Rare Disease Service Review for Lysosomal Storage Diseases

Laura Stephens, Senior Clinical Scientist

University Hospitals Plymouth NHS Trust

NHS
University Hospitals Plymouth
NHS Trust

Background

- Lysosomal storage diseases (LSDs): group of 70+ inherited metabolic disorders occurring due to gene defects in lysosomal proteins.
- Accumulation of excess substrate in tissues can cause organ dysfunction and increased mortality.
- Enzyme replacement therapy (ERT) only available for some LSDs, but average time to diagnosis is still 5 - 10 years.
- No clear pathway for identifying patients with LSDs at University Hospitals Plymouth.

Aims

- Review current journeys through the healthcare system of patients tested for LSDs.
  - Main focus on Fabry, Pompe and Gaucher disease
  - First encounter → referral into secondary care → point of testing
- Identify missed opportunities for diagnosis.
- Uncover potential improvements to diagnostic pathway.

Methods

Map diagnostic journeys of 60 patients between 2013 – 2023

ALL patients diagnosed with an LSD
AND
RANDOM selection of adults/paediatrics with negative tests

Answer clinical questions for each patient using data collection tool

Initial presentation
Family history
Specialisms referred to
Recognised LSD symptoms
Diagnosis and timeframe

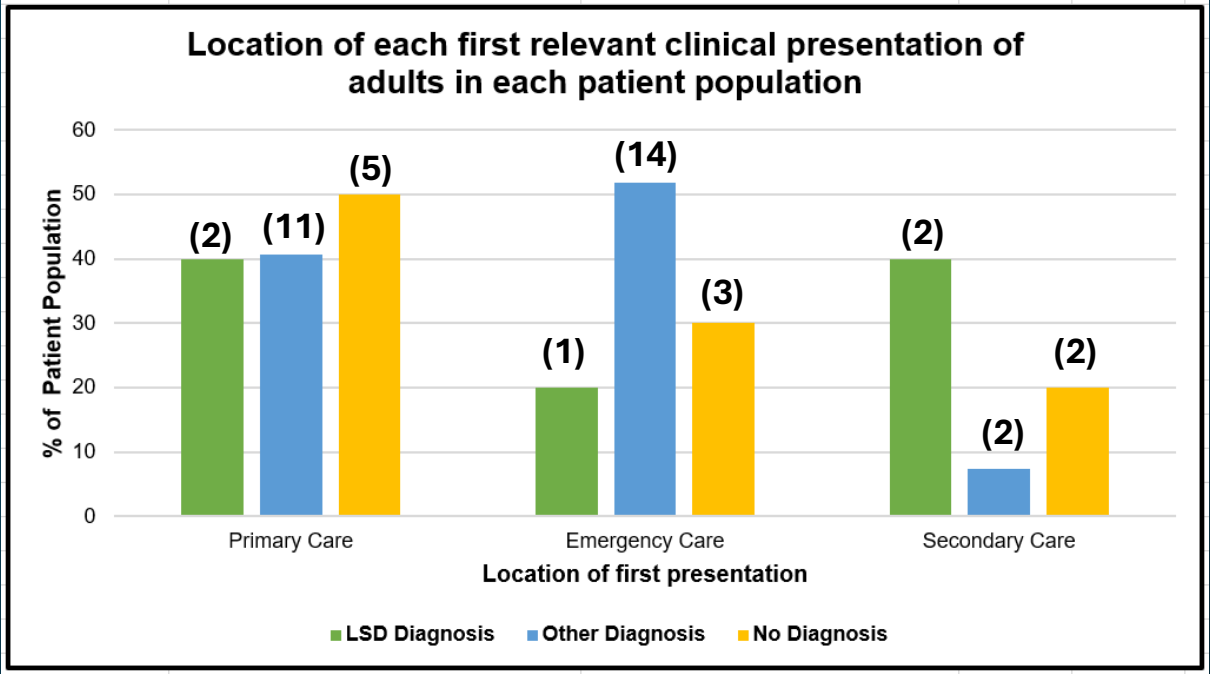
Identify data trends and discuss findings with relevant specialisms

Specialisms in which the selected LSDs are typically investigated

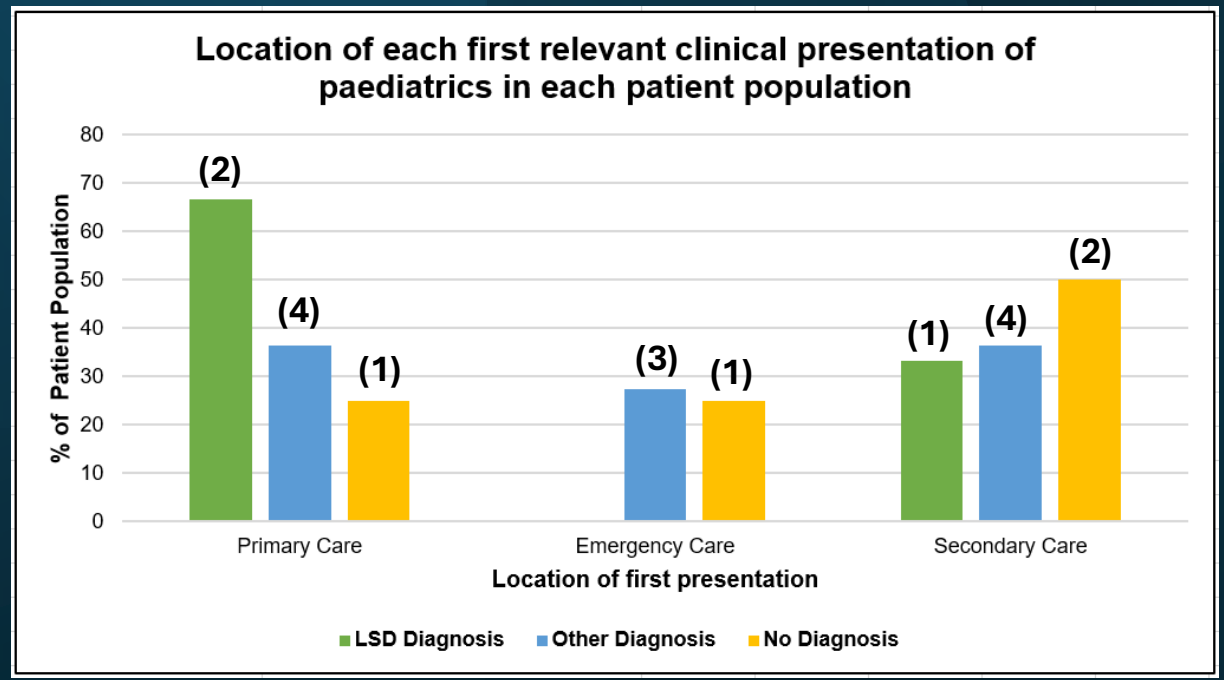
RESULTS

Location of first presentation

Adult patients (n = 42)



Paediatric patients (n = 18)



Symptoms by location of initial presentation: adults (n = 42)

Primary care	
Symptom	**Count**
Hepatosplenomegaly	3
Abdominal pain	3
Hypotonia	3
Haematological	3
Stroke symptoms	2
Bone pain	1
Psychomotor retardation	1
Cardiac failure	1
Neuropathic pain	1
Hypertrophic cardiomyopathy	1
Worsening headaches	1
Tremor	1
None	1

ED	
Symptom	**Count**
Stroke	10
Hepatosplenomegaly	2
Haematological	2
Hypotonia	2
Hypertrophic cardiomyopathy	2
Seizures	1
Sensorineural hearing loss	1
Restrictive lung disease	1
Increased SOB	1
Stroke symptoms	1

Secondary care	
Symptom	**Count**
Bone pain	2
Hepatosplenomegaly	2
Osteoporosis	1
Haematological	1
Proteinuria	1
None	1

Symptoms by location of initial presentation: paediatrics (n = 18)

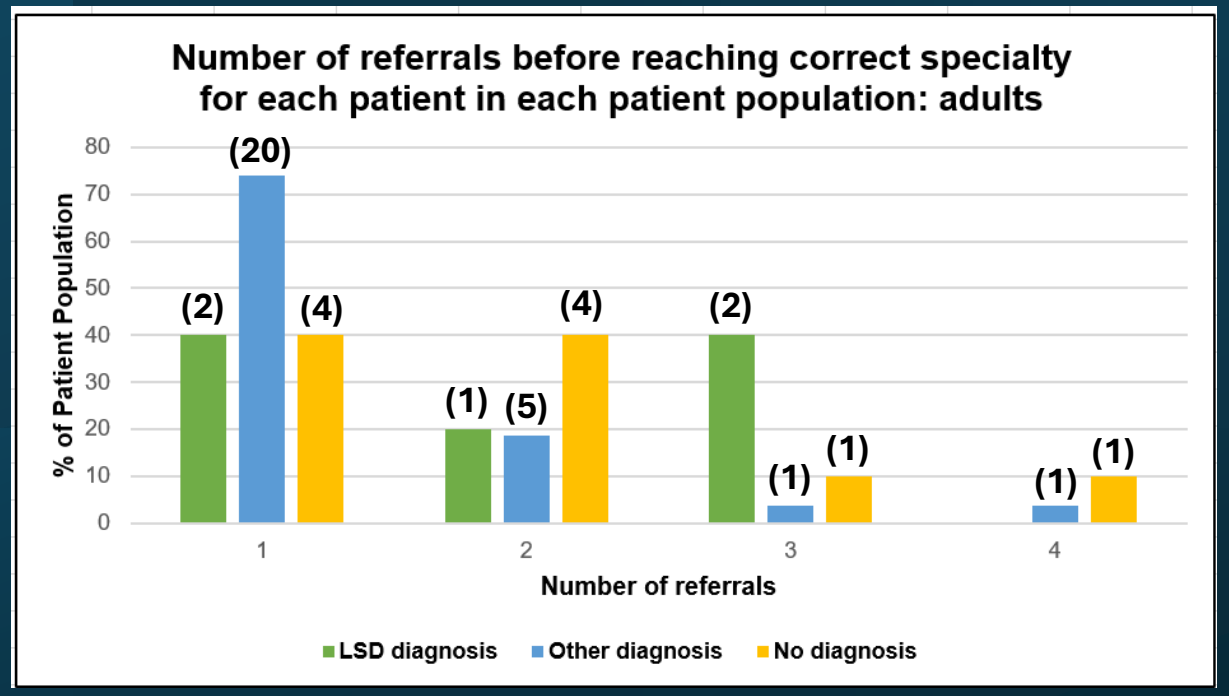
Primary care	
Symptom	**Count**
Psychomotor retardation	2
Developmental delay	2
Regression	2
Hypotonia	2
Mental retardation	1
Speech delay	1
Hypertrophic cardiomyopathy	1
Sensorineural hearing loss	1
Abnormal eye movements	1
Feeding difficulties	1
Faltering growth	1

ED	
Symptom	**Count**
Seizures	3
Abnormal eye movements	2
Hepatosplenomegaly	1
Regression	1

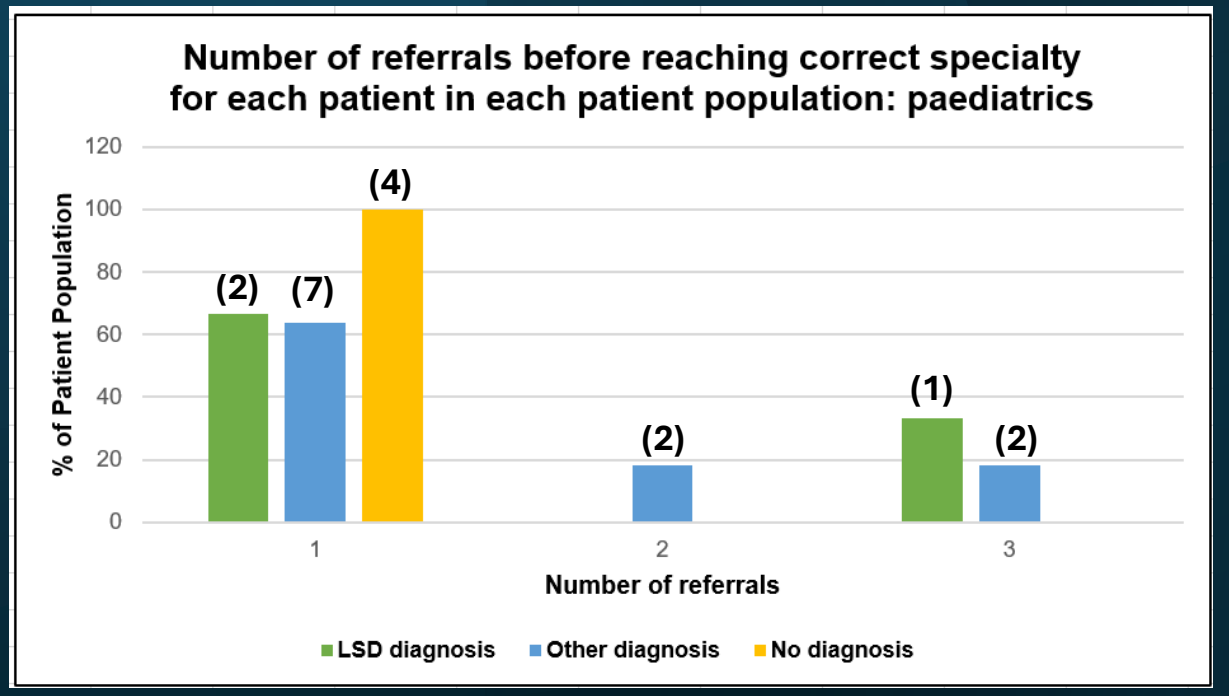
Secondary care	
Symptom	**Count**
None	2
Regression	1
Kyphosis	1
Hypotonia	1
Sensorineural hearing loss	1
Abdominal pain	1
Hepatosplenomegaly	1
Bone pain	1

Number of specialisms referred to for each patient

Adult patients (n = 42)

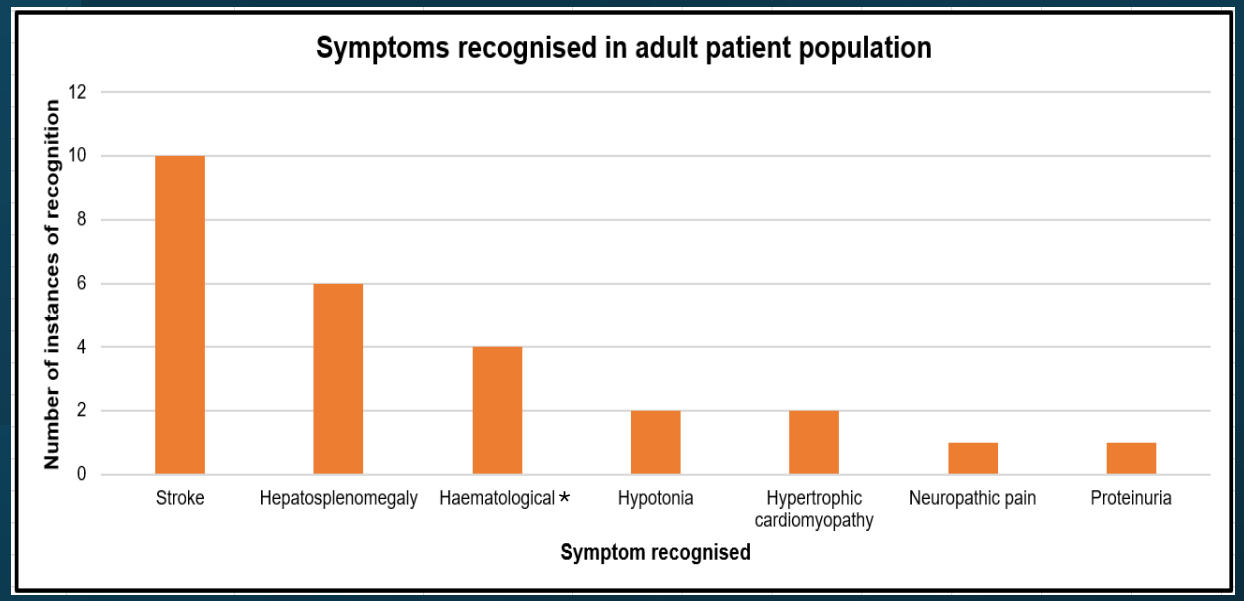


Paediatric patients (n = 18)



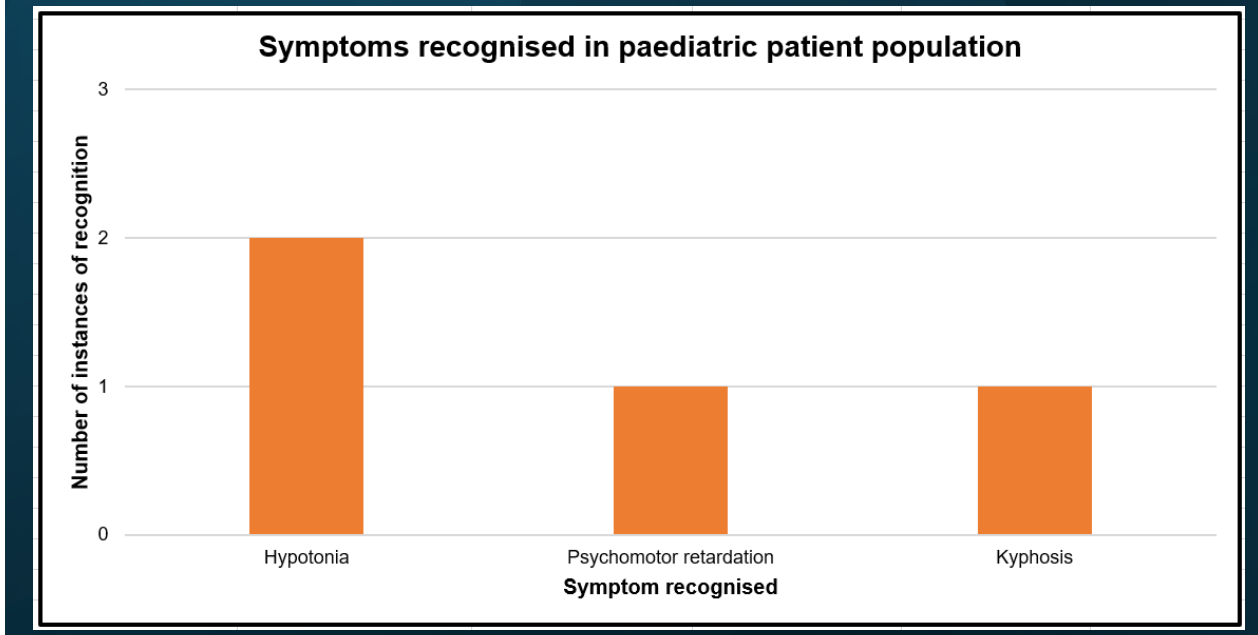
Recognised symptoms associated with LSDs

Adult patients
(24/42 patients had symptoms recognised)



*Recognised haematological symptoms: 2x thrombocytopenia, 1x anaemia, 1x pancytopenia

Paediatric patients
(4/18 patients had symptoms recognised)



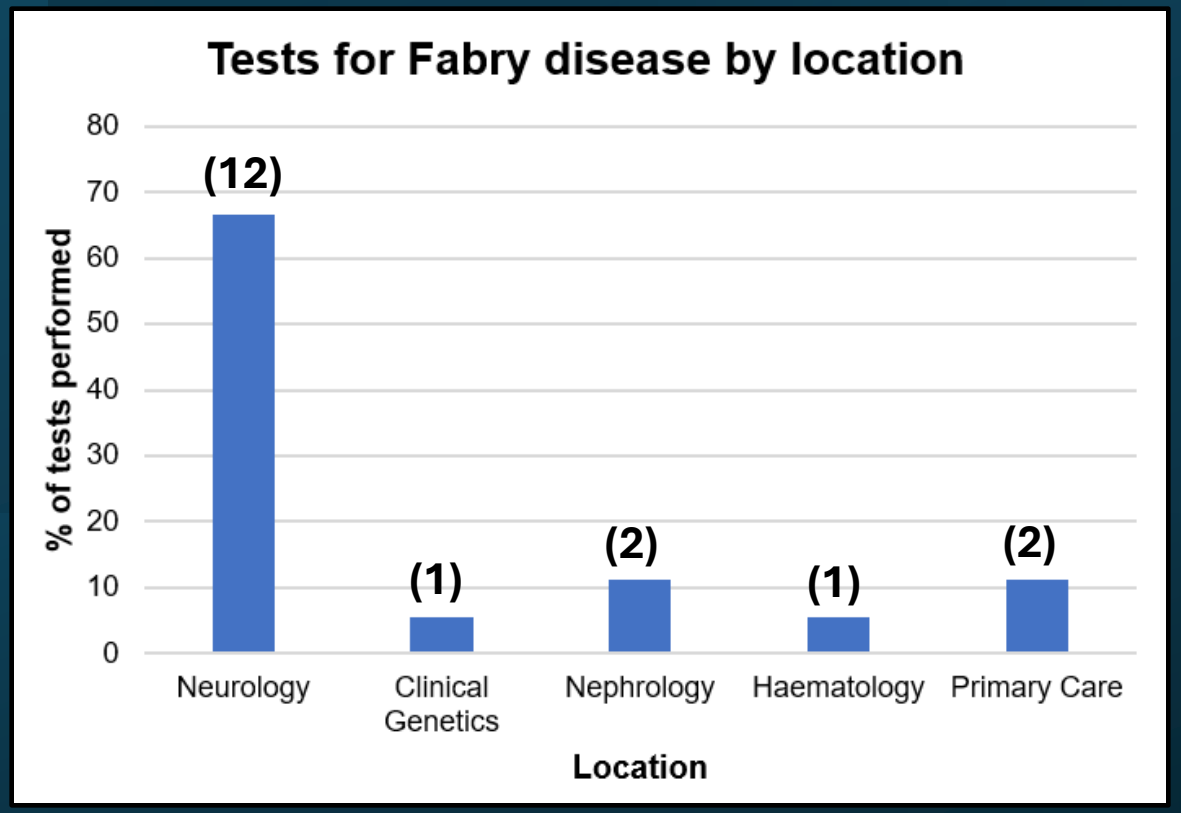
Instances of family history (all patients)

	Number of instances of FHx	Disease (number of occurrences)	
LSD Diagnosis	2	Gaucher (2)	
Other Diagnosis	2	Fabry (1), MPS I (1)	
No Diagnosis	2	Fabry (1), Pompe (1)	
Total	**6**	Fabry	2
		Pompe	1
		Gaucher	2
		MPS I	1

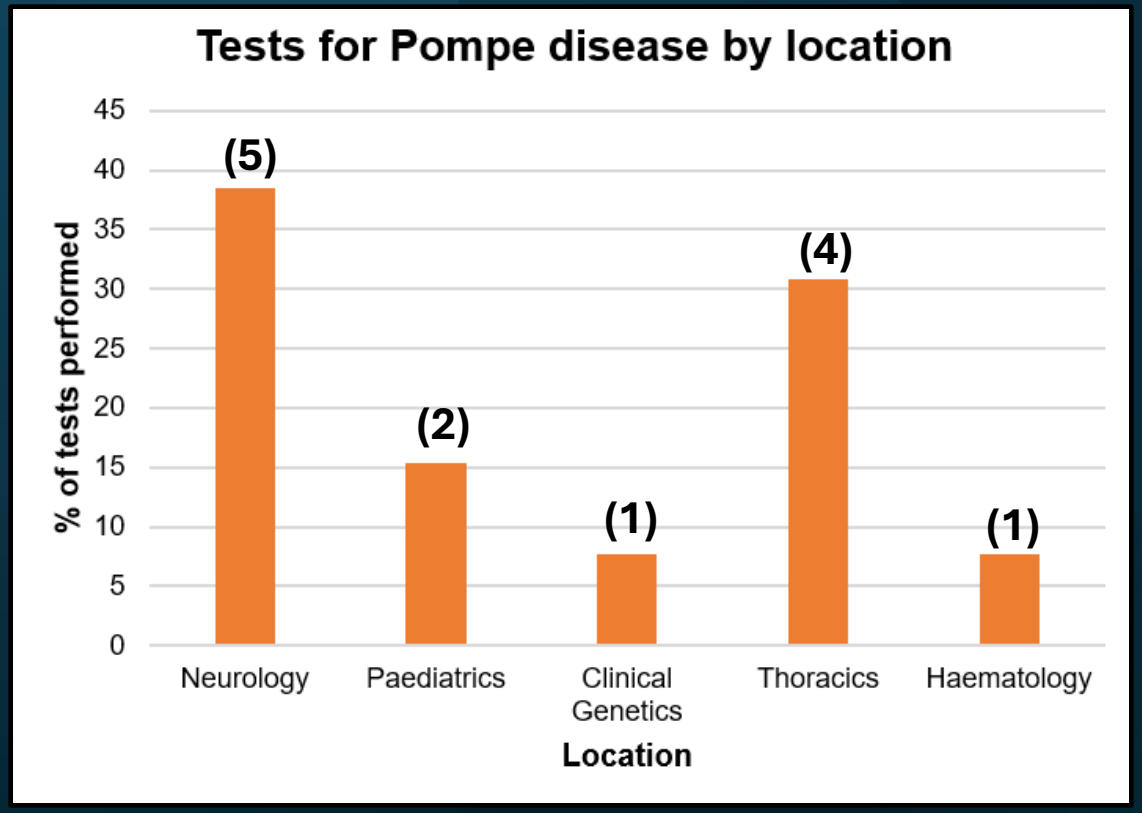
(4/6 patients reached correct discipline due to noted family history)

Locations for LSD testing in secondary care

Fabry Disease

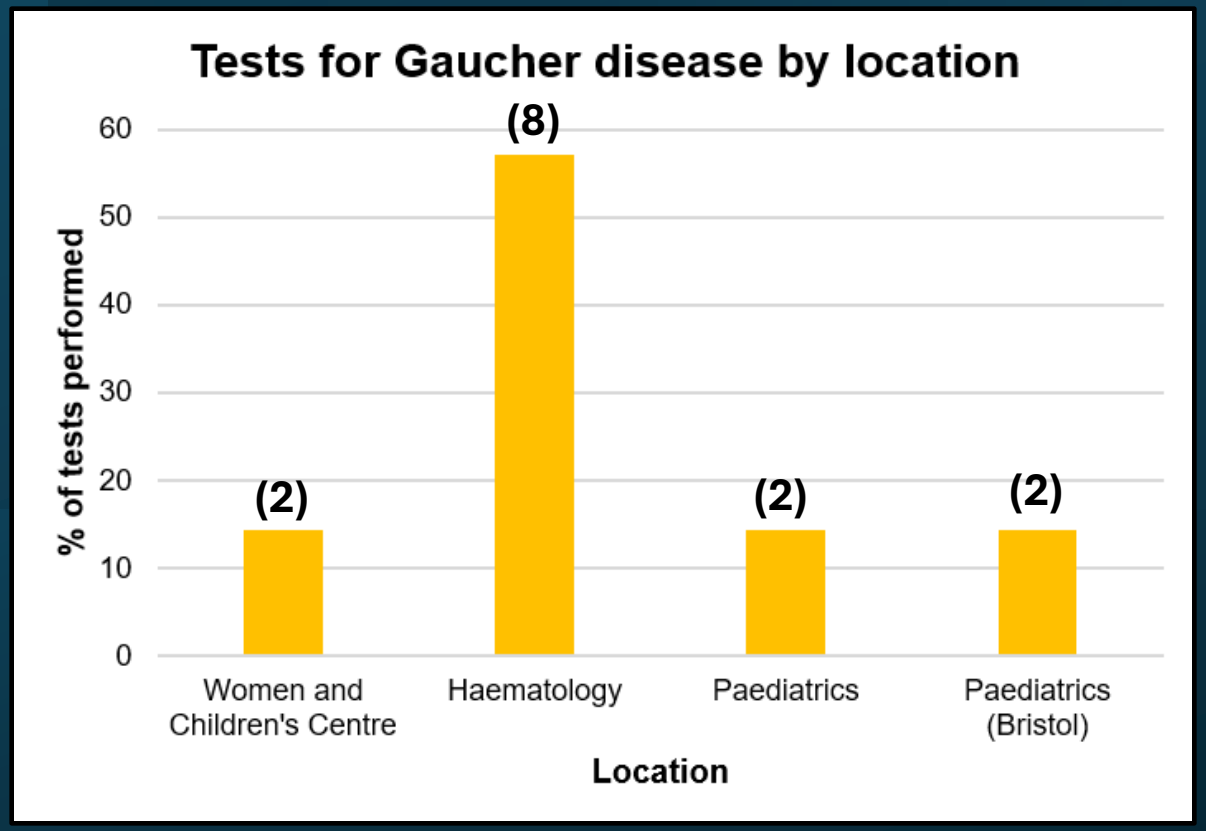


Pompe Disease

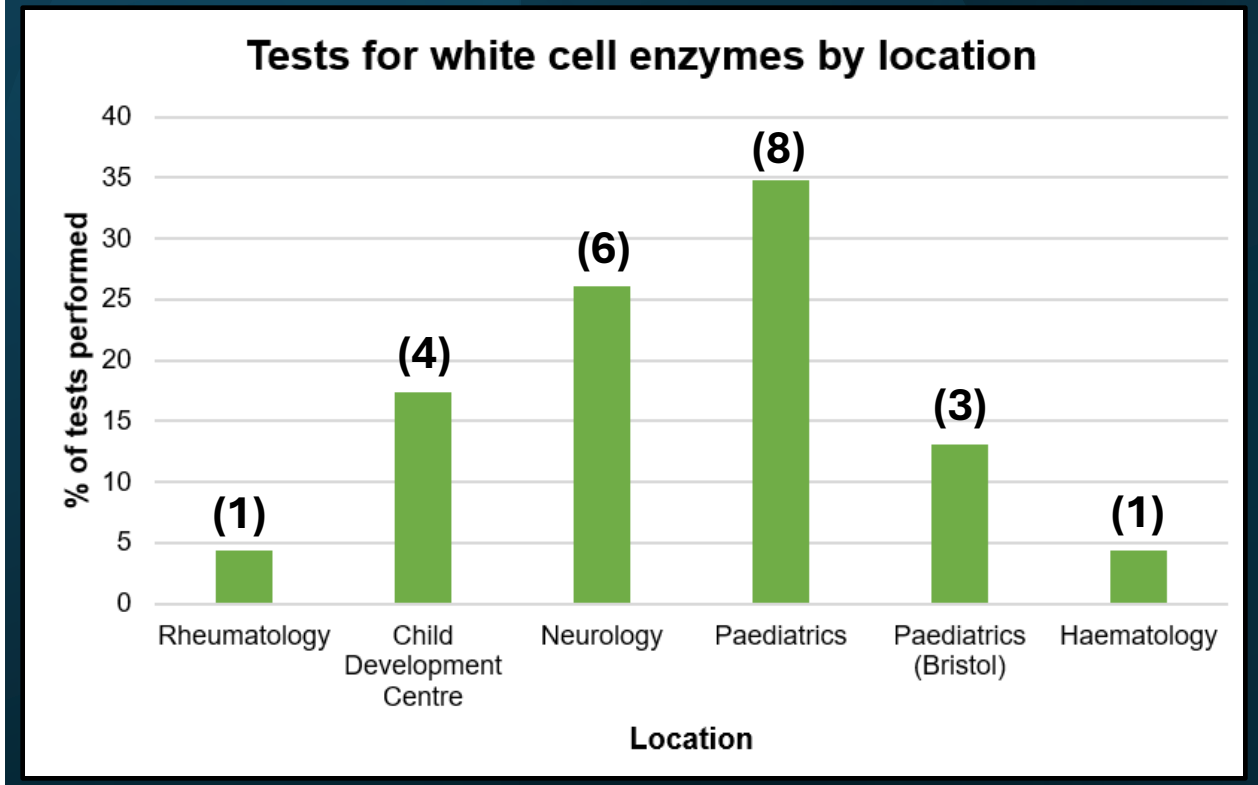


Locations for LSD testing in secondary care

Gaucher Disease

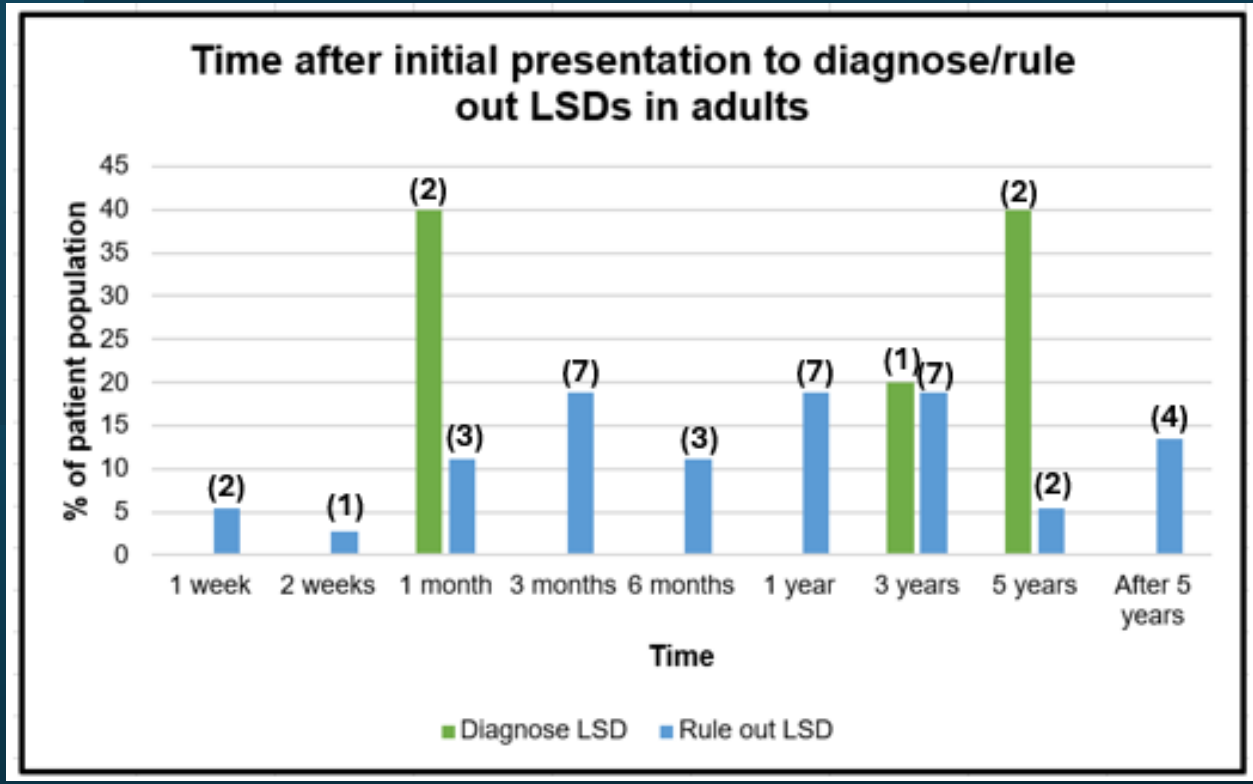


White cell enzymes

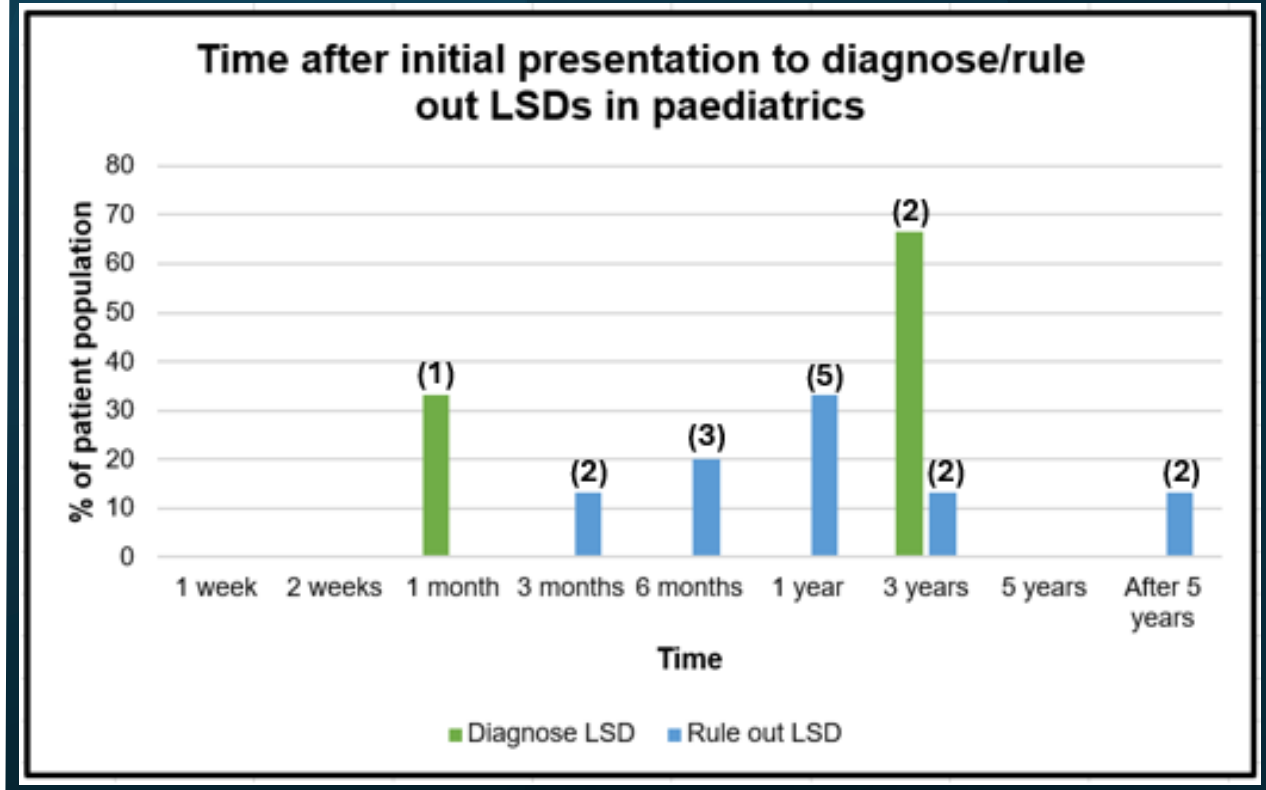


Time from initial presentation to diagnosis/rule out of an LSD

Adult patients (n = 42)



Paediatric patients (n = 18)



Case Study: Fabry Disease (42 y/o M)

Initial presentation:
Patient originally presented to ED with **stroke symptoms**, which later changed to a thunderclap headache.

Entering secondary care:
Following emergency care. The patient was found to have not had a stroke, but a subarachnoid haemorrhage (SAH).

Referrals:
- After entering secondary care, the patient was seen in **neurology**, who continued to follow the patient up for their SAH until he was discharged.
- Referred to **cardiology** the following year for arrythmia investigations due to persistent dizziness, fatigue and headaches; nothing notable was found from this.
- The patient subsequently had a stroke the following year and was referred back to **neurology**.

Reason for entering correct discipline: **recognised symptoms** upon both referrals to neurology; first time due to stroke symptoms (although this ended up being an SAH) and the second time because the patient did have a stroke.

Testing: **Fabry disease** (genetics). HRM and sequence analysis of GLA gene found that the patient was hemizygous for the c. 427 G>A A143T mutation in exon 3; which is consistent with Anderson-Fabry disease.

Timings:
- Initial presentation → diagnosis (2016): **within 3 years**.
- Entering the correct discipline in secondary care → diagnosis: **within 1 month**.

Outcome: Patient was commenced on enzyme replacement therapy shortly after diagnosis and is now doing well.

Case Study: Pompe disease (18 y/o F)

Initial presentation: Patient originally presented to her GP with **hypotonia**; specifically weakness in her lower legs. There was no further follow-up from this appointment as the patient moved to Plymouth shortly afterwards.

Entering secondary care: Following emergency care. Patient attended ED following abdominal pain and vomiting. Initial blood tests revealed raised ALT and imaging revealed an abnormal liver US; querying fatty liver.

Referrals:

- Originally referred to **hepatology** after findings.
- Continued to have abdominal pain and vomiting, so was also subsequently referred to **gastroenterology**.
- Eventually referred to **neurology** by hepatology: whilst being monitored by hepatology over a 2-year period; the patient developed worsening leg pain and weakness – with shooting pains down both calves, occasional leg numbness, reduced power, frequent falls and neuropathic pain. Eventually, the patient could no longer walk to her studies or uphill.

Reason for entering correct discipline: recognised symptoms of worsening pain, numbness and hypotonia in legs.

Testing: Pompe disease (positive result); confirmed by lymphocyte alpha glucosidase analysis from a muscle biopsy.

Timings:

- Initial presentation → diagnosis (2020): **within 5 years**.
- Entering the correct discipline in secondary care → diagnosis: **within 1 year**.

Outcome: Patient was commenced on enzyme replacement therapy shortly after diagnosis and is now doing well.

Case Study: Gaucher disease (5 y/o F)

Initial presentation: Patient presented to private secondary care abroad with persistent **abdominal pain**, **splenomegaly** and **bone pain**. She also had a family history of juvenile idiopathic arthritis; which her mother has.

Entering secondary care: **Privately entered secondary care** abroad due to symptoms. The patient was subsequently transferred to paediatrics at Derriford after moving to the UK.

Referrals:

- Seen privately in **paediatrics in secondary care abroad**; to investigate the presenting symptoms.
- Upon moving to the UK, the patient was seen in **paediatrics at Derriford**; where the patient's family history of juvenile arthritis was investigated.
- Following worsening and persistence of presenting symptoms, with the patient developing difficulties walking, the patient was referred to the **paediatric metabolic unit at BRI** for further investigations.

Reason for entering correct discipline: **Other** – privately seen in secondary care abroad before moving to the UK.

Testing: **Gaucher disease** (positive result). Subsequent GBA1 gene analysis found that the patient had a compound heterozygous mutation associated with type III Gaucher disease.

Timings:

- Initial presentation → diagnosis (2015): **within 3 years**.
- Entering the correct discipline in secondary care → diagnosis: **within 3 years**.

Outcome: Patient is now receiving ERT and tocilizumab for confirmed juvenile idiopathic arthritis. Currently doing well.

Summary trends

- Those diagnosed with an LSD typically had 1-3 referrals to different specialisms in secondary care.

- **Most commonly recognised LSD symptoms in patients:**
  - Stroke (Fabry Disease)
  - Hypotonia (Pompe Disease)
  - Hepatosplenomegaly (Gaucher Disease)

- **Highest number of test requests by location:**
  - Neurology (Fabry and Pompe Disease, white cell enzymes in adults)
  - Haematology (Gaucher Disease)

- Varied time from initial presentation to diagnosis of 1 month to 5 years for those diagnosed with an LSD (1 week to >5 years for those where an LSD was ruled out)

What next?

Need for increased awareness of LSD presentations to result in more timely management for those which are treatable.

- ❖ Creation of local metabolic handbook.
- ❖ Provision of GP education and Grand Round talks.
- ❖ Generation of joint MDTs between relevant specialisms.

Acknowledgements

- Roanna George, Consultant Clinical Scientist (North Bristol NHS Trust)
- Amanda Archer, Diagnostic Pathway Specialist in Rare Diseases (Sanofi)
- Michelle Rolfe, National Sales Manager – Rare Diseases (Sanofi)

References

1. Platt FM, d'Azzo A, Davidson BL, Neufeld EF, Tifft CJ. Lysosomal storage diseases. *Nat Rev Dis Primer* (2018); 4(1): 27. Available at: https://www.nature.com/articles/s41572-018-0025-4

2. Chunli Y, Qin S, Hui Z. Enzymatic Screening and Diagnosis of Lysosomal Storage Diseases. *N Am J Med Sci* (2013); 6(4): 186-193. Available at: https://stacks.cdc.gov/view/cdc/39973

Any Questions?

NHS
University Hospitals Plymouth
NHS Trust