







Lupus spectrum ambiguity has long-term negative implications for patients

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ABSTRACT

Lupus is a complex disease that is often difficult to diagnose. Risks of diagnostic delays include non-specific signs and symptoms that mimic other diseases and a lack of diagnostic criteria and referral pathways for non-specialists. To address these issues, we convened a series of virtual meetings with members of our Addressing Lupus Pillars for Health Advancement clinical care team. Meeting participants included lupus physicians, treatment developers from biotechnology, patient advocacy group representatives from the Lupus Foundation of America and advocacy/government consultants. Causes and consequences of ambiguity in diagnosis and diagnostic delays were evaluated through historical, experiential and evidence-based accounts (survey data, literature reviews and patient testimonials). Discussions highlighted the need for a clearer understanding of the definition of lupus, the natural history of the disease and the need for advancements in biotechnology to support an accurate and timely diagnosis with the potential development of a lupus spectrum.

THE ADDRESSING LUPUS PILLARS FOR HEALTH ADVANCEMENT PROJECT

The Addressing Lupus Pillars for Health Advancement (ALPHA) Project is a global initiative spearheaded by the Lupus Foundation of America (LFA) to identify and address the most pressing barriers to improving lupus outcomes. The ALPHA Project is led by a Global Advisory Committee (GAC) of lupus experts from around the globe (see list in online supplemental file 1). In the first phase of the project, completed in 2019, the GAC identified key barriers to improving lupus outcomes through a series of interviews and an online survey of lupus clinicians and researchers from around the world.¹ In phase II, completed in 2020, the GAC identified and prioritised actionable solutions for three different types of barriers: those to clinical care, drug development and access to care.² This report is the first of a series of reports and toolkits in phase III, the solution implementation phase, of the ALPHA Project. This report summarises a series of meetings and

deliberations held by members of the GAC as an important first step to operationalise the highest priority solution for addressing barriers to clinical care: defining the lupus spectrum.

OVERVIEW OF THE JOURNEY TO DIAGNOSIS OF PATIENTS WITH LUPUS

Lupus is a complex disease with interpersonal and intrapersonal symptom variability across a patient's lifespan. In addition, clinical presentation with non-specific signs and symptoms that mimic other diseases such as rheumatoid arthritis or undifferentiated connective tissue disease complicates the diagnostic journey for many patients. This, in turn, can lead to a delay in access to health-care providers well versed in lupus and subsequent access to appropriate lupus treatments. At present, there are no clear, validated diagnostic criteria for lupus, and SLE classification criteria are often used as a reference to determine if a patient is indeed presenting with SLE. In this meeting report, we outline the patient perspective on barriers to diagnosis, how they impact patients, and provide recommendations for reducing time to diagnosis by recognising and defining lupus as a spectrum disorder.

Reports from a global patient-reported survey found that 27%–37% of people with lupus were diagnosed within 1 year from the onset of their symptoms, while an average one-third of patients were diagnosed after 5 years, with the median reported delay being 2 years.^{3,4} Even more striking are results from a study of 2527 patients with lupus in the UK that showed an average delay in diagnosis of over 6 years, and that 47% of respondents were originally misdiagnosed.⁵

DIAGNOSTIC DELAYS

Diagnosing lupus is considerably challenging, particularly early in the disease process



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where patients present with inadequate or non-specific sequelae. Moreover, pathognomonic diagnostic tools are lacking the molecular prowess necessary to support diagnosticians in clinical decision-making. We recognise that when patients present clinically without cardinal features of lupus (ie, ANA positivity, photosensitivity, etc), incomplete SLE or probable lupus, making a clear diagnosis might prove challenging, even for the more skilled and experienced specialist. Still, consequences of diagnostic delays, especially in patients with major organ involvement, are vast and include higher disease activity, higher rates of damage accrual, fatigue and a lower quality of life over the long term.⁶ An in-depth understanding of causes for delays in diagnosis may drive the development of solutions that promote earlier diagnosis, intervention and better long-term outcomes.⁷

Limited exposure and experience among primary care physicians

Primary care physicians (PCPs) and emergency room doctors are the gatekeepers to specialty care and often the first providers to encounter a patient with lupus.⁸ However, non-specialists often have difficulty interpreting non-specific symptoms and signs of potential lupus that should, but often do not, result in referral to dermatologists, nephrologists or other physicians specialising in rheumatological care.⁹ LFA global patient survey data demonstrated that only 20% of respondents who initially reported their symptoms to a PCP recall any mention of lupus from the doctor at the first visit.⁸ Respondents reported that a probable lupus diagnosis was mentioned among rheumatologists and dermatologists at a higher rate (58% and 49%, respectively) compared with a PCP.⁸ These findings support observations in a community-based survey showing that rheumatologists are four times as likely to accurately diagnose lupus compared with primary care providers.¹⁰ Short of conducting exhaustive lupus education for PCPs, there may be opportunities to develop an acronym or other resource outlining subtle features of lupus to help the public and non-specialists identify 'red flag' symptoms that indicate possible or incomplete lupus. Marketing and advocacy campaigns that raise awareness about 'red flag' lupus symptoms would be instrumental in improving quality of care. The development of risk prediction models that identify people at risk of lupus may also be useful for reducing delays in diagnosis and treatment.¹¹

Misdiagnosis and provider mistrust

Even when patients have access to experts in rheumatological diseases, misattribution of symptoms to a different disease may occur because initial signs and symptoms of lupus, particularly of SLE, are like those of other diseases. In some cases, it may take years for patients to display enough symptoms for their providers to clearly diagnose them with lupus. Recent patient survey data collected by the LFA from 1313 patients with lupus in the USA noted that the most common lupus symptoms such as

fatigue and/or joint pain/swelling also occur in other autoimmune conditions.¹² As a result, people with lupus are frequently misdiagnosed with rheumatoid arthritis, fibromyalgia, chronic fatigue, skin disorders, psychological disorders such as anxiety and depression or receive no answers at all.^{12 13} Patients rely heavily on medical providers for medical interpretation of symptoms and appropriate treatment. Misdiagnosis and diagnostic ambiguity cause patients to second guess themselves, alter healthcare-seeking behaviours and reduce trust in physicians.¹⁴ Hundreds of inquiries to LFA's health education specialists reflect patients' needs for further support, guidance and information.

Shown below is one example of a recent patient inquiry:

Need information on LUPUS, Sjogren and Antithrombin 3 deficiency. I've gone through different treatments and drugs, and they aggravate the diseases instead of calming it down. 1993 was first diagnosis of LUPUS due to a severe stroke. In 2019 [a hospital provider] added the Sjogren and AT3 [deficiency]. Tried to get care through my local doctors, but I am a woman and ethnic, I've been accused of wanting drugs or I'm mentally ill. Need info, to educate myself, been worse this year not sure who to trust! (anonymous patient)

Risk factors for poor health communication include limited health literacy, limited English proficiency and provider–patient language discordance, race/ethnicity discordance and provider implicit bias. These factors might explain findings in one LFA study which demonstrated that out of 3156 patients, 50% described symptoms to their physician as being less severe than they really were. When asked, 'In your opinion, is there anything your doctor(s) could've done differently to reach an accurate lupus diagnosis sooner?', 42% of patient survey respondents believed their doctor did everything they could, while 22% of them believed they could have received an accurate lupus diagnosis faster if their doctor(s) had listened to them and 'taken them seriously'. One-fourth of patients said at least one of their doctors told them their condition was psychological or 'all in their head'.⁸ Accordingly, patients communicating with LFA health educators suggested they have often been labelled as *drug seekers*. A clearer definition of the lupus spectrum-based signs and symptoms along with molecular biomarkers may reduce diagnostic ambiguity in medical decision-making among physicians and ease the psychological toll and physical burden of the journey to diagnosis for patients.

Lupus diagnosis and SLE classification criteria: a conundrum that delays diagnosis?

Diagnostic criteria are used to make a diagnosis in variety of conditions. In a heterogeneous disease like SLE, that has not been possible to date because diagnostic criteria are quite difficult to develop given the complexity of SLE that often evades conventional formularies. Instead,

diagnosis of SLE relies heavily on the adaptation of SLE classification criteria, clinical judgement and probabilistic diagnostic reasoning.^{15 16} However, there are differing views on the legitimacy of using SLE classification criteria in diagnostic scenarios. Large rheumatology organisations including the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR) do NOT support application of diagnostic criteria, only classification criteria. However, other experts suggest that SLE classification criteria should not be used for making a diagnosis but can be used as a reference.^{15 17} We agree that development of diagnostic criteria for a disease with evasive heterogeneity is an arduous task and propose that a cadre of molecular and diagnostic tools are necessary to expand our understanding of lupus as a spectrum disease.

Recent studies suggest that Systemic Lupus International Collaborating Clinical (SLICC) 2012 and EULAR/ACR 2019 criteria have superior specificity in classifying SLE at 93.8% and 97.3%, respectively.¹⁸ Still, these criteria have lower sensitivity for classifying early lupus, probable lupus, incomplete lupus or other lupus endotypes.¹⁹ In general, application and subsequent underperformance of SLE classification criteria can have devastating long-term consequences for patients.²⁰ Patients who do not meet the threshold for conventional SLE classification criteria often suffer longer and must manage their disease while simultaneously encountering physicians who may have clinical reasoning flaws or experiential biases that lead to a lack of agreement on the medical interpretation of their symptoms. Hypothetically, if a 'spectrum' definition of lupus were developed, disseminated and adopted, it could prompt providers to refer patients to rheumatological experts even if their symptoms were not as common or completely typical of lupus. This approach might, in turn, accelerate the diagnostic journey and decrease the time to diagnosis and at the very least give specialists the opportunity to provide treatment directed to a symptom or sign without absolute certainty of the diagnosis.

HARMONISING AND SIMPLIFYING: THE CASE FOR DEFINING THE LUPUS SPECTRUM

The disagreement across the rheumatological profession about what constitutes lupus has been pervasive, even in epidemiological studies. For example, data from the US Centers for Disease Control and Prevention-funded lupus registry suggest that cases of SLE in the US population include roughly 161 000 with definite SLE and 322 000 with definite or probable SLE.²¹ Case definitions were based on ACR 1997 and SLICC 2012 classification criteria. By contrast, the LFA estimates that 1.5 million people in the USA are living with lupus based on patient self-reported data. The truth may lie somewhere in between, but it is difficult to determine because there is no comprehensive definition of lupus erythematosus that captures the full spectrum observed in all cases. The resulting wide range

of estimates of incidence of lupus has important implications for dollars earmarked for government-funded lupus research as well as decisions made by the pharmaceutical industry about where to make investments for development of new, more powerful drugs.

Recognising the diagnostic challenges of lupus and the limitations of classification criteria as diagnostic tools, ALPHA GAC members agreed that it would be useful to consider defining lupus spectrum or umbrella of related immune-mediated inflammatory disorders.² Immune-mediated mechanisms connect a wide spectrum of inflammatory diseases with lupus. Previously published data from the ALPHA GAC demonstrated that lupus nephritis, cutaneous lupus erythematosus (CLE), antiphospholipid antibody syndrome, mild or early ANA+ syndromes and secondary Sjogren's syndrome fall under this umbrella of diseases.⁵ Defining lupus as an immune-mediated spectrum involving persistent and shared inflammatory mechanisms that can result in varied clinical phenotypes across several lupus endotypes may be reasonable and limit delays in diagnosis.

PROS AND CONS OF AMBIGUITY IN THE SPECTRUM

Adopting a spectrum definition of lupus could help address diagnosis-related challenges to support earlier diagnosis and improve access to care. A simplified and more inclusive construct may also be easier for non-specialists to operationalise in routine practice settings. This could limit the time to a lupus spectrum diagnosis experienced by those whose symptoms do not fit into the narrower definition of SLE used today. These individuals may have difficulty accessing specialty care, as illustrated by a study that found that over half of patients diagnosed after a year cited long wait times for specialist appointments, compared with 39.4% of those diagnosed within a year.¹² This suggests that earlier diagnosis is associated with more prompt access to a specialist and more appropriate clinical care from someone familiar with lupus.

Although a spectrum definition of lupus could improve access to care, it could also lead to overdiagnosis, which can be just as psychologically, emotionally and physically harmful as diagnostic delays. Widening definitions of disease and decreases in treatment thresholds could put patients at risk of exposure to toxic treatments that are costly and can have consequential side effects. Thus, caution must be applied when examining and making clinical judgements about patients with indeterminate symptoms common across immune-mediated diseases not conceptually unique to lupus. Moynihan and colleagues caution that technological advancements often leave people with permanent labels and decrease the likelihood of receiving appropriate care for their condition if misdiagnosed.²² For lupus in particular, a diagnosis can lead to the patient feeling stigmatised, overwhelmed or even afraid. As described above, misdiagnosis can lead to a mistrust in the healthcare system and alter care-seeking patterns. If there is a move to define lupus as a spectrum,

it will be important to identify strategies to reduce the likelihood of overdiagnosis to avoid such challenges.

In working to avoid overdiagnosis, some patients may have an uncertain diagnosis, at least temporarily. Diagnostic delays are, in part, attributed to the heterogeneity of lupus, which means a patient may need to have multiple lupus symptoms before their clinical care team can be confident in a diagnosis. Embracing a lupus spectrum concept may improve the quality of communication between healthcare providers and their patients about necessary diagnostic uncertainty and ambiguity. A spectrum definition would also disentangle issues with patient trust in the physicians' technical judgement when presenting with indiscriminate sequelae that may be lupus or lupus related, without assigning a firm and irrevocable diagnosis. A spectrum definition would serve as a conduit for a collaborative process between patients and providers for developing follow-up visits and subsequent treatment plans that address the patient's medical needs even in the absence of a definitive diagnosis.

In the context of drug development and research, a lupus spectrum definition would have advantages and disadvantages. Identifying outcome measures that address the full heterogeneity is already difficult, given that the variability is so great that two individuals with active disease may have non-overlapping manifestations.² These challenges may be exacerbated by expanding the definition of lupus to include a spectrum of closely related conditions. At the same time, current approaches to drug development may result in overly narrow indications, inhibiting clinicians from prescribing medications to all who might benefit. If the field were to move to a spectrum definition for lupus, this should be done with consideration for the impacts—both positive and negative—on drug development efforts. For example, a spectrum definition of lupus may expand the research pool from which molecular subsets for precision medicine approaches are derived.²³ This might promote clinical trial design based on molecular subsets, similar to basket trials already used in oncology, as opposed to relying on organ system-based and serology-based classification criteria.

STRATEGIES FOR DEFINING THE LUPUS SPECTRUM

Surveillance of the natural history of disease

To develop a comprehensive definition of the clinical lupus spectrum, the field will need detailed data about the pathology, epidemiology, molecular signatures and symptoms of the related disorders that may fall within the lupus spectrum. Such research is ongoing and should continue. These data can guide development of diagnostic criteria that capture the full spectrum of clinical lupus, including isolated CLE. Moreover, concept models that split or clump the definition depending on the audience will be important to consider. For example, policymakers or others in the public domain may gravitate towards using the term 'lupus' due to its simplicity and sensibility, similar to cancer and autism. On the other

hand, for industry, drug discovery, biomarker development and treatment decisions, the specific 'type' of lupus (based on clinical, genetic and molecular signatures) becomes more relevant.

Diagnostic developments

In parallel with consideration of a spectrum definition of lupus, biomarker multiomic research aimed at earlier identification of disease and its subsets should continue. Such diagnostic developments would aid early and accurate diagnosis, monitoring disease progression and 'personalised medicine' for people with lupus. Efforts to identify and validate such biomarkers are currently underway.^{24–26} Multiomics, or the comparison of various data sets from different '-omics' groups (eg, genomics, epigenetics, transcriptomics, proteomics and metabolomics), will likely contribute to a comprehensive understanding of the pathogenic mechanisms and are currently being tested to identify biomarkers in SLE.²⁷

Using patient-reported data, which can capture the patients' experience with lupus, will also be important when considering a move to a spectrum definition of lupus and when developing biomarkers or multiomics analysis. Such data may include information on the patients' symptoms, function, well-being and the overall burden of lupus.²⁷ Digital health tools, such as mobile applications and wearable medical devices, can collect these data from patients with lupus in real time and longitudinally broadening the current understanding of the disease and of what is most important to patients. This expanded wealth of information may support the concept of lupus as a spectrum and must be factored into the development of a lupus spectrum definition.

Educating providers on communications about diagnostic ambiguity

Although a spectrum definition may lead to more prompt diagnosis for some individuals, many are likely to still experience diagnostic uncertainty. In such situations, it is important for clinicians to help patients understand and navigate the ambiguity of their diagnosis. For example, clinicians should help patients understand why their phenotype may be indicative of lupus and what additional monitoring or treatment steps will need to occur before a diagnosis can be confirmed or an alternative diagnosis made. The use of a spectrum definition may ultimately be helpful in these conversations, as patients with possible lupus come to understand that they are near the end of the spectrum but may eventually have symptoms that are clearly indicative of lupus. It will be important for providers to be educated on how to have conversations with patients whose diagnosis may be unclear even if they fall within the lupus spectrum.

Recommendations for next steps

Determining whether it would be appropriate to move to a definition of lupus as a spectrum will require consultation with and consensus from stakeholders across the

lupus global landscape, including professional medical societies, regulatory health agencies and sponsors in clinical research. These stakeholders will be crucial to driving the development and acceptance of a new definition and ensuring that all patients who experience symptoms of lupus are diagnosed accurately and in a timely manner. Before developing a spectrum definition, however, there are other foundational steps the global lupus community must take. ALPHA GAC recommendations for next steps include the following:

- ▶ Conduct additional research into the natural history of disease and studies on environmental and modifiable lifestyle triggers that initiate and cause progression of lupus.
- ▶ Continue to improve definitions of lupus endotypes with clinical and molecular signatures, including additional research on biomarkers.
- ▶ Conduct prevention trials to advance understanding of whether predictive biomarkers can contribute to earlier diagnosis, possible prevention, likely treatment response and impact of lifestyle changes on disease course.
- ▶ Leverage the professional networks of medical associations to:
 - Implement provider training and tools to improve patient care, including in cases where there is diagnostic uncertainty.
 - Send alerts and resources on the latest developments in the field.
 - Develop a clear pathway for referral from primary care practitioner to specialist.
- ▶ Leverage emerging research and work with the US Food and Drug Administration and other global regulatory health agencies to consider the expansion of the definition of lupus for drug development efforts.

CONCLUSION

Lupus is a complex, heterogeneous disease for which no diagnostic criteria exist. As a result, patients may see multiple providers and spend months or years seeking an accurate diagnosis. Diagnostic delays and errors have vast consequences for patients with lupus. Moving to a spectrum definition of lupus might address some of these challenges. By drawing on insights from experienced rheumatologists and other practitioners who specialise in lupus care, implementing a spectrum definition may help bridge knowledge gaps related to diagnoses, reduce time to diagnosis and lessen the overall burden on the patient.

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REFERENCES

- 1 Manzi S, Raymond S, Tse K, *et al*. Global consensus building and prioritisation of fundamental lupus challenges: the ALPHA project. *Lupus Sci Med* 2019;6:e000342.
- 2 Tse K, Sangodkar S, Bloch L, *et al*. The ALPHA project: establishing consensus and prioritisation of global community recommendations to address major challenges in lupus diagnosis, care, treatment and research. *Lupus Sci Med* 2021;8:e000433.
- 3 Lupus Foundation of America LRA, Lupus and Allied Disease Association. Lupus patient voices: report on externally-led patient-focused drug development meeting; 2017.
- 4 Cornet A, Andersen J, Myllys K, *et al*. Living with systemic lupus erythematosus in 2020: a European patient survey. *Lupus Sci Med* 2021;8:e000469.
- 5 Morgan C, Bland AR, Maker C, *et al*. Individuals living with lupus: findings from the lupus UK members survey 2014. *Lupus* 2018;27:681–7.
- 6 Kerder A, Richter JG, Fischer-Betz R, *et al*. Delayed diagnosis adversely affects outcome in systemic lupus erythematosus: cross sectional analysis of the LuLa cohort. *Lupus* 2021;30:431–8.
- 7 Faurschou M, Dreyer L, Kamper A-L, *et al*. Long-term mortality and renal outcome in a cohort of 100 patients with lupus nephritis. *Arthritis Care Res* 2010;62:873–80.
- 8 Daly RPR, Davidson P. Lupus diagnosis: process and patient experience. *Arthritis Rheumatol* 2017;69.
- 9 Guidelines for referral and management of systemic lupus erythematosus in adults. American College of rheumatology AD hoc

- Committee on systemic lupus erythematosus guidelines. *Arthritis Rheum* 1999;42:1785–96.
- 10 Narain S, Richards HB, Satoh M, *et al.* Diagnostic accuracy for lupus and other systemic autoimmune diseases in the community setting. *Arch Intern Med* 2004;164:2435–41.
 - 11 Rees F, Doherty M, Lanyon P, *et al.* Early clinical features in systemic lupus erythematosus: can they be used to achieve earlier diagnosis? A risk prediction model. *Arthritis Care Res* 2017;69:833–41.
 - 12 McClamb D, Oberholtzer L, Marion A, *et al.* 1304 factors in lupus diagnosis. *Lupus Sci Med* 2021.
 - 13 Li Q-Z, Karp DR, Quan J, *et al.* Risk factors for ANA positivity in healthy persons. *Arthritis Res Ther* 2011;13:R38.
 - 14 Sloan M, Harwood R, Sutton S, *et al.* Medically explained symptoms: a mixed methods study of diagnostic, symptom and support experiences of patients with lupus and related systemic autoimmune diseases. *Rheumatol Adv Pract* 2020;4:rkaa006.
 - 15 Bertsias GK, Pamfil C, Fanouriakis A, *et al.* Diagnostic criteria for systemic lupus erythematosus: has the time come? *Nat Rev Rheumatol* 2013;9:687–94.
 - 16 Grimes DA, Schulz KF. Refining clinical diagnosis with likelihood ratios. *Lancet* 2005;365:1500–5.
 - 17 Aggarwal R, Ringold S, Khanna D, *et al.* Distinctions between diagnostic and classification criteria? *Arthritis Care Res* 2015;67:891–7.
 - 18 Aringer M, Johnson SR. Systemic lupus erythematosus classification and diagnosis. *Rheum Dis Clin North Am* 2021;47:501–11.
 - 19 Adamichou C, Nikolopoulos D, Genitsaridi I, *et al.* In an early SLE cohort the ACR-1997, SLICC-2012 and EULAR/ACR-2019 criteria classify non-overlapping groups of patients: use of all three criteria ensures optimal capture for clinical studies while their modification earlier classification and treatment. *Ann Rheum Dis* 2020;79:232–41.
 - 20 Aringer M, Costenbader K, Daikh D, *et al.* 2019 European League against Rheumatism/American College of rheumatology classification criteria for systemic lupus erythematosus. *Arthritis Rheumatol* 2019;71:1400–12.
 - 21 Lawrence RC, Felson DT, Helmick CG, *et al.* Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum* 2008;58:26–35.
 - 22 Moynihan R, Doust J, Henry D. Preventing overdiagnosis: how to stop harming the healthy. *BMJ* 2012;344:e3502.
 - 23 Reynolds JA, Bruce IN. A molecular taxonomy for systemic autoimmune rheumatic diseases (SARDs): learning lessons from oncology? *Rheumatology* 2020;59:2193–4.
 - 24 Sasaki T, Bracero S, Keegan J, *et al.* Longitudinal immune cell profiling in patients with early systemic lupus erythematosus. *Arthritis Rheumatol* 2022;74:1808–21.
 - 25 Munroe ME, Young KA, Guthridge JM, *et al.* Pre-clinical autoimmunity in lupus relatives: self-reported questionnaires and immune dysregulation distinguish relatives who develop incomplete or classified lupus from clinically unaffected relatives and unaffected, unrelated individuals. *Front Immunol* 2022;13:866181.
 - 26 Md Yusof MY, Psarras A, El-Sherbiny YM, *et al.* Prediction of autoimmune connective tissue disease in an at-risk cohort: prognostic value of a novel two-score system for interferon status. *Ann Rheum Dis* 2018;77:1432–9.
 - 27 Bell K, Dykas C, Muckian B, *et al.* Patient-reported outcome information collected from lupus patients using a mobile application: compliance and validation. *ACR Open Rheumatol* 2022;4:99–109.