

# Urea Cycle Disorders – Legacy of Hope

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**RARE DISEASES**  
CLINICAL RESEARCH NETWORK

 Urea Cycle  
Disorders Consortium

*Legacy of*  
**HOPE**

 National Urea Cycle Disorders Foundation  
families research education support ... Hope



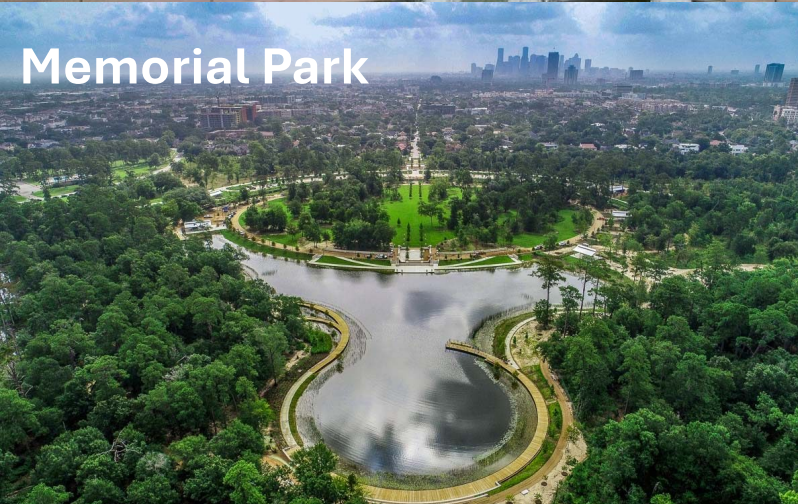
Museums



Texas Medical center



Memorial Park



Houston zoo



JSC - NASA



Hermann Park



Houston zoo



*Restaurants!*



# *Cindy LeMons*

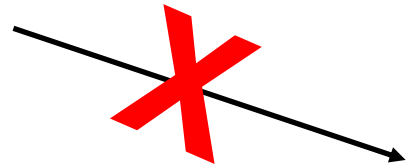
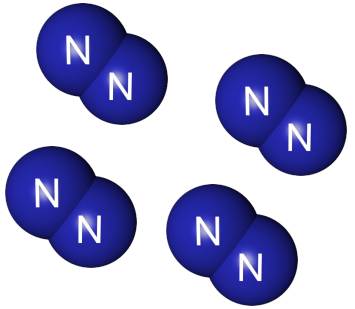


# Outline of the talk

- **Brief historical perspective of urea cycle disorders**
- **Challenges with research in UCDs and how we can improve outcomes for UCDs**
  - ✓ Role of patients and patient advocacy groups
  - ✓ Collaborative research networks
- **Where we are in the field of UCDs and how talks this morning will tie into the Legacy of Hope theme**

# All living things need nitrogen

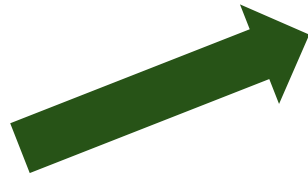
Atmosphere



Proteins of  
all tissues



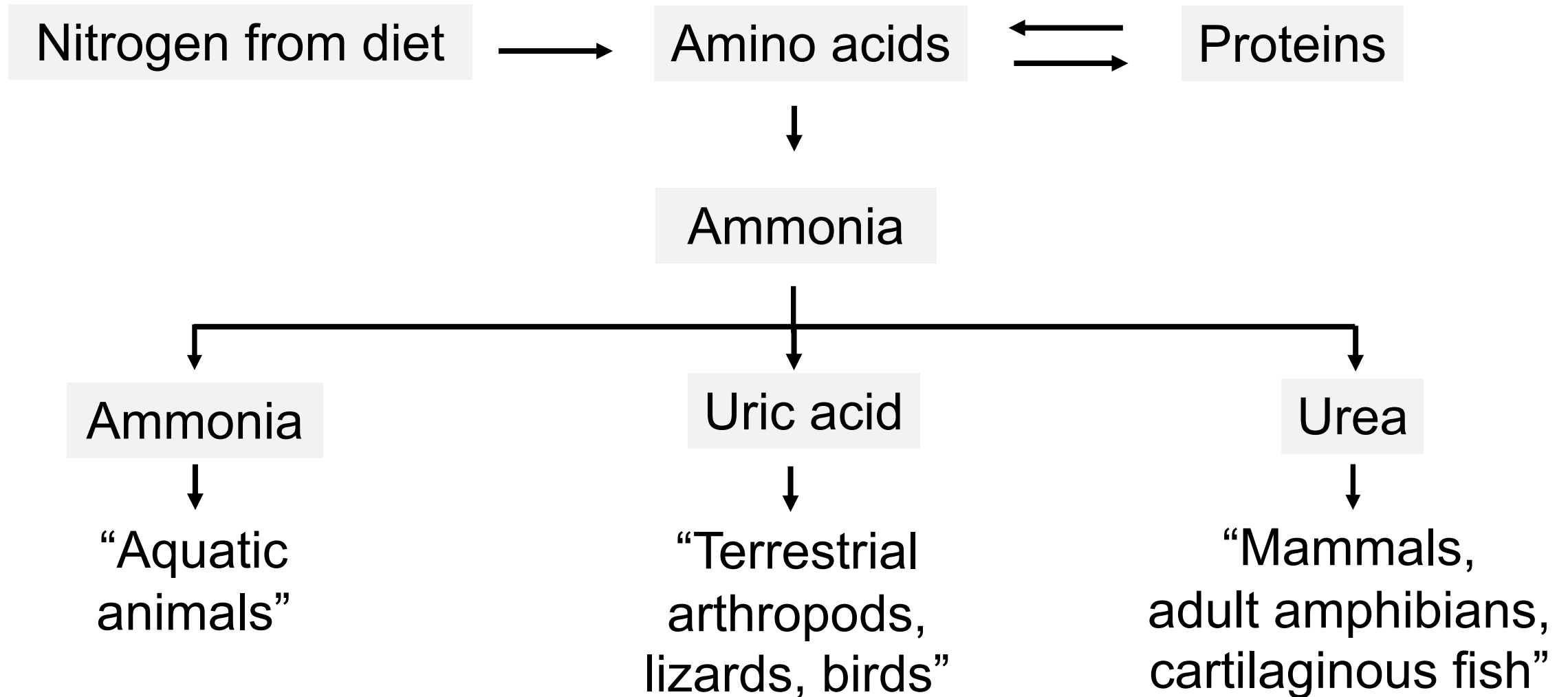
Food



Genetic  
information



# How is excess nitrogen excreted in animals?

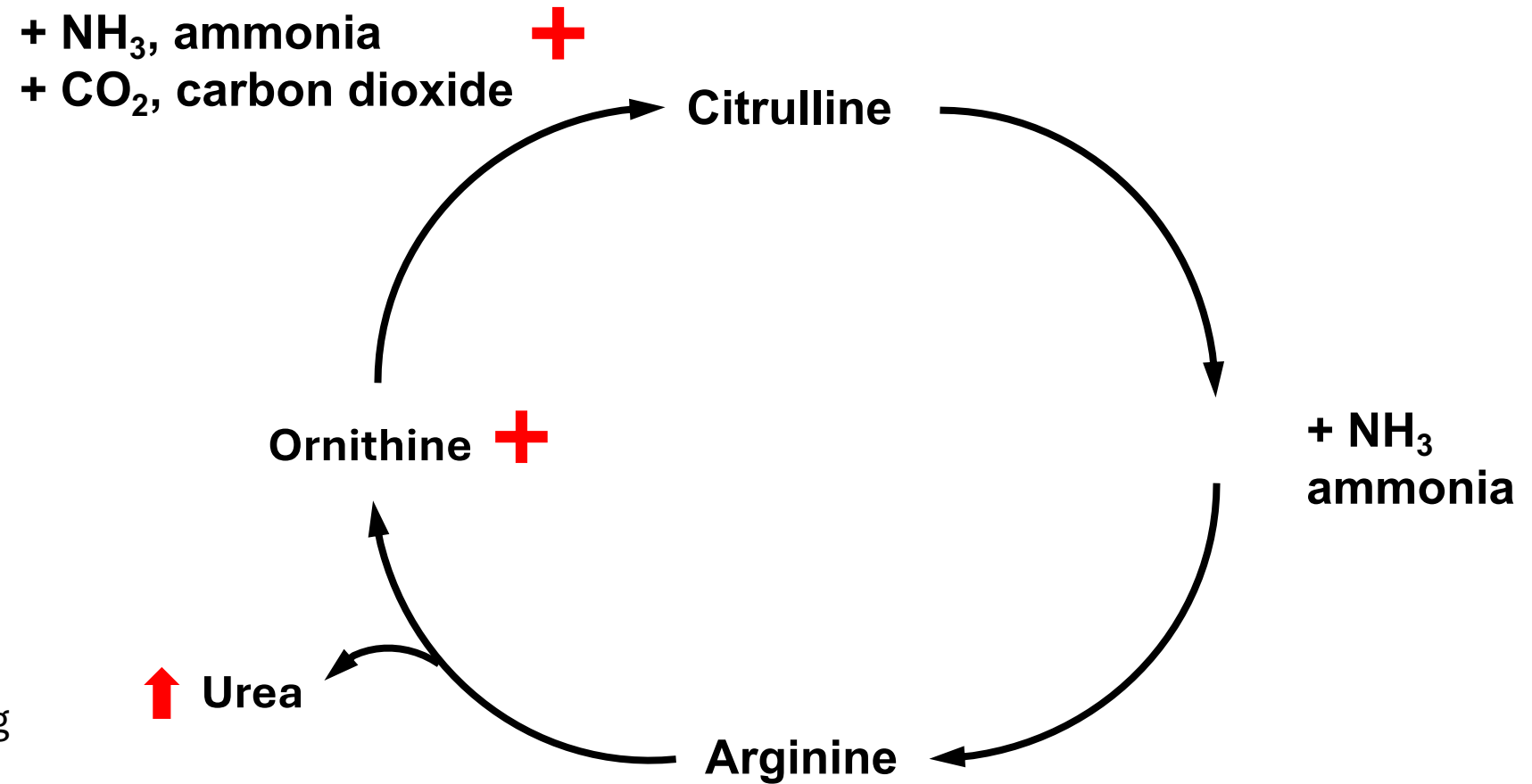


# How is urea synthesized in mammals?

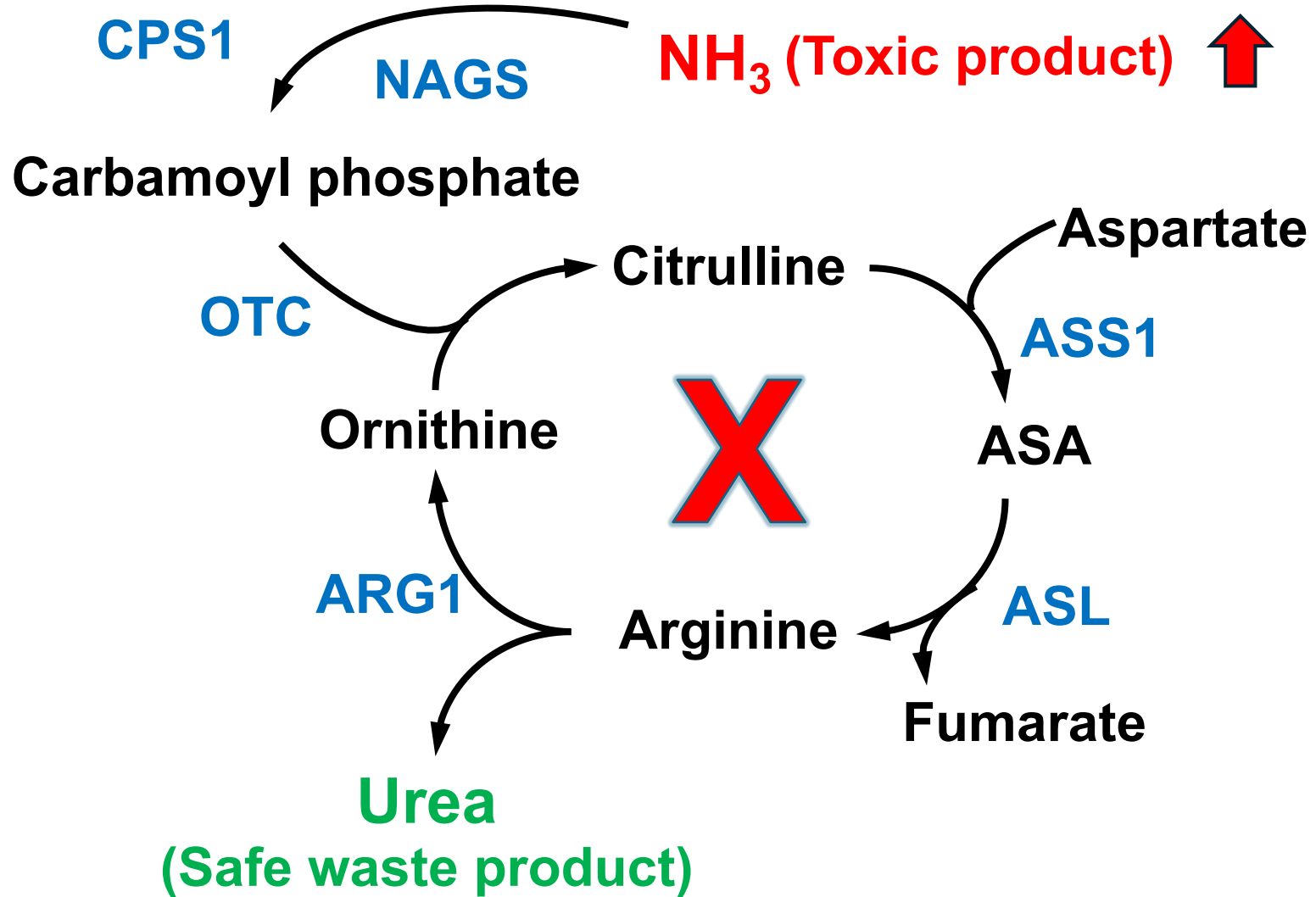
Hans Krebs



Picture from Nobelprize.org

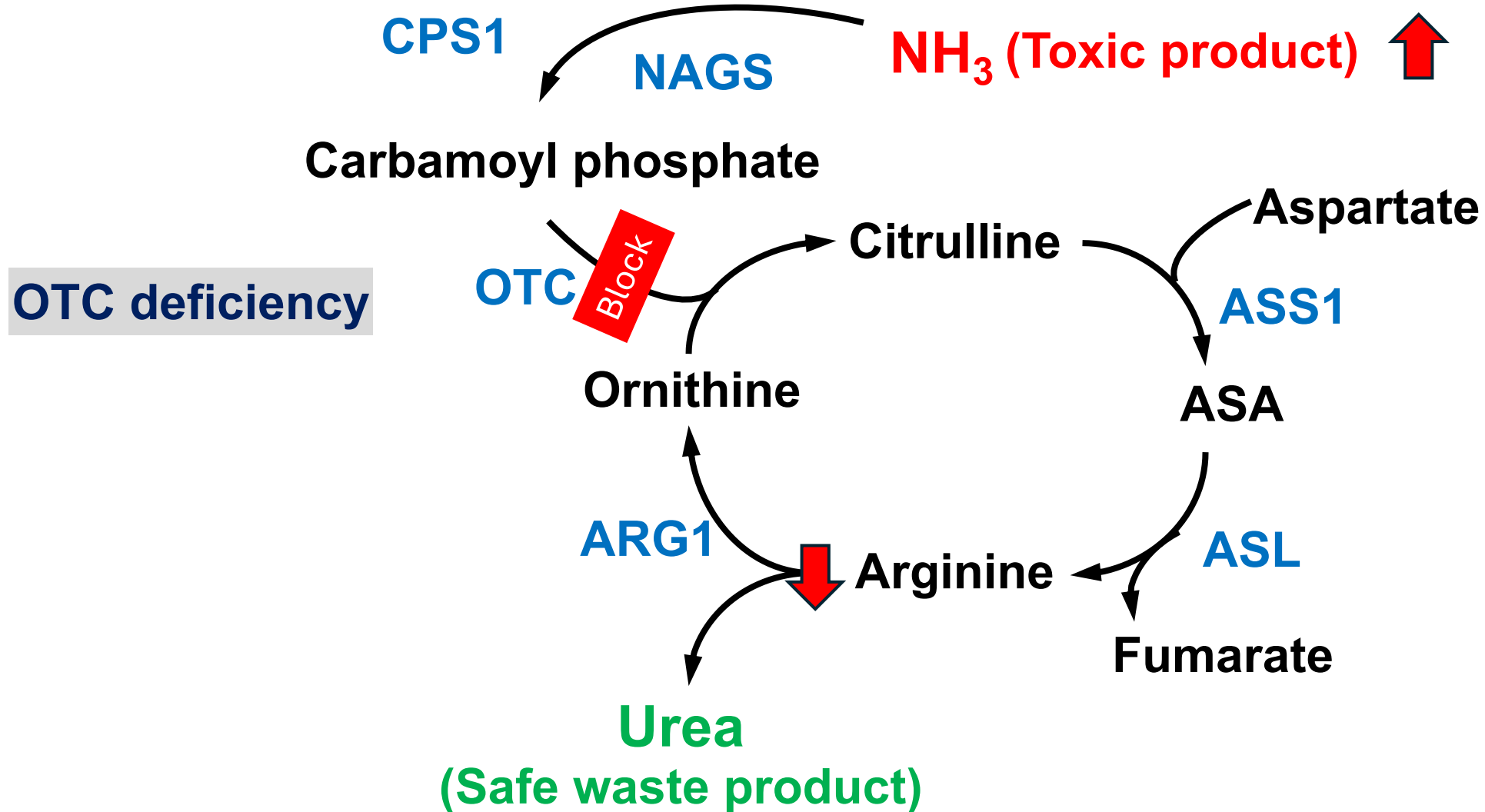


# Urea Cycle

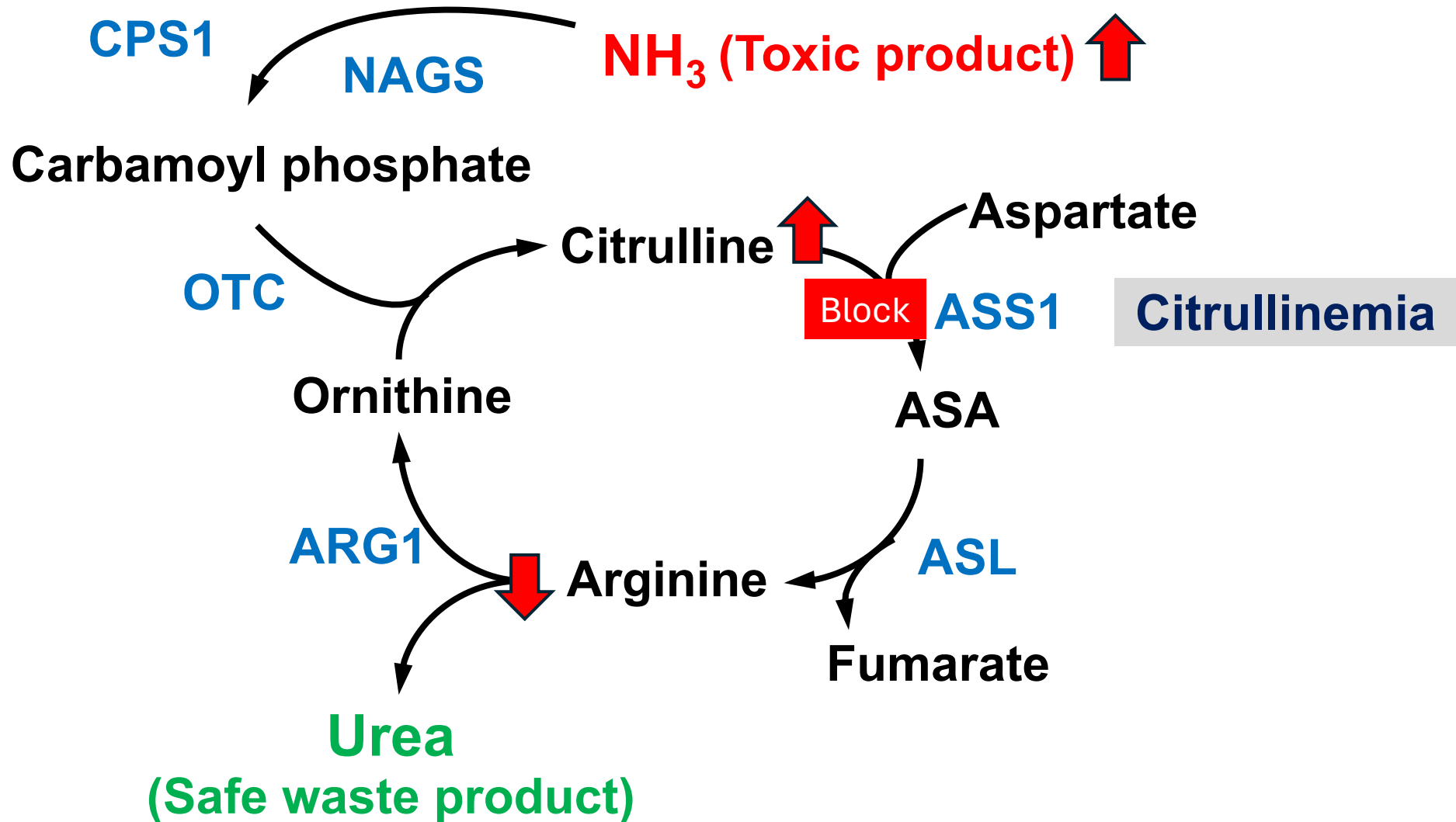




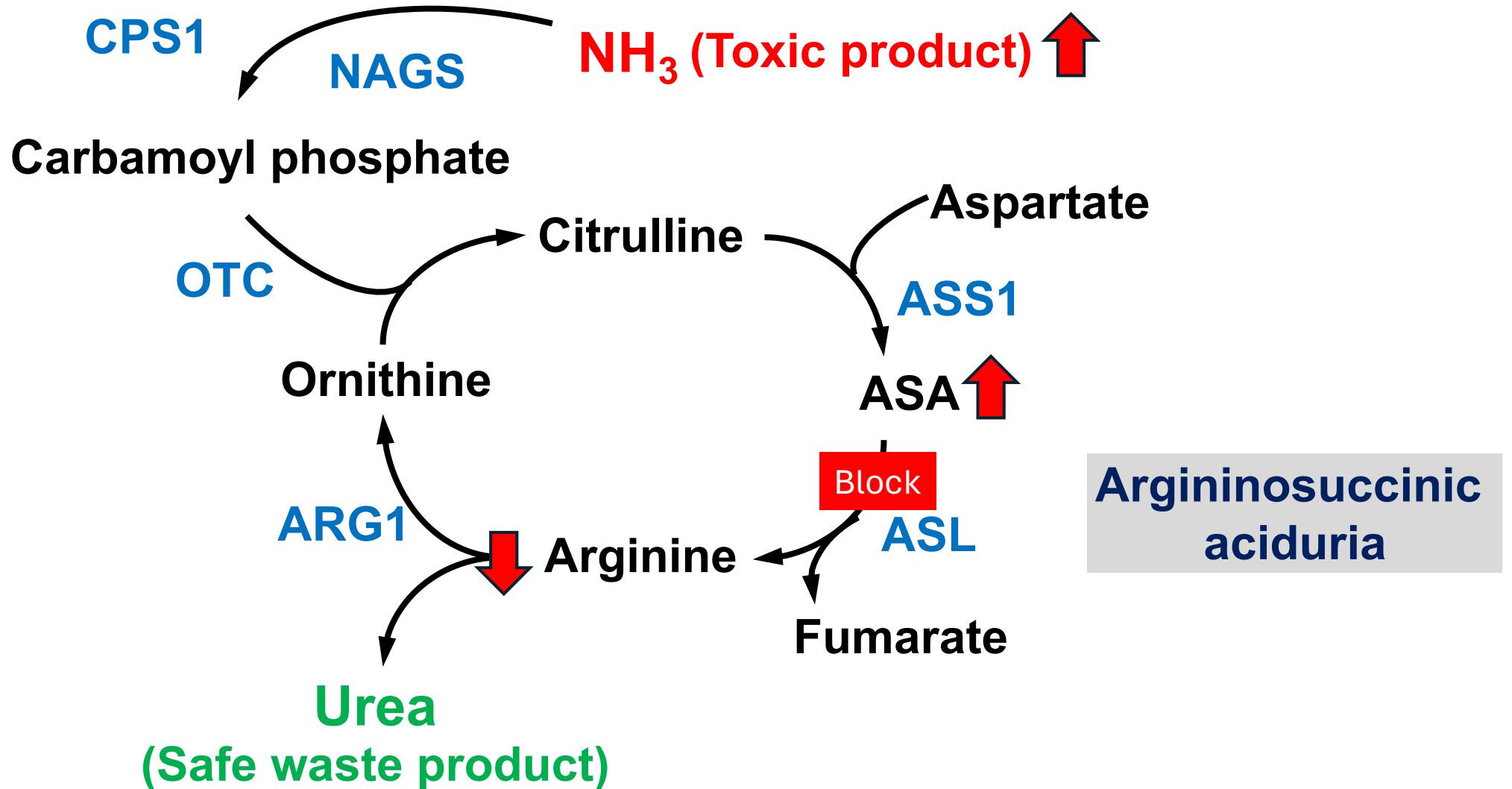
# Urea Cycle Disorders (UCDs)



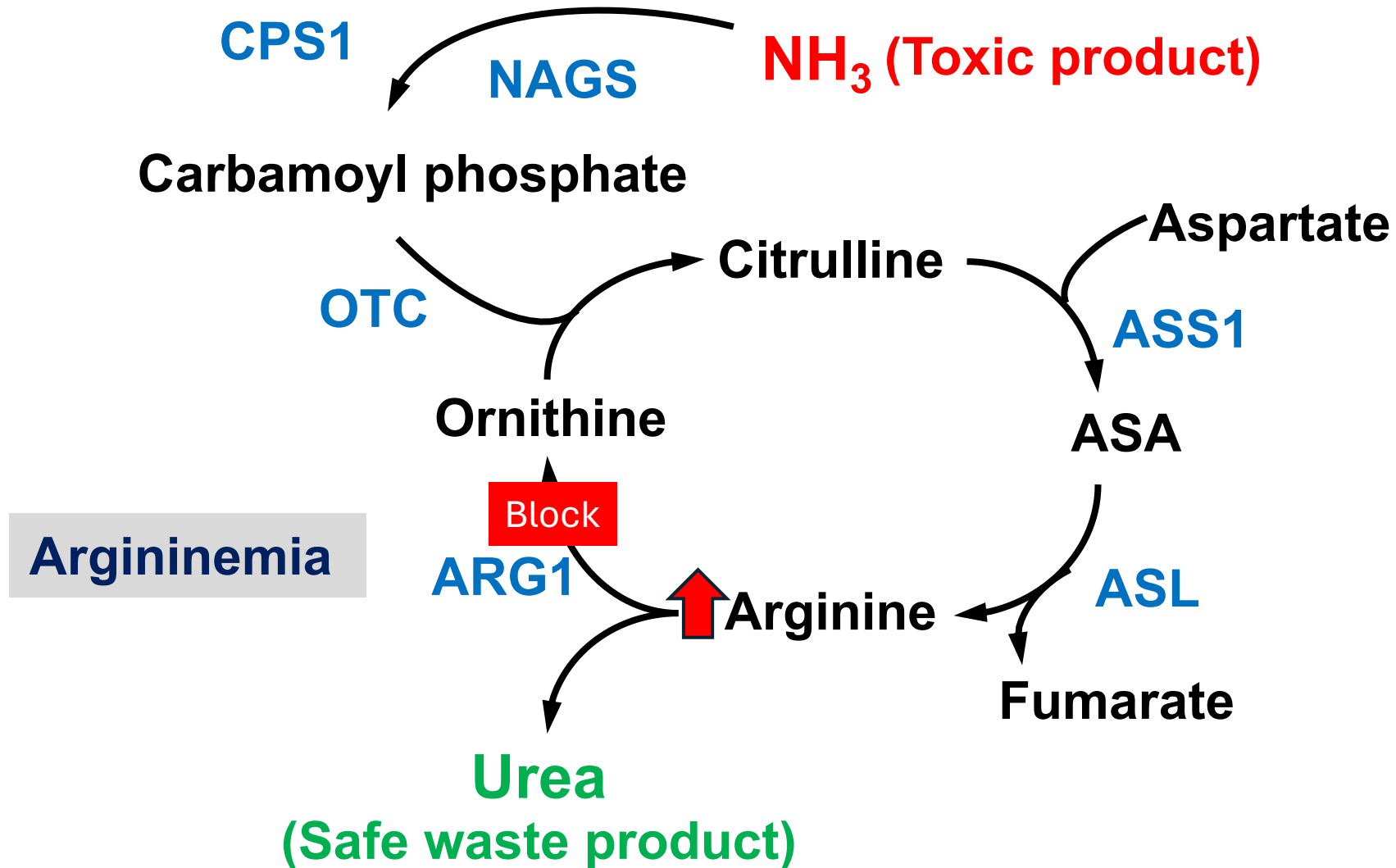
# Urea Cycle Disorders (UCDs)



# Urea Cycle Disorders (UCDs)



# Urea Cycle Disorders (UCDs)





# A historical perspective of UCDs

## 1. ASA, *Lancet* 1958

**A DISEASE, PROBABLY HEREDITARY,  
CHARACTERISED BY SEVERE MENTAL  
DEFICIENCY AND A CONSTANT GROSS  
ABNORMALITY OF AMINOACID  
METABOLISM**

J. D. ALLAN

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CONSULTANT PEDIATRICIAN, STOCKPORT AND MACCLESFIELD  
HOSPITALS

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BIOCHEMIST, ROYAL MANCHESTER CHILDREN'S HOSPITAL,  
PENDLEBURY, LANCs

## 2. OTCD, *Lancet* 1962

Preliminary Communication

### HYPERAMMONÆMIA

**A New Instance of an Inborn Enzymatic Defect of  
the Biosynthesis of Urea**

A. RUSSELL

M.D. Durh., M.R.C.P.

B. LEVIN

M.D. Lond., B.Sc., PH.D.

V. G. OBERHOLZER

B.A. Oxon.

L. SINCLAIR

M.B., B.Sc. Lond., M.R.C.P.

Queen Elizabeth Hospital  
for Children,  
London, E.2

## 3. Citrullinemia, *Pediatrics* 1963

### CITRULLINURIA

W. C. McMurray, Ph.D., J. C. Rathbun, F.R.C.P.(C.), F. Mohyuddin, M.Sc.,  
and S. J. Koegler, M.D., D.C.H.

Departments of Biochemistry and Paediatrics, University of Western Ontario, and the Wards of War  
Memorial Children's Hospital, and the Children's Psychiatric Research Institute, London, Canada

## 4. Argininemia, *Z Kinderheilkd* 1969

> *Z Kinderheilkd.* 1970;107(4):298-312.

**[Hyperargininemia with arginase deficiency. A new  
familial metabolic disease. I. Clinical studies]**

[Article in German]

H G Terheggen, A Schwenk, A Lowenthal, M van Sande, J P Colombo

PMID: 5438971

## 5. CPS1D, *Arch Neuro* 1970

### Congenital Hyperammonemia

**Association With Hyperglycinemia and  
Decreased Levels of Carbamyl Phosphate Synthetase**

*John M. Freeman, MD; John F. Nicholson, MD; Robert T. Shimke, MD;  
Lewis P. Rowland, MD; and Sidney Carter, MD, New York*

## 6. NAGSD, *NEJM* 1981

**N-ACETYLGLUTAMATE SYNTHETASE DEFICIENCY:  
A DISORDER OF AMMONIA DETOXICATION**

C. BACHMANN

S. KRÄHENBÜHL

J. P. COLOMBO

University of Berne

Berne, Switzerland

G. SCHUBIGER

K. H. JAGGI

O. TÖNZ

Children's Hospital

Lucerne, Switzerland

# Urea Cycle Disorders

UCDs	Estimated prevalence
<b>Enzyme deficiencies</b>	
NAGS deficiency	< 1 per 2,000,000
CPS1 deficiency	1 per 62,000
OTC deficiency	1 per 14,000
ASS1 deficiency (Citrullinemia type 1)	1 per 60,000
ASL deficiency (Argininosuccinic aciduria)	1 per 60,000
ARG1 deficiency (Argininemia)	1 per 353,000
<b>Transporter defects</b>	
Citrin deficiency (Citrullinemia type 2)	1 per 20,000 in Japan
HHH syndrome	Prevalence unknown
<b>Secondary Urea Cycle Disorders</b>	
Lysinuric protein intolerance, Carbonic anhydrase VA deficiency	Prevalence unknown

# Early treatment of UCDs

*Lancet* 1979

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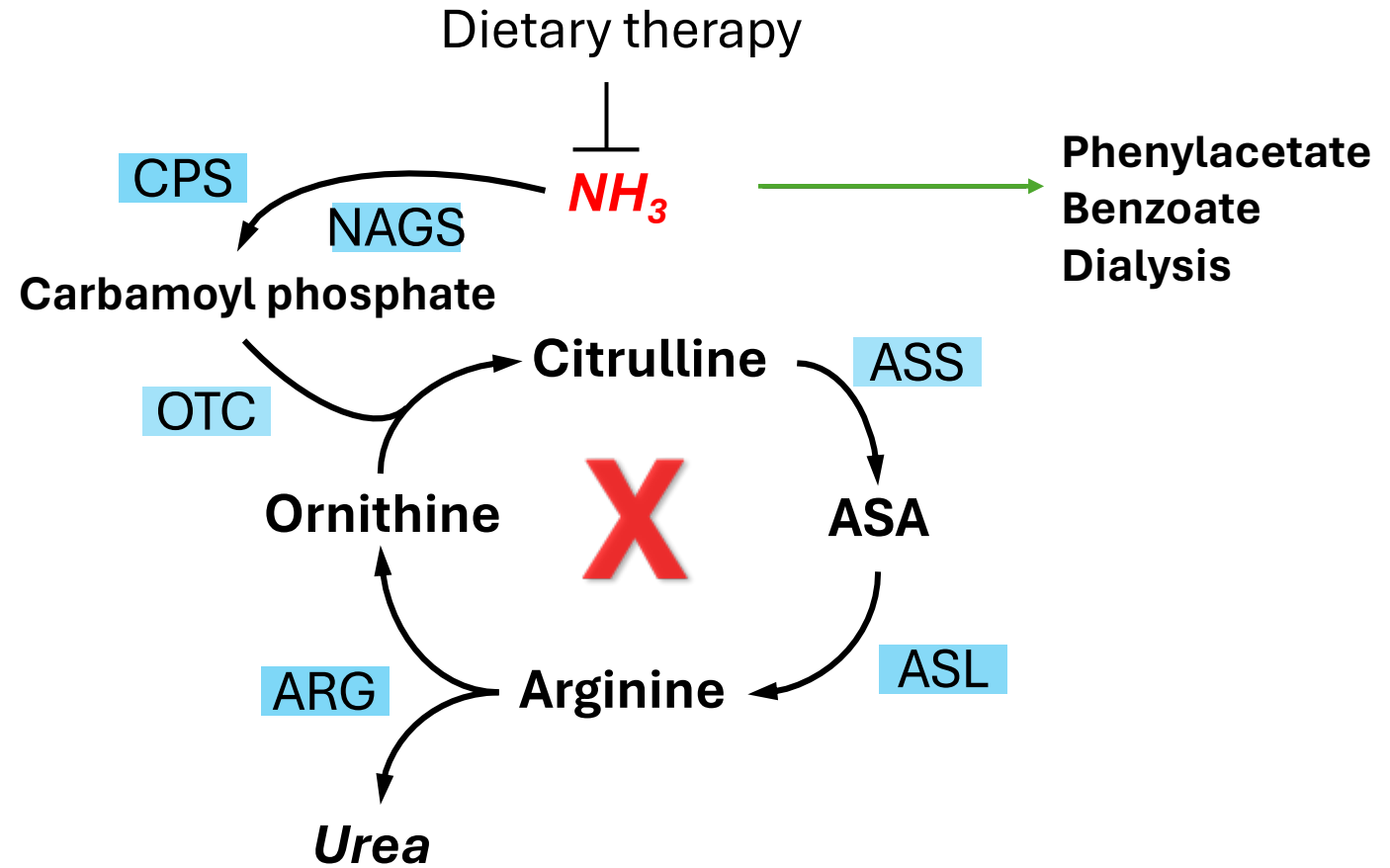
Occasional Survey

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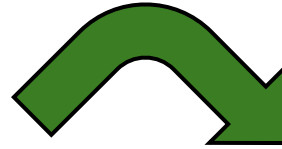
## NEW PATHWAYS OF NITROGEN EXCRETION IN INBORN ERRORS OF UREA SYNTHESIS

SAUL W. BRUSILOW      DAVID L. VALLE  
MARK L. BATSHAW

*Departments of Pediatrics and Neurology, Johns Hopkins  
University School of Medicine, and John F. Kennedy Institute,  
Baltimore, Maryland 21205, U.S.A.*



# Early data on outcomes in UCDs were not encouraging



## Prior to nitrogen-scavenging therapy

### Shih VE and colleagues, 1976

- ✓ N= 28 children with UCDs
- ✓ 1-yr survival = 14%
- ✓ Survivors with ID = 75%

## Soon after nitrogen-scavenging therapy became available

### Msall M and colleagues, 1984

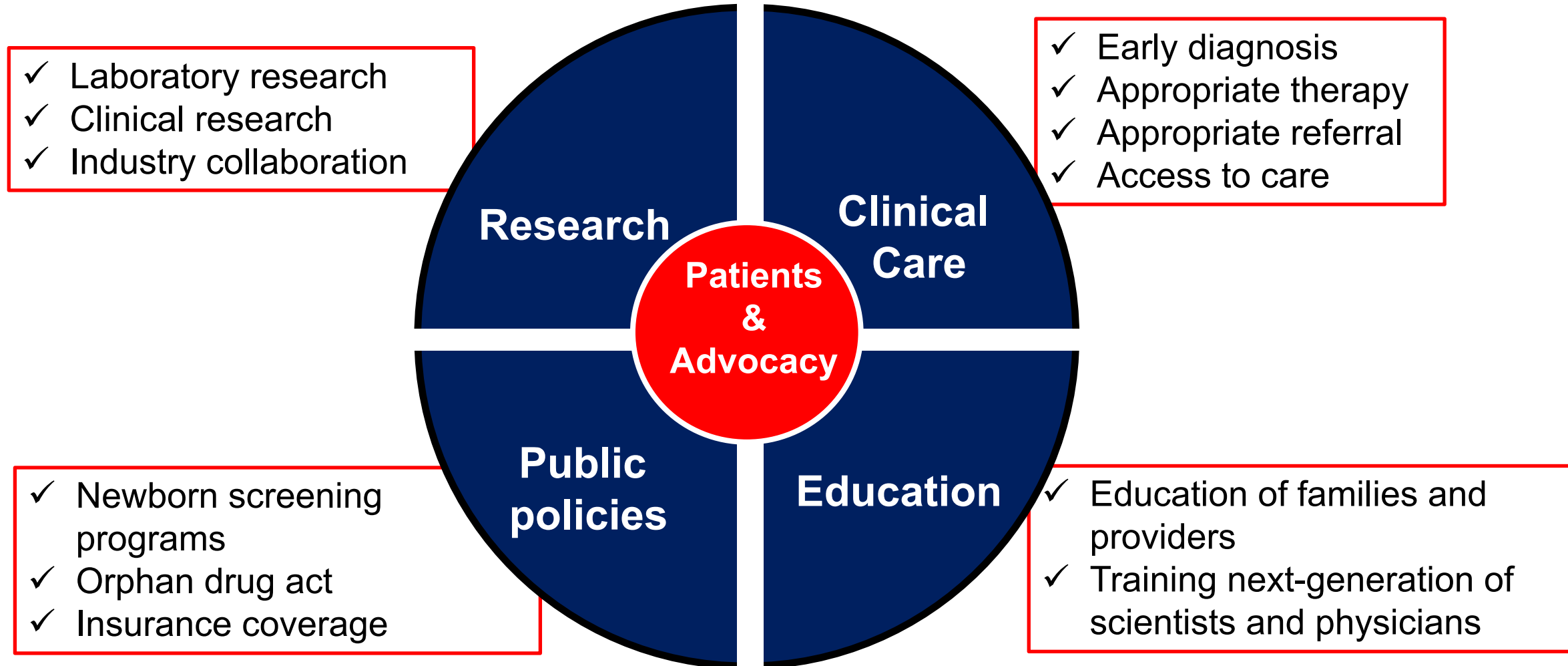
- ✓ N=26 children with UCDs
- ✓ 1-yr survival = 92%
- ✓ Survivors with ID = 80%
- ✓ Average "IQ" was in the 40s



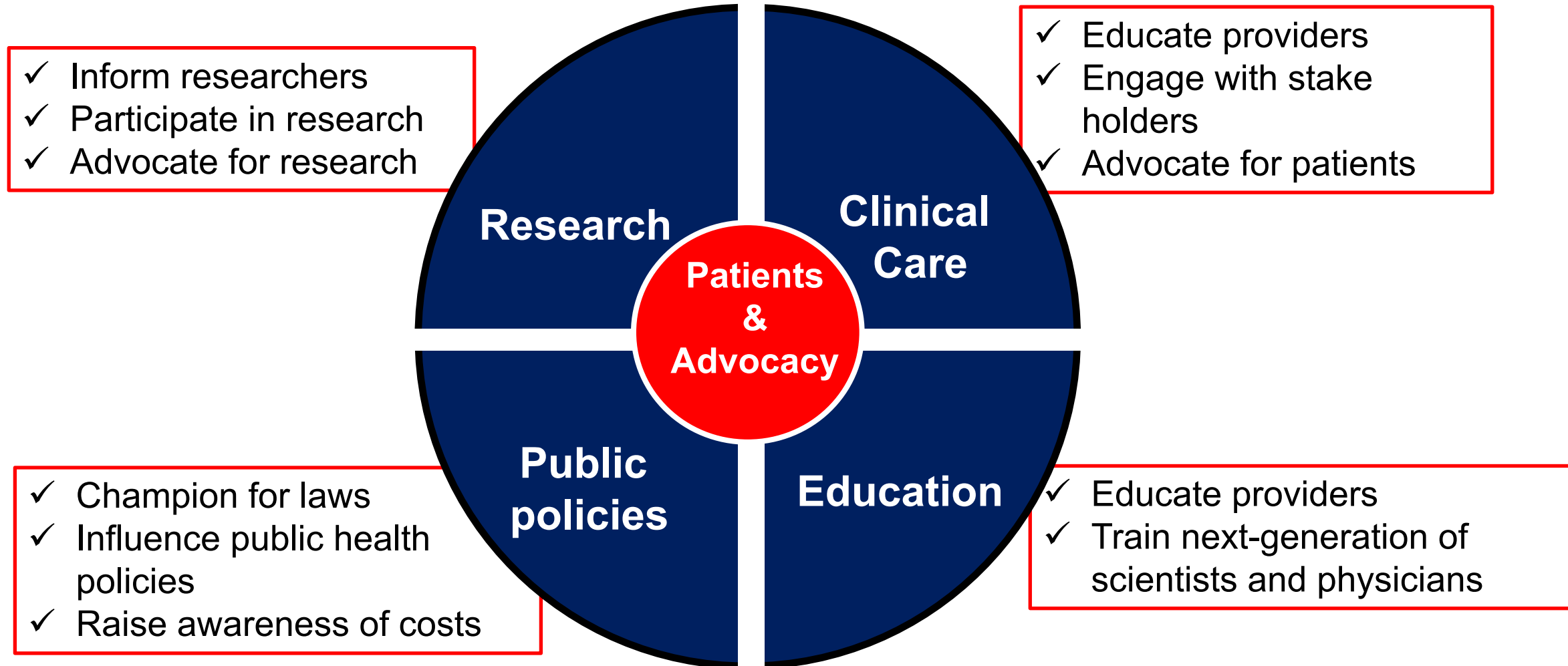
# What are some challenges in advancing research and clinical care in UCDs?

- Natural history of disease is not well studied
- Rarity means:
  - Few specialists
  - Few expert centers for research and treatment
  - Conducting clinical trials is usually difficult
- Often, no high-quality evidence to guide treatment

# How can outcomes for rare disorders like UCDs be improved?



# What are the roles of patients and patient advocacy groups in improving outcomes



# Patient advocacy groups for UCDs



National  
Urea  
Cycle  
Disorders  
Foundation

**METABOLIC  
SUPPORT UK**

Your rare condition.  
Our common fight.



**Citrin Foundation**

*OTHERS*



# Exemplars of NUCDF's role in advancing clinical care and research in UCDs

## 1994 - 1996

- ✓ NUCDF champions NaPB

## 2004 - 2006

- ✓ UCDC (6 sites)
- ✓ LS of UCDs
- ✓ NIH support
- ✓ O' Malley Foundation funding

## 2013 - 2019

- NUCDF funds 2 UCDC sites
- Co-hosts International UCD symposium
- Checkammonia.com
- Partner in PCORI grant
- CureUCD Center

## 1988 - 1991

- ✓ NUCDF Founded
- ✓ Families invited

## 2000 - 2003

- ✓ NBS advocacy
- ✓ Rare disease advocacy
- ✓ Rare Diseases Act
- ✓ 1<sup>st</sup> treatment guidelines

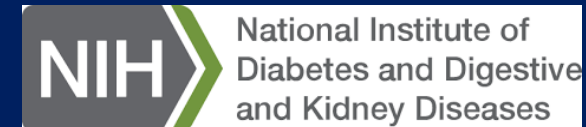
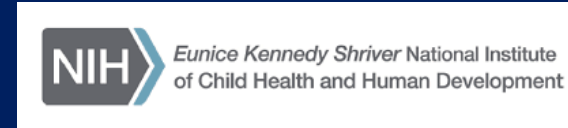
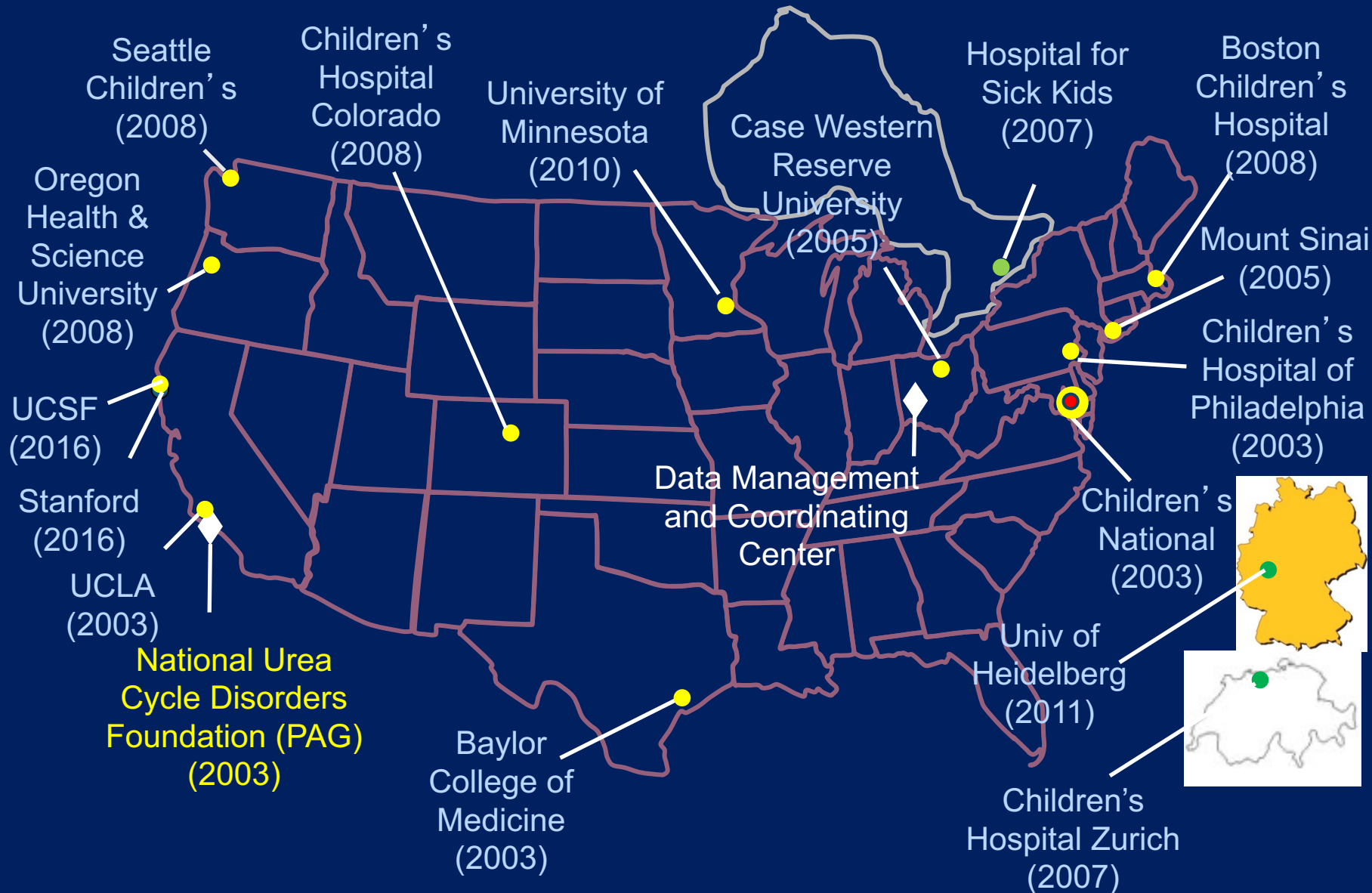
## 2008 - 2012

- ✓ UCDC growth (12 sites)
- ✓ NUCDF fellowship
- ✓ Collaboration/Advice for industry (E.g., Vitaflo, Hyperion, Orphan Europe)

## 2019 - 2023

- ✓ COVID-19 education
- ✓ UCDC/NUCDF host International Symposium on UCDs
- ✓ MyRareDiet App

# Urea Cycle Disorders Consortium



# UCDC Studies

Protocol	Study	Status	Accrual
5101	Longitudinal study of UCDCs	Enrolling	956
5102	RCT of low vs. high dose arginine in ASLD	Completed	12
5104	Neural injury in UCDCs – neuroimaging study	Completed	46
5105	NCG for treatment of HA	Completed	48
5107	Brain nitrogen metabolism in OTCD	Completed	49
5110	NO flux in ASS1D	Completed	6
5111	Orphan Europe Carbaglu surveillance protocol	Enrolling	5
5113	Biomarkers of neurological injury and recovery	Enrolling	21
5114	NO supplementation in ASLD	Completed	12
5115	Manipulating gut microbiome in UCDCs	Completed	4
5116	Sequencing as NBS for proximal UCDCs	Completed	NA
5117	PCORI – liver transplant vs. conservative treatment	Completed	313
5118	Non-invasive assessment of chronic liver disease	Completed	28
5119	Prevalence of electrographic seizures in UCDCs	Enrolling	
5120	Noninvasive Biomarkers of Hepatic Fibrosis in Urea Cycle Disorders	Enrolling	34
5121	Comparison of Standard Neuropsychological Battery and NIH Toolbox	Enrolling	31
5122	Hepatic Histopathology in UCD	Enrolling	66

# Collaborative network/registry-based approach for UCDs



~ 960 individuals with UCDs



**Society of Pediatric Liver Transplantation**



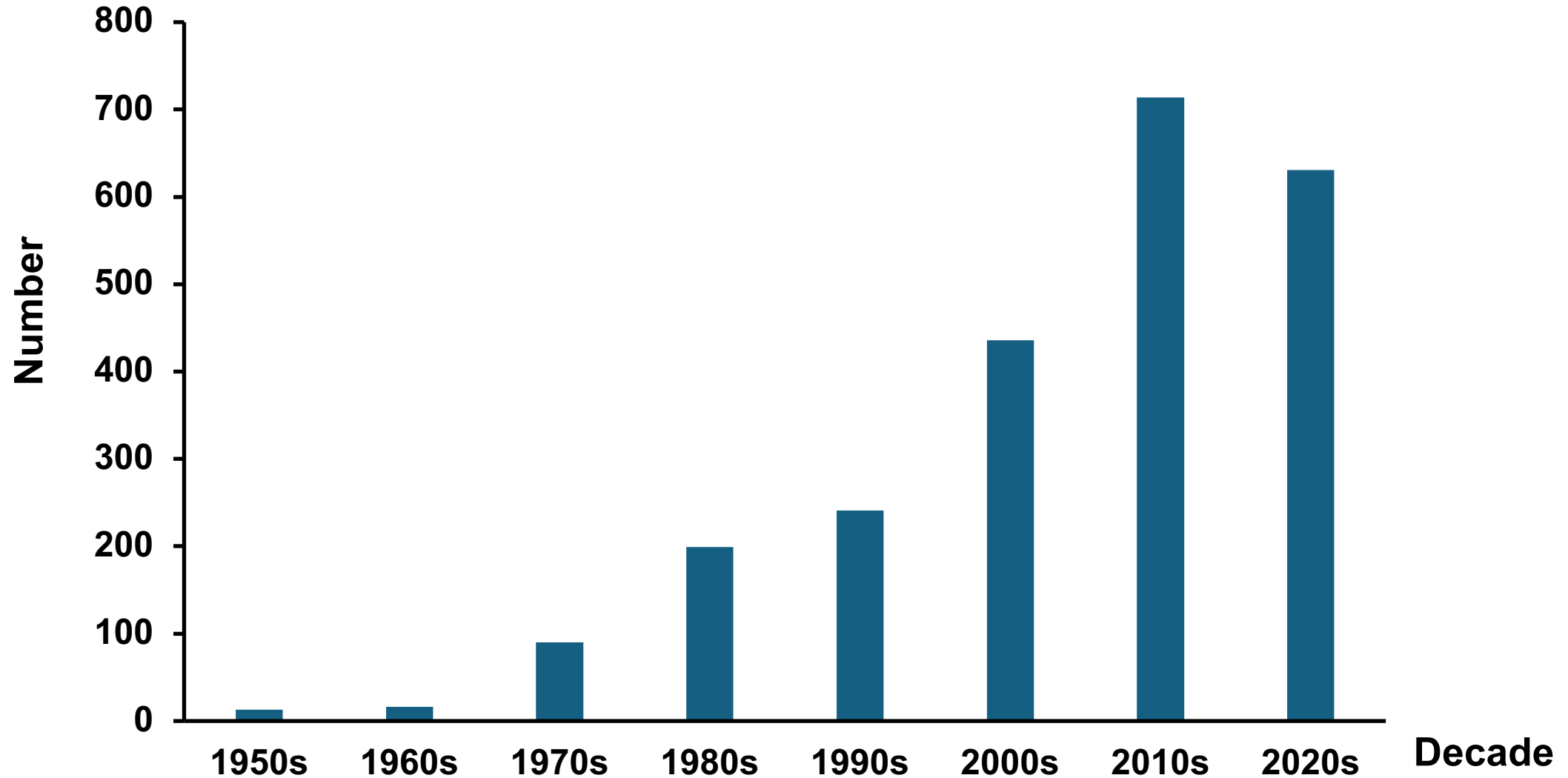
~ 700 individuals with UCDs



**Multicenter collaborative efforts  
without a formal structure**



# There has been a significant increase in the number of medical articles on “UCDs”




# How does one find studies in UCDs?

NIH National Library of Medicine  
National Center for Biotechnology Information

ClinicalTrials.gov

Find Studies ▾ Study Basics ▾ Submit Studies ▾ Data and API ▾ Policy ▾ About ▾

ClinicalTrials.gov is a place to learn about clinical studies from around the world.

 The U.S. government does not review or approve the safety and science of all studies listed on this website. [Read our full disclaimer](#) for details. +

**Focus Your Search** (all filters optional)

**Condition/disease** ⓘ

**Other terms** ⓘ

**Intervention/treatment** ⓘ

**Location**

Search by address, city, state, or country and select from the dropdown list

**Study Status** ⓘ

All studies

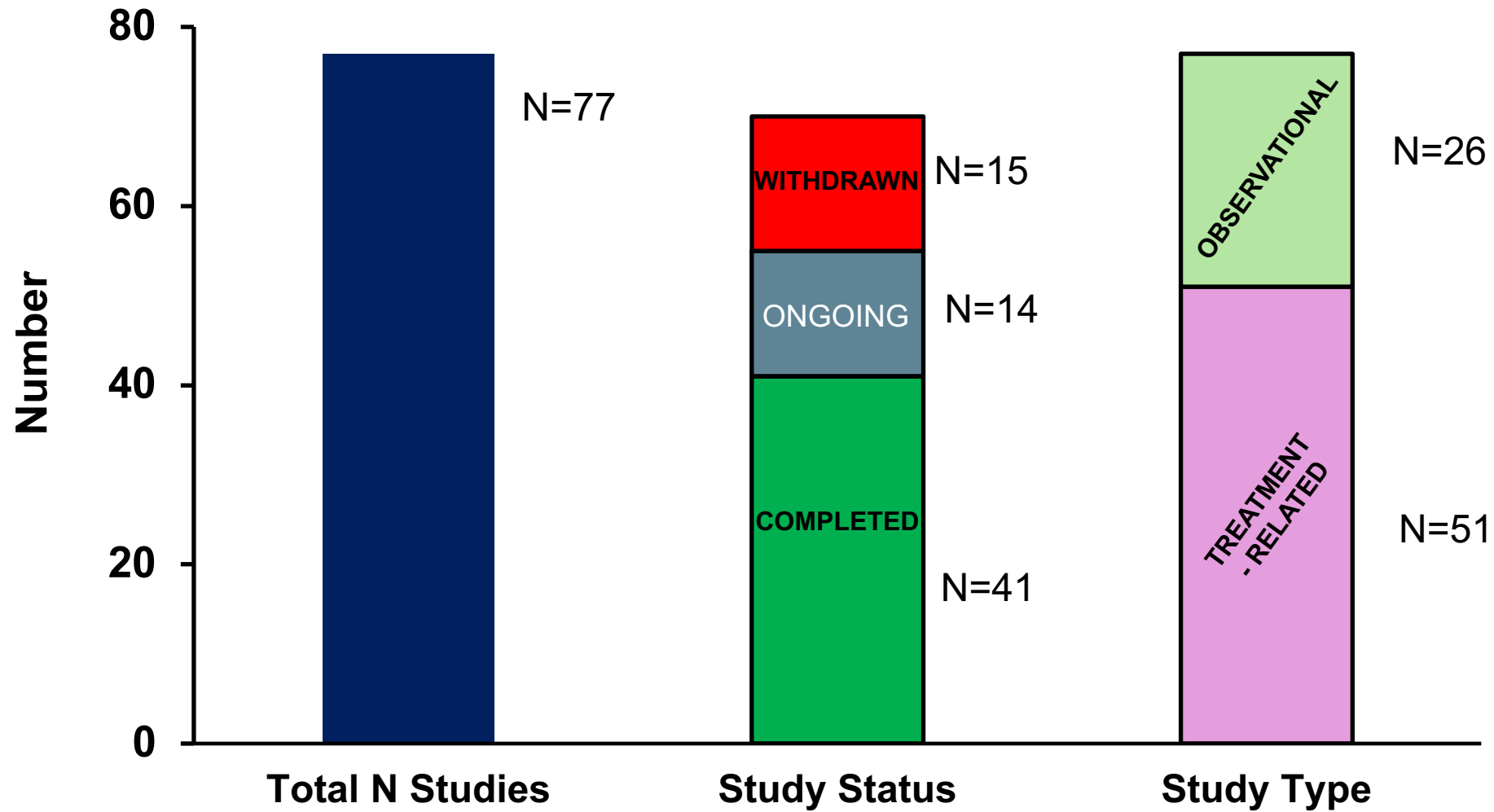
Recruiting and not yet recruiting studies

Search

<https://clinicaltrials.gov>

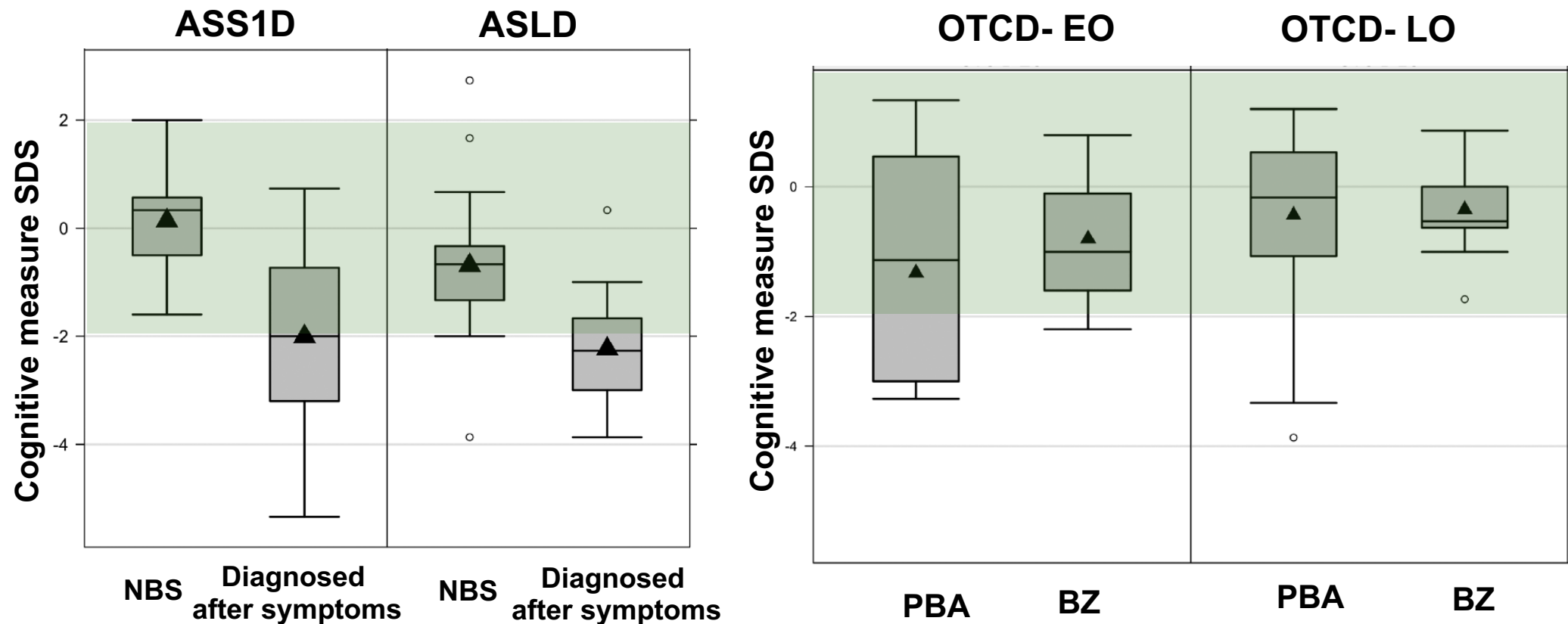
- Search for clinical studies by
- ✓ Condition
  - ✓ Location of clinical trial sites
  - ✓ Age of participants
  - ✓ Study type
  - ✓ Title
  - ✓ Sponsor
  - ✓ ...and others

# Studies on UCDs listed on clinicaltrials.gov



# What do the current outcomes for UCDs look like?

Data from 503 individuals with UCDs from North America and Europe



# How can we further improve outcomes for UCDs?

- ✓ NBS, genomic screening
- ✓ Better interpretation of genetic testing – **Aimee Dudlee**
- ✓ Neuromonitoring – **Andrea Gropman**
- ✓ Monitoring for complications - **Lindsay Burrage**

**Diagnosis/  
monitoring**

- ✓ Dietary therapy – **Erin MacCleod**
- ✓ Making informed decisions – **Nicholas Ah Mew**
- ✓ Liver transplantation - **George Mazariegos**

**Clinical  
Care**

- ✓ **Industry updates**
- ✓ Genomic therapies – **Shawn McCandless**
- ✓ Clinical Trials – **Susan Berry**

**Newer  
therapies**

- ✓ **Discussions**

**Education**



# Thanks to the team at Baylor College of Medicine



Brendan Lee



Lindsay Burrage



Saima Ali

## Neuropsychology

David Schwartz  
Kristin Adkins

## Hepatology/Radiology

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Benjamin Shneider,  
Prakash Masand

## Past BCM members

Juan Marini  
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Susan Carter

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C.Soler-Alfonso, K.Glinton, L. Burrage, B. Lee,  
K. Divin, J. Andre, N. Aquino, C. Harlen



Texas Children's®

Baylor  
College of  
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BCM IDDRC

# Thanks to the UCDC Team

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Sandesh Nagamani, MD

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Mina Nguyen-Driver, Psy.D  
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Yuri Shishido, PhD  
Arianna Stefanatos, PhD  
Rachel Tangen, PhD  
**Greta Wilkening, PhD**

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Eileen King, PhD  
DMCC members

## Study Coordinators

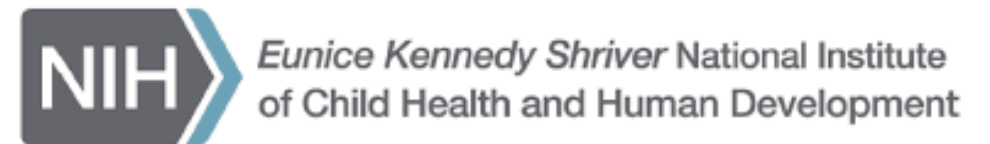
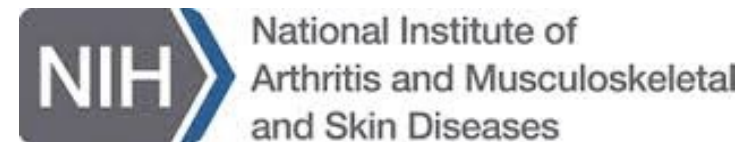
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Liora Caspi  
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Ruby Escalante  
Florian Gleich  
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Rhonda Jones  
Genya Kisin  
Elijah Kravets  
Andi Martinson  
Catherine Miller  
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Spencer Quinn  
Erika Rodriguez-Guzman  
Kara Simpson, MS, CGC  
Julia Smith  
Henna Tiwary  
Hayden Vreugdenhil  
Ashley Wilson  
Keaton Zimbelman  
Kalil King

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Dietmar Hopp Foundation



*Thank you*

*Cindy*





*Thank you*

*Tresa  
Warner*

