

The JUMP (Journey to Understand MMA and PA) Study

A Natural History Study

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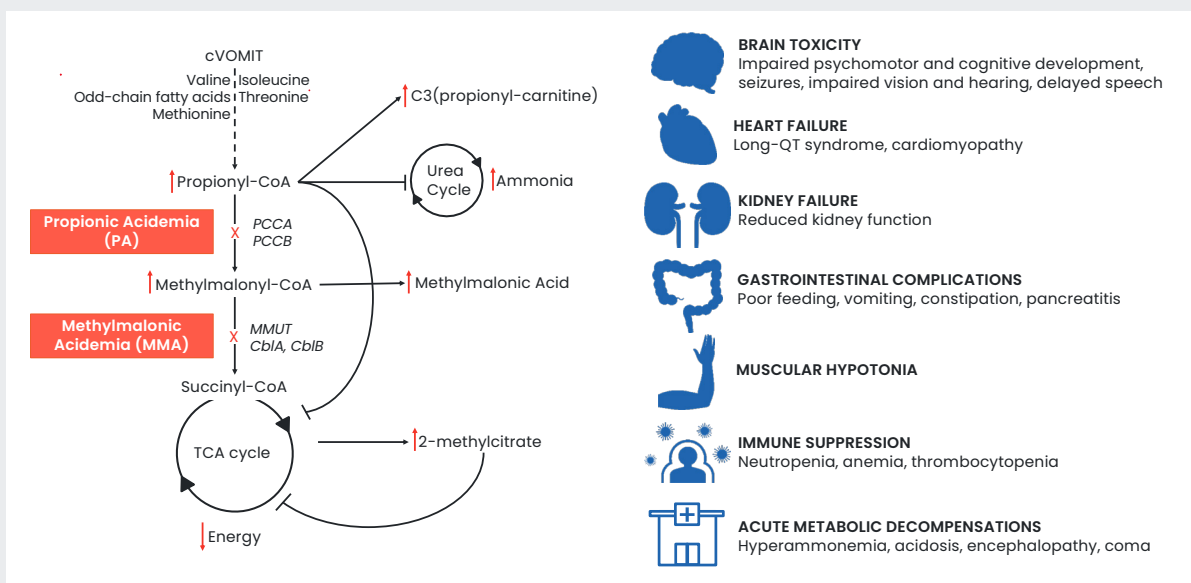
ABSTRACT

Methylmalonic acidemia (MMA) and propionic acidemia (PA) are extremely rare organic acidemias affecting renal, immune, CNS, hepatic, hematologic, and cardiovascular systems. The incidence in the United States is ~1 in 70,000 for MMA and ~1 in 240,000 for PA.* These diseases are associated with significant morbidity and mortality in infancy and childhood, and for survivors, significant debilitating end-organ damage into adulthood. Because they are so rare, there is a great need to better understand these diseases to improve patient care and accelerate drug development.

HemoShear Therapeutics, Inc. is developing HST5040, an oral small molecule in clinical trials to treat MMA and PA. HemoShear has engaged with AllStripes Research, a healthcare technology platform dedicated to rare disease research, to conduct a natural history study named JUMP (Journey to Understand MMA and PA). The objectives of JUMP are to obtain real-world evidence to inform the design of MMA and PA clinical trials and generate evidence for potential surrogate markers likely to predict disease severity and/or clinical benefit. The AllStripes platform enables participants to access and manage their medical records while also contributing their aggregated and de-identified health information to research projects.

The JUMP study will recruit up to 120 patients diagnosed with MMA or PA through age 18 in the US, Canada, and the UK. The study has been piloted with up to 10 participants for an initial assessment before the project is launched to the greater MMA and PA community. An overview of the platform, study design, and pilot results of five patients are provided.

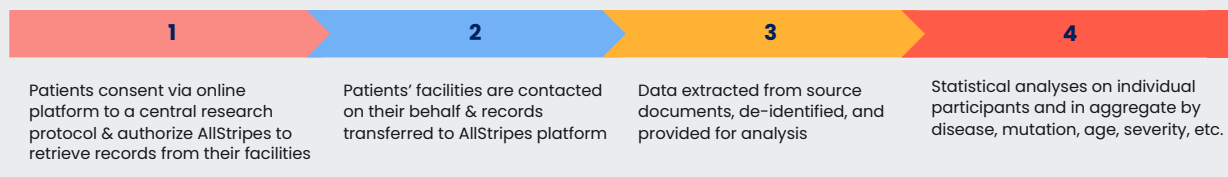
METHYLMALONIC ACIDEMIA (MMA) AND PROPIONIC ACIDEMIA (PA)



SCOPE OF NATURAL HISTORY STUDY

- JUMP is a collaboration between HemoShear and AllStripes to accelerate understanding of MMA and PA for all stakeholders – families, academia, clinicians, and industry
- HemoShear will analyze the de-identified data from medical records from MMA and PA patients to better understand the clinical features, natural history, and progression of disease over time
 - Retrospective:** data abstracted from electronic health records and paper records, neuropsychological, developmental, and academic assessments
 - Prospective:** genetic testing, periodic collection of blood samples from participants, and completion of health-related questionnaires in addition to collection of medical records throughout the duration
- The study goal is to recruit ~120 participants (60 PA: 60 MMA)

DATA COLLECTION AND ANALYSIS



SUMMARY

What Are We Seeking to Learn from JUMP?

- Assess annual frequency of acute metabolic decompensations requiring hospitalizations, emergency room visits, and home emergency protocol use (events and duration in days) by disease diagnosis and age
- Evaluate how biomarkers correlate with disease diagnosis and clinical severity, and how levels change over time, with diet, or with interventional treatments
- Assess clinical severity according to the frequency and severity of acute metabolic decompensations and major disease-related morbidities

Encouraging Initial Results from the Pilot Study

- Full analysis for completeness of data abstracted into study modules is ongoing, but initial results are promising for the number of entries across five patients
- The Healthcare Encounters module can be utilized to determine the frequency and duration of days of an ED and/or hospital visit over the age range of the patient
- This approach has the potential to minimize the need for clinicians and institutions to input data into natural history databases

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PRELIMINARY PILOT DATA ON FIRST FIVE PARTICIPANTS

Figure 1. Demographic and Diagnosis Data from Five Participants Analyzed in JUMP Pilot

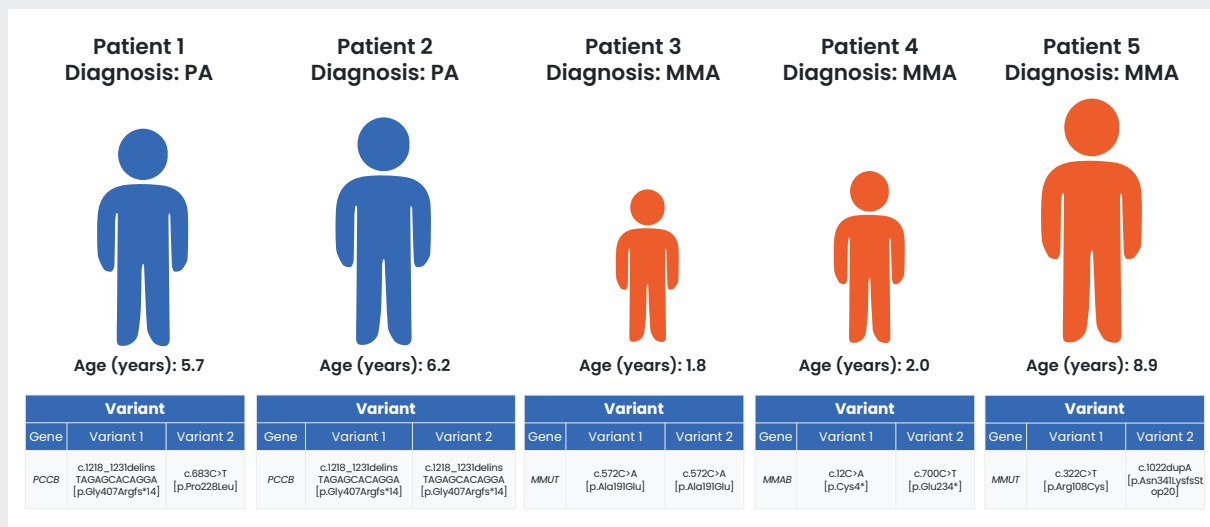


Table 1. Data Categories Collected for Analysis

Category	Study module (abstraction)	Number of data entries across 5 patients
Clinical manifestation	MMA / PA symptoms and comorbidities	80
	Developmental milestones and progression	5
Clinical measurement	Echocardiogram	14
	Electrocardiogram	25
	Growth monitoring	146
	Imaging (x-rays, CT scan, ultrasounds)	135
Laboratory monitoring	Vision testing	1
	Neurocognitive Testing	0
	Carnitine (total, free) and acylcarnitine (C3, C2) profile	18
	Ammonia, anion gap, creatinine	149
	Methylmalonic acid and 2-methylcitric acid (plasma)	47
Management	Amino acids	78
	Blood count With differential	54
	Medications and supplements	21
	Alimentation (formula, feeding tube use)	11
	General assistive devices	1
	Therapy assessments	8
Hospitalization & crisis	Surgeries and procedures	16
	Healthcare encounters (ED, hospitalization)	116
Quality of Life	Acute metabolic decompensations (AMD)	36
	Activities of Daily Living and Quality of Life	0

Figure 2. Hospitalization and Emergency Department Visit Frequency and Duration

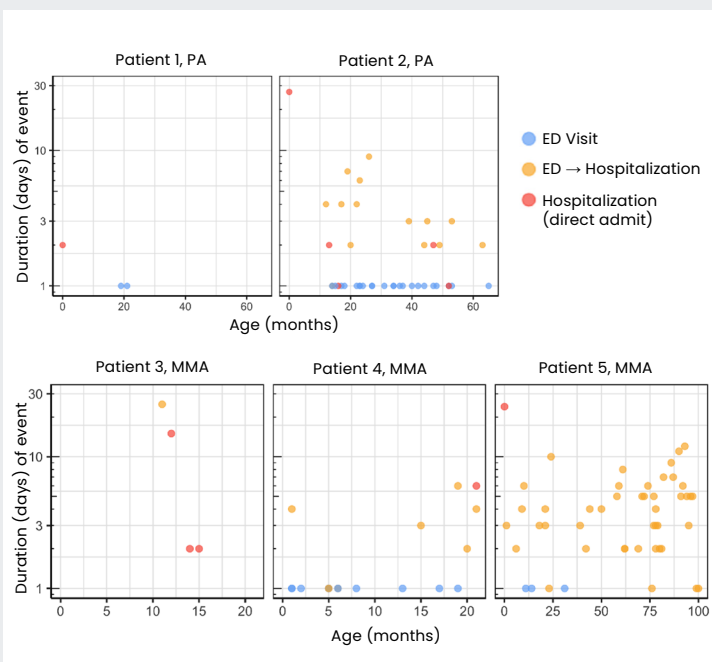
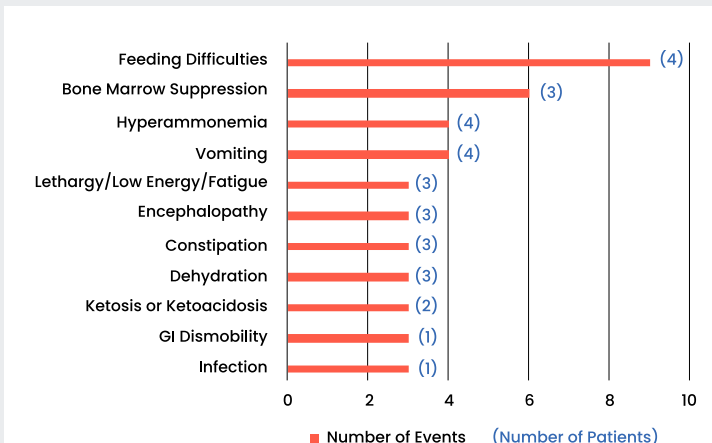


Figure 3. Frequent Symptoms and Comorbidities in PA and MMA Patients



This figure reflects the most frequently reported symptoms and comorbidities as defined by at least 3 events in medical records. This analysis is preliminary, may change based on the analysis of additional medical records, and may not reflect the experience of the larger MMA and PA population.