ignore these results for future treatment targets. Considering this, we believe that it is too premature to implement the LUCID strategy in daily clinical practice. However, a subsequent trail studying the effect of a liberal approach on mortality in patients with DM2 patients is justified, taking admission HbA1c into consideration when choosing the glucose target and designing the trial. Probably there is not a one-size-fits-all approach, and a personalized approach may be the way forward also in patients with DM2. ■

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Deep Learning–based Classification of Fibrotic Lung Disease: Can Computer Vision See the Future?

Despite existing diagnostic criteria and guidelines for identifying and classifying fibrotic lung disease such as idiopathic pulmonary fibrosis (IPF) (1, 2), their diagnosis can be challenging. Current guidelines emphasize the role of high-resolution computed tomography (HRCT), and place particular importance on identifying the presence of underling usual interstitial pneumonia (UIP), which suggests a diagnosis of IPF (1). However, this approach is binary: it requires patients be classified based on the predominant pattern on HRCT, while in practice patients may have some evidence of UIP features but a different predominant disease pattern (1, 2). Clinically, current UIP diagnosis also relies on subjective readings of the HRCT that may vary from radiologist to radiologist (3). These issues are of particular concern because of the importance of UIP in identifying patients likely to have faster disease progression and worse prognosis (4–7). Thus, missed or inaccurate diagnosis has the potential to have significant clinical impact, and there has been great interest in

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developing tools to improve the detection and classification of UIP on HRCT (3).

Deep learning is a form of machine learning that utilizes multi-layered, or deep, neural networks to learn from complex data such as imaging. Deep learning based tools have proliferated in radiologic research over the past decade and have shown great promise in the analysis of HRCTs for diseases ranging from lung cancer to IPF (8–10). One of the strengths of deep learning algorithms is that they may capture patterns not seen or ignored by the human eye, potentially improving disease classification and quantification (11).

In this issue of the *Journal*, Walsh and colleagues (pp. 883–891) report the results of their study using the Systematic Objective Fibrotic Imaging Analysis Algorithm (SOFIA), a previously developed and validated deep convolutional neural network tool, to identify UIP in 516 patients from the Australian IPF registry (12, 13). For each participant's HRCT, SOFIA generates 500 unique, 4-slice image montages. Then, for each montage, the device calculates the probabilities for each of 4 categories: definite UIP, probability UIP, indeterminate UIP, and not UIP. These probabilities (which sum to 1.0) are then averaged, and the device provides the patient level probability for each category (13). The investigators then used Cox proportional hazards and logistic regression models to determine the relationships between SOFIA UIP probabilities with transplant-free survival and with 12-month disease progression, respectively. Multiple forms of analysis were performed including using predicted probabilities as continuous measures as well as grouped into categories based on the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) approach. Univariate analyses, bivariable analyses that included both SOFIA based information and expert radiologist assessment, and multivariable models that were additionally adjusted for age, gender, radiologist-defined computed tomography disease severity, and other clinical measures of disease severity, were all performed as well.

In general, the authors found that not only did SOFIA UIP probabilities, both as a continuous variable and into grouped into PIOPED categories, predict transplant free survival and disease progression in univariate analyses, but also when evaluated using bivariable analyses that included radiologist defined disease extent. In fact, in those bivariate analyses only the SOFIA based measures were associated with adverse outcomes, not the radiologist defined disease extent. Similar findings were present in multivariable analyses adjusted for total disease extent and clinical variable associated with adverse outcomes in fibrotic lung disease like age and lung function. Importantly, the predictive utility of SOFIA UIP was maintained in subgroup analyses of patients with UIP on HRCT or histopathology versus and in those with other fibrotic patterns.

A particularly interesting finding of this study was the predictive probability of SOFIA in the subset of patients with indeterminate UIP on HRCT. Using the PIOPED based binning strategy, SOFIA reclassified over a quarter of HRCTs classified as indeterminate UIP by expert radiologists as intermediate, high, or pathognomonic probability of UIP, and this reclassification predicted transplant-free survival in the multivariable model, with a hazard ratio of 1.73 (95% confidence interval, 1.40–2.14) in the indeterminate UIP subgroup. The reclassification of a large proportion of indeterminate UIP HRCT cases is perhaps unsurprising when considering that the interobserver agreement between two radiologists for the ATS/ERS/JRS/ALAT (American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society) criteria is only moderate, even among expert thoracic radiologists with over ten years of experience (3). Still, these results highlight the potential utility of a deep learning model to identify subtle fibrosis patterns and improve clinical diagnosis, especially in indeterminate cases that are more challenging to determine.

Despite this study's many strengths, it has several limitations as well. The number of analyses and comparisons raises the question of multiple testing, and 34.6% of the cohort was receiving antifibrotic therapy, potentially affecting the analysis of transplant-free survival, as patients with more severe disease are more likely to be receiving therapy. Still, the biggest limitations of this work are not unique to this specific study but related to the field of artificial intelligence in medicine more generally. For example, when there are multiple possible algorithms for diagnosing or classifying a disease such as pulmonary fibrosis available, how do we know which to choose? And once one is chosen, who will fund its certification as software as a medical device with regulators, especially when it is unclear who would pay for its clinical use? Finally, who is responsible if the algorithm is wrong and misdiagnoses a patient as having a disease when they do not, or vice versa? Before a deep learning model like SOFIA is brought to the clinical setting, these questions and others need answering. In the meantime, work such as this by Walsh and colleagues demonstrates the potential power of deep learning in medicine and the need to answer these difficult questions so that patients can benefit from the insight artificial intelligence can provide. ■

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The Value of Chest Radiography in Tuberculosis Preventive Treatment Screening in Children and Adolescents

Despite existing guidelines and strong commitments to increase tuberculosis preventive treatment (TPT) uptake, the World Health Organization (WHO) estimates that less than one-third of young children (<5 yr) who had household contact with an infectious tuberculosis (TB) case received TPT in 2020 (1). Increased TB transmission resulting from COVID-19 health system disruption accentuates the threat posed to vulnerable young children and people living with HIV, who are key TPT target groups. Recently, WHO extended TPT recommendations to HIV-uninfected older children and adolescents (5–19 yr) who are household TB contacts, and coverage in this group is currently estimated to be less than 5% globally (1, 2).

Barriers to implementation of child TB contact screening and management include the need for pragmatic screening options to deliver community-based TPT (3). Chest radiography has a critical role, both to support a clinical diagnosis of TB and to rule out active disease before initiating TPT; but access to chest radiography is a major hurdle in resource-limited settings (4). It has been demonstrated that symptom-based TB contract screening is safe, and that chest radiography adds little value in asymptomatic young children who receive TPT (5–7). However, despite the available evidence, many clinicians remain uncomfortable providing TPT without a chest radiograph to rule out TB disease, given that chest radiography is routinely performed before TPT commencement in settings without resource constraints.

The value of chest radiography also requires further clarification in older children and adolescents, since the WHO now recommends that older child and adolescent TB contacts with evidence of infection (or on the basis of known exposure to a bacteriologically confirmed infectious TB case, if a test for infection is unavailable) should receive TPT once TB disease has been excluded (2). The role of chest radiography in this older age group requires better evidence as this is a group that, compared with young child contacts, are more likely to have coprevalent subclinical bacteriologically positive TB detectable by chest radiography (8). Therefore, they are at greater risk of suboptimal outcomes and drug resistance acquisition if not appropriately treated.

Assessing the Value of Chest Radiograpy for Tuberculosis Contact Screening

In this issue of the *Journal*, Huang and colleagues (pp. 892–900) evaluated the diagnostic and prognostic value of chest radiography in children exposed to TB in Peru and measured the efficacy of isoniazid preventive therapy (IPT) in those with radiographic abnormalities (9). They enrolled 4,468 children with household exposure to bacteriologically confirmed TB who had symptom assessment and chest radiography done. The majority (56%) of contacts were 6 years of age or older, and only 0.1% were HIV positive. Chest radiography was limited to an anteroposterior film, and these were interpreted by experienced readers blinded to the clinical presentation. Those without coprevalent TB (at baseline) were followed for 1 year to assess disease progression (incident TB) risk as well as the protective efficacy of IPT.

Asymptomatic children with abnormal chest radiographs were found to be 25 times more likely to have coprevalent TB and 26 times more likely to be diagnosed with incident TB during follow-up than asymptomatic children with normal chest films (9). The authors concluded that chest radiography is strongly supported as a routine screening tool for the evaluation of child TB contacts, where this is readily available, given that even atypical radiographic findings in asymptomatic children may indicate incipient or subclinical disease.

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