SUMMARY OF SAFETY AND EFFECTIVENESS DATA

1. General Information

Device Generic Name:	Analyzer, Medical Image
Device Trade Name:	*RapidScreen*™ RS-2000
Applicant's Name and Address:	Deus Technologies, LLC. 1700 Research Blvd. Suite 104 Rockville, MD 20850
PMA Number:	P000041
Date of Panel Recommendation:	March 5, 2001
Date of Approval to Applicant:	July 12, 2001

2. Indications for Use

The *RapidScreen*™ RS-2000 is a computer-aided detection (CAD) system intended to identify and mark regions of interest (ROIs) on digitized frontal chest radiographs. It identifies features associated with solitary pulmonary nodules from 9 to 30 mm in size, which could represent early-stage lung cancer. The device is intended for use as an aid only after the physician has performed an initial interpretation of the radiograph.

3. Contraindications

There are no contraindications for use of this device.

4. Warnings and Precautions

See Essential Prescribing Information.

5. Device Description

The RS-2000 algorithm consists of the following features: (1) use of 87 proprietary cancer and non-cancer descriptive feature parameters derived from clinical and image information; (2) use of patented multi-resolution analysis approach to detect various sizes, contrasts, and conspicuities of suspects; and (3) use of patent-pending multiple-stage classification processes including heuristic decision rules, artificial neural network, and fuzzy logic for accurate classification. The RS-2000 algorithm was developed based on the following database: (1) more than 1,000 chest radiographs containing T1 lung cancer confirmed by CT, follow-up, or biopsy and (2) more than 10,000 cancer-free chest x-ray images, confirmed with 3-10 years of follow-up.

The 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 RS-2000 system, the

7

operator inserts the chest radiograph into the film digitizer and uses the bar code reader or keypad to input the film ID. The CCD digitizes the film, and the RS-2000 algorithms process the digital image, detecting and marking ROIs with characteristics similar to SPNs. The analysis results generated by the 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 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 RS-2000 when analyzing a chest image.

The RS-2000 system searches a chest image for round-shaped opaque structures with a diameter smaller than 30 mm (in the scale of the original film), characteristics that may be indications 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 25 mm in radius in the scale of the original film.

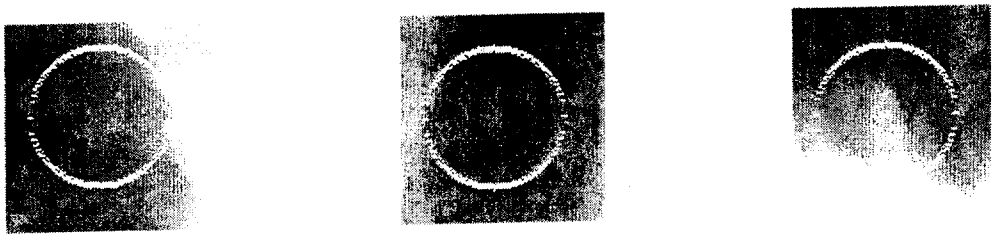

Figure 1. Examples of marked lung nodules.

The system has been designed to mark only image patterns associated with lung nodules. However, normal anatomical structures in chest images, 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.

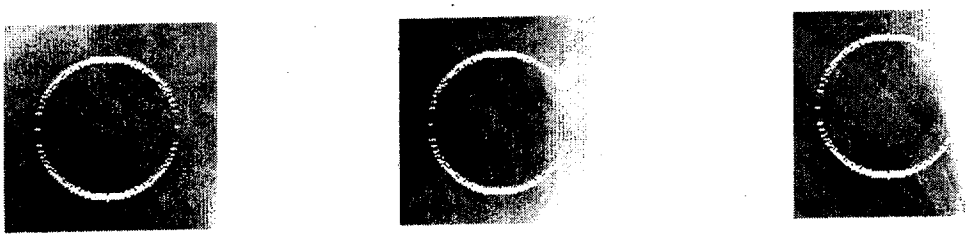

Figure 2. Examples of normal structures that may be marked as potential lung nodule.

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

To interpret a case, a physician first reviews the chest radiographs for initial interpretation in the conventional manner. The physician then refers to the results from the 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 RS-2000 functions as an aid to physicians, a "second opinion" in reviewing chest radiographs, by calling attention to the ROIs.

6. Alternative Practices and Procedures

The current method of detecting SPNs is the review of plain chest radiographs or CT examinations.

7. Marketing History

The RS-2000 system has not been marketed anywhere in the world.

8. Potential Adverse Effects of Device on Health

There are no known direct risks to safety or health of the patient caused by, or related to, the physical use of the RS-2000 system. The indirect risks are that 1) the physician may be dissuaded from working up an earlier finding if the device fails to mark that site, thus missing a possible cancer, or 2) the physician may be misled into working up a benign finding that would not otherwise have been acted upon.

9. Non-Clinical Studies

Non-clinical studies were designed and conducted to develop, analyze, and improve the design of the RS-2000 System. In-depth design reviews 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 RS-2000 System.

System Reproducibility

Deus Technologies conducted an investigation of the reproducibility of each software module and hardware component.

Deus Technologies also conducted a study to test the reproducibility of the RS-2000 System. The results, expressed in terms of the variability of device sensitivity for the detection of T1 lung cancer, were a mean device sensitivity of 80% with a standard deviation of 4.5%. The standard deviation of device sensitivity is due to the variability in the process of digitizing the images. Reproducibility for each single set of digitized data is perfect; i.e., the standard deviation is zero for this part of the processing.

Safety

The RS-2000 System was tested and found to be in compliance with:

Underwriter's Laboratories safety requirements UL3101
FCC Part 15 Class A computing device
ESD Immunity Testing to IEC1000-4-2: 1995
RF Immunity Testing to IEC1000-4-3: 1995
EFT Immunity Testing to IEC1000-4-4: 1995
Surge Immunity Testing to IEC1000-4-5: 1995
RF Common Mode Immunity Testing to IEC1000-4-6: 1996
Voltage Dips & Interruptions Immunity Testing to IEC1000-4-11: 1994

Software Validation

Deus Technologies provided documentation showing that the software used in this device was developed under an appropriate software development control program and procedures. All identified hazards were addressed and the software was validated.

10. Clinical Studies

Since the device is never in the vicinity of the patient, there are no direct safety issues for the patient. Effectiveness was assessed in terms of a risk-benefit ratio, thereby assessing indirect safety issues as well. Clinical studies of the RS-2000 were designed to determine improvement (over unaided readings) in sensitivity (i.e., cancer detection, or increase in true positives) compared to increase in work-ups of lesions that turn out to be benign (i.e., in false positives).

Deus Technologies conducted two phases of clinical studies to demonstrate the effectiveness and safety of the RS-2000 system. These studies were conducted using radiographs from male heavy smokers, 45 years of age or older, with a high risk for cancer.

The clinical studies were conducted at the Imaging Sciences and Information System (ISIS) Research Center, Department of Radiology, Georgetown University Medical Center, from 1998 to 2000, and consisted of a pilot study and a full-scale double-blinded Receiver Operating Characteristics (ROC) study.

Pilot Study

A pilot study was performed to gather data necessary to design the pivotal study. In it, 180 normal (cancer-free) cases and 20 T1 lung cancer cases (size ranging from 10 to 30 mm) were selected from a large-scale prospective lung cancer-screening project on male heavy smokers over 45 years of age, performed in the 1970s at the Mayo Clinic, Johns Hopkins University, and Memorial Sloan-Kettering, in which every chest radiograph was read by two radiologists. This project contained over 10,000 cases, (with each case consisting of chest radiographs taken for 5 consecutive years). The cancer cases selected included 14 that had been found by at least one of the two original radiologists and 6 other more subtle cases that had been missed by both. The chest radiographs from the 6 missed cases were confirmed retrospectively to contain visible lung cancers by a panel of radiologists based on medical records and follow-up films from the screening project. Ten radiologists read the films, independently and blinded as to subsequent diagnosis and outcome. The results of this study were used to plan the pivotal study.

Pivotal Study

The pivotal study was designed to test three hypotheses, one primary and two secondary.

- Radiologists using the RS-2000 will increase their ROC performance for primary lung cancers **up to 30 mm** in diameter.
- Radiologists using the RS-2000 will increase their ROC performance for primary lung cancers up to 30 mm in diameter that had previously been **missed** by both screening radiologists (called *Actionable Priors* or simply *Priors).*
- Radiologists using the RS-2000 will increase their ROC performance for primary lung cancers **9 to 15 mm** in average diameter (smaller cancers).

A set of 240 study cases, consisting of 80 cancer cases and 160 non-cancer cases, were chosen from the same prospective lung cancer-screening project as was used in the pilot study.
The 80 cancer cases were primary lung cancers, from different patients, with lesions 9.5 to 27.5 mm in size, each proven pathologically by biopsy with location confirmed by a panel of radiologists. Of these 80 cancers, 62 (77%) were cases where one or both screening radiologists had either detected or suspected cancer at the time of the original reading. These cases are referred to as *Currents*. The other 18 (23%) cases (*Priors*) were originally missed by both screening radiologists, but could be seen in retrospect by the panel of radiologists.

All 80 cancer cases were intermixed with the 160 cancer-free cases using a computer randomization method. These cancer free cases were randomly drawn from the same screening project 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.

A group of 15 community board-certified radiologists interpreted these study cases. Each of the 15 initially interpreted all 240 films without RS-2000 (RS) assistance (called *Independent-without-RS*). Then, after at least one month to minimize recall, they re-interpreted the 240 cases in the two-part so-called *Sequential ROC Test*, in which each chest radiograph was interpreted

11

first without RS assistance (referred to as *Sequential-without-RS*) and then immediately thereafter was re-interpreted with the system's assistance (*Sequential-with-RS*).

Device Cancer Detection Sensitivity

The RS-2000 System detected 66% of the total cancers (9.5 – 27.5 mm in size) and 68% of cancers 9.5-15 mm in size.

False Positives for Lung Cancer per Image

The RS-2000 System placed 1321 marks on the 240 cases included in the ROC study. Of these, 53 marks were on cancer locations. Therefore 1268 marks were false positives, for an average of 1268/240 = 5.3 false positive marks for lung cancer per image.

Results Obtained from the ROC Study

The MultiReader MultiCase (MRMC) ROC method of Dorfman, Berbaum, and Metz (*Receiver Operating Characteristic Rating Analysis: Generalization to the Population of Readers and Patients with the Jackknife Method.* Investigative Radiology 1992; 27:723-731.) was used for statistical analysis of the three reading conditions (Independent-without-RS, Sequential-without-RS, and Sequential-with-RS).

The results for the primary and two secondary hypotheses are presented in Tables 1 through 3 and Charts 1 through 3, respectively.

Table 1. Comparison of radiologists' ROC performance in the detection of lung cancers 9.5–27.5 mm in size.

Comparison	Az Without RS	Az With RS	Improve-ment	95% Confidence Interval	P
Sequential-with-RS vs. Independent-without-RS	0.8288	0.8654	0.0366	(0.011,0.062)	0.0058 v.s.
Sequential-with-RS vs. Sequential-without-RS	0.8347		0.0307	(0.017,0.045)	<0.0001 v.s.

Az = Area under the ROC curve
RS = RS-2000 System
Improvement = (Az With RS) - (Az Without RS)
95% Confidence Interval = 95% CI of Improvement
v.s. = Very significant

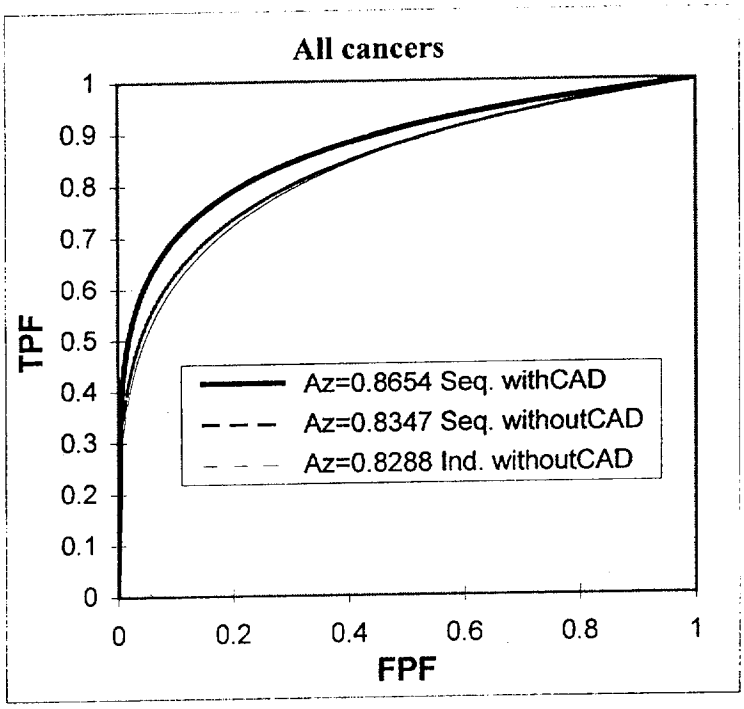

Chart 1: The ROC curves for each of the three reading conditions, for all cancer cases and all normal cases, with combined results for all radiologists. (TPF = True Positive Fraction and FPF = False Positive Fraction)

Table 1 and Chart 1 confirm the primary hypothesis above. While not shown in the Table or Chart, the radiologists' sensitivity increased by 7% (from an averaged radiologists' sensitivity of 71% in Independent-without-RS to 78% when RS was used as an aid in Sequential-with-RS) with concomitant increase of false positive fraction from 21% to 22%.

Table 2. Comparison of radiologists' ROC performance in the detection of lung cancers originally missed by the two screening radiologists.

Comparison	Az Without RS	Az With RS	Improve-ment	95% Confidence Interval	p
Sequential-with-RS vs. Independent-without-RS	0.7231	0.7443	0.0212	(-0.031,0.074)	0.4268 n.s.
Sequential-with-RS vs. Sequential-without-RS	0.7022		0.0421	(0.0041,0.08)	0.0299 sig.

Az = Area under the ROC curve
RS = RS-2000 System
Improvement = (Az With RS) - (Az Without RS)
95% Confidence Interval = 95% CI of Improvement
n.s. = non-significant
sig. = Significant

13

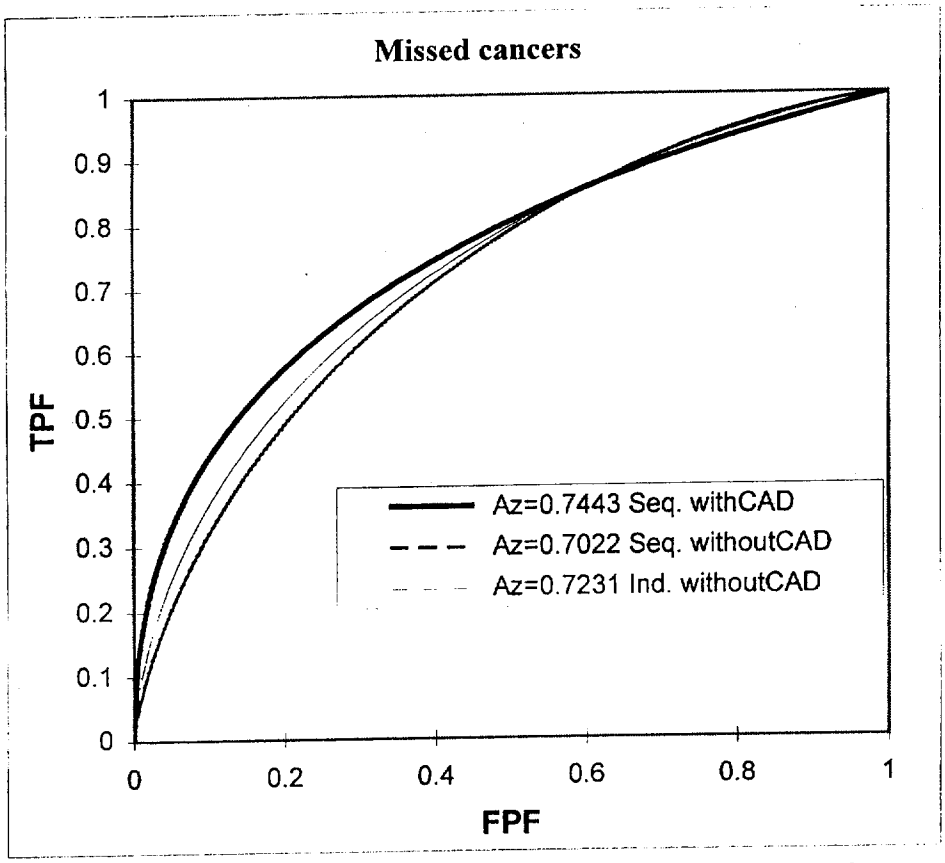

Chart 2: The ROC curves for each of the three reading conditions, for the cancer cases that were originally missed by the two screening radiologists and all normal cases, with combined results for all radiologists.

The increase of Az comparing the Independent readings to the reading with the RS was not significant (p=0.4). However, the comparison between the Sequential readings was significant. Because of heightened vigilance of readers during a clinical trial, the ROC performance in actual clinical practice is bound to be poorer than either reading during this clinical trial. Therefore we conclude that these results support the first secondary hypothesis showing that radiologists perform better using the RS than they do without the RS, on cancers that had been missed by the two screening radiologists.

Table 3. Comparison of radiologists' ROC performance in the detection of lung cancers 9.5-15 mm in average diameter.

Comparison	Az Without RS	Az With RS	Improve-ment	95% Confidence Interval	p
Sequential-with-RS vs. Independent-without-RS	0.7975	0.8477	0.0502	(0.01,0.09)	0.0161 sig.
Sequential-with-RS vs. Sequential-without-RS	0.8002		0.0475	(0.022,0.073)	0.0005 v.s.

Az = Area under the ROC curve
RS = RS-2000 System
Improvement = (Az With RS) - (Az Without RS)
95% Confidence Interval = 95% CI of Improvement
sig. = Significant
v.s. = Very Significant

14

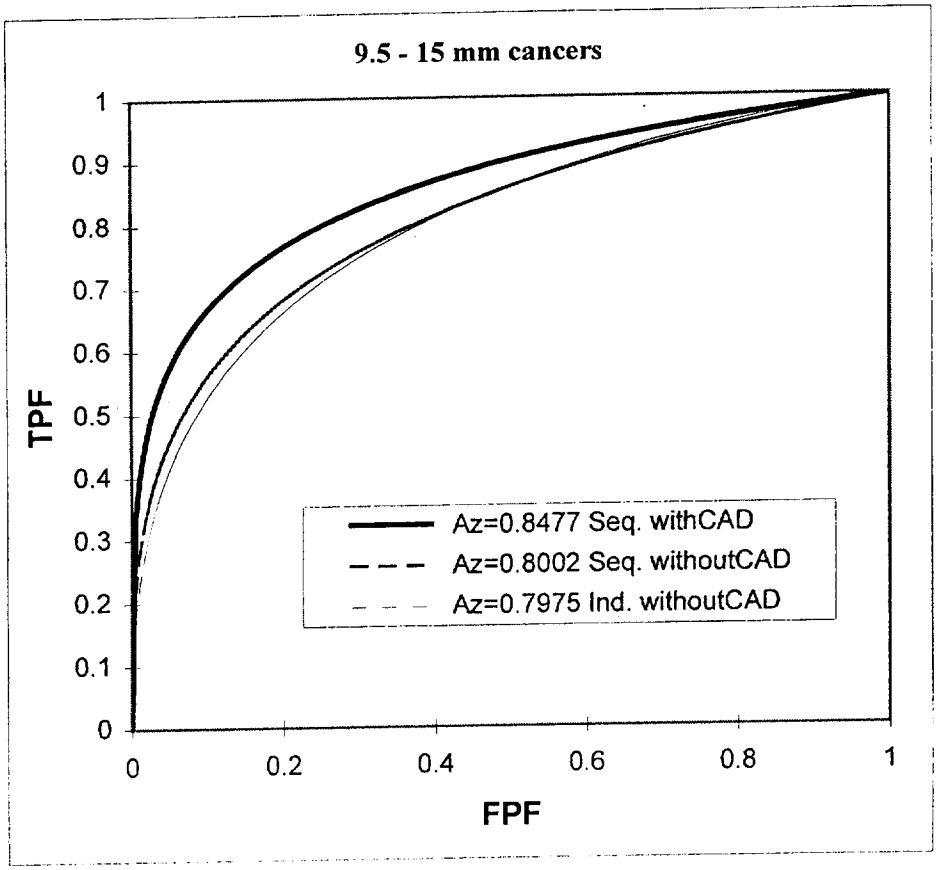

Chart 3: The ROC curves for each of the three reading conditions, for the subset of cancer cases 9.5 to 15 mm and all normal cases, with combined results for all radiologists.

These results support the second secondary hypothesis and show that the RS increases the ROC performance of radiologists for the smaller lung cancers and that these results are statistically significant. While not shown in the Table or Chart, the radiologists' sensitivity increased by 10% (from an averaged radiologists' sensitivity of 64% in Independent-without-RS to 74% when RS was used as an aid in Sequential-with-RS) with concomitant increase of false positive fraction from 20% to 22%.

Additional Analysis

In addition, the improvement in ROC performance of the radiologists for cancers 15-19 mm in size was also investigated. The results are presented in Table 4 and Chart 4.

Table 4. Comparison of radiologists' ROC performance in the detection of lung cancers 15-19 mm in average diameter.

Comparison	Az Without RS	Az With RS	Improve-ment	95% Confidence Interval	p
Sequential-with-RS vs. Independent-without-RS	0.8399	0.8704	0.0305	(0.0007,0.06)	0.0452 sig.
Sequential-with-RS vs. Sequential-without-RS	0.8565		0.0139	(-0.009,0.037)	0.2389 n.s.

Az = Area under the ROC curve
RS = RS-2000 System
Improvement = (Az With RS) - (Az Without RS)
95% Confidence Interval = 95% CI of Improvement
sig. = Significant
n.s. = non-significant

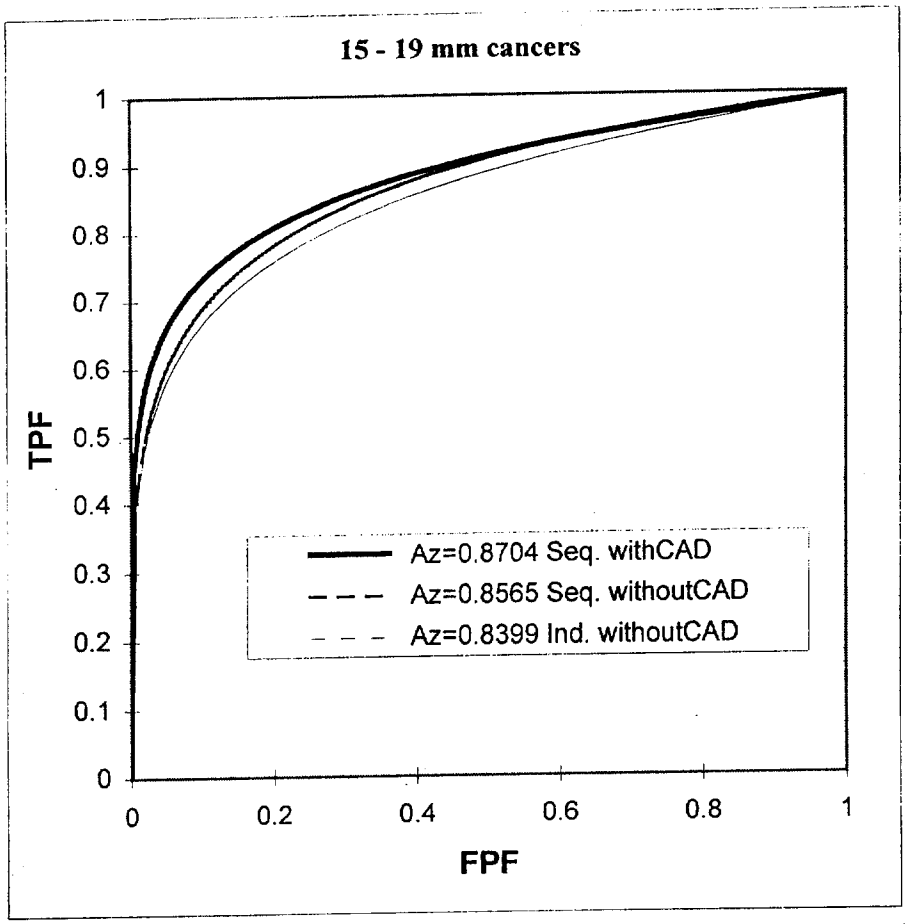

Chart 4: The ROC curves for each of the three reading conditions, for the subset of cancer cases 15 to 19 mm and all normal cases, with combined results for all radiologists.

These results show that there is some improvement in the detection of mid-sized lung cancers with the assistance of RS-2000, but statistical significance in shown only when comparing the Independent reading with the reading assisted with RS-2000. In this case statistical significance is not shown for the comparison of the two Sequential readings. As previously discussed, if either of the unaided readings is statistically significantly improved with the RS-2000, we conclude that the device improves ROC performance in actual clinical practice.

16

Therefore, while there is statistically significant improvement with use of the RS-2000 for cancers in the entire size range from 9.5 to 27.5 mm, and for the smaller cancers among those, 9.5 to 15 mm, the larger the cancers the less significance there is. Thus the smaller the cancers, which are also those for which the radiologists' ROC performance was poorer, the more significant the aid offered by use of the RS-2000.

Other Effectiveness Issues

In these studies, the ROC curves were all calculated without taking into account whether or not a cancer identified on the chest radiograph was attributed to the correct location, thus increasing the areas under all ROC curves. Also, with any device that improves sensitivity for detecting some disease, there is a potential for harm to the patient from a concomitant increase of false positives. These result in extra work-ups and possible interventions for lesions that turn out to be benign, and in the case of the RS-2000 could involve computed tomography (CT) examinations or even open thoracotomies for biopsies.

If the first follow-up step of the work-up for every possible lung cancer identified on chest radiograph with the aid of the RS-2000 were to be a chest CT, as recommended in the labeling, then the harm to the patient with a benign lesion would mainly be due to the extra radiation from the CT. Moreover CT should correct any mislocations of cancers on the chest radiograph, as well as help discriminate between benign and malignant lung lesions.

11. Conclusions Drawn from Studies

- The RS-2000 system can detect solitary pulmonary nodules in chest radiographs, an important indication of early-stage lung cancer.
- A physician using the RS-2000 system can increase her or his ROC performance on chest x-ray radiographs for lung cancers 9.5-27.5 mm in size, which are usually early-stage lung cancers, of which only 15% are currently detected without computer aid (according to the American Cancer Society).
- This aid is least effective for the larger lesions and progressively more effective for the smaller lesions, which tend to be the earliest and most curable cancers.
- The results show the effectiveness of the device in male heavy smokers over 45 years of age. Its effectiveness for other demographic groups was not determined in the clinical testing.

12. Panel Recommendation

The Radiological Devices Panel met on March 5, 2001 to discuss this PMA for the RapidScreen™ RS-2000 device. Following a thorough discussion of the issues, the Panel unanimously recommended approval of the PMA with five conditions. The conditions all applied to the labeling and were intended to ensure that users understand exactly what the device has been shown to achieve.

The specific conditions were the following:

1. Revise the labeling to state: The device was validated with adult male smokers 45 years of age or older with a high risk for cancer.

2. Identify in the labeling the degree of benefit that can be expected from the device.

3. The labeling should provide a more explicit description of the regions of interest (ROIs) that the device is likely to mark, so as to alert users that the device will generate substantial numbers of false positives and will leave substantial numbers of false negatives.

4. The labeling should state explicitly and specifically what the device has been shown to achieve, especially with respect to the sensitivity shown for the device.

5. Revise the warning in the labeling as follows: add "If the procedure in this warning is not followed, potential cancers may be missed." to "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."

13. CDRH Decision

The PMA was granted Expedited Review status for the two reasons indicated below.

1. No CAD system is currently approved for assisting physicians in identifying suspicious areas on chest radiographs.
2. The device is expected to provide a substantive health benefit by assisting in the early detection of lung cancer.

CDRH concurred with the recommendation of the panel and worked with the applicant to resolve the outstanding labeling issues.

The sponsor's manufacturing and control facilities were inspected March 29 - April 9, 2001, and were determined to be in compliance with the Quality Systems Regulations. CDRH issued an approval order on July 12, 2001.

14. Approval Specifications

Directions for use: See labeling.

Warnings, Hazards to Health from use of the device: See Indications, Contraindications, Warnings, and Precautions in the labeling.

Conditions of Approval: CDRH approval of this PMA is subject to full compliance with the conditions described in the approval order.

7/12/01