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Improving Screening Mammography Outcomes through Comparison with Multiple Prior Mammograms

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Abstract

Objective—To evaluate the impact of comparison with multiple prior examinations on screening mammography outcomes relative to comparison with a single prior.

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IRB: Our study was approved by our Institutional Review Board and was compliant with requirements of the Health Insurance Portability and Accountability Act (HIPAA).

Disclosures: Weiwen Lin, PhD, is the Chief Executive Officer of Jambeyang Research, LLC. None of the remaining authors have any interests to disclose.

Materials and Methods—Following institutional review board approval, we retrospectively analyzed 46,288 consecutive screening mammograms in 22,792 women at our institution. We subdivided these examinations into three groups: those interpreted without priors, with one prior, and with two or more priors. For each group we determined the recall rate. We also calculated the positive predictive value of recall (PPV_1) and cancer detection rate (CDR) for the single and multiple prior groups. Generalized estimating equations with logistic link function were used to determine the relative odds of recall as a function of the number of comparisons with adjustment for age as a confounding variable. Fisher's exact test was performed to compare the PPV_1 and CDR in the different cohorts.

Results—Recall rates for mammograms interpreted with no priors, one prior and two or more priors were 16.6%, 7.8%, and 6.3%, respectively. After adjusting for age, the odds ratio of recall for the multiple prior relative to the single prior group was 0.864 (95% CI: 0.776, 0.962; p=0.0074). There were also statistically significant increases in PPV_1 of 0.05 (p=0.0009) and CDR of 2.3/1000 (p=0.0481) for mammograms compared with multiple priors relative to a single prior.

Conclusions—Comparison with two or more prior mammograms resulted in a statistically significant reduction in the screening mammography recall rate and increases in the CDR and PPV_1 relative to comparison with a single prior.

Introduction

A large body of evidence including randomized controlled trials and modern evaluations of organized screening programs indicates that screening mammography reduces breast cancer mortality on the order of 20–40% for women aged 40 years and older. [1]. However, false positives are a frequently cited "harm" of mammographic screening, which may result in patient anxiety, added radiation exposure, biopsies and increased healthcare costs [2,3]. The US Preventive Services Task Force has cited excessive false positives as a reason not to support routine screening of women in their forties and to recommend less frequent screening among older women [4]. Consequently, although the mortality benefit of screening mammography arguably far outweighs its potential harms, reduction of false positives should be a priority in order to ensure that support for and access to screening mammography is maintained. Since millions of women are screened each year in the US, even a small reduction in the recall rate may have widespread benefit.

Several previous studies have demonstrated that comparison with at least a single prior mammogram is an effective strategy for reducing the screening mammography recall rate; some of these studies have shown that a prior comparison also increases the biopsy yield of cancer although none have shown an increase in the cancer detection rate [5–12]. Currently there is no established standard as to whether comparison should be made to a single prior or more than one prior examination, although we hypothesized that there would likely be a difference in outcomes between these approaches. Therefore, we chose to test the incremental efficacy of comparing with two or more prior examinations relative to only a single prior. We did not aim to compare the performance within these study groups to interpretation without any priors as this has already been studied. Our study objective was to determine whether there is a significant difference in recall rate, positive predictive value of

recall and cancer detection rate when comparison is made to a single prior versus more than one prior examination.

Materials and Methods

After institutional review board approval, we performed a retrospective search of our mammography database for screening mammograms performed at a single screening facility at an academic medical center between 6/14/2010 and 3/3/2015. Although we did not apply specific exclusion criteria to the study, women at our facility are eligible for screening, hence inclusion in this study, if they are over the age of 30 or over the age of 25 if they are BRCA1 gene mutation carriers, have not had a breast cancer diagnosis within the past 5 years, have no new localized breast symptoms such as a lump or focal pain, have no suspicious abnormalities on clinical breast exam, and did not receive an abnormal assessment (BIRADS 0,3,4,5 or 6) on the most recent prior screening or diagnostic mammogram. This yielded a dataset of 46,288 consecutive screening mammograms performed in 22,792 women. We collected data on patient age, breast density, personal and family history of breast cancer, dates of comparison mammograms recorded in the clinical report, recommendation for recall, and subsequent cancer diagnosis. All prior examinations recorded in the mammographic report were counted as prior examinations, whether screening or diagnostic, regardless of how long ago the examination was performed, and regardless of whether film screen or digital.

During the study period, our facility performed only digital mammography. Screening mammograms were displayed according to the hanging protocol on our PACS workstation, which was standardized for all of the radiologists. In the initial step of this protocol the two most recent prior mammograms, whether screening or diagnostic, were displayed next to the current study using a 6 image per monitor display (figure 2). The subsequent 2 steps displayed two images per monitor, with the current CC views next to the most recent prior CC views, followed by the current and most recent prior MLO views. In these steps of the hanging protocol, the more remote prior images were tiled beneath the most recent priors, but the radiologist could choose whether or not to view the more remote priors in this step. In the final step of the hanging protocol, the current images were displayed in full resolution. If at least two digital priors were not available, then the most recent available screen film mammograms were hung on the alternator for comparison, such that the radiologist always had at least 2 prior mammograms for comparison. Finally, any additional prior digital or film mammograms were available in the PACS system or in the patient folder, respectively; these additional priors were reviewed at the discretion of the radiologist.

Women who present for mammography at our institution are encouraged to obtain their outside prior comparison mammograms. If these are not available at the time of their visit, they are asked to sign a release form that allows our facility to request outside prior mammograms. The screening mammogram is reported the day after it is performed regardless of whether priors are available for comparison. If and when outside priors are obtained, the radiologist will addend the original mammogram report and issue a revised final assessment, which is recorded in the mammography database. In our study, if an addendum was issued to the original screening mammogram report for prior comparison, we

counted all of the priors that were compared in the original report and subsequent addendum, and recorded the final assessment based on the addendum report. Information regarding cancer diagnosis was obtained through query of our institutional pathology records with a minimum follow up interval of 7 months.

We subdivided the screening mammograms into three groups: those interpreted with no prior mammograms for comparison, those compared with one prior, and those compared with two or more priors. The latter two groups constitute the study comparison groups. For each of these subsets of examinations, we subsequently determined the recall rate. Recall rate was defined as the percentage of screening examinations given a BI-RADS 0, 3, 4, or 5 assessment [13]. In addition, we calculated the positive predictive value of recall (PPV_1) and cancer detection rate (CDR) for the groups with one prior and two or more priors. PPV_1 was defined as the percentage of positive screening exams (BIRADS 0, 3, 4, and 5) that resulted in a cancer diagnosis within one year [13]. CDR was defined as the number of cancers detected at screening mammography per 1,000 examinations [13].

Generalized estimating equations (GEE) with logistic link function were used to determine the relative odds of recall as a function of the number of comparison exams without and with adjustment for age as a confounding variable. The GEE model (rather than conventional logistic regression) was used in order to be able to account for repeated observations regarding recall on the same patient over the study period. Fisher's exact test was performed to compare the PPV_1 and CDR between the study groups; the GEE model was not used for these metrics because patients diagnosed with breast cancer during the study period were removed from the screening pool for the duration of the study according to our institutional lumpectomy protocol, and therefore repeated observations of cancer diagnosis would not have been made in the same patient. A nominal p-value < 0.05 was considered statistically significant. Comparison of PPV_1 and CDR was made only between the single and multiple prior groups as these groups by definition consisted of only incidence screening exams. The group without priors predominantly consisted of prevalence screens, and would therefore be expected to have a higher cancer yield relative to incidence screens without prior comparison [14]. Therefore, to avoid the confounding effect of prevalence screens on PPV_1 and CDR and to isolate the effect of prior comparison, we only studied the single and multiple prior groups.

Results

A total of 3,789 screening mammograms were interpreted with no prior comparison mammograms, 5,758 exams were interpreted with a single prior, and 36,741 exams were interpreted with two or more priors (table 1). Screening recall rates for mammograms interpreted with no priors, one prior and two or more priors were 16.6%, 7.8%, and 6.3%, respectively (table 1).

The estimated unadjusted odds ratio (OR) of recall for mammograms with multiple priors versus a single prior was 0.789 (95% CI: 0.711, 0.877; $p<0.0001$) (table 2). However, as the patients in the single prior and no prior groups were younger than those in the multiple prior group (table 1), we repeated our analysis controlling for age as a confounding variable. After

adjusting for patient age, the OR of recall for the multiple prior group relative to the single prior group was 0.864 (95% CI: 0.776, 0.962; p=0.0074), a finding which was statistically significant (table 2).

There also were statistically significant increases in the positive predictive value of recall and the cancer detection rate for mammograms compared with multiple priors relative to a single prior (table 3,4). The PPV_1 for the single and multiple prior groups was 0.056 (95% CI: 0.035, 0.077) and 0.105 (95% CI: 0.093 0.118), respectively (table 3). The two tailed p-value for the test of independence on the table was 0.0009, indicating strong evidence of a difference in PPV_1 depending on whether patient had a single or multiple priors.

Of the patients who received BI-RADS 4 or 5 assessments, tissue diagnoses were available for all patients in the single prior group and for all except 4 patients in the multiple prior group. The CDR per 1000 exams for the single and multiple prior groups was 4.3 (95% CI: 2.8, 6.4) and 6.6 (95% CI: 5.8, 7.5), respectively (table 4). The two tailed p-value for the test of independence on the table was 0.0481, indicating some evidence of a difference in CDR depending whether patient had a single or multiple priors. There were no statistically significant differences in the characteristics of cancers detected in the single versus multiple prior comparison groups (table 5).

Discussion

After adjusting for age, our study showed a statistically significant 14% decrease in the odds of recall for screening mammograms compared with two or more priors relative to comparison with only one prior. Although several previous studies have shown that comparison with at least a single prior mammogram reduces the screening recall rate relative to no comparisons [5–12], there has been no study to our knowledge that specifically evaluated the effect of comparing with a single versus multiple priors. The findings of our study are relevant because the default approach in many practices is to compare to a single prior mammogram. However, it has long been standard in our own practice to compare with at least two priors. We have based this approach on our experience that priors may either obviate recall of borderline findings that have a stable appearance (Figure 1) or facilitate recall in those cases that show progressive change. Specifically, because the appearance of normal breast tissue often changes from year to year due to variable positioning and technique, the likelihood of demonstrating stability increases with the number of prior examinations compared, by increasing the chances of identifying a prior examination with very similar positioning and technique as the current examination. Similarly, the likelihood of demonstrating progressive change in a real lesion, even slow change, increases with the number of prior examinations.

In the analog film environment, the ability to compare to multiple prior examinations was limited by the need to hang comparison films on an alternator, which required additional effort on the part of clerical staff or radiologist, as well as more physical space on the alternator. However, in the digital environment, comparison with multiple prior examinations is facilitated by the greater ease of display built into the digital workstation. In our digital-based practice we have established a default hanging protocol that simultaneously displays

the current and two prior examinations, as this overview makes stability or change over time more readily apparent (Figure 2).

In our study, the statistically significant reduction in recall rate in the multiple prior group was accompanied by statistically significant increases in the PPV_1 and cancer detection rate relative to the single prior group. Previous studies that compared screening mammography interpretation with or without the use of prior examinations have shown an increase in the biopsy yield of cancer when prior films were compared [5–12]. However, none have shown a concomitant increase in the cancer detection rate. This may reflect the fact that all but one of these studies included prevalence screening exams in the group without priors, whereas we explicitly performed comparison between two groups of incidence screens, which by definition consisted of studies with prior comparison exams. The CDR will be higher for prevalence than for incidence screens [14]. Therefore to assess the true effect of prior comparison on CDR, previous investigators would have to distinguish between incidence screening examinations interpreted without priors and prevalence screens. In order to address this issue, Burnside compared only incidence screens interpreted with and without priors, and found that prior comparisons did increase the CDR at diagnostic mammography, but not at screening [10]. In that study the authors postulated that subtle changes over time might be viewed with greater suspicion in the diagnostic setting, leading to increased sensitivity. However the results of our study suggest that similar effects may be observed in the screening environment as well. Indeed, certain signs of malignancy, such as developing asymmetry, by definition present as interval change, and would not be otherwise detectable without comparison to prior examinations (Figure 3) [15].

Limitations of our study include its retrospective design, which may lead to selection bias. The majority of mammograms in our study were interpreted with two or more priors (when these were available for comparison) since this is the standard approach in our practice. As a result, women in the single prior group were younger than those in the multiple prior group. The younger women most likely had fewer prior exams because they had undergone screening for a shorter time period than the older women. As younger age has been shown to be associated with higher recall rates [16], we controlled for age in our statistical analysis. The recall rate reduction in the multiple prior group relative to the single prior group remained statistically significant after controlling for age, confirming that the number of priors compared is an independent predictor of recall. Although the higher cancer detection rate in the multiple prior group could in part be due to more advanced age, age alone would be unlikely to account for the magnitude of the CDR increase observed in our study. We report a relative increase in the CDR of 2.3/1000 in the multiple prior versus single prior group, whereas the average age difference between these groups was only six years (mean age of the single and multiple prior groups was 55.5 and 61.5 years, respectively). The age specific incidence of breast cancer for women in the US obtained from the 2008–2012 SEER database was 2.4/1000 for age 50–59 and 3.4/1000 for age 60–64 [17]. Based on these SEER data, we would expect a relative increase in CDR of approximately 1/1000 for the multiple prior group on the basis of age relative to the single prior group, whereas we observed more than twice that increase, suggesting that prior comparison has an effect on CDR that is independent of age. Nevertheless, future studies with age-matched cohorts would be helpful to confirm our findings.

In spite of the age difference between the single and multiple prior groups, the absolute difference in the proportion of women with dense breasts was small (43% versus 39% with dense breasts in the single versus multiple prior groups). Therefore breast density was not an important confounder of study outcomes.

Approximately 31% of our population had a strong family history of breast cancer, which was defined by having at least one first degree relative with breast cancer. This likely contributed to our high CDR overall. However, there was a small absolute difference between the single and multiple prior groups with respect to family history of breast cancer (29.8% vs. 31.8%, respectively). Therefore family history was also not an important confounder of study outcomes, and we do not believe this should limit the generalizability of our study findings.

Notably, there were a higher percentage of patients with a personal history of breast cancer in the multiple prior group than in the single prior group (8.2% vs 4.5%). Our institutional lumpectomy protocol excludes patients with breast cancer diagnoses within the past 5 years from screening and triages these patients to diagnostic mammography. In addition, many of our breast cancer survivors choose continued follow-up with diagnostic rather than screening exams beyond 5 years after diagnosis. These factors would attenuate any disproportionate contribution of the personal history cohort to CDR and PPV_1.

Another limitation of this study is that we were only able to obtain information regarding cancer diagnoses from our institutional pathology database as we did not have linkage to a tumor registry for the study period. However, we cannot posit a sensible reason why the few additional cancers that may be identified in a tumor registry would be more or less likely to be in the single versus multiple prior cohort.

Another confounding factor in our study is the fact that the median time interval to the last prior comparison mammogram was 12 months longer in the single prior group as compared to the multiple prior group. Therefore we cannot exclude the possibility that the availability of more recent priors may have contributed to the recall rate reduction in the multiple prior group. In a small reader study, Sumkin showed that the specificity was significantly better when using a single comparison mammogram from 1 year prior relative to 2 years prior [18]. However, there is a paucity of data on this subject. One might speculate that if a prior study is too remote, it will bear little resemblance to the current study; interpretation of the current study in this situation would be akin to reading a prevalence screening exam without the benefit of prior comparisons. However, when the comparison interval is within a couple years of the current exam, as was the case in our study, one might speculate that longer term stability of a low suspicion finding would be more reassuring and thus more likely to avert recall than stability of only one year. Further studies utilizing a more balanced dataset controlling for time interval to last prior examination would be necessary to clarify this issue.

A final limitation of our study was the fact that we did not differentiate between the number of comparison exams within the multiple prior group in our analysis. We sought only to establish that comparing with multiple priors is better than comparing to a single prior.

Future studies that establish the optimal number of reference exams, whether it be two or more priors, would be of value.

In summary, we have shown that the screening mammography recall rate decreases while the PPV_1 and CDR increase when two or more prior examinations are used for comparison relative to comparison with a single prior examination. Our findings suggest that, at screening mammography, radiologists who compare with more than a single prior examination will have more true–positive and fewer false–positive outcomes.

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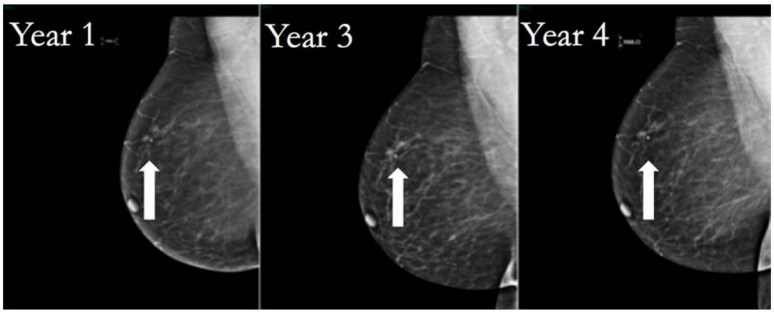

Fig. 1.

59 year old female with an asymmetry in the upper right breast (arrows), which was not recalled at screening mammography based on long-term stability in comparison to multiple prior examinations.

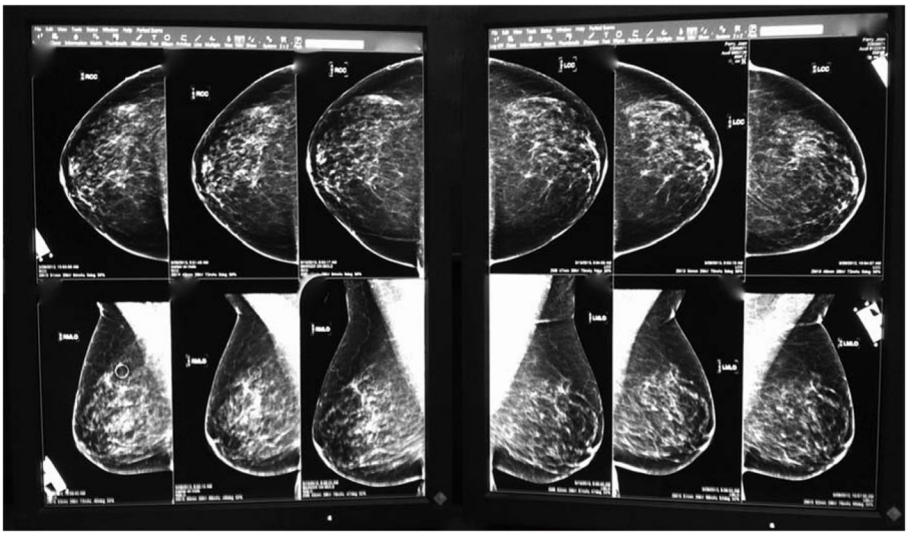

Fig. 2.

Workstation hanging protocol with simultaneous display of two prior comparison mammograms (current examination at center, partially on each monitor). For workstations not capable of displaying 6 images per monitor, the current and most recent examination may be displayed simultaneously, followed by the current and older examination.

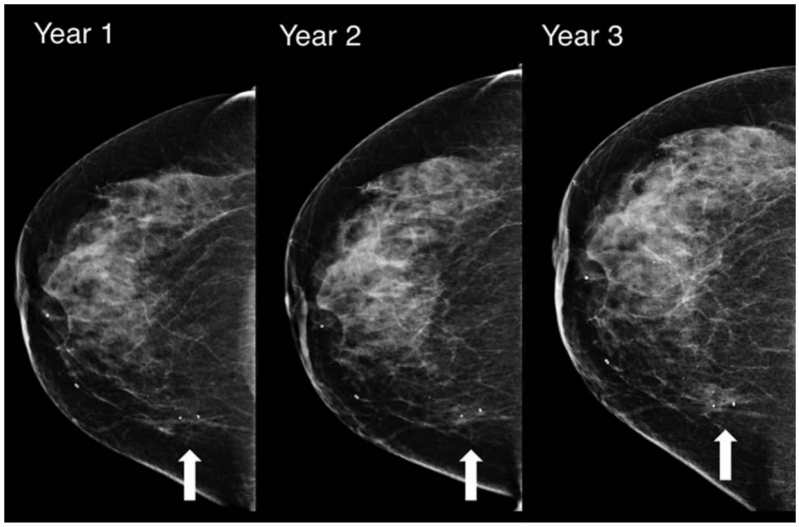

Fig. 3.

75 year old female with infiltrating ductal carcinoma presenting as a developing asymmetry (arrows) in the medial breast at screening mammography.

TABLE 1

Screening mammography recall rates and patient characteristics for study groups defined by the number of prior comparisons

Priors compared	0	1	≥2	Combined
Number of screening mammograms	3,789	5,758	36,741	46,288
Exams recalled	631 (16.7%)	449 (7.8%)	2,307 (6.3%)	3,387 (7.3%)
Median time interval to last prior mammogram in months (range)	N/A	26 (0.68–321)	14.1 (0.06–251)	14.9 (0.06–321)
Breast Density A,B[a]	1835 (48%)	3259 (57%)	22559 (61%)	27653 (60%)
Breast Density C,D[b]	1,954 (52%)	2,499 (43%)	14,182 (39%)	18,635 (40%)
Mean age in years (mean±SD)	49.5 ± 11.5	55.5 ± 11.7	61.5 ± 11.1	59 ± 12.2
Personal history of breast cancer				
Yes	35 (1.4%)	178 (4.5%)	2995 (8.2%)	3,208 (6.9%)
No	2,559 (67.5%)	2,875 (49.7%)	24,121 (65.7%)	29,555 (63.9%)
Unknown	1,195 (31.5%)	1,661 (28.8%)	9,625 (26.1%)	12,481 (27.0%)
Family history of breast cancer				
None[c]	1935 (51.0%)	2875 (49.9%)	17,936 (48.8%)	22,746 (49.1%)
Strong[d]	986 (26.0%)	1,718 (29.8%)	11,688 (31.8%)	14,592 (31.5%)
Unknown	868 (22.9%)	1165 (20.2%)	7117 (19.4%)	9,150 (19.8%)

[a] Density A=almost entirely fatty, B=scattered areas of fibroglandular density

[b] Density C=heterogeneously dense, D=extremely dense

[c] No first degree relatives with breast cancer.

[d] At least one first degree relative with breast cancer.

TABLE 2

Relative odds of recall at screening mammography as a function of the number of prior comparison mammograms without and with adjustment for age as a confounding variable

Number of comparisons	Unadjusted OR* (95% CI)	p value	Adjusted OR§ (95% CI)	p value
1 vs. 0	0.430 (0.379, 0.489)	< 0.0001	0.470 (0.413, 0.536)	< 0.0001
≥2 vs. 0	0.340 (0.309, 0.374)	< 0.0001	0.406 (0.366, 0.451)	< 0.0001
≥2 vs. 1	0.789 (0.711, 0.877)	< 0.0001	0.864 (0.776, 0.962)	0.0074

*Unadjusted ORs refers to GEE logistic model estimates not adjusting for confounding variables.

§Adjusted ORs refer to GEE logistic model estimates after adjusting for age as a confounding variable.

TABLE 3

PPV_1 for screening mammograms interpreted with a single prior versus 2 or more prior comparisons

No. of Comparisons	True Positive	False Positive	PPV_1 (95% CI)
1	25	424	0.056 (0.035, 0.077)
≥2	243	2,064	0.105 (0.093, 0.118)
Combined	268	2,488	0.097 (0.086, 0.011)

Two-tailed p-value for test of independence on the table = 0.0009, as calculated by Fisher's exact test

TABLE 4

Cancer detection rate for screening mammograms interpreted with a single prior versus 2 or more prior comparisons

No. of Comparisons	No. of Cancers	Total Screening Exams	CDR per 1,000 exams (95%CI)
1	25	5,758	4.3 (2.8, 6.4)
≥2	243	36,741	6.6 (5.8, 7.5)
Combined	268	42,499	6.3 (5.6, 7.1)

Two-tailed p-value for test of independence on the table = 0.0481, as calculated by Fisher's exact test

TABLE 5

Characteristics of cancers detected at screening mammography interpreted with a single prior versus 2 or more prior comparisons

Characteristic	1 prior	≥2 priors	p-value*
Invasive ductal or lobular carcinoma	14 (56%)	134 (55%)	0.505
<1 cm	5 (20%)	68 (28%)	
node negative	5 (20%)	73 (30%)	
DCIS	10 (40%)	71 (29%)	0.505
Minimal	15 (60%)	139 (57%)	0.648
Unknown	1 (4%)	38 (16%)	
Total	25	243	

*Two-tailed p-value for test of independence as calculated by Fisher's exact test