



# ERNDIM 2025 SYMPOSIUM

ERNDIM

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Thursday 9<sup>th</sup>  
Friday 10<sup>th</sup>  
October 2025  
Madrid SPAIN  
Crowne Plaza Madrid  
Centre Retiro

## Rare/interesting cases

Dr. Cristiano Rizzo  
U.O.C. Malattie Metaboliche OPBG  
Roma- Italy

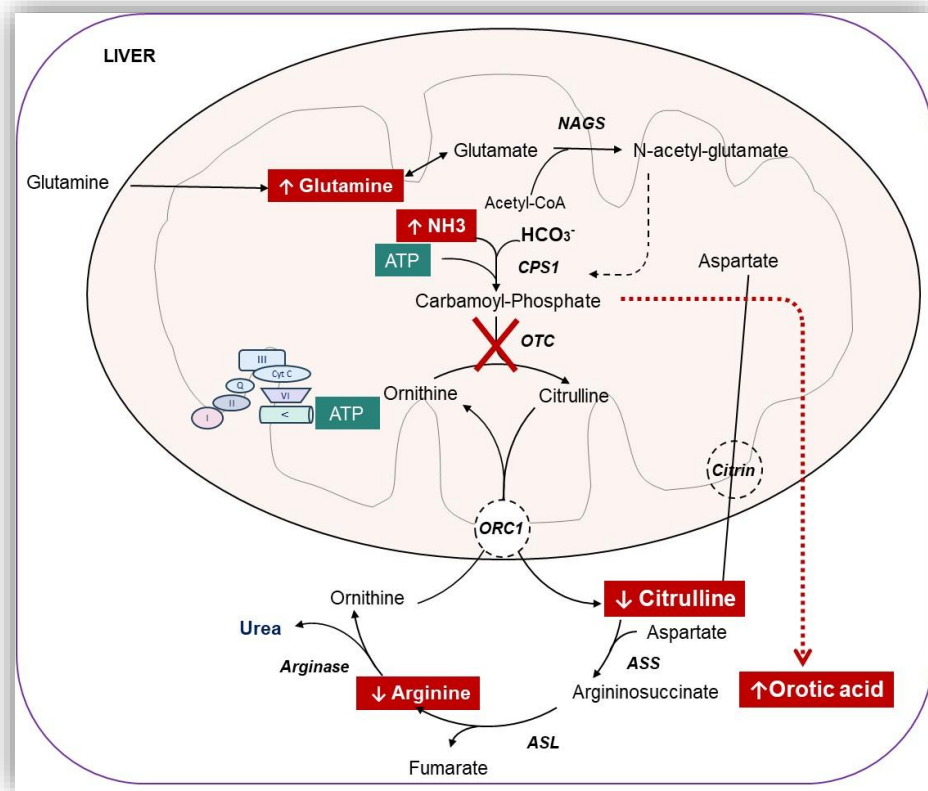
**Friday 10<sup>th</sup> October 2025 -Madrid**

[admin@erndim.org](mailto:admin@erndim.org)

# Hyperammonemia & FLHCC

μml/L	NH <sub>3</sub> (n.v. <50)	Gln (n.v. 200-800)	Cit (n.v. 10-35)	Orn (n.v. 50-190)	Arg (n.v. 30-90)
Pt1 12 Y	500	1046	12	51	8
Pt2 22 Y	300	2070	25	3	45

Orotic aciduria (<10μmol/mMcreat)
723
392



➤ Molecular analysis of *OTC* (gene for UCDs):  
**NEGATIVE**

??

# Hyperammonemic Encephalopathy and secondary OTC deficiency in Fibrolamellar Hepatocellular Carcinoma

**Cristiano Rizzo**

Unit of Metabolic Diseases

Ospedale Pediatrico Bambino Gesù, Rome, Italy



European  
Reference  
Network

MetabERN



Bambino Gesù  
OSPEDALE PEDIATRICO

# Hyperammonemia & FLHCC

- Fibrolamellar hepatocellular carcinoma (FLHCC) is a rare cancer of the liver
- **FLHCC** accounts for less than 1% of all primary liver cancers
- Majority of HCCs manifests in **late childhood & young adulthood** patients (< 40 yrs)
- **Clinical presentations:** abdominal liver masses, lymph nodes involvement, and diffuse metastasis and recurrences
- **No management guidelines:** surgery, chemotherapy CT (CP, DOX, 5-FU, INF $\alpha$ , FOLFOX, *GEMOX* ) and immunotherapy (*sorafenib*, *bevacizumab*, nivolumab, *atezolimumab*)
- **Paraneoplastic syndromes:** **Hyperammonemic Encephalopathy (HAE)**, gynecomastia, and venous thrombosis

# Hyperammonemia & cancers

## ➤ Cancer-related

- **Liver involvement:** HCC
- **Liver infiltration:** haematologic malignancies (NHL) & solid tumours (gastric, pancreatic, CRC, etc...)
- **Portosystemic shunting:** neuroendocrine tumours (NET)

## ➤ Treatment-related

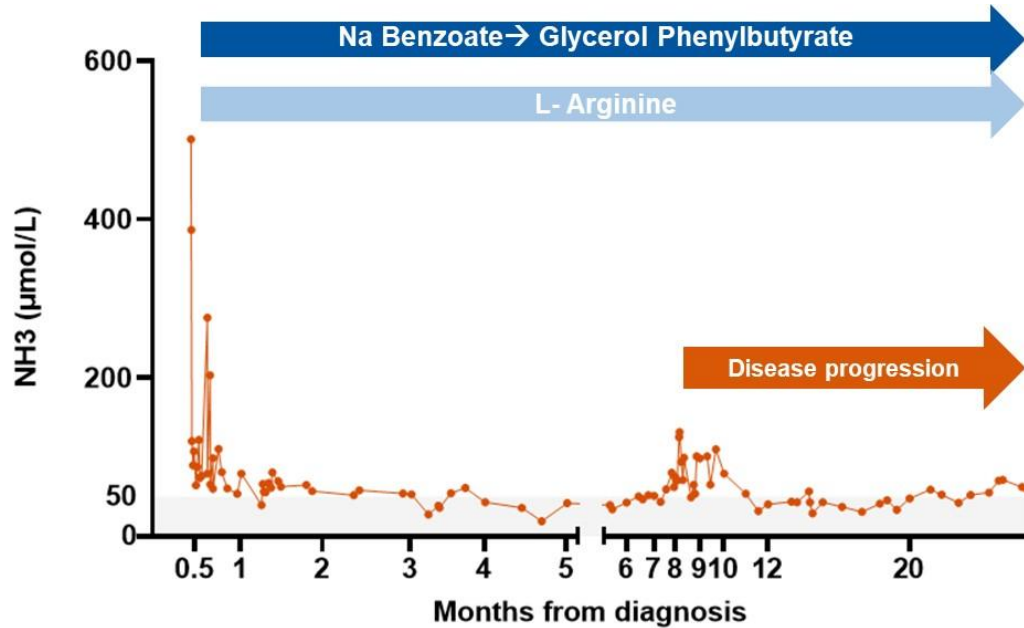
- **Chemotherapy:** L-Asparaginase, Ara-C, 5-FU, FOLFOX, cyclophosphamide)
- **Immunotherapy:** Tyrosine kinase inhibitors (sorafenib, sunitinib)

### HAE pathomechanism:

- ↑ AA consumption by tumour
- portosystemic shunt
- CT-induced tumor lysis & ↑ N<sub>2</sub> production

# OPBG cohort

## ➤ Pt 1 (12y):



PLADO + Sorafenib



PLADO + Bevacizumab



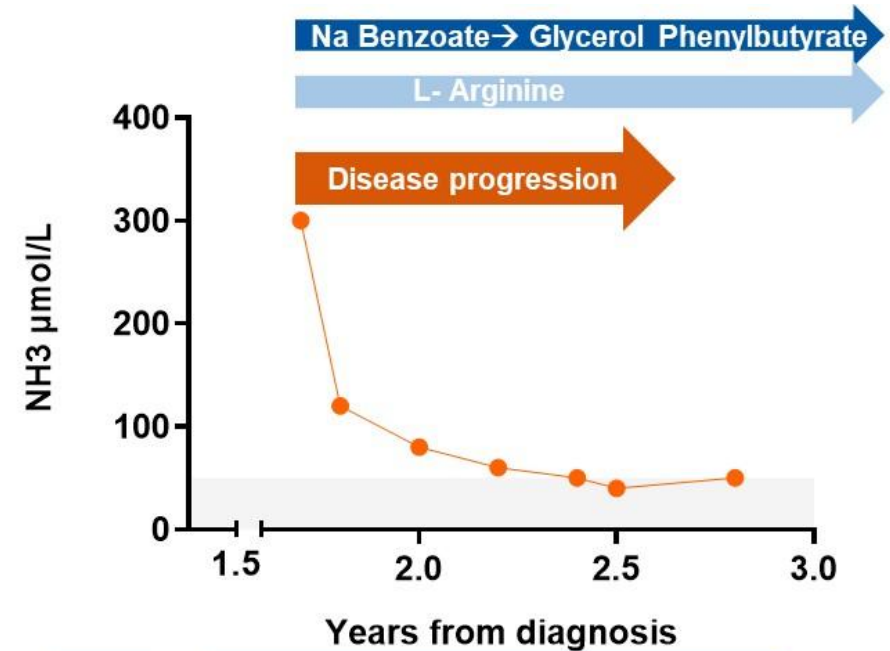
Atezulizumab + Bevacizumab



GEMOX



## ➤ Pt 2 (22y):



CT



# Hyperammonemia & FLHCC

## Case series

- 20 patients with HAE in FLHCC
- 8 males, 12 females
- median age 22.5 yrs (13-32)

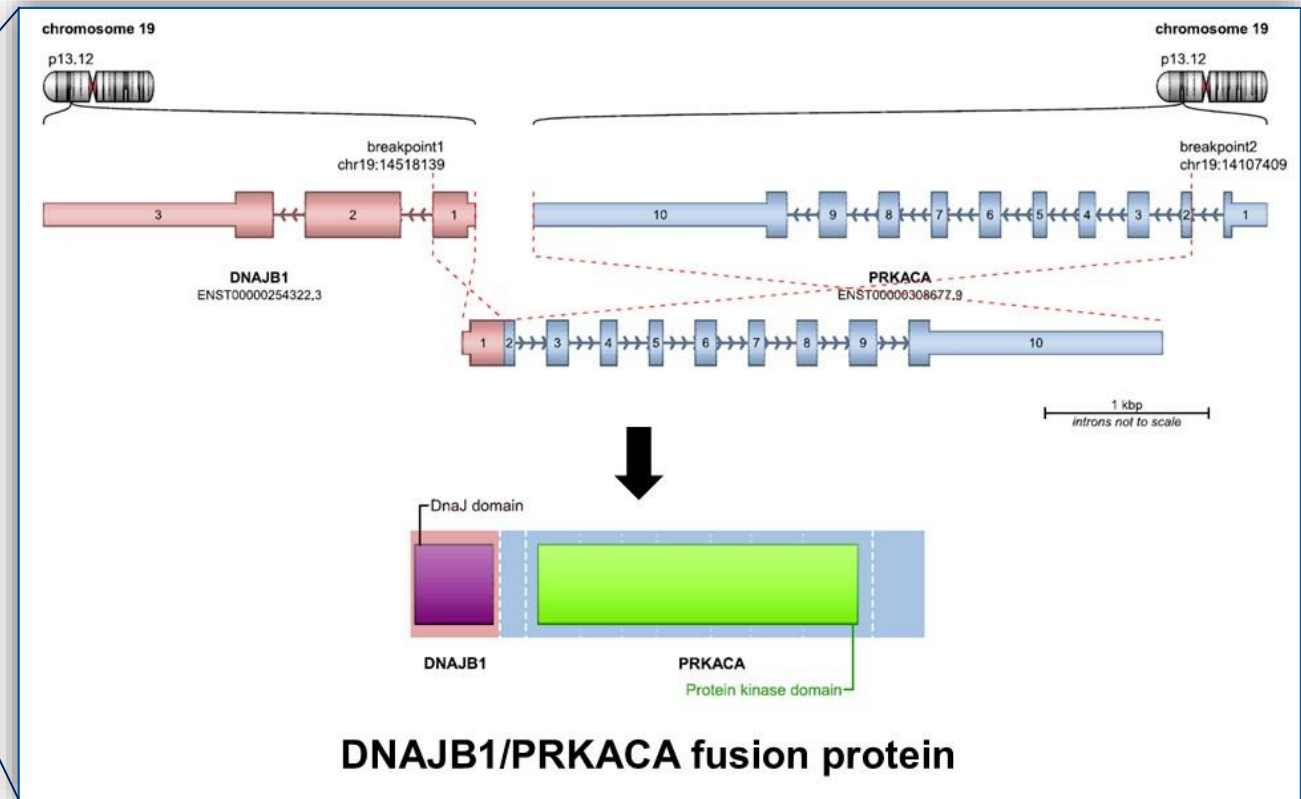
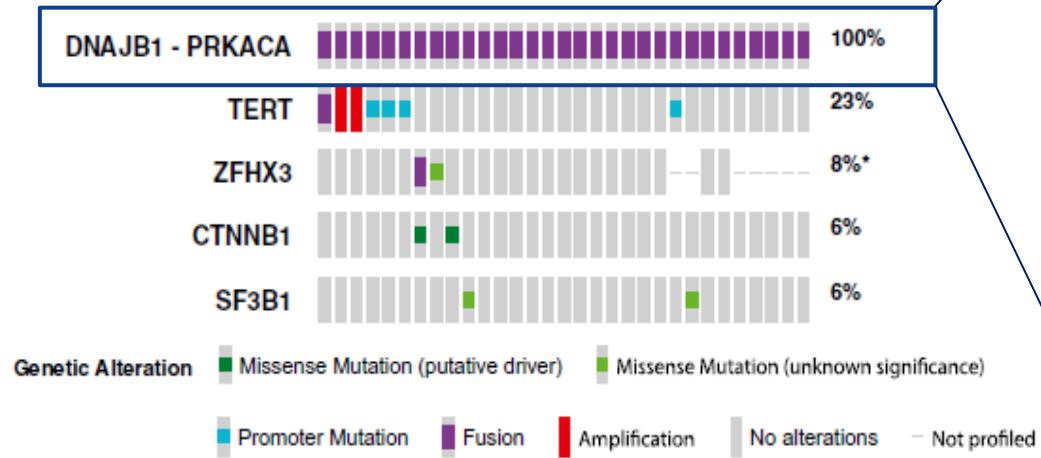
## FLHCC

- **Liver affection:**  
single (13/20), multiple (7/20)
- **Disease extent:**  
localized (1/20), metastatic (19/20)
- **Chemo/Immunotherapy:** 16/20
- **Surgery:** 8/20

HAE in FLHCC			
<b>NH3 max</b>	314 $\mu\text{mol/L}$ (137-694)		
<b>OTC profile</b>	12/13		
<b>Timing</b>	<b>at diagnosis</b>	<b>after CT</b>	<b>at progression</b>
	4/20	9/20	4/20
<b>Treatment</b>	<b>lactulose / rifaximine</b>	<b>NH3 scavenger L-arginine</b>	<b>CVVH</b>
	8/19	15/19	3/19
<b>Recurrency</b>	<b>resolution</b>	<b>recurrency</b>	<b>death</b>
	7/17	8/17	3/17

# Hyperammonemia & FLHCC

## ➤ Oncoprint in FLHCC



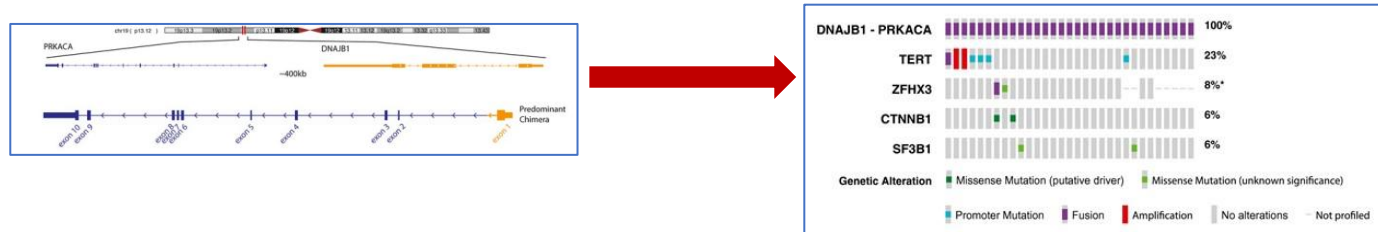
**Oncogenic driver in FLHCC**

# Functional OTC deficiency as a cause of hyperammonemia in FLHCC

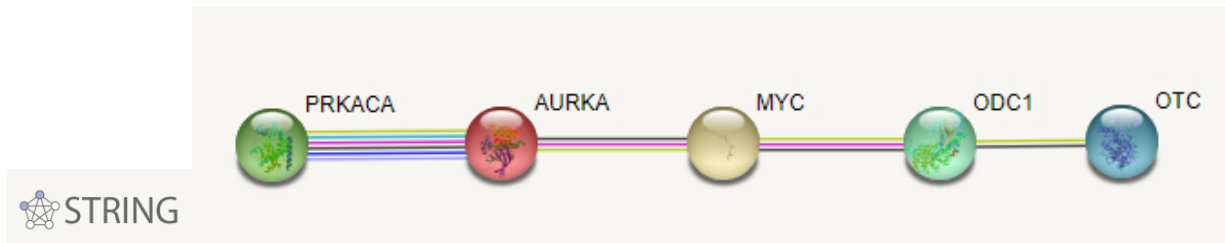
A Proposed Physiopathological Pathway to Hyperammonemic Encephalopathy in a Non-Cirrhotic Patient with Fibrolamellar Hepatocellular Carcinoma without Ornithine Transcarbamylase (OTC) Mutation.

Surjan RC, Dos Santos ES, Basseres T, Makkissi FF, Machado MA.  
Am J Case Rep. 2017 Mar 8;18:234-241. doi: 10.12659/ajcr.901682.

## Heterozygous deletion on Chr19 results in a fusion gene DNJB1-PRKACA



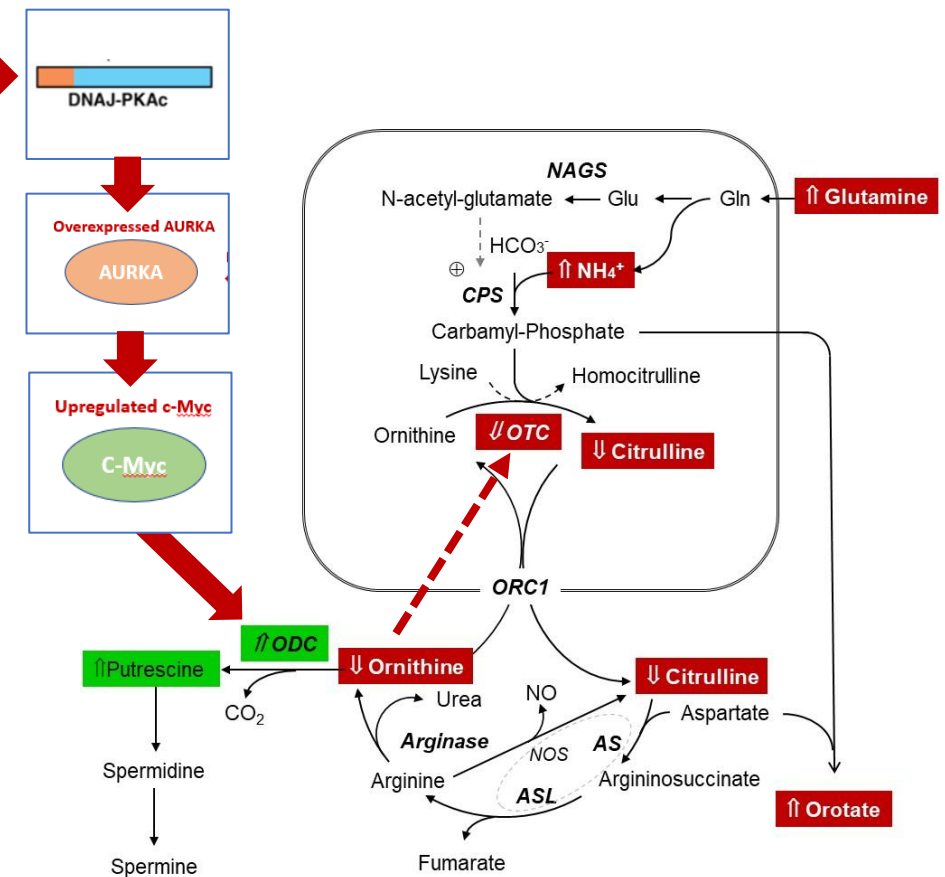
*The fusion gene increases the expression of AURKA, leading to overexpression of c-Myc that upregulates ODC, thus consuming ornithine for polyamines synthesis. The reduced ornithine availability causes a functional OTC deficiency*



Molecular profiling and analysis of genetic aberrations aimed at identifying potential therapeutic targets in fibrolamellar carcinoma of the liver.

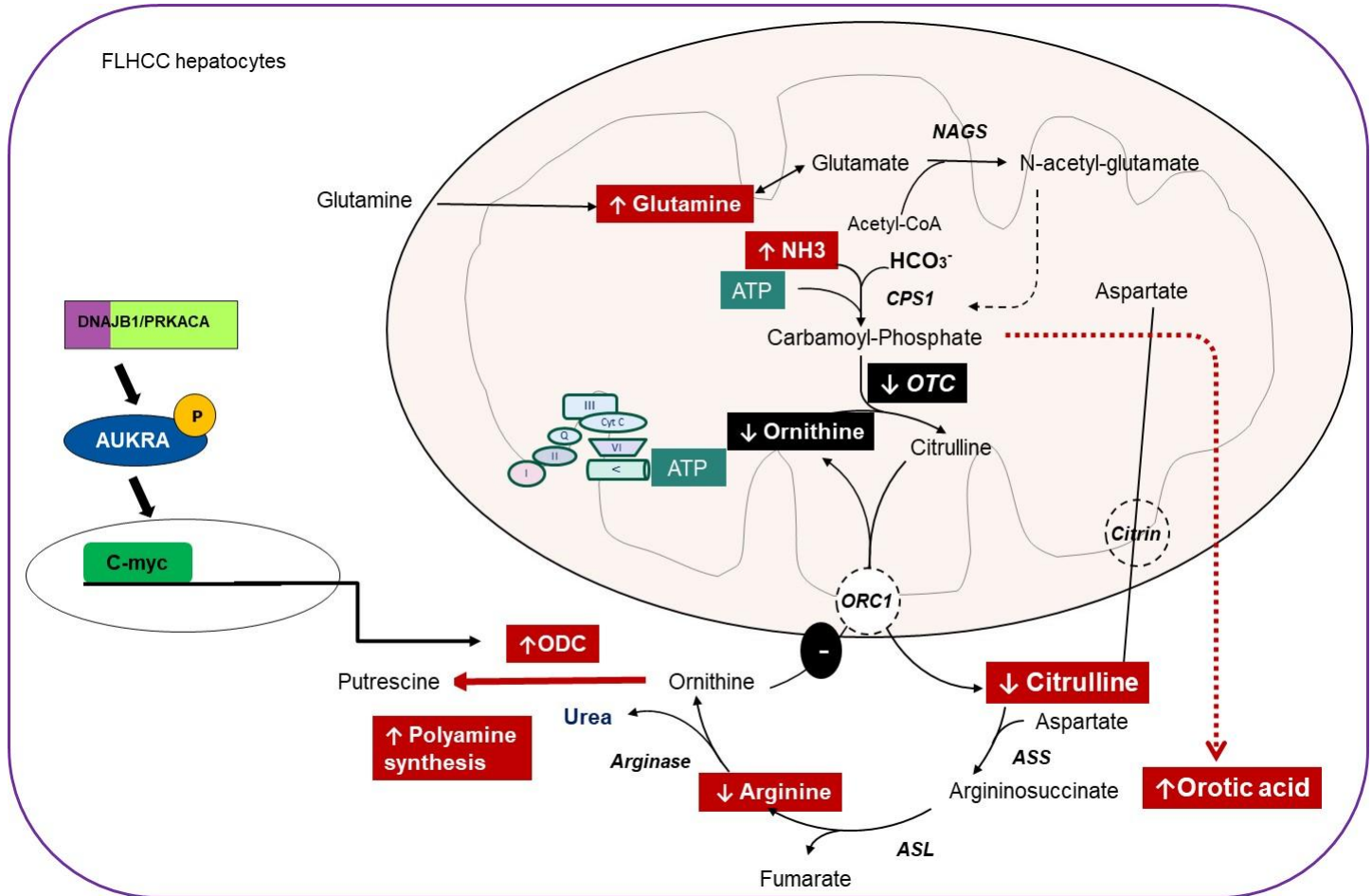
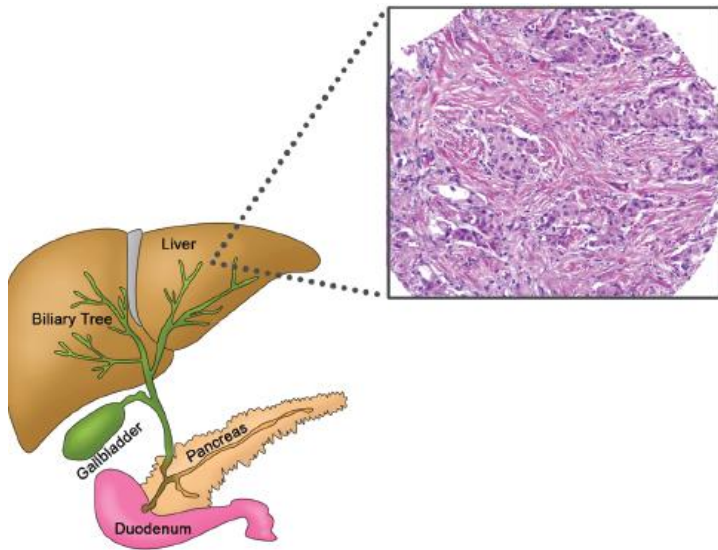
El Dika I, Bowman AS, Berger MF, Capanu M, Chou JF, Benayed R, Zehir A, Shia J, O'Reilly EM, Klimstra DS, Solit DB, Abou-Alfa GK.

Cancer. 2020 Sep 15;126(18):4126-4135. doi: 10.1002/cncr.32960. Epub 2020 Jul 14.



# Hyperammonemia & FLHCC

## ➤ Pathomechanism of HAE



# OPBG cohort

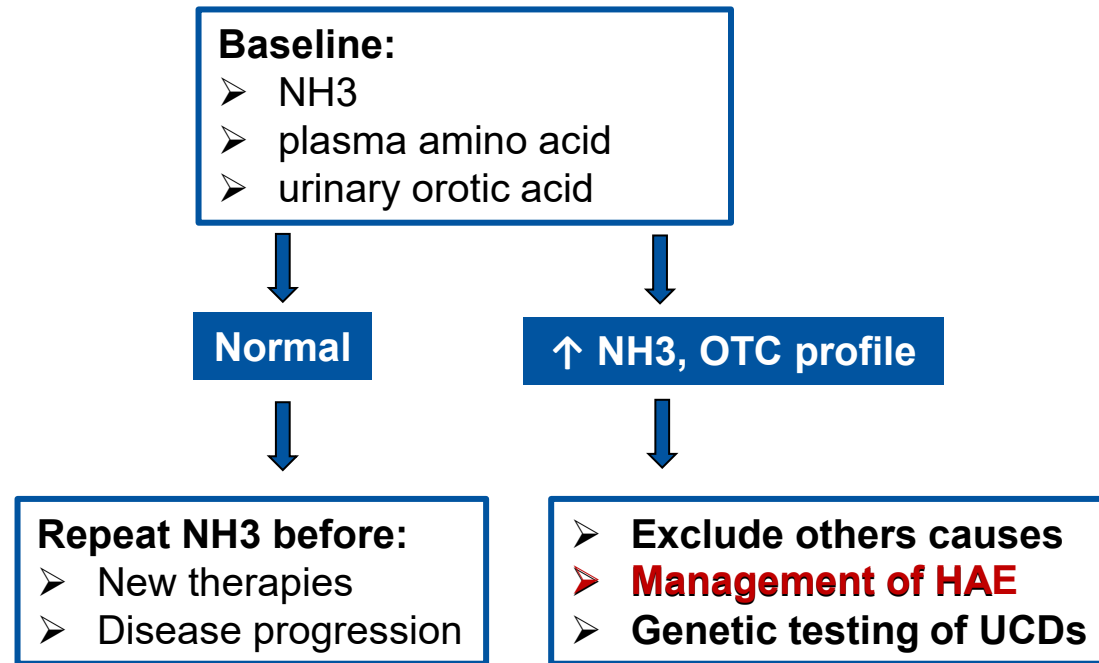
	NH3	DNAJB1/ PRKACA	Age onset	Tumor size	Disease extent	Treatment	Follow-up
<b>Pt 1</b>	✓	✓	12y	114 mm	metastatic	PLADO + immunotherapy	Refractory →exitus
<b>Pt 2</b>	✓	✓	22 y	116 mm	metastatic	CT+ immunotherapy	Progression
<b>Pt 3</b>	✓	✓	14 y	114 mm	liver	surgery	no recurrence
<b>Pt 4</b>	✓	✓	11 y	80 mm	liver	surgery	no recurrence
<b>Pt 5</b>	✓	✓	27 y	88 mm	liver	surgery +sorafenib	local recurrence

**HYPERAMMONIEMIC  
ENCEPHALOPATHY**

# Hyperammonemia & FLHCC

## ➤ Diagnosis of HA in FLHCC

All patients with FLHCC  
(regardless of stage/liver fx & before CT)



# Conclusion

- HAE in cancer patients is mainly related to **tumour necrosis/growth** or **chemotherapy**
- HAE is a severe and relatively frequent complication in **FLHCC**
- DNAJB1/PRKACA fusion protein, specific but non-unique for FLHCC, represents a key oncogenic role
- Overexpression of ODC results in reduced ornithine with **UCDs** with an OTC-like profile
- Ornithine shifts towards **polyamine synthesis**, and other tumorigenic compounds
- Increase the **awareness** of the occurrence of HAE in FLHCC and on the **pathomechanism**
- Add FLHCC among the **secondary “non-metabolic”** causes of HAE

# Acknowledgments

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## Division of Anatomic-pathology, OPBG

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Isabella Giovannoni  
Rita Alaggio

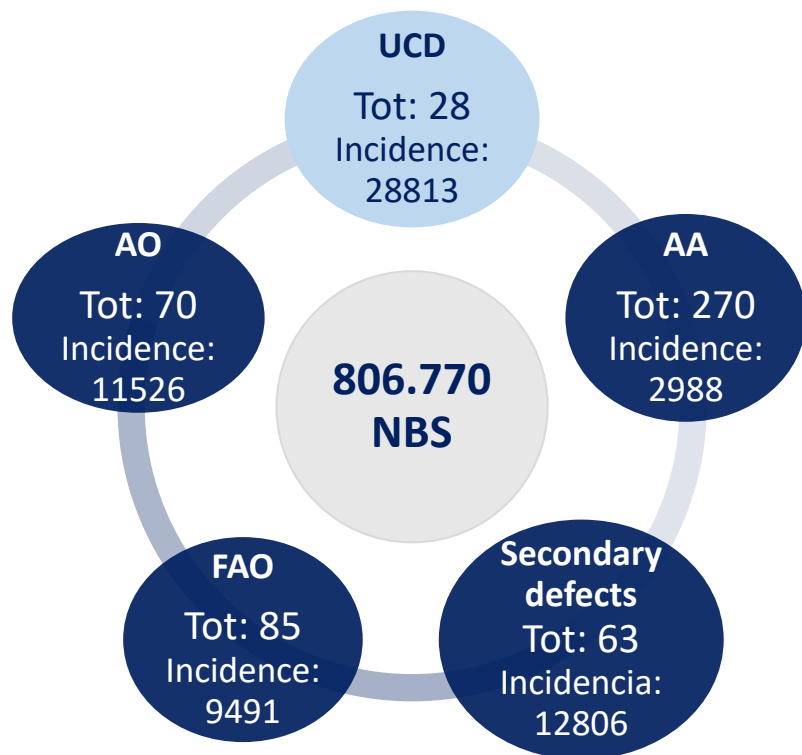
# CASES OF “MILD” OR “LOW” CITRULLINEMIA IN EXPANDED NEONATAL SCREENING

Cristiano Rizzo U.O.C. Malattie Metaboliche OPBG

# Citrulline in newborn screening

Expanded Newborn Screening in Italy Using Tandem Mass Spectrometry: Two Years of National Experience.

Ruoppolo M, Malvagia S, Boenzi S, Carducci C, Dionisi-Vici C, Teofoli F, Burlina A, Angeloni A, Aronica T, Bordugo A, Bucci I, Camilot M, Carbone MT, Cardinali R, Carducci C, Cassanello M, Castana C, Cazzorla C, Ciatti R, Ferrari S, Frisso G, Funghini S, Furlan F, Gasperini S, Gragnaniello V, Guzzetti C, La Marca G, La Spina L, Lorè T, Meli C, Messina M, Morrone A, Nardecchia F, Ortolano R, Parenti G, Pavanello E, Pieragostino D, Pillai S, Porta F, Righetti F, Rossi C, Rovelli V, Salina A, Santoro L, Sauro P, Schiaffino MC, Simonetti S, Vincenzi M, Tarsi E, Uccheddu AP.



## ➤ NBS data in Italy between 2019-2020 :

	tests	806.770
<b>UCD, AA, AO, FAO, Secondary defects</b>	<b>Tot</b>	<b>516</b>
	<b>Incidence (1/X)=</b>	<b>11563</b>
<b>Urea Cycle Defects</b>	Cit I	14
	Cit II	0
	ASA	13
	ARG	1
	<b>Tot</b>	<b>28</b>
	<b>Incidence (1/X)=</b>	<b>28813</b>



**5.2% of MME diagnosed via NBS secondary to elevated Citrulline (Cit)**

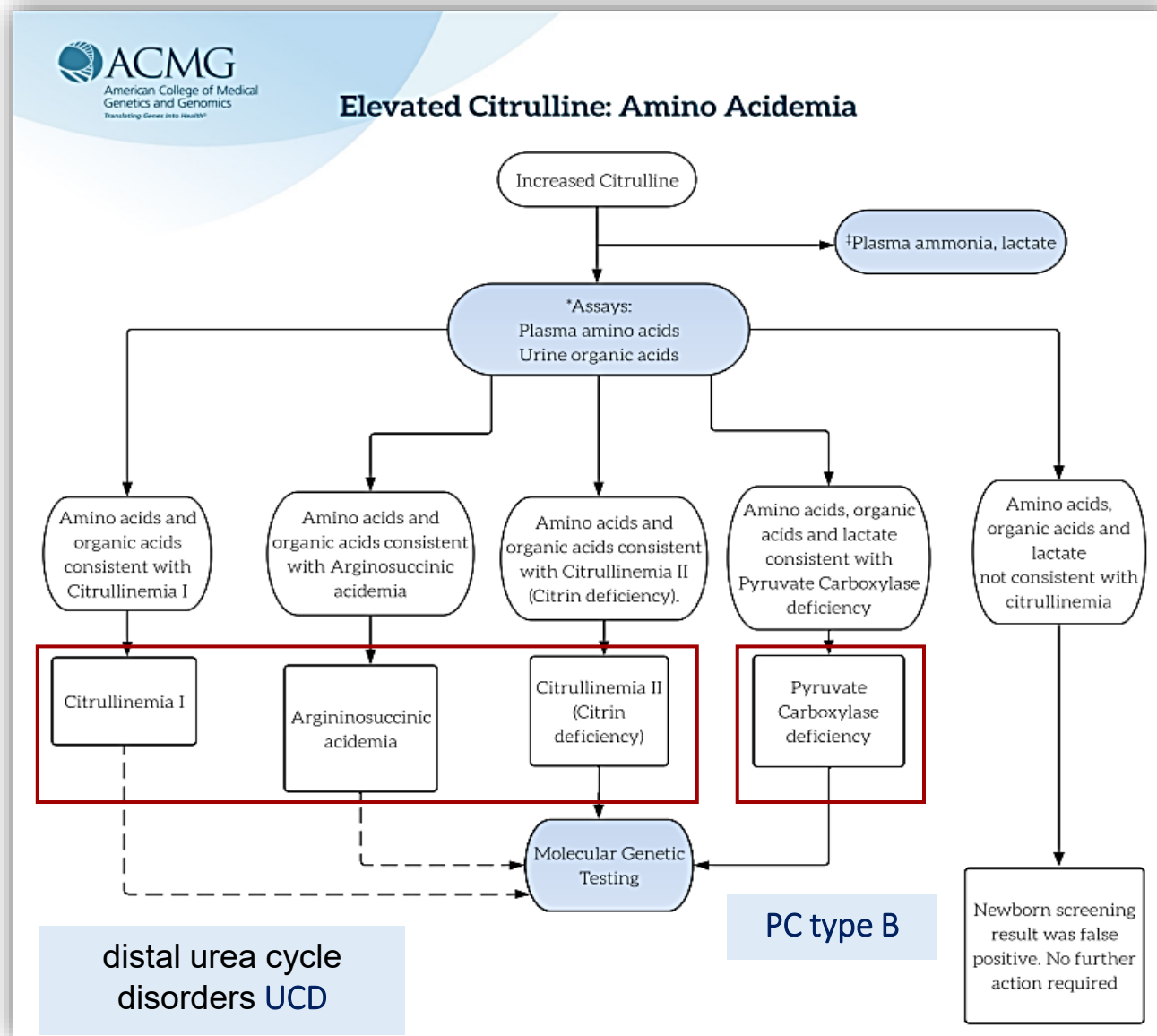
\*Non presi in considerazione dati per IC,FC, patologie materne

# Citrulline in newborn screening

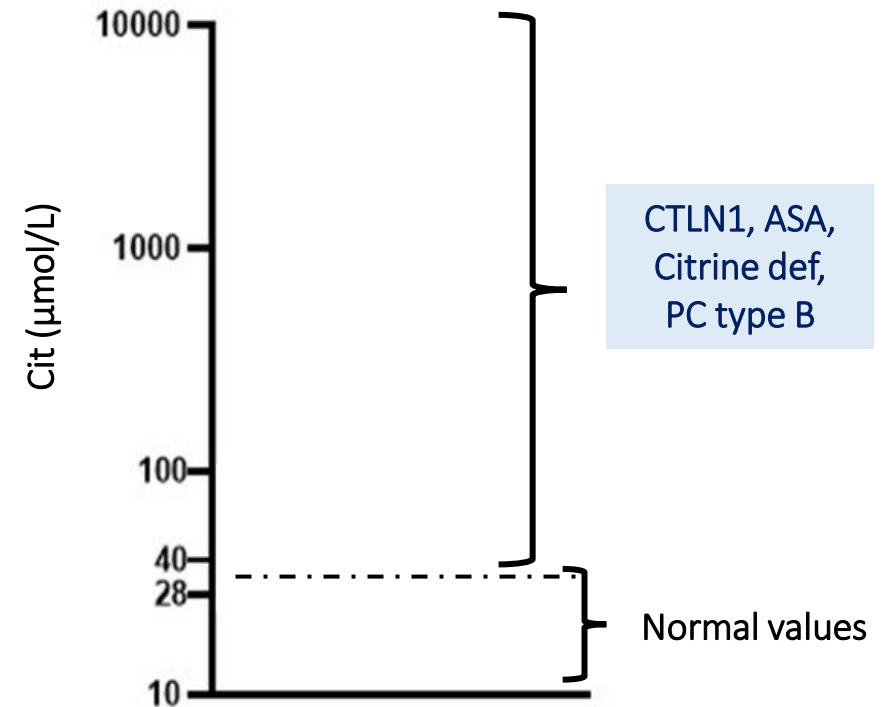
## ➤ UCD: high-risk NBS

	Gln	Cit	Arg	Orn	ASA	Orotic
NAGS	▲	▼	▼	▼		absent
CPS	▲	▼	▼	▼		absent
OTC	▲	▼	▼	▼		▲
Citrullinemia	▲	▲	▼			▲
ASLD	▲	▲			▲	▲
Argininemia	▲		▲			▲
HHH	▲			▲		▲
citrin defect		▲				absent

# Citrulline in newborn screening



## ➤ NBS citrulline levels :

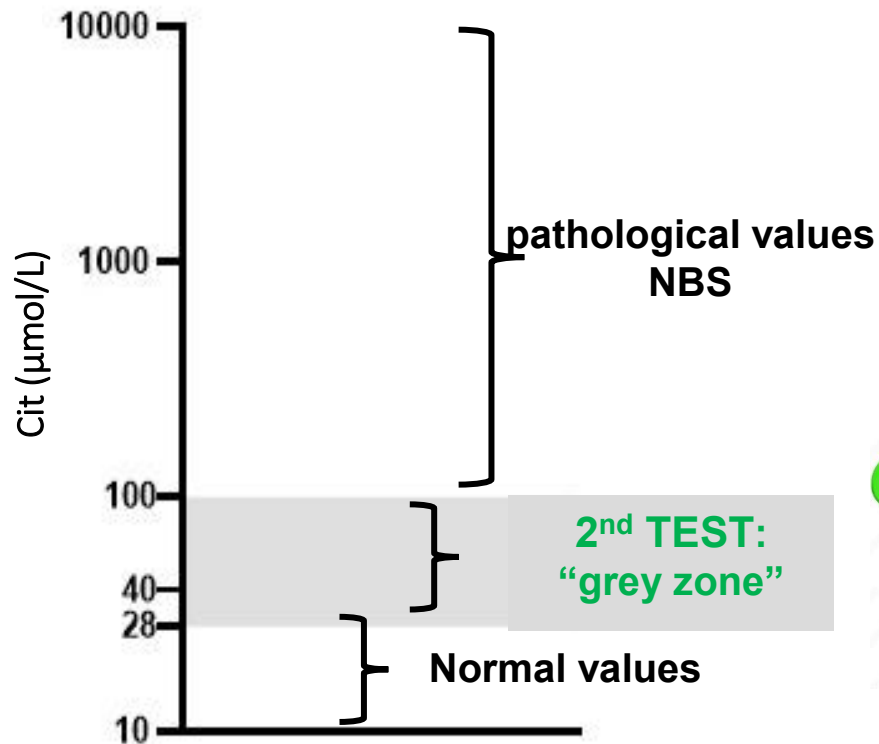


# Citrulline in newborn screening

The diagnostic challenge of mild citrulline elevation at newborn screening.

Siri B, Olivieri G, Angeloni A, Cairoli S, Carducci C, Cotugno G, Di Michele S, Giovanniello T, La Marca G, Lepri FR, Novelli A, Rossi C, Semeraro M, Dionisi-Vici C.

Mol Genet Metab. 2022 Apr;135(4):327-332. doi: 10.1016/j.ymgme.2022.02.008. Epub 2022 Feb 20.



## Mild increase in citrulline in NBS (<100 $\mu\text{mol/L}$ ):

- 2 screening center (Lazio & Abruzzo)
- **Years:** 2018-2020
- % recall : 0.06% = 98
- **False Positives** : 88%
- **10 confirmed cases with elevated CIT in the new test**

# Citrulline in newborn screening

	age (days)	Cit (6.43 – 26.1)	ASA (absent)	Cit/Phe (0.11 - 0.56)
Pt 1 (F)	3	44.1	absent	0.64
Pt 2 (F)	3	40.1	absent	0.66
Pt 3 (M)	2	35.6	absent	0.47
Pt 4 (F)	3	46.6	absent	0.78
Pt 5 (F)	2	43.6	absent	1.12
Pt 6 (F)	3	46.2	absent	0.67
Pt 7 (M)	3	35.7	absent	0.74
Pt 8 (F)	2	22.3	20.9	0.55
Pt 9 (M)	3	46.1	absent	0.63
Pt 10 (F)	3	27	absent	0.64

➤ **9 Pts:** ↑ Cit: **43.6 μmol/L** (IQR 31.3; 46.15)  
↑ Cit/Phe: **0.64** (IQR 0.59; 0.72)

➤ **1 Pt :** ASA **20.9 μmol/L**

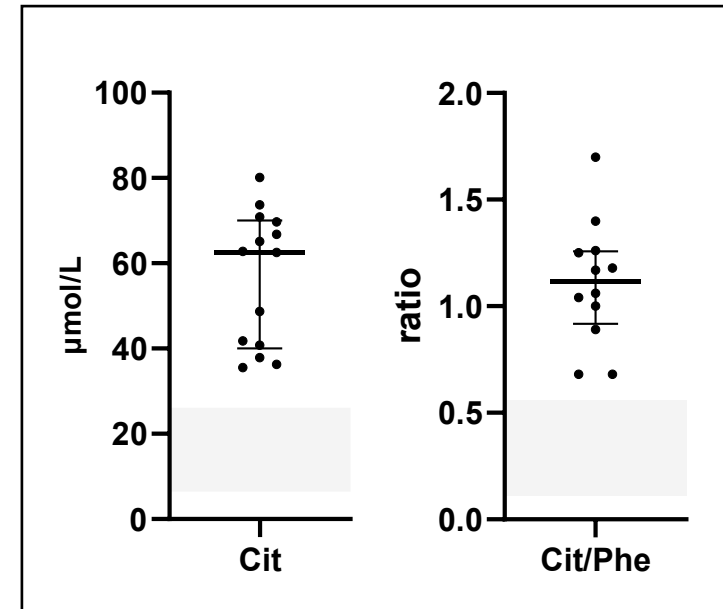
\*IQR: range  
interquartile  
amminoacidi: μmol/L

# Citrulline in newborn screening

➤ Pt 1-7:

	Age (days)	Cit	Cit/Phe
		(6.43-26.1)	(0.11-0.56)
Pt1	3	46.1	0.64
	16	65.1	1.25
	3	40.1	0.66
Pt2	11	62.5	1.00
	24	62.8	1.17
	2	35.6	0.47
Pt3	21	66.7	0.68
	3	46.6	0.78
	11	69.7	1.18
Pt4	18	73.7	1.70
	2	43.6	1.12
	10	40.8	1.04
Pt5	22	48.7	1.26
	3	46.2	0.67
	13	80.1	1.40
Pt6	3	35.7	0.74
	8	36.3	0.68

re-test Cit > 40  $\mu\text{mol/L}$



\*IQR: range interquartile aminoacidi:  $\mu\text{mol/L}$

# Heterozygous for CTLN1(7/10)

➤ Pt 1-7:

	Age (days)	Cit	Cit/Phe
		(6.43-26.1)	(0.11-0.56)
Pt1	3	46.1	0.64
	16	65.1	1.25
Pt2	3	40.1	0.66
	11	62.5	1.00
	24	62.8	1.17
Pt3	2	35.6	0.47
	21	66.7	0.68
Pt4	3	46.6	0.78
	11	69.7	1.18
	18	73.7	1.70
Pt5	2	43.6	1.12
	10	40.8	1.04
	22	48.7	1.26
Pt6	3	46.2	0.67
	13	80.1	1.40
Pt7	3	35.7	0.74
	8	36.3	0.68

7 pts: Carrier per CTLN1

**ASS1:** c.535 T > C (p.Trp179Arg)/WT (exon 7)

**ASS1:** c.1087C > T (p.Arg363Trp)/WT (exon 13)

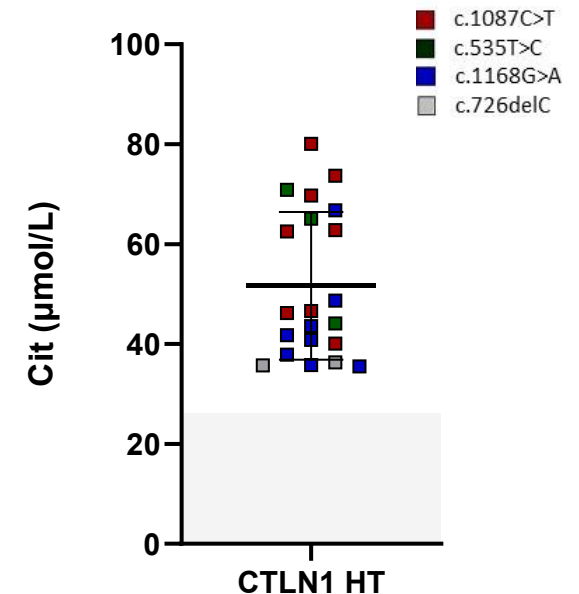
**ASS1:** c.1168 G > A (p.Gly390Arg)/WT (exon 14)

**ASS1:** c.1087C > T (p.Arg363Trp)/WT (exon 13)

**ASS1:** c.1168 G > A (p.Gly390Arg)/WT (exon 14)

**ASS1:** c.1087C > T (p.Arg363Trp)/WT (exon 13)

**ASS1:** c.726delC (p.Thr243fsTer12)/WT (exon 10)



False positives

\*IQR: range interquartile  
aminoacidi: µmol/L

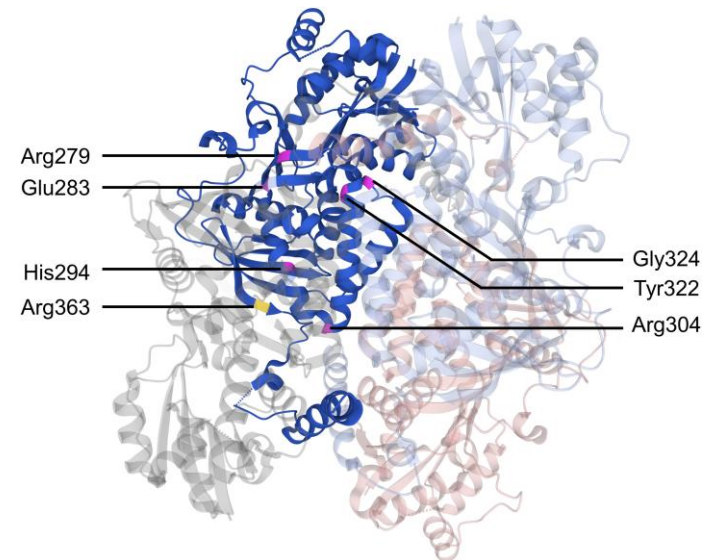
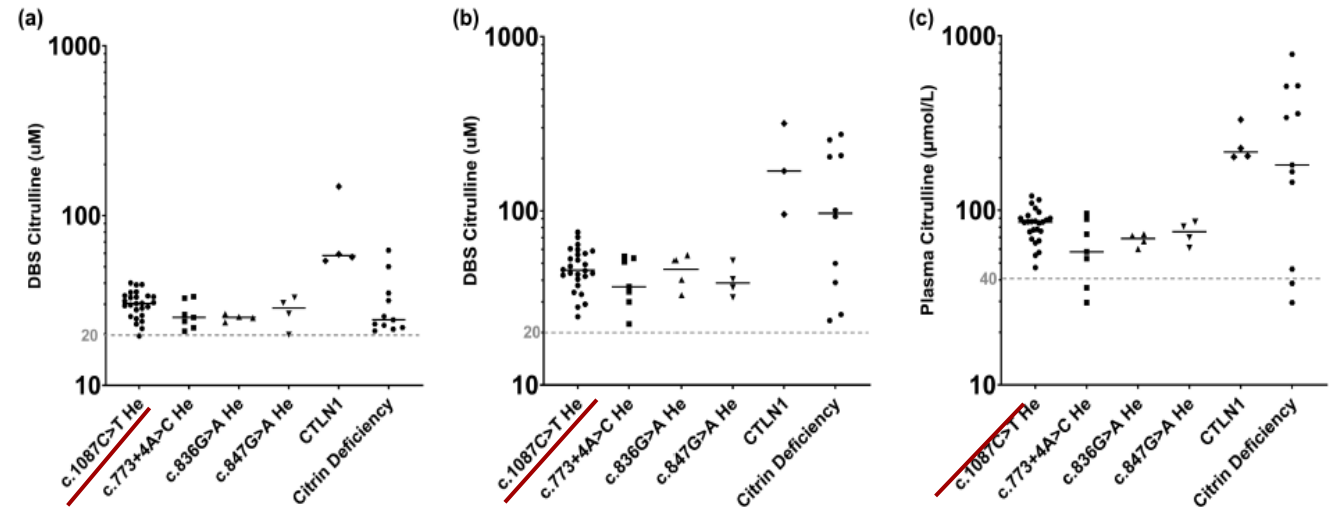
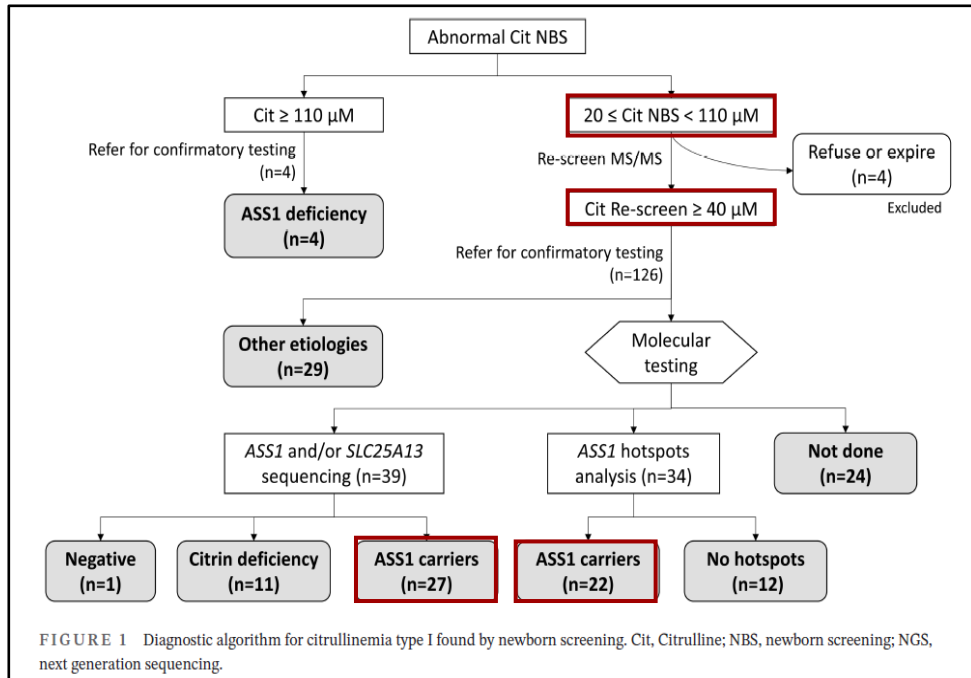
# Asymptomatic ASS1 Carriers

Asymptomatic ASS1 carriers with high blood citrulline levels.

Chen HA, Hsu RH, Chang KL, Huang YC, Chiang YC, Lee NC, Hwu WL, Chiu PC, Chien YH.

Mol Genet Genomic Med. 2022 Sep;10(9):e2007. doi: 10.1002/mgg3.2007. Epub 2022 Jun 21.

False positives

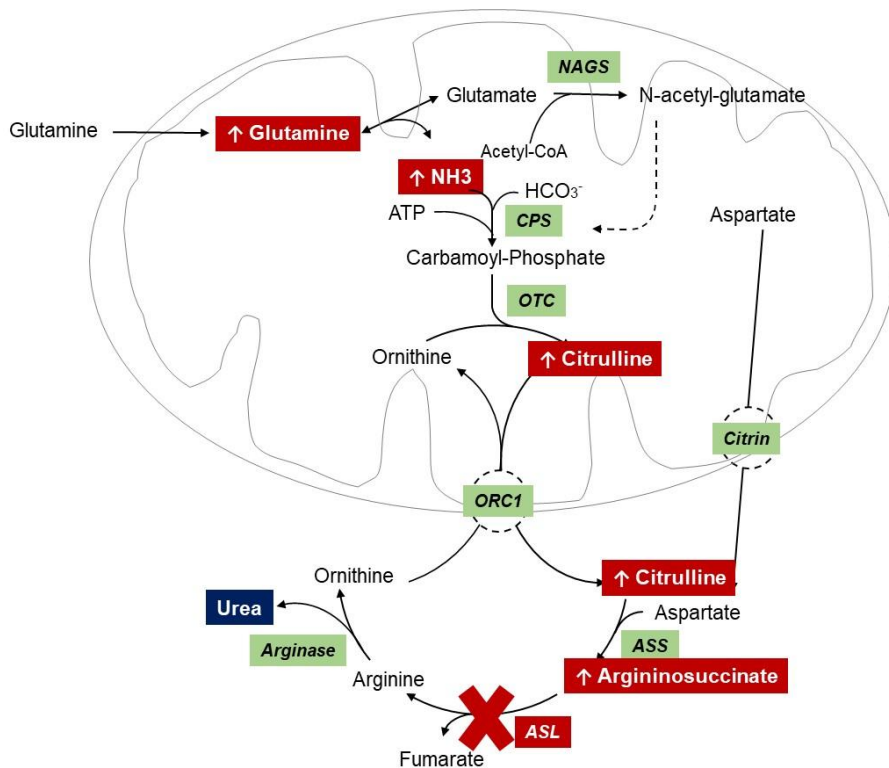


**Cit SNE-associated variants:**  
**Exons 11-15 in the interaction region between the two dimers**

# Distal defects of the urea cycle

➤ Pt 8:

Age (days)	Cit (6.43-26.1)	ASA (assente)	Phe (34-86)	Cit/Phe (0.11-0.56)
2	22.3	20.9	40.3	0.55
18	46.7	47.1	59.4	0.79



## ASLD ASA (OMIM#207900)

- ❖ Without episodes of decompensation
- ❖ **AA pl:** Cit 29-65 μmol/L and ASA 0-37 μmol/L
- ❖ Therapy with L-Arginina → STOP a 5m
- ❖ Negative ASA after L-Arginine suspension
- ❖ Normal neurocognitive development at 13 months

“Mild ASA”

- 👉 Molecular analysis of ASL: compound heterozygosity c.532G>A/c.1267G>A
- 👉 Predicted enzyme activity (Zielonka et al.): 40-60%

# Citrulline in newborn screening

Secondary conditions

➤ Pt 9:

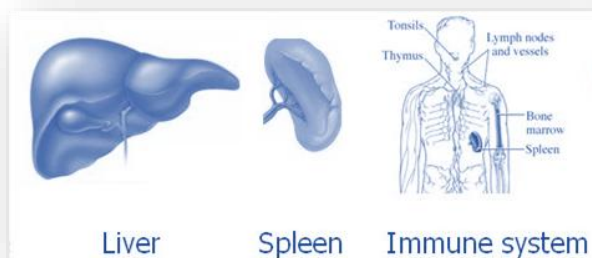
Age (days)	Cit (6.43-26.1)	ASA (absent)	Ala (121-561)	Val (55-230)	Phe (34-86)	Cit/Phe (0.11-0.56)
3	46.1	absent	602	130	73.4	0.63
84	79.6	absent	865.5	248.5	93.8	0.85

➤ First months of life :



episodio di IVU  
**↑↑ LDH, Ferritin**  
 ↑ GGT  
 ↑ AST

**profile MAS-like**



↑↑ Cit  
**↑↑↑ LDH, Ferritin**  
 ↑ AST>>ALT



**Growth retardation**  
**Protein rejection**  
 Epatomegalia, ↑ AST>>ALT  
 ↑↑↑ LDH, Ferritina  
 AApl: ↑↑ Cit, ↓↓ pl. Lys, Orn, Arg  
 AAu: ↑↑ Lys, Orn, Arg



**profile UCD-like**

# Citrulline in newborn screening

Secondary conditions

## Metabolic Serendipities of Expanded Newborn Screening.

Yahyaoui R, Blasco-Alonso J, Gonzalo-Marín M, Benito C, Serrano-Nieto J, González-Gallego I, Ruiz-Sala P, Pérez B, González-Lamuño D.

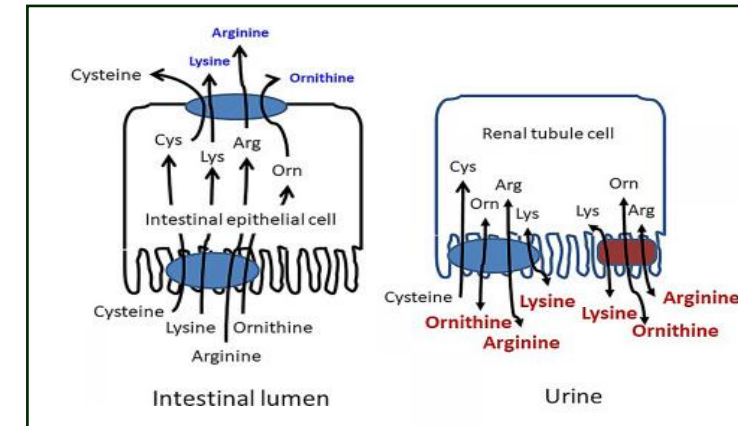
Genes (Basel). 2020 Aug 29;11(9):1018. doi: 10.3390/genes11091018.

### ➤ Patient OPBG

	Pt.1	Pt.2	Pt.3	Pt.4	Pt.5	Pt.6	Pt.9	Yahyaoui
symptoms at onset	↑ ALT/AST	IEA	Sindrome di Fanconi	Sindrome di Fanconi	Confusion, epilepsy	SLE	↑ Cit allo SNE	↑ Cit allo SNE
age at diagnosis	3 days	2 days	15 days	10 days	31 days	10 days	1 day	1 day
LDH UI/L	2476	2972	1712	2507	975	2058	5167	na
Ferritine µg/dl	184	2162	10	356	/	818	2412	na
Citrulline µM/L	102	18	59	220	61	93	78.5	61.8

Protein intolerance with lysinuria

Homozygosis c.726G > A (p.Trp242Ter) in *SLC7A7*



# Citrulline in newborn screening

Secondary conditions

## ➤ Pt 16 aa

**Reye syndrome:** IEA - Lactic acidosis - Hiperammonemic encephalopathy

UCD-like profile	Gln	↑↑
	Cit	↑↑
	Arg	↑↑
MSUD-like profile	Val	↑↑
	Ile	↑↑
	Le	↑↑
	Allo-Ile	↑↑



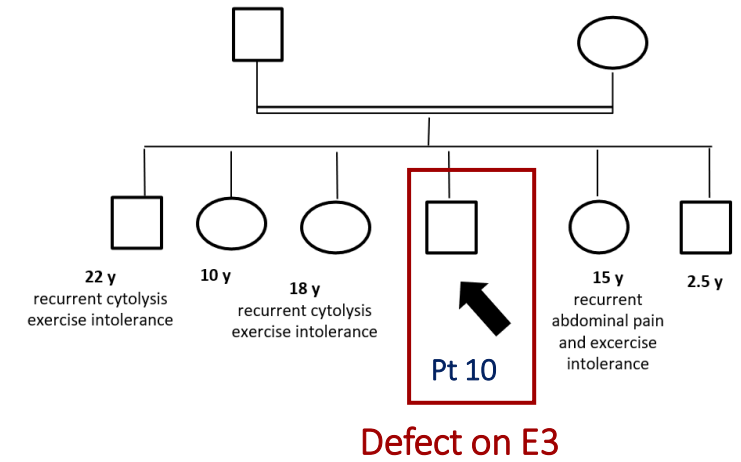
Dihyrolipoamide dehydrogenase Defect (DLDD) or E3 defect

Homozygosity for c.685G >T (p.Gly229Cys) in **DLD**

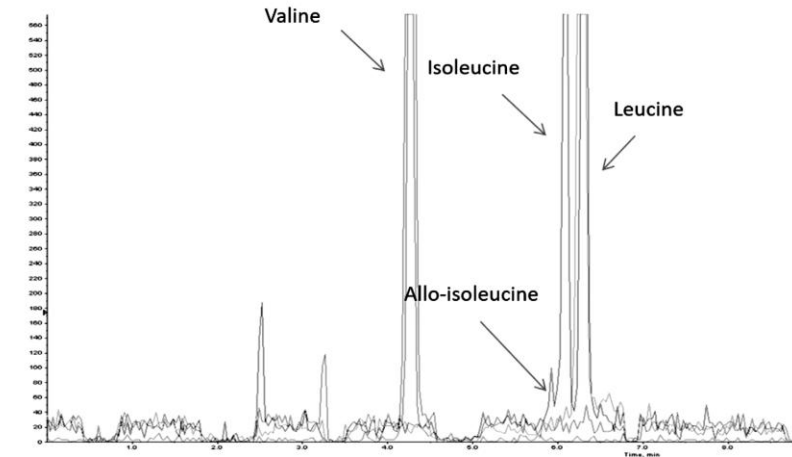
**Organic acids :** alpha-Ketoacids

## ➤ Pt 10

Age	Cit*	Phe	Allo-Ile	Val	Xle	Cit/Phe	Xle/Phe
	(6.43-19)	(34-86)	(assente)	(55-230)	(63-254)	(0.11-0.56)	(1.12-4.79)
3 days	27	42	2.8	256	213	0.64	5.07



**Presence of Allo-Ile\*\***



\*Cit cut-off è datato 2005  
\*\* analisi retrospettica

# Dihydrolipoamide Dehydrogenase deficiency

Elevated plasma citrulline: look for dihydrolipoamide dehydrogenase deficiency.

Haviv R, Zeharia A, Belaiche C, Haimi Cohen Y, Saada A.

Eur J Pediatr. 2014 Feb;173(2):243-5. doi: 10.1007/s00431-013-2153-x. Epub 2013 Aug 31.

**Table 1** Markers in DLD patients and in control patients

Variable	DLD patients/ number of cases	Control patients/ number of cases	P value
Elevated serum transaminases	12/17	13/19	0.892
Hyperammonemia	3/17	6/19	0.349
Metabolic acidosis	12/17	6/19	0.019
Elevated plasma citrulline	7/17	0/19	0.001
Elevated plasma glutamine	6/17	5/19	0.359
Elevated plasma tyrosine	1/17	4/19	0.199
Elevated plasma alanine	7/17	6/19	0.734



- **Citrulline:** 205 μM (59 to 382 μmol/L)
- 2 pts with neurological phenotype and ↑ **Cit al NBS\*\***
- Variant with ↑ Cit in **DLD** c.685G>T (p.Gly229Cys)

\*\* during decompensation

Newborn screening for dihydrolipoamide dehydrogenase deficiency: Citrulline as a useful analyte.

Quinonez SC, Seeley AH, Seeterlin M, Stanley E, Ahmad A.

Mol Genet Metab Rep. 2014 Aug 15;1:345-349. doi: 10.1016/j.ymgmr.2014.07.007. eCollection 2014.

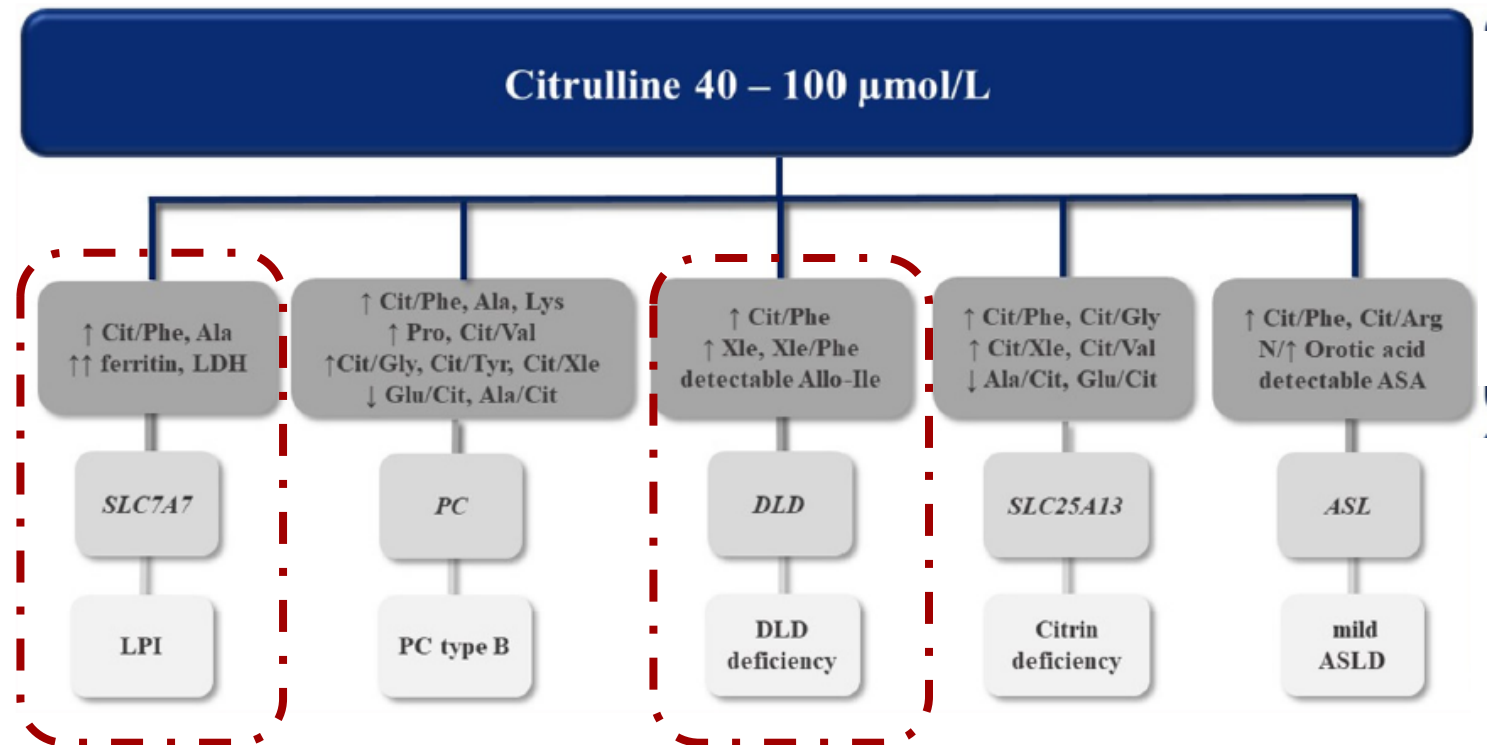
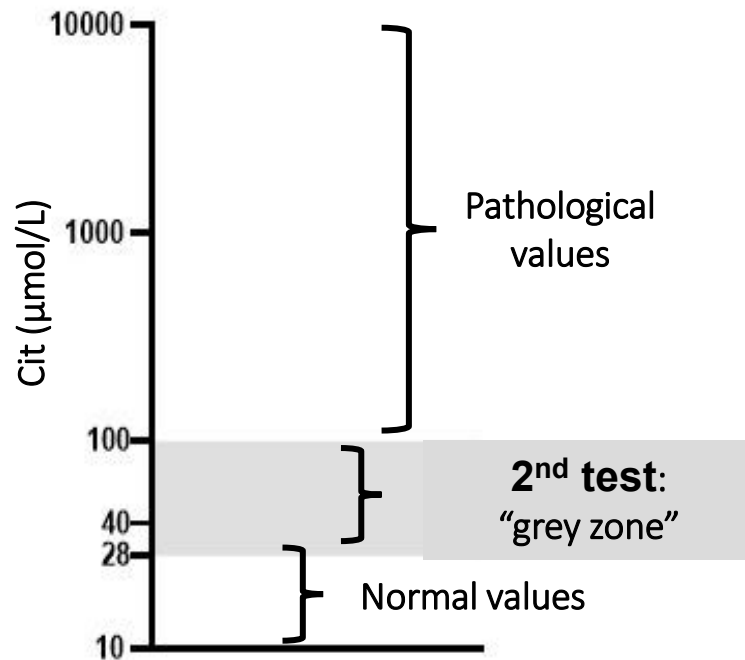
- **Pt 1 ( 7 m):** Hypoglycemia + Hyperglycemic Acidosis + Lethargy  
**AApl:** ↑Leu e Allo-Ile (9)
- **Pt 2 (1 d) :** Hypoglycemia + Hyperlactatemic Acidosis + Encephalopathy  
**AApl:** Allo-Ile, in acute ↑BCAA e Allo-Ile

	Pt.1		Pt.2
	24 h	13 days	3 days*
Cit	↑**	N	N
Allo-Ile	+	+	+
Xle	↑	N	↑
Xle/Phe	N	↑	↑
Xle/Ala	N	N	na
Val	N	N	na
Ala	N	N	na

\* re-test after 17 days from NBS

# Citrulline in newborn screening

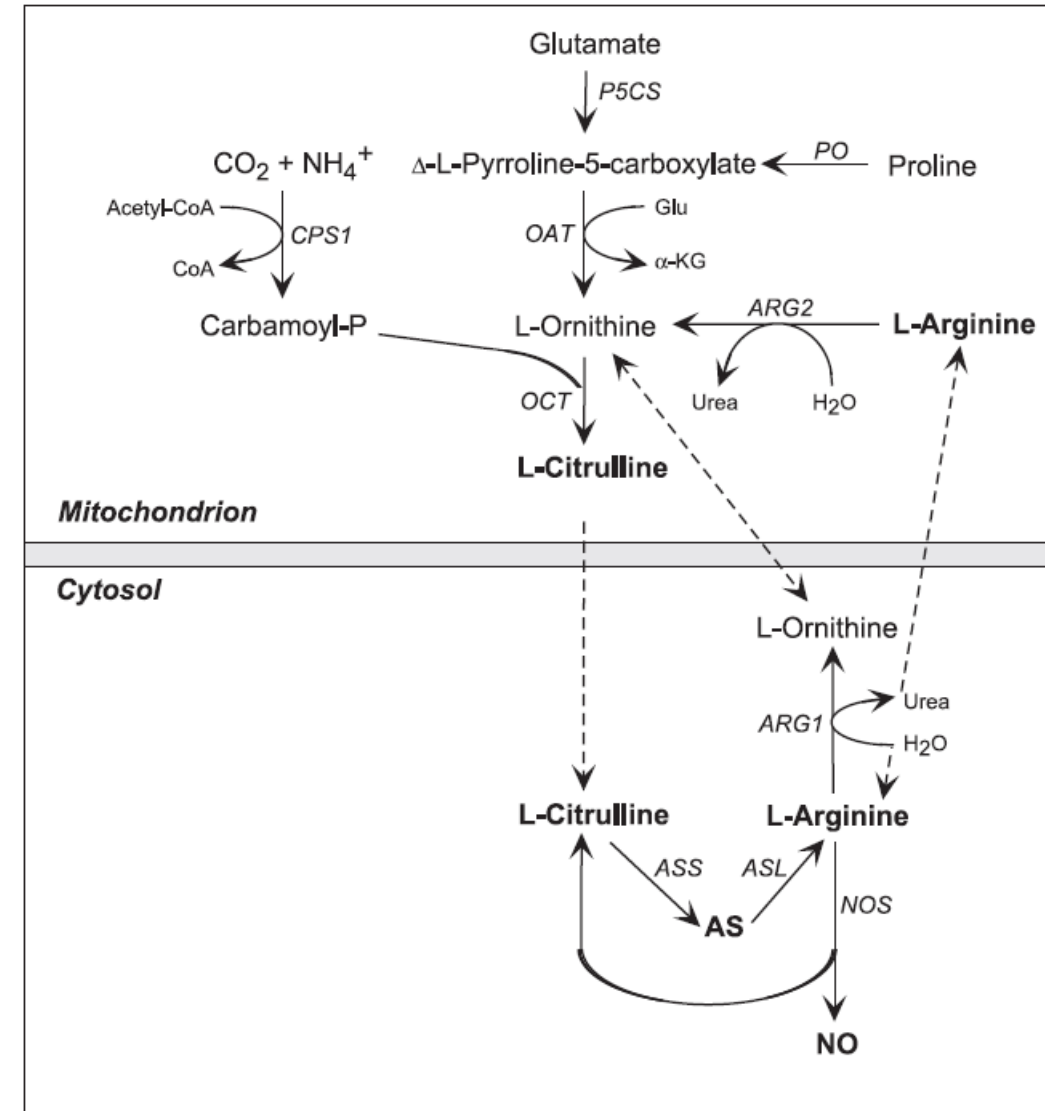
➤ Diagnostic algorithm proposed for implementation in NBS:



# Low citrulline levels

- Low citrulline levels are a characteristic hallmark in proximal UCD (CPS and OTC deficiency)
- MELAS (mitochondrial encephalomyopathy, lactic acidosis with stroke-like episodes syndrome)
- Citrulline can be used as a marker for the MT-ATPase6 defect

A. Naini et al. / Journal of the Neurological Sciences 229–230 (2005) 187–193



# Low Citrulline MT-ATPase6

DBS Acylcarnitines profile					
Age	C3 (<2.5 μmol/L)	C5-OH (<0.44 μmol/L)	Citrulline (>8 μmol/L)	C3/Citr (<0.22 μmol/L)	C5-OH/Citr ( <0.04 μmol/L)
<b>Pt1</b>					
3 d	5.54	0.38	6.90	0.81	0.06
3 m	2.46	0.36	6.10	0.40	0.06
3.5 m	6.60	0.61	4.30	1.53	0.14
4 m	1.41	0.22	4.00	0.35	0.05
<b>Pt2</b>					
3 d	0.63	0.49	8.70	0.07	0.05
4 d	2.01	0.63	12.10	0.17	0.05
19 d	0.48	0.31	5.60	0.09	0.06
6 m	1.84	0.59	7.00	0.26	0.08
<b>Pt3</b>					
3 d	5.18	0.49	3.50	1.48	0.14
4 d	2.91	0.38	2.0	1.46	0.19
6 d	1.45	0.38	3.90	0.37	0.10
1.5 m	2.55	0.40	1.90	1.34	0.21
3 m	2.18	0.58	3.00	0.73	0.19
6 m	1.52	0.12	1.9	0.8	0.06

**Pt1:** Lactic acidosis, developmental growth delay, axial hypotony, mixed apnea, non-compaction of the left ventricle, retinal and cochlear alteration of BEPPS and VEP-flash (at birth). MRI: T2 hyperintensity in BG, DWI, WM reduction and cerebral cerebellar atrophy (4 m)

**Pt2:** developmental growth delay, axial hypotony and poor suction, hypertrophic cardiomyopathy, SVPT, hyperammonemia, hyporegenerative anemia (at birth)

**Pt3:** Lactic acidosis, sideropenic anemia, developmental growth delay, axial hypotony with dyskinesia (at birth). Central and obstructive apnea (3 m), cerebral MRI and MRS: negative (3 m); Epileptic spasms (7m)

**Organic Acids:** krebs ↑ (pt1; pt2; pt3):  
3-methylglutaconic ↑ pz3

Low citrulline with the C5OH/Citr content could be used as a marker for the MT-ATPase6 defect

# Conclusion

- ↑ Cit in NBS identifies "Primary Conditions": Distal UCD defects
- "Mild ASA" phenotype: mild, based on biochemical values?
- New "Secondary Conditions":
  - E3 defect (DLDD) and lysinuric protein intolerance (LPI)
  - If mild ↑ Cit is confirmed, activate the diagnostic algorithm:
    - allo-isoleucine (DLD) and LDH and ferritin (LPI)
    - Molecular screening: ASS1, ASL, SLC25A13, PC, SLC7A7, DLD
- "Gray zone" 40-100 μmol/L: ASS1 heterozygosity. False positives?
- ↓ Cit with C5OH/citr ratio in NBS allows identification of ATPase6

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