

Clinical Relevance and Potential Utility of Diagnostic Tests

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Summary: Since the 1970s, diagnostic tests have been evaluated using a hierarchical six-level framework. Within this framework, clinical relevance and potential utility represent level 4 and 5 evidence and is typically assessed by means of randomized controlled trials where diagnostic tests are randomized and the decisions made by clinicians (level 4 evidence) or the tangible outcomes observed in patients (level 5 evidence) are tabulated. Using such an evidence-based framework within dentistry would be particularly useful for assessing diagnostic tests aimed at detecting subtle changes or involving ionizing radiation. Diagnosing subtle anatomical, crevicular fluid, or microbiological changes in the oral cavity of symptom-free patients has the potential to drastically increase dental disease prevalence and dental treatment utilization. Experiences with diagnostic tests in other disease areas such as prostate cancer indicates that such redefining of disease leads to uncertainties in assessing harm-benefit ratios because it often is unclear whether those subtle changes that *can* be detected and treated *need* to be treated, and whether those subtle changes that *need* to be treated, *can* be detected and treated. Diagnostic tests involving ionizing radiation can have potentially adverse health consequences, and additional pressures exist to provide evidence that their benefits outweigh harms. Considering the high prevalence of radiation usage and the lack of individual-patient dose-monitoring, there is a need to determine which radiographs improve patient outcomes. The high potential impact of dental diagnostic testing on dental utilization combined with the high prevalence of dental visits make it that an evidence-based framework of the assessment of diagnostic tests would offer a welcome addition to the dental knowledge database.

Key words: diagnostic testing, patient benefits, ionizing radiation, harms

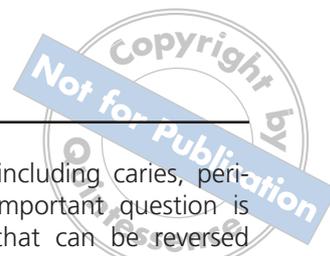
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INTRODUCTION

The methodology for assessing the value of diagnostic tests was largely established in the 1970s and has now been widely adopted by evidence-based treatment centres and the Agency for Health Care Research and Quality Assessment Technology Program (Thornbury et al, 1975; McNeil and Adelstein, 1976; Fineberg et al, 1977; Fryback, 1983; Tatsioni et al, 2005). The methodology consists of a six-level hierarchical framework with the lowest level being the technical feasibility of the diagnostic technology and the optimization of its usage (level 1) and the highest level being the societal impact of diagnostic testing (level 6) (Table 1). Most relevant to this report, assessing the clinical relevance and potential utility of diagnostic tests, is determining how diagnostic testing impacts on treatment decisions (level 4 evidence) and more importantly, how diagnostic testing provides tangible patient benefits in

terms of how a patient feels, functions, or survives (level 5 evidence).

The clinical utility of dental diagnostic tests varies widely. For instance, correct imaging of the inferior alveolar nerve (IAN) vis-a-vis the implant body is of such importance in avoiding IAN damage that even a suggestion of randomizing patients to have access (or not to have access) to radiographic techniques for IAN visualization would be unethical (Worthington, 2004). On the other extreme, the use of a cephalographic radiograph to document the end of orthodontic therapy is of such dubious clinical utility that spending resources on a formal evidence-based assessment of the value of such practices appears to be a waste of resources. Between such extremes, there are those dental diagnostic tests where it remains unclear and controversial whether diagnostics testing leads to tangible patient benefits and where a formal assessment of diagnostic test value would be most productive.



Two areas of diagnostic testing have the potential to have a significant impact on the profession of dentistry and will be discussed further. First, there are those diagnostic tests aimed at detecting subtle changes in the oral cavity. Enamel de- and re-mineralizations, subtle bone-remodelling processes as a potential sign of periodontitis, or biochemical or microbiological markers of inflammation have the potential to drastically increase dental 'disease' prevalence and are increasingly used to advocate for early intervention. An evidence-based assessment of the utility of such diagnostic tests is overdue. Second, there are those diagnostic tests that may be harmful in and of themselves. Ionizing radiation is the most prominent member of this class of diagnostic tests and, with certain countries reporting that over 50% of the population is exposed to dental radiation, there is a need to provide an evidence-based assessment of the benefits.

DIAGNOSTIC TESTS AIMED AT DETECTING SUBTLE CHANGES

Substantial resources have been spent in dental research on the development of diagnostic tests aimed at detecting subtle changes. Examples include those diagnostic tests aimed at detecting bacterial or host enzymatic activity in gingival crevicular fluid, methods aimed at detecting subtle enamel demineralizations, microbiological testing for a cariogenic bacterial challenge or purported periodontal pathogens, and differential dark field microscopy. Their success in terms of adoption in clinical practice has varied widely.

For many of these diagnostic tests, the clinical relevance of what is being detected is not completely understood and epidemiological evidence relating the subtle changes to clinically relevant outcomes is often lacking. For instance, the role of bacteria in the periodontitis process (not gingivitis) continues to be an often-changing and increasingly complex story that remains to a large extent unsupported by epidemiological evidence of causality. Developing diagnostic tests aimed at detecting these bacteria have a long scientific road ahead to establish clinical utility. Similarly, the benefits of detecting early enamel lesions rest on biological plausibility, not epidemiological evidence. Small clinical studies suggest that most enamel demineralizations may not progress (Backer Dirks, 1966), that many frank cavities are observed without observing a preceding white spot (Katz et al, 2005), and that 'bad' remineralizations (hidden cavities) may occur (Koulourides and Cameron, 1980). Treatments effective on preventing subtle enamel lesions may not be effective in preventing frank cavitations (Zimmer et al, 2001). Consequently, diagnostic tests aimed at detecting subtle enamel demineralizations have unclear clinical significance. For

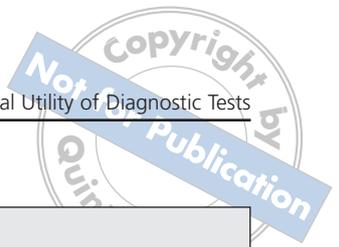
many chronic diseases, possibly including caries, periodontitis and oral cancer, the important question is whether those subtle changes that can be reversed need to be reversed, and whether those subtle changes that need to be reversed can be reversed. Making diagnostic tests aimed at detecting subtle oral changes in otherwise healthy patients without answers to such questions make it possible to drastically increase treatment utilization, cost, and potentially harm to the patient, without materially changing the clinically relevant dental disease outcomes.

Dental diagnostic tests aimed at detecting subtle changes should be based on level 5 evidence (Table 1) - the conduct of randomized controlled trials where patients are randomly assigned either to access or no access to diagnostic tests and where the clinically relevant outcomes in both groups are compared. Diagnostic tests such as prostate-specific antigen (PSA) testing are currently being evaluated using such an approach (Schroder, 2005). Hopefully, diagnostic testing for chronic dental diseases will follow such examples and provide the same type of reliable evidence that is available for medical diagnostic tests.

DIAGNOSTIC TESTS THAT INVOLVE IONIZATING RADIATION

While the radiation doses with dental radiography are typically considered to be very low, there is a concern regarding potential adverse health effects. Some suggest that the lowest dose for which good epidemiological evidence exists of an increased cancer risk with an acute exposure is 10 to 50 millisievert. This dose is higher than most typical dental radiographic exposures (Brenner et al, 2003). Cumulative dental radiography doses can cross this threshold and can be of concern since some of the most radiosensitive organs in the body, the thyroid and the meninges, can be in the direct field of the radiation beam. Several studies have raised concerns that dental radiography may be associated with intracranial meningiomas (Preston-Martin et al, 1980, 1983, 1989; Rodvall et al, 1998; Longstreth et al, 2004), thyroid cancers (Hallquist et al, 1994; Wingren et al, 1997), salivary gland tumors (Horn-Ross et al, 1997) and adverse reproductive outcomes (Goldberg et al, 1998; Hujoel et al, 2004; De Santis et al, 2005).

Studies showing such associations typically have little impact on diagnostic practices in dentistry both because the results are often at odds with interpolations of the atomic blast experiments, and because radiation doses have been continuously decreasing. These two reasons combined with advocacy of the ALARA principle (as low as reasonable achievable) have left diagnostic X-ray practices under-evaluated over the past 40 years.

**Table 1 Hierarchical levels of evidence for diagnostic tests**

Level	Description	Examples of study purpose	Examples
1	Technical feasibility and optimization	Determine which cutoff is optimal for yes-no tests	Optimization of the BANA test (Loesche et al, 1997)
2	Diagnostic accuracy	Sensitivity and specificity; % agreement, likelihood ratio tests	(Bretz et al, 1990)
3	Diagnostic thinking impact	Change in diagnostic thinking based on availability of diagnostic test	Caries and radiographs (Hopcraft and Morgan, 2005)
4	Therapeutic choice impact	Change in therapeutic decisions based on diagnostic test	Orthodontic treatments (Han et al, 1991)
5	Patient outcome impact	Outcomes in patients with and without access to diagnostic test	Oral cancer screening and mortality (Sankaranarayanan et al, 2005)
6	Societal impact	Cost-effectiveness of screening	-

The ALARA-principle however is toothless. In the absence of evidence-based assessments of clinical utility, both the orthodontist who requests, in addition to the standard orthodontic series, a CT-scan of the mandibular joints for every patient with a midline discrepancy, and the orthodontist who only request a panoramic radiograph to determine missing teeth can be said to practice according to the ALARA principle. Yet the radiation doses to radiosensitive organs can differ by magnitudes as much as 100. With lack of knowledge regarding radiation doses common, and the absence of a reliable cumulative patient record of lifetime received radiation doses, there is little or no control over a person's total lifetime exposure to dental radiography.

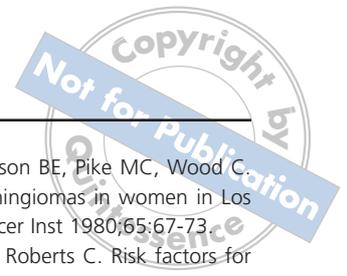
The recent National Academy of Sciences report (Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation NRC, 2005) that there is no such thing as a safe radiation dose emphasizes the need to develop evidence-based guidelines, not opinion-based guidelines as to which practices involving ionizing radiation provide unequivocal tangible patient benefit. Higher levels of evidence (e.g., randomized trials) on the value of X-rays in many dental specialties have the potential to provide a firm scientific footing as to which, if any, radiographic practices indeed provide tangible patient benefits in terms of treatment outcomes. Such studies would provide the opportunity to determine what visualization techniques for which procedures/interventions/monitoring do impact on the ultimate outcome that the patient perceives.

CONCLUSIONS

The primary goal of a diagnostic test is to improve patient clinical outcomes. While it is often assumed, based on biological plausibility, that most dental diagnostic tests achieve this goal, direct evidence in support of this is often lacking. Given that the current diagnostic tests of interest have the potential to drastically increase dental disease prevalence, and given that diagnostic tests that involve radiation will do harm on a population-level, and given the world-wide high utilization of dental diagnostic tests, the adoption of the six-level framework for assessing and evaluating dental diagnostic tests could be a welcome addition to the dental knowledge database.

REFERENCES

- Backer Dirks O. Post-eruptive changes in dental enamel. *J Dent Res* 1966;45:503-511.
- Brenner DJ, Doll R, Goodhead DT, Hall EJ, Land CE, Little JB, et al. Cancer risks attributable to low doses of ionizing radiation: assessing what we really know. *Proc Natl Acad Sci USA* 2003;100:13761-13766.
- Bretz WA, Lopatin DE, Loesche WJ. Benzoyl-arginine naphthylamide (BANA) hydrolysis by *Treponema denticola* and/or *Bacteroides gingivalis* in periodontal plaques. *Oral Microbiol Immunol* 1990;5:275-279.
- Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation NRC. *Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII Phase 2: The National Academy Press*; 2005.



- De Santis M, Straface G, Cavaliere AF, Caruso A, Cichocki F, Venga L, et al. First trimester maternal thyroid X-ray exposure and neonatal birth weight. *Reprod Toxicol* 2005;20:3-4.
- Fineberg HV, Bauman R, Sosman M. Computerized cranial tomography. Effect on diagnostic and therapeutic plans. *JAMA* 1977;238:224-227.
- Fryback DG. A conceptual model for output measures in cost-effectiveness evaluation of diagnostic imaging. *J Neuroradiol* 1983;10:94-96.
- Goldberg MS, Mayo NE, Levy AR, Scott SC, Poitras B. Adverse reproductive outcomes among women exposed to low levels of ionizing radiation from diagnostic radiography for adolescent idiopathic scoliosis. *Epidemiology* 1998;9:271-278.
- Hallquist A, Hardell L, Degerman A, Wingren G, Boquist L. Medical diagnostic and therapeutic ionizing radiation and the risk for thyroid cancer: a case-control study. *Eur J Cancer Prev* 1994;3:259-267.
- Han UK, Vig KW, Weintraub JA, Vig PS, Kowalski CJ. Consistency of orthodontic treatment decisions relative to diagnostic records. *Am J Orthod Dentofacial Orthop* 1991;100:212-219.
- Hopcraft MS, Morgan MV. Comparison of radiographic and clinical diagnosis of approximal and occlusal dental caries in a young adult population. *Community Dent Oral Epidemiol* 2005;33:212-218.
- Horn-Ross PL, Ljung BM, Morrow M. Environmental factors and the risk of salivary gland cancer. *Epidemiology* 1997;8:414-419.
- Hujoel PP, Bollen AM, Noonan CJ, del Aguila MA. Antepartum dental radiography and infant low birth weight. *JAMA* 2004;291:1987-1993.
- Katz BP, Ofner S, Eckert GJ, Zandona Ferreira AG, Ando M, et al. De- and re-mineralization. *Caries Res* 2005;39:319 (abstract).
- Koulourides T, Cameron B. Enamel remineralization as a factor in the pathogenesis of dental caries. *J Oral Pathol* 1980;9:5,255-269.
- Loesche WJ, Kazor CE, Taylor GW. The optimization of the BANA test as a screening instrument for gingivitis among subjects seeking dental treatment. *J Clin Periodontol* 1997;24:718-726.
- Longstreth WT, Jr., Phillips LE, Drangsholt M, Koepsell TD, Custer BS, Gehrels JA, et al. Dental X-rays and the risk of intracranial meningioma: a population-based case-control study. *Cancer* 2004;100:1026-1034.
- McNeil BJ, Adelstein SJ. Determining the value of diagnostic and screening tests. *J Nucl Med* 1976;17:6,439-448.
- Preston-Martin S, Mack W, Henderson BE. Risk factors for gliomas and meningiomas in males in Los Angeles County. *Cancer Res* 1989;49:6137-6143.
- Preston-Martin S, Paganini-Hill A, Henderson BE, Pike MC, Wood C. Case-control study of intracranial meningiomas in women in Los Angeles County, California. *J Natl Cancer Inst* 1980;65:67-73.
- Preston-Martin S, Yu MC, Henderson BE, Roberts C. Risk factors for meningiomas in men in Los Angeles County. *J Natl Cancer Inst* 1983;70:863-866.
- Rodvall Y, Ahlbom A, Pershagen G, Nylander M, Spannare B. Dental radiography after age 25 years, amalgam fillings and tumours of the central nervous system. *Oral Oncol* 1998;34:265-269.
- Sankaranarayanan R, Ramadas K, Thomas G, Muwonge R, Thara S, Mathew B, et al. Effect of screening on oral cancer mortality in Kerala, India: a cluster-randomised controlled trial. *Lancet* 2005;365:1927-1933.
- Schroder FH. Detection of prostate cancer: the impact of the European Randomized Study of Screening for Prostate Cancer (ERSPC). *Can J Urol* 2005;12 Suppl 1:2-6; discussion 92-93.
- Tatsioni A, Zarin DA, Aronson N, Samson DJ, Flamm CR, Schmid C, et al. Challenges in systematic reviews of diagnostic technologies. *Ann Intern Med* 2005;142(12 Pt 2):1048-1055.
- Thornbury JR, Fryback DG, Edwards W. Likelihood ratios as a measure of the diagnostic usefulness of excretory urogram information. *Radiology* 1975;114:561-565.
- Wingren G, Hallquist A, Hardell L. Diagnostic X-ray exposure and female papillary thyroid cancer: a pooled analysis of two Swedish studies. *Eur J Cancer Prev* 1997;6:550-556.
- Worthington P. Injury to the inferior alveolar nerve during implant placement: a formula for protection of the patient and clinician. *Int J Oral Maxillofac Implants* 2004;19:731-734.
- Zimmer S, Bizhang M, Seemann R, Witzke S, Roulet JF. The effect of a preventive program, including the application of low-concentration fluoride varnish, on caries control in high-risk children. *Clin Oral Investig* 2001;5:40-44.

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