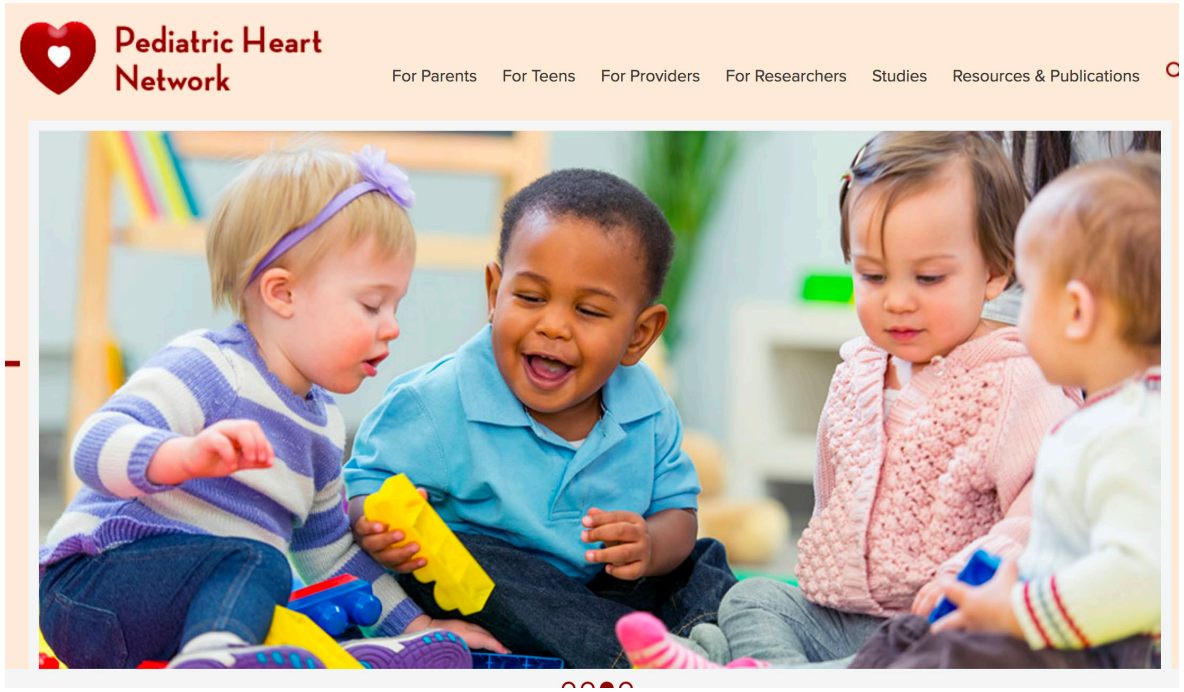
Challenges in Pediatric Drug Trials

- Rapid growth and development in children
  - Impacts pharmacokinetics and pharmacodynamics
- Need for surrogate study endpoints
  - Long life expectancy makes endpoints difficult to define
  - Different endpoints may be needed at different ages
- Rare diseases/Small patient populations
  - Single center studies can not provide adequate sample size
  - Limited market/revenue for pharmaceutical industry
- Ethical considerations for clinical research in children

Pediatric Heart Network



Trial	Primary Endpoint
Single Ventricle Reconstruction Blalock-Taussig vs. Sano Shunt	Survival
Infant Single Ventricle Enalapril vs. Placebo	Somatic Growth
Kawasaki Disease Methylprednisolone vs. Placebo	Coronary Artery Z score
Marfan Losartan vs. Atenolol	Aortic Root Z score

FUEL: Primary Results

- Udenafil at 87.5 mg twice daily was well tolerated and showed clinical improvement in exercise capacity in adolescents with Fontan
- Most pronounced at VAT with significant improvement in:
  - VO_2 at VAT
  - VE/VCO_2 at VAT
  - Work rate at VAT
- The reasons for these findings are due to the unique response to exercise in the Fontan physiology

Fontan Exercise Capacity and Study Results

- Max VO_2 has been a generally accepted marker of hospitalization and death
- Max VO_2 may not be an ideal efficacy measure in SV
- Limited ability to increase CO to meet exercise need
  - Lack of a sub-pulmonary pumping ventricle.
  - Baseline CVP rises significantly during exercise
  - Limits ability to increase pre-load and thus CO
- Unique physiologic ceiling for max VO_2 in the Fontan

Veldtman et al. Cong Heart Dis 2017; Navaratnam et al. AJC 2016

Fontan Exercise Capacity and Study Results

- VO_2 at VAT, which measures sub-maximal exercise, is more relevant for the Fontan circulation.
- At submaximal exercise, patients with Fontan do not reach the point of an unsustainably high CVP
- VAT occurs at about 70% of max VO2 in Fontan circulation (vs. 55% in 2V Physiology)
  - Max VO2 ceiling is lower

Atz et al. AJC 2017; Agnolotti et al. JTCVS 2017

FUEL Results: Impact on Practice

- In adults with congenital heart disease, maximal VO2 of approximately 45 to 50% of predicted is threshold value for increased risk of heart failure and death.
- A medication that addresses the central deficiencies of Fontan physiology and results in improved exercise performance may allow for a longer period of symptom free survival

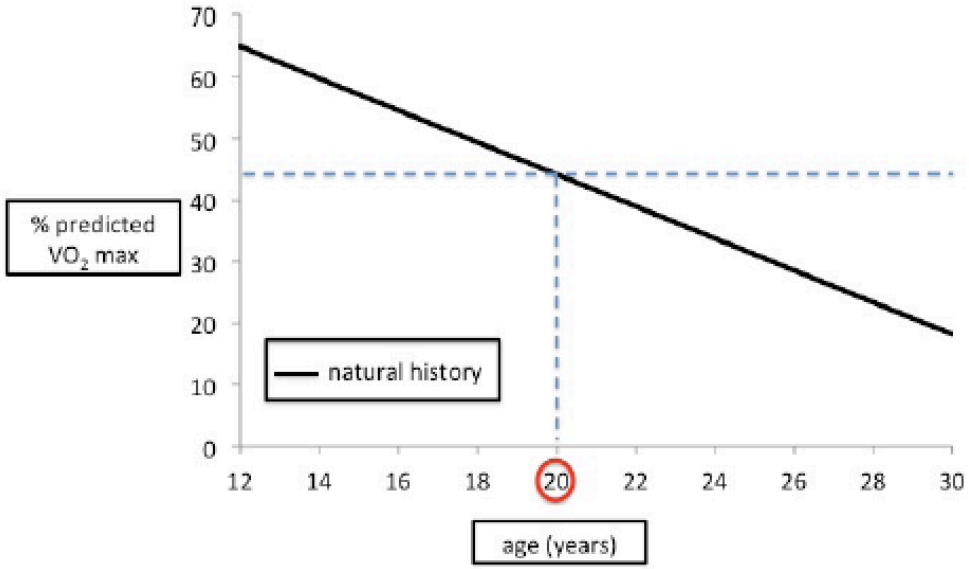


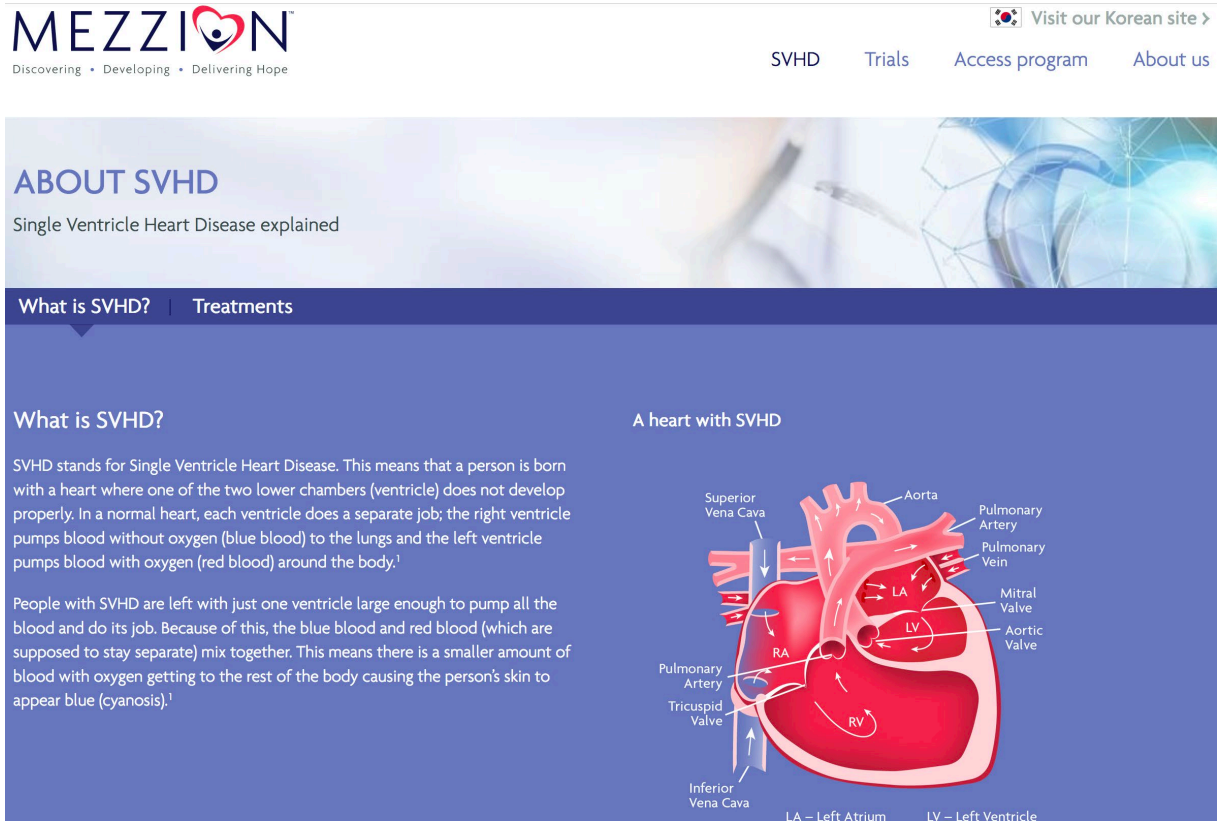
Figure 2. Projected decline in percent predicted maximal VO_2 versus age in years from the PHN Fontan population based on a 2.6% decline per year. Note that the threshold value of 45% is reached by 20 years of age (horizontal dotted line)

Giardini et al. AJC 2007; Diller et al. Circulation 2005

FUEL Results: Press Release

“Landmark pediatric drug trial finds certain exercise benefits in teens with complex single ventricle congenital heart disease with Fontan physiology.”

Drug therapy aims to delay decline in the Fontan teens’ well-being



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