During the course of its work, the committee assembled a list of research needs based on committee judgment. The list below is not intended to be comprehensive. However, it is indicative of the kinds of research needed, and by itself is far-reaching in terms of the kinds of research and disciplines required as well as the many diseases included in the autoimmune disease category.

**Dissect heterogeneity across and within autoimmune diseases to decipher common and disease-specific pathogenic mechanisms**

- Examine common innate inflammatory pathways (e.g., damage-associated molecular patterns, pathogen-associated molecular patterns, pattern recognition receptors, inflammasomes, and associated signaling pathways), dysregulated cellular processes, and altered metabolism across multiple autoimmune diseases to understand the biologic mechanisms underlying development, progression, remission, and exacerbation of autoimmune diseases in children and adults
- Apply machine learning methods that combine layers of “omics” data (e.g., genomics, proteomics, metabolomics) to generate new mechanistic hypotheses and inform discovery of novel drug targets
- Elucidate mechanisms by which sex-specific factors (such as hormones, X and Y chromosomes, birth control products, endocrine disrupting chemicals) influence autoimmune disease, examining the effect of puberty, pregnancy, and menopause to understand sex differences in autoimmune diseases
- Identify autoantigens across autoimmune diseases using new technologies that allow T cell receptors identified by single cell RNA sequencing from tissue to be interrogated without bias transfecting mRNA libraries into reporter antigen presenting cells
- Dissect molecular mechanisms associated with poor outcomes
- Design research that bridges animal models and human studies to better understand common mechanisms in inflammation for specific autoimmune diseases

**Study rare autoimmune diseases and develop supporting animal models**

- Study autoimmune diseases that affect fewer individuals but often have a high morbidity/earlier mortality to reveal novel, shared, or dominant molecular pathways and novel or improved therapeutic options
  - Dominant pathways in the less common autoimmune diseases may reveal shared molecular pathways with other autoimmune diseases to facilitate drug-repurposing, rapid trials and possible therapies that could rapidly impact clinical care
- Develop animal models to better understand the mechanisms of rare autoimmune disease

**Define autoantibodies and other biomarkers that can diagnose and predict the initiation and progression of autoimmune diseases**

- Determine the pathophysiological relationship of antibodies to autoimmune disease—for example, which autoantibodies are biomarkers of autoimmune diseases, which are effectors, and the reasons for the differences
- Determine the temporal relationship of antibodies to autoimmune disease—for example, how and why some autoantibodies appear decades before clinical illness and others appear simultaneously with first symptoms
- Understand differences in autoantibody profiles by age, sex, and sex-and-age, race, ethnicity, and ancestry, for individual autoimmune diseases and in relation to their ability to predict and diagnose autoimmune disease
- Examine whether infections (e.g., SARS-CoV-2) and/or chemicals (e.g., bisphenol A) influence autoantibody levels/types and/or immune complex formation that are diagnostic or pathological for autoimmune diseases
- Explore the pipeline for development and validation of autoantibodies as disease biomarkers and surrogate endpoints of disease
• Identify novel biomarkers and complex “signatures” that predict and diagnose autoimmune diseases including cytokines, microRNAs and other markers

**Determine the biologic functions of genetic variants and gene–environment interactions within and across autoimmune diseases using novel, cutting-edge technologies**

• Study early-onset (e.g., childhood-onset) and rare autoimmune diseases to identify pathologic genetic variants and potential mechanistic insights
• Systematically map genetic variants of individual autoimmune diseases to biologic functions in different populations in order to 1) translate genotype to phenotype, 2) define immune pathways that may predict response to treatment, and 3) inform understanding of the effect of environmental exposure in autoimmune diseases
• Understand genomic and pharmacogenomic data as they relate to the individual, that are disease specific, or provide insight across multiple autoimmune diseases
• Explore chimeric antigen receptor-T cell / natural killer cell therapies to benefit immune regulation
• Use and improve artificial intelligence, computational science, and other technologies to understand gene–environment interactions

**Examine the role of environmental exposures and social determinants of health in autoimmune diseases across the lifespan**

• Systematically examine the effect of environmental exposures (e.g., chemical, infectious, dietary) and social determinants of health in children and adults, including stress, for individual and/or multiple autoimmune diseases, including disease flares
• Determine the effect of environmental exposures on immune pathways in patients and animal models of autoimmune disease
• Utilize a life-course approach along with advanced methodologies (e.g., computational science) to identify and examine the potential effect of interacting co-exposures that may increase susceptibility to disease, and to understand how these factors affect onset, progression, and severity of disease
• Conduct a systematic investigation of the effects of nutrients, dietary antigens, exercise, aging, and microbiome in normal tissue development and homeostasis in the pre-clinical phase of disease and during disease and recovery
• Explore novel methodologies to identify distinct and interacting biological and biopsychosocial factors contributing to observed sex/gender differences in autoimmune diseases, including the effect of puberty, menopause, and pregnancy on autoimmune diseases

**Determine 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.**

• Investigate the occurrence of and risk factors for disease complications (e.g. functional impairment, disability, growth impairment), co-occurring autoimmune diseases, coexisting morbidities (e.g., cardiovascular disease, cancer), and psychosocial conditions (e.g., fatigue, depression, pain)
• Investigate the effects of complications and coexisting morbidities on clinical outcomes (e.g., adherence to therapy, disease activity, disease damage), functional outcomes (activity and participation in daily and community life, education and work status), health-related quality of life, and healthcare utilization and costs.
• Conduct research to improve understanding of the long-term consequences of autoimmune diseases in children
• Develop and test treatment models, targeting those at highest risk, that prevent, detect, and address complications and coexisting morbidities in persons living with autoimmune disorders, incorporating chronic disease self-management strategies and other approaches
• For complications for which there are no highly effective treatments, such as pain and fatigue, develop, identify, and test new therapies
• Develop and test interventions to improve or address lack of or inadequate social support in order to improve symptom and disease management and daily life, including interventions for parents of children with autoimmune disorders
Foster research to advance health equity for all autoimmune disease patients

• Investigate genetic, biological, social determinants, and environmental mechanisms of autoimmune diseases in different racial, ethnic, and other underrepresented groups, as well as across sexes and over the lifespan
• Identify individuals at high risk of autoimmune diseases and implement prevention strategies
• Investigate disparities and determinants of disparities in disease stage at presentation and progression of disease, including complications, coexisting morbidities, functional impairments, and disability
• Explore novel methodologies to identify distinct and interacting biological and biopsychosocial factors contributing to observed sex differences in autoimmune diseases
• Collaborate with consumers, community-based organizations, and other partners to develop and evaluate health care delivery and/or policy interventions to address identified disparities and generate evidence to support their feasibility, sustainability, and dissemination
• Build long-term partnerships between patients, communities, clinicians, and scientists to increase participation of underserved populations in interventional clinical trials and other clinical and translational research studies
• Conduct dissemination/implementation research to determine best practices and to improve outcomes for all
• Conduct research on how to increase recruitment of underserved populations in clinical research, and in interventional clinical trials in particular
• Conduct research on how best to target interventions for patients with worse outcomes and/or underserved populations

Assess the direct and indirect costs of autoimmune diseases

• Examine insurance claim data to assess inpatient, emergency room, outpatient, physician visit, pharmacy (including disparities between different therapies), laboratory, and medical device costs associated with autoimmune diseases
• Examine the costs of lost wages, job turnover, and other work-productivity issues
• Examine the costs of premature mortality
• Examine the costs of associated home care and child care

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