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Antibiofilm Effects of Kaempferol Against Oral Pathogens: A Systematic Review

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ABSTRACT

Dental caries and periodontitis are biofilm-mediated diseases involving oral pathogens such as *Streptococcus mutans* and *Porphyromonas gingivalis*, which form structured biofilms resistant to antimicrobials and host defences. Kaempferol, a dietary flavonol with antibacterial and antibiofilm properties, has attracted interest; however, its effects against oral pathogens have not been systematically reviewed. This systematic review evaluated the antibiofilm activity and mechanisms of kaempferol against oral pathogens. A Systematic Literature Review approach guided by PRISMA 2020 was conducted, searching PubMed, ScienceDirect, Scopus, and SpringerLink. Eligible original studies investigated purified kaempferol or kaempferol as an identified constituent in relation to oral-pathogen biofilm formation, viability, or biofilm-associated virulence. Studies involving the genus *Kaempferia* were excluded. Two reviewers independently screened studies, extracted data, and assessed methodological quality using the QUIN tool. Three studies met the inclusion criteria. Kaempferol reduced biofilm formation and biomass, with the most consistent effects reported against *S. mutans* in a concentration-dependent manner. Reported mechanisms included inhibition of glucosyltransferase activity and glucan synthesis, suppression of acidogenicity, bacterial membrane disruption with intracellular content leakage, and induction of reactive oxygen species. Activity varied by chemical form, with the free aglycone showing greater activity than its glycosides. All studies had a medium risk of bias. Evidence remains limited to laboratory settings. Overall, limited and heterogeneous evidence suggests that kaempferol inhibits oral-pathogen biofilms through multiple mechanisms, predominantly beyond direct bacterial killing. These findings support its potential as an adjunctive anti-virulence agent, although standardised multispecies and *in vivo* studies are needed before clinical translation.

Keywords: kaempferol; antibiofilm; flavonol; oral pathogens; *Streptococcus mutans*

INTRODUCTION

Dental caries and periodontitis remain among the most common chronic diseases affecting humans, imposing a substantial burden on quality of life and health systems worldwide [1]. Both conditions are initiated and sustained by microbial biofilms that accumulate on the tooth surface and within the gingival sulcus [2]. Within these biofilms, communities of bacteria embedded in a self-produced extracellular matrix cooperate through metabolic and signalling interactions, giving rise to a stable, structured consortium that is considerably more tolerant of antimicrobials, host immune responses and environmental stress than the corresponding planktonic cells [2,3]. This biofilm lifestyle is widely regarded as the principal reason that mechanical debridement and adjunctive antimicrobials frequently fail to achieve durable control of oral infection [3].

Among the oral microbiota, *Streptococcus mutans* is the principal cariogenic pathogen. It metabolises dietary carbohydrates to organic acids and, through its glucosyltransferases (Gtfs), synthesises insoluble glucans that form the scaffold of cariogenic biofilm and promote firm adhesion to enamel [4]. In the periodontal environment, *Porphyromonas gingivalis* is a keystone pathogen whose virulence factors, including gingipains, fimbriae and lipopolysaccharide, subvert host immunity and drive dysbiosis, while

species such as *Fusobacterium nucleatum* act as bridging organisms that support multispecies biofilm maturation [5,6]. Across these species, biofilm formation is not merely a growth state but a central virulence determinant, which makes it an attractive therapeutic target [3,6].

Conventional antimicrobial strategies for oral biofilm, such as chlorhexidine and systemic antibiotics, are effective but constrained by well-recognised limitations, including tooth staining, dysgeusia, mucosal irritation and, importantly, the selective pressure that drives antimicrobial resistance [7]. These concerns have stimulated interest in anti-virulence approaches, in which the aim is to attenuate pathogenicity, in particular biofilm formation, without directly killing the bacteria, thereby reducing the selective pressure for resistance [8]. Naturally occurring compounds, and flavonoids in particular, have attracted considerable attention in this context because of their broad bioactivity, dietary origin and favourable safety profile [8,9]. Flavonoids can interfere with biofilm development through several routes, including inhibition of adhesins and matrix-synthesising enzymes, disruption of membrane integrity, and modulation of quorum-sensing signalling [9,10].

Kaempferol (3,5,7-trihydroxy-2-(4-hydroxyphenyl) -4H-1-benzopyran-4-one) is a dietary flavonol distributed widely in fruits, edible plants, tea and medicinal herbs [11]. In addition to its antioxidant and anti-inflammatory properties, kaempferol exhibits antibacterial, antifungal, and antibiofilm activity against a range of microorganisms, and its mechanisms and sources have been reviewed in general terms [11]. A growing body of primary work indicates that kaempferol is also active against oral pathogens, including growth inhibition of *S. mutans* and *P. gingivalis* [11]. It has been reported to suppress *S. mutans* glucosyltransferase activity and acid production at sub-inhibitory concentrations [8,12], and to reduce biofilm formation and biomass of *S. mutans* with efficacy approaching that of chlorhexidine [13]. Kaempferol and its acylated derivatives have shown concentration-dependent inhibition of biofilm formation by the periodontal pathogens *P. gingivalis* and *F. nucleatum* [14]. Notably, the antibiofilm activity of kaempferol appears to depend on its chemical form, with the free aglycone generally more active than certain glycosylated derivatives [14].

Despite this accumulating evidence, the literature on kaempferol and oral biofilm remains fragmented. Studies differ considerably in the pathogens examined, the chemical form of kaempferol tested, the concentrations applied and the assays used to quantify biofilm, and no review has yet synthesised this evidence specifically for oral pathogens. Existing reviews address either the antimicrobial activity of kaempferol against microorganisms in general [11] or the broader class of flavonoids and polyphenols in oral health [10], leaving the specific question of kaempferol and oral biofilm unresolved. A further source of confusion that complicates the field is the frequent conflation of kaempferol with the botanically unrelated genus *Kaempferia* (for example, *K. galanga* and *K. parviflora*, and the chalcone panduratin A derived from *K. pandurata*), which share a similar name but not the compound itself; such studies should be clearly distinguished from genuine investigations of kaempferol.

Given the therapeutic interest in anti-virulence agents for oral biofilm control and the lack of a focused evidence synthesis, a systematic review is warranted. The objective of this review was to systematically identify, appraise and synthesise the available *in vitro* and *in vivo* evidence on the antibiofilm effects of kaempferol against oral pathogens and on the mechanisms that underlie these effects.

MATERIAL AND METHODS

Protocol and reporting

This systematic review was designed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement [17]. The review question was structured using the PICOS framework: the Population comprised oral pathogenic microorganisms; the Intervention/Exposure was kaempferol, applied either as a purified compound or as an identified bioactive constituent of a plant material; the Comparator was an untreated negative control and, where available, a positive antimicrobial control; the Outcomes were biofilm formation, biofilm biomass or viability, and biofilm-associated virulence; and the eligible Study designs were *in vitro* and *in vivo* experimental studies.

Eligibility criteria

Studies were included if they were original experimental articles that evaluated the effect of kaempferol on the biofilm formation, biofilm biomass or viability, or biofilm-associated virulence factors of one or more oral pathogens, and reported extractable quantitative or qualitative outcome data. Studies were excluded if they met any of the following criteria: (i) they investigated the plant genus *Kaempferia* (for example *Kaempferia galanga*, *Kaempferia parviflora*, or panduratin A isolated from *Kaempferia pandurata*) rather than the flavonol kaempferol, as these are botanically and chemically distinct from the compound of interest; (ii) they assessed microorganisms with no established role in oral disease; (iii) they did not report any biofilm-related outcome; (iv) they were reviews, conference abstracts without primary data, editorials, or in silico studies without experimental validation; or (v) the full text was not available in English.

Information sources and search strategy

A systematic search was conducted across four electronic databases, PubMed, ScienceDirect, Scopus, and Springer, from inception to [month year]. The search combined controlled vocabulary and free-text terms related to the exposure and the outcome using Boolean operators, as follows: ("kaempferol") AND ("biofilm" OR "antibiofilm" OR "quorum sensing" OR "virulence") AND ("oral" OR "dental" OR "*Streptococcus mutans*" OR "*Porphyromonas gingivalis*"

OR "*Aggregatibacter actinomycetemcomitans*" OR "*Fusobacterium nucleatum*" OR "periodontal" OR "caries"). The reference lists of all eligible articles and relevant reviews were manually screened to identify additional studies.

Study selection

All retrieved records were exported to a reference manager, and duplicates were removed. Two reviewers independently screened titles and abstracts against the eligibility criteria, followed by full-text assessment of potentially relevant articles. Disagreements were resolved by discussion until consensus was reached, or by consultation with a third reviewer. The study selection process is summarised in the PRISMA 2020 flow diagram (Figure 1).

Data extraction

Two reviewers independently extracted data from the included studies using a standardised extraction form. The following items were recorded: first author and year of publication, country, study design, target oral pathogen and strain, the form of kaempferol tested (purified compound, isolated fraction, or constituent incorporated into a material), the concentrations evaluated, the biofilm assay used, the comparator, the main antibiofilm outcomes, and the reported mechanism of action.

Risk of bias assessment

The methodological quality of the included *in vitro* studies was appraised independently by two reviewers using the QUIN tool for the assessment of risk of bias in *in vitro* dental studies [16]. Each criterion was scored and an overall percentage grade derived, with studies categorised as having a low (>70%), medium (50–70%) or high (<50%) risk of bias. Disagreements were resolved by discussion. The results of this appraisal are presented in the Results.

Data synthesis

Owing to the anticipated heterogeneity in the oral pathogens studied, the chemical form and concentration of kaempferol applied, and the biofilm assays employed, a quantitative meta-analysis was not considered appropriate. The findings were therefore synthesised qualitatively in a narrative format, organised by target pathogen and by reported mechanism of action.

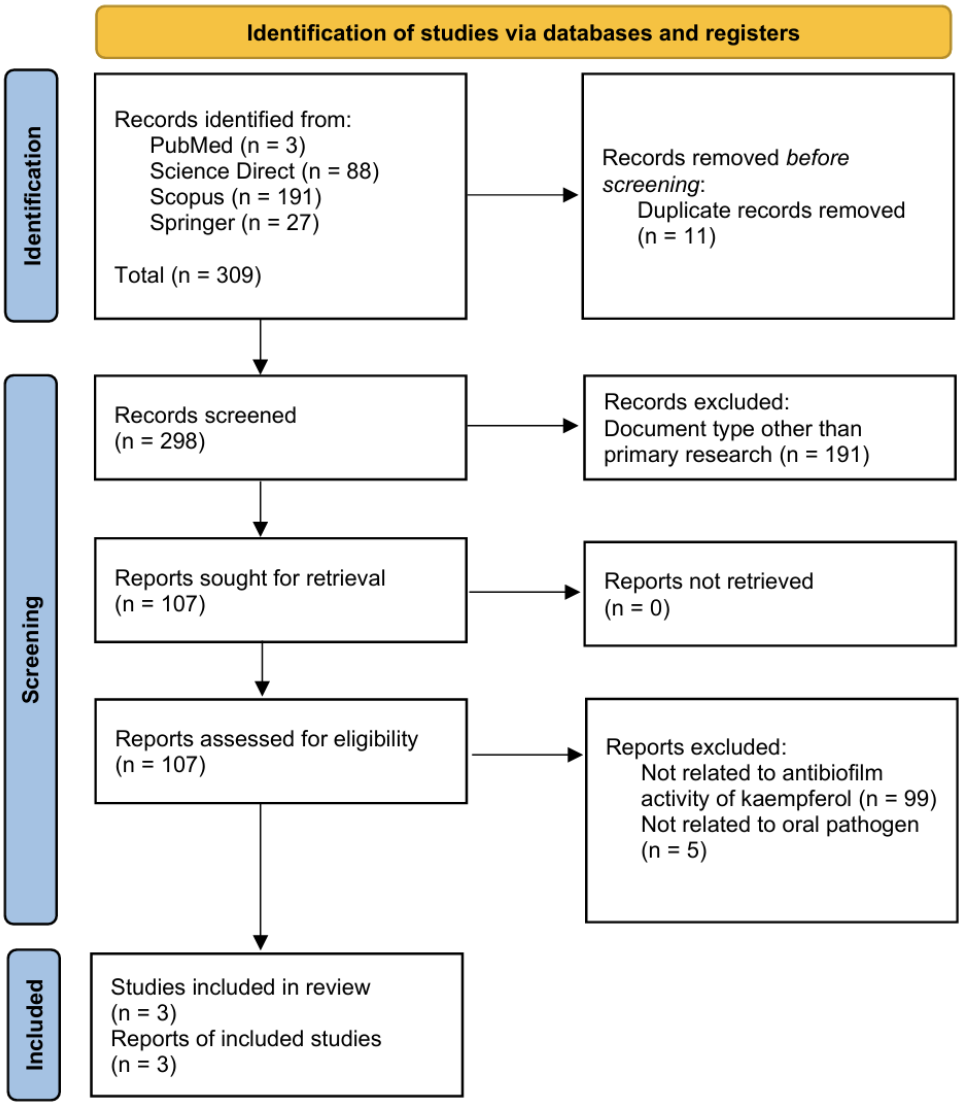


FIGURE 1: PRISMA 2020 flow diagram of study identification, screening, eligibility assessment, and inclusion.

RESULT

Study Selection

The database search identified 309 records (PubMed, n = 3; ScienceDirect, n = 88; Scopus, n = 191; Springer, n = 27), of which 298 remained after 11 duplicate records were removed. During title and abstract screening, 191 records were excluded as document types other than primary research, leaving 107 reports that were sought for retrieval and assessed for eligibility. Of these, 104 were excluded: 99 because they were not related to the antibiofilm activity of kaempferol and 5 because they were not related to an oral pathogen, so that 3 studies met all eligibility criteria and were included in the qualitative synthesis.

A recurrent reason for exclusion at the full-text stage was the misattribution of studies on the genus *Kaempferia* to kaempferol; such studies were excluded as pre-specified. The study selection process is shown in the PRISMA flow diagram (Figure 1).

Characteristics of the included studies

The included studies evaluated kaempferol against cariogenic and periodontal pathogens using *in vitro* biofilm models. They differed in the chemical form in which kaempferol was applied, ranging from a purified compound isolated from a plant extract to a flavonol incorporated into a dental restorative material, and in the assays used to quantify biofilm. The principal characteristics of the included studies are summarised in Table 1.

TABLE 1: Characteristics of the included studies.

Study (year)	Oral Pathogen(s)	Form of Kaempferol	Concentrations tested	Biofilm Assay	Comparator
Carvalho *et al.* (2026) [15]	Streptococcus mutans ATCC 25175	Incorporated into an etch-and-rinse adhesive system	1%, 2%, 4% (w/w)	MTT metabolic activity; medium turbidity	Adhesive without kaempferol
Zhou *et al.* (2022) [14]	Porphyromonas gingivalis ATCC 33277	Free aglycone (with quercetin and two acylated	0.03–0.24 mM	Crystal violet	Untreated control
Moktan *et al.* (2025) [13]	Streptococcus mutans MTCC 497	two acylated flavonol glycosides)	1× MIC (1.562 µg/µL)	Crystal violet; biofilm dry weight; SEM; live/dead	Clorhexidin digluconat

Risk of bias within studies

The methodological quality of the three included studies, appraised with the QUIN tool, is summarised in Table 2. All three studies were judged to carry a medium risk of bias. The recurrent limitations were the absence of operator and outcome-assessor details, the lack of blinding, and no reported randomisation of specimen or well allocation, which are common shortcomings in *in vitro* antibiofilm research.

Carvalho et al. achieved the highest score, largely because it was the only study to report a priori sample-size calculation [15]. Reporting of aims, comparison groups, methodology, outcome measurement, statistical analysis, and presentation of results was adequate in all three studies. No study was rated low or high risk; this uniform medium rating should temper the strength of the conclusions drawn from the synthesis.

TABLE 2: Risk-of-bias assessment of the included studies (QUIN tool).

QUIN criterion	Moktan 2025 [13]	Zhou 2022 [14]	Carvalho 2026 [15]
Clearly stated aims/objectives	2	2	2
Sample size calculation	0	0	2
Sampling technique	NA	NA	NA
Details of comparison group	2	2	2
Detailed methodology	2	2	2
Operator details	0	0	0
Randomisation	0	0	1
Method of outcome measurement	2	2	2
Outcome assessor details	0	0	0
Blinding	0	0	0
Statistical analysis	2	2	2
Presentation of results	2	2	2
Total score / applicable max	12 / 22	12 /2	15 / 22
Score (%)	54.5%	54.5%	68.2%
Overall risk of bias	Medium	Medium	Medium

Antibiofilm effects against cariogenic pathogens

Two of the included studies evaluated kaempferol against *Streptococcus mutans*, the principal cariogenic pathogen. Moktan et al. isolated kaempferol as the active fraction (F1) from the ethyl acetate extract of *Bergenia ciliata* flowers and reported that, at its minimum inhibitory concentration, kaempferol inhibited *S. mutans* biofilm formation by approximately 80%, a value comparable to that of the chlorhexidine positive control (approximately 83%), and reduced biofilm dry weight by approximately 92% [13]. Carvalho et al. incorporated kaempferol into an experimental adhesive system at 1%, 2%, and 4% and assessed the metabolic activity of the *S. mutans* biofilm formed on the adhesive surface by MTT reduction; all kaempferol-containing groups exhibited significantly lower biofilm metabolic activity than the kaempferol-free control, with the effect increasing at higher concentrations [15]. Taken together, these studies indicate that kaempferol reduces both the biomass and the metabolic activity of *S. mutans* biofilm, whether applied as an isolated compound or incorporated into a restorative material.

Antibiofilm effects against periodontal pathogens

One included study evaluated kaempferol against the periodontal pathogens *Porphyromonas gingivalis* and *Fusobacterium nucleatum*. Zhou et al. tested kaempferol as a free aglycone alongside quercetin and two acylated flavonol glycosides and reported that kaempferol inhibited biofilm formation by both species in a concentration-dependent manner over the range 0.03–0.24 mM [14]. However, among the compounds tested, kaempferol was the least potent: its minimum inhibitory concentration against *P. gingivalis* exceeded 0.48 mM, compared with 0.03 mM for quercetin, and the glycosylated derivatives and quercetin produced stronger biofilm inhibition than kaempferol at equivalent concentrations. This indicates that, although kaempferol is active against periodontal-pathogen biofilm, its intrinsic potency in this context may be lower than that of related flavonoids.

Reported mechanisms of action

The included studies described several, largely non-bactericidal, mechanisms underlying the antibiofilm activity of kaempferol. Moktan et al. provided the most detailed mechanistic account, demonstrating that kaempferol compromised *S. mutans* membrane integrity, as shown by scanning electron microscopy and propidium iodide uptake, and triggered the intracellular generation of reactive oxygen species with consequent lipid peroxidation and leakage of proteins, carbohydrates and nucleic acids [13]. In the study by Carvalho et al., the reduction in biofilm metabolic activity was attributed to the recognised capacity of kaempferol to inhibit *S. mutans* growth and cariogenic virulence factors, including glucosyltransferase activity and acid production [15]. Zhou et al. linked the antibiofilm activity of kaempferol and the related flavonoids to iron chelation, proposing that sequestration of iron, which is essential for the growth of anaerobic periodontal pathogens, contributes to the observed inhibition of biofilm formation [14].

Influence of the chemical form of kaempferol

The included evidence suggests that the antibiofilm activity of kaempferol is influenced by the chemical form in which it is presented. Kaempferol was active as a free aglycone [14], as a compound isolated from a plant matrix [13], and when incorporated into a dental material [15]. In the comparative study by Zhou et al., the free aglycone was less potent than quercetin and its own acylated glycoside derivatives against periodontal pathogens [14], indicating that structural modification and the surrounding matrix may modulate the delivery and activity of kaempferol at the biofilm interface.

DISCUSSION

This systematic review synthesised the available evidence on the antibiofilm effects of kaempferol against oral pathogens and the mechanisms that underlie them. The principal finding is that kaempferol consistently reduced biofilm formation, biomass, or metabolic activity of oral pathogens in a concentration-dependent manner, most reproducibly for *Streptococcus mutans*, and that this effect was mediated through several, predominantly non-bactericidal, mechanisms. These observations are consistent with the broader characterisation of kaempferol as a multi-target antimicrobial flavonol [11] and support the view that flavonoids are promising anti-virulence agents for oral biofilm control [8,9].

The mechanisms identified across the included studies converge on the core processes of biofilm development rather than on bacterial killing. Interference with glucosyltransferase activity and glucan synthesis would be expected to weaken the extracellular polysaccharide scaffold on which cariogenic biofilm depends, while suppression of acidogenicity reduces the cariogenic potential of the biofilm without necessarily reducing viable counts [4,8,12]. The membrane-disrupting and reactive-oxygen-species-inducing actions reported for *S. mutans* [13], together with the iron-chelating activity proposed for periodontal pathogens [14], indicate that kaempferol acts on multiple, partly species-specific targets. This mechanistic breadth is characteristic of flavonoids and may be advantageous, as multi-target agents are generally less prone to the emergence of resistance than single-target antibiotics [8].

An important and recurring observation is that the activity of kaempferol depends on its chemical form and delivery context. Kaempferol was active as a free aglycone, as a compound isolated from a plant matrix, and when incorporated into a dental material, yet in the only head-to-head comparison it was less potent than quercetin and its own acylated glycoside derivatives against periodontal pathogens [14]. This is consistent with reports that minor structural differences among flavonols substantially alter antibacterial and antibiofilm potency, and that glycosylation, acylation and the

surrounding formulation modulate solubility, membrane permeability and target binding [9,14]. For translational purposes, this suggests that the delivery vehicle, whether a mouthrinse, a gel or a restorative material, may be as important as the compound itself, as illustrated by the retained antibacterial effect of kaempferol once incorporated into an adhesive system [15].

From a clinical perspective, the appeal of kaempferol lies in its anti-virulence mode of action. By attenuating biofilm formation and virulence rather than eradicating the microbiota, such an approach could help control cariogenic and periodontal biofilm while exerting less selective pressure for resistance than conventional antimicrobials, and while better preserving the commensal oral flora [8]. The favourable dietary origin and safety profile of kaempferol further support its candidacy as an adjunctive agent. These considerations, however, remain hypotheses generated by a small and preliminary body of work rather than conclusions supported by clinical data.

This review has several limitations, which largely reflect the state of the primary literature. First, the number of eligible studies was small, and the body of evidence is immature, so the conclusions must be regarded as preliminary. Second, the included studies were markedly heterogeneous in the pathogens examined, the chemical form of kaempferol, the concentration units applied (percentage by weight, millimolar, and micrograms per microlitre), and the biofilm assays used, which precluded any quantitative meta-analysis and limited direct comparison between studies. Third, in several studies kaempferol was not tested in isolation but as a constituent of a plant extract or a material, making it difficult to attribute the observed effects to kaempferol alone. Fourth, all included studies were judged to carry a medium risk of bias, principally because of the absence of reported randomisation, blinding, and operator or assessor details. Fifth, the evidence was derived almost entirely from monospecies *in vitro* biofilm models, which do not reproduce the polymicrobial complexity of oral biofilm, and *in vivo* confirmation was lacking. Finally, the restriction to English-language publications and the reliance on the indexed databases searched may have introduced language and publication bias.

Several priorities for future research follow from these limitations. Standardised *in vitro* protocols, with harmonised concentration units and biofilm quantification methods, would allow more direct comparison and eventual quantitative synthesis. Studies using multispecies biofilm models, and ultimately *in vivo* and clinical investigations, are needed to establish relevance to the oral environment. Mechanistic work, including quorum-sensing and gene-expression analyses, would help confirm the molecular targets proposed here. Dose-response studies of purified kaempferol, head-to-head comparisons with quercetin and other flavonols, evaluation of optimised delivery systems, and assessment of biocompatibility and safety would collectively clarify whether kaempferol can be developed into a practical adjunct for oral biofilm control.

CONCLUSION

Within the limits of a small and heterogeneous body of evidence, this systematic review indicates that kaempferol inhibits biofilm formation by oral pathogens, most consistently *Streptococcus mutans*, in a concentration-dependent manner and through multiple, predominantly non-bactericidal mechanisms, including inhibition of glucosyltransferase activity and glucan synthesis, membrane disruption, induction of reactive oxygen species, and iron chelation. Its activity is modulated by chemical form and delivery context, and in direct comparison, it was less potent than quercetin. All included studies carried a medium risk of bias. Kaempferol therefore shows promise as an adjunctive anti-virulence agent for oral biofilm control, but standardised *in vitro* protocols, multispecies biofilm models and *in vivo* confirmation are required before clinical application can be considered.

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