Het verhaal van baby Pia

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September 2019- Team Pia

- Bij **Pia B.** werd op de leeftijd van 6 maanden de genetische aandoening **SMA 1** vastgesteld, spinale musculaire atrofie type 1.
- Baby's met die ziekte geraken progressief volledig verlamd en hebben een **levensverwachting van minder dan 2 jaar**.
- Pia werd onmiddellijk behandeld met **Spinraza,** een intrathecale therapie, te herhalen om de 4 maanden, dat de productie van het ontbrekend SMN eiwit weer opkrikt. Dit product is sinds 2018 in Belgie goedgekeurd en terugbetaald

Dubbele frustratie:

- (te) late diagnose en start behandeling (cfr. piloot project NBS in Brussel/ Wallonie)
- net te oud om aan klinische testfase van **Zolgensma** (gentherapie Novartis-AveXis) deel te nemen in ons land.



Sms actie Team Pia

- Zolgensma was reeds goedgekeurd in de VS. Kostprijs: ongeveer **1,9 miljoen euro**.
- De ouders lanceerden een nationale sms-actie **Team Pia** , wat heel veel aandacht kreeg in media en sociale media.
- Resultaat : 1,9 miljoen euro op nog geen 3 dagen…. **Meer dan een miljoen Belgen** stuurden een sms'je ter waarde van twee euro
- Mede onder druk van de grote media aandacht werd deze gentherapie tenslotte in Belgie toegediend, vooraleer het door EMA was goedgekeurd



Hoe gaat het nu met baby Pia

Baby Pia kan in september naar een gewone school
19/02/2021



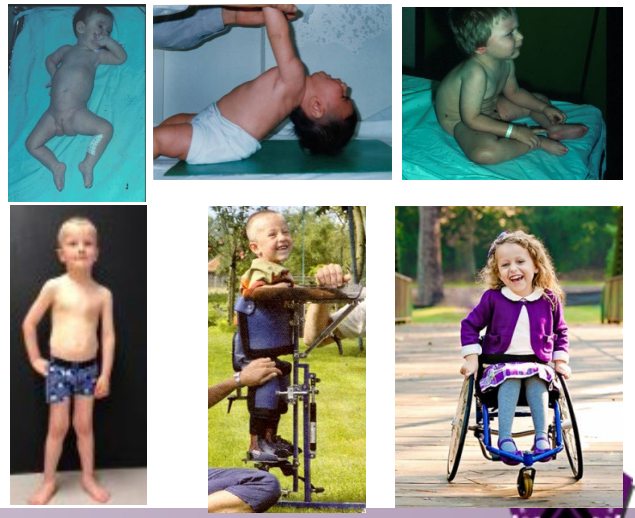
Baby Pia, één jaar na de campagne: "Wat als ze straks vindt dat wij het helemaal verkeerd hebben aangepakt?" 12/09/2020

WILRIJK - **Een half jaar nadat baby Pia het medicijn Zolgensma toegediend kreeg dankzij de financiële steun van heel het land, is ze uitgegroeid tot peuter Pia. Een gelukkig meisje van 16 maanden dat fysiek een enorme progressie maakte en probleemloos haar levensverwachting van maximaal twee jaar zal overschrijden. Allemaal dankzij het geneesmiddel van 1,9 miljoen euro. "Dat is echt waar super, maar we hadden op sommige vlakken op meer gehoopt."**

Spinal muscular atrophy (SMA)

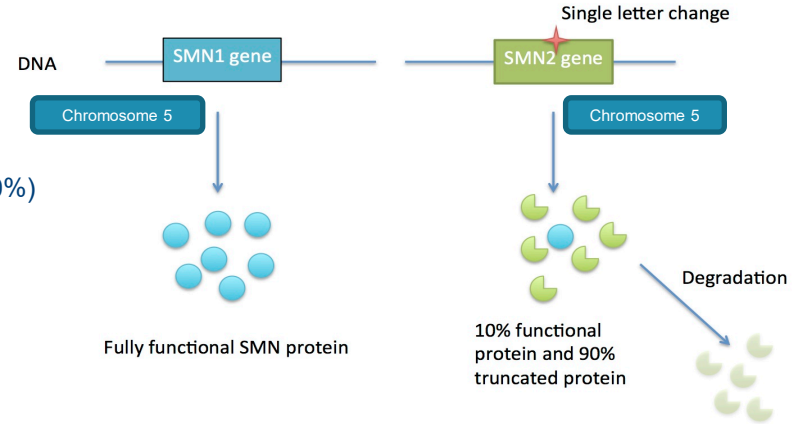
- Recessively inherited degenerative disease affecting spinal motor neurons
- Homozygous mutations in SMN1 gene resulting in deficiency of SMN protein
- Incidence 1/6,000 to 10.000 newborn, carrier 1/35-50
- Clinical heterogeneity : SMAI, SMAII,SMA III, SMA IV, correlating with copy number of paralogous SMN2 gene

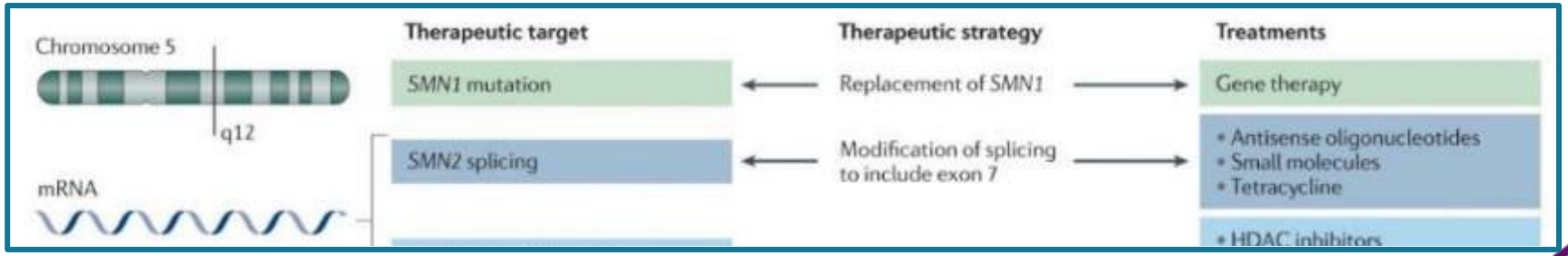
Type of SMA	Age at onset	Highest function	Natural age of death
SMA I (severe, Werdnig-Hoffmann)	0–6 months	Never sits	< 2 years
SMA II (intermediate)	7–18 months	Sits, never stands	> 2 years
SMA III (mild, Kugelberg-Welander)	> 18 months	Stands and walks	Adult
SMA IV	2nd or 3rd decade	Walks in adulthood	Adult



SMN genetics

- 2 genes for SMN production
- Situated on chromosome 5
- SMN1: main provider of functional SMN protein (+/- 90 %)
- SMN2: back up gene with slightly modified protein (+/- 10%)
- SMA patients: deletion of SMN1 → depending on functional production of SMN2

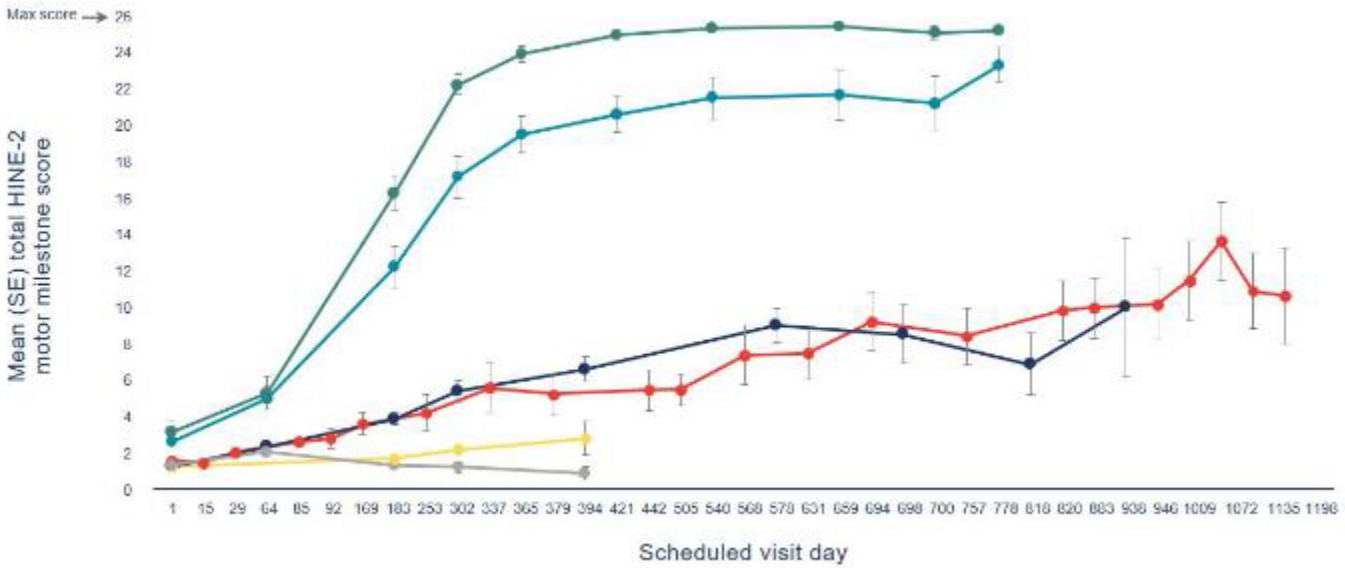




Treatment options for SMA

SMN2 splicing	Advantages	Limitations	Belgium
Spinraza (Antisense Oligonucl.)	• Highly specific, targets only *SMN2* • All SMA patients at any age • Very few side effects	• CNS only • Repetitive invasive IT injection • Side effects due to IT injection • Additional costs due to inpatient admission • Highest costs converted to life expectancy • US $ 750,000 first year, US$ 350,000/year	Reimbursed for all types of SMA at any age
Evrisdy (Small molecule)	• Orally administred • Systemic distribution • All SMA patients > 2 months	• Daily administration • Neonatal administration excluded • Potential off-target effects and increased side effects on the long term • US $ 100,000-340,000/year, weight dependent	CUP
Gene therapy			
Zolgensma (Gene therapy with AAV9 vector)	• One time dosing IV • Systemic distribution	• Restricted to patients with >= 3copies *SMN2* • Excluded for patients with antibody titers > 50 mg/ml • Vey limited knowledge of long term effects of scAAV9 • Age limitation due to inability to cross BB barrier and maximal viral load that can be administered • Re-injection impossible (antibodies) • Side effect (eg. liver toxicity) • Extremely high but one time cost US$ 2,1 million	Reimbursement request submitted

Nusinersen: a valid treatment option for SMA



NURTURE (pre-symptomatic Infantile-onset SMA; 3 *SMN2* copies; n=10; 2/2020 data cut)

NURTURE (pre-symptomatic infantile-onset SMA; 2 *SMN2* copies; n=15; 2/2020 data cut)

CS3A (Infantile-onset SMA; 2 *SMN2* copies; n=17; final analysis)*

ENDEAR and SHINE SPINRAZA® (infantile-onset SMA; 2 *SMN2* copies; 6/2017 data cut)

ENDEAR sham-control/SHINE SPINRAZA® (infantile-onset SMA; 2 *SMN2* copies; n=23; 6/2017 data cut)

ENDEAR sham-control (infantile-onset SMA; 2 *SMN2* copies; n=40; final analysis)

Adapted from Swoboda et al.[1]

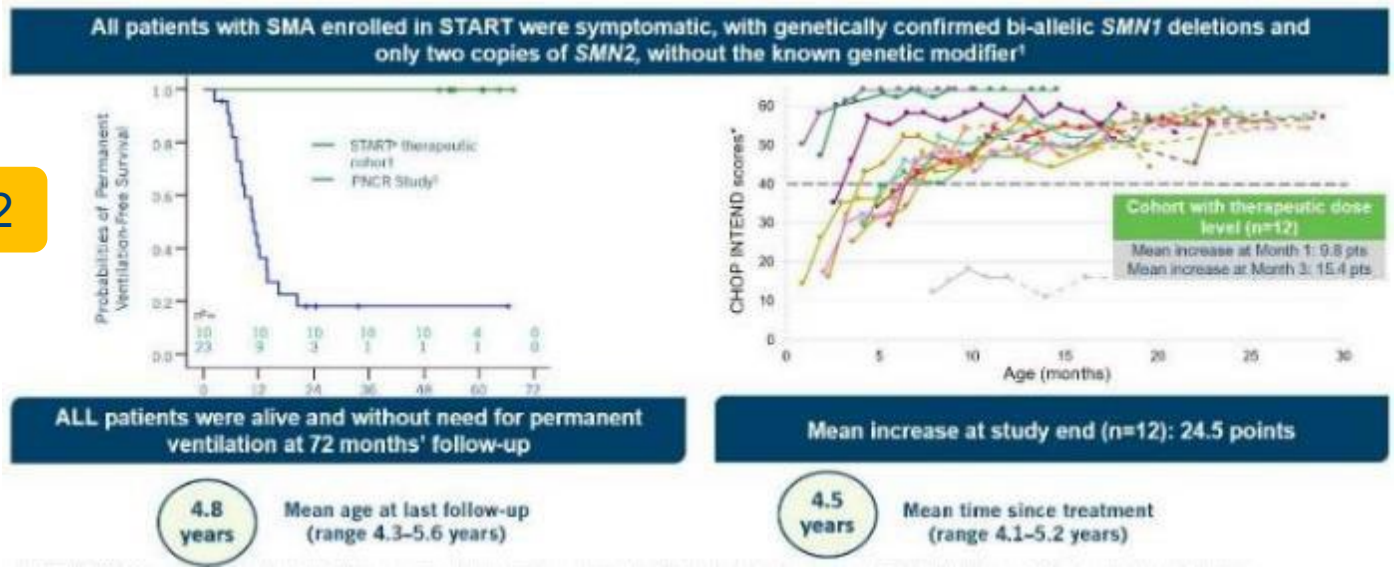
significant benefit of presymptomatic Spinraza® treatment

versus treating after symptom onset

Swoboda et al. Presented at Cure SMA Annual Conference 2020; Slide provided by Biogen

Onasemnogene abeparvovec (Zolgensma®)

N= 12



11 sat alone — **11** of 12 patients **sat unassisted**[3]

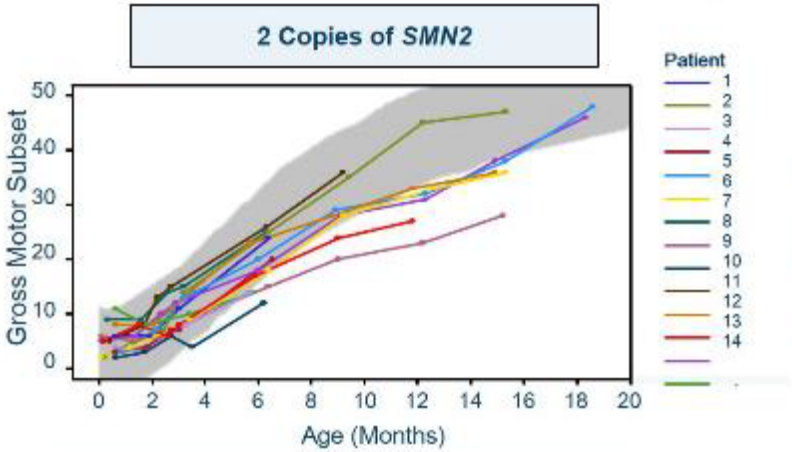
2 walked alone — **Two** children crawled, pulled to a stand, stood, and **walked independently**[1,3]

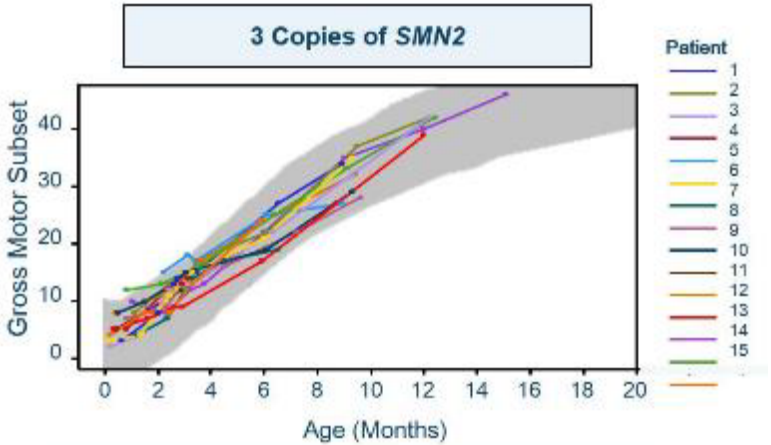
improvement in survival and motor outcomes in SMA type 1 patients

Mendell et al. *NEJM* 2017; slide provided by Novartis Gene Therapies

Onasemnogene abeparvovec (Zolgensma®)

SPR1NT — Two or three *SMN2* copies — Infants ≤6 weeks of age





7 of 14 (50%) have **gross motor performance** similar to normal development

14 of 14 (100%) have **fine motor performance** similar to normal development

15 of 15 (100%) have **gross motor performance** similar to normal development

14 of 15 (93%) have **fine motor performance** similar to normal development

presymptomatic treatment results in **nearly normal development** in patients with up to 3 *SMN2* copies

Slide provided by Novartis Gene Therapies

What is the treatment expectation for SMA1?[1]

CURRENT TREATMENT OUTCOMES

Type I SMA[3–8]

- Type I until death
- Short life expectancy (<2 years)

TREATMENT EXPECTATIONS FOR NEW PHENOTYPE

Caregivers may expect their children, treated with disease modifying therapies, to

- Show improvements in survival
- Have fewer respiratory and swallowing complications
- Reach motor milestones that historically are not reported in infants with Type I SMA
- Sit and stand without support
- Show improvements in mobility on the long-term/ walking?

Reaching any of these milestones would vary from infant to infant and would be dependent on different variables, including **length of disease, complications already present, functional level and timing for therapy initiation**

SMA, spinal muscular atrophy.

1. Tizzano EF & Finkel RS. *Neuromuscul Disord* 2017;27:883–889; 2. Dubowitz V. *Eur J Ped Neuro* 1999;3:49–51; 3. Kolb SJ & Kissel JT. *Neurol Clin* 2015;33:831–846; 4. Viollet L & Melki J. *Handbook of Clin Neuro: Ped Neuro Part III* 2013;113:1395–1411; 5. Butchbach M. *Front Mol Biosci* 2016;3:7; 6. D'Amico A et al. *Orphanet J Rare Dis* 2011;6:71; 7. Lunn MR et al. *Lancet* 2008;371:2120–2133; 8. Prior TW. *Genet Med* 2010;12:145–152.

Considerations (1)

- Hype versus Hope in treatment development for severe diseases
- Role of (social) media in treatment expectations
- Role of clinician - Pressure to treat with compounds not yet approved by EMA
- Combination of two very expensive therapies

Considerations (2)

- Interpersonal solidarity (sms actie) versus contractual solidarity
- “publicity” for SMA, an orphan disease, impact on societal acceptance of costs of orphan drugs.

“Factors that make the measurement of societal value in the area of funding orphan drug particularly difficult are:

- *the **low level of public awareness** of, and engagement with, the orphan-drug issue*
- *the 'zero-sum' framing commonly used to describe the policy challenge posed by orphan drugs”*

Dragojlovic N et al.. Challenges in measuring the societal value of orphan drugs: insights from a Canadian stated preference survey. Patient. 2015 Feb;8(1):93-101.

Considerations (3)

- Costs of therapies
- Add-on to costs of a longer survival with impairments
- Urgency to implement neonatal screening

What numbers are we talking about

- Prevalence of SMA1 patients in Belgium: 18
  - based on Belgian Neuromuscular Disease Registry,
  - = literature data : prevalence 0,04-0,28/100,000) (Verhaart et al. 2017)
- Incidence of SMA1 patients in Belgium: 10,4 new cases/year
  - based on New Born Screening data from Brussel/Wallonie (Dangouloff et al. 2020)

Cost impact per SMA1 patient

Treatment	Cost
Spinraza	Approx € 600,000 first year, € 300,000/year from year two
Zolgensma	€ 2 million, once

- Estimated costs of care per SMA patient according to German study
  - 100,000 Euro per year (SMA1)
  - 90,000 Euro per year (SMA2)*
    - 68 % live up to 25 years, then survival reaches normal life span (mean lifelong cost : 7,7 milj Euro)
  - 52,44O Euro per year (SMA3)
    - normal life span (mean lifelong cost : 4,5 milj Euro)

**Klug. C, Orphanet J Rare Dis 2016*

Systematic literature review of the economic burden of spinal muscular atrophy and economic evaluations of treatments

Dangouloff T. Orphanet J Rare Dis. 2021; 16: 47

Aim:

- Systematic literature review on cost of SMA and economic evaluations of treatments (annual cost of care of patients with SMA: 9 studies/ evaluations of the cost-effectiveness of SMA treatments: 6 studies).

Results:

- The average annual cost of SMA1ranged from **$75,047 to $196,429** per year.
- The yearly costs for the forms of the later-onset form SMA2, SMA3, and SMA4 were more variable, ranging from **$27,157 to $82,474**.

Systematic literature review of the economic burden of spinal muscular atrophy and economic evaluations of treatments

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Results:

- The incremental cost-effectiveness ratio (ICER) of Spinraza compared to standard of care in SMA1 ranged from **$210,095 to $1,150,455** per quality-adjusted life years (QALY) gained ,The ICER for Zolgensma ranged from **$32,464 to $251,403**.
- For pre-symptomatic patients, the ICER value ranged from **$206,409 to $735,519**.
- The ICERs for later-onset forms of SMA were more diverse ranging from **$275,943 to $8,438,049**.

Conclusion

This review confirms the **substantial cost burden of standard of care** for SMA patients and the **high cost-effectiveness ratios of the approved drugs** at the current price

Considerations (4)

- Turning a lethal disease into a disease with significant impairements
- How do we assess Quality of Life in SMA
- What are meaningfull improvements

On which ground is it ethically accepted to prolong life in an irreversible proces ?

Provision of life saving or life prolonging measures or therapies is only ethically accepted *“if they respect patients well being…”*

What is patient’s well being ?
How do we assess patient’s well being?
How do we estimate patient’s well being?



Neuromuscular disorders (NMD)

- Improved multidisciplinary approach and management, improved longevity
- New insights in pathophysiology, hope for future treatments
- Improved contextual aspects (technical assisting devices, integration/education, resources…and other determinants of QoL)

Evolution in socio-medical perception of disease burden and clinical decision making process in NMD

Evolution in socio-medical perception in management of NMD

- Eighties: struggle for use of non-invasive ventilation in stable congenital myopathies
- Nineties : debate about ethical aspects of ventilating chronic progressive NMD (Duchenne, ALS,…)
- Early this century: debate about permanent ventilating neonates with poor neuromuscular prognosis (SMA I, ..)
- Today debate on ethical aspects and cost of therapies for degenerative NMD

Quality of Life

- Generally assumed that a **reduced physical ability** and **greater disease severity** are the main factor determining impaired quality of life
- QoL is a subjective and multidimensional concept: a whole series of factors: personal, cognitive, social, contextual, relational, environmental, can impact greatly on QoL

Life satisfaction among NMD patients

1, Strongest correlation with life satisfaction:

- Emotional well being
- Self assessed health
- Social life
- Family support
- Percieved control
- Recreational opportunities
- Sexual relations



2. Impairment and disability do not affect significantly life satisfaction and quality of life



Rahbek J Paediatric Rehabilitation 2005;Bach et al, *Arch Phys Med Rehab 1991 ;* Kohler M,Am J Resp Crit Care Med 2005; G. Zamani et al. Neuromuscular Disorders 2017

Quality of life: the disability **paradox**

- Phenomenon that people who have serious health conditions, with lasting impairments and disabilities, can nevertheless experience **a good quality of life,** although this may seem counterintuitive to most external observers: happy patients, with low quality of life as rated by the general public
- Concerns about **impact of subjective assessment of quality of life** of these patients by health care providers by using their own values when facing the limitations of the impaired individual
- **Underestimation of QoL** interferes with disclosure practice and decision making proces

Albrecht and Devlieger ,1999; Gerhart *Ann Emerg Med 1994*; Campell ME: *Psychology 1996* ; Zamani G, et al. *Neuromuscul Disord*. 2016;Lim Y, et al., *Qual Life Res 2014*; de Moura MC et al. *Arq Neuropsiquiatr. 2015*

Het verhaal van baby Pia…

Stof voor boeiende debatten rond medische, ethische, economische en maatschappelijke kwesties ivm ontwikkeling, prijs, toepassingen en evaluatie van geneesmiddelen voor weesziekten!