In the name of God

case presentation

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- Gender: woman
- Age: 31-year-old
- Source of History: Patients, Reliable
- Married
- Born & live in brugerd
- Education:diploma
- House wife

Chief complaint:

- paroxysmal headache with hot flushes and profuse sweating and palpitation last 30 min to few hr
- Headache relieve spontaneously or with NSAID
- Spells were 3 to 4 times a week

Present illness:

- A 31-year-old woman with the history of chronic headache and ET from last year .
- She was treated by a hematologist
- And for this reason she did abdominal ultrasound and cbc test every four months

Present illness:

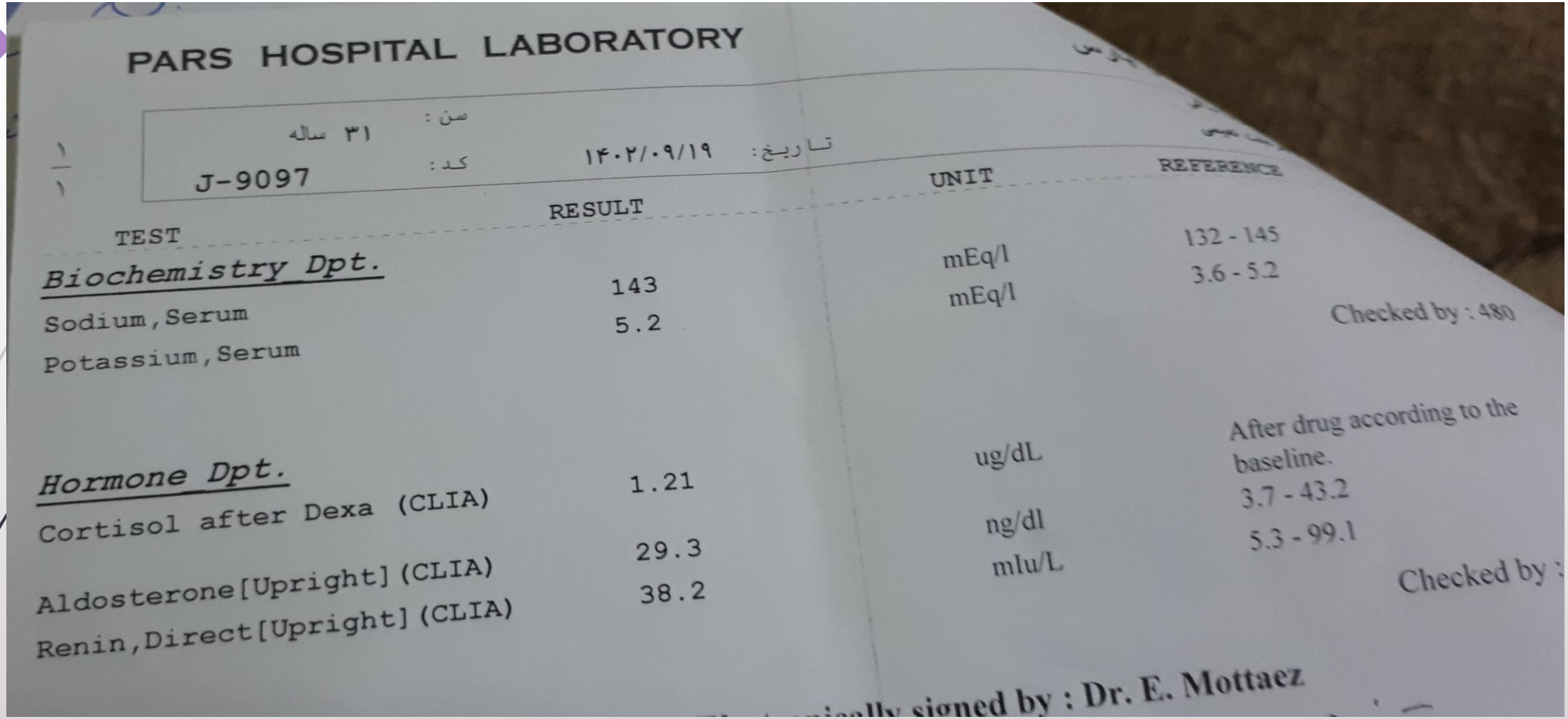
- In periodic sonography for monitoring of ET 2 mass in renal region was reported
- she refer to nephrologist
- An abdominal ct scan shows bilateral mass in adrenals

lab test result: 28.08.1402

test	result		method	reference
Urine noremetanephrine24h	**1361**	Mic/24h	Elisa	Less than 600
Urine metanephrin24h	22	Mic/24h	Elisa	Less than 350
Urine VMA24	5.3	Mg/24h	Chemical	Up to 13.5
Urine volume24h	710	Ml/24h		600-1800

Present illness:

- referred to endocrinologist
- Repeat lab test



PARS HOSPITAL LABORATORY

سن : ۳۱ ساله
کد : J-9097
تاریخ : ۱۴۰۲/۰۹/۱۹

TEST	RESULT	UNIT	REFERENCE
Biochemistry Dpt.			
Sodium,Serum	143	mEq/l	132 - 145
Potassium,Serum	5.2	mEq/l	3.6 - 5.2
			Checked by : 480
Hormone Dpt.			
Cortisol after Dexa (CLIA)	1.21	ug/dL	After drug according to the baseline.
Aldosterone[Upright](CLIA)	29.3	ng/dl	3.7 - 43.2
Renin,Direct[Upright](CLIA)	38.2	mIu/L	5.3 - 99.1
			Checked by :

Electronically signed by : Dr. E. Mottaez

PARS HOSPITAL LABORATORY

سن : ۳۱ ساله
کد : K-1501
تاریخ : ۱۴۰۲/۰۹/۲۲

TEST	RESULT	UNIT	REFERENCE
Biochemistry Dpt.			
Volume,24 hr,Urine	1750	ml/24hrs	600 - 2500
Creatinine,24hr,Urine			
Creatinine,Urine	49	mg/dl	
Creatinine,24 hr,Urine	857	mg/24hrs.	600 - 1800
Creatinine/Kg,24 hr,Urine	12	mg/kg/24hrs	11 - 20
Weight	72	kg	
Volume,24 hr,Urine	1750	ml/24hrs	600 - 2500
Chromatography(HPLC) Dpt.			
24 hrs urine Volume.....	1750	ML	
VMA,24hr,Urine(HPLC)	4.7	mg/24hrs	2 - 12
VMA/CR,Ratio,Urine	5.4	mg/gr	0 - 8

Chromatography (HPLC) Dpt.

24 hrs urine Volume.....	1750	ML	
VMA,24hr,Urine(HPLC)	4.7	mg/24hrs	2 - 12
VMA/CR,Ratio,Urine	5.4	mg/gr	0 - 8

Hormone Dpt.

Metanephrin,24hr,Urine(ELISA) ✓	258.1	mcg/24hrs	0 - 350
Metanephrine/Cr,Ratio,Urine	301.2	mcg/g	27-270
Normetanephrin,24hr,Urine(ELI: ✓	H 2796.1	mcg/24hrs	0 - 600
Normetanephrine/Cr,Ratio,Urin	3262.7	mcg/g	69-750
Volume,24 hr,Urine	1750	ML	600 - 2500

Electronically signed by : Dr. E. Mottaez

Present illness:

- She was hospitalized in Taleghani hospital (1402.10.09)

- Lab test
- Radiologic study
- Medical therapy
- Surgical planning
- Other consultant

Family history

- Her mother underwent partial bilateral nephrectomy at 44 y due to bilateral renal mass
- Her mother underwent brain surgery due to cerebellar mass and fell into a coma and then died at 48
- Other mother family have no problem

Family history

- **Her father died due to cardiac arrest at 52**
- **Her brother has blood concentration and is forced to donate blood**
- **She has a healthy brother and sister**
- **She has two kid without any problem**

Drug history:

- ASA
- hydroxyurea500
- Novafen -prn

PHYSICAL EXAMINATION:

- General appearance:
- A 31-year-old woman, orient

- Vital sign:
  - BP:110/70 mmhg
  - HR=80
  - RR= 14
  - BMI= 25.53 kg/m2
  - W=72Kg
  - H=168 Cm

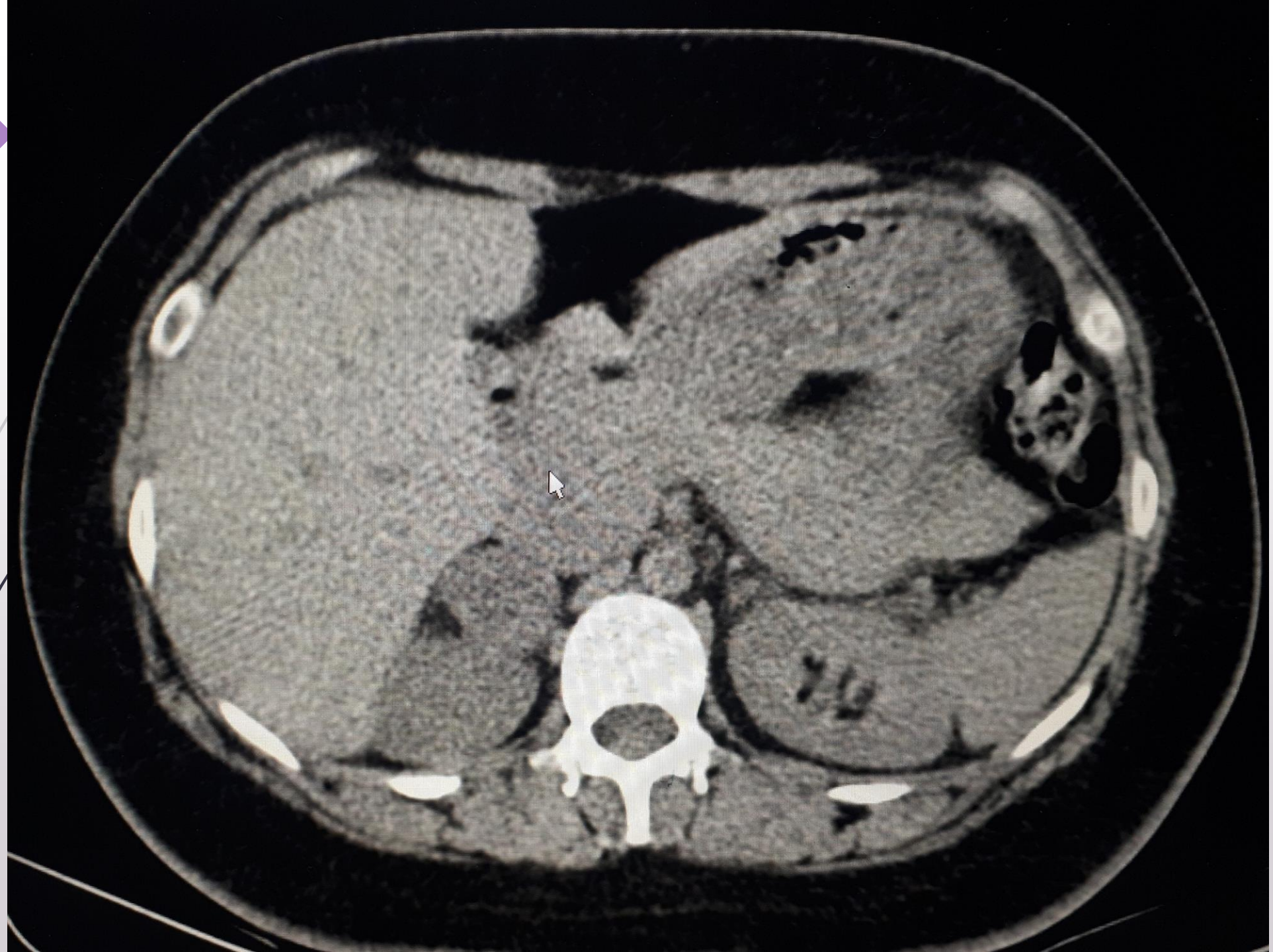
REVIEW OF SYSTEM:

- Headache (+) Nausea & vomiting (-) Visual problems(-)
- Weight changes (-) appetite changes (-) sexual problems (-)
- Skin: pigmentation (-) sweating (+) Dry & fragile hair (-)
- Ear , nose, mouth: NL
- Cardiovascular: NL palpitation (+)
- Respiratory: NL
- Gastrointestinal: NL
- Musculoskeletal: NL
- Neurological: NL
- Psychiatric: NL

خدمت درخواستی: سی تی اسکن شکم و لگن بدون تزریق (با پروتکل آدرنال)

در این بررسی که با مقاطع آگزیال از قسمتهای فوقانی شکم تا انتهای لگن بدون بعمل آمده، نتایج زیر بدست آمده:

- کبد دارای اندازه و پارانشیم یکنواخت و طبیعی است و نشانه ای از توده فضاگیر در آن دیده نمی شود.
- کیسه صفرا و مجاری صفراوی نمای عادی دارند.
- طحال دارای اندازه و پارانشیم یکنواخت و طبیعی است و نشانه ای از توده فضاگیر در آن دیده نمی شود.
- پانکراس دارای ابعاد طبیعی بوده، در هیچیک از نواحی سر، تنه و دم ضایعه ای دیده نمی شود.
- **تصویر ۲ ضایعه هیپودنس به دیامتر ۳۳۰۰*۶۰ در آدرنال سمت راست و ۱,۵۰۰ در سمت چپ با دانسیته ۲۷۰۰ رویت شد. جهت بررسی دقیق تر سی تی با پروتکل آدرنال توصیه می شود.**



Problem list:

- A 31-year-old woman with the history of headache & ET
- Paroxysmal headache, palpitation and sweating
- Normetanephrine elevation in lab test
- Bilateral adrenal mass in radiologic study
- Cerebellar and renal mass in her mother

AGENDA:

- What is this patients diagnosis?
- What is the next plan & treatment for this patent?
- what is the next plan for her family members?

Pheochromocytoma

- Pheochromocytoma has the highest degree of heritability among all tumors; up to 40% of cases result from germline mutations.
- Currently, it is recommended that genetic testing should be considered in all patients
- Genetic testing is particularly important in patients presenting at a young age, with a

family history of pheochromocytoma or with extraadrenal, multiple, recurrent, and metastatic tumors.

- hereditary pheochromocytomas are often multifocal and bilateral.
- Most catecholamines produced by the pheochromocytomas and paragangliomas are metabolized to metanephrines within tumor cells rather than after secretion

Who to Test According to Presentation?

- anyone with paroxysmal profuse sweating, pallor, tremor, and tachycardia, especially in a subject with episodic hypertension
- known mutation of susceptibility genes and/or a family history of pheochromocytoma
- adrenal mass or mass at an extraadrenal location that may represent a paraganglioma;
- anyone who has had episodic hypertension, stroke, tachycardia, or an arrhythmia in response to anesthesia, surgery, medications, or food

several familial disorders associated with adrenal pheochromocytoma

- **Multiple Endocrine Neoplasia Syndromes**
- **Von Hippel–Lindau Syndrome**
- **Neurofibromatosis Type 1**
- **Succinate Dehydrogenase Gene Family**

BIOCHEMICAL DIAGNOSIS OF PHEOCHROMOCYTOMA

- Guideline on pheochromocytomas and paragangliomas recommended that testing for the tumors should include measurement of plasma or urinary metanephrines.
- the plasma test is superior to both urine tests in patients screened due to hereditary risk, an incidentaloma, or past history of the tumors.
- For the plasma test, sampling blood in the seated position is a common cause of false-positive results. Blood for this test should be collected with patients supine for at least 20 to 30 minutes before sampling.
- sympathetic paragangliomas almost invariably produce only norepinephrine, with or without methoxytyramine.

What is this patients diagnosis?

- The patient diagnosis is pheochromocytoma in the context of von hippel lindau disease
- The incidence of VHL is 1 case in 36000 live birth

Vertebral marrow : ترمال

قوس نورال خلفی : intact

تعدادی فیبروم کوچک در پارانشیم به صورت اینترامورال و اینترامورال ساب سروزال به حداکثر دیامتر ۱۳۰۰ در خلف فوندوس رویت شد (FIGO=4/5)

تصویر ندول ۱۰۰۰ در آدرنال چپ و ناحیه round 27×25mm در آدرنال راست رویت شد تطبیق با هیستوری بیمار و CT با پروتکل آدرنال و یافته های آزمایشگاهی توصیه می شود.

Disc dehydration در لول های L5-S1, L4-L5 رویت شد.

دیسک بالج با اثرفشاری بر تکال ساک و left paracentral annular tear در لول L4-L5 رویت شد.

دیسک بالج با اثرفشاری بر تکال ساک در لول L5-S1 رویت شد.

Subarticular recess : ترمال

نورال فورامن ترمال

فضای ساب آراکنوئید : ترمال

نخاع در نواحی قابل مشاهده : دارای قطر و سیگنال ترمال است.

ریشه های عصبی : ترمال

آنرومی عضلات پاراسپاینال وجود ندارد.

خدمت درخواستی : MRI مغز با و بدون ماده حاجب

تکنیک تصویر برداری:ام ار ای مغز بدون کنتراست

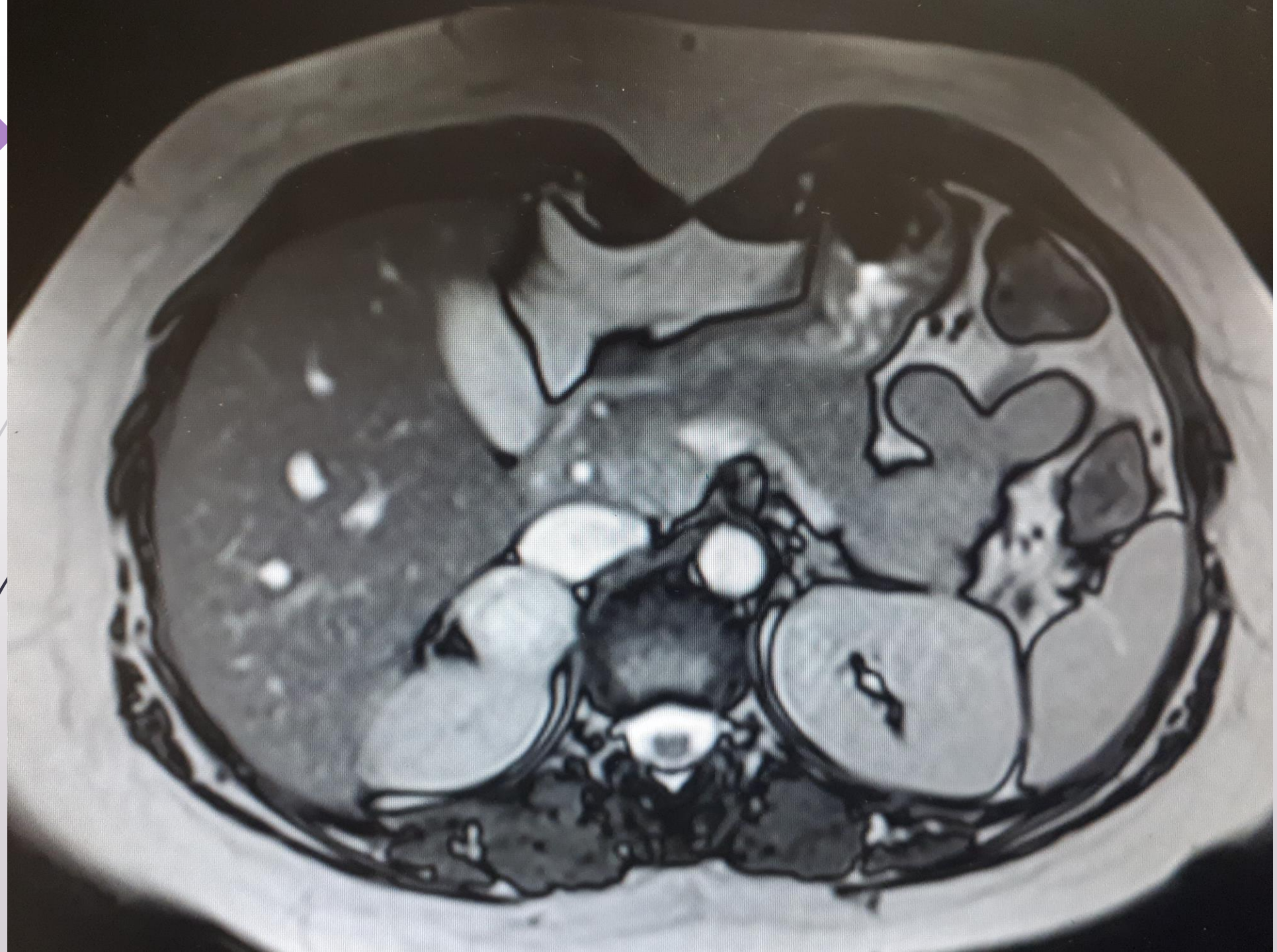
یافته ها :

تصویر چند فوکوس کوچک با سیگنال مشابه CSF به حداکثر سایز ۴۰۰ در ماده سفید پری وتریکولار دوطرف رویت شد.

تصویر چند ساختار کوچک enhancing در هردو لوب مخچه به حداکثر سایز ۵۰۰ در سمت راست و به سایز ۴۰۰ در تمپورال راست رویت شد با توجه به هیستوری بیمار احتمال همانژوبلاستوما متعدد در مراحل اولیه برای بیمار مطرح است،تطبیق با یافته های کلینیکی و imaging فالوآپ توصیه می شود.

هتروژنیسته هیپوفیز نیز رویت شد تطبیق با MRIهیپوفیز توصیه می شود.

فضاهای اکسترا آگزیال :در سایز و شکل با توجه به سن بیمار نرمال هستند



Consults

- Ophthalmology counseling:
  - absence of retinal hemangioma
- Neurosurgery counseling;
  - no therapy is needed

Von Hippel–Lindau Syndrome

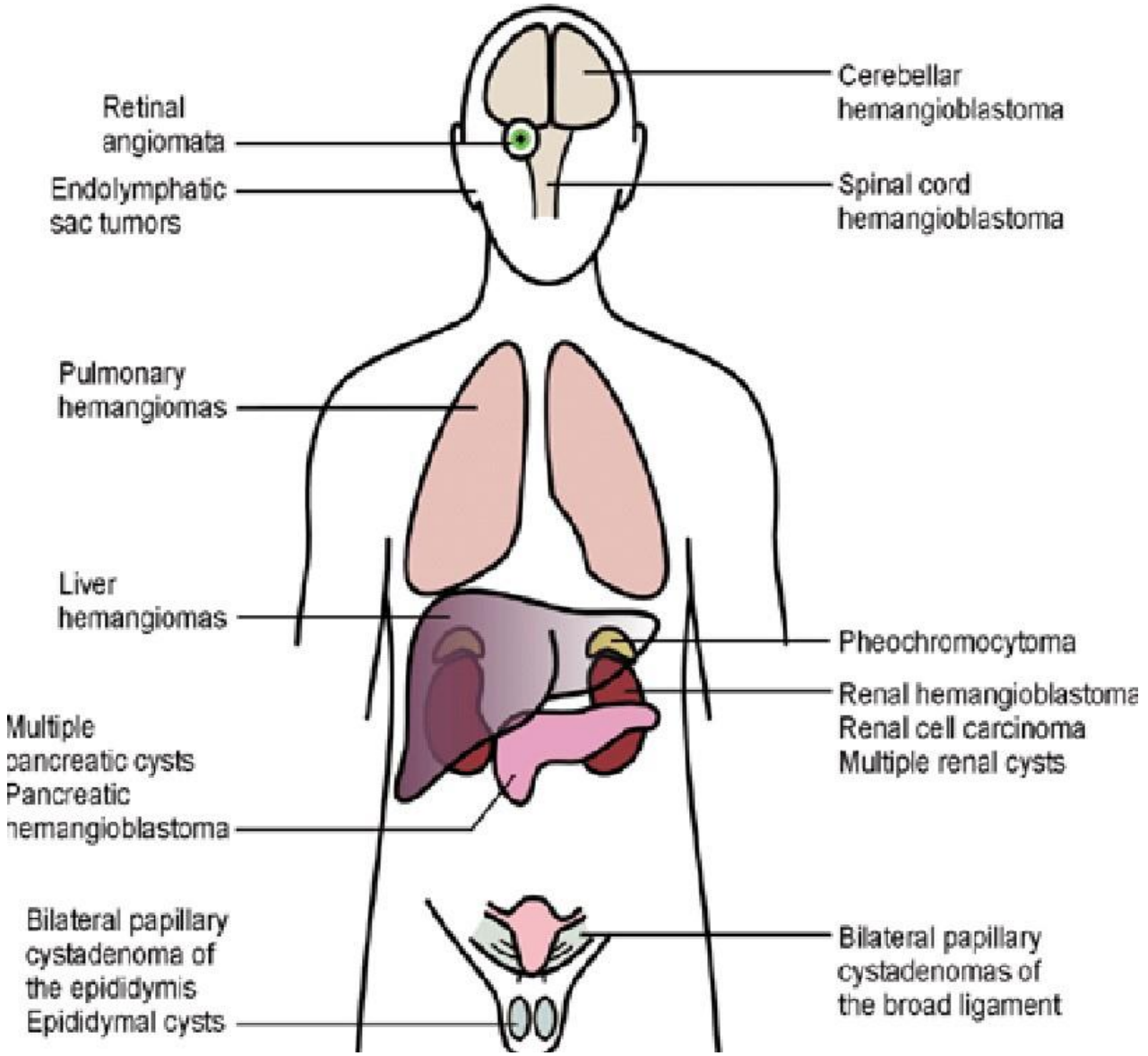
Autosomal dominant genetic condition

(mutation in the tumor suppressor gene on chromosome 3p25.3)

characterized by visceral cysts, benign masses, and the potential for malignant transformation in multiple organ systems

Clinical features:

* Eye tumor (retinal hemangioblastomas)
* Brain tumor (CNS hemangioblastomas)
* Kidney tumor(renal cell carcinoma)
* Adrenal gland tumor (pheochromocytoma)
* pancreatic tumors(pancreatic serous cystadenoma)
* Cafe au lait spots
* CVS (strokes, and heart attacks)


Retinal angiomata
Endolymphatic sac tumors
Pulmonary hemangiomas
Liver hemangiomas
Multiple pancreatic cysts
Pancreatic hemangioblastoma
Bilateral papillary cystadenoma of the epididymis
Epididymal cysts
Cerebellar hemangioblastoma
Spinal cord hemangioblastoma
Pheochromocytoma
Renal hemangioblastoma
Renal cell carcinoma
Multiple renal cysts
Bilateral papillary cystadenomas of the broad ligament

Clinical manifestations of von Hippel-Lindau disease

Clinical manifestations of von Hippel-Lindau disease

	Ages at diagnosis	Most common ages at dx	Frequency in patients CNS
CNS			
Retinal hemangioblastomas	0-68 yrs	12-25 yrs	25-60 percent
Endolymphatic sac tumors	12-46 yrs	24-35 yrs	10-25 percent
Cerebellar hemangioblastomas	9-78 yrs	18-25 yrs	44-72 percent
Brainstem hemangioblastomas	12-36 yrs	24-35 yrs	10-25 percent
Spinal cord hemangioblastomas	12-66 yrs	24-35 yrs	13-50 percent
Viscera			
Renal cell carcinoma or cysts	16-67 yrs	25-50 yrs	25-60 percent
Pheochromocytomas*	4-58 yrs	12-25 yrs	10-20 percent¶
Pancreatic tumor or cyst	5-70 yrs	24-35 yrs	35-70 percent
Epididymal cystadenomas	17-43 yrs	14-40 yrs	25-60 percent of males*
Adnexal papillary cystadenoma of mesonephric origin (broad ligament cystadenoma)	16-64 yrs	16-46 yrs	Estimated 10 percent of females

* Includes the 20 percent of lesions that occur outside the adrenal gland, also called paragangliomas.

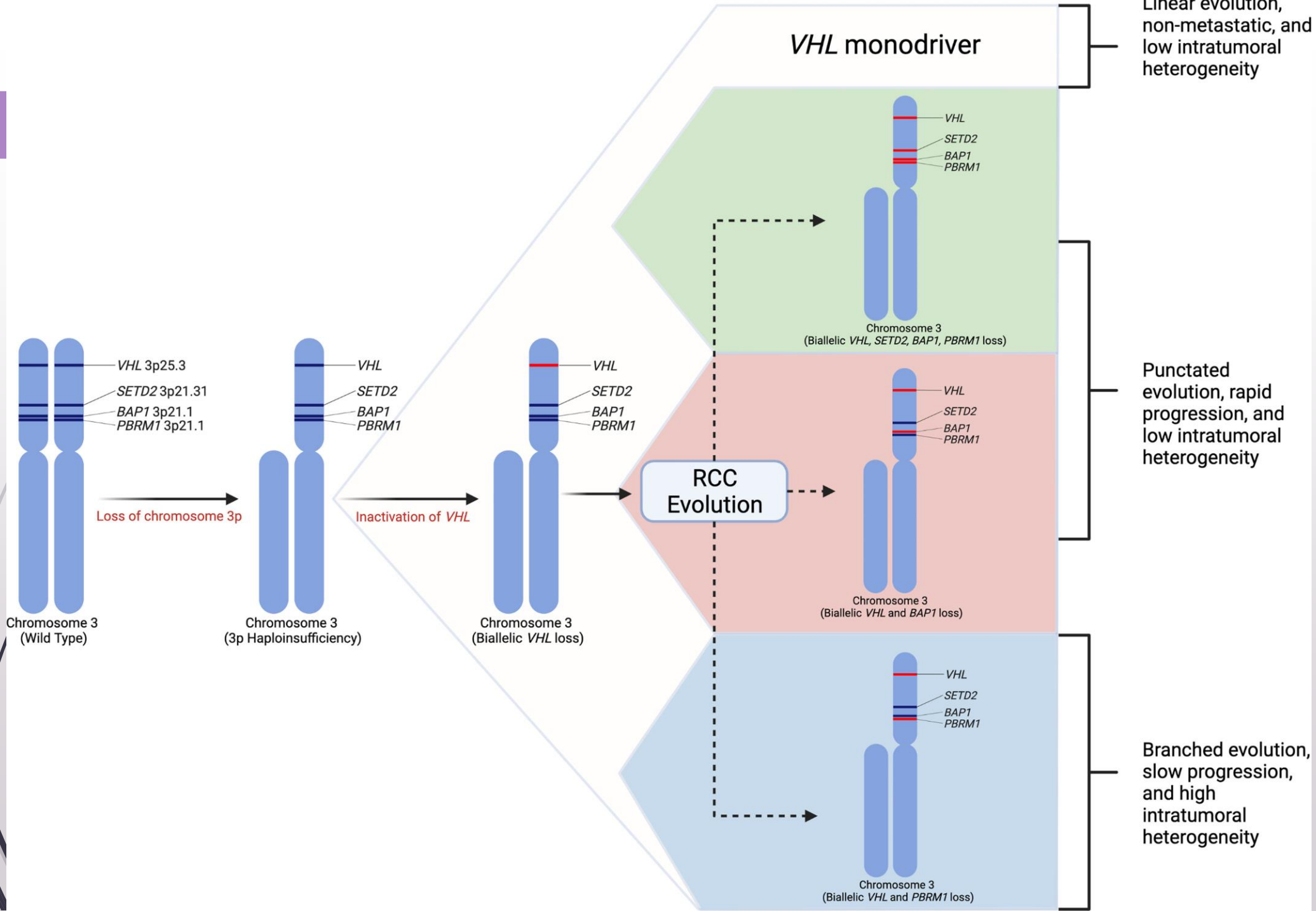
von Hippel-Lindau disease

- *In one evaluation of 271 patients with apparently sporadic pheochromocytoma*
- ***A germline VHL pathogenic variant was identified in 30 patients overall (11 percent) and in 42 percent of those who presented at age 18 or younger.***
- *Patients with VHL disease and catecholamine production due to pheochromocytoma almost exclusively produce* ***normetanephrines***
- *Conventional imaging may not be sufficient because of the potential for extra-adrenal lesions:*123I-MIBG scan , 18F-F DOPA PET/CT , 68Ga-DOTA-SSAs PET/CT

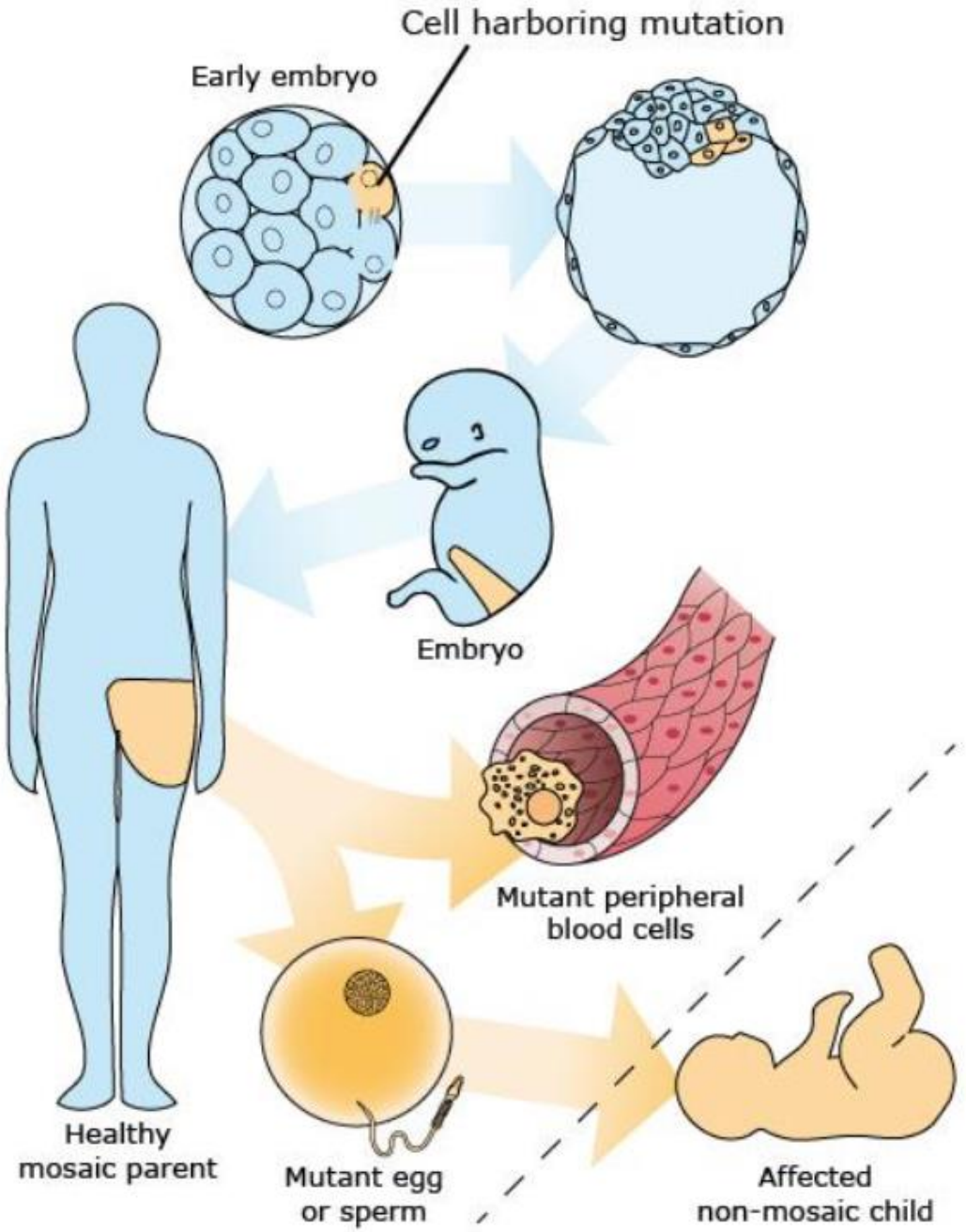
DIAGNOSIS

- *The diagnosis of VHL disease is typically established through detection of a germline pathogenic (typically loss of function) variant in the VHL gene.*
- *Rarely, in patients who do not have access to genetic testing, the diagnosis of VHL disease can be based on clinical criteria (eg, those with one VHL-associated lesion and a family history of VHL, or those with multiple VHL-associated lesions)*
- *Genetic testing is typically performed on isolated DNA from a fresh blood sample, which is obtained primarily from lymphocytes. saliva or buccal*
- *Rare patients may have the clinical features of VHL without a detectable pathogenic variant from analysis of a blood sample due to mosaicism for the VHL pathogenic variant*

the person inherits a germline mutation that renders one VHL allele inactive and an acquired "second hit" to the other VHL allele in a somatic cell leaves that cell without tumor suppressor ability


VHL monodriver
Linear evolution, non-metastatic, and low intratumoral heterogeneity
VHL 3p25.3
SETD2 3p21.31
BAP1 3p21.1
PBRM1 3p21.1
Chromosome 3 (Wild Type)
Loss of chromosome 3p
VHL
SETD2
BAP1
PBRM1
Chromosome 3 (3p Haploinsufficiency)
Inactivation of VHL
VHL
SETD2
BAP1
PBRM1
Chromosome 3 (Biallelic VHL loss)
RCC Evolution
VHL
SETD2
BAP1
PBRM1
Chromosome 3 (Biallelic VHL, SETD2, BAP1, PBRM1 loss)
VHL
SETD2
BAP1
PBRM1
Chromosome 3 (Biallelic VHL and BAP1 loss)
VHL
SETD2
BAP1
PBRM1
Chromosome 3 (Biallelic VHL and PBRM1 loss)
Punctated evolution, rapid progression, and low intratumoral heterogeneity
Branched evolution, slow progression, and high intratumoral heterogeneity

Von Hippel-Lindau disease transmission from a mosaic parent to child

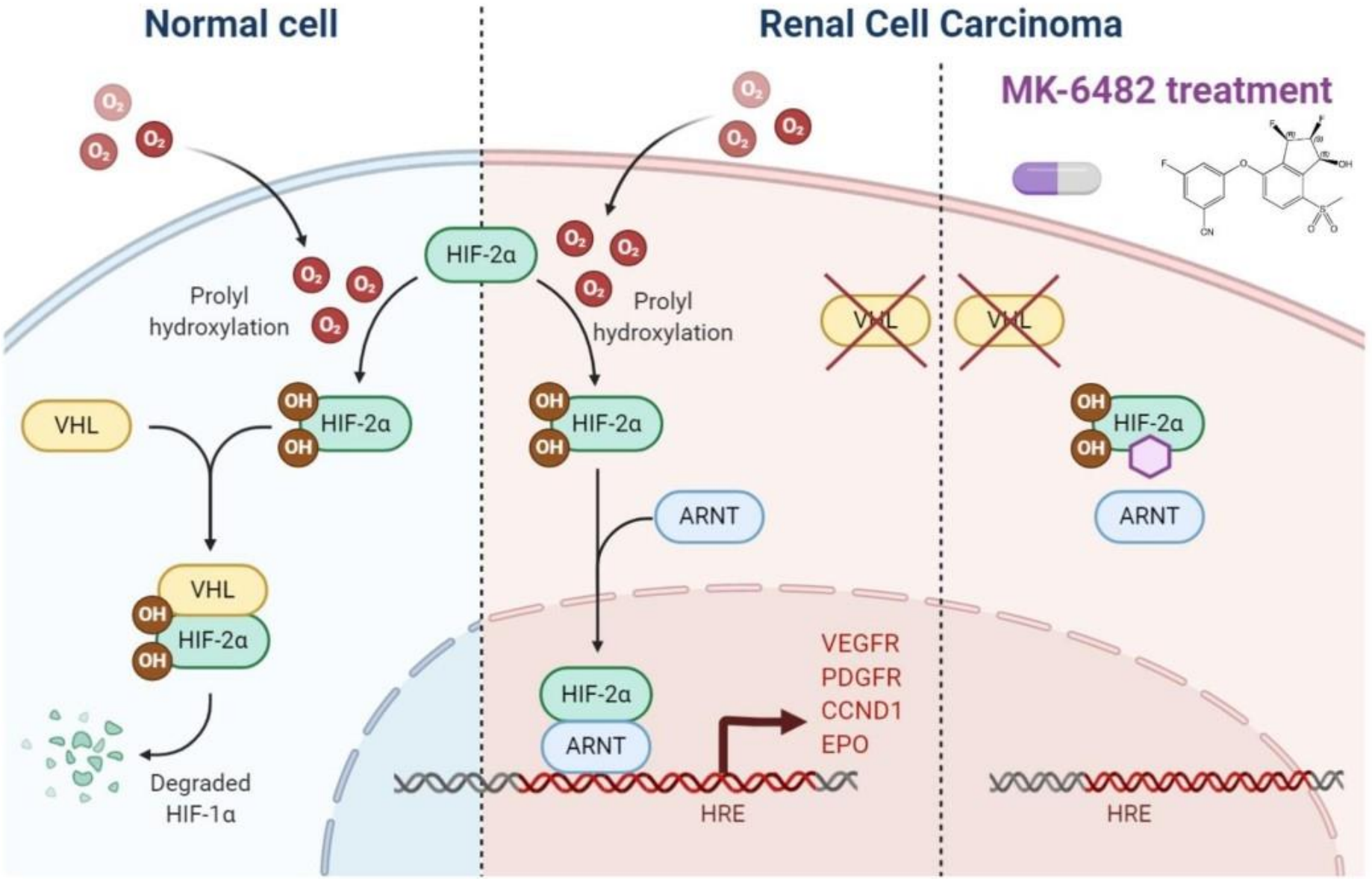


For VHL disease, this de novo mutation occurs in about a 20% of patients.

pVHLs form a complex with several other proteins This multiprotein complex ubiquitinates different substrates, thus marking them for degradation.

Cells lacking pVHL fail to degrade HIFs in the presence of oxygen, thus permitting accumulation of high levels of stable proteins and activating the transcription of a large cohort of hypoxia-responsive genes constitutively

hypoxia-induced mRNAs, such as those for erythropoietin (EPO), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and enzymes involved in glycolysis through HIF-mediated transcription. Tumors associated with VHL disease are often highly vascular, possibly because of overproduction of these mRNAs. Paraneoplastic polycythemia is frequently observed as a result of increased EPO production.


Normal cell
Renal Cell Carcinoma
MK-6482 treatment
Prolyl hydroxylation
Prolyl hydroxylation
HIF-2α
VHL
VHL
VHL
OH
OH
HIF-2α
ARNT
Degraded HIF-1α
VEGFR
PDGFR
CCND1
EPO
HRE
HRE

What is the next plan & treatment for this patent?

- She was treated with alfa blocker
- Refer to urologist for bilateral adrenalectomy

- Genetic test and regular surveillance for patient and relatives

SURVEILLANCE PROTOCOLS

- Complete blood cell (CBC) count is used to look for evidence of polycythemia vera due to EPO expression by renal cysts and cerebellar hemangioblastomas.
- Electrolytes and renal function (BUN and creatine) are used for electrolyte measurement and renal baseline function
- Measurement of plasma catecholamines and urinary catecholamine metabolites

SURVEILLANCE PROTOCOLS

- Ophthalmic ultrasonography
- Abdominal/genitourinary ultrasonography
- Abdominal CT scanning without and with contrast: Renal, pancreatic, and adrenal gland lesions
- Abdominal MRI: Renal, pancreatic, and adrenal gland lesionsBrain CT scan with and without contrastCNS MRI with and without contrast

Surveillance Modality (Tumors being screened)	AGE[1]						Pregnancy[11]
	<5 years	**Beginning at age 5y**	**Beginning at age 11y**	**Beginning at age 15y**	**Beginning at age 30y**	**Beginning at age 65y[1]**	
History and Physical Examination[2]	Yearly from age 1 year	Yearly	Yearly	Yearly	Yearly	Yearly	Prior to conception[11]
Blood Pressure and Pulse (Pheochromocytomas/paragangliomas)	Yearly from age 2 years	Yearly	Yearly	Yearly	Yearly	Yearly	Prior to conceptionr[11]
Dilated Eye Examination[3] (Retinal Hemangioblastomas)	Every 6-12 months, beginning before age 1 year	Every 6-12 months	Every 6-12 months	Every 6-12 months	Yearly	Yearly	Prior to conception, then Every 6-12 months[11]
Metanephrines[4] (Pheochromocytomas/paragangliomas)	——	Yearly	Yearly	Yearly	Yearly	Stop routine[1]	Prior to conception[11]
MRI Brain and Spine w/wo Contrast[5,6,7] (CNS Hemangioblastomas)	——	——	Every 2 years[8]	Every 2 years[8]	Every 2 years[8]	Stop routine[1]	Prior to conception[11]
Audiogram (Endolymphatic sac tumors)	——	——	Every 2 years	Every 2 years	Every 2 years	Stop routine[1]	——
MRI Abdomen w/wo Contrast[5,6,7] (Renal cell carcinomas, Pheochromocytomas/paragangliomas, Pancreatic neuroendocrine tumors/cysts)	——	——	——	Every 2 years[9]	Every 2 years[9]	Stop routine[1]	Prior to conception[11]
MRI Internal Auditory Canal[10] (Endolymphatic sac tumors)	——	——	——	Once	——	——	No specific changes

Management

- *FDA granted regulatory approval to belzutifan a hypoxia-inducible factor-2alpha (HIF-2alpha) inhibitor in adult patients with VHL disease who require therapy for associated CNS hemangioblastoma and do not require immediate surgery . Belzutifan also has regulatory approval from the FDA for VHL-associated RCC and pancreatic neuroendocrine tumors.*

THANKS FOR YOUR ATTENTION