Best practices in collaborative care and the potential impact of novel therapies

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Disclosures

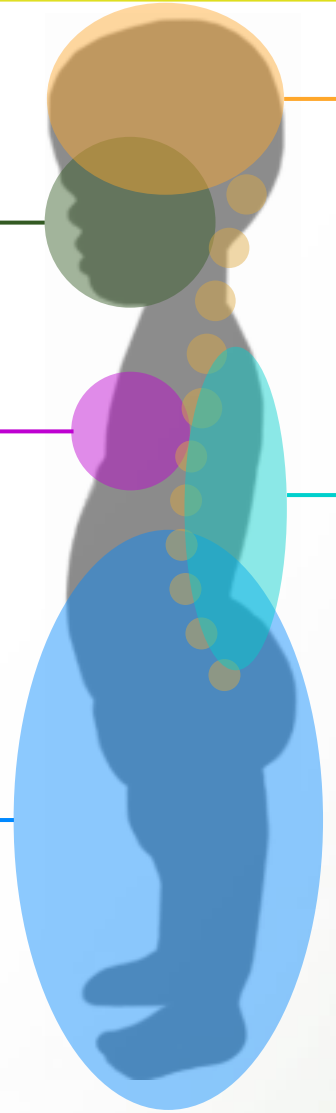
- **Principal Investigator:**
  - Alexion, Ascendis, Novo Nordisk, and Pfizer/OPKO
- **Adjudication Committee:**
  - Aeterna Zentaris
- **Speaker Bureau:**
  - Ascendis, BioMarin, and Novo Nordisk
- **Advisory Board:**
  - Ascendis, BioMarin, Novo Nordisk, and Pfizer

Objectives

- Assess the need for multidisciplinary care for people with achondroplasia
- Discuss the evolving role of the pediatric endocrinologist in the pharmacologic treatment of achondroplasia and available therapies
- Explore the need to regularly monitor the growth and development of children and adolescents with achondroplasia, utilizing disease-specific tools
- Discuss best practices for endocrinologists as part of a collaborative team

Assess the need for multidisciplinary care for people with achondroplasia

Children with achondroplasia may experience complications in multiple systems[1-3]



EAR, NOSE, AND THROAT
- Recurrent otitis media
- Hearing loss
- Dental malocclusion

CARDIOVASCULAR AND RESPIRATORY SYSTEMS
- Obstructive sleep apnea
- Hypertension

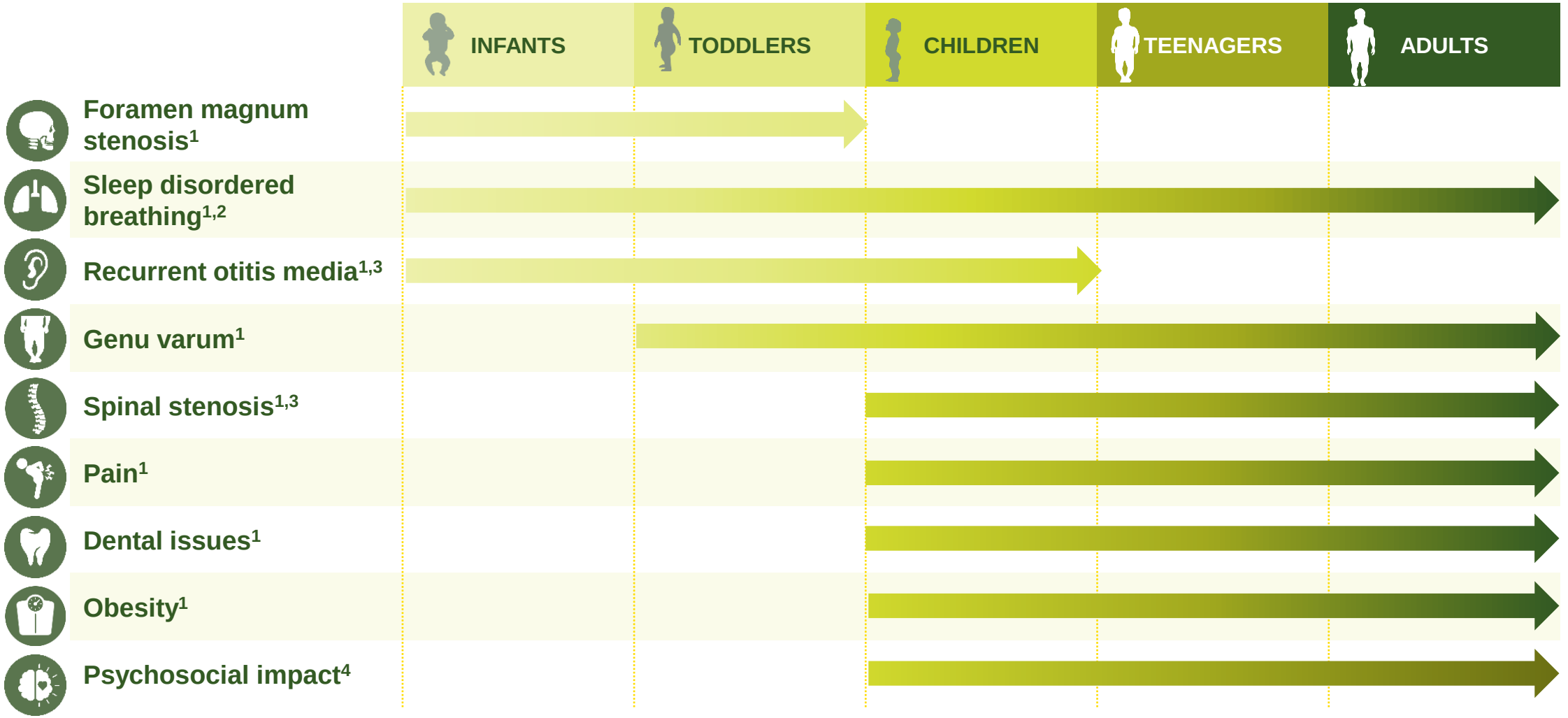
EXTREMITIES
- Genu varum
- Rhizomelic shortening of upper and lower extremities

NERVOUS SYSTEM
- Foramen magnum stenosis
- Central sleep apnea

BACK
- Spinal stenosis
- Thoracolumbar kyphosis
- Lumbar hyperlordosis
- Pain

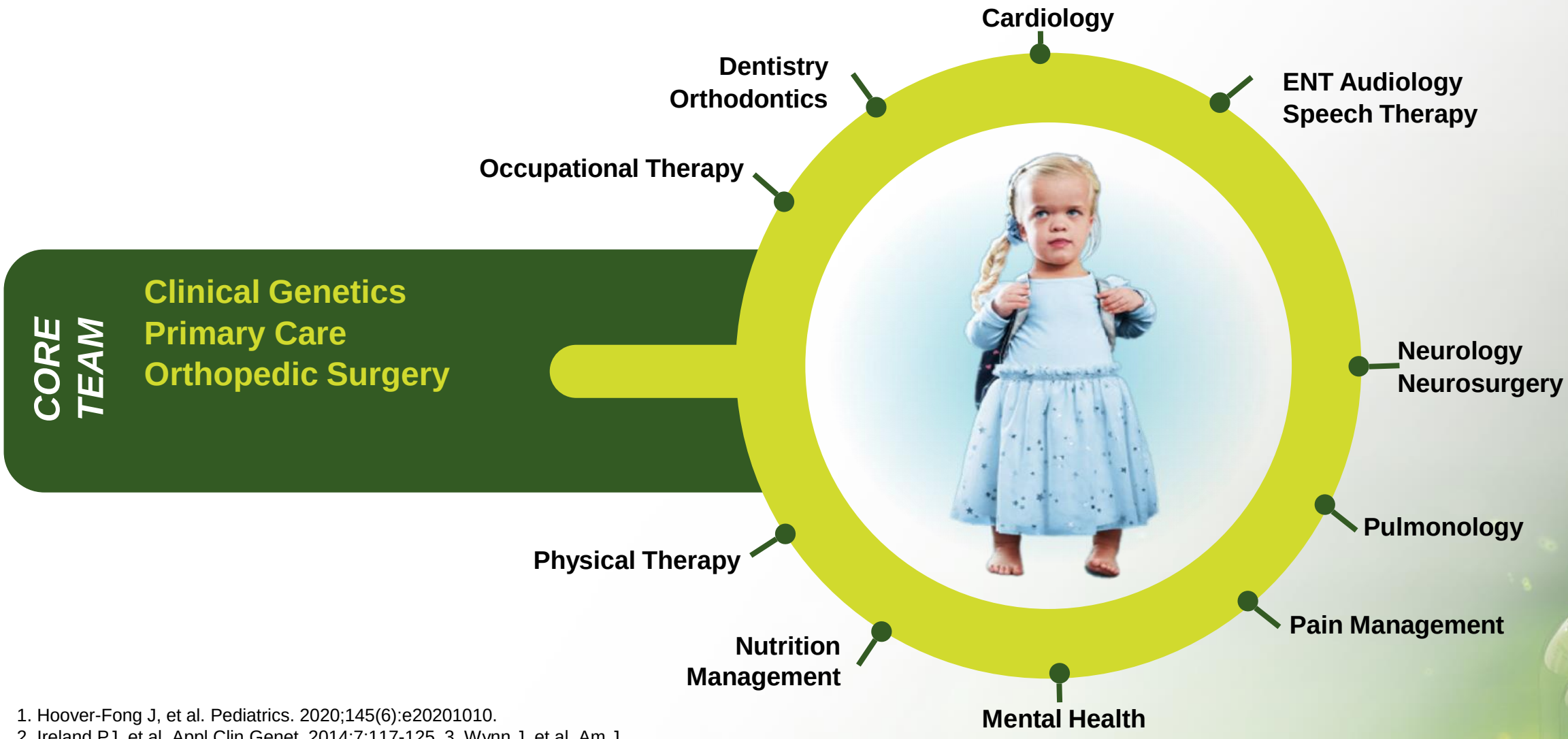
1. Ireland PJ, et al. Appl Clin Genet. 2014;7:117-125. 2. Hunter AGW, et al. J Med Genet. 1998;35:705-712. 3. Horton WA, et al. Lancet. 2007;370:162-172.

These complications occur at during different stages of life



1. Hoover-Fong J, et al. Pediatrics. 2020;145(6):e20201010. 2. Tenconi R, et al. Am J Med Genet A. 2017;173(4):868-878. 3. Wright MJ, Irving MD. Arch Dis Child. 2012;97(2):129-134. 4. Nishimura N, Hanaki K. J Clin Nurs. 2014;23(21-22):3045-3056.

Multidisciplinary care is needed[1-4]



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4. Ahoor MH, Amizadeh Y, Sorkhabi R. Middle East Afr J Ophthalmol. 2015;22(4):522-524.

Picture: Annika, a clinical tiral participant receiving Voxzogo

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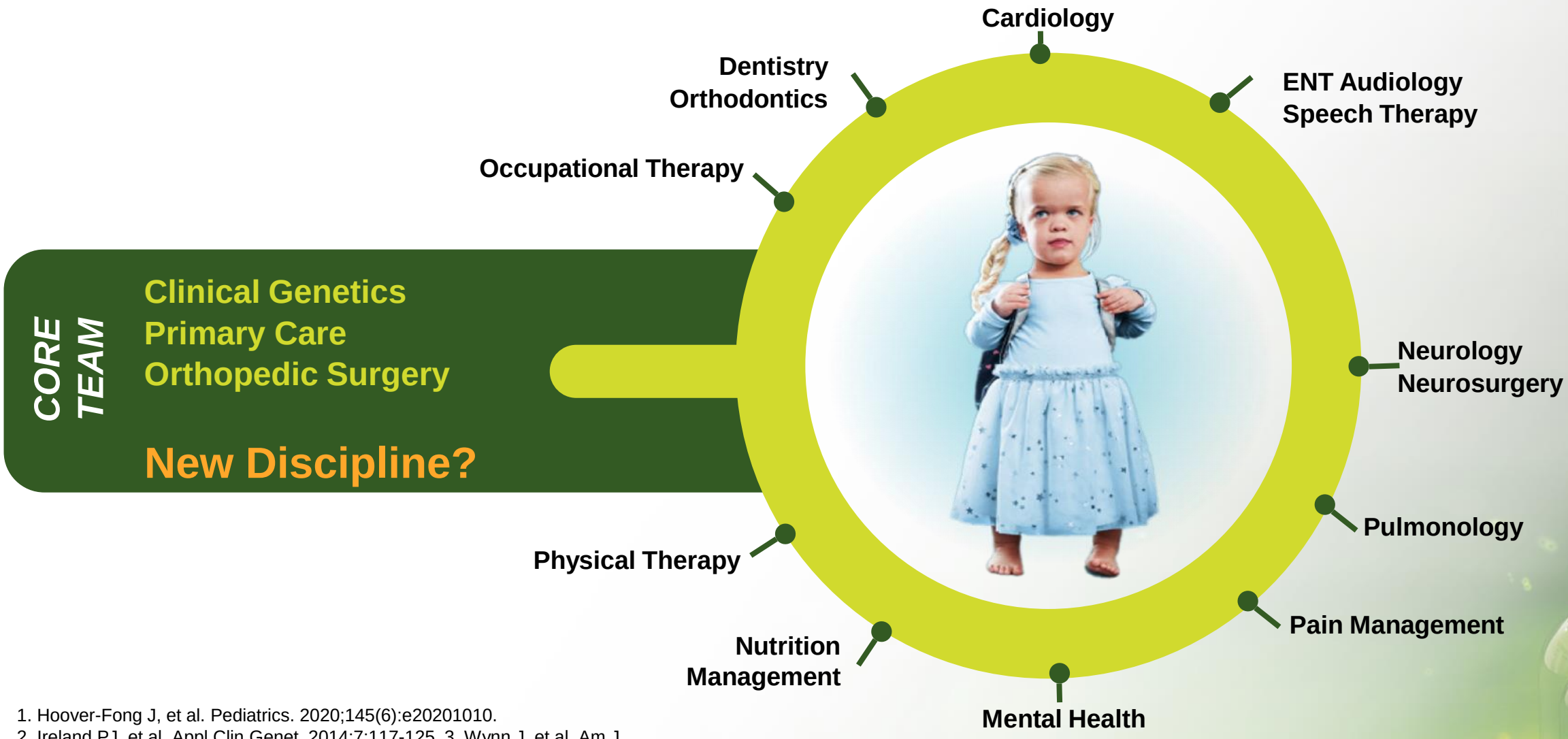

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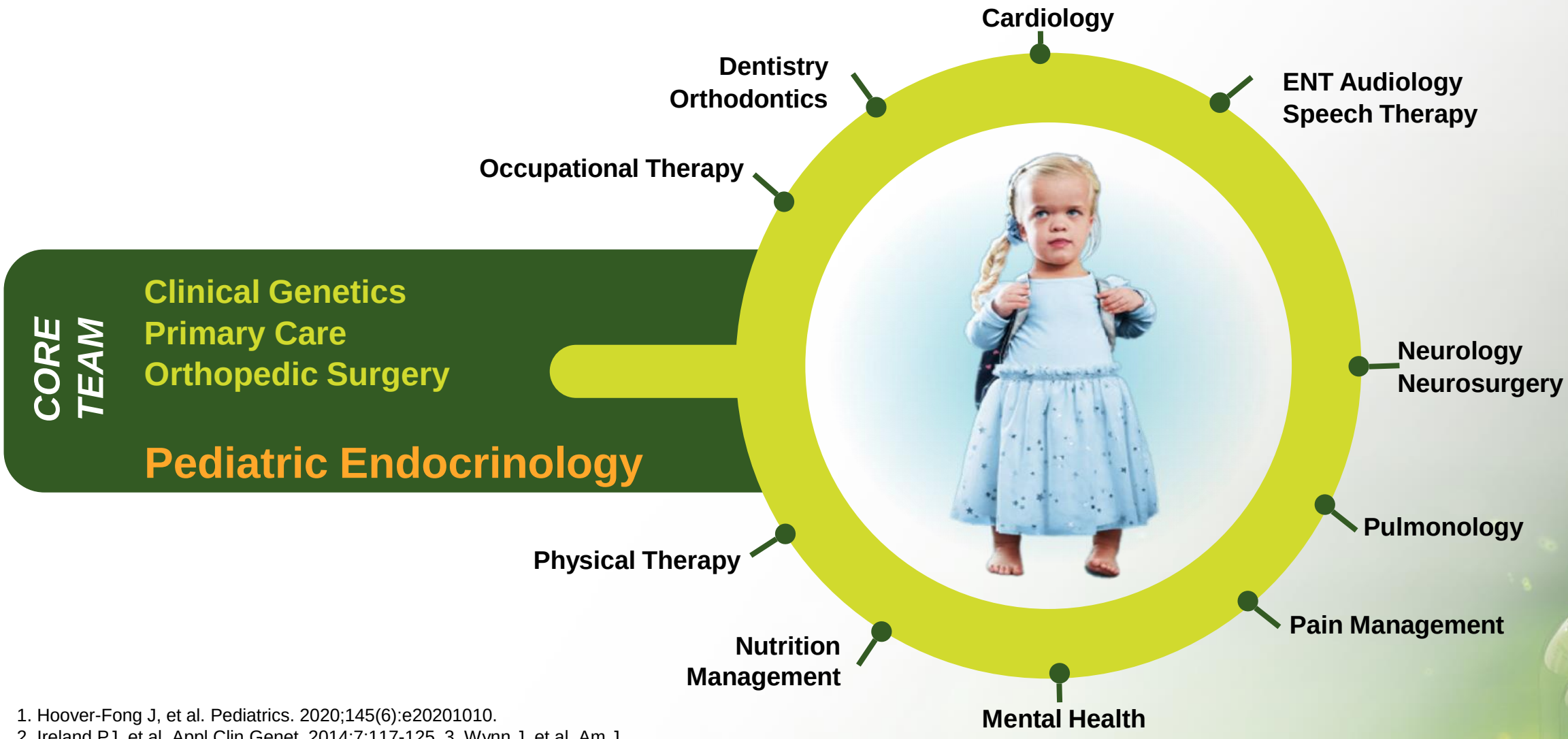

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Discuss the evolving role of the pediatric endocrinologist in the pharmacologic treatment of achondroplasia and available therapies

Vosoritide (Voxzogo by BioMarin)

- First and only FDA-approved therapy for children with achondroplasia
- CNP-analog that targets overactive FGFR3 signaling
  - Positive regulator of endochondral bone growth
- Indicated for linear growth in children ≥ 5yo with open epiphyses
- Daily SQ injection given at home
- Efficacy: 52-wk double-blind randomized placebo-controlled trial[1]
  - Improved AGV: +1.57cm/yr
  - Improved Z-score: +0.28 SD
- Safety[1]:
  - Common A/Es: injection site reactions (73%), transient erythema or swelling
  - Serious A/Es: transient decrease in BP (12%), with 3% being symptomatic (vomiting and/or dizziness); resolves within 30min
    - Counseling: to be given after proper hydration and meal

1. Savarirayan, et al. Once-daily, subcutaneous vosoritide therapy in children with achondroplasia: a randomized, double-blind, placebo-controlled, multicentre trial. Lancet 2020; 396:684-92.

Why Pediatric Endocrinology?

Experience in monitoring growth

- Follow patients frequently (every 3-6mo)
- Familiar with weight-based dose adjustments

Familiar with multi-disciplinary care models

- Turner syndrome

Comfortable with SQ injection training

- In-house vs coordinating home training

Experience with metabolic bone disease

- Hypophosphatasia and X-linked hypophosphatemic rickets

Infrastructure to address insurance coverage

- Benefits investigation, prior authorization, and appeals for high-cost specialty injectables

Barriers for pediatric endocrinologists

Unfamiliarity with achondroplasia

- Condition where historically ped endo not typically involved

Access to patients

- Current core team: primary care, clinical genetics, and orthopedic surgery

1. Hoover-Fong J, et al. Health Supervision for People With Achondroplasia. Pediatrics. 2020; vol 145 number 6.

Solutions to overcome barriers

Resource: AAP Clinical Care Guidelines 2020

- Health Supervision for People with Achondroplasia[1]

Educational campaign for both caregivers and providers

- Disease-state awareness and therapeutic options

Achondroplasia Doctor Finder

1. Hoover-Fong J, et al. Health Supervision for People With Achondroplasia. Pediatrics. 2020; vol 145 number 6.

Explore the need to regularly monitor the growth and development of children and adolescents with achondroplasia, utilizing disease-specific tools

Growth charts

Must use condition-specific, gender-specific charts

- Achondroplasia GC are available through EPIC
- If non-EPIC user, downloadable GCs are available
  - Neumeyer L, Merker A & Hagenäs L; Achondroplasia clinical charts; version 2020

01

Traditional ped endo anthropometrics

- Standing height
- Weight
- BMI

02

Additional achondroplasia anthropometrics

- Arm span
- Sitting Height
- Head circumference (in all ages)
- Leg length (Standing height – Sitting height)

03

Typically need two individuals for accurate measurements

04

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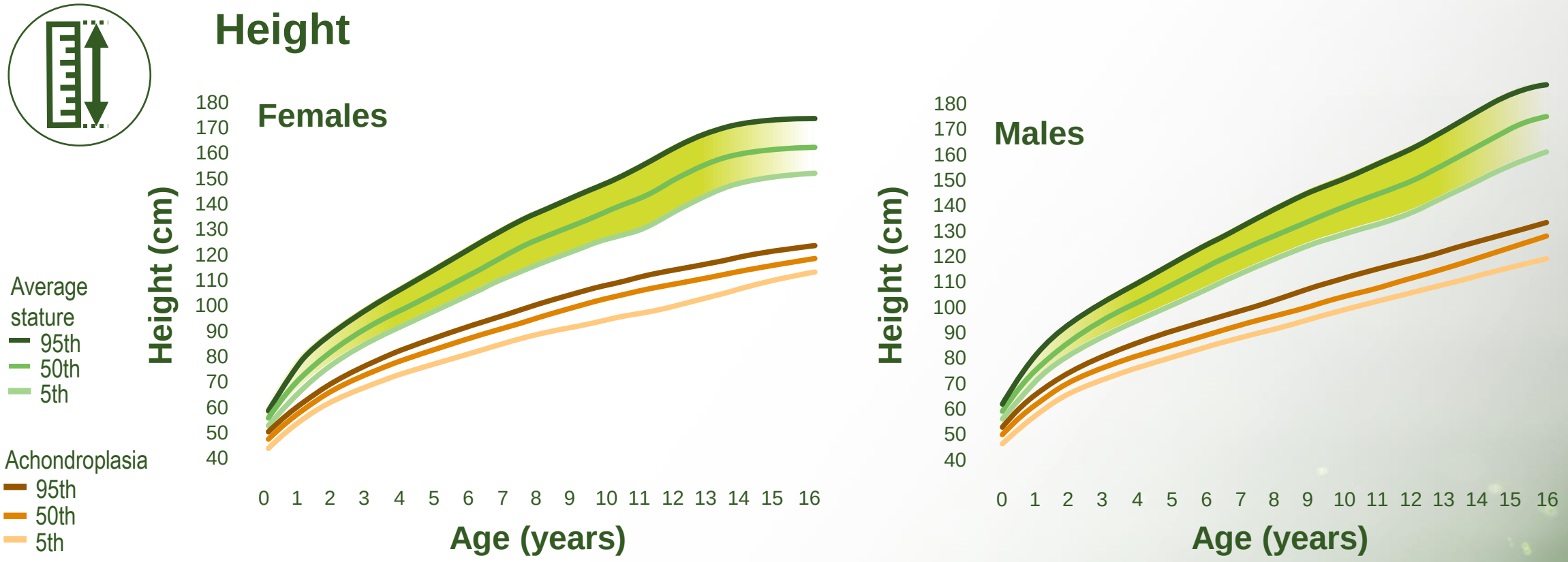
Achondroplasia-Specific Growth Charts

Height



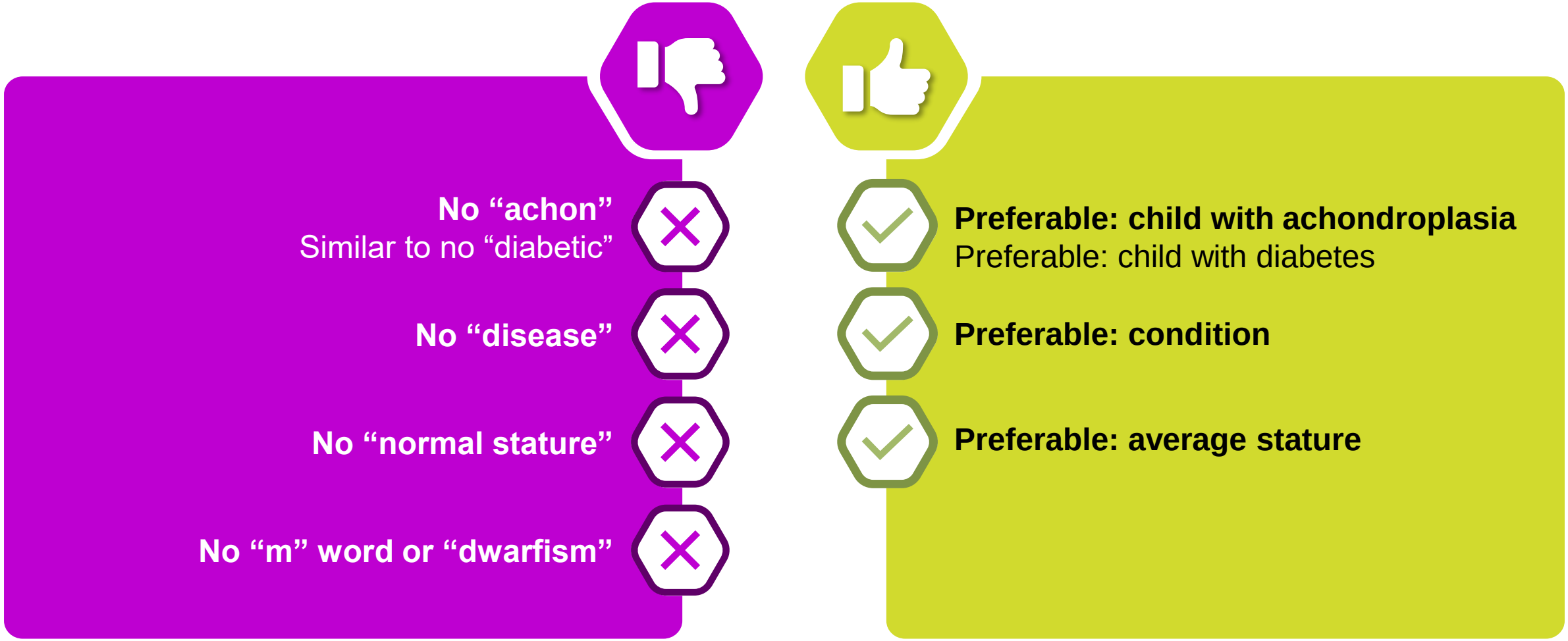
For individuals with achondroplasia, adult height is roughly ***–6.0 SDS*** *for both sexes*

Hoover-Fong JE, Schulze KJ, McGready J, Barnes H, Scott CI. Age-appropriate body mass index in children with achondroplasia: interpretation in relation to indexes of height. Am J Clin Nutr. 2008;88(2):364-371. doi: 10.1093/ajcn/88.2.364. Reproduced by permission of Oxford University Press on behalf of the American Society for Nutrition.

References: 1. Hoover-Fong J, et al. Pediatrics. 2020;145(6):e20201010. 2. Hoover-Fong J, et al. Am J Clin Nutr. 2008;88(2):364-371.

Discuss best practices for endocrinologists as part of a collaborative team

Sensitivity



Sensitivity (cont.)

Little People of American (LPA)

- Strong patient advocacy and social group
- Vocal minority has stigmatized treatment for height alone
  - Reports of patients with leg-lengthening surgery receiving criticism
  - Similar but less emotionally charged than ISS in ped endo GH therapy

Managing expectations with treatment

- Currently, FDA-approved indication is for linear growth *only*
  - Not proportionality
  - Not early neurosurgical complications
  - Five years of age and older
- Studies ongoing to evaluate long-term effects on proportionality and treatment <5yo for neurosurgical complications
- Improved growth velocity is marginal (compared to ped endo GH therapy)
  - Recall pivotal phase 3: +1.57cm/yr
  - Longer term data are still needed by final adult height
  - Cumulative increases over years of Rx *may* lead to significant gains that *may* affect activities of daily living
  - 2yr extension data[1]: maintenance of improved height velocity from baseline
  - Maximal duration of therapy (early initiation combined with continuation until growth plate fusion) is likely to provide the maximum benefit

1. Savarirayan, et al. Safe and persistent growth-promoting effects of vosoritide in children with achondroplasia: 2-year results from an open-label, phase 3 extension study. Genetics in Medicine. 2021; 23:2443-2447.

Coordinating care with team

Pediatric endocrinology will be the newest addition to the core team

Essential that there is open communication between members

- Particularly true if therapy is started
- Ongoing frequent monitoring
- It takes a village

Final Thoughts: 2 words

- Expanding knowledge into a new condition for pediatric endocrinology
- Using our existing skill sets and infrastructure

Excitement

Hope

- First and only FDA-approved therapy for achondroplasia – vosoritide
  - Start with linear growth
  - Potential other benefits TBD with more time