Laboratoriumdiagnostiek van neuroblastoom en feochromocytoom

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UZ Leuven (chemie)

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To do’s/acties

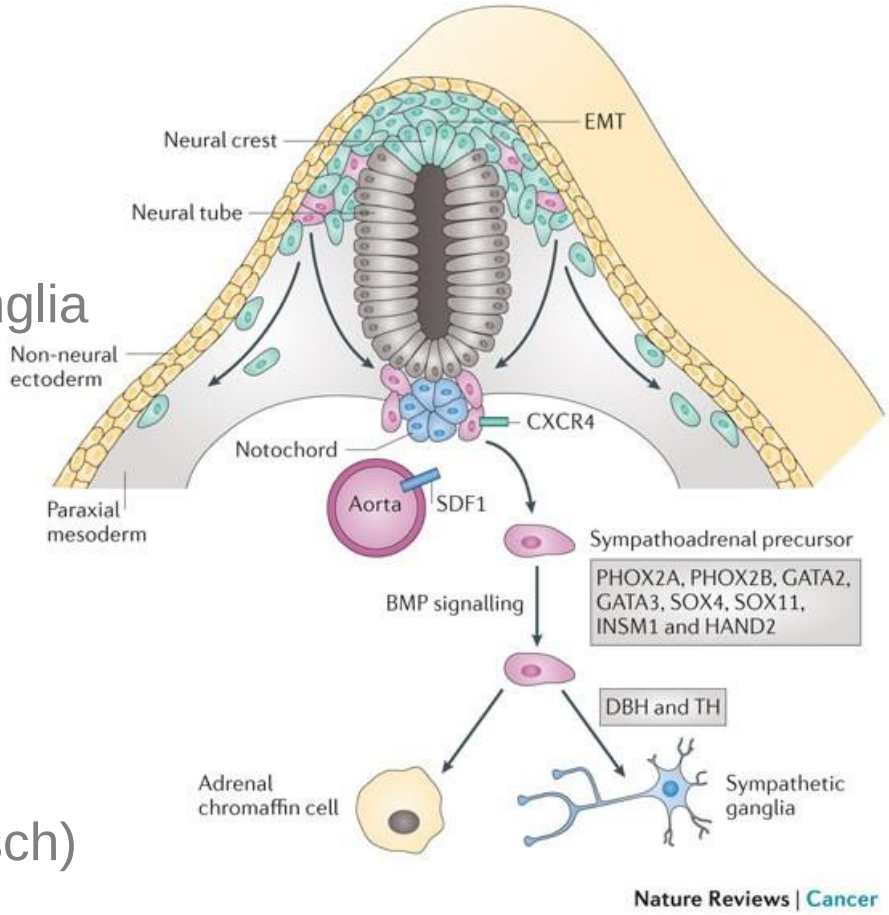
Wat?

Neuroblastomen

- Kinderen (10 gevallen per miljoen kinderen onder 15j)
- Immature embryogene neuroblastcellen
- Heterogeen
- Meestal in abdomen (bijniermerg of lumbale sympathische ganglia in 65%)

Paragangliomen

- Eerder volwassenen (2-8 gevallen per miljoen inwoners)
- Mature chromaffine cellen, (para)sympathische ganglia
- Sympathisch of parasympatisch
- **Feochromocytoom**: intra-adrenale paraganglioom (sympathisch)



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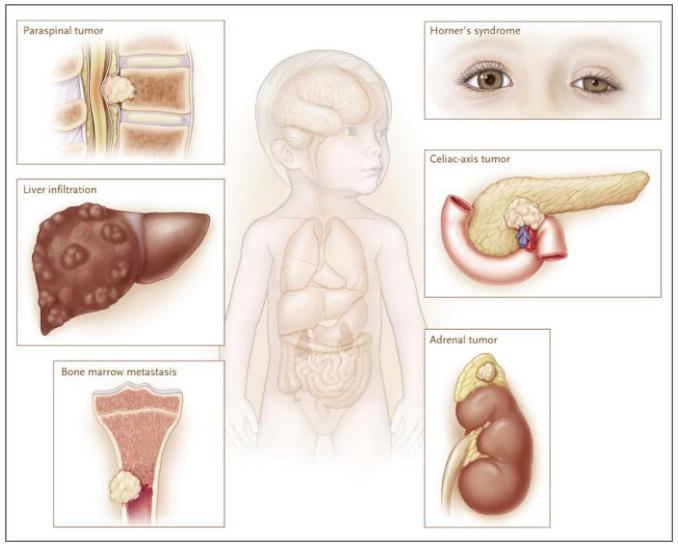
Wat?

Neuroblastomen

- Meest voorkomende extracraniële solide tumor bij kinderen
- 18 maanden
- 8,5% van alle pediatrische maligniteiten

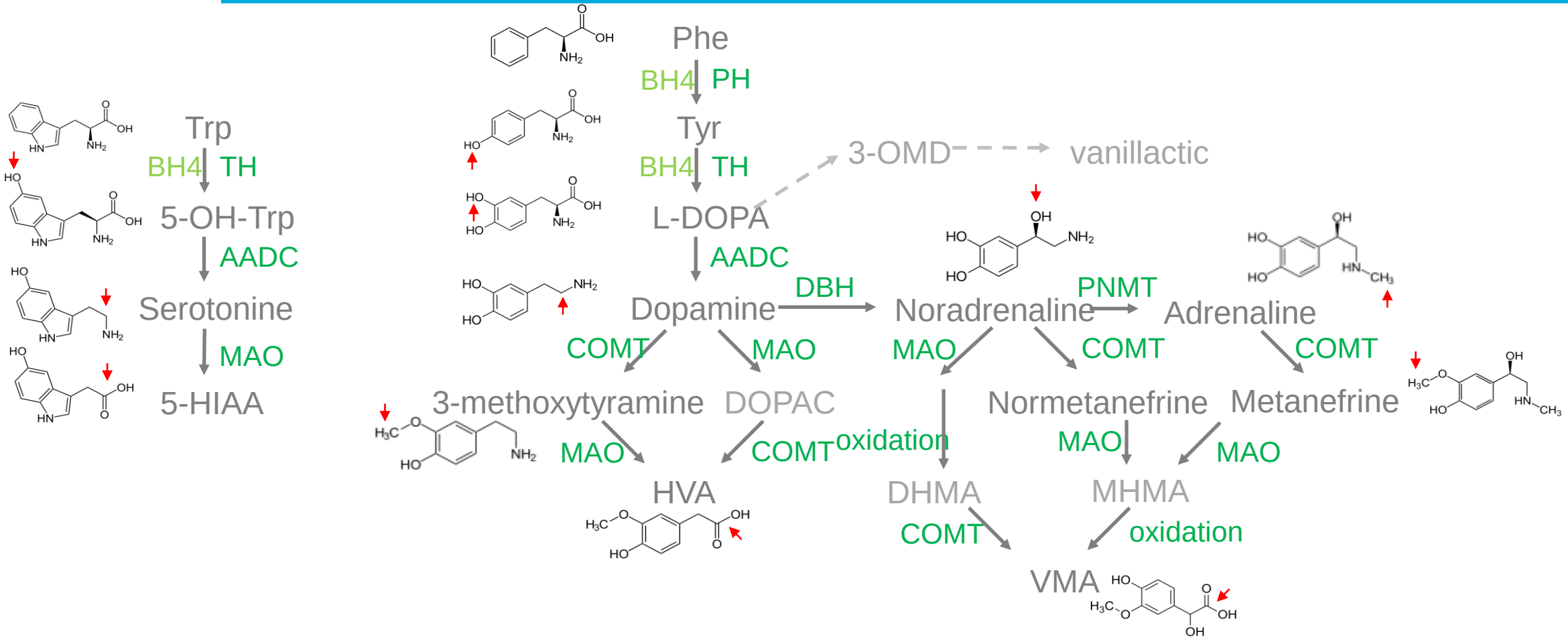


Maris JM. Recent advances in neuroblastoma. N Engl J Med. 2010 Jun 10;362(23):2202-11. doi: 10.1056/NEJMra0804577. PMID: 20558371; PMCID: PMC3306838.

Feochromocytomen en paragangliomen (PPGL)

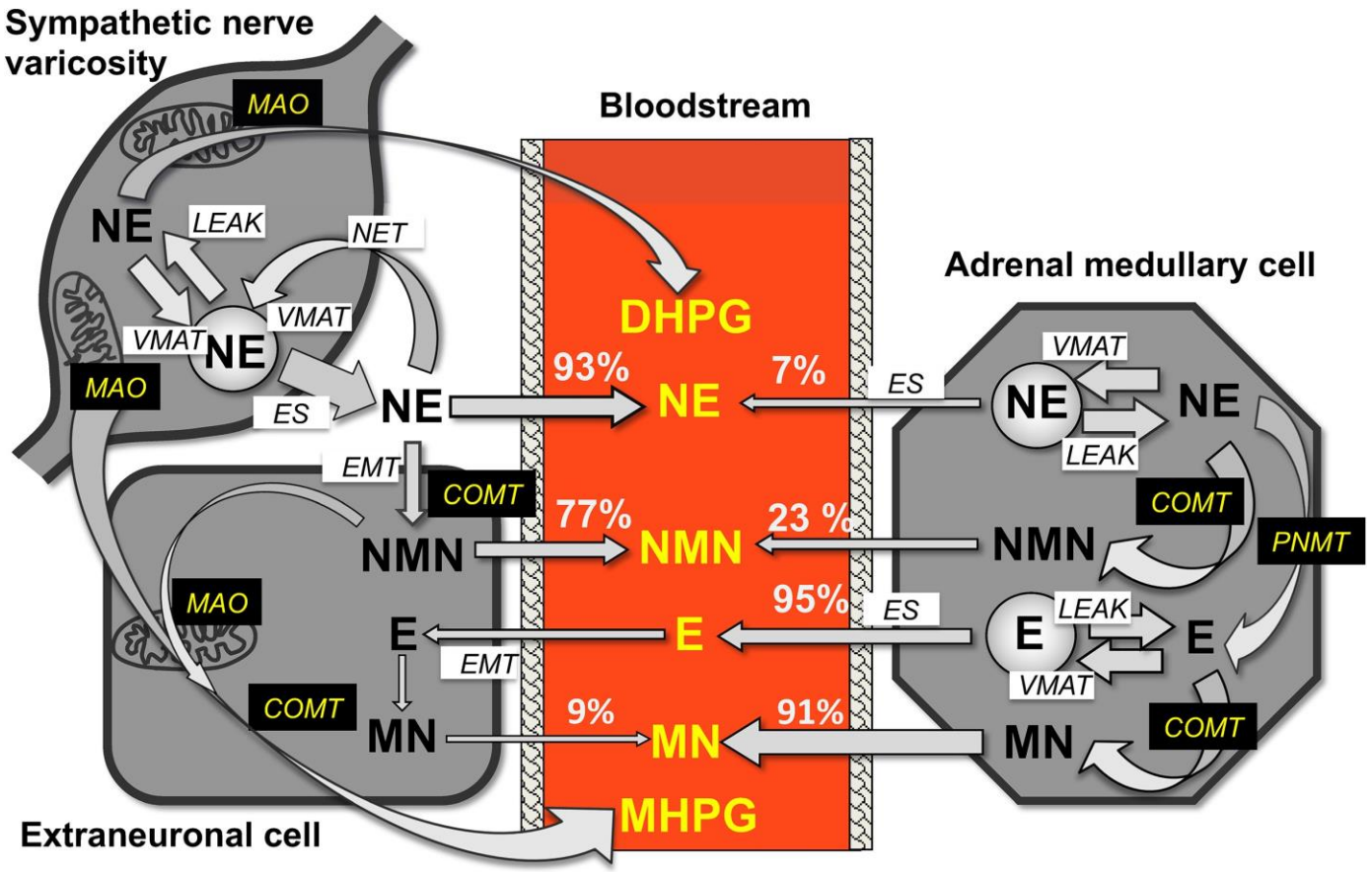
- 40-60 jaar
- Hypertensie: 0.2-0.6% versus 85-95%
- Klassieke triade (episode)
  - Palpitaties
  - Hyperhidrosis
  - Hoofdpijn
- “Crisis”: acute ernstige presentatie van een catecholamine-geïnduceerde hemodynamische instabiliteit → mortaliteit van 6% (28% als in shock)
- Feochromocytoom: 10% maligne
- Extra-adrenale paraganglioma: 30-40% maligne
- Bijnierincidentaloom (7%)
- Hereditaire syndromen (30-40%)

Catecholamines en metabolieten



5-HIAA: 5-OH-indolacetic acid; 5-OH-tryptamine; 3-O-methyldopa; AADC: L-aromatic aminoacid decarboxylase; BH4: tetrahydrobiopterine; COMT: catechol-O-methyl-transferase; DBH: dopamine-beta- hydroxylase (co-factor: ascorbic acid); DHMA: dihydroxymandelic acid; DOPA: 3,4diOH-phenylalanine; DOPAC: 3,4-diOH-phenylacetic acid; HVA: homovanillic acid; MAO: monoamine oxidase (cofactor: FAD); MHMA: 3-methoxy-4-OH-mandelic aldehyse; PH: phenylalanine hydroxylase, PNMT: phenylethanolamine N-methyltransferase (co-factor: S-adenosyl-L-methionine); TH: tyrosine hydroxylase; VMA: vanillylmandelic acid

Catecholamines en metabolieten



Eisenhofer G, Pamporaki C, Lenders JWM. Biochemical Assessment of Pheochromocytoma and Paraganglioma. Endocr Rev. 2023 Sep 15;44(5):862-909. doi: 10.1210/endrev/bnad011. PMID: 36996131.

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To do’s/acties

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- Welke urine en plasma biomarkers worden aangeraden voor de diagnostiek van neuroblastomen?
- Welke urine en plasma biomarkers worden aangeraden voor de diagnostiek van PPGL?
- Wat is de diagnostische performantie van de eerder genoemde biomarkers in urine in vergelijking met plasma bij PPGL?
- Wat is de diagnostische performantie van de eerder genoemde biomarkers in patiënten met een bijnierincidentaloom?

Biomarkers voor de diagnostiek van neuroblastoom

- Klassiek: vanillylamandelzuur (VMA) en homovanillinezuur (HVA) in urine
- >90% secreteren catecholamines en metabolieten
- Diagnostische performantie VMA en HVA in urine?
  - Sensitiviteit 73-92%
  - Specificiteit 96-100%

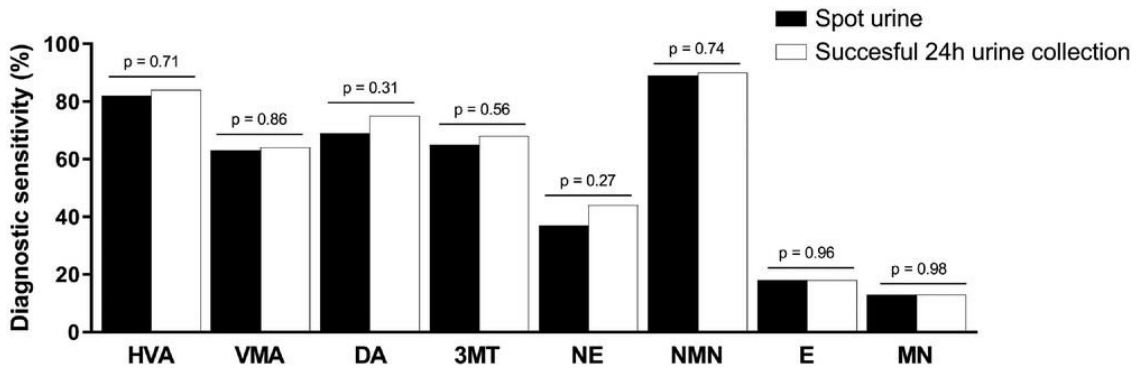
→Panel van acht metabolieten in urine

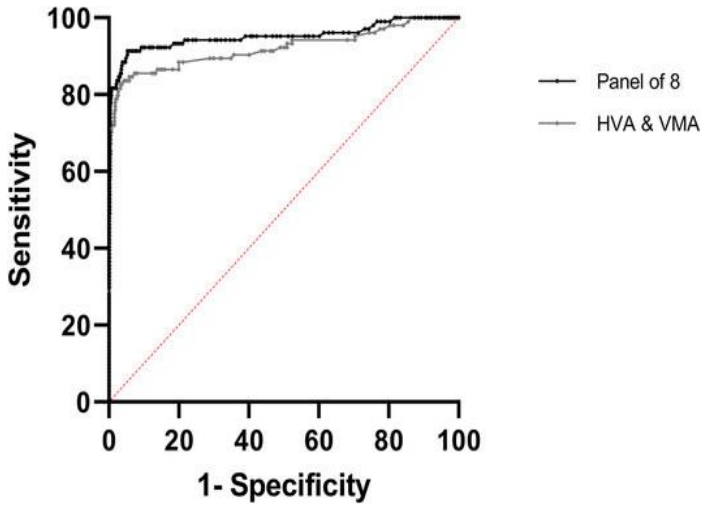
VMA, HVA, adrenaline (A), noradrenaline (NA), dopamine (DA), metanefrine (MN), normetanefrine (NMN), 3-methoxytyramine (3MT)

Biomarkers voor de diagnostiek van neuroblastoom

SIOPEN Catecholamine Working Group

	HVA + VMA	Panel of 8 metabolites
24-Hour urine HPLC-FD		
Sensitivity ($n = 171$)	85 (78.6–89.5)	95 (90.9–97.8)
Spot urine HPLC-FD		
Sensitivity ($n = 62$)	84 (72.6–91.2)	94 (84.1–97.9)
Spot urine UPLC-MS/MS		
Sensitivity ($n = 104$)	86 (77.5–91.2)	94 (87.7–97.6)
Specificity ($n = 571$)	92 (89.4–93.9)	75 (71.4–78.5)

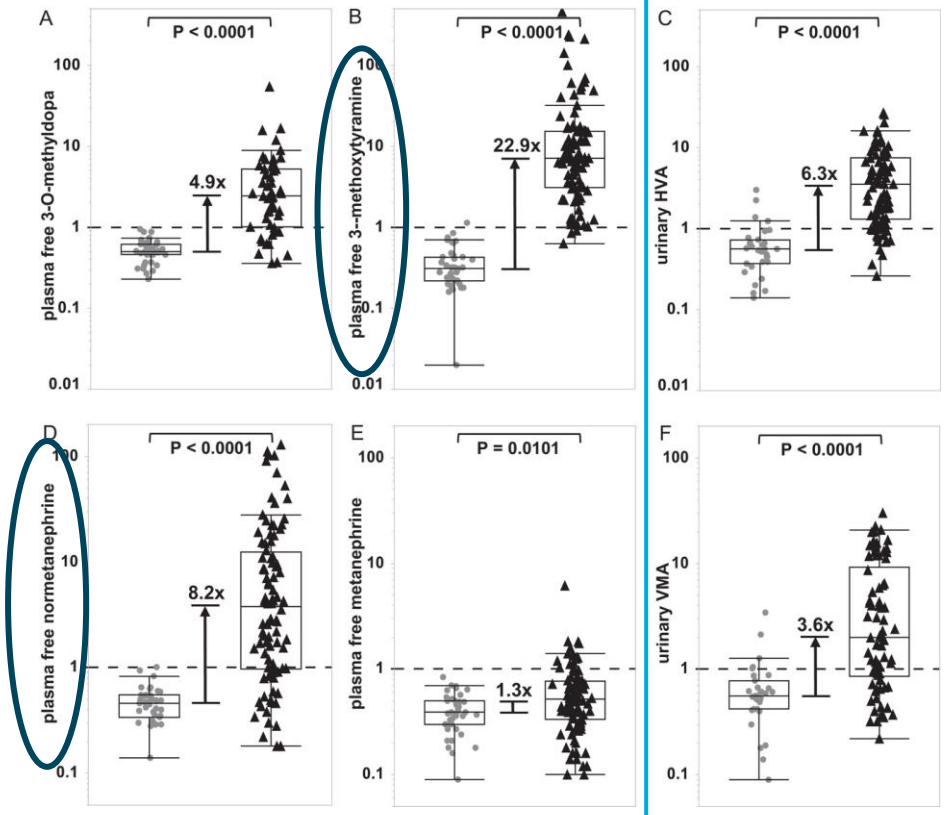




Matser YAH, Verly IRN, van der Ham M, de Sain-van der Velden MGM, Verhoeven-Duif NM, Ash S, Cangemi G, Barco S, Popovic MB, van Kuilenburg ABP, Tytgat GAM; SIOPEN Catecholamine Working Group. Optimising urinary catecholamine metabolite diagnostics for neuroblastoma. Pediatr Blood Cancer. 2023 Jun;70(6):e30289. doi: 10.1002/pbc.30289. Epub 2023 Apr 3. PMID: 37010353.

Biomarkers voor de diagnostiek van neuroblastoom

Plasma?



	Plasma MTY + NMN	Urinary HVA + VMA
Sensitivity	97.9% [a] [95.0%–100.0%] (94/96)	82.2% [74.3%-90.1%] (74/90)
Specificity	95.1% [88.5%–100.0%] (39/41)	84.8% [72.6%-97.0%] (28/33)
AUC		
Raw data	0.994 [b] [0.980-0.999]	0.945 [0.890-0.973]
Normalized data	0.996 [c] [0.983-0.999]	0.880 [0.800-0.931]
Positive predictive value	97.9% [96.5%-99.3%] (94/96)	93.4% [90.6%-96.2%] (71/76)
Negative predictive value	95.1% [91.7%-98.5%] (39/41)	80.0% [73.2%-86.8%] (28/35)

Peitzsch M, Butch ER, Lovorn E, Mangelis A, Furman WL, Santana VM, Hero B, Berthold F, Shulkin BL, Huebner A, Eisenhofer G. Biochemical testing for neuroblastoma using plasma free 3-O-methyldopa, 3-methoxytyramine, and normetanephrine. Pediatr Blood Cancer. 2020 Feb;67(2):e28081. doi: 10.1002/pbc.28081. Epub 2019 Nov 14. PMID: 31724812.

Biomarkers voor de diagnostiek van PPGL

- The Endocrine Society Clinical Practice Guideline (2014)

  - "We recommend that initial biochemical testing for PPGLs should include measurements of plasma free metanephrines or urinary fractionated metanephrines."

  - "We suggest using liquid chromatography with mass spectrometric or electrochemical detection methods rather than other laboratory methods to establish a biochemical diagnosis of PPGL."

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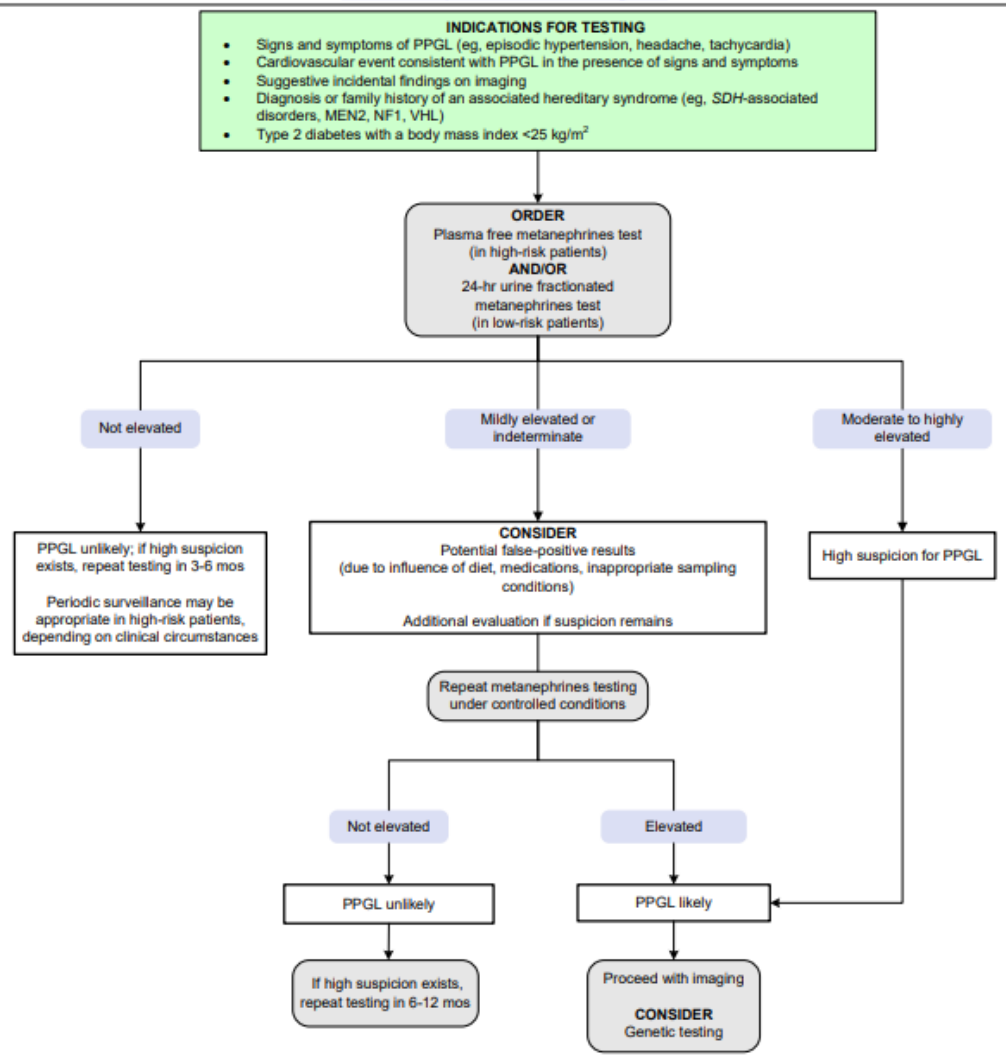
ARUP Consult

Pheochromocytoma - Paraganglioma Biochemical Testing

Click here for topics associated with this algorithm



Abbreviations

MEN2	Multiple endocrine neoplasia type 2
NF1	Neurofibromatosis type 1
PPGL	Pheochromocytoma and paraganglioma
VHL	Von Hippel-Lindau syndrome

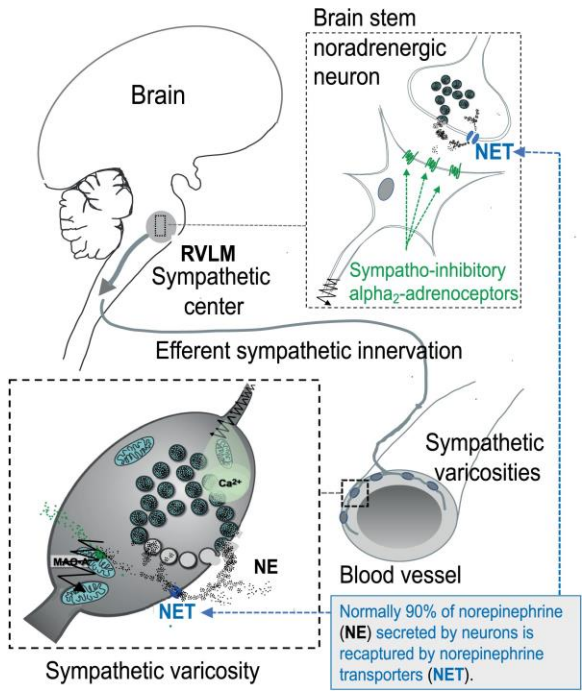
Content Reviewed: December 2023 Last updated: December 2023

Biomarkers voor de diagnostiek van PPGL

	Sensitivity		Specificity	
	Hereditary	Sporadic	Hereditary	Sporadic
Plasma Tests (n)	(76)	(138)	(339)	(305)
Free metanephrines	97% (91-100)	99% (96-100)	96% (94-98)	82% (77-86)
Catecholamines	69% (58-79)	92% (86-95)	89% (86-92)	72% (67-77)
Urine Tests (n)	(68)	(107)	(324)	(211)
Fractionated metanephrines	96% (82-99)	97% (91-99)	82% (77-86)	45% (37-52)
Total metanephrines	60% (46-73)	88% (79-94)	97% (91-99)	89% (81-94)
Catecholamines	79% (68-87)	91% (91-95)	96% (94-98)	75% (69-81)
VMA	46% (35-58)	77% (67-84)	99% (98-100)	86% (80-91)

Eisenhofer G, Pamporaki C, Lenders JWM. Biochemical Assessment of Pheochromocytoma and Paraganglioma. Endocr Rev. 2023 Sep 15;44(5):862-909. doi: 10.1210/endrev/bnad011. PMID: 36996131.

- Chromogranine A
  - Niet zo sensitief en specifiek
  - Hereditaire syndromen (RET mutatie, SDHB mutatie)
- Clonidine suppressie test



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Diagnostische performantie biomarkers in urine versus plasma voor de diagnostiek van PPGL

Group[a]	Sensitivity, %	Specificity, %
All patients (NMN and MN)		
Plasma free	96.6 (228/236)[b]	94.9 (1727/1820)[c]
Urinary free	92.9 (210/226)	94.5 (1660/1756)[c]
Urinary deconjugated	92.9 (210/226)	92.8 (1630/1757)
All patients (NMN, MN, and MTY)		
Plasma free	97.9 (231/236)[b]	94.2 (1714/1820)[c]
Urinary free	93.4 (211/226)	94.2 (1655/1756)[c]
Urinary deconjugated	92.9 (210/226)	92.1 (1619/1757)
High pretest prevalence (NMN, MN, and MTY)		
Plasma free	96.7 (145/150)[b]	92.8 (569/613)
Urinary free	89.6 (129/144)	92.8 (542/583)
Urinary deconjugated	89.5 (128/143)	91.8 (536/584)
Low pretest prevalence (NMN, MN, and MTY)		
Plasma free	100 (86/86)	94.9 (1145/1207)[c]
Urinary free	100 (82/82)[d]	95.0 (1114/1173)[c]
Urinary deconjugated	98.8 (82/83)[d]	92.3 (1083/1173)

Eisenhofer G, Prejbisz A, Peitzsch M, Pamporaki C, Masjkur J, Rogowski-Lehmann N, Langton K, Tsourdi E, Pęczkowska M, Fliedner S, Deutschbein T, Megerle F, Timmers HJLM, Sinnott R, Beuschlein F, Fassnacht M, Januszewicz A, Lenders JWM. Biochemical Diagnosis of Chromaffin Cell Tumors in Patients at High and Low Risk of Disease: Plasma versus Urinary Free or Deconjugated *O*-Methylated Catecholamine Metabolites. Clin Chem. 2018 Nov;64(11):1646-1656. doi: 10.1373/clinchem.2018.291369. Epub 2018 Aug 10. PMID: 30097498.

Diagnostische performantie biomarkers in urine versus plasma voor de diagnostiek van PPGL

- Plasma: Preanalytiek!

  Sympathoadrenale systeem

  - Positie van de patiënt
  - Via katheter
  - Temperatuur (buiten en staal)
  - Dieet en medicatie
  - Acuut zieke patiënten
  - Nierlijden?

Drug category	Pharmacodynamic actions	Main impact
Stimulants		
Nicotine	•Activation of nicotinic cholinergic receptors	Increased adrenal epinephrine secretion
Caffeine	•Mobilization of intracellular calcium stores	Increased adrenal epinephrine secretion
Sympathomimetics		
Amphetamine Methamphetamine	•Increased release of monoamines from vesicular stores of sympathetic nerves •Inhibition of monoamine oxidase •Blockade of neuronal cell membrane norepinephrine (NE) transporters (NET)	Increased NE concentrations in the neuronal cytoplasm Reversed transport of NE by NET from cytoplasm to extracellular space Increased NE escape from reuptake
Ephedrine Pseudoephedrine	•Activation of alpha and beta-adrenergic receptors •Inhibits function of vesicular monoamine transporters •Inhibits NE reuptake (indirectly)	Increased NE release Increased NE release from secretory vesicles
Norepinephrine reuptake blockers		
Tricyclic antidepressants Venlafaxine/Duloxetine Cocaine	•Blockade of neuronal cell membrane NE transporters •Centrally mediated sympathoinhibition	Decreased sympathetic nerve firing and secretion of NE from sympathetic nerves, but opposing increased escape of NE from reuptake after neuronal secretion
Alpha$_2$ adrenoreceptor antagonists		
Phenoxybenzamine Mirtazapine Yohimbine	•Antagonism of alpha2-adrenoreceptors at central sympathoinhibitory sites and on sympathetic neurons	Increased sympathetic nerves firing secretion of NE from sympathetic nerves
Monoamine oxidase (MAO) inhibitors	•Blockade of the deamination of the O-methylated catecholamine metabolites	Increased plasma and urinary metanephrines with normal catecholamines
Atypical antipsychotics		
Quetiapine, Clozapine, Risperidone	•Inhibition of dopaminergic, adrenergic, and serotoninergic receptors •Antagonism to α_2-adrenoreceptors	Increased secretion of NE from sympathetic nerves

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Diagnostische performantie biomarkers in patiënten met een bijnierincidentaloom

- Definitie:

  Bijniermassa op beeldvorming te zien, waarbij de beeldvorming voor een niet-adrenale indicatie was

- Prevalentie: 3% op 40 jaar → 10% op 70 jaar
- Diverse etiologie
- European Society of Endocrinology Clinical Practice Guideline (2023):
  - "We recommend that every patient with an adrenal incidentaloma should undergo careful assessment including clinical examination for symptoms and signs of adrenal hormone excess."
  - "We recommend excluding pheochromocytoma by measurement of plasma free metanephrines or urinary fractionated metanephrines."

    Enkel indien HU ≥ 10 op CT zonder contrast

Etiology	Prevalence of the different entities among adrenal incidentalomas
Adrenocortical adenoma or macronodular bilateral adrenal hyperplasia	80%-85%
•Nonfunctioning	40%-70%
•Mild autonomous cortisol secretion	20%-50%
•Primary aldosteronism	2%-5%
•Overt Cushing's syndrome	1%-4%
Other benign mass	
•Myelolipoma	3%-6%
•Cyst and pseudocyst	1%
•Ganglioneuroma	1%
•Schwannoma	<1%
•Hemorrhage	<1%
Pheochromocytoma	1%-5%
Adrenocortical carcinoma	0.4%-4%
Other malignant mass (mostly adrenal metastases)	3%-7%

Fassnacht M, Tsagarakis S, Terzolo M, Tabarin A, Sahdev A, Newell-Price J, Pelsma I, Marina L, Lorenz K, Bancos I, Arlt W, Dekkers OM. European Society of Endocrinology clinical practice guidelines on the management of adrenal incidentalomas, in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol. 2023 Jul 20;189(1):G1-G42. doi: 10.1093/ejendo/lvad066. PMID: 37318239.

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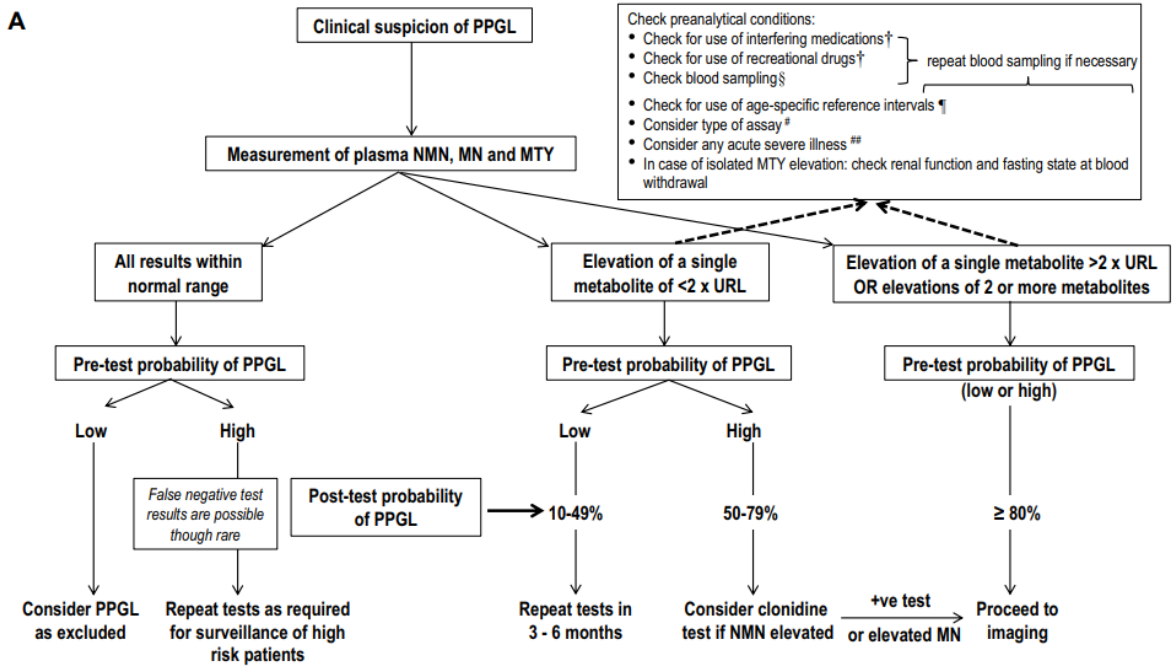
Neuroblastoom

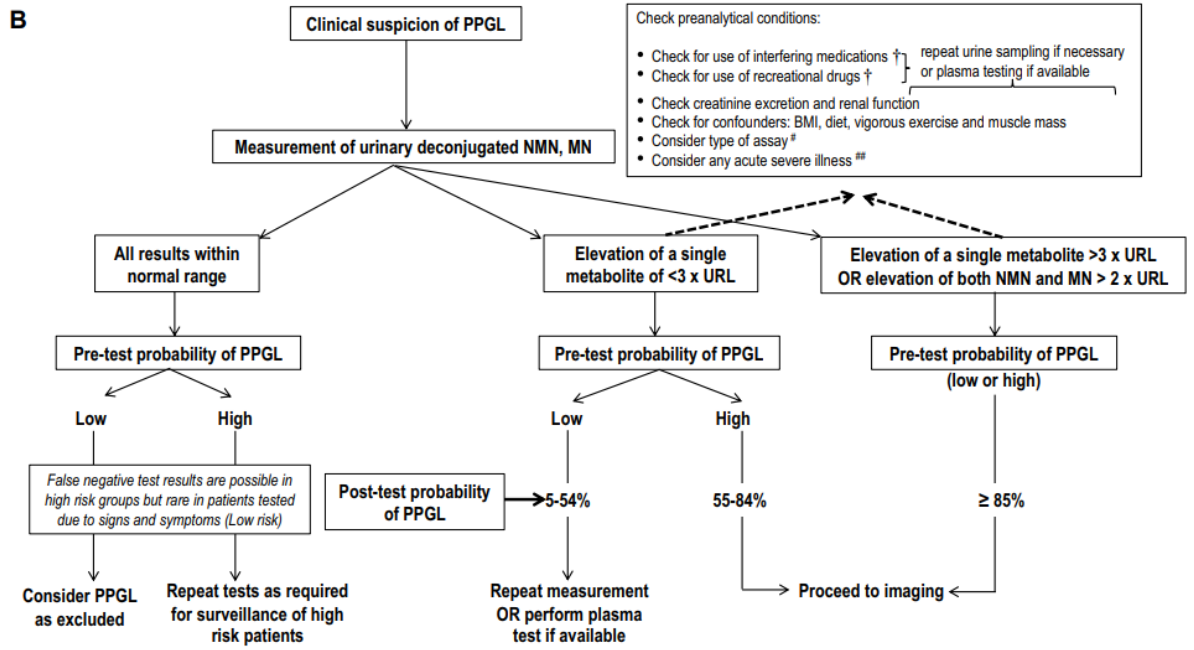
- Meerwaarde van panel van 8 metabolieten?
- Urine of plasma?
- The European Standard of Clinical Practice (2021):

  Evaluatie bij diagnose:

  “Urine catecholamine metabolites (VMA and HVA minimum), measured in mol/mmol of creatinine. It is recommended that dopamine is also measured. It can be performed in a single urine sample.”

Feochromocytoom en paraganglioom





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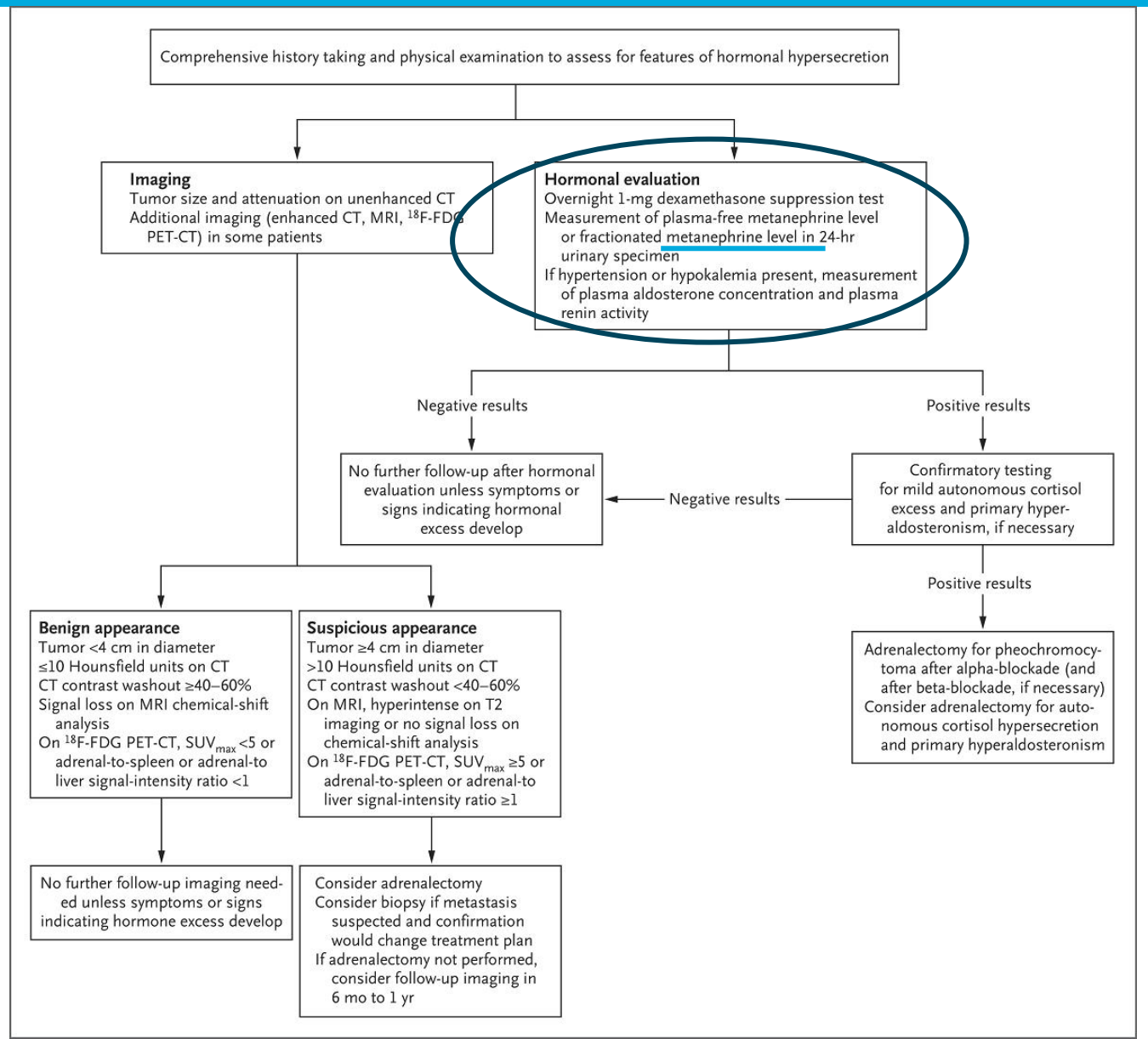
Bijnierincidentaloom



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- Implementatie plasma catecholamines en metanefrines