Helsedirektoratet

Returadresse: Helsedirektoratet, Postboks 220 Skøyen, 0213 Oslo, Norge

Helse- og omsorgsdepartementet
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Deres ref.:	19/01077-5
Vår ref.:	20/19167-8
Saksbehandler:	Bente Bryhn
Dato:	11.02.2021

Utvidelse av tilbudet om genetiske masseundersøkelser av nyfødte i Norge til å inkludere spinal muskelatrofi (SMA)

Helsedirektoratet har mottatt og behandlet søknad fra Helse Sør-Øst RHF om utvidelse av nyfødtscreeningprogrammet til å omfatte screening for spinal muskelatrofi (SMA).

Vi viser til vedlagt søknad fra Helse Sør-Øst RHF:
Søknadsbrev av 2.11.2020 fra Helse Sør-Øst RHF med følgende vedlegg:

- Brev av 21.09.2020 fra Oslo universitetssykehus HF
- Utfylt søknadsskjema for nasjonale og flerregionale behandlingstjenester
- Rapport av 3.3.2018: *Evidence-based Review of Newborn Screening for Spinal Muscular Atrophy (SMA): Final Report (v5.2).*

Bakgrunn
Nyfødtscreeningen i Norge er organisert som en nasjonal tjeneste, ved Oslo universitetssykehus HF. Departementet har i forskrift 17. desember 2010 nr. 1706 om godkjenning av sykehus, bruk av betegnelsen universitetssykehus og nasjonale tjenester i spesialisthelsetjenesten § 4-1 bestemt at regionale helseforetak skal søke departementet om godkjenning for nasjonale tjenester.

Helsedirektoratet er fra og med 1. januar 2019 tillagt myndighet til å godkjenne etablering av nye nasjonale tjenester, og beslutte endring eller nedleggelse av etablerte nasjonale tjenester. Når det gjelder bioteknologiloven og tilhørende forskrifter har direktoratet fortolkningsansvar for lovverket, og er fagmyndighet.

Beslutning om utvidelse av nyfødtscreeningprogrammet til å omfatte testing for flere sykdommer tas av regjeringen gjennom behandling av endring i *forskrift om genetisk masseundersøkelse av nyfødte.* Før forskriften kan endres, skal forslaget sendes på høring.

I forkant av dette gjør direktoratet en faglig vurdering av søknaden.

Helsedirektoratet har i brev av 06. april 2020 til Helse- og omsorgsdepartementet anbefalt prosess og roller ved endring av nyfødtscreeningprogrammet for å ivareta alle hensyn og krav i

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regelverk som regulerer virksomheten, samt ivareta en hensiktsmessig prosess ved endring av programmet. HOD har i brev av 12. juni 2020 støttet direktoratets beskrivelse av prosess og roller. Se vedlagt beskrivelse.

Behandling av søknad om utvidelse av nyfødtscreeningprogrammet
I behandling av søknad om endring av nyfødtscreeningprogrammet, har Helsedirektoratet vurdert følgende:

- *Vurdering av søknaden ift. kriterier for screeningprogrammer*

Søknaden er vurdert i forhold til kriteriene for screeningprogrammer, som er basert på WHO sine kriterier for screeningprogrammer. I dette inngår en vurdering av metode for screening og test som benyttes for å avdekke sykdommen det screenes for.

- *Søknad om nasjonale tjenester*

Direktoratet har vurdert søknaden opp mot kriterier for godkjenning av nasjonale tjenester.

Vurdering av søknaden ift. kriterier for screeningprogrammer
Helsedirektoratet har utarbeidet 16 kriterier for nasjonale screeningprogrammer i Norge med utgangspunkt i WHO sine 10 kriterier for screening. Se vedlegg.

Direktoratet har vurdert den foreslåtte endringen av nyfødtscreeningprogrammet opp mot kriteriene:

Tilstand

- *Tilstanden skal være et viktig helseproblem*
- *Tilstandens naturlige forløp skal være tilstrekkelig kjent*
- *Tilstanden skal ha en symptomfri fase som kan detekteres*

Spinal muskelatrofi (SMA)
SMA er en autosomal recessiv sykdom som i hovedsak skyldes bi-allelisk delesjon av survival motor neuron 1 (*SMN1*) genet. Tilstanden medfører tap av alfa-motornevroner i ryggmargen med progressiv muskelatrofi og muskelsvekkelse, og til tap av ferdigheter og forkortet livslengde. Type 1 og 2 utgjør 70-90 % av tilfellene og gir symptomdebut fra de første seks levemåneder til 6-18 levemåneder. I de mest alvorlige tilfellene vil barna aldri kunne sitte selvstendig. Av genetiske sykdommer har SMA historisk vært den vanligste årsaken til tidlig barnedød. SMA opptrer med ulik alvorlighetsgrad og klassifiseres i henhold til fenotype. De fleste som blir født med SMA har de alvorlige formene SMA type 1 eller 2. I Norge har det i gjennomsnitt vært diagnostisert 7 nye SMA-pasienter per år de siste årene.

Over 95 % av alle SMA-pasienter er homozygote for delesjon av S*MN1,* enten hele genet eller viktige deler av genet (ekson 7-8), og dette brukes til primærdiagnostikk av SMA. Alle har i tillegg et variabelt antall kopier av *SMN2* genet. På grunn av en genvariant i *SMN2* gir dette «reservegenet» kun lave, men likevel viktige mengder av SMN proteinet ved fravær av det normale *SMN1* genet. Antallet kopier av *SMN2* korrelerer derfor med SMA alvorlighetsgrad: Jo høyere antall kopier av *SMN2*, jo mildere fenotype.

Testing for *SMN1* delesjoner i kombinasjon med bestemmelse av *SMN2* kopiantall har vist seg å være en effektiv strategi for tidlig å identifisere SMA pasienter som vil ha stor nytte av tidlig oppstart av effektiv behandling.

Test

- *Det må finnes en sikker, presis og validert test*
- *Kriterier og prosedyrer for videre oppfølging av testpositive må være definert*
- *Testmetoden skal være akseptabel for målgruppen*

Nyfødtscreening for SMA

SMA har vært anbefalt inkludert i nyfødtscreeningen i USA siden juli 2018 og erfaringene er positive. Flere land i Europa har igangsatt pilotprogrammer eller planlegger innføring (blant annet Nederland, Sverige og Danmark).

SMA kan detekteres i blod fra nyfødte med en test som er utviklet og validert ved Center for Disease Control and Prevention i USA. Norge har implementert screening for alvorlig T-celle defekter/immunsvikt (SCID) i nyfødtscreeningprogrammet. Screeningmetodikken som benyttes til SCID screening vil også benyttes til screening for SMA i programmet. Metoden er også utprøvd på verifiserte prøver i Norge etter samtykke fra foreldre til barn med SMA og utprøvingen viste 100 % sensitivitet og spesifisitet. Positive tester vil verifiseres gjennom retesting og oppfølgende analyser.

Screening gjøres ved å teste for *SMN1*-delesjonen som over 95 % av pasientene er homozygote for, og deretter vurdere antall kopier av *SMN2.* Da det finnes en "vanlig" mutasjon i Norge ut over delesjonen, planlegger OUS i tillegg å undersøke dette hos nyfødte som får påvist kun én delesjon (heterozygote).

Et viktig spørsmål ved SMA-screening er å forutsi hvilken type SMA pasienten vil utvikle. Det er en klar sammenheng mellom antall *SMN2* kopier og klinisk fenotype på gruppenivå. Det anbefales å igangsette behandling hvis det er tre eller færre kopier av *SMN2.* Gruppen med flere enn 3 *SMN*2 kopier følges tett klinisk med tanke på eventuell utvikling av symptomer og mulig senere oppstart av behandling.

Nyfødtscreeningprogrammet har planlagt oppfølgingsprogram og rutiner ved utvidelse av programmet. Se vedlagt brev fra OUS med nærmere beskrivelse av dette.

Behandling

- *Det må finnes tiltak eller behandling som gir bedre effekt i tidlig stadium enn ved klinisk diagnostikk*
- *Tiltak/behandling må være etablert og godt dokumentert*
- *Tiltak/behandling skal være akseptabel for målgruppen*

Beslutningsforum godkjente februar 2018 å ta i bruk nusinersen (Spinraza®) ved SMA på gitte vilkår som i praksis er tilfredsstilt hos de fleste barn med nydiagnostisert SMA. Behandlingen gis i dag til barn under 18 år i Norge. Behandlingen er svært kostbar, men har godt dokumentert effekt. Jo tidligere behandlingen kommer i gang, jo bedre er effekten av behandlingen og prognosen. SMA skyldes tap av motornevroner grunnet mangel på SMN overlevelsesproteinet, og behandlingens mål er å hindre dette.

Effekten av behandlingen vil være bedre jo tidligere den igangsettes, og behandling bør om mulig

igangsettes før symptomdebut, da dette gir bedre effekt og prognose. SMA egner seg derfor godt for nyfødtscreening etter at effektiv behandling er blitt tilgjengelig og tatt i bruk.

Eventuelle nye legemidler eller behandlinger for SMA må vurderes gjennom Nye metoder på lik linje med andre.

Screeningprogrammet

- *Screeningprogrammet skal redusere sykdomsspesifikk dødelighet eller sykelighet av tilstanden*
- *Helsegevinstene må være større enn de negative effektene*
- *Personvern og juridiske aspekter må være ivaretatt*
- *Screeningprogrammet skal være akseptabelt fra et etisk perspektiv*
- *Informasjon om deltakelse i screeningprogrammet må være kunnskapsbasert og bidra til informerte valg*
- *Screeningprogrammet skal tilfredsstille kravene til kostnadseffektivitet*
- *Det må foreligge en plan for ledelse, kvalitetssikring og evaluering av programmet*

Gjennomføring av screening

Det er dokumentert gjennom flere studier at SMA-screening er gjennomførbart og effektivt for å avdekke tilfeller før symptomdebut og dermed kunne starte behandling tidlig for å oppnå betydelig bedret prognose. Regionsykehusene i Norge har erfaring med behandling av barn med SMA, og tilgjengelige data og erfaring også i Norge viser at tidlig diagnostikk og behandlingsstart gir en signifikant effekt og reduksjon av sykelighet hos disse pasientene.

Effekten av behandlingen er vurdert i Nye Metoder og besluttet tatt i bruk i 2018.

Når det gjelder selve *screeningtesten* innebærer ikke utvidelse av programmet noen endring når det gjelder undersøkelsesmetoden i programmet.

Helsedirektoratet mener at en utvidelse av programmet ikke innebærer noen nye *juridiske og personvernmessige* problemstillinger, sammenliknet med dagens program.

Etikk: Sett fra pasient og familie sin side vil inklusjon av SMA i nyfødtscreeningprogrammet innebære et gode. Endringen innebærer at det vil avdekkes tilfeller av SMA på et tidligere tidspunkt, før sykdomsdebut/symptomdebut. Det fører til tidligere behandlingsstart, bedret prognose og redusert sykelighet. Behandlingen er allerede tatt i bruk i Norge og er vurdert til å være sikker og effektiv. Den genetiske undersøkelsen innebærer ingen ekstra belastning for barna. Testen er validert og kvalitetssikret, og spesifisitet og sensitivitet er 100 %. Omfang av pasienter som oppdages vil anslagsvis være samme antall som i dag, men behandlingen for flertallet av disse vil igangsettes tidligere. Tidlig oppdagelse innebærer at spesialisthelsetjenestens behandlingskostnader kommer tidligere i forløpet, men på lengre sikt kan det også bety sparte kostnader fordi pasientene får bedre funksjon, økt selvstendighet og redusert behov for hjelpetiltak.

Informasjon*:* Søknaden gjelder utvidelse av programmet, og nyfødtscreeningprogrammet har utarbeidet informasjon til foreldrene om programmet. Det er viktig at informasjonen oppdateres i forbindelse med endringer i programmet.

Økonomiske konsekvenser
Eventuell inkludering av SMA i nyfødtscreeningen vil kreve marginalt med ekstra ressurser da den kan legges «oppå» dagens SCID-screening og laboratoriet ved Oslo universitetssykehus HF har alt nødvendig utstyr.

Funn av SMA medfører behov for svært kostbar behandling som også i dag gis til barn under 18 år, jfr. beslutning i Beslutningsforum i 2018. Direktoratet viser til at det i 2017 ble utført en metodevurdering av Statens legemiddelverk som grunnlag for Beslutningsforum sin behandling og beslutning om at Spinraza skulle tas i bruk i Norge til behandling av barn med SMA, på nærmere angitte kriterier.
Metodevurderingen fra Statens legemiddelverk *Nusinersen (Spinraza) ved behandling av spinal muskelatrofi SMA* fra 09.10.2017[1] inneholder vurdering av økonomiske konsekvenser ved behandlingen som i dag tilbys denne pasientgruppen.

Helse Sør-Øst RHF har stilt spørsmål om pasientgruppen vil bli større enn i dag, ved innføring av screening. Direktoratet har innhentet vurderinger fra Nevromuskulært kompetansesenter (se vedlegg). Det er vurdert at antall nye pasienter årlig ikke vil avvike vesentlig fra i dag ved en eventuell innføring av screening for SMA.

Vurderingene i søknaden og avklaringer med Nevromuskulært kompetansesenter gir et tilstrekkelig bilde av omfang av behandlinger og samlet sett anses dette å være tilstrekkelig for å vurdere økonomiske konsekvenser av den omsøkte endringen av screeningprogrammet. Det er derfor heller ikke bestilt en egen helseøkonomisk analyse av forslag om innføring av screening for SMA i nyfødtscreeningprogrammet, ettersom de økonomiske kostnadene ved selve screeningen er minimale, pasientpopulasjonen ikke vil øke i omfang, og aktuell behandling allerede gis til barn under 18 år i Norge.
Helsedirektoratet har i møte og i påfølgende brev av 03.02.2021 til Helse Sør-Øst redegjort for vurderinger og avklaringer knyttet til omfang av pasienter og økonomiske konsekvenser av innføring av screening for SMA. Helse Sør-Øst har deretter avklart med de øvrige tre RHF-ene at RHF-ene ikke har forbehold til søknad om utvidelse av screeningprogrammet. Se vedlagt brev av 03.02.2021 fra Helsedirektoratet og epost av 11.02.2021 fra Helse Sør-Øst RHF.

Prioriteringskriteriene
I vurdering av søknaden har direktoratet vurdert forslaget opp mot prioriteringskriteriene alvorlighet, nytte og ressursbruk. SMA er uten tvil en svært alvorlig sykdom med store konsekvenser for pasientene og deres familie. Tiltaket vil ha stor nytte for pasientgruppen og i et samfunnsmessige perspektiv. Ressursbruk er vurdert ift. endring av programmet, og er tidligere vurdert og avveid ifm. innføring av behandling for disse pasientene i Norge. Konklusjonen er at ressursbruken er forholdsmessig ift. gevinst og nytte i form av redusert sykelighet.

Søknad om utvidelse av Nasjonal behandlingstjeneste for screening av nyfødte og avansert laboratoriediagnostikk ved medfødte stoffskiftesykdommer

[1] https://nyemetoder.no/metoder/nusinersen-spinraza

Helse Sør-Øst RHF har søkt om en utvidelse av Nasjonal behandlingstjeneste for screening av nyfødte og avansert laboratoriediagnostikk ved medfødte stoffskiftesykdommer. Etablering eller utvidelse av en nasjonal behandlingstjeneste forutsetter at tjenestens innhold bidrar til økt kvalitet, likeverdig tilgjengelighet til utredning eller behandling og økt kostnadseffektivitet. Det er i regelverk for etablering og drift av nasjonale tjenester i spesialisthelsetjenesten forutsatt at den utredning og behandling som tjenesten utfører er å anse som faglig forsvarlig og bygger på metoder som har vitenskapelig dokumentert effekt. Det er redegjort for alle disse tre forutsetningene i foreliggende søknad og vedlagt dokumentasjon.

Søknaden gjelder utvidelse av innholdet i Nasjonal behandlingstjeneste for screening av nyfødte og avansert laboratoriediagnostikk ved medfødte stoffskiftesykdommer til å omfatte SMA. Den nasjonale behandlingstjenesten har allerede tatt i bruk screeningmetodikk som kan benyttes til også å avdekke SMA. Det fremgår av søknaden at metoden er utprøvd og anses å ha 100 % sensitivitet og spesifisitet.

Screening av nyfødte er forskriftsfestet og basert på informert samtykke. Nyfødtscreeningprogrammet er tilgjengelig for alle barn som blir født i Norge. En utvidelse av programmet innebærer at alle nyfødte kan bli testet for SMA. Det er allerede etablert et nasjonalt screeningprogram og en nasjonal behandlingstjeneste som ivaretar drift og gjennomføring av programmet: Det fremgår av søknaden at en utvidelse av screeningprogrammet til også å omfatte SMA har marginale tilleggskostnader. Utvidelsen anses derfor som kostnadseffektiv.

Søknaden om utvidelse av dagens screeningprogram er forankret i tjenestens faglige referansegruppe. 13. oktober 2020 ble søknaden om å utvide screening av nyfødte til også å omfatte SMA ble oversendt av Helse Sør-Øst RHF til fagdirektørene i Helse Vest RHF, Helse Nord RHF og Helse Midt-Norge RHF. Det fremgår i mail av 21. januar 2021 fra Helse Sør-Øst RHF at fagdirektørene har behandlet saken og støtter søknaden om utvidelse.

Under forutsetning av at screening for SMA blir tatt inn i forskriften for genetisk masseundersøkelse av nyfødte, vil Helsedirektoratet godkjenne søknaden om en utvidelse av Nasjonal behandlingstjeneste for screening av nyfødte og avansert laboratoriediagnostikk ved medfødte stoffskiftesykdommer.

Konklusjon
Helsedirektoratet anbefaler at nyfødtscreeningprogrammet utvides til å inkludere test for Spinal muskelatrofi (SMA).

Vennlig hilsen

Johan Georg Røstad Torgersen e.f.
direktør

Torunn Janbu
avdelingsdirektør

Dokumentet er godkjent elektronisk

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Vår referanse:	Deres referanse:	Dato:
19/01077-5		02.11.2020

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Søknad om å utvide tilbudet om genetiske masseundersøkelser av nyfødte i Norge til å inkludere spinal muskelatrofi (SMA)

Helse Sør-Øst RHF viser til brev fra Helsedirektoratet av 23. juni 2020 vedrørende søknad om utvidelse og endring av Nyfødtscreeningprogrammet – nyfødtscreening for spinal muskelatrofi (SMA) og sender i samarbeid med Oslo universitetssykehus HF søknad om utvidelse/endring av Nyfødtscreeningprogrammet – se vedlegg.

Om den videre prosessen:

Helsedirektoratet beskriver i sitt brev prosess for utredning og videre vurdering av søknaden. Direktoratet skriver blant annet at det i den videre vurderingen «om nødvendig vil bli innhentet ytterligere informasjon/kunnskapsgrunnlag, inkludert etiske vurderinger, helseøkonomiske og/eller kostnadsberegninger. Ved behov for oppdatert kunnskapsoppsummering eller metodevurdering utarbeider Folkehelseinstituttet dette etter bestilling fra Helsedirektoratet.» Videre skriver Helsedirektoratet: «Ved oversendelse av søknad påtar Helse Sør-Øst seg samtidig ansvar for de økonomiske-/budsjettmessige konsekvensene dersom nyfødtscreeningprogrammet endres til å omfatte SMA».

Helse Sør-Øst RHF understreker at vi ved å oversende søknaden *til videre behandling* ikke kan påta oss de økonomiske/budsjettmessige forpliktelsene før disse er utredet. Vi viser samtidig til protokoll fra Bestillerforum i Nye metoder 24. februar 2020: «Forslag om "Nasjonal behandlingstjeneste for screening av nyfødte - utvidelse av tilbudet med screening for spinal muskelatrofi (SMA)" oversendes Helsedirektoratet for videre oppfølging. Bestillerforum RHF understreker at innføring av screening kan påvirke kostnad-nyttevurderingene for kommende behandlinger og at en metodevurdering bør gjennomføres raskt.» Det er følgelig klart at metodevurdering eller tilsvarende utredning må foreligge før de regionale helseforetakene kan konkludere i denne saken. Helsedirektoratet har da også skissert en omfattende prosess for videre søknadsbehandling, og denne innebærer en generell høring.

Om søknaden:

Genetiske masseundersøkelser av nyfødte er et effektivt tilbud for rask identifisering av barn med utvalgte alvorlige, medfødte sykdommer. Nasjonal behandlingstjeneste for nyfødtscreening og avansert laboratoriediagnostikk ved Oslo universitetssykehus HF har et nasjonalt mandat for genetiske masseundersøkelser av nyfødte. Dagens tilbud omfatter testing for 25 sykdommer. Utvidet testing fra 2 tilstander (fenylketonuri og medfødt hypertyreose) til 23 tilstander ble implementert fra 1. mars 2012 og fra 1. januar 2018 ble 2 tilstander til (3-OH 3 metylglutaryl CoA lyasedefekt (HMG) og alvorlig kombinert immunsvikt (SCID) og andre alvorlige T-celle defekter) inkludert i screeningtilbudet.

Gjennomføringen av selve nyfødtscreeningen vil kreve lite ekstra ressurser da den kan legges «oppå» dagens SCID-screening og laboratoriet ved Oslo universitetssykehus HF har alt nødvendig utstyr. Funn av SMA medfører imidlertid behov for svært kostbar behandling som også gis i dag.

SMA tilfredsstiller de viktigste kriterier for nyfødtscreening:

- Det er en alvorlig sykdom
- Det finnes en effektiv behandling for de alvorligste symptomene
- Behandlingen er mer effektiv jo tidligere barna identifiseres
- Klinisk diagnostikk dvs. etter sykdomsdebut medfører forsinket identifisering av aktuelle barn og forsinket behandling
- Det finnes en tilfredsstillende test som kan avsløre sykdommen med høy spesifisitet og sensitivitet (lav falsk positiv og falsk negativ rate)
- SMA kan screenes ved multiplexing av SMN1 med TREC/SCID-metoden

Søknaden er utformet i tråd med kriterier for nasjonale screeningprogrammer og i samråd med tjenestens faglige referansegruppe. Oslo universitetssykehus opplyser at søknaden er forankret i referansegruppen for Nasjonal behandlingstjeneste for nyfødtscreening og avansert laboratoriediagnostikk den 13.12.19. Ledelsen ved Oslo universitetssykehus HF har for øvrig bekreftet ved oversendelsen at helseforetaket stiller seg bak søknaden.

Helse Sør-Øst RHFs vurdering:

Vi har forelagt søknaden for fagdirektørene i de øvrige regionale helseforetake, som støtter at søknaden oversendes Helsedirektoratet for videre utredning og behandling etter den prosessen direktoratet redegjør for i sitt brev av 23. juni 2020. Fagdirektørene i Helse Vest RHF, Helse Midt-Norge RHF og Helse Nord RHF støtter også vår vurdering om at de regionale helseforetakene ikke kan påta seg ansvaret for de økonomiske-/budsjettmessige konsekvensene før disse er utredet (metodevurdering/ kunnskapsoppsummering, etiske vurderinger, helseøkonomiske og/eller kostnadsberegninger).

Blant annet fordi en utvidelse skal vurderes opp mot ulike regelverk, som alle har sine egne prosesser (screeningprogram, behandlingstjeneste, Nye metoder) har det allerede vært en lang prosess for den nasjonale behandlingstjenesten å få søknaden fram. Helse Sør-Øst RHF oppfatter at behandlingstjenesten nå har anvendt de søknadsskjemaer og fulgt den søknadsprosessen som Helsedirektoratet har bedt om, så langt det er mulig. Ettersom søknaden gjelder en utvidelse av en eksisterende behandlingstjeneste og ikke etablering av en ny behandlingstjeneste, passer ikke søknadsskjemaet for behandlingstjenester godt. Dette er likevel utfylt etter beste evne og følger søknaden om utvidelse av screeningprogrammet som vedlegg. Helse Sør-Øst RHF vil følgelig be Helsedirektoratet starte en realitetsbehandling av søknaden, selv om det skulle avdekkes mangler i det som nå er oversendt. Skulle det være opplysninger som mangler eller ikke er oppgitt i rett skjema, skal vi bidra til å rette opp i dette parallelt med at den videre utredningen som Helsedirektoratet har skissert igangsettes.

Med vennlig hilsen

Jan Frich
viseadministrerende direktør

Siv Cathrine Høymork
avdelingsdirektør

Vedlegg: Søknad fra Oslo universitetssykehus av 23. september 2020 om å utvide tilbudet til genetiske masseundersøkelser av nyfødte i Norge til å inkludere spinal muskelatrofi (SMA)
Søknaden lagt inn i skjema anbefalt av Helsedirektoratet
Rapport ved innføring av SMA-screening i USA (13. mars 2018)

HELSE NORD | HELSE MIDT-NORGE | HELSE VEST | HELSE SØR-ØST

Søknadsskjema for nasjonale og flerregionale behandlingstjenester

Søknaden sendes elektronisk som PDF-dokument til eget helseforetak innen angitte frister

De regionale helseforetakene har etablert prosedyrer i egen region for innsending av søknader med interne frister m.m. Samlet søknad fra det regionale helseforetaket om opprettelse/endring av nasjonale tjenester med prioritering av forslagene skal sendes Helse- og omsorgsdepartementet med kopi til Helsedirektoratet innen 15. januar hvert år.

Søknadsprosessen er forankret i forskrift og HODs veileder som er utarbeidet med bakgrunn i forskrift. Veilederen er retningsgivende for korrekt utfylling av skjemaet. Mangler i utfyllingen av skjema kan føre til at søknadsbehandlingen forsinkes eller at søknaden ikke blir behandlet.

Søknader fra fagmiljøene skal gjennom en behandlings- og prioriteringsprosess i eget helseforetak før helseforetaket oversender søknaden til det regionale helseforetaket (RHF). Det er det regionale helseforetaket som avgjør hvilke søknader som sendes over til videre behandling i Helse- og omsorgsdepartementet. RHF-ene skal i felleskap samordne og prioritere søknadene ut fra nasjonale behov, før oversending til Helse- og omsorgsdepartementet (HOD). Helse- og omsorgsdepartementet nettside for nasjonale tjenester gir blant annet tilgang til forskrift og veileder for nasjonale tjenester, https://www.regjeringen.no/no/tema/helse-og-omsorg/sykehus/innsikt/nasjonale-tjenester/id614574/.

Vedlagt søknadsskjemaet følger mandat og sammensetning av referansegruppene, innledning/ veiledning for søknader om nye nasjonale behandlingstjenester, samt mal for samarbeidserklæringer og kompetansespredningsplan.

Regionale og nasjonale frister 2020

- Kontakt eget helseforetak for interne frister
- 4. november - helseforetakenes søknadsfrist til RHF
- November/desember - behandling i regionalt helseforetak
- 14. desember - behandling i Interregionalt fagdirektørmøte
- 15.01.21 - søknadsfrist til Helsedirektoratet

Forankring av ny behandlingstjeneste			
Regionalt helseforetak	HSØ		
Helseforetak	OUS		
Ansvarlig avdeling/klinikk		Avdelingsleder/ klinikkleder	Rolf D. Pettersen/Terje Rootwelt
		Faglig ansvarlig for tjenesten	Rolf D. Pettersen
Navn på tjenesten Bruk et dekkende navn på den helsehjelp det ønskes å etablere behandlings-tjenestens for.	Nasjonal behandlingstjeneste for **genetiske masseundersøkelser av nyfødte**		
Engelsk navn på tjenesten[1]	**Norwegian National Unit for Newborn Screening**		

Hva søkes det om

x **Nasjonal behandlingstjeneste**

I så fall:

x Er dette et nytt tilbud. **Utvidet tilbud i etablert nasjonal behandlingstjeneste for genetiske masseundersøkelser av nyfødte**
☐ Er dette sentralisering av aktivitet som allerede foregår andre steder, eller
☐ Fungerer det de facto som behandlingstjeneste allerede i dag?

☐ **Flerregional behandlingstjeneste**

I så fall:

☐ Er dette en eksisterende behandlingstjeneste som ønskes delt, eller
☐ Eksisterende behandling/diagnostikk som ønskes sentralisert til to steder, eller
☐ Et nytt tilbud som ønskes etablert to steder i landet. Søknader om flerregionale behandlingstjenester skal sendes fra hvert av de involverte RHF-ene. Det forutsettes at søknadene samordner beskrivelsen av hvordan behandlingstjenesten er tenkt organisering.

Hvilke regionale helseforetak er involvert:

Dersom søknaden forutsetter bruk av ny metode, skal denne ha gjennomgått en metodevurdering før det søkes opprettet ny tjeneste, jf. nasjonalt system for innføring av nye metoder i helsetjenesten.

☐ Ikke aktuelt for denne søknaden
☐ Metodevurdering er gjennomført
☐ Metodevurdering er ikke gjennomført
x Søknad om metodevurdering er sendt

Kommentarer: Søknad om metodevurdering ble sendt Bestillerforum 18. februar 2020. Følgende svar ble mottatt fra Nye metoder 3. april 2020:
Deres forslag om metode til nasjonal metodevurdering – ID2020_016 Nasjonal behandlingstjeneste for screening av nyfødte – utvidelse av tilbudet med screening for spinal muskelatrofi (SMA) – ble tatt opp i Bestillerforum RHF sitt møte 30.03.2020. Beslutningen ble som følger: «Forslag om Nasjonal behandlingstjeneste for screening av nyfødte – utvidelse av tilbudet med screening for spinal muskelatrofi (SMA)» oversendes Helsedirektoratet for videre oppfølging. Bestillerforum RHF understreker at innføring av screening kan påvirke kostnad-nytte vurderingene for kommende behandlinger og at en metodevurdering bør gjennomføres raskt.
Til deres informasjon legger jeg ved dokument fra HOD til Helsedirektoratet datert 20. mars 2020 «Styringsstruktur for nasjonale screeningprogrammer».
Vi setter dere i kopi når vi i dag oversender saken til Helsedirektoratet.

Vi fikk så brev 23. juni fra HDir som etter dialog med HOD hadde avklart hvordan prosesser med utvidelse av nyfødtscreeningen skulle foregå. Ny søknad skulle sendes til HSØ. Vi hadde møte med HSØ ved Siv Cathrine Høymork og Kirsti Tørbakken 21. august med avklaring av innhold i fornyet søknad inkl. at denne burde sendes både på dette skjema og som eget brev.

Er det tidligere søkt om nasjonal status for samme eller tilsvarende tjeneste?

☐ Ja
X Nei

Hvis ja, når var dette (årstall)?

Beskrivelse av tjenesten – formål, innhold og avgrensning

1. Hvilken eller hvilke pasientgrupper og diagnoser skal tjenesten omfatte

Søker om utvidelse av etablert nasjonal behandlingstjeneste med nyfødtscreening for spinal muskelatrofi (SMA).

2. Hvilke ICD-10 koder er aktuelle

Hvilke ICD-10 koder er aktuelle:

G12

3. Hvilken type helsehjelp dreier det seg om

x Diagnostikk alene

☐ Diagnostikk og behandling

☐ Behandling eller behandlingskombinasjoner, inkludert rehabilitering

Kommentarer:

4. Gi en beskrivelse av innholdet i tjenesten, inkl. henvisningskriterier

SMA er en autosomal recessiv sykdom som i hovedsak skyldes bi-allelisk delesjon i survival motor neuron 1 (*SMN1*) genet. Tilstanden medfører tap av alfa-motornevroner i ryggmargen med progressiv muskelatrofi og muskelsvekkelse. Av genetiske sykdommer har SMA historisk vært den vanligste årsaken til tidlig barnedød. SMA opptrer med ulik alvorlighetsgrad og klassifiseres i henhold til fenotype. SMA Type 1, tidligere omtalt som "Werdnig-Hoffmann sykdom», er den mest alvorlige. Disse barna viser symptomer på muskelsvikt allerede i løpet av de seks første levemåneder og vil aldri kunne sitte selvstendig. Ca. 60 % av tilfeller med SMA er type 1. Ca. 30 % av pasientene diagnostiseres med SMA type 2 med tegn til muskelsvakhet i de første 6-18 levemåneder. Barna klarer å sitte, men klarer aldri å gå uten hjelp. De som har senere debut og klarer å gå eller har stått/gått før 18 måneder klassifiseres som SMA type 3. Enkelte klinikere inkluderer i tillegg to ytterpunkter. SMA type 0 henviser til en tilstand som debuter i fosterlivet med alvorlig svakhet og pustevansker ved fødsel. SMA type 4 utgjør en mindre gruppe pasienter som først utvikler muskelsvakhet i voksen alder.
Over 95 % av alle SMA pasienter er homozygote for delesjon av S*MN1,* enten hele genet eller viktige deler av genet (ekson 7-8), og dette brukes til primærdiagnostikk av SMA. Alle har i tillegg et variabelt antall kopier av *SMN2* genet, som er en paralog av *SMN1*. Pga

en genvariant i *SMN2* gir dette «reservegenet» kun lave, men likevel viktige mengder av SMN proteinet ved fravær av det normale *SMN1* genet. Antallet kopier av *SMN2* korrelerer derfor med SMA alvorlighetsgrad; jo større antall kopier av *SMN2*, jo mildere fenotype. Barn med kun to eller tre kopier av *SMN2* har stor sannsynlighet til å debutere med SMA type 1 eller 2, og SMA pasienter med 4 eller flere *SMN2* kopier har lav sannsynlighet for til å debutere med SMA type 1. I tillegg indikerer nye studier at mindre enn 10 % av alle SMA pasienter vil debutere hos barn som er eldre enn 3 år, og disse vil typisk ha SMA type 3.
Dette viser at testing for *SMN1* delesjoner i kombinasjon med bestemmelse av *SMN2* kopiantall vil være en effektiv strategi for tidlig å identifisere SMA pasienter som vil ha stor nytte av tidlig oppstart av effektiv behandling. Tjenesten ønsker å screene alle nyfødte for SMA for raskest mulig diagnostikk og behandling. For ytterligere informasjon se vedlegg til søknad.

5. Hva er det totale omfanget av primærdiagnostikk, primærbehandling, komplikasjonsoppfølging og langsiktig oppfølging i den planlagte tjenesten

Tjenesten vil ha ansvar for screening og varsling av barn med SMA for videre oppfølging i klinikken. Denne oppfølgingen kan enten skje ved lokal eller regional barneavdeling eller ved Barne- og ungdomsklinikken i OUS. OUS vil være tilgjengelig for faglig dialog og kan etter forespørsel motta alle barn der det etterspørres. Oppstart av Spinrazabehandling er etter føringer fra Beslutningsforum sentralisert til OUS.

6. Hvilke deler av pasientforløpet skal inngå i tjenesten

Screening, diagnostikk og varsling for medisinsk oppfølging.

7. Hvordan skal det samarbeides om pasientforløpet før og etter den sentraliserte tjenesten

Etablert nasjonal faggruppe innen barnenevrologi som i dag ivaretar nasjonal koordinering av Spinrazabehandling vil naturlig fortsette å være et viktig nasjonalt samarbeidsorgan for oppfølging av barn etter positiv nyfødtscreening.

8. Hva omfattes ikke av tjenesten

Gi en beskrivelse av grenseoppgang mot annen virksomhet og eventuelle gråsoner som må avklares

SMA behandling inngår ikke i den nasjonale tjenesten, se over.

9. **Insidens:** Oppgi forventet pasientvolum i form av antall nyhenviste pasienter pr. år som vil bli behandlet ved behandlingstjenesten. Beskriv også grunnlaget for beregningene. Oppgi eventuelt supplerende tall (inngrep, prosedyrer m.v.).

Forventet pasientvolum: Alle nyfødt vil testes, ca 55.000 per år. Antall positive forventes å være ca 7 per år.

Grunnlag for beregningene: Basert på kliniske data fra OUS og nasjonalt samt internasjonale tall.

Eventuelt supplerende tall:

Konsekvenser av sentralisering

10. Hva er begrunnelsen for å sentralisere behandlingen

Benytte samme etablerte behandlingstjeneste som pt har mandat til genetiske undersøkelser av alle nyfødte.

11. Hvilke helsemessige gevinster i form av bedre prognose eller livskvalitet vil etablering av en nasjonal behandlingstjeneste føre til for målgruppen

Rask diagnose og behandling gir mindre sykelighet, lidelse for pasientene og samfunnsmessige kostnadsbesparelser, se vedlegg.

12. Beskriv eventuelle praktiske og sosiale konsekvenser en sentralisering av aktuell behandling har for pasienter og pårørende

Tilbudet finnes ikke i Norge i dag. Hvis det skal etableres, må dette skje som del av etablert nasjonal behandlingstjenesten som allerede har etablert logistikk, utstyr og kompetanse for å kunne utføre denne tjenesten.

13. Hvilke konsekvenser kan opprettelse av en nasjonal behandlingstjeneste ha for fagmiljø og gjenværende pasientgrupper med beslektede behov ved de sykehus som i framtiden ikke skal utøve aktuell behandling

Etablering av nyfødtscreening for SMA vil styrke og effektivisere pasientbehandlingen ved SMA og anses ikke å ville påvirke annen pasientbehandling lokalt.

14. Vil en sentralisering av eksisterende behandling være mer kostnadseffektiv enn dagens organisering av behandlingen[2]

Ja – kfr vedlegg. Raskere, bedre og mer kostnadseffektiv behandling. Kfr vedlagt søknad.

15. Er spørsmålet om sentralisering av aktuell behandling avklart med tilsvarende avdelinger i andre helseregioner

☐ Ja, se vedlagte erklæringer fra avdelings/klinikkdirektører ved aktuelle avdelinger.

X☐ Nei

Kommentarer: Søknaden er forankret i referansegruppen for Nasjonal behandlingstjeneste for screening av nyfødte og avansert laboratoriediagnostikk ved medfødte stoffskiftesykdommer. HSØ vil sende dokumentasjon på forankring i alle 4 RHF.

Kunnskapsgrunnlag, resultatmål og kompetansespredning

16. Gi en beskrivelse av tjenestens kunnskapsgrunnlag, jf. veilederens § 4.3.

For beskrivelse av kunnskapsgrunnlag henvises til vedlagte brev med utdypning og henvisninger til følgende referanseliste.

1. Performance of Expanded Newborn Screening in Norway Supported by Post-Analytical Bioinformatics Tools and Rapid Second-Tier DNA Analyses. Tangeraas T, Sæves I, Klingenberg C, Jørgensen J, Kristensen E, Gunnarsdottir G, Hansen E, Strand J, Lundman E, Ferdinandusse S, Salvador C, Woldseth B, Bliksrud Y, Sagredo C, Olsen Ø, Berge M, Trømborg A, Ziegler A, Zhang J, Sørgjerd L, Ytre-Arne M, Hogner S, Løvoll S, Kløvstad Olavsen M, Navarrete D, Gaup H, Lilje R, Zetterström R, Stray-PedersenA, Rootwelt T, Rinaldo P, Rowe A, Pettersen R. Int. J. Neonatal Screen. 2020;6(3):51.
2. Second-Tier Next Generation Sequencing Integrated in Nationwide Newborn Screening Provides Rapid Molecular Diagnostics of Severe Combined Immunodeficiency. Strand J, Aftab Gul K, Erichsen HC, Lundman E, Berge MC, Trømborg AK, Sørgjerd LK, Ytre-Arne M, Hogner S, Halsne R, Gaup HJ, Osnes LT, Kro GAB, Sorte HS, Mørkrid L, Rowe AD, Tangeraas T, Jørgensen JV, Alme C, Bjørndalen TEH, Rønnestad AE, Lang AM, Rootwelt T, Buechner J, Øverland T, Abrahamsen TG, Pettersen RD, Stray-Pedersen A. Front. Immunol. 2020;11:1417.
3. Evidence-based Review of Newborn Screening for Spinal Muscular Atrophy (SMA): Final Report (v5.2). Prepared for: MATERNAL AND CHILD HEALTH BUREAU
   By: The Evidence-based Review Group: Committee Representatives for the SMA Evidence Review. *03/13/2018* Alex R. Kemper
4. Delay in diagnosis of spinal muscular atrophy: A systematic literature review. Lin CW et al. Pediatr Neurol. 2015;53:293-300.
5. Diagnostic journey in Spinal Muscular Atrophy: Is it still an odyssey? Pera MC; Coratti G; Berti B; D'Amico A; Sframeli M; Albamonte E; de Sanctis R; Messina S; Catteruccia M; Brigati G; Antonaci L; Lucibello S; Bruno C; Sansone VA; Bertini E; Tiziano D; Pane M; Mercuri E. PLoS ONE [Electronic Resource]. 15(3):e0230677, 2020.
6. Verhaart IEC, Robertson A, Wilson IJ, Aartsma-Rus A, Cameron S, Jones CC, Cook SF, Lochmüller H. Prevalence, incidence and carrier frequency of 5q-linked spinal muscular atrophy - a literature review. Orphanet J Rare Dis. 2017;12:124
7. One Year of Newborn Screening for SMA - Results of a German Pilot Project. Vill K; Kolbel H; Schwartz O; Blaschek A; Olgemoller B; Harms E; Burggraf S; Roschinger W; Durner J; Glaser D; Nennstiel U; Wirth B; Schara U; Jensen B; Becker M; Hohenfellner K; Muller-Felber W. Journal of neuromuscular diseases. 6(4):503-515, 2019.
8. Correlation between SMA type and SNM2 copy number revisited: An analysis of 625 unrelated Spanish patients and a compilation of 2834 reported cases. Calucho M, Bernal S, Alias L, March F, Vencesla A, Rodriguez-Alvarez FJ et al. Neuromuscul Disord 2018;28:208-15.
9. Cost-Effectiveness of Nusinersen and Universal Newborn Screening for Spinal Muscular Atrophy. Ali Jalali, Erin Rothwell, Jeffrey R. Botkin, Rebecca A. Anderson, Russell J. Butterfield, Richard E. Nelson. J Pediatr 2020;x:1-7
10. PMU30 COST-EFFECTIVENESS ANALYSIS OF NEWBORN SCREENING FOR SPINAL MUSCULAR ATROPHY (SMA) IN THE UNITED STATES. Arjunji, R ; Zhou, J ; Patel, A ; Edwards, M.L ; Harvey, M ; Soverino, M ; Dabbous, O. Value in health, 2020-05, Vol.23, p.S238-S238 https://www.sciencedirect.com/science/article/pii/S1098301520309931
11. High-throughput genetic newborn screening for spinal muscular atrophy by rapid nucleic acid extraction from dried blood spots and 384-well qPCR. Czibere L et al. Eur J Hum Genet. 2020;28(1):23-30
12. Newborn screening for SMA in Southern Belgium. Boemer F et al. Neuromuscul Disord. 2019;29(5):343-349.
13. The implementation of newborn screening for spinal muscular atrophy: the Australian experience. Didu S. T. Kariyawasam, Jacqueline S. Russell, Veronica Wiley, Ian E. Alexander and Michelle A. Farrar. GENETICS in MEDICINE | Volume 22 | Number 3 | March 2020
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    The Hague: Health Council of the Netherlands, 2019; publication no. 2019/15.
    https://www.healthcouncil.nl/documents/advisory-reports/2019/07/23/neonatal-screening-for-spinal-muscular-

atrophy
15. The independent Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG). Feb. 27, 2020. https://www.iqwig.de/en/press/press-releases/spinal-muscular-atrophy-sma-newborn-screening-promises-a-benefit.12933.html
16. Nusinersen versus sham control in infantile-onset spinal muscular atrophy Finkel RS et al. N Engl J Med 2017; 377:1723-1732.
17. Nusinersen versus sham control in later-onset spinal muscular atrophy. Mercuri E et al. N Engl J Med 2018; 378:625-635.
18. Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the Phase 2 NURTURE study. De Vivo DC et al. Neuromuscul Disord 2019; 29:842-856.
19. European ad-hoc consensus statement on gene replacement therapy for spinal muscular atrophy. Janbernd Kirschner, Nina Butoianu, Nathalie Goemans, Jana Haberlova, Anna Kostera-Pruszczyk, Eugenio Mercuri, W. Ludo van der Pol, Susana Quijano-Roy, Thomas Sejersen, Eduardo F. Tizzano, Andreas Ziegler, Laurent Servais, Francesco Muntoni. European Journal of Paediatric Neurology 2020.
DOI: https://doi.org/10.1016/j.ejpn.2020.07.001
20. Newborn blood spot screening test using multiplexed real-time PCR to simultaneously screen for spinal muscular atrophy and severe combined immunodeficiency. Taylor JL et al. Clin Chem. 2015;61(2):412-9.
21. Presymptomatic diagnosis of spinal muscular atrophy through newborn screening. J Pediatrics; 2017;190 (11):124-129.e1.
22. Treatment Algorithm for Infants Diagnosed with Spinal Muscular Atrophy through Newborn Screening. Glascock J et al. J Neuromuscul Dis. 2018; 5(2):145-158.
23. Revised Recommendations for the Treatment of Infants Diagnosed with Spinal Muscular Atrophy via Newborn Screening Who Have 4 Copies of SMN2. Glascock J et al. J Neuromuscul Dis. 2020;7:97-100
24. Infants Diagnosed with Spinal Muscular Atrophy and 4 *SMN2* Copies through Newborn Screening – Opportunity or Burden? Wolfgang M¨uller-Felber, Katharina Vill, Oliver Schwartz, Dieter Gläser, Uta Nennstiel, Brunhilde Wirth, Siegfried Burggraf , Wulf Röschinger , Marc Becker, Jürgen Durner, Katja Eggermann, Christine Müller, Iris Hannibal, Bernd Olgemöller, Ulrike Schara, Astrid Blaschek and Heike Kölbel. J Neuromuscul Dis. 2020; 7(2): 109–117.
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26. Single-dose gene-replacement therapy for spinal muscular atrophy. Mendell JR et al. N Engl J Med 2017; 377:1713-1722.
27. Gene Therapy for Spinal Muscular Atrophy: Safety and Early Outcomes**.** Megan A. Waldrop, Cassandra Karingada, Mike A. Storey, Brenna Powers, Megan A. Iammarino, Natalie F. Miller, Lindsay N. Alfano, Garey Noritz, Ian Rossman, Matthew Ginsberg, Kathryn A. Mosher, Eileen Broomall, Jessica Goldstein, Nancy Bass, Linda P. Lowes, Chang-Yong Tsao, Jerry R. Mendell and Anne M. Connolly**.** Pediatrics September 2020, 146 (3) e20200729; DOI: https://doi.org/10.1542/peds.2020-0729
28. *Direct Medical Costs of Spinal Muscular Atrophy in the Catalonia Region: A Population-Based Analysis. Darba J. Clinical Drug Investigation. 202040(4):335-341*
29. https://www.sma-europe.eu/opening-a-new-horizon-for-children-born-with-sma/

17. På hvilken måte vil tjenesten gi økt kvalitet og kompetanse på området

Raskere og mer effektiv diagnostikk i tråd med fokus på pasientens helsetjeneste.

18. Hvilke resultatmål[3] skal etableres for tjenesten jf. veilederens punkt om oppgaver, § 4-4

Påvisning av alle nyfødte med SMA innen 14 arbeidsdager etter fødsel med nær 100% sensitivitet og 100% PPV.

19. Tjenesten skal sørge for veiledning, kunnskaps- og kompetansespredning til helsetjenesten, andre tjenesteytere og brukere. Dette omfatter blant annet kunnskap om henvisningskriterier, pasientforløp og innhold i tjenesten. Gjør rede for hvordan behandlingstjenestens oppgaver med kompetansespredning er tenkt ivaretatt, jf. veilederens punkt om oppgaver, § 4-4.

Tjenestens primære målgrupper: Pasienter, pårørende og helsearbeidere innen fagfeltet.

Deltagelse i fagmøter med pasientorganisasjoner og helsearbeidere.

Informasjon på tjenestens nettsider.

Info om tjenesten vil blant annet gis i tre etablerte og spesielt relevante fora:

1) Halvårlige samarbeidsmøter for alle barneavdelinger om medfødte stoffskiftesykdommer og nyfødtscreening
2) Barnenevrologisk interessegruppe (BIG) som er en aktiv undergruppe i Barnelegeforeningen med to møter per år
3) Etablert nasjonal faggruppe for Spinrazabehandling

Redegjør for hvordan kompetansespredning er tenkt ivaretatt:

Presentasjoner i fagmøter og publisering av informasjon på avdelingens nettside.

☐ Det er utarbeidet egen kompetansespredningsplan, se vedlegg.

Kompetansespredningsplan vil bli lagt inn i oppdatert versjon av dagens plan.

20. Oppgi inntil 10 vitenskapelige publikasjoner de siste 5 år som har utgått fra personer i det fagmiljøet som søker, og som er relevante for den tjenesten som søkes. Listen bør inkludere publikasjonens PubMed-nummer.

Performance of Expanded Newborn Screening in Norway Supported by Post-Analytical Bioinformatics Tools and Rapid Second-Tier DNA Analyses.
Tangeraas T, Sæves I, Klingenberg C, Jørgensen J, Kristensen E, Gunnarsdottir G, Hansen E, Strand J, Lundman E, Ferdinandusse S, Salvador C, Woldseth B, Bliksrud Y, Sagredo C, Olsen Ø, Berge M, Trømborg A, Ziegler A, Zhang J, Sørgjerd L, Ytre-Arne M, Hogner S, Løvoll S, Kløvstad Olavsen M, Navarrete D, Gaup H, Lilje R, Zetterström R, Stray-PedersenA, Rootwelt T, Rinaldo P, Rowe A, Pettersen R. Int. J. Neonatal Screen. 2020, 6(3), 51.

Second-Tier Next Generation Sequencing Integrated in Nationwide Newborn Screening Provides Rapid Molecular Diagnostics of Severe Combined Immunodeficiency.
Strand J, Aftab Gul K, Erichsen HC, Lundman E, Berge MC, Trømborg AK, Sørgjerd LK, Ytre-Arne M, Hogner S, Halsne R, Gaup HJ, Osnes LT, Kro GAB, Sorte HS, Mørkrid L, Rowe AD, Tangeraas T, Jørgensen JV, Alme C, Bjørndalen TEH, Rønnestad AE, Lang AM, Rootwelt T, Buechner J, Øverland T, Abrahamsen TG, Pettersen RD, Stray-Pedersen A.
Front. Immunol. 2020;11:1417.

Next-generation sequencing of newborn screening genes: The accuracy of short-read mapping.
Trier C, Fournous G, Strand JM, Stray-Pedersen A, Pettersen RD, Rowe AD.
npj Genomic Medicine. 2020. In press.

21. Er det etablert nasjonale/flerregionale forskningsnettverk på området. Gi i så fall en beskrivelse av hvilke miljø som inngår i forskningsnettverket.

Etablert nasjonal faggruppe for Spinrazabehandling diskuterer aktuelle forskningsprosjekter.

Internasjonalt samarbeid

22. Vil behandlingstjenesten samarbeide med utenlandske institusjoner. Gi i så fall en beskrivelse av hvilke institusjoner/miljø som inngår i samarbeidet.

Mange land har pågående prosesser for å inkludere SMA i sitt nyfødtscreeningprogram. Vi samarbeider særlig med våre søstertjenester i Sverige og Danmark.

23. Er fagmiljøet med i internasjonale forskningsnettverk. Gi i så fall en beskrivelse av hvilke miljø som inngår i nettverket.

Vi er med i ERN (European reference network) for metabolske sykdommer (hvor nyfødtscreening er tema) og har søkt om medlemskap i EURO-NMD (nevromuskulære sykdommer) hvor SMA inngår.

Fagmiljø og ressurstilgang

24. Gi en beskrivelse av miljøets kompetanse, inkl. hvilke typer nøkkelpersonell tjenesten er avhengig av

Avdelingen har ledende tverrfaglig kompetanse innen nyfødtscreening, bioinformatikk, genetikk, medisinsk oppfølging og var først i Europa med nasjonalt tilbud innen screening for SCID og andre alvorlige T-celle defekter.

For mer dokumentasjon av aktivitet og kompetanse henvises til tjenestens årlige rapporter https://forskningsprosjekter.ihelse.net/senter/rapport/L-OUS-16/2019

25. Gjør spesifikt greie for hvordan kompetansen er tenkt vedlikeholdt i årene framover

Som en integrert del av mandat innen genetiske masseundersøkelser av nyfødte.

26. I veilederen forutsettes det at minst tre fagpersoner kan ivareta behandlingstilbudet i en nasjonal behandlingstjeneste. Oppgi minst tre personer som skal ivareta behandlingen (navn, tittel, fagområde)

Dette vil inngå som en integrert del av nyfødtscreeningen med hele nyfødtscreeningmiljøet (24,9 årsverk pt) som ansvarlige. OUS barnenevrologisk avdeling vil være nær samarbeidspartner for diagnostikk og oppfølging. Vi har således et meget robust fagmiljø som vil kunne ivareta dette oppdraget.

27. Tjenestens faglige referansegruppe, jf. veilederen kapittel III og vedlagte kjernemandat
Nasjonale tjenester skal opprette referansegruppe med ett medlem fra hver region, en representant for tjenesten og brukerrepresentasjon der dette er hensiktsmessig. Deltakere fra andre aktører kan vurderes. Leder av tjenesten skal oppnevnes blant RHF-representanter utenfor den regionen tjenesten er hjemmehørende. Referansegruppen har spesifikke oppgaver knyttet til oppfølging av tjenesten, se veileder og kjernemandat, men er ikke en styringsgruppe.

Er det spesielle momenter som må vektlegges ved sammensetning av gruppen:

Dagens etablerte referansegruppe søkes videreført.

28. Hvilke ressurser, inkludert infrastruktur, avsettes for den nasjonale behandlingstjenesten?
(eksempelvis antall og type stilling pr avdeling/enhet som er eller vil bli involvert i tjenesten, driftsmidler, utstyr, areal og annet)

Avdelingen har 24,9 årsverk og all nødvendig kompetanse og utstyr til å kunne starte SMA screening.

29. Gjør rede for utfordringer knyttet til ressurstilgang. Dette kan for eksempel være utfordringer knyttet til DRG/ISF-finansiering av pasientgruppen(e), eller forhold knyttet til å ivareta kompetansetjenesteoppgavene som ligger inne som del av det å påta seg en nasjonal behandlingstjeneste.

Se over. Det er ingen utfordringer med ressurstilgang for gjennomføring av selve screeningen. Etterfølgende behandling er svært kostbart, men det gis allerede i dag i praksis til alle barn, bare med forsinket oppstart. Etablering av nyfødtscreening vil således øke effekten av behandling som allerede gis i dag og heller redusere samlede kostnader (mindre behov for øvrig helsehjelp med bedre funksjon), kfr vedlagte brev.

30. Hvordan er utfordringene tenkt løst? Det må komme klart fram om det ligger ressursmessige forutsetninger fra HF-et for å påta seg oppgaven. Dette er ett av punktene som RHF-et må ta konkret stilling til før (eventuell) videresending av søknaden for videre behandling.

31. Finansiering av tjenesten er avklart med eget helseforetak

☒ Ja

☐ Under avklaring

☐ Nei

Kommentarer: Finansieres av basisbevilgninger og takst per screeningprøve til de ulike HF. Selve SMA screeningen vil gi en marginal kostnadsbelastning. Kfr vedlagte søknad.

Andre momenter

32. Er det andre momenter som bør trekkes fram, som det ikke er spurt om ellers i skjemaet

Svært dyr behandling tilbys allerede i dag i praksis til alle barn med SMA etter klinisk diagnose. Det er viktig å komme i gang raskest mulig slik at effekten av denne kostbare behandlingen optimaliseres.

Vedlegg

☐ Dokumentasjon som viser at spørsmålet om etablering av en nasjonal behandlingstjeneste er diskutert med ledelsen for tilsvarende fagmiljø i alle helseregioner og om det er enighet om behovet for en slik tjeneste, jf. vedlagte mal for samarbeidserklæringer

☐ Gjennomført metodevurdering (dersom dette er gjennomført på søknadstidspunktet)

☐ Plan for kompetansespredning og oppbygging av kompetanse til andre deler av helsetjenesten (dersom dette er utarbeidet på søknadstidspunktet).

[1] Se Veilederen under vedlegg for mer informasjon om utforming av engelske navn på tjenesten.

[2] Potensialet for helsemessig tilleggsgevinst og kostnadseffektivitet ved sentralisert behandling bør så langt mulig være dokumentert. Forhold som (antatt) antall pasienter, tilgang til nødvendig infrastruktur, og helhetlige pasientforløp utover egen helseregion bør kunne dokumenteres og legges ved søknadene. Det legges vekt på at de nevnte opplysningene er dokumentert, for eksempel i form av vitenskapelige artikler, kunnskapsoppsummeringer, medisinske metodevurderinger, kost-nytte vurderinger, ekspertuttalelser, kartleggingsundersøkelser, rapporter, og lignende (jf. vedlegg 5 - Innhold og dokumentasjon i søknader om nasjonale tjenester). Veilederen omtaler også effektivitet som nasjonale helhetlige kvalitetshensyn, som skal sikre rasjonell ressursutnyttelse på nasjonalt nivå, og bedre kostnadseffektivitet i nasjonal sammenheng.

[3] Resultatmål skal ta utgangspunkt i det nasjonale oppdraget, og skal gi informasjon om hva som ønskes oppnådd ved etablering av tjenesten, hva som planlegges gjort og hvorfor, samt hvordan dette skal måles. I veilederens side 12 og 13 er det listet opp eksempler på hva som kan inngå i resultatmål.

Oslo universitetssykehus

OUS ved
Adm Dir Bjørn Atle Bjørnbeth
Fagdirektør medisin Hilde Myhren
Ansvarlig for nasjonale tjenester i OUS Marianne Torbjørnsen

Nyfødtscreeningen
Barne- og ungdomsklinikken

Vår ref.:	Deres ref.:	Saksbeh.:	Dato:
			21.09.2020

Søknad om å utvide tilbudet om genetiske masseundersøkelser av nyfødte i Norge til å inkludere spinal muskelatrofi (SMA)

Nasjonal behandlingstjeneste for screening av nyfødte er organisatorisk forankret i Barne- og ungdomsklinikken i OUS og har nasjonalt mandat for genetiske masseundersøkelser av nyfødte. Tjenesten er regulert av Forskrift om endringer i forskrift 29. juni 2007 nr. 742 om genetisk masseundersøkelse https://lovdata.no/dokument/LTI/forskrift/2017-10-13-1614. Formålet med forskriften er å legge til rette for en faglig forsvarlig gjennomføring av genetisk masseundersøkelse av nyfødte for alvorlige, medfødte sykdommer. Dagens tilbud omfatter testing for 25 sykdommer. Utvidet testing fra 2 tilstander (Fenylketonuri og medfødt hypotyreose) til 23 tilstander ble implementert fra 1. mars 2012 (1). Fra 1. januar 2018 ble også 3-OH 3-metylglutaryl CoA lyasedefekt (HMG) og alvorlig kombinert immunsvikt (SCID) og andre alvorlige T-celle defekter inkludert i screeningtilbudet (2).
Genetiske masseundersøkelser av nyfødte er et effektivt tilbud for rask identifisering barn med utvalgte alvorlige, medfødte sykdommer. Tidlig identifisering er viktig for igangsetting av behandling før barn blir skadelidende. Dette bidrar til å nå et av målene i FNs erklæring fra 2015 "Transforming our World: The 2030 Agenda for Sustainable Development" som Norge var med å vedta, nemlig Delmål 3.2 «*Innen 2030 få slutt på dødsfall som kan forhindres blant nyfødte og barn under fem år.*»

Nyfødtscreening er basert på informert samtykke (ikke skriftlig), og det legges betydelig innsats i informasjon til foreldre, fagpersoner og allmennheten. Tjenesten har egen nettside med detaljert informasjon om formål, sykdomsbeskrivelser, behandling av de ulike tilstander og rutiner *www.oslo-universitetssykehus.no/nyfodtscreeningen*. Nettsiden har også informasjonsvideo om tilbudet.
Det er nær 100 % oppslutning om screeningtilbudet, og i perioden 2012 til 2018 er det kun 107 kjente reservasjoner mot testing.
Behandlingstjenestens årsrapporter og referansegruppens faglige vurderinger er tilgjengelig på https://forskningsprosjekter.ihelse.net/senter/rapport/L-OUS-16/2018.

Beskrivelse av tilstand i henhold til screeningkriterier

- *Tilstanden skal være et viktig helseproblem*
- *Tilstandens naturlige forløp skal være tilstrekkelig kjent*
- *Tilstanden skal ha en symptomfri fase som kan detekteres*

Spinal muskelatrofi (SMA)
SMA er en autosomal recessiv sykdom som i hovedsak skyldes bi-allelisk delesjon av survival motor neuron 1 (*SMN1*) genet (3,4,5). Tilstanden medfører tap av alfa-motornevroner i ryggmargen med progressiv muskelatrofi og muskelsvekkelse. Av genetiske sykdommer har SMA historisk vært den vanligste årsaken til tidlig barnedød. SMA opptrer med ulik alvorlighetsgrad og klassifiseres i henhold til fenotype. Forekomst av SMA er ca 1: 8 000 i nordeuropeisk befolkning (6), men angis generelt til 1:10.000. De fleste som blir født med SMA har de alvorlige formene SMA type 1-2. Det har i gjennomsnitt vært diagnostisert 7 nye SMA-pasienter per år de siste årene i Norge (med 55.000 fødsler årlig).

SMA type 1, tidligere omtalt som "Werdnig-Hoffmann sykdom», er den mest alvorlige formen for SMA og utgjør ca 50-60 % av alle nye tilfeller med SMA. Barna med SMA type 1 viser symptomer på muskelsvikt allerede i løpet av de seks første levemåneder og vil aldri kunne sitte selvstendig. Tidligere var dødeligheten 95 % innen to år ved SMA type 1.
SMA type 2 utgjør ca 20-30 % av alle tilfeller med SMA. Disse barna diagnostiseres med tegn på muskelsvakhet i alderen 6-18 levemåneder. Barna klarer å sitte, men klarer aldri å gå uten hjelp. SMA type 2 medfører også tap av ferdigheter og forkortet livslengde.
SMA type 3 utgjør en mindre gruppe av alle nye tilfeller med SMA. Barn med SMA type 3 har symptomdebut etter 18 måneders alder, og barna har klart å gå eller å ha stått . SMA type 3 er oftest også en alvorlig nevrologisk sykdom.
Enkelte klinikere inkluderer i tillegg to ytterpunkter. SMA type 0 henviser til en sjelden tilstand som debuter i fosterlivet med alvorlig svakhet og pustevansker ved fødsel. SMA type 4 utgjør en mindre gruppe pasienter som først utvikler muskelsvakhet i voksen alder.

Over 95 % av alle SMA-pasienter er homozygote for delesjon av S*MN1,* enten hele genet eller viktige deler av genet (ekson 7-8), og dette brukes til primærdiagnostikk av SMA. Alle har i tillegg et variabelt antall kopier av *SMN2* genet, som er en paralog av *SMN1*. Pga en genvariant i *SMN2* gir dette «reservegenet» kun lave, men likevel viktige mengder av SMN proteinet ved fravær av det normale *SMN1* genet. Antallet kopier av *SMN2* korrelerer derfor med SMA alvorlighetsgrad; jo større antall kopier av *SMN2*, jo mildere fenotype. Barn med kun to eller tre kopier av *SMN2* har stor sannsynlighet til å debutere med SMA type 1 eller 2, og SMA pasienter med 4 eller flere *SMN2* kopier har lav sannsynlighet for å debutere med SMA type 1. Blant våre egne norske pasienter har kun en av 67 debutert etter 3 år, mens man internasjonalt sier at 3 år er gjennomsnittlig debutalder ved type 3 (4,5).

De fleste SMA-pasienter både i Norge og i utenlandske studier har 2 eller 3 kopier av *SMN2*, noen har 4 kopier og kun svært få (0,7 %) har flere enn 4 (7). Tidligere studier har angitt ca 15 % med 4 kopier av *SMN2* (8), mens en fersk tysk screeningstudie fant 38% (7). En mulig høyere andel pasienter med 4 kopier av SMN2 ved screening enn ved klinisk diagnose er et viktig punkt som diskuteres videre under, men samlet sett viser dette at testing for *SMN1* delesjoner i kombinasjon med bestemmelse av *SMN2* kopiantall vil være en effektiv strategi

for tidlig å identifisere SMA pasienter som vil ha stor nytte av tidlig oppstart av effektiv behandling.

Beskrivelse av tilstand i henhold til screeningkriterier

- *Det må finnes en sikker, presis og validert test*
- *Kriterier og prosedyrer for videre oppfølging av testpositive må være definert*
- *Testmetoden skal være akseptabel for målgruppen*

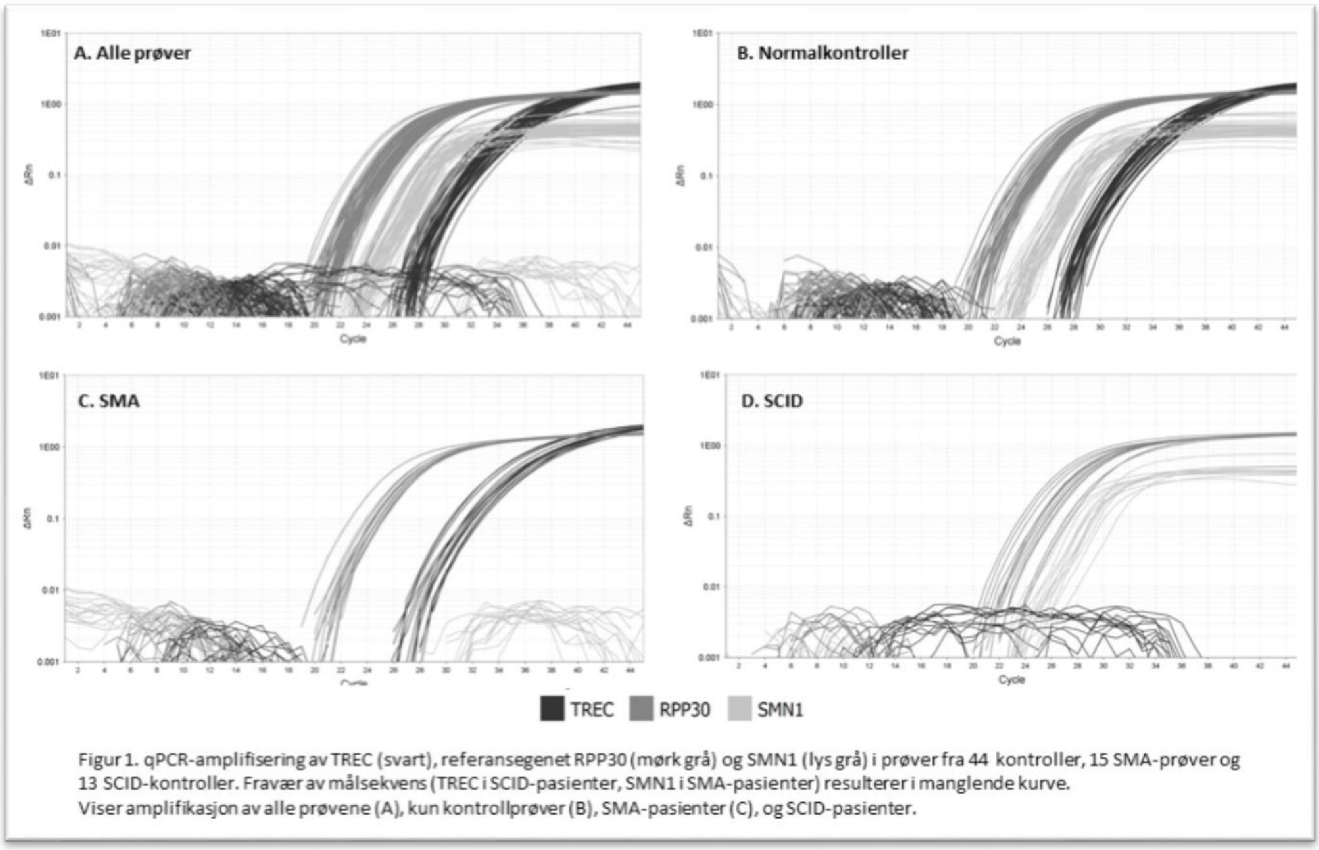
Nyfødtscreening for SMA
I USA anbefaler man per i dag nyfødtscreening for minst 34 tilstander; http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/index.html. SMA har vært anbefalt inkludert i nyfødtscreeningen i USA siden juli 2018, se vedlegg (ref 3) for deres vurderingsrapport fra mars 2018. Erfaringene fra USA er positive (9,10). Flere land i Europa har igangsatt pilotprogrammer inkl. Tyskland (7,11), Belgia (12) og Australia (13) eller planlegger innføring (Nederland (14), Sverige og Danmark), da det er bred oppfatning om at SMA egner seg spesielt godt for nyfødtscreening nå som effektive behandlinger finnes og det er bred enighet om at jo tidligere behandling igangsettes, jo bedre effekt (15, 16, 17, 18, 19).
Screening gjøres ved å teste for *SMN1*-delesjonen som over 95 % av pasientene er homozygote for, og deretter vurdere antall kopier av *SMN2* (3, 11,12,13,14, 20,21). Da det finnes en «vanlig» mutasjon i Norge ut over delesjonen, planlegger vi i tillegg å undersøke nyfødte med kun én påvist delesjon for dette (se under).

Et viktig spørsmål ved SMA-screening er å forutsi hvilken type SMA pasienten vil utvikle. Det er en klar sammenheng mellom antall *SMN2* kopier og klinisk fenotype på gruppenivå (se over). Både amerikanske (22) og europeiske (19) retningslinjer har anbefalt å igangsette behandling hvis det er 3 eller færre kopier av *SMN2* hvilket tilsier høy sannsynlighet for å utvikle SMA 1 eller SMA 2. Den (antatt) mindre gruppen med flere enn 3 *SMN*2 kopier følges tett klinisk med tanke på evt. utvikling av symptomer og da evt. senere oppstart av behandling. Annen behandling (inkl. per os medisin) som er under utvikling, kan bli aktuelt for denne pasientgruppen. USA har nå i 2020 endret sine anbefalinger (23) til at også nyfødte med 4 kopier av *SMN2* bør starte behandling. Europeiske anbefalinger (19) anbefaler fortsatt oppstart ved 3 eller færre kopier, og vi vil legge dette til grunn, men følge dette tett fremover. Det er foreløpig usikkert hvor mange nyfødte med 4 (evt en sjelden gang flere) *SMN2* kopier som vil utvikle symptomer i småbarnsalder og da uansett vil trenge behandling. Tidligere har man anslått at kun ca. 15 % har 4 kopier av *SMN2*, men i den tyske pilotscreeningen (7) hadde hele 38 % av nyfødte med SMA 4 kopier av *SMN2*. Hvis dette er tilfelle også i Norge, vil vi finne et par nyfødte hvert år som foreløpig ikke skal behandles, men som må følges klinisk for evt senere oppstart av behandling. Dette utgjør en etisk utfordring («patients in waiting»)(24), men så lenge det gis god informasjon, og man har et etablert oppfølgingsopplegg med trygghet for at det finnes effektiv behandling hvis/når symptomer oppstår, oppfattes det som at fordelen med tidlig behandling oppveier denne ulempen (14). Det er jo også hos denne pasientgruppen med senere og langsommere debut at den diagnostiske forsinkelsen er størst; dvs ved tett oppfølging vil disse barna få en klart tidligere diagnose og tjene på en tidligere oppstart av behandling de også. Hvorvidt det er noen få pasienter som aldri ville fått symptomer og da kun får en ulempe ved screening, er ikke avklart.

Norge har som første land i Europa implementert screening for alvorlig T-celle defekter/immunsvikt (SCID) (2). Testen baseres på en PCR analyse med kvantitering av antall TREC kopier i screeningprøven. Dette gir et unikt grunnlag for å innføre SMA testing ved å multiplekse den etablerte TREC metoden med kvantitering av *SMN1* ekson 7 og påvisning av delesjoner (25). Ved positivt funn brukes digital droplet PCR til bestemmelse av antall *SMN2* kopier. Ettersom screeningmetodikken som benyttes for SMA allerede er etablert gjennom SCID screening, har Norge muligheten til å bli det første eller et av de første landene i Europa som kan gi tilbud om nasjonal SMA-screening og derved også bli internasjonalt ledende i behandlingen av SMA.

Praktisk gjennomføring av SMA-screening

SMA-screening gjøres i samme oppsett som dagens SCID-screening (20,25). SMA kan detekteres i blod fra nyfødte med en enkel test utviklet og validert ved Center for Disease Control and Prevention i USA (20,25). Testen benyttes allerede til SMA-screening i en rekke amerikanske delstater. Teknologien som benyttes er en kvantitativ PCR som måler antall kopier av exon 7 av *SMN1,* genet som er defekt i SMA. Metodene er vel kjente og etablert i mange laboratorier i USA og Europa. Vi er godt kjent med de aktuelle teknikkene.
Vi har fått skriftlig samtykke fra foreldre til barn med kjent SMA til å bruke lagrede nyfødtscreeningprøver for å verifisere at metodene fungerer. Denne utprøvingen med 15 SMA-pasienter og 200 kontroller har vist 100 % sensitivitet og spesifisitet. Vi har også bekreftet i laboratoriet at positive SCID-prøver vil detekteres som de skal, selv om analysen multiplexes med SMA-testing (Figur 1).



Figur 1. qPCR-amplifisering av TREC (svart), referansegenet RPP30 (mørk grå) og SMN1 (lys grå) i prøver fra 44 kontroller, 15 SMA-prøver og 13 SCID-kontroller. Fravær av målsekvens (TREC i SCID-pasienter, SMN1 i SMA-pasienter) resulterer i manglende kurve.
Viser amplifikasjon av alle prøvene (A), kun kontrollprøver (B), SMA-pasienter (C), og SCID-pasienter.

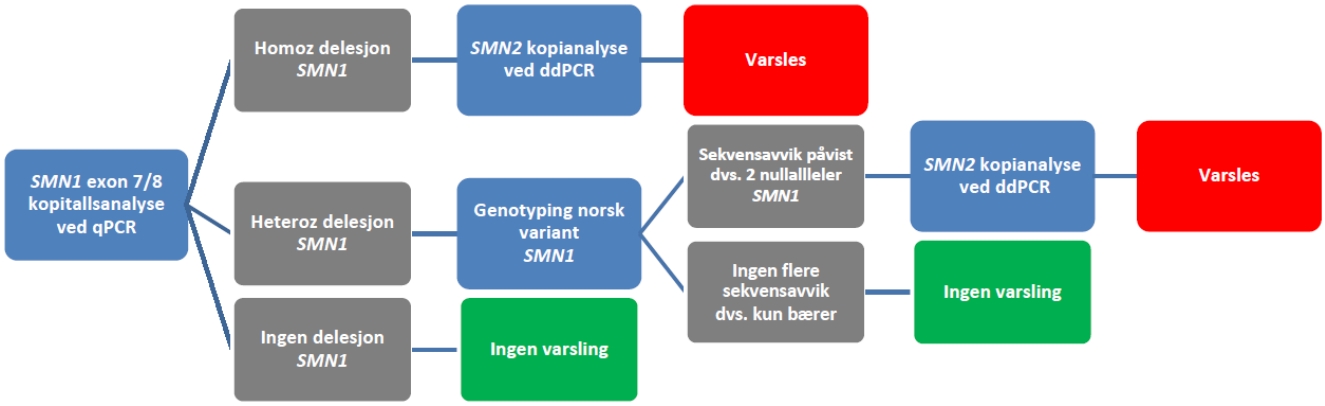
Positive funn vil alltid bekreftes med retesting og oppfølgende analyser før en eventuell varsling. Den oppfølgende analysen er digital droplet PCR (ddPCR), som nøyaktig kvantifiserer antall kopier av *SMN1* og *SMN2*. Metoden er testet ut ved Nyfødtscreeningen, og viser riktig resultat for alle SMA-pasienter med kjent genotype med bruk av DNA ekstrahert fra filterkort (tabell 1). Vi har også testet at vi ved testen identifiserer bærere på korrekt måte.

Tabell 1. Antall SMN1 og SMN2-kopier analysert med ddPCR i norske pasienter med SMA.

Prøve	SMN1-kopier	SMN2-kopier
Pasient 1	0	3
Pasient 2	0	3
Pasient 3	0	3
Pasient 4	0	3
Pasient 5	0	2
Pasient 6	0	2
Pasient 7	0	3
Pasient 8	0	3
Pasient 9	0	2
Pasient 10	0	2
Pasient 11	0	3
Pasient 12	0	3
Pasient 13	0	4
Pasient 14	0	2
Pasient 15	0	2

Antall kopier *SMN2* er relevant for videre oppfølging og behandling av pasienten (se over), og er en støtte i videre utredning. Positive funn regnes som prøver med 0 kopier *SMN1*. I disse tilfellene vil Nyfødtscreeningens leger kontakte foreldrene, og barnet kalles inn til videre undersøkelser ved Oslo universitetssykehus, Rikshospitalet eller eget lokal-/regionssykehus i samarbeid med OUS. Screeningalgoritmen er presentert i figur 2. Funnet fra Nyfødtscreeningen vil etter varsling bekreftes i annet diagnostisk laboratorium.

Ca. 5 % SMA-pasienter er ikke homozygote for en delesjon i *SMN1* genet, men har i tillegg til delesjon av *SMN1* på det ene kromosomet en annen type genfeil på det andre kromosomet. Dersom det ved qPCR påvises kun én delesjon i *SMN1*, utføres genotyping mhp deteksjon av den norske varianten NM_000344.3(SMN1): c.93_96dup, p.(Ile33*). Hvis det så påvises et sekvensavvik i *SMN1* dvs at barnet har to nullalleller av *SMN1*, utføres kvantitering av antall *SMN2* kopier ved ddPCR før varsling. Screening for SMA vil benytte seg av samme prøvemateriale som SCID-screeningen, dvs DNA ekstrahert fra en enkelt filterkortbit på 3,2 mm. Det kreves ikke mer prøvemateriale, og det vil ikke være noen endring i prøvetakning eller prøveforsendelse på barselavdelingene.



Figur 2. Algoritme for SMA-screening.
Ved Nyfødtscreeningen ekstraheres DNA fra barnets blodprøve på filterkort. DNA testes med kvantitativ PCR (qPCR) mhp. delesjon av *SMN1* for SMA-screening sammen med TREC analysen i SCID-screeningen.
Dersom det påvises to delesjoner i *SMN1*, utføres digital droplet PCR (ddPCR) mhp. kvantitering av antall *SMN2* kopier, samtidig som svaret meldes ut som patologisk. Dersom det ved qPCR påvises kun én delesjon i *SMN1*, utføres genotyping mhp. den norske varianten NM_000344.3(SMN1):c.93_96dup, p.(Ile33*). Hvis det påvises et sekvensavvik i *SMN1* dvs. at barnet har to nullalleller av *SMN1*, utføres kvantitering av antall *SMN2* kopier ved ddPCR, samtidig som svaret meldes ut som patologisk.
Forklaring/forkortelser i figuren over: qPCR:kvantitativ PCR. ddPCR: digital droplet PCR. genotyping *SMN1*: fragmentanalyse eller sekvensering mhp. deteksjon av den norske genvarianten.

Nyfødtscreeningen flyttet januar 2020 til et nytt og større laboratorium hvor alt er lagt til rette for denne og senere utvidelser av nyfødtscreeningprogrammet. Fra vår side er det mulig og ønskelig med oppstart med SMA-screening januar 2021.
Kostnadene ved innføring av SMA-screening vil primært være relatert til ca. 0,3 mill NOK årlig til reagenser samt overlege i 50 % stilling for medisinsk validering og klinisk oppfølging.

Beskrivelse av behandling i henhold til screeningkriterier

- ***Det må finnes tiltak eller behandling som gir bedre effekt i tidlig stadium enn ved klinisk diagnostikk***
- ***Tiltak/behandling må være etablert og godt dokumentert***
- ***Tiltak/behandling skal være akseptabel for målgruppen***

Behandling av SMA

Beslutningsforum godkjente februar 2018 å ta i bruk nusinersen (Spinraza®) ved SMA på gitte vilkår som i praksis er tilfredsstilt hos de fleste barn med nydiagnostisert SMA. Dette er antisense oligonukleotid basert «genterapi» som øker SMN proteinnivåene ved å endre avlesningen av *SMN2* genet. Behandlingen er svært kostbar, men har godt dokumentert effekt i litteratur (15, 16, 17,18) og etter vår egen erfaring (internt kvalitetsregister).
All internasjonal og nasjonal erfaring tilsier at jo tidligere behandlingen kommer i gang, jo bedre er effekten av behandlingen og prognosen (15, 16, 17, 18). SMA skyldes tap av motornevroner grunnet mangel på SMN overlevelsesproteinet, og behandlingens mål er å hindre nettopp dette. Tidlig økning av overlevelsesproteinet reduserer nevrontap.

Engangsbehandling med intravenøs adeno-assosiert virus (AAV)-basert genterapi for SMA er også godkjent og tatt i bruk hos spedbarn i USA. Den innledende studien publisert i NEJM var svært lovende (26), og resultatene opprettholdes i oppfølgingsstudier (27). USA godkjente medikamentet onasemnogene abeparvovec-xioi (Zolgensma®) i mai 2019, og EMA i mai 2020. Medikamentet er til metodevurdering i Norge. For denne behandlingen ser det foreløpig ut til å være enda viktigere med tidlig diagnose (= nyfødtscreening).

Beskrivelse av screeningprogrammet i henhold til screeningkriterier

- ***Screeningprogrammet skal redusere sykdomsspesifikk dødelighet eller sykelighet av tilstanden***
- ***Helsegevinstene må være større enn de negative effektene***
- ***Personvern og juridiske aspekter må være ivaretatt***
- ***Screeningprogrammet skal være akseptabelt fra et etisk perspektiv***
- ***Informasjon om deltakelse i screeningprogrammet må være kunnskapsbasert og bidra til informerte valg***
- ***Screeningprogrammet skal tilfredsstille kravene til kostnadseffektivitet***
- ***Det må foreligge en plan for ledelse, kvalitetssikring og evaluering av programmet***

Tilgjengelig dokumentasjon fra USA, Tyskland, Belgia og Australia (7,9,10, 11, 12, 13) viser at SMA-screening er gjennomførbart og effektivt og viktig for å gi pasienter med SMA optimal behandling. Barne- og ungdomsklinikken ved OUS har stor erfaring med behandling av barn med SMA, og alle tilgjengelige data og egen erfaring (internt kvalitetsregister) viser at rask diagnostikk og behandlingsstart vil redusere sykelighet hos pasientene.
Krav til kostnadseffektivitet ved omsøkt utvidelse er et viktig punkt.
Gjennomføringen av selve nyfødtscreeningen krever lite ekstra ressurser da den kan legges «oppå» dagens SCID screening, og vårt laboratorium har alt nødvendig utstyr.
Funn av SMA medfører imidlertid behov for svært kostbar behandling (Spinraza evt senere Zolgensma og Risdiplam og andre nye medisiner). Imidlertid gis kostbar Spinraza-behandling allerede i dag i praksis til alle barn med nyoppdaget SMA. Så lenge man ikke starter behandling på den mindre gruppen nyfødte med flere enn tre kopier av *SMN2,* vil ikke nyfødtscreening føre til at flere settes på Spinraza-behandling enn ved klinisk diagnostikk. Oppstart av behandling vil dog skje noen måneder til noen få år tidligere ved screening. Det vil kunne bety ett til noen få år ekstra med «vedlikeholdsbehandlig» med Spinraza (mens dette vil være uten betydning for engangsbehandling med Zolgensma). Det er ikke overdiagnostikk ved screening, kfr tysk screeningerfaring (7) med tilnærmet lik insidens ved screening som forutgående klinisk diagnostikk.
Et forbehold er hvis man senere endrer indikasjonen for behandling til også å inkludere nyfødte med 4 kopier av *SMN2*. Da vil antallet som behandles fra nyfødtperioden kunne øke litt, men fortsatt begrenset. Av de 66 norske pasientene med symptomdebut før 3 års alder hadde 4 pasienter flere enn 3 kopier, og alle disse ville kvalifisert for Spinraza-behandling per i dag.
All publisert dokumentasjon og egen erfaring med Spinraza tilsier at forventet effekt av denne kostbare behandling vil være betydelig større med igangsetting av behandling i nyfødtperioden. Dette øker «effekt/kostnads ratioen» betydelig. Dessuten forventes hjelpebehovet grunnet nevrologisk skade/funksjonssvikt å reduseres betydelig hos pasientene med følgende reduserte kostnader til annen behandling og ikke minst oppfølging lokalt i kommunene som resultat. Helt generelt er behandling SMA-pasienter med funksjonssvikt betydelig kostnadskrevende (28). Mindre nevrologisk skade gir også mindre lidelse og funksjonshemming for de barna dette gjelder, og mulighet for deltagelse i vanlige

aktiviteter av essensiell betydning for barns psykiske og somatiske helse. Samlet sett tilsier dette en betydelig kostnadseffektivitet ved innføring av nyfødtscreening for SMA med marginalt økte medikamentkostnader, reduserte kostnader til oppfølging av pasienter og betydelig bedret klinisk effekt av behandlingen.
Europeiske pasientforeningene er sterke tilhengere av innføring av nyfødtscreening (29).

Nyfødtscreeningen har nasjonalt mandat for genetiske masseundersøkelser av nyfødte, og som for de 25 andre tilstandene i tilbudet vil også SMA-screening være forskriftsfestet og underlagt krav til informert samtykke. Ledelse, kvalitetssikring og evaluering av programmet vil bli ivaretatt innenfor de generelle forskrifter, krav til ledere i OUS, oppfølging av nasjonal referansegruppe og årlige rapportert til Helsedirektoratet. Alle nasjonale tjenester blir også normalt evaluert hvert 5. år.
All oppstart av Spinraza-behandling i Norge har etter føringer fra Beslutningsforum skjedd ved OUS. Alle barna er inkludert i et kvalitetsregister hvor oppfølgingsdata regelmessig registreres for å følge effekten av behandlingen. Dette vil videreføres ved evt inkludering av SMA i nyfødtscreeningen slik at effekten av denne utvidelsen vil følges og dokumenteres.

Utviklingen innen persontilpasset medisin går nå meget raskt; først innen screening og diagnostikk, men også innen behandling. Antallet genterapiforsøk for sjeldne diagnoser har eksplodert (www.ClinicalTrials.gov), og en rekke andre målrettede behandlingsformer er også på vei. For de sjeldne, genetiske sykdommene hvor effektiv behandling er eller blir tilgjengelig, gjelder i stor grad at tidlig diagnose for å kunne igangsette behandling før alvorlig skade har inntrådt, er avgjørende for prognosen. Nyfødtscreeningen som nasjonal behandlingstjeneste, må raskt og effektivt kunne tilpasse sitt tilbud til dette.

Ønske om utvidelse av nyfødtscreening med SMA i Norge
Vi mener SMA tilfredsstiller de viktigste kriterier for nyfødtscreening:

- Det er en alvorlig sykdom
- Det finnes en effektiv behandling for de alvorligste symptomene
- Behandlingen er mer effektiv jo tidligere barna identifiseres
- Klinisk diagnostikk dvs. etter sykdomsdebut medfører forsinket identifisering av aktuelle barn og forsinket behandling
- Det finnes en tilfredsstillende test som kan avsløre sykdommen med høy spesifisitet og sensitivitet (lav falsk positiv og falsk negativ rate)
- SMA kan screenes ved multiplexing av *SMN1* med TREC/SCID metoden

Utvidelse av nyfødtscreeningen krever at Helse- og omsorgsdepartementet vedtar endring i Forskrift om endringer i forskrift 29. juni 2007 nr. 742 om genetisk masseundersøkelse til å inkludere testing for SMA.

Søknad om SMA-screening er tidligere forankret i møte i den nasjonale referansegruppen for Nyfødtscreeningen 13.12.19.

Vennlig hilsen

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Evidence-based Review of Newborn Screening for Spinal Muscular Atrophy (SMA): Final Report (v5.2)

03/13/2018

Prepared for:
MATERNAL AND CHILD HEALTH BUREAU

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EXECUTIVE SUMMARY

Overview

This report summarizes the evidence regarding the benefits and harms of newborn screening for spinal muscular atrophy (SMA) and the capability of state newborn screening programs to offer comprehensive testing and follow up for the condition.

This executive summary highlights key findings from the final version of the complete report developed for the United States Secretary of Health and Human Services' Advisory Committee on Heritable Disorders in Newborns and Children (Advisory Committee) regarding newborn screening for SMA. This summary is not intended to replace the complete report, which describes the methods for evidence identification and synthesis, and a full discussion of findings. This summary instead provides a high-level review of findings from the complete report.

SMA: Epidemiology and Clinical Course

SMA is a heterogeneous group of inherited neuromuscular disorders caused by degeneration of motor neurons in the anterior horn of the spinal cord. The focus of this review is on SMA caused by mutations in the Survival Motor Neuron 1 (*SMN1*) gene. Most cases are caused by a deletion of exon 7 in both alleles of *SMN1*, although up to 5% of cases are caused by this deletion in one allele and a deleterious mutation in the other allele. Prior to screening, the estimated birth prevalence of SMA was about 1 in 11,000.

There is a broad phenotypic spectrum, typically classified across five types. Type 0 often leads to fetal loss or newborns with significant involvement and death in early infancy. Type I leads to progressive weakness in the first six months of life and, without targeted intervention, death prior to 2 years of age. Type II is associated with progressive weakness by 15 months of life and, without targeted intervention, respiratory failure and death after the third decade of life. Types III and IV are associated with progressive weakness that develops after 1 year of life or in adulthood, and most individuals have a normal lifespan. Although there are gaps in knowledge regarding the distribution of SMA by type, about 54% of cases are Type I and 18% are Type II. Humans have another gene, *SMN2*, which is similar to *SMN1* except for a single nucleotide change in exon 7, leading to an unstable form of the *SMN1* gene product; however, some (estimated <10%) of the protein is functional. *SMN2* can be present with variable copy numbers, which can influence the disease process. Most cases of Type 1 have one or two copies of *SMN2*. One study found that 20% of cases of Type I SMA have 3 *SMN2* copies.

Prospective Newborn Screening for SMA

Screening is based on detection of a deletion in exon 7 in *SMN1*. Multiple screening methods are available, some of which only detect infants with deletions in both alleles (homozygotes). Other methods detect both deletions and deleterious mutations. Those methods detect carriers as well as newborns who have one deletion and a deleterious mutation in the other allele (i.e., compound heterozygotes). From 2-6% of cases of SMA are estimated to be compound heterozygotes or have de novo mutations. Screening for SMA can either be stand alone or multiplexed with screening for severe combined immunodeficiency (SCID).

At the time of this report, Massachusetts and Utah had just started statewide screening (January 2018) and 3 others (Minnesota, North Carolina, Wisconsin) were preparing to screen for SMA in

the next 12 months. Only one state was conducting prospective screening, as a research project. This project began in January 2016 in three hospitals in New York. The screening process in New York detects either one allele with a deletion in exon 7 (e.g., compound heterozygotes or carriers) or deletions in both alleles, who are likely to have SMA. As of January 2018, 10,362 newborns had been screened. One SMA case was detected and the carrier rate is 1:72. No cases of compound heterozygotes leading to the diagnosis of SMA have been identified.

Anticipated Harms of Screening

Screening for the exon 7 deletion is highly specific. If screening includes the detection of carriers, a substantial number of newborns require follow-up. Insufficient evidence is available to weigh the harms associated with carrier detection against the benefit of detection of compound heterozygotes.

Early Detection and Treatment for SMA

Determining the *SMN2* copy number can provide some prognostic information, although the disease course cannot be perfectly predicted. Treatment decisions are based on these genetic findings and close monitoring by specialists.

There is only one FDA-approved targeted treatment for SMA. Nusinersen is an antisense oligonucleotide that alters splicing of *SMN2* pre-mRNA to increase the amount of full-length *SMN2* mRNA, leading to an increase in the amount of functional SMN protein. A strong-quality Phase 3 efficacy study enrolled infants with SMA with two copies of the *SMN2* gene with symptoms before 6 months of age and who were screened for study participation by 7 months of age. This study was terminated early because the event-free (i.e., not requiring mechanical ventilation) survival was significantly different (hazard ratio for death or permanent assisted ventilation: 0.53 (95% CI: 0.32-0.89) by 56 weeks after the start of the study. Motor-milestone response was improved in the treatment group (41% vs. 0), including 22% achieving full head control and 10% rolling over. A *post-hoc* analysis not published in a peer-reviewed journal found that those subjects with disease duration ≤12 weeks had a greater likelihood of ventilator-free survival and improved motor developed.

No peer-reviewed published reports were identified that evaluated outcomes for individuals with SMA identified presymptomatically compared to usual case detection. A presentation not yet published in the peer-reviewed literature described 9 infants with Type I SMA after one year of nusinersen treatment who had been detected presymptomatically. Of these, 9 had normal head control, 7 could roll, 6 could sit, 6 could crawl, 5 could cruise, and 3 could stand unaided and had age-expected motor development.

Impact on the Health of the Population

Based on the limited data available, compared with clinical detection, newborn screening of the 4 million newborns born in the US each year could avert death or the need for mechanical ventilation in 48 (range: 16-100) infants by one year of life. Insufficient data are available to model outcomes after one year of life. Natural history suggests that there is a significant risk between 1 and 2 years of life for mortality and decline in motor function. However, insufficient data are available to model the impact of nusinersen on these affected infants after one year. In addition, insufficient data are available to model developmental outcomes.

Impact on Public Health Systems

Most newborn screening programs surveyed stated that it would take between 1 and 3 years to implement screening for SMA. Screening for SMA requires fewer additional resources to implement when multiplexed with SCID, which is included on most state newborn screening panels. SMA screening methods have high (100%) positive predictive value and no false positives have been reported to date when screening for deletions of exon 7 on both alleles. Challenges for states adding SMA to their screening panels include whether to screen and report carriers, developing management plans for late-onset cases, and the cost of therapy.

LIST OF ABBREVIATIONS

Abbreviation	Definition
Advisory Committee, ACHDNC	Advisory Committee on Heritable Disorders in Newborns and Children
ERG	Evidence-based Review Group
FDA	United States Food and Drug Administration
HINE	Hammersmith Infant Neurological Examination
MS/MS	Tandem mass spectrometry
NBS	Newborn Screening
PCR	Polymerase Chain Reaction
RT	Real-time
RUSP	Recommended Uniform Screening Panel
SMA	Spinal Muscular Atrophy
SMN1	Survival Motor Neuron 1
SMN2	Survival Motor Neuron 2

1 SCOPE AND METHODS OF THE REVIEW

Scope of Review

This report was developed to support the Secretary of Health and Human Services' (HHS) Advisory Committee on Heritable Disorders in Newborns and Children ("Advisory Committee") in making recommendations to the Secretary, HHS, about whether newborn screening for spinal muscular atrophy (SMA) should be added to the Recommended Uniform Screening Panel (RUSP).

Nomination and Request for Review

SMA disease was first nominated to the Advisory Committee for inclusion in the RUSP in November 2008. At that time, the Advisory Committee did not request a systematic review of the potential benefits and harms of screening for SMA disease, stating that such a review would be "premature…based on the submitted evidence." The Advisory Committee's Nomination and Prioritization Workgroup recommended *a) implementation of prospective pilot studies of the screening method by one or more traditional public health laboratories to test the reproducibility of the preliminary findings by Dr. Prior's laboratory. This time frame also could allow for an assessment of potential therapies of drugs and other treatment benefits rather than just relying on the nutritional support and respiratory care options at this time."* A follow-up nomination was presented to the Advisory Committee on May 11, 2017, at which time the Committee requested a formal review of evidence for newborn screening for SMA from the external Evidence-based Review Group (ERG).

Purpose of the Condition Review of Evidence

The role of the ERG is to conduct a systematic review of evidence on likely net benefit or harm of expanding newborn screening to include SMA, regarding potential health outcomes of affected newborns, the projected health impact at the population level, and the public health impact on the state newborn screening programs. The review will summarize evidence about the impact on individual newborns, population health, and public health systems, with specific attention to decision-making criteria considered by the Advisory Committee.[1] The ERG is not charged with making specific recommendations to the Committee.

Case Definition

SMA is a heterogeneous group of inherited neuromuscular disorders that affect control of muscle movement. SMA is caused by degeneration of motor neurons in the anterior horn of the spinal cord that results in progressive motor weakness. Many types of SMA have been identified that can be distinguished by the types of muscles and genes affected, as well as range in age of onset, severity of muscle weakness, and patterns of clinical features. Some types of SMA may lead to death in early infancy, while some forms may appear as mild muscle weakness in adulthood.

The focus of this review is on SMA caused by mutation of the Survival Motor Neuron 1 (*SMN1*) gene located on chromosome 5q (locus 5q13), with infantile or childhood onset. Mutations in *SMN1* account for most of the SMAs.

Methods – Systematic Evidence Review

The methods guiding this systematic evidence review (SER) followed approaches outlined in the Condition Review Workgroup – Manual of Procedures (2012, 2014) and revised in 2016 to address requirements in the 2014 Reauthorization of the Newborn Screening Saves Lives Act (Public Law No: 113-240, 12/18/2014). These procedures are based on the Agency for Healthcare Research and Quality (AHRQ) SER Methods Guide,[2,3] the United States Preventive Services Task Force (USPSTF) Procedures Manual,[4] and other established evidence review standards, with adaptations to address the nature of research on rare disorders (e.g., few large RCTs) and the established review and comment timeline of the Committee. This section describes specific procedures that guided this Condition Review of newborn screening for SMA.

Literature Search

Published Literature Search

An experienced medical librarian conducted the initial literature search for evidence on newborn screening and treatment of SMA. We identified published literature from MEDLINE, EMBASE, CINAHL, and Cochrane from database inception (earliest 1966, MEDLINE) using the following MeSH terms and associated key words used for each database. Cited reports were included for review were limited to full-text available in English, human subjects only (animal research excluded). Any non-full-text reports (e.g., research letters, grey literature, conference presentations or posters, etc.) with direct relevance to informing key questions were retained for consideration and discussed among the reviewers regarding inclusion. Publication dates were limited to reports after January 1, 2000, after *SMN1* mutations were identified as cause of SMA, and genetic testing developed and established for diagnosing SMA.[5]

Specific search terms and results for each database are included in Appendix A.

- Publication Dates: January 1, 2000 through January 11, 2018.
- Databases: PubMed, EMBASE, CINAHL, Cochrane Reviews
- Keywords and Search Terms: "spinal muscular atrophies of childhood"[Mesh] OR "spinal muscular atrophies"[tiab] OR "spinal muscular atrophy"[tiab] OR "Werdnig-Hoffman"[tiab] OR "Kugelberg-Welander"[tiab] OR SMA[tiab].

Literature Screening Inclusion and Exclusion Criteria

Preliminary Screening

Inclusion Criteria. Articles that reported on studies with human subjects and published in English were included. All study designs were considered, including case reports, case series, observational, studies, uncontrolled, and controlled intervention trials.

Exclusion Criteria. Non-human studies, studies with no English language abstracts, and articles with no new data were excluded.

Literature Review Eligibility Criteria

Following the initial Title and Abstract screen, additional inclusion and exclusion criteria were added to refine the search (e.g., minimum sample size requirements,and outcomes reported).

Additional eligibility criteria regarding included Populations, Interventions, Comparators Outcomes, Timing, and Settings for each key topic area (KTA) and question (KTQ) are outlined below. Further details of the article screening and flow diagram can be found in Appendix A.

Full-text review exclusion criteria followed standard rules, with sample size requirements determined after the initial scan of available literature, and are as follows:

- Not Full-text article
- No original data or analyses
- No KTA/KTQ addressed
- No human subjects with SMA
- Other (includes sample size requirements not met)

Published Literature Search Results

Total numbers of articles identified in the search was 2,782 (PubMed 2,273; Embase 891; CINAHL 249; Cochrane 131). From these, 579 duplicates were removed, and 2,193 articles were systematically screened and reviewed. With database articles combined, an additional 287 reports were screened for relevance to SMA or duplicates, for a total of 1,832 articles entered into the Distiller SR program for systematic review. Initial title and abstract screening was conducted by two independent reviewers for relevance and general exclusion and inclusion. An inclusion from at least one reviewer retained an article for further full-text review. After title and abstract screening, 805 articles were excluded, and 1027 were advanced for full-text review. Two independent reviewers reviewed the title, abstract, and full-text for inclusion based on specific relevance to key questions. At this full-text review stage, disagreements between reviewers were reconciled through discussion or by a third independent reviewer as needed. After the full-text review, 787 articles were excluded, leaving 240 for review and summary.

Screening and Treatment related articles were fully abstracted for content detail, and assessed for quality of evidence using well-established risk of bias rating forms[6-10] with modifications for newborn screening as needed. Global ratings for included, full-text reports are indicated in the results. Detailed rating forms and copies of the Quality Assessment Forms used are provided in Appendix A.

Other Key Topic articles (e.g., Incidence and Epidemiology, Natural History and Clinical Course with Clinical Detection) were summarized in each results section as context. Technical method details of the Systematic Evidence Review (PRISMA diagram with flow of articles screened, screening search and results, quality assessment ratings and forms) are outlined in Appendix A. Evidence tables of abstracted details for screening and treatment articles reviewed are included in Appendix E.

Key Questions for Evidence Review: SMA

The key topic areas and questions for the systematic evidence review were developed from the general analytic framework used by the Evidence-based Review Group (Condition Review Manual of Procedures-Rev v2.0, 2012, 2014) and the specific needs of the Advisory Committee. The technical expert panel on SMA guided refinement of the specific key questions to ensure relevance to the target condition. The Key Questions guiding the review of evidence for newborn

screening for a new condition can be organized into four main topic areas, I. Natural History and Clinical Detection, II. Screening and Short-Term Follow Up, III. Treatment and Long-Term Follow Up, and IV. Public Health Impact. The final Key Questions are outlined below, with the refined inclusion and exclusion criteria listed within the Population, Interventions, Comparators, Outcomes, Timing, and Setting (PICOTS) parameters consistent with standard evidence review methods.

Natural History and Epidemiology with Usual Clinical Detection

Key (Context) Question 1: What is the natural history and epidemiology of SMA? Specifically, what are the estimated incidence rates for associated SMA phenotypes, and the typical course of disease (i.e., ages of reported clinical onset and symptoms, diagnosis, treatment initiation, and death)? What are the phenotypes particularly affecting newborns and children (onset <21 years of age)? What factors predict morbidity or mortality?

Screening, Short-Term Follow-Up, and Diagnostic Confirmation

Key Question 2: What is the direct and indirect evidence that newborn screening for SMA disease leads to improved health outcomes compared to usual clinical care?

- Population: n>5, Newborns with no known risk for SMA and detected early, or newborns with increased family risk for SMA who were identified presymptomatically
- Interventions: Any care received subsequent to the screening test
- Comparators: Contemporaneous or historical controls affected by SMA
- Outcomes: Overall Survival; Survival with major morbidity
- Timing: Any duration of follow-up
- Settings: All settings

Key Question 3: Screening and Short-term follow up/diagnostic confirmation methods

A. What is the analytic validity or clinical validity of the newborn screening approaches used to detect SMA Types I – III using high-throughput methods in generalizable populations?
B. What diagnostic testing methods are available to confirm or identify these phenotypes?
C. What screening or diagnostic methods, if any, are available to predict or inform age of onset or disease severity during newborn screening?

There are two standard measures of analytic validity, sensitivity and specificity. To estimate these requires validated proficiency testing samples. Few such data exist. Consequently, one must use screening studies, which represent the combination of analytic and clinical validity.

- Population: n>5, Newborns without known diagnosis of, or risk factor for SMA; de-identified dried-blood spots
- Interventions: Any screening methods for SMA conducted in the first month of life. For analytic validity, studies should also report proficiency
- Comparators: Diagnosis by genotype and follow-up evaluation or genotype alone

- Outcomes: Sensitivity, specificity, positive predictive value, negative predictive value, reliability, and yield (i.e., prevalence)
- Timing: Any duration of follow-up
- Settings: All settings

Key Question 4: What are the harms associated with newborn screening for SMA to the individual or the family?

- Population: n>5, Newborns screened for SMA and their families
- Interventions: Any newborn screening for SMA
- Comparators: Any population or none
- Outcomes: Systematic assessment of harms, including harm related to false-positive screening results, false-negative screening results, early identification of later-onset disease, or perceived harms or acceptability of screening for SMA
- Timing: Any duration of follow-up
- Settings: All settings

Treatment and Long-term Follow Up

Key Question 5: What are the standard treatments for SMA and evidence for their effectiveness? Do follow-up protocols exist for the management of SMA that do not require immediate initiation of treatment? What is known about the effectiveness of follow-up protocols in modifying intermediate health outcomes?

Does early initiation of treatment improve primary health outcomes (overall survival, other important health outcomes) when the condition is caught early or through newborn screening compared with usual clinical care? How does this vary by phenotype?

- Population: n>3, Newborns and others diagnosed with SMA through newborn screening or other methods of presymptomatic detection and diagnosis in childhood
- Interventions: nusinersen or other approved disease-modifying therapies
- Comparators: Contemporaneous or historical controls with SMA disease or no comparison
- Outcomes: Survival and key health status measures specific to SMA (e.g., motor function, time to ventilator dependence)
- Timing: Any duration of follow-up
- Settings: All settings

In assessing the impact of early intervention, it is important to distinguish whether cases were identified early through newborn screening or risk (e.g., family history of SMA) versus identification of symptoms under usual care (i.e., clinical detection). Those children detected based on symptom onset may have more severe disease, and thus could have worse outcomes.

Key Question 6: Does initiation of treatment modify the intermediate health outcomes when SMA is detected through newborn screening or other methods of presymptomatic detection and diagnosis in childhood compared with usual clinical care? How does this vary by phenotype?

How strong is the association between changes in intermediate outcomes of (e.g., biomarkers) of SMA and changes in health outcomes?

- Population: n>3, Newborns and others diagnosed with SMA through newborn screening or other methods of presymptomatic detection and diagnosis in childhood
- Interventions: nusinersen or other approved disease-modifying therapies
- Comparators: Contemporaneous or historical controls with SMA disease or no comparator
- Outcomes: Changes in intermediate outcomes, such as improvements in biomarkers or physiologic changes which are related to other health outcomes.
- Timing: Any duration of follow-up
- Settings: All settings

Key Question 7: What are the effects of treatment on secondary health outcomes?

- Population: n>3, Newborns and others diagnosed with SMA through newborn screening or other methods of presymptomatic detection and diagnosis in childhood
- Interventions: nusinersen or other approved disease-modifying therapies
- Comparators: Contemporaneous or historical controls with SMA disease or no comparator
- Outcomes: Other important health outcomes, physical or psychosocial, for the patient or family members
- Timing: Any duration of follow-up
- Settings: All settings

Key Question 8: What are the harms associated with treatments for SMA in early childhood, for symptomatic and presymptomatic patients? How does this vary by phenotype?

- Population: Any child (or caregiver of child) identified with SMA receiving a current treatment
- Interventions: nusinersen or other approved disease-modifying therapies
- Comparators: Any population or none
- Outcomes: Any systematic assessment or description of harm
- Timing: Any duration of follow-up
- Settings: All settings

Key Question 9: What is the impact of newborn screening on the Public Health of the population on projected numbers affected? On relevant primary, intermediate, and secondary health outcomes?

Key Question 10*:* What is the impact of implementing newborn screening of SMA on the Public Health System? What is the feasibility of population-based screening for SMA within the United States? What is the readiness of state newborn screening programs to expand screening panels to include SMA?

Technical Expert Panel

A panel of Technical Experts was identified to advise this review throughout its development; members are listed in Table 1. We first met with technical experts to review our scope of review and methods, identify current issues in research and practice, and to describe the typical care standards for newborn screening and treatment procedures to ensure relevance and applicability of the review. Technical Expert Panel (TEP) members also met to provide input and feedback throughout development of the decision analysis model to estimate the impact of newborn screening on the population. During the review, additional experts were identified and interviewed to further inform unpublished newborn screening implementation and laboratory practices. Further information about the methods to develop the decision model and the role of the TEP members in the process is detailed in Section 4 – Applying Decision Modeling to Project Population Benefit.

Table 1. List of Technical Expert Panel Members

Name	Affiliation
Jeffrey R. Botkin, MD, MPH	*Professor of Pediatrics* *Adjunct Professor of Human Genetics and Internal Medicine* *Chief, Division of Medical Ethics and Humanities* *Associate Vice President for Research* **University of Utah School of Medicine**
Michele Caggana, ScD, FACMG	*Deputy Director, Division of Genetics* *Director, Newborn Screening Program* *Faculty Member, Wadsworth School of Laboratory Sciences* **New York State Department of Health Wadsworth Center**
Richard S. Finkel, MD	*Chief, Division of Neurology* **Nemours Children's Hospital**
Susan T. Iannaccone, MD, FAAN	*Warren A. Weinberg, MD Chair in Pediatric Neurology and Learning* *Associate Director, Paul Wellstone Muscular Dystrophy Center* *Professor of Pediatrics and Neurology & Neurotherapeutics* **UT Southwestern Medical Center**
Jill Jarecki, PhD	*Chief Scientific Officer* **Cure SMA**
Allison Kingsley	*Member and Former Chair, Family Advisory Council* *Member, Family as Faculty* **Nationwide Children's Hospital**
Kathryn J. Swoboda, MD, FACMG	*Katherine B. Sims, MD, Endowed Chair in Neurogenetics* *Director, Neurogenetics Unit, Center for Genomic Medicine* **Massachusetts General Hospital**

2 REVIEW OF EVIDENCE: NEWBORN SCREENING FOR SPINAL MUSCULAR ATROPHY

Key Questions for Evidence Review for SMA NBS

The key topic areas and questions for the systematic evidence review were developed from the general analytic framework used by the ERG and the specific needs of the Advisory Committee. The technical expert panel on spinal muscular atrophy (SMA) will help to refine the specific key questions. The Key Questions guiding the evidence review fall into 4 main topic areas: 1) Natural history and epidemiology with clinical detection, 2) Screening and Short-term follow up, 3) Treatment and long-term care and management, and 4) Public Health Impact – Population-Level Benefit and Public Health System Impact.

Epidemiology and Natural History of SMA with Usual Clinical Detection

Key (Context) Question 1: *What is the epidemiology and natural history of SMA? Specifically, what are the estimated incidence rates for SMA and the typical course of disease (i.e., ages of reported clinical onset and symptoms, diagnosis, treatment initiation, and death)? What are the phenotypes particularly affecting newborns and children (onset <21 years of age)? What factors predict phenotype or severity?*

Estimated Incidence of SMA with Clinical Detection

Incidence of SMA in the United States has been estimated through a population-based carrier screening study (n≥68,403). The authors reviewed clinical laboratory data including clinical indication for testing, family history, and ethnicity. All individuals referred for testing were reported to be asymptomatic. The proportion with a deletion of exon 7 in *SMN1* was evaluated and observed frequencies were used to derive carrier frequency and incidence estimates under assumptions of Hardy-Weinberg equilibrium. Using a measured carrier frequency of 1 in 54, and a detection rate of 92.1%, the authors estimated the incidence of SMA in the United States as 1 in 11,000.[11] As Table 2 shows, the estimated birth prevalence of SMA in the U.S. is generally consistent with those reported from other countries, which range from about 8.5 to 10.7 individuals with SMA per 100,000.[12,13] Studies with base years prior to the late 1990s cover periods before the development and established use of genetic testing for *SMN1* deletions for screening and diagnostic testing, and may be less reliable.[12-14]

Table 2. Published Reports of Estimated Birth Prevalence of SMA

*First Author, Pub Year	N (region)	Base Years	Estimated Birth Prevalence	95% CI
Sugarman, 2012[11]	68,471 (US)	2008-2009	1: 11,000 (9.1 in 100,000)	3.8 to 19.1 in 100,000
Prior, *2010*[15]	40,103 (OH)	NR	1 in 10,026 (10 in 100,000)	1 in 4,517 to 1 in 38,541
Jedrezejowska, 2010[12]	Poland	1998-2005	1 in 9320, 1 in 7127 (Warsaw)	1: 2304 to 1:11,236
Arkblad, 2008[13]	Sweden	1980-2006	1 in 11,800 (8.5 in 100,000)	6.2 – 11.3 in 100,000

Natural Course and Phenotypes

The phenotypic spectrum of SMA manifests on a continuum with symptom onset ranging from prenatal- through adult-onset. The disease spectrum is divided into 5 types, based on age of onset. In addition subtypes are classified based on the combination of age of onset and highest motor milestone achieved. Within each of these classifications, there is phenotypic heterogeneity.[16,17]

Table 3. SMA Types and Clinical Features

SMA Type	Age When Symptoms Typically Apparent	Symptoms and Systems Affected	Progression/ Natural History
Type 0	Prenatal	Born with congenital arthrogryposis (SMA Type 0), already weak at birth.	Lifespan <6 months
Type I (infantile, or Werdnig Hoffmann disease)	<6 months Most are asymptomatic at birth	SMA Type 1 children are never able to sit independently. Infants develop symptoms of diffuse motor weakness prior to 6 months. They lose the ability to swallow safely	Most progress to respiratory failure and death prior to 2 years of age.
Type II	~6 – 15 months	SMA Type 2 children are never able to stand. They achieve the ability to sit independently for brief periods of time and after this may lose motor milestones. Variably they develop respiratory muscle weakness and may develop difficulty swallowing safely.	Progressive muscle weakness with respiratory failure and death after the 3rd decade of life without intervention.
Type III	>12 months through adolescence	SMA Type 3 children may be able to stand and walk, but with weakness noted later. The child may have delayed walking or may walk at an appropriate age but have an abnormal, weak gait. Many lose the ability to walk independently over time. Respiratory muscle weakness onset is variable and typically occurs in adolescence or adulthood.	Progressive muscle weakness, many lose ambulation, most have a normal lifespan.
Type IV	Adulthood	Onset of weakness is observed in adulthood and may present with diffuse myalgia and progressive muscle atrophy.	Mild progressive muscle weakness, normal lifespan.

Birth prevalence by SMA Type

Birth prevalence estimates by SMA Type from studies reporting these estimates are listed in Table 4 below. These studies include those published after 2000 which stated using genetic diagnosis for at least some cases as available. Type 1 birth prevalence ranged from 3.5 to 7.1. Published reviews have reported 4 to 6 in 100,000[18] using overlapping though different subsets of studies.

Table 4. Published Reports of Birth Prevalence Estimates of SMA by Type

First Author, Pub Year	Region **Base Years**	**Population**	SMA **Est. Incidence**	Type 1 **Est. Incidence**	Type 2 **Est. Incidence**	Type 3 **Est. Incidence**
Zaldivar, 2000[19]	Cuba 1996-2002	1,018,454	5.0	3.5	NR	NR
Vaidla, 2006[20]	Estonia 1994-2003	129,832	11.6	6.9	NR	NR
Jedrezejowska, 2010[12]	Poland 1998-2005	2,963,783	10.3	7.1	1.2	2.0
Arkblad, 2008[13]	Sweden 1980-2006	531,746	8.5	3.6	2.1	2.8
Darin, 2000[21]	Sweden 1979-1994	343,941	6.1	3.8	0.9	1.5

Est. incidence per 100,000 live births. Genetic diagnosis used for all or some cases.

International SMA Consortium SMA Classifications

In 1992, a group of experts developed a classification scheme for SMA subtypes based on a combination of age of onset and highest motor milestone achieved. Distinctions within each Type further differentiate functional outcomes.[16,22] These classifications are outlined in Table 5 below, with typical *SMN2* copy numbers.

Table 5. SMA Classifications from the 1992 International SMA Consortium

SMA Type	Age of Onset	Highest Motor Milestone Achieved	*SMN2* Copy Number	Life Span
IA	<1 week	Never sits	1	<1 month
IB	1 week – 3 months	Never sits	2, 3	<2 years
IC	3 – 6 months	Never sits	2, 3	<2 years
IIA	6 – 15 months	Sits independently Loses ability to sit	2, 3, 4	>2 years
IIB	6 – 15 months	Sits independently Maintains ability to sit	2, 3, 4	>2 years
IIIA	<3 years	Walks independently	3, 4	Adult
IIIB	>3 years	Walks independently	3, 4	Adult
IV	>21 years	Walks independently	4, 5	Adult

Natural History of SMA – Clinical Detection

Clinical Symptom Onset and Diagnosis

A review of studies published between 2000 and 2014 derived an overall mean age of onset, diagnosis, and diagnostic delay in SMA under clinical detection, weighted by number of patients.[23] Among studies reporting mean ages of onset and confirmed diagnosis, delayed diagnosis was calculated. Under clinical detection, the weighted mean delay in diagnosis for SMA Type I, II, and III was 3.6, 14.3, and 43.6 months, respectively. Mean delays in diagnosis were inversely related to phenotype severity. These data are summarized in the following table.

Table 6. Weighted Mean Age of Onset, Diagnosis, and Diagnostic Delay in SMA with Clinical Detection

	Type I	Type II	Type III
Mean age of onset, months			
No. of patients for weighted mean	420	357	63
No. of studies for weighted mean	10	8	5
Mean (SD) Range	(0.6) 0.6 – 9.0	8.3 (1.6) 1.2 – 72.0	39.0 (32.6) 3.0 – 82.8
Mean age of confirmed diagnosis, months			
No. of patients for weighted mean	271	219	60
No. of studies for weighted mean	4	4	3
Mean (SD) Range	6.3 (2.2) 0.6 – 9.0	20.7 (2.6) 1.2 – 72.0	50.3 (12.9) 3.0 – 82.8
Mean delay in diagnosis, months			
No. of patients for weighted mean	264	105	25
No. of studies for weighted mean	3	1	1
Mean (SD) Range	3.6 (1.9) 1.0 – 5.9	14.3 (0.0) 14.3	43.6 (0.0) 43.6

SD = standard deviation; SMA = Spinal muscular atrophy.
Studies reporting mean ages and published in 2000 to 2014 included. Case reports and studies reporting only median ages excluded.
Data weighted by total number of patients evaluated in included studies.

Survival and Independence from Ventilation Support

SMA Type I/Infantile Onset

With increasing availability of noninvasive ventilation and other supportive care for SMA Type I patients, natural history studies have shown a higher likelihood of survival of affected in the 1990s relative to early periods. Using data from the International Spinal Muscular Atrophy Patient Registry and additional clinical information for 143 patients with SMA Type I, Oskoui and colleagues found that patients born in 1995-2006 had a 70% reduction in risk of death over a mean follow up of 49.9 months compared with those born between 1980 and 2006 ($p<0.001$).[24]

When controlling for demographic and clinical care variables, year of birth was not significantly associated with age at death, whereas ventilator use (<16 hours/day) and gastronomy tube feeding each were significantly associated with reducing the risk of death.[24]

Survival and SMN2 Copy Number

Outcomes for patients with SMA type I are influenced by the number of copies of *SMN2*. A natural history study on survival among patients (enrolled 2005-2009) with SMA Type I, by *SMN2* copy number, report an overall median age at which death or ventilator support is reached as 13.5 months of age [interquartile range 8.1-22.0 months].[25] Among 32 infants with SMA Type

I, the likelihood of event-free survival was about 30% and 0% at 12 and 24 months, respectively, for patients with 2 copies of *SMN2* (n=23), and about 90% and 50% at 12 and 24 months for patients with 3 *SMN2* copies (n=9). A study following 26 SMA Type I patients and 27 healthy controls enrolled between December 2012 and Sept 2014 reported very similar probabilities of event-free survival of about 40% and 15% at 12 and 24 months, respectively, for patients with 2 *SMN2* (n=16), and 85% at 12 and 24 months for those with 3 or more *SMN2* (n=9).[26]. The overall median age of death or ventilator support in this group of infants with 2 *SMN2* copies was 8 months (CI, 6, 17; n=20).

SMA Type II and III

Natural history studies have reported generally normal life expectancies for patients with SMA Type II and III with advances in medical care, though patients may live with severe physical disabilities,[27,28] including the need for respiratory support.[16]

Motor Function

Clinical outcomes measures assessing motor function for SMA treatment vary by age and developmental skill levels across SMA phenotypes (Type I – III).[29] Key motor function measures that have been assessed as reliable and valid for use with individuals with SMA are reviewed below, with observed functioning levels in SMA patients not treated with nusinersen.

SMA Type I

Hammersmith Infant Neurological Examination (HINE). The Hammersmith Infant Neurological Examination (HINE) is a standardized instrument for assessing infants from 2-24 months of age for a wide array of neurologic and motor impairments.[30] Since its initial development, the scale has been modified and expanded to capture a broader array of gross motor ability and to be less susceptible to bias from fatigue or position[31] and to serve as a tool to monitor children with SMA.[32] The HINE has three sections (neurologic examination; developmental milestones, and behavioral assessment).

The second section (HINE-2) has been used to assess outcome for many of the SMA studies. The HINE-2 consists of eight domains (see Figure 1).[33] The possible score for each domain ranges from 0 to 3 (head control), 4 (voluntary grasp, rolling, standing, walking), or 5 (sitting, ability to kick in supine, crawling or bottom shuffling) for a total possible score of 34.

The HINE was validated on 135 infants with no perinatal risk, including 12-month old (n=92) and 18-month old (n=43) infants.[34] Based on the assessed milestones achieved, the range of HINE-2 scores for 12 month old infants was 24 to 34, and for 18-month old infants was 31 to 34. The proportion of infants in each age group (12 and 18 months) achieving each milestone is shown in Figure 1.

HINE-2 in Infants with SMA Type I. In a retrospective study of individuals (n=33) with infantile-onset (Type I) SMA who were 1 to 8 months of age at the onset of symptoms, none of the more severely affected infants achieved a major milestone such as rolling over, independent sitting, crawling, standing, or walking.[33] Individuals with later-onset (Type II and Type III) SMA may demonstrate progressive decline in HFMSE scores.[35]

Figure 1. HINE-2 Developmental Milestones Scoring

Milestone					
Head control	Unable to maintain head upright (normal up to 3 months)	Wobbles (normal up to 4 months)	Maintained upright all the time (normal from 5 months)		
Sitting	Cannot sit	Sits with support at hips (normal at 4 months) 	Props self up (normal at 6 months) 	Stable sitting (normal at 7–8 months)	Pivots (rotates) (normal at 9 months) 
Voluntary grasp (note L or R side)	No grasp	Uses whole hand	Index finger and thumb, but immature grasp	Pincer grasp	
Ability to kick (supine)	No kicking	Kicks horizontally but legs do not lift	Upward (vertical) (normal at 3 months) 	Touches leg (normal at 4–5 months) 	Touches toes (normal at 5–6 months) 
Rolling	No rolling	Rolls to side (normal at 4 months)	Prone to supine (normal at 6 months)	Supine to prone (normal at 6 months)	
Crawling or bottom shuffling	Does not lift head	On elbow (normal at 3 months) 	On outstretched hand (normal at 4 months) 	Crawling flat on abdomen (normal at 8 months) 	Crawling on hands and knees (normal at 10 months) 
Standing	Does not support weight	Supports weight (normal at 4 months)	Stands with support (normal at 7 months)	Stands unaided (normal at 12 months)	
Walking		Bouncing (normal at 4 months)	Cruising (walks holding on) (normal at 12 months)	Walking independently (normal at 15 months)	
SCORE	0	1	2	3	4

Available at https://www.togetherinsma-hcp.com/en_us/home/disease-education/motor-function-measures.html.

Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders. The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) was developed to assess children with SMA type I for children 4 months through 4 years of age. The CHOP INTEND has been used in multisite clinical trials with strong inter-rater reliability >0.8 [1449], and validated for use with patients with SMA Type I, correlating with disease severity.[36] The total possible score is 64 and evaluates across the following 16 domains (0-4)[37]:

- Upper extremity spontaneous movement
- Lower extremity spontaneous movement
- Hand grip

- Head in midline with visual stipulation
- Hip adductors
- Rolling elicited from legs
- Rolling elicited from arms
- Shoulder and elbow flexion and horizontal abduction
- Shoulder flexion and elbow flexion
- Knee extension
- Hip flexion and foot dorsiflexion
- Head control
- Elbow flexion
- Neck flexion
- Head/neck extension
- Spinal incurvation

One weak-quality study found "excellent" test-retest reliability (r=0.987) for the HINE-2 and reported the correlation over time between changes in the HINE-2 and the CHOP INTEND to be 0.691 (p=0.001) among 19 infants with SMA treated in an open-label phase 2 study.[38] Factors that lowered the study quality included a lack of information about who conducted the tests and whether there was blinding regarding the outcome of the previous tests. Although one of the study goals was to assess feasibility, no measure of feasibility was reported.

CHOP-INTEND Scores: Infants with SMA Type I and Healthy Infants. An observational study compared CHOP-INTEND scores for infants with SMA Type I with 2 *SMN2* copies (n=16) with aa control group sample of healthy infants (n=14) enrolled at a mean age of 3.7 months and 3.3 months, respectively.[26] Figure 2Table 7 summarizes the findings, with healthy infants ingaveraging 50.1 on the CHOP-INTEND, whilewhile infants with SMA had a mean score of 20.2.[26] Infants with SMA showed progressive declines in motor function and CHOP-INTEND scores across the 24-month follow-up period.[25,26]

Table 7. CHOP INTEND Scores for Infants with SMA Type I with 2 *SMN2* Copies and Healthy Controls

Patient Group	Mean CHOP INTEND Score	Mean Age (months)	Age of Clinical Onset
Healthy Infants (n=14)	50.1 (sd 10.2) range 32-62	3.3	NA
SMA Type I, 2 *SMN2* copies (n=16)	20.2 (sd 7.4) range 10-33	3.7	<1 month (6/16) 1-2 months (5/16) 2-3 months (3/16) 4-5 months (1/16)

SMA Type II and Type III

An observational study of 65 patients with SMA Type II and III (age 20 months to 45 years) showed no significant changes across a 12-month follow-up period in motor function, pulmonary function, and muscle strength measures.[39] Children younger than 5 years who were ambulatory showed some motor function gains, and scoliosis surgery during the 12 months led to declines in motor function. Study of functional outcomes through up to 48-months follow-up (mean follow up 25 months, SD 13 months) indicated slow declines in motor function and pulmonary function. Declines were more pronounced after 2 years.[40]

Although observational studies of disease progression across the lifespan were not identified, a recent cross-sectional study of 180 patients with SMA Types I-IV, aged 1 – 77.5 years, and median disease duration of 18 years (range 0 – 65.8 years) described muscle strength, motor function, and patterns of weakness relative to age and SMA type.[41] Findings showed that patients with SMA Types II and III in early phases of disease may achieve new motor skills and show temporary increases in muscle strength, declines in motor skills and muscle strength over time occurs across all SMA types. Results indicate that rates of disease progression and functional decline may occur into adulthood, and may be more pronounced during specific periods of life (i.e., the second, third and fifth decades of life in SMA types II, III, and IV, respectively). Although the age at loss of specific motor functions appears to be associated with disease severity, the cross-sectional study design limits interpretation of these findings.

With the FDA-approval of nusinersen for SMA in December 2016, outcomes for infants and children with SMA Type 1 have improved. Evidence to inform this changing natural history will be reviewed in the nusinersen treatment outcomes section.

Summary: Epidemiology and Natural History of SMA

- SMA is a heterogeneous group of inherited neuromuscular disorders caused by degeneration of motor neurons in the anterior horn of the spinal cord. The focus of this review is on SMA caused by mutations in the Survival Motor Neuron 1 (*SMN1*) gene. Most cases are caused by a deletion of exon 7 in both alleles of *SMN1*, although up to 5% of cases are caused by this deletion in one allele and a deleterious mutation in the other allele.
- Prior to screening, the estimated birth prevalence of SMA was about 1 in 11,000.
- There is a broad phenotypic spectrum, typically classified across five types, based on maximum motor milestones achieved and age of onset. Type 0 often leads to fetal loss or newborns with significant involvement and death in early infancy. Type I leads to progressive weakness in the first six months of life and, without targeted intervention, death prior to 2 years of age. Type II is associated with progressive weakness by 15 months of life and, without targeted intervention, respiratory failure and death after the third decade of life. Types III and IV are associated with progressive weakness that develops after 1 year of life or in adulthood, and most individuals have a normal lifespan.
- Although there are gaps in knowledge regarding the distribution of SMA by type, about 54% of cases are Type I and 18% are Type II. Humans have another gene, *SMN2*, which is similar to *SMN1* except for a single nucleotide change in exon 7, leading to an unstable form of the *SMN1* gene product; however, some (estimated <10%) of the protein is functional. *SMN2* can be present with variable copy numbers, which can influence

disease severity and process. Most cases of Type 1 have one or two copies of *SMN2*. One study found that 20% of cases of Type I SMA have 3 copies.

Screening, Short-Term Follow-Up, and Diagnostic Confirmation

Key Question 2: *Methods. What are the screening and short-term follow up/diagnostic confirmation methods available and what is the evidence regarding effectiveness?*

Key Question 3: *Newborn Screening Outcomes. What is the direct and indirect evidence that newborn screening for SMA disease leads to improved health outcomes compared to usual clinical care?*

Key Question 4: *Harms of Screening. What are the harms associated with newborn screening for SMA to the individual or the family?*

Genetics of SMA

SMN1. In the majority of patients, SMA is caused by deletions or mutations affecting the *SMN1* gene located at chromosome 5q13.2. Wirth and colleagues found that 96% of SMA patients have mutations in SMN1 linked to 5q13, and that 96.4% of those cases are due to a deletion of exons 7 and 8, or exon 7 only, in both alleles of the gene, and 3.6% are compound heterozygotes in SMN1, with a deletion or gene conversion on one allele, and a mutation on the other allele.[42] *De novo* mutations occur at about 2%.[43] In a sample of 523 SMA Type I, II, and III patients with typical clinical features, the proportion of each Type with homozygous deletion of exon 7 of SMN1 was 96%, 93.5%, and 82.4%, respectively.[42]

SMN2. Deletions of the *SMN1* gene disrupt the availability of proteins needed for motor neurons. *SMN1* and *SMN2* genes are highly interrelated, with overlapping functions. *SMN1* produces full-length functional protein, and *SMN2* produces 5–10% full-length functional protein. Generally, having about 50% functional full-length SMN protein is sufficient to function normally. Higher numbers of *SMN2* copies moderates the impact of *SMN1* deletions on severity of SMA disease and subsequent outcomes.[16,25,44,45]

A recent study combined data from a cohort of 625 SMA Spanish patients and 2,834 SMA patients worldwide, extracted from articles published since 1999.[46] The most frequently reported *SMN2* copy numbers in pooled Type I patients (n=1,256) is 2 *SMN2* copies (73%), in pooled Type II patients (n=1,160) is 3 *SMN2* copies (78%), and in pooled Type III patients (n=1,043) is 3 *SMN2* copies (49%) and 4 *SMN2* copies (44%). The table below summarizes the distribution of *SMN2* copy numbers in patients with SMA Type I, II, and III as reported in the combined data on n=3,459 patients.

Table 8. Distribution of *SMN2* Copy Number by SMA Type in Patients Worldwide†

***SMN2* copy number**	Type I **(n=1,256)**	Type II **(n=1,160)**	Type III **(n=1,043)**
1	88 (7%)	4 (<1%)	0 (0%)
2	919 (73%)	190 (16%)	54 (5%)
3	245 (20%)	902 (78%)	515 (49%)
4	3 (<1%)	59 (5%)	455 (44%)
5	1 (<1%)	3 (<1%)	16 (2%)
6	0 (0%)	0 (0%)	3 (<1%)

†Data from published articles since 1999, and a Spanish cohort of 645 patients with SMA.[46]

Screening and Diagnosis of SMA

High-Throughput Screening. Screening methods for SMA target detection of *SMN1* gene deletions by amplifying DNA to evaluate *SMN1* copy numbers. Since demonstrating use of RT-PCR as a feasible method of screening for SMA[47], other methods and variations of this approach have been validated for use in high-throughput applications, including post-PCR high-resolution melting analysis[48], liquid bead arrays[15], and *SMN1*-specific locked nucleic acid (LNA) probe and primer [49] with analytic validity for detecting homozygous deletions of exon 7 based on testing for the presence of intron 7 of the *SMN1* gene, as well as a multiplexed RT-PCR assay to simultaneously test for SCID and SMA. Additional testing may involve targeted mutation analysis or sequencing to confirm homozygous *SMN1* deletion and to determine *SMN2* copy numbers (e.g., digital droplet PCR [ddPCR], Sanger sequencing). RT-PCR approaches have yielded nearly 100% positive predictive values in identified screen positives.

Diagnosis. SMA diagnoses include confirmation of genetic testing and additional sequencing of *SMN1*, determination of *SMN2* copy numbers, and clinical examination and evaluation of biomarkers which may be elevated in patients affected by SMA. Most DNA diagnostic laboratories use multiplex ligation probe amplification (MLPA) methods for deletion analysis of exon 7 of the *SMN1* gene. This test is also commonly used in carrier testing with potential probands and carriers. This type of targeted mutation testing in conjunction with sequence analysis can also detect individuals who are compound heterozygotes with a deletion of exon 7 in one *SMN1* allele and an intragenic point mutation in the other allele. Of these compound heterozygote cases, sequence analysis of the *SMN* gene will detect known, previously reported mutations, but not all (e.g., exonic deletions or duplications and location of point mutations if the *SMN1* gene or *SMN2* gene is not deleted will not be detected). Certain point mutations have been described in more than one SMA patient, informing location and pathology of future identification of these mutations in the *SMN1* gene.[42]

Population-based Screening for SMA

In the United States, as of January 2018, 2 states have begun implementing statewide newborn screening for SMA (MA, UT), at least 3 states are planning and preparing for statewide screening in the next 12 months (MN, WI, NC), and one state is conducting a research project to screen for SMA in 3 hospitals (NY). The states currently conducting statewide screening began January 29, 2018, with results not yet available. (See Section IV for more information about

readiness of states to adopt screening for SMA.) Pilot screening results from NY are included in the following section, informed by published report and interview and personal communications with NYS NBS program.

The literature search identified two published reports on outcomes from prospective, population-based screening for SMA in the United States (New York State)[50] and in Taiwan.[51]

New York Pilot Study

The New York State newborn screening program, in partnership with Columbia University with funding from Biogen, is conducting a pilot research study to determine feasibility of newborn screening for SMA.[50] Pilot screening started January 2016 in 3 hospitals in New York City. Consent to participate was obtained from 93.03% of parents approached.

The New York research pilot study genotyping assay uses a multiplex TaqMan real-time (RT) polymerase chain reaction (PCR) assay on dried blood spot specimens, with screen positive results confirmed by an outside laboratory. The RT-PCR assay was validated to screen and detect any deletion of exon 7 in either of the two *SMN1* genes. These results were considered screen positive (0 *SMN1* gene with exon 7), carriers (1 *SMN1* gene with exon 7), or normal (2 *SMN1* genes with exon 7).

Screening results from January 2016 through January 2017 reported 59 carriers and 1 screen positive for homozygote deletion of *SMN1* exon 7.[50] Screening results updated through January 2018 are summarized in the following table.

Table 9. Newborn Screening for SMA: NY State Pilot Results (Jan 2016 – Jan 2018)

	N	% **(95% Confidence Interval [CI])**	**Observed Incidence**
Babies screened	10,362*	---	
Normal (No exon 7 deletions in *SMN1*)	10,217	98.60% (CI 98.37% – 98.83%)	
Suspected Carrier (Exon 7 deletion in one *SMN1* gene)	144	1.39% (CI 1.17% – 1.63%)	1 in 72
Suspected Case (Exon 7 deletions in both *SMN1* genes)	1	0.0097% (CI 0.00% – 0.05%)	
True Positive, Diagnosed	1		1 in 10,362

*updated numbers provided by Dr. Michelle Caggana, personal communication.

An outside laboratory confirmed the positive screen for homozygous deletion of *SMN1* exon 7 and also determined the presence 2 *SMN2* copies, suggesting possible SMA Type I phenotype. The newborn was clinically evaluated at 7 days of age, with normal physical and neurological exam, and at age 13 days enrolled the infant into an open-label trial of nusinersen for clinically presymptomatic infants with SMA. The infant received her first dose of nusinersen at 15 days of

age, and, by report, as of the last assessment at 12 months, the baby appeared normal and had achieved all developmental milestones.

Taiwan Pilot Screening for SMA

A screening trial was conducted at the National Taiwan University Hospital newborn screening center between November 2014 and September 2016 to assess feasibility of presymptomatic detection and diagnosis of SMA. First-tier screening procedures used a RT-PCR genotyping assay for *SMN1/SMN2* intron 7 to detect homozygous deletion of *SMN1* exon 7. Second-tier screening included exon 7 mutation and *SMN2* copy number with digital droplet PCR (ddPCR) with the same dried blood spot, and multiplex ligation-dependent probe amplification (MLPA) using a whole blood sample.

Of the 120,267 newborn screened, 15 had a positive 1st tier (RT-PCR) screen. The ddPCR confirmed homozygous deletion of *SMN1* for 7 newborns, and found that 8 of the positive 1st tier screens had 1 copy of *SMN1*. The ddPCR also determined *SMN2* copy numbers of the 7 babies confirmed with *SMN1* deletion. MLPA confirmed both *SMN1* and *SMN2* copy number results.

Screening results from newborn screening in Taiwan are presented in Table 10 below.

Table 10. Newborn Screening for SMA: Results from Taiwan (Nov 2014 - Sept 2016)

	N	Observed Incidence
Babies screened	120,267	
1st-tier (RT-PCR) positive (*SMN1* = 0)	15	
2nd tier (ddPCR, MLPA) positive (*SMN1*=0)	7	
True Positive (confirmed)	7	1 in 17,181 (5.82 in 100,000) (CI 1 in 8323 to 1 in 35,468) (2.82 to 12.01 in 100,000)

The first tier (RT-PCR) yielded a false-positive rate of 53%. Inclusion of the second tier ddPCR with the same dried blood spot excluded the 8 false positives, for an overall positive predictive value of 100%. The observed incidence of 1 in 17,181 was lower than other SMA incidence estimates of about 1 in 10,000, although expected estimates falls within the wide confidence interval. Of the 7 newborns identified with SMA, diagnosis was confirmed between 4 and 11 days of age, at which time 6 were asymptomatic. Screening was conducted prior to the availability of a disease-modifying treatment or approval of nusinersen. At last reported follow up, 1 infant had died at 3 months of age, 3 were asymptomatic and normal (2.5 to 25 months), and 3 were experiencing some muscle weakness or loss of motor milestones (1.5 to 23 months). Two of the 7 infants were enrolled in a treatment trial. One infant had been asymptomatic at the time of diagnosis (8 days) and had 2 *SMN2* copies but showed some weakness at 3 weeks of age when treatment began. The other infant was diagnosed at 11 days of age, had 3 *SMN2* copies, started trial treatment at 1.5 months, and was normal at last follow up at 6 months of age.

Potential Harms of Newborn Screening for SMA

No information was identified regarding the harms of carrier detection or the detection of compound heterozygotes who have a variant of unknown significance. To date, no confirmed false-negative screening results have been reported among the newborns who were screened for SMA.

Summary – Screening and Short Term Follow Up

- Genotyping assays to target mutation analysis of *SMN1* RT-PCR effectively screen for SMA caused by homozygous deletion of exon 7 of *SMN1*. From 2% to 6% of cases may be caused by deletion in one allele and a mutation in the other allele. Not all mutations have been clearly linked to the development of SMA (e.g., variants of uncertain significance).
- Confirmation of homozygous deletions of *SMN1* can be done with ddPCR or targeted sequencing. Use of MLPA is a standard genetic test used by DNA diagnostic laboratories. *SMN2* copy numbers is also important to inform disease severity, and can be evaluated with ddPCR or other method.
- Of 10,362 newborns screened to date in New York, 1 infant was identified with SMA (2 *SMN2* copy numbers) consistent with Type I. This newborn was referred, diagnosed and began treatment presymptomatically by 15 days of age. By report, at 12 months follow up, the infant has met all developmental milestones within normal limits, and has not required respiratory support.
- Little is known about the harm related to cascade testing or the process of follow-up for asymptomatic individuals at risk for developing SMA.

Treatment and Long-Term Follow Up

Key Question 5: *What are the standard treatments for SMA and evidence for their effectiveness? Do follow-up protocols exist for the management of SMA that do not require immediate initiation of treatment? What is known about the effectiveness of follow-up protocols in modifying intermediate health outcomes?*

Does early initiation of treatment improve primary health outcomes (overall survival, other important health outcomes) when the condition is caught early or through newborn screening compared with usual clinical care? How does this vary by phenotype?

Key Question 6: *Compared with usual clinical care, does initiation of treatment when SMA is detected through newborn screening or other methods of pre-symptomatic identification modify intermediate health outcomes of SMA? How does this vary by phenotype? How strong is the association between changes in intermediate outcomes of (e.g., biomarkers) of SMA and changes in health outcomes?*

Key Question 7: *Does initiation of treatment when SMA is detected through newborn screening or other methods of pre-symptomatic identification modify secondary health outcomes of SMA?*

Key Question 8: *What are the harms associated with treatments, interventions, or follow-up care for SMA in early childhood, for symptomatic and presymptomatic patients?*

SMA Treatment

FDA-approved Treatment

Nusinersen is currently the only FDA-approved targeted treatment for SMA. Developed by Biogen under the trade name Spinraza, nusinersen was approved by the FDA on December 23, 2016, and "*is indicated for the treatment of spinal muscular atrophy (SMA) in both pediatric and adult patients.*"[52]

Nusinersen is an antisense oligonucleotide drug that alters splicing of the *SMN2* pre-mRNA to increase the amount of full-length *SMN2* mRNA. Full-length *SMN2* mRNA is translated into mRNA to increase the amount of functional SMN protein, which has been compromised by the loss of *SMN1* deletions or mutations. Patients typically receive 4 loading doses in the 2 months, followed by maintenance every 4 months via intrathecal injection (i.e., lumbar puncture, spinal tap).

An International Standard of Care Committee for Spinal Muscular Atrophy was formed in 2005 to establish guidelines for clinical practice.[53,54] More recently, an *ad-hoc* group of clinicians, researchers, and advocates formed the *SMA NBS Multidisciplinary Working Group* has formed to develop clinical guidelines to guide practice and treatment decisions for nusinersen.[55]

Supportive Care

Prior to nusinersen, supportive or palliative care was the mainstay of treatment. Although supportive care could extend life and decrease the time to ventilator dependence[24,56] the disease course was not substantially altered. Examples of supportive care include:

1) *nutritional support and careful monitoring of nutritional intake and swallow function*, with placement of feeding tubes as needed, and 2) *respiratory support* including chest physiotherapy devices, cough assist devices, and pulse oximetry monitoring, and also the use of respiratory

support devices including bi-level positive airway pressure via face/nose mask or tracheostomy tube to treat sleep disordered breathing.

Emerging/Experimental Therapies

A number of experimental therapies for SMA have been developed and are currently in clinical testing. These include *SMN1* gene replacement therapy, small molecules designed to alter *SMN2* mRNA splicing, and other small molecule approaches aimed at motor neuron protection and muscle enhancement. Two reports were identified describing early stage, Phase 2 results on experimental therapies. Although these studies report on experimental interventions not approved for clinical use and have thus been excluded from the evidence review, they are described briefly to highlight emerging therapies for SMA.

Olesoxime

One strong-quality trial[57] tested this potentially neuroprotective agent against placebo among subjects 3-25 years of age with Type II or Type III SMA. There were 108 subjects randomized to olesoxime and 57 to placebo. After 24 months, there was no significant difference (p=0.0676) in the change of the primary outcome score (the Motor Function Measure domains 1 and 2).

Gene Therapy

One moderate-quality study evaluated gene therapy among 15 patients with Type I SMA.[58] The primary outcomes of this Phase 1 trial were safety and ventilator-free survival. Three subjects received a lower dose than the remaining 12 subjects. Mean ages at treatment were 6.3 months and 3.4 months for the low and high dose groups, respectively. By at least 20 months of age, all children were alive and did not require mechanical ventilation (one child required ventilation at 29 months of age because of hypersalivation; after salivary-gland ligation, ventilation was required 15 hours/day).

Among the 12 infants who received the higher dose: 11 could sit unassisted for 5 seconds and 9 for at least 30 seconds; 11 had head control, 9 could roll over, 2 could crawl, pull to stand, stand independently, and walk independently; and, 11 could speak. Eleven of the 12 infants had CHOP INTEND scores >40 by about 10 months of age, while scores for the 3 infants receiving the lower dose remained below 40 throughout the 20 month follow up. The factors that influenced the quality rating included lack of information about whether those conducting outcome assessments were blinded from the patients dosing group and from previous assessments. Additional clinical trials are in development to assess efficacy in patients with Type 1, and safety and efficacy in patients with Type II.

Effectiveness of Treatment

Outcomes

Several outcome measures have been used to assess the effectiveness of nusinersen. Across the studies, primary endpoint/outcome measures have targeted a) survival, b) ventilator dependence (>16 hours/day for 21 days), and c) motor development and function. Intermediate biomarkers include ulnar compound muscle action potential amplitude (CMAP), electrical impedance myography (EIM) high reactance slope, and survival motor neuron (SMN) mRNA levels in blood, and serum protein analytes.[59] Some biomarkers appear to predict functional clinical outcomes, and have been assessed in clinical trials as secondary endpoints. However, survival and ventilator dependence, and select measures of motor development, have been refined to be

sensitive to treatment effects and disease progression in SMA populations and validated for use as a primary outcome for this clinical population across developmental stages.[25,26,39,40,59] These primary outcome measures are reviewed briefly below.

Overview of Studies on Nusinersen

Studies of nusinersen funded by its manufacturer, Biogen, include: CHERISH (Phase 3 randomized trial in patients with later-onset SMA; clinicaltrials.gov registry NCT02292537); ENDEAR (Phase 3 trial in patients with infantile-onset SMA; clinicaltrials.gov registry NCT102193074), NURTURE (Phase 2 open-label study of subjects with presymptomatic infants with SMA; clinicaltrials.gov registry NCT02386553), EMBRACE (Phase 2 study of subjects not eligible for CHERISH or ENDEAR; clinicaltrials.gov NCT02462759), and SHINE (an open-label extension study of nusinersen studies; clinicaltrials.gov NCT02594124). These trials are in different stages of completion. Results have been reported in scientific journals on a Phase 2 trial with SMA patients with Type II and III (ages 2 to 14 years of age), and on Phase 2 and Phase 3 trials (ENDEAR) for infants with SMA (clinical symptom onset <6 months of age). No peer-reviewed publications with results are available from NURTURE, CHERISH, EMBRACE, or SHINE. Some studies have more than one publication or report with interim results. To be clear in the description of the evidence, we do not use the study names below but instead focus on the study characteristics and results.

Table 11 summarizes the published treatment reports included for consideration in this review, with overall quality assessment rating. Detailed ratings of these published reports are presented in Appendix A. Evidence from these studies is reviewed below. Table 12 lists the Grey literature reports (published and unpublished in searchable databases) included in this review. As described in the Methods, quality rating is not assigned to grey literature because they lack the granular elements necessary to assess quality.

Table 11. Treatment Evidence – Peer-Reviewed Reports

First Author	Pub Year	SMA Type (Study Type)	Overall Quality Rating
Chiriboga[60]	2016	Type II, III (Ph1/2)	Weak
Hache[61]	2016	Type II, III (AEs, Ph1/2)	Weak
Finkel[62]	2016	Type I symptomatic (Ph2)	Moderate
Finkel[63]	2017	Type I symptomatic (Ph3)	Strong

AEs=adverse events

Table 12. Treatment Evidence – Grey Literature

Published Grey Literature[†]			
First Author	**Pub Year**	**SMA Type**	**Source**
Mercuri[64]	2017	Type II, III (Ph3)	Conference poster
Servais[65]	2017	Infantile-onset Symptomatic (Ph3)	Conference poster
Hwu[66]	2017	Infantile-onset, Presymptomatic (Ph2)	Conference poster, interim results
DeVivo[67]	2017	Infantile-onset, Presymptomatic (Ph2)	Conference presentation, interim results
Unpublished Grey Literature[‡]			
First Author	**Pub Year**	**SMA Type**	**Source**
Crawford[68]	2017	Presymptomatic	Conference poster
Jones[69]	2016	Types II, III, IV	Conference poster

[†]Published in searchable database
[‡]Not published in searchable database, posters provided by CureSMA Scientists.

Effectiveness of Nusinersen – Clinical Detection

The following section presents the studies identified for inclusion, organized by SMA Type/symptom onset.

SMA Type II and III (Onset ≥ 6months, Ages 2 to 14 years)

Phase 1/2

A phase one study to assess safety and evaluate pharmacokinetics enrolled 28 subjects with Type II and Type III SMA between the ages of 2 and 14 years.[60] Six subjects each received nusinersen 1 mg, 3 mg, 6 mg, and ten received nusinersen 9 mg. Of these, 24 subjects enrolled in an extension study (observational), with results reported 9-14 months after their initial dose.

Adverse Events. No significant adverse events were reported.[60,61] However, lumbar puncture was associated with headache (11% of lumbar punctures), back-pain (11% of lumbar punctures), and post-lumbar puncture syndrome (11% of lumbar punctures).[61]

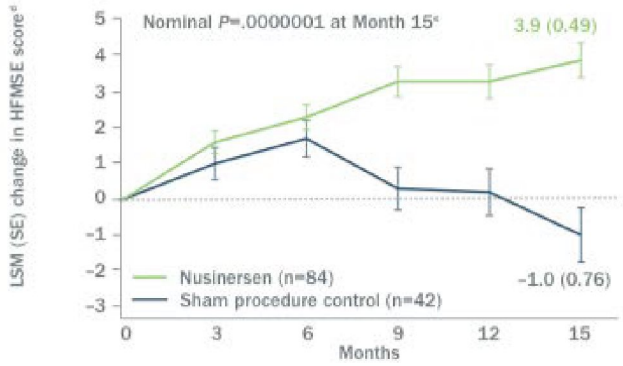
Outcomes. Subjects who received nusinersen 9 mg. had a statistically significant improvement (p=0.016) in the Hammersmith Functional Motor Scale Expanded (HFMSE).[70]

The overall quality of evidence from this study was rated as weak due to lack of information about who conducted the assessments, study blinding, and the aggregate grouping of subjects (ages 2 to 14 years) without further stratification or information about differences by age or disease duration.

Phase 3

Study abstracts were identified reporting on a Phase 3 clinical trial was conducted following the completed Phase 2 trial[60] described above. Study design, safety, and endpoint results were described through an oral presentation and poster session at the American Academy of Neurology Annual meeting (April 2017). This Phase 3 randomized, controlled trial (RCT) included 126 participants 2 to 12 years of age with later-onset SMA (likely to develop Type II or Type III SMA).[64] Most (88%) had 3 *SMN2* copies. Participants were randomly assigned (2:1) to receive nusinersen (n=84) or sham-control (n=42) group, stratified based on age at screening (<6 vs. ≥6 years). The average age at screening for trial participation was 3 years in the control group and 4 years in the treatment group.

Figure 2. Changes in HFMSE Scores (Motor Skills) Across 15 Months Intervention: Nusinersen vs. Control Group[64]



Adverse Events. Nusinersen was considered safely tolerated, with treatment group participants experiencing significantly less adverse events than the control group.

Outcomes. Changes from baseline to the month 15 endpoint were significantly greater for the treatment group participants (see Figure 2). Children receiving nusinersen demonstrated significantly greater gains in motor function at follow up than control group participants, who experienced a decline in function during this period. No further information was reported for outcomes by age or disease duration.

Participants completing this trial were invited to enroll in an ongoing, open-label extension study for follow up after 15 months.

SMA Type I, Early Infantile-onset (<6 months of age), Symptomatic Infants

Phase 2

Between May 3, 2013, and July 9, 2014, 20 subjects were recruited into a Phase 2 open-label study of nusinersen for infants diagnosed with SMA, with symptom onset before 6 months of age.[62] Subjects had to have symptoms develop between from 3 weeks-6 months and be no more than 7 months old at the time of recruitment. The first four subjects began with loading doses of nusinersen 6 mg (days 1, 15, 85) and then 12 mg on day 253 and every 4 months later. The remaining 16 subjects received nusinersen 12 mg for each dose. The two groups were similar. Among those who received loading doses of nusinersen 6 mg., all 4 had 2 *SMN2* copies and among those who received the loading dose of nusinersen 12 mg., 13 had 2 *SMN2* copy numbers, 2 had 3 copy numbers, and 1 had an unknown number (due to death before sample was collected

and analyzed). Subjects were to be followed until the endpoint of death or permanent mechanical ventilation.

Adverse Effects. In an interim analysis done on January 26, 2016, there were no serious adverse events associated with nusinersen.[62]

Outcomes. Improvements were observed overall in motor function from the time of study enrollment. Those with 3 *SMN2* copies relative to those with 2 *SMN2* copies appear to have greater improvement. A comparison group of infants from a separate natural history case series showed no improvement or declines in motor function.[25]

At last analysis, 13 of 20 infants were alive (65% survival). This represented a significant divergence (p=0.0014) in survival probabilities derived from a comparative natural history case series of 17 infants with SMA (<20% survival in a similar follow up interval).[25]

This report was rated as moderate quality because of the lack of information regarding who conducted the outcome assessments and whether raters were blinded to previous scores.

Phase 3

Following the completion of the Phase 2 trial,[62] a larger strong-quality Phase 3 efficacy trial was conducted.[63] Infants from 31 treatment centers with infantile-onset SMA with two copies of the *SMN2* gene with symptoms before 6 months of age were eligible for this phase three trial. Screening for participation had to begin by 7 months of age and this phase could take up to 3 weeks. Subjects were randomized (2:1) to nusinersen or sham therapy, with loading doses on days 1, 15, 29, and 64, and maintenance doses on days 183 and 302. The primary outcomes included motor-milestone response and ventilator-free survival. Motor-milestone response was based on the HINE-2 score, excluding voluntary grasp. A response was improvement in at least one category and more categories with improvement than categories with worsening.

An interim analysis on June 15, 2016[63] led to early termination of this study. At this point, there were 80 in the treatment group and 41 in the control group who had received at least one procedure; and 73 in the nusinersen group and 37 in the control group enrolled for ≥ 6 months before the last visit.

Outcomes. Infants who received nusinersen were more likely to have event-free survival after 1 year than those who did not receive nusinersen (61% in the nusinersen group and 32% in the control group had event-free survival after 1 year, p=0.005).

For the motor-milestone response in the final analysis, 41% of infants had a response versus none in the control group. This included: full head control (22%), rolling over (10%), independent sitting (8%), and standing (1%).[63]

Results from additional analyses of these Phase 3 trial data were presented in a poster session (October 2017) at the International Annual Congress of the World Muscle Society in Saint Malo, France,[65] examining treatment outcomes further stratified by total disease duration ≤12 weeks and >12 weeks. This poster session report found that compared with infants with disease symptoms for more than 12 weeks, those with a shorter disease duration (≤12 weeks) had greater likelihood of ventilator-free survival and improved scores on the HINE-2.

Figure 3. Phase 3 Nusinersen Treatment Outcomes for Infantile-onset SMA (Type I) with Clinical Detection, by Disease Duration (≤ 12 weeks vs. > 12 weeks)

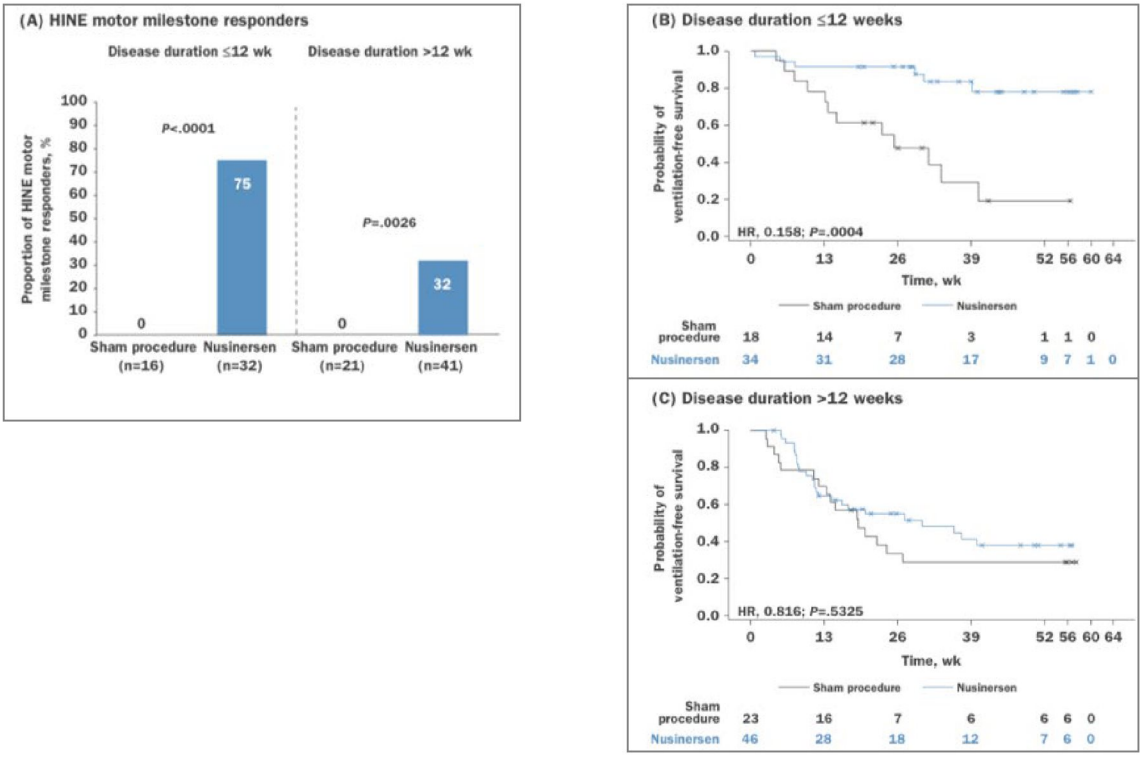


Figure A shows motor outcomes by treatment group for disease duration ≤ 12 weeks vs. > 12 weeks. Figures B and C show event-free survival probabilities for disease duration (≤ 12 weeks (Fig. B) and disease duration > 12 weeks (Fig. C).

Effectiveness of Nusinersen - Presymptomatic Detection

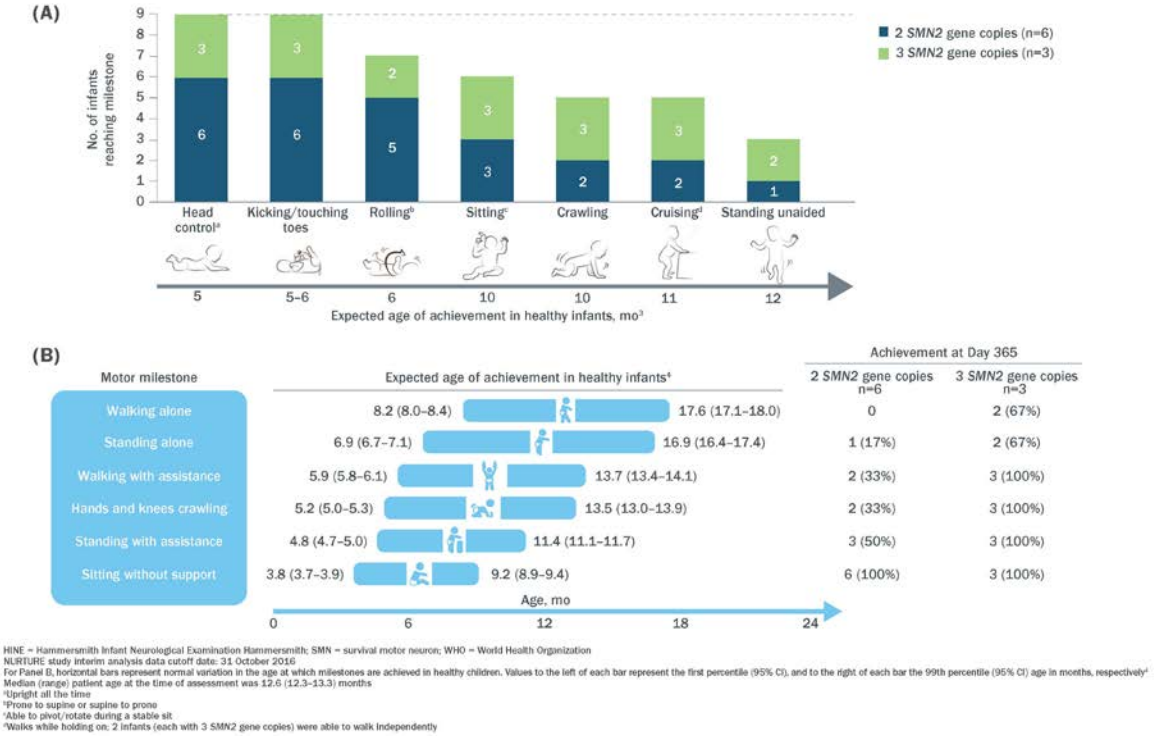
No peer-reviewed published reports were identified that evaluated outcomes for individuals identified presymptomatically compared to usual clinical case detection. However, interim results from an ongoing Phase 2 study of nusinersen for infants diagnosed with SMA who are presymptomatic have been reported[66,67] and are described below.

SMA Type I, Presymptomatic Infants (<6 months of age)

A published abstract (April 2017)[67] provides updates regarding the status of a phase 2 study of infants with presymptomatic SMA. This ongoing study is enrolling infants with presymptomatic, confirmed SMA, who received first study dose of nusinersen ≤6 weeks of age. At the time of presentation, 20 infants with presymptomatic SMA were enrolled. Early detection and diagnosis of participating infants was through: a sibling with SMA (n=15), newborn screening pilot/initiative (n=3), prenatal screening (n=1), and known carrier status (n=1). A poster[66] presented at the International Annual Congress of the World Muscle Society (October 2017) described interim outcomes. Of the 20 subjects enrolled, none required respiratory intervention nor had died. Among the 9 infants enrolled for one year, 9 met HINE motor milestones for head control and kicking, 7 achieved rolling, 6 sitting, 5 crawling, 5 cruising, and

3 standing unaided. Of these 3, all achieved age-expected HINE motor milestones. Infants with 3 *SMN2* (n=3) copies achieved milestones throughout the 1 year follow up period, while fewer infants with 2 *SMN2* copies (n=6) achieved developmental milestones after about 6 months of age. Figure 4 shows the interim results for these motor milestone outcomes on Day 365.[66]

Figure 4. Achievement of (A) HINE and (B) WHO Motor Milestones after 1 Year of Nusinersen: Day 365 Study Visit (N=9)



HINE = Hammersmith Infant Neurological Examination Hammersmith; SMN = survival motor neuron; WHO = World Health Organization
NURTURE study interim analysis data cutoff date: 31 October 2016
For Panel B, horizontal bars represent normal variation in the age at which milestones are achieved in healthy children. Values to the left of each bar represent the first percentile (95% CI), and to the right of each bar the 99th percentile (95% CI) age in months, respectively[4]
Median (range) patient age at the time of assessment was 12.6 (12.3–13.3) months
[a]Upright all the time
[b]Prone to supine or supine to prone
[c]Able to pivot/rotate during a stable sit
[d]Walks while holding on; 2 infants (each with 3 *SMN2* gene copies) were able to walk independently

At least one infant with 2 *SMN2* copies who has continued to achieve milestones within normal limits was identified through newborn screening for SMA.[50] After screening positive as a newborn, the infant was referred and clinically diagnosed at 7 days of age, enrolled in the trial at age 13 days, and began nusinersen at age 15 days. At 12-month follow up, the infant has met all developmental milestones within normal limits and continued to be asymptomatic.

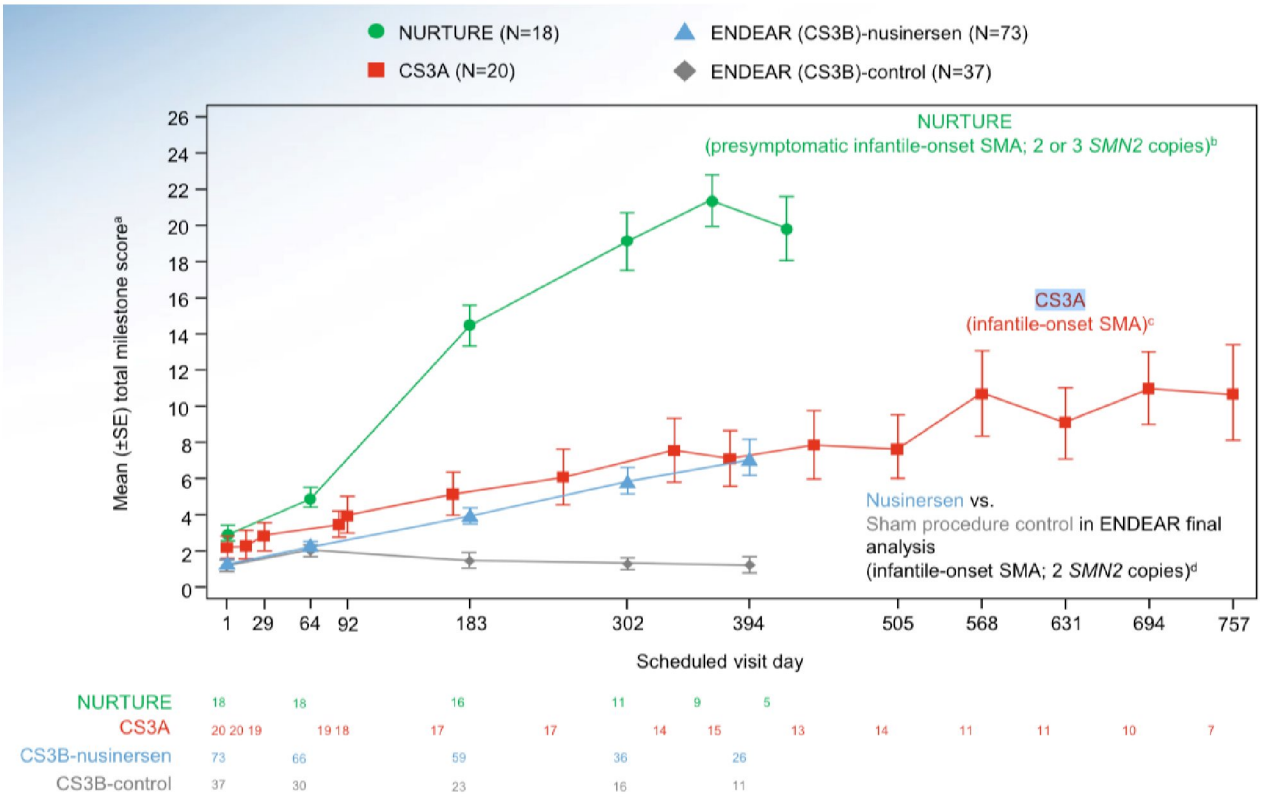
An unpublished poster presented at Cure SMA's Annual SMA Conference[68] included additional information about the presymptomatic infants in this trial who had siblings with SMA (n=15). Thirteen of the 15 had completed the 183 Day assessment. Among these, 8 had siblings who could not sit independently. Five of these 8 infants who received nusinersen presymptomatically (62.5%) could sit independently. Six of these 8 infants were >7 months of age (when most babies sit on their own), suggesting that 62.5% is a lower bound estimate of discordance between siblings on achieving this sitting milestone. In addition, of the other 5 presymptomatic infants whose sibling could sit but not walk, 2 infants receiving nusinersen presymptomatically could walk on their own (40%).[68] These results are better than seen in 265 siblings with SMA described in the Cure SMA sibling database, 1996-2016, which showed that among sibling pairs with SMA, the majority (87%) have concordant phenotypes and motor milestone achievement.[69]

These reports are from unpublished, non-refereed conference presentations and have not undergone peer-review.

Treatment Timing – Relative Effects by SMA Type (Symptom Onset)

The figure below synthesizes findings across studies of nusinersen. This figure has been presented in multiple conference presentations (e.g., the Annual Meeting of the Academy of Neurology (April 2017).[69,71] It illustrates the HINE-2 over time for subjects enrolled in three studies, including infants with SMA Type I a) identified and treated presymptomatically (green line), b) identified and treated symptomatically (red and blue lines), and c) identified symptomatically but not treated with nusinersen (grey line). Although this implies that presymptomatic identification is associated with better outcomes, the duration of follow-up is shorter than for those subjects enrolled in the other studies.

Figure 5. Mean Total Milestone Score in Studies of Nusinersen



Summary: Evidence Regarding Treatment Outcomes for Early Detection

Data support that therapies such as nusinersen or gene therapy lead to a decreased risk of ventilator dependence or death and improved motor outcome within the first two years of life in those with SMA type I. Emerging data highlight the importance of *SMN2* copy number in predicting disease severity and potentially for treatment outcome. Most data are unpublished and the duration of follow-up is limited to about 2 years of life, with many reports limited to about 1 year of life.

No study has directly compared outcomes for presymptomatic compared to symptomatic identification for SMA. Evidence supporting the benefit of early detection of SMA includes:

- A *post-hoc* analysis not available in the peer-reviewed literature suggesting that nusinersen treatment outcomes are improved when symptoms have been present for no more than 12 weeks compared to treatment that begins later.
- Unpublished data regarding a Phase 2, open-label study of nusinersen for asymptomatic subjects beginning therapy by six weeks of life, suggesting improved motor milestone development through about 1 year of life compared to symptomatic subjects at interim analysis with 9 of 20 patients.

3 PUBLIC HEALTH IMPACT – POPULATION OUTCOMES

Key Question 9: *What is the impact of newborn screening on the Public Health of the population in terms of projected numbers affected by screening and projected health outcomes?*

Overview of Process

Evidence Evaluation and Methods Workgroup

In April 2011, an Evidence Evaluation and Methods Workgroup met to consider methods and approaches utilized by the external Evidence-based Review Group (ERG) for the Secretary of Health and Human Services' Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC). One of the recommendations from this group was to incorporate the application of decision analysis into the evidence review process. An April 2012 publication[72] coauthored by some of the workgroup members noted that a decision analytic model "could provide an estimate of the range of cases prevented, deaths prevented, and/or number of children requiring treatment, as well as other health outcomes, for universal screening compared to clinical ascertainment." Since the recommendations were made, decision analytic modeling has been used as part of the evidence review process for hyperbilirubinemia, Pompe disease, mucopolysaccharidosis type I disease (MPS I), and, most recently, X-linked adrenoleukodystrophy (X-ALD). Spinal muscular atrophy (SMA) is the fifth condition to incorporate decision analytic modeling into the evidence review and synthesis process.

Objectives of Decision Analysis

Decision analysis is a systematic approach to decision making under conditions of uncertainty that has been applied to clinical and public health problems.[73] Decision analytic models can be used to simulate randomized clinical trials for new health interventions, to project beyond the clinical trial time frame, or to compare treatment protocols not directly compared in head-to-head trials. The decision analytic approach allows the decision maker to identify which alternative is expected to yield the most health benefit. It can also allow researchers to characterize the uncertainty associated with projections of clinical and economic outcomes over the long-term,[74] which is important given the lack of long-term outcomes data for most conditions considered for newborn screening.

A decision analytic model (or decision tree) defines the set of alternatives and short- and long-term outcomes associated with each alternative. In the application to screening for SMA, this approach was anticipated to aid in the estimation of the range of health outcomes that could be expected for universal newborn screening of SMA disease compared with clinical identification.

Applying Decision Analysis to Screening for SMA Disease

Published literature for rare phenomena including SMA disease is very limited with respect to data for prevalence, natural history, or response to treatment. For this review, we are able to utilize preliminary data from pilot screening programs in New York[50] and Taiwan[51], in combination with additional published and unpublished data. By utilizing modeling, we could supplement the evidence base identified through the systematic review by providing projections of key health outcomes at the population level for newborn screening compared with clinical identification. This process also serves to highlight evidence gaps and areas with the most uncertainty, thereby enhancing the overall decision making process.

Expert Panel Meeting Process

Clinical and scientific experts in the screening and treatment of SMA disease were identified and invited to serve on the Technical Expert Panel (see Table 1Table 1). TEP members were asked to provide input on the design and assumptions of the decision analysis model, including the identification of key health outcomes to be included in the analysis. A series of three TEP meetings (see Table 13) were conducted to identify sources for input probabilities for each outcome in the model; to provide feedback on the structure of the initial and revised decision analytic models, including the relevant timeframe for key health outcomes; and to develop assumptions where little or no data were available. All meetings were conducted via webinar. TEP participants received a discussion guide that included background information, a schematic of the model structure, proposed data inputs, and proposed modeling inputs for discussion by the group. The identification of data sources and the development of a decision analytic model is typically an iterative process.

Table 13. Timeline of Decision Analytic Modeling for SMA Disease Screening

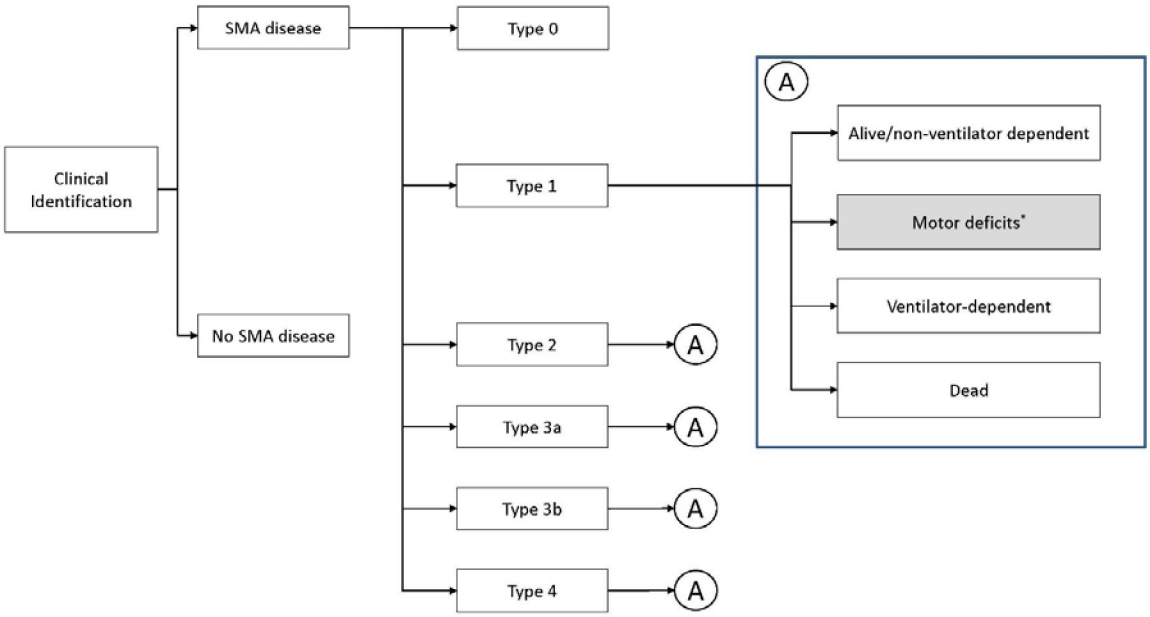
Date	Milestone
May 2017	SMA disease nominated for addition to uniform newborn screening panel; referred to external CRW
July 2017	Initial development of decision analytic model to evaluate newborn screening for SMA disease
July 2017	TEP meeting #1 – review model structure
October 2017	TEP meeting #2 – review revised model structure and preliminary evidence review summary
December 2017	TEP meeting #3 – review revised model structure and input assumptions
January/February 2018	Final SMA evidence review report and decision analysis findings presented to ACHDNC

Methods

An initial decision analysis model was developed concurrently with the evidence review process. The initial model was reviewed with the expert panel in July 2017. A schematic of the final SMA newborn screening decision model is shown in Figure 5.Figure 6.

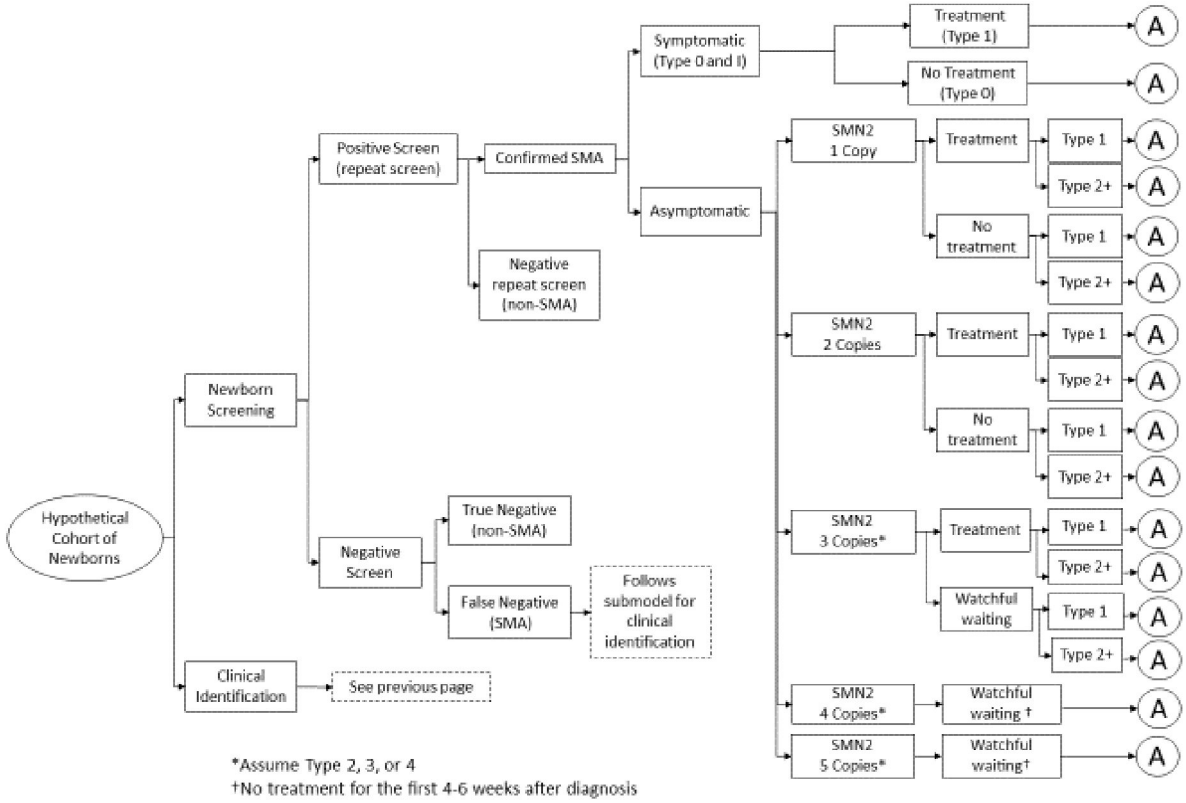
Figure 6. SMA Model Schematic

5aa. Clinical Identification Submodel



*May not be included in the final model

5.b. Universal Newborn Screening Submodel



*Assume Type 2, 3, or 4
†No treatment for the first 4-6 weeks after diagnosis

The key features of the decision analytic model are as follows:

- Target population: Annual newborn cohort for the US (i.e., 4 million newborns), excluding newborns at higher risk for SMA disease (i.e., with a family history of SMA). Estimation of health benefits is restricted to infants with Type I SMA
- Interventions: A strategy of universal newborn screening is compared with diagnosis through clinical identification. The analysis assumes that identified cases of severe SMA disease meeting treatment criteria will be treated with nusinersen whether they are diagnosed through newborn screening or through clinical identification. In other words, the key difference in determining outcomes between the two modeled cohorts—newborn screened or clinically identified—indicates the benefits of earlier diagnosis and earlier treatment.
- Timeframe: 1 year
- Key health endpoints: Mortality and ventilator-dependence

Two additional TEP meetings were held in October and December 2017 to review the decision tree and proposed set of parameter inputs for the decision model. Parameter inputs were based on published and unpublished data. The model structure and parameter estimates were revised following each TEP meeting based on additional data sources identified and supplemented by expert opinion in cases where no data were available. The sources of published and unpublished data are listed in Table 14. The final set of parameter inputs and associated ranges for the analysis are shown in Table 15 through Table 20 below.

Table 14. Key Data Sources for Decision Model Input Parameters

Reference	Citation
Calucho M, Bernal S, Alías L, March F, Venceslá A, Rodríguez-Álvarez FJ, et al. Correlation between SMA type and *SMN2* copy number revisited: an analysis of 625 unrelated Spanish patients and a compilation of 2,834 reported cases. Neuromuscular Disord 2018; in press.	46
Chien YH, Chiang SC, Weng WC, Lee NC, Lin CJ, Hsieh WS, et al. Presymptomatic diagnosis of spinal muscular atrophy through newborn screening. J Pediatr. 2017;190:124-9.	51
Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, et al. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. N Engl J Med. 2017;377(18):1723-32.	63
Hwu W-L, De Vivo DC, Bertini E, Foster R, Bhan I, Gheuens S, et al. Outcomes after 1 year treatment in infants who initiate nusinersen in a pre-symptomatic stage of spinal muscular atrophy (SMA): interim results from NURTURE study. [Presentation] 22nd International Annual Congress of the World Muscle Society, Saint Malo, France. 4 October 2017.	66
Kraszewski JN, Kay DM, Stevens CF, Koval C, Haser B, Ortiz V, et al. Pilot study of population-based newborn screening for spinal muscular atrophy in New York state. Genetics in Medicine. 2017;epub ahead of print.	50
Servais L, Farrar M, Finkel RS, Kirschner J, Muntoni F, Sun P, et al. Nusinersen demonstrates greater efficacy in infants with shorter disease duration: final results from the ENDEAR study in infants with spinal muscular atrophy (SMA). [Presentation] 22nd International Annual Congress of the World Muscle Society, Saint Malo, France. 4 October 2017.	65
Sugarman EA, Nagan N, Zhu H, Akmaev VR, Zhou Z, Rohlfs EM, et al. Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of >72,400 specimens. Eur J Hum Genet. 2012;20(1):27-32.	11
Swoboda K, Zhang R, Bower A, Latroul J. Project Cure SMA data report for TEP committee. Boston: Massachusetts General Hospital; 2017 [updated 16 Jan 2018; cited 17 Jan 2018].	75

Overall Approach

The model estimates outcomes for two identical cohorts of newborns not at higher risk for SMA, one cohort receives newborn screening for SMA and one cohort does not. Therefore, the two strategies for identifying patients with SMA compared in the model are:

1. Newborn screening for all newborns not at higher risk for spinal muscular atrophy, and
2. No newborn screening/cases are identified via clinical identification.

The key endpoints are 1-year mortality and 1-year survival without ventilator dependence for Type I SMA cases. The model also estimates the number of newborns identified by type (Type I, Type II+), as well as screening program outcomes for the newborn screened cohort. Each parameter in the model is defined with a 'most likely' estimate and a range for sensitivity analyses. Ranges are projected for each outcome. The model was programmed using Treeage software.

Key Assumptions

Incidence of SMA is based on published data on clinically-identified cases of SMA.[11] The incidence of SMA (overall and by type) with newborn screening (Table 15, Table 16) is assumed to be consistent with the estimates presented in the evidence (Table 2, Table 4).

Screening probabilities were derived from the New York pilot program (Table 17). In the base case analysis, conditional probabilities for symptomatic and asymptomatic SMA cases given a confirmed SMA diagnosis are based on the New York and Taiwan pilot studies. Initial screening data from Taiwan and New York state indicate a slightly lower incidence but only 8 cases to date have been identified across both pilot programs. Probabilities of SMA type conditional on being symptomatic and asymptomatic are derived from Calucho et al (Table 17).[46]

Estimation of health benefits is restricted to Type I SMA. Under clinical identification, it is assumed that all patients with Type I SMA are treated with nusinersen. Current clinical practice may also include patients with other types; however, only outcomes for SMA Type I are reflected in the decision model.

Under newborn screening, it is assumed that the diagnosis of SMA will be confirmed before 2 weeks of age (by 11 days in the Taiwan screening pilot.[51]) At that time, all symptomatic patients will be treated with nusinersen. For asymptomatic patients, treatment decisions will be based on *SMN2* copy number, with the CURE SMA foundation recommending that all infants with 2 or 3 copies of *SMN2* be treated.[55] The proportion of Type I patients conditional on copy number is estimated using data from a registry of SMA patients to derive possible distributions of type conditional on copy number.[75] Timing and eventual onset of symptoms for asymptomatic SMA cases for newborn screening are unknown. SMA Type I cases identified through newborn screening are assumed to be treated earlier than a hypothetical identical cohort of SMA Type 1 cases that are clinically identified.

Outcomes at age 12 months for newborns treated with SMA are derived from two data sources: (1) a randomized, double-blind, sham-controlled phase 3 efficacy and safety trial of nusinersen in symptomatic infants with SMA[63,65] and (2) an ongoing open-label, single-arm, phase 2 study evaluating nusinersen among presymptomatic infants with SMA.[66] Outcomes for clinically identified newborns are projected based on data from the overall group results from the Finkel et al. paper (Table 18).[63]

We use the comparison between early- and late-treated cohorts of symptomatic SMA type 1 patients to estimate the effectiveness of treatment associated with earlier identification and treatment under newborn screening (Table 18 through Table 20).[65] There may be additional benefits if treatment is considerably earlier in asymptomatic patients identified under newborn screening and we will explore this in sensitivity analysis.

Table 15. Incidence of SMA

Description	Most Likely	Range (min-max)*	Source
Probability of SMA diagnosis through clinical identification (all forms)	0.000091	0.00004-0.00019	Sugarman et al. 2012,[11] range derived from min/max CI estimates in Table 2 (1 in 11,000; range: 3.8-19.1/100,000)
Probability of SMA diagnosis through newborn screening (all forms)	0.000091	0.00004-0.00019	Assumed†

*Minimum and maximum values derived from 95% confidence interval assuming a binomial distribution
†This number does not represent the incidence of SMA through newborn screening. It is assumed that under newborn screening, the incidence of SMA is the same as under clinical identification.

Table 16. Conditional Probability of SMA Type, Clinical Identification

Type	Most Likely	Range (Min-Max)*	Source
Type I**	0.54	0.41-0.67	Table 4. Subtype incidence
Type II	0.18	0.11-0.24	Table 4. Subtype incidence
Type III	0.25	0.19-0.31	Table 4. Subtype incidence
Type IV	0.03	0.02-0.05	Zerres et al., 1995;[28] assumption

*Minimum and maximum values derived from 95% confidence interval assuming a binomial distribution
**Includes Type 0

Table 17. Parameter Inputs, Newborn Screening for SMA

Probability	Best Case	Range (min-max)†	Source
Abnormal screen	0.0132	0.0118-0.0164	Calculated using data from Kraszewski et al. 2017;[50] personal communication Jan 2018 from NY Pilot
Positive confirmatory test given abnormal screen	0.0069	0.0002-0.0378	Calculated using data from Kraszewski et al. 2017;[50] personal communication Jan 2018 from NY Pilot
Carrier given abnormal screen	0.9931	0.9622-0.9998	
Probability of SMA given negative screen (false negative)	0	0-0.05	Calculated using data from Kraszewski et al. 2017;[50] personal communication; range assumed by authors based on expert opinion
Probability of being symptomatic by 11 days of life, given SMA diagnosis, assumed Type I‡	0.125	0.003-0.527	Calculated using data from Kraszewski et al. 2017[50] and Chien et al. 2017[51]
Probability of being asymptomatic by 11 days of life, given SMA diagnosis‡**	0.875	0.474-0.997	
2 copies of *SMN2*, asymptomatic	0.476	0.419-0.531	Derived from Calucho et al., in press[46]
Type I (2 copies *SMN2*)	0.910	0.857-0.953	
Type II-IV (2 copies of *SMN2*)	0.090	0.047-0.143	
3 copies of *SMN2*, asymptomatic	0.473	0.416-0.528	
Type I (3 copy *SMN2*)	0.082	0.042-0.136	
Type II-IV (3 copy of *SMN2*)	0.918	0.864-0.958	
4 copies of *SMN2*, asymptomatic	0.046	0.027-0.077	
Type I (4 copy *SMN2*)	0.051	0.002-0.320	
Type II-IV (4 copy of *SMN2*)	0.949	0.681-0.998	
5 copies of *SMN2*, asymptomatic	0.006	0.001-0.023	
Type I (4 copy *SMN2*)	0.000	0.000-0.842	
Type II-IV (4 copy of *SMN2*)	1.000	0.158-1.00	

*The 51st percentile of the 95% CI range was used as base case value to calibrate to 1 in 11000 incidence.
*Minimum and maximum values derived from 95% confidence interval assuming a binomial distribution
†The 50th percentile of the 95% CI range was used as base case.
‡In the base case, the conditional probabilities of symptomatic and asymptomatic SMA cases are based on the findings of the pilot screening programs in New York and Taiwan.
**Base case assumes no cases with 1 copy *SMN2* are asymptomatic.

Table 18. Clinical Outcomes of Symptomatic SMA Type 1 Cases with Nusinersen Treatment by 52 Weeks of Age[63]

Description	Most Likely	Range (min-max)*	Source
Probability of death among all treated infants†	0.183	0.079-0.356	Finkel et al. 2017[63]
Probability of ventilator dependence among all treated infants†	0.265	0.089-0.532	Finkel et al. 2017[63]

*Minimum and maximum values derived from 95% confidence interval assuming a binomial distribution
†"All treated infants" refers to the nusinersen-treated infants in the phase 3 clinical trials (see Finkel et al. 2017), derived

Table 19. Treatment Effectiveness for Symptomatic SMA Patients at 52 Weeks of Age by Disease Duration ≤12 weeks (Early) vs. >12 weeks (Later)[65]

Description	Most Likely (%)	Range (%, min-max)*	Source
Probability reduction of death between infants treated early† compared to infants treated later‡	63.8	45.8-79.3	Derived from Servais et al. 2017[65]
Probability reduction of ventilator-dependence between infants treated early† compared to infants treated later‡	65.1	39.1-86.2	Derived from Servais et al. 2017[65]

*Minimum and maximum values derived from 95% confidence interval assuming a binomial distribution

Table 20. Treatment Effectiveness for Asymptomatic SMA Patients (Treated at Less Than 6 Weeks of Age) at 52 Weeks

Description	Most Likely (%)	Range (%, min-max)*	Source
Probability reduction of ventilator-dependence and death†	100	70.1-100	Derived from Hwu et al. 2017‡[66]

*Minimum and maximum values derived from 95% confidence interval assuming a binomial distribution
†Probability reduction of death is assumed to be equal to the probability reduction of ventilator-dependence
‡This assumption is based on Hwu et al. (2017) that reported no deaths and no ventilator-assistance after one year among 9 genetically diagnosed presymptomatic infants who completed their one-year assessment and are likely to develop Type I or Type II SMA.

Results

Projected Cases of SMA Disease

We projected the annual number of SMA cases and associated phenotypes that would be identified with newborn screening compared with clinical identification (Table 21).

Table 21. Projected Cases for Newborn Screening for SMA Disease Compared With Clinical Identification for a Cohort of 4 Million Children in the US*

	Universal **Newborn Screening**	**Clinical Identification**
Type I	196 (82 - 413)	196 (82 - 413)
Symptomatic	45 (1 - 192)*	196 (82 - 413)
Asymptomatic	151 (133 - 363)*	--
Type II+	167 (70 - 351) - all asymptomatic at time of diagnosis (11 days)	167 (70 - 351)*
Total	364 (152 - 764)	364 (152 - 764)

*by 11 days of life
†At any age, clinical identification indicates all cases are symptomatic

Projected Health Outcomes for SMA Cases

We projected the health outcomes (i.e., mortality and ventilator-dependent cases) among SMA type 1 cases diagnosed through newborn screening (presumably treated before 6 weeks as in the clinical trial) and through clinical identification

Table 22. Projected 52-Week Outcomes for Type 1 SMA Cases (and Treated Before 6 Weeks), Base Case Estimate (Range)

	Universal **Newborn Screening**	**Clinical Identification**	**Cases or Deaths Averted**
Ventilator-dependent cases	4 (0 - 18)	52 (17 - 109)	48 (16 - 100)
Deaths	3 (0 - 13)	36 (15 - 75)	33 (14 - 68)

*Not at higher risk for SMA
†Ranges represent one-way sensitivity analysis on each parameter

Limitations

The analysis uses a simplified model to evaluate projected short-term outcomes for identified cases of SMA disease under a universal screening recommendation. The model includes 12-month outcomes of survival and ventilator-dependence, but does not quantify any additional health benefits (e.g., motor function) that could be associated with earlier identification and treatment of SMA disease. Since most deaths in untreated Type I SMA occur between 12 and 24 months, it is likely that most of the benefits of asymptomatic detection enabled by NBS will

occur beyond age 12 months; therefore, the results of this analysis are very conservative. The analysis also does not consider short- or long-term outcomes for later-onset SMA disease. For many of these later-onset cases, especially Type II SMA, newborn screening may yield additional benefits, especially if they are treated while asymptomatic. If the Cure SMA treatment algorithm is followed and all infants with 3 copies of *SMN2* are treated (presumably before 6 weeks of age) nearly all SMA type II infants will be assured asymptomatic treatment (based on data from Feldkotter et al. 2002[76]). The potential harms of treatment (i.e., adverse events associated with treatment) are not included. The analysis did not evaluate economic outcomes such as costs or cost-effectiveness of alternative screening modalities.

Limited data were available for a number of parameter inputs. In particular, very little data were available for the conditional probabilities of SMN copy number (Table 16) given a genetically confirmed diagnosis of SMA and treatment outcomes for asymptomatic SMA cases.

Given the rare nature of newborn screened conditions, data are typically scarce for conditions being considered for addition to the recommended uniform screening panel. Compared to other conditions that have been nominated and considered for addition to the panel, data for the consideration of SMA were considerably more sparse with respect to time horizon for outcome measurement (52 weeks) for both the estimation of treatment effectiveness and outcomes for cases treated with nusinersen under clinical identification (comparator strategy).

Summary

Earlier diagnosis and treatment is likely to result in reduced deaths and cases of ventilator-dependence by 1 year of life for newborn screening compared with clinical identification for Type I SMA. Additional benefits will likely accrue to other subtypes of SMA.

4 PUBLIC HEALTH SYSTEM IMPACT ASSESSMENT FOR SMA

Key Question 10: *What is the impact of implementing newborn screening of SMA on the Public Health System? What is the feasibility of population-based screening methods for SMA? What is the state of Readiness of State Newborn Screening Programs to Screen for SMA?*

- One state Newborn Screening (NBS) program has initiated a pilot study for SMA. Six others have mandates to screen population-wide or to conduct pilot studies, all of which are expected to begin before December 2018. Although a few NBS programs received funding to conduct pilot studies, all of the NBS programs conducting pilots will need to secure additional funding or increase their NBS fee in order to sustain screening once their pilot study is completed.
- The greatest facilitator for SMA implementation is that the screening test can be multiplexed with screening for severe combined immunodeficiency (SCID) which will allow for efficiency and will cut down on resources (equipment and personnel) needed. Programs conducting pilot studies are not able to multiplex because it requires consent.
- Challenges with SMA implementation that were frequently reported include: determining program policies around carrier reporting, determining what to do with late onset cases, cost of treatment, insurance/Medicaid reimbursement issues, and treatment equity.
- Most NBS programs in this assessment either will not or have not determined whether they would identify and report carriers upon initiation of population screening. There are many issues with detecting carriers including having genetic counselors available to contact and communicate with patients, the burden on follow-up programs, and causing unnecessary anxiety for patients/families.
- Administrative challenges and process issues can extend the time frame for implementation. Some of these challenges include increasing the newborn screening fee and/or obtaining funds, changing administrative rules, getting legislator buy-in and authority to screen. These processes often take several years.
- Implementation activities for SMA which include selecting and validating the screening test, developing the follow-up protocol, communicating with specialists, purchasing equipment, and hiring additional personnel is expected to take one to three years for the majority of NBS programs.
- Cost challenges include those related to confirmatory testing and treatment. Many NBS programs stated they are on a two-year legislative cycle and can only request a fee increase at this time. The long-term burden of this cannot be understated.

Key Questions: *What is the impact of implementing newborn screening of SMA on the Public Health System? What is the feasibility of population-based screening methods for SMA? What is the state of readiness of State Newborn Screening Programs to Screen for SMA*?

As part of the evidence review procedures, a Public Health System Impact (PHSI) assessment of expanding newborn screening for SMA was conducted by the Association of Public Health Laboratories (APHL) from August to December 2017. APHL evaluated individual state NBS programs' capability to implement screening for SMA. A survey had been previously developed

by APHL for other PHSI assessments and minor revisions were made. The process and results from the SMA assessment are described in this report.

Methods

Feasibility and Readiness

Feasibility is based on the degree to which the following exist:

- An established and available screening test
- A clear approach to diagnostic confirmation
- Acceptable treatment plan, and
- Established approach to long-term follow-up plans

Some of the key issues related to feasibility extend beyond the public health system and into personal medical care services.

Readiness refers to the overall national ability to adopt a condition into state NBS panels and is classified as:

- Ready: most NBS programs could implement within 1 year
- Developmental Readiness: most NBS programs could implement within 1–3 years
- Unprepared: most NBS programs would take more than 3 years to implement

The public health system impact assessment examines length of time it takes NBS programs to complete implementation activities. It is important to note that there are several activities that need to take place within a NBS program before implementation activities begin. Examples include getting authority to screen, meeting with state Advisory Committees, increasing the NBS fee and/or getting funds to screen, and obtaining legislative buy-in, identifying technology for screening and establishing growth of follow-up programs to accommodate management of an additional disorder screening. Each NBS program is unique with the process it goes through to add a new condition, however, these procedures often take several years to complete and should be considered in addition to the time it takes to complete implementation activities.

Fact Sheet

The fact sheet, which was created in collaboration with APHL, members from the Evidence-based Review Group (ERG) and individuals from state NBS programs (Appendix B). The fact sheet provided background information pertaining to SMA to assist individuals with completing the survey (Appendix C). The fact sheet was sent to NBS program directors along with an SMA survey. The SMA fact sheet included information such as incidence of the disorder, screening methods, resources/materials, workstation resources and capacity, personnel requirements, quality control and reported screening results, estimated costs, short-term follow up, and treatments. Fact sheet information includes screening outcomes and cost projections from a limited number of state NBS programs considering SMA screening or conducting a pilot study of SMA screening.

Survey

APHL developed a web-based survey instrument intended to evaluate NBS programs' readiness to implement comprehensive screening for SMA. The same survey has been pilot-tested in the

past and used for previous PHSI assessments (Appendix C). Minor revisions were made to the survey to make it specific to SMA. A question in the beginning of the survey was revised to exclude NBS programs that had conducted a budget analysis and include those that had only completed preliminary cost discussions. NBS programs that contract screening services did not receive questions pertaining to the screening test itself or to laboratory capabilities. There were also questions related to screening for carriers specifically for NBS programs that indicated they planned on screening for carriers. The survey instrument included questions related to implementation challenges, resources/factors that can hinder or aid in implementation and timeframe to complete implementation activities.

The survey link was sent to one NBS program designee (e.g., program director) in 53 U.S. states and territories (including Washington DC) via email. The survey email emphasized that the individual completing the survey should collaborate with necessary stakeholders (e.g., laboratory experts, follow-up staff, medical specialists, Title V directors, advocates, public health commissioners) prior to completing the survey link. The timeframe to complete the survey was from October 5, 2017 to November 17, 2017. All survey data was submitted electronically to APHL.

Webinar and Outreach

APHL conducted a webinar on October 4, 2017 to discuss the purpose of the PHSI assessment, benefits of completing the survey, and the SMA Factsheet. APHL discussed the PHSI assessment and survey at several meetings and conference calls. Throughout October and November 2017, APHL conducted active follow-up with survey non-responders through phone calls and emails to improve participation.

Interviews

NBS programs that had a mandate to screen for SMA, were conducting a pilot study, or had performed a budget analysis for SMA were excluded from the web-based survey; NBS program directors and representatives from such programs were interviewed by telephone. These respondents were provided the interview questions in advance and were asked to consult with stakeholders in their public health system. Stakeholders were encouraged to be on the call. APHL designed a combination of open- and close-ended interview questions (Appendix D) meant to assess challenges and facilitators. The interview tool included questions related to progress with regards to implementation, factors that will aid and hinder implementation, costs and timeframe for implementation activities. The questions were catered slightly for each program.

Data Analysis

Data were kept secure and reviewed for accuracy. Quantitative and qualitative data from the surveys were aggregated and analyzed using Qualtrics and Excel. Interview data were de-identified for anonymity.

Interview Results

Five NBS programs were excluded from the web-based survey and were invited by email to participate in an interview. Two of the five NBS programs did not respond and thus were not interviewed. We also reached out to two additional NBS programs known to have mandates or known to be launching a pilot to screen for SMA in the next year, both of which agreed to an

interview. Additionally, we also reached out to an NBS program that is not currently screening for SCID; since SMA will be multiplexed with SCID we wanted to get this NBS program's unique perspective. That state provided written responses to our interview questions. In total, we collected in-depth interview information from six state NBS programs. We spoke specifically to the NBS program director and in many cases, representatives from their laboratory and follow-up system. See Table 23 for NBS programs that have mandates or have/will begin pilots for SMA.

Table 23. NBS Programs with Mandates/Pilots

State	Legislative Mandate	Pilot Screening	Start Date/ Anticipated Start Date (Estimate)	Begin with Whole vs. Select Population	Completed APHL Interview
MA	X	X	January 2018	Whole	
MN	X		March 2018	Whole	X
MO	X		December 2018	Whole (No reporting at first)	X
NC		X	April 2018	Select	X
NY*		X	January 2016	Select	X
UT	X		January 2018	Whole	
WI		X	May 2018	Whole	X

Five of the six state NBS programs that were interviewed were conducting an SMA pilot study, have a pilot study planned in the next year, or have a mandate to screen for SMA. Each NBS program varies with regard to its progress made towards considering implementation.

State NBS Program Conducting SMA Pilot

As of January 29, 2018, two states (MA and UT) have begun statewide screening for SMA. The New York NBS program has been conducting a pilot for SMA since January 2016 at three state hospitals under an opt-in, consent-based protocol, as described in the systematic evidence review.

The NBS program conducting the pilot study (New York) explained that their biggest challenges for implementing SMA screening were deciding whether to report carriers, securing genetic counseling resources, and deciding how to handle late-onset cases. The affordability of treatment was noted as a system-wide challenge. The program has developed educational material and follow-up materials that will likely need to be adapted for population-based screening.

State NBS Programs with Mandates or Planning Pilot Studies

The four state NBS programs interviewed that have mandates or are planning pilot studies are in the early stages of implementation. Two of them will begin screening population-wide, while the other two will begin screening as a pilot study and then move to population-wide screening. They have all had discussions and made progress towards implementation activities including designing their screening algorithm, validating their method, acquiring equipment, thinking about staffing needs, designing educational materials and follow-up protocols, and identifying and communicating with medical specialists (See Figure 7). With regards to reporting, three of

the NBS programs do not plan to identify carriers and one is undecided. All of them stated that they would need to either increase their NBS fee or acquire additional funding to sustain long-term screening.

Figure 7. Implementation Status for States with Mandates or Planning Pilots

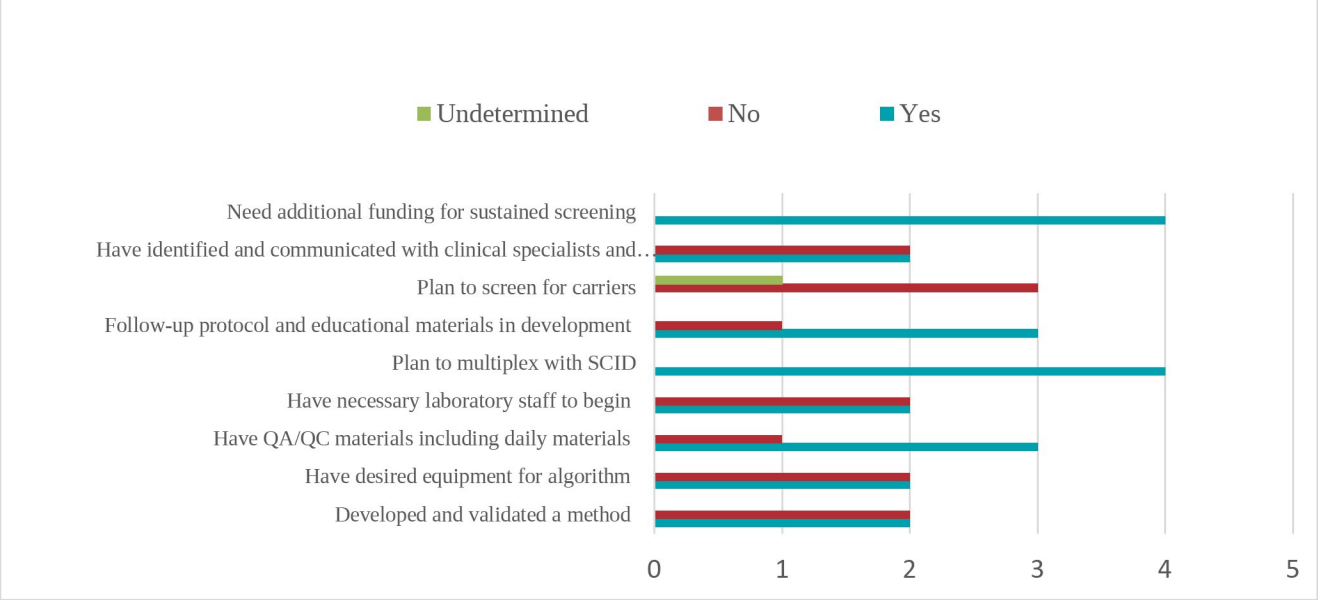
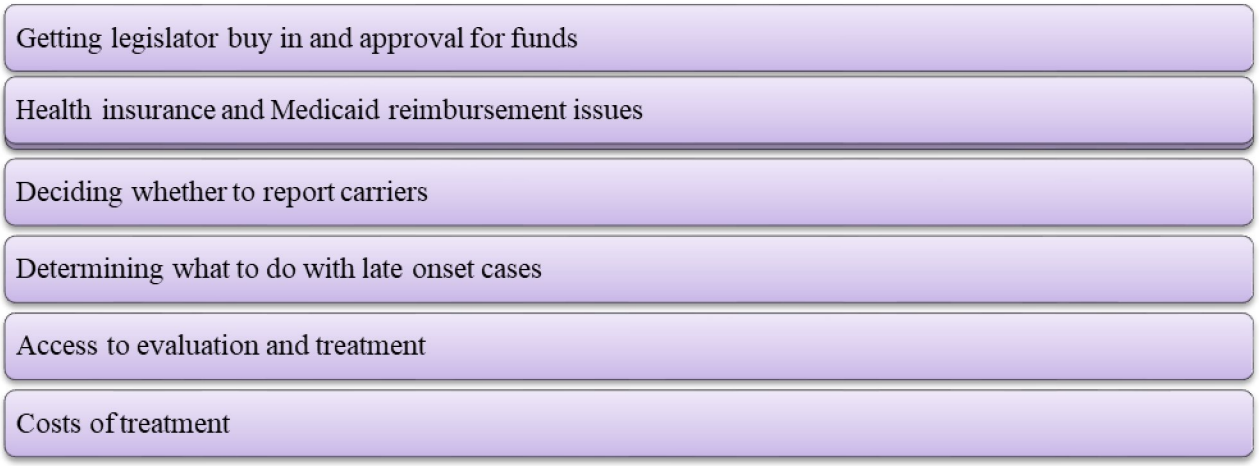


Figure 8. Challenges for SMA Implementation Mentioned During Interviews



Laboratory

The NBS program directors interviewed discussed their readiness for screening for SMA. Most directors mentioned that the biggest facilitator to screening was that SMA is capable of being multiplexed, or screened in tandem, with SCID. A benefit to screening in this manner is that it is efficient and often does not require the addition of equipment or personnel, except if *SMN2* copy number is being examined (a diagnostic but not a screening requirement). None of the NBS programs that are beginning with pilot screening are multiplexing with SCID because issues with

consent and funding make this prohibitive. All of the NBS program directors interviewed plan to multiplex once they transition from the pilot study to population-based screening.

It has been estimated that 1.5 to 2 full time employees (FTE) are needed for population-based multiplexed SCID and SMA testing to process 100,000 specimens annually. Generally, the NBS program directors indicated that they believed they had adequate laboratory personnel to begin SMA screening. Two of the 4 NBS program directors interviewed explained that they would need to add 1 laboratory FTE once population-based screening begins. Additionally, the SMA screening method can be validated in six months or less according to the laboratory personnel we interviewed. When SMA is multiplexed with SCID, the SCID assay also needs to be re-validated. The NBS program directors interviewed did not foresee challenges with either the validation process or screening method itself for SMA and expected to receive support from the US Centers for Disease Control and Prevention (CDC). Additionally, those interviewed planned on receiving quality assurance/quality control (QA/QC) materials from the CDC but stated that if a large number of states began screening for SMA at the same time, there could availability issues for these materials.

Three of the four NBS programs interviewed with mandates or planning pilot studies have decided to use a one-tier algorithm and one NBS program may use a two-tiered approach similar to the one used by the NBS program currently conducting a pilot. In order to conduct SMA screening, an NBS program needs real time PCR equipment and digital liquid handlers. This is the same equipment required to screen for SCID. NBS program directors interviewed explained that they would not need additional equipment to screen for the SMA, providing they were using a one-tier screening algorithm and examining the *SMN1* gene only. One of the NBS program directors planned to assess *SMN2* copy number as part of their screening algorithm and mentioned that they would need to purchase digital droplet PCR equipment. Another NBS director said they needed to purchase a liquid handler. The NBS programs interviewed explained that they would need minimal supplies including NBS reagents such as PCR master mix, *SMN1* and control gene primers and probes. Some NBS programs are developing a laboratory developed assay for SMA screening, while others plan to use a kit that is being developed by PerkinElmer.

Diagnosis and Follow-Up

The program directors interviewed discussed their readiness for dealing with the follow-up and diagnostic component for SMA. The majority of NBS programs with a mandate or beginning a pilot study are creating workgroups with medical experts and other stakeholders to develop follow-up protocols and educational materials for SMA screening. One NBS program was in the process of determining if it would screen for carriers and the other three NBS program directors explained they did not intend to screen for carriers. It was noted that the NBS programs would have to hire additional follow-up personnel if they screen for carriers. NBS programs that do not plan to identify or report carriers explained that they can utilize their current follow-up staff or add less than 1.0 FTE for follow-up, at least for the first year of screening. The NBS program that had not decided whether to report carriers were hoping to get guidance from their NBS Advisory Committees and other experts in this area. Many of them discussed the issues with reporting carriers including having genetic counselors available to contact and communicate with patients, the burden on follow-up, costs of follow-up, and causing unnecessary anxiety for patients/families.

The NBS program directors interviewed stated that they have begun to identify confirmatory and diagnostic centers they will utilize in their states for SMA. Most of them explained that they were comfortable with the number of centers given the incidence of the disorder. They also noted that they were working with pediatric neurologists, which is a new group of specialists that will be handling referrals for them. Whenever a new group of specialists is required for screening for a new disorder, it takes time to identify and develop these new relationships. Some of those interviewed explained that they were concerned that patients in certain geographical areas would have difficulty getting access to evaluation and treatment. Those interviewed noted that there would also be certain cost equity issues that could pose as challenges including insurance/Medicaid coverage and reimbursement of ancillary costs (e.g., traveling to treatment centers).

Costs

During the interviews, the NBS program directors discussed some of the preliminary cost estimates their programs have developed for SMA implementation. The directors estimated that the addition of SMA will add between 10 cents and $1 to the cost of the NBS test when multiplexed with SCID. Programs interviewed were only considering adding newborn screening for SMA as a multiplex, add-on to SCID screening. When multiplexed with SCID, SMA screening uses the same molecular testing equipment and staffing to conduct both TREC (SCID) and *SMN1* exon 7 real-time PCR for the primary, first-tier screen. Additional marginal costs to screen included expenses for disposable supplies (i.e., reagents, primers, probes) and added labor for laboratory technician (ranging from 0 to 1.0 FTE initially) and short-term follow-up (ranging from 0-0.3 FTE initially).

The higher end of this estimated 0.10 to $1.00 cost per specimen to add SMA reflected a program that is currently considering purchasing additional equipment (i.e., digital droplet PCR equipment) to include second-tier screening to assess *SMN2* copy number. This second-tier screening procedure would determine *SMN2* copy numbers to further inform phenotype severity, but is not required for initial identification of newborns affected with SMA. Purchase of this equipment was broadly estimated at approximately $93,000 to $140,000 in the start-up year, and about $50 per specimen for each affected baby. Another state that was considering similar second-tier screening for *SMN2* dosage planned to use digital PCR equipment available in another laboratory within the state laboratory for second-tier testing of any positive screens (estimated at 1 in 11,000 screens). (See Appendix B, the Screening Implementation Fact Sheet for SMA, for further detail).

State programs providing cost estimates were not planning on including results for 1 *SMN1* copy number in the first-tier screen, which would allow detection of carriers with 1 SMN 1 copy. Reporting carriers would require additional staffing for follow up and counseling for these results.

Although treatment costs do not directly impact the budget of all state public health departments, newborn screening for SMA would impact health services and treatment for infants requiring treatment in the first few months of life, as well as those with later-onset forms who are require long-term management to monitor disease progression. Specific costs of treatment for SMA have been reported in the literature at $125,000 per dose.[77] With 6 doses required in the first year, and 3 doses per year after that, total annual costs are $750,000 in year 1, and $375,000 each year thereafter. These costs include the pharmacological treatment, and do not include costs to

administer the drug via intrathecal injection (i.e., lumbar puncture/spinal tap). Adding newborn screening for SMA would impact many sectors, patients and families, other consumers, and the broader health care delivery system, and may indirectly impact the budgets of state newborn screening programs indirectly.

Overall, NBS program directors stated that they had funds to screen in the short-term, but would need to increase their newborn screening fee or obtain additional funding for sustained screening for SMA. One NBS program director discussed that his program has seen the addition of three disorders in less than a year without having a fee increase. Many NBS programs stated they are on a two-year legislative cycle and can only request a fee increase at this time. The long-term burden of this cannot be understated. This assessment did not evaluate confirmatory testing or treatment costs.

State NBS Program Not Screening for SCID

Currently, there are four states in the U.S. not universally screening for SCID. Since the SMA screening test is generally multiplexed with SCID, APHL chose to interview a NBS program not screening for SCID to evaluate some of their unique challenges. This NBS program has no plans to screen for SMA in the near future. It has taken ten years to transition screening from a regional laboratory to their state laboratory and nearly three years to implement SCID screening (expected start date for SCID is January 2018). Funding was mentioned to be this program's biggest challenge. It was also mentioned that space and personnel are limited and not expected to change until significant financial resources are available for expansion. A NBS fee increase would be necessary if and when they decide to implement screening for a new disorder, which was estimated to take at least three years after SCID implementation. NBS programs like this one would likely take longer to implement SMA because other disorders and priorities would come first. Qualitative data from interviews along with survey data was useful in assessing readiness and feasibility.

Survey Results

A total of 46 completed surveys were received from 53 U.S. states and territories, for a response rate of 87%. Five state NBS programs were excluded because of either a pilot or mandate to screen. Of the 41 responses included in the analysis, 27 came from state NBS programs that have laboratory and follow-up components, 11 came from programs that contract NBS laboratory services regionally, and 3 came from programs that contract NBS laboratory services commercially. Results from the survey can be found in the figures below.

Figure 9. Status of SMA Screening in your NBS Program

Full Question Text: Within the last 3 years has your program (check all that apply).

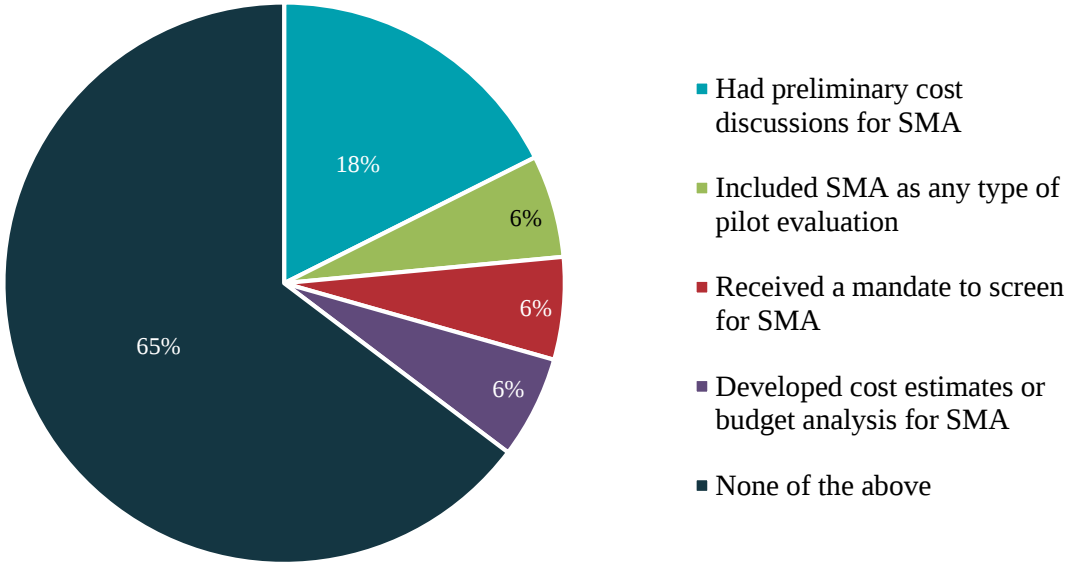


Figure 10. Duration for SMA Authorization

Full Question Text: If SMA was added to the Recommended Uniform Screening Panel (RUSP) tomorrow, how long would it take to get authorization to screen for SMA your state?

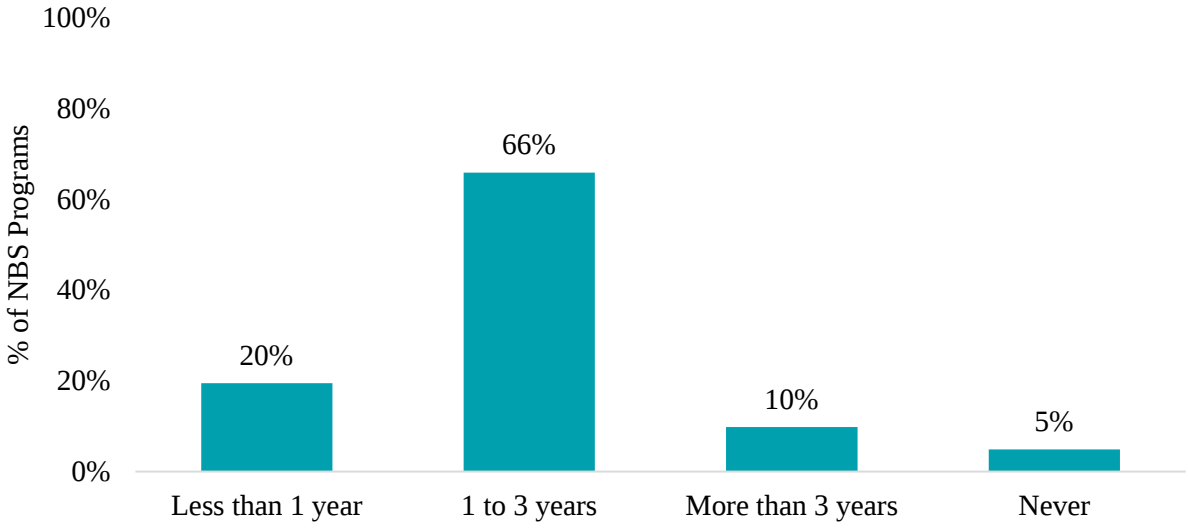


Figure 11. Duration for SMA Funds

Full Question Text: Once you received authorization to screen, how long would it take to have funds allocated for SMA?

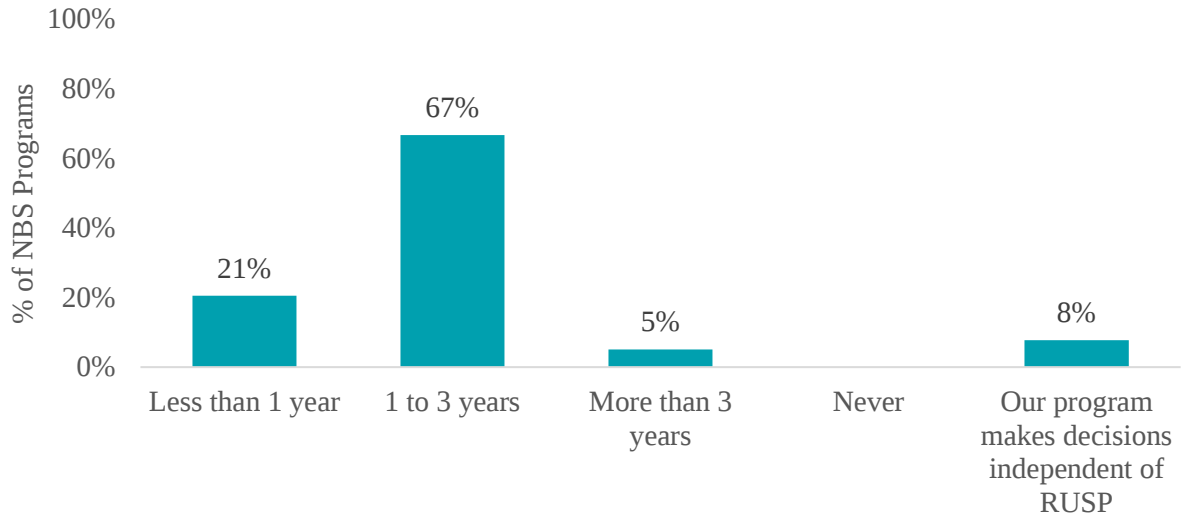


Figure 12. SMA Implementation Challenges

Full Question Text: Please select the top 3 challenges related to SMA implementation.

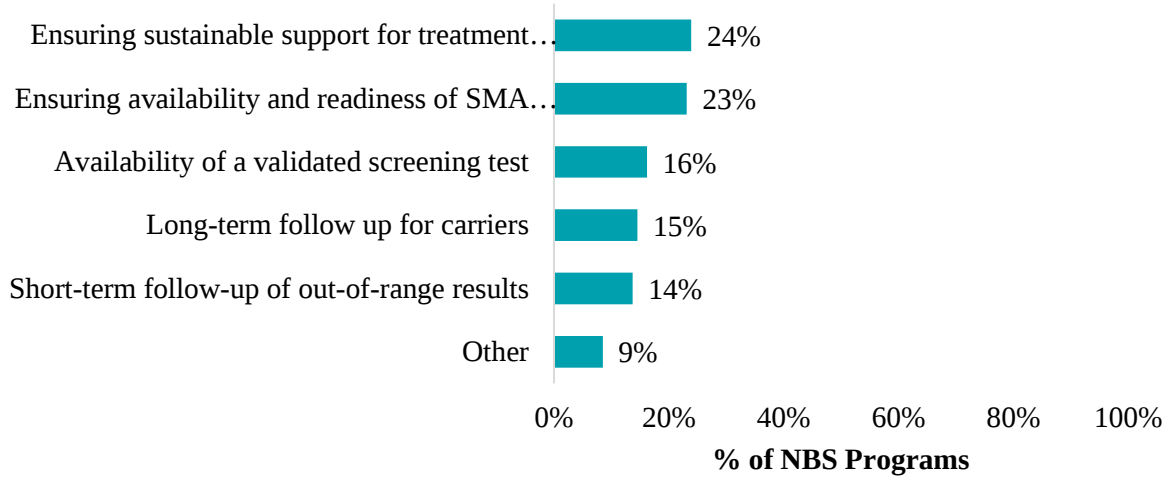


Figure 13. SMA Screening Approach for Carriers

Full Question Text: Which describes the type of screening approach your program would choose. Question excludes those that contract screening regionally or commercially.

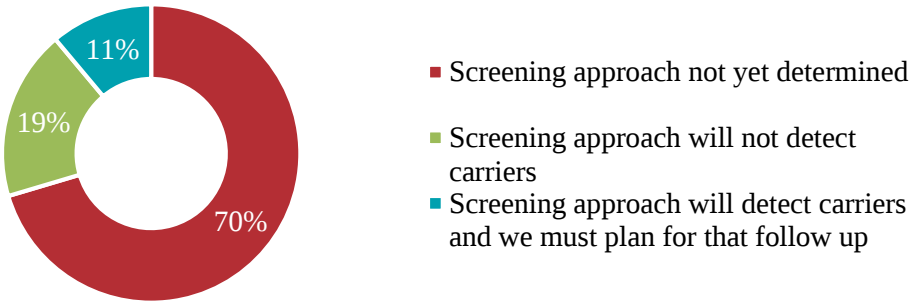
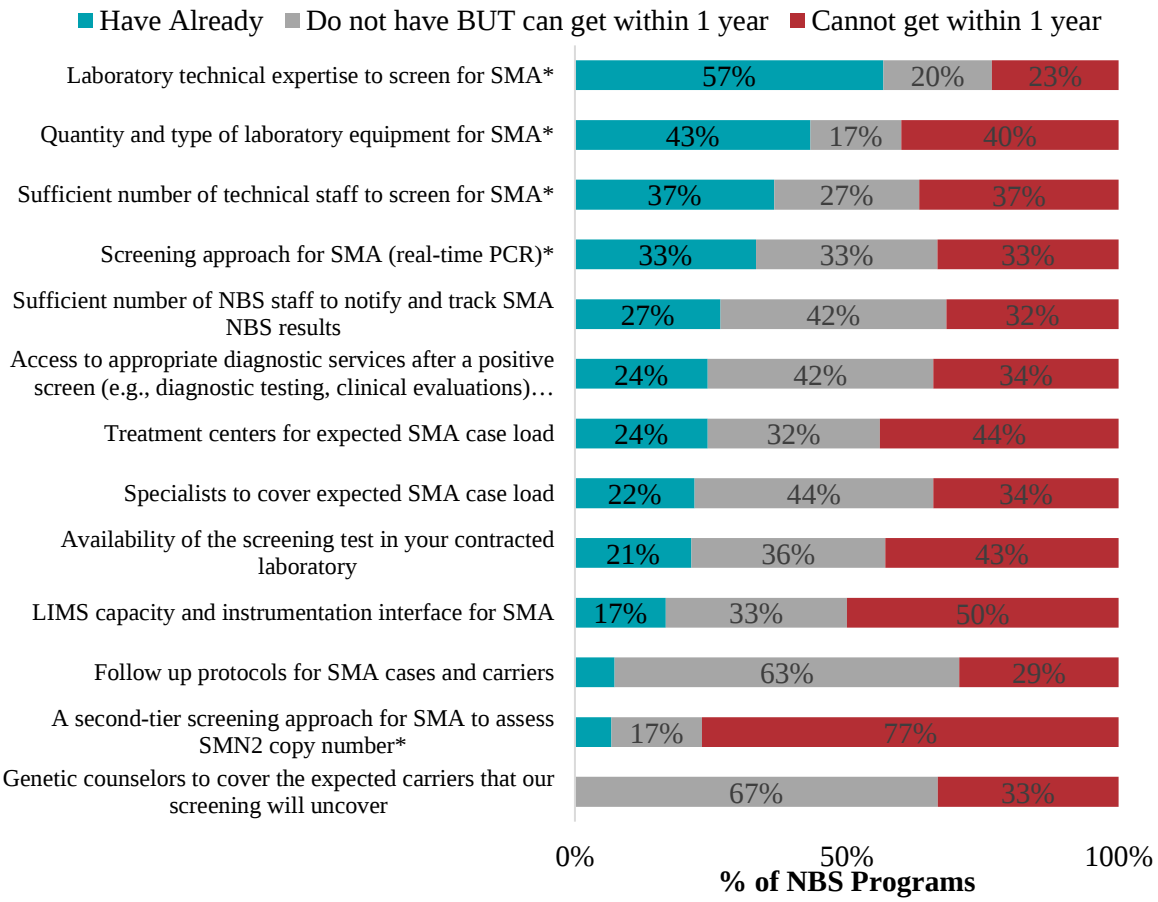


Figure 14. SMA Implementation Resources

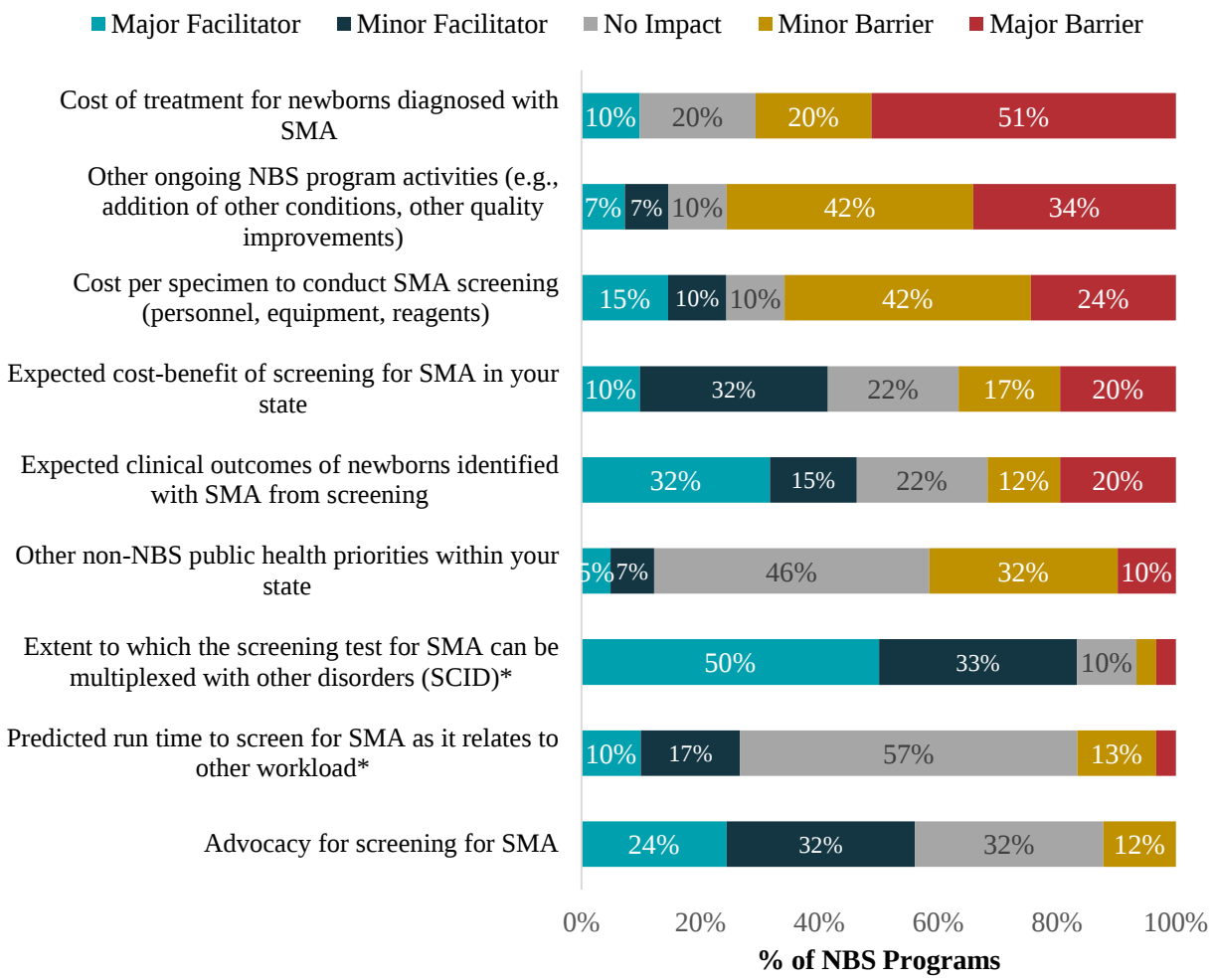
Full Question Text: Please indicate your NBS program's readiness to implement screening for SMA by evaluating the following resources



*Question only asked to labs with a state NBS program or commercial contract.

Figure 15. SMA Implementation Factors

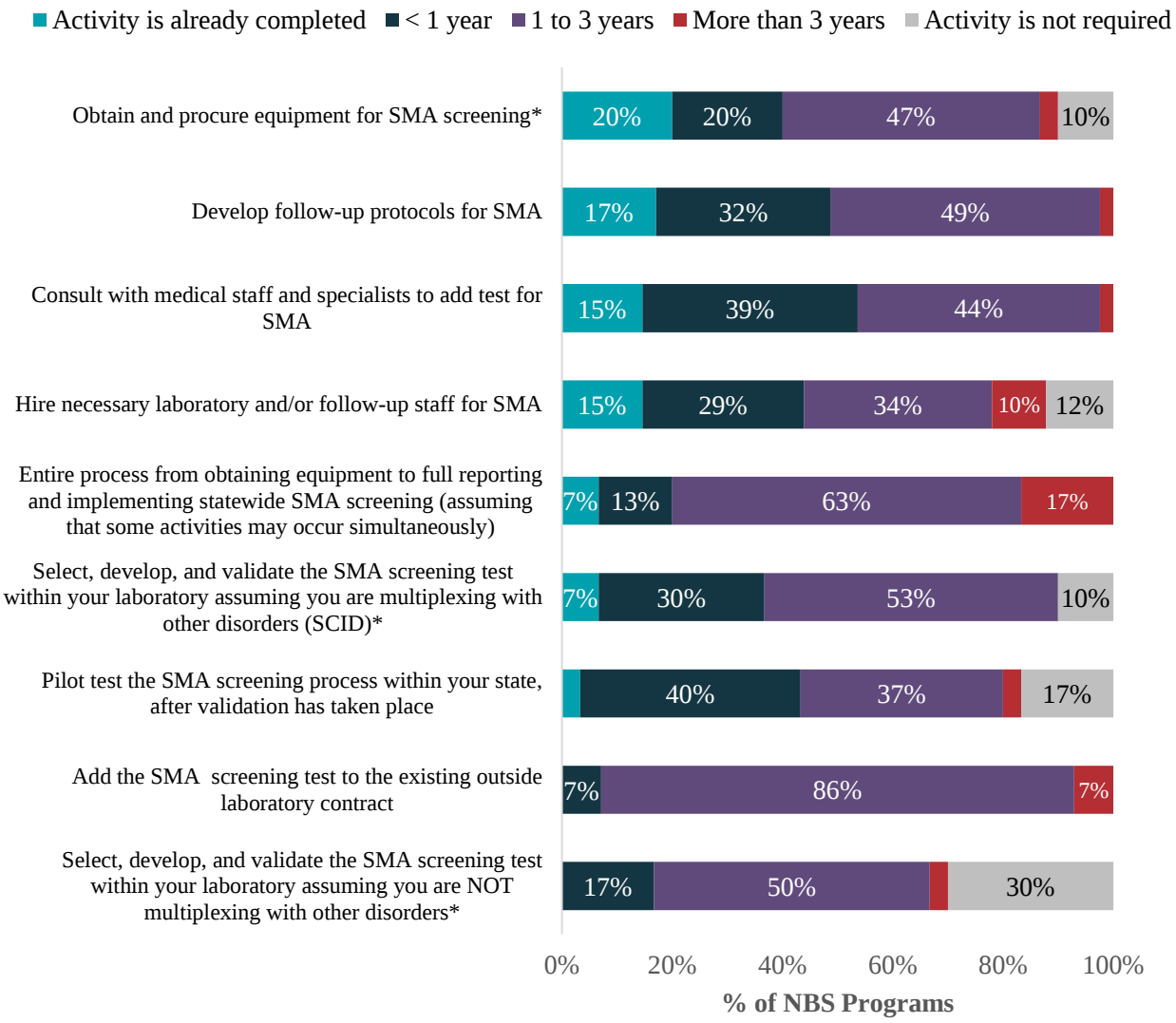
Full Question Text: To what extent do the factors below impede or facilitate the adoption of screening for SMA in your NBS program?



*Question only asked to labs with a state NBS program or commercial contract.

Figure 16. Duration for Implementation Activities

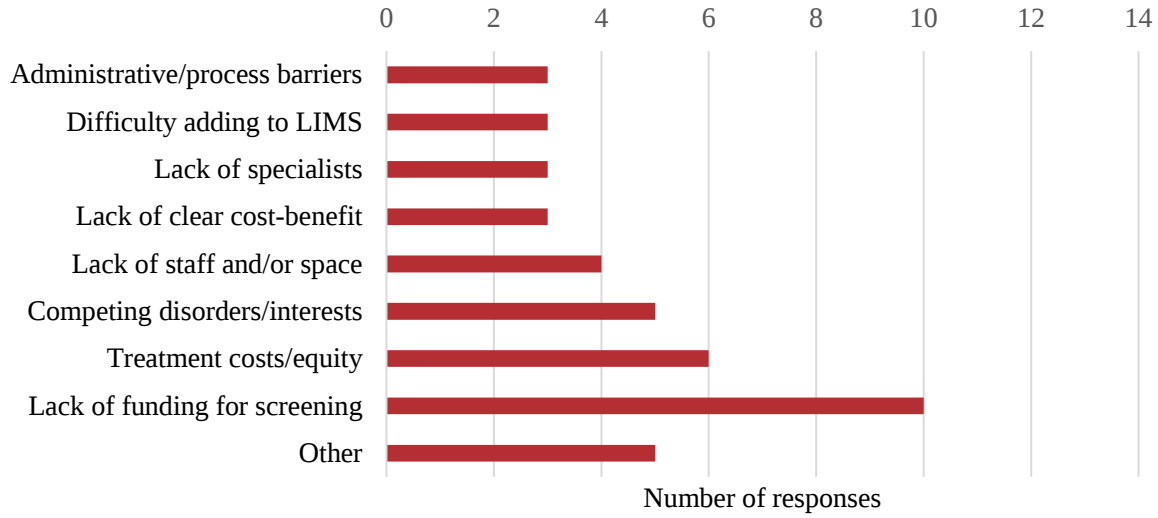
Full Question Text: How long would it take your NBS program to complete the following activities?



*Question only asked to labs with a state NBS program or commercial contract.

Figure 17. Most Significant Barriers to Implementation

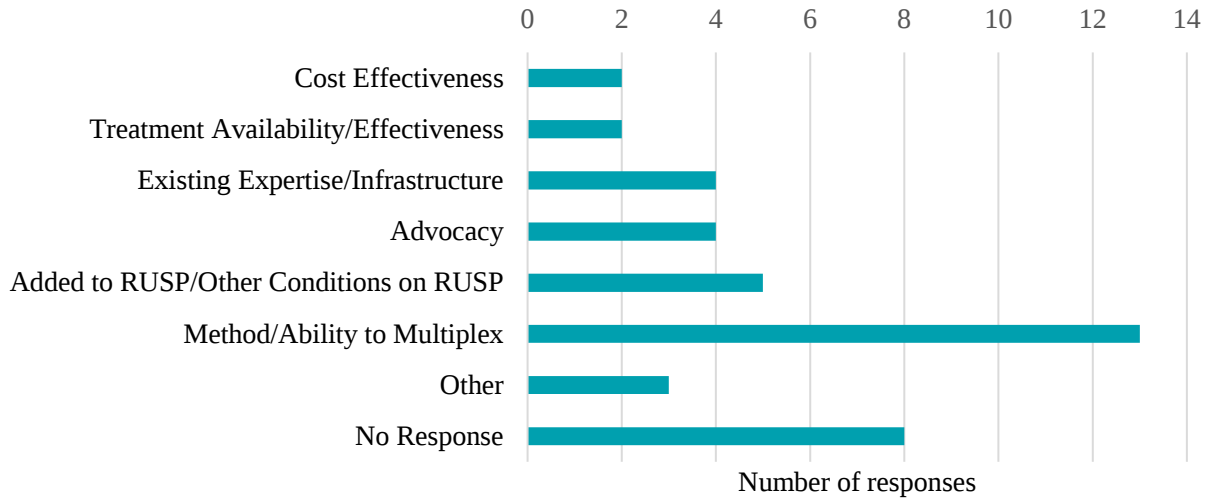
Full Question Text: What is the most significant barrier to implementing screening for SMA in your program?



Open-ended and multiple responses were captured for this question. Ten NBS programs cited lack of funding for screening their most significant barrier. Six programs cited treatment costs and equity of treatment as their most significant barrier. Other responses included competing disorders/interests, lack of staff and/or space, lack of clear cost-benefit, lack of specialists, difficulty adding to their Laboratory Information Management systems (LIMs), and administrative/process barriers.

Figure 18. Most Significant Facilitators to Implementation

Full Question Text: What is the most significant facilitator to implementing screening for SMA in your program?



Open-ended responses were captured for this question. Thirteen NBS programs cited the ability to multiplex as the most significant facilitator for SMA screening. Five programs cited SMA

being added to the RUSP or other conditions added to the RUSP as being the most significant facilitator for SMA screening. Other responses included advocacy, existing expertise/infrastructure, treatment availability, and cost-effectiveness.

Conclusions

The PHSI attempted to assess NBS programs' readiness and feasibility to implement new disorders to the RUSP. Although APHL was not able to evaluate opinions and experiences from every state NBS program, the survey response rate of 87% was a strength. An additional strength of the PHSI was that it was able to assess both real experiences through interviews as well as perceptions about implementing SMA via a survey based on NBS programs' experiences with implementing other disorders.

Feasibility

1. Does an established and available screening test exist?

   As described in the systematic evidence review, the first tier screen for SMA entails using real-time PCR to detect homozygous *SMN1* deletion of exon 7. SMA is capable of being multiplexed with SCID, allowing for quicker, more efficient testing. Some state NBS programs may choose to conduct a second-tier screen to get information about *SMN2* copy number. The CDC is expected to have quality assurance/quality control and proficiency testing materials available for SMA.

2. Is there a clear approach to diagnostic confirmation?

   SMA can be confirmed through diagnostic confirmation which evaluates the SMN1 gene and copy number along with clinical characteristics. Refer to the systematic evidence review.

3. Is there an acceptable treatment plan?

   Please refer to the systematic evidence review for treatment effectiveness. 71% of survey respondents noted that cost of treatment was a major or minor for implementation. More guidance is needed in this area.

4. Is there a long-term follow up plan?

   Please refer to the systematic evidence review for the evidence regarding the effectiveness of long-term management.

Readiness

When asked how long it would take to get authority to screen for SMA once it was added to the RUSP, 66% of respondents (n=41) indicated that it would take them 1 to 3 years; 19% indicated it would take less than a year; 10% indicated it would take more than 3 years; and 5% indicated it would never happen, respectively. When asked how long it would take after authorization to get funds allocated for SMA, 67% of respondents (n=39) responded it would take 1 to 3 years; 21% indicated it would take less than a year; 5% stated it would take more than 3 years; and 7% stated their program makes decisions independent of RUSP respectively. When asked how long it would take to complete implementation activities for their program, 63% of respondents (n=30) agreed between 1 and 3 years; 17% stated more than 3 years; 13% said less than 3 years; and 7% stated that it was already complete respectively. NBS programs that contract their laboratory services did not answer this question. Eighty-six percent (86%) of contract laboratories (n=14) stated, however, that it would take between 1 to 3 years to add SMA to their

existing contract. Although APHL did not get a response from every state, it is reasonable to conclude that NBS programs across the U.S. are, at best, developmentally ready to implement SMA screening. The time it takes for the addition of the condition to the RUSP, obtaining legislative approval, and funding for screening may significantly slow down the process.

Readiness varies by state newborn screening program. For example, 33% of survey respondents cited that they had the screening approach for SMA (real-time PCR); 33% could get the screening test within one year; and 33% cited they could not get it within the year. Although laboratories that contract services were underrepresented in our analysis 6 out of 14 (43%) of them noted that they would not be able to get the screening test in their contracted laboratory within one year. Additionally, 22% of survey respondents cited that they already had specialists to cover the expected SMA case load; 44% cited they did not have but could get within 1 year; and 34% cited that they did not believe they could get specialists within the year. 50% of NBS programs surveyed stated that they would not be able to update their LIMS system for SMA within a year. 77% of NBS programs could not get a second-tier method for SMA to assess *SMN2* copy number, however, this is not a criterion for screening.

Advocacy was reported as a major or minor facilitator for 56% of survey respondents (n=41). Approximately 83% of the survey respondents (n=30) reported that the extent to which the screening test for SMA can be multiplexed with SCID was a major or minor facilitator to implementation. 33% of NBS programs that do not screen for SCID (n=3), however, saw multiplexing the test as a major or minor barrier. Likewise, the cost of treatment for SMA was seen as a major or minor barrier for 71% of survey respondents (n=41). Other ongoing NBS activities including adding conditions was seen as a major or minor barrier for 76% of respondents (n=41).

Limitations

There were several limitations with the PHSI assessment. In many of the survey questions, respondents were asked to assume approval had occurred and funds allocated. This was not meant to underestimate the importance and time commitment involved with these steps, but rather to have responders consider specific implementation activities outside of funding and legislation. It is plausible that getting approval and acquiring funds could add years to the timeframe for implementation. Additionally, although NBS program directors likely relied on experiences implementing other conditions, the questions in the survey were hypothetical and responses were subjective. Interviews assisted in gathering additional information pertaining to real world barriers and facilitators as well as screening outcomes.

Summary

Most NBS programs surveyed stated that it would take between 1 and 3 years to complete implementation activities from obtaining equipment to full reporting and implementing screening statewide. The NBS states interviewed (n=5) who are conducting or preparing pilot studies or population screening have begun implementation activities. Each plans to be screening, either with a pilot or population-wide, by December 2018. Screening for carriers, determining what to do with late-onset cases, cost of treatment, and treatment equity were commonly reported challenges in this assessment. There continue to be administrative barriers that delay the implementation process; examples include increasing the newborn screening fee and/or obtaining funds, changing administrative rules, getting legislator buy-in and authority to screen. Also, competing public health interests continue to be an issue hindering implementation of conditions.

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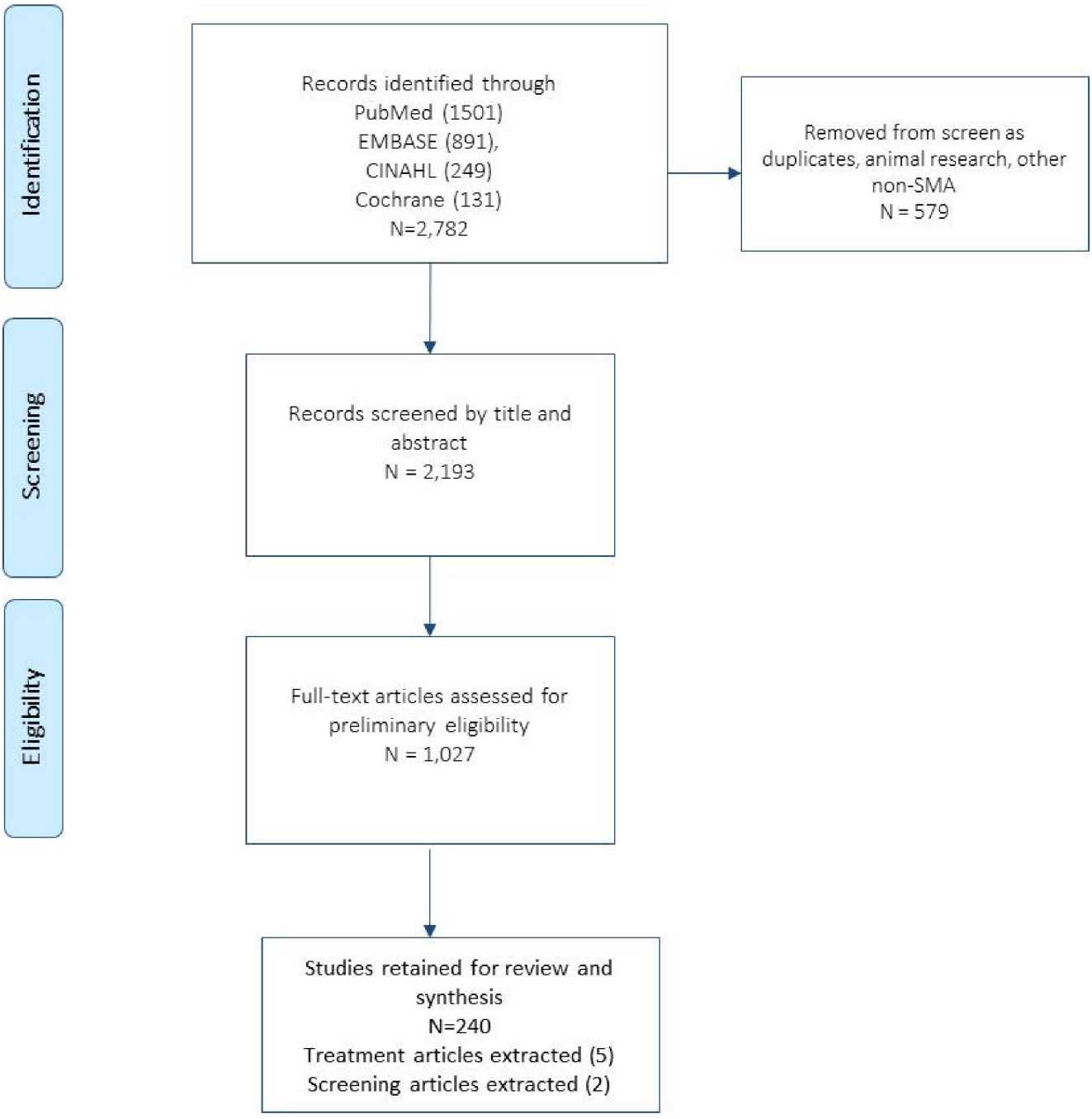
Appendix A. SYSTEMATIC EVIDENCE REVIEW TECHNICAL METHODS

PRISMA[78] Flow Diagram of Literature Search for Newborn Screening for SMA



Search Terms and Results

SMA Literature Search, Jan 2000 – June 1 2017, Update: May 2017 - Jan 12, 2018 (pubs through Jan 11).

PubMed

Set	Terms	1/1/00 – **6/1/17**	**5/1/17 - 1/12/18**
#1	"Spinal Muscular Atrophies of Childhood"[Mesh] OR "Spinal Muscular Atrophies"[tiab] OR "Spinal Muscular Atrophy"[tiab] OR "Werdnig-Hoffman"[tiab] OR "Kugelberg-Welander"[tiab] OR (SMA[tiab] AND type[tiab])	6781	7060
#2	("Pediatrics"[Mesh] OR pediatric[tiab] OR pediatrics[tiab] OR paediatric[tiab] OR paediatrics[tiab] OR juvenile[tiab] OR juveniles[tiab] OR "Infant"[Mesh] OR infant[tiab] OR infants[tiab] OR infantile[tiab] OR "Child"[Mesh] OR child[tiab] OR children[tiab] OR childhood[tiab] OR preadolescent[tiab] OR preadolescents[tiab] OR prepubescent[tiab] OR "Adolescent"[Mesh] OR adolescent[tiab] OR adolescents[tiab] OR youth[tiab] OR youths[tiab] OR teenager[tiab] OR teenagers[tiab] OR teenaged[tiab] OR teen[tiab] OR teens[tiab]) NOT ("Adult"[Mesh] NOT ("Adolescent"[Mesh] OR "Child"[Mesh] OR "Infant"[Mesh]))	3539012	3617824
#3	#1 AND #2	2504	
#4	#3 AND English[la] AND ("2000"[Date - Publication] : "3000"[Date - Publication])	1414	
#3	#1 AND #2		2590
#4	#3 AND English[la] AND ("2017/05/01"[Date - Entrez] : "3000"[Date - Entrez])		87

EMBASE

Set	Terms	1/1/00 – 6/1/17	5/1/17 – 1/12/18
#1	'hereditary spinal muscular atrophy'/exp OR "Spinal Muscular Atrophies":ab,ti OR "Spinal Muscular Atrophy":ab,ti OR "Werdnig-Hoffman":ab,ti OR "Kugelberg-Welander":ab,ti OR (SMA:ab,ti AND type:ab,ti)	11,169	11,815
#2	([infant]/lim OR [child]/lim OR [adolescent]/lim OR pediatric:ti,ab OR pediatrics:ti,ab OR paediatric:ti,ab OR paediatrics:ti,ab OR juvenile:ti,ab OR juveniles:ti,ab OR infant:ti,ab OR infants:ti,ab OR infantile:ti,ab OR child:ti,ab OR children:ti,ab OR childhood:ti,ab OR preadolescent:ti,ab OR preadolescents:ti,ab OR prepubescent:ti,ab OR adolescent:ti,ab OR adolescents:ti,ab OR youth:ti,ab OR youths:ti,ab OR teenager:ti,ab OR teenagers:ti,ab OR teenaged:ti,ab OR teen:ti,ab OR teens:ti,ab) NOT (([young adult]/lim OR [adult]/lim OR [middle aged]/lim OR [aged]/lim OR [very elderly]/lim) NOT ([embryo]/lim OR [fetus]/lim OR [newborn]/lim OR [infant]/lim OR [child]/lim OR [adolescent]/lim))	3469359	3569446
#3	#1 AND #2 AND [embase]/lim NOT [medline]/lim	867	
#4	#3 AND [english]/lim AND [2000-2017]/py	705	
#3	#1 AND #2 AND [embase]/lim NOT [medline]/lim		963
#4	#3 AND [english]/lim AND [1-5-2017]/sd NOT [12-1-2018]/sd		186

CINAHL

Set	Terms	1/1/00 – **6/1/17**	**5/1/17 – 1/12/18**
#1	(MH "Muscular Atrophy, Spinal+") OR TI ("Spinal Muscular Atrophies" OR "Spinal Muscular Atrophy" OR "Werdnig-Hoffman" OR "Kugelberg-Welander" OR (SMA AND type)) OR AB ("Spinal Muscular Atrophies" OR "Spinal Muscular Atrophy" OR "Werdnig-Hoffman" OR "Kugelberg-Welander" OR (SMA AND type))	867	949
#2	TI (pediatric OR pediatrics OR paediatric OR paediatrics OR juvenile OR juveniles OR infant OR infants OR infantile OR child OR children OR childhood OR preadolescent OR preadolescents OR prepubescent OR adolescent OR adolescents OR youth OR youths OR teenager OR teenagers OR teenaged OR teen OR teens) OR AB (pediatric OR pediatrics OR paediatric OR paediatrics OR juvenile OR juveniles OR infant OR infants OR infantile OR child OR children OR childhood OR preadolescent OR preadolescents OR prepubescent OR adolescent OR adolescents OR youth OR youths OR teenager OR teenagers OR teenaged OR teen OR teens)	487004	517.236
#3	#1 AND #2, limit to English and 2000 – present	215	
#3	#1 AND #2, limit to English and 5/1/2017 – present		34

Cochrane

Set	Terms	1/1/00 – **6/1/17**	**5/1/17 – 1/12/18**
#1	[mh "Spinal Muscular Atrophies of Childhood"]	17	17
#2	"Spinal Muscular Atrophies":ab,ti or "Spinal Muscular Atrophy":ab,ti or "Werdnig-Hoffman":ab,ti or "Kugelberg-Welander":ab,ti or (SMA:ab,ti and type:ab,ti)	109	109
#3	#1 AND #2	113	
#3	#1 AND #2, 2017 – present		18

Quality Ratings of Evidence

A. Quality Assessment of Evidence: Screening and Treatment Articles

B. Quality Assessment Forms by Study Design

Study Design	Quality Assessment Forms
Randomized Clinical Trials (RCT)	**Quality Assessment Tool For Quantitative Studies**[9] Follow this link to view the form.
Screening Pilot Studies	**QUADAS-2 Modified for SMA**[6] Follow this link to view the form.
Case-Control	**Newcastle Ottawa Scales**[8] Follow this link to view the form.
Cohort Studies	**Newcastle Ottawa Scales**[8] Follow this link to view the form.
Case Series	**Quality Assessment Tool**[10] Follow this link to view the form. (modified)
Case Studies	**Quality Assessment Tool**[10] Follow this link to view the form.(modified)

A. Quality Assessment of Evidence: Screening and Treatment Articles

A. Quality Assessment of Evidence: Screening and Treatment Articles

Key: Risk of Bias
Low
Unclear
High

SCREENING				Patient Selection		Newborn Screening Test		
RefID	**Publication**	**Therapy**	**Global Publication Rating**	**Risk of Bias**	**Applicability**	**Conduct and Interpretation of Test**	**Reference Standard**	**Flow and Timing**
4627	Kraszewski 2017	Screening	Strong					
4632	Chien 2017	Screening	Strong					

A. Quality Assessment of Evidence: Screening and Treatment Articles

Key: Strength of Publication
Strong
Moderate
Weak
Not reported

TREATMENT

RCT											
RefID	Publication	Therapy	Global Publication Rating	Selection Bias	Study Design	Confounders	Blinding	Data collection	Attrition	Intervention Integrity	Analyses
4625	Finkel 2017	Nusinersen	Strong								

CASE SERIES				Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Also Noted		
RefID	Publication	Therapy	Global Publication Rating	Study objective	Case definition			Outcome reporting	Patient Follow-up		Results Descrip-tion	Patient Blinding	Caregiver Blinding	Other
10	Bishop 2017	Nusinersen	Weak											
66	Finkel 2016	Nusinersen	Moderate											
152	Chiriboga 2016	Nusinersen	Weak											
154	Hache 2016	Nusinersen	Weak											
626	Mendell 2017	Gene therapy	Moderate											

Randomized Trials and Quasi-Experimental Designs

QUALITY ASSESSMENT TOOL FOR QUANTITATIVE STUDIES

http://www.ephpp.ca/PDF/Quality%20Assessment%20Tool_2010_2.pdf

COMPONENT RATINGS

SELECTION BIAS

(AQ1) Are the individuals selected to participate in the study likely to be representative of the target population?

1 Very likely

2 Somewhat likely

3 Not likely

4 Can't tell

(AQ2) What percentage of selected individuals agreed to participate?

1 80 - 100% agreement

2 60–79% agreement

3 less than 60% agreement

4 Not applicable

5 Can't tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

STUDY DESIGN

BQ1. Indicate the study design

1 Randomized controlled trial

2 Controlled clinical trial

3 Cohort analytic (two group pre + post)

4 Case-control

5 Cohort (one group pre + post (before and after))

6 Interrupted time series

7 Other specify

8 Can't tell

BQ2. Was the study described as randomized? If NO, go to Component C.

No Yes

BQ2a. If Yes, was the method of randomization described? (See dictionary)

No Yes

BQ2b. If Yes, was the method appropriate? (See dictionary)

No Yes

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

CONFOUNDERS (e.g.,, race, sex, marital status/family, age, SES, education, health status, pre-intervention score on outcome measure).

(Q1) Were there important differences between groups prior to the intervention?

1 Yes

2 No

3 Can't tell

(Q2) If yes, indicate the percentage of relevant confounders that were controlled (either in the design (e.g. stratification, matching) or analysis)?

1 80 – 100% (most)
2 60 – 79% (some)

3 Less than 60% (few or none)

4 Can't Tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

BLINDING

(Q1) Was (were) the outcome assessor(s) aware of the intervention or exposure status of participants?

1 Yes

2 No

3 Can't tell

(Q2) Were the study participants aware of the research question?

1 Yes

2 No

3 Can't tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

DATA COLLECTION METHODS

(Q1) Were data collection tools shown to be valid?

1 Yes

2 No

3 Can't tell

(Q2) Were data collection tools shown to be reliable?

1 Yes

2 No

3 Can't tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

WITHDRAWALS AND DROP-OUTS

(Q1) Were withdrawals and drop-outs reported in terms of numbers and/or reasons per group?

1 Yes

2 No

3 Can't tell

4 Not Applicable (i.e. one time surveys or interviews)

(Q2) Indicate the percentage of participants completing the study. (If the percentage differs by groups, record the lowest).

1 80 -100%
2 60 - 79%

3 less than 60%

4 Can't tell

5 Not Applicable (i.e. Retrospective case-control)

RATE THIS SECTION	STRONG	MODERATE	WEAK	
See dictionary	1	2	3	Not Applicable

INTERVENTION INTEGRITY

(Q1) What percentage of participants received the allocated intervention or exposure of interest?

1 80 -100%
2 60 - 79%

3 less than 60%

4 Can't tell

(Q2) Was the consistency of the intervention measured?

1 Yes

2 No

3 Can't tell

(Q3) Is it likely that subjects received an unintended intervention (contamination or co-intervention) that may influence the results?

4 Yes

5 No

6 Can't tell

ANALYSES

(Q1) Indicate the unit of allocation (circle one)
community organization/institution practice/office individual

(Q2) Indicate the unit of analysis (circle one)
community organization/institution practice/office individual

(Q3) Are the statistical methods appropriate for the study design?

1 Yes

2 No

3 Can't tell

(Q4) Is the analysis performed by intervention allocation status (i.e. intention to treat) rather than the actual intervention received?

1 Yes

2 No

3 Can't tell

GLOBAL RATING

COMPONENT RATINGS

Please transcribe the information from the gray boxes on pages 1-4 onto this page. See dictionary on how to rate this section.

A	**SELECTION BIAS**	**STRONG**	**MODERATE**	**WEAK**
		1	2	3
B	**STUDY DESIGN**	**STRONG**	**MODERATE**	**WEAK**
		1	2	3
C	**CONFOUNDERS**	**STRONG**	**MODERATE**	**WEAK**
		1	2	3
D	**BLINDING**	**STRONG**	**MODERATE**	**WEAK**
		1	2	3
E	**DATA COLLECTION METHOD**	**STRONG**	**MODERATE**	**WEAK**
		1	2	3
F	**WITHDRAWALS AND DROPOUTS**	**STRONG**	**MODERATE**	**WEAK**
		1	2	3

GLOBAL RATING FOR THIS PAPER (circle one):

1	STRONG	(no WEAK ratings)
2	MODERATE	(one WEAK rating)
3	WEAK	(two or more WEAK ratings)

With both reviewers discussing the ratings:

Is there a discrepancy between the two reviewers with respect to the component (A-F) ratings?

No Yes

If yes, indicate the reason for the discrepancy

1 Oversight

2 Differences in interpretation of criteria

3 Differences in interpretation of study

Final decision of both reviewers (circle one):	**1**	**STRONG**
	2	**MODERATE**
	3	**WEAK**

SCREENING PILOT STUDIES

QUADAS-2 *Modified* for SMA

(http://www.bristol.ac.uk/medialibrary/sites/quadas/migrated/documents/quadas2.pdf)

Domain 1: Patient Selection *Describe how participants were selected:*				
A. Risk of Bias	YES	NO	Unclear	
1. Was a consecutive or random sample of samples screened?	YES	NO	Unclear	
2. Did the study avoid inappropriate exclusions?	YES	NO	Unclear	
3. Could the selection of patients have introduced bias?	Low Risk	High Risk	Unclear	
B. Applicability				
1. Was this a pilot test of a newborn screening test (i.e., not anonymized samples)?	YES	NO	Unclear	
2. Did newborn screening occur within a defined population?	YES	NO	Unclear	
3. Is there concern that the study does not reflect population-based newborn screening?	YES	NO	Unclear	
Domain 2: Newborn Screening Test *(Repeat for each test used).* *Describe the newborn screening test:*				
1. Were the results of the newborn screening test interpreted without knowledge of the diagnostic test results?	YES	NO	Unclear	
2. Was the threshold for a positive screen clear?	YES	NO	Unclear	
3. Was the threshold for a positive screen pre-specified?	YES	NO	Unclear	
4. Were alternative thresholds for a positive screen clear?	YES	NO	Unclear	
5. Could the conduct or interpretation of the screening introduce bias?	Low Risk	High Risk	Unclear	NA
Domain 3: Reference Standard *Describe the reference standard:*				
1. Is the reference standard likely to correctly classify the condition?	YES	NO	Unclear	
2. Is the reference standard likely to correctly classify the condition?	YES	NO	Unclear	
3. Was the reference standard interpreted without knowledge of the newborn screening result?	YES	NO	Unclear	

Domain 1: Patient Selection *Describe how participants were selected:*				
4. Could the reference standard, its conduct, or its interpretation have introduced bias?	Low Risk	High Risk	Unclear	
Domain 4: Flow and Timing				
1. Did all positive newborn screens receive the reference standard?	YES	NO	Unclear	
2. Was the same reference standard used for all who received diagnostic testing?	YES	NO	Unclear	
3. Were all screening results used in the analysis?	YES	NO	Unclear	
4. Could the newborn screening flow have introduced bias?	Low Risk	High Risk	Unclear	

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE CASE CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?
   a) yes, with independent validation ✸
   b) yes, eg record linkage or based on self reports
   c) no description

2) Representativeness of the cases
   a) consecutive or obviously representative series of cases ✸
   b) potential for selection biases or not stated

3) Selection of Controls
   a) community controls ✸
   b) hospital controls
   c) no description

4) Definition of Controls
   a) no history of disease (endpoint) ✸
   b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for _____ (Select the most important factor.) ✸
   b) study controls for any additional factor ✸ (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure
   a) secure record (eg surgical records) ✸
   b) structured interview where blind to case/control status ✸
   c) interview not blinded to case/control status
   d) written self report or medical record only
   e) no description

2) Same method of ascertainment for cases and controls
   a) yes ✸
   b) no

3) Non-Response rate
   a) same rate for both groups ✸
   b) non respondents described
   c) rate different and no designation

****Final Draft****

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average _____ (describe) in the community ✹
   b) somewhat representative of the average _____ in the community ✹
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort ✹
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
   a) secure record (eg surgical records) ✹
   b) structured interview ✹
   c) written self report
   d) no description

4) Demonstration that outcome of interest was not present at start of study
   a) yes ✹
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for _____ (select the most important factor) ✹
   b) study controls for any additional factor ✹ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
   a) independent blind assessment ✹
   b) record linkage ✹
   c) self report
   d) no description

2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow up period for outcome of interest) ✹
   b) no

3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for ✹
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ✹
   c) follow up rate < ____% (select an adequate %) and no description of those lost
   d) no statement

CASE SERIES

Adapted from - https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/case_series

#	CASE SERIES – Quality Assessment Criteria	Y	N	CD-NA-NR
1.	Was the study objective clearly stated?			
2.	Was there a case definition for the study population?			
3.	Was the case definition applied to each case?			
4.	Were the subjects comparable?			
5.	Were the outcome measures defined and implemented consistently across all study participants?			
6.	Was the length of follow-up adequate?			
7.	Was the proportion who had complete follow-up appropriate for the study objectives and outcome measures?			
8.	Were the results well-described?			

CASE STUDIES

#	CASE STUDIES – Quality Assessment Criteria	Y	N	CD-NA-NR
1.	Was the study objective clearly stated?			
2.	Was there a case definition?			
3.	Was the case definition applied?			
4.	Were the outcome measures defined and implemented consistently across all study participants?			
5.	Was the length of follow-up adequate?			
6.	Were the results well-described?			

Appendix B. PHSI ASSESSMENT: FACT SHEET FOR SMA SCREENING

Condition	SMA
Description	SMA is an autosomal recessive disorder characterized by degeneration of motor neurons in the spinal cord and caused by mutations in the *SMN1 gene*. The clinical severity of SMA is highly variable ranging from a fatal disease of infancy to a disorder causing mild muscle weakness in adults and a normal lifespan. SMA Type I affects infants by 6 months of age. SMA Type II usually affects infants before age 18 months of age. SMA Types III and IV are typically considered late onset.
Expected Incidence	Incidence estimated from clinical detection is approximately 1 in 11,000.[11] • Detection by prospective newborn screening pilots of SMA: • *NYS NBS*- 1 in 10,326 screened positive; carrier status identified in 1 in 75 infants out of 10,326 infants screened. • *Taiwan*- 1 in 17,181 infants screened positive out of 120,267 infants screened (data collected from November 2014 to September 2016).[51]
Screening Methods	
Measurement method	First tier screen entails real-time PCR with TaqMan probe to evaluate the *SMN1* exon 7 deletion. Targeted sequencing is used as a QA measure to rule out allelic dropout due to variants in the TaqMan primer/probe binding regions in carriers. Note: This sequencing is not expected to detect a second mutation in SMA cases compound heterozygous for the deletion and another rare mutation. Second tier screen (optional) entails real-time PCR or digital droplet PCR (more accurate and precise) to determine *SMN2* copy number.
Data Source(s)	NYS NBS Program is conducting a pilot and has screened 6,200 infants.
Screening Marker	*SMN1* exon 7 • ≥ 2 copies = normal • 1 copy = carrier • 0 copies= positive screen *SMN2* gene to aid in determining phenotype and severity.
Screening Strategy	First tier screen entails using real-time PCR to detect homozygous *SMN1* deletion of exon 7. Second tier screen entails using real-time PCR or digital droplet PCR to detect *SMN2* copy number.

Condition	SMA
Resources and Materials	
Minimum Instrumentation, Equipment and Requirements Necessary to Process 100,000 Specimens Annually (Includes Conventional Redundancies)	Required materials include reagents such as PCR master mix, *SMN1* and control gene primers and probes; real time PCR equipment; liquid handling system (automated would be required for population level screening in most states). To process 100K annually in NYS: QuantStudio 12K Flex: 3-6 (if runs processed concurrently) Custom Janus liquid handler (8 x 96-well plate capacity): 1-2
Equipment Suppliers and Availability of Kits, Reagents and Consumables	PerkinElmer is in the process of developing a kit; currently lab-developed tests are being used. CDC,[49,79] Taiwan[51] and NYS[50] have published assays (reagents are all commercially-available).
Workstation Resources and Capacity	
Tech Time to Prepare Specimens	NYS: DNA extraction on Janus: 3 hr per 8 x 96-well plates SCID/SMA assay setup: 20 min per 1 x 384-well plate; add 5 min per each additional 384-well plate
Instrument Time	1 hr, 40 min per instrument run
Maximum Number of Specimens to Be Analyzed at One Workstation During An 8 Hour Shift	NYS SMA assay, pilot study: Currently 20-50 specimens analyzed/day; straightforward scale-up providing the assay is multiplexed with SCID. NYS SMA/SCID assay: Max=2 x 384-well plates (with 1 FTE, 1 Janus [max=16 x 96-well plates / day] and 1 QuantStudio [max=2 x 384-well plates / day])
Minimum Space Requirements (Supporting Equipment Not Included)	NYS (W x H x D): Custom Janus 8-deck liquid handler: 108” x 48” x 36” Janus Mini: 56” x 48”x 36” QuantStudio 12K Flex: 56” x 28” x 32”
Personnel Requirements	
FTE Needed to Process 100,000 Specimens Annually	1.5–2 FTE for population-based multiplexed SCID and SMA testing (includes DNA extractions, assay setup, analysis and interpretation, punching and testing samples requiring retesting, LIMs merge, report generation).
FTE Needed to Follow-Up with Expected Caseload Annually	0.3 FTE to follow 25-40 cases expected per year in NYS.
Other Considerations	
LIMs Adjustments	Variable (dependent on vendor); fields and import procedures should be similar to SCID.
Training	Variable. Carrier status detection and reporting; *SMN2* detection and reporting issues

Condition	**SMA**
QC and Reported Screening Results	
Availability of Quality-Control Specimens	Being developed by CDC
Reported Rate of Second-Tier Test	*SMN2* test in NYS: 1 in 9,100 infants screened
Reported Rate of Repeat Requests (Independent Specimen)	0%
Rate of Referrals	NYS: 1 in 9,100 infants screened
Reported Outcomes	# by type(s): SMA Type I = 1 in 9,100 infants screened Carriers = 92 (1 in 68) False positives = 0 False negatives = expected ~5-7% • Other point mutations possible • 5% SMA cases - compound heterozygous for exon 7 deletion and other point mutations would currently be reported as carriers in NYS
Estimated $$ Costs	
Equipment Cost (Overhead)	Not available
Estimated Cost of Laboratory Reagents or FDA-Approved Kit	The addition of the *SMN1* primers and probes multiplexed with SCID is expected to increase the cost of the assay by 10 cents per 10 µl reaction. Dependent on contractual agreements, decision to multiplex with SCID or not, method used.
Estimated Reagent Rental Cost	Not Available
Estimated Personnel Cost To Screen 50,000 to 100,000 Specimens Annually (Follow-Up Not Included)	Dependent on # FTE, state personnel, fringe and overhead rates.
Estimated Personnel Cost for Additional Follow-Up of Presumptive Positives	Dependent on # FTE, state personnel, fringe and overhead rates.
Estimated Diagnostic Assay Cost	Not Available
Estimated Diagnostic Molecular Testing Costs	Not Available

Condition	**SMA**
Short-Term Follow-Up	
Description	A genetic test to examine *SMN1* is necessary for diagnosis. Genetic testing of *SMN2* is beneficial for prediction of phenotype/prognosis. Additionally, family history is evaluated and a physical exam is performed.
Case Definition (typically manifests in infancy/childhood)	Spinal muscular atrophy is an autosomal recessive disease affecting the motor neurons of the anterior horn with resulting progressive motor weakness. Approximately 94–98% of individuals with SMA have homozygous deletion of the Survival Motor Neuron 1 (*SMN1*) gene and variable number of *SMN2* genes resulting in a phenotypic range of disease presentation, severity and age at onset.
Diagnostic Method & Criteria	Homozygous *SMN1* exon 7 deletion *SMN2* copy number to aid in determining phenotype Clinical manifestations
Availability of Diagnostic Testing Laboratories	The diagnostic testing can be performed in a number of laboratories.
Current Treatment(s)	
Description and Current Treatment Guidelines with Clinical Identification	Spinraza (Nusinersen) treatment was approved by the FDA in December 2016 and is recommended for pediatric and adult patients, including pre-symptomatic infants with SMA. The treatment increases production of SMN protein derived from the *SMN2* gene. Gene therapy research is currently experimental and not yet approved.
Specialty Providers or Centers	Neuromuscular disease centers and neurologists.

Appendix C. SMA PUBLIC HEALTH SYSTEM IMPACT ASSESSMENT SURVEY

The purpose of this survey is to inform the Secretary of Health and Human Services Advisory Committee on Heritable Disorders in Newborns and Children about the ability to add newborn screening (NBS) for Spinal Muscular Atrophy (SMA) using information gathered from most of the Newborn Screening (NBS) programs in the U.S.

Please refer to the SMA screening factsheet to answer the following questions about the ability to add NBS for SMA in your NBS program. Please also consult with others in your NBS program, including laboratory and follow-up staff, medical professionals and specialists, prior to completing the survey. When unsure about a response, **please provide your best estimate**.

1. Within the last 3 years, has your NBS program [Check all that apply]

- Included SMA as part of the routine NBS panel (*end survey*)
- Included SMA as any type of pilot evaluation (*end survey*)
- Received a mandate to screen for SMA (*end survey*)
- Developed cost estimates or budget analysis for SMA *(end survey)*
- Had preliminary cost discussions for SMA (go to question 2)
- None of the above (*go to question 2*)

2. Which of the following provides NBS laboratory services for your NBS program?

- Your own state's public health or NBS laboratory (includes state university laboratory for which there is an intra-state agency agreement)
- A contracted regional NBS laboratory or other not-for-profit laboratory
- A contracted commercial laboratory
- None of the above

3. If SMA was added to the Recommended Uniform Screening Panel (RUSP) tomorrow, how long would it take to get authorization to screen for SMA in your state? All

- Less than 1 year
- 1 to 3 years
- More than 3 years
- Never (go to question 5)

4. Once you received authorization to screen, how long would it take to have funds allocated for SMA? All

- Less than 1 year
- 1 to 3 years
- More than 3 years
- Never
- Our program makes decisions independent of RUSP

FOR QUESTIONS 5-8, PLEASE ASSUME THAT SMA HAS BEEN AUTHORIZED FOR ADDITION TO YOUR STATE'S PANEL AND THAT FUNDS FOR LABORATORY TESTING AND FOLLOW UP HAVE BEEN MADE AVAILABLE.

5. Please select the top 3 challenges related to SMA implementation. All

- Availability of a validated screening test
- Short-term follow-up of out-of-range results
- Ensuring availability and readiness of SMA specialists
- Ensuring sustainable support for SMA
- Long-term follow up for carriers
- Other – please specify

6. Which best describes the type of screening approach your program would choose: All except for contract

- Screening approach will detect carriers and we must plan for that follow up
- Screening approach will not detect carriers
- Screening approach not yet determined

7. Please indicate your NBS program's readiness to implement screening for SMA by evaluating the following resources.

Resource	Have Already	Do Not Have BUT Can Get Within One Year	Cannot Get Within One Year
Screening approach for SMA (real-time PCR) All except regional contract			
A second-tier screening approach for SMA to assess *SMN2* copy number All except regional contract			
Quantity and type of laboratory equipment for SMA All except regional contract			
Laboratory technical expertise to screen for SMA All except regional contract			
Sufficient number of technical staff to screen for SMA All except regional contract			
Availability of the screening test in your contracted laboratory* Regional contract and commercial contract			
LIMS capacity and instrumentation interface for SMA All, except regional contract			
Sufficient number of NBS staff to notify and track SMA NBS results All			
Access to appropriate diagnostic services after a presumptive positive from a screen (e.g., diagnostic testing, clinical evaluations) for SMA All			
Genetic counselors to cover the expected carriers that our screening will uncover Those who responded positively to the first point in Q6			
Specialists to cover expected SMA case load All			
Treatment centers for expected SMA case load All			
Follow up protocols for SMA cases and carriers All			

*This question only applies if you reported using a contracted laboratory at question.

8. To what extent do the factors below impede or facilitate the adoption of screening for SMA in your NBS program? Please see the definitions below*

Factor	Major Barrier	Minor Barrier	No Impact	Minor Facilitator	Major Facilitator
Predicted run time to screen for SMA as it relates to other workload. All except regional contract					
Extent to which the screening test for SMA can be multiplexed with other disorders (SCID) All except regional contract					
Advocacy for screening for SMA All					
Other ongoing NBS program activities (e.g., addition of other conditions, other quality improvements) All					
Cost per specimen to conduct SMA screening (personnel, equipment, reagents) All					
Cost of treatment for newborns diagnosed with SMA All					
Expected clinical outcomes of newborns identified with SMA from screening All					
Expected cost-benefit of screening for SMA in your state All					
Other non-NBS public health priorities within your state All					

*Major barrier- Will prevent testing from being done effectively and/or timely.
Minor barrier- May compromise testing so it is not performed effectively and/or timely.
Minor facilitator- May allow testing to be done effectively and/or timely.
Major facilitator- Will allow testing to be done effectively and/or timely.

9. How long would it take to complete the following activities assuming your current NBS program and laboratory infrastructure?

Activity	< 1 year	1 to 3 years	More than 3 years	Activity is already completed	Activity is not required
Obtain and procure equipment for SMA screening All except regional contract					
Select, develop, and validate the SMA screening test within your laboratory assuming you are multiplexing with other disorders (SCID) All except regional contract					
Select, develop, and validate the SMA screening test within your laboratory assuming you are NOT multiplexing with other disorders All except regional contract					
Hire necessary laboratory and follow-up staff for SMA All					
Consult with medical staff and specialists to add test for SMA All					
Develop follow-up protocols for SMA All					
Add the SMA screening test to the existing outside laboratory contract* Regional contract and commercial contract					
Pilot test the SMA screening process within your state, after validation has taken place All except regional contract					
Entire process from obtaining equipment to full reporting and implementing statewide SMA screening (assuming that some activities may occur simultaneously) All except regional contract					

*This question only applies if you reported using a contracted laboratory at question 2.

10. What is the most significant barrier to implementing screening for SMA in your program? All
11. What is the most significant facilitator to implementing screening for SMA in your program? All
12. Please share any additional information regarding implementation of screening for SMA. All

Appendix D. SMA INTERVIEW QUESTIONS FOR STATE NBS PROGRAMS

Interview Questions for NBS Programs That Are Screening for Spinal Muscular Atrophy

BACKGROUND

1. When did screening begin in your state? OR When do you plan to begin screening in your state? Where are you at with the implementation process now?
2. What has been your biggest challenge with implementing screening for SMA?
3. What has been the strongest facilitator for implementing screening for SMA?

LABORATORY

4. Please discuss your algorithm for SMA screening.
5. Discuss process and length of time it took to validate the method for SMA. Do you use a kit? In-house method? Multiplex with another assay?
6. What equipment does your program have to screen for SMA? What do you need to purchase to add SMA (equipment, reagents/supplies, other disposables, ancillary equipment, etc.)?
7. Are there/anticipate any issues/challenges with your method?
8. Are QA/QC and PT materials available from CDC?
9. What is the tech time (and expertise) required to process specimens? How many specimens does that cover annually? Will you or have you had to add FTEs in the lab to add SMA? If so, how many FTEs, and for what position level(s)?
10. Are you finding any challenges with screening for SMA from the laboratory perspective? If so, what?

DIAGNOSIS AND FOLLOW-UP

11. Have you developed a follow up protocol and/or educational materials for SMA? If so please describe it and how it was developed.
12. Approximately how many added FTEs are you anticipating for SMA follow up? Will you have to add FTEs in follow up to add SMA? If so, how many FTEs and for what position level(s)?
13. Are you finding any challenges with follow-up with regards to SMA screening? If so, what are they?
14. Is your program planning to identify carriers? If so, please elaborate on the challenges that may arise.
15. With regards to SMA, have you identified the following:
    - The confirmatory testing center/lab you will use?
    - Specialty/diagnostic centers for molecular genetic sequencing of positive screens?
    - Clinical specialists for referral and diagnosis of confirmed positive screens?
16. Based on your experience, what is the availability of molecular diagnostic centers on a national level? How is this important if SMA is added to the RUSP?
17. Discuss the availability of the specialty centers in your state? Rest of the country? Is that adequate given the expected incidence?

COSTS

18. Has your program developed cost estimates or a budget analysis to adopt SMA screening?
19. IF NO, have you had preliminary cost discussions? Are you able to elaborate?
20. What do you anticipate will be the greatest cost challenge as it relates to SMA?
21. What do you anticipate will be the greatest cost facilitator as it relates to SMA?

Thank you for your time!

Appendix E. EVIDENCE TABLES – SMA SYSTEMATIC EVIDENCE REVIEW

- Population-based Screening Pilots
- Treatment for SMA

Refid		Bibliography	STATED OBJ	STUDY DES	SS TOT	SS CHARAC	SCRNG_PROC	
SCREENING PILOTS								
4627	2017	4627. Kraszewski, J et al., (2017). Pilot study of population-based newborn screening for spinal muscular atrophy in New York state Genetics In Medicine.	To determine feasibility and utility of newborn screening for spinal muscular atrophy (SMA) in New York State.	CASECONTROL	3826	NYC, 3 hospitals	Validated multiplex TaqMan real-time quantitative polymerase chain reaction assay using dried blood spots for SMA. Screened from January 2016 to January 2017 at three hospitals in New York City Assays were run in triplicate on an Applied Biosystems 7900HT Real-Time PCR System or Quantstudio 12K Flex Real Time PCR System Reported carrier status	-Approximately 5% false negatives because of SMN point mutations, but none were ID'd in this screen. -One SMA type 1 (likely) infant was ID'd and enrolled in the open lab nusinersen trial. Thus far she has reached all normal motor milestones
4632	2017	4632. Chien, Y. (2017). Presymptomatic Diagnosis of Spinal Muscular Atrophy Through	To demonstrate the feasibility of presymptomatic diagnosis of spinal muscular atrophy (SMA) through newborn screening (NBS).	CASESERIES	120267	newborns from Nat'l Taiwan Univ Hosp undergoing routine metabolic screening	A real-time polymerase chain reaction (RT-PCR) genotyping assay for the SMN1/SMN2 intron 7 c.888+100A/G polymorphism was performed to detect homozygous SMN1 deletion using dried blood spot (DBS) samples. Then the exon 7 c.840C>T mutation and SMN2 copy number were determined by both droplet digital PCR (ddPCR) using the original screening DBS and multiplex ligation-dependent probe amplification (MLPA) using a whole blood sample.	Of the 120 267 newborns, 15 tested positive according to the RT-PCR assay. The DBS ddPCR assay excluded 8 false-positives, and the other 7 patients were confirmed by the MLPA assay. Inclusion of the second tier DBS ddPCR screening assay resulted in a positive prediction value of 100%. The incidence of SMA was 1 in 17 181 (95% CI, 1 in 8323 to 1 in 35 468). Two of the 3 patients with 2 copies of SMN2 and all 4 patients with 3 or 4 copies of SMN2 were asymptomatic at the time of diagnosis. Five of the 8 false-positives were caused by intragenic recombination between SMN1 and SMN2.

Refid	Bibliography	KTA_TREATMENT_comment	STATED OBJ	STUDY DES	SS TOT	Type1	SS CHARAC	US Ss	TX_DESCRIP	TX_Major Outcomes	2ndary Outcomes	OTHER FINDINGS
GREY LITERATURE												
1445	2017 1445. Kuntz et al. (2017). Nusinersen in Infants Diagnosed with Spinal Muscular Atrophy (SMA): Study Design and Initial Interim Efficacy and Safety Findings from the Phase 3 International ENDEAR Study Neurology, 88:16 Supplement 1.(#issue#), #Pages#	NUS Ph3 ENDR	To report interim efficacy, safety, and tolerability results from the Phase 3, double-blind, sham-procedure controlled, 13-month ENDEAR study in infants with SMA.	EXPER	122	Type1	-age ≤7 months at screening -genetic diagnosis of SMA with symptoms, and 2 SMN2 copies -Key exclusion criteria include hypoxemia during screening	US	-2:1 nusinersen vs. sham control patients -13 month study-12mg dosage	Motor skills used as primary endpoint	Primary endpoint assessed at the time of interim analysis was the proportion of patients achieving a level of improvement in motor milestones, ≥2 point increase (or maximal score) in ability to kick or ≥1 point increase in the motor milestones of head control, rolling, sitting, crawling, standing or walking, and improvement in more categories of motor milestones than worsening, defined as a responder for this primary analysis (according to HINE section 2)	
4628	2017 4628. Mercuri E et al. (2017). Efficacy and Safety of Nusinersen in Children With Later-Onset Spinal Muscular Atrophy (SMA): Results of the Phase 3 CHERISH Study. #journal#, #volume#(#issue#), #Pages#	NUS Ph3 CHER	NURTURE (NCT02386553) is an ongoing phase 2, open-label, single-arm study, evaluating intrathecal nusinersen (12-mg equivalent dose) in infants with presymptomatic spinal muscular atrophy (SMA)	EXPER	17	Type1	-Presymptomatic infants -Most (12/17) had 2 SMN2 copies -Most were aged ≤1 month at enrollment.	US	-open-label, single-arm study, evaluating intrathecal nusinersen (12-mg equivalent dose)	-primary endpoint is time to death or respiratory intervention (tracheostomy/any ventilation support for ≥6 hours/day continuously for ≥7 days)	- the proportion of infants developing clinical symptoms of SMA and -achievement of motor milestones. -Changes in compound muscle action potential (CMAP) -adverse events (AEs)	intervention or death. -Improvements in mean Hammersmith Infant Neurological Examination (HINE) motor milestones scores vs Baseline have been observed. -Infants have generally gained weight over time consistent with normal development, and mean CMAP scores have mostly improved vs Baseline. -There were no severe AEs reported, 5 infants experienced a serious AE. Three infants experienced AEs considered possibly related to study drug.
4629	2017 4629. Servais L et al. (2017). Nusinersen Demonstrates Greater Efficacy in Infants With Shorter Disease Duration: Final Results From the ENDEAR Study in Infants With Spinal Muscular Atrophy (SMA) #journal#, #volume#(#issue#), #Pages#	NUS Ph3 ENDR-by DisDuration	To evaluate outcomes in infants in the pre-symptomatic stage of SMA who have received intrathecal nusinersen for 1 year.	EXPER	20	Type1,2	Age ≤6 weeks at first dose Pre-symptomatic stage of SMA Genetic diagnosis of 5q SMA 2 or 3 SMN2 gene copies	US	Loading doses Days: 1, 15, 29, 64 Maintenance doses Days: 183, 302, 421, 540, 659, 778, 897, 1016 etc.) Interim analysis performed at 365	No infants died or required a respiratory intervention (defined as invasive or non-invasive ventilation for ≥6 hours/day continuously for ≥7 days or tracheostomy)	Infants achieved motor milestones beyond those achieved by their siblings with SMA; -At the Day 365 study visit, all infants (9/9) achieved HINE motor milestones for head control and kicking, 7/9 achieved rolling, 6/9 sitting, 5/9 crawling, 5/9 cruising and 3/9 standing unaided – Three (33%) infants achieved all HINE motor milestones expected for age: 1/6 with 2 SMN2 gene copies (17%) and 2/3 with 3 SMN2 gene copies (67%). • All infants (9/9) achieved WHO motor milestones for sitting, 6/9 achieved standing with assistance, 5/9 crawling, 5/9 walking with assistance, 3/9 standing alone and 2/9 walking alone (Figure 2B). • Mean CHOP INTEND scores improved from baseline, with greater mean change from baseline in infants with 3 SMN2 gene copies (Figure 3). – All could sit independently and 1 could stand with assistance. – Nusinersen was well tolerated and no specific safety concerns were identified	Four infants, all with 2 SMN2 gene copies, exhibited protocoldefined symptoms of SMA-->low weight and failure of WHO milestones
4630	2017 4630. Hwu W-L, De Vivo DC, Bertini E, Foster R, Bhan I, Gheuens S, Farwell W, Reyna SP (#year#). Outcomes After 1 Year of Treatment in Infants Who Initiate Nusinersen in a Pre-symptomatic Stage of Spinal Muscular Atrophy (SMA): Interim Results From the NURTURE Study #journal#, #volume#(#issue#), #Pages#	NUS Ph2 NURT	CHERISH (NCT02292537) was a Phase 3, multicenter, randomized, double-blind, sham procedure–controlled study to assess the efficacy and safety of nusinersen in children with later-onset SMA (most likely to develop SMA Type II or III).	EXPER	120	Type 2, 3	• Children with symptomatic SMA 2–12 years of age were randomized 2:1 (stratified based on screening age <6 vs. ≥6 years) to receive 4 doses of intrathecal nusinersen (12 mg nonscaled) or sham procedure control over 9 months during this 15-month study. • Key inclusion criteria included confirmed 5q SMA and onset of SMA clinical symptoms at ≥6 months of age.		global, randomized, double-blind, sham procedure–controlled study	-The primary endpoint was change from baseline in Hammersmith Functional Motor Scale Expanded (HFMSE) score at Month 15.	– Proportion of children who achieved a ≥3.0-point increase from baseline in HFMSE score; – Proportion of children who achieved any new World Health Organization (WHO) motor milestone; – Number of new WHO motor milestones achieved per child; – Change from baseline in Revised Upper Limb Module (RULM) test score; – Proportion of children who achieved standing alone; – Proportion of children who achieved walking with assistance. • Safety and tolerability also were assessed.	Interim analysis, there was a significant difference of 5.9 points in mean HFMSE score changes from baseline to Month 15 with a 4.0-point mean improvement with nusinersen vs. a mean decline of 1.9 points with sham procedure control. (P=.0000002) -At end of study analysis, the treatment difference was: nusinersen, 3.9-point improvement; sham procedure control, 1.0-point decline; P=.0000001 -Treatment-emergent adverse events (AEs), severe AEs, and serious AEs (SAEs) were reported less frequently in nusinersen-treated vs. sham procedure control–treated children. – Back pain, headache, and vomiting were observed at a ≥5% higher frequency in the nusinersen group 72 hours following drug administration. These are known complications following lumbar puncture (LP) and appeared to be related to the LP procedure. • There were no treatment discontinuations due to AEs. • There was no evidence of adverse effects on platelet counts, renal function, or hepatic enzymes.
4631	2017 4631. De Vivo DC et al. (2017). Interim Efficacy and Safety Results from the Phase 2 NURTURE Study Evaluating Nusinersen in Presymptomatic Infants With Spinal Muscular Atrophy. #journal#, #volume#(#issue#), #Pages#	NUS Ph2 NURT	To assess the efficacy and safety of nusinersen in infants with SMA with disease duration ≤12 or >12 weeks.	EXPER	121	Type1	INCLUSION: • Onset of clinical signs and symptoms consistent with SMA at ≤6 months of age, Genetic diagnosis of 5q SMA , 2 SMN2 copies • ≤7 months of age at screening EXCLUSION: • Hypoxaemia (oxygen saturation of <96% awake or asleep without ventilation support) • SMA symptoms at birth or within ≤1 week after birth		Screened before 21 days Dosed at: Days 1, 15, 29, 64 (loading), 183, 302, 394, etc. (maintenance)	– Proportion of Hammersmith Infant Neurological Examination (HINE) motor milestone responders (more categories improving than worsening, excluding voluntary grasp); – Event-free survival (i.e., time to death or permanent ventilation).	– Proportion of Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) responders (≥4-point improvement from baseline); – Survival rate	•Significant between-group differences (nusinersen vs. sham procedure) in the proportion of HINE responders were observed in infants with disease duration ≤12 weeks (75% vs. 0%; P<.0001) and those with disease duration >12 weeks (32% vs. 0%; P=.0026 • There was a significant treatment benefit of nusinersen in event-free survival in infants with disease duration ≤12 weeks (hazard ratio [HR], 0.158; P=.0004; and a trend favouring nusinersen treatment in those with disease duration >12 weeks (HR, 0.816; P=.5325 • Similar results were noted for other endpoints with nusinersen, demonstrating benefit in all subgroups and greater efficacy in infants with disease duration ≤12 weeks (Figure 3A–C).

Refid		Bibliography	KTA_TREATMENT_comment	STATED OBJ	STUDY DES	SS TOT	Type1	SS CHARAC	US Ss	TX_DESCRIP	TX_Major Outcomes	2ndary Outcomes	OTHER FINDINGS	7. HARMS or ADVERSE EFFECTS
PEER-REVIEWED PUBLICATIONS														
66	2016	66. Finkel, R. S. et al. (2016). Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study Lancet, 388(10063), 3017-3026	NUS Ph2	This open-label, phase 2, escalating dose clinical study assessed the safety and tolerability, pharmacokinetics, and clinical efficacy of multiple intrathecal doses of nusinersen (6 mg and 12 mg dose equivalents) in patients with infantile-onset spinal muscular atrophy.	EXPER	20	Type1	-24 males, 16 females -31 white, 2 black, 2 asian, 2 multiple races, 2 other	US Ss	Oopen-label, escalating dose phase 2 study was designed to assess the safety and tolerability, pharmacokinetics, and clinical effi cacy of nusinersen. Nusinersenwas doses: 1-2 mg/mL (6 mg dose equivalent) or 2-4 mg/mL (12 mg dose equivalent) with artifi cial cerebrospinal fl uid (CSF). Loading period of dosing over the fi rst 3 months to achieve a target spinal cord drug concentration, and then, after 6 months, chronic dosing once every 4 months to sustain the tissue concentration. Intrathecal dosing via lumbar puncture with topical anaesthesia using standard techniques for infants.	Safety assessments included adverse events, physical and neurological examinations, vital signs, clinical laboratory tests (serum chemistry, haematology, and urinalysis), CSF laboratory tests (cell counts, protein, and glucose), and electrocardiographs. Survival, including the surrogate of avoiding the need for permanent ventilation, was divergent as compared with natural history cohorts	-two assessments of motor function: the motor milestones portion of the Hammersmith Infant Neurological Exam—Part 2 (HINE-2) and the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) motor function test		
152	2016	152. Chiriboga, C. A.,Swoboda, K. J.,Darras, B. T.,Iannaccone, S. T.,Montes, J.,De Vivo, D. C.,Norris, D. A.,Bennett, C. F.,Bishop, K. M. (2016). Results from a phase 1 study of nusinersen (ISIS-SMN(Rx)) in children with spinal muscular atrophy Neurology, 86(10), 890-7	NUS Ph1	To examine safety, tolerability, pharmacokinetics, and preliminary clinical efficacy of intrathecal nusinersen in type 2 and 3 SMA patients-Phase I.	EXPER	28	Type 2, 3	-symptomatic, medically stable patients with type 2 and type 3 SMA aged 2–14 years -a life expectancy of ≥2 years per investigator judgement -excluded for: respiratory insufficiency, hospitalization for surgery or pulmonary event within the past 2 months, active infection at screening, history of brain or spinal cord disease or bacterial meningitis, presence of implanted CSF drainage shunt, clinically significant laboratory	US Ss	LP was performed under anesthesia/sedation per institutional guidelines. Before intrathecal injection of study drug, 5–6 mL of CSF was collected for analysis. Following injection, participants were observed for 24 hours. Follow-up visits were performed on days 8 and 29 for all participants and on day 85 for participants in the 6- and 9-mg dose groups. A second LP to collect CSF for safety and pharmacokinetics was performed on day 8 in the 1-, 3-, and 6-mg dose groups and on days 8 or 29 in the 9-mg dose group (n 5 5 at each time point). Participants were assessed 9–14 months postdose at enrollment into the long-term extension study, using assessments identical to those employed in the single-dose study.	LP was performed under anesthesia/sedation per institutional guidelines. Follow-up visits were performed on days 8 and 29 for all participants and on day 85 for participants in the 6- and 9-mg dose groups. A second LP to collect CSF for safety and pharmacokinetics was performed on day 8 in the 1-, 3-, and 6-mg dose groups and on days 8 or 29 in the 9-mg dose group (n 5 5 at each time point). Participants were assessed 9–14 months postdose at enrollment into the long-term extension study, using assessments identical to those employed in the single-dose study.	adverse events (AEs), physical/neurologic examinations, vital signs, clinical laboratory tests (serum chemistry, hematology, urinalysis, and ECGs		
154	2016	154. Hache, M. et al. (2016). Intrathecal Injections in Children With Spinal Muscular Atrophy: Nusinersen Clinical Trial Experience J Child Neurol, 31(7), 899-906	NUS Ph1	To summarize lumbar puncture experience in children with spinal muscular atrophy during a phase 1 open-label study of nusinersen and its extension.	EXPER	28	Type 2, 3	-Ages 2-14 -61% female, 39% male -10/28 patients ambulatory -13/28 patients with scoliosis	US Ss	A total of 3 lumbar punctures were scheduled during the 2 trials for drug delivery and/or follow-up collection of cerebrospinal fluid for safety and pharmacokinetic analyses. Participants underwent the first lumbar puncture on day 1 for cerebrospinal fluid collection and nusinersen dosing, the second lumbar puncture on day 8 or day 29 for cerebrospinal fluid collection, and the third lumbar puncture during the extension study for cerebrospinal fluid collection and redosing with nusinersen 9 to 14 months after the initial lumbar puncture.	68% of lumbar punctures had no complications reported.			-The most common adverse effects were headache, back pain, and post-dural syndrome (headache and sometimes vomiting), all were manageable with ibuprofen or other OTC treatments
4625	2017	4625. Finkel, R. S. et al., (2017). Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy N Engl J Med, 377(18), 1723-1732	NUS Ph3 ENDR	To report the final results of the ENDEAR trial, a 13-month, international, randomized, multicenter, sham-controlled, phase 3 trial that assessed the clinical efficacy and safety of nusinersen in infants who had received a genetic diagnosis of spinal muscular atrophy, had two copies of SMN2 (which is subject to copy-number variation), and had had onset of symptoms at 6 months of age or younger.	EXPER	121	Type1	genetic documentation of a homozygous deletion or mutation in the SMN1 gene, 2 copies SMN2 had onset of clinical symptoms that were consistent with SMA at 6 months of age or younger	US Ss	- doses were administered on days 1, 15, 29, and 64 and maintenance doses on days 183 and 302. -Efficacy end points were assessed on days 64, 183, 302, and 394 (±7 days for each visit). -Safety monitoring visits occurred on days 16, 30, 65, 184, and 303. -Follow-up after the procedure consisted of weekly assessments by telephone and a visit to the study center on day 394 (±7 days).	Primary endpoint was the evaluation of motor skills by HINE and HINE 2	-HINE and HINE 2 -event free survival--time to death or permanent use of ventilator for 21 continuous days -CHOP INTEND -CMAP	-51% of infants on nusinersen vs 0% of control infants had motor milestone response -Infants on nusinersen were also less likely to need permanent ventilation and were less likely to die than control group -The shorter the presentation of symptoms prior to dosage the better the outcome for infants	Nusinersen groups were comparable to controls in adverse events
4626	2017	4626. Mendell, J. et al. (2017). Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy N Engl J Med, 377(18), 1713-1722	GeneTher	To study functional replacement of the mutated gene encoding survival motor neuron 1 (SMN1) in this disease	EXPER	15	Type1	-genetically confirmed diagnosis of SMA1, homozygous SMN1 exon 7 deletions, and two copies of SMN2. - mean age of patients at the time of treatment was 6.3 months (range, 5.9 to 7.2) in cohort 1 (low dose) and 3.4 months (range, 0.9 to 7.9) in cohort 2 (high dose).	US Ss	Fifteen patients with SMA1 received a single dose of intravenous adeno-associated virus serotype 9 carrying SMN complementary DNA encoding the missing SMN protein. Three of the patients received a low dose (6.7×1013 vg per kilogram of body weight), and 12 received a high dose (2.0×1014 vg per kilogram).	-determination of safety on the basis of any treatment-related adverse events of grade 3 or higher	-time until death -the need for permanent ventilatory assistance -motor-milestone achievements (particularly, sitting unassisted) and -CHOP INTEND scores	an age of at least 20 months and did not require permanent mechanical ventilation vs. 8% in historical cohorts not requiring ventilation -All the patients in cohorts 1 and 2 had increased scores from baseline on the CHOP INTEND scale and maintained these changes during the study -11 of 12 patients in cohort 2 were able to sit unassisted for at least 5 seconds, 10 for at least 10 seconds, and 9 for at least 30 seconds -11 achieved head control, -9 could roll over -2 were able to crawl, pull to stand, stand independently, and walk independently.	2 events were treatment-related grade 4 events on the basis of laboratory values: 1- Patient 1 in cohort 1 had elevations in serum aminotransferase levels 2- One patient in cohort 2 required additional prednisolone to attenuate elevated serum ALT and AST levels -A single intravenous infusion of adeno-associated viral vector containing DNA coding for SMN in patients with SMA1 resulted in longer survival than in historical cohorts with this disease.

Helsedirektoratet

Returadresse: Helsedirektoratet, Postboks 220 Skøyen, 0213 Oslo, Norge

Nevromuskulært kompetansensenter (NMK)
Universitetssykehuset Nord-Norge
Postboks 33
9038 Tromsø

Deres ref.:	
Vår ref.:	20/19167-9
Saksbehandler:	Bente Bryhn
Dato:	03.12.2020

Utvidelse av tilbud om genetisk masseundersøkelse av nyfødte til å omfatte SMA-testing - spørsmål om behandling av barn med SMA

Helsedirektoratet viser til vedlagt søknad fra Helse Sør-Øst RHF angående utvidelse av nyfødtscreeningprogrammet.

Helsedirektoratet skal behandle søknaden, og vil deretter komme med en anbefaling til Helse- og omsorgsdepartementet.
Endelig avgjørelse om eventuell utvidelse av nyfødtscreeningprogrammet vil tas av departementet etter høring av endring av forskrift for masseundersøkelser av nyfødte.

I forbindelse med behandling av søknaden har vi noen spørsmål vi håper dere kan bidra til å belyse. I søknaden står det anslag på årlig antall pasienter.

Vi har spørsmål om forventet omfang av pasienter etter innføring av screening, og omfang av pasienter i dag.
Vi ønsker at dere gir en tilbakemelding med deres vurdering av følgende spørsmål:

- Antall i Norge i dag: Hvor mange pasienter med SMA under 18 år får i dag behandling med Spinraza, og hvor mange pasienter med SMA (under 18 år) får ikke behandling med Spinraza?
- Er start- eller stoppkriterier for behandling med Spinraza endret etter RHF-enes beslutning fra 22. oktober 2018 [1]?
- Vil antall pasienter som får diagnosen SMA endres hvis det innføres screening for SMA – eller forventes omtrent det samme antallet pasienter som i dag (bare at behandlingen igangsettes tidligere grunnet screening av nyfødte)?
- Vil man oppdage noen flere pasienter gjennom screening enn man oppdager i dag gjennom klinisk diagnostikk?
- Finnes det, og i så fall hva er andelen, pasienter med SMA som har andre mutasjoner enn de som kan gi mulighet for behandling med Spinraza?
- Hva er forskjell i prognose for barna ved tidlig og senere intervensjon/behandling?

[1] Nusinersen (Spinraza) (nyemetoder.no)

Helsedirektoratet
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- Vil eventuell screening av nyfødte for SMA påvirke tidspunkt og kriterier for oppstart av behandling, og i så fall, hvordan?
- Er det forskjell på behandlingen ved tidlig eller senere oppstart av behandling?

Vi ber om tilbakemelding om dette innen 11. desember. Tilbakemelding sendes til postmottak@helsedir.no, skriv ref. 20/19167, og kopi til bente.bryhn@helsedir.no

Vennlig hilsen

Torunn Janbu e.f.
avdelingsdirektør

Bente Bryhn
seniorrådgiver

Dokumentet er godkjent elektronisk

Helsedirektoratet
Postboks 220 Skøyen
0213 OSLO

Deres ref:	Vår ref:	Saksbehandler:	Dato:
20/19167-9	2020/10984-3	Andreas Dybesland Rosenberger	07.12.2020

Ref. 20/19167 Besvarelse fra Nevromuskulært Kompetansesenter

Besvarelse vedrørende «Utvidelse av tilbud om genetisk masseundersøkelse av nyfødte til å omfatte SMA-testing – spørsmål om behandling av barn med SMA»

Nevromuskulært Kompetansesenter (NMK) takker for muligheten til å komme med tilbakemelding på aktuelle spørsmål knyttet til behandling av søknaden om inkludering av SMA i nyfødtscreeningsprogrammet.

De etterfølgende svarene følger rekkefølgen på spørsmålene som ble stilt:

1) 59 pasienter < 18 år får i dag behandling med Spinraza i Norge. I tillegg er 9 pasienter overført til voksennevrologiske avdelinger etter at de har fylt 18 år. 1 pasient er død (ikke oppfattet som relatert til behandlingen). To av pasientene vurderes nå med tanke på eventuell avslutning av Spinraza-behandlingen. Vi har ikke full oversikt over hvor mange med SMA <18 år som ikke får Spinraza, men vi regner med at muligheten for slik behandling nå er godt kjent i Norge, og at vi derfor har fått kjennskap til de fleste som er diagnostisert. Vi kjenner til ett barn med type 3 som ikke har startet. Dessuten kjenner vi til to spedbarn der behandlingen aldri ble startet og som mest sannsynlig ikke lever lenger.

2) Den nasjonale faggruppen for Spinraza-behandling ble i forbindelse med RHF-enes beslutning i oktober 2018 gitt anledning til å endre stopp-kriteriene i samsvar med oppdatert kunnskap og erfaring. Faggruppen har på denne bakgrunn sendt inn forslag om visse justeringer, blant annet fordi man fant at de etablerte stoppkriteriene ikke fanger opp effekten godt nok. Faggruppen har også foreslått enkelte endringer når det gjelder startkriteriene, inkludert mulighet for å starte behandling der pasienten presymptomatisk har fått påvist delesjon i *SMN1*-genet og har 2 eller 3 kopier av *SMN2*-genet. I sjeldne tilfeller, for eksempel ved kjent SMA hos søsken, kan en slik situasjon oppstå også uten screening. Faggruppen har også foreslått å kunne starte

behandling hos type 3 med debut etter 3 års alder, men med tilleggskriterium at det foreligger klar progresjon av sykdommen. Dette har imidlertid svært sjelden vært en aktuell situasjon så langt. Man har dessuten ønsket å stramme noe inn på oppstartkriterier ved type 1 ved å si at det ikke skal være klare symptomer ved 1 ukes alder.

3) Dersom det innføres screening for SMA, vil mutasjon forenlig med sykdommen avdekkes i nyfødtperioden. Dermed vil det på tidlige alderstrinn være flere diagnostiserte, og flere av dem vil da være asymptomatiske, særlig de med ≥4 kopier. Disse kan i noen tilfeller få sen klinisk debut, i enkelte tilfeller først i voksen alder. Imidlertid tydet preliminære resultater fra et pilotprosjekt i Tyskland på at nyfødtscreening for SMA ikke førte til relevant økning i insidens (K.Vill et al, *J Neuromuscul Dis* 2019)

4) Ved screening vil pasientene oppdages tidligere. Dermed vil flere ha diagnosen i tidlig alder. Dersom screening innføres, vil det være viktig å ta stilling til hvem som skal få behandling med en gang og hvem som skal avvente, eventuelt til symptomer melder seg (særlig aktuelt for de som får påvist ≥4 kopier).

5) Man regner med at ca 5% av pasienter med klinisk SMA har en sykdom som ikke skyldes mutasjon i *SMN1*-genet.

6) Ut ifra dagens kunnskap er det fyldig dokumentasjon for at tidlig start av behandling gir en klart bedret prognose, slik det også er referert i søknaden om etablering av screening av nyfødte for SMA i Norge (R.S.Finkel et al. *New Engl J Med* 2017; E.Mercuri et al *New Engl J Med* 2018; D.C.De Vivo et al, *Neuromuscul Disord* 2019).

7) Eventuell screening av nyfødte for SMA vil opplagt føre til tidligere behandlingsstart fordi mange vil få behandlingen presymptomatisk, og for de som eventuelt skal avvente til symptomdebut, vil behandling kunne settes i gang straks symptomene melder seg. Slik situasjonen er i dag, kan det ta tid før riktig diagnose stilles. Dermed forsinkes behandlingen med risiko for dårligere prognose. Når det gjelder kriterier for oppstart, må en ved screening basere avgjørelsen på antall kopier av *SMN2*-genet, snarere enn på type SMA. Det er likevel en klar sammenheng mellom de to. Ved SMA type 1 er det oftest 2 kopier, ved type 2 oftest 3 kopier, mens 4 kopier oftest sees ved type 3.

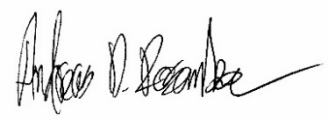
8) I dag er Spinraza den eneste årsaksrettede behandling som er tilgjengelig i Norge både ved tidlig og senere oppstart. Pasientgruppen forventes fortsatt å ha noe behov også for annen type behandling/tverrfaglig habilitering selv om de får Spinraza, men i mindre utstrekning. Særlig forventes et redusert slikt behov når årsaksrettet behandling innsettes tidlig, og så langt man har oppfølgingsdata, ser det altså ut til å

være svært mye å vinne ved presymptomatisk oppstart (D.C.De Vivo et al, *Neuromuscul Disord* 2019). Dersom det åpnes for bruk av ekte genterapi (Zolgensma), må det nedfelles kriterier for hvem som skal få slik terapi. Det samme gjelder dersom det perorale medikamentet risdiplam blir tilgjengelig i Norge.

Basert på tilgjengelig forskningskunnskap og erfaringene fra Spinraza-behandling i Norge, støtter NMK søknaden om utvidelsen av genetisk masseundersøkelse av nyfødte til også å omfatte SMA.

Håper dette er til hjelp i videre behandling av søknaden.

Vennlig hilsen



Andreas Dybesland Rosenberger
Senterleder Nevromuskulært Kompetansesenter
Universitetssykehuset Nord-Norge

Dokumentet er elektronisk godkjent og kan derfor være uten signatur.

Bente Bryhn

Prosess ved utvidelse av nyfødtscreeningprogrammet

1. Helse Sør-Øst RHF v/Nasjonal behandlingstjeneste for screening av nyfødte og avansert laboratoriediagnostikk ved medfødte stoffskiftesykdommer, Oslo universitetssykehus HF, utarbeider søknad om utvidelse/endring av nyfødtscreeningprogrammet.

2. Søknaden skal utarbeides i tråd med kriterier for nasjonale screeningsprogrammer[1] og i samråd med tjenestens faglige referansegruppe, og oversendes Helsedirektoratet for vurdering. Søknaden skal omfatte forslag til ny beskrivelse av tjenestens innhold.

3. Helsedirektoratet vurderer søknaden og innhenter om nødvendig ytterligere informasjon/kunnskapsgrunnlag, inkludert etiske vurderinger, helseøkonomiske og/eller kostnadsberegninger. Ved behov for oppdatert kunnskapsoppsummering eller metodevurdering utarbeider Folkehelseinstituttet dette etter bestilling fra Hdir. Ved behov innhentes også ytterligere innspill og råd fra RHF-ene og fagmiljø.
Søknaden vurderes etter regelverket for nasjonale tjenester, bioteknologiloven og forskriften for masseundersøkelser av nyfødte. I tillegg gjøres en helhetsvurdering av søknaden opp mot
screeningkriteriene, prioriteringskriteriene, etiske implikasjoner og andre konsekvenser av endringen, inkludert økonomiske konsekvenser

4. Hdir oversender en anbefaling til HOD

5. HOD sender forslag om endring av *Forskrift om masseundersøkelser av nyfødte* på høring

6. Etter høring beslutter HOD eventuell endring av forskrift, og Helsedirektoratet gir beskjed til Helse Sør-Øst RHF om at søknaden er godkjent og at endringen implementeres i Nasjonal behandlingstjeneste for screening av nyfødte og avansert laboratoriediagnostikk ved medfødte stoffskiftesykdommer, Oslo universitetssykehus HF

Bakgrunn: Helsedirektoratet har i brev av 06. april 2020 til Helse- og omsorgsdepartementet anbefalt prosess og roller ved endring av nyfødtscreeningprogrammet for å ivareta alle hensyn og krav i regelverk som regulerer virksomheten, samt ivareta en hensiktsmessig prosess ved endring av programmet. HOD har i brev av brev av 12. juni 2020 støttet direktoratets beskrivelse av prosess og roller.

[1] Kriterier for nasjonale screeningprogrammer er beskrevet i direktoratets notat av november 2018 og rapport om nasjonale screeningprogrammer fra 2015. Kriteriene er basert på WHO sine kriterier.

Screeningkriteriene

Tilstand

1. Tilstanden skal være et viktig helseproblem
2. Tilstandens naturlige forløp skal være tilstrekkelig kjent
3. Tilstanden skal ha en symptomfri fase som kan detekteres

Test

4. Det må finnes en sikker, presis og validert test
5. Kriterier og prosedyrer for videre oppfølging av testpositive må være definert
6. Testmetoden skal være akseptabel for målgruppen

Behandling

7. Det må finnes tiltak eller behandling som gir bedre effekt i tidlig stadium enn ved klinisk diagnostikk
8. Tiltak/behandling må være etablert og godt dokumentert
9. Tiltak/behandling skal være akseptabel for målgruppen

Screeningprogrammet

10. Screeningprogrammet skal redusere sykdomsspesifikk dødelighet eller sykelighet av tilstanden
11. Helsegevinstene må være større enn de negative effektene
12. Personvern og juridiske aspekter må være ivaretatt
13. Screeningprogrammet skal være akseptabelt fra et etisk perspektiv
14. Informasjon om deltakelse i screeningprogrammet må være kunnskapsbasert og bidra til informerte valg
15. Screeningprogrammet skal tilfredsstille kravene til kostnadseffektivitet
16. Det må foreligge en plan for ledelse, kvalitetssikring og evaluering av programmet

Helsedirektoratet

Returadresse: Helsedirektoratet, Postboks 220 Skøyen, 0213 Oslo, Norge

Helse Sør-Øst RHF
Postboks 404
2303 HAMAR

Deres ref.:
Vår ref.: 20/19167-15
Saksbehandler: Bente Bryhn
Dato: 03.02.2021

Angående søknad om utvidelse av nyfødtscreeningprogrammet - screening for SMA - økonomiske konsekvenser

Helsedirektoratet viser til søknad fra Helse Sør-Øst RHF om utvidelse av nyfødtscreeningprogrammet til å omfatte screening for spinal muskelatrofi (SMA).

Søknaden fra Helse Sør-Øst RHF består av følgende dokumenter: Brev av 2.11.2020 fra Helse Sør-Øst RHF med vedlegg:
- Brev av 21.09.2020 fra Oslo universitetssykehus HF,
- Utfylt søknadsskjema for nasjonale og flerregionale behandlingstjenester
- Rapport av 3.3.2018: *Evidence-based Review of Newborn Screening for Spinal Muscular Atrophy (SMA): Final Report (v5.2)*

Helse Sør-Øst RHF skriver i brevet av 02.11.20:
"*søknaden er forelagt for fagdirektørene i de øvrige regionale helseforetakene, som støtter at søknaden oversendes Helsedirektoratet for videre utredning og behandling etter den prosessen direktoratet redegjør for i sitt brev av 23. juni 2020. Fagdirektørene i Helse Vest RHF, Helse Midt-Norge RHF og Helse Nord RHF støtter også vår vurdering om at de regionale helseforetakene ikke kan påta seg ansvaret for de økonomiske-/budsjettmessige konsekvensene før disse er utredet.*"

Som det fremgår av søknaden vil en eventuell inkludering av SMA i nyfødtscreeningen kreve marginalt med ekstra ressurser knyttet til selve screeningundersøkelsen/screeningprogrammet, da den kan legges «oppå» dagens SCID-screening og laboratoriet ved Oslo universitetssykehus HF har alt nødvendig utstyr. Kostnadene er opplyst[1] til årlig å være om lag 400 000 + sosiale kostnader for en 50 % legestilling.

Funn av SMA medfører imidlertid behov for svært kostbar behandling.
Dette er behandling som også i dag gis til barn under 18 år under nærmere bestemte forutsetninger, jfr. beslutning i Beslutningsforum i oktober 2018. I 2017 ble det utført en metodevurdering av Statens legemiddelverk. Metodevurderingen var grunnlag for Beslutningsforum sin behandling og beslutning om at Spinraza skulle tas i bruk i Norge til behandling av barn med SMA, på nærmere angitte kriterier. Blant kriteriene er at det skal

[1] I epost fra avdelingsleder for Nyfødtscreeningen, Rolf D. Pettersen 4.11.20

Helsedirektoratet
Avdeling spesialisthelsetjenester
Bente Bryhn
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Org.nr.: 983 544 622 • postmottak@helsedir.no • www.helsedirektoratet.no

etableres og jevnlig vurderes start- og stoppkriterier og at alle pasienter skal registreres i det nasjonale medisinske kvalitetsregisteret. I sin beslutning skriver Beslutningsforum blant annet: "*Tilgjengelig dokumentasjon viser at effekten av nusinersen (Spinraza) er størst hos de yngste barna og de barna som starter behandlingen tidlig i sykdomsforløpet.*"

Metodevurderingen fra Statens legemiddelverk om bruk av Nusinersen (Spinraza) ved behandling av spinal muskelatrofi SMA fra 09.10.2017[2] inneholder kostnadsestimater og vurdering av økonomiske konsekvenser ved behandlingen.

Spinraza er definert som genterapi og ble godkjent etter bioteknologiloven av Helsedirektoratet i brev av 03.03.2018.

Formålet med nyfødtscreening for SMA er å identifisere pasientene før symptomer oppstår, for dermed å kunne igangsette behandling. I søknaden fremgår det at testen som brukes har høy spesifisitet og sensitivitet. Behandlingen som tilbys er etablert som behandlingstilbud i Norge fra 2018, og det er vel dokumentert at behandlingen gir gevinst i form av redusert sykelighet og forlenget levetid for pasientgruppen.

Helse Sør-Øst RHF har i møte med direktoratet stilt spørsmål om pasientgruppen vil bli større enn i dag, ved en eventuell innføring av screening for SMA i nyfødtscreeningprogrammet. Oslo universitetssykehus HF har i søknaden opplyst at omfanget av pasienter ikke vil avvike vesentlig fra i dag. Direktoratet har i forbindelse med behandling av søknaden også innhentet vurderinger fra Nevromuskulært kompetansesenter i Tromsø. De uttaler at antall nye pasienter årlig ikke vil avvike vesentlig fra i dag ved en eventuell innføring av screening for SMA. Indikasjon for behandling er den samme, enten pasientene diagnostiseres via screening eller ved klinisk indikasjon. Se vedlagt kopi av brev til og fra Nevromuskulært kompetansesenter.

Helsedirektoratet mener på bakgrunn av dette at vurderingene i søknaden og avklaringer med Nevromuskulært kompetansesenter gir et tilstrekkelig bilde av at omfang av pasienter ikke vil øke og således at man har tilstrekkelig informasjon for å vurdere økonomiske konsekvenser av den omsøkte endringen av screeningprogrammet. Kostnader ved behandling for SMA er redegjort for i Statens legemiddelverk sin analyse fra 2017. Direktoratet har derfor ikke bestilt en egen helseøkonomisk analyse av forslag om innføring av screening for SMA. De økonomiske kostnadene ved selve screeningen er minimale, pasientpopulasjonen vil ikke øke i omfang, og aktuell behandling gis allerede til barn med SMA under 18 år under nærmere bestemte forutsetninger[3]Norge.

Direktoratet har i møte med Helse Sør-Øst RHF 02.02.21 redegjort for at direktoratet mener de økonomiske konsekvensene, samt øvrige vurderingstema nå er tilstrekkelig opplyst for å kunne ta stilling til en utvidelse av nyfødtscreeningprogrammet til også å omfatte screening for spinal muskelatrofi (SMA).

Direktoratet ber om en bekreftelse på at det ikke gjenstår forhold ved søknaden som gir grunn til forbehold fra RHF-ene. Vi ber om at Helse Sør-Øst avklarer med øvrige RHF og gir en

[2] https://nyemetoder.no/metoder/nusinersen-spinraza
[3] Spinraza til barn (nyemetoder.no)

tilbakemelding så raskt som mulig og senest 10. februar til postmottak@helsedir.no med kopi til bente.bryhn@helsedir.no, vår referanse 20/19167.

Vennlig hilsen

Torunn Janbu e.f.
avdelingsdirektør

Bente Bryhn
seniorrådgiver

Dokumentet er godkjent elektronisk

Kopi:
Helse Sør-Øst RHF, Kirsti Tørbakken

Helsedirektoratet

Returadresse: Helsedirektoratet, Postboks 220 Skøyen, 0213 Oslo, Norge

Nevromuskulært kompetansensenter (NMK)
Universitetssykehuset Nord-Norge
Postboks 33
9038 Tromsø

Deres ref.:	
Vår ref.:	20/19167-9
Saksbehandler:	Bente Bryhn
Dato:	03.12.2020

Utvidelse av tilbud om genetisk masseundersøkelse av nyfødte til å omfatte SMA-testing - spørsmål om behandling av barn med SMA

Helsedirektoratet viser til vedlagt søknad fra Helse Sør-Øst RHF angående utvidelse av nyfødtscreeningprogrammet.

Helsedirektoratet skal behandle søknaden, og vil deretter komme med en anbefaling til Helse- og omsorgsdepartementet.
Endelig avgjørelse om eventuell utvidelse av nyfødtscreeningprogrammet vil tas av departementet etter høring av endring av forskrift for masseundersøkelser av nyfødte.

I forbindelse med behandling av søknaden har vi noen spørsmål vi håper dere kan bidra til å belyse. I søknaden står det anslag på årlig antall pasienter.

Vi har spørsmål om forventet omfang av pasienter etter innføring av screening, og omfang av pasienter i dag.
Vi ønsker at dere gir en tilbakemelding med deres vurdering av følgende spørsmål:

- Antall i Norge i dag: Hvor mange pasienter med SMA under 18 år får i dag behandling med Spinraza, og hvor mange pasienter med SMA (under 18 år) får ikke behandling med Spinraza?
- Er start- eller stoppkriterier for behandling med Spinraza endret etter RHF-enes beslutning fra 22. oktober 2018 [1]?
- Vil antall pasienter som får diagnosen SMA endres hvis det innføres screening for SMA – eller forventes omtrent det samme antallet pasienter som i dag (bare at behandlingen igangsettes tidligere grunnet screening av nyfødte)?
- Vil man oppdage noen flere pasienter gjennom screening enn man oppdager i dag gjennom klinisk diagnostikk?
- Finnes det, og i så fall hva er andelen, pasienter med SMA som har andre mutasjoner enn de som kan gi mulighet for behandling med Spinraza?
- Hva er forskjell i prognose for barna ved tidlig og senere intervensjon/behandling?

[1] Nusinersen (Spinraza) (nyemetoder.no)

Helsedirektoratet
Avdeling spesialisthelsetjenester
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Org.nr.: 983 544 622 • postmottak@helsedir.no • www.helsedirektoratet.no

- Vil eventuell screening av nyfødte for SMA påvirke tidspunkt og kriterier for oppstart av behandling, og i så fall, hvordan?
- Er det forskjell på behandlingen ved tidlig eller senere oppstart av behandling?

Vi ber om tilbakemelding om dette innen 11. desember. Tilbakemelding sendes til postmottak@helsedir.no, skriv ref. 20/19167, og kopi til bente.bryhn@helsedir.no

Vennlig hilsen

Torunn Janbu e.f.
avdelingsdirektør

Bente Bryhn
seniorrådgiver

Dokumentet er godkjent elektronisk

Helsedirektoratet
Postboks 220 Skøyen
0213 OSLO

Deres ref:	Vår ref:	Saksbehandler:	Dato:
20/19167-9	2020/10984-3	Andreas Dybesland Rosenberger	07.12.2020

Ref. 20/19167 Besvarelse fra Nevromuskulært Kompetansesenter

Besvarelse vedrørende «Utvidelse av tilbud om genetisk masseundersøkelse av nyfødte til å omfatte SMA-testing – spørsmål om behandling av barn med SMA»

Nevromuskulært Kompetansesenter (NMK) takker for muligheten til å komme med tilbakemelding på aktuelle spørsmål knyttet til behandling av søknaden om inkludering av SMA i nyfødtscreeningsprogrammet.

De etterfølgende svarene følger rekkefølgen på spørsmålene som ble stilt:

1) 59 pasienter < 18 år får i dag behandling med Spinraza i Norge. I tillegg er 9 pasienter overført til voksennevrologiske avdelinger etter at de har fylt 18 år. 1 pasient er død (ikke oppfattet som relatert til behandlingen). To av pasientene vurderes nå med tanke på eventuell avslutning av Spinraza-behandlingen. Vi har ikke full oversikt over hvor mange med SMA <18 år som ikke får Spinraza, men vi regner med at muligheten for slik behandling nå er godt kjent i Norge, og at vi derfor har fått kjennskap til de fleste som er diagnostisert. Vi kjenner til ett barn med type 3 som ikke har startet. Dessuten kjenner vi til to spedbarn der behandlingen aldri ble startet og som mest sannsynlig ikke lever lenger.

2) Den nasjonale faggruppen for Spinraza-behandling ble i forbindelse med RHF-enes beslutning i oktober 2018 gitt anledning til å endre stopp-kriteriene i samsvar med oppdatert kunnskap og erfaring. Faggruppen har på denne bakgrunn sendt inn forslag om visse justeringer, blant annet fordi man fant at de etablerte stoppkriteriene ikke fanger opp effekten godt nok. Faggruppen har også foreslått enkelte endringer når det gjelder startkriteriene, inkludert mulighet for å starte behandling der pasienten presymptomatisk har fått påvist delesjon i *SMN1*-genet og har 2 eller 3 kopier av *SMN2*-genet. I sjeldne tilfeller, for eksempel ved kjent SMA hos søsken, kan en slik situasjon oppstå også uten screening. Faggruppen har også foreslått å kunne starte

behandling hos type 3 med debut etter 3 års alder, men med tilleggskriterium at det foreligger klar progresjon av sykdommen. Dette har imidlertid svært sjelden vært en aktuell situasjon så langt. Man har dessuten ønsket å stramme noe inn på oppstartkriterier ved type 1 ved å si at det ikke skal være klare symptomer ved 1 ukes alder.

3) Dersom det innføres screening for SMA, vil mutasjon forenlig med sykdommen avdekkes i nyfødtperioden. Dermed vil det på tidlige alderstrinn være flere diagnostiserte, og flere av dem vil da være asymptomatiske, særlig de med ≥4 kopier. Disse kan i noen tilfeller få sen klinisk debut, i enkelte tilfeller først i voksen alder. Imidlertid tydet preliminære resultater fra et pilotprosjekt i Tyskland på at nyfødtscreening for SMA ikke førte til relevant økning i insidens (K.Vill et al, *J Neuromuscul Dis* 2019)

4) Ved screening vil pasientene oppdages tidligere. Dermed vil flere ha diagnosen i tidlig alder. Dersom screening innføres, vil det være viktig å ta stilling til hvem som skal få behandling med en gang og hvem som skal avvente, eventuelt til symptomer melder seg (særlig aktuelt for de som får påvist ≥4 kopier).

5) Man regner med at ca 5% av pasienter med klinisk SMA har en sykdom som ikke skyldes mutasjon i *SMN1*-genet.

6) Ut ifra dagens kunnskap er det fyldig dokumentasjon for at tidlig start av behandling gir en klart bedret prognose, slik det også er referert i søknaden om etablering av screening av nyfødte for SMA i Norge (R.S.Finkel et al. *New Engl J Med* 2017; E.Mercuri et al *New Engl J Med* 2018; D.C.De Vivo et al, *Neuromuscul Disord* 2019).

7) Eventuell screening av nyfødte for SMA vil opplagt føre til tidligere behandlingsstart fordi mange vil få behandlingen presymptomatisk, og for de som eventuelt skal avvente til symptomdebut, vil behandling kunne settes i gang straks symptomene melder seg. Slik situasjonen er i dag, kan det ta tid før riktig diagnose stilles. Dermed forsinkes behandlingen med risiko for dårligere prognose. Når det gjelder kriterier for oppstart, må en ved screening basere avgjørelsen på antall kopier av *SMN2*-genet, snarere enn på type SMA. Det er likevel en klar sammenheng mellom de to. Ved SMA type 1 er det oftest 2 kopier, ved type 2 oftest 3 kopier, mens 4 kopier oftest sees ved type 3.

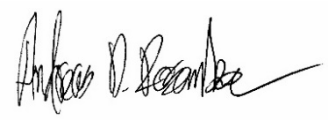
8) I dag er Spinraza den eneste årsaksrettede behandling som er tilgjengelig i Norge både ved tidlig og senere oppstart. Pasientgruppen forventes fortsatt å ha noe behov også for annen type behandling/tverrfaglig habilitering selv om de får Spinraza, men i mindre utstrekning. Særlig forventes et redusert slikt behov når årsaksrettet behandling innsettes tidlig, og så langt man har oppfølgingsdata, ser det altså ut til å

være svært mye å vinne ved presymptomatisk oppstart (D.C.De Vivo et al, *Neuromuscul Disord* 2019). Dersom det åpnes for bruk av ekte genterapi (Zolgensma), må det nedfelles kriterier for hvem som skal få slik terapi. Det samme gjelder dersom det perorale medikamentet risdiplam blir tilgjengelig i Norge.

Basert på tilgjengelig forskningskunnskap og erfaringene fra Spinraza-behandling i Norge, støtter NMK søknaden om utvidelsen av genetisk masseundersøkelse av nyfødte til også å omfatte SMA.

Håper dette er til hjelp i videre behandling av søknaden.

Vennlig hilsen



Andreas Dybesland Rosenberger
Senterleder Nevromuskulært Kompetansesenter
Universitetssykehuset Nord-Norge

Dokumentet er elektronisk godkjent og kan derfor være uten signatur.

Bente Bryhn

Prosess ved utvidelse av nyfødtscreeningprogrammet

1. Helse Sør-Øst RHF v/Nasjonal behandlingstjeneste for screening av nyfødte og avansert laboratoriediagnostikk ved medfødte stoffskiftesykdommer, Oslo universitetssykehus HF, utarbeider søknad om utvidelse/endring av nyfødtscreeningprogrammet.

2. Søknaden skal utarbeides i tråd med kriterier for nasjonale screeningsprogrammer[1] og i samråd med tjenestens faglige referansegruppe, og oversendes Helsedirektoratet for vurdering. Søknaden skal omfatte forslag til ny beskrivelse av tjenestens innhold.

3. Helsedirektoratet vurderer søknaden og innhenter om nødvendig ytterligere informasjon/kunnskapsgrunnlag, inkludert etiske vurderinger, helseøkonomiske og/eller kostnadsberegninger. Ved behov for oppdatert kunnskapsoppsummering eller metodevurdering utarbeider Folkehelseinstituttet dette etter bestilling fra Hdir. Ved behov innhentes også ytterligere innspill og råd fra RHF-ene og fagmiljø.
Søknaden vurderes etter regelverket for nasjonale tjenester, bioteknologiloven og forskriften for masseundersøkelser av nyfødte. I tillegg gjøres en helhetsvurdering av søknaden opp mot
screeningkriteriene, prioriteringskriteriene, etiske implikasjoner og andre konsekvenser av endringen, inkludert økonomiske konsekvenser

4. Hdir oversender en anbefaling til HOD

5. HOD sender forslag om endring av *Forskrift om masseundersøkelser av nyfødte* på høring

6. Etter høring beslutter HOD eventuell endring av forskrift, og Helsedirektoratet gir beskjed til Helse Sør-Øst RHF om at søknaden er godkjent og at endringen implementeres i Nasjonal behandlingstjeneste for screening av nyfødte og avansert laboratoriediagnostikk ved medfødte stoffskiftesykdommer, Oslo universitetssykehus HF

Bakgrunn: Helsedirektoratet har i brev av 06. april 2020 til Helse- og omsorgsdepartementet anbefalt prosess og roller ved endring av nyfødtscreeningprogrammet for å ivareta alle hensyn og krav i regelverk som regulerer virksomheten, samt ivareta en hensiktsmessig prosess ved endring av programmet. HOD har i brev av brev av 12. juni 2020 støttet direktoratets beskrivelse av prosess og roller.

[1] Kriterier for nasjonale screeningprogrammer er beskrevet i direktoratets notat av november 2018 og rapport om nasjonale screeningprogrammer fra 2015. Kriteriene er basert på WHO sine kriterier.

From: Jan Frich <Jan.Christian.Frich@helse-sorost.no>
Sent: 11. februar 2021 20:07
To: Postmottak (Ekstern post til arkivet)
Cc: Bente Bryhn; 'Tollåli Geir'; Gustafsson, Bjørn Inge; Schem, Baard-Christian; HSORHF PB Postmottak; Siv Cathrine Høymork; Spørck Randi Midtgård
Subject: Angående søknad om utvidelse av nyfødtscreeningprogrammet - screening for SMA - økonomiske konsekvenser

Follow Up Flag: Følg opp
Flag Status: Completed

Til Helsedirektoratet,

Deres ref. 20/19167-15

Angående søknad om utvidelse av nyfødtscreeningprogrammet - screening for SMA - økonomiske konsekvenser

Takk for brev. Saken er behandling i det interregionale fagdirektørmøtet 11.2.2021.

Det ikke foreligger noen spesifikke forbehold fra RHFene når søknad om utvidelse av nyfødtscreeningprogrammet med SMA-screening
oversendes Helse- og omsorgsdepartementet.

Vennlig hilsen

Jan Frich
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