

## Summary of Safety and Effectiveness Data

### **1 GENERAL INFORMATION**

Device Generic Name:	Mammogram Image Analysis System
Device Trade Name:	Kodak Mammography CAD Engine
Applicant's Name and Address:	Eastman Kodak Company 343 State Street Rochester, NY 14650
Date of Panel Recommendation:	Not applicable, refer to section XII
PMA (Pre-market Approval Application):	P030007
Date of GMP Inspection:	September 15, 2004
Date of Notice of Approval to Applicant:	November 23, 2004

### **2 INDICATIONS FOR USE**

The Kodak Mammography CAD Engine is a software package intended to identify and mark regions of interest on routine screening and diagnostic mammograms to bring them to the attention of the radiologist after the initial reading has been completed. Thus, the software 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 this device.

### **4 WARNINGS AND PRECAUTIONS**

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

### **5 DEVICE DESCRIPTION**

The Kodak Mammography CAD Engine is a software package designed to identify and mark regions of interest on digitized routine screening and diagnostic film mammograms. The Kodak Mammography CAD Engine is used in combination with three specific accessories, including the Kodak Case Input Station / for Mammography CAD System (CIS), the Vidar Diagnostic Pro (a specific high-resolution digitizer), and the Kodak Report Station / for Mammography CAD System. The Kodak Mammography CAD Engine, the Kodak Case Input Station / for Mammography CAD System (CIS), the Kodak Report Station / for Mammography CAD System, and the high resolution x-ray film digitizer constitute a complete CAD system. The software package is installed on off-the-shelf computing

equipment (see below) by trained Kodak employees using documented installation procedures and instructions. Users will be provided with an integrated user manual which includes instructions on mandatory, regular quality control procedures.

The high resolution digitizer, cleared under the premarket notification K993599, is responsible for converting the traditional film images into a digital format. The digitizer is controlled by a software program, the Kodak Case Input Station / for Mammography CAD System (CIS), which ensures that the images are being digitized in the proper orientation and notifies the Kodak Mammography CAD Engine that the images are ready to be processed. The CIS was cleared under the premarket notification K031132. Once the images have been processed by the Kodak Mammography CAD Engine, the Kodak Report Station / for Mammography CAD System is notified that the results are ready to be viewed. The Report Station allows the user (typically a radiologist) to view or print low resolution versions of the images with or without marks suggesting potential cancers. The Report Station was cleared under the premarket notification K031248.

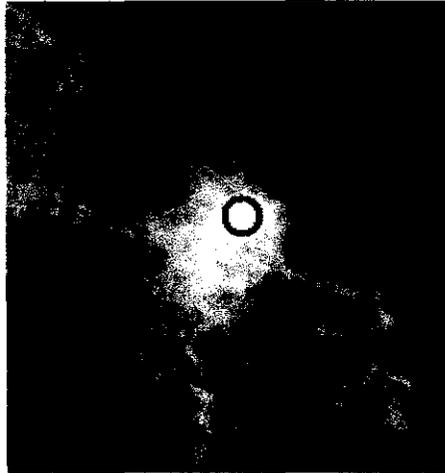
Acceptable computing equipment for use with the Kodak Mammography CAD Engine must have the following minimum specifications: Microsoft® Windows® XP Professional edition, a 2-gigahertz (GHz) processor, 500 megabytes (MB) of Random Access Memory (RAM), and a 20-gigabyte (GB) hard drive.

Mammograms are digitized by a high-resolution digitizer under control of Kodak Case Input Station / for Mammography CAD System . A barcode, a manually entered reference number, or a name identifies the case for the rest of the software package.

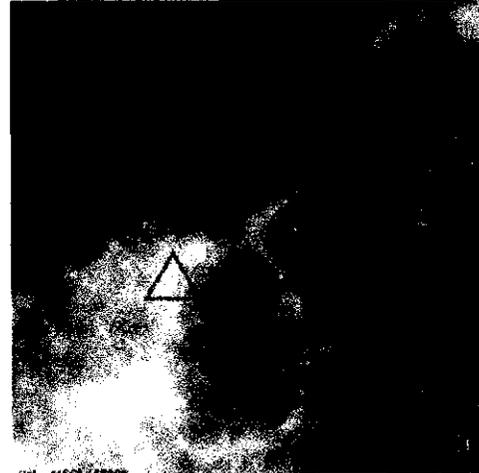
The Kodak Mammography CAD Engine executes a Computer-Assisted Detection (CAD) algorithm designed to examine the digitized mammograms for signs of cancer. This algorithm focuses on two primary signs of cancers, densities (of multiple types) and clustered micro-calcifications (MCCs). The Kodak Mammography CAD Engine can detect densities (or masses) with an equivalent diameter between 5 mm and 50 mm. The Kodak Mammography CAD Engine can also detect MCCs that contain a number of micro-calcification spots with spot-to-spot distance less than 6 mm, and with each micro-calcification spot bigger than 0.2 mm and smaller than 0.6 mm in diameter. A cluster contains at least 3 micro-calcifications.

Candidate locations (areas of potential cancer) are extracted from all images acquired during the mammogram. Typically a mammography session, or case, consists of two or four images. The Kodak Mammography CAD Engine then makes the final marks available in an electronic CAD report.

The electronic report can be displayed using the Kodak Report Station / for Mammography CAD System (an equivalent printed report can also be generated). The Kodak Report Station / for Mammography CAD System overlays marks on low resolution representations of the original digitized mammograms for anatomical orientation and reference. Potential masses are marked by a hollow blue circle, as seen in Figure 1, and potential MCCs are marked with a hollow green triangle, as seen in Figure 2.



**Figure 1 Mass Mark Location**



**Figure 2 Multiple MCC mark locations**

The directions for use specify that a radiologist will first read the case on film in the conventional, unaided manner. Next, the radiologist is instructed to review the marks on the Kodak Report Station / for Mammography CAD System (or on the printed report). As a result, the radiologist may want to re-review regions marked by the CAD system to verify that they do not warrant work-up. The directions for use clearly specify that the lack of a CAD mark in a suspicious region does not warrant a reversal of a work-up decision arrived at during the unaided read.

## **6 ALTERNATIVE PRACTICES AND PROCEDURES**

Film mammograms are typically placed on motorized viewers or light boxes. The radiologist reviews the mammogram for signs of cancer, often with the help of a magnifying glass or a hot light. The Mammography Quality Standards Act (MQSA) documents practices and procedures to maximize the accuracy of reading mammograms.

Some centers use “double reading”, meaning that a second radiologist reviews each mammogram. It has been reported in clinical literature that more cancers are found through double reading without undue increase in work-up rate.

There are also other systems that perform image analysis like that performed by the Kodak Mammography CAD Engine. These systems are commonly referred to as “Mammography CAD” systems.

## **7 MARKETING HISTORY**

The Kodak Mammography CAD Engine has never been marketed domestically or internationally.

## **8 POTENTIAL ADVERSE EFFECTS OF DEVICE ON HEALTH**

There are no known direct risks to safety or health of the user or the patient that are related to the use of the device. Indirect inherent risks are that (a) the device may not mark actionable areas; and (b) the device may mark regions that are not actionable. These possibilities are

explained in the Warnings section of the device labeling. Proper use of the marks generated by the device is explained in the Directions for Use section of the device labeling.

## **9 SUMMARY OF PRE-CLINICAL STUDIES**

Several pre-pivotal studies were conducted throughout the development and design of the Kodak Mammography CAD Engine as described in section 9.1-9.4 below.

### **9.1 CAD Algorithm Sensitivity and Specificity**

During the development of the Kodak Mammography CAD Engine, over 2,000 cases, with over 8,000 individual images, were collected and digitized from five mammography centers using a formal clinical protocol for algorithm development and validation purposes. The cases were randomly placed into one of three sets, training, testing, and clinical. The clinical cases were sequestered from software developers and were used in the clinical studies described in section 10 below. The training and testing sets were used by the software engineers to develop and test the Kodak Mammography CAD Engine in house. The cases consisted of biopsy-confirmed cancer cases and normal cases that had confirmation of normality in a follow-up of at least 2 years. For the biopsy-confirmed cancer cases, the cancerous regions were electronically outlined by a site radiologist.

The algorithm was trained using data from the training set and then tested using the test set. Algorithm results were initially measured using different thresholds resulting in multiple sensitivity/false positive rate combinations. Bi-monthly test results were generated and analyzed to determine the product-readiness. The final benchmark demonstrated a sensitivity of 93.8% with 0.88 false positive marks per normal image.

### **9.2 Comparison Study**

A subset of the test and training databases were analyzed using a commercially available CAD system. These results were compared to the marks generated by an earlier version of the Kodak Mammography CAD Engine and analyzed. The analysis provided useful reference data for further development.

### **9.3 Pilot Reader Study**

A small reader study with two readers and about 80 cases was conducted to evaluate the algorithm when used by radiologists. The study demonstrated that CAD marks can assist a radiologist in finding more cancers than in the unaided read.

### **9.4 Software Validation and Verification**

Kodak developed and validated the Kodak Mammography CAD Engine in compliance with software standard AAMI/ANSI SW 68, Medical Device Software Lifecycle Processes. Validation of the Kodak Mammography CAD Engine is conducted as per the requirements of this standard.

## 10 SUMMARY OF CLINICAL STUDIES

Four clinical studies were conducted to evaluate the precision and clinical performance of the Kodak Mammography CAD Engine as described in 10.1 to 10.5 below.

The **Precision Study** had two objectives:

**P1** Measure **sensitivity** of the CAD algorithm in isolation using biopsy-proven cancer cases; measure **false positive rate** on follow-up confirmed normal cases.

**P2** Confirm **reproducibility** of the CAD algorithm in conjunction with the digitization process, using algorithm results based on repeated digitization of the same films on a group of different digitizers.

The **Reader Study** also had two objectives:

**S1** Estimate the **increase in work-up rate**, resulting from the use of CAD, as compared to independent double reading by radiologists.

**S2** Estimate the ability of the CAD algorithm, as an aide to radiologists, to identify cancers earlier, based on their **performance on visible, actionable priors**. Priors are mammograms temporally preceding the mammogram on which a cancer was found.

### 10.1 Precision Study-P1 (Sensitivity Study)

Five hundred eighty-eight cases were collected and digitized from five mammography centers using a clinical protocol. These cases were sequestered from the algorithm development group.

Biopsy-confirmed cancer cases were retrospectively collected using a randomized selection protocol. Only densities in a size range of 5-50mm and micro-calcification clusters of at least 3 micro-calcifications within a 6mm circle were included. Exclusion criteria consisted of cases that did not have four views (two for uni-laterals), cases with breast implants, cases without standard mammographic quality, cases without sufficient patient information, and cases where there was an inability to adequately digitize an image.

The site radiologist identified the truth regions on film, and these regions were transferred into electronic form in XML format. Therefore, algorithm performance was assessed automatically and objectively, without human intervention. The site radiologist was asked to identify each truth region as either a mass or a micro-calcification cluster (MCC) and to identify the primary sign of cancer for the case: "mass" or "MCC". Of the 394 cancer cases, 262 were identified as mass, 172 were identified as MCC, and 40 were identified as both mass and MCC.

Normal cases were also collected from the same five sites using a defined protocol. Similar exclusion criteria applied, but for normal cases, a confirming normal follow-up exam was required to exclude the possibility of the presence of undetected, developing cancer. One hundred ninety-four normal cases were added to the study, for a total of 588 cases in the study.

The Kodak Mammography CAD Engine was used to evaluate the 588 cases. A case was considered a true positive if a mark was placed on at least one cancerous lesion in at least one

view. Sensitivity was determined as the fraction of true positives over all cancer cases. False positives per image (FPI) were calculated as an average of false positive marks per image on all normal cases. The lower and upper bounds of the 95% confidence interval for sensitivity and FPI was determined using bootstrapping over cases with 2.5% on each tail (see Table I-1).

**Table I-1 P1: Kodak Mammography CAD Engine Sensitivity**

	Total Cases	Detected by Kodak Mammography CAD Engine	Sensitivity	95% CI Lower Bound	95% CI Upper Bound
Primary "Mass" Cases	262	228	87.0%	83.1%	91.0%
Primary "MCC" Cases	172	156	90.7%	86.0%	94.8%
All Cases	394	344	87.3%	84.0%	90.6%

The average FPI was determined to be 1.0 false positive mark per normal image, with a 95% CI of +/- 0.1 FPI.

## 10.2 Precision Study-P2 (Reproducibility Study)

The algorithm implemented in the Kodak Mammography CAD Engine is digital, and since no physical source of variation or noise comes into play, it was expected to produce the same output every time it was presented with the same input. In contrast, the process of digitizing a film involves film positioning and processing illumination, and a light quantum collection to reproduce a high range of optical densities at a high resolution with high fidelity. Subtle grey scale variations found in subtle lesions will present with slight variation in digitized images. Reproducibility is expected to be higher for well-characterized lesions that are clearly visible in both views. The reproducibility study analyzed reproducibility in relation to lesion characteristics.

Twenty-two cases, with one lesion visible in both views, were selected from the clinical and testing data sets. These cases were digitized at least nine times each, on three different digitizers. In the P1 Study, eighteen of these cases were reported as true positives in the base-line run and six of the cases were detected in both views.

Reproducibility was measured as the largest number of equal outcomes among the 30 runs e.g., 27 true positives out of 30 have a reproducibility of 90% as do 27 false positives out of 30 (see Table I-2).

**Table I-2 P2: Kodak Mammography CAD Engine Reproducibility**

	Number of Cases	Reproducibility	95% CI Lower Bound	95% CI Upper Bound
All Cases	22	92%	87%	98%
Baseline True Positives	18	94%	88%	100%
Baseline Both Views	6	100%	100%	100%

Confidence intervals were determined using bootstrapping over cases, digitizers, and individual runs on the digitizers.

### **10.3 Reader Study**

While the Precision Study was designed to measure the performance of the Kodak Mammography CAD Engine alone, the Reader Study was designed to measure performance of the Kodak Mammography CAD Engine used by a radiologist. The study was conducted at two of the five sites (Rose Medical Center and the University of Colorado Health Science Center) and only data from those two sites were used.

A set of 228 cases was composed of normal, current, and prior cases. All cancer cases with available prior exams from precision study P1 from the two sites were reviewed by a site radiologist. Information about the case was available at the review. The site radiologist determined whether the biopsy-confirmed lesion on the current exam was retrospectively visible on the prior exam. In this manner, a total of 47 visible “prior” cases were included and available for the study. The prior exam was taken an average of 15 months (6-36 months) earlier than the current exam.

The remaining cancer cases from the two sites from Precision Study P1 were randomized, and an additional 29 “current” cases were included for a total of 76 cancer cases. Additionally, 152 normal cases were collected at the two study sites.

Eight MQSA-qualified radiologists with 4 to 14 years (average 8 years) of experience participated in the study. These radiologists had read between 1,000 and 15,000 mammograms in the year preceding the study. The radiologists had not seen the cases before the study and were blinded to the proportion of cancer cases and the nature of the cases (however, they all evidently and reasonably expected a higher proportion of cancers than in a regular screening environment). The radiologists were given a training session on the mechanics of the study and were given hands-on training with 14 cases. After assessing each case without and with CAD marks, the radiologists were shown the truth for each of these training cases.

The radiologists were first presented with the films without any additional information (except surgical scars) and were requested to provide a Breast Imaging and Reporting Data System (BIRADS) rating for each breast. Next, the readers were presented with the CAD marks, and were again requested to provide an updated BIRADS rating. The radiologists were instructed that they could not reverse a diagnosis from positive to negative. Additional information was collected for specific analyses of the study. Results of this study are presented in sections 10.4 and 10.5.

### **10.4 Reader Study-S1 (Work-up Rate Study)**

In Reader Study-S1, an independent double reading study, two radiologists independently read a case. If one or both of the radiologists recommended work-up, the case was recalled for further studies. The study and analysis was designed to compare unaided, radiologist double reading to computer-aided reading.

Unaided and aided sensitivity for individual radiologists was determined as that fraction of cancer breasts that received a BIRADS rating of 0, 4, or 5. False positive rate on normal,

single breast cases was used to model the work-up rate. The average sensitivity and false positive rates for individual radiologists, including 95% CI intervals, were determined using bootstrapping over cases and radiologists.

Eight radiologists independently read all cases resulting in 28 possible independent double reading combinations. The average sensitivity and false positive rates for double reads, including confidence intervals, were again determined using bootstrapping over cases and all 28 pairs of double reads.

Finally, the increase in sensitivity and false positive rate from unaided to aided double reading was determined by joint bootstrapping of all three methods over radiologists and/or pairs of radiologists. The increases for both aided and double reading were statistically significant (see Table I-3).

**Table I-3 S1: Kodak Mammography CAD Engine Work-Up Rate Increases**

	Sensitivity	95% CI Interval	False Positive Rate	95% CI Interval
<b>Unaided Read</b>	71%	59-83%	33%	19-47%
<b>Double Read</b>	85%	78-91%	50%	40-59%
<b>CAD-Aided Read</b>	75%	64-86%	38%	25-52%

Tables I-4 and I-5 provide sub-analysis data of sensitivity for prior and current cancers

**Table I-4 Sub-Analysis of Unaided and Aided Sensitivity**

Sensitivity	Unaided	Aided	Change
All Data	71%	75%	4%
Priors	58%	63%	5%
Currents	91%	93%	3%

and for BIRADS 1 and 2 normal cases.

**Table I-5 Sub-Analysis of Unaided and Aided False Positive Rates**

False Positive Rate	Unaided	Aided	Change
All Data	33%	38%	5%
BIRADS 1	23%	30%	6%
BIRADS 2	45%	49%	4%

Both double and aided read demonstrate a statistically significant increase of sensitivity and false positive rate at a similar *relative* rate (i.e. ratio of false positives rate increase to sensitivity increase).

### 10.5 Reader Study-S2 (Inferential Study)

Reader Study-S2 was designed to infer what proportion of visible cancers that was missed, by single radiologist reading, could be found earlier if the Kodak Mammography CAD Engine was used. The study consisted of two parts: determination of actionability of prior cases and estimation of the Kodak Mammography CAD Engine performance on those cases.

The unaided BIRADS ratings for the 47 prior cases were selected from the reader study. The eight radiologists that had assigned an unaided BIRADS rating of 0, 4, or 5 were identified for each case. Weighted averaging was used to determine the weighted number of actionable cases, e.g., a case identified as “actionable” by 3 out of 8 radiologists was weighted by a factor 3/8.

Four radiologists were requested to identify the BIRADS 0, 4 or 5 rating. Actionability based only on suspicious regions that developed into cancer, and weighting these based on the assessments of four radiologists only, resulted in a total of 22.3 actionable cases.

BIRADS ratings for the same cases were also collected for the aided read, and a change in actionability was accepted if the change was based on a lesion that was correctly identified by the Kodak Mammography CAD Engine. In this manner, the number of actionable cases was increased to 23.8.

Kodak Mammography CAD Engine results for actionable cases were combined, using the same weighted averaging scheme mentioned above. The times between current and prior exams were averaged in a weighted manner. 39.4% of visible prior cases were correctly identified by the Kodak Mammography CAD Engine. Therefore, at least 39.4% of missed cancers could have been diagnosed 14.8 months earlier with the help of the Kodak Mammography CAD Engine (see Table I-6).

**Table I-6 S2: Kodak Mammography CAD Engine Prior Analysis (4 Readers, Correct Location)**

	Cases Deemed Actionable	Weighted	Identified by Mammography CAD Engine	Weighted
0 out of 4	6	0.0	1	0.0
1 out of 4	11	2.8	5	1.3
2 out of 4	14	7.0	10	5.0
3 out of 4	8	6.0	7	5.3
4 out of 4	8	8.0	7	7.0
<b>Total</b>	<b>47</b>	<b>23.8</b>	<b>30</b>	<b>18.5</b>
				<b>39.4%</b>

A 95% confidence interval of +/- 14% was determined by bootstrapping over readers and cases.

## **11 CONCLUSIONS DRAWN FROM STUDIES**

The clinical precision studies measured the sensitivity of the Kodak Mammography CAD Engine at 87% (CI 84.0-90.6%) on all cancers, with a false positive rate of approximately one mark per image.

The clinical reader studies demonstrated that use of the Kodak Mammography CAD Engine would have helped the radiologist to identify 39.4% (CI +/- 14%) of missed cancers 14.8 months earlier.

The work-up rate is necessarily increased because the Kodak Mammography CAD Engine is intended to alert radiologists to additional regions of interest, and not to reverse any unaided findings. In relation to the sensitivity improvement, the work-up rate increase is comparable to independent human reading.

## **12 PANEL RECOMMENDATIONS**

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Radiological Devices Panel, and FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

## **13 CDRH DECISION**

The sponsor's manufacturing and control facilities were inspected on September 15, 2004, and they were found to be in compliance with Good Manufacturing Practice Regulations.

Based on the review of the information submitted the PMA (which includes all amendments), the device has been found to be reasonably safe and effective for its intended use when used in accordance with the instructions for use. CDRH worked with Kodak and refined the labeling so that it accurately described the capabilities of the device as demonstrated by the clinical trials that were conducted.

FDA issued an approval order on November 23, 2004.

## **14 APPROVAL SPECIFICATIONS**

Directions for use: See attached labeling.

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

Post-approval Requirements and Restrictions: See approval order.