MILKEN INSTITUTE
CENTER FOR
STRATEGIC PHILANTHROPY

SARCOIDOSIS

A Giving Smarter Guide

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ABOUT US

About the Milken Institute

The Milken Institute is a nonprofit, nonpartisan think tank.

For the past three decades, the Milken Institute has served as a catalyst for practical, scalable solutions to global challenges by connecting human, financial, and educational resources to those who need them. Guided by a conviction that the best ideas, under-resourced, cannot succeed, we conduct research and analysis and convene top experts, innovators, and influencers from different backgrounds and competing viewpoints. We leverage this expertise and insight to construct programs and policy initiatives.

These activities are designed to help people build meaningful lives in which they can experience health and well-being, pursue effective education and gainful employment, and access the resources required to create ever-expanding opportunities for themselves and their broader communities.

About the Center for Strategic Philanthropy

The Milken Institute Center for Strategic Philanthropy advises philanthropists and foundations seeking to develop and implement transformative giving strategies.

FOREWORD

The cough, the shortness of breath, the instant fatigue, the sudden and terrifying inability to do things I would normally have been able to do—and the doctors kept telling me I wasn't sick. Test after test showed that my results were within the normal range. I was a healthy young woman, they said, and so I believed them. After all, they said, I didn't look sick.

Based on outward appearances, this should have been true. I had been a star athlete in junior high and high school, running track and breaking record after record. I played basketball, volleyball, and soccer, excelling in all. When it came time for college, the scholarship offers were many. Still, the pain, tightness, and the feeling like I couldn't get enough air all grew worse. But I trusted the doctors who told me I wasn't sick. I managed to convince myself that I was healthy—but my body was telling me otherwise. After a year of running at the collegiate level, I gave up my scholarship, not knowing what was wrong, unable to explain my ailments to anyone. Again, I didn't look sick.

When I sought the advice of the medical professionals, there were doctors who didn't validate my concerns; doctors who were insensitive and dismissive of my symptoms; doctors whose offices I left in tears, feeling worse than when I arrived. There were doctors who insisted it was psychosomatic or related to my mental health, even doctors who claimed it was related to my large breasts and the types of bras I wore. There were doctors who just didn't give a damn because I was the patient they didn't feel like treating, who saw me as the Black woman in their office that didn't belong, who would ask me again and again if I actually had health insurance. There were doctors whose pride and egos led them to talk over me, who were afraid to admit that my symptoms were beyond their areas of expertise, and who refused to refer me elsewhere or to consult other physicians. These doctors made me doubt myself and my own health needs; they made me question whether this was all in my head. I went undiagnosed for far too many years. All because I didn't look sick.

And then, a turning point. My primary care physician commented that I always seemed to be coughing when I came in for an appointment and referred me to a pulmonologist. After a lung tissue biopsy, I finally had a diagnosis: pulmonary sarcoidosis. Had I not revealed that my mother died of congestive heart failure and pulmonary sarcoidosis secondary, I may not have been diagnosed at all. This was 22 years after my first symptoms appeared.

Sarcoidosis is generally defined as a systemic inflammatory disease characterized by the presence of granulomas (tiny masses or nodules of tissue) in one or more organs. For some, this is a short-term experience, with weight loss, fatigue, and fever being common symptoms. But for others like myself, it is long-lasting and severe. Pulmonary sarcoidosis is the most common form of sarcoidosis. Patients will experience a host of symptoms related to lung function, including a persistent dry cough, shortness of breath, wheezing, and chest pain. Sarcoidosis also has a higher incidence among African Americans. There is no known cause of sarcoidosis, nor is there any consensus around diagnosis or treatment.

Following the diagnosis, I was prescribed Prednisone, an anti-inflammatory steroid medication that can cause dreadful side effects. Essentially, there are no other options. When it comes to sarcoidosis, there are far too few therapies, far too few pharmaceutical companies that are willing to approve or make the investments into researching other therapies, and far too few medical professionals willing to explore therapies that go beyond steroids.

While Prednisone reduces inflammation, it can cause changes in mood and increased appetite resulting in weight gain—what some refer to as "moon face." Long-term use of medications like Prednisone can also result in steroid-induced diabetes. The higher the dose of steroids, the higher the blood sugar numbers. The higher the blood sugar numbers, the more insulin you require. Balancing the two is nearly impossible at times. Sustained steroid use has a domino effect, with potential health complications resulting, including Cushing syndrome (a condition where your body has too much steroid), bone loss, and osteoporosis.

Although the bars are invisible, those of us with sarcoidosis are prisoners constrained by hospital admissions. We are tethered to heart monitors, IV lines, and oxygen medications. We are offered few answers and even fewer promises from our care teams. But in this respect, I am more fortunate than others. Access to quality care and treatment remains an issue for those with sarcoidosis, particularly among low-income families with little or no access to affordable health care.

My sarcoidosis story, which so many refused to hear for far too long, is one of many that patients with sarcoidosis have. But I am hopeful that others will be luckier than me. The Ann Theodore Foundation has partnered with the Milken Institute in creating a path forward to provide funding to research and identify the scientific cause of sarcoidosis, to create and develop a collaborative effort across different scientific and medical disciplines to identify consistent criteria for a proper diagnosis, and to create and develop proposals for effectively treating the disease.

The Ann Theodore Foundation and the Milken Institute invite you to read the following Giving Smarter Guide to learn more about sarcoidosis and to realize more fully where philanthropy might play a role in supporting the sarcoidosis medical research community. We hope you will support and join us on this journey to bring more attention to sarcoidosis and listen to those whose stories need to be heard.

Carol Lafond
Advisor to the Anne Theodore Foundation

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EXECUTIVE SUMMARY

Sarcoidosis is a debilitating and sometimes fatal inflammatory condition that can affect nearly every organ in the body. Immune cells cluster throughout the body, causing many people who have sarcoidosis to struggle with extreme fatigue, difficulty breathing, joint pain, fever, and eye inflammation. In some cases, the symptoms may last from one to two years, but for others it could be a lifelong battle with sarcoidosis, which has no cure. The existing treatments may address the inflammation, but many of them have significant side effects that include diabetes or weight gain. If left unmanaged, sarcoidosis can lead to severe organ damage and even death.

This condition has been observed to affect 0.06 percent of the US population, but it is likely more common. Sarcoidosis is relatively unknown and poorly understood by the medical and scientific communities, as well as the public, which leads to many people being misdiagnosed. Sarcoidosis can drastically affect a person's quality of life, so it is important to address it as quickly as possible. Unfortunately, sarcoidosis attracts fewer federal research dollars than other inflammatory conditions, even those that are less prevalent. There is a need for alternative funding sources to enable people who work in the sarcoidosis space to improve care and the quality of life for individuals with sarcoidosis. Philanthropy is uniquely positioned to propel sarcoidosis research forward and make quick and meaningful advances in the community's understanding of the disease. In this report, the Milken Institute Center for Strategic Philanthropy (CSP) lays out key opportunities to support critical scientific work that can improve the lives of people with sarcoidosis.

State of the Field

Sarcoidosis is likely caused by a combination of genetic risk and environmental exposures, but the exact mechanisms of disease development and progression are not well understood. The experience of individuals with sarcoidosis can vary based on severity, organs affected, and length of the disease course, and these variables complicate science's ability to understand the disease. Sarcoidosis also affects African American women at a higher rate than any other group in the United States. Although treatments are available, they are not consistently effective, and in some cases, could exacerbate the condition.

Although little is known about the disease's cause, funding for sarcoidosis research has been lower than that for related research fields. Figures 7 and 8 in this report show that most funding from the National Institutes of Health has been focused on lung sarcoidosis even though sarcoidosis affects a variety of organs. In addition, research on the common treatments for sarcoidosis remains limited.

Philanthropic Opportunities

Long-term underinvestment in research translates to many opportunities for philanthropic investment to advance the field. Such initiatives can help grow the knowledge base for sarcoidosis, attract more researchers to the field, and create additional resources and therapies for people affected by sarcoidosis. The opportunities outlined in this guide were derived from an in-depth literature review of the science, an examination of funding opportunities for sarcoidosis research, and conversations with more than 20 experts in the field.

1. **Support the Development of New Tools to Characterize the Biology Underlying Sarcoidosis**
   Although physicians and scientists do not know the specifics of sarcoidosis onset or progression, current evidence points to both genetic and environmental triggers of the disease. Finding new ways to understand how and why sarcoidosis affects so many different segments of the population is paramount to progress. Improved understanding of the biology of the disease will eventually lead to new therapies.

2. **Support Clinical Trials**
   Although physicians currently rely on treatments that suppress the immune system or resist inflammation, study of the long-term efficacy and side effects of these treatments has been insufficient. The lack of understanding of the long-term effects of current treatments has led to inconsistent clinical practices, and patients may not be receiving the right type of care. Supporting additional clinical trials to determine optimal dosage, assess potential side effects, and understand other vital characteristics will improve clinical care.

3. **Provide Sarcoidosis Education to Research and Clinician Communities**
   The sarcoidosis research and clinical communities are currently small. Intentionally growing the field will introduce new perspectives and ideas to push it forward. Sarcoidosis is not well known among clinicians, which leads to high rates of misdiagnosis. Making more clinicians aware of sarcoidosis will help streamline both referral to sarcoidosis specialists and access to effective interventions.

4. **Build a More Collaborative Research Environment**
   When researchers and clinicians learn about each other's efforts, collaboration and innovation often follow. These collaborations can promote information sharing, consensus building, and greater community-driven action. Promoting collaborative efforts and pooling resources will lead to more widely applicable study outcomes and more standardized clinical practices.

BIOLOGY OF SARCOIDOSIS

Sarcoidosis is a potentially fatal disease hallmarked by clusters of immune cells, called granulomas, in various organs throughout the body. The disease presents differently in individual patients, creating unique challenges for diagnosis and treatment. Sarcoidosis is most commonly observed in the lungs, likely because the presence of granulomas in the airways causes noticeable symptoms such as coughs, chest pain, fatigue, and shortness of breath (Bargagli and Prasse 2018). However, granulomas can occur in nearly any organ system. For some, sarcoidosis is asymptomatic and self-correcting, meaning that the disease will remedy itself within a few years. For others, if unmanaged, the disease may progress aggressively, leading to organ damage and, in rare cases, death.

FIGURE 1: SARCOIDOSIS CAN AFFECT MULTIPLE ORGANS

MEDICAL TERM	ORGAN AFFECTED	PERCENTAGE OF PEOPLE WITH SARCOIDOSIS IMPACTED
Neurosarcoidosis	Brain	3-10%
Optical Sarcoidosis	Eyes	20-30%
Pulmonary Sarcoidosis	Lungs	90%
Cardiac Sarcoidosis	Heart	20-25%
Cutaneous Sarcoidosis	Skin	30%
Hepatic Sarcoidosis	Liver	90%

Sources: Ungprasert and Matteson (2017); Pasadhika and Rosenbaum (2015); Tavana et al. (2015); Birnie et al. (2017); Wanat and Rosenbach (2015); Kumar and Herrera (2019)

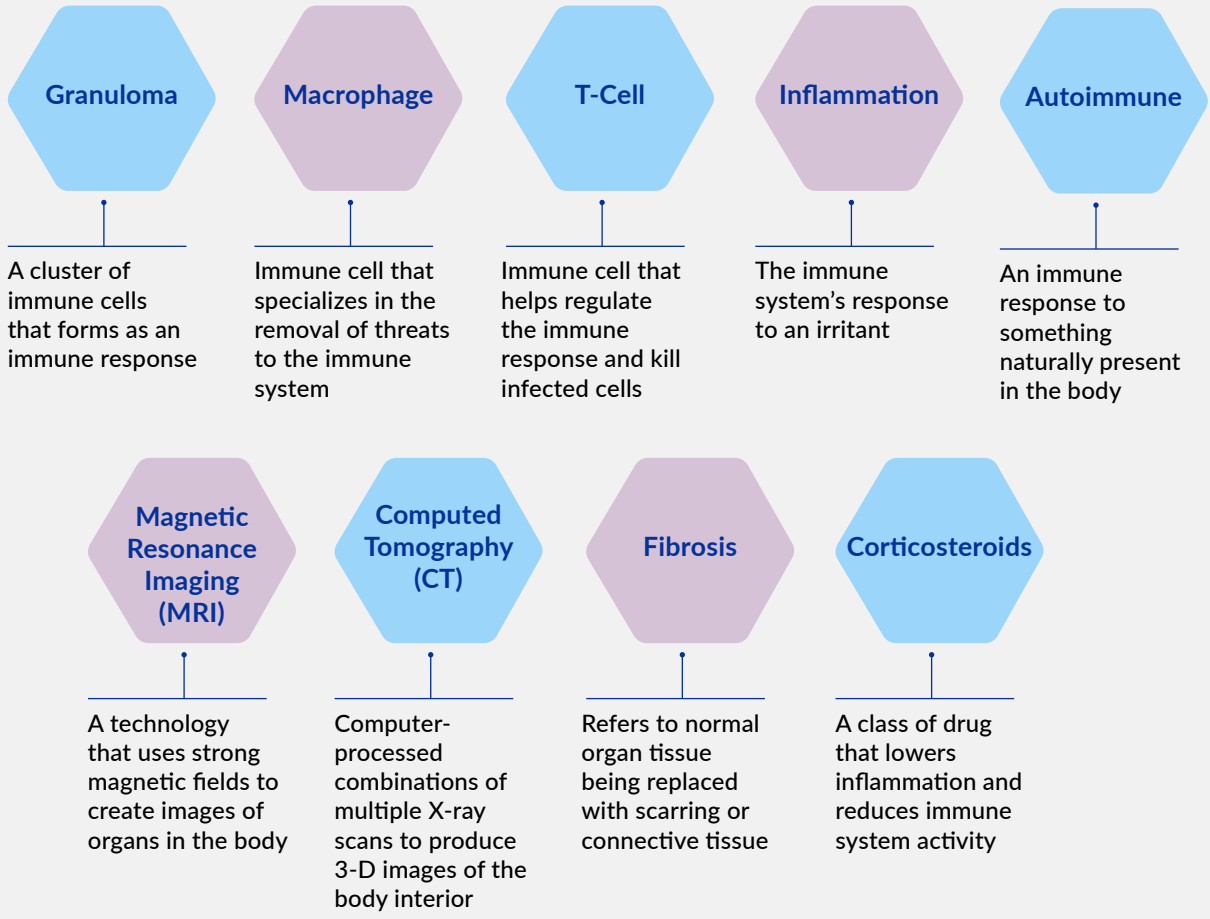
Sarcoidosis can appear as either an acute or chronic disease. Acute sarcoidosis is characterized by arthritis, fever, and enlarged lymph nodes, among other symptoms. Patients with acute sarcoidosis typically go into remission in one to two years, sometimes without interventions. Acute sarcoidosis symptoms usually present rapidly, but chronic sarcoidosis has a much slower and more insidious disease progression. Chronic sarcoidosis patients tend to experience shortness of breath, and clusters of immune cells may cause severe tissue damage over time. Chronic sarcoidosis symptoms may be absent for a period of time, but granulomas are almost always present in the lungs upon diagnosis (Bargagli and Prasse 2018). Researchers are engaged in an ongoing conversation about

whether sarcoidosis is one disease or a family of diseases because different populations tend to have different forms of sarcoidosis (e.g., Japanese populations diagnosed with sarcoidosis may have higher rates of eye and heart involvement than other populations) (Brito-Zerón et al. 2019).

Researchers are engaged in an ongoing conversation about whether sarcoidosis is one disease or a family of diseases because different populations tend to have different forms of sarcoidosis.

Granulomas are typically composed of immune cells such as macrophages and T-cells, both of which play a major role during the body's immune response (Sakthivel and Bruder 2017). Granulomas are thought to be protective, isolating foreign substances that the body cannot eliminate. If the granulomas persist for too long, however, they become damaging (Pagán and Ramakrishnan 2018). The specifics of why these granulomas form and why they last long enough to cause damage are not fully understood.

FIGURE 2: KEY TERMS IN SARCOIDOSIS



Source: Milken Institute (2021)

Causes of Sarcoidosis

Although the exact causes of sarcoidosis are not yet known, scientists believe that a combination of a person's genetic makeup and environmental factors triggers sarcoidosis. There are several types of potential causes of sarcoidosis:

Inherited Risk

Although there are no confirmed genetic determinants of sarcoidosis, some studies have shown that incidence varies greatly by race. In addition, sarcoidosis runs in families, and individuals with a first-degree relative with sarcoidosis have nearly four times the risk of developing the disease compared to the general population. Together, these findings suggest that genetics plays a role in sarcoidosis development (Spagnolo and Schwartz 2013).

FIGURE 3: PREVALENCE OF SARCOIDOSIS

By Sex

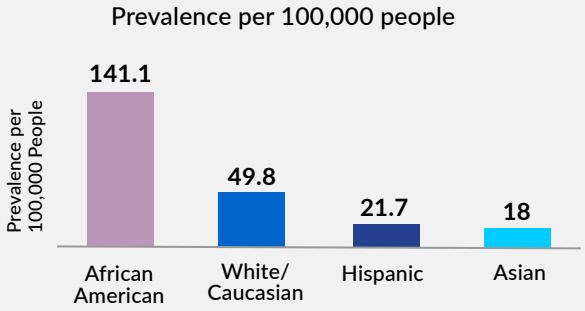
Men and women have **key differences** in some features of sarcoidosis, but the causes for these differences are **unclear**

Men tend to be diagnosed in their **mid- to late-40s**, compared to women who are more often diagnosed in their **mid-50s**

Women may have more **musculoskeletal symptoms** than men

By Race

In the United States, African Americans, and especially women, are more impacted by sarcoidosis



Sources: Arkema and Cozier (2020); Arkema and Cozier (2018); Baughman et al. (2016)

Environmental Exposures

Environmental exposures, such as bacteria, are considered likely triggers of sarcoidosis (Moller et al. 2017). Additional environmental risks include air pollution, mold, mildew, metal dust, and silicon products. Granulomas can form in response to external triggers as a normal immune response.

First responders at the 9/11 World Trade Center attacks developed sarcoidosis at a higher rate than the general population after their exposure to airborne toxins from the building collapse (Hena et al. 2019). Their development of sarcoidosis was likely a normal immune response that lingered for too long.

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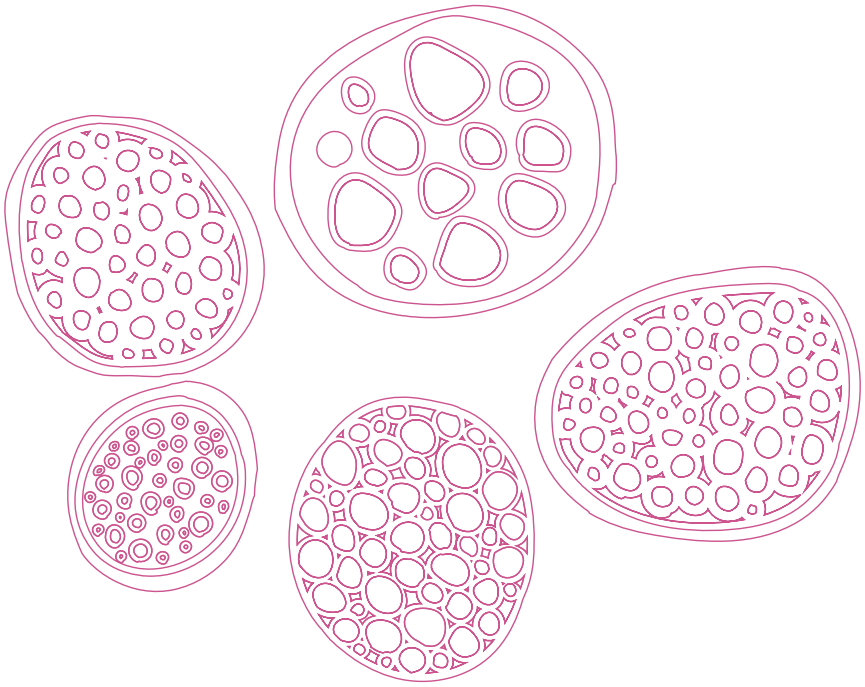
Autoimmune Risk

Recent research suggests that sarcoidosis is an autoimmune disorder. Molecular studies have identified similarities between sarcoidosis and rheumatoid arthritis, and other autoimmune conditions. Sarcoidosis can also co-exist with autoimmune conditions, suggesting overlapping triggers or pathologies. Environmental exposures or other unknown factors could cause the immune system to become hyperactive, creating granulomas. Despite the associations made with other autoimmune diseases, a potential autoimmune-related risk factor has not been identified (Starshinova et al. 2020).



SARCOIDOSIS IMPACT

Symptoms Can Decrease Quality of Life

Individuals with sarcoidosis may face a myriad of symptoms daily, including fatigue, difficulty breathing, joint pain, anxiety, and depression (Bargagli and Prasse 2018; Drent et al. 2015). Inflammation in the body is thought to induce negative mood states that can cause anxiety and depression (Felger 2018). Caregivers may also experience a decline in their own social and psychological well-being.

Sarcoidosis carries economic burdens as well. An analysis of insured patient metrics showed that annual costs of care for an individual with sarcoidosis average over $32,000 (Baughman et al. 2016). These costs are a major burden to people in middle- or lower-income brackets (especially people who are uninsured) and generally lead to worse long-term outcomes because of the inability to afford care.

Annual costs of care for an individual with sarcoidosis average over $32,000.

Prevalence of Sarcoidosis

Due to misdiagnosis and underdiagnosis, exact numbers of people affected by sarcoidosis are difficult to find. The best estimates at this time suggest that around 0.06 percent of the US population has been diagnosed with sarcoidosis. However, there is a great deal of variability among demographics. In Caucasian populations in US, rates have been measured around 0.05 percent, while rates for African American women are as high as 2.0 percent (Arkema and Cozier 2018). Worldwide, geographic location seems to be a strong predictor of sarcoidosis prevalence. Sweden and Canada have relatively high prevalence rates of sarcoidosis, while Caribbean populations may have lower rates (Coquart et al. 2015; Cozier 2016; Hena 2020).

Geographic, Lifestyle, and Socioeconomic Determinants

Geographic location and race may also influence the risk of certain types of sarcoidosis. Cardiac sarcoidosis is more prevalent in Japan, while hypercalcemia and spleen sarcoidosis are more prevalent in African Americans (Gwadera et al. 2019; Kusano and Satomi 2016). In addition,

FIGURE 4: GEOGRAPHY OF SARCOIDOSIS

COUNTRY	PREVALENCE PER 100,000 PEOPLE
Japan	4
South Korea	5
Finland	28
France	30
Germany	46
United States	60
Switzerland	121
Canada	143
Sweden	160

Source: Arkema and Cozier (2020); Costabel, Wessendorf, and Bonella (2016)

women may have a higher rate of sarcoidosis in the eyes and skin (Noe and Rosenbach 2017; Rothova et al. 1989). Current data suggest that obesity, smoking, and genetics are key factors modifying the risk for developing sarcoidosis (Cozier, Govender, and Berman 2018; Rivera et al. 2019).

Individuals with lower incomes tend to have more severe cases of sarcoidosis and worse outcomes. Certain occupations, such as agricultural workers, automotive workers, and teachers, are associated with higher incidences of sarcoidosis, likely because of the environmental risks.

FIGURE 5: POTENTIAL RISK FACTORS

Individuals with a **close relative who has sarcoidosis**

Occupations including agriculture, manufacturing, and firefighting

Environmental factors such as pollution and mold

African Americans and individuals in **Nordic countries**

Sources: Arkema and Cozier (2020); Newman et al. (2004)

Age of Onset

There is no consensus about the age of onset or periods of high risk of developing sarcoidosis. Multiple periods of higher risk of developing sarcoidosis are possible, with different studies showing a variety of age ranges, including 25-29, 30-35, and 65-69 years (Baughman et al. 2016; Gerke et al. 2017; Salah et al. 2018; Ungprasert, Ryu, and Matteson 2019).

Prognosis

The prognosis for patients with sarcoidosis depends on the severity of the case. About one-third of people with sarcoidosis are asymptomatic, and some recover without treatment (Valeyre et al. 2015). Between 1 percent and 5 percent of patients with any type of sarcoidosis die from complications (Gerke 2014). The organs at highest risk of being affected are the lungs, heart, liver, and nervous system. Heart sarcoidosis is more common than clinical diagnosis suggests; up to five times as many cases of heart sarcoidosis are found post mortem compared to in the clinic (Birnie et al. 2016b).

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People with heart sarcoidosis can be at risk of sudden death due to heart damage. Chronic pulmonary sarcoidosis causes shortness of breath, fatigue, and organ damage, among other symptoms. Chronic pain conditions can also develop from sarcoidosis, greatly reducing quality of life (Tavee and Culver 2011).

Impact on Individual Organs

Sarcoidosis patients may have multiple organs develop granulomas, but different organs are likely to be affected at different rates (Sauer et al. 2017). The lungs appear to be the most commonly involved organ in sarcoidosis because they are implicated in greater than 90 percent of diagnosed cases (Tavana et al. 2015). Cutaneous sarcoidosis, which appears in the skin, is also common and occurs in approximately 30 percent of all sarcoidosis patients (Wanat and Rosenbach 2015). Cardiac sarcoidosis is estimated to be present in 20-25 percent of sarcoidosis patients (Birnie et al. 2016b). The ocular form, affecting 20-30 percent of patients, is often the first manifestation in individuals who develop sarcoidosis (Pasadhika and Rosenbaum 2015). Neurosarcoidosis is relatively uncommon because this manifestation occurs in 3-10 percent of the patient population (Ungprasert and Matteson 2017). Although not commonly studied, the liver is often implicated in multi-organ cases of sarcoidosis. A recent study found that up to 90 percent of sarcoidosis patients have liver granulomas but that the majority of cases are asymptomatic (Kumar and Herrera 2019).

Diagnosis

There is no universally accepted standard to diagnose sarcoidosis. Imaging techniques, such as an MRI or CT scan, are commonly used to visualize granulomas. However, this approach is complicated by the fact that granulomas are present in multiple diseases. Biopsies can be taken from the suspected organs to differentiate sarcoidosis granulomas from other granulomatous diseases such as tuberculosis or cancer, but this highly invasive method can still miss the diagnosis. In more advanced cases, fibrosis, which refers to organ scarring or hardening, may be present rather than granulomas. Because of these complexities, sarcoidosis is generally diagnosed by ruling out the possibility of other diseases.

Treatment

Treatment plans are not standardized and vary dramatically among clinics. In some cases, granulomas may be present without any inflammation or additional symptoms. Some clinicians treat granulomas in the absence of other symptoms, while other physicians believe that treatment of acute sarcoidosis could lead to chronic sarcoidosis. The aggressiveness of the treatment plan may also depend on which organ is affected.

With routine monitoring and checkups, physicians could determine whether a case will spontaneously resolve or may cause harm, although determining the difference between these cases has proven difficult. If sarcoidosis is found on the skin or in the eye, topical anti-inflammatory drugs or eye drops can be used to treat the granulomas (Jadotte et al. 2018; Pasadhika and

Rosenbaum 2015). For any other affected organ, systemic drugs are typically used. Löfgren's syndrome, an acute form of sarcoidosis, typically resolves over one to two years, so treatment is directed toward managing symptoms and not eradicating the granulomas. The most prevalent treatment types used in clinical care or being tested for future use are described below.

FIGURE 6: COMMON SARCOIDOSIS TREATMENTS

INTERVENTION	DESCRIPTION	POSSIBLE SIDE EFFECTS
Corticosteroids	The most common treatment for sarcoidosis, though it is associated with a host of side effects	Weight gain, hypertension, diabetes, headaches, dizziness, nausea, diarrhea
Immunosuppressants	A group of drugs that inhibit immune cell activity and are not effective in all patients. These are capable of lessening sarcoidosis symptoms	Gastrointestinal, liver, and renal toxicity, lower white blood cell count
Protein Inhibitors	Drugs that affect a specific molecular target and are approved as treatments for other diseases but have shown promise in sarcoidosis	Allergic reaction, higher risk of serious infection
Repository Corticotropin Injection	An injection of hormones that reduces inflammation and may improve quality of life	Anxiety, swelling, allergic reaction, infection
Lifestyle Changes	Diet, exercise, and cognitive behavioral therapy can improve sarcoidosis symptoms but will likely not address the granulomas	

Sources: Sellarés et al. (2020); Strookappe et al. (2015); Bast, Semen, and Drent (2018); Moor et al. (2020)

Corticosteroids

Corticosteroids, which are naturally produced in the body and affect a wide range of biological processes, are usually the first line of treatment for sarcoidosis (Judson et al. 2013). Steroids will not cure the disease and are only used to reduce inflammation. The most commonly prescribed is prednisone. There is no consensus for the appropriate dosage (Baughman and Lower 2018). Although corticosteroids can be effective for some patients, prolonged use is linked to a plethora of side effects, including hypertension, weight gain, and diabetes (Judson et al. 2015).

Although corticosteroids can be effective in the short term for some patients, prolonged use is linked to a plethora of side effects, including hypertension, weight gain, and diabetes.

Some physicians believe that steroid use may cause a transition from acute to chronic sarcoidosis. Corticosteroid dosage can be reduced, and patients can be prescribed other therapies to prevent or alleviate side effects.

Immunosuppressive Drugs

If a patient does not respond well to corticosteroids or needs a very high dose, immunosuppressive drugs such as methotrexate are usually the next treatment option. Some immunosuppressive drugs are cytotoxic, cytotoxic, damaging cells and causing side effects that include dizziness, headaches, hair loss, and liver damage (Conway and Carey 2017). Little research has compared the efficacy of different immunosuppressive drugs. Methotrexate, which prevents immune cells from activating or multiplying, is currently being studied to determine its effectiveness as an alternative to steroids.

Protein Inhibitors

Therapies that interact with specific proteins may be used when general corticosteroids or immunosuppressants have little to no effect on the patient's condition or result in severe side effects. The targets are molecules with important roles in the cell life cycle, but they can behave abnormally and disrupt the immune system. These drugs are also used in other diseases, such as rheumatoid arthritis, but have not been as rigorously tested in sarcoidosis patients and have not been formally approved for sarcoidosis treatment.

Repository Corticotropin Injection

Repository corticotropin injection (RCI) is a mixture of hormones injected into the muscle or under the skin to reduce inflammation. It is the only drug other than prednisone that has been approved by the US Food and Drug Administration (FDA) to treat sarcoidosis (Chopra et al. 2019). This is another option for people with corticosteroid-resistant sarcoidosis. RCI has been used to reduce the dose of corticosteroids, which may in turn reduce side effects (Baughman et al. 2017). RCI tends to be effective in reducing the severity of symptoms and improving quality of life.

Lifestyle Changes

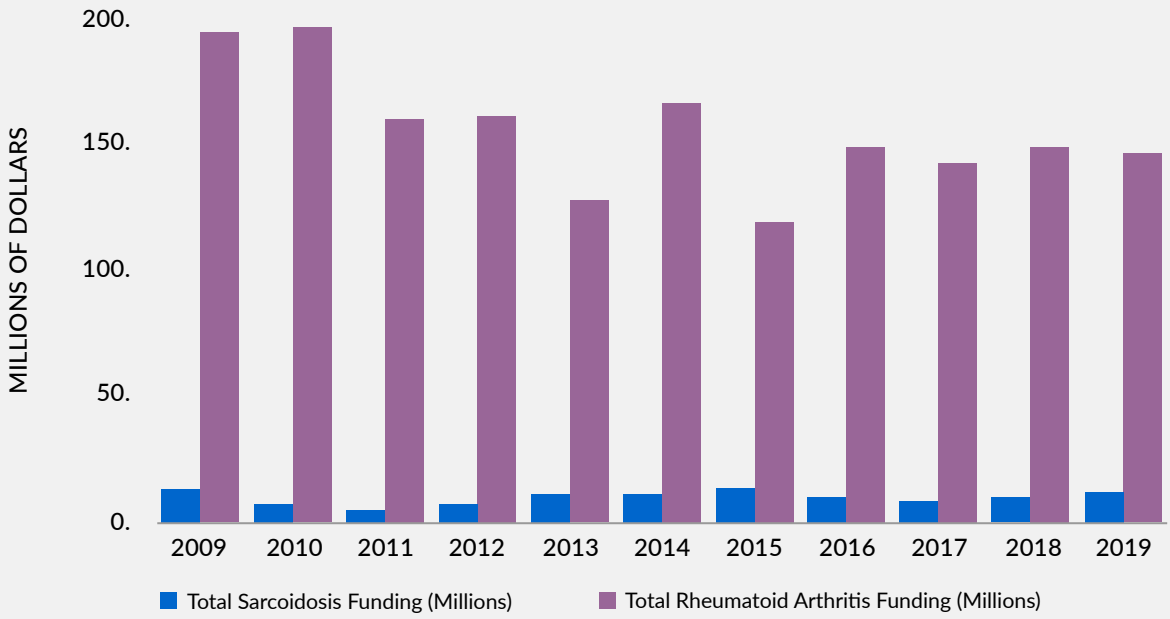
Several studies have shown that physical training may help reduce fatigue, one of the most commonly reported symptoms in patients with sarcoidosis (Strookappe et al. 2015). Changes in diet can also help manage inflammation, especially diets rich in vitamins C and E, as well as foods such as walnuts and vegetable oil, which have high levels of healthy fats (Bast, Semen, and Drent 2018). Cognitive behavioral therapy can help alleviate anxiety and depression, which can develop in sarcoidosis patients (Drent et al. 2015; Moor et al. 2020). These lifestyle changes may help control inflammation or improve quality of life, but they will likely not address the presence of granulomas, especially in chronic sarcoidosis.

FUNDING FOR SARCOIDOSIS

CSP's analysis showed that the federal government funds the vast majority of sarcoidosis research in the US through the National Institutes of Health (NIH). The majority of NIH funding for sarcoidosis is focused on pulmonary sarcoidosis and clinical trials. There is a distinct underfunding of studies examining the most commonly prescribed treatments for sarcoidosis, as well as an underfunding of the sarcoidosis field overall.

Between fiscal years 2009 and 2019, the federal government provided more than $110 million for sarcoidosis research. Annual funding for sarcoidosis varied during this time, with annual amounts ranging between $4.8 million and $13.7 million. These data are published in funding databases Federal Reporter (FedReporter) and the NIH Research Portfolio Online Reporting Tool (NIHReporter).

FIGURE 7: ANNUAL SARCOIDOSIS FUNDING, 2009–2019



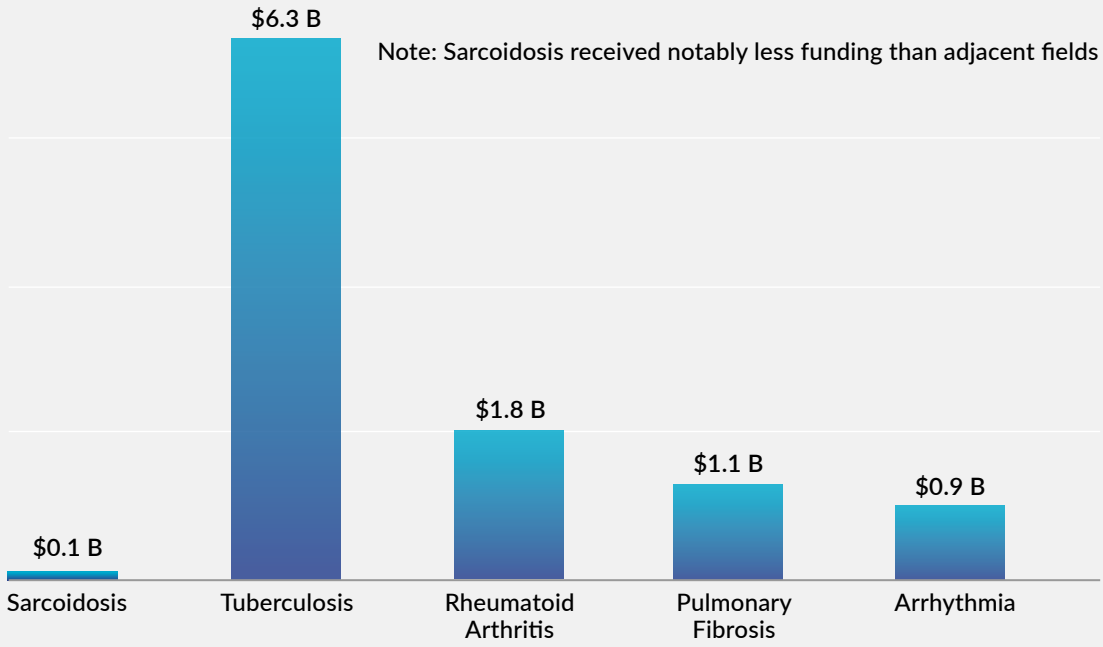
Note: Funding levels for sarcoidosis were low and somewhat variable in this decade

Sources: NIHReporter (FY2009-FY2019); FedReporter (FY2009-FY2019)

Sarcoidosis Has Comparatively Little Investment

Experts in the field frequently expressed the sentiment that sarcoidosis is underfunded. From 2009 to 2019, funding for adjacent fields, such as tuberculosis, rheumatoid arthritis, pulmonary fibrosis, and arrhythmia, was much more robust. The incidence of rheumatoid arthritis is four to five times higher than the incidence of sarcoidosis. However, funding levels for rheumatoid arthritis are 15 times higher than those of sarcoidosis.

FIGURE 8: SARCOIDOSIS FUNDING COMPARED TO ADJACENT FIELDS, 2009–2019



Sources: NIHReporter (FY2009-FY2019); FedReporter (FY2009-FY2019)

Pulmonary Sarcoidosis Drives Overall Funding

Sarcoidosis can affect nearly every organ in the body, and therefore it is vital to understand how funding is stratified. Because NIH is structured by medical specialties and disorders, certain institutes or grants may focus on studying single organs rather than the multi-system condition.

Note: The majority of NIH funding went through NHLBI

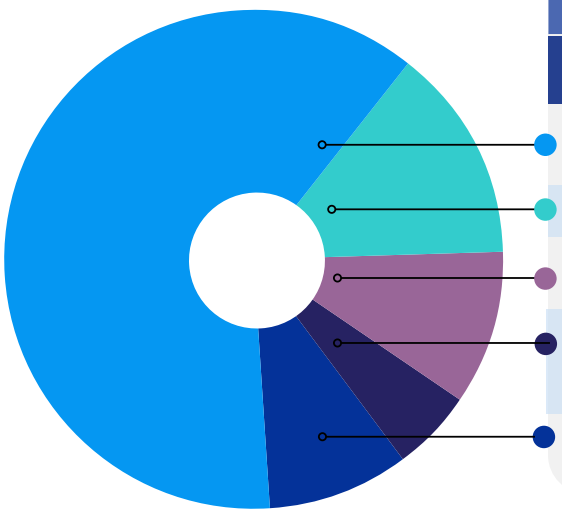


FIGURE 9: NIH SARCOIDOSIS FUNDING, 2009–2019

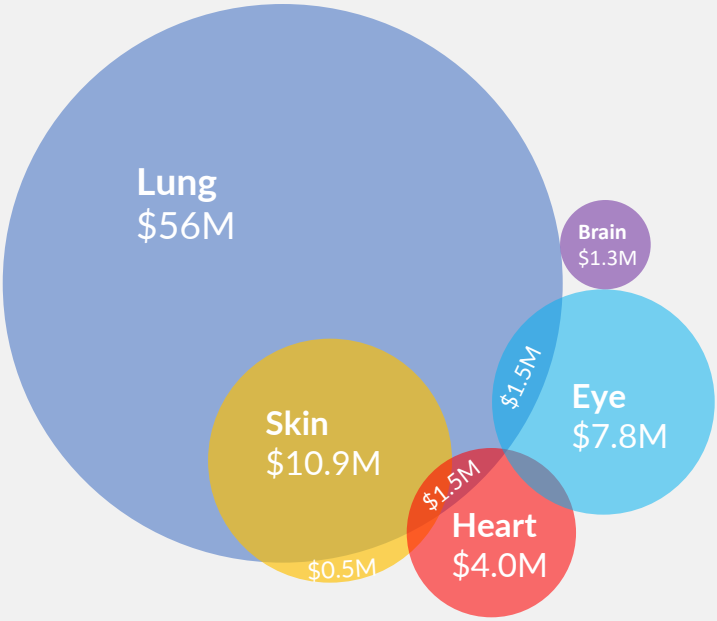
INSTITUTE	10-YEAR SARCOIDOSIS FUNDING
National Heart, Lung, and Blood Institute (NHLBI)	$68,152,423
National Eye Institute (NEI)	$15,425,214
National Institute of Allergy and Infectious Diseases (NIAID)	$10,723,596
National Institute of Environmental Health Sciences (NIEHS)	$6,018,002
Other	$9,875,643

Source: Arkema and Cozier (2020); Costabel, Wessendorf, and Bonella (2016)

The institutional focus on specific organ systems rather than multi-organ disease has led to unequal funding of research on specific organs rather than the disease in general. Funding for pulmonary sarcoidosis accounted for the vast majority (61 percent) of sarcoidosis funding between 2009 and 2019, totaling around $70.5 million.

FIGURE 10: ORGAN-SPECIFIC SARCOIDOSIS FUNDING, 2009–2019

Note: Majority of sarcoidosis funding was allocated for pulmonary sarcoidosis



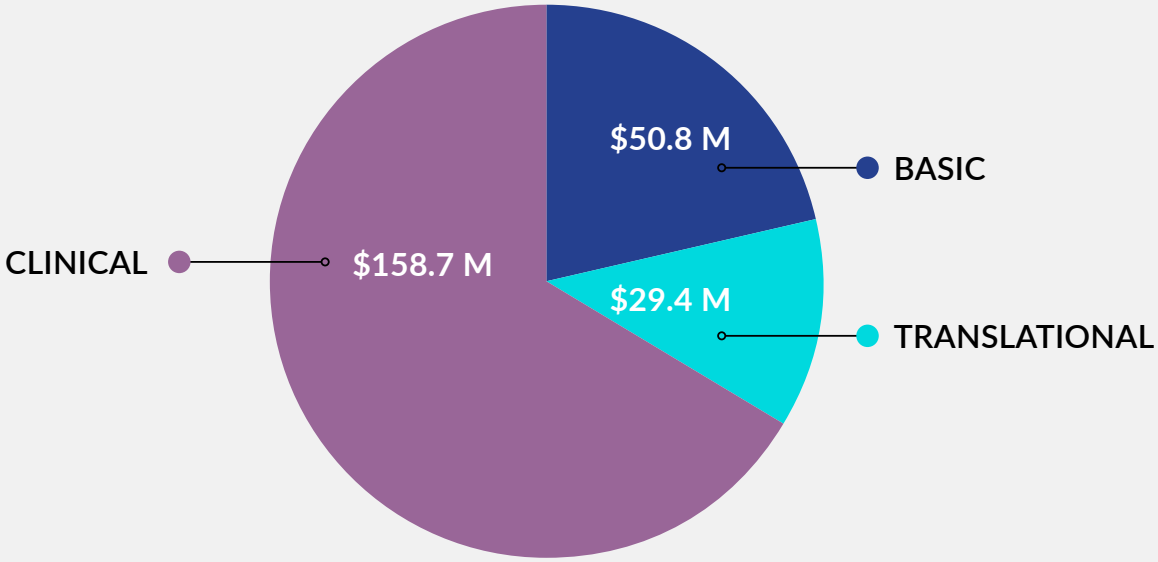
Sources: NIHReporter (FY2009-FY2019); FedReporter (FY2009-FY2019)

Basic Science Is Underfunded

To better understand the trends, CSP examined the types of studies that have been funded. They include basic research, which encompasses laboratory experiments that help to understand innate biology; translational research, which adapts the basic biological findings to develop therapeutics and clinical tools; and clinical research, which includes treatments and clinical trials. We found that clinical studies account for two-thirds of the total funding between 2009 and 2019. Translational science received about 21 percent of the total funding, and basic science received the remaining 12 percent. This funding trend runs counter to how other disease fields are funded, where basic science often accounts for a majority of funded studies. Basic science funding allows scientists to generate new hypotheses, identify molecular targets that could lead to new or repurposed treatments, and achieve greater understanding of disease mechanism and progression.

FIGURE 11: SARCOIDOSIS SPENDING BY STUDY TYPE, 2009–2019

Note: Clinical studies accounted for the majority of sarcoidosis funding



Sources: NIHReporter (FY2009-FY2019); FedReporter (FY2009-FY2019)

Common Treatments Are Not Well Studied

Sarcoidosis experts have noted the lack of studies examining the effects of the most commonly prescribed therapeutics. Between 1985 and 2019, less than $3 million in federal funding was devoted to testing prednisone, a corticosteroid used in front-line treatment for sarcoidosis. Furthermore, one lab led all of the prednisone studies, which tested whether the corticosteroid could be replaced with a therapeutic with fewer harmful side effects. The funding for other studies on commonly used drugs was also relatively low and led by a small number of researchers. Additional studies examining the varying efficacies and side effects of these drugs should be prioritized, especially for commonly prescribed treatments. Expanding the knowledge base of the effects of common treatments is important for patient communities, and justifying the use of one treatment over another could be life-changing.

These studies can more quickly impact individuals with few financial resources. Prednisone is often the most affordable option for patients, despite its many long-term side effects. If individuals cannot afford a safer option, they will either have to continue using prednisone or take no medication at all.

BARRIERS HINDERING SARCOIDOSIS PROGRESS

CSP has identified seven barriers to progress for sarcoidosis understanding, treatment, and patient care practices. These barriers, which are not mutually exclusive, cross nearly all points of research and treatment. Understanding these barriers is key to identifying how philanthropic investment can be most impactful.

1. Poorly Understood Cellular and Molecular Biology

Despite the work to date to understand the biology of sarcoidosis, little is known about what causes the disease, its progression, genetic risk factors, or how to distinguish acute and chronic cases of sarcoidosis. Although some genes have been implicated in sarcoidosis, it is unclear whether they cause the disease. The immune system is believed to play a substantial role in the development and progression of sarcoidosis. However, scientists have not yet determined how immune factors impact or drive sarcoidosis. Without this knowledge, the development of specifically targeted novel therapeutics will remain difficult.

2. Incomplete Understanding of How Social Determinants Influence Sarcoidosis Development

Sarcoidosis disproportionally affects African American women, along with people of Nordic origin. Sarcoidosis onset is thought to be influenced by both genetic susceptibility and environmental exposure, at times influenced by occupation, but the exact mechanisms are not well defined. Because medications that can be used instead of steroids are more expensive, individuals with low income are commonly prescribed only corticosteroids, which can cause severe side effects and additional comorbidities.

Furthering the knowledge of how socioeconomic status, occupation, and geography influence sarcoidosis rates is severity are essential to improving science's understanding of the disease, developing effective therapeutics, and enacting preventative measures.

3. Inadequate Animal Models

No widely accepted animal models for studying sarcoidosis currently exist. Some scientists have used rodents to study sarcoidosis, but many experts do not find them representative of the human disease. The creation and widespread use of validated animal models will enable scientists to study the molecular biology of sarcoidosis and further our collective understanding of the disease. A single animal model may not model a human disease; rather, models can replicate different facets to enable study of a disease from multiple angles. The totality of these models is informative but requires investment in hypothesis building, tool development, and validation.

4. Lack of Specific Diagnostic Tools and Protocols

The most common techniques to diagnose sarcoidosis involve imaging, such as CT scans and biopsy. Although these tools can help physicians, a sarcoidosis diagnosis generally requires ruling out other potential conditions rather than confirming sarcoidosis directly. Biopsies can achieve this objective, but they are invasive and inconsistent. Other techniques may be even less reliable. For clinicians to more accurately and quickly diagnose sarcoidosis, new diagnostic methods for sarcoidosis must be developed.

5. No Standardized Clinical Practices

Individual physicians have different criteria for screening people for sarcoidosis. Some rely exclusively on a biopsy, while others use imaging techniques. This lack of diagnostic consensus makes it difficult to understand which practices are most beneficial to patients and can make diagnosis and navigating information and care more difficult. Similarly, there is no consensus on appropriate treatments once a diagnosis is made. One physician may prescribe a drug when sarcoidosis is first detected, while another may wait for active inflammation. Corticosteroids are often the first-line treatment, but there is less agreement on subsequent interventions if corticosteroids fail to alleviate symptoms. In addition, a lack of public awareness has led to misdiagnosis and mismanagement of sarcoidosis, worsening outcomes overall.

6. Insufficient Treatment Toolbox

Not all treatments have the same efficacy in every person, and only seven clinical studies have compared the relative efficacies and side effects of pharmacological interventions for sarcoidosis. Without additional data on these therapies, it has been exceedingly difficult to create effective treatment plans that change the course of the disease.

Fewer than 10 treatments are commonly used for sarcoidosis, all with serious side effects and limited efficacy. The lack of basic, foundational knowledge of the disease and preclinical testing platforms such as animal models has stunted the development of novel therapeutics. All of these circumstances combine to complicate the treatment of patients.

7. Need for a Larger Research Workforce and Greater Clinical Awareness

The sarcoidosis research community is small, and many researchers and clinicians focus on pulmonary or cardiac sarcoidosis even though the condition impacts other organ systems. Researchers note that inconsistent and low levels of funding have made sarcoidosis research less appealing to young researchers and pushed veterans out of the field. Without a sufficient workforce, it will be difficult to create and sustain forward momentum.

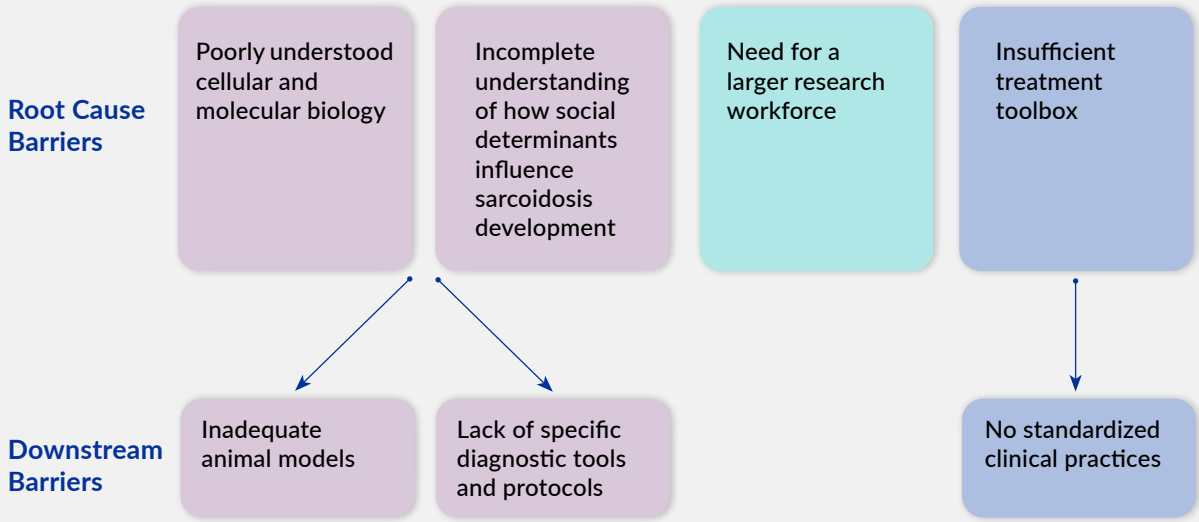
The Interconnectivity of Sarcoidosis Barriers

Upstream challenges drove many barriers identified by CSP. Analysis of the barriers revealed four *root cause* barriers in the sarcoidosis field:

- poorly understood cellular and molecular biology,
- incomplete understanding of how social determinants influence sarcoidosis development,
- need for a larger research workforce and greater clinical awareness, and
- limited characterization for existing therapeutics.

Overcoming these root cause barriers will generate long-term impact but will likely require long-term and substantial investment to address them adequately.

FIGURE 12: INTERCONNECTIVITY OF BARRIERS



Source: Milken Institute (2021)

OPPORTUNITIES FOR PHILANTHROPY

The field has many barriers to overcome, but philanthropy has a unique opportunity to build tools and infrastructure that would have a long-lasting impact on many individuals' lives.

1. Characterize the Biology and Progression of Sarcoidosis Through the Application and Development of New Tools

Progress toward a fundamental understanding of the disease, as well as clinical management, has been slowed by a lack of accessible tools to study or diagnose sarcoidosis effectively. For the field to move forward more efficiently, the molecular interactions that underlie the disease and its progression and robust characterization of its manifestations must be known.

Support molecular target discovery: To diagnose and treat sarcoidosis better, experts need to better understand the specific molecular changes that lead to its onset and progression. Technologies used to examine other conditions can be applied to advance sarcoidosis research and expand the ability to manage sarcoidosis.

Focus on specific populations: Race, sex, and socioeconomic status are compounders of discrepancies in patient outcomes, and African American women are the group most impacted by the disease in the United States. A specific focus on understanding why sarcoidosis is more prevalent in certain populations can also lead to tailored treatment development.

Fund the development of animal models: Animal models are essential to novel therapeutics and are key tools for understanding the molecular underpinnings of sarcoidosis. Support to develop multiple animal models reflective of different facets of the disease is key to improving our understanding of sarcoidosis.

2. Support Clinical Trials

Researchers and clinicians noted both the insufficient evidence for the current standard practices and insufficient funding to develop and test new therapeutics for sarcoidosis.

Testing existing therapeutics: Many experts noted the lack of data to justify the use of one treatment versus another. Furthermore, drugs that have been approved for other conditions may also provide symptomatic relief in people with sarcoidosis. What is needed are randomized, controlled trials of existing therapeutics to offer additional resources to people with sarcoidosis.

Developing novel therapeutics: Additional work on the molecular biology of sarcoidosis is needed to inform the development of novel therapeutics. Once more potential therapeutic targets are uncovered, support for studies to develop new therapies targeting these mechanisms will be essential.

3. Expand the Sarcoidosis Research and Clinician Communities

Experts in the field indicated that the community is rather small and that sarcoidosis is not well known by the public. A larger and more consistent research and clinical community is essential to creating long-lasting change.

Expand fields of study: Sarcoidosis should be studied by researchers from many disciplines, such as rheumatologists, immunologists, and neurologists. Providing funding opportunities for specific fields outside of sarcoidosis will not only expand the number of scientists focused on sarcoidosis but also improve the diversity of ideas and spur innovative solutions.

Increase funding stability: Any scientific community needs reliable and consistent funding to sustain research. To ensure that researchers can make significant progress on sarcoidosis projects, support and resources must be maintained.

Create avenues to pilot data: Typically, academics utilize start-up funds or smaller grants to collect enough data to apply for larger grants, usually from NIH. Funding directed toward testing early hypotheses and collecting early data could help to attract follow-on funding from NIH.

Focus on people: Fellowships would directly support individual scientists and can attract younger people and scientists from diverse backgrounds to the field. Although this type of funding already exists in sarcoidosis research, additional opportunities would increase the capacity and diversity of the scientific community.

Support awareness campaigns: Targeted awareness campaigns could lead researchers and clinicians to make more connections among their work, patient needs, and the disease. In addition, with the right knowledge, clinicians will be better able to make appropriate referrals to a sarcoidosis specialist, saving a patient time and stress and benefiting their overall health.

4. Build Infrastructure to Unite the Community

A variety of resources could be developed for people within and outside of the community to study and better understand the varying presentations of sarcoidosis. Creating opportunities for collaborative efforts will help bring people together and support the growth of the research space.

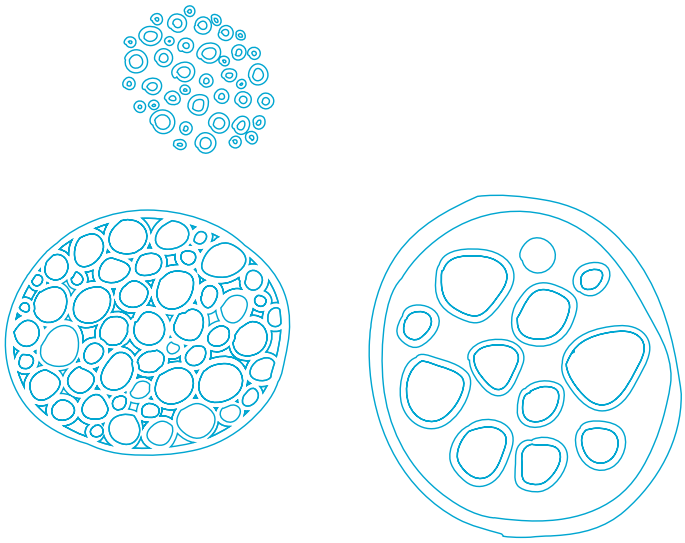
Create a biobank of patient samples: A tissue bank, and support for researchers to study biological samples, could inform understanding of the causes, commonalities, and differences among individual cases of sarcoidosis. A centralized biobank can utilize patient samples from diverse backgrounds to allow for more inclusive studies and findings on sarcoidosis. Study of these samples could lead to the identification of more reliable biomarkers for diagnosis, treatment, and prognosis. Philanthropy can increase the reach and scale of current biobanks.

Build a clinical studies network: A network would facilitate coordination among clinical trials, funding of studies using the network, and participation of more people from various locations. This network could also foster consensus for diagnostic approaches. The Foundation for Sarcoidosis

Research (FSR) is the largest non-profit dedicated to sarcoidosis research and patient care, and is building such a network to run clinical trials.

Develop patient registry: A central collection of medical information from a group of patients to support the assessment of outcomes that can determine what traits, treatments, and lifestyle changes affect the prognosis of sarcoidosis would be life-changing for many patients. Philanthropy can increase the diversity of these registries, specifically for patients who are African American, female, of low socioeconomic status, or from certain occupations. A robust patient registry can help to clarify the best treatment plans. A partnership with FSR, which has a well-established network, would be an effective approach.

Support scientific meetings: Philanthropy can also support researchers who travel to conferences or disease-focused foundations in hosting successful convenings for the research community. Providing opportunities for researchers to meet to share their ideas and work can help build collaborative efforts and the community.



CONCLUSION

Sarcoidosis is a severely underfunded and poorly understood condition that can have drastic effects on people's lives. Even now, physicians and scientists are unsure of the number of people affected by sarcoidosis because of mis- and underdiagnosis. The field has been underfunded for decades, and philanthropy has a unique opportunity to support sarcoidosis research and create the forward momentum that is so desperately needed. Sarcoidosis can be a life-altering and life-threatening condition, but philanthropic investments can help people with sarcoidosis in the short and long terms.

Taking advantage of the opportunities outlined here could alleviate the most pressing barriers to sarcoidosis research. Philanthropy can be a powerful catalyst for change and innovation, which can lead to further funding from public and nonprofit sources to sustain growth. By finding ways to bring people together to collaborate, better understand the underlying biology of sarcoidosis, and make more therapeutic options available, philanthropy can drastically improve the overall health of people who live with sarcoidosis.

APPENDIX

Key Stakeholders

The organizations presented here are the leading organizations making progress in expanding the knowledge base of sarcoidosis and building the sarcoidosis community.

Professional Societies

- World Association of Sarcoidosis and Other Granulomatous Disorders

  The mission of WASOG is to bring together clinicians and scientists interested in sarcoidosis and other interstitial lung diseases together.

- American Lung Association

  The ALA is a leading organization working to save lives by improving lung health through education, advocacy, and research.

Nonprofit Research Funders

- Foundation for Sarcoidosis Research

  FSR works with some of the world leaders in sarcoidosis, invests in patient-centered research efforts, and provides educational resources to patients worldwide

- CHEST Foundation

  CHEST Foundation is the patient-focused philanthropic arm for the American College of Chest Physicians, and is dedicated to championing lung health.

- Pulmonary Fibrosis Foundation

  The Pulmonary Fibrosis Foundation is focused on being a trusted resource for all who are affected by pulmonary fibrosis, which can be caused by sarcoidosis.

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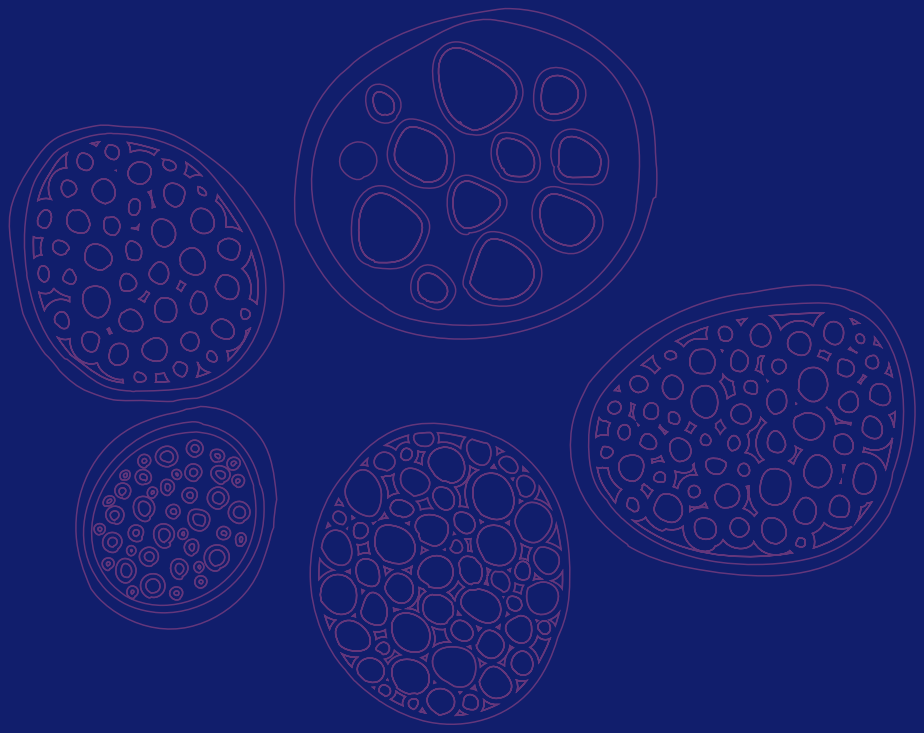

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