Next to a possible biomarker function, another advantage of gene expression signatures in blood, sputum, nasal brushes, or samples from lower airways or lung parenchyma is that they also provide insights in pathobiological mechanisms associated with COPD and COPD-associated traits, which could potentially lead to discovery of novel treatment targets. In the case of the study by Moll and colleagues, blood transcriptional risk score genes were enriched for pathways related to PPAR-α (peroxisome proliferator-activated receptor α) signaling and B-cell activation, which are possibly involved in COPD susceptibility and lung function decline.

In conclusion, gene expression profiling is a promising tool for the development of clinically relevant biomarkers in lung diseases like COPD and can reveal novel treatment targets leading to to improved personalized treatment of the disease. The data published by Moll and colleagues in this issue of the *Journal* provide an excellent example of a clinically relevant biomarker that can be easily and noninvasively assessed. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Maarten van den Berge, M.D., Ph.D.
University Medical Center Groningen
University of Groningen
Groningen, the Netherlands

Alen Faiz, Ph.D.
Faculty of Science
University of Technology Sydney
Sydney, New South Wales, Australia

ORCID ID: 0000-0002-9336-7340 (M.v.d.B.).

References

1. Becker EJ, Faiz A, van den Berge M, Timens W, Hiemstra PS, Clark K, *et al.* Bronchial gene expression signature associated with rate of subsequent FEV_1 decline in individuals with and at risk of COPD. *Thorax* [online ahead of print] 10 May 2021; DOI: 10.1136/thoraxjnl-2019-214476.
2. Moll M, Boueiz A, Ghosh AJ, Saferali A, Lee S, Xu Z, *et al.* Development of a blood-based transcriptional risk score for chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2022;205:161–170.
3. Fazleen A, Wilkinson T. Early COPD: current evidence for diagnosis and management. *Ther Adv Respir Dis* 2020;14:1753466620942128.
4. Woodruff PG, Barr RG, Bleecker E, Christenson SA, Couper D, Curtis JL, *et al.*; SPIROMICS Research Group. Clinical significance of symptoms in smokers with preserved pulmonary function. *N Engl J Med* 2016;374: 1811–1821.
5. McDonald VM, Fingleton J, Agusti A, Hiles SA, Clark VL, Holland AE, *et al.*; participants of the Treatable Traits Down Under International Workshop; Treatable Traits Down Under International Workshop participants. Treatable traits: a new paradigm for 21st century management of chronic airway diseases: Treatable Traits Down Under International Workshop report. *Eur Respir J* 2019;53:1802058.
6. Christenson SA, Steiling K, van den Berge M, Hijazi K, Hiemstra PS, Postma DS, *et al.* Asthma-COPD overlap. Clinical relevance of genomic signatures of type 2 inflammation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2015;191:758–766.
7. Christenson SA, van den Berge M, Faiz A, Inkamp K, Bhakta N, Bonser LR, *et al.* An airway epithelial IL-17A response signature identifies a steroid-unresponsive COPD patient subgroup. *J Clin Invest* 2019;129: 169–181.
8. Steiling K, van den Berge M, Hijazi K, Florido R, Campbell J, Liu G, *et al.* A dynamic bronchial airway gene expression signature of chronic obstructive pulmonary disease and lung function impairment. *Am J Respir Crit Care Med* 2013;187:933–942.
9. van den Berge M, Steiling K, Timens W, Hiemstra PS, Sterk PJ, Heijink IH, *et al.* Airway gene expression in COPD is dynamic with inhaled corticosteroid treatment and reflects biological pathways associated with disease activity. *Thorax* 2014;69:14–23.
10. Brandsma CA, van den Berge M, Postma DS, Jonker MR, Brouwer S, Paré PD, *et al.* A large lung gene expression study identifying fibulin-5 as a novel player in tissue repair in COPD. *Thorax* 2015;70:21–32.
11. Boudewijn IM, Faiz A, Steiling K, van der Wiel E, Telenga ED, Hoonhorst SJM, *et al.* Nasal gene expression differentiates COPD from controls and overlaps bronchial gene expression. *Respir Res* 2017;18:213.
12. Faiz A, Imkamp K, van der Wiel E, Boudewijn IM, Koppelman GH, Brandsma CA, *et al.* Identifying a nasal gene expression signature associated with hyperinflation and treatment response in severe COPD. *Sci Rep* 2020;10:17415.
13. Imkamp K, Berg M, Vermeulen CJ, Heijink IH, Guryev V, Kerstjens HAM, *et al.* Nasal epithelium as a proxy for bronchial epithelium for smoking-induced gene expression and expression quantitative trait loci. *J Allergy Clin Immunol* 2018;142:314–317.e15.
14. Ditz B, Sarma A, Kerstjens HAM, Liesker JJW, Bathoorn E, Vonk JM, *et al.* The sputum transcriptome better predicts COPD exacerbations after the withdrawal of inhaled corticosteroids than sputum eosinophils. *ERJ Open Res* 2021;7:00097-2021.

Repurposing Propofol as a Prognostic Probe for Return of Consciousness

There is a growing realization that behavioral and neurophysiologic responses to general anesthesia can provide useful information regarding underlying brain health. For example, in response to concentrations of propofol or ether-derived inhaled anesthetic agents (e.g., sevoflurane and isoflurane) associated with loss of consciousness, people with healthy brains often have prominent anterior electroencephalographic α and θ spindles, which exhibit phase–amplitude coupling with slow δ waves (1). In contrast, surgical patients with preexisting cognitive impairment often fail to develop these typical, prominent anterior electroencephalographic spindles in response to propofol or inhaled general anesthetics (2). Furthermore,

Originally Published in Press as DOI: 10.1164/rccm.202111-2504ED on November 24, 2021

in patients with underlying neurologic vulnerability who experience postoperative delirium, electroencephalographic suppression tends to occur at relatively low concentrations of anesthetic agents (3, 4). General anesthetic agents might therefore be viewed as a neural stress test revealing brain health or vulnerability that might not otherwise be overtly manifest.

In this issue of the *Journal*, Duclos and colleagues (pp. 171–182) present results from a small clinical study in which they administer propofol to 12 patients who are in a minimally conscious state or who have unresponsive wakefulness syndrome, previously referred to as a persistent vegetative state (5). The idea behind this study is that the function and integrity of certain brain networks can be inferred by analyzing data from a combination of electroencephalographic channels. Propofol typically causes disruption of certain networks, which have been proposed to undergo adaptive reconfiguration, or in other words, a reorganization of functional connections that might help preserve overall network homeostasis. The authors leverage this concept, which has been demonstrated in both awake individuals performing a task and in the spontaneous activity of the anesthetized brain. They propose the adaptive reconfiguration index as a surrogate for network resilience; when there is little change in network configuration on exposure to propofol, the index is low, and when brain networks respond like that of a healthy individual, the index is high (5). Interestingly, three patients who had high adaptive reconfiguration indices in response to propofol all fully regained consciousness within three months. None of the patients with low adaptive reconfiguration indices regained consciousness. The intriguing hypothesis emerges that the combination of propofol with a readily derived, standard 18-channel–based electroencephalographic index can be used as a pragmatic, bedside prognosticator in the ICU for patients in a minimally conscious state (5).

Adaptive reconfiguration of brain networks during general anesthesia was first proposed on the basis of a study of propofol in healthy volunteers (6). Despite clear changes in functional connectivity in the anesthetized state, large-scale EEG-based networks still maintained a hub-like organization, much like a network of airports (6). It was later found that this preservation of global organization was likely driven by a reconfiguration of network hubs in the brain, with a reversal of posterior and anterior areas with rich functional connectivity (7). Returning to the airport analogy, it would be as if the major hub airport in Michigan shifted rapidly from Detroit to Lansing—the general type of network organization would be the same (there would still be a hub airport and a more local one), but the location of the high-traffic hub areas would be different. Such a shift in airport hubs would no doubt lead to different patterns or directions of air travel. Similarly, by using the more principled approach of computational modeling, it was found that the location of the functional hubs in the brain define the directionality of functional connectivity (8). In a past case report by some of the authors on the study and us, it was found that propofol induced the same characteristic shifts in hub location and directional connectivity in a patient with unresponsive wakefulness syndrome as it typically did in healthy volunteers (9). This was unexpected, but even more surprising was that this patient recovered, prompting the question of whether a reconfiguration of hub topology while he was still unconscious indicated that his brain networks were still healthy enough to respond flexibly.

Duclos and colleagues have now addressed this question in a larger patient cohort, demonstrating the further promise of using propofol to probe the response and resiliency of brain networks in patients with pathological states of unconsciousness (5). Although the adaptive reconfiguration index was 100% accurate in this study in predicting the return of full consciousness within three months, this finding should still be regarded as preliminary because only 3 of 12 patients regained full consciousness in the time frame of interest (5).

Importantly, the adaptive reconfiguration index is only informative in the context of a brief and reversible brain perturbation, leading to network disruption and allowing network reconfiguration. Such perturbation is reliably provided by a propofol challenge. The adaptive reconfiguration index, unlike alternative analytical approaches such as the perturbational complexity index (10, 11), performs poorly at diagnosing specific disorders of consciousness. Indeed, the very basis of a high index is that networks respond in a pathologic state as healthy individuals do. Thus, the adaptive reconfiguration index is proposed to have only prognostic rather than diagnostic value. One important question that is not sufficiently addressed by Duclos and colleagues is how the adaptive reconfiguration index performs for people who have covert consciousness, also known as cognitive–motor dissociation (11). Such individuals are conscious of the world and are aware of sensations, including pain (11). Hence, they are uniquely vulnerable. In our quest to alleviate pain and suffering, we would not wish to miss this diagnosis.

In conclusion, this provocative study provides a striking example of innovative and safe drug repurposing. Propofol was introduced in the 1970s as an intravenous sedative and anesthetic agent (12). Today, it is used extensively and safely for these purposes in operating rooms, procedural settings, and ICUs. Duclos and colleagues have performed a small, but rigorous, assessment suggesting that, after 60 years of rendering millions of people reversibly unconscious, propofol might now be able to reinvent itself as an oracle that can reliably reveal whose persistent unconsciousness is reversible and whose is not. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Michael S. Avidan, M.B. B.Ch.
Department of Anesthesiology
Washington University School of Medicine
St. Louis, Missouri

George A. Mashour, M.D., Ph.D.
Department of Anesthesiology
University of Michigan Medical School
Ann Arbor, Michigan

References

1. Hight DF, Kaiser HA, Sleigh JW, Avidan MS. Continuing professional development module: an updated introduction to electroencephalogram-based brain monitoring during intended general anesthesia. *Can J Anaesth* 2020;67:1858–1878.
2. Koch S, Windmann V, Chakravarty S, Kruppa J, Yürek F, Brown EN, *et al.*; BioCog Study Group. Perioperative electroencephalogram spectral dynamics related to postoperative delirium in older patients. *Anesth Analg* 2021;133:1598–1607.
3. Fritz BA, Maybrier HR, Avidan MS. Intraoperative electroencephalogram suppression at lower volatile anaesthetic concentrations predicts postoperative delirium occurring in the intensive care unit. *Br J Anaesth* 2018;121:241–248.

4. Fritz BA, King CR, Ben Abdallah A, Lin N, Mickle AM, Budelier TP, *et al.*; ENGAGES Research Group. Preoperative cognitive abnormality, intraoperative electroencephalogram suppression, and postoperative delirium: a mediation analysis. *Anesthesiology* 2020;132:1458–1468.
5. Duclos C, Maschke C, Mahdid Y, Nadin D, Rokos A, Arbour C, *et al.* Brain responses to propofol in advance of recovery from coma and disorders of consciousness: a preliminary study. *Am J Respir Crit Care Med* 2022; 205:171–182.
6. Lee U, Oh G, Kim S, Noh G, Choi B, Mashour GA. Brain networks maintain a scale-free organization across consciousness, anesthesia, and recovery: evidence for adaptive reconfiguration. *Anesthesiology* 2010;113:1081–1091.
7. Lee H, Mashour GA, Noh G-J, Kim S, Lee U. Reconfiguration of network hub structure after propofol-induced unconsciousness. *Anesthesiology* 2013;119:1347–1359.
8. Moon J-Y, Lee U, Blain-Moraes S, Mashour GA. General relationship of global topology, local dynamics, and directionality in large-scale brain networks. *PLoS Comput Biol* 2015;11:e1004225.
9. Blain-Moraes S, Boshra R, Ma HK, Mah R, Ruiter K, Avidan M, *et al.* Normal brain response to propofol in advance of recovery from unresponsive wakefulness syndrome. *Front Hum Neurosci* 2016; 10:248.
10. Sinitsyn DO, Poydasheva AG, Bakulin IS, Legostaeva LA, Iazeva EG, Sergeev DV, *et al.* Detecting the potential for consciousness in unresponsive patients using the perturbational complexity index. *Brain Sci* 2020;10:917.
11. Edlow BL, Claassen J, Schiff ND, Greer DM. Recovery from disorders of consciousness: mechanisms, prognosis and emerging therapies. *Nat Rev Neurol* 2021;17:135–156.
12. Dankoski E. The 2018 Lasker∼DeBakey Clinical Medical Research Award recognizes John Baird Glen for the discovery of propofol. *J Clin Invest* 2018;128:4198–4200.

Pediatric Pneumonia: Another Problem Plagued by Inequity in Health Care

Although pediatric pneumonia has decreased substantially in the advent of improved early-life nutrition, living conditions, vaccinations, and HIV diagnosis and treatment, it remains a leading cause of preventable morbidity and mortality among children <5 years of age (1). The disparate burden of pediatric pneumonia is largely borne by those living in low- and middle-income countries (LMICs), where there is often a higher prevalence of risk factors for pneumonia in the face of fewer resources for diagnosis and treatment. Appropriate identification and timely treatment of severe pneumonia, which is often complicated by hypoxemia, is critical because of the associated high risk of morbidity and mortality (2). Treatment of severe pediatric pneumonia requires systemic access to appropriately trained staff and life-saving interventions such as antibiotics, supplemental oxygen, and in the most severe cases, ventilatory support. This remains an unmet need in many resource-poor and remote locales.

In this issue of the *Journal*, Simkovich and colleagues (pp. 183–197) leveraged the resources and infrastructure of the HAPIN (Household Air Pollution Intervention Network) trial to identify healthcare facilities that they defined as adequately resourced to manage severe pediatric pneumonia as part of implementing a pneumonia surveillance strategy in rural regions of four LMICs—Guatemala, Peru, Rwanda, and India (3). They defined adequately resourced healthcare facilities as those that were open daily and had overnight beds, an available physician, a pulse oximeter, supplemental oxygen, respiratory support devices, X-ray or ultrasound, and antibiotics. They surveyed administrative leaders of 350 healthcare facilities ranging from community centers and health posts to formal health centers and hospitals in the HAPIN study area, finding that only 13% of facilities had adequate resources to manage severe pneumonia, but this varied substantially across regions, from 3% in Guatemala to 42% in India. Overall, 37% of facilities had pulse oximeters and 44% had supplemental oxygen, although this also varied by country. Mean travel times to an adequately resourced facility were 31–99 minutes, with the shortest in India and the longest in Peru. Only 43–63% of the study population lived within 30 minutes of a facility that was adequately resourced to care for severe pneumonia, and 5% of the population in Peru lived outside of a two-hour travel time.

These findings bring to the forefront yet another example of the inequity of resource availability to care for highly prevalent, treatable medical problems worldwide (4, 5). We applaud the authors for positing a potential intervention to address a step in the cascade of care for pneumonia diagnosis and treatment (Figure 1). They propose that universal availability of pulse oximetry could reduce time to diagnosis of severe pneumonia based on modeling of travel time to healthcare facilities in the hypothetical situation that all facilities were supplied with pulse oximetry. Availability would theoretically reduce time to diagnosis, and, as a result, time to referral, by 3 minutes in India and up to 19 minutes in Peru. It is not clear from these data, however, how this might translate to improved access or reduced time to receipt of appropriate care for severe pneumonia.

Although pulse oximetry is an easy-to-use, low-cost tool, is its universal availability sufficient to impact reduction of the morbidity and mortality of childhood pneumonia on a population level in diverse settings? Pulse oximetry improved outpatient diagnosis of pediatric pneumonia that would otherwise have been missed based on World Health Organization referral guidelines in a Malawian study (6), but in a Nigerian study, only 19% of

Supported by NIH/NHLBI grant K23 HL129888 (E.F.A.).

Originally Published in Press as DOI: 10.1164/rccm.202110-2325ED on November 17, 2021