

---

# Research on Therapies for Rare Diseases

---

Roger J. Lewis, MD, PhD  
Department of Emergency Medicine  
Harbor-UCLA Medical Center  
David Geffen School of Medicine at UCLA  
Berry Consultants, LLC



@RogerJLewis

# Financial Disclosures

---

- Employee
  - County of Los Angeles, Department of Health Services, Harbor-UCLA Medical Center
  - David Geffen School of Medicine at UCLA
  - Los Angeles Biomedical Research Institute
  - Berry Consultants, LLC
- Special Government Employee
  - Food and Drug Administration/CBER
- Support from
  - National Institutes of Health/NINDS
  - National Institutes of Health/NHLBI
- Other consulting
  - Octapharma

# Challenges and Opportunity

---

- Challenges
  - Fewer patients, fewer data, less information
  - Goal is to maximize information gained and impact, given data limitations
- Opportunities
  - Regulatory and statistical standards may be less stringent
  - Greater ability/willingness to use ancillary information (e.g., prior information, non-concurrent controls, natural history data)

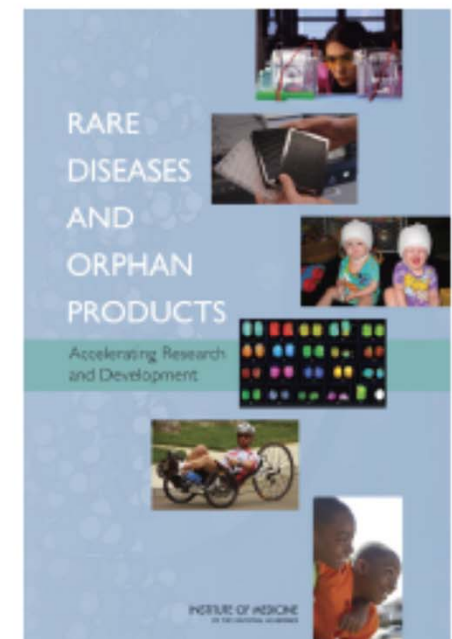
# Areas to Discuss

---

- Goals
- Population
- Randomization/Interventions
- Selection of Outcomes
- Analysis strategies
- Impact/Regulatory Strategy
- Cautions

# Rare Diseases and Orphan Products

## Accelerating Research and Development





U.S. Department of Health & Human Services



National Institutes of Health



National Center  
for Advancing  
Translational Sciences

Research

Funding &  
Notices

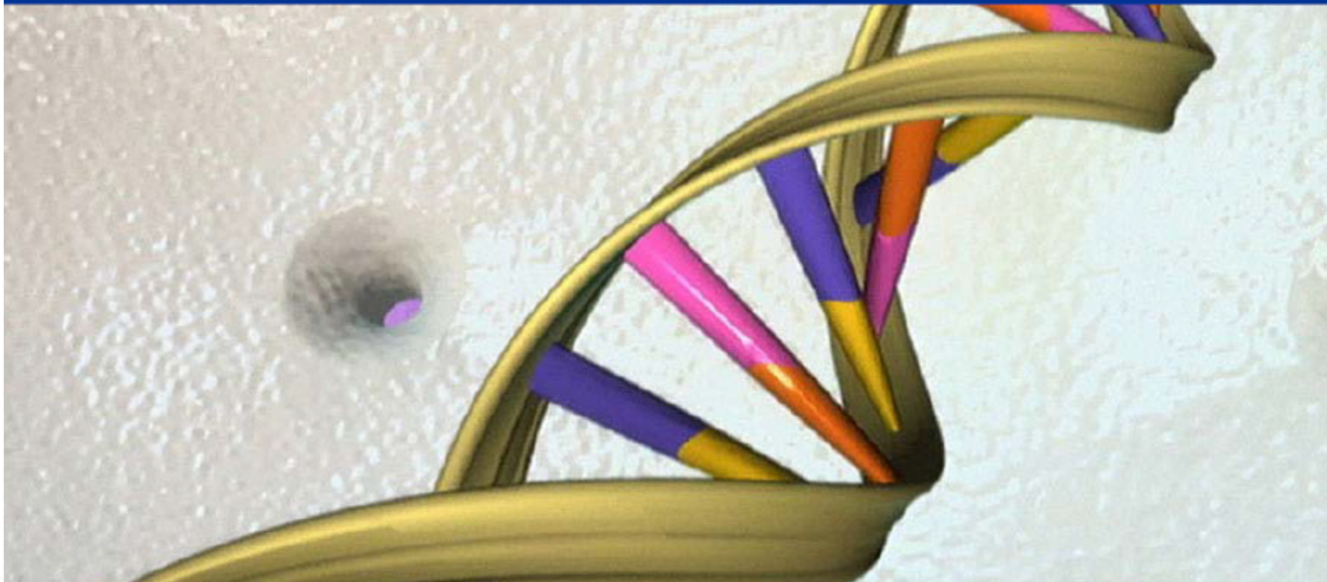
News & Media

About Translation

About NCATS

[Home](#) > [About NCATS](#) > [NCATS Programs & Initiatives](#)  
> [Therapeutics for Rare and Neglected Diseases \(TRND\)](#)

## Therapeutics for Rare and Neglected Diseases (TRND)



# Goals

---

- The size of the treatment effect sought must be reasonable given feasible sample size
- Degree of statistical certainty sought should consider the “patient horizon”
  - If a substantial fraction of all patients with disease are in the trial, treating patients well within the trial is an important goal
  - The sooner you can draw a conclusion, the sooner patient care can be improved or the research priorities can be revised
- Balance when you can get an answer versus getting a perfect answer

# Population

---

- Common dilemma
  - Enrolling as many patients as possible, even though they will be heterogeneous; versus
  - Enrolling a more homogeneous population, to hopefully increase the signal-to-noise ratio
- If both approaches are feasible, more data are almost always better
  - Heterogeneity of population has to be anticipated and managed clinically and statistically
  - Treatment must be plausibly effecting across heterogeneous patient population



# Randomization/Interventions

---

- Randomization
  - Randomization is almost always worth it, as non-randomized and single-armed trials are very difficult to interpret
  - Consider within subject randomization, e.g., N-of-1 trials
- Ideally, interventions should have great benefit to reduce the required sample size (always true?)
- Ways to increase potential treatment effect
  - Start with high doses, if acceptable risk/benefit ratio
  - Titrated/tailored dosing strategies (e.g., within patient titration)

# Selection of Outcomes

---

- Want to maximize the signal-to-noise ratio
- Strategies to consider
  - Outcomes that are “proximate” to treatment, e.g., shorter term neurological outcomes
  - Most informative (avoid dichotomization, “ceiling” and “floor” effects)
  - Disease specific versus general measures
  - May be better acceptance of “mechanistic” outcomes versus clinical outcomes in the rare disease setting
- Test outcomes in order of decreasing likelihood of success (“gatekeeping” strategy)

## RESEARCH ARTICLE

# Bayesian model of disease progression in GNE myopathy

M. Quintana<sup>1</sup> | J. Shrader<sup>2</sup> | C. Slota<sup>3,6</sup> | G. Joe<sup>2</sup> | J.C. McKew<sup>3</sup> | M. Fitzgerald<sup>1</sup> |  
W.A. Gahl<sup>4</sup> | S. Berry<sup>1,5</sup> | N. Carrillo<sup>3,4</sup>

<sup>1</sup>Berry Consultants, Austin, Texas

<sup>2</sup>Department of Rehabilitation Medicine,  
Clinical Center, National Institutes of  
Health, Bethesda, Maryland

<sup>3</sup>Therapeutics for Rare and Neglected  
Diseases Program, National Institutes of  
Health, Bethesda, Maryland

<sup>4</sup>National Human Genome Research  
Institute, National Institutes of Health,  
Bethesda, Maryland

<sup>5</sup>Kansas University Medical Center,  
Kansas City, Kansas

<sup>6</sup>RTI Health Solutions, Durham,  
North Carolina

**Correspondence**

M. Quintana, Berry Consultants, Austin  
Texas.

Email: melanie@berryconsultants.net

**Funding information**

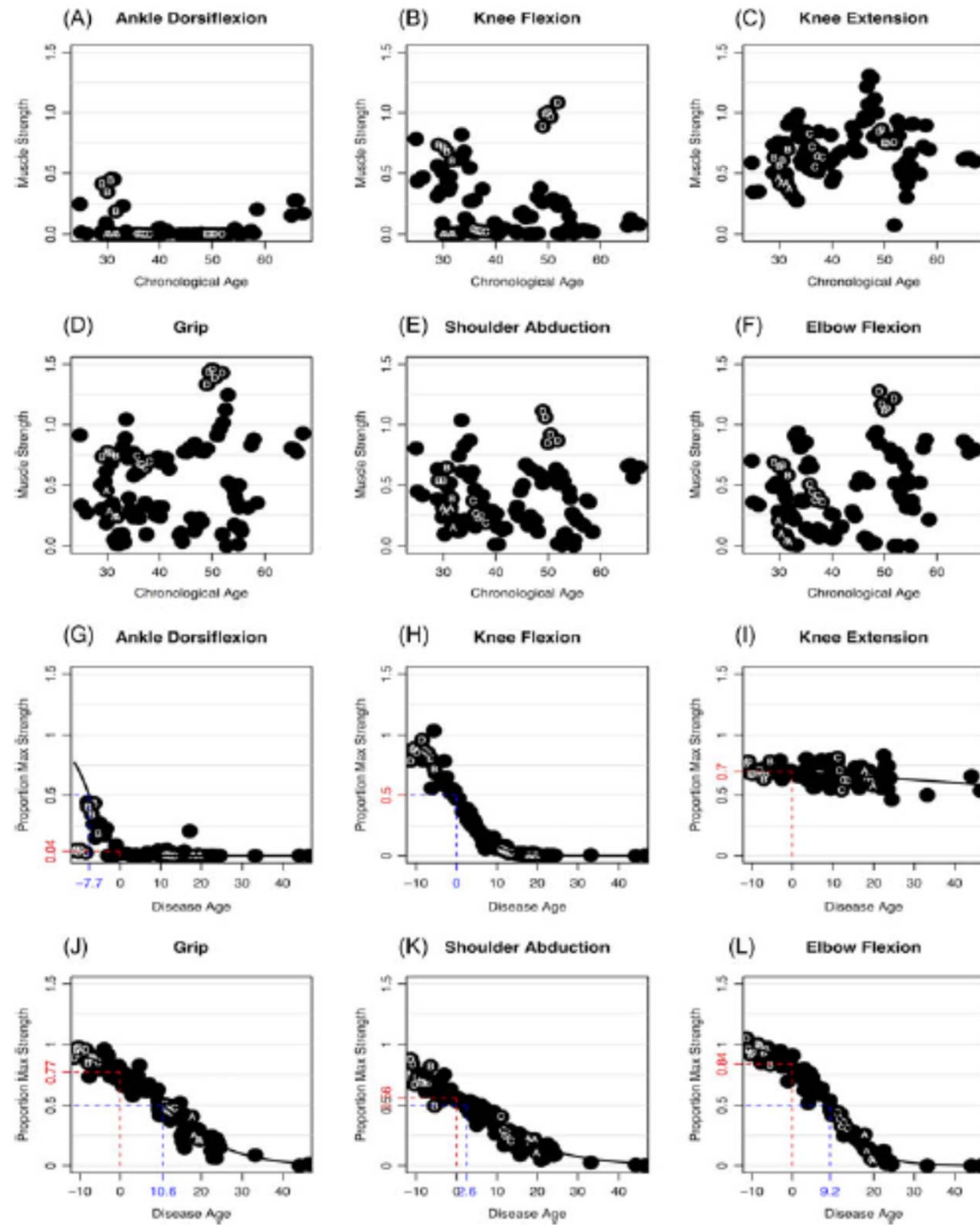
National Human Genome Research  
Institute (NHGRI); National Center for  
Advancing Translational Sciences  
(NCATS); NIH Clinical Center

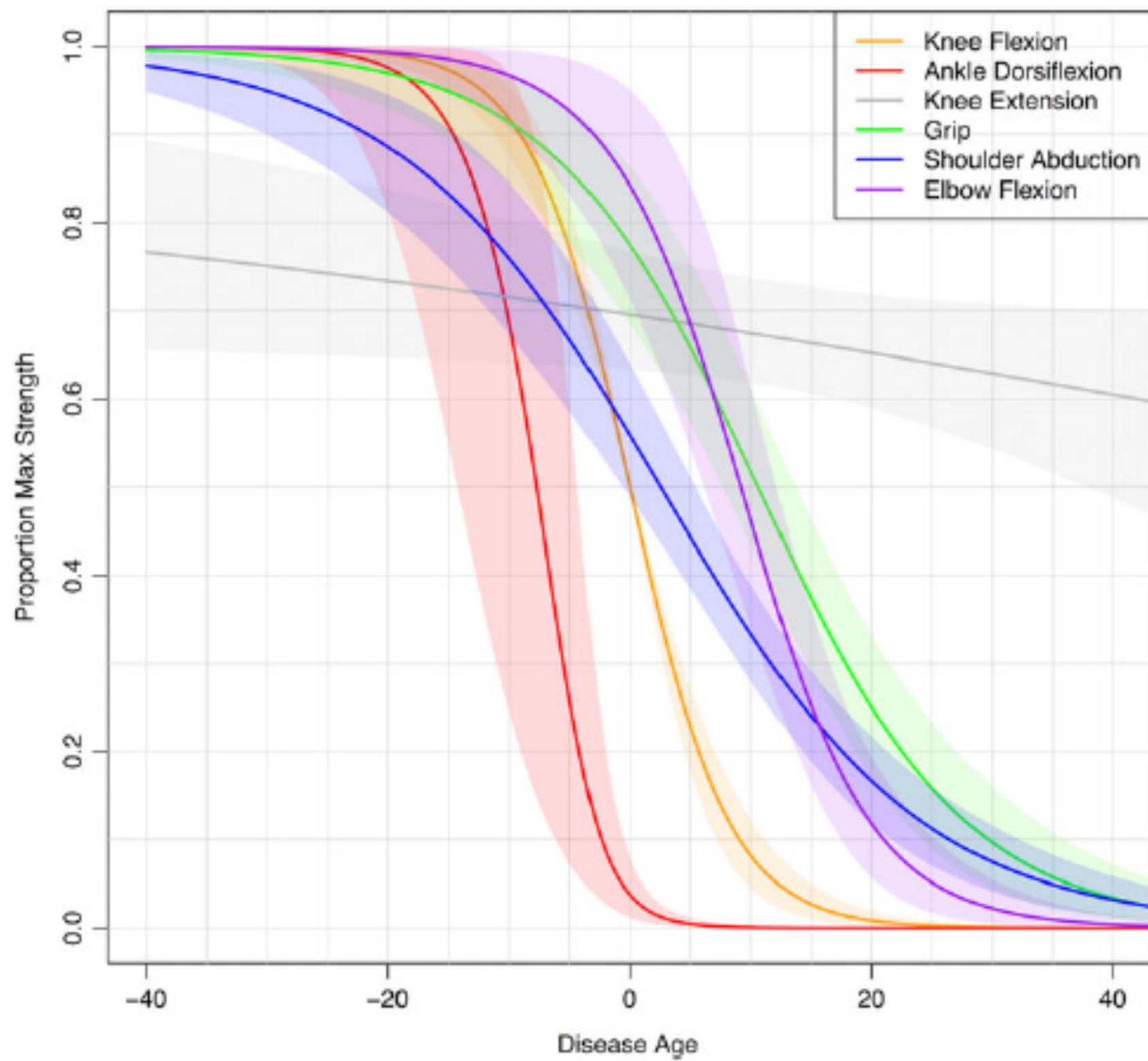
**One Sentence Summary:** A Bayesian repeated measures model based on quantitative muscle strength data from a prospective Natural History Study was developed to determine disease progression and design clinical trials for GNE myopathy, a rare and slowly progressive muscle disease.

GNE myopathy is a rare muscle disease characterized by slowly progressive weakness and atrophy of skeletal muscles. To address the significant challenges of defining the natural history and designing clinical trials for GNE myopathy, we developed a Bayesian latent variable repeated measures model to determine disease progression. The model is based on longitudinal quantitative muscle strength data collected as part of a prospective Natural History Study. The GNE Myopathy Progression Model provides an understanding of disease progression that would have otherwise required a natural history of unfeasible duration. "Disease age," the model-generated measure of disease progression, highly correlates with a variety of clinical, functional and patient-reported outcomes. With the incorporation of a treatment effect parameter to the GNE Disease Progression Model, we describe a novel GNE Myopathy Disease Modification Analysis that significantly increases power and reduces the number of subjects required to test the effectiveness of novel therapies when compared to more traditional analysis methods. The GNE Myopathy Disease Progression Model and Disease Modification Analysis can be applied to muscle diseases with prospectively collected muscle strength data, and a variety of rare and slowly progressive diseases.

**KEYWORDS**

Bayesian, clinical trial, disease progression model, GNE myopathy, muscle disease





# Analysis Strategies

---

- Use of prior information
  - Historical controls
  - Natural history studies (e.g., with objective performance criteria)
  - Prior probabilities
- Never dichotomize
- Measure baseline characteristics whenever possible
  - Adjusted analyses will generally have greater power
  - Generally avoid “change from baseline” analysis strategies

# Impact/Regulatory Strategy

---

- Consider what level of evidence would be necessary to alter clinical practice
- If goal is to potentially affect regulatory approval (including labeling) then involve FDA early
- Consider involvement of patient advocacy groups from beginning of trial planning, through execution and dissemination of results

# Cautionary Comments

---

- Enthusiasm is not the same as data
- Rigor is as important as always
  - Pre-specification vs post hoc or explanatory analyses
- Ethical standards
  - Desperate patients are inherently vulnerable
  - Involvement of patient groups is important