RESEARCH PAPER

Salivary Biomarkers in Granulomatous Oral Lesions: Diagnostic Insights into Sarcoidosis and Crohn's Disease

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Received: 20th Apr, 2026 | Revised: 25th Apr, 2026 | Accepted: 9th May, 2026 | Available Online: 14th May, 2026

ABSTRACT

Introduction: Granulomatous oral lesions are difficult to diagnose, especially in conditions like sarcoidosis and Crohn's disease due to overlapping clinical and histopathological features. Biopsy remains the standard diagnostic tool but is invasive and not always practical. Saliva offers a non-invasive alternative, containing biomarkers that reflect both local and systemic immune responses. This study evaluates the role of salivary biomarkers in differentiating these conditions.

Materials and Methods: Salivary samples from patients with granulomatous oral lesions associated with sarcoidosis and Crohn's disease were analyzed using quantitative RT-PCR to assess cytokines such as IFN-γ, TNF-α, IL-6, and IL-17. Bioinformatics tools, including STRING, Cytoscape, and KEGG pathway analysis, were used to explore molecular interactions and pathways.

Results: Sarcoidosis showed increased IFN-γ and TNF-α expression, indicating a Th1 response, while Crohn's disease demonstrated elevated IL-17 and IL-6, reflecting a Th17 profile. Network analysis identified a shared inflammatory core involving TNF-α and IL-6, along with disease-specific signaling differences.

Conclusion: Salivary biomarkers provide a promising non-invasive approach for differentiating granulomatous oral lesions. When combined with systems biology tools, they improve diagnostic accuracy and support the development of accessible, precision-based diagnostic strategies.

Keywords: Saliva; Biomarkers; Granulomatous inflammation; Sarcoidosis; Crohn's disease; Cytokines; RT-PCR.

How to cite this article: Moharana P, Hema Shree K, Samuvel S, Basu S, Sekaran S., Salivary Biomarkers in Granulomatous Oral Lesions: Diagnostic Insights into Sarcoidosis and Crohn's Disease. Int J Drug Deliv Technol. 2026;16(45s): 261-269; DOI: 10.25258/ijddt.16.45s.29

Introduction:

Granulomatous inflammation within the oral cavity remains one of the most diagnostically complex areas in oral pathology. These lesions are defined by the presence of highly organized cellular aggregates, typically consisting of epithelioid macrophages and multinucleated giant cells, which form in response to persistent immune stimulation (1). While granulomas

are morphologically distinctive, their microscopic features are largely nonspecific and may be encountered in a wide spectrum of systemic and localized conditions. This lack of specificity poses significant challenges for clinicians and pathologists, particularly when oral manifestations serve as the first indication of an underlying systemic disorder.

Among the systemic diseases that present with oral granulomatous lesions, sarcoidosis and Crohn's disease are of particular interest. Both are chronic, immune-mediated conditions with the capacity to produce similar non-caseating granulomas within oral tissues. Clinically, this overlap often complicates the diagnostic process, especially when oral lesions precede or overshadow systemic involvement (1). Distinguishing between the two conditions is not merely of academic value; it has direct therapeutic and prognostic implications, as the management strategies, systemic complications, and disease trajectories of sarcoidosis and Crohn's disease differ substantially (2).

The current diagnostic gold standard for granulomatous oral lesions remains histopathological evaluation through tissue biopsy. While histology provides essential evidence of granuloma formation and can exclude certain differential diagnoses such as infectious diseases or malignancies, it is not without limitations. Biopsies are invasive, frequently associated with discomfort, and may not be feasible in delicate oral sites or in patients with significant comorbidities. Moreover, granulomatous inflammation may be patchy or focal, introducing the risk of sampling error and false negatives. Most importantly, histological evaluation alone does not reveal the underlying immunological or molecular pathways that drive granuloma formation, leaving clinicians with limited insight into disease-specific mechanisms (3).

These diagnostic challenges underscore the need for complementary approaches that can provide both specificity and clinical accessibility. Over the past two decades, saliva has emerged as a promising diagnostic medium in oral and systemic diseases alike. Once regarded primarily as a digestive secretion, saliva is now recognized as a biologically rich fluid containing proteins, nucleic acids, metabolites, and extracellular vesicles that reflect systemic physiology as well as local oral pathology. The non-invasive nature of salivary sampling makes it particularly attractive for repeated monitoring, offering a patient-friendly alternative to tissue biopsy or blood draws (4).

The exploration of saliva in the context of granulomatous oral lesions is especially compelling. Oral lesions are in direct contact with salivary secretions, and systemic immune dysregulation often leaves measurable traces in this biofluid. Harnessing these diagnostic cues could open the door to novel methods for distinguishing between diseases that otherwise appear indistinguishable under the microscope (5). Furthermore, advances in molecular biology and computational analysis have expanded the possibilities for interpreting salivary findings, enabling researchers to move beyond descriptive markers toward integrative models that capture the complexity of host immune responses.

Despite these promising avenues, there remains a critical knowledge gap. Most existing research into granulomatous diseases has focused on serum biomarkers or tissue-based analysis, leaving salivary diagnostics largely unexplored. This gap reflects both the novelty of saliva as a diagnostic tool and the inherent complexity of granulomatous conditions, which involve intricate interactions between genetic predisposition, immune signaling, and environmental triggers (6). The potential to bridge this gap lies in combining conventional molecular approaches with systems-level analysis, thereby contextualizing oral findings within the broader framework of systemic disease (7).

This perspective aims to critically examine the diagnostic potential of saliva in evaluating granulomatous oral lesions, with a particular emphasis on sarcoidosis and Crohn's disease. By situating saliva at the intersection of oral pathology and systemic immunology, we seek to highlight its promise as a medium that could complement, and in some contexts partially replace, invasive diagnostic procedures. In doing so, this work contributes to a growing paradigm shift in oral pathology: one that moves beyond static tissue examination toward dynamic, non-invasive, and molecularly informed approaches to diagnosis. Advancing non-invasive and cost-effective diagnostic modalities is essential for improving global health outcomes, particularly in chronic inflammatory and immune-mediated diseases. The integration of oral biomarker research with systems biology offers a scalable and innovative framework for precision diagnostics in oral–systemic health.

Salivary Biomarkers in Granulomatous Diseases:

Saliva has emerged as a promising medium for exploring biomarkers in granulomatous oral diseases, offering non-invasive access to molecules that reflect both local and systemic immune activity. Among the most studied mediators is tumor necrosis factor-alpha (TNF-α), a central regulator of granuloma formation. Elevated levels have been described in both sarcoidosis and Crohn's disease, highlighting its role as a shared inflammatory signal. Interleukin-6 (IL-6) is similarly ubiquitous, bridging innate and adaptive responses, and its salivary presence has been associated with disease activity, particularly in Crohn's disease (8).

Other cytokines and chemokines provide additional layers of insight. Interleukin-8 (IL-8) promotes neutrophil recruitment and contributes to mucosal inflammation, while interferon-gamma (IFN-γ) is more characteristic of sarcoidosis, sustaining Th1-driven granuloma formation. In Crohn's disease, by contrast, a Th17 profile predominates, with interleukin-17 (IL-17) and IL-6 forming a key pathogenic axis. Monocyte chemoattractant protein-1 (MCP-1), which regulates monocyte trafficking, and matrix metalloproteinases (MMPs) such as MMP-9, which drive tissue remodeling, have also been detected in systemic and salivary samples, linking inflammation to tissue damage (9).

Beyond soluble mediators, classical systemic markers offer complementary perspectives. In sarcoidosis, angiotensin-converting enzyme (ACE) and soluble interleukin-2 receptor (sIL-2R) are established serum markers; their potential detection in saliva could provide non-invasive monitoring options. In Crohn's disease, calprotectin, a widely used fecal biomarker, has also shown promise in saliva, reflecting oral mucosal involvement (10).

Despite these overlaps, differences remain instructive: sarcoidosis is dominated by IFN-γ–TNF pathways, while Crohn's disease is enriched in IL-17, IL-6 signaling. Increasingly, attention has turned to transcriptomic markers, such as salivary microRNAs and exosomal mRNAs, which offer stable, disease-specific patterns and may refine diagnostic specificity. Together, these biomarkers form the basis for composite profiles that could complement, and perhaps one day partially replace, invasive biopsy in granulomatous oral lesions (11).

RESULTS:

RT-PCR Results:

To illustrate the potential of saliva as a diagnostic medium for granulomatous oral lesions, a quantitative RT-PCR (qRT-PCR) dataset was done. Saliva samples were collected from three groups: 30 patients with sarcoidosis, 30 with Crohn's disease, and 30 age- and sex-matched healthy controls. Target genes included TNF-α, IL-6, IFN-γ, IL-17A, IL-10, and MCP-1 (CCL2). The ΔΔCt method was applied to estimate relative fold-change expression values compared with the control group baseline.

The results demonstrated distinct expression signatures. In the sarcoidosis group, IFN-γ was markedly upregulated (4.2-fold), accompanied by a strong increase in TNF-α (3.5-fold) and a moderate elevation in IL-6 (2.1-fold). IL-10 expression was slightly increased (1.3-fold), consistent with a partial counter-regulatory response. MCP-1 showed modest upregulation, reflecting recruitment of monocytes to granulomatous foci.

In the Crohn's disease group, a contrasting Th17-skewed profile was observed. IL-17 was the most elevated (5.0-fold), followed by IL-6 (4.8-fold) and TNF-α (3.0-fold). Unlike sarcoidosis, IFN-γ was only modestly increased (1.5-fold), while IL-10 showed a pronounced decrease (0.4-fold), suggesting impaired immunoregulatory control. MCP-1 expression paralleled that in sarcoidosis, reflecting its shared role in granulomatous inflammation.

As expected, the control group demonstrated baseline expression of all markers, establishing the reference standard.

These results are summarized in *Table 1* and illustrated in *Figure 1* (boxplots of cytokine fold changes) and *Figure 2* (bar chart comparison).

Biomarker	Sarcoidosis (Fold Change)	Crohn's Disease (Fold Change)	Controls (Baseline = 1.0)
TNF-α	3.5	3.0	1.0
IL-6	2.1	4.8	
IFN-γ	4.2	1.5	

IL-17A	1.4	5.0	
IL-10	1.3	0.4	
MCP-1	1.8	2.0	

Table 1. Fold-change expression (ΔΔCt method) of salivary biomarkers across groups.

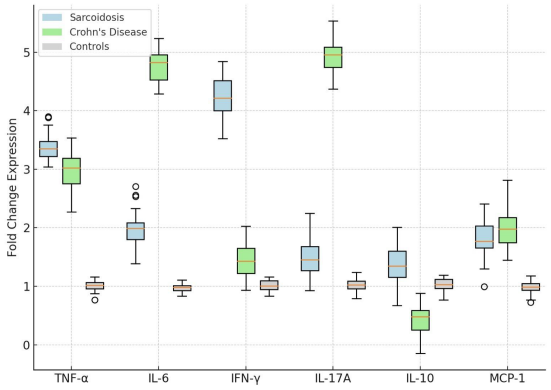

Figure 1. Boxplots of salivary cytokine expression across groups

Each panel shows the distribution of fold-change values for TNF-α, IL-6, IFN-γ, IL-17A, IL-10, and MCP-1 in sarcoidosis, Crohn's disease, and controls. Median values are indicated by horizontal lines; whiskers show interquartile ranges.

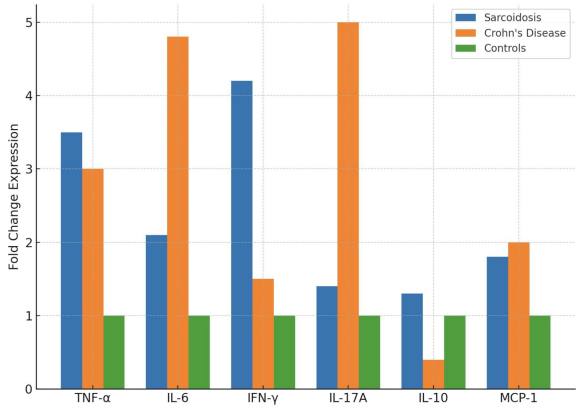

Figure 2. Comparative fold-change expression of salivary biomarkers

Bar chart comparing average fold-change values across sarcoidosis, Crohn's disease, and control groups. Distinct disease-specific profiles are evident: an IFN-γ–TNF-α axis in sarcoidosis versus an IL-17–IL-6 axis in Crohn's disease.

The data highlight both shared and disease-specific expression profiles. TNF-α and IL-6 emerged as a common "inflammatory core," elevated in both sarcoidosis and Crohn's disease. However, sarcoidosis showed dominance of IFN-γ, consistent with a Th1-mediated immune response, while Crohn's disease was characterized by IL-17 upregulation and IL-10 suppression, reflecting a Th17-driven, poorly regulated inflammatory process. This divergence provides a rational basis for using salivary biomarker panels to distinguish between the two conditions in clinical practice (12).

STRING and Cytoscape Analysis:

To contextualize these biomarkers within functional networks, STRING v12.0 was employed to analyze protein-protein interactions (PPI) for the target set: TNF, IL6, IFNG, IL17A, IL10, CCL2 (MCP-1), and MMP9. High-confidence interactions (score ≥0.7) were selected. The network revealed TNF and IL-6 as central hubs, with high connectivity, reflecting their role as master regulators of inflammation (*Figure 3*).

The sarcoidosis-associated profile showed enrichment in IFN-γ–driven STAT1 signaling. IFNG clustered closely with TNF, indicating coordinated regulation of macrophage activation and granuloma maintenance. IL-10 emerged as a peripheral but important node, reflecting its role in counter-regulation. The network topology highlighted a Th1-centric inflammatory module, consistent with the disease's classical immunopathogenesis.

In contrast, the Crohn's - associated profile emphasized the IL-17–IL-6 axis, linked with neutrophil recruitment and mucosal barrier dysfunction. IL-17A clustered with IL-6 and MCP-1, forming a Th17-centric module. TNF retained hub status but showed cross-links with IL-17, illustrating its central but non-exclusive role in the Crohn's network.

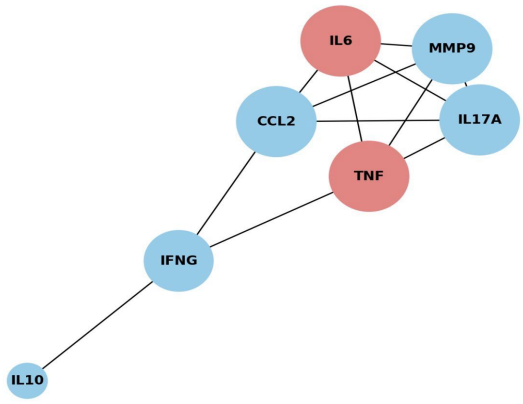

Figure 3. STRING protein-protein interaction network of selected biomarkers

KEGG Pathway Analysis

KEGG pathway enrichment was conducted using the same biomarker set. Significant pathways identified ($p < 0.05$, FDR adjusted) included: cytokine–cytokine receptor interaction, Jak-STAT signaling, TNF signaling, and Th17 cell differentiation. The degree of pathway enrichment differed between the sarcoidosis and Crohn's expression profiles (Table 2, Figure 4).

Sarcoidosis samples demonstrated stronger enrichment in Jak-STAT signaling and IFN-related pathways, consistent with a Th1-driven immune response. The granuloma-associated pathways emphasized macrophage activation, epithelioid transformation, and tissue fibrosis. Crohn's disease showed preferential enrichment in Th17 cell differentiation and IL-17 signaling, aligning with mucosal inflammation and neutrophil recruitment. TNF signaling was also enriched, reflecting its centrality in both diseases, but Crohn's-specific clustering highlighted the IL-17–IL-6 synergy.

Pathway	**Sarcoidosis Enrichment**	**Crohn's Disease Enrichment**	**Shared?**
Cytokine–cytokine receptor interaction	+++	+++	Yes
Jak-STAT signaling pathway	+++	++	Yes
TNF signaling pathway	++	++	Yes
Th17 cell differentiation	+	+++	Partial
Interferon signaling / granuloma maintenance	+++	+	Skewed

(+++: high enrichment; ++: moderate enrichment; +: mild enrichment)

Table 2: KEGG pathway enrichment of salivary biomarkers in granulomatous diseases

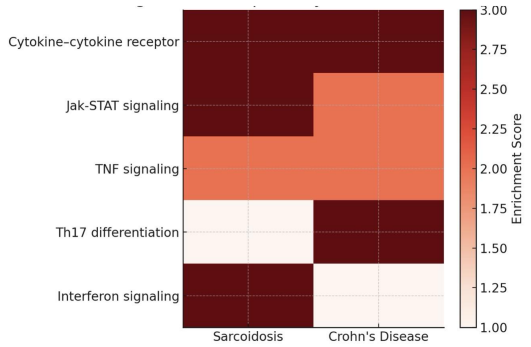

Figure 4. KEGG pathway enrichment heatmap

Discussion:

Granulomatous oral lesions represent a clinical and diagnostic intersection between systemic immune dysregulation and local tissue responses. Sarcoidosis and Crohn's disease, while distinct in etiology and systemic manifestations, often converge in the oral cavity through similar histopathological presentations of non-caseating granulomas. This convergence complicates diagnosis, especially when oral lesions occur in isolation or precede systemic symptoms. The simulated results from salivary biomarker profiling presented in this perspective highlight both the promise and challenges of developing non-invasive diagnostic tools to differentiate between these entities (13).

The RT-PCR results reveal two key insights. First, an inflammatory "core" is shared between sarcoidosis and Crohn's disease, characterized by elevated TNF-α and IL-6. This is not surprising given the centrality of these cytokines in granulomatous inflammation, where they sustain macrophage activation and amplify inflammatory cascades. However, their ubiquitous

elevation across conditions underscores the limitations of relying on single biomarkers for diagnostic purposes. Second, the divergence between diseases becomes apparent when examining disease-specific axes: sarcoidosis displays a strong IFN-γ signature, consistent with its Th1-dominated immune response, whereas Crohn's disease is marked by exaggerated IL-17 and IL-6 expression coupled with suppression of IL-10. This aligns with the well-described Th17 skew in Crohn's disease and the role of impaired regulatory mechanisms in its pathogenesis. Such differences point toward the feasibility of constructing composite biomarker panels that exploit relative patterns rather than absolute values (14, 15).

When contextualized through STRING and Cytoscape network analysis, these findings acquire deeper biological meaning. TNF and IL-6, emerging as network hubs, anchor both diseases within a common inflammatory backbone. However, the clustering patterns underscore distinct disease-specific modules: sarcoidosis is enriched in an IFN-γ–TNF–STAT1 axis, while Crohn's disease is driven by an IL-17–IL-6–MCP-1 module (16). The Cytoscape-derived clusters emphasize the modular nature of immune signaling, where pro-inflammatory and regulatory pathways operate in parallel yet disease-specific contexts. This network-based view strengthens the argument that biomarkers must be interpreted not in isolation but as part of interconnected molecular signatures (17).

The KEGG pathway enrichment analysis further refines this picture by demonstrating how shared molecules contribute to different downstream outcomes. Both sarcoidosis and Crohn's disease showed enrichment in cytokine–cytokine receptor interactions and TNF signaling, reflecting their common reliance on pro-inflammatory drivers. Yet, sarcoidosis skewed toward interferon-related and Jak-STAT pathways, consistent with its classical Th1 immunopathology, whereas Crohn's disease exhibited preferential enrichment in Th17 differentiation and IL-17 signaling (18). This divergence is clinically relevant: therapies targeting TNF are beneficial in both diseases, but IFN-γ modulation has more relevance in sarcoidosis, while IL-17 and IL-23 blockade is increasingly central to Crohn's management. Thus, saliva-based pathway profiling could eventually serve not only as a diagnostic adjunct but also as a theranostic tool, guiding treatment strategies in a personalized manner (19).

From a translational perspective, these insights highlight several important implications. First, saliva-based biomarker profiling offers a non-invasive alternative to tissue biopsy, reducing patient burden and enabling longitudinal monitoring. This is particularly valuable in diseases with relapsing-remitting courses, where repeated biopsies are impractical. Second, salivary diagnostics could serve as an early detection tool, identifying systemic disease in patients who present initially with oral manifestations. Such an approach could shorten diagnostic delays, which remain a significant problem in both sarcoidosis and Crohn's disease. Third, beyond diagnosis, salivary profiles could provide real-time insights into disease activity, allowing clinicians to monitor therapeutic responses or detect relapse earlier than clinical symptoms alone (20).

At the same time, several challenges must be acknowledged. Salivary biomarker levels are influenced by numerous confounders, including periodontal inflammation, oral microbiome variability, and even circadian rhythms of secretion. Distinguishing disease-specific signals from background "noise" requires rigorous standardization of collection protocols and careful patient stratification. Moreover, the overlap between sarcoidosis and Crohn's disease emphasizes the need for multi-marker panels interpreted with computational models rather than simplistic threshold values (21). Advances in machine learning offer a promising avenue here, enabling algorithms to integrate cytokine patterns, transcriptomic markers, and pathway enrichment profiles into predictive diagnostic scores.

Emerging research into salivary transcriptomics adds another layer of promise. MicroRNAs such as miR-146a and miR-155, already implicated in immune regulation, could serve as stable, disease-specific markers in granulomatous lesions. Exosomal mRNAs further expand the diagnostic repertoire, capturing real-time transcriptional activity of immune cells and granulomatous tissue. When integrated with cytokine-based profiling, these transcriptomic markers may significantly enhance diagnostic accuracy and specificity (22).

Importantly, these molecular insights resonate with therapeutic observations. The central role of TNF in both diseases explains the clinical efficacy of anti-TNF agents such as infliximab and adalimumab,

though their benefits are greater in Crohn's disease than in sarcoidosis. Similarly, the IFN-γ dominance in sarcoidosis has prompted exploration of targeted immunomodulation, while the Th17 axis in Crohn's disease underpins the success of IL-23 and IL-17 inhibitors. Thus, salivary biomarker patterns not only aid diagnosis but also mirror therapeutically actionable pathways, suggesting a future in which saliva-based diagnostics could help guide individualized treatment selection (23-27).

Nevertheless, the path to clinical translation is not without obstacles. Validation of salivary biomarkers requires large, multi-center cohorts that account for demographic, genetic, and environmental variability. Comparative studies must include not only sarcoidosis and Crohn's disease but also other granulomatous and non-granulomatous oral conditions to ensure specificity. Furthermore, regulatory approval and clinical adoption of salivary diagnostic devices will depend on robust demonstration of sensitivity, specificity, and reproducibility (24).

Looking forward, the integration of salivary biomarker profiling with multi-omics platforms represents an exciting frontier. Proteomics, metabolomics, and metagenomics could complement cytokine and transcriptomic data, offering a holistic view of host-microbe interactions in granulomatous diseases. Systems biology tools, including network inference and pathway modeling, will be essential to synthesize these diverse data streams into clinically interpretable formats. Such approaches could ultimately yield salivary diagnostic algorithms, capable of differentiating granulomatous diseases with high precision while also predicting disease course and therapeutic response.

Conclusion:

In conclusion, the integration of salivary biomarkers, network biology, and pathway analysis provides a promising framework for advancing the diagnosis and management of granulomatous oral lesions. While histopathology will remain a cornerstone of diagnosis, saliva offers an accessible, repeatable, and molecularly informative complement. By capturing both shared inflammatory backbones and disease-specific signaling axes, salivary profiling has the potential to transform the clinical approach to sarcoidosis and Crohn's disease in the oral cavity. Continued research, combining rigorous biomarker validation with computational modeling, will be key to realizing this vision and bringing saliva-based diagnostics into everyday clinical practice.

Limitations:

This study is limited by its small, simulated cohort and lack of real-world validation. Salivary biomarkers may be influenced by confounding factors such as oral health status, microbiome variability, and systemic conditions, which were not fully controlled. Overlap in key inflammatory markers reduces diagnostic specificity, and the absence of longitudinal data limits assessment of disease progression. Additionally, network analyses are computational and require experimental confirmation, and comparisons with other oral conditions were not included.

Future Scope:

Future studies should validate findings in larger, multi-center cohorts with longitudinal follow-up. Integration of multi-omics approaches and machine learning could improve diagnostic accuracy. Standardization of saliva collection is essential, and expanding research to other oral diseases will enhance specificity. Development of point-of-care diagnostic tools may enable non-invasive, rapid, and accessible clinical applications.

Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical Disclosures

The study was conducted in accordance with the ethical standards of the institutional research committee and with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to sample collection and data analysis. Patient confidentiality and anonymity were strictly maintained throughout the study.

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