Beyond the randomized clinical trial: innovative data science to close the pediatric evidence gap

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Abstract

Despite the application of advanced statistical and pharmacometric approaches to pediatric trial data, a large pediatric evidence gap still remains. Here, we discuss how to collect more data from children by using real-world data from electronic health records, mobile applications, wearables, and social media. The large datasets collected with these approaches enable, and may demand, the use of artificial intelligence and machine learning to allow the data to be analyzed for decision-making. Applications of this approach are presented, which include the prediction of future clinical complications, medical image analysis, identification of new pediatric endpoints and biomarkers, the prediction of treatment non-responders and the prediction of placebo-responders for trial enrichment. Finally, we discuss how to bring machine learning from science to pediatric clinical practice. We conclude that advantage should be taken of the current opportunities offered by innovations in data science and machine learning to close the pediatric evidence gap.

Introduction

Historically, the evidence basis of pediatric treatments has lagged behind those in adult patients. A key aspect of this is the lack of pediatric data, which originates from the logistic, ethical and legal challenges of performing clinical investigations in children.(1) Additionally, the pediatric population is more heterogeneous than the adult population, with maturational differences in pharmacokinetics, pharmacodynamics and disease etiology across the pediatric age-range from preterm neonates to adolescents.(1) Consequently, data collected in children within a narrow age-range might still leave us with limited information regarding the treatment of children outside the studied age-range. Finally, similar to other patient populations, optimal treatment will also differ for individuals within the same age-group for instance because of obesity, genetic polymorphisms or disease severity and should be improved with more personalized treatment approaches.(2)

To date, academic hospitals and industry perform clinical studies and randomized clinical trials (RCTs) on current and new drugs in children. Many academic studies focus on commonly used drugs in hospitalized patients, as the in-patient situation facilitates the collection of data. Generally, to minimize the study burden on pediatric subjects, the frequency and amount of data collection is limited and often not standardized. For example, to limit the number of venous samples, drug concentrations in plasma might be quantified in scavenged samples that were taken as part of standard of care.(3) Population pharmacometric modelling approaches have been successfully used to deal with these unbalanced data to better understand pediatric pharmacology.(1, 3) More recently, we have seen an increased use of mechanistic or physiologically-based models, which leverage prior knowledge regarding the physiological changes in organ weight, blood flow, and protein expression during a child's life.(2, 4, 5) An important aspect of such models is their improved predictive performance when used to extrapolate from adults to children.(6)

These pharmacometric modelling approaches are now, despite limited data, being used with success to support neonatal and pediatric drug development as well as dosing of commonly used off-label drugs.(1, 4, 7) However, recent failures of randomized clinical trials in children have taught us that there is more to these studies than confirming model-based predictions.(8) These failures have been attributed to different reasons such as an increased placebo effect in children, different disease etiology compared to adults, and inadequate dose selection.(8) Another important cause is the failure to recruit sufficient patients, which can force investigators to costly increases of the study duration or even premature termination of a study due to low feasibility of recruiting the target sample size.(9, 10) Failed drug trials—and the general lack of pediatric clinical trials being performed particularly in primary health care—contribute to the high prevalence of off-label drug use in children, especially in the first years of life.(11) It is clear that despite

the advances in approaches to data collection and analysis, a large need for additional research in pediatrics still remains.

To tackle the limitations of conventional clinical research, we need to move beyond the RCTs and their analysis with traditional statistical and advanced pharmacometric techniques. In this narrative review, we will discuss novel approaches to collecting data in pediatric patients to get more information from both clinical trials and real-world data. In addition, we will discuss how large datasets that are derived from new data collection approaches enable, and may demand, the use of innovative data science approaches such as machine learning. Finally, we will discuss both applications and challenges to the widespread use of machine learning in pediatric medicine. Together, these innovations have the potential to greatly support our ability to generate high quality evidence to guide optimal pediatric clinical care, thereby closing the pediatric evidence gap.

Advances in pediatric data collection

Improving our capacity for pediatric data collection is necessary for closing the pediatric evidence gap. Pediatric (randomized) clinical studies are costly and time-consuming to perform, and a sole reliance on these studies may limit our capacity for medical research in children. These studies are generally site-centric, meaning that most data is collected in a hospital or physical study site. Figure 1 illustrates how the capacity for pediatric data collection can be increased by moving beyond site-centric pediatric studies towards real-world data and new techniques for patient-centric data collection.(12) Below we elaborate on the different opportunities and challenges (ethical and privacy) of these advances in data collection in pediatrics.

Real-world data collection

The collection of real-world data through electronic health records (EHRs) has sharply increased in the last decade, which opens up an unprecedented potential for data collection with more subjects, more variables, and lower costs.(13) The use of EHR data for research purposes comes with its own set of challenges, due to the large amount of data and variables to be analyzed. Machine learning techniques are often required to maximize the information extracted from EHR records. In addition to large amounts of structured data, a part of the information in EHR is hidden in clinical or lab notes, which complicates data analysis when this information is required to answer a particular question.(12)

To extract information from such notes into structured data, techniques like natural language processing may provide a great opportunity for answering pediatric research questions.(14, 15) These techniques enable analyses that would be impossible to perform on the text data itself when it would be too time-consuming to do a manual extraction of the relevant features from the text data. For example, in radiology,

natural language processing was used to automatically notate whether a certain condition or finding is mentioned within the text of the report.(16) In another example, Liang and others used natural language processing to allow the use of unstructured information from EHR for the development of a deep learning model for automatic pediatric diagnoses that surpassed the accuracy of junior, but not senior, physicians.(17) Finally, the data extracted using natural language processing might be required to identify patients eligible for inclusion in cohorts for observational research.(15)

While effectiveness research with real-world data can be problematic due to the difficulty in controlling for confounding variables and non-randomized treatment decisions, real-world data offer many other opportunities.(12, 18, 19) First, real-world data might be used to generate or select hypotheses on the most effective treatment that can then be tested in a RCT. Alternatively, real-world data might be used to confirm that the findings in a well-controlled RCT also apply to the wider, more heterogeneous pediatric population or establish that some subpopulations require additional research.(18) Additionally, real-world data can also be used to better characterize patients outside clinical studies as natural history cohorts which can subsequently be used as an external control to replace placebo arms in pediatric trials.(19) While externally-controlled studies require additional considerations to deal with potential biases compared to traditional RCTs, this approach might provide an opportunity for performing studies in cases where sufficiently powered RCTs are difficult to perform due to rarity of the indication or reluctance of parents to consent to a placebo-controlled trial.(19-21) Finally, real-world data may be more suitable than RCTs for answering drug safety questions regarding rare adverse effects or adverse effects that present themselves years after the initial drug exposure.(18, 22)

To deliver the best medical practice tomorrow, it is important that we harness the full potential of the data collected today. At the moment, data in EHR is still primarily collected for medical practice, and may sometimes be ill-suited for secondary use as research data. This is compounded by the fact that physicians are primarily responsible for treating patients and not for generating high-quality research data.(18) In a learning healthcare system, real-world data are not only collected to treat the individual patient, but also readily usable to improve clinical practice by contributing to the generation of knowledge and innovations.(18, 23) Examples of initiatives include the PEDSnet learning healthcare system, a large clinical data research network that currently holds data of over six million children from 2009 onwards and has enabled the generating of real-world evidence in a variety of clinical settings, including obesity, leukemia and long-term safety of (maternal) drug use.(24) Also important are initiatives like the European EHR4CR project(25) that support the integration of data from different EHR systems, as this allows the creation of larger datasets, and the external validation of findings in datasets from different sites.(13, 18)

Patient-centric data collection

In addition to data from site-centric RCTs, in which most data is collected in one or more physical study sites(22), the collection of patient-centric data has the potential to increase the capacity for data collection (Figure 1).(22, 23) Patient-centric data refers to data collected from the patient at home or during other parts of their daily routine. Depending on the context, data could be collected using mobile applications, wearables and social media. A specific advantage of patient-centric data is the increase of study data without increasing the study burden associated with additional study visits that may in the case of children affect their parents or caregivers as well. The opportunities of patient-centric data collection are particularly important for studying chronic diseases in children that do not require hospitalization or frequent hospital check-ups as part of their treatment. Another potential application would be the long-term follow-up of previously hospitalized patients.

Mobile applications

In its simplest form, a mobile application might be an electronic diary, designed to collect self-reported outcomes which can be reported by children when they are beyond a certain age or by the parents in case of younger children. Compared to a paper diary, electronic diaries are reported to improve compliance with alerts, and to reduce the risk of errors during data entry.(26) In other cases, the primary aim of the application is to promote healthy behavior in the child through motivation or education, for example in applications that help older children with self-management of asthma or type 1 diabetes.(27) The interactions by the child and/or their parents with these applications may offer great opportunities for data collection.

Wearables

The use of wearables creates the possibility of continuous data collection in an at-home setting, which supports characterizing the intra- and inter-individual variability in disease and drug response, as well as quantifying exposure-response relationships for drugs in the pediatric population.(28) The latter is especially true if the clinical outcome or a surrogate endpoint can be quantified at home. Similar to mobile applications, the wearable itself might not only be used to collect data, but also to motivate desirable behavior. For example, Hooke *et al*. evaluate the use of activity trackers to promote physical activity in children with acute lymphoblastic leukemia in an effort to reduce treatment-induced fatigue.(29)

Wearables can also include biochemical sensors to non-invasively measure electrolytes, metabolites and proteins in an at-home setting. Wearables worn on the skin can be used to measure analytes directly in sweat, but can also non-invasively extract analytes such as proteins and glucose from the skin's interstitial fluid.(30) While many analytes of interest cannot yet be measured using wearable sensors, future

developments in this area will likely expand the applicability of these techniques for patient-centric collection of pediatric biochemical data.

While these wearables may provide great opportunities for data collection in otherwise difficult to study patient populations like children, it is important to note that the field of clinical application of wearables is still in its infancy when we consider its clinical utility, even for adult patients.(31) There are a variety of challenges that need to be met in scientific, logistic, ethical and privacy aspects, as covered extensively by a recent review by Izmailova *et al*.(26) For example, commercially available wearables frequently do not report the raw data, but only the summary or secondary data that has been processed with undisclosed and proprietary algorithms. This complicates the interpretation of wearable data, especially when collecting data from multiple types of wearables with differing terminology and data standards. For the pediatric application of wearables, additional validation will be required to ensure devices are also fit-for-purpose for children of a particular age-group, and whether the data measured with these devices have the same relevance for the clinical outcome. Finally, the use of wearables by study participants might affect their behavior (e.g. they might walk more when wearing a wearable that tracks their daily step count), which could be a problem depending on the research question and design of the study. Despite these challenges, their ability for continuous data collection at low burden to the patient could provide a great opportunity in the effort to fill the pediatric evidence gap, especially if the link can be made to clinical outcomes and biomarkers.

Social media data

The use of social media has increased dramatically over the last decade. It has been reported that children that use medication might use these platforms to share experiences that are not communicated to their healthcare practitioner.(32) As such, social media might contain information useful to pediatric pharmacovigilance that is not available elsewhere. Recent studies explored patient reports of adverse effects on social media platforms such as Twitter(33) and patient fora.(34) This information was explored by counting how many times different adverse effects were mentioned in combination with a certain drug. These studies could serve as a method for signal detection of rare adverse effects, or to supplement information on known adverse effects that are underestimated in children.

At the moment, the use of social media data for pharmacovigilance is still in its infancy. In a recent study from the IMI project WEB-RADR, natural language processing techniques that were used to automatically label social media posts with drugs and adverse effects combinations were only correct in about 40% of the cases.(35) Using these imprecise techniques, the authors found no indication that posts on general social media platforms like Facebook and Twitter would have an added value to traditional methods of pharmacovigilance. Another challenge identified in the WEB-RADR project is that some drugs are hardly

discussed in social media posts, thus having little to no potential for advancing pharmacovigilance.(35) The use of social media posts in pharmacovigilance might be more beneficial with further advances in natural language processing and by directing research efforts towards patient fora which would carry a higher percentage of relevant posts than general social media platforms.

Ethical and privacy aspects of pediatric data collection

Innovations in data collection will support our ability to effectively treat pediatric patients in the future, especially when the collected data is FAIR (Findable, Accessible, Interoperable, Reusable) to allow secondary analyses to be performed by the broader research community. These benefits need to be balanced with the right to privacy of the patients whose data is used in this research. Maintaining and further developing ethical and data security standards are crucial to ensure ongoing support by patients and their parents of data collection for research purposes.(36) Maintaining data security is particularly challenging for patient-centric data collection where sensitive data are collected on a mobile phone or wearable, as data leaks could occur when the device is lost or during data transfer from the device to the central database.

Appropriate security measures need to be in place to minimize the risk of violating the patient's privacy. In this respect, the removal of identifying information can contribute to maintain privacy when using data for research purposes. However, when the research question requires that data from different databases are linked, some form of patient identifier might be needed to do this.(37) A potential solution to this issue is to add a small amount of noise to the data to ensure patients cannot be identified.(37) Another interesting approach is to 'share the answers, not the data'. In this case, a data analysis or model might be run on the data, and only the aggregated results are returned to the researchers.

The issue of consent is particularly complex for pediatrics. Depending on the age of the child, (written) informed consent might be obtained from the parents, the child or both. However, in the case of re-use of the data, there are questions that remain unanswered.(38) Can the parental informed consent be considered to be valid for re-use of the data years later, even if the patient has since reached adolescence or adulthood? It is recognized that retrospectively obtaining informed consent for large datasets of observational real-world data could likely result in lengthy and costly procedures, which would limit their use in practice.(37) However, for some observational analyses of de-identified data, the need for informed consent can be waived by institutional review board, if appropriate privacy measures are taken.(37)

Machine Learning for evidence generation

Innovations in pediatric data collections provide great opportunities for research and hold great promise in closing the pediatric evidence gap, but this promise can only be fulfilled if these data are used effectively to address clinically relevant questions. To do so is challenging due to the size and complexity of datasets

collected with these novel techniques. Collecting new types of data will therefore go hand in hand with the increasing use of artificial intelligence and machine learning in pediatrics.

The term machine learning is often used interchangeably with the term artificial intelligence (AI).AI is an area in the discipline of computer science that aims to create intelligently perceiving, reasoning, and acting machines. A subset of AI is machine learning, which encompasses a wide range of advanced data analysis techniques. Depending on techniques used, machine learning algorithms can predict both numerical outcomes (e.g. a disease severity score) or class labels (e.g. healthy versus diseased).

With respect to the different classes of machine learning techniques, linear models are an easy to interpret class of machine learning techniques for the analysis of structured data (Figure 2). Linear regression, which is the most common linear modelling technique, can be used for both prediction and hypothesis testing, but is not suitable when there are many variables in the dataset. In those cases, penalized regression techniques can be used, which have a penalty term to constrain overfitting. Examples of such techniques include LASSO(39) and ridge regression.(40) A second class of machine learning techniques are tree-based models, such as Classification And Regression Trees(41) and random forests.(42) Depending on specific type of technique, the output of a tree-based model might be a form of a decision tree, which can still be relatively well explained. A third class of machine learning techniques is deep learning or deep neural networks. Deep learning has been used extensively for image analysis and text mining outside the medical world, and has recently started to be used on medical images and electronic health records (Figure 2).(43) Complex deep learning models can have a good predictive performance when dealing with unstructured data due to flexibility of such models (Figure 2). However, deep learning models are often difficult to explain, as it is generally difficult to understand how the input data leads to the model prediction.

Of note, it is important to recognize that machine learning will supplement, and not replace, traditional statistics in pediatric research. The use of traditional statistical tests or linear models might be more appropriate if the primary goal of the analysis is not to obtain a prediction model.(44, 45) This includes situations when the goal of the analysis is hypothesis testing ('Does the treatment work better than placebo?') or estimation of treatment effect ('What effect does the treatment have on the outcome?'). However, there are various clinical problems in which the predictions made by machine learning can contribute to closing the pediatric evidence gap, as will be illustrated with examples in the next section.

Applications of machine learning in pediatrics

The opportunities offered by the various machine learning techniques can benefit pediatric practice in a variety of ways. In this section, we will discuss different applications of machine learning in pediatrics including: the prediction of future clinical complications, medical image analysis, identification of new

pediatric endpoints and biomarkers, prediction of treatment non-responders, and the prediction of placebo-responders to allow pediatric trial enrichment.

Predicting future clinical complications

The ability to predict clinical complications in the future can be used to deliver more personalized medicine in pediatrics. For this purpose, machine learning plays a crucial role due to its improved potential predictive performance compared to traditional statistical methods, especially when the data are unstructured or otherwise complex. Children that are predicted to be at high risk for a certain event, can subsequently be monitored and treated more intensively. In recent research, new algorithms have been explored to make good predictions using data from previous studies or real-world data. Box 1 shows three case studies in which machine learning techniques were used to make predictions about future clinical complications such as childhood obesity(46), late onset sepsis(47) and neonatal hyperbilirubinemia(48).

Box 1. Prediction of clinical complications in pediatrics using machine learning

Case study 1. Childhood obesity

Dugan *et al.* (2015) explored predictors of childhood obesity, with the aim of eventually being able to provide targeted obesity prevention for high-risk children. The answers on a dynamic questionnaire and measurements of clinical staff were mined from over 7000 children below the age of 2 years. These features were used to predict the prevalence of obesity after their second birthday. Using tree-based machine learning, an accurate model predicting childhood obesity was obtained, which included predictors like pre-existing obesity, ethnicity, height and maternal depression.

Case study 2. Neonatal sepsis

Mani *et al.* (2014) evaluated the usefulness of different classification algorithms to predict late onset sepsis in neonates, using early results of laboratory tests and nursing observations. The best classification algorithm surpassed the clinician in both the sensitivity and specificity of predicting neonatal sepsis. After validation, clinical implementation could allow earlier treatment of sepsis while reducing the number of patients unnecessarily treated with antibiotics.

Case study 3. Neonatal hyperbilirubinemia

Daunhawer *et al.* (2019) used machine learning techniques to predict neonatal hyperbilirubinemia. An ensemble classifier combining the logistic regression LASSO and random forests was able to predict accurately whether a neonate would undergo phototherapy treatment in the next 48 hours. The predictions were made using clinical variables, such as birth weight and health information about the mother. This model could support a more personalized bilirubin monitoring approach, with more intensive monitoring of high-risk patients.

Medical image analysis

Deep learning models have been particularly effective in image analysis, mainly in radiology.(49) A deep learning model can learn to classify images as healthy or diseased, or can notate the areas in the image that correspond to organs or other anatomical structures. For example, a deep learning model was able to

identify the segmentation of white matter, grey matter and cerebrospinal fluid in the brains of babies.(50) The automation of these tasks with a deep learning model can reduce the time spent on an image by limiting the radiologist's task to checking and adjusting the lines drawn by the algorithm. In another example, a deep learning model was able to identify the skeletal maturity of children by assessing hand radiographs.(51) Another common application is the detection of malignant tumors in medical images, which could serve as a second opinion to detect malignancies that might have been missed by the radiologist.(52, 53)

In addition to increasing efficiency, deep learning models could also extract information from image data that is not included in the radiologist report. This would include features that are too complex and time-consuming to extract manually or features that are not currently being used in clinical decision making.(54) With automated extraction of additional information from medical images, deep learning-based image analysis can be used to perform research on imaging-based pediatric biomarkers that would not be feasible with manual image analysis.

Identifying endpoints and biomarkers in pediatrics

The development and validation of pharmacodynamic endpoints for children is recognized as an important methodological step in closing the evidence gap of pediatric medicine.(55) Having suitable disease-specific pharmacodynamic endpoints for children is essential for demonstrating efficacy and for establishing the exposure-response relationship of drugs needed for pediatric drug labeling. Additionally, these measures of patient disease severity or well-being can guide treatment decisions in clinical practice. For this, the efficacy and safety endpoints used in adults may not be fit-for-purpose across the pediatric age-range: the clinical endpoint might not occur until later in life, might not be directly measurable, or the clinical presentation of the disease might differ too much from any adult counterpart.(55)

Machine learning can be used in biomarker and endpoint discovery by performing variable selection and dimension-reduction when there are multiple variables considered to be potentially relevant for pediatric outcome. For example, Hartley *et al.* used EEG data to derive a summary measure for nociceptive brain activity in infants.(56) In this example, the EEG-based measure of pain was learned from the context, i.e. by comparing the response profiles after non-noxious or noxious stimulation. In another example, a supervised learning approach was used to derive a measure of iatrogenic withdrawal severity in children by combined analysis of nurse's expert opinion of the child's withdrawal severity, and the observed withdrawal symptoms.(57) Finally, machine learning may be used to identify early biomarkers that correspond to long-term clinical endpoints or quality-of-life.(58) For example, a machine learning tool is currently being developed to analyze cough sound data as a digital biomarker of acute respiratory disease in children.(59)

Predicting treatment responders

Machine learning techniques can also be used to identify non-responders, i.e. children that are unlikely to respond to a particular treatment. The clinical benefit lies in avoiding therapy that might give adverse effects at low chance of beneficial effects, as well as reducing the need for trial-and-error approaches for treatment personalization.(60)

For the adults, machine learning techniques have been used to predict non-responders to drug treatment in different settings, including oncology, immunology, and postoperative pain.(60-62) Depending on the similarity of disease between adults and children, and the explicability and the biological plausibility of the machine learning model, models developed in adults might be also applicable in the pediatric setting after validation. In other cases, the pediatric pathophysiology might be too different or the disease might be absent in adults. In this case, efforts would be warranted to develop new machine learning models to predict drug response in children, so that they can also benefit from these innovations.

Predicting placebo responders to improve trial success

Prospective (randomized) clinical trials remain the gold standard to get drugs registered for the pediatric population. However, some of these RCTs fail to demonstrate efficacy in children.(8) These failures have been attributed to a numbers of reasons, one of which is the high placebo response observed in indications such as depression, migraine, and bipolar disorder.(8) A high placebo response would limit the ability of a trial to demonstrate efficacy or would require a very large sample size to do so. Additionally, it has been shown that younger children tend to have a stronger placebo response than older children.(63) This would make it especially difficult to demonstrate efficacy in younger children, which is problematic considering that the off-label drug use is highest in children in the first year of life.(11)

One way to limit the impact of placebo response on trial outcomes, would be to identify baseline predictors of placebo response so that trials can be enriched pre-randomization with subjects that are less likely to respond strongly to placebo.(8) This strategy has been used in pediatric trials, resulting for example in the successful application for a pediatric indication of rizatriptan for acute treatment of migraine.(64) For adults, it has been proposed machine learning techniques may have better predictive power when using multiple variables to predict placebo response, as was demonstrated for depression in a geriatric population.(65) The use of machine learning techniques to reduce the placebo response in pediatric trials, might therefore increase the success rate of pediatric drug trials and support pediatric drug labeling.

Bringing machine learning to pediatric practice

While promising, more work needs to be done before the machine learning applications mentioned in the previous section are ready for widespread clinical use in children. Methods for predicting placebo response

need to be developed for different therapeutic indications, and prove their worth in practice by increasing the success of pediatric registration trials (Figure 3, left column). Biomarkers and endpoints suggested by machine learning need to be validated, and supported by the relevant stakeholders (Figure 3, middle column). When this is the case, having better pediatric endpoints and biomarkers will impact not only pediatric practice, but also pediatric research. Considerable work is also required to bring a machine learning model to the clinic as a medical decision support tool, as this requires extensive external validation of the model, the development of a user-friendly software tool, and assessment of the impact of the use of this tool in clinical practice (Figure 3, right column). Below, we will discuss the issue of validation of machine learning models for clinical use, and the particular challenges of implementing medical decision support tools in pediatric clinical practice.

Validation for clinical use in pediatrics

Machine learning models enable us to use complex data to achieve improved predictions of health and disease in children compared with traditional methods. However, it is important that the trained model does not "overfit" the data. An overfitted machine learning model has good predictive performance in the dataset it was trained on, but poor performance when predicting for new cases. Validation of the model on an independent test data set is therefore essential to ensure the scientific quality and the clinical utility of the model (Figure 3, right column). Obtaining suitable datasets for this external validation can be challenging, especially in pediatric research, which underlines the importance of efforts to promote data sharing and the use of real-world data for research purposes.(66)

Considering the heterogeneity of the pediatric population aged 0 to 18 years, it is also important to consider that a model might have a good predictive performance for children in a particular age-group, but a poor performance for others (e.g. preterm neonates vs term neonates). This risk is particularly high if certain age-groups are underrepresented or absent in the dataset used to develop the model.(67) Transparency about the validity of the model, and for which pediatric population this validity has been shown, is therefore crucial.

Finally, it is important to recognize that even externally-validated model predictions are not guaranteed to improve patient outcome when used in clinical practice. Some have therefore proposed that the clinical use of models as medical decision support tools should supported by studies that demonstrate their impact on relevant clinical endpoints (Figure 3, right column).(68) Considering the added difficulty to perform such trials in children, we argue that it is important to consider the need for such trials on a case-by-case basis, depending on the potential risk and benefits of the use (and non-use) of machine learning tools in clinical decision making. In cases where dedicated pediatric trials are not feasible, modeling and simulation

workflows used in pharmacometrics might be used to assess the likely clinical benefit-risk ratio of decision support tools by integrating available data from adult and pediatric patients.(69)

Implementation of medical decision support tools

Implementation of findings from machine learning studies into pediatric clinical practice will not happen without focused efforts and close involvement of the various stakeholders. Currently, the widespread clinical implementation of scientific evidence is a lengthy process (>15 years on average) and only achieved in about half of the cases.(70) Wittmeier and colleagues have argued in favor of systematic step-wise approaches to bring scientific knowledge to pediatric clinical practice. An important aspect of this is to engage in activities that have been shown to successfully support implementation, such as educational outreach and meetings, use of local opinion leaders, computerized reminders, audit and feedback.(71) For the implementation of machine learning as a medical decision support tool in pediatrics, there are additional challenges to overcome (Figure 3, right column).(36)

Because the predictions or classifications of machine learning tools can incorporate information of multiple variables, they are not as readily integrated in clinical guidelines as knowledge that relies on a single variable (e.g. age or bodyweight) for decision making. Therefore, software packages might be needed so that physicians can easily use models in medical decision making (Figure 3, right column). It is important to stress that such software packages should be quick and simple to use, and ideally linked to the EHR system so that there is no need for error-prone data entry of a large number of variables by the clinician.

The need to integrate machine learning tools into software packages does complicate their implementation, as they can be classified by the FDA as a medical device if the physician is not able to independently evaluate the basis of the recommendation.(72) With complex machine learning models, this is likely the case. Many software packages that provide recommendations based on models obtained with machine learning would therefore require lengthy regulatory approval procedures before they can be used in clinical practice.

In addition, to being easy to use, the advice of the model should be explicable by the clinician. Here, lies a key challenge for machine learning tools, especially for techniques like neural networks which provide more 'black box' predictions.(73) The integration of such 'black box' predictions in clinical decision making is problematic, because it means a departure from the paradigm of evidence-based medicine.(74) Additionally, shared decision making between the patient and physician also requires that decisions supported by machine learning tools can also be explained.(67, 73) Therefore, explicability for both the physician and the patient is likely a requirement for meaningful contributions to the decision process. Ongoing efforts to improve the explicability of complex machine learning models are therefore crucial to support their clinical acceptance and implementation.(75)

Conclusions

Innovations in data collection and analysis could revolutionize many aspects of medical science and clinical practice in the upcoming decades. With the increased use of real-world data within a learning healthcare system and patient-centric data collection there is a potential to significantly expand our capacity for pediatric data collection. There are many useful potential applications of the predictive performance of machine learning models, and future work may integrate these applications with mechanistic modelling to improve understanding of the underlying biology. And even though efforts are required to bring these innovations to the clinic, it is crucial that we capitalize on this opportunity to close the pediatric evidence gap.

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Figure legends

Figure 1. Innovative pediatric data collection beyond the site-centric randomized clinical trial (RCT). Data from these pediatric clinical studies can be supplemented by increased use of real-world pediatric data from electronic health records. Additional information can be obtained without increasing patient burden by using patient-centric data collection tools, such as mobile applications, wearables and social media data. Site-centric RCTs refer to studies in which data collection is limited to one or more hospitals or physical study sites. Patient-centric data refers to data collected from the patient at home or during other parts of their daily routine.

Figure 2. Explicability of the various machine learning techniques. On the far left, linear models have a clear explanation, but require that the data is structured. Linear regression, the most common linear modelling technique, can be used for both prediction and hypothesis testing, but is not suitable when there are many variables in the dataset. On the opposite end of the spectrum, deep learning models are generally difficult to interpret and explain, and not suitable for hypothesis testing. However, due to the flexibility of deep learning models, they are able to handle complex and unstructured data such as image and text data. Depending on the data (structured or unstructured) and the goal of the analysis (raw predictive performance or testing hypotheses), different techniques will be most appropriate.

Figure 3. How applications of machine learning in pediatrics can support pediatric clinical practice.

Site-centric RCT

Advantages
- High degree of control
- High robustness of conclusions
- Low complexity of data analysis

Disadvantages
- High demand on research budget
- Patient recruitment challenging
- Intensive data collection only feasible in hospital
- Strict inclusion and exclusion criteria limit the broad applicability of findings
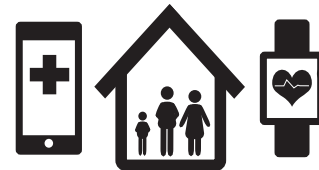
+

Real-world data

Advantages
- Large number of subjects and variables
- Low demand on research budget
- Covers entire patient population

Disadvantages
- Limited control
- Complex data clearning
- Complex data analysis
- Confounding complicates interpretation of results

Patient-centric data

Advantages
- Continuous data collection
- Low patient burden
- Daily life of non-hospitalized patients

Disadvantages
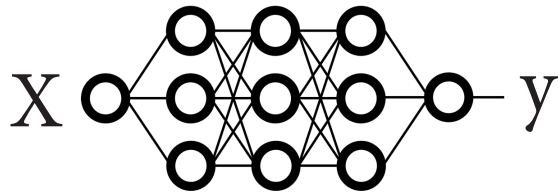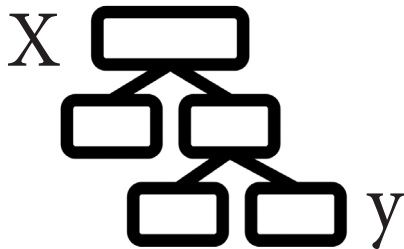- Limited control
- Complex data analysis
- No expert supervision

Linear models   **Tree-based models**   **Deep learning models**

$$y = X\beta$$

Easy to explain   Difficult to explain

Explicability

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┌─────────────────────────────────────────────┐
│              Machine learning                 │
└─────────────────────────────────────────────┘
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- Placebo responder prediction
- Endpoint and biomarker discovery
- Prognosis prediction
- Medical image analysis
- Drug response prediction

Pediatric trial enrichment

Endpoint and biomarker validation

External model validation

Development of medical decision support tool

Support pediatric registration trials

Assess impact of clinical use on clinical outcomes

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┌─────────────────────────────────────────────┐
│         Pediatric clinical practice           │
└─────────────────────────────────────────────┘
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