DPT 2009: Common Sample

Diagnosis:

Salla disease, Sialic acid storage disease, Finnish type sialuria

Patient information on form at referral

A 6 year old girl

- prominent cerebellar ataxia
- mild mental retardation and previous hypotonia.
- Only able to speak a few words.

Patient: this sample was obtained from a 6 year old female patient suffering from Salla disease. This urine was provided by Dr. J.-E. Månsson, Molndal, Sweden. The diagnosis had been confirmed by the finding of homozygosity for the Finnish sialin mutation R39C.

Total sialic acid	98 mmol/mol Creat.
Free sialic acid	79 mmol/mol Creat.

Reference

Full clinical details

Unrelated parents - no known Finnish ancestors

6 months

- hypotonic but otherwise normal psychomotor development

14 months

- gross motor development delayed (level 9 months)

18 months

- able to crawl

1½ y. - 4½ y.

- psychomotor development slowly progressed.
- slowly increasing hypertonicity of lower limbs

Full clinical details

4 ½ y.

- Active, cooperative but slightly retarded.
- Unable to walk unsupported, cerebral ataxia, severe dyskinetic movements resembling myoclonic jerks.
- Signs of spastic parapareses, brisk tendon reflexes, pseudoclonus of ankles
- Spoke only few words

6y.

- Slowly continuing deterioration, greater motor disability
- Speaking few words, with severe dysarthria and judged to be slightly intellectually delayed.

Lab findings

Amino acids
Organic acids
MPS

} No relevant abnormalities

Free Sialic acid 132 mmol/mol creatinine

Oligosaccharide tlc with Bials reagent (Orcinol $FeCl_3$) for N-acetyl neuraminic acid

Sialuria OMIM

- Infantile sialic acid storage disease (OMIM #269920)
- Salla disease, milder form (OMIM #604369)

Main symptoms

- hypotonia, cerebellar ataxia, mental retardation
- visceromegaly, coarse features also present in infantile cases.
- Progressive cerebellar atrophy and dysmyelination documented by MRI.
- Enlarged lysosomes on electron microscopy
- large amounts of free sialic acid in the urine

Type into OMIM
cerebellar ataxia, hypotonia, mental retardation, speech delay
sialuria Finnish type is no. 12 from 22 hits

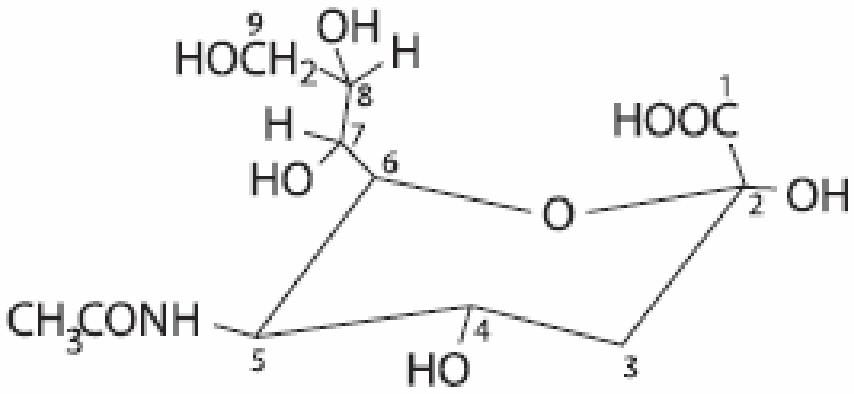
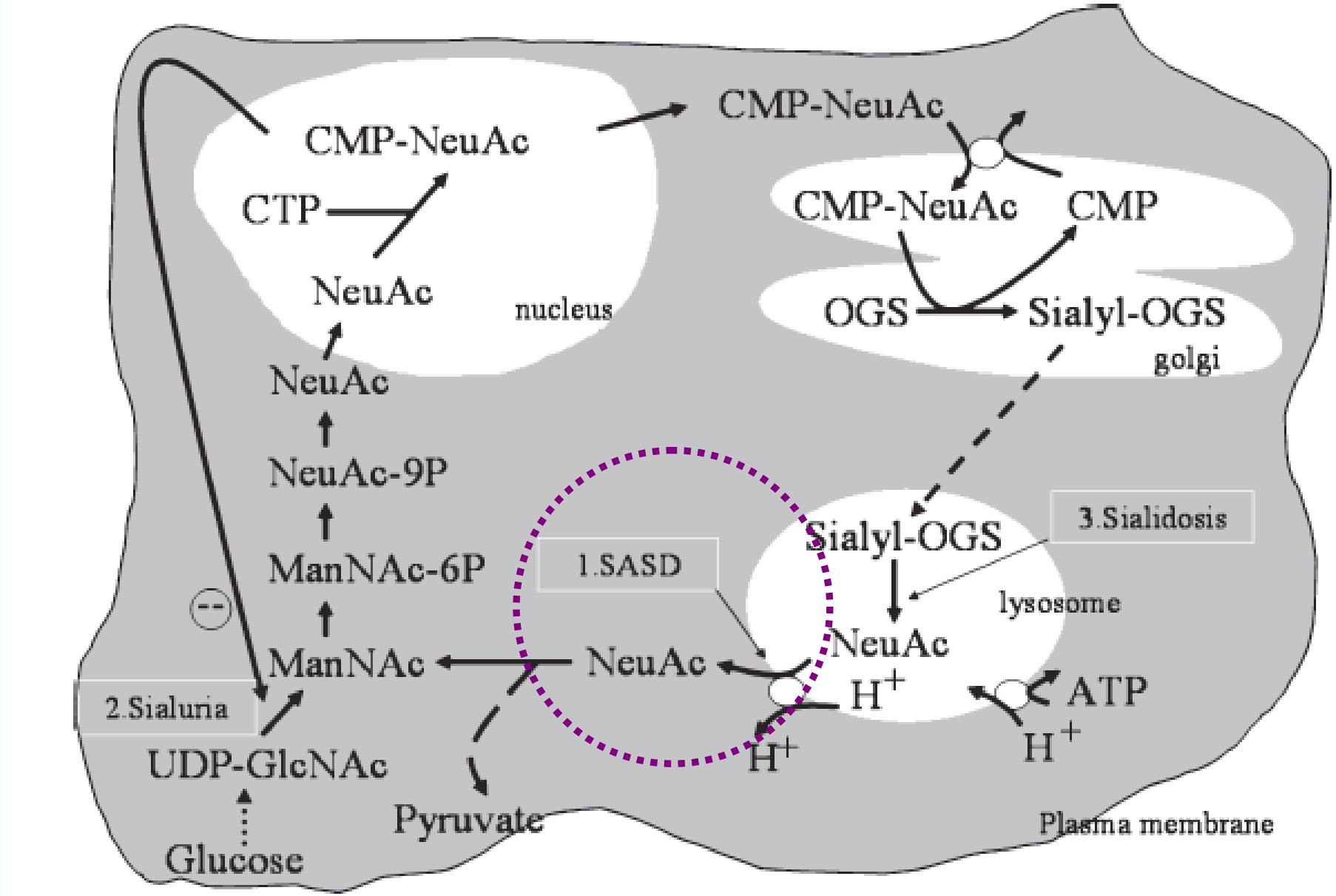


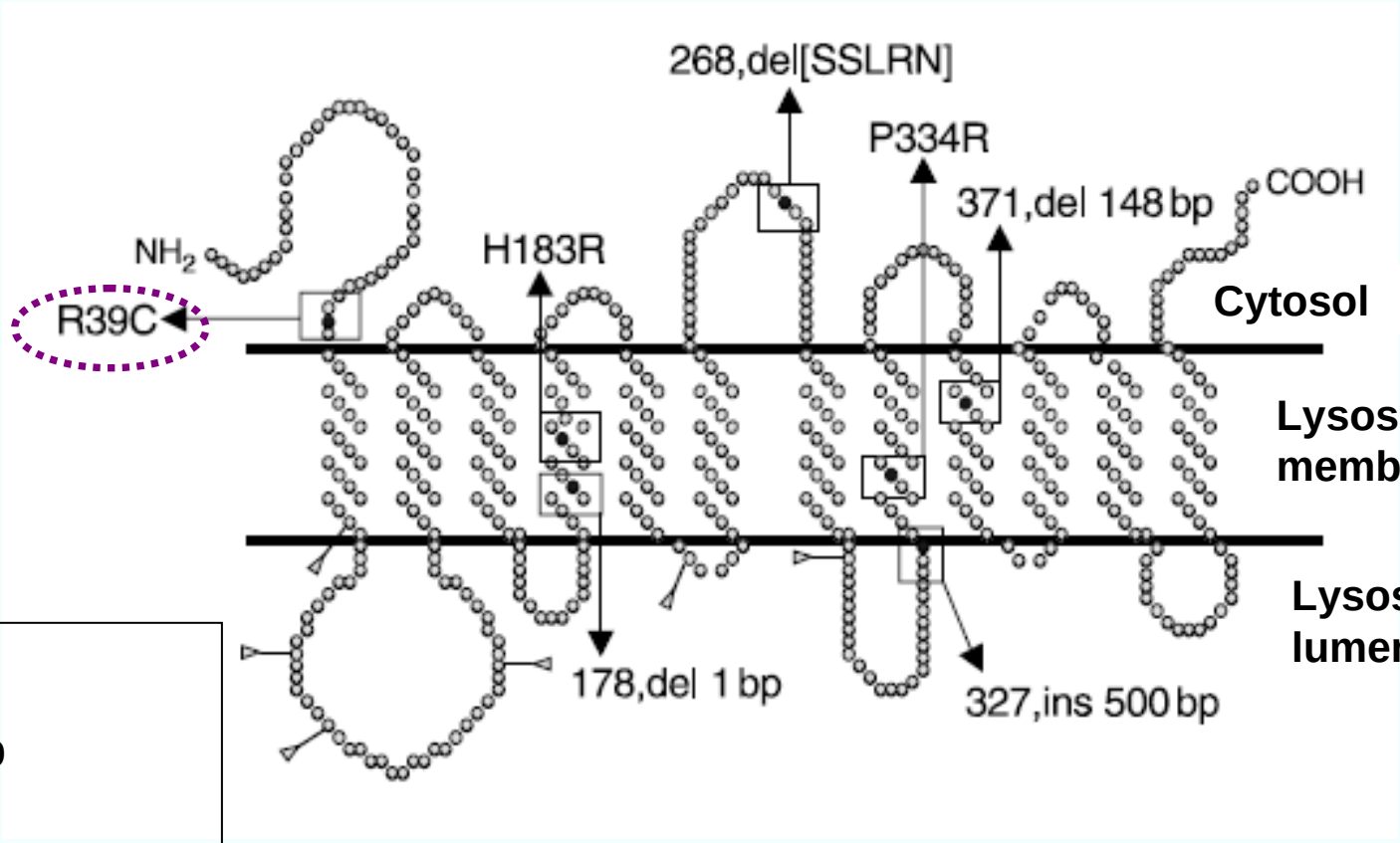
Fig. 4.3.1 Structure of N-acetylneuraminic acid (NeuAc)


CMP-NeuAc
CTP
NeuAc
nucleus
CMP-NeuAc
CMP-NeuAc
CMP
OGS
Sialyl-OGS
golgi
NeuAc
NeuAc-9P
ManNAc-6P
ManNAc
2.Sialuria
UDP-GlcNAc
Glucose
Pyruvate
1.SASD
NeuAc
H+
H+
Sialyl-OGS
3.Sialidosis
lysosome
NeuAc
ATP
H+
Plasma membrane

Lysosomal transporter defects

Salla disease / Infantile sialic acid storage disease

Transporter for sialic acid = Sialin *SLC17A5*

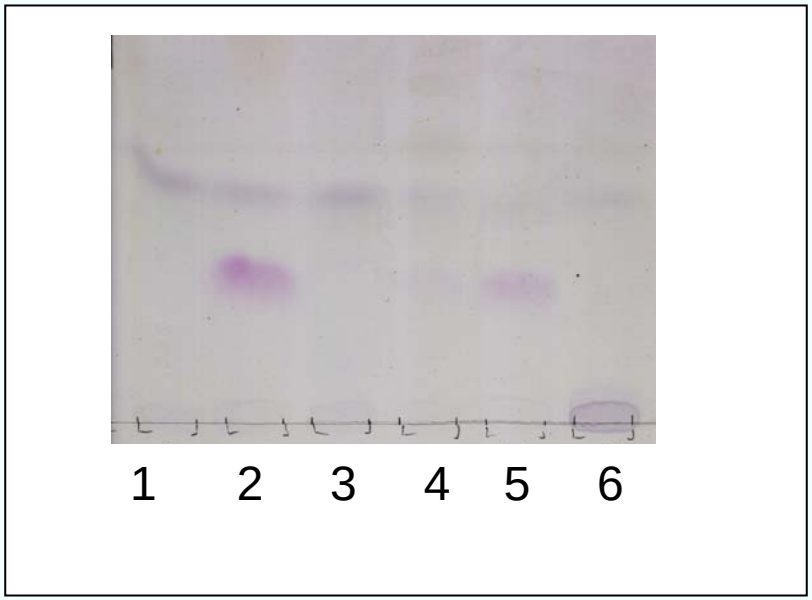


6q14-q15

495 amino acids

12 trans-membrane domains

Sample F:
Salla disease, Sialuria



Salla disease

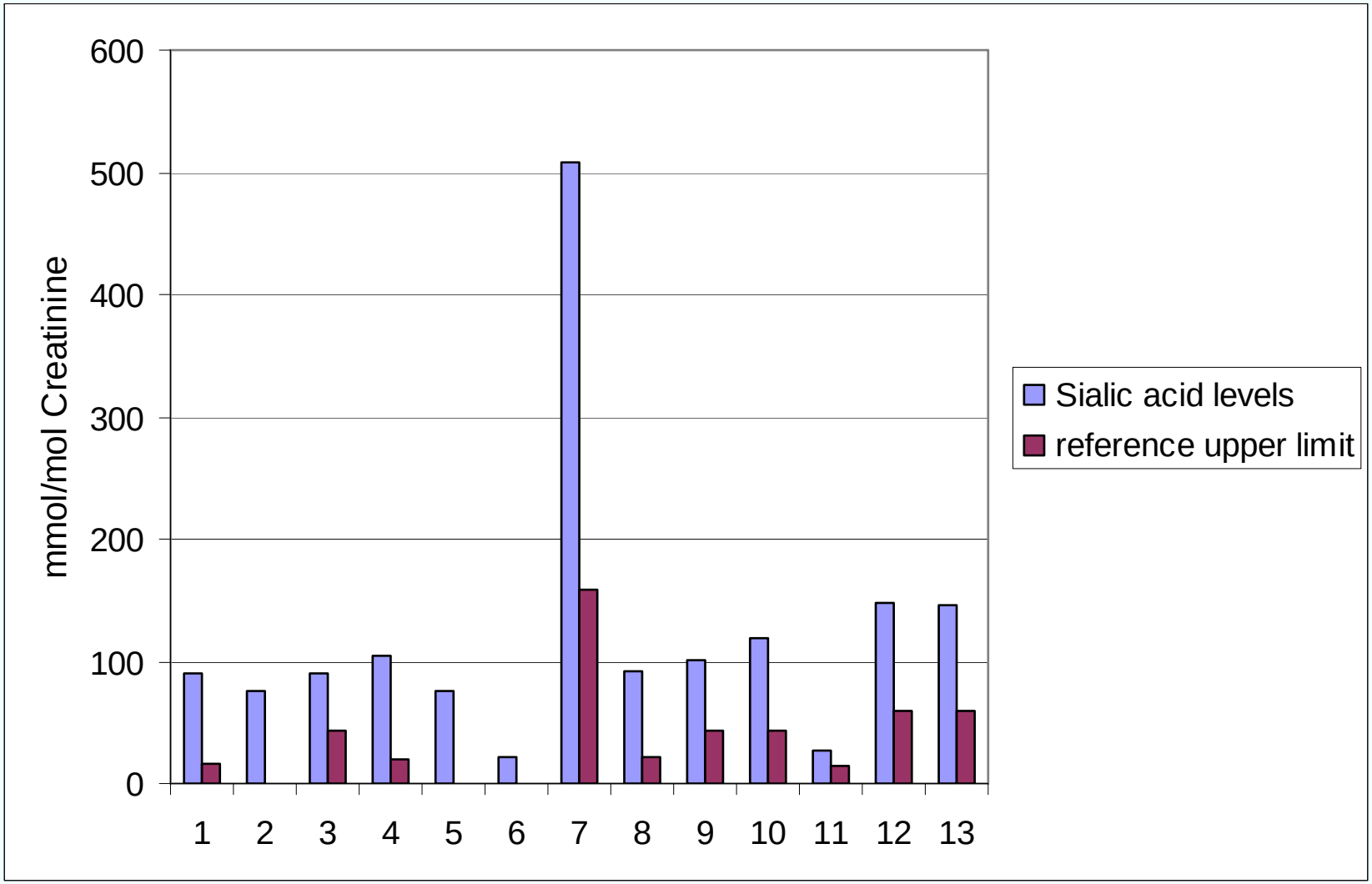
Courtesy M. Rohrbach

Nenad Blau · Marinus Duran
K. Michael Gibson

Laboratory Guide to the Methods in Biochemical Genetics

4.3 Sialic Acid 335
Frans W. Verheijen

Sialic acid levels



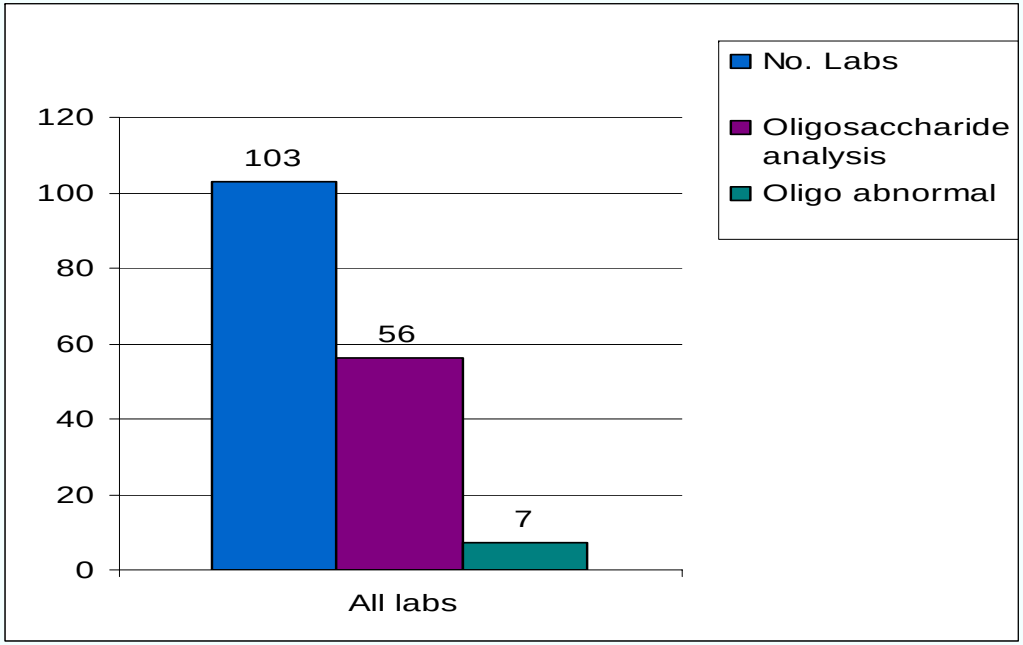
Lab findings

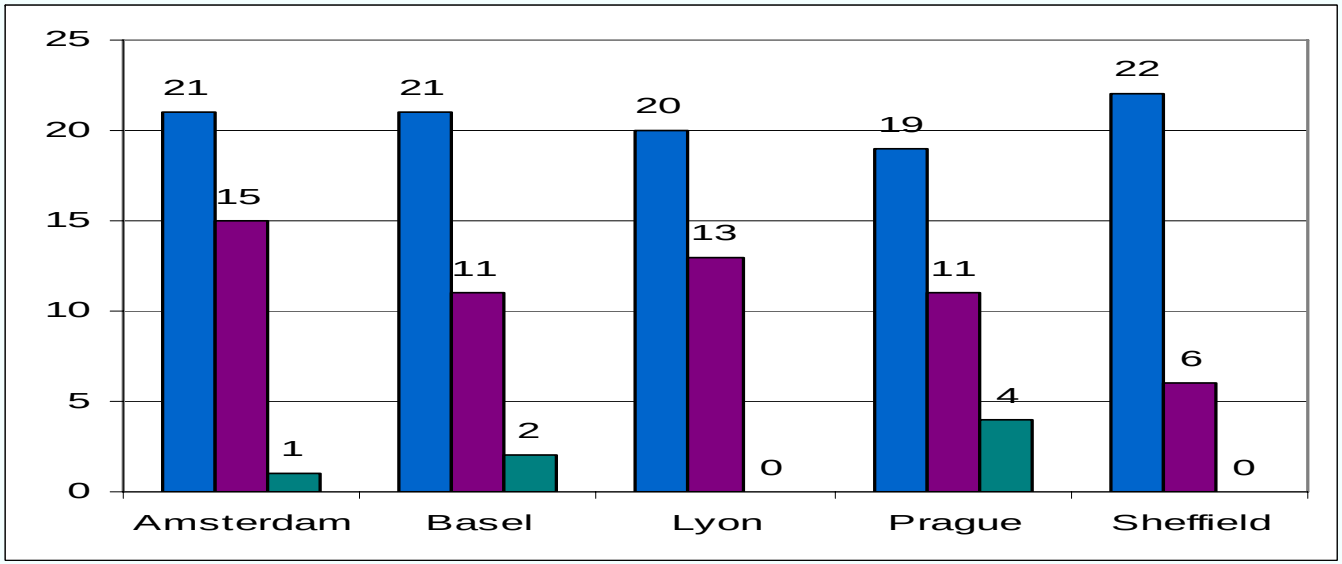
	Creatinine n=102	Creatinine n= 81(-Basel)	Creatinine n= 21 Basel
median	2.3	2.4	1.4
mean (S.D.)	2.18 (0.51)	2.4 (0.37)	1.43 (0.3)
interlab CV%	26%	14%	9%
lowest	0.55	0.93	0.55
highest	4.4	4.4	2.2

Creatinine between centres

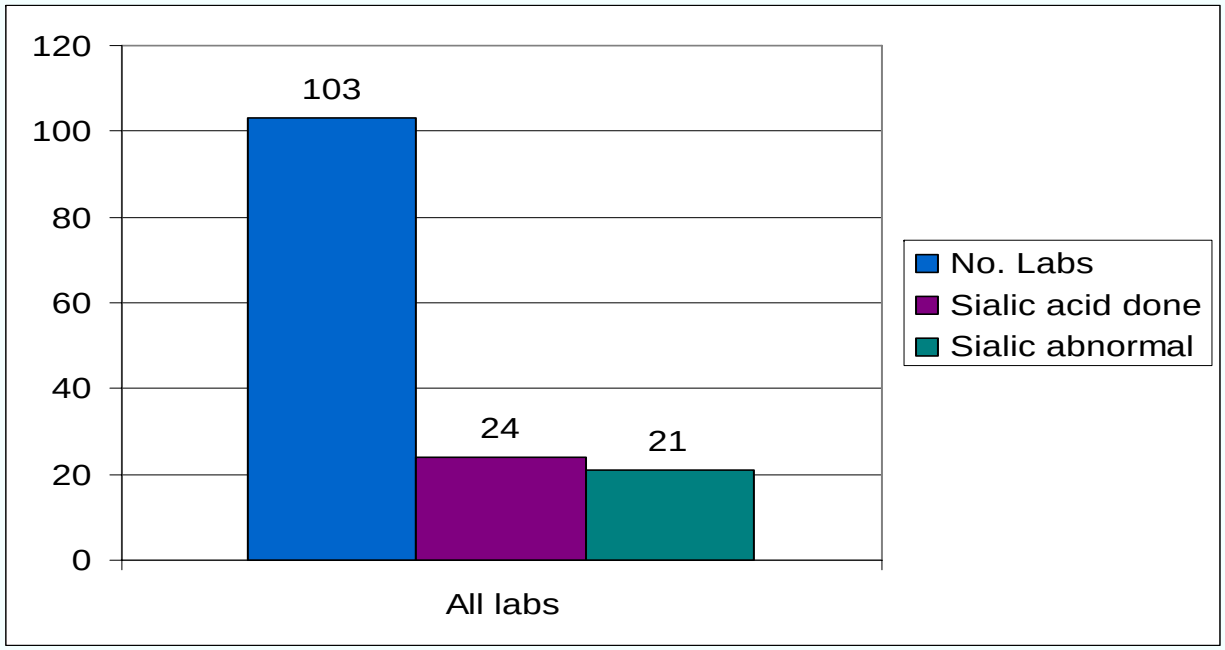
Medians	Creatinine [mmol/l]
All centers	**2.3**
Amsterdam	2.3
Basel	1.43
Lyon	2.4
Sheffield	2.4
Prague	2.3

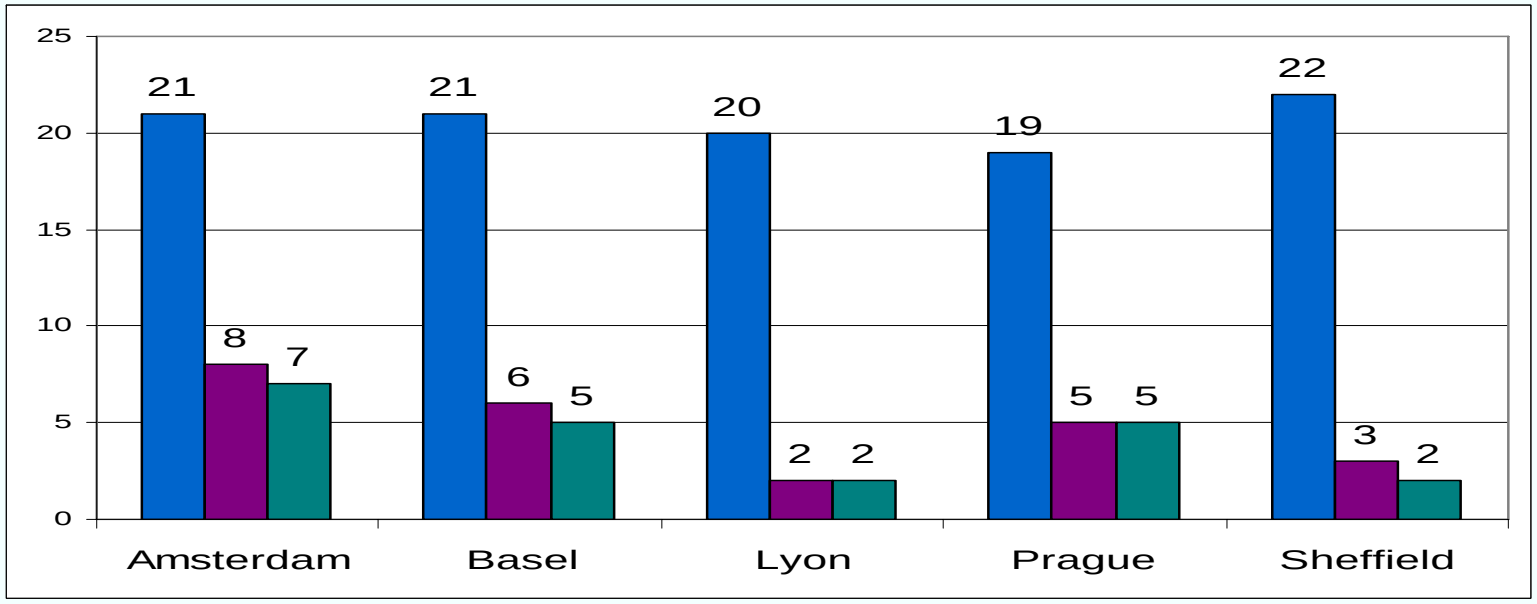
Lab findings: Oligosaccharides





Lab findings: free sialic acid

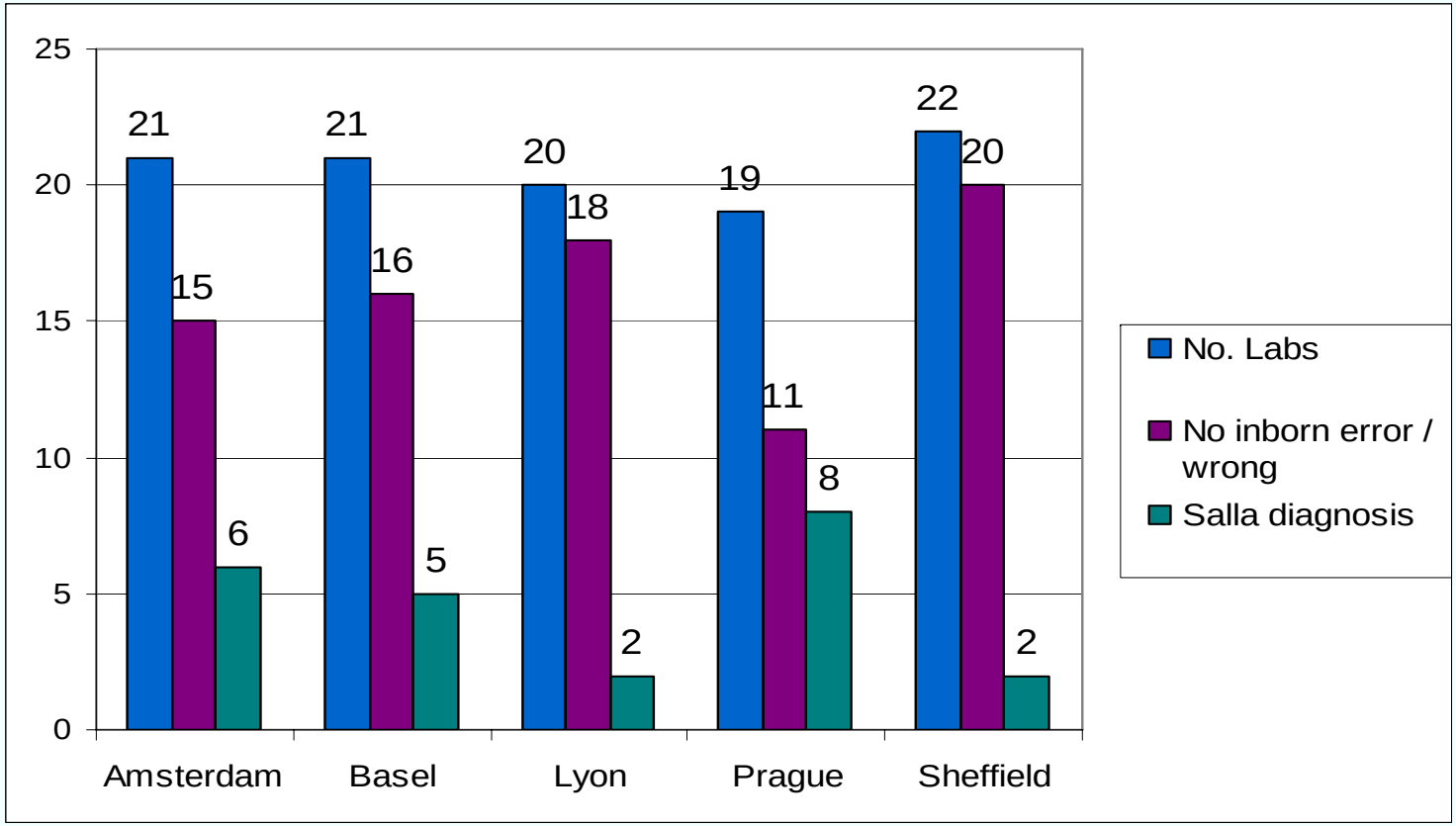




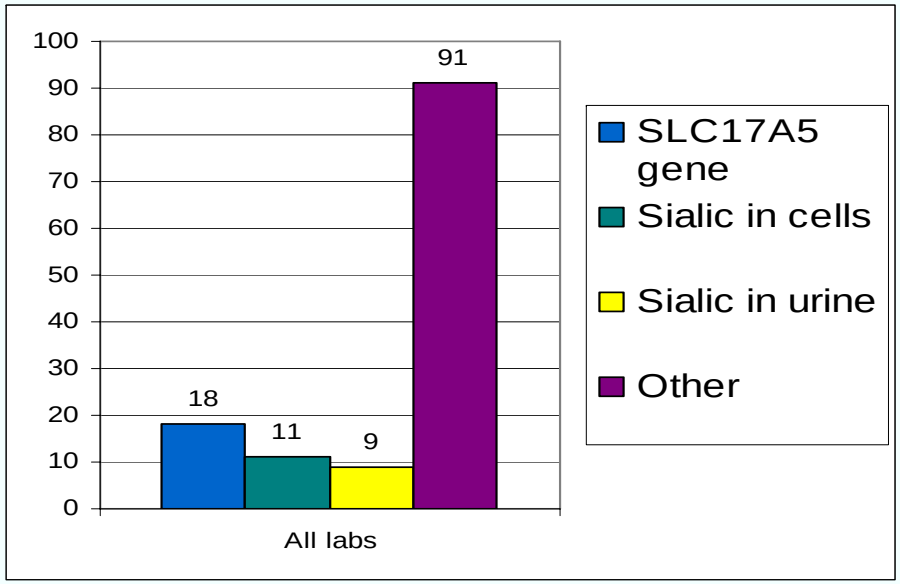
Diagnostic Proficiency

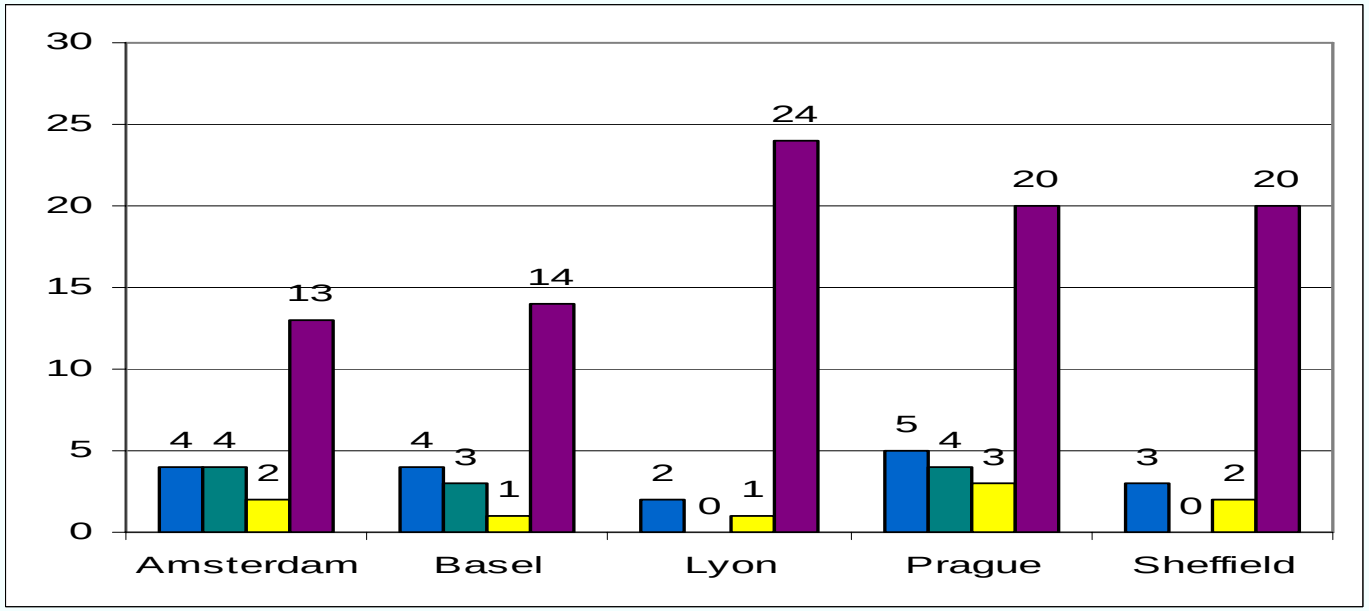
All labs

Salla disease	23 (22%)
No IEM / Other diagnosis	80



Recommendations





Conclusions and lessons

- We learn more from difficult than easy cases
- Sialic acid increase in Salla disease is not great
- Quantitation with age matched controls necessary
- Oligosaccharide analysis interpretation tricky