HTA in Childhood Diseases: Evidentiary Challenges

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Enpr-EMA Annual Meeting

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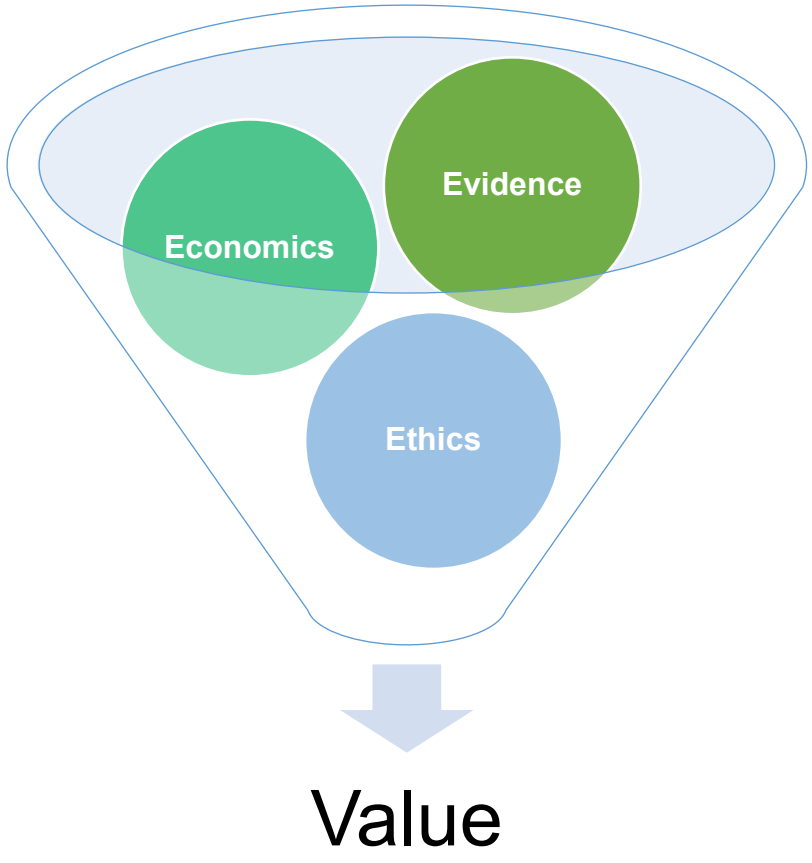
SickKids 2025

HTA Challenges in an Emerging Era of Precision Medicine



What is Value? For Whom?

Do They Use the Same Measures for Value?

- Diagnostic company
- Pharma company
- The positive patient
- The negative patient
- The other patient
- The insurance fund
- The provider
- The pharmacist
- The ethicist
- The researchers
- The policy maker
- …

Investment	RoI	Margin	Risk	of Dx Component
Investment	RoI	Margin	Risk	of Rx Component
Hope for Health		Fear for restricted Coverage		
No unnecessary side effect		Alternative?		
Insurance cost	Negative impact on my coverage?			
Budget Impact	Savings	Certainty	Fairness	
Efficiency	Reimbursement	Patient Retainment		
Complexity	Shelf Life / Storage	Value Chain		
Societal Impact	Risk	Access	Fairness	
Innovation	Knowledge	Margin	Risk	
Voter impact	Economics	X-National	Fairness	

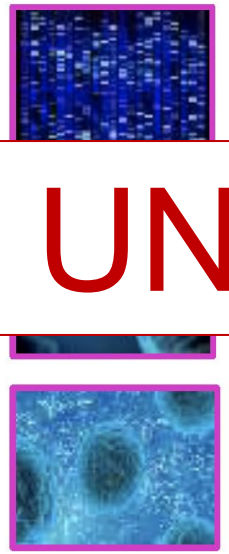
… Do They Apply the Same Weights?

Holtorf, ISPOR 2018

Towards Precision Value Frameworks

Core Components that Value Frameworks Addressing Precision Medicine Should Consider

1. Incorporating diagnostic performance
2. Alignment of evidence and reimbursement for the test component
3. Clarify acceptable study designs and evidentiary expectations for the test component
4. Clarifying evidence expectations for different diagnostic applications
5. Incorporate value of "ruling out" treatment options



6. Addressing next generation testing special considerations

9. Integration of precision medicine with AI, machine learning & decision support

UNCERTAINTY

Faulkner, ISPOR 2018; Faulkner et al, VIH 2020

Table 3. Novel Considerations of Evidence and Value Associated with Precision Medicine.

- Uncertainties around standards and expectations for validation of individual biomarkers in a test or of the algorithm driving test interpretation
- Uncertainties around number needed to test to support good value for money, particularly as we move towards multi-marker testing
- Uncertainties around insufficiently validated biomarkers
- …of identifying patient risk factors or diseases not …y the broader test
- …overuse, harms, or ethical considerations after use …mechanism
- Potential for a test to indicate the use of more than one targeted therapy
- Potential to identify treatments that have not been proven in specific indication
- Payment requirements as numbers of biomarker tests expand
- Value of the precision mechanism in establishing or increasing efficiency of clinical pathways
- Health system effects of precision medicine beyond obvious standard clinical or economic metrics

Value Frameworks: Deliberating on Uncertainty

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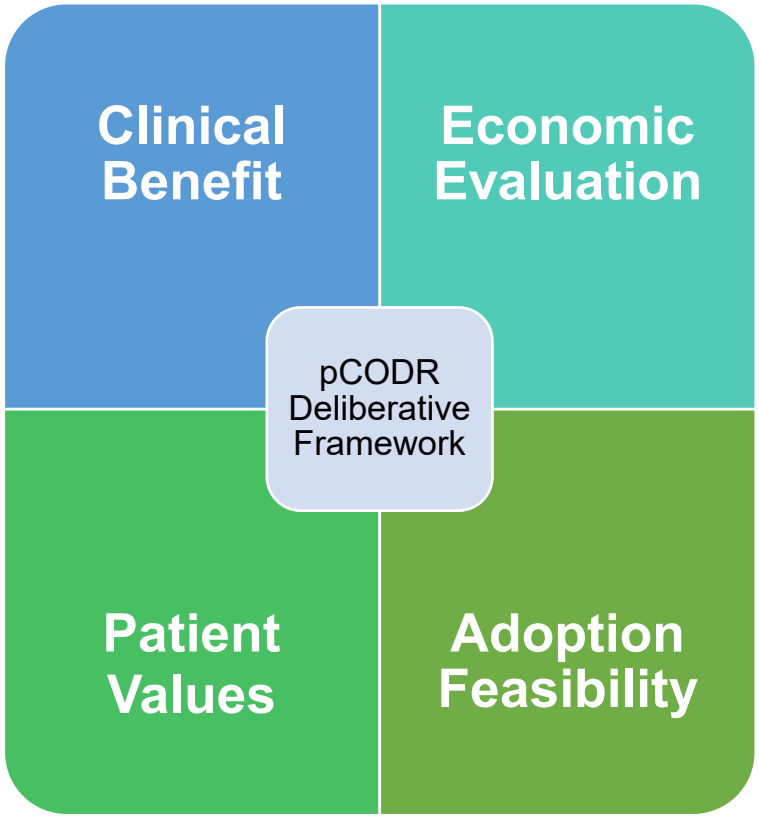
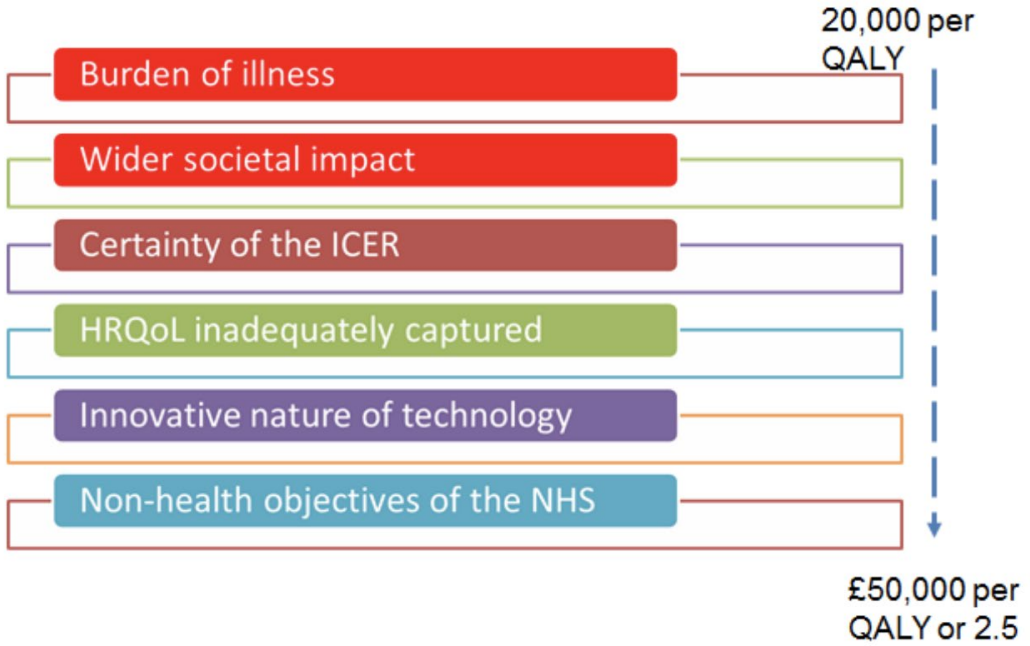
CADTH



NICE National Institute for Health and Care Excellence



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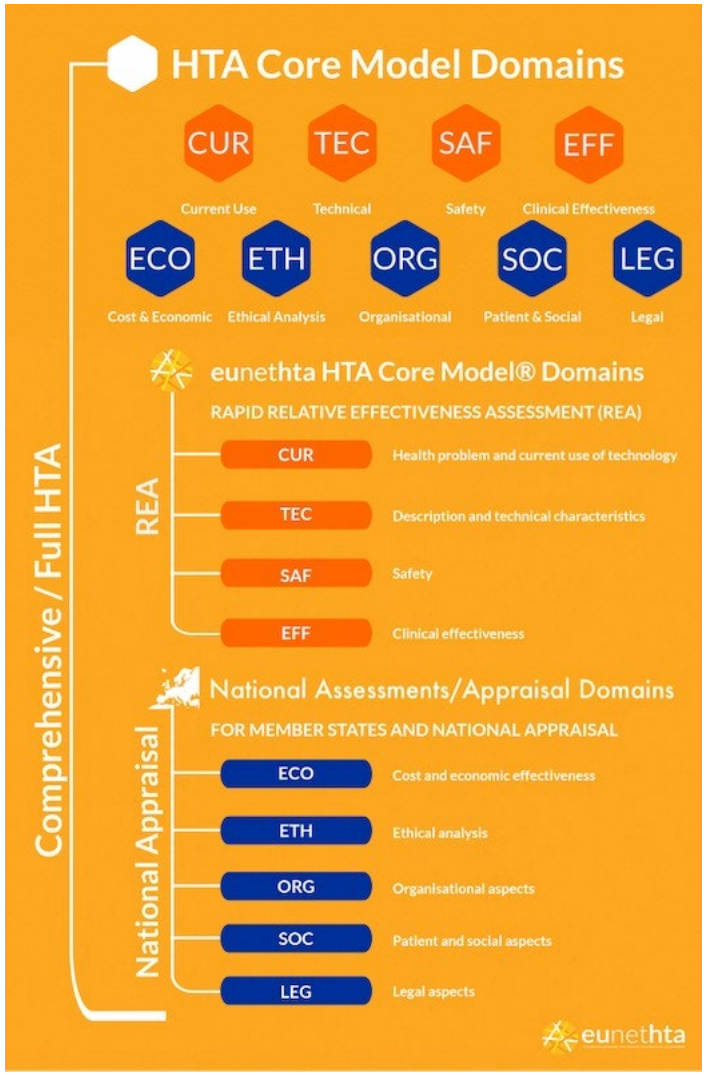
EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT



Pediatric Drug Access: Dynamics and Challenges

Health system challenges

Industry
- Market dynamics
- Political economy

Regulator
- Evidence of safety and efficacy
- Pediatric indication

HTA
- HTA submission
- Priority-setting for review

Payer
- Opportunity cost
- Political environment

HTA challenges

Evidence
- Biology
- Epidemiology
- Trial enrolment

Economics
- Life-course dynamics
- Child and family utilities
- Externalities

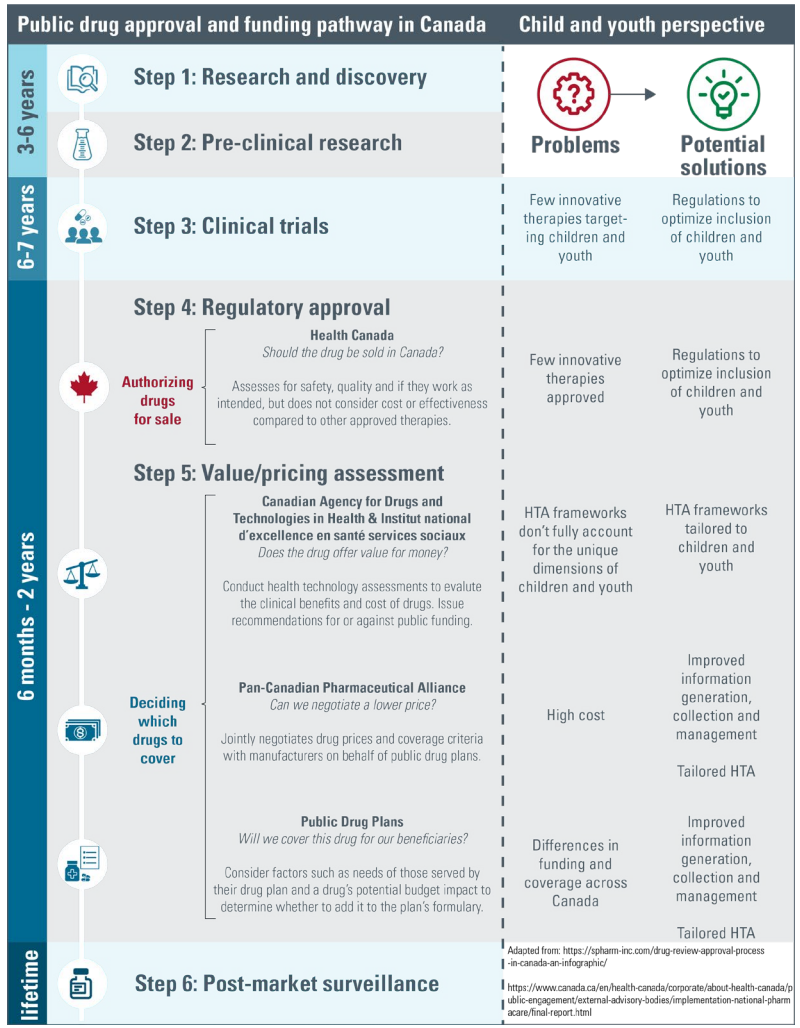
Ethics
- Procedural
- Substantive
- Spatial

Inequities in Access

Welcome to Our World: Evidentiary Uncertainty in Pediatric HTA

Challenges in generation of pediatric clinical evidence:

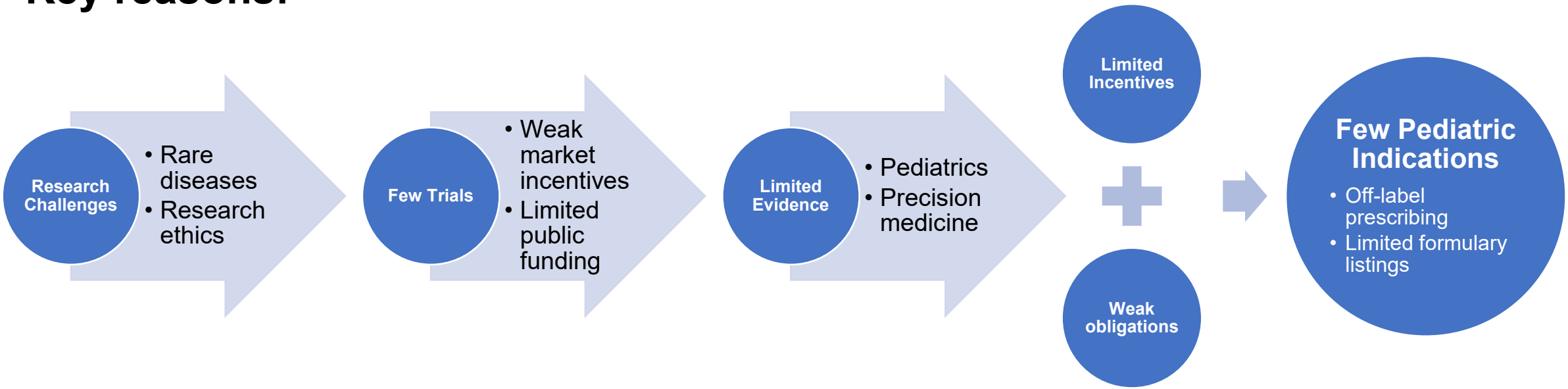
- Disease nosology & drug indications
- Pediatric trials: design, recruitment, analysis
- Pharmaceutical market dynamics and regulation
- Life-course effects



The Pediatric Pipeline: Bends and Bottlenecks

*Few innovative therapies for children and youth are being **developed** and **approved** for sale and funding consideration in most developed health systems*

Key reasons:

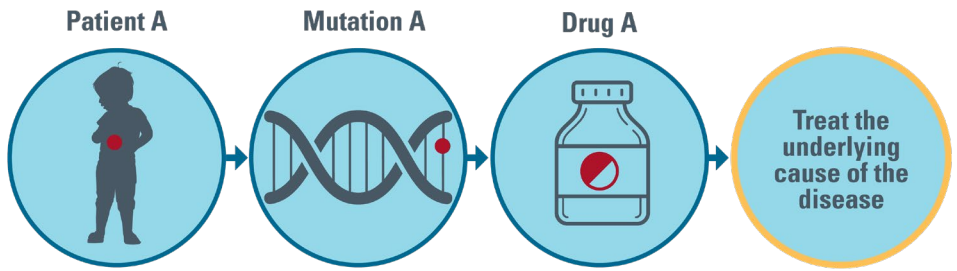


Precision Therapies…in Pediatrics

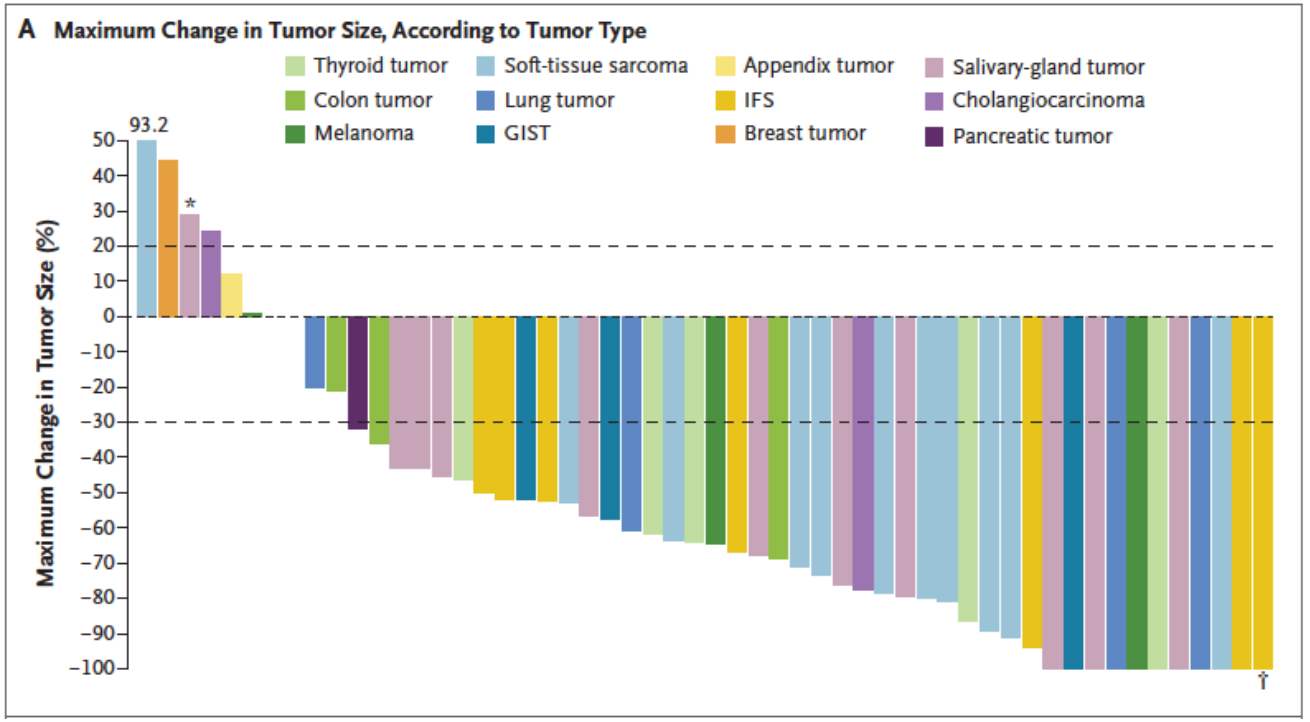
Treatment targeted to fix/fight an underlying (genetic) cause of disease

Promising new avenues for treatment of complex and often rare diseases

Frequently very expensive, big impacts on healthcare budgets

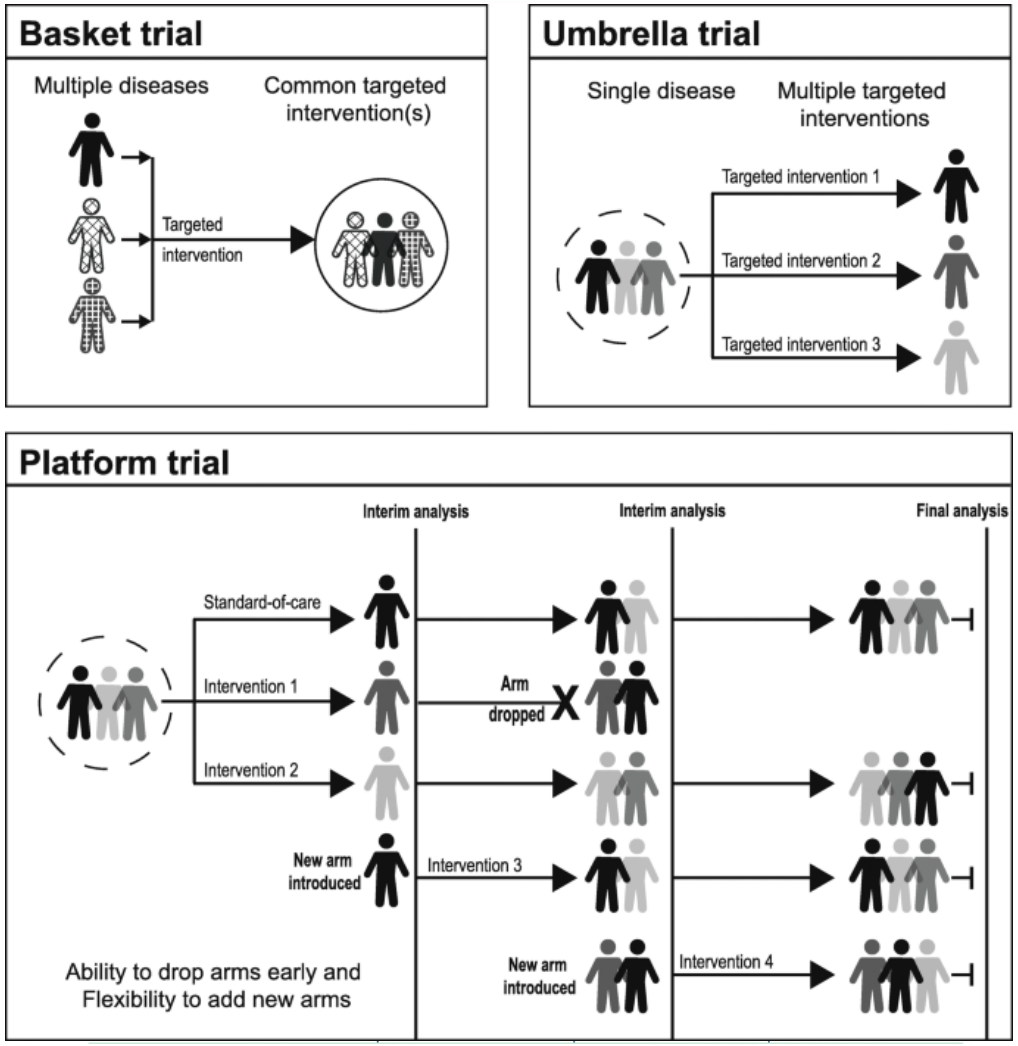


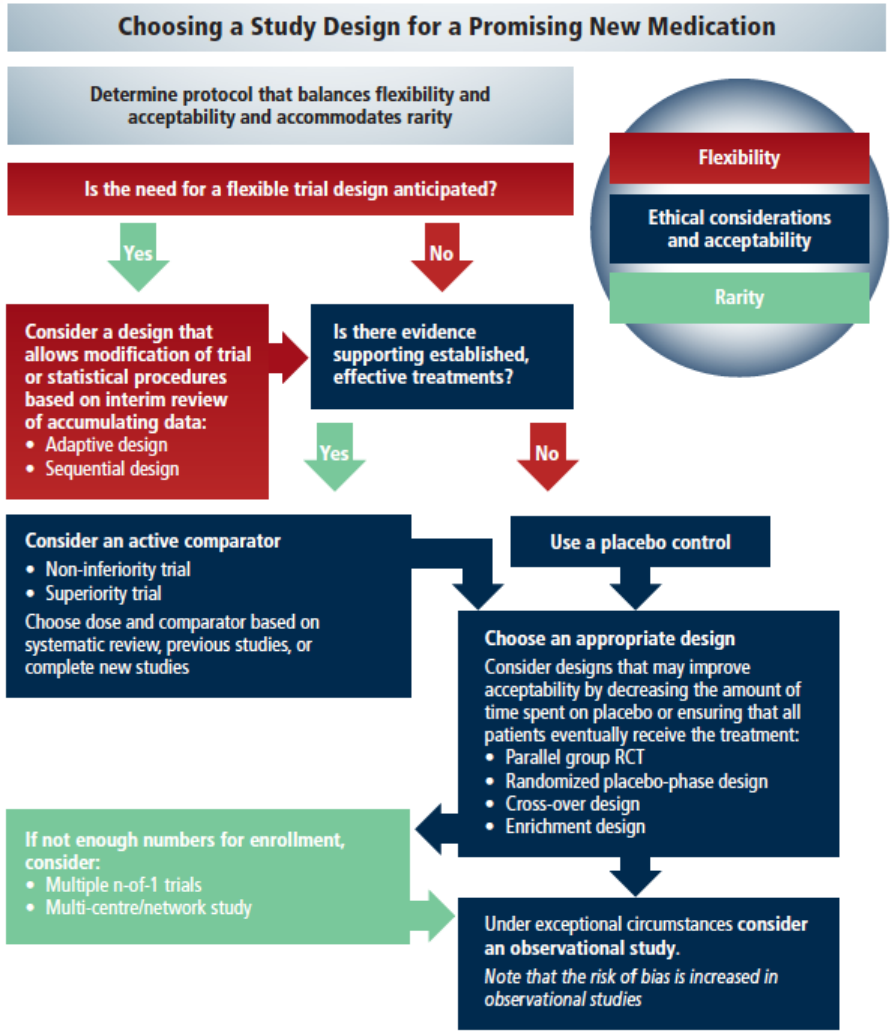
Larotrectinib for TRK-fusion+ cancers



Drilon NEJM 2018

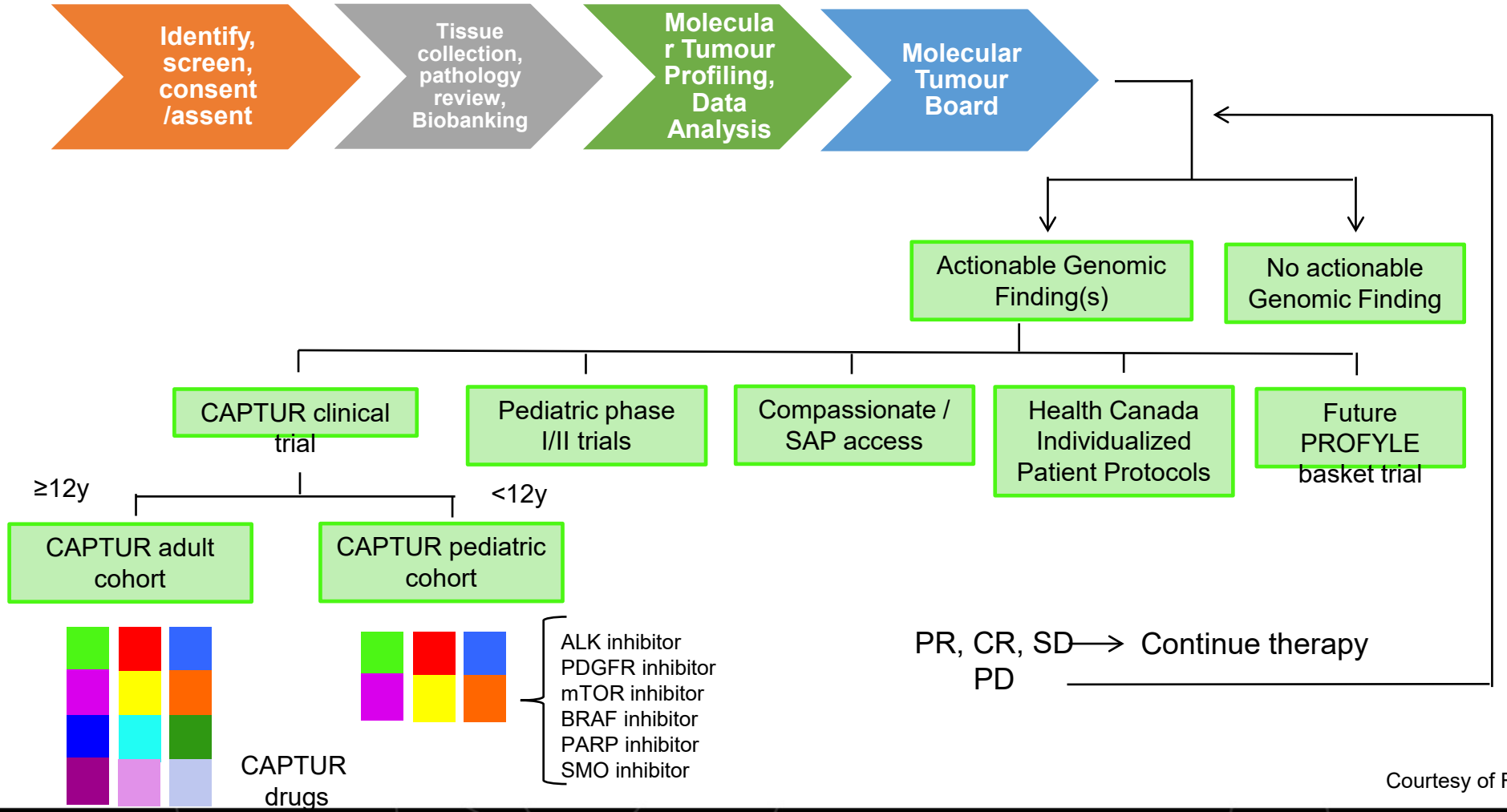
Adapting to Uncertainty: Innovation in Pediatric Trial Design





CCA 2014

Precision Oncology in Pediatrics: Trial Innovation in Practice



Courtesy of R Deyell. PROFYLE 2020

Pediatric-specific Regulatory Reform

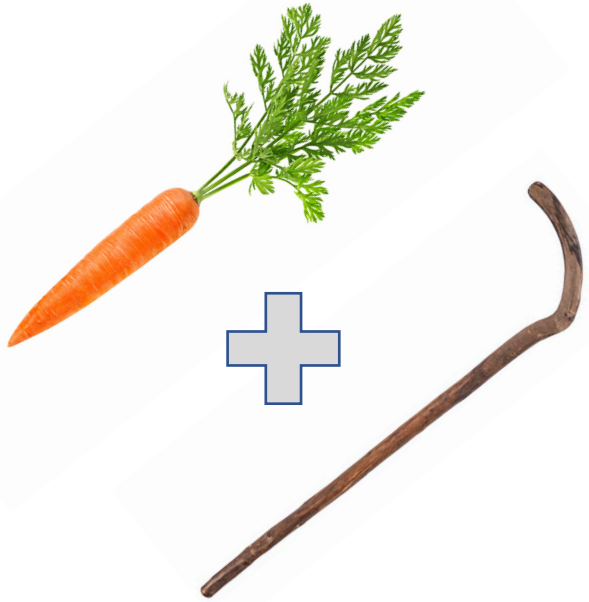
Legislation to support pediatric drug development and approval

US Food and Drug Administration:

- BPCA (2002, 2012)
- PREA (2003, 2012)
- RACE for Children Act (2020)

EU European Medicines Agency:

- Pediatric Regulation (2007)



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Life-course Impacts of Therapy

Table 3. Relative Risk of Selected Severe (Grade 3) or Life-Threatening or Disabling (Grade 4) Health Conditions among Cancer Survivors, as Compared with Siblings.

Condition	Survivors (N=10,397)	Siblings (N=3034)	Relative Risk (95% CI)
	percent		
Major joint replacement*	1.61	0.03	54.0 (7.6–386.3)
Congestive heart failure	1.24	0.10	15.1 (4.8–47.9)
Second malignant neoplasm†	2.38	0.33	14.8 (7.2–30.4)
Cognitive dysfunction, severe	0.65	0.10	10.5 (2.6–43.0)
Coronary artery disease	1.11	0.20	10.4 (4.1–25.9)
Cerebrovascular accident	1.56	0.20	9.3 (4.1–21.2)
Renal failure or dialysis	0.52	0.07	8.9 (2.2–36.6)
Hearing loss not corrected by aid	1.96	0.36	6.3 (3.3–11.8)
Legally blind or loss of an eye	2.92	0.69	5.8 (3.5–9.5)
Ovarian failure‡	2.79	0.99	3.5 (2.7–5.2)

* For survivors, major joint replacement was not included if it was part of cancer therapy.
† For both groups, this category excludes basal-cell and squamous-cell carcinoma (grade 2). For siblings, this category includes a first cancer.
‡ Values are for women only.

Oeffinger NEJM 2006

Outcome Measures: Widening the Value Lens

Populations

- **Experts**
  - Providers
  - Payers
  - Others
- **Patients**
  - Patients
  - Families
- **Publics**
  - General
  - Specific

Methods

- DPE
- DCE
- PRO/E

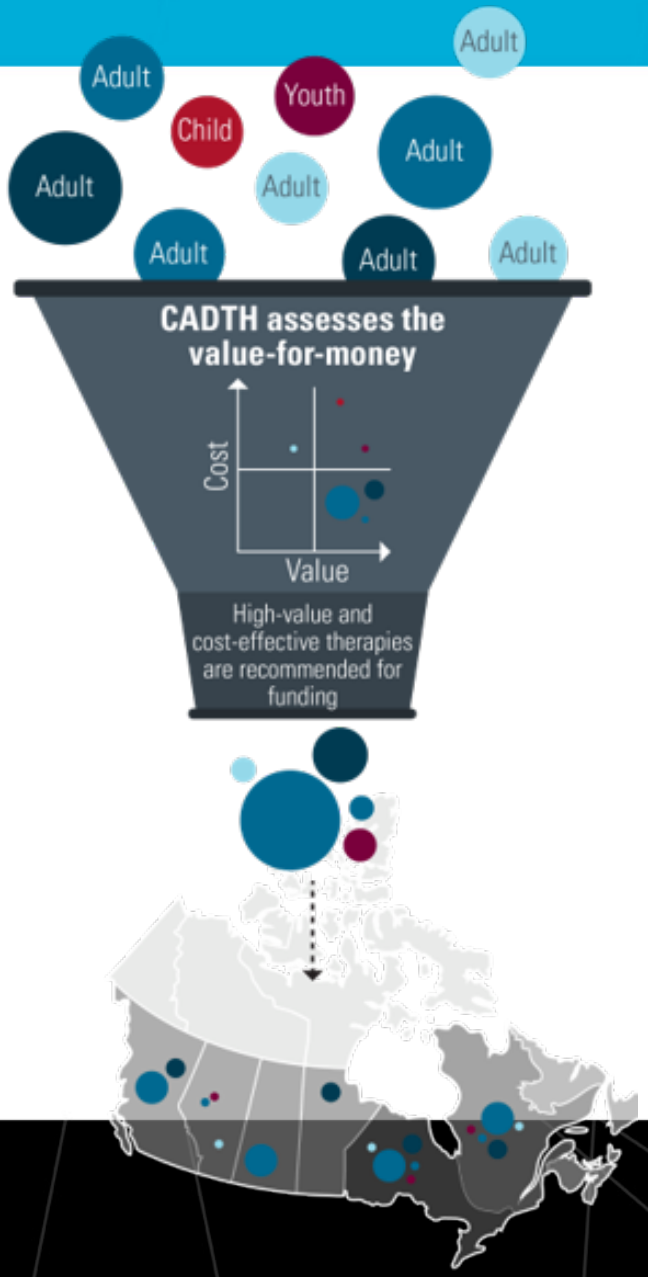
Limited and Unequal Access to Pediatric Precision Therapies

Few pediatric therapies in the discovery and development pipeline

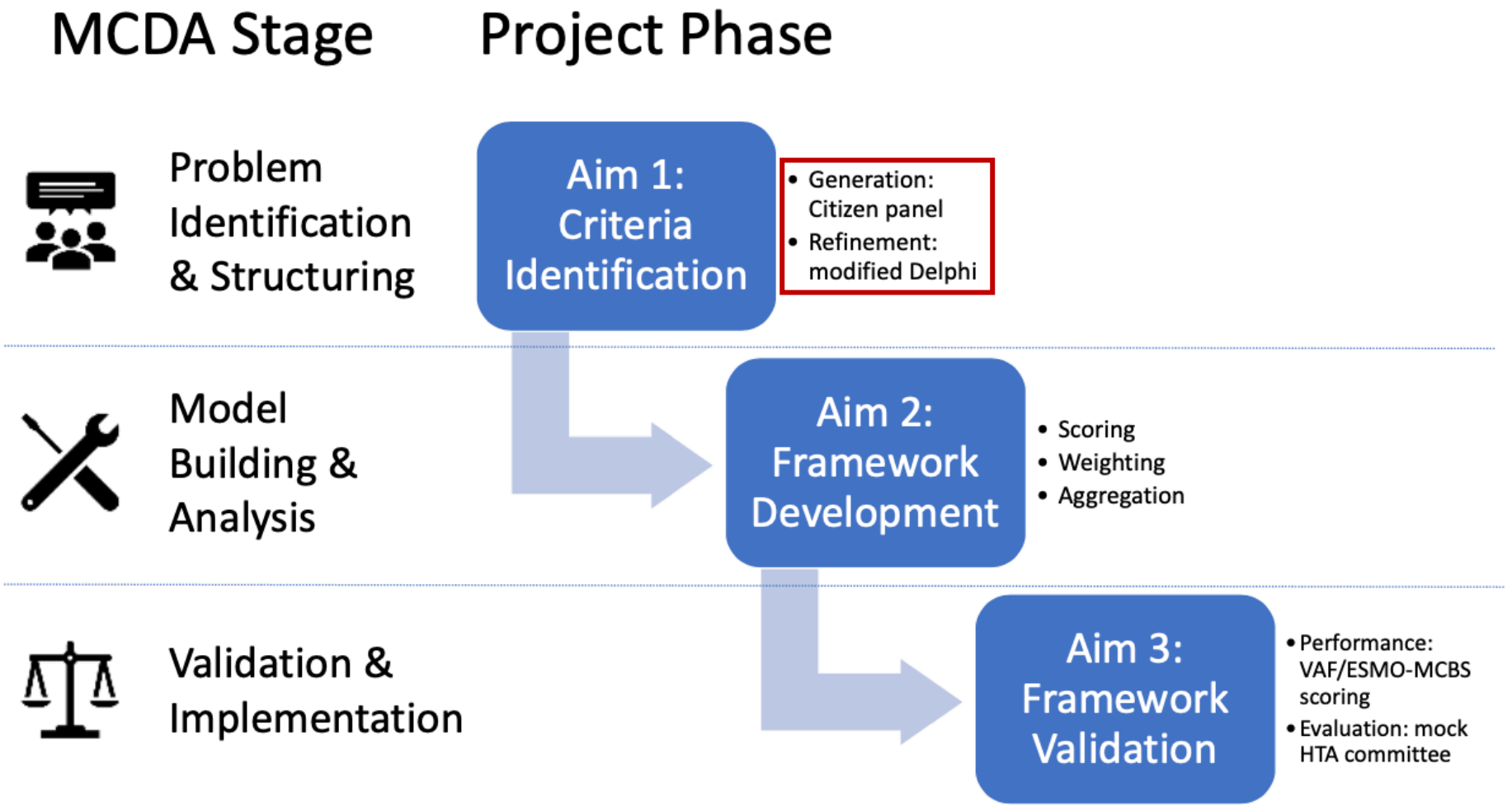
Incomplete HTA assessments of value specific to child health

High-cost, but potentially high-benefit technologies putting pressures on health budgets

Inequitable access due to patchwork coverage across Canada

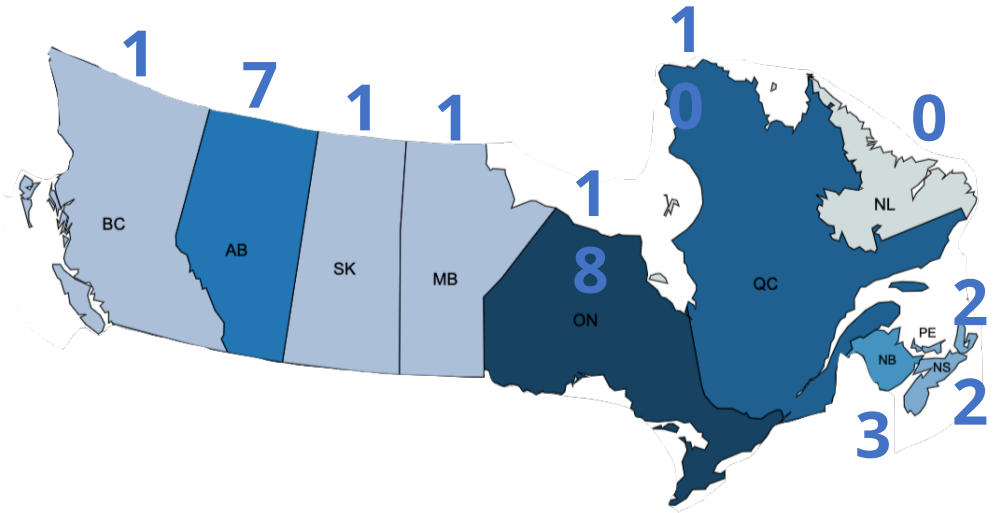


Value Framework: Project Overview



Citizen Panels

45 Participants



Female	Male	Other
31	13	1

Lived Experience
12

Age	
16-21	14
22-34	7
35-49	14
50-64	9
≥ 65	1

Citizens Panel-Identified Criteria

Child-specific Criteria

- Caregiver Return-to-work
- Childhood Development
- Child Return-to-school
- Fair Innings
- Family Impacts
- Future Potential
- Hope

Existing Criteria

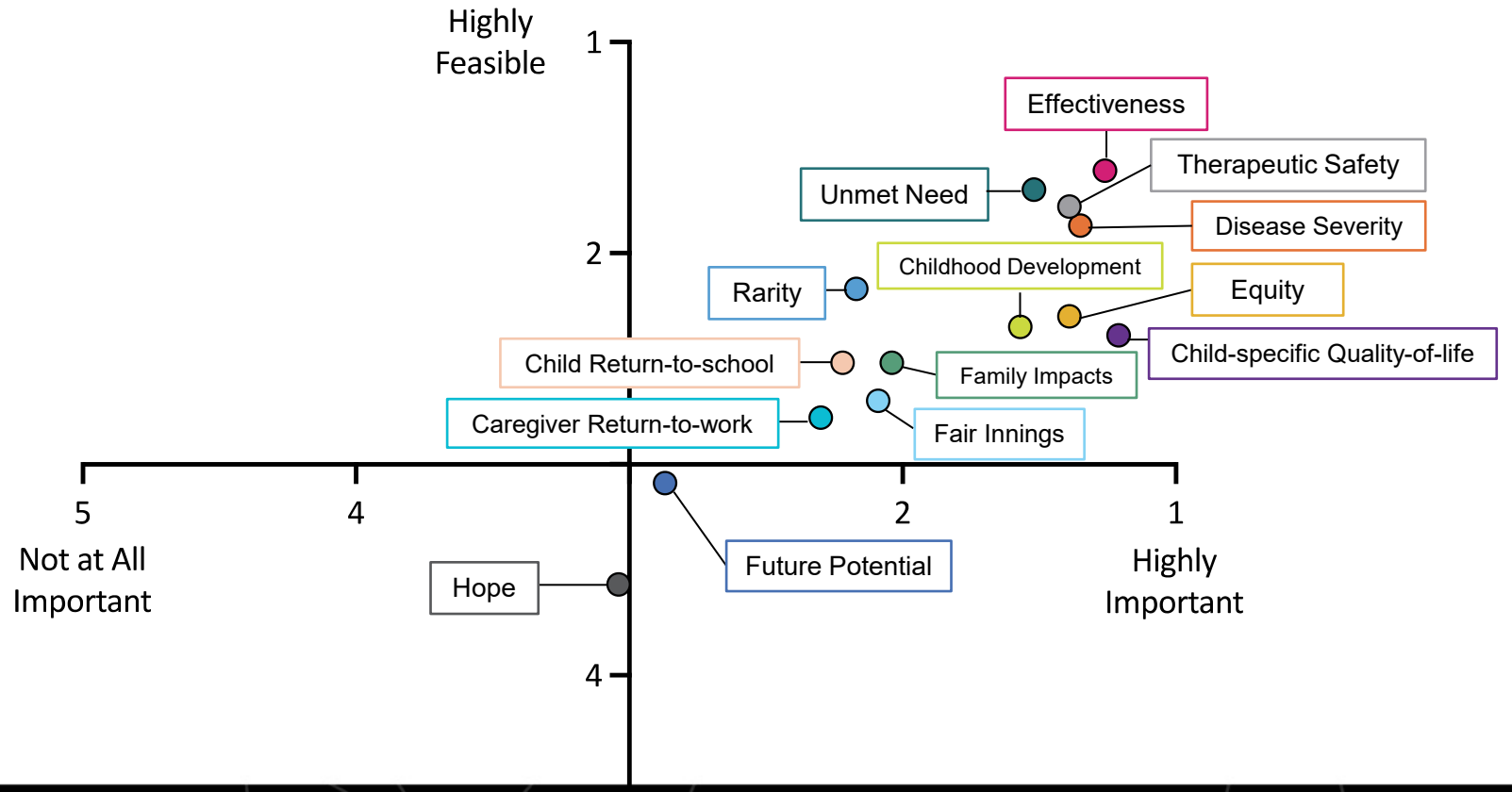
- Child-specific Quality-of-Life
- Disease Severity
- Effectiveness
- Equity
- Rarity
- Therapeutic Safety
- Unmet Need

Modified Delphi Process

- Two online surveys followed by virtual participant meetings
- Twenty-three participants
- **Diversity of stakeholders:**
  - Patients and/or Caregivers (3), Academics (5), Clinicians (4), Regulators (1), Industry (1) Civil society (2), HTA organizations (3), Government decision-makers (2), Ethics and Equity (2)
- **Provincial representation:**
  - British Columbia (4), Alberta (3), Ontario (12), Quebec (1), New Brunswick (1), Nova Scotia (2)

Survey Results: Importance and Feasibility

Mean participant (*N* = 23, 100% response) ratings for the 14 criteria



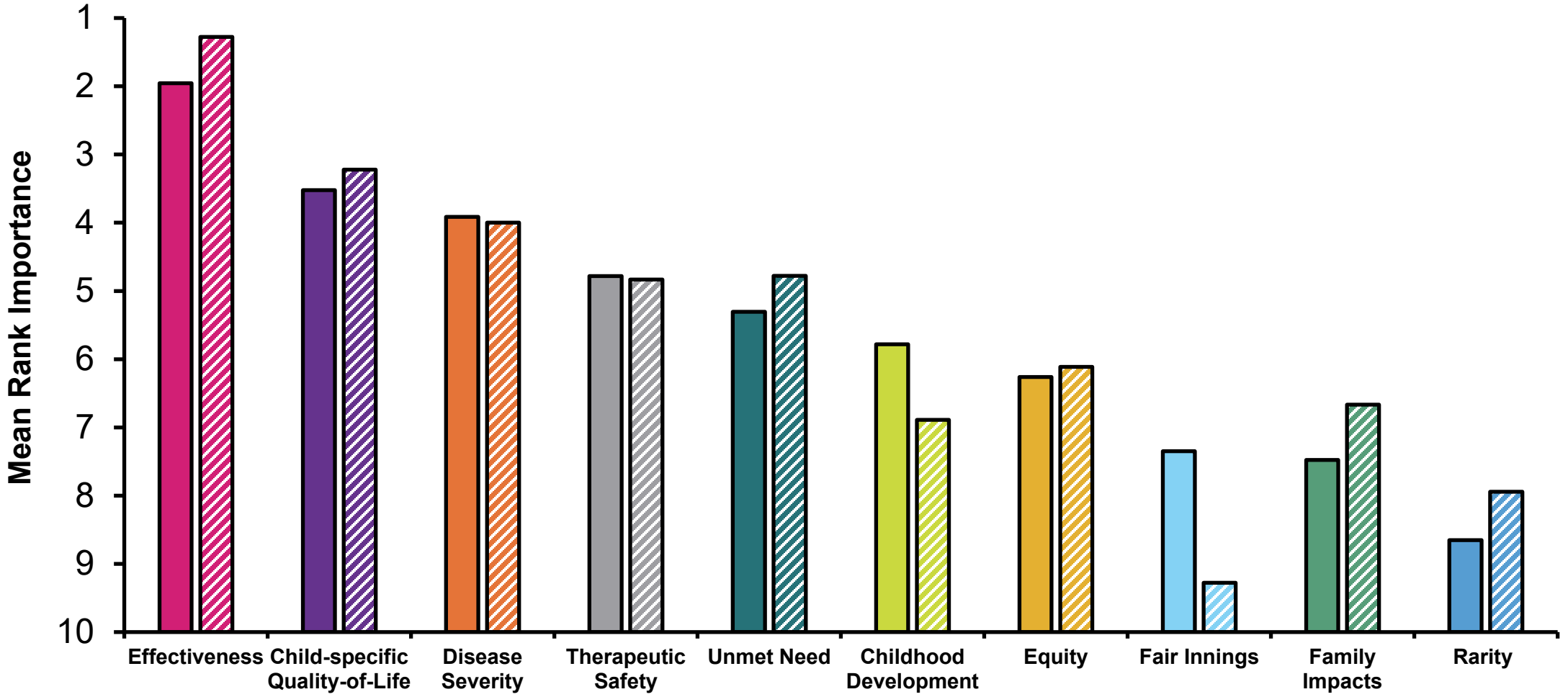
Survey Results: Ranking of Importance

Mean participant (*N* = 23, 100% response) rankings for the 10 criteria

	Mean	Median	*SD*
Effectiveness	1.96	1.00	2.16
Child Quality-of-Life	3.52	3.00	1.88
Disease Severity	3.91	4.00	2.35
Therapeutic Safety	4.78	5.00	2.65
Unmet Need	5.30	5.00	2.57

	Mean	Median	*SD*
Child Development	5.78	5.00	1.91
Equity	6.26	6.00	2.12
Fair Innings	7.35	7.00	2.17
Family Impacts	7.48	8.00	2.17
Rarity	8.65	9.00	1.47

Survey results: Ranked importance of 10 criteria pre/post-deliberations



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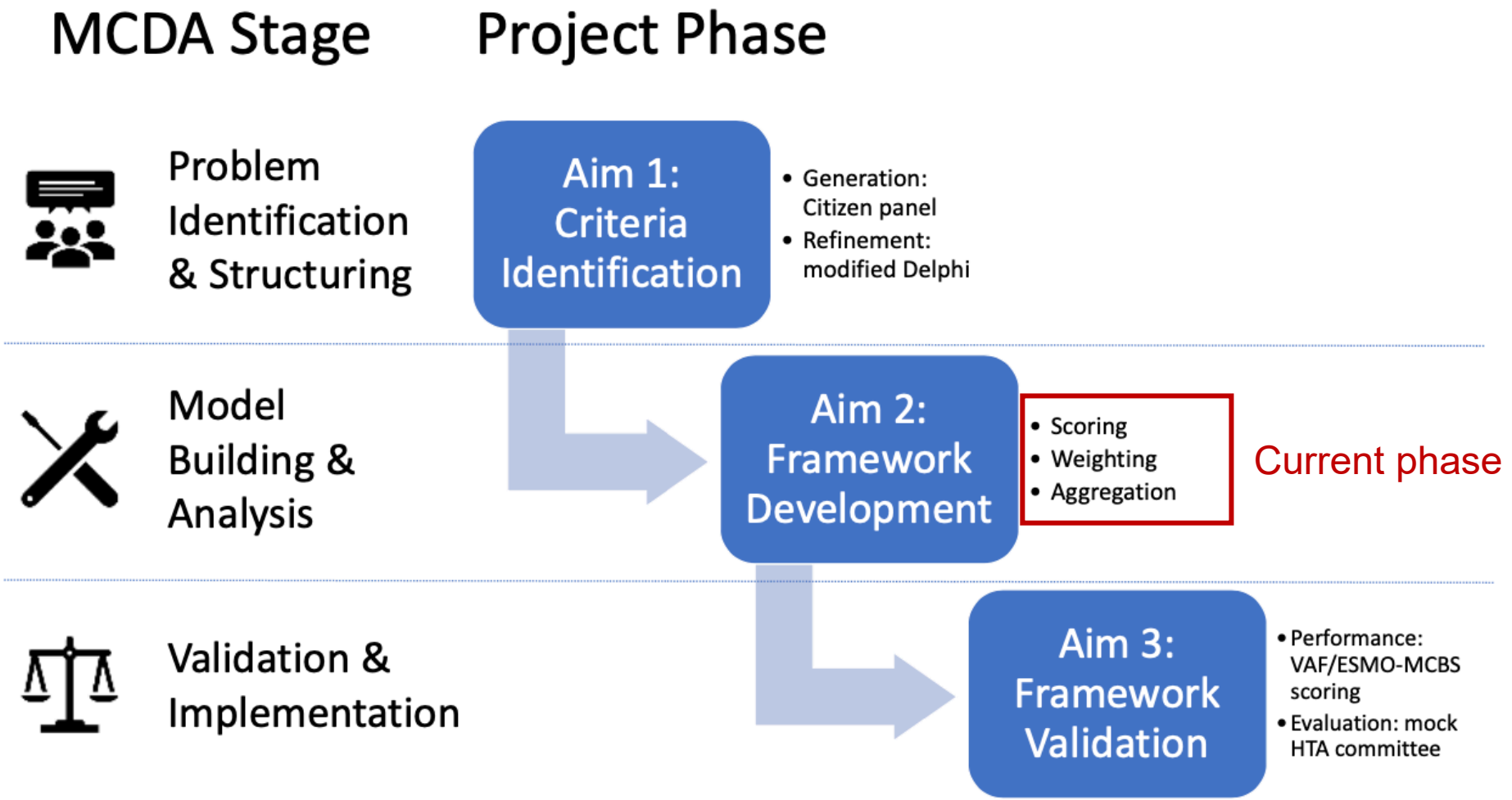

Criteria weighting and scoring

	Weighted Ave.	Starting weight	Adjust factor	Final weight
Effectiveness	1.28	15	4	19
Child-spec HQoL	3.22	15	3	18
Disease severity	4.00	15	2	17
Unmet need	4.78	10	1	11
Therapeutic safety	4.83	10	0	10
Equity	6.11	10	0	10
Family impacts	6.67	10	-1	9
Childhood development	6.89	5	-2	3
Rarity	7.94	5	-3	2
Fair innings	9.28	5	-4	1
				100

			SCORE			
CRITERIA	**DEFINITION**	**WEIGHT**	**0**	**1**	**2**	**3**
Effectiveness	**The ability of a treatment to improve key disease-specific outcomes, compared to existing treatments or standards of care.**	**19**	**No evidence of improvement in key disease-specific outcome(s)**	**Minimal improvement in key disease-specific outcome(s)**	**Moderate improvement in key disease-specific outcome(s)**	**Significant improvement in key disease-specific outcome(s)**
Child-specific Health-related Quality-of-Life	**The impact of a treatment on a child's well-being, including social, emotional, and physical dimensions of daily life, as measured by instruments that have been adapted or specifically developed for children and youth, compared to existing treatments or standards of care.**	**18**	**No evidence of impact on QoL (using a validated scale)**	**Minimal improvement in QoL (using a validated scale)**	**Moderate improvement in QoL (using a validated scale)**	**Significant improvement in QoL (using a validated scale)**

Implications for Research and Policy

- Value framework validation and implementation
  - VAF-ESMO-MCBS performance score comparisons
  - Mock committee deliberations with Canadian (and European?) HTA bodies
- Comparative analyses of regulatory and HTA approaches to novel paediatric (precision) medicines internationally, including in Europe
- Window of opportunity to incorporate paediatric-specific evidentiary and values considerations in EU HTA legislation
- **Questions/ideas?**

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