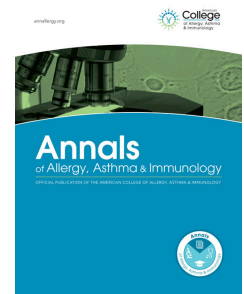


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Precision Medicine for Lung Diseases: A National Heart, Lung, and Blood Institute Perspective

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Perspective

Precision Medicine for Lung Diseases: A National Heart, Lung, and Blood Institute Perspective

Personalized medicine is not new. For centuries physicians have provided individualized care based on the nuanced clinical presentations of patients and the severity of their diseases. However, analytical advances over the past decade have sparked a hope that we may soon be able to deliver medical care with unprecedented resolution and effectiveness. To distinguish that new era of personalized medicine from the kind practiced by Galen in ancient Rome, a new term has been coined. *Precision medicine* describes a molecule-based approach to personalized medicine, one which can utilize precise biological measures (biomarker assays, genetic and epigenetic information, imaging studies, and quantitative clinical phenotypes) to determine the right treatment for the right patient at the right time. Analogous opportunities exist for precise prevention.

At this time, the full promise of precision medicine remains an optimistic goal for most diseases. A host of issues related to the availability of highly targeted treatments, the expectations of regulatory agencies, the structure of clinical care guidelines, and the practices of healthcare payors must all be resolved before patients with common lung diseases can fully benefit from this new form of precision care. Nevertheless, significant progress is being made toward the goal of precision medicine, especially for diseases such as asthma in which immunologic abnormalities play a prominent role. This perspective highlights efforts by NHLBI to promote the research needed to advance this field for lung diseases. That research includes deep phenotyping of patient cohorts, large scale genomic studies, biomarker-directed clinical trials, mechanistic studies of particular pathobiological processes, and development of novel, molecule-targeted therapies.

The Division of Lung Diseases (DLD) in NHLBI has emphasized the research needed to advance precision medicine for more than a decade. Recognizing that a detailed mechanistic understanding of the pathobiology of disease is needed to develop precise treatments and prevention strategies, we have invested heavily in investigator-initiated research (R01) grants, which comprise the bedrock of NIH-supported research on pathobiology. Over the past ten years DLD has funded approximately 700 R01 grants each year at an average Total Cost of about \$353 M per year. Interestingly, the fraction of these R01 grants that involve human subjects or specimens in the research has steadily increased over that period, from 38% in 2009 to 50% in 2018, perhaps reflecting greater accessibility to the tissues, experimental tools, and data required to study human biology directly. This research is generating the detailed understanding of molecular and cellular biology needed to develop therapies that target specific pathobiological processes towards the goal of precision therapies.

In parallel with this basic research, DLD has initiated several clinical research programs that seek to characterize and explain the inter-individual heterogeneity of pulmonary diseases. The first of these, begun in 2001, was our Severe Asthma Research Program (SARP), whose investigators have used common protocols to study 2358 individuals with asthma in detail, including 1007 with severe asthma.¹ SARP has led in defining subgroups within asthma and characterizing phenotypic, cellular, and molecular variations among these groups, and its model is being followed in other diseases. The SubPopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS), begun in 2009, is performing detailed, longitudinal phenotyping of 2981 individuals, largely with COPD.² We have also funded recruitment and characterization of more than 10,000 smokers with or at risk of COPD in the COPDGene study.³ The Genomic Research in AAT-Deficiency and Sarcoidosis study (GRADS) has completed deep phenotyping

of 200 individuals with alpha-1 antitrypsin deficiency and 400 with sarcoidosis,⁴ and the Pulmonary Vascular Disease Phenomics Program (PVDOMICS) is currently recruiting and characterizing 1200 patients with pulmonary hypertension.⁵ The clinical and biomarker data generated by these large programs are providing unprecedented opportunities for better understanding the substantial variations in presentation and disease course that are typical of lung diseases.

Another major program of NHLBI is helping investigators obtain extensive genomic data from biospecimens collected in these deep phenotyping studies and to better understand the molecular bases of lung and sleep disorders. NHLBI began the Trans-Omics for Precision Medicine (TOPMed) program in 2014 to obtain genomic data that can inform advances in precision medicine. TOPMed (<https://www.nhlbiwgs.org>) has done whole genome sequencing (WGS) with DNA from more than 70 well-phenotyped cohorts involving about 150,000 participants. More than 50,000 of the WGS are related to lung diseases, primarily from studies of asthma or COPD, but also including cohorts with idiopathic pulmonary fibrosis (IPF), sarcoidosis, or obstructive sleep apnea. Racial and ethnic disparities can be readily examined in the cohorts selected for sequencing in TOPMed. The asthma studies include 40% African Americans and 40% Hispanics; sarcoidosis cases are 100% on African American; and the sleep apnea cohort has 50% African American participants.

TOPMed data are an incredibly rich resource for research related to precision medicine. The first 100,000 WGS data revealed more than 640 million SNPs and indels, including more than 4.8 million that altered the amino acid sequence (missense and indels in coding regions) and 141,000 nonsense mutations that truncated the protein. Work is underway to characterize copy number and other structure variants, telomere length, and somatic mutations and to define

polygenic risk scores (PRS) that are highly predictive for common, complex disease phenotypes. Biospecimens from thousands of subjects are also being analyzed by TOPMed to obtain RNA-sequence, DNA methylation, and metabolomic data. These other omics data will facilitate identification of regulatory elements (cis- or trans-) that control gene expression at transcription levels and will allow integrative modeling of gene regulation, protein expression, and metabolomics.

A final area of research that is critical to precision medicine is the conduct of clinical trials that can inform optimal choices among multiple treatments for individual patients. DLD recently funded the first clinical research network in NHLBI that is specifically designed for that purpose. Precision Interventions for Severe and/or Exacerbation Prone Asthma (PrecISE) (<https://preciseasthma.org/preciseweb/>) is developing an adaptive protocol based, in large part, on knowledge generated by investigator-initiated studies of pathobiology and on phenotypic clustering analyses in SARP and other asthma cohorts. To determine the therapeutic response of individual patients, PrecISE will utilize disease phenotypes, endotypes, and predictive biomarkers in a multi-stage, precise, adaptive trial with multiple interventions. Severe asthma is particularly well suited for this highly innovative program, since multi-scale information has already confirmed the concept that severe asthma results from interactions among multiple, diverse pathobiologic mechanisms over time. PrecISE will leverage this evidence base to define more precise, biologically based approaches for asthma management.

PrecISE may provide a model for future trials in other pulmonary diseases. Targeted, adaptive testing enhances the flexibility and efficiency of trials by enriching the patient population with a specific etiology and predicting responsiveness rather than treating large patient groups as homogeneous populations. The combination of multi-scale information and multi-stage,

adaptive clinical trial designs, can be used to predict and stratify patients, based on pathobiology, and to determine the therapeutic responsiveness of specific disease endotypes. Such designs can also be used to inform and optimize large trials in the future, increasing efficiency. The ultimate result will be biologic and precision-based treatment approaches to disease management and secondary prevention, plus generation of new data to inform future development and validation of biomarkers for predicting and monitoring therapeutic responsiveness.

Finally, NHLBI recognizes that progress in precision medicine will require combining information from a wide variety of sources – integration of data generated by a host of investigators using many different scientific approaches. Such integrated analyses can be performed only if data are shared among investigators on a scale that far surpasses previous collaborative efforts of our scientific community. To facilitate the intensive data mining needed for discovery research in support of precision medicine, NHLBI recently began a project called STAGE (<https://www.nhlbiidaatastage.org/>). STAGE will soon host the large volume of TOPMed genomic data in a public cloud environment where investigators can perform analyses by bringing their own tools to the data or employing user-friendly tools provided by STAGE. We strongly encourage researchers to take advantage of the opportunity that STAGE will provide to generate novel hypotheses and to expand ongoing research by utilizing additional data obtained from large, heterogeneous populations with lung disease. We believe these collective efforts will bring to reality to goal of precision medicine for pulmonary diseases.

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