
DEUS

TECHNOLOGIES

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February 13, 2001

Food and Drug Administration
Center for Devices and Radiological Health
PMA Document Mail Center (HFZ-401)
9200 Corporate Blvd.
Rockville, MD 20850

Attention: Mr. Robert J. Doyle

SUBJECT: Posting of sections of PMA #P000041 (*RapidScreen*TM RS-2000) on the
FDA Web Site

Dear Mr. Doyle:

In response to your email of February 5, concerning permission to publish the Summary of Safety and Effectiveness and Labeling sections from the above referenced PMA on the FDA web site, attached please find hard copies of these two sections. Also attached is a floppy diskette containing MS-Word 2000 electronic versions of the same two files.

If there are additional questions regarding our submission, please contact Jesse Lin, Director of Quality Assurance, at 301.762.4442 x312, or the undersigned at x303.

Sincerely,



Dr. Michael H.Y. Yeh
President and Chief Executive Officer
Deus Technologies

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I-A. Summary of Safety and Effectiveness

1.0 General Information

<i>Device Generic Name:</i>	Image Analysis System
<i>Device Trade Name:</i>	RapidScreen™ RS-2000
<i>Applicant's Name and Address:</i>	Deus Technologies, LLC. 1700 Research Blvd. Suite 104 Rockville, MD 20850
<i>PMA Number:</i>	P000041
<i>Date of Panel Recommendation:</i>	March 5, 2001
<i>Date of Approval to Applicant:</i>	<i>(To be completed by FDA)</i>

2.0 Indications for Use

The RapidScreen™ RS-2000 system is a computer-aided detection (CAD) system intended to identify regions of interest (ROIs) on digital chest images that may have features associated with solitary pulmonary nodules (SPNs), an important indication for early-stage lung cancer. The system functions on PA or AP chest radiographs and brings the ROIs to the attention of physicians after the initial reading of the radiographs. Thus, the system assists physicians in minimizing observational overlooks by marking ROIs on the digital image of the original radiograph that may warrant a second review.

To interpret a case, the physician performs an initial interpretation of the original chest radiograph in the conventional manner. The physician then reviews the digital images generated by the RapidScreen™ RS-2000 system with the ROIs marked. The physician then re-evaluates the original chest radiographs, paying particular attention to the regions corresponding to the ROIs on the images and re-assesses the original interpretation, if necessary. The RapidScreen™ RS-2000 system has been shown in clinical trials to assist radiologists in increasing the detection of small primary lung cancers.

3.0 Contraindications

There are no contraindications for use of this device.

4.0 Warnings and Precautions

Warning and Precautions for use of the device are provided in *Section IV-A, Labeling*.

5.0 Device Description

Developed by Deus Technologies, the RapidScreen™ RS-2000 system is a computer-aided detection (CAD) system to aid physicians in detection of regions of interest (ROIs) on PA or AP chest radiographs, after their initial reading has been completed. The ROIs detected by the RapidScreen™ RS-2000 system have characteristics similar to solitary pulmonary nodules (SPNs), an important indication of early primary lung cancer,

commonly overlooked by physicians. The *RapidScreen*™ RS-2000 system is designed to serve as a “second opinion” to focus physician’s attention on ROIs that may be indication of early stage lung cancer.

The *RapidScreen*™ RS-2000 system consists of the following major hardware components: (1) *Processor* (including a bar code reader, keypad, CCD film digitizer and processing computer), and (2) *Display* (including a laser printer and a video monitor). To operate the *RapidScreen*™ RS-2000 system, the operator inserts the chest radiograph into the film digitizer and uses the bar code reader or keypad to input the film ID. The CCD film digitizer, previously approved by FDA for marketing, then digitizes the film, and the *RapidScreen*™ RS-2000 algorithms process the digital image, detecting and marking ROIs with characteristics similar to SPNs. The analysis results generated by the *RapidScreen*™ RS-2000, i.e., the annotated image corresponding to the film with marked ROIs, is displayed on the video monitor and printed in hard copy by the laser printer.

The *RapidScreen*™ RS-2000 system’s algorithms look for characteristics commonly associated with lung nodules. The system ranks its findings by likelihood and then marks those regions above a fixed threshold of likelihood. Following sections describe the algorithms used by the *RapidScreen*™ RS-2000 when analyzing a chest image.

The *RapidScreen*™ RS-2000 system searches a chest image for round-shaped opaque structures with diameter smaller than 30 mm (in the scale of the original film), characteristics that may be indication of lung nodules. When the features associated with such a structure in the chest image meet the generally accepted criteria for a lung nodule, the system places a marker over the centroid of that structure on the image, as shown in Figure 1. The system marks these ROIs using a circle equivalent to 2.5 cm in radius in the scale of the original film.



Figure 1. Examples of marked lung nodules.

The system has been designed to mark only image patterns associated with lung nodules. However, normal anatomical structures in the chest image, such as rib crossings and end-on vessels, sometimes satisfy the algorithms’ criteria for selection and may also be marked. Such structures are shown in Figure 2.

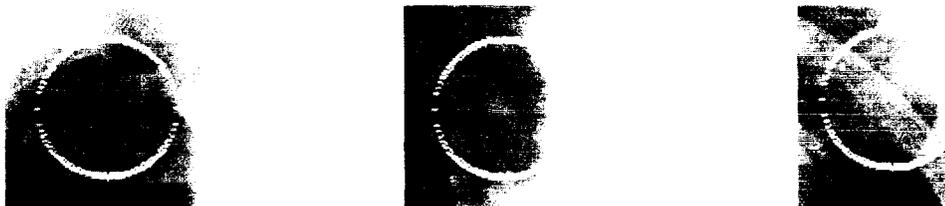


Figure 2. Examples of normal structures that may be marked as potential lung nodule.

The software algorithms have been optimized to identify image patterns of round-shape within the 7 to 30 mm diameter range. The system does not process lateral view chest radiographs.

To interpret a case, physician first reviews the chest radiographs for initial interpretation in the conventional manner. Physician then refers to the results from the *RapidScreen*™ RS-2000 system (i.e., the corresponding display image or printout with marked ROIs). The physician would then refer back to the original films, paying particular attention to the marked areas and re-assessing the original interpretation. Thus, the *RapidScreen*™ RS-2000 functions as an aid to physicians, a “second opinion” in reviewing chest radiographs by calling attention to the ROIs.

6.0 Alternative Practices and Procedures

The current radiological practice for reviewing chest radiographs involves a physician’s review of the films on a lightbox or motorized film viewer. Currently, double reading of chest radiographs is an uncommon practice among physicians. However, studies have shown that double reading results in an 8-15% increase in sensitivity for lung nodule detection. The proposed use of *RapidScreen*™ RS-2000 can provide the effects of double reading by calling physicians’ attention to ROIs that may have features associated with SPNs for a “second look” after their initial reading.

7.0 Marketing History

The *RapidScreen*™ RS-2000 system was first introduced in 1998 at the Radiological Society of North America annual conference (RSNA’98) in Chicago, IL. Since then, the product has been tested in Taiwan. No adverse effects have been reported from users, and it has not been withdrawn for any reason.

8.0 Potential Adverse Effects of Device on Health

There are no known direct risks to safety or health caused by, or related to, the use of the *RapidScreen*™ RS-2000 system. The indirect risks are that the device may fail to identify and mark some actionable lung nodules or will mark some areas that do not require further action. (Refer to Warnings in *Section IV-A, Labeling*). The primary potential adverse effect is missing cancer. However, the potential for a missed lesion is not increased over normal chest radiograph analysis when the *RapidScreen*™ RS-2000 is used according to instructions.

9.0 Non-Clinical Studies

Non-clinical studies were designed and conducted to develop, analyze, and improve the design of the *RapidScreen*™ RS-2000 System. In-depth design and review were performed to determine the requirements for a user-friendly system. Hardware, software, and the interactions between them and between systems and operators were also

considered during the design and development of the RapidScreen™ RS-2000 System. Brief descriptions of these studies are provided in paragraphs 9.1 to 9.4, below.

9.1 System Reproducibility

Deus Technologies conducted an investigation of reproducibility at each software module and hardware component level. The investigation of the reproducibility of the film digitizer was conducted to develop software algorithms and improve the consistency of the digitizer's output, i.e., the image data. The capability of each software module is evaluated for the tolerance of shift- and intensity-noise from the digitizer.

A non-clinical study was conducted to provide data for the reproducibility of the RapidScreen™ RS-2000 System as a computer aid for the detection of T1 lung cancer. Defined as the degree of deviation from perfect reproducibility (100%), the intra-machine reproducibility index of sensitivity is approximately 95% from 60 films containing well-characterized T1 lung cancers processed ten (10) times by three (3) systems. The inter-machine reproducibility index of sensitivity is approximately 97%. These reproducibility indices demonstrate that there is only minimal inter-machine and intra-machine variability in the detection of T1 lung cancer.

9.2 Assessment of Algorithm Performance

Deus Technologies performed a quantitative assessment of the RapidScreen™ RS-2000 System algorithms based on testing from an in-house library that containing a very large number of chest radiographs and digital chest images with confirmed cancers and known cancer locations. The in-house library of chest radiographs and digital chest images were collected according to Deus Technologies' data collection protocol. The chest radiographs (after digitization) and digital chest images are used to refine and cross-validate the algorithms. This in-house library contains chest x-ray radiographs of different screen-film systems and digitized images by different types of digitizers collected from several different countries. The in-house results provided a preliminary demonstration that the system performs with a high level of sensitivity in the detection of the image patterns whose characteristics may be associated with SPNs and lung cancers.

9.3 Safety

The RapidScreen™ RS-2000 System is tested for compliance with the following electrical safety and EMC standards: (1) FCC Part 15 class A and (2) UL2601-1. The device also has a number of additional safety features, including: (1) all major components are in compliance with UL and FCC standards, (2) use of all UL certified cables and major components, and (3) other interlocks and mechanical safeguards.

9.4 Software Validation

Deus Technologies has provided documentation showing that the software used in this device was developed under an appropriate software development control program and procedures. Deus Technologies has performed a hazard analysis from both the patient and user perspectives and has addressed all identified hazards. Deus Technologies has

also performed an appropriate validation process. These processes provide the foundation for assuring that the software will operate as described.

10.0 Clinical Studies

Deus Technologies has conducted two phases of comprehensive clinical studies in order to demonstrate the effectiveness and safety of the *RapidScreen*™ RS-2000 system when it is used as a computer aided detection (CAD) tool to assist radiologists in the detection of early-stage lung cancers from chest radiographs. Descriptions of these two studies are provided in paragraphs 10.1 and 10.2 below.

10.1 Purpose

The trials were conducted to prove the efficacy and safety of the *RapidScreen*™ RS-2000 system when used as a CAD tool to assist physicians in the detection of early-stage lung cancers from chest radiographs.

10.2 Periods and Site

There were two phases of clinical trials conducted at the Imaging Sciences and Information System (ISIS) Research Center, Department of Radiology, Georgetown University Medical Center, from 1998 to 2000: a Pilot study and a full-scale double-blinded Receiver Operating Characteristics (ROC) study.

Phase I Trial: Pilot Study

The two main purposes of the pilot study are (1) to investigate the feasibility of *RapidScreen*™ RS-2000 system in helping radiologists to detect early stage (T1) lung cancers, and (2) to determine the sample size for the full-scale double-blinded clinical trial. The cases selected from a large-scale prospective lung cancer-screening project (over 10,000 cases) were used for this pilot study. Ten percent (10%) of the selected cases are T1 stage (early stage) lung cancer. Among these cancer cases, 70% of them had been discovered by the original screenings of two radiologists, and the rest 30% cancer cases are more subtle cases that had been missed by the two original radiologists' analyses. These subtle lung cancers were confirmed retrospectively by expert thoracic radiologists through review of medical records and follow-up films from that screening project. In this pilot study, a group of radiologists from different clinical practices were recruited to read the films.

These study radiologists were able to detect 55% to 75% of the cancer cases. The *RapidScreen*™ RS-2000 system detected 10% to 20% additional cases of cancer that the study radiologists had missed. Thus, if the study radiologists were to use the information from the *RapidScreen*™ RS-2000, they would increase the number of cancer cases detected by 8% to 16% for all cancer cases selected for this pilot study.

Among the subset (30%) of total cancer cases that were more subtle and had be originally missed by two screening radiologists, the study radiologists were able to detect either 0% to 33% of them, whereas the *RapidScreen*™ RS-2000 detected 67% of these cases. Combining the *RapidScreen*™ RS-2000 and study radiologist's performances, the *RapidScreen*™ RS-2000 could provide a 33% to 67% improvement in sensitivity for

cancer detection for the radiologists on these more subtle cases.

For the rest cancer-free cases, it was also found that the unnecessary work-up rate would change from 16.8% to 15.9% when *RapidScreen*™ RS-2000 system was used as an aid in lung cancer detection. Such a change is statistically insignificant.

In summary it was shown that:

- The *RapidScreen*™ RS-2000 system could potentially improve radiologists' sensitivities by 8% to 16% in the detection of overall early-stage (T1) lung cancers;
- The *RapidScreen*™ RS-2000 system could potentially provide 33% to 67% improvement of sensitivity for radiologists in detection of more subtle early-stage lung cancers; and
- The unnecessary work-up rate for radiologists remained unchanged when the *RapidScreen*™ RS-2000 system was used as an aid to detect early-stage lung cancer.

Phase 2 Full-Scale Clinical Trial: Double-blinded ROC study

The ROC Study was designed to test three hypotheses: one primary and two secondary hypotheses. The primary hypothesis was that radiologists using *RapidScreen*™ RS-2000 would increase their detection of primary lung cancers (T1 stage). The secondary hypotheses were that radiologists using *RapidScreen*™ RS-2000 would increase their detection of primary lung cancers that had previously been missed by two screening radiologists and that they would increase their detection of primary lung cancers 9-14 mm in average diameter.

To evaluate these three hypotheses, Receiver Operator Characteristic (ROC) analysis was used. Again a set of study cases was chosen from a large-scale prospective lung cancer-screening project containing over 10,000 cases, (each case consists of chest radiographs taken for 5 consecutive years) based on the estimation from our pilot study experience. These known cancer cases were primary lung cancer cases of different patients with lesions 9 to 27 mm in size, each proven pathologically with biopsy and confirmed by an Expert Panel in this study. Of these cancer cases, 77% were cases wherein one or both former screening radiologists had either detected or suspected cancer at the time of the original reading. These cases are referred to herein as *Current Cancer Cases*. The rest 23% cases were originally missed by both former screening radiologists, but could be seen in retrospective analysis and were confirmed by the Expert Panel in this trial. This subset of cases (23% of all cancer cases in this clinical study) is referred to herein as *Actionable Prior Cancer Cases*. All cancer cases were intermixed with all the cancer-free cases using computer randomization methods. These cancer free cases were randomly drawn from the same screening project of heavy smokers and had been determined to be cancer free by at least three years of clinical follow-up and usually by at least two years of cancer free chest radiographs. Accordingly, a group of study radiologists (observers) certified by the American Board of Radiology were recruited to interpret these study cases. Each study radiologist interpreted the films initially without *RapidScreen*™ RS-2000 assistance (called *Independent ROC Test* or *Independent without CAD*). Then, a minimum of one month later, the radiologists reinterpreted them in the so

called *Sequential ROC Test*, in which each film was interpreted without the RapidScreen™ RS-2000 assistance first (referred to *Sequential without CAD*) and then re-interpreted with the system assistance (*Sequential with CAD*). The MultiReader MultiCase (MRMC) ROC method of Dorfman, Berbaum, and Metz (DBM) was then used for statistical analysis of these three reading conditions (Independent without CAD, Sequential without CAD, and Sequential with CAD).

Potential Improvement of Radiologists’ Detection Using RapidScreen™ RS-2000 System

The potential improvement from the use of the RapidScreen™ System can be determined by combining machine performance and radiologist performance case-by-case and radiologist-by-radiologist. Such results provide a goal for radiologists using the RapidScreen™ system to attempt to reach and indicate the potential improvement if radiologists fully utilized the computer output in their decision-making. We found that the potential improvement was greatest for the cases that the radiologists found most difficult.

For lesions 9-14 mm, the radiologists on average could have detected an additional 24% cases (a potential increase from 58% to 82% or 24% improvement in sensitivity). For lesions 15-19 mm, the average potential increase is 20% cases (a potential increase in sensitivity from 68% to 88% or a 20% improvement in sensitivity). For lesions 20-27 mm, the average potential increase is 6% cases (a potential increase from 78% to 84% or 6% improvement in sensitivity). Combining the radiologists’ detections with those of the computer, overall they detected 84%, an increase from 65% to 84%, a potential 19% improvement in sensitivity.

Results Obtained from the ROC Study

Hypothesis 1: Radiologists using RapidScreen™ RS-2000 will improve their performance in the detection of lung cancers 9-27 mm in size. Results relevant to this hypothesis are presented in Table 1 and Chart 1.

Table 1. Comparison of radiologists’ performance parameters in the detection of lung cancers 9 – 27 mm in size during the Independent ROC and Sequential ROC (with and without RS-2000 aid) tests.

DBM's MRMC Analysis	unaided Az	Sequential with CAD Az	P	95% CIs
Sequential with CAD vs. Independent without CAD	0.8288	0.8654	0.0058	(-0.062, -0.011)
Sequential with CAD vs. Sequential without CAD	0.8347	0.8654	<0.0001	(-0.045, -0.017)

Legend:

- Az = Area under the ROC curve
- 95% CI = 95% confidence interval

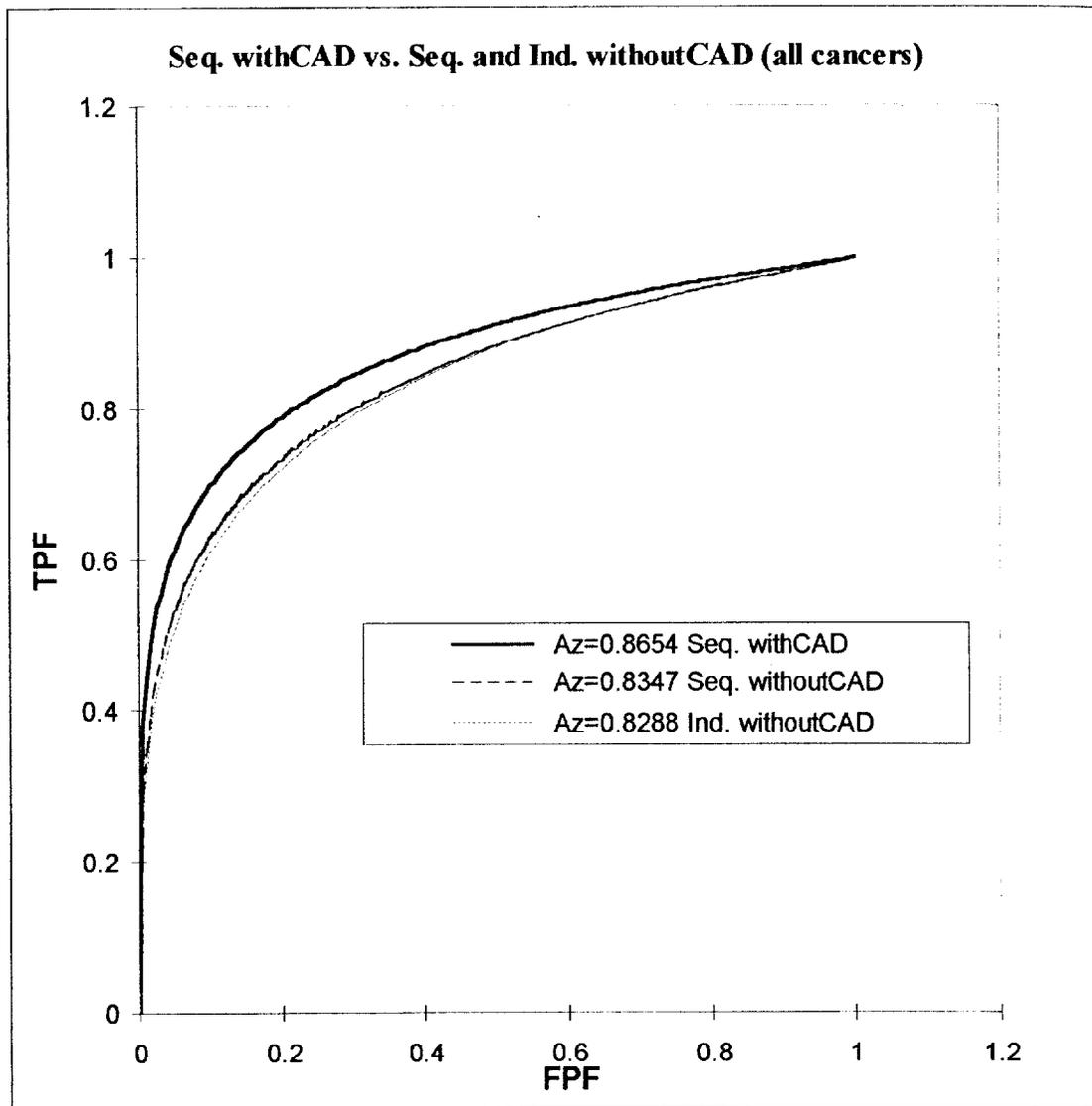


Chart 1: The ROC curves for each of the three reading conditions for all cancer cases and all normal cases with combined results for all radiologists.

These results confirm Primary Hypothesis 1. Two different comparisons were made in this plot (Chart 1). In the first, the first reading of the radiologists (Independent without CAD) was compared to their interpretations with *RapidScreen*™ RS-2000 in the second read (Sequential with CAD). The Az (area under the curve) during the first read (Independent without CAD) was 0.8288 and in the second read with *RapidScreen*™ RS-2000 was 0.8654. This improvement has a p value of 0.0058. The second comparison was with the sequential reading in which the radiologists used the *RapidScreen*™ RS-2000 in its recommended clinical use pattern (i.e., Sequential with CAD vs. Sequential without CAD). In this comparison, the Az of the reading without *RapidScreen*™ RS-2000 was 0.8347 and with *RapidScreen*™ RS-2000 was again 0.8654. The $p < 0.0001$. It is noted that the two curves corresponding to situations without computer assistance are not statistically significant ($p=0.6$), even though the curve corresponding to Sequential without CAD is higher than that Independent without CAD. This increase of Az value is,

we believe, mainly due to the higher alertness in the sequential test mode. Comparing radiologists' sensitivity with RS-2000 (Sequential with CAD) to their current clinical practice without CAD (less than 65% in Independent without CAD) in Chart 1, an approximate 10% increase of sensitivity can be seen in detection of T1 cancer 9-27 mm in size with slight increase of false positive fraction.

As in Table 1, the difference between the Az is greater when comparing the first reading (Sequential without CAD) to the reading using RapidScreen™ RS-2000 (Sequential with CAD), but the p value is larger (0.0058 vs. 0.0001). This is likely due to the greater standard deviation of scores seen among radiologists in the first read (Independent without CAD) for both the cancer and normal cases than in the second read without RapidScreen™ RS-2000. This might suggest that radiologists' detection performance might be less variable when they work with computer assistance.

Hypothesis 2: Radiologists using RapidScreen™ RS-2000 will increase their detection rate of T1 cancers originally missed by two screening radiologists prospectively. Results relevant to this hypothesis are presented in Table 2 and Chart 2.

Table 2. Comparison of radiologists' performance parameters in the detection of lung cancers originally missed by two screening radiologists prospectively during the Independent ROC and Sequential ROC (with and without RS-2000 aid) tests.

DBM's MRMC Analysis	unaided Az	Sequential with CAD Az	P	95% Cis
Sequential with CAD vs. Independent without CAD	0.7231	0.7443	0.4268	(-0.074, 0.031)
Sequential with CAD vs. Sequential without CAD	0.7022	0.7443	0.0299	(-0.08, -0.0041)

Legend:

Az = Area under the ROC curve

95% CI = 95% confidence interval

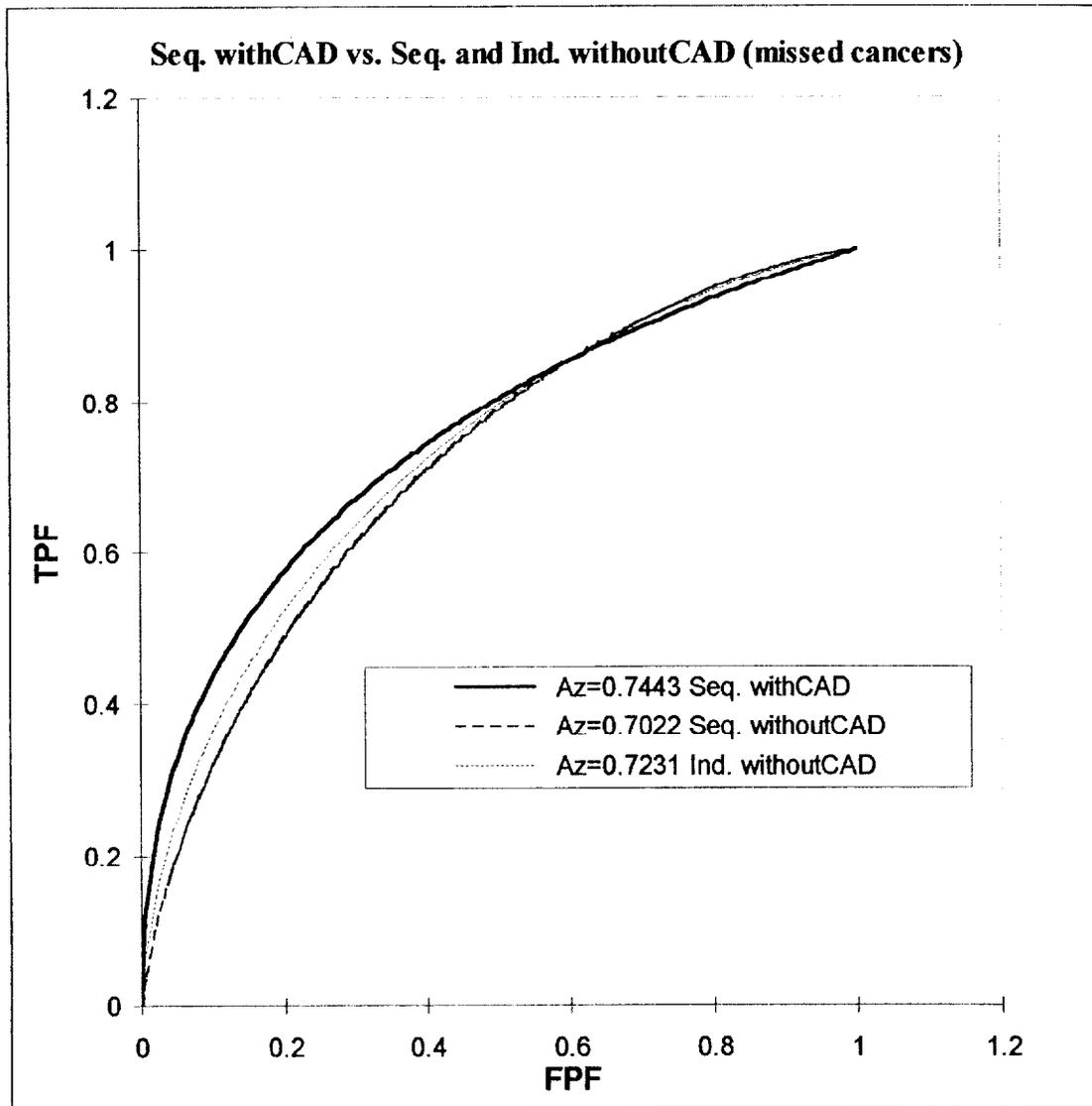


Chart 2: The ROC curves for each of the three reading conditions for the cancer cases that were originally prospectively missed and all normal cases with combined results for all radiologists.

In Chart 2, the results show that the use of *RapidScreen*™ RS-2000 resulted in an increase in Az for cases originally missed by radiologists (*Actionable Priors*). The p value (0.03) for the sequential test (without and with CAD) is small enough to indicate that this increase in Az is significant. However, the increase of Az comparing the independent reading to the reading with *RapidScreen*™ RS-2000 assistance is not significant (p=0.4). This may be due to larger reader variation in first reading and smaller sample size for the missed cancer cases (*Actionable Prior* cases). These results support Secondary Hypothesis 2 showing that radiologists using *RapidScreen*™ RS-2000 detect more cancers in a group where the cancers had been prospectively missed by two radiologists.

Hypothesis 3: That radiologists using *RapidScreen™* RS-2000 will increase their detection of T1 cancers 9 to 14 mm in size. Results relevant to this hypothesis are presented in Table 3 and Chart 3.

Table 3. Comparison of radiologists’ performance parameters in the detection of lung cancers 9 – 14 mm in size during the Independent ROC and Sequential ROC (with and without RS-2000 aid) tests.

DBM’s MRMC Analysis	unaided Az	Sequential with CAD Az	P	95% Cis
Sequential with CAD vs. Independent, without CAD	0.7975	0.8477	0.0161	(-0.09, -0.01)
Sequential with CAD vs. Sequential without CAD	0.8002	0.8477	0.0005	(-0.073, -0.022)

Legend:

Az = Area under the ROC curve

95% CI = 95% confidence interval

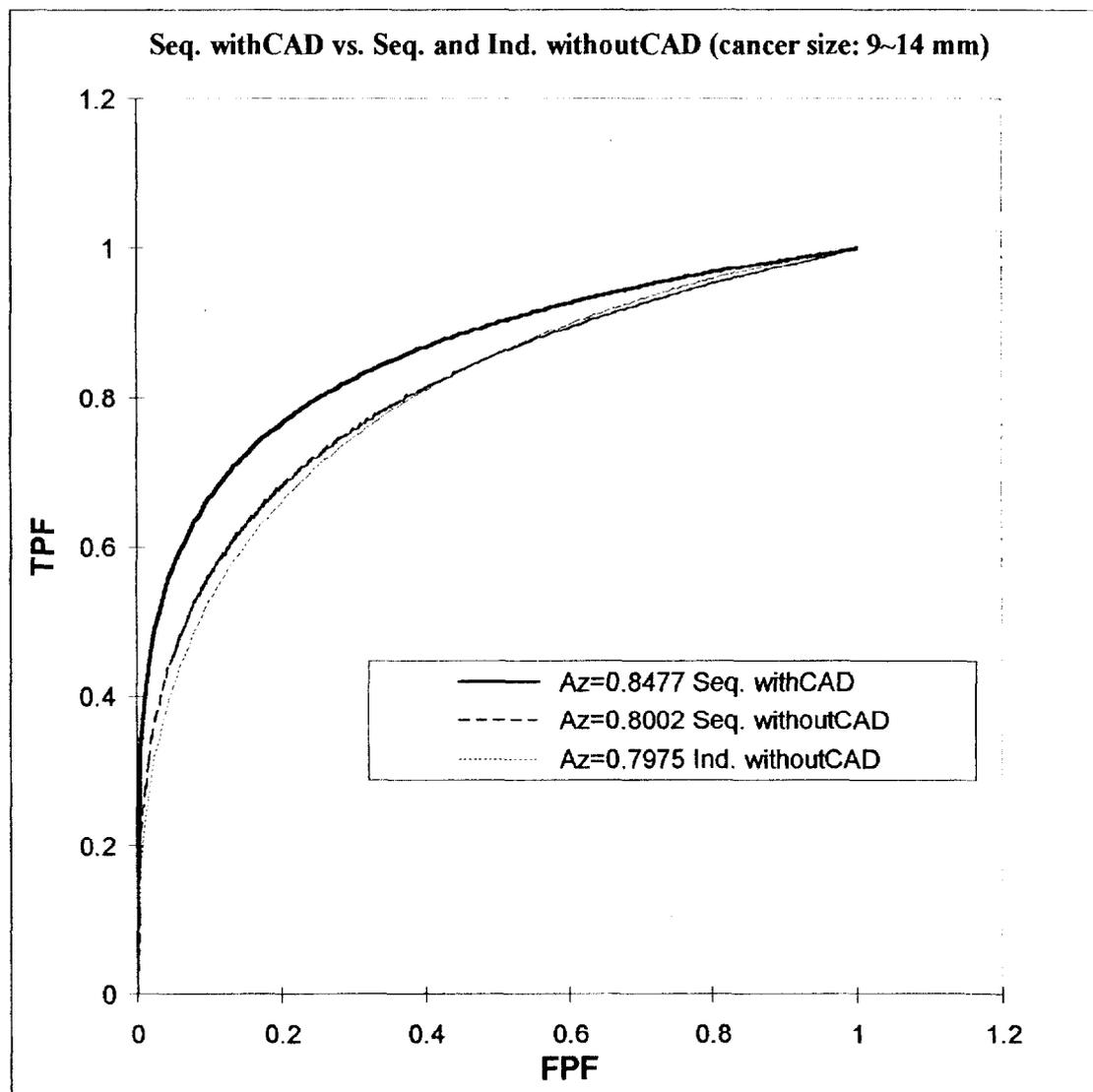


Chart 3: The ROC curves for each of the three reading conditions for the cancer cases that measured 9 to 14 mm and all normal cases with combined results for all radiologists.

In Chart 3, the results support Secondary Hypothesis 3 and show that *RapidScreen*™ RS-2000 increases the detection of small lung cancers and that these results are highly statistically significant. Comparing radiologists' sensitivity with RS-2000 (Sequential with CAD) to their current clinical practice without CAD (less than 58% in Independent without CAD) in Chart 3, an approximate 15% increase of sensitivity can be seen in detection of T1 cancer 9-14 mm in size with slight increase of false positive fraction.

In addition, we investigated the detection improvement for T1 cancers 15-19 mm in size. The results are presented in Table 4 and Chart 4.

Table 4. Comparison of radiologists' performance parameters in the detection of lung cancers 15 - 19 mm in size during the Independent ROC and Sequential ROC (with and without RS-2000 aid) tests.

DBM's MRMC Analysis	unaided Az	Sequential with CAD Az	P	95% CIs
Sequential with CAD vs. Independent without CAD	0.8399	0.8704	0.0452	(-0.06, -0.0007)
Sequential with CAD vs. Sequential without CAD	0.8565	0.8704	0.2389	(-0.037, 0.009)

Legend:

Az = Area under the ROC curve

95% CI = 95% confidence interval

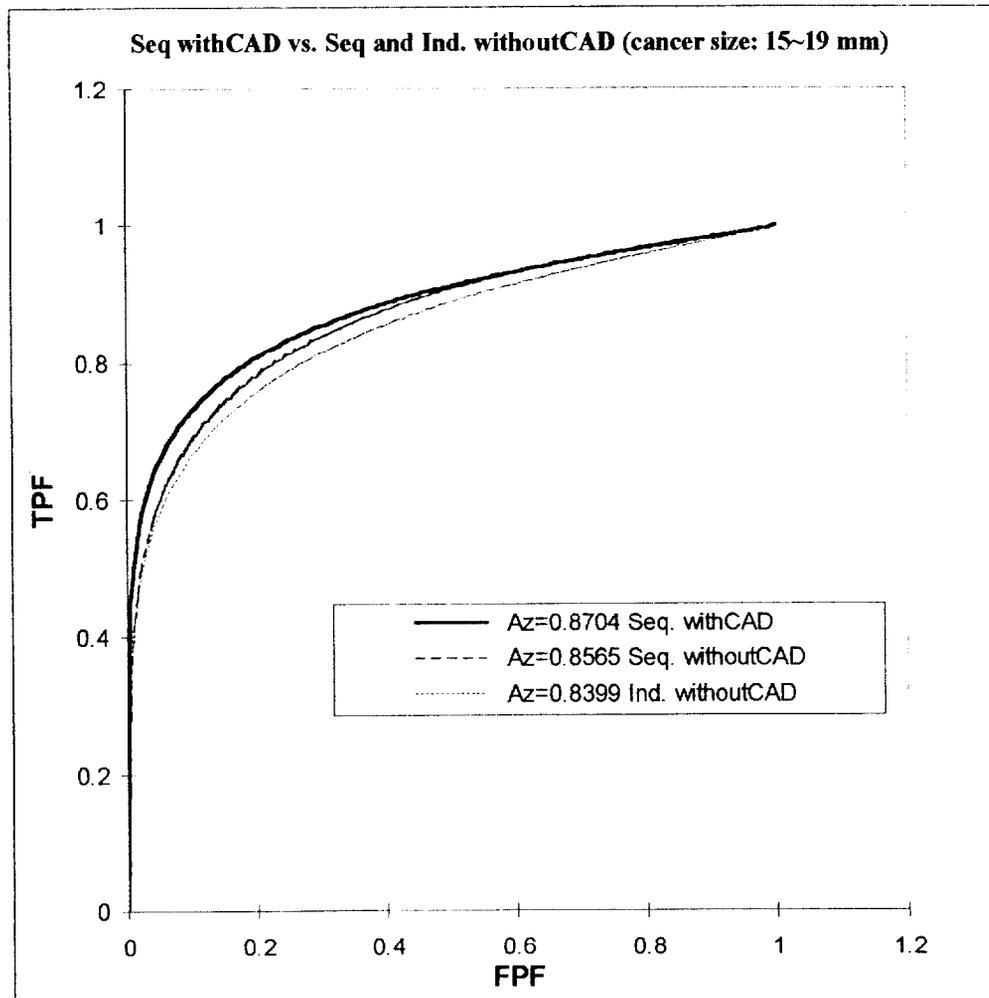


Chart 4: The ROC curves for each of the three reading conditions for the cancer cases that measured 15 to 19 mm and all normal cases with combined results for all radiologists.

In Chart 4, the results show that there is some improvement in the detection of mid sized lung cancers with the assistance of RapidScreen™ RS-2000, but statistical significance is shown only when comparing the independent reading with the reading assisted with RapidScreen™ RS-2000. Thus improvement is shown comparing the standard clinical practice in which no computer assistance is given to the situation where computer assistance by RapidScreen™ RS2000 is provided. Statistical significance is not shown when the radiologists are reading with a higher degree of alertness knowing that the computer information would be immediately available.

Safety Considerations in the Use of the RapidScreen™ RS2000

Safety was shown by demonstrating that the failure of the RapidScreen™ System to detect the cancer had only an average 1% effect (0.26 case average per radiologist in machine negative cases) in decreased cancer detection in the machine false negative cases and that for all but one reader, this was offset by the improved detection rate of cancers that occurred in machine positive cases. Only one reader decreased his /her overall detection rate when using RapidScreen™ RS-2000 system and this was a minimal decrease.

Cost-Benefit information was provided. Analysis of the study data showed that radiologists using RapidScreen™ exhibited only a small increase in false positive detections on cancer-free films. In this study, for each two additional cancer cases detected, one additional CT would be performed in a patient without cancer. In previously reported screening trials, an average of 18 patients without cancer had indeterminate or suspicious findings resulting in further evaluation for each cancer detected. One additional CT for two cancers detected is a very low cost for high patient benefit and is a very low ratio of additional workup compared to the prior reported lung cancer screening trials.

11.0 Conclusions Drawn from Studies

1. The RapidScreen™ RS-2000 system can detect solitary pulmonary nodule in chest radiographs, an important indication of early-stage lung cancer.
2. A physician using RapidScreen™ RS-2000 system can increase the detection of T1 early-stage lung cancer 9-27 mm in size in chest x-ray radiographs:
 - A. A physician can detect more T1 early-stage lung cancer 9-14 mm in size with the RapidScreen™ RS-2000 aid than without the RapidScreen™ RS-2000 aid.
 - B. A physician can detect more T1 early-stage lung cancer 15-19 mm in size with the RapidScreen™ RS-2000 aid than without the RapidScreen™ RS-2000 aid.
3. Physicians using RapidScreen™ RS-2000 system can reduce the likelihood of missing small (T1) lung cancers, most of which are early-stage lung cancers.

12.0 Panel Recommendation

(To be completed by FDA)

13.0 CDRH Decision

(To be completed by FDA)

14.0 Approval Specifications

(To be completed by FDA)

generated by the *RapidScreen*™ RS-2000 system with the ROIs marked. The physician then re-evaluates the original chest radiographs, paying particular attention to the regions corresponding to the ROIs on the images and re-assesses the original interpretation, if necessary. The *RapidScreen*™ RS-2000 system has been shown in clinical trials to assist radiologists in increasing the detection of small primary lung cancers.

3. Contraindications

There are no contraindications for use of the device.

4. Warnings

Warnings: Radiological Interpretation

- The physician should perform interpretation only upon the films and not the markers shown on the *RapidScreen*™ RS-2000 output (paper printout or video monitor display).
- The device is a detection aid, not an interpretive or diagnostic aid. It should be used only after the first reading by physician.
 - The device marks regions that contain lung nodules and others that do not represent lung nodules, and thus the radiologist must still use his/her interpretative skills on regions marked by the device.
 - The device will not enhance what the user sees; rather it helps to identify regions on chest radiographs that should be reexamined.
- The device will not identify all areas that are suspicious for cancers.
 - The device will miss some lung nodules and a user should not be dissuaded from working up a finding if the device fails to mark that site.
 - The device is not designed to detect lung nodules in lateral view chest radiographs.
 - Conditions of film quality that diminish chest radiographic sensitivity, such as under- or over-exposed films, also diminish the sensitivity of the device.
- Physician's individual practice patterns may influence the results obtained when using this device. Therefore, each facility and physician should carefully monitor the results that this device has on their practice of chest radiography in order to optimize its effectiveness.

Warnings: Device Operation

- Remove all potentially obstructive objects before loading the films in the digitizer, motorized viewer, and light box to prevent the possibility of injury due to moving parts or damage to the device.
- Ensure that the device is connected to a power receptacle that is properly grounded and provides voltage and current within the specifications of the device to prevent the possibility of electrical shock or fire hazard.

- Do not place liquid containers on the device. In the event of a spill, shut down power to all components prior to cleaning to prevent the possibility of electrical shock. Do not operate the device if internal components are exposed to liquids. Contact authorized Deus Technologies service personnel.
- While adjusting the position of the video monitor by moving the articulated arm, use both hands to hold both ends of the video monitor panel. Avoid moving the video monitor too close to the digitizer to prevent damage to the monitor, digitizer, or both.

Warnings: Installation and Maintenance

- Shut down power to all components prior to cleaning to prevent the possibility of electrical shock.

5. Precautions

Precautions: Device Operation

- Operators should review the User Manuals and receive training as required before using the device.
- To ensure proper device operation, use only barcode labels readable by the barcode reader of the device.
- In order for the displayed annotated images produced by the device to correctly correspond to the film position at the motorized viewer or light box, be certain to orient the film correctly when scanning, as per instruction in the User Manuals.
- For proper operation of the device:
 - The quality of the original chest radiographs (e.g. contrast) should meet relevant chest radiography standards and be acceptable to the physician.
 - The device should only be used on PA or AP view of chest radiographic with films size of 14" x 17" or 14" x 14".
 - No lateral view films can be processed.
 - Do not attempt to place films in the scanner that are bent or damaged, as they may jam.
- To prevent damage to the device, shut down the device according to the procedures recommended in the Operator's Manuals.

Precautions: Installation and Maintenance

- This device contains one user serviceable part – the laser printer. The user needs to regularly check and replace toner and add paper to the laser printer. Contact Deus Technologies for any other problems.

- To prevent damage to the device, do not attempt to install or repair the *RapidScreen™* RS-2000 System. Only trained personnel, authorized by Deus Technologies, are qualified to install or repair the device. For service training, contact Deus Technologies at 301-762-4442.
- To prevent damage to the device, maintain equipment in a well-ventilated, air-conditioned environment.
- Disconnect power cord before moving or servicing.

6. Adverse Effects

There are no known direct risks to safety or health caused by, or related to the use of the device. The indirect risks are that the device may fail to identify and mark some actionable lesions and will mark some lesions that do not require further action (See Warnings above). The primary potential adverse effect in a chest x-ray examination is missing lung cancer; however, the potential for missed cancer is not increased when the *RapidScreen™* RS-2000 system is used as labeled.

7. Brief Description of Functions of *RapidScreen™* RS-2000

The *RapidScreen™* RS-2000 system's algorithms look for characteristics commonly associated with lung nodules. The system ranks its findings by likelihood and then marks those regions above a fixed threshold of likelihood. The following sections describe the algorithms used by the *RapidScreen™* RS-2000 when analyzing a chest image.

The *RapidScreen™* RS-2000 system searches a chest image for round-shape opacity structures (with diameter smaller than 30 mm), which may be indicative of lung nodules. When the features associated with such a structure in the chest image meet the generally accepted criteria for a lung nodule, the system places a marker (currently using a circle with 2.5 cm in radius corresponding to the scale of the original film) over the centroid of that structure on the image as shown in Figure 1.



Figure 1. Examples of marked lung nodules.

The system has been designed to mark only image patterns associated with lung nodules. However, normal anatomical structures (such as rib crossings and end-on vessels) in the chest image sometimes satisfy the algorithms' criteria for lung nodules and also will be marked, as shown in Figure 2.

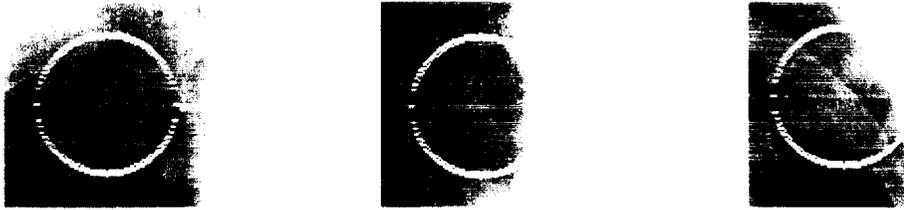


Figure 2. Examples of normal structures that can be marked as potential lung nodules.

By design, the system will not mark objects that are larger than 30 mm in diameter on the original films. The software algorithms have been optimized to identify image patterns of round-shape with 7 to 30 mm in size.

To interpret a case, the radiologist first reviews the chest radiographs for initial interpretation in the conventional manner. The radiologist then may refer to the results from the *RapidScreen*™ RS-2000 system (i.e., the corresponding printouts with marked ROIs that may have characteristics similar to SPNs). The radiologist must go back to the original films and pay particular attention to these areas associated with the ROIs on the *RapidScreen*™ RS-2000 printouts, and re-assesses his/her original interpretation, if necessary. The *RapidScreen*™ RS-2000 thus functions as an aid to radiologists in reviewing chest radiographs by calling attention to regions of interest.

8. Clinical Study

Deus Technologies has conducted two comprehensive clinical studies in order to demonstrate the effectiveness and safety of the *RapidScreen*™ RS-2000 system when it is used as a computer aided detection (CAD) tool to assist radiologists to detect early-stage lung cancers from chest radiographs.

Purpose

The trials are to prove the efficacy and safety of the *RapidScreen*™ RS-2000 system when it is used as a CAD tool to assist physicians in the detection of early-stage lung cancers from chest radiographs.

Periods and Site

There are two phases of clinical trials conducted at Division of Imaging Sciences and Information System (ISIS), Department of Radiology, Georgetown University Medical Center from 1998 to 2000: a Pilot study and a full-scale double-blinded Receiver Operating Characteristics (ROC) study.

Clinical Trials

Phase I Trial: Pilot Study

In the Pilot study, 180 normal (cancer-free) cases and 20 early-stage lung cancer cases (size ranging from 10 to 30 mm) were collected from a large-scale prospective lung cancer-screening project. The cancer cases included those that had been found by two original radiologists (14 cases) and other more subtle cases that had been missed by the two original radiologists (6 cases). The subtle lung cancers in the six cases are confirmed

retrospectively by expert thoracic radiologists in the pilot study based on medical records and follow-up films from that screening project. In this Pilot study, 10 study radiologists were recruited to read the films.

The ten study radiologists were able to detect 55 to 75% of the 20 cancers. The *RapidScreen™* RS-2000 system detected 2 to 4 additional cases of cancer that the study radiologists had missed so that if the study radiologists were to use the information from the *RapidScreen™* RS-2000, they would increase the number of cancer cases detected by 8 to 16 percent (potential improvement on cancer detection sensitivity). Among the subset of those six cancers that had be originally missed by two screening radiologists, the study radiologists now detected either one or two of the six cases, whereas the *RapidScreen™* RS-2000 detected four of these cases. Combining the *RapidScreen™* RS-2000 and study radiologist's performances, each study radiologist could have a potential improvement in detecting two or three additional cancers. Thus use of the *RapidScreen™* RS-2000 could provide 33% to a 50% improvement in sensitivity for cancer detection for the radiologists on the more subtle cases. Among 180 normal cases, it was also found that the unnecessary work-up rate changes from 16.8% to 15.9% when *RapidScreen™* RS-2000 system was used as an aid in lung cancer detection. Such a change is statistically insignificant.

In summary, it was found that:

- *RapidScreen™* RS-2000 system could potentially improve radiologists' sensitivities by 8% to 16% in detection of overall early-stage lung cancers;
- *RapidScreen™* RS-2000 system could potentially provide 33% to 50% improvement of sensitivity for radiologists in detection of more subtle early-stage lung cancers; and
- The unnecessary work-up rate for radiologists remains unchanged when *RapidScreen™* RS-2000 system was used as an aid to detect early-stage lung cancer.

Phase 2 Trial: Double-blind ROC study

The ROC Study was designed to test three hypotheses: A primary hypothesis and two secondary hypotheses. The primary hypothesis was that radiologists using *RapidScreen™* RS-2000 would increase their detection of lung cancers 9-30 mm in size. The secondary hypotheses were that radiologists using *RapidScreen™* RS-2000 would increase their detection of lung cancers that had previously been missed by two screening radiologists and that they would increase their detection of lung cancers 9-14 mm in average diameter. To evaluate these three hypotheses Receiver Operator Characteristic (ROC) analysis was used. A total of 240 cases were collected from a large-scale prospective lung cancer-screening project, 80 cancer cases and 160 cancer free cases. The 80 cancer cases are primary lung cancer cases 9.5 to 27 mm in size, each proven pathologically and confirmed by an Expert Panel in this ROC study. Of the 80 cancer cases, 62 were cases that one or both former screening radiologists had either detected or suspected at the time of the original reading and are called *Current Cancer Cases* (see clinical trial protocol DEUS.DOC 99-04). 18 were cases that were originally missed by both former screening radiologists, but could be seen in retrospect and confirmed by the Expert Panel in this

clinical trial. These 18 cases are called *Actionable Prior Cancer Cases*. These cancer cases were intermixed using computer pseudorandomization methods with the 160 cancer free cases. These cancer free cases are randomly drawn from the same screening project of heavy smokers and had been shown to be cancer free by at least three years of clinical follow-up and usually by at least two years of cancer free chest radiographs. The 240 cases were interpreted by 15 study radiologists (observers) certified by the American Board of Radiology. Each study radiologist interpreted the original films initially without RapidScreen™ RS-2000 assistance. Then, a minimum of one month later, reinterpreted them in the so called sequential ROC test (See Section III-B, *Clinical Study of the Effectiveness and Safety of RapidScreen™ RS-2000 System – Summary*) in which each film was interpreted without the RapidScreen™ RS-2000 assistance first and then re-interpreted with the system assistance. The MultiReader MultiCase (MRMC) ROC method of Dorfman, Berbaum, and Metz was then used for statistical calculation.

The following summarizes the detection performance of RapidScreen™ RS-2000 system:

Cancer Detection Sensitivity

The RapidScreen™ RS-2000’s cancer detection sensitivity in the ROC study is shown in Chart 1.

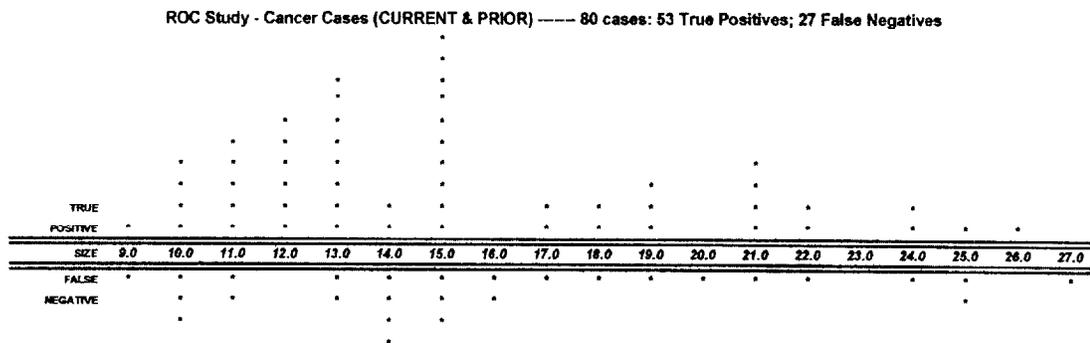


Chart 1 shows the cancer cases sorted by size along the x-axis. The marks above and below the double lines indicate machine performance. The marks above the line indicate machine detection, those below the line, machine false negative. The RapidScreen™ RS-2000 System detected 53 of the total 80 cancers (66 %) and 26 of 38 cancers (68%) 9-14 mm in size.

False Positives per Image

The RapidScreen™ RS-2000 System placed 1321 marks on the 240 cases included in the ROC study. 53 of these marks were on cancer locations. Therefore 1268 marks were false positive locations. $1268/240 = 5.3$ false positive marks on average per image.

The following are described the results obtained from the ROC study:

Hypothesis 1: Radiologists using RapidScreen™ RS-2000 will improve their performance in the detection of lung cancer 9-27 mm in size.

Table 1. Comparison of radiologists' performance parameters in the detection of lung cancers 9 – 27 mm is size during the Independent ROC and Sequential ROC (with and without RS-2000 aid) tests.

DBM's MRMC Analysis	unaided Az	Seq. with CAD Az	p	95% CIs
Sequential with CAD vs. Independent without CAD	0.8288	0.8654	0.0058	(-0.062, -0.011)
Sequential with CAD vs. Sequential without CAD	0.8347	0.8654	<0.0001	(-0.045, -0.017)

Legend:

Az = Area under the ROC curve

95% CI = 95% confidence interval

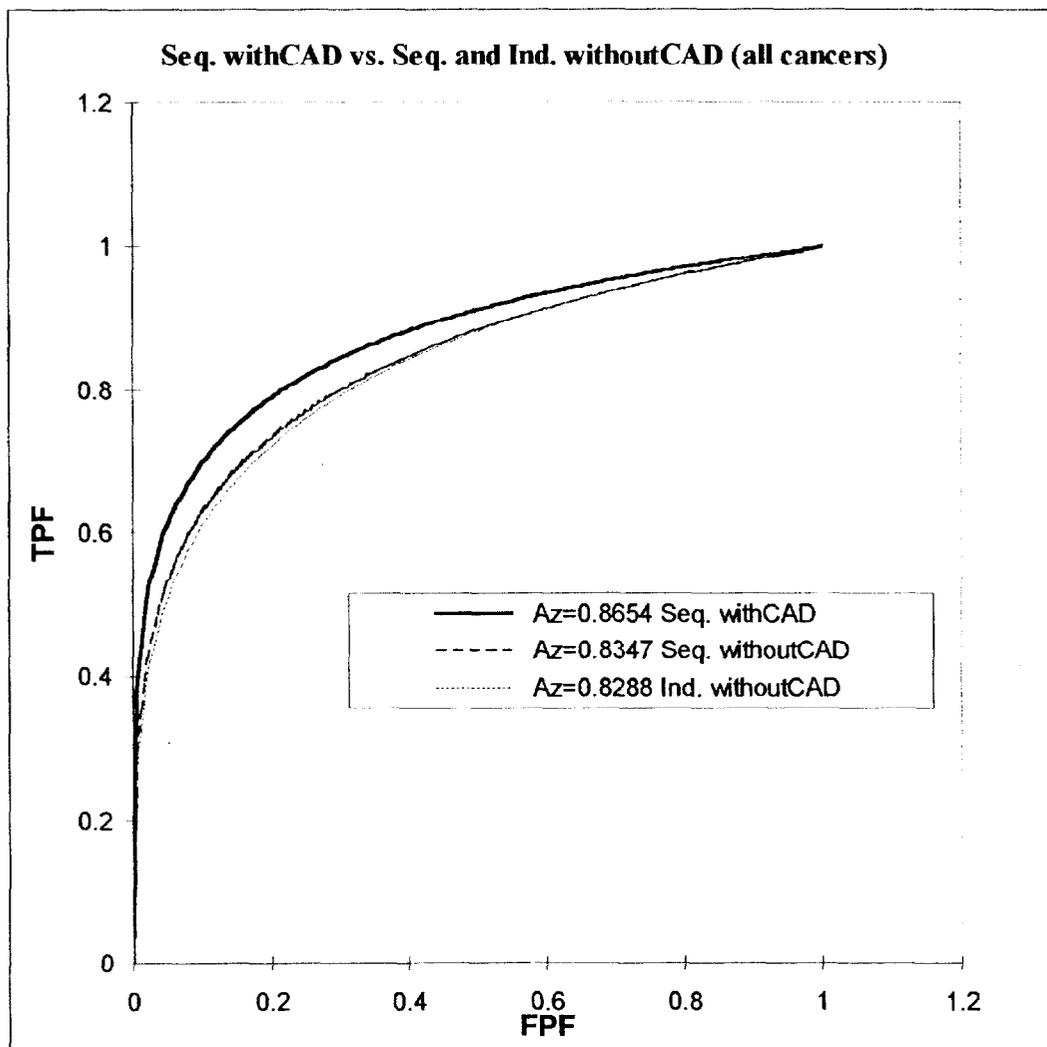


Chart 2: This chart presents the ROC curves for each of the three reading conditions for all cancer cases and all normal cases with combined results for all radiologists.

These results confirm Primary Hypothesis (1). Two different comparisons were made in this plot (Chart 2). In the first, the first reading of the radiologists (Independent Without CAD) was compared to their interpretations with *RapidScreen*™ RS-2000 in the second read (Sequential with CAD). The Az during the first read (Independent without CAD) was 0.8288 and in the second read with *RapidScreen*™ RS-2000 was 0.8654. This improvement has a p of 0.0058. The second comparison was with the sequential reading in which the radiologists used the *RapidScreen*™ RS-2000 in its recommended clinical use pattern (i.e., Sequential with CAD vs. Sequential without CAD). In this comparison, the Az of the reading without *RapidScreen*™ RS-2000 was 0.8347 and with *RapidScreen*™ RS-2000 was again 0.8654. The $p < 0.0001$. It is noted that the two curves corresponding to without computer assistance are not statistically significant ($p=0.6$), even though the curve corresponding to Sequential without CAD is higher than that Independent without CAD. This increase of Az value is, we believe, mainly due to the higher alertness in the sequential test mode.

The difference seen between the Az is greater comparing the first read vs. with *RapidScreen*™ RS-2000 compared to the sequential read, but the p value is larger. This is likely due the greater standard deviation of scores seen among radiologists in the first read (radiologist current practice) for both the cancer and normal cases than in the second read without *RapidScreen*™ RS-2000. This might suggest that radiologists' detection performance might be less variable when they work with computer assistance.

Hypothesis 2: Radiologists using *RapidScreen*™ RS-2000 will increase their detection rate of cancers originally missed by two screening radiologists prospectively.

Table 2. Comparison of radiologists' performance parameters in the detection of lung cancers originally missed by two screening radiologists prospectively during the Independent ROC and Sequential ROC (with and without RS-2000 aid) tests.

DBM's MRMC Analysis	unaided Az	Seq. with CAD Az	p	95% CIs
Sequential with CAD vs. Independent without CAD	0.7231	0.7443	0.4268	(-0.074, 0.031)
Sequential with CAD vs. Sequential without CAD	0.7022	0.7443	0.0299	(-0.08, -0.0041)

Legend:

Az = Area under the ROC curve

95% CI = 95% confidence interval

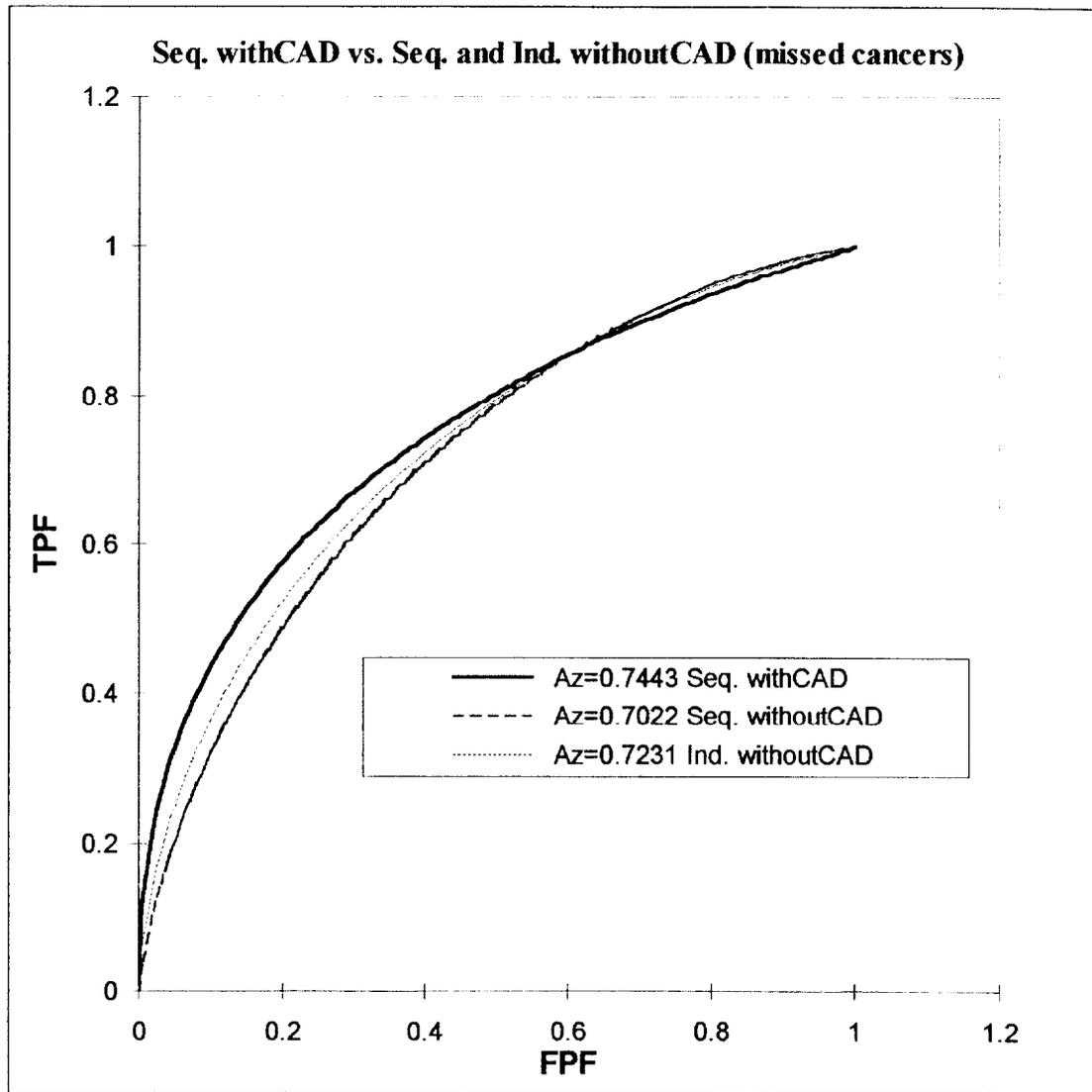


Chart 3: This chart presents the ROC curves for each of the three reading conditions for the cancer cases that were originally prospectively missed and all normal cases with combined results for all radiologists.

In Chart 3, the results show that the use of *RapidScreen*™ RS-2000 resulted in an increase in Az for cases (*Actionable Priors*) originally missed by radiologists. The p value (0.03) for sequential test is small enough to indicate that this increase in Az is significant. However, the increase of Az comparing the independent reading to the reading with *RapidScreen*™ RS-2000 assistance is not significant (p=0.4). This may be due to larger reader variation in first reading and small sample size for the missed cancer cases (18 *Actionable Prior* cases). These results support the Secondary Hypothesis 2 showing that radiologists using *RapidScreen*™ RS-2000 detect more cancers in a group where the cancers had been prospectively missed by two radiologists.

Hypothesis 3: That radiologists using *RapidScreen*™ RS-2000 will increase their detection of cancers 9 to 14 mm in size.

Table 3. Comparison of radiologists' performance parameters in the detection of lung cancers 9 – 14 mm is size during the Independent ROC and Sequential ROC (with and without RS-2000 aid) tests.

DBM's MRMC Analysis	unaided Az	Seq. with CAD Az	p	95% CIs
Sequential with CAD vs. Independent without CAD	0.7975	0.8477	0.0161	(-0.09, -0.01)
Sequential with CAD vs. Sequential without CAD	0.8002	0.8477	0.0005	(-0.073, -0.022)

Legend:

Az = Area under the ROC curve

95% CI = 95% confidence interval

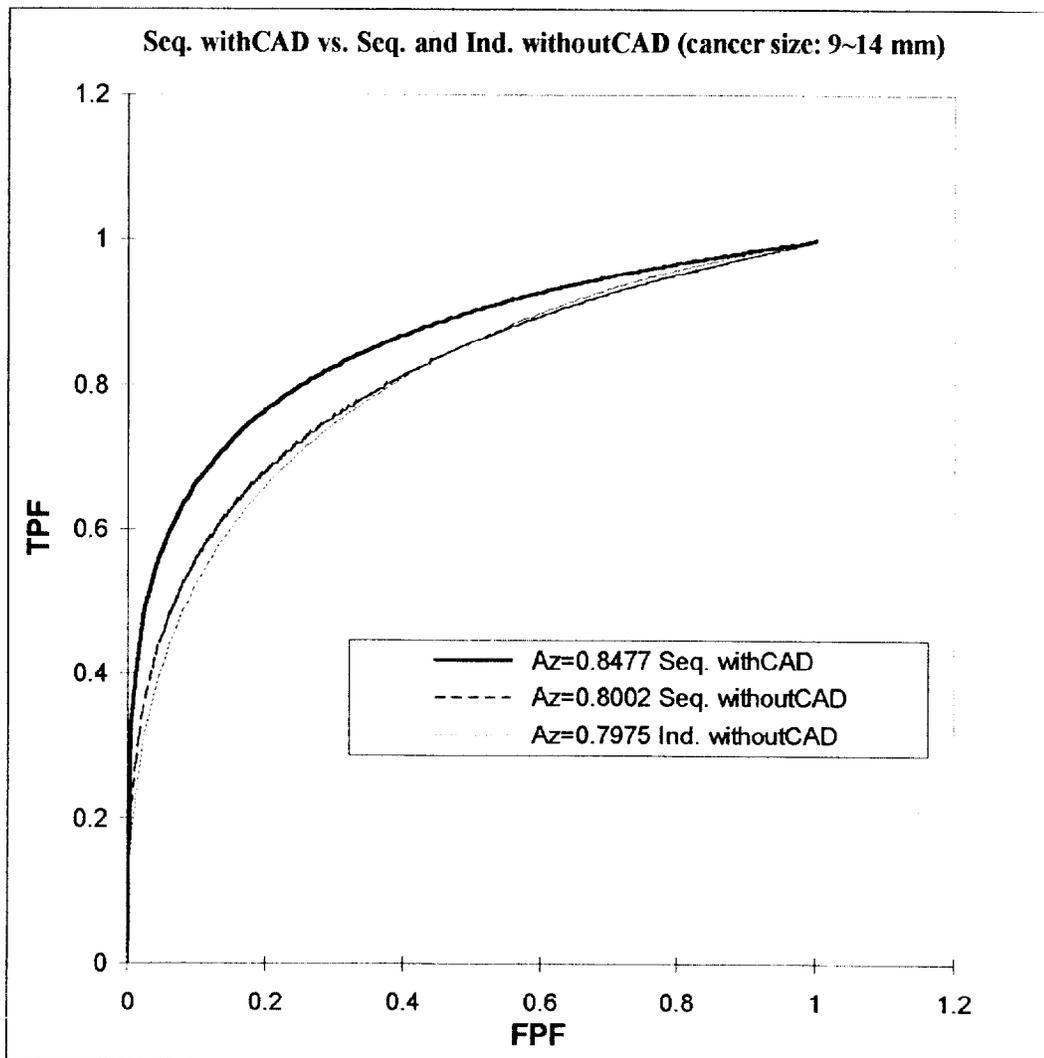


Chart 4: This chart presents the ROC curves for each of the three reading conditions for the cancer cases that measured 9.5 to 14 mm and all normal cases with combined results for all radiologists.

In Chart 4, the results support Hypothesis 3 and show that *RapidScreen*™ RS-2000 increases the detection of small lung cancers and that these results are highly statistically significant.

In addition, we looked at the detection improvement for nodules 15-19 mm in size.

Table 5. Comparison of radiologists' performance parameters in the detection of lung cancers 15 - 19 mm is size during the Independent ROC and Sequential ROC (with and without RS-2000 aid) tests.

DBM's MRMC Analysis	unaided Az	Seq. with CAD Az	p	95% CIs
Sequential with CAD vs. Independent without CAD	0.8399	0.8704	0.0452	(-0.06, -0.0007)
Sequential with CAD vs. Sequential without CAD	0.8565	0.8704	0.2389	(-0.037, 0.009)

Legend:

Az = Area under the ROC curve

95% CI = 95% confidence interval

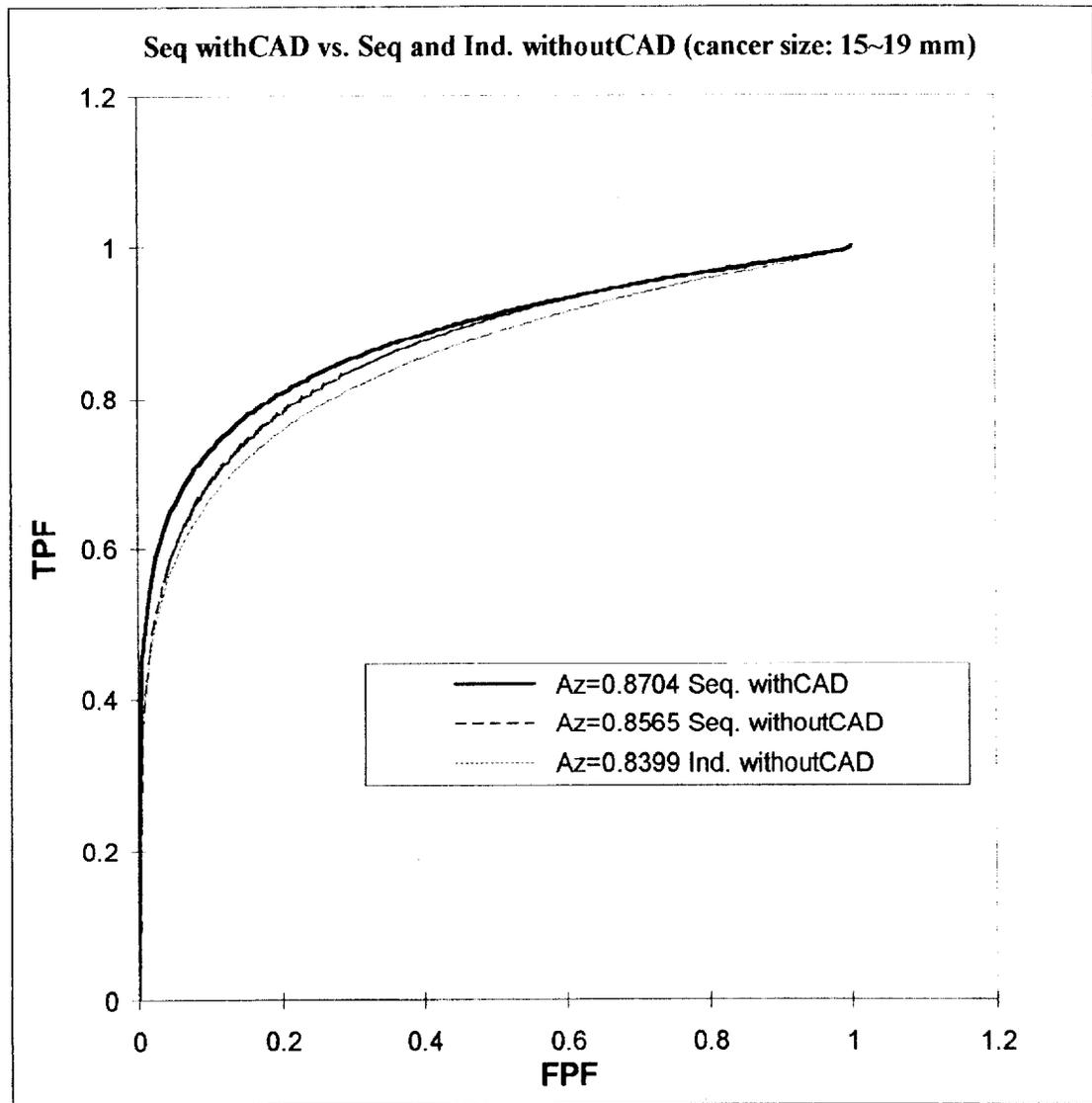


Chart 5: This chart presents the ROC curves for each of the three reading conditions for the cancer cases that measured 15 to 19 mm and all normal cases with combined results for all radiologists.

In Chart 5, the results show that there is some improvement in the detection of mid sized lung nodules with the assistance of *RapidScreen™* RS-2000, but statistical significance is shown only when comparing the independent reading with the reading assisted with *RapidScreen™* RS-2000. Thus, improvement is shown comparing the standard clinical practice in which no computer assistance is given to the situation where computer assistance by *RapidScreen™* RS-2000 is provided. It is not shown when the radiologists are reading with a higher degree of alertness knowing that the computer information would be immediately available.

9. Conformance to Standards

The *RapidScreen*™ RS-2000 System is under testing for the compliance with the following Electrical Safety and EMC Standards:

UL2601-1
FCC Part 15 Class A

10. How Supplied

Standard configuration for the *RapidScreen*™ RS-2000 system includes the following major components:

- Processor (containing the bar code reader, keypad, CCD film digitizer and processing computer)
- Display (containing a laser printer and a video monitor)

11. Operator's Manual

The following manuals are provided with the *RapidScreen*™ RS-2000 system:

RapidScreen™ RS-2000 User Manual – Describes how to handle films for digitization and processing by the *RapidScreen*™ RS-2000 system.

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