prisms 2022 Envisioning the Possibilities

Medical Management of SMS Across the Lifespan

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Friday August 5th, 2022

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SMS Management of SMS Across the Lifespan
Workshop Goals

I. **Medical management recommendations for SMS**
- At Diagnosis
- Across the lifespan – surveillance and transition to adulthood
- Caveats from SMS Natural History study that warrant attention & management intervention

II. **Problem Identification in SMS - Personalized problem management**
- Health promotions strategies & transition to adulthood
- Hands-on approach/practical tips that work for the child with SMS and entire family

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Smith-Magenis Syndrome (SMS)
Overview – OMIM 182290
Neurodevelopmental Disorder

Distinct pattern of physical, developmental & behavioral features

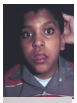
Identified worldwide in all ethnic groups

Estimated incidence 1/15,000 births

Majority occur sporadically (*de novo*)

Delayed diagnosis common

- Interstitial deletion 17p11.2 (~90%)
- Mutations in RAI1 gene (~10%)
- New molecular tools (e.g., CMA) for diagnosis



b. 1919 (65y @ DX)

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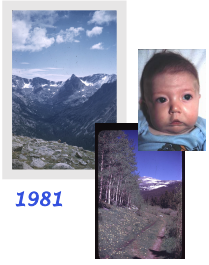
Decades of Discovery

1980's ~ **Recognition of new syndrome**

1981: first IBM PC
1982: first portable computer

1975 MIM



1981

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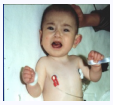
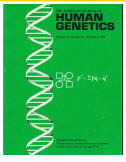
Initial Clinical Description of del 17p11.2

2 infants with
Failure to thrive
Cardiac defects
Facial clefts



1982 Abstract
Amer. Society of Human Genetics



1986 Delineation of SMS
Smith & Magenis

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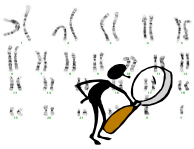
Genetic Counseling in 1981
Identification of del 17p11.2



DIAGNOSIS
What is it?

ETIOLOGY/CAUSE
What caused it? - *chromosome abnormality*
Is it inherited?

RECURRENCE RISK
Is there are risk for other children?

MANAGEMENT/TREATMENT & REFERRAL
What does the diagnosis mean for my child?
What treatments help improve function?
What about my child's development?

SUPPORT & ADVOCACY
Where can I get more information?
Is there a support group?

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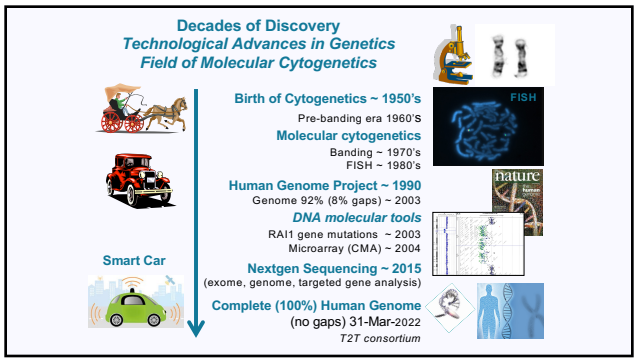
Decades of Discovery
Technological Advances in Genetics
Field of Molecular Cytogenetics
Smart Car
Birth of Cytogenetics ~ 1950's
Pre-banding era 1960'S
Molecular cytogenetics
Banding ~ 1970's
FISH ~ 1980's
FISH
Human Genome Project ~ 1990
Genome 92% (8% gaps) ~ 2003
DNA molecular tools
RAI1 gene mutations ~ 2003
Microarray (CMA) ~ 2004
Nextgen Sequencing ~ 2015
(exome, genome, targeted gene analysis)
Complete (100%) Human Genome
(no gaps) 31-Mar-2022
T2T consortium

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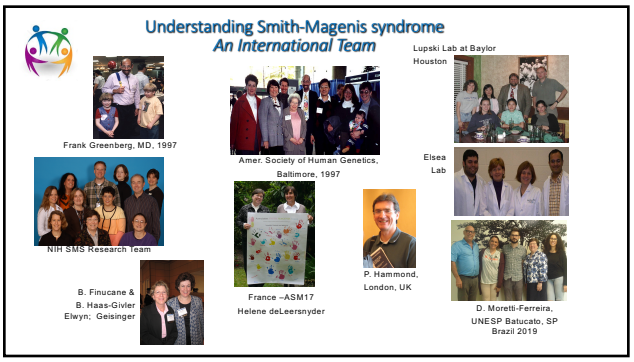
Understanding Smith-Magenis syndrome
An International Team
Frank Greenberg, MD, 1997
Amer. Society of Human Genetics, Baltimore, 1997
Lupski Lab at Baylor Houston
Elsea Lab
NIH SMS Research Team
B. Finucane & B. Haas-Givler Elwyn; Geisinger
France –ASM17 Helene deLeersnyder
P. Hammond, London, UK
D. Moretti-Ferreira, UNESP Batucato, SP Brazil 2019

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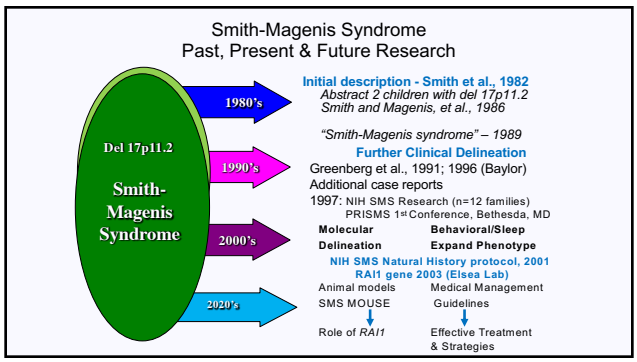
Smith-Magenis Syndrome
Past, Present & Future Research
Del 17p11.2
Smith-Magenis Syndrome
1980's
1990's
2000's
2020's
Initial description - Smith et al., 1982
Abstract 2 children with del 17p11.2
Smith and Magenis, et al., 1986
"Smith-Magenis syndrome" – 1989
Further Clinical Delineation
Greenberg et al., 1991; 1996 (Baylor)
Additional case reports
1997: NIH SMS Research (n=12 families)
PRISMS 1st Conference, Bethesda, MD
Molecular Delineation
Behavioral/Sleep Expand Phenotype
NIH SMS Natural History protocol, 2001
RAI1 gene 2003 (Elsea Lab)
Animal models
SMS MOUSE
Role of RAI1
Medical Management
Guidelines
Effective Treatment & Strategies

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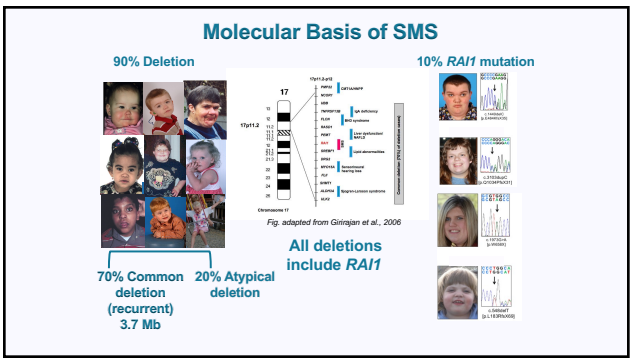
Molecular Basis of SMS
90% Deletion
10% RAI1 mutation
Fig. adapted from Girirajan et al., 2006
All deletions include RAI1
70% Common deletion (recurrent) 3.7 Mb
20% Atypical deletion

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Smith-Magenis Syndrome (del 17p11.2)
Recognized Neurodevelopmental Disorder (NDD)
Deletion or mutation of RAI1 (haploinsufficiency)
Facial & other characteristic physical features
Developmental delay
Cognitive impairment
Marked expressive speech delay
Sensory processing dysfunction
Disturbed sleep pattern (chronic)
Advanced sleep phase
Increased daytime napping
Inverted circadian melatonin rhythm
Phase advanced 24-Body temperature
Self-injurious, repetitive & other maladaptive behaviors
Psychiatric co-morbidities
(ADHD, ASD, OCD, PDD-NOS)
Excellent long-term memory

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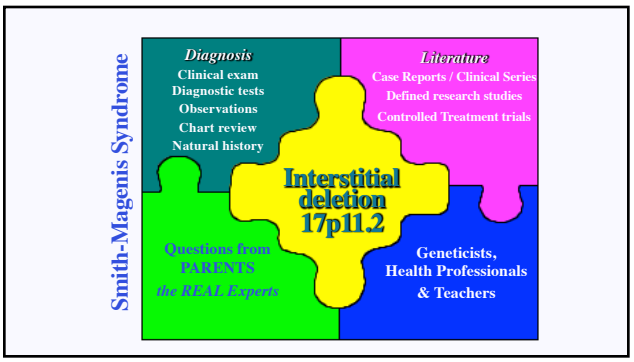
Smith-Magenis Syndrome
Diagnosis
Clinical exam
Diagnostic tests
Observations
Chart review
Natural history
Literature
Case Reports / Clinical Series
Defined research studies
Controlled Treatment trials
Interstitial deletion 17p11.2
Questions from PARENTS the REAL Experts
Geneticists, Health Professionals & Teachers

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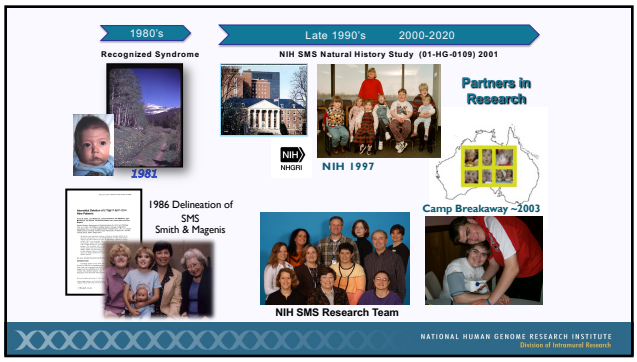

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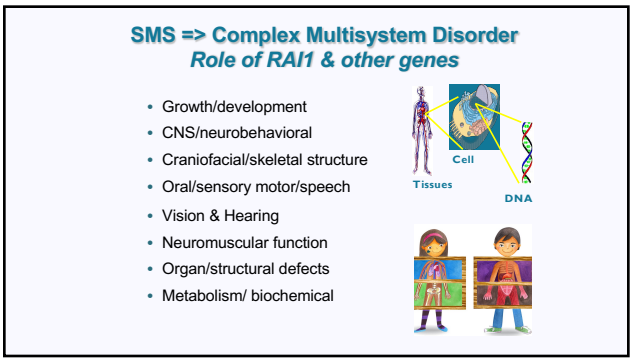

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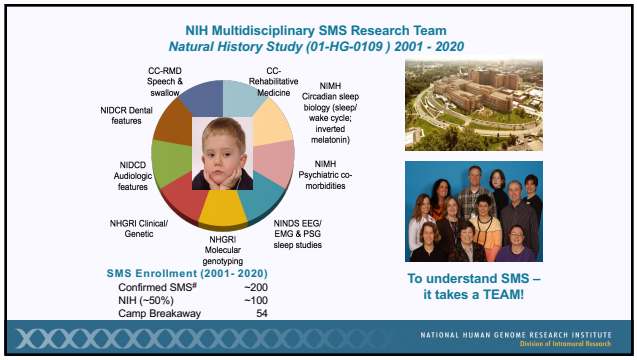

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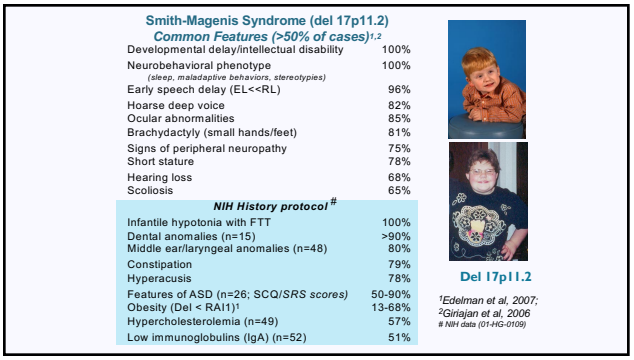

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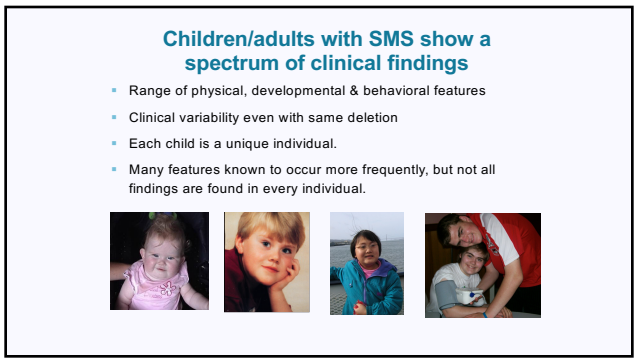

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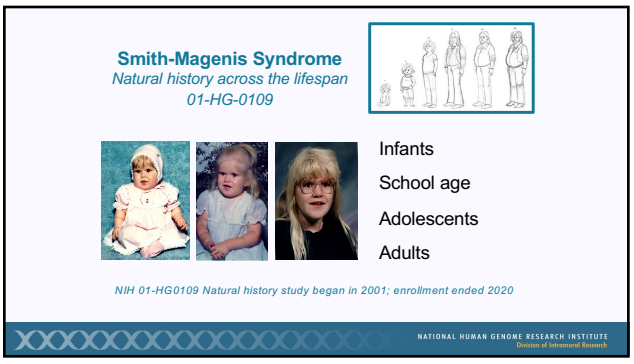

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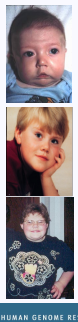
Smith-Magenis Syndrome
Variable Features



Cardiac defects[1]	25-50%
Renal abnormalities[1]	<25%
Low thyroxine levels[1]	25-50%
Low immunoglobulins[1,2]	25-50%
History seizures	11%-30%
Abn. EEG w/o seizures	21%
Forearm abnormalities	16%
Cleft lip/palate[1]	<25%

[1] GeneReviews (2022 March Revision): Available from: https://www.ncbi.nlm.nih.gov/books/NBK1310/
[2] NIH immunologic data ~ 50%

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Division of Intramural Research

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Deletion vs. *RAI1* mutation SMS

Feature	Del 17p11.2[1],	*RAI1* mutation (<30cases)[2,6]
Developmental delay/ intellectual delay	100%	100%
Infantile hypotonia[2,3]	>90%	44-61%
Speech/motor delay	>75%	70%
Sleep disturbance	75-100%	100%
Hoarse, deep voice	>80%	100%
Self-injurious behavior	75-92%	100%
Self hug	50-80%	100%
Hand/self biting	80%	60%
Craniofacial features	>75%	80%
Obesity [3]	13%	67%
Middle ear/laryngeal anomalies	>75%	54.5%
Short stature	50-75%	<10%
Hearing loss	50-75%	10%
Cardiac defects (1 *RAI1 case*[6])	<25%	0% (2022 <3%)
Renal anomalies	<25%	0%

[1]*GeneReviews, Smith et al., last revised Mar. 2022;* [2]*Girirajan, et al, 2005;* [3]*Edelman et al., 2007;* [4]*Vilboux et al., 2011;* [5]*Dubourg et al., 2014,* [6]*Onesimo et al., 2022*

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SMS ~ After Diagnosis
Support/Advocacy

PRISMS (www.prisms.org)
SMS Foundation-UK
SMS-Australia
Sirius (Germany)
ASM17 (France)
Icelandic SMS Society
SMS Brazil

Management issues
- Medical/primary care
  - Management Guidelines
- Behavior & sleep
- Therapies (PT, OT, speech)

Educational planning
- Speech delay
- Motor delays
- Vocational skills

Psychosocial issues
- Support
- Respite needs

Multidisciplinary team approach!
Primary care physician & other specialists,
Genetics, & Family

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SMS Medical Management Guidelines & Checklist

Written by PAB Management Guidelines Working Group ACM Smith, K Boyd, C Brennan and J Charles) with review and final approval by PRISMS Professional Advisory Board (PAB) 24 January 2018.

Available at: https://www.prisms.org/us/living---with---sms/medical---management---guidelines/

Treatment Recommendation series (PCRC - 2022)

PCRC
PRISMS Clinic and Research Consortium

Written by Gail Reiner, DNP, FNP-C, Myra Woolery, PhD, RN, APRN-CNS, CPON, & Ann C.M. Smith, MA, DSc (Hon.), CGC)

Available at: https://www.prisms.org/constipation-treatment-recommendations-for-sms/

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EDUCATION | AWARENESS | RESEARCH

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At DIAGNOSIS ~ Baseline
Medical Review of Body Systems
(head to toe body functions)

- Physical and neurologic examination
- Growth parameters: height, weight & head circumference
  - Monitor for obesity (often noted by 6-9y)
- Swallowing dysfunction (poor suck/swallow), oral-sensory-motor deficits
  - referral as warranted for full evaluation
- Vision – eye exam: strabismus, microcornea, iris anomalies; visual acuity; keratoconus (adults).
- Middle ear dysfunction / hearing issues
  - ENT (ear/nose & throat) evaluation - attention to ear physiology & palatal abnormalities (cleft, velopharyngeal insufficiency);
  - Hearing: routine audiologic surveillance throughout the lifespan
    middle ear dysfunction (flat tympanograms)
    monitor for conductive and sensorineural hearing loss

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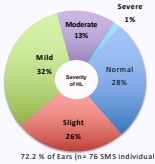
Smith-Magenis Syndrome
Hearing Loss (n=76 individuals)#

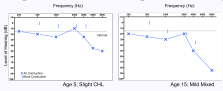
Hearing loss	~80%
Loss on at least one assessment	91%
Severity: "*slight* to *mild*"	~58%
Type of HL (age related)	
Conductive (<10 yr)	35%
Sensorineural (>10y)	48%
Hyperacusis	74%



72.2 % of Ears (n= 76 SMS individuals)

Longitudinal Hearing Sensitivity

Pattern of fluctuation & progression with age



Source: #NIH SMS Research Team, NIDCD/NHGRI, NIH, Brendal et al., 2016,

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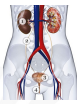
At Diagnosis ~ Baseline Imaging to *Assess for Structural Defects*

Cardiac anomalies (<45% in deletion cases)

Rare in *RAI1* cases: 1st report of cong. pulmonary valve stenosis (Onesimo et al., 2022)

- Evaluation by cardiologist
- Echocardiogram to check for structural changes in the heart
- Follow-up only as needed



Genitourinary (GU) anomalies (<25%)[1]

- Renal ultrasound to check for structural kidney anomaly
- Urinary tract anomalies (duplication of collecting system) are common
- Urologic workup if a history of frequent urinary tract infections exists
- Routine urinalysis to evaluate for occult urinary tract infection
- Other studies only as needed

[1] *RAI1* mutation cases no reported renal anomalies to date

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Review of Body Systems at Initial Diagnosis, cont.

head to toe body functions

- **Skeletal anomalies**
  - Spine X-rays (baseline): vertebral anomalies/SBO & scoliosis (~60%)
  - Mild/moderate scoliosis (esp. mid thoracic region) may be progressive;
  - Monitor and, if significant, may require corrective surgery.
  - MRI if concern for tethered cord or spinal stenosis (few adults)
- **Gastrointestinal issues**: GERD; constipation issues (bowel habits) with referral as history warrants.
- **Dermatologic (skin) assessment**: dry skin; hyperkeratosis (thicker skin); evidence of self-injury (skin picking; biting; nail damage)
- **EEG**: History of clinical seizures (~11-20%) and/or concern for sub-clinical events; staring spells; catamenial seizures in females (pubertal onset)
- **Neuroimaging (MRI/CT scan)** in accordance with neurologic findings (e.g., seizures and/or motor asymmetry)
- **Sleep history**: sleep/wake schedule and respiratory function.
  - Evidence of snoring or sleep disordered breathing => PSG/sleep study to evaluate for OSA

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Routine Laboratory Studies

(at diagnosis and annually)

- Complete blood count (CBC)
- Comprehensive metabolic panel (substances in blood, including liver enzyme function)
- Thyroid function studies, including free T4 and TSH
- Fasting lipid profile (evaluation for hypercholesterolemia)
- Quantitative immunoglobulins (IgG, IgA, IgM)
- Routine urinalysis to evaluate for occult urinary tract infections.
- Vitamin D level

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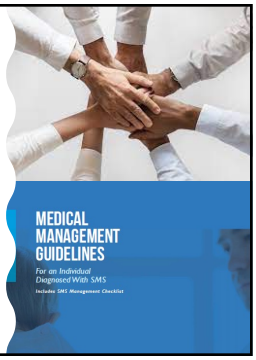
Multidisciplinary Team Approach

Allied Health/Education

- Multidisciplinary developmental or neuropsychological evaluation (depending on age),
- PT/OT (gross & fine motor development and functional impairments
- Comprehensive speech/language pathology evaluation
- Behavioral/emotional screening (standardized screen checklists for primary caregivers and teachers
- School age: Individualized Educational Plan (IEP) for learning/behavioral accommodations.
- Assessment of family support & psychosocial & emotional needs to assist in designing family interventions.



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Look to Future for SMS

Global networks of support

Syndrome delineation 4 decades ago

SMS disease-specific centers of excellence

- USA: PRISMS Clinics & Research Consortium ~ March 2021

  SMS Clinics (n=6) – multispecialty comprehensive, clinically appropriate care for the SMS community.
- UK: Cerebra Network for Neurodevelopmental Disorders (SMS focus)

Future – is now!!

- Natural history study => Available outcome measures needed to document efficacy in future treatment trials/studies.
- Vanda trial: HETLIOZ® (tasimelteon) a melatonin agonist – 1st FDA approved treatment for sleep in SMS Dec. 2020
- Advancing knowledge about treatment/management approaches
- Expanding horizons for persons with SMS

PCRC
PRISMS Clinic and Research Consortium

The Cerebra Centre for Neurodevelopmental Disorders

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PRISMS Clinics and Research Consortium (PCRC)

SMS Clinics across the USA (n=6)

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Envisioning the Possibilities

Evidence-Based "Best Practice" Interventions

Gail Reiner, D.N.P., FNP-C
UCSD/Rady Children's Hosp – SMS Clinic

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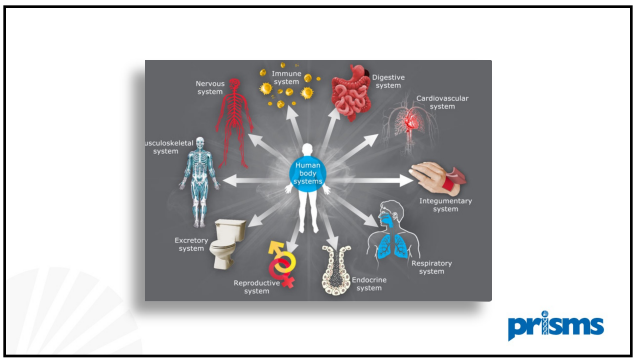

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Purpose of this time together is to provide an overview of SMS

Perspective we share is that SMS individuals are NOT just SMS!

Possibilities through research and expert care involve HOPE

Persistent truth:
ALL BEHAVIOR HAS MEANING

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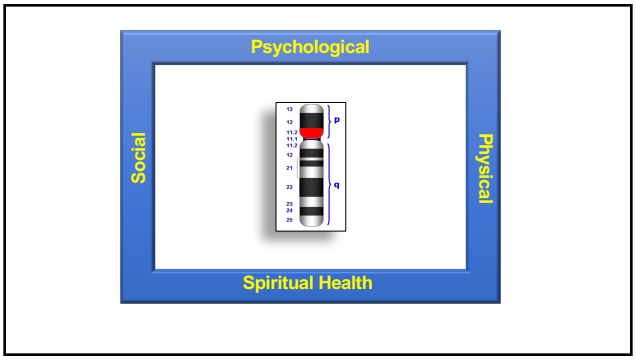

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Evidence-Based "Best Practice" Interventions

Personalized across Lifespan from Current Evidence (SMS and Relevant Research)

1. Natural History Study
2. Prisms.org
3. Review Articles
4. Retrospective Studies
5. Case Reports
6. Clinical Trials
7. Experts' Consensus
8. Patient and Family Reports (Ann Smith Curated)
9. Social Media

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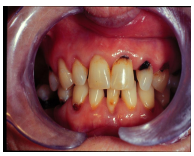
Accelerated caries formation → Alkaline toothpaste, cleanings every 4 months, Sealants, bleach trays every 2 weeks, water pic



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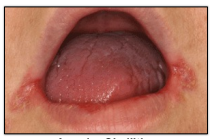
Sialorrhea, Cheilosis, Cheilitis → B vitamin levels, Vitamin B-complex, Ear, Nose, Throat Physician Consult



Angular Cheilitis

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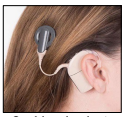
Hearing deficit → Hearing testing every 1-3 years, hearing aids, Total communication Cochlear implants



Cochlear Implant

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Dysacusis, Hyperacusis → Avoid triggers, noise-cancelling headphones, music With ear buds

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Strabismus, Retinal Hypoplasia, Kerataconus → Neuro-ophthalmology or genetic ophthalmology Consult, careful consideration for surgery

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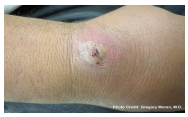
MRSA secondary to skin picking → Super-fatted soap, emollients
Bleach baths weekly
Bactroban Rx (topical antibiotic)
Habit reversal therapy



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Evidence-Based "Best Practice" Interventions

Personalized across Lifespan from Current Evidence (SMS and Relevant Research)

Hypotonia, Exercise intolerance, Fatigue	Correcting for anemia and thyroid dysfunction Ubiquinol, B-complex
Peripheral Neuropathy	Skin checks daily as performed for diabetics Early onset wound care as needed
Seizures	Avoid valproate, topiramate, leviteracetam Med as mood stabilizer and best anti-epileptic
Flat feet, eversion, tight heel cords	Orthotics, orthopedic evaluation, physiotherapy, botox, surgery, acceptance
Poor balance and weak leg strength	Physiotherapy optimizing balance and leg strength
Ataxia, imbalance	Evaluate for cerebellar hypoplasia, balance training

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Evidence-Based "Best Practice" Interventions

Personalized across Lifespan from Current Evidence (SMS and Relevant Research)

- Impulsivity with parent desire to avoid prescriptives ⇒ N-Acetyl cysteine 600mg up to 2400mg/day; Habit reversal, relaxation training
- Depression with parent desire to avoid prescriptives ⇒ St. John's wort, L-methylfolate
- Running away ⇒ Door alarms, GPS watch, "Take me Home Sheriff"
- Bullying, loneliness, desire for intimacy ⇒ Special Olympics, SMS business cards, Kids on block
- Grief and loss ⇒ Memory box, expressive arts, pet therapy

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Evidence-Based "Best Practice" Interventions

Personalized across Lifespan from Current Evidence (SMS and Relevant Research)

- Gastroparesis, slow-transit constipation ⇒ Avoid constipating foods, Bowel regimen
- Menorrhagia, inability to manage menstrual periods ⇒ Continuous hormone suppression; Surgery
- Hyperphagia ⇒ Green, Yellow, Red Foods, Locked cupboards; Low calorie snacks
- Fecal smearing ⇒ Assess for fecal impaction, constipation and Enlarged colon, bowel program, Sensory alternatives

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Evidence-Based "Best Practice" Interventions

Personalized across Lifespan from Current Evidence (SMS and Relevant Research)

- Dry skin ⇒ Superfatted soap without perfumes or dyes; emollients; linoleic acid; cotton, wool, silk fabrics
- Increased risk of diabetes ⇒ Blood sugar once or twice a year; Aerobic exercise to reduce insulin resistance

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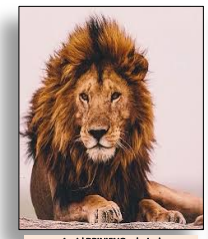

Avoid DRINKING calories!
Water is the beverage of LIONS!

Eat a RAINBOW every day!

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Stretching
Strengthening
Balance
Cardiorespiratory

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