

Natural History of SMA and Impact of Standards of Care on Survival and Motor Function

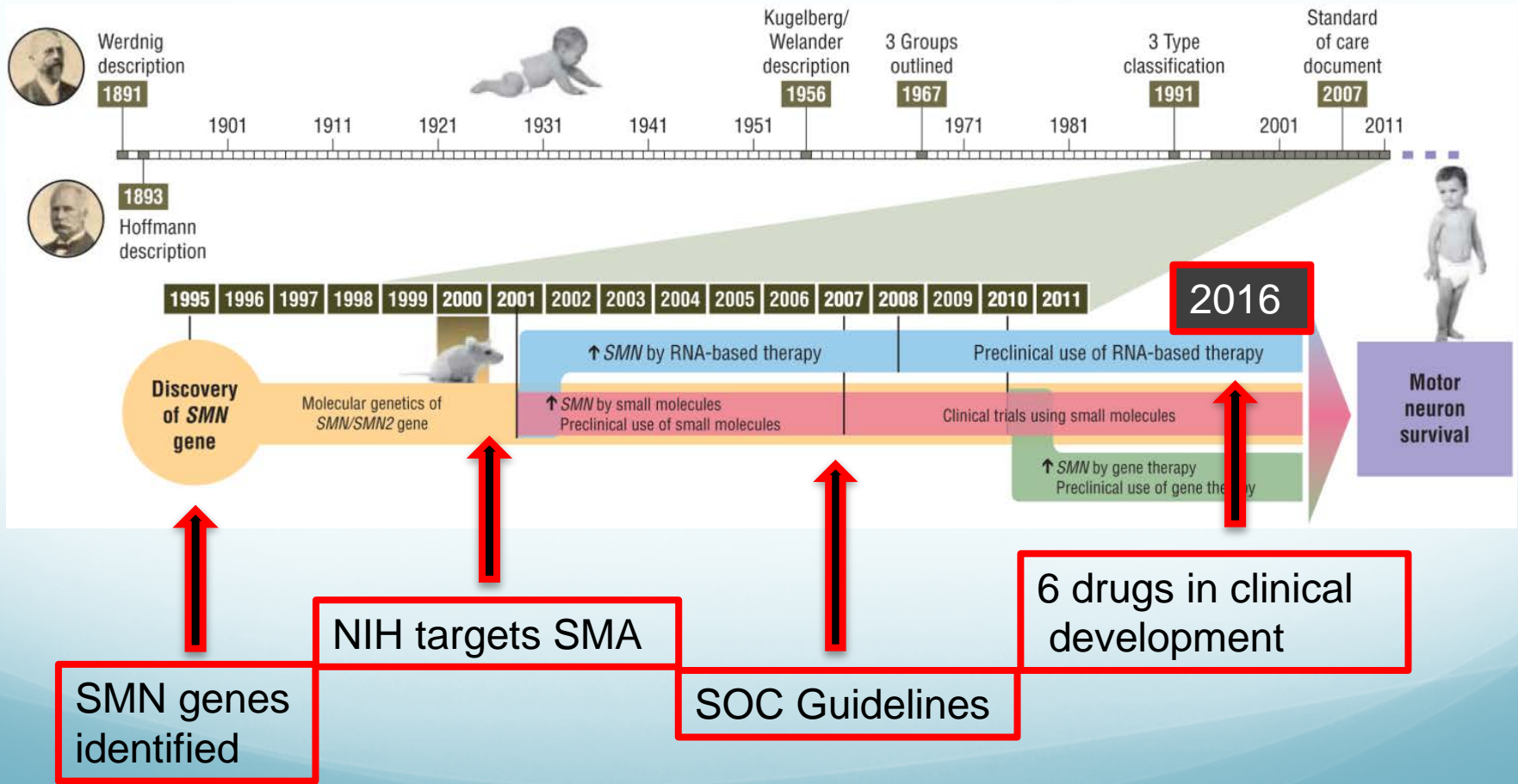
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Disclosures, SMA-related

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- DSMB: Roche, AveXis

Spinal Muscular Atrophy



The Clinical Spectrum of SMA

Type	Age at Symptom Onset		Incidence %	Prevalence %	Maximum Motor Function	SMN2 copy number	Life expectancy
0	Fetal		<1	0	Nil	1	Days -Weeks
1	< 6 Months	1A: B-2 Weeks 1B: <3 Months 1C: >3 Months	60	15	Never sits	1, 2,3	< 2 years
2	6-18 Months		25	70	Never walks	2, 3,4	20-40 years
3	1.5-10 Years	3A: <3 Years 3B: > 3 Years	15	15	Walks Rregression	3, 4, 5	normal
4	>35 Years		<1	1	Slow decline	4, 5,6	normal

SMA, Type 1

Infantile form, “Werdnig-Hoffmann Disease”



Typical type 1 SMA infant
at age 4 months



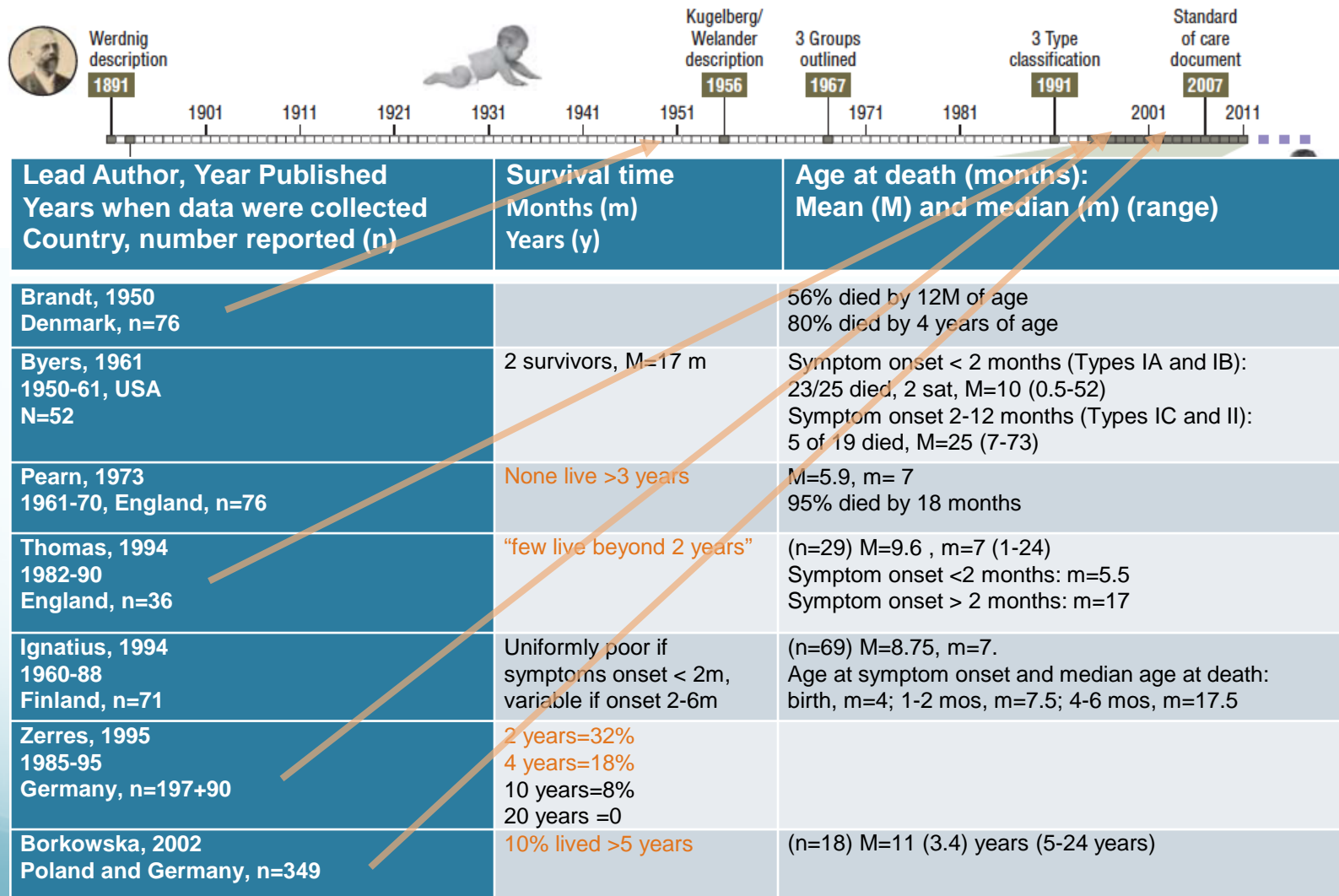
4 years
SMN2CN = 3



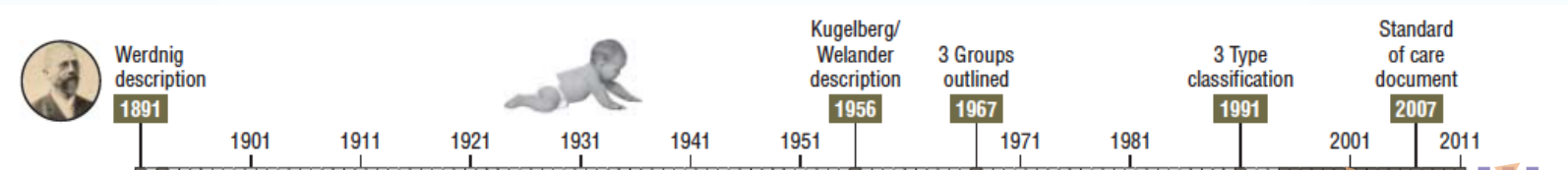
3 years
SMN2CN = 2

Early Natural History Studies

not genetically confirmed, no supportive care



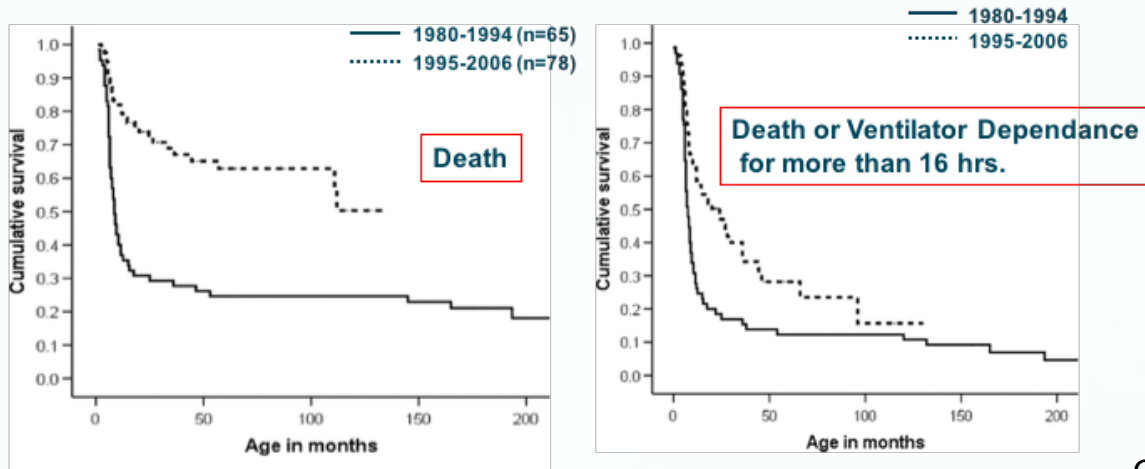
Contemporary Natural History Studies genetically confirmed, some supportive care



Timeline of key events in the history of SMA research:

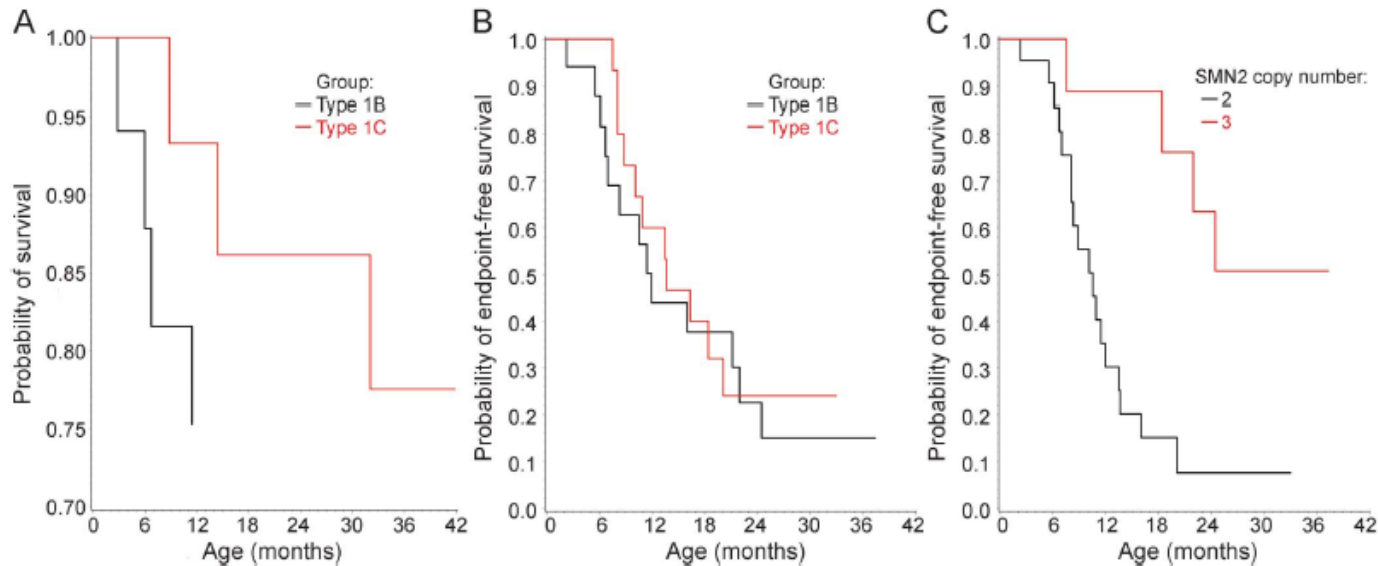
- 1891: Werdnig description
- 1901
- 1911
- 1921
- 1931
- 1941
- 1951
- 1956: Kugelberg/Welander description
- 1967: 3 Groups outlined
- 1971
- 1981
- 1991: 3 Type classification
- 2001
- 2007: Standard of care document
- 2011

Lead Author, Year Published Years when data were collected Country, number reported (n)	Survival time Months (m) Years (y)	Age at death (months): Mean (M) and median (m) (range)
Ioos, 2004 France, n=68 (1B=33, 1C=35)	IB: 18% alive with TV (8-17Y) IC: 74% alive (? range)	IB: (n=27 of 33, 82% mortality), M=18 (29) IC: (n=9 of 35, 26% mortality), M=4 Years (3.75Y)
Bach, 2007 1996-2006; USA, n=74+18	82% alive at M=66.1±44.8m	Unsupported (n= 18), M=9.6±4.0 Supported (n=74), 13 died: M=32.9±50.4, one at 270
Oskoui 2007, USA mainly 1980-1994 (n=65) 1995-2006 (n=78)	m=8.5m m=indeterminate	M=19.1, m=7.3 (1.0-193.5) M=22.1, m=10.0 m (2.5-112.0)
Rudnik-Schöneborn, 2009 2000-05 diagnosis Germany, n=66	Alive at 2Y: Overall: 6% SMN2CN2: 2% SMN2CN3: 67%	Mortality in 57 (86.3%): All patients: M=9.0 (few days-55 months), m=6.7 SMN2CN=2 (n=57): M=7.8, m=6.5 (0.5-30) SMN2CN=3 (n=3): M=28.9, m=19 (10.1-55.1)
Lemoine, 2012 2002-09 USA, n=49	4 year survival: Proactive: 72% Supportive: 33%	Proactive care (n=23; 6 deaths): m=7.6 (IQR 6.5,10.5) Supportive care (n=26; 16 deaths), m=8.8 (IQR 4.7, 23.7).
Finkel. 2014 (2005-09 enrolment) followed for up to 3Y USA, n=34	Combined endpoint: Type IB, m=11.9 Type IC, m=13.6	Death (n=9): m=9 (2-14) Death or requiring >16 hours of BiPAP/day: Overall group: 13.5 m (IQR: 8.1-22) SNM2CN = 2: 10.5 m (IQR: 8.1-13.6 m)



Oskoui et al, 2007

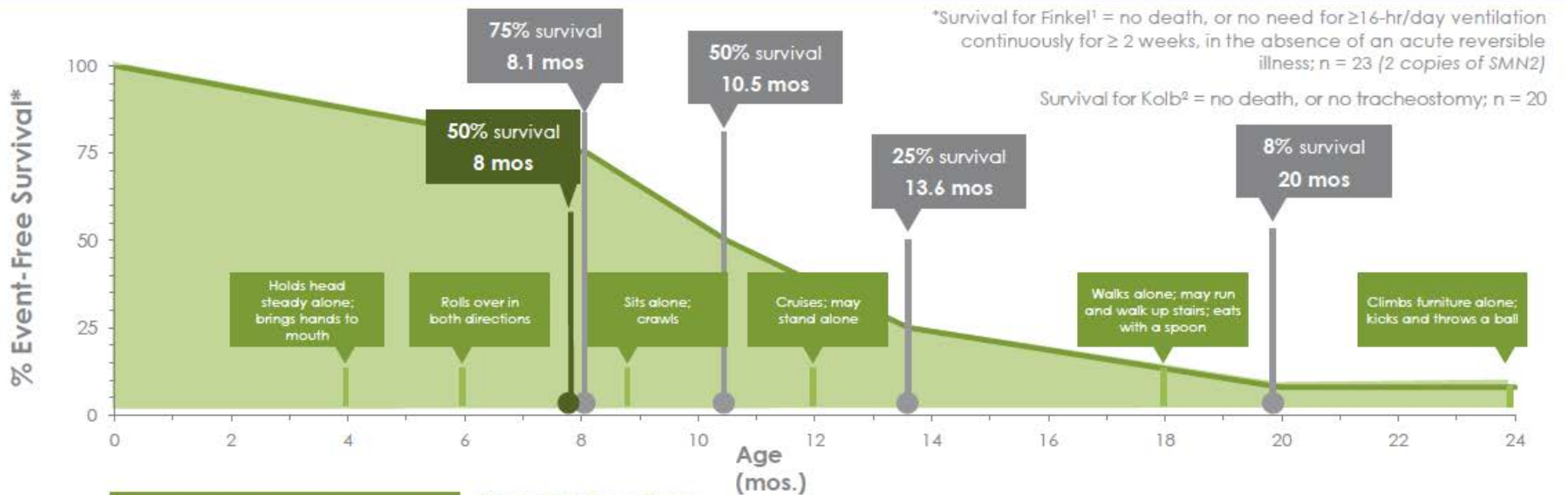
Figure 1 Time-to-event curves for SMA-I



Kaplan-Meier curves for SMA-I. (A) Probability of survival with advancing age by SMA-I subtype (type 1B, n = 18; type 1C, n = 16). (B) Probability of not reaching the combined endpoint of death or the need for a minimum of 16 hours/day of noninvasive ventilation support for a minimum of 14 continuous days, in the absence of an acute reversible illness or perioperatively, with advancing age by SMA-I subtype. (C) Probability of not reaching the combined endpoint with advancing age by SMN2 copy number (2 copies, n = 23; 3 copies, n = 9). SMA-I = spinal muscular atrophy type I. Finkel et al, 2014

Natural History of SMA Type 1

More than 90% of SMA Type 1 patients will not survive or will need permanent ventilation support by age 2



Onset of SMA Type 1 by 6 months

Symptoms may present

“floppy baby” syndrome
 muscle weakness (legs more than arms)
 poor head control
 belly breathing
 bulbar muscle weakness (weak cry, difficulty swallowing, aspiration)
will never sit unsupported
loss of motor function:

- NeuroNEXT -- CHOP INTEND decrease of 10.5 points/yr.
- PNCR -- CHOP INTEND decrease of 1.27 points/yr.

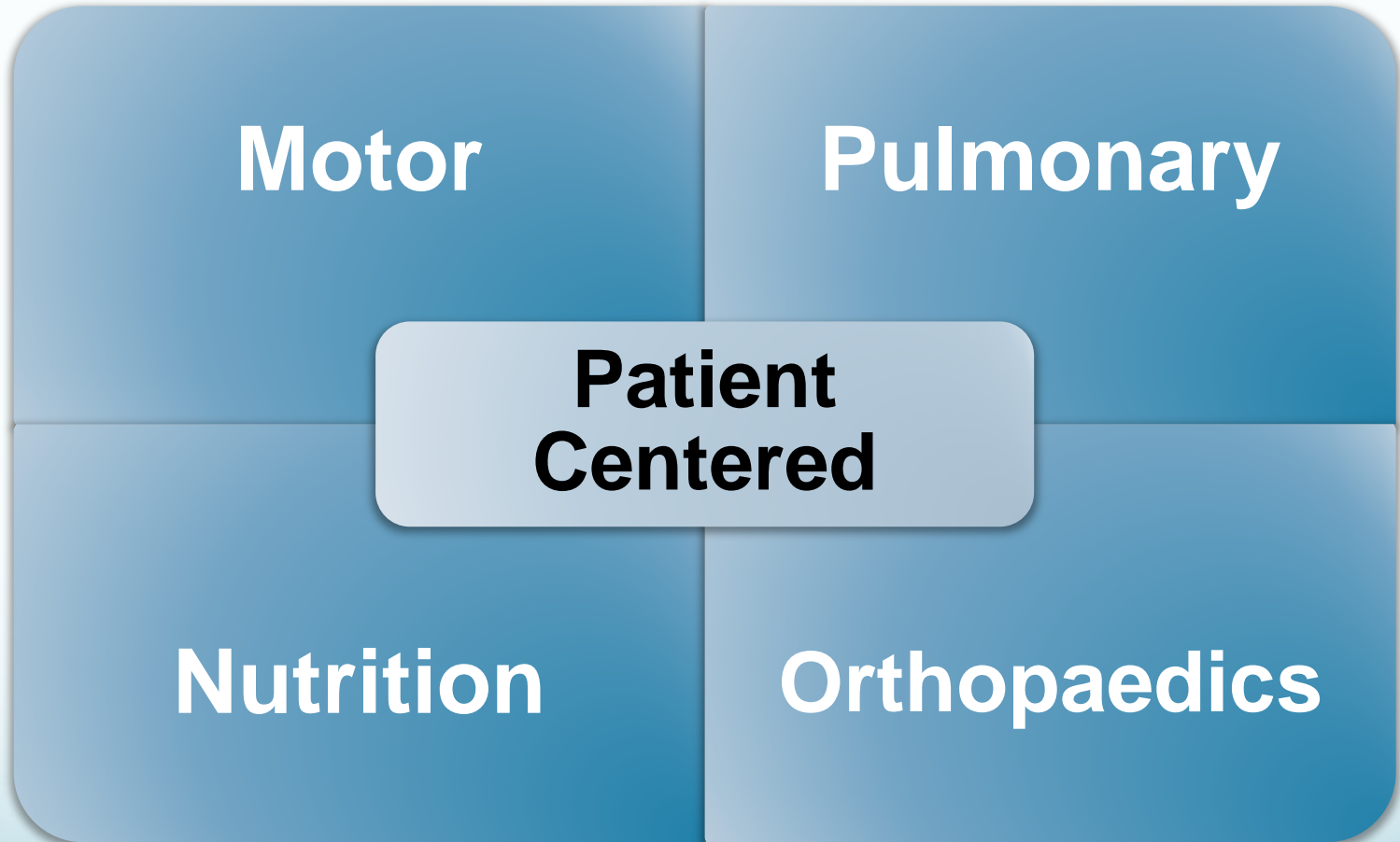
■ Milestone for a healthy infant

■ SMA Type 1 survival rates per Finkel¹

■ SMA Type 1 survival rate per Kolb²

1. PNCR (Finkel)
 2. NeuroNEXT (Kolb)

4 Clinical Domains of SMA



Management Issues for Type 1 SMA

Evolving Topics

- Diagnosis
- Nutritional
- Respiratory
- Orthopaedic
- Acute care
- Physiotherapy/Rehabilitation

Active Discussion

- Maximize motor function
- Enable communication
- Comfort care
- Ethics
- Quality of Life
- Access to new treatments

Consensus Statement for Standard of Care in Spinal Muscular Atrophy

Journal of Child Neurology / Vol. 22, No. 8, August 2007

Updated Standard-of-Care guidelines are being finalized

Comfort Care

- Palliative care focus
 - Oral secretions
 - Breathing comfort
 - Nutrition comfort
 - Activity options, e.g. hydrotherapy

Impact of Enhanced SOC

- Better nutrition and ventilation often leads to improved survival
- *No improvement in motor function, however.*
- Improved quality of life?

Summary

- Infants with SMA type 1 present with typical pattern of weakness and breathing impairment
- After an initial precipitous decline there may be a plateau phase with slower decline
- Survival depends upon age of presentation, SMN2 copy number, avoidance of pulmonary infections and extent of supportive care
- Motor function does not improve from the time of diagnosis.

Thank you