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Letters to the Editor
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Artificial Intelligence in Rare Disease Diagnosis: A Clinical Milestone with Ethical Considerations

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Dear **Editor**,

Artificial intelligence (AI) holds substantial promise for transforming the diagnosis of rare diseases. By analyzing large datasets from genomics, imaging, and electronic health records, AI systems can detect subtle diagnostic patterns that may be overlooked by even experienced clinicians (1). For patients with orphan diseases who often endure years of uncertainty, this capability could meaningfully shorten the diagnostic journey and improve outcomes.

However, the rapid integration of AI into rare disease diagnostics raises significant ethical and clinical challenges. A primary concern is interpretability: deep learning models often function as "black boxes," providing diagnostic outputs without clear reasoning (2). This opacity can undermine transparency and shared decision-making, both of which are essential in rare disease care.

Ethical considerations extend beyond interpretability. Concerns around data privacy are acute, given the sensitive nature of genomic and health data. Emerging strategies such as synthetic data generation offer potential solutions by enabling the creation of privacy-preserving datasets that mimic real patient data while complying with regulations like the General Data Protection Regulation (GDPR) and the Health Insurance Portability and Accountability Act (HIPAA) (3). Such approaches can facilitate AI training and international collaboration without exposing personal health information. Informed consent processes must also be adapted for AI-driven diagnostics, clearly explaining to patients how their data will be used and how AI contributes to their care. Furthermore, accountability for AI-related errors must be defined, clarifying whether responsibility lies with the developer, the clinician, or both.

Bias in training data remains another challenge. Most algorithms are developed using datasets from high-income countries, underrepresenting populations from low-resource settings (4). This can reduce diagnostic accuracy in ethnically and geographically diverse groups, as evidenced by recent findings of performance gaps in AI-assisted genetic disease diagnosis within underrepresented communities (5).

Over-reliance on AI also poses risks. A 2024 multicenter simulation study showed that clinicians sometimes deferred to AI outputs even when these conflicted with their clinical judgment (6). In rare disease contexts, where nuanced reasoning and contextual knowledge are essential, this could erode critical thinking and harm patient outcomes.

To ensure safe and equitable clinical adoption, we propose a concise roadmap:

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1. Diverse and representative datasets to train AI models, improving performance across populations.
2. Independent AI audit mechanisms to evaluate algorithm accuracy, fairness, and robustness in real-world settings.
3. Collaborative decision-making frameworks where AI supports, rather than replaces, clinician expertise.

In conclusion, AI has the potential to revolutionize rare disease diagnosis, but its benefits must be realized within a framework grounded in transparency, equity, and ethical responsibility. We call upon regulators, AI developers, and healthcare providers to work collaboratively to establish rigorous ethical guidelines, enforce accountability, and ensure that technological progress translates into genuine and equitable patient benefit.

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