Rhythm Research and Development Event

September 25, 2019

Forward Looking Statements

This presentation contains certain statements that are forward-looking within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, and that involve risks and uncertainties, including statements regarding Rhythm's expectations for 2019 and 2020, anticipated timing for enrollment, design and completion of clinical trials, the timing for filing of an NDA, the release of results of clinical trials, estimates of treatable patient populations, the efficacy of setmelanotide in patients with new indications, and Rhythm's strategy, prospects and plans. Statements using word such as "expect", "anticipate", "believe", "may", "will" and similar terms are also forward-looking statements. Such statements are subject to numerous risks and uncertainties, including but not limited to, our ability to enroll patients in clinical trials, the outcome of clinical trials, the impact of competition, the ability to achieve or obtain necessary regulatory approvals, risks associated with data analysis and reporting, our expenses, and other risks as may be detailed from time to time in our Annual Reports on Form 10-K and quarterly reports on Form 10-Q and other reports we file with the Securities and Exchange Commission. Except as required by law, we undertake no obligations to make any revisions to the forward-looking statements contained in this presentation or to update them to reflect events or circumstances occurring after the date of this presentation, whether as a result of new information, future developments or otherwise.

Today's Agenda

Introductions

Hunter Smith, Chief Financial Officer

Welcome and Overview

Keith Gottesdiener, M.D., Chief Executive Officer

Science Behind New Indications

Alastair Garfield, Ph.D., Vice President of Translational Research and Development

Update on Epidemiology Estimates

Keith Gottesdiener, M.D., Chief Executive Officer

Rhythm Engine, Basket Study and Update on Phase 2 Bardet-Biedl Syndrome Patients

Murray Stewart, M.D., Chief Medical Officer

Bardet-Biedl and Alström Syndromes Community Building and Patient Finding

Nithya Desikan, Chief Commercial Officer

Closing Remarks and Q&A

Welcome

Keith Gottesdiener, M.D.
Chief Executive Officer

Welcome to Rhythm's Fall 2019 R&D Event

4 **new indications** being added to Phase 2 Basket Study

Growing database now with sequences of

13,567

people with early-onset, severe obesity

Sequencing yield and updated **epidemiology** for pivotal and basket indications

Rhythm Engine and what it's designed to accomplish

Progress in programs for **Bardet-Biedl and Alström syndromes**

Rhythm Achievements on the Road to Changing the Paradigm with a Much-needed Therapy for Rare Genetic Disorders of Obesity

Translational Research and Genetics

- Added **high-impact heterozygous (HET)** obesity to **Basket Study** and presented preliminary clinical data demonstrating consistent weight and hunger responses
- Launched **Uncovering Rare Obesity**, a free genetic testing program
- Launched **TEMPO** registry and **GO-ID** trial

Clinical Advancement

- Secured **Breakthrough Therapy** and **EMA PRIME** designations for POMC, LEPR, BBS & Alström
- Achieved **positive Phase 2** Bardet-Biedl & Alström syndromes results
- Enrolled first patient in pivotal Phase 3 study in BBS & Alström
- **Completed enrollment in** POMC Phase 3 trial
- Completed enrollment in LEPR **Phase 3 trial**
- Initiated Phase 2 trial for **once-weekly** formulation of setmelanotide
- **Met all primary and key secondary endpoints** for weight loss and reduction in hunger in **POMC and LEPR Phase 3 trials**

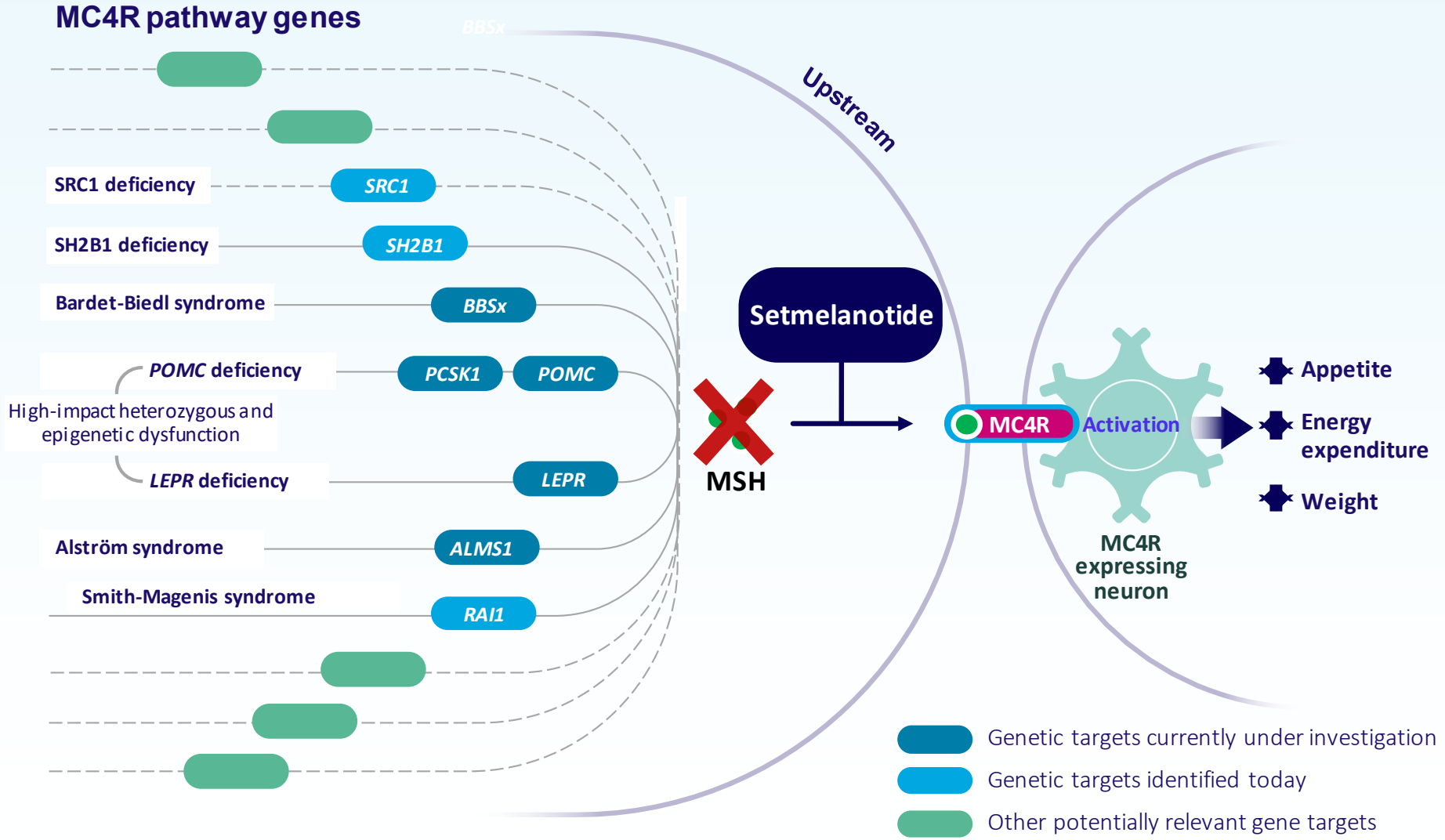
Expand Basket Study and provide update on genetic sequencing and patient finding

Today's Focus is on New Indications and Patient Finding

These Rhythm initiatives remain on track

- POMC and LEPR deficiency obesities pivotal data and registration
  - Presentations of data at major medical meeting expected during 4Q2019
  - U.S. New Drug Application submission on track to be completed 4Q2019/1Q2020
- High-impact HETs progressing in Rhythm Basket Study; update coming in 2020
- Commercialization approach for POMC/LEPR - 1H2020

Setmelanotide has Potential to Address Multiple Genetic Disorders that Disrupt MC4R Pathway Function

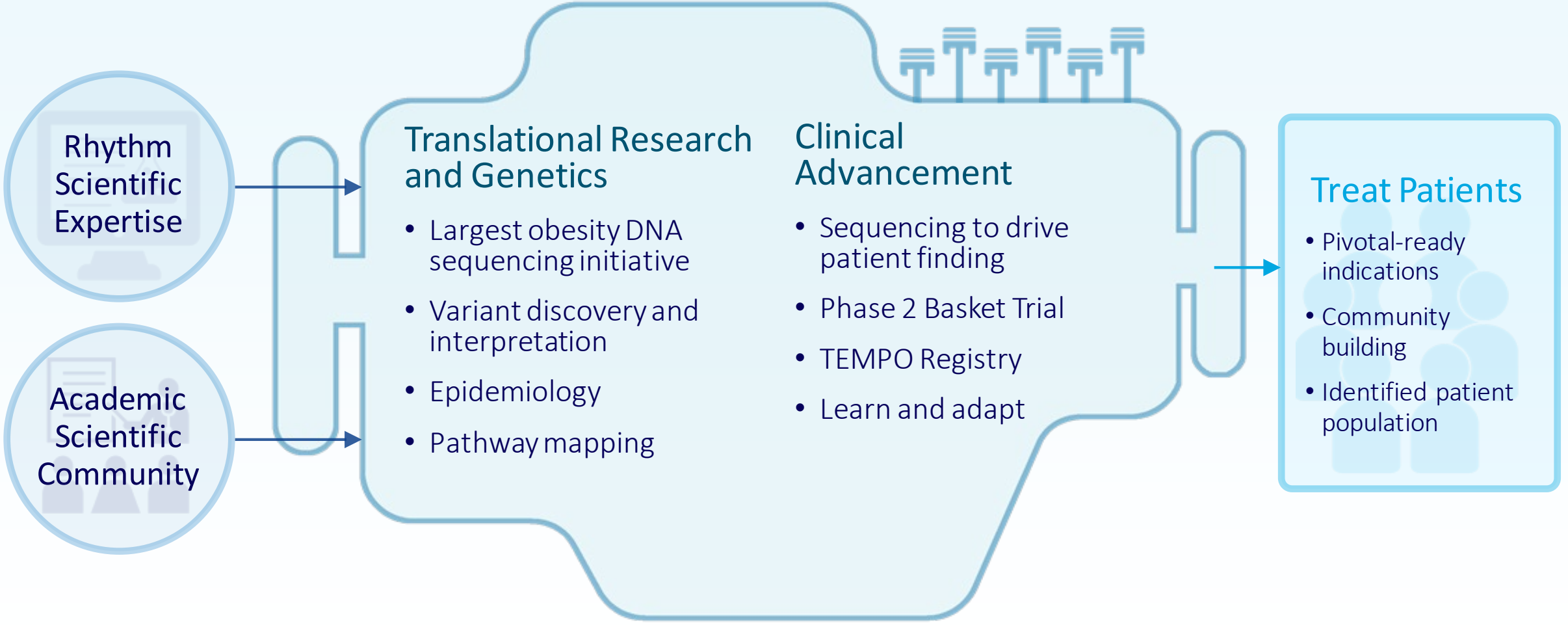


- POMC deficiency obesity
- LEPR deficiency obesity
- Bardet-Biedl syndrome
- Alström syndrome

- High-impact heterozygous deficiency obesity
- Epigenetic disorders

- SRC1 deficiency obesity
- SH2B1 deficiency obesity
- Smith-Magenis syndrome
- MC4R deficiency obesity

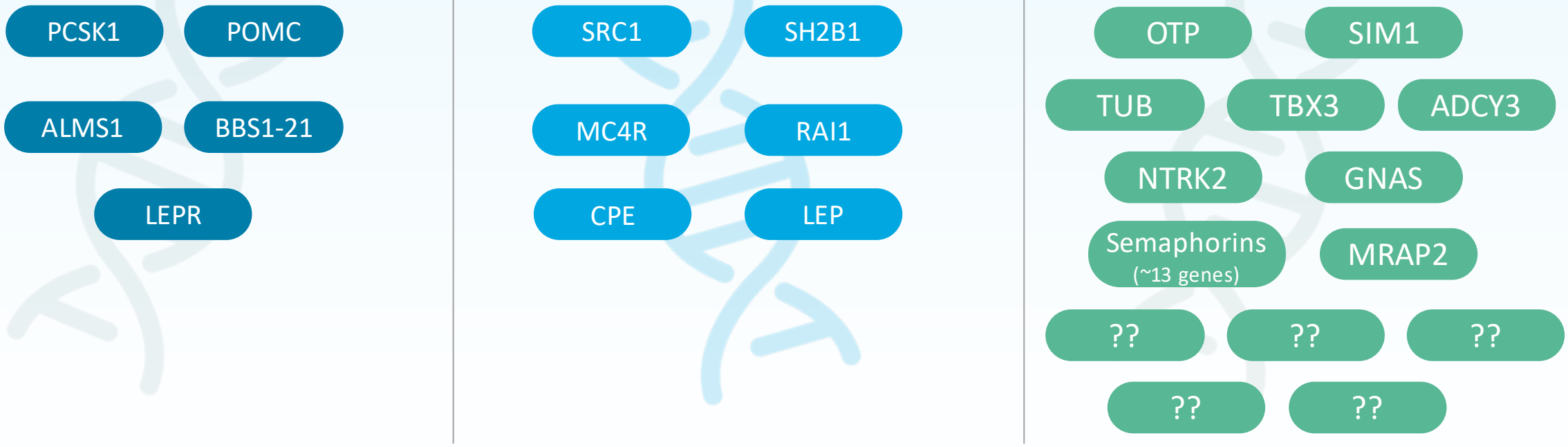
Rhythm Engine Drives Understanding and Treatment of Rare Genetic Disorders of Obesity



Science Behind New Indications

Alastair Garfield, Ph.D., Vice President of
Translational Research and Development

Numerous MC4R Pathway Genes Implicated in Rare Genetic Disorders of Obesity

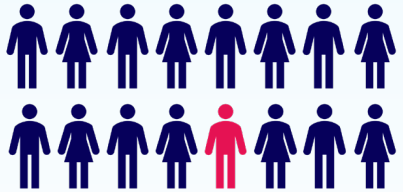


Rhythm PHARMACEUTICALS

MC4R Pathway Disorders: Genetic or Syndromic Diagnosis

Genetically-identified

POMC, LEPR deficiency obesities;
High-impact HETs



Patients diagnosed after genetic screening

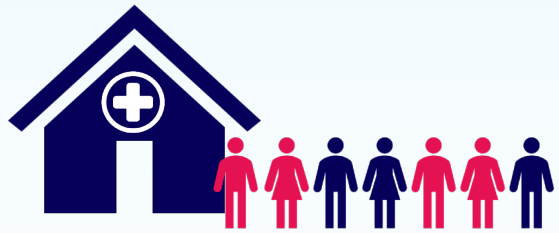
SRC1 deficiency obesity

MC4R deficiency obesity

SH2B1 deficiency obesity

Clinically-identifiable, syndromic

BBS and Alström syndrome

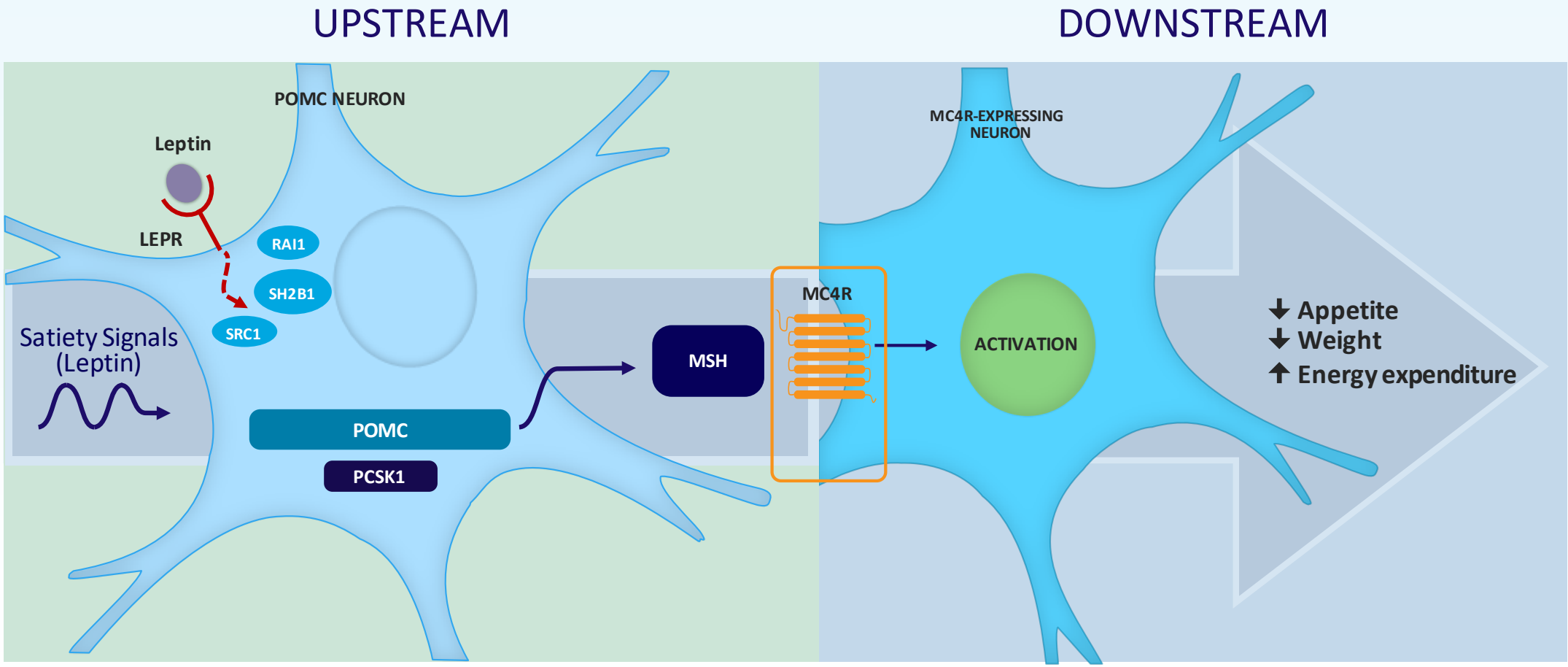


Patients often known to the medical system

Smith-Magenis syndrome

Images are for illustrative purposes only and not intended to imply or suggest actual prevalence estimates or patient identification yields.

New MC4R Pathway Indications Based on Proven Scientific Rationale



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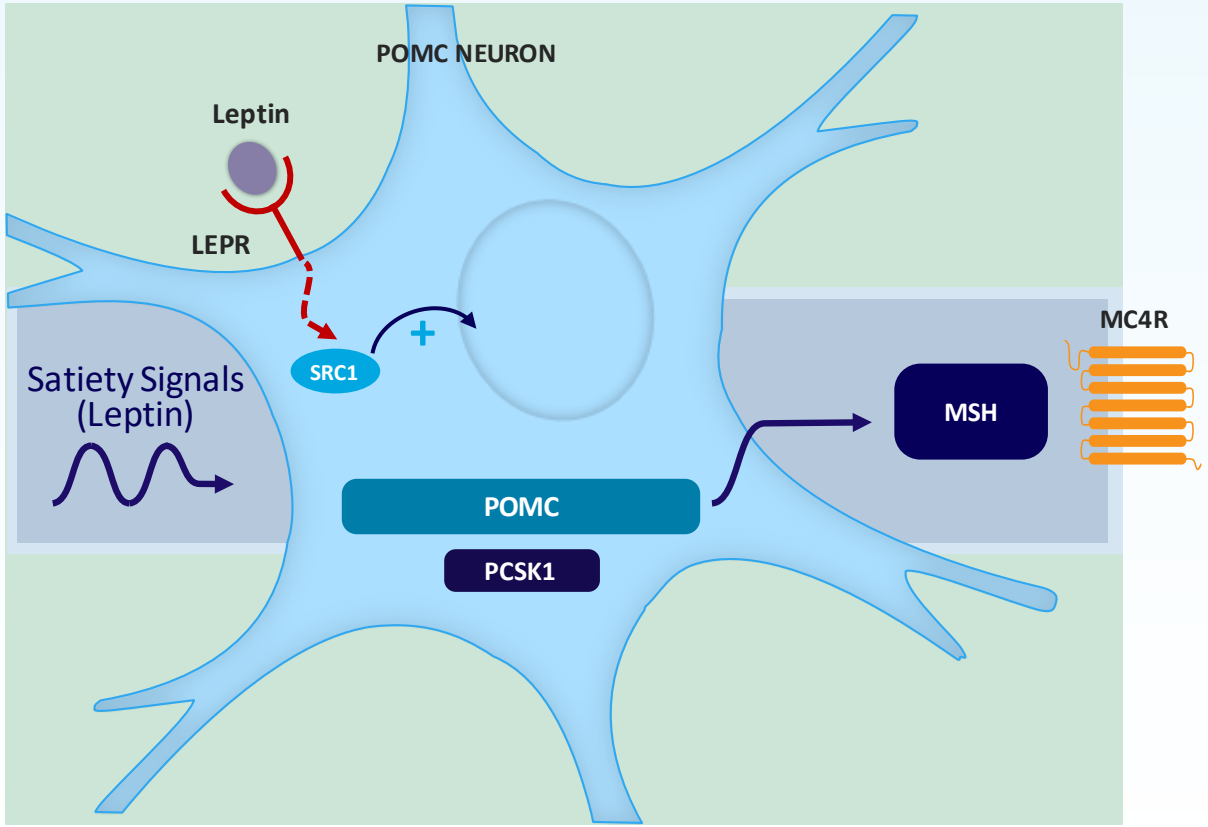
SRC1 is a Transcriptional Coactivator that Drives POMC Expression



Pathway Relevance: Drives POMC Expression

- Transcriptional coactivator activated downstream of LEPR
- Found in POMC neurons

Autosomal Dominant

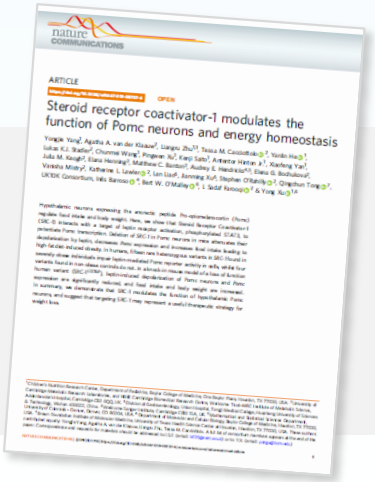
- Obesity arises due to heterozygous gene variants

Clinical Presentation

- Early onset obesity and hyperphagia
- Hyperleptinemia

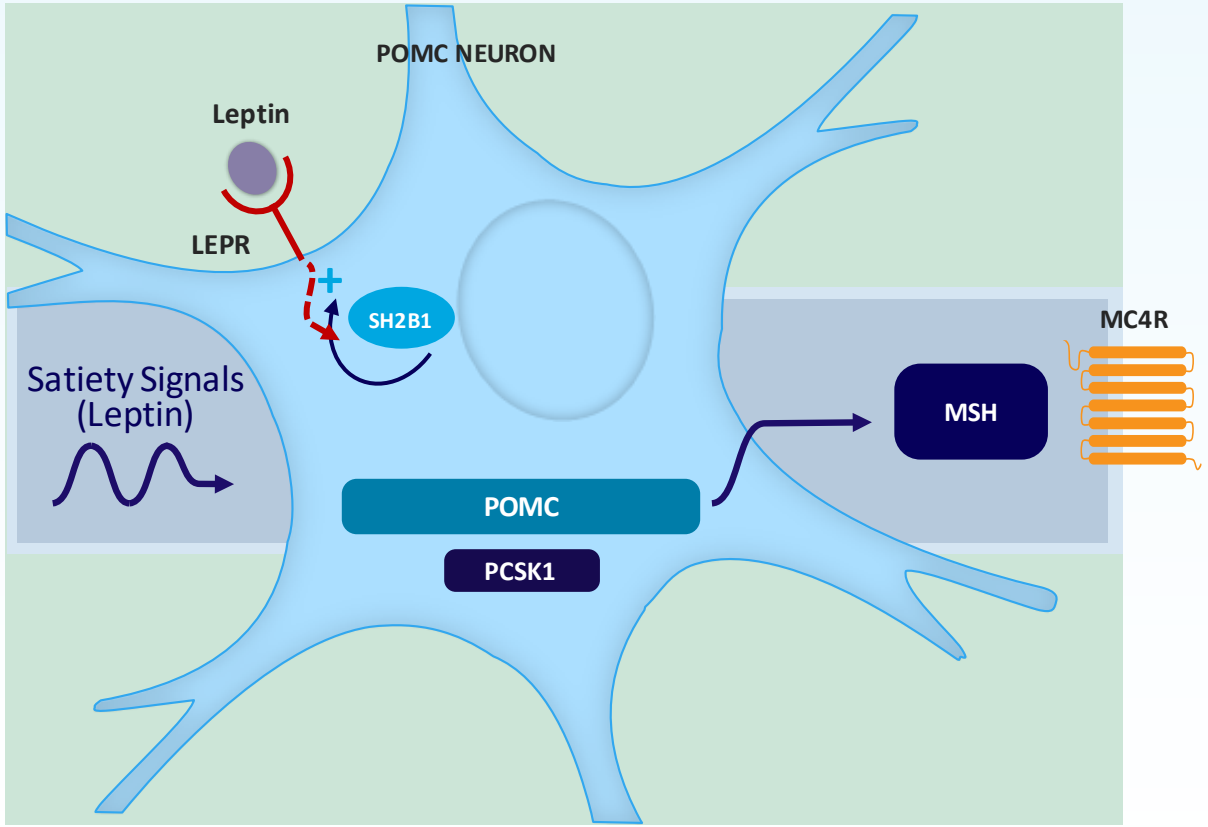
Citations

- Yang et al 2019, Nat Comm. 10, Article 1718



Rhythm PHARMACEUTICALS

SH2B1 is an Adapter Protein that Regulates LEPR Activity



Pathway Relevance: **Regulates LEPR activity**

- Adapter protein
- Found in POMC neurons

Autosomal Dominant

- Obesity arises due to heterozygous gene variants or chromosomal deletions

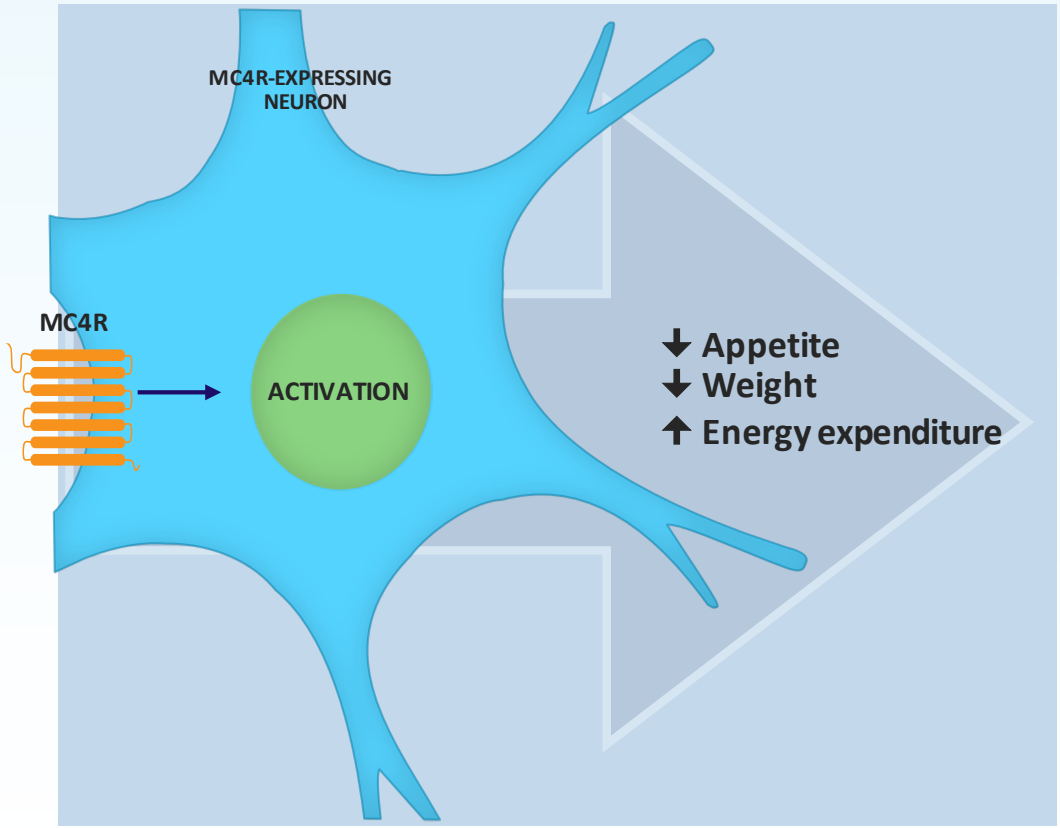
Clinical Presentation

- Early onset obesity and hyperphagia
- Hyperinsulinemia

Citations

- Doche et al 2011, JCI, 122; 4732
- Ockukova et al 2010, Nature, 463; 666

MC4R: Receptor for POMC Ligand MSH



Pathway Relevance: **Receptor for POMC ligands**

- Required for satiety effects of α/β-MSH

Autosomal Dominant

- Obesity arises due to heterozygous gene variants

Clinical Presentation

- Early onset obesity and hyperphagia

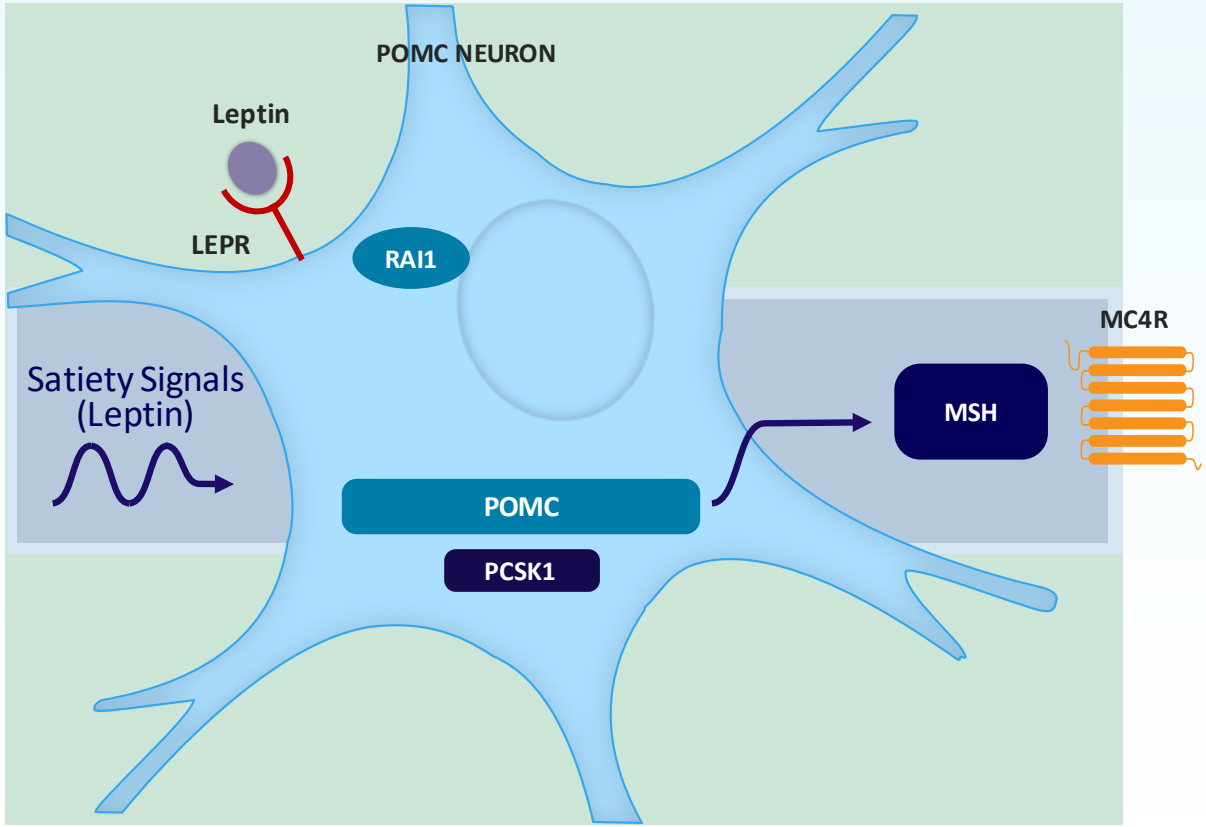
Setmelanotide

- Pharmacological target for setmelanotide
- Rhythm conducted small, 4-week PhIb study in MC4R deficiency obesity
- Rhythm biochemical studies indicate that setmelanotide can rescue specific MC4R variants
- Current indication is focused on rescuable MC4R variant carriers

Citations

- Farooqi et al 2003, NEJM, 348; 1085
- Collett et al 2017, Molecular Metabolism, 6; 1321

Smith-Magenis Syndrome Obesity: RAI1 Affects POMC Expression



Pathway Relevance: Decreased Pathway Function Upstream of MC4R

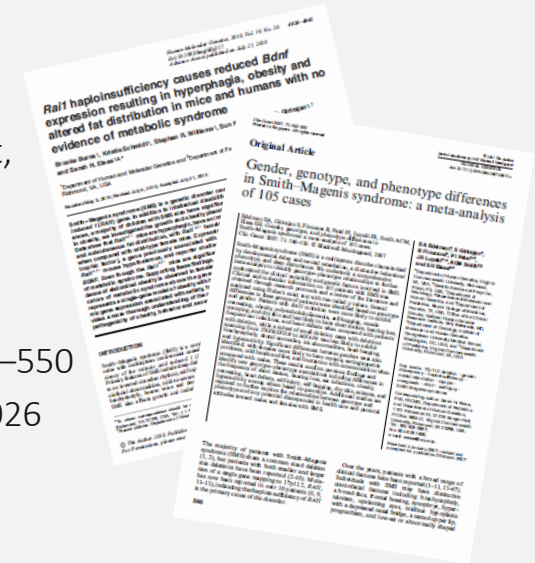
- Causal gene is RAI1
- Transcription factor for a number of pathway genes

Autosomal Dominant

- Gene variants and chromosomal deletions

Clinical Presentation

- Adolescent obesity and hyperphagia
- Sleep disturbance, cognitive impairment, craniofacial anomalies, low energy expenditure


Rai1 haploinsufficiency causes reduced Bdnf expression resulting in hyperphagia, obesity and altered fat distribution in mice and humans with no evidence of metabolic syndrome

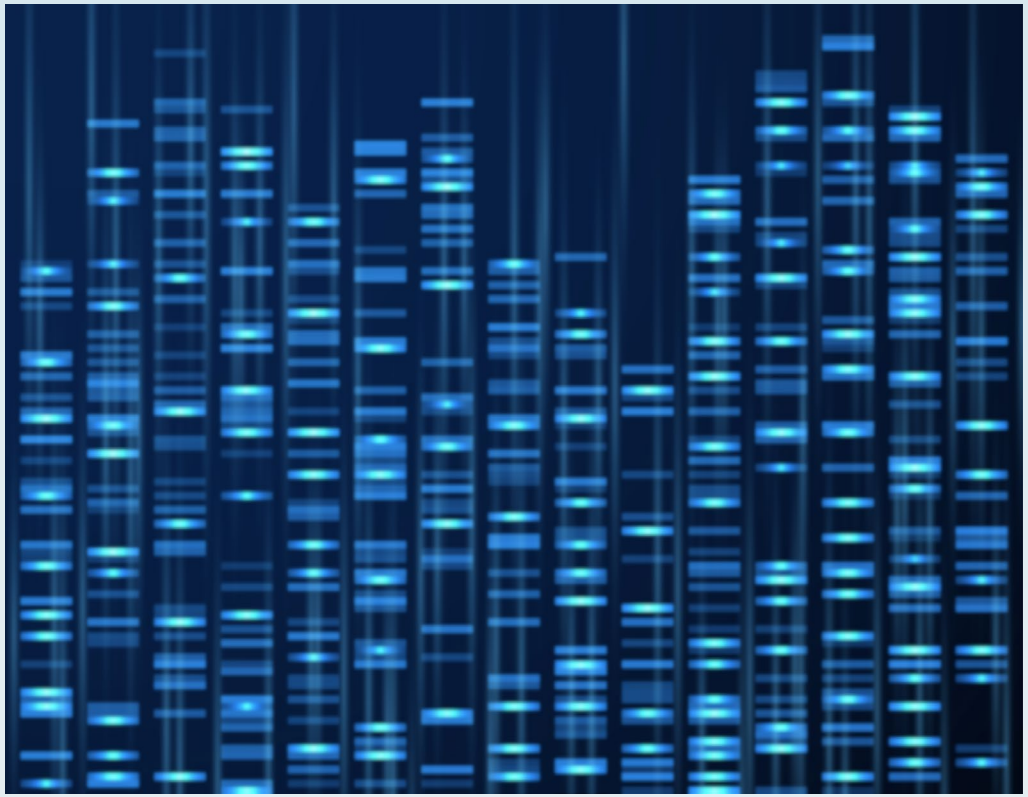
Original Article

Gender, genotype, and phenotype differences in Smith–Magenis syndrome: a meta-analysis of 105 cases

Citations

- Edelman et al 2007, Clin Genet; 71: 540–550
- Burns et al 2010, Hum. Mol. Gen; 19; 4026

Leveraging Sequencing Data to Build a Better Understanding of Genetics Underlying Obesity



101 Gene Panel for Obesity

- Clinically relevant obesity genes
- Research based genes
- Not all associated with MC4R pathway

There's an Art to the Science of Rhythm's Genotyping Strategy

Rhythm's growing **DNA sequencing database** for clinically obese individuals

Severe obesity
+
rare genetic variants

Epidemiology

Rhythm's robust internal infrastructure drives epidemiological analysis of MC4R-pathway obesity disorders based on clinically relevant cohort data (obese and lean)

Biochemical Screening

Rhythm has established a deep biochemical **screening strategy** for **functional testing** of genetic variants in trial eligible MC4R-pathway obesity disorders

Individuals with a *rare genetic variant* that contributes to their *severe obesity*

Epidemiology Estimates for MC4R Pathway-driven Disorders

Keith Gottesdiener, M.D.
Chief Executive Officer

Building the Largest Genetic Database for Severe Obesity

Clinical Characteristics:

Early-onset obesity

Obesity is **severe**

BMI> 40* as adults

Rhythm's growing database has

13,567

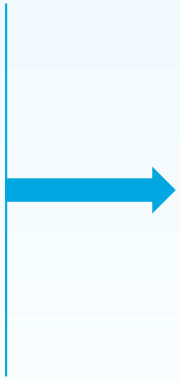
samples**

* For children under 12, included those who are 1.4 X 95th percentile for weight; ** As of June 2019.

Sequencing Focused on Genetically-identified Rare Disorders of Obesity

Individuals with severe obesity sequenced

13,567



Number of genetically-identified individuals who may be eligible for **Rhythm Basket Study**:

1,584

Yield = 11.7%

With 'rarity filter' of <1% frequency applied

Severe obesity
+
rare genetic variant

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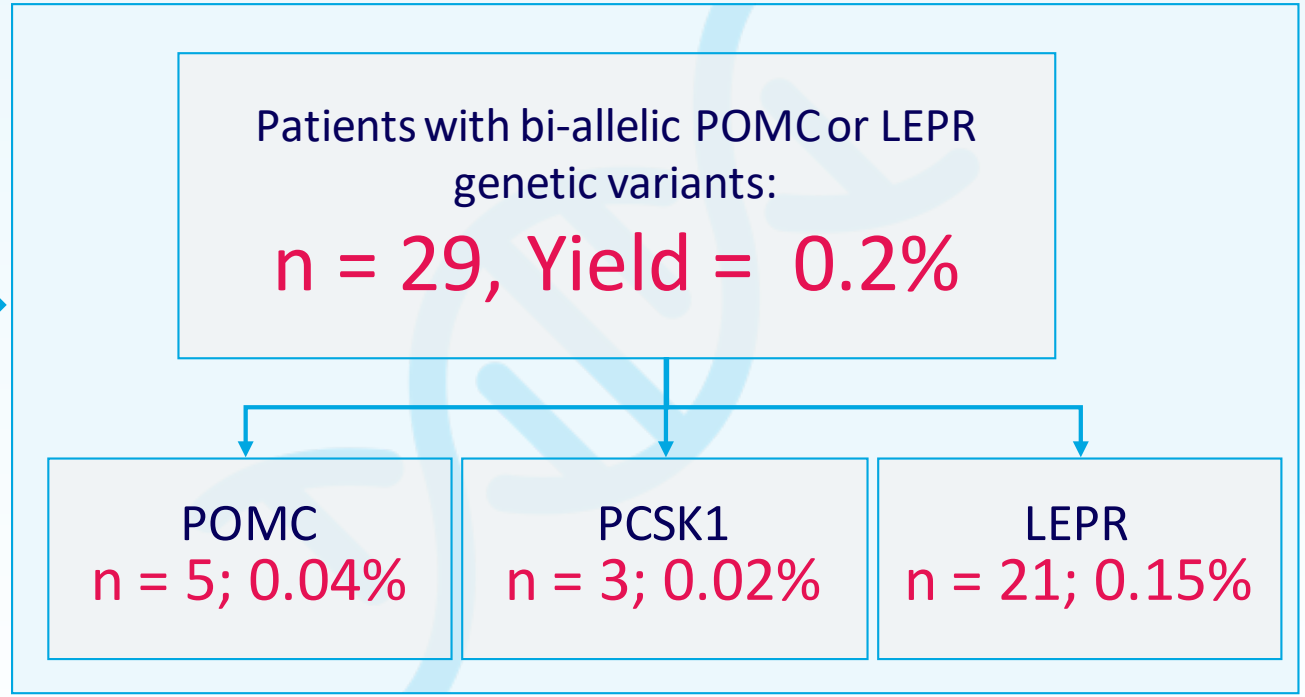
Sequencing Yield Supports Ultra-rare Populations in POMC and LEPR Deficiency Obesities

Individuals with severe obesity sequenced

13,567

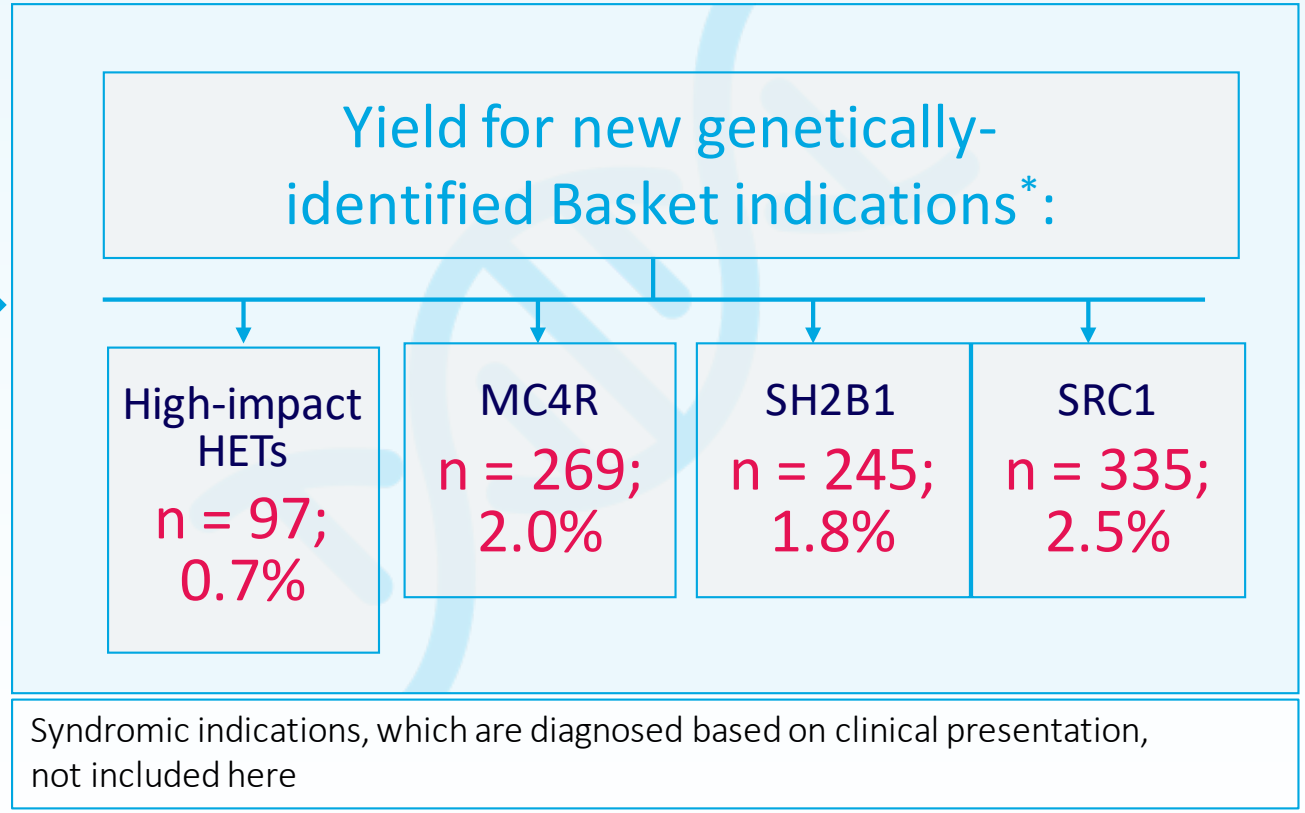


Consistent with Rhythm's U.S. clinical epidemiology estimates of 100-500 for POMC deficiency obesity and 500-2,000 for LEPR deficiency obesity

Sequencing Yield for New Basket Indications Points to Significant Opportunity

Individuals with severe obesity sequenced

13,567



Syndromic indications, which are diagnosed based on clinical presentation, not included here

*Basket yield includes 683 individuals with other variants; some patients have more than one variant.

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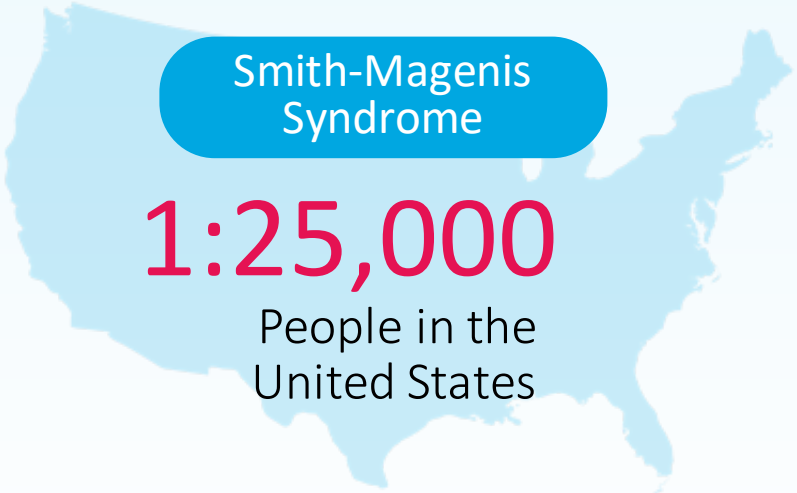
Obesity Affects a Meaningful Portion of Patients with Smith-Magenis Syndrome



10%
of patients have RAI1 variants

90%
of patients have 17p11.2 chromosomal deletion

U.S. epidemiology estimate of SMS patients living with severe obesity:

67%
of SMS patients with RAI1 variant live with obesity*

13%
of SMS patients with 17p11.2 deletion live with obesity*

U.S. epidemiology estimate of SMS patients living with severe obesity	> 2,400

* Elsea and Girirajan, European Journal of Human Genetics, 16;412-421 (2008)

Translating Rhythm Sequencing Data to U.S. Prevalence Estimates

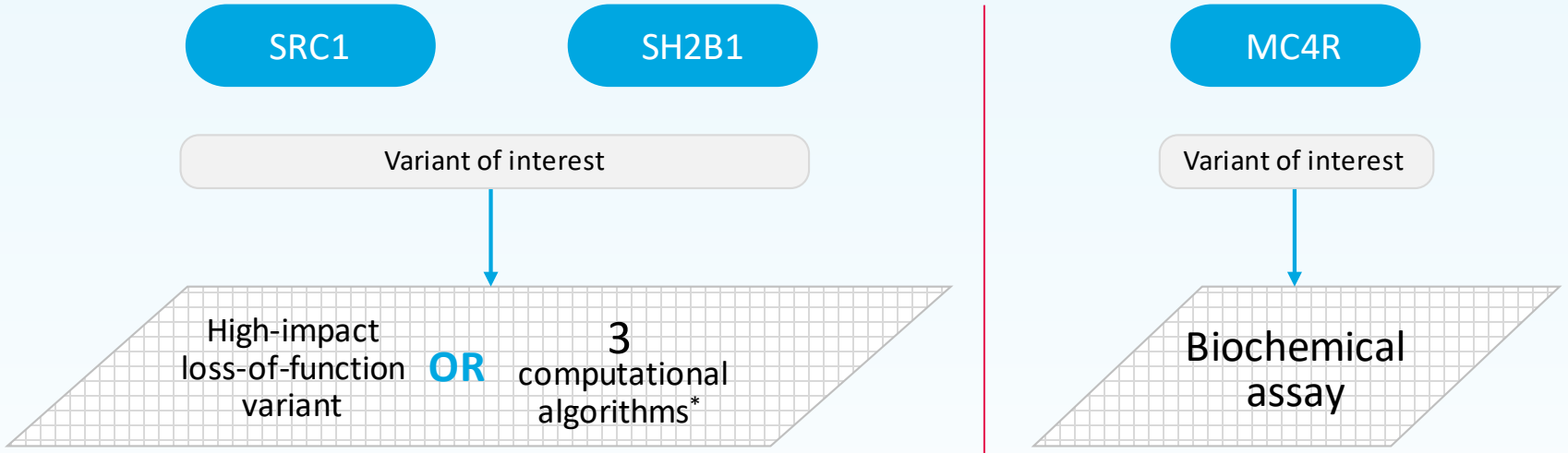
Individuals with obesity and rare variant

↓

Functional and computational filters

↓

Prevalence estimates:
Obesity associated with variant



>23,000** patients with **SRC1** deficiency obesity

>24,000** patients with **SH2B1** deficiency obesity

>10,000** patients with MC4R deficiency obesity with a potentially rescuable variant

*** PolyPhen**: Adzhubei IA, et al. Nat Methods 7(4):248-249 (2010); **SIFT**: Vaser R, et al. Nat Protocol 4:1073-1081 (2009); **Mutation Taster**: Schwarz J.M., et al. Nat. Methods 11(4):361-362 (2014) ** Company estimates calculated based on the following assumptions: US pop 327 million; 1.7% has early onset, severe obesity (Hales et al in JAMA – April 2018: Trends in Obesity and Severe Obesity Prevalence in US Youth and Adults by Sex and Age, 2007-2008 to 2015-2016); Allele frequency based on Rhythm genetic sequencing (June 2019)

U.S. Prevalence Estimates for MC4R Pathway-driven Rare Genetic Disorders Obesity

New indications > 60,000*

SRC1 deficiency obesity
SH2B1 deficiency obesity
Smith-Magenis syndrome
MC4R deficiency obesity

High-impact HETs: > 20,000*

Pivotal indications: up to 5,000*

POMC deficiency obesity
LEPR deficiency obesity
Bardet-Biedl syndrome
Alström syndrome

* Company estimates calculated based on the following assumptions: US pop 327 million; 1.7% has early onset, severe obesity (Hales et al in JAMA – April 2018: Trends in Obesity and Severe Obesity Prevalence in US Youth and Adults by Sex and Age, 2007-2008 to 2015-2016); Allele frequency based on Rhythm genetic sequencing (June 2019); Company also estimates that EU prevalence is similar for each indication.

Rhythm Engine and the Basket Study

Murray Stewart, M.D., Chief Medical Officer

Rhythm Engine: Identifying Patients, Discovering Diseases and Advancing a Therapy

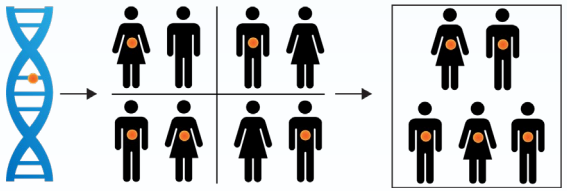
GO ID genotyping

UNCOVERING RARE OBESITY

Sponsored genetic testing program

Biobanks

Phase 2 Basket Study



TEMPO

TRACING THE EFFECT OF THE MC4R PATHWAY IN OBESITY

Uncovering Rare Obesity Program Broadens Access to Genetic Testing and Facilitates Diagnosis of Rare Genetic Disorders of Obesity

Raise Awareness

Elevate awareness and increase suspicion of rare genetic disorders of obesity (RGDO)

Increase Frequency of Genetic Testing

Providing simple and efficient genetic testing program

Improve Access to Genetic Testing

Offering no-cost genetic testing option

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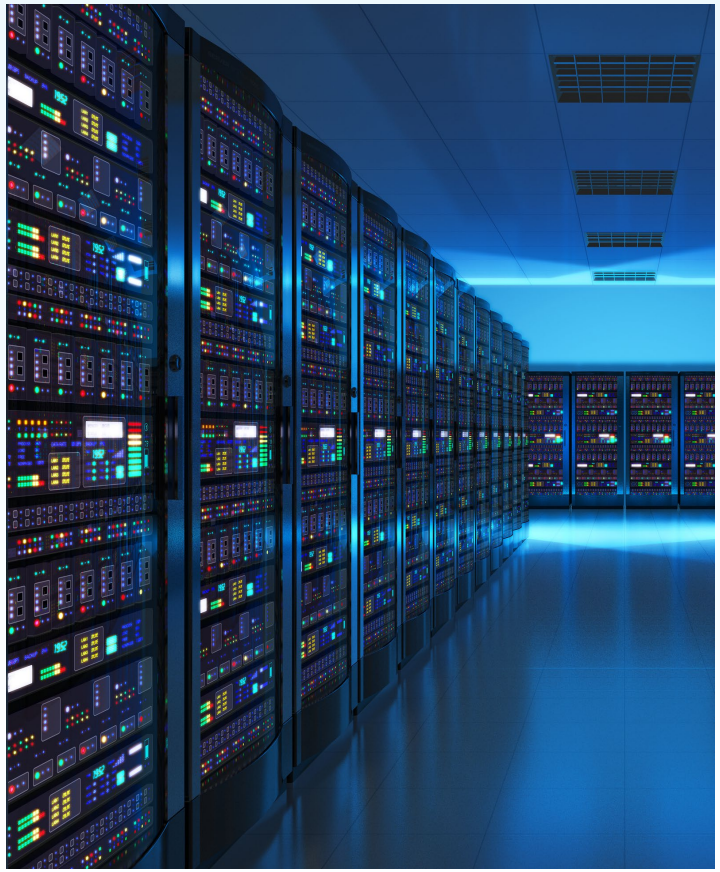
Biobanks Providing Large Data Sets for Patient Identification and Furthering Disease Understanding



Established collaborations with

9

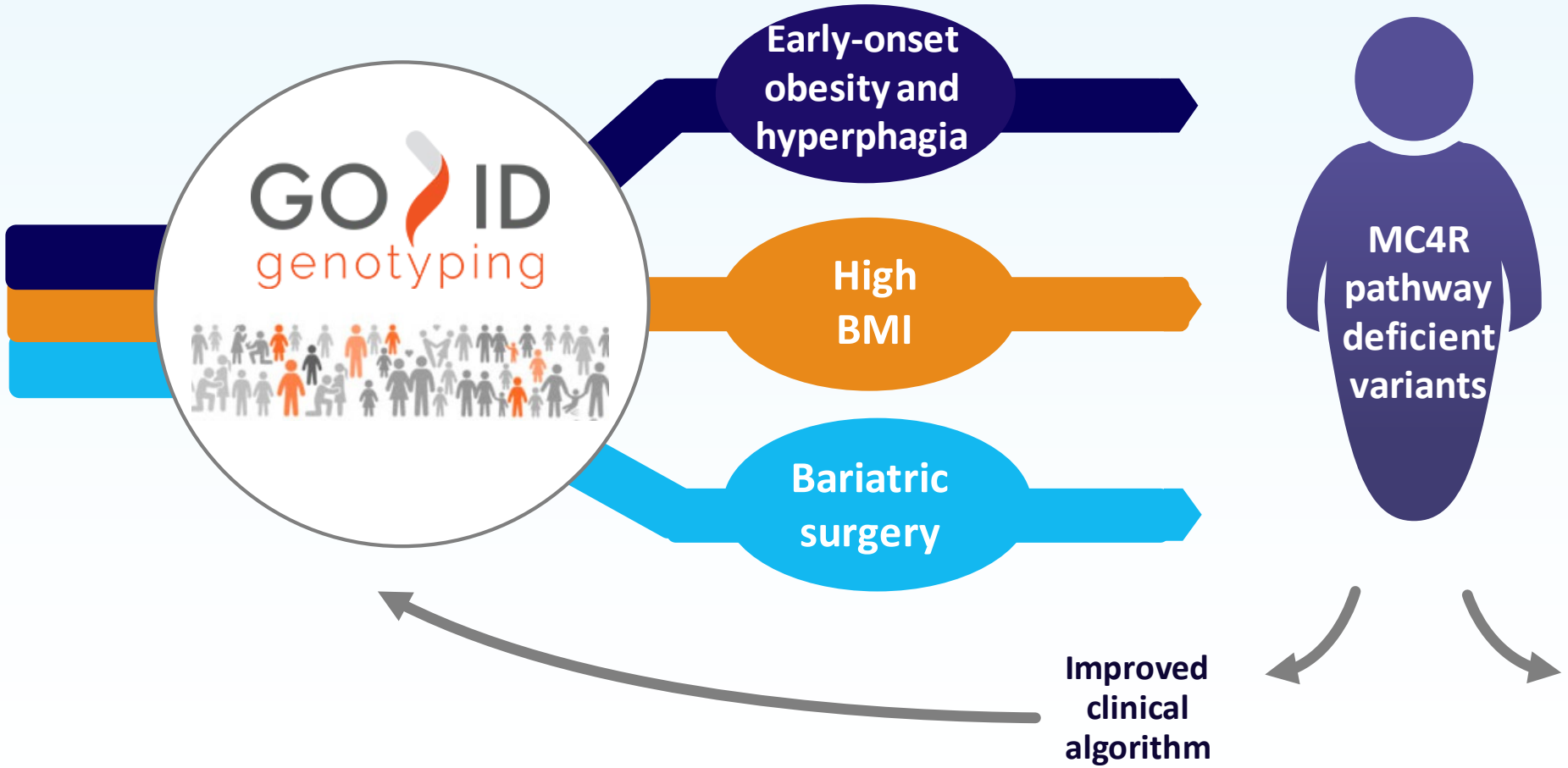
well-known biobanks giving Rhythm access to sequencing data from

23,000

individuals with severe obesity

- Identification of eligible patients for potential trial enrollment and treatment
- Data for variant characterization
- Evaluation of clinical features that may be predictive of genotypes of interest

GO-ID Driving Genetic Testing and Patient Finding while Evaluating and Enriching Distinct Patient Subsets



81
sites

9
countries

Significant overlap with Basket Study

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Community Building Through the TEMPO Registry

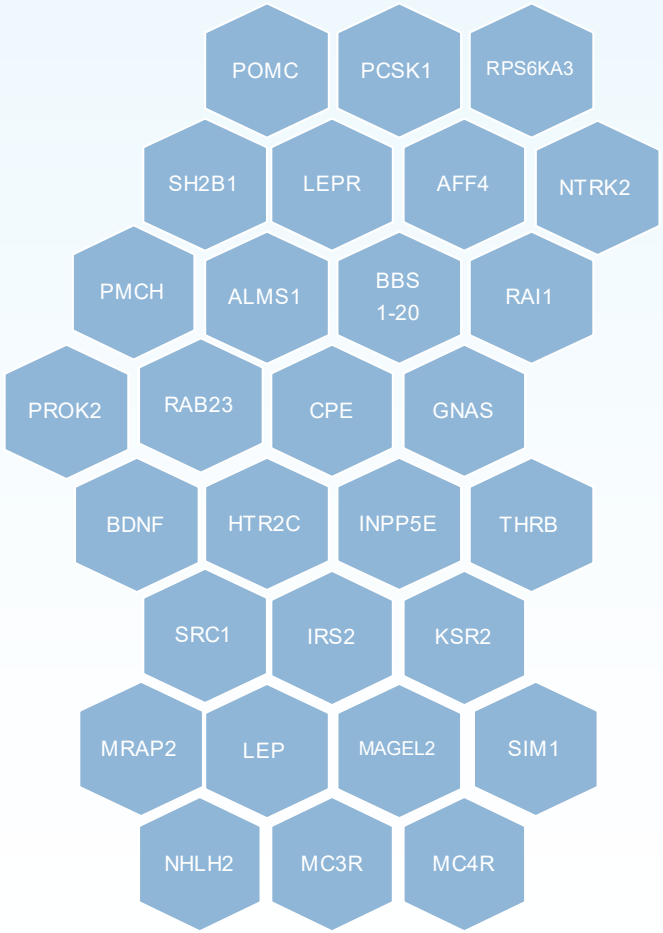
TEMPO

TRACING THE EFFECT OF THE MC4R PATHWAY IN OBESITY

Designed to complement existing patient registries (e.g. CRIBBS for BBS) and to facilitate **better understanding of rare genetic disorders of obesity** in the medical community

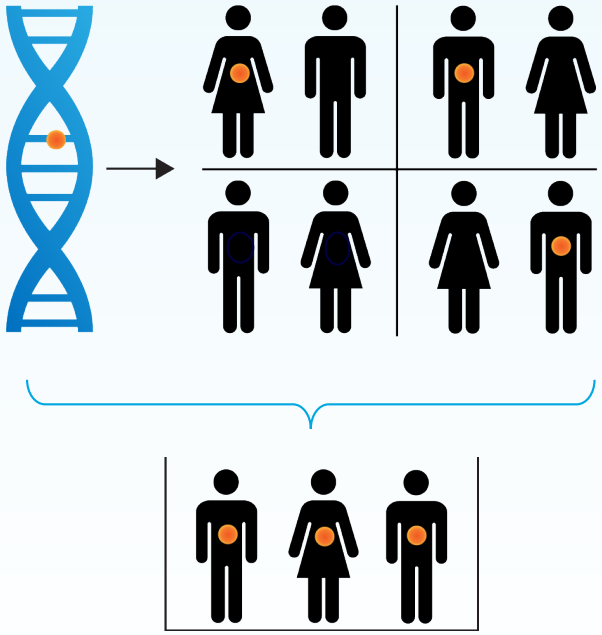
- Target enrollment of ~1,000 patients
- Genetic screening through GO-ID
- Potential enrollment in Phase 2 basket studies

TEMPO is for individuals with specific variants in the MC4R pathway genes, that include at least one of the following:



Basket Study Key to Proof of Concept, Advancing Indications to Phase 3

- Improve understanding of interplay of genetic variation and MC4R pathway function
- Aim for seamless integration with sequencing efforts
- Rapid proof-of-concept in new indications
- Delivers pivotal indications into phase 3 trials



- Multiple cohorts of HETs patients enrolled
- Enrolling patients in new indications

Images are for illustrative purposes only and not intended to imply or suggest actual prevalence estimates or patient identification yields.

Updated Phase 2 Data in BBS Show Continued Responses at ~Two Years

	Gene	Treatment, weeks	Weight Change from Baseline	Hunger Score Change from Baseline
Patient 1	BBS1	123	**-36.7%**	-33%
Patient 2	BBS2	119	**-15%**	-71%
Patient 3	BBS10	121	**-28%**	-100%*
Patient 4	BBS12	108	**-25%**	67%
Patient 6	BBS5	83	**-10.8%**	-38%
Patient 7	BBS4	73	**-17.9%**	-14%**

- Six of nine pts responded - All maintain weight loss at ~two years
- Mean percent weight reduction of responders = **22.2%** after ~two years on therapy
- Three patients discontinued treatment
  - Patient 5 (pediatric patient with BBS1 variant and type 1 diabetes) experienced 53.3% reduction in hunger and reduction in hemoglobin A1c (10.1% to 7.6%) before withdrawing. Pt subsequently entered long-term extension study
  - Two patients (one non-genetically confirmed) withdrew due to lack of weight loss

*Pt. has cognitive impairment, so Food Problem Diary (FPD) score maintained by caregiver; **Pt. did not have baseline hunger measure. The first score was a 7, which was not recorded until after the patient had received treatment. Current score is a 6.

Updated Phase 2 Data in Alström Syndrome Show Variable Responses

	Age at enrollment/ Sex	Baseline Weight (kg)	Treatment, weeks	% Weight Change from Baseline	% Hunger Score Change from Baseline†
Patient 1	12/M	78.6	95	**-20%**	-25%
Patient 3*	15/F	70.7	84	**1%**	-38%
Patient 4	16/F	91.6	68	**-6%**	0%

- Patient 1 showed strongest response and HCP started decreasing the dose after 32 weeks of treatment; currently 0.5 mg/day and has reached healthy body weight
- Patient 3 maintaining weight and reduced hunger – HbA1c decreased by 3% from 11% to 8%
- All 3 continuing patients plan to enter long-term extension trial

*As previously disclosed, patient 2 (data not shown) discontinued at ~14 weeks

Community Building and Patient Finding

Nithya Desikan, Chief Commercial Officer

Community Building Off and Running

Disease Journey

- Reducing barriers to diagnosis

Advocacy Relations

- Building relationships with multiple advocacy groups in US and EU

Established Registries

- CRIBBS (Bardet-Biedl syndrome registry)
- Large cohorts of known patients

Field Medical Outreach

- GOLD academies building awareness and community
- Field team members connecting with HCPs

Mapping the BBS Patient Journey to Diagnosis and Beyond

Working to Reduce Barriers to Diagnosis

Solomon, Living with BBS

Variability:
Variability of presentation and progression of the disease

Initial concerns dismissed:
Caregivers collect "proof" to raise HCP suspicion

Medical Team:
Specialists brought in as symptoms increase and worsen with no coordinated care

Specialists may include:
Pediatricians, ENTS, ophthalmologist, endocrinologist, nephrologist and/or therapist

Discovering BBS:
Happens by chance for most via an encounter with someone familiar with BBS; or someone diagnosed with it.

Patient Advocacy Collaborations Advance Common Mission to Improve Lives of Patients, Families Affected by Bardet-Biedl, Alström Syndromes

- Increase disease awareness and reduce barriers to diagnosis
- Gain feedback on clinical trial design and materials
- Support pathway to regulatory approval

CMO Murray Stewart at the 2019 9th Alstrom Syndrome International Family Conference and Scientific Symposium

Bardet Biedl Syndrome Foundation

BBS UK
Bardet-Biedl Syndrome UK

Alström Syndrome UK
Strength for today, hope for the future

ASI
Alström Syndrome International

Community Building: Genetic Obesity Leadership and Network Development

GOLD Academy
Genetic Obesity Leadership Development

Launched in 2019 to educate health care providers, develop management strategies and build a peer-to-peer network

Established education modules on rare genetic disorders of obesity, hyperphagia, clinical characteristics, potential diagnosis and management strategy

20

GOLD Academy faculty

20

programs completed or in process

>500

Health care providers have or are expected to participate

Patient Finding Efforts have Resulted in Many Identified Patients with BBS and Alström syndrome*

Field Medical teams survey of physicians confirms original prevalence of estimates for Bardet-Biedl, Alström syndromes

Estimated Clinical Epidemiology

2,500 in U.S.

2,500 in EU

Bardet-Biedl syndrome

500 in U.S.

500 in EU

Alström syndrome

Rhythm Physician Interactions

224

physicians who treat BBS patients

93

physicians who treat patients with Alström syndrome

BBS Patients Identified

500-800* in U.S.

1,000 - 1,500* in EU

Patients with Alström Syndrome Identified

50-70* in U.S.

200-225* in EU

*Assessment of numbers of patients relies on HCP recall, which may result in over or under reporting

Conclusion

Rhythm Expects Significant Progress in 2019 and 2020

✓	Updated interim data for HET obesity
✓	Positive topline data from both POMC and LEPR Phase 3 studies
✓	Expand Phase 2 basket studies into four additional MC4R pathway disorders
2H19	Complete pivotal enrollment in BBS and Alström Phase 3 study
4Q19-1Q20	Initial NDA submission for setmelanotide in POMC and LEPR
2020	Additional data in high impact HETs obesity and additional Basket indications
2020	Topline data from BBS and Alström Phase 3 study

Rhythm Is Transforming the Care for Patients with Rare Genetic Disorders of Obesity Driven by deficiencies within the MC4R Pathway

Discovering MC4R pathway disorders that cause obesity and identifying patients

Rhythm has expanded the Basket Study into **4 new indications**, all with strong scientific ties to the MC4R pathway

Sequencing has improved our understanding of:

- **POMC and LEPR**
- **New indications**, for which the estimated prevalence is substantial

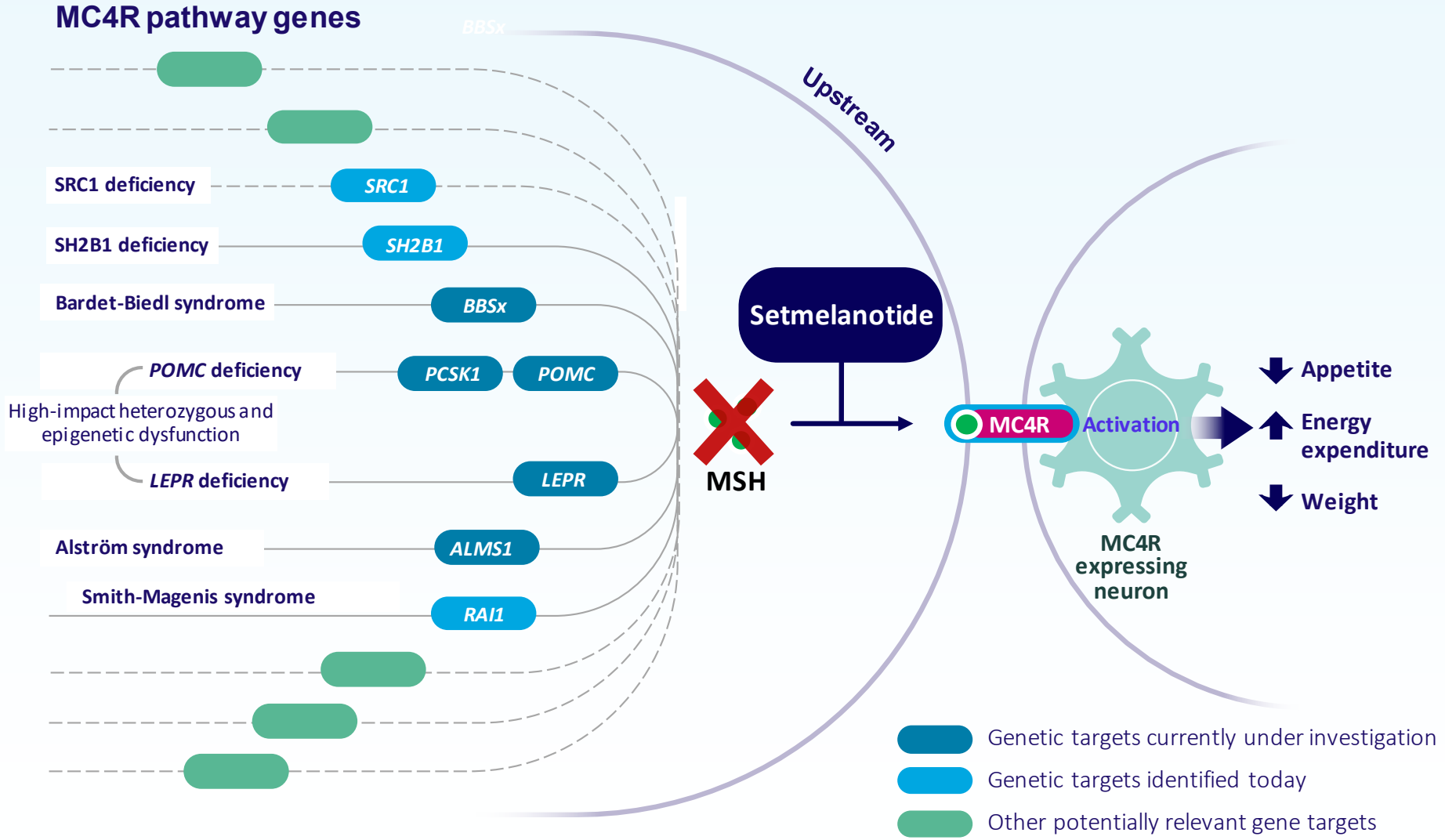
Significant progress in Bardet-Biedl and Alström syndromes programs

- Patients in Phase 2 trial showing deepening of response over longer-term
- Patient finding efforts are exceeding expectations

Rhythm Engine is executing on a scientific approach to identifying patients with rare genetic disorders of obesity related to the MC4R pathway


Rhythm
PHARMACEUTICALS

Setmelanotide has Potential to Address Multiple Genetic Disorders that Disrupt MC4R Pathway Function



- POMC deficiency obesity
- LEPR deficiency obesity
- Bardet-Biedl syndrome
- Alström syndrome

- High-impact heterozygous deficiency obesity
- Epigenetic disorders

- SRC1 deficiency obesity
- SH2B1 deficiency obesity
- Smith-Magenis syndrome
- MC4R deficiency obesity