rhythm

Targeting rare MC4 pathway defects that result in life-threatening obesity

ASCPT
March 2018

Executive Summary

Targeting MC4 Pathway Defects that Result in Life-Threatening Obesity

Orphan Focus

Strong data in MC4 pathway deficiencies; basis for multiple rare genetic disorders of obesity

- Focus on rare genetic deficiencies targeting MC4 pathway disorders, where setmelanotide has potential to serve as replacement therapy
- Demonstrated proof-of-concept (POC) in POMC deficiency obesity (POMC), LepR deficiency obesity (LepR) and Bardet-Biedl syndrome (BBS)
  - **Dramatic reductions in both weight and hunger**
  - **FDA awarded "Breakthrough Therapy Designation" for POMC and LepR**

Development Plans

Significant potential opportunity across multiple indications

- Phase 3 trials underway in POMC and LepR deficiency obesity; BBS expected to initiate in 2018
- Additional MC4 pathway POC trials initiated in BBS, Alström Syndrome, POMC Heterozygous (Hetz), and POMC Epigenetic disorders
- Focused development program with rapid paths expected to approval

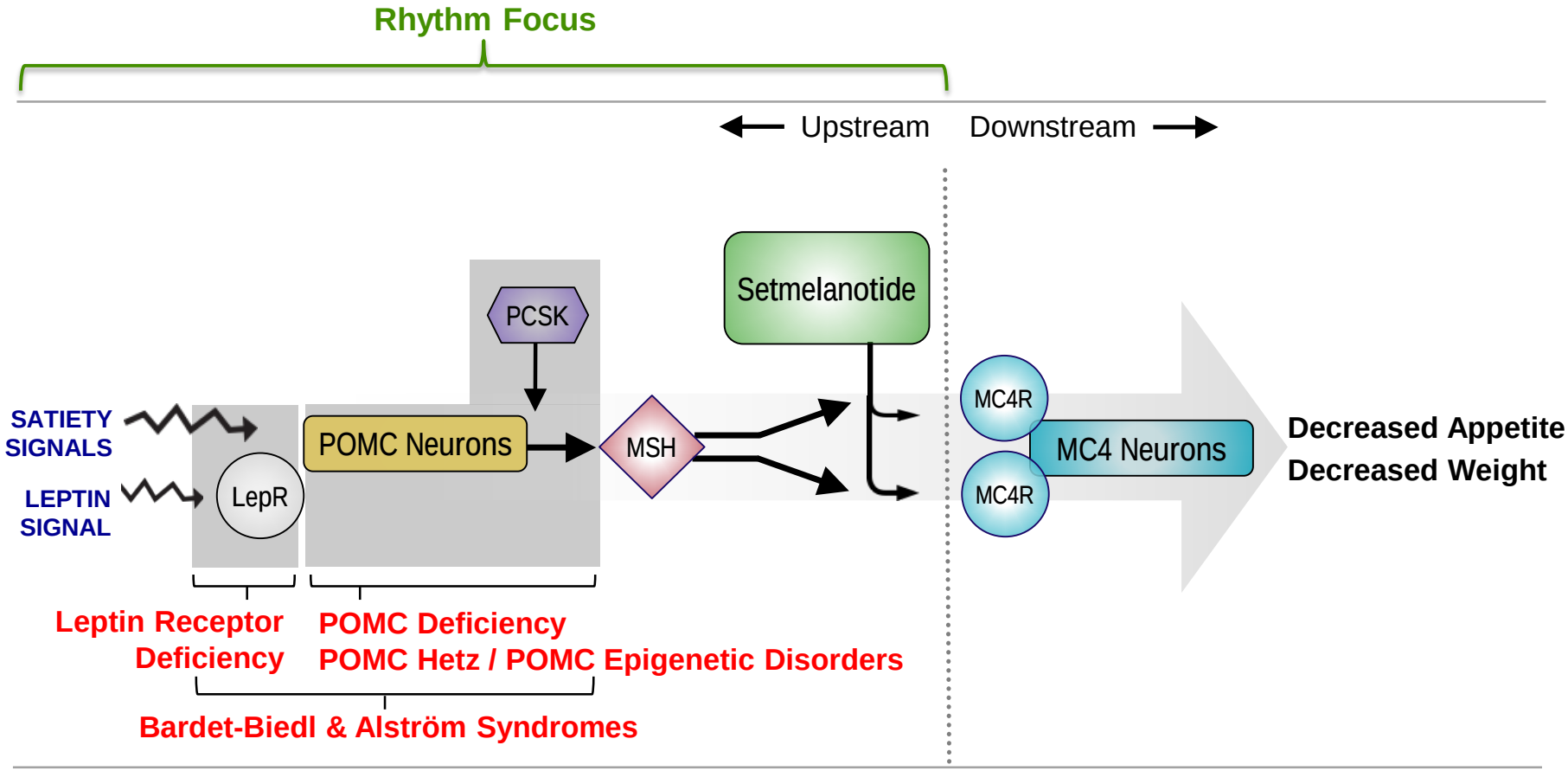
Challenges

- Ultra-rare disorders: challenge to recruitment and commercial plans
- Building rare genetic disorders of obesity community, knowledge, centers of excellence
- Partnership with FDA, EMA and other regulatory agencies
- Design of clinical trials, safety data base, development program

Targeting Upstream MC4 Pathway Defects

- These genetic defects result in severe obesity and hyperphagia
- Setmelanotide, an MC4R agonist, has potential to serve as “replacement therapy”

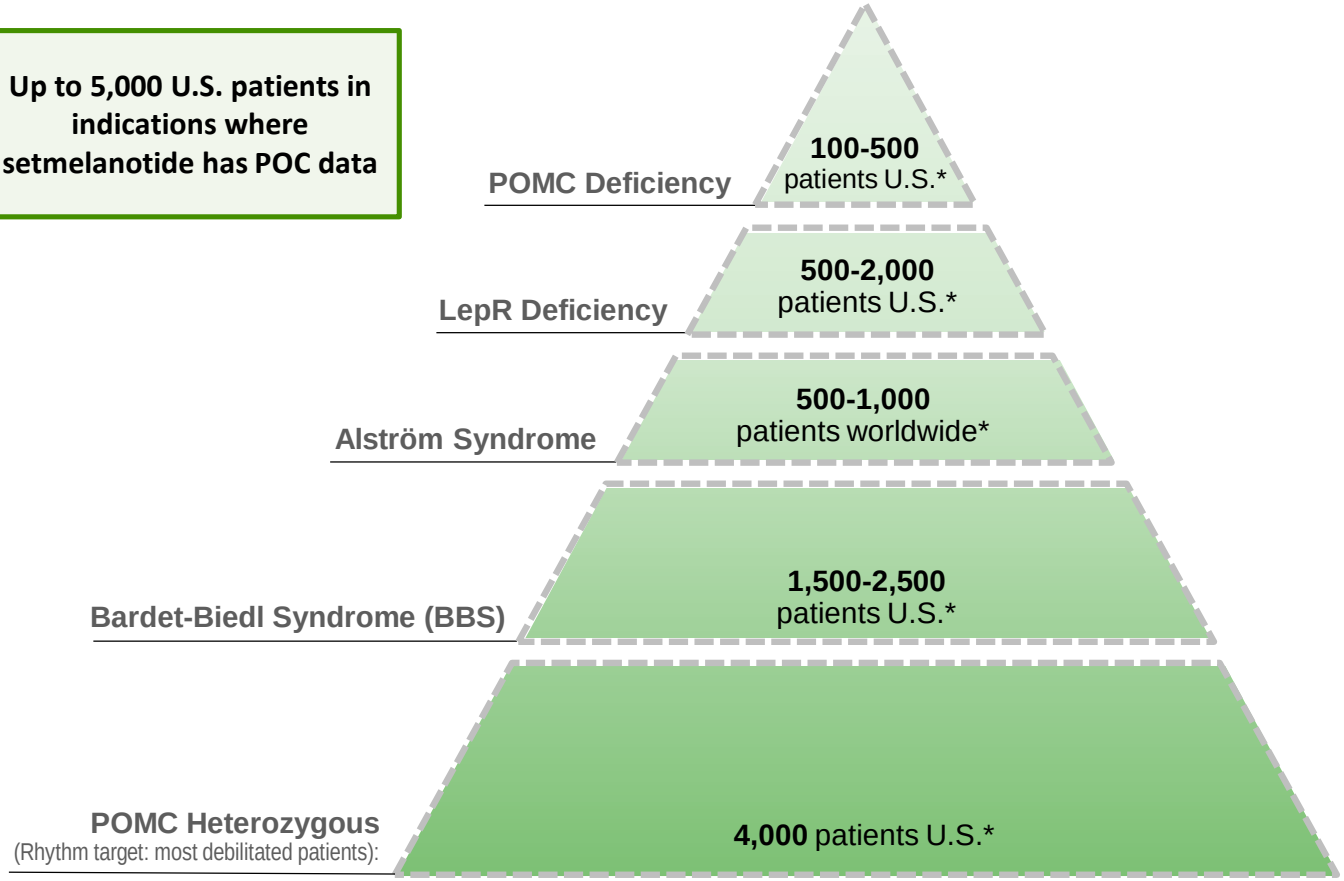
MC4 Pathway



Creemers et al. *Diabetes* 2012; 61:383. Challis et al. Human Molecular Genetics 2002; 11: 1997. Buono et al. *Clinical Chemistry* 2005; 51: 1358. Farooqi. Genetics of Obesity Study (GOOS), unpublished data

Setmelanotide Addresses a Significant Unmet Medical Need†

Up to 5,000 U.S. patients in indications where setmelanotide has POC data



European patient populations believed to be at least as large as those in the U.S. (1)
Potentially a total of 10,000 U.S. and E.U. patients in POMC, LepR and BBS indications

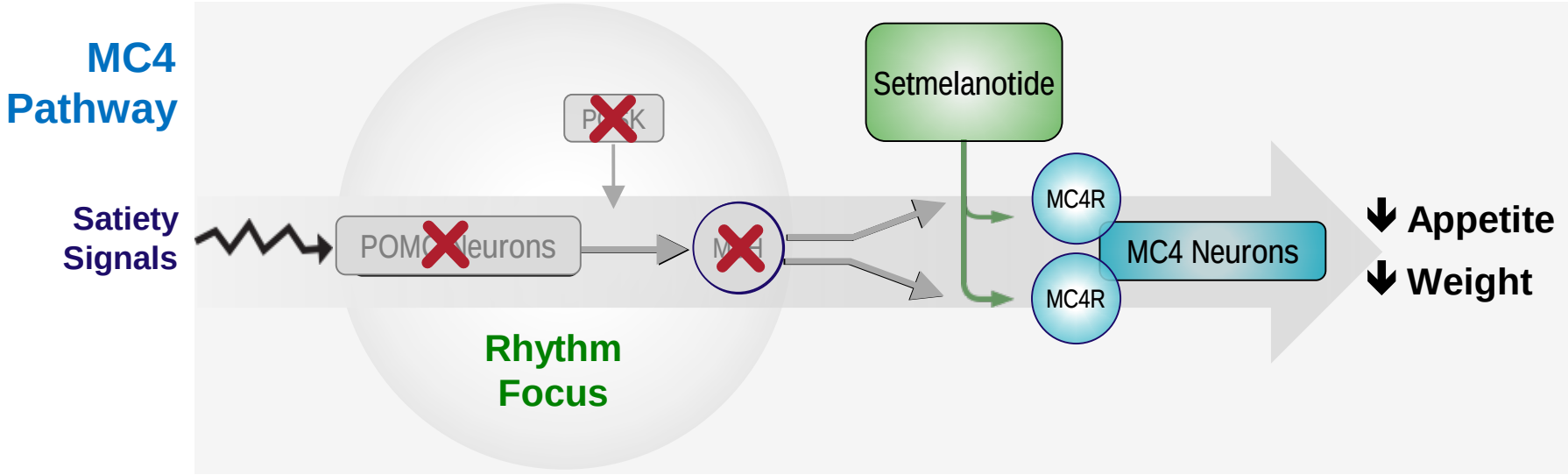
* The patient numbers above are based on company estimates
† Epidemiological estimates not yet available for POMC epigenetic disorders
(1) Rhythm believes that the addressable patient population in Europe is at least as large as in the U.S. However, Rhythm does not have a comparable epidemiological data from the European Union and these estimates are therefore based solely on applying relative population percentages to the Company-derived estimates

Setmelanotide Clinical Development

POMC Deficiency Obesity

POMC Homozygous Patients

- Ultra-rare disorder caused by two different homozygous genetic defects
- Causes severe, early-onset obesity and profound hyperphagia
- 50 patients reported to date; Company estimates U.S. addressable population of 100–500 patients
  - Ongoing Rhythm genetic epidemiology study suggests significant potential upside to these patient numbers



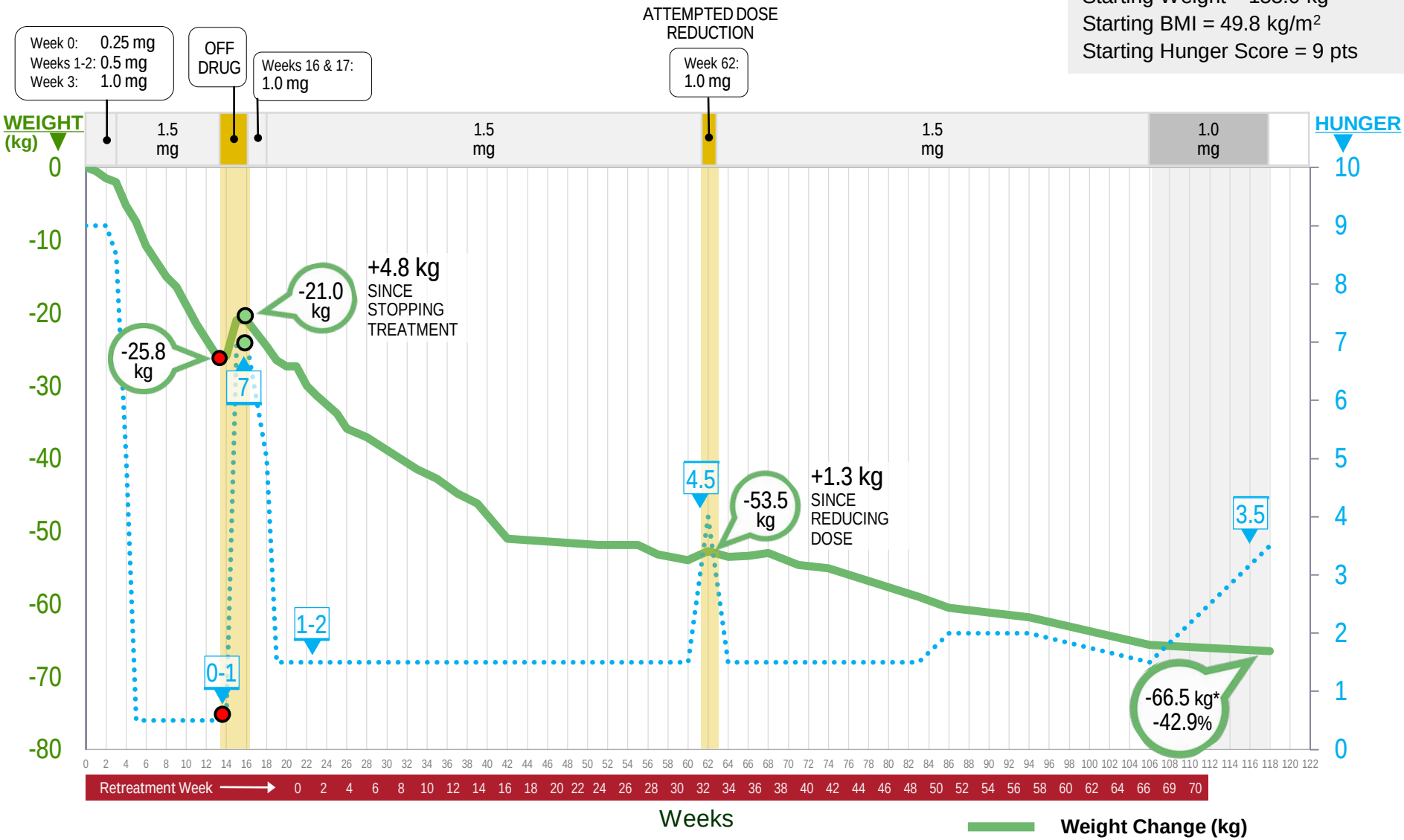
Clinical Status

- Phase 2 data (N=2 patients) published in NEJM
- FDA and EMA have helped at every stage, working to address the challenges
- FDA Breakthrough Designation
- Phase 3 ongoing
  - n=10, ~1-year duration, primarily open-label design

POMC Deficiency Obesity Phase 2 Study: Patient #1

Now on Treatment >2 Years

20 yr old female
Starting Weight = 155.0 kg
Starting BMI = 49.8 kg/m^2
Starting Hunger Score = 9 pts



* Figures represent cumulative weight lost in kgs

Strategy & Priorities

Priorities For Setmelanotide:

- Improve methods of **evaluation and diagnosis** of rare genetic obesity patients through:
  - Enhanced diagnostic capabilities
  - Partnership with KOLs and pediatric endocrinologists
  - Defining the mutations (variants) that are pathogenic
- Facilitate an **integrated genetic obesity community** through:
  - The rare genetic obesity community is underdeveloped, outside of the Prader Willi Syndrome community
  - Need to build services that support patient awareness, education, advocacy and treatment
  - This is almost “start from scratch”
- Communicate the **burden of rare genetic obesity** syndromes to:
  - Promote advocacy for patient sequencing, and
  - Support pricing and reimbursement of setmelanotide

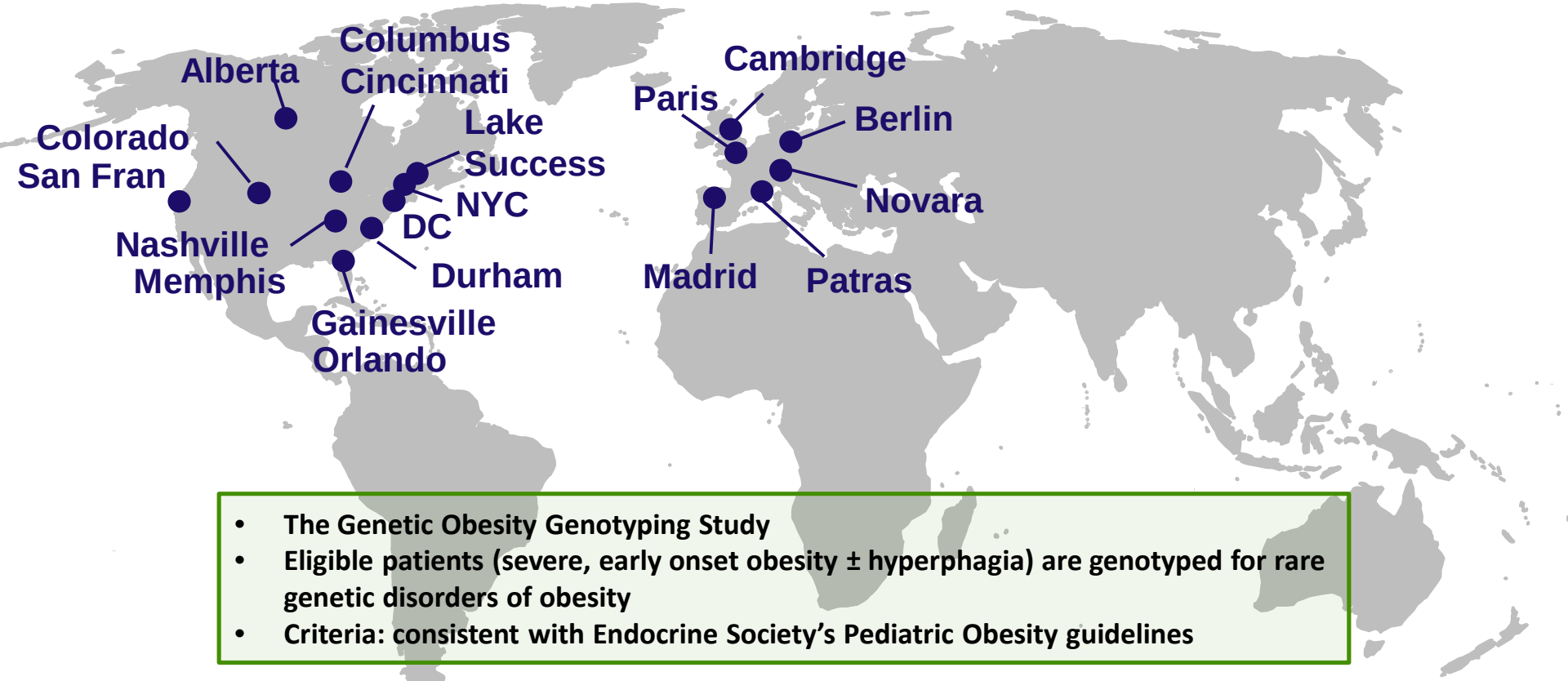
Critical Issue:

- Diagnosing and bringing to treatment the appropriate patients with rare genetic disorders of obesity

Genotyping Study: Sites in North America and Europe*

Goal of the Genotyping Study

To develop a screening algorithm for selecting patients to be genotyped and diagnosed with rare genetic obesities



- The Genetic Obesity Genotyping Study
- Eligible patients (severe, early onset obesity ± hyperphagia) are genotyped for rare genetic disorders of obesity
- Criteria: consistent with Endocrine Society's Pediatric Obesity guidelines

* Representative sites participating are indicated on the map


rhythm