


# “There’s so much to be done”: a qualitative study to elucidate research priorities in childhood-onset systemic lupus erythematosus

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## ABSTRACT

**Objective** There is a pressing need for high-quality, comprehensive research to describe the natural history, best treatments, access to care and disparities in care for patients with childhood-onset SLE (cSLE). Building on a previously published survey study of cSLE clinicians and researchers to describe research priorities in cSLE, the primary objective of this study was to conduct expert interviews to define high-priority areas for cSLE research.

**Methods** Individuals with identified multidisciplinary expertise in cSLE were recruited worldwide using purposive sampling technique. Experts participated in open-ended, semistructured qualitative interviews. Interviews were designed to elicit expert perspectives on research priorities, optimal research approaches, and factors that facilitate and hinder advancing cSLE research. Interviews were digitally recorded, transcribed and de-identified for analysis. Analysis for underlying themes of cSLE expert perspectives was performed using a constant comparative approach.

**Results** Twenty-nine experts with diverse clinical and research backgrounds participated. Themes emerged within five domains: (1) expanding disease knowledge; (2) investigator collaboration; (3) partnering with patients and families; (4) improving care to optimise research; and (5) overcoming investigator barriers. Choosing a singular area of focus was difficult; experts identified many competing priorities. Despite the numerous priorities that emerged, experts described several existing and potential opportunities for advancing cSLE research.

**Conclusions** In addition to the priorities identified by cSLE experts in this study, the opportunities for advancing cSLE research and care that were proposed should be used as a foundation for creation of a cSLE research agenda for both research and funding allocation.

## INTRODUCTION

SLE is a chronic, relapsing autoimmune disease affecting multiple organ systems; an estimated 10%–20% of patients with SLE have childhood-onset SLE (cSLE), defined as SLE diagnosed prior to 18 years of age.<sup>1</sup> cSLE has been shown to be more aggressive than adult-onset disease; children and adolescents suffer greater complications

## Key messages

### WHAT IS ALREADY KNOWN ON THIS TOPIC

▶ Although there have been significant advancements in the understanding and treatment of childhood-onset SLE (cSLE), significant knowledge gaps remain.

### WHAT THIS STUDY ADDS

▶ This qualitative study examined perspectives from a diverse group of clinicians and researchers with expertise in areas relevant to cSLE to identify barriers as well as research strategies to advance understanding and care of patients with cSLE.  
▶ Experts had difficulty selecting a singular area of focus to delegate resources reflective of many areas of need; identified priorities encompassed expanding knowledge of the disease itself, partnering with patients and improving their care to optimise research, and enabling investigator collaboration as well as overcoming individual investigator barriers.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

▶ The proposed solutions to barriers to advancement of cSLE research in this study should help guide a cSLE research agenda and may inform future funding priorities.

of the disease than adults, including more widespread organ involvement and higher disease activity.<sup>2 3</sup> Given the early onset of cSLE, patients often experience significant burden due to comorbidities and immunosuppressive treatment over their lifespan.<sup>1 3</sup> Although there are similarities between cSLE and adult-onset disease, there are unique considerations in the paediatric population, such as puberty, neurodevelopment, disease and medication effect on growth, drug metabolism, and medication efficacy,<sup>2</sup> in addition to the need to partner with the child’s caregiver/family. Knowledge gaps remain in these areas, and there is a pressing need for high-quality,

comprehensive research efforts to define the natural history, best treatments, access to care and disparities in care for patients with cSLE.<sup>4</sup>

In 2015, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) released an SLE research plan on behalf of the National Institutes of Health (NIH) which included broad areas for potential focus. cSLE (defined as a special population within the plan) made up a very small part of the overall research objectives. More recently, the Addressing Lupus Pillars for Health Advancement (ALPHA) project, a two-phase study, conducted expert interviews to inform a global survey of SLE experts to identify, prioritise and develop strategies for advancing SLE research, care and access as phase I of the study. Although paediatric rheumatologists were included in both the initial interview and survey components, only 6% of survey respondents primarily practised paediatric rheumatology. Responses of phase I of the ALPHA survey indicated that the lack of attention to paediatric issues is a barrier to SLE drug development and clinical care<sup>5</sup>; however, specific aspects of these issues were not detailed. Subsequently, phase II of the ALPHA study proposed actionable solutions to the identified research barriers from phase I of the study. Increased representation of paediatric patients in clinical trials was named as a solution to the previous barriers that had been identified in phase I of the study.<sup>6</sup>

To expand on the NIAMS-identified objectives and ALPHA study results, the Childhood Arthritis and Rheumatology Research Alliance (CARRA) and the Lupus Foundation of America (LFA) partnered to identify key knowledge gaps and strategies for advancing cSLE research. An initial objective of this collaboration was to prioritise cSLE research domains by surveying rheumatologists, nephrologists and dermatologists with expertise in cSLE.<sup>7</sup> The previously published survey study identified the highest prioritised domains as SLE nephritis, clinical trials, biomarkers, neuropsychiatric disease and refractory skin disease.<sup>7</sup>

Building on this survey study, the objective of the current qualitative interview study was to further characterise and elaborate on high-priority areas of cSLE research. This follow-up study examined perspectives from multidisciplinary and international providers with expertise in cSLE care and research aiming to identify (1) areas of high priority in cSLE research; (2) best research approaches to address these areas; and (3) barriers and facilitators to advancing cSLE research.

## METHODS

### Study design and patient and public involvement

Individual interviews were conducted to elicit perspectives from cSLE experts, to further characterise and elaborate on the priority domains, and identify new domains. Patients were not recruited to be part of this study and there was no public involvement.

**Table 1** Expert demographics (N=29)

	n (%)
<b>Gender</b>	
Male	7 (24)
Female	22 (76)
<b>Specialty/area of practice</b>	
Paediatric rheumatology	21 (72)
Other	8 (28)
<b>Location</b>	
USA	19 (66)
Canada	6 (21)
Other	4 (14)
<b>Years in practice after completion of training</b>	
<5	3 (10)
6–15	12 (41)
16–25	6 (21)
26+	8 (28)

### Setting and participants

Using purposive sampling, 39 individuals with a range of expertise in cSLE were invited to participate in semi-structured, individual interviews. Investigators identified experts through review of authors for cSLE research publications, review of investigators and collaborators within CARRA, and discussion with leaders in cSLE research. We aimed to sample individuals with expertise in clinical care and/or research related to cSLE, specific clinical and research areas (eg, central nervous system/mental health, nephrology, dermatology, cardiology, immunology) and a variety of research approaches (basic science, genetics, clinical trials, clinical and outcomes research, quality improvement/implementation science). Adult rheumatologists with clinical and/or research expertise in transition to adult care were included, as were several paediatric rheumatologists outside North America for a global perspective.

Twenty-nine individuals from 6 different countries and 23 different institutions were interviewed. The majority of participants practised within the USA and Canada (collectively making up 87% of the interviewees) (table 1).

Experts came from paediatric rheumatology (72%), paediatric nephrology, child psychiatry, adolescent medicine, adult rheumatology and medicine/paediatric rheumatology. They varied in their years of experience after completing training, with providers who had been in practice from 6 to 15 years making up the largest group (41%), followed by those practising more than 25 years (28%).

### Data collection

Two interviewers (AC and LC) trained in qualitative interviewing techniques employed a semistructured guide (online supplemental 1) designed to explore experts' ideas and recommendations on advancing cSLE

research. Topics included (1) advances and deficits in the current state of cSLE research, to identify priority areas encompassing disease pathology, comorbidities and healthcare utilisation; (2) optimal research methodologies to investigate identified priority areas; and (3) barriers and facilitators to advancing cSLE research. To further define their thoughts on addressing high-priority research areas, participants were asked: 'If you could give \$10 million to cSLE research, is there a type of project that you think would have the biggest impact?' Interviews were conducted by phone between January and May 2020 and averaged approximately 35 min (range 20–70 min). They were digitally recorded, transcribed and de-identified. Interviewees consented verbally at the time of the interview.

### Data analysis

Consistent with a constant comparative approach to analysis, experts' views on the state of cSLE research were iteratively examined to uncover the range of priorities among them.<sup>8 9</sup> AC and LC read and synthesised each expert's interview transcript to capture their observations and recognise points of difference and consensus across experts that would indicate shared priorities.

Nearly half of the interview transcripts were independently analysed and synthesised by both LC and AC, followed by a joint review for alternative interpretations or missed themes. Their independent identification of themes converged within the first set of six interview transcripts. The remaining transcripts were synthesised by AC without secondary review. Next, the themes and excerpted text were organised into broad domains (eg, collaboration, funding, drug development). Together the authors (LC, AC, AH and AMK) explored the compilation of themes, domains and text to characterise the nature of the experts' perspectives and explore intersections within and across themes.

## RESULTS

The priorities proposed by experts included not only 'what' to study, but the infrastructure and support needed to carry out that research. Several notable themes emerged and were categorised into five domains: (1) expanding disease knowledge; (2) investigator collaboration; (3) partnering with patients and families; (4) improving care to optimise research; and (5) overcoming investigator barriers. Illustrative quotes are shown in [table 2](#).

### Expanding disease knowledge

#### Genetics and environment

Experts indicated a need for greater understanding of the underlying genetic pathways of the disease for both identifying risk in preclinical states and determining best treatments ([table 2](#), Q1). Experts pointed out that genetic knowledge as it relates to disease phenotype brings us closer to targeted medications (Q2–Q3). They also

acknowledged a need to better understand the relationship between 'genetic predisposition' and environment in order to assess susceptibility. Studying the impact of environmental risk factors (violence, poverty, trauma, socioeconomic status, etc) on the development and course of disease may advance approaches to treatment (Q4).

#### Need for biomarkers

Experts described cSLE as a heterogeneous disease and emphasised the need for biomarkers to better characterise each individual's disease. They also identified biomarkers as critical to predicting organ involvement as well as a way to enable targeted therapy and potentially lead to new drug targets (Q5–Q6). Experts noted the need for biomarkers and targeted therapy frequently in the context of research devoted to cSLE nephritis and neuropsychiatric disease, given the significant morbidity associated with these disease manifestations (Q7).

#### Paediatric clinical trials

Experts described the efficacy of therapies for cSLE as being largely extrapolated from adult data and highlighted the need for paediatric clinical drug trials to advance therapeutic options in cSLE. Experts voiced frustration that if a medication is not effective in an adult study, then it will never be known if it would be effective in treating patients with cSLE, and that there is a delay between medications' use in adult care versus use in paediatric care (Q8). Medications were also discussed from the perspective of adherence and the need for medications that are more palatable to patients with less side effects and that work quickly (Q9).

#### Longitudinal outcomes

Experts said that longitudinal studies are critical to better understanding the long-term effects of treatment as well as long-term organ damage and mortality, especially in the context of nephritis and neuropsychiatric disease (Q10). When designing such studies, experts suggested researchers consider the quality, standardisation and organisation of data sources such as electronic medical records (EMRs) or registries. Many experts noted that longitudinal design is particularly suited to studies of transition from child to adulthood and to examining the long-term effects of medications. Patient registries were discussed as a tool to follow patients longitudinally, specifically the CARRA registry (Q11). It was noted, however, that longitudinal data capture may be limited by insurance changes and transition to adult care (Q12). The increasing sophistication of the EMR was noted as an opportunity to capture these data, but the cost of such studies was identified as a limiting factor. Additionally, experts said that standardised data collection is needed across centres/sites to consistently share information for registries and databases to be useful.

**Table 2** Illustrative quotes for qualitative themes for advancing cSLE research

Expanding disease knowledge	
Genetics and environment	<p>Q1 “It would be very nice down the road if we can identify the patient early in the course of the lupus development – probably people are talking about preclinical – means before you have the full blown picture of lupus skin, are we able to identify those patient and say probably because of your genetic marker and the symptoms that we’re seeing, this might evolve into lupus down the road and it would be ideal if we have medication to stop this from happening at the preclinical levels.” —Expert AA</p> <p>Q2 “You look at all of their gene expression, all of their immune profiles, all of their phenotypes or clinical presentations in the very beginning after treatment and during maintenance and figure out who are the different types of the people, which ones respond to which treatments...knowing ahead of time, like targeting which immune pathway works for what group of patients. Because that would help you, A, personalize the treatment, but also, B, potentially look for new treatment targets like drug targets, specifically.” —Expert BB</p> <p>Q3 “Like this molecular fingerprint needs Cytoxin right away and this molecular fingerprint does best with MMF...And there’s molecular reasons why these pathways are selected. I think that’s where things are going.” —Expert E</p> <p>Q4 “So, this idea of adverse childhood events and the impact of trauma, violence, and chronic stress on the hypothalamic axis in the way that increases the risk for autoimmunity, but also worsen the outcomes and the way mental health plays into that. So, I think there are probably some disease modifying factors that include kind of the psychosocial realm and the environment that...probably are very rich for improving outcomes.” —Expert B</p>
Need for biomarkers	<p>Q5 “There is always room for improvement in biomarkers that would allow us to identify which patients would have certain organ involvement, which patients would have more severe disease course. So, kind of a biomarkers for assessment of disease severity, not just activity and damage.” —Expert U</p> <p>Q6 “But if you asked me to prioritize, I would say biomarkers, looking at precision-based treatments based on pathophysiology, and then sorting through clinical phenotypes.” —Expert B</p> <p>Q7 “So early identification of [neuropsychiatric] problems is key. Because then you can follow up on the cognitive function over time and determine if is this getting worse, getting better? Is it related to disease activity or not? Or is cognitive impairment an irreversible kind of status that we can change it over time? There are a lot of questions related to cognitive impairment that need to be answered.” —Expert AA</p>
Clinical trials	<p>Q8 “A lot of our treatment is still guided by research that is being done on adults that the conclusions of which have sort of been superimposed and assumed to apply to a pediatric population which may or may not be the case. There are still a dearth of clinical trials that are being done in pediatric lupus, though more probably over the last decade than ever before but still very few.” —Expert Q</p> <p>Q9 “We can spend all our money and time discovering these things, but if they’re not palatable and if they – unfortunately, most lupus medicines take a while to work, and so you’re not feeling better for a whole month after taking this medicine and it’s like, what am I doing this for?” —Expert V</p>
Longitudinal outcomes	<p>Q10 “I would have a longitudinal electronic database where every new onset-lupus patient got entered in, demographic data, family history and got urine and blood samples and then every follow-up visit – the same thing with a blood and urine sample was collected and stored. And so, we would have really on a whole bunch of patients a lot of clinical and molecular data to really understand what was going on and response to medications.” —Expert E</p> <p>Q11 “I think it’s still sort of in its early phases in terms of the kind of longitudinal data that the CARRA registry has on lupus patients. But it will be a very, very powerful tool in the years to come to answer some of those questions.” —Expert Q</p> <p>Q12 “I think because often [young adults with lupus] change services and often cities, so you don’t get all the doctors from the beginning and they even lose follow up...mostly I would say it’s difficult in getting access to data because you don’t have all the information, but when they are adults you don’t have all the information from when they were kids.” —Expert O</p>
Investigator collaboration	

Continued

**Table 2** Continued

Multicentre collaboration	Q13	“20 years ago, there wasn’t such a thing as a multi-PI R01 and now there is because everybody recognizes now that you really have to do collaborative research in certain fields, that it’s just not possible to do it otherwise.” — Expert X
International priorities and collaboration	Q14	“If you talk to the people in India or in South America or in Africa about lupus, they will give you different answers [about priorities]. They don’t have the expensive drugs. They have an insane high burden of TB and other infections. They have poor health literacy and access to care. They have slightly different priorities...obviously, we care about the global health of kids with lupus. So somehow it has to come into it.” —Expert G
	Q15	“I think that North American and European collaboration could be better...we collaborate more on the, let’s say, the general aspects of the disease. But for certain, let’s say, biomarker studies, genetic studies, of course there is always room for improvement for transatlantic collaboration.” — Expert U
Multidisciplinary collaboration	Q16	“And that instead of producing research that simply deals with clinical rheumatology, people are exploring aspects of the disease that require the expertise of all these other disciplines and looking at things in a more – looking at this very complicated disease in a more nuanced and a deeper way.” —Expert Q
	Q17	“They’re going to get done by team science, right? A clinician putting the phenotype together, paired with a translational scientist who has a PhD who knows how to design the right experiments, so that we’re doing this in the best quality, highest yield way.” —Expert B
	Q18	“I guess myself, what my interest is in is trying to get to the basic understanding...of what causes this immune dysregulation in lupus. And so, I think you do need collaboration between geneticists and molecular biologists, immunologists and clinicians who can all come together to really understand what lupus is from their own perspectives but also in a dialogue with each other so that you can move forward.” —Expert V
Relationship with pharmaceutical industry	Q19	“So better alignment of the pharmaceutical companies’ motivations and needs with the FDA’s perspective...and with the clinicians’ desires and patients’ desires in terms of the drugs, is important...So that all falls under the area of policy and money and prioritization – advocacy.” — Expert G
Partnering with patients and families		
Recruiting and engaging patients	Q20	“Our clinics are very, very busy...When you have that kind of pace, it’s hard to spend the time that you need to really involve the family and give the feeling that we’re all on the same team.” — Expert K
	Q21	“It is easier to participate in studies for the person who speaks English, the person who has technology available to them, the person who has time to be on calls during working hours when we’re having our calls. But the person who doesn’t speak English or...can’t get away from their job to get on a phone call at 10:00...we’re not good at engaging them.” — Expert G
	Q22	“Often times consent for studies are done with [a teen’s] parents in the room and it’s really important to allow that teen to have that conversation confidentially without their parents there...you want the teen to feel empowered and they’re more likely to participate if they feel like this is really about them and their answers count and whether or not they can choose to consent or not and it’s not something they have to do because their parents tell them to or want them to.” —Expert T
	Q23	“My recommendation would be engaging the patient at different levels of your project because your project has different phases. It starts from the conceptualization of the idea and again you move on with phase one, phase two – application, analysis, interpretation – until you get to publication and dissemination.” — Expert AA

Continued

**Table 2** Continued

Including outcomes important to patients	Q24	“I think that PROs give you a different perspective on how to assess outcomes and especially in the diseases...where we don't actually know how to measure whether somebody's in remission...So just because somebody's protein goes away, does that really mean their lupus is in remission? And in a setting where the doctors are not 100 percent sure how to measure it, it seems to me it's even more important for us to be listening to how patients might measure it.” —Expert X
	Q25	“I think there's a need for more patient-reported outcome measures to...hear from the adolescent about what they feel measures of success would be. ...So, for example, I would say that the teenagers are more interested in achieving success in terms of functional outcomes. So, ability to participate in the way they want in school, in sport, in other extracurricular activities, to be able to secure a job without feeling limited by their illness, making sure socially they're okay, emotionally from a mental health perspective that they're okay.” —Expert T
Improving care to optimise research		
Quality improvement: intersection of healthcare delivery and outcomes	Q26	“One of the goals of the CARRA registry was to be able to define variation across these centers. And to say, center X is doing really great, what are they doing, versus center Y, which is maybe – has even better outcomes, and what are they doing? So that we can share learning and develop new research studies to try to improve care.” —Expert I
	Q27	“So things as simple as are we documenting whether or not they got their – even their primary vaccinations? And if so then another project is how we make sure that they get a pneumococcal vaccine because they need to have one, because – to protect them...We're looking at detecting vascular necrosis early. Detecting osteoporosis early. What do we implement that helps us to detect these things, and if so what kinds of treatment or prophylaxis do we offer patients? ... How do we make sure that patients are having their lipids checked every year? And how do we ensure that we're looking for growth changes?... Can't use QI to look at which drug treatment is the best, or is the new drug better than what we have? But we certainly use QI to make changes every day in how we take care of patients.” —Expert G
	Q28	“I should just say the family – what's happened with that kid's support and what the family is doing intersects with what the healthcare delivery system is doing, is really important in how well a kid does – not only psychosocially, but also medically. And so, maybe if we can't cure the disease – I mean, we sometimes say, until we know how to cure and until we have drugs that work better, let's at least make sure that we use optimally what we have... So I think that's a place for high impact.” —Expert G

Continued

Table 2 Continued

Optimising mental health	Q29	"I'd also put money into a patient navigator...somebody to go into our patients' homes and practice medicine in their environment, as opposed to in our environment...because if you have the navigators in these homes, and you're making sure they are getting to the appointments, so then we have data [collected during home visits] and we are able to shoot it out of EPIC into like some bioinformatic platform." —Expert L
	Q30	"I also think that sometimes people just sort of change what they're doing because they're just worried about their patient, but their patient's actually okay and they can keep going with the protocol. I just get a sense with some of these protocols – and maybe I'm wrong. But I worry because there's no oversight, really." —Expert F
	Q31	"...there are people on our research team that specialize in doing quality assessments of protocol adherence – for example, and making sure that when we're applying a tool like a SLEDAI score that we're accurately scoring it or that when we're enrolling a patient in a prospective study that we're actually seeing them the proper number of times per year and that we're not missing ordering specific labs that are in the protocol." —Expert M
	Q32	"We don't currently have a good way to, A, figure out is it from having a chronic illness and not having good resiliency to cope with it, or is it the disease itself that's causing it...And then we also don't know how to provide the necessary services." —Expert BB
	Q33	"I think we still have many unanswered questions in terms of how the psychological stress of the disease or life impacts the disease and how that impacts patient outcomes in the long term and whether there are areas that we could target in young adulthood and adolescence and childhood that we're not doing a great job of targeting right now that could have long-term effects on patient outcomes in lupus and in their lives in general." —Expert Q
	Q34	"[Anxiety and depression] are common just because you're a teenager, but also complicated by the fact that they have a chronic condition that they're having to wrap their head around and that this isn't gonna go away...it's very clear that...resources or therapy or medications for mood-related things, there's a strong appetite for that." —Expert T
Improving adherence and transition to adult care	Q35	"And at least identifying when there's not adherence and getting over the connotation of non-adherence as being a bad thing and making sure that our patients and our research subjects understand that we're asking them to adhere and we're needing to earn their adherence as opposed to expecting their compliance – so to speak." —Expert M
	Q36	"I think if you could take a cohort of adolescents who are getting treatment for serious lupus...and you could study them and ask about health outcomes, over a ten-year period, and understand what contributes to medication adherence and what contributes to resilience and successful transition to adulthood in a work environment, I think that would be huge." —Expert N
	Q37	"And when [patients transitioning to adult care] lose us as their family support, things just don't go well. So, how do you instill that kind of knowledge and self-care in these patients who don't know how to do that or don't understand what it means?" —Expert F
Overcoming investigator barriers and identifying opportunities		
Protected time	Q38	"As physicians, our time gets sort of fractionated into these teeny little pieces like threedays a week we're in clinic all day.... And then the other days you get pulled into meetings, things appear on your calendar. There's almost no space to think and write and be creative. And, without that, I don't think we can move this work forward." —Expert B
Funding for research	Q39	"So, that is really probably what, in the long run, will be the best solution is to have all these experts advocating on behalf of the children with those diseases, and convince the powers above to come out with RFAs for – specifically for childhood SLE conditions." —Expert S
	Q40	"I'm seeing more young investigators not able to stick with it...the funding situation has gotten so difficult that it's really hard for them to stay in the game and they get discouraged." —Expert R
Mentoring for young investigators	Q41	"And it's really tough then to, A, find the people to do it who have the time to do it and, B, have the mentors who can teach the next generation to do it and I think that's a huge problem that we need to address." —Expert D

CARRA, Childhood Arthritis and Rheumatology Research Alliance; cSLE, childhood-onset SLE; FDA, Food and Drug Administration; MMF, Mycophenolate mofetil; PROs, patient-reported outcomes; QI, quality improvement; RFA, request for applications; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; TB, tuberculosis.

## Investigator collaboration

### Multicentre collaboration

Given the rarity of the disease, collaboration among centres was identified by experts as a necessity in advancing cSLE research. Investigators need to come together to advance this work with multicentre studies (Q13). Experts pointed to CARRA as a vehicle for research collaboration, especially with the patient registry; it has served to examine variation in care among centres and improve care overall.

### International priorities and collaboration

Experts outside of North America explained that international collaboration is particularly important for this rare disease because it increases the number of patients available to participate in studies, in turn enabling samples that represent the total population of children with cSLE. While in North America and Europe the focus is on advancing research, other areas of the world have more urgent needs for investment in basic healthcare, education and advocacy for patients with cSLE (Q14). They also pointed out challenges to fostering international collaboration (eg, regulatory barriers, Institutional Review Board approvals). One expert stated that international collaboration has been more successful on ‘the general aspects of the disease’ but would benefit from collaboration on biomarker studies and genetic studies (Q15).

### Multidisciplinary collaboration

Multidisciplinary collaboration was also identified as essential to advancing cSLE research. Experts noted that understanding the multiple impacted organ systems in cSLE requires expertise from specialists across disciplines (eg, nephrologists, neurologists, dermatologists) to investigate the disease in a ‘nuanced and deeper way’ (Q16). Beyond subspecialties the need for partnership between clinicians and scientists from a variety of backgrounds (eg, immunologist, translational scientist, molecular biologist, geneticist, etc) was also emphasised, with experts indicating that a ‘team science’ approach is needed, including the potential of more basic science representation at CARRA meetings as an opportunity for collaboration (Q17–Q18).

### Relationship with pharmaceutical industry

Experts noted the general cost of drug development and the unique challenges of drug development in rare diseases as barriers to new cSLE medication options. One expert noted that there needs to be better alignment between the pharmaceutical companies’ motivations and the Food and Drug Administration’s needs (Q19).

## Partnering with patients and families

### Recruiting and engaging patients

Experts identified recruitment of patients in research as an important research priority, and barriers to recruitment such as lack of adequate staff or time on the part of the provider were discussed (Q20). One expert pointed out that attention to a diverse recruiting staff could encourage more patients, particularly those that would strengthen

the representatives of the population in studies. Experts indicated that increased inclusion of diverse patients in research is necessary to capture a representative patient population which limits our understanding of the disease (Q21). The need to engage patients, not only parents, in studies was also emphasised especially in the adolescent population (Q22). Experts emphasised the need to include the family in any research that involves clinical intervention and the importance of involving patients at each ‘phase’ of a project to get their input (Q23).

### Including outcomes important to patients

Experts acknowledged, some emphatically, the importance of registering patients’ definitions of success to guide the interpretation of assessments and interventions (Q24). In particular, patient-reported outcomes (PROs) are mechanisms to challenge assumptions about success that may be built into the design of a study. Examples of patients’ concerns include effects of cSLE on education, employment, extracurricular activities and psychosocial well-being (Q25).

## Improving care to optimise research

### Quality improvement: intersection of healthcare delivery and outcomes

Several experts acknowledged the importance of quality improvement efforts to standardise care across individuals and institutions (Q26). One expert provided examples of the benefits of quality improvement studies, such as monitoring vaccinations, detecting avascular necrosis and osteoporosis, and lipid monitoring (Q27). Experts also noted that how an individual is able to navigate the complex healthcare system—which can be overwhelming for a patient and family—is tied to a patient’s outcome. Effective healthcare delivery is intimately tied to understanding the patient’s support system and the psychosocial impact of the disease (Q28). Therefore, financially prioritising research and support (such as patient navigators) around healthcare delivery was seen as a necessity for advancing cSLE care and ultimately research (Q29). Additionally, standardising the implementation of studies in clinical settings was a concern, particularly in terms of recruitment and ensuring the buy-in and commitment from clinicians to carry out study activities consistently (Q30–Q31).

### Optimising mental health

Experts raised questions about the effect of psychological stress from the disease or disease activity and long-term outcomes. They called out the clinical conundrum of determining whether patients’ psychiatric symptoms are a manifestation of primary disease activity or an expression of coping with chronic disease and encouraged devoting resources to develop diagnostic tools to differentiate between the two (Q32). Experts also noted the relationship between mental health and poor adherence to treatment and suggested that improvement in mental health screening may significantly impact outcomes (Q33–Q34).



### Improving adherence and transition to adult care

While some experts said that there has been progress on research around adherence, it was identified as a priority given that non-adherence remains a major barrier to the care and outcomes of patients with cSLE (Q35). Experts highlighted the need for research around best practices for promoting adherence, especially for therapies where patients do not experience immediate effect. Experts frequently discussed research and support around adherence in relation to the transition from paediatric to adult care. This was identified as a very vulnerable time for patients and an area where more resources should be dedicated to promoting successful transition to an adult rheumatologist (Q36–Q37).

### Overcoming investigator barriers and identifying opportunities

#### Protected time and funding for research

Many experts identified the lack of time to obtain funding and complete projects as a major barrier to advancing cSLE research. They explained that providers have competing demands, and the obligations of clinical care leave little time to conduct high-quality studies (Q38). Providing time and funding for collaborative projects helps enable patients to be enrolled in studies and for collaborative research organisations to succeed, for example.

Experts noted that current models of compensation—largely based on procedures and volume—are problematic for paediatric rheumatologists given rarity of diseases that they treat, which limits the institutional resources that they are allocated. Experts highlighted the importance of advocating for funding, with one interviewee stating that advocacy is needed to “convince the powers above to come out with [Requests for Applications] for childhood SLE conditions” (Q39). They also expressed the need for more robust funding mechanisms for cSLE projects, with special attention to opportunities for young investigators and trainees considering a research career (Q40).

#### Mentoring for young investigators

Experts expressed concern about the next generation of researchers due to the major obstacles with funding and beginning in a research-focused career in cSLE (Q41). They were selective about mentees because of this difficulty and the credentials and passion required to persevere. To be successful in a cSLE research career, experts said that young investigators need strong mentorship from more senior researchers, a need that currently cannot be met by the limited pool of senior researchers and their availability. One expert identified adult rheumatologists as a potential mentoring resource given the similarities between cSLE and adult-onset SLE. Other solutions proposed include creating mentorship programming specific to cSLE research with protected time for mentors and organised opportunities for networking among senior cSLE researchers and early investigators.

### A path forward: establishing a paradigm for advancing cSLE research

Experts noted the challenges in establishing a clear direction for cSLE research. When asked how they would spend a hypothetical grant of \$10 million for cSLE research, nearly a quarter of them explicitly emphasised the difficulty choosing a single focus and some divided the money across multiple methodologies or lines of enquiry. Collection of patient biosamples (blood, urine and tissue) from diagnosis through their disease course for longitudinal characterisation of disease was the most frequent response, with over a third of experts detailing a project related to better understanding of disease biomarkers. These projects were often discussed as a mechanism to enable more targeted drug development. Despite the question’s focus on cSLE research, a fifth of experts indicated that they would spend the money on improving healthcare access and delivery, which was identified as both a major barrier to advancing cSLE research and an important determinant of the patient’s overall outcome.

One expert suggested the following approach to prioritisation in response to the 10-million-dollar question:

I would probably target pathogenesis of the disease with genetic and immunophenotypic disease stratification to somehow get into the disease mechanism as much as possible...one of my teachers said, when you have the biggest emergency there is still time to run once around the hospital and to refresh your thoughts, and then kind of do the best rational thing, the optimal rational thing. So, sometimes you need time to reflect on different aspects and see what is feasible, what is doable, and would have the biggest impact. —Expert U

Another expert asserted the importance of starting from a paradigm rather than a priority, explicating the tension between numerous and varied priorities, and calling out how difficult it is to prioritise research efforts when there is “so much to be done.”

So this is a problem we have in the field – we have a problem that there’s so much to be done, it’s really difficult to prioritize. And the question is – what is the basis for prioritization? Is the basis number of people affected...or should you give higher priority to things that are easier to do? Is it based on feasibility or should you give higher priority to things that are an emerging cool technology or biology...We don’t have agreement on what we should say are the features on which to prioritize...we’ve prioritized kidney disease and neuro – brain disease because it’s a higher mortality and morbidity. That’s another way to prioritize things...But what we really need isn’t to know what to work on. What we really need is to know how to work on it...People have been trying, trying, trying in both the pediatric and adult arena to address a whole array of lupus phenomenon. And our lack of progress isn’t because we don’t know where to focus.

So prioritization is helpful if you want to know where to put all your money or where to start. But I don't think that the lack of progress is because of people not working in a certain area...we haven't figured out a path of investigation – a path of research that advances the science and the knowledge well enough. —Expert G

Similarly, two other experts stated the value of being intentional about setting such a direction, with one (Expert X) noting that in the field of autoinflammatory disease “they now have paradigms for how to study it and we still don't have a good paradigm for how to understand and study lupus.”

## DISCUSSION

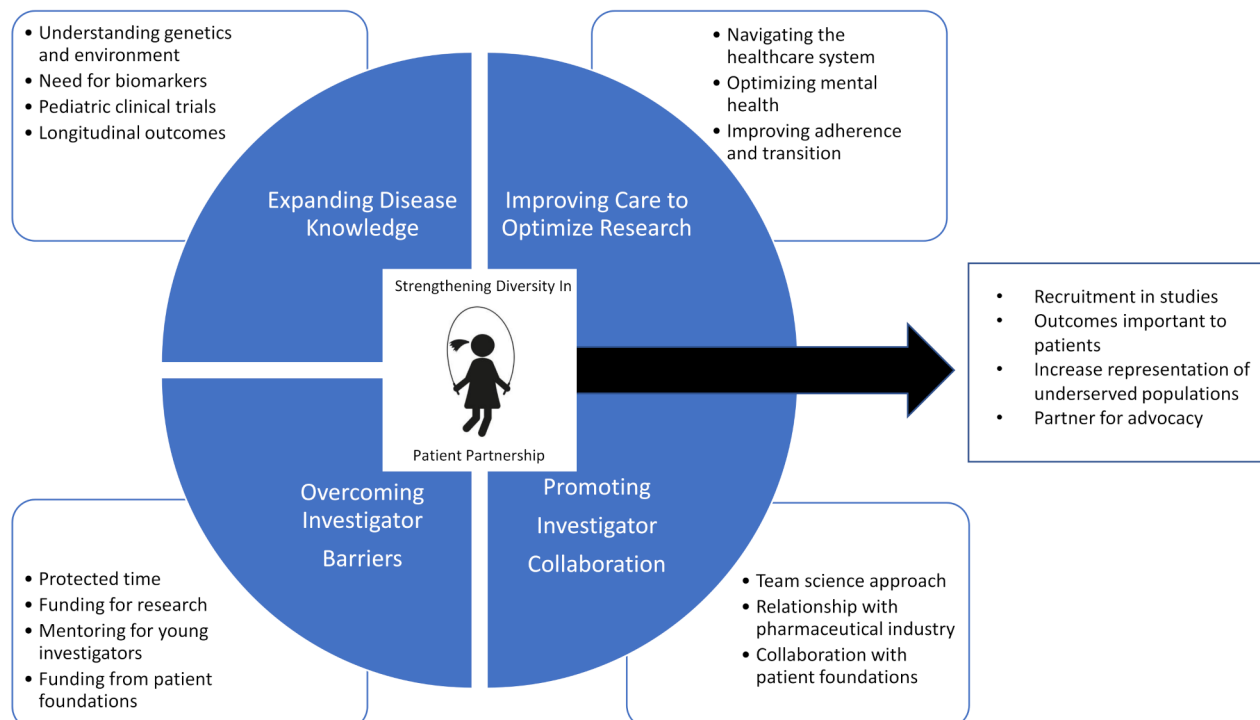
While there have been advances in understanding disease mechanisms and treatment of cSLE in the last decade, significant needs remain, underscoring the necessity of a focused research agenda for allocation of available resources. Expanding on the findings from the ALPHA study<sup>5,6</sup> and CARRA-LFA survey regarding cSLE research priorities,<sup>7</sup> we elucidated approaches to address cSLE research priorities, exploring both barriers and opportunities to advancing cSLE research. Multidisciplinary experts in our study identified research priorities represented by five domains: (1) expanding disease

knowledge; (2) investigator collaboration; (3) partnering with patients and families; (4) improving care to optimise research; and (5) overcoming investigator barriers. Many interviewees had difficulty selecting a single priority, and the need for a broader paradigm framework for cSLE investigation was identified. Additionally, and notably, partnership with patients emerged as a unifying factor for advancing research (figure 1).

We identified not only barriers but also numerous opportunities for progress (box 1). Our findings represent an initial step in formulating a research agenda and funding priorities for the cSLE community.

Experts identified a need for a path of investigation in lupus research, described as a paradigm framework to guide ‘how’ to do the research, which would also inform ‘what’ to research. A comparison was made to the field of autoinflammatory disease research, which has seen recent significant advances due to international and interdisciplinary collaboration, and harnessing of genomic and molecular technologies to link genotype to biological pathways to phenotype.<sup>10</sup> This has resulted in better diagnostic tools and target immunosuppressive treatment in autoinflammatory disease. A similar paradigm for lupus research, addressing the complexity and heterogeneity of the disease, would be optimal to guide lupus investigation towards improving patient care. Experts emphasised the importance of a research agenda that promotes

## Improving Care of cSLE Patients through Advancing cSLE Research



**Figure 1** A visual representation of study themes. The figure proposes that research priorities for cSLE are captured by five interrelated themes, which include disease knowledge, investigator collaboration, improving care to optimise research, investigator barriers and patient partnership (depicted in the centre of the figure). Patient engagement, patient partnership and health equity in research endeavours are central to the development of any proposed research agenda, and the other four themes rely on engagement of patients and health equity for their advancement. cSLE, childhood-onset SLE.

## Box 1 Opportunities for advancing childhood-onset SLE (cSLE) research

### Collaboration

- ▶ Interdisciplinary collaboration across subspecialties and scientific disciplines to engage in a team science approach.
- ▶ Multicentre and multinational collaboration to develop larger representative cSLE patient cohorts with diverse disease manifestations.
- ▶ Efforts to reduce regulatory barriers to collaboration (eg, Institutional Review Board, Food and Drug Administration).

### Longitudinal data

- ▶ Address gaps in clinical care, with attention to enhance standardised, comprehensive and longitudinal data collection.
- ▶ Longitudinal patient registry data collection from paediatric disease onset through adulthood.
- ▶ Data management and infrastructure support across centres/sites to share standardised electronic medical record data and link to other data sources (eg, registries, administrative data).

### Patient involvement in research

- ▶ Improve healthcare delivery, with particular focus on underserved populations, to empower participation in research.
- ▶ Engage patients and families to determine meaningful research questions and outcomes and to enhance recruitment of diverse populations.
- ▶ Include patient-reported outcomes in study design.
- ▶ Include diverse staff on research teams.

### Investigator support

- ▶ Increase funding opportunities for early investigators to pursue cSLE-related projects.
- ▶ Dedicated mentorship programming for cSLE research, including funded protected time for cSLE mentors.
- ▶ Facilitated networking among senior researchers and early investigators.

collaboration among investigators with different expertise (immunology, genetics, basic science, translational science, etc). With regard to translating findings to the clinical setting, experts also identified biomarker and drug development as prominent priority areas, acknowledging the unique regulatory and ethical considerations that exist in studies involving paediatric patients.

One promising model of investigation is the Accelerating Medicines Partnership (AMP),<sup>11 12</sup> which has enabled successful collaboration between the NIH, pharmaceutical companies and non-profit organisations, bringing together individuals of varying backgrounds and expertise to push the science forward. The AMP initiative has supported 'team science' studies in the adult SLE population, for example, with one published study using single-cell RNA sequencing technology to examine heterogeneity of lupus nephritis and skin disease, and identifying cellular changes on skin biopsy as a potential biomarker for lupus nephritis.<sup>11</sup> A trans-NIH initiative (across specialties) could be another potential opportunity for multidisciplinary collaboration to understand lupus disease heterogeneity given the multiorgan involvement in cSLE. Fostering team science collaboration inclusive of cSLE (both within cSLE and SLE research in general) will

be critical to advancing research and discovery in cSLE, furthering knowledge of potential targets for more effective and less toxic medications (box 1). Furthermore, although there has been advancement in cSLE trials in recent years,<sup>13</sup> treatment development in cSLE will likely require innovative smaller trials with specific endpoints given the rarity and heterogeneity of the disease.<sup>14</sup>

Another potential area for collaborative research is creating purposeful synergy between existing and newly created cSLE observational registries in order to optimise the breadth and depth of the data collected. Longitudinal observational registries which capture the full breadth of patient demographics, disease manifestations, treatments and response are critical to understanding cSLE's natural history and short-term and long-term outcomes. Harmonisation of data fields can allow for comparison or combination of related registries, which may be essential when describing less common disease manifestations or treatments. These registries are even more powerful when paired with biosample collection, allowing for determination of both clinical and biologic factors which may contribute to fluctuations in disease activity and outcomes.

Although there was significant emphasis on research of the disease itself and its manifestations, patients' barriers to engaging with the healthcare system (eg, transportation to clinic, reliable methods to communicate with providers) were a less expected, yet significant finding. This echoes priorities in the 2015 National Public Health Agenda for Lupus developed by a collaborative of the LFA, the Centers for Disease Control and Prevention, the National Association of Chronic Disease, and leading lupus and public health advocates,<sup>15</sup> calling for improved lupus care coordination, self-management programmes, resources and identification of health disparities. Notably, SLE mortality risk is significantly impacted by race, with black females having increased mortality from SLE as compared with other individuals with SLE.<sup>16 17</sup> Additionally, although individuals from racial minority groups make up a large proportion of patients with SLE in the USA, white participants are over-represented in SLE randomised control trials.<sup>18</sup> Health equity research is therefore greatly needed to eliminate ongoing health disparities in SLE.<sup>15</sup>

To address the lack of adequate representation of racial minority groups in SLE research, a 2019 conference among patients with SLE, SLE physicians, clinical trialists, treatment developers from biotechnology, social scientists, patient advocacy groups and US government representatives explored solutions for increasing diversity in SLE research studies.<sup>19</sup> Best practices for clinicians and researchers were developed, which included reflecting on how personal and institutional culture lead to racial bias in research questions and study design, the need to avoid making assumptions about the 'kind' of patient who would participate in a trial, and increasing recruitment of under-represented minorities to the field of rheumatology. Experts in our study expressed several

opportunities to address these issues, including having a diverse research staff, including outcomes that are important to patients and utility of funding for patient navigators (box 1).

cSLE researchers face significant challenges—namely funding and protected time from clinical obligations—that impede their participation in multicentre studies or to procure data for registries to support longitudinal studies of diverse cohorts. As experts pointed out, this milieu discourages the number of early career faculty who pursue research careers, leading to fewer cSLE investigators and an inevitable lack of diversity in their research backgrounds. Academic institutions have created programmes to address this need,<sup>20–22</sup> but it remains a critical issue across paediatric subspecialties and particularly in cSLE research given the small size of the paediatric rheumatology field.

As one of the smallest paediatric subspecialties, often with small institutional divisions,<sup>23</sup> interinstitutional mentorship is crucial for trainees and early career faculty in paediatric rheumatology. The ACR/CARRA Mentoring Interest Group<sup>24 25</sup> has established connections between individuals at different institutions for career mentorship. Even with funding (such as a mentored career development award, eg, NIH K award), the number and availability of mentors for cSLE research are limited. Grants that protect time for mentors, K24-like funding and Request for Application opportunities related to research mentorship from the LFA or Lupus Research Alliance are potential solutions to foster investigator mentoring (box 1). Patient advocacy efforts through private foundations could also fill such a role (figure 1).

There are a number of strengths in our study. To our knowledge, this is the largest qualitative study of cSLE experts regarding cSLE research priorities. The group of experts had diverse backgrounds, including their disciplines (eg, nephrology, dermatology, medicine/paediatrics rheumatology), years in practice and research backgrounds. There was also international representation. A limitation of our study is that patients were not included in our study, risking misalignment between patients' priorities and those of experts. A follow-up study is planned to include patients' perspectives, priorities and perceived barriers to being involved in research.

In conclusion, the findings of this study highlight the importance of a collaborative research framework and the interdependence of the essential components needed to advance cSLE research and patient care. These findings can inform an actionable research agenda that incorporates the complexity of foundational challenges that investigators in cSLE research face. Funding and limited infrastructure remain a major limitation, yet the potential solutions posited by experts should be prioritised in future request for applications for work related to cSLE.

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