Executive Summary of the NHLBI Workshop Report: Leveraging Current Scientific Advancements to Understand Sarcoidosis Variability and Improve Outcomes

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Abstract

Sarcoidosis is a systemic granulomatous disease that primarily affects the lung; it is associated with significant disparities, more commonly impacting those in the prime of their lives (age 20–50 yr, with a second peak after age 60 yr), black individuals, and women. However, the burden of disease, the ability to diagnose and prognose organ involvement and course, as well as specific treatment options, management options, and disease pathogenesis remain poorly understood. As a result, the National Heart, Lung, and Blood Institute undertook a sarcoidosis workshop, “Leveraging Current Scientific Advancements to Understand Sarcoidosis Variability and Improve Outcomes,” to help address these issues by defining the scientific and clinical priorities to improve sarcoidosis care. The overarching recommendations from this workshop are outlined in the following summary and detailed in the accompanying articles.

The recommendations included establishing collaborations and networks to conduct research based on consensus definitions of disease phenotypes and standards of care, and to provide clinical outreach to areas with a burden of disease to improve care. These collaborative networks would also serve as the hub to conduct clinical trials of devastating phenotypes (e.g., cardiac, neurologic, and fibrotic disease) not only for treatment but to enhance our understanding of the burden of disease. In addition, the networks would be used to leverage state-of-the-art “omics” and systems biology research, as well as other studies to advance understanding of disease pathogenesis, and development of biomarkers and therapeutic targets, with a goal to translate this information to improve care of individuals with sarcoidosis.

Keywords: sarcoidosis; disparities; NHLBI; workshop

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Sarcoidosis is a rare systemic disease of unknown etiology, usually diagnosed in those in the prime of their life, between 20 and 50 years of age. The prevalence of sarcoidosis and disease manifestations vary by sex, race, and age. One study suggests that sarcoidosis rates are increasing (1), but it is unclear whether this trend relates to improved detection or to changing

environmental factors. The organ involvement, disease manifestations, and clinical course are highly variable, with devastating disease resulting from pulmonary, cardiac, and neurologic disease in some individuals and complete resolution of disease in others. The overall health and economic burden of sarcoidosis are not well understood, although the

mortality rate appears to be rising (2). Some investigators and physicians have questioned whether the face of sarcoidosis is changing or whether, instead, our lack of understanding of disease manifestations has led us to perceive changes.

The National Heart, Lung, and Blood Institute (NHLBI) hosted its last workshop on sarcoidosis in 2002 (3). Some of the

research goals established at that workshop have since been addressed; some genetic variants associated with sarcoidosis disease risk have been identified, and our understanding of the pathogenesis and potential etiology of disease has been advanced. However, research results have been limited, in part due to the single-center approach to research with limited study power and validation, which impede research translation. In general, sarcoidosis research has been limited to T0 (basic mechanisms), T1 (proof-of-concept studies in humans), or T2 (e.g., limited clinical applications or findings in early-stage trials), with few examples of T3/T4 (translation of research to routine clinical practice) studies. Many fundamental aspects of sarcoidosis remain poorly

understood and/or have not advanced, including our appreciation of the burden of disease, the ability to diagnose and prognose organ involvement and course, as well as treatment, which remains nonspecific in the face of limited evidence-based recommendations. Given the ongoing gaps in knowledge and many unanswered questions, additional efforts are required to advance our understanding of this disease and to improve the care of those affected.

Overview of the NHLBI Workshop

With the above in mind, the NHLBI Division of Lung Diseases and Center for

Translational Research and Implementation Science sponsored a multidisciplinary patient-focused and -oriented workshop on August 31 and September 1, 2015, to leverage current scientific knowledge and define platforms to address disease disparities and improve outcomes in sarcoidosis. The workshop assembled investigators with varied scientific and clinical expertise reflecting the poorly understood disease mechanisms contributing to the highly variable clinical manifestations of sarcoidosis, including pulmonologists, cardiologists, neurologists, researchers focused on epidemiology, “omics,” and immunology, as well as a number of National Institutes of Health (NIH) institutes and offices, including the Office of Research on Women’s Health, the

Table 1. Themes emerging from the workshop

Area of Emphasis	Specific Themes
Clinical aspects	<ul style="list-style-type: none"> ● Promote a patient-centered approach to care and treatment of sarcoidosis ● Standardize care with guidelines to promote optimal care and guide research ● Establish standardized disease phenotypes to promote clinical care and research ● Define clinical spectrum by collecting clinical data, including diagnosis, clinical follow-up, response to treatment ● Better characterize disease manifestations with poor outcomes, the factors that predict them, and the means to intervene earlier to prevent disease morbidity ● Use EHR or other large databases to capture big data and data sets ● Foster the next generation of clinical providers and sarcoidosis specialists, as well as a network of sarcoidosis specialists
Research agenda	<ul style="list-style-type: none"> ● Establish a longitudinal network and registry from which research can be conducted ● Use other disease approaches and available data sets, as models to help advance research (e.g., multiple sclerosis, rheumatology, Cystic Fibrosis Network) ● Advance clinical research and understanding of disease and disease pathogenesis in parallel to optimize research impact, conducting disease across the spectrum of translational research, from T0, to T1 to T2 to T3, and ideally moving to T4 ● Utilize team science, multifaceted, multidisciplinary approach, as well as individual investigator-initiated studies ● Determine biomarkers for diagnosis, prognosis, response to therapy ● Define mechanism of disease to determine new drug-susceptible targets and treatments ● Develop better animal models and/or cell models to study mechanism and response to therapy ● Utilize new tools such as “omics,” epigenetics, and creative study designs for clinical trials ● Leverage existing data and cohorts, like GRADS ● Foster the next generation of researchers
Community involvement/engagement	<ul style="list-style-type: none"> ● Promote the NIH roadmap for community involvement in research and care, with a two-way highway ● Utilize CTSA/NCATS infrastructure for the studies to be conducted, including the community outreach that is a part of most CTSAs, and to translate discoveries to care more quickly, via the CTSA Program Data to Health (CD2H) informatics ● Promote education of patients and providers to optimize care ● Address disparities at the primary care clinic, whether in inner cities or rural areas and help individuals find the care that is needed ● Develop clinical guidelines that utilize and emphasize precision medicine approaches
Sarcoidosis as a public health model	<ul style="list-style-type: none"> ● Improve reporting of disease to track it and its health outcomes ● Primary prevention to stop new cases from occurring as well as secondary and tertiary prevention ● Partner with other agencies and groups: PCORI, FDA, NIH, FSR, HRSA, and others

Definition of abbreviations: CTSA = Clinical and Translational Science Award; EHR = electronic health record; FDA = Food and Drug Administration; FSR = Foundation for Sarcoidosis Research; GRADS = Genomic Research in Alpha-1 Antitrypsin Deficiency and Sarcoidosis; HRSA = Health Resources and Services Administration; NCATS = National Center for Advancing Translational Sciences; NIH = National Institutes of Health; PCORI = Patient-Centered Outcomes Research Institute.

National Institute of Neurological Disorders and Stroke, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and others. The goal of this workshop was to define the gaps in knowledge relating to sarcoidosis manifestations, pathogenesis, and treatment and to outline a strategic patient-focused plan and prioritized roadmap to address gaps in a multidisciplinary comprehensive manner, an approach that differed from that used in the 2002 workshop (3). Groups of investigators were assembled ahead of the meeting to address specific areas, including (1) the clinical, economic, and social burden of sarcoidosis; (2) the genetic, immunological, and environmental underpinnings of sarcoidosis; (3) the current state and potential applications of “omics” and systems biology research in sarcoidosis; (4) gaps in access to and quality of care, as well as health disparities in sarcoidosis; and (5) the interventions for high-risk disease, focusing on cardiac, neurologic, and pulmonary sarcoidosis. These areas and approaches to remedy gaps were discussed at the workshop, followed by a consensus discussion (Table 1) to determine recommendations to move the field forward. A summary of these discussions is detailed in the articles that follow (4–7).

In brief, current understanding of the epidemiology, clinical manifestations, and treatments were outlined. The implications of these areas regarding quality of life, health and psychosocial status, economics (lost days of work, costs of care, etc.), and/or patient-reported outcomes are not well understood (5). Significant advances in our understanding of the genetic, immunologic, and environmental triggers have been established over the past 10–15 years (8, 9). However, additional research is required to link these mechanistic observations to clinical phenotypes and disease course to advance our care and treatment of patients (e.g., response to immune-modulating therapies) (10). Use of systems biology is proposed to be an effective approach to provide encouraging results in sarcoidosis, exploring genomic profiles as prognostic markers and defining pathogenesis (4). The NHLBI-funded multicenter study GRADS (Genomic Research in Alpha-1 Antitrypsin Deficiency and Sarcoidosis) will provide compelling new “omics” data (referring to a comprehensive analysis of all related molecules, such as RNA, proteins, etc.), including RNA-sequencing and

microbiome data from bronchoalveolar lavage cells and blood on a variety of sarcoidosis phenotypes (10).

It is evident that significant disparities currently exist when comparing various health care providers in terms of sarcoidosis detection and management, which relates in part to limited access to health care and specialists, causing delays in diagnosis, and lack of standardized treatment and follow-up approaches. The estimated impact of health disparities and barriers to care in sarcoidosis is not well defined (11), partly due to lack of standardized management guidelines, particularly for severe disabling disease in underserved communities. Education of providers and patients in underserved areas is essential to reducing disparities. Long-term patient-oriented studies to quantify health disparities and to provide evidence-based guidelines, such as

was accomplished for rheumatoid arthritis (12), are recommended to reduce disparities, improve care and access, and inform the design of future scientific studies. A focus on severe debilitating organ involvement, particularly neurologic, cardiac, severe pulmonary, and/or multiorgan involvement, would be most beneficial. Unfortunately, the best therapeutic options for these more severe forms of sarcoidosis are poorly defined, and optimal therapy likely differs depending on organ involvement (7).

A number of overlapping health care challenges (Table 1), along with common solutions proposed for addressing them (Tables 2 and 3), emerged from this workshop. First and foremost, a sustainable platform for optimizing care and facilitating effective research studies is needed to reduce disparities and to support

Table 2. Patient-centered research outcomes

Category of Outcome	Assessment of Outcome
Clinical outcomes—patient centered	Cognitive failure Symptoms, including respiratory, fatigue, cognitive function Physical activity, including activities of daily living, assessment with new technologies (e.g., Fitbit) Depression Diet, exercise, sense of well-being Disease status and whether in remission Sleep
Clinical outcomes—organ function	Biopsy BAL PFTs Assessment of exercise, such as timed walk Chest radiography and CT scan Electrocardiogram Echocardiogram Organ-specific outcomes for cardiac, neurologic, and other disease Overall functional status and assessment of disease involvement Endpoints for clinical trials including PFTs, CXR, BAL, QOL, similar to the rheumatology and multiple sclerosis models
Assessment of morbidity and disease impact	QOL Employment status Return to work if hospitalized or unable to work Health care utilization, specialty referrals Admission and readmission rates Compliance and disease follow-up Care and treatment and cost-effectiveness
Assessment of disparities	Access to care Referrals to sarcoidosis experts and specialists Assessment of quality of care Follow-up

Definition of abbreviations: BAL = bronchoalveolar lavage; CT = computed tomography; CXR = chest X-ray; PFT = pulmonary function test; QOL = quality of life.

the careers of dedicated sarcoidosis researchers and clinicians. Consensus definitions of disease and disease phenotypes (e.g., high-risk disease), and guidelines for diagnosis, treatment, and follow-up need to be established. Given the multiorgan presentation of sarcoidosis, these efforts need to include multifaceted approaches, including relevant subspecialists (pulmonologists, cardiologists, neurologists, psychiatry, etc.), professional societies, patient advocacy

groups, foundations, and other resources. Sarcoidosis patient registries should occur through these sites and/or on state and national levels to more accurately assess the incidence, prevalence, and manifestations of disease (Table 2). A model such as those used in other rare diseases, such as cystic fibrosis, multiple sclerosis, and rheumatoid arthritis, could be considered and/or platforms like the HIV/AIDS Network could be reconceptualized.

The Foundation for Sarcoidosis Research has initiated a sarcoidosis clinical network, with plans to extend the network to many other sites across the United States and Europe; this and/or other platforms can be leveraged to provide a national sarcoidosis clinical and research network, including communities with a high burden of disease and individuals without access to care who would benefit most from access to care. Investigators and groups with similar missions and interests, such as

Table 3. Specific care and research themes and approaches to be considered to advance sarcoidosis care and reduce disparities

Overarching Research Themes	Approaches to Advance Sarcoidosis Care
Clinical management and research	<ul style="list-style-type: none"> • Best practice for treatment and to limit toxicity • Telemedicine and/or leveraging novel technology for care • Centers of excellence participating and interacting with the community where disparities exist • Communication between experts and primary care providers, utilizing referrals as needed • Patient-powered network to influence priorities/outcomes, including community-based participatory research • Focus efforts on patients at risk for inadequate care and poor outcomes • Optimize EHR to characterize predictors of poor outcomes or care and implement and confirm findings and improve care • Establish new methods and techniques to optimize diagnosis • Evaluate and measure disease activity and severity of sarcoidosis, including neurologic and cardiac disease • Develop biomarkers of disease risk, prognostication and response to treatment • PET scanning and other radiographic biomarkers of disease • Develop registries of clinical evaluation, diagnostics, and therapeutics to assess outcomes and validate other studies • Evaluate those with severe forms of disease as well as those with less severe forms and remission to understand differences and changes that can be used for therapeutic approaches • Access drug repositories to increase pipeline, repurposing of new therapies • Utilize novel approaches for treatment trials
Disease pathogenesis and mechanism	<ul style="list-style-type: none"> • Biomarkers—change over time • Epitope discovery to determine inciting agents • Epigenetics to link exposure/inciting antigens and disease • Use of “omics” technologies including molecular “signatures,” metabolomics, and others • Other model of granuloma <i>ex vivo</i> as model of sarcoidosis, to determine similarities and differences • Immunologic time course and mechanism from initiation of disease to end stage • Define innate and adaptive immune response and ways to optimize the adaptive response as a potential therapy • Determine whether the immune response in sarcoidosis is dysregulated or aberrant • Evaluate T-cell, macrophage, epithelial, and other immune cell contribution to disease onset and persistence as well as the cross-talk between these cells • Define the vascular effect of sarcoidosis • Determine mechanisms of fibrosis, pathways to healing, progression, and reoccurrence • Obtain transplanted tissues from sarcoidosis for studies • Utilize tissue from multiple organs to compare and contrast difference in pathogenesis • Animal models to recapitulate human immune response, test findings from human cells and therapies, assess disease persistence • Determine the mechanistic underpinnings of small-fiber neuropathy, fatigue, cardiac and other organ involvement and progression

Definition of abbreviations: EHR = electronic health record; PET = positron emission tomography.

those involved in multiple sclerosis, Crohn's disease, common variable immunodeficiency, tuberculosis, and others, should be included to expand and incorporate other research models and approaches to advance our understanding of disease. This platform would allow studies of disease pathogenesis (Table 3), including investigator-initiated grants and projects focused on a specific theme (e.g., NIH R01 mechanisms or other similar grant support), translation of research from cell models to humans, and research spanning the clinical and translational spectrum, from T0 to T4. In addition, large data sets that have already been collected should be mined to address the questions noted herein, including insurance data sets, the GRADS data set (10), Veterans Affairs data, and other NIH cohorts such as the Framingham Study (13) and others (14). It is time for all stakeholders interested in impacting this disease to come together to provide a unified multidisciplinary broad spectrum of approach; with this approach we will be able to start moving this field forward in a larger, more concerted effort to ultimately devise innovative approaches for prevention of disease and devastating outcomes, to reduce the burden and severity of disease.

Proposed Steps to Address Current Health and Science Gaps in Sarcoidosis

- **Step 1:** Standardize definitions of disease phenotypes and organ-specific measures of dysfunction, as well as templates for collection of data/quality of life measures to facilitate clinical management and future clinical studies.
- **Step 2:** Establish centers of excellence that are qualified to manage a cohort of rigorously phenotyped patients with sarcoidosis with longitudinal follow-up data and to collect serial biospecimens by standardized methodologies. This resource can be used to investigate the genetic/epigenetic/immunologic basis of sarcoidosis, with a particular focus on longitudinal changes associated with severe disease phenotypes. This resource can also be used to develop clinical tools that enable personalized approaches to treatments.
- **Step 3:** Establish standards of care and related outcomes for patients with various phenotypes of sarcoidosis, based

on the best available evidence, and then fill in the knowledge gaps with future clinical studies/trials.

- **Step 4:** Devise new outreach strategies to communities with a high prevalence and/or burden of sarcoidosis and increase early referrals of at-risk patients to centers of excellence for advanced management and clinical trials.
- **Step 5:** Prioritize clinical trials that evaluate interventions for life-threatening complications of sarcoidosis and consider new trial strategies such as "randomized withdrawal design" (15) for trials addressing rarer sarcoidosis complications such as neurosarcoidosis. Biospecimens from these subjects with sarcoidosis in these trials should also be collected for future biomarkers/pathogenesis studies.
- **Step 6:** Apply "omics" and systems biology research to improve the molecular characterization of sarcoidosis disease phenotypes and to uncover novel disease mechanisms that could represent new disease biomarkers or therapeutic targets.
- **Step 7:** Develop animal models that recapitulate features and mechanisms found in chronic and severe sarcoidosis phenotypes, and for preclinical testing of novel therapeutics.
- **Step 8:** Integrate and use health care electronic medical records systems to (1) assess sarcoidosis disease burden in the United States longitudinally; (2) determine the disease trajectories among patients with different disease phenotypes; (3) analyze the impact of pain, fatigue, depression, and cognitive dysfunction and other disabilities on patients; and (4) determine the contribution of treatment complications, aging, and comorbid conditions to long-term morbidity and mortality in sarcoidosis
- **Step 9:** Conduct research trials using the established network to develop innovative approaches including both preventive and therapeutic interventions to reduce the burden and severity of disease among those most greatly affected. ■

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