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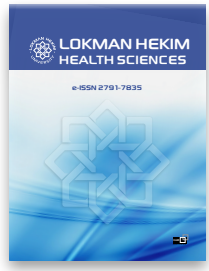

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SYSTEMATIC REVIEW

Artificial Intelligence Applications in Pediatric Genetics: Clinical and Research Implications and Ethical Considerations

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Abstract

Introduction: Artificial intelligence (AI) is transforming healthcare, and pediatric genetics has emerged as a particularly promising field for its implementation due to the complexity of rare genetic disorders and the rapidly increasing volume of genomic data. AI-based technologies may improve diagnostic accuracy, facilitate genomic interpretation, and support precision medicine approaches in pediatric patients.

Methods: This study was designed as a structured narrative review informed by a systematic literature search. A comprehensive search was conducted in PubMed, Scopus, and Web of Science databases for English-language publications published between January 2019 and January 2026. Relevant original studies, reviews, consensus statements, and ethically focused publications related to AI applications in pediatric genetics were included.

Results: AI-supported tools, including deep learning-based facial dysmorphology analysis and machine learning-driven genomic variant prioritization systems, have demonstrated significant potential in improving phenotype-genotype correlation, diagnostic efficiency, and personalized management strategies. AI applications also contribute to predictive modeling, disease-risk stratification, and large-scale multi-omics research. However, important ethical and legal concerns remain, including informed consent in minors, algorithmic bias, data privacy, transparency, and equitable access to AI technologies.

Discussion and Conclusion: AI has considerable potential to transform pediatric genetic practice by enhancing diagnostic precision and supporting individualized clinical care. Nevertheless, successful and equitable integration into routine practice requires robust ethical governance, prospective validation in diverse populations, transparent algorithms, and multidisciplinary clinician oversight. AI should be regarded as a decision-support tool that augments rather than replaces clinical expertise.

Keywords: Artificial intelligence; Dysmorphology; Ethical governance; Genomic medicine; Machine learning; Pediatric genetics; Rare diseases; Variant interpretation

Artificial intelligence (AI) has rapidly emerged as a transformative technology in healthcare by enabling advanced data analysis, automated pattern recognition, and predictive modeling.[1–3] AI-supported systems increasingly contribute to diagnostic accuracy, clinical decision-making, and personalized treatment strategies across multiple medical disciplines. Within this landscape, pediatric genetics is a particularly suitable domain for

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AI implementation, given the complexity of genotype-phenotype relationships and the rapidly expanding volume of genomic data generated by next-generation sequencing technologies.[4–6]

Rare genetic disorders collectively affect millions of children worldwide and frequently present with heterogeneous clinical manifestations, overlapping phenotypes, and delayed diagnosis. Despite substantial technological advances in genomic sequencing, many pediatric patients still experience prolonged diagnostic journeys requiring extensive clinical evaluation and repeated testing. AI offers the potential to mitigate these challenges by integrating phenotypic, genomic, and clinical datasets into unified analytical frameworks that support early and accurate diagnosis.[4,6,7]

Recent developments in machine learning and deep learning have enabled automated facial dysmorphology recognition, phenotype-driven gene prioritization, and predictive modeling of disease progression.[1,7–9] These approaches may significantly improve early diagnosis and individualized management strategies, particularly in childhood-onset genetic disorders where timely intervention can have a profound impact on long-term outcomes.[1,3,10]

The primary aim of this review was to provide a clinically oriented synthesis of emerging AI applications in pediatric genetics rather than to quantitatively evaluate pooled evidence.

Materials and Methods

Eligible publications included original research articles, systematic reviews, and consensus statements with direct clinical applicability to pediatric genetic practice, published in English between January 2019 and January 2026. Foundational studies published before 2019 (e.g., the initial description of the human phenotype ontology (HPO), American College of Medical Genetics and Genomics (ACMG) variant interpretation guidelines, and early phenotype-driven prioritization algorithms) were selectively included when they provided essential conceptual frameworks not superseded by more recent literature. Editorials, conference abstracts, and non-peer-reviewed sources were excluded.

A comprehensive literature search was conducted in January 2026 across PubMed, Scopus, and Web of Science databases. The search strategy combined key terms related to AI ("artificial intelligence," "machine learning," "deep learning") and genetics ("genetics," "genomic medicine," "clinical genetics," "medical genetics") using Boolean operators. Database-specific adaptations of the search syntax were applied where necessary.

The initial search identified 1,995 records (PubMed: n=301; Web of Science: n=303; Scopus: n=1.391). After removal of duplicates, 1,625 unique records remained. Following title and abstract screening, 1,425 articles were excluded due to lack of relevance to AI applications in genetic or genomic medicine or absence of pediatric applicability. A total of 200 articles were assessed for full-text eligibility. 162 articles were excluded because they primarily focused on non-clinical computational methodologies, lacked relevance to pediatric populations, lacked sufficient methodological detail, or did not address practical applications in genetic or genomic medicine.

This study was designed as a structured narrative review informed by a systematic literature search strategy. The primary objective was to provide a clinically oriented synthesis of current and emerging AI applications in pediatric genetics rather than to perform a quantitative evidence synthesis or meta-analysis.

Because the review included heterogeneous evidence types, including original studies, reviews, consensus statements, methodological reports, and ethical guidance documents, formal systematic review procedures such as preferred reporting items for systematic reviews and meta-analyses methodology, protocol registration, duplicate reviewer screening, and formal risk-of-bias assessment tools were not applied. Instead, the included literature was qualitatively critically appraised for clinical applicability, methodological transparency, population diversity, and relevance to pediatric genetic practice.

Study selection and eligibility assessment were performed by the sole author. This may represent a methodological limitation and may increase the risk of selection bias.

38 studies were ultimately included in the final review (Fig. 1). Studies not exclusively conducted in pediatric populations were also considered if they demonstrated applications of AI in genetic or genomic analysis with clear translational relevance to pediatric genetic practice. The full list of included studies is provided in Supplementary Table S1.

Clinical and Research Consequences

A summary of key studies, their AI methods, clinical applications, dataset characteristics, reported performance, and major limitations is presented in Table 1.

The diagnostic evaluation of pediatric rare diseases remains one of the most challenging areas of clinical

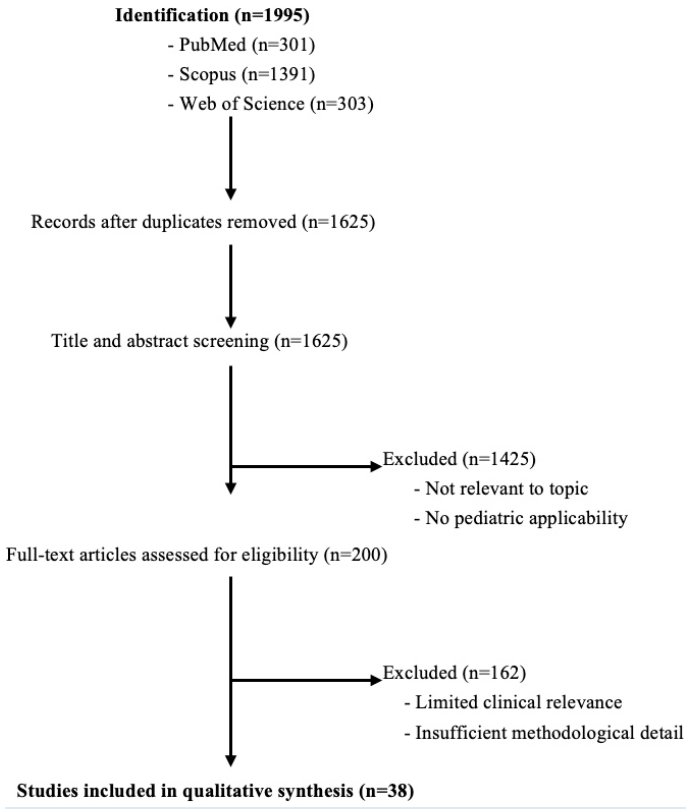

Figure 1. Preferred reporting items for systematic reviews and meta-analyses 2020 flow diagram of study selection.

medicine. AI-based diagnostic systems enable automated integration of HPO-based clinical data with genomic sequencing results, facilitating phenotype-genotype correlation and reverse phenotyping approaches.[5,7,9,11] These tools allow clinicians to reinterpret genomic findings as patients are followed longitudinally, improving diagnostic precision over time.[2,4,8,12]

Deep learning-based facial recognition systems have demonstrated high accuracy in identifying syndromic conditions in real-world clinical settings by analyzing dysmorphic facial features.[5,8,9] By assisting clinicians in narrowing differential diagnoses and guiding targeted genetic testing, such systems are particularly valuable during early childhood when phenotypic findings may be subtle or non-specific. It is important to emphasize that these tools serve as decision-support systems; even when an AI algorithm suggests a particular syndromic diagnosis, the final clinical determination requires confirmation through comprehensive physical examination and integration with other clinical findings by an experienced clinician.

The widespread clinical adoption of whole-exome and whole-genome sequencing has significantly increased diagnostic yield but also introduced substantial interpretative complexity. AI-supported variant interpretation platforms integrate multidimensional datasets including evolutionary conservation metrics, functional prediction algorithms, population frequency databases, and phenotype ontologies.[4,6,13] Machine learning-based prioritization reduces analytical burden and improves consistency in variant classification in accordance with ACMG recommendations.[13] AI-assisted reanalysis further enables iterative diagnostic reassessment as new gene-disease associations are discovered.[12,14]

Beyond diagnosis, AI applications are increasingly extending into predictive and preventive pediatric medicine. Integrative AI models combining genomic, biochemical, imaging, and longitudinal clinical data allow prediction of disease progression and individualized risk assessment.[1–3] Such predictive systems may support early identification of clinical deterioration, optimize surveillance strategies, and enable personalized therapeutic decision-making in inherited metabolic, neurodevelopmental, and cancer predisposition disorders. Taken together, these developments contribute to a continuously learning healthcare system in which genomic data remain clinically informative throughout childhood and adulthood.[2,10,15]

AI technologies are reshaping genetic research by enabling large-scale multi-omics analysis and discovery of novel disease mechanisms.[10,15,16] Machine learning approaches facilitate the identification of gene-disease associations and biological pathways that may remain undetected using conventional analytical methods. Collaborative frameworks such as federated learning allow model development across multiple institutions without direct sharing of sensitive genomic data, improving generalizability while preserving patient privacy and regulatory compliance.[17,18] This approach has the additional advantage of enabling algorithm training on more diverse datasets, potentially reducing algorithmic bias and improving performance across different populations.

Ethical and Legal Challenges

The clinical implementation of AI in pediatric genetics introduces significant ethical and legal challenges. Genomic information represents permanently identifiable health data with implications extending across an individual's lifespan and potentially affecting family members.[4,12,17] Pediatric genomic testing further raises concerns because consent decisions are typically made by parents or guardians while long-term consequences affect the child's future autonomy, commonly described as the

Table 1. Key applications, foundational studies, and methodological considerations of artificial intelligence in pediatric genetic practice

Study (Year)	AI method	Clinical application	Dataset characteristics	Key reported performance	Major limitation(s)
Gurovich et al.[8]	Deep learning (CNN)	Facial dysmorphology analysis for syndromic diagnosis	~17,000 images; predominantly European ancestry	Top-10 accuracy: 91%	Limited ethnic diversity; single-modality (facial images only)
Hsieh et al.[9]	Deep learning (Gestalt Matcher)	Rare disease matching using facial phenotype descriptors	~30,000 images; multi-ethnic but imbalanced	AUC: 0.91 for known syndromes	Performance drops significantly for ultra-rare syndromes; requires further prospective validation
Schaefer et al.[1]	Various ML methods	Scoping review of ML in rare diseases	211 included studies	N/A (review)	Heterogeneous methodologies; limited clinical implementation data
Dias and Torkamani[6]	Machine learning	Genomic variant prioritization	Multiple datasets (simulated and real)	Performance varies across models; reported improvements in variant prioritization accuracy compared to traditional pipelines	Lack of standardized benchmarking and persistent "black box" interpretability challenges
Richards et al.[13]	N/A (guidelines)	ACMG variant interpretation guidelines	N/A (consensus)	N/A	Pre-AI framework; does not incorporate AI-based evidence or probabilistic modeling approaches
Teo et al.[18]	Federated learning	Systematic review of federated ML in healthcare	612 studies	N/A (review)	Limited real-world clinical implementation; interoperability and data privacy constraints
Obermeyer et al.[19]	Algorithmic bias analysis	Racial bias in healthcare algorithm	~50,000 patients	Significant racial bias detected	Not specific to genomics or pediatric populations; highlights broader risks of algorithmic bias in clinical AI systems

AI: Artificial intelligence; AUC: Area under the curve; CNN: Convolutional neural network; ML: Machine learning; N/A: Not applicable.

child's "right to an open future."[4,12,16] This concept creates particular tension in the context of AI-based predictive analytics: when algorithms identify risks for adult-onset conditions during childhood, clinicians and families must navigate the complex decision of whether and how to disclose information that may impact the child's future autonomous decision-making.

Management of Incidental and Secondary Findings

AI-driven genomic analysis, particularly when using broad variant-prioritization algorithms, may inadvertently uncover incidental or secondary findings unrelated to the initial diagnostic question.[12,16] These may include adult-onset conditions, carrier status for recessive disorders, or even misattributed parentage. Clinicians using AI tools must therefore establish clear protocols for handling incidental findings, including predefined policies on when, how, and whether to disclose this information to families, balancing immediate clinical utility with the child's future autonomy.[4]

Data Ownership and Long-Term Data Stewardship

Pediatric genomic data used to train or validate AI models cannot be fully anonymized due to their inherent uniqueness.[17] This raises critical questions regarding data ownership: Who holds the rights to a child's genomic data after it is used to train a commercial AI algorithm? Current regulatory frameworks, including general data protection regulation, provide a "right to be forgotten," but its technical implementation for already-trained AI models remains unresolved.[16] Commercial AI developers may have conflicting incentives regarding long-term data stewardship, creating potential tensions between profit motives and ethical obligations to research participants.

Obligations for Longitudinal Reanalysis

AI algorithms improve over time as new data and methodological advances emerge. Studies have demonstrated that AI-assisted reanalysis can identify new diagnoses in a substantial proportion of previously unsolved cases.[12,14] However, without clear guidelines, a two-tiered system may emerge where patients at academic medical centers benefit from continuous reanalysis while those in resource-limited settings do not, potentially exacerbating existing healthcare disparities. Establishing systematic reanalysis pipelines requires significant infrastructure, funding, and personnel – an obligation that remains largely unaddressed in current policy frameworks.

Algorithmic Bias and Transparency

Algorithmic bias remains a major concern, as AI systems trained on genetically homogeneous datasets may perform worse in underrepresented populations and unintentionally reinforce healthcare disparities.[17,19] Furthermore, limited transparency of complex AI models – the so-called "black box" problem – complicates attribution of medicolegal responsibility among clinicians, healthcare institutions, and AI developers, highlighting the importance of explainable AI in clinical decision-making.[3,17,20]

Limitations and Methodological Considerations

The findings and claims discussed above must be interpreted in light of several important limitations. First, while deep learning-based facial recognition systems have demonstrated high diagnostic accuracy in controlled research settings,[5,8,9] it is critical to note that most training datasets are predominantly composed of individuals of European ancestry. For example, Gurovich and colleagues reported 91% top-10 accuracy using facial analysis[8] yet their model's generalizability to more diverse populations – including individuals of African, Asian, or Latin American descent – remains unproven, a limitation explicitly acknowledged by the original authors. This raises the possibility that reported accuracy figures may overestimate real-world performance in non-European populations.

Second, AI-supported variant interpretation platforms rely heavily on reference databases (e.g., gnomAD, ClinVar) that exhibit substantial ancestry bias, with underrepresented populations having higher rates of variants of uncertain significance. Consequently, diagnostic yield improvements reported in the literature[4,6,13] may not be equitably distributed across all pediatric patient populations. Third, the "black box" problem mentioned earlier complicates not only medicolegal attribution but also clinical adoption in resource-limited settings where explainability is particularly valued.

Fourth, most published studies on AI in pediatric genetics focus on retrospective cohorts or curated datasets, which may not reflect the phenotypic heterogeneity and data incompleteness encountered in routine clinical practice. Prospective validation studies in unselected, consecutive patient populations remain scarce. Fifth, the promising predictive analytics applications described above[1–3] are largely derived from single-center or simulation-based studies; their performance in real-time clinical decision support, particularly for progressive or ultra-rare conditions, requires further prospective evaluation.

Finally, our discussion is limited by the absence of a systematic review methodology, and the cited references serve as illustrative examples rather than an exhaustive synthesis of the literature. Future research should prioritize diverse, multi-ethnic training cohorts, standardized reporting of subgroup performance metrics, and prospective clinical trials to establish generalizable evidence for AI-based diagnostic tools in pediatric genetics. In addition, publication bias may have influenced the available evidence, as studies reporting positive performance outcomes are more likely to be published. Study selection was conducted by a single reviewer, which may increase the risk of selection bias. The evidence discussed in this review includes heterogeneous publication types with varying methodological strengths; therefore, conclusions should be interpreted within the context of the underlying evidence level.

Despite these challenges, AI-supported tools have the potential to substantially improve daily clinical practice in pediatric genetics by facilitating earlier diagnosis, optimizing genomic data interpretation, and supporting individualized patient management strategies. AI-assisted phenotype recognition and variant prioritization may reduce diagnostic delays and enable more efficient utilization of genetic testing resources. Predictive analytics may further assist clinicians in risk stratification, longitudinal monitoring, and personalized surveillance planning for children with genetic disorders.[1–3] Successful implementation ultimately requires clinician oversight, interdisciplinary collaboration, and integration into existing clinical workflows to ensure safe, equitable, and patient-centered care.

Conclusion

AI has the potential to significantly transform pediatric genetic practice, improving diagnostic efficiency, enhancing genomic interpretation, and enabling precision-based patient management. However, the successful integration of AI into clinical workflows depends on careful attention to ethical governance, data security, algorithmic fairness, and transparency. Rather than replacing clinical expertise, AI should be regarded as a decision-support partner that augments diagnostic reasoning and clinical judgment.

Future research should specifically: (1) Conduct prospective, multi-center validation of at least two existing facial recognition tools (e.g., GestaltMatcher and DeepGestalt) in cohorts where <30% of participants are of European ancestry; (2) report performance metrics stratified by ancestry, age, and phenotypic complexity in all AI studies; (3) develop and publicly release a standardized benchmarking dataset for pediatric genomic AI that includes diverse populations; and (4) establish within the next 5 years a regulatory framework requiring prospective clinical trial data for AI-based diagnostic tools before regulatory approval in pediatric populations.

Only through rigorous evaluation and responsible governance can the full potential of AI be safely and equitably realized for children with genetic disorders and their families.

Ethics Committee Approval: Ethical approval was not required for this study since this is a review article.

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Appendix 1. Summary of included studies and key supporting literature on artificial intelligence in pediatric genomic medicine

No	Study	Type	AI method	Clinical application/relevance
1	Gurovich et al.[8]	Original study	Deep learning	Facial dysmorphology analysis
2	Hsieh et al.[9]	Original study	Deep learning	Rare disease matching via facial phenotype
3	Amiri H and Kohane[21]	Original study	Machine learning	Outcome prediction in undiagnosed diseases
4	Arlt et al.[22]	Original study	Deep learning	Facial phenotyping in CdLS
5	Berger et al.[23]	Original study	Automated reanalysis	Variant reinterpretation
6	Beyreli et al.[24]	Original study	Deep multitask learning	Gene risk prediction (NDD)
7	Jackson et al.[25]	Original study	AI-based variant reinterpretation	Genetic disease prevalence estimation
8	Kabir et al.[26]	Original study	Machine learning	Congenital anomaly gene prediction
9	Kaczmarek et al.[27]	Original study	Machine learning	Pathogenic variant identification
10	Kadlubowska and Schrauwen[28]	Review	—	Molecular diagnosis in pediatric neurology
11	Kingsmore et al.[29]	Original study	Federated learning	Newborn genomic screening
12	Kobayashi et al.[30]	Original study	AI-based analysis	Clinical variant reclassification
13	Peterson et al.[31]	Original study	NLP+ML	Prioritization for WGS
14	Porras et al.[32]	Original study	Machine learning	Genetic syndrome screening
15	Cohen et al.[33]	Original study	Genomic analytics	Rare disease genome analysis
16	Rivera-Munoz et al.[34]	Original study	Exome sequencing	Phenotypic expansion
17	Yang et al.[35]	Original study	Deep learning	Noonan syndrome detection
18	Ye et al.[36]	Original study	AI+rapid WGS	Rare disease diagnosis
19	Obermeyer et al.[19]	Analytical study	Algorithmic analysis	Bias in healthcare AI
20	Schaefer et al.[1]	Review	—	Machine learning in rare diseases
21	Rajkomar et al.[2]	Review	—	Machine learning in medicine
22	Marques et al.[3]	Review	—	Ethical challenges of AI
23	Ilić and Sarajlija[4]	Review	—	AI in pediatric rare disease diagnosis
24	Duong and Solomon[5]	Review	—	AI in clinical genetics
25	Dias and Torkamani[6]	Review	—	AI in genomic diagnostics
26	Smedley and Robinson[7]	Methodological	—	Phenotype-driven gene prioritization
27	Topol[10]	Perspective	—	AI in medicine framework
28	Robinson and Mundlos[11]	Methodological	—	Human Phenotype Ontology
29	Krier et al.[12]	Review	—	Genomic sequencing in clinical practice
30	Richards et al.[13]	Guideline	—	ACMG variant interpretation standards
31	Beam and Kohane[14]	Perspective	—	Big data and AI in healthcare
32	Emmert-Streib et al.[15]	Editorial	—	AI and multi-omics
33	World Health Organization[16]	Guideline	—	Ethics and governance of AI
34	He et al.[17]	Review	—	AI implementation in medicine
35	Teo et al.[18]	Systematic review	—	Federated learning in healthcare
36	Amann et al.[20]	Review	—	Explainability in AI
37	Coghlan et al.[37]	Review	—	Ethics in pediatric genomic AI
38	Gripp[38]	Review	—	AI facial analysis in genetics

This table includes heterogeneous evidence types, including original studies, reviews, guidelines, methodological reports, perspectives, and editorials, to provide a clinically oriented overview of current AI applications in pediatric genomic medicine. ACMG: American College of Medical Genetics and Genomics; AI: Artificial intelligence; CdLS: Cornelia de Lange syndrome; WGS: Whole genome sequencing; NDD: Neurodevelopmental disorders.