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Surrogate Endpoints for Clinical Trials Urea Cycle Disorders

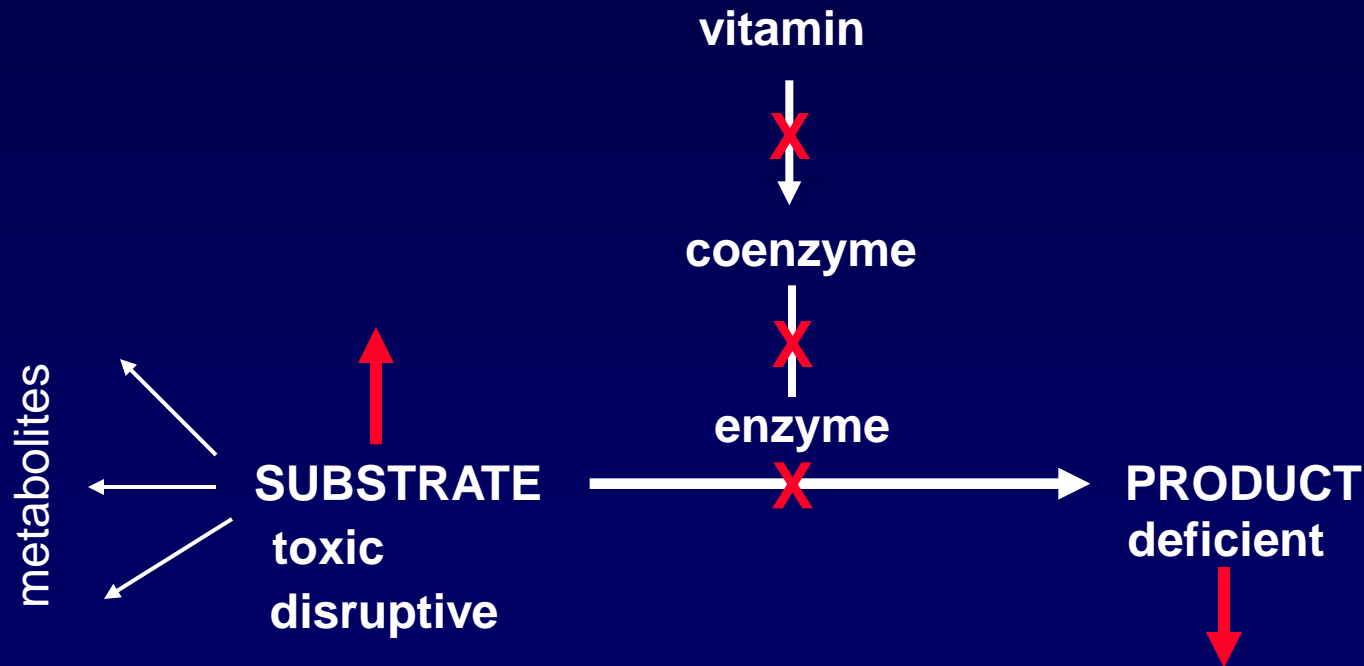


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Inborn errors of metabolism

- Ultra-rare diseases
- Single gene single protein disorders
- Derangement of biochemical homoeostasis
- Pathophysiology involves substrate or products of enzymes
- Only few have effective treatments
- Some are treated with “natural” substances

Patho-biochemistry of inborn errors of metabolism



IEM classification

	Micromolecules	Macromolecules
Substrates / Products	amino acids organic acids Carbohydrates fatty acids	Glycogen Glycosaminoglycans Glycoproteins sphingolipids
Pattern	acute/rapid/ cumulative	slowly progressive
Pathology	toxic , energy depletion	anatomical/toxic
Therapy	dialysis, diet, Vitamins/ cofactors, scavenger drugs , enzyme inhibitors organ transplantation	Proteins, BMT, biosynthesis inhibitors, organ transplantation

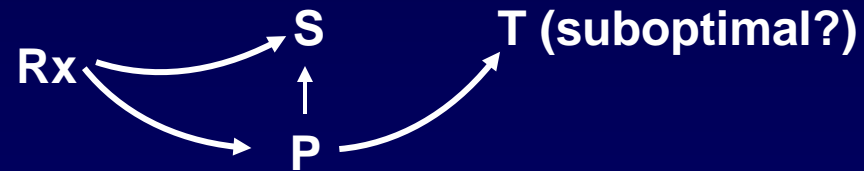
Why surrogate markers for IEM

- Cause: Single gene, single protein single function
- Pathophysiology better understood
- Substrate/toxin model
- Gene or protein treatment is/will be available
- Rare diseases, true endpoint hard to study
- True endpoint affected by many confounders

A surrogate marker (S)

Rx \longrightarrow S \longrightarrow T (optimal)

An optimal surrogate marker mediates all treatment effect on the true endpoint (T)



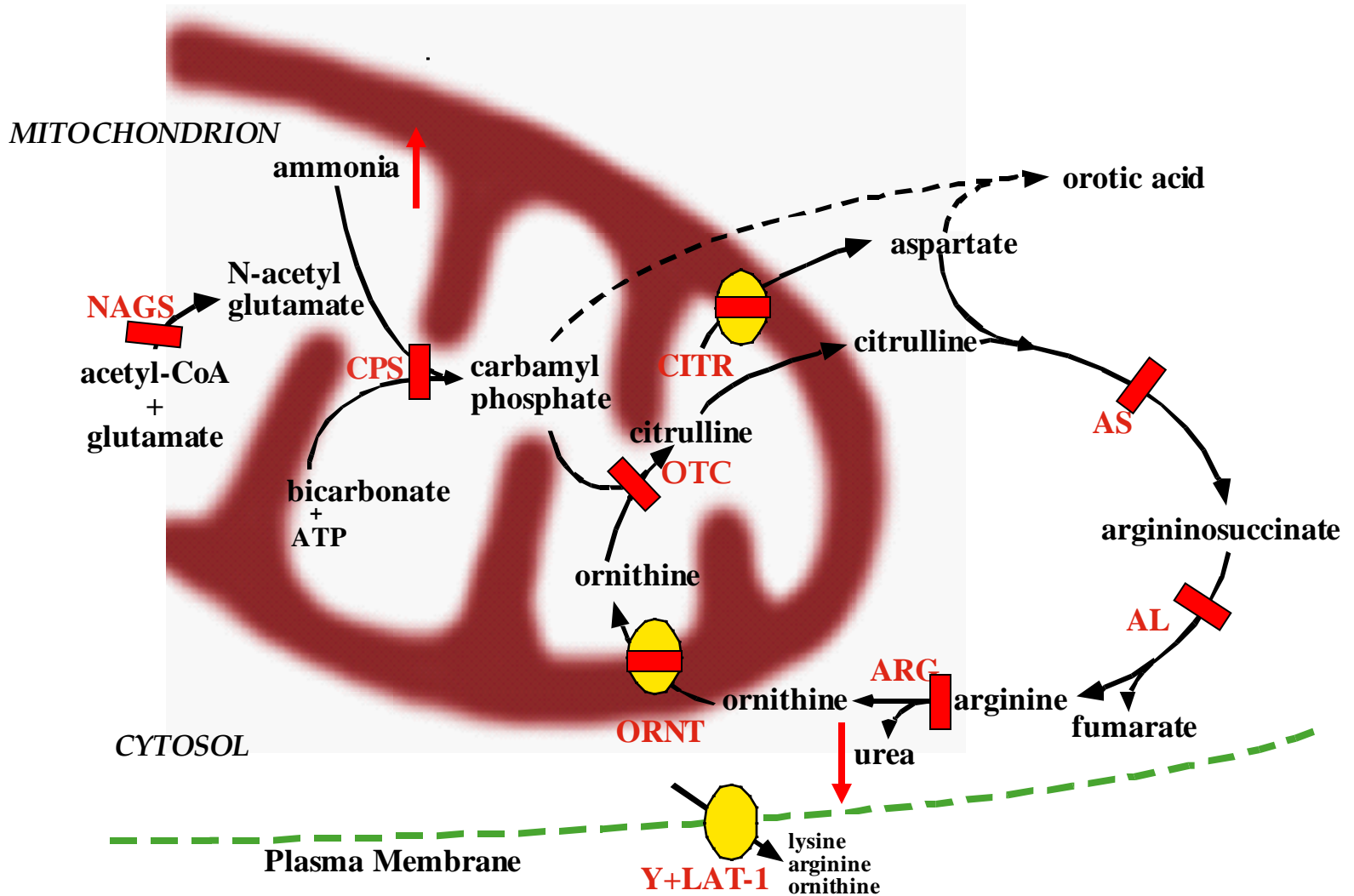
A correlate does not a surrogate make: What makes a good surrogate marker?

- Is the only causal pathway of the disease process**
- Therapy works through its effect on surrogate**
- Timing and sufficient duration to affect outcome**
- Can be reliably measured**

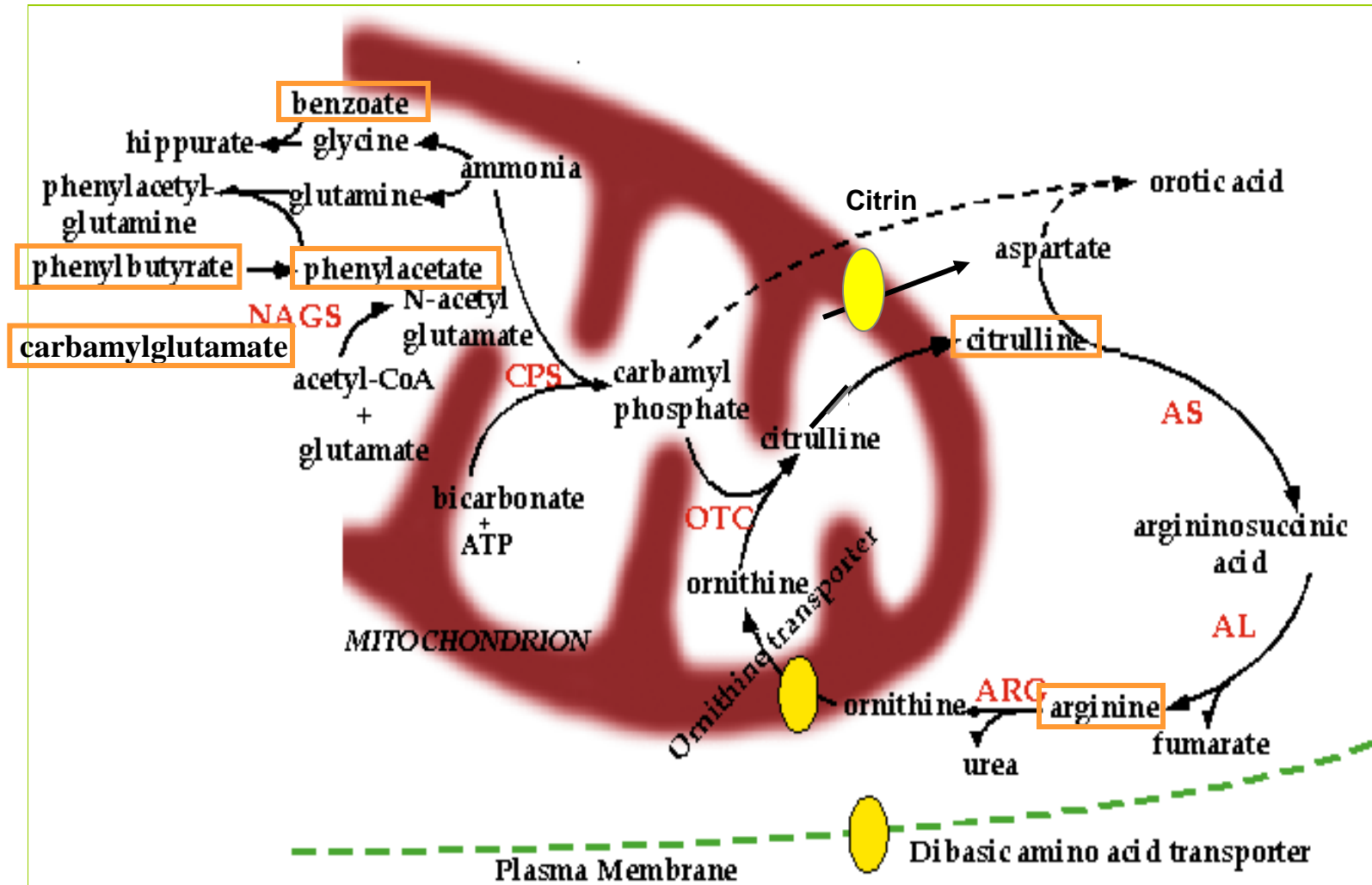
Neonatal hyperammonemia



Urea cycle disorders



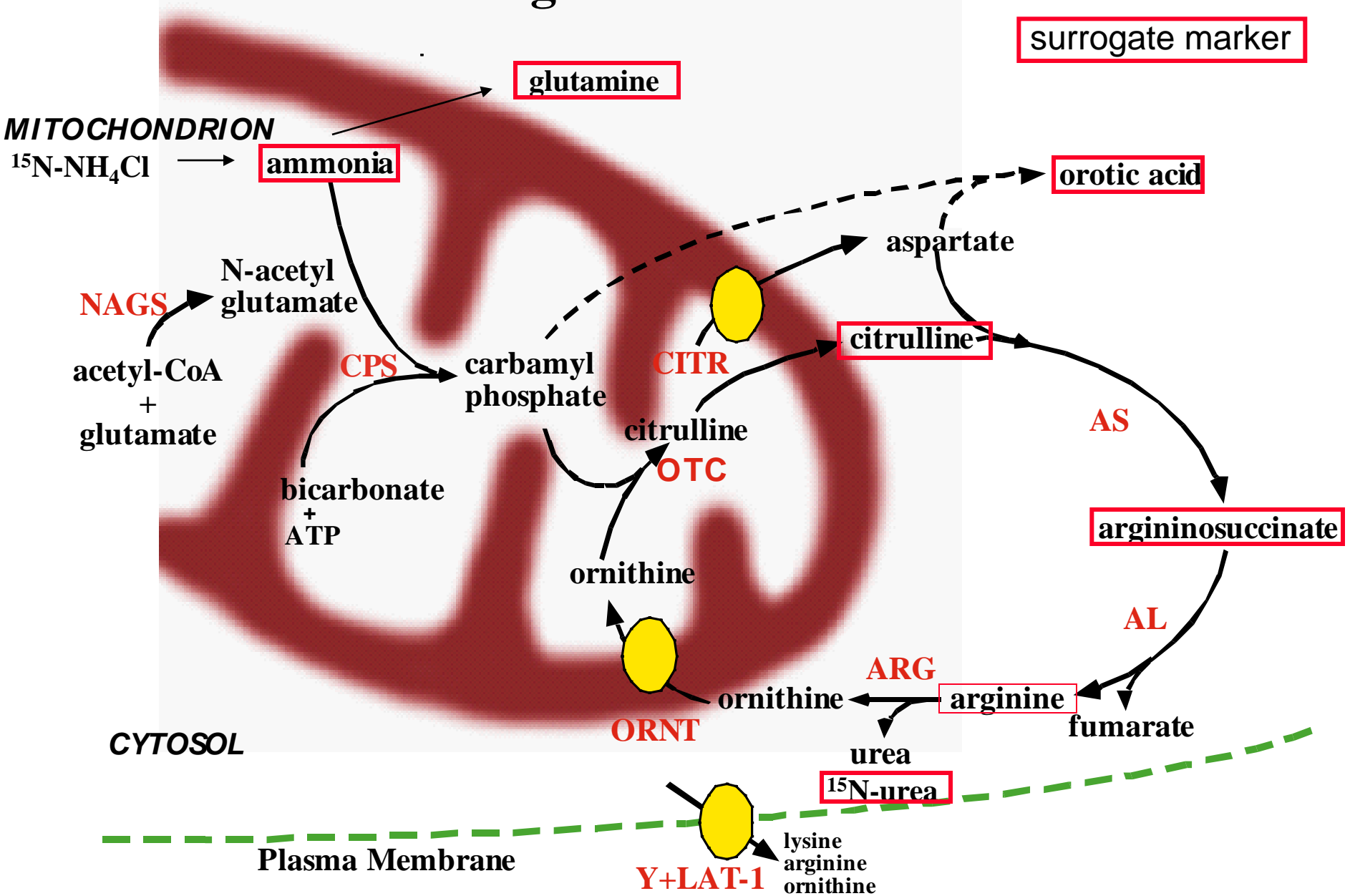
Drug therapy for UCD



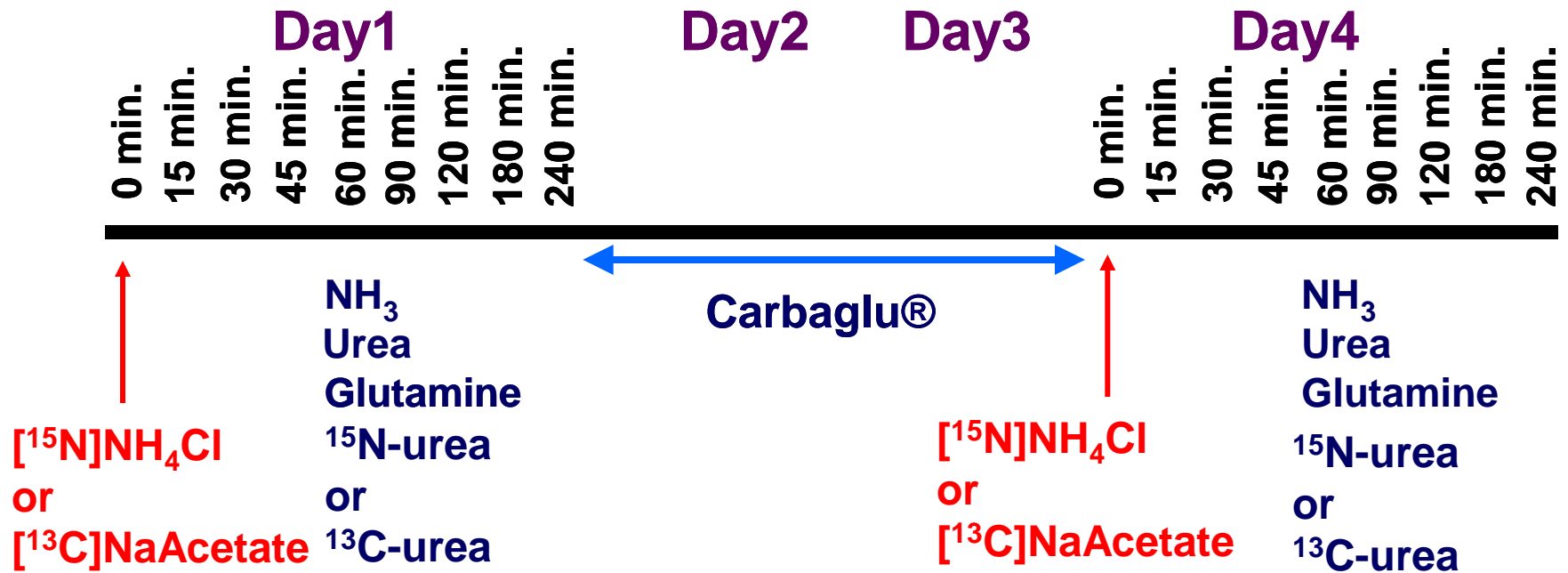
True endpoints for urea cycle disorders

- Improved survival rate
- Prevention or reduction in severity of brain damage
- Normal linear growth
- Increased protein tolerance
- Reduction or elimination of hyperammonemia episodes

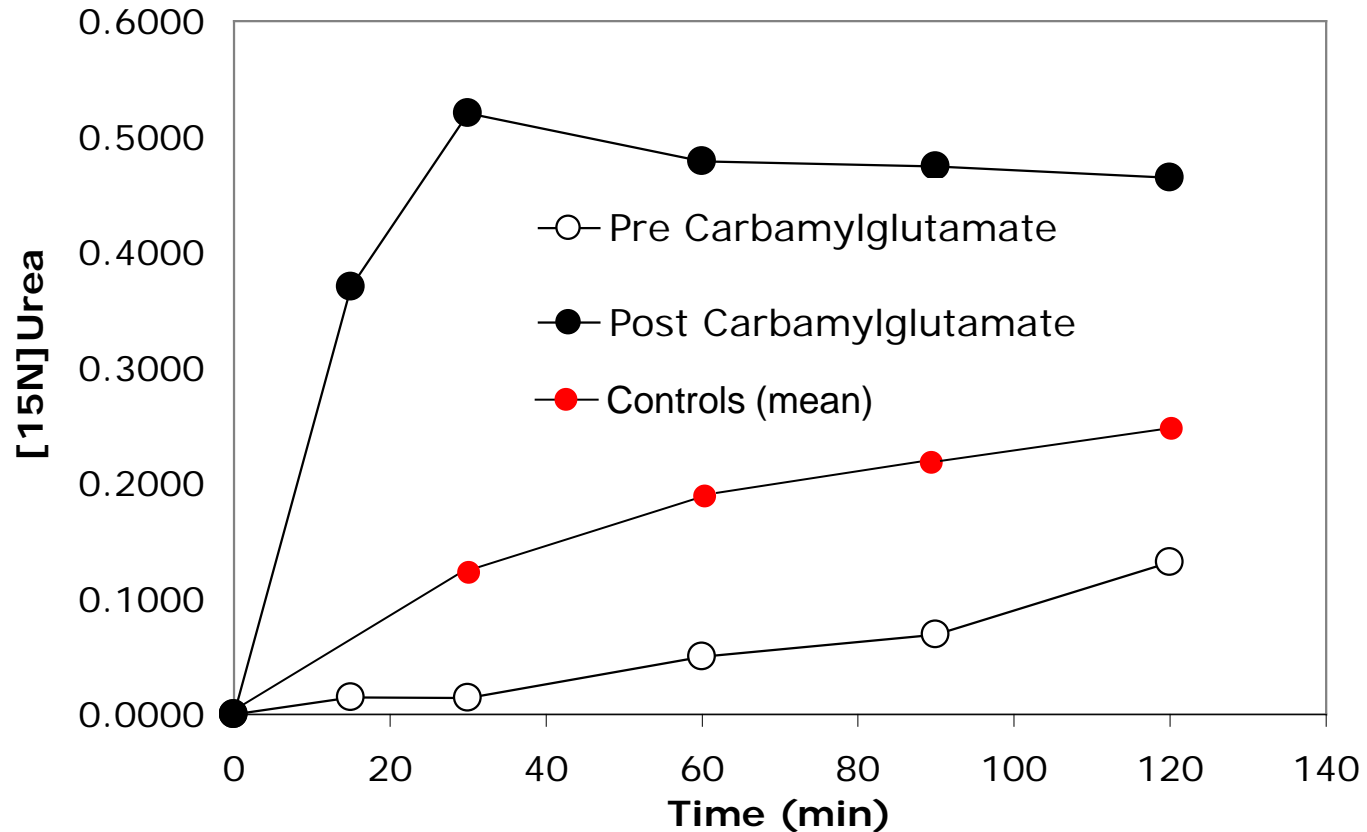
Surrogate markers for UCD



Short-term clinical trial of N-carbamylglutamate



Correction of ureagenesis with N-carbamylglutamate (Carbaglu) in NAGS deficiency



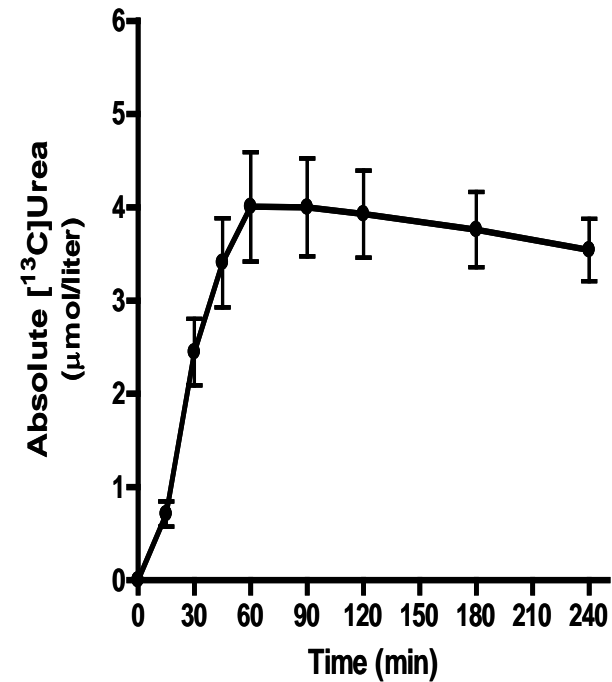
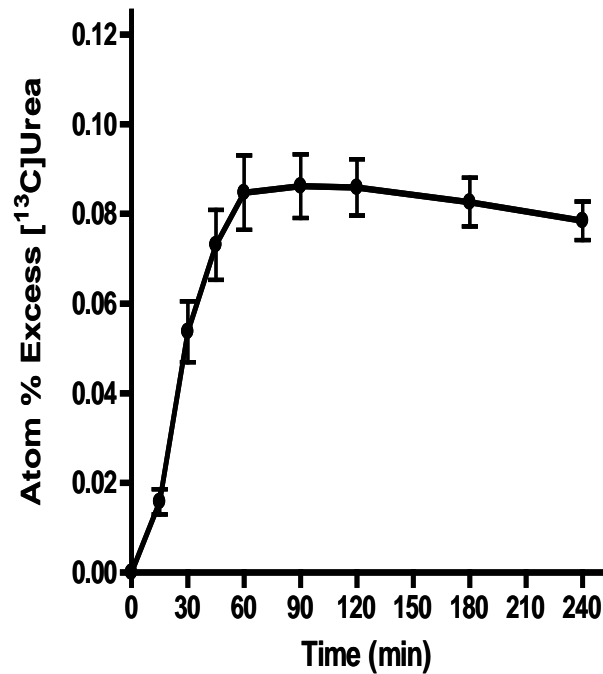
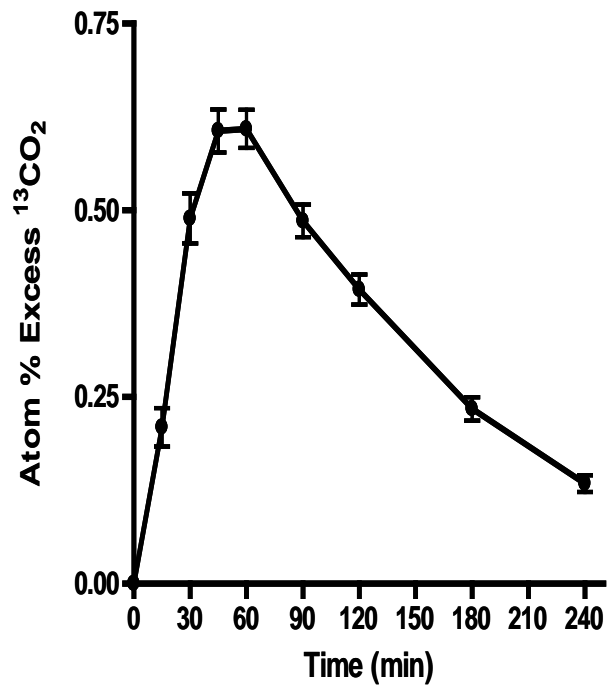
NAGS deficiency

Effect of 3-day treatment with N-carbamylglutamate

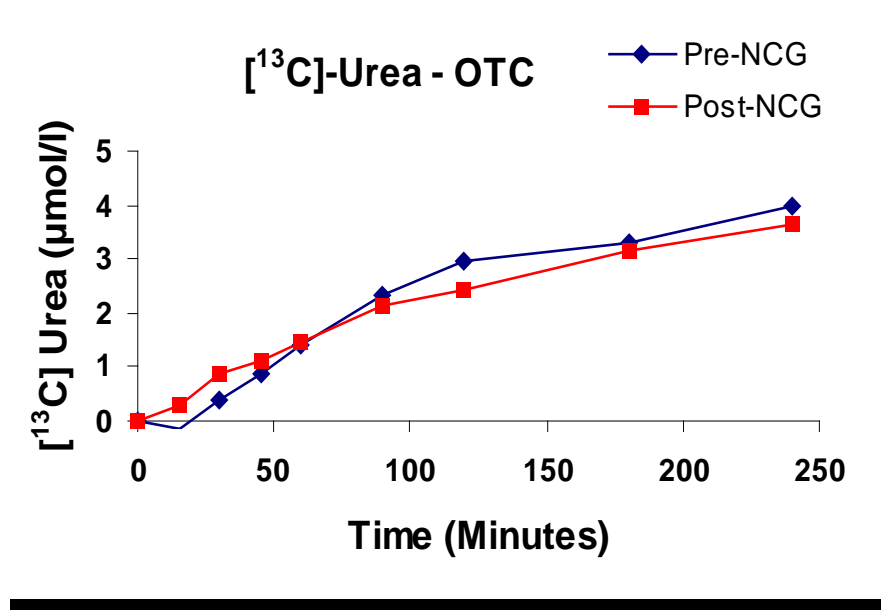
Time (min)	ammonia		urea		[15N]urea	
	pre	post	pre	post	pre	post
0	20	11	4	7	0.0000	0.0000
15			3	8	0.0146	0.3701
30			3	8	0.0143	0.5204
60	51	11	3	7	0.0499	0.4787
90			3	7	0.0691	0.4743
120	70	8	4	7	0.1315	0.4647
<i>P</i>			0.0001		0.002	



[¹³C] incorporation into Urea in 17 healthy adults



OTC deficiency

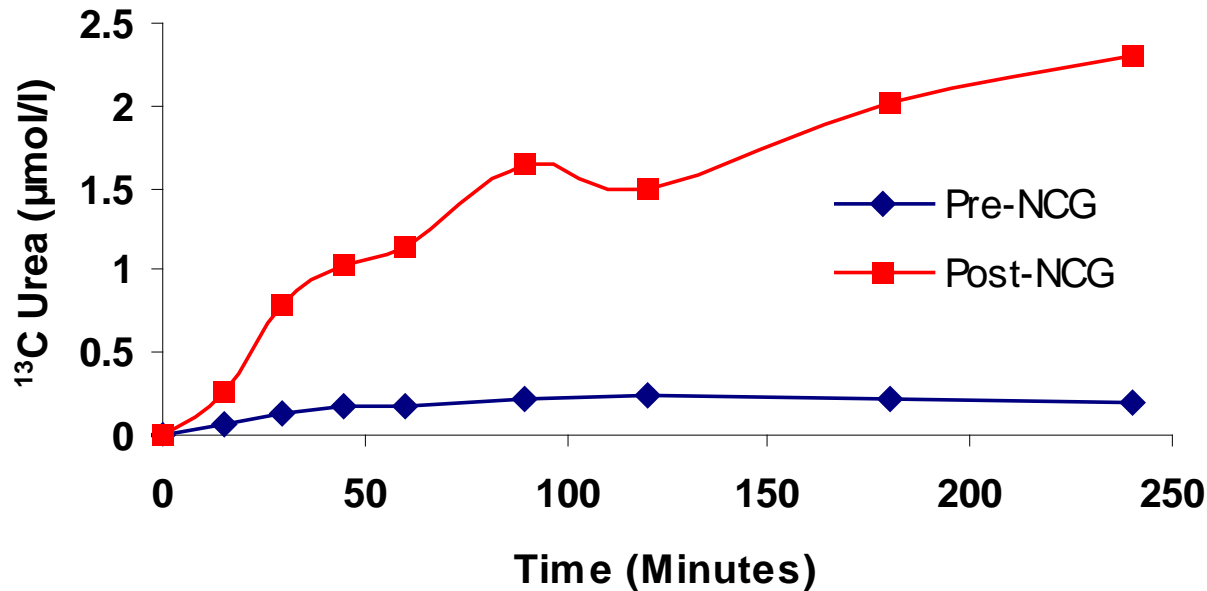


Marker	Pre-NCG	Post-NCG
NH ₃ (µM)	23 ± 5	23 ± 9
Urea (mM)	4.8 ± 0.2	4.9 ± 0.2
Gln (µM)	819 ± 70	839 ± 44
Urine Orotate	0.5, 5	5.2, 24



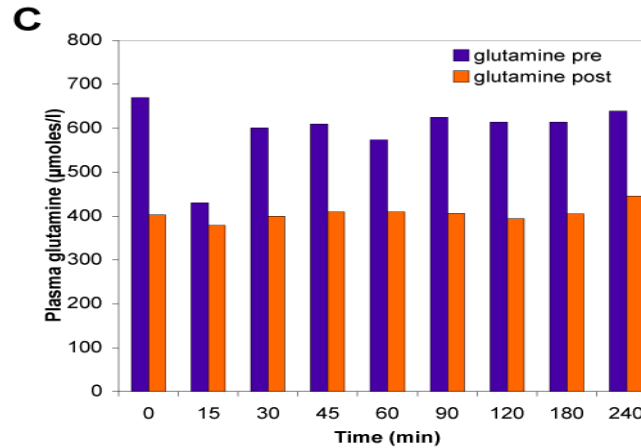
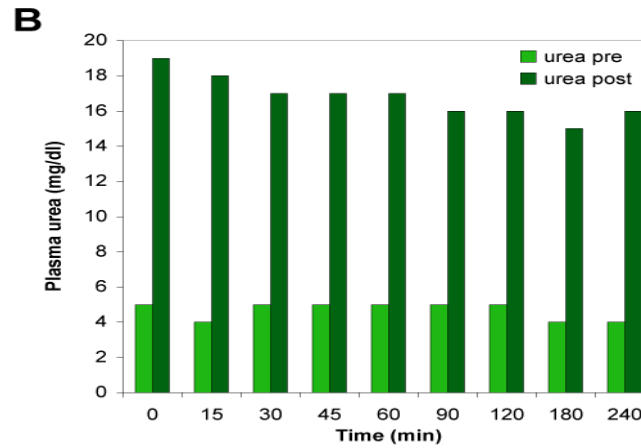
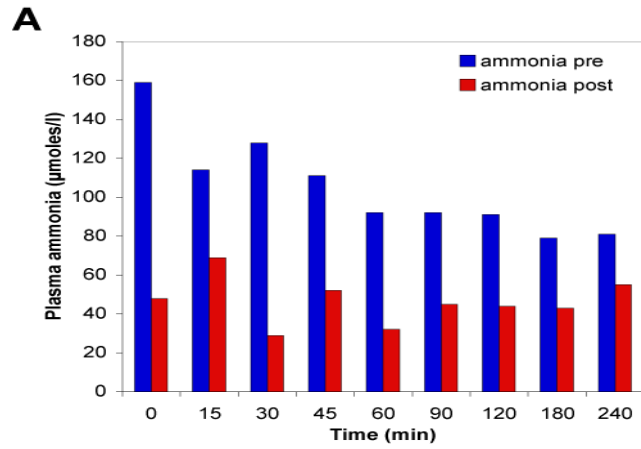
NAGS subject

¹³C-Urea - NAGS deficiency



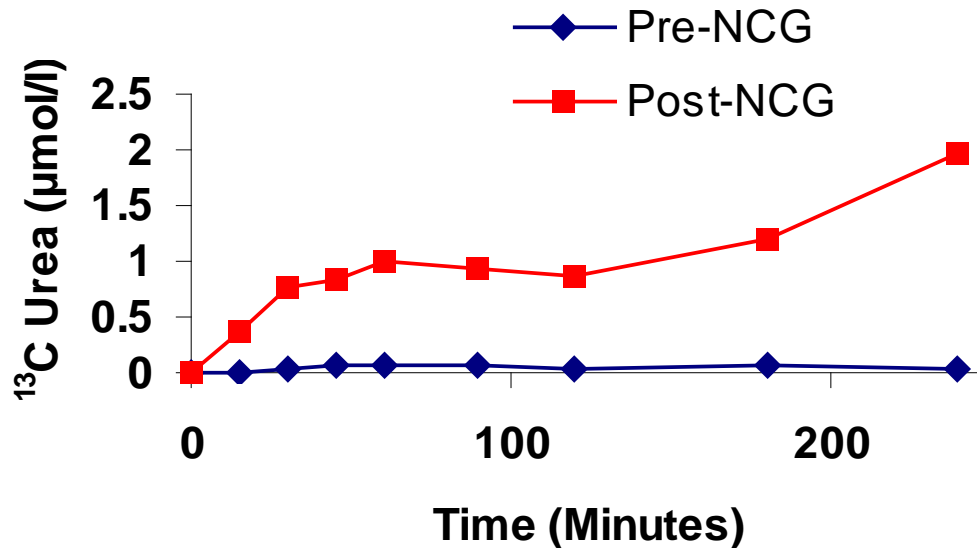
Marker	Pre-NCG	Post-NCG
Ammonia(µM)	105 ± 26	46 ± 12
Urea (mM)	1.7 ± 0.2	6.0 ± 0.4
Glutamine (µM)	597 ± 68	405 ± 18





Subject 13 – NCG study

^{13}C -Urea - Subject 13



marker	Pre-NCG	Post-NCG
Ammonia (μM)	20 +/- 6	18 +/- 3
Urea (mM)	0.4 +/- 0.05	1.4 +/- 0.1
Glutamine (μM)	618 +/- 75	363 +/- 31



Odor: true or surrogate marker?

