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March 2026 Response to the National Institutes of Health Request for Information

NIH-Wide Strategic Plan for Fiscal Years 2027–2031

Submitted by: The Alpha-1 Foundation

The Alpha-1 Foundation appreciates the opportunity to provide input regarding the development of the National Institutes of Health Strategic Plan for Fiscal Years 2027–2031.

Patients and families affected by Alpha-1 Antitrypsin Deficiency (Alpha-1) depend heavily on the biomedical research enterprise supported by NIH, particularly the leadership of the National Heart, Lung, and Blood Institute (NHLBI) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

Alpha-1 Antitrypsin Deficiency is a serious genetic disorder that causes progressive lung disease, early onset chronic obstructive pulmonary disease (COPD), bronchiectasis, and liver disease in both children and adults. Although classified as a rare disease, Alpha-1 represents an important model for translational and precision medicine research because its genetic basis and disease mechanisms are well characterized.

As a result, Alpha-1 provides a unique scientific platform that can accelerate discovery, therapeutic development, and regulatory innovation across multiple diseases. The Alpha-1 Foundation encourages NIH to recognize Alpha-1 as a model rare disease ecosystem demonstrating how coordinated research investment can produce meaningful progress for both rare and common diseases.

The upcoming NIH Strategic Plan presents an important opportunity to strengthen the nation's commitment to rare disease research, cross-institute coordination, and translational science that accelerates therapies from discovery to patient access.

Alpha-1 as a Model Translational Disease Platform

Rare diseases often present challenges for research due to small patient populations and fragmented data. Alpha-1 offers the opposite it has a well-organized national research ecosystem that can serve as a model for NIH strategy.

The Alpha-1 research infrastructure includes:

• Patient registries and natural history data
• Biobanks and genetic datasets
• Clinical trial networks
• Active collaboration with academic research centers

This infrastructure has enabled Alpha-1 research to generate insights that extend far beyond the rare disease community.

The Alpha-1 research ecosystem is also well-positioned to serve as a model for the integration of artificial intelligence (AI) and advanced analytics into biomedical research. The combination of longitudinal patient registries, genomic data, and clinical outcomes creates an ideal environment for the development of AI-driven approaches to:

• Predict disease progression
• Identify novel biomarkers
• Optimize clinical trial design and patient selection

Strengthening Rare Disease Research Across NIH

Rare diseases collectively affect more than 30 million Americans, yet most rare conditions still lack effective treatments.

The Alpha-1 Foundation encourages NIH to continue elevating rare diseases as a core priority across NIH research initiatives, including:

• Support case detection initiatives (including COPD screening)
• Expanded investment in genomics and gene-based therapies
• Support for natural history studies and patient registries
• Development of biomarkers and clinical endpoints for rare disease trials
• Expansion of rare disease clinical trial infrastructure
• Integration of artificial intelligence and machine learning to enhance biomarker discovery, natural history modeling, and trial efficiency

Research on Alpha-1 Antitrypsin Deficiency has contributed significantly to scientific understanding of:

• Chronic obstructive pulmonary disease (COPD) and bronchiectasis
• Lung inflammation and tissue destruction
• Genetic liver disease
• Precision medicine approaches for inherited disorders

Investments in rare disease research often produce broad scientific returns that benefit both rare and common diseases.

Improving Coordination Across NIH Institutes

Many rare diseases affect multiple organ systems and therefore span the missions of several NIH Institutes and Centers.

Alpha-1 Antitrypsin Deficiency affects both the lungs and the liver, requiring collaboration across multiple NIH institutes, including:

Manifestation	NIH Institute
Lung disease (emphysema, COPD)	National Heart, Lung, and Blood Institute
Liver disease	National Institute of Diabetes and Digestive and Kidney Diseases
Genetic mechanisms	National Human Genome Research Institute

The next NIH strategic plan should expand mechanisms that allow institutes to:

- Co-fund rare disease initiatives
- Share patient data infrastructure
- Coordinate clinical trial networks
- Support multidisciplinary translational research
- Develop interoperable, AI-ready data platforms that enable secure sharing and analysis of rare disease datasets across Institutes

Improved coordination will allow NIH to better address diseases that cross traditional research boundaries.

Expanding Collaboration Between NIH, FDA, and CMS

Scientific discovery alone does not deliver therapies to patients. Successful translation requires coordination across research, regulatory, and healthcare systems.

The Alpha-1 Foundation encourages stronger collaboration between NIH and:

- U.S. Food and Drug Administration (FDA)
- Centers for Medicare & Medicaid Services (CMS)

Such coordination is essential to:

- Identify clinical endpoints acceptable for regulatory approval
- Support innovative clinical trial designs appropriate for rare diseases
- Ensure timely patient access and reimbursement once therapies are approved
- Leverage AI-enabled analyses of real-world data and natural history cohorts to

support regulatory decision-making and post-market evidence generation, particularly in small patient populations

These goals align closely with the objectives of the 21st Century Cures Act, which emphasized accelerating medical innovation, strengthening patient engagement in research, and improving coordination among federal health agencies.

Maintaining Leadership in Lung Disease Research

Lung diseases remain among the leading causes of death and disability in the United States. However, pulmonary research funding has historically lagged behind the burden of disease.

The Alpha-1 Foundation encourages NIH to maintain strong leadership and investment within the National Heart, Lung, and Blood Institute.

Priority research areas should include:

- COPD and genetic emphysema
- Identification of biomarkers for disease progression
- Lung tissue repair and regeneration
- Gene correction therapies
- Environmental and occupational lung injury

Research on Alpha-1 Antitrypsin Deficiency has provided fundamental insights into protease-antiprotease imbalance and lung tissue destruction, mechanisms that have informed broader COPD research.

Continued investment in lung science will accelerate progress across multiple respiratory diseases affecting millions of Americans.

Advancing Research on Rare Liver Diseases

Alpha-1 Antitrypsin Deficiency is also one of the most common genetic causes of pediatric and adult liver disease.

The Alpha-1 Foundation strongly supports continued NIH investment in pediatric liver disease research, including programs such as the Childhood Liver Disease Research Network (ChiLDReN).

Supported by the National Institute of Diabetes and Digestive and Kidney Diseases, ChiLDReN plays a critical role in advancing research on rare liver diseases affecting infants and children, including Alpha-1 Antitrypsin Deficiency.

The Alpha-1 community encourages NIH to expand research in:

- Rare genetic liver diseases
- Pediatric liver disease progression
- Molecular therapies, including gene editing and RNA-based therapeutics
- Biomarkers predicting liver disease progression

For patients living with Alpha-1 Antitrypsin Deficiency, NIH-supported research represents hope for transformative therapies and ultimately a cure.

By strengthening rare disease science, expanding cross-institute collaboration, integrating AI-driven research capabilities, and accelerating translational coordination, NIH can advance progress not only for Alpha-1 patients but also for millions of Americans affected by genetic and chronic diseases.

The upcoming NIH Strategic Plan presents an opportunity to strengthen the United States' leadership in biomedical innovation while accelerating solutions for patients with rare and chronic diseases.

Alpha-1 provides a powerful example of how coordinated research investment can produce meaningful progress for both rare and common diseases. The Alpha-1 research ecosystem demonstrates how patient organizations, academic researchers, and federal agencies can work together to accelerate biomedical discovery and improve patient outcomes.

The Alpha-1 Foundation stands ready to partner with NIH to advance these priorities.

Scott Santarella
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