COMMENTARY

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Will artificial intelligence widen the therapeutic gap between children and adults?

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The impending rise of artificial intelligence (AI)-powered healthcare offers exciting hope for improved care and outcomes in children with serious illnesses.[1] The historical precedent in healthcare, however, suggests that advancements in adult care do not necessarily result in proportional progress in pediatrics. This disparity was first noted in the mid-20th century when tragedies that involved drugs with well-studied and known adult safety profiles, such as sulfonamide elixir and thalidomide, resulted in harm to children due to limited pediatric clinical trial inclusion.[2] As a result, legislation in 1962 required drug companies to include package labels that restricted or dissuaded the use of medications in children that were not properly studied in this population.[2] Subsequently, physicians became reluctant to prescribe many medications, and pharmaceutical companies had little incentive to enroll children in trials as an unfavorable result could negatively impact sales in the adult market, and a successful outcome would only marginally increase the market pool.[3] This lack of access led Dr. Harry Shirkey to describe children as "therapeutic orphans" in 1968.[2] After more than half a century of legislation aimed at increasing pediatric representation in research and drug development (Figure 1), enrollment of children in clinical trials remains disproportionately low,[4] with children included in as few as 12% of trials for diseases with a burden equal to, or greater in, the pediatric versus adult population.[5]

The growth of AI in healthcare has the potential to benefit both children and adults, but without proactive steps, this new technology threatens to widen the already existing therapeutic gap between adults and children. Just as the safety of pharmaceuticals cannot be assumed in children given they are not simply "little adults",[6] this same rationale must be applied to the development of AI tools. It is well recognized that the generalizability of AI models is reflective of the data on which they are trained.[7] Abstracting studies from clinicaltrials.gov that have been completed or are actively recruiting as of August 11, 2023, that include the keywords "Artificial Intelligence" or "Machine Learning", we identified 1426 relevant AI trials. Of these trials, 281 (20%) are indexed to include children within the study population. Of note, the number of these studies that ultimately included children is likely lower, as trials

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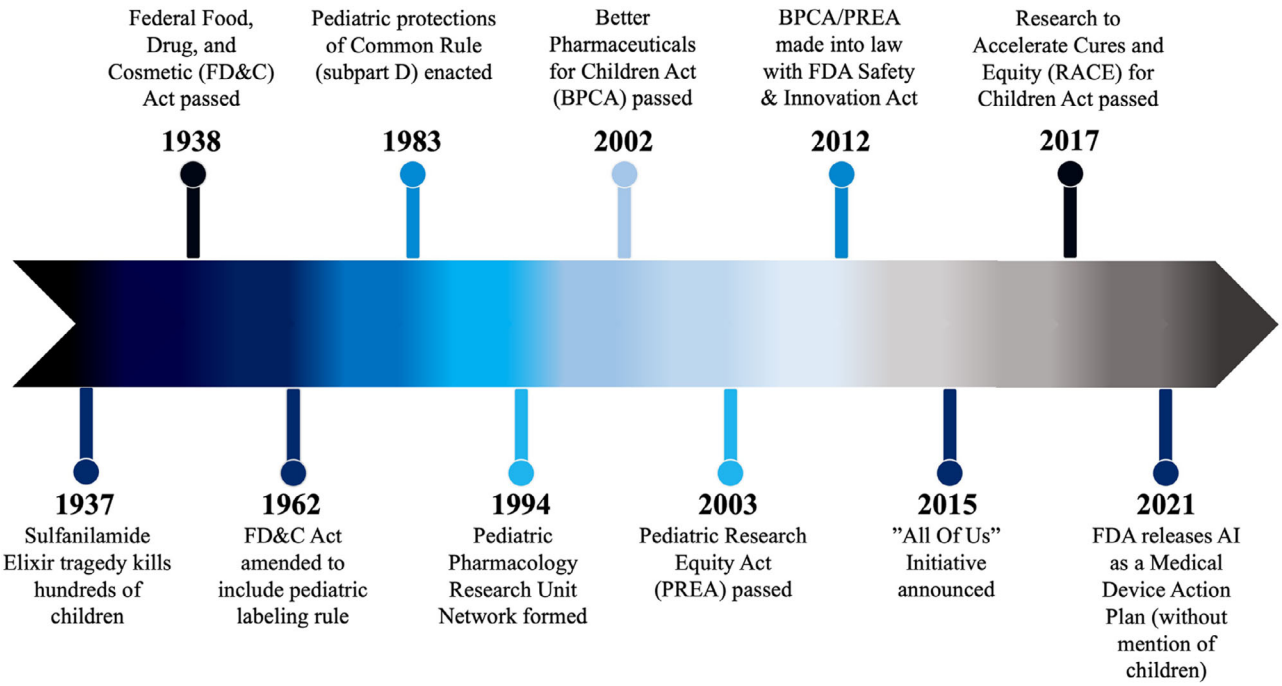

FIGURE 1 Timeline of significant events in pediatric therapeutic orphan history. FDA, Food and Drug Administration.

are included for conditions without relevant pediatric correlates, such as prostate cancer (ie: NCT02943824), coronary artery disease (NCT04146766), and Alzheimer's disease (NCT05569083). Additionally, only 58 (4%) trials were pediatric-specific (no adults included in the recruitment cohort), further highlighting the limited focus on children in these early AI clinical trials.

The insufficient inclusion of children in AI training and development has multiple implications. First, this disparity could result in fewer AI-powered clinical tools available for children. A white paper by the American College of Radiology provides early evidence of this disparity, reporting that of the 200 Food and Drug Administration (FDA) approved AI-powered radiologic devices, only 3% are labeled for pediatric use.[8] Second, a model developed with adult data may have poor predictive value if used in children, such as a recent AI model to detect fractures in adults that was neither reliable nor sensitive when used in children.[9,10] Similarly, a model developed to identify pneumonia in adults underperformed a comparative model developed for children when applied to a pediatric population.[11] While only a few studies to date have specifically evaluated the impact of excluding children from AI development,[9,10] there is strong evidence of bias and poor performance in patients from underrepresented racial, ethnic, and geographic backgrounds as a result of these groups being excluded from model development.[12,13] Even if a disease is present in both adults and children, such as sepsis or pneumonia, the clinical manifestations may be different and cannot be assumed from adult data if children are not included in the development. Moreover, the limited focus on developing models that are relevant to pediatric-specific conditions suggests those with diseases confined to childhood, such as diseases of prematurity and various genetic and metabolic diseases, may not find similar advances as those that present across the lifespan. Including sufficient pediatric data in model development and validation is necessary to ensure children benefit from and are not harmed by these technical advancements. Below, we briefly highlight three potential contributors to this disparity of pediatric inclusion in AI research and development and propose possible mitigation strategies.

PROBLEM 1: LACK OF AWARENESS

While the harm of excluding children from clinical research was brought to light in the mid-20th century through tragedy and legislation, the broader impact of excluding children from AI development is still nascent.[8] At baseline, clinicians report limited understanding of AI principles and the implications of its impending role in patient care,[14] with fewer than half of clinicians possessing basic knowledge of AI,[15] and only 6% of medical students confident in explaining the risks and benefits of AI.[16] At a larger scale, the FDA has recently prioritized developing unbiased models in terms of race, ethnicity, and socioeconomic status, however, there is no mention of children in this discussion.[17] If action is not taken to increase clinician awareness and promote policy prioritization of the importance of AI in pediatrics, the quality of care received by children will suffer.

Solution 1

Just as pediatricians learn to use a wide array of diagnostic and therapeutic tools in their training, so too should fundamentals of AI be incorporated into all levels of medical education. It is not that pediatricians should become computer scientists, but should rather be equipped in medical school and beyond to critically assess new models.[18] This includes becoming familiar with common AI terminology, understanding the appropriate role of various AI-powered tools in clinical decision-making, and evaluating the appropriateness of a given model for use in the pediatric population.[19] Additionally, advocacy by professional organizations, both pediatric and subspecialty-specific, is imperative for the development of policies to protect children, while simultaneously facilitating their inclusion in AI research. The American Academy of Pediatrics, for example, has played a leading role in child-health advocacy that has impacted policy change at a national level,[20] though the safe inclusion of children in AI development has yet to be included among these initiatives.[21] The American College of Radiology has recently taken a strong stance supporting the inclusion of children in AI development,[8] a position if adopted by other organizations can play a defining role in broader AI policy development, such as in the FDA's plans and guidelines for AI roll-out.[17]

PROBLEM 2: LACK OF INVESTMENT

Companies developing AI-powered tools will likely aim to enter a market with abundant data and a large pool of consumers/patients anticipating the products' release. Given the rarity of many pediatric diseases and the smaller proportion of ill children versus adults in the general population, a lack of investment in AI for childhood diseases could threaten to recapitulate historical patterns seen in drug development and approval.[2] The developer seeking to design an AI model to identify novel cancer therapeutics, for example, will be more inclined to target adult lung carcinoma, a disease with over 234 000 new diagnoses in the United States yearly,[17] rather than the most common pediatric solid tumor, neuroblastoma, which has about 700 new diagnoses per year.[22] Moreover, as a vulnerable population, including children in the design and application of AI-powered tools is a more time-consuming and higher-risk endeavor for developers,[23] potentially compounding the dissuading market influences.

Solution 2

In 2002, the Better Pharmaceutical for Children Act was approved as a policy to provide limited market exclusivity for pharmaceutical companies that conducted pediatric clinical trials.[4] Subsequently, the Pediatric Research Equity Act in 2003 mandated that all new drug applications, biologics, and supplements provide pediatric testing data.[4] This carrot-and-stick approach proved effective at improving pediatric pharmaceutical trial inclusion. Amending these laws to include healthcare-related AI may offer robust motivation for commercial engagement to mitigate the developing disparity. The Research to Accelerate Cure and Equity Act passed in 2017 required all new targeted therapies with a potential pediatric use to include children in the trials without exemption, a model which if adapted to AI development would help promote the inclusion of children in device development for conditions with relevant pediatric correlates.[24] Additionally, the National Institutes of Health (NIH) currently has an "Inclusion across the lifespan" requirement for grant applications,[25] a policy if closely enforced in AI-related funding decisions has the potential to foster relevant research with children in mind.

PROBLEM 3: LACK OF DATA

Perhaps the most pervasive barrier to the inclusion of children in AI is the lack of pediatric data available for model development and evaluation.[1] The reasons for this limited data are multifactorial; only 22% of the US population is younger than 18 years,[26] children are less likely to be hospitalized than adults (where most actionable clinical data are collected),[27] and many pediatric diseases are rarer and distinct from adult diseases.[28] Further, few public databases exist for children, and clinical data are often buried within institutional medical records, making access to a sufficient volume of high quality multi-institutional data challenging.[28] For example, of the 29 publicly available chest radiograph databases, only seven include any pediatric data, and two are exclusively for children.[29] Moreover, companies employing AI in health care, such as Google Health's Deep Mind and IBM's Watson Health, have published landmark studies consisting of solely adult data, suggesting the landscape of pediatric representation among proprietary data is similarly limited.[30–32]

Solution 3

One method of streamlining pediatric data acquisition is the use of learning health systems, such as PedsNET, a networked institutional architecture that has been successfully piloted and allows for observational research and clinical trials to be completed in routine clinical encounters.[28] Additionally, creating robust publicly available clinical databases, such as those available for adults,[33,34] can further increase developer access to pediatric data. Early efforts include a recent $50-million allocation for the Childhood Cancer Data Initiative at the NIH,[35] and the more established Kids Inpatient Database, containing health systems data from roughly 7 million pediatric hospitalizations. While these efforts are positive steps, further proactive

efforts to establish additional multi-institutional databases across a wide array of diseases and datatypes (genomic, routine laboratory, clinical outcomes, etc) will be critical for achieving the sample sizes and diversity of data necessary to establish robust AI models.[25] As of January 25, 2023, the NIH has made efforts to increase data availability by requiring new grant applications to include a data sharing budget and plan, however, early evidence suggests the intended open data sharing has not yet materialized in implicated publications.[36] Further monitoring of compliance to this policy in subsequent grant considerations would be prudent, and further policy could facilitate these data to be deposited in a public repository, as is common practice in genomics.[37]

ACKNOWLEDGING RISKS OF AI

As we enumerate the need to ensure children are not left behind in AI development, we must also acknowledge the potential harms and problems with including children in AI research. As the efficacy of AI in healthcare slowly emerges, establishing clear guidelines and regulations around the use of pediatric data will be essential. Currently, children are considered a protected population in clinical research according to subpart D of the common rule, which should continue to hold as they are integrated into AI research and development.[38] Inherently there will be known and unknown risks to children participating in these trials, including data breaches, emotional and psychological distress, or even physical harm if the algorithm is inaccurate, necessitating a need for clear consent and assent with the guardians and patients, respectively.[39] For example, when considering sharing data with commercial developers, even data that are de-identified present a lingering risk of privacy breaches when large datasets are used,[40] because AI could develop the ability to "re-identify" individuals despite removal of Health Insurance Portability and Accountability Act identifiers. Moreover, while commercialization of pediatric data may increase the number of models applicable for children, these avenues may not offer the same protections for children, nor will a company's primary interests necessarily align with that of the patient and family.[41] While no official guidelines have yet been developed for pediatric inclusion in AI, a recent framework called ACCEPT-AI outlines important considerations for safely including children in these developments, offering recommendations that can be used independently or integrated into existing/future AI guidelines.[39] Researchers and regulatory bodies must anticipate and address these issues so children are not harmed by reckless inclusion nor excluded from potential future benefits of AI development. Furthermore, the National Academy of Medicine is developing recommendations for a governance framework for AI use in medicine.[42] This governance structure must include pediatric-specific concerns to mitigate these potential harms to children in the future.

CONCLUSION

While this commentary does not aim to be an exhaustive review, it is clear from the current landscape of AI clinical trials that applications toward child health are lacking relative to adults, and failure to include children could result in suboptimal AI tools for this population in the future. Without proactively including children in model development and implementation we risk further cementing children in their status as therapeutic orphans. By increasing awareness through education and advocacy, providing proper incentives and mandates to developers and clinicians, and streamlining data acquisition, however, AI can instead serve as a powerful tool in pediatrics, and potentially play a role in narrowing the therapeutic gap between children and adults.

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CONFLICT OF INTEREST

Dr. Kodish serves on the Data Sharing Review Board for Incyte and receives compensation for this activity. All other authors declare no conflict of interest.

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