Developing an evidence framework for establishing treatment effectiveness in rare diseases.

2016 CADTH Symposium

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Disclosure

- I have no conflicts of interest to disclose

Outline

- Objectives
- Background & rationale
- Methods
- Results to-date
- Conclusions
- Next steps

Learning objectives

1. To understand the challenges in the generation and synthesis of rare disease research
2. To learn how alternative designs to randomized controlled trials address the identified challenges and to understand their tradeoffs
3. To understand the potential of expanded evidence synthesis practices in improving the quality of medical decision-making

Rare diseases - epidemiology

- Approximately **7,000 rare diseases** have been characterized to-date
  - Always increasing, especially with advances in technology
- Estimated that **1 in 12 people are affected** by rare disease

  ~ 3 million Canadians!
- Typically **genetic** in origin with ~50% presenting during childhood
- Often manifest as serious **chronic, progressive, life-shortening** conditions

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- Typically manifest as serious **chronic, progressive, life-shortening** conditions

A lot of **uncertainty** remains!

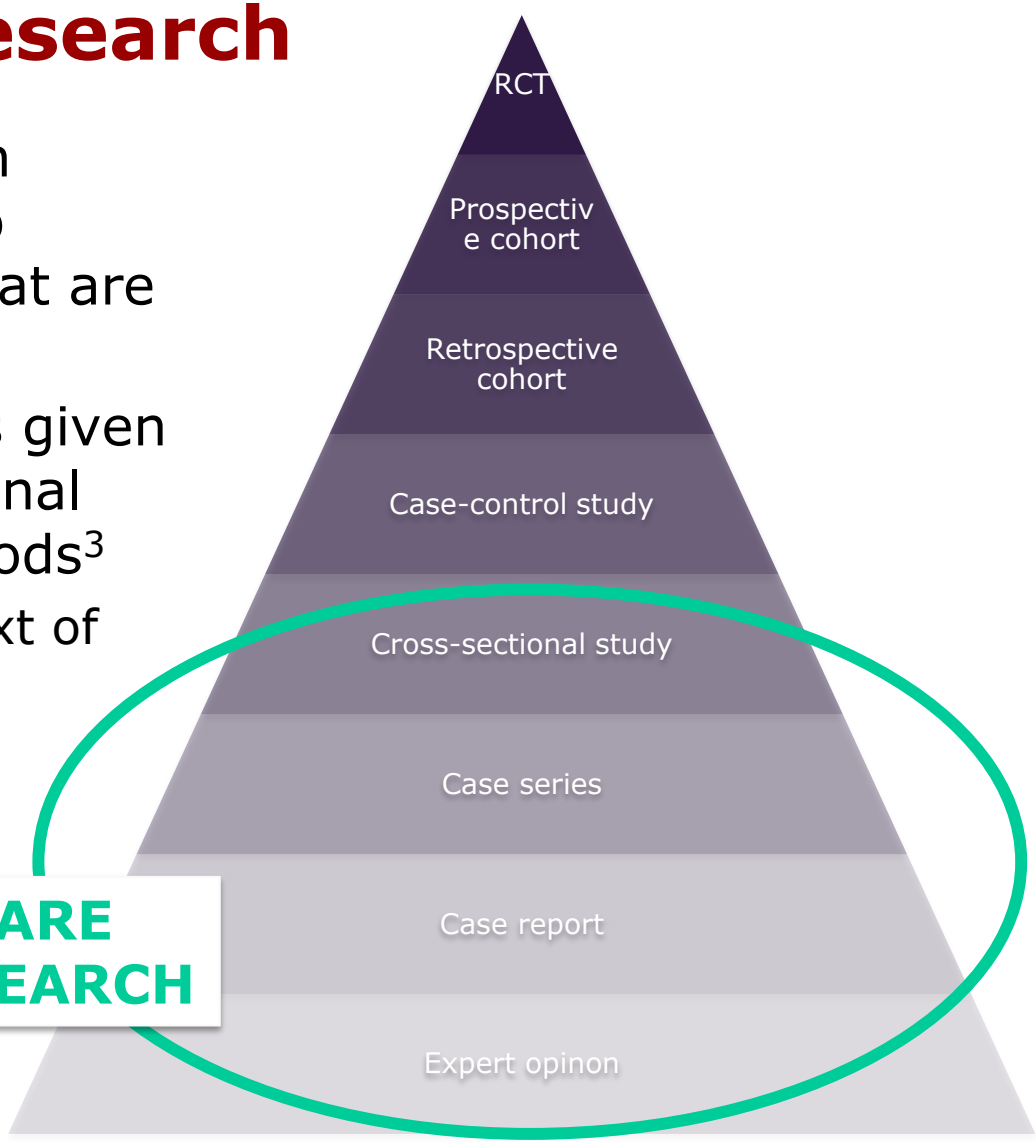
- Variation in prevalence
- Huge spectrum of clinical severity

Rare diseases - research

- **Challenging** to implement strong primary study designs (e.g., randomized studies) to evaluate the efficacy and effectiveness of intervention(s)[1]
  - **Small and clinically heterogeneous patient population**
  - Geographically dispersed
  - Lack of validated measures of disease progression
  - Lack of funding

Rare diseases - research

- Researchers must rely on **alternative methods** to evaluate effectiveness that are **more prone to bias**[2]
- Lower quality evidence is given little weighting in traditional evidence synthesis methods[3]
  - particularly in the context of policy-decision making



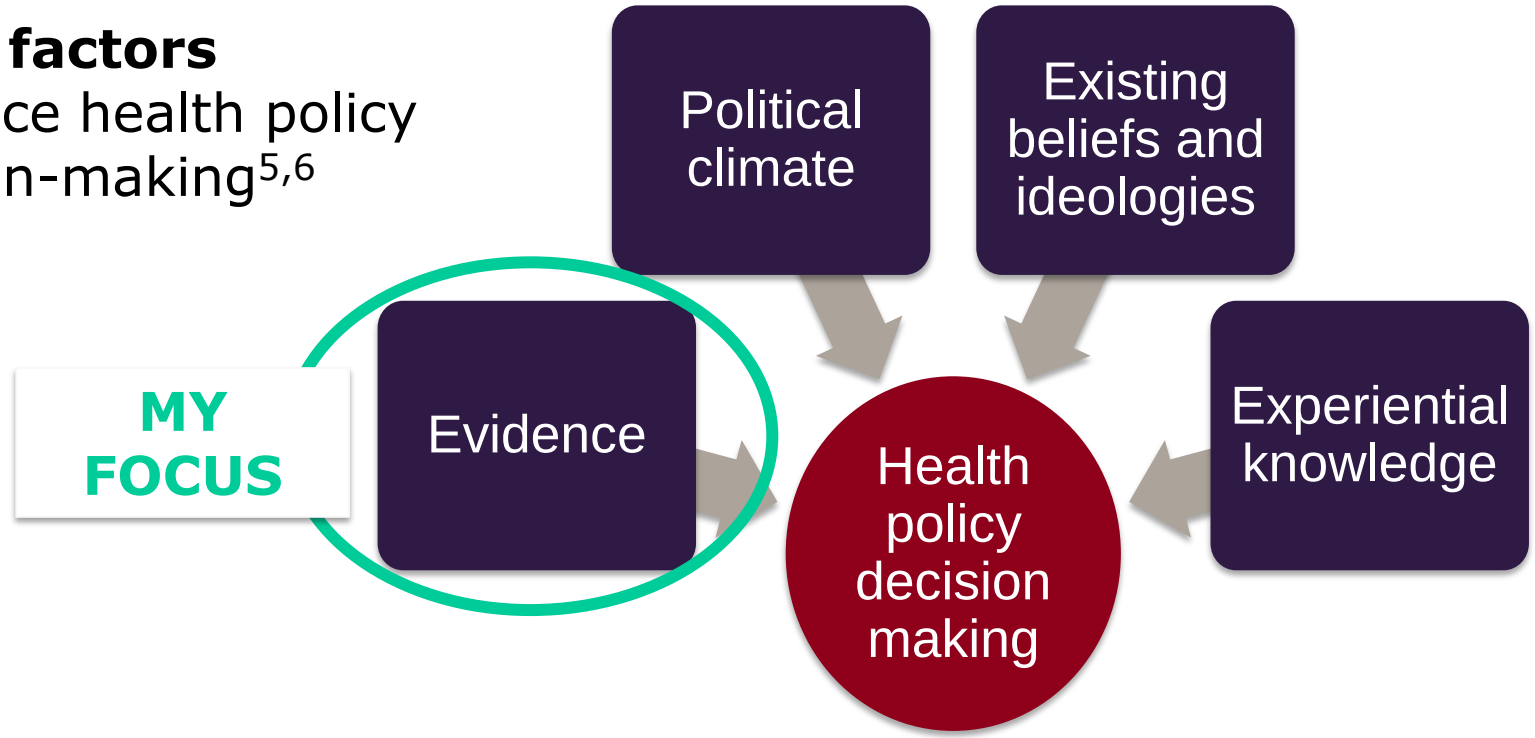
Traditional evidence hierarchy adapted from Ho et al. 2008[4]

Rare diseases – decision making

- Given the lack of strong evidence and the typically high cost of orphan drugs, **debates about the effectiveness of interventions** for rare diseases are common among stakeholders[5]

Rare diseases – decision making

- Given the lack of strong evidence and the typically high cost of orphan drugs, **debates about the effectiveness of interventions** for rare diseases are common among stakeholders[5]
- **Other factors** influence health policy decision-making[5,6]



Rare diseases – decision making

- Disagreements about the evidence:
  - What constitutes a **meaningful outcome**?
  - What is the **minimal clinically important difference**?
  - Is the **study design appropriate**?

- Expansion of current evidence synthesis practices to **improve the quality of decision-making** regarding the development, availability, and reimbursement of treatments for rare diseases?

PhD thesis

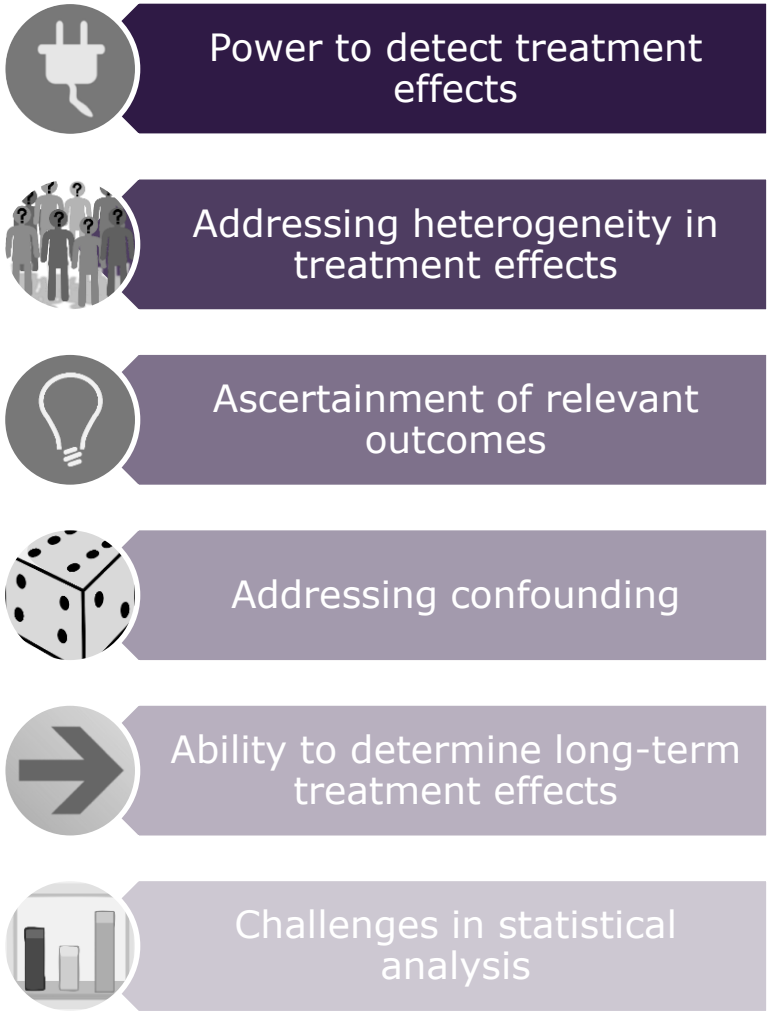
- Overall objective:
  - to develop **methods for synthesizing treatment effectiveness evidence for rare diseases** and to **investigate the value of those methods** from the perspective of various stakeholders

- Specific to this presentation:
  - to **conceptualize the value added to current knowledge from a range of study designs** for rare diseases, while specifically recognizing risks of bias with each

Methods

- Literature search to identify key papers in the following areas:
  - Evidence typologies for evaluating treatment effectiveness
  - Risk of bias assessment
  - Methods and frameworks for evaluating interventions for rare diseases
- Selected papers were **qualitatively synthesized** to identify:
  - challenges specific to the rare disease context
  - ability of specific study designs to address these challenges
  - risk of bias

Results – challenges in rare disease research



- Identified **six main challenges** in generating evidence of treatment effectiveness for rare diseases
- Challenges are **inter-related** and not mutually exclusive
  - Representative of different **tradeoffs** among study designs in rare disease research

1. Power to detect treatment effects

	
RCTs	+/-
PCTs	+/-
N-of-1 trials	+/-
Adaptive trials	+/-
Registries	+
Cohort studies	+
Case series	-

+ addressing this aspect is a strength of this design
+/- addressing this aspect is variable
- addressing this aspect is a weakness of this design
RCTs (randomized controlled trials); PCTs (pragmatic controlled trials)

2. Addressing heterogeneity in treatment effects

		
RCTs	+/-	-
PCTs	+/-	+
N-of-1 trials	+/-	+
Adaptive trials	+/-	-
Registries	+	+
Cohort studies	+	+
Case series	-	+

+ addressing this aspect is a strength of this design
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3. Ascertainment of relevant outcomes

			
RCTs	+/-	-	+/-
PCTs	+/-	+	+
N-of-1 trials	+/-	+	+/-
Adaptive trials	+/-	-	+/-
Registries	+	+	+/-
Cohort studies	+	+	+
Case series	-	+	+

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4. Addressing confounding

				
RCTs	+/-	-	+/-	+
PCTs	+/-	+	+	+
N-of-1 trials	+/-	+	+/-	+/-
Adaptive trials	+/-	-	+/-	+/-
Registries	+	+	+/-	-
Cohort studies	+	+	+	-
Case series	-	+	+	-

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RCTs (randomized controlled trials); PCTs (pragmatic controlled trials)

5. Ability to determine long term treatment effects

					
RCTs	+/-	-	+/-	+	-
PCTs	+/-	+	+	+	+/-
N-of-1 trials	+/-	+	+/-	+/-	-
Adaptive trials	+/-	-	+/-	+/-	-
Registries	+	+	+/-	-	+
Cohort studies	+	+	+	-	+
Case series	-	+	+	-	+/-

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RCTs (randomized controlled trials); PCTs (pragmatic controlled trials)

6. Challenges in statistical analysis

						
RCTs	+/-	-	+/-	+	-	+/-
PCTs	+/-	+	+	+	+/-	+/-
N-of-1 trials	+/-	+	+/-	+/-	-	+/-
Adaptive trials	+/-	-	+/-	+/-	-	+/-
Registries	+	+	+/-	-	+	+/-
Cohort studies	+	+	+	-	+	+/-
Case series	-	+	+	-	+/-	-

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Example – MPSI (Hurler syndrome)

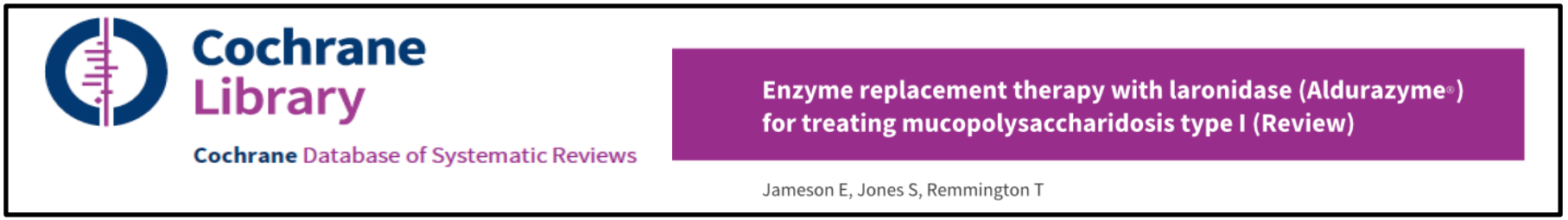
- Lysosomal storage disorder
- Birth prevalence: 1 in 100,000[7]
- Broad spectrum of clinical manifestations affecting multiple organ systems

TREATMENTS

- Hematopoietic stem cell transplant (HSCT) before age 2 is current standard of care[8]
  - Slows progression of cognitive impairments
- Enzyme replacement therapy (ERT) with laronidase (Aldurazyme®)[8]
  - Does not cross blood brain barrier
  - Very expensive!

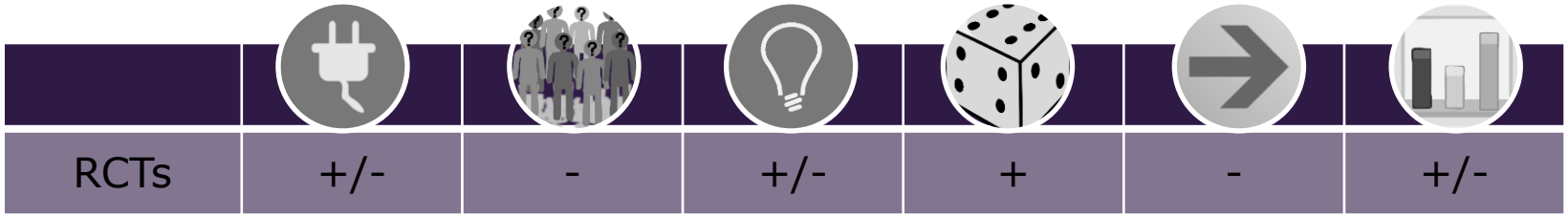
Example – evidence synthesis

- Recent Cochrane review for ERT as treatment for MPSI:



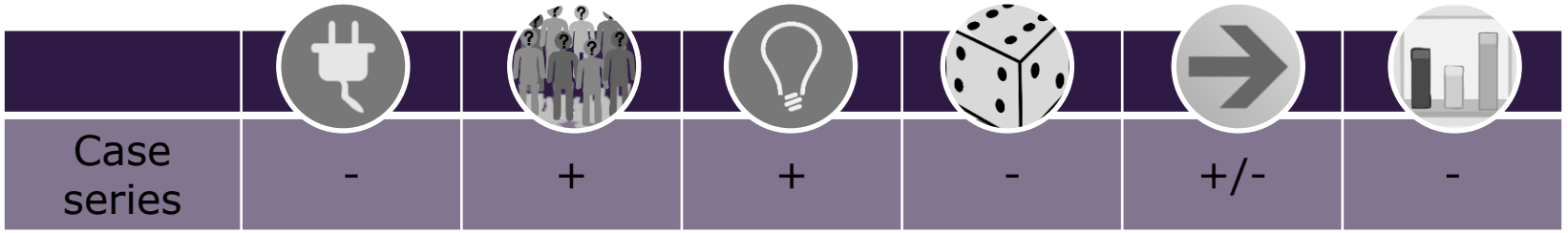
- Included a single RCT:

Example – RCT (MPSI)



- Randomized, double-blind, placebo-controlled, multicenter, multinational clinical trial
- Sample size n=45; several exclusions
- Primary outcome → composite **6-Minute Walk Test (6MWT)** and **forced vital capacity (FVC)**
  - Several secondary outcomes
- Follow-up = 26 weeks
- Results:
  - 6MWT - 38.1m increase in treatment group
  - FVC – 5.6% increase in treatment group

Example – observational study/case series (MPSI)



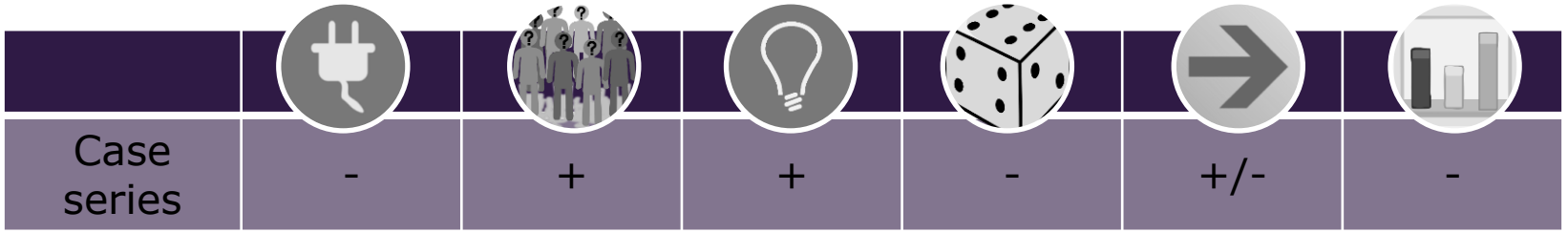
TRANSPLANTATION

BLOOD, 26 MARCH 2015 • VOLUME 125, NUMBER 13

Long-term outcome of Hurler syndrome patients after hematopoietic cell transplantation: an international multicenter study

Mieke Aldenhoven,[1] Robert F. Wynn,[2] Paul J. Orchard,[3] Anne O'Meara,[4] Paul Veys,[5] Alain Fischer,[6] Vassili Valayannopoulos,[7] Benedicte Neven,[6] Attilio Rovelli,[8] Vinod K. Prasad,[9] Jakub Tolar,[3] Heather Allewelt,[9] Simon A. Jones,[10] Rossella Parini,[11] Marleen Renard,[12] Victoria Bordon,[13] Nico M. Wulffraat,[14] Tom J. de Koning,[15] Elsa G. Shapiro,[16] Joanne Kurtzberg,[9] and Jaap Jan Boelens[1]

Example – observational study/case series (MPSI)



Case series	-	+	+	-	+/-	-

- Multicenter, multinational, retrospective, observational
- Sample size n=217; excluded attenuated phenotypes
  - 21% received ERT + HSCT
- Primary outcomes → **neurodevelopmental** outcome (DQ/IQ) & **growth**
- Follow-up = average of 9 years (range 3-23 years)
- Results:
  - Male sex, lower baseline DQ/IQ, higher age at HCT, use of total body irradiation and higher age at evaluation = statistically significant predictors of inferior neurodevelopmental outcome
  - ERT not a predictor of any outcomes

Conclusions

- Generation of high quality evidence in determining treatment effectiveness in rare diseases is challenging
- Challenges are inter-related and strategies to overcome the challenges often result in tradeoffs in risk of bias among study designs
- Information from this project will help policy-advisors and clinicians, researchers, patients, and families to make informed medical decisions

Next steps

- **Review additional study designs**
  - crossover trials and other alternative trial designs
  - case studies
- **Consultation with various stakeholders** to better understand their views about evidence for rare diseases and their opinions on different approaches to summarize evidence
- **Produce framework** to provide guidance for approaches to systematically reviewing treatment effectiveness evidence in rare diseases and
  - application in two case studies (MPSI and Pompe disease)

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8. D'Aco K, et al. Diagnosis and treatment trends in mucopolysaccharidosis I: findings from the MPS I Registry. *Eur J Pediatr* 2012;171:911–9

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Questions?

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