Neuroendocrine tumours in children

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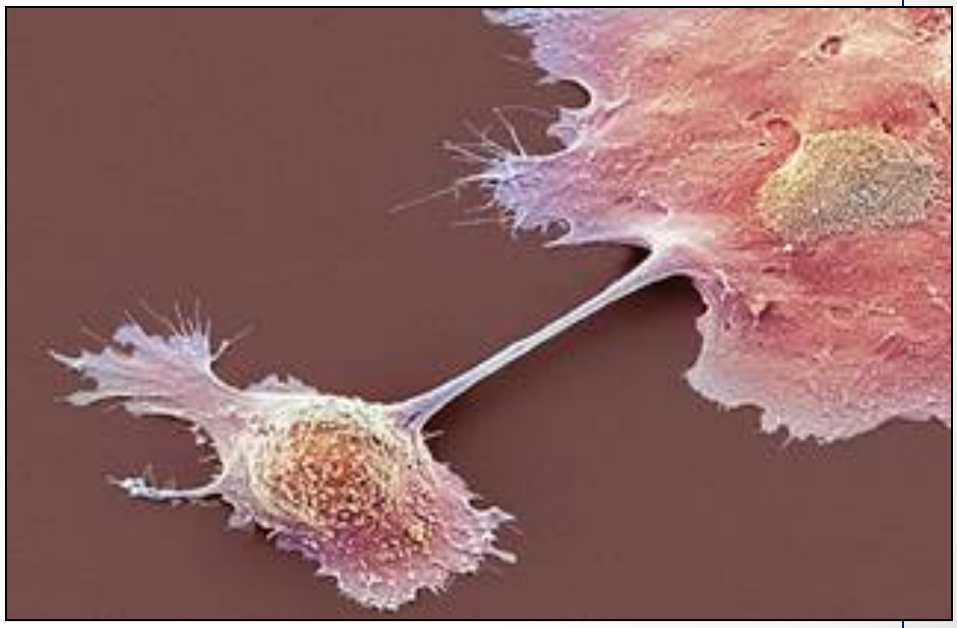
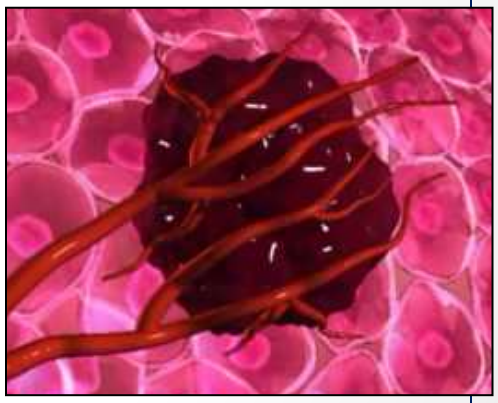
Introduction

- NETs in children
- Screening
- Family trees
- MEN1
- MEN2a
- MEN2b
  - FMTC
  - Phaeochromocytomas and Paragangliomas
- VHL
- Case study



Neuroendocrine tumours in children

- Relatively rare amongst children
- Majority occur sporadically and are non-hereditary
- Despite this, carcinoid tumours may also be associated with hereditary syndromes
- Most endocrine tumours in children
  - Clinically benign
  - Low grade malignancies
- NETS
  - Known for late diagnoses
    - Liver or bone metastases
    - Multi year history of symptoms before malignancy identified
  - Few reports in children
    - At least 10% of children have metastatic disease at presentation

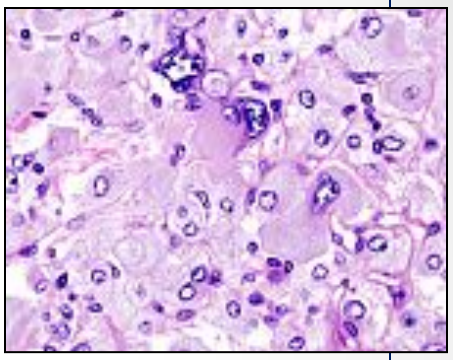


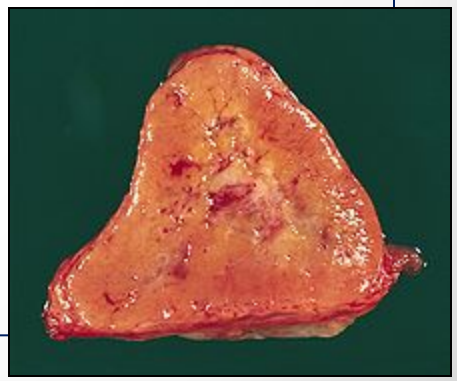
Distribution of NETS in children and young adults <30 years

Tumour type	Percentage of NET in this age group
Bronchial NET	28
Medullary carcinoma of the breast	18
Appendiceal NET	18
Colon and rectal NET	9
Jejunal and ileal NET	5
Small cell carcinoma (ovary)	5
Unknown primary NET	5
Pancreatic and gastric NET *	4
Medullary carcinoma thyroid *	4
Small cell carcinoma (cervix)	4

Other NETs

- Phaeochromocytoma
  - MEN 2A
  - MEN 2B
  - VHL disease
  - NF1
  - Peak incidence between 9 -12 years of age
    - Nearly 10% occur in children
    - 10% of these are malignant
- Paraganglioma
  - Extra adrenal in origin
  - Parasympathetic nervous system



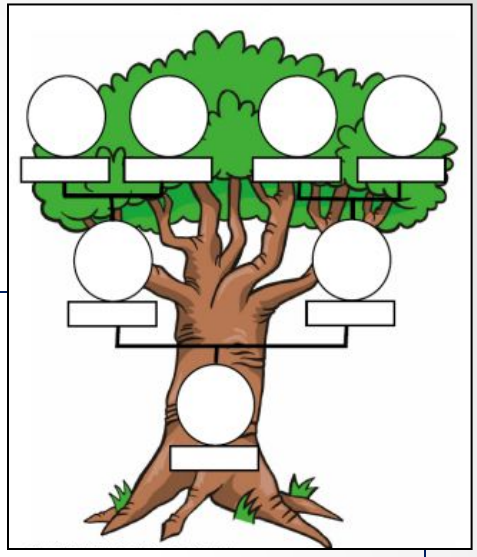


Screening

- MEN 1 & 2 and VHL
  - Autosomal dominant
    - Only one mutation in one pair of genes is needed to cause the condition
    - 50% chance of having a boy or a girl with the same condition
  - Most commonly present in early adulthood and onwards
  - Can now target individuals at risk
  - Genetic screening allows the children from affected families who have NOT inherited the mutation
    - Reassured
    - Avoid regular clinical monitoring
    - Issues re: Informed consent, counselling and confidentiality

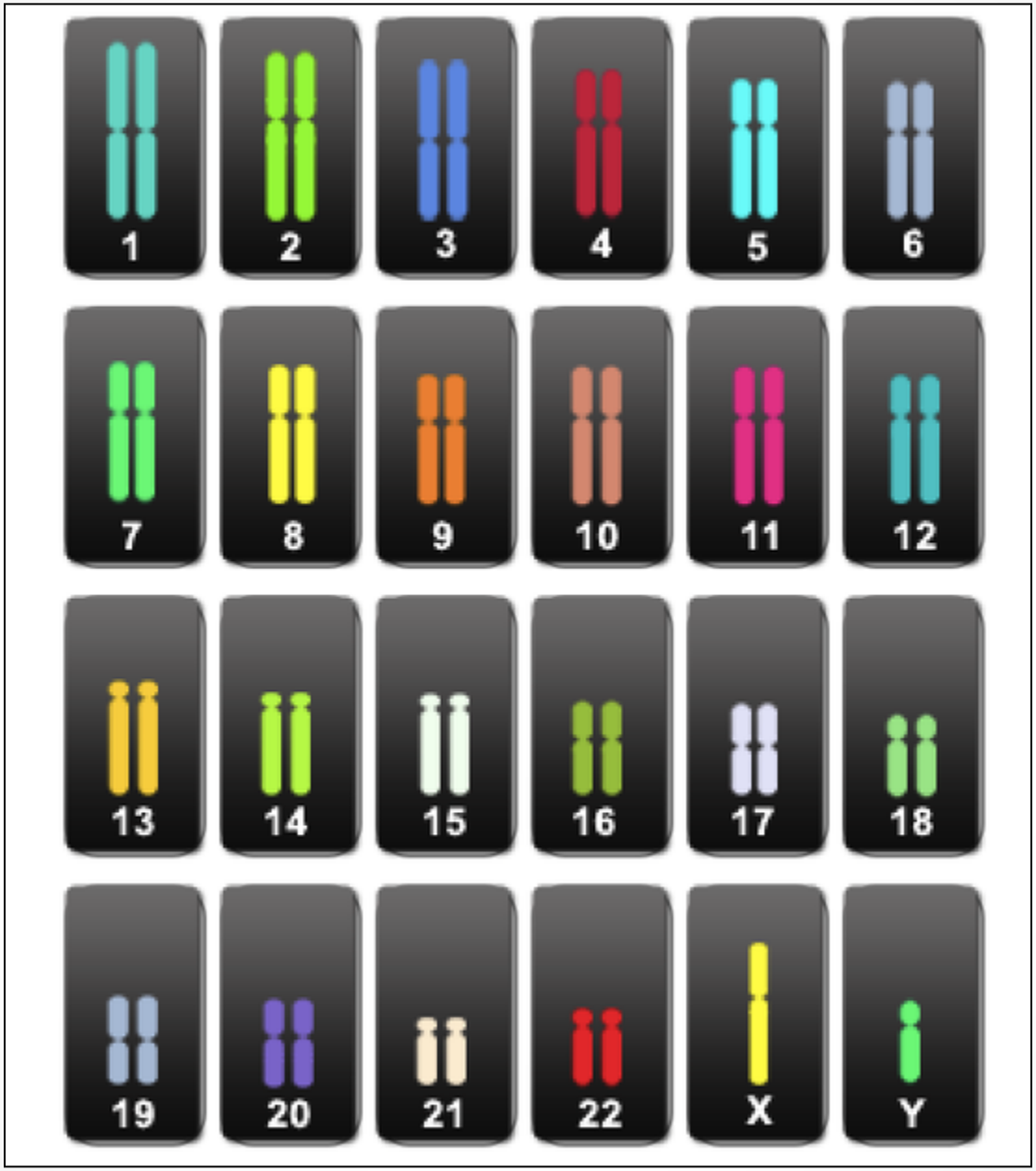
TYPE	SYSTEM	CLINICAL / BIOCHEMICAL	RADIOLOGY	AGE TO START	FREQUENCY
MEN-1	Parathyroid	Serum calcium (parathyroid hormone)		10-15 yrs	Annual
	Pancreas	Pancreatic polypeptide, Gastrin	US pancreas	10-15 yrs	Annual
			MRI pancreas	10-15 yrs	3 yearly
	Pituitary	Prolactin, IGF-1		10-15 yrs	Annual
			MRI pituitary	10-15 yrs	5 yearly
MEN-2	Thyroid	*(mutation known)* Prophylactic thyroidectomy		5 yrs	
		(mutation not yet known) Pentagastrin test for calcitonin		5 yrs	Annual
	Adrenal (*phaeochromocytoma*)	Blood pressure 24-hour urine collections (x3) – catecholamines (*plus corresponding serum metanephrines*)	US adrenals	5 yrs	Annual
			MRI adrenals	5 yrs	3 yearly
	Parathyroid	Serum calcium		10 yrs	Annual
VHL	Eyes	Fundoscopy	Fluorescein angiography	5 yrs	Annual
	CNS	Full examination		10 yrs	Annual
			MRI brain & spinal cord	10 yrs	3 yearly
	Renal	Abdonimal examination	US kidneys	5 yrs	Annual
			MRI kidneys	5 yrs	3 yearly
	Adrenal (*phaeochromocytoma*)	Blood pressure 24-hour urine collections (x3) – catecholamines (*plus corresponding serum metanephrines*)	US adrenal	5 yrs	Annual
			MRI adrenals	5 yrs	3 yearly
FPS	Cervical chain/ carotid bodies	Examination	US head and neck	10-15 yrs	Annual
	Adrenal	Blood pressure 24-hour urine collections (x3) – catecholamines (*plus corresponding serum metanephrines*)	US adrenals	8-10 yrs	Annual
	Parasympathetic chain		MRI chest/abdo/pelvis	8-10 yrs	Annual

Family trees



- Biological relationships between family members
- Any medical conditions
  - Reveal patterns of inheritance
  - Assesses likelihood of genetic diseases in relatives
  - Individuals can then be offered targeted surveillance

  Including children
- Builds rapport with patients
  - Develop trust, to ask questions
  - Correct any misconceptions about symptoms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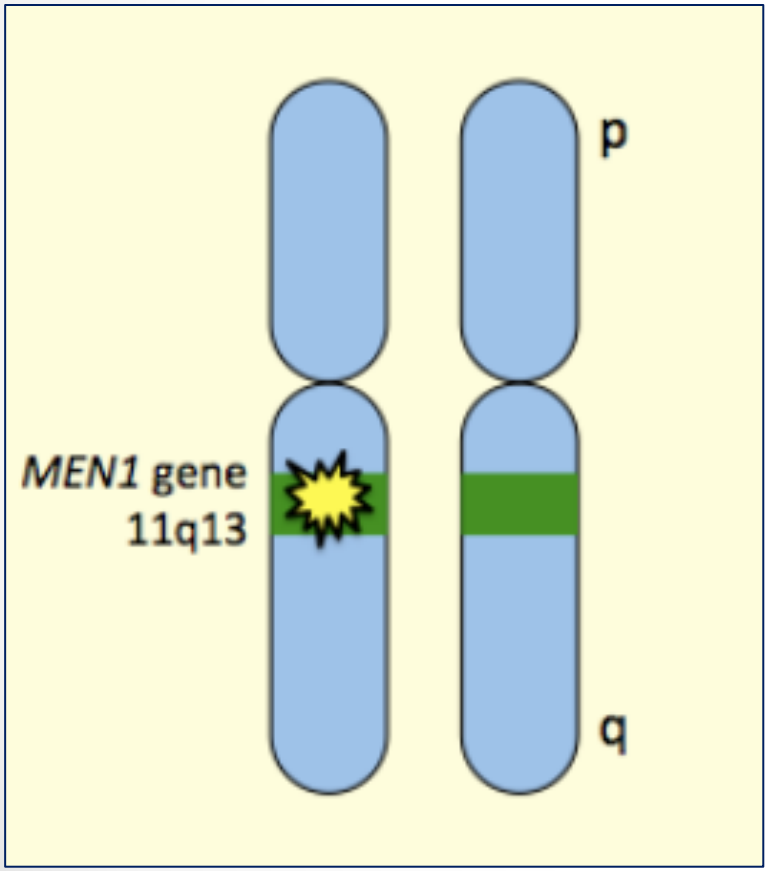
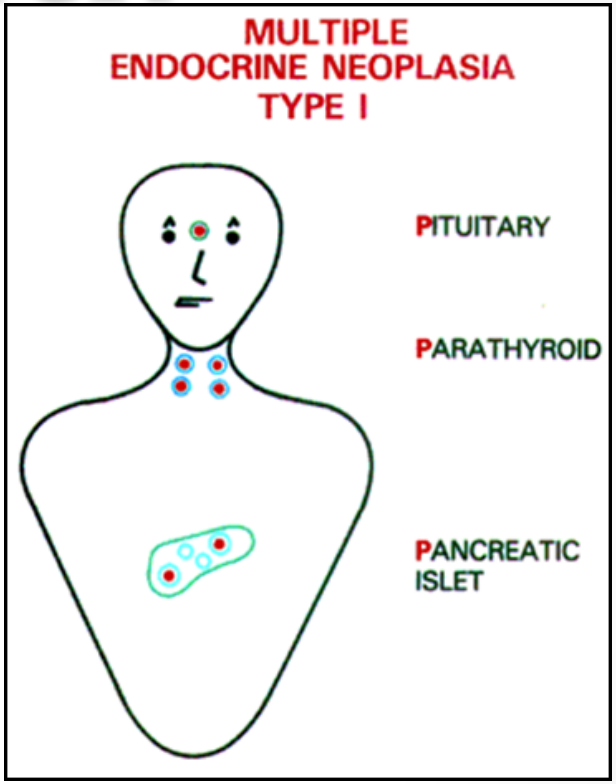
MEN 1



- Parathyroid tumours
  - 90% of MEN1 patients
- Pituitary tumours
  - 30% of MEN1 patients
- Pancreatic Islet cell tumours
  - 75% of MEN1 patients
- Carcinoid tumours
  - Chest / stomach
  - Lipomas
  - Thyroid
  - Adreno-cortical tumours

MEN 1 screening in children

- Children of an identified MEN1 patient
  - Screened genetically initially
  - Screened clinically from age 10
    - Annual measurements
      - Calcium, PTH
      - Pancreatic polypeptide and gastrin
        - Imaging
      - Prolactin, IGF-1
        - Imaging



TYPE	SYSTEM	CLINICAL / BIOCHEMICAL	RADIOLOGY	AGE TO START	FREQUENCY
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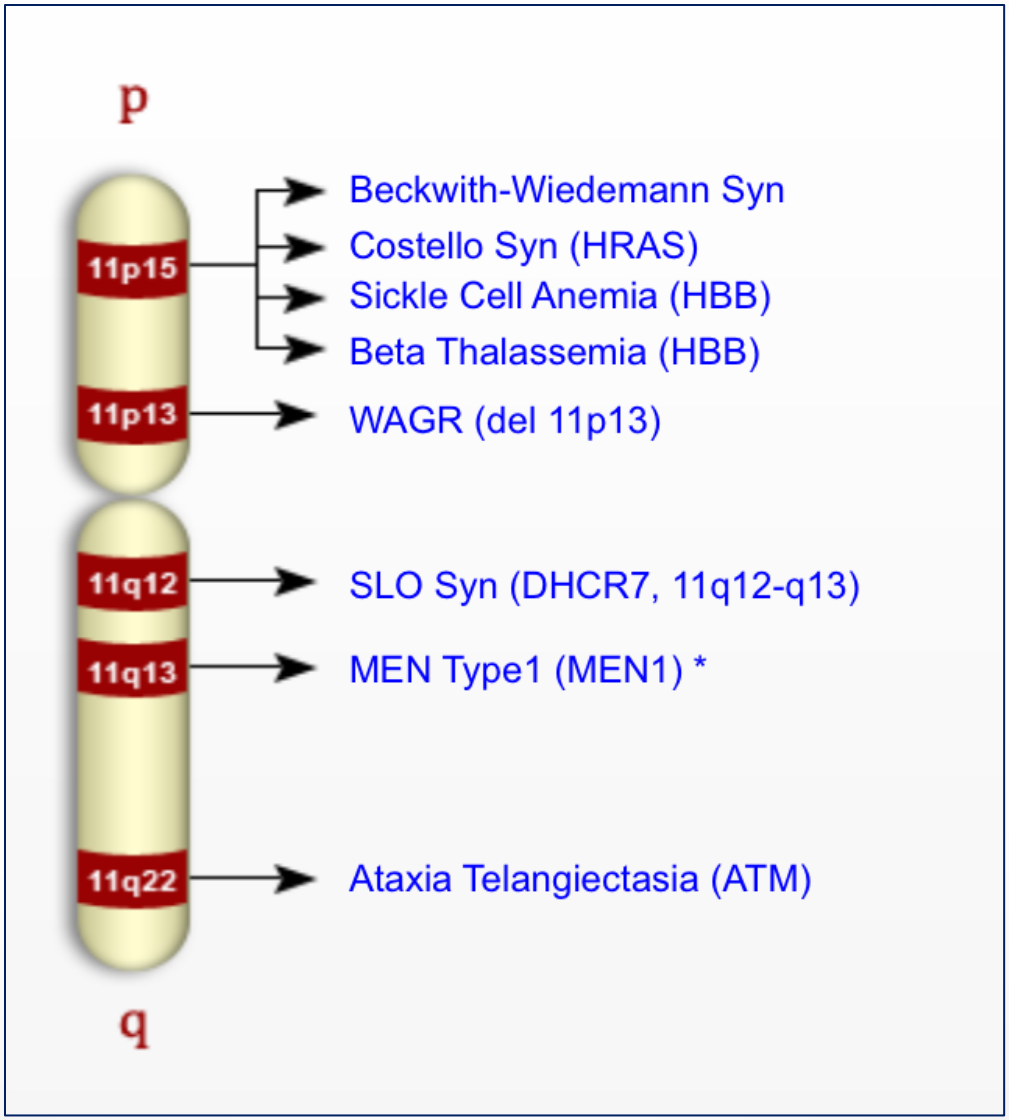
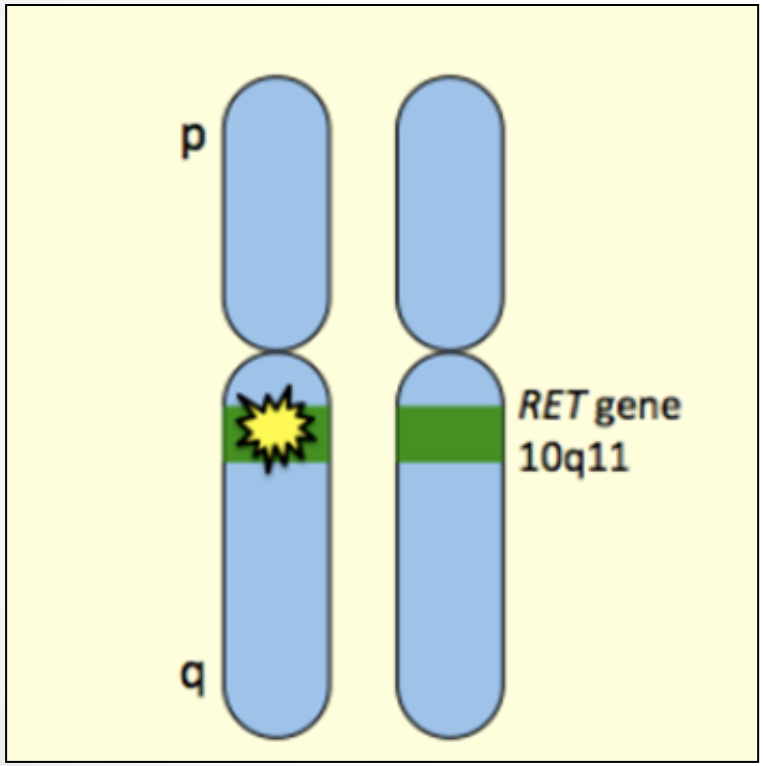
			MRI pancreas	10-15 yrs	3 yearly
	Pituitary	Prolactin, IGF-1		10-15 yrs	Annual
			MRI pituitary	10-15 yrs	5 yearly

Chromosome 11



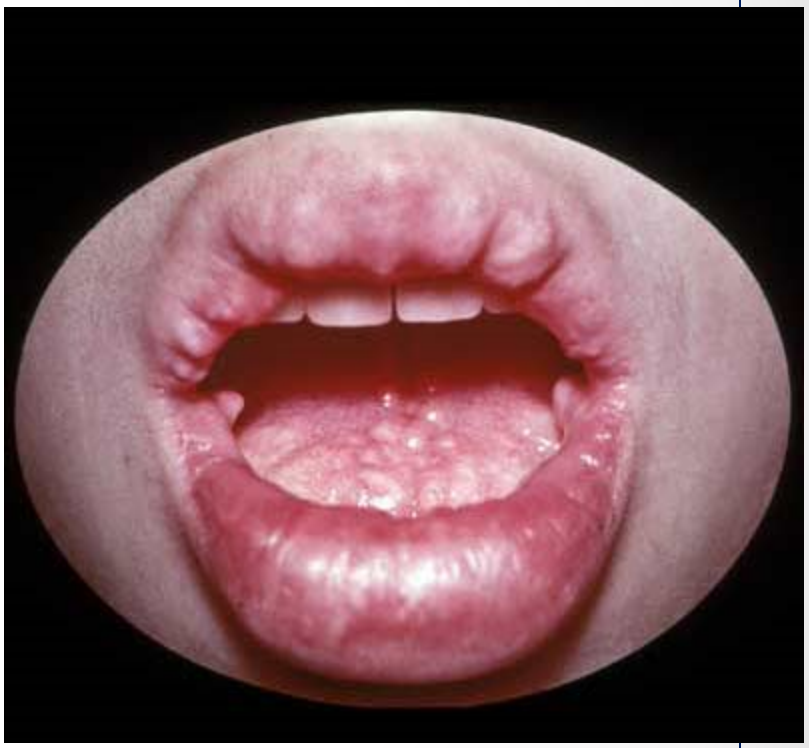
MEN 2a

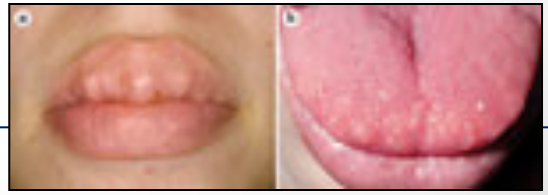


- Thyroid gland
  - MTC
  - Child with a known MEN2a gene change
    - Total thryoidectomy before age of 5yrs
  - Newly diagnosed adults
    - Screen children asap
- Parathyroid glands
- Adrenal glands
  - Phaeochromcytomas
    - 24hr urine collections

MEN 2b

- Thyroid gland tumours
- Phaeochromocytomas
- Benign lumps on the lips, in the mouth and throughout the gut
  - Children
    - More likely to have feeding problems, bowel problems
      - Present with FTT



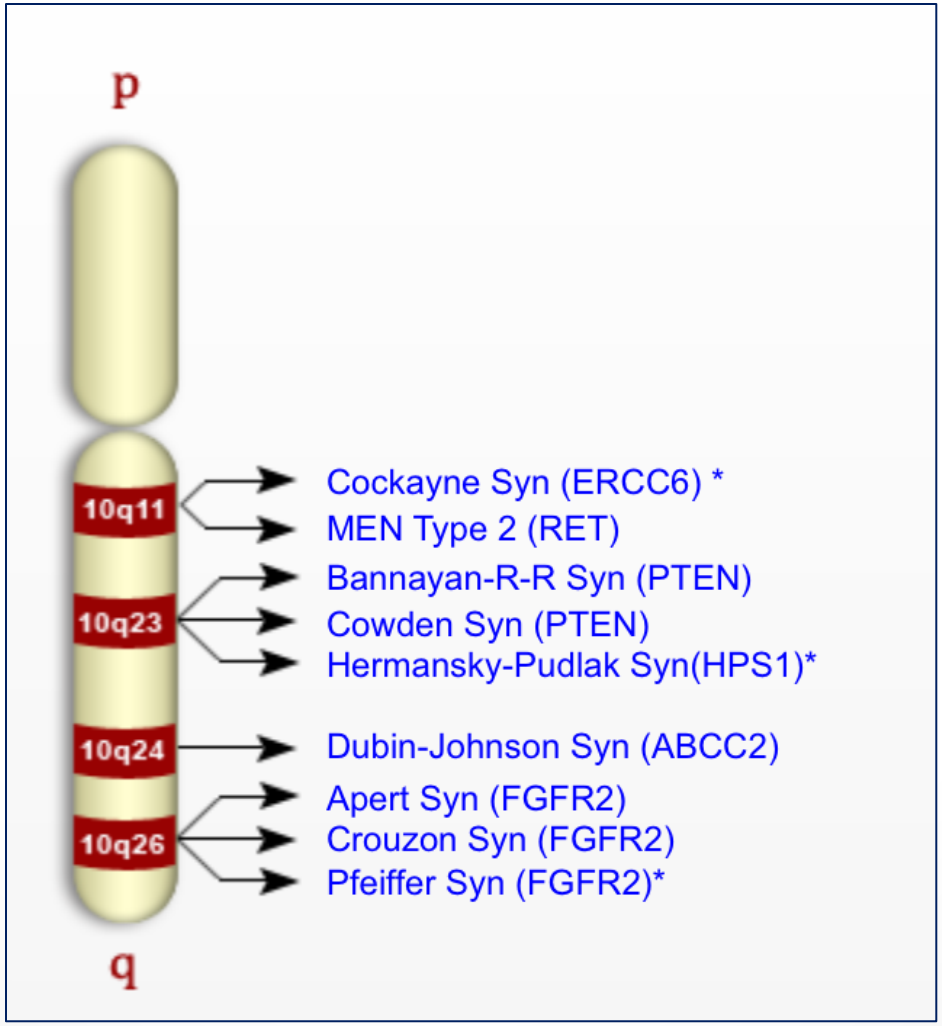


MEN 2 screening

- Screened genetically
  - MTC assoc with MEN2b
    - Can occur in first year of life
  - MEN2b – age 1yr
  - MEN2a – age 5yrs
- Clinical screening
  - Thyroid
  - Adrenal

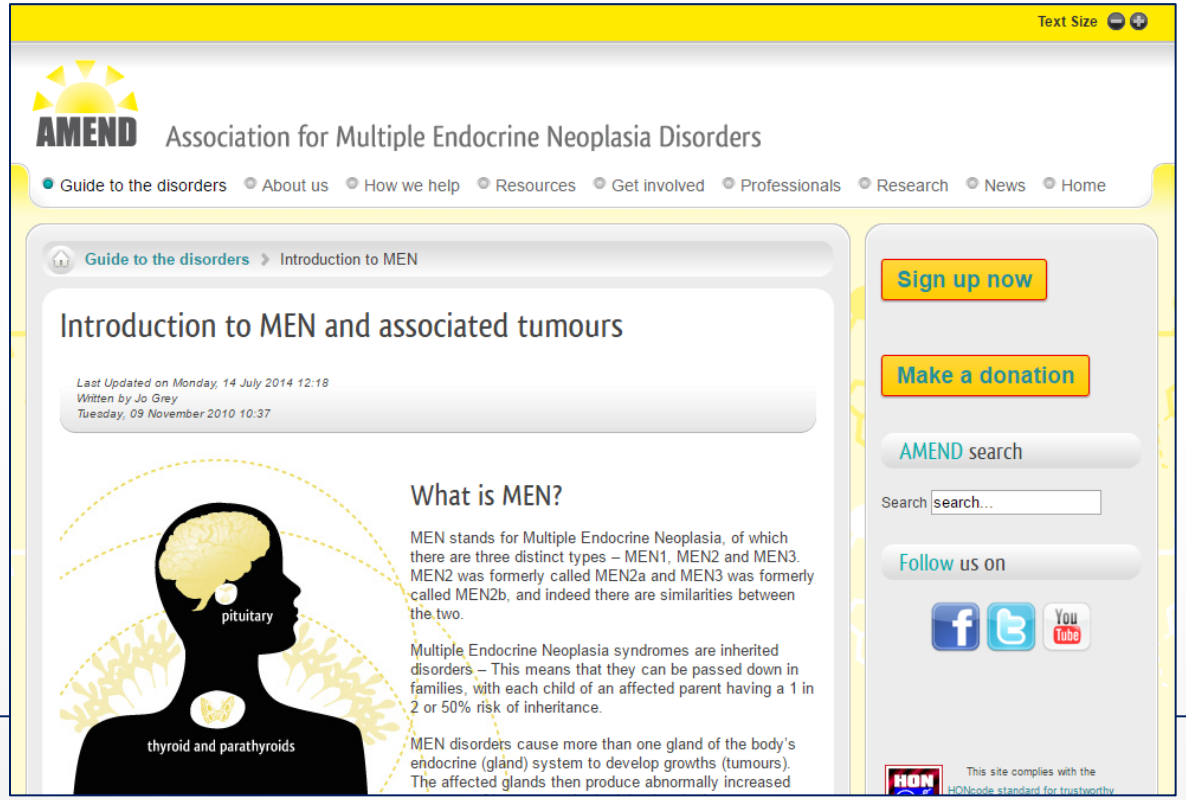
MEN-2	Thyroid	*(mutation known)* Prophylactic thyroidectomy		5 yrs	
		(mutation not yet known) Pentagastrin test for calcitonin		5 yrs	Annual
	Adrenal (*phaeochromocytoma*)	Blood pressure 24-hour urine collections (x3) – catecholamines (*plus corresponding serum metanephrines*)	US adrenals	5 yrs	Annual
			MRI adrenals	5 yrs	3 yearly

Chromosome 10



Patient support

- AMEND
  - UK Patient support group
  - www.amend.org.uk



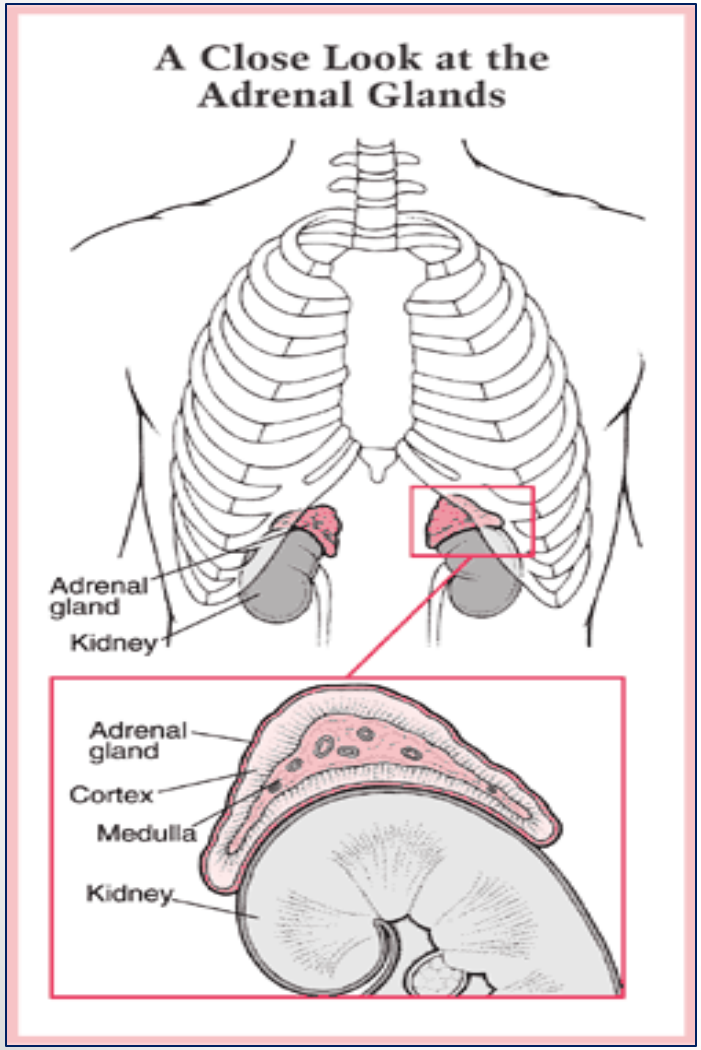
Children's area

Daniel has MEN1 and Lisa has MEN2. With the help of their pet cats and animated friends, they explain their conditions simply.


SUPERHERO ADVENTURE INSIDE THE HUMAN BODY!
MEDIKIDZ
EXPLAIN
MULTIPLE ENDOCRINE NEOPLASIA TYPE 1
SUPERHERO ADVENTURE INSIDE THE HUMAN BODY!
MEDIKIDZ
EXPLAIN
MULTIPLE ENDOCRINE NEOPLASIA TYPE 2

Phaeochromocytomas

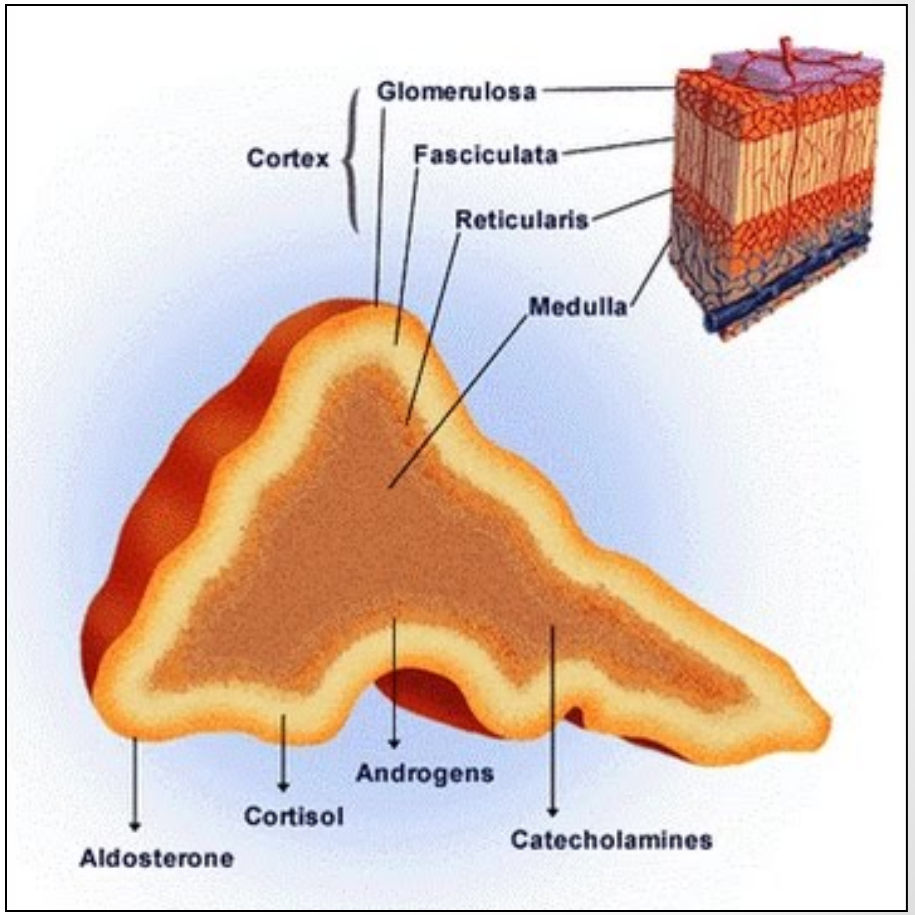
Adrenal Gland A & P



- Adrenal cortex
  - Outer portion
- Adrenal medulla
  - Inner portion

Adrenal Cortex

- Mineralocorticoids
  - ALDOSTERONE
    - Helps regulate BP by controlling how much salt is retained in the body
- Glucocorticoids
  - CORTISOL
    - The body's natural steroid, 3 main functions:
      - Helps control the blood sugar level
      - Helps the body deal with stress
      - Helps to control BP and blood circulation
- Sex Steroids / Androgens
  - DHEA
  - DHEA-S
  - Androstenedione
    - Secondary sexual characteristics

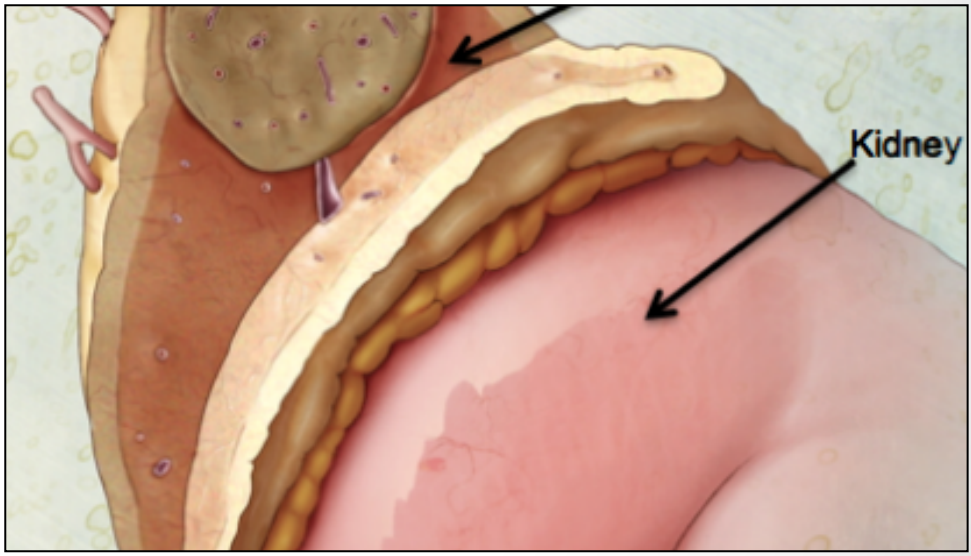


Adrenal Medulla

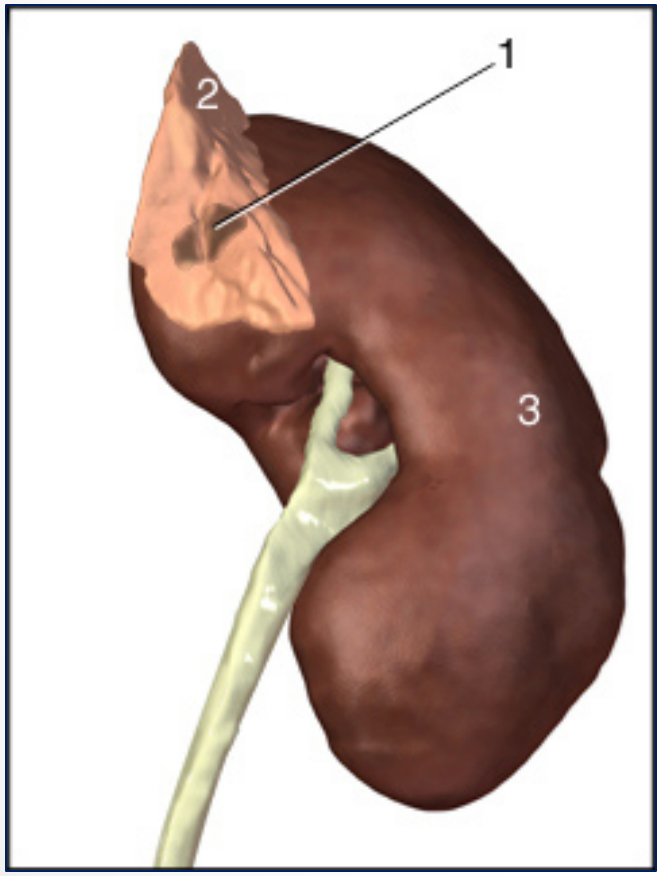
- Catecholamines
  - Adrenaline
    - Released in response to signals from the sympathetic nervous system
    - Increases
      - Blood sugar
      - Muscle glycogen breakdown
      - Blood flow to muscle
      - Respiration
  - Noradrenaline
    - Similar effects to adrenaline, as well as maintains BP
  - Dopamine
    - Precursor to adrenaline and noradrenaline
      - Neurotransmitter

Phaeochromocytoma

- Neuroendocrine tumour
- Usually benign, *can* be malignant
- Excretes excess catecholamines
- Uncommon cause of ↑ BP ∴ can easily be missed
- We have occasional bursts of cats when we are upset or stressed
  - Those with phaeos have it all the time



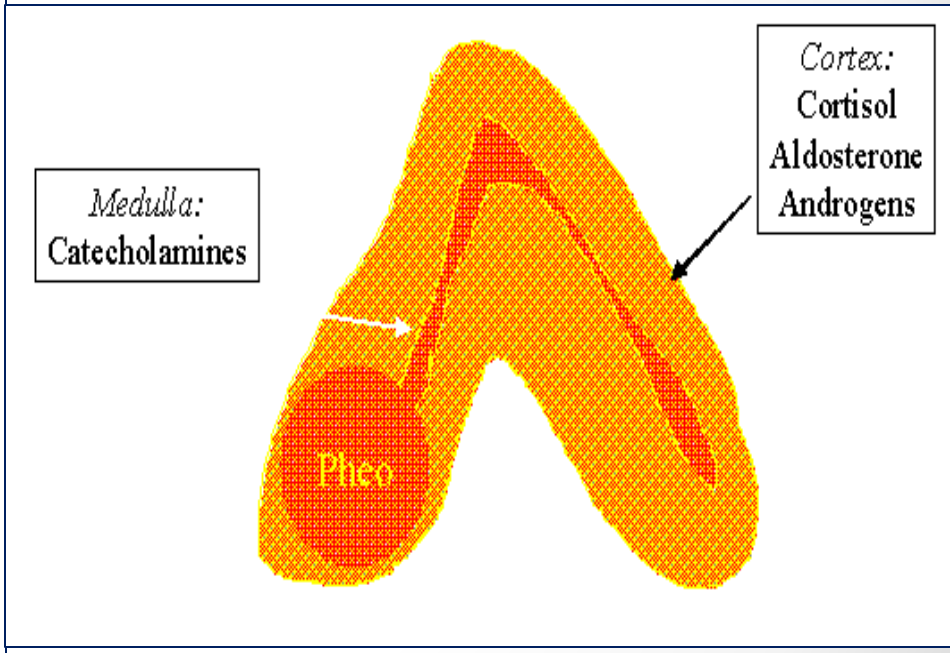
Phaeochromocytoma



- Only present in 10% of VHLs
- French study in the 90s
  - Phaeos were the first manifestation of VHL disease in 51% of pts
  - Only manifestation for up to age 21 yrs, or even indefinitely
- Easy to miss the diagnosis
- *Usually* arise in the adrenals, may also originate in paraganglia outside the adrenals

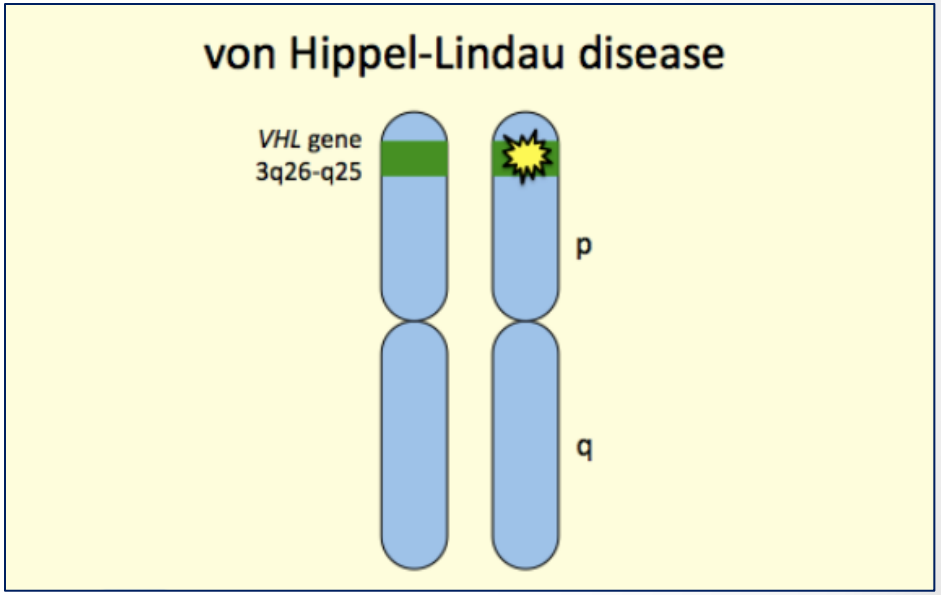
Phaeochromocytoma

- Symptoms ?
  - ↑BP
  - Headache
  - Perspiration / episodic sweating
  - Palpitations
  - Anxiety attacks
    - May be incorrectly attributed to anxiety or depression
- Can cause life threatening conditions
  - Hypertensive crisis
  - Mets - Stroke
  - Cardiac failure - MI



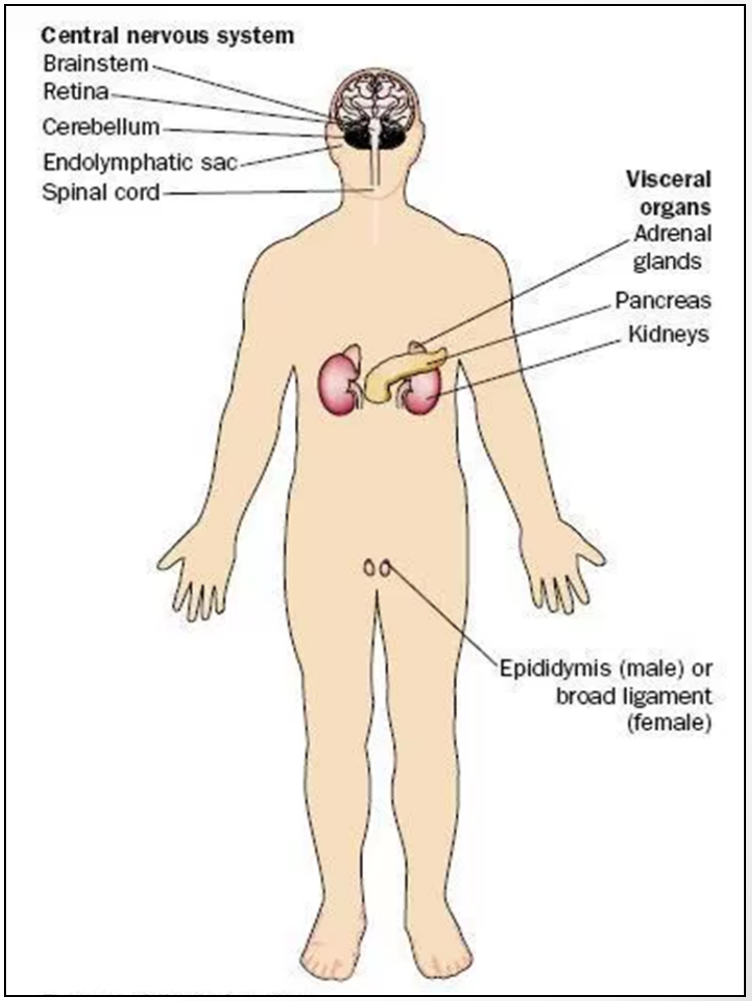
Von Hippel-Lindau disease

- Chromosome 3
- Tumour suppressor gene
- Can identify the gene
  - Pre-symptomatic screening
- Autosomal dominant
  - Each child of an affected individual has a 1 in 2 chance (50%) to inherit the gene alteration
- Children referred
  - Fellow adult endocrine teams managing in their affectedparent

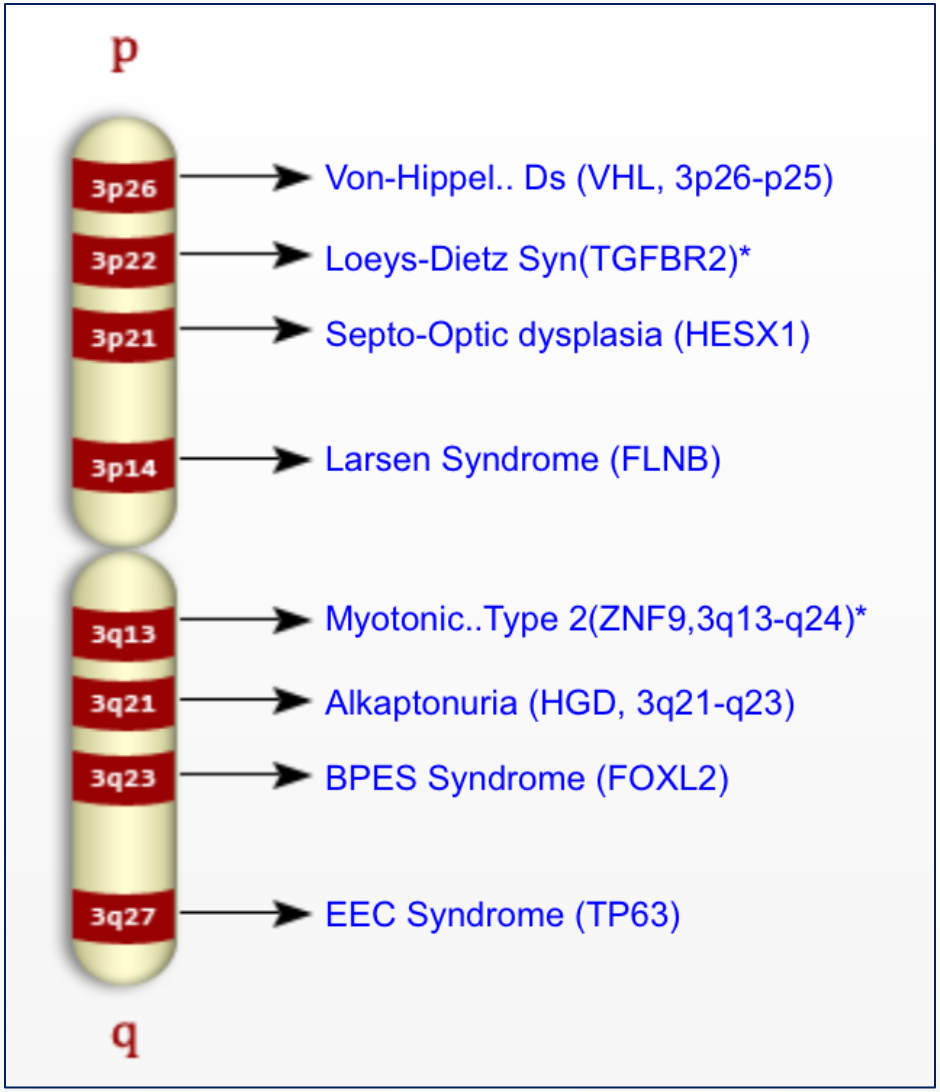


Von Hippel Lindau disease

- Incidence
  - 1 in 40,000
  - Average age of presentation
    - 26 yrs of age
- Haemangioblastomas
  - Brain, spinal cord, retina
- Renal cysts
- Phaechromocytomas



Chromosome 3



Screening in VHL

- Genetics
  - Analysis of the index case is key to identifying further members of the family at risk
  - Can be done from age 5yrs
    - Enable clinical screening

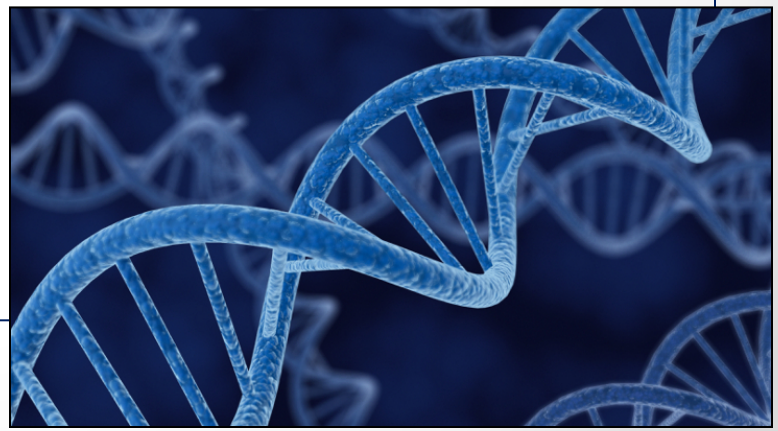
Reduction in morbidity compared to their parents

- Ophthalmology review
  - Fundoscopy screening
- Adrenals
  - Phaeochromocytomas
- Renal carcinomas
  - Now leading cause of death amongst VHL patients
    - Successful treatment for CNS haemangioblastomas
    - Imaging

VHL	Eyes	Fundoscopy	Fluorescein angiography	5 yrs	Annual
	CNS	Full examination		10 yrs	Annual
			MRI brain & spinal cord	10 yrs	3 yearly
	Renal	Abdonimal examination	US kidneys	5 yrs	Annual
			MRI kidneys	5 yrs	3 yearly
	Adrenal (*phaeochromocytoma*)	Blood pressure 24-hour urine collections (x3) – catecholamines (*plus corresponding serum metanephrines*)	US adrenal	5 yrs	Annual
			MRI adrenals	5 yrs	3 yearly

Case study

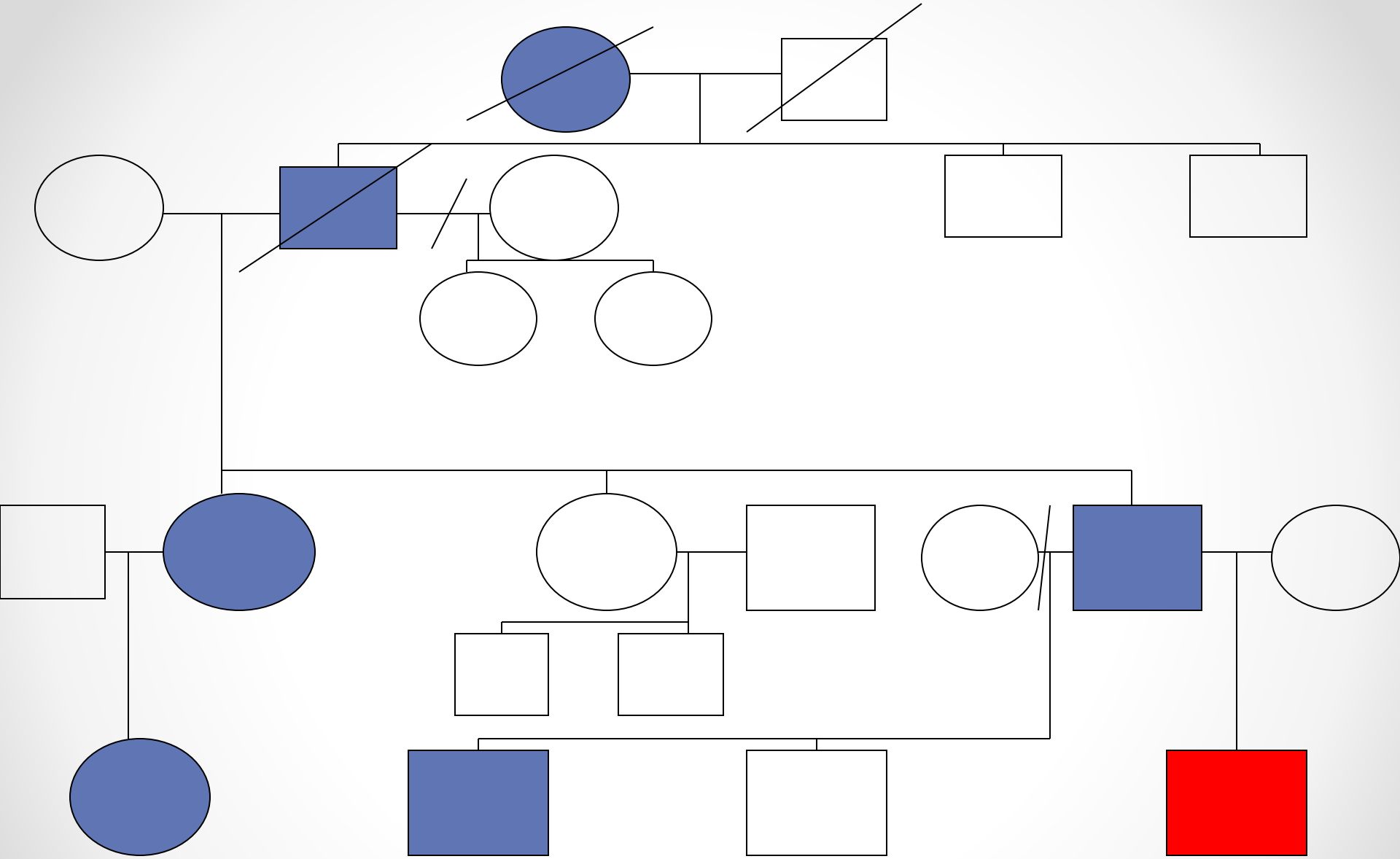
- Male child Tom
- DOB 10.11.01
- Family history of VHL
- Positive for the familial mutation in exon 3 of the VHL gene
- Commenced screening programme
  - 2006 age 5yrs



Family history

- Father
  - Retinal angiomatosis
  - Bilateral phaechromocytomas 23yrs
  - Cervical spine haemangioblastoma 33yrs
  - Bilateral renal cell carcinomas 34 7 35yrs
- Half-brother
  - Right phaechromocytoma age 14yrs
    - 3 year old son

- Paternal aunt
  - Bilateral phaechromocytomas 7 and 21yrs
  - Cerebral haemangioblastoma 16yrs
  - Retinal haemangioblastoma 18yrs
  - Right renal carcinoma 28yrs
  - Pancreatic NET 36yrs
- Cousin (female)
  - Bilateral phaechromocytomas 12yrs and 14yrs
  - Pancreatic NET 19yrs
- Brother
  - Age 3yrs

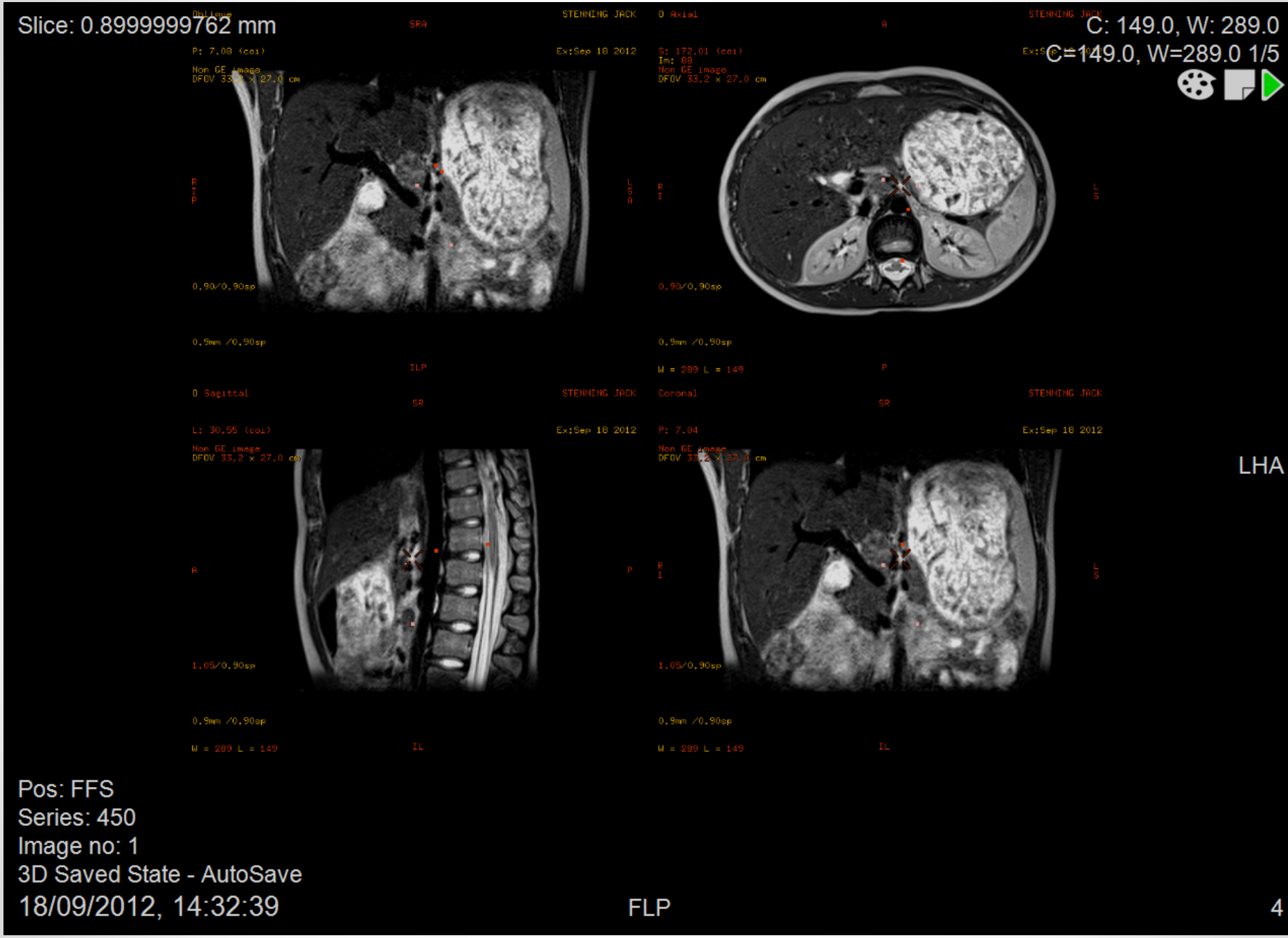


Clinical screening

- 2007, 2008, 2009
  - All normal
- 2010
  - January
  - Urine catecholamine (noradrenaline) slightly elevated
    - 370nmol/day (N=below 194)
  - Repeat and watch as asymptomatic
  - May
    - 433nmol/day
  - June
    - MRI adrenal normal
  - October
    - 372nmol/day
- 2011
  - February
    - 477nmol/day
- 2012
  - Lesion seen on abdominal MRI
  - Repeat MRI with contrast
  - MIBG scan

MRI Abdomen 12.10.12

- Review of imaging for endocrine VHL MDT 31.10.2012
- There is a 3cm MIBG positive paraganglioma in the upper retroperitoneum interposed between in the aorta, IVC and portal vein. No local invasion seen. Slow increase in size since 2008.
- Small areas of soft tissue in the distal aorto-caval region but these are currently indeterminate.
- Normal kidneys, adrenals and pancreas
- Excision of paraganglioma January 2013, age 11yrs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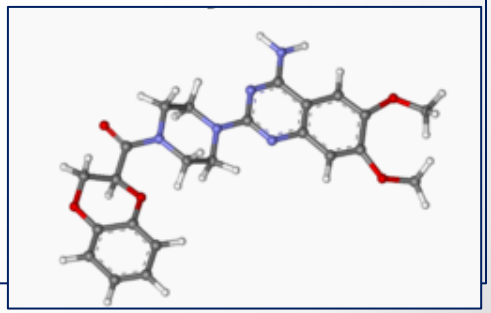
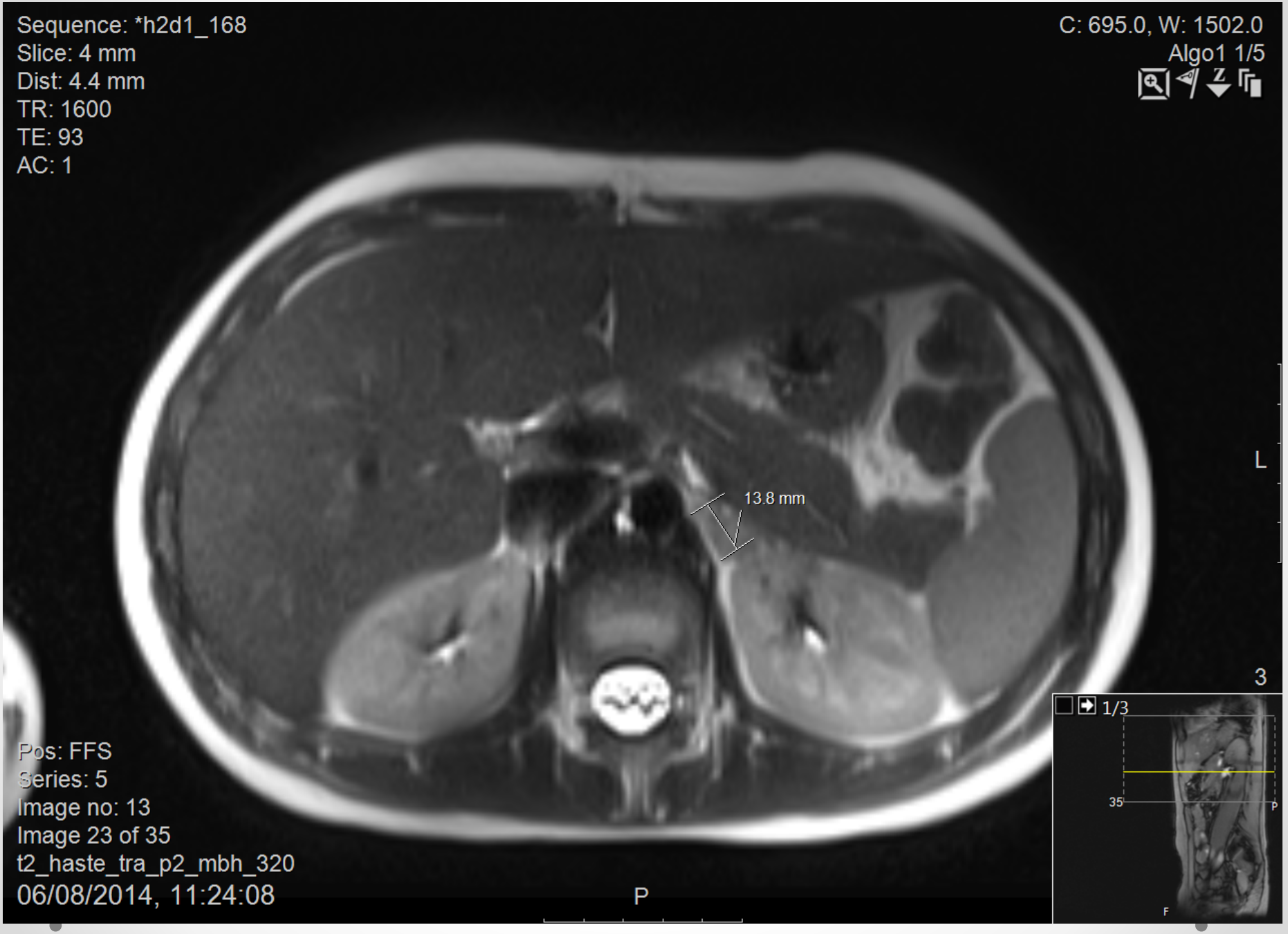
Clinical management

- April 2012
  - Paraganglioma
    - Small
    - No plans for surgery
    - Intermittent symptoms and continued raised catecholamines
    - Commence Doxazocin 0.5mg once daily
      - Increase to twice a day after a week if tolerated
      - Continue until surgery planned
  - Doxazocin
    - Alpha blockade
      - Reduces BP



MRI Abdomen 6.8.14

- New 9mm peripherally enhancing left adrenal nodule which demonstrates restricted diffusion likely to represent a small phaechromocytoma.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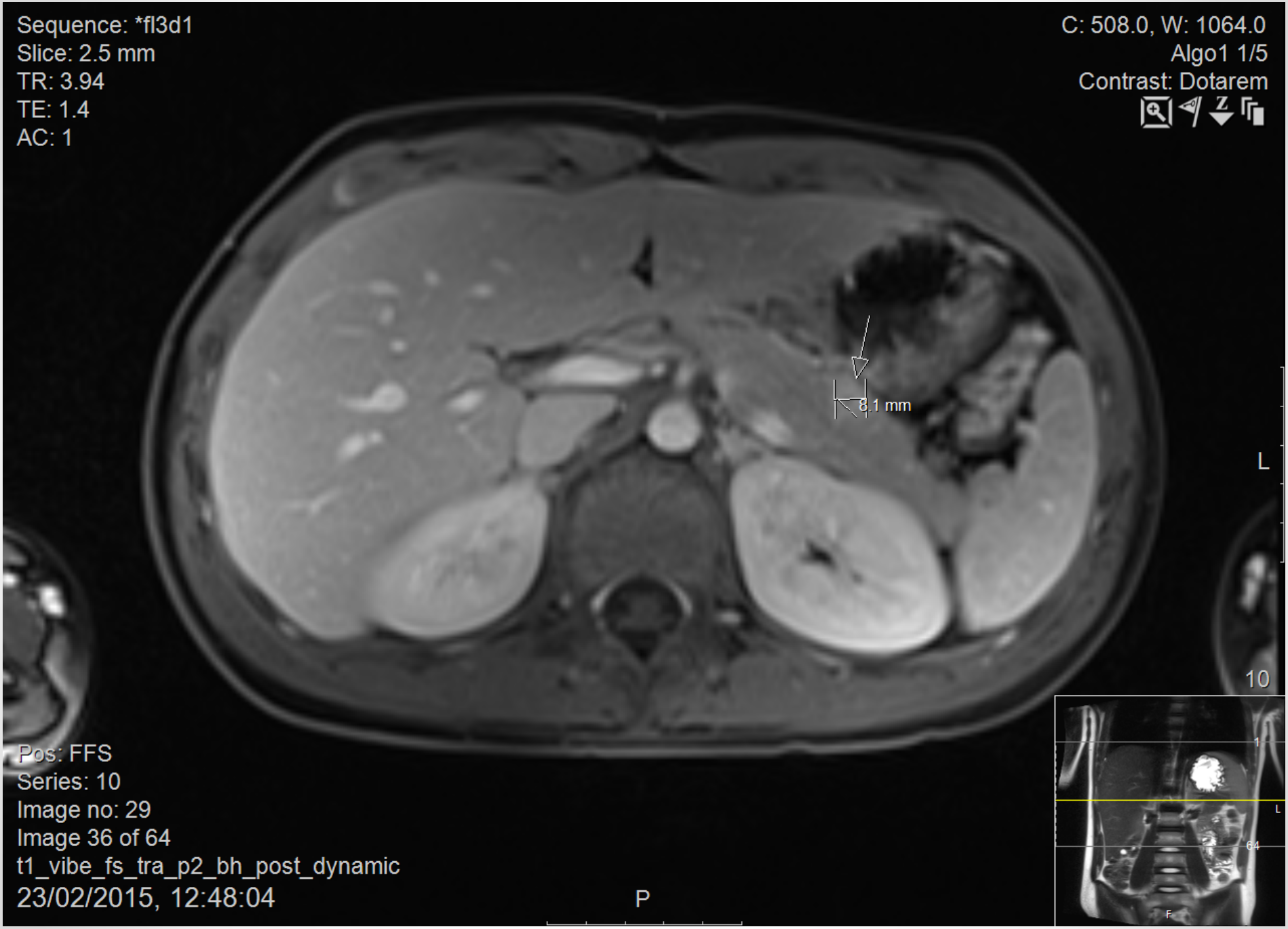
Clinical management

- 2014
  - November age 13yrs
    - Now wants to be seen without his Mum
    - ? Phaeochromocytoma
    - Tom very stressed and upset
    - Psychological input offered
- 2015
  - Further imaging..

MRI Pancreas 23.2.15

- The anterior lesion in the tail of the pancreas is still present and demonstrates an arterial blush.
- This remains suggestive of an islet cell tumour.
- No other pancreatic lesion is demonstrated.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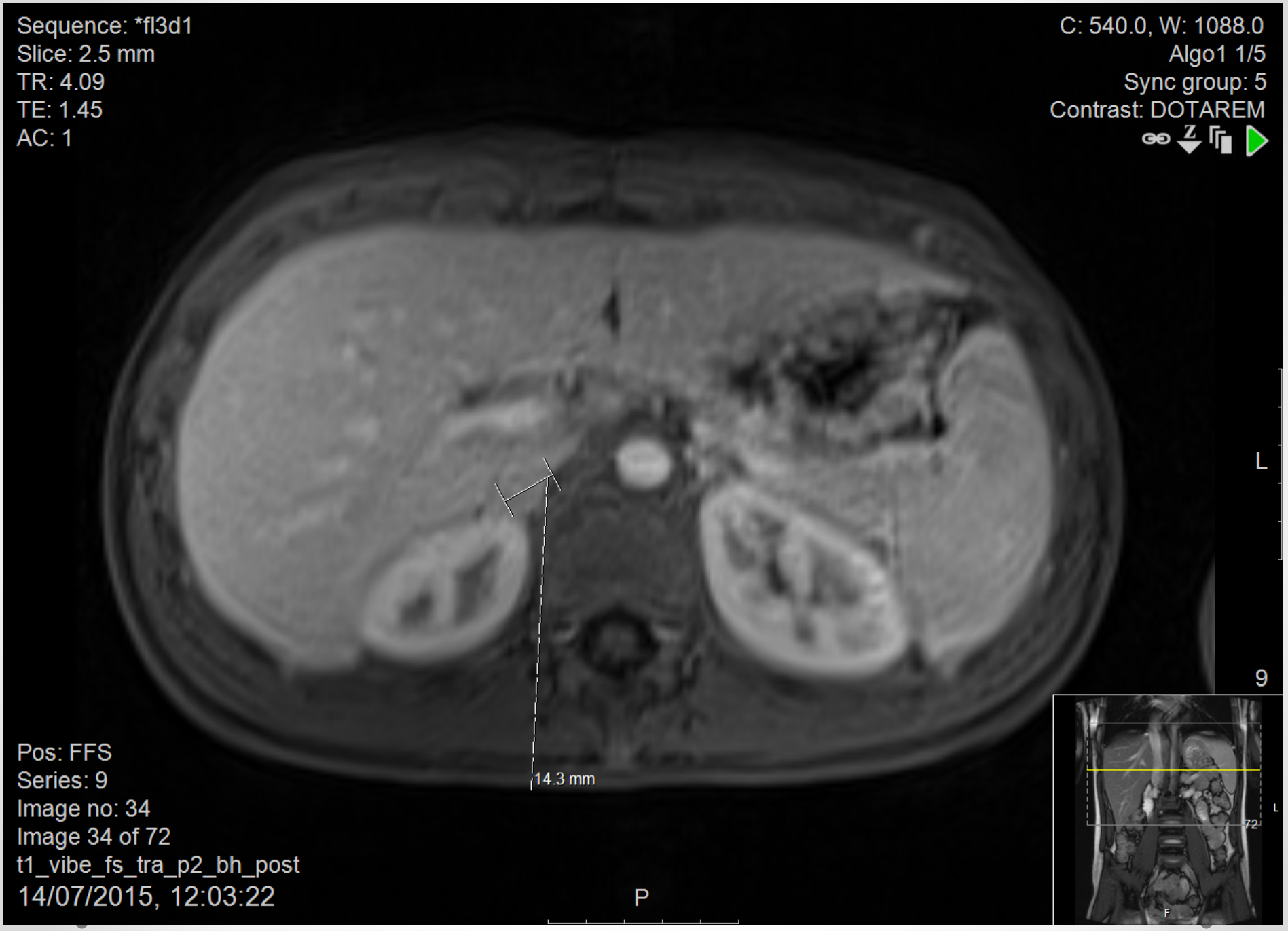
MRI adrenals 14.7.15

- The right adrenal mass in the body of the adrenal has further increased in size now measures 13 mm.
- The left adrenal nodule in the lateral limb is stable measuring 15 mm.
- Both lesions have similar properties and the appearances are in keeping with small phaeochromocytomas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Algo1 1/5
Sync group: 5
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L
9
14.3 mm
Pos: FFS
Series: 9
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Image 34 of 72
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14/07/2015, 12:03:22
P
72
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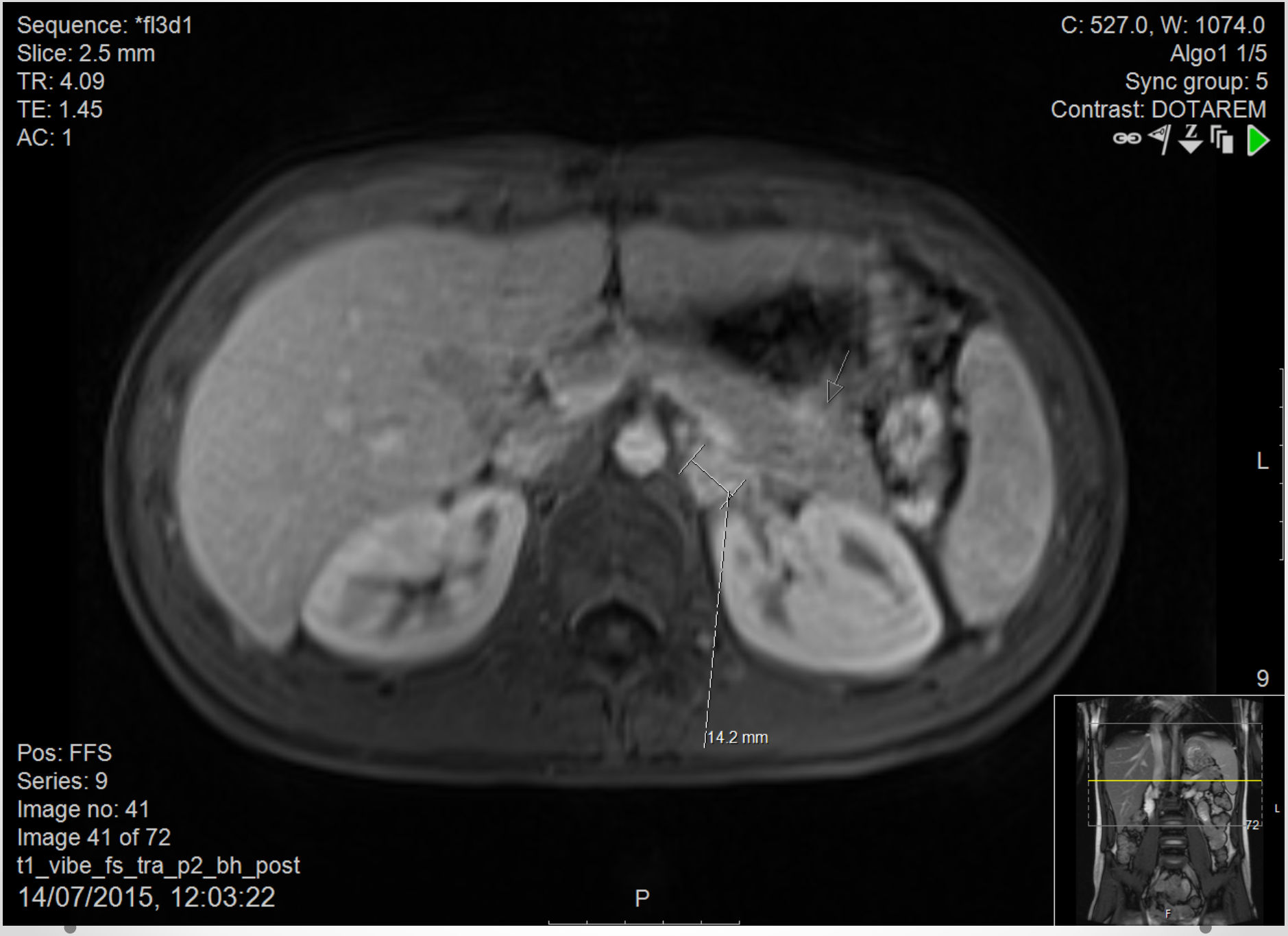
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Sync group: 5
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L
9
14.2 mm
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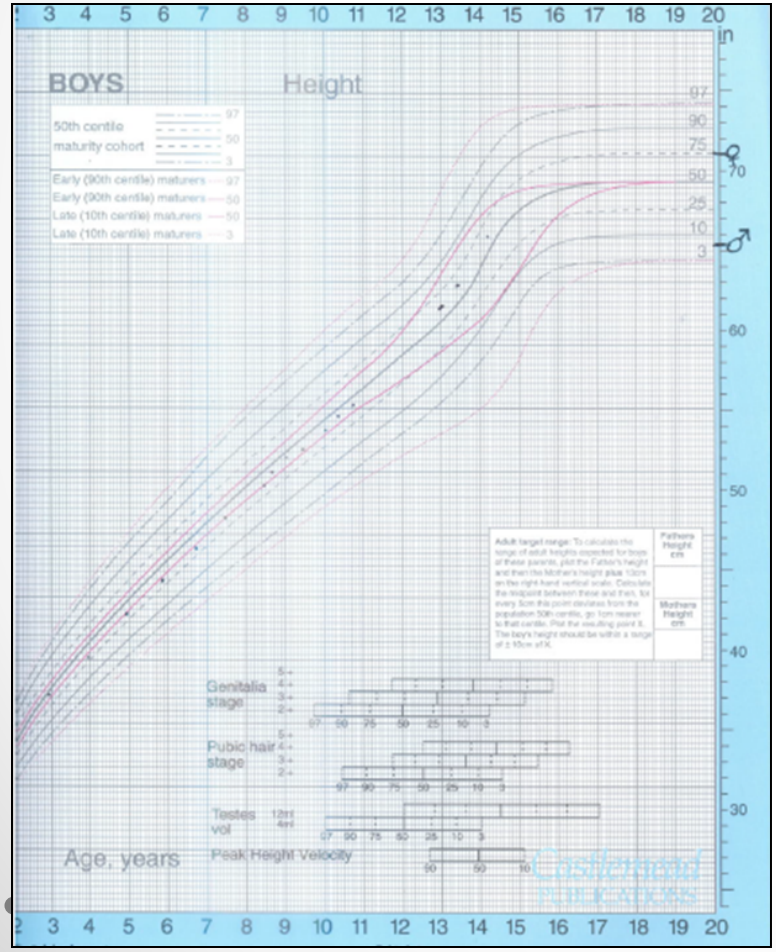
Series: 9
Image no: 41
Image 41 of 72
t1_vibe_fs_tra_p2_bh_post
14/07/2015, 12:03:22
P
72
F
L

Continued management

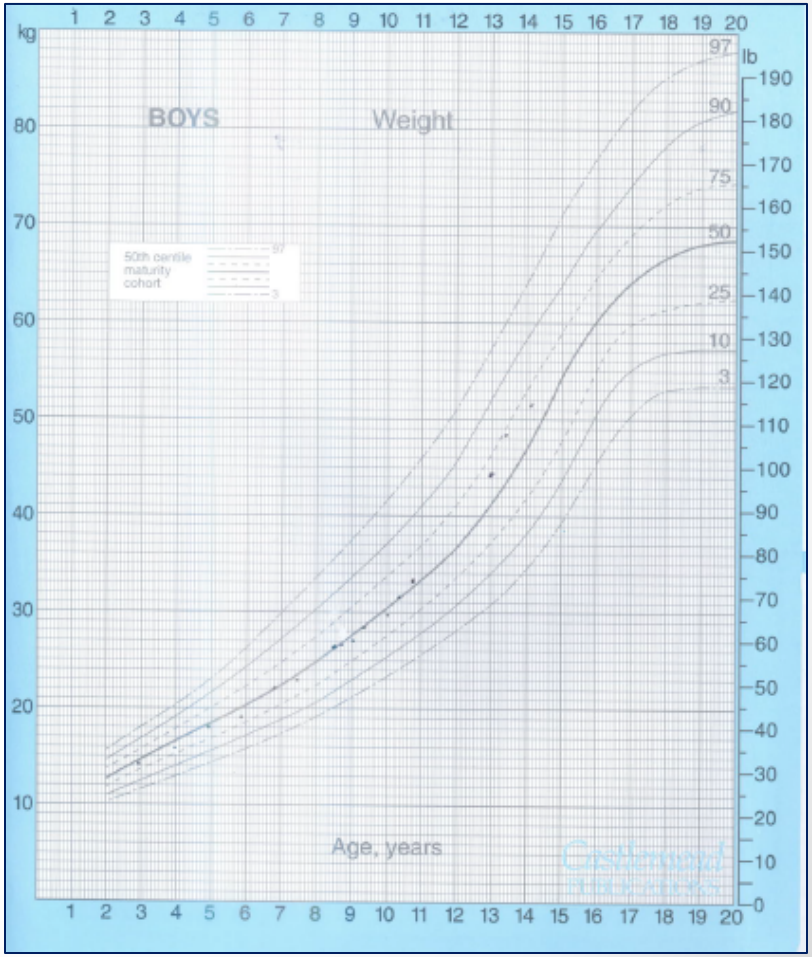
- 2015
  - July
  - Bilateral phaeochromocytomas
  - Now proceed to surgery
  - December had surgery
- 2016
  - April – surgical follow up
  - As you know he underwent a right laparoscopic adrenalectomy for a pheochromocytoma within the Von Hippel Lindau syndrome in December last year, from which he made a rapid and uncomplicated post-operative recovery.
  - On examination today, all incisions have healed well.
  - We knew pre-operatively that he had bilateral phaeochromocytomas however the right was the largest and we hoped to proceed with a staged adrenalectomy to preserve adrenal function for as long as possible.
  - Unfortunately, post-operative urinary nor-metadrenaline has not decreased substantially although his mother tells me he remains normotensive and asymptomatic.
  - I discussed the findings with him and his mother today and I have suggested that he seeks an early appointment with the paediatric endocrine team to discuss the potential for going back on to doxazosin. He particularly would like to avoid further surgery for at least a year. He is of course in his GSCE year currently.

Auxology

Height

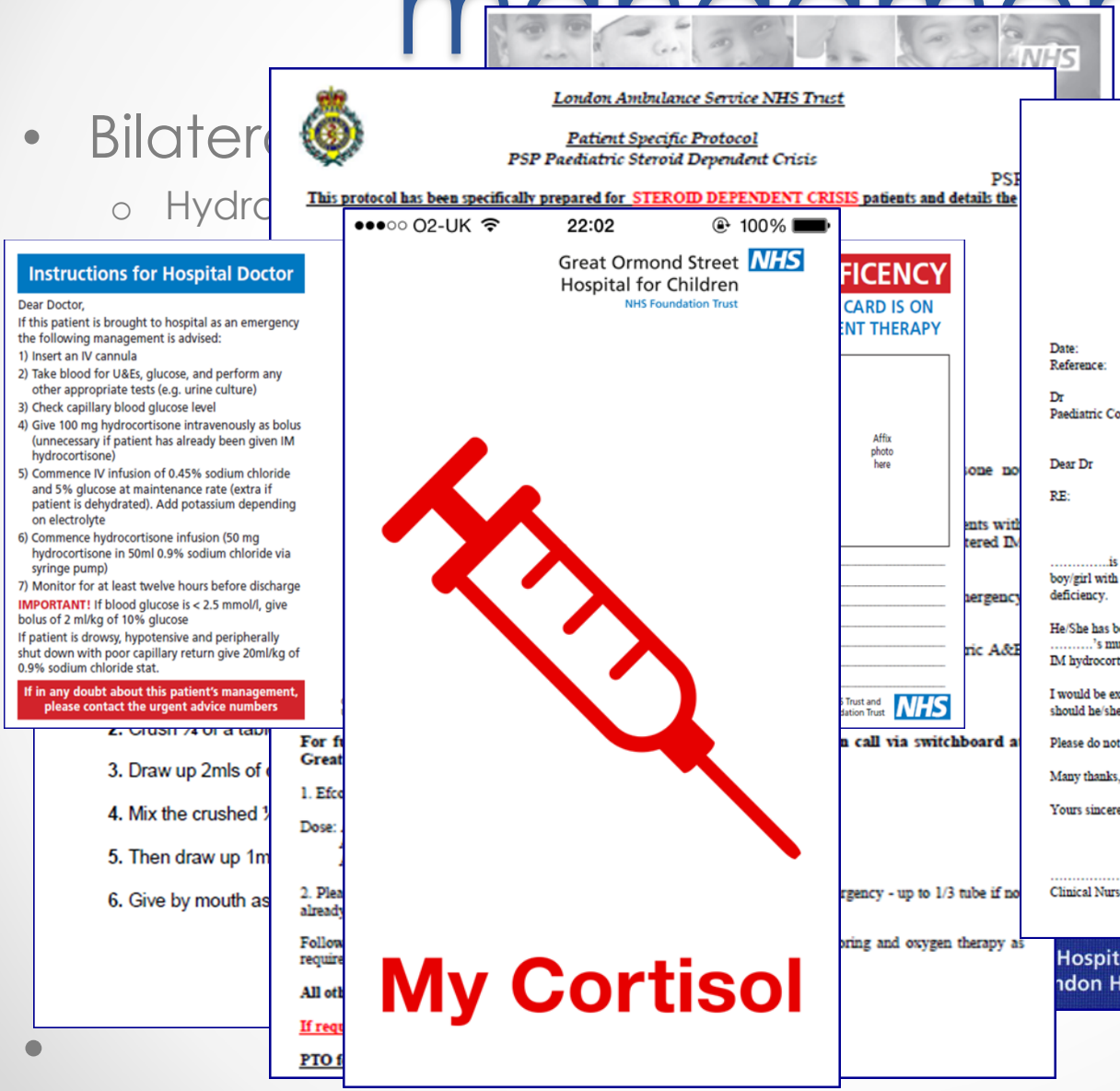


Weight



Potential further management

- Bilater
  - Hydr



Conclusion

- Management of children with NETs very complex
- Importance of screening emphasised
  - Genetics and clinical
    - Inform families
    - Reduce need for screening
    - Reduction in morbidity compared to their parents
    - Can screen from age 5yrs
      - MEN2b genetics from age 1yr
- Potentials for further management
  - Nursery / School
    - Hydrocortisone management

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