A Preliminary Evaluation of Multi-probe Resonance-frequency Electrical Impedance Based Measurements of the Breast

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Rationale and Objectives: The aim of this study was to preliminarily assess the performance of a new, resonance-frequency electrical impedance spectroscopy (REIS) system in identifying young women who were recommended to undergo breast biopsy following imaging.

Materials and Methods: A seven-probe REIS system was designed and assembled and is currently being prospectively tested. During examination, contact is made with the nipple and six concentric points on the breast skin. Signal sweeps are performed, and outputs ranging from 200 to 800 kHz at 5-kHz intervals are recorded. An initial set of 140 patients, including 56 who eventually had biopsies, 63 who had negative results on screening mammography, and 21 recalled for additional imaging but later determined to have negative results, was used. An initial set of 35 features, 33 representing impedance signal differences between breasts and two representing participant age and average breast density, was assembled and reduced by a genetic algorithm to 14. The performance of an artificial neural network-based classifier was assessed using a case-based leave-one-out method.

Results: The substantially greater asymmetry between signals of mirror-matched regions ascertained from biopsy ("positive") compared to nonbiopsy ("negative") cases resulted in an artificial neural network classifier performance (area under the curve) of 0.830 ± 0.023. At 90% specificity, this classifier, optimized for "recommendation for biopsy" rather than "cancer," detected 30 REIS-positive cases (54%), including six of nine (67%) actual cancer cases and six of nine women (67%) recommended for surgical excision of high-risk lesions.

Conclusions: Asymmetry in impedance measurements between bilateral breasts may provide valuable discriminatory information regarding the presence of highly suspicious imaging-based findings.

Key Words: Electrical impedance spectroscopy; EIS; resonance frequency; risk stratification; breast cancer; artificial neural network; technology assessment.

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The early detection of breast cancers in younger women (aged < 50 years) is a mammographically difficult and time-consuming task, primarily because of the low prevalence of disease and denser breast tissue (on average) that results in lower detection sensitivity and specificity (1–3). In recent years, a number of alternative and/or improved approaches have been investigated for this purpose. Full-field digital mammography, whole breast ultrasound, and magnetic resonance imaging are frequently used for this purpose (4). Other newer technologies, such as digital breast tomosynthesis and breast cone-beam computed tomography, are also being investigated (5,6). These new breast imaging modalities have demonstrated the ability to achieve improved detection performance in specific groups of women compared to film and/or digital mammography (7–9), resulting for example in the recent recommendation for periodic breast magnetic resonance imaging examinations in women at high risk as an adjunct to mammography (10). Often these technologies result in the detection of different cancers; hence, the information obtained is complementary to mammography (4). However, all of these imaging modalities have well-understood advantages and disadvantages, in particular when, and if, applied to a substantial fraction of the screened population with no known risk factors.

Despite these advances and the fact that mortality from breast cancer is decreasing, there is a serious continuing controversy about the efficacy of current screening practices in the United States (11,12). As related to women who are of prescreening age and those not complying with screening
recommendations at an older age, there has been an interest in
developing an inexpensive, non-radiation-based examination
tool that is simple to use and interpret, which could be used
during annual examinations at physicians' offices in conjunc-
tion with the clinical breast examination. The underlying
concept is that with the use of this new examination tool,
any abnormalities in these women would be detected at an
eyear time (and potentially at an earlier stage). Because of
low cancer prevalence among younger women (aged < 50
years), there may be an important role for tools that could
stratify these women into two groups, the majority of those
who are at "average risk" and but a small fraction of those
(eg, ≤10%) who are at significantly higher than average risk
for having or developing breast cancer. Hence, women who
do not participate in periodic imaging-based screening
because of their age, or their personal choice, and are found
to be "positive" on the basis of the stratification-type exa-
mination should be recommended to seek imaging-based evalu-
ation because they were determined to belong to a "defined
high-risk group" (13). This approach is therefore based on
a "rule-in" concept rather than a "rule-out" one. Namely,
such a stratification tool is in no way a competitor of
imaging-based surveillance. Under this paradigm, every
additional cancer that would be ultimately detected as a result
of the practice, and the imaging that would follow, will
likely be detected substantially earlier. As important perhaps,
stratification-type examination (tool) with these operational
characteristics could become extremely important for indi-
vidualized screening recommendations if annual imaging-
based examinations, in particular at an earlier age (<50 years),
is ultimately deemed to no longer be the standard of practice.

Electrical impedance spectroscopy (EIS) is one of the
approaches that have been investigated for this purpose. Since
the first imaging-based EIS system to detect breast abnormali-


demonstrated that measured EIS output signals contain some
discriminatory information (24). However, when applied to
women in the clinic, the performance levels of EIS-based
classifiers remain relatively low. For example, the T-Scan 2000
has not been successful in terms of the stated objective, as
reported sensitivity was in the range of 20% to 30% at high
specificity levels. Only one study reported 27% sensitivity at
94% specificity in a group of women that included 36 with
cancer and 476 with negative findings (21).

We have been investigating a substantially different non-
imaging-based EIS concept, in that the response signals we
ascertain and analyze are specifically at and near the resonance
frequency for the breast tissue being measured. We focus our
analysis on asymmetry in measured EIS signals from mirror-
matched regions of bilateral breasts of the examined woman
(25–27). Hence, we have termed this approach "resonance-
frequency EIS" (REIS). The approach aims to identify younger
women who are not routinely screened by an imaging
modality but are at a higher than average risk for having or
developing breast cancer. These women could then be
recommended to undergo imaging-based follow-up. In a prelimi-
ary evaluation of a prototype REIS system with only one pair of
probes, we demonstrated that there is relevant information in the
measured signals and that performance was statistically
significantly better than chance (26). Recently, we developed,
assembled, and installed a new multiprobe REIS system (27).

Under institutional review board-approved protocol, we are
currently conducting a prospective clinical data collection to
assess the performance of this multiprobe REIS system. In this
study, the initial set of REIS examinations acquired from 140
women with verified diagnostic results was used to develop
and test an artificial neural network (ANN)-based machine
learning classifier. From the classification results of these women
into "positive" (women actually recommended for biopsy) and
"negative" (women not recommended for biopsy), we report
here the preliminary assessment results.

MATERIALS AND METHODS

The Multiprobe REIS System

Under an exclusive agreement between the University of
Pittsburgh and Dhirajt Electronics Consulting LLC (Roches-
ter, NY), we designed and assembled a unique multiprobe REIS
system (Fig 1) that enables measuring and recording multi-
channel output signal sweeps ranging from 200 to 800 kHz
(27). In brief, the system consists of a mechanical support, an
electronic box with two sensor cups, and a notebook computer
that includes the management software of the system control
and data acquisition and recording. The two sensor cups have
different surface curvatures specifically designed to fit "smaller"
and "larger" breasts. Each sensor cup has seven mounted metallic
probes. One probe is located at the center of the cup, and the
other six probes are mounted uniformly, or symmetrically
distributed, along an "outer" circle with a 60-mm radius. The
probes (contacts) protrude approximately 4 mm from the base
The multiprobe resonance-frequency electrical impedance spectroscopy system installed in our clinical breast imaging facility.

of the cups to facilitate good contact with the breast. During an REIS examination, the center probe is intended to enable easy contact with the nipple. The other six external probes provide contact with six fixed points on the breast skin surface at a fixed distance to the nipple (center probe). Specifically, the six external probes are located at the 12, 2, 4, 6, 8, and 10 o'clock positions (Fig. 1). The curvature of the cups and the distance between the probes were based on actual multiple measurements using a mock-up device. The two sensor cups are mounted on the “front” and “back” of the electronic box. The complete assembly can be easily rotated 180° to allow the use of either cup by the person conducting the REIS examination and is easily movable (up or down) to a desired height. The maximum electric voltage and current applied to the sensor probes are <1.5 V and <30 mA, respectively. Hence, applying a sensor cup to the breast skin is similar to physically holding a 1.5-V battery between one’s fingers.

The REIS Examination

After launching the REIS control software, a trained technologist performs the REIS examination as follows: (1) The technologist adjusts the height of the sensor box (lowers or raises) along a vertical rail (weight balanced for ease of use) to fit the height of the participant’s breast and locks it in place. The center probe is typically positioned slightly above the natural position of the participant’s nipple while standing. (2) The technologist selects the sensor cup to be used on the basis of the participant’s breast size and locks it in place. (3) The woman is asked to “lift” her breast slightly with her hand and position the nipple in contact with the center probe and then gently “pull herself into” the cup by holding one or both support sidebars designed specifically for this purpose. (4) The technologist keys a digital identification number specific to each REIS examination in a data entry window and then, using the computer mouse, initiates the REIS examination by clicking on a “start” command button displayed on the computer screen. Once the system detects automatically that all seven probes are in “good contact with the breast,” signal acquisition commences. (5) The technologist visually monitors the signal scanning process on the computer screen to ensure that contact between the breast skin and probes was maintained during the entire scanning period. If adequate contact is lost during the REIS examination, the system generates unsmoothed signal output curves, and the examination results are discarded. A repeated examination is then conducted and recorded. A complete examination of each breast takes 8 seconds to scan, record, and save all measured output signals from as many as eight detection channels. During a complete REIS examination, the same positioning and scanning protocol are performed on both breasts.

Acquired Output Signals

The recorded signal sweeps in each detection channel, namely, a single pair of probes, includes three sets of output signals. Each records 121 output values for frequencies ranging from 200 to 800 kHz in 5-kHz increments. The three sets of output signal sweeps represent signal amplitude ($a$), signal phase ($p$), and signal magnitude ($I = \sqrt{a^2 + p^2}$), as shown in Figure 2. At the resonance frequency, the signal magnitude ($I$) reaches a minimum output signal value, and the phase signal crosses the $p = 0$ line (i.e., converts from a negative to a positive value). During each REIS examination, all generated and recorded six pairs of the three output signal sets are automatically saved in a computer database for future data analysis.

Study Participants

Under an institutional review board–approved protocol, we have been performing REIS examinations on consenting women between the ages of 30 and 50 years who meet our inclusion criteria. Participants are classified on the basis of actual diagnostic results (outcomes) into one of three groups. The “positive” group includes women who had been recommended for biopsy following an imaging-based diagnostic workup (Breast Imaging Reporting and Data System [BI-RADS] category 4 or 5), and the REIS relevant examination was performed prior to the biopsy (typically on the same day approximately half an hour prior to the scheduled biopsy). The second group includes women who previously had negative screening results.
and were visiting our facility for their scheduled annual screening examinations. Status verification in these women included at this time solely the negative mammograms of the scheduled screening examination. Currently, we do not have long-term follow-up on these women, as it is scheduled to be performed in 2 years, but the expectation value for future positive findings within 1 or 2 years is extremely low. The third group includes women who had been recalled for diagnostic follow-up (BI-RADS category 0) as a result of prior screening mammograms but were later (after diagnostic workup) determined not to require biopsy (BI-RADS category 1 or 2; no BI-RADS category 3 in this group). At this time, our inclusion criteria for women who had been recalled for diagnostic follow-up, or those who had been recommended for biopsy, does not include restrictions regarding the type of abnormality in question (eg, mass, cluster of microcalcifications, focal asymmetry) or the specific location or depth of the suspected abnormality within the breast (26).

The multiphasic prospective clinical data collection task we are embarking on will be executed over the next 2 years and has several planned sequential analytic steps. As a preliminary assessment, the first acquired set of 140 cases is reported here. We analyzed an initial set of 140 REIS examinations acquired with a new multiprobe-based REIS system on women with known imaging-based and/or pathology-based outcomes. Among these women, 56 were “positive” (recommended for biopsy) and 84 were “negative” (nonbiopsy). The latter group (“negative”) included 63 who had not been recalled (screening negative) and 21 who had been recalled (screening BI-RADS category 0) for additional imaging procedures but were later determined not to need biopsy (BI-RADS category 1 or 2); hence, these cases are considered “negative” for the purpose of this analysis. Among the 56 “positive” cases (BI-RADS category 4 or 5), imaging-based examinations (ie, mammography, ultrasound, and magnetic resonance imaging) showed that 37 depicted suspicious masses, asymmetric density, or architectural distortions; eight depicted microcalcification clusters alone; and 11 depicted both masses and microcalcification clusters. Among the 56 biopsied lesions in this data set, 16 were reported as “palpable” masses in the corresponding diagnostic reports (clinical breast examination), but only two of these eventually represented “high-risk” lesions, and none of the cancers was palpable. For the purpose of this analysis, the biopsy (“positive”) group included three types of cases: (1) verified cancer cases, (2) cases with high-risk lesions recommended for surgical excision as a result of the biopsy that followed, and (3) biopsy-proven benign cases. The biopsy results showed that the “positive” group included nine cancer cases, nine high-risk cases, and 38 benign cases. Among the nine cancer cases, four depicted masses only, two were associated with microcalcification clusters only, and three depicted both abnormalities. Among the nine “high-risk” cases, six depicted masses only, two depicted microcalcification clusters only, and one depicted both abnormalities.

The average mass size in the biopsy group, as measured by ultrasound, was 1.37 ± 1.28 cm (range, 0.4–7 cm). The cancer mass sizes ranged from 0.85 to 2.0 cm. Among the 56 biopsied cases, nine were located in the “periareolar” or “retroareolar” regions, and three were located posteriorly, close to the chest wall. The remaining 44 biopsied lesions were reasonably well distributed in all breast regions. The average age of the women whose REIS data were included in this analysis was 43.8 ± 3.8 years (range, 35–50 years). Among the 140 cases in this data set, two were subjectively rated by the radiologists during the imaging-based examinations as being “almost all fatty” (1.4%), 32 were rated as “scattered fibroglandular densities” (22.9%), 93 were rated as “heterogeneously dense” (66.4%), and 13 were rated as “extremely dense” (9.3%).

The Initial Feature Pool

A large number of EIS signal-related features were extracted as the initial feature set from the six sets of EIS signal sweeps acquired between the center probe and each of the six “external” probes. We named each probe on the basis of the location (orientation) of the external contact point at 12, 2, 4, 6, 8, and 10 o’clock (Fig 1). On the basis of the underlying assumption that, similar to asymmetry in tissue patterns, two breasts have a higher level of impedance symmetry in negative cases than in abnormal cases (20–25,26), we focused our analysis on signal differences between geometrically corresponding locations obtained from the two breasts of each participant. Figures 3 and 4 show typical signal sweeps (magnitude only) for a biopsy (“positive”) case and a nonbiopsy (“negative”) case, respectively.

The initial feature pool of 35 included 33 EIS signal-based features and two non-EIS-based features. The definitions of the initial 33 EIS signal-based features follow. Feature 1 was defined as the maximum absolute difference between the ranges of all six resonance frequencies for each of the breasts as computed for the left and right breasts ($F_i = \max|\Delta f_i - \Delta f_{\text{Ri}}|$).
The remaining 32 EIS signal-based features were divided into two distinct groups (features 2 to 17 in group 1 and features 18 to 33 in group 2). In the first group, we averaged a number of EIS signal values of the six EIS sweeps (including both signal magnitude and phase) for each breast. Except for one feature that was computed as a mean of two averaged EIS signal values from the two breasts, the remaining 15 features were all computed by subtraction (differences) of two averaged EIS signal values from the two breasts. These 16 features were as follows:

1. Features 2 and 3: We computed two average resonance frequencies, including \( f_{L} = \left( \sum_{i=1}^{6} f_{i} \right) / 6 \) for the left breast and \( f_{R} = \left( \sum_{i=1}^{6} f_{i} \right) / 6 \) for the right breast and defined the following two features. Feature 2 was the mean of the two averaged resonance frequencies \( (F_{2} = \frac{f_{L} + f_{R}}{2}) \) and was the only feature that did not represent a subtracted value but rather represented the overall resonance frequency value as measured for the specific case. Feature 3 was the absolute difference between the two averaged resonance frequency values \( (F_{3} = |f_{L} - f_{R}|) \).

2. Feature 4: By identifying the EIS signal magnitude value at the resonance frequency \( (|T|) \) of each sweep and computing the average value of all six EIS sweeps \( (T = \left( \sum_{i=1}^{6} T(f_{i}) \right) / 6) \), we defined feature 4 as \( F_{4} = |T_{L} - T_{R}| \), representing the absolute difference in averaged EIS magnitude values at the respective resonance frequencies.

3. Features 5 to 10: Near each resonance frequency, we extracted six EIS signal magnitude values of an EIS sweep \( (|T_{i}|) \) at six recorded frequencies, including two values smaller than the resonance frequency \( (f_{-10} = f - 10 \text{ kHz} \) and \( f_{-5} = f - 5 \text{ kHz} \) and four values larger than the resonance frequency \( (f_{+5} = f + 5 \text{ kHz} \) to \( f_{+20} = f + 20 \text{ kHz} \) in 5-kHz increments). For each of these extracted EIS signal magnitude values, we subtracted the EIS signal magnitude value at the resonance frequency of the same EIS sweep \( \Delta I_{i} = |T_{i} - T_{i}| \). After computing the average EIS signal magnitude differences \( \Delta I \) among all six probe pairs \( \Delta I_{i} = \left( \sum_{i=1}^{6} \Delta I_{i} \right) / 6 \) for each breast, we defined six features \( (F_{5} = |\Delta I_{L} - \Delta I_{R}|) \), where \( j = 5, 6, \ldots, 10, \) and \( i = -10, -5, +5, +10, +15, \) and +20, representing the six frequency differences near the resonance frequency (in kilohertz) of the EIS signal sweeps. Thus, features 5 to 10 represented the absolute differences of the averaged EIS signal magnitude values between left and right breasts at these six frequencies.

4. Feature 11: Similar to the computation of feature 3, representing the difference in value between two frequencies, we computed another frequency difference value between two breasts on the basis of the EIS signal phase sweep (Fig. 2). For each EIS signal phase sweep, we identified the frequency at which the EIS phase value reaches a plateau \( (\phi_{\text{Max}}) \). We then computed the average frequency value of the six EIS
signal phase sweeps \( \langle \mu_p^{\text{Max}} \rangle = \frac{\sum_{j=1}^{n} f_j}{6} \) for the left and the right breasts. We defined feature 11 as \( F_{11} = [\langle \mu_p^{\text{Max}} \rangle - \langle \mu_p^{\text{Max}} \rangle], \) representing the absolute difference between two averaged frequencies at which EIS phase values reach plateaus for the two breasts.

5. Features 12 to 17: Similar to features 5 to 10, we computed EIS signal phase value differences rather than EIS signal magnitude value differences for the same set of six frequencies of interest. Features 12 to 17 were defined as the absolute differences between two breasts of two averaged phase values at the specific frequencies, namely, \( F_{i} = (\bar{p}(f_{j})_{L} - \bar{p}(f_{j})_{R}), \) where \( j = 12, 13, \ldots, 17, \) and \( i = -10, -5, +5, +10, +15, \) and +20 kHz different from the resonance frequencies, respectively.

Features 18 to 33 in the second group were defined and computed in a similar manner to Features 2 to 17 in the first group, with the exception that only one pair of mirror-matched EIS signal sweeps (rather than averages of all six sweeps) from the left and the right breasts were selected for computing these 16 features. Specifically, for each REIS examination (case), we compared the resonance frequency differences for the six sets of mirror-matched EIS pairs of sweeps. We then selected the one matched pair of EIS sweeps (eg, at 10 o'clock on the right breast and 2 o'clock on the left breast) that had the maximum resonance frequency difference among all six matched pairs of EIS sweeps. Table 1 summarizes the distribution of cases that had a maximum resonance frequency difference between the two breasts at each of the six mirror-matched pairs in the data set used in this study. After selecting the examination-specific matched pair, we discarded all other (five) pairs and repeated the same computation process that was used to define and compute features 2 to 17 (\( F_{2} \) to \( F_{17} \)). This process resulted in a second group of 16 EIS signal-related and phase-related features (\( F_{18} \) to \( F_{33} \)).

Last, we added to the feature pool the participant’s age (\( F_{34} \)) and the radiologist’s subjectively rated density BI-RADS score during the mammographic interpretations (\( F_{35} \)). Because breast density and age are well known to be correlated with risk, the rationale of adding the two non-REIS-based input variables (“features”) was to test whether or not our classifier optimization scheme is sensitive to inclusion or exclusion of these variables (“features”).

Optimization and Performance Assessment of the Machine Learning Classifier

The selection of an “optimal” feature set through the process of pruning redundant features is an important step in developing any data-driven computerized scheme designed for this purpose. In previous studies, we established a feature selection protocol using a genetic algorithm (GA) that has been tested and applied frequently to optimize different machine learning classifiers, including Bayesian belief networks (28), ANNs (29), and k-nearest neighbor algorithm-based template-matching schemes (30). In this study, we applied a similar GA-based feature selection method to reduce the feature pool and build an optimal ANN. The feed-forward ANN built in this study included three layers. The first (input) layer included \( N \) neurons that connect to \( N \) selected features, the second layer included \( M \) hidden neurons, and the third (decision) layer included one neuron that generates a likelihood score of a test case being “positive” for the endpoint of interest (or not). A publicly available GA software package (31) was modified and used with a specifically designed binary coding method and a GA fitness function (29) to select an optimal feature set and ANNs for the specific ANN performance, a limited number of training iterations (1000) and a large ratio between the momentum (0.9) and learning rate (0.01) were used. During the GA optimization step, the initial 100 chromosomes in the first generation were randomly generated by the scheme. After a specific GA chromosome was selected, a case-based leave-one-out method was used to assess the performance of the ANN-based classifier. The 140 classification scores generated by this process were input into a ROC fitting and analysis program (ROCKET 0.9 Beta Version; http://www-radiology.uchicago.edu/krl/) to compute the area under the ROC curve (\( A_{z} \) value). Thus, after each training cycle, the GA generated a performance score (\( A_{z} \)) for each chromosome. The GA chromosomes that produce higher \( A_{z} \) values have higher probabilities of being selected in generating new chromosomes using the method of crossover and mutation. The GA operation was terminated when it reached a global maximum performance level or a predetermined number of growth generations or iterations (ie, 100 in this study).

After the highest performing ANN-based classifier was determined, we recomputed the performance level when classifying the 140 cases in our data set into “positive” and “negative” groups. Using the case-based leave-one-out testing method we recorded the final ANN-generated classification scores for each test case over the entire positive and negative set of cases. The performance level (eg, area under the ROC curve) and its variability (95% confidence interval) were analyzed. We note that the classifier was optimized for an “actionable” endpoint (ie, recommendation to biopsy) rather than for cancer as an endpoint. This was done specifically for the purpose of the intended use of our proposed approach rather than as a screening tool to identify cancer cases. Under this scenario, we clearly underestimate the ability to identify cancer cases had the classifier been optimized for actual cancer as an endpoint, but the results for “biopsy recommendations” are more generalizable in this scenario because of the number of cases in the different groups. However, under this suboptimal optimization, we computed the changes in sensitivity levels for different types of cases (ie, verified cancer cases, “high-risk” cases recommended for surgical excision of the lesions, and all other biopsy
TABLE 1. Number of Occurrences by Orientation (Location) of the Mirror-matched Probe Pair (of Six Pairs) That Showed Maximum Resonance Frequency Differences Between Two Breasts

<table>
<thead>
<tr>
<th>Probe pair position on the left and right breasts (o'clock)</th>
<th>12 and 12</th>
<th>2 and 10</th>
<th>4 and 8</th>
<th>6 and 6</th>
<th>8 and 4</th>
<th>10 and 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>34</td>
<td>27</td>
<td>18</td>
<td>19</td>
<td>10</td>
<td>32</td>
</tr>
</tbody>
</table>

RESULTS

An example of the three recorded breast EIS output signal sweeps for one measurement channel (one pair of probes) is shown in Figure 2. The six sets of EIS signal magnitude sweeps between the center probe and each of the six “external” probes are shown in Figure 3 for a participant with a biopsy-confirmed cancer and in Figure 4 for a participant determined by mammography to be negative. As previously discussed by other investigators (20) and shown in our own previous studies (25, 26), these figures demonstrate that in general, “negative” cases tend to exhibit a higher level of electrical impedance symmetry between the two breasts than “positive” cases.

After using a GA for selecting an optimal feature set, we built and tested an ANN-based classifier that included 14 input features (neurons) and four hidden neurons. The 14 selected features included six from those representing differences in averaged EIS signal or phase (the first feature group), namely, \( F_6 \), \( F_{10} \), \( F_{11} \), \( F_{12} \), \( F_{13} \), and \( F_{15} \), and eight features selected from the differences of EIS signals in individual mirror-matched probe pairs (the second feature group), namely, \( F_{19} \), \( F_{20} \), \( F_{21} \), \( F_{25} \), \( F_{26} \), \( F_{28} \), \( F_{29} \), and \( F_{30} \). The distribution of these 14 selected features also shows that two features represented frequency differences (\( F_{11} \) and \( F_{19} \)), six represented EIS signal magnitude differences (\( F_6 \), \( F_{10} \), \( F_{20} \), \( F_{21} \), \( F_{25} \), and \( F_{29} \)), and six represented EIS signal phase differences (\( F_{12} \), \( F_{13} \), \( F_{15} \), \( F_{26} \), \( F_{28} \), and \( F_{30} \)). Interestingly, the two non-REIS signal-based features, age (\( F_{33} \)) and breast density (\( F_{33} \)), were not selected by the GA for inclusion in the optimized classifier, supporting the general expectation that, unlike mammography, REIS examinations are largely independent of patient age and/or breast tissue density.

The overall performance of the ANN-based classifier resulted in an area under the ROC curve (Fig 5) of \( A_c = 0.830 \) (95% confidence interval, 0.755-0.890). Table 2 shows performance levels of the ANN training and testing results as a function of the number of training iterations. Table 3 summarizes the detection results of the classifier, optimized for “biopsy” as an end point, at three predetermined specificity levels. The results are provided by biopsy outcome, type of abnormality, and density BI-RADS score. For example, the ANN classifier detected 30 “positive” (biopsy) cases, or 54% sensitivity at 90% specificity.

DISCUSSION

As the number of women who participate in breast cancer screening programs increases, so too does the demand placed on the health care system to deliver high-quality care to an ever increasing number of women through adequate access and high-quality (accurate) interpretation, at a reasonable cost. Despite the continuing controversy about the efficacy of screening, in particular as related to younger women, we believe that individualized risk-based screening will ultimately be established and accepted in this country (and other countries as well). Despite the markedly lower prevalence of breast cancer at a younger age, there is great interest in improving the early detection of breast abnormalities in younger women because of the large potential benefits. The identification of younger women who are at higher than average risk for having and/or developing breast cancer is an important and difficult task. This may even be more important in younger women who are not enrolled in annual mammographic screening (<40 years old in the United States and <50 years old in many other countries) or in women who choose for personal reasons not to participate in recommended imaging-based screening programs. Among several alternative approaches to risk stratification that do not require radiation, electrical impedance–based technology has been investigated.
Table 3. Detection Performance of the Classifier by Drop-Out.

<table>
<thead>
<tr>
<th>Setting</th>
<th>4B-FRADS</th>
<th>3B-FRADS</th>
<th>2B-FRADS</th>
<th>0B-FRADS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Train</td>
<td>0.70 ± 0.02</td>
<td>0.61 ± 0.02</td>
<td>0.55 ± 0.02</td>
<td>0.52 ± 0.02</td>
</tr>
<tr>
<td>Test</td>
<td>0.69 ± 0.04</td>
<td>0.57 ± 0.04</td>
<td>0.52 ± 0.04</td>
<td>0.49 ± 0.04</td>
</tr>
</tbody>
</table>

Table 2. ANI Overall Classification Performance Lasso by Drop-Out.

<table>
<thead>
<tr>
<th>Setting</th>
<th>4B-FRADS</th>
<th>3B-FRADS</th>
<th>2B-FRADS</th>
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<tbody>
<tr>
<td>Train</td>
<td>0.70 ± 0.02</td>
<td>0.61 ± 0.02</td>
<td>0.55 ± 0.02</td>
<td>0.52 ± 0.02</td>
</tr>
<tr>
<td>Test</td>
<td>0.69 ± 0.04</td>
<td>0.57 ± 0.04</td>
<td>0.52 ± 0.04</td>
<td>0.49 ± 0.04</td>
</tr>
</tbody>
</table>
(67%) marked by radiologists as located posteriorly near the chest wall were correctly detected at 90% specificity. Although interesting, we caution against the generalization of these results because of the limited data in different categories after subsetting.

The REIS-based approach does not require radiation exposure. At the same time, it is not an imaging-based device. Identifying either the types or the locations of any breast abnormalities has not been attempted to date. Despite the limitations of this preliminary study, in particular in terms of sample size, our results suggest that REIS-based technology could potentially be used as a prescreening tool aimed at identifying a case-based risk for having or developing breast cancer. The ultimate goal of the approach that we are exploring is to provide a fast, low-cost, easy-to-use, and non-radiation-based prescreening tool that can be incorporated into physicians' practices for periodic examinations of women who do not participate in annual mammography-based screening or those who are at a younger age (between 35 years old and the commencement of periodic mammography screening). In this respect, REIS can be seen as an adjunct or an alternative examination to the clinical breast examination. Any cancer identified under this scenario would not have been found until later and possibly at a greater stage during an eventual detection.

We note that REIS-based examinations are not intended in any way to compete with imaging-based screening mammography, and they are not intended for screening women with known high-risk factors. As related to imaging-based screening, the REIS exam should be considered a “rule-in” approach; namely, given a positive REIS result, the physician should consider recommending an imaging-based follow-up examination, rather than using it as a “rule-out” approach (i.e., women should not use negative REIS results as an excuse to avoid imaging-based screening).

At this stage, our data set is limited, but we included both a relatively large set of “positive” cases (in this case, women who after imaging-based diagnostic workup had findings that were suspicious enough to warrant biopsy) and negative cases. The ratio of approximately 2:1 between negative and positive cases is higher than many preliminary optimizations of machine learning classifiers. Also, the testing procedures we implemented that included “recalled” but later determined to be “negative” cases address at least in part the problem of generalization in terms of covering the “domain” from which the negative cases were selected. We note that in recruiting women to participate in this study, we did focus on recruiting prebiopsy (“positive” for the purpose of this study) cases. This is a necessary, commonly implemented, and generally accepted strategy in the medical imaging field for the purpose of developing and optimizing classifiers.

Despite the encouraging results showing that asymmetry in impedance signal measurements between the bilateral breasts may provide valuable discriminatory information regarding the presence of highly suspicious imaging-based findings resulting in a recommendation for biopsy, we must emphasize that this is a preliminary study that suffers from a number of limitations. First, this study included a limited number of REIS examinations representing only a small subset of the examinations we plan to acquire in our ongoing prospective clinical data collection effort. Second, a direct comparison with results from other EIS-based studies is not possible, because the participant pool is different, and in this study, we optimized the classifier for a surrogate endpoint, rather than cancer (15–22). Third, all abnormalities included in this study had been originally detected on imaging-based procedures, potentially biasing the results. We do not have data on performance when the REIS approach and classification scheme is applied to occult abnormalities during imaging. Last, whether the clinical use of this REIS approach would eventually result in a significant increase in unnecessary interventions due to false-positive findings was not investigated in this preliminary study. Therefore, much work is needed in this area before we can conclude whether this approach should be prospectively tested for possible wide clinical use.

ACKNOWLEDGMENT

We thank the Magee-Womens Research Institute & Foundation, Glimmer of Hope Fund, for supporting this effort.

REFERENCES