Good afternoon Muscular Dystrophy Community,

My name is Dr. Kathryn Wagner. I am a laboratory and clinical researcher in muscular dystrophy and above all, I am a doctor to hundreds of children and adults with muscular dystrophy at the Center for Genetic Muscle Disorders at Kennedy Krieger Institute in Baltimore, Maryland. I have been a co-director of one of the early Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers at the University of Pennsylvania and Johns Hopkins School of Medicine and more recently, a principal investigator in the University of Massachusetts, Harvard University, Kennedy Krieger, Wellstone Center focused on Facioscapulohumeral muscular dystrophy research. I have been fortunate to witness and participate in the explosion of discoveries and advancements in understanding of these diseases thanks in large part to this NIH funding. However, my patients and I have not yet witnessed a transformation in treatment that is expected from these discoveries.

Mrs. Walters has given you a perfect description of Facioscapulohumeral muscular dystrophy. It is a rare disorder, but one of the most common muscular dystrophies, affecting approximately 1 in 15,000 of the US population. It is a genetic disorder, frequently affecting multiple members of a family, children and adults, men and women, inherited from one generation to the next. It is a chronic and disabling disorder, causing progressive and irreversible weakness of the face, arms, trunk and legs. It is currently an incurable and untreatable disorder. There are no accepted pharmacological treatments to slow the progression of the disease. Treatments are limited to supportive care such as orthopedic bracing, physiotherapy and pain management.

Until recently, FSHD was also an enigmatic disease. It has been known since the 1990s that a contraction of repetitive elements on the tip of the long arm of chromosome 4 was linked to the
disease. But how this contraction led to disease was unknown. The lack of an understanding of the pathophysiology of the disease, the lack of patient materials such as cells and muscle samples and the lack of animal models stymied the field from moving forward. This began to change in the early 2000s. Increased funding for FSHD led to an understanding that the chromosome 4 contraction causes misexpression of genes which are normally silent. The DUX4 retrogene is aberrantly expressed in FSHD skeletal muscle and turns on a battery of other genes. The MD-Care Act ensured the funding in 2008 of a Wellstone Center at Boston Biomedical Research Institute with collaborators at Harvard and Kennedy Krieger focused on FSHD. In the first 5-year cycle of funding, our Wellstone Center established a biorepository of DNA, cells, and muscle tissue samples from over 50 FSHD patients and their first degree unaffected family members. It was a tremendous outpouring from the FSHD community, each individual literally donating a piece of him or herself to provide investigators with the necessary tools. These biomaterial tools are now available to all FSHD researchers throughout the world. Animal models of FSHD have also been recently developed including a zebrafish model expressing Dux4, a transgenic mouse model expressing a portion of the abnormal human chromosome 4 and a xenograft mouse model transplanted with human FSHD muscle. Our Wellstone Center focusing on FSHD was recently renewed and is now well poised to take advantage of these recent advances.

Our and other groups funded by NIH are developing novel therapeutic initiatives for FSHD, with the goal of reducing the expression of the Dux4 gene or its downstream targets and improving strength and quality of life. For the first time, a high-throughput drug screen in FSHD cells is underway. Gene therapy studies to knock down DUX4 expression in the new animal models have also begun. These are exciting new preclinical initiatives, to develop therapies directed at the specific pathophysiology of FSHD. The next step will be translating these preclinical discoveries to pharmacologic and gene therapy clinical trials in FSHD patients. The field is preparing for this imminent reality by defining biomarkers of disease that can be followed in clinical trials including molecular biomarkers, MRI biomarkers and
functional and quality of life outcome measures. These current studies are only possible due to the investment the NIH has made in FSHD research. The future clinical studies are only possible with continued support such as the MD-CARE Act and through partnership with industry.

Industry is becoming interested in FSHD now for the first time. Previously, without an understanding of the pathophysiology and without animal models, there had only been one clinical trial with a novel drug and only a half dozen trials total in FSHD. Now, thanks to these recent advances, pharmaceutical companies are partnering with academia providing drug libraries to screen and developing novel therapeutics targeted to the misexpressed genes.

The momentum is building to bring novel therapies into the clinic for FSHD patients. This next step will require expanding funding to capitalize on the advances made since initiation of the MD-CARE Act and expanding a currently limited workforce. There are simply not enough people working on muscular dystrophy due to limited funding. Through the Wellstone Centers, the MD-CARE Act has provided funding to support and educate trainees. We are training a new cadre of muscular dystrophy clinical and basic researchers to go further and provide meaningful therapies to FSHD families.

The patients that you have heard from today, the patients and family members in the audience and the larger muscular dystrophy community at home and at work are looking to their federal government for a meaningful treatment for their disease. The investment has been initiated but the payoff has not yet been realized. None of the muscular dystrophies you have heard about today have any meaningful treatment. The families are not only dealing with the burden of their disease but they are raising money for research, participating in clinical trials and donating their tissue. Industry is partnering and spending significant resources on developing novel therapeutics for these diseases. But there is no substitute for the MD-CARE Act which brings patients, researchers, NIH and Congress to work together against muscular dystrophy. As a physician who is face to face with patients who are looking to me for treatment, and as a scientist attempting to discover some genuine new understanding of disease,
I need to work collaboratively with the best academic and industry scientists towards a common goal of developing new classes of drugs for muscular dystrophy. The MD-CARE Act and Wellstone Centers make this possible and have given me hope that I will be able to do what I am here to do, which is deliver treatments to alleviate the suffering of those with muscular dystrophy.