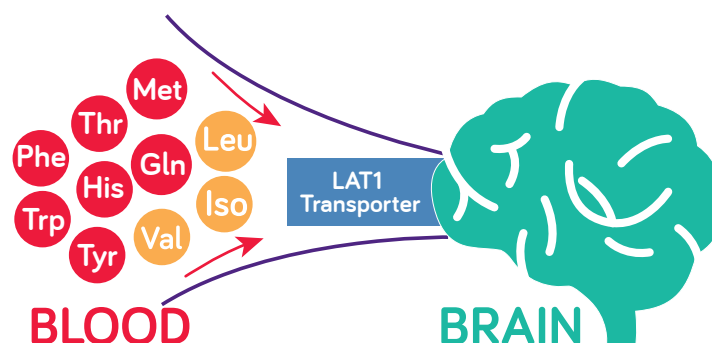


# UNDERSTANDING THE SCIENCE AND RESEARCH BEHIND COMPLEX MSD MEDICAL FOODS

## COMPLEX MSD IS THE ONLY SPECIALIZED FORMULA FOR MSUD SUPPORTED BY OVER 10 YEARS OF CLINICAL DATA

In 2005, the Clinic for Special Children (CSC) in Strasburg, PA collaborated with Nutricia North America (Applied Nutrition Corp. at the time) to develop Complex MSD, a range of specialized formulas\* for the dietary management of maple syrup urine disease (MSUD).

Complex MSD has a unique amino acid profile; it was designed based on the known competitive cerebral uptake of the branched-chain amino acids (BCAAs: leucine, isoleucine, and valine) and 7 other amino acids (phenylalanine, tryptophan, methionine, tyrosine, histidine, threonine, and glutamine) at the blood-brain barrier.<sup>1</sup> These 10 amino acids are shuttled into the brain via the LAT1 transporter. The quantities of each amino acid transported into the brain depend on the concentrations of their competitors in the blood.<sup>2</sup> Accordingly, for patients with MSUD, LAT1 uptake of the BCAAs into the brain is estimated to be very high because blood concentrations of BCAAs are chronically elevated.



Utilizing this known competition, Dr. Strauss and his colleagues developed a model to estimate the uptake of each LAT1 amino acid into the brain for a given plasma amino acid profile.<sup>1-3</sup> This model was the basis for developing the amino acid composition of Complex MSD. The amounts of the 7 non-BCAAs were increased in the formulation, as compared to high biological value proteins. The intention of the amino acid composition was to help safeguard the brain against the amino acid deprivation that is caused by chronic elevations of leucine in MSUD.

Complex Junior MSD Drink Mix (the original Complex MSD formula) was designed to include essential fatty acids, vitamins, and minerals to help support normal development and reduce nutrient deficiencies historically documented in other patients with inborn errors of amino acid metabolism.<sup>4-6</sup>

The Clinic for Special Children conducted a prospective 3-year clinical trial of Complex Junior MSD Drink Mix in 15 young children with classical MSUD. The results, published in 2010, showed that young patients managed with Complex Junior MSD demonstrated normal growth and development. Patients showed improved metabolic control over previous formula usage. Additionally, hospitalization frequency and duration were reduced.<sup>3</sup>

\*Complex MSD formulas are medical foods for the dietary management of maple syrup urine disease and must be used under medical supervision.

## GROUNDBREAKING 2020 PUBLICATION ON MSUD FEATURES A SUBSET OF PATIENTS MANAGED WITH COMPLEX MSD MEDICAL FOODS

In a 2020 publication, Dr. Kevin Strauss and colleagues presented a retrospective study on the clinical outcomes of 184 MSUD patients, the largest single-center MSUD cohort publication.<sup>7</sup>

Between 2005 and 2018, a subset of 41 patients<sup>†</sup> were managed with Complex MSD as their metabolic formula, a key component of MSUD nutrition management. These patients are the basis for contemporary dietary management recommendations by the authors.

The 41 patients followed strict nutritional protocols when well and during illness. Routine clinical management included frequent amino acid monitoring (every 1-2 weeks) and monthly clinic visits to assess growth, monitor neurological development, and obtain more extensive laboratory studies. These monitoring tools helped determine patients' current leucine tolerance. Dietary intake of leucine, supplemental valine and isoleucine, and metabolic formula were adjusted as needed based on these factors.



To hear first-hand from the author about the publication and the formula design, visit [NutriciaLearningCenter.com](https://www.NutriciaLearningCenter.com) to view our recorded webinar presented by Dr. Strauss.



### Key Outcomes for the Patients on Complex MSD formulas:

- Complex MSD formulas are safe and help support metabolic control
- Normal growth and nutritional status
- Continued decreased hospitalization rate compared to pre-Complex MSD usage
- Normal achievement of childhood milestones compared to unaffected age-matched siblings

### Complex MSD is safe and helps supports metabolic control

Complex MSD formulations were shown to be safe and displayed acceptable plasma amino acid levels. Plasma concentrations of phenylalanine, tryptophan, methionine, tyrosine, histidine, threonine, and glutamine stayed within 2 standard deviations (SD) of the reference mean. Average BCAA plasma concentrations remained within acceptable limits (+3 SDs above the reference mean).

### Normal growth and nutritional status

All 41 patients had normal trajectories for weight, length, and head circumference when compared to the World Health Organization reference curves. Biochemical markers of nutritional status<sup>‡</sup> were normal for all patients, even those obtaining 85% or more of their daily protein from Complex MSD.

<sup>†</sup>All 41 patients were *BCKDHA* c.1312T>A homozygous, a genetic variant of classical MSUD characteristic of the North American Old Order Mennonites. CSC's primary patient population is Old Order Mennonite and Amish.

<sup>‡</sup>Nutrition-focused laboratory studies included serum electrolytes, creatinine, glycohemoglobin, hemoglobin, albumin, total protein, hepatic transaminases, alkaline phosphatase, cell counts, red cell indices, total iron binding capacity, ferritin, 25-hydroxyvitamin D, folate, vitamin B12, and carnitine profiles.

## Continued decreased hospitalization rate compared to pre-Complex MSD usage

Overall, MSUD patient hospitalizations have decreased dramatically since the Clinic for Special Children's creation in 1989. Implemented changes to disease management, including the development and use of Complex MSD beginning in 2005, have contributed to the continued decrease in hospital days for this MSUD population.

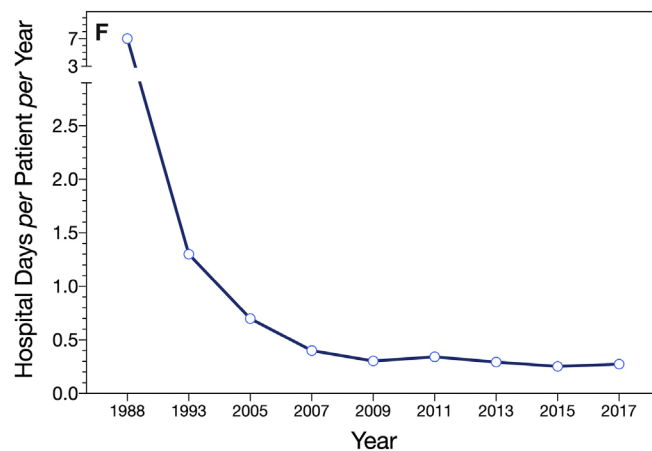
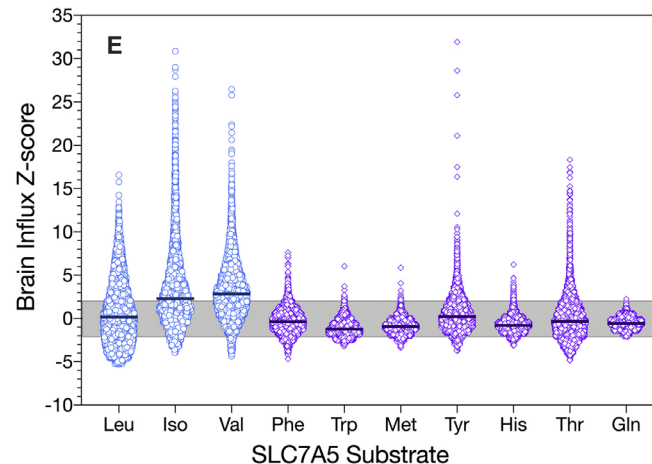


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## Estimated brain amino acid uptake partially preserved

Complex MSD partially preserved the estimated uptake of the 7 LAT1 amino acids (shown in Fig. E as purple diamonds) into the brain, which in principle helps to compensate for the amino acid imbalance characteristic of MSUD.

While the management and care of MSUD have greatly improved, MSUD remains a life-threatening disorder. In addition, patients are at increased risk of cognitive impairment and other psychological and psychosocial challenges as they get older.



SLC7A5 is another term for LAT1. Figure used with author's permission.<sup>7</sup>

## Patients demonstrated the need for high nutritional reliance on metabolic formula

As expected, weight-adjusted leucine tolerance decreased as patients grew older, and the reliance on BCAA-free metabolic formula as a source of BCAA-free protein increased to about 90% in adolescents. Throughout the lifespan, total protein intake (from intact sources and BCAA-free formula) was 25-50% above the RDA.

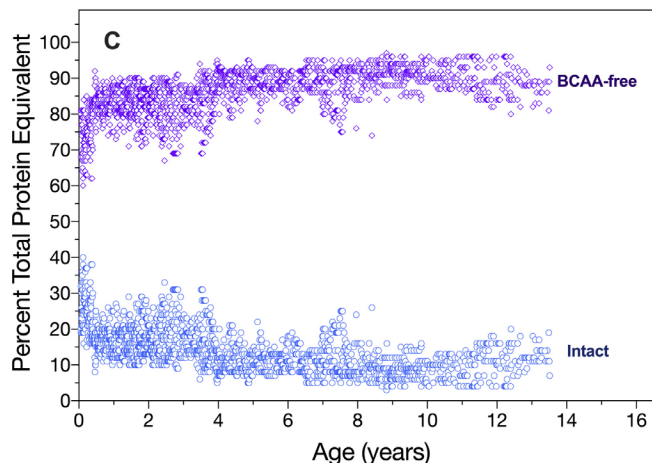
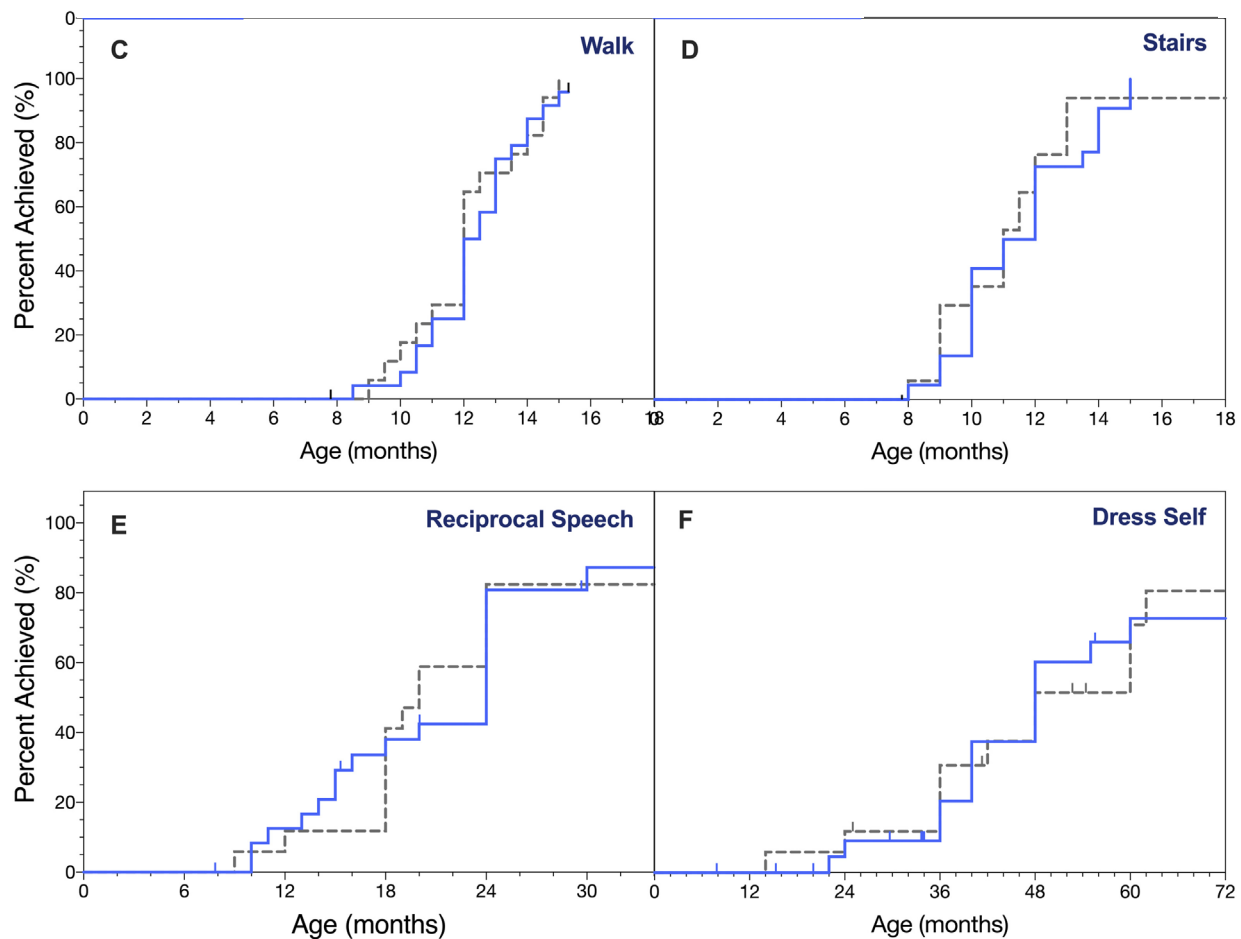


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## Normal achievement of childhood milestones compared to unaffected, age-matched siblings

In addition to normal growth, patients managed with Complex MSD (blue lines) achieved childhood milestones, such as walking (C), climbing stairs (D), reciprocal verbal communication (E), and self-dressing without assistance (F) at ages comparable with their unaffected siblings (grey dotted lines).



Figures used with author's permission.<sup>7</sup>

**Summary:** Complex MSD is a unique range of MSUD formulas with over 10 years of published data on safety and efficacy. The products are safe, well-tolerated, and support normal growth, nutritional status, and early milestone acquisition in classical MSUD patients. When paired with improvements in clinical management, Complex MSD helps to support metabolic control and reduced hospitalizations.

### REFERENCES

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