



MAY 2022

Enhancing NIH Research on Autoimmune Disease

Autoimmune diseases occur when the body's immune system malfunctions and mistakenly attacks healthy cells, tissues, and organs. There is no consensus on what illnesses are autoimmune diseases—counts range from more than 80 to around 150 diseases, depending on the source—and definitional boundaries of autoimmunity and autoimmune disease are evolving. The diseases present heterogeneously, can affect any part of the body, and can occur at any age. Common autoimmune diseases include celiac disease, rheumatoid arthritis, psoriasis, multiple sclerosis, inflammatory bowel disease (IBD), and type 1 diabetes. Individuals with an autoimmune disease often develop more than one, and face an increased risk of cancer, cardiovascular disease, and a wide variety of other complications and illnesses. Many autoimmune diseases, but not all, affect women predominantly, with female-to-male ratios reaching 6:1 or higher for some diseases. As a group, they rank among the 10 leading causes of death for females. With no known cures, autoimmune diseases are chronic, lifelong, and can cause significant physical and psychosocial impairment, impeding activities of daily living, productivity, and quality of life.

Strong data on the U.S. incidence and prevalence of autoimmune diseases are limited. The last U.S. study that examined autoimmune diseases as a whole, in 2009, estimated the prevalence of autoimmune diseases to be 7.6 to 9.4 percent—equivalent to 25 to 31 million people today. But this estimate was based on only 29 diseases and does not account for increased rates in the past decade shown by trend data, including increases in the prevalence of IBD and type 1 diabetes in children. There is no single pattern of racial and ethnic disparities in incidence or prevalence among autoimmune diseases; for some conditions, the highest rates are in Black, American Indian, and Alaska Native populations, while for others, the highest rates are in White populations. Disparities in the severity and prognosis of autoimmune diseases and in the provision of care have been observed. There is little U.S. data on the costs of specific autoimmune diseases or of autoimmune diseases overall. One study found the annual direct costs of multiple sclerosis to be second only to congestive heart failure, and another estimated the average total lifetime cost for patients with Crohn's disease to exceed \$600,000.

To form a clearer picture of the National Institutes of Health's (NIH's) autoimmune disease research portfolio, the challenges that NIH faces in supporting autoimmune disease research to benefit the greatest need, and possible solutions to those challenges, Congress requested the National Academies of Sciences, Engineering,



and Medicine assess the NIH autoimmune disease research portfolio with attention to issues such as risk factors, diagnostic tools and barriers, and treatments and prospects for cures; the occurrence of multiple autoimmune diseases in individuals; and the interplay of autoimmune diseases and coexisting conditions. In addition, the expert committee was asked to identify barriers to NIH-sponsored autoimmune disease research, research gaps, and promising areas for future research, as well as to evaluate Institute and Center (IC) structure to identify strengths and weaknesses in coordinating research. The committee's resulting consensus study report, *Enhancing NIH Research on Autoimmune Disease*, addresses this charge.

CONTEXT AND FRAMEWORK FOR THIS REPORT

To build context for identifying knowledge and research gaps in autoimmune disease research, and opportunities for addressing them, the committee selected 11 autoimmune diseases for special focus and examination. Selection factors included those autoimmune diseases that are in congressional language requesting the study, are overrepresented in women, may affect multiple systems, are associated with coexisting illness, and collectively illustrate the spectrum of autoimmune disease. The committee also considered the availability of NIH data on research funding for the diseases. Sjögren's disease, systemic lupus erythematosus, antiphospholipid syndrome, rheumatoid arthritis, psoriasis, IBD (Crohn's disease and ulcerative colitis), celiac disease, primary biliary cholangitis, multiple sclerosis, type 1 diabetes, and autoimmune thyroid disease, which includes Graves' disease and Hashimoto's thyroiditis, were chosen.

Investigating the 11 diseases highlighted the complexity of autoimmune diseases—their epidemiology and impact, etiology and risk factors, presentation and disease course, complications and coexisting illnesses, and treatments and responses to therapy. The committee found a lack of long-term (20 years or more), population-based epidemiology studies on autoimmune disease that could enable researchers to accurately estimate disease incidence and prevalence, assess trends, and identify differences among population subgroups. It also found an absence of multidisciplinary research using a life-course framework to track how exposures—such as infections, trauma, diet, and occupational exposures—over the lifetime affect the development and course of autoimmune diseases. There is no mandatory reporting system or national registry for autoimmune diseases in the United States. This is in contrast to cancer, for which the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program serves as an authoritative source for U.S. statistics.

While the committee determined that the characteristics that distinguish autoimmune diseases provide valuable information about the pathogenesis of each disease, it also recognized, and chose to highlight and discuss, the commonalities among autoimmune diseases, which could direct crosscutting research to accelerate efforts to prevent, delay, diagnose, treat, and cure disease. Considering the diseases as a group based on common mechanisms might provide novel insights beyond those gained by focusing on the affected organ or system, or on individual diseases. Crosscutting areas for research include genetics, environmental factors, biomarkers, sex-driven disease characteristics, coexisting morbidities, and mechanistic pathways. The committee believes that the emerging and evolving science now makes these connections more achievable than ever before.

To review the NIH research portfolio on autoimmune disease, the committee examined a set of inputs (spending), activities (research conducted), and outputs (clinical trials, publications, and other indicators) of NIH's investment. It also examined the different types of NIH-funded grants and awards; the process for reviewing and awarding grants; the funding and operation of extramural and intramural programs; NIH-wide and individual IC missions and strategic plans; autoimmune disease-related initiatives involving collaboration; and NIH approaches to coordinating research.

The committee's review confirms that much extraordinary work related to autoimmune disease has been undertaken. The committee was struck by the number of research grants (8,470) it identified as related to autoimmune disease during the fiscal year 2008–2020 period and the extent to which knowledge associated with these projects has been disseminated to the research community through publications, translated into potential interventions, or driven innovation through patents. At the same time, there are barriers to NIH's ability to maximize the outcomes of this research portfolio. For example, there is variation in IC strategic plans regarding autoimmune diseases, and mechanisms for coordinating autoimmune disease research among ICs appear limited. Most significant, however, is the absence of a research plan that spans all ICs to provide an overall strategic NIH plan for autoimmune diseases. Absent the latter, NIH lacks a comprehensive, transparent, and strategic approach to how it plans and evaluates progress made on autoimmune disease research. The committee identified five essential elements for accelerating and improving autoimmune disease research.

Essential Elements for Rapid Advancement and Improvement in Autoimmune Disease Research

1. Strategic research planning to set priorities
2. An emphasis on coordinating across ICs and enhancing collaborative research given the crosscutting nature of autoimmune diseases
3. An orientation toward innovation
4. A focus on evaluating the autoimmune research portfolio in order to determine progress made across NIH
5. Resources to support planning, collaboration, and innovation

While the committee recognizes that the diffuse and investigator-initiated nature of NIH research and of autoimmune disease research in particular has many well-described and accepted advantages, NIH does not optimally promote these essential elements. In organizing its recommendations into four action areas, the committee seeks not only to address an opportunity to fill gaps that may fall between the work of diverse ICs but also to capture and leverage an understanding of the crosscutting nature of autoimmune diseases.

CREATE AN OFFICE OF AUTOIMMUNE DISEASE/AUTOIMMUNITY RESEARCH WITHIN THE OFFICE OF THE NIH DIRECTOR

After considering multiple options for enhancing autoimmune disease research and resulting outcomes, and considering the pros and cons, costs, and feasibility issues for each, the committee determined that the best option to address these challenges and opportunities would be to create an Office of Autoimmune Disease/Autoimmunity Research within the Office of the NIH Director. It found significant merit in this option, provided the Office had its own research budget and would substantially control certain key budgetary decisions about autoimmune disease research activities conducted elsewhere in NIH.

A successful crosscutting Office should have the capacity to suggest and advance creative new scientific approaches, partners, and paradigms. Effective Offices recognize the importance of living within institutional cultures and constraints, but they can suggest and direct new ways of doing business that others may not see, have the time or expertise to consider, or the resources to pursue. This, in the view of the committee, is how a new Office of Autoimmune Disease/Autoimmunity Research would provide its greatest value.

Objectives of Office of Autoimmune Disease/Autoimmunity Research

- Facilitate cross-NIH multidisciplinary collaboration and stimulate innovation around autoimmune disease research
- Engage in priority setting, strategic planning, and implementation
- Budget for and allocate available research funds in alignment with the strategic plan
- Manage and evaluate research efforts
- Communicate with key stakeholders
- Provide visible leadership on autoimmune disease research

Realizing that creating an Office may take some time, the committee makes two specific recommendations relating to data collection that could be implemented independent of the Office.

ESTABLISH LONG-TERM SYSTEMS TO COLLECT POPULATION-BASED SURVEILLANCE AND EPIDEMIOLOGICAL DATA

Progress on autoimmune disease requires substantially more sophisticated and refined epidemiology on the individual and aggregate impact of autoimmune disease. Information gaps include trends in prevalence and incidence; comprehensive evaluations of the disease risk factors and disease impact on patients and families, including direct and indirect costs; the impact on different populations; the trajectory from the period before these diseases manifest and through the life course; and the impact of specific treatments and interventions.

The committee found a lack of long-term (20 years or more), population-based epidemiology studies on autoimmune disease. Such studies would allow for assessing trends, identifying differences among population subgroups, and determining the prevalence and incidence of under-researched autoimmune diseases and conditions, such as celiac disease.

To fill this gap, the committee recommends that NIH establish long-term systems to collect and ensure optimum usability of population-based surveillance and epidemiological data on autoimmune diseases and measures of autoimmunity. A model for such studies is the SEER Program for cancer. In addition, NIH should support the optimization of existing data sources.

ESTABLISH POPULATION AND PATIENT COHORTS

Few studies provide information on the long-term progression of autoimmune disease beginning in the period before disease manifests through the life course. Population cohorts can provide data that are critical for studying mechanisms leading to autoimmune diseases and to understanding the heterogeneity of disease expression and changes with time and over various life stages. To understand how early life exposures and the timing of these exposures influence health at different life stages at individual patient and population levels, it is essential to support long-term (10–20+ years) patient cohort studies. Such studies would also lead to new opportunities for developing clinical treatments and behavioral interventions. Moreover, the studies could be designed to address a wide variety of disease outcomes and health effects.

The committee recommends that NIH support the development of population cohorts that extend from the period before disease manifests to the development of symptoms and disease, and should support patient cohorts that will allow the examination of the progression, coexisting morbidities, and long-term (20+ years) outcomes of autoimmune diseases. Data collection should include, but need not be limited to, genome-wide associations; environmental and occupational exposures; autoantibody, cytokine, and T cell assays, particularly in new-onset disease; response to therapeutic interventions, including timing of treatment (e.g., to assess whether early treatments prevent disease progression); and development of co-occurring autoimmune diseases.

ESTABLISH A COMPREHENSIVE RESEARCH AGENDA

Addressing the research gaps the committee identified requires a comprehensive national research agenda for autoimmune diseases that involves coordination and collaboration among researchers, research groups, and stakeholders. This agenda should prioritize clinical and basic research that addresses key knowledge gaps, including, but not limited to:

- dissecting heterogeneity across and within autoimmune diseases to decipher common and disease-specific pathogenic mechanisms;
- examining rare autoimmune diseases and develop supporting animal models to better understand the mechanisms of these rare autoimmune diseases;
- defining autoantibodies and other biomarkers that can diagnose and predict the initiation and progression of autoimmune diseases;
- determining the biologic functions of genetic variants and gene–environment interactions within and across autoimmune diseases using novel, cutting-edge technologies;
- examining the role of environmental exposures and social determinants of health in autoimmune diseases across the lifespan;

- determining the impact of coexisting morbidities, including co-occurring autoimmune diseases and complications of autoimmune diseases, across the lifespan, and develop and evaluate interventions to improve patient outcomes;
- fostering research to advance health equity for all autoimmune disease patients; and
- assessing the direct and indirect costs of autoimmune diseases.

CONCLUSION

Millions live with autoimmune disease and there are indications that some autoimmune diseases are on the rise. NIH spending on autoimmune disease research has remained constant at about 2.8 percent of its total obligations between 2008 and 2020. From 2015 to 2020, total NIH obligations increased by 40 percent, whereas autoimmune disease spending increased by approximately 34 percent. If resources increase for autoimmune disease research, a strategy for prioritizing, leveraging, and ensuring that funds are invested in the areas of highest scientific priority would be essential. And if budgets remain constrained, the need for strategic prioritization is even greater.

The quantity and quality of the research NIH conducts on autoimmune diseases are impressive. The committee believes that a strategic plan for all NIH autoimmune disease research and a well-configured and well-funded Office to support the coordination and collaboration of all ICs that can play a role in advancing the field represent an opportunity for NIH both to optimize its significant resources and to maximize the ground covered by the research it conducts.

Committee for the Assessment of NIH Research on Autoimmune Diseases

Bernard M. Rosof (*Chair*)
Zucker School of Medicine at Hofstra/Northwell

Glinda S. Cooper
Innocence Project

Deidra C. Crews
Johns Hopkins University School of Medicine

William R. Duncan
East Tennessee State University

DeLisa Fairweather
Mayo Clinic

Sonia Friedman
Brigham and Women's Hospital

Lisa I. Iezzoni
Harvard Medical School

Andrea M. Knight
University of Toronto

Scott M. Lieberman
Carver College of Medicine,
University of Iowa

Michael D. Lockshin
Barbara Volcker Center for Women and Rheumatic Disease, Hospital for Special Surgery

Jill M. Norris
Colorado School of Public Health,
University of Colorado Anschutz Medical Campus

Emily C. Somers
University of Michigan Schools of Medicine and Public Health

Barbara G. Vickrey
Icahn School of Medicine at Mount Sinai

Study Staff

Rose Marie Martinez
Study Director
Senior Director, Board on Population Health and Public Health Practice

Leila Meymand
Senior Program Assistant (*until January 2022*)

Grace Reading
Senior Program Assistant

Dara Rosenberg
Research Associate

Kristin White
Associate Program Officer

Y. Crysti Park
Administrative Assistant

Study Sponsor

National Institutes of Health

To read the full report, please visit
<https://www.nationalacademies.org/autoimmune-disease>

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

The nation turns to the National Academies of Sciences, Engineering, and Medicine for independent, objective advice on issues that affect people's lives worldwide.

www.nationalacademies.org