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Artificial intelligence in clinical variant interpretation: Opportunity or overpromise?

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The rapid expansion of genomic sequencing has changed the scale of clinical genetic testing. Exome and genome sequencing are now part of clinical practice and generate large numbers of genetic findings that require interpretation. However, our ability to generate genomic data has outpaced our ability to determine the clinical significance of every identified variant. This challenge is particularly evident in rare disease diagnostics, where variant interpretation may require substantial time and specialist expertise (1, 5).

The increasing use of advanced sequencing technologies has also resulted in the identification of a growing number of variants of uncertain significance (VUS). Clinical interpretation of these variants requires a comprehensive assessment of population frequency, computational predictions, functional evidence, segregation data, and the consistency of the variant with the patient's phenotype. (1) With the growing amount of information available for each variant, this assessment can be time-consuming and difficult to perform consistently. AI may be helpful by bringing relevant evidence together and directing attention to variants that need further review (2, 5).

The potential value of AI, however, should be considered in the context of what clinical variant interpretation actually requires. The ACMG/AMP framework classifies variants using multiple categories of evidence, including population, computational, functional, and segregation data (1). A computational prediction is therefore only one component of the interpretation process. A model may predict that a variant is likely to affect protein function, but this prediction alone does not establish pathogenicity. Clinical interpretation requires assessment of the available evidence as a whole and consideration of its relevance to the individual patient.

This distinction becomes particularly important for VUS. Recent evaluation of automated variant interpretation tools against ClinGen Expert Panel classifications showed that the tools performed better for clearly pathogenic or

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benign variants than for VUS, for which concordance was substantially lower. Some tools also showed a tendency to classify uncertain variants as pathogenic (4). This finding raises a clinically important concern: the problem is not simply that an automated prediction may be wrong, but that it may convey a level of certainty that is not supported by the available evidence. AI can help prioritize a VUS and identify evidence that warrants further review, but it cannot replace the biological evidence required for reclassification (1, 3, 5).

The quality and representativeness of the datasets used to develop and validate AI models are important determinants of their clinical utility. In particular, the underrepresentation of certain ancestral populations in genomic datasets may limit the generalizability of model predictions across diverse populations. In addition, reported performance can depend on the dataset, variant labels, and evaluation strategy used for benchmarking (3). High performance on a particular dataset should therefore not automatically be interpreted as evidence of clinical validity in other populations or clinical settings. This issue is especially relevant in genetic medicine, where an interpretation may have implications not only for the individual patient but also for family members undergoing testing.

Interpretability is another important consideration. Some advanced prediction models, particularly complex deep learning approaches, may provide useful predictions without offering a clear explanation of how those predictions were generated (3). In clinical practice, this can make it difficult for a reviewer to determine why a particular prediction was made and whether the underlying evidence is appropriate for the case. AI systems intended for clinical use should therefore provide sufficient transparency for their outputs to be critically assessed rather than simply accepted.

Despite these limitations, AI has a legitimate and potentially important role in clinical variant analysis. Variant interpretation involves searching and reviewing information from multiple sources, comparing candidate variants, and determining which findings require further investigation. AI can assist with these tasks by aggregating information, prioritizing variants, and supporting evidence review (2,5). Its value may therefore lie less in making the final classification and more in helping clinicians manage the increasing volume and complexity of genomic evidence.

It is also important to distinguish variant-effect prediction from automated clinical variant interpretation. A tool designed to predict the functional effect of a variant is not equivalent to a system that attempts to integrate multiple ACMG/AMP criteria and provide an overall classification. The latter is a more complex task because evidence may be incomplete, conflicting, or dependent on the clinical context (1, 4). The clinical utility of an AI system should consequently be judged according to the specific task for which it has been developed and validated.

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For me, the greatest concern is the use of AI in the final clinical decision-making process. Although AI can process and integrate large amounts of information, it does not possess human clinical judgment or an understanding of the individual and emotional context of a patient. Genetic interpretation is not limited to assigning a classification to a variant; the consequences of that interpretation may affect patients and families in deeply personal ways. For this reason, the final clinical decision should remain with qualified professionals who can consider the available evidence within the broader clinical and human context (1, 4, 5).

In clinical practice, AI should assist rather than determine the interpretation of a genetic variant. It may help clinicians find and review relevant evidence and identify variants that require closer assessment. The responsibility for weighing that evidence and making the final classification, however, should remain with qualified clinical geneticists and laboratory professionals (4, 5).

The promise of AI in clinical variant interpretation is therefore real, but it should not be confused with the promise of autonomous interpretation. AI can help address the growing volume of genomic information and may make evidence review more efficient and systematic. However, limitations in biological knowledge, data quality and diversity, model interpretability, and the persistent uncertainty surrounding many variants remain important barriers to fully automated clinical interpretation (3, 5).

AI has a clear role to play in clinical genomic analysis as the volume and complexity of genomic evidence continue to increase. It can make the process of finding and reviewing relevant information more manageable, particularly when many lines of evidence need to be considered. AI may facilitate the retrieval and systematic evaluation of relevant evidence when variant interpretation requires integrating multiple, sometimes conflicting, sources of information. Nevertheless, incomplete or discordant evidence still requires careful assessment and clinical judgment by qualified professionals. For this reason, its role in clinical variant interpretation should remain supportive, with the final assessment and clinical decision resting with qualified professionals.

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