

A review of the effectiveness of quantitative light-induced fluorescence (QLF) to detect early caries.

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Introduction

With the decrease in caries prevalence within the Western world, attention of clinicians and researchers alike has been drawn to the detection, quantification, monitoring and ultimately diagnosis of early carious lesions. For many years the techniques for the remineralisation of such lesions have been described, yet their clinical implementation has been hindered by the inability to clinically detect demineralised enamel in a condition amenable to remineralising therapies or regimes. The advent of a number of novel diagnostic devices in recent years has offered the possibility of detecting very early lesions and thus the ability to instigate preventative and reversal therapies. Devices, such as the Electronic Caries Monitor (ECM), DiagnoDent, Digital imaging Fibre-optic Trans-illumination (DiFOTI), and Quantitative Light-induced Fluorescence (QLF), also offer the research community the ability to further elucidate the carious process and study the effect of new therapies and products on the demineralisation / remineralisation dynamic.

As with any new device, a number of variables must be obtained, through careful study, to ensure that the device is valid and thus suitable for use in research and in the clinical decision making process. Validation is therefore an essential step in the acceptance of any new technique. The purpose of this paper is to review the validation evidence supporting the use of QLF as a diagnostic aid for early carious lesions.

Validity

A valid device is one that measures what it claims to measure. This is normally assessed by comparing the questioned device with a currently accepted 'gold-standard' for the variable under question and then comparing the results, often using correlation statistics. Valid devices are usually also reliable devices and ones with acceptable levels of accuracy, defined by their sensitivity and specificity scores. The combination of reliability, accuracy and validity are often combined in to a single term, effectiveness. A discussion of the effectiveness of any one system would therefore properly include a discussion of all of the above factors.

Before assessing the research supporting the QLF device, it is worthwhile considering the effectiveness of the current diagnostic tests used in dentistry, including those for caries detection. In this way, it is possible to place the values produced by the QLF research into context. A new device should offer an improvement within one of the factors assessed; i.e. increased reliability or improved sensitivity. See Tables 1,2 and 3.

Considering the evidence for current tests we can assess the literature concerning QLF and determine if the device offers an improvement in any one of the areas considered when establishing effectiveness.

The QLF Theory and Technique

Well described by a number of authors in recent publications (van der Veen, Ferreira Zandona et al. 1998; van der Veen and de Josselin de Jong 2000; Angmar-Mansson and ten Bosch 2001; Tranaeus, Heinrich-Weltzien et al. 2001), the theory behind QLF is described only briefly here. Under certain conditions, human enamel will auto-fluoresce. Bjelkhagen was the first to describe the reduced fluorescence seen in demineralised enamel (Bjelkhagen, Sundstrom et al. 1982) and a cause for this loss was proposed by Angmar-Mansson and ten Bosch, 1987 (Angmar-Mansson and ten Bosch 1987). They suggested that the increased porosity seen in carious lesions led to a decrease in the refractive index of the lesion from that of sound enamel to one closer to water. The increase in scattering results in a significant decrease in light-path lengths with a resultant decrease in absorption and therefore a visible decrease in auto-fluorescence.

The introduction of the theory into a viable technique was started by Sundström (Sundstrom, Hafstrom-Bjorkman et al. 1989) following his earlier work on spectroscopic studies (Sundstrom, Fredriksson et al. 1985). The light source was a laser and this was housed in a distant location to the subjects for safety reasons. Further development occurred when images were captured on CCD cameras and imported visualised on computers, enabling longitudinal monitoring and assessment of individual carious lesions (Hafstrom-Bjorkman, Sundstrom et al. 1992). de Josselin de Jong et al developed a method for the quantification of mineral loss from lesions visualised using the system, employing a reconstruction technique based upon sound enamel surrounding the lesion (de Josselin de Jong, Sundstrom et al. 1995). The need for a laser light-source was removed when a portable arc-lamp unit was developed and shown to be as effective as the cumbersome laser-based system (al-Khateeb, Oliveby et al. 1997) (Ando, van der Veen et al. 1997).

The system was commercialised and made available as a complete unit including the necessary analysis software (QLF, Inspektor Research Systems BV, Amsterdam, The Netherlands). Further developments included new cameras suitable for intra-oral use, a calibration system and a repositioning system to ensure that longitudinal images were correct aligned (de Josselin de Jong and van der Veen 2000). The analysis software also developed, and an image subtraction system is now available for *in vivo* longitudinal studies (QLFPatient, Inspektor Research Systems BV, Amsterdam, The Netherlands). See Figure 1.

Smooth Surface Caries

The vast majority of the validation and reliability research concerning QLF has centred on smooth surface caries. A summary of the studies conducted to date are shown in Table 4. Studies have generally centred on the comparison of QLF to total mineral loss or lesion depth. The gold-standard employed in these studies is invariably transverse micro-radiography (TMR) or a variant, longitudinal micro-radiography (LMR) with a correlation coefficient, r , used as the statistical tool. Studies assessing the sensitivity and specificity have employed histology or clinical visualisation as a comparator. The choice of gold-

standard and the use of correlation statistics as the statistical tool of choice have been criticised and are discussed later in this paper. Table 4 summarises the studies conducted on this subject.

In 1999, ten Bosch reviewed the literature on QLF calibration (validation) and determined that the mean correlation coefficient was $0.75 (\pm 0.08)$ when compared to TMR/LMR for mineral loss measurements (ten Bosch 2000). A small revision is now possible, with the benefit of additional studies, of $0.76 (\pm 0.1)$. If the studies are separated into those employing the laser source and those employing a light source, the means are $0.76 (\pm 0.1)$ and $0.81 (\pm 0.1)$ respectively. There is, however, no statistical difference between the laser and light studies, $p=0.258$. When bovine and human enamel studies are compared, the coefficients are $0.72 (\pm 0.07)$ and $0.78 (\pm 0.09)$, respectively, again with no statistical difference between the two substrate types ($p=0.221$). When considering the relationship with lesion depth and QLF the mean correlation was $0.73 (\pm 0.10)$.

When considering diagnostic performance the specificity and sensitivity of the test are the values of interest. Again, studies considering these are shown in Table 4. The mean sensitivity and specificity for QLF assessment of smooth surface caries is $0.76 (\pm 0.02)$, $0.85 (\pm 0.09)$. However, these values alone are of little use to the clinician. A variable that is often ignored in discussions of caries diagnosis is that of the predictive values, which can be defined as:

Positive predictive value (PPV): Given a positive result, the chance that the patient has a carious lesion

Negative predictive value (NPV): Given a negative result, the chance that the patient is caries free

In order to calculate the predictive values, the prevalence of the disease (in this case caries) under scrutiny must be known. Prevalence therefore influences the effectiveness of a test. For example, if we take the mean sensitivity and specificity values for QLF, the predictive values for detecting a carious lesion in a population with a low caries prevalence of 0.1 would be, PPV 0.36, NPV 0.96. Or, given a positive result by QLF we can only be 36% certain that the tooth is carious, but, given a negative result we can 96% certain that the tooth is caries free and does not require treatment. If we now use QLF in a screening programme of high caries risk children, with, for example, a prevalence of 0.8, we obtain the following predictive values: PPV 0.95 and NPV 0.46, almost a reversal of the previous results. This compares to bitewing radiography which, in a low risk population provides a PPV of 0.73 and a NPV of 0.97, and in a high risk population the values would be 0.98 and 0.47 for PPV and NPV respectively.

Occlusal caries

Occlusal surfaces represent the most commonly effected site for new lesions in younger individuals and represent a diagnostic dilemma for clinicians (Kidd and Joyston-Bechal 1997). The presence of stain, complex anatomy and the failure of established tests, such as

radiography, to provide diagnostic assistance ensure that any device that improved the detection and diagnosis of occlusal demineralisation would be well received (Kidd and Joyston-Bechal 1997). See Figure 2.

Since the last review of the QLF validation (ten Bosch 2000) a number of studies have been undertaken examining the effectiveness of QLF of occlusal surfaces, these are summarised in Table 5. The mean sensitivity for occlusal caries detection is 0.61 (± 0.14) and the mean specificity is 0.59 (± 0.18). The values are considerably lowered by the study of (Ferreira Zandona, Analoui et al. 1998), and if these are removed the values are; sensitivity 0.68 (± 0.13) and specificity 0.70 (± 0.03). Is it valid to disregard the results from the Ferreira Zandona study? The study was the only one to investigate artificial lesions, using different kinds of occlusal structures; straight wall, converging and diverging wall and were created in bovine discs. The study compared laser fluorescence with dye-enhanced laser fluorescence and also investigated the effect of plaque on these readings. The 'gold-standard' employed was examiner assessment, rather than TMR or histology, and therefore the comparisons differ from the other studies which have employed. While there is no criticism of the study design or its execution, the differences between it and the other validation studies are sufficient to justify its removal when considering the sensitivity and specificity of occlusal caries detection using QLF.

Table 6 illustrates how QLF compares with other diagnostic tests when sensitivity and specificity are compared, as well as positive and negative predictive values; Table 7 illustrates these values for other surfaces assessed by QLF. Youden's value quoted in Table 6 is a combination of the sensitivity and specificity, often known as Youden's index.

Only one study has produced an 'r' value, or correlation, for QLF. Described elsewhere in these proceedings (Higham) the study by (Pretty, Laloo et al. 2003) aimed to produce an interpretive index for QLF values in relation to occlusal demineralisation. This was done by initially correlating QLF values to histological, clinical and radiographic scores using the scale of Ekstrand (Ekstrand, Kuzmina et al. 1995; Ekstrand, Ricketts et al. 1997). The exercise was also undertaken using the DIAGNODent device. Both data types (ΔQ and ΔF) produced by QLF were compared to the gold standard, histology, and the most favourable result was obtained by ΔF at the 5% threshold compared to histology, giving an r value of 0.82. ΔQ correlations resulted in an r value of 0.74. DIAGNODent scored 0.62 when compared to the histological standard. Table 8 places these r values into context with traditional and other novel tests for occlusal caries.

The comparisons demonstrate that QLF compares favourably with other methods for detecting occlusal caries. When the combination of specificity and sensitivity values, Youden's index, is considered, QLF scores highest, along with ECM (Ashley, Blinkhorn et al. 1998) (See Table 6). All of the studies contributing to the QLF data set for these comparisons have been derived from *in vitro* studies. Longer term clinical trials are indicated assessing occlusal surface survival rates following screening either with QLF or a more traditional method. The use of histology as a gold-standard and the relative merits of correlations to establish links with agreement are discussed later in this paper and are of particular importance in relation to occlusal diagnosis.

Root caries

QLF is based upon the auto-fluorescence of enamel. While a number of theories have been suggested for how this is so, many believe that it is the underlying dentine that is responsible for the fluorescence, with the presence of a lesion preventing the light source reaching the chromophores in the dentine layer, thus producing the darkened areas associated with mineral loss. This has been supported by a number of authors who have stated that without dentine, there is a marked reduction or even complete loss of enamel fluorescence (Amaechi and Higham 2002), (Heinrich-Weltzien, Kuhnisch et al. 2003) (van der Veen, Ando et al. 2002). One study, has, however arrived at a contrary conclusion, the reasons for which are not understood (Rousseau, Vaidya et al. 2002). Root surface dentine therefore does fluoresce under QLF conditions, although the effect of demineralisation differs from that of enamel. Rather than a decrease in fluorescence, there is a slight increase in areas of demineralisation (van der Veen and ten Bosch 1993). One study has shown that the QLF device cannot detect this slight increase in fluorescence and requires the addition of a fluorescent dye to detect the lesions (Pretty, Ingram et al. 2003). See Table 9. Table 10 presents data regarding root caries detection using other diagnostic methods.

The study by (Gonzalez-Cabezas, Dunn et al. 2001) employed natural lesions from extracted teeth that featured the clinical presentations of root caries including stain, calculus, early cavitations and combinations of these. Certainly many of these are known confounders to QLF analysis; however the ROC area under the curve was encouraging. Perhaps QLF is monitoring colour changes in the root lesions? Colour change is the basis of most visual indices for root caries, and QLF has been demonstrated to effectively monitor colour differences (Pretty, Edgar et al. 2001).

Van der Veen (van der Veen and ten Bosch 1993; van der Veen and ten Bosch 1996; van der Veen, Tsuda et al. 1996) explored the use of sodium fluorescein penetration into root lesions and their subsequent detection and quantification using a fluorescent system. This has been adapted for use with QLF and a correlation between mineral loss measured by TMR and ΔF values of 0.89 upon demineralisation and 0.8 following remineralisation have been described (Pretty, Ingram et al. 2003). Again issues of using TMR as a gold standard and correlations for measuring agreement apply to these findings and are discussed later in the paper. Again, as with the previous study the results are encouraging although none of the teeth employed in this study offered the confounding clinical presentation that was so well represented in the (Gonzalez-Cabezas, Dunn et al. 2001) study. See Figure 3.

With the rising age of Western populations and a simultaneous increase in the retention of teeth into old-age, root caries (along with occlusal caries in younger populations) detection and diagnosis is likely to become a major research focus in the future (Murray 1998). With a study determining that neither DIAGNODent nor ECM ($r=0.45$, $r=0.48$ respectively) can accurately assess the depths of these lesions, QLF may have a role in the advancement of primary root caries assessment (Wicht, Haak et al. 2002).

Secondary caries

Secondary, or caries adjacent to restorations, is given as the most common reason for restoration replacement (Mjor and Toffenetti 2000), see Figure 4. The aetiology is complex, with differing situations seen in *in vitro* lesions compared to *in vivo* examples. Whether or not secondary caries is related to residual caries, a true association with marginal failure of a restoration or simply a new, unrelated carious event in a susceptible site is unclear. However, the need to detect such demineralisation early in its development is clear and the ability to instigate remineralising therapies for restoration repair is dependant on such diagnoses. A number of studies have explored the use of QLF to detect such lesions and these are summarised in Table 11. Table 12 contains data from studies assessing the effectiveness of other methods for detection of secondary caries. There is a disappointingly small number of studies providing sensitivity and specificity data for secondary caries. This was noted by Bader et al who produced an excellent review of caries diagnostic systems. They described the lack of adequate literature describing root caries, secondary caries and caries in the primary dentition (Bader, Shugars et al. 2001; Bader, Shugars et al. 2002).

Secondary caries, does, however, seem to have been of interest to researcher's using QLF and several studies have been conducted. The r value ($r = 80$) is satisfactory (given the caveats later in this paper) and the mean effectiveness is 0.91 for sensitivity and 0.85 for specificity. These values are encouraging although the range of variables when assessing secondary caries is large, and include the restored surface (smooth/occlusal), restorative material, bonding material, size and shape of restoration, access to margins, effect of fluoride containing materials and whether or not the caries is residual or truly a new carious event. Interestingly it should be noted that work by (Lennon, Buchalla et al. 2002) is developing the use of QLF to detect, during the caries removal phase of restorative work, residual caries. Their study found that the fluorescent method had superior sensitivity and specificity over visual/tactile, DIAGNODent and caries detecting dye. Certainly further work is required but it is a promising adjunct to the secondary caries studies currently being undertaken.

Like root caries, secondary caries is likely to increase in prevalence given the changing demographics and oral health habits of Western populations. The increase in the use of fluoride containing restorative materials suggests that QLF may have applications in the assessment of these products as well as a possible tool for *in vivo* detection. Further validation studies in which the variables described previously are controlled are required before effectiveness can be claimed.

Orthodontic demineralisation

The occurrence of enamel demineralisation adjacent to buccal brackets is a well described side-effect of fixed orthodontic therapy (Wisth and Nord 1977; Southard, Cohen et al. 1986). The presence of brackets, bands and orthodontic wires hinders effective oral hygiene and surfaces normally associated with a low incidence of demineralisation

(especially in younger individuals) – the buccal surfaces – exhibit characteristic white spots of initial demineralisation. Studies suggest that many of these early lesions will remineralise fully, although some develop into frank cavitation and require restorative intervention. The detection, therefore, of orthodontic demineralisation is therefore important to the effective instigation of a remineralising therapy (Marcusson, Norevall et al. 1997). In addition, orthodontic patients offer a model for demineralisation on smooth surfaces that can be employed in the assessment of new remineralising products or regimes (Pretty, Pender et al. 2003).

One of the first QLF *in vivo* studies was conducted on post-debonded orthodontic patients (Al-Khateeb, Forsberg et al. 1998). While small, 7 subjects, the study was a pioneer in the application of the device *in vivo* and the QLF images and data have been reproduced in a number of other publications to support the use of QLF. (Al-Khateeb, Forsberg et al. 1998) work detected significant differences in both lesion area and fluorescence between the beginning of the study and 12 months later. See Table 13 for a summary of the research.

An *in vitro* assessment of longitudinal demineralisation and remineralisation using orthodontic cleats was undertaken by (Pretty, Pender et al. 2003) which found similar results to those in the previous study. This work differed in that the orthodontic components were still attached to the teeth and therefore suggests that QLF may have a role in monitoring demineralisation *during* orthodontic treatment. This would be an obvious requisite in any preventative programme. Benson's work on the QLF and orthodontics compared the detection of a variety of levels of demineralisation (again *in vitro*) using a photographic technique and QLF, developing effectiveness scores for each and then he determined the reliability of each method.

While there are only a few studies examining QLF in orthodontic patients, the data suggests that this may be a successful application for QLF. There are several reasons why these subjects may be especially suited to QLF;

- a) The surfaces under examination (central and lateral incisors typically) are flat
- b) The surfaces are easily imaged using QLF, either manually or by the use of a head-rest
- c) Small amounts of demineralisation are typical, QLF was designed to monitor such lesions
- d) Younger patients, who can be enrolled as subjects within clinical trials assessing products or therapies
- e) The demineralisation is generally 'square' in nature (i.e. following the outline of the bracket) and thus is readily analysed by either the traditional QLF software or the new subtraction system
- f) The buccal surfaces are normally plaque free and can be readily dried
- g) Motivated patients / subjects

While these factors explain why QLF assessment of orthodontic patients would be appropriate, it does not guarantee validity. There is currently insufficient data to claim validity, although the initial studies suggest an acceptable level of sensitivity and

specificity combined with an excellent reliability score. Further research into this area is being conducted in Liverpool and other centres.

Erosion

While the title of the paper describes effectiveness in caries detection, it is worthwhile mentioning the possible application of QLF to erosion, especially as this form of tooth loss is of increasing interest to cariologists and is increasing in prevalence.

There are only two studies considering the possibility of QLF monitoring erosion. Both are summarised in Table 14. It is, of course, too early to determine if QLF will offer a means by which erosion can be monitored. The relatively high r value described by (Pretty, Edgar et al. 2003) is promising, although the exact mechanism by which QLF images erosion is not fully understood. Theories currently centre on the interaction of crater depth and softened surface layer. The technique has been used in a product separation study (*in vitro*) where mouthrinses were compared for their erosive potential (Pretty, Edgar et al. 2003). This work is described elsewhere in these proceedings (Higham, Chapter XX). As with many other aspects of this emerging technology, further validity research is required.

Reliability of QLF measurements

As described in the introduction, any discussion on the effectiveness of a device must include a description of the reliability of the system. Reliability, or the ability to reproduce the same measurement from the same system on multiple occasions, is usually expressed in terms of inter-examiner and intra-examiner reliability. Statistical reporting usually involves intra-class correlation co-efficients (ICC) or Kappa. As QLF produces continuous, rather than categorical, data, ICC is the preferred method. It should be noted, however, that several authors have expressed concern over the use of ICC for measuring examiner agreement, claiming that it is inappropriate (Bland and Altman 1990). There does seem, if one reviews the literature, a consensus currently that ICC's are acceptable (Moret, Mesbah et al. 1993; Yen and Lo 2002).

The studies assessing the reliability of the QLF device are provided in Table 15 and Table 16 provides some examples of reliability using alternate devices. The mean intra- and inter-examiner reliability scores, for both image capture and the subjective analysis stage can be classed as excellent (Landis JR 1977). Indeed, many of the new devices are highly reproducible and this is in comparison to some of the traditional techniques, such as clinical visual, where there is often a large discrepancy in inter-examiner scores, often due to personal thresholds.

The data suggest that QLF is highly objective. There are two subjective stages in QLF analysis; the image capture and the subsequent analysis. Neither seem to have a negative effect. Its closest companion in optical caries diagnosis, DIAGNODent, also has a subjective stage – i.e. the placement of the probe on the tooth, but it also appears to be highly reproducible. The studies undertaken thus far have only considered two of the possible surface types that have been discussed; smooth and those adjacent to orthodontic

components. There is a need to determine the effect of surface type on reliability by assessing root surface, occlusal surfaces and secondary caries. This research is currently being undertaken and should be reported shortly.

Factors affecting the validity of QLF

(ten Bosch 2000), when assessing QLF research for this conference, described two possible confounding factors; dehydration and inadequate sample thickness. Currently there are many other factors that can contribute to a less than optimal QLF assessment. These include; presence of plaque, poor angulation, poor focus, presence of stain, presence of underlying dentine, camera/mirror fogging, and the presence of enamel defects. A discussion of each of these is beyond the scope of this paper, and they have been summarised by (Amaechi and Higham 2002). The development of QLF as a tool for measuring both plaque and tooth stain have developed from the observance of these features on QLF images, and thus, far from hindering the development of the device, have extended the use of the system into other areas of dental research.

Concerns over the usage of TMR as a gold-standard in QLF validation studies

In his summary of research into QLF validation in 1999, ten Bosch described some of the inherent difficulties using TMR as a comparator for QLF (ten Bosch 2000). One of the main differences in function is that TMR will measure the mineral loss from a cut, polished, thin section of enamel, whereas QLF measures the entire lesion. The selection of a single or even multiple slices under TMR investigation to provide a representation of the whole lesion is therefore problematic. Carious lesions, especially natural lesions, are non-homogenous and therefore a great deal of variability in depth and mineral loss can occur. The TMR process necessitates a loss of lesion containing tissue, in both the initial cut and then in subsequent grinding and polishing. (ten Bosch 2000) describes this confounding factor in more detail, but summarises by stating that the low values of 'r' for smooth surface caries validation using QLF may well be associated with the TMR process. Research effort into assessing alternate gold-standards may prove fruitless – TMR has been proven to be the method of choice, and studies comparing QLF data to another 'standard' may be criticised for not employing TMR (Featherstone 1986).

Concerns over the usage of correlation statistics in validation studies

Direct measurement of mineral loss from teeth is, at least in the *in vivo* situation, impossible and therefore indirect measures have been developed, of which QLF is one. In order to validate the device, studies comparing data from QLF have been compared to a gold-standard, which, in most of the reports described within this paper, has been a microradiographic technique. Following acquisition of the data, the two different methods are compared using a scatter-plot and correlation analysis is performed resulting in an *r* value. The general consensus is that the closer this value is to 1, the greater the agreement

is between the two measurements. If the new device correlates closely to the gold standard then it is argued that it is valid. (Bland and Altman 1986) has raised concerns over this assumption and published an opinion paper in the Lancet.

Bland and Altman's arguments can be stated as:

- a) Correlation measures the strength of a relationship between two values, rather than the agreement between them. Agreement occurs only if points lie on the line of equality, whereas a strong correlation will occur if the data points lie along any straight line
- b) Changes in the scale of measurement will not effect correlation, but will effect agreement
- c) Correlation is highly dependant on the range of the true quantity in the sample, if it is wide then the correlation will be greater than if narrow. Any study involving demineralisation will, by virtue of the inherent variability and susceptibility of teeth to acid attack, provide a whole range of values and hence this may have contributed to any high correlations
- d) Tests of significance may demonstrate that methods are related, although this is almost assumed as the both claim to measure the same variable
- e) Data which are in poor agreement have been shown to produce high correlations, Bland provides the example of Serfontein & Jaroszewicz in which the gestational ages of babies were determined. Babies aged at 35 weeks by one method had gestations between 34 and 39.5 weeks by another, yet the correlation between the two methods was high, $r = 0.85$ (Serfontein and Jaroszewicz 1978).

The difficulty in using any of the methods suggested by Bland and Altman as an alternative to correlations is that the devices which are compared in caries research provide different values, and thus different scales. The use of mean difference and similar statistical techniques is that they require the same data types to be used. For example, (Ricketts, Watson et al. 1998) used difference from mean when they compared microradiographs and confocal microscopy as validating techniques in occlusal caries. For each system, the measurement value was distance of the advancing front of the lesion from the enamel-dentinal junction (EDJ). The data were provided in mm. Their analysis followed the recommendations of Bland and Altman and provided an initial scatter-plot, without any regression line, to illustrate the possible relationship between the two methods and then a plot demonstrating the difference in depth measurements between the two systems. They reported their findings as mean difference, which, for dentinal lesions was 0.41mm and the limits of agreement, which were +0.73 and +0.09.

It would be impossible, for example, to perform this same analysis if one were comparing QLF data, say ΔF at 5% threshold, with TMR data, ΔZ . We are therefore forced to continue to use correlation statistics which, if Bland is to be accepted, are inherently incorrect measurements of agreement and validation. It would appear that the correlation statistics will over emphasise agreements and may even suggest that agreement exists where there is none. This concern is also voiced by (Brunette 1996) who states that while correlations are easily understood, and graphically make intuitive sense to consumers of the

literature, they can over-emphasise the relationship particularly in homogenous sample groups. (Streiner and Norman 1989) state that correlation coefficients are an inappropriate and liberal measure of validity that will invariably over estimate the agreement between the comparators.

An example of this potential over-estimate is the work of Oldham and co-workers who were comparing Wright peak flow meters, they found a correlation of 0.992, but when they adjusted their set-up they obtained a "material improvement" of 0.996 (Oldham, Bevan et al. 1979). (Bland and Altman 1986) states that if a correlation coefficient of 0.99 can be improved upon then the context of what is an acceptable correlation may need to be revisited. Considering these points it is important that validation studies do not use the r value to indicate agreement, only to illustrate a relationship between two variables. A strong relationship is *one* possible indicator for validation. Alternative statistical techniques to prove validity should be investigated prior to commencing a trial to ensure that an appropriate study design is employed.

Conclusion

The summaries contained within the tables associated with this paper present the current state of QLF research with respect to effectiveness. However, if one was to apply the stringent meta-analysis criteria of (Bader, Shugars et al. 2001; Bader, Shugars et al. 2002) very few studies would satisfy the acceptance criteria. One of the underlying problems, and this is faced constantly in caries research, is that so many of the studies are *in vitro*. This is of particular importance when we wish to validate a diagnostic device that is intended for use *in vivo*. Operating conditions are obviously different and the effect that these may have on sensitivity and specificity is unknown. The selection of teeth and their preparation for *in vitro* studies is undertaken to ensure that the best specimens are used, not a luxury that is afforded to the clinical researcher. However, there is a mass of research being undertaken using the device and the indications are that it will be of great importance in dental diagnostic science.

Further research must be undertaken to validate QLF although the study designs must change, further replication of the current pilot studies will offer little additional evidence. Studies should have a low caries prevalence (this is a harder diagnostic challenge) should be, ideally, conducted *in vivo* and should employ appropriate statistics for analysis of the data produced. Trials such as that conducted by the Indiana group and international collaborators (ten Cate, Lagerweij et al. 2000) should be replicated elsewhere and a true picture of the device's effectiveness in the clinical setting gained. Certainly there is further *in vitro* work to be undertaken, validation and elucidation of the potential for QLF to monitor erosion and the effect of material type on the detection of secondary caries are required.

QLF, based upon the current data, is valid and reliable in the *in vitro* setting. Evidence is currently weak to support this statement in relation to *in vivo* work, but there have been no studies that provide any contrary evidence and therefore research should be focussed on strengthening the evidence base. QLF promises to be a useful device in the detection and

diagnosis of smooth and occlusal caries, root caries, secondary caries, and demineralisation adjacent to orthodontic components. It may have use in the monitoring of the erosive process. Little progress has been made on the detection of inter-proximal lesions, although excellent work by (Buchalla, Lennon et al. 2002) may enable this difficult surface to be investigated with QLF.

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FIGURE 1

- a) QLF camera
- b) Example of the traditional QLF capture system
- c) Example of the VidRep system
- d) Example of a calibration image

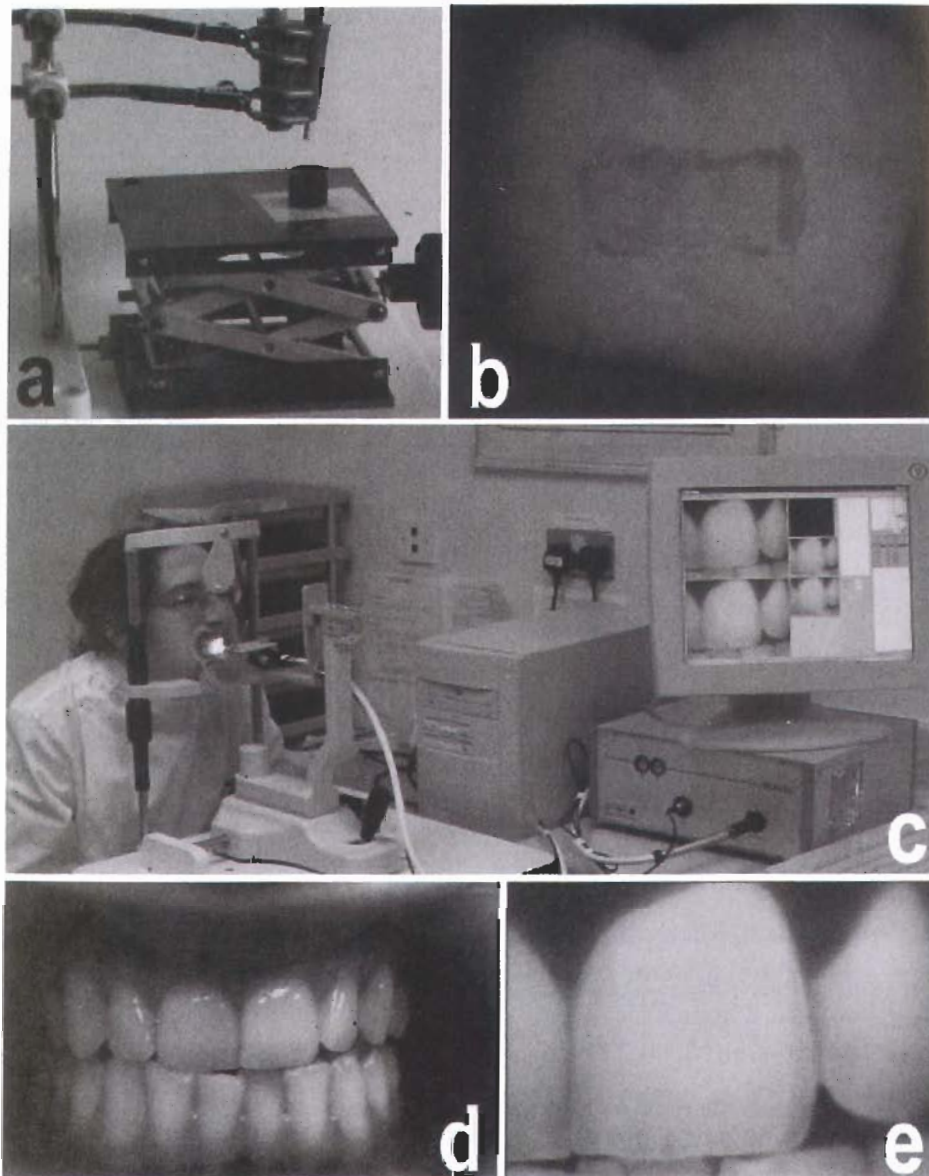


FIG. 1: a) QLF camera in an in vitro set-up.
b) An image captured in vitro.
c) The VidRep system used with the QLF handpiece held on a head-rest.
d) White light image and (e) the QLF image taken using this system.

FIGURE 2

Occlusal caries. Radiographic techniques (a) have been shown to be inferior to clinical visual assessment using a well-defined index (b). Does QLF (d & e) offer the ability to measure these lesions, monitor them longitudinally and provide a guide of when to restore and when to instigate a remineralising therapy?

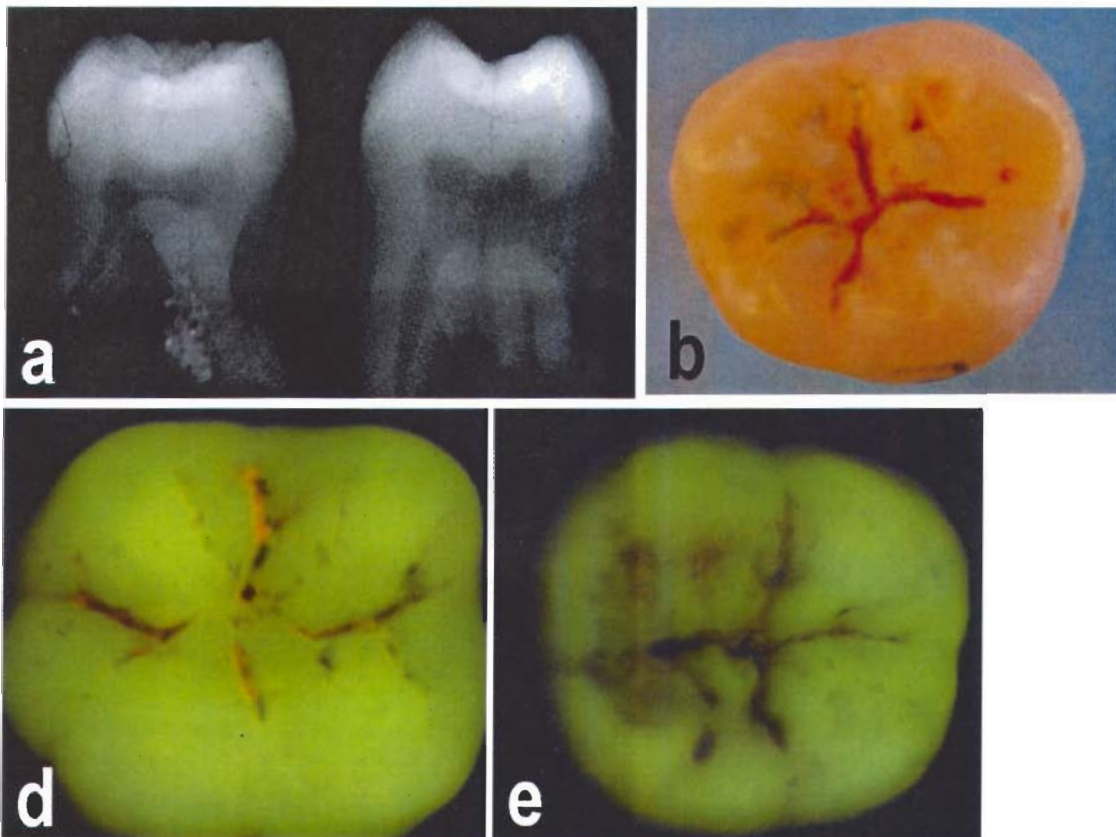
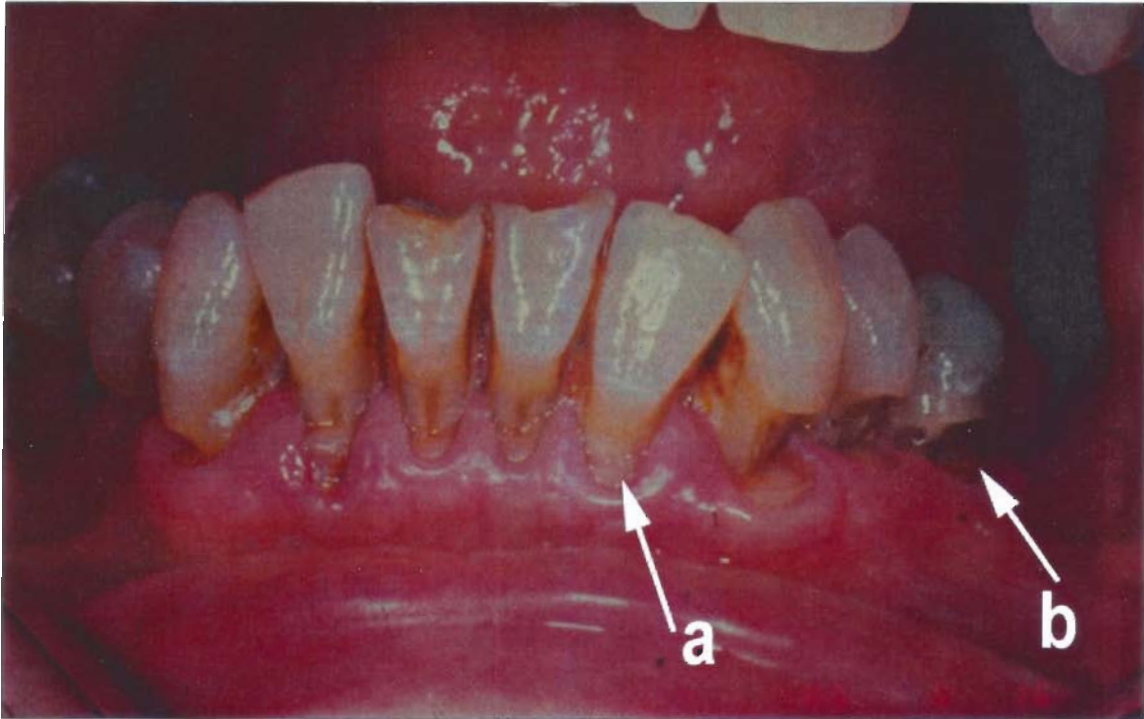


FIGURE 3

Root Caries and abrasion cavities in a middle-aged patient.



The diagnosis of a caries-free surface in (a) is a simple matter, but the assessment of surface (b) is more problematic. More representative of the work of (Gonzalez-Cabezas, Dunn et al. 2001), than that of (Pretty, Ingram et al. 2003), would either method enable an *in vivo* assessment of this lesion leading to an appropriate clinical decision?

FIGURE 4

Secondary decay. On clinical examination, the amalgam restoration in this first molar (a) appears to be failing on the buccal and occlusal surfaces, as does the occlusal amalgam on the premolar (b). Diagnostic test values suggest that only 53% of failing restorations will be detected by radiographic examination, (c) demonstrates potential caries adjacent to the palatal composites. Does QLF (d & e) offer the possibility of detecting enamel demineralisation adjacent to restorations earlier, and hence reduce the need for replacement?

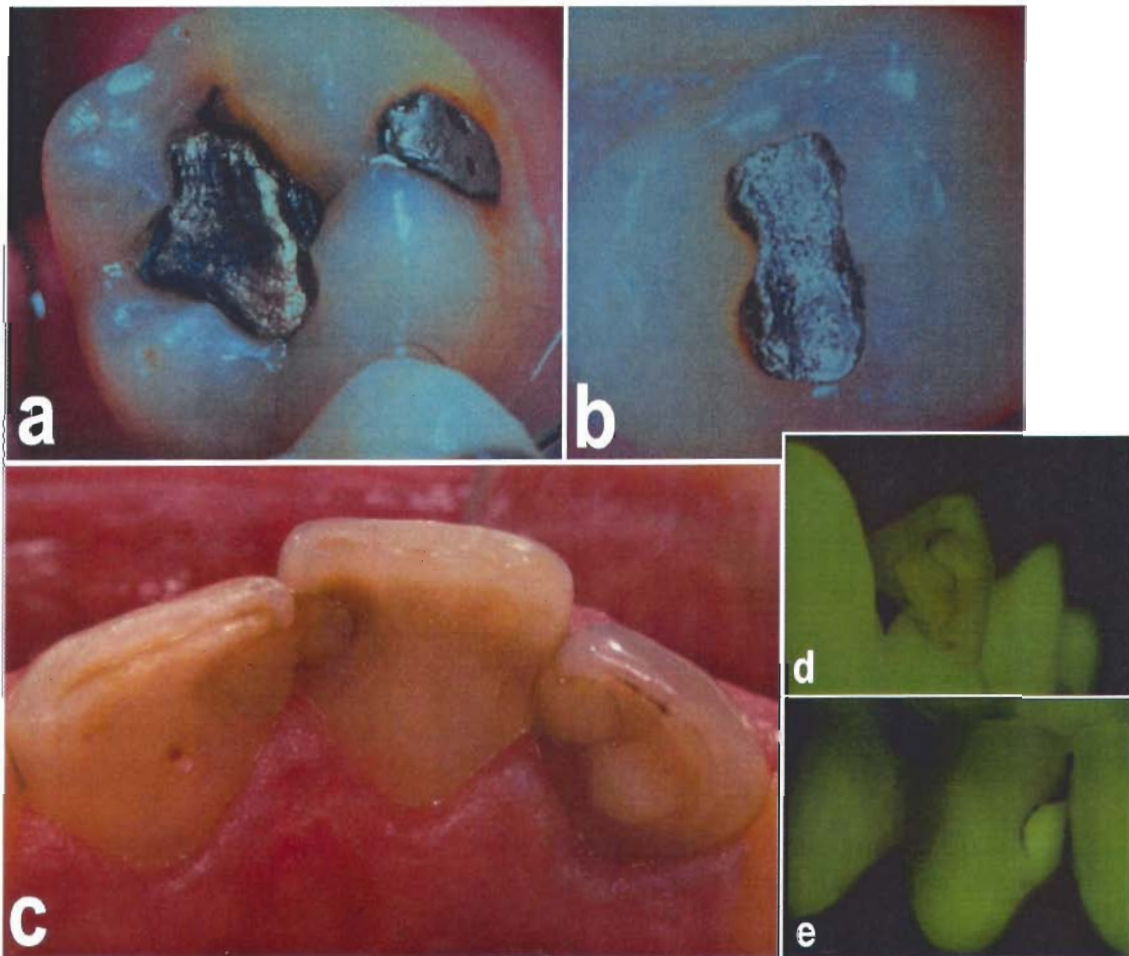


TABLE 1

Effectiveness of some common diagnostic tests for the detection of caries. Modified from (Bader, Shugars et al. 2001)

Method	Number of studies		Number of examiners		Lesion Prevalence (%)		Sensitivity			Specificity			
					Mean	Median	Mean	Median	Range	Mean	Median	Range	
Visual	Occlusal surfaces												
		Cavitated	4	1	1	56	51	63	51	53	89	89	22
		Dental	10	9	4	50	44	37	25	92	87	91	59
		Enamel	2	2	2	21	21	66	66	12	69	69	7
		Any	4	12	7	78	75	59	62	62	72	74	39
Proximal surfaces													
	Cavitated	1	1	-	nr*	-	94	-	-	92	-	-	
Visual-Tactile	Occlusal surfaces												
		Cavitated	1	1	-	nr-	-	94	-	-	92	-	-
		Dental	2	12	6	29	29	19	19	10	97	97	7
		Any	2	4	4	40	40	39	39	44	94	94	13
	Proximal surfaces												
	Cavitated	3	3	3	5	6	52	32	64	98	99	2	
	Dental	1	3	-	nr	-	50	-	-	71	-	-	
Radiographic	Occlusal surfaces												
		Dental	26	4	3	54	55	53	54	79	83	85	50
		Enamel	4	2	2	18	18	30	28	25	76	76	10
		Any	7	5	4	82	84	39	27	67	91	95	18
	Proximal surfaces												
	Cavitated	7	3	3	13	9	66	66	63	95	97	13	
	Dental	8	39	5	27	27	38	40	42	95	96	7	
	Enamel	2	10	10	25	25	41	41	11	78	78	4	
	Any	11	6	3	62	66	50	49	85	87	88	26	
Occlusal Surfaces													

[illegible]

TABLE 2

Accuracy of some digital and conventional radiographic tests for the detection of caries. Modified from Pretty & Maupome (2003)

System	Occlusal AUC	Interproximal AUC
<i>MPDx</i> ¹	0.83	0.74
<i>Dixi</i> ²	0.81	0.82
<i>Sidexis</i> ³	0.8	0.8
<i>RVG(Old)</i> ⁴	0.89	0.77
<i>RVG(New)</i> ⁴	0.9	0.77
<i>Visualix</i> ⁵	0.78	0.76
<i>Ektaspeed Plus</i> ⁶	0.82	0.87
<i>Insight</i> ⁶	0.81	0.83

¹ Dental/Medical Diagnostic Systems Inc., Woodland Hills, CA, USA

² Planmeca, Helsinki, Finland

³ Sirona, Bensheim, Germany

⁴ Trophy, Paris, France

⁵ Gendex, Milan, Italy

⁶ Eastman Kodak, Rochester, NY, USA

AUC – Area under the (ROC) Curve

TABLE 3

Diagnostic performance of caries diagnostic tests for occlusal and approximal caries.

After (Verdonschot, Angmar-Mansson et al. 1999).

Diagnostic method	Occlusal caries mean D_z	Approximal caries mean D_z	Approximal caries mean D_z ‡
<i>Visual inspection</i>	0.85	1.55	-
<i>Radiography</i>	0.91	1.35	4.23
<i>FOTI₁</i>	1.08	2.16	1.72
<i>ERM</i>	1.40	-	-

‡ After mathematical correction for misclassification

i Visual inspection upon FOTI

TABLE 4

Smooth surface caries validation and accuracy studies

Authors	Journal	Year	Optical source	Experimental Material	Result	Method of de- or remineralisation	Gold standard employed	Comments
(Hafstrom-Bjorkman, Sundstrom et al. 1992)	Caries Res	1992	Laser	Human enamel slabs (n=10)	$r_{sp} = 0.86$	Demin in pH cycling model	LMR	$r = 0.97$ for individual slices
(Emami, al-Khateeb et al. 1996)	Acta Odont	1996	Laser	Human enamel slabs (n=36)	$r = 0.73$	Demin natural incipient lesions	LMR	Repeatability was $\pm 1.0\%$
(ten Cate, de Josselin de Jong et al. 1996)	Caries Res (Abs)	1996	Laser	Bovine enamel blocks (n=54)	$r = 0.65$	Demin in buffered solution	TMR	Lesion depth rather than mineral loss
(al-Khateeb, ten Cate et al. 1997)	Adv Dent Res	1997	Laser	Human / bovine blocks (n=25b, 30h)	$r = 0.79$ (laser) $r = 0.84$ (light)	Demin and remin using a pH cycle	TMR and chemical	When the two methods (laser & light) compared, $r = 0.93$
(al-Khateeb, Oliveby et al. 1997)	Caries Res	1997	Laser	Human enamel blocks (n=72)	$r = 0.76$	Demin in pH cycle, remin <i>in situ</i>	TMR	
(Ando, Hall et al. 1997)	Caries Res	1997	Light	Bovine enamel blocks (n=144)	$r = 0.69$	Demin in buffered solution	TMR, CLSM	
(Hall, DeSchepper et al. 1997)	Adv Dent Res	1997	Laser	Bovine enamel cores (n=84)	$r = 0.83$	Demin in buffered solution	TMR, histology	When lesion depth assessed, $r = 0.70$

(Lagerweij, van der Veen et al. 1999)	Caries Res	1997	Laser & Light	Human enamel blocks (n=40)	r = 0.63 (light) r = 0.70 (laser 1)	Demin in buffered solution	TMR	A further laser device (ring illum), r= 0.36
(Ando, Analoui et al. 1999)	Caries Res Abs	1999	Laser & Light	Human enamel blocks	r = 0.86 (light) r = 0.83 (laser)	Demin in buffered solution	TMR	DIAGNODent was also used, with r = 0.59
(Naganuma 2000)	Indiana Proceedings	2000	Light ??	??	r = 0.88		TMR	Look up
(Ando, van Der Veen et al. 2001)	Caries Res	2001	Light & Laser	Whole human teeth (n=30, deciduous teeth)	r = 0.88 (light) r = 0.84 (laser)	Demin in buffered solution	TMR	
(Ando, van Der Veen et al. 2001)	Caries Res	2001	Light & Laser	Whole human teeth (n=30, permanent teeth)	r = 0.62 (light) r = 0.53 (laser)	Demin in buffered solution	TMR	
(Hall, DeSchepper et al. 1996)	Indiana Proceedings	1996	Laser		Sens: 0.75 Spec: 0.90			
(ten Cate, Lagerweij et al. 2000)	Indiana Proceedings	2000	Light	Exfoliated natural teeth (n = 100)	Sens: 0.79 Spec: 0.75	Natural lesions	TMR	
(Shi, Tranaeus et al. 2001)	Caries Res	2001	Laser	Human premolars (n=71)	Sens: 0.76 Spec: 0.92 r = 0.69	Natural lesions	TMR and Histology	When assessing lesion depth r = 0.85

TABLE 5

Occlusal surface caries validation and accuracy studies, † No plaque, ‡ Plaque covered

Authors	Journal	Year	Optical source	Experimental Material	Result	Method of de- or remineralisation	Gold standard employed	Comments
(Ando, Analoui et al. 1999)	Caries Res Abs	1996	Laser	Natural teeth (n=6)	Sens: 0.76† Spec: ----	Natural lesions	Histology	
(Tranaeus, Lussi et al. 1997)	J Dent Res Abs	1997	Laser	Human molars (n=100)	Sens: 0.71 Spec: 0.73	Natural lesions	Histology	QLF scored lower than ECM in this study
(Ferreira Zandona, Analoui et al. 1997)	J Dent Res Abs	1997	Laser	Human whole enamel samples (n=49)	No differences in sensitivity, poorer specificity than visual	Natural lesions	Histology	
(Ferreira Zandona, Analoui et al. 1998)	Caries Res	1998	Laser	Bovine enamel disks (n=240)	ROC: 0.70 Sens: 0.54† Spec: 0.29† Sens: 0.43‡ Spec: 0.55‡	Demin in buffered solution	Examiner assessment	
(Ferreira Zandona, Analoui et al. 1998)	Caries Res	1998	Laser	Whole human teeth (n=150)	Sens: 0.49 Spec: 0.67	Natural lesions	Histology and CSLM	
(ten Cate, Lagerweij et al. 2000)	Indiana Proceedings	2000	Light	Exfoliated teeth	Sens: 0.77 Spec: 0.71	Natural lesions	TMR	

(Pretty, Laloo et al. 2003)	J Dent Res Abs	2003	Light	Whole teeth (n=75)	r = 0.82	Natural lesions	Histology and radiography
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TABLE 6

Effectiveness measures from a variety of diagnostic tests applied to the detection of occlusal caries.

	Diagnostic system	Sensitivity	Specificity	Youden's J	Positive predictive value	Negative predictive value
(Ashley, Blinkhorn et al. 1998)	ECM	0.65	0.73	0.38	0.78	0.58
(Ashley, Blinkhorn et al. 1998)	Visual	0.60	0.73	0.33	0.77	0.55
(Ashley, Blinkhorn et al. 1998)	FOTI	0.21	0.88	0.09	0.72	0.42
(Ashley, Blinkhorn et al. 1998)	Bitewing radiographs	0.19	0.80	0.01	0.60	0.40
(Pretty, Laloo et al. 2003)	QLF	0.68	0.70	0.38	0.77	0.59
(Alwas-Danowska, Plasschaert et al. 2002)	Visual	0.50†	0.91†	0.41†	TBC	TBC
(Alwas-Danowska, Plasschaert et al. 2002)	DIAGNODent	0.94†	0.52†	0.46†	TBC	TBC
(Bamzahim, Shi et al. 2002)	DAIGNODent	0.8	1	0.80	TBC	TBC
(Bamzahim, Shi et al. 2002)	ECM	0.75	0.88	0.63	TBC	TBC

† Calculated from data in publication

TABLE 7

Positive and negative predictive values of QLF on various enamel surfaces

Surface	High risk population (0.8)		Low risk population (0.1)	
	PPV	NPV	PPV	NPV
Smooth	0.95	0.43	0.36	0.96
Occlusal	0.901	0.35	0.20	0.95
Secondary caries	0.96	0.70	0.40	0.98
Orthodontic	0.98	0.62	0.65	0.98

PPV = Positive predictive value

NPV = Negative predictive value

TABLE 8

Correlations expressed in Spearman Rank correlation coefficients (r) between diagnostic outcomes and actual lesion depth for occlusal caries detection. Extended from original by (Verdonschot, Angmar-Mansson et al. 1999)

Publication	Diagnostic method	r
(Wenzel and Fejerskov 1992)	Visual inspection	0.57†
(Tveit, Espelid et al. 1994)	Visual inspection	0.76†
(Ekstrand, Ricketts et al. 1997)	Visual inspection	0.90
(Pretty, Laloo et al. 2003)	Visual inspection	0.88
(Wenzel and Fejerskov 1992)	Radiography	0.54†
(Ekstrand, Ricketts et al. 1997)	Radiography	0.77
(Pretty, Laloo et al. 2003)	Radiography	0.83
(Ricketts, Kidd et al. 1996)	ECM	0.62
(Ekstrand, Ricketts et al. 1997)	ECM	0.82
(Bamzahim, Shi et al. 2002)	ECM	0.83
(Huysmans, Longbottom et al. 1998)	ECM	0.78
(Pretty, Laloo et al. 2003)	DIAGNODent	0.62
(Bamzahim, Shi et al. 2002)	DIAGNODent	0.93
(Pretty, Laloo et al. 2003)	QLF	0.82

† Calculated from data in publication

TABLE 9

Detection of root caries using QLF.

Authors	Journal	Year	Optical source	Experimental Material	Result	Method of de- or remineralisation	Gold standard employed	Comments
(Gonzalez-Cabezas, Dunn et al. 2001)	Caries Res Abs	2001	Light	Extracted teeth with natural lesions	ROC – AUC 0.78	Natural lesions	Confocal microscopy	Similar to ECM, and DD.
(Pretty, Ingram et al. 2003)	J Oral Rehab	2003	Light (with fluorescein)	Whole roots	Demin: $r = 0.89$ Remin: $r = 0.84$	Demin in buffered solution, remin in artificial saliva	TMR	Images required manipulation prior to analysis

TABLE 10

Effectiveness of other diagnostic systems at detecting root lesions

Authors	System	Gold standard employed	Result – r values
(Wicht, Haak et al. 2002)	ECM	PLM	0.48
(Wicht, Haak et al. 2002)	DIAGNODent	PLM	0.45
(Zoellner, Bragger et al. 2000)	Visual index	Histology	0.87
(Almqvist, Wefel et al. 1988)	Absorptiometry	Chemical	0.93

TABLE 11

Studies concerning the detection of secondary caries using QLF

Authors	Journal	Year	Optical source	Experimental Material	Result	Method of de- or remineralisation	Gold standard employed	Comments
(Hall, DeSchepper et al. 1996)	Caries Res Abs	1996	Laser	Bovine enamel slabs (n=7)	Significant differences detected (p<0.001) Sens: 0.95 Spec: 0.85 Agreement: 0.90	Demin in buffered solutions	TMR	
(Benedict, DeSchepper et al. 1996)	J Dent Res Abs	1996	Laser	Human teeth restored with amalgam (n=20)	Sens: 0.88† Spec: 0.85† r = 0.66	Demineralised in buffered solutions	Visual	Used negative images during the QLF analysis stage
(DeSchepper, Hall et al. 1996)	Caries Res Abs	1996	Laser	Bovine enamel restored with amalgam (n=50)		Demin in buffered solutions	Clinical	
(Tranaeus, de Josselin de Jong et al. 1997)	Caries Res Abs	1997	Light & Laser	Human teeth (n = 20, 4 restorative materials)	Laser: r = 0.75 Light r = 0.80	Natural lesions restored leaving residual marginal demineralisation	LMR	
(Gonzalez-Cabezas, Fontana et al. 2000)	Indiana Conference	???	?		?	?	?	To follow
(Pretty, Smith et al. 2003)	Dental Materials	2003	Light	Whole human teeth (n=15, 5 different materials)	Significant differences detected (p<0.001)	Demineralised in buffered solutions	TMR	No influence on detection of material used

† Means calculated from publication

TABLE 12

Studies concerning the detection of secondary caries using other diagnostic systems

Author(s)	System	Results	Gold-standard	Comment
(Boston 2003)	DIAGNODent	For enamel caries: Sens: 0.67, Spec: 0.79 For dentinal caries: Sens: 0.73, Spec: 0.84	Histology	15 extracted teeth used, adjacent to resin based materials only.
(Rudolph, van Loveren et al. 1996)	Visual	Sens: 0.92, Spec: 0.55	TMR	150 extracted molars and premolars used. Employed detection of greyish discoloration
(Nummikoski, Martinez et al. 1992)	Digital subtraction radiography	??	??	To follow
(Espelid and Tveit 1991)	Radiographically	Sens: 61.8, Spec: 93.05	Visual	Used different materials with varying levels of radio-opacity
(Espelid, Tveit et al. 1991)	Radiographically II			To follow
(Choksi, Brady et al. 1994)	FOTI	Radiographs > FOTI > Clinical visual	Need for restoration	In vivo study

TABLE 13

Studies concerning the detection of orthodontic demineralisation

Authors	Journal	Year	Optical source	Experimental Material	Result	Method of de- or remineralisation	Gold standard employed	Comments
(Benson 2003)7]	Eur J Orthod	2003	Light	Whole human teeth (n=30)	Sens: 0.86 Spec: 0.95	Demin in buffered solution	Visual	
(Pretty, Pender et al. 2003)8]	Eur J Orthod	2003	Light	Whole human teeth (n=15)	Statistical differences detected between each time interval (p<0.001)	Demin in buffered solution, remineralised in artificial saliva	N/A	

TABLE 14

Erosion studies using QLF

Authors	Journal	Year	Optical source	Experimental Material	Result	Method of de- or remineralisation	Gold standard employed	Comments
(Kuhnisch, Heinrich-Weltzien et al. 2001)	Caries Res Abs	2001	Light	Whole teeth	Significant changes found over time $r = 0.87$	Citric acid erosion	None	Proof-of-concept study
(Pretty, Edgar et al. 2003)	J Dent Res Abs	2003	Light	Whole teeth		Citric acid erosion	TMR	

TABLE 15

Studies assessing the reliability of QLF

Authors	Journal	Year	Optical source	Experimental Material	Result	Method of de- or remineralisation	Gold standard employed	Comments
(Tranaeus, Shi et al. 2002)	Caries Res	2002	Light	In vivo images of natural lesions (n=15, 3 examiners)	Image Capture: 0.96† Intra-exam: 0.96† Inter-exam: 0.97†	Natural lesions	N/A	Intra-class correlation coefficients
(Pretty, Hall et al. 2002)	Br Dent J	2002	Light	Whole human teeth (n = 20, 10 examiners)	Intra-exam: 0.93 Inter-exam: 0.92	Demin in solution	N/A	Examiners in three different centres.
(Benson, Pender et al. 2003)	Eur J Orthod	2003	Light	Whole human teeth (n=30)	Agreement: 0.1 ±0.63 Reliability r = 0.84	Demin in buffered solution	N/A	Assessment of orthodontic demineralisation

† Means calculated from publication

TABLE 16

Reliability data using other diagnostic devices

Study	Device	Results (ICC)	Comment
(Wicht, Haak et al. 2002)	DIAGNODent	Inter-exam: 0.96	When assessing root surface lesions
(Alwas-Danowska, Plasschaert et al. 2002)	DIAGNODent	Intra-exam: 0.89 Inter-exam: 0.87	Using both the original and revised DIAGNODent devices on occlusal surfaces
(Bamzahim, Shi et al. 2002)	DIAGNODent	Inter-exam: 0.97	When assessing occlusal surface lesions
(Lussi, Imwinkelried et al. 1999)	DIAGNODent	Intra-exam: 0.89† Inter-exam: 0.69†	Kappa scores when assessing occlusal lesions
(Tranaeus, Karlsson et al. 2001)	DIAGNODent	Intra-exam: 0.89† Inter-exam: 0.86	In vivo study assessing smooth surfaces
(Bamzahim, Shi et al. 2002)	ECM	Inter-exam: 0.71	When assessing occlusal surface lesions
(Wicht, Haak et al. 2002)	ECM	Inter-exam: 0.95	When assessing root surface lesions
(Holt and Azevedo 1989)	FOTI	Inter-exam: 0.76	Proximal lesions, kappa statistics.
(Cleaton-Jones, Daya et al. 2001)	FOTI	Inter-exam: 0.90	Primary dentition, kappa statistics
(Lavonius, Kerosuo et al. 1997)	FOTI	Inter-exam: 0.42	When assessing occlusal lesions

†Means calculated from publication