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# Reflected near-infrared light versus bite-wing radiography for the detection of proximal caries: A multicenter prospective clinical study conducted in private practices

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ABSTRACT

*Objectives:* The aim of the present prospective multicenter clinical study was to compare the detection of proximal caries with near-infrared light reflection (NILR) versus bitewing radiography (BWR).

*Materials and methods:* Intraoral scans were performed on 100 patients in five dental clinics using an intraoral scanner (iTero Element 5D, Align Technology, Tempe, AZ, USA) that includes a near-infrared light source (850 nm) and sensor. Reflected near-infrared light images of posterior teeth were used by the individual dentists to detect proximal caries and the results were compared to the BWRs. In a total of 3499 proximal surfaces of molars and premolars which were examined, 223 carious lesions were detected by BWR, while NILR detected 549 carious lesions. Caries detection using both methods was also done by an expert team of five dentists, highly experienced in NILR image interpretation, who used the same sets of clinically-obtained data. Sensitivity, specificity, and accuracy were calculated for caries detection by both the dentists and the expert team. Fifty-nine of the detected carious lesions were clinically treated and the observations during caries excavation were compared with those done with NILR and BWR. Statistical analysis to compare between NILR and BWR diagnosis was performed using non-parametric two-sided McNemar's Chi-Square test with the significance level set at $p < 0.05$. Kappa coefficients were calculated to assess the level of agreement between the two caries detection methods.

*Results:* Accuracy of NILR detection of early enamel lesions was 88% and that of carious lesions involving the dentino-enamel junction (DEJ) was 97%. Accuracy was found to be higher at 96% and 99%, respectively, when the same data were examined by the expert team. Direct observation during caries-excavation treatment suggested that NILR detected early enamel lesions that were not detectable with BWR alone.

*Conclusions:* Within the limitations of the present study, NILR was more sensitive than BWR in detecting early enamel lesions and comparable to BWR in detecting lesions that involved the DEJ.

*Clinical relevance:* Reflected near-infrared light images that are generated simultaneously with 3D intra-oral scanning may be used reliably for detection, screening, and monitoring of proximal caries, thus potentially minimizing the traditional use of ionizing radiation.

## 1. Introduction

Diagnosis of early carious lesions in pits and fissures is based mainly on visual-tactile detection of the lesions. Such methods are not effective when early lesions in proximal surfaces of molars and premolars are considered [1]. Bitewing radiography (BWR) has been used for many decades as the standard of care for the detection of early proximal lesions, yet this traditional method has its limitations. A meta-analysis

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published in 2015 analyzed 117 studies (13,375 teeth and 19,108 surfaces) reporting on the accuracy (sensitivity/specificity) of radiographic detection of natural primary carious lesions under clinical or in vitro conditions. The authors found that for detecting any kind of proximal lesions, sensitivity in clinical and in vitro studies was only 0.24 (95% CI 0.21/0.26) and 0.42 (95% CI 0.31/0.34), respectively, and specificity was 0.97 (95% CI 0.95/0.98) and 0.89 (95% CI 0.88/0.90). When evaluating the accuracy of detecting lesions involving dentin, sensitivity was reported to be higher at 0.36 (95% CI 0.24/0.49) and specificity was 0.95 (95% CI 0.94/0.96) [2].

Furthermore, radiography requires the use of ionizing radiation for imaging, which limits its use in monitoring initial carious-lesion progression due to patient risk [3–6]. Consequently, alternative methods were sought that would allow detection and monitoring of proximal caries and could safely be applied in children, low-risk-for caries populations, and pregnant women [7]. The most promising of these alternative methods were based on the optical properties of the enamel and included methods based on transillumination with near-infrared light [8–14] as well as laser fluorescence [15,16].

Intact enamel is found to be relatively transparent when transilluminated with near-infrared light. However, carious lesions cause scattering and thus partial reflection of such light, which enables distinguishing between sound and carious enamel. This allowed the development of devices that use near-infrared light reflection (NILR) for detection of proximal caries. When using NILR technology, teeth are illuminated with the near-infrared light and the reflection is registered and presented as a grayscale image. Within this image, sound enamel, which is transparent to light, appears dark and the carious lesion, which scatters and reflects the near-infrared light, appears brighter on the dark background of the surrounding enamel [17,18,19].

Jablonski-Momeni et al. [17] studied the clinical performance of a NILR system (VistaCam iX Proxi, Dürr Dental, Bietigheim-Bissingen, Germany) in comparison with BWR and concluded that NILR is comparable to BWR in detection of carious lesions.

Recently, two NILR-based systems were studied in vitro and compared with bitewing radiography for their ability to detect early carious lesions in proximal surfaces of molars and premolars; images of the lesions in micro-CT scans were used as a reference "ground truth" [18,19]. Lederer et al. [18] found that BWR demonstrated sensitivity of 0.31 and 0.55 for detection of lesions in the enamel and lesions involving dentin, respectively, with high sensitivity at 0.94 and 1.00.

A more recent study [19], which was conducted with a similar methodology (with micro-CT representing the "ground truth") found that another NILR system (iTero Element 5D, Align Technology, Tempe, AZ, USA) provided clear and reliable results. The authors attributed this in part to the finding that the iTero Element 5D scanner does not show any reflection artifacts. The two NILR systems were not compared directly in the same study, yet Litzenburger et al. [19] reported a higher sensitivity than that reported by Lederer et al. [18] when using the VistaCam iX Proxi system in detecting initial defects in the enamel compared to BWR [19]. In this last in vitro study, NILR resulted in an overall accuracy of 64.8%, an overestimation of 15.6% and an underestimation of 19.6%. For BWR, an overall accuracy of 71.2%, with no overestimation and an underestimation of 26.4%, was reported. These recent in vitro findings [19] have yet to be validated in a clinical setting.

The aim of the present prospective multicenter clinical study was to compare the detection of proximal caries with near-infrared light reflection (NILR) versus bitewing radiography (BWR).

The null hypothesis was that detection of carious lesions by the NILR system will be non-inferior to that of BWR.

## 2. Materials and methods

### 2.1. Study design

The study was designed to compare the detection of proximal caries in posterior teeth, using two different methods: near-infrared light reflection (NILR), using the iTero Element 5D scanner, and bitewing radiography (BWR), which was referred to as a "ground truth" control. Additionally, the study was designed to find out to what extent the evaluator experience in interpreting NILR images may affect the sensitivity, specificity, and accuracy of detecting proximal caries using the NILR method, compared to BWR control. The study was a multicenter, prospective, study conducted in five general-practice clinics in Canada and Germany.

Patients attending five general-practice clinics between April and November 2020 were offered to participate in the study. A total of 100 patients consented and were included in the study ($n = 20$ per clinic). Inclusion criteria were kept broad and exclusion criteria minimal. Included were all subjects who were 14 years or older (18 years or older in Germany) and who were scheduled for bilateral bitewing radiographs as part of their regular standard care. Excluded were subjects who reported to be pregnant and those with a history of epileptic seizures. Previously restored surfaces, non-proximal surfaces and anterior teeth were excluded from the present study analysis.

The study was approved by the Ethics Committee of the State Medical Association of Rhineland-Palatinate, Germany for the sites in Germany (May 10, 2020, under application number 2020–14,908_2-MPG § 23b) and by the Advara Institutional Review Board (IRB) for the Canadian sites (March 13, 2020, under protocol number: Pro0042394).

### 2.2. Sample size calculation

The sample size was calculated from the sample size equation for comparing paired nominal data by using McNemar's test:

$$n = \frac{\left[z_{\alpha/2}\sqrt{p_{01}+p_{10}} + z_{\beta}\sqrt{p_{01}+p_{10}-(p_{01}-p_{10})^2}\right]^2}{(p_{10}-p_{01})^2}$$

Where $P_{01}$ is the percentage of surfaces that can be detected as caries by X-ray but not NILR (NILR missed detection rate), $P_{10}$ is the percentage of surfaces that can be detected by NILR but not X-ray (NILR over detection rate), Z stands for the critical value of standard normal distribution, α is the significance level and β is the non-inferiority margin. A similar formula was obtained for the one-sided non-inferiority test by substituting $z_{\alpha/2}$, $p_{10}$ with $z_{\alpha}$ and $p_{10} + M$:

$$n = \frac{\left[z_{\alpha}\sqrt{p_{01}+p_{10}+M} + z_{\beta}\sqrt{p_{01}+p_{10}+M-(p_{01}-p_{10}-M)^2}\right]^2}{(p_{10}+M-p_{01})^2}$$

For this equation, a significance level of $\alpha = 0.05$, a power of $1-\beta = 0.8$, a non-inferiority margin of $M = 5\%$, and an assumed detection rate of $p_{01} = 0.1\%$, and $p_{10} = 0.06\%$ were used.

The minimum sample size required was calculated to be 128 proximal tooth surfaces. Assuming a drop-off rate of 20%, an additional 26 surfaces were added with a total minimal sample size of 154 surfaces. The actual sample size that was used in the study was 3499 non-treated proximal surfaces of molars and premolars.

### 2.3. The iTero element 5D scanner

The iTero Element 5D scanner (Align Technology, Tempe, AZ, USA) is an integrated intraoral dental imaging system that simultaneously captures both 3D color images of the dentition and reflected near-infrared light images (NILR) that are intended to aid in caries detection.

The translucency of the scanned tooth structure to near-infrared light (NIL, 850 nm) translates to the brightness level in the resulting captured image wherein the higher the translucency of the object, the darker it appears. Intact enamel is translucent to NIL and appears dark, whereas dentin and interferences in the enamel are reflective and scatter the NIRL and appear brighter than intact enamel. NILR images from multiple angles are captured and stored automatically during the scan. One

scan generates both color and NILR images as opposed to other NILR devices, which often require changing of the device "head" and a separate additional scan for both sets of images. The "View mode" includes a "Review Tool" that enables the user to view an area of interest in both color 3D and gray scale NILR visualization (Fig. 1). While using the "Review Tool", the color and NILR images displayed in the viewfinder match the position of the simulated loupe over the 3D model display and are continuously updated when moving the simulated loupe along the display. NILR images of proximal surfaces with carious lesions are presented in Fig. 2.

### 2.4. Diagnostic procedure and interpretation

Data acquisition was performed by each of the five individual dentists (Fig. 3). The following interpretation of the NILR and BWR images was done (a) by each of the individual dentists and (b) by a expert team (see below). In 59 of the cases, validation of the extent of the lesion was done during caries excavation (Fig. 3).

Clinical examination and BWRs used during this study were those that are used as the standard of care in the diagnosis of proximal caries in each of the participating clinics. Radiography was done in each clinic with the X-ray machine and setting that are routinely used in that clinic.

The same standard of care was provided for all site patients, including the patients who did not participate in this clinical study. No additional radiographs were taken for the sole purpose of this trial. In addition to the standard of care, the subjects were scanned using the iTero Element 5D scanner system. The scanner operator received online directions on the use of the iTero Element 5D scanner and interpretation of the NILR results.

At each of the study sites, a dental professional captured a full scan of the maxillary and mandibular arches of each subject using the iTero Element 5D scanner. The resulting 3D scan included a NILR image in gray scale, which was automatically presented next to the 3D image of a given tooth/pair of teeth (Fig. 1).

#### 2.4.1. Interpretation by the dentists

NILR and BWR images were used to detect proximal caries. To minimize bias, NILR or BWR images were interpreted by the dentist in alternating order: either the NILR image first and the BWR second or vice versa. In each case, the operator assessed and documented the findings of the first diagnostic method (BWR or NILR imaging) before performing the second method.

For each subject, the dentist graded carious lesions in the BWR and the NILR scan according to American Dental Association (ADA) staging guidelines for BWR [20]. The results of each diagnostic modality were documented using a Caries Evaluation Form. Analysis of sensitivity, specificity, and accuracy was done on the data as interpreted by the dentists independently of a similar analysis of the same data as interpreted by the expert team (see below) (Fig. 3).

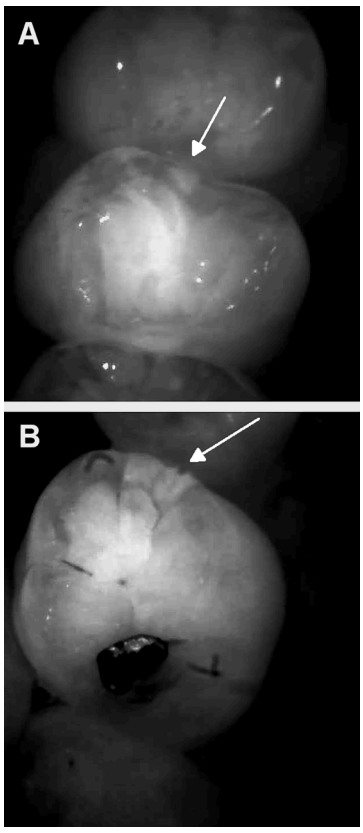


**Fig. 2.** A. Mesial surface of tooth #15 with a carious lesion detected by NILR. The lesion (arrow) is of triangular shape and does not reach the DEJ and was recorded as an early enamel lesion. B. Mesial surface of tooth #16 with a carious lesion detected by NILR. The lesion is trapezoid in shape (arrow) reaching the DEJ and was recorded as a lesion involving the DEJ.

#### 2.4.2. Interpretation by an expert team

A team of experts also evaluated the same data that was clinically collected by the dentists (Fig. 3). The data that was clinically acquired by the dentists was transferred for parallel evaluation by the expert team as anonymized, unmatched NILR scan and BWR datasets.

The expert team consisted of five dentists who had been recruited

**Fig. 1.** Screenshot of the "View mode" of the iTero Element 5D scanner. When the simulated loupe is positioned over a given area of the color 3D model, the corresponding 2D NILR gray-tone image is presented next to the color 3D image of the same teeth.

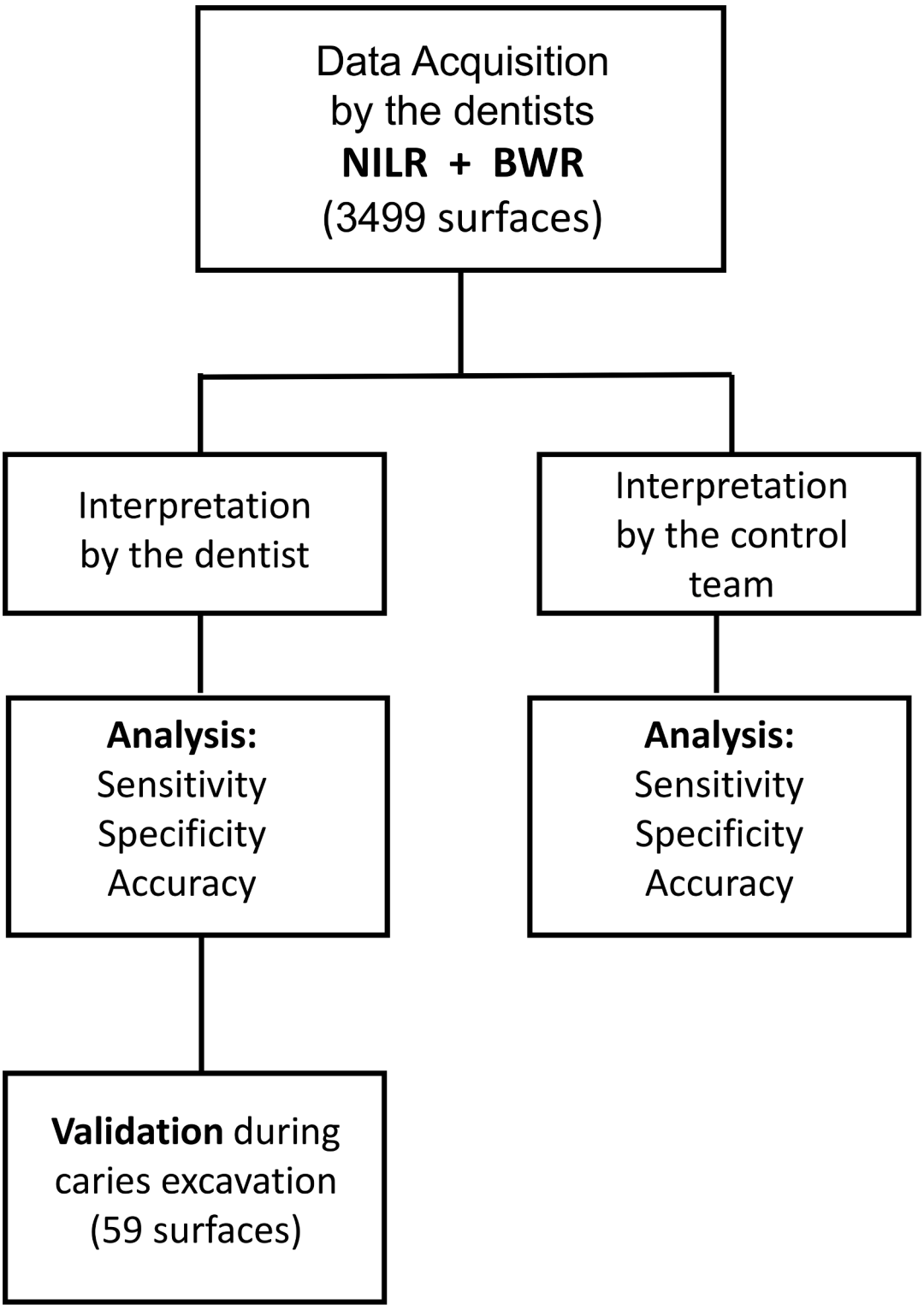


**Fig. 3.** Flowchart of the experimental design. Data acquisition was performed by 5 dentists in their individual clinical settings. This included BWR and NILR scans. A total of 3499 proximal surfaces of molars and premolars were included in the present study. Caries detection was done (a) by each of the individual dentists and (b) the same images were also examined by a team of 5 dentists who had a vast experience in interpretation of NILR images and provided an agreed-upon interpretation of the same data. Analysis of sensitivity, specificity and accuracy was performed for the results obtained by both evaluation groups. In 59 of the cases direct observation was possible during caries excavation, thus allowing validation of the diagnosis made using BWR and NILR.

and trained by the sponsor (Align Technology, Tempe, AZ, USA) for research and development purposes. They had 2 years of experience in evaluating thousands of NILR images of carious lesions, prior to the present study. The team members were pre-calibrated and inter-rater reliability was assessed using the methodology described by McHugh (2012) [21].

Four members of the team independently evaluated each NILR scan and each BWR at a random sequence and unrelated to each other, giving

a diagnosis of the presence or absence of proximal caries. Later, if majority agreement for a given NILR scan or BWR was not reached, a fifth team member evaluated the data and provided a majority decision. In order to avoid as far as possible any bias in interpretation, the NILR and BWR images were viewed as isolated independent images with no connection possible between an individual NILR image and the BWR image of the same tooth. Analysis of sensitivity, specificity, and accuracy was done independently of a similar analysis of the data as interpreted by the individual dentists (Fig. 3).

#### 2.4.3. Validation during caries excavation

A follow-up call to the dental office took place one month after the initial visit to review patient records and capture any clinical information recorded since the trial visit was concluded. Treatment of carious lesions was performed in accordance with the clinical decision of the dentist, as part of the patient's routine dental treatment. Fifty-nine of the surfaces included in the study underwent restorative procedures. In the cases in which restorative treatment was performed, the dentists were asked to document the true extent of the lesions as observed during caries excavation.

### 2.5. Outcome measures

The primary goal of this study was to test a non-inferiority hypothesis of the iTero Element 5D NILR technology compared to BWR in detecting proximal caries. Sensitivity, specificity, and accuracy values were calculated for NILR scan vs. BWR, which was referred to as "ground truth". Analysis of the results was also categorized and dichotomized by the extent of the lesion as determined by the "ground truth". This was done to differentiate the detection ability of lesions extending into the dentin from lesions limited to the enamel. Lesions that presented with a triangular shape and did not reach the dentino-enamel junction (DEJ) in either the BWR or the NILR image were categorized as "early enamel lesions" while those reaching the DEJ and having a more trapezoid form were categorized as "lesions with DEJ involvement". The latter were assumed to be lesions penetrating the dentin [22].

Secondary goals of the study were (a) to evaluate the caries detection ability of a dentist under clinical conditions using the NILR system and compare it to that of a team with vast experience with reading NILR images and (b) to compare the results observed and registered during caries excavation in a follow-up treatment, when available, with the results of the BWR and the NILR system.

### 2.6. Statistical analysis

Data was analyzed and presented as sensitivity, specificity, and accuracy. Sensitivity evaluates how good the test is at detecting a positive disease, specificity estimates how likely patients without disease can be correctly ruled out and accuracy measures how correct a diagnostic test identifies and excludes a given condition [23].

Specificity was calculated as the number of true positive assessments divided by the number of all positive assessments, specificity was calculated as the number of true negative assessments divided by the number of all negative assessments and accuracy was calculated as the number of correct assessments divided by the number of all assessments.

The non-parametric two-sided McNemar's Chi-Square test was used for paired nominal data. This test enables the comparison of the detection proportions between the two methods.

Kappa coefficients were calculated to assess the agreement between the two methods [24].

Differences in detecting the existence of primary proximal carious lesions (sensitivity and specificity) between the iTero Element 5D scanner and BWR and the corresponding 90% confidence interval for the differences were calculated.

A minimum of 154 tooth surfaces was initially calculated as a sample size that will ensure a power of 0.8, with an alpha = 0.05.

Moderate agreement (Kappa$\geq$0.4) was expected between the iTero Element 5D scanner and BWR. Non-inferiority of the iTero Element 5D scanner was expected as compared with BWR and evaluated by the McNemar's Chi-Square test.

Statistical evaluation was first performed for the caries detection carried out by the clinical site dentists followed by caries detection of the same clinically obtained data carried out by the expert team.

## 3. Results

### 3.1. Dentist reported results

The results of proximal caries detection by the dentists are presented in Table 1 and Table 2.

From a total of 3499 proximal surfaces of molars and premolars which were examined, 223 carious lesions were detected by BWR (157 early lesions and 66 lesions involving the DEJ) while NILR detected 549 carious lesions (395 early lesions and 154 lesions involving the DEJ) (Table 1).

When compared to the "ground truth" of BWR, the sensitivity of NILR detection of early enamel caries was 51.6% and the specificity was 90.4%. The sensitivity of NILR detection of carious lesions with DEJ involvement was 84.8% and specificity was 97.1%. These findings represent an accuracy of 88.6% for early enamel lesions and 96.9% for lesions with DEJ involvement. A statistically significant difference was found between the detection ability of NILR and BWR ($p < 0.0001$) (Table 2).

Non-inferiority of the NILR detection when compared to BWR was established and was highly significant ($p < 0.0001$, Table 2).

### 3.2. Expert team results

The results of proximal caries detection by the expert team are presented in Table 3 and Table 4. The expert team evaluation presented a higher NILR sensitivity for early enamel lesions (73.0%) and lesions with DEJ involvement (88.5%) when compared to the dentists at the clinical sites (Table 4). NILR specificity was also reported to be slightly higher from the expert team compared to the dentists from the clinical sites, with a resultant accuracy of 96.0% for the early enamel lesions and 99.4% for lesions with DEJ involvement. A statistically significant difference between the detection ability of NILR and BWR was found when evaluated by the expert team ($p<0.0001$) (Table 4).

The non-inferiority of the NILR detection compared to the BWR results as reported by the expert team was statistically significant (Table 4).

### 3.3. Validation during caries excavation

Direct observation of the lesions during caries excavation occurred during restorative treatment of 59 of the lesions. The treatment was scheduled and carried out as part of the patient's routine dental care.

Matching between the NILR findings and the clinical direct observation was found in 34/35 lesions that were limited to the enamel and in 23/24 of the lesions with DEJ involvement (Table 5). This represents a

**Table 1**
Numbers of carious (positive) and non-carious (negative) proximal surfaces of posterior teeth, as recorded by five dentists in their clinical environment.

| Depth of Lesion | Detection Method | NILR Positive | NILR Negative |
|---|---|---|---|
| Early Enamel | BWR Positive | 81 | 76 |
| | BWR Negative | 314 | 2965 |
| DEJ involvement | BWR Positive | 56 | 10 |
| | BWR Negative | 98 | 3335 |

Note: 63 surfaces that presented in the BWR with deep carious lesions in the dentin were not included in the NILR analysis.

**Table 2**
Sensitivity, specificity, and accuracy of caries detection by NILR when compared to a "ground truth" of BWR. Evaluation by five individual dentists.

| | Early Enamel Lesions | DEJ Involvement |
|---|---|---|
| Sensitivity | 51.6% | 84.8% |
| Specificity | 90.4% | 97.1% |
| Accuracy | 88.6% | 96.9% |
| Two-Sided McNemar's Chi-Square test (p-value) | < 0.0001[a] | < 0.0001[a] |
| Asymptotic Non-Inferiority Test (p-value) | < 0.0001[b] | < 0.0001[b] |
| One-Sided Binominal test (p-value) | < 0.0001[c] | < 0.0001[c] |
| Kappa Coefficient | 0.24[d] | 0.50[e] |

[a] Indicating a statistically significant difference between the detection ability of NILR and BWR;.
[b] The false positive (FP) rate is non-inferior to false negative (FN) rate with non-inferiority margin as 0.05, which indicates that NILR is non-inferior to BWR in detecting proximal caries;.
[c] The false positive (FP) count is significantly higher than false negative (FN) count, which indicates NILR can detect more proximal caries than BWR;.
[d] Fair agreement is observed between NILR and BWR for early enamel lesion detection;.
[e] Moderate agreement is observed between NILR and BWR for detection of lesions that involve the DEJ.

**Table 3**
Numbers of carious (positive) and non-carious (negative) proximal surfaces of posterior teeth as detected and recorded by a expert team using the same database as collected and used by the five individual dentists (Table 1).

| Type of Lesion | | NILR Positive | NILR Negative |
|---|---|---|---|
| Early Enamel | BWR Positive | 76 | 28 |
| | BWR Negative | 106 | 3216 |
| DEJ involvement | BWR Positive | 62 | 8 |
| | BWR Negative | 11 | 3418 |

Note: 73 surfaces that the adjudication team found to present in the BWR with deep carious lesions in the dentin were not included in the NILR analysis.

sensitivity of 97% and 96%, respectively.

Matching between the BWR findings and the clinical direct observation during caries excavation was found in 5/35 lesions that were limited to the enamel and in 13/24 of the lesions with DEJ involvement (Table 5). This represents a sensitivity of 14% and 54%, respectively.

## 4. Discussion

Intraoral scanners started as a technology to replace physical records taken using impression materials; however, in recent years a paradigm shift has occurred regarding the scope and role of intraoral scanning in the dental practice [25,26,27]. This multicenter clinical study investigated the potential of caries detection of a 3D intraoral scanner with combined simultaneous NILR capabilities.

The NILR device was found to be non-inferior to BWR, which has been the traditional "gold standard" for proximal caries detection in posterior teeth. Furthermore, the NILR device was more sensitive than BWR in the detection of early carious lesions in the enamel, which was verified in the cases that were subjected to caries excavation.

The results of both the dentists and the expert team support the study's null hypothesis: NILR was statistically non-inferior to BWR in detecting primary proximal carious lesions. One-sided binomial tests of the results reported by the expert team indicated that while NILR did detect more early enamel proximal lesions than BWR, it did not detect more of the advanced lesions reaching the DEJ and the dentin.

When proximal caries detection was performed by the individual dentists, the agreement level between the two diagnostic modalities

**Table 4**
Sensitivity, specificity, and accuracy of caries detection by NILR when compared to a "ground truth" of BWR. Evaluation by a expert team, using the same database as collected and used by the 5 dentists (Tables 1,2).

| | Early Enamel Lesions | DEJ Involvement |
|---|---|---|
| Sensitivity | 73.0% | 88.5% |
| Specificity | 96.8% | 99.6% |
| Accuracy | 96.0% | 99.4% |
| Two-Sided McNemar's Chi-Square test (p-value) | <0.0001[a] | 0.65 (>0.05)[b] |
| Asymptotic Non-Inferiority Test (p-value) | <0.0001[c] | <0.0001[c] |
| One-Sided Binominal test (p-value) | <0.0001[d] | 0.32 (>0.05)[e] |
| Kappa Coefficient | 0.51[f] | 0.86[g] |

[a] There is a statistically significant difference between the detection ability of NILR and BWR when evaluated by the expert team;.
[b] There is no statistically significant difference between the detection ability of the NILR and BWR when evaluated by the expert team;.
[c] The false positive (FP) rate is non-inferior to the false negative (FN) rate with non-inferiority margin as 0.05, which means NILR is non-inferior to BWR in detecting proximal caries when evaluated by the expert team;.
[d] The false positive (FP) count is significantly higher than the false negative (FN) count, which means NILR can detect more proximal caries than BWR;.
[e] The false positive (FP) count is not significantly higher than the false negative (FN) count, which means NILR cannot detect more proximal caries than BWR;.
[f] Moderate agreement was observed between NILR and BWR after adjudication;.
[g] Almost perfect agreement was observed between the NILR and BWR after adjudication.

**Table 5**
Clinical observations during caries excavation: Match vs. mismatch with NILR and BWR caries detection.

| | Lesions observed to be limited to enamel while conducting caries excavation | Lesions observed to reach dentin while conducting caries excavation |
|---|---|---|
| NILR Detection Match | 34 | 23 |
| NILR Detection Mismatch | 1 | 1 |
| NILR Sensitivity | 97% | 96% |
| BWR Detection Match | 5 | 13 |
| BWR Detection Mismatch | 30 | 11 |
| BWR Sensitivity | 14% | 54% |
| P-value of One-Sided Proportional Test | < 0.0001[a] | =0.0014[b] |

[a] Significant difference between NILR and BWR in detecting lesions limited to the enamel;.
[b] Significant difference between NILR and BWR in detecting lesions involving the DEJ.

(NILR and BWR) was fair (Kappa = 0.24) for lesions limited to the enamel and moderate (Kappa = 0.50) for lesions reaching the DEJ. When evaluation of the same data was performed by the expert team, the agreement level was moderate (Kappa = 0.51) in the case of lesions limited to the enamel and high (Kappa = 0.86) in lesions reaching the DEJ. The difference between the evaluation by these two groups is most likely due to differences in experience/training related to the use of the NILR method. The difference between the results of the expert team and the dentists indicates that the operators' expertise does have a moderate effect on their diagnostic abilities using NILR, as seen also with other imaging techniques [28].

The data collected during caries excavation is of significant clinical importance. During caries excavation, the presence and extent of carious lesions were recorded and dichotomized to "Limited to enamel" and "Reaching the DEJ". The number of cases that were available for such analysis was limited to 59, due to the Covid-19 epidemic that followed/continued.

The data clearly indicates that BWR is limited in the detection of early carious lesions. The calculated sensitivity for BWR (compared to the visualization during caries excavation) was 14% for lesions limited to the enamel and 54% for lesions reaching into the dentin.

The BWR sensitivity, compared to the above clinical observation during caries excavation, was approximately 10% lower than that previously reported for enamel lesions and 20% higher for lesions involving the dentin [2]. In the present analysis, NILR sensitivity to detect both lesions limited to the enamel and those extending into the dentin was significantly higher than that of BWR (97% and 96% respectively).

The lesions that were defined as "with DEJ involvement" are most likely lesions penetrating the dentin, as is commonly observed in histological ground-section images of carious teeth. Using the trapezoid shape of the lesion and its oblong contact with the DEJ, as seen in NILR images, dentists were able to correctly determine if the lesion crossed the DEJ and extended into the dentin in 66.6% (NILR) of the verified dentinal lesions.

BWR, the selected comparator, has been the "gold standard" for diagnosing proximal caries in clinical practice in most countries. That said, a recent meta-analysis has shown BWR to perform with low sensitivity for detection of proximal caries *in-vivo* [2]. Schwendicke et al. [2] found that BWR sensitivity was 0.24 (95% CI 0.21/0.26), which translates to 76% of all proximal lesions being missed by BWR under clinical conditions [2]. The results of the present study are in agreement with these findings as the results indicate that 69.4% of the lesions that were confirmed during clinical caries excavation were not detected by BWR.

Russotto et al. [29] tested near-infrared light transmission (NIRT) (DIAGNOcam, Kavo, Biberach, Germany) in private practice in a study with a similar design to the current study. In their study, BWR performed significantly better than NIRT in regard to sensitivity analysis (59.1% vs. 45.6%, $p < 0.001$) while NIRT performed significantly better than BWR regarding specificity analysis (98% vs 93.3%, $p < 0.001$). However, NIRT showed sensitivity similar to that of BWR when only enamel carious lesions were concerned [30].

The strength of the present study is that (a) it is based on the observations of 3499 proximal surfaces of posterior teeth, which is a relatively large sample size, (b) an expert team evaluation was performed and compared to the evaluation of the individual dentists and (c) an additional "ground truth" comparator based on direct visualization of the lesion during caries excavation was applied.

Yet, the present study has some limitations. One limitation was the lack of standardization of the radiographic equipment that was used in the participating clinics. Another limitation was the lack of an absolute "ground truth" value to compare against the NILR test groups. Methods such as histological sections or the use of micro-CT were inapplicable for this clinically oriented design. Consequently, BWR was used as the "ground truth" in this study, despite its limitations. Another inherent limitation of all similar clinical studies is that the proximal surfaces that were diagnosed as intact cannot and should not be excavated to verify the diagnosis [30]. The use of NILR in addition to BWR may allow dentists to overcome the last limitation. The fact that the expert team was trained by the sponsor of the study may apparently be considered as another limitation of the study, yet the data was presented to the expert team members as isolated individual images, which has most likely prevented any potential bias in the evaluation.

## 5. Conclusions

Within the limitations of the present study, it may be concluded that: The non-inferiority hypothesis of NILR compared to BWR in detecting proximal caries was approved. A team of observers experienced in NILR imaging evaluated the two methods with higher accuracy and agreement levels compared to individual dentists in their clinical settings, who were less experienced with the NILR method. NILR had higher sensitivity than BWR in the detection of early enamel lesions and comparable sensitivity to BWR in detecting lesions that involved the DEJ.

## Statement of ethics (IRB)

The study protocol was approved by the appropriate ethics committees in accordance with laws and regulations of the countries in which the research was conducted (Canada and Germany). Written informed consent was obtained from each individual participating in this study after adequate explanation of the aims, methods, objectives and potential risks of the study.

All participating dentists and designated office coordinators were trained on the clinical study protocol and Good Clinical Practices (GCP) by representatives of the Sponsor and the sites were monitored by the Sponsor in accordance with the monitoring plan.

## Disclosure statement

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## CRediT authorship contribution statement

Prof. Zvi Metzger: Conceptualization, methodology, writing original draft, review & editing. Dr. Dana G. Colson, Dr. Peggy Bown, Dr. Timo Weihard, Dr. Tim Nolting and Dr. Ingo Baresel: Clinical investigation.

## Declaration of Competing Interest

All authors deny any conflict of interest related to the present study.

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