Review

AI in Variant Analysis: Fast Track to Genetic Diagnoses

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AI in Variant Analysis: Fast Track to Genetic Diagnoses

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Abstract

While falling costs have increased access to genomic sequencing, the impact of clinical sequencing is often hindered by the challenge of interpreting complex genetic data. The high prevalence of variants of unknown significance (VUSs) can lead to false reassurance or psychological distress, as patients and non-expert clinicians may misinterpret inconclusive results. We propose that artificial intelligence (AI) may serve as a critical clinical decision-support tool to improve the efficiency of genetic testing, especially in variant analysis. We advocate integrating AI throughout the genetic diagnostic workflow and outline current approaches to AI-assisted variant analysis to enable efficient personalized treatment. We also discuss anticipated challenges in this pursuit and offer recommendations to ensure precision, accuracy, reproducibility, and transparency.

Keywords: variant analysis; clinical decision support; genomics; explainable ai; precision medicine; diagnostic odyssey

Introduction

The average time to receive a genetic diagnosis across high-income countries ranges from 4 to 19 years [1,2]. Current practices force patients with genetic diseases into a 'diagnostic odyssey,' subjecting them to rounds of unnecessary clinic visits, procedures, and medications. This process closes or narrows their window of intervention, ultimately enabling disease progression and long-term disease damage. One critical component in addressing the diagnostic odyssey is high-throughput genetic testing, which has become widely accessible and cost-effective [3]. Even out-of-pocket sequencing costs are a fraction of the overall odyssey, which produces $86,000 to $516,000 in avoidable costs per patient [4].

Early disease identification and therapeutic intervention should be the norm. However, physicians report limitations in their genetics training [5–7], and many express reduced interest in genetic screening due to the rarity of genetic conditions [8]. On the contrary, 25-30 million Americans have a genetic disease (~ 1 in 11) [9]; therefore, health care providers should widely adopt genetic testing to fulfill this demand.

Variant analysis—the rate-limiting step in genetic testing [10]—classifies variants by their pathogenicity to guide clinical decision-making. Inaccurate interpretation at this stage fundamentally alters patient management, preventing the use of targeted therapies, initiating surveillance, or performing preventive procedures [11]. These errors also extend to the family, obscuring the need for cascade screening or preimplantation genetic diagnosis [12]. Consequently, misinterpreted variants contribute to avoidable morbidity and mortality through missed preventative interventions, while simultaneously inflicting psychological harm via false reassurance or unnecessary anxiety [13]. The

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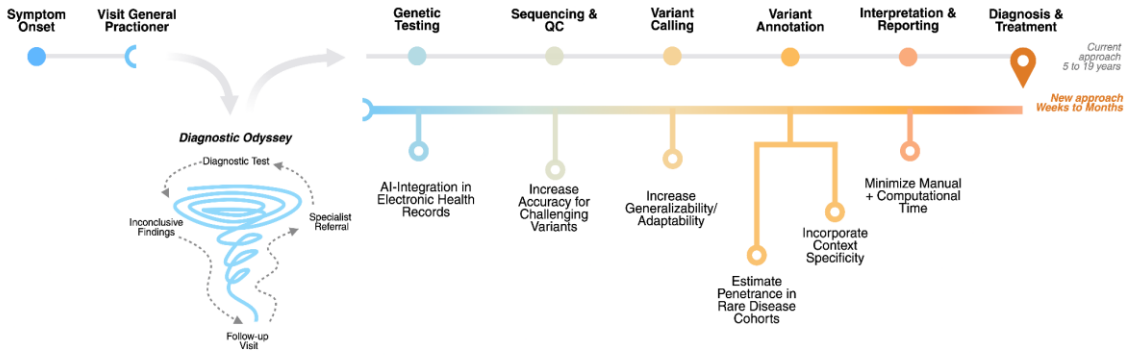
standard of care uses ACMG/AMP and/or ESHG guidelines [14,15] for variant interpretation, but the process as a whole remains labor-intensive and relies heavily on experts. Results can be inconsistent and often yield variants that lack sufficient evidence to be classified as benign or pathogenic [11,16,17], complicating patient care. However, automation that leverages all available clinical, molecular, and population data in a standardized, reproducible manner could help reduce these issues. Artificial intelligence (AI), tools with "human-like reasoning" built from a variety of machine learning (ML) models and/or large language models (LLMs) (reviewed in [18–22]), can optimize labor- and knowledge-intensive steps throughout the genetic testing process.

In this perspective (**Figure 1**), we highlight opportunities, challenges, and recommendations for incorporating AI into variant analysis to support clinical genetic testing and research.



Challenge	Recommendation	Impact
Privacy & Safety	Adhere to GDPR, HIPPA, ISO/IEC, and GINA; use secure data handling practices	Protect sensitive information and maintain patient trust
Data Quality & Bias	Use high-quality, representative datasets; avoid "big data hubris"	Reduce bias, improve prediction accuracy, and ensure fairness
Model Transparency	Incorporate explainable AI (XAI) methods; ensure models are auditable	Improve trust, interpretability, and ethical accountability
Validation & Life Cycle	Implement post-market testing and total product life cycle monitoring	Ensure ongoing efficacy and safety of AI tools

Figure 1. Comparing the years-long diagnostic odyssey to an AI-enabled streamlined pathway.

The schematic contrasts the slow, cyclic traditional approach with targeted AI opportunities that accelerate variant analysis and shorten time to diagnosis. The table summarizes potential challenges using our proposed AI-assisted approach, along with recommended solutions and their expected clinical impact. Created in BioRender. Taluri and Wilk. (2026) https://BioRender.com/6xxko8q

Approach to Variant Analysis

AI is emerging at a time when clinical genetics faces its greatest gap between knowledge and practice.

To prevent the diagnostic odyssey, physicians must first recognize patients who would benefit from genetic testing. Genetic diseases typically present with a constellation of signs (e.g., dysmorphism, early-onset, and/or multi-system involvement); therefore, AI can assist in determining when genetic testing may be appropriate (e.g., FACE2GENE [23]). For instance, AI-integrations in EHRs could detect potential patients, even those with subtle clinical presentations [24,25]. AI can also support physicians' continuing education through adaptive educational modules that account for each individual's time constraints, goals, and baseline knowledge [26].

After sequencing, variant analysis processes the data in four key steps: variant calling, annotation, prioritization, and interpretation. AI/ML tools have already streamlined variant calling by reducing manual filtering and improving scalability. Examples of this include Google's DeepVariant [27], DNAscope [28,29], DeepTrio [30], Clair3 [31], Medaka [32], and HELLO [33]. These

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tools offer speed and generalizability across sequencing platforms [34–36]. Following variant identification, variant annotation contextualizes a patient's variants using sequence data, conservation, population frequency, and functional impact. This step requires synthesizing information across diverse databases. LLMs, a subtype of AI models that process and generate human language [18], excel at automating this process. Mining resources like ClinVar and gnomAD (i.e., large databases of patient variants) have been assessed in the context of their genetic sequences to predict a variant's consequences on the primary structure (e.g., SpliceAI, AlphaMissense, and Evo2) [37,38]. Other ML models have enhanced variant annotation through feature-based learning (e.g., REVEL, CADD, PrimateAI-3D) [39–41]

Full-stack variant analysis pipelines, including AI-MARRVEL [42], Qiagen's Franklin [43], Illumina's Emedgene [44], and Nostos Genomics [45], have already automated variant interpretation and prioritization. Despite these advances, variants of uncertain significance (VUSs) remain the most common variant classification, accounting for ~35-37% of variants associated with rare diseases and cancer [46–48]. This ambiguity presents a critical clinical challenge; non-experts may misinterpret a VUS as 'normal' (false reassurance) or as a definitive diagnosis (unnecessary anxiety), leading to inappropriate care [13]. Reclassification is inherently difficult, as assigning a variant to benign, likely benign, likely pathogenic, or pathogenic annotations requires ≥90% certainty of its clinical relevance [14]. This threshold is challenging to meet, especially when context-specific data are limited and/or when considering non-coding (e.g., regulatory sequences [49] and splice sites [50]), low-penetrance, or hypomorphic variants [14,51]. Emerging tools aim to address this, such as DYNA, a disease-specific LLM that compares context-specific networks to score pathogenicity of coding and non-coding variants [52]. In a study of >17k cardiomyopathy VUSs from ClinVar, DYNA reclassified ~9% as pathogenic, likely pathogenic, benign, or likely benign [52]. Another promising approach to improving classification is to estimate penetrance. In rare diseases, small cohorts make it difficult, or even impossible, to calculate penetrance using traditional methods. However, Forrest et al. [53], developed disease-specific ML models to calculate disease probability and penetrance using EHR and genetic data.

AI-assisted variant analysis can clarify genetic test results (e.g., AI-enabled ACMG scoring within EHR and clinical trial eligibility screening [54]), enabling clinicians to weigh genomic evidence alongside clinical findings. With data-driven rationales to support clinical diagnostics, clinicians are better-equipped to make more efficient and accurate decisions. Clinicians can thereby reduce trial-and-error prescribing by linking variants to targeted therapies and trials. Ultimately, AI-assistance will increase genetic screening rates, preventing delays in care.

Challenges and Recommendations

Integrating AI into clinical genetics shows great promise, but we expect challenges ahead (**Figure 1**).

Trust in scientists is declining in the US [55], and global opinion toward AI remains cautious [56]. To restore public confidence, developers should collaborate with patients and clinicians when designing AI tools, leveraging their domain-specific expertise to improve model performance and ensure relevance [57,58].

Genetic data has historically raised significant legal, ethical, and privacy concerns due to its uniquely identifiable nature. Using this data with AI could raise additional concerns; therefore, training data and software must comply with national/international laws and standards [59–63]. Models for variant analysis should also adhere to established clinical standards from reputable organizations, such as ACMG, AMP, CAP [14], and ESHG [15,64].

A major shortcoming of many AI tools stems from the data they are trained on. Overreliance on large, uncurated datasets can introduce bias, inaccuracies, and outdated information, leading to large errors in predictions [65–68] and AI "hallucinations" [69]. Instead, datasets should be reliable and representative of the affected patient population [57,70–75]. This is especially critical in biomedical applications, where underrepresentation can perpetuate disparities [71–73,76–79]. However,

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implementing retrieval-augmented generation (RAG) systems (curated knowledgebases) has already aided biomedical applications and reduced AI hallucinations [80,81].

ML/AI models offer powerful capabilities for streamlining variant analysis by integrating multimodal data (e.g., genetic sequences, EHRs, biomedical knowledge graphs, and large-scale text mining) but often at the cost of interpretability, with many functioning as a "black box" [60,82]. To ensure fairness and accuracy, especially in clinical contexts, models must be auditable and explainable. An auditable model acts as a "glass box," where processes can be systematically examined and traced (e.g., by logging decision logic [83] and data sources used as evidence [44], [45], [84], [85] [83], [86]. Explainable AI (XAI) techniques further enable users to dissect models and their predictions to assess the influence of individual features. Numerous XAI approaches are currently available–even for complex LLMs–despite their scale of parameters and training [87–89]. Some AI-assisted variant analyses and workflows already incorporate explainable AI (XAI) methods, such as scoring and ranking the importance of features that drive their predictions [44,53,9091].

Confirming the correctness and translatability of AI-prioritized variants requires multi-tiered validation and continual monitoring. Models must be benchmarked and tested against high-quality, expert-curated datasets (e.g., ClinVar or specific disease cohorts) to ensure high sensitivity (>90%) in real-world scenarios [90], and predictions should be verified through orthogonal biological tests. Potential orthogonal evidence-based methods include segregation analysis [92], confirming variant tracks with phenotypes in a family, and *in vivo* or *in vitro* functional assays [11,92], providing experimental evidence supporting variant damage to a gene product. AI tools should follow a full product lifecycle approach, including international predetermined change control plans (PCCPs) for ML-enabled medical devices [93], with real-world performance tracked for safety and efficacy. Because models evolve, outputs may change and even contradict earlier reports; this should be expected and documented so clinicians and patients can modify care as needed [93].

Conclusions

Incorporating ML and AI into variant analysis can transform and expedite the genetic testing process with actionable clinical intelligence, enabling earlier diagnostics and potentially life-saving interventions. When designed with transparency and community engagement, these tools accelerate variant interpretation without compromising clinical judgement or patient trust. By prioritizing ethical design, high-quality data, and explainable models, AI-assisted genomics advances the principle of beneficence by improving accuracy and efficiency, while ensuring nonmaleficence through bias control, ultimately streamlining the path from genetic discovery to bedside treatment and, ultimately, improving long-term patient outcomes.

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