MRI fat fraction distribution in Duchenne muscular dystrophy (DMD): Effect size comparison to identify optimal biomarker for early efficacy assessment

M. Hammond[1], J. Harris[1], B. Luna[1], F. Roche[2], M. Berger[1], F. Vincent[2], S. Zabbatino[1], R. Scheyer[3], S. Holland[1]

1 Medpace Core Laboratories, Cincinnati, OH, United States; 2 Medpace Core Laboratories, Lyon, France; 3 Medpace, Cincinnati, OH, United States

1 INTRODUCTION

- MRI proton density fat fraction (PDFF) is a sensitive and objective quantitative biomarker of fat replacement in affected muscle for DMD and other neuromuscular trials[1,2]
- Change in mean MRI-PDFF does not capture the heterogenous underlying distribution of fatty infiltration within a region of interest (ROI)
- Other MRI-PDFF metrics reflecting pathologically relevant changes in fat distribution may be better able to detect efficacy of disease modifying treatments

2 AIMS

- Test a strategy to determine the optimal metric for the MRI-PDFF biomarker for early efficacy assessment based on maximizing the standardized effect size to boost statistical power

3 METHODS

- MRI scans of the vastus lateralis (VL) stratified by baseline fat fraction and soleus optimized for PDFF quantitation[3,4] over 1-year and 3-years of follow-up were extracted from an anonymous clinical trial data repository (Table 1)

Table 1: Mean baseline fat fraction and standard deviation (SD) of each group

Group	Mean PDFF ± SD
VL>15% (n=8)	44.5 ± 22.8%
VL≤15% (n=7)	8.5 ± 3.9%
Soleus (n=5)	5.7 ± 1.7%

- Fat fraction was obtained by applying an ROI (Fig. 1) optimized for reducing mean fat fraction variability[5,6] to the MRI-PDFF map

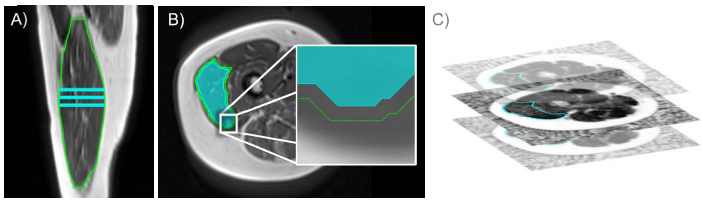

Fig. 1: ROIs were produced from 3-slices centered on the muscle (A) segmented on T1-weighted images with an axial contraction (B) that was co-registered with the MRI-PDFF map (C)

- The relative standardized effect size (Cohen's *d*) of the skewness, kurtosis, and every 5% quantile was evaluated compared to the Cohen's *d* of mean MRI-PDFF (d/d_m) over 1-year and 3-years of follow-up in a DMD population

$$\text{Cohen's } d = \frac{(\text{Group Mean at Follow-up}) - (\text{Group Mean at Baseline})}{\text{Pooled SD}}$$

$$d/d_m = \text{Cohen's } d \text{ of metric} \,/\, \text{Cohen's } d \text{ of Mean PDFF}$$

- Optimization was based off d/d_m at 1 year, consistency at 1 and 3 years, consistency between muscles, and applicability over different baseline fat fraction populations

4 RESULTS AND DISCUSSION

- Skewness and kurtosis are not good candidates as they are independent of MRI-PDFF magnitude and d/d_m was not consistent across timepoint, muscle, or baseline fat fraction
- For VL≤15%, d/d_m approached a maximum near the 90–95% quantiles at 1-year (Fig 2; d/d_m = 138% at 90% quantile)
- For V>15%, d/d_m was maximum near the 5–10% quantiles and then was fell to ~90% at the 40% quantile until the 95% quantile (Fig 2)

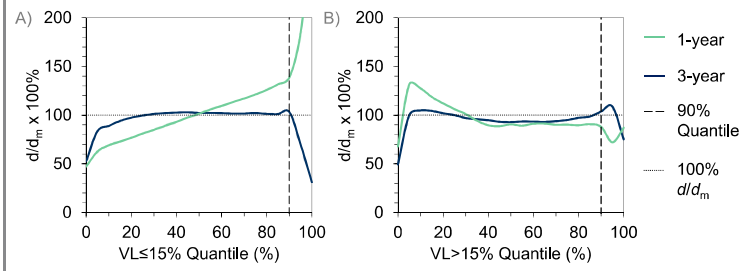

Fig. 2: Relative effect size (d/dm) percentages at each quantile from 0% to 100% in the VL≤15% (A) and VL>15% (B) groups

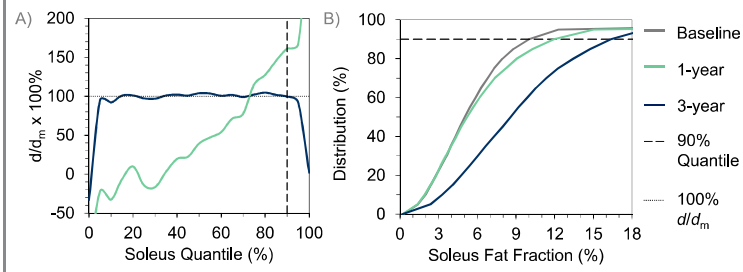

Fig. 3: Relative effect size (d/dm) percentages at each quantile from 0% to 100% in the soleus (A) and composite empirical distribution of fat fraction (B)

- In the soleus, the d/d_m trend followed a similar pattern as the VL≤15% group (1-year d/d_m = 161% at 90%)
- At 3-years, $d/d_m \approx 100\%$ across quantiles 5-95% in all groups
- Recommend applying contraction to ROI to ensure all of ROI is within muscle and reduce sensitivity to outliers caused by incorrect segmentation

5 CONCLUSIONS

- The 90% quantile of the MRI-PDFF distribution within the ROI is an optimal MRI-PDFF-based biomarker to assess treatment efficacy, especially early in disease progression

6 REFERENCES

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7 CONTACT

Max Hammond, PhD; m.hammond@medpace.com

Josh Harris, MS; j.harris1@medpace.com