

**SUMMARY OF SAFETY AND
EFFECTIVENESS DATA (SSED)**

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

A. GENERAL INFORMATION

Device Generic Name: System, Computer Aided Detection (CAD), Lung CT

Device Trade Name: ImageChecker® CT CAD Software System – (Model LN-1000)

Applicant's Name and Address: R2 Technology, Inc.
1195 W. Fremont Avenue
Sunnyvale, CA 94087

PMA Number: P030012

Date of Panel Recommendation: February 3, 2004

Date of Approval to Applicant: July 8, 2004

B. INDICATIONS FOR USE

The ImageChecker® CT CAD Software System is a Computer-Aided Detection (CAD) system designed to assist radiologists in the detection of solid pulmonary nodules during review of multidetector CT (MDCT) scans of the chest. It is intended to be used as an adjunct, alerting the radiologist – after his or her initial reading of the scan – to regions of interest (ROIs) that may have been initially overlooked.

C. CONTRAINDICATIONS

There are no contraindications for the use of this device.

D. WARNINGS AND PRECAUTIONS

Warnings and Precautions for use of the device are stated in the attached product labeling.

E. DEVICE DESCRIPTION

System Overview

The ImageChecker® CT System is an image analysis and visualization system designed to assist radiologists in the review of multidetector CT (MDCT) exams of the chest for the detection of solid pulmonary nodules between 4 and 30mm in size. The device is not intended as a detection aid for either part-solid or non-solid lung nodules.

The ImageChecker® CT System is a combination of dedicated computer software and hardware. The system is comprised of the ImageChecker® CT Workstation (K023003) and the ImageChecker® CT CAD Software. This combination of the workstation and software, the Model LN-1000, is the subject of this PMA filing. The two components are related as indicated in Figure 1.

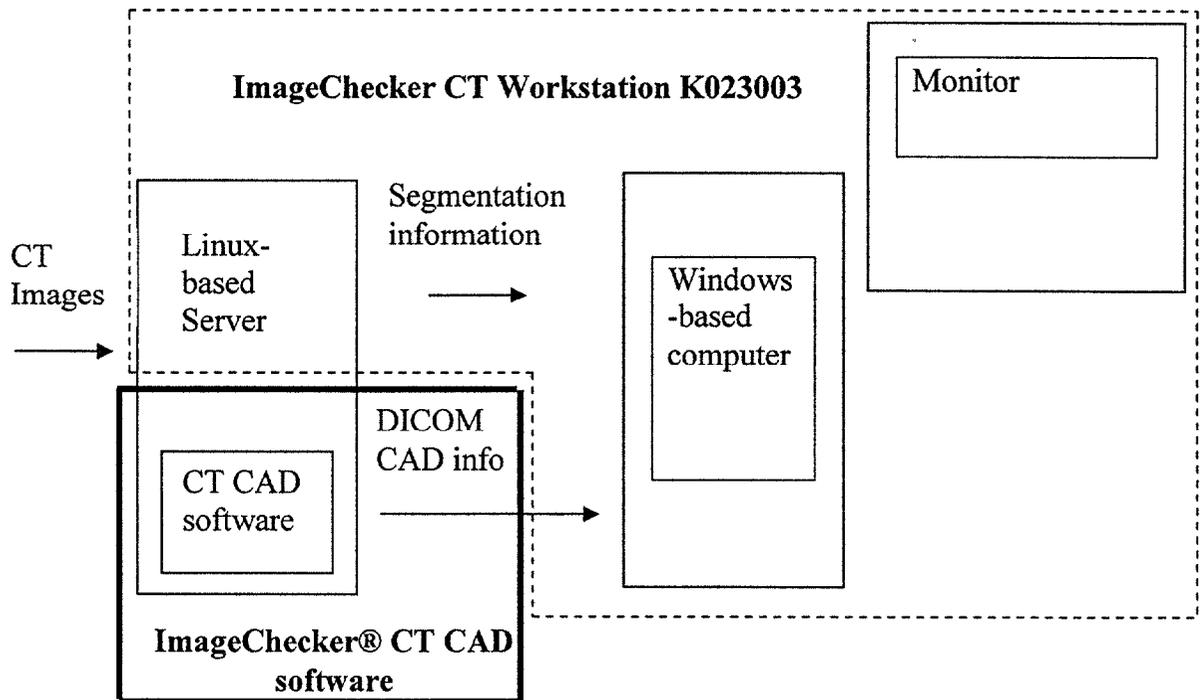


Figure 1. Overview of the ImageChecker® CT system illustrating the two devices that comprise the system and the relevant hardware and software components.

The ImageChecker® CT CAD software applies proprietary signal processing algorithms to the large digital datasets generated during scanning. These algorithms analyze the complete set of images and search for findings with features suggestive of a solid pulmonary nodule. The system marks these “candidate” nodules for further review by the radiologist.

After the initial exam acquisition by the CT scanner, copies of the exam are sent automatically to the review workstation for the user to review as well as to the processing server for segmentation and CAD analysis. The processing server then sends a report to the workstation. All image and information exchanged between the components of the system and external devices (such as CT acquisition devices, PACS systems) are controlled using standard DICOM (Digital Imaging and Communications in Medicine) protocols.

The following sections give a brief overview of the individual devices that comprise the ImageChecker® CT System.

ImageChecker® CT Workstation

The ImageChecker®-CT Workstation is indicated for use as a general medical imaging workstation, and is used to receive, store, transmit, and display images from a multidetector CT scanner (MDCT). The Center for Devices and Radiological Health (CDRH) cleared the workstation for marketing on 11/4/2002 (K023003) as ImageChecker® CT Model LN-500. The ImageChecker® CT Workstation combined with the ImageChecker® CT CAD Software that is the subject of this PMA submission will be distributed as the Model LN-1000.

The ImageChecker®-CT Workstation LN-1000 is comprised of two off-the-shelf personal computers, one with a Linux-based operating system (OS) and one with a Microsoft Windows-based operating system (OS), and a display monitor.

The processing software performs several functions:

- receives MDCT exams using the DICOM standards;
- takes the CT images and segments different anatomical structures into normal structures (e.g. vessels) and other composite features; and
- stores the location and characteristics of the segmented composite features in a DICOM Structured Report object.

The workstation display software provides tools for the radiologist that aid in the review process. During the review, the radiologist instructs the display software by means of a standard keyboard and mouse. The images and findings are communicated to the radiologist by means of a color flat panel display. When the radiologist completes his or her review, the system provides a summary report that lists any findings and measurements associated with the study. The user can also print this summary.

The workstation is able to display the findings that are identified by the CAD software (see next section). The radiologist using the workstation is able to view the CAD findings – after a preliminary review of the study – using a simple button press on the user interface. The user can then view areas that the CAD software identifies.

ImageChecker® CT CAD software

The ImageChecker® CT CAD software is an adjunctive software package that analyzes the CT images after they have been pre-processed by the workstation software and identifies regions of interest that may be solid pulmonary nodules. The regions of interest are identified by means of the propriety signal processing algorithms that analyze the images and search for findings with features suggestive of a solid pulmonary nodule (see Figure 2).

The ImageChecker® CT CAD software was developed from a database of over 350 MDCT exams of the chest that contained solid nodules identified by a consensus of radiologists. The series included cases acquired on both Philips/Marconi and Siemens CT systems and at both low and standard doses. All cases were reconstructed at ≤ 3 mm (0.5 – 3.0 mm) collimation. The CAD algorithms take the images after they have been

segmented by the workstation software, and calculate geometric and other feature measurements associated with each candidate region. A final stage of the CAD algorithm classifies these regions and chooses the ones most likely to represent solid pulmonary nodules.

The location information about these identified regions of interest is sent to the workstation using a DICOM CAD Structured Report (DICOM CAD SR).

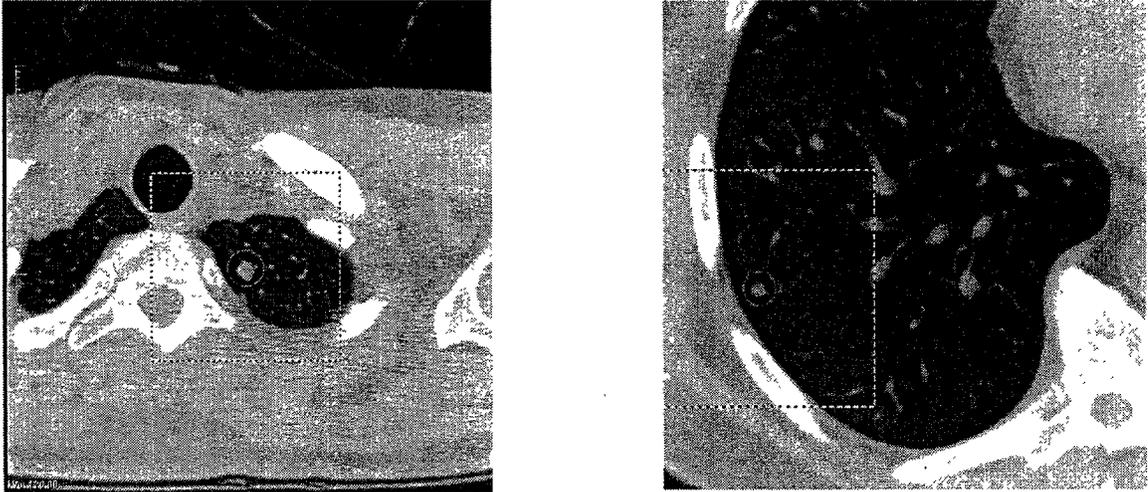


Figure 2. Examples of CAD-marked pulmonary nodules

The ImageChecker® CT CAD software is optimized to analyze certain types of DICOM MDCT images with the technical specifications for these images listed below (see the User Manuals for additional details).

multidetector CT (MDCT)	4 or more rows
acquisition collimation	0.5 – 3.0 mm
reconstruction	0.5 – 3.0 mm
exposure	(20 keV; 15 mAs
slice spacing	contiguous, no overlaps
series	(3 cm in length; < 1000 images
minimal FOV	entire intrathoracic cavity must be included
contrast	with or without intravenous contrast

CAD should only be applied to CT exams meeting these requirements and deemed acceptable for clinical reading by a radiologist. A wider variety of cases can be reviewed on the ImageChecker® CT workstation – these specifications only refer to the CAD analysis.

F. ALTERNATIVE PRACTICES AND PROCEDURES

Currently, there is no alternative to assist radiologists in the detection of lung nodules on multidetector CT chest scans other than double reading.

G. MARKETING HISTORY

The same version of the ImageChecker® CT CAD Software System was launched for commercial sale in the European Union at the European Congress of Radiology in March 2003.

H. 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 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.

I. NON-CLINICAL STUDIES – SOFTWARE VERIFICATION AND VALIDATION

Acceptable documentation has been submitted demonstrating that R2 Technology, Inc. has developed the software for this device under an appropriate software development program; that they have performed a hazard analysis from both the patient's and user's standpoint, and addressed those hazards; and carried out an appropriate validation process. These procedures provide the foundation for assuring, to the extent possible, that the software will operate in a manner described in the specifications, and in no other way.

J. CLINICAL STUDIES

Overview of Clinical Studies

R2 Technology, Inc. has conducted three pivotal clinical studies to evaluate the safety and effectiveness of the ImageChecker CT CAD software in the model LN-1000. The studies were based on a retrospective case collection project involving multiple clinical sites in various regions across the U.S. The clinical studies did not attempt to assess the effectiveness of the device on an asymptomatic lung cancer screening population. The applicability of this device to such a CT screen population has not been established.

Objectives

The first pivotal study was designed to generate a “truth” set of cases containing solid pulmonary nodules, as well as cases with no nodules, to be used as a reference truth for subsequent studies. The second pivotal study was an Observer/ROC (Receiver Operating Characteristic) study, designed to measure the performance enhancement of radiologists using the System. The third study was a retrospective study to characterize the stand-alone sensitivity of the CAD system.

Sites and Cases for Case Collection Project and Subsequent Studies

Five (5) regionally diverse sites contributed 151 cases to the study; two sites in the

Northeast, and one site each from the South, the Midwest, and the West. Of these sites, three were private imaging centers and two were academic medical centers (see Table 1).

Name	State	Number of Nodule-present Cases Used in Studies	Number of Non-nodule Cases Used in Studies	Total Cases
Atlantic Medical Imaging	NJ	11	10	21
MRI & CT Diagnostics	VA	15	23	38
South Jersey Radiology	NJ	14	35	49
University of Iowa	IA	18	9	27
UC, San Francisco	CA	5	11	16
Total		63	88	151

All cases were acquired consecutively from the sites' digital archives according to the inclusion and exclusion criteria identified in the case collection protocols.

The nodule-present cases collected included only those in which a diagnosis of cancer, either primary lung cancer or an extrathoracic neoplasm, had been documented. Other co-existing disease processes resulting in the formation of nodules (e.g. TB, histoplasmosis, rheumatoid lung) were allowed, as were cases containing other underlying pathology such as lobar pneumonia, emphysema, and heart failure.

A total of 63 nodule-present cases dating from November 2001 through December 2002 were included in the studies. The study population consisted of 56% females and 44% males, with a median age of 66 (range 20-86). The malignancies consisted of primary lung cancer in 24 (38%) of these cases, and documented extra-thoracic primary cancer with suspected metastatic disease to the lung in the remaining 39 (62%) cases. Forty-six percent (46%) of the exams were performed following injection of intravenous contrast media.

The nodule-absent cases collected were those in which no nodules were deemed to be present by the principal investigator at each site. A total of 88 nodule-absent cases dating from June 2002 through December 2002 were included. This group consisted of 53% females and 47% males, with a median age of 55 (range 18-85). Other disease processes could be present, including the presence of pulmonary masses (>3cm). Patients with histories of cancer, radiation therapy, or even previous thoracotomy, were allowed. Fifty-two percent (52%) of the exams included intravenous contrast media.

STUDY #1 – IDENTIFICATION OF REFERENCE TRUTH

The objective of this study was to generate a 'truth' set of unanimous actionable nodules, as identified by a panel of 3 experienced radiologists ('Reference Truth Panel'), to serve as a reference truth for all subsequent studies.

To achieve this objective, multiple panel sessions were scheduled in which three radiologists independently read a variable number of cases (min = 12, max = 25) until all 151 study cases had been independently interpreted by three readers.

The Reference Truth Panels identified a total of 142 findings in the 151 cases that met the size (4–30mm) and peak density (greater than –100HU) requirements, and which all three panelists agreed were actionable. This set of findings is defined as solid actionable nodules. The presence or absence of at least one of these findings in a quadrant was used as the reference truth for Study #2 below.

The findings ranged in size from 4–28mm. The majority of these findings were between 4 and 8 mm in diameter (46%, 66/142), with the largest categories being the 5–6 mm (15%, 21/142) and 6–7 mm (15%, 22/142) findings.

STUDY #2 – EFFECT OF CAD SYSTEM ON IMPROVING ACCURACY OF IDENTIFICATION OF ACTIONABLE NODULES

The objective of this study was to demonstrate that review of CAD output improves performance of radiologists reviewing MDCT with respect to their ability to accurately identify actionable nodules. The study employed a receiver operating characteristic (ROC) methodology. Ninety (90) cases were randomly selected from the 151 cases in a stratified manner. The cases were divided into four quadrants, yielding 360 regions for evaluation. Each of 15 radiologists independently reviewed the 360 quadrants, first without computer-aided detection (CAD) and then immediately with CAD. The results of this study were used for all of the final analyses of the data.

Each reader rated each quadrant on a 0–100 ‘actionability scale’ as to his or her level of confidence that the quadrant contained at least one actionable nodule. Ratings were provided both before and after viewing the CAD marks.

For purposes of measuring reader performance, quadrants were defined as ‘actionable’ if the Reference Truth Panel described in Study #1 unanimously agreed that at least one of the findings in the quadrant was (1) a solid lung nodule and (2) actionable (i.e., required intervention or short-term follow-up). Otherwise the quadrant was defined as non-actionable for the purpose of ROC analysis.

Before describing the statistical analysis, one example case is described. Figure 3 shows one case where the CAD software pointed out a nodule that was initially missed by four radiologists. The patient was a 67 year-old male, with a history of bladder cancer. A small 4.4 mm noncalcified nodule was present in the right lung, in the lower quadrant, marked by the CAD algorithm. Only eleven of the 15 radiologists rated that quadrant as containing an actionable nodule in their initial review – whereas three more radiologists increased their ratings after viewing the CAD marks.

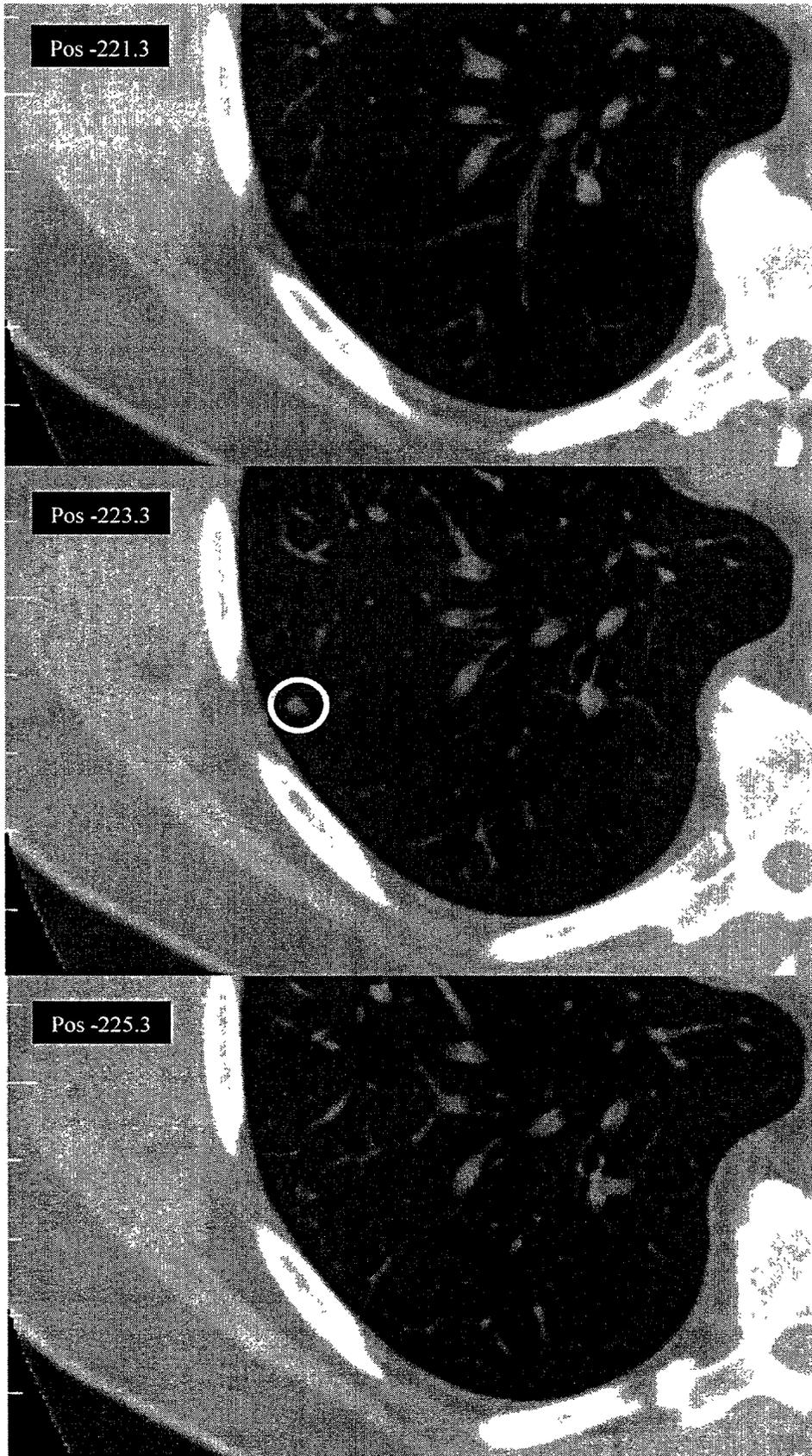


Figure 3. Example case of a missed nodule where CAD reduced misses.

An area under the ROC curve (AUC) was computed for each of the 15 radiologists before and after CAD. The average curve of all 15 radiologists is shown below in Figure 4. The area under the ROC curve increased with the use of CAD. If the full plot is viewed as a unit square, the area separating the two curves is 0.024.

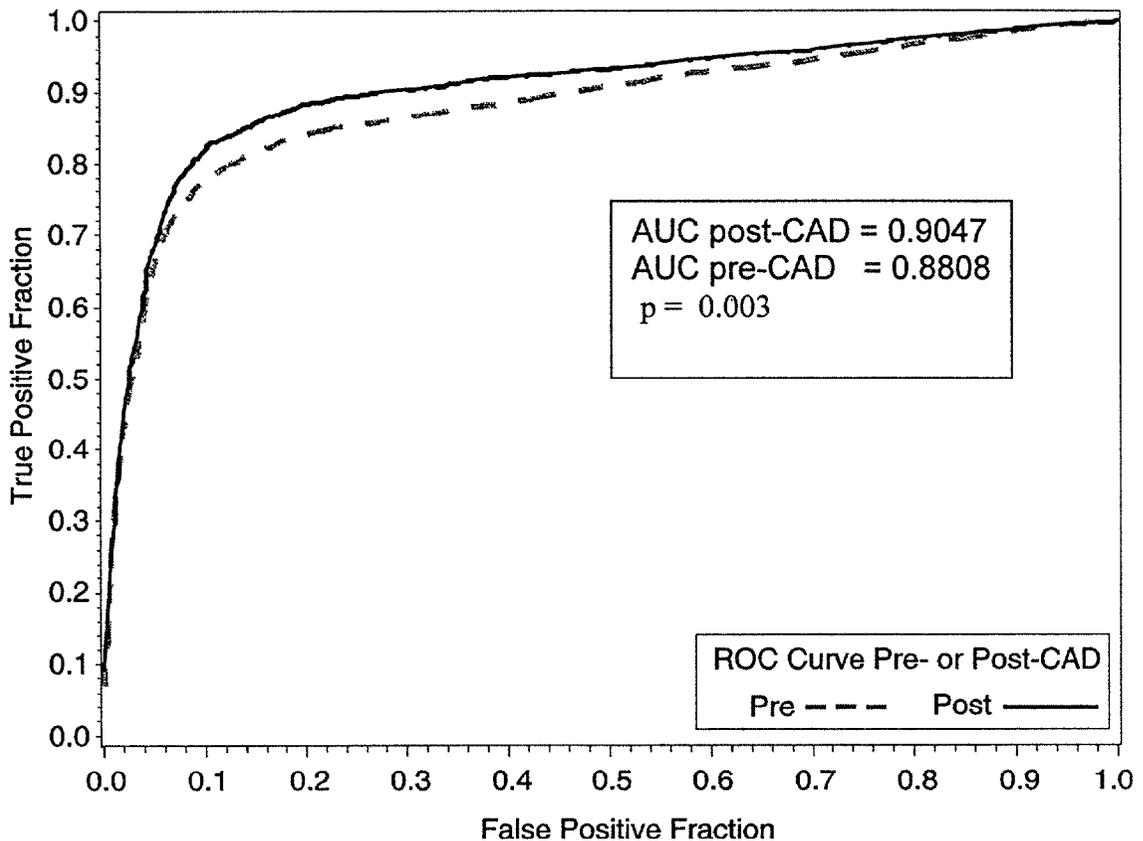


Figure 4. Average ROC curve showing pre-CAD (dashed line) and post-CAD (solid line) performance for 90-case (360 quadrant) study.

The primary analysis of statistical significance was based on the Dorfman-Berbaum-Metz (DBM) ANOVA-after-jackknife approach¹ (adapted for the fact that the quadrants are ‘clustered’ data) and the results are presented in Table 2 below.

The average reader improvement in AUC (estimated using the ANOVA-after-jackknife) was 0.0240 ± 0.0077 ($p=0.0033$) with a 95% confidence interval of (0.0084, 0.0395). Thus, the study showed a statistically significant improvement in the area under the ROC curve with the use of CAD.

Secondary analyses of statistical significance were conducted to determine the dependence of the study results on the use of the consensus reference truth from Study #1 for ROC evaluation. This was done since a reference truth based on a consensus panel assessment of actionability is weaker than one based on biopsy.

¹ Dorfman DD, Berbaum KS and Metz, CE. Receiver Operating Characteristic Rating Analysis. Invest Radiol 1992; 27: 723-731.

The first of these variations in the reference truth involved using the findings identified by at least 2 of the 3 members of the Reference Truth Panel in Study #1 (n=310 findings). The ANOVA-after-jackknife analysis was recomputed, with the results as shown below in Table 2. The average reader improvement in AUC was again statistically significant.

To further examine the effect of variability in the unanimous three-panelist Reference Truth Panel, three-, two- and single-panelist reference truths were constructed from the data collected in Study #1. Implementing this variable truth is difficult within the framework of the ANOVA-after-jackknife analysis, therefore the secondary analysis employs a bootstrap analysis². The bootstrap is a computationally-intensive non-parametric method that allows complex analyses to be repeated many times using different randomly generated datasets (all based on the original data) to approximate the variability that would occur if the entire study were repeated many times. As a test of the validity of the bootstrap mechanism, the analysis was performed first using the unanimous reference truth. As shown in Table 2, the results of the primary ANOVA-after-jackknife analysis and the bootstrap analysis using the unanimous reference truth are very similar.

Table 2. Study analyses of the significance of the improvement in area under the ROC curve when reference truth or statistical methods were varied			
Analysis Method	Estimated Improvement in AUC	p-value	95% CI
Primary: ANOVA-after-jackknife, with unanimous reference truth	0.0240	0.003	(0.0084, 0.0395)
Secondary: ANOVA-after-jackknife, with 2/3 majority reference truth	0.0213	0.001	(0.0097, 0.0329)
Secondary: Bootstrap with unanimous reference truth	0.0246	<0.001	(0.0089, 0.0446)
Secondary: Bootstrap with random 3-panel reference truth	0.0224	<0.001	(0.0076, 0.0403)
Secondary: Bootstrap with random 2-panel reference truth	0.0216	0.002	(0.0077, 0.0387)
Secondary: Bootstrap with random 1-panel reference truth	0.0209	<0.001	(0.0080, 0.0370)

Several approaches were used, based on the bootstrap re-sampling approach, to incorporate random reference truths for the random cases against which the random

² Rutter, C. Bootstrap Estimation of Diagnostic Accuracy with Patient-clustered Data. Acad Radiol 2000; 7: 413-419.

readers' performance could be estimated. Based on varying the reference truth in this way, the average reader improvement in AUC (estimated using the 1000 bootstrap samples with variability in the reference truth) ranged from 0.0209 – 0.0224, as shown in Table 2. Thus again, the results with the varied random reference truth demonstrate that the study showed a statistically significant improvement in the area under the ROC curve with the use of CAD.

An additional secondary analysis was performed to determine if the effect of the presence or absence of intravenous contrast in the cases affected the overall study results. The ROC primary ANOVA-after-jackknife analysis (based on the unanimous Reference Truth Panel findings) was redone, stratifying the 90 cases into those that included contrast and those that didn't. Analysis of both the 45 non-contrast and 45 contrast media cases showed improvement with CAD (delta AUC for each set of cases was greater than 0.02).

Finally, an analysis at the patient level, rather than at the quadrant level, was conducted to determine if there was evidence to show a positive effect of the use of CAD using a methodology closer to the clinical use of the product.

Each case in the study was assigned to one case cohort based on what truth nodules were present (depending on the definition of the "truth" reference standard). For example, the cases that contained at least one unanimous actionable nodule were placed in a case cohort that would be considered true nodule-present cases. Each case was assigned a rating of "actionable" if at least one quadrant had a rating of 50 or greater (on our 0–100 scale). A threshold of 50 was chosen based on the way the readers were instructed to use the scale (a rating of 50 was 'indeterminate') and the actual ratings data showed a bimodal distribution, with most ratings clearly above 50 or below 50. Thus we can calculate the effect of CAD at the patient level in terms of reduction in observational oversights (i.e., the number of times a patient had a rating change from below 50 pre-CAD to above 50 post-CAD in a case that contained a truth nodule) and change in the false positive rate (the same ratings change for a patient with no nodules). This analysis showed that, at the case level, there were 22 corrections of 86 oversights (25.6%) and an increase in the false-positive rate (8 increases in 57 cases; 14.0%).

In summary, the primary analysis of the ImageChecker CT CAD Software System study shows a statistically significant improvement in the AUC for an ROC analysis for detecting solid pulmonary nodules between 4 and 30 mm in diameter. This result is robust when different reference truth definitions are used in the analysis.

STUDY #3 – MEASUREMENT OF CAD ALGORITHM PERFORMANCE

This objective of this study was to test that the ImageChecker CT CAD Software System can mark solid pulmonary nodules equal to or greater than 4 mm in size with a high level of sensitivity and a low number of false marks per normal case. The CAD software is designed to specifically identify those solid, spherical nodules whereas radiologists identify many other actionable findings (e.g. ground glass opacities), some of which were included in the set of 142 nodules from Study #1.

To evaluate the performance, all 142 unanimous actionable solid nodules arising from Study #1 were first independently shown to a new panel of five radiologists (the ‘Nodule Classification Panel’), each with a minimum of 6 months experience reading MDCT of the chest. The radiologists were asked to categorize each finding according to its 3-dimensional appearance, and determine how closely that appearance approximated a classic pulmonary nodule. The definition of ‘nodule’ was taken from a standard text³, and the term “classic” was as pictured in the same text⁴. The descriptor ‘solid’ referred to a nodule with a peak density > -100HU.

After all 142 reference truth nodules were reviewed by the Nodule Classification Panel, each candidate nodule was then categorized based on how many of the five Nodule Classification Panel radiologists rated it as classic. The subset of pulmonary nodules deemed to be classic in appearance (‘classic nodules’) by at least 4 of the 5 readers (n = 64) was defined as the primary target population for testing purposes.

All 151 cases were analyzed by the ImageChecker CT CAD Software System, and an automatic scoring tool matched the CAD marks with the locations of the nodules. The CAD sensitivity results are shown in Table 3. The accompanying false marker rate, as measured on cases with no reference truth nodules, was a median of two marks pre case.

Nodule Classification Panel members rating nodule as classic	# of nodules	CAD Sensitivity*	95% Lower Limit	95% Upper Limit
4/5, 5/5 “classic”	64	83%	73%	92%
3/5	13	69%	44%	94%
0/5, 1/5, 2/5	65	32%	21%	44%

*CAD Sensitivity is defined as the number of nodules marked by CAD divided by the total number of nodules in each category.

A further analysis of the CAD sensitivity for cases with and without intravenous contrast media showed consistent results in the cases with contrast compared to the cases without contrast. The sensitivity for the classic nodules in cases with contrast was 94% (16/17, 95% CI 83%-100%) and for the classic nodules without contrast was 79% (37/47, 95% CI 67%-90%). The sensitivity for all solid nodules (classic and non-classic) in cases with intravenous contrast media is 55% (34/62, 95% CI 43%-67%) and in cases without contrast was 61% (49/80, 95% CI 51%-72%). The false marker rate measured on the nodule-absent cases was the same in both groups and the same as the summary numbers above.

³ Fraser RS, Muller NL, Colman N, Paré PD, Eds. *Fraser and Paré’s Diagnosis of Diseases of the Chest*, Fourth Edition, Volume 1. W.B. Saunders, Philadelphia, 1999; page xxxv. The definition is: “Round opacity, at least moderately well marginated and no greater than 3 cm in maximum diameter.”

⁴ *ibid*, Figure 18-31, page 458.

These results confirm that the ImageChecker CT CAD Software System performs at a high level of sensitivity for classic pulmonary nodules, with low false marker rates per normal case.

K. CONCLUSIONS DRAWN FROM STUDIES

For multidetector CT (MDCT) exams of the chest:

The ImageChecker® CT CAD Software System shows a statistically significant average reader improvement in AUC, 0.024 (p=0.003) in radiologists' ROC performance for detecting solid pulmonary nodules between 4 and 30mm in size.

L. PANEL RECOMMENDATIONS

At a meeting held on February 3, 2004, the FDA Radiological Devices Panel recommended approval of the PMA for the ImageChecker® CT CAD Software System (Model LN-1000) with the following conditions:

1. provide a reanalysis of the data presented in the submission on a per patient as opposed to a per lung quadrant basis,
2. provide a reanalysis showing the algorithm's performance on contrast and non-contrast CT subpopulations,
3. revise the labeling to include instructions on the importance of the radiologist always reading the film before using the CAD and never changing an original positive reading to a negative one after reviewing the CAD marked image -- "Always interpret all images before turning on the CAD. Never dismiss a finding because CAD did not identify it.",
4. present a training program to instruct physicians on the proper use of the device, and
5. conduct post market surveillance to determine the clinical significance of using the device.

M. CDRH DECISION

CDRH concurred with the first four panel recommendations listed above and asked the sponsor to provide the additional analyses and change the labeling accordingly. These analysis are provided in the clinical section of this document. CDRH also agreed with the panel that the study demonstrated the safety and effectiveness of the device.

The recommendation for a post market study was rejected by CDRH as unnecessary. Review of the panel transcript revealed that the panel members were interested in the sensitivity and specificity of the device for detecting malignancy. The device however is indicated as an adjunct in the detection of solid pulmonary nodules, not malignancy. The radiologist reviews the markings made by the CAD and confirms or denies the importance of the region of interest detected. The determination of malignant potential is dependent upon the physician. CDRH and the Panel both agreed that finding additional solid pulmonary nodules was of sufficient clinical significance to be an acceptable endpoint for the study as well as an acceptable indication for use. Therefore a study designed to evaluate the sensitivity and specificity of the device for finding cancer was not necessary in the pre- or post-market setting.

CDRH has determined the ImageChecker® CT CAD Software System (Model LN-1000) to be safe and effective to assist radiologists in the detection of solid pulmonary nodules during review of multidetector CT (MDCT) scans of the chest.

FDA inspected the R2 Technology, Inc. manufacturer and determined the facilities to be in compliance with the Quality System Regulation (21 CFR 820) by memorandum dated, June 25, 2004.

CDRH issued an approval order on July 8, 2004.

N. APPROVAL SPECIFICATIONS

Direction for use: See the Device Labeling.

Hazards to Health from Use of the Device: See Indication, Contraindications, Warnings, Precautions and Adverse Events in the labeling.

Post-approval Requirements and Restrictions: See approval order.

Draft R2 Technology, Inc.

Revised Draft: JMK 06/16/2004

Revised: DAM/WSH 06/18/2004

Revised: NXP 06/22/2004

Revised: DAM 06/23/2004 and 06/24/2004

Revised: WSH, SP and JMK 06/28/2004

Revised: JMK 06/29/2004

Revised: RAP, JMK 07/01/2004

Revised: KEO 07/02/2004

Revised: NCB, DAM, TXN 07/05/2004

Revised: DAM, JMK 07/07/2004

Revised: TXN, JMK 07/13/2004