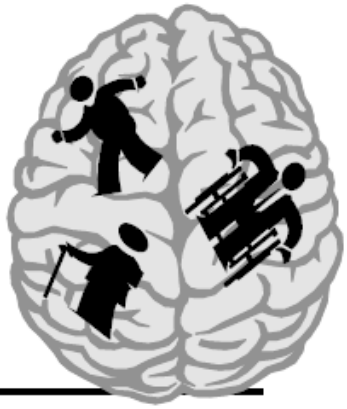
Degenerative Diseases



Fall 2008 Volume 8 Issue 1

Newsletter of the Degenerative Diseases Special Interest Group
Neurology Section, APTA

A Message from the Chairperson

Hello to all DDSIG members! It is with great honor and pleasure that I begin my new position as DDSIG Chair. I would first like to extend my sincere thanks to the previous DDSIG Chair Herb Karpatkin and Nominating Committee Chair Cathy Curtis for their dedication and superb contributions to the SIG. I also want to extend a warm welcome and CONGRATULATIONS! to Kirk Personius who was elected to the DDSIG Nominating Committee. As we join with other DDSIG Executive Committee members Donna Fry (Vice Chair), Robbin Howard (Secretary), Evan Cohen (Nominating Committee Chair and Newsletter Editor) and Daniel White (Nominating Committee), I anticipate an exciting and productive year ahead for our SIG.

I hope that you will enjoy reading the articles in this newsletter. The article entitled "Toolbox of Outcome Measures for Individuals with ALS" gives an overview of evidence-based assessments that physical therapists can use when evaluating their patients with ALS. This article is the first of a series of "toolbox" articles highlighting each of the major neurodegenerative diseases (Parkinson disease, multiple sclerosis, and Huntington's disease) that will appear in the next three DDSIG newsletters. Deb Kegelmeyer has written a very interesting and informative article entitled "Beneficial Effects of Exercise in Individuals with Dementia and Alzheimer's Disease" that reviews

Continued on page 8

Table of Contents

DD SIG Officers

Combined Sections Meeting 2008
Nashville, Tennessee

DDSIG Programming at CSM 2008

It was another banner year at CSM for the DDSIG programming. DDSIG Vice-Chair, Donna Fry, PT, PhD, and Toni Chiara, PT, PhD gave an excellent presentation on "Respiratory Muscle Training in Individuals with Multiple Sclerosis – An Evidence-Based Approach". This dynamic and informative presentation included the discussion of how to assess respiratory muscle function and develop pulmonary exercise programs for individuals with MS based on research that they and others have conducted.

The DDSIG Roundtable was hosted by DDSIG Nominating Committee Chair Evan Cohen, PT, MA, NCS. "Management of the Complex Patient with a Degenerative Neurologic Condition" drew a diverse crowd of participants from within and outside the Neurology Section.

Combined Sections Meeting 2008
Las Vegas, Nevada

DDSIG Programming at CSM 2009

We are looking forward to another year of excellent programming at CSM 2009. Be sure to plan to attend the following presentations:

- "Use of Clinical Decision Making Frameworks to Guide Examination and Intervention with Neurodegenerative Disease: A Presentation of Selected Cases" by DDSIG Secretary Robbin Howard, PT, DPT, NCS and Julie Hershberg, DPT, NCS.

- "Dimensions of Care for People with Neurological Terminal Illness: A Roundtable Discussion" led by Rich Briggs, PT, MA, Chair of the Oncology Section's Hospice and Palliative Care SIG and Evan Cohen, PT, MA, NCS.

TOOLBOX OF OUTCOME MEASURES FOR INDIVIDUALS WITH ALS

by Anne Kloos, PT, PhD, NCS
Associate Clinical Professor, The Ohio State University

Amyotrophic lateral sclerosis is a devastating neurodegenerative disease that affects approximately 30,000 individuals in the United States. Destruction of motor neurons in the cerebral cortex, brainstem, and spinal cord results in progressive muscle weakness and atrophy that ultimately leads to an inability to perform activities of daily living (ADLs) and participate in community, social, and civic life. Due to the variety and various combinations of regions affected in ALS, physical therapists must conduct a careful and comprehensive examination of each patient to determine the extent of their impairments, and how those impairments are related to their activity limitations and participation restrictions. Re-examination at regular intervals using evidence-based outcome measures is necessary to determine the extent and rate of progression of the disease and the need for therapeutic interventions.

Therapists may consult the section in the *Guide to Physical Therapist Practice* on Practice Pattern 5E for guidelines regarding the examination of patients with ALS.[1] According to the Guide, a comprehensive initial assessment is composed of the patient history, a systems review, and tests and measures. Table 1 contains a toolbox of tests and measures that can be used to assess and evaluate an individual with ALS. Therapists can refer to the World Federation of Neurology's *Guidelines for the Use and Performance of Quantitative Outcome Measures in ALS Clinical Trials* for a more detailed description of the standard test and measures used in clinical trials.[2] When selecting assessments, therapists should take into account the patient's goals and individual characteristics such as the extent and area of involvement, rate of disease progression, and stage of the disease. It is important to include participation tests and measures (e.g., environmental barriers, quality of life measures) as they may be more positively impacted by physical therapy interventions than impairment and activity level measures due to the progressive nature of the disease. Specific tests and measures may include:

- *Aerobic Capacity and Endurance*. Fatigue is a common complaint in individuals with ALS and may be caused by a variety of factors including motor neuron loss, depression, poor pulmonary function, and poor quality of sleep. Abnormal physiologic and metabolic responses to aerobic exercise tests have been reported in individuals with ALS.[3]
- *Anthropometric Characteristics*. Edema may be present in the distal limbs due to a lack of muscle pumping action in severely weakened limbs.
- *Arousal, Attention, and Cognition*. While most individuals with ALS do not exhibit significant cognitive deficits, a small subgroup of patients exhibit symptoms of frontotemporal dementia. Flaherty-Craig et al. recently proposed a 20-minute cognitive screening evaluation that identified frontal lobe dysfunction (i.e., verbal fluency, abstract reasoning, and judgment) in individuals with ALS to a similar extent to that of more comprehensive assessments.[7] If cognitive screens are abnormal, referral for a neuropsychological evaluation may be indicated.
- *Assistive, Adaptive, Orthotic, Protective, and Support devices*. As upper and lower motor neuron symptoms progress, individuals with ALS will need to use a variety of assistive (e.g., canes, walkers, wheelchairs), adaptive (e.g., modified writing and eating utensils, key turners, remote controls, buttoners and zipper pulls) , orthotic (e.g., ankle-foot orthoses, splints), protective (e.g., braces, cushions), and supportive (e.g., neck collars, slings) devices and equipment to maintain mobility, perform activities of daily living, and prevent injury and pain.
- *Circulation*. Cardiovascular impairments affecting heart rate and blood pressure have been reported in individuals with ALS, particularly in advanced stages.[8]
- *Cranial Nerve Integrity*. Cranial nerve involvement in ALS leads to bulbar muscle impairments resulting in dysarthria, dysphagia, and sialorrhea. Patients with ALS should be referred to a nutritionist and speech language pathologist for more extensive evaluation of bulbar function.
- *Environmental, Home, and Work Barriers*. Due to the progressive nature of the disease, the patient's home and work environments need to be regularly reassessed for architectural and transportation barriers.
- *Ergonomics and Body Mechanics*. Ergonomics and good body mechanics are important for preventing injuries and excessive fatigue in weakened muscles. Caregivers should also be assessed in these areas when the patient requires physical assistance from them.
- *Gait, Locomotion, and Balance*. As symptoms of weakness and spasticity worsen, individuals with ALS experience increasing balance and gait problems that can result in falls. Low total Tinetti Balance Test scores, indicating impaired balance, were found to be moderately to strongly related to lower extremity muscle weakness and activity limitations in individuals with ALS,[13] and one study reported that the Tinetti Balance Test is a reliable measure for individuals in the early or early-middle stages of ALS.[14] A recent study found that Timed Up and GO (TUG) times increased linearly over 6 months, were negatively correlated with strength and functional measures, and predicted falls using a cutoff of 14 seconds in 31 patients with ALS.[15]
- *Integumentary Integrity*. Skin integrity is usually not a problem in patients with ALS since sensation is usually preserved. Regular skin inspection is recommended, particularly when the patient becomes immobile.

(Continued on page 4)

Outcome Measures in ALS — Continued from Page 3

- *Motor Function (Motor Learning and Motor Control)*. Dexterity, coordination, and motor control may be impaired by motor neuron loss and associated spasticity and muscle weakness. Hand and upper extremity function has been measured using the Purdue pegboard test in clinical trials.[16] This test is reliable and normal values are published.[17,18]

- *Muscle performance.* Progressive motor neuron loss in ALS leads to declines in muscle strength, power and endurance. Assessment of Maximum Voluntary Isometric Contraction (MVIC) using a strain gauge tensiometer system is considered to be the most direct technique for investigating motor unit loss, and has been used extensively in clinical trials.[19-22] Advantages of this method are that it produces highly reliable and sensitive data, accurately measures muscle strength in weak, as well as strong muscles, is relatively safe, and does not induce fatigue in the majority of patients.[2] Disadvantages are that MVIC testing requires specialized equipment and extensive training to use.[2] One study that compared test reliability of MMT and MVIC scores in patients with ALS when administered by uniformly trained physical therapists found that the tests had equal reproducibility.[23]

- *Pain*. Pain is a common complaint in patients with ALS and may have many different causes. It may arise directly from muscle strains, joint sprains, and acute injuries or secondarily from joint immobility, subluxations, or malalignments that may be due to underlying weakness and/or severe spasticity. Areas of the body that are most often affected by pain are the neck and back, and the shoulders.

- *Posture*. Progressive cervical and upper thoracic weakness in ALS can cause the head to drop forward. To compensate for the altered head position, some patients will adopt a lordotic posture during ambulation or a slouched posture during sitting.

- *Psychological Function*. Patients with ALS often experience fear, anxiety, and depression. The ALS Depression Inventory 12 (ADI-12) is a newly developed ALS-specific screening instrument for depression that excludes statements addressing activities that depend on an intact motor system.[24] Patients with ALS who test positive on depression and anxiety screens may need to be referred to a psychologist or psychiatrist for further evaluation.

- *Range of Motion (ROM)(Including Muscle Length).* Decreased ROM due to muscle weakness can result in muscle and tendon shortening (commonly in the Achilles tendon), joint contractures (commonly claw-hand deformity), joint subluxation and adhesive capsulitis (commonly in shoulders).

- *Reflex Integrity.* Assessment of deep tendon reflexes, pathological reflexes (e.g., Babinski's and Hoffman's reflexes), and muscle tone using the Modified Ashworth Scale[29] is necessary to determine the extent of upper motor neuron versus lower motor neuron involvement.

- *Self-Care and Home Management (Including ADL and IADL)*. The ALS Functional Rating Scale (ALSFRS)[30] and the revised version which includes additional respiratory items (ALSFRS-R),[31] are most often used in clinical trials to measure functional status and change in patients with ALS. The individual is asked to rate his/her function for the 10-12 items on a scale from 4 (normal function) to 0 (unable to attempt the task). Both scales have been found to be valid and reliable for measuring the decline in function that results from loss of muscular strength when administered in the clinic and via telephone interview, and to predict 9 month survival in individuals with ALS.[30-33] Basic and instrumental activities of daily living and the need for adaptive equipment may also be assessed by an occupational therapist.

- *Sensory Integrity.* While sensory pathways are usually spared in ALS, some patients may report sensory symptoms which may warrant a sensory evaluation.

- *Ventilation and Respiration.* Since respiratory failure is the major cause of death in ALS, respiratory status and function should be closely monitored. Patients may be referred to a pulmonologist for more extensive pulmonary function testing.

- *Work, Community, and Leisure Integration*. ALS-specific quality of life (QOL) measures include the ALS Assessment Questionnaire 40 (ALSAQ-40)[39] and a newly developed ALS-specific QOL instrument (ALSSQOL).[40] The ALSAQ-40 contains 40 items that assess five health domains: mobility, ADLs, eating and drinking, communication, and emotional functioning. The validity and reliability of the ALSAQ-40 and a shorter version of it, the ALSAQ-5, have been reported.[39,41,42] The ALSSQOL contains 59 items that assess psychological, support, existential, and spiritual domains, in addition to a physical domain. The test was found to have concurrent, convergent, and discriminant validity for the overall instrument and convergent validity for its subscales.[40]

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[Continued on Page 5]

Outcome Measures in ALS — Continued from Page 4

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[Continued on Page 6](#)

Outcome Measures in ALS — Continued from Page 5

Table 1: Toolbox of Outcome Measures for Individuals with Amyotrophic Lateral Sclerosis (ALS)*

Category	Test or Measure
Aerobic Capacity and Endurance	Aerobic capacity during functional activities, or during standardized exercise test (early stages) Cardiovascular and pulmonary signs and symptoms in response to exercise or increased activity Fatigue Severity Scale (FSS)[4] Multidimensional Fatigue Inventory (MFI)[5]
Anthropometric Characteristics	Girth measurements of extremities
Arousal, attention, and cognition	Ability to follow multistep commands Alert, oriented times 4 Mini Mental State Examination (MMSE)[6] Screen for frontal lobe dysfunction[7†]
Assistive, Adaptive, Orthotic, Protective, and Supportive Devices	Assessments of different devices and equipment used during functional activities including the safety during use, alignment, fit, and the patient's ability to care for the devices or equipment
Circulation	Blood pressure measurement Heart rate and rhythm
Cranial Nerve Integrity	Screen of cranial nerves V, VII, IX, X, and XII (III, IV, & VI affected in later stages) Assessment of oral motor function, phonation and speech production through interview and observation
Environmental, home and work barriers	Evaluation of patient's home and work environments for current and potential barriers, and access and safety issues
Ergonomics and Body Mechanics	Assessment of ergonomics and body mechanics during self-care, home management, work, community, or leisure activities (may include caregivers)
Gait, Locomotion, and Balance	Timed walk test[2] Tinetti Performance Oriented Mobility Assessment (POMA)[9†] Timed Up and Go (TUG) Test[10†] Berg Balance Scale (BBS)[11] Functional Reach Test (FRT)[12]
Integumentary Integrity	Skin inspection at contact points with devices and equipment and the sleeping surface
Motor Function (Motor Learning and Motor Control)	Observations of quality of movement during functional activities Standard coordination tests (e.g., finger-to-nose, heel to shin, rapid alternating movements, finger opposition tests) Purdue pegboard test[16]
Muscle Performance (Strength, Power, and Endurance)	Maximum Voluntary Isometric Contraction (MVIC) using a strain gauge tensiometer system[2] Manual muscle testing (MMT) Isokinetic muscle strength testing Hand-held dynamometry
Pain	Pain numerical rating scale Pain visual analog scale (VAS)
Posture	Assessment of spinal alignment, particularly cervical and upper thoracic posture

Continued on Page 7

Table 1—Continued

Category	Test or Measure
Psychological Function	ALS Depression Inventory 12 (ADI-12)[24†] Beck Depression Inventory (BDI)[25] Center of Epidemiologic Study-Depression Scale (CES-D)[26] Hospital Anxiety and Depression Scale (HADS)[27] Spielberger State-Trait Anxiety Inventory (STAI)[28]
Range of Motion (ROM)	Goniometry End feel assessment Multisegment flexibility tests
Reflex Integrity	Deep tendon reflexes Pathological reflexes Modified Ashworth Scale[27]
Self-Care and Home Management	ALS Functional Rating Scale (ALSFRS) [30†] ALS Functional Rating Scale-Revised (ALSFRS-R) [31†] Appel ALS Scale (AALS) [34] ALS Severity Scale (ALSSS) [35] Norris Scale[36] Functional Independence Measure (FIM™) [37] Schwab and England Scale[38]
Sensory Integrity	Sensory testing
Ventilation and Respiration/ Gas Exchange	Respiratory rate, rhythm, and pattern Auscultation of breath sounds Cough effectiveness testing Vital capacity (VC) testing or Forced vital capacity (FVC) testing
Work, Community, and Leisure Integration	ALS Assessment Questionnaire 40 (ALSAQ-40) [39†] ALS-Specific Quality of Life (ALSSQOL) [40†] SF-36 Health Survey[43] Schedule for Evaluation of Individual Quality of Life-Direct Weighting (SEIQoL-DW) [44] Sickness Impact Profile (SIP) [45]

*All named instruments have been used in ALS clinical trials; †reliability and/or validity of the instrument has been studied in individuals with ALS (see text for specifics)

Contribute to your DDSIG!

Do you have any resources to share with our SIG? Home exercise materials, videos, books or even ideas for others to follow up with would help to advance our SIG and help our patients to achieve their goals!

Do you have ideas for a case study or a research project involving degenerative diseases? Contact us and we may be able to point you in the right direction regarding collaborators or other ideas!

Interested in contributing an article to the DDSIG Newsletter? Contact us and let us know what you are interested in writing!

Call for Nominations

THE DD SIG WANTS YOU!

The Degenerative Diseases Special Interest Group is seeking nominations for two positions for the coming year: Secretary and Nominating Committee Member.

If you are interested, or know someone who is, please contact a member of the Nominating Committee

Message from the Chair—continued from Page 1

some recent animal and human studies showing the beneficial effects of exercise on cognitive functions.

This year has been a great year for DD programming at APTA conferences! We started the year with well-received programming at CSM 2008 in Nashville. A big thank you goes out to Vanina Dal Bello-Haas, Ed Gappmaier, Donna Fry, Toni Chiara, and Evan Cohen for their outstanding presentations! Vanina also organized an awesome three-day continuing education series on degenerative diseases that was very well attended last summer at the 2008 APTA Annual Conference & Exposition in San Antonio. Looking ahead, the DDSIG has plans to offer more great programming at CSM 2009 in Las Vegas. Plan ahead to attend the DDSIG business meeting to hear a presentation by Robbin Howard and Julie Hershberg on "Use of Clinical Decision Making Frameworks to Guide Examination and Intervention with Neurodegenerative Disease: A Presentation of Selected Cases". Evan Cohen (DDSIG) and Richard Briggs (Hospice/Palliative Care SIG) will also be leading a roundtable discussion on "End of Life Care".

We continue to strive to provide our members with degenerative disease-related updates and resource materials and welcome all input from members as to how we can best serve your needs. To that end, one of our goals this year is to update the DDSIG website to provide additional information and resources for our members. All members are encouraged to become actively involved in the DDSIG by suggesting ideas for programming, providing resources for the website, writing articles for the newsletter, attending meetings, and running for offices. Working together we can build a strong DDSIG that will lead the future of physical therapy for individuals with degenerative diseases.

Enjoy the fall season and the rest of the year,

Anne

BENEFICIAL EFFECTS OF EXERCISE IN INDIVIDUALS WITH DEMENTIA AND ALZHEIMER'S DISEASE

by Deb Kegelmeyer PT, DPT, MS, GCS

Alzheimer's Disease (AD) is a neurodegenerative disorder that impacts 10% of those aged 65 and 47% of those 85 years old and older.[1-3] Most cases are sporadic (non-genetic) with only 5%-10% being familial.[2, 3] Treatment of AD rarely includes exercise but emerging evidence points to the potential benefits of early exercise to not only improve function and overall health but to also provide neuroprotective benefits. Understanding the pathogenesis of AD can help to better explain how exercise may be beneficial to both cognitive and physical function. Alzheimer's disease leads to neuronal death which initially is most pronounced in the hippocampus but spreads to encompass motor and sensory areas by the late stages of the disease.[2] It is well known that the brains of individuals with AD contain neuritic plaques containing b-amyloid and neurofibrillary tangles (NFTs), but these may be byproducts rather than mediators of AD pathogenesis.[4] Neurofibrillary tangles consist of a hyper-phosphorylated form of the protein tau and newer studies suggest that the mutant tau protein is the primary neurotoxic entity.[4] Once the neuritic plaque has formed, secondary cascades of inflammation, excitotoxicity and likely apoptosis mediate additional damage.[4] Exercise is most likely to impact this secondary cascade through its positive impact on angiogenesis, neurogenesis, formation of new dendrites, neural sprouting and increases in supporting structures like glia.[5]

Participation in regular aerobic exercise has been linked to improved cognitive function in healthy animals and adult humans.[5-10] In animal studies aerobic exercise produced neuroprotective effects, delayed b-amyloid accumulation, and improved cognitive function as measured by memory and learning tests.[5] Human studies reported that increased physical activity correlated with better cognitive function and less dementia.[6-8] Rosano et.al. found that there was a significant association (r = 0.19–0.32) between physical and cognitive function in well-functioning adults after adjustment for other factors such as education.[6] Prospective observational studies have provided evidence that physical activity in middle age reduces the risk of developing Alzheimer's disease or dementia in general and preserves cognitive function.[5] These studies indicate that those who exercise greater than 3 times per week are 34% less likely to develop dementia.[9] Older adults who exercise improve executive function and by extension exercise may also provide the same type of benefits to those with AD.[5]

Few studies have examined the effect of exercise on cognition in individuals with AD. One study found that subjects with moderate to severe AD (n=23) had significantly improved cognition (i.e., Mini-Mental Status scores) after participating in an aerobic exercise program utilizing either a walking program or stationary bicycle for a mean time of 7 weeks (range 5-12 weeks).[10] All subjects lived at home with a caregiver. In addition to cognition, significant improvements ($p<0.01$ - 0.001) were found in nutritional status (Mini Nutritional Assessment), behavioral problems (Neuropsychiatric Inventory) and risk of falls (Tinetti test). In contrast, there was no significant change in performances of basic and instrumental activities of daily living following exercise.

Although the majority of observational and randomized control studies in humans have reported a beneficial effect of exercise on cognition, certain factors may be important for the mediation of this effect (see review article by Kramer and Erickson).[8] Studies which demonstrated a positive association between exercise and prevention of cognitive decline all utilized aerobic exercise programs (i.e., walking, swimming, and bicycling), whereas some studies that found no association used non-aerobic exercise such as strengthening and/or range of motion exercises.[8] Therefore, the type of exercise chosen may determine whether or not the exercise will have a beneficial effect on cognitive function. Results of studies also differed depending on which cognitive domain was assessed. Studies with the largest positive results tended to assess executive functions (i.e., planning, scheduling, working memory, dealing with distraction and multi-tasking). Other cognitive domains may not undergo the same beneficial effects of exercise. It is also important to note that cognitive benefits were often achieved without significantly changing fitness level or leading to improvement in gait and balance function such as decreasing the number of falls. Thus, it appears that exercise-induced improvements in cognitive function are separate from changes in fitness or functional levels.

Newer studies are looking for evidence that exercise directly impacts brain function (see review article by Kramer et al.).[11] The use of functional magnetic resonance imaging (fMRI) has allowed researchers to examine changes in activation patterns and brain volume in response to exercise. One study demonstrated that aged adults who participated in a 6 month progressive walking program (3 times a week for 45 minutes) had brain activation patterns similar to young controls. Those who did a stretching and toning program had significantly different activation patterns than the young controls and the aerobically trained aged.[11, 15] Brain volume changes associated with exercise were studied in college students and two groups of aged individuals; one group performed 1 hour of walking 3 times a week and the other group did no aerobic exercise. The aged adults who did aerobic training demonstrated an increase in gray matter volume in the frontal and temporal cortex and in anterior white matter and improvements on cognitive testing (i.e., Flanker task, verbal learning and memory tests). Neither the college students nor the control subjects demonstrated any changes in brain volumes.[11, 15] These studies suggest that the benefits of exercise on cognitive function may be due to changes in brain morphology. Future studies are necessary to determine what impact exercise can have on disease processes like AD. Based on the

Continued on Page 10

neuroprotective effect of exercise on other neurodegenerative diseases like Parkinson disease,[12, 13] there is reason to believe it can also be neuroprotective in the face of AD.

The cardiovascular status of a person may affect whether exercise improves cognitive status. Studies suggest that some individuals with severe cardiovascular disease, particularly if it results in decreased cardiac output, respond to exercise by supplying blood to the muscle at the expense of the brain. These individuals may not have the cardiovascular reserve to increase blood flow and promote angiogenesis in response to exercise and instead might actually develop a worsening of their cognitive status.[14] There is some evidence that this scenario is possible, but in studies to date the majority of subjects demonstrated positive effects. Therapists should be aware of this possibility when considering prescribing exercise to maintain/improve cognition with individuals with severe cardiovascular disease.[14] In summary, we know that exercise and activity have positive effects on cognition with executive function being primarily impacted in both animal and human studies. There are few studies directly examining the effect of exercise on cognition in those with AD but benefits have been shown in animal models. It appears that aerobic exercise is key and based on studies of exercise in both healthy and diseased individuals there is likely a dose dependent response.

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Merci!
Danke!
Grazie!
Thanks!

The Leadership of the DDSIG would like to extend its gratitude to the outgoing members of the Executive Committee: Herb Karpatkin, PT, MS, MSCS, the outgoing DDSIG Chairperson, and Catherine Curtis, PT, EdD, the outgoing DDSIG Nominating Committee Chairperson.

Herb and Catherine, please accept our sincerest thanks for your service to the SIG and your profession. Your contributions will long be remembered. We hope that you will both continue your involvement with the DDSIG!

The DDSIG Leadership would like to extend it warmest welcome to the newly elected Leaders. Anne Kloos, PT, PhD returns to the DDSIG Leadership as the incoming Chairperson. Kirk Personius, PT, PhD was elected to the open position on the DDSIG Nominating Committee

Thanks are also due to Evan Cohen, PT, MA, NCS, who will assume the role of Nominating Committee Chairperson for the coming year.

Bienvenue!
Willkommen!
Benvenuto!
Welcome!

Degenerative Diseases

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