Modeling and Bridging Biomarkers to Support Pediatric Extrapolation

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Drouville, *In the fish tank*

Drouville is a patient, graphic designer and artist from Argentina who has survived multiple myeloma and a relapse.

ADEPT7- Advancing the Development of Pediatric Therapeutics Complex Innovative Trial Design
September 1, 2021

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Extrapolation of Efficacy for Pediatric Labeling

Efficacy is a causal inference that is extrapolated from the “source” population to the “target” population based on a descriptive inference (i.e., sufficiently similar, under a totality of evidence).

The (reasonable) clinical assumption that **the course of the disease** and **the response to treatment** are the two key “descriptive” attributes on which to extrapolate efficacy was proposed a priori by FDA in 1992.†

How can Modeling and Bridging Biomarkers Support this Clinical Assumption?

†“Specific Requirements on Content and Format of Labeling for Human Prescription Drugs: Proposed Revision of “Pediatric Use” Subsection in the Labeling” Federal Register/Vol. 57, No 201, dated October 16, 1992

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Modeling to support extrapolation

Viral exacerbation at 40x magnification

Biomarker-Disease Modeling

- Used to define prognostic enrichment biomarkers
- Biomarker endpoint that reflects earlier phase of disease- could be useful to extrapolate in diseases affecting children and adults

Input	Modeling	Output
• **Clinical Study Data**	• **Baseline severity** • **Longitudinal endpoints** • **Baseline/Longitudinal biomarkers** • **Other co-variates- age, demographics, genetics, etc…**	• **Disease trajectory** • **Predictors** • **Clinical trial simulator**

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Modeling to Selecting the Dose Matching Adult Exposures

- **Population PK, Non-Compartmental Analysis**
- **Physiologically- Based PK**
  - Accounts for physiologic changes that occur during development
  - Incorporates blood flow rates, organ volumes, transporter expression, receptor ontogeny
  - Select dose, predict exposures
  - Facilitate extrapolation of Drug-Drug Interaction Studies to pediatrics

Can Modeling Also Support Use of Bridging Biomarkers to Extrapolate Efficacy?

Cleary et al, Model-based drug-drug interaction extrapolation strategy from adults to children-risdiplan in pediatric patients with spinal muscle atrophy. Clin Pharmacol Ther 2021; Aug 4 ahead of print

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Link between a biomarker and clinical outcome captured within a physiologic model?

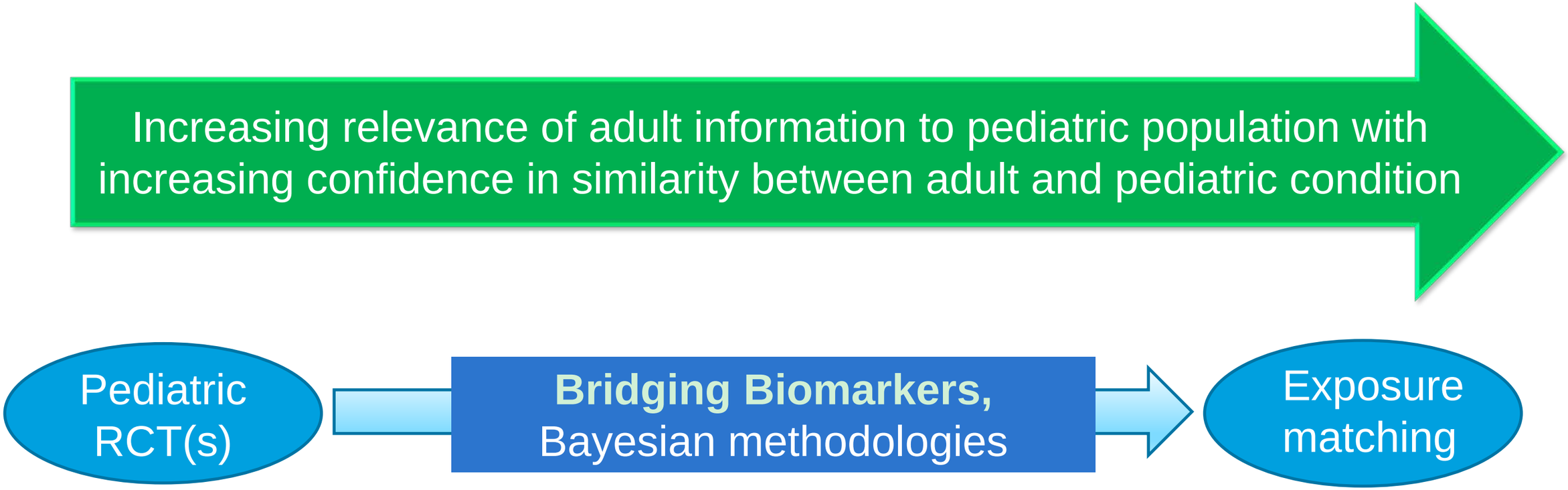
Quantitative Pharmacologic Systems model incorporating

- Disease pathophysiology
- Known systems of the therapeutic target
- Organ maturation
- Receptor ontogeny

- Incorporates data from multiple sources

- Bridging biomarkers may support extrapolation of efficacy from adults without this modeling.

Extrapolation of Efficacy: Relies upon disease/response similarity



Building the Totality of Evidence

Common Themes in Rare Disease and Pediatric Programs

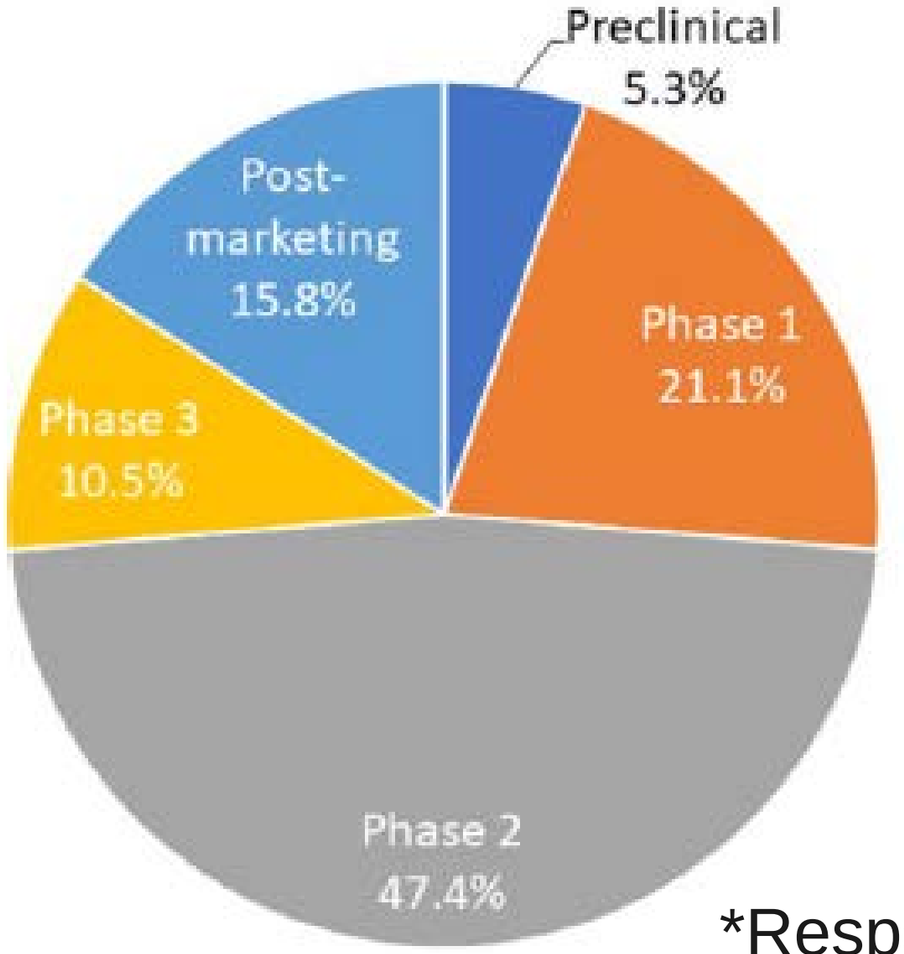
- Major unmet clinical need- patients are waiting
- Enroll minimum number of participants into trials necessary
- Rely on innovative approaches, but Complex and Innovative designs should expedite not impede pediatric labeling
- Need to focus on the uncertainties
- A mathematical solution (modeling) is helpful for dose selection, disease progression, trial simulation
- Early and timely regulatory input is critical

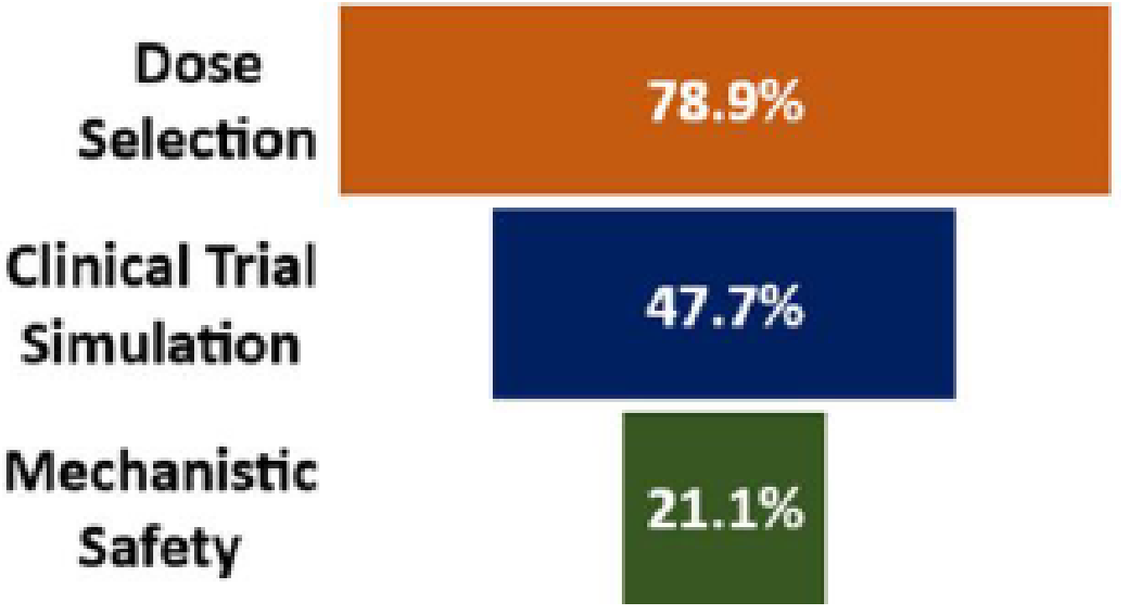
FDA: Model Informed Drug Development (MIDD)

- Provides an opportunity for drug developers and FDA to discuss the application of MIDD approaches to the regulatory evaluation of products in development

- Advice about how particular MIDD approaches can be used in a specific drug development program

FDA MIDD Program- dose selection in Phase 2 or Clinical Trial Simulation

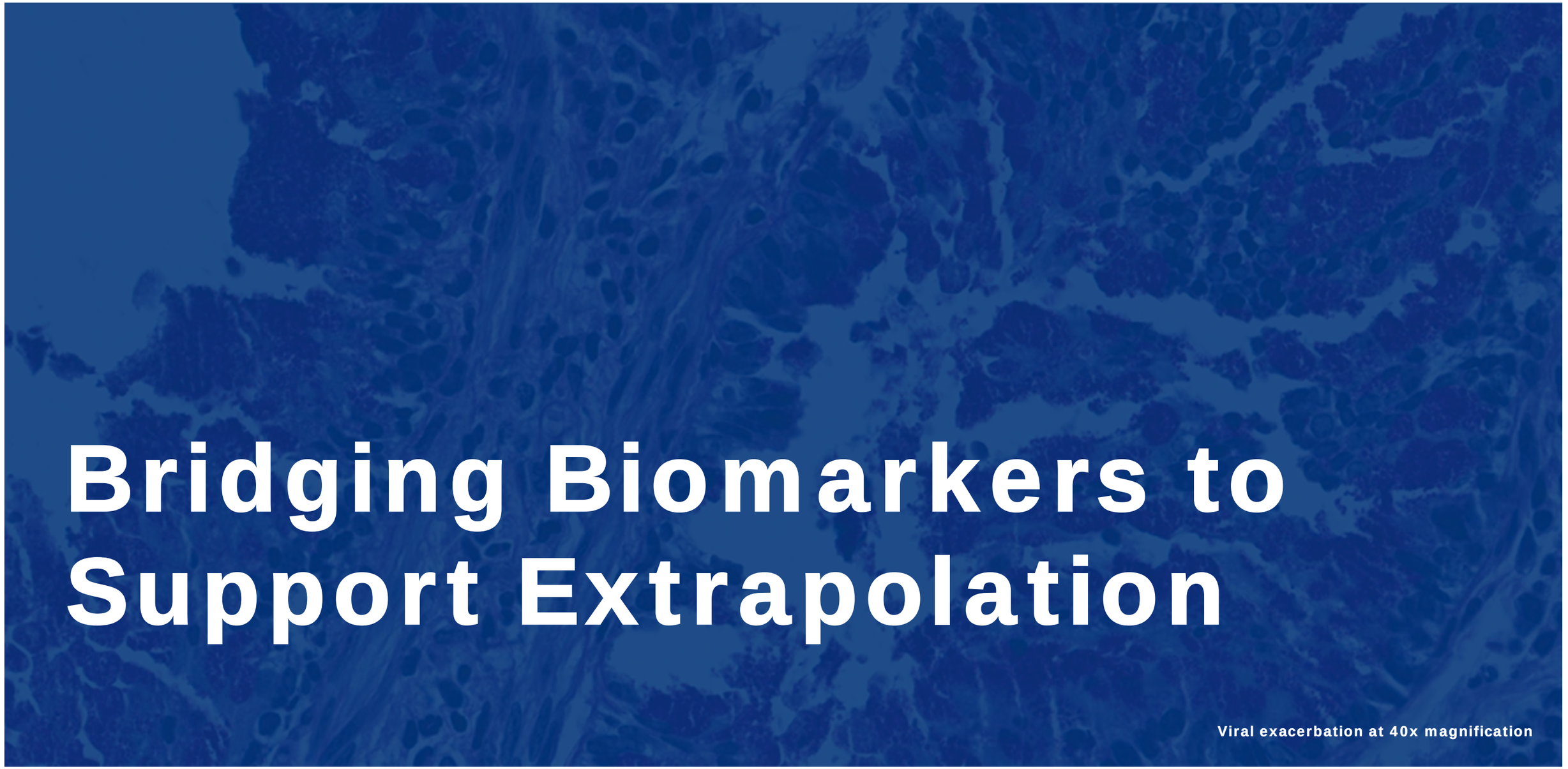




*Responses from 19 of 30 participating companies

Galluppi et al. Industrial perspective on the benefits realized from the FDA's Model-Informed Drug Development paired meeting pilot program. Clin Pharmacol Ther. 2021 May 15. Online ahead of print

Bridging Biomarkers to Support Extrapolation



Viral exacerbation at 40x magnification

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Context of Use and Level of Uncertainty is Important

- Bridging biomarkers could support similarity of disease, similarity of response
- A surrogate biomarker (eg change in dystrophin to support accelerated approval of eteplirsen for Duchenne) ≠ bridging biomarker used to support extrapolation from adult efficacy to peds
- Consider Target Populations- different levels of uncertainty
  - Age of children
  - Drug target/physiology expected to change with advancing age?
  - Other indications

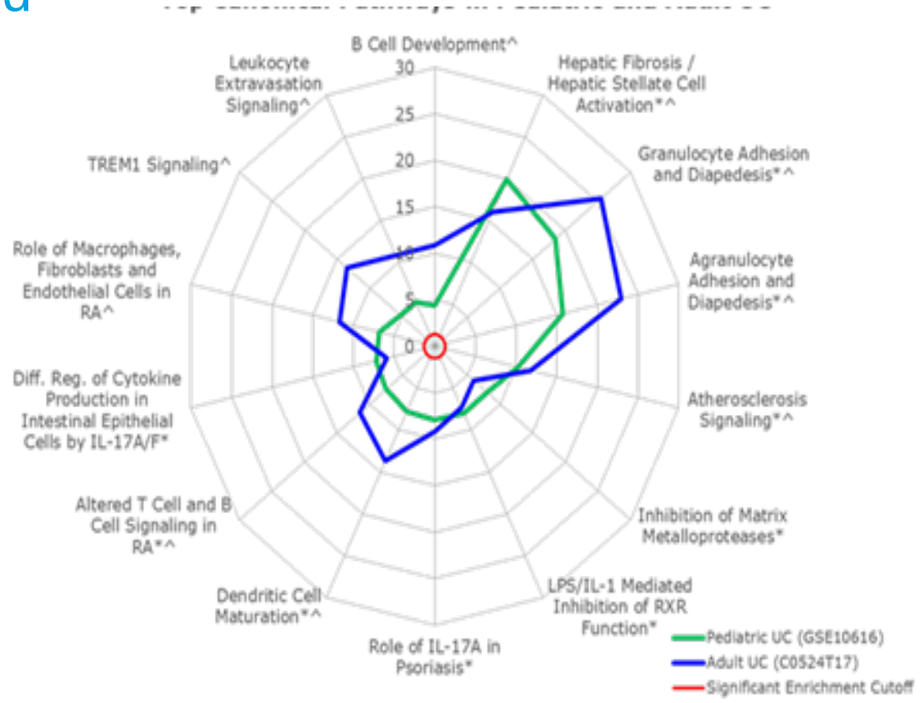
Context of Use: Demonstrating Similarity of Disease

Data were generated during PURSUIT demonstrating similarity of disease in adult UC and peds UC at baseline

Similarity in the molecular profile of disease and response to golimumab was demonstrated in adult and pediatric UC populations

Data were used to support extrapolation approach in PIP and PSP regulatory documents

Top canonical pathways in the **pediatric (green)** and **adult (blue)** ulcerative colitis disease profile.



Top 11 predicted upstream transcriptional regulators responsible for pediatric and adult ulcerative colitis expression profiles

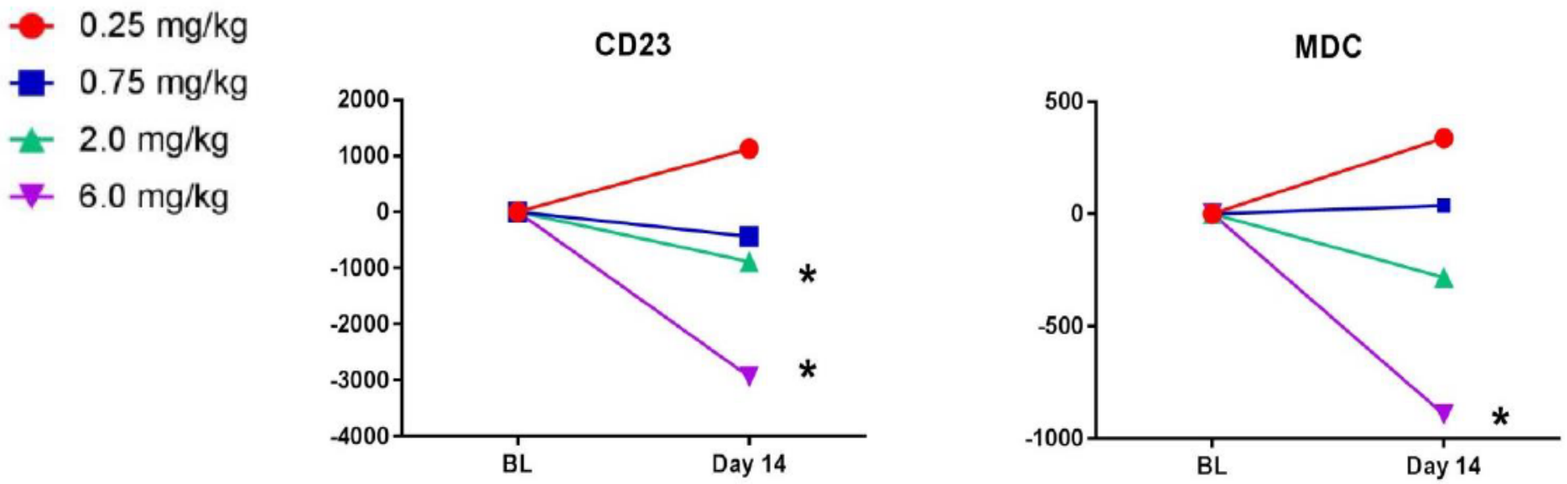
Upstream regulators	Activation z-score	
	Pediatric UC (GSE10616)	Adult UC (C0524T17)
lipopolysaccharide	11.27	12.84
IL1B	9.48	10.38
TNF	9.17	11.36
NFkB (complex)	8.15	9.21
IFNG	7.78	10.07
phorbol myristate acetate	7.76	8.62
CSF2	7.60	7.59
IL1A	7.59	8.09
SB203580	-7.39	-7.64
poly rI:rC-RNA	7.37	8.61
IL6	7.37	7.62

Li et al. J Pediatr Gastroenterol Nutr. 2018 Jul;67(1):45-52.

Context of Use: Dose Selection/possible bridging biomarker

Response PD biomarkers in Phase 2a are supportive of dose selection for an anti-inflammatory drug in Duchenne muscular dystrophy

- Pre-selected serum biomarkers reflective of inflammation and responsive to corticosteroids
- 6 of 7 pre-specified proteins showed dose response in Phase 2a



Once biomarkers are shown to correlate with exposures and clinical outcomes in a reference population (adults), can a similar change support extrapolation of efficacy to a target population (children)?

Conklin et al. Pharmacol Res. 2018 Oct;136:140-150.

Building Bridging Biomarkers to Support Pediatric Extrapolation

In Phase 2 adult studies:

- **Identify response biomarkers that are physiologically relevant to disease pathophysiology and drug mechanism of action**
- **Demonstrate change in biomarkers from baseline by exposure, clinical response / benefit**

Align PK and efficacy assessments

In pediatric studies:

Demonstrate similar change in biomarkers at a similar exposure in responders (and not in non-responders)

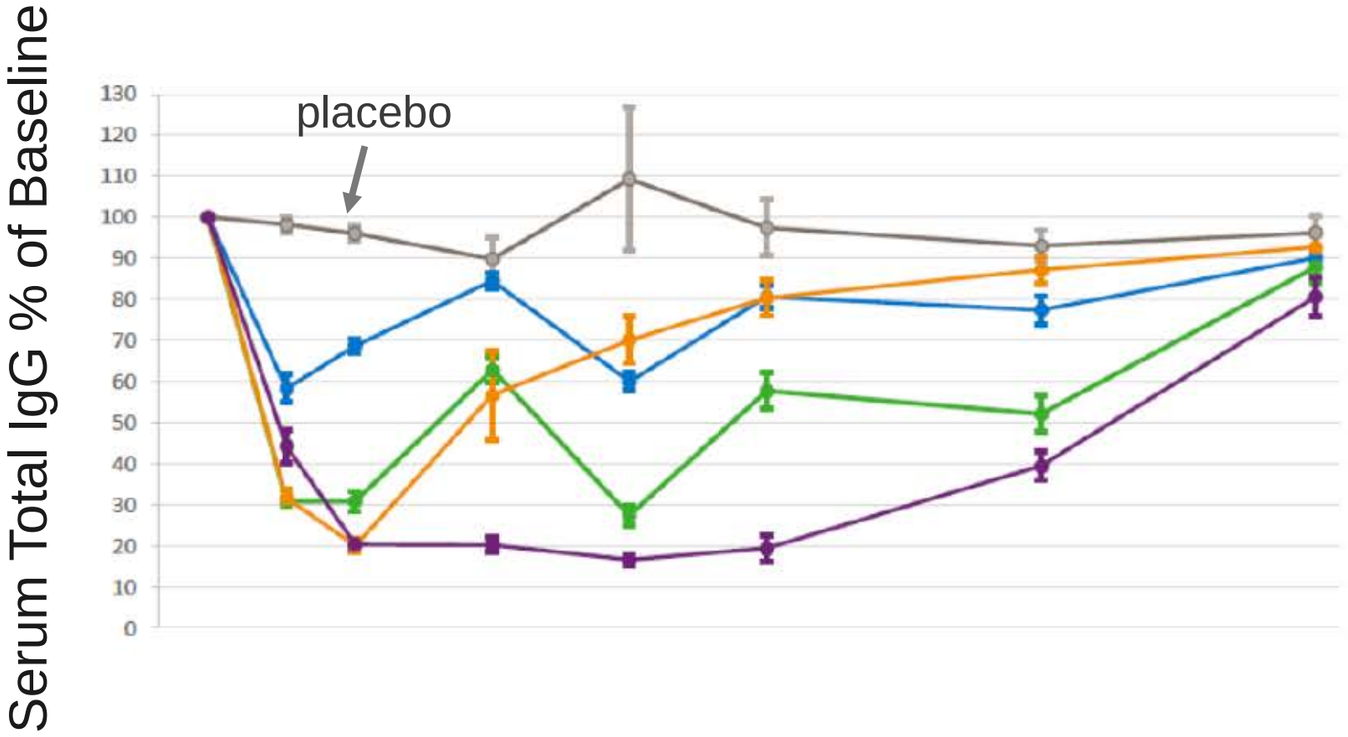
Supportive of :

- **Similarity of response**
- **Extrapolation of efficacy**

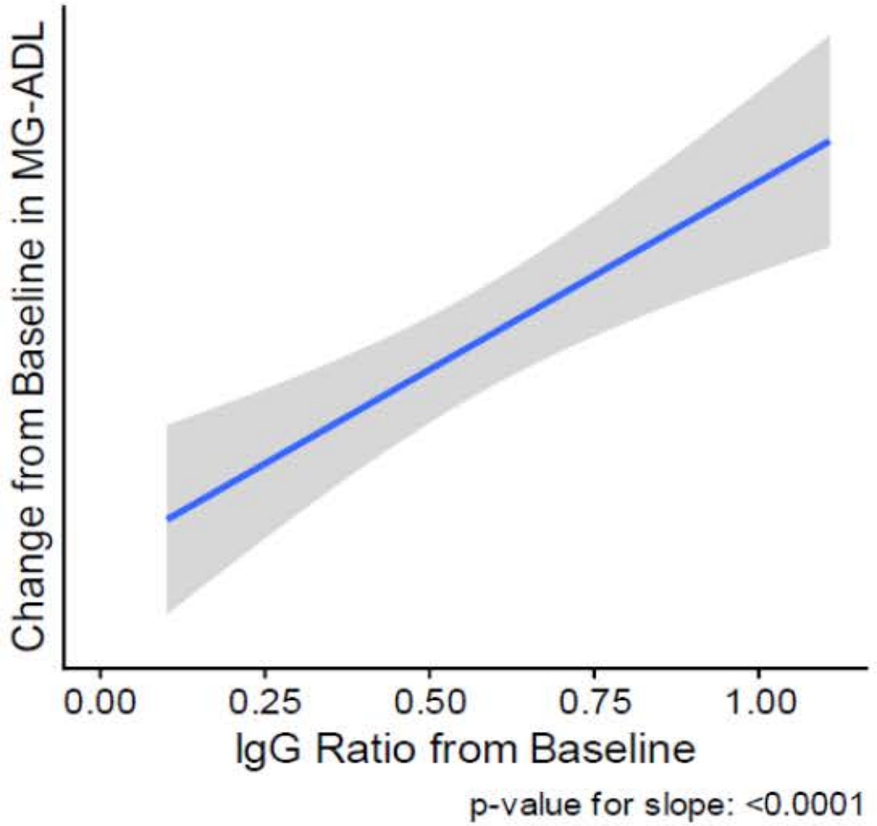
Context of Use: Bridging Biomarker to Support Extrapolation

Nipocalimab for gMG: decrease in serum IgG correlates with dose and clinical benefit

Serum Total IgG Concentrations



Comparison of MG-ADL Score and IgG Levels



Conclusions

- Modeling is useful for dose selection, disease progression, and clinical trial simulation
- Context of Use is important to consider when selecting and applying bridging biomarkers to the totality of evidence required for extrapolation.
- Change in pre-selected bridging biomarkers correlated with exposure/dose and response in adults could support pediatric extrapolation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