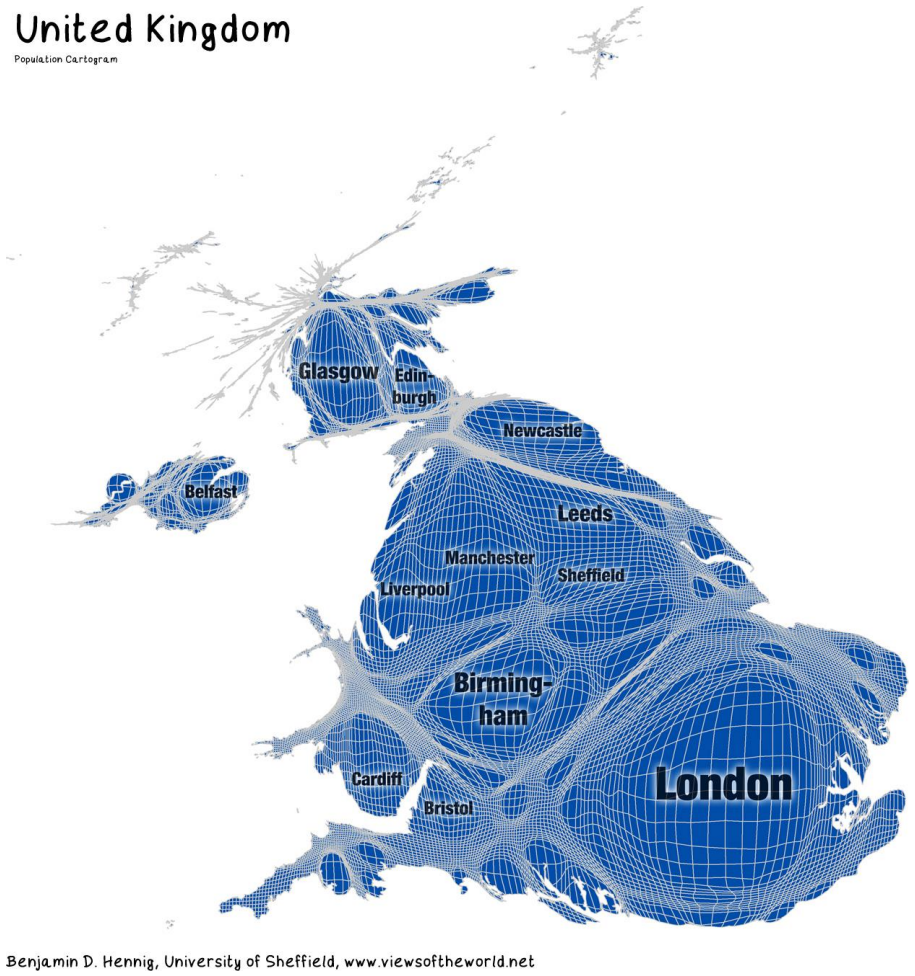
An Audit of UK VHL Surveillance Clinic Guidelines 2018



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- An audit of VHL screening practices was discussed at the Clinical leads meeting 2017 as a way of reviewing current practice against expert guidelines.
- Several centres identified significant differences in practice and how identifying these might support the commissioning and introduction of more comprehensive and standardised programs.
- Anecdotally patients have also commented on differences in annual surveillance being offered to different family members.

Genereviews (https://www.ncbi.nlm.nih.gov/books/NBK1463/)

VHL **should be suspected** in individuals with or without a family history of **VHL** who have:

- retinal angioma, especially in a young individual
- spinal or cerebellar hemangioblastoma
- adrenal or extra-adrenal pheochromocytoma
- renal cell carcinoma (RCC), if the individual is younger than age 47 years or has a personal or family history of any other tumour typical of **VHL**
- multiple renal and pancreatic cysts
- neuroendocrine tumours of the pancreas (pNET)
- endolymphatic sac tumours (ELST)
- less commonly, multiple papillary cystadenomas of the epididymis or broad ligament

VHL diagnostic criteria

Simplex case (an individual with no known family history of **VHL** syndrome) presenting with **two or more characteristic lesions**:

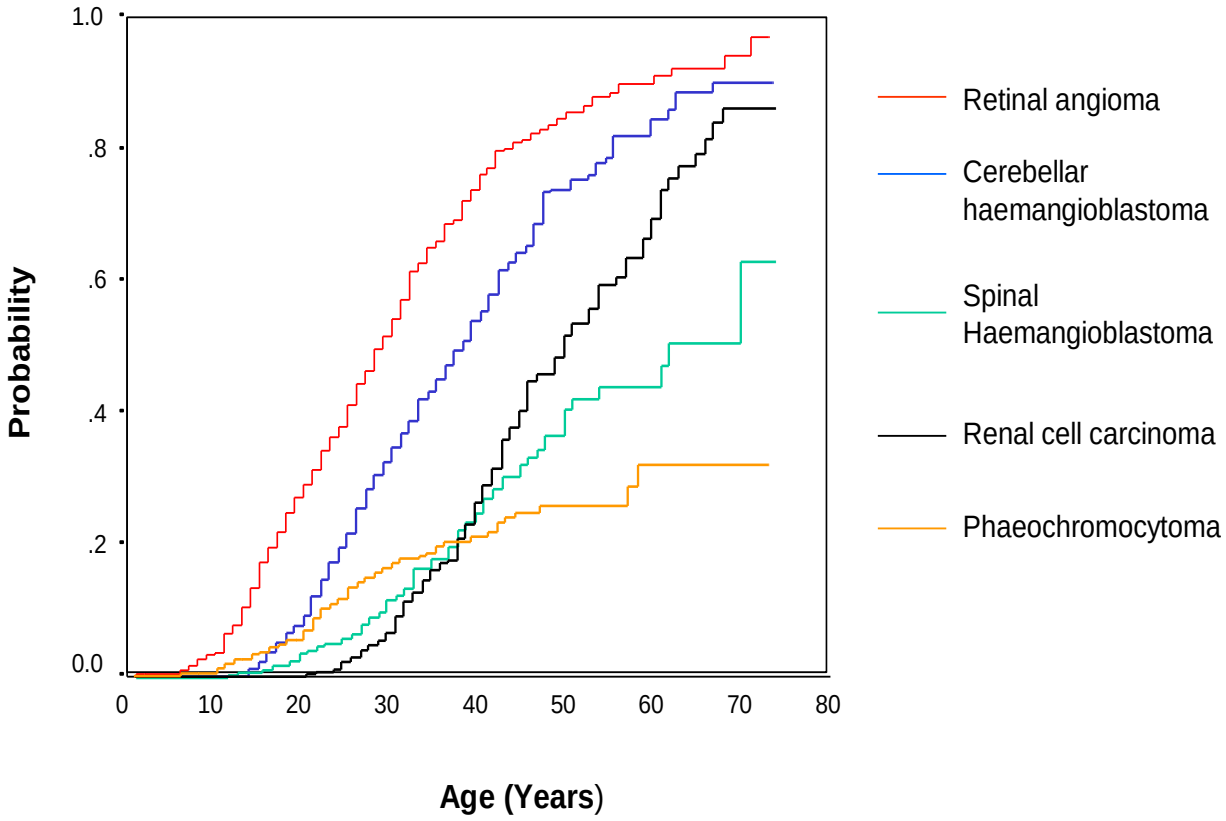
- Two or more hemangioblastomas of the retina, spine, or brain or a single hemangioblastoma in association with a visceral manifestation (e.g., multiple kidney or pancreatic cysts)
- Renal cell carcinoma
- Adrenal or extra-adrenal pheochromocytomas
- Less commonly, endolymphatic sac tumours, papillary cystadenomas of the epididymis or broad ligament, or neuroendocrine tumours of the pancreas

VHL diagnostic criteria 2

An individual with a family history of **VHL** syndrome in whom **one or more of the following is present**:

- Retinal angioma
- Spinal or cerebellar hemangioblastoma
- Adrenal or extra-adrenal pheochromocytoma
- Renal cell carcinoma
- Multiple renal and pancreatic cysts

Age related risks in VHL



Genotype–Phenotype Correlations in von Hippel-Lindau Disease

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Suggested routine surveillance protocol for von Hippel–Lindau disease

Screen for retinal angioma: Annual ophthalmic examinations (direct and indirect ophthalmoscopy), beginning in infancy or early childhood.
Screen for CNS haemangioblastoma: MRI scans of the head for every 12–36 months, beginning in adolescence.
Screen for renal cell carcinoma and pancreatic tumours: MRI (or ultrasound) examinations of the abdomen every 12 months, beginning from the age of 16 years.
Screen for phaeochromocytoma: Annual blood pressure monitoring and 24-h urine studies for catecholamine metabolites. More intense surveillance (e.g. annual measurement of plasma normetanephrine levels, adrenal imaging, beginning from the age of 8 years should be considered in families at high-risk for phaeochromocytoma).

Maher *et al.* Eur J Hum Genet. 2011 Jun; 19(6): 617–623.

- 22 regional genetics centres contacted May 2018
- 21 responses received to March 2019
- 2 additional centres identified-plan to request surveillance data
- 2 centres have no formal surveillance clinic
  - Exeter (low numbers)
  - GOSH (Barts and RFH)

For VHL Surveillance Clinics

- 18/19 are led by the regional genetics Service
- 1/19 is led by Endocrinology

- For the genetics led clinics
  - 3 combined with ophthalmology alone
  - 2 combined with ophthalmology and urology
  - 1 combined with ophthalmology and radiology
  - 1 combined with ophthalmology and endocrinology
  - 1 combined with ophthalmology and radiology
  - 2 combined with endocrinology
  - 1 combined with neurology
  - 1 combined with endocrinology, urology and neurology
  - 1 combined with paediatrics and neurosurgery
  - 6 Genetics alone

Screen for retinal angioma: Annual ophthalmic examinations (direct and indirect ophthalmoscopy), beginning in infancy or early childhood.

- 18 clinics provided data
- All offered or co-ordinated surveillance
  - 13 from age 5 years
  - 1 from age 5-8 years
  - 1 from age 3 years
  - 1 from age 5-10 years
  - 1 from age 2 years
  - 1 from age 7-10 years

- 2 cases of retinal angioma reported under age 5 years

Screen for CNS haemangioblastoma: MRI scans of the head for every 12–36 months, beginning in adolescence.

- 18 clinics provided data
- All offered or co-ordinated surveillance for cerebellar and spinal lesions
  - Baseline MRI from age 15-18 years with offer of 3 yearly screening
  - 1 clinic offered baseline MRI from age 15-18 years with offer of 5 yearly screening
  - 1 offered baseline MRI at age 11 years
  - 1 offered baseline MRI at age 14 years with 1-2 yearly screening
  - 1 offered baseline MRI at age 8 with offer of 3 yearly screening

- No centres reported CNS disease under age 5 years

- ELST screening via CNS MRI or symptom enquiry (single lesion from 2012-2017)

Screen for renal cell carcinoma and pancreatic tumours: MRI (or ultrasound) examinations of the abdomen every 12 months, beginning from the age of 16 years.

- 18 clinics provided data
- All offered or co-ordinated surveillance for RCC and pNET
  - Screening was MRI, alternating ultrasound and MRI or ultrasound alone
  - MRI/CT was offered for suspected lesions

- For MRI only age at start was 10, 15, 15, 15, 16, 18, not stated
- For US only age at start was 8*, 10, 10, 10, 16
- For US/MRI age at start was 8, 12**, 15**, 15**, 16, 16, 16**

* Combined with plasma chromogranin A
**MRI 2 or 3 yearly or starting at age 18.

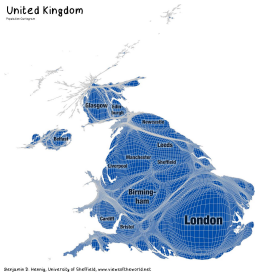
Screen for renal cell carcinoma and pancreatic tumours: MRI (or ultrasound) examinations of the abdomen every 12 months, beginning from the age of 16 years.

- 2 centres reported RCC disease under age 18 years
- Earliest age of pNET detection was 12 years
- All centres referred RCC to urology or urology MDT
  - 3 centres at 20-25 mm
  - 2 centres at 30 mm
  - Rest at diagnosis any size

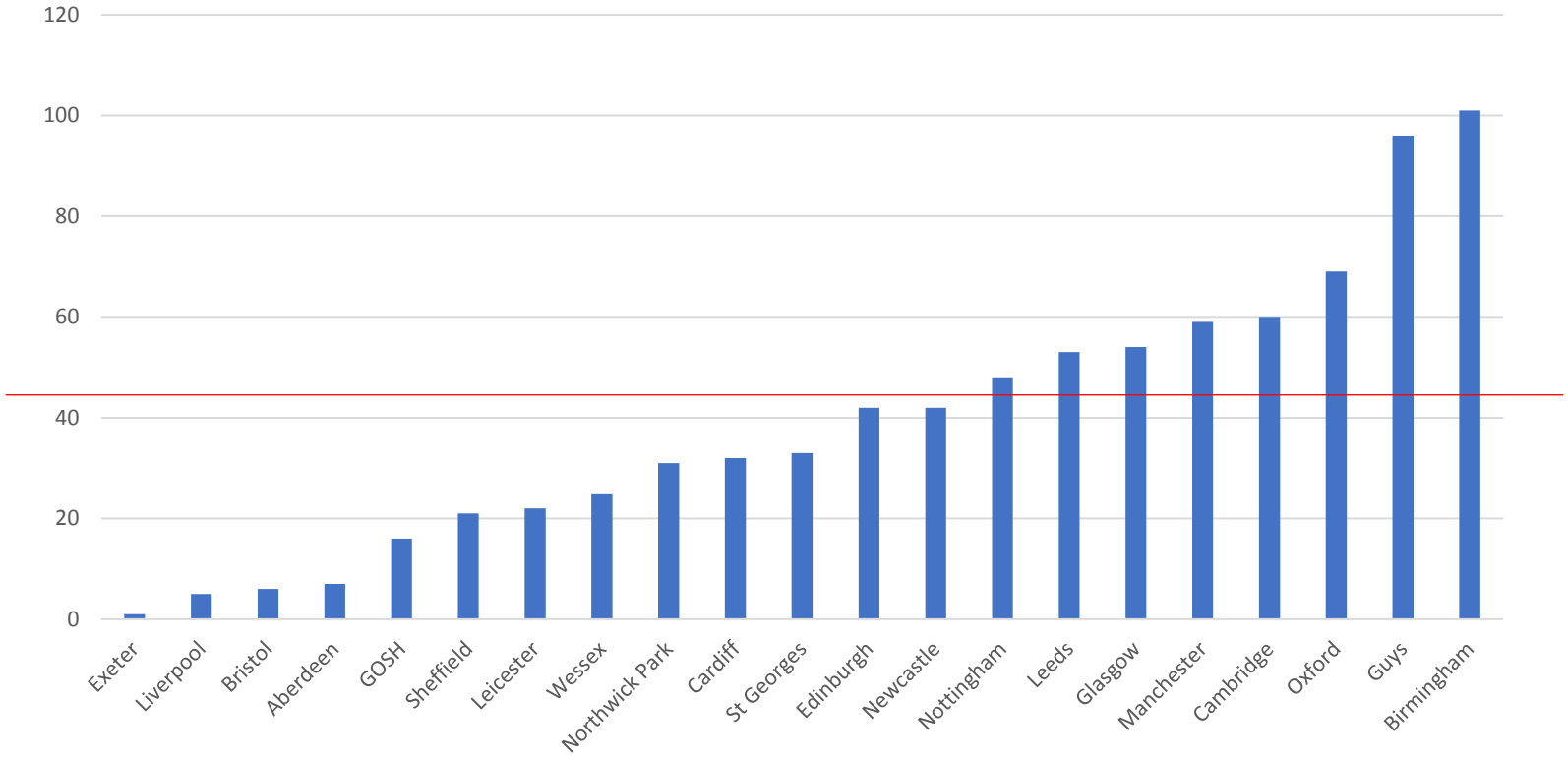
Screen for phaeochromocytoma: Annual blood pressure monitoring and 24-h urine studies for catecholamine metabolites. More intense surveillance (e.g. annual measurement of plasma normetanephrine levels, adrenal imaging, beginning from the age of 8 years should be considered in families at high-risk for phaeochromocytoma).

- 18 clinics provided data
- All offered or co-ordinated surveillance for phaeochromocytoma
  - Screening offered using BP, spot urine, 24 hour urine, pMETs, imaging (as part of abdo imaging)
  - From age 10 in 6 centres
  - From age 11 in 1 centre
  - From age 8 in 3 centres
  - From age 7 in 1 centre
  - From age 5 in 4 centres (1 center included MRI)
  - From age 3 in 1 centre (high risk FH)
  - From age 5 in 1 centre (high risk FH)

Several comments about ‘earlier’ screening if high risk FH and pMETS in childhood if high risk

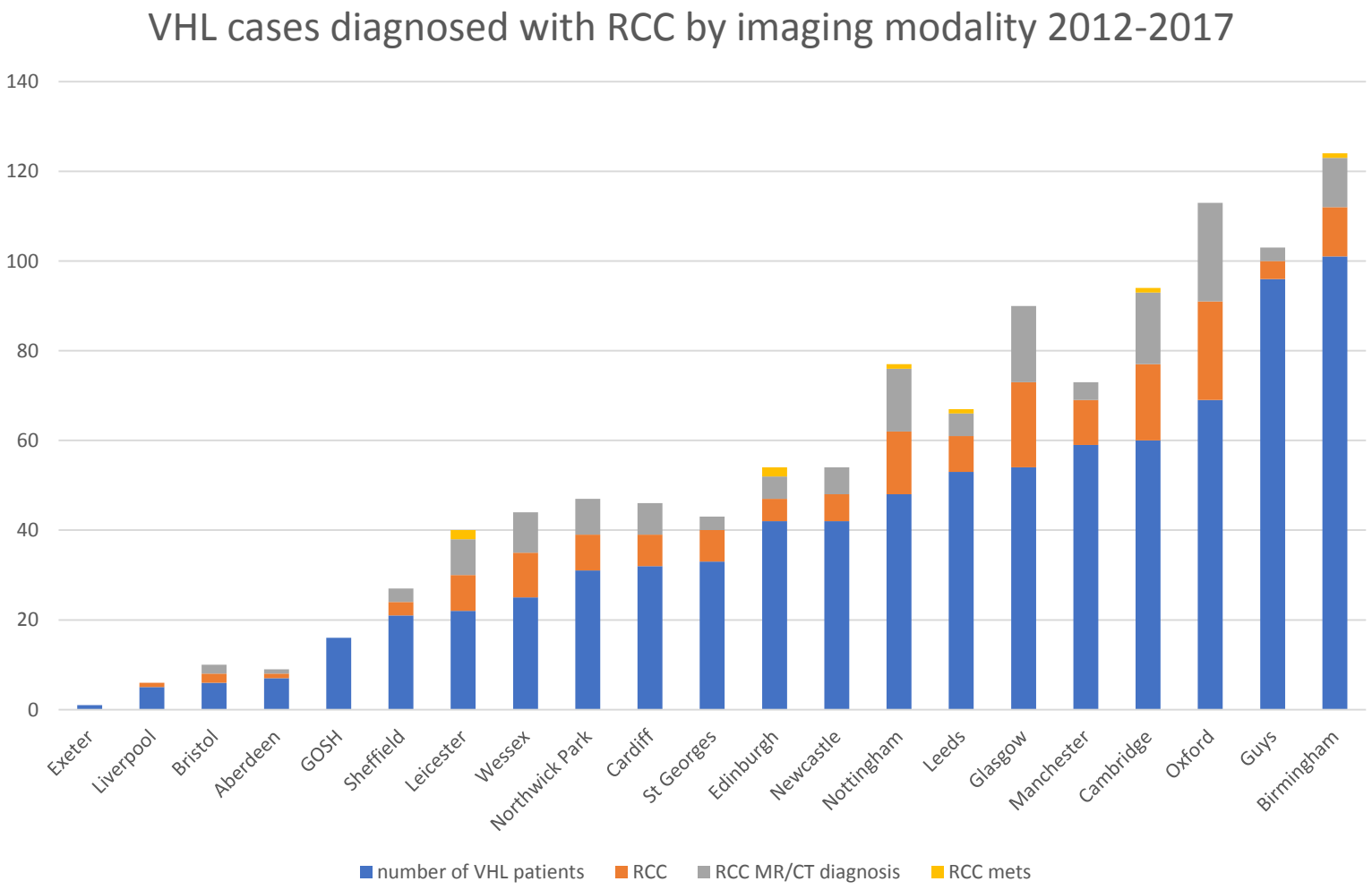


Number of VHL patients under follow up
2012-2017

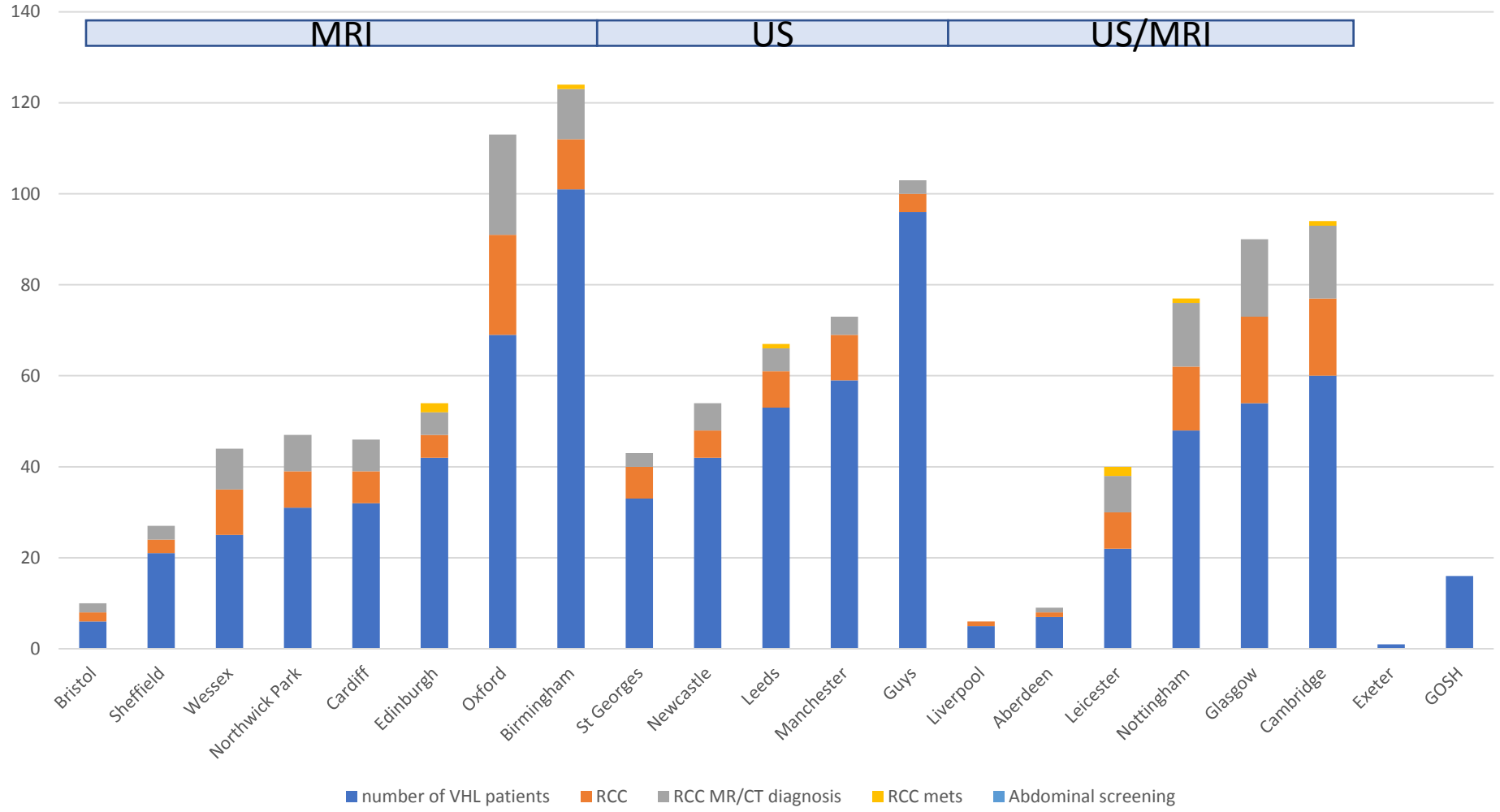


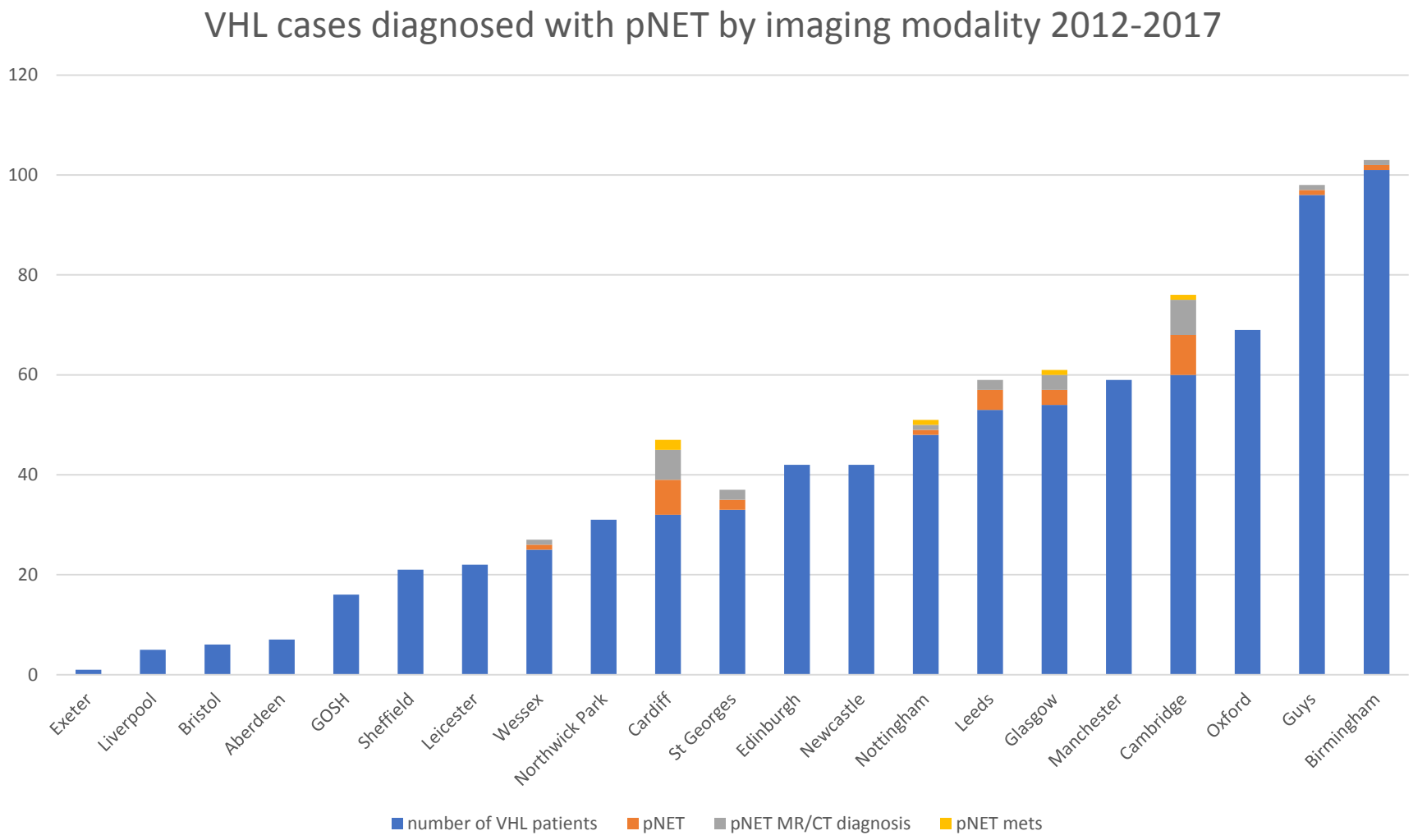
- Total = 823 VHL patients (385M:438F)
- Age range = 1-88 years
- 731 with pathogenic mutation
- 64 with no mutation identified (7.7%)

- 74 at 50% risk (35M:39F)
- 40 with known familial mutation (54%)

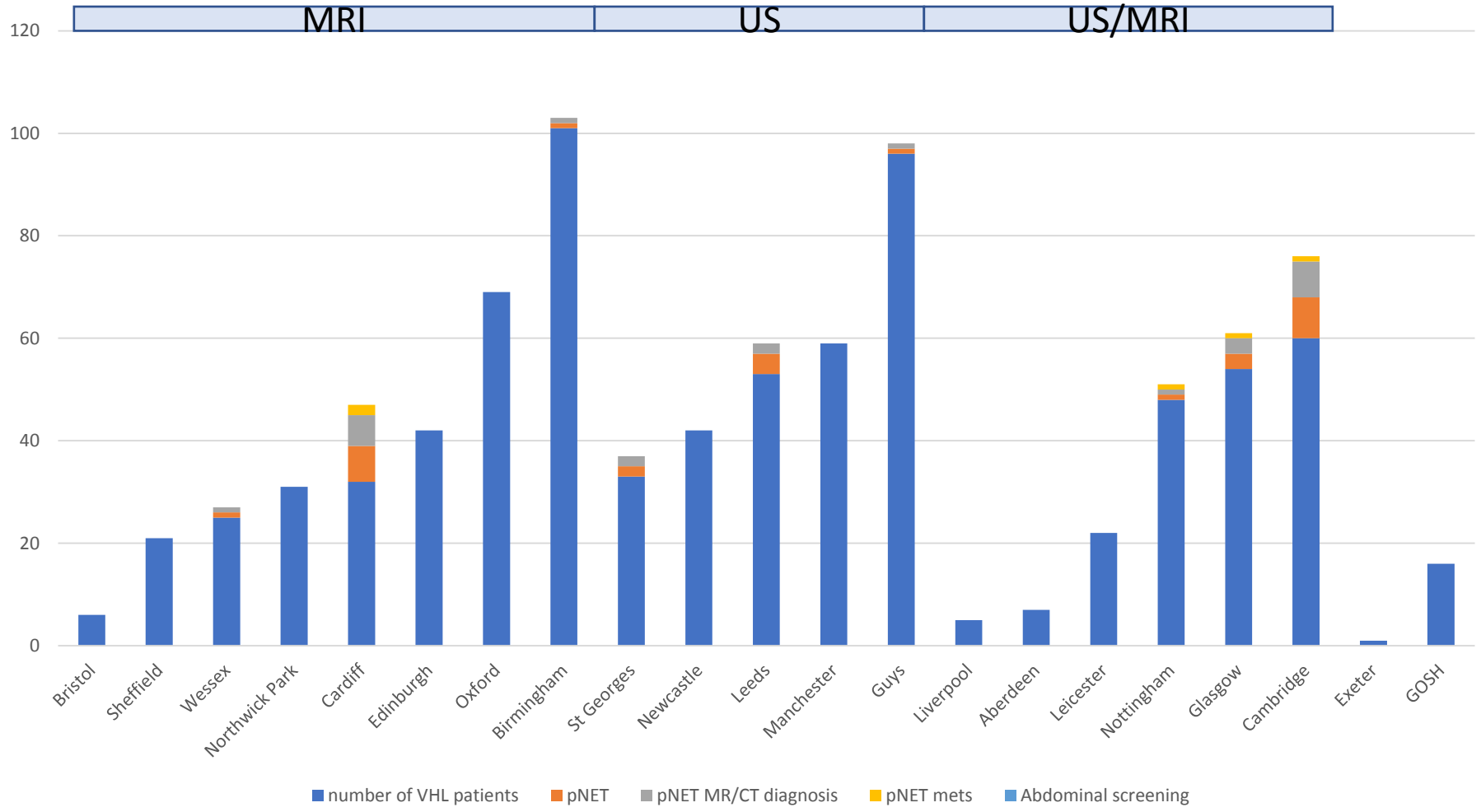

VHL cases diagnosed with RCC by imaging modality 2012-2017
140
120
100
80
60
40
20
0
Exeter
Liverpool
Bristol
Aberdeen
GOSH
Sheffield
Leicester
Wessex
Northwick Park
Cardiff
St Georges
Edinburgh
Newcastle
Nottingham
Leeds
Glasgow
Manchester
Cambridge
Oxford
Guys
Birmingham
number of VHL patients
RCC
RCC MR/CT diagnosis
RCC mets

RCC cases stratified by centre routine abdominal screening modality 2012-2017

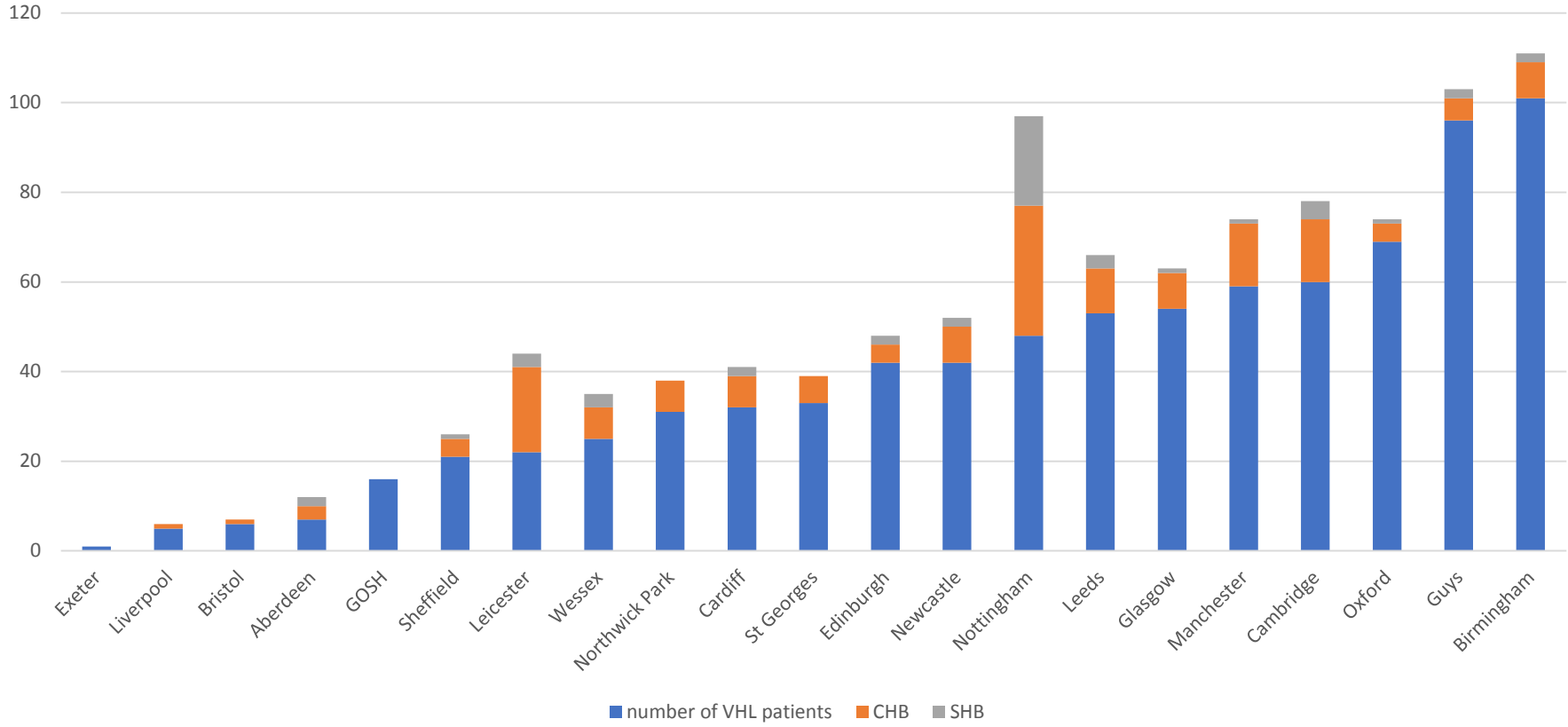



VHL cases diagnosed with pNET by imaging modality 2012-2017
120
100
80
60
40
20
0
Exeter
Liverpool
Bristol
Aberdeen
GOSH
Sheffield
Leicester
Wessex
Northwick Park
Cardiff
St Georges
Edinburgh
Newcastle
Nottingham
Leeds
Glasgow
Manchester
Cambridge
Oxford
Guys
Birmingham
number of VHL patients
pNET
pNET MR/CT diagnosis
pNET mets

pNET cases stratified by centre routine abdominal screening modality 2012-2017



Cases of cerebellar and spinal haemangioblastoma (surgery) by centre 2012-2017

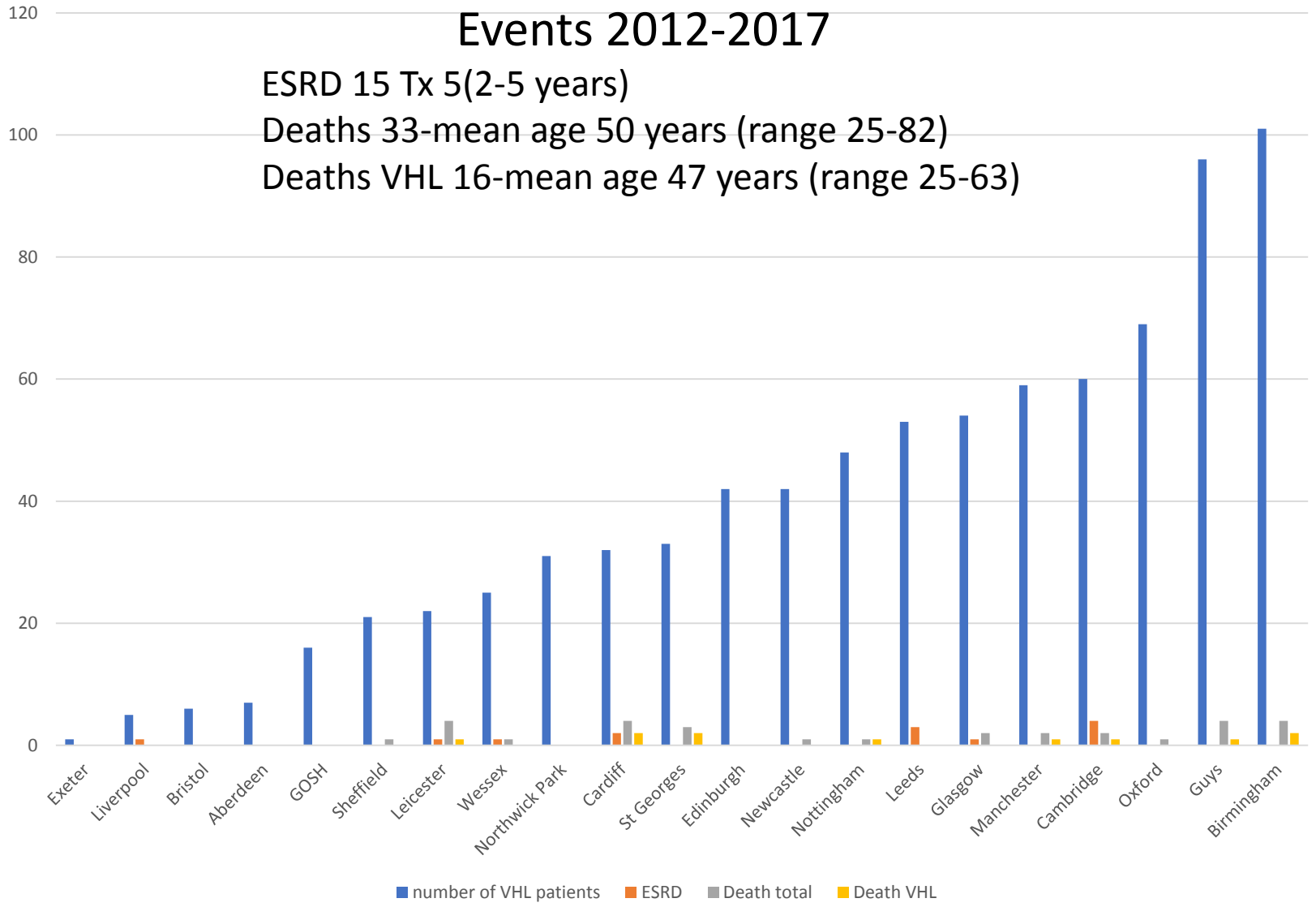


Events 2012-2017

ESRD 15 Tx 5(2-5 years)

Deaths 33-mean age 50 years (range 25-82)

Deaths VHL 16-mean age 47 years (range 25-63)



Isolated CNS Haemangioblastomas

Woodward *et al* 2007

- 4% have a detectable *VHL* mutation and all presented before age 40 years
- Small proportion may have a VUS
- 5% with no mutation developed further VHL type tumour

- All centres returned data
- If isolated (including negative VHL gene test)
  - No centres offered FDR screening
  - No standard policy regarding discontinuation of surveillance
  - Examples include
    - Screen to 40 (3 centres) or 50 (6 centres)
    - Screen 2 yearly to 60
    - Reduced screening after age 30 years
    - Discontinue after negative genetic test
    - Case by case basis
    - 1-2 yearly
    - No policy

Summary

- Of the 21 centres that provided surveillance information on behalf of themselves or another service ALL met the audit guideline.
- There was considerable variation in the age at which screening was offered and with which method for CNS haemangioblastoma, RCC, pNET and phaeochromocytoma detection! Risk stratification is not routinely used.
- From the data provided between 2012 and 2017 there were no clear differences in or patterns of outcome due to these differences. Further analysis based on size of lesion is being carried out.
- There is a need to provide clear guidance about screening and surveillance for patients of all ages presenting with an apparently isolated CNS haemangioblastoma.
- Further data will be required to provide the evidence to support changes to or standardization of VHL screening

- Data collection will continue for a short period prior to circulating the final audit report
- Targeted follow up questions may be required for clarification
- Feedback about how this audit was conducted would be very welcome!
- A National Register is being established (ERM)

Thank you to all the centres that supported this audit- it was a huge task!