Poster # P.126

Genotype-unmatched Controls are Feasible for Drug Development in Duchenne Muscular Dystrophy (DMD)

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Introduction

- Clinical trials of genotype-specific treatments in DMD traditionally compare treated patients to controls with the same dystrophin genotype to avoid confounding due to genotype effects on outcomes (Kinali et al. 2009, McDonald et al. 2017, Mendell et al. 2016, Frank et al. 2020).
- However, requiring matched genotypes also reduces the pool of eligible controls and challenges recruitment, especially for rare genotypes or genotypes with multiple approved or investigational treatment options.
- A previous meta-analysis found that genotype class effects on 1-year changes in the North Star Ambulatory Assessment (ΔNSAA) total score were small in magnitude and precisely estimated, indicating that such effects can be accounted for and that genotypically unmatched controls may be feasible in DMD (Muntoni et al. 2021).
- Use of these findings in a clinical trial requires a quantitative understanding of how genotypically unmatched controls would impact power and sample size requirements for specific trial designs.

Study Objectives

We assessed the suitability of genotypically unmatched control groups in DMD trials by:

1. Conducting an illustrative analysis of a genotypically unmatched control group and assessing the degree to which statistical adjustments, informed by pre-existing estimates of genotype effects, can avoid bias due to genotype differences
2. Quantifying the sample size implications of using genotypically unmatched versus matched controls in standard two-arm trials and in platform trials of multiple targeted therapies

Illustrative Analysis of a Simulated Trial with Genotypically Unmatched Controls

Trial construction

- A clinical trial was simulated based on real data drawn from multiple data sources: the DEMAND III clinical trial placebo arm and five real world or natural history (RWD/NHD) sources (iMDEX, Leuven, PRO-DMD-01, NSUK, CCHMC). Patients had confirmed DMD based on genetic testing and/or muscle biopsy.
- Included patients were required to meet the following criteria at baseline:
  - Age ≥ 5 years
  - Steroid therapy for ≥ 6 months
  - NSAA total score > 10
  - Follow-up visit with non-missing NSAA total score within 9-15 months
  - Non-missing data on variables used for adjustment: deflazacort use, height, weight, BMI, 10-meter walk/run (10MWR) velocity
- Included patients were grouped into the following hypothetical trial arms (**Table 1**):
  - Treatment arm (n=58): patients from the DEMAND III placebo arm, all with exon 51 skip-amenable DMD genotypes
  - Genotypically matched control arm (n=45): patients with exon 51 skip-amenable genotypes drawn from sources other than DEMAND III
  - Genotypically unmatched controls (n=58): patients with DMD genotypes amenable to skipping exons other than exons 51, 53, 44, and 45, also drawn from sources other than DEMAND III

Trial analysis and results

- Treatment effects on 1-year ΔNSAA total scores were estimated as the differences between the hypothetical treatment group and the genotypically unmatched and matched control groups, adjusting for baseline age, NSAA total score, deflazacort use, height, weight, BMI and 10MWR velocity via multivariable regression.
  - The true treatment effect in each case is zero, i.e., no difference between the hypothetical treatment and controls arms, since there are no differences in therapy – thus any apparent non-zero treatment effect is an indicator of genotype bias.
  - In the presence of genotype effects, failure to account for genotype bias could result in under- or overestimation of true treatment effects.
- The treatment effect estimated using the unmatched control group without accounting for genotype differences indicated a bias of 1.7 NSAA units (**Figure 1**).
- To mitigate this bias, a treatment effect corrected for genotype mix was calculated by subtracting from the original unmatched treatment effect an estimate of the genotype effect obtained from a prior meta-analysis (Muntoni et al. 2021), and accounting for the increased variance due to uncertainty in the genotype effect estimate (**Figure 2**).
- Once corrected for the genotype differences, the bias was < 0.3 NSAA units. The correction also increased the standard error of the treatment effect from 0.85 to 1.15 NSAA units (**Figure 1**).

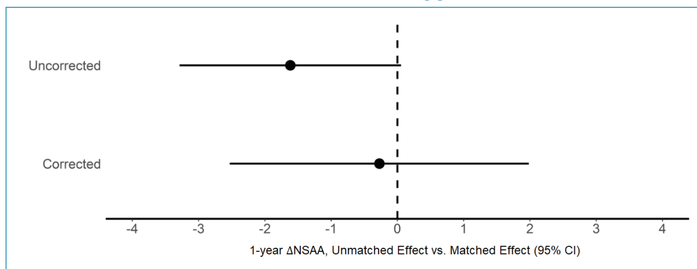
Table 1. Patient Baseline Characteristics in Simulated Trial

	Treatment	Matched Control	Unmatched Control
N	58	45	58
Age (years)	8.3 ± 2.0	8.0 ± 2.4	9.1 ± 2.8
Steroid type			
Deflazacort	24 (41.4%)	22 (48.9%)	39 (67.2%)
Prednisone	34 (58.6%)	23 (51.1%)	19 (32.8%)
Steroid duration (months)	26.2 ± 19.8	27.4 ± 21.7	35.9 ± 29.7
Height (cm)	121.5 ± 9.3	119.3 ± 11.1	125.5 ± 14.3
Weight (kg)	26.6 ± 7.6	28.1 ± 10.4	31.5 ± 10.8
BMI (kg/m²)	17.8 ± 3.5	19.2 ± 4.3	19.4 ± 3.8
NSAA total score	21.2 ± 8.1	22.7 ± 6.5	25.4 ± 6.4
10MWR (seconds)	7.3 ± 3.5	6.8 ± 7.6	5.2 ± 1.8
10MWR velocity (meters/second)	1.6 ± 0.5	1.9 ± 0.6	2.1 ± 0.5

Means and standard deviations are shown for continuous characteristics; counts and percentages are shown for categorical characteristics.

Abbreviations: 10MWR: 10-meter walk/run, BMI: body mass index, NSAA: North Star Ambulatory Assessment, SD: standard deviation

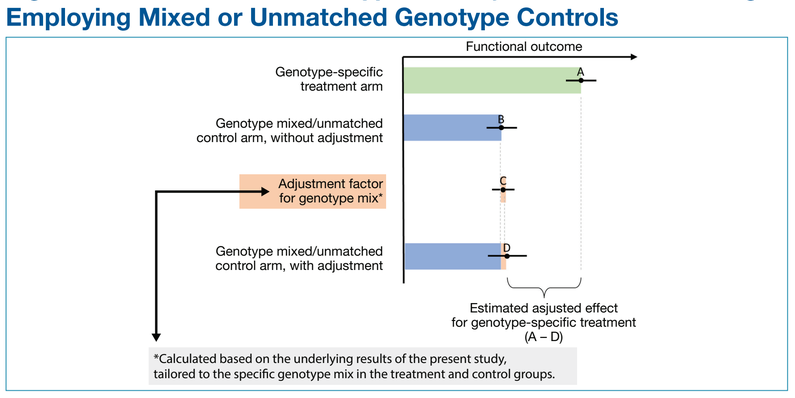
Figure 1. Bias in Estimated Treatment Effects with and without Correction for Differences in Genotype Mix



Control Group	Estimate	Standard Error	Lower 95%	Upper 95%
Matched	0.9397	0.9113	-0.8464	2.7259
Unmatched (Uncorrected)	-0.6769	0.8524	-2.3475	0.9937
Unmatched (Corrected)	0.6667	1.1510	-1.5892	2.9226

Abbreviations: CI: confidence interval; NSAA, North Star Ambulatory Assessment

Figure 2. Schematic for Genotype Mix Adjustment in Trial Designs Employing Mixed or Unmatched Genotype Controls



Power and Sample Size Assessments

Trials with one treatment arm and one control arm

- Power analyses were conducted to assess the sample size implications of genotypically unmatched controls, considering the increased uncertainty (standard error) associated with performing a genotype correction as described above.
- Sample sizes required to achieve 80% power for treatment effect sizes of 2.5, 3, 4, and 5 NSAA units were higher for a genotypically unmatched design compared to a matched design, with larger sample size increases for smaller treatment effects (**Table 2**).
- For trial planning purposes, the following formula describes the relationship between the total sample size required in an unmatched design (N_1) versus a matched design (N_0) to achieve the same power:

$$N_1 = N_0 \times \frac{V(\Delta)}{V(\Delta) - V(g) \cdot N_0/2}$$

  $V(\Delta)$ denotes the variance in the outcome and $V(g)$ denotes the variance of the genotype correction (equal to zero in a matched design)

- This formula indicates that the number of additional patients required in an unmatched versus matched design will be smaller when estimated genotype effects are more precise (smaller $V(g)$) and/or when the expected treatment effect is larger (smaller N_0).

Table 2. Per Arm Sample Size (Equal Allocation) Required for 80% Power by Targeted Treatment Effect

Mean ± SD Targeted Treatment Effect (Difference in ΔNSAA)	Per Arm Sample Size			
	Unmatched Control Group	Matched Control Group	*Difference*	*Multiplier*
2.5	195	49	146	3.98
3	71	34	37	2.09
4	27	19	8	1.42
5	15	12	3	1.25

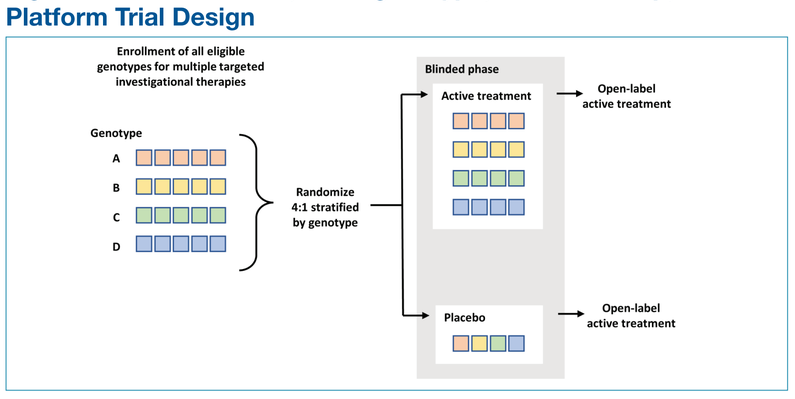
Notes:
[1] Assuming Type I error controlled at 5% and SD of 4.4 units for change in NSAA

Abbreviations: NSAA: North Star Ambulatory Assessment, SD: standard deviation

Platform trials with multiple therapies targeting different genotypes

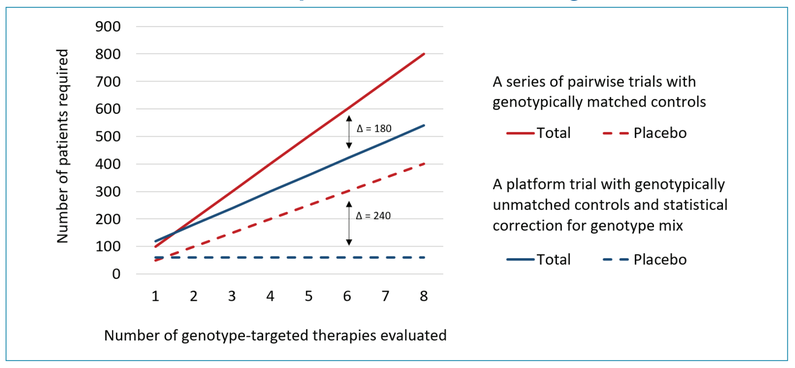
- A platform trial design is a trial design in which multiple therapies, each targeting a potentially different genotype, are studied under a single protocol (**Figure 3**).
  - An advantage of this design is that assignment to active therapy vs. placebo can be double-blind, since all patients entering the trial are eligible for at least one of the trialed treatments.
  - A challenge for platform designs in DMD has been that the control group would be genetically heterogenous compared to each treatment group – which could bias typical approaches to estimating treatment effects.
  - This bias can be addressed by applying the genotype correction methods described above, drawing on externally-derived estimates of the genotype effects, though this bias reduction comes at the expense of increased sample size requirements per arm.
- We evaluated the total sample size required for a multi-genotype platform trial design with statistical correction for genotype effects, versus the total sample size required across a series of pairwise, genotypically matched randomized controlled trials for each treatment.
  - The pairwise genotypically matched trials were assumed to each have 1:1 allocation between treatment (n=50) and placebo (n=50) arms
  - The genotype correction was assumed to increase per-arm sample size requirements from n=50 to n=60 for all arms in the platform design
- The platform design with genetically unmatched controls was found to have smaller sample size requirements than a series of pairwise trials – both in terms of the total sample size required and the number of patients assigned to placebo (**Figure 4**).
  - The larger the number of studied treatments, the greater the reduction in sample size requirements with a platform design vs. a series of traditional pairwise trials.
  - With six studied treatments, for example, the genotypically mixed platform design would require 180 fewer total patients — and 240 fewer assigned to placebo — than a series of genotypically matched pairwise trials.

Figure 3. A Randomized, Multi-genotype, Parallel Group, Blinded Platform Trial Design



Note: In this hypothetical platform trial, patients are enrolled from four genotype groups (A, B, C, D), each of which is amenable to one of four trialed treatments. Patients are randomized and blinded with, in this example, one patient of each genotype assigned to a common placebo arm for every 4 such patients assigned to active therapy. This trial design could include strictly concurrent treatment groups (e.g., if run by a single sponsor with a multi-genotype pipeline) or could admit non-concurrent treatment arms (e.g., including different mechanisms and drug developers over time).

Figure 4. Comparison of a Genotypically Unmatched Platform Design with a Series of Genotypically Matched Pairwise Trials: Numbers of Patients Required in Total and Assigned to Placebo



Limitations

- The illustrative trial analysis is based on the same clinical data as the prior genotype effect estimates. In practice, statistical correction for genotype effects should be used in a new clinical trial, or with new external control groups, for which the data are independent of the genotype effect estimates.

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Conclusions

- Accounting for genotype differences between treatment and control groups, via statistical adjustments informed by pre-existing estimates of genotype effects, reduced bias to a negligible level (< 0.3 units) in a hypothetical clinical trial simulated using real data.
- While such genotype adjustments increase per-arm sample size requirements, they also enable multi-genotype platform trial designs which, in turn, substantially reduce total sample size requirements and need for placebo exposure.
- Comparisons with genotypically unmatched controls, with careful consideration of baseline prognostic factors, are feasible in DMD drug development and could help limit placebo exposure among patients eligible for genotype-targeted treatments.

Disclosures

This study was conducted within the collaborative Trajectory Analysis Project (cTAP), a precompetitive coalition of academic clinicians, drug developers, and patient foundations formed in 2015 to overcome the challenges of high variation in clinical trials in DMD. cTAP has received sponsorship from Astellas (Mitobridge), Avidity Biosciences, BioMarin Pharmaceutical, Bristol Meyers Squibb, Catabasis, Daiichi Sankyo, Edgewise Therapeutics, Entrada Therapeutics, FibroGen, Italfarmaco SpA, Marathon Pharmaceuticals, NS Pharma, Pfizer, PTC Therapeutics, Roche, Sarepta Therapeutics, Shire, Solid Biosciences, Summit Therapeutics, Ultragenyx, Vertex Pharmaceuticals, Parent Project Muscular Dystrophy, Charley's Fund, and CureDuchenne, a founding patient advocacy partner and provider of initial seed funding to cTAP.

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