
ANAH
ASEAN NETWORK of
ADRENAL HYPERTENSION
Breaking Boundaries in Adrenal Disorders
ANAH - AFES Joint Symposium 2025
14 - 16 Nov 2025 | Ariyana Convention Center, Da Nang city, Vietnam

ASEAN NETWORK of ADRENAL HYPERTENSION

*Breaking Boundaries in Adrenal Disorders*

**ANAH-AFES Joint Symposium 2025**

14 - 16 Nov 2025 | Ariyana Convention Centre, Da Nang City, Vietnam

*Meet the Professor*

# Ruling OUT pheochromocytoma / paraganglioma

Gregory A. Kline MD FRCPC
Medical Director, UC Adrenal Research Group
Clinical Professor of Medicine
University of Calgary

# Textbook vs Reality

- Most texts/review articles teach how to diagnose **("rule-in")** PPGL
- Most patients referred for query PPGL do NOT have PPGL
  - The role of the endocrinologist is usually to **RULE-OUT**
    - "spells" – very broadly defined!
    - Hypertension (sustained)
    - Adrenal mass
    - Anxiety
    - Paroxysmal high BP

# Key Points

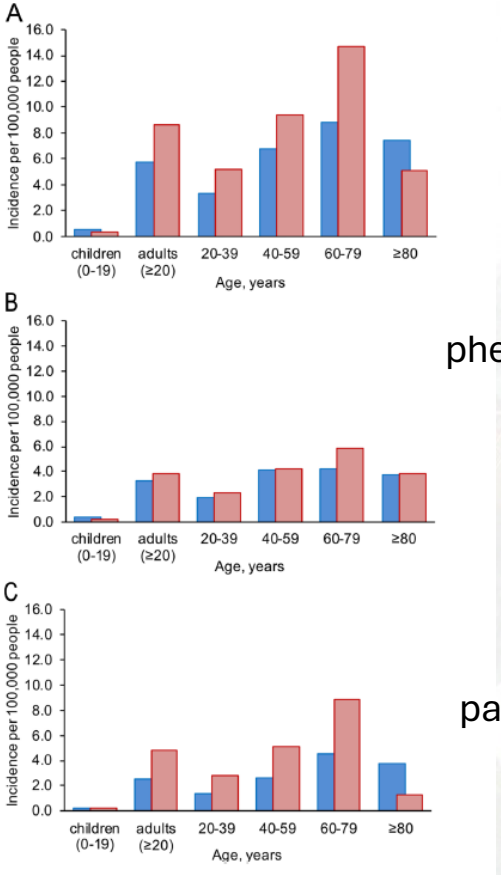
1) PPGL is rare thus pre-test probability always starts LOW
2) Beware the reported reference interval
3) Inpatient metanephrines are highly unreliable on their own
4) PPGL are rarely anatomically occult
5) Adrenal pheo lesions are not low density
6) Supine age-adjusted plasma nor/metanephrine as the best test
7) A way forward based on **PRE-TEST PROBABILITY**

## Pre-Test Probability

| LOW | MODERATE - HIGH |
|---|---|
| Primary goal:<br>RULE OUT<br>(confirm absence) | Primary goal:<br>RULE IN<br>(confirm presence) |

# 1) PPGL is rare but often considered

- Incidence 0.66 per 100,000 people per year*
- 0.32 cases of **pheo** per 100,000 people per year
- **<u>In adults only,</u>**
- 3.27 and 3.84 **pheo** per 100,000 adults per year (M/F)
- Ages 60-79,
- 8.8 and 14.7 **pheo** per 100,000 older adults per year (M/F)




All PPGL
Men-blue
Women - red

pheochromocytoma

paraganglioma

*European Journal of Endocrinology* (2020) **184**, 19–28

# Biochemistry

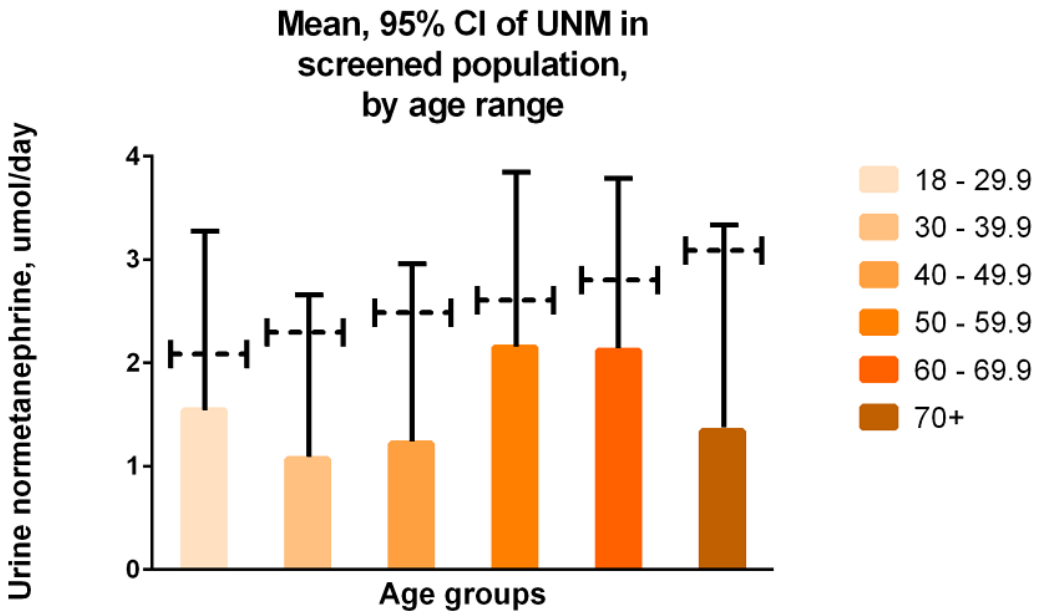
- Overall prevalence of 0.57% **among those who were tested**

*European Journal of Endocrinology*
(2020) **184**, 19–28

# PPGL is RARE

- Pre-test probability will be LOW unless:
- * prior PPGL in the patient or family
- * known genetic syndrome
- * higher density/atypical adrenal lesion
- * very high metanephrines
- **As you decide next steps, let your pre-test probability GUIDE YOU**

# 2) Know your reference intervals




Among a population where case-finding using Urine metanephrines takes place:

a. Positivity rate: **20.2%**
b. Given expected prevalance, most abnormals in 13,000 tests will be FP
a. The importance of the derivation population

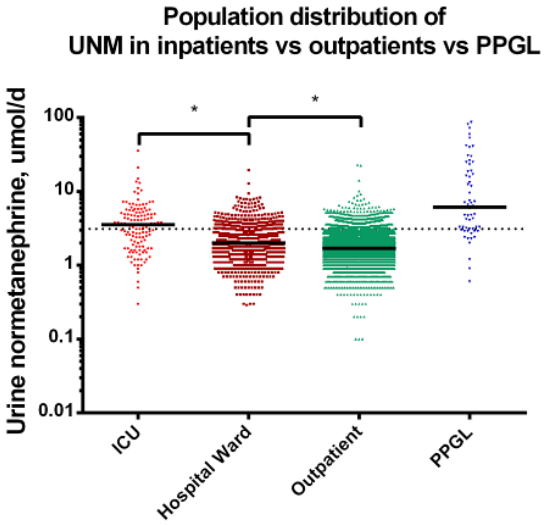
Dashed horizontal line = age-dependent lab ULN

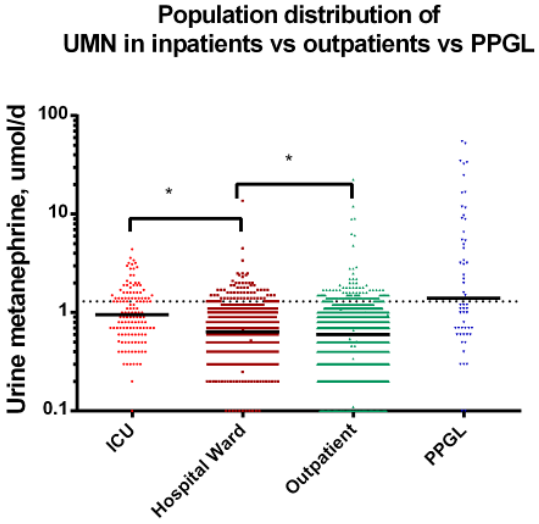
*Clinical Biochemistry 77 (2020) 26–31*

# 3) What about inpatients?

- Urine MN/NM database April 2012 – June 2018
- PPGL epi database, same time frame
- ***Inpatient measures = 1102 (wards 842, ICU 132)***

Kline GA et al. Am J Med 2021 Aug 1;134(8):1039-46.




Any elevation in either NM or MN or both:

Outpt: 18.7%

Hospital ward: 34.4%

Critical care: 67.4%

**Large overlap between PPGL and inpts**

Kline GA et al. Am J Med 2021 Aug 1;134(8):1039-46.

# When does PPGL become a likely diagnosis?

| location | analyte | 98% spec, Umol/d | PPV with Prev 0.7% |
|---|---|---|---|
| Outpt | NM | > 4.35 | 17% |
| | MN | > 1.35 | 15% |
| Ward | NM | > 6.95 | 14% |
| | MN | > 1.95 | 14% |
| ICU/CCU | NM | > 14.25 | 10% |
| | MN | > 3.30 | 11% |

Kline GA et al. Am J Med 2021 Aug 1;134(8):1039-46.

# 4) Imaging: pheo lesions are not occult

**CANADA (2013-2018)**

- N=239
- Adrenal location = 49%
- Abdominal location = 12%
- Thoracic = 1%
- H&N = 37%
- Size (median, IQR) = 3.2 cm [2.0-5.0]

*European Journal of Endocrinology* (2020) **184**, 19–28

**DENMARK (1977-2015)**

- N=567
- Adrenal location = 86%
- Size (median, range) = 4.0 cm (1.1-23.0)

*The Journal of Clinical Endocrinology & Metabolism*, 2021, Vol. 106, No. 5, e2251–e2261

# Imaging

**USA (1980-2018)**

- N=390
- Adrenal location = 100% (by design)
- Size (median, range) = 5.1 cm [1.0-28.0]

*Am J Surg Pathol* • Volume 45, Number 9, September 2021

**SPAIN (1980-2016)**

- N=106
- Adrenal location = 86%
- Size (median, IQR) = 4.3 cm (3.0-6.0)

Iglesias P, Revista Clínica Española 2021 Jan 1;221(1):18-25.

# Imaging

**PHILLIPINES (2010-2021)**

- N=30
- Adrenal location = 100%
- Size (mean) = 7.0 cm
- 83% > 4 cm

Hernandez E, Journal of the ASEAN Federation of Endocrine Societies. 2024 Sep 9;39(2):41.

**UK (1977-2015)**

- N=167
- Adrenal location = 86%
- Size (median, range) = 4.5 cm (1.0-21.0)

Aggarwal S, J Clin Endocrinol Metab 2024 Jan;109(1):e389-96.

# 5) Density of Lesions: pheos are not adenomas

- multi-centre retrospective, n=376 confirmed PPGL
  - 99.5% had unenhanced CT HU > 10
  - Washout data unreliable
- N= 46 PCC vs 98 adrenal adenomas
  - 100% of PCC had unenhanced CT HU > 10
  - Washout criteria not specific for PCC

Canu L et al. J Clin Endocrinol Metab 2019 Feb;104(2):312-8.

Patel J et al. Am J Roentgenol 2013 Jul;201(1):122-7.

# APPLICATION: this is NOT like PA or Cushings

1. Truly “occult” PPGL is exceedingly rare within a very rare disease
2. **PPGL lesions are BIG**
3. **PPGL lesions are DENSE**
    1. If you are puzzled by the biochemistry this is one time when imaging could be done instead of sorting out the labs.
    2. Absence of an obvious lesion in CT chest/abd/pelvis markedly decreases post-test probability
    3. If a lesion is found but is < 10 HU (adrenal) – highly unlikely to be PCC
    4. If a lesion is found and is > 10 HU, you shift from RULING OUT to RULING IN

# 6) Plasma metanephrines

- Plasma normetanephrine is strongly influenced by upright posture
- Seated plasma normetanephrine is highly age-dependent
- Use of a plasma normetanephrine reference interval that is not posture or age-adjusted can have just as many false positives as urine normetanephrine

# 7) PRE-TEST PROBABILITY and NEXT STEPS

## Low Pre-test probability: RULE OUT

1. Consider the reference interval upper limit
2. Most PPGL have results > 2-3 x URL,
3. Inpatients can have results > 5 X URL
4. If you have access: supine, age-adjusted plasma normetanephrine
5. Easiest way forward may be imaging: if you don't see an obvious, higher density lesion and pre-test probability was low, STOP. The patient almost certainly does not have PPGL.
6. Consider the differential diagnosis and re-direct or follow periodically

## HIGH Pre-test probability: RULE IN

1. Family history/genetics, prior PPGL, very high biochemical screen, high-density lesion on imaging
2. Not much more needed! Advanced imaging…?
3. Surgery likely warranted; it's OK to be wrong if pre-test probability was high and atypical lesion present

# Case 1

- 45 year old nurse with 8 month history of episodic high BP, several emergency room visits for high BP
- No target organ damage, BP can be up to 180/110
- No family history of PPGL-like disease
- Pre-test probability: LOW
- 24 hour urine normetanephrine 3.9 nmol/d (< 3.0 umol/d)
- 24 hour urine metanephrine 0.3 umol/d (< 0.9 umol/d)
- *Ideal screening population reference interval URL < 4.3 umol/d*
  - NORMAL
  - **STOP**

# Case 2

- 79 year old man admitted to neurosurgical ICU with intra-cerebral hemorrhage
- BP highly variable, often very high
- Day 4 – abdominal distention, CT abdomen
- Incidental 2.2 cm low density (-12 HU) left adrenal mass
- 24 hour urine normetanephrine 9.9 umol/d (< 4.3 umol/d)
- 24 hour urine metanephrine 1.4 umol/d (<1.3 umol/d)
- Pre-test probability: **LOW**
- Decision: **STOP** (maybe later --- ? PA)

# Case 3

- 47 year old woman with chronic depression/anxiety and “spells”
- Using SNRI (venlafaxine), cannot be stopped.
- No family history of PPGL
- 24 hour urine normetanephrine 4.8 umol/d (< 3.9) repeatedly
- Historically – clonidine suppression test ?
- Supine plasma normetanephrine with age-adjusted interpretive range not available
- Pre-test probability: LOW
- CT chest/abd/pelvis – no lesions seen = **STOP**

# Case 4

- 25 year old man with incidental adrenal lesion found after motorcycle crash
- CT – 4.5 cm heterogeneous adrenal lesion, 37 HU unenhanced
- Mild hypertension but no other symptoms
- Outpatient 24 hour urine normetanephrine 7.9 umol/d, metanephrine 3.4 umol/d
- Pre-test probability: HIGH
- Decision - **surgery**

# What else could it be?

- Anxiety/PTSD
- Food, wine, drugs, procedures
- Chest pain, abdominal pain, constipation, cardiomyopathy, MSOF
- Baro-reflex injury, POTS, OSA, carcinoid syndrome, LMS, autonomic neuropathy, RAS, hyperventilation, pseudopheochromocytoma, arteriosclerotic hemodynamics, acute intermittent porphyria etc.


# Thank you!

gakline@ucalgary.ca