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# Action Plan for Lupus Research

Prepared by the National Institute of Arthritis and  
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# Action Plan for Lupus Research

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## Introduction

Systemic lupus erythematosus (SLE, or lupus) is one of more than 80 known autoimmune diseases. An autoimmune disease is one in which the body's immune system—its normal defense against harmful invaders including viruses and bacteria—turns its attack against the body's own organs, tissues, and cells. In some autoimmune diseases, the target of the attack is limited to a particular part of the body—the blood vessels, moisture-producing glands of the eyes and mouth, or insulin-producing cells of the pancreas, for example. In lupus, the attack is systemic, meaning it affects many organs and organ systems including the skin, joints, heart, lungs, kidneys, and brain. The results can be disabling or even deadly.

Disease activity often waxes and wanes. Periods of relatively mild disease may be followed by flares, or periods of increased disease activity involving one or more organ systems, which can lead to irreversible organ damage. Some flares are evident through clinical symptoms such as a skin rash, increased fatigue, joint inflammation, oral or nasal ulcers, or seizures. In other cases, the only evidence of a flare is a laboratory test showing a low white blood cell or platelet count or protein in the urine, for example.

By the most conservative estimates, there are at least 322,000 Americans with definite or probable lupus.<sup>1</sup> Recent independent surveys have suggested a prevalence as high as 1.5 million.<sup>1</sup> Women with the disease outnumber men nine to one. Lupus often strikes women in their early working and childbearing years, interfering with the ability to work, have or raise a family, or in some cases, even care for themselves.

The most heterogeneous of the autoimmune diseases, lupus is also one of the most difficult to understand and treat. Sixty years ago, about 50 percent of those with lupus died within five years of their diagnosis. Today, thanks to advances brought about by research, 97 percent of lupus patients are living five years after diagnosis, and 90 percent continue to survive after 10 years. The transformation of lupus from a disease with a high mortality rate to one that is chronic has led to an increased need for better therapies that can manage long-term symptoms. Ongoing research is likely to lead to new therapies with fewer side effects.

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<sup>1</sup> <http://www.cdc.gov/arthritis/basics/lupus.htm>

The past two decades of research have yielded a wealth of new information and extraordinary growth in improving our understanding of lupus. As a result, opportunities now exist to identify potential genetic, epigenetic, environmental, and infectious causes of lupus, and to develop novel approaches for lupus treatment and prevention. To achieve these goals, the National Institutes of Health (NIH) places a high priority on cross-disciplinary research and the participation of other government agencies and private organizations in these efforts.

To facilitate collaboration among the NIH Institutes, other federal agencies, voluntary and professional organizations, and industry groups that have an interest in lupus, the NIH established the [Lupus Federal Working Group](#) (LFWG) in 2003 at the request of Congress. The LFWG is led by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and includes representatives from all relevant Department of Health and Human Services (HHS) agencies and other federal departments having an interest in lupus. This includes the National Institute of Allergy and Infectious Diseases; the National Institute of Neurological Disorders and Stroke; the National Institute of Diabetes and Digestive and Kidney Diseases; the National Heart, Lung, and Blood Institute; the NIH Office of Research on Women's Health; and other agencies of the federal government, including the HHS Office on Women's Health, the U.S. Food and Drug Administration (FDA), and the Centers for Disease Control and Prevention (CDC). Voluntary organizations and representatives from the private sector also attend and participate in the meetings of the LFWG.

In fiscal year 2005, the House Appropriations Committee directed the NIH to develop a plan to guide the nation's investment in lupus research. To identify the opportunities, priorities and needs in lupus research that should be considered for inclusion in the plan, the NIH convened a workshop with scientific experts. The highlights of their conclusions were reported in 2007 in [The Future Directions of Lupus Research](#).

In July 2014, the Congressional Lupus Caucus requested that the NIAMS, as convener of the LFWG, develop a new coordinated action plan for lupus research on behalf of the NIH. Over the next year, the Institute issued two Requests for Information to solicit comments from the public, and held a webinar with external experts and lupus groups to obtain input on research directions that should be included in the coordinated Action Plan. A detailed description of the development of this plan is provided in Appendix 1. This document represents a synthesis of internal and external input on promising future directions for lupus research. It will help to inform priority-setting processes among all lupus-related organizations and serve as a guide for investigators as they develop independent approaches to address the numerous scientific opportunities in lupus.

Through the development process, four key questions emerged.

- First, is lupus one disease or many? In recent years, new research tools have improved the molecular characterization of lupus, providing support for the view that lupus actually represents a spectrum of related, but distinct, conditions. Many of the suggested research directions described in this plan will help researchers identify and define subgroups in a clinically meaningful way. If lupus represents a collection of related diseases, it will be important to determine whether these diseases have different causes and mechanisms that would require distinct prevention and treatment strategies. It also will have important implications for the grouping of patients participating in observational and interventional clinical trials.
- Second, how can new and emerging research tools and technologies advance our understanding of disease mechanisms? Many contributors to the plan expressed enthusiasm about the potential for cutting-edge tools (e.g., genetic analysis and gene editing, high-throughput and systems biology approaches, state-of-the-art imaging modalities, and mobile technologies) to move research forward. The research tools developed in recent years will enable scientists to explore disease mechanisms and follow patients clinically in ways that have not been possible previously.
- Third, how can we facilitate the development of new and emerging treatment paradigms? Since 2007, when the last plan was published, researchers have made tremendous progress in identifying individuals who are at-risk for lupus, as well as molecular markers that appear before the onset of clinical symptoms. Researchers now hope to translate such discoveries into strategies for early intervention or even disease prevention. For individuals with established lupus, researchers are focused on designing new trials that could test emerging candidate drugs in combination or sequentially with existing therapies.
- Finally, how can various sectors work together to more effectively conduct and support lupus research and research training? Many members of the community have highlighted the need for innovative partnerships between federal agencies, patient and professional groups, and industry. For example, novel partnerships could advance the goal of precision medicine—an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle—for people with lupus.

This research plan highlights many opportunities to increase our understanding of lupus at the molecular, individual, and population levels, which should ultimately allow the translation of new knowledge into safer and more effective treatments and, eventually, curative strategies. The report is organized to mirror current understanding of the disease, and to reflect opportunities for advancement. It supplements and enhances ongoing plans and activities of the NIH, such as the [NIAMS Long Range Plan \(2015-2019\)](#), as well as the work of the LFWG and the NIH [Autoimmune Diseases Coordinating Committee](#).

## Chapter 1: Etiology and Prevention

Although the cause of lupus remains unknown, there is strong evidence that genetics, epigenetics, environmental, and infectious and non-infectious factors play a role. New ideas, concepts and technologies have improved understanding of the factors that may predispose people to lupus and trigger its development and clinical course. Scientists' perseverance in gathering biospecimens and clinical histories from lupus patients and their relatives has opened new research avenues. Emerging opportunities to study genes and pathways, epigenetics, and gene-environment interactions are expected to improve understanding of lupus initiation and progression, and ultimately lead to development of better tools for diagnosis, prognosis, prevention, and treatment.

NIH-supported research has been key in the discovery of potential factors that influence susceptibility to lupus. Since the publication of the original *Future Directions of Lupus Research* report in 2007, researchers have made substantial advances related to understanding the etiology of lupus. Genome-wide association studies have identified numerous genetic variants associated with lupus, although the functions of identified variants and their contribution to disease remain largely unknown. In most cases, lupus is thought to be caused by a combination of many genetic variations, each with modest effects, although recent studies have pointed to the existence of rare variations with more substantial effects in certain lupus patient subsets. Research on genetic variants and the mechanisms by which they affect disease initiation and progression can provide new insights into lupus pathogenesis.

While genetics may play a crucial role in the development of lupus, researchers agree that environmental factors contribute to disease initiation and progression in genetically susceptible individuals. Recent data suggest that environmental factors may directly influence disease risk by interacting with the genome to alter gene expression. Analyses of gene-environment interactions are expected to provide information about the role of epigenetic alterations (e.g., DNA methylation patterns in T cells), chromatin remodeling, RNA transcripts and their encoded proteins, and microRNAs in lupus. Research on genes or variants that interact with certain

environmental factors (e.g., gut microbes, dietary components, infectious agents) to trigger disease may provide important insights into lupus development, progression, and severity.

## Research Objectives

Broad areas of potential research directions include:

### Genetics and Genomics

- Investigate the genetic architecture that influences susceptibility to autoimmune diseases
- Investigate the potential role of epistatic interactions between multiple lupus susceptibility genes in a single individual
- Use bioinformatics tools to identify new genetic variants and target pathways in lupus
- Identify and determine the function of causal variants within lupus-associated genetic elements
- Use *in vivo* models to determine the effects of identified risk variants and their relative contributions to autoimmunity and disease
- Use induced pluripotent stem cell (iPSC) or genomic editing technologies to improve our understanding of lupus risk and its preclinical stages
- Characterize epigenomic events in specific cell types and subtypes from individuals with and without defined risk genotypes to understand the effects of epigenetic alterations within the context of known genomic variants
- Conduct studies in well-defined longitudinal patient cohorts so that changes in -omics readouts can be linked to phenotypic alterations
- Conduct whole exome or genome sequencing to define extreme human phenotypes of lupus, and to identify somatic mutations in critical cell populations in humans and in animal models of lupus
- Use molecular phenotyping to facilitate studies of etiology and disease mechanisms by identifying molecular signatures that can be used to stratify heterogeneous groups of patients into more homogeneous populations

### Environment

- Investigate the contribution of environmental factors (e.g., diet, lifestyle, human microbiome) to risk of developing lupus or developing flares in individuals with established lupus
- Understand the mechanisms by which exposure to sunlight may trigger lupus symptoms
- Investigate factors that may be associated with lupus flares, such as ultraviolet (UV) light, stress, medications, physical activity, sleep deprivation, and infections (viral or other)



- Investigate maternal (pre-conception or gestational) and early-childhood exposures that may alter the risk of development of lupus in children
- Use detailed epidemiologic studies and proteomic analyses to clearly identify signatures of prior microbial or other environmental exposures
- Foster collaboration between environmental experts and clinical investigators to better assess and measure relevant exposures using emerging new tools such as wearable biosensors
- Link potential environmental exposures to molecular disease mechanisms (e.g., epigenetic changes, Toll-like receptor triggering, NETosis, other pathways)
- Understand the interplay between genetics and environment in the development of lupus
  - Understand how environmental factors may cause epigenetic changes in critical cell types (e.g., T cell DNA methylation)
  - Study the impact of environmental factors that cause oxidative stress
- Differentiate disease-causing genetic and environmental factors from those that affect disease propagation and events in later-stage disease, such as chronic tissue damage

### Epidemiology

- Conduct longitudinal studies of patients as they develop lupus, including collecting biological specimens and clinical data, in order to understand disease initiation and identify exposures related to the development of lupus
- Investigate time windows of increased vulnerability or susceptibility to the development of lupus (e.g., *in utero*, early childhood, adolescence, or adulthood)
- Understand the molecular factors that influence age of onset of lupus
- Leverage the expansion of insurance coverage and electronic medical record data availability to enhance epidemiological studies, potentially including geographic exposure, medication, and healthcare utilization data
- Leverage the availability of data from social networking and biometric wearables to enhance epidemiological studies to include environmental factors and the patient voice and experience
- Study changes in lupus prevalence and incidence over time across the age-spectrum of disease

## Chapter 2: Mechanisms of Disease

To lay the groundwork for future therapies, researchers are studying the altered biological processes that lead to the wide array of immune system abnormalities that characterize lupus. Recent findings suggest that both arms of the immune system—the innate and adaptive

immune systems—are involved in the disease, and various interplays between the two systems may result in the initiation and propagation of autoimmunity. Over the past few years, researchers have learned more about the role of Toll-like receptors (TLRs) and other innate immune system receptors in lupus pathogenesis. They also have improved understanding of immune cell subsets (e.g., T cell subsets, B cell subsets, dendritic cells) and their signaling pathways. Other work has shed light on the role of neutrophils, an abundant, yet short-lived white blood cell involved in the innate immune response, in lupus. For example, recent studies have indicated that neutrophil death by a mechanism called NETosis likely provides cellular material that may elicit an autoimmune response.

Although immune dysregulation plays a major role in lupus, structural and functional properties of target organs (kidneys, heart, lungs, blood vessels and brain) may contribute significantly to the development of tissue damage and clinical manifestations. Recent advances indicate that target organ processes may be related to the induction and maintenance of damage, including expression of proteins related to organ function. Researchers have begun to increase their focus on autoantigens in target tissues, local immune responses in target organ tissue, and the role of molecular pathways within resident tissue cells in organ damage. This is particularly relevant in lupus nephritis, which is at least as severe in males as it is in females, suggesting that the molecular pathways involved in renal damage must be aggressive in both sexes. In the past few years, researchers have gained a better understanding of the mechanisms of accelerated atherosclerosis in lupus and have learned more about how interferon-alpha damages blood vessels. By better understanding mechanisms of organ damage in lupus, researchers can test approaches to modify these processes, and perhaps minimize or prevent some of the most serious complications of the disease.

## Research Objectives

Broad areas of potential research directions include:

### Immune and Inflammatory Mechanisms

- Understand the contribution of dysregulated cellular processes (e.g., cell death, defective clearance of dead cells, autophagy, oxidative stress) in development and progression of lupus
- Elucidate the role of viruses, hormones, systemic inflammation and other factors as disease initiators or triggers of disease flares
- Understand the biological basis for sex differences in immune and inflammatory systems that contribute to the sex differences in lupus

- Understand the relative roles of membrane bound and cytosolic innate immune sensors and their signaling pathways and triggers on the initiation and pathogenesis of lupus; identify critical steps that can be targeted for therapy
- Explore the role of gene-regulatory elements, such as transcription factors, enhancers/super-enhancers, and microRNAs on the regulation of cellular functions related to lupus
- Study the innate and adaptive immune responses to endogenous retroelements (i.e., viral nucleic acids embedded in the genome), in both animal models and humans
- Characterize immune cell tolerance defects in lupus, including regulatory cells (e.g., Treg cells, Breg cells) and other immune-dampening systems that may be altered in lupus
- Investigate methods to induce tolerance, potentially through peptide vaccination
- Elucidate the role of the major histocompatibility complex locus and its related functions in lupus susceptibility and initiation
- Define the factors and mechanisms that cause autoantibody specificity (e.g., why do some patients develop antibodies to anti-DNA leading to glomerulonephritis, while others develop antibodies to red blood cells leading to autoimmune hemolytic anemia?)
- Understand the regulation and contribution of different B cell populations to lupus pathogenesis, and develop models to track the generation and progression of autoreactive B cells
- Explore new methods to target autoreactive B cells and plasma cells (e.g., therapeutic targeting of nuclear export proteins) in lupus
- Continue to use emerging technologies (e.g., CRISPR) to create new animal models with lupus genotype alleles; replicate these studies in human cell lines
- Understand the role of the microbiome in autoimmune disease initiation and progression, and how manipulation of the microbiome may alter disease course, in both humans and lupus animal models
- Identify markers and pathogenic pathways activated in patients with early/pre-clinical disease versus those with established disease and those in remission
- Understand disease-triggering immunological mechanisms in people who have a high risk for lupus or in patients with non-specific early symptoms of potential lupus
- Understand specific elements of the interferon-alpha signature that associate with disease severity, poor prognosis, or response to therapy
- Differentiate distinct molecular pathways that might separate what we now define as lupus on clinical grounds into distinct biological diseases that can be studied individually
- Understand the mechanisms that link complement deficiencies to the development of lupus

- Investigate the role of glycans in blood and vascular systems leading to immune dysregulation in lupus

### Target Organ Damage

- Study the biological basis for sex differences in target organs and tissues that contribute to the sex differences in lupus
- Understand physiological mechanisms and risk factors of renal damage
  - Elucidate mechanisms of renal injury, progression, and recovery
  - Understand the role of autoantibodies and immune complexes in the pathogenesis of kidney injury
- Determine whether animal models can be developed for membranous lupus nephritis
- Apply brain imaging techniques and clinical assessment tools (e.g., [NIH Toolbox](#)) to explore central nervous system lupus
- Investigate the contribution of cytokines and autoantibodies to the various presentations of neuropsychiatric lupus, including cognitive dysfunction
- Investigate the effects of interactions between components of the immune system on metabolism in lupus, as well as on traditional cardiovascular risk factors, such as premature atherosclerosis
- Understand the connection between cardiovascular disease in lupus and immune dysregulation
- Elucidate the mechanisms and pathways of lupus skin involvement and factors leading to skin damage
- Investigate organ-specific differences in RNA expression and the possible effects of those differences on disease and end-organ damage

## Chapter 3: New Treatments and Interventions

The goals of treatments for lupus typically have focused on decreasing inflammation and pain while preventing tissue damage and complications. However, no effective targeted therapies exist for the most severe manifestations of the disease (e.g., lupus nephritis, cardiac involvement, and neuropsychiatric lupus). Many of the existing medications have serious side effects, and no medications have been approved for the treatment of lupus in children. In 2011, the FDA approved Benlysta® (belimumab) for the treatment of lupus in adults, making it the first drug in 56 years to be approved for the condition. Despite this significant milestone, developing new drugs for lupus remains challenging. Some of the most important work in lupus in the coming years will focus on improving the ability to diagnose and treat the disease and its complications. Improvements in these areas will depend largely on further developments in four key areas: preclinical and translational research, the identification and validation of

biomarkers and surrogate endpoints for use in clinical trials, therapeutic development activities, and well-designed interventional studies.

In the past few years, several advances related to the development of new therapies have occurred. New efforts have begun to explore the value of “repurposing” drugs approved for other conditions to treat lupus. Progress has been made on identifying new biomarkers (e.g., interferon-alpha signature) and exploring potential new therapeutics, including epigenetic modulators, and agents that target the type I interferon pathway. Researchers also are increasingly incorporating into clinical trials measures of outcomes that are most important to patients, such as improved symptom and quality of life assessments, increased tolerability of drug regimens, and more effective management of co-morbid conditions. There also is interest in increasing the number of studies that compare the effectiveness of various interventions.

## Research Objectives

Broad areas of potential research directions include:

### Biomarker Development and Validation

- Characterize longitudinal samples to identify molecular signals or other biomarker signatures that could be predictors of a flare
- Develop and validate biomarkers for specific outcomes (e.g., end-stage renal disease, cardiovascular disease)
- Relate various biomarkers to clinical subtypes, disease activity, and genetic predisposition to improve disease stratification
- Advance proteomics and integrate with other –omics approaches to identify novel biomarkers
- Analyze biomarker and/or pharmacogenomic data from studies in well-defined cohorts to identify predictors of response, as well as toxicity to specific therapies

### Drug Development

- Develop organ specific therapies, such as for kidney disease
- Design early-stage clinical trials to assess candidate therapeutics
- Conduct dose finding studies for therapeutics to improve efficacy and decrease side effects
- Develop methods for targeted delivery of drugs to the immune system, tissue resident cells, or organs (e.g., monoclonal antibody-toxin conjugates to target and directly kill specific cells)
- Establish therapeutic target-based drug levels to ensure current and future therapeutics are being titrated effectively in individual patients

- Develop new therapeutics, or improved formulations of existing therapeutics, that can be used as more effective long-term treatments for lupus with improved safety compared to therapies currently in clinical use

### Clinical Trials

- Study and develop new experimental immunotherapies and improve existing immunotherapies
- Improve disease management by determining optimal dosing of steroids to maximize effectiveness and minimize toxicity
- Design clinical trials to determine whether treat-to-target approaches minimize damage to organs such as the kidney, joints, or brain, and improve patient outcomes
- Study novel combinations of existing and emerging therapies guided by mechanism-based models with agents that target these mechanisms
- Develop evidence-based criteria for if or when maintenance therapy can be discontinued or whether drug holidays are feasible
- Repurpose existing drugs to treat lupus-related disease
- Study the comparative effectiveness of existing medications for specific lupus indications
- Improve study designs to maintain statistical and clinical rigor in the short-term and generalizability in the long-term
  - Develop new adaptive or other alternative clinical trial designs
  - Match endpoints to other key aspects of trial design, such as inclusion/exclusion cutoffs
  - Include concrete endpoints, biomarkers, and relevant patient-reported outcomes (PROs) for all phases of clinical trials
  - Incorporate results of basic studies of disease mechanisms into clinical trials
  - Collect correlative data and specimens in clinical trials to facilitate linking –omics patterns to phenotypes
  - Conduct long-term follow-up of participants in clinical research to optimize interpretation and generalizability of results

### Patient-Centered Research Opportunities

- Identify individuals at highest risk of developing lupus and develop targeted preventive interventions for those groups
- Improve assessment of pain, fatigue, physical function, and other symptoms by employing validated PROs (e.g., PROMIS<sup>®</sup>—the Patient Reported Outcomes Measurement Information System<sup>®</sup>) in lupus; understand how outcomes change over

time, how they are affected by interventions and treatment, and how lupus patients compare to patients with other diseases

- Clinically validate adult and pediatric PROs as response criteria for clinical trials
- Investigate the effects of sociodemographic differences in patient populations on clinical responses to different medications
- Develop approaches to enable precision medicine in lupus
- Identify social determinants of health among patients with lupus
- Bring patients in as “field researchers” to contribute data through social media and biometric devices to facilitate patient-centered approaches to autoimmune disease research

## Chapter 4: Diagnosis and Clinical Care

As with any disease, early diagnosis of lupus often leads to the most successful treatment. In its early stages, lupus can resemble a number of diseases, many of which require different courses of treatment. Moreover, the disease manifestations can develop at different times and often are not all present at once. Therefore, the accumulation of enough signs and symptoms to fulfill the diagnostic criteria for lupus takes time. The lack of a specific diagnostic test for lupus results not only in delayed diagnosis and treatment, but also more severe disease manifestations, and worse patient outcomes.

Treating lupus can be difficult, as well. The features of lupus vary widely among individuals, as do optimal treatment plans, which are tailored to the individual’s needs and may change over time. Some goals of treatment are to prevent flares, to treat them when they do occur, and to minimize organ damage and complications. In light of the potentially harmful side effects of many of the existing therapies (e.g., corticosteroids), researchers are working to develop ways to limit or offset the use of such medications. Researchers also are looking for ways to improve diagnosis and clinical care through the use of biomarkers and new approaches for clinical monitoring and treatment.

### Research Objectives

Broad areas of potential research directions include:

#### Biomarkers Usage in Clinical Practice

- Clinically validate existing biomarkers and develop and validate new biomarkers for pediatric and adult cohorts
- Standardize methods for assessing and reporting biomarkers and PROs

- Investigate risk factors and biomarkers associated with a variety of outcomes to enable more effective, earlier intervention
- Utilize both existing and emerging biomarkers with acceptable sensitivity and specificity to personalize treatment for individual patients
- Develop methods to improve the information obtained from tissue biopsies (e.g., genetic makeup and molecular profile) so that it can be used to guide the choice of therapeutics or stratification into an appropriate clinical trial
- Identify biomarkers of steroid response to ensure adequate dosing
- Develop companion biomarkers for available therapies to identify responders early

### Clinical Monitoring and Treatment

- Incorporate new imaging technologies into patient care
- Clinically validate existing lupus quality indicators and develop new quality measures to address important gaps
- Develop organ-specific surrogate outcomes measures
- Develop steroid-sparing treatments or other treatment regimens to decrease long-term damage by toxic therapies
- Develop evidence-based standards for steroid use for lupus treatment
- Investigate the basis of the major disease subsets of lupus, such as glomerulonephritis, cutaneous lupus, autoimmune hemolytic anemia, anti-phospholipid syndrome, neonatal lupus, and others
- Develop non-invasive tests to predict and monitor lupus activity
- Develop simpler ways to assess lupus disease activity (e.g., PRO-wearable devices, downloadable apps)
- Encourage patients to contribute PRO data through social media and biometric devices to facilitate personalized medicine approaches to autoimmune diseases; include a focus on children due to their ongoing development to gain an understanding of the effect of lupus on children's health-related quality of life
- Use PROs to monitor treatment response and assess the efficacy and safety of interventions
- Investigate differential treatment responses that are affected by race, sex, age, and ethnicity, as well as their influence on differential organ involvement
- Increase ethnicity-specific risk assessment and monitoring
- Investigate factors affecting long-term outcomes in lupus (e.g., renal failure, cardiovascular disease, osteoporosis) in order to define preventive strategies to improve outcomes



## Chapter 5: Behavioral, Biopsychosocial and Health Services Research

While research continues to elucidate the biological underpinnings of lupus occurrence and treatment, it is imperative to continue to improve the patient experience. Behavioral and social science research constitute an important component of treating the whole individual, not just the disease. The use of PROs is critical to capturing the patient's voice and understanding the impact of lupus on an individual's functioning and quality of life. The NIH Common Fund's PROMIS® initiative has aided the development and validation of robust PRO tools to gather information on many health-related concerns, such as pain, fatigue, depression, and physical functioning. PROMIS tools can be utilized to measure changes over time in response to treatment and can be integrated into clinical trials, point-of-care visits, and large-scale surveys.

In addition, outcomes for patients have been associated with the health care systems in which they participate. The ability of lupus patients to access subspecialty providers can have a significant impact on disease progression and complications. Socioeconomic status, location, and insurance status are key components of health services delivery, and have been correlated with outcomes for lupus patients. The widespread adoption of electronic health records provides novel data sources for future exploration of these factors.

### Research Objectives

Broad areas of potential research directions include:

#### Behavioral Research

- Determine the effect of lupus-related cognitive impairment on disease outcomes; test existing instruments (e.g., the [NIH Toolbox](#)) or develop new tools to assess and mitigate the impairment
- Understand the relationship between patient preferences and outcomes, and identify methodologies to improve treatment adherence and patient-provider interactions
- Define how genetic and epigenetic factors influenced by the environment impact neuro-cognitive function and illness-related behaviors
- Examine the effects of exercise, stress, sleep, and fatigue on disease processes (e.g., presentation, symptom flares) and patient functioning (e.g., depression)
- Develop behavioral interventions to assist patients in managing their disease
- Integrate new technologies, such as mobile-health technologies (e.g., smart phone apps), to enhance research on the role of behavioral factors in lupus disease outcomes

### Biopsychosocial Research

- Develop new, or apply existing methodologies to assess cognitive functioning in lupus patients, and determine the impact of cognitive abilities on disease management and progression
- Develop, validate, and implement outcome assessment tools (e.g., PROMIS® measures) as endpoints for lupus clinical trials
- Develop and validate biopsychosocial strategies and interventions for the management of lupus to assist patients in coping with their disease
- Identify, test, and provide interventions that encourage healthy behaviors at the community level

### Health Services Research

- Develop models to improve local access to culturally sensitive care
- Develop and implement strategies to improve communication between physicians and patients
- Develop measures of patient engagement with health care providers and insurers
- Leverage emerging data infrastructure tools (e.g., electronic health records, mobile technologies) to standardize and improve the quality and safety of healthcare delivered to individuals with lupus
- Use large, systematic population samples that include detailed geographical data, health records, and PROs to identify new factors contributing to observed disparities in individuals with lupus
- Examine the effects of socioeconomic status and ethnicity on access to care, and assess their contribution to aggregate disease burden
- Develop strategies to improve coordination of care between primary care physicians and specialists, especially for economically disadvantaged patients where care is likely to be fragmented
- Understand nationwide variation in lupus care and treatment; identify and test interventions to enhance or standardize care to improve patient outcomes

## Chapter 6: Special Populations

As already stated, lupus is a heterogeneous disease with complex and variable manifestations. Epidemiological studies have identified significant sex, racial, and ethnic disparities in outcomes for lupus patients. Although some lupus manifestations (e.g., lupus nephritis) are not sex-specific, the biological basis of the female predisposition in lupus susceptibility requires further exploration. While the sex disparity is commonly attributed to hormonal effects, other mechanisms, such as defective tolerance and inefficient apoptosis of autoreactive cells, have

also been implicated. Detailed and definitive explanations are still needed, and additional research is being pursued.

In addition, racial and ethnic disparities in lupus present interesting challenges for researchers to explore. Compared to Whites, African Americans show a 3-to-5-fold higher prevalence of lupus, and have more severe clinical manifestations and organ damage from the condition, especially to the kidneys. In addition, long-term longitudinal outcome studies, such as the Lupus in Minorities: Nature vs. Nurture (LUMINA) multiethnic cohort, have shown that disease manifestations are as serious in Hispanics as in African Americans.

Lupus often strikes women in their early working and childbearing years, and it can interfere with a woman's ability to work, raise a family, or, in some cases, even care for themselves. Women with inactive disease who become pregnant generally experience excellent outcomes. However, during active disease, complications are common. In recent years, researchers have identified clinical signals and biomarkers that can indicate poor pregnancy outcomes, allowing earlier interventions. Researchers are now beginning to explore long-term developmental outcomes of children born to women with lupus.

Finally, while rare, childhood-onset lupus patients often experience more severe disease manifestations and higher disease burden as they live longer with the disease. The epidemiology of lupus in children is poorly understood. Further, the effect of the disease on the development and maturation that occurs during childhood and adolescence has not been well-delineated. This is especially true for disease assessment and treatment. Additionally, little is known about the special needs of children with lupus with respect to social and emotional well-being.

In 2001, the scientific community formed the Childhood Arthritis and Rheumatology Research Alliance (CARRA), an organization of pediatric rheumatologists committed to advancing the health and quality of life of children with rheumatic diseases and arthritis. Researchers within the CARRA seek to answer critical research questions to elucidate the causes of rheumatic diseases in children, determine the best treatments, and track long-term outcomes. The CARRAnet registry was established with support from the American Recovery and Reinvestment Act as part of CARRA to create a unified, scalable informatics infrastructure and to engage families, patients, and communities in addressing critical clinical research questions. A number of clinical trials leverage the CARRA infrastructure. For example, the Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE) study, which tested the use of statins to prevent atherosclerosis in pediatric lupus patients, was conducted as part of the CARRA.

## Research Objectives

Broad areas of potential research directions include:

### Health Disparities

- Investigate the various genetic, cognitive, environmental, sociological, and healthcare system factors observed in lupus health disparities, and how these interact and contribute to disparities in incidence/prevalence, age of onset, severity, rate of progression, and long-term outcomes
- Develop strategies and interventions to eliminate disparate outcomes and reduce disease in affected populations
- Develop culturally competent clinical practice and treatment guidelines
- Support research on the role of modifiable risk factors in contributing to disparities in lupus morbidity and mortality (e.g., poverty, employment, stress, access to providers)

### Lupus and Pregnancy

- Define and evaluate clinical biomarkers to predict adverse pregnancy outcomes in women with lupus, and develop clinical monitoring plans to effectively manage risks during pregnancy
- Study long-term outcomes in children of mothers with lupus to provide science-based information on pregnancy and breastfeeding

### Childhood-Onset Lupus

- Identify best practices for multidisciplinary approaches to treatment and transitioning from pediatric/adolescent care to adult care
- Determine if and how childhood-onset lupus (particularly onset before puberty) is distinct from adult-onset lupus
- Define clinical parameters to determine when research studies should be performed separately in pediatric and adult cohorts, and when joint protocols with both children and adults with lupus are appropriate
- Determine clinical targets (e.g., blood pressure, lipid levels) for children with lupus that indicate optimal disease management and better long-term outcomes

### Lupus Across the Lifespan

- Investigate lupus in elderly populations
- Determine the long-term effects of lupus in terms of organ damage, physical function, and comorbidities

## Chapter 7: Training and Collaborations

The future of lupus research will rely on a well-trained workforce, as well as robust collaborations between federal, non-profit, and private organizations. As noted earlier, the NIAMS leads the LFWG, which provides a forum for representatives from all relevant stakeholders to share information and coordinate lupus-related activities.

Currently, several federally supported population-based [lupus registries](#) are serving to generate better prevalence and incidence estimates for lupus. In addition, lupus biospecimen repositories, such as the Lupus Family Registry and Repository supported by the NIAMS, are available to the research community.

Many novel partnerships have been developed in recent years. For example, the NIH [Accelerating Medicines Partnership \(AMP\) Rheumatoid Arthritis \(RA\)/Lupus Network](#) was launched in February 2014, as part of a public-private partnership between the NIH, FDA, ten biopharmaceutical companies, and multiple non-profit organizations. The AMP RA/Lupus Network is a unique program designed to accelerate discoveries and to improve patient care as rapidly as possible. In addition, in 2015, through a grant from the CDC, an initiative to create a [National Public Health Agenda for Lupus](#) was launched to address strategies for promoting and prioritizing a public health approach to lupus. The effort will provide a blueprint for all stakeholders to guide action surrounding future policy, planning and advocacy initiatives across four domains: epidemiology and surveillance, environmental strategies, health system strategies, and community-clinical linkages.

### Research Objectives

Broad areas of potential research directions include:

#### Training

- Enhance primary care physician and pediatric resident training programs to improve diagnosis and management of lupus
- Develop training programs for researchers to obtain outstanding clinical research and animal model expertise, ensuring robust experiences in experimental design to improve the rigor and reproducibility of research results
- Facilitate cross-disciplinary research through training opportunities in bioinformatics, systems biology, imaging, brain biology, and other disciplines with potential for advances in lupus research and patient care
- Develop a growing cadre of young investigators with experience using large-scale databases, including but not limited to Medicare and Medicaid systems and private insurers, to conduct epidemiological and health services research

- Promote lupus research opportunities among the scientific community in order to attract the best and brightest researchers to the lupus field

### Collaborations

- Integrate pediatric subspecialties into existing and new partnerships, networks, and registries
- Increase interdisciplinary collaborations between clinicians and basic scientists in areas such as molecular biology and structural biology
- Expand partnerships between pharmaceutical companies and federal, academic, and non-profit organizations to enable access to licensed products for conducting pre-clinical studies in animal models, or for development of new products for adults and children aimed at genetically-based drug targets
- Identify impediments and develop evidence-based solutions to enhance lupus patient participation in clinical trials and studies, particularly among minorities
- Engage and incorporate patient advocates in clinical trial networks as liaisons between researchers and patients to improve clinical trial recruitment

### Conclusion

The lupus community has many avenues available to improve the health and well-being of individuals affected by lupus. The potential research directions presented here have been informed by significant consultation with the research community, patient advocacy groups, and the general public. However, it is not an exhaustive list. This *Action Plan for Lupus Research* will help to inform priority-setting processes among all lupus-related organizations. It is intended to serve as a guide for investigators as they develop independent approaches to address the numerous scientific opportunities in lupus. Basic, translational, and clinical research discoveries and emerging technologies will present additional opportunities to advance our understanding of lupus and how best to manage and ultimately prevent and cure the condition. The NIH and stakeholders in the academic, non-profit, and private sector will continue to work to support the best science and advance lupus research with the resources available.

## Appendix 1: Overview of the Development Process

The structure of the FY 2015 *NIH Action Plan for Lupus Research* is similar to that of the 2007 report on the *Future Directions of Lupus Research*, with chapters focusing on etiology, disease mechanisms, development of new treatments, diagnosis and clinical care, special populations, and health services research. In addition, new chapters have been added focusing on behavioral and biopsychosocial research, and research training and collaborations. The [NIAMS Long-Range Plan for FY 2015-2019](#) serves as companion piece to the new Action Plan since many of the needs and opportunities presented in that document are highly relevant to lupus research. The NIAMS will continue to partner with other NIH Institutes, Centers, and Offices, health advocacy and professional organizations, and industry to advance lupus research.

In December 2014, the NIAMS began developing the plan by gathering input from the NIH components that invest in lupus research. Several NIH Institutes, Centers, and Offices provided information on ongoing programs, research advances, and future research directions. To obtain public input on topics to include, the NIAMS also issued a Request for Information (RFI) in December 2014 (Appendix 2). The RFI was posted on the NIAMS website and in the NIH Guide for Grants and Contracts, and it encouraged feedback from researchers, professional and patient advocacy organizations, health care providers, and patients and their families. The comment period spanned 59 days. Respondents were asked to provide input on the most significant advances and publications since 2007, the most important scientific opportunities in lupus research, areas that are ready for progress in the short term, gaps to be addressed in order to advance lupus research, and topics to add or remove from the Broad Goals and Priorities elaborated in the 2007 plan. General comments were also encouraged. NIAMS received 36 responses through the RFI.

The Institute then prepared a draft Action Plan that incorporated the information gathered from the NIH components and the RFI. To obtain focused input on the draft plan, the NIAMS held a webinar with lupus researchers and lupus-related organizations on May 27, 2015 (Appendix 3). The webinar included approximately 60 individuals, comprising lupus researchers with broad expertise, scientific and lay representatives from lupus-related organizations, and programmatic and subject matter experts from several NIH ICs. Participants were encouraged to gather and share the views of the broader research community by consulting a diverse set of colleagues in advance of the webinar. Updates on the progress of the planning process were provided at the February 2015, June 2015, and September 2015 NIAMS Advisory Council meetings, and at the October 2014, April 2015, and October 2015 Lupus Federal Working Group meetings. Copies of the slides prepared for those updates were shared with the staff to the Congressional Lupus Caucus.

In July 2015, the draft Action Plan was posted on the NIAMS website for 51 days, and comments were gathered via an RFI published in the NIH Guide for Grants and Contracts (Appendix 2). Respondents were asked to provide feedback on the draft plan. NIAMS received 10 responses through the RFI. All comments were reviewed carefully by Institute staff and incorporated into the document, as appropriate. The final Action Plan was provided to the Congressional Lupus Caucus, posted on the NIAMS website, and widely disseminated to the community.



## Appendix 2: Requests for Information Published in the NIH Guide For Grants and Contracts

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### Request for Information (RFI) on the Future Directions of Lupus Research

Notice Number: [NOT-AR-15-007](#)

#### Key Dates

**Release Date:** December 17, 2014

**Response Date:** January 30, 2015

#### Related Announcements

[NOT-AR-15-018](#)

[NOT-AR-15-009](#)

#### Issued by

National Institute of Arthritis and Musculoskeletal and Skin Diseases ([NIAMS](#))

#### Purpose

The NIAMS is leading an effort to evaluate progress on [The Future Directions of Lupus Research](#) (lupus plan), which was released in 2007, and to develop a coordinated action plan for future lupus research at the request of the Congressional Lupus Caucus. To help inform this process, we welcome comments from the public including significant accomplishments since the release of the lupus plan, important opportunities in lupus research, and suggestions for updating the Broad Goals and Priorities elaborated in the 2007 lupus plan.

#### Background

NIH's mission is to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability. The National Institute of Arthritis and Musculoskeletal and Skin Diseases, and a number of other Institutes and Centers support lupus-related research at the NIH, and the NIAMS facilitates collaboration among the NIH Institutes, other Federal agencies, and voluntary and professional organizations with shared interests in lupus.

Systemic lupus erythematosus (SLE, or lupus) is a complex, heterogeneous, multisystem autoimmune disease that predominantly affects women of childbearing age. Lupus severity ranges on a spectrum from mild to severe, and in its most severe forms lupus can cause significant morbidity and mortality. No effective targeted therapies exist for the most severe forms of the disease, including lupus nephritis, and lupus affecting the central nervous system.

A major challenge remains to find new targeted therapies that can achieve a high degree of disease activity reduction (i.e., remission) or disease cure, and therapies that have fewer immunosuppressive side effects.

The fiscal year 2005 House Appropriations Committee Report Language directed the NIH to develop a plan to guide the nation's investment in lupus research. To identify the opportunities, priorities and needs in lupus research that should be considered for inclusion in the research plan, a workshop consisting of scientific experts in the field of lupus was organized for two days of presentations and discussion. The highlights of their conclusions were reported, in [The Future Directions of Lupus Research](#) released in 2007.

Through the individual and collaborative activities of researchers, clinicians, and stakeholders in the lupus community, there have been significant advances in understanding of disease mechanisms, evolution of new partnerships, and advances in drug discovery and development that have fostered candidate therapeutics, FDA approval of a new therapeutic, and improvements in the care and quality of life for affected individuals. At this time, there are new challenges and opportunities that would benefit from an assessment of progress and current needs, as requested by the Congressional Lupus Caucus.

### **Information Requested**

Through this Request for Information (RFI), NIAMS invites researchers in academia and industry, health care professionals, patient advocates, representatives of health advocacy organizations, members of scientific or professional organizations, and other interested members of the public to provide comments from their perspective on progress made toward the Broad Goals and Priorities in the 2007 lupus plan, and on current opportunities in lupus research.

We also welcome input that includes, but is not limited to, the following topics:

- The most significant advances/publications since 2007 in your area of interest/expertise.
- The most important scientific opportunities in lupus research.
- Identification of areas that are ready for progress in the short term.
- Description of gaps to be addressed in order to advance lupus research.
- Topics to add or remove from the Broad Goals and Priorities elaborated in the 2007 plan (listed below), so that the current state of the science is reflected.

## **Appendix A: The Future Directions of Lupus Research**

### ***Broad Goals and Priorities***

#### **Lay the Foundation for Lupus Prevention**

Lupus prevention may become an attainable goal in the next decade. To achieve this goal it will be critical to advance and coordinate research efforts to:

- Identify populations at risk
- Identify risk of disease
- Family studies
- Genetics
- Evaluation of the best options for prevention

#### **Identify Triggers of Disease**

The interplay between genes and environmental factors needs to be dissected and defined in individual patients and in patient subsets. Critical to this goal will be to define triggers:

- Endogenous: genes, hormones
- Exogenous: infectious agents, chemical exposures, biopsychosocial factors

#### **Define Target Organ Damage Mechanisms**

The goal is to prevent progression of target organ damage. It will be critical to acquire technologies for the assessment of multiple and overlapping mechanisms of disease occurring over time that cause irreversible damage. These include identification of:

- Inherent target organ susceptibility factors
- Mechanisms of injury: immune, inflammatory, vascular
- Mechanisms of progression: repair failure, abnormal clearance, persistence of triggering agent
- Mechanisms of recovery
- Role of local cells
- Measurement of injury: non-invasive rapid assays

#### **Understand Autoantibodies**

The role of autoantibodies in disease and their use as biomarkers needs to be fully understood. Research priorities and opportunities exist on:

- Defining the genes that regulate tolerance to self and production of autoantibodies
- Role in pathogenesis via traditional and functional mechanisms
- Interaction with target organ targets
- Initiation/induction of tissue damage
- Targeting their effector function for therapeutic purposes
- Role and use as biomarkers

### **Expand Biopsychosocial Research**

The goal is to increase our understanding of behavioral, psychological and societal factors that affect the course and the long term outcomes in the disease. Modifiable factors could be identified through research on:

- Epidemiology
- Impediments to access of care and maintaining status quo of therapies
- Quality of life
- Self-report vs. physician report
- Interactions with institutions, government, etc., and their effect on long-term outcomes
- Interaction with other psychiatric disease
- Mind/body interactions
- Cognitive affliction
- Coping styles
- Support groups
- Family
- Transition from pediatric to adult
- Disparities
- Poverty, race/ethnicity
- Origin and mechanisms of fatigue

### **Discover and Validate Biomarkers**

The goal during the next few years will be to use modern approaches to discovery and validation of existing biomarkers for lupus diagnosis, prognosis and evaluation of therapies.

Promising biomarkers are likely to emerge from research on:

- Genetics
- Polymorphisms and gene products evaluated by novel technologies such as microarrays and proteomics
- Validation studies in well characterized patient cohorts

- Analysis of potential use of selected biomarkers and their combinations in clinical subsets

### **Move Forward Treatment and Therapy**

New treatments for lupus are being tested by the private sectors. The goal of the NIH and academic research will be to ensure a continuous supply of new targets for intervention and adequate trial methodologies. Research likely to contribute to this goal will be focused on:

- Identification of targets for non-immunosuppressive therapies
- Target organ repair
- Collateral damage – musculoskeletal, cardiovascular, chronic fatigue, mild myalgia
- Prevention of collateral damage
- Treatment of symptoms (e.g., cognitive rehabilitation, control of fatigue)

### **Resources and Infrastructure**

To achieve the goals of this plan, critical resources will be needed, and they will have to be implemented in creative and dynamic ways to ensure rapid progress. Implementation will require careful attention to achieving an adequate balance between investigator-initiated research and network/collaborative large projects. The following is a list of some of those resources. Their acquisition and maintenance will require collaborative approaches by the funding organization, the academic centers and the private sector.

#### *Patient Collections*

Issues affecting the collection and sharing of patient cohorts that will have to be addressed include:

- Accessibility
- Control populations
- Registry maintenance facilitation
- Specimen collection with clinical trials
- More patients for intervention

#### *Partnerships*

A collaborative environment that facilitates sharing of data, specimens and information will enhance research and research careers in lupus. For example, immunologists and rheumatologists should seek direction from other areas like reproductive medicine,

neurophysiology, cell biology, and hematology. Some principles that may guide their development include:

- Free exchange between academic investigators and industry
- Free exchange between investigators
- Educate institutions on collaborative efforts
- Participation of patient groups

#### *Training*

- Education – physicians for new therapies
- New investigators

The collected comments will be reviewed and considered as we evaluate progress and develop updated Broad Goals and Priorities in response to the request from the Congressional Lupus Caucus.

#### **How to Submit a Response**

Responses to this RFI must be submitted electronically by email to the following address: [niamslupusplanupdate@mail.nih.gov](mailto:niamslupusplanupdate@mail.nih.gov). Please indicate in your response the topic(s) you are addressing, and which of the Broad Goals and Priorities it is related to. Responses will be accepted until January 30, 2015.

Responses to this RFI are voluntary. Please do not include any personally identifiable or other information that you do not wish to make public. Proprietary, classified, confidential, or sensitive information should not be included in your response.

This request is for information and planning purposes only and should not be construed as a solicitation or as an obligation on the part of the United States Government. The NIAMS or the NIH will not make any awards based on responses to this RFI, nor will the NIAMS or the NIH otherwise pay for the preparation of any information submitted or for the Government's use of such information.

The NIAMS will use the information submitted in response to this RFI at its discretion and will not provide comments to any responder's submission. Respondents are advised that the Government is under no obligation to acknowledge receipt of the information received or provide feedback to respondents with respect to any information submitted. The Government reserves the right to use any non-proprietary technical information in any resultant solicitation(s).

## **Inquiries**

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## **Request for Information (RFI) on the Action Plan for Lupus Research**

**Notice Number:** [NOT-AR-15-018](#)

### **Key Dates**

**Release Date:** July 23, 2015

**Response Date:** September 11, 2015

### **Related Announcements**

[NOT-AR-15-007](#)

[NOT-AR-15-009](#)

### **Issued by**

National Institute of Arthritis and Musculoskeletal and Skin Diseases ([NIAMS](#))

### **Purpose**

In July 2014, the Congressional Lupus Caucus requested that the NIAMS, as convener of the [Lupus Federal Working Group](#) (LFWG), develop a new coordinated action plan for lupus research on behalf of the NIH. In response, the NIAMS has led NIH efforts to develop the Action Plan for Lupus Research over the past year, and is now requesting comments and feedback on the draft.

## Background

NIH's mission is to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability. The National Institute of Arthritis and Musculoskeletal and Skin Diseases, and a number of other Institutes and Centers support lupus-related research at the NIH. The NIAMS facilitates collaboration among the NIH Institutes, other Federal agencies, and voluntary and professional organizations with shared interests in lupus by leading the LFWG.

Systemic lupus erythematosus (SLE, or lupus) is a complex, heterogeneous, multisystem autoimmune disease that predominantly affects women of childbearing age. Lupus severity ranges on a spectrum from mild to severe, and in its most severe forms lupus can cause significant morbidity and mortality. No effective targeted therapies exist for the most severe forms of the disease, including lupus nephritis, and lupus affecting the central nervous system. A major challenge remains to find new targeted therapies that can achieve a high degree of disease activity reduction (i.e., remission) or disease cure, and therapies that have fewer immunosuppressive side effects.

The fiscal year 2005 House Appropriations Committee Report Language directed the NIH to develop a plan to guide the nation's investment in lupus research. To identify the opportunities, priorities and needs in lupus research that should be considered for inclusion in the research plan, a workshop consisting of scientific experts in the field of lupus was organized for two days of presentations and discussion. The highlights of their conclusions were reported in [The Future Directions of Lupus Research](#), released in 2007. Through the individual and collaborative activities of researchers, clinicians, and stakeholders in the lupus community, there have been significant advances in understanding of disease mechanisms, evolution of new partnerships, and advances in drug discovery and development that have fostered candidate therapeutics, FDA approval of a new therapeutic, and improvements in the care and quality of life for affected individuals. At this time, there are new challenges and opportunities that would benefit from an assessment of progress and current needs, as requested by the Congressional Lupus Caucus.

Over the past year, NIAMS has led the efforts to develop the draft Action Plan for Lupus Research (action plan). The structure of the draft action plan is similar to the 2007 report on the Future Directions of Lupus Research, with chapters focusing on etiology, disease mechanisms, development of new treatments, diagnosis and clinical care, special populations, and health services research. In addition, new chapters have been added focusing on behavioral and biopsychosocial research, and research training and collaborations. NIAMS solicited input on information to be included in the action plan via a data call in December 2014 to other NIH



Institutes and Centers, issuance of a Request for Information (RFI) on the Future Directions of Lupus Research ([NOT-AR-15-007](#)) in December 2014, and a webinar held in May 2015. NIAMS also provided regular updates to the LFWG, NIAMS Advisory Council, and Congressional Lupus Caucus staff. NIAMS staff have considered all of the feedback collected through the NIH data call, the previous RFI, and the webinar in drafting the action plan.

### **Information Requested**

Through this RFI, NIAMS invites feedback on the draft Action Plan for Lupus Research from researchers in academia and industry, health care professionals, patient advocates, representatives of health advocacy organizations, members of scientific or professional organizations, and other interested members of the public. Organizations are strongly encouraged to submit a single response that reflects the views of their organization and membership as a whole.

Please provide your comments and feedback. The final Action Plan for Lupus Research will be presented to the NIAMS Advisory Council and Lupus Federal Working Group, provided to the Congressional Lupus Caucus, and posted on the NIAMS website in Fall/Winter 2015.

### **How to Submit a Response**

Responses to this RFI must be submitted electronically by email to the following address: [niamslupusplanupdate@mail.nih.gov](mailto:niamslupusplanupdate@mail.nih.gov). Responses will be accepted until September 11, 2015.

Responses to this RFI are voluntary. Please do not include any personally identifiable or other information that you do not wish to make public. Proprietary, classified, confidential, or sensitive information should not be included in your response.

This request is for information and planning purposes only and should not be construed as a solicitation or as an obligation on the part of the United States Government. The NIAMS or the NIH will not make any awards based on responses to this RFI, nor will the NIAMS or the NIH otherwise pay for the preparation of any information submitted or for the Government's use of such information.

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## Appendix 3: Webinar Participants

NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES

WEBINAR DISCUSSION ON

**The Future Directions of Lupus Research**

May 27, 2015, 1:00-4:00 P.M.

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