Automated Enteropathy: Discovering the Potential of Machine Learning in Environmental Enteropathy

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See ''Artificial Intelligence-based Analytics for Diagnosis of Small Bowel Enteropathies and Black Box Feature Detection'' by Syed et al on page 833.

Advances in computational techniques have driven countless recent developments in both research and clinical capacity. Supervised machine learning (1), a term for computational models that learn to provide specific input/output from training data of that same form, has already been the focus of multiple efforts to advance clinical practice, in particular, for use in the analysis of images such as in assessment of radiology and histology (2–4).

Sana Syed et al at the University of Virginia are leaders in the US investigation of environmental enteropathy (EE), otherwise known as environmental enteric dysfunction (EED), a disease felt to be the major global cause of stunted growth (5). EE/EED is endemic to developing nations and felt to be linked to recurrent enteric infection in areas without access to clean water. With a subclinical presentation and no reliable biomarker (6), EE/EED requires a systematized approach to interpreting histologic evidence, an area of utmost importance to ongoing work in addressing a condition affecting hundreds of millions of children. Syed previously collaborated in several other parts of this effort, not least of which included serving on a team attempting to standardize histopathological markers of EE/EED across regions (7).

In this issue, Syed et al (8) explore use of a more intricate model of machine learning known as deep learning, deploying tools called ''Convolutional Neural Networks'' (CNN) to assess digitized images of histological samples and ideally to differentiate between normal tissue and enteropathy caused by EE/EED and celiac disease (CD). Deep learning is a simple, flexible, and surprisingly effective set of modeling components that has received significant investment in recent years in software, hardware, and academic research (1). These algorithms are adept at image analysis, as they remove the need for ''feature engineering'' wherein researchers hand design low-level features used by the model to identify specific components of the image. The implications of success in automating initial histopathological screening are profound for clinical practice broadly but specifically in the context of EE/EED in which trained personnel can often be a rate-limiting step in the areas in which the disease is most prevalent. If successful, this technique and other methods can be applied more broadly to well characterized histopathological conditions, potentially leading to a screening tool for rapid characterization of an intestinal biopsy. Such a tool would have immense clinical impact, improving turnaround time and reliably identifying normal biopsy samples and referring abnormal samples for confirmation by an experienced pathologist. With regard to EE/EED, an automated scoring system provides a high utility tool for future research, allowing for rapid, cost-effective, and standardized histologic scoring to serve as correlation with novel efforts in assessing the impact of shifts in the microbiome or RNAseq efforts in affected patients (9).

Convolutional models such as the authors employ have demonstrated substantial success in image analysis, and this article describes an excellent first step in deploying it for histopathological analysis. Syed et al have achieved impressive results, evaluating 3 different models of deep learning (shallow CNN, resNET50, and multi-zoom resNET50) to generate a combined accuracy of 98.3% in an exclusive classification task between EE/EED, CD, and control samples. They also undertook an effort using the previously utilized ''Grad-CAM'' technique to alleviate the ''black box'' issue, the fact that while a system may be highly accurate, the reasoning behind its decision-making typically remains vague. The ability to characterize the decisions that lead to a classification is both reassuring and intriguing, as it may actually create the ability to identify new histological markers that are either subtle or challenging for pathologists to identify.

The generated accuracy of 98.3% is impressive but comes with some caveats. When dealing with small datasets, such as the one used in this work, it is common for nongeneralizable factors or irrelevant idiosyncrasies to give deep learning models artificially elevated performance numbers (10). In other words, with a small N it is possible for to create false pathways based on irrelevant findings but yielding correct answers. Due to limitations of available biopsy samples, the investigators were not able to provide a large dataset to their CNNs to learn EE characteristics. And while their accuracy is impressive, with a low N (only 48 available EE biopsies), it is hard to determine the significance and reproducibility of this finding with novel samples. This issue will be rapidly remedied as the investigators apply their model more broadly.

By expanding this work and continuing to provide training material from different sources, Syed et al will be able to estimate the accuracies of these methods to higher statistical significance. The use of combined model architectures in this study is also of note, as it exemplifies a technique that may help sustain the high accuracy of this approach as the N increases. Combining models fall under the term ''mixture of experts,'' a method to more reliably characterize images by using a principle similar to the ''wisdom of the crowd.'' By allowing multiple models to assess data, their findings can be aggregated to essentially create a meta-analysis of their conclusions. This approach has shown substantial capability (11), and training additional models to support an expanded ''mixture of experts'' may be of use as their dataset expands.

In summary, this is an important step in the process of developing automated screening tools capable of providing true decision support to our colleagues in pathology. The implications of developing this specific capability in EE/EED are profound, offering both an expansion of histopathological services in developing nations as well as possible research tools for improving our understanding of a condition impacting hundreds of millions of children.

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Received December 11, 2020; accepted February 17, 2021.

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The author reports no conflict of interest.

DOI: 10.1097/MPG.0000000000003115

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High-volume Plasmapheresis in Children With Acute Liver Failure: Another Brick in the Wall in the Current Management?

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See ''Safety of High-Volume Plasmapheresis in Children With Acute Liver Failure'' by Jørgensen et al on page 815.

Pediatric acute liver failure (PALF) is a rare but devastating condition with a transplant-free survival between 10% and 40% depending on etiology (1–3). Significant advances in standard medical treatment (SMT) has seen more patients with ALF recover without the need for liver transplantation. In some cases, however, mortality remains high without liver transplantation because of the sepsis, cerebral edema, and multiple organ failure that follows abrupt loss of hepatic function.

In recent years, we have seen the emergence of extracorporeal liver support systems (ELSS) with the aim of supporting patients with ALF or acute on chronic liver failure (AoLF) as a bridge to spontaneous recovery or successful liver transplantation (4,5). Although various ELSS including albumin dialysis (namely Molecular Adsorbent Recirculating System; MARS), plasmapheresis, and high-volume continuous renal replacement therapy (CRRT) have demonstrated an improvement in biochemical and clinical parameters in patients with ALF, no significant effect on patient survival has been shown (6,7). A recent prospective multicenter randomized controlled trial of 182 adult patients with ALF has shown that high volume plasma exchange (PE) with SMT as compared with SMT alone improved transplant-free survival and was able to modulate the proinflammatory response though removal of damage-associated molecular patterns (DAMPs) (8). Current experience of PE in children are limited to small case series in children with ALF using exchange of plasma volume corresponding to 1.3 to 4 times their estimated plasma volume (9–13).

In this issue of the Journal, Jørgensen et al (14) describe the use of high-volume PE in a group of children presenting with ALF. Between 2012 and 2019, 16 children with ALF and elevated bilirubin >200 μmol/l or toxic hepatitis were treated with 3 consecutive daily sessions of high-volume PE, replacing 10% of body weight with fresh frozen plasma. Among these 16 children, 8 survived without liver transplantation, 2 survived after liver transplantation, and 6 children died. High-volume PE was well tolerated without major side effects. Furthermore, transaminases, bilirubin, and international normalized ratio all decreased during the 3 days of high-volume PE. Because of the broad criteria used for the initiation of high-volume PE, there was significant heterogeneity in the severity of illness between the group of children who survived with their native liver and the group of children who died or required liver transplantation. The children who survived with their native liver had significantly lower liver injury scores, were not listed for transplantation, and a majority of them had no signs of encephalopathy or multiple organ dysfunction at the time of PE treatment. Although it is possible that high-volume PE may have contributed to transplantation-free survival in this group of patients, it may be argued that these children might have recovered with SMT alone.

An ideal ELSS should be able to perform both the synthetic and detoxification function of the liver by removing toxins preventing further aggravation of liver injury, providing a favorable environment for liver regeneration and preventing the development of irreversible neurological damage, multiple organ failure, and uncontrolled infection. The reason for the lack of consistent survival benefit among the different ELSS may be explained by differences in the detoxification function of these systems. It may also be because of the methodological limitations of numerous studies that included heterogenous patient groups with different etiologies and natural histories, as well as the lack of patient stratification according to severity.

Currently, the only definitive treatment for patients with ALF who meet poor prognostic criteria is liver transplantation. Unfortunately, many patients die before a suitable organ is found or are too sick to be on the transplant list. Therefore, the important question for the clinician is to decide, which patient may benefit the most from extracorporeal liver support system as a bridge to recovery or liver transplantation. A first group of patients who may benefit from ELSS are patients with potential liver regeneration capacity. Spontaneous recovery of liver function with supportive management has

Received March 10, 2021; accepted March 21, 2021.
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The authors report no conflicts of interest.

DOI: 10.1097/MPG.0000000000003134