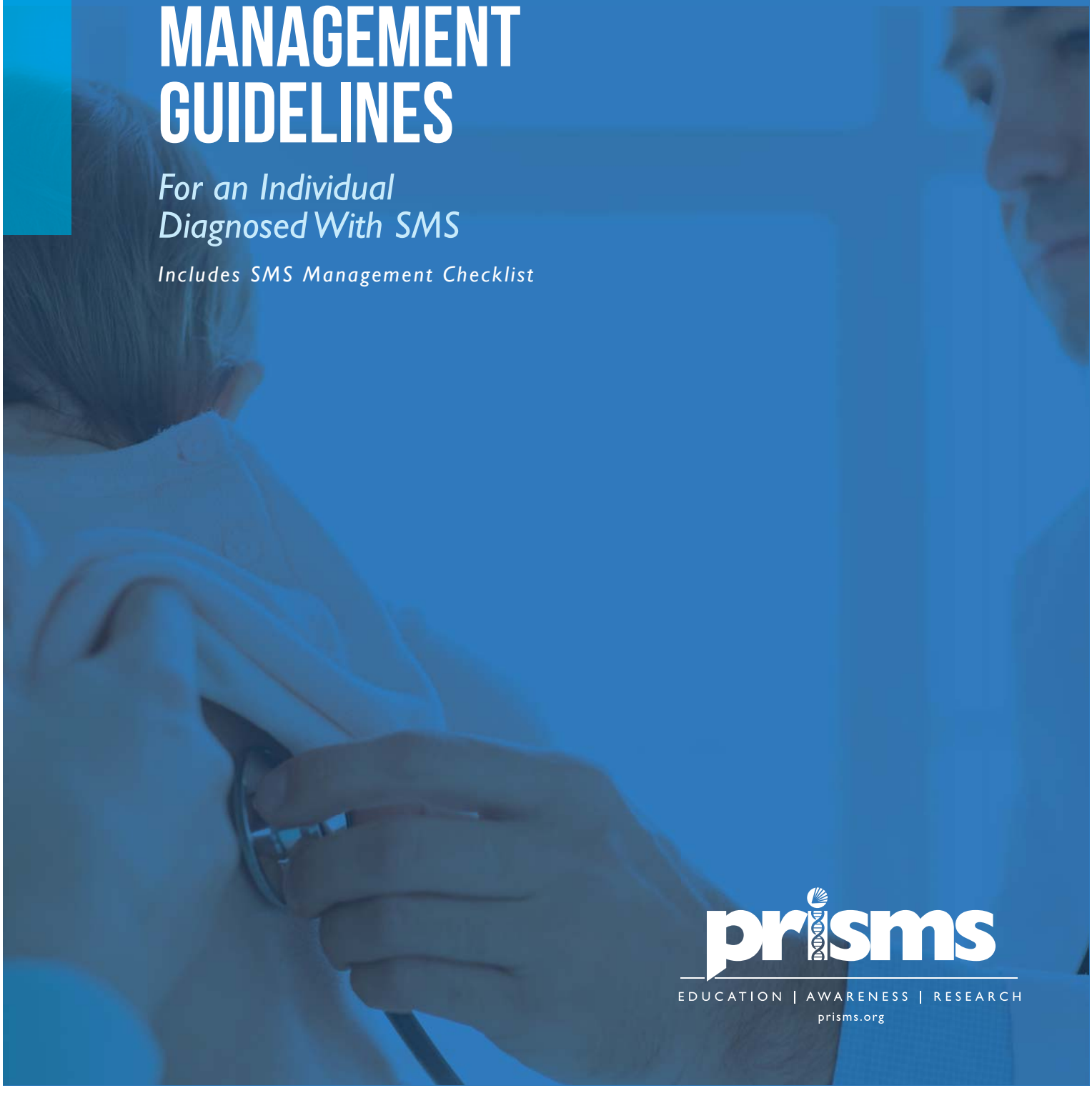
PRISMS PROFESSIONAL ADVISORY BOARD

MEDICAL MANAGEMENT GUIDELINES

For an Individual Diagnosed With SMS

Includes SMS Management Checklist



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Management involves evaluation for manifestations of Smith-Magenis Syndrome (SMS) and treatment to mitigate associated symptoms and conditions. Variability among individuals and developmental changes are important to recognize. These guidelines were developed and approved by PRISMS Professional Advisory Board. First published as part of the in-depth review of SMS that appears in GeneReviews (Last update June 2012), these guidelines were updated and approved by PRISMS Professional Advisory Board[1]. The terminology used here that is USA-focused may be adapted, as appropriate, for use in other countries.

Source: PRISMS Professional Advisory Board

Authors (PRISMS Professional Advisory Board):
Ann CM Smith, MA, DSc (hon), CGC, Chair Emeritus[1]
Kerry E Boyd, MD, FRCP(C)[1]
Christine Brennan, PhD CCC-SLP[1]
Jane Charles, M.D., FAAP[1]
Sarah H Elsea, PhD, FACMG, Chair
Brenda M Finucane, MS, CGC
Rebecca Foster, PhD
Barbara Haas-Givler, MEd, BCBA
Santhosh Girirajan, MD, PhD
Andrea Gropman, MD, FAAP, FACMG

[1] PAB Management Guidelines Working Group

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Parents and Researchers Interested in Smith-Magenis Syndrome

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Source: Written by PRISMS' Management Guidelines Working Group (ACMS, KB, CB and JC) with review and final approval by PRISMS Professional Advisory Board 24 January 2018.

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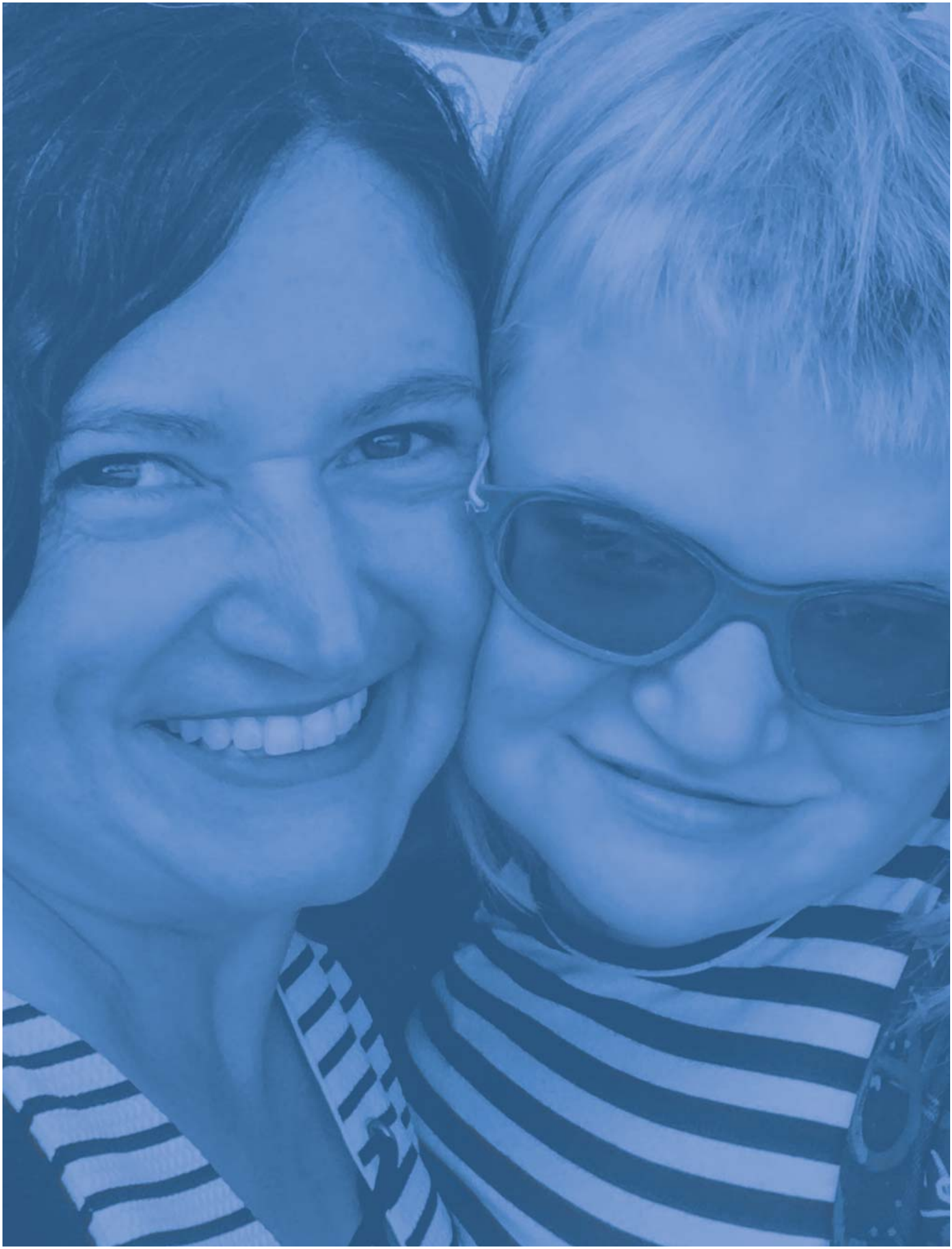


EVALUATIONS FOLLOWING INITIAL DIAGNOSIS

Medical

- Complete review of systems (‘head to toe’ body functions)
- Physical and neurologic examination
- Growth: Pediatric height, weight, head circumference; adult height, weight, BMI (obesity risk). Obesity is especially prevalent in individuals with RAI1 mutations.
- Ophthalmologic evaluation with attention to evidence of strabismus, microcornea, iris anomalies, and refractive error
- Otolaryngologic evaluation to assess ear, nose, and throat problems, with specific attention to ear physiology and palatal abnormalities (cleft, velopharyngeal insufficiency)
- Swallowing dysfunction (poor suck/swallow), oral-sensory-motor deficits with referral as warranted for full diagnostic evaluation
- Routine audiologic surveillance throughout the lifespan is recommended as part of standard clinical care to monitor for conductive and/or sensorineural hearing loss. Middle ear dysfunction is a common finding, frequently characterized by flat tympanograms.
- Immunologic evaluation due to an increased susceptibility to sinopulmonary infections, including pneumonia; however, the prevalence of allergies and autoimmune diseases is not increased. Evaluation by immunologist with prophylactic strategies to prevent infections may benefit select patients.

- Cardiac anomalies: Echocardiogram to evaluate for possible cardiac anomalies (occurs in <45% of individuals with SMS); follow-up according to the type of cardiac anomaly identified
- Gastroesophageal and intestinal issues: Signs and symptoms of gastroesophageal reflux disease (GERD). Discussion of bowel habits and concern for chronic constipation with referral to gastroenterology as history warrants.
- Genitourinary (GU) anomalies: Ultrasound examination to evaluate for possible renal/urologic anomalies (occurs in ~20% of individuals with SMS), including urologic workup if a history of frequent urinary tract infections exists
- Skeletal anomalies: Spine radiographs to evaluate for possible vertebral anomalies that include spina bifida occulta, and to document and monitor degree of scoliosis. Mild to moderate scoliosis (prevalence rate of 60%), usually of the mid-thoracic region, can be progressive, and, if significant, may require corrective surgery.
- Dermatologic (skin) assessment with attention to common complaints: Rosy cheeks (drooling or eczema related), dry skin (trunk, extremities), hyperkeratotic skin over surface of hands, feet, knees (occurs in <20%), and/or evidence of self-injurious behavior (i.e., skin picking, biting, and/or nail damage).
- Sleep history with attention to sleep/wake schedules and respiratory function. Sleep diaries may prove helpful in documenting sleep/wake schedules. Evidence of snoring or sleep-disordered breathing warrants a polysomnography (overnight sleep study) to evaluate for obstructive sleep apnea.
- EEG in individuals who have clinical seizures (prevalence 11-30%) to guide the choice of antiepileptic agents. For those without overt seizures, EEG may be helpful to evaluate for possible subclinical events in which treatment may improve attention and/or behavior; a change in behavior or attention warrants reevaluation. A video EEG may be helpful to correlate staring or behavioral changes with EEG.
- Neuroimaging (MRI or CT scan) as determined by specialists, in accordance with neurological findings such as seizures and/or motor asymmetry.
- Routine blood chemistries, fasting lipid profile (evaluation for hypercholesterolemia), quantitative serum immunoglobulins (IgG, IgA, IgM) including vaccine titers (pneumococcus especially), and thyroid function studies.
- For individuals with SMS documented to have larger distal deletions extending into 17p12, consider:

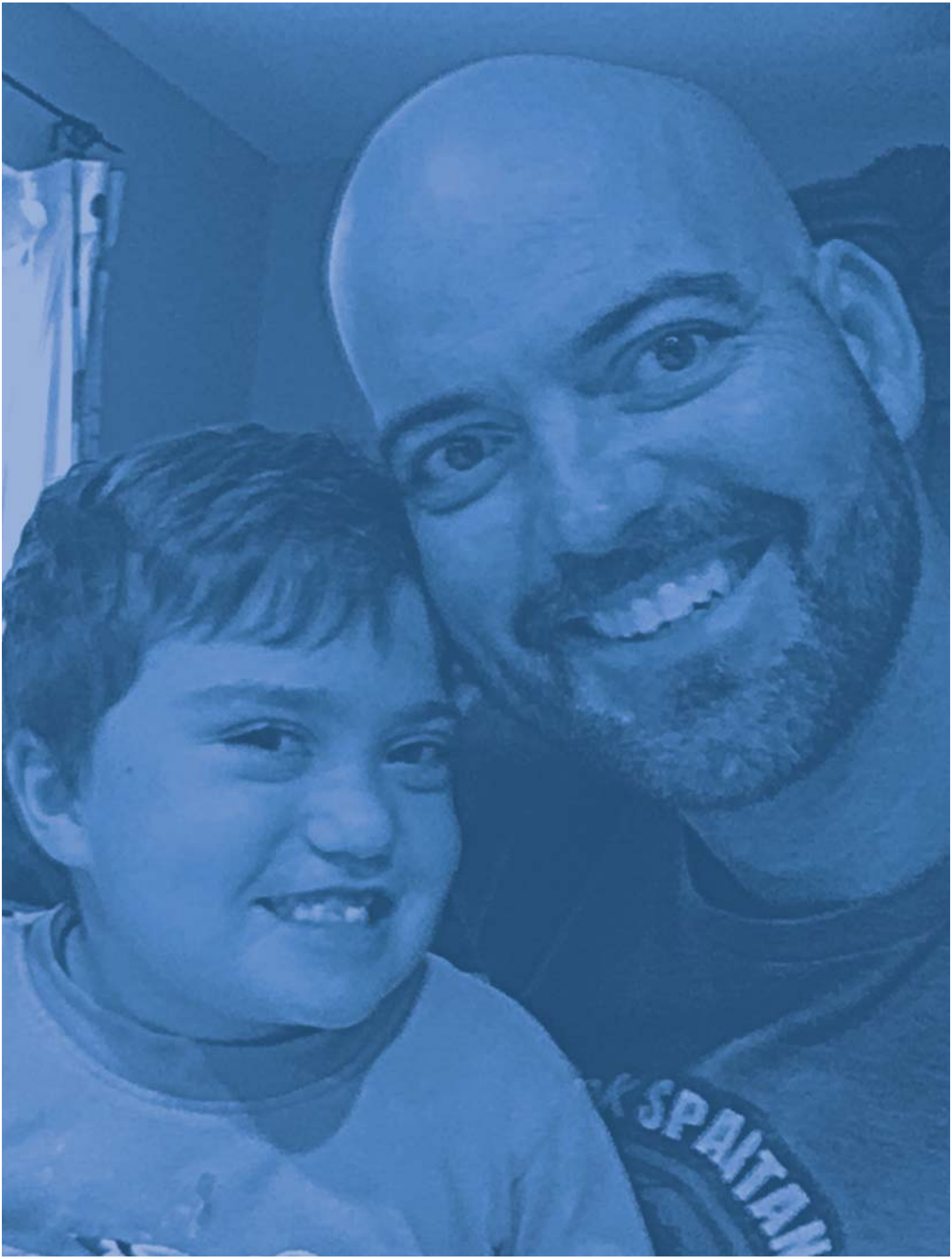
  Though rare, specific adrenal screening is warranted. Baseline and adenocorticotropic hormone-stimulated serum cortisol levels should be checked in cases of suspected hypoadrenalism.

  Detailed assessment and attention to peripheral neurologic function in individuals with SMS with large deletions involving PMP22 gene, which is associated with hereditary neuropathy with liability to pressure palsy (HNPP). When suspected, electromyogram/nerve conduction studies may be considered.

Multidisciplinary /Allied Health/ Education

Multidisciplinary assessments to guide individualized ongoing special education plans, therapeutic interventions, and transition to adulthood. Referrals for therapies, including speech/ language, physical, occupational, and sensory integration may be indicated (See next section).

- Multidisciplinary developmental or neuropsychological evaluation (depending on age), including assessment of motor, speech, language, personal-social, behavioral, emotional, cognitive (including executive functioning/attention/memory), academic, adaptive functioning, and vocational skills. Testing should be completed periodically based on provider recommendations.
- Early evaluation by physical and/or occupational therapists to assess fine and gross motor developmental and functional impairments.
- Comprehensive speech/language pathology evaluation with assessment of caloric intake, signs and symptoms of gastroesophageal reflux disease (GERD), swallowing abilities, and oral motor skills with referral as warranted for full diagnostic evaluation.
- Annual behavioral and emotional screening using standardized broad screen behavior checklists for primary caregivers and teachers (when available).
- If school age, child should have an individualized education plan for learning and behavioral accommodations. If the child is on medication, an individualized health plan should be in place by the school nurse or a designated health professional.
- A comprehensive behavior support plan for home and school should be considered as soon as problem behaviors arise, typically starting in early elementary school.
- Annual assessment of family support and psychosocial and emotional needs to assist in designing family interventions.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TREATMENT OF MANIFESTATIONS

Medical

- Immunizations

  Ongoing pediatric care with regular immunizations as recommended by American Academy of Pediatrics, including pneumonia with boosters [≥ 2year PPV (Pneumococcal polysaccharide vaccine); or adult >19y (PPSV23)]_

  - Helpful Resource Link: https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/immunization/Pages/Immunization-Schedule.aspx

- Growth measurements (height, weight, head circumference)

  Short stature: Birth length is typically within the normal range; however, decreased height velocity persists through age 3 (SMS average ≤ 5th percentile). However, by age 12, the median SMS height is ~25th percentile. Individuals with RAI1 mutations are often taller.

  While growth hormone treatment has been reported, controlled studies have not evaluated its effectiveness.

  Risk of obesity (increased BMI), often noted by age 6-9 years, is further impacted by dietary preferences, hyperphagia, food foraging at night (especially at older ages), psychotropic medication side effects (increase appetite/weight gain), and/or general sedentary lifestyle. Obesity is especially prevalent in individuals with RAI1 mutation.

  - Use of a “hands on” approach to stay active, have fun, and stay fit ideally should begin at a young age. Start early, make it fun and personalize interventions that encourage staying active. Family involvement is strongly recommended.

- Incorporate technology (pedometer, iPhone apps, food diaries with stickers) to promote healthy living.
- Decrease overall sedentary time (limit screen time) and encourage movement and physical activity.
- A comprehensive fitness approach includes balance, strengthening, stretching and cardiorespiratory fitness with water-walking, aerobics or swimming ideal for those with orthopedic limitations.

Vision
Treatment with corrective lenses as indicated for ophthalmologic abnormalities
Hearing
Treatment of recurrent otitis media with tympanostomy tubes as needed.
Conservative management should consider that the risk for hearing loss in those with SMS is high. Hearing loss may fluctuate and decline over time. Auditory amplification if hearing loss is identified. Ear wax buildup is readily treated.
Hyperacusis, a heightened perception to sound, is reported in 74% of individuals with SMS. Reactions may be effected by mood, sleep or circumstances. Hyperacusis is important to recognize, permitting caregivers the opportunity to implement management strategies. Helpful strategies include offering explanations and warnings before anticipated sound exposure (e.g., fireworks), use of headphones or earplugs to dampen the sound, and/or complete avoidance or lowered risk of the upsetting sounds (e.g., mylar balloons instead of rubber balloons that pop).
Neurological
Management of seizures in accordance with standard practice.
Cardiac
Treatment of cardiac and renal anomalies in accordance with standard medical practice.
Gastrointestinal
Constipation and/or encopresis are common in SMS.
Chronic constipation (59%) or alternating constipation with overflow incontinence (diarrhea) warrants referral to gastroenterology and possible further procedures (barium enema).
Increased fluid intake, stool softeners, dietary management, and behavioral interventions, as used for general population, may be helpful.
Signs and symptoms of gastroesophageal reflux disease (GERD), concern for swallowing abilities, and/or aspiration pneumonia should prompt referral for further/full diagnostic evaluation.

- Scoliosis
  - Clinical monitoring for evidence of scoliosis progression, especially during adolescence; radiographs should be obtained when clinically indicated to document change in spinal curvature.
  - Scoliosis should be treated in accordance with standard medical care. Surgical intervention is rarely required.
- Orthopedics
  - Orthopedic and/or physical therapy evaluation to assess developmental, functional and balance impairments.
  - Use of orthotics may be helpful for positional foot deformities, tight heel cords/toe walking, and/or gait disturbances.
  - Efforts to enhance functional mobility and/or exercises to improve abdominal/truncal tone are encouraged.
- Dermatologic
  - Skin assessment should be part of the routine medical examination.
  - Moisturizing creams can be effective in treating dry skin; lotions that contain either 10% urea or 5-10% lactic acid are recommended in cases of extremely dry skin.
  - Long-sleeved garments may help minimize injury caused by chronic self-biting and skin picking behavior.
  - Fingered gloves and frequent manicures/pedicures for nail hygiene may help minimize cuticle mutilation and biting, picking, and/or pulling out of finger- or toenails.
  - Use superfatted soaps, which do not include scent or deodorants.
- Monitoring of hypercholesterolemia (recognized in >50% of individuals with SMS); treatment with diet or medication as indicated.
- Evaluation by immunologist with prophylactic strategies to prevent infections may benefit select patients.

Multidisciplinary/Allied Health/Education

Refer to early childhood intervention programs, multidisciplinary assessments to guide individualized ongoing special education plans, behavioral and family support interventions, and transition to adulthood planning. Therapies including speech/language, physical, and occupational therapies:

- Speech/Language Pathology

  During early childhood, speech/language pathology services focus on identifying and treating swallowing and/or feeding problems, as well as optimizing oral sensorimotor development.

  While receptive language is a relative strength for individuals with SMS, both expressive and receptive language needs should both be addressed.

  Motor speech issues, including apraxia, may also be present and warrant intensive intervention for articulation to improve.

  A multimodal approach to communication is recommended. Language therapy should be designed to help children gain access to spoken language and limit frustration due to poor expressive communication. Augmentative communication approaches (including but not limited to sign language) are standard for children with severe expressive language delay/impairment. Picture exchange communication systems (PECS), and voice output systems, and touch voice apps may also be helpful in reducing frustration from inability to communicate effectively. Interventions should aim to improve functional communication, and be tailored to the needs of the child.

  Therapeutic goals of increasing sensory input, fostering movement of the articulators, increasing oral motor endurance, and decreasing hypersensitivity are needed to develop skills related to swallowing and speech production.

- Physical and Occupational Therapy

  Physical and occupational therapy (PT/OT) referrals are important to assess developmental and functional deficits and provide support and treatment.

  OT services should focus on fine motor development, fostering visual and auditory perceptual skills, and increasing activities of daily living.

  Atypical patterns of sensory processing may be apparent at any age. Insight about the vulnerabilities and relative strengths in patterns of sensory processing may aid caregivers of individuals with SMS in adapting activity demands, modifying the environment, and facilitating appropriate and supportive social interactions. The potential for more problematic or atypical behaviors with increased age underscores the need for early and ongoing intervention and caregiver education.

- Behavioral Interventions

  Behavioral therapies including special education techniques that emphasize individualized instruction, structure, and routine to help minimize behavioral outbursts in the school setting.

Behavioral interventions, including full comprehensive behavior plans in home and school settings, can be implemented to address attention seeking behaviors, refusal behaviors, oppositionality, emotional lability, adherence to medical regimens and daily tasks, self-harm and aggression toward others, toileting, feeding, and other maladaptive behaviors.

- Early Intervention

Evaluation for Early Intervention (EI) for young children ages birth-3 years. EI is a system of services that helps babies and toddlers with developmental delays or disabilities with a focus on intervention to facilitate development of skills that typically develop during the first three years of life (can include the following skills: speech/communication, motor, cognitive, social/emotional, self-help). In the U.S., EI evaluations and intervention are available in every state.

- Helpful Resource Link: For a flowchart for the EI referral and evaluation process, see http://ectacenter.org/~pdfs/topics/families/ifsp_process_chart.pdf

- Education/School

A school age child's educational plan should be individualized based on strengths and needs.

- The following link provides information about the process for creating an individualized educational plan (IEP). It also provides terms and legal rights for children within the USA.

- https://www2.ed.gov/parents/needs/speced/iepguide/index.html

If the child is on medication, a health plan should be put in place by either a school nurse or another medical specialist. The health plan should be created with input from the family and the educational team.

- Helpful Resource: Flowchart to determine need for a health plan (*See page 10*)

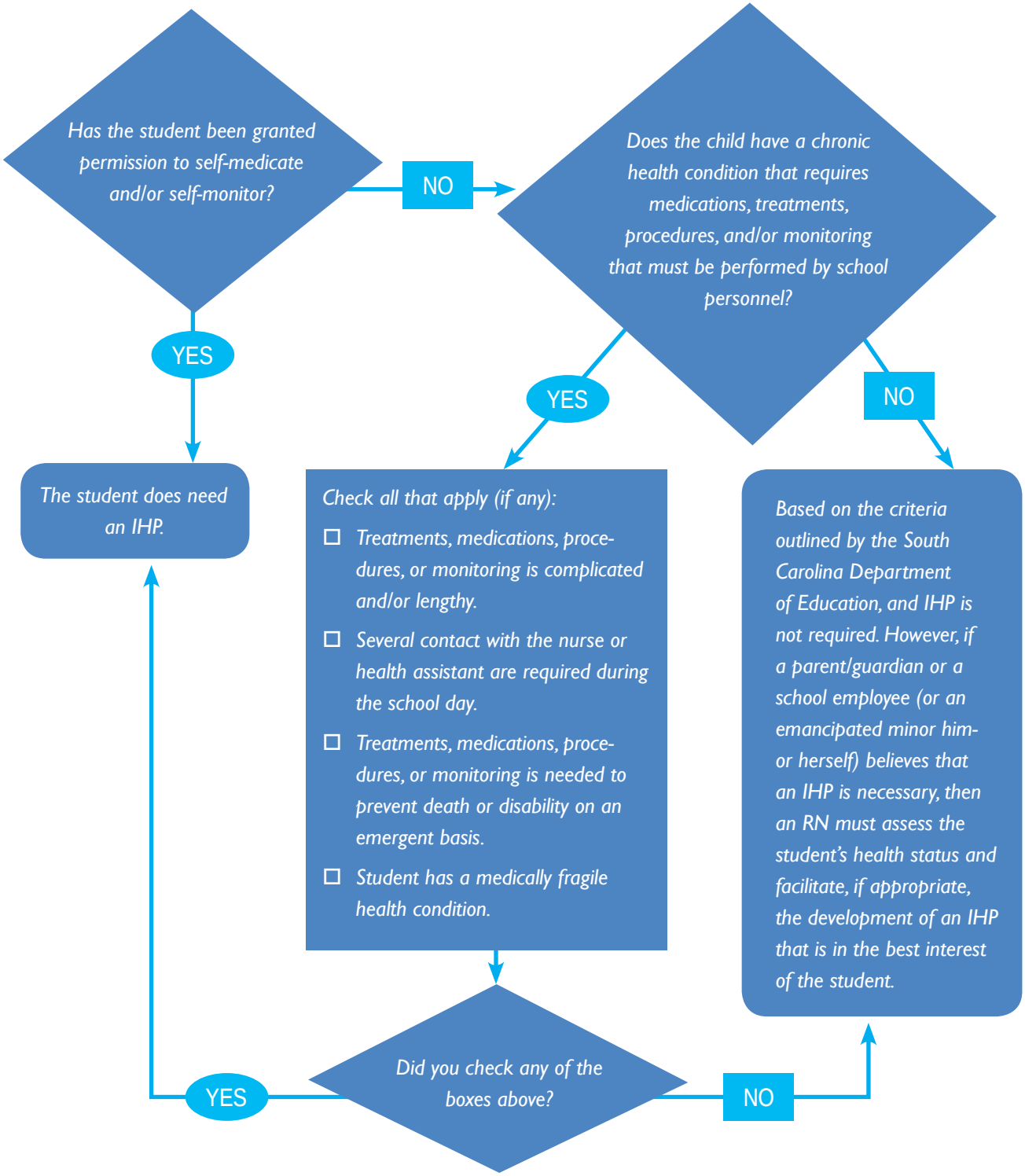
Behavioral concerns at school

- School programs should be highly structured with a close teacher:student ratio. In addition, some students may need one-on-one support. Curricula should be tailored to meet the needs of the child. Importantly, careful consideration of the biological, psychological (e.g. cognitive, communication, emotional) and behavioral profile of SMS should be considered when addressing the needs of these students. Students with SMS typically require consistent structure and a full schedule of high-interest activities due to their short attention spans and impulsive natures. Most children with SMS are highly adult oriented, with a sometimes insatiable need for individual attention. As a result, they are often in competition with their peers for staff attention. Behavioral outbursts are usually precipitated by a need for attention, an unexpected change in routine, or a lack of clear expectations or structure.

- An accommodation for a scheduled nap or "quiet time" should be included in the educational plan during school years. Ideally this should occur late morning or after lunch, but not late afternoon (>3pm).

- If behaviors disrupt the child's learning, the school educational team should arrange for a functional assessment of behavior (FBA) by a qualified professional (psychologist or board certified behavior analyst). Following the assessment, a positive behavioral intervention plan should be implemented, then reviewed and updated as needed. The emphasis of the plan

Flowchart: Does This Student Need an IHP



should be on antecedent strategies to support the student with SMS and opportunities to practice appropriate behaviors. Identification and avoidance of triggers are more effective than consequence-based behavior modification approaches, particularly as it applies to behaviors such as self-injury and aggression.

- Behavioral data should be collected and re-analyzed on a regular basis to assess the effectiveness of the plan. The plan should be revised after data analysis and team review.
- PRISMS' Resource Links: "On the Road to Success with SMS"; www.prisms.org/education/publications-and-resources/
- Helpful Resource Link: http://www.specialeducationguide.com/pre-k-12/behavior-and-classroom-management/functional-behavior-assessment-and-behavior-intervention-plans

Transition to Adulthood

For children in middle school (approximately age 13-14 years) transition planning should begin. Transition planning is a process mandated in the USA by the Individuals with Disabilities Education Act (IDEA) for all students who have an Individualized Education Program (IEP) in K-12 education. The purpose is to facilitate the student's move from school to post-school activities. The transition planning must start before the student turns 16, be individualized, be based on the student's strengths, preferences, and interests, and include opportunities to develop functional skills for work and community life.

- Helpful Resource Link: (https://ldaamerica.org/transition-planning-requirements-of-idea-2004)

Guardianship: Consideration and planning for guardianship should begin between the ages of 16-18 years so that it is in place before the child's 18th birthday. In the USA pursuing guardianship after 18 years involves additional legal steps. When persons with SMS become 18 years of age, they will likely need assistance managing their affairs, requiring assistance and guidance from family, friends or a legal guardian. A guardianship or conservatorship is a legal mechanism that grants an adult legal power to make decisions for another person, one who is considered incapable of making decisions himself or herself. Strict monitoring must be in place to protect the best interests and preferences of each person.

Adulthood

The Individual Service Plan (ISP) is the written details of the supports, activities, and resources required for the adult individual to achieve personal goals.

The Individual Service Plan is developed to articulate decisions and agreements made during a person-centered process of planning and information gathering. The general welfare and personal preferences of the individual are the key consideration in the development of all plans.

The ISP team, (the individual, medical specialists, specific provider staff, and guardians and caregivers), should include these aspects when accessing the needs of the individual: Personal choices and preferences, significant health care, mental health or behavioral needs and related maintenance needs and safety and financial skills.

Psychotropic Medications

There is limited research on the efficacy of psychotropic medications in the treatment of co-morbidities (cognitive impairment, learning disabilities, behavior disorders, obsessive compulsive features, anxiety and mood symptoms) associated with SMS.

There are no published clinical trials on the use and effectiveness of psychotropic medications such as psycho-stimulants, antipsychotics, anti-epileptics, antidepressants, sedative-hypnotics or canniboids, in children or adults with SMS. No single regimen shows consistent efficacy (Laje et al., 2010a). Based on the single extensive retrospective review of psychotropic medication use in a cohort of 62 patients with SMS (58% female), use of polypharmacy and/or serial trials demonstrated minimal effectiveness (Laje et al., 2010; www.prisms.org/about-sms/living-with-sms/medication/.

Lacking evidence for SMS-specific medications, clinicians must rely on best practices of managing underlying reasons emotional and/or behavior disturbances (health, environment, life stressors) and engaging in medication trials specific to the presenting problems, e.g. melatonin and sleep routines for sleep disturbance.

Psychotropic medications should be initiated by an experienced physician (preferably in the context of a multidisciplinary team) one at a time aiming for least effective doses and amounts of medication.

Regular medication reviews are required to monitor efficacy, side effects and to avoid long term use and polypharmacy.

Sleep

Sleep management in SMS remains a challenge for physicians and parents. No well-controlled treatment trials have been reported.

Sleep environment

- The first recommendation is to institute a good sleep routine. This includes a consistent bedtime and bedtime routine, quiet/non-stimulating activities, use of white noise or a rhythmic sound, and a comfortably cool/dark room.
- Parents often implement similar solutions to “SMS-proof” the child’s bedroom to minimize self-injury, maximize sleep cycle, and provide some degree of assurance that their child will not wake and wander about and/or injure themselves.
- Enclosed bed system for containment during sleep. Different brands of enclosed bed systems are available.

Physiology/obstructive sleep apnea (OSA) concerns

- Evidence/concern about possible OSA, snoring and/or other signs of sleep abnormalities warrant sleep-deprived EEG or polysomnography. Documented sleep apnea should be managed in accordance with standard practice; this may include tonsillectomy and adenoidectomy if airway obstruction is present.

Medication to manage sleep

- Sleep disturbance, often recognized in early childhood, remains a chronic issue in SMS that is associated with a reversal of melatonin secretion (daytime high), which is a hallmark of the syndrome.
- Early anecdotal reports of therapeutic benefit from melatonin taken at bedtime remain encouraging, providing variable improvement of sleep without reports of major adverse reactions. Dosages should be kept low, so it is out of the system by the next day. However, melatonin dispensed over the counter is not regulated by the FDA; thus, dosages may not be exact. A monitored trial of four to six weeks on melatonin may be worth considering individuals with sleep disturbance.
- Open label trials using b1-adrenergic antagonist (beta blocker: acebutolol 10 mg/kg) has shown efficacy for use in SMS (deLeersnyder et al., 2001). This approach targets the inverted circadian melatonin rhythm. The combination use of a morning beta-blocker coupled with administration of an evening dose of melatonin helped to restore circadian plasma melatonin rhythmicity, decrease daytime sleepiness, improve daytime behavior, and enhance sleep in children with SMS (DeLeersnyder et al., 2006). Contraindications to the use of ß1-adrenergic antagonists include asthma, pulmonary problems, some cardiovascular disease, and diabetes mellitus.
- Prior to beginning any trial, the child's medical status and baseline sleep pattern must be considered.

Impact on Caregivers/Family

The combination of intellectual disability, severe behavioral abnormalities, and sleep disturbance takes a significant toll on parents and siblings.

Parents report high rates of depression and anxiety, and family stress is significantly higher in families of people with SMS than in those of children with nonspecific developmental disabilities.

Family support services, respite care, and resources should be included as essential components of a holistic management plan for people with SMS.

SURVEILLANCE

Recommended annually

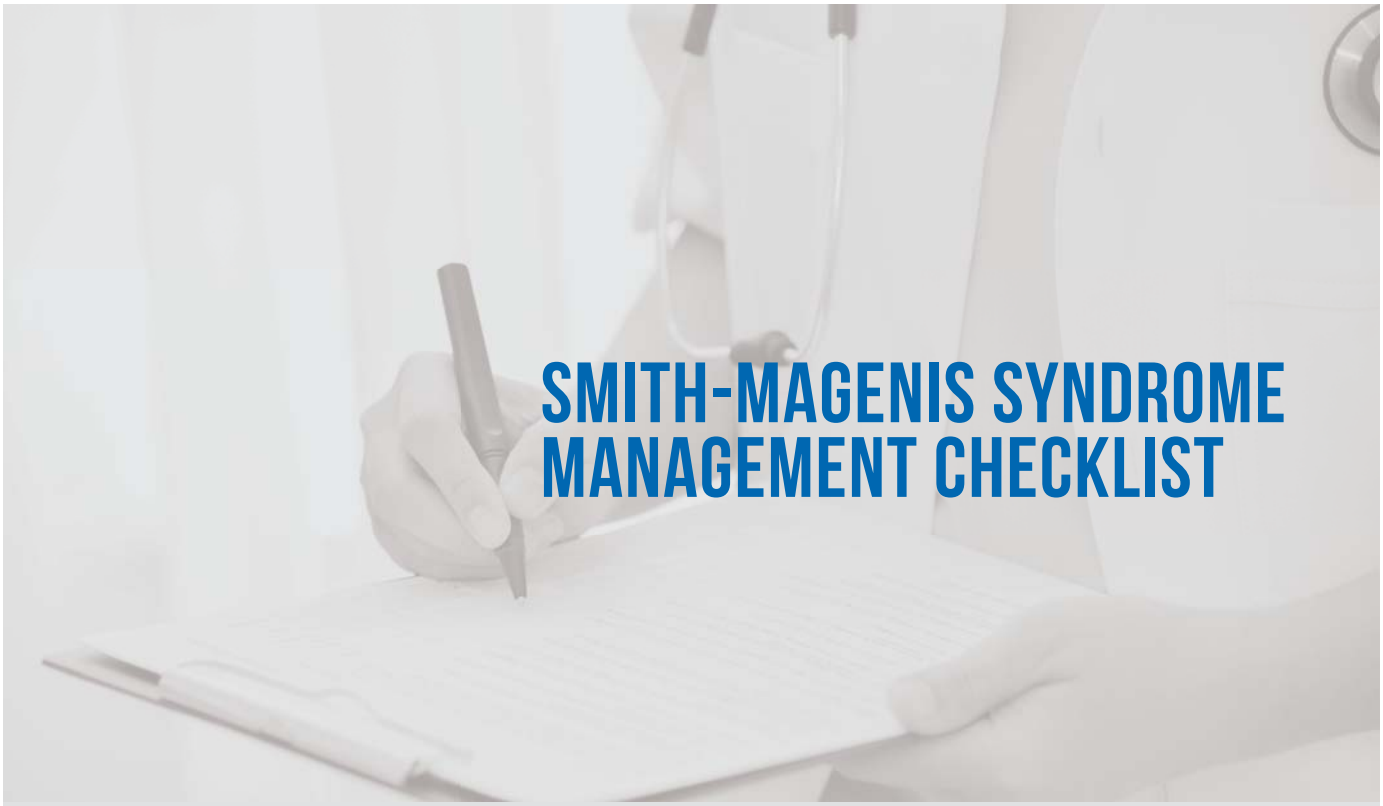
Medical

- Growth parameters (height, weight, truncal obesity)
- Healthy lifestyle habits (eating whole foods, avoiding simple carbohydrates and sugary drinks such as soda and juices, physical activity, exercises to improve muscle tone), restrict nighttime eating (“food foraging”) and attempt good sleep hygiene.
- Ophthalmologic evaluation for vision and eye anomalies (strabismus, microcornea, iris, refractory errors, detached retina).
- Routine and careful assessment and management of middle ear dysfunction (otitis media) and other sinus abnormalities is recommended; for most persons with SMS, surveillance by an otologist will be necessary.
- Audiologic surveillance to monitor for conductive or sensorineural hearing loss should be a standard part of routine care to facilitate early identification and intervention, when necessary. Hyperacusis in 74% is important to recognize.
- Routine blood chemistries (liver function, blood count, etc.), thyroid function, including free T4 and TSH; fasting lipid profile (evaluation for hypercholesterolemia).
- Quantitative serum immunoglobulins (IgG, IgA, IgM) including vaccine titers (pneumococcus especially) at initial diagnosis, with additional studies as clinically indicated.
- Routine urinalysis to evaluate for unrecognized urinary tract infections.

- Musculoskeletal: Clinical monitoring for scoliosis with radiographs in cases where spinal curvature appears to progress. Attention to balance and gait abnormalities, reflexes, tight heel cords, and/or joint hypermobility (pes planus vs pes cavus) may warrant orthopedic evaluation and/or fitting for orthotics.
- Peripheral neuropathy: 75% non-progressive but follow-up on disturbed gait.
- Constipation is common (>75%); monitor regularly for constipation and manage proactively.
- Medication review: medications affecting metabolism, sedation, polypharmacy (includes alternative/OTC, supplements and prescribed medications), and potential drug interactions.
- Sleep history review: evidence of snoring, obstructive sleep apnea, and/or signs of sleep abnormalities should prompt need for full sleep study (polysomnography). Age-related developmental changes in sleep patterns (e.g., adolescent “settling” issues) and daytime nap habits warrant discussion to optimize management of chronic sleep disorder from childhood to adulthood.
- Screen for seizures and staring spells, if present consider EEG
- Adults age 21 and older: Deletion of 1 copy (haploinsufficiency) of the folliculin (FLCN) gene, which maps within the common SMS deletion interval, poses a risk for Birt-Hogg-Dubé (BHD) syndrome, with a theoretical concern about increased kidney cancer risk.

Multidisciplinary Allied Health/Education

- Multidisciplinary team evaluations that assess motor skills, sensory processing, and speech-language abilities are critical to monitor progress, update goals, and develop appropriate an individualized educational program (IEP) (ages 3-22 years in the USA). Periodic neurodevelopmental assessments and/or developmental/behavioral pediatric consultation can be an important adjunct to the team evaluation.
- Annual assessment of patient emotional, social and behavioral functioning, and family well-being.
- Update Functional Behavioral Assessment (FBA) and Individual Education Plan (IEP) as needed for behavior challenges.
- Adulthood: An Individual Service Plan (ISP; USA) should be established to help facilitate the transition to adulthood. In the USA Planning should incorporate supports, activities, and resources required for the adult individual to achieve personal goals. Plans should consider all of the following: general welfare, preferences of the individual with SMS, medical, emotional, social, and behavioral needs, maintenance needs including safety and financial skills. Planning should be a collaborative effort by the individual, parents/guardians/caregivers, medical specialists, and educational and therapeutic specialists.



SMITH-MAGENIS SYNDROME MANAGEMENT CHECKLIST

	CHECKLIST This checklist is intended for use by physicians caring for a child with Smith-Magenis syndrome
1. GROWTH	
• Birth parameters usually in normal range. Failure to thrive (FTT)and short stature are often observed at early ages (17p11.2 deletion cases especially). • Obesity with increased BMI appreciated with age, especially for RAI1 mutation cases. • Hyperphagia, food foraging at night (especially. at older ages), psychotropic medication side effects (increase appetite; weight gain), and/or general sedentary lifestyle contribute to risk of obesity.	☐ Obesity: A “hands on” approach to stay active, have fun, and stay fit ideally should begin at a young age. Weight management requires dietary changes and food portioning in combination with increased movement and physical activity, limiting overall time spent in sedentary activity, and avoidance of nighttime eating. Encourage movement and exercises that are fun.

Source: PRISMS Management Guidelines Working Group (Ann CM Smith, Kerry Boyd, Jane Charles, Christine Brennan) with review and final approval by PRISMS Professional Advisory Board on January 24, 2018. Format adapted from the Health Watch Table from Surrey Place [www.surreyplace.on.ca/Clinical-Programs/Medical Services/Pages/PrimaryCare.aspx].

	CHECKLIST This checklist is intended for use by physicians caring for a child with Smith-Magenis syndrome
2. HEENT (Head, Eyes, Ears, Nose, Throat)	
• Vision: ~ 85% have eye abnormalities, including strabismus, myopia, iris anomalies, and microcornea. • Retinal detachment, which may be related to high myopia and self-injurious/aggressive behaviors, occurs in ~20% (age 10 years - adult). • Hearing: Chronic ear infections & middle ear dysfunction is common (>50%), with hearing loss documented in >75%. Conductive loss is more common at younger ages and mixed and/or sensorineural loss at older ages. Hearing loss may fluctuate and worsen with age. Hyperacusis is recognized in ~75%. • Throat: Almost all have delayed speech, ~ 65% have palatal abnormalities such as velopharyngeal insufficiency (VPI) and cleft palate. A deep, hoarse voice is common. • Prone to recurrent sinus infections and/or upper respiratory infections (including pneumonia), which occur in 50-75%. • Speech/language – communication delays (~90%): diminished vocalization/sound production and feeding difficulties' in infancy; significant oromotor dysfunction; expressive language skills more delayed than receptive language.	☐ Refer to an ophthalmologist following initial diagnosis and annually thereafter ☐ Refer to an ENT surgeon regarding palatal abnormalities following initial diagnosis and annually thereafter. ☐ Routine and careful assessment of middle ear function; annual audiologic surveillance across the lifespan to facilitate early identification and intervention. ☐ Recognition of hyperacusis to permit implementation of helpful management strategies: explanations and warnings before anticipated sound exposure (e.g., fireworks); use of headphones or earplugs to dampen the sound; and/or complete avoidance of the upsetting sounds. ☐ Immunologic evaluation with infectious prophylaxis considered in accordance with standard practice. Quantitative serum immunoglobulins (IgG, IgA, IgM) and vaccine titers (pneumococcus especially) at initial diagnosis, with additional studies as clinically indicated. ☐ Refer to a speech and language pathologist in early childhood to address feeding difficulties, optimize functional communication and oral motor abilities; encourage use of sign language and total communication approach to reduce maladaptive behaviors by improving communication. ☐ Consider referring to an occupational therapist (OT) or physical therapist (PT) regarding oral sensorimotor development.
3. DENTAL	
• Children and Adults: ~ 75% have dental • anomalies including tooth agenesis (premolars), taurodontism and/or root dilacerations. • Poor dental hygiene may lead to cavities.	☐ Arrange early and regular dental assessments ☐ Review brushing and flossing techniques with each dental cleaning. Strategies to assist with oral hygiene and gingival care usually require parental supervision (e.g., rechargeable toothbrush with 2-minute timer)

	CHECKLIST This checklist is intended for use by physicians caring for a child with Smith-Magenis syndrome
4. CARDIOVASCULAR	
• ~ 50% have congenital cardiovascular abnormalities (17p11.2 deletion cases); structural defects of heart have not been reported in RAI1 mutation cases. • Hypercholesterolemia in childhood is common (57%). • While the risk for premature atherosclerosis in adulthood is unknown, screening for premature atherosclerotic disease may be warranted given rare reports of cerebrovascular accidents.	☐ Obtain an echocardiogram at time of initial diagnosis. ☐ Refer to a cardiologist at initial diagnosis with follow up arrangements with congenital heart disease clinics, depending on the abnormalities detected. ☐ In adulthood, follow-up as clinically indicated. ☐ Monitoring of hypercholesterolemia by annual lipid profiles; treatment with diet or medication at older ages in accordance with standard practice.
5. GASTROINTESTINAL	
• Feeding problems and gastro-esophogeal reflux disease (GERD) are common. • Over 75% have history of constipation, which can greatly influence behavior, comfort level, mood, activity level & appetite.	☐ Undertake a clinical assessment in infancy with attention to feeding problems and evidence of GERD ☐ Monitor regularly for constipation and manage proactively.
6. GENITOURINARY	
• Congenital renal or urinary tract abnormalities occur in ~35% of 17p11.2 deletion cases but are not reported in RAI1 mutation cases. • Nocturnal enuresis is common (80%) in children and may remain an issue into school age.	☐ Obtain a renal ultrasound at initial diagnosis ☐ Screen for urinary tract infections with an annual urinalysis or as indicated.

	CHECKLIST This checklist is intended for use by physicians caring for a child with Smith-Magenis syndrome
7. MUSCULOSKELETAL	
• Delayed gross and fine motor skills • ~ 75% of children develop scoliosis, which may become more severe with age. • Markedly flat or highly arched feet (pes planus or pes cavus) and unusual gait (foot flap), tight heel cords (equinus; decreased dorsiflexion), and/or persistent toe-walking (60%) are generally appreciated in childhood. Low tone (truncal hypotonia) persists into adulthood.	☐ Obtain spine X-rays at diagnosis to assess for vertebral anomalies then annually to assess for scoliosis. ☐ Assessment/fitting for orthotics may be helpful. ☐ Exercises/activities that focus on improving abdominal and truncal tone are recommended.
8. NEUROLOGY	
• Children: ~ motor delay with hypotonia (particularly in infancy); truncal hypotonia persists into adulthood (lordotic postural issues). • ~ 75% have peripheral neuropathy, often associated with decreased pain and temperature sensation. • Hereditary neuropathy with liability to pressure related palsies may occur in those with relatively large chromosomal deletions including the PMP22 gene. • ~ 10% - 30% have evident and subclinical epilepsy. Onset of seizures associated with menses (catamenial) at puberty have been seen in some females. • Mild intention tremor of hands may be noted in early childhood.	☐ Undertake a neurological assessment at diagnosis and annually thereafter as clinically indicated ☐ Provide periodic neurodevelopmental assessments during infancy and childhood. Assessments should be completed approximately every three years unless an acute change in clinical presentation or imaging results necessitates more frequent testing. ☐ Consider subclinical seizures if behavior change occurs ☐ To evaluate type and etiology of seizures, consider electroencephalography (EEG), and Computed Axial Tomography (CAT) scan and Magnetic Resonance Imaging (MRI) scan of head as indicated during infancy and childhood. Consider medication for seizures, taking into account side effects (wakefulness, weight gain).

	CHECKLIST This checklist is intended for use by physicians caring for a child with Smith-Magenis syndrome
9. ENDOCRINE	
• ~ 25% are mildly hypothyroid. • Hypercholesterolemia is common (>50)%) • Hypoadrenalism (adrenal insufficiency), though rare, can occur, particularly in children.	☐ Undertake annual thyroid function and fasting lipid testing ☐ Start screening for hypercholesterolemia in childhood and consider dietary modification for hypercholesterolemia and the possible role of medication ☐ Assess for hypoadrenalism in the event of any serious illness
10. INFECTIOUS DISEASE / IMMUNIZATION	
• Lowered serum immunoglobulins profiles, observed >50%, may contribute to chronic otitis media, sinusitis and/or upper respiratory infections.	☐ Arrange qualitative immunoglobulin testing at diagnosis ☐ Immunization in accordance with AAP guidelines ☐ Undertake periodic review if recurrent infections ☐ Evaluation by immunologist with prophylactic strategies to prevent infections may benefit select patients

	CHECKLIST This checklist is intended for use by physicians caring for a child with Smith-Magenis syndrome
11. SLEEP	
• Virtually 100% have sleep disturbances. These are usually associated with an inverted circadian rhythm of melatonin release (daytime high, nighttime low). Inverted melatonin rhythm occurs in >90%. • Frequent nighttime awakenings, shortened sleep periods, absence of REM sleep, and daytime napping are common. • Wandering at night and/or food foraging is common and may present safety issues. • Chronic sleep debt impacts daytime functioning. Daytime sleepiness with sudden short naps are common.	☐ Undertake a sleep study with attention to sleep disturbance, short sleep cycle, early rising, frequent night awakenings, and daytime napping ☐ If there is evidence of snoring, symptoms of obstructive sleep apneaand/or other signs of sleep abnormalities, arrange a sleep study and multiple sleep latency testing. ☐ Consider evening melatonin (< 3 mg) and morning acebutolol (presumed to counter daytime melatonin release) ☐ Melatonin and acebutolol (beta-blocker) have been used with some success. Over-the-counter melatonin dosages may be inexact and acebutolol use has some contraindications ☐ Consider strategies to address nighttime safety issues (e.g., enclosed bed system) ☐ An accommodation for a scheduled nap or “quiet time” should be included in the educational plan during school years. Ideally this should occur late morning or after lunch, but not late afternoon (>3pm).

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12. COMMUNICATION, MOTOR, AND SENSORY PROCESSING	
• Evaluations and services will be needed early (as soon as a diagnosis is confirmed) and will very likely be required through the school years.	☐ Arrange assessments by a speech-language pathologist (SLP), Physical Therapist (PT), and Occupational Therapist (OT) in infancy and periodically thereafter as appropriate. ☐ In the USA, SLP, PT, and OT services may be available free of charge in the US through early intervention programs for children under the age of 3. ☐ Use of sign language and total communication programs, including sign, computer assisted devices and tablets, augmentative communication, voice output systems, and/or picture exchange (PECS) may serve as additional forms of communication to traditional speech-language therapy that focuses solely on spoken communication. This will promote improved communication skills, which may have a positive impact on behavior. Note that using alternative forms of communication will not hinder the development of speech or spoken communication, but will promote development of language abilities. ☐ Need for PT, OT or SLP to be determined annually at school meetings.

	CHECKLIST This checklist is intended for use by physicians caring for a child with Smith-Magenis syndrome
13. BEHAVIORAL/MENTAL HEALTH	
• Maladaptive behaviors prominent in the neurobehavioral phenotype of SMS include a unique constellation of repetitive (stereotypic) and self-injurious behaviors (SIB) (e.g., teeth grinding, self-hugging, head banging, self-hitting and/or biting, and inserting objects into body orifices). The pattern/range of maladaptive behaviors may change with age. For example, onset of ~~nail yanking~~ onychotillomania (i.e., pulling out finger- and toe-nails) often occurs in late childhood or adulthood rather than in infancy or preschool years. • Impaired behavioral regulation, cognitive inflexibility (i.e., difficulties tolerating change/transitions), and frustration intolerance, combined with intellectual and communication difficulties, likely contribute to challenging behaviors (i.e., impulsivity, aggression, tantrums, disobedience, hyperactivity, avoidance, elopement). • Clinical behavioral diagnoses include autism spectrum disorder (ASD), intellectual disability (ID), attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and obsessive-compulsive disorder (OCD). • Socialization skills, while deficient, emerge as relative strengths in adaptive functioning compared to delays in communication and daily living skills. • Relative strengths exist in visual processing (i.e., visual learners alert to environment and attentive to meaningful visual details); long-term memory for faces, places, and people; engaging personality; and good sense of humor. • Caregivers of individuals with SMS demonstrate high rate of anxiety and depression symptoms and report difficulties with caregiver well-being and self-care.	☐ In children, arrange early intervention with specific preventative behavioral strategies and special education techniques that emphasize individualized instruction. ☐ Behavior support plans can be implemented to help mitigate behavioral concerns at home and school. Psychologists, , teachers, and occupational therapists typically develop and implement such plans ☐ Use of computer-assisted technology may be helpful to promote adaptive communication skills, which in turn can lessen maladaptive behaviors. ☐ Sensory dysregulation is a factor contributing maladaptive behaviors. Providing compensatory positive sensory experiences may help reduce behavioral concerns. ☐ Psychotropic medications: There is limited research on the efficacy of psychotropic medications in the treatment of co-morbidities (cognitive impairment, learning disabilities, behavioral disorders, obsessive compulsive features, anxiety and mood symptoms) associated with SMS. Clinicians must rely on best practices of managing underlying reasons emotional and/or behavior disturbances (health, environment, life stressors) and engaging in medication trials specific to the presenting behavioral problems. Psychotropic medications should be initiated by an experienced physician (preferably in the context of a multidisciplinary team), one at a time, aiming for lowest effective doses. Regular medication reviews are required to monitor efficacy, side effects and to avoid long term use and polypharmacy. ☐ An annual interdisciplinary team assessment of socio-emotional needs and behavioral difficulties is warranted. These should include the use of well-validated parent, teacher (if available), and self-report (if cognitively able to complete) measures. ☐ Plan respite care, family psychological, and social supports. ☐ Facilitate contact with advocacy organizations, such as Parents and Researchers interested in Smith-Magenis Syndrome (PRISMS- www.prisms.org), to provide support and education.

	CHECKLIST This checklist is intended for use by physicians caring for a child with Smith-Magenis syndrome
14. SCHOOL/ACCOMMODATION & SERVICES[#]	
• Services – ongoing need (PT/OT/speech) beginning in early childhood through school years. • Transition planning should begin when children are in middle school. Transition planning will facilitate a student's move from school to post-school activities. [#]The terminology used here is USA focused and may be adapted, as appropriate, for use in other countries.	☐ Early Intervention (EI) for birth-3 years. EI is a system of services for infant/toddlers with developmental delays or disabilities focus on intervention to facilitate development of skills that typically develop during the first three years of life (can include the following skills: speech/communication, motor, cognitive, social/emotional, self-help). For infants and child prior to the third birthday, there will also be an individualized family service plan (IFSP). ☐ For school age, child should have an Individualized Education Plan (IEP) for learning and behavioral accommodations. "Otherwise health impaired" is often the category used to designate services. ☐ If the child is on medication, an Individualized Health Plan (IHP) should be in place by the School RN. ☐ If behaviors are disrupting the child's learning, the school is required to do a Functional Behavioral Assessment (FBA) and implement a Positive Behavior Intervention Plan (BIP) ☐ LINK: management/functional-behavior-assessment-and-behavior-intervention-plans. ☐ The IEP should be updated annually or when learning or behavior issues arise. Consider eligibility classification to be "Otherwise Health Impaired" to accommodate medical concerns and behavioral challenges. ☐ Needs for PT, OT or ST to be determined annually at IEP meeting. ☐ Transition planning, which begins in middle school (~ age 13-14y), is a process mandated in the US by the Individuals with Disabilities Education Act (IDEA) for all students who have an Individualized Education Program (IEP) in K-12 education. The purpose is to facilitate the student's move from school to post-school activities. The transition planning must start before the student turns 16, be individualized, be based on the student's strengths, preferences, and interests; and include opportunities to develop functional skills for work and community life.

	CHECKLIST This checklist is intended for use by physicians caring for a child with Smith-Magenis syndrome
15. OTHER ISSUES	
• Transition to Adulthood • Transition Medicine (shift from pediatric to adult healthcare)	☐ Guardianship/medical decision maker ☐ Adulthood: The Individual Service Plan (ISP) is the written details of the supports, activities, and resources required for the adult individual to achieve personal goals. The general welfare and personal preferences of the individual are the key consideration in the development of all plans to articulate decisions and agreements made during a person-centered process of planning and information gathering. The ISP team, (the individual, medical specialists, specific provider staff, and guardians and caregivers), is focused on assessment of the individual's needs, including personal choices and preferences, significant health care, mental health or behavioral needs and related maintenance needs and safety and financial skills. ☐ Limited data and recommendations are currently available for adults (GUIDE) but more information is emerging as identified – LINK to PRISMS GUIDE ☐ Transition Medicine provides appropriate medical care and social support services to the growing population of adolescents/young adults with SMS as they move from pediatric to adult healthcare.

The SMS Checklist was developed by PRISMS' Management Guidelines Working Group (Ann CM Smith, Kerry Boyd, Jane Charles, Christine Brennan) with review and final approval by PRISMS Professional Advisory Board 24 January 2018. The checklist format was adapted from the Health Watch Table from Surrey Place [www.surreyplace.on.ca/Clinical-Programs/Medical Services/Pages/PrimaryCare.aspx.)

Resources: www.prisms.org - The official website for Parents and Researchers Interested in Smith-Magenis Syndrome

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NOTES

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