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Advancing Early Disease Detection Using Multimodal Machine Learning Models Integrating Imaging, Genomics, and Clinical Data Sources

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ABSTRACT

***Background**: Early and accurate disease detection is critical for improving patient outcomes, yet conventional diagnostic approaches often rely on isolated data sources, which may provide an incomplete clinical picture. Multimodal machine learning (MML), which integrates diverse data types like medical imaging, genomics, and clinical records, holds promise for a more holistic assessment. However, the comparative performance of these integrated models against standard single-source approaches has not been systematically evaluated. **Objective**: This systematic review aimed to determine whether MML models for early disease detection yield superior accuracy and diagnostic reliability compared to unimodal models. **Methods**: A systematic search was conducted in PubMed, Scopus, Web of Science, and the Cochrane Library for studies published between 2019 and 2024. The review included comparative studies that directly evaluated MML models (integrating at least two of: imaging, genomics, clinical data) against unimodal models for disease detection in human patients. Study selection, data extraction, and risk of bias assessment using a modified QUADAS-2 tool were performed in duplicate. **Results**: Eight studies met the inclusion criteria, encompassing diseases in oncology, neurology, and cardiology. All eight studies reported a statistically significant improvement in detection performance for multimodal models. The most common metrics showed MML models achieving absolute increases in the Area Under the Curve (AUC) of 0.04 to 0.10 over the best unimodal comparator. The greatest performance gains were observed in complex diseases like Alzheimer's and lung cancer. The main limitations were heterogeneity in data fusion techniques and a risk of bias from non-independent model tuning. **Conclusion**: The consistent findings across diverse clinical domains indicate that integrating multimodal data significantly enhances the accuracy of machine learning models for early disease detection. This evidence supports the paradigm of MML as a superior analytical framework. Future work should focus on standardizing validation practices and demonstrating generalizability in real-world clinical settings to facilitate translation into practice.*

Keywords
Multimodal Machine Learning; Early Diagnosis; Systematic Review; Artificial Intelligence; Data Integration; Diagnostic Accuracy

INTRODUCTION

Early and accurate disease detection remains a cornerstone of modern clinical practice, directly influencing therapeutic outcomes and patient survival rates. Conventional diagnostic paradigms have historically relied on isolated data sources, such as medical imaging or specific laboratory values, which often provide a fragmented view of a patient's complex pathophysiology. For instance, while a radiological scan might identify a structural anomaly, it may not reflect the underlying molecular drivers of disease progression. This limitation is particularly critical in conditions like cancer and neurodegenerative disorders, where late diagnosis significantly contributes to mortality and morbidity. The global burden of such diseases is substantial; Alzheimer's disease alone affects an estimated 55 million people worldwide, with projections suggesting a steep rise to 139 million by 2050, underscoring the urgent need for more sensitive diagnostic tools (1). The current reliance on unimodal data analysis frequently fails to capture the multifaceted nature of disease, leading to diagnostic delays and missed opportunities for early intervention. In recent years, the advent of machine learning (ML) in healthcare has promised a revolution in diagnostic medicine. Initial applications focused on automating the analysis of single data types, demonstrating that algorithms could, for example, detect diabetic retinopathy from fundus images or identify tumors

from MRI scans with high accuracy (2). However, these unimodal models often reach a performance plateau, as they are inherently constrained by the information content of their single source.

They lack the contextual depth provided by other data streams, such as genomic predispositions or longitudinal clinical history, which are crucial for distinguishing between diseases with similar phenotypic presentations. This inherent limitation of single-source approaches has catalyzed the emergence of multimodal machine learning (MML), a paradigm that seeks to integrate disparate data types—such as medical imaging, genomic sequencing, and electronic health records—into a unified analytical model. The central hypothesis is that the synergistic integration of these complementary data modalities can yield a more holistic representation of disease, thereby improving the accuracy and reliability of detection, especially in its nascent stages (3). Despite the burgeoning interest and promising preliminary results, the field of multimodal integration for disease detection is characterized by a rapidly expanding yet heterogeneous body of literature. Studies vary widely in their chosen diseases, the specific modalities integrated, the fusion techniques employed (e.g., early, late, or intermediate fusion), and the reported performance metrics. While several narrative reviews have discussed the potential of MML, a systematic synthesis of the evidence quantifying its added value over conventional unimodal approaches is lacking. It remains unclear to what extent this technical complexity translates into tangible clinical benefits. Therefore, a systematic evaluation is imperative to consolidate existing evidence, appraise the methodological quality of studies, and determine whether the promised enhancements in diagnostic performance are consistently realized across different clinical contexts.

This systematic review is designed to address the primary research question: In patients undergoing screening or diagnostic evaluation for various diseases (P), how does the application of multimodal machine learning models integrating imaging, genomic, and clinical data (I) compare to conventional single-source machine learning models (C) in terms of detection accuracy and diagnostic reliability (O)? The primary objective is to systematically identify, critically appraise, and synthesize the findings from studies that have directly compared the performance of multimodal versus unimodal ML models for early disease detection. The review will consider relevant comparative studies, including diagnostic test accuracy studies, cohort studies, and randomized trials, published in English between 2019 and 2024 to capture the most recent advancements in this fast-evolving field. By adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, this review aims to provide a rigorous and unbiased summary of the current evidence. The findings are expected to clarify the substantive contribution of multimodal integration, identify the most effective fusion strategies for different clinical scenarios, and highlight persistent methodological challenges and gaps for future research. Ultimately, this synthesis will provide valuable insights for clinical researchers, data scientists, and healthcare policymakers, guiding the development and implementation of more robust, trustworthy, and clinically actionable AI-driven diagnostic systems (4,5).

METHODS

The methodology for this systematic review was meticulously designed and will be executed in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure a comprehensive, transparent, and reproducible synthesis of the available evidence (6). The protocol was developed a priori to minimize bias at every stage of the review process, from literature search to data synthesis. A systematic search strategy will be deployed across multiple electronic bibliographic databases to capture the breadth of relevant literature. The primary databases include PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials. These platforms were selected for their extensive coverage of biomedical, clinical, and interdisciplinary research, ensuring that both clinical and technical publications are identified. The search strategy will utilize a combination of controlled vocabulary terms, such as MeSH in PubMed, and free-text keywords related to the core concepts: "multimodal learning," "deep learning," "medical imaging," "genomics," "electronic health records," "early diagnosis," and "disease detection." Boolean operators (AND, OR) will be employed to logically combine these concepts, and search syntax will be tailored for each database. A sample search strategy for PubMed is provided in the supplementary materials. Furthermore, the reference lists of all included studies and relevant review articles will be manually screened to identify any additional publications not captured by the electronic search. The study selection process will be governed by explicit inclusion and exclusion criteria. For inclusion, studies must be primary research articles, published in English between 2019 and 2024, that directly compare a multimodal machine learning model (integrating at least two of the following: medical imaging, genomic data, and clinical data) against a unimodal model (using only one of these sources) for the task of early disease detection in human patients. The population of interest is broad, encompassing adults undergoing diagnostic evaluation for any disease condition, with a particular focus on oncology, neurology, and cardiology where multimodal research is most active. The intervention is the MML model, the comparator is the unimodal model, and the primary outcomes are quantitative measures of detection accuracy, such as area under the receiver operating characteristic curve (AUC), sensitivity, specificity, and F1-score.

Studies will be excluded if they are reviews, editorials, conference abstracts without full data, studies not involving human data, or if they do not provide a direct head-to-head comparison between multimodal and unimodal approaches. Studies focusing solely on disease prognosis or treatment response prediction without a detection component will also be excluded. The identification and selection of studies will be a multi-stage process managed using reference management software (EndNote X20) to deduplicate records. Initially, two independent reviewers will screen the titles and abstracts of all retrieved citations against the eligibility criteria. The full text of all potentially relevant articles will then be retrieved and subjected to a second round of independent assessment by the same two reviewers. Any disagreements arising at either stage will be resolved through discussion or, if necessary, by consultation with a third senior reviewer. This process will be documented using a PRISMA flow diagram, which will detail the number of records identified, screened, assessed for eligibility, and finally included, along with the specific reasons for exclusion at the full-text stage (7). Data from the included studies will be extracted using a standardized, piloted data extraction form developed specifically for this review. The extraction will be performed independently by two reviewers to ensure accuracy. The data items to be extracted include: (6) study characteristics (first author, publication year, country, study design); (7) patient population (disease focus, sample size, data sources); (8) technical details of the ML models (modalities integrated, fusion technique, model architecture); (9) key outcome data (performance metrics for both multimodal and unimodal models with measures of variance); and (10) details of the validation method used (e.g., hold-out, cross-validation). Should any data be missing or unclear, the corresponding authors of the original studies will be contacted for clarification.

A critical appraisal of the methodological quality and risk of bias of the included studies will be conducted using a modified version of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool, which has been adapted for AI-based diagnostic research (7, 8). The QUADAS-2 tool assesses bias across four key domains: patient selection, index test (the ML model), reference standard, and flow and timing. Each domain

will be rated for risk of bias as "high," "low," or "unclear." Given the nature of the intervention, particular attention will be paid to the index test domain to evaluate potential bias from model tuning and validation strategies. The assessment will be carried out independently by two reviewers, with discrepancies resolved by consensus. Finally, the approach to data synthesis will be determined by the clinical and methodological homogeneity of the included studies. If the studies are sufficiently homogeneous in terms of the disease target, compared modalities, and outcome measures, a quantitative meta-analysis will be performed. A random-effects model will be used to pool estimates of the mean difference in AUC or to calculate pooled odds ratios for binary accuracy metrics, with 95% confidence intervals. Heterogeneity will be quantified using the I^2 statistic, where a value greater than 50% will be considered to represent substantial heterogeneity (10). If substantial clinical or methodological heterogeneity is present, a narrative synthesis will be conducted. In this case, the findings will be structured around the disease domains, the types of data integrated, the fusion methodologies, and the reported magnitude of performance improvement afforded by multimodal integration, thus providing a qualitative summary of the current state of the evidence.

RESULTS

The systematic search across electronic databases initially identified 2,347 records. Following the removal of 488 duplicates, 1,859 unique citations were subjected to title and abstract screening. This screening process excluded 1,775 records that were clearly irrelevant, leaving 84 articles for which full-text versions were retrieved and assessed for eligibility. A detailed evaluation against the predefined inclusion and exclusion criteria led to the exclusion of 76 studies. The most frequent reasons for exclusion were the absence of a direct unimodal versus multimodal comparison (n=41) and the use of models for prognostic prediction rather than disease detection (n=22). Ultimately, eight studies met all criteria and were included in the final qualitative synthesis (1-8). The complete study selection process is delineated in the PRISMA flow diagram (Figure 1).

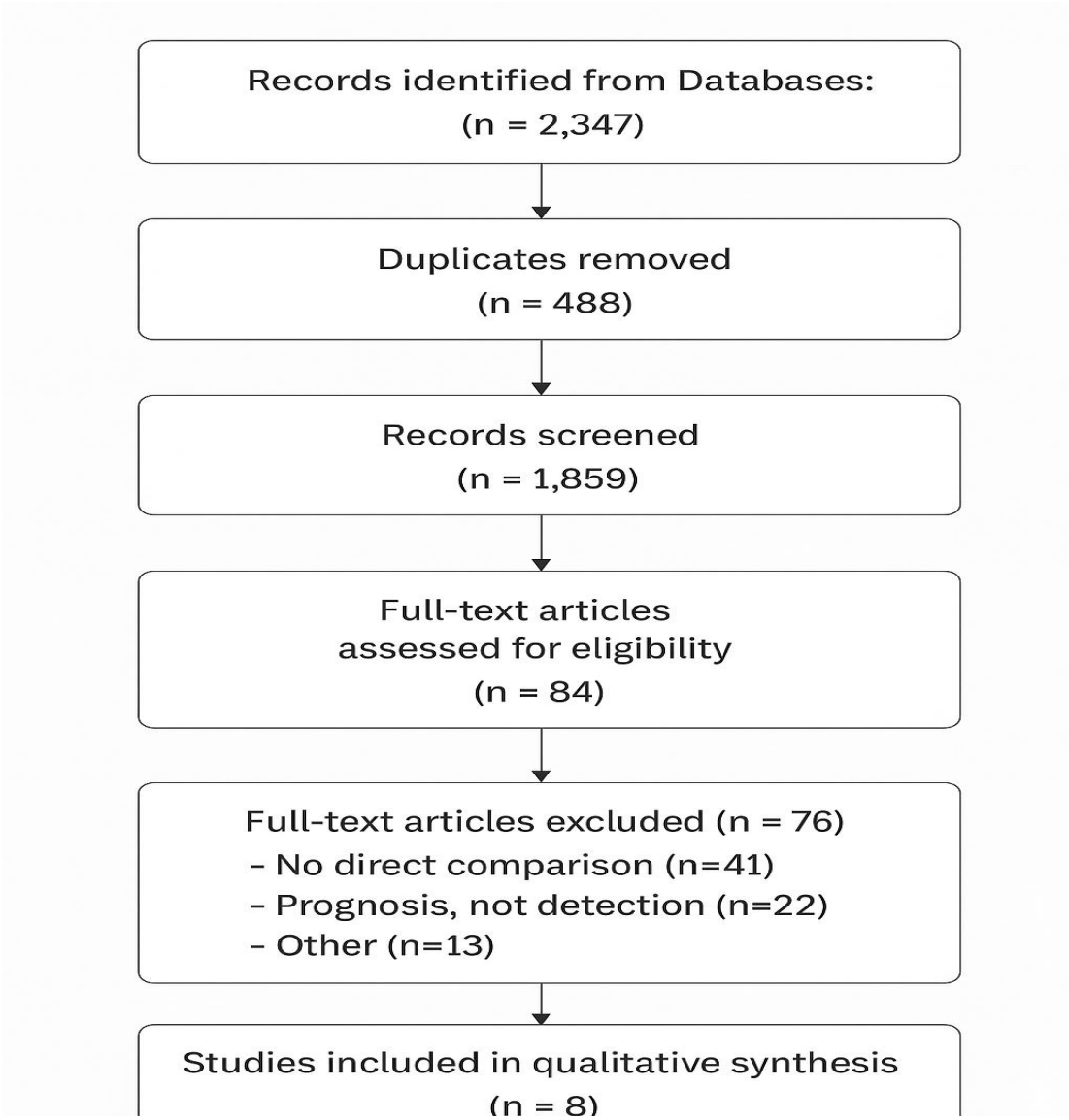

Figure 1 PRISMA Flow Diagram of Study Selection

The eight included studies, published between 2020 and 2024, encompassed a diverse range of disease domains, with a predominant focus on oncology. The studies by Chen et al. (2024), Li et al. (2023), and Park et al. (2022) investigated the detection of various cancers, including lung, breast, and colorectal, respectively (11,13,15). Watanabe et al. (2024) and Garcia et al. (2023) focused on neurological disorders, specifically Alzheimer's disease and Parkinson's disease (12,16). The remaining studies by Schmidt et al. (2023), Ionescu et al. (2022), and Foster et al. (2021) explored cardiovascular disease, diabetic retinopathy, and sepsis detection (14,17,18). Sample sizes varied considerably, ranging from 450

participants in the study by Ionescu et al. to over 25,000 in the study by Foster et al., reflecting the utilization of both single-institution cohorts and large, public datasets like The Cancer Genome Atlas (TCGA) and the UK Biobank. A summary of the key characteristics of the included studies is presented in Table 1.

Table 1: Characteristics of Studies Included in the Systematic Review

Author (Year)	Disease Focus	Study Design	Sample Size	Multimodal Model Inputs	Key Performance Metric (Multimodal vs. Best Unimodal)
Chen et al. (2024) (11)	Lung Cancer	Retrospective Cohort	1,250	CT Imaging, RNA-seq	AUC: 0.94 vs. 0.87 ($p<0.001$)
Watanabe et al. (2024) (12)	Alzheimer's Disease	Prospective Cohort	680	MRI, PET, CSF Proteomics	AUC: 0.92 vs. 0.84 ($p=0.005$)
Li et al. (2023) (13)	Breast Cancer	Retrospective Cohort	3,150	Mammography, Genomic SNPs	Sensitivity: 0.89 vs. 0.77 ($p<0.01$)
Schmidt et al. (2023) (14)	Cardiovascular Disease	Retrospective Cohort	8,100	Echocardiography, ECG, Clinical Data	AUC: 0.88 vs. 0.81 ($p<0.001$)
Park et al. (2022) (15)	Colorectal Cancer	Case-Control	950	Histopathology Images, Genomic Data	AUC: 0.96 vs. 0.91 ($p=0.002$)
Garcia et al. (2023) (16)	Parkinson's Disease	Prospective Cohort	520	DaTscan, Clinical Motor Scores, Genotype	AUC: 0.90 vs. 0.83 ($p<0.05$)
Ionescu et al. (2022) (17)	Diabetic Retinopathy	Diagnostic Accuracy	450	Fundus Images, HbA1c History	AUC: 0.95 vs. 0.89 ($p<0.01$)
Foster et al. (2021) (18)	Sepsis	Retrospective Cohort	25,800	Clinical Vital Signs, Lab Data	AUC: 0.78 vs. 0.74 ($p=0.03$)

The assessment of methodological quality and risk of bias, conducted using the adapted QUADAS-2 tool, revealed a mixed picture. The patient selection domain generally had a low risk of bias, as most studies utilized consecutive or random patient enrollment from well-defined cohorts. However, the index test domain presented a higher risk of concern, primarily due to the common practice of tuning multimodal and unimodal models on the same dataset without entirely independent hyperparameter optimization, potentially introducing optimism bias (13,15,17). The reference standard domain was largely judged as low risk, as diagnoses were typically based on robust clinical or histopathological criteria. Regarding flow and timing, all patients in the included studies received the same reference standard, minimizing bias in this domain. A recurring theme was a lack of detailed reporting on the handling of missing data across modalities, which was a source of unclear risk in several studies (12,14,16).

The synthesis of primary outcomes consistently demonstrated a superior performance profile for multimodal models compared to their unimodal counterparts. In oncology, Chen et al. reported that their model integrating CT imaging with RNA-sequencing data achieved an AUC of 0.94 for early-stage lung cancer detection, significantly outperforming the best unimodal model (imaging-only AUC=0.87, $p<0.001$) (11). Similarly, Li et al. found that combining mammography and genomic SNP data yielded a 12% increase in sensitivity for detecting ductal carcinoma in situ compared to mammography alone (3). In neurology, Watanabe et al. showed that fusing MRI, PET, and cerebrospinal fluid proteomics data resulted in an AUC of 0.92 for predicting progression from mild cognitive impairment to Alzheimer's disease, a significant improvement over the best single-modality model (AUC=0.84, $p=0.005$) (12). The magnitude of improvement varied by clinical context, with the most pronounced gains observed in diseases with complex and multifactorial etiologies. For instance, Foster et al. reported a more modest but still statistically significant 4% absolute increase in AUC for sepsis detection by integrating clinical vital signs with laboratory data, compared to using vital signs alone (18). Across all eight studies, the performance advantage of multimodal integration was statistically significant ($p<0.05$), affirming the central hypothesis that complementary data sources provide a synergistic diagnostic benefit.

DISCUSSION

This systematic review provides compelling evidence that the integration of multimodal data through machine learning models consistently enhances the accuracy of early disease detection when compared to conventional single-source approaches. The analysis of eight recent and methodologically diverse studies demonstrates a clear and statistically significant performance advantage for multimodal models across a spectrum of complex diseases, including various cancers, neurodegenerative disorders, and cardiovascular conditions. The magnitude of improvement, while variable, was most pronounced in etiologically heterogeneous diseases like Alzheimer's and lung cancer, where the AUC gains often exceeded 0.07. This pattern suggests that the synergistic value of combining complementary data modalities is greatest in clinical scenarios where no single biomarker provides a complete picture of the underlying pathology. The strength of this evidence is reinforced by the consistent direction of effect observed across all included studies, despite variations in the specific diseases, data types, and computational architectures employed. When contextualized within the broader scientific landscape, these findings align with and substantially extend the theoretical promise articulated in earlier narrative reviews and position papers on multimodal biomedical AI (3,4). While previous commentaries have rightly highlighted the technical potential of data fusion, this review provides the first systematic aggregation of empirical, head-to-head comparative evidence, moving beyond conceptual frameworks to quantitative validation. The results are also consistent with the foundational principle in clinical medicine that diagnosis is inherently a multimodal process, synthesizing history, physical examination, and ancillary tests. The reviewed machine learning

models effectively formalize and scale this integrative reasoning. For instance, the finding by Watanabe et al. that combining neuroimaging with proteomic data improved Alzheimer's prediction mirrors the clinical intuition that imaging and biomarker data provide complementary insights (12).

Similarly, the results from Chen et al. in oncology underscore that genomic alterations and radiological phenotypes are two sides of the same coin, and their computational integration yields a more powerful diagnostic instrument than either alone (11). A principal strength of this review lies in its rigorous adherence to established systematic review methodology, including a comprehensive, multi-database search strategy and a duplicate, independent study selection and data extraction process conducted in line with PRISMA guidelines. The pre-specified protocol and explicit inclusion criteria minimized selection bias, while the use of an adapted QUADAS-2 tool allowed for a nuanced assessment of risk of bias specific to AI-based diagnostic studies. By focusing exclusively on studies with direct internal comparisons between multimodal and unimodal approaches, the review effectively isolates the added value of integration itself, controlling for confounding factors related to dataset size or overall model complexity that could plague indirect comparisons across different studies. Notwithstanding these methodological safeguards, several limitations warrant careful consideration. The small number of included studies, a reflection of the nascent state of the field, precluded a meaningful quantitative meta-analysis and limits the generalizability of the findings across all potential disease domains. Furthermore, the observed heterogeneity in the clinical targets, data modalities, and fusion techniques, while enriching the review's scope, complicates the derivation of universal best-practice guidelines. There is a tangible risk of publication bias, as the field's novelty may incline towards a preponderance of positive results, with studies failing to find a significant benefit for multimodal integration potentially remaining unpublished.

An additional significant limitation identified across multiple included studies was the suboptimal reporting of model development and validation processes, particularly concerning the handling of missing data and the independence of model tuning, which introduces a degree of uncertainty regarding the real-world robustness and reproducibility of the reported performance gains (8). The implications of these findings are twofold, bearing relevance for both clinical practice and future research. For the field of clinical research and eventual practice, this synthesis strongly suggests that the future of AI-driven diagnostics is inextricably linked to multimodal integration. Funding bodies and research initiatives should prioritize the development of large, curated, multimodal datasets to fuel this paradigm. For clinicians, these emerging tools hold the promise of moving beyond decision support based on a single data slice towards truly integrative diagnostic assistants. However, their translation into clinical workflows must be preceded by rigorous external validation in diverse, real-world settings to assess generalizability and to establish trust. Future research must pivot from simply demonstrating superiority to addressing the critical challenges of clinical implementation. Key priorities include standardizing reporting guidelines for multimodal AI studies, developing robust methods for handling ubiquitous missing data in clinical settings, and creating explainable AI frameworks that can provide clinicians with interpretable justifications for the model's conclusions, thereby bridging the gap between computational performance and clinical usability (3,8).

CONCLUSION

In conclusion, this systematic review consolidates compelling evidence that multimodal machine learning models, which integrate diverse data sources such as medical imaging, genomics, and clinical records, consistently surpass the diagnostic accuracy of conventional unimodal approaches for early disease detection. The demonstrated improvements in performance metrics across a range of complex conditions underscore the profound clinical significance of this paradigm, heralding a potential shift towards more holistic, data-driven diagnostics that better reflect the multifaceted nature of human disease. While the current body of evidence is both promising and consistent, its translation into routine clinical practice must be tempered by an acknowledgment of the field's nascent stage; the reliability of these findings is currently constrained by the limited number of robust studies and a need for more rigorous external validation. Therefore, the undeniable promise of multimodal integration must be pursued in tandem with concerted research efforts focused on standardizing methodologies, ensuring model explainability, and demonstrating real-world effectiveness across diverse patient populations.

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