Common sample 2008

MPS III A

Referral sample information

Referral from neurological clinic

A seven years old boy

- slowly progressing expressive dysphasia
- abnormal perinatal history (umbilical strangulation)
- CT revealed enlarged cisterna magna and possibly cerebellum hypoplasia
- EEG did not reveal specific epileptic grafoelements

Screening for IEMs requested

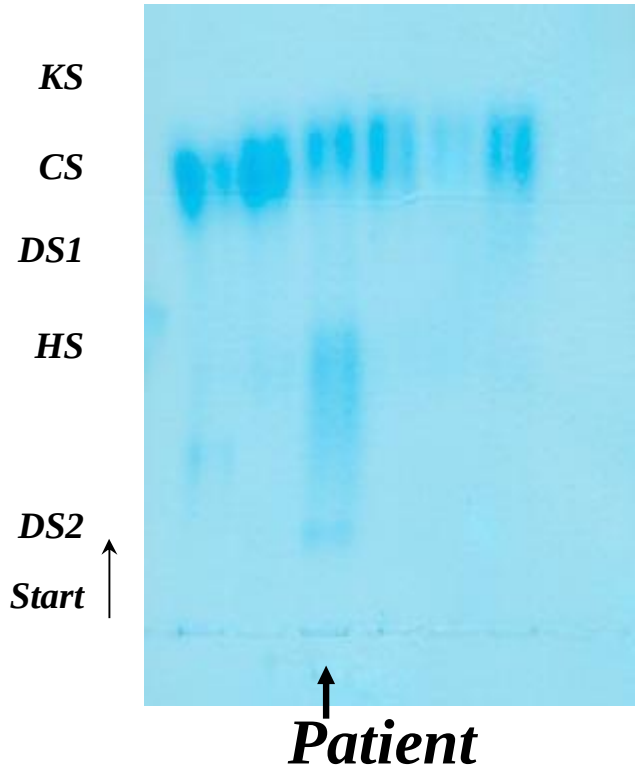
Initial IEM analysis

GAG concentration:

24,7 g/mol creat

(age matched ref range < 10)

Normal profile AA, org. acids



Out-patient clinic (1 month later)

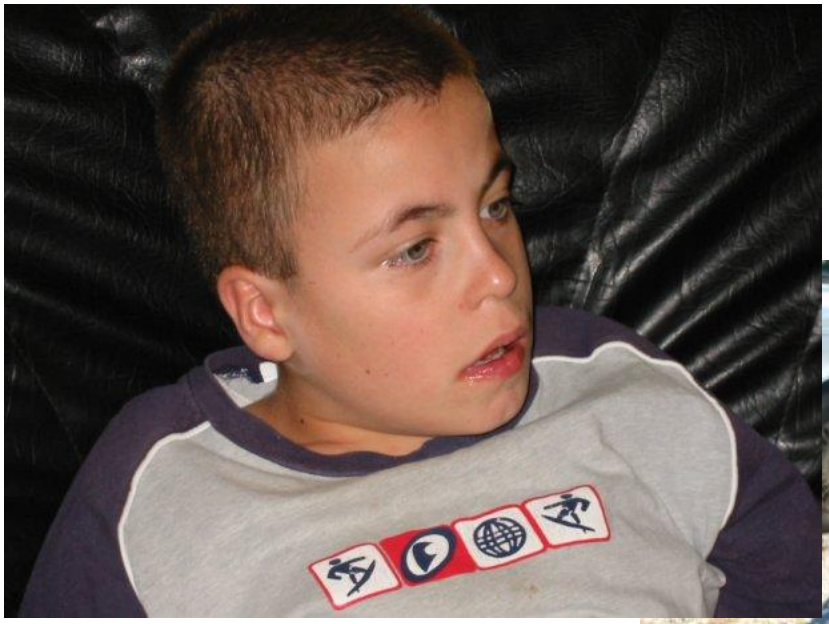
- Perinatal history- umbilical cord strangulation
- Normal development up to 2 years of age, then regression of speech development
- Mother of patient complains about **insomnia and psychomotor restlesness**

- Attending **school for hearing impaired**
- **Umbilical hernioplasty** at 7 years

- **No facial dysmorphia**
- **Very mild changes resembling dysostosis multiplex**

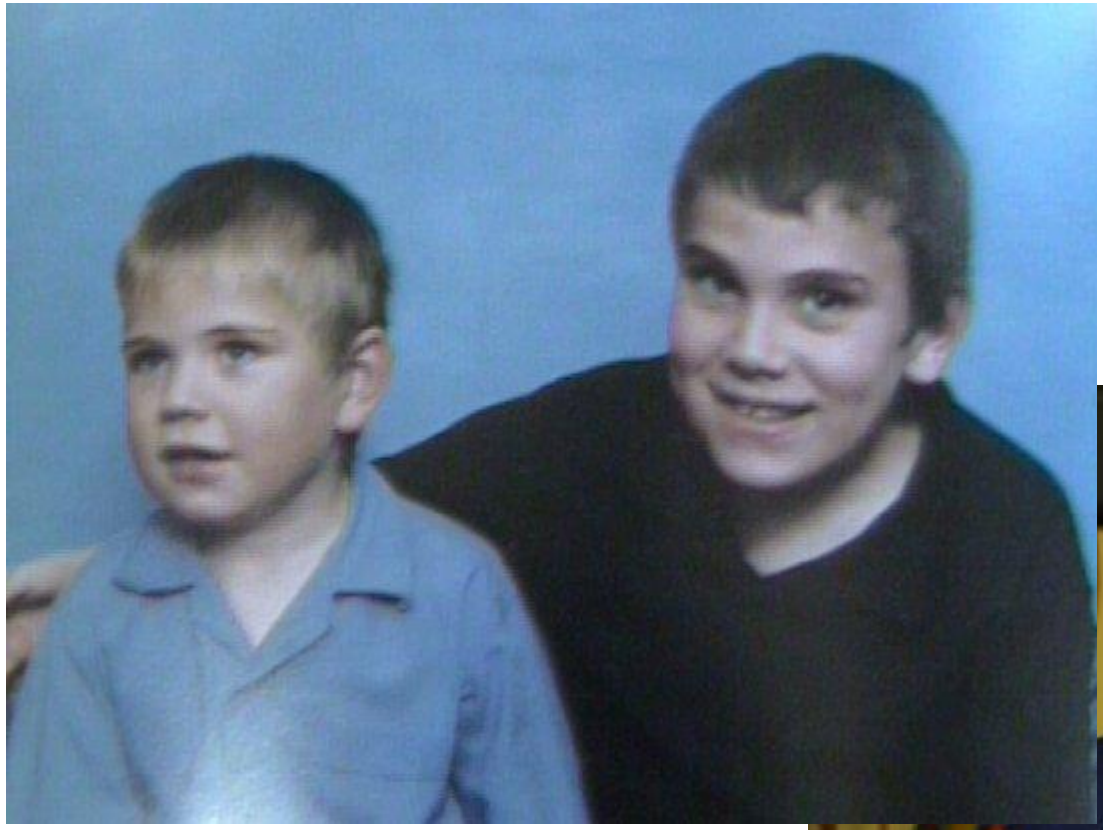
Courtesy E.Hrubá

Facial features in MPS III



http://www.mpssociety.org.au/mps_picture_gallery.htm

Facial features in MPS III



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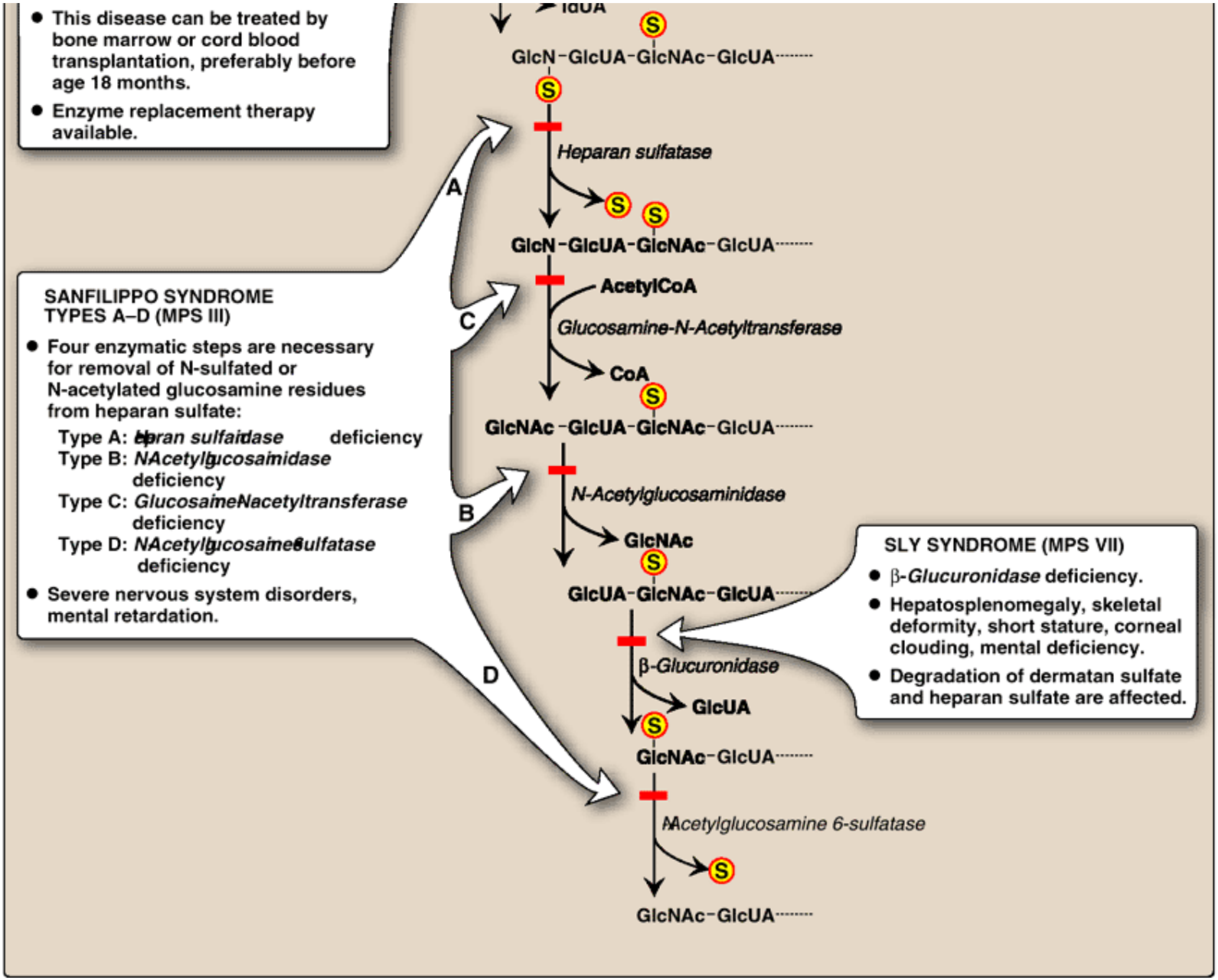

• This disease can be treated by bone marrow or cord blood transplantation, preferably before age 18 months.
• Enzyme replacement therapy available.
SANFILIPPO SYNDROME TYPES A–D (MPS III)
• Four enzymatic steps are necessary for removal of N-sulfated or N-acetylated glucosamine residues from heparan sulfate:
Type A: Heparan sulfatase deficiency
Type B: N-Acetylglucosaminidase deficiency
Type C: Glucosamine-N-acetyltransferase deficiency
Type D: N-Acetylglucosamine-6-sulfatase deficiency
• Severe nervous system disorders, mental retardation.
IdUA
GlcN–GlcUA–GlcNAc–GlcUA
Heparan sulfatase
GlcN–GlcUA–GlcNAc–GlcUA
AcetylCoA
Glucosamine-N-Acetyltransferase
CoA
GlcNAc–GlcUA–GlcNAc–GlcUA
N-Acetylglucosaminidase
GlcNAc
GlcUA–GlcNAc–GlcUA
β-Glucuronidase
GlcUA
GlcNAc–GlcUA
N-Acetylglucosamine 6-sulfatase
GlcNAc–GlcUA
A
B
C
D
SLY SYNDROME (MPS VII)
• β-Glucuronidase deficiency.
• Hepatosplenomegaly, skeletal deformity, short stature, corneal clouding, mental deficiency.
• Degradation of dermatan sulfate and heparan sulfate are affected.

Diagnosis confirmation (MPS IIIA)

- Heparin sulfamidase in leucocytes (4-MU)

  0.06 nmol/mg prot/hr (ref range 1.4-5.5)

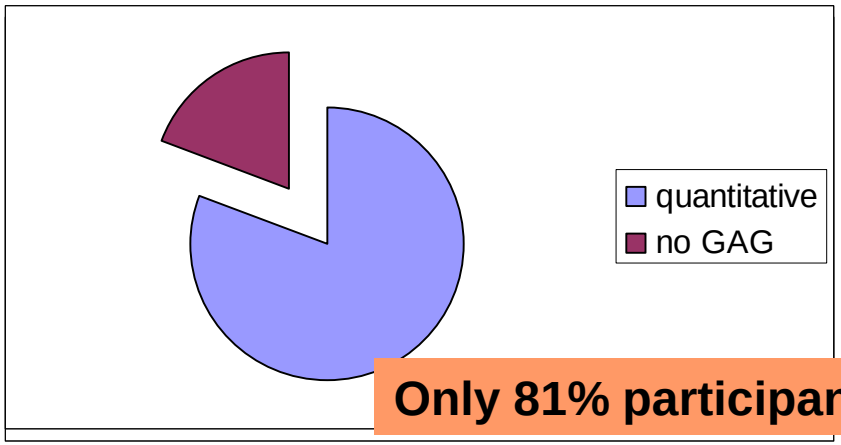
- Enzymes for MPS IIIB and MPS IIIC

N-Ac-alpha-D-glucosaminidase	11. 7 (7.3-18.3)
N-Ac-transferase	28.5 (13-46)

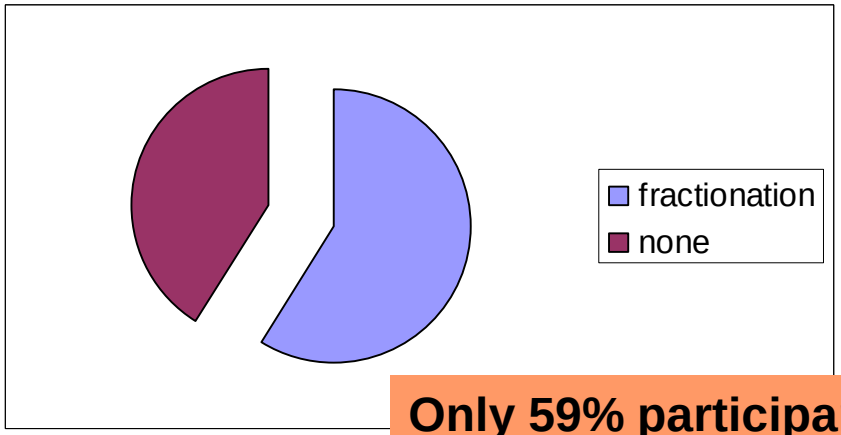
- Control enzymes within ref. Ranges

beta-galactosidase	136 (95-272)
beta-hexosaminidase	1660 (870-3200)

GAG analysis



Only 81% participants measured GAG



Only 59% participants performed TLC/elfo

Analytes in urine (n=88)

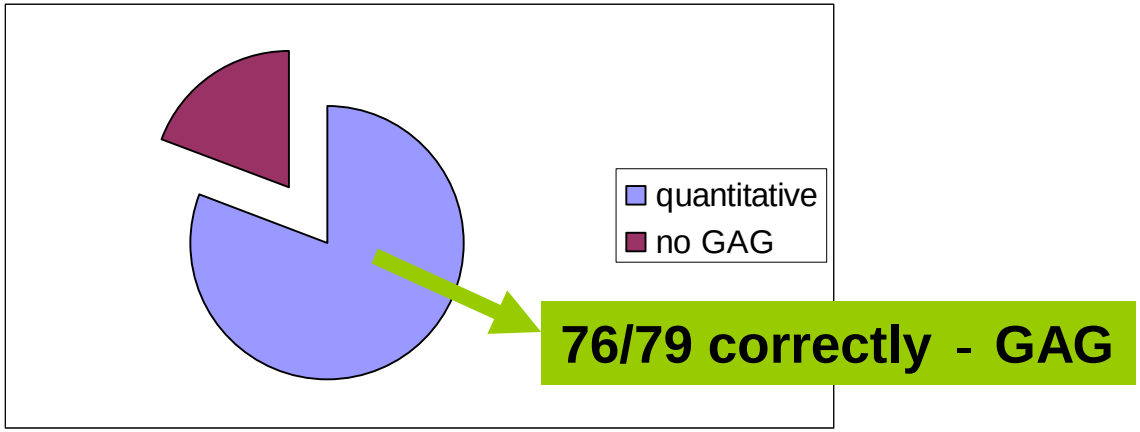
	Creatinine [mmol/l]	GAG [mg/l]	GAG [g/mol creat]
median (5; 95 centile)	3.2 (2,3; 3,8)	85 (43; 142)	29 (12; 47.7)
mean (S.D.)	3.2 (0.7)	89 (34)	29.6 (12.2)
interlab CV%	**22%**	**38%**	**41%**
lowest	1.7	11	3.4
highest	7.2	221	79

Analytes in urine (n=68)

Medians	Creatinine [mmol/l]	GAG [mg/l]	GAG [g/mol creat]
All centers	**3.2**	**85**	**29.0**
Amsterdam	3.2	99	30.8
Basel	3.1	87	33.0
Lyon	3.3	69	**20.6**
Sheffield	2.7	77	31.0
Prague	3.2	83	30.6

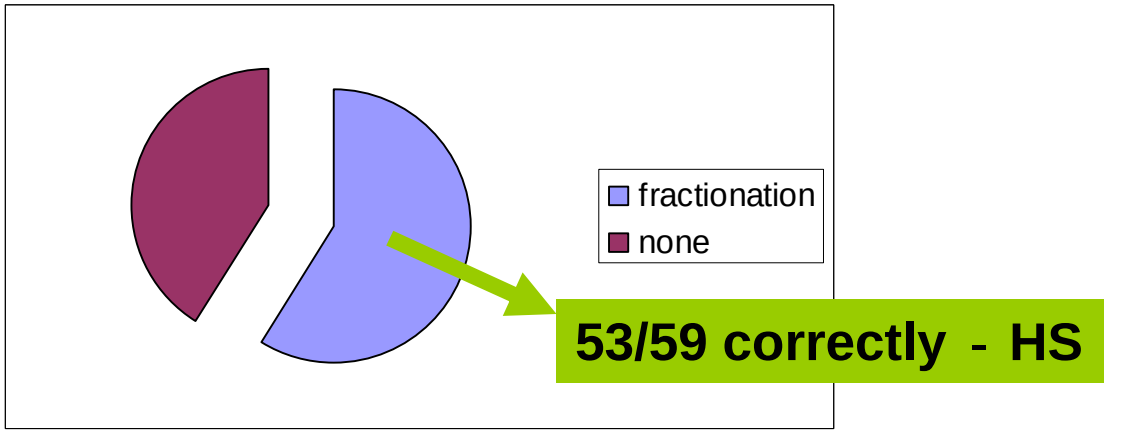
GAG analysis

Quantitative



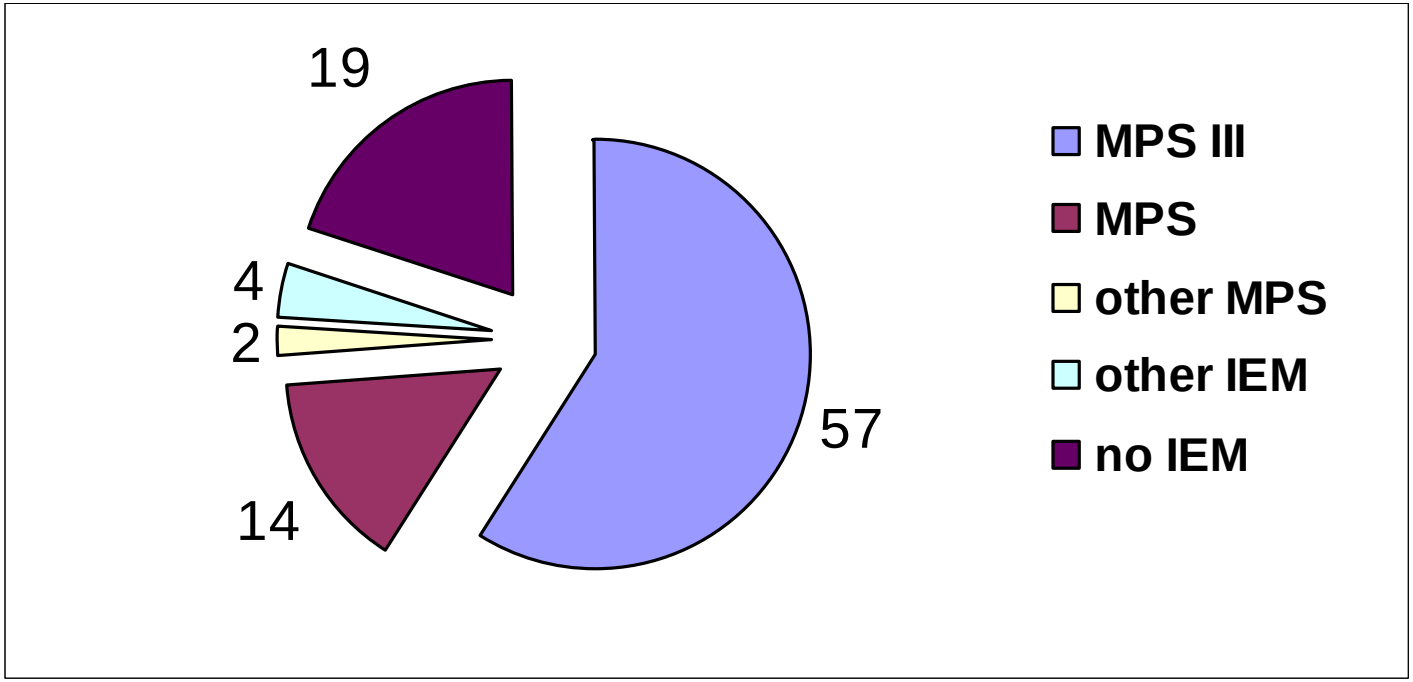
76/79 correctly - GAG

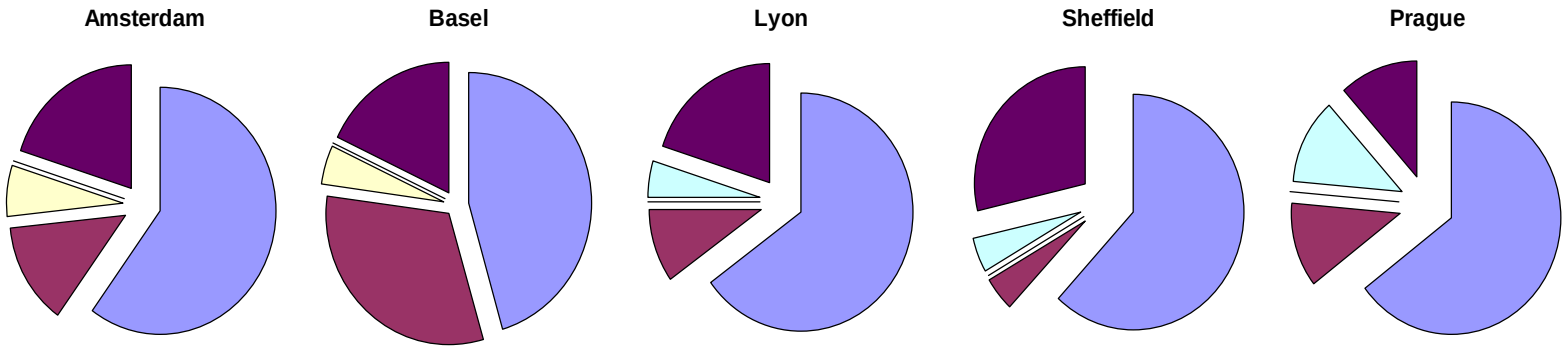
Qualitative



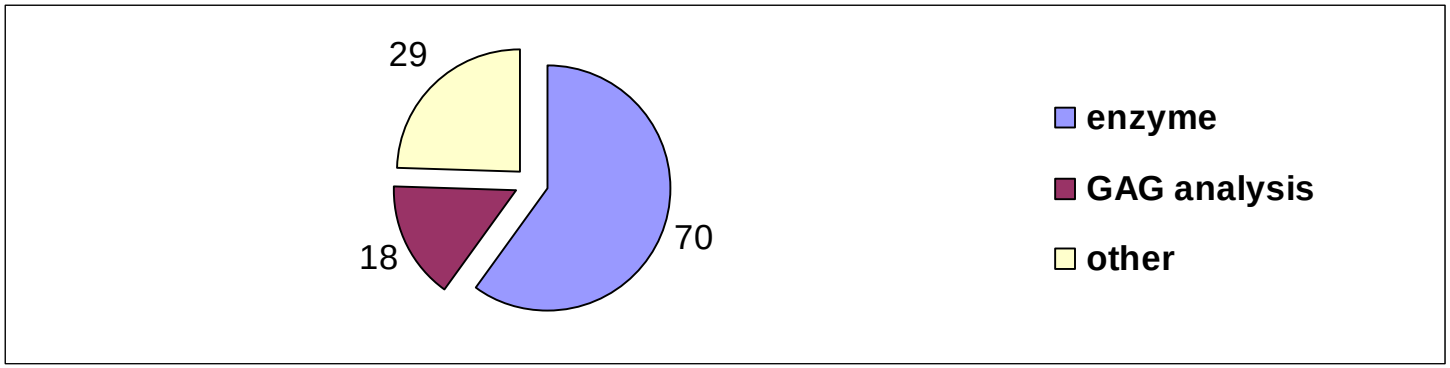
53/59 correctly - HS

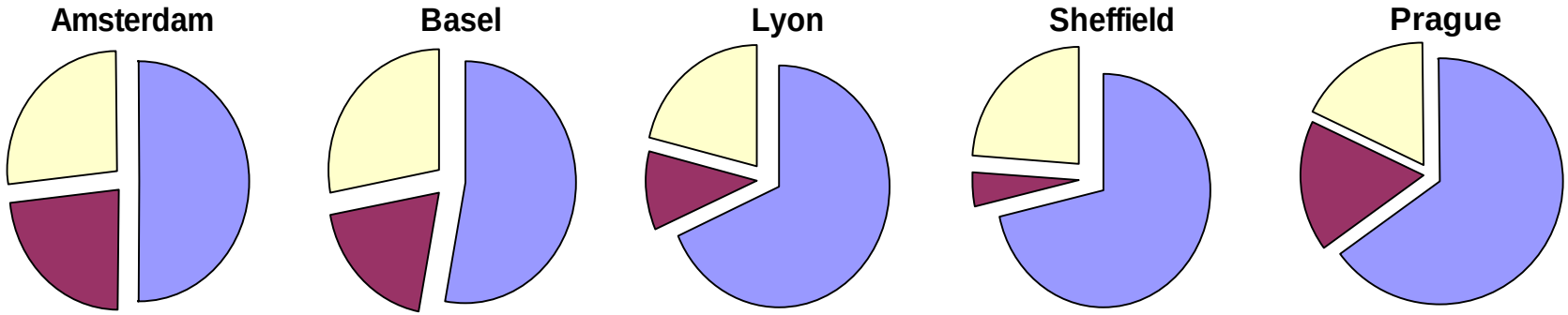
Interpretative proficiency





Recommendations





Feedback from participants/organizeres

- Sample selection (two MPS III in Amsterdam)
- Clinical description not resembling MPS

Taken home messages

- MPS III can be easily missed clinically
- Room for improvement
  - quantitative GAG analysis should be widely available and perhaps screened blindly in selective screening
  - ↓ CV in GAG and creatinine analysis
  - GAGs fractionation may become more common