The JUMP (Journey to Understand MMA and PA) Study
A Natural History Study

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ABSTRACT

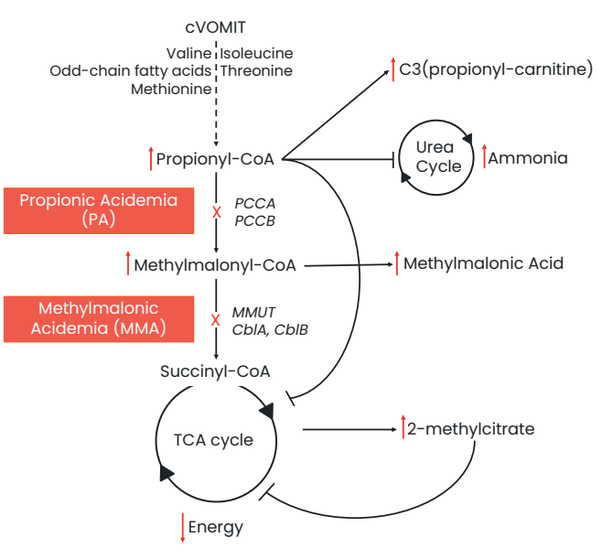
Methylmalonic acidemia (MMA) and propionic acidemia (PA) are extremely rare organic acidemias affecting renal, immune, CNS, hepatic, hematologic, and cardiovascular systems. These diseases are associated with significant morbidity and mortality in infancy and childhood, and for survivors, significant 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.

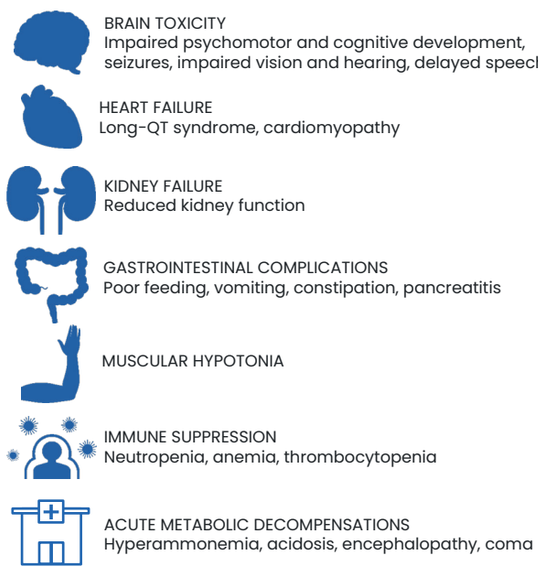
HemoShear Therapeutics is developing HST5040, an oral small molecule in clinical trials to treat MMA and PA. HemoShear has engaged with AllStripes Research, a healthcare technology platform dedicated to rare disease research, to conduct a natural history study named JUMP (Journey to Understand MMA and 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. Participants or their legal guardians will provide informed consent, authorize the release of their medical records, and provide self-reported information through the secure online platform. The AllStripes staff will request and collect medical files from all the participants' treating institutions. In addition, participants can also opt in to provide blood samples for periodic monitoring of key metabolites and undergo a genetic test to confirm the diagnosis of MMA or PA. Data collected will be abstracted, de-identified, and shared with HemoShear for analysis. Data gleaned from medical records will include the frequency and length of hospitalizations, emergency home treatment protocol use, surgeries, developmental history, laboratory values, alimentation method and intake, and neurocognitive testing. The pilot study is looking for up to 10 participants to consent to participate in an initial assessment before the research 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)

- Methylmalonic acidemia (MMA) and propionic acidemia (PA) are rare, autosomal recessive intoxication-type disorders of propionic acid metabolism.
- The incidence in the United States is ~ 1 in 70,000 for MMA and ~ 1 in 240,000 for PA.*
- PA and MMA, which can be identified by newborn screening, are characterized by the accumulation of toxic primary and secondary metabolites derived from unmetabolized precursors (cVOMIT) originating from the diet, endogenous catabolism, or the intestinal microbiota.
- These multi-systemic diseases affect renal, gastrointestinal, immune, central nervous system, hepatic, hematologic, and cardiovascular systems, resulting in morbidity and mortality in infancy and childhood, and for survivors, debilitating end-organ damage and death into adulthood.





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

1	2	3	4
Patients consent via online platform to a central research protocol & authorize AllStripes to retrieve records from their facilities	Patients' facilities are contacted on their behalf & records transferred to AllStripes platform	Data extracted from source documents, de-identified, and provided for analysis	Statistical analyses on individual participants and in aggregate by disease, mutation, age, severity, etc.

JUMP
Journey to Understand MMA and PA

HEMOSHEAR THERAPEUTICS

AllStripes

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PRELIMINARY PILOT DATA ON FIRST FIVE PARTICIPANTS

Table 1. Demographic data from five participants analyzed in JUMP pilot

Patient	Diagnosis	Age (years)	Variant		
			Gene	Variant 1	Variant 2
1	PA	5.7	*PCCB*	c.1218_1231delins TAGAGCACAGGA [p.Gly407Argfs*14]	c.683C>T [p.Pro228Leu]
2	PA	6.2	*PCCB*	c.1218_1231delins TAGAGCACAGGA [p.Gly407Argfs*14]	c.1218_1231delins TAGAGCACAGGA [p.Gly407Argfs*14]
3	MMA	2.0	*MMAB*	c.12C>A [p.Cys4*]	c.700C>T [p.Glu234*]
4	MMA	1.8	*MMUT*	c.572C>A [p.Ala191Glu]	c.572C>A [p.Ala191Glu]
5	MMA	8.9	*MMUT*	c.322C>T [p.Arg108Cys]	c.1022dupA [p.Asn341LysfsStop20]

Figure 1. Hospitalization and Emergency Department Visit Frequency and Duration

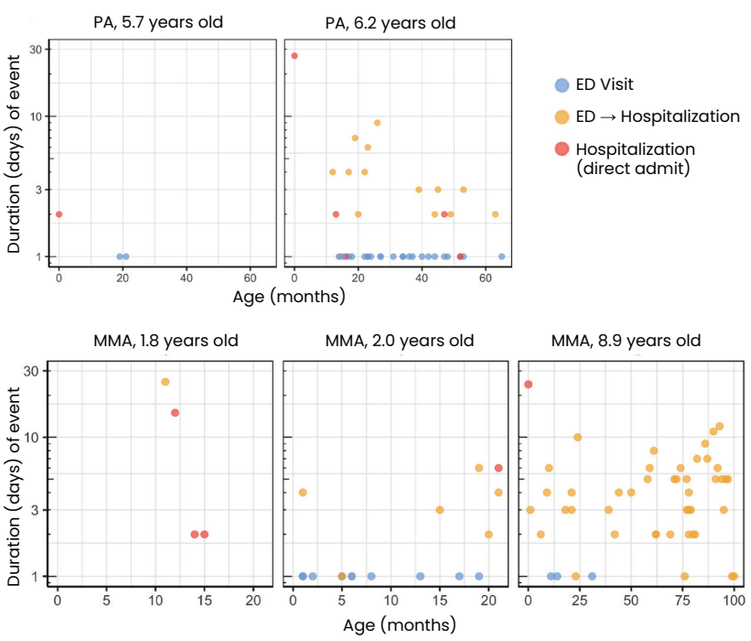

Table 2. Data categories collected for analysis

Category	Study module (abstraction)	Number of data entries across 5 patients
Patient information and diagnosis	Demographics	5
	MMA or PA diagnosis (NBS, biochemical, genetic)	5
	Pre-diagnostic journey (care, diagnosis, symptoms)	5
	Genetic testing	5
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
	Vision testing	1
	Neurocognitive Testing	0
Laboratory monitoring	Carnitine (total, free) and acylcarnitine (C3, C2) profile	18
	Ammonia, anion gap, creatinine	149
	Methylmalonic acid and 2-methylcitric acid (plasma)	47
	Amino acids	78
	Blood count With differential	54
Management	Medications and supplements	21
	Alimentation (formula, feeding tube use)	11
	General assistive devices	1
	Therapy assessments	8
	Surgeries and procedures	16
Hospitalization & crisis	Healthcare encounters (ED, hospitalization)	116
	Acute metabolic decompensations (AMD)	36
Quality of Life	Activities of Daily Living and Quality of Life	0

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

*Chapman et al., 2018, Mol Genet Metab Rep.