helpful to women in developed countries including the USA where efficacy of mammography is found to be limited in women with dense breasts, women under age 40 and women that are at high-risk for breast cancer. The product being developed by UELS, is a non-invasive, hand-held, battery-powered breast scanner that enables minimally trained community health workers (CHWs) to administer "CBE-like" breast exams, quickly and with greater clinical efficacy. iBE is designed to 'optimize and standardize' every health worker's ability to objectively identify and report breast lesions at early stages in conditions with limited or no medical infrastructure. iBE has the potential to "optimize" CBE by improving on its overall effectiveness to detect Stage I and IIa breast cancers with minimally trained CHWs. iBE will also "standardize" clinical breast exams by assisting every CHW to administer and record breast exams objectively, consistently and with the ability to share the results easily using the mobile device app.

As realized in this research project, iBreastExam has the potential to bring forth an entirely new approach to breast cancer early detection.

23. Inventions, Patents and Commercial Development Opportunities.

23(A) Were any inventions, which may be patentable or otherwise protectable under Title 35 of the United States Code, conceived or first actually reduced to practice in the performance of work under this health research grant? Yes_____ No___X_____

If "Yes" to 23(A), complete items a – g below for each invention. (Do NOT complete items a - g if 23(A) is "No.")

a. Title of Invention:

b. Name of Inventor(s):

c. Technical Description of Invention (describe nature, purpose, operation and physical, chemical, biological or electrical characteristics of the invention):

d. Was a patent filed for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No____
If yes, indicate date patent was filed:

e. Was a patent issued for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No____
If yes, indicate number of patent, title and date issued:
Patent number:
Title of patent:
Date issued:

f. Were any licenses granted for the patent obtained as a result of work performed under this health research grant? Yes_____ No____

If yes, how many licenses were granted?_____

g. Were any commercial development activities taken to develop the invention into a commercial product or service for manufacture or sale? Yes___ No____

If yes, describe the commercial development activities:

23(B) Based on the results of this project, are you planning to file for any licenses or patents, or undertake any commercial development opportunities in the future?

Yes___X_____ No_____

If yes, please describe your plans:

Based on the results from this project, UE LifeSciences is working to commercialize iBreastExam as a medical device for global impact. Accomplishments of the engineering aims have led UELS to design, develop and build a commercial-grade product from innovative academic science. Mihir Shah, the principal investigator for this research project will be serving as the Chief Executive Officer of UE LifeSciences. In addition, UELS has assembled a team of engineers, scientists, and clinicians to implement a business plan to fully commercialize iBreastExam technology. UELS will be seeking new funding opportunities, pursuing distributorship partnerships globally and fostering collaborations with non-profits, governmental agencies as well as private healthcare providers.

24. Key Investigator Qualifications. Briefly describe the education, research interests and experience and professional commitments of the Principal Investigator and all other key investigators. In place of narrative you may insert the NIH biosketch form here; however, please limit each biosketch to 1-2 pages. *For Nonformula grants only – include information for only those key investigators whose biosketches were not included in the original grant application.*

Provided in grant application.