



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

P970058

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

R2 Technology, Inc.
c/o Howard M. Holstein
Hogan & Hartson
555 13th Street, N.W.
Washington, D.C. 20004

JUN 26 1998

Re: P970058
M1000 ImageChecker
Filed: December 16, 1997
Amended: February 17, 1998, February 20, 1998,
April 10, 1998, April 22, 1998, and June 9, 1998

Dear Mr. Holstein:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the M1000 ImageChecker.

The ImageChecker M1000 is a computer system intended to identify and mark regions of interest on routine screening mammograms to bring them to the attention of the radiologist after the initial reading has been completed. Thus, the system assists the radiologist in minimizing observational oversights by identifying areas on the original mammogram that may warrant a second review.

We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

This device is approved upon the condition that within 60 days of receipt of this letter, you submit a protocol in the form of a PMA supplement for a postapproval study to more accurately assess the effect which the device will have on true positive and false positive work up rates. CDRH will work interactively with you as you develop this protocol. You further agree to perform the study itself within a reasonable period of time following acceptance of the protocol.

CDRH will notify the public of its decision to approve your PMA by making available a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at <http://www.fda.gov/cdrh/pmapage.html>. Written requests for this information can also be made to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., Rm. 1-23, Rockville, MD 20857. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

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Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

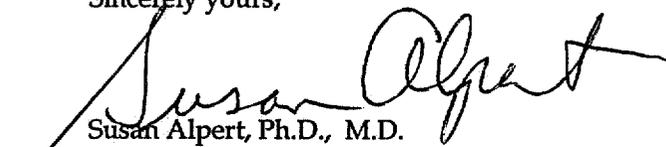
You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

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

If you have any questions concerning this approval order, please contact Robert J. Doyle at (301) 594-1212.

Sincerely yours,


Susan Alpert, Ph.D., M.D.
Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

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Issued: 3-4-98

CONDITIONS OF APPROVAL

APPROVED LABELING. As soon as possible, and before commercial distribution of your device, submit three copies of an amendment to this PMA submission with copies of all approved labeling in final printed form to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration (FDA), 9200 Corporate Blvd., Rockville, Maryland 20850.

ADVERTISEMENT. No advertisement or other descriptive printed material issued by the applicant or private label distributor with respect to this device shall recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act, all advertisements and other descriptive printed material issued by the applicant or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects and contraindications.

PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT. Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effected" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations which require a PMA supplement cannot be briefly summarized, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

A "Special PMA Supplement - Changes Being Effected" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It allows for the addition of, but not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgment by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effected." This acknowledgment is in addition to that issued by the PMA Document Mail Center for all PMA supplements submitted. This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant(s) involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

POSTAPPROVAL REPORTS. Continued approval of this PMA is contingent upon the submission of postapproval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Postapproval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. The postapproval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

(1) Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).

(2) Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:

(a) unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and

(b) reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each identified report when so notified by FDA.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

(1) A mix-up of the device or its labeling with another article.

(2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and

(a) has not been addressed by the device's labeling or

(b) has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.

(3) Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION. The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984. This regulation was replaced by the reporting requirements of the Safe Medical Devices Act of 1990 which became effective July 31, 1996 and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to the FDA whenever they receive or otherwise become aware of information, from any source, that reasonably suggests that a device marketed by the manufacturer or importer:

- (1) May have caused or contributed to a death or serious injury; or
- (2) Has malfunctioned and such device or similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for a PMA, the manufacturer shall submit the appropriate reports required by the MDR Regulation within the time frames as identified in 21 CFR 803.10(c) using FDA Form 3500A, i.e., 30 days after becoming aware of a reportable death, serious injury, or malfunction as described in 21 CFR 803.50 and 21 CFR 803.52 and 5 days after becoming aware that a reportable MDR event requires remedial action to prevent an unreasonable risk of substantial harm to the public health. The manufacturer is responsible for submitting a baseline report on FDA Form 3417 for a device when the device model is first reported under 21 CFR 803.50. This baseline report is to include the PMA reference number. Any written report and its envelope is to be specifically identified, e.g., "Manufacturer Report," "5-Day Report," "Baseline Report," etc. Any written report is to be submitted to:

Food and Drug Administration
Center for Devices and Radiological Health
Medical Device Reporting
PO Box 3002
Rockville, Maryland 20847-3002

Copies of the MDR Regulation (FOD # 336&1336) and FDA publications entitled "An Overview of the Medical Device Reporting Regulation" (FOD # 509) and "Medical Device Reporting for Manufacturers" (FOD #987) are available on the CDRH WWW Home Page. They are also available through CDRH's Fact-On-Demand (F-O-D) at

800-899-0381. Written requests for information can be made by sending a facsimile to CDRH's Division of Small Manufacturers Assistance (DSMA) at 301-443-8818.

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SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name: Image Analysis System

Device Trade Name: ImageChecker M1000 System

Applicant's Name and Address: R2 Technology, Inc.
325 Distel Circle
Los Altos, CA 94022

PMA Number: P970058

Date of Panel Recommendation: May 11, 1998

Date of Approval to Applicant: June 26, 1998

II. INDICATIONS FOR USE

The ImageChecker M1000 is a computer system intended to identify and mark regions of interest on routine screening mammograms to bring them to the attention of the radiologist after the initial reading has been completed. Thus, the system assists the radiologist in minimizing observational oversights by identifying areas on the original mammogram that may warrant a second review.

III. CONTRAINDICATIONS

There are no contraindications for use of this device.

IV. WARNINGS AND PRECAUTIONS

Warning and Precautions for use of the device are stated in the attached product labeling. (Attachment A)

V. DEVICE DESCRIPTION

The ImageChecker M1000 System consists of the following major components: 1)Processor (containing a bar code reader, 50µm laser film digitizer and processing computer), 2)Ethernet or Modem link and, 3)Motorized Viewer (containing a bar code reader and video monitors).

Original mammograms are displayed in the conventional manner on the Motorized Viewer without any obstruction or marking. A bar code reader is provided as part of the ImageChecker M1000 System to identify case films and allow random access to the queue of low resolution images so they can be displayed in the same sequence as the films on the viewer transport.

A bar code identification number is placed on the upper left hand corner of a document such as the patient's film jacket, requisition slip, patient history sheet or mammography insert. When this bar code is inserted into the bar code reader in the Processor films a faint beep indicates the number has been read and the ID will

appear in the ID window on the touch sensitive screen. The reader is a commercial self-scanning unit that uses LED illumination and CCD sensing to decode the labels.

For each of the films, the video monitors display the corresponding low resolution images and markers which are generated by the ImageChecker M1000 System's processor. These markers identify likely sites of microcalcifications or masses, by comparing the results of R2 Technology's proprietary image processing techniques to generally accepted clinical criteria. The signal processing techniques are sensitive to clusters of bright spots and densities with radiating lines visible in the film which may be sites with microcalcifications or masses, respectively. The system uses two different markers; a triangle for a cluster of bright spots and an asterisk for a density with radiating lines.

To interpret a case, the radiologist reviews the mammograms (typically two views each of the left and right breasts) mounted on the Motorized Viewer for interpretation in the conventional manner. The radiologist then activates the ImageChecker M1000 System display unit to review the low resolution marked images on the two video display monitors installed on the console below the light boxes. The radiologist may then review the original mammograms again, paying particular attention to any areas of the images designated by the markers and revise his/her assessment, if necessary. The ImageChecker M1000 System thus functions as an aid to radiologists in reviewing mammograms by calling attention to regions of interest that have features that may be associated with breast cancer.

The ImageChecker algorithms look for characteristics commonly associated with cancer. The system ranks its findings by likelihood and then marks those regions above a fixed threshold of likelihood with a fixed upper limit of no more than three microcalcification ROIs or two mass ROIs per film. The following sections describe the algorithms used by the ImageChecker M1000 System when analyzing a mammogram.

Microcalcifications

The ImageChecker M1000 System searches an image for clusters of bright spots which are suggestive of microcalcification clusters. When features in the mammogram meet the generally accepted criteria for microcalcifications the System places a triangular marker over the centroid of that region on the low resolution images as shown in Figure 4.

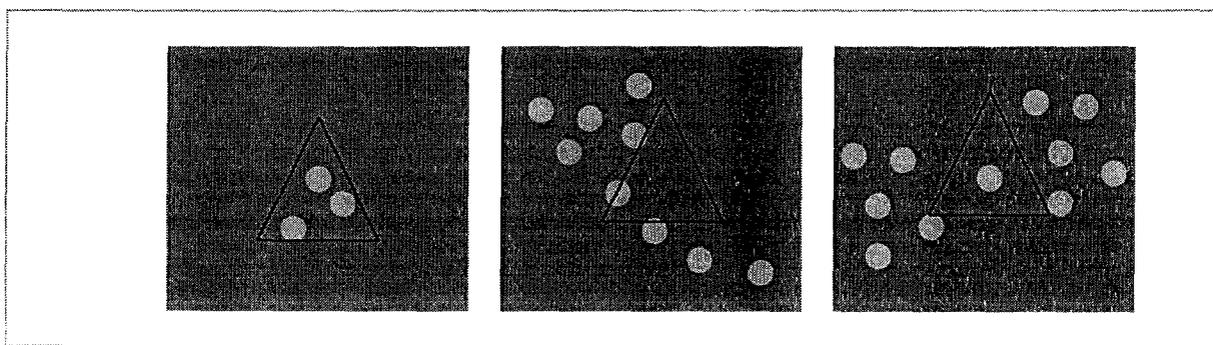


Figure 4. Marker positioning examples for microcalcifications

The System has been designed to mark only patterns associated with microcalcifications. However, normal structures in the breast sometimes satisfy the algorithm's criteria for patterns associated with microcalcifications and will also be marked as shown in Figure 5.

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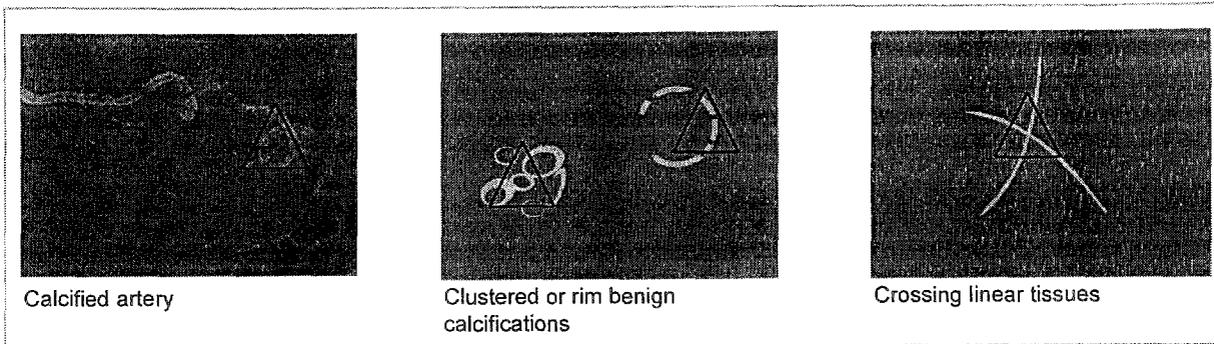


Figure 5. Examples of normal structures that can be marked as potential microcalcifications.

The System will not mark every cluster of bright spots. By design, the ImageChecker M1000 System will not mark:

- Very small clusters with less than 3 elements.
- Clusters where each bright spot in the cluster is separated by more than 2.5mm.

Masses

The ImageChecker M1000 System image-processing software also searches for patterns of dense regions with radiating lines suggestive of masses or architectural distortions.

To do this, it uses an “annulus.” The annulus consists of concentric inner and outer circles with a diameter of 6mm and 32mm, respectively. The annulus is “moved” over the mammogram. The outer circle defines the limits of the search area. See Figure 6, below. A marker is placed when the software encounters line segments radiating from a common origin (the inner annulus).

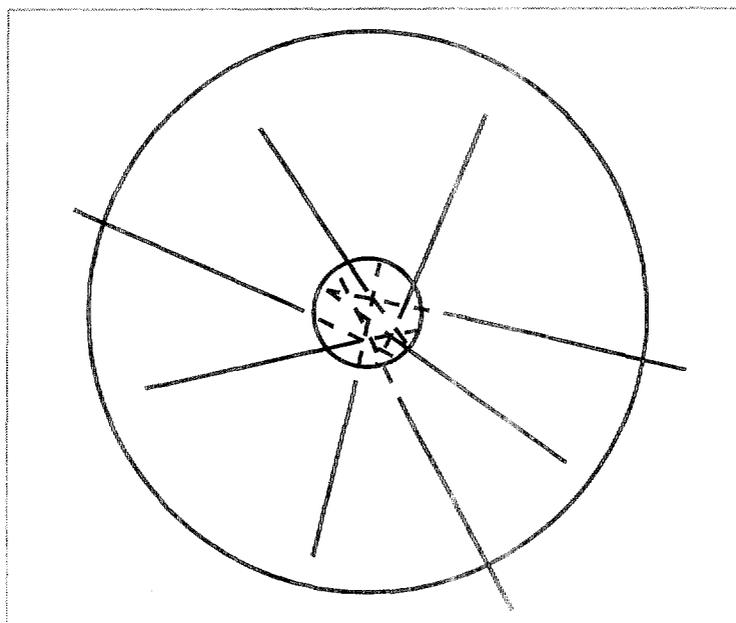


Figure 6. Radiating lines originating from the inner annulus.

In addition to radiating lines, the software is sensitive to the presence (or absence) of a central density. When no central density is found, the radiating lines must be more pronounced to be marked. See Figure 7, below. The ImageChecker M1000 System uses an asterisk to mark patterns associated with masses. The marker is positioned on the low resolution images at the point of maximum convergence.

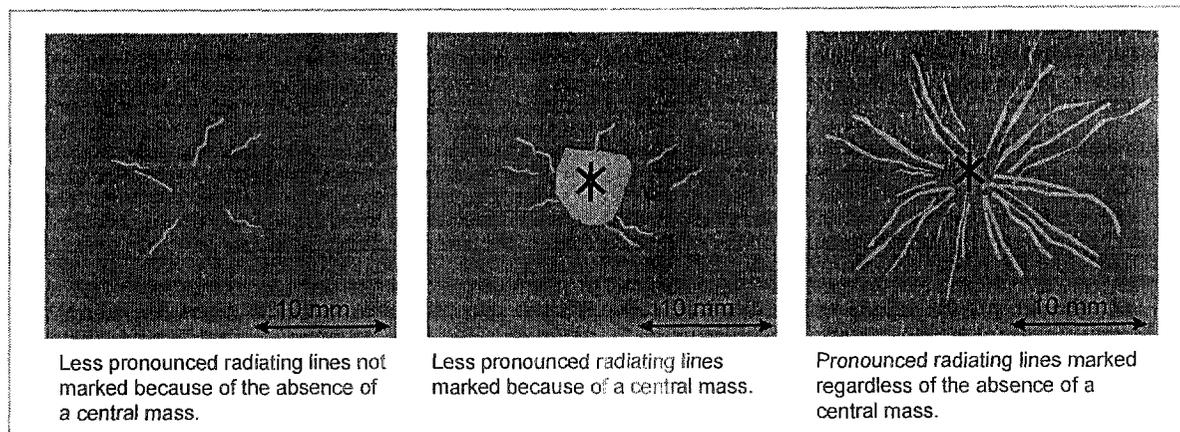


Figure 7. Relative effect of central density and radiating lines on whether feature is marked.

Normal structures in the breast can sometimes satisfy the algorithm's criteria for patterns associated with masses and will then be marked as shown in Figure 8.

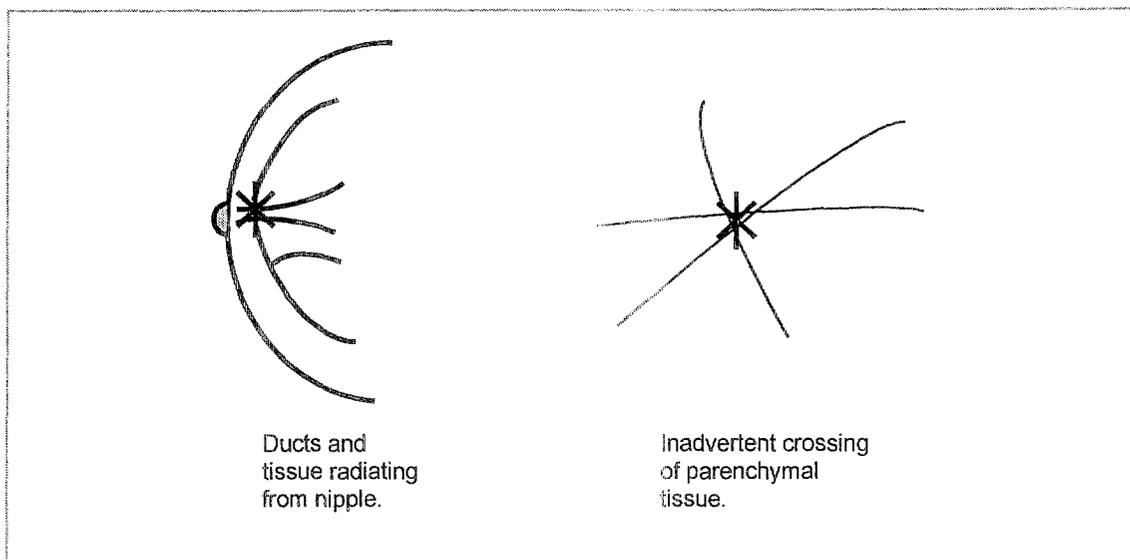


Figure 8. Examples of normal breast structures that can be marked as a potential mass.

Masses can be thought of as occupying a continuum ranging from well-defined to highly spiculated as shown in Figure 9.

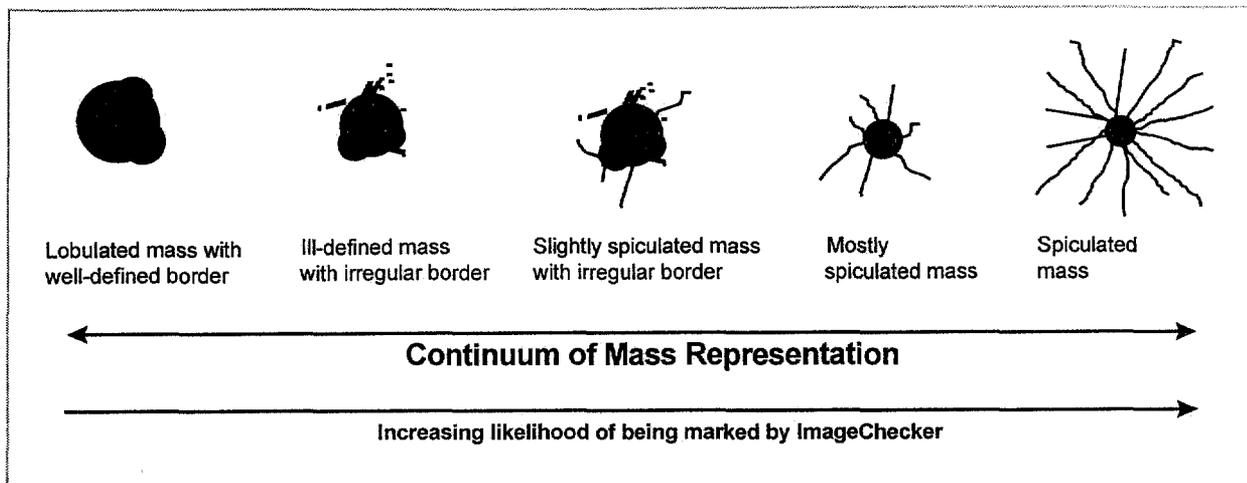


Figure 9. Mass characteristics and their relative likelihood of being marked.

The software algorithm has been optimized to identify and mark patterns associated with masses of 10 to 20 mm in size.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

The current procedure for reviewing mammograms involves a radiologist's review of the films on a lightbox or motorized film viewer. Commonly, the radiologist will use a magnifying glass to facilitate the identification of subtle features on the film. Only a small number of radiologists currently double read mammograms. Studies have shown that double reading results in an 8-15% gain in sensitivity.

VII. MARKETING HISTORY

The product was first introduced at the European Congress of Radiology in Vienna, Austria in March of 1997, and the first device was sold in Germany that same month. Since then, the product has been marketed in Norway, Sweden, Finland, France as well as Germany. No adverse effects have been reported from these countries, and it has not been withdrawn for any reason.

VIII. 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 which do not require further action (See Warnings above). The primary potential adverse effect of a screening test is missing disease; however, the potential for missed lesions is not increased over routine screening mammography when the ImageChecker is used as labeled.

IX. NON-CLINICAL STUDIES

Non-clinical studies were conducted from 1994 through January of 1997. These studies were designed to develop, analyze, and improve the design of the ImageChecker M1000 System.

System Reproducibility - The applicant performed an initial evaluation of system reproducibility based on test radiographs of the CIRS 50/50 4.5cm tissue equivalent breast phantom, manufactured by Nuclear Associates

(Model 18-222). This phantom was actually designed to stress the imaging capability of mammography film screen systems to their limits. It is not an accurate representation of the human breast that can produce realistic mammographic images. Therefore, it has significant limitations with regard to R2's application. The results with this phantom provided a preliminary demonstration that the ImageChecker M1000 System performs according to specifications when subjected to objective, quantitative criteria.

Assessment of Algorithm Performance - The applicant performed a quantitative assessment of the ImageChecker Algorithms based on testing from an in-house library of several hundred mammograms with known malignancies. The in-house library was not collected according to a formal protocol and no conclusions can be made regarding how representative the material is of the general screening population. The results provided a preliminary demonstration that the System performs with a high level of sensitivity in the detection of features associated with microcalcifications and masses.

In addition, significant in-house testing was conducted to determine the requirements for the image analysis algorithm. Informal evaluations and in-depth interviews were conducted to characterize the interactions between hardware and software to develop a user-friendly system configuration.

Safety - The ImageChecker M1000 System is in compliance with the following electrical safety and EMC standards: 1) UL2601-1, 2) IEC 60601-1, and 3) FCC Part 15 Class A. The device also has a number of additional safety features including: 1) leakage current ≤ 0.5 mA, 2) use of hospital grade NEMA connectors on all major components, and 3) other interlocks and mechanical safeguards.

Software Validation - The applicant provided documentation showing that the software used in this device was developed under an appropriate software development program. They have performed a hazard analysis from both the patient and user perspectives and addressed the identified hazards. They also performed an appropriate validation process. These processes provide the foundation for assuring that the software will operate as described in the specifications.

X. CLINICAL STUDIES

Preliminary studies were conducted to provide data regarding estimates of sensitivities to abnormal cases as well as guidance to finalize the protocols used in the Clinical Studies.

Use of the ImageChecker M1000 Information - The objective of this study was to evaluate how radiologists would utilize the ImageChecker M1000 System information in the course of routine mammogram interpretation. An independent testing firm (Corning HTA) designed and carried out a prospective study in which five (5) certified radiologists (radiology experience range 6-39 years) each read the same set of 180 cases. In the case set, the number of cancers was enriched, *i.e.* the prevalence was artificially high for purposes of the study. Cases were acquired from the Johns Hopkins Medical Institutions, Baltimore, MD.

For each case, the radiologists reviewed the films and recorded their interpretation according to normal clinical procedure. They next viewed the R2 display and re-evaluated the cases. The data sets were subjected to statistical analysis using a paired t-test.

There were no statistically significant differences in the performance of the radiologist with, versus without, the ImageChecker M1000 System ROI information. This result was not surprising given that both test environment and the artificially high number of cancers in the sample would result in heightened attentiveness among the radiologists and, therefore, reduce the likelihood of an observation oversight. Nevertheless, the finding provided preliminary support for the hypothesis that the ImageChecker M1000 System would not unduly affect the radiologist and result in a significant increase in work-up rates.

Retrospective-Directed Study of Prior Mammograms - A retrospective-directed study was undertaken in cooperation with the Palo Alto Medical Clinic, Department of Radiology, in Palo Alto, California to assess the ability of the ImageChecker M1000 System to mark appropriate ROIs on prior mammograms determined to be malignant after a subsequent mammogram. The study identified, in the population of consecutive cases from 1993 and 1994, those patients who had core biopsy confirmed diagnoses of malignant microcalcifications, and had a mammogram on file taken prior to the one upon which the diagnosis was made (*i.e.* a prior set of films in which the radiologist had interpreted the case as not warranting follow-up). In cases where there was more than one prior mammogram on file, the most recent prior was used for the study comparison. These prior mammograms were processed and displayed on the ImageChecker M1000 System and the results compared with the known lesion location.

Of the study sample of 22,000 cases reviewed over the 2 year period there was a total of 50 malignant microcalcifications diagnosed. There were 14 cases where prior (*i.e.* negative finding) films could not be retrieved (*e.g.* films had been returned to the referring physician). Of 36 patients for whom the most recent prior films could be located, 15 were not included in the analysis for the following reasons:

The lesion was not visible to the unaided eye.

There were multiple foci found, demanding a multi-factorial design which was beyond the scope of the pre-clinical study.

Of the remaining 21 cases, 17 were correctly identified by the ImageChecker M1000 System. From these preliminary data, it appeared evident that the ImageChecker M1000 System may provide assistance to the radiologist by identifying areas on the original mammogram that warrant a second review.

Pivotal Clinical Studies

R2 Technology, Inc. has conducted three studies to evaluate the performance of the ImageChecker M1000 System. The first study was a prospective, multicenter trial designed to demonstrate that, when used in a normal clinical setting, the System does not significantly increase the number of patient work-ups. The second study was a multicenter trial designed to measure the sensitivity of the System in correctly identifying obvious, actionable abnormalities in prior screening mammograms of cancer patients. This study provides a direct indication of the utility of the device for reducing false negative readings due to observational oversights. The third study measured the overall sensitivity of the System in identifying lesions in mammograms with biopsy-proven cancer, as well as the intra- and inter-system precision of marking ROIs associated with cancer.

For purposes of clarity, the terms "Currents" and "Priors" are defined as follows:

"Currents" are the mammographic screening films from asymptomatic patients where the cancer was first detected.

"Priors" are the most recent prior mammographic screening films acquired in the previous 9-24 months before the cancer was detected.

Protocol 1: Prospective Utilization Study

Study Goals

The goal of this multicenter, prospective study was to support the claim that the use of the ImageChecker M1000 System does not result in a significant increase in the number of patient work-ups when used as directed in a normal clinical setting.

Baseline Data Review

Historical data for a minimum four (4) month period was collected from hospital statistics describing:

Overall number of screening mammograms and work-up rate on a month-by-month basis.

Each individual radiologist's number of screening mammograms and work-up rate on a month-by-month basis.

Requirements for Participating Physicians

MQSA Certified, Read at least 100 routine screening cases/month.

Post-Installation Training and Data Collection Requirements

Approximately one month after installation of the system, the prospective arm of study was initiated. During this one month training period, the medical and technical staffs were trained in the operation of the device and any workflow changes were established, particularly those associated with the extra step of digitizing the mammograms prior to being reviewed by the radiologist. The prospective arm of the study was run for a minimum of four (4) months.

All asymptomatic screening mammography cases were run on the ImageChecker M1000 System. On a daily basis, paper printouts were collected for each screening case processed by the ImageChecker System.

On a monthly basis the following information was collected:

Overall number of screening mammograms and work-up rate during the month.

Each individual radiologist's number of screening mammograms and work-up rate during the month.

At the end of each month, a reconciliation was performed to confirm the monthly statistic regarding number of cases read and number of recalls for each participating radiologist, to account for any filed Problem Reports. If any cases were not included, the disposition of that patient was determined and any recommendation for further work-up was recorded.

Results

Fourteen (14) radiologists from five (5) institutions met the study criteria and were included in the study. The baseline number of cases read by these radiologists pre-installation was 23,682. The number of cases read post-installation was 14,817.

Individual radiologist's pre-installation work-up rates ranged from 2.2% to 15.2% with a group mean of 8.3%. Their post-installation work-up rates ranged from 2.4% to 11.3% with a group mean of 7.6%.

Due to variability from month to month and radiologist to radiologist, any change in call-back rates resulting from use of the device was too small to be detected.

Conclusion

The study data indicated that use of the ImageChecker did not create a significant increase in the work-up rate.

Protocol 2: Retrospective-Directed System Sensitivity Study

Study Goals

The goal of this multicenter study was to measure the capability of the ImageChecker M1000 System to correctly mark microcalcifications and masses in prior screening mammograms ("Priors") which, on review by a panel of five radiologists, were considered "actionable" (*i.e.*, recognizable by radiologists as requiring further work-up). The capability of the ImageChecker M1000 System to correctly mark abnormalities in those Priors considered actionable by a panel of radiologists will measure the efficacy of the device in minimizing the possibility of false negatives during mammographic screening due to observational oversights.

Collection and Preparation of Case Material

All consecutive asymptomatic screening films that led to a cancer diagnosis (Currents) in a 2 or 3 year period from 1994 to 1996 were identified from the thirteen (13) participating institutions. For this study, the most recent prior screening films acquired in the previous 9 to 24 months before the Current exam were collected. As such, the Priors represented all consecutive Priors that were available from all consecutive Currents acquired at that time.

To create the "gold standard" for each Current case, one of the radiologists from the institution that provided the Currents defined the biopsy-proven lesion location(s) on an overlay and the primary and secondary lesion characteristic(s). They also provided an assessment recommendation using the American College of Radiology BIRADS Categories:

- N Negative, no evidence of malignancy
- B Benign Findings, routine follow-up recommended
- P Probably Benign Findings, short interval follow-up recommended
- A Incomplete, requires immediate recall for additional views, US, etc.
- S Suspicious Abnormality, biopsy should be considered after work-up
- M High Probability of Breast Cancer, biopsy recommended after work-up

Several independent, MQSA certified radiologists acted as Designated Radiologists to assess the Priors. The Designated Radiologists were provided full information about the Currents and created a "gold standard" overlay for the Priors to account for any differences between Currents and Priors due to positioning of the breast during mammography. By necessity, the Designated Radiologists also provided an initial assessment of lesion visibility since it would be impossible to develop an overlay if no lesion were visible on the Prior. Such "Invisible Priors" were largely excluded from review by the Panel Radiologists, except for 20 cases which were included as a quality control measure.

Priors were also excluded from review by the Panel Radiologists if the case were unilateral (that is, the woman had a mastectomy) or if there had been previous breast surgery. Such cases would have required significant explanation of the patient's history to the Panel Radiologists which would have created a reading bias.

Data Review

For each Case Set the Visible Priors were mixed with Invisible Priors, Currents and Normals in the following approximate proportions:

- 75 Visible Priors.
- 5 Invisible Priors.
- 20 Currents (biopsy confirmed cancers) common to all radiologists.
- 20 Normal cases common to all radiologists.

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Four different Case Sets were run which included a total of 286 Visible Priors. Different radiologists participated in the review of each of the Case Sets. Under no circumstances could a radiologist participate in a panel if any Priors in the set were acquired from his/her institution.

Normal cases were defined as routine screening mammograms that were read as normal by an MQSA certified radiologist AND were confirmed by one or more follow-up exams that were also read as normal.

The 20 Currents were selected with the proportion of cases containing microcalcifications or masses made consistent with the overall distribution of microcalcifications and masses among the Currents. Cases defined according to the BIRADS assessment category as "M" (High Probability of Cancer, Recommend Biopsy) were considered too obvious and were thought to be inappropriate to measure the sensitivity of the radiologists on the panel. Therefore, cases were selected only from those that had a BIRADS assessment of "A" (Immediate Recall for Additional Views, 17/20) or "S" (Suspicious Abnormality, 3/20).

The 20 Normal Cases and 20 Current Cases allowed for an assessment of radiologist performance under the test conditions and inter-radiologist comparisons for justification of pooling.

The panel radiologists were instructed that there was a mixture of positive and negative cases, but were not advised of the prevalence of each type. The patient's age and information about any film markers was provided. Radiologists were asked to operate at their usual clinical threshold when reviewing the cases.

For each case, the Panel Radiologists provided:

Location of the single most suspicious region, if any, documented by circling the area on an overlay, if any.

Primary characteristic of the most suspicious lesion, if any.

Location of the second most suspicious region, if any, documented by circling the area on an overlay, if any.

Primary characteristic of the second most suspicious lesion, if any.

Assessment recommendation using the American College of Radiology BIRADS Categories (defined above).

The "gold standard" overlays were used to evaluate the findings of each of the Panel Radiologists. A "Consensus on Actionability" was developed for each case based on the number of Panel Radiologists that identified the correct location and classification of primary or secondary lesions on at least one view and categorized the case as actionable (BIRADS categories "A", "S" or "M").

All Priors were run on the ImageChecker M1000 System. The ImageChecker findings were scored by the Designated Radiologist. The System was judged to have marked the case correctly if it identified the correct location and classification of the lesion on at least one view when compared to the "gold standard" overlays.

Summary of Findings

493 Priors were collected. The average patient age was 63 years with a range of 34-86 years. Of the 493 Priors, 141 were classified as "Invisible" by the Designated Radiologist and excluded from review by the Panel Radiologists. A total of 20 of these cases were included in the Case Sets as a quality control measure.

Of the 352 remaining Visible Priors, 62 were excluded from review by the Panel Radiologists due to previous breast surgery or because the case was unilateral (that is, the woman had a mastectomy) to eliminate the possibility of bias. In fact, as these cases would have immediately raised the Panel Radiologists attention, this approach is very conservative. This left 290 Visible Priors.

Four additional cases were not included due to oversight (2) or the cases were not resolved with respect to some aspect of the patient history by the time of the final Case Set (2). Thus, 286 Visible Priors were reviewed by the Panel Radiologists.

Table 1: Summary of the Analysis of "Priors"

Radiologist Consensus on Actionability	Number of Cases	Number Correctly Marked	Percent Correctly Marked
0/5	83	28	33.7%
1/5	53	28	52.8%
2/5	38	24	63.2%
3/5	38	28	73.7%
4/5	38	30	78.9%
5/5	36	33	91.7%

Radiologists Consensus on Actionability	Number of Cases	Number Correctly Marked	Percent Correctly Marked	95% lower Limit	95% CI Upper Limit
Majority 3/5, 4/5, 5/5	112	91	81.3%	73.9%	83.1%
Super Majority 4/5, 5/5	74	63	85.1%	76.9%	87.5%
100% Consensus 5/5	36	33	91.7%	82.5%	95.7%

Table 1 summarizes the results of the analysis of Priors. 95% confidence intervals were calculated based on Clopper-Pearson exact likelihood limits with equal probability in each tail (side). The results demonstrate that:

22.7% (112/493) of all Priors were judged actionable by a majority of radiologists (3/5, 4/5 or 5/5). 81.3% (91/112) of these cases were correctly marked by the ImageChecker M1000 System.

15.0% (74/493) of all Priors were judged actionable by a super-majority of radiologists (4/5 or 5/5). 85.1% (63/74) of these cases were correctly marked by the ImageChecker M1000 System.

7.3% (36/493) of all Priors were judged actionable by all radiologists (5/5). 91.7% (33/36) of these cases were correctly marked by the ImageChecker M1000 System.

Table 2: Summary of the Analysis of "Priors" by Primary Feature

Microcalcifications	Number of Cases	Number Correctly Marked	Percent Correctly Marked
Majority 3/5, 4/5, 5/5	39	37	94.9%
Super Majority 4/5, 5/5	26	25	96.2%
100% Consensus 5/5	13	13	100.0%

Masses	Number of Cases	Number Correctly Marked	Percent Correctly Marked
Majority 3/5, 4/5, 5/5	73	54	74.0%
Super Majority 4/5, 5/5	48	38	79.2%
100% Consensus 5/5	23	20	87.0%

Table 2 summarizes the results of the analysis of Priors by primary feature. The results demonstrate that:

94.9% (37/39) of all calcifications and 74.0% (54/73) of all masses judged actionable by a majority of radiologists (3/5, 4/5 or 5/5) were correctly marked by the ImageChecker M1000 System.

96.2% (25/26) of all calcifications and 79.2% (38/48) of all masses judged actionable by a super-majority of radiologists (4/5 or 5/5) were correctly marked by the ImageChecker M1000 System.

100% (13/13) of all calcifications and 87.0% (20/23) of all masses judged actionable by a all radiologists (5/5) were correctly marked by the ImageChecker M1000 System.

The overall results demonstrate that the ImageChecker M1000 System can correctly mark a high percentage of microcalcifications and masses from Priors that were judged actionable by a majority of radiologists. Those Priors were acquired in the preceding 9-24 months before the cancer was diagnosed.

Protocol 3: Precision Studies

Study Goals

A series of Precision Studies was performed to measure: a) The sensitivity of the ImageChecker M1000 System to correctly mark microcalcifications and masses on Current mammograms from patients with biopsy-proven cancer and, b) The intra- and inter-system precision of marking ROIs associated with cancer.

Precision Study 1

The goal of the first Precision Study was to demonstrate the overall sensitivity of the ImageChecker M1000 System to mark lesions on current mammograms from patients with biopsy-proven cancer. This study provides a direct measure of the sensitivity of the device in marking microcalcifications and masses.

Case Material

All consecutive asymptomatic screening films (Currents), that led to the cancer being diagnosed and were confirmed by biopsy, were obtained. For each institution, the period from which Current cases were acquired was either 2 or 3 years from 1994, 1995 and 1996.

Collection and Preparation of Case Material

Based on the Cancer Case List provided by the Principal Investigator at each site, all patient jackets were requisitioned. Cases were excluded for the following documented reasons:

- Symptomatic patient
- No films/Jackets available
- Lack of information
- Not mammographically evident

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Wrong year for study
Other (Non-malignant case, etc.)

In this manner, all available consecutive asymptomatic screening films where cancer was first identified (Currents) were obtained. In addition, the following basic information about the case was recorded:

Patient age
Date of Service
Availability of earlier mammogram in the previous 9-24 months
Pathology findings

For each case, the radiologist from the institution that provided the Currents provided:

Location of the confirmed cancer by circling the area on an overlay.
Primary characteristic of this lesion.
Secondary characteristic of this lesion, if any.
Location of a second confirmed cancer, if any, by circling the area on an overlay.
Primary characteristic of the second lesion, if any.
Secondary characteristic of the second lesion, if any.
Assessment recommendation using the American College of Radiology BIRADS Categories (defined above).

This review and documentation process by radiologist from the institution that provided the Currents, created the "gold standard" for Currents.

Cases were brought to R2 Technology for processing on the ImageChecker M1000 System. The digitized films were archived on CD-ROM and magnetic tape. Copy films were printed at 100 μ m resolution and a paper printout of the low resolution images with the ImageChecker M1000 results was created.

When archiving and processing were complete, the films were returned to the hospital and the radiologist that originally created the "gold standard" for the case evaluated the ImageChecker marks on a paper printout and scored the System. That is, the radiologist determined whether the ImageChecker M1000 System had marked the case correctly by judging whether the System identified the correct location of the lesion and classification of the lesion (primary or secondary) on at least one view when compared to the "gold standard" overlays.

Table 3: Summary of Findings for Precision Study 1

Primary Feature	Number of Cases	Number Correctly Marked	Percent Correctly Marked	95% CI Lower Limit	95% CI Upper Limit
Microcalcifications	404	396	98.0%	96.6%	99.4%
Masses	679	507	74.7%	71.3%	77.9%
Total	1083	903	83.4%	81.1%	85.6%

Table 3 summarizes the results of the analysis of Currents by primary feature. 95% confidence intervals were calculated based on Clopper-Pearson exact likelihood limits with equal probability in each tail (side). 1083 consecutive cancer cases were acquired. These cancers were identified from the standard screening mammography programs for asymptomatic women at thirteen (13) institutions. These institutions

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represented private care institutions, dedicated breast centers, academic centers and managed care institutions. The results demonstrate that:

For cancers with microcalcification features, 98.0% (396/404) were correctly marked by the ImageChecker M1000 System.

For cancers with mass features, 74.7% (507/679) were correctly marked by the ImageChecker M1000 System.

Overall, 83.4% (903/1083) of all consecutive cancer cases were correctly marked by the ImageChecker M1000 System.

Finally, an analysis of the average number of marks per case (normally 4 films per case) was tallied as a function of primary feature. As expected, the number of marks per case was higher for cancer versus non-cancer cases. This finding reflects not only the expected increase in the number of marks due to the cancer but indirectly reflects the generally more complex nature of the breast containing cancer as well as the multifocal nature of the disease.

Primary Feature	Number of Cases	Marks/Case
Microcalcification	404	7.65
Mass	679	6.96
All Cancer	1083	7.22
Normals	100	3.58

Overall, the results demonstrate that the ImageChecker M1000 System can correctly mark a high percentage of lesions on Current mammograms from patients with biopsy-proven cancer. This study provides a direct measure of the sensitivity of the device to mark microcalcifications and masses from a large, consecutive and representative sample of cancers identified during standard screening mammography of asymptomatic women.

Precision Study 2

The goal of the second Precision Study was to demonstrate the intra- and inter-system reliability of the ImageChecker M1000 System in identifying and marking ROIs associated with cancer.

Selection of Case Material

Twenty-five (25) well-characterized cases were selected from the Current cases where the primary lesion was correctly marked in both views. Fourteen (14) Microcalcification cases and eleven (11) Mass cases, for a total of 25 cases, were selected. For expediency, only the two views from the side documented to have cancer were processed resulting in a total of 50 films. Each of the 50 films was run ten (10) times on three (3) different ImageChecker M1000 Systems.

The ImageChecker M1000 System was scored as having marked the case correctly if it identified the correct location and classification of the biopsy-proven lesion when compared to the gold standard.

Summary of Findings

Primary Feature	Number of Cases	Number of Films	Number Repetitions	System 1 Correctly Marked	System 2 Correctly Marked	System 3 Correctly Marked
Microcalcifications	14	28	10	280/280	279/280	280/280
Masses	11	22	10	220/220	220/220	220/220
Total	25	50	10	500/500	499/500	500/500

Table 4 summarizes the results of the intra- and inter-system precision study. The results demonstrate a near perfect reproducibility of result within and across systems. Of the 1500 evaluations (50 films x 10 passes per system x 3 systems) the ImageChecker M1000 System correctly marked the correct location with the appropriate marker on 1499/1500 evaluations for a precision rate of 99.93%.

These results demonstrate that the ImageChecker M1000 System consistently identifies microcalcification and mass features and is highly reproducible within and across systems.

System Reliability

Five (5) ImageChecker M1000 Systems were installed at the five (5) institutions participating in the prospective study between February and May of 1997. The system downtime, for any reason, was estimated as 7 days for the 31 months of system operation at all sites.

XI. CONCLUSIONS DRAWN FROM STUDIES

Study 1

The study data indicated that use of the ImageChecker did not create a significant increase in the work-up rate.

Study 2

The results of study 2 demonstrate that the ImageChecker M1000 System can correctly mark a high percentage of abnormalities from Priors that were judged actionable by a majority of radiologists. This capability demonstrates the effectiveness of the device in minimizing the possibility of false negative readings during mammographic screening due to observational oversights.

Study 3, Part 1

The results of study 3, part 1, demonstrate that the ImageChecker M1000 System can correctly mark a high percentage of abnormalities on Current mammograms from patients with biopsy-proven cancer. This study provides a direct measure of the sensitivity of the device to mark microcalcifications and masses from a large, consecutive and representative sample of cancers identified during standard screening mammography.

Study 3, Part 2

The results of study 3, part 2, demonstrate that the ImageChecker M1000 System is a highly robust system with highly reproducible results.

XII. PANEL RECOMMENDATIONS

A meeting of the FDA Radiological Devices Panel took place on May 11, 1998, to discuss, make recommendations and vote on the applicant's submission, PMA 970058, as amended. The panel members voted unanimously that the PMA was approvable with the condition that the applicant work with the FDA to address the labeling precautions and warnings concerns raised during discussion.

XIII. CDRH DECISION

CDRH concurred with the recommendation of the panel. The panel recommendations were adopted, and the FDA worked with the applicant in augmenting the Warnings and Precautions listed in the attached labeling. In addition, FDA required R2 Technology to submit a protocol and perform a postapproval study to more accurately assess the effect which the device will have on true positive and false positive work-up rates, and to revise its product brochure to include in the data those cancers missed because of misinterpretation.

The applicant's manufacturing and control facilities were inspected March 28 - April 3, 1998, and the facilities were found to be in compliance with the Good Manufacturing Practice (GMP) Regulations.

XIV. APPROVAL SPECIFICATIONS

Directions for use: See attached labeling.

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

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

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

ImageChecker M1000 - Device Labeling

1. Brief Device Description

The ImageChecker M1000 System is a computer system with image analysis and visual display capabilities. The System digitizes a mammogram which is then analyzed by proprietary signal processing algorithms which highlight “regions of interest” (ROIs) with the following characteristics:

- Clusters of bright spots (*i.e.*, regions suggestive of microcalcification clusters).
- Dense regions with radiating lines (*i.e.*, regions suggestive of masses or architectural distortions).

The ImageChecker M1000 System marks particular ROIs because of their physical characteristics. That is, the marked ROIs are associated with a visually perceptible structure that has some of the generally accepted geometric characteristics of microcalcifications or masses. The marked areas may be something other than an actual abnormality, but these are recognized as such by the radiologist upon review of the original mammogram.

Importantly, the ImageChecker M1000 System is not a diagnostic device, as only the original mammograms may be used for interpretation by the radiologist. By design, the device produces only low resolution images on its monitors to preclude their use for diagnostic interpretation. The device design and mode of operation are consistent with current standard mammography clinical practices, as governed by the requirements of the Mammography Quality Standards Act (MQSA) of 1992. Users are cautioned to always comply with the Mammography Quality Standards Act of 1992 (MQSA) for the United States, or the appropriate national standards when implementing the ImageChecker M1000 System in clinical protocols.

2. Indications for Use

The ImageChecker M1000 is a computer system intended to identify and mark regions of interest on routine screening mammograms to bring them to the attention of the radiologist after the initial reading has been completed. Thus, the system assists the radiologist in minimizing observational oversights by identifying areas on the original mammogram that may warrant a second review.

3. Contraindications

There are no contraindications for use of the device.

4. Warnings

Warnings: Radiological Interpretation

- The radiologist should base interpretation only upon the films and not use the markers shown on the low-resolution display for interpretation.
- The device is a detection aid, not an interpretative aid. It should only be used after the first reading.
 - The device marks many things which do not represent cancer, and the user must still use her or his interpretative skills on items marked by the device.
 - The device will not enhance what the user sees, rather it helps to identify regions on mammograms that should be reexamined.
- The device will not identify all areas that are suspicious for cancer.
 - Some lesions will be missed by the device 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 right-left asymmetries or changes from other mammograms.
 - The device is not designed to detect vague opacities, skin thickening, or nipple retractions.
 - Conditions of the breast that diminish mammographic sensitivity, such as density of normal tissue, also diminish the sensitivity of the device.
 - The device is more sensitive for the detection of microcalcifications (98.0%) than masses (74.7%), that is, it will miss about 2% of microcalcifications and 25% of masses.
- Individual practice patterns may influence the results obtained when using this device. Therefore, each facility and radiologist should carefully monitor the results which this device has on their practice of mammography in order to optimize its effectiveness.

Warnings: System Operation

- Remove all potentially obstructive jewelry and clothing before loading the films in the Processor or Motorized Viewer to prevent the possibility of injury due to moving parts or damage to the System.
- The symbol next to the power connector indicates potential shock hazard. Ensure that the system is connected to a power receptacle that is properly grounded and provides voltage and current within the specifications of the system 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 liquid. Contact authorized R2 Technology service personnel.

Warnings: Installation and Maintenance

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

5. Precautions

Precautions: System Operation

- Operators should review the User Manuals and receive training as required before using the System.
- Perform the Processor and Scanner Tests weekly to ensure the System's performance, as per the User Manuals.
- To ensure proper system operation, use only barcode labels provided by R2 Technology.
- In order for the low-resolution display images to correctly correspond to the film position at the display unit, be certain to orient and order the films correctly when scanning, as per the User Manuals.
- For proper operation of the System:
 - The technical quality of the original mammography films (*e.g.*, contrast) should meet relevant MQSA standards and be acceptable to the mammographer.
 - The system should only be used on standard size mammographic film: 18cm x 24cm or 24cm x 30cm.
 - Safety and effectiveness has not been independently established for analyzing mammograms from patients with breast implants. For patients with breast implants, only Implant Displaced Views (Ecklund or stand-off) can be processed by the system and only in cases with a maximum of 2.5cm (1") of the breast implant imaged on the film.
 - No diagnostic films (*e.g.*, magnification views or spot compression views) can be processed.
 - Cases where segmented views of the breast are shown cannot be analyzed, *i.e.*, the breast was too large to be imaged on one film so a "mosaic" version was taken.
 - Do not attempt to place films in the scanner that have labels or tape with edges within 1mm of the edge of the film as they may jam.
 - Do not attempt to place films in the scanner that are bent or damaged as they may jam.
- To prevent damage to the system, shut down the System according to the procedures recommended in the Operator's Manuals.

Precautions: Installation and Maintenance

- This product contains no user serviceable parts. To prevent damage to the system, do not attempt to install or repair the ImageChecker M1000 System. Only trained personnel, authorized by R2 Technology, are qualified to install or repair the System. For service training, contact R2 Technology at 1 (888) 472-7877.
- To prevent damage to the system, maintain equipment in a well-ventilated, air-conditioned environment.
- Disconnect power cord before moving or servicing.

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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 which do not require further action (See Warnings above). The primary potential adverse effect of a screening test is missing disease; however, the potential for missed lesions is not increased over routine screening mammography when the ImageChecker is used as labeled.

7. Clinical Studies

R2 Technology, Inc., has conducted three comprehensive clinical studies in order to demonstrate the safety and effectiveness of the ImageChecker M1000 System.

Study 1

A multicenter, prospective study was conducted to evaluate a concern about the potential increase in the number of work-ups resulting from the use of the device. Baseline pre-installation data consisting of 23,682 cases were acquired from five (5) institutions over a four month period. Fourteen (14) MQSA certified radiologists participated in the study. The baseline data were compared to the post-installation data of 14,817 cases derived from the same institutions and readers over a similar time period. The study data indicated that use of the ImageChecker did not create a significant increase in the work-up rate.

Study 2

The second study was a multicenter retrospective-directed analysis of mammograms from patients whose cancer was diagnosed following a subsequent screening mammogram. It was designed to test the ability of the device to identify abnormalities in prior screening mammograms.

All available consecutive screening films where the cancer was first detected (Currents) were obtained as well as the most recent prior screening films acquired in the previous 9-24 months, all of which were read as “normal” at the time (Priors).

A blinded review of these Priors was conducted by a panel of five radiologists and they were subsequently analyzed by the M1000 Image Checker. The results are shown in the following Table.

Radiologists Consensus on Actionability	Number of Cases	Number Correctly Marked	Percent Correctly Marked	95% lower Limit	95% CI Upper Limit
Majority 3/5, 4/5, 5/5	112	91	81.3%	73.9%	83.1%
Super Majority 4/5, 5/5	74	63	85.1%	76.9%	87.5%
100% Consensus 5/5	36	33	91.7%	82.5%	95.7%

Study 3

The third study measured: a) The overall sensitivity of the System in identifying lesions in mammograms with biopsy-proven cancer found during screening mammography, and b) The intra- and inter-system precision of marking ROIs associated with cancer.

Study 3A - Thirteen (13) institutions representing dedicated breast centers, academic centers and managed care institutions provided case data. All available consecutive screening films where the cancer was diagnosed (Currents) were obtained for a total of 1,083 cases. Given that the incidence of breast cancer is 40-50 cases per 10,000 screening mammograms, the material collected represents all cancers that were detected from a pool of approximately 250,000 asymptomatic screening mammograms.

Summary of Findings for Study 3A

Primary Feature	Number of Cases	Number Correctly Marked	Percent Correctly Marked	95% CI Lower Limit	95% CI Upper Limit
Microcalcifications	404	396	98.0%	96.6%	99.4%
Masses	679	507	74.7%	71.3%	77.9%
Total	1083	903	83.4%	81.1%	85.6%

Study 3B - Twenty-five (25) well-characterized Current cancer cases were processed by the device to demonstrate the intra- and inter-system reliability of the ImageChecker M1000 System in marking characteristics associated with cancer. The two films from the side with cancer were run 10 times on three different ImageChecker M1000 Systems. The ImageChecker M1000 was scored to have marked the case correctly if it identified the correct location and classification of the biopsy-proven lesion when compared to the gold standard.

Summary of Findings

Primary Feature	Number of Cases	Number of Films	Number Repetitions	System 1 Correctly Marked	System 2 Correctly Marked	System 3 Correctly Marked
Microcalcifications	14	28	10	280/280	279/280	280/280
Masses	11	22	10	220/220	220/220	220/220
Total	25	50	10	500/500	499/500	500/500

8. Principles of Operation

The ImageChecker algorithms look for characteristics commonly associated with cancer. The system ranks its findings by likelihood and then marks those regions above a fixed threshold of likelihood with a fixed upper limit of no more than three microcalcification ROIs or two mass ROIs per film. The following sections describe the algorithms used by the ImageChecker M1000 System when analyzing a mammogram for the main features associated with breast cancer - microcalcifications and masses.

Microcalcifications

The ImageChecker M1000 System searches an image for clusters of bright spots which are suggestive of microcalcification clusters. When features in the mammogram meet the generally accepted criteria for microcalcifications the System places a triangular marker over the centroid of that region on the low resolution images as shown in Figure 1.

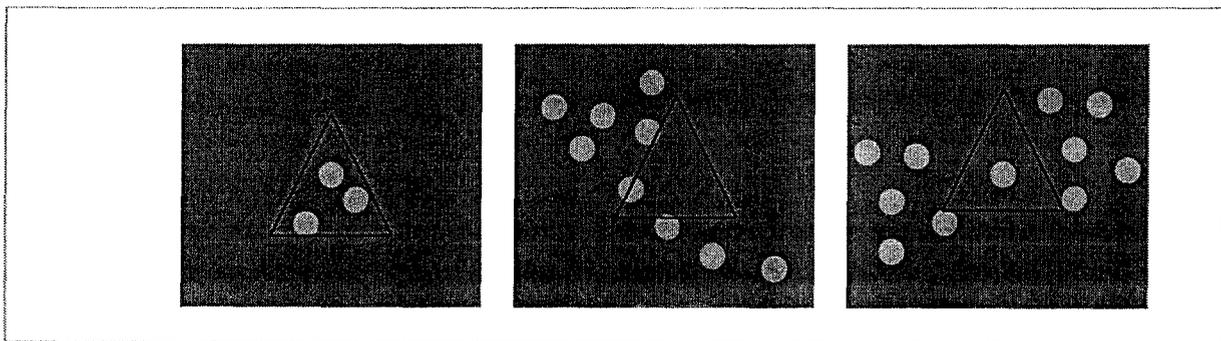


Figure 1. Marker positioning examples for microcalcifications

The System will not mark every cluster of bright spots. By design, the ImageChecker M1000 System will not mark:

- Very small clusters with less than 3 elements.
- Clusters where each bright spot in the cluster is separated by more than 2.5mm.

Masses

The ImageChecker M1000 System image-processing software also searches for patterns of dense regions with radiating lines suggestive of masses or architectural distortions.

To do this, it uses an “annulus”. The annulus consists of concentric inner and outer circles with a diameter of 6mm and 32mm, respectively. The annulus is “moved” over the mammogram. The outer circle defines the limits of the search area. See Figure 2, below. A marker is placed when the software encounters line segments radiating from a common origin (the inner annulus).

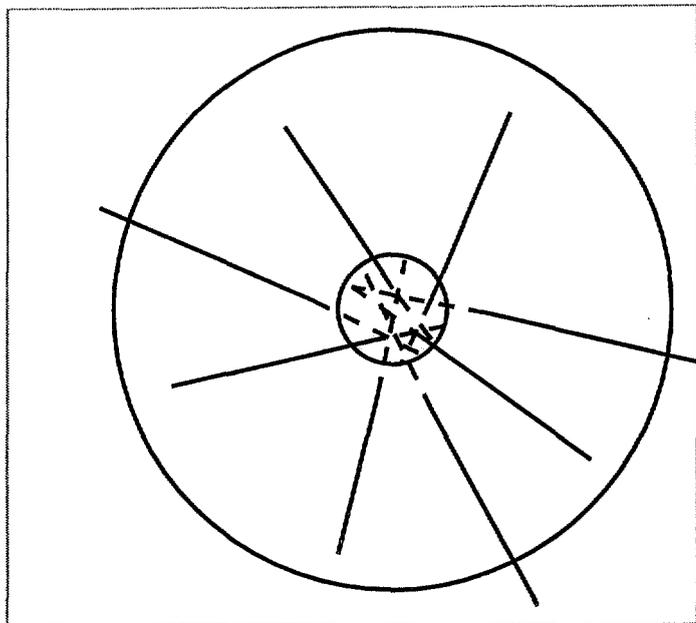


Figure 2. Radiating lines originating from the inner annulus.

In addition to radiating lines, the software is sensitive to the presence (or absence) of a central density. When no central density is found, the radiating lines must be more pronounced in order to be marked. See Figure 3, below. The ImageChecker M1000 System uses an asterisk to mark patterns associated with masses. The marker is positioned on the low resolution images at the point of maximum convergence.

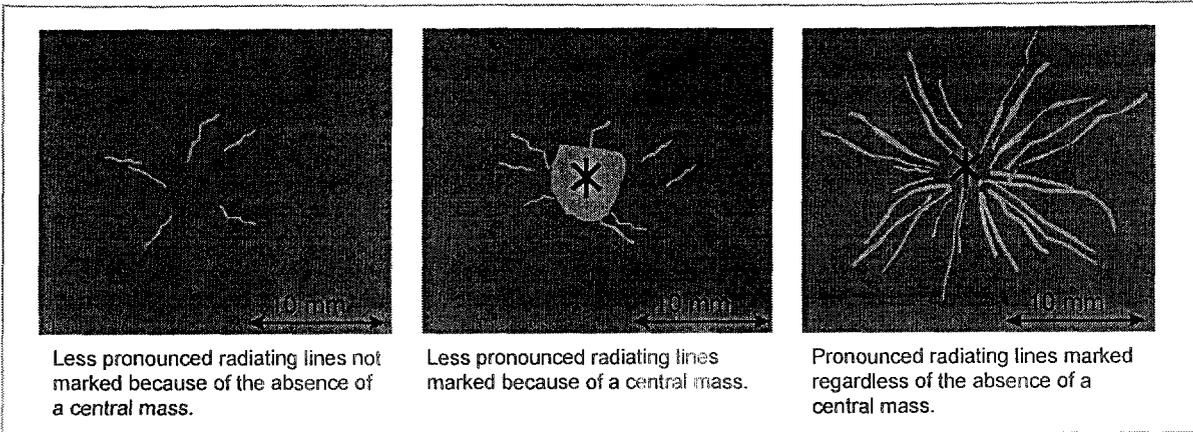


Figure 3. Relative effect of central density and radiating lines on whether feature is marked.

Normal structures in the breast can sometimes satisfy the algorithm's criteria for patterns associated with masses and will then be marked as shown in Figure 4.

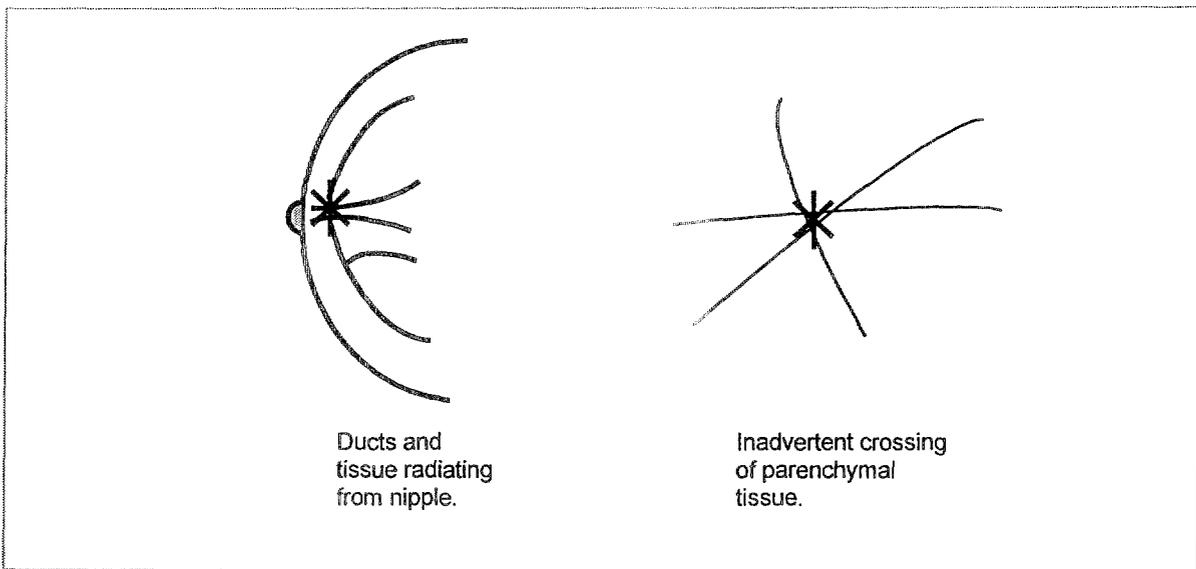


Figure 4. Examples of normal breast structures that can be marked as a potential mass.

Masses can be thought of as occupying a continuum ranging from well-defined to highly spiculated. This continuum, as well as the likelihood of the mass being marked by the ImageChecker, are shown in Figure 5.

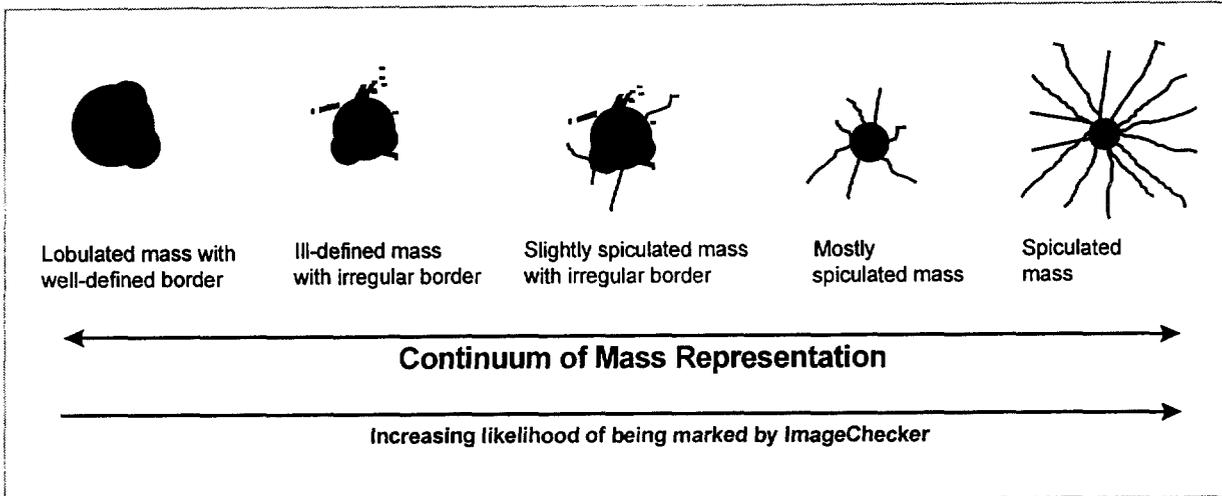


Figure 5. Mass characteristics and their relative likelihood of being marked.

9. Conformance to Standards

The ImageChecker M1000 System is in compliance with the following Electrical Safety and EMC Standards:

USA: UL2601-1, IEC 601-1, FCC Part 15 Class A

Europe: EN60601-1, EN60601-1-2,

Canada: CSA601.1, DOC Regulation CRC, c.1374; ICES-003

Japan: JIS-1001

10. How Supplied

Standard configuration for the ImageChecker M1000 System includes the following major components:

- Processor (containing the bar code reader, 50 micron laser film digitizer and processing computer)
- Ethernet or Modem link
- Motorized Viewer (containing a bar code reader and video monitors)

11. Operator's Manual

The following Operator's Manuals are provided with the ImageChecker M1000 System:

1. Processor User Manual - Describes how to handle films for digitization and processing by the ImageChecker M1000 System.

2. Viewer User Manual - Describes how to hang films on the Motorized Viewer as well as display controls for the low resolution images with markers that were processed by the ImageChecker M1000 System.
3. Processor Quick Guide - A Quick reference manual that summarizes information in the Processor User Manual.
4. Viewer Quick Guide - A Quick reference manual that summarizes information in the Viewer User Manual.
5. Algorithm Description - Provides an overview of the ImageChecker M1000 System algorithms and describes the basic processing parameters and criteria for feature detection.

12. References

Selected references are provided below:

1. American Cancer Society, Breast Cancer Facts and Figures 1996.
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