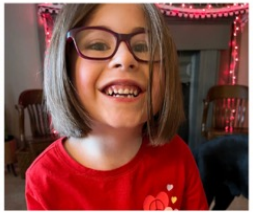
FOUNDATION FOR PRADER-WILLI RESEARCH CANADA

PWS Research: Progress & Possibilities

Theresa Strong
Director of Research Programs
Foundation for Prader-Willi Research
Daniel's mom




Agenda

1. Update on PWS Research Activities
2. A look ahead
3. Questions & Discussion

FOUNDATION FOR PRADER-WILLI RESEARCH

Mission: to eliminate the challenges of PWS through the advancement of research and therapeutic development

Focus: accelerate progress towards the discovery, evaluation and approval of new therapies for PWS, optimizing clinical care

Vision: a world in which all individuals with PWS are physically healthy, mentally well and able to live full and independent lives

.

FPWR: Strategic Directives

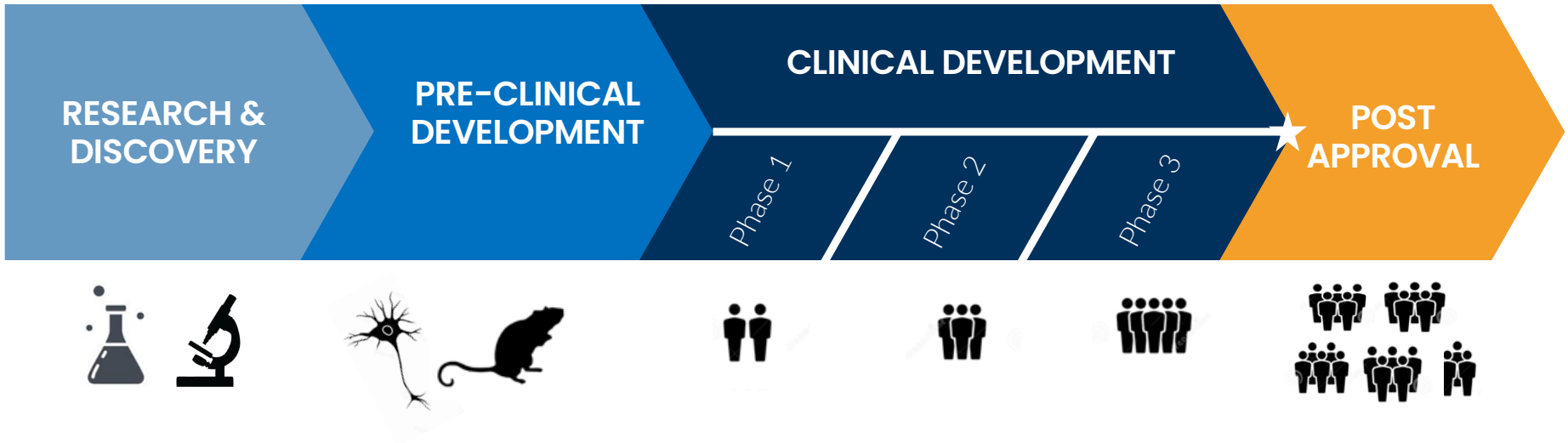
- **Focus on translational research** that advances lab and clinic observations into new therapies that improve the health and well-being of of people with PWS.
- **Balance short-term and long-term investments** to address the pressing need for improvements in treatments and care while working to develop transformative therapies that will require more time.
- **Build PWS research capacity** by supporting investigators who are new to the PWS field, fostering collaborations, providing research tools that can be widely used.
- **Invest in a diverse research portfolio**

What research should we prioritize?

DRUG DEVELOPMENT

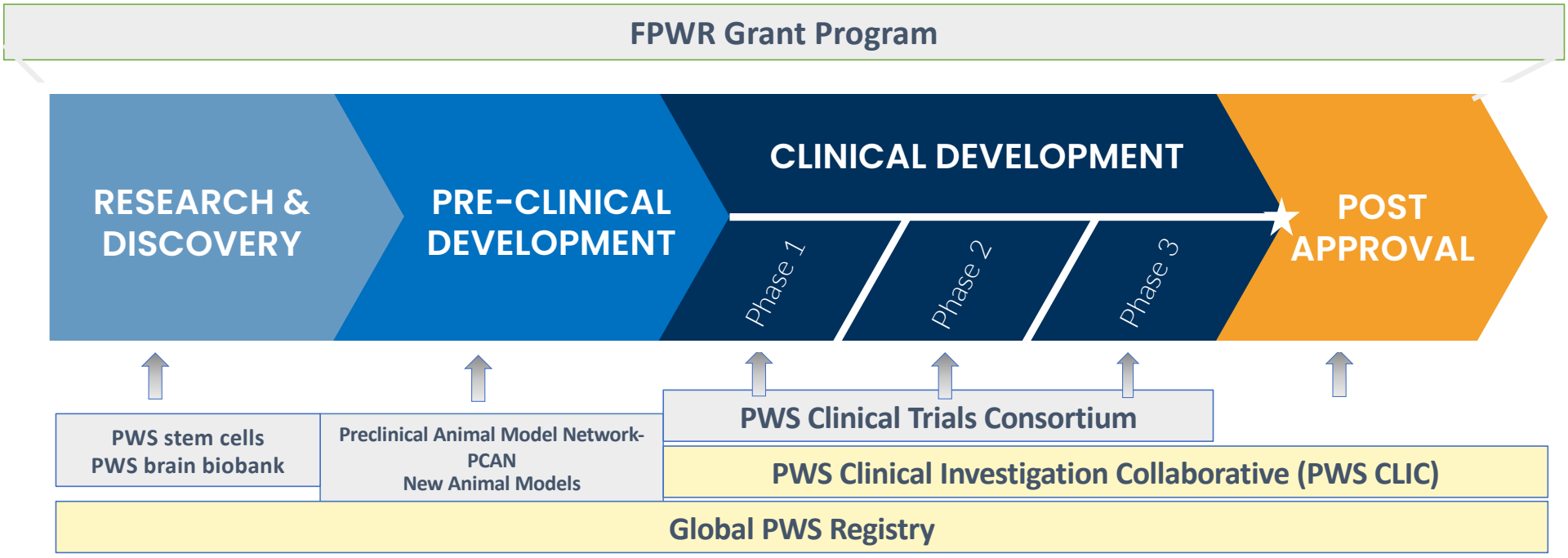
PIPELINE TO NEW THERAPIES

Our goal: accelerate every step in this process



FPWR Initiatives to Advance Research

Across the therapeutic development pipeline



PWS CLIC
CLINICAL INVESTIGATION COLLABORATIVE

https://www.fpwr.org/pws-clic

Mission: *to improve the quality of clinical research and medical care for people with PWS across the lifespan through collaborative investigation and research to support evidence-based care*

PWS Clinical Investigation Collaborative

30 CLIC Sites Across the US and Canada

Building a shared clinical databased to pool information and answer clinical questions

FOUNDATION FOR PRADER-WILLI RESEARCH

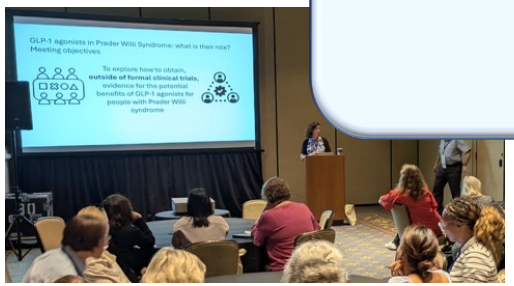
PWS Clinical Workshops

GLP-1 Agonists in PWS: What is their role?

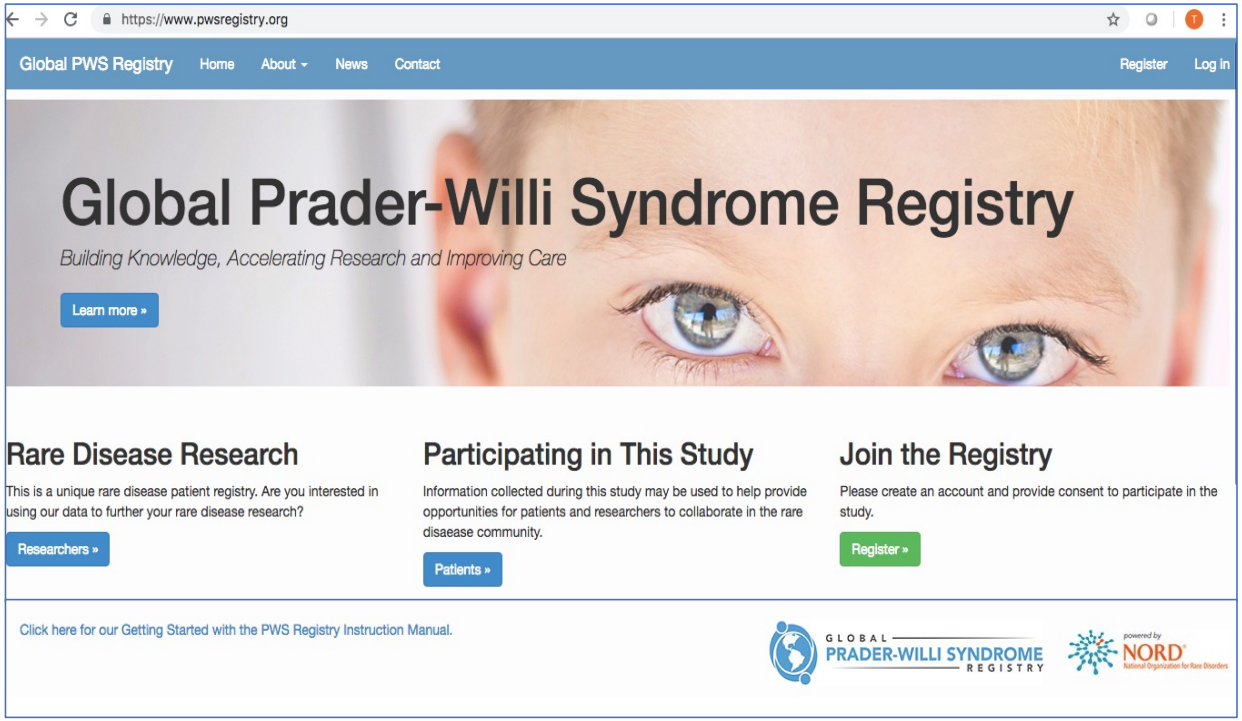
Therapeutics for behavior and mental health concerns in PWS

Health Equity in PWS Clinical Research and Care

Aging in PWS: Optimizing care for individuals with PWS across the lifespan



Financial support:



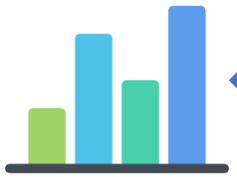
www.pwsregistry.org
NORD's IAMRARE platform

- Launched in 2015
- Parent reported data: diagnosis, GI, neurology, endocrine,
- behavior, medications, quality of life
- Currently ~2,600 participants from 35 countries
- ***Version 2.0 will be launched before the end of the year – new capabilities, translations***

How are we using the Global PWS Registry?

Learn about the scope of PWS symptoms to optimize clinical care

Build knowledge to inform therapeutic development for pharmaceutical companies, regulatory agencies



Bring quantitative data to support anecdotal evidence in documenting the unmet medical needs of our patient community

GLOBAL PRADER-WILLI SYNDROME REGISTRY

PWS Registry - Supporting Clinical Trials and Clinical Care

>25 **Recruitment**: supporting recruitment for clinical trials and research studies

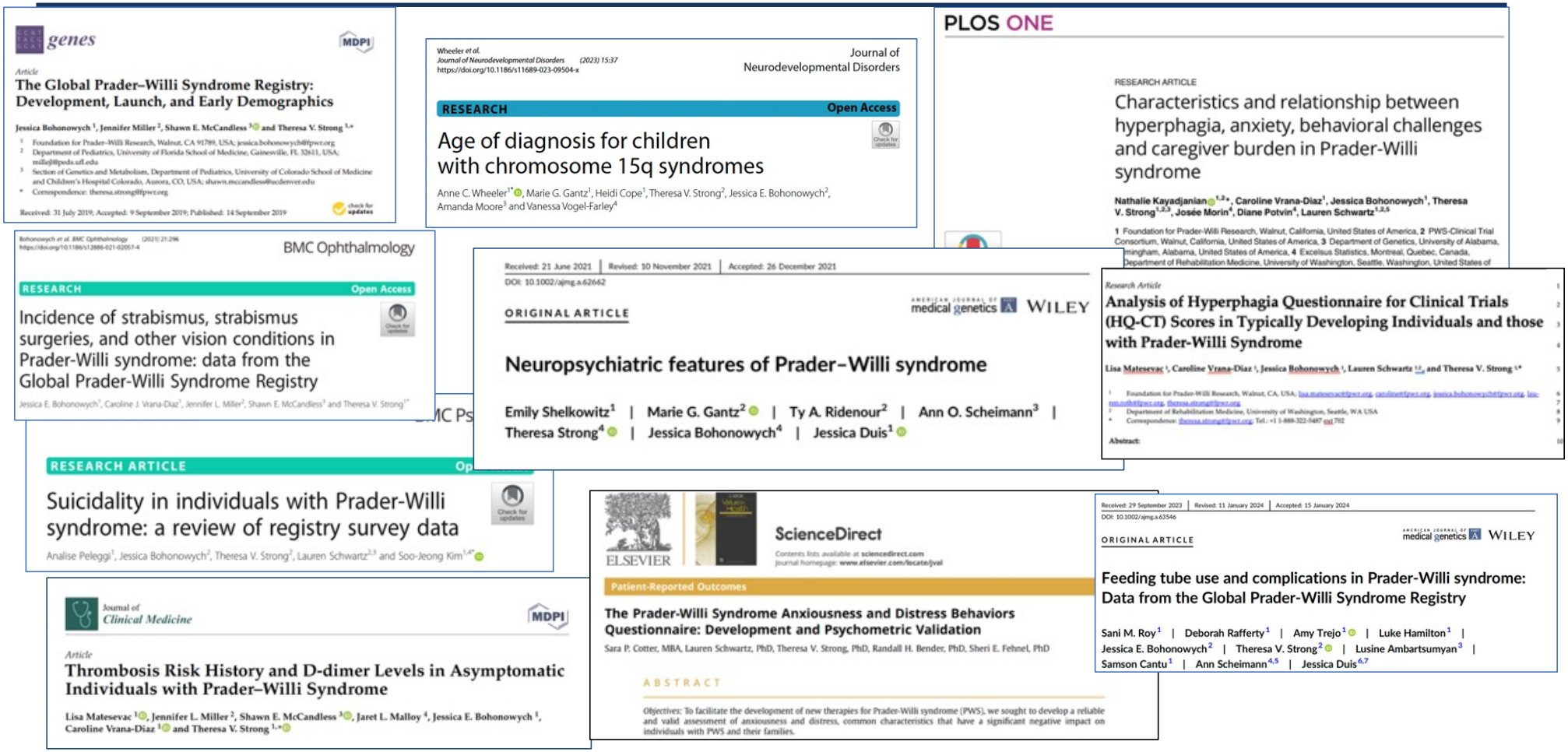
>20 **Data**: providing data to inform protocol development, regulatory interactions & submissions, and clinical care

>5 **Outcome Measures**: Development and improved understanding of clinical outcome assessments

GLOBAL PRADER-WILLI SYNDROME REGISTRY

Strength of the Global PWS Registry

GLOBAL PRADER-WILLI SYNDROME REGISTRY



genes

Article

The Global Prader–Willi Syndrome Registry: Development, Launch, and Early Demographics

Jessica Bohonowych [1], Jennifer Miller [2], Shawn E. McCandless [3] and Theresa V. Strong [1,*]

Received: 31 July 2019; Accepted: 9 September 2019; Published: 14 September 2019

Wheeler et al. Journal of Neurodevelopmental Disorders (2023) 15:37 https://doi.org/10.1186/s11689-023-09504-x

Journal of Neurodevelopmental Disorders

RESEARCH Open Access

Age of diagnosis for children with chromosome 15q syndromes

Anne C. Wheeler[1*], Marie G. Gantz[1], Heidi Cope[1], Theresa V. Strong[2], Jessica E. Bohonowych[2], Amanda Moore[3] and Vanessa Vogel-Farley[4]

PLOS ONE

RESEARCH ARTICLE

Characteristics and relationship between hyperphagia, anxiety, behavioral challenges and caregiver burden in Prader-Willi syndrome

Nathalie Kayadjanian[1,2*], Caroline Vrana-Diaz[1], Jessica Bohonowych[1], Theresa V. Strong[1,2,3], Josée Morin[4], Diane Potvin[4], Lauren Schwartz[1,2,5]

Bohonowych et al. BMC Ophthalmology (2021) 21:296 https://doi.org/10.1186/s12886-021-02057-4

BMC Ophthalmology

RESEARCH Open Access

Incidence of strabismus, strabismus surgeries, and other vision conditions in Prader-Willi syndrome: data from the Global Prader-Willi Syndrome Registry

Jessica E. Bohonowych[1], Caroline J. Vrana-Diaz[2], Jennifer L. Miller[2], Shawn E. McCandless[3] and Theresa V. Strong[1*]

Received: 21 June 2021 | Revised: 10 November 2021 | Accepted: 26 December 2021

DOI: 10.1002/ajmg.a.62662

ORIGINAL ARTICLE

American Journal of medical genetics A WILEY

Neuropsychiatric features of Prader–Willi syndrome

Emily Shelkowitz[1] | Marie G. Gantz[2] | Ty A. Ridenour[2] | Ann O. Scheimann[3] | Theresa Strong[4] | Jessica Bohonowych[4] | Jessica Duis[1]

Research Article

Analysis of Hyperphagia Questionnaire for Clinical Trials (HQ-CT) Scores in Typically Developing Individuals and those with Prader-Willi Syndrome

Lisa Matesevac [1], Caroline Vrana-Diaz [1], Jessica Bohonowych [1], Lauren Schwartz [1,2], and Theresa V. Strong [1,*]

RESEARCH ARTICLE

Suicidality in individuals with Prader-Willi syndrome: a review of registry survey data

Analise Peleggi[1], Jessica Bohonowych[2], Theresa V. Strong[2], Lauren Schwartz[2,3] and Soo-Jeong Kim[1,4*]

ELSEVIER

ScienceDirect

Contents lists available at sciencedirect.com

Journal homepage: www.elsevier.com/locate/jval

Patient-Reported Outcomes

The Prader-Willi Syndrome Anxiousness and Distress Behaviors Questionnaire: Development and Psychometric Validation

Sara P. Cotter, MBA, Lauren Schwartz, PhD, Theresa V. Strong, PhD, Randall H. Bender, PhD, Sheri E. Fehnel, PhD

ABSTRACT

Objectives: To facilitate the development of new therapies for Prader-Willi syndrome (PWS), we sought to develop a reliable and valid assessment of anxiousness and distress, common characteristics that have a significant negative impact on individuals with PWS and their families.

Journal of Clinical Medicine

Article

Thrombosis Risk History and D-dimer Levels in Asymptomatic Individuals with Prader–Willi Syndrome

Lisa Matesevac [1], Jennifer L. Miller [2], Shawn E. McCandless [3], Jaret L. Malloy [4], Jessica E. Bohonowych [1], Caroline Vrana-Diaz [1] and Theresa V. Strong [1,*]

Received: 29 September 2023 | Revised: 11 January 2024 | Accepted: 15 January 2024

DOI: 10.1002/ajmg.a.63546

ORIGINAL ARTICLE

American Journal of medical genetics A WILEY

Feeding tube use and complications in Prader-Willi syndrome: Data from the Global Prader-Willi Syndrome Registry

Sani M. Roy[1] | Deborah Rafferty[1] | Amy Trejo[1] | Luke Hamilton[1] | Jessica E. Bohonowych[2] | Theresa V. Strong[2] | Lusine Ambartsumyan[3] | Samson Cantu[1] | Ann Scheimann[4,5] | Jessica Duis[6,7]

Global PWS Registry: Fostering Collaborations

GLOBAL PRADER-WILLI SYNDROME REGISTRY

angelman SYNDROME FOUNDATION

Dup15q Alliance FOR 15Q 11.2–13.1 MULTIPLICATIONS

Wheeler *et al.*
Journal of Neurodevelopmental Disorders (2023) 15:37
https://doi.org/10.1186/s11689-023-09504-x

Journal of Neurodevelopmental Disorders

RESEARCH Open Access

Age of diagnosis for children with chromosome 15q syndromes

Anne C. Wheeler[1*], Marie G. Gantz[1], Heidi Cope[1], Theresa V. Strong[2], Jessica E. Bohonowych[2], Amanda Moore[3] and Vanessa Vogel-Farley[4]

fast FOUNDATION FOR ANGELMAN SYNDROME THERAPEUTICS

FOUNDATION FOR PRADER-WILLI RESEARCH

RTI INTERNATIONAL

Received: 29 September 2023 | Revised: 11 January 2024 | Accepted: 15 January 2024
DOI: 10.1002/ajmg.a.63546

ORIGINAL ARTICLE

AMERICAN JOURNAL OF medical genetics PART A WILEY

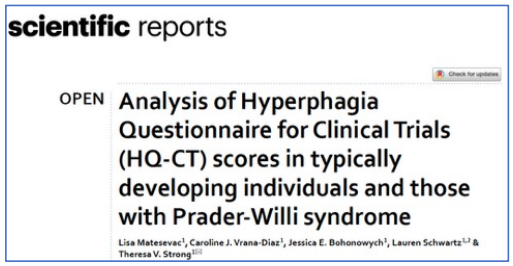
Feeding tube use and complications in Prader-Willi syndrome: Data from the Global Prader-Willi Syndrome Registry

Sani M. Roy[1] | Deborah Rafferty[1] | Amy Trejo[1] | Luke Hamilton[1] | Jessica E. Bohonowych[2] | Theresa V. Strong[2] | Lusine Ambartsumyan[3] | Samson Cantu[1] | Ann Scheimann[4,5] | Jessica Duis[6,7]

Sani Roy, Cook Children's

PWS-Specific Clinical Outcome Assessment Development

Hyperphagia Questionnaire For Clinical Trials (HQ-CT)


scientific reports

OPEN Analysis of Hyperphagia Questionnaire for Clinical Trials (HQ-CT) scores in typically developing individuals and those with Prader-Willi syndrome

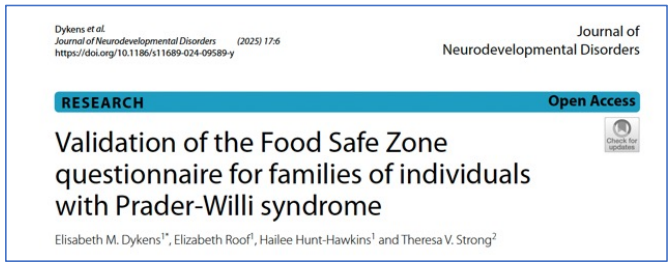
Lisa Matesevac[1], Caroline J. Vrana-Diaz[1], Jessica E. Bohonowych[1], Lauren Schwartz[1,2] & Theresa V. Strong[1]

Assesses hyperphagic behaviors

Primary endpoint in most PWS trials

Tested in 600+ PWS participants & 400+ typical controls

Food Safe Zone


Dykens et al. Journal of Neurodevelopmental Disorders (2025) 17:6 https://doi.org/10.1186/s11689-024-09589-y

Journal of Neurodevelopmental Disorders

RESEARCH Open Access

Validation of the Food Safe Zone questionnaire for families of individuals with Prader-Willi syndrome

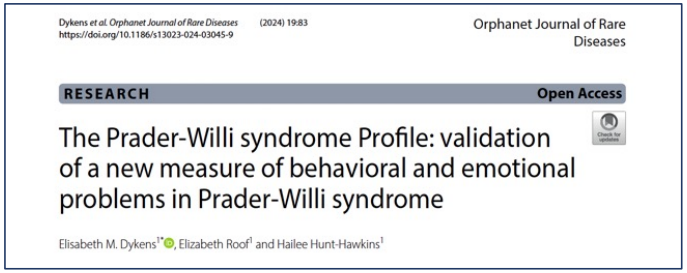
Elisabeth M. Dykens[1*], Elizabeth Roof[1], Hailee Hunt-Hawkins[1] and Theresa V. Strong[2]

Assesses how parents maintain a food safe environment for their child with PWS.

Tested by 491 caregivers in the Registry

Now used in multiple clinical trials in conjunction with the HQ-CT.

PWS Profile


Dykens et al. Orphanet Journal of Rare Diseases (2024) 19:83 https://doi.org/10.1186/s13023-024-03045-9

Orphanet Journal of Rare Diseases

RESEARCH Open Access

The Prader-Willi syndrome Profile: validation of a new measure of behavioral and emotional problems in Prader-Willi syndrome

Elisabeth M. Dykens[1*], Elizabeth Roof[1] and Hailee Hunt-Hawkins[1]

Assesses major behavioral characteristics of PWS

Full validation was done with 500+ parents/caregivers;

Registry participants completed every 6 months- longitudinal data and stability over time.

Elisabeth Dykens, Vanderbilt U

Study Design with Responsible Return of Results for a Fully Remote Genome Sequencing Study in Individuals with Prader-Willi Syndrome

Caroline J. Vrana-Diaz[1], Jessica Bohonowych[1], Jaimie L. Richards[2,3], Brandon M. Wilk[3], Manavalan Gajapathy[3], Yael Bar-Peled[5], Anna C. Harris[5], Jessica J. Denton[5], Donna Brown[3], Elizabeth A. Worthey[3], Theresa V. Strong[1,4]

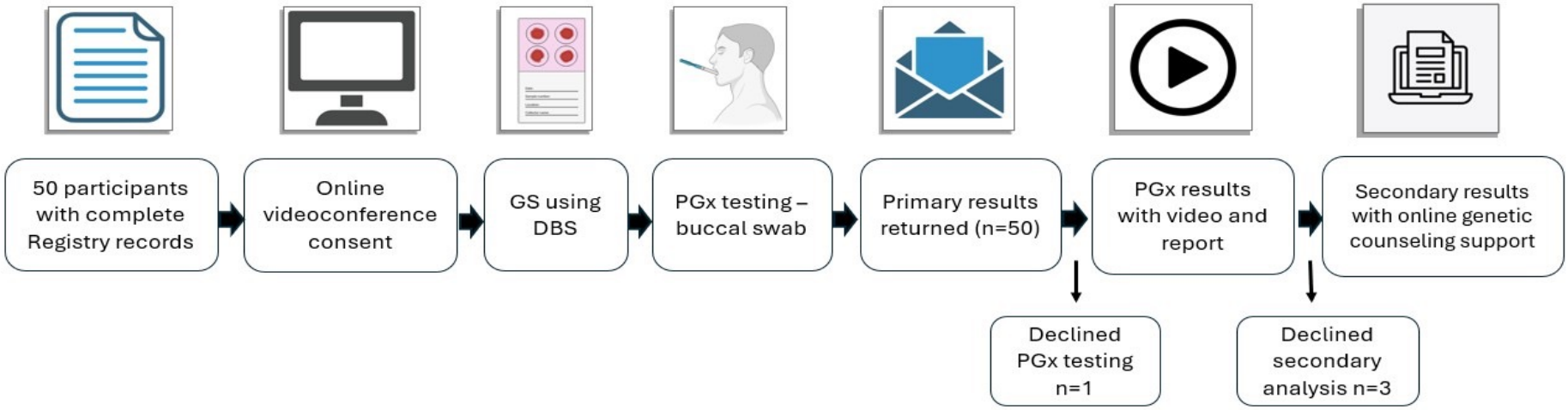
[1] Foundation for Prader-Willi Research, Covina, CA, USA; [2] Division of General Internal Medicine and Population Science, University of Alabama at Birmingham Heersink School of Medicine, Birmingham, AL, USA; [3] Center for Computational Genomics and Data Science, Department of Genetics, University of Alabama at Birmingham Heersink School of Medicine, Birmingham, AL, USA; [4] Department of Genetics, University of Alabama at Birmingham Heersink School of Medicine, Birmingham, AL, USA; [5] Department of Clinical and Diagnostic Sciences, University of Alabama at Birmingham, Birmingham, AL, USA

Overview and Context

Clinical symptoms in PWS occur with varying degrees of frequency and severity among individuals.

Potential explanation for symptom variability → presence of variants throughout the genome that influences the expression of certain PWS characteristics.

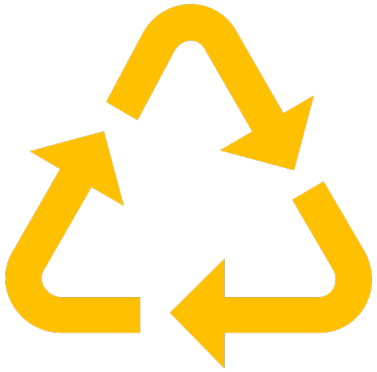
Study to assess the feasibility of a fully remote, patient group-led, whole genome sequencing (WGS) study in PWS



Highlights of Data/Results

<u>3 Levels of Returning Results</u>

- Primary Findings Report
- Pharmacogenomics (PGx) Report
- Secondary Findings Report

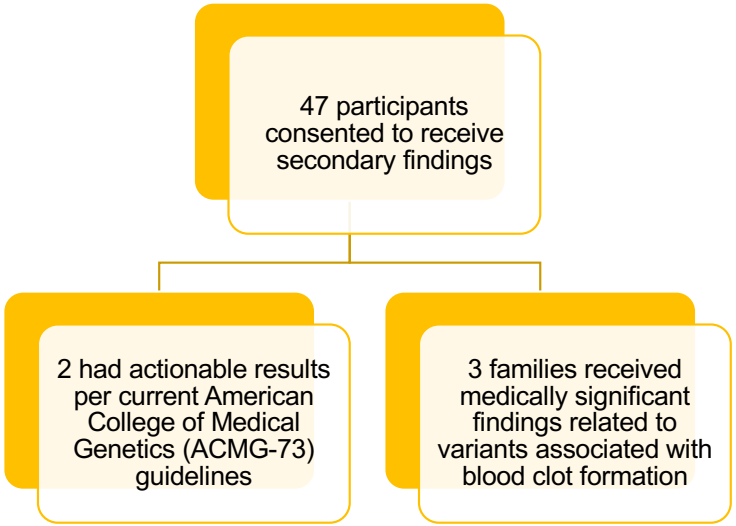


<u>Collaborative/Iterative Process</u>

- Consent Discussion
- PGx report development
- Participant-facing materials
- Participant choices re: data sharing & return of results

<u>Patient-Focused</u>

- Reducing Burden
- Home sample collection
- Return of results important to families
- Qualitative interviews to discuss experiences



Serious Medical Events and PWS-associated Behaviors in *PATH for PWS*:

A Non-Interventional, Observational, Natural History Study

PATH for PWS™
Paving the way for Advances in Treatments & Health for PWS

FOUNDATION FOR PRADER-WILLI RESEARCH

Purpose & Overview

- ***Four-year, prospective, observational study to advance the understanding of serious medical events in individuals with PWS, age 5+***
- Fully remote study completed through the Global PWS Registry
- Parent-reported retrospective medical history, updates q 6 months:

  Height & Weight Prescription Medications

  Behavior assessments: Hyperphagia (HQ-CT), Food Safe Zone, PWS Profile
- Detailed report on all serious medical events and thrombotic events, accompanying medical records uploaded if available
- Enrollment began late 2018

Enrollment and Retention

Target: 500 participants

700 Participants consented
647 Completed initial surveys

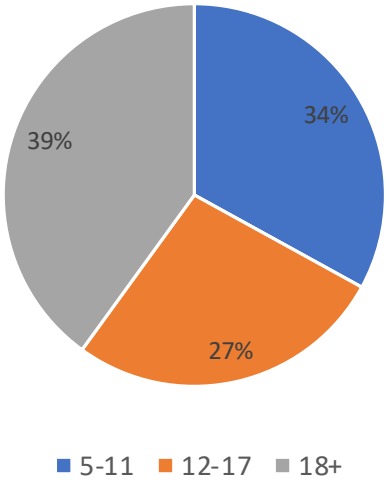
11 participant deaths
3 caregiver deaths
5 moved to group homes
4 unenrolled
89 become inactive

535 completers

83% stayed enrolled and active through the end of the 4-year study

Participant Demographics

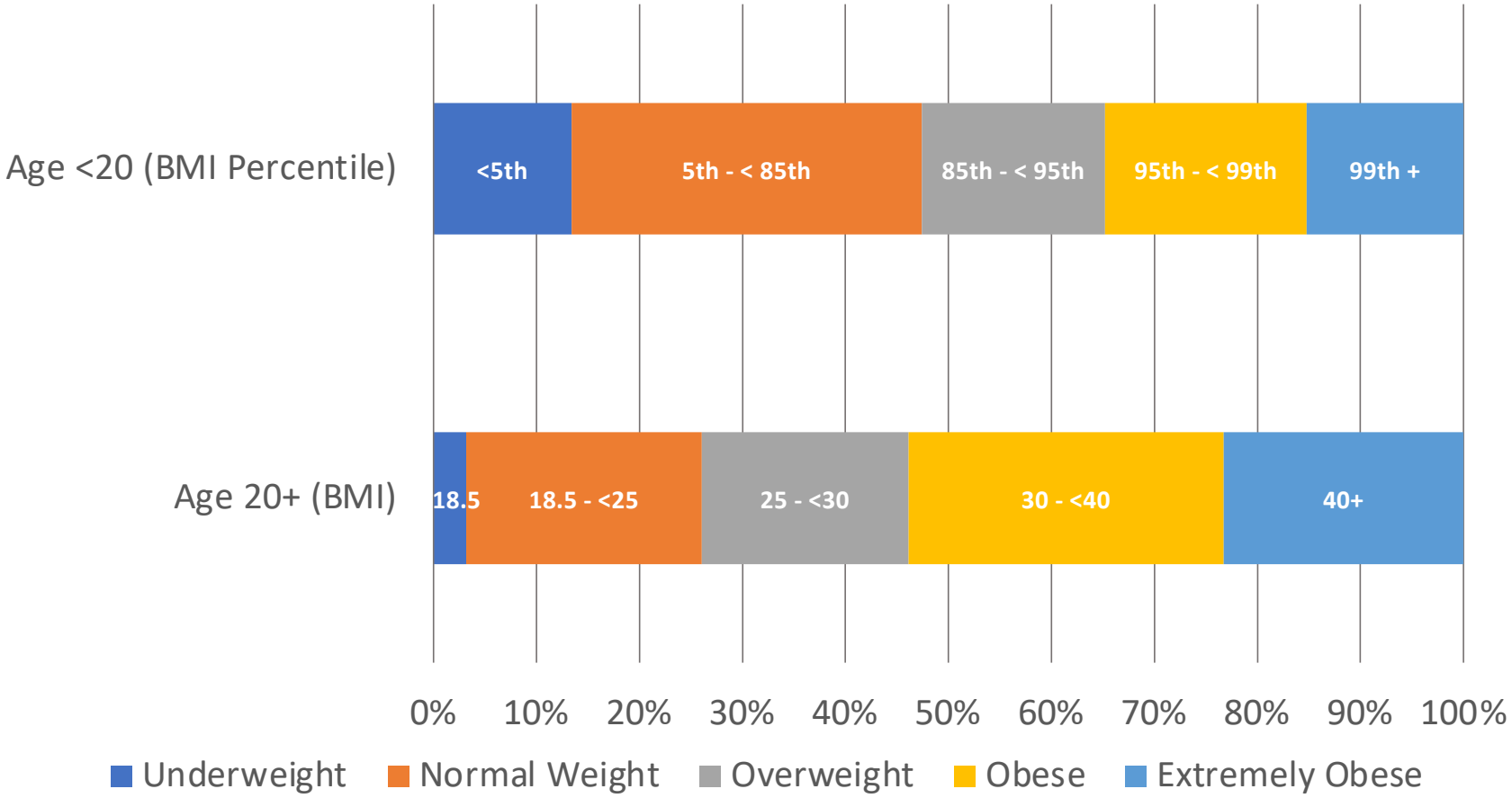
Age at Enrollment



34%	Age 5-11	(n= 218)
27%	Age 12-17	(n=177)
24%	Age 18-29	(n= 156)
15%	Age 30+	(n=96)

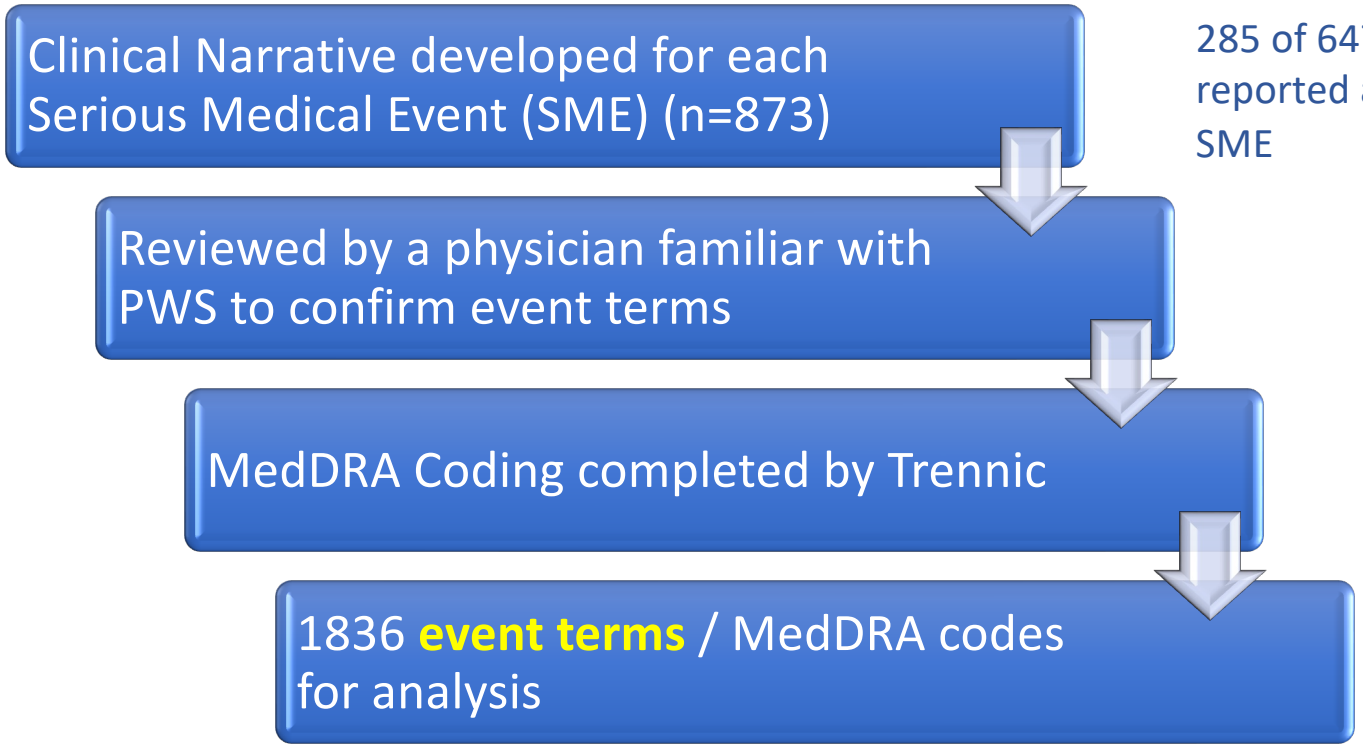
- Equal distribution of male and female participants
- Genetic Subtype [81% provided confirmation of genetic dx]
  - 53% Deletion
  - 33.3% UPD
  - 8.5% Not determined/not reported
  - 2.6% Imprinting Defect
  - 1.4% Translocation
  - 1.2% Non-Deletion (methylation +, FISH neg)
- Participants from 4 countries
  - 88% US
  - 8% Canada
  - 3% Australia
  - 1 % New Zealand
- ~31% (n=201) have participated in clinical trials during PATH

Distribution of Body Mass Index at Entry



75% of adults overweight or obese

PATH for PWS

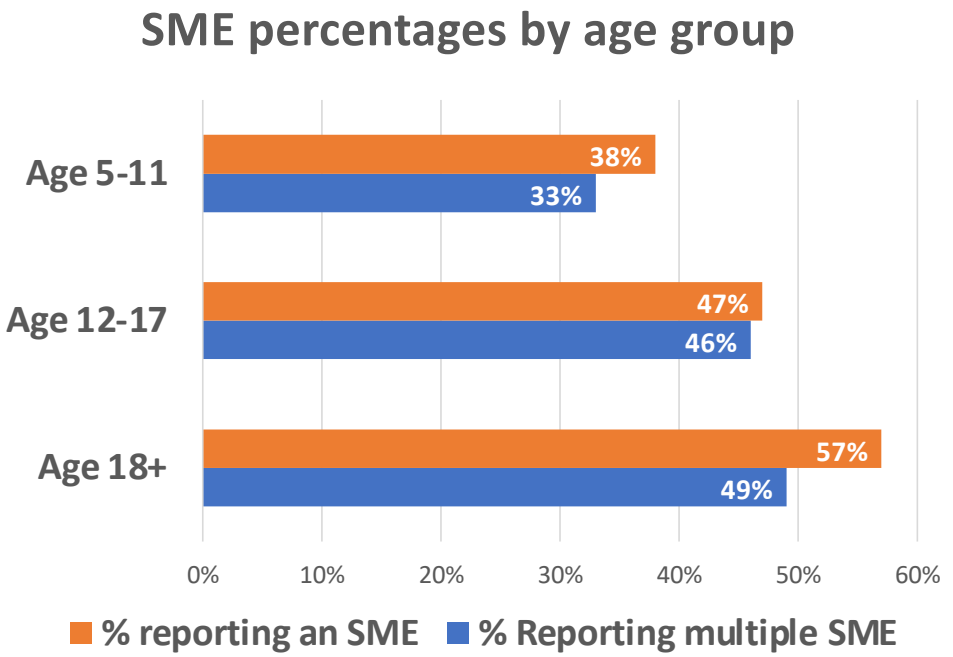


285 of 647 participants reported at least 1 SME

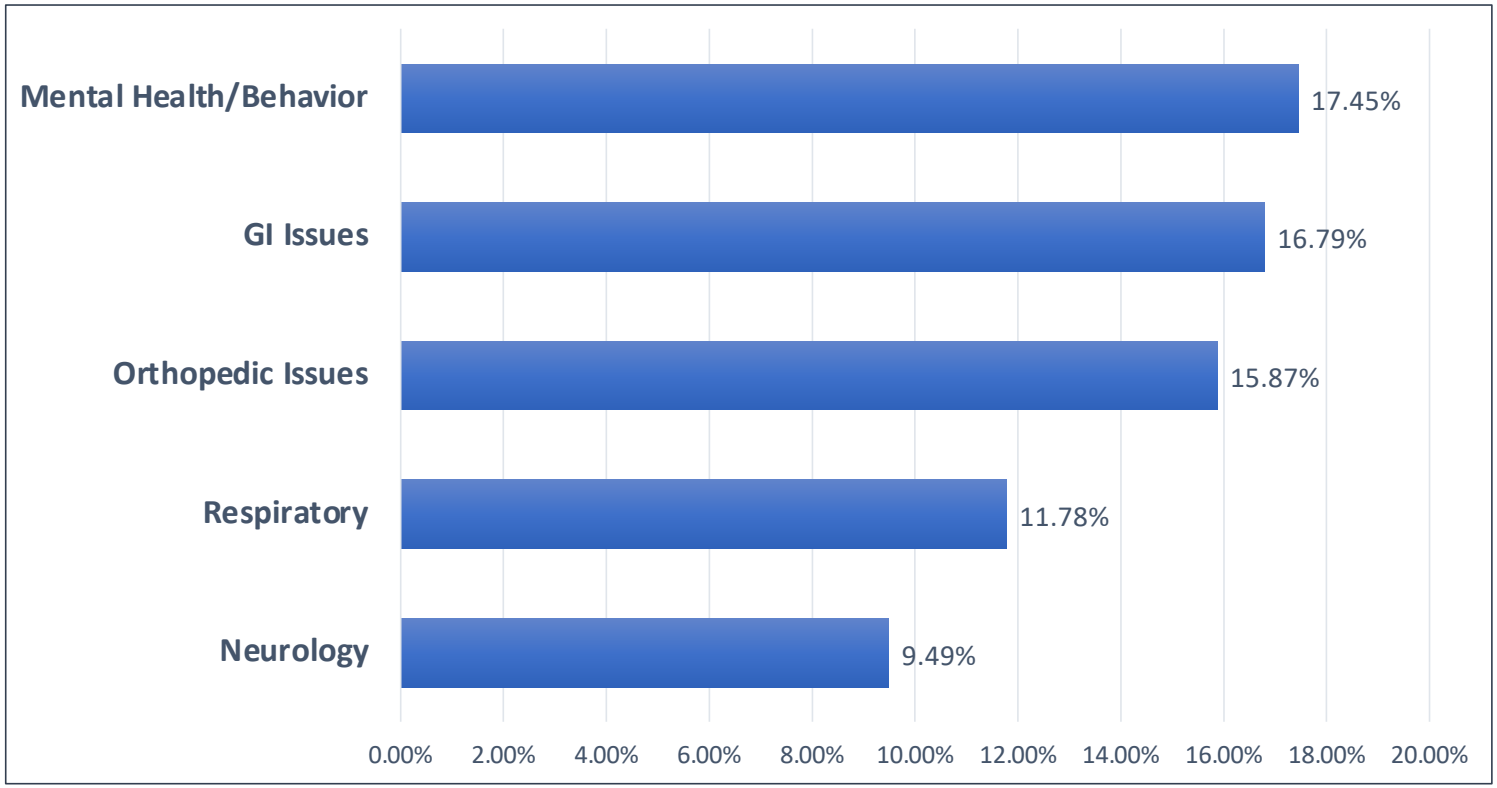
1 Medical Event	3 Event Terms
ER Visit for Abdominal Pain	Vomiting Bowel Obstruction Intestinal Procedure

Serious Medical Events

- 285 of 647 of PATH participants reported at least one serious medical event during the study period
- Of those who documented a serious medical event, 67% have had multiple events
- Incidence of serious medical events increases with age
- Incidence of multiple events increases with age



Serious Medical Event Term Categories

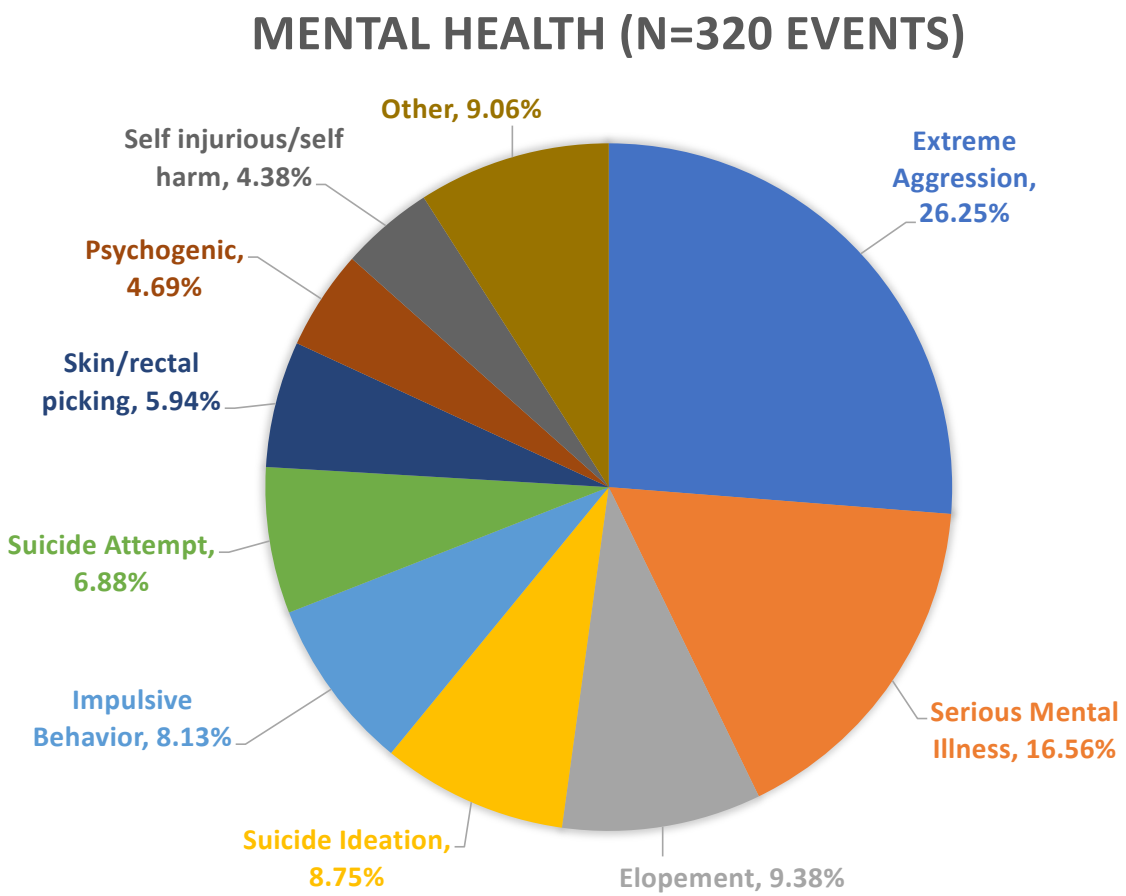


% of total event terms

n=1836 total event terms

More than 70% of total event terms fell into the above categories
Of special interest – 12 blood clots, one of which was fatal

Serious Medial Event Terms: Mental Health



Occurred in 89 participants

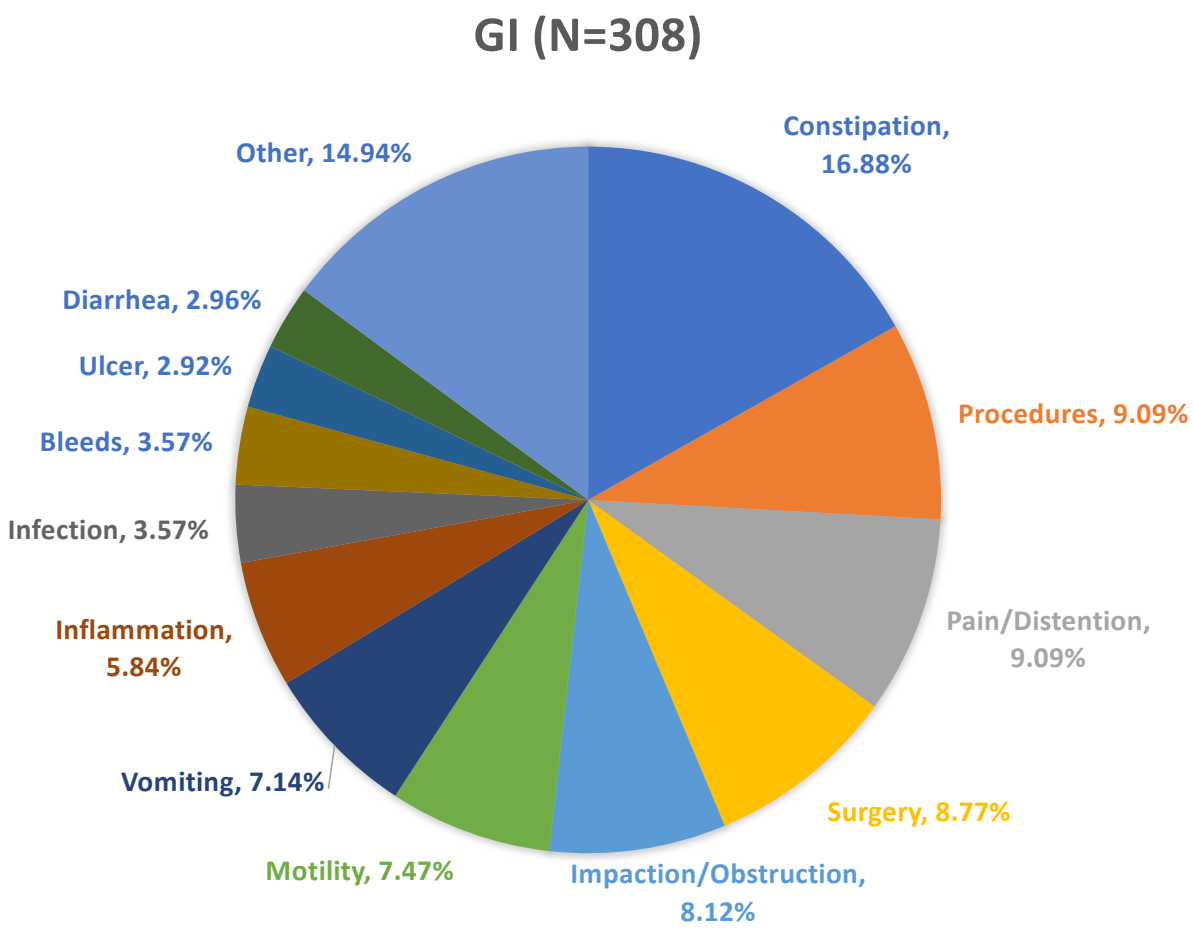
- 42 females
- 47 males

Subtype Breakdown

- UPD: 42 participants
- Deletion: 32 individuals
- Other: 15 individuals

PATH for PWS™

GI Serious Medical Event Terms

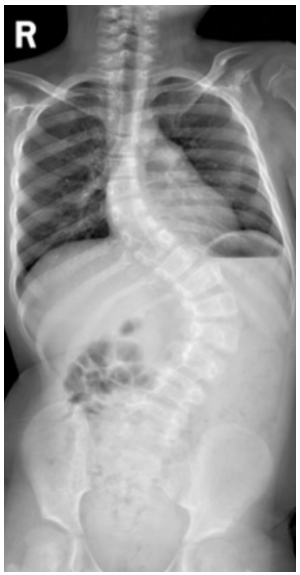


Wide range of GI problems

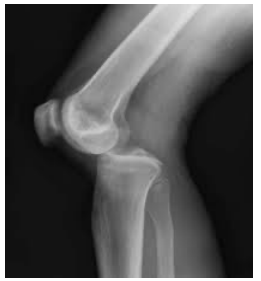
18% of PATH participants reported at least one GI serious medical event

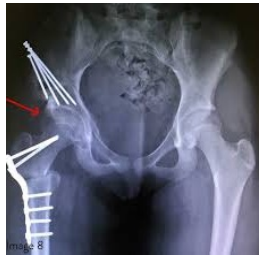
Orthopedic problems and surgeries

- 59 fractures and sprains (~10% of the PATH population)
  - 50 fractures reported over 4.5 years
  - Many associated with falls, some with extreme aggression events
  - Approx 2x the rate typical population [1.2%/year]
- 37 knee dislocations & surgeries in 18 individuals
  - Several repeat dislocations, some requiring surgical intervention
  - Approx 50x increased risk of knee dislocation in PATH participants vs. general population
- 5 Hip dysplasia / hip replacement surgeries
- 58 scoliosis-related spine surgeries



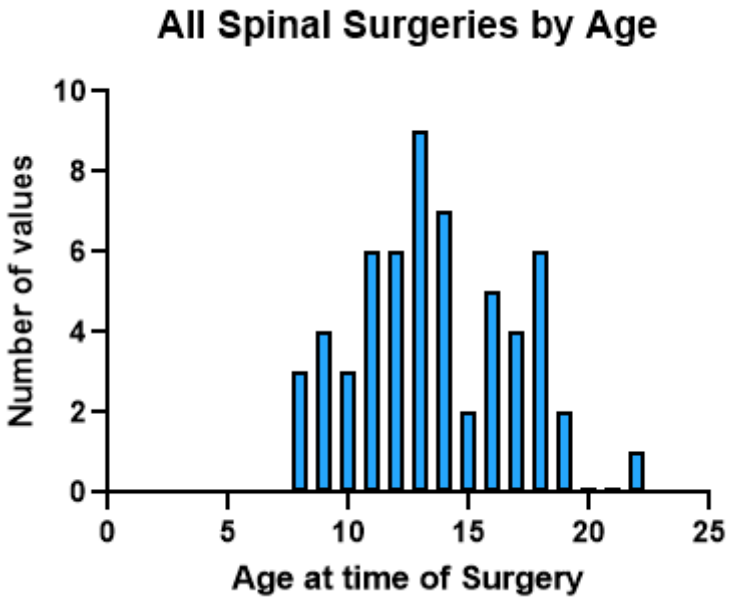
BMC Pediatrics 24: 118 (2024)

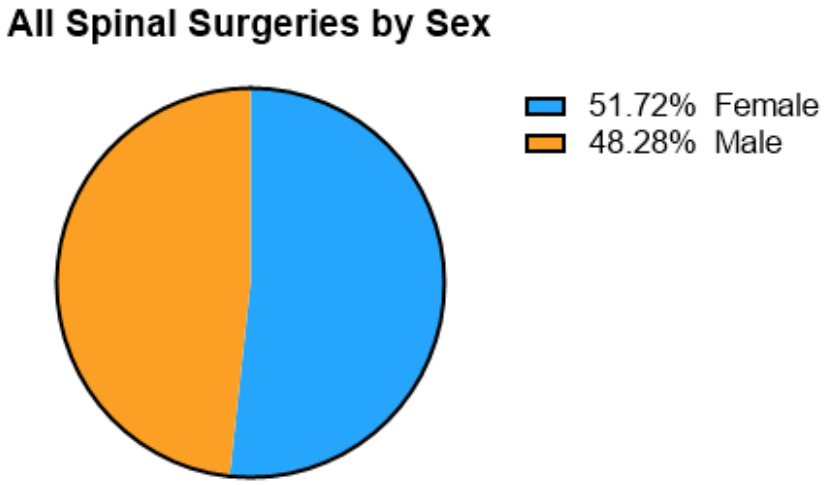




Spinal Surgeries in PATH Participants

58 surgeries in 44 individuals



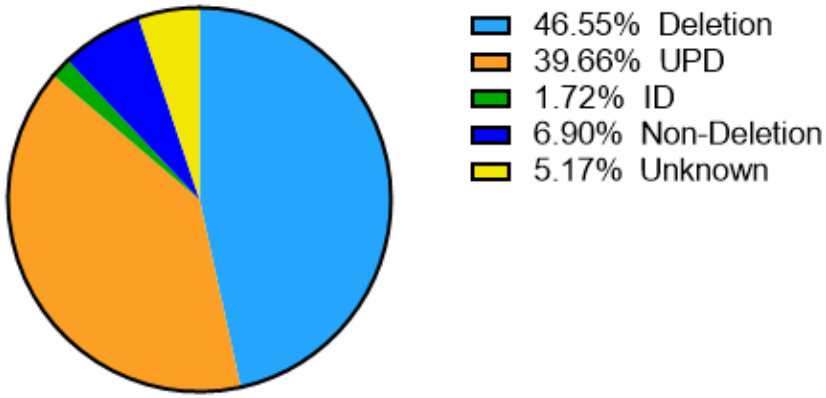


* Very different from general population

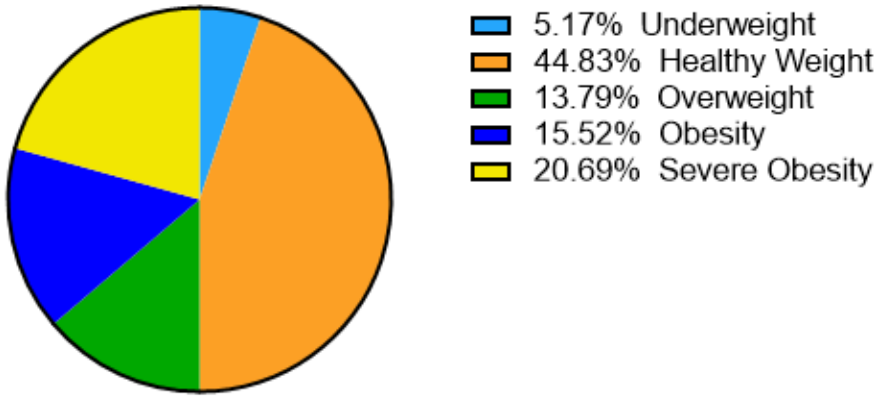
Spinal Surgeries in PATH Participants

58 surgeries in 44 individuals

All Spinal Surgeries by Subtype



All Spinal Surgeries by BMI Category

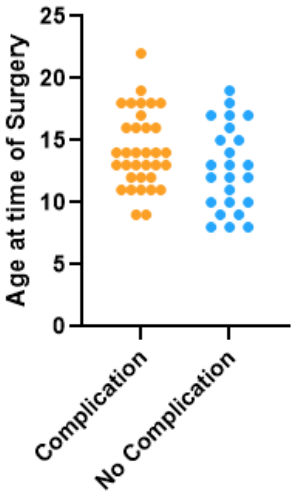


Genetic subtype and BMI are similar to baseline PATH population

Frequency of Complications – Spinal Surgeries

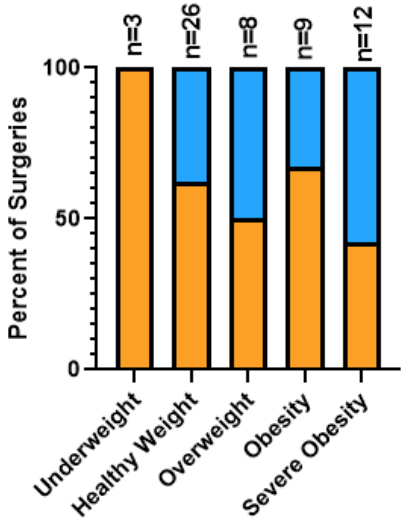
34 of 58 surgeries (59%) were associated with at least 1 significant complication
63 complications reported in 30 individuals (68% of individuals)

Age



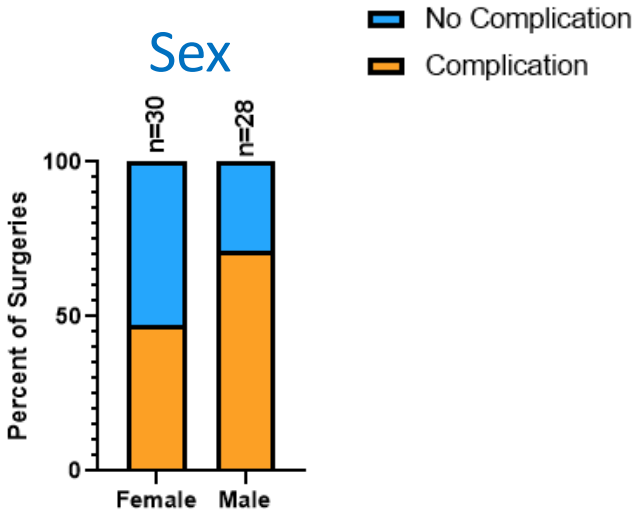
No difference

BMI



No difference

Sex



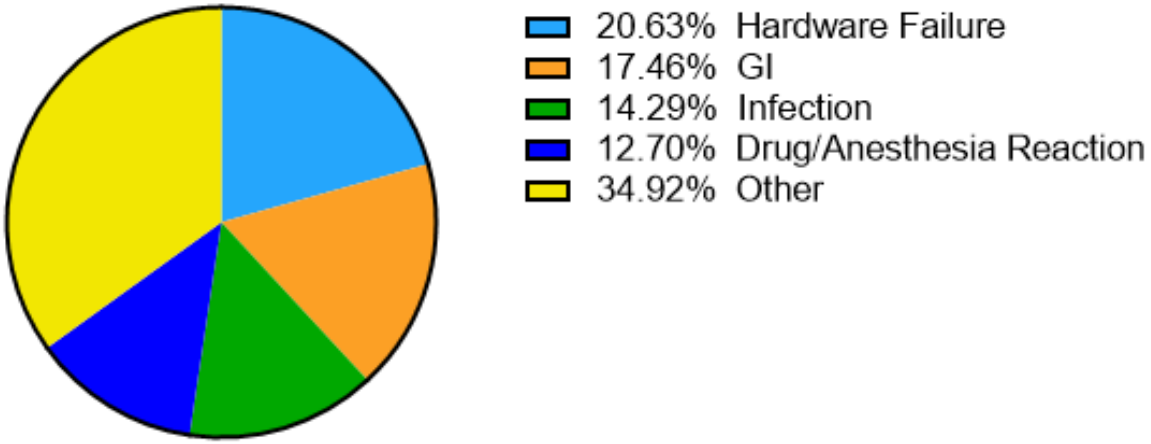
Trend towards more complications in males

Types of Surgical Complications

PATH for PWS™

Other: less than 5 incidents each

- CSF Leak
- Headache
- Muscle spasm/intractable pain
- Nerve damage
- Tracheostomy
- Worsening kyphosis
- Tachycardia
- Incontinence
- Paralysis
- Pneumothorax



Care team should be aware of the high rate of complications in PWS patients undergoing scoliosis surgery

Analysis of Hyperphagia (HQ-CT), Environmental Control (FSZ) and BMI

- There were 621 participants with at least one measurement who were included in the baseline analyses
- Most participants had at least 7 HQ-CT & FSZ measures
- There were 582 individuals with 2 or more measurements that were included in longitudinal analyses

Correlation between Age, BMI Group, HQ-CT and FSZ

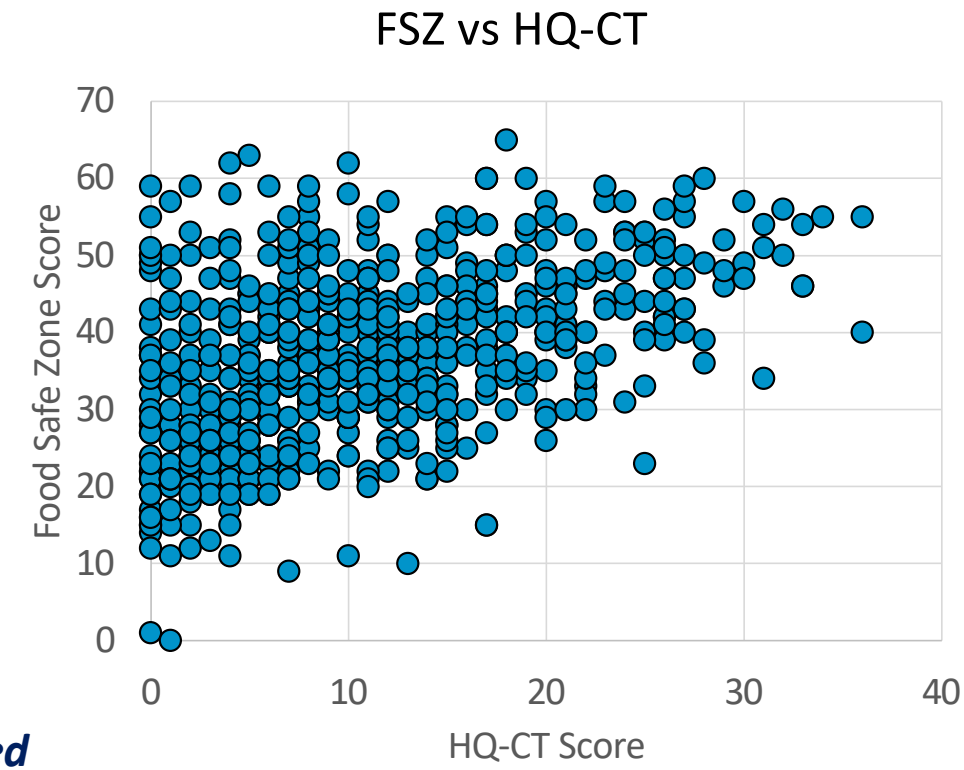
Baseline data

Correlation coefficients

	Age	BMI	HQ-CT	FSZ
Age		0.17	0.04	0.37
BMI			0.2	0.1
HQ-CT				0.48

Positive correlation coefficients indicate that the two measures are increasing together.

Coefficients in orange: p-value less than 0.05.

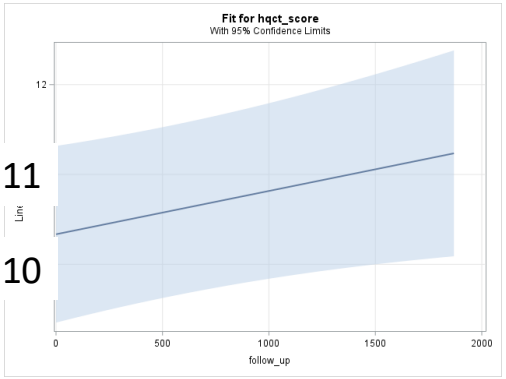


Higher HQ-CT scores are associated with increased measures to limit food access (FSZ), but also increased BMI.

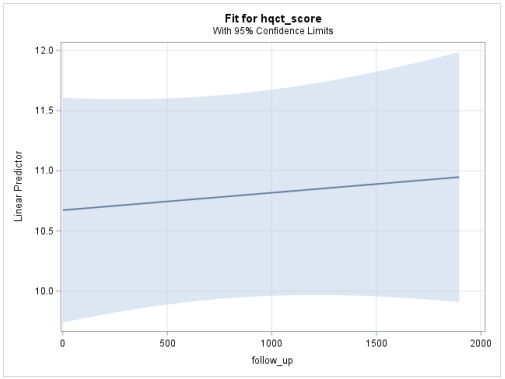
PATH for PWS

Longitudinal Analysis: Changes in HQ-CT by Age Group

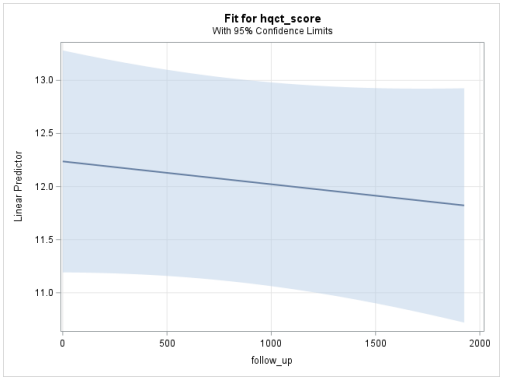
Age 5 - 11



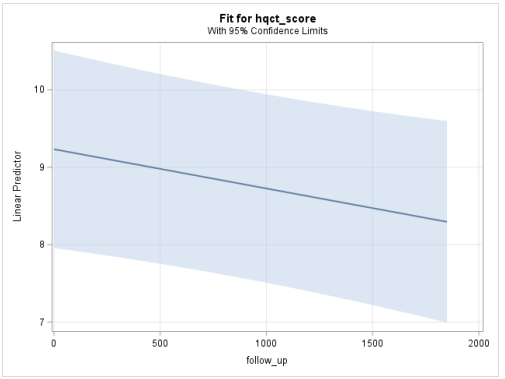
Age 12 - 17



Age 18 - 29



Age 30+



- HQ-CT is increasing the most among young children aged 5 – 11
- Increases continues during adolescence but at a slower rate
- HQ-CT levels off in early adulthood
- Slight decrease in scores observed in older individuals, age 30+
  - Controlled living situation, established routines may contribute (Matesvac et al 2023)

PATH Study Conclusions

- The PATH for PWS study, with its robust participation, provides a rich dataset to better understand serious medical events changes in behavior over time in PWS
- Extreme behaviors and mental illness are a significant concern.
- GI serious medical events are common and diverse, with many are related to poor GI motility
- Specific medical problems much more likely in the PWS population compared to the general population: e.g., knee dislocations, blood clots, seizures
- Spinal surgeries are common and are frequently associated with significant complications
- Hyperphagia as measured by HQ-CT scores increases over time in children and adolescents, and level off or drop slightly in older adults; Food Safe Zone scores go up over time

PATH for PWS™

Paving the way for Advances in Treatments & Health for PWS

SOLENO THERAPEUTICS

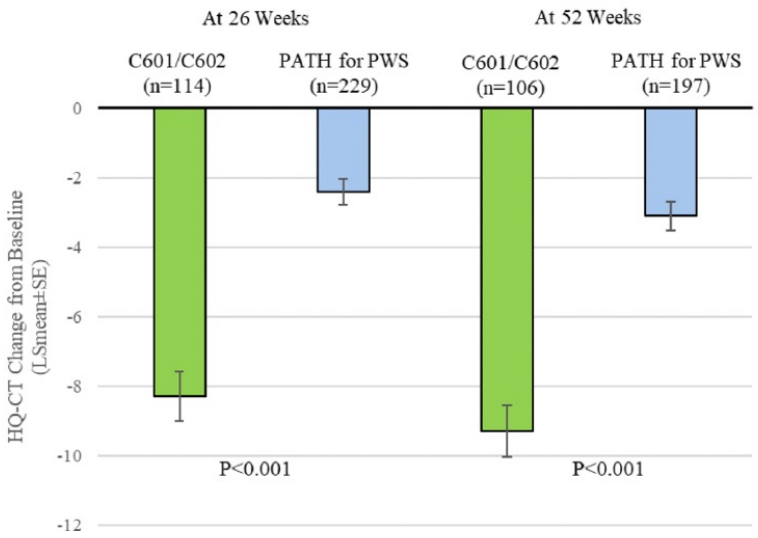
Comparison of Hyperphagia and Other Behaviors: DCCR (Soleno Therapeutics) Phase 3 C601-C602 (open label extension, 1 year) with PATH for PWS Natural History Study

Methodology for Comparison

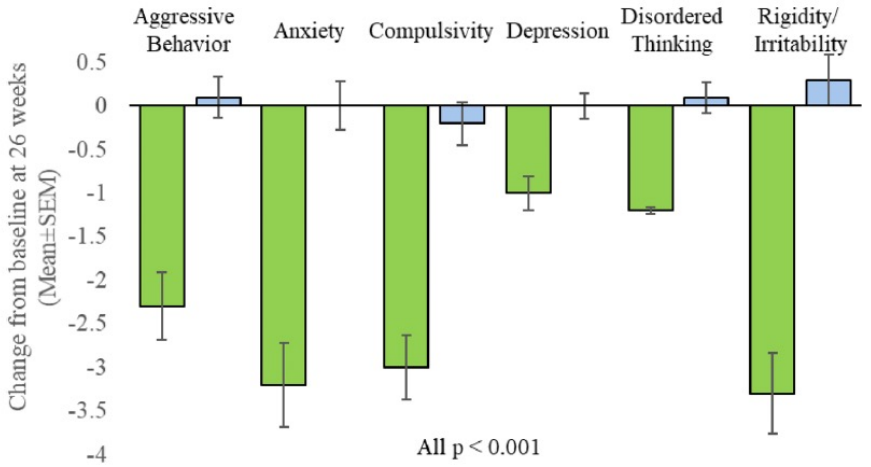
- Subset of *PATH for PWS* participants who met criteria for inclusion in the Soleno C601/602 study: age, weight, HQ-CT score
- Parameters and timepoints analyzed:
  - HQ-CT - hyperphagia
  - PWS Profile (PWSP)
    - Aggressive Behaviors, Anxiety, Rigidity/Irritability, Compulsivity, Depression and Disordered Thinking
  - Compared at 26 weeks (6 mo) and 52 weeks (1 year)
- Analysis was performed by an independent CRO

Comparison of DCCR to *PATH for PWS*: HQ-CT & PWS Profile - Change From Baseline

Change in Hyperphagia



Change in behaviors



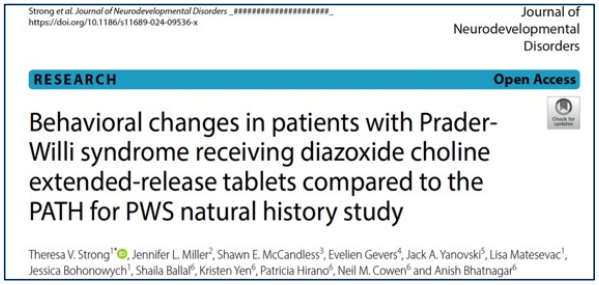
PATH for PWS

DCCR

Compared to participants in PATH for PWS who were not receiving the drug, participants treated with DCCR for 6 months or 1 year with DCCR showed:

Highly significant improvements in hyperphagia ($p < 0.001$)

Significantly greater improvements in PWS associated behaviors - aggression, anxiety, compulsivity, rigidity/irritability, depression and disordered thinking


Strong et al. Journal of Neurodevelopmental Disorders _####################_
https://doi.org/10.1186/s11689-024-09536-x

Journal of Neurodevelopmental Disorders

RESEARCH Open Access

Behavioral changes in patients with Prader-Willi syndrome receiving diazoxide choline extended-release tablets compared to the PATH for PWS natural history study

Theresa V. Strong[1*], Jennifer L. Miller[2], Shawn E. McCandless[3], Evelien Gevers[4], Jack A. Yanovski[5], Lisa Matesevac[1], Jessica Bohonowych[1], Shaila Ballaf[6], Kristen Yeri[6], Patricia Hirano[6], Neil M. Cowen[6] and Anish Bhatnagar[6]

Soleno proceeded with a randomized withdrawal study that also showed significant reduction in hyperphagia in those continuing to receive DCCR

PATH for PWS™
Paving the way for Advances in Treatments & Health for PWS

vykat™ XR
(diazoxide choline) extended-release tablets

Approved in the US in March 2025

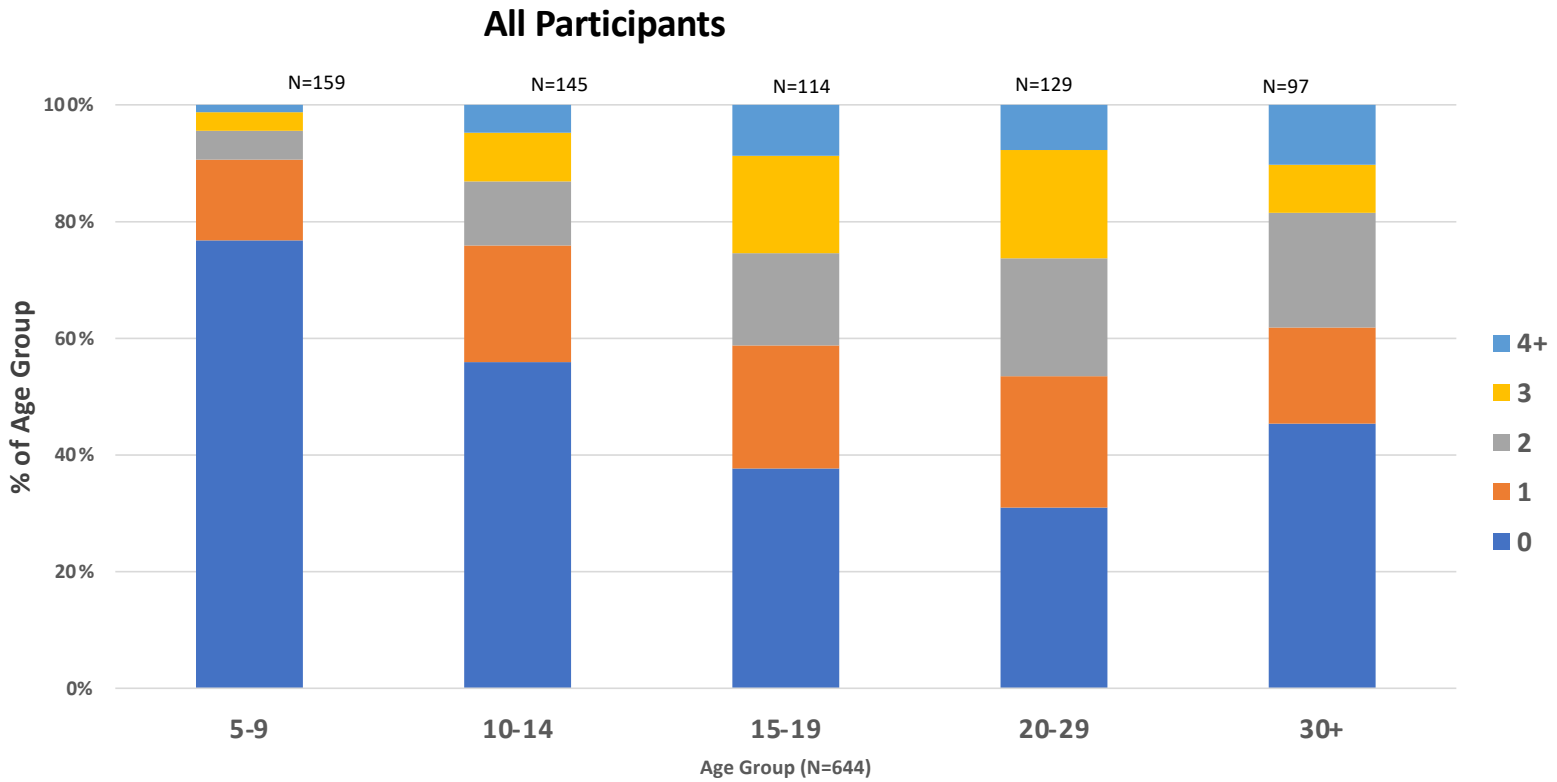
SOLENO THERAPEUTICS

Use of Psychiatric Medications in *PATH for PWS* Participants

PATH for PWS™
Paving the way for Advances in Treatments & Health for PWS

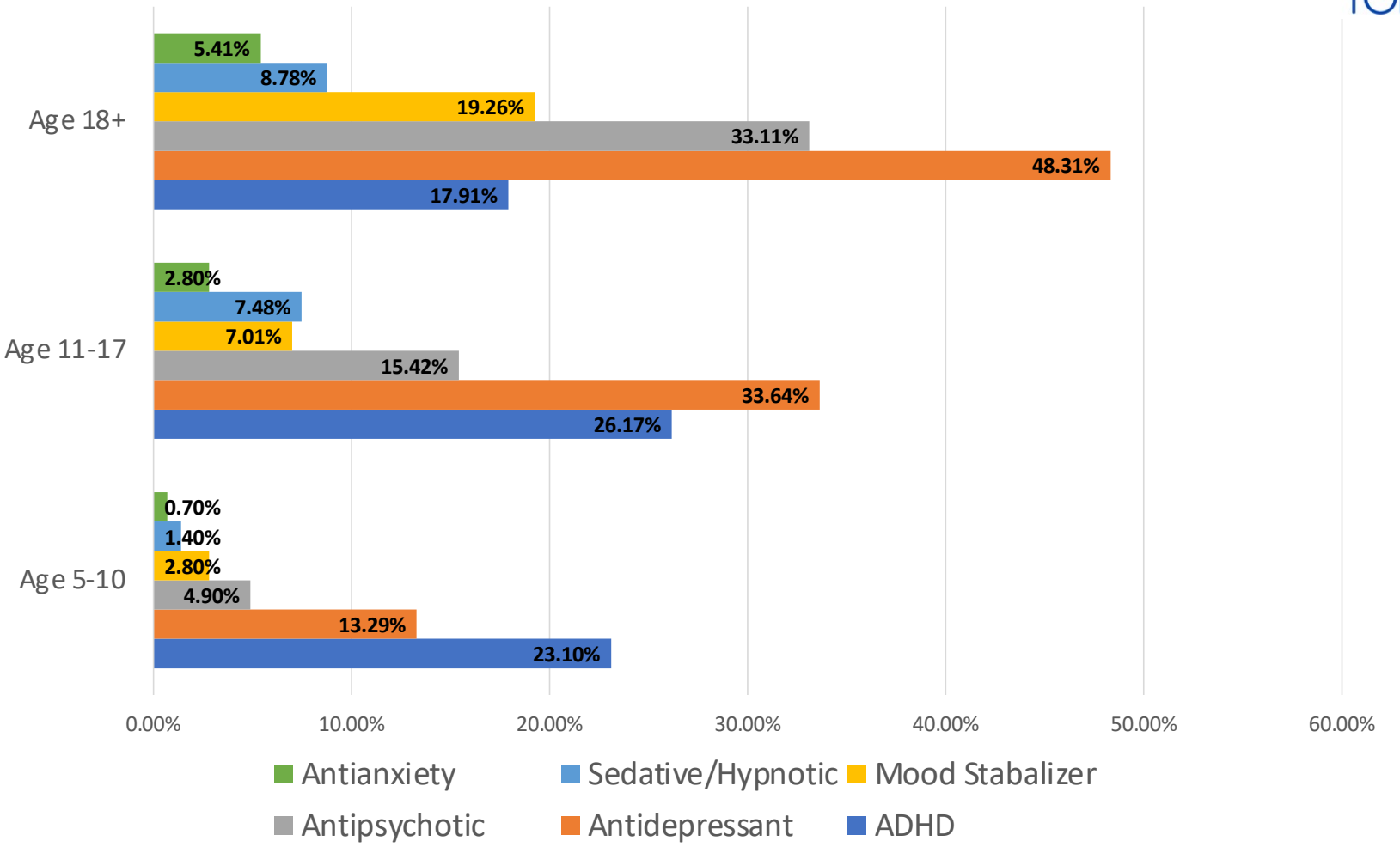
FOUNDATION FOR PRADER-WILLI RESEARCH

Psychotropic Medication Use by Age



Research need: Better data on prescribing rationale, efficacy, and long-term outcomes.

Percentage Taking 1 or More Behavior/Psych Medication by Type



How Do PWS Patients Compare?

Group	PATH for PWS	General Population
Adolescents (12–19)	**~60%** on ≥1 psych med; ~20% on ≥3 meds	6.3% on any; 1.8% on ≥2 meds
Adults (20–65)	**~2/3** on ≥1 med; high polypharmacy	16.5% on any prescription med
Antidepressants	SSRIs used by **35–40%** aged 15+	~13% antidepressant use overall
ADHD meds	Non-stimulant ADHD med use **20%** in teens/adults	ADHD med use 3.2% in adolescents

- Use of psychiatric medications is common
- Evidence of safety and effectiveness is limited
- More studies are needed to understand the benefits vs. risks of psychiatric medication use in the PWS population

PWS Clinical Trials

Active, Recently Completed, and Planned Investigational Drug Trials for PWS

COMPANY / INSTITUTION	PRODUCT	NCT #	PRECLINICAL / PHASE 1 / PHASE 2 / PHASE 3 / APPROVAL
SOLENO	DCCR	03440814	PHASE 3 COMPLETED, FDA Approved March 2025
ot4b	OXYTOCIN	04283578	PHASE 3 COMPLETED, FRANCE, add'l ongoing or planned
ACADIA	CARBETOCIN	06173531	PHASE 3 Completed
HARMONY	PITOLISANT	04257929	PHASE 3 ENROLLING
AARDVARK	ARD-101	05153434	PHASE 3 ENROLLING
PALOBIOFARMA	PBF-999		PHASE 2 Ongoing
CONSYNANCE	CSTI-500	05504395	PHASE 1 PK/PD COMPLETED
TONIX	OXYTOCIN	pending	PHASE 2 PLANNED

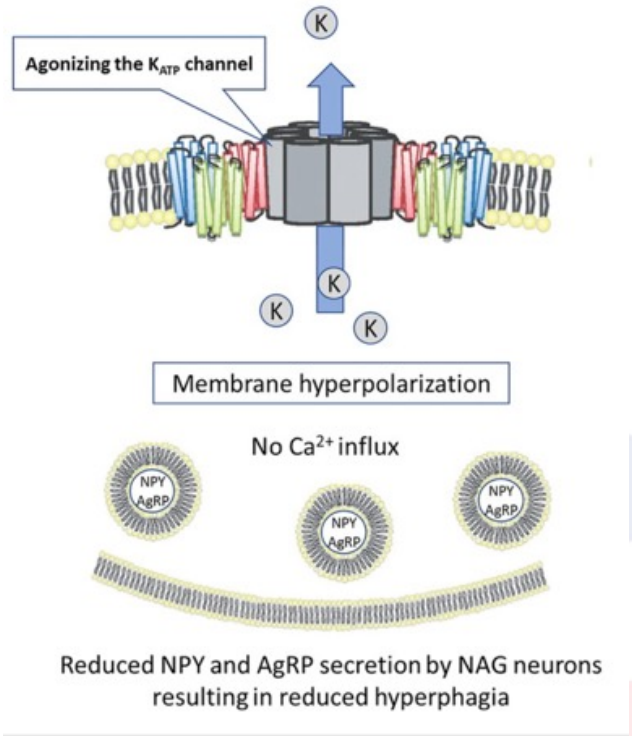
To stay up to date on PWS clinical trials: https://www.fpwr.org/pws-clinical-trials
For more info on Aardvark, Acadia and Palobiofarma clinical trials, see: https://ipwso.org/research-and-clinical-trials-update-meetings/

vykat™ XR
(diazoxide choline) extended-release tablets

www.vykatxr.com

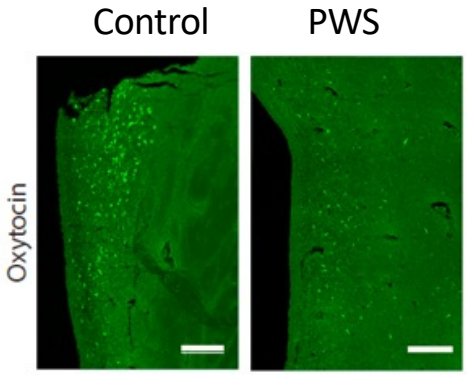
SOLENO THERAPEUTICS

- Approved in March 2025 in the US - the first FDA-approved treatment for hyperphagia in individuals with PWS, age 4+
- Marketing Authorization Application submitted to the EMA in May 2025
- MOA – thought to work by opening K_{ATP} channels, reducing release of appetite stimulating neuropeptides (NPY, AgRP)
- Most common side effects: hypertrichosis (hair growth), edema, hyperglycemia (high blood sugar)



Reduced NPY and AgRP secretion by NAG neurons resulting in reduced hyperphagia

Oxytocin as a potential therapeutic for PWS



Oxytocin reduced in the brains of individuals with PWS
Bochukova et al. doi: 10.1016/j.celrep.2018.03.018

Impaired processing and release of oxytocin in PWS cells and mouse models
Chen et al doi: 10.1172/jci.insight.138576

Administration of oxytocin to a PWS mouse model improves neonatal feeding, social development
Muscatelli et al, doi: 10.3389/fnmol.2022.1071719, doi: 10.1038/s41380-021-01227-6, doi: 10.1038/s41386-022-01313-5

Outcomes of Clinical Studies of Oxytocin in PWS have been Mixed

Oxytocin-based therapies for treatment of Prader-Willi and Schaaf-Yang syndromes: evidence, disappointments, and future research strategies
doi: 10.1038/s41398-022-02054-1

ACADIA®

Study of carbetocin nasal spray for the treatment of hyperphagia in PWS

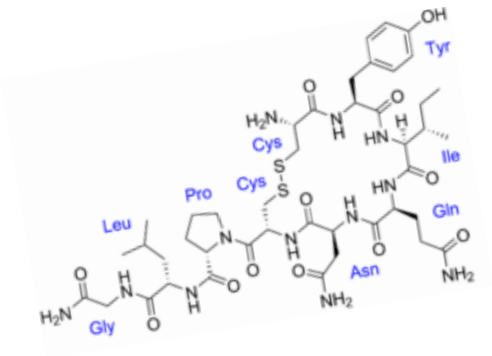
Phase 3: 170 participants: US, Canada, France, Germany, Spain, UK

12-week administration of carbetocin 3x per day

Primary outcome – reduction of hyperphagia as measured by HQ-CT

Sept 24, 2025 – Study did not meet primary or secondary outcomes

Other Oxytocin-based clinical trials



Administered to infants
Study completed in France – compassionate use
Additional studies planned internationally: European Phase 3

Phase 2 planned in US for 2026
Uses a magnesium-potentiated formulation of oxytocin

Excessive daytime sleepiness is extremely common in PWS

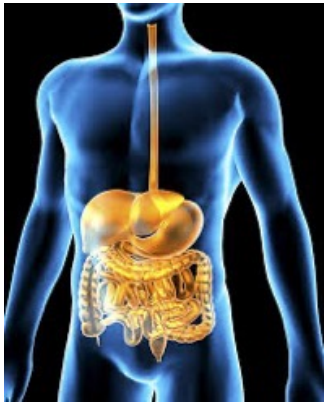
Can interfere with learning, socialization; impacts on mood

Pitolisant is a histamine-3 receptor (H3R) antagonist/inverse agonist, which has been shown to be effective in treating excessive daytime sleepiness in narcolepsy, cataplexy

Phase 3, double blind, placebo-controlled study is evaluating Pitolisant in people with PWS, age 6-65, who have daytime sleepiness; OLE

Trial sites in the US, Australia, Belgium, Canada, Czechia, Denmark, France, Germany, Italy, Poland, Romania, Spain, Sweeden, UK

Novel drug to reduce hunger in PWS



Phase 3 international study (HERO) ongoing – double blind placebo-controlled study with an OLE

ARD-101: Oral drug, gut-restricted activation of the bitter taste receptors (TAS2R)

Stimulates release of satiety hormones (CCK, etc)

Additional studies in development for hyperphagia

Phosphodiesterase 10 inhibitor (PDE10) (PBF-999)

Phase 2, single site study soon to be completed in Spain

Planning Phase 3 for late 2026

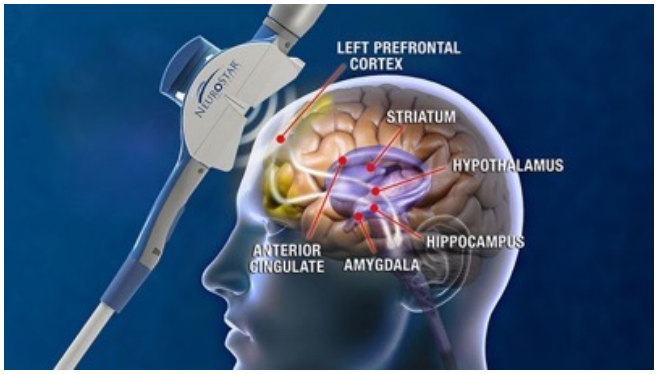
Europe, US, Australia

CSTI-500 is a triple reuptake inhibitor: serotonin, dopamine, norepinephrine

Strategy to allow personalized dosing

Phase 1 PK/PD completed; Phase 2 in planning stage

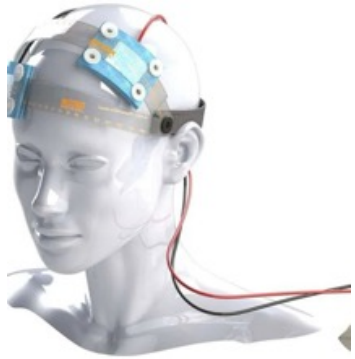
Device / Neuromodulation Approaches for the Treatment of PWS



Transcranial magnetic stimulation

Deep brain stimulation.

Bright Light Therapy



Transcranial Direct Current Stimulation

Vagus nerve stimulation

Qi et al, *Neuromodulation for the treatment of PWS- A systematic review*
doi: 10.1016/j.neurot.2024.e00339

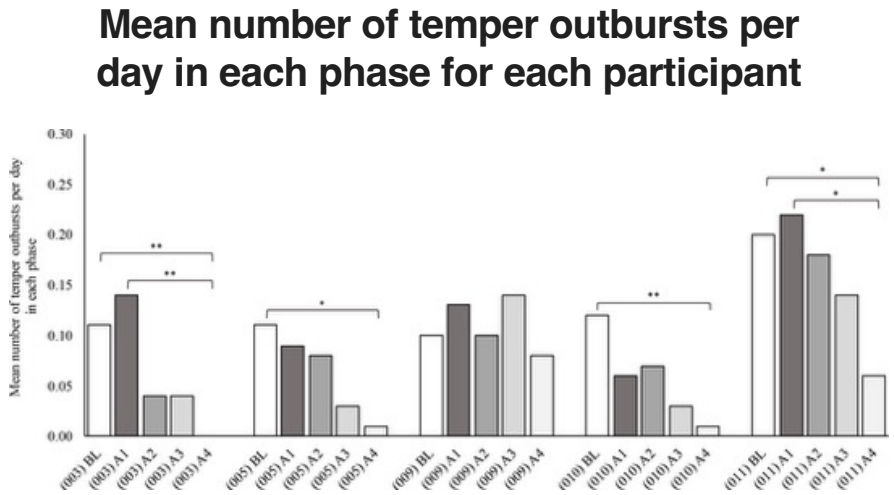
VNS4PWS

A Phase 3, Randomized, Double-Blind, Dose-Ranging, Evaluation of Transcutaneous Vagus Nerve Stimulation (tVNS) to Reduce Temper Outbursts in People with Prader-Willi Syndrome (PWS)

Sponsored by the Foundation for Prader-Willi Research (FPWR)

VNS Reduced Temper Outbursts in Pilot Studies

- Initial aim was to reduce hyperphagia – no notable impact
- iVNS reduced temper outbursts in 2 of 3 participants (Manning, 2015)
- Transcutaneous VNS led to significant reductions in temper outburst frequency
  - 6 – 9 months treatment time needed to observe improvement
- Reductions in CBI and improvement in global outcomes scales
- No significant side effects noted



Manning, *et al* 2019

STUDY AIMS

VNS 4 PWS: A phase 3 study to determine if VNS is safe and reduces temper outbursts in PWS

Evaluate safety, acceptability and efficacy of tVNS in reducing temper outbursts in PWS (10 – 40 years)

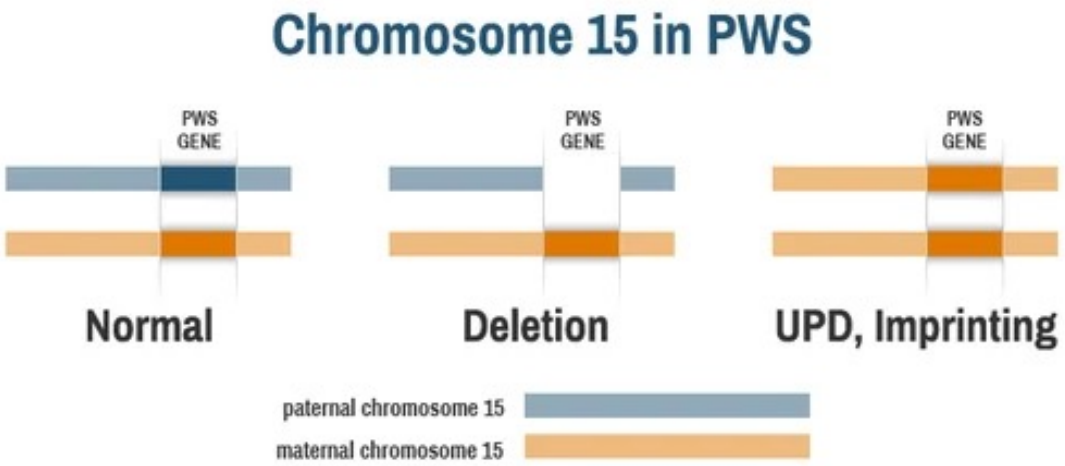
Evaluate the potential benefit beyond the temper outbursts, including hyperphagia, QOL, and caregiver burden

Determine the clinical characteristics of responders versus non-responders

15 sites in the US
85 of 102 enrolled to date, 10 in screening
Canadian citizens can participate – need to travel to the US

Looking ahead…….

Genetic Therapy for PWS



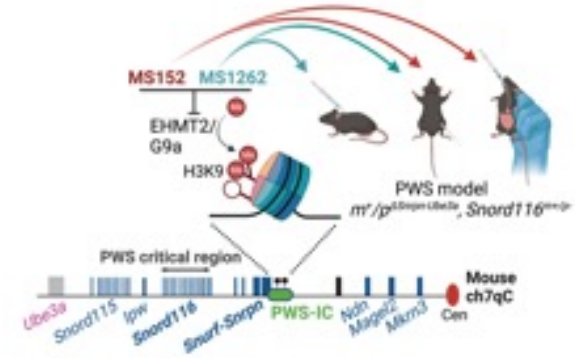
All individuals with PWS have the PWS region genes present, but silent, on the maternal chr15

The region is complex – more than one gene likely contributes to the PWS characteristics

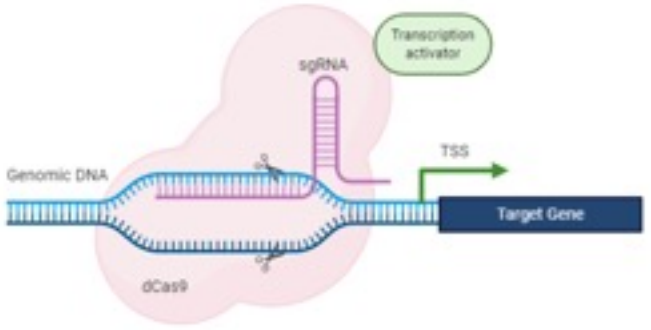
Addresses the underlying cause of PWS – potential to be transformative *

*many questions remain

Genetic Therapies for PWS
FPWR funded projects



Small molecule epigenetic modulators
Wang et al, doi: 10.1016/j.ymthe.2024.05.034
Y-h Jiang, Yale University

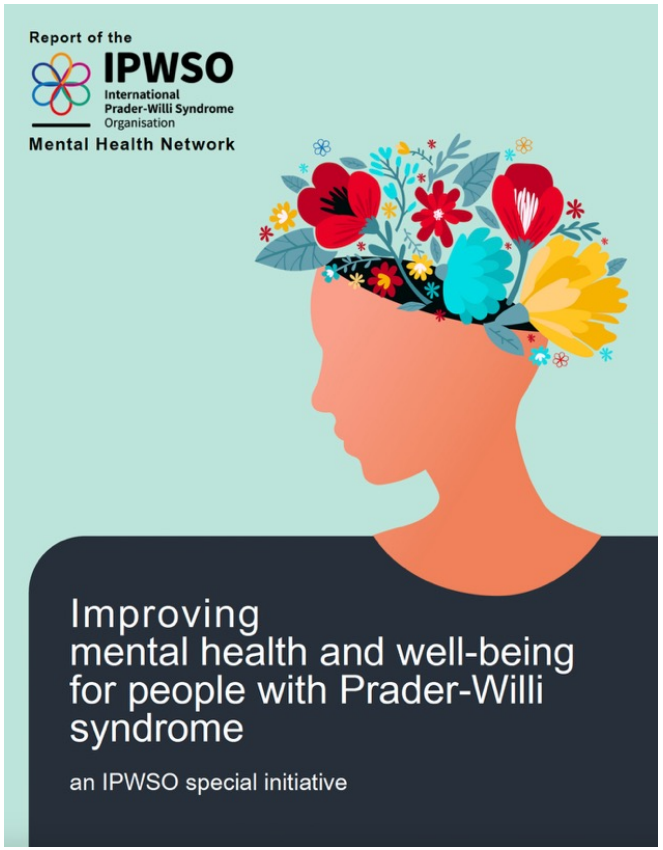


CRRISPR mediated gene activation in the PWS region
Rohm et al, doi: 10.1016/j.xgen.2025.100770
C. Gersbach, Duke University

SMCHD1 inhibition:
https://www.fpwr.org/fpwr-funded-projects/how-does-the-epigenetic-regulator-smchd1-regulate-the-pws-cluster-in-humans
M Blewitt, WEHI

Improving Mental Health and Well-Being: Outcomes from the IPWSO Mental Health Initiative

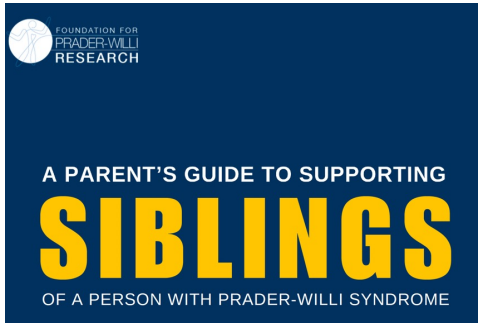
Anthony J Holland, MD



- Outcomes of a workshop at the 2022 IPWSO Workshop in Ireland, with continuing input by a subgroup of those participants
- Focus on mental health – expanded to include well-being and quality of life
- Consideration of the basis of hyperphagia, anxiousness in PWS
- Report available for download

https://ipwso.org/information-for-medical-professionals/mental-health/

Sibling concerns



References and Support:

- https://www.fpwr.org/supporting-siblings
- https://ipwso.org/information-for-families/siblings/
- Kamble et al. *Experiences and Support Needs of Siblings of Individuals with Prader-Willi Syndrome-Findings from a Two-Stage Qualitative Study*. J Appl Int Dis Res 2025
- Pule & Hughes. *Anxiety, Depression and Stress in Parents and Siblings of People Who Have Prader-Willi Syndrome: Morbidity Prevalence and Mitigating Factors*. J Intellect Disabil Res. 2025

How can I support PWS research?

Sign up for the Global PWS Registry and complete surveys

Sign up for the “Clinical Trial Alert” – this also includes non-clinical trial opportunities: https://www.fpwr.org/pws-clinical-trials

Learn about / consider participating in a clinical trial

Volunteer to be an Advocate Reviewer (caroline@fpwr.org)

Participate in a fundraiser

MY HQ

VANDERBILT UNIVERSITY

Age 10 & Up
15 min Zoom call
Elizabeth.roof@Vanderbilt.edu
https://www.fpwr.org/blog/help-advance-pws-treatments-by-joining-the-my-hq-project

Acknowledgements

Thank you:
Research Participants & Caregivers

At FPWR:
Lisa Matesevac, AuD
Jessica Bohonwych, PhD
Caroline Vrana-Diaz PhD
Marc Ridilla, PhD
Lauren Schwartz, PhD

Collaborators
Vanderbilt University
Elisabeth Dykens, PhD
Elizabeth Roof, MA
NORD/RDCA-DAP
Aliza Fink, D.Sc

Study Investigators for PATH Medical Review
Jennifer Miller, MD — U Florida
Shawn McCandless, MD — Colorado U
Jim Strong, MD — Grandview Medical Ctr, AL
Deepan Singh, MD – psychiatric medication

PATH COMMUNITY PARTNERS

Thank you, fundraisers!