Spinal muscular atrophy

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Abstract | Spinal muscular atrophy (SMA) is a neurodegenerative disorder caused by mutations in *SMN1* (encoding survival motor neuron protein (SMN)). Reduced expression of SMN leads to loss of α-motor neurons, severe muscle weakness and often early death. Standard-of-care recommendations for multidisciplinary supportive care of SMA were established in the past few decades. However, improved understanding of the pathogenetic mechanisms of SMA has led to the development of different therapeutic approaches. Three treatments that increase SMN expression by distinct molecular mechanisms, administration routes and tissue biodistributions have received regulatory approval with others in clinical development. The advent of the new therapies is redefining standards of care as in many countries most patients are treated with one of the new therapies, leading to the identification of emerging new phenotypes of SMA and a renewed characterization of demographics owing to improved patient survival.

Classic spinal muscular atrophy (SMA) is an autosomal recessive disease caused by mutations in *SMN1* on chromosome 5 leading to reduced expression of survival motor neuron protein (SMN). This causes dysfunction and degeneration of α-motor neurons in the spinal cord and brainstem, in addition to progressive muscle atrophy and weakness of limb, trunk, bulbar (which control swallowing) and respiratory muscles. Other genetic forms of SMA are not discussed in this Primer owing to their distinct pathobiology.

Historically, SMA has been subdivided into three main types with paediatric onset (types 1 to 3) and two less common types (TABLE 1), one with antenatal onset (type 0) and one with adult onset and milder phenotype (type 4). This classification is based on the age of onset and maximum motor function achieved in untreated patients, and does not capture the change in disease phenotype due to treatment with the new therapies nusinersen, onasemnogene abeparvovec and risdiplam. This is best exemplified in SMA type 1 (OMIM 253300), which is the most frequent subtype of SMA; in the absence of treatment this subtype is characterized by onset before 6 months of life, inability to achieve independent sitting, rapidly progressive motor, respiratory and bulbar deterioration and >90% mortality by 2 years of age. By contrast, most treated infants with SMA type 1 survive for >2 years and, especially if treated soon after diagnosis, have functional improvements and milestone achievements that have not been observed in untreated infants. The three new therapies have also changed the clinical approach to patients with SMA with the need to adapt standards of care to the new emerging phenotypes and to identify and treat patients as early as possible to prevent severe disease manifestations and to achieve maximal therapeutic benefit.

This Primer provides a comprehensive introduction to SMA including disease epidemiology, inheritance pattern and pathophysiology, highlighting aspects of pathophysiology that are critical for therapeutics development. This Primer also discusses standard-of-care recommendations for diagnosis and multidisciplinary management of SMA, and changes to diagnosis and management owing to the effect of the commercially available therapies on clinical phenotypes and quality of life (QOL). Moreover, this Primer provides an overview of the existing therapeutic approaches including those that have been approved and others in clinical development.

Epidemiology

The worldwide incidence of SMA is ~1 in 10,000 live births[1–3] or ~7.8–10 in 100,000 live births[4]. In the USA, the estimated pan-ethnic incidence was 1 in 11,000 live births when determined using genetic laboratory data[3]. The incidence in Europe is ~1 in 3,900–16,000 live births[5,6] (median 11.9 in 100,000 live births) when estimated with data collected from both genetic laboratories and from an international registry as part of the activities of the global network TREAT-NMD. Inter-country variability in reported incidence rates relates to many factors, including the size of the region, sources of data (clinics versus studies of carrier rates) and involvement of cross-border testing (testing of specimens received from other countries). Data from 2020–2021 have provided more evidence on the incidence of SMA. In these studies, the incidence of SMA was 1 in 18,957 live births

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in Massachusetts (USA), 1 in 28,137 live births in New York (USA), 1 in 11,554 live births in New South Wales (Australia)[7–9] and 1 in 6,910 births in Germany[10]. The incidence in New York state is 2.6–4.7 times lower than the expected incidence of about 1 in 6,000 to 1 in 11,000 live births. In a Global SMA Patient Registry representing 29 countries, the sex distribution was about equal, suggesting similar incidence of SMA in boys and girls[5].

Of note, the incidence of SMA is lower than expected when calculations are based on carrier frequency. The reasoning is that such calculations may overestimate incidence by including fetuses with a 0/0 *SMN1*/*SMN2* genotype (that is, no SMN is produced), which is embryonically lethal in other species[11], as well as the inclusion of unaffected individuals with no functional *SMN1*, but a high number of *SMN2* copies (usually four or more). Individuals with five or more *SMN2* copies may never develop SMA. Conversely, underestimation of carrier frequency can occur as some mutations, namely, de novo mutations, point mutations and multiple *SMN1* copies on the same chromosome, are not routinely assessed by current testing methodology.

When all patients with 5q-SMA were considered in 2004, ~58% had SMA type 1, 29% had SMA type 2, and 13% had SMA type 3 (REF.[12]). In 2017, ~60% had SMA type 1, ~20% had SMA type 2 and ~20% had SMA type 3 (REFS.[5,6]). The prevalence of SMA type 1 is lower than the other subtypes owing to shorter life expectancy; however, prevalence is rapidly increasing with improved survival owing to the increased availability of disease-modifying drugs. The prevalence of SMA is often reported as 1–2 per 100,000 persons, with significant inter-country variability ranging from 0.01 to 2.43 per 100,000 persons globally and 0.00 to 4.11 per 100,000 persons in Europe.

The average global carrier frequency of SMA is 1 in 50 (range 1 in 40 to 1 in 60)[2]. A pan-ethnic study in 2012 found that carrier frequency in North America was highest in white individuals (1 in 47) and lowest in Hispanic individuals (1 in 68) and Black individuals (1 in 72)[3]. The latter may be an underestimation[3] because Black individuals have a high frequency of a two-copy duplication allele, which may lead to a high number of individuals with two copies of *SMN1* on one allele and no copies on the other allele, a combination that is not detected by testing methodologies used in clinical laboratories. A study reviewing the first experiences of neonatal screening for SMA in nine countries found that the incidence ranges from 1 in 5,000 to 1 in 28,000 in Ontario[13].

Access to preconception carrier screening, prenatal diagnosis and application of advanced reproductive technologies is likely to lower the incidence of SMA in many parts of the world. However, increased implementation of standards of care and treatment of patients with SMA with new disease-modifying drugs is likely to increase disease prevalence globally.

Table 1 | **Historical classification of SMA**

SMA type	Typical age at presentation (range)	Maximal motor function achieved with supportive care	Feeding and communication	Pulmonary function	Survival[a] with supportive care
0	Fetal	Nil	Nil	Very poor	Days–weeks
1	3 months (0–6 months)	No sitting or rolling	Poor, requires support	Poor, requires support	Months (median ~10 months)
2	12 months (7–18 months)	Sits, no walking	Variably affected	Reduced, often needs support	Years (median >20 years)
3	3 years (1.5–10 years)	Walks (limited)	Normal	No symptoms, mild reduction possible	Normal
4	>18 years	Walks (normal)	Normal	Normal	Normal

SMA, spinal muscular atrophy. [a]Survival includes 'event-free survival' (ventilation support for <16 h/day for ≥14 days).

Mechanisms/pathophysiology

Genetics

In 1990, all three types of SMA were mapped to chromosome 5q11.1–13.3. This complex region contains a large 500-kb duplication and the telomeric *SMN1* gene (encoding SMN)[14] and its paralogue, centromeric *SMN2* (FIG. 1). Each *SMN* gene comprises nine exons (including exons 1, 2a, 2b, 3, 4, 5, 6, 7 and 8 (encoding the 3′ untranslated region (UTR))). *SMN1* pre-mRNAs are generally spliced to retain all exons. A single functional, coding variant c.840C>T in exon 7 of *SMN2* inactivates an exonic splicing enhancer and simultaneously creates an exonic splicing silencer. This change is translationally silent but affects splicing so that exon 7 is excluded from most *SMN2* transcripts, resulting in truncated, rapidly degraded SMN protein[15–17]. Because exon 7 is sometimes retained, each copy of *SMN2* produces ~10% full-length, functional SMN[15]. The clinical manifestations of SMA, including impaired α-motor neuron development and degeneration, are driven by reduced expression levels of the SMN protein[18].

About 95% of patients with 5q-SMA harbour homozygous deletions of both exons 7 and 8 or only exon 7 of *SMN1* regardless of the phenotype of disease[19]. Other patients carry a *SMN1* point mutation and a deletion in the other *SMN1* allele, or, very rarely, biallelic small-scale mutations in any of the *SMN1* exons[19]. De novo mutations occur at a relatively high rate (~2%) owing to the instability of this 5q region[19]. In patients with less severe manifestations (SMA types 2 and 3), gene conversion (that is, the change of the *SMN1* exon 7 to that of *SMN2*)

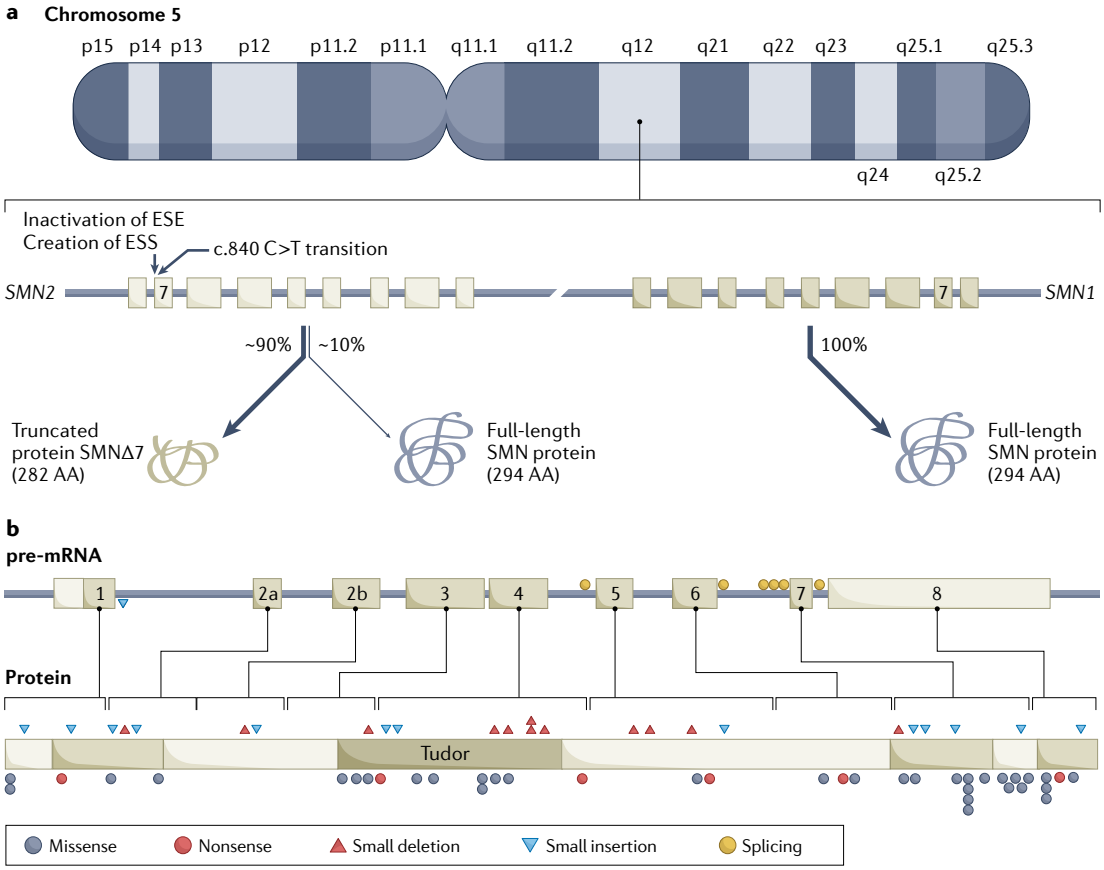

Fig. 1 | **Schematic diagram of human *SMN1* and *SMN2* on chromosome 5. a** | Patients with spinal muscular atrophy have deletions or point mutations in both copies of *SMN1* (encoding survival motor neuron protein (SMN)). A C-to-T transition in exon 7 of *SMN2* inactivates an exonic splicing enhancer (ESE) and simultaneously creates an exonic splicing silencer (ESS) that leads to skipping of exon 7 during transcription and, therefore, production of truncated, non-functional SMN. However, a small amount (~10%) of full-length mRNA is produced from *SMN2*, resulting in functional, full-length SMN protein[201]. **b** | Protein domains of SMN, with proteins it binds to and location of mutations in humans[202] are indicated. AA, amino acids. Part **a** adapted with permission from REF.[201], Elsevier. Part **b** reprinted with permission from REF.[202], Elsevier.

often occurs rather than genuine deletions of *SMN1* (which occurs in SMA type 1)[19,20]. The reverse phenomenon (that is, *SMN2* gene conversion into *SMN1*) can also occur[19,20].

SMN2 expression and splicing

Both *SMN1* and *SMN2* are constitutively transcriptionally active and are regulated by multi-kilobase promoters[21–23], transcription factors, epigenetic determinants[24–27] and long non-coding RNAs[28–30] (FIG. 2). Transcriptional activity of both genes may be modulated by developmental state[23,27], cell stress[24] and autoregulatory mechanisms[27]. Of note, early therapeutic development efforts for SMA focused on small molecule transcriptional activation of *SMN2* (REFS.[31,32]), but drug candidates were insufficiently potent, specific and/or safe for chronic administration. As transcriptional activity of *SMN2* determines the pre-mRNA template available for splice-modulating therapeutics and as splicing often occurs co-transcriptionally[33], combinatorial transcriptional and splice-modifying therapy remains an attractive goal[27,29,34].

As discussed above, the alternative splicing of *SMN2* exon 7 is a crucial event in SMA pathogenesis[16,17]. Multiple *cis*-acting (intronic and exonic splice enhancer and silencing motifs) and *trans*-acting (RNA-binding proteins) factors regulate exon 7 splicing[35–37], and human disease severity is lessened by single-nucleotide polymorphisms that tip the balance of these factors[38,39] (FIG. 2). For example, the single base substitution c.859G>C in the exon 7 encoding sequence of *SMN2* creates a new exonic splicing enhancer element that results in increased full-length transcripts and reduced disease severity[38]. Alterations in the abundance of specific RNA-binding proteins could also modify disease severity[40]. The frequency of exon 7 inclusion may vary with cell type, with normal motor neurons producing low levels of full-length *SMN* mRNA from *SMN2* compared with other cells in the spinal cord[41]. This inefficient retention of *SMN2* exon 7 in motor neurons could result in particularly low SMN levels in this cell type and vulnerability to disease[41].

Individuals without SMA, having at least one functional copy of *SMN1*, may have a varying number of *SMN2* copies, with 10–15% of unaffected individuals having no *SMN2* copies[11,42,43]. However, *SMN2* copy number and phenotypic severity have a clear inverse correlation in patients with SMA. In a large cohort

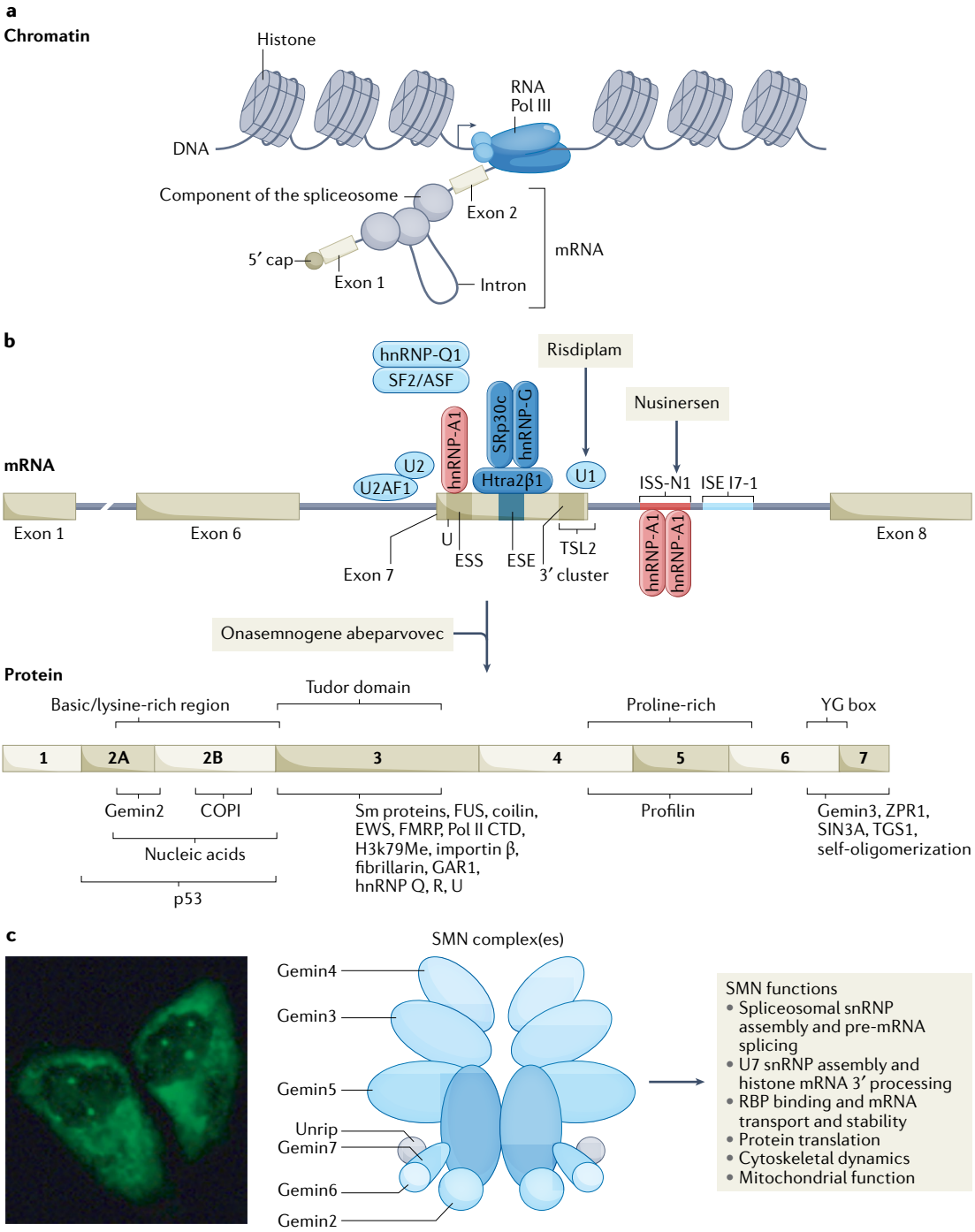

Fig. 2 | **SMN complex composition and function. a** | *SMN* within chromatin undergoing transcription and RNA polymerase making *SMN* pre-mRNA. Transcription of *SMN1* and *SMN2* is regulated by sequence motifs within the promoters and epigenetic determinants. **b** | Splicing of *SMN2* pre-mRNA (upper schematic), highlighting some of the intronic and exonic *cis* elements and *trans*-acting factors that modulate survival motor neuron protein (SMN) exon 7 inclusion[203]. Exon inclusion requires recruitment of the U1 small nuclear ribonucleoprotein (snRNP) to the 5′ splice site of intron 7 and the U2 snRNP to the 3′ splice site of intron 6, along with its auxiliary factor U2AF. This process is modulated by several essential serine/arginine (SR)-rich proteins and heterogeneous nuclear ribonucleoproteins (hnRNPs) that recognize exonic and intronic splicing enhancer and silencers (ESE, ESS, ISE and ISS). In *SMN1*, SF2/ASF recruitment is facilitated by an ESE near the 5′ end of exon 7, but for *SMN2* the C-to-T variant results in a uridine within this motif that ablates the ESE and creates an ESS, which recruits hnRNP-A1, promoting exon 7 exclusion. Exon 7 inclusion in *SMN2* pre-mRNAs can be re-established by steric blocking of ISS-N1 with nusinersen to prevent hnRNP-A1 recruitment or by promoting recruitment of the U1 snRNP using risdiplam. Full-length SMN protein (lower schematic) has distinct functional domains (indicated above the schematic) and interacts with several proteins (indicated below the schematic). **c** | SMN complex composition and function[49,204]. The SMN complex (centre) is localized to the nucleus and cytoplasm (left) and has been proposed to have several functions (right). CTD, C-terminal domain; Pol, polymerase; RBP, RNA-binding protein; TSL, terminal stem loop. Part **b** adapted from REF.[203], CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/). Part **b** adapted with permission from REF.[49], Elsevier. Part **c** adapted with permission from REF.[204], Elsevier.

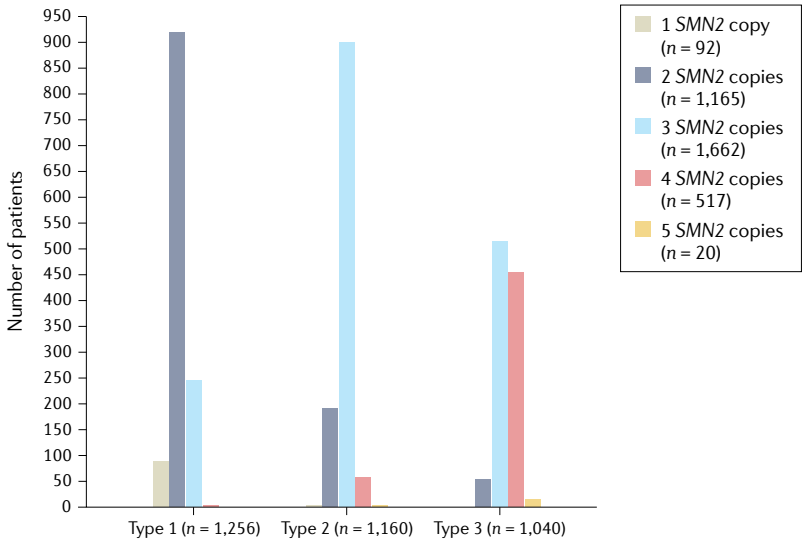

Fig. 3 | ***SMN2* copies and SMA types.** Differences in the distribution of *SMN2* genotypes across patients with spinal muscular atrophy (SMA) type 1, type 2 and type 3. Most patients with SMA type 1 have two *SMN2* copies, followed by three *SMN2* copies and one *SMN2* copy. Most patients with SMA type 2 have three *SMN2* copies, followed by two, four and one *SMN2* copy, whereas among patients with SMA type 3, the numbers with three or four *SMN2* copies are similar and patients with two or five *SMN2* copies are rare[43].

study[43], 80% of patients with SMA type 1 had one or two copies of *SMN2*, 78% of patients with SMA type 2 has three copies of *SMN2*, and 93% of patients with SMA type 3 had three or four copies of *SMN2* (FIG. 3); similar frequencies have been found in other studies[4,42,44]. Nonetheless, clinical severity of SMA is not predicted only by *SMN2* copy number, particularly in those with SMA types 2 and 3. Indeed, individual patients with SMA type 1, 2 or 3 with two or three copies of *SMN2* have been reported, and five copies of *SMN2* have been detected in unaffected family members with homozygous *SMN1* deletions and in patients with SMA type 3, suggesting that *SMN2* copy number is not the sole modifier of disease severity[4,38,45–47]. Other identified modifier genes include *PLS3* and *NCALD*[46–48] (see section SMN structure and function, below).

SMN structure and function

After mRNA processing, full-length *SMN* mRNA is translated into a 38-kDa SMN protein, which is ubiquitously expressed. SMN has distinct functional and binding domains[49]; the importance of these domains is highlighted by missense or small deletion mutations found in rare patients with compound heterozygosity (FIG. 1b). SMN most often exists in an oligomerized form, binding to itself via the YG box, and to multiple other proteins including gemin 2–gemin 8. SMN lacking exon 7 is particularly unstable owing to the significantly reduced ability to oligomerize, in addition to the creation of a degron motif that results in rapid degradation[50–52]. SMN can form a series of distinct protein complexes with differing functions (FIG. 2c). Furthermore, post-translational modifications of SMN can modulate localization, stability and function[53–59].

In multiple cell types, SMN is localized diffusely in the cell cytoplasm and in punctate structures in the nucleus called gems, the number of which correlates with disease severity in patient-derived fibroblasts[60]. In neurons, SMN is found in granules in axons where it traffics rapidly bidirectionally[61,62].

The first identified and most well-defined role of SMN is in maintaining the fidelity of spliceosomal small nuclear ribonucleoprotein (snRNP) assembly (FIG. 2c) of the major (U2-dependent) and minor (U12-dependent) spliceosomes[63–65]. SMN deficiency leads to a preferential defect of the U12 spliceosmal complex, which causes splicing defects of a restricted number of genes in which this intronic splicing is necessary[66]. One of the affected genes is *TMEM41B* (encoding stasimon)[67]. Stasimon is localized to the endoplasmic reticulum (ER), but its function is poorly understood. The splicing pattern of stasimon is altered in a mouse model of severe SMA, which shows weakness and early death. Viral delivery of full-length stasimon prevents loss of motor neuron proprioceptive excitatory synaptic inputs, but not motor neuron loss. It has also been proposed that SMN enables the formation of other mRNA-binding protein complexes including messenger ribonucleoprotein (mRNP) transport granules that enable mRNA axonal transport and local translation at the distal end of developing neurons in animal and cellular models[62,67–71]. Whether such mRNP granules are reduced in patients with SMA is unknown. SMN is also directly implicated in other cellular pathways including gene transcription[72] and protein translation[73].

The identification of human disease modifier genes that act independently of SMN expression such as *PLS3* (encoding plastin 3, an actin-binding protein) and *NCALD* (encoding neurocalcin-δ, a calcium-binding protein) highlight the importance of actin cytoskeletal dynamics, synaptic vesicle release and endocytosis as consequences of SMN deficiency[46–48]. Higher levels of plastin 3 seem to lessen disease severity in female patients with SMA, whereas reduced NCALD expression may be protective. Overexpression of plastin 3 (REF.[48]) and suppression of NCALD[74] have been shown to have protective effects in SMA mice, perhaps by improving endocytic pathways at the neuromuscular junction (NMJ). Nonetheless, targeting these proteins therapeutically may be challenging, as substantial changes in their expression is associated with other disease phenotypes[75,76].

Another emerging cellular pathway that is disrupted downstream of SMN deficiency is mitochondrial respiratory chain function in motor neurons[77–79] and muscle[80,81], possibly secondary to generation of mitochondrial reactive oxygen species as shown in SMN-deficient cells[77]. Indeed, a muscle spectroscopy study suggested that adults with SMA type 3 or 4 have decreased mitochondrial ATP synthetic function, revealed by altered intramuscular inorganic phosphate accumulation and blunted blood lactate rise during exercise that correlates with muscle weakness[81]. Whether SMN deficiency causes motor neuron disease via loss of a single function or a multitude of functional effects that varies across cell types and/or stages of development remains to be determined.

SMN levels in blood vary significantly between individuals[82], but intra-individual levels are relatively

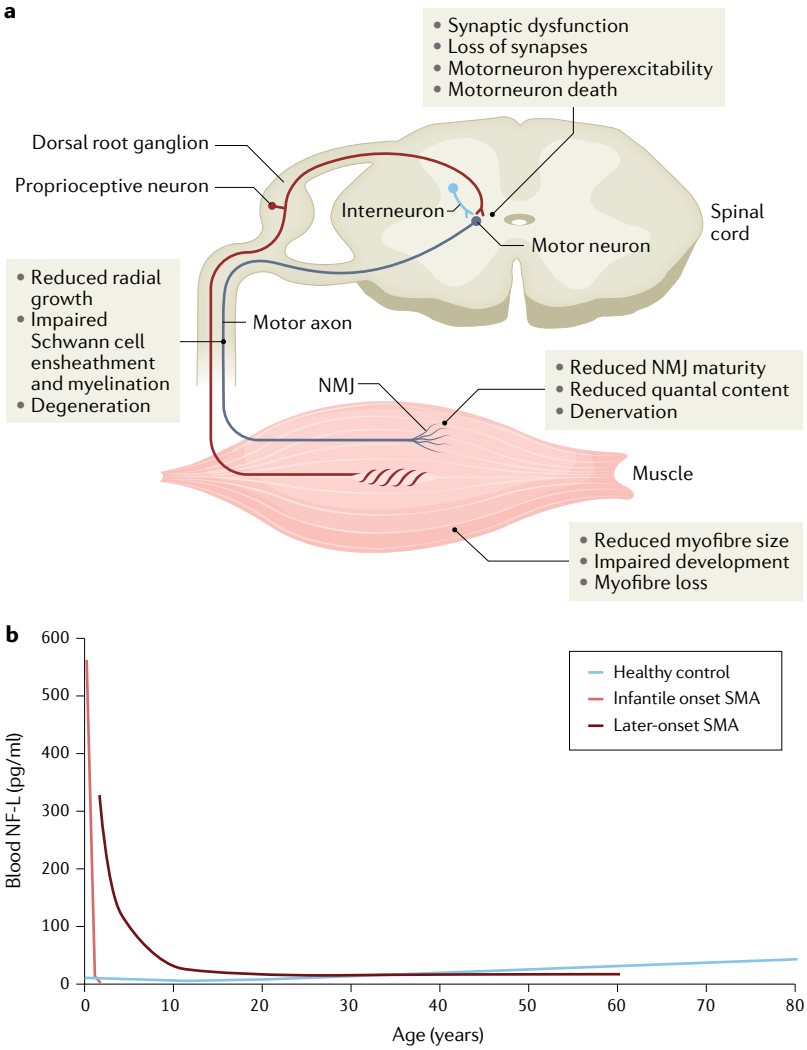

Fig. 4 | **Spinal cord, motor neurons, motor axons, neuromuscular junctions and muscle. a** | α-motor neurons connect to skeletal muscles via neuromuscular junctions (NMJs) and receive synaptic inputs including from proprioceptive neurons residing in dorsal root ganglia. Survival motor neuron (SMN) deficiency in spinal muscular atrophy (SMA) leads to multiple defects in this loop and ultimately motor neuron degeneration. Developmentally immature motor axons have been demonstrated as an early feature of SMN deficiency, already present prenatally[94]. **b** | Serum neurofilament levels (blood NF-L) in healthy controls[205,206] and in patients with SMA[207]. Infants with SMA type 1 have increased neurofilament levels in the first week of life, even if they are clinically asymptomatic, particularly those with only two copies of *SMN2*. Treatment with nusinersen decreases neurofilament levels, and a correlation between rate of neurofilament decline at 60 days and clinical outcome at 10 months has been suggested. Elevated serum neurofilament levels are also a feature of children with SMA type 2, although their peak may be later and their levels are lower than in patients with SMA type 1. Adults with SMA have not been reported to have significantly elevated neurofilament levels compared with healthy controls.

stable over short periods, allowing blood SMN levels to be used as a biomarker of drug engagement for the orally delivered risdiplam[83]. SMN levels are not reliably measured in the cerebrospinal fluid; therefore, central nervous system (CNS) protein levels cannot be monitored in living patients. Measurement of SMN levels in post-mortem CNS and muscle samples suggest decreasing SMN levels during development, with a 6.5-fold decline between fetal and postnatal stages in healthy individuals[84,85]. SMN complex activity in snRNP assembly is also particularly high in the brain and spinal cord during late embryonic and early postnatal development in mice[86]. Collectively these data imply a need for SMN protein during development when global transcriptional activity may be high. In support of this, a study in motor neuron-like NSC-34 cells demonstrated that SMN complex activity is molecularly linked with global transcriptional activity via interaction of SMN with the 7SK snRNP complex, such that snRNP abundance can be tuned to dynamic splicing needs[87].

Overexpression of SMN has generally been considered safe in humans and animal models[88]. However, this view has been questioned by studies in which long-term SMN large overexpression resulting from an intracerebroventricularly delivered viral vector in a mouse model of severe SMA seemed to disrupt the normal stoichiometry of the SMN complex, resulting in cytoplasmic aggregation of SMN protein in dorsal root ganglion cells and motor neurons, disrupted gene expression and ultimately neuronal loss[89]. Limited data from two human autopsies after onasemnogene abeparvovec treatment suggest an increase in full-length *SMN* mRNA expression in laser-captured motor neurons, but no SMN protein aggregation observed by immunohistochemistry[90]. Autopsy studies in nusinersen-treated subjects showed increased full-length *SMN* mRNA and SMN protein staining intensity in spinal cord tissues, but not in brain tissues, correlating with a caudal to rostral gradient of tissue drug concentration after lumbar intrathecal delivery[85].

Impaired motor unit development and degeneration

Disruption of the SMA motor unit (motor neurons and the muscle fibres they innervate) underlies the most evident clinical manifestation of SMA (skeletal muscle weakness). Examination of human autopsy tissues and mouse models indicates that initial disease stages are characterized by impairments of development that affect the motor neuron cell body, axon and target myofibres. Specific defects include slowed acquisition of motor neuron excitatory synaptic inputs and mature motor neuron firing patterns[91–93]; motor axon radial growth, Schwann cell ensheathment and myelination[94]; NMJ synapse structural elaboration and increased quantal content[95–97]; and myofibre growth[98] (FIG. 4a). Longitudinal studies in SMA mouse models suggest developmental delay that begins during the late gestational and neonatal periods[94]. An ultrastructural study of SMA type 1 human motor axons examined in autopsy tissues suggested impairments of motor axon radial growth that may occur during mid-gestation[94]. These pathologies show topographical specificity with medial motor column and medial lateral motor column motor neurons more affected than lateral motor column motor neurons in SMA mouse models[99]. Moreover, severity within a given spinal segment is variable[91]. This variability has been suggested to be due to variation in individual cell SMN levels, based on data from induced pluripotent stem cell-derived motor neurons[100].

In both mouse models of SMA and patients with SMA, degenerative pathologies include withdrawal of the terminal motor axon from the NMJ postsynaptic terminal[101], degeneration of proximal motor axons, loss

of cell body synaptic inputs and motor neuron cell body death. Moreover, myofibres are lost after prolonged denervation and are replaced by fibro-adipose tissue. Those SMA motor units that are mostly developmentally immature are particularly vulnerable to early and precipitous degeneration that involves all compartments of the motor neuron. This early loss of motor neurons corresponds to high levels of cerebrospinal fluid and blood neurofilaments, neuronal specific cytoskeletal proteins released from neurons during degeneration[102] (FIG. 4b). Neurodegeneration during later disease stages is probably slower and may principally involve the distal motor components. Proposed molecular mediators of neurodegeneration in SMA include activation of the p53 pathway downstream of altered splicing of *Mdm2* and *Mdm4* (REFS.[103,104]). Importantly, inhibition of p53 can prevent motor cell body death, but has minimal impact on terminal axonal degeneration in SMA mouse models[104]. Other molecular mediators suggested to have roles in SMA motor neuron degeneration include JNK[105,106], ER stress[107,108] and DNA damage[109].

Slowed development beginning in utero and rapid postnatal degeneration in SMA underlie the need for very early therapeutic delivery for optimal therapeutic outcomes. Indeed, preclinical mouse studies and human clinical trials have repeatedly demonstrated markedly enhanced efficacy with early postnatal, presymptomatic drug initiation[110]. Although SMN deficiency in motor neurons is a primary driver of disease, it remains unresolved whether SMN deficiency outside the CNS contributes meaningfully to disease manifestations, particularly in patients. SMA mouse models have pathologies in the heart, liver, pancreas, gut and vasculature, with resulting tissue hypoxia[111–113], and peripheral restoration of SMN contributes to improved survival[114]. As nusinersen is delivered to the CNS only and omnasemnogene abeparvovec is diluted from replicating cells, it is possible that treated patients with SMA will develop pathologies in other tissues due to long-term SMN deficiency[115]. Given the distinct mechanisms of action and biodistributions of these therapies, treatment with more than one of these therapeutics may enhance efficacy[116]. In addition, a priority for the future is to identify novel therapeutic targets downstream of SMN deficiency. Clinical trials are ongoing to evaluate whether an antibody to promyostatin (SRK-105), which was designed to inhibit myostatin and enhance myofibre growth, will provide benefit alone or in combination with SMN induction therapy (ClinicalTrials.gov identifier NCT03921528) as some preclinical data suggest[117,118].

Box 1 | **New phenotypes of SMA**

The increased survival and improved function of patients with spinal muscular atrophy (SMA) owing to nusinersen, onasemnogene abeparvovec and risdiplam treatment is associated with new phenotypes of this disease, such as in patients with SMA type 1 who can sit or patients with SMA type 2 who can walk. Moreover, progression of the SMA is different in treated patients compared with untreated patients[212]. There is increasing evidence that the newly observed clinical features do not always fully overlap with the functional abilities known to occur in untreated patients[212]. Treated patients with SMA type 1 who achieve sitting often develop an early kyphosis and a posture that is not observed in infants with SMA type 2 (REF.[212]). Similar differences have been found in many other motor, respiratory and nutritional manifestations that will require careful monitoring[212]. Improvement in endurance has also been observed in treated patients[213].

Moreover, with the increasing focus on identifying and starting treatment in presymptomatic newborn infants with SMA, an entirely different phenotype of this disease is emerging. Many of these infants have normal development[129] and will require different means of monitoring their long-term response to treatments. Work is in progress to revise the existing care recommendations of SMA to take into account new phenotypes and the new features of disease.

Diagnosis, screening and prevention

Clinical manifestations

Individuals with SMA are diagnosed when they are either symptomatic or presymptomatic. Presymptomatic patients are identified when a positive family history of SMA prompts genetic testing or from population-based newborn screening (see section Screening, below).

Although SMA is a continuum of phenotypic expression, the presenting symptoms differ significantly between subtypes (TABLE 1). Common features of SMA across the spectrum include a pure motor neuronopathy and axonopathy with areflexia and fasciculations, preserved sensation and a typical pattern of muscle weakness that is more severe for proximal muscles and muscles of the lower extremities. Infants with SMA type 1 have severe manifestations, with profound hypotonia and progressive respiratory and swallowing difficulties. In a restricted number of patients (type 0) there is antenatal onset of symptoms with reduced or absent fetal movements and severe signs at birth including contractures. Patients with SMA type 2 have a similar pattern of muscle weakness as observed in those with type 1, even if less severe, and invariably develop scoliosis and some respiratory impairment. Presenting signs may be milder in those with SMA type 3 and are mainly related to a tendency to fall, lower limb weakness and fatigue, although ~50% of patients will lose the ability to walk independently, often at the time of puberty. Cognition is normal in patients with SMA type 3 or 4, with emerging data indicating cognitive impairment in some patients with SMA type 1 or 2, which may be more appreciable owing to longer-term survival of treated patients[119,120] (BOX 1). Upper motor neuron signs or CNS symptoms (such as seizures or impaired vision or hearing) are not seen in patients with SMA. The age of onset of symptoms varies with the type of SMA (TABLE 1).

Diagnosis

Historically, electromyography (EMG) and muscle biopsy were performed to establish the diagnosis of SMA. However, these tests are no longer routinely performed and a patient with suspected SMA undergoes genetic testing as the initial diagnostic step.

Genetic diagnosis. Genetic diagnosis is quite straightforward as ~95% of patients with SMA harbour homozygous deletions of exons 7 and 8 or only of exon 7 in *SMN1*. Biallelic mutations in *SMN1* provide genetic confirmation of 5q-SMA; however, new recommendations highlight the need to also determine *SMN2* copy number as it provides information on disease severity in symptomatic patients and identifies which presymptomatic patients should undergo treatment.

SMN1 deletions and *SMN2* copy number can be determined by several techniques, including quantitative real-time PCR, multiplex ligation-dependent probe amplification (MLPA), digital PCR and next-generation sequencing methods. MLPA is considered the gold standard for *SMN2* copy number determination, although data have shown limitations in the precision of this technique, particularly for copy numbers more than two[121]. In addition, two different MLPA methods may lead to diverging results even within the same laboratory[122], highlighting the need to implement tests of reliability and quality control procedures when assessing *SMN2* copy number. Real-time PCR and digital droplet PCR have also been developed for more precise *SMN2* copy number quantification, and next-generation sequencing techniques have also demonstrated good results[123].

Other testing. Serum creatine kinase levels, which are often determined in patients with muscle weakness, may be mildly elevated in those with SMA, although generally not >1,000 IU/l, and may falsely lead to suspicion of a myopathy, in which case EMG can aid in distinguishing a neurogenic from a myopathic aetiology. Serum creatinine levels are typically low in patients with SMA type 1 or 2, reflecting reduced muscle mass. Chest radiography in patients with SMA type 1 often reveals a bell-shaped thorax and a 'parasol' rib deformity, reflecting intercostal muscle weakness and relatively preserved diaphragm function.

Following genetic confirmation of SMA, parents or carers and adult patients should receive counselling to address recurrence risk and explain the genetic basis of the condition. This can be carried out by the neurologist, genetics counsellor or geneticist. The physician should then identify the patient's subtype of SMA, based upon presenting symptoms and signs and age at symptom onset, and establish a prognosis and consider treatment options (see section Management, below). Informative biomarkers, such as the ulnar nerve compound motor action potential amplitude and blood neurofilament levels, may provide additional prognostic information and serve as predictive biomarkers for response to a medication[102], although their use is limited to research protocol studies.

Screening

Individuals with SMA can be identified by three methods: preconception carrier screening, prenatal testing of the fetus and testing following birth. Preconception carrier screening testing can be performed for severe genetic conditions. Carrier screening is relevant in those with or without a positive family history of SMA, given the relatively high carrier frequency of deletions in *SMN1* (0.98–2.02%, depending on ethnicity)[3]. The American College of Medical Genetics recommends offering carrier testing to all couples regardless of race or ethnicity, even without a family history of SMA[124]. Identification of positive carrier status should lead to testing of the gamete of the donor or the individual's partner and genetic counselling. Of note, nationwide carrier screening in Israel has not changed the rate of postnatal diagnosis of SMA[125].

Prenatal testing of the fetus can be performed using chorionic villus sampling or amniocentesis, and possibly with extraction of fetal cells from the maternal circulation[126]. Prenatal testing is performed less frequently than in previous years owing to the advent of therapeutic options for SMA, as fewer parents are opting for termination of pregnancy, but prenatal testing may become more relevant if fetal therapy for SMA becomes feasible[127].

Newborns can also be tested for SMA following birth through targeted diagnostic testing in those with a positive family history of SMA using commonly available testing laboratories, or through unbiased population screening. Population screening is performed in many countries, and encompasses testing for a panel of diseases, including SMA, typically in a health department laboratory using blood from a heel-stick blood spot sample prior to a baby's discharge from the delivery centre. It is usually an 'opt-out' programme. DNA is extracted from the blood sample and is analysed for homozygous deletion of exons 7 or 8 in *SMN1*. Newborn screening identifies ~95% of babies born with SMA, although it is not able to identify those with a deletion on one allele and a mutation on the other allele which requires gene sequencing to identify.

Up to mid-2022, ~97% of babies born in the USA had been screened for SMA, with anticipation that almost all babies will undergo screening in future[128]. Similar screening programmes are underway in several other countries in Europe and the Asia–Pacific regions. Of note, implementation of newborn screening for SMA has generated several important findings, namely, a better estimation of the true incidence of SMA (see section Epidemiology, above), the opportunity to initiate treatment before symptom onset (including three presymptomatic clinical treatment trials), improved understanding of how prognostic and predictive biomarkers respond to treatment (such as blood SMN protein and neurofilament levels), and improved understanding of the economic effects of earlier treatment.

Prevention

The need for neonatal screening for SMA is strongly supported by the increasing evidence of the efficacy of the available treatment options in presymptomatic patients. The NURTURE study is a phase II, open-label, single-arm study of nusinersen treatment in 25 presymptomatic infants[129] with *SMN1* mutations and two or three copies of *SMN2* (therefore who are likely to develop SMA type 1 or 2) identified on the basis of newborn screening or testing prompted by a positive family history for SMA. All patients were treated within the first 6 weeks of life and did not have obvious clinical signs of SMA. Interim analysis of this trial from March 2022 found that all 25 children were alive (median follow-up of 4.9 years) with continuing gains in motor skills. All 25 children could sit unsupported. Independent sitting was achieved by all participants at an age when typically developing children acquire this milestone (by the age of 9 months). Independent walking was attained by 92 patients (in all 10 patients with three copies of *SMN2* by 18 months of age, and in 13 of 15 of patients with

two copies of *SMN2*, in 6 of 13 by 18 months of age, the upper limit of normal). No patient required tube feeding, tracheostomy or ventilation for longer than 16 h/day. Moreover, 84% did not require any respiratory intervention (three patients required part-time non-invasive ventilation support). Similar results have also been reported in recent congresses on the use of onasemnogene abeparvovec (NCT03505099) and risdiplam (NCT03779334). In the SPR1NT gene therapy study (NCT03505099), 29 presymptomatic infants (14 with two *SMN2* copies and 15 with three *SMN2* copies) were treated with onasemnogene abeparvovec. All 14 patients with two *SMN2* copies survived to the 14-month assessment point and all sat independently and 9 walked independently at 18 months[130]. All 15 patients with three *SMN2* copies were alive and 14 of 15 sat independently and walked by 24 months of age[131]. Collectively, these results provide further strong evidence that early initiation of treatment provides larger clinical benefits than in symptomatic patients with a high possibility to achieve age-appropriate motor milestones.

Management

Until recently, SMA was managed by early recognition and treatment of clinical signs related to progressive weakness of limb, trunk, respiratory and bulbar muscles. This management plan was facilitated by the availability of standard-of-care recommendations published in 2007 (REF.[132]) and revised in 2018 (REFS.[133,134]). The recommendations highlight the need for a multidisciplinary assessment with a physician coordinating the assessments from different specialists and the interaction among them, and a focus on anticipatory proactive care. The most recent recommendations include nine topics: diagnosis and genetics; physical therapy and rehabilitation; orthopaedic care; nutrition, growth and bone health care; pulmonary care; acute care management; other organ system involvement; medication; and ethics and palliative care. Recommendations include those for patients with all subtypes of SMA subdivided according to their functional status (non-sitters, sitters and walkers). These guidelines have been widely adopted by clinicians all over the world, have been translated into several languages and promoted by patient advocacy groups and international neuromuscular networks. We briefly report some of the highlights of the revised standard-of-care recommendations.

Physiotherapy and orthopaedic management

Physiotherapy and orthopaedic management aims to optimize or preserve weakened muscle function and prevent severe deformities such as joint contractures or scoliosis, which are frequent in patients with SMA. Orthopaedic management of progressive scoliosis focuses on early indication for surgical procedures.

Other primary rehabilitation goals are related to the need to assess strength and motor function. These functions are assessed using appropriate tools, such as the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)[135] and the Hammersmith Infant Neurologic Examination Section 2 (HINE-2)[136] for infants and the Hammersmith Functional Motor Scale Expanded (HFMSE)[137] and the Revised Upper Limb Module for SMA (RULM)[138] for children and adults. These tools are routinely used in many clinical centres and assess different aspects of motor function. These scales include clinically meaningful items that are relevant to the patient's age, developmental stage and degree of motor impairment, and have been used in several natural history studies and intervention drug trials to assess trajectories of change and response to treatments[139–145]. The HINE-2 can be administered without special training or expertise and captures incremental acquisition of motor milestones, making it attractive for use in less specialized clinics. Assessment of the response to these treatments in adults has been more challenging owing to the smaller rate of change than in infants and young children, and sometimes from a floor effect. Efforts are underway to create more sensitive and age-appropriate motor function tests for adults.

Respiratory care

Recommendations for respiratory care include regular assessment of respiratory function with measurements of forced vital capacity and overnight sleep studies to measure oxygen and CO_2 levels. Other recommendations, which are strongly suggested, are assessments for impaired airway clearance, and the provision of necessary or proactive support via mechanical non-invasive ventilation and assisted cough techniques.

Management of bulbar impairment

Special attention should be devoted to swallowing dysfunction in patients with SMA type 1 or severe SMA type 2, and regular assessments of growth, involving speech therapists and nutritionists with SMA expertise. Gastrointestinal symptoms, such as gastroesophageal reflux and poor bowel motility or constipation, are common in patients with SMA and should also be monitored. The availability of the new treatments for SMA management has expanded to promote effective oral communication in patients with SMA type 1.

Acute care

Recommendations for acute care of SMA include management of acute events with protocols to be used in a hospital setting and anticipatory care with home illness management plans, including preliminary meetings with local emergency services and planning of safe transportation to medical facilities. Monitoring and addressing acute respiratory decompensation, dehydration and hypoglycaemia are emphasized.

New therapies

As previously mentioned, nusinersen, onasemnogene abeparvovec and risdiplam (FIG. 5) have received regulatory approval by the FDA and EMA for the treatment of SMA, and are available in many countries worldwide. Other drugs for SMA are also under clinical investigation. These treatments all increase SMN expression via distinct molecular mechanisms, and have different administration routes and tissue biodistributions. In high-income countries, while most patients with diagnosed SMA, including those with a new diagnosis, have access to and

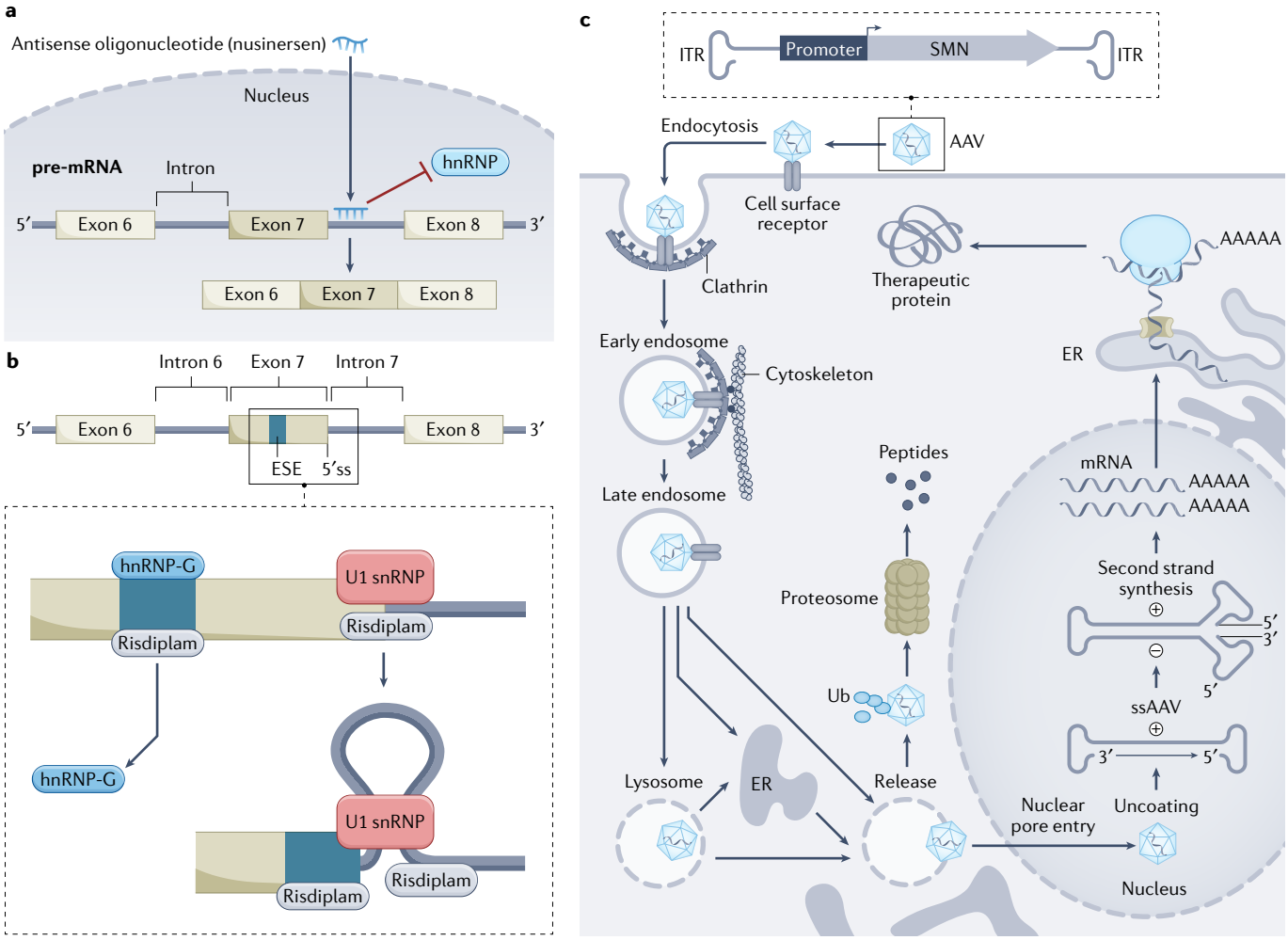

Fig. 5 | **Mechanism of action of approved SMA therapies. a** | The splice-switching antisense oligonucleotide nusinersen binds to an intronic splice silencer site in intron 7 and sterically hinders recruitment of heterogeneous nuclear ribonucleoproteins (hnRNPs) that stimulate exclusion of exon 7 (REF.[208]). **b** | The binding of the small molecule risdiplam to two sites in the *SMN2* pre-mRNA is thought to induce a conformational change in the small ribonucleoproteins involved in *SMN2* splicing, increasing *SMN2* exon 7 inclusion[209]. **c** | Onasemnogene abeparvovec comprises an adeno-associated virus 9 (AAV9) that is used to deliver a functional copy of *SMN* cDNA to cells[210,211]. ER, endoplasmic reticulum; ESE, exonic splicing enhancer; ITR, inverted terminal repeat; SMA, spinal muscular atrophy; SMN, survival motor neuron; ssAAV, single-stranded AAV; Ub, ubiquitin. Part **a** adapted from REF.[208], Springer Nature Limited. Part **b** adapted from REF.[209], CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/). Part **c** adapted from REF.[210], Springer Nature Limited. Part **c** adapted from REF.[211], Springer Nature Limited.

payment coverage for at least one of the new therapies, barriers to access remain. For example, in the USA, coverage policies vary among commercial insurers, who make their coverage determinations independently, and public insurance programmes (Medicare and Medicaid), which have rigid templates to provide coverage on a case-by-case basis. In countries with government-paid health care, approval of the drugs by the health authorities does not translate necessarily into easy access for all; families have to seek help from companies through expanded access programmes or raise private funding to pay for these very expensive treatments[146]. Still, in many countries around the world, patients have no access at all to these disease-modifying treatments. Notwithstanding the issues discussed above, these therapies are becoming the new standards of care for SMA and are redefining the natural history of this disease.

Nusinersen was the first drug to successfully complete randomized sham-controlled clinical trials in early-infantile and late-infantile onset SMA[147,148], and to be approved by the FDA in 2016, followed by approval in several other countries worldwide. The first study (ENDEAR) included infants with SMA type 1 <7 months of age, and demonstrated the achievement of new motor milestones, such as head control and independent sitting, in >50% of treated infants compared with none receiving the sham procedure. The risk of death or permanent assisted ventilation was also significantly reduced in treated patients[147]. In another study (CHERISH), better motor responses on the HFMSE and RULM were observed in 57% of nusinersen-treated children versus 26% of children who received the sham procedure[148]. Moreover, preliminary results of the extension study (SHINE) illustrated in recent conferences confirm long-term efficacy and a good safety profile.

Further real-world data and data from early access programmes have demonstrated the safety and efficacy of nusinersen in much larger and diverse populations of patients, from young infants with the most severe neonatal onset form[149–152], to children[141,153–155] and adults[144,156–169] with milder phenotypes, and presymptomatic infants identified mainly by newborn screening. As of early 2022, >12,000 patients with SMA had been treated with nusinersen[170,171]. While the initial studies focused on infants and children, there has been an increasing number of studies reporting data in adults, confirming the safety and efficacy of nusinersen.

A review in 2021 of all the published papers reporting the use of nusinersen in patients with SMA type 2 or 3 (REF.[172]) showed positive changes on at least one of the functional measures used to assess efficacy, suggesting a favourable benefit in motor function across patients with SMA type 2 or 3 of all ages. Of note, these results were different from those in natural history studies including untreated cohorts, which consistently had negative findings[172]. A study of higher-dose nusinersen is in progress (DEVOTE; NCT04089566).

Onasemnogene abeparvovec (adeno-associated virus 9 (AAV9)-mediated delivery of *SMN1*) was first investigated in an open-label, dose-escalation phase I clinical trial in 15 infants with SMA type 1 (REF.[173]). This study found that onasemnogene abeparvovec was overall well tolerated, although a number of patients had transient abnormal liver function tests with elevated serum levels of aminotransferase, which was well controlled with prednisolone. Safety and efficacy findings were maintained at 5 years[174], with a median time since dosing of 5.2 years. All 13 patients whose family agreed to long-term follow-up were alive and 2 of the 3 patients in the low-dose cohort did not require permanent ventilation support. Motor milestones were maintained and two participants in the higher therapeutic dose cohort achieved additional milestones.

These results led to FDA approval of onasemnogene abeparvovec in 2019 for the treatment of individuals with SMA up to 24 months of age, which was followed by approval in many other countries worldwide with a more variable range in patient coverage policies. Two subsequent larger, open-label, multicentre phase III studies in the USA[175] and Europe[176] had similar results and safety profiles, with >90% of infants participating in the study surviving at 18 months of age and a significant improvement in motor function (evaluated using the sitting independently item of the Bayley Scale of Infant Development, version III and the CHOP INTEND motor scale) compared with an external comparator group. The STR1VE EU study[176] included patients with minimal bulbar dysfunction or respiratory support between 6 and 12 h/day who were excluded from the previous studies. These patients also had lower motor functional scores at baseline, and showed some improvement in motor function even if this improvement was lower than in patients who did not require support at baseline[176].

Moreover, since the approval of onasemnogene abeparvovec, there are some reports of real-world data[177–180] confirming the observations from clinical studies in infants treated before 6 months of age. Moreover, the real-world studies included patients >8.5 kg in weight, who were not included in clinical trials, and suggested that some adverse events, such as elevated serum levels of aminotransferase, were more frequent in heavier infants but were always well controlled by prednisolone[181]. One real-world study observed three patients with thrombotic microangiopathy[178], which was found in preclinical studies but not in the clinical trials. Other possible adverse events found in preclinical studies, such as dorsal root ganglia and cardiac involvement, have not been observed in patients. Other studies are in progress to assess the safety of the biodistribution, safety and tolerability of intravenous administration of high doses of AAV vector in children up to 21 kg in weight (SMART; NCT04851873) and to establish safety and efficacy of intrathecal AVXS-101 delivery (STRONG; NCT03381729).

Risdiplam is approved in the USA for use in all patients with SMA, from birth to adulthood, and in other countries from 2 months of age and older, following the completion of two large clinical trials. In the first study (FIREFISH), patients with symptomatic SMA type 1 (REFS.[182,183]) had significantly increased survival and functional improvement compared with a natural history cohort study, with achievement of motor milestones such as head control and sitting independently. The second study (SUNFISH) in patients with SMA type 2 or non-ambulant SMA type 3 between 2 and 25 years of age showed a difference in motor function on both the Motor Function Measure (MFM) and RULM associated with increased production of SMN protein in blood compared with a placebo group[184]. Risdiplam was well tolerated and had an excellent safety profile in both studies. This drug is available for compassionate use, early-access programmes and more recently commercially, but real-world data are not yet available. The RAINBOWFISH study (NCT03779334), currently in progress (as of June 2022), is an open-label study of risdiplam in presymptomatic patients under 6 weeks of age.

Logistic and financial considerations limit the access to these three expensive drugs. This has created an ethical dilemma that will not be easily solved. As a result of newborn screening many patients are now treated before the onset of symptoms. One proposed treatment algorithm recommends treating all patients with two, three or four copies of *SMN2* and assessing those with one or five copies on a case-by-case basis[185]. The greatest urgency to treat is in babies with two copies of *SMN2*, as clinical experience has found that symptoms can evolve within 1–2 weeks of diagnosis, and treatment after symptom onset has a less favourable response than treatment before onset[129,180]. Health-care authorities in different countries, and even sometimes among provinces in one country, have developed different coverage policies. Authorization for the treatment of presymptomatic patients with four copies and for symptomatic patients with SMA type 2 or 3 varies widely. This has led to uneven access in both high-income and in low-income and middle-income countries. In some countries, these drugs have gained approval by the health-care authorities but no or limited payment coverage is provided. Families eager to access a drug for their child that is not available in their country — owing to it not being approved by

health-care authorities or to restrictive policies — have in some cases resorted to crowd-sourcing funds to purchase a drug for their child. This has become more common and has led to a cottage industry of medical tourism for families with financial means to gain access to these drugs from another country. This unfair situation will hopefully ease as health-care authorities and the drug manufacturers come to more widespread agreement on financial terms and coverage policies.

Quality of life

Several studies have found a good subjective QOL in children and adults with SMA[186–191]. Although Duchenne muscular dystrophy and other muscle disorders are associated with a high frequency of issues such as anxiety and depression, the incidence of depressive symptoms in patients with SMA is similar to that in the general population[192]. The available studies have found no association between QOL and changes in motor function, and, in one study, self-reported QOL was higher in patients with SMA and more severely affected motor function than in patients with milder disability[188].

One reason for the lack of association between motor disability and QOL may be because most studies assessing QOL in patients with SMA have focused on health-related QOL (HRQOL), and, therefore, on physical integrity and health-related issues, rather than on self-reported, subjective measures of QOL[193]. When HRQOL measures are used, the lack of correlation between motor disability and QOL is consistent among SMA and other neuromuscular disorders, thus showing that changes in motor function do not correlate with changes in HRQOL measures[194]. Another possible explanation may be that weaker patients who are stable seem to view their QOL better than higher-functioning patients with progressing symptoms.

A workshop focusing on patient-reported outcome measures (PROMs) in SMA, suggested that other measures, such as assessment of activities of daily living and carer burden, are likely to capture clinically relevant changes that are more closely associated with functional motor changes[195]. This finding has led to efforts to validate the assessment of activities of daily living, such as in the Paediatric Evaluation of Disability Inventory Computer Adaptive Test (PEDI-CAT)[196] and the Spinal Muscular Atrophy Independence Scale (SMAIS), which can be used in patients with SMA from the first years of life[195]. Scales assessing carer burden such as the SMA Health Index (SMA-HI), developed for use in older children and adults, are also important[197].

Despite the increasing attention to QOL and, more generally, to PROMs, a few gaps remain to be addressed. These gaps include assessment of fatigability and reduced endurance, which are among the most frequently reported concerns of adults with SMA[195]. The assessments should include perceived fatigue (subjective) and physiological fatigue, both of which are important for maintaining posture and activities during continuous or prolonged tasks or in performing repetitive movements[195,198–200]. Increasing evidence from treated patients suggests that changes following treatment often involve reduction in fatigability that has a significant effect on several facets of activities of daily living and on QOL. Large structured studies are also needed to systematically explore the possible changes in QOL following treatment with nusinersen, onasemnogene abeparvovec and risdiplam.

Outlook

The field of SMA has completely changed owing to the advent of nusinersen, onasemnogene abeparvovec and risdiplam, which have become standards of care. These developments require a new classification of patients with SMA that encompasses the emerging phenotypes of treated individuals, and a renewed characterization of demographics particularly in terms of population frequency of the infantile onset form. The prevalence of treated SMA type 1 is rapidly increasing and in time will become the most prevalent form of the disease, particularly if treatment is widely available in all countries.

These remarkable steps forward also highlight areas in which our knowledge of SMA and its response to therapeutic intervention is incomplete. Patients with SMA expected to develop SMA type 1 with two copies of *SMN2* often have markedly elevated serum neurofilament levels at birth, indicating very early degeneration that highlights an essential role for SMN during in utero development[102]. Important knowledge gaps are whether long-term improvement can be achieved in these infants, even with treatment as part of a newborn screening programme, and whether there are long-term consequences of SMN deficiency during development.

For SMN restoration therapies, whether the differences in mode of administration and biodistribution lead to long-term different trajectories in patients is unknown. Moreover, whether there is a difference between drugs acting exclusively in the CNS and drugs that also have an effect peripherally is unknown. Also still to be studied is whether combinatorial therapies achieve an even more complete biodistribution and SMN restoration than monotherapy. Several ongoing studies are investigating combinatorial therapies, including combined SMN protein-enhancing drugs (nusinersen treatment following onasemnogene abeparvovec (RESPOND; NCT04488133)) and myostatin inhibitors combined with either nusinersen (TOPAZ; NCT03921528) or risdiplam (NCT05115110).

In addition, patients with more chronic SMA have a more modest therapeutic response, suggesting that SMN deficiency is unlikely to be the only target for functional response in this group. Whether their less-striking clinical response is simply a reflection of the fact that irreversible loss of motor neurons has already occurred or is a consequence of SMN deficiency in peripheral tissues including muscle, and which SMN-independent approaches could be considered in these patients, are still to be determined.

In this respect, ongoing trials with drugs with different mechanisms of action, such as those targeting the force of muscle contraction or NMJ efficiency, are in early clinical trials. It remains a challenge for all patients with SMA to gain access to these transformative drugs.

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Author contributions

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Competing interests

E.M., C.J.S., F.M., B.T.D. and R.S.F. are all principal investigators for clinical studies and consultants for Roche, Biogen, Novartis and Scholar Rock.

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