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## **Psychological Health and Well-Being in Systemic Sclerosis: State of the Science and Consensus Research Agenda**

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## **ABSTRACT**

**Objective:** There is relatively little research on important patient-reported outcomes that affect quality of life in systemic sclerosis (SSc) and even less research on psychological, behavioral, and educational intervention strategies. The objective was to review existing evidence and to develop a consensus research agenda for behavioral health and psychological research in SSc.

**Methods:** An international panel of recognized experts in behavioral and psychological health in SSc, rheumatologists, patients, and patient advocates was convened to identify areas of concern for patients with SSc and to develop a research agenda. As part of this process, the PubMed and PsychInfo databases were searched from inception for the keywords “scleroderma” in conjunction with keywords related to each identified topic area. All relevant original and review articles were examined.

**Results:** Key areas where behavioral health and psychological approaches may be useful to assess and improve quality of life in SSc include depression, fatigue, pain, pruritus, body image distress, and sexual function. Less researched areas that warrant attention include sleep, fear of disease progression and dependency, family and couples relationships, and healthcare factors.

**Conclusion:** Qualitative and quantitative studies are needed to (1) develop and evaluate assessment tools for SSc patient-reported outcomes; (2) assess potential causal and maintaining factors, as well as trajectories, of important problems faced by patients; and (3) develop and test psychological, behavioral, and educational interventions to reduce distress and increase overall well-being. Collaborative approaches that include multiple centers and that actively involve patients and patient advocates in the research process are needed.

Systemic sclerosis (SSc) is a multisystem disorder characterized by disturbance in fibroblast function, microvascular disease and immune system activation, culminating in fibrosis of skin and internal organs (1, 2). SSc is associated with extensive morbidity, including disfiguring skin thickening, finger ulcers, joint contractures, pulmonary hypertension, interstitial lung disease, chronic diarrhea, and renal failure (1, 2). The rate of disease onset is highest between 30-50 years of age with risk for women 4-5 times that for men (3, 4). Median survival time from diagnosis is approximately 11 years, and patients are 3.7 times more likely to die within 10 years of diagnosis (44.9% mortality) than age, sex, and race-matched individuals without SSc (12.0% mortality) (3).

Because there is no cure for SSc, improving quality of life is an important clinical challenge. There is relatively little research, however, on patient-reported outcomes related to quality of life in SSc or behavioral, psychological, and educational interventions. To begin to address this important knowledge gap, a panel of internationally-recognized experts in behavioral and psychological health in SSc, patients and patient advocates from the Scleroderma Society of Canada, and Canadian Scleroderma Research Group researchers was convened for a two-day meeting to identify important areas of concern for people living with SSc and to develop a consensus research agenda. The following sections present a summary of results from the meeting, including a description of important areas where research is needed, summaries of existing research in each area, and recommendations for future research.

## **METHODS**

The PubMed and PsychInfo databases were searched from inception for the keywords “scleroderma” and “systemic sclerosis” in conjunction with keywords related to each identified topic area. All relevant original and review articles were examined.

## RESULTS

### Depression

Depression is common among patients with chronic medical conditions and is associated with emotional suffering, impaired functional outcomes, greater healthcare utilization and increased comorbidity and mortality (5). Rather than simply a consequence of medical illness, mood disturbances appear to impact physical health through biological pathways, such as immune system dysfunction and inflammation, and through behavioral processes (5, 6), including poor adherence to medical treatment regimens (7), a reduced likelihood of adapting health-promoting behaviors, such as smoking cessation (8), and greater social isolation (9).

*Existing Research:* A systematic review of studies in SSc found that rates of depressive symptoms above cutoff scores for potential clinical significance on self-report questionnaires range from 36-65%, depending on the questionnaire and cut-off used (10). The 20-item Center for Epidemiologic Studies Depression Scale (CES-D) and the 9-item Patient Health Questionnaire (PHQ-9) are reliable and valid measures of depressive symptoms that perform similarly in SSc (11, 12).

A cross-sectional study of 376 SSc patients found that both sociodemographic variables (unmarried, less education) and disease factors (more tender joints, breathing problems, gastrointestinal symptoms) were associated with greater depressive symptom scores (13). Other smaller studies have found that overall disease severity, disability, gastrointestinal function, body image, pain, sexual function, and factors related to coping, disease-related cognitions, social support, and resilience are related to mental health (14-23). Notably, positive and negative affect appear to be distinct emotional states that relate differentially to coping, pain, and disability in SSc (24).

**Research Directions:** Studies that use “gold standard” structured clinical interviews are needed to understand the prevalence and impact of depression in SSc. Longitudinal studies that track disease progression concurrent with depressive symptoms will clarify the trajectory of depression in SSc and the interface between mood and disease progression. Similarly, studies are needed to specifically address how symptoms of depression influence and are influenced by inflammation and immune system dysfunction.

Since the existing literature indicates a substantial impact of depressive symptoms on clinical outcomes, interventions to address depression in SSc should be developed and tested. Tailored cognitive-behavioral therapy interventions that address multiple problems have been used successfully in other chronic diseases, such as rheumatoid arthritis (25), and should be tested in SSc given the varied problems faced by patients with the disease.

## **Fatigue**

Persistent fatigue from chronic illness involves ongoing exhaustion that is disproportionate to exertion and not alleviated by rest (26). Fatigue is one of the most important factors impacting quality of life in many chronic diseases (26), but it is typically not assessed by researchers and clinicians (27, 28).

**Existing Research:** Studies have reported that fatigue is present in approximately 75% of SSc patients (29, 30), may be the most bothersome symptom experienced by patients (31), and is robustly associated with physical function, even after controlling for education level, disease subtype, pain, sleep quality, and depressive symptoms (30). Fatigue is a robust independent predictor of level of activity and work disability (32-34). A recent systematic review found that fatigue scores from SSc patients on the Multidimensional Fatigue Inventory (35) were similar to scores from patients with other rheumatic diseases and cancer patients currently undergoing

treatment, and higher than scores from general population samples and cancer patients in remission (36). Fatigue scores in one study of 659 SSc patients were independently associated with number of medical comorbidities, breathing problems, gastrointestinal symptoms, depression and pain, as well as smoking, which may be related to breathing problems and other medical issues (37).

Only one study has investigated sleep disturbances in SSc (38). Of 27 patients in the study, mean sleep time was <6.5 hours, and more than half of patients reported abnormally poor sleep.

**Research Directions:** Reliable and valid tools to assess fatigue in SSc are needed. Evidence of the validity of several fatigue measures among patients with rheumatoid arthritis, including the Functional Assessment of Chronic Illness Therapy Fatigue Scale, visual analog scales, and the Multidimensional Assessment of Fatigue Scale, may extend to the assessment of fatigue in SSc, but this should be empirically evaluated. Research on fatigue in cancer has benefited from the development of a case definition for Cancer-Related Fatigue (39), which has improved the ability of researchers to identify patients with a high enough level of fatigue to warrant specific intervention, and this approach may be useful in SSc. Beyond assessment, research is needed to establish the etiology of fatigue in SSc, including the relationship between fatigue and inflammatory and neurosignaling processes. Basic neuroscience research has linked inflammation and proinflammatory cytokines to symptoms of fatigue and other *sickness behaviours*, including malaise, listlessness, loss of appetite, and depressed mood (40). The presence of chronic inflammation and enhanced cytokine production is one of the pathways that cause significant organ damage in SSc (41), and its role in fatigue should be clarified. Research in cancer and other rheumatic diseases shows that fatigue is amenable to intervention, including



exercise, sleep hygiene, psychosocial, and pharmacological interventions (42). Similar approaches should be tested among patients with SSc. The assessment of sleep problems is an important area to include in research on fatigue in SSc.

## **Pain**

Pain in rheumatic disease is associated with higher rates of physician visits, greater disability, and reduced health-related quality of life (43, 44). Improved pain management is an important priority for patients with rheumatic diseases (45). There are, however, relatively few studies on pain in SSc, and the complex etiology of pain in SSc remains unclear.

**Existing Research:** Pain is reported in 60-83% of patients with SSc (18, 29, 46, 47), and pain severity is comparable to levels found in other chronic pain conditions and rheumatic diseases (18, 48, 49). Patients with diffuse SSc report only slightly higher pain severity than patients with limited disease (47). Pain is an independent predictor of activity levels and work disability (32, 34). Patients in a focus group study (46) described multiple sources of pain, including joint and musculoskeletal pain, skin pain, pain associated with Raynaud's phenomenon, gastrointestinal and digestive pain, and pain in distal extremities (tightness, calcinosis and ulcers). Skin scores, patient-reported leg swelling, and patient-reported joint tenderness (50), severe Raynaud's symptoms, active ulcers, moderate to severe synovitis, gastrointestinal symptoms, and painful comorbid conditions (47), in addition to depressive symptoms (47), have been found to be independently associated with pain in multivariate analyses.

**Research Directions:** Qualitative and quantitative studies are needed to better understand the nature and sources of pain in SSc. Single-item visual analog (50) and numerical rating scales (47), as well as the 15-item McGill Pain Questionnaire - Short Form (MPQ-SF) (18, 51) have

been used to assess pain intensity in SSc. The Outcome Measures in Rheumatology (OMERACT) initiative determined that visual analog scales are valid outcome measures for Raynaud's phenomenon and digital ulcerations from SSc (52), but did not assess pain measures more broadly. Studies are needed that assess the relative merits of easily administered single-item measures versus the MPQ-SF, which differentiates affective and sensory pain. Studies that examine differences between and within patients longitudinally are needed to better understand the progression of pain. Vascular and inflammatory processes related to pain are important targets for future studies. Neuropathic pain has also been documented in SSc and warrants attention (53). Psychosocial interventions for pain that have been developed and tested in arthritis, including cognitive-behavioral therapy, relaxation, biofeedback and meditation (54), should be adapted and tested in SSc.

## **Pruritus**

Pruritus, or itching, has been defined as a “poorly localized, non-adapting, usually unpleasant sensation that provokes a desire to scratch” (p. 5) (55). Pruritus appears to be common during the early stages of SSc, and is an important problem for many patients (56-58). Clinical reviews agree that pruritus tends to subside as the disease progresses, although different time periods for this have been suggested (56-58). In some cases, pruritus may persist for many years (56). Until recently, there was no research on pruritus in SSc.

***Existing Research:*** A recent study of 400 patients,  $\geq 1$  year since onset of non-Raynaud's symptoms (59), found that 45% reported pruritus on most days in the last month. Patients with early disease (1–1.9 years since onset) reported significantly

higher rates (69%) than patients at least 2 years post-onset (44%). Pruritus was associated with skin involvement, gastrointestinal symptoms, breathing problems, Raynaud's symptoms, and finger ulcers, although only gastrointestinal symptoms predicted pruritus in multivariate analysis.

**Research Directions:** Existing research on pruritus in SSc is limited by the use of single-item dichotomous assessment, and the development and validation of an easily administered and scored continuous pruritus severity measure is needed. Most existing measurement scales for pruritus tend to be difficult to administer and score and/or not well-validated (59). Recently, a pilot study was conducted among dermatology patients with the ItchyQoL (60), a 22-item, multidimensional tool that is easily scored and assesses symptoms, functional limitations, and emotions related to pruritus. Only rudimentary validation data are available, however, and the ItchyQoL should be tested in SSc, including an assessment of its performance against a single item visual analog or numerical rating scale (59). More data are needed on the trajectory of pruritus, as well as causal and maintaining factors and the extent to which it impacts quality of life and function. In addition, trials that investigate the management of pruritus in SSc should be conducted.

### **Body Image Distress**

Disfigurement in visible and socially relevant areas of the body (e.g., hands, neck, face, mouth) is a central feature of SSc. Patients with disfigurement that occurs in the context of medical disease or injury often struggle with body image and experience difficulty maintaining healthy social interactions due to changes in appearance (61). Social anxiety is common among individuals with facial disfigurement, and the fear of negative evaluation from others can lead to

avoidance of social situations (62). Body image is directly related to self-esteem and quality of life (63), but there is relatively little empirical research examining body image in SSc.

**Existing Research:** SSc patients rate disfigurement as a significant source of stress (31). Several different measurement tools have been used to assess body image and appearance concerns, although only the adapted Satisfaction with Appearance Scale has been validated for use in SSc (64). Two studies (31, 65) have reported that women with SSc have diminished appearance self-esteem as measured with the Appearance subscale of the State Self-Esteem Scale (66). Two other studies found that higher levels of body image dissatisfaction, self-rated attractiveness, and fear of negative evaluation were associated with symptoms of depression and anxiety and poorer psychosocial functioning (16, 67). One of these studies reported that body image dissatisfaction was predicted by younger age and more severe SSc (67).

**Research Directions:** Experts have emphasized the need for measures that assess specific dimensions of body image (e.g., evaluation of appearance, investment in appearance, body image avoidance) and that are appropriately adapted and validated in specific patient groups (68). Measures of important body image constructs, including social avoidance related to body image in SSc, are needed. Existing measures, such as the Body Image Avoidance Questionnaire (69), which focuses on social avoidance behaviors associated with weight-related concerns, should be adapted for behaviors related to acquired disfigurement from SSc. Studies are also needed to address patient and disease factors leading to body image distress and to further clarify if body image is associated with quality of life outcomes independent of depression. Finally, social interaction skills training programs (70, 71) and cognitive-behavioral therapy for social anxiety (62) have been recommended as strategies to reduce social avoidance. These

interventions focus on the development of social skills that allow people with disfigurements to effectively anticipate and manage the reactions of others and to increase their confidence and self-esteem in social settings (63). Interventions based on these principles should be developed and tested for SSc.

## **Sexual Function**

Impaired sexual function refers to problems such as reduced desire and enjoyment, impaired arousal, difficulty reaching orgasm, and painful sex (72). Physical and psychological consequences of SSc that can lead to impaired sexual function include skin tightening and discomfort, shrinking of the mouth, joint pain, Raynaud's phenomenon, gastrointestinal symptoms, pulmonary restrictions, depression, fatigue, distressing changes in appearance, vaginal tightness and dryness in women, and reduced penile blood flow in men (73-75). However, there is relatively limited research on sexual function in SSc (56).

***Existing Research:*** More than half of women with SSc report sexual impairment (74). Sexual impairment is significantly greater among women with SSc compared to healthy controls (76) and the general population (21). A recent systematic review found that women with diffuse SSc experienced levels of sexual impairment similar to or higher than women with breast cancer, HIV, and gynaecological cancer, and that women with limited SSc experienced levels of impairment greater than women with breast cancer (77). Common problems include vaginal dryness, painful intercourse, and fewer and less intense orgasms (78). Vaginal discomfort, vaginal pain, and fatigue (21), as well as disease duration and overall marital dissatisfaction (76), have been associated with poorer sexual function. Among men with SSc, the only published study (N=43) reported that 81% experienced erectile dysfunction, with mean onset 3 years post-diagnosis (79).

**Research Directions:** Validated measures of sexual impairment for SSc are needed, ideally measures with comparison data from community and other chronic illness samples. Possibilities include the Female Sexual Function Index (80) for women and the International Index of Erectile Function (81) for men. In addition, measures or supplementary scales that capture factors specific to SSc should be considered. Large-sample studies that investigate multiple predictors of sexual impairment, including both physical symptoms of SSc and psychological factors, and studies that chart the course of impairment longitudinally over the course of disease development should be conducted. Studies are also needed that focus on spouses or partners and that address couples' interactions. Finally, methods of delivering accurate information to patients and facilitating patient-physician communication about sexuality, as well as formal interventions based on observational findings and clinical recommendations, need to be developed and tested.

#### **Other Perceived Stressors/Unidentified Research Areas**

SSc patients are affected by many disease-related stressors (82), as well as stressors related to obtaining appropriate health care, yet many of these have received little attention in published literature.

**Existing Research:** A recent study from the Netherlands (N=123) found that dependency on others, being misunderstood by others, and fear of the future were among the top concerns endorsed by patients (31), but these have otherwise received little research attention. Several studies have assessed anxiety among patients with SSc, although all were conducted with small patient samples and used self-report questionnaires that did not permit the estimation of prevalence of specific anxiety disorders (83-85). A survey of more than 500 Canadians with SSc, which was conducted by the Canadian Scleroderma Research Group and the Scleroderma

Society of Canada (unpublished) found that accessing healthcare and managing healthcare needs are important sources of stress. Specific issues included limited health insurance coverage, cost of treatments, as well as delays in diagnosis and, in some cases, numerous physician referrals prior to diagnosis. Consistent with this, a previous study of 408 Canadian patients found that the median time between the onset of Raynaud's phenomenon and diagnosis was 2.0 years (86).

Only one study, which investigated challenges reported by 75 mothers, has investigated family roles in SSc (87). That study found that mothers had difficulties playing with their children, doing household chores, and shopping.

**Research Directions:** More research is needed on understudied disease-related stressors, including anxiety, and how these interact with other aspects of behavioral health (e.g., depressive symptoms and fatigue), as well as on difficulties SSc patients face with the healthcare system, such as delays in diagnosis. Large-sample longitudinal studies in SSc are needed to be able to examine how patients cope with disease- and healthcare-related stressors. Religious or spirituality-based coping, for instance, is important for many patients, but has been largely ignored in SSc (86). Studies are needed that address interpersonal roles and relationships of persons with SSc, as well. In addition to parenting roles, research is needed on relationships and distress in couples coping with SSc. In cancer, modest elevations in distress are observed in couples coping with cancer regardless of the sex of the patient, and research suggests that couples react to this challenging diagnosis as an emotional system (89).

### **Behavioral and Educational Interventions**

Recent European League Against Rheumatism recommendations for the treatment of SSc (90) did not include any recommendations for lifestyle or behavioral interventions and noted, "There are also other treatment options for the management of SSc patients, such as

physiotherapy, education, new experimental therapies, etc, which...could not be included because of the lack of expert consensus” (p. 626). Recent studies (91, 92) show that patient-identified psychological factors are important, but unmet treatment needs in SSc.

***Existing Research:*** Several published reports have described the use of individual- and group-based self-help and self-management programs in small numbers of patients (e.g., 3-6) with SSc (93-95). Poole et al. (96) developed a self-management program for SSc based on the principles of Lorig’s widely disseminated Arthritis Self-Management Program (97). The intervention program consisted of a booklet with modules on topics related to coping with SSc and a DVD showing face, hand, arm and leg exercises. Preliminary results using a pre-post design among 49 patients, however, did not find consistent evidence of benefit for most of the outcomes tested. The authors concluded that the program may be more useful for newly diagnosed patients than for patients with long-standing disease and that the booklet and DVD format may not work as well as a small-group format. Nielson (98) recently presented preliminary results from 19 patients in an uncontrolled study of a daily, two-week multidisciplinary treatment program that included both psychological (e.g., cognitive therapy) and physical (e.g., physiotherapy) elements, as well as disease education, and found improvements in emotional distress, illness-related cognitions, pain coping, and the extent patients felt SSc interfered with their lives. Kwakkenbos et al. (99) studied the efficacy of a short psycho-educational group intervention among 41 patients in a pre-post design and reported favorable changes in helplessness and acceptance of limitations, but not in disease acceptance or depressive symptoms. The authors concluded that more intensive treatment would likely to be more effective in improving depressive symptoms when targeted to patients with high levels of depressive symptoms.



**Research Directions:** Educational and psychotherapy interventions based on cognitive-behavioral principles should be developed and tested in SSc. As with other complex illnesses, inclusion of multiple symptoms, including pain, depressive symptoms, fatigue, sleep disturbance, and body image dissatisfaction is warranted. A stepped care model for psychological interventions might improve efficacy of treatment by matching treatments to patient needs (100). Many patients with SSc do not have direct access to health professionals with experience in SSc. Therefore, the incorporation of new developments in e-health therapy and computer-based interventions could increase access to care (101-103). Technological approaches may also facilitate the delivery of group-based or interactive self-management interventions for patients outside of large metropolitan areas. The SSc-specific program developed by Poole et al. should be tested in larger samples in an interactive format and should be compared with potentially more accessible general self-help programs, such as Lorig's Chronic Disease Self-Management Program (104).

### **Biological Perspectives**

The field of psychoneuroimmunology focuses on the mechanisms through which behavior is associated with health via a network of endocrine and neural pathways linking the central nervous system, neuroendocrine organs, autonomic nervous system, and the immune system. There is a bidirectional communication infrastructure where top-down processes affect the periphery, but also, conversely, where the periphery can influence central nervous system function and ultimately experiential phenomena such as mood, cognitive functioning, perceived energy level or fatigue, and pain sensitivity (105, 106). Little is known about the interplay between psychological and disease factors in SSc. However, extensive research has been conducted in other rheumatic disorders, notably rheumatoid arthritis.

In rheumatoid arthritis, prospective studies indicate that psychological stress affects markers of disease activity (107), including pain, fatigue, and disability. There is evidence that psychological stress affects levels of inflammatory cytokines, the chemical messengers that are the key promoters of the autoimmune inflammatory dysregulation seen in rheumatoid arthritis (108). Experimental studies have found that inflammatory cytokines such as interleukin-2 and interferon-alpha induce depressed mood, cognitive difficulties, and fatigue (109, 110). Furthermore, depression correlates with increased inflammatory cytokines such as interleukin-6 in medically healthy populations (111, 112) and in rheumatoid arthritis (113).

Although depressive symptoms are common in SSc (10), it is unclear whether pathophysiological disease processes in SSc promote depressive symptoms. Thus, it will be important to determine if there are endogenous processes in SSc that predispose patients to experience depressive affect, fatigue, and poor sleep.

## **CONCLUSIONS**

SSc is a devastating disease that causes great suffering and even death for many patients. Nonetheless, many individuals with SSc are able to live relatively long and satisfying lives, and psychological and behavioral health research has great potential to improve their overall well-being.

The low prevalence of SSc has historically made research on behavioral and psychological health and well-being difficult, although substantial progress in recent years provides a solid foundation for more and better research. This report has summarized a group of psychological and behavioral aspects of SSc, a number of which are under-recognized by health practitioners and research scientists, but highly disturbing to patients, including depression, fatigue, pain, pruritus, body image distress, sexual functioning, and poor sleep. As detailed in

this report, a concerted effort is needed to (1) develop reliable and valid assessment tools for SSc patient-reported outcomes; (2) assess potential causal and maintaining factors, as well as trajectories, of important problems faced by patients; and (3) develop and test psychological, behavioral, and educational interventions to reduce distress and increase overall well-being. Inclusively, research is needed to better understand interrelationships between key problem areas. For instance, depression, pain and fatigue have been shown to be interrelated (37, 47). Similarly, body image, depression and sexual function are likely to be closely related. Across all problem areas, qualitative studies are needed to better understand patients' experiences.

Increasingly, it is recognized that the ability to produce high-quality research in the context of a rare disease, such as SSc, requires collaborative approaches. The US National Institutes of Health, for instance, created the Rare Diseases Clinical Research Network to support consortia dedicated to research on rare diseases. The meeting, *Improving Health and Well-Being in Scleroderma: Establishing a Collaborative Behavioral Health Research Agenda*, that resulted in this proposed psychological and behavioral health research agenda was an effort to begin to link behavioral scientists from across the world in order to better understand the challenges faced by patients with SSc, and to develop research to address these in a way that produces tangible benefits for patients.

In addition to multi-disciplinary, multi-center, and international collaborations among scientists, the active involvement of patients and patient advocates in the research process is crucial for developing relevant research questions that address important needs and produce results that are useful for clinical care. Knowledge translation and exchange has been defined as “the exchange, synthesis, and ethically-sound application of knowledge—within a complex set of interactions among researchers and users—to accelerate the capture of the benefits of

research...through improved health, more effective services and products, and a strengthened health care system” (p. 4) (114). Essentially, in SSc research, this is a process that would integrate the knowledge and experiences of individuals with SSc as participants at each stage of the research process. At its fullest, it is an active partnership among researchers, clinicians, patients, and patient advocates who work together to develop funding and scientific infrastructures, generate research questions, develop assessment tools and interventions, define outcomes, analyze data, interpret results, and disseminate findings (114, 115).

Beyond an endorsement of collaborative efforts, it is important to emphasize specific research models that will likely move psychological and behavioral health research forward in a way that benefits patients. SSc is a complex, multi-faceted disease with multiple symptom manifestations and health care needs that vary across and within patients over time. More qualitative research is needed to better elucidate problems faced by persons living with SSc, as well as coping mechanisms (46, 116). In terms of quantitative research, as we noted, collaborative approaches are necessary to obtain data from sufficiently large numbers of patients so that results accurately reflect the experiences of patients with SSc.

In summary, the last several years have seen a great deal of activity in research on behavioral and psychological aspects of living with SSc, but there is much to be done. We hope that this proposed agenda will serve both to identify important questions in need of research and to emphasize the need for increased collaboration in order to produce research of high utility to individuals with SSc.

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