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Nusinersen treatment of spinal muscular atrophy – a systematic review

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ABSTRACT

INTRODUCTION: 5q spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder caused by insufficient survival motor neuron protein. Untreated SMA involves death or permanent respiratory support (type 1), inability to walk (type 2) or ability to walk (type 3). The incidence of SMA is 1 in 7,500 live births, equivalant to eight children being born with SMA in Denmark annually.

METHODS: We undertook a systematic review of the efficacy of nusinersen as SMA treatment. We included randomised controlled trials and cohort studies. Our primary endpoints were survival without permanent respiratory support and change in motor function.

RESULTS: We identified 658 articles and included 13 of these (two randomised controlled trials and 11 cohort studies). Nusinersen increased survival without permanent respiratory support in SMA type 1 and increased motor function development in types 1-3. Nusinersen treatment before symptom onset in children with presymptomatic SMA produced near-normal motor development. So far, nusinersen has only minor safety concerns mostly related to the lumbar puncture.

CONCLUSIONS: Nusinersen increased survival without permanent ventilatory support in children with SMA type 1. Improvements in SMA type 2 and 3 were less evident. Better outcomes were seen in young children with a short disease duration, particularly in children receiving nusinersen before symptom onset. Newborn SMA screening may facilitate presymptomatic treatment with splice modification (nusinersen, risdiplam) or gene implantation therapy (AVXS-101, zolgensma).

KEY POINTS

Nusinersen improves survival without permanent respiratory support in type 1 and presymptomatic spinal muscular atrophy.

Nusinersen improves motor function development in patients with type 1 and type 2 spinal muscular atrophy with the largest improvements seen at early age and in patients with a short disease duration.

Genetic screening for spinal muscular atrophy and pre-symptomatic nusinersen start may lead to near-normal motor development.

5q spinal muscular atrophy (SMA) is an autosomal recessive disease that causes progressive muscle atrophy and weakness [1]. The incidence of SMA is 1 per 7,500 live births; thus, approximately eight children with SMA are born in Denmark annually [2, 3].

SMA is caused by a homozygous deletion or mutation in exon 7 of the survival motor neuron (SMN) 1 gene [1]. This leads to faulty splicing of the pre-mRNA that codes for SMN protein. Functional SMN protein is needed for development of motor neurons. Another gene, SMN2, produces only 5-10% functional SMN protein due to a splice-site variant, which excludes exon 7 from the RNA transcript [1]. Nusinersen is an antisense oligonucleotide that targets pre-mRNA splicing of the SMN2 gene. Accordingly, nusinersen increases inclusion of exon 7 in the SMN2 mRNA splicing and hereby increases the amont of functional SMN protein [4].

Disease severity in children with SMA is modified by the number of SMN2 copies where children with a higher copy number generally have a milder phenotype [5]. The phenotype of SMA is based on age at symptom onset and the highest motor milestone achievement; it can be divided into a) prenatal presentation (type 0), b) never achieving the ability to sit independently and onset before six months of age (type 1), c) never achieving the ability to walk without support and onset between six and 18 months of age (type 2), and d) later presentation with the ability to walk unassisted (type 3) [6].

SMA type 1 is seen in 60% of children with SMA [7]. Most children with SMA type 1 have one or two SNM2 copies (but may have three SNM2 copies), whereas most patients with SMA types 2 and 3 have three or more SMN2 copies [8, 9]. Having SMA and no SMN2 copies is not compatible with life. If untreated, children with SMA type 1 will die or require permanent respiratory assistance before the age of two years (median lifespan: one year), preceded by a steady decrease in motor function [9]. The prognosis varies in untreated SMA type 2 and 3, but patients experience a gradual decrease in motor function over time [10].

We undertook a systematic review of the efficacy of nusinersen in the treatment of SMA. Our primary endpoints were survival without permanent respiratory support and changes in motor function.

METHODS

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11].

Data sources and searches

We undertook a systematic search of MEDLINE (via PubMed), Embase (OVID), Web of Science (core) and the Cochrane Central Register of Controlled Trials. We used the following search terms: 'Spinraza' OR 'Nusinersen' OR 'ISIS 396443' OR 'ISIS-SMNRx'. We accessed the databases during 2019 and the latest update was made on 13 November 2019.

Study selection criteria

We included randomised controlled trials (RCTs) and prospective cohort studies on the clinical efficacy of intrathecally administered nusinersen in the treatment of SMA. We excluded phase 1 trials and abstracts from meetings or conferences. Duplicate studies were removed, and the remaining titles and abstracts were screened according to the inclusion criteria. Reasons for exclusion were provided for seemingly eligible studies.

Data collection

From each study, the following data were extracted: study characteristics, number of participants, age at symptom onset, nusinersen treatment duration and relevant endpoints.

Risk of bias

All studies were assessed for bias from randomisation (selection bias), blinding (performance and detection bias) and missing outcomes (attrition bias) [12].

Outcomes

Our two main outcomes were:

1) "Survival without permanent respiratory support" defined as no death or need for permanent respiratory support (non-invasive ventilation or tracheostomy more than 16 hours/day for more than 21 days).

2) Change in motor function assessed by validated rating scales (see description below) or achievement of milestones, such as walking or sitting.

Assessment scales for motor development

a) The Hammersmith Infant Neurologic Examination (HINE) is a 37-item scale of neurologic function in infants; HINE Part 2 (HINE-2) focuses on motor development and ranges 0-26 points [13].

b) The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders is used to evaluate motor skills in infants. It consists of 16 items and ranges 0-64 points [14].

c) The Hammersmith Functional Motor Scale - Expanded (HFMSE) is a scale for assessment

of motor function beyond infancy. It consists of 33 items and ranges 0-66 points [15].

d) The 6-Minute Walk Test is a validated assessment tool for outcomes in ambulatory SMA patients and other neuromuscular conditions [16].

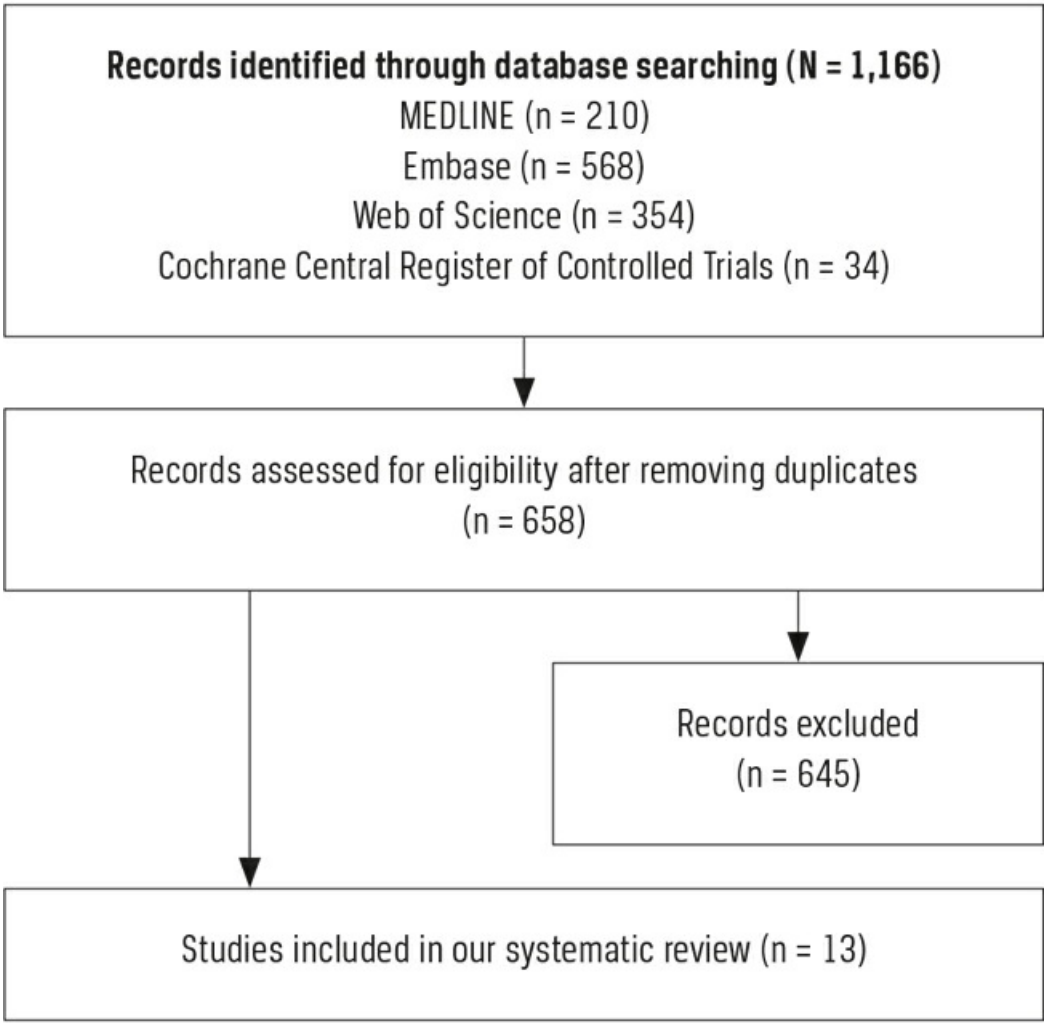
e) The Upper Limb Module is used to evaluate upper limb function in weaker, non-ambulatory SMA patients [17]. As an extension of this scale, the Revised Upper Limb Module is used to evaluate upper limb function in both non-ambulatory and ambulatory patients [18].

RESULTS

Study selection

We identified 1,166 articles, and 658 articles remained after duplicate deletion (**Figure 1**, PRISMA flow chart). We included 13 studies in the systematic review (two RCTs and 11 prospective cohort studies) [11].

FIGURE 1 / PRISMA flow chart. Identification of studies included in our systematic review.



PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Three seemingly eligible studies were excluded due to a) already published data [19], b) invalid motor function data [20] and c) inclusion of a more recent study with longer follow-up from the same cohort [21, 22].

Efficacy of nusinersen on spinal muscular atrophy

An overview of included studies are shown in **Table 1** (presymptomatic SMA), **Table 2** (SMA type 1), and **Table 3** (SMA types 2 and 3).

TABLE 1 / Study characteristics and main findings of presymptomatic (genetically diagnosed) 5q spinal muscular atrophy.

Reference	Study type	Treatment groups	Age at 1st nusinersen dose, median or mean (range), days	Main findings
De Vivo et al, 2019 [8]	Cohort	25 children with genetically diagnosed SMA: 15 with 2 SNM2 copies, 10 children with 3 SMN2 copies	22 (3-42)	*After a median 2.9 yrs of nusinersen treatment* All children were alive without permanent ventilation and were able to sit unassisted 88% walked independently CHOP INTEND increased during 6 mo.s when they reached a plateau around 60 points and then remained stable while children continued to increase on HINE and WHO milestone outcomes HINE increased by 21 points in children with SMA type 2 and 23 in children with SMA type 3
Vill et al, 2019 [2]	Cohort	6 children with 2 or 3 SMN2 copies	23 (15-35)	*After a median 7 mo.s (range 1-12) of nusinersen treatment* 0 of the 6 children developed SMA symptoms during follow-up

CHOP INTEND = The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE = The Hammersmith Infant Neurologic Examination; SMA = 5q spinal muscular atrophy; SMN = survival motor neuron.

TABLE 2 / Study characteristics and main findings of 5q spinal muscular atrophy type 1.

Reference	Study type	Treatment groups	Age at symptom onset, median or mean (range)	Age at 1st nusinersen dose, median or mean (range)	Main findings
Finkel et al, 2016 [4]	Cohort	20 children with SMA compared with a non-treated natural history SMA cohort	60 (21-154) days	141 (36-210) days	*Improvements after 2-32 mo.s of nusinersen treatment compared with natural history SMA cohort* Improved survival without need for permanent ventilatory support, p = 0.0014, 1 infant died Mean CHOP INTEND increase of 11.5 points, p = 0.0080 Significant increase in HINE score in 16 of 19 children Improvement of ≥ 2 levels in ≥ 1 category of HINE scale in 13 children
Finkel et al, 2017 [23]	RCT	Nusinersen group: 80 children	Nusinersen group: 7.9 (2-18) wks	Nusinersen group: 163 (52-242) days	*Improvements after 6-13 mo.s in the nusinersen group compared with controls* Decreased hazard for death or permanent assisted ventilation in the nusinersen group compared with controls, hazard ratio = 0.53, p = 0.005 Motor-milestone response in 51% (nusinersen group) vs 0% (controls), p < 0.001 CHOP INTEND response in 71% (nusinersen group) vs 3% (controls), p < 0.001 Study terminated early at interim analysis due to significant motor milestones improvements in nusinersen treated children with SMA
		Control group: 41 children	Control group: 9.6 (1-20) wks	Control group: 181 (30-262) days	
Pechmann et al, 2018 [24]	Cohort	61 children with SMA	3 (0-6) mo.s	21 (1-93) mo.s	*Improvements after 6 mo.s of nusinersen treatment compared with baseline* HINE motor milestone response in 34,4%, mean HINE increase of 1.4 points 77% increased ≥ 4 points on CHOP INTEND, mean CHOP INTEND increase of 9.0 points No significant difference between children with ≤ 2 SMN2 copies compared to children with ≥ 3 SMN2 copies CHOP INTEND increase from baseline in children treated before age 7 mo.s was higher than for children treated after age 7 mo.s, 14.4 vs 7.0 points
Aragon-Gawinska et al, 2018 [25]	Cohort	33 children with SMA	4 (2-6) mo.s	21 (8-113) mo.s	*Improvements after 6 mo.s of nusinersen treatment compared with baseline* All patients were alive at 6-mo. follow-up Median HINE increase of 1.5 points, p < 0.001 Median CHOP INTEND increase of 4 points No significant difference between children with ≤ 2 SMN2 copies compared with children with ≥ 3 SMN2 copies
Farrar et al, 2018 [26]	Cohort	8 children previously diagnosed with SMA	5 (3-6) mo.s	102 (28-434) mo.s	*Improvements after median 5 mo.s (1-11) of nusinersen treatment compared with baseline* All survived without permanent ventilatory support In the newly diagnosed cohort, 7 of 8 children gained motor function
		8 children newly diagnosed with SMA	3 (1-5) mo.s	8 (3-12) mo.s	
Olsson et al, 2019 [27]	Cohort	12 children with SMA	2 (0.3-4) mo.s	14 (1-92) mo.s	*Improvements after 11 mo.s (2.5-19) of nusinersen treatment compared with baseline* Median CHOP INTEND increase of 13 (3-30) points Younger age at baseline was related to better motor improvement
Pane et al, 2019 [22]	Cohort	85 children with SMA	-	5 (2-191) mo.s	*Improvements after 12 mo.s of nusinersen treatment compared with baseline* Statistically significant difference in CHOP INTEND and the HINE-2 for the whole group (p < 0.001), the subgroups with 2 SMN2 copies, p < 0.001, and those with 3 SMN2 copies, p < 0.001 Mean CHOP INTEND increase of 6 (–6-32) points Mean HINE increase of 1.3 (–3-12) points, p < 0.001, but the increase on the HINE was statistically significant only in children younger than 2 yrs of age Lower age at baseline was associated with better outcomes
LoMauro et al, 2019 [28]	Cohort	27 children with SMA	-	5-9 mo.s	*Improvements after 12-16 mo.s of nusinersen treatment compared with baseline* Median CHOP INTEND increase of 11 points

CHOP INTEND = The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE = The Hammersmith Infant Neurologic Examination; SMA = 5q spinal muscular atrophy; RCT = randomised controlled trial; SMN = survival motor neuron.

TABLE 3 / Study characteristics and main findings of 5q spinal muscular atrophy type 2-3.

Reference	Study type	Treatment groups	Age at symptom onset, median or mean (range)	Age at 1st nusinersen dose, median or mean (range)	Main findings
Mercuri et al, 2018 [1]	RCT	Nusinersen group: 84 children	Nusinersen group: 10 (6-20) mo.s	Nusinersen group: 4 (2-9) yrs	*After 15 mo.s of nusinersen treatment* The between-group difference favoured the nusinersen group by an increase on HFMSE by 5.9 (95% CI: 3.7-8.1) points, p < 0.001, which prompted early termination of the trial 57% in the nusinersen group and 26% in the control group had an increase from baseline to month 15 in the HFMSE score of ≥ 3 points, p < 0.001 Lower age and treatment early after symptom onset were associated with better HFMSE improvements
		Control group: 42 children	Control group: 11 (6-20) mo.s	Control group: 3 (2-7) yrs	
Darras et al, 2019 [30]	Cohort	Type 2 SMA: 11 children	Type 2: 11 (3-15) mo.s	Type 2: 4 (2-15) yrs	*Improvements after 3 yrs of nusinersen treatment compared with baseline* Type 2: mean HFMSE increase of 10.8 points, and mean Upper Limb Module increase of 4.0 points Type 3: mean HFMSE increase of 1.8 points, and mean 6-Minute Walk Test increase of 92 m
		Type 3 SMA: 17 children	Type 3: 22 (6-60) mo.s	Type 3: 9 (3-15) yrs	
Walter et al, 2019 [29]	Cohort	19 children with SMA	11 (1-40) yrs	35 (18-59) yrs	*Improvements after 10 mo.s of nusinersen treatment compared with baseline* No significant HFMSE improvement Minor improvement on the Revised Upper Limb Module and 6-Minute Walk Test

CI = confidence interval; HFMSE = The Hammersmith Functional Motor Scale – Expanded; RCT = randomised controlled trial.

Nusinersen treatment initiated before symptom onset in children with pre-symptomatic spinal muscular atrophy

Nusinersen treatment before the first neurological symptoms has been shown to improve survival and motor development in children with genetically diagnosed SMA (Table 1). In the "NURTURE" study, 25 children with homozygous SMN1 deletion and 2-3 SMN2 copies were alive and did not require permanent ventilatory support after 2.9 years of nusinersen initiated before symptom onset. These children's motor development was almost normal [8]. Furthermore, seven children with genetic SMA (2-3 SMN2 copies) remained asymptomatic after eight months (range: 1-12 months) of nusinersen treatment [2]. This should be compared with historical cohorts of SMA type 1 where the median age at permanent respiratory support was 10.5 month and only 8% were alive at age 20 months, and to SMA type 2 defined as never achieving the ability to walk without support and symptom onset between six and 18 months of age [6, 9].

Nusinersen for children with type 1 spinal muscular atrophy

Nusinersen improved both survival without permanent respiratory support and motor development (Table 2). Improvements were strongest in younger children, and there was no difference between children with two or three SMN2 copies [4, 22-28].

The "ENDEAR" RCT showed a hazard ratio for death or permanent ventilation of 0.53 (p = 0.005) in favour of nusinersen-treated children versus sham control children and a clinically meaningful and statistically significant increase in motor milestones of 51% (p < 0.001), which resulted in the early termination of the study [23]. Similarly, cohort studies support stable or increased motor function in nusinersen-treated SMA children followed for more than one year. Not all children showed great improvements, and younger age at nusinersen initiation was related to enhanced motor development, whereas the number of SMN2 copies did not influence outcomes [4, 22, 24-28].

Nusinersen for children with types 2 and 3 spinal muscular atrophy

Nusinersen improved motor function development over more than three years assessed by HFMSE, 6-Minute Walk Test and The Upper Limb Module (Table 3) [1, 29, 30]. However, lower age at nusinersen initiation and shorter disease duration were associated with an enhanced treatment response. The "CHERISH" RCT showed a significantly better motor function development in the nusinersen group than in sham control children, particularly in young children with a short disease duration, and this study was terminated early after the interim analysis [1]. Furthermore, the benefit of nusinersen on motor function may be present after three years, which was more evident in type 2 than in type 3 SMA children [30]. However, a cohort study with inclusion of older children with type 3 SMA (mean age at treatment initiation of 35 years, range: 18-59 years) only found small and clinically non-significant motor function improvement after ten months of nusinersen treatment [29].

Side effects to nusinersen

An integrated safety analysis of seven completed clinical trials (376 participant years) found that the overall incidence of serious adverse effects was lower in the treated group than in those receiving a sham procedure (41% versus 61%). The frequency and types of adverse effects were consistent with symptoms of SMA or lumbar puncture. Headache was the only symptom with a higher frequency in the nusinersen group than in the control group, and no patients had any indication of increased intracranial pressure or communicating hydrocephalus. Thus, no evidence has been found to support the previous clinical concern for benign increased intracranial pressure. A follow up study (SHINE) is collecting long-term safety data [31].

DISCUSSION

Our systematic review was designed to investigate the efficacy of nusinersen in children with SMA types 1, 2 and 3. We found that nusinersen was seemingly efficient in treating all three SMA phenotypes, with the strongest evidence being found in the youngest children, and there were few safety concerns regarding drug administration. Children with SMA who were treated before neurological symptoms presented (presymptomatic SMA) had a near-normal motor development. For SMA type 1, nusinersen improved both survival without permanent respiratory support and development of motor function. These effects were strongest in younger patients without significant difference between children with two or three SMN2 copies. For SMA types 2 and 3, nusinersen improved or stabilised motor function development, but lower age at nusinersen treatment and shorter disease duration were associated with an enhanced response.

The efficacy and safety profile of nusinersen is supported by other recently published systematic reviews [32-34].

Our systematic review has several potential limitations. First, studies were heterogenous in their inclusion criteria and outcomes, making it difficult to pool data. Second, the efficiency of nusinersen in children with long disease duration remains unclear. Third, some studies may have been biased because a pharmaceutical company sponsored the two included RCTs and was also involved in some of the cohort studies. Fourth, we cannot ignore the risk of publication bias which may cause an overestimation of treatment efficacy. Fifth, at this point, we cannot determine the long-term efficacy of nusinersen due to limited long-term follow-up. Sixth, most studies were open-label, non-controlled trials due to ethical concerns. Seventh, studies vary in the composition of SMA types, often pooling type 2 and type 3. Eigth, most SMA studies are small because SMA is a rare disease. Ninth, research in SMA is rapidly growing, and articles published after November 13, 2019 have not been included, e.g., Hagenacker et al [35].

In Denmark, the Danish Medicines Council assesses new hospital drugs according to efficacy and price compared with existing therapy. To date, nusinersen is not a recommended standard treatment care for persons with SMA in Denmark, but it is given to children with: a) presymptomatic SMA with two or three SMN2 copies; b) SMA type 1 with two or three SMN2 copies, symptom onset before the age six months, and no need for permanent ventilatory support at treatment onset; and c) SMA type 2 with at least two SMN2 copies, symptom onset before the age of two years, a maximum disease duration of four years at treatment onset, no need for permanent ventilatory support and at least 95% oxygen saturation without ventilatory support. They recommend discontinuing treatment in type 2 patients if there is a) worsening of respiratory status not due to infection (based on time on ventilator or a decrease in SaO2 without extra oxygen support during three weeks) or b) aggravation of motor function as measured on the HFMSE in two consecutive measurements compared with values at start of treatment [36]. The cost of nusinersen treatment is very high. In Denmark, the listed price for a single dose is 772,000 DKK (equivalent to 112,784 US dollars), and the dosing schedule consists of six doses the first year and three doses the following year [37]. The actual price may be subject to varying discounts in different countries, and the price paid in Denmark is not disclosed. We have previously published a case series on three of the children in Denmark who were treated with nusinersen as part of an early access programme [38].

Future research is needed to determine a) the efficacy of nusinersen in SMA patients with advanced disease, b) the long-term benefit of nusinersen and c) predictors (e.g., biomarkers) for a favourable treatment response. Other promising treatment regimens, particularly for presymptomatic SMA, are underway such as single-dose gene replacement therapy (AVXS-101, zolgensma). However, long-term data of treatment efficacy are not yet available [39]. As of today, the cost of this treatment is a one-time payment of 2.1 million US dollars, and it is currently available in the United States only [40].

CONCLUSIONS

Nusinersen increased survival without permanent ventilatory support in children with SMA type 1. Improvements in SMA type 2 and 3 were less evident. Lower age at nusinersen treatment and shorter disease duration were associated with a better response. Enhanced outcomes were seen in young children with a short disease duration, particularly in children with genetic SMA receiving nusinersen before symptom onset. There were only minor safety concerns. Newborn SMA screening may be implemented to facilitate presymptomatic treatment.

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