28 Summary and Future Applications of Precision Medicine in Pulmonary, Critical Care, and Sleep Medicine

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Introduction

We are at the dawn of precision medicine, a transitional period fueled by technological advances in high-throughput assays for various types of biological data, imaging, sensors, data science, and computing. The application of these methods to large and deeply phenotyped cohorts coupled with our current understanding of disease pathogenesis are moving us closer to the widespread development and implementation of personalized therapies. The adoption of precision medicine across pulmonary, critical care, and sleep remains uneven, however, as can be gleaned by contrasting the reviews provided in preceding chapters. Here, we summarize salient findings from each book section and major themes related to the future of precision medicine research and its implementation.

Genetics and Pharmacogenetics in Pulmonary, Critical Care, and Sleep Medicine

High-throughput genomic techniques have led to the discovery of loci linked to various pulmonary diseases and uncovered potential targets for drug development. In the case of rare diseases, where one or few loci confer a high proportion of disease susceptibility, substantial progress has been made in precision medicine. As discussed in the chapter on Diffuse Pulmonary Disorders, genotype-driven precision therapies are available or under study for patients with neonatal respiratory distress syndrome, cystic fibrosis, pulmonary alveolar proteinosis, pulmonary Langerhans cell histiocytosis, and alpha-1 antitrypsin deficiency (AATD) [1–6]. For these diseases and other rare ones of unknown origin, genetic evaluation can proceed in a relatively straightforward manner thanks to the availability of genome sequencing. A major barrier now is that ultra-

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rare, novel variants of uncertain significance are often identified via sequencing, and determining which of these may actually lead to observed traits is not straightforward [7]. Even when causal loci are identified, there may not be a treatment available. Identification of causal loci is nonetheless a helpful starting point that may lead to treatment identification as has been demonstrated successfully in some cases [8]. Genetic counselors play an important role in helping patients and their families navigate the process of searching for loci linked to disease and taking actions based on results.

For complex diseases, although most genomic findings have not yet changed clinical practice, some may soon lead to advances in precision medicine. For example, genetic studies of idiopathic pulmonary fibrosis (IPF) have begun to clarify why this disease occurs and identify new potential therapeutic targets. Because IPF is a diagnosis of exclusion, assigned only after various other conditions that present similarly have been ruled out, and IPF prognosis is poor, any clues regarding its origin are of great importance [9]. Further, distinguishing IPF from other interstitial lung diseases matters, as currently available anti-fibrotic therapies have been studied and approved for IPF patients but not those with other fibrosing idiopathic interstitial pneumonias [9]. Common and rare genetic factors conferring disease risk in IPF include variants in surfactant protein C (*SFTPC*), surfactant protein A2 (*SFTPA*), telomerase reverse transcriptase (*TERT*) and RNA component (*TERC*) [10–13], and Mucin 5B, Oligomeric Mucus/Gel-Forming (*MUC5B*) [14, 15]. Distinct genotypes found in these and other genes, which have implicated surfactants, mucociliary function, cell-cell adhesion and telomere maintenance as playing important roles in IPF pathobiology, may determine clinical phenotypes and novel therapies for IPF. The next stage is the conduct of prospective clinical trials to translate current IPF genetics observations into findings that may be implemented in clinical practice [16].

As demonstrated by genomics studies of COPD, genome-wide association studies (GWAS) with progressively larger sample sizes and increased coverage of genetic variants have been useful to identify reproducible disease risk loci. The largest COPD GWAS to date, consisting of 35,735 COPD cases defined by moderate to very severe airflow limitation and 222,076 controls with data on more than 6 million genetic variants, identified 82 genome-wide significant loci, at least 60 of which replicated in an independent cohort [17]. Effect sizes of these loci were relatively small (odds ratios 1.06–1.21) and together accounted for 7.0% of the COPD phenotypic variance, indicating that individual GWAS results are unlikely to serve as biomarkers. However, the identification of novel drug targets and pathways that may lead to the discovery of COPD endotypes is made possible by the study of these genes, as suggested by subsequent functional work of COPD-associated genes such as family with sequence similarity 13 member A (*FAM13A*), cholinergic receptor nicotinic alpha 3 subunit (*CHRNA3*), cholinergic receptor nicotinic alpha 5 subunit (*CHRNA5*), hedgehog interacting protein (*HHIP*), and matrix metallopeptidase 12 (*MMP12*). Beyond the many common variant associations identified for COPD, it is worth noting that the most validated genetic risk factor that accounts for 1–5% of COPD cases is the *SERPINA1* variant that results in alpha-1 antitrypsin deficiency (AATD) [18]. Because this variant has not been identified via GWAS, further studies on the role of rare variants in subtypes of COPD may yield insights into other rare endotypes.

In the case of asthma, the most well-known and highly replicated genetic association signal is within the 17q21 locus, spanning genes ORMDL sphingolipid biosynthesis regulator 3 (*ORMDL3*) and gasdermin B (*GSDMB*) [19–21]. Although the exact mechanisms via which these genes are related to asthma is not yet known, functional studies are making progress in understanding their role in disease pathogenesis: overexpression of either *ORMDL3* or *GSDMB* in mouse bronchial epithelium leads to increased airway remodeling and responsiveness [22, 23], and GSDMB protein induces pyroptosis of airway epithelia cells during inflammation [24]. Various immune pathway genes have also been associated with

asthma, and contrasting association results obtained with specific asthma endotypes and other allergic diseases has helped clarify molecular processes that are unique versus shared across these conditions. Much work remains to yield novel therapies or identify novel genetics markers that are specific to asthma endotypes on the basis of GWAS findings.

In contrast to IPF, asthma and COPD, lung cancer is primarily caused by environmental exposures, such as tobacco smoke, that cause *non-inherited* somatic mutations [25]. While heritable genetic factors may influence individual response to environmental exposures and play a direct role in a minority of lung cancer cases, studies of somatic mutations have been the focus of much work and have advanced precision medicine for some types of lung cancer. Specifically, targeted treatments for various mutations involved in non-small cell lung cancer (NSCLC), which accounts for approximately 85% of all cases [26], have been identified. Notable examples include mutations of epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase (*ALK*), and ROS Proto-Oncogene 1, Receptor Tyrosine Kinase (*ROS1*) [27, 28]. Testing of specific mutations that drive lung tumorigenesis where there is a chemotherapeutic drug available to target cells that harbor that mutation is currently recommended, and high-throughput sequencing has enabled the continued detection of additional driver mutations that contribute to lung cancer development and progression [29]. Many questions remain in lung cancer, including gaining traction on small cell lung cancer (SCLC), which is characterized by rapid growth, early metastasis, high molecular complexity, a large number of mutations in each tumor, and a very low 2-year survival rate [30, 31], as well as the identification of a broader range of mutations in NSCLC.

With the exception of lung cancer loci that have targeted drugs, few pharmacogenetic loci have been identified and widely replicated for most respiratory diseases. This is due in part to the limited number of large cohorts with appropriate and similarly captured drug response measures, which make studying these traits particularly challenging. Pharmacogenomics studies of bronchodilator and glucocorticoid response have been conducted for people with asthma and COPD, under the rationale that inter-individual variability in the response to these drugs has a genetic component and that genetic variants may be useful to predict drug response or their side effects. Early reports from candidate gene studies of Adrenoceptor Beta 2 (*ADRB2*), the primary receptor target of β_2-agonists, found that variants of this gene were associated with bronchodilator response in people with asthma or COPD, but more recent meta-analysis have found few or no consistent associations between genotype and treatment response in COPD [32] and asthma [33]. Although some promising GWAS associations have been measured and are supported by functional data, such as spermatogenesis-associated serine-rich 2 like (*SPATS2L*) with bronchodilator response [34] and glucocorticoid-induced 1 (*GLCCI1*) with inhaled corticosteroid response [35], overall, pharmacogenetic studies over the past decade have failed to deliver medically actionable results, and it is unlikely that common genetic variants will serve as biomarkers of β_2-agonist or steroid responsiveness [36].

Biomarkers in Pulmonary, Critical Care, and Sleep Medicine

As described in several chapters, the search for, and discovery of, biomarkers has led to the evolution of syndrome definitions from symptom-centered diagnoses to more precise definitions based on genetics and other molecular changes. In pulmonary infections, the development of metagenomic testing has led to the identification of specific pathogens associated with illness in children without a previously identifiable pathogen [37]. The combination of metagenomics with novel sequencing platforms has also facilitated the analysis of sputum samples to identify bacterial pathogens with a turnaround time of 6 hours [38]. Additional expansion of these methods will enable rapid diagnosis and therapeutic changes in real time, rather than on culture-based methods,

the current standard. Further, a deeper understanding of pathogens associated with infections is transforming how we prescribe and de-escalate therapy with antibiotics, which is of particular importance in the setting of increasing antibiotic resistance worldwide [39].

The search for biomarkers related to chronic airways obstruction has shown promise to discover endotypes of asthma, COPD and asthma-COPD overlap (ACO). Although COPD and asthma are considered distinct diseases, they share clinical manifestations, such as airway inflammation and obstruction. Consequently, the therapies used in their management overlap, as they are directed towards reducing airway inflammation and reversing bronchoconstriction. Some biomarkers have been developed for Type 2-driven asthma, while some for non-Type 2 asthma, COPD and ACO are only in the early stages of development. For example, eosinophils are used to predict therapeutic response and guide treatment in both asthma and COPD [40–42], including targeted treatments such as mepolizumab [43]. IgE, which correlates with the presence and severity of asthma, is another widely used biomarker that has driven the development of biologics like omalizumab [44]. With the exception of COPD related to AATD, no COPD-specific endotypes with clinically relevant treatments exist. Plasma fibrinogen qualified as the first FDA-approved biomarker for COPD, to be used for patient selection for enrollment into clinical trials to enrich for those who are at risk of disease worsening [45]. While identifying elevated plasma levels of fibrinogen as a biomarker is a step forward, fibrinogen lacks disease specificity and does not establish an endotype. Biomarker studies of asthma and COPD have made evident that no single gene or molecular biomarker will be sufficient to differentiate endotypes of these complex and multifactorial diseases. In fact, biomarker panels incorporating multiple markers in combination have shown increased efficacy over single biomarkers. Accurate and reproducible endotyping would be of great utility for the study and management of chronic airways obstructive diseases, enabling the development of treatments that target specific dysregulated pathways.

As is the case for obstructive airway disease, interstitial lung disease (ILD) refers to a large group of complex and highly heterogeneous diseases. Although shared characteristics of those with ILD include changes to the lung interstitium, distorted pulmonary architecture, and altered gas exchange ability of the lung, various molecular pathways underlie these traits. There are no molecular biomarkers in widespread clinical use for ILD, including IPF, although several exciting candidates are under study. For both IPF and non-IPF ILD, there is an urgent need to identify and validate biomarkers for early diagnosis, and monitor disease progression and outcomes [46]. Among the promising biomarkers for ILD and/or IPF are: 1) surfactant protein A (SFTPA) and surfactant protein D (SFTPD) [47], which are also supported by genetics studies [12, 48]; 2) telomere length, supported by the observations that a) telomere shortening is associated with cell death of airway epithelial cells and could explain the occurrence of disease in older individuals [49] and b) association of mutations in telomerase reverse transcriptase (encoded by the *TERT* gene) and telomerase RNA (encoded by *TERC*) that lead to abnormal telomere shortening have been observed in 8–15% of patients with familial pulmonary fibrosis [50, 51]; and 3) matrix metallopeptidase 7 (MMP7), the most studied and validated biomarker in IPF, whose elevated levels are associated with disease in multiple compartments (e.g., BAL, serum, lung tissue) and is related to extracellular matrix remodeling and fibroproliferation [52–56].

In addition to nucleic acid and protein biomarkers, imaging biomarkers have been adopted as diagnostic and therapeutic response tools, especially in lung cancer [57]. However, as illustrated in the chest imaging chapter, precision imaging is becoming an invaluable tool for the study and phenotyping of patients with chronic lung diseases such as COPD [58]. Therefore, the integration of biospecimen-derived and imaging biomarkers has the potential to transform disease

classification and therapeutics. For IPF, detection of interstitial lung abnormalities via imaging are the best, albeit limited, approach for early detection of fibrosis [59, 60]. Another example of how imaging can be used for patient phenotyping is the use of machine learning to evaluate cardiac MRI changes of right ventricle (RV) failure in pulmonary hypertension, as work has demonstrated that patients with loss of effective contraction in the septum and free wall of the RV, along with reduced basal longitudinal motion, have worse RV failure. The combination of these cardiac MRI findings with traditional clinical characteristics and hemodynamics led to improved survival prediction and showed better separation of median survival between high- and low-risk groups [61]. Therefore, imaging integration with clinical characteristics improves patient identification and outcome prediction.

Phenotyping in Pulmonary, Critical Care, and Sleep Medicine

Phenotyping of pulmonary, critical care, and sleep-related conditions has become intertwined with the search for omics and imaging-based biomarkers. Although progress in phenotyping is made possible by the identification of biomarkers, the identification of biomarkers is made easier when distinct phenotypes of people are captured. Thus, phenotyping using clinical data and approaches besides high-throughput omics and imaging techniques remains relevant in precision medicine. The challenge of disease heterogeneity was salient for the complex conditions described, including IPF, COPD, sepsis, and acute respiratory distress syndrome (ARDS). The combination of deep phenotyping and identification of molecular profiles that characterize pathophysiologically heterogeneous conditions is currently the best approach to drug discovery. For example, the use of blood eosinophil count is a promising predictive biomarker of clinical response to inhaled corticosteroids in COPD [62–64]. Much work remains in the identification of more specific biomarkers and therapies for COPD and other diseases, as can be gleaned from the chapters focused on complex respiratory conditions.

Sepsis and ARDS each cause substantial morbidity and mortality, and precision medicine approaches are sorely needed to improve outcomes related to them. Their study is challenged not only by disease heterogeneity but also by the fact that the entire course of disease is measured in days to weeks rather than months to years. Promising results from large-scale gene expression and targeted proteomics plasma studies suggest that biologically distinct patterns of expression may identify differential response to routine treatments applied in the intensive care unit (ICU). In sepsis, a gene expression signature with dysregulated adaptive immune signaling has evidence for a differential response to systemic steroid therapy [65, 66], whereas in ARDS, a hyperinflammatory pattern identified in plasma using targeted proteomics was favorably associated with randomized interventions including high positive end-expiratory pressure, volume conservative fluid therapy, and simvastatin therapy [67–70]. In the case of pulmonary arterial hypertension (PAH), a whole blood transcriptomic classifier led to the identification of a specific signature in vasodilator-responsive PAH that differentiates it from non-responsive PAH [71]. Replication of these critical care and PAH findings and the conduct of prospective studies evaluating expression signatures may lead to clinically useful results.

Sleep medicine is one of the most data-rich fields in medicine because of the increasing conduct of sleep studies that include remote collection of data from positive airway pressure (PAP) devices. The use of sophisticated analytical methods to identify distinct patterns of data captured during sleep has led to the characterization of distinct obstructive sleep apnea endotypes associated with adverse cardiovascular events [72]. Machine learning and computational tools [73, 74] are being further leveraged to develop better classification methods for various sleep disorders. These advances in phenotyping coupled to the discovery of biomarkers may yield striking changes in sleep precision medicine.

The Role of Sensors, Wearables and Health Information Technologies in Pulmonary, Critical Care, and Sleep Medicine

Along with efforts to capture molecular, imaging and phenotype data using traditional clinical and research approaches, precision medicine captures additional complementary data on the environment, behavior, patient-reported symptoms and outcomes, and medication use. The latter are made possible by advances in health information and sensor technologies, which have resulted in the creation of a wide range of mobile health (mHealth) platforms for disease self-management, research, and inclusion of novel data streams into provider-facing applications [75]. The use of these platforms has tremendous potential to benefit patients, providers, and the entire healthcare system although their documented clinical utility has not been established in most cases. While over 325,000 mobile applications (apps) are currently available, most are limited to providing information [76], and a relatively small proportion are dedicated to respiratory health. Functions provided by respiratory apps include medical education, messaging, diary logs, disease self-management, and educational games [77]. One of the largest mobile health tracking studies thus far was the Asthma Mobile Health Study. This project demonstrated the feasibility of using a mobile app to monitor asthma symptoms, but the lessons learned at study completion apply to most mobile health efforts: sustaining initial enthusiasm of an app is very difficult, there is selection bias in those enrolling and providing information, and data security concerns limit some subjects' willingness to share data [78]. Wearables, devices worn on the body to track bodily functions, have become a part of daily life. Most wearables are worn on a wrist or chest with functions that include tracking exercise, weight loss, sleep, and coping with stress [79]. Incorporating wearable data into respiratory studies may be an effective way to capture additional subject data to aid in phenotyping. Use of these technologies is still in the early stages, and despite some early progress, several barriers must be overcome before mHealth is widely adopted and recommended by healthcare providers.

Concern for pollution's effect on health and broad demand for accessible environmental monitoring have led researchers and manufacturers to develop a number of low-cost, portable pollution sensors that are able to capture increasingly finer-scaled geographic differences in pollution. Such sensors broaden the scope of environmental studies that are possible: rather than rely on measures taken by regulatory monitors that are not able to account for the spatial and temporal heterogeneity of personal exposures, we are nearly able to measure individual exposure profiles. Although pollution measurements taken with low-cost sensors are less accurate and reliable than reference monitors, several studies have shown the feasibility and validity of using them to capture air pollution information across an area by deploying sensors in fixed-location networks, attaching them to vehicles, placing them in indoor spaces, and having people wear them to monitor personal exposures [80–82]. Ultimately, capturing personal exposure measures and integrating them into health monitoring tools will lead to improved precision medicine.

Precision Therapies in Pulmonary, Critical Care, and Sleep Medicine

In parallel to the advances in genomics, biomarkers, and phenotyping, therapeutics have improved by specific knowledge of underlying molecular changes associated with distinct diseases. Of pulmonary diseases, precision medicine advances are most notable in lung cancer, for which, as mentioned above, some so-called driver mutations can be targeted with specific chemotherapeutic agents. The demonstration that patients with NSCLC with activating mutations in EGFR could be successfully treated with the tyrosine kinase inhibitor gefitinib [83], led to the search for other specific mutations in NSCLC that could be drug targets. The subsequent identification of ALK and development of ALK inhibitors [84], as well as many other oncogenic drivers, has been associated with improved out-

comes in lung cancer over the last 15 years [85]. Efforts to identify driver mutations in lung cancer continue, and greater personalized approaches to cancer therapy will result from an improved understanding of lung tumor evolution, by allowing physicians to anticipate which lung tumors will develop resistance to chemotherapeutic agents and which lung tumors have a propensity to recur or metastasize. Cystic fibrosis has also made significant advances in targeted therapies. The development of cystic fibrosis transmembrane conductance regulator (CFTR) modulators that correct for specific deficiencies in the CFTR channel [86–88] are a first generation of drugs that can potentially transform this devastating disease. Advances in lung cancer and cystic fibrosis offer hope that other domains of pulmonary, critical care, and sleep medicine may soon have precise therapeutics, based on knowledge of specific molecular changes that characterize diseases.

Lung transplantation, used as a rescue therapy for patients with advanced lung disease, requires close monitoring to identify allograft rejection. Identification of allograft rejection is currently based on clinical signs and invasive procedures, such as lung biopsy, and thus, novel methods to improve detection of allograft rejection would greatly improve care of patients after transplantation. A promising non-invasive approach to identify early rejection may be the quantification of donor-derived cell-free DNA, as a study demonstrated that subjects with average levels in the upper tertile had a 6.6-fold higher risk of developing allograft failure [89]. This and other biomarker studies may soon improve management of immunosuppression.

Mechanical ventilation is a life-saving intervention used to treat patients in the ICU that requires immediate attention to patient tolerance and real-time adjustments to minimize the risk of ventilator-induced injury and ventilator dyssynchrony [90]. Thus, mechanical ventilation is one of the most important practices in the ICU that is personalized to maximize the benefit of physiologic support while avoiding harm to patients. The sophisticated design of modern ventilators has enabled safer practice of telemedicine in the ICU by allowing clinicians to evaluate patients remotely through video streams. Tele-ICU practices have also facilitated the redesign of care processes to improve outcomes in critical care [91], a demonstration of the power of thoughtful design of clinical interventions that use telemedicine.

Cigarette smoking is a key risk factor for multiple pulmonary diseases, particularly COPD and lung cancer. Consequently, smoking cessation is an essential intervention in clinical practice. Despite evidence of increased interest in quitting smoking over the past few decades (49.2% in 2000 versus 55.4% in 2015), successful quitting happens in less than 10% of smokers in the United States according to the Centers for Disease Control and Prevention [92]. Although these outcomes are multifactorial, pharmacogenetics of nicotine plays a role. Both GWAS and candidate gene studies have identified loci associated with response to smoking cessation agents. Specifically, there is evidence that polymorphisms in cytochrome genes (*CYP2A6, CYP2B6*), which are involved in nicotine metabolism, and cholinergic receptors (*CHRNA3, CHRNA4, CHRNA5, CHRNB4*) are associated with nicotine replacement therapy outcomes [93, 94]. Pharmacogenomic profiling may thus serve as an adjunctive measure in the selection of smoking cessation strategies [94].

Ongoing and Future Efforts in Pulmonary, Critical Care, and Sleep Precision Medicine

Several large studies are underway to identify endotypes for various pulmonary, critical care, and sleep conditions. A notable initiative aimed at driving precision medicine is the U.S. National Heart, Lung, and Blood Institute (NHLBI)'s Trans-Omics for Precision Medicine (TOPMed) Program. The early phase of this program included the generation of whole-genome sequencing data for patients with well-defined clinical phenotypes and outcomes from earlier NHLBI-funded studies [95]. As the program has continued, the subjects sequenced are increas-

ingly diverse and various layers of omics data are being incorporated. Results from TOPMed are expected to lay a foundation for precision medicine to substantially improve in several complex respiratory diseases.

As noted in the chapter on Precision Medicine for All, an important limitation of precision medicine now is the lack of information on minority populations [96]. For example, despite significant advances in the understanding of the human genome and decreased sequencing costs, only 22% of GWAS participants are non-European [97]. Because some observed racial/ethnic and sex disparities in respiratory disease prevalence and severity may have a genetic basis, genetics and other omics studies must include diverse groups to inform precision medicine efforts. In addition to this issue being addressed by large studies such as TOPMed, individual researchers and healthcare providers need to be aware of the limitations of precision medicine approaches that result from studies based on non-diverse populations.

Translating genetic associations to disease understanding remains a major challenge, as the number of loci obtained via GWAS and next-generation sequencing studies outpaces the ability of functional studies to identify biological mechanisms. Factors that contribute to the slow translation include: 1) the time-consuming nature of functional studies given the need to tailor experiments to a particular complex disease phenotype and type of polymorphisms in a genomic region; 2) in order to test genes and variants for function, complex diseases have to be simplified into assays that may not capture the cell-specific, developmental, or environmental context necessary for functional elucidation of gene/variant function; and 3) several loci of interest are in gene deserts or genes with no annotated function, making the design of functional experiments even more difficult. Ongoing efforts to identify cell types using single-cell methods for expression, protein, and other molecular quantitative trait loci (e.g., splicing, histone modification) across various conditions and using high-throughput assays to annotate variant effects [98] will increase our understanding of genetic associations. Some of these issues extend to other biomarkers even though they are "closer to phenotype" than genetic variants.

Beyond validating the accuracy of biomarkers, key issues related to their widespread use are establishing their practicality, availability, and cost-effectiveness [99]. Non-invasive biomarkers are more practical for clinical use than invasive ones [100], and thus, finding biomarkers in readily obtained bio-samples to represent more invasive ones may be a necessary step for some conditions such as fibrotic lung diseases. As stated in the chapter on Implementing COPD Precision Medicine in Clinical Practice, the fact that clinically valuable COPD genetic findings related to AATD are not yet readily adopted in clinical practice, raises an important consideration for implementation of genetic findings. Education and advances in regulatory processes are critical if we want to witness the full promise of precision medicine.

For precision medicine to thrive, current and future trainees in the specialty need to be aware of the principles of precision medicine, how these influence our current understanding of disease biology, diagnostics and therapeutics, and how they will transform pulmonary, critical care, and sleep medicine. Education in precision medicine cannot be overlooked and needs to be incorporated in fellowship training curricula, as well as educational conferences. The chapter on education for the practice of precision medicine expounds these ideas and provides guidance on a path forward.

Conclusion

Precision medicine is advancing with the availability and improvement of high-throughput assays for various types of biological data, imaging, sensors, data science and computing. Some rare pulmonary diseases and lung cancer already have personalized therapies available, while most complex respiratory, critical care, and sleep conditions are in the early stages of precision medicine. The study of highly heterogeneous diseases with large and deeply phenotyped cohorts is leading to the discovery of genetic and other molecu-

lar biomarkers that underlie distinct phenotypes. As early examples show, the identification of reproducible endotypes that leverage a broad range of data for each person leads to a better understanding of disease pathobiology, thereby enabling successful preventive strategies and novel drug discovery. The widespread implementation of precision medicine will require inclusion of diverse individuals in research and clinical studies, consideration of cost-effectiveness of novel interventions, and improved education of healthcare providers.

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