A contemporary analysis of the Australian clinical and genetic landscape of spinal muscular atrophy: a registry based study

Lakshmi Balaji,[a,b,*] Robin Forbes,[c] Anita Cairns,[d] Hugo Sampaio,[a] Andrew J. Kornberg,[e] Lauren Sanders,[f,g] Phillipa Lamont,[h] Christina Liang,[i] Kristi J. Jones,[j,k] Kristen Nowak,[l] Cullen O'Gorman,[m,n] Ian Woodcock,[e] Nancy Briggs,[o] Eppie M. Yiu,[c,e,p] Michelle A. Farrar,[a,b] and Didu Kariyawasam[a,b]

[a]Department of Neurology, Sydney Children's Hospital Randwick, NSW, Australia
[b]Discipline of Paediatrics and Child Health, School of Clinical Medicine, UNSW Medicine and Health, University of New South Wales, Sydney, NSW, Australia
[c]Australian Neuromuscular Disease Registry, Neuroscience Research Group, Murdoch Children's Research Institute, Parkville, VIC, Australia
[d]Queensland Children's Hospital, Brisbane, QLD, Australia
[e]Department of Neurology, The Royal Children's Hospital Melbourne, Parkville, VIC, Australia
[f]The University of Melbourne, VIC, Australia
[g]St Vincent's Hospital, Melbourne, VIC, Australia
[h]Royal Perth Hospital, Perth, WA, Australia
[i]Royal North Shore Hospital, St Leonards, NSW, Australia
[j]Discipline of Child and Adolescent Health, University of Sydney, Sydney, NSW, Australia
[k]Children's Hospital at Westmead, Westmead, NSW, Australia
[l]University of Western Australia, Perth, WA, Australia
[m]Princess Alexandra Hospital, Brisbane, QLD, Australia
[n]University of Queensland, Brisbane, QLD, Australia
[o]Mark Wainwright Analytical Centre, University of New South Wales, Sydney, NSW, Australia
[p]Department of Paediatrics, The University of Melbourne, Parkville, VIC, Australia

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Summary

Background New paradigms of diagnosis and treatment have changed the neurodegenerative trajectory for individuals with spinal muscular atrophy (SMA). Registries are a critical tool to provide real-world data on treatment patterns, their effects and health care provision within this evolving paradigm of care. This study aimed to evaluate the phenotypic and genotypic landscape, treatment patterns and health impact of SMA in Australia through the national registry.

Methods This cross-sectional study investigated demographic, clinical and genetic information, sequelae of weakness, treatment patterns and patient-reported outcomes amongst individuals with SMA enrolled in the Australian Neuromuscular Disease Registry (ANMDR) from 1st January 2020 to 30th April 2023. Descriptive statistics were used for analysis and Chi-Squared or Fisher's exact tests for associations.

Findings 195 individuals with SMA enrolled into the ANMDR. 5/195 (2.6%) were deceased by censor date. Of (n = 190) individuals living with SMA, 104/190 (54.7%) were children. Minimum Australian prevalence was 0.73/100,000. *SMN2* copies were inversely associated with phenotype in those with homozygous *SMN1* deletions ($p < 0.0001$). Treatment was utilised in 154/190 (81%) of the population, with 65/137 (47.6%) of individuals perceiving improvements with therapeutic intervention on Patient/Parent Global Impression of Improvement scale ($p < 0.0001$). Engagement with multidisciplinary care practitioners was significantly higher among children with SMA than adults (93% versus 12%, $p < 0.0001$).

Interpretation Despite diagnostic and therapeutic advances, mortality and the multi-systemic health impact of SMA continue to be experienced within the Australian population. Healthcare provision must align with patient-centred outcomes, adapting to meeting their changing but ongoing care requirements. The study identified the

Abbreviations: IQR, Interquartile range; NBS, Newborn bloodspot screening; OA, Onasemnogene abeparvovec; PBAC, Pharmaceutical Benefits Advisory Committee; PBS, Pharmaceutical Benefits Scheme; PGI-S, Patient/parent Global Impression of Severity; PGI-I, Patient/parent Global Impression of Improvement; PREM, Patient reported experience measure; PROM, Patient reported outcome measure; REDCap, Research Electronic Data Capture system; QoL, Quality of Life; SMA, Spinal Muscular Atrophy; SMN gene, Survival Motor Neuron gene; TGA, Therapeutic Goods Administration; TREAT-NMD, Translational Research in Europe for the Assessment and Treatment of Neuromuscular Diseases

*Corresponding author. Department of Neurology, Sydney Children's Hospital Randwick, NSW, Australia.
E-mail address: l.balaji@unsw.edu.au (L. Balaji).

considerable unmet need for multidisciplinary care, not only for adults with SMA but also for the emerging cohort of treated children, emphasising the imperative for comprehensive healthcare provision to address their evolving needs.

Funding No funding was received for this study.

Keywords: Spinal muscular atrophy; Registry; Prevalence; Epidemiology; Rare disease; Comorbidities

Research in context

Evidence before this study

We performed search on PubMed using the keywords "spinal muscular atrophy" and "registry" (("muscular atrophy, spinal"[MeSH Terms] OR ("muscular"[All Fields] AND "atrophy"[All Fields] AND "spinal"[All Fields]) OR "spinal muscular atrophy"[All Fields] OR ("spinal"[All Fields] AND "muscular"[All Fields] AND "atrophy"[All Fields]) OR (((((("spinal"[All Fields] NOT "spinalization"[All Fields]) NOT "spinalized"[All Fields]) NOT "spinally"[All Fields]) NOT "spinals"[All Fields]) AND ("muscular atrophy"[MeSH Terms] OR ("muscular"[All Fields] AND "atrophy"[All Fields]) OR "muscular atrophy"[All Fields] OR ("muscular"[All Fields] AND "atrophies"[All Fields]) OR "muscular atrophies"[All Fields])) OR "5qSMA"[All Fields]) AND ("registries"[MeSH Terms] OR "registries"[All Fields] OR "registry"[All Fields] OR "registry s"[All Fields] OR ("registries"[MeSH Terms] OR "registries"[All Fields] OR "registry"[All Fields] OR "registry s"[All Fields]) OR ("directory"[Publication Type] OR "directories as topic"[MeSH Terms] OR "registers"[All Fields])). Studies in the past 10 years were included, to deliberately reflect the clinical landscape and impact of SMA for individuals within the new diagnostic and treatment era. One hundred studies were identified, of which 32 were registry based. Registry reports described epidemiology, demographic and clinical/genetic information (n = 9), drug effects (n = 6) and side effects (n = 1), registry establishment and methodology (n = 14), natural history (n = 3), proposed classification of combination disease-modifying treatment (n = 1), sex-specific vulnerability in SMA (n = 1), and patient-reported experiences (n = 2). These studies were from European (n = 16), North and Latin American (n = 7), and Middle-Eastern (n = 2) countries, and from global registries (n = 7). No studies were identified from the core countries within the Asia–Pacific (APAC) region. There was paucity of comprehensive reports describing evidence on genotype-phenotype correlation, clinical sequalae of weakness, treatment patterns in the era of newborn screening and SMN-augmenting therapies and patient-reported experience measures. This study is, thus, the first registry-based output from within the APAC region, that concomitantly includes an in-depth evaluation of clinical, genetic and patient-centric outcomes."

Added value of this study

As the first study of the Australian national registry, this work provides new knowledge of the demographic, genetic and therapeutic characteristics on the Australian SMA population. The analysis of treatment patterns and comorbidities provides insights into the range of unmet needs, particularly in the adult population and highlights potential challenges for the healthcare system in the provision of sustainable resource allocation and care planning, to provide equity of access and optimise health outcomes for all Australians living with SMA.

Implications of all the available evidence

Whilst the advent of new pathways for diagnosis and therapeutic intervention have provided opportunities for a change in clinical trajectory for many individuals with SMA, new challenges have evolved through this proactive paradigm of care. This body of work emphasises that access to SMN-augmenting treatments can change patient experience of health, but healthcare access to supportive care to actualise the potential of therapeutics is variable, and requires a collaborative and streamlined approach to care coordination. Within a publicly funded healthcare system, real-world data mined from registries will continue to be essential to interrogate new ways of implementation of health services so that equity of access to best practice is met for all individuals with SMA.

Introduction

Spinal muscular atrophy (SMA) is characterised by progressive muscle weakness, leading to increasing neurodisability, plateauing, and regression of motor skills and in some forms, limited survival. Since the introduction of survival motor neuron (SMN) targeted therapies in 2016, there has been a continuing shift in the clinical trajectory of SMA, transforming it from a condition with limited survival in severe forms to a treatable one with improved survival and motor function trajectories.[1] The therapeutic repertoire for SMN-augmenting therapies includes an antisense oligonucleotide (nusinersen), a gene transfer therapy (onasemnogene abeparvovec), and a small molecule based on SMN2 splice correction (risdiplam). Despite all three agents having efficacy in clinical trial populations,

real-world data has attested to the fact that individual clinical, disease and electrophysiological characteristics, including but not limited to disease duration, functional score at intervention and clinical status, all combine to change the clinical trajectory with treatment.[2] Thus, for a heterogeneous population with a rapidly evolving clinical profile, including individuals diagnosed through newborn screening (NBS) programs and individuals living with SMA, a contemporary understanding of the clinical and management landscape remains imperative to customise healthcare approaches and guide service provision, and to optimise health outcomes across the lifetime of affected individuals.[3] The integration of real-world data with clinical research and healthcare delivery systems is essential in this context, providing valuable insights into the multifaceted experiences and needs of individuals living with SMA across all stages of the disease spectrum.

The incidence of SMA was 1 in 11,458 in an Australian population-based study,[4] thus qualifying it as a rare disease. Registries serve as a critical tool to enhance knowledge, monitor interventions[5] and facilitate translational efforts[6] in rare diseases such as SMA. They provide real-world evidence of the use, safety and efficacy of therapies and self-reported quality-of-life measures[7] in populations not included or reported in clinical trials. In addition, registries can provide relevant regional information and the opportunity to amalgamate substantial datasets for comprehensive analysis.[8]

There is lack of collated current data on SMA prevalence, genotypes, treatment patterns and impact within an Australian context, particularly the effects of treatment reported by individuals living with SMA. These knowledge gaps among stakeholders hinder the customisation of clinical care to address the specific needs of affected individuals, as mandated by national strategic policy and recommendations for rare disease care,[9,10] and preclude the ability to plan and implement a more equitable, person-centred, evidence-based model of healthcare. In addition, with a growing prevalent population of children approaching transition, healthcare approaches that span the entire lifetime of affected individuals remain essential to support health outcomes and guide service provision.[3] Systematic evaluation of registry data from the diverse and geographically unique Australian population is, thus, pertinent, particularly in the context of expanding regulatory access to SMN-augmenting therapies and implementation of newborn screening (NBS) programs worldwide. It endeavours to bridge knowledge disparities, inform policy and foster collaborative research within the dynamic healthcare milieu.

The primary aims of this study were to establish an understanding of the current epidemiology and genetic and phenotypic spectrum of SMA in Australia, leveraging national data collected through the Australian Neuromuscular Disease Registry (ANMDR). The secondary aims were to analyse the impact of the condition on people living with SMA, including the prevalence of sequelae of weakness, analysis of contemporary treatment patterns and healthcare engagement of the Australian population, as well as mortality in the era of SMN-augmenting therapies.

Methods

Australian Neuromuscular Disease Registry (ANMDR)

The latest iteration of the ANMDR was established and relocated to the Murdoch Children's Research Institute (MCRI) in 2020, amalgamating the original Australian neuromuscular disorders registry which was established in 2010 (under the auspices of the Office of Population Health Genomics in Western Australia) and the Parent Project Muscular Dystrophy Australian Duchenne registry. The aims of the ANMDR are to collect cross-sectional and longitudinal clinical, genetic and sociodemographic data from Australians living with neuromuscular disorders, to facilitate clinical research, and to inform therapeutic goods allocation and service provision within a national context. It is a member of the TREAT-NMD Global Registry Network.

The ANMDR has ethics approval from the Royal Children's Hospital Human Research and Ethics Committee (HREC 54969).

Potential new participants are recruited by self-referral from the website or other promotional material, and/or by promotion by their treating clinicians through expression of interest on https://www.australiannmdregistry.org.au/. Consent is obtained only by registry staff by phone or in-person. Participants with genetic confirmation of their neuromuscular disorder, of all ages, living as well as deceased, are eligible for enrolment.

The Registry utilises the Treatment of Neuromuscular Diseases (TREAT-NMD) disease-specific datasets for data collection.[11] Data is participant-reported and clinician-verified where necessary. Data is collated into and managed using the REDCap (Research Electronic Data Capture) system, a secure, web-based software platform, designed to support data capture for research studies, hosted at the MCRI.[12] Auditing is performed periodically to resolve missing or incomplete information. Data collection for SMA is performed by registry staff at enrolment and updated biannually.

Study design and participant eligibility

This national cohort study examined cross-sectional data collected by the ANMDR, with analysis censored on 30th April 2023. Ethics approval for the current study was granted by the Sydney Children's Hospital Network Human Ethics Committees (HREC 2022/ETH01174) and approval for use of collated data was provided by the ANMDR advisory committee.

Participants included children (0–18 years) and adults (>18 years) enrolled in the ANMDR from 1st January 2020 to 30th April 2023. All individuals with genetically confirmed *SMN1*-related SMA in Australia were included. Individuals who were deceased prior to 1st January 2020 and those with non-SMN related neuromuscular conditions were excluded. Intentional grouping or clustering of participants based on geographic or other factors was not implemented. Each participant was enrolled individually based on eligibility.

Study measures

The ANMDR dataset has 120 unique data items in the core dataset version 2. In the present study, measures relevant to this study's research questions were gathered from participants' most recent data update prior to censoring (Table S1, Appendix p 1–5). These included sociodemographic characteristics such as age and gender, clinical characteristics including SMA phenotype, genetic information, current motor function and clinical sequelae of weakness. Presymptomatic was defined as a state in which symptoms were not displayed on clinical examination in individuals with genetically confirmed SMA. For those manifesting clinical symptoms, phenotype was recorded based on traditional classification (type 1: onset <6 months, type 2: onset 7–18 months, type 3: onset 18 months to 18 years; type 4: onset >18 years)[13] and functional type.[14] For the latter, individuals were classified based on current motor function into non-sitters (unable to sit unassisted), sitters (unassisted sitting with head erect for at least 10 s) and walkers (able to take at least 5 independent steps with a straight back).[2,14]

SMN genetics including analysis of *SMN1* variants and *SMN2* copy numbers were obtained from laboratory reports.

The clinical sequelae of weakness collated included scoliosis, use of wheelchair for mobility, respiratory difficulties requiring ventilatory support {invasive (delivery of positive pressure to the lungs via endotracheal or tracheostomy tube) and non-invasive (positive pressure ventilation) of any duration}, and ability to feed {assigned as exclusively oral, mixed (oral and tube) or exclusive tube feeding (nasogastric tube or gastrostomy)}. The requirement of surgical repair for scoliosis and the ages at repair were noted across various types of SMA.

The utilisation of SMN-augmenting therapies (nusinersen, onasemnogene abeparvovec and risdiplam: ages at initiation, instances of discontinuation/switch to another, and the underlying reasons for such decisions) were documented through self-reports. Patterns of healthcare engagement were measured and recorded as the occurrence of one or more consultations with a specific healthcare specialty or service in the previous 6 months {neurologist, other subspecialist under the umbrella of multidisciplinary care (such as cardiologist, respiratory physician, endocrinologist, orthopaedic surgeon), physiotherapist, occupational therapist, orthotist and general practitioner} and number of elective inpatient hospitalisations (for administration of SMN-augmenting therapy/other medical or surgical indications).

Clinical Outcomes {Patient/Parent Reported Outcome Measures (PROMs)} were gathered through self-reported scales. The *Patient/parent Global Impressions scale of Severity* (PGI-S), a self-administered, validated questionnaire,[15] was employed for reporting disease severity; individuals or parents/caregivers of individuals were asked to rate disease severity at enrolment (baseline) on a 4-point scale from 1 ('not at all affected') to 4 ('severely affected'). Additionally, the PGI-Improvement (PGI-I), a single item validated questionnaire, was utilised to assess the individuals' or parents/carers' perception of how their condition changed in the previous 6 months on a 7-point scale from 1 ('very much improved') to 7 ('very much worse').

Data analysis

Statistical analyses were carried out using Excel or Prism–GraphPad by Dotmatics at graphpad.com, version 10.0.02. Aligned with the aims of this study, separate analyses were undertaken in cohorts living and deceased with SMA. Categorical variables were summarised using frequencies and percentages; continuous variables were expressed as median values and interquartile ranges (IQR). Minimum prevalence was defined as the aggregate number of individuals in the Registry divided by the total population of Australia, sourced from the Australian Bureau of Statistics (reference period Mar 2023).[16] The separation of health care provision into paediatric (birth-18 years inclusive) and adult (>18 years) services in Australia prompted the analysis of disease impact and care patterns in these two categories. The Chi-square test was employed to assess associations between age group and current motor function and patterns of health care engagement. Fisher's exact test was used to assess associations between SMA type and *SMN2* copy number, and utilisation of SMN-augmenting therapies, PGI-S and PGI-I. A two-sided p-value <0.05 was interpreted as statistically significant. Missing data for *SMN2* copy number, PGI-S and PGI-I were imputed using mice package in R.[17] Twenty-five datasets were imputed using the predictive mean matching method.[18] The imputation model included the variables of *SMN2* copy number, *SMN1* genotype, SMA type, sex, age at data cut-off, rehabilitative interventions undertaken in the last 6 months since registry update, use of SMN-augmenting therapies and PGI-S and PGI-I scores. Fisher's exact test was run on each imputed dataset. The mean p-values for imputed analyses were reported, along with minimum, maximum and median values (Table S3, Appendix p 7–8). Based on the study sample size, the Wilson score method was used to calculate the 95%

confidence intervals for SMA prevalence and the precision of data. This cohort achieved 80% power with a significance level of 0.05 to detect a difference between two group proportions on a binary categorical variable with equal group sizes, if proportions were 0.7 and 0.5.

Role of funding source
The funding sources of the ANMDR had no role in the design, data collection, data analysis or writing of this report.

Results
The registry had received expressions of interest from 265 individuals at censoring. Of these, 51 were not enrolled for a variety of reasons including: not contactable, not SMA, residing overseas, or lacking genetic confirmation of SMA (especially for adults); 19 individuals declined participation. The final enrolment was 195 individuals during the study interval and included 190 individuals living with SMA and 5 deceased by censor date. Referral centres spread across six Australian states and two territories, encompassing tertiary children's services (n = 7), adult hospitals (n = 19) and primary care services (n = 7), with highest recruitment from the state of Victoria (Table 1).

Mortality
The 5 deceased individuals were children (3 males, 2 females) and the median age (years, IQR) of death was 1 (0.3–10.6). The phenotypic distribution was SMA type 0 (n = 1), SMA type 1 (n = 3) and SMA type 2 (n = 1); 4/5 did not initiate SMN-augmenting therapies and all (5/5) were non-sitters at the time of death (Table S2, Appendix p 6).

Demographics of individuals living with SMA
The minimum Australian prevalence of SMA in 2023 was 0.73/100,000 individuals (95% CI 0.63–0.84/100,000). Highest prevalence rate of 4.29/100,000 were observed in the first decade of life, followed by a steady decrease with increasing age (Fig. 1). Of this living study population, 104/190 (54.7%) were children; sex distribution was nearly equal {male = 92 (48.4%), female = 98 (51.6%)}. The median age (years, IQR) at analysis of individuals with SMA in Australia was 15.9 (7.2–33). A diagnosis of SMA was established after referral to clinical services with clinical symptoms (173/190; 91.1%), through newborn screening programs (10/190; 5.2%), prenatal screening (2/190; 1.1%) and through cascade screening (5/190; 2.6%). Of the cohort, 40 (21.1%) had family history of SMA, among which 32 belonged to sibships from 16 pedigrees. No individual had a parent or child with SMA.

Clinical characteristics of individuals living with SMA
At analysis, 7/190 (3.7%) individuals were presymptomatic, diagnosed through newborn screening (n = 5), prenatal screening (n = 1) and family screening (n = 1). Of the 183/190 (96.3%) individuals who had clinical symptoms and signs of SMA, the predominant SMA subtypes were SMA2 and SMA3 {75/183 (50%) and 64/183 (35%), respectively} (Table 2). Individuals with SMA1 {42/183 (22.9%)} and SMA4 {2/183 (1.1%)} formed the remainder of the population.

State/territory	Number (n) of individuals enrolled in ANMDR	Minimum prevalence[a]
Victoria (VIC) Jurisdictionally includes Tasmania (TAS)	80	1.19/100,000
New South Wales (NSW) and Australian Capital Territory (ACT) Jurisdictionally include Northern Territory (NT)	55	0.63/100,000
Queensland (QLD)	28	0.52/100,000
Western Australia (WA)	19	0.67/100,000
South Australia (SA)	8	0.49/100,0000
Australia wide	**190**	**0.73/100,000[b]**

[a]95% CI 0.63–0.84/100,000. [b]Australian Bureau of Statistics (March 2023), National, state and territory population.

Table 1: **Statewise prevalence of SMA in Australia.**

There were higher proportions of individuals with presymptomatic and SMA1 among children than adults {Children: presymptomatic: 7/104 (6.7%), SMA1: 38/104 (36.5%), SMA2: 36/104 (34.6%), SMA3: 23/104 (22.1%), SMA4: 0; Adults: presymptomatic: 0, SMA1: 4/86 (4.7%), SMA2: 39/86 (45.3%), SMA3: 41/86 (47.7%), SMA4: 2/86 (2.3%), $p < 0.0001$}.

At census cutoff, current motor function classified approximately half of individuals (102/190; 53.6%) as sitters, 48/190 (25.2%) individuals as non-sitters and 40/190 (21.1%) as walkers. The cohort of sitters included individuals who achieved milestones beyond sitting but lost them over time (52/102; 51%), others who plateaued at sitting (25/102; 24.5%) and those who were sitting as part of an upward motor milestone trend (25/102; 24.5%). Adults with SMA were more likely to have lower current motor function than children (Non-sitters: adults 35/48 (72.9%), children 13/48 (27.1%); Sitters: adults 40/102 (39.2%), children 62/102 (60.8%); Walkers: adults 11/40 (27.5%), children 29/40 (72.5%), $p < 0.0001$).

The clinical sequelae of weakness were evident in all SMA types. Scoliosis was present in 122/190 (64.2%) across all SMA subtypes and ages (Fig. 2A), with surgical repair undertaken in 57/122 (46.7%), employing a range of techniques such as insertion of growing rods, arthrodesis and other methods (Luque instrumentation, Harrington rods and non-adjustable rod placements). Frequency and median age (years, IQR) of initial scoliosis surgery across subtypes were 2/22 (9.1%) and 12.2 (11.9–12.6) for SMA1, 40/64 (62.5%) and 10.9 (9.9–12.7) for SMA2, 15/35 (42.9%)

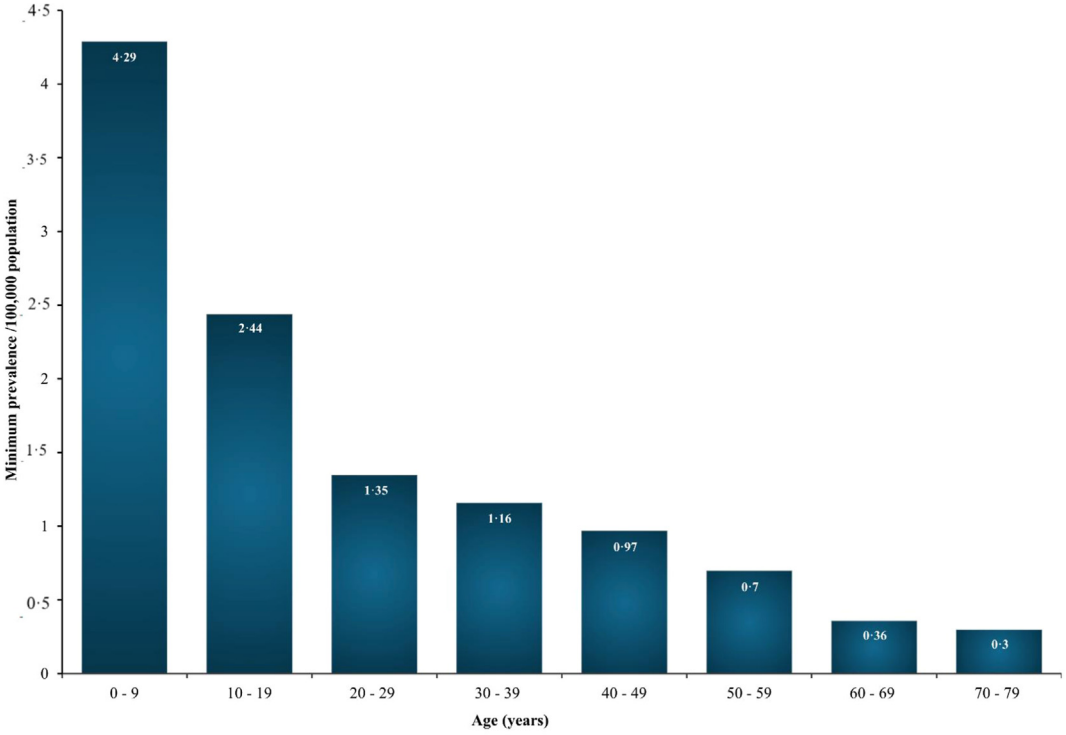

Fig. 1: **Minimum prevalence of SMA in Australia presented by age deciles**. *Australian Bureau of Statistics (March 2023), National, state and territory population.

and 13[11–14] for SMA3. The type of SMA was associated with whether surgery for scoliosis was required ($p < 0.0001$), with nearly two-thirds of SMA2 individuals requiring surgical stabilisation.

Mobilisation with a wheelchair was required in 159/190 (83.6%), non-invasive ventilation for respiratory difficulties utilised in 60/190 (31.6%) and tube feeding in 43/190 (22.6%) individuals (Fig. 2).

No individual within the cohort was on invasive ventilatory support at the time of data analysis; it was transiently required previously in 7 individuals, all children, during respiratory illness and surgery. A total of 60/190 (31.6%) individuals required NIV. This included 2 individuals (2/60, 3.3%) with SMA1 requiring full-time support (>16 h/day). The remainder of individuals, 58/60 (96.7%) required part-time use. 43/190 (22.6%) individuals required tube feeding. Exclusive tube feeding was required for 4 individuals {4/43 (9.3%)}, all with SMA1; supplementary tube feeds were provided for 39 {39/43 (90.7%)}.

	Type 1 (n = 42)	Type 2 (n = 75)	Type 3 (n = 64)	Type 4 (n = 2)	Presymptomatic (n = 7)
Gender, number (%)					
Male	18 (43)	41 (55)	29 (45)	1	3
Female	24 (57)	34 (45)	35 (55)	1	4
Age, years					
Median (IQR)	4.6 (2.1–6.8)	15.0 (8.2–33.2)	30.5 (14.6–45.5)	59.7 (53.9–65.4)	2.8 (1.3–9.3)
Age group, number (%)					
Children	38 (90)	37 (49)	23 (36)	0	7
Adults	4 (10)	38 (51)	41 (64)	2	0
Current motor function, number (%)					
Non sitter	13 (31)	28 (37)	7 (11)	0	0
Sitter	24 (57)	44 (59)	29 (45)	1	4
Walker	5 (12)	3 (4)	28 (44)	1	3

Table 2: **Clinical characteristics of individuals living with SMA in Australia.**

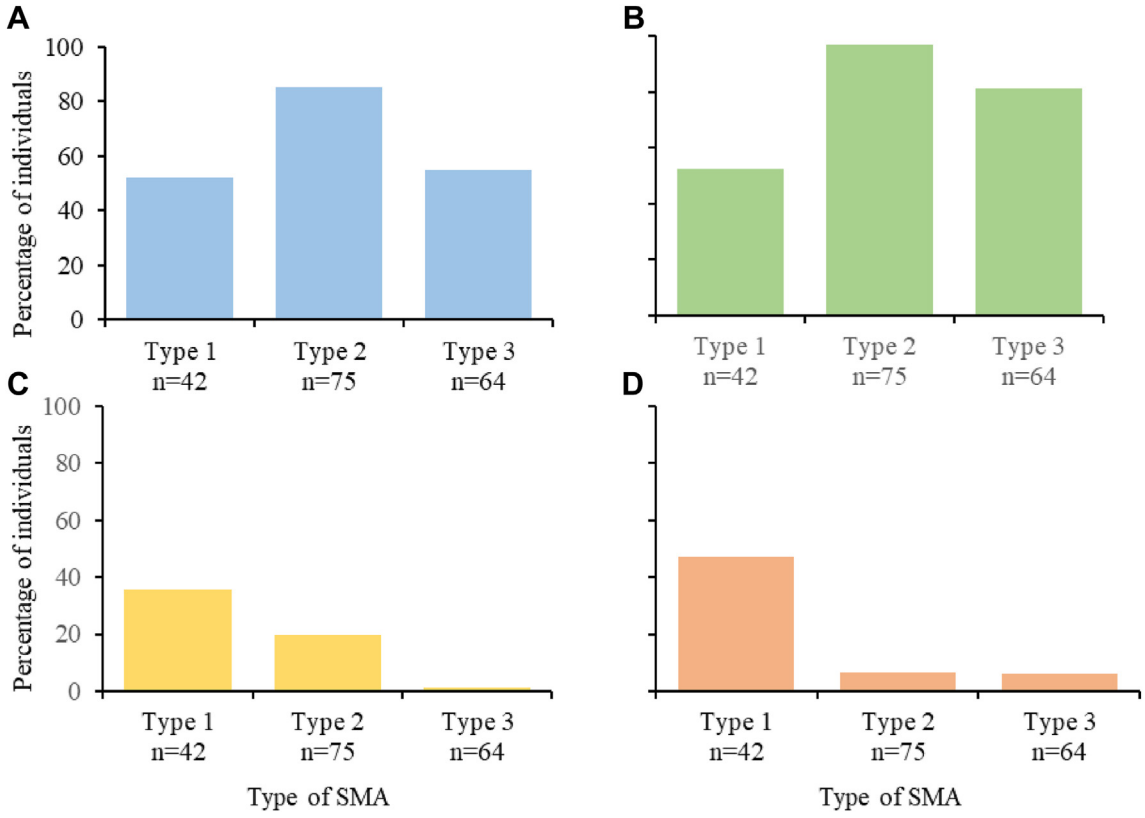

Fig. 2: **The frequency of clinical sequelae of weakness in individuals with SMA types 1–3. A. Scoliosis B. Use of wheelchair for mobility C. Respiratory insufficiency and use of non-invasive ventilation and D. Use of tube feeding**. *SMA type 4 not included (n = 2).

Spectrum of genetic variants and genotype-phenotype correlations

Of the population living with SMA, 177/190 (93.1%) had homozygous deletions in *SMN1* exon 7, whilst compound heterozygosity accounted for pathogenicity in 11/190 (5.8%) and homozygosity for pathogenic sequence variants in *SMN1* in 2/190 (1.1%) individuals.

The numbers of *SMN2* copies were available in 102/190 (53.6%) individuals of the cohort. An inverse association between the phenotype and copy numbers was observed among individuals with homozygous *SMN1* deletions (Observed and imputed mean $p < 0.0001$, Fig. 3); 24/26 (92.3%) of individuals with 2 *SMN2* copies manifested SMA type 1, while 4/5 (80%) of those with ≥4 *SMN2* copies had milder SMA types 3 and 4; 3 *SMN2* copies conferred a range of phenotypes from SMA types 1 to 3. In contrast, for individuals with compound heterozygosity and biallelic sequence variants in *SMN1*, the study did not find evidence of an association between the number of *SMN2* copies and SMA type (Observed $p = 0.21$, imputed mean $p = 0.12$); of note, one individual with compound heterozygosity and 1 *SMN2* copy (confirmed on repeat testing) had SMA type 4 and another with 3 *SMN2* copies had severe SMA1 with clinical sequelae of weakness; individuals with 2 copies of *SMN2* in this cohort had a range of phenotypes (SMA1 n = 2, SMA2 n = 2, SMA3 n = 3).

SMA management

Among those living with SMA, SMN-augmenting therapies were utilised by 154/190 (81%) individuals,

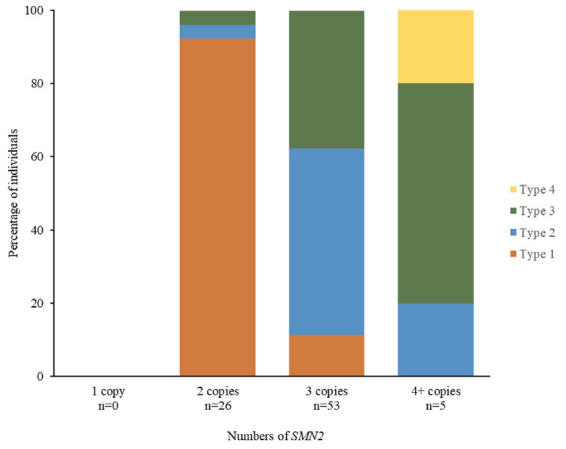

Fig. 3: **Genotype–Phenotype associations in SMA among individuals with homozygous deletions of EXON 7 *SMN1***.

comprising 100/104 (96%) children and 54/86 (63%) adults (p = 0.05) (Fig. 4). No individual stopped treatment. The utilisation of therapies varied across the types of SMA; SMA1: 42/42 (100%), SMA2: 58/75 (77.3%), SMA3: 47/64 (73.4%), SMA4: 1/2. All except one of the presymptomatic individuals (6/7) received therapy. The frequency of utilisation of individual therapies at any time was 137/154 (88.9%) for nusinersen, 27/154 (17.5%) for onasemnogene abeparvovec and 46/154 (30%) for risdiplam. Among children, the median age (years, IQR) for initiation of SMN-augmenting therapy (including access through clinical trials) was 2.8 (0.5–8.6) for nusinersen, 0.7 (0.3–1.2) for onasemnogene abeparvovec and 6.6 (2.9–13) for risdiplam. In the adult group, the median ages (years, IQR) at initiation of nusinersen and risdiplam were 30.8 (27.5–43.2) and 22.9 (18.5–29.6), respectively. Over the study interval, 21/137 (15.3%) switched from nusinersen to onasemnogene abeparvovec and 25/137 (18.2%) to risdiplam. This was due to a range of factors including evolving scoliosis {7/46 (15.2%)}, procedural side effects {5/46 (10.9%)}, perceived insufficient benefit {3/46 (6.5%)}, elective choice {30/46 (65.2%)} and unknown reason {1/46 (2.1%)}. Nearly half (7/15, 46.6%) of adults on risdiplam were adolescents who transitioned to adult services and switched from nusinersen to risdiplam.

The patterns of healthcare engagement among children and adults are shown in Table 3. Children had a higher proportion of one or more attendances to healthcare facilities than the adult group; there were significant differences between the groups in engagement with multidisciplinary clinics, occupational therapy and orthotics services.

Clinical outcomes

PGI-S and PGI-I were available for 137/154 individuals utilising SMN-augmenting therapies and all 36 individuals not utilising therapies. In this study, there was no association observed between disease severity, as perceived by the individuals/parents, and the utilisation of therapies (Observed p = 0.79, imputed mean p = 0.74). However, an association emerged when comparing the utilisation of therapies with the PGI-I (observed and mean imputed $p < 0.0001$), with 65/137 (47.6%) individuals on therapy noting improvement (Fig. 5).

Discussion

This study highlights the diverse needs of the SMA population, notes the shift in epidemiology of SMA with emergence of new cohorts and encapsulates the role of registries in contributing to healthcare planning. Our findings show that the Australian SMA population is diverse in terms of age, genetics, functional abilities and engagement with healthcare and treatment patterns, delineated by paediatric and adult healthcare services. Importantly, although SMN-augmenting therapies provide improvement, the health impact and continuing care needs of the population are substantial and highlight an unmet need for multidisciplinary care for adults with SMA and the growing cohort of treated children. As an SMA flagship nation for delivering first-in-kind interventions and pioneering NBS programs within the Asia-Pacific,[19,20] the findings of the national registry have translational utility and guide the implementation of similar initiatives across the region and beyond.

Traditionally perceived as a condition of infancy and early childhood, the health outcomes for severe type 1 SMA in Australia have seen a significant shift, now

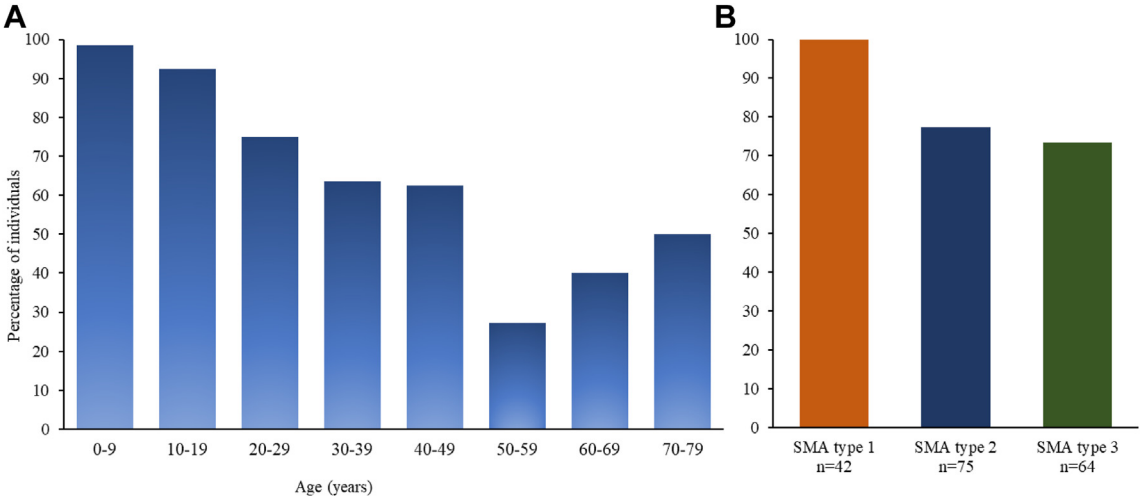

Fig. 4: **Utilisation of SMN-Augmenting therapies among alive individuals with SMA by A. Age deciles and B. SMA type***. *Presymptomatic (n = 7) and SMA type 4 (n = 2) not included.

including extended lifespan. The highest prevalence was of those <10 years, with a notable proportion of type 1 individuals, reflecting the emergence of a new cohort of treated children with ongoing muscle weakness impacting respiratory, bulbar and musculoskeletal functions, and requiring ongoing supportive care. Even so, permanent invasive ventilatory support continues to not be standard Australian practice, linked with reimbursement criteria.[21] In addition, restricted life expectancy persists, including children initiating SMN-augmenting therapies and others with symptomatic type 1 SMA whose families' chose palliative care. The changing epidemiology of SMA also included a small but growing presymptomatic population as a consequence of newly instigated NBS programs coupled with early initiation of therapies. Approximately half of the cohort were adults living with SMA, with variable engagement in healthcare. Whilst this cohort predominantly comprised individuals with milder types of 2, 3 and 4, our findings attest to the lifetime impact of weakness on this population. Adults with SMA had lower motor function than treated children; this is perhaps reflective of the ramifications of a chronically progressive condition of long duration in adults compared to cessation of a precipitous neurodegenerative process in the severe form through SMN augmentation in children; this aligns with previous observation that disease duration is a key modifier of future motor function.[22]

This changing epidemiology has several ramifications for clinical practice. Whilst prior to the era of therapeutics, the clinical course of SMA was predictable and founded on SMA phenotype and *SMN2* copy number, clinicians now need to account for disease duration, current motor function, modality of diagnosis and clinical status at therapy induction[2] to set therapeutic expectations and inform treatment strategies. As our findings show, as an increasingly lifetime condition that spans from birth to adulthood, collaborative working, exchange of expertise between stakeholders in adult and child neurological services and formalised and streamlined transition processes remain essential to provide supportive foundation for individuals with SMA. In addition, it is essential that stakeholders collaborate to find new ways of implementing therapeutic strategies and rehabilitative technologies in sustainable and well-resourced pathways for the expanding SMA population.

For children with SMA, our findings emphasise the imperative to guide management more proactively within the framework of multidisciplinary care to capitalise on the benefits of SMN-augmenting therapies.[14] While the therapies may lead to improved motor function in treated children, longer times in erect postures of sitting and standing on the background of residual

	Children (birth to 18 years) N = 104	Adults (>18 years) N = 86
Utilisation of healthcare resources		
Therapy[a] utilisation, number (%)	100 (96)	54 (63)
One or more consultations in the previous 6 months, number (%)		
Neurologist	104 (100)	72 (84)
Multidisciplinary clinic	97 (93)	10 (12) $P < 0.0001$
Physiotherapist	92 (88.4)	53 (61.6)
Occupational therapist	68 (65.3)	16 (18.6) $P < 0.0001$
Orthotist	64 (61.5)	7 (8) $P < 0.0001$
Other rehabilitation services[b]	104 (100)	82 (95.3)
Primary care physician	60 (58)	70 (81)
Elective hospital admissions		
Per individual in the previous 12 months (median, IQR)[c]	2.0 (1.0–3.0)	1.0 (0–1.0)

[a]SMN-augmenting therapy. [b]Includes home-based exercises, massage, hydrotherapy, stretches, respiratory physiotherapy sessions, speech & language therapy sessions, inputs for home safety equipment. [c]Includes planned admission for scoliosis/other orthopaedic surgeries, sleep study, intrathecal nusinersen, imaging under anaesthetic.

Table 3: **Healthcare engagement patterns among children and adults with SMA.**

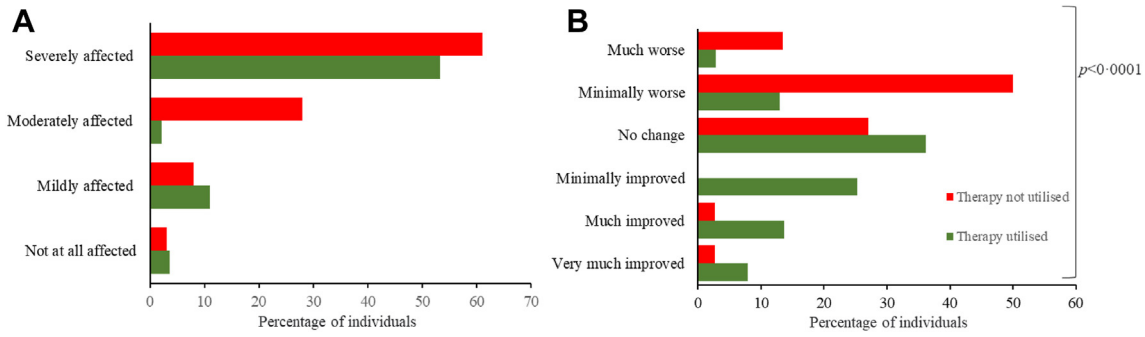

Fig. 5: **Parent/Patient reported outcome measures among individuals with SMA and utilisation of SMN-Augmenting therapies. A. Parent/Patient global impression of severity (PGI-S)[#] and B. Parent/Patient global impression of improvement (PGI-I)[@].** [#]PGI-S: 1-not at all affected; 2-minimally affected; 3-moderately affected; 4-severely affected. [@]PGI-I: 1-very much improved; 2-moderately improved; 3-minimally improved; 4-no change; 5-minimally worse; 6-moderately worse; 7-very much worse.

weakness may promote the evolution of scoliosis.[23] We noted a high frequency of scoliosis in children with SMA type 1; this cohort was younger than the typical age for surgical intervention, which is usually during the second decade of life[24,25]—this emphasises the need for additional healthcare provision and resource allocation to meet the anticipated demand. Whilst current standards of care highlight the need for proactive surveillance of musculoskeletal comorbidities and recommend deferring instrumentation till after the period of growth, our findings provide the rationale for orthopaedic care to be an integral part of management for all individuals with SMA.

From a genotype perspective, our findings provide knowledge to strengthen the prediction of phenotype and prognosis, particularly within the context of implementation of NBS programmes nationally and globally. The modification of phenotype by *SMN2* copy number was evident in individuals with exon7 homozygous deletions in *SMN1*, but not in those with intragenic pathogenic variants. This aligns with observations of previous studies,[26–28] and supports current reliance on *SMN2* gene copies for decision-making in screen positive newborns, noting that most NBS programs detect the former (i.e. *SMN1* exon7 homozygous deletions).[29] Repeat *SMN*2 copy number testing is now recommended in cases with discordant genotype-phenotype associations and will be important as resolving predicting tool in individuals with compound heterozygosity.[30] While NBS programmes in other jurisdictions have reported up to 40% of neonates with ≥4 *SMN2* copies,[31] the small number of individuals with the same in the ANMDR consolidates observations in the Australian NBS program.[4] The registry serves as a vital resource in these times when therapies are not reimbursed for presymptomatic individuals with ≥4 *SMN2* copies, providing valuable insights into epidemiology and clinical trajectory, and informs national and regional healthcare and policy.

Treatment strategies within the study reflect a combination of therapies approved and reimbursed across Australia and individual choices to initiate SMN-augmenting therapies, with an uptake of 81%. This broader access, facilitated by the Australian healthcare system, mirrors similar observations noted in Germany,[6] Canada and Italy.[32] In addition to studies reporting the efficacy of SMN-augmenting therapies in adults with SMA from the perspective of motor function, our findings include the perspectives of people living with SMA to provide important PROMs highlighting the positive effect of the therapies. Our study demonstrates the value of PROMs through integration of participants' perspectives into research.

This research vitally informs healthcare planning for the future. As the prevalent population survives and ages, it will be imperative to plan health services to streamline access to care across the population. Whilst services to promote motor function and autonomy are integral, those that encompass the whole-person impact of neurodisability remain fundamental to address the multisystem ramifications of SMA. These include coordinated access to psychological, peer-group and schooling support, financial and housing planning, and reproductive and genetic counselling at age-appropriate stages. Our findings underscore the need for community-based resources tailored to adults with SMA who perhaps have less access to and engagement with hospital and specialist services. The current healthcare system needs expansion of services to support not only early treated infants with functional gains along a normative developmental trajectory,[33] but also adolescents and adults with substantial care needs which are currently unmet.

The major strength of this study is that it addresses the knowledge gap regarding the clinical and epidemiologic status of SMA in Australia. As the first national registry study, these findings provide a foundation for future work that evaluates the enduring effects of interventions. Although the sample is not representative of the SMA population of the country in its entirety (as is expected with any registry with voluntary enrolment), limiting analysis of incidence and mortality rate, the study cohort encompasses individuals from all states and territories of Australia, is sociodemographically heterogenous, and thus, offers a comprehensive, real-world experience of SMA landscape. In this registry-based study, a diverse range of individuals, of all ages and stages of disease, have been included. They are from various geosocioeconomic backgrounds and have variable access to healthcare. The rigour of registry-data collection with clinician verification of genetic investigations and other measures is also a strength of the evidence-base, aiming to reduce bias inherent to retrospective data collection and recall. However, unmeasured confounding is a potential limitation of this study, which can only be overcome with a system of mandatory registry participation. While an association between the number of *SMN2* copies and disease severity was identified in this study, collaboration across registry networks is important to leverage larger data sets, enhance statistical power and allow appropriate estimates of association that are clinically relevant. Future considerations while reevaluating the establishment of registries and methodologies may include making enrolment a prerequisite for access to therapies, ensuring representative data, as implemented in certain jurisdictions.[34]

Conclusions

Our data elucidates the paradigmatic transition driven by enhanced standards of care and access to novel therapies for SMA across the genotypic and phenotypic spectrum of the condition. The study supports the current reliance on *SMN2* copy numbers for decision-

making in screen-positive newborns and advocates delivery of healthcare services tailored to the diverse needs of the population. Traditionally a disease of infancy and childhood, the severe type 1 SMA in this changed paradigm has extended lifespan, and may now be anticipated into adulthood. From our findings, if equitable access to best practice care (including access to innovative genetic treatments and early diagnosis) is to be actualised as mandated by the national policy, it is imperative for stakeholders to collaborate to explore innovative, sustainable ways of integrating these technologies into healthcare through well-resourced avenues, whilst also providing holistic support and care for the changing needs of the affected population.

Contributors

LB and MAF conceptualized the study. All co-authors supported recruitment for the ANMDR. RF curated the data. EMY is the principal investigator of the ANMDR. LB, MAF and EMY had access to and verified the data underlying the study. LB performed the analysis and drafted the first manuscript. NB performed statistical analyses. All authors contributed to interpretation and approved the final version of the manuscript. MAF and DK provided overall supervision. All authors were responsible for the decision to submit for publication.

Data sharing statement

Data that underlie the results reported in this article may be available to suitably qualified researchers upon approval of request submitted to the ANMDR and supported by the steering committee. Enquires should be addressed to anmdr@mcri.edu.au.

Declaration of interests

RF has received speaker honoraria from Biogen and travel support from Novartis, PTC Therapeutics and Pfizer. AJK is the site principal or sub-investigator for Novartis Clinical Trials, and has received honoraria for advisory board participation from Sanofi and Novartis. LS has received speaker fees for lectures and development of educational material from Biogen, Pfizer, AbbVie and travel support from Abbott. CL has received honoraria from Biogen for speaker engagements and from Biogen and Roche for advisory board participation. KJJ has received honoraria for lectures, presentations, and speaker bureau engagements from Novartis Global gene Therapy Network Steering Committee. COG has received speaker fees from Biogen. IW has received honoraria for work performed including educational activities and attendance at advisory board meetings from Biogen, Novartis, Roche. EMY is the principal investigator of the Australian Neuromuscular Diseases Registry (ANMDR) at the Murdoch Children's Research Institute. EMY is a site principal or sub-investigator for Biogen and Novartis clinical trials in spinal muscular atrophy, and the institution has received funds for contract research related to the conduct of these trials. EMY has received honoraria for advisory board participation from Biogen and Roche, including honoraria paid to their institution from Biogen for advisory board participation. MAF is the recipient of NHMRC investigator grant (APP1194940). MAF is a site principal investigator for Biogen, Roche and Novartis Gene Therapies, Inc., clinical trials, and their institution has received funds for contract research related to the conduct of these trials. MAF has received honoraria for educational events from Biogen, Novartis Gene Therapies, and Roche. MAF has received honoraria for contributions to scientific advisory boards for Biogen, Roche and Novartis Gene Therapies, Inc., MAF is a medical director of Muscular Dystrophy New South Wales (not for profit, unpaid). DK has received the NHMRC Investigator grant 2024 (2026317), and has received honoraria from Biogen, Roche and Novartis for presentations, for participation on Advisory Board from Biogen, and travel support from Biogen.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2024.101237.

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