Developing a Standard of Care

for VCP disease / IBMPFD / MSP-1

Organizational Meeting

DECEMBER 2020

Today's Agenda:

1. Cure VCP Disease Overview – 5 minutes
2. Project Overview – 5 Minutes
3. Introductions – 10-15 Minutes
4. Domain and Current Research Discussion – 30 Minutes
5. Next Steps – 5 minutes

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CURE VCP DISEASE, INC.

Our Mission

- To bring together patients, clinicians and researchers to help accelerate treatments and therapies for VCP disease

Only patient advocacy organization for VCP disease / IBMPFD / MSP-1

Founded February 2018

Led by a seven-member Board of Directors and 3 member Medical Advisory Team

- No staff
- Volunteer led

Nathan and Allison Peck,
co-founders of Cure VCP Disease

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Cure VCP Disease Patient Community and Activities

2019 Patient Meeting

50+ in attendance

Monthly Educational Webinars

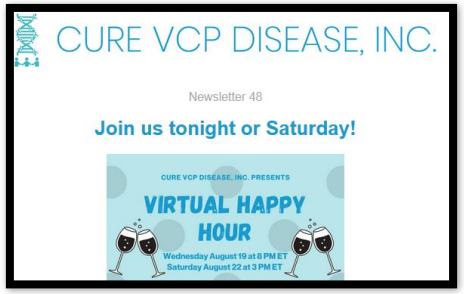
25-50 participating each month

International Patient Registry

70 Enrolled, 7 countries represented

Periodic Newsletter

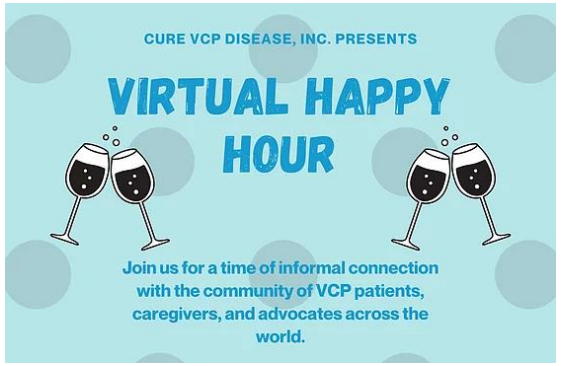
200 + subscribed



Social Media Presence

Monthly Patient Support Group

20+ participating each month



Website

500+ monthly visitors

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Project Need, Goal and Proposal

Need: Because this condition is ultra-rare with disparate phenotypes, patients will see a multitude of doctors, some of whom might only see one VCP patient. The diagnosis, treatment and management of each patient is dependent upon each provider's independent knowledge

Project: Establish a Standard of Care through Expert Consensus

Proposal:

1. Survey a multitude of clinicians
2. Divide the condition into different domains with an expert or experts for each domain
3. Hold a virtual meeting in the April 2021 timeframe where each expert presents (15-20 minutes per domain)
4. Publish results of meeting in a medical journal
5. Distribute and publicize the publication to patients and physicians through the Cure VCP Disease network.

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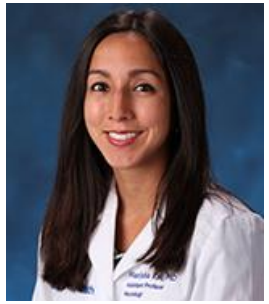
Current Standard of Care Leadership Team



Manisha K. Korb, MD – Assistant Professor at University of California-Irvine, Department of Neurology

http://www.ucihealth.org/find-a-doctor/k/manisha-korb

Tahseen Mozaffar, MD, PhD - Professor of Neurology and Orthopaedic Surgery, Director of UC Irvine-MDA ALS and Neuromuscular Center and Neuromuscular Program at University of California-Irvine, at School of Medicine

https://www.faculty.uci.edu/profile.cfm?faculty_id=4612

Virginia Kimonis, MD - Professor and Clinical Geneticist-Scientist at University of California-Irvine, Department of Pediatrics

http://www.ucirvinehealth.org/find-a-doctor/k/virginia-kimonis

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5739971/

Conrad (Chris) Weihl, MD, PhD - Professor of Neurology at Washington University School of Medicine in St. Louis

https://hopecenter.wustl.edu/?faculty=chris-weihl-md-phd

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4208462/

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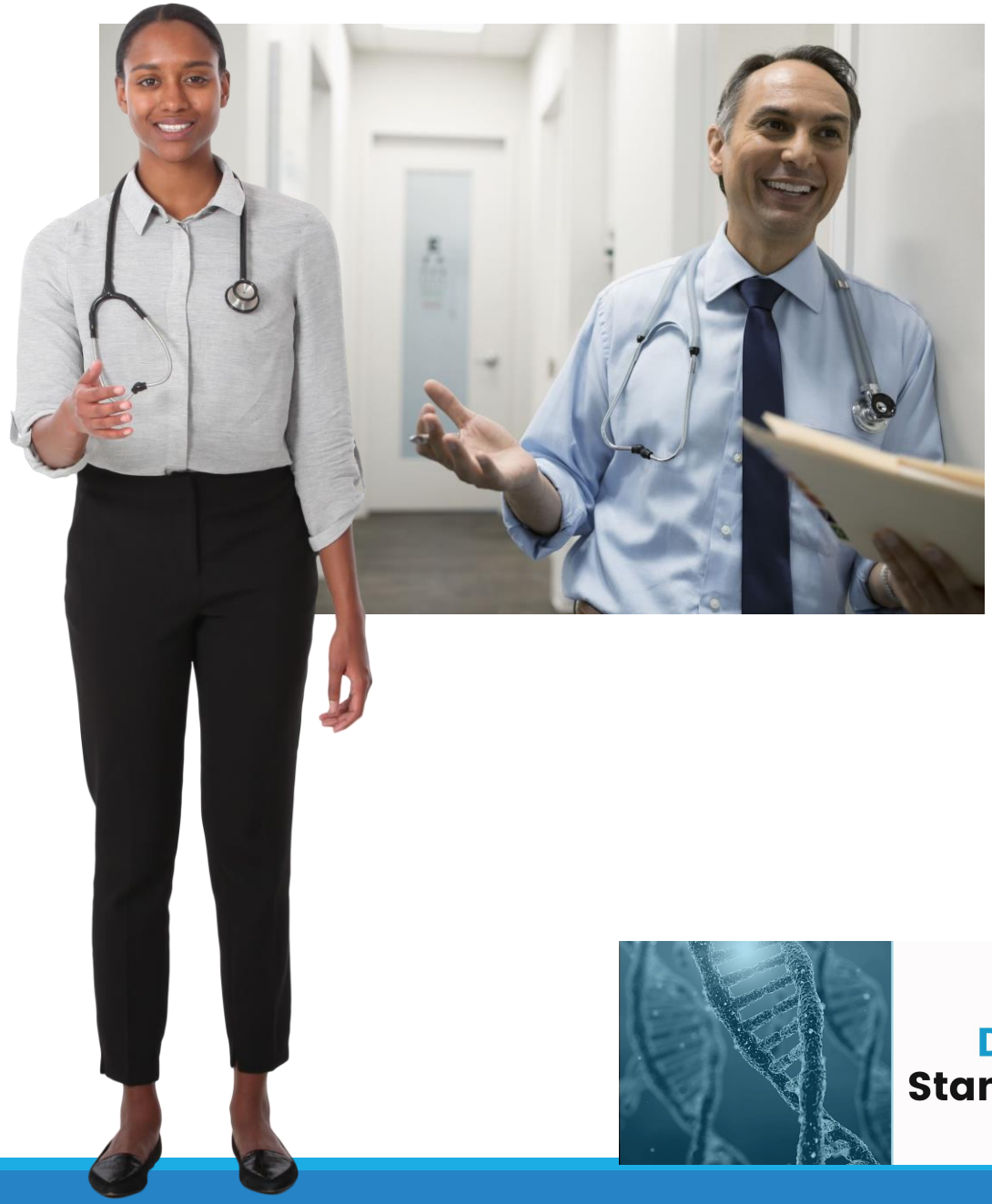
Brief Introductions

Name
Location
Clinic / Institution
Your Clinical Specialty

Challenge: Can we do this in less than 10 minutes?



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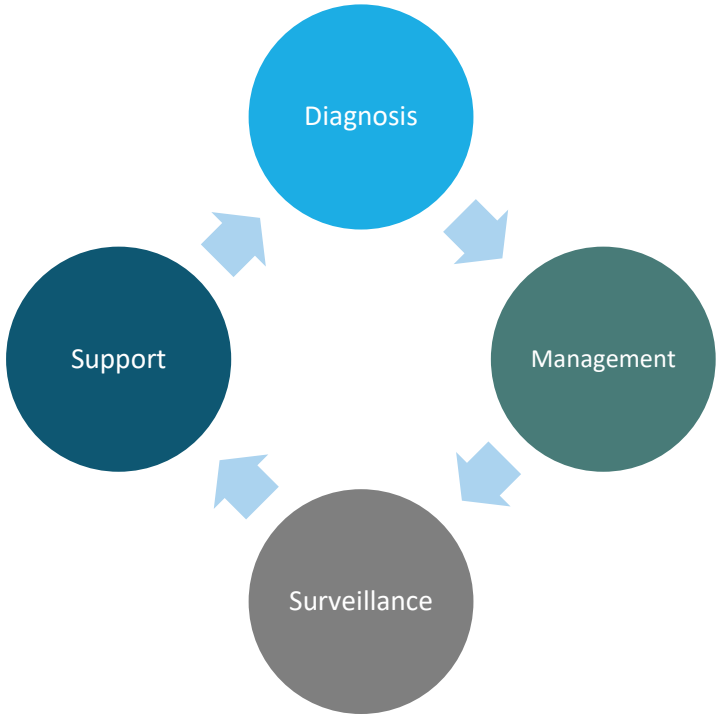
Domains for Project

Domain	Clinician	Domain	Clinician
1. Genetic Diagnosis		3. Motor Neuron	
a. How to Diagnose		a. ALS	
i. Genetics		b. Charcot Marie Tooth (CMT)	
ii. Muscle Biopsy		4. Paget's disease of the bone	
iii. Brain Imaging		5. Dementia	
b. Family Planning		6. Other Phenotypes	
2. Muscle		a. Parkinsonism	
a. Upper and Lower Extremity		b. GI Issues	
i. Disability Declaration		7. Nutrition	
ii. Assistive Devices		8. Supplements	
b. Respiratory Guide		9. Physical Therapy	
c. Cardiology		10. Occupational Therapy	
		11. Exercise	
		12. Social Support	



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VCP disease / IBMPFD / MSP Overview

- Early 2000s: Kimonis et al. described 5 families who had inclusion body myopathy, PDB, and frontotemporal dementia, thus naming the syndrome IBMPFD.
- Linkage analysis identified chromosome 9p13 missense mutations in the *VCP* gene (aka p97) as the pathogenic cause
- As early as 2002, other genes were identified in patients with similar clinical syndromes, which are now grouped into the category of Multisystem Proteinopathy (MSP).
- VCP mutations still comprise about half of all the mutations identified in MSP

Genetic Diagnosis

Diagnosis

Consider testing for VCP mutation in patients with family history of myopathy or motor neuron disease and/or dementia, even if individual family members are limited to one feature of MSP

If VCP genetic testing is negative, consider mutations in heterogeneous nuclear ribonucleoprotein A2B1 and A1 (*hnRNPA2B1* and *hnRNPA1*; MSP 2 and 3) genes, sequestosome 1 (*SQSTM1;* MSP4), matrin 3 (*MATR3;* MSP5), T-cell restricted intracellular antigen 1(*TIA1*), and optineurin (*OPTN*).

Molecular genetic testing can be done with targeted single-gene testing or use of a multigene panel.

Diagnosis of Myopathy

Diagnosis

Clinical Exam

Slowly progressive weakness and atrophy of skeletal muscles

Typically proximal and distal weakness of upper and lower extremities, foot drop, and scapular winging; occasional involvement of paraspinal muscles

EMG and nerve conduction study

Often shows mixed myopathic and neurogenic features

Pattern can reflect ALS or CMT variants

Muscle biopsy

Cytoplasmic rimmed vacuoles containing proteins such as tau, amyloid, and TDP-43

Increased fiber size variation, internalized nuclei, and abnormal accumulation of ubiquitylated proteins

Muscle MRI

Patchy regions of atrophied muscle replaced by fatty connective tissue in nearly all muscles.

In the thighs and lower legs, both posterior and anterior compartment muscle involvement is common

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Diagnosis of Paget's Disease of the Bone (PDB)

Diagnosis

Clinical Exam

Bone pain, pathological fractures, hearing loss, and arthritis

Imaging

X-rays: coarse trabeculation, bone expansion, cortical thickening, and sclerotic lesions

Bone scintigraphy: anomalous concentration of radionuclides in sclerotic lesions

Lab Testing

Blood alkaline phosphatase

Less common labs: bone-specific alkaline phosphatase, procollagen type 1 amino-terminal propeptide (P1NP), serum and urine C-terminal telopeptide (uCTX and sCTX), and urine N-terminal telopeptide (uNTX), urine pyridinoline studies

Diagnosis of Frontotemporal Dementia (FTD)

Diagnosis

Clinical Exam

Behavioral variant FTD, with changes in personality, behavior and executive function, is the more common subtype associated with VCP

Neuropsychiatric testing: executive dysfunction, disinhibition, language dysfunction, with relatively preserved memory

Imaging

CT head or MRI brain showing atrophy in frontal and temporal lobes

Brain histology

Not specific or necessary for diagnosis

Shows gliosis, spongiosis, and neuronal intranuclear inclusions

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Other Phenotypes associated with VCP

Diagnosis

ALS

Parkinson's disease

Cardiomyopathy

Charcot Marie Tooth disease

Anal incompetence

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Current Management Strategies

IBM and ALS
Best managed with a multi-disciplinary team approach, including neurologists, physical and occupational therapists, speech therapists, respiratory therapists, and social workers.
Riluzole and edaravone are the only approved therapies to mildly slow the course of ALS.
Still no effective treatment for slowing the progression of IBM.

PDB
Bisphosphonates have some efficacy in suppressing bone remodeling and ameliorating the bone pain of PDB.
Early treatment may prevent pathological fractures and bone deformities.

FTD
Lacks disease-modifying therapy.
Lifestyle modifications: implementing a daily routine, avoiding confrontation, participating in activities they enjoy, and removing triggers for maladaptive behaviors.
Selective serotonin reuptake inhibitors may have some benefit for the behavioral symptoms.

Additional Supportive Management

Weight control to avoid obesity

Supplements

Regular aerobic and resistance exercise to maintain stamina

Physical therapy and stretching exercises to promote mobility and prevent contractures

Mechanical aids (canes, walkers, orthotics, wheelchairs) for ambulation/mobility

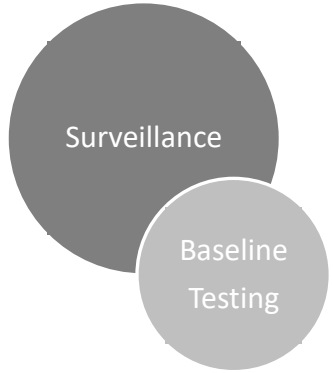
Surgical intervention for foot deformity and scoliosis

Respiratory aids when indicated

Social and emotional support

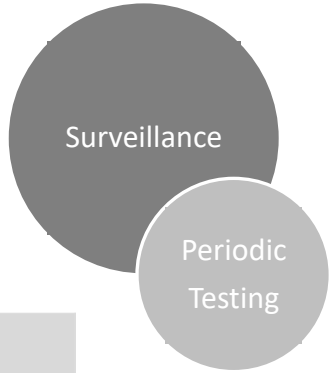
Assisted living arrangements for muscle weakness and/or dementia

Recommended Evaluations Following Initial Diagnosis



System/Concern	Evaluation
Muscle	Assessment of muscle strength, muscle wasting, & tendon reflexes. EMG &/or muscle biopsy may be necessary
Cardiac	Baseline echocardiogram & ECG
Lungs	Baseline pulmonary function studies
Bone	Blood alkaline phosphatase, urine pyridinoline studies, & bone scan studies followed by skeletal x-ray to evaluate distribution & severity of Paget disease of bone
Neurologic	Baseline neuropsychological studies of behavior & mental status
Other	Consultation w/clinical geneticist &/or genetic counselor

Recommended Surveillance



System/Concern	Evaluation	Frequency
Cardiac	Echocardiogram & ECG to monitor for evidence of cardiomyopathy	•Obtain baseline studies. •If normal, reevaluate at 2-3-yr intervals or if symptomatic.
Lungs	Pulmonary function studies	Annual
	Sleep study	As needed
Bone	Alkaline phosphatase, skeletal x-rays, &/or bone scans to monitor therapy & (if symptomatic) PDB	•Annual alkaline phosphatase •Bone scan only when alkaline phosphatase ↑ or symptoms of pain or bony deformity observed
Neurologic	Assessment of behavior & mental status	At baseline & every 2-3 yrs

Genetic Counseling

Support

Autosomal dominant inheritance

Estimated 80% of affected individuals have an affected parent

Approximately 20% have the disorder from a *de novo* pathogenic variant

Prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible considerations

Support Resources

- **Cure VCP Disease, Inc.**
PO Box 6533
Americus GA 31709
Email: curevcpdisease@gmail.com
www.curevcp.org

- **Association for Frontotemporal Degeneration (AFTD)**
Phone: 866-507-7222 (Toll-free Helpline); 267-514-7221
Email: info@theaftd.org
www.theaftd.org

- **Muscular Dystrophy Association - USA (MDA)**
222 South Riverside Plaza
Suite 1500
Chicago IL 60606
Phone: 800-572-1717
Email: mda@mdausa.org
www.mda.org

- **Medline Plus**
Paget's Disease of the Bone

- **Muscular Dystrophy UK**
61A Great Suffolk Street
London SE1 0BU
United Kingdom
Phone: 0800 652 6352 (toll-free); 020 7803 4800
Email: info@musculardystrophyuk.org
www.musculardystrophyuk.org

- **Myositis Association**
1737 King Street
Suite 600
Alexandria VA 22314
Phone: 800-821-7356 (toll-free); 703-299-4850
Fax: 703-535-6752
Email: tma@myositis.org
www.myositis.org

- **National Institute of Neurological Disorders and Stroke (NINDS)**
PO Box 5801
Bethesda MD 20824
Phone: 800-352-9424 (toll-free); 301-496-5751; 301-468-5981 (TTY)
Frontotemporal Dementia Information Page

VCP Standard of Care Survey

www.curevcp.org/standardofcare

1. How many patients do you manage who are genetically confirmed to have VCP disease?
2. What factors are most important in prompting you to order genetic testing for VCP mutation?
3. If testing for VCP mutation yields a negative finding, do you order genetic tests to look for other mutations when you have high clinical suspicion for IBMPFD?
4. Do you routinely do muscle biopsies on your patients who have suspected or confirmed VCP disease?
5. What would make you suspect the myopathy has a component of motor neuron disease? If a patient has motor neuron disease associated with VCP, do you treat with riluzole or edaravone?
6. Do you routinely do a nerve conduction study/ EMG on suspected or confirmed VCP patients?
7. How often do you screen for Paget's disease of the bone, and what tests do you order to check for this? Blood alkaline phosphatase, urine pyridinoline studies, bone scane, skeletal x-ray are some diagnostic options. If a patient has evidence of Paget's disease, do you treat with a Bisphosphonate or other agent?
8. Do you routinely order a brain MRI or neuropsychologic testing on your genetically confirmed VCP disease to screen for frontotemporal dementia? Do you repeat an MRI brain at certain intervals to screen for development of FTD?
9. Do you refer your VCP patients for genetic counseling?
10. How often do you screen for cardiomyopathy with an echocardiogram and/or EKG?
11. How often do you screen for respiratory dysfunction with PFTs? Do you recommend respiratory exercises or respiratory devices (cough assist, BIPAP, other)?
12. Do you advise your VCP patients to follow any particular dietary plan or use any supplements?
13. Do you refer your VCP patients for physical therapy?
14. Do you advise your VCP patients to engage in regular exercise? If so, what type, what frequency, and what resistance?
15. Do your VCP patients have access to a multidisciplinary clinic with a neurologist, PT, OT, ST, RT?
16. Do you refer VCP patients to colleagues at other centers who have expertise in IBMPFD?
17. Do you refer your VCP patients to counseling for depression, and if so, when?
18. Do you refer your VCP patients to support groups or particular websites?

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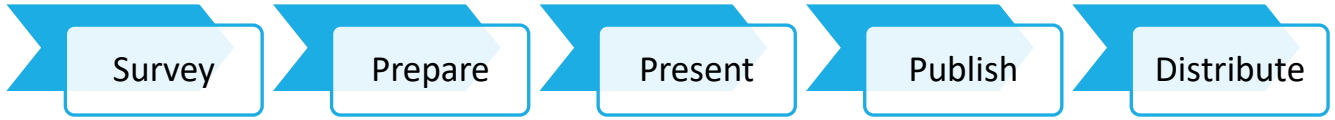
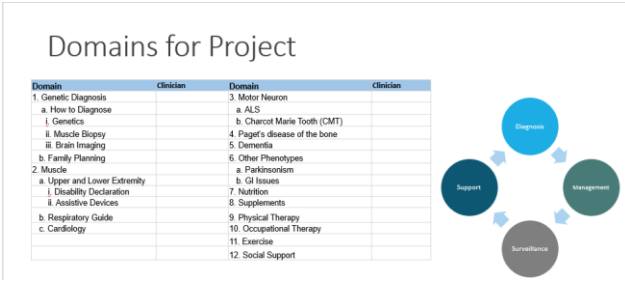
Next Steps



- Please fill out the online survey by 1/31/2021 if you have not already
- Please refer us to any other experts in the VCP domains who you think may be willing to participate and contribute
- We will ask for volunteers / assign each expert to their respective topics in their field
- We ask each expert to present some level of evidence (even if it is just your opinion) and draft a short paragraph regarding your presentation piece
- Please prepare a 15-20 minute presentation along with the other experts in your domain to discuss your topic
- We are aiming for April 2021 for a 3 hour international virtual consortium to establish a consensus on updated guidelines for VCP diagnosis, management, and surveillance
- After the consortium, we will pool together the transcript of expert presentations and publish a consensus on the guidelines in a medical journal
- We envision these guidelines will be distributed through the Cure VCP Disease network to healthcare providers and patients for increased awareness of the disease and improved standards of care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b. Respiratory Guide		9. Physical Therapy	
c. Cardiology		10. Occupational Therapy	
		11. Exercise	
		12. Social Support	

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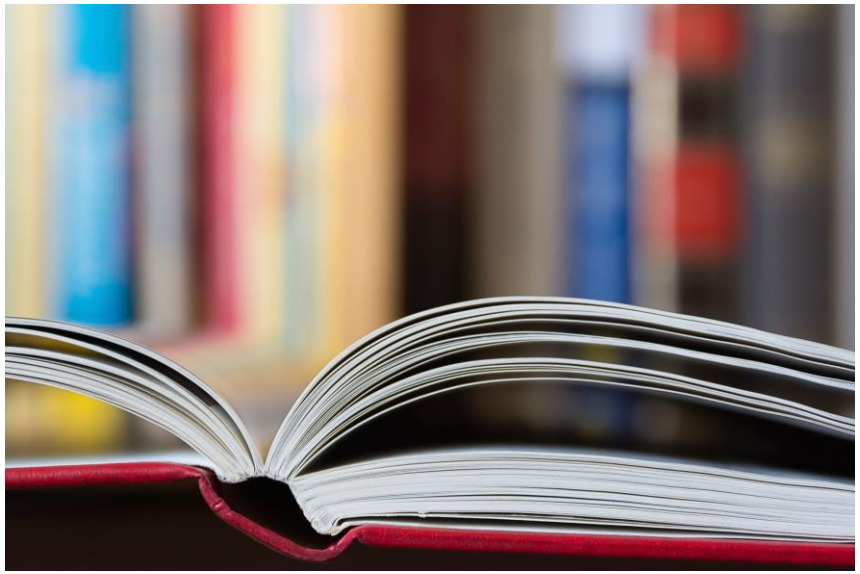
References

Korb MK, Kimonis VE, Mozaffar T. (2020) Multisystem proteinopathy: where myopathy and motor neuron disease converge. *Muscle and Nerve:*1-13. https://doi.org/10.1002/mus.27097

Kimonis, V. Inclusion Body Myopathy with Paget Disease of Bone and/or Frontotemporal Dementia. 2007 May 25 [Updated 2019 Sep 12]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1476/



Thank you for attending today's organizational meeting.

We look forward to continued correspondence with you and hope to see you in April 2021 for our virtual international standard of care consensus meeting.

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