Value assessment of nusinersen, Spinraza®, Biogen Idec

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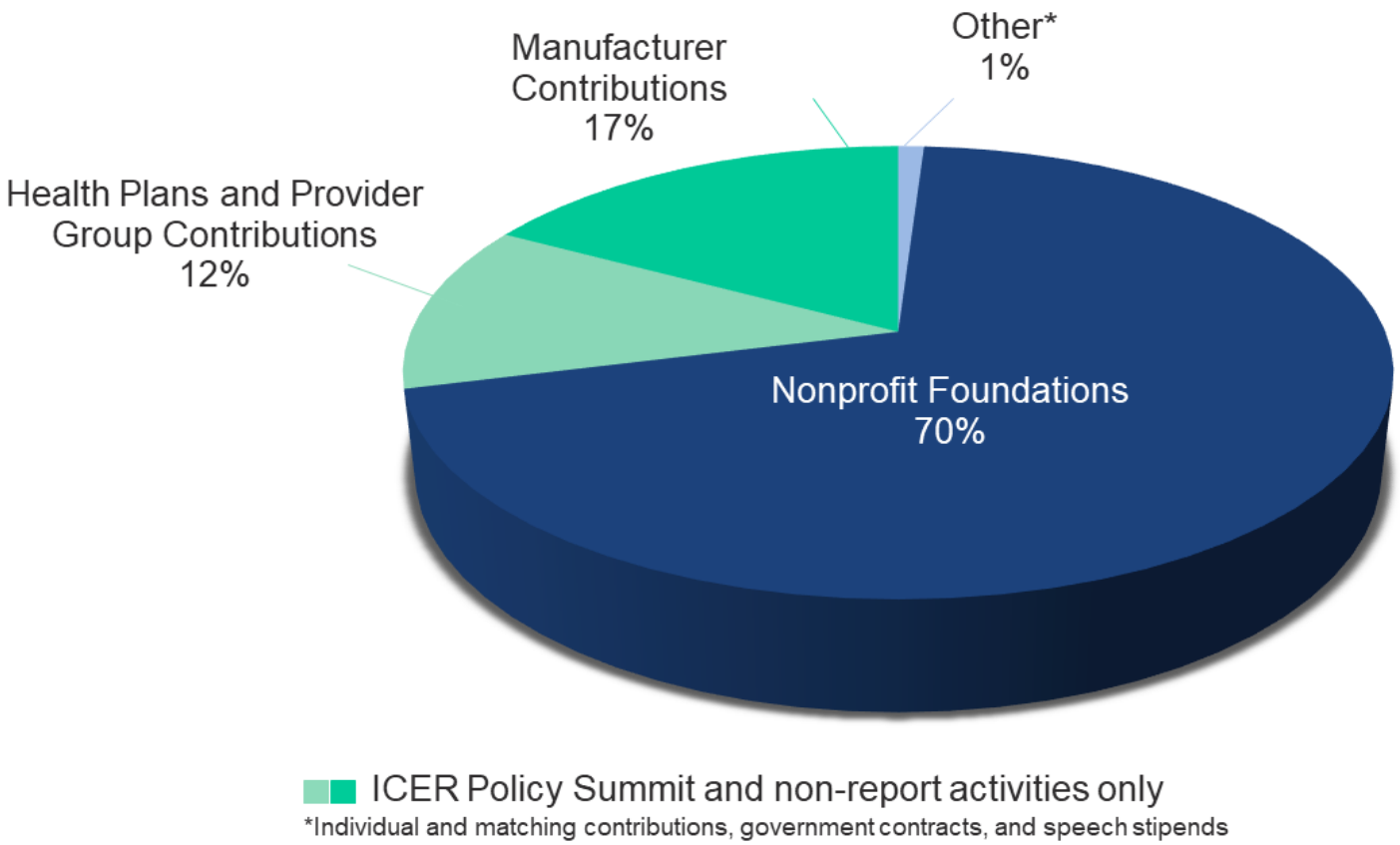
Sources of Funding, 2020
https://icer-review.org/about/support/



Potential Elements in Determining a Reasonable Price for Pharmaceuticals

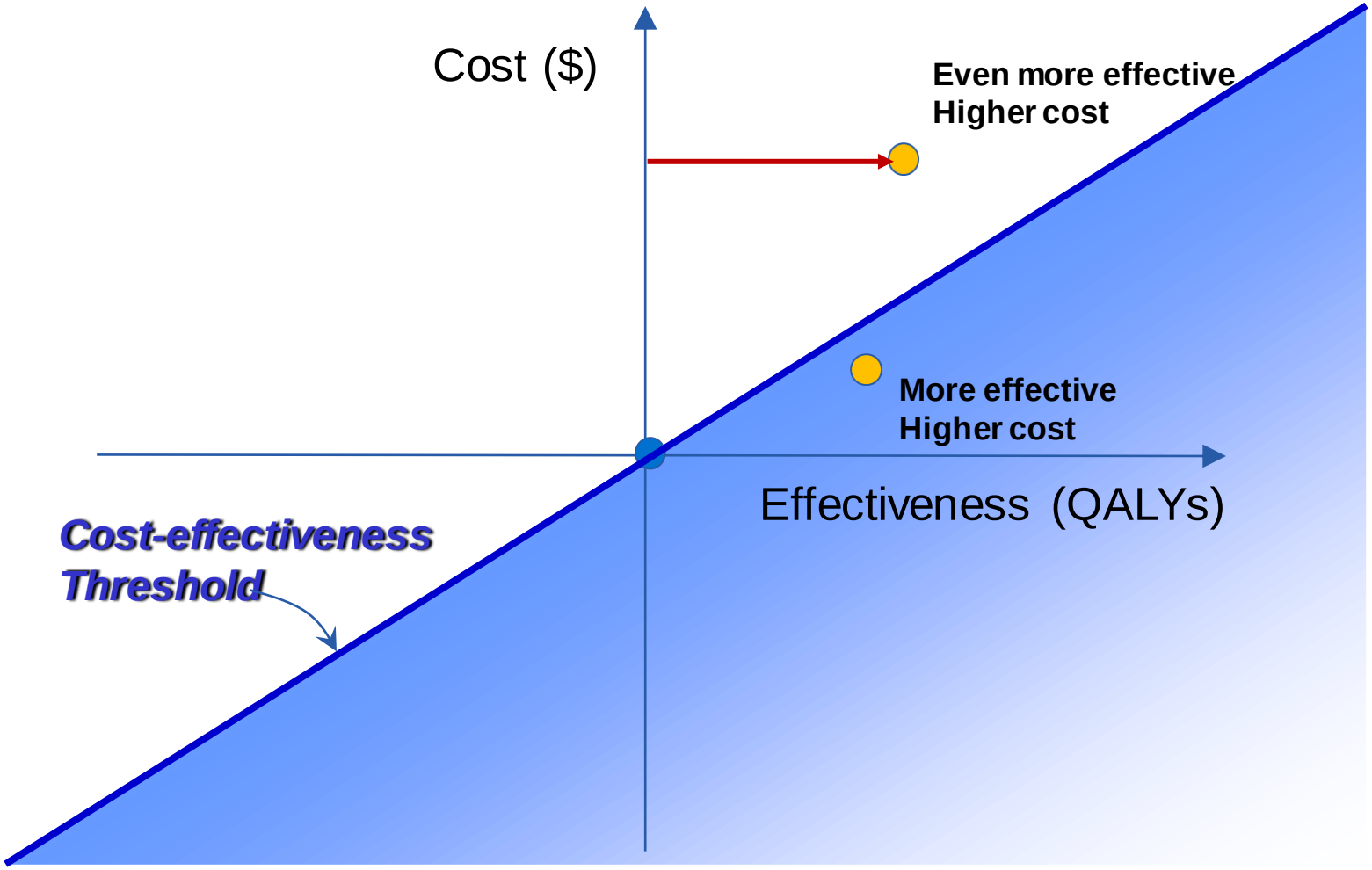
- Costs of development and/or production plus "reasonable" profit
  - Often considered appropriate for older generic drugs without barrier to entry

- Added "value" to patients and health systems
  - More apt for new drugs with limited or no competition
  - Cost-effectiveness analysis is the accepted approach in the US and abroad for comparing health gains and overall cost impact across different treatment options

What is in each cost-effectiveness model?

- Clinical outcomes
  - Specific clinical benefits, e.g. ability to sit, to walk
  - Side effects
  - Quality of life with each outcome
  - Life years gained
  - Putting them all together
    - the quality-adjusted life year (QALY)
- Costs
  - All health services
    - Drugs, tests, doctor visits, hospitalizations, etc.
  - Can include broader effects like productivity

Cost-effectiveness thresholds (Cost per QALY)



Cost-effectiveness thresholds

- **Societal "willingness to pay"**
  - World Health Organization ~1-3x per capita GDP/QALY
  - American College of Cardiology: $50,000-$150,000 per added QALY
- **Individual "willingness to pay" research**
  - ~$100,000 per QALY in the US
- **"Opportunity cost" research**
  - ~$104,000/QALY in the US
- **ICER: $100,000-$150,000 per QALY**
  - Opportunity cost paradigm plus flexibility for consideration of additional elements of value not well captured by modeling
  - Recent commercial market activity suggests $100,000/QALY as standard
- **In 2018 the NY DURB selected $150,000/QALY threshold price for Orkambi, a treatment for an ultra-rare subpopulation with CF**

Objective

- To provide results of an ICER value assessment report on Spinraza first issued on May 24, 2019

- Updates on evidence that has emerged recently

SMA Assessment Team

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SMA Types

SMA Type	% of SMA cases	Age of Onset	Highest Achieved Motor Function	Natural Age of Death	Typical Number of *SMN2* Copies
I	60%	<6 months	Sit with support only	<2 years	1-3
II	20-30%	6–18 months	Sit independently	>2 years	2-3
III	10-20%	>18 months	Walk independently	Adulthood	3-4

Presymptomatic SMA (SMN 2-3) Results

	2 *SMN2* (n=15)	3 *SMN2* n=10	All N=25	
Alive	15 (100)	10 (100)	25 (100)	
Required Respiratory Intervention				
≥ 6 Hours/Day for ≥7 Days	4 (24)	0	4 (16)	
≥16 Hours/Day for >21 Days (Permanent Ventilation)	0	0	0	
Motor Milestones				
Independent Sitting	15 (100)	10 (100)	25 (100)	
Walking with Assistance	13 (80)	10 (100)	23 (92)	
Walking Alone	8 (53)	9 (90)	17 (68)	22 (88)

ICER Evidence Ratings for Spinraza

SMA Population	Spinraza
Infantile-Onset (Type I)	A
Later-Onset (Type II and III)	B+
Presymptomatic	B+

Potential Other Benefits and Contextual Considerations

- Spinraza was the first FDA-approved treatment that modified disease progression
  - Zolgensma, a novel gene therapy has followed;
  - Risdiplam is under review
- Treatment likely to shift to presymptomatic infants with introduction of routine screening at birth
- Minor improvements in motor functioning can allow patients greater ability for self-care and independence
- Return to school (children) or work (caregivers)
- Reduce other resources used (e.g., at school) and encourage more interaction in communities

Cost-Effectiveness

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Methods Overview

- **Model**: A new model with two phases: Short term (trial/study duration) + long-term (extrapolation)
- **Setting**: United States
- **Perspective**:
  - Health care sector (direct medical care and drug costs)
  - Modified Societal (includes estimates of patient productivity gains, lost household income, cost of home improvements and remediation
- **Time Horizon**: Lifetime
- **Discount Rate**: 3% per year (costs and outcomes)
- **Primary Outcomes**: Cost per quality-adjusted life year (QALY) gained; cost per life year (LY) gained

Key Assumptions

- Motor function milestones achieved at the end of the follow up are sustained until death.
- Utility benefit was assumed in the treatment arms for patients achieving interim motor function milestones such as head control, rolling, crawling, and standing.
- In the treatment arms, patients in the “not sitting” health state at the end of the short-term model are assumed to have the same survival as those on “permanent ventilation.”
- Patients with SMA Type I who are in “sitting” health state are assumed to have mortality similar to that of SMA Type II patients.
- Patients with SMA Type I who are in “walking” health state are assumed to have mortality similar to that of SMA Type III patients.
- Patients on Spinraza who did not achieve motor function milestones at 24 months discontinued the treatment. We assumed no other patients discontinue Spinraza in the model.

Short-Term Model Effectiveness Inputs

	SMA Type 1	Later Onset (SMA Type 2/3)	Presymptomatic SMA
Spinraza	ENDEAR (Finkel 2017); SHINE (Castro 2018)	CHERISH (Mercuri 2018)	NURTURE (De Vivo 2017)
Best Supportive Care (BSC)	ENDEAR (Finkel 2017)	CHERISH (Mercuri 2018)	N/A

Studies in red indicate non-comparative evidence.

Patient Utilities

Health State	Utility in BSC Patients	Utility in Spinraza Patients	Source for BSC Values (Derivation)
Permanent Ventilation	0.19	0.19	Thompson et al. (caregivers)
Not Sitting	0.19	0.29	
Sitting	0.60	0.65	Tappenden et al. (clinicians)
Walking	--		Age-matched general population utility

The increase in utility associated with Spinraza patients was included to capture benefits that would not be captured within the broad health states.

Results

Results Overview

- Results are presented in terms of:
  - Cost per quality-adjusted life-year (QALY) gained
  - Cost per life year gained (LYG)
  - Selected scenario analyses

- Results provided use a health care sector perspective. The modified societal perspective results were very similar.
- Caregiver “burden” was not included as inclusion may lead to counter-intuitive results.

Infantile-Onset (Type I) SMA Model

	Total Costs	QALYs	LYs	Incremental Results	
				Cost/QALY Gained	Cost/LYG
Spinraza	**$3,884,000**	**3.24**	**7.64**	**$1,112,000**	**$590,000**
BSC	$789,000	0.46	2.40	--	--

Later-Onset (Type II/III) SMA Model Base Case Results

	Total Costs	QALYs	LYs	Incremental Results	
				Cost/QALY Gained	Cost/LYG
Spinraza	**$9,148,000**	**12.28**	**18.90**	**$8,156,000**	**Dominated**
BSC	$1,442,000	11.34	18.90	--	--

Presymptomatic SMA Model – Spinraza
Assuming new data on % reaching walking alone

	Total Costs	QALYs	LYs	Incremental Results	
				Cost/QALY Gained	Cost/LYG
Spinraza	**$12,705,000**	**24.76**	**28.80**	**$643,000**	**$617,000**
BSC	$801,000	6.25	9.51	--	--

Threshold Prices for Spinraza based on new data in Presymptomatic SMA (per dose)

	Per QALY*	Per LYG*
Threshold Price at $50,000/QALY	$5,000	$5,333
Threshold Price at $100,000/QALY	$15,333	$16,000
Threshold Price at $150,000/QALY	$25,667	$27,000
Threshold Price at $200,000/QALY	$36,000	$37,667

*Annual price to reach thresholds includes any potential mark-up and represents treatment price in years 2+.

Key Model Limitations

- Relatively small numbers of patients and lack of long-term data produce important residual uncertainty in future outcomes.

- The broad health states in the model could miss benefits that are associated with “minor” improvements with Spinraza treatment.
  - NB: increased quality of life added in the non-sitting and sitting states for Spinraza

Comparisons with Published Models (Zuluaga-Sanchez et al.)

- For Type I SMA the cost per QALY gained >€550,000. This was >€310,000 for Type II/III SMA.
- This model appears to be very similar to that initially submitted to the National Institute of Health and Care Excellence (NICE) with different utilities used.
- The NICE committee commented that: "*The company's transition probabilities are optimistic and do not reflect clinical practice.*"; "*The modelled long-term overall survival benefit is based on optimistic assumptions and is highly uncertain*"; and that "*Utility values in the economic model are highly uncertain*."
- It is noted that patients receiving Spinraza could not worsen, whilst a proportion improved each cycle.

Summary

- Spinraza improves patient health outcomes compared to best supportive care alone for all subpopulations of SMA. Its greatest impact appears to be when used for presymptomatic infants.

- However, in proportion to the clinical benefits, the added cost of Spinraza therapy exceeds commonly used thresholds for cost-effectiveness for all patient subpopulations. The modified societal perspective scenario analysis did not notably improve the cost-effectiveness of Spinraza.

- Reduced prices to meet different cost-effectiveness thresholds have been presented.

- There are important potential other benefits and contextual considerations related to Spinraza treatment for SMA. For treatments of ultra-rare disorders, decision-makers have often given additional consideration to these factors.