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Gaps in Aging Research as it Applies to Rheumatologic Clinical Care

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Synopsis

The incidence and prevalence of rheumatologic conditions is increasing and the Rheumatology workforce must be aware of aging-specific issues. In this article, we review specific barriers to our understanding of the biology of aging and aging-related mechanisms that may underlie development of rheumatologic diseases in older adults. We summarize gaps in the assessment, outcomes measurement and treatment of these diseases in this unique population. Lastly, we highlight potential solutions to these barriers and suggest possible ways to bridge the gap, from a research and education standpoint, so we can be better prepared to effectively manage older adults with rheumatologic conditions.

Keywords

Older adults; Rheumatology; Barriers; Education; Research

By 2030, the size of the 65 years and above age group is expected to reach 71.5 million, or 20% of the total US population. The majority of the older population is projected to be between age 65 and 74 years until 2034 when all of the baby boomers will be over 70.[1] By extension, the number of older adults with degenerative and inflammatory rheumatologic

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diseases will increase in the subsequent decades and both the Rheumatology and Geriatric Medicine work force must be prepared to manage these conditions.

Osteoarthritis (OA), a degenerative joint disease commonly affecting hands, knee, hip, and spine, is the most common source of chronic joint pain among older adults. Estimates from 2005 suggest that OA affects approximately 27 million people in the United States alone.[2] As age is a major risk factor for OA, its incidence and prevalence is expected to increase with aging of the population.[3] Besides OA, advanced age is also associated with a higher incidence and prevalence of inflammatory rheumatologic diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), polymyalgia rheumatica (PMR) and giant cell arthritis (GCA). The incidence of RA continues to increase until age 75–80 years.[4] While SLE is an autoimmune multisystem disease that most commonly affects women of child-bearing age, up to 18% of cases have an onset after age 50.[5] There are conflicting data regarding whether late-onset SLE has a more benign clinical course as compared to SLE in younger populations.[6,7] Some reports suggest lower disease severity in late-onset SLE as compared with younger SLE patients.[6] Other research suggests greater disease activity and damage, and poorer survival; these findings are likely due to greater frequency of comorbid conditions and greater organ damage at the time of diagnosis.[5] Rheumatologic diseases such as PMR and GCA exclusively affect older adults. While the exact mechanisms leading to the development of PMR and GCA remains unclear, aging-related changes in the innate and adaptive immune systems are implicated.[8]

The reasons underlying the rising incidence of these rheumatologic diseases in older age, especially for those conditions traditionally believed to affect mostly younger populations, are not fully understood. Rheumatologists' primary goals are to maintain function, reduce progression to chronic deformities, and minimize toxicity from therapy. Furthermore, how these diseases manifest in older populations may be very different from younger populations. Finally, we still have much to learn about the process of aging, per se, and its impact on rheumatologic diseases. In 2014, a seminal publication by the trans-National Institute of Health's Geroscience Interest Group outlined 'Seven Pillars of Aging' and discussed how these biological processes intersect and connect with chronic disease.[9] While not specifically focused on rheumatologic disease, many of these pillars and the mechanistic relationships between aging and chronic diseases can be applied to clinical rheumatology. For example, the pillars of inflammation, epigenetics, adaptation to stress, and proteostasis are all known or suspected to play prominent roles, to different degrees, in rheumatologic conditions. These relationships and especially the interphase with behavioral and social sciences are slowly being uncovered. Finally, our understanding of the processes that promote aging and how these influence rheumatologic diseases may help identify treatment targets, thus helping in clinical care and decision-making unique to older adult populations.

Further, older adults pose unique challenges to the assessment and management of rheumatologic disease. This population often suffers from multimorbidity (defined as 2+ chronic conditions), polypharmacy, frailty, cognitive impairment, and fragmented social support systems.[10–12] In this article, we will cover specific barriers to our understanding of the biology of aging in rheumatology, and gaps in the assessment, outcomes measurement and treatment of this unique population. We will highlight potential solutions to these

barriers and how to bridge the gap so we can be better prepared to effectively manage older adults with rheumatologic conditions.

Gaps/Challenges in Current Geriatric Rheumatology Clinical Care

Gaps in Understanding of the Biology of Aging

Advanced age is a major risk factor for many rheumatologic diseases,[13,14] as it is for many other diseases (e.g., atherosclerosis, neurodegenerative disease, etc.) but the specific aging-related pathogenic mechanism underlying this association is unclear. Aging is a systemic phenomenon, thus it is conceivable that aging-related diseases of different organ systems may well be connected through the same underlying mechanisms. This concept of common aging mechanisms leading to a host of diseases related to aging has led NIH to initiate and promote Geroscience research in an effort to understand the link between aging and aging-related chronic diseases.[9] During the 2013 Geroscience summit, seven interconnected processes emerged as potential drivers of the aging process that may govern the pathogenesis of aging-related diseases.[9] A greater understanding of the underlying mechanisms may provide insights into treatment targets for aging-related diseases, including rheumatologic diseases, and ultimately contribute to increasing disease-free life span. Below, we will review “the seven pillars” of aging and how they may be associated with rheumatologic diseases in older adults.

1. **Adaptation to stress**: Human beings are chronically exposed to stress—physical, social and psychological, to which neurohumoral, metabolic and immunologic responses are mounted.[15] Chronic stress has been associated with both onset and worse outcomes in rheumatologic diseases. At the level of the individual there exist differences in vulnerability to stressors and responses, with some individuals demonstrating either suboptimal or exaggerated responses.[15] This is linked to the question of how age may influence psychological, physiological, and biological resiliencies. The relationship between stress response, aging pathways and aging are seen in invertebrate models, but clear evidence from human studies are lacking.[16] Finding the relationship between stress and leucocyte telomere shortness[17] coupled with the finding that telomere length at birth is affected by prenatal stress[18] are noteworthy especially since telomere shortening in chondrocytes and leucocytes have been observed in OA.[19,20] Understanding such differences in adaptation to stress, and why some patients may be more resilient than others, may provide key insights into pathogenic mechanisms. Further, identifying biomarkers for the aging-process that may help detect vulnerable subjects early in the stage of disease when interventions may be effective are key areas that merit further research.

2. **Epigenetics**: Epigenetics refers to the changes in genome without affecting DNA sequence, and includes DNA methylation, posttranslational histone code, and noncoding RNAs.[9] Aging-related epigenetic changes may influence the rate of aging and are being evaluated in other chronic

age-dependent diseases (cancer and Alzheimer's disease) using genome wide association studies.[21] Epigenetic mechanisms have been implicated in the pathogenesis of SLE, RA, scleroderma, and OA.[22] Aging-related epigenetic changes (e.g., DNA methylation) have also been linked to abnormal T-cell function that may in turn contribute to the high incidence of autoimmunity in old age.[23] Further, the emergence of evidence for the role of epigenetic drift in RA (that could result in resistance to apoptosis such as in fibroblast-like synoviocytes), OA and other diseases is relevant but warrants more investigation.[22] Lastly, the possibility of reversal of aging by targeting epigenetic mechanisms is an exciting area of research and may provide novel approaches of treatment of age-related rheumatologic diseases.[24]

3. **Inflammation or "inflamm-aging"**: First described by Francesci et al, "inflamm-aging" refers to chronic, low-grade inflammatory response to chronic antigenic burden, implicated in aging-related diseases.[25] Inflammaging is in contrast to acute inflammation, which is an acute immunologic response to injury or other stimuli.[26] Evidence for aging being a proinflammatory state comes from studies where elevated systemic levels of proinflammatory cytokines are noted in healthy older adults compared to young adults as well as in other states of unsuccessful aging.[25,27–29] How chronic inflammation contributes to aging and aging-related diseases is unclear, although immune senescence seems to play a role through depletion of immunologic reserve. Cell senescence was initially described by Hayflick and colleagues as a phenomenon wherein normal cells lose the ability to proliferate after multiple cycles of proliferation in in-vitro cell cultures.[30] Senescent cells produce a host of proteins, known as Senescence-Associated Secretory Phenotypes (SASP),[31] which contribute to chronic inflammation in aging. One of the key SASP proteins, IL-6, has been associated with many rheumatologic diseases, including RA, OA, PMR and GCA.[32–34] The role of senescent T cells in the pathogenesis of rheumatoid arthritis has been widely reviewed.[35] Cellular senescence of chondrocytes has also been implicated in the pathology of OA.[36] However, mechanistic studies demonstrating the role of SASP proteins or inflamm-aging in pathogenesis of aging-related rheumatologic diseases are lacking and merit evaluation. 'Senolytics', a new class of drugs targeting the removal of senescence cells with the goal of slowing aging and age-related diseases, have been successfully tested in animals.[37] However, the feasibility and effectiveness of this approach in humans and in rheumatologic diseases is unclear.

4. **Macromolecular damage/Oxidative stress injury:** The Harman Free Radical Theory of Aging states that oxidative damage to DNA, other cellular components and tissues accumulate over time and lead to aging, disease and death.[38,39] A state of oxidative stress occurs when there is a macromolecular damage of DNA, lipids or proteins, resulting in imbalance

between production of reactive oxygen species/free radicals (chemical species with unpaired electrons) and anti-oxidant defense mechanisms in the body.[40] Support for macromolecular damage and oxidative stress in aging is supported by a study showing decrease in oxidative stress markers and increase in lifespan with caloric restriction.[41] While the specific role of the oxidative stress injury with aging and aging-related diseases are still under investigation, association between markers of oxidative stress with aging and aging-related diseases have been reported and summarized in a recent review of published literature.[40,42] Levels of oxidative stress markers were shown to increase with age in a small series of human subjects.[43–45] The aging associated diseases shown to be associated with oxidative stress markers include, among others, Alzheimer's disease,[45,46] atherosclerosis/cardiovascular disease,[47,48] and cancer.[49] Regarding the association of oxidative stress marker and arthritis, epidemiologic studies indicate that agents causing oxidative stress, such as silica, smoking and infections are associated with onset and flare of a number of autoimmune disorders.[50,51] Oxidative damage can cause DNA damage, resulting in autoantigenesis and contribute to the induction of autoimmune diseases such as SLE and RA.[52,53]

5. **Metabolic pathways**: Many metabolic processes (glycolysis, fatty acid oxidation, amino acid oxidation, lipogenesis, and ketogenesis) decline with aging. It is unclear whether this decline is a result of aging or a cause of aging. Further, medications targeting metabolic pathways have shown impact upon lifespan, (e.g. rifamycin through mTOR[54] and metformin through AMPK,[55]) indicating an intersection of metabolic pathways and aging, with implications for aging related diseases. An area of interest for rheumatologists and an area of active research is the effect of glucose transport (GLUT1) on human T cell growth and proliferation as well as inflammatory response.[56] More research is needed to clarify the role of metabolic pathways in pathogenesis of aging-related rheumatalogic diseases.

6. **Proteostasis**: With aging, proteostasis or intracellular protein homeostasis is difficult to maintain and its imbalance is detected in normal aging and in aging-related diseases (Alzheimer's or Parkinson's disease).[57] Proteostasis pathways are also implicated in inflammation and are of interest in aging-related rheumatologic diseases.[58] The posttranslational protein modifications most observed in diseases, including RA, are glycosylation, citrullination, and carbamylation.[59]

7. **Stem cell regeneration**: Some stem cells are declining with age but can be rejuvenated by therapy suggesting that aging is not associated with irreversible loss of stem cells, as evidenced from aging muscle.[60] This has implications for therapy in age-related rheumatologic diseases. Synovial membrane derived mesenchymal stem cells are detected at higher levels in OA synovial fluid.[61] As synovial membrane mesenchymal stem cells can

develop into multiple cell types,[62] its potential for cartilage regeneration is of interest in aging-related arthritides.

Gaps in Assessment and Outcome Measurement

As clinicians, our evidence base for guiding management, including assessment tools specifically designed for older adults, is limited. Many use a "one size fits all" approach to assess and measure outcomes in younger and older adults. This may not be appropriate as older adults' values, priorities and expectations regarding treatment may not be the same as for younger populations.

Prognostication, Goal Setting, and Time Horizons in Older Adults—As in many fields of medicine, prognostication is an important part of our assessment and development of a treatment plan. This is particularly important when the clinician needs to balance the potential benefits, risks, and cost of chronic therapies (including biologic agents) in the aging rheumatic disease population. The oncology field has cancer-specific as well as function-based (e.g. Karnofsky Performance Scale) survival prediction tools.[63,64] Similarly, the cardiology field has developed prognostication tools for cardiac conditions such as congestive heart failure[65] and refractory angina.[66] Unfortunately, we lack specific tools to help us prognosticate for older adults with rheumatologic conditions. It is important to consider both the absolute and relative risk reduction of a proposed therapy in a frail population that has a limited life expectancy. Until we have rheumatic disease-specific prognostic tools, rheumatologists may consider using disease-agnostic prognostic instruments such as the on-line ePrognosis calculator (http://eprognosis.ucsf.edu/index.php).

With age, questions of prognosis and how aggressively to manage patients are closely linked with individual goals, priorities, and motivations to engage in medical care. Understanding the goals of our older patients has direct implications for how we, as clinicians, seek to address their rheumatologic conditions. We are learning that older adults make health related decisions in different ways than younger adults facing similar health decisions.[67] Research in the field of Lifespan Development Psychology demonstrates how motivations and specific goals vary with age. Motivation affects the degree to which older adults use prior experience, affect, and deliberative skills to make decisions.[67] For example, a growing literature highlights the role of age-related shifts in the ratio of gains and losses. Older adults who face an accumulation of losses of internal and external resources will often prioritize maintenance goals and prevention of losses (i.e., function). Additional research points to shifting time horizons.[68,69] Older adults frequently view their future time as more limited, this shift in time horizons may shape motivational priorities and health care decisions. Specifically, older adults often prioritize present-oriented goals aimed at optimizing current well-being, focusing on positive emotions, and maintaining rewarding relationships.[70] As we approach older patients and consider goal setting, please remember the following quote, "Don't ask what is the matter with me, ask *what* matters to me." [71,72] To date, little attention has been given to understanding how time horizons, for example, impact the way we, as Rheumatologists, approach our aging patients and navigate conversations about treatment expectations and relevant outcome assessments. Incorporating how older adults are uniquely

motivated to change behavior and interact with the health care system has not been systematically evaluated or consistently practiced.

Patient Reported Outcomes in Older Adults—While various measures have been validated and are widely used throughout the literature, it is debatable whether these instruments fully capture the scope of outcomes that are most meaningful to older populations. In this regard, older adults identify as meaningful the particular consequences of chronic degenerative musculoskeletal pain, including back pain. In particular, older adults identify the well-established biospsychosocial consequences of chronic pain including functional, psychological, and social impairments.[73,74] Older adults also highlight the adverse impact of pain on fatigue, sleep, and social isolation – consequences that are less commonly assessed in clinical practice.[73] Broadening our assessments from pain to associated functional, psychological and social outcomes will be important to consider for our aging population.[75,76]

Newer, efficient, state-of-the-science instruments are now available that assess appropriate and relevant domains/outcomes in older adults. Since 2014, the NIH has heavily invested in developing robust patient-centered outcome measures using PROMIS (Patient Reported Outcomes Measurement Information System) that are available for testing in subpopulations: http://www.nihpromis.org.[77–79] Data collected using PROMIS will provide clinicians and researchers with efficient and reliable information about the effect of therapy. How PROMIS instruments may be used in the development and implementation of treatment plans, and used at the point of care to enhance communication, management, and understanding of chronic rheumatologic conditions is an active area of investigation. Research is underway to evaluate how PROMIS performs in older populations with chronic musculoskeletal pain.[80]

Another critically important area that is fertile for further research is how to assess and evaluate chronic rheumatologic diseases in cognitively impaired older adults.[81] Joint pain, a common manifestation of rheumatologic diseases, is often assessed by self-report. Presence of dementia and cognitive impairment poses challenges in assessment of pain due to impairment in the ability to report pain, due to difficulty in recalling and in verbalizing.[82,83] Thus, presence of dementia and cognitive impairment is associated with under-recognition and under-treatment of pain.[84–86] Currently available behavioral assessment tools, such as DOLOPLUS-2[87] and PACSLAC,[88] which rely on non-verbal cues, can be used for the assessment of pain in patients with dementia or cognitive impairment, especially in nursing homes.[89] These tools, however, are underdeveloped and have poor psychometric properties.[90]

Gaps in Managing/Treating Older Adults with Rheumatologic Conditions

We lack guidelines that are specific to older adults for most rheumatologic conditions. Older adults are often excluded from clinical trials for various reasons including multimorbidity, polypharmacy, and fragmented social support systems.[10,11] By not including medically complex older adults in trials we are unable to fully understand the harm, benefit and cost ratio of therapies for this specific population. We often extrapolate clinical decisions from

guidelines based upon data from younger populations to older patients. The next section will address this in the context of multimorbidity, individualized interdisciplinary management, as well as immunizations – all areas critical to consider when treating older adults with rheumatologic conditions.

Multimorbidity and Polypharmacy—Given the prevalence of multimorbidity, there has been a push to better understand rheumatologic conditions in the context of co-existing chronic conditions. It is uncommon to care for a patient in rheumatology who has isolated knee OA or RA in the absence of cardiovascular, pulmonary or renal disease. While researchers have traditionally avoided the complexity of multiple chronic conditions, it is inevitable that rheumatologists face these each day. For example, the use of non-steroidal anti-inflammatory medications that are often better tolerated by young adults, are generally avoided in older adults due to their adverse effects including increased cardiovascular events or worsening renal impairment. Future research should include heterogeneous populations with multiple chronic conditions in sufficient numbers to measure benefits and harms of interventions.

Polypharmacy is a direct consequence of multimorbidity. Rheumatologists and geriatricians have to be cognizant of drug interactions as a result of polypharmacy, which makes caring for older adults more complex. Research suggests that the age of a patient influences rheumatologists' decision to escalate care in RA.[91] Future research should consider how ageism plays a role in the quality of care delivered to older adults with rheumatologic diseases. We also need to carefully consider how, in the face of polypharmacy and multimorbidity, escalation or de-escalation of the medication list impacts outcomes for this population.

Individualized Inter-Disciplinary Management—For older adults with rheumatologic conditions, individualizing the approach to management is critical. Older adults have unique home life circumstances and divergent abilities to adhere to and sustain management plans. We must therefore carefully design interventions that are feasible and safe for this population. Developing and implementing individualized plans of care for older adults must be weighed carefully against feasibility, generalizability, and cost effectiveness. Implementing an individualized care plan for an older adult with rheumatologic conditions (among other comorbidities) involves an interdisciplinary team, often including (as available): rheumatologist, geriatrician, physical and/or occupational therapist, psychologist or behavioral interventionist. As outlined in a review on persistent pain in older adults, combining pharmacologic, nonpharmacologic, and rehabilitative (activity based) approaches in addition to a strong therapeutic alliance between the patient and physician is essential in setting, adjusting, and achieving realistic goals of therapy.[75]

Immunizations—One area of specific interest in geriatric rheumatology and one that bridges the biology of aging and clinical implications is vaccine efficacy in later life. Age-related changes in immune function includes decline in efficacy of vaccinations in older adults.[92] Based on a review of 31 vaccine antibody response studies conducted from 1986 to 2002, Goodwin and colleagues calculated 7–53% efficacy of the influenza vaccine in older adults compared to 70–90% in younger adults.[92] These authors suggested that future

research is needed for more immunogenic vaccine formulations specifically for older patients. A recent study found that a high-dose trivalent influenza vaccine, with four times as much hemagglutinin, confers superior protection than standard trivalent vaccine.[93] Herpes zoster, reactivation of latent varicella, is more common in older adults and those who are immunocompromised (including patients with inflammatory arthritides and taking disease modifying anti-rheumatic drugs).[94] The herpes zoster vaccine is recommended for RA patients 50 years of age and older.[95] Additional literature is emerging suggesting that younger adults with autoimmune diseases or inflammatory conditions have rates of herpes zoster that are comparable to or greater than the rates in older adults and that this population should be considered for vaccination at a younger age cut off.[96] How this would impact our vaccination practices as patients with rheumatologic diseases age is unknown. Further research is needed in older adults with rheumatologic diseases and multimorbidity to determining vaccine efficacy and scheduling. We know there is tremendous variability in the implementation of guidelines at local levels,[97] and innovative, possibly automated, systems of vaccine delivery by non-physician providers may be most effective.

Bridging the Gap: A Call to Action

With aging of the population, there is an urgent need for our workforce to be prepared to manage the rapidly rising population of older adults with rheumatologic conditions. A recent New York Times article highlighted, “where are the geriatricians?”[98] One potential solution to this shortage is to train subspecialists, including rheumatologists, and other providers in the rheumatology work force in the appropriate assessment and management of older adults with rheumatologic conditions.

In this article we have discussed the gaps and challenges in the understanding of the biology of aging pertaining to the underlying pathophysiology of age-related rheumatologic diseases as well as assessment, outcomes measurement and treatment of rheumatologic diseases in later life. Below, we summarize possible ways to bridge the gap, through more research and education, which we hope will translate into guidelines that will improve care and foster healthy aging for millions of older adults with rheumatologic diseases.

In the opinions of these authors, and from a **research** standpoint, we must consider the following:

- Develop aging animal models that are more similar to aging humans for preclinical studies;
- Use age-appropriate animals in evaluating immune-based treatments for rheumatologic diseases that primarily affect older adults;
- Align preclinical models and clinical trial populations including more appropriate disease phenotype, and ensure that measured outcomes are clinically relevant (i.e., outcomes measured in the animal model relate to the human disease);

- Increase our understanding of the relationship between aging processes and the pathogenesis, clinical manifestation, and treatment of rheumatologic diseases;
- Consider adopting the worldwide strategy of One Health Initiative: interdisciplinary collaboration and communication between medical and veterinary health care and health research to provide multidirectional flow of knowledge and synergistic gains for both disciplines;[99]
- Focus research efforts on older adults with multimorbidity and polypharmacy, rather than excluding this medically complex population. Clinical research that involves older adults may benefit from including patient stakeholder input from this group—the group for whom the intervention is intended to benefit. Given the relative lack of guidelines specific to older adults, now may be a prime opportunity to solicit older adults with rheumatic diseases to participate on guideline panels in order to incorporate their voice and experience;[100]
- Develop novel interventions that can be implemented and disseminated in real-world practice (i.e., the older adult will have access to the intervention);
- Develop prognostication tools for individual rheumatologic diseases to help guide treatment decisions of these diseases in frail older adults;
- Develop a cadre of future investigators who serve as opinion leaders in geriatric rheumatology:
  - NIA has heavily invested in developing research and leadership careers of talented new investigators who are well poised to change theory, practice and health outcomes related to the health of older adults. The prestigious Beeson award—recently re-named the Paul B. Beeson Emerging Leaders Career Development Award in Aging (K76 NIA mechanism) serves this purpose;
  - A private/public partnership also exists, the NIA Grants for Early Medical/Surgical Specialists' Transition to Aging Research (GEMSSTAR), to help early career physicians establish a track record in aging-related aspects of their specialty;
  - Leverage the trans-NIH institutes Geroscience Initiative, and increase the participation of, particularly, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and the National Institute of Allergy and Infectious Diseases (NIAID):
    - Co-sponsor conferences and target areas of shared research interests

- To enhance the pipeline of geriatric rheumatology investigators in academia, we must continue to provide pertinent funding opportunities, perhaps in conjunction with support from foundations (for example, the John A. Hartford Foundation, http://www.jhartfound.org) and organizations (for example, The Atlantic Philanthropies, the Association of Specialty Professors, part of the Alliance for Academic Internal Medicine have a long track record of integrating geriatrics within subspecialties) with complementary priorities and shared agendas;
- We must cultivate, motivate and nurture the current and next generation of mentors in this field. A lack of appropriate role models and mentorship may be one of the primary reasons for why talented young investigators leave academia;[101]

From an **education** standpoint, the following should be considered:

- Facilitate networking opportunities at national meetings in the form of special interest groups—gathering like-minded individuals will help drive both research and clinical agendas forward;
- Develop core curricula for geriatric rheumatology that may be disseminated to training programs and that includes other professional trainees/providers;
- Develop educational modules that are accessible on-line (via pogo-e, for example, https://www.pogoe.org/about);
- Disseminate research findings to a greater audience/community of clinicians:
  - Peer reviewed manuscript publication—recent years have seen increased emphasis/focus on aging issues among vulnerable populations;[102]
  - Present research findings at conferences and workshops;
  - Leverage social media forums that provide an avenue to heighten awareness of research findings that are clinically applicable to a geriatric rheumatology population;
  - Partner with advocacy groups and patient stakeholders to make our clinical and research voices heard by the community;

As outlined in this article, there is a need to bridge fundamental gaps in our research and clinical knowledge to improve the care of older adults with rheumatologic diseases. We have an enormous responsibility and opportunity to develop and deliver age-appropriate relevant, effective and high-value clinical care that will improve outcomes in older adults with

rheumatologic disease. By heightening awareness of the intersection of aging with rheumatology we hope to inspire the next generation of investigators and clinicians to approach their careers and patient care with a commitment to aging.

References

1. Bureau UC; Commerce UDo, editor. The Next Four Decades: The Older Population in the United States: 2010 to 2050. https://https://www.census.gov/prod/2010pubs/p25-1138.pdf2010:P25-1138
2. 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. [PubMed: 18163497]
3. Loeser RF. Age-related changes in the musculoskeletal system and the development of osteoarthritis. Clin Geriatr Med. 2010; 26:371–86. [PubMed: 20699160]
4. Crowson CS, Matteson EL, Myasoedova E, et al. The lifetime risk of adult-onset rheumatoid arthritis and other inflammatory autoimmune rheumatic diseases. Arthritis Rheum. 2011; 63:633–9. [PubMed: 21360492]
5. Arnaud L, Mathian A, Boddaert J, Amoura Z. Late-onset systemic lupus erythematosus: epidemiology, diagnosis and treatment. Drugs & aging. 2012; 29:181–9. [PubMed: 22263748]
6. Boddaert J, Huong DL, Amoura Z, Wechsler B, Godeau P, Piette JC. Late-onset systemic lupus erythematosus: a personal series of 47 patients and pooled analysis of 714 cases in the literature. Medicine (Baltimore). 2004; 83:348–59. [PubMed: 15525847]
7. Lalani S, Pope J, de Leon F, Peschken C. Members of Ca NFoL. Clinical features and prognosis of late-onset systemic lupus erythematosus: results from the 1000 faces of lupus study. J Rheumatol. 2010; 37:38–44. [PubMed: 20008925]
8. Mohan SV, Liao YJ, Kim JW, Goronzy JJ, Weyand CM. Giant cell arteritis: immune and vascular aging as disease risk factors. Arthritis Res Ther. 2011; 13:231. [PubMed: 21861860]
9. Kennedy BK, Berger SL, Brunet A, et al. Geroscience: linking aging to chronic disease. Cell. 2014; 159:709–13. [PubMed: 25417146]
10. Rogers WH, Kazis LE, Miller DR, et al. Comparing the health status of VA and non-VA ambulatory patients: the veterans' health and medical outcomes studies. The Journal of ambulatory care management. 2004; 27:249–62. [PubMed: 15287215]
11. Reid MC, Bennett DA, Chen WG, et al. Improving the pharmacologic management of pain in older adults: identifying the research gaps and methods to address them. Pain Med. 2011; 12:1336–57. [PubMed: 21834914]
12. Tinetti ME, Fried TR, Boyd CM. Designing health care for the most common chronic condition--multimorbidity. JAMA. 2012; 307:2493–4. [PubMed: 22797447]
13. Michet CJ Jr, Evans JM, Fleming KC, O'Duffy JD, Jurisson ML, Hunder GG. Common rheumatologic diseases in elderly patients. Mayo Clinic proceedings. 1995; 70:1205–14. [PubMed: 7490924]
14. Boots AM, Maier AB, Stinissen P, Masson P, Lories RJ, De Keyser F. The influence of ageing on the development and management of rheumatoid arthritis. Nat Rev Rheumatol. 2013; 9:604–13. [PubMed: 23774902]
15. Epel ES, Lithgow GJ. Stress biology and aging mechanisms: toward understanding the deep connection between adaptation to stress and longevity. J Gerontol A Biol Sci Med Sci. 2014; 69(Suppl 1):S10–6. [PubMed: 24833580]
16. Lithgow, GMR. Determination of aging rate by coordinated resistance to multiple forms of stress. In: Guarente, LPL.; Wallace, DC., editors. Molecular Biology of Aging. New York, NY: Cold Spring Harbor Laboratory Press; 2008. p. 427-81.
17. Blackburn EH, Epel ES. Telomeres and adversity: Too toxic to ignore. Nature. 2012; 490:169–71. [PubMed: 23060172]
18. Price JD, Beauchamp NM, Rahir G, et al. CD8+ dendritic cell-mediated tolerance of autoreactive CD4+ T cells is deficient in NOD mice and can be corrected by blocking CD40L. Journal of leukocyte biology. 2014; 95:325–36. [PubMed: 24082013]

19. Price JS, Waters JG, Darrah C, et al. The role of chondrocyte senescence in osteoarthritis. Aging cell. 2002; 1:57–65. [PubMed: 12882354]
20. Zhai G, Aviv A, Hunter DJ, et al. Reduction of leucocyte telomere length in radiographic hand osteoarthritis: a population-based study. Ann Rheum Dis. 2006; 65:1444–8. [PubMed: 17038452]
21. Brunet A, Berger SL. Epigenetics of aging and aging-related disease. J Gerontol A Biol Sci Med Sci. 2014; 69(Suppl 1):S17–20. [PubMed: 24833581]
22. Gay S, Wilson AG. The emerging role of epigenetics in rheumatic diseases. Rheumatology (Oxford). 2014; 53:406–14. [PubMed: 24026248]
23. Tserel L, Kolde R, Limbach M, et al. Age-related profiling of DNA methylation in CD8+ T cells reveals changes in immune response and transcriptional regulator genes. Sci Rep. 2015; 5:13107. [PubMed: 26286994]
24. Gray SG. Perspectives on epigenetic-based immune intervention for rheumatic diseases. Arthritis Res Ther. 2013; 15:207. [PubMed: 23510070]
25. Franceschi C, Bonafe M, Valensin S, et al. Inflamm-aging. An evolutionary perspective on immunosenescence. Annals of the New York Academy of Sciences. 2000; 908:244–54. [PubMed: 10911963]
26. Freund A, Orjalo AV, Desprez PY, Campisi J. Inflammatory networks during cellular senescence: causes and consequences. Trends Mol Med. 2010; 16:238–46. [PubMed: 20444648]
27. Cohen HJ, Pieper CF, Harris T, Rao KM, Currie MS. The association of plasma IL-6 levels with functional disability in community-dwelling elderly. J Gerontol A Biol Sci Med Sci. 1997; 52:M201–8. [PubMed: 9224431]
28. Wei J, Xu H, Davies JL, Hemmings GP. Increase of plasma IL-6 concentration with age in healthy subjects. Life sciences. 1992; 51:1953–6. [PubMed: 1453878]
29. Hager K, Machein U, Krieger S, Platt D, Seefried G, Bauer J. Interleukin-6 and selected plasma proteins in healthy persons of different ages. Neurobiol Aging. 1994; 15:771–2. [PubMed: 7534383]
30. Hayflick L, Moorhead PS. The serial cultivation of human diploid cell strains. Experimental cell research. 1961; 25:585–621. [PubMed: 13905658]
31. Coppe JP, Patil CK, Rodier F, et al. Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. PLoS biology. 2008; 6:2853–68. [PubMed: 19053174]
32. Caplanne D, Le Parc JM, Alexandre JA. Interleukin-6 in clinical relapses of polymyalgia rheumatica and giant cell arteritis. Ann Rheum Dis. 1996; 55:403–4.
33. Alvarez-Rodriguez L, Lopez-Hoyos M, Mata C, et al. Circulating cytokines in active polymyalgia rheumatica. Ann Rheum Dis. 2010; 69:263–9. [PubMed: 19254903]
34. Roche NE, Fulbright JW, Wagner AD, Hunder GG, Goronzy JJ, Weyand CM. Correlation of interleukin-6 production and disease activity in polymyalgia rheumatica and giant cell arteritis. Arthritis Rheum. 1993; 36:1286–94. [PubMed: 8216422]
35. Weyand CM, Yang Z, Goronzy JJ. T-cell aging in rheumatoid arthritis. Current opinion in rheumatology. 2014; 26:93–100. [PubMed: 24296720]
36. Loeser RF. Aging and osteoarthritis: the role of chondrocyte senescence and aging changes in the cartilage matrix. Osteoarthritis and cartilage/OARS, Osteoarthritis Research Society. 2009; 17:971–9.
37. Zhu Y, Tchkonia T, Pirtskhalava T, et al. The Achilles' heel of senescent cells: from transcriptome to senolytic drugs. Aging cell. 2015; 14:644–58. [PubMed: 25754370]
38. Harman D. Aging: a theory based on free radical and radiation chemistry. J Gerontol. 1956; 11:298–300. [PubMed: 13332224]
39. Kirkwood TB. Understanding the odd science of aging. Cell. 2005; 120:437–47. [PubMed: 15734677]
40. Richardson AG, Schadt EE. The role of macromolecular damage in aging and age-related disease. J Gerontol A Biol Sci Med Sci. 2014; 69(Suppl 1):S28–32. [PubMed: 24833583]
41. Bokov A, Chaudhuri A, Richardson A. The role of oxidative damage and stress in aging. Mech Ageing Dev. 2004; 125:811–26. [PubMed: 15541775]

42. Jacob KD, Noren Hooten N, Trzeciak AR, Evans MK. Markers of oxidant stress that are clinically relevant in aging and age-related disease. Mech Ageing Dev. 2013; 134:139–57. [PubMed: 23428415]
43. Humphreys V, Martin RM, Ratcliffe B, et al. Age-related increases in DNA repair and antioxidant protection: a comparison of the Boyd Orr Cohort of elderly subjects with a younger population sample. Age and ageing. 2007; 36:521–6. [PubMed: 17913757]
44. Trzeciak AR, Mohanty JG, Jacob KD, et al. Oxidative damage to DNA and single strand break repair capacity: relationship to other measures of oxidative stress in a population cohort. Mutation research. 2012; 736:93–103. [PubMed: 22273780]
45. Montine TJ, Peskind ER, Quinn JF, Wilson AM, Montine KS, Galasko D. Increased cerebrospinal fluid F2-isoprostanes are associated with aging and latent Alzheimer's disease as identified by biomarkers. Neuromolecular medicine. 2011; 13:37–43. [PubMed: 20632131]
46. Lovell MA, Gabbita SP, Markesbery WR. Increased DNA oxidation and decreased levels of repair products in Alzheimer's disease ventricular CSF. Journal of neurochemistry. 1999; 72:771–6. [PubMed: 9930752]
47. Kedziora-Kornatowska K, Czuczejko J, Pawluk H, et al. The markers of oxidative stress and activity of the antioxidant system in the blood of elderly patients with essential arterial hypertension. Cell Mol Biol Lett. 2004; 9:635–41. [PubMed: 15647786]
48. Demirbag R, Yilmaz R, Gur M, et al. Lymphocyte DNA damage in patients with acute coronary syndrome and its relationship with severity of acute coronary syndrome. Mutation research. 2005; 578:298–307. [PubMed: 15985271]
49. Muller WU, Bauch T, Stuben G, Sack H, Streffer C. Radiation sensitivity of lymphocytes from healthy individuals and cancer patients as measured by the comet assay. Radiat Environ Biophys. 2001; 40:83–9. [PubMed: 11357715]
50. Miller FW, Alfredsson L, Costenbader KH, et al. Epidemiology of environmental exposures and human autoimmune diseases: findings from a National Institute of Environmental Health Sciences Expert Panel Workshop. J Autoimmun. 2012; 39:259–71. [PubMed: 22739348]
51. Sanz-Cameno P, Medina J, Garcia-Buey L, et al. Enhanced intrahepatic inducible nitric oxide synthase expression and nitrotyrosine accumulation in primary biliary cirrhosis and autoimmune hepatitis. Journal of hepatology. 2002; 37:723–9. [PubMed: 12445411]
52. Perl A. Oxidative stress in the pathology and treatment of systemic lupus erythematosus. Nat Rev Rheumatol. 2013; 9:674–86. [PubMed: 24100461]
53. Altindag O, Karakoc M, Kocyigit A, Celik H, Soran N. Increased DNA damage and oxidative stress in patients with rheumatoid arthritis. Clin Biochem. 2007; 40:167–71. [PubMed: 17196579]
54. Inoki K, Kim J, Guan KL. AMPK and mTOR in cellular energy homeostasis and drug targets. Annu Rev Pharmacol Toxicol. 2012; 52:381–400. [PubMed: 22017684]
55. Scarpello JH. Improving survival with metformin: the evidence base today. Diabetes Metab. 2003; 29(6):S36–43.
56. Macintyre AN, Gerriets VA, Nichols AG, et al. The glucose transporter Glut1 is selectively essential for CD4 T cell activation and effector function. Cell Metab. 2014; 20:61–72. [PubMed: 24930970]
57. Kaushik S, Cuervo AM. Proteostasis and aging. Nature medicine. 2015; 21:1406–15.
58. Liu-Bryan R, Terkeltaub R. Emerging regulators of the inflammatory process in osteoarthritis. Nat Rev Rheumatol. 2015; 11:35–44. [PubMed: 25266449]
59. Mastrangelo A, Colasanti T, Barbati C, et al. The Role of Posttranslational Protein Modifications in Rheumatological Diseases: Focus on Rheumatoid Arthritis. J Immunol Res. 2015; 2015:712490. [PubMed: 26090496]
60. Conboy IM, Rando TA. Aging, stem cells and tissue regeneration: lessons from muscle. Cell Cycle. 2005; 4:407–10. [PubMed: 15725724]
61. Jones EA, Crawford A, English A, et al. Synovial fluid mesenchymal stem cells in health and early osteoarthritis: detection and functional evaluation at the single-cell level. Arthritis Rheum. 2008; 58:1731–40. [PubMed: 18512779]

62. de Sousa EB, Casado PL, Moura Neto V, Duarte ME, Aguiar DP. Synovial fluid and synovial membrane mesenchymal stem cells: latest discoveries and therapeutic perspectives. Stem Cell Res Ther. 2014; 5:112. [PubMed: 25688673]
63. Mor V, Laliberte L, Morris JN, Wiemann M. The Karnofsky Performance Status Scale. An examination of its reliability and validity in a research setting. Cancer. 1984; 53:2002–7. [PubMed: 6704925]
64. Pal SK, Katheria V, Hurria A. Evaluating the older patient with cancer: understanding frailty and the geriatric assessment. CA Cancer J Clin. 2010; 60:120–32. [PubMed: 20173172]
65. O'Connor CM, Whellan DJ, Wojdyla D, et al. Factors related to morbidity and mortality in patients with chronic heart failure with systolic dysfunction: the HF-ACTION predictive risk score model. Circ Heart Fail. 2012; 5:63–71. [PubMed: 22114101]
66. Povsic TJ, Broderick S, Anstrom KJ, et al. Predictors of long-term clinical endpoints in patients with refractory angina. Journal of the American Heart Association. 2015; 4
67. Strough J, de Bruin WB, Peters E. New perspectives for motivating better decisions in older adults. Front Psychol. 2015; 6:783. [PubMed: 26157398]
68. Lockenhoff CE, Carstensen LL. Aging, emotion, and health-related decision strategies: motivational manipulations can reduce age differences. Psychol Aging. 2007; 22:134–46. [PubMed: 17385990]
69. Lockenhoff CE, Carstensen LL. Decision strategies in health care choices for self and others: older but not younger adults make adjustments for the age of the decision target. The journals of gerontology Series B, Psychological sciences and social sciences. 2008; 63:P106–9.
70. Charles ST, Carstensen LL. Social and emotional aging. Annu Rev Psychol. 2010; 61:383–409. [PubMed: 19575618]
71. Reuben DB, Tinetti ME. Goal-oriented patient care--an alternative health outcomes paradigm. N Engl J Med. 2012; 366:777–9. [PubMed: 22375966]
72. Bynum JP, Barre L, Reed C, Passow H. Participation of very old adults in health care decisions. Medical decision making: an international journal of the Society for Medical Decision Making. 2014; 34:216–30. [PubMed: 24106235]
73. Makris UE, Melhado T, Lee SC, et al. Illness representations of restricting back pain: the older Person's perspective. Pain Med. 2014; 15:938–46. [PubMed: 25075398]
74. Gatchel RJ, McGeary DD, McGeary CA, Lippe B. Interdisciplinary chronic pain management: past, present, and future. The American psychologist. 2014; 69:119–30. [PubMed: 24547798]
75. Makris UE, Abrams RC, Gurland B, Reid MC. Management of persistent pain in the older patient: a clinical review. JAMA. 2014; 312:825–36. [PubMed: 25157726]
76. Fraenkel L, Falzer P, Fried T, et al. Measuring pain impact versus pain severity using a numeric rating scale. J Gen Intern Med. 2012; 27:555–60. [PubMed: 22081365]
77. Amtmann D, Cook KF, Jensen MP, et al. Development of a PROMIS item bank to measure pain interference. Pain. 2010; 150:173–82. [PubMed: 20554116]
78. Cella D, Riley W, Stone A, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005–2008. J Clin Epidemiol. 2010; 63:1179–94. [PubMed: 20685078]
79. Cella D, Yount S, Rothrock N, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS): progress of an NIH Roadmap cooperative group during its first two years. Medical care. 2007; 45:S3–S11.
80. Deyo RA, Ramsey K, Buckley DI, et al. Performance of a Patient Reported Outcomes Measurement Information System (PROMIS) Short Form in Older Adults with Chronic Musculoskeletal Pain. Pain Med. 2015
81. Hadjistavropoulos T, Herr K, Turk DC, et al. An interdisciplinary expert consensus statement on assessment of pain in older persons. Clin J Pain. 2007; 23:S1–43. [PubMed: 17179836]
82. Cole LJ, Farrell MJ, Duff EP, Barber JB, Egan GF, Gibson SJ. Pain sensitivity and fMRI pain-related brain activity in Alzheimer's disease. Brain: a journal of neurology. 2006; 129:2957–65. [PubMed: 16951408]
83. Gibson SJ, Helme RD. Age-related differences in pain perception and report. Clin Geriatr Med. 2001; 17:433–56. v–vi. [PubMed: 11459714]

84. Feldt KS, Ryden MB, Miles S. Treatment of pain in cognitively impaired compared with cognitively intact older patients with hip-fracture. J Am Geriatr Soc. 1998; 46:1079–85. [PubMed: 9736099]
85. Nygaard HA, Jarland M. Are nursing home patients with dementia diagnosis at increased risk for inadequate pain treatment? International journal of geriatric psychiatry. 2005; 20:730–7. [PubMed: 16035124]
86. Morrison RS, Siu AL. A comparison of pain and its treatment in advanced dementia and cognitively intact patients with hip fracture. Journal of pain and symptom management. 2000; 19:240–8. [PubMed: 10799790]
87. Pautex S, Herrmann FR, Michon A, Giannakopoulos P, Gold G. Psychometric properties of the Doloplus-2 observational pain assessment scale and comparison to self-assessment in hospitalized elderly. Clin J Pain. 2007; 23:774–9. [PubMed: 18075404]
88. Fuchs-Lacelle S, Hadjistavropoulos T. Development and preliminary validation of the pain assessment checklist for seniors with limited ability to communicate (PACSLAC). Pain Manag Nurs. 2004; 5:37–49. [PubMed: 14999652]
89. Lints-Martindale AC, Hadjistavropoulos T, Barber B, Gibson SJ. A psychophysical investigation of the facial action coding system as an index of pain variability among older adults with and without Alzheimer's disease. Pain Med. 2007; 8:678–89. [PubMed: 18028046]
90. Zwakhalen SM, Hamers JP, Abu-Saad HH, Berger MP. Pain in elderly people with severe dementia: a systematic review of behavioural pain assessment tools. BMC geriatrics. 2006; 6:3. [PubMed: 16441889]
91. Kievit W, van Hulst L, van Riel P, Fraenkel L. Factors that influence rheumatologists' decisions to escalate care in rheumatoid arthritis: results from a choice-based conjoint analysis. Arthritis care & research. 2010; 62:842–7. [PubMed: 20535795]
92. Goodwin K, Viboud C, Simonsen L. Antibody response to influenza vaccination in the elderly: a quantitative review. Vaccine. 2006; 24:1159–69. [PubMed: 16213065]
93. DiazGranados CA, Dunning AJ, Kimmel M, et al. Efficacy of high-dose versus standard-dose influenza vaccine in older adults. N Engl J Med. 2014; 371:635–45. [PubMed: 25119609]
94. O'Connor KM, Paauw DS. Herpes zoster. Med Clin North Am. 2013; 97:503–22. ix. [PubMed: 23809711]
95. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis care & research. 2016; 68:1–25. [PubMed: 26545825]
96. Yun H, Yang S, Chen L, et al. Risk of Herpes Zoster in Auto-immune and Inflammatory diseases: Implications for Vaccination. Arthritis Rheumatol. 2016
97. Papadopoulou D, Sipsas NV. Comparison of national clinical practice guidelines and recommendations on vaccination of adult patients with autoimmune rheumatic diseases. Rheumatology international. 2014; 34:151–63. [PubMed: 24322451]
98. Hafner K. As Population Ages, Where Are the Geriatricians? New York Times 2016. Jan 25.2016
99. Malfait AM, Little CB. On the predictive utility of animal models of osteoarthritis. Arthritis Res Ther. 2015; 17:225. [PubMed: 26364707]
100. Fraenkel L, Miller AS, Clayton K, et al. When Patients Write the Guidelines: Patient Panel Recommendations for the Treatment of Rheumatoid Arthritis. Arthritis care & research. 2016; 68:26–35. [PubMed: 26545701]
101. Ogdie A, Shah AA, Makris UE, et al. Barriers to and Facilitators of a Career as a Physician-Scientist Among Rheumatologists in the US. Arthritis care & research. 2015; 67:1191–201. [PubMed: 25708626]
102. Pruchno R. Veterans Aging. Gerontologist. 2016; 56:1–4. [PubMed: 26767775]

Key Points

- The incidence and prevalence of rheumatologic diseases (including osteoarthritis, rheumatoid arthritis, systemic lupus erythematosus, polymyalgia rheumatica) is increasing and the Rheumatology workforce must be aware of aging-specific issues.
- Understanding the biology of aging and aging-related mechanisms that underlie rheumatologic diseases may help identify treatment targets and improve outcomes for older adults.
- Older adults pose unique challenges to the assessment and management of rheumatologic disease as this population often suffers from multimorbidity, polypharmacy, frailty, cognitive impairment, and fragmented social support systems.
- An effective approach to older adults with rheumatologic conditions will require a better understanding of the mechanisms underlying the disease, time horizons and expectations of the patient, and outcomes that are mutually relevant to patient and provider.
- Training rheumatologists in principles of geriatric medicine, and geriatricians in musculoskeletal health as it applies to an aging population will be critical.