Award Number: W81XWH-11-1-0545

TITLE: Building a Better Model: A Comprehensive Breast Cancer Risk Model Incorporating Breast Density To Stratify Risk and Apply Resources.

PRINCIPAL INVESTIGATOR: Jennifer Harvey

CONTRACTING ORGANIZATION: The Rector and Visitors of the University of Virginia
Charlottesville, VA 22903

REPORT DATE: October 2014

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
Oct 2014	Annual	25 Sep 2013 - 24 Sep 2014

4. TITLE AND SUBTITLE

Building a Better Model: A Comprehensive Breast Cancer Risk Model Incorporating Breast Density To Stratify Risk and Apply Resources.

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-11-1-0545

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Jennifer Harvey, W Cohn, M Yaffe

E-Mail: jah7w@virginia.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
The Rector and Visitors of the University of Virginia, PO Box 400195, Charlottesville, VA 22904-4195. (Department of Radiology & Medical Imaging, PO Box 800170, Charlottesville, VA 22908-0170; Department of Public Health Sciences, PO Box 800717, Charlottesville, VA 22908-0717).
Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Toronto, Ontario, Canada M4N 3M5

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Purpose: Development and validation of a personalized breast cancer risk assessment model that includes automated measurement of breast density.
Scope: Assemble a cohort of women with known breast cancer risk factors and digital mammogram files for women diagnosed with breast cancer using existing data sources and match them to controls (Harvey/Knaus). Validate and refine automated breast density software (Yaffe/Harvey). Build and validate the initial comprehensive model (Knaus/Yaffe/Harvey).
Major Findings: During this second year, we have recruited over 3200 women (622 cases). Breast density measurement has been evaluated for accuracy using a second test set showing very good correlation with 2D methods, for precision using repeated measures with excellent correlation, and variation between vendors. A survey instrument was developed, vetted using focus groups, and administered (nearing completion) to evaluate screening knowledge, practices, and willingness to change practice.

15. SUBJECT TERMS
Breast cancer; risk model; mammography; breast density

16. SECURITY CLASSIFICATION OF:	17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
			USAMRMC

a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPHONE NUMBER *(include area code)*
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BC100474: Building a Better Model: A Personalized Breast Cancer Risk Model Incorporating Breast Density to Stratify Risk and Improve Application of Resources

INTRODUCTION:

This project is aimed at meeting informational needs by moving the nation from guidelines based on population averages to recommendations based on an individual's risk beginning with personalized mammography screening decisions. This will be done by increasing the ability to predict a women's risk of developing breast cancer by adding a strong risk factor—breast density—to current risk-assessment equations or algorithms. Our plan is, over three years, to build and initially validate a comprehensive breast cancer risk model. The overall work will require the recruitment of 1000 cases (breast cancer patients) and 3000 controls (non-breast cancer patients) from whom we will collect extensive risk factor information and breast density based on digital mammograms previously obtained at UVa. Breast cancer risk information is largely already available for cases though patients will be requested to validate and complete data. The recruitment of 3000 control patients will require engagement with the community through appropriate messaging and marketing. The measurement of breast density using automated methods will be optimized during this study through the evaluation of outlier correction, comparison of several different software methods, precision measurement, and evaluation of variation by mammography machine vendor. Once the model is complete, tested nationally, and proven accurate, it will be available for widespread use within five to six years.

BODY:

Research accomplishments are listed by Task.

Task 1: Develop procedures for team communication and coordination (month 1)

Completed. A listserve was developed for the group early on. Bi-weekly conference calls are held on Tuesdays at noon. An agenda precedes the call by at least one day. Quarterly Team meetings have been held at UVa (12 Dec 2011, 16 March 2012, 05 June 2011, 4 Dec 2012, 8 March 2013, 17 June2013, 9 Dec 2013, 24 March 2014, 12 June 2014). Bi-annual team meetings have been held, alternating at UVa (09Sept 2011, 24 Sep 2012, 23 Sep 2013, 12 May 2014) and Toronto (20 April 2012, 03 May 2012, 16 Sept 2014). All PIs, advocates, and key personnel attended these meetings.

Task 2: Submit protocol to Institutional Review Board/Human Investigation Committee (months 1-3)

Completed. Study protocol, consent, and recruitment materials were drafted, submitted to UVa IRB and to DoD for review. All have been approved. The UVa IRB reviews all open protocols and consent forms annually; once approval has been received locally, the updated documents will be sent to DoD for their review and approval. All annual reviews have been completed.

Task 3: Establish secure database (months 1-2)
Completed. A secure database has been established behind a secure firewall. The database is HIPAA compliant. Data fields and dictionary were defined. Minor changes were made to clarify choices. Data linkages have been validated. Data has been successfully extracted with a small number of unanswered items. These primarily relate to details about breast cancer diagnosis (histologic type, grade, etc.). These data are being entered using our Breast Cancer Database and Clinical Data Repository in an ongoing fashion.

Task 4: Perform outlier correction for 3D Cumulus (CumulusV) (months 2-6)
Completed. The first round of outlier correction was completed during Year 1. Cumulus V was used to analyze a set of 260 mammograms for volumetric density, and those results were compared with estimations of area density made by Dr. Harvey using our two-dimensional Cumulus 2D area method. During a work visit to Toronto from October 29 to November 3, 2011 Dr. Harvey evaluated any discordant readings using color maps to visually correlate the density map with the mammographic image. In January 2012, Olivier Alonzo-Proulx performed the calibration of the seven mammography units of UVA, including three units at the Breast Care Center, three units at the Northridge site including the mobile clinic and one system at Orange Medical Center. Both the detectors and the thickness readout mechanisms were characterized on each of the units in order to make retrospective and prospective volumetric breast density measurements.

Further modifications were made to the density algorithm and the images were reevaluated. The new data were reviewed during Dr. Harvey's visit to Toronto (16 Apr to 20 Apr 2012). Some results are shown in Figure 1 and demonstrate an improved correlation between the gold standard Cumulus 2D and CumulusV. Correlations were also made using Volpara, a commercially available volumetric density measurement tool. Some results are shown in Figure 2 where the correlation between the two algorithms is seen to be quite high. The Volpara measurement systematically indicates lower volume, since it excludes the contribution of skin.

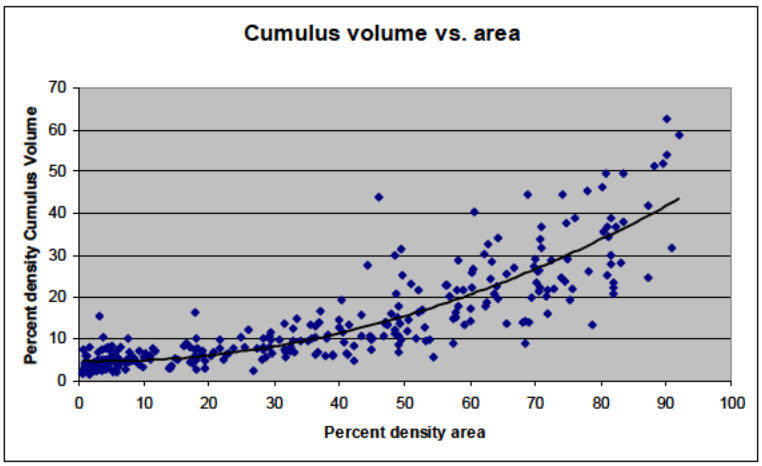


Figure 1: Cumulus 2D area (measured by Dr. Harvey) density vs. Cumulus V volume. The quadratic correlation is R= 0.87.

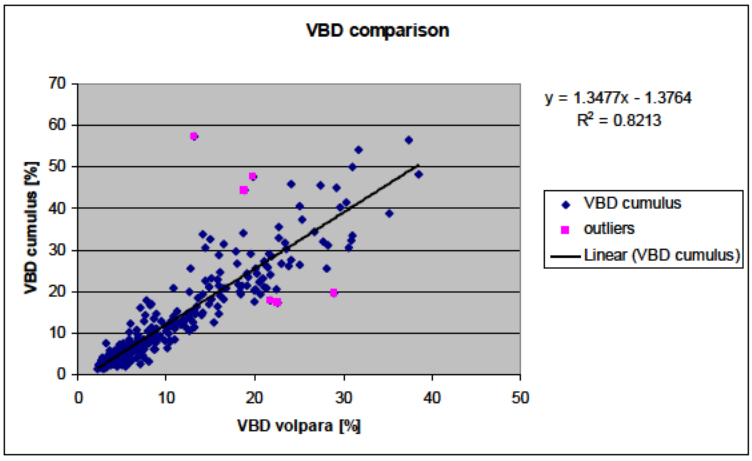
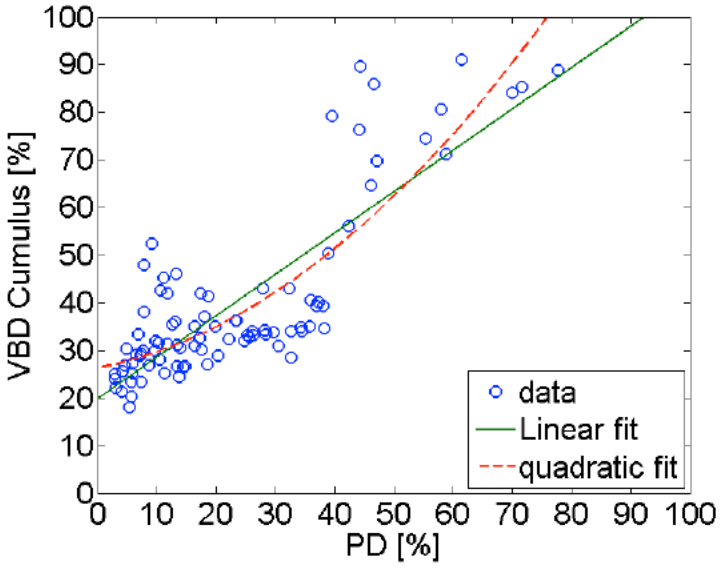


Figure 2: Cumulus volume vs. Volpara volume

A limitation of the above dataset is the fact that the mammograms were acquired over a long period of time, during which the machines may have been serviced or altered. Several detectors have been replaced since those images were obtained and this may have resulted in the calibration not representing the actual state of the imaging system at the time that the mammograms were acquired.

Second dataset. To test CumulusV using more recent mammograms, a new dataset was collected and retesting was completed during Year 2. The new dataset included 100 images from a GE unit and 100 images from a Hologic unit. These were reviewed during Dr. Harvey's visit to Toronto October 2012. The three volumetric methods (CumulusV, Volpara, Quantra) were compared to the gold standard area based method, Cumulus 2D (Figures 3-5). Volpara had the best correlation.



R = 0.8279

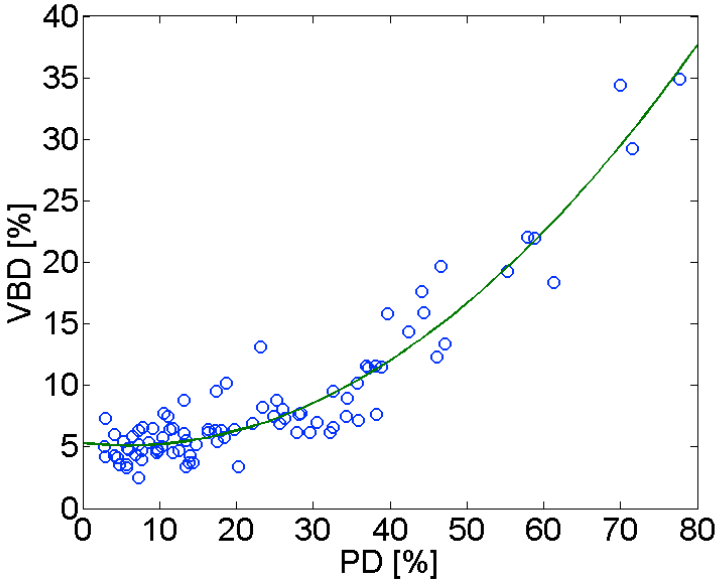
Linear fit:

$y = 0.868x + 19.9\ \%$

Quadratic fit:

$y = 0.0096x^2 + 0.2410x + 26.3\ \%$

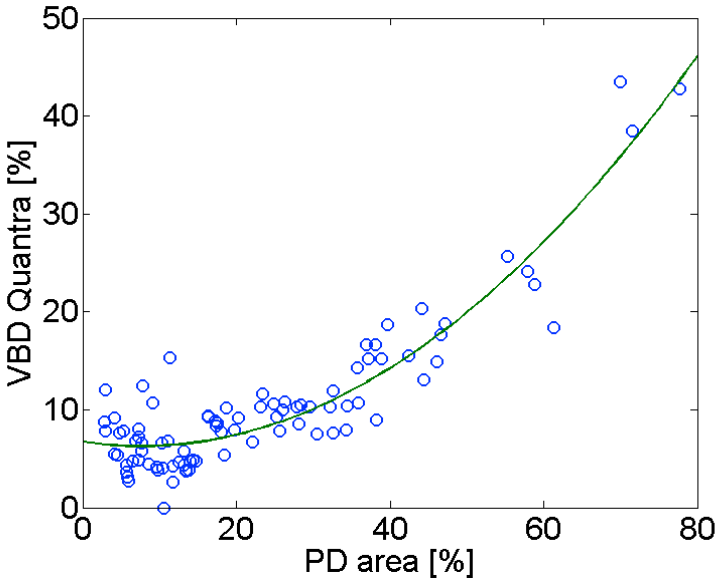
Figure 3. CumulusV density measures compared with Cumulus 2D (area) method. There is not a marked difference between the new dataset and the prior.



R= 0.884

$y = 0.0059x^2 - 0.0688x + 5.3$ %

Figure 4. Volpara density measurements compared with Cumulus 2D (area). This method has strongest correlation with the area based method with an R value of 0.884.



R= 0.854

$y = 0.0077x^2 - 0.122x + 6.9$ %

Figure 5. Quantra density measurement compared with Cumulus 2D (area). This method had good correlation with the area based measurement.

Tiled Images. The issue of how to address women with large breasts who have multiple images in the same projection (view) to cover the area of the breast was evaluated. We performed a retrospective study to evaluate this topic. The data was presented at the International Workshop for Mammography (IWDM) in Gifu, Japan, in July 2014. The paper was published in the conference proceedings. There is the abstract:

> **Abstract.** Tiled images are sometimes obtained for women with large breasts, which is a limitation of receptor size. In this retrospective HIPAA compliant study, automated breast density measurements for tiled images are compared with full MLO and CC views. Women with tiled views between July and December 2007 followed by full views within 15 months were included. Volumetric breast density (VBD) for tiled MLO views had very good correlation with full views ($r = 0.88$), while correlation between tiled and full CC views was poor ($r = 0.31$). VBD for all women requiring tiled CC views was low (<10%). In conclusion, VBD measured from a tiled MLO view is a reasonable substitute for a full MLO measure. Attributable risk of breast density for women requiring tiled CC views may be sufficiently low compared other factors such as high body mass index

Task 5: Populate and validate database with existing data (months 3-6) HARVEY
Completed.
5a. Link existing radiology data sets with Clinical Data Repository (month 3-4). Our current breast cancer database is Microsoft Access format. The entries, while clear to us, are variable in style. For example, the term half-sister may have been entered as "half-sister," "half sister," or "1/2 sister." These variables reduce the accuracy of prepopulation of our database very challenging and with many errors. Because of this, we will use the database to obtain information about our case patients prior to their arrival to clinic that can be used to help patients complete the form. In addition, information that is missing or answered "I don't know" will be completed using the existing database (many patients do not know specific details about their breast cancer).
5b. Identify missing data that can be obtained via chart review (month 3-4). This will be an ongoing process as cancer case patients complete their survey. For case patients that are no longer in the area or have passed away, we populated the information using both the MS Access database and chart review.
5c. Conduct chart review for selected cases (month 4-6). Comparison of information from the Breast Cancer Database and medical records showed good consistency (for example, details of treatment for cancer cases were the same between sources). Both sources have been used to help fill in missing data.

Task 6: Case ascertainment (month 6) KNAUS
6a. Apply inclusion/exclusion criteria to populated database (month 6).
6b. Date of diagnosis and age identification for matching with controls (month 6).
6c. Identify specific missing data fields that can be obtained by interview (month 6).

Completed. Case ascertainment was performed using a combination of our Clinical Data

Repository and our MS Access Database. Over 2000 eligible cases were identified.

Task 7: Control ascertainment (month 7) KNAUS
7a. Apply inclusion/exclusion criteria to potential controls (month 7)
7b. Match to cases within five years of diagnosis of breast cancer (month 7).
7c. Identify up to 15 potential controls for each case (month 7

Completed. Over 28,000 potential control patients have been identified. The cases and potential controls were contained in a MS Excel spreadsheet so that when a patients presented to the clinic, the research staff could easily see if she qualified for the study.

Task 8: Develop Automated 2D Cumulus program (months 7-12) YAFFE
8a. Create a volumetric composition map using 3D Cumulus on Dr. Harvey's previously validated 340 mammogram dataset (months 7-9)
8b. Perform quasi-2D density analysis on dataset maps (month 10).
8c. Optimize algorithm during Dr. Harvey's visit to Toronto (month 11)

Completed. The current 2D method of Cumulus has a well validated association with breast cancer risk. However this method is labor intensive and used only in research. Because 2D methods of measuring breast density are not dependent upon having accurate measurements of breast thickness, an automated 2D Cumulus measurement may prove more reliable than 3D methods. Dr. Yaffe's group has developed an automated 2D method. Figure 7 shows the automated 2D (area) results on the same dataset presented in Task 4 (figures 1 and 2). The same limitation, the age of the mammograms, applies here. The correlation between the automatic area and the cumulus area is similar to that seen in Figure 1. However, the relation between the area measurements is linear, compared to the quadratic relation between Cumulus volume and Cumulus area. The value of R = .88 is actually better than is found in tests of inter-observer variability with well trained readers.

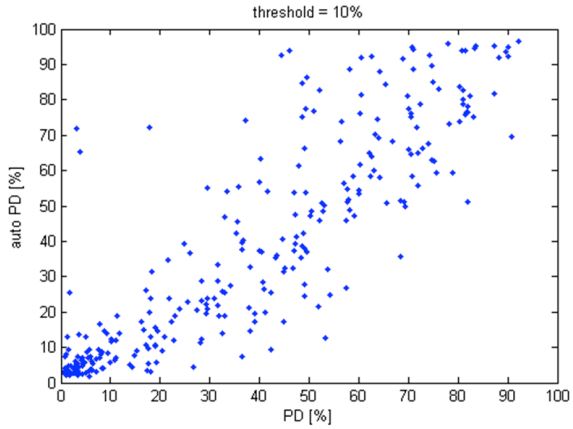


Figure 7: comparison between the PD (percent density using Cumulus area) and the automatic PD. The correlation is R=0.88 and the linear least square fit between the two PD measurements is y=0.97x+2.2%,

Task 9: Evaluate precision of 3D Cumulus method (months 7-12) HARVEY
9a. Develop IRB protocol and obtain approval (months 7-8)

Completed. Precision reflects the consistency of a repeated measurement. It does not necessarily reflect the accuracy or validity of the measurement. Precision is important however to the model since changes in breast density will translate to changes in breast cancer risk. Therefore, noise in measurement should be minimal.

Thirty women were recruited under this protocol, which was approved by the UVa IRB and the CDMRP. All women presented for screening mammography. Each patient underwent the standard of practice 4-view mammogram. Following this, a different technologist obtained a second craniocaudal image of the left breast. Density analysis of these 30 paired images was performed to assess the precision, or accuracy of a repeated measure. The paired images were analyzed using Cumulus 2D manually performed by Dr. Harvey and three automated volumetric methods using CumulusV, Volpara, and Quantra. The precision was excellent for all methods but best results were obtained using Volpara.

The manuscript was prepared, submitted, and accepted for publication by the journal *Radiology*. The abstract is below.

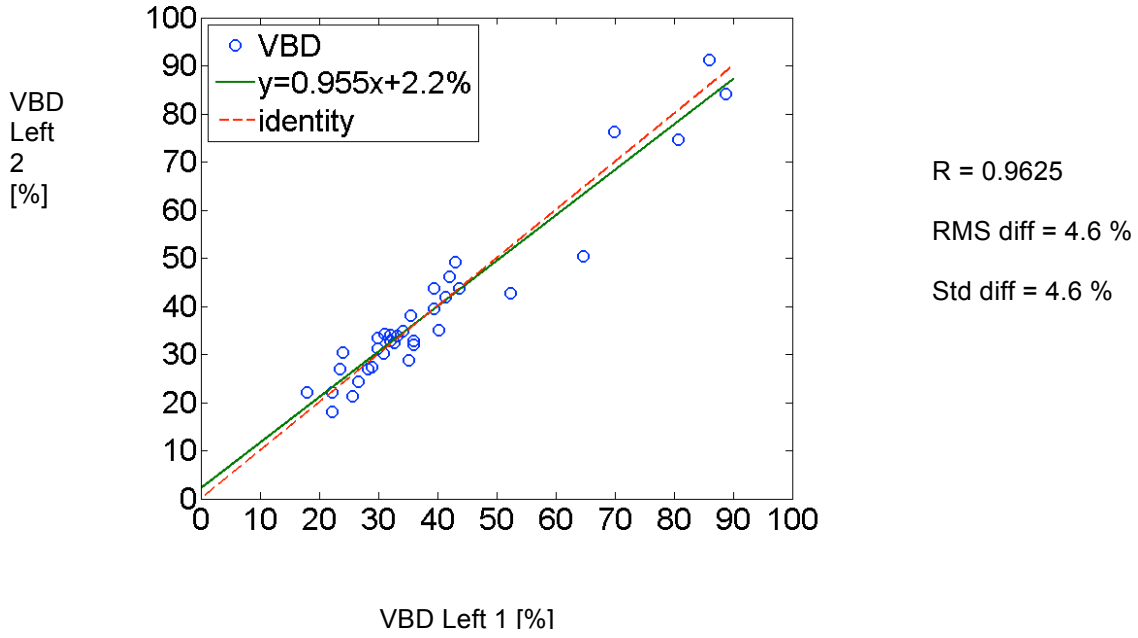
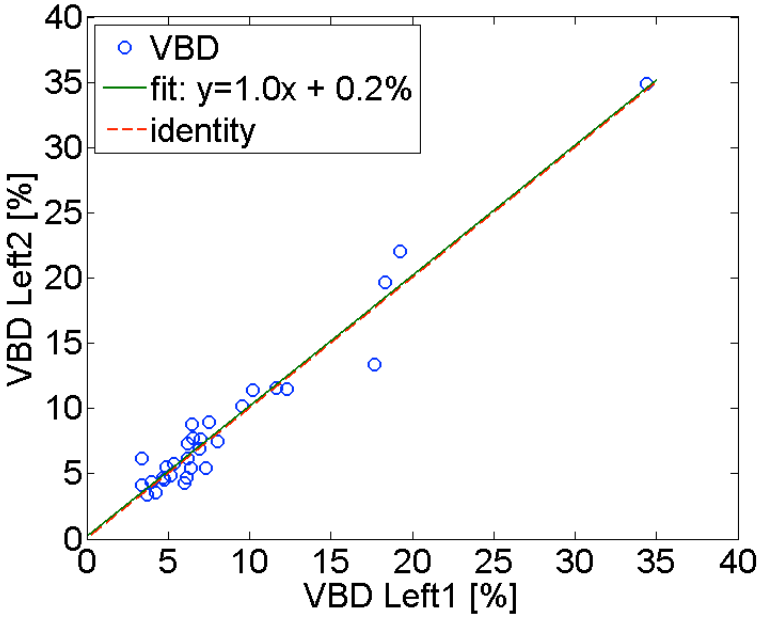


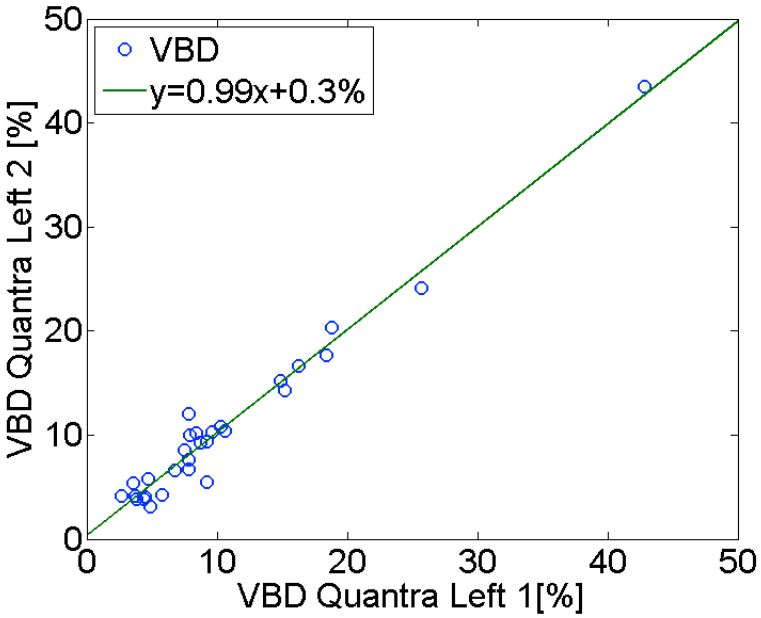
Figure 8. Precision of CumulusV. Excellent precision is present using this method with an R value of 0.96.



R = 0.976

RMS diff. = 1.4 %

Figure 9. Precision using Volpara density measurement. Precision is similarly very high with an R value of 0.976.



R = 0.984

Std diff = 1.48 %

Figure 10. Precision using Quantra density measurement. Also excellent precision with R value of 0.984.

Background: Automated measures of breast density must have low variability to be useful in a breast cancer risk model. A small change in density could imply considerable differences in risk.

Methods: Thirty women undergoing screening mammography were recruited to undergo a repeated left craniocaudal view by a second technologist in this prospective, IRB-approved, HIPAA compliant study. Breast density was measured using an area method (Cumulus ABD) and three automated volumetric methods (CumulusV, Volpara, Quantra). Discrepancy was obtained for each algorithm by subtracting the second from the first measurement (Δ_{1-2}).
Results: Variability was higher for Cumulus ABD and CumulusV compared with Volpara or Quantra. The *within-breast* density measurement standard deviations were 3.32% (95% CI 2.65, 4.44%), 3.59% (95% CI 2.86, 4.48%), 0.99% (95% CI 0.79, 1.33%) and 1.04% (95% CI 0.82, 1.39%) for Cumulus ABD, CumulusV, Volpara, and Quantra, respectively. Although, the mean discrepancy between the repeat breast density measurements was not statistically different from zero for any of the four algorithms, larger absolute breast density discrepancy (Δ_{1-2}) values were associated with larger breast density values for Cumulus ABD and CumulusV, but not for Volpara and Quantra.
Conclusion. The variability in a repeated measurement of breast density is lowest for Volpara and Quantra; these algorithms may be more suited to incorporation into a risk model.

Task 10: Case enrollment (months 7-24) KNAUS
Task 11: Control enrollment (months 8-24) HARVEY

Completed. After building the dataset, iPads were programmed for survey data acquisition by the patient. This has been a very efficient, secure system to administer the survey. The data is uploaded to the secure server immediately, and the data is removed from the iPad after completion. A token system has been set up for patient anonymity. Patients can also access the survey from home using their token.

Study recruitment was completed on December 31, 2013. A total of 825 cases and 2598 control patients were enrolled for a total of 3423. The characteristics of the case and control population are relatively similar (Table 1).

Table 1. Characteristics of the Study Population

Variable	Cases – Survivors	Controls
Age	62.6 years (SD = 11.5)	61.2 years (SD = 9.7)
Race	83.6% White; 15.2% Black	88.2% White; 11.1% Black
Height	64.2 inches (SD = 2.7)	64.2 inches (SD = 2.9)
Weight	170.1 pounds (SD = 41.1)	160.2 pounds (SD = 36.9)
Educational level	25.7% graduate degree; 18.9% college degree; 25.3% some college; 19.1% high school	29.0% graduate degree; 25.1% college degree; 20.2% some college; 14.9% high school

All study images were collected and density analyzed using CumulusV, Quantra, and

Volpara.

As part of the study, we also requested an optional donation of a blood sample from patients. The blood sample process was set up after recruitment was underway. We obtained 1297 blood samples (166 cases, 1091 controls). These banked samples are stored in a minus 80 degree Celsius freezer purchased through another grant. These may be helpful if serum hormone levels are needed to further refine the model.

Task 12: Establish accuracy of 3D Cumulus using different machines (months 13-18) YAFFE

Completed. In order to determine whether the density measurements of mammograms performed on machines from different vendors have significantly different results, and if a "machine type" variable is necessary in the model to control for the variability, a study was performed.

The new dataset used in Task 4 was also used for this task. All women in this dataset had both GE and Hologic mammograms within 15 months. There were 65 patients that qualified for this study.

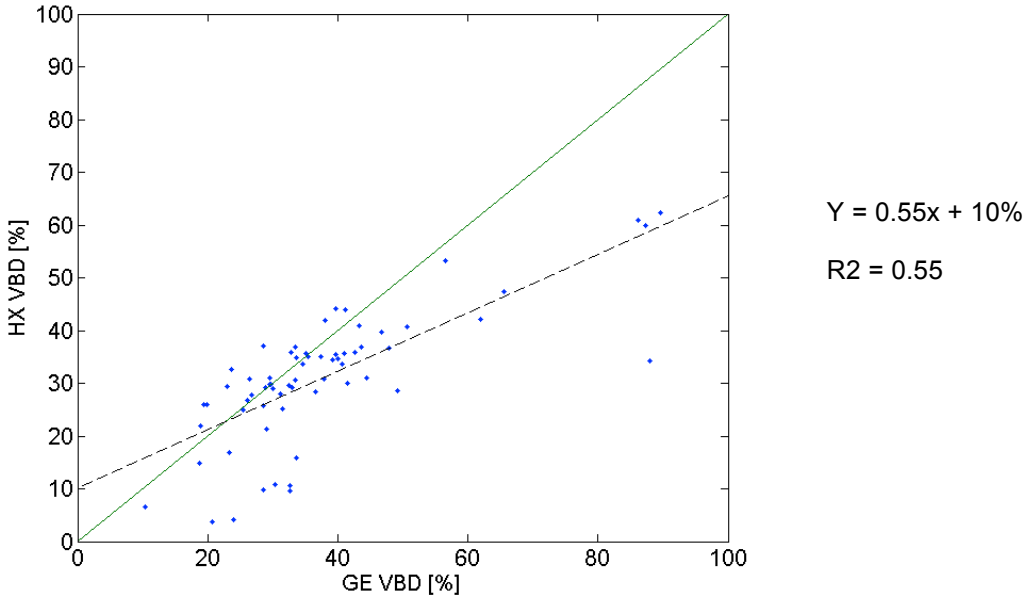


Figure 11. Volumetric breast density (VBD) using CumulusV of mammograms obtained using GE and Hologic machines on the same patient within 15 months. There is moderate correlation. Density measures using images from Hologic machines are uniformly lower than GE.

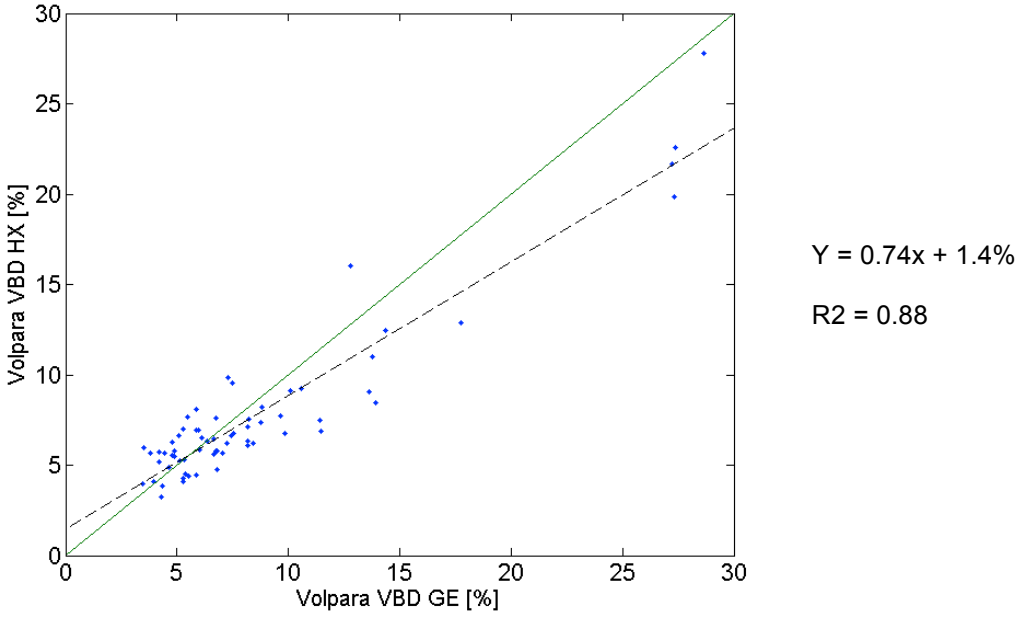


Figure 12. Volumetric breast density (VBD) using Volpara of mammograms obtained using GE and Hologic machines on the same patient within 15 months. There is improved correlation compared with CumlusV. Volpara is less dependent on accurate breast thickness readouts provided by the manufacturers.

Task 13: Finalize database for analysis (months 24-25) KNAUS
Completed in March 2014.

Task 14: Community engagement and publicity campaign (months 1-24) HARVEY
Completed
During the first few months of the study, we conducted two focus groups, which were very helpful. The project title is: The UVa Mammography Project: Shaping the Future of Breast Cancer Screening. Our advocates were invaluable in this process.

We created a project website (http://www.healthsystem.virginia.edu/pub/ct/ct15885, live date July 2012). We are not using Twitter. However, Vernal Branch, one of our advocates, has posted tweets about the project through the Virginia Breast Cancer Foundation.

The UVa Breast Program Facebook page has increased to 1712 "likes" and we have made 109 posts during the last year. At least 10 of these posts were specific to study questions- breast density awareness, risk factors for breast cancer, etc.

A rack card and letter to potential case/control patients was developed to aid recruitment. We are very grateful to our advocates and focus groups for their hard work on these items.

Representatives from the project were present to provide information at the Charlottesville Four Miler Training Program and for the Charlottesville Four Miler Race.

Task 15: Conduct focus groups (months 12-20) HARVEY

Completed

The Staff of the Center for Survey Research (CSR) conducted ***two initial focus groups*** in ***January 2012***. The results were very enlightening. The purpose was :

1. To understand what participants know about breast cancer screening and risk
2. To explore participants' reactions to information about breast density as a risk factor
3. To discuss the Harvey study and motivations for recruiting participants in the study
4. To discuss names for the study

The two focus groups were women without a personal history of breast cancer and women who were breast cancer survivors. The Non-Cancer Group met on January 17, 2012. Eleven participants were recruited who are patients of Dr. Harvey at the Northridge Office or referrals from the UVa Medical staff. The Survivors Group met on January 24, 2012. Nine participants were recruited who are members of a cancer support group coordinated by Diana Cole, at the Emily Couric Clinical Cancer Center, or referrals from Breast Surgery.

Agenda for the Focus Groups:

1. Discussed screening and how participants make decisions about screening
2. Kathy Repich presented Dr. Harvey's slides on risk factors and the existing models for measuring risk
3. Discussed participants' reactions to the presentation and their knowledge of the risk factors
4. Discussed recruitment for the study and what would motivate people to participate in the study
5. Presented ideas for naming the project and gave participants an opportunity to rate them and share others

The non-cancer focus group cited the following as motivating factors for participation in the study: convenience, legitimacy, importance, size of the study, self-education, learn about risk factor models, and altruism ("To help my daughter"). Cancer survivors cited the following as additional motivating factors for participation: to reduce false positives for others, altruism ("I had treatment options because of other trial participants") and "the idea that someday, there may be customized recommendations."

The results of the focus groups lead us to these considerations for messaging on recruitment materials: highlight convenience of participation, address patient privacy, highlight size / scope / potential impact of the study, assess effectiveness of giveaways as recruitment tool – non-cancer group not in favor public display of study participation, and altruism ("Your participation could impact future generations."). We subsequently decided not to give away study logo items (t-shirts, tote bags), but to thank participants

with a thank you note highlighting their altruism. The note also includes a $5 gas card as a token of appreciation.

Two additional focus groups were held in ***January and February 2013***. The purpose was to vet the telephone survey instrument. The additional review was very helpful to address phrasing and to clarify end points.

Task 16. Conduct message testing telephone survey (months 12-20). Harvey

Completed. The telephone survey was developed with the UVa Center for Survey Research based on women's responses to the second set of focus groups. Our advocates were very helpful in the development and review of the survey.

The goals of the survey were:

- Assess Virginia women's current knowledge about cancer screening recommendations and breast density
- Evaluate willingness of women to change their breast cancer screening practices based on new recommendations
- Identify characteristics of women who are willing and unwilling to change their screening practices
- Inform design of future educational campaigns to promote new tailored recommendations

The survey used a triple frame scientific random sample that include listed landline phone numbers (random from phone directory), landline RDD-Random Digit Dialing (includes unlisted phone numbers), and cell phone numbers (RDD from cell phone exchanges at Virginia billing centers).

The survey topics include:

- Demographics
- Personal history
- Current breast cancer screening practices
- Risk perception
- Understanding of breast density
- Understanding of current guidelines
- Willingness to change screening practices
- Information sources

The results have been analyzed. The following abstract was presented at the American Association for Public Health:

What do women know about breast density?

RESULTS FROM A POPULATION SURVEY OF VIRGINIA WOMEN

Breast density reduces the sensitivity of mammography and is a moderate independent breast cancer risk factor. Virginia is one of fourteen states that

currently require providers to notify patients when they have dense breasts. However, little is known about what women in the general population know and understand about breast density. This survey study assessed knowledge about breast density, its impact on mammography and its relationship to breast cancer risk. A random sample of 1,024 Virginia women between age 35-70 years and without breast cancer, reached by landline and cell phone, completed a 24-minute interview. Thirty-six percent of respondents had been informed about their breast density by a doctor. Few respondents (5.3%) were able to answer all three breast density knowledge questions correctly. Women with a higher perceived risk of breast cancer, familiarity with its risk factors, or familiarity with current recommendations for screening were more likely to have accurate breast density knowledge; those in rural regions were less likely. Seventy-five percent of respondents reported being either somewhat or very familiar with risk factors for breast cancer, but less than 1% proved able to list breast density as a risk factor. These results suggest that while women are becoming aware of the term "breast density", they may not understand its relationship to cancer detection by mammography and, especially, its relation to breast cancer risk. Improved public health education about breast density is necessary to augment new legislation to help women evaluate and manage their breast cancer risk.

The following abstract regarding women's willingness to change screening behaviors has been developed but not yet presented (submitted to American Society of Preventive Oncology):

Are Women willing to change Breast cancer screening guidelines?

Purpose: In 2009, the US Preventative Task Force released new guidelines for screening mammography that sparked both public and professional controversy. While the guidelines are evidence based, they are not personalized to a woman's individual risk factors. This interview study was designed to evaluate the willingness of women to change their breast cancer screening practices based on new personalized recommendations.
Materials and Methods: A random sample of 1,024 Virginia women between age 35-70 years and without breast cancer, reached by landline and cell phone, completed a 24-minute interview.
Results: Just over half (54.6%) of women are definitely or probably willing to reduce their frequency of breast cancer screening compared to 81.9% who are definitely or probably willing to increase screening. The most cited disadvantage for reduced screening was delayed detection of breast cancer (77%) while the most cited advantage for increased screening is earlier detection (82%). Women are willing to change their type of screening (92.3%). Women who were more likely to be willing to reduce screening are those with a lower perceived risk of breast cancer, less familiarity with risk factors and recommendations. When asked what they needed to know to make a change, women cited advice of a doctor (52.1%), research/evidence (38.9%) and comparison with old

recommendations (22.5%) most frequently. Advice of a radiologist was only stated by 2.3% of the women.
Conclusion: These results suggest that most women will be willing to change their breast cancer screening frequency especially if recommended by their primary care physician. Women do not view their radiologist as having a primary role in delivering screening recommendations; this underscores the need to educate primary healthcare providers regarding breast screening recommendations.

Task 17. Model Development (Months 24-36) KNAUS
a. Initial Model Development.

The database was closed in May, 2014, following completion and cleaning of data. Analysis has been performed.

Controls were matched to cases in a 2:1 ratio based on age group, race, and education, using the GREEDY algorithm. Case-control selections were made using the weighted sum of the absolute differences between the case and control matching factors. Conditional logistic regression using the partial likelihood function from Cox proportional hazard's regression was used to fit risk prediction equations to the matched case-control study dataset, with stratification for each case matched set.
A full model was estimated including all available covariates for use as a model performance reference standard. Reduced Models were then estimated including covariates in the full model that had a Wald Chi-Square/degrees of freedom ratio > 1.0 (A) and then again including covariates with p value < 0.10 (B) . A Minimal Model was then estimated including covariates from Model B with Wald/Chi-square/DF >5.0). The performance of the full, reduced, and minimal models was measured using the C index and the maximum R-Square statistic.

Multivariable analysis was conducted using 860 cases and 1,683 controls with 1 or more breast studies reported for the surveyed population. The matching process yielded balanced matching factor values between cases and controls, with no significant differences in age group ($p = 0.95$), race ($p = 0.13$), or education ($p = 0.86$).

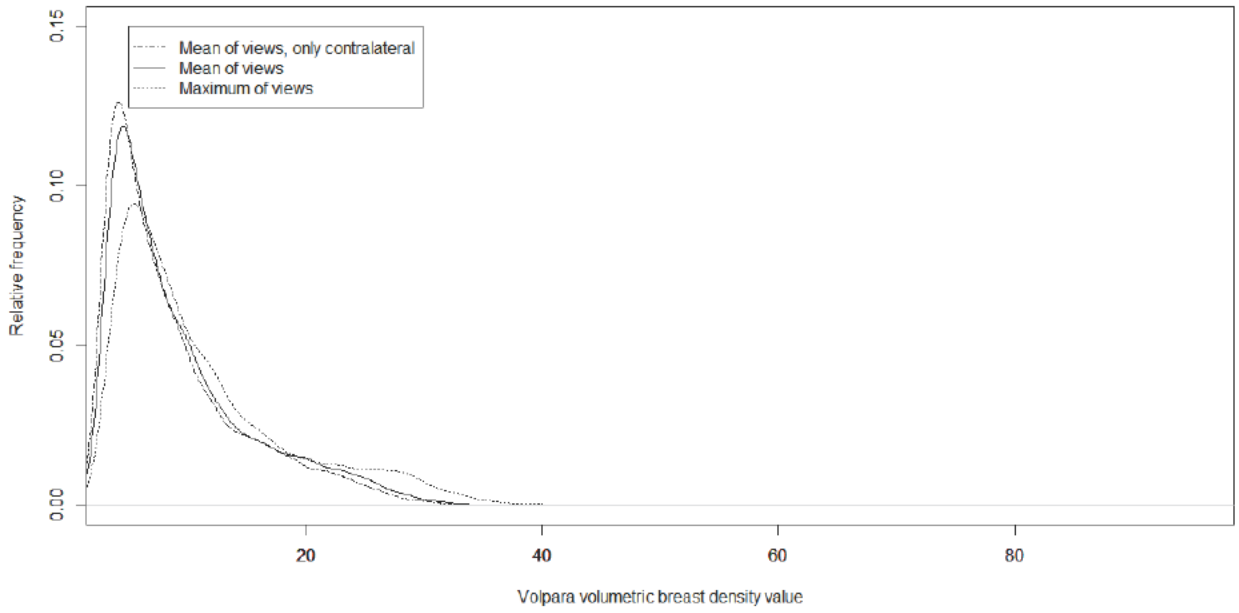


Figure 13. Distribution of Volpara densities.

The results of the preliminary model were presented at the San Antonio Breast Cancer Symposium in December, 2014.

Table 2. Model Development Results

Model Development Results			
Model	Number of Covariates	Maximum Adjusted R^2	C Statistic
Full Model (All available covariates)	62	0.62	0.86

Reduced Model A: (Full Model with Wald Chi-Square/DF > 1.0)	34	0.59	0.85
Reduced Model B: (Reduced A with Wald Chi-Square p value < 0.10)	21	0.56	0.84
Minimal Model: (Reduced Model B covariates with Wald Chi-Square/DF > 5.0)	13	0.54	0.82

The addition of volumetric breast density improved breast cancer risk discrimination. Our model uses an automated measurement of breast density used as a continuous variable that proved to be one of the top five predictors of breast cancer risk in our population. Discrimination is key in model development if screening recommendations are to be individualized. Even the minimal model that includes only 13 covariates demonstrates improved discrimination (0.82) compared with the Tyrer-Cuzick (IBIS) model (0.74).

b. Evaluate normal temporal changes of breast density.
In progress. Our priority is to publish results of the relationship of volumetric breast density to risk and of the breast cancer risk model.

c. Evaluate best breast density measurement associated with breast cancer risk.
The above analysis in A was performed using Volpara. The C-statistic for CumulusV was not statistically significant, while the results for Quantra were significant but not as strong.

d. Develop plan for external validation of the model.
We have identified several sites as candidates for validation. However, the cost to conduct these studies will be quite high. We are currently exploring the option of data-splitting (using 2/3 of data to build model, then use 1/3 to validate). This would allow us to publish the results as a useable model and let others perform secondary validation.

KEY RESEARCH ACCOMPLISHMENTS:

- Obtained IRB and CDMRP approval for study
- Established a secure database
- Established data elements for survey and set up iPads as survey instruments
- Identified over 2,000 potential cases and over 28,000 controls

- Completed study enrollment. Final recruitment included 3423 women have been recruited and have completed the survey (825 cases and 2598 controls). Of all study patients, 1297 submitted blood samples (optional) (166 cases, 1091 controls).
- Performed outlier correction for area versus CumulusV and Volpara density measurement software programs. The quadratic correlation with manual area density measurement for corrected CumulusV is R= 0.87. Second dataset showed R values of 0.84 for CumulusV, 0.88 for Volpara, and 0.85 for Quantra. Study of patients with tiled images also performed with results presented at the International Workshop on Breast Imaging in Gifu, Japan, 2014, and published in the conference proceedings.
- Developed Automated Cumulus2D software program and compared with manual area density measurements; R=0.88.
- Precision study completed. The R values for repeated left craniocaudal mammogram images are 0.96 for Cumulus, 0.98 for Volpara, and 0.98 for Quantra. Accepted for publication in *Radiology*.
- Study completed to evaluate differences in density measures between mammography machine vendors. Density measurements from Hologic machines are uniformly lower than from GE images when using CumulusV (R= 0.55). However, the relationship is more linear and consistent when using Volpara (R = 0.88).
- Conducted two focus groups with the help of our advocates and the Center for Survey Research. This formed our messaging for naming the study and recruitment materials. Two additional focus groups conducted to aid in survey instrument development and testing.
- Survey instrument developed, tested, and administered to a total of 1024 women. Results demonstrate low knowledge of breast density as a risk factor and that women will rely on their primary health care providers for advice regarding screening strategies. This will require education of health care providers regarding knowledge of breast density moving forward.
- Engaged community through the Charlottesville Women's Four Miler Race and Training Program, Midlife Women's Forum, Relay for Life, and a study website (http://www.healthsystem.virginia.edu/pub/ct/ct15885). FaceBook page (UVa Breast Care Program) increased to1712 Likes with over 100 posts in the last year.
- Produced initial breast cancer risk model using Volpara automated software density program. The C-statistic of 0.86 for the full model with a minor decrease to 0.82 with the reduced model. Breast density was one of the top 5 risk factors in the model. This is considerably higher than the C-statistic of the comprehensive Tyrer-Cuzick risk model, of 0.74.

REPORTABLE OUTCOMES:

- A process for specimen handling has been established for women donating a blood sample. The samples are divided into 20 serum aliquots and buffy coat for DNA.

- Grant from the Charlottesville Women's Four Miler, $2400, May 2012, for iPads (survey instrument)
- Grant from the Charlottesville Women's Four Miler, "Breast Cancer Plasma and DNA Bank: use for development of integrative breast cancer risk prediction method. " $77,733, September 2012. Funds to freeze and store blood samples obtained through this project.
- Two abstracts presented at the International Breast Density Workshop, San Francisco, California, June 9-10, 2013.
    - **Comparison of Breast Density Measurements with a Mammographic Volumetric and Area Algorithm and Magnetic resonance imaging.** O Alonzo-Proulx, JG Mainprize, J Harvey[2] and MJ Yaffe
    - **Estimation of the Precision of Cumulus Area Density and Two Automated Volumetric Breast density Algorithms.** O Alonzo-Proulx, G Mawdlsey, M. Ge, J Harvey and MJ Yaffe
- Conducted survey of 1024 Virginian women demonstrating low knowledge of breast density as a risk factor and willingness to change breast cancer screening based on provider recommendations. Results presented at APHA meeting.
- Preliminary model results demonstrate excellent discrimination of the model even when reduced to 13 variables. This significantly out performs current risk models. These results were presented at the San Antonio Breast Cancer Symposium.

CONCLUSION:

We have completed nearly all promised tasks designated for our study. During this third year, we completed recruitment that was very successful. Community engagement through attendance at events, a website, and Facebook page was very helpful in this success. We completed and have a manuscript accepted regarding precision of automated breast density measurement (Radiology). We completed a telephone survey of 1024 Virginian women was completed, with results showing the women have low baseline knowledge of breast density as a risk factor and that they are willing to change screening behaviors if directed by their primary health care provider. These results were presented at the AHPA meeting. The preliminary model has been assembled demonstrating excellent discrimination (C-statistic) that is much higher than models currently in use. These results were presented at the San Antonio Breast Cancer Symposium.

We have requested and received a no-cost extension of funds. During the next year, we plan to further evaluate our data. We will be better evaluating the relationship of automated breast density and cancer risk/risk factors, and plan to publish those results. We continue to study our dataset regarding modeling risk.

REFERENCES:

None

APPENDICES:

None.