rhythm

Key Opinion Leader Symposium:
The MC4R Pathway and Rare Genetic Disorders of Obesity

December 13, 2018

Forward-Looking Statements

This presentation contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this presentation, including statements regarding our strategy, future operations, future financial position, future revenues, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words “anticipate,” “believe,” “estimate,” “expect,” “intend,” “may,” “plan,” “predict,” “project,” “target,” “potential,” “will,” “would,” “could,” “should,” “continue,” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. The forward-looking statements contained in this presentation reflect Rhythm’s current views with respect to future events, and Rhythm assumes no obligation to update any forward-looking statements except as required by applicable law.

Forward-looking statements represent our management’s beliefs and assumptions only as of the date hereof. You should read our filings with the Securities and Exchange Commission, including the prospectus for our initial public offering, as well as our Form 10-Q, including the Risk Factors set forth therein, and the documents that we have filed as exhibits to the registration statement for our initial public offering, and the Form 10-Q, completely and with the understanding that our actual future results may be materially different from what we expect. We have included important factors in the cautionary statements included in such documents, particularly in the Risk Factors sections, that we believe could cause actual results or events to differ materially from the forward-looking statements that we make.

All references will be available in version of presentation available for download at www.rhythmtx.com.

Today's Agenda

Welcome and Introduction

Keith Gottesdiener, M.D.

Chief Executive Officer, Rhythm Pharmaceuticals

Genetic Disruption of the MC4 Receptor Pathway: A Therapeutic Target for Obesity

Lee M. Kaplan, M.D., Ph.D.

Director, Obesity, Metabolism & Nutrition Institute at Massachusetts General Hospital

Associate Professor of Medicine, Harvard Medical School

Bardet-Biedl Syndrome

Robert Haws, M.D.

Director of Clinical Research, Marshfield Clinic Research Institute

Director, Center of Excellence for Bardet-Biedl Syndrome

Bardet-Biedl Syndrome and Alström Syndrome Clinical Development Updates

Murray Stewart, D.M., F.R.C.P.

Chief Medical Officer, Rhythm Pharmaceuticals

Q&A

Transforming the Care of Patients with Genetic Obesity

The MC4R pathway regulates hunger to maintain body weight. Genetic defects in the MC4R pathway cause insatiable hunger, leading to severe, refractory and early-onset obesity

There are currently no therapies for people living with rare MC4R pathway disorders

Potential First-in-Class Therapy

Setmelanotide is an MC4R agonist designed to rescue the pathway from defects that occur upstream of MC4R receptor as replacement therapy to restore lost activity in the MC4R pathway:

- **Dramatic reductions in weight and hunger observed in four rare homozygous disorders upstream of MC4 receptor**:
  - Awarded *FDA Breakthrough Therapy* and *EMA PRIME* designations received and *pivotal Phase 3 trials ongoing* in all four indications
- **Phase 2 development ongoing in two additional MC4R-pathway disorders**: Preliminary efficacy demonstrated in heterozygous and epigenetic MC4R-pathway disorders; updated data expected early 2019

Multiple Avenues to Accelerate Growth

- **Rhythm Basket Study:** Facilitates rapid enrollment and exploration of setmelanotide's potential in patients with new genetic targets or syndromes tied to the MC4R pathway
- **GO-ID Genotyping Study and TEMPO Registry**: Enables clinical study enrollment, patient identification and exploration of new genetic variants tied to MC4R loss of function
- **Pipeline Expansion:** Leverage expertise to treat additional rare genetic obesity disorders

Genetic Disruption of the MC4 Receptor Pathway: A Therapeutic Target for Obesity

Lee M. Kaplan, MD, PhD

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December 13, 2018

Something to consider …

In 1985, HIV infection was a death sentence …[1]

… in 2018, HIV infection barely affects life expectancy[2]

Why haven't we made the same progress in obesity?

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References: 1. CDC Fact Sheet. Today's HIV/AIDS Epidemic. https://www.cdc.gov/nchhstp/newsroom/docs/factsheets/todaysepidemic-508.pdf. Accessed December 6, 2018. 2. WHO Fact Sheet; HIV/AIDS. https://www.who.int/news-room/fact-sheets/detail/hiv-aids. Accessed December 7, 2018.

The challenge of obesity

In the past 40 years, **not a single country** in the world has experienced a reduction in the prevalence of obesity

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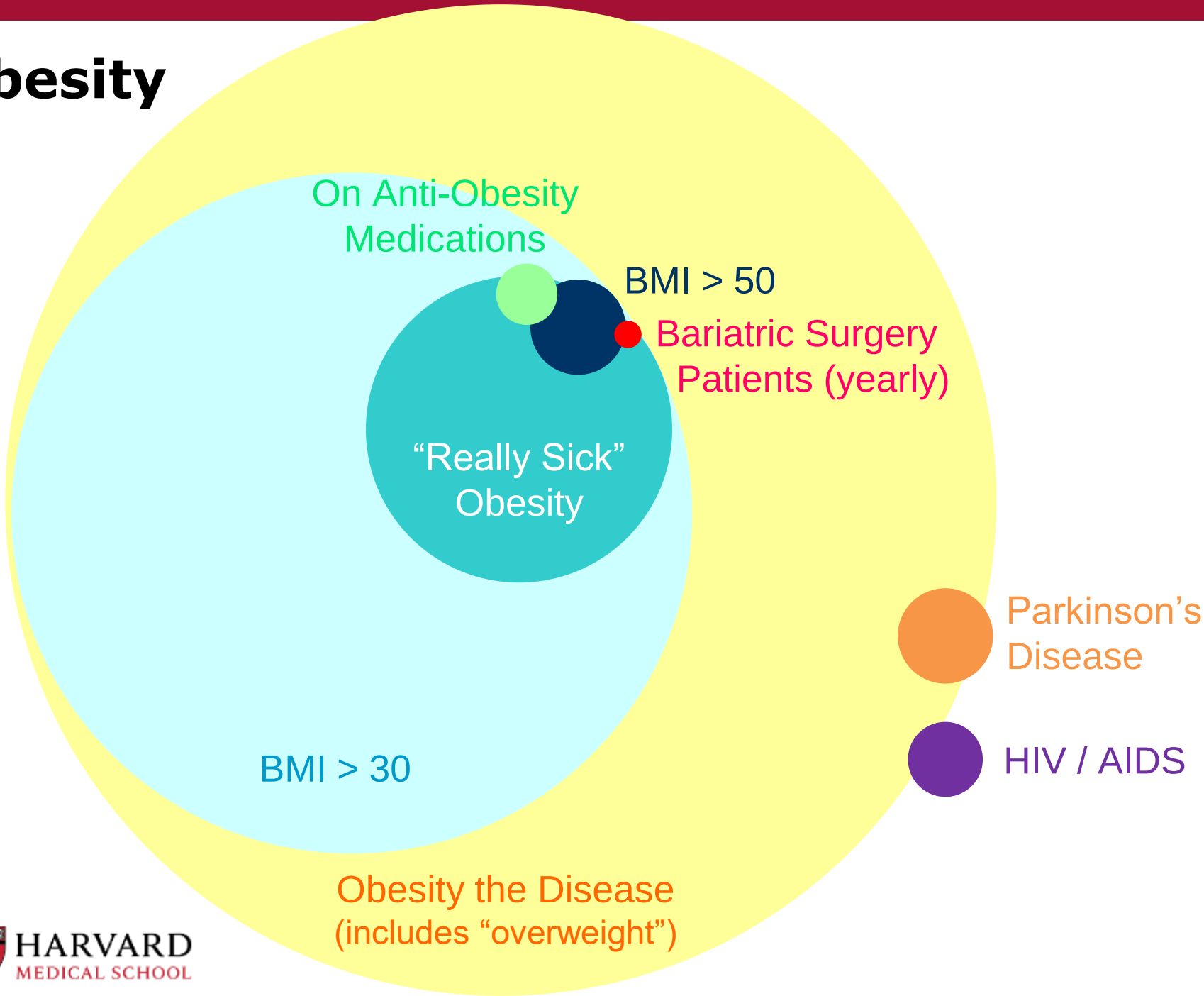
Reference: Ng M. *Lancet.* 2014;384(9945):766-781.

Obesity



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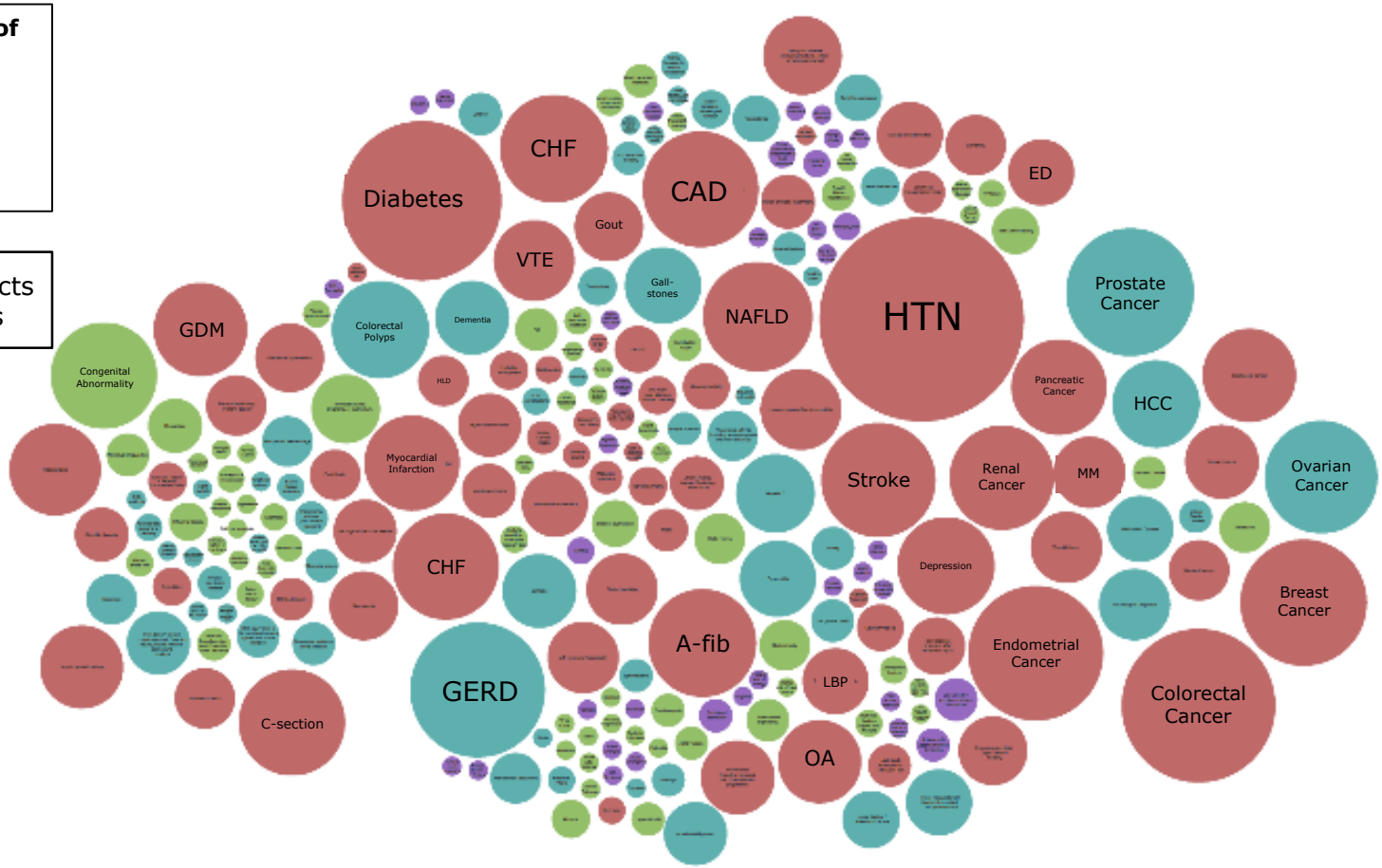
229+ obesity comorbidities affecting EVERY organ system and medical specialty

Color GRADE	Strength of evidence
4	Very strong
3	Strong
2	Moderate
1	Weak

Size of circle reflects number of articles



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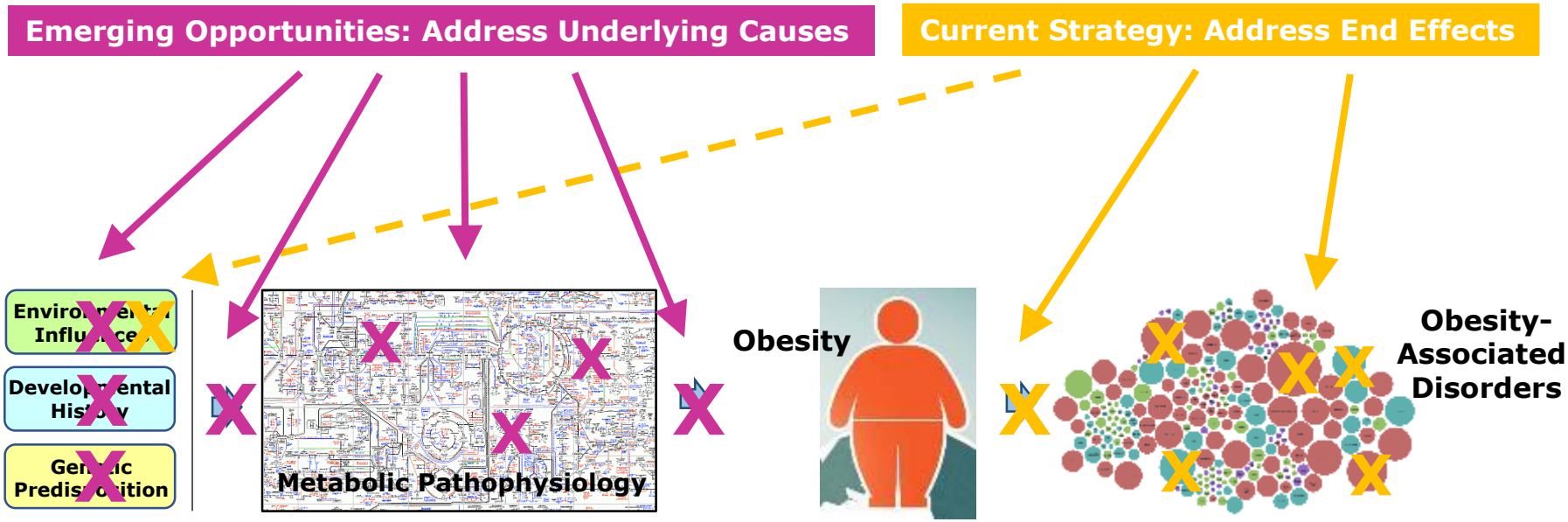
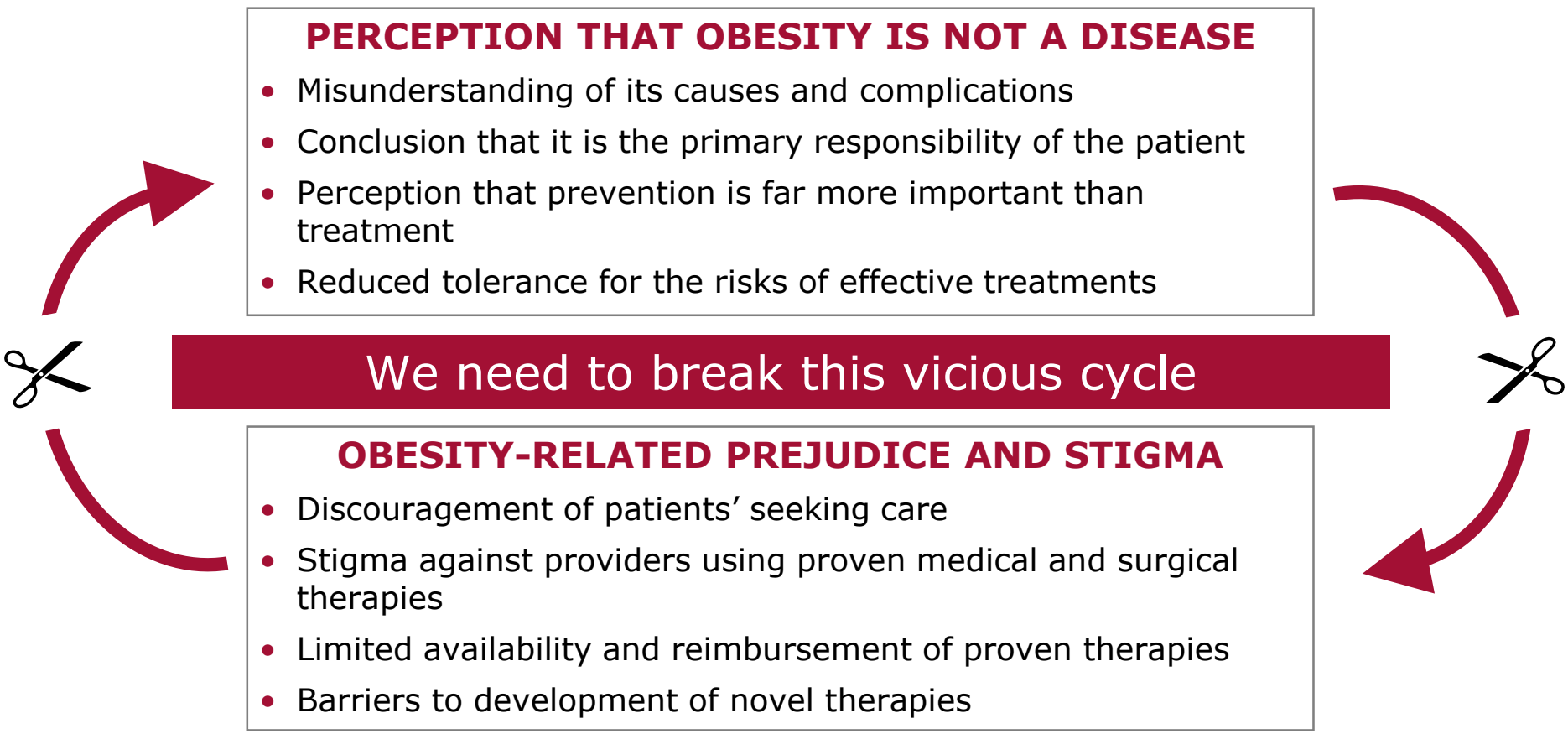
Reference: Yuen MM et al. A Systematic Review and Evaluation of Current Evidence Reveals 195 Obesity-Associated Disorders (OBAD). Presented at: ObesityWeek 2016; October 31-November 4, 2016; New Orleans, LA. Poster T-P-3166. Manuscript in preparation.

Where do we intervene?



Major challenges to effective obesity care[1,2]



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References: 1. Bray GA et al. *Endocr Rev*. 2018;39(2):79-132. **2.** Heymsfield SB et al. *NAM Perspectives*. Discussion Paper, National Academy of Medicine, Washington, DC. doi: 10.31478/201809b.

Breaking the cycle: Patently blameless obesity

- Obesity from brain trauma[1]
- Obesity from brain tumors[1]
- Obesity from brain irradiation[1]
- Obesity from therapeutic drug therapy[1]
- **Syndromic obesity**[2]
- **Genetic obesity**[2]

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References: 1. Lee M, Korner J. *Pituitary*. 2009;12(2):87-95. **2.** Huvenne H et al. *Obes Facts*. 2016;9(3):158-173.

Body fat mass is tightly regulated by central physiological mechanisms

The hypothalamus regulates appetite and energy expenditure

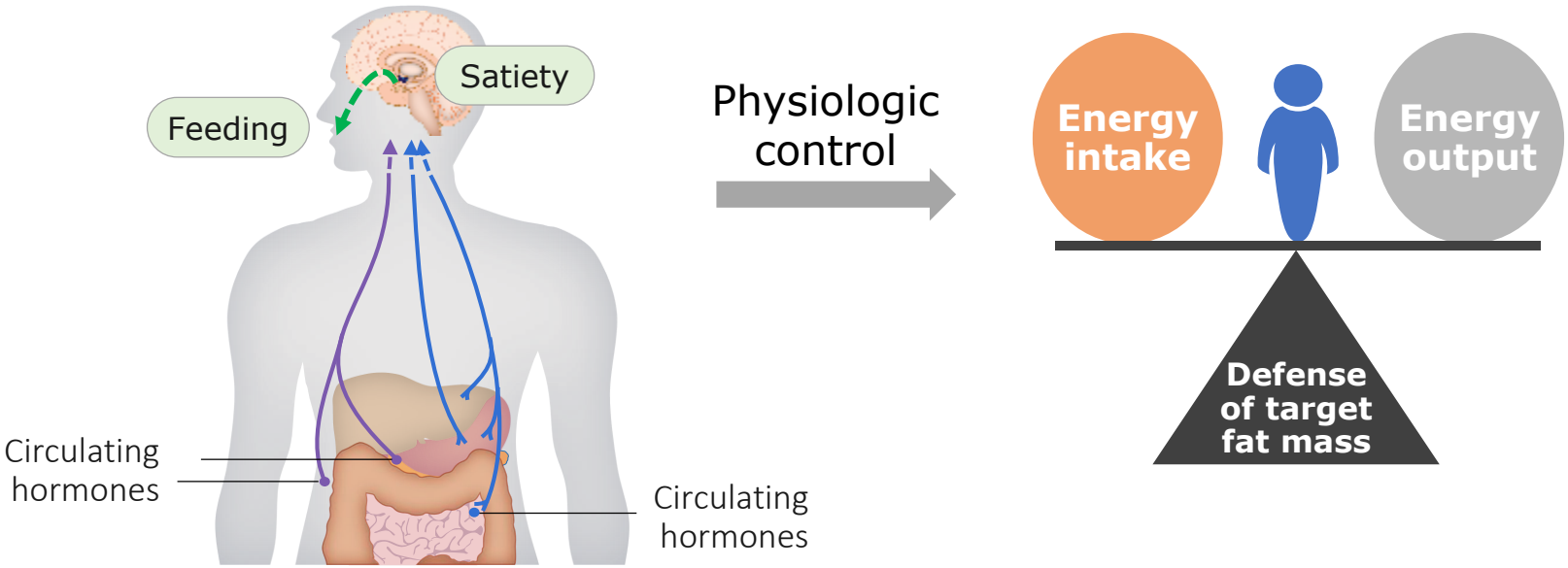

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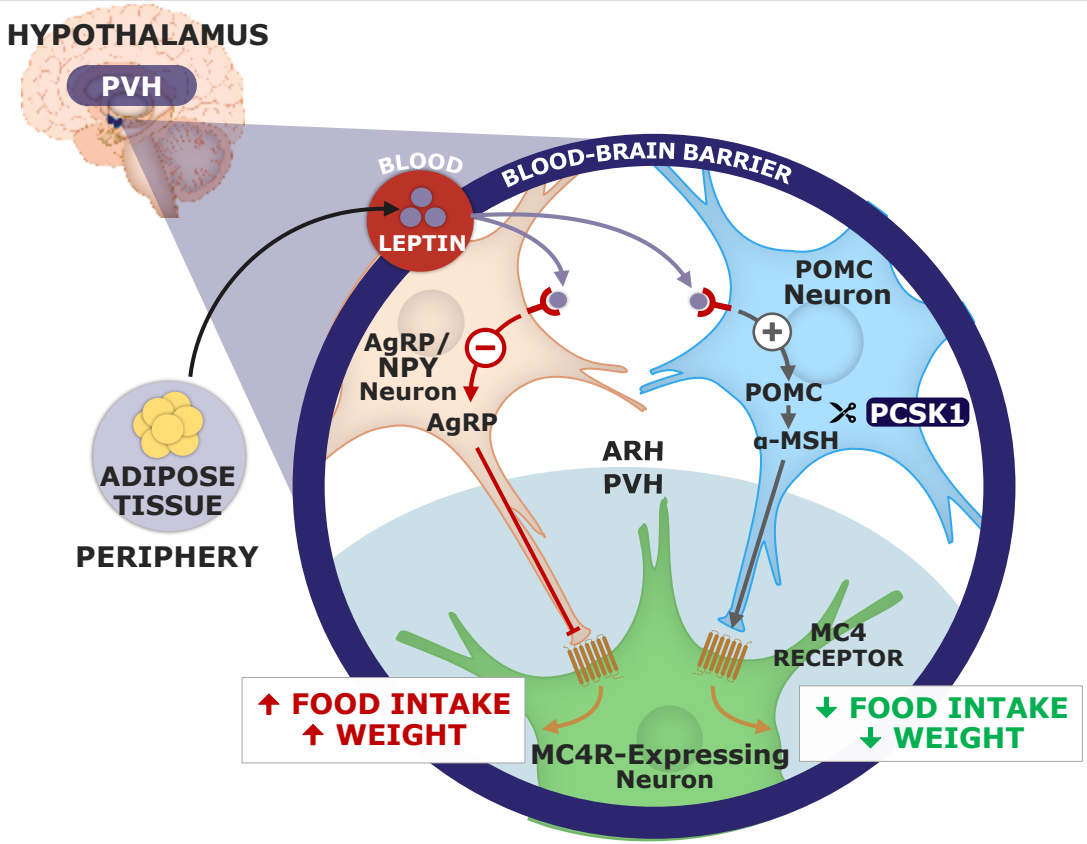
Figure modified from *Science.* 299:846 (2003). Reprinted with permission from AAAS.

Reference: van der Klaauw AA, Farooqi IS. *Cell*. 2015;161(1):119-132.

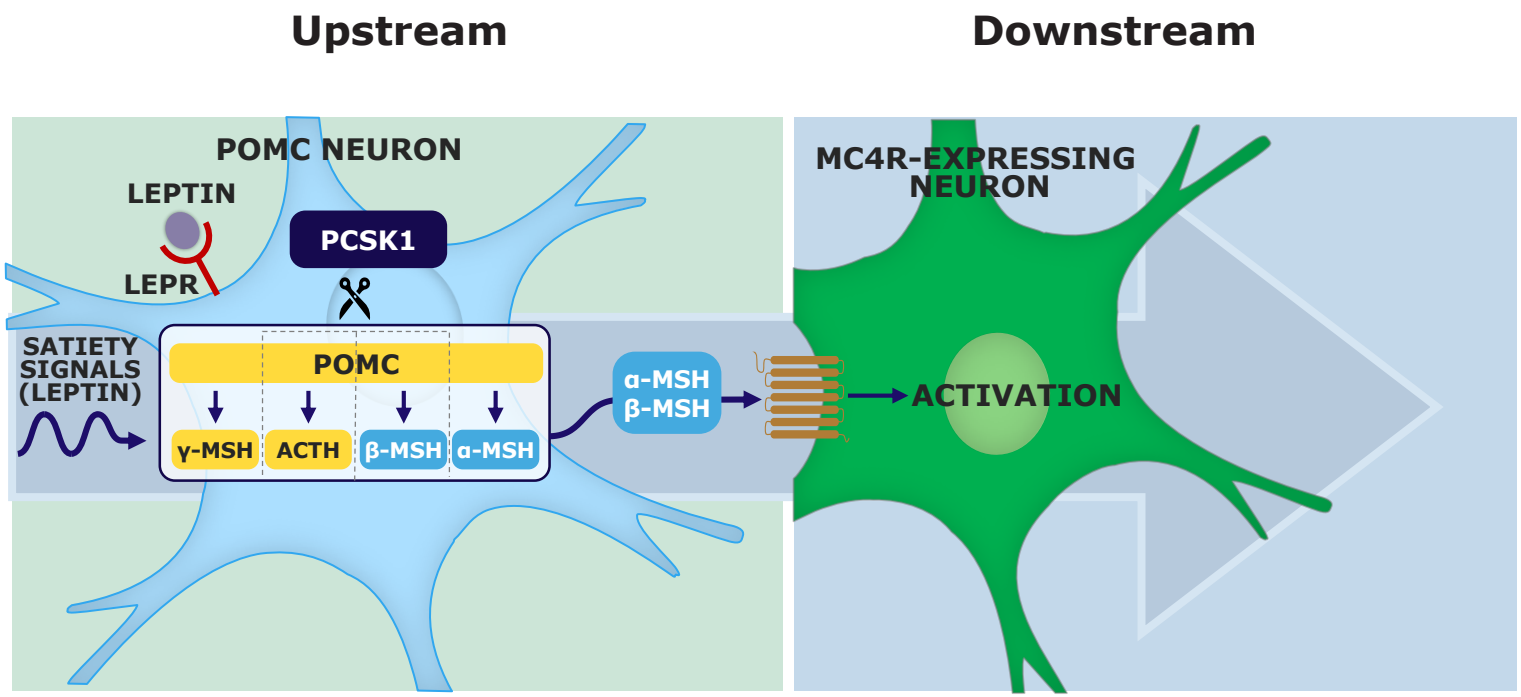
Hypothalamic regulation of appetite and energy expenditure



AgRP, agouti-related protein; ARH, arcuate nucleus; MC4R, melanocortin-4 receptor; MSH, melanocyte stimulating hormone; NPY, neuropeptide Y; POMC, pro-opiomelanocortin; PVH, paraventricular nucleus of hypothalamus.

Reference: Yazdi FT et al. *PeerJ.* 2015;3:e856.

Role of melanocortin signaling



ACTH, adrenocorticotropic hormone; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; MSH, melanocyte stimulating hormone; PCSK1, pro-protein convertase subtilisin/kexin type 1; POMC, pro-opiomelanocortin.

References: 1. Huvenne H et al. *Obes Facts.* 2016;9(3):158-173. **2.** Kostovski M et al. *Pril (Makedon Akad Nauk Umet Odd Med Nauki)*. 2017;38(3):121-133. **3.** Kuehnen P et al. *PLoS Genet.* 2012;8(3):e1002543. **4.** da Fonseca ACP et al. *J Diabetes Complications*. 2017;31(10):1549-1561.

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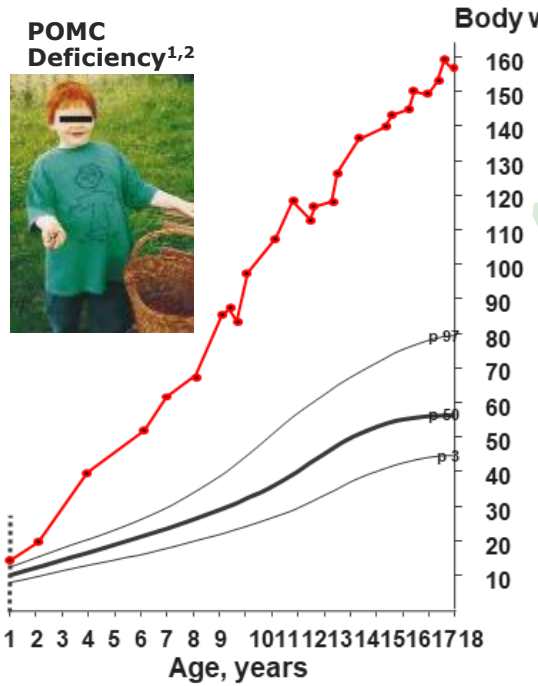
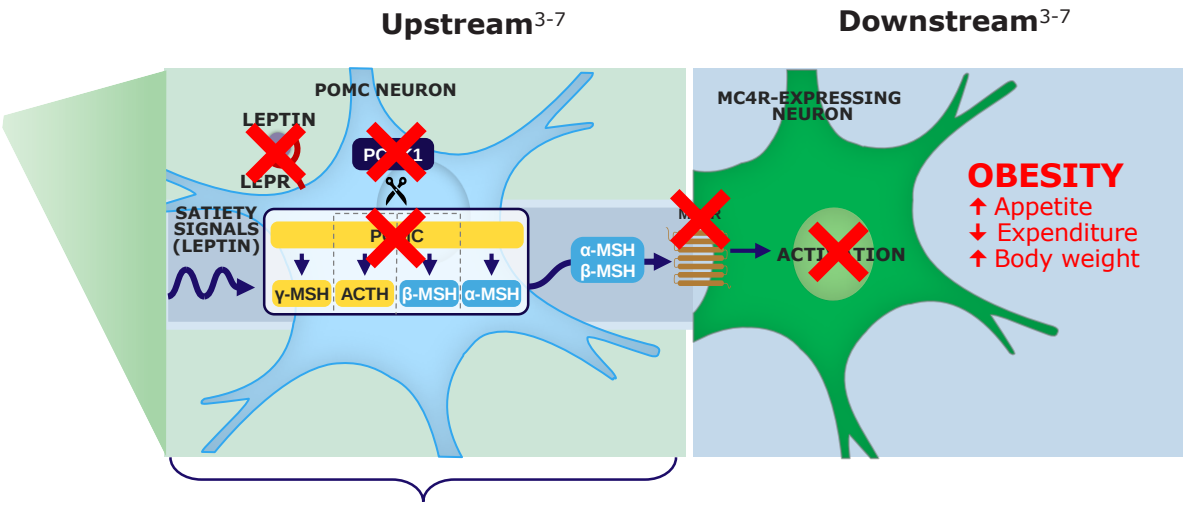
Mutations in the MC4R pathway cause profound, early-onset obesity





BBS[8] and Alström syndrome[9]?

ACTH, adrenocorticotropic hormone; BBS, Bardet-Biedl syndrome; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; MSH, melanocyte stimulating hormone; PCSK1, pro-protein convertase subtilisin/kexin type 1; POMC, pro-opiomelanocortin.

Photo: Reprinted by permission from Springer Nature: Krude H et al. *Nat Genet*. 1998;19(2):155-157. Graph: From Kühnen P et al. *N Engl J Med*. 2016;375(3):240-246. © 2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

References: 1. Kühnen P et al. *N Engl J Med.* 2016;375(3):240-246. **2.** Krude H et al. *Nat Genet.* 1998;19(2):155-157. **3.** Yazdi FT et al. *PeerJ.* 2015;3:e856. **4.** Krashes MJ et al. *Nat Neurosci.* 2016;19(2):206-219. **5.** Cone RD. *Endocr Rev.* 2006;27(7):736-749. **6.** Sohn JW et al. *Trends Neurosci.* 2013;36(9):504-512. **7.** van der Klaauw AA, Farooqi IS. *Cell.* 2015;161(1):119-132. **8.** Guo DF et al. *PLoS Genet*. 2016;12(2):e1005890. **9.** Marshall JD et al. *Curr Genomics.* 2011;12(3):225-235.

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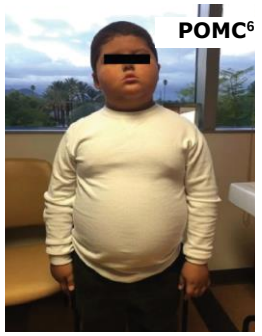
Rare genetic disorders of obesity: monogenic obesity[1-3]

- Obesity caused by **loss-of-function mutations** of genes contributing to the regulation of energy balance and fat mass
  - Relevant genes often involved in hypothalamic development and function
  - Many participate in signaling along the melanocortin-dependent pathway
  - Commonly presents as severe, early-onset obesity with hyperphagia and endocrine dysfunction
- Examples
  - LEPR deficiency
  - POMC deficiency
  - PCSK1 deficiency
  - MC4R deficiency
  - LEP deficiency



LEP, leptin; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; PCSK1, pro-protein convertase subtilisin/kexin type 1; POMC, pro-opiomelanocortin.
Left photo: Reproduced from Hannema SE et al. *Horm Res Paediatr*. 2016;85(6):412-420. Permission provided under the terms of the Creative Commons Attribution License: https://creativecommons.org/licenses/by/4.0/legalcode. Middle photo: Reprinted by permission from Springer Nature: Krude H et al. *Nat Genet*. 1998;19(2):155-157. Right photo: Republished with permission of Walter de Gruyter GmbH & Co. KG, from Hilado MA, Randhawa RS. *J Pediatr Endocrinol Metab*. 2018;31(7):815-819; permission conveyed through Copyright Clearance Center, Inc.

References: 1. da Fonseca ACP et al. *J Diabetes Complications*. 2017;31(10):1549-1561. **2.** Huvenne H et al. *Obes Facts*. 2016;9(3):158-173. **3.** Stijnen P et al. *Endocr Rev*. 2016;37(4):347-371. **4.** Hannema SE et al. *Horm Res Paediatr*. 2016;85(6):412-420. **5.** Krude H et al. *Nat Genet*. 1998;19(2):155-157. **6.** Hilado MA, Randhawa RS. *J Pediatr Endocrinol Metab*. 2018;31(7):815-819.

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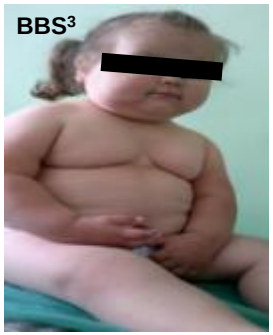
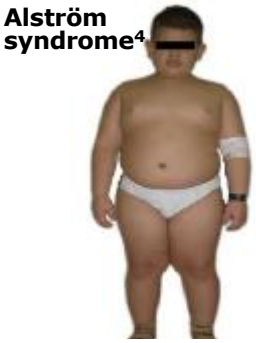
Rare genetic disorders of obesity: syndromic obesity[1,2]

- Obesity associated with specific, characteristic phenotypic changes
  - Commonly presents as severe, early-onset obesity with hyperphagia and other phenotypic changes (often related to brain or skeletal development)
  - Results from disruption or dysfunction of one or a small group of genes
- Examples
  - Bardet-Biedl syndrome
  - Alström syndrome
  - Prader-Willi syndrome





BBS, Bardet-Biedl syndrome; CNS, central nervous system.

References: 1. Huvenne H et al. Obes Facts. 2016;9(3):158-173. 2. Chung WK. Pediatr Blood Cancer. 2012;58(1):122-128. 3. Pasińska M et al. J Mol Genet Med. 2015;9:4. 4. Marshall JD et al. Curr Genomics. 2011;12(3):225-235.

Summary

- Severe, genetic forms of obesity are rare[1]
- Differentiation of specific obesity subtypes is important[2]
  - Specific diagnosis allows for development of an effective treatment plan
- Identifying genetic variants may help identify an individual's risk of developing obesity[3]
- Genetic testing of patients with early-onset obesity and hyperphagia guides the choice of effective treatment[4]

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References: 1. Huvenne H et al. *Obes Facts.* 2016;9(3):158-173. **2.** Kostovski M et al. *Pril (Makedon Akad Nauk Umet Odd Med Nauki).* 2017;38(3):121-133. **3.** Kuehnen P et al. *PLoS Genet.* 2012;8(3):e1002543. **4.** da Fonseca ACP et al. *J Diabetes Complications.* 2017;31(10):1549-1561.

We need a new perspective on obesity…

- That does **not** rely on a person's appearance
- That emphasizes the **underlying biology**
- **Genetic obesity** is an ideal place to start

Creating an effective anti-obesity strategy

We know where we want to go…

…starting with forms of obesity with a discrete mechanism provides a strong advantage

Genetic Disruption of the MC4 Receptor Pathway: A Therapeutic Target for Obesity

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December 13, 2018

Bardet-Biedl Syndrome

Robert Haws, MD
Director, Clinical Research Center
Marshfield Clinic Research Institute
Marshfield Clinic
Marshfield, WI

Marshfield Clinic
Research Institute

Overview of the Presentation

1. The discovery of the syndrome
2. The epidemiology of BBS
3. The genetics of BBS
4. The cilia
5. Diagnosing BBS and patient identification
6. Clinical features of BBS
7. Health concerns for individuals with BBS
8. The impact of obesity

BBS, Bardet-Biedl syndrome.

The History of BBS

- Georges Louis Bardet[1-3]
  - French physician and associate of Louis Pasteur
  - In 1920, he submitted his thesis on 2 French girls with polydactyly, **hypothalamic obesity,** and retinitis pigmentosa
- Artur Biedl[1,4]
  - Hungarian pathologist
  - In 1922, he further described the syndrome with cognitive impairment, polydactyly, and **obesity**

References: 1. Haws M et al. *New Horiz Transl Med*. 2015;2(4-5):102-109. **2.** Bardet G. *Obes Res*. 1995;3(4):387-399. **3.** BBS UK. Bardet-Biedl Syndrome Medical Information Booklet. 2016. http://lmbbs.org.uk/LMBBS/file/Medical%20Booklet%202016(1).pdf. Accessed November 27, 2018. **4.** Biedl A. *Obes Res*. 1995;3(4):404.

The History of BBS (continued)

- 1866 descriptions by ophthalmologists John Zachariah Laurence and Robert Charles Moon of retinitis pigmentosa, choroidal atrophy, short stature, renal anomalies, T2DM, speech delay, and ataxia[1-3]
- 1925 paper by Solis-Cohen and Weiss suggested that the patients described by Drs. Laurence and Moon had the same disorder as the individuals described by Drs. Bardet and Biedl[3]
- Lawrence-Moon-Bardet-Biedl syndrome[3]
- Lawrence-Moon-Biedl syndrome[4]
- Bardet-Biedl syndrome[5]
  - OMIM #209900
  - 24+ genes
- Lawrence-Moon syndrome[3]
  - OMIM #245800
  - Gene PNPLA6
  - Important differences between BBS and LMS are **obesity** and renal disease in BBS vs short stature, minor renal anomalies, and ataxia/spastic paraplegia in LMS[3,5]

BBS, Bardet-Biedl syndrome; LMS, Lawrence-Moon syndrome; OMIM, Online Mendelian Inheritance in Man; T2DM, type 2 diabetes mellitus.

References: 1. Laurence JZ, Moon RC. *Obes Res.* 1995;3:400-403. **2.** Forsythe E, Beales PL. *Eur J Hum Genet.* 2013;21(1):8-13. **3.** Online Mendelian Inheritance in Man (OMIM). Laurence-Moon Syndrome; LNMS. https://www.omim.org/entry/245800. Accessed November 26, 2018. **4.** BBS UK. Bardet-Biedl Syndrome Medical Information Booklet. 2016. http://lmbbs.org.uk/LMBBS/file/Medical%20Booklet%202016(1).pdf. Accessed November 27, 2018. **5.** Online Mendelian Inheritance in Man (OMIM). Bardet-Biedl Syndrome 1; BBS1. https://www.omim.org/entry/209900. Accessed November 26, 2018.

Epidemiology of BBS

Prevalence[1-3]

- North America: 1 in 100,000
- Switzerland: 1 in 160,000
- Kuwaiti Bedouin tribes[2]: 1 in 13,500
  - Consanguinity
- Newfoundland: 1 in 18,000[3,4]
  - Founder effect

Individuals of all races and numerous countries have been identified with BBS[5]

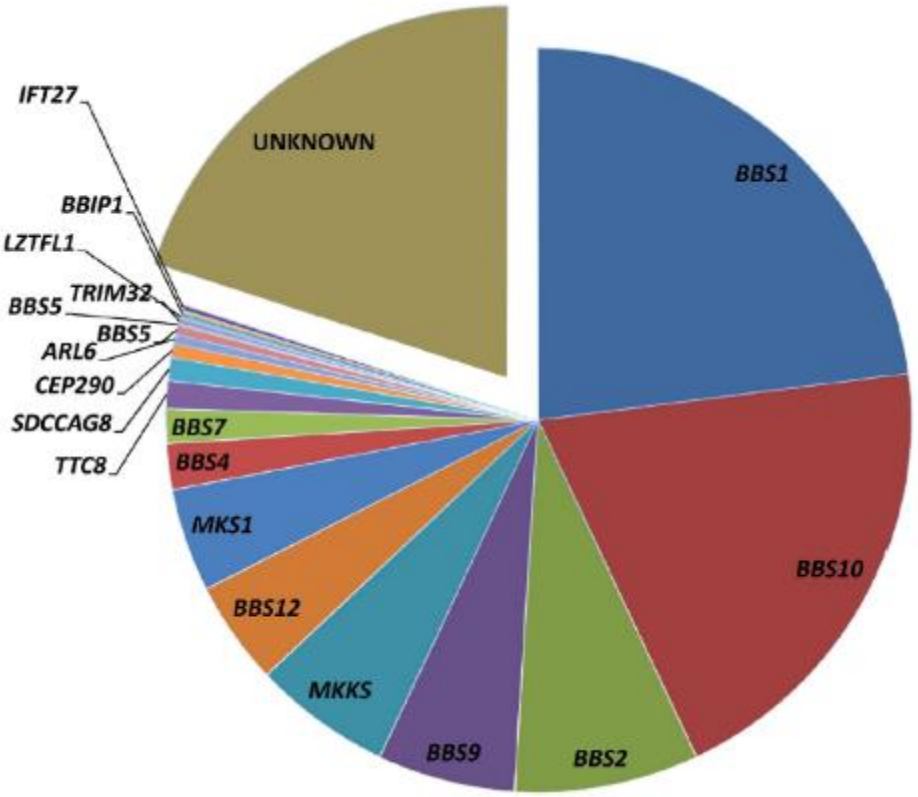
BBS, Bardet-Biedl syndrome.

References: 1. Haws M et al. *New Horiz Transl Med*. 2015;2(4-5):102-109. **2.** Forsythe E, Beales PL. *Eur J Hum Genet*. 2013;21(1):8-13. **3.** Forsythe E et al. *Front. Pediatr*. 2018;6:23. doi: 10.3389/fped.2018.00023. **4.** Moore SJ et al. *Am J Med Genet A*. 2005;132A(4):352-360. **5.** Stryjeck C et al. *Obes Rev*. 2018;19(1):62-80.

BBS as a Genetic Disorder

- 24 known genes and growing[1]
- Primarily autosomal recessive inheritance with exceptions suggesting oligogenic inheritance patterns[2]
  - Triallelism and mutational burden
  - Numerous syndromes are allelic disorders to BBS
    - McKusick-Kaufman syndrome, Meckel-Gruber syndrome, nephronophthisis, Joubert syndrome, and Senior-Løken syndrome
  - Families reported with children with different syndromes but same genes[2,3]
  - Multiple syndromes in one individual[1,3]

Frequency of BBS-causing mutations[2]



Reproduced from Haws M et al. *New Horiz Transl Med*. 2015;2(4-5):102-109.

BBS, Bardet-Biedl syndrome.

References: 1. Online Mendelian Inheritance in Man (OMIM). Bardet-Biedl Syndrome 1; BBS1. https://www.omim.org/entry/209900. Accessed November 26, 2018. **2.** Haws M et al. *New Horiz Transl Med*. 2015;2(4-5):102-109. **3.** Novas R et al. *FEBS Lett*. 2015;589(22):3479-3491.

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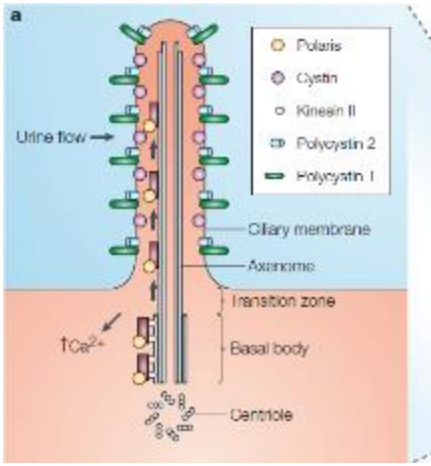
BBS as a Ciliopathy

- Cilia are ubiquitous hair-like structures that permit cells to interact with other cells and their environment[1-3]
  - Allow us to see, hear, smell, maintain balance, have 5 fingers on our hands, and a heart that points to the left[1-3]
  - Cilia are spread throughout the entire body so features of BBS and other ciliopathies are found in many organ systems and cause diverse health problems[3]
  - There are dozens of ciliopathies ranging from common to ultra-rare[4,5]



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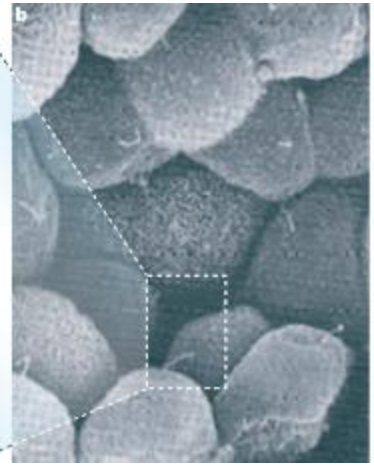
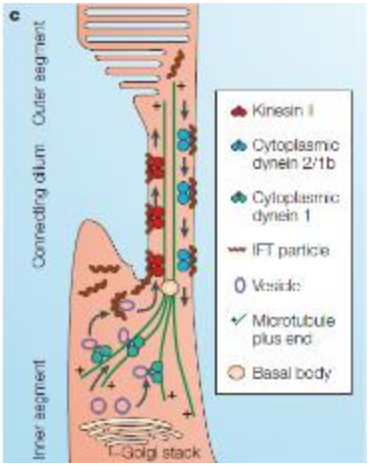


Reproduced from Hildebrandt F, Otto E. *Nat Rev Genet.* 2005;6(12):928-940, with permission of Springer Nature.



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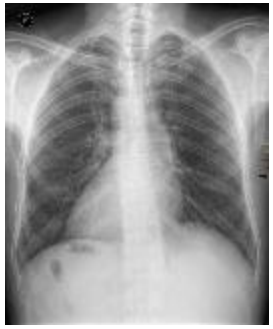

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BBS, Bardet-Biedl syndrome.

References: 1. Hildebrandt F, Otto E. *Nat Rev Genet*. 2005;6(12):928-940. **2.** Bisgrove BW et al. *Development*. 2006;133(21):4131-4143. **3.** Hildebrandt F et al. *N Engl J Med.* 2011;364(16):1533-1543. **4.** Wheway G et al. *Front Cell Develop Biol.* 2018;6(8):1-13. **5.** Haws M et al. *New Horiz Transl Med*. 2015;2(4-5):102-109.

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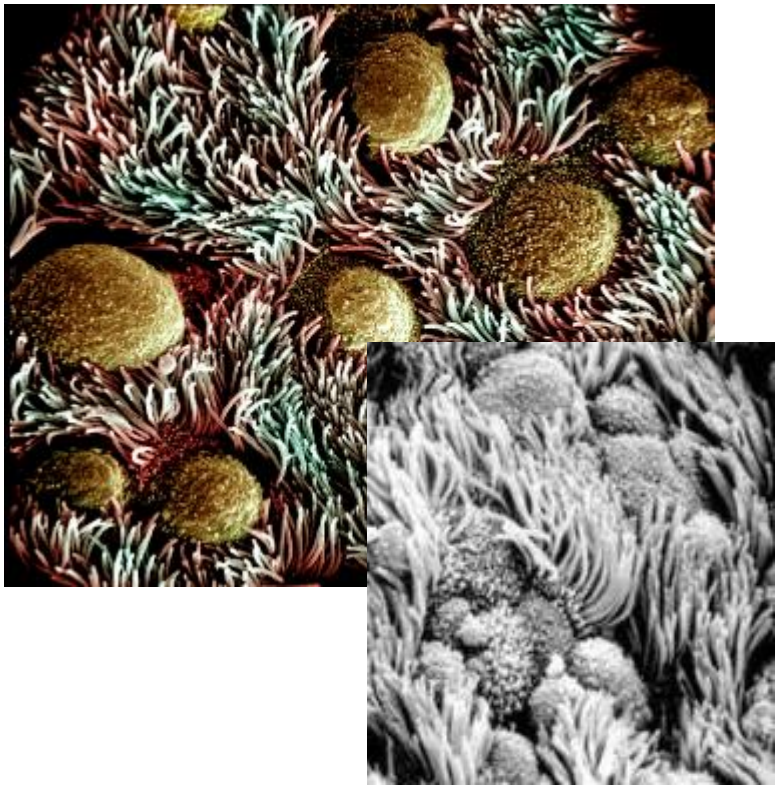
The Cilium

Motile cilia



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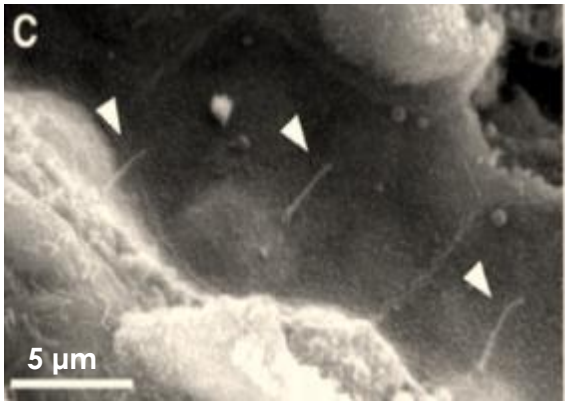

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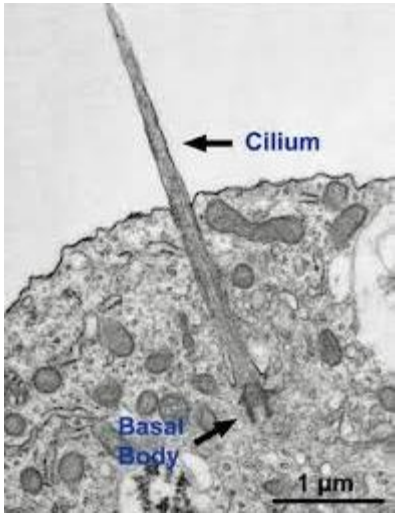

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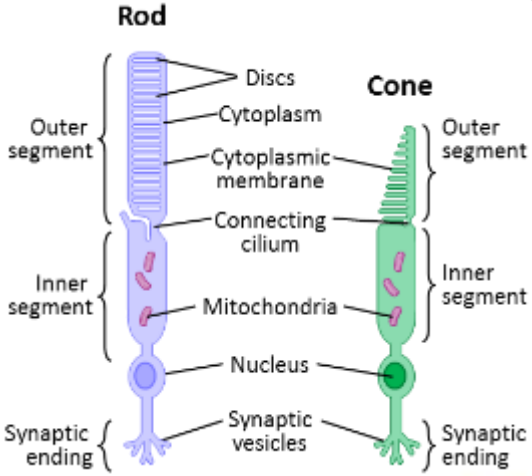
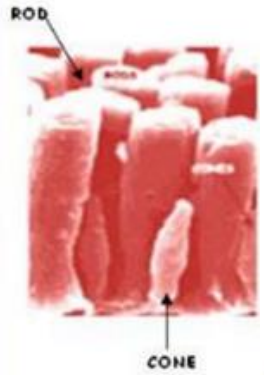
Primary cilia





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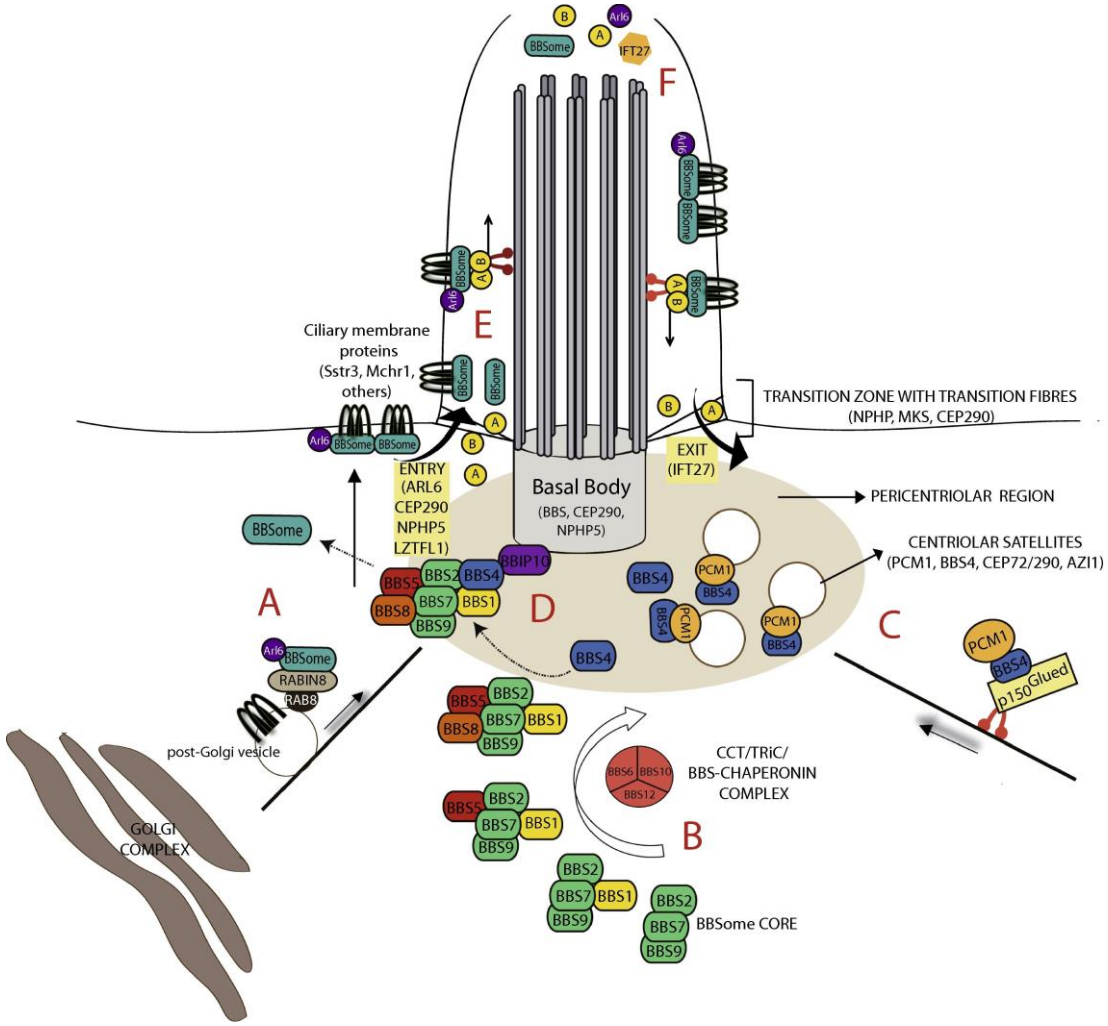
BBS Proteins in Ciliogenesis: The BBSome



Reproduced from Novas R et al. *FEBS Lett.* 2015;589(22):3479-3491, with permission of John Wiley and Sons. © 2015 Federation of European Biochemical Societies.

BBS, Bardet-Biedl syndrome.

Reference: Novas R et al. *FEBS Lett.* 2015;589(22):3479-3491.

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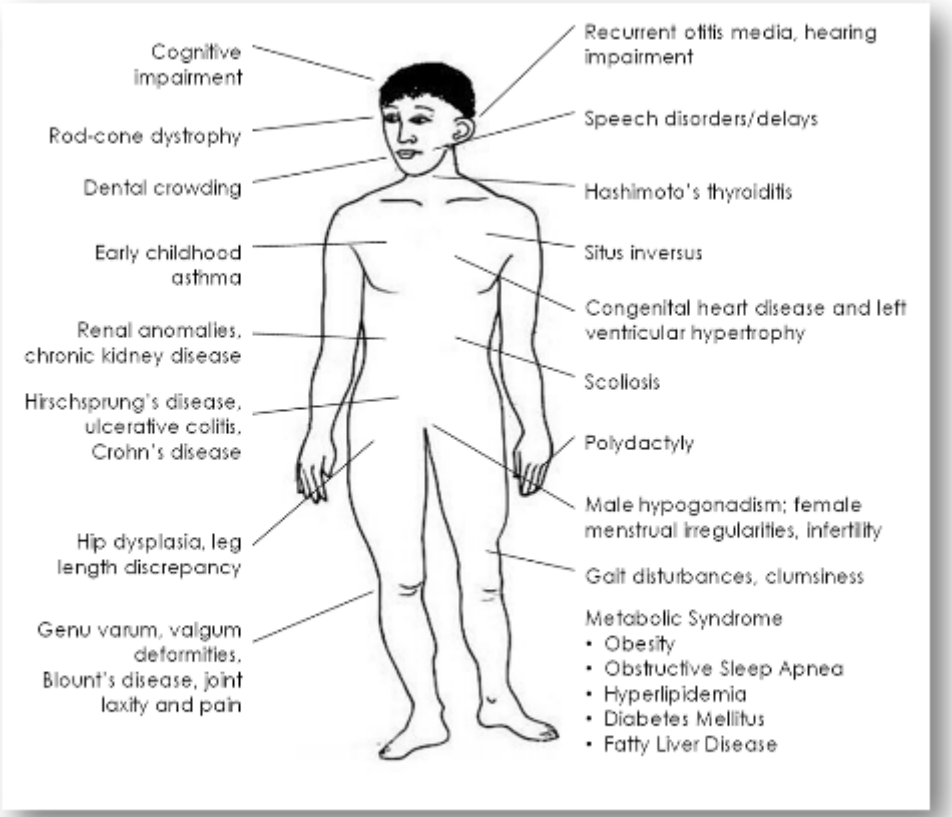
The Impact of BBS on Health[1,2]

- Cardinal features of BBS
  1. Obesity
  2. Polydactyly
  3. Rod-cone dystrophy
  4. Learning difficulties
  5. Male hypogonadism
  6. Renal anomalies
- Secondary features of BBS
  1. Dental anomalies
  2. Speech delay
  3. Congenital heart disease/ cardiomyopathy
  4. Poor coordination
  5. Strabismus/cataracts/astigmatism
  6. Hepatic fibrosis



Reproduced from Haws M et al. *New Horiz Transl Med.* 2015;2(4-5):102-109.

BBS, Bardet-Biedl syndrome.

References: 1. Haws M et al. *New Horiz Transl Med*. 2015;2(4-5):102-109. **2.** Forsythe E et al. *Front Pediatr*. 2018;6:23. doi: 10.3389/fped.2018.00023.

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Modified Diagnostic Criteria for BBS

- Primary features (four features are required to be present):
  - Rod-cone dystrophy
  - Polydactyly
  - Obesity
  - Learning difficulties
  - Male hypogonadism
  - Renal anomalies

OR

- Three primary plus two secondary features of:
  - Speech disorder/delay
  - Strabismus/cataracts/astigmatism
  - Brachydactyly/syndactyly
  - Developmental delay
  - Polyuria/polydipsia (nephrogenic diabetes insipidus)
  - Ataxia/poor coordination/imbalance
  - Mild spasticity (especially lower limbs)
  - Diabetes mellitus
  - Dental crowding/ hypodontia/small roots/high arched palate
  - Left ventricular hypertrophy/congenital heart disease
  - Hepatic fibrosis

BBS, Bardet-Biedl syndrome.

Reference: Beales P, et al. *J Med Genet.* 1999;36(6):437-446.

Patient Identification

How are individuals with BBS identified?[1-3]

- Siblings with BBS
- Prenatal echogenic kidneys and polydactyly
- Early-onset obesity and developmental delays
- Apparent vision loss and learning difficulties
- Progressive renal disease and other comorbidities
- Retinitis pigmentosa diagnosis that just does not quite fit
- Retinitis pigmentosa genetic screening

BBS, Bardet-Biedl syndrome.

References: 1. Forsythe E, Beales P. *Eur J Hum Genet*. 2013;21:8-13. **2.** Haws M et al. *New Horiz Transl Med*. 2015;2(4-5):102-109. **3.** Centogene NGS Panel – Genetic Testing for Bardet Biedl syndrome. https://www.centogene.com/science/centopedia/ngs-panel-genetic-testing-for-bardet-biedl-syndrome.html. Accessed December 5, 2018.

Primary Concerns of Individuals With BBS[1-3]

- Obesity
- Blindness
- Behavior
- Kidney disease

"That is what for us is the most frightening part about the whole syndrome. Being blind isn't going to kill them one day, but being morbidly obese will."

- Parent of a child with BBS

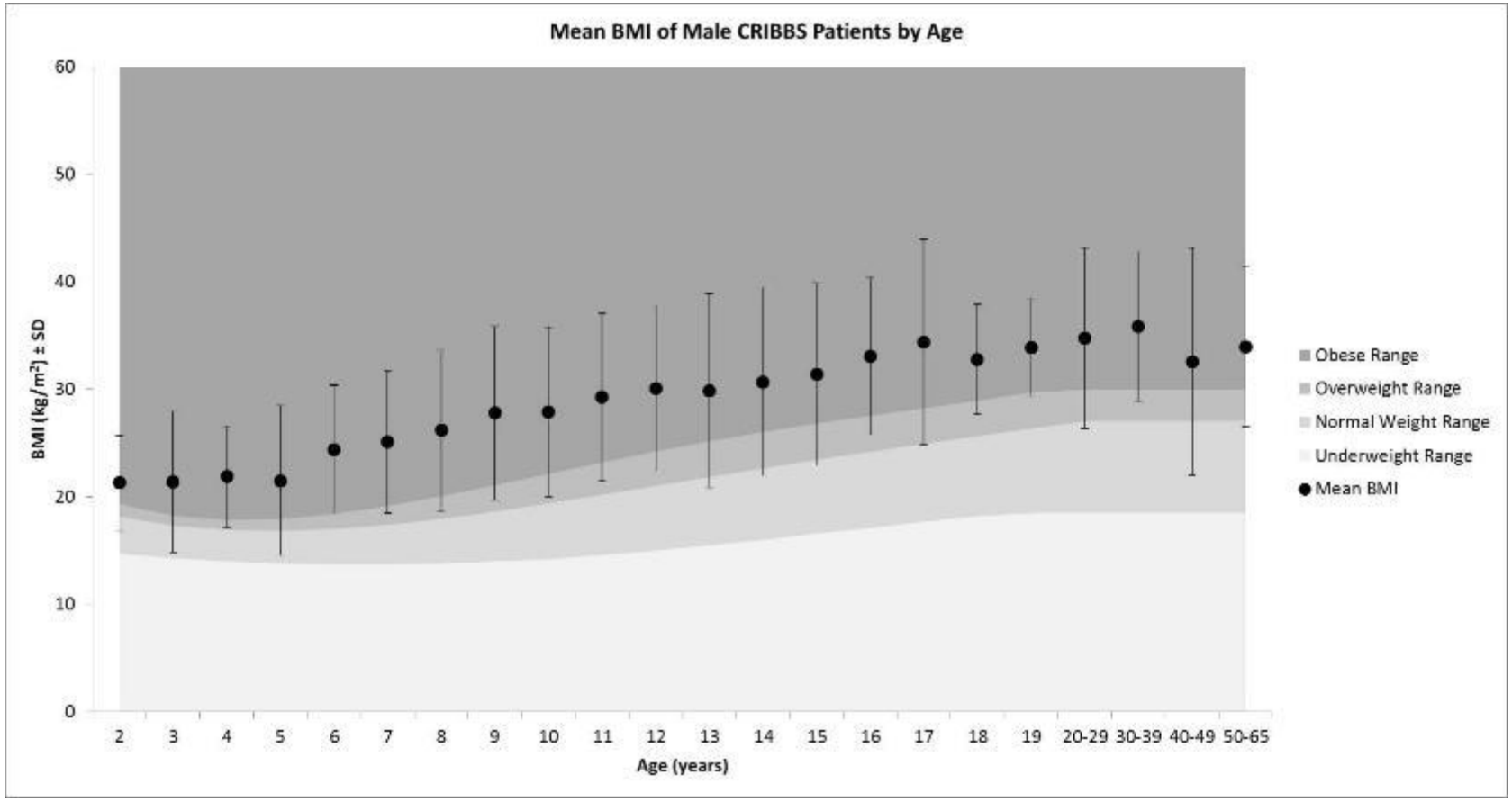
References: 1. Haws M et al. *New Horiz Transl Med*. 2015;2(4-5):102-109. **2.** Forsythe E, Beales PL. *Eur J Hum Genet*. 2013;21(1):8-13. **3.** Zacchia M et al. *Kidney Dis (Basel)*. 2017;3(2):57-65.

Obesity and BBS

"Weight is a huge issue BBS families deal with. People are automatically so much more drawn to help and give compassion to children with vision loss than they are with obesity. People just think we should control the things our kids eat better and get them out to exercise more. I know I would think the same thing if I didn't have Lucy to show me how difficult that really is."

- Parent of a child with BBS

CRIBBS Registry Data



BMI, body mass index; CRIBBS, Clinical Registry Investigating Bardet-Biedl Syndrome.

Reference: CRIBBS Registry. Marshfield Clinic Research Foundation. https://cribbs.marshfieldclinic.org/.

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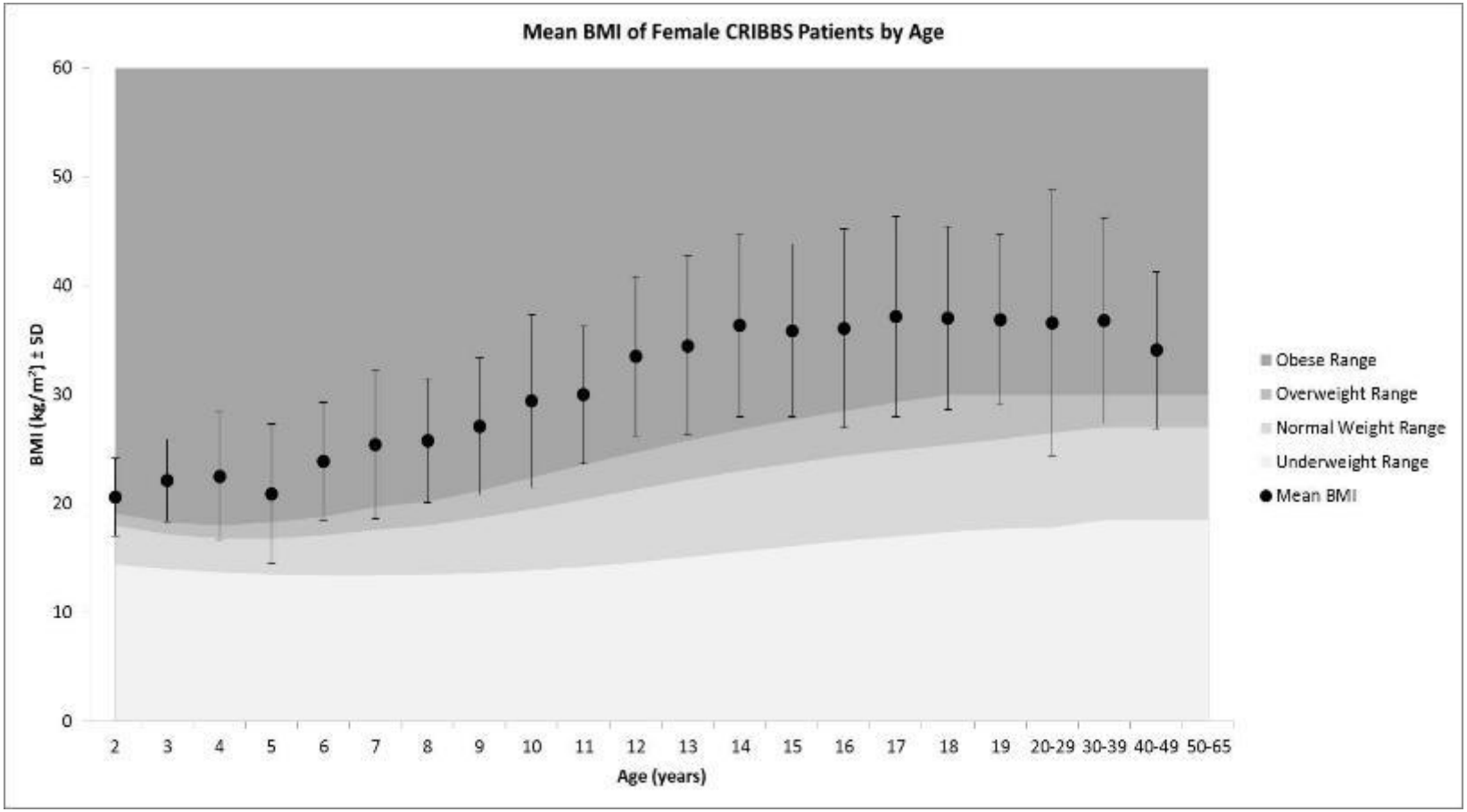
CRIBBS Registry Data (continued)



BMI, body mass index; CRIBBS, Clinical Registry Investigating Bardet-Biedl Syndrome.

Reference: CRIBBS Registry. Marshfield Clinic Research Foundation. https://cribbs.marshfieldclinic.org/.

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Health Consequences in Individuals With BBS[1-3]

- Obesity
- Diabetes mellitus
- Hypertension
- Dyslipidemia
- Obstructive sleep apnea
- Blindness
- Nonalcoholic steatohepatitis
- Chronic kidney disease
- Musculoskeletal disorders
- Mental health disabilities

References: 1. Forsythe E, Beales PL. *Eur J Hum Genet*. 2013;21(1):8-13. **2.** BBS UK. Bardet-Biedl Syndrome Medical Information Booklet. 2016. http://lmbbs.org.uk/LMBBS/file/Medical%20Booklet%202016(1).pdf. Accessed November 27, 2018. **3.** Zacchia M et al. *Kidney Dis (Basel)*. 2017;3(2):57-65.

BBS and Alström Syndrome Clinical Development Updates

Murray W. Stewart, MD, FRCP
Chief Medical Officer

Rhythm's approach to BBS

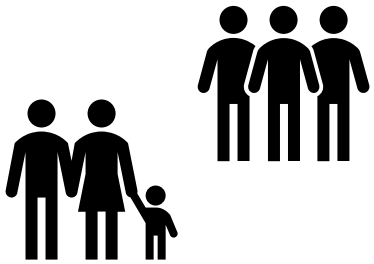
Clinical development program

- Trial design and protocol for Phase 3 trial in patients with BBS and Alström Syndrome

Proposed Indication	Proof of Concept	PRE-CLINICAL	PHASE 1	PHASE 2	PHASE 3
SETMELANOTIDE					
POMC Deficiency	✓				
LEPR Deficiency	✓				
Bardet-Biedl Syndrome	✓				
Alström Syndrome	✓				
POMC Heterozygous Deficiency					
POMC Epigenetic Disorders					

Building the community

- Collaborating with patient advocacy groups and registries



Phase 2 Study Results Support Advancement to Phase 3 Study

	Variant	Sex	Age, years	Treatment, weeks	Weight Change	Hunger Score Reduction
Patient 1	BBS1	Male	25	65	-26% (-37.7 kg)	44%
Patient 2	BBS2	Female	61	55	-15% (-14.5 kg)	86%
Patient 3	BBS10	Female	16	64	-24% (-29.1 kg)	N/A
Patient 4	BBS12	Female	17	50	-24% (-23.1 kg)	83%
Patient 6	BBS5	Female	16	15	-6.8% (-8.32 kg)	66%
Patient 7	BBS4	Female	14	17	-6.6% (-5.81 kg)	21%

- **Three additional patients discontinued treatment**
  - **Patient 5** (a pediatric patient with BBS1 variant and type 1 diabetes) had a 53.3% reduction in hunger and reduction in hemoglobin A1c (10.1% to 7.6%) before withdrawing
  - **Patient 8** (13-year old male; non genetically confirmed) and **Patient 9** (31-year old male; BBS1 variant) withdrew due to lack of weight loss

1. Haws RM et al. Effect of the Melanocortin-4 Receptor Agonist Setmelanotide on Obesity and Hyperphagia in Individuals Affected by Bardet-Biedl Syndrome. ESPE 2018. Abstract RFC6.3.

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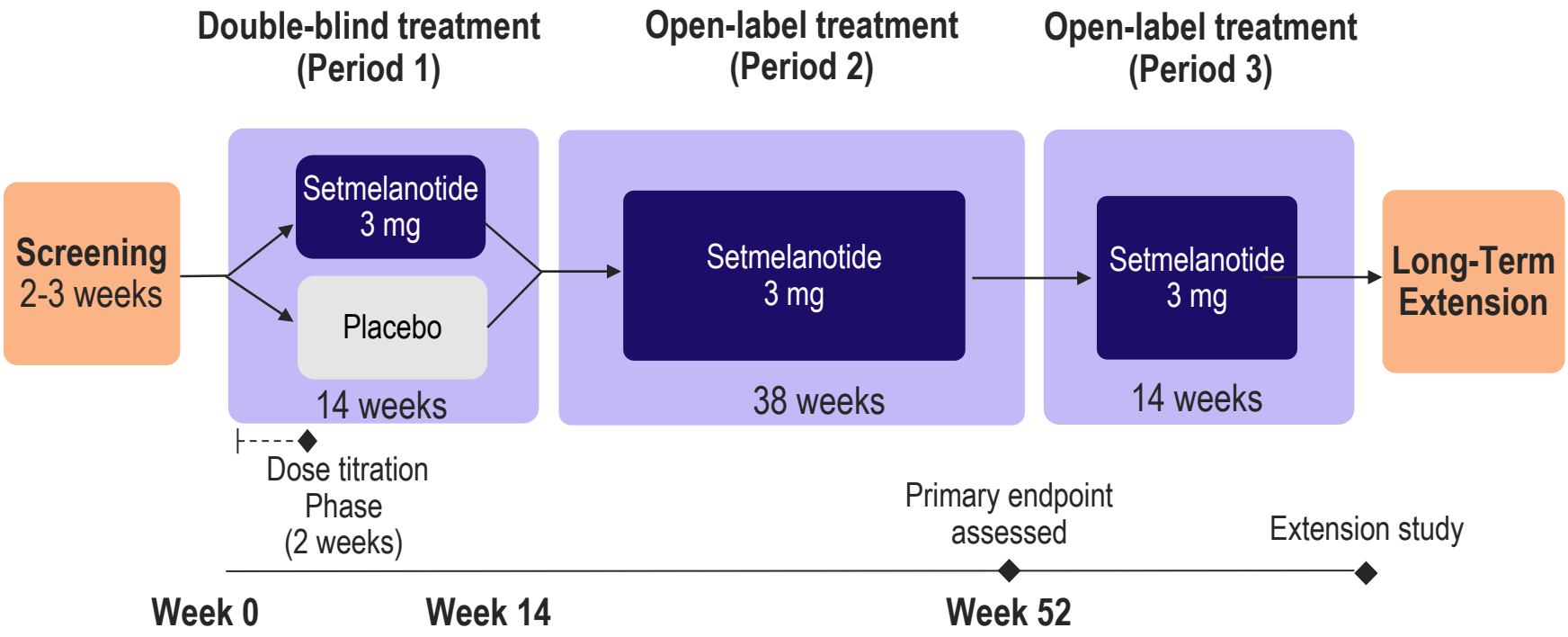
Phase 3 Study Design Endorsed



Primary Endpoint: Proportion of patients (12 years of age and older) who have at least a 10% reduction in body weight at Week 52

Phase 3 Study Update

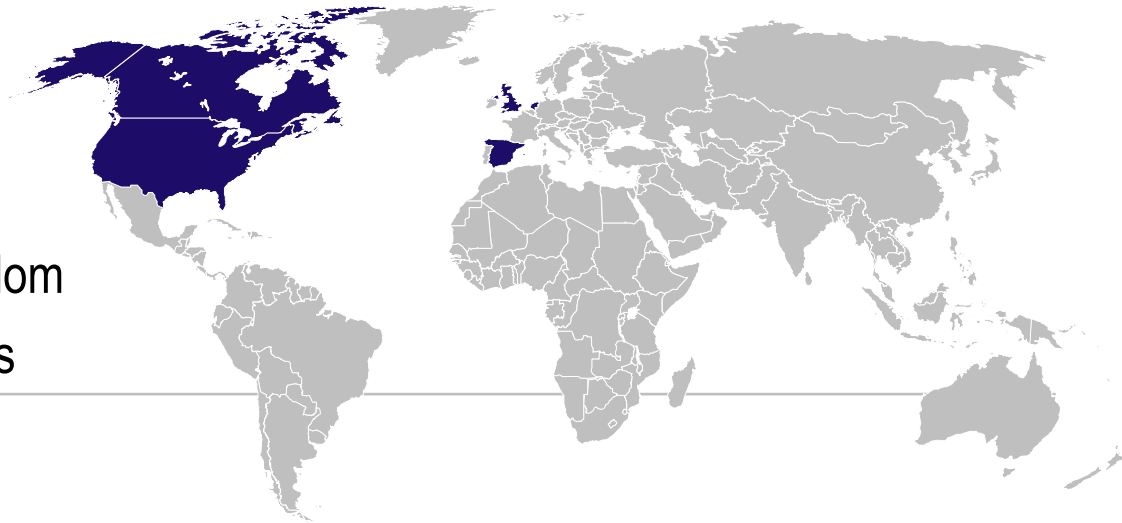
Protocol	▪ Final comments from FDA have been incorporated
Study enrollment milestones	▪ **First patient with BBS enrolled**
Study enrollment goals	▪ Enrollment **minimum**: • 20 BBS patients • 6 Alström Syndrome patients

Phase 3 Study Update

Participants expected to be enrolled and randomized across study centers worldwide

Centers of excellence	▪ Marshfield Clinic Health System
	  ▪ Bob Haws, MD
	▪ University College of London Great Ormand Street Institute of Child Health
	  ▪ Phil Beales, MD

Confirmed countries	▪ Canada ▪ Netherlands ▪ Spain ▪ United Kingdom ▪ United States



Principles of Advocacy

Collaborate with patient advocacy groups to advance the common mission of improving the lives of those living with Rare Genetic Disorders of Obesity

- Increase disease awareness and speed to diagnosis
- Gain feedback on clinical trial design and materials; support enrollment
- Support pathway to regulatory approval
- Support access to treatment and services

Estimated Patients Worldwide

BBS

- 1:100,000 in North America
- 1,500–2,500 patients in US
- 1,000 patients diagnosed and being followed up as part of large cohorts in EU[1,2]

Current CRIBBS Enrollment: 451 patients

- **Goal:** Bring together complex genetic and clinical information from patients with BBS to accelerate research into effective treatments

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Alström Syndrome

- 500–1,000 cases reported worldwide

1. >500 families from BBS UK website: 2 >500 patients with confirmed genotypes from FRA (personal communication)

Summary

- We estimate that BBS affects 1,500–2,500 patients in US
- BBS patients present with hyperphagia and obesity and currently have no effective treatment options
- Setmelanotide has demonstrated efficacy in Phase 2 studies
- Achieved alignment with regulatory authorities in US and EU
- Rhythm has started a global Phase 3 study
- The BBS community is supportive and enthusiastic
- BBS is just one example of setmelanotide's potential

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Q&A


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