PARAGON HEALTH INSTITUTE POLICY BRIEF

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The Regulation of Uncertainty

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KEY TAKEAWAYS

Policymakers struggle to regulate healthcare AI products because, unlike traditional software, AI can produce unpredictable results.

To ensure safety and effectiveness as AI products evolve, the FDA can evaluate AI products on an ongoing basis (even when products are already in the market) by partnering with developers and health systems.

With ever greater investments and regular technological breakthroughs, artificial intelligence is taking most industries, including healthcare, by storm. However, the use of artificial intelligence (AI) in healthcare has challenged federal and state regulators aiming to protect consumer safety because, unlike traditional medical software, AI may produce unpredictable outputs. Moreover, the unpredictability itself can be irregular. Hypothetically, four identical inputs to a particular AI system might produce the same output but a fifth instance might not. Reliability fears attending this issue are exacerbated by the opacity surrounding the technology[1]. Some AI systems perform calculations so numerous that their developers cannot fully explain the resulting predictions despite their accuracy. This lack of explainability, when combined with unexpected outputs of potentially serious medical consequences, have raised questions about the need and extent of regulations governing health AI technologies[2]. For all their good intentions, we believe overly restrictive rules on health AI may have a detrimental effect on healthcare AI progress and endanger the prospects for regulation that effectively confronts the safety concerns related to AI uncertainty.

A major impediment to addressing AI uncertainty through a traditional regulatory approach is the technology's diversity. AI encompasses numerous programming methodologies that do not all share the possibility of unpredictable outputs. Some systems are adaptive and should become more accurate over time because they continue to refine their outputs from new data acquired through real world medical use. In contrast, Large Language Models may occasionally produce gibberish or factually inaccurate statements because of their underlying architecture. Depending on the healthcare context, such an output variability could result in patient harm, especially if used blindly or without appropriate supervision. If this kind of output variability incites unnecessarily broad overregulation, life-saving and cost-reducing solutions may never reach patients or health organizations. Moreover, the lingering fear of unnecessary overregulation may prevent reasonable safety rules from subsequently garnering industry support.

AI used in medical prevention, diagnosis, and treatment is classified as a medical device and is regulated by the FDA. The agency's approach, developed before AI technology was a major consideration, has focused on validating safety and efficacy prior to a device's market availability for clinicians and consumers. However, the FDA's draft guidance issued on January 6, 2025 recognizes the need for a total product lifecycle approach, which includes not only premarket but also post-market setting[3]. We argue that to increase the expediency at which best health AI technologies are brought to patients and clinicians while at the same time improve their safety and efficacy, a larger paradigm shift is necessary that places a heavier emphasis on post-market surveillance. There exists

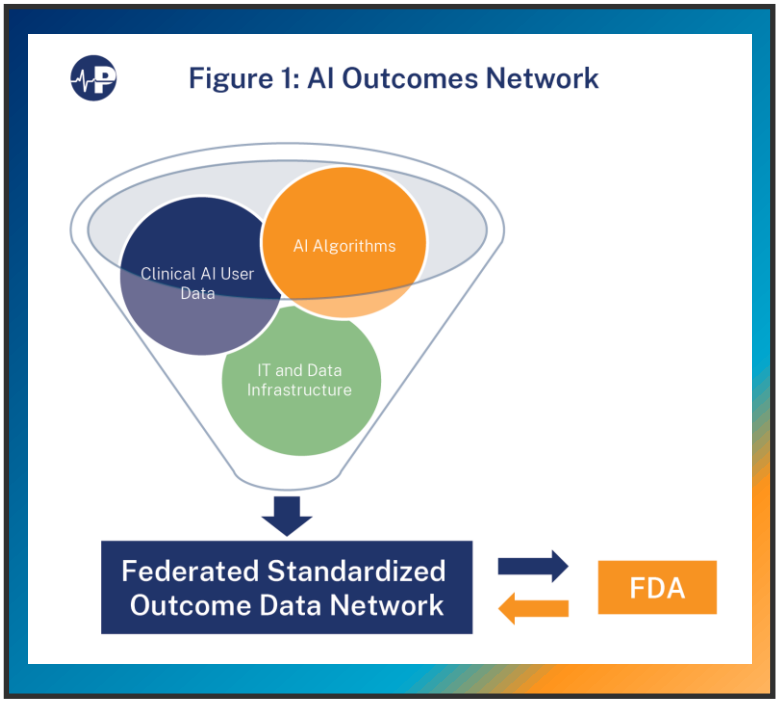
some precedent and legal framework for surveillance after market entry. Section 522 of the federal Food, Drug, and Cosmetic Act empowers the FDA, at its discretion, to require a post-market surveillance study from a device manufacturer[4]. However, this has been more of an exception than a routine, since fewer than ten Section 522 studies have been initiated per year in the last decade[5]. The new draft guidance hopes to change this with a voluntary convention for post-market monitoring plans for premarket approval (PMA) studies.

Reorienting AI surveillance to post-market performance will not be as simple as suggesting monitoring plans. Instead, a new framework will be needed to estimate uncertainty potential as well as patient risk. Given that the FDA has already suggested it is understaffed to adequately monitor all AI devices[6], the effective monitoring of post-market AI performance should enlist the efforts of not only AI developers but also healthcare providers who use these technologies and have direct access to the relevant data. Their cooperation, though, necessitates both incentive as well as a streamlined process that avoids excessive labor and unnecessary data collection. Post-market surveillance of health AI technologies would be aided by a formation of federated standardized outcome data networks whose key ingredients are depicted in Figure 1.

On the incentive side, healthcare providers and developers want to prevent avoidable patient injury as well as decrease their liability when such events occur. Participation in a program monitoring an AI system's market performance could provide access to information on negative device trends earlier than would be the case with formal agency announcements as well as demonstrate good faith efforts to maximize patient safety. Moreover, healthcare providers and developers won't volunteer to participate unless the FDA has 1) a compelling framework for establishing which AI systems pose the greatest patient risk, 2) clear criteria for predicting the occurrence of AI output variability, 3) an easy-to-implement methodology for capturing meaningful information from an AI system already approved for market use, 4) a financial model for post-market surveillance that promotes innovation and continuous improvement.

These four issues, if used to mitigate the risks of unpredictable AI outputs, could shape the near-term success of AI in American healthcare.

- The first will force regulators to improve medical device risk assessment according to features such as programming methodology, training data characteristics, medical use context, and input-output relationships.
- The second may positively influence healthcare providers' perceptions of AI reliability and accelerate the technology's adoption.
- The third may transform operation of the medical device market and introduce a collaborative governance model that mutually benefits regulators, developers, and the healthcare providers who depend on them, paving the way for similar work outside of AI medical devices.
- The fourth recognizes that a well-designed post-market surveillance system requires investment and maintenance that need to be undertaken in a manner that brings value to all parties.



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[1] Youssef A, Pencina M, Thakur A, Zhu T, Clifton D, Shah NH. External validation of AI models in health should be replaced with recurring local validation. Nat Med. 2023 Nov;29(11):2686-2687. doi: 10.1038/s41591-023-02540-z. PMID: 37853136.

[2] Aboy M, Minssen T, Vayena E. Navigating the EU AI Act: implications for regulated digital medical products. NPJ Digit Med. 2024 Sep 6;7(1):237. doi: 10.1038/s41746-024-01232-3. PMID: 39242831; PMCID: PMC11379845.

[3] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-use-artificial-intelligence-support-regulatory-decision-making-drug-and-biological; accessed January 27, 2025

[4] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postmarket-surveillance-under-section-522-federal-food-drug-and-cosmetic-act; accessed January 27, 2025

[5] U.S. Food & Drug Administration, "522 Postmarket Surveillance Studies Database," January 27, 2025, https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pss.cfm. See also Bradley Merrill Thompson, "Unpacking Averages: Assessing FDA's Postmarket Surveillance Under Section 522," Epstein, Becker Green, October 1, 2024, https://www.healthlawadvisor.com/unpacking-averages-assessing-fdas-postmarket-surveillance-under-section-522

[6] Warraich HJ, Tazbaz T, Califf RM. FDA Perspective on the Regulation of Artificial Intelligence in Health Care and Biomedicine. JAMA. 2025;333(3):241–247. doi:10.1001/jama.2024.21451