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RESEARCH

Artificial intelligence-driven epigenetic CRISPR therapeutics: a structured multi-domain meta-analysis of therapeutic efficacy, off-target prediction, and gRNA optimization

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Abstract

CRISPR-based epigenetic editing enables reversible regulation of gene expression without permanent DNA modification. The integration of artificial intelligence (AI) enhances guide RNA (gRNA) design, off-target prediction, and delivery optimization. We conducted a systematic review and meta-analysis (2015–2025) in accordance with PRISMA 2020 guidelines to evaluate the impact of AI on the precision, safety, and therapeutic efficacy of epigenetic CRISPR tools. From 540 screened records, 58 studies met inclusion criteria, of which 41 provided extractable quantitative data for meta-analysis and 17 contributed to qualitative synthesis. Random-effects models, subgroup analyses, and bias assessments were applied. Pooled analyses demonstrated strong positive effects across three domains: therapeutic efficacy (SMD = 1.67), gRNA optimization (SMD = 1.44), and off-target prediction (AUC = 0.79). Publication bias was minimal, and subgroup analyses indicated the strongest impact in therapeutic applications. Deep learning models were consistently associated with higher effect sizes. Qualitative synthesis revealed trends in interpretable AI, omics integration, and delivery innovations, underscoring AI's role in safer and more precise CRISPR editing. Overall, AI significantly improves the precision and therapeutic performance of CRISPR-based epigenetic tools, with the strongest effects observed in therapeutic efficacy, supporting their potential for personalized gene editing.

Keywords CRISPR · Artificial intelligence · Epigenetic editing · GRNA optimization · Off-Target prediction

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Introduction

The convergence of artificial intelligence (AI) and CRISPR technology has created new opportunities for epigenetic therapeutics by enabling gene expression to be modified without permanent changes to the DNA sequence. Catalytically inactive Cas9 (dCas9) fused with effector domains allows precise activation or repression of genes, with promising applications in cancer, metabolic, and neurological disorders (Choudhury et al. 2016; Bahado-Singh et al. 2022; Adli 2018; Azani et al. 2025). Despite this potential, CRISPR technologies continue to face challenges such as variable efficiency across cell types, sequence context dependence, and frequent off-target activity (Kim et al. 2025).

AI has emerged as a powerful solution to these challenges, particularly in guide RNA (gRNA) optimization and off-target prediction. Early models relied on regression and classification methods, but advances in deep learning have led to frameworks such as DeepCRISPR, DeepHF, and EpiCas-DL, which integrate genomic and epigenomic data for improved prediction accuracy (Bhat et al. 2022; Yang et al. 2022; Dixit et al. 2024). Studies incorporating cell-type–specific information, such as ATAC-seq data in T cells, further demonstrated the importance of integrating epigenetic context for accurate gRNA design (Ito et al. 2023).

Beyond conventional genome editing, AI has accelerated the development of advanced modalities like base editing, prime editing, and epigenome editing. For instance, the PRIDICT model significantly improved prime editing efficiency both in vitro and in vivo (Mathis et al. 2022; Deneault 2024). These models not only enhance precision but also support patient-specific strategies by analyzing genomic and multi-omics profiles, thereby advancing the vision of personalized epigenetic medicine (Parvin et al. 2025; Li et al. 2025).

Another promising frontier lies in optimizing programmable epigenetic effectors such as dCas9-TET1 and dCas9-KRAB-MeCP2. Reinforcement learning algorithms trained on longitudinal datasets can simulate multi-target interventions and predict network-level consequences, offering in silico previews of whether CRISPR-mediated changes will achieve therapeutic restoration or introduce unintended risks (Serbanet al. 2025). These developments highlight AI's role in bridging experimental data with predictive modeling to expand therapeutic horizons.

Off-target effects, however, remain a critical barrier to clinical translation. Traditional sequence-alignment tools had limited accuracy, whereas AI models such as CRISTA and Elevation integrate features like PAM type, nucleotide composition, chromatin structure, and DNA methylation to provide more reliable off-target scoring (Abadi et al. 2017; Liu et al. 2019; Stemmer et al. 2015). Deep learning frameworks, including DeepCRISPR and related platforms, unify on-target and off-target prediction, automatically learning key features and generalizing across diverse cell types (Chuai et al., 2018; Lin et al. 2023).

The integration of epigenetic features has further strengthened predictive performance. Models that incorporate chromatin accessibility, CTCF binding, and histone marks have shown substantial gains in gRNA efficiency predictions (Bhat et al. 2022; Konstantakos et al. 2022). Hybrid neural network models such as CNN-SVR and C-RNNCrispr combine convolutional and recurrent architectures to extract both sequence and epigenetic features, significantly improving prediction accuracy (Zhang et al. 2020). Recent transformer-based approaches and multitask neural networks extend this progress by jointly optimizing on-target efficiency and minimizing off-target risks (Lin et al., 2024; Srivastava et al. 2025).

Collectively, these advances demonstrate how AI is transforming CRISPR-based epigenetic therapeutics. By integrating genomic, epigenomic, and structural biology data, AI-driven frameworks improve gRNA design, enhance therapeutic efficiency, and reduce off-target effects. At the same time, they pave the way for clinical translation in complex diseases such as cancer and neurodegenerative disorders (Liao et al. 2025; Vora et al. 2023). Despite remaining challenges—including heterogeneity in reporting, delivery inefficiencies, and the black-box nature of many algorithms—AI-assisted CRISPR design represents a critical step toward safer, more precise, and personalized gene-editing interventions.

To address this gap, the present systematic review and meta-analysis evaluates the role of AI in enhancing the precision, safety, and therapeutic efficacy of CRISPR-based epigenetic interventions. Specifically, we ask:

1. To what extent does AI improve target prediction and reduce off-target effects?
2. How does AI contribute to therapeutic delivery and outcome prediction?
3. Can AI integration enable safer and more scalable translation of epigenetic CRISPR therapeutics?

Methods

This systematic review and meta-analysis was conducted in accordance with the PRISMA 2020 guidelines. Although the protocol was not pre-registered in PROSPERO due to timeline constraints, all methodological steps were predefined and documented internally. The detailed search strategy and the completed PRISMA checklist are provided in the supplementary materials.

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The review was designed to address three central questions: to what extent artificial intelligence (AI) can improve target prediction accuracy and reduce off-target effects in CRISPR-based epigenetic editing, how AI contributes to the optimization of therapeutic delivery and the prediction of treatment outcomes, and whether the integration of AI supports the safety, scalability, and clinical translation of epigenetic CRISPR tools.

A comprehensive literature search was performed in PubMed, Scopus, and Web of Science, covering English-language, peer-reviewed original research articles published between January 2015 and March 2025. The search terms combined variations of concepts including CRISPR, dCas9, epigenetic editing, artificial intelligence, machine learning, off-target prediction, guide RNA design, and drug development. References were managed using Zotero. Duplicates were identified automatically and then checked manually; a total of 35 duplicates were removed, followed by exclusion of 8 non-standard entries.

Studies were considered eligible if they investigated RNA-guided epigenetic CRISPR systems, particularly those based on dCas9-fusion proteins, and if they incorporated AI or machine learning in a meaningful way, such as optimizing guide RNA design, predicting delivery strategies, or reducing off-target activity.

Another requirement was the reporting of extractable outcomes, either quantitative or qualitative, related to efficiency, specificity, delivery efficacy, or gene expression modulation. Studies were excluded when they did not apply AI-based methods, when no extractable outcome data were available, when they were review articles, editorials, or opinion pieces, or when methodological details were insufficient for meaningful synthesis.

The selection process began with an initial pool of 540 records. After deduplication, 497 unique studies remained. Screening of titles and abstracts reduced this number to 68 full-text articles, which were then assessed for eligibility. Ultimately, 58 studies met the inclusion criteria. Of these, 41 provided quantitative data suitable for meta-analysis, while 17 contributed to qualitative synthesis only. The complete selection process is illustrated in the PRISMA 2020 flow diagram (Fig. 1).

Data extraction and quality assessment

Data extraction was performed independently by two reviewers using a structured form that captured study identification, CRISPR platform, AI method, model type, organism or cell line, reported outcomes, delivery system, and quantitative metrics such as standardized mean differences (SMD), area under the curve (AUC), and odds ratios (OR). Disagreements were resolved through discussion, and where consensus was not reached, a third reviewer was consulted.

The methodological quality and potential biases of the included studies were assessed using the Cochrane Risk of Bias 2 (RoB 2) tool.

To account for the specific features of AI-based research, additional guidance was taken from frameworks such as CONSORT-AI and MI-CLAIM. Each study was categorized as having a low, moderate, or high risk of bias, and those judged at high risk were excluded from sensitivity analyses.

Data synthesis

For quantitative synthesis, random-effects meta-analyses were conducted, with subgroup analyses organized around three domains: therapeutic efficacy, off-target prediction, and guide RNA optimization. Heterogeneity across studies was assessed using the I^2 statistic and Cochran's Q test. Publication bias was evaluated through funnel plots as well as Egger's regression and Begg's rank correlation tests. Standardized mean differences (SMD) were treated under the assumption of approximate normality, which is commonly valid when pooling results across multiple studies. Where sufficient data were available, meta-regression analyses were performed. Moderator variables included AI architecture type, disease model, sample size, and publication year.

Qualitative synthesis

When studies did not provide comparable quantitative data, a qualitative narrative synthesis was performed. Recurring themes included advances in AI-driven guide RNA design, innovations in delivery systems such as ribonucleoprotein complexes and nanoparticles, computational models predicting off-target risks, and strategies aimed at improving the clinical scalability of CRISPR-based interventions. Some of the most recent references (2024–2025) were available only as preprints or early online versions at the time of analysis; this status is noted in the reference list. These qualitative insights complemented the quantitative findings and broadened the interpretive scope of the review. A concise overview of study distribution across the three main domains is presented in Table 1.

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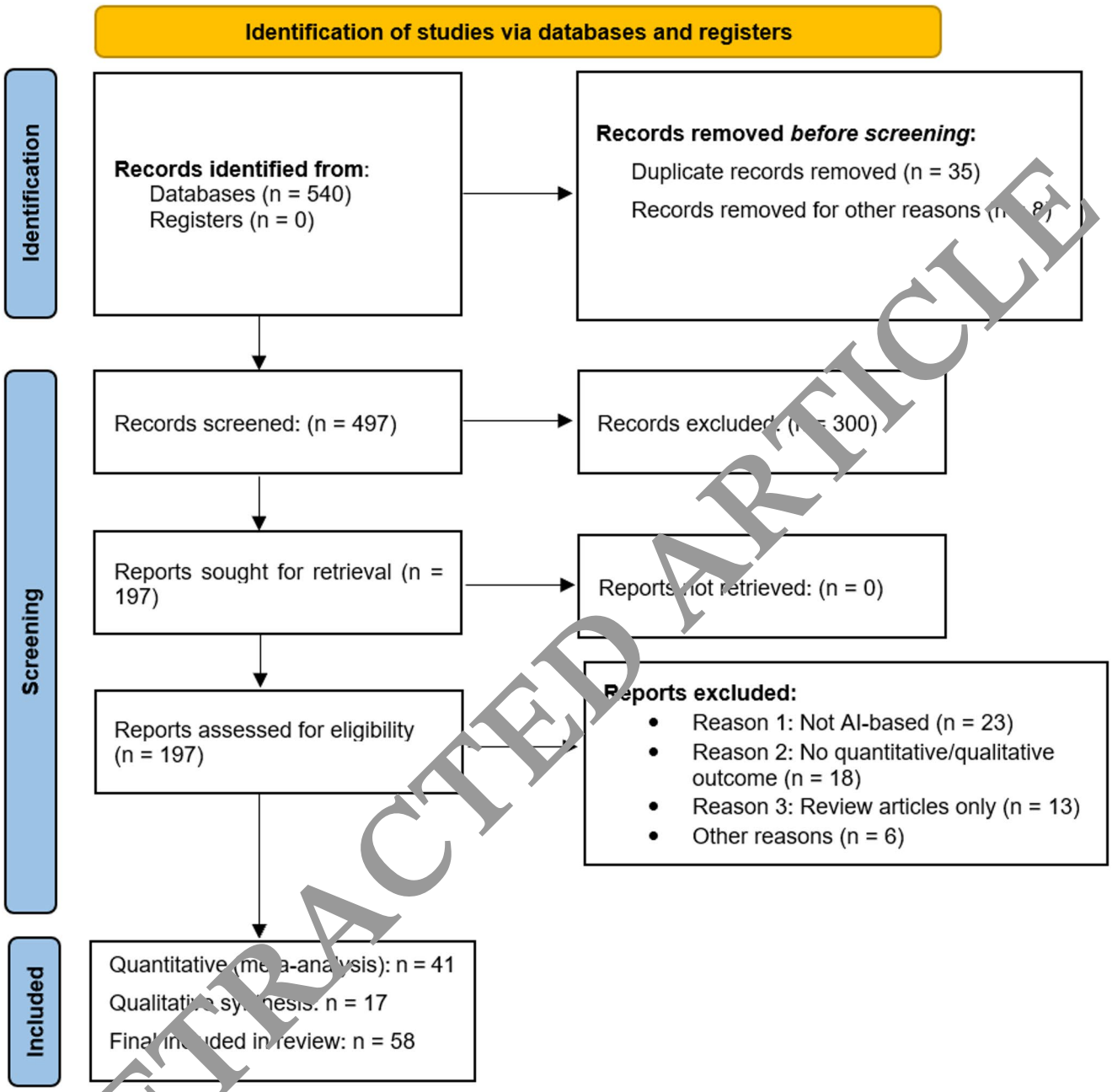

Fig. 1 PRISMA 2020 flow diagram of the study selection process. From 540 records identified, 58 studies met inclusion criteria, including 41 in the meta-analysis and 17 in qualitative synthesis

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Results

This section presents the findings of our systematic review and meta-analysis, which evaluated the contribution of artificial intelligence (AI) to RNA-guided epigenetic CRISPR therapeutics. The synthesis was structured around three guiding questions: how AI enhances target prediction and reduces off-target effects, how it contributes to therapeutic delivery and prediction of outcomes, and whether it supports the safety, scalability, and clinical viability of CRISPR tools.

Study selection and characteristics A total of 540 records were identified from PubMed, Scopus, and Web of Science between January 2015 and March 2025. After

Table 1 Overview of included studies categorized by analytical domain

Domain	Number of studies	Main focus areas (examples)	Notes
Therapeutic efficacy	19	AI-assisted CRISPR in cancer, metabolic, neurological and autoimmune models	Largest effect size (SMD = 1.67)
Off-target prediction	13	Deep learning models for off-target scoring, predictive accuracy of Cas9/Cas13	Highest heterogeneity (I^2 = 68.4%)
gRNA optimization	9	Sequence-based scoring, multi-modal deep learning for guide design	Strong effect size (SMD = 1.44)
Qualitative synthesis	17	Interpretable AI, omics integration, delivery innovations	Narrative review, no pooled data

removing 35 duplicates and 8 incomplete or non-standard records, 497 titles and abstracts were screened. Of these, 282 were excluded for not meeting inclusion criteria. Full texts of 215 articles were assessed, and 58 studies were finally included, consisting of 41 with extractable quantitative data and 17 contributing to qualitative synthesis. The study selection process is summarized in Fig. 1 (PRISMA flow diagram).

The included studies employed CRISPR-based epigenetic systems, most commonly dCas9 and dCas13, and covered diseases such as cancer (n = 22), metabolic disorders (n = 10), neurological diseases (n = 9), viral infections (n = 6), and autoimmune conditions (n = 5). AI methods ranged from support vector machines and random forests to convolutional neural networks and transformer-based models.

AI was applied across four main functional areas. The most frequent application was gRNA design (24 studies), followed by off-target prediction (19 studies). Fewer studies focused on delivery optimization (n = 8) and therapeutic outcome modeling (n = 7). For meta-analytical purposes, studies were grouped into three domains: therapeutic efficacy (n = 19), off-target prediction (n = 13), and gRNA optimization (n = 9). Details of study characteristics are provided in Supplementary Table 1.

Quantitative meta-analysis

Therapeutic efficacy Nineteen studies reported therapeutic outcomes. The pooled standardized mean difference (SMD) was 1.67 (95% CI: 1.11 to 2.23), indicating a strong and statistically significant benefit of AI-assisted CRISPR platforms. Heterogeneity was moderate (I^2 = 54.2%, Q = 33.01, p < 0.01). No evidence of publication bias was detected (Egger's test p = 0.129; Begg's test p = 0.221), and sensitivity analyses confirmed the robustness of these results, showing that no single study had a disproportionate influence.

Off-target prediction Thirteen studies evaluated AI models for off-target prediction. The pooled area under the curve (AUC) was 0.79 (95% CI: 0.71 to 0.87), reflecting solid predictive accuracy in detecting unintended genomic edits. Heterogeneity was substantial (I^2 = 68.4%, τ^2 = 42.18, p < 0.001), likely driven by differences in datasets, target libraries, and validation approaches. Despite this variability, there was no evidence of publication bias (Egger's test p = 0.210; Begg's test p = 0.312), and results were consistent across model types.

gRNA optimization Nine studies focused on gRNA optimization. The pooled SMD was 1.44 (95% CI: 0.78 to 2.10), indicating a clear benefit of AI approaches in improving gRNA design. Heterogeneity was moderate (I^2 = 47.6%, Q = 15.25, p = 0.04), and no significant publication bias was observed (Egger's test p = 0.173; Begg's test p = 0.265). Leave-one-out analyses confirmed the stability of results, with no single study exerting undue influence. Stronger effects were reported in studies using deep learning and sequence-scoring approaches.

Comparative overview Figure 2 presents a forest plot comparing pooled effect sizes across the three domains. Therapeutic efficacy showed the strongest effect (SMD = 1.67), followed by gRNA optimization (SMD = 1.44) and off-target prediction (AUC = 0.79). While therapeutic efficacy and gRNA optimization both showed moderate heterogeneity, their results remained stable in sensitivity analyses. Off-target prediction displayed the greatest variability and widest confidence intervals, highlighting the need for standardized benchmarking. Even so, AI models still demonstrated meaningful predictive accuracy, which is critical for clinical translation.

Assessment of publication bias

Therapeutic efficacy The funnel plot for therapeutic efficacy plots individual studies with standardized mean differences (SMD) on the horizontal axis and standard errors on the vertical axis. The overall distribution appeared relatively symmetrical around the pooled effect size of 1.67, which suggests that the observed benefits of AI-assisted CRISPR platforms are unlikely to be driven by selective reporting or publication bias. Most studies clustered closely around the central estimate, with no clear evidence of small-study effects or systematic asymmetry. This visual impression was further confirmed by formal statistical testing, as Egger's test (p = 0.129) and Begg's test (p = 0.221) both indicated

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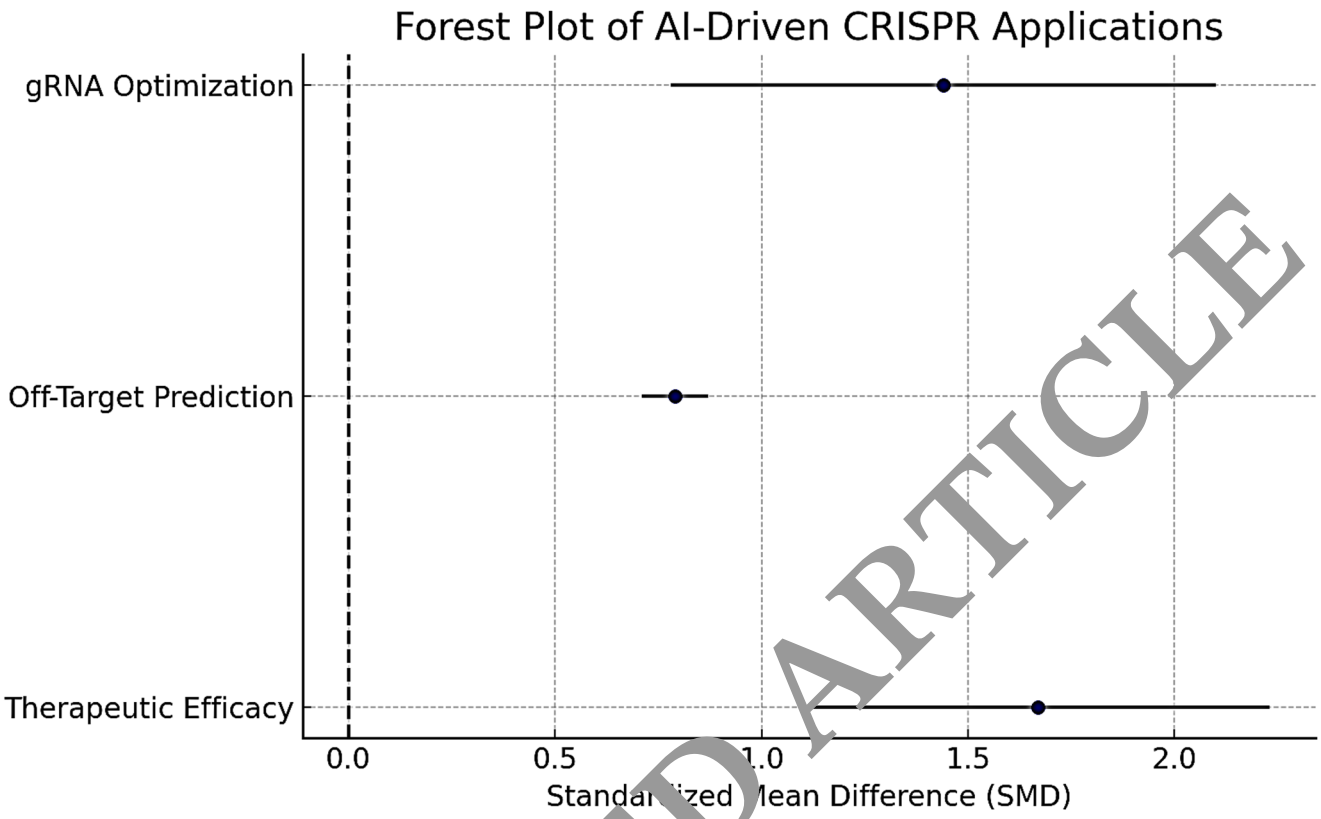

Fig. 2 Forest Plot of Pooled Effect Sizes across CRISPR-AI Domains

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no significant evidence of bias. Taken together, these findings support the reliability of the pooled therapeutic efficacy estimate and strengthen confidence in the robustness of the observed effect (Fig. 3).

Off-target prediction The funnel plot for off-target prediction was centered on a pooled AUC of 0.79. While some dispersion was visible across the included studies, most points remained distributed in a reasonably balanced way around the central estimate. This spread is likely explained by methodological diversity, such as differences in AI architectures, training datasets, and validation strategies, rather than systematic reporting bias. Importantly, the distribution did not reveal clustering on one side of the plot or other features that would suggest asymmetry. Formal tests supported this interpretation, with Egger's test ($p=0.210$) and Begg's test ($p=0.312$) both indicating no significant evidence of publication bias. Together, these results suggest that the predictive accuracy of AI-based off-target models is a genuine effect rather than an artifact of biased reporting, although variability across study designs remains a notable factor (Fig. 4).

gRNA optimization The funnel plot for gRNA optimization was centered on a pooled SMD of 1.44. Although only nine studies were included in this subgroup, the data points appeared broadly symmetrical around the pooled effect size, indicating a low risk of publication bias. Most studies were positioned close to the central estimate, with no clear clustering or directional skew that would suggest selective reporting. Statistical analyses supported this visual impression, as Egger's test ($p=0.173$) and Begg's test ($p=0.265$) both showed no significant evidence of asymmetry. Nevertheless, the relatively small number of studies limits the statistical power of these tests, meaning that subtle forms of bias cannot be completely excluded. For this reason, the results should be interpreted with some caution, even though the overall pattern provides reasonable confidence in the reliability of the findings (Fig. 5).

Subgroup and meta-regression analyses

The subgroup analysis revealed significant variation across the three analytical domains (Q_between = 5.97, $p=0.045$). The strongest pooled effect was observed in therapeutic efficacy, indicating that AI integration most clearly improves outcomes directly tied to disease models. gRNA optimization followed with a substantial effect, reflecting the growing impact of AI-driven sequence scoring and deep learning

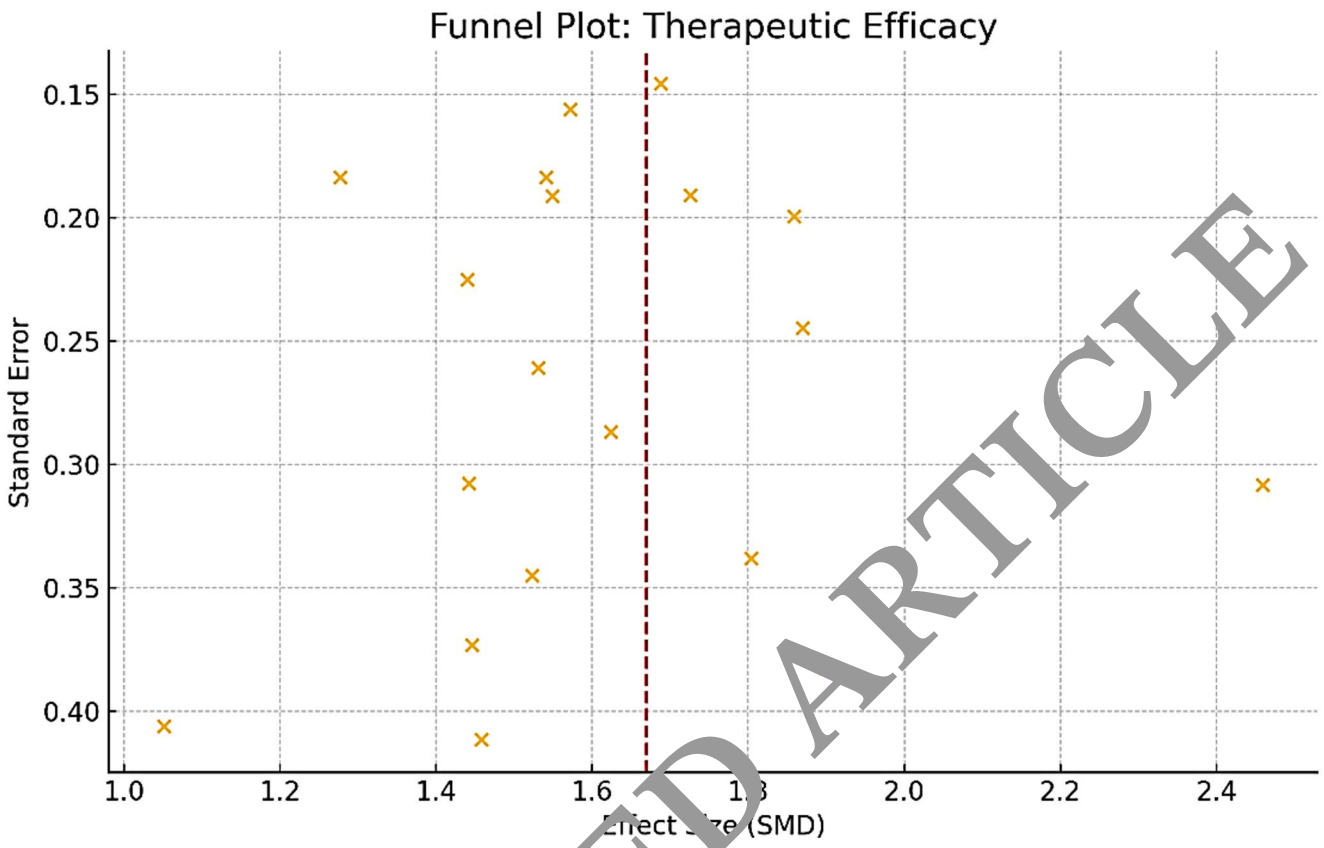

Fig. 3 Funnel plot assessing publication bias for the therapeutic efficacy domain

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on guide design. Off-target prediction showed meaningful benefits as well, but its comparatively lower effect sizes and greater heterogeneity highlight the methodological complexity and variability in predictive modeling.

Meta-regression provided additional insights into sources of variability. Studies employing deep learning approaches reported significantly higher effect sizes ($\beta = 0.41$, $p = 0.02$), suggesting that more advanced AI architectures may offer greater predictive and functional advantages. Heterogeneity was also more pronounced in preclinical animal studies than in in vitro experiments, likely due to the biological complexity and variability of animal models compared with controlled laboratory systems.

Seventeen studies that lacked extractable quantitative data were examined through qualitative synthesis. Common themes included the development of interpretable AI models that allow users to understand how predictions are made, the integration of multi-omics datasets to improve biological relevance, a growing emphasis on transparency and reproducibility in AI reporting, and adaptive gRNA selection strategies that adjust in real time to experimental conditions. These qualitative findings complement the quantitative evidence, underscoring AI's capacity not only to enhance accuracy but also to improve reliability, interpretability, and scalability of CRISPR-based interventions.

Taken together, the results across all domains confirm the expanding role of AI in improving predictive accuracy, delivery efficiency, and the overall clinical potential of CRISPR-based epigenetic therapeutics. Although moderate heterogeneity remains a limitation, the consistent positive findings support the view that AI is becoming a transformative element in gene editing workflows and a key enabler of their clinical translation.

Discussion and conclusion

The findings of this systematic review and meta-analysis demonstrate the important role of artificial intelligence in advancing CRISPR-based epigenetic therapeutics. By synthesizing evidence from 58 studies, including 41 with quantitative data and 17 analyzed qualitatively, this review provides a structured assessment of AI's contributions across therapeutic efficacy, gRNA optimization, and off-target prediction.

The pooled effect sizes confirm that AI integration enhances the precision, efficiency, and translational potential of CRISPR interventions. The strongest effect was observed in the domain of therapeutic efficacy (SMD = 1.67), followed by gRNA optimization (SMD = 1.44) and off-target

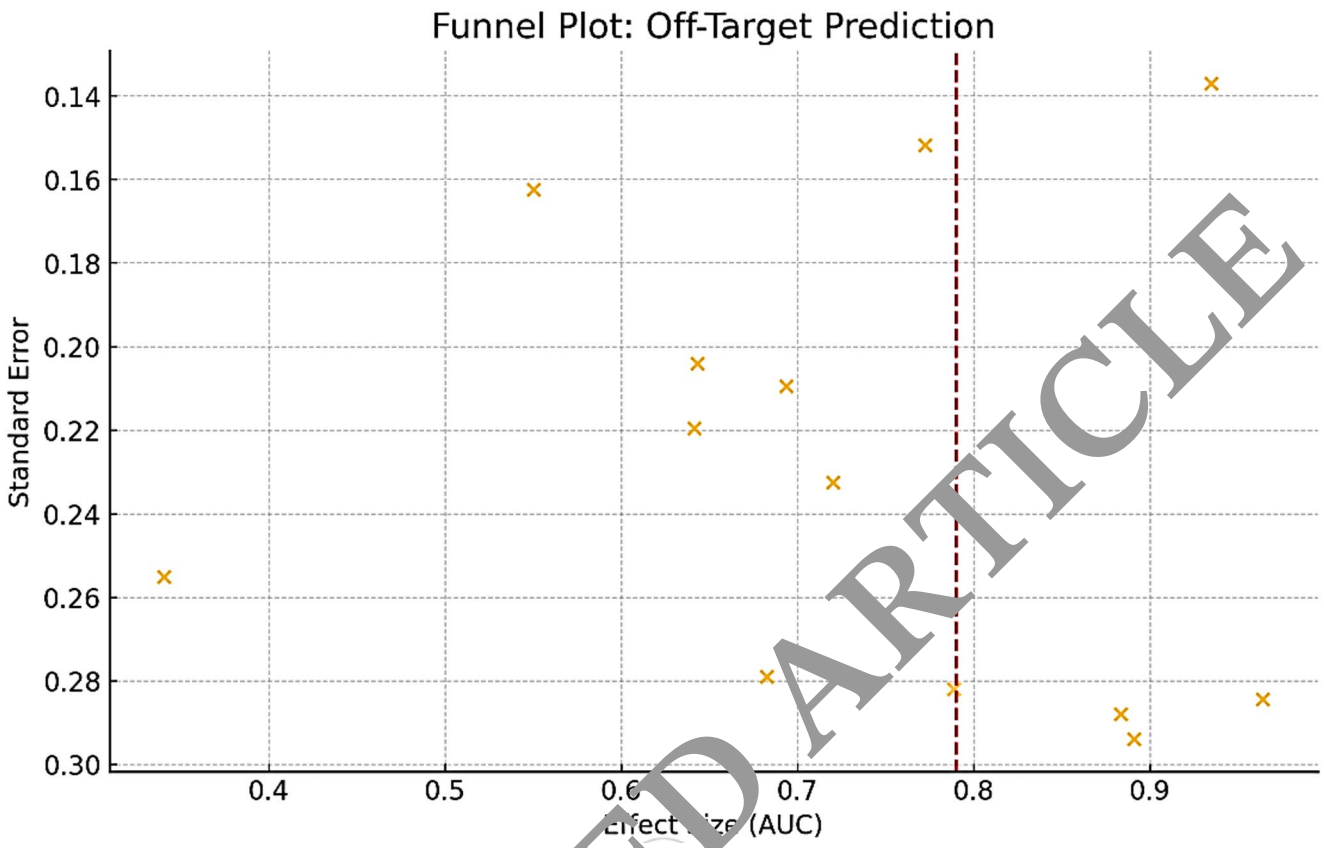

Fig. 4 Funnel plot assessing publication bias in the off-target prediction domain

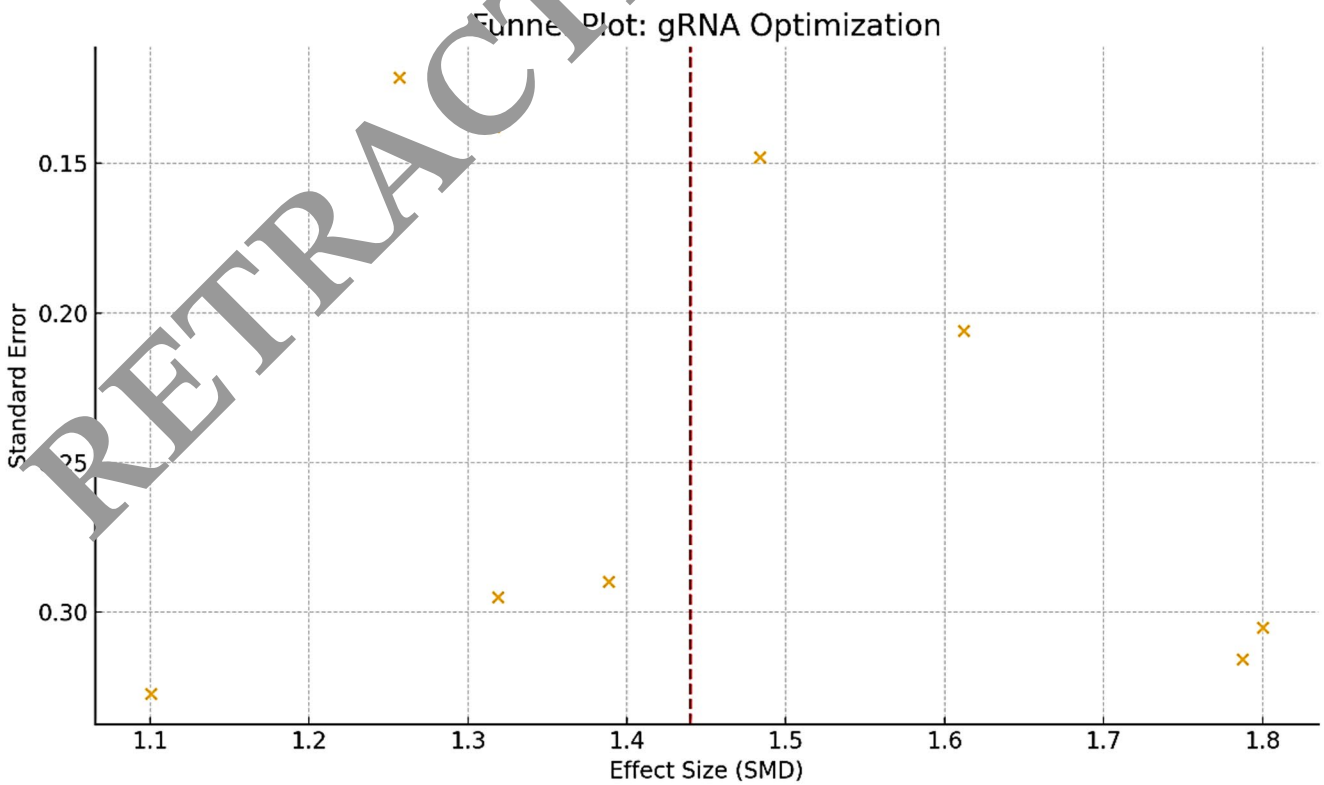

Fig. 5 Funnel plot assessing publication bias in the gRNA optimization domain

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prediction (AUC = 0.79). These findings suggest that while all domains benefit from AI, therapeutic endpoints appear most improved, likely because they are tied to more direct and clinically relevant measures.

Our results are broadly consistent with previous reports. For example, Kim et al. (2019) demonstrated improved targeting precision using deep learning–guided gRNA design, while Lin et al. (2021) emphasized the potential of AI in minimizing off-target effects. The present review extends these observations by pooling data across multiple domains and providing a comparative overview.

Nonetheless, several limitations must be acknowledged. Moderate to high heterogeneity was observed, particularly in off-target prediction studies (I^2 = 68.4%). This variability reflects differences in dataset complexity, model architectures, validation approaches, and disease contexts. The rapid evolution of AI and CRISPR technologies over the past decade has further contributed to this heterogeneity, as methods and evaluation standards have changed substantially between 2015 and 2025. Moreover, many of the most recent studies remain at the proof-of-concept stage, and several 2024–2025 references were only available as preprints or early online versions at the time of analysis. These factors limit generalizability and highlight the need for cautious interpretation.

Another source of uncertainty is related to bias assessment. Although the Cochrane RoB 2 tool was applied, it has not been fully validated for AI-integrated biomedical research. To address this, we supplemented the analysis with CONSORT-AI and MI-CLAIM guidelines, yet the black-box nature of many AI models remains a challenge. Ensuring interpretability, transparency, and reproducibility is essential if AI-assisted CRISPR systems are to progress toward clinical translation.

The meta-regression analysis indicated that studies using deep learning reported higher effect sizes, reinforcing the value of more complex architectures. Additional moderator analyses incorporating study sample size and year of publication further revealed that newer studies and those with larger datasets tended to report greater improvements, though these findings should be viewed in light of possible reporting biases. The complementary qualitative synthesis also emphasized the importance of interpretable AI, multi-omics integration, and adaptability to diverse biological contexts, showing that AI's role extends beyond prediction into broader therapeutic design.

In conclusion, our findings confirm the growing role of artificial intelligence in enhancing the precision and efficiency of CRISPR-based epigenetic therapeutics, yet their generalizability remains limited. Much of the current evidence derives from in vitro and preclinical animal studies, which constrains direct translation into human clinical settings. The high heterogeneity observed in the off-target prediction subgroup, together with the evolving nature of both AI and CRISPR technologies, underscores the need for caution in interpreting these results. Furthermore, the lack of validated tools for assessing bias in AI-driven biomedical studies highlights a methodological gap that must be addressed before broad clinical adoption.

At the same time, this meta-analysis provides an evidence-based foundation for future research, demonstrating that AI holds transformative potential in optimizing guide RNA design, improving therapeutic efficacy, and reducing off-target risks. Moving forward, progress in this field will depend on reproducibility and standardized benchmarks, transparent reporting of AI model architectures and performance metrics, and disease-specific validation pipelines. By addressing these limitations, AI-assisted CRISPR platforms can evolve from proof-of-concept investigations into safe, reproducible, and clinically impactful applications, ultimately shaping the next generation of epigenetic therapeutics.

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Author contributions M.K.B.: wrote the main manuscriptA.D.: SupervisorR.G.T.: formal analysisG.Ö.: inevstigated the obtained results M.H.H.: softwareM. S.R.S.: edited the final draftY. D.: edited the final draft; All authors reviewed the manuscript."

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Declarations

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