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QUALITY ASSURANCE IN LABORATORY TESTING FOR IEM

Laboratory aspects of new defect in Purine & Pyrimidine metabolism

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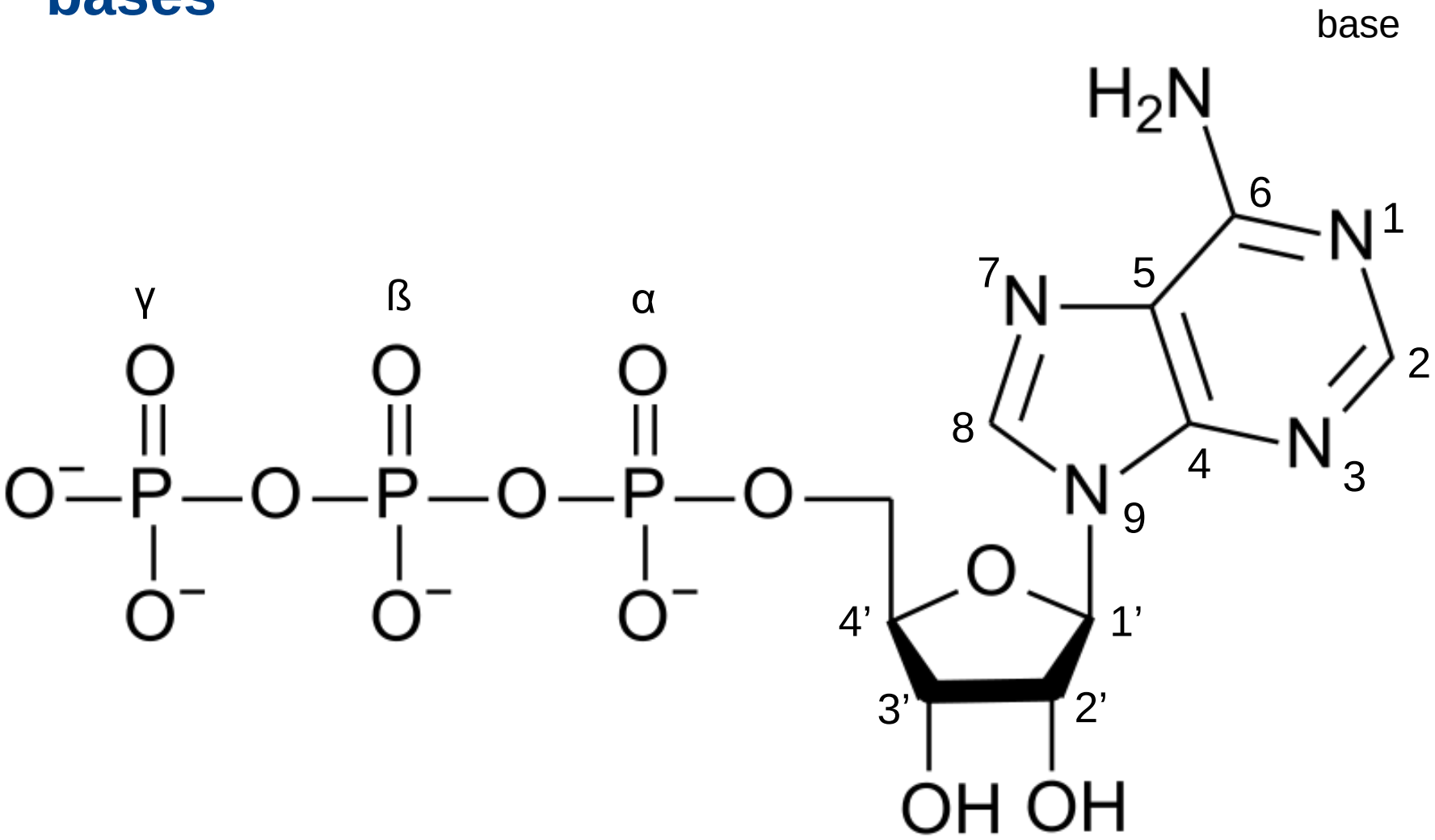
ERNDIM Workshop, 4th September 2018

Athens, Greece

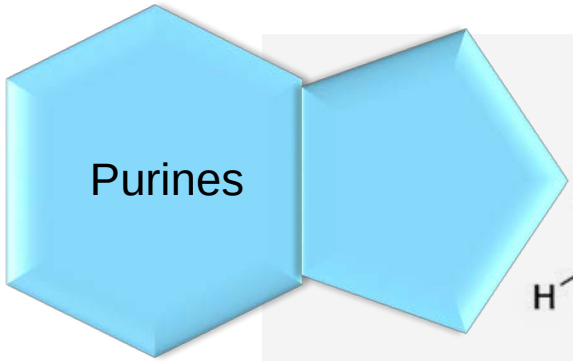
Outline

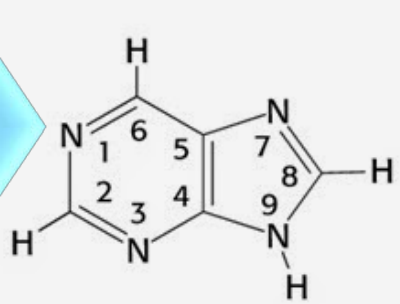
1. Short introduction to purines and pyrimidines
2. New defects identified over last decade
3. Looking ahead

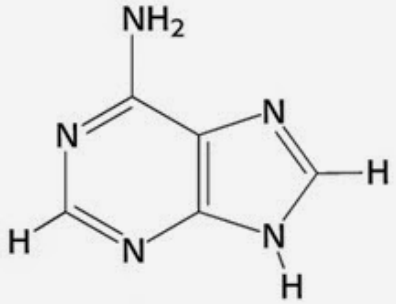
Back to basics: nucleotides, nucleosides and bases

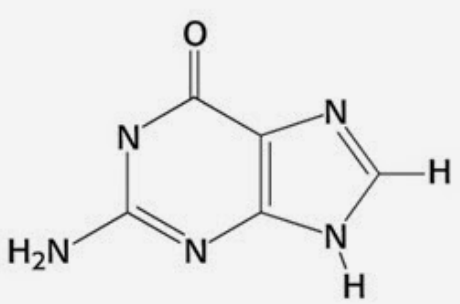


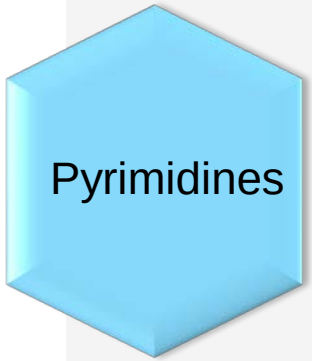
Purines and pyrimidines in nucleic acids

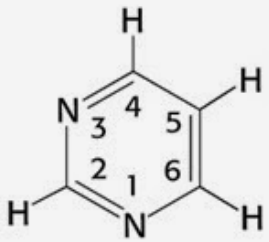


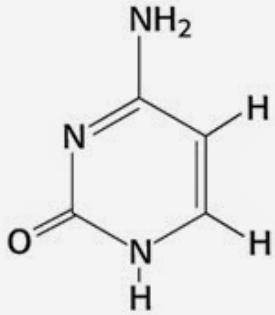


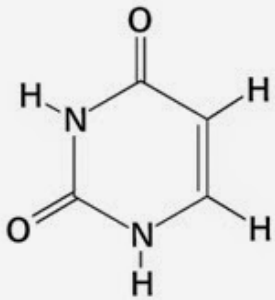


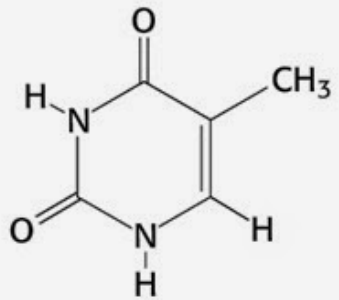












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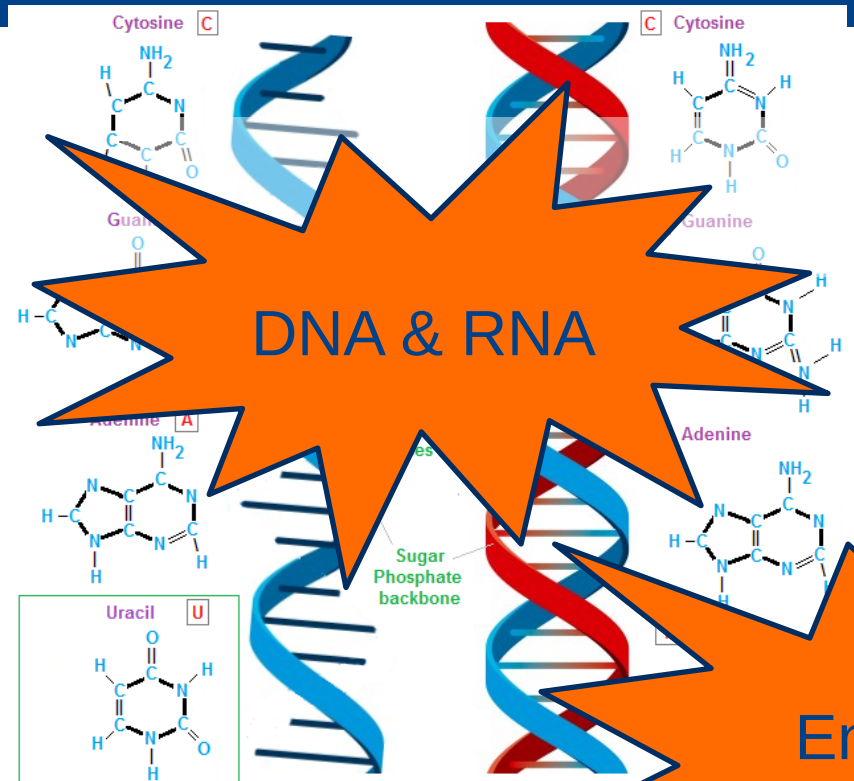
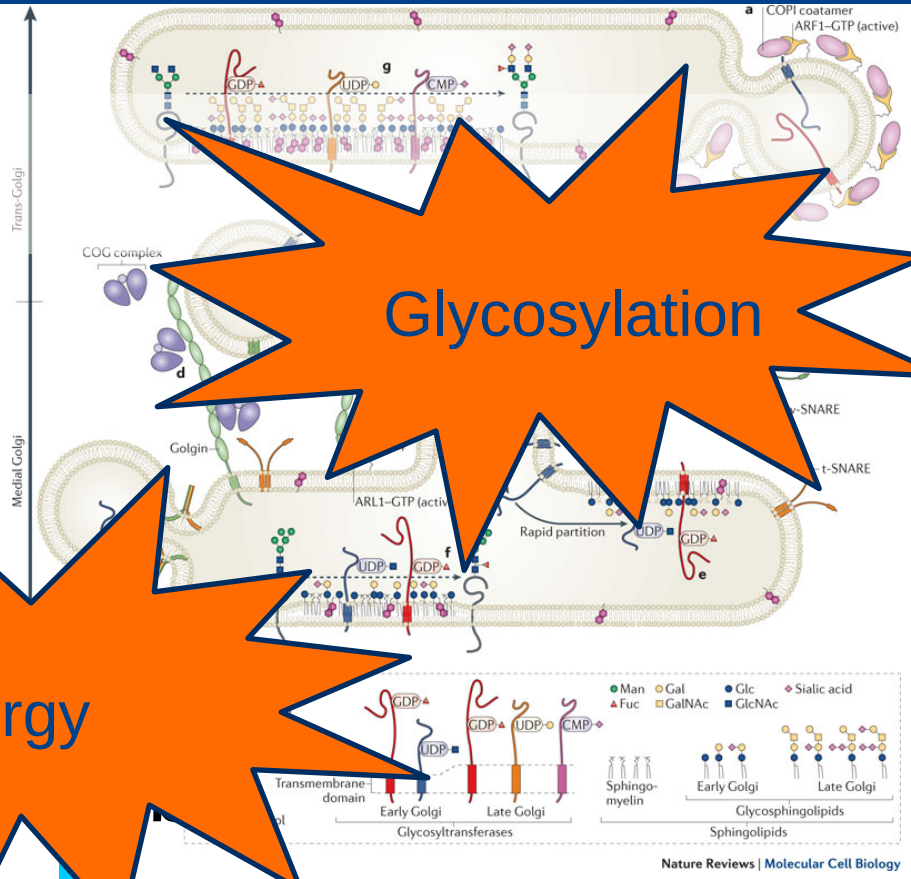
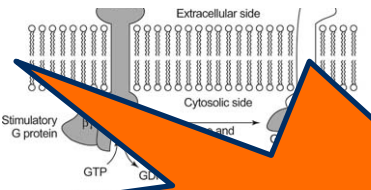


DNA & RNA

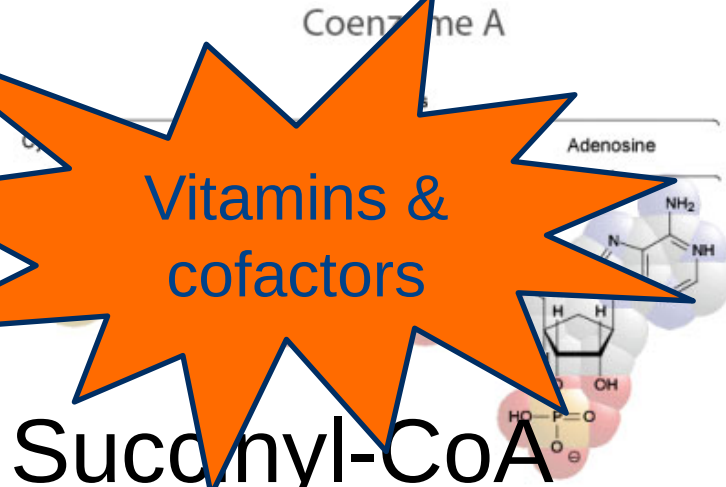


Glycosylation

Energy



Cell signalling



Vitamins & cofactors

Ado-Cbl

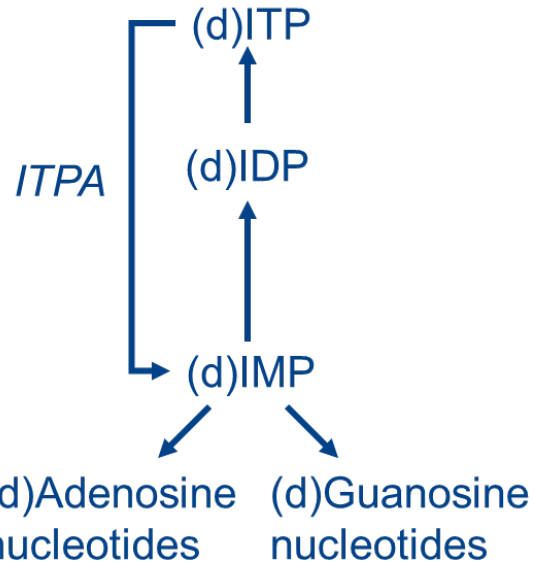
Methylmalonyl-CoA → Succinyl-CoA

Recently described defects in purine and pyrimidine metabolism

- Dihydro-orototate dehydrogenase (DHODH) deficiency
- Adenosine kinase deficiency
- ITPA encephalopathy
- CAD-deficiency

ITPA encephalopathy

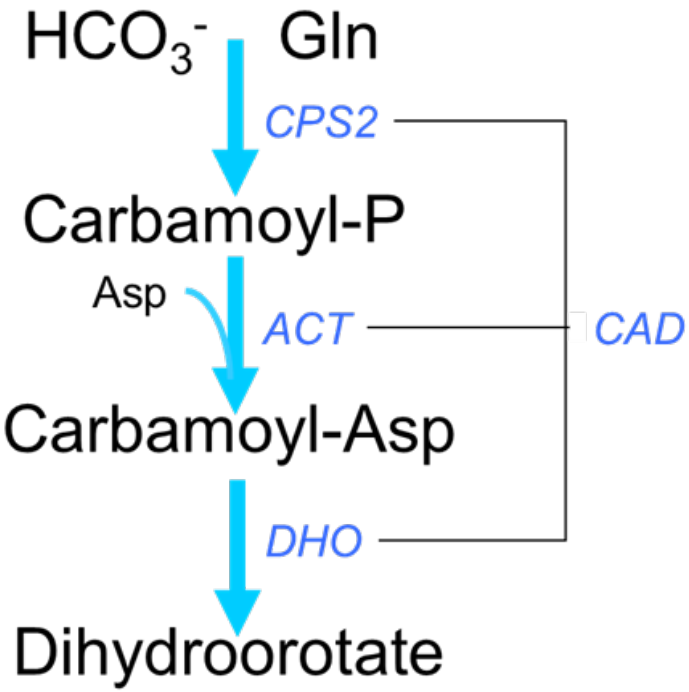
- Described by Kevelam et al in 2015
- Severe encephalopathy,
- cerebral atrophy
- delayed myelination
- Seizures
- Lack of psychomotor development
- Cardiomyopathy



- Caused by truncating mutations in *ITPA*
- Severely decreased ITPase activity in cultured skin fibroblasts
- Immensely different from effect of *ITPA* polymorphisms

CAD-deficiency

- Defect of pyrimidine *de novo synthesis*
- No abnormalities in selective metabolic screening
- Saskia's topic

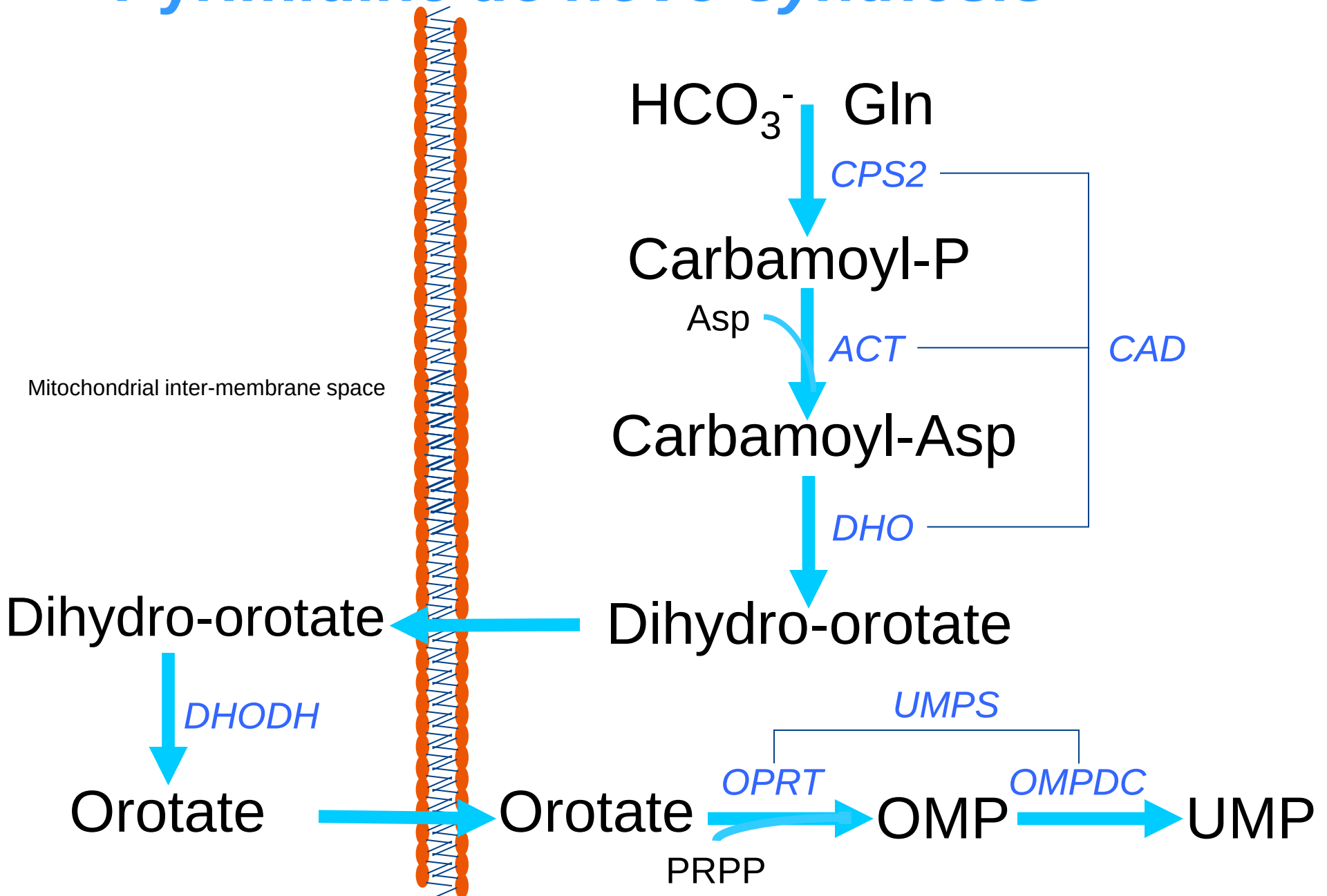


Dihydro-orotate dehydrogenase deficiency- Clinical picture

- Identified as cause of Miller syndrome
  - Ng et al Nature Genetics 42, 30-35 (2010)
  - Rainger et al Hum Mol Genet 18, 3969 – 3983 (2012)

- Main clinical symptoms:
  - Cranofacial dysmorphisms
    - Micrognathia
    - Orofacial clefts
    - Malar hypoplasia
    - Cup-shaped ears
  - Absence of ray 4 or 4+5 in hands and feet
  - Hypo-/aplasia of posterior limb elements
  - Normal intelligence

Pyrimidine *de novo synthesis*



Dihydro-orotate dehydrogenase deficiency- Urinary metabolites

	Rainger 2012	Duley 2016*	Maastricht lab 2012
Dihydro-orotate	Not detected	39 (<0.5)	87(< 4)
Orotate	0 – 38 (< 5)	33 (< 5)	78 (< 4)
N-carbamoylaspartate	Not reported	Not reported	152 (n.d.)
Orotidine	Not reported	Not reported	38 (< 8)

(µmol/mmol creatinine) (ref)

*Duley et al.
Mol Gen Met 119, 83 -90 (2016)

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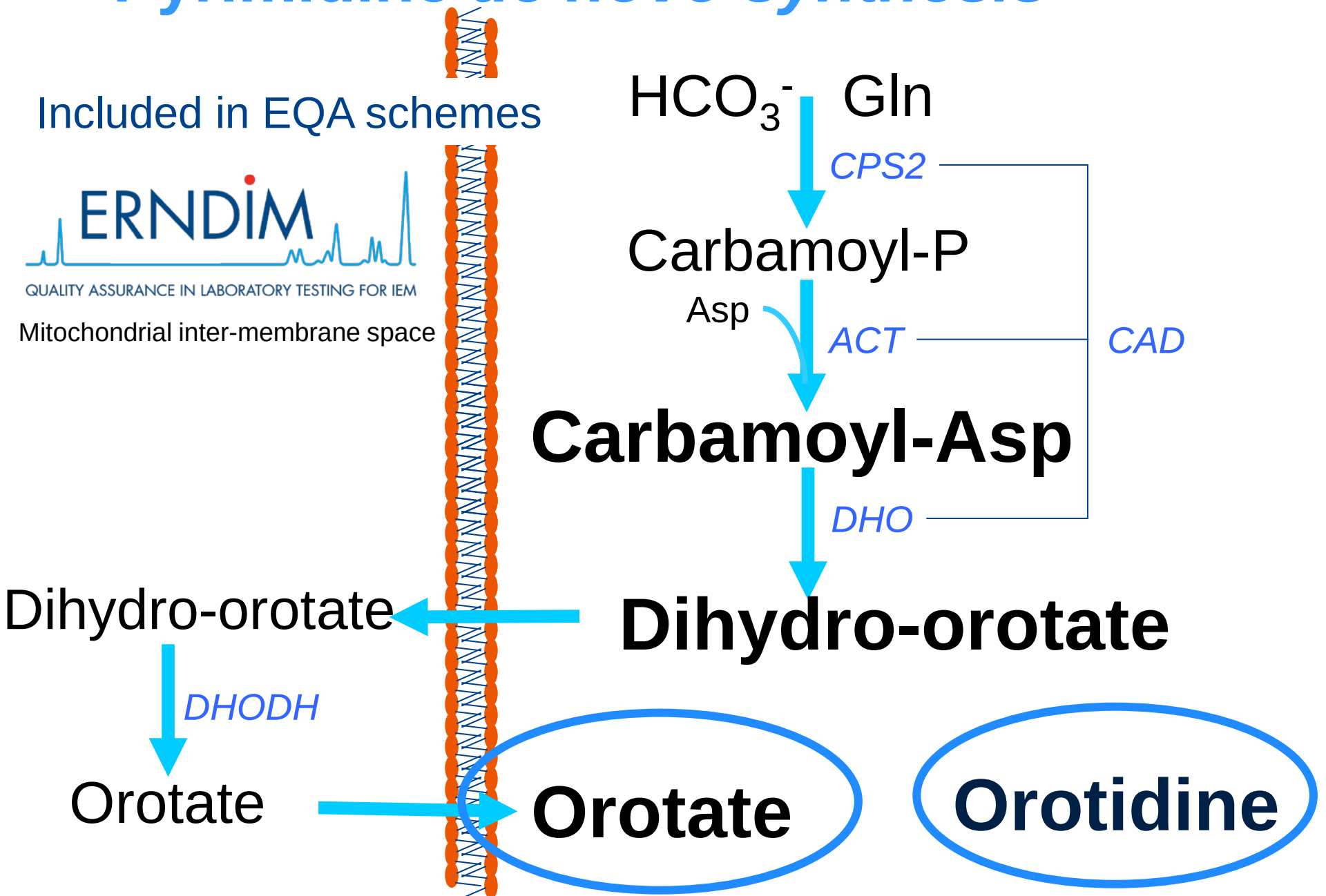
Pyrimidine *de novo synthesis*

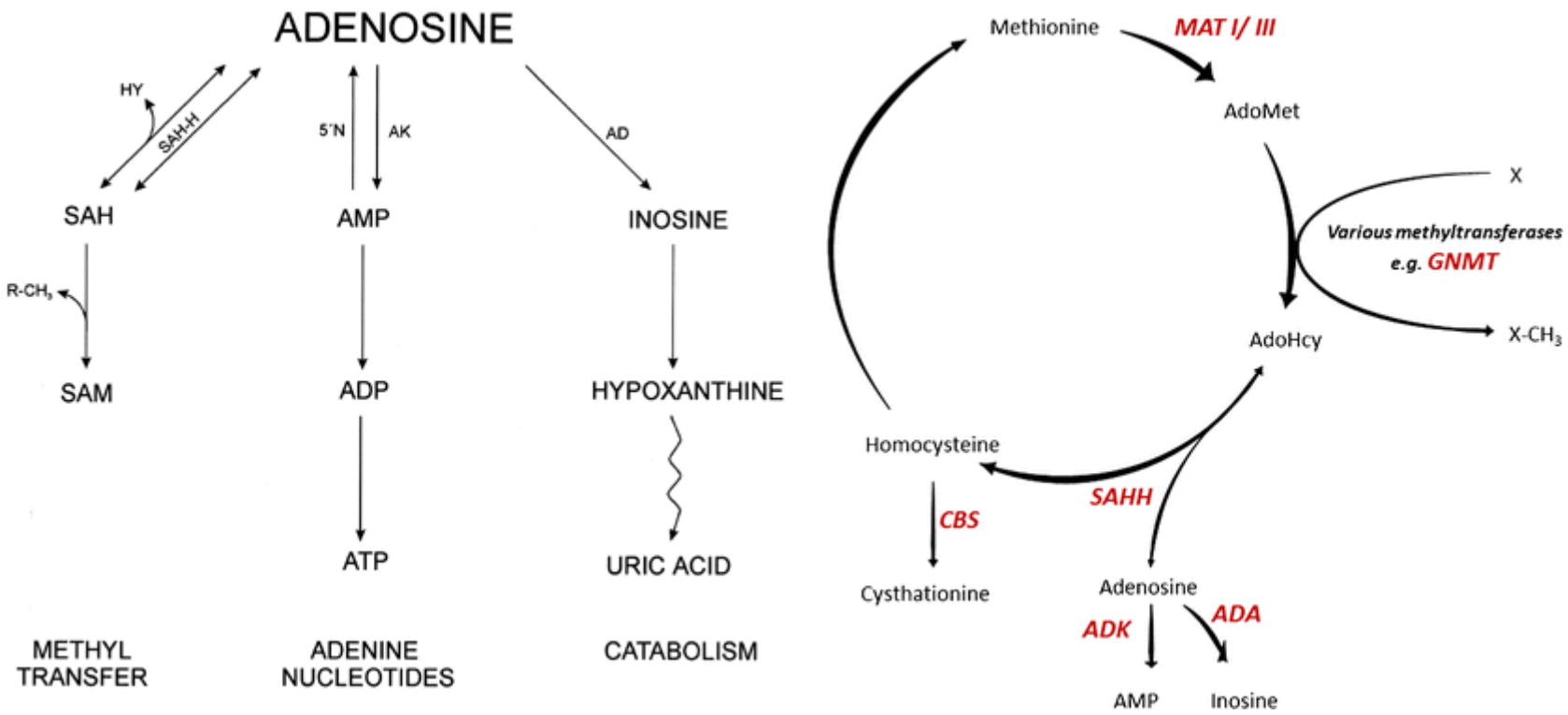


Adenosine kinase deficiency - Clinical picture

- Described as inborn error of metabolism in 2011 by Bjursell et al.
- Clinical spectrum revisited in 2016 by Staufner et al.

- Main clinical symptoms:
  - Mild to severe (neonatal onset) liver dysfunction
  - Recurrent hypoglycaemia due to hyper insulinism
  - Epilepsy
  - Global developmental retardation
  - Frontal bossing

Adenosine kinase deficiency-metabolism



Sleep Research Online 2(2): 33-41, 1999

Staufner, C., Lindner, M., Dionisi-Vici, C. et al. J Inherit Metab Dis (2016) 39: 273. https://doi.org/10.1007/s10545-015-9904-y

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Adenosine kinase deficiency – special laboratory

Key Metabolite	Reported values (min – max)	Reference
Methionine (p)	6 – 886 µM	< 45 µM
AdoMet (p)	160 – 1892 nM	71 – 118 nM
AdoHCy (p)	40 – 438 nM	9 – 14 nM
Adenosine (u)	4 – 45 mmol/mol cr	< 4 mmol/mol cr

Included in EQA schemes

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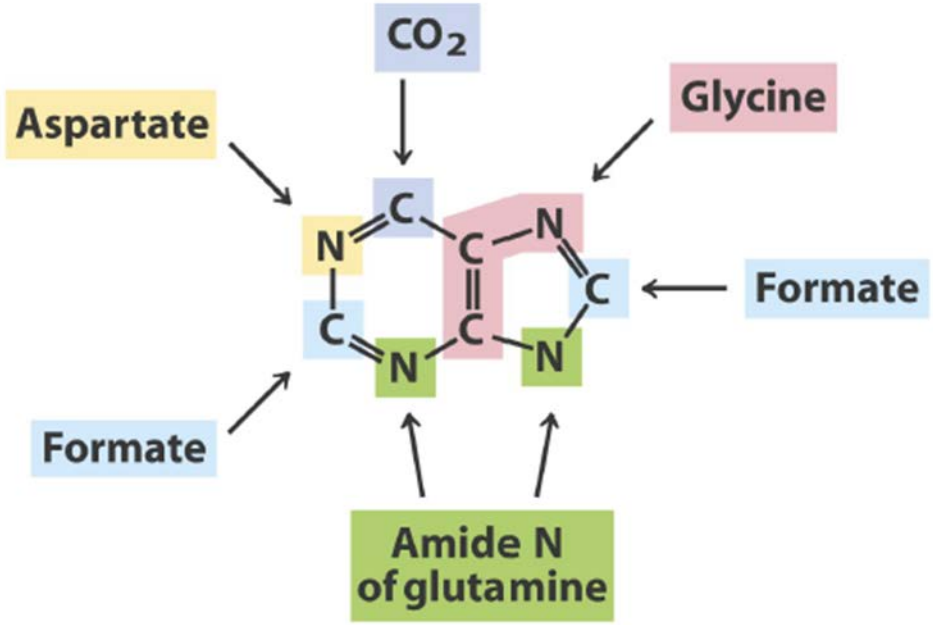
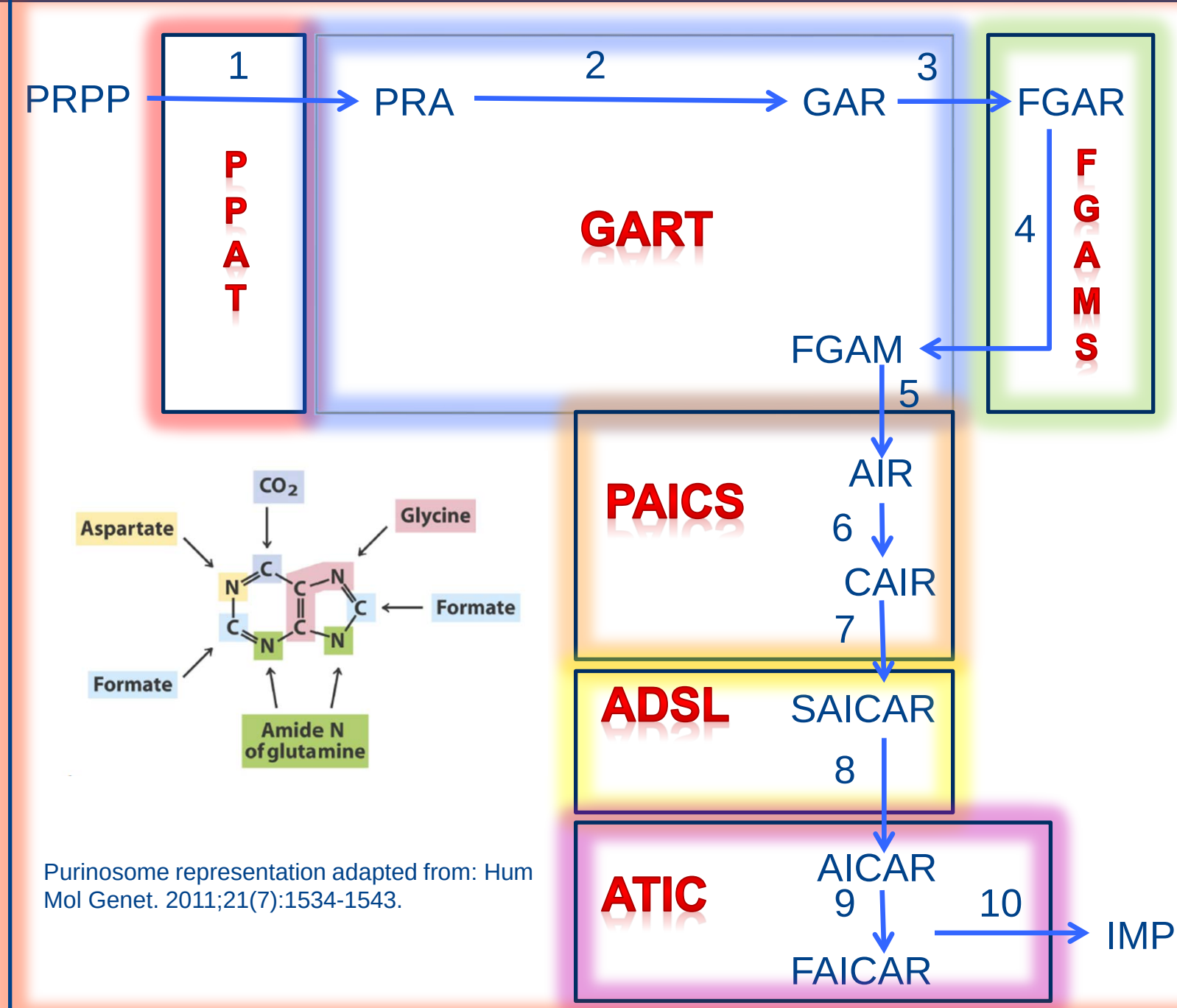
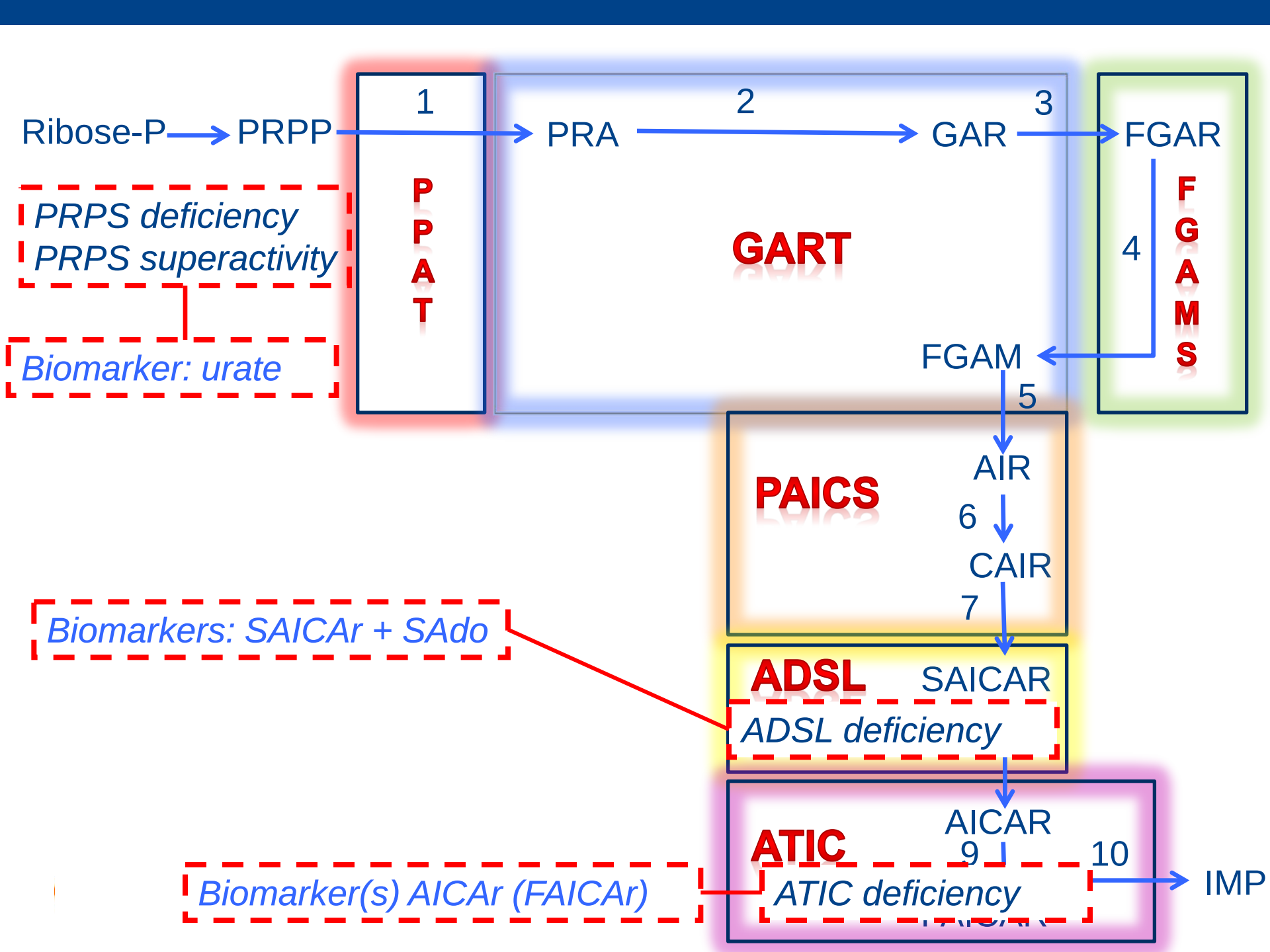
Looking ahead to the near future

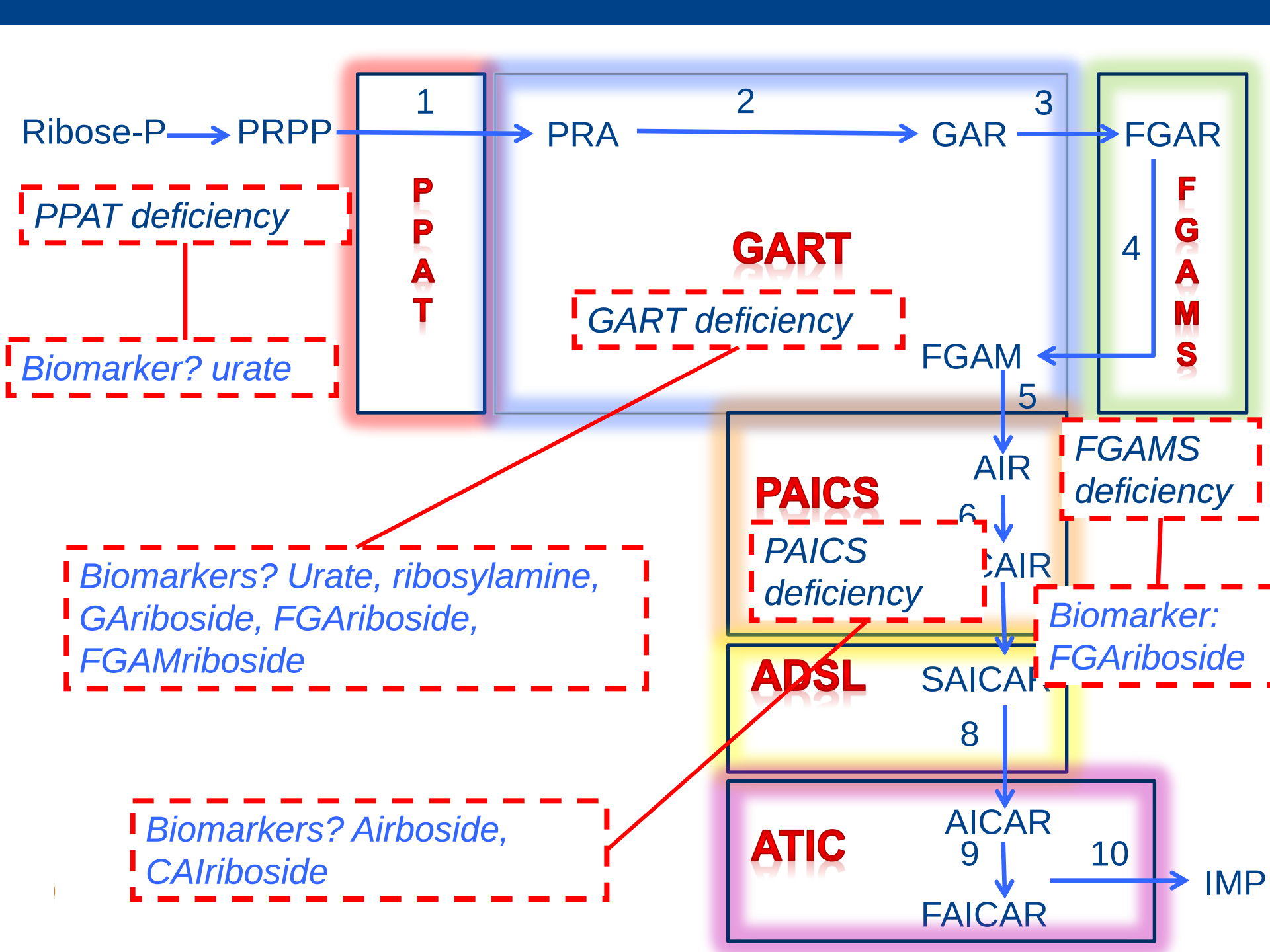
What new defects can we still expect in purine and pyrimidine metabolism?





Purinosome representation adapted from: Hum Mol Genet. 2011;21(7):1534-1543.


Ribose-P
PRPP
1
PPAT
PRPS deficiency
PRPS superactivity
Biomarker: urate
2
PRA
3
GAR
GART
FGAR
4
FGAMS
FGAM
5
PAICS
AIR
6
CAIR
7
Biomarkers: SAICAr + SAdo
ADSL
SAICAR
ADSL deficiency
AICAR
9
ATIC
10
IMP
Biomarker(s) AICAr (FAICAr)
ATIC deficiency


Ribose-P
PRPP
1
PPAT
PRA
2
GAR
3
FGAR
4
FGAMS
PPAT deficiency
Biomarker? urate
GART
GART deficiency
FGAM
5
AIR
PAICS
6
PAICS deficiency
CAIR
FGAMS deficiency
Biomarker: FGAriboside
Biomarkers? Urate, ribosylamine, GAriboside, FGAriboside, FGAMriboside
ADSL
SAICAR
8
Biomarkers? Airboside, CAIriboside
ATIC
AICAR
9
10
IMP
FAICAR

Thank you

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