



ScreenPoint Medical BV
% Dr. Nico Karssemeijer
CEO
Stationsplein 26
Nijmegen, 6512 AB
NETHERLANDS

November 21, 2018

Re: K181704

Trade/Device Name: Transpara™

Regulation Number: 21 CFR 892.2090

Regulation Name: Radiological Computer Assisted Detection And Diagnosis Software

Regulatory Class: Class II

Product Code: QDQ

Dated: October 17, 2018

Received: October 19, 2018

Dear Dr. Karssemeijer:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm> identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's

requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see <https://www.fda.gov/CombinationProducts/GuidanceRegulatoryInformation/ucm597488.htm>); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to <http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm>.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (<https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/>) and CDRH Learn (<http://www.fda.gov/Training/CDRHLearn>). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (<http://www.fda.gov/DICE>) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

A handwritten signature in blue ink that reads "Michael D. O'Hara". The signature is written over a large, light blue watermark of the letters "FDA".

Robert Ochs, Ph.D.

Director

Division of Radiological Health

Office of In Vitro Diagnostics

and Radiological Health

Center for Devices and Radiological Health

Enclosure

Indications for Use

510(k) Number (if known)

K181704

Device Name

Transpara™

Indications for Use (Describe)

The ScreenPoint Transpara™ system is intended for use as a concurrent reading aid for physicians interpreting screening mammograms, to identify regions suspicious for breast cancer and assess their likelihood of malignancy. Output of the device includes marks placed on suspicious soft tissue lesions and suspicious calcifications; region-based scores, displayed upon the physician's query, indicating the likelihood that cancer is present in specific regions; and an overall score indicating the likelihood that cancer is present on the mammogram. Patient management decisions should not be made solely on the basis of analysis by Transpara™.

Type of Use (Select one or both, as applicable)

Prescription Use (Part 21 CFR 801 Subpart D)

Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

This section applies only to requirements of the Paperwork Reduction Act of 1995.

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510(k) Summary Transpara™

K181704

This 510(k) summary of safety and effectiveness information is prepared in accordance with the requirements of 21 CFR § 807.92.

1. Submitter

Manufacturer:

ScreenPoint Medical BV

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Stationsplein 26, 6512AB, Nijmegen, The Netherlands

Date:

November 18, 2018

2. Device

Device trade name	Transpara™
Device	Radiological Computer Assisted Detection and Diagnosis Software
Classification regulation	21 CFR 892.2090
Panel	Radiology
Device class	II
Product code	QDQ
Submission type	Traditional 510(k)

3. Legally marketed predicate device

Device trade name	OsteoDetect
Legal Manufacturer	Imagen Technologies, Inc.
Device	Radiological Computer Assisted Detection and Diagnosis Software
Classification regulation	21 CFR 892.2090
Panel	Radiology
Device class	II
Product code	QBS

4. Device description

Transpara™ is a software-only device for aiding radiologists with the detection and diagnosis of breast cancer in mammograms. The product consists of a processing server and an optional viewer. The software applies algorithms for recognition of suspicious calcifications and soft tissue lesions, which are trained with large databases of biopsy proven examples of breast cancer, benign lesions and normal tissue. Processing results of Transpara™ can be transmitted to external destinations, such as medical imaging workstations or archives, using the DICOM mammography CAD SR protocol. This allows PACS workstations to implement the interface of Transpara™ in mammography reading applications.

Transpara™ automatically processes mammograms and the output of the device can be used by radiologists concurrently with the reading of mammograms. The user interface of Transpara™ has different functions:

- a) Activation of computer aided detection (CAD) marks to highlight locations where the device detected suspicious calcifications or soft tissue lesions. Only the most suspicious soft tissue lesions are marked to achieve a very low false positive rate.
- b) Regions can be queried using a pointer for interactive decision support. When the location of the queried region corresponds with a finding of Transpara™ a suspiciousness level of the region computed by the algorithms in the device is displayed. When Transpara™ has identified a corresponding region in another view of the same breast this corresponding region is also displayed to minimize interactions required from the user.
- c) Display of the exam based Transpara™ Score which categorizes exams on a scale of 1-10 with increasing likelihood of cancer.

Transpara™ is configured as a DICOM node in a network and receives its input images from another DICOM node, such as a mammography device or a PACS archive. The image analysis unit includes machine learning components trained to detect calcifications and soft tissue lesions and a component to pre-process images in such a way that images from different vendors can be processed by the same algorithms

5. Indications for use

Transpara™ is a software medical device for use in a healthcare facility or hospital with the following indications for use:

The ScreenPoint Transpara™ system is intended for use as a concurrent reading aid for physicians interpreting screening mammograms, to identify regions suspicious for breast cancer and assess their likelihood of malignancy. Output of the device includes marks placed on suspicious soft tissue lesions and suspicious calcifications; region-based scores, displayed upon the physician's query, indicating the likelihood that cancer is present in specific regions; and an overall score indicating the likelihood that cancer is present on the mammogram. Patient management decisions should not be made solely on the basis of analysis by Transpara™.

Intended user population

Intended users of *Transpara™* are physicians qualified to read screening mammograms.

Intended patient population

The device is intended to be used in the population of women undergoing screening mammography.

Warnings and precautions

Transpara™ is an adjunct tool and not intended to replace a physicians' own review of a mammogram. Decisions should not be made solely based on analysis by Transpara™.

6. Predicate device comparison

The indication for use of Transpara™ is similar to that of the predicate device. Both devices are intended to be used by clinicians interpreting radiological images, to help them with localizing and characterizing abnormalities. The devices are both intended to be used concurrently with the reading of images and are not intended as a replacement for the review of a clinician or their clinical judgement.

The indication for use of Transpara™ and the predicate device differ in the disease specific findings the devices detect, the type of medical images the devices process, and the intended patient population. However, these differences do not raise new questions regarding safety and effectiveness of the device when used as labeled.

The overall design of Transpara™ is similar to that of the predicate device. Differences in technological characteristics of Transpara™ and the predicate device do not raise different questions of safety and effectiveness.

7. Summary of non-clinical performance data

In the design and development of Transpara™, ScreenPoint applied the following voluntary FDA recognized standards:

Standard ID	Standard Title	FDA Recognition #
ISO 14971:2007	Medical Devices - Application Of Risk Management To Medical Devices	5-40
IEC 62304:2015	Medical Device Software - Software Life Cycle Processes	13-79
DEN180005	Evaluation of automatic class III designation for OsteoDetect – Decision summary with special controls	N/A

The following guidance documents were used to support this submission:

- Guidance for Industry and FDA Staff - Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices (Issued on May 11, 2005)

- Computer-Assisted Detection Devices Applied to Radiology Images and Radiology Device Data – Premarket Notification [510(k)] Submissions (Issued on July 3, 2012)
- Guidance for Industry and FDA Staff - Clinical Performance Assessment: Considerations for Computer-Assisted Detection Devices Applied to Radiology Images and Radiology Device Data - Premarket Approval (PMA) and Premarket Notification [510(k)] Submissions (Issued on July 3, 2012)

Software performance testing

Transpara™ is a software-only device. The level of concern for the device is determined as Moderate Level of Concern.

Verification testing consisted of software unit testing, software integration testing and software system testing. The purpose of the verification test was to assure that the software application satisfied the software requirements.

Validation testing consisted of determining stand-alone performance of the algorithms in Transpara™ using a multi-vendor testset of mammograms acquired from multiple centers in multiple EU countries. This test dataset was not used for training of Transpara™ algorithms and included mammograms of asymptomatic women acquired with devices from four manufacturers: Hologic, GE, Philips and Siemens. Sensitivity and specificity of the CADe marks for detection of malignant calcification groups and soft tissue lesions were determined with 95% confidence intervals obtained by bootstrapping. Sensitivity for calcifications was 94.1 (90.6-97.1) with a false positive rate of 0.23 (0.22-0.25) marks per image. For soft tissue lesions sensitivity was 72.0 (67.4-76.5) with a false positive rate of 0.033 (0.028-0.037) marks per image.

The Transpara™ Score indicates the likelihood that a mammographically visible cancer is present in an exam. The score combines the results of the Transpara™ algorithms. The score is calibrated in such a way that the number of screening mammograms in each category is approximately equal. The figure shows that in the independent testing database 78% of exams with screen-detected cancers fall in category 10, while very few occur in the lowest categories (Fig. 1)

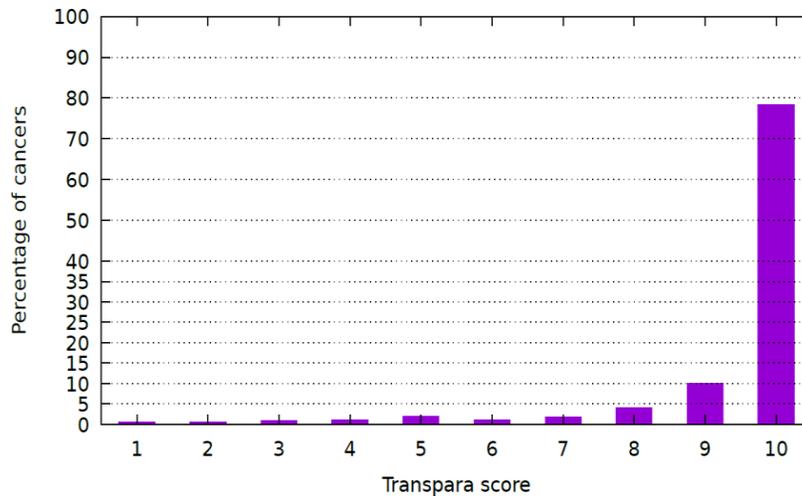


Figure 1: The Transpara™ Score indicates the likelihood that a mammographically visible cancer is present in an exam. The graph shows that in the testing database over 78% of exams with cancers fall in category 10, while very few occur in the lowest categories.

Transpara™ operates on “FOR PRESENTATION” images from different manufacturers. Since manufacturers use different proprietary processing algorithms, which may evolve over time or have flavors which can be selected by the user, the performance of the Transpara™ detection algorithms should not be affected by differences in image processing methods applied by manufacturers. In addition, algorithms should be able to work with images that have a different pixel spacing. Stability tests have been performed to verify that performance of Transpara™ remains stable when processing and pixel spacing varies.

Based on results of verification and validation tests it is concluded that Transpara™ is effective in the detection of soft lesions and calcifications at an appropriate safety level in mammograms acquired with mammography devices for which the software has been validated.

8. Summary of clinical tests

A pivotal reader study has been conducted to determine whether the performance of radiologists in detecting breast cancer in mammograms increases when they use the Transpara™, compared to when they read mammograms unaided. The primary effectiveness endpoint of the study is a significant increase of area under the ROC (AUC). The following guidance document was used to design and conduct the study:

- Guidance for Industry and FDA Staff - Clinical Performance Assessment: Considerations for Computer-Assisted Detection Devices Applied to Radiology Images and Radiology Device Data - Premarket Approval (PMA) and Premarket Notification [510(k)] Submissions (Issued on July 3, 2012)

In the study, both conditions are tested with a balanced fully-crossed multi-reader multi-case (MRMC) retrospective study. Study outcomes are comparisons of area under the receiver operating characteristic curve, sensitivity and specificity, and reading time.

In the study fourteen MQSA qualified radiologists read 240 cases twice, once with and once without Transpara™, with a washout period of one month or more in between. The reader study was conducted in the United States. The study set contained digital mammograms of asymptomatic women that were retrospectively collected at two clinical centers using Lorad Selenia (Hologic) and Mammomat Inspiration devices. The selected cases consisted of series of consecutive samples. The study set included 100 cases with cancer, 40 false positive recalls from screening, and 100 normal exams.

Reading was performed using a setting similar to a screening procedure in the United States. All readers completed the reading sessions as scheduled following the study protocol. There were no adverse events reported in the clinical reader study.

Statistical analysis of the MRMC study was done using analysis of variance models that take repeated measures into account.

Results showed that radiologists significantly improved their detection performance when using Transpara™, with the average AUC increasing from 0.866 to 0.886 (+0.020, 95% CI = 0.010 – 0.030, $P=0.0019$). (Figure 2). Per reader, the changes in AUC ranged from -0.3% to +5.4%, being higher with Transpara™ for twelve out of the fourteen radiologists (equal AUC for one reader and decrease of 0.3% with Transpara™ for another).

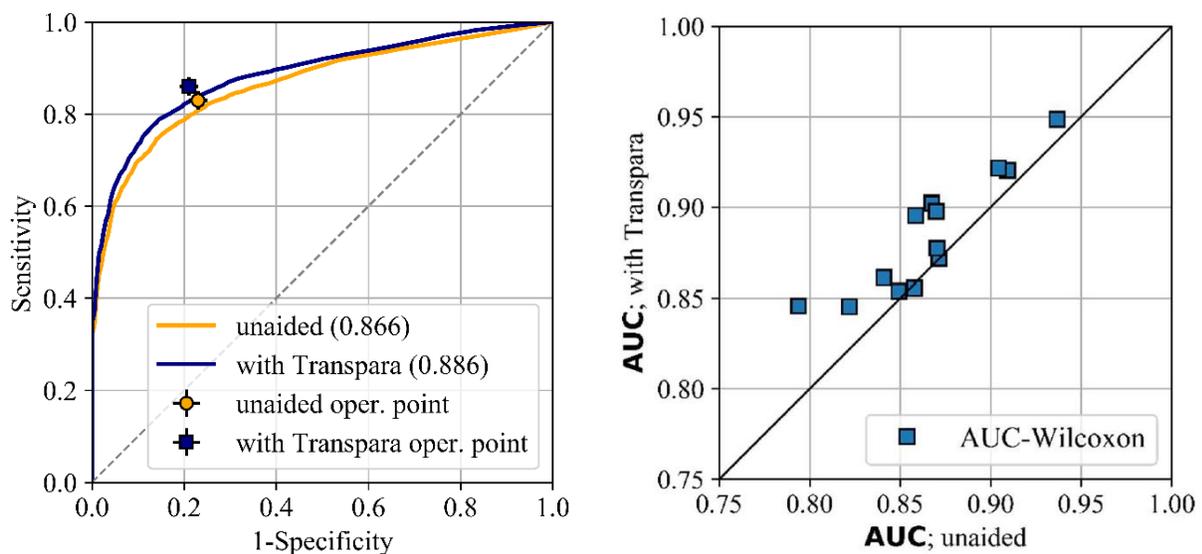


Figure 2. Average ROC performance of the readers under both reading conditions (left), and AUC performance of the individual readers in aided and unaided condition (right). In the ROC plot the operating point computed with the BI-RADS ≥ 3 criterion is shown.

Analysis by lesion type was performed by only including the True and False positive exams of the given type in the evaluation. Performance was higher with Transpara™ whether reading cases with soft tissue lesions or reading cases with calcifications. For soft tissue lesions, the AUC increased from 0.886 to 0.902 (mean difference = +0.016, standard error = 0.007), while for calcifications, the AUC was 0.878 in the unaided and 0.898 in the aided mode (mean difference = +0.020, standard error = 0.012).

On average, reading time per case was similar in the unaided sessions (146 s, 95% CI: 143-149 s) and the sessions with Transpara™ (149 s, 95% CI: 146-152 s). Reading time increased for nine out of fourteen radiologists (range 0.5-10%) while it decreased for five (range 0.3%-22%)

The standalone breast cancer detection performance of *Transpara*™ was observed to approach the average performance of the clinical study radiologists when reading mammograms unaided (radiologists' AUC = 0.866 versus *Transpara*™ AUC=0.887). Compared to each individual radiologist, *Transpara*™ had higher AUC (range 1.5-9.3%) than eleven out of the fourteen radiologists, and lower AUC than the other 3 (range 1.7-4.7%).

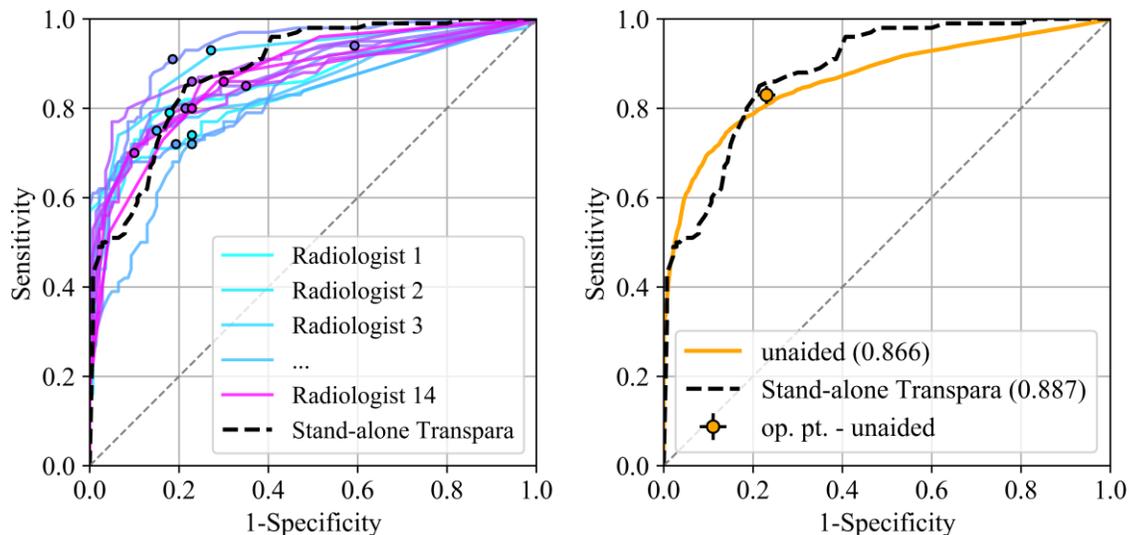


Figure 3. Comparison of ROC curves between the radiologists (reading mammograms unaided, left individual radiologists, right shows the average of the 14 radiologists) and *Transpara*™ as a stand-alone. Radiologists' operating points at BI-RADS 3 thresholds are indicated with the circle markers. Op. pt. indicates the mean operating point of the radiologists.

Discussion

The primary endpoint of the clinical study was met. With the use of device AUC of the readers increase significantly ($p=0.0019$). Secondary descriptive analyses show that the

impact of Transpara™ on radiologists' performance depends negligibly on lesion type, image type and used workflow, while there is not an increase in reading time.

In conclusion, study results provide evidence for safety and effectiveness of Transpara™. With use of the device it is likely that false positives and false negatives are reduced. A decrease in false positives and false negative was also found in the clinical test performed with the predicate device, in a study with similar design. Therefore, the outcome of the clinical study supports substantial equivalence of Transpara™ with the predicate device.

9. Conclusions

The data presented in this 510(k) includes all required information to support the review by FDA. Non-clinical and clinical performance tests demonstrate that Transpara™ is safe and effective.

One difference with the predicate device is a difference in the indications for use, because it detects different disease specific findings in different radiological images. The risks associated with use of the device are comparable because they are both intended to be used in a similar same way as aid for the clinician. Main risks are related to false positives and false negatives of the devices and these are mitigated by special controls defined in DEN180005.

Results of the primary analysis of the clinical test demonstrate that use of Transpara™ improves detection of breast cancer in mammograms. Hypothesis testing was not pre-specified for secondary analyses. Descriptively, improvement was observed to depend negligibly on lesion type and reading time was not observed to increase with the use of Transpara™. In addition, sensitivity of the readers tended to increase with the use of Transpara™ without decreasing specificity. Finally, in standalone testing, Transpara™ breast cancer detection performance was observed to approach the average performance of the clinical study radiologists when reading mammograms unaided.

ScreenPoint has applied a risk management process in accordance with FDA recognized standards to identify, evaluate, and mitigate all known hazards related to Transpara™. These hazards may occur when accuracy of diagnosis is potentially affected, causing either false-positives or false-negatives. All identified risks are effectively mitigated and it can be concluded that the residual risk is outweighed by the benefits.

Considering all data in this submission, the data provided in this 510(k) supports the safe and effective use of Transpara™ for its indications for use and substantial equivalence to the predicate device.