Goodmorning, my name is Kelly Crisp, and it is my pleasure to be here with you today. I am a speech pathologist at Duke University where I have the privilege of assisting Dr. Harrison Jones with his research. This morning I’ll be sharing the results of our lab’s recent investigation into the effects of respiratory muscle training or RMT in adults with late onset Pompe disease.
Here is the obligatory disclosures slide which you can read online at your leisure; there were several authors on this presentation, myself included, who received some level of funding from grants provided by Genzyme corporation to conduct the research I am describing today.
This is a list of references also available online if you are interested.
I’d like to start by providing some brief background information about Pompe disease. Pompe is also known as glycogen storage disorder type 2. It is an autosomal recessive muscle disease with an incidence of approximately 1 in 40,000 that results from some level of deficiency of the lysosomal enzyme acid alpha glucosidase, also known as GAA. Pompe can be thought of as a single disease with varying clinical manifestations across a spectrum. The two primary phenotypes are infantile onset Pompe disease, which is the more severe form arising from a complete or nearly complete deficiency of GAA present from birth. Late onset Pompe disease appears sometime after the first year of life, usually in later adulthood, and arises from a partial GAA deficiency. The timing of symptom onset and severity of symptoms is correlated to the amount of residual GAA in LOPD.
Progressive skeletal and respiratory muscle weakness are common in both phenotypes and respiratory muscle weakness is THE primary cause of morbidity and mortality in LOPD. This weakness has significant implications for these patients: it often manifests initially in sleep disordered breathing requiring nighttime ventilation and then penetrates into daytime ventilation, causing hypoventilation, hypercapnia, and hypoxia. Other implications include cough impairment, dysarthria initially manifested as reduced loudness, shortness of breath with activity, and eventually respiratory failure. Many patients with LOPD will require full time mechanical ventilation prior to their death.

Enzyme replacement therapy, known as ERT, has been shown to attenuate the rate of decline in respiratory muscle strength in LOPD. Although modest improvements in respiratory strength of about 3% may be noted immediately after ERT is initiated, these strength gains do not persist over time, however, and decreases in respiratory strength will continue, albeit at a slower rate. Respiratory muscle training, which has been studied fairly widely in healthy normals, athletes, and other respiratory diseases, and to a more limited extent, individuals with NMD, seems a potentially viable treatment option for addressing progressive respiratory muscle weakness in individuals with Pompe disease that merits further investigation.
When we are talking about RMT, we are referring to a combination of both inspiratory muscle training or IMT and expiratory muscle training or EMT. Because both muscle systems are involved in Pompe disease, it seems particularly important to train both the inspiratory and expiratory muscles in this population. The application of RMT to Pompe disease was first reported by Dr. Jones in 2011 in which he described large increases in both inspiratory and expiratory muscle strength in a case study of 2 adults with LOPD.

The results of this case study led to a more systematic line of inquiry with goals of determining the safety, feasibility, and preliminary estimates of effect size of RMT in Pompe following an intensive 12 week RMT regimen. We have now studied this regimen 11 times in 10 unique participants, including two pediatric subjects with infantile-onset Pompe disease, the results of which were published earlier this year. We subsequently repeated the study protocol with one of those pediatric participants and my colleague Kaylea Nicholson will be presenting the very interesting results of that experiment today in the next session.

In this presentation I’ll be publicly sharing the results from our 8 adult participants with LOPD for the first time.
There were three a priori hypotheses regarding the effects of our RMT regimen:

First, that maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP) would increase following 12 weeks of intensive RMT.

Second, that this regimen would produce changes at least large in magnitude, using Cohen’s d values. Effect sizes were defined conservatively as negligible for values less than 0.6, modest for values between 0.6 and 1.0, large for values greater than 1.0, and very large for values greater than 2.0.

Lastly, we hypothesized that peak MIP/MEP values would be seen at posttest, immediately following 12 weeks of training, and that evidence of detraining would be found when values were reassessed following 3 month withdrawal of RMT.
Four men and four women with a confirmed diagnosis of LOPD and a mean age 49 years participated in the study. All were on stable enzyme replacement therapy regimens at the time of their participation; 1 for less than 1 year, 4 for 1-3 years, and 3 had been on ERT for more than 3 years. Again, ERT and all other aspects of their medical care remained constant for the duration of the study.
Our study was setup as an **A-B-A single subject experimental design replicated across subjects**, with A1 as the baseline or pre-treatment status, B as the 12 week active treatment phase of the study, and A2 as the posttest status immediately following conclusion of the B phase and continuing through 3 month withdrawal to post-detraining.

Participants completed **12 visits over 24 weeks**, with this graphic depicting the various study activities included in each visit. Participants were evaluated by a pulmonologist with expertise in Pompe disease at Visit 1 to ensure safe and meaningful participation in the study. **In depth assessment of respiratory status** including spirometry, MIP/MEP, and peak cough flow or PCF, **along with gross motor assessment**, was completed over two days at Pretest in visits 1 and 2 and at Posttest at visits 8 and 9 and again over 1 day at Post-Detraining visit 12. **MIP and MEP**
were additionally measured at each visit during the B phase of the study as well as during visits 10 and 11 during 3 month withdrawal.
We used a standard protocol including a calibrated digital pressure gauge and standard verbal instructions to **obtain reliable measures of our primary dependent variables, MIP and MEP.**

**Four test sessions per day** were conducted at pretest, posttest, and post-detraining, with **each session’s data point representing the mean of the 3 maneuvers** with the largest values and least amount of variability.
Our procedures for measuring our secondary and descriptive variables are briefly described here. These included spirometry conducted in the pulmonary function lab, and gross motor measures collected by a trained physical therapist including the 6 minute walk test, time to climb 4 stairs, time to move supine to stand, and time to walk 10 meters. The study protocol was amended to include assessment of Peak Cough Flow or PCF in subjects 4 to 8. Volitional cough was measured with a calibrated oral pneumotoachograph system 6 times at pretest and posttest and 3 times and post-detraining. The mean of these values is reported in L/s.
RMT was completed for 12 weeks during the B phase of our study.

Participants saw a trained SLP for RMT therapy sessions every other week. We used the handheld pressure-threshold respiratory trainer devices noted here to provide inspiratory and expiratory pressure-threshold resistance set at 60-70% of each participants MIP and MEP. The trainers were hand-calibrated using a novel gas pressure circuit comprising the trainer, a 3L syringe, and a pressure gauge in subjects 4-8. As mentioned previously MIP and MEP were measured following our standard procedures before each therapy session to allow the pressure thresholds to be adjusted to provided progressive resistance.
Participants completed RMT during their 6 therapy sessions with the SLP and during a home exercise program. In each RMT therapy session, the participants completed 3 sets of 25 repetitions of both IMT and EMT while the treating SLP shaped performance and monitored accuracy and negative side effects. The accuracy target was 88% or better with no more than mild side effects, with participants being monitored for things like pain, dizziness, and shortness of breath after each set. To help us monitor the safety of our RMT regimen, we also asked participants to rate their self-perceived level of effort on a scale of 0-10 after each set, with 0 representing no work at all and 10 representing the hardest work imaginable. If they reported an effort rating greater than 8 or if they were unable to achieve at least 88% accuracy at the current pressure-threshold, the resistance was adjusted downward to prevent over-training.

The home exercise program comprised 3 sets of 25 repetitions of both IMT and EMT per day, 5 days per week, for a total of 750 reps weekly. They tracked completion of their home exercise program including effort ratings and accuracy in a daily log which was reviewed by the treating SLP in the next RMT therapy session.

Taken together this represents a cumulative dose of 9000 RMT repetitions, 4500 EMT and 4500 IMT, over 12 weeks.
We found substantial changes in both MIP and MEP following this intensive 12 week regimen.

When we average the performance of the individual participants, we found that mean MIP increased 20% from pretest to posttest, with a mean d value of 2.3 corresponding to a very large effect size.

Following 3 month withdrawal, when we compare posttest to post-detraining, mean MIP increased an additional 12%, with a mean d value of 1.4 corresponding to a large effect size.

When we look at the treatment effect for MIP over the entire 6 month study duration, we found that MIP increased a total of 35%, with a very large effect size represented by a mean d value of 3.8.
We also found substantial changes in MEP.

**Again averaging the performance of the individual participants**, mean MEP increased 16% from pretest to posttest, with a mean d value of 1.8 corresponding to a large effect size.

Following 3 month withdrawal, again comparing posttest to post-detraining, mean MEP decreased slightly by 1%, corresponding to a small negative d value of -0.7.

When we look at the treatment effect for MEP over the entire 6 month study duration, we found that MEP increased a total of 15%, with a large effect size represented by a mean d value of 1.4.
Here’s another way to look at the data, with this graph depicting the raw values for mean MIP and MEP at pretest, posttest, and post-detraining. Here we can see that our participants had fairly substantial respiratory muscle weakness at pretest, particularly in the inspiratory muscles, with a mean MIP of 48 cm h20 and a mean MEP of 78 cm h20. The change in MIP represented by the red line shows an increase to 57 cm h20 at posttest with a peak value of 61 cm h20 at post-detraining. The change in MEP depicted by the blue line shows the increase from 78 cm h20 at pretest to 90 cm of h20 at posttest, with MEP decreasing just slightly to 88 cm h20 following 3 month withdrawal at post-detraining.
The results from our secondary and descriptive variables including **spirometry, gross motor, and peak cough flow were inconsistent**. When we did see changes that appeared as if they **might be meaningful, which we defined as exceeding 5%, there was not much of a pattern evident**. We came to understand that these were **likely not the best measures to really inform functional outcomes**.

In terms of spirometry values, **very large changes in respiratory strength** are probably needed before you would start to see **changes in respiratory volumes**.

Regarding physical activity, we thought that the measures selected may allow us to assess the contribution of respiratory muscle weakness on gross motor function, but it seems that lower extremity weakness is actually a more significant limiting factor.

**Peak cough flow seems** likely to be more directly associated with changes in respiratory muscle strength, with our pilot data showing a mean increase of 5% across participants though there were some robust responders with the range going up to 38%.
Discussion: Pretest to posttest

- Mean MIP increased 20%
  - Very large effect sizes for increases in inspiratory strength
    \((d=2.33)\)
- Mean MEP increased 16%
  - Large effect sizes for increases in expiratory strength
    \((d=1.82)\)
- Increases in both MIP and MEP seen in 7/8 subjects

Taken together, these data demonstrate that RMT is potentially a powerful treatment for addressing progressive respiratory muscle weakness in LOPD. We saw very large increases in inspiratory muscle strength and large increases in expiratory muscle strength immediately following our 12 week regimen. Seven of the eight participants responded to the therapy with increases in both MIP and MEP.
The response to three month withdrawal was complex. We saw an additional 12% increase in inspiratory muscle strength over this period, in contrast to relatively stable MEP values at post-detraining, decreasing by 2%. These data point to a possible differential response to RMT in the inspiratory and expiratory muscles, with maximum MEP appearing a posttest whereas maximum MIP was achieved at post-detraining.
Bringing this all back to our three a priori hypotheses, it was indeed true that an intensive 12 week RMT regimen resulted in increased inspiratory and expiratory muscle strength in LOPD. Again, the data are quite compelling, with an average of 20% increase in MIP and a 16% increase in MEP following RMT. It was also true that these changes were large in magnitude, with very large d values for MIP and large d values for MEP, changes which were persistent over 3 months of detraining. The results for our third hypotheses were mixed, however; peak values were seen at posttest for MEP with a slight 2% decline in strength over 3 month withdrawal. However, this hypotheses was false for MIP as we actually saw further gains of 12% over the 3 month withdrawal period. Again this was an unexpected finding that suggests a possible differential response for the inspiratory and expiratory muscles.
Training at 60-70% of MIP/MEP and completing 9000 repetitions over 12 weeks does in fact appear feasible, as our self-reported adherence data demonstrated over 90% compliance with the prescribed regimen. Although dose and intensity are quite high in our study, higher than that found in nearly all the other RMT literature, it does appear to be safe – when adhered to as prescribed and side effects are appropriately monitored and self-reported. There was one participant, our first adult subject, who demonstrated a transient drop in her MIP/MEP values which was occurred after she continued to train through fairly significant pain with her home exercise program without reporting this to the PI. Her measures of respiratory strength did fully rebound after a period of recovery, suggesting that no permanent damage was done, but this isolated example does illustrate the importance of having safeguards in place to prevent overtraining, particularly in more fragile populations such as those with neuromuscular disease.
While these pilot data are certainly promising, there is still a great amount that we don’t know about RMT in Pompe and other primary muscle conditions. Further research should examine the effects of RMT on ventilation and respiration, secretion management, and airway protection. We also need better functional outcomes to fully understand the impact of RMT, which likely need to be more directly related to breathing.

We have found that RMT is potentially a very powerful treatment, but we don’t know enough about dose yet — in Pompe or in other conditions. Further research is needed to clarify the dose-response relationship with manipulation of variables such as pressure threshold, number of repetitions, and total duration of training. Detraining and maintenance are also important issues that merit further study, particularly in patients with neuromuscular disease and progressive respiratory muscle weakness, so we may better understand how RMT could contribute to reducing morbidity and mortality of these patients over time.

In summary, we have some very compelling pilot data demonstrating that RMT holds great promise for addressing respiratory muscle weakness in patients with Pompe disease, but there is still a lot left to learn.
Thank you very much for your interest. We’d be happy to answer any questions?

What does this have to do with speech pathology: Depending on who is asking, the answer may be not much at all. While there is some evidence that the main contributing factor to dysarthria in patients with Pompe is likely respiratory muscle weakness which manifests itself as decreased loudness, the link between increased respiratory muscle strength and changes in speech parameters is likely not direct. We think that there may very well be a role for speech pathologists to expand our scope of practice into working more directly with breathing, though, even without a direct link to a speech or swallowing diagnosis. Our skills as behavioralists make us very qualified to conduct this sort of therapy and do it well, since it isn’t a one-size-fits-all type of treatment that can be doled out without supervision, particularly in medically fragile populations such as those with NMD. Our knowledge base as experts in upper airway anatomy and physiology also uniquely qualify us to play a role in the management of breathing.

Why did MIP continue to increase during withdrawal? We don’t have a great explanation for this finding, as the response of the inspiratory muscles certainly did not follow the typical pattern of detraining we expected to see and did see in the expiratory muscles. The high dose and intensity of our regimen may have played a role in explaining this finding which is not typical of the response seen in other RMT literature. Another possible explanation is that increases in inspiratory muscle strength during the
active treatment phase of the study allowed the participants to increase their activity levels, which may have resulted in continued strengthening of the diaphragm. Only by engaging in exertional activities like running or perhaps coughing would there be further opportunity to continue to strengthen the expiratory muscles once RMT was discontinued, so perhaps this may be part of the reason there was a differential response in the two measures of respiratory strength. We did not include activity monitoring as part of this study, so it is difficult to say, but this may be something worth including in future investigation in this population.