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Pulmonary Hypertension and Precision Medicine through the “Omics” Looking Glass

Pulmonary vascular diseases (PVDs) are a heterogeneous group of disorders that affect the pulmonary circulation (1). Pulmonary hypertension (PH) is one of the best studied of these PVDs and has a complex pathobiology. PH can be idiopathic, genetic, or associated with other pulmonary, cardiac, or systemic diseases or other factors, including drugs and toxins (2). Interestingly, despite the recent availability of multiple medications, PH outcomes remain poor (3). Current treatment strategies have been developed for the “average patient with PH” and primarily target pulmonary vasoconstriction instead of using personalized or phenotyping-based methods. As one would expect, this “one-size-fits-all” approach has been very successful for some patients but has not

worked well for others. The current approach to treatment does not take into account recent and ongoing advances in genomics, metabolomics, imaging, etc. (4–11).

In 2016, the White House launched a Precision Medicine Initiative to put forth a new model of patient-powered research (12). This initiative promised to accelerate biomedical discoveries and provide knowledge, tools, and therapies that are “personalized” to the individual patient. The major objectives of the Precision Medicine Initiative are to create better treatments for disease, build a national research cohort, commit to protecting patient privacy, modernize the regulatory landscape, and facilitate public–private partnerships (12). These objectives for personalized disease treatment require a coordinated national effort from multiple private and public organizations and institutions. In line with the Precision Medicine Initiative, the NHLBI put together a workshop to develop a strategic plan for lung vascular research (13) that spurred the American Thoracic Society to publish a statement on PH phenotypes (14). These activities served as the basis for the initiative recently launched by the NHLBI Division of

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Lung Diseases to redefine PH through an “omics” approach (PVDOMICS). This is the largest initiative for PVD undertaken by the NHLBI since the PH registry (15), which provided major insight into PH. Public investment in the PH registry stimulated decades of groundbreaking research into this devastating disease that eventually led to the many therapies we have today. The recent PVDOMICS network promises to take our understanding of PVDs to the next level. Several nationally ranked teams of basic, translational, and clinical investigators with expertise in PVDs were awarded funds to (1): reclassify subsets of patients with PH regardless of the existing conventional World Health Organization classification system (2); define novel, clinically relevant therapeutic indices that may be useful for intermediate or primary outcomes in clinical trials (3); identify biomarkers of PH for detection and prevention research; and (4) define novel vascular disease phenotypes through endophenotyping approaches, including genomics, proteomics, metabolomics, etc. (5, 14). Recently, these teams of experts convened a workshop with other NHLBI initiatives, patient advocacy organizations, regulatory agencies, and pharmaceutical industry experts to discuss current and prospective research priorities and their alignment with the NHLBI Strategic Vision on precision medicine for PVDs (Figure 1).

In this issue of the *Journal*, Newman and colleagues (pp. 1661–1670) report on the outcome of the workshop that

was sponsored by the Division of Lung Diseases of the NHLBI and the Cardiovascular Medical Research and Education Fund (16). The goal of the workshop was to identify ways to focus and leverage the activities of the recently launched NHLBI PVDOMICS initiative. This is a collaborative protocol-driven network to reclassify populations of patients with PH and define novel vascular disease phenotypes based on endophenotyping activities using several omics-based methods. This report provides a summary of the opinions and conclusions of the workshop participants that are intended to help the NHLBI as it determines priorities in its Strategic Vision. This workshop report is certainly timely in both the areas of PH and other PVDs as well as in the area of precision medicine. A major strength of this report is that it brings together stakeholders from different areas, including basic, translational, and clinical researchers in addition to clinicians, patient advocate organizations, regulatory agencies, and pharmaceutical industry experts. The report also offers several useful suggestions on how to move the field forward within the context of the currently ongoing initiatives by the National Institutes of Health and the Cardiovascular Medical Research and Education Fund. The group discussed the current inadequacies of therapies for PH using the “one-size-fits-all” approach. They addressed the overall limited response to PH therapies and highlighted multiple potential reasons. Specifically, they discussed the lack of mechanistic-defined patient phenotypes, the heterogeneous and ambiguous World Health Organization groups, the lack of satisfactory clinical trial endpoints in spite of 25 years of therapies, and the limited understanding of the mechanism(s) of action for some treatments in PH. To overcome the limitations of the current practice, the experts discussed the use of a personalized approach. To build on recent advances and discoveries, the group discussed the role of the PVDOMICS network and how each team could better integrate the link between phenotypes and biology through clinical phenotyping and endophenotyping methods. The workshop report discussed the use of “big data” metaanalytics and machine learning (“deep patient”) approaches prior to clinical trials as well as determining the right clinical trial for an individual patient. Furthermore, they highlighted the current lack of robust primary and secondary endpoints for PH clinical trials, and discussed how “patient preference” should be included as an important measure of treatment efficacy.

In the absence of a therapeutic intervention, these initiatives would have greater potential if they supplemented their current descriptive approach with a plan to identify mechanisms of disease. Another missed opportunity is the lack of correlation to robust outcomes and endpoints. Biomarkers and phenotypes identified by the initiatives would be much more valuable if validated against mortality/survival, which is the ultimate endpoint. This would allow these exciting ventures to transcend the opportunities missed in the design of most industry-sponsored clinical trials to date (17, 18). These initiatives have a great promise to provide groundbreaking findings and highly valuable insights into PVDs. Including robust endpoints and patient-centered outcomes will hopefully maximize the return on the public investment and minimize the chances of following the precision rabbit down the alluring omics hole. ■

Figure 1. Some of the ongoing efforts in precision medicine for pulmonary vascular diseases. NIH = National Institutes of Health; PAH = pulmonary arterial hypertension; PVDs = pulmonary vascular diseases. Illustration by Jacqueline Schaffer.

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