GLYTACTIN RESEARCH SUMMARY

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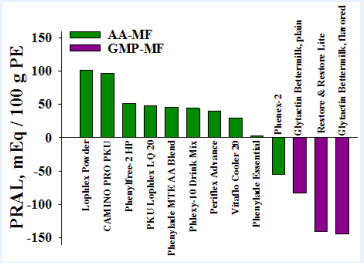
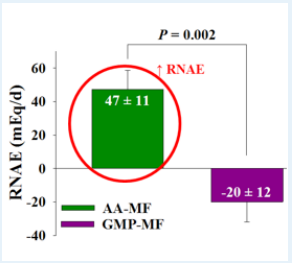
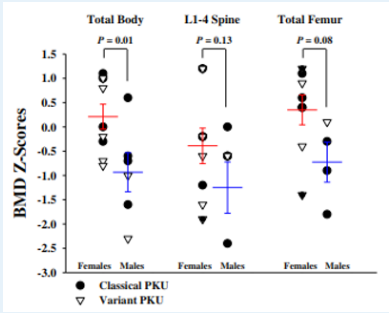
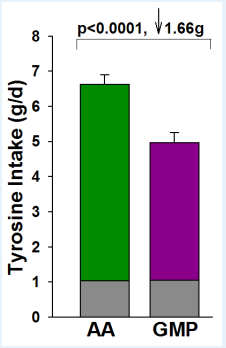
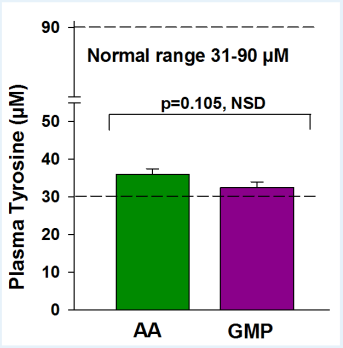
Additional Data Insights from the 30 subject Prospective, Randomized, Crossover Study (Ney DM, et al. – AJCN 2016).

Study	Participants & Analysis	Findings	Supporting Data	Conclusions by Authors
Stroup BM, et al. Amino acid medical foods provide a high dietary acid load and increased urinary excretion of renal net acid, calcium, and magnesium compared with glycomacropeptide medical foods in phenylketonuria. J Nutr Metab. 2017 May; 2017:1909101 PMID: 28546877	Subset of 8 participants • Ages: 16-35 years • Gender: 4 females, 4 males • Classical PKU (n=4) Variant PKU (n=4) • Excess body fat: 2 females, 3 males **Data collected:** • 3-day food diaries for each arm of study • Dietary acid loads of all medical foods utilized in the study • 24-hour urine samples	• 25% of participants had low Bone Mineral Density-for-age, both were males • Dietary protein, calcium, and magnesium intake were similar • AA-MF provided 1.5–2.5-fold higher Potential Renal Acid Load (PRAL) and resulted in 3- fold greater renal net acid excretion • **Urinary excretion of calcium and magnesium were reduced by 40% and 30% respectively while consuming Glytactin GMP-MF**	 	• The high dietary acid load of AA-MF likely contributing to the etiology of skeletal fragility in PKU • Glytactin GMP-MF promotes retention of calcium and magnesium which can then be used for bone mineralization
Stroup BM, et al. Sex differences in body composition and bone mineral density in phenylketonuria: a cross-sectional study. Mol Genet Metab Rep 15 (2018) 30-35	Subset of 15 participants • Ages: 15-49 years • Gender: 9 females, 6 males • Classical PKU (n=8) Variant PKU (n=7) • Participants reported life-long compliance with AA-MF **Data collected:** • DXA scan evaluated to determine impact of AA-MF on bone mineral density	• Only 50% percent of male participants had total body BMD Z-scores above −1.0 • Males tended to consume more grams of protein equivalents per day from AA-MF than females (means ± SE, males: 67 ± 6 g, females: 52 ± 4 g) • Males showed a trend for higher urinary calcium excretion compared to females • Males had a low-normal lean mass based on the appendicular lean mass index (ALIM), but were similar to the female participants		• Males with PKU have lower BMD compared with females with PKU which may be related to higher intake of AA-MF and greater calcium excretion • Calcium and magnesium excretion is lower with Glytactin GMP-MF
Ney DM, et al. Metabolomic changes demonstrate reduced bioavailability of tyrosine and altered metabolism of tryptophan via the kynurenine pathway with ingestions of medical foods in phenylketonuria. Mol Genet Metab. 2017 Jun;121(2):96-103. PMID 28400091	Subset of 18 subjects • Age: 15-49 years • Gender: 10 females, 8 males • Classical PKU (n=11) • Variant PKU (n=7) **Data collected:** • Metabolomic analysis was conducted on plasma (n= 18) and urine (n= 9) samples	• **Intake of Tyr and Trp was ~50% higher with AA-MF but concentrations in the blood were not significantly different** • For subjects with variant PKU, plasma serotonin levels were 3-fold higher and these levels increased with ingestion of Glytactin GMP-MF • Urinary excretion of tyramine (headaches) and phenol sulfate (nephrotoxic) were 50–90% higher with ingestion of AA-MF • With AA-MF, a greater portion of Tyr is metabolized through the kynurenine pathway which is associated with inflammation-related neuropsychiatric diseases	 	• Bioavailability of Tyrosine and Tryptophan are improved with Glytactin GMP-MF, possibly due to the prebiotic properties of GMP • Glytactin GMP prevents the diversion of Trp away from serotonin synthesis thus increasing plasma levels and reducing the inflammatory response

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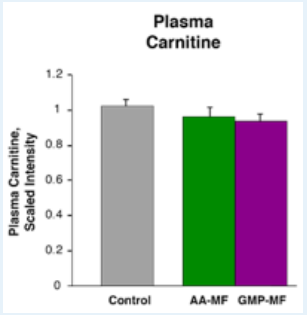
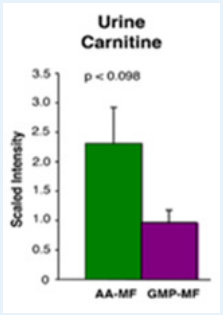
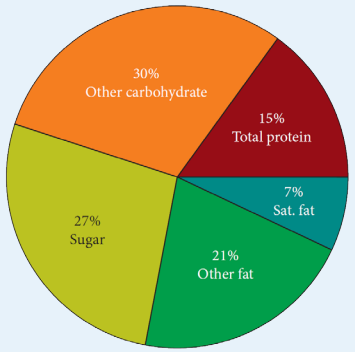
Study	Participants & Analysis	Findings	Supporting Data	Conclusions by Authors
Stroup BM, et al. Metabolomic markers of essential fatty acids, carnitine, and cholesterol metabolism in adults and adolescents with phenylketonuria. J Nutr 2018;148:194-201 PMID: 29490096	• **Study design 1:** Analyzed the Fatty Acid (FA) profiles of Red Blood Cell Membranes in 25 adult subjects with classical and variant PKU and 143 controls • **Study design 2:** Metabolomics analysis of plasma samples of 10 adults and adolescents with PKU compared to age-matched controls • **Study design 3**: Metabolomics analysis of urine samples of 9 adults and adolescents with PKU	• PKU subjects had higher n-6/n-3 ratio in RBC and plasma oxidized derivatives of 18:2n-6 and lower ratio of 20:4n-6/20:3n-6 in RBC, consistent with compensation for inflammation • **Despite higher L-carnitine intake from AA-MF, plasma carnitine is similar between AA-MF and Glytactin GMP-MF** • Urine excretion of carnitine and trimethylamine N-oxide (TMAO) was higher with AA-MF	 	• Bioavailability of L-carnitine is improved with Glytactin GMP-MF, possibly due to the prebiotic properties of GMP • Lower TMAO levels with Glytactin GMP-MF may indicate reduced risk for atherosclerosis and cardiovascular disease
Stroup BM, et al. Metabolomic insights into the nutritional status of adults and adolescents with phenylketonuria consuming a low- phenylalanine diet in combination with amino acid and glycomacropeptide medical foods. J Nutr Metab. 2017 Dec; 2017:6859820. PMID 29464117	30 adult and adolescent subjects with classical and variant PKU • Ages: 15-49 years • Gender: 18 females, 12 males • Classical PKU (n=20) • Variant PKU (n=10) **Data collected:** • Analysis of micronutrient intake utilizing 3 day food records from each arm of intervention • Fasting Phe levels • Metabolomic analysis of plasma and urine	• Intake for sugar was excessive at 27% of total energy (goal <10%) for both AA-MF and Glytactin arms • Macronutrient composition of the low-Phe diet did not change between AA-MF and Glytactin arm of the study • Inadequate intake of Potassium and Choline with both AA-MF and Glytactin GMP-MF • **If taking MF without micronutrient supplementation >70% of participants would have inadequate intake of 11 micronutrients: biotin, choline, pantothenate, Vitamin D and E, potassium, calcium, iodine, magnesium, selenium, and zinc** • Content of sulfur containing AA's in AA-MF are 3x higher than WHO recommendations	Macronutrient Composition of Low-Protein Diet plus Medical Foods  Inadequate and Excessive Intakes as a Percentage of Subjects | | <AMDR or DGA | >AMDR or DGA | |---|---|---| | Total protein | 7% | 0% | | Total carbohydrate | 10% | 20% | | Sugar | — | 97% | | Total fat | 17% | 17% | | Saturated fat | — | 13% |	• Medical foods containing less sugar (like the new Glytactin RTD Lite, Build, Restore Lite, and BetterMilk Lite products) are needed for the PKU community • Vitamin and mineral supplementation of medical foods, like in Glytactin's complete GMP–MF, is necessary in order to prevent nutrient deficiency in PKU • Per the original study, compliance with completion of MF was 1.5 fold higher with Glytactin MF thus promoting improved micronutrient intake