Essential Prescribing Information

Caution: Federal law restricts this device to sale by or on the order of a physician.

1. Device Description

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 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 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 digitizes a chest radiograph, processes the digitized image, and produces an annotated hard-copy image with a laser printer or soft-copy image on the video monitor. The output image is the corresponding digital chest image with marked ROI's, represented by circles with a 2.5 cm radius on the original films. These marked ROI's indicate areas on the chest image that have characteristics similar to SPN's.

Importantly, only the original chest radiographs are to be used for diagnostic interpretation by physicians. The RS-2000 is a CAD device and its output is designed only as an aid to the interpretation process after the initial reading of the film.

2. Indications for Use

The 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 the device.

4. Warnings

The RS-2000 has only been clinically validated with male smokers over 45 years of age. Its effectiveness for other populations is therefore unknown.

Radiological Interpretation

- Because the RS-2000 marks a large number of sites that are not cancer, which may lead to an increase in the number of work-ups of lesions that turn out to benign, CT examination is strongly recommended as the next step in patient evaluation.
- The physician should only perform interpretation using the films and use the markers shown on the RS-2000 output (paper printout or video monitor display) only as a guide.
- The device will not identify all areas that represent cancers, and users should never be dissuaded from working up an earlier finding even if the device fails to mark that site. If this warning is ignored, some cancers that would have been worked up will not be.
  - The device is not designed to detect lung nodules in lateral view chest radiographs.
  - Conditions of film quality, such as under- or over-exposure, that diminish chest radiographic sensitivity, may also diminish the sensitivity of the device.
- In addition to marking approximately 2 out of 3 cancers, the device will typically place up to 6 marks per radiograph, most of which do not represent lung cancer. Thus the physician must still use his/her interpretive skills on regions marked by the device.
- The RS-2000 is not an image enhancement device; rather it helps to identify overlooked regions on chest radiographs that should be reexamined.

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

5. Precautions

Device Operation

- Physicians and operators should review the User Manual and receive training before using the device.
- To ensure proper device operation, use only barcode labels readable by the barcode reader of the device.
- Be certain to orient the film correctly when scanning; follow the instructions in the User Manual.
- 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 chest radiographic views with films size of 14" x 17" or 14" x 14".
  - Do not attempt to place films that are bent or damaged in the scanner, as they may jam.
- To prevent damage to the device, shut down the device according to the procedures recommended in the User Manual.
- 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.

Installation and Maintenance

- Regularly check and replace toner and add paper to the laser printer.
- Do not attempt to install or repair the 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 ext. 312.
- To ensure proper operation of the device, maintain equipment in a well-ventilated, air-conditioned environment (temperature range 60 to 85 degrees Fahrenheit (^{o}F) (15 to 30 degrees centigrade (^{o}C)).
- For proper operation the system requires 100 to 127 VAC, 47 to 63 Hz; 10A maximum.
- Disconnect power cord before moving or servicing.
- Perform routine monthly assessments of the system by following the instruction for Routine System Check provided in Section 10.4 of the user's manual.

6. Adverse Effects

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.

7. Functions of the RS-2000

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-shape opacity structures (with a 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 (using a circle with 25 mm in radius corresponding to the scale of the original film) over the centroid of that structure on the image as shown in Figure 1.

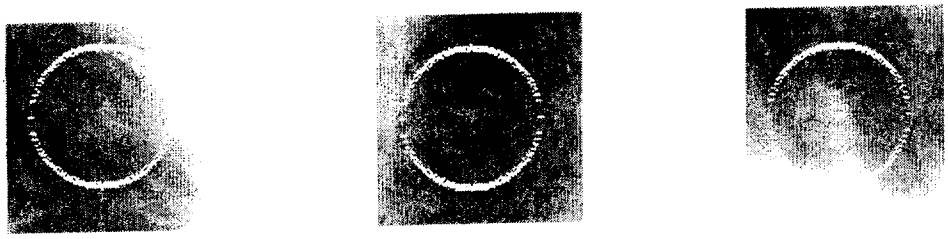

Figure 1. Examples of marked lung nodules.

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 chest images sometimes satisfy the algorithms' criteria for lung nodules and will also be marked, as shown in Figure 2.

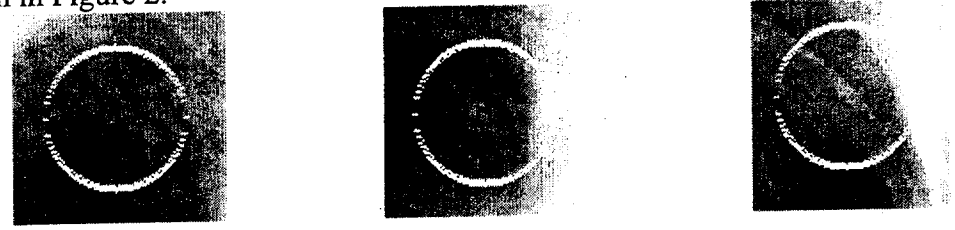

Figure 2. Examples of normal structures that can be marked as potential lung nodules.

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 in the 5 to 30 mm size range.

To interpret a case, the radiologist first reviews a chest radiograph for initial interpretation in the conventional manner. The radiologist then refers to the results from the RS-2000 system (i.e., the corresponding printouts with marked ROI's that may have characteristics similar to SPN's). The

radiologist then must go back to the original films and pay particular attention to these marked areas associated with the ROI's on the RS-2000 printouts, and check his/her original interpretation, as necessary. The RS-2000 thus functions as an aid to radiologists in reviewing chest radiographs by calling attention to ROI's with characteristics similar to SPN's.

8. Clinical Study

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 including indirect safety issues as well. Clinical studies of the RS-2000 were designed to determine the 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 a pivotal study to demonstrate the effectiveness and safety of the RS-2000 system. These studies were conducted at the Imaging Sciences and Information System (ISIS) Research Center, Department of Radiology, Georgetown University Medical Center, from 1998 to 2000, using radiographs selected from a 1970s lung cancer screening trial, performed with male heavy smokers, 45 years of age or older, with a high risk for cancer, in which all chest films were read by two radiologists.

The pivotal study was a full-scale double-blinded reader study, using receiver operating characteristics (ROC) for analysis. It 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 selected from over 10,000 screening cases. 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 were seen in retrospect by the panel of radiologists.

The 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 first without RS-2000 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 Detection 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 results are presented in Tables 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

These results confirm the primary hypothesis above. While not shown in the table, 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

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 without RS is bound to be poorer than either reading during this clinical trial. Therefore it is reasonable to 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

These results support the second secondary hypothesis and show that the RS-2000 increases the ROC performance of radiologists for the smaller lung cancers and that these results are statistically significant. While not shown in the table, 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.

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 WithRS) - (Az Without RS)
95% Confidence Interval = 95% CI of Improvement
sig. = Significant
n.s.= non-significant

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 is 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 mentioned, if either of the unaided readings is statistically significantly improved with the RS-2000, it is reasonable to conclude that the device improves ROC performance in actual clinical practice.

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 Warnings, 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.

9. Conformance to Standards

The *RapidScreen*™ RS-2000 System was tested and found compliant with the following Electrical Safety and EMC Standards:

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

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. Manuals

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.

Training Manual for Physicians - Describes how physicians should handle different RS-2000 detection results.

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