

SUBJECT VISIT PLAN RECORD

Inclusion Criteria

Patients with suspected PPGLs

Male and female patients (all ages, including children above 5 years) with suspected PPGLs are included on the basis of one or more of the following:

- (i) Patients with a previous history of PPGLs.
- (ii) New onset of hypertension or hypertensive episodes and/or symptoms suggestive of PPGLs (sweating, headache, pallor, palpitations, or other suspicious spells).
- (iii) Therapy-resistant hypertension, defined as an office blood pressure of >140/90 mmHg despite treatment with ≥ 3 antihypertensive agents at full dose (including a diuretic).
- (iv) Family history of PPGL or genetic mutations known to predispose individuals to develop PPGLs.
- (v) Presence of an adrenal or retroperitoneal mass discovered incidentally during abdominal imaging studies carried out for investigations unrelated to clinical suspicion of PPGLs.
- (vi) Any other situation involving reasonable clinical suspicion of a PPGL (e.g., patients with a vasopressor response during anesthesia, surgery or angiography).

Patients with suspected GEP tumors

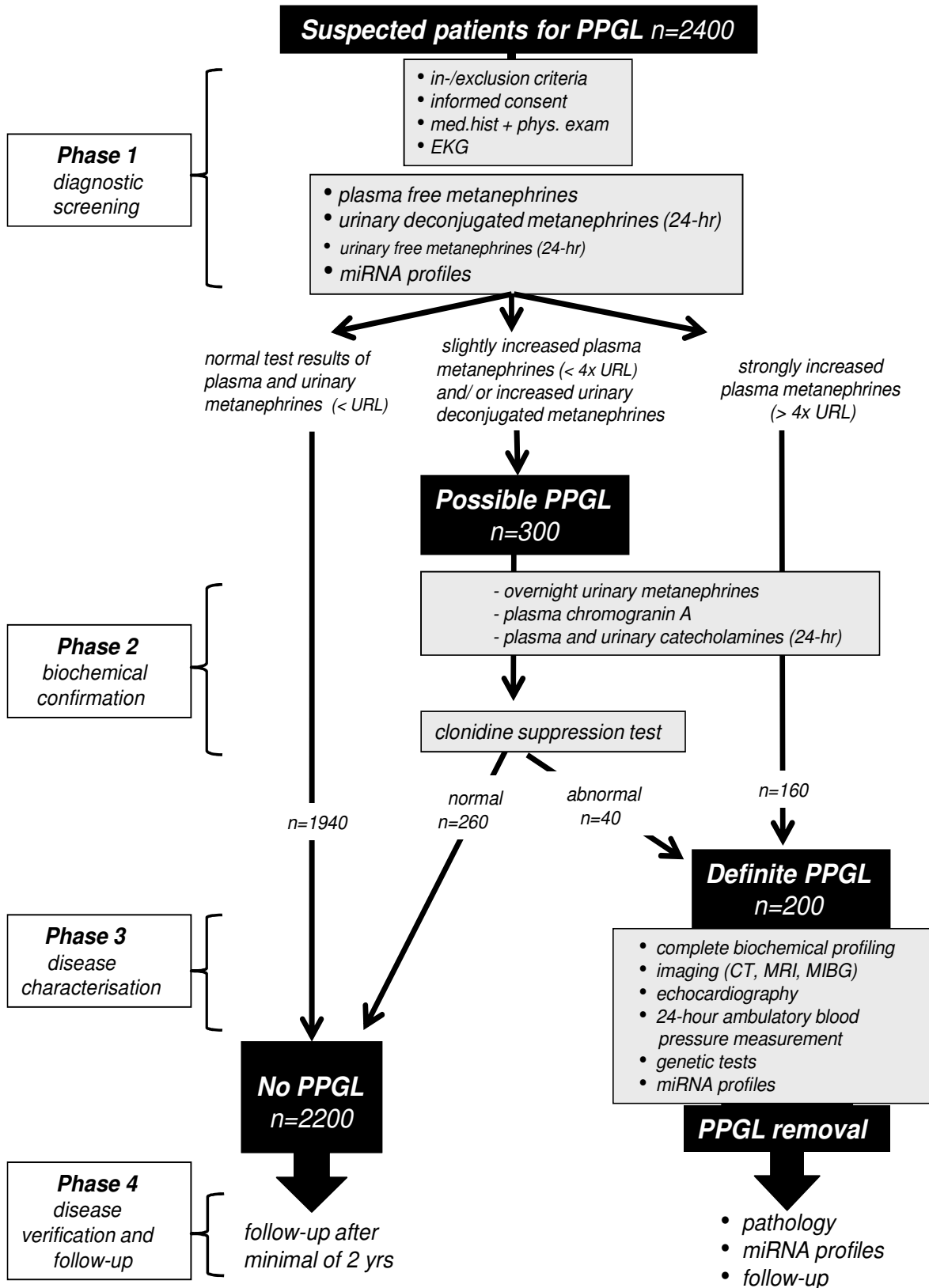
Adult male and female patients (all ages above 18 yr) with proven or suspected GEP tumors are included on the basis of one or more of the following:

- (i) Patients referred or recruited because established GEP tumors.
- (ii) Patients suspected to have GEP tumors based on clinical signs and presenting features (e.g., flushing, diarrhea, steatorrhea, wheezing, dyspepsia, ulcers, hypoglycemia, heart disease, deep vein thrombosis, anorexia, nausea, vomiting, constipation, hypotension, fainting, skin disorders, dumping syndrome, pernicious anaemia, autoimmune disorders, diabetes, gall bladder disease).
- (iii) Patients suspected to have GEP tumors based on previous biochemical testing and/or imaging studies.

Exclusion Criteria

- (i) Subjects with impaired mental capacity that precludes informed consent.
- (ii) Subjects who require medications that would interfere with or invalidate primary outcome parameters (e.g., tricyclic antidepressants).
- (iii) Pregnant women will not be included as part of either normotensive or hypertensive control groups. Apart from this pregnancy or advanced age does not constitute criteria for exclusion from the protocol. However, pregnant women are excluded from receiving clonidine under the protocol and from all portions of the protocol involving administration of radioactivity. In women of childbearing age (up to age 50) a pregnancy test is performed. In those with a positive result, MRI will be used as an imaging modality but no PET scanning, MIBG scanning or contrast CT will be performed under the protocol.
- (iv) Children will not be included as part of either normotensive or hypertensive control groups. Children below 5 years of age are also excluded from all portions of the protocol. Apart from the above, children aged 5 to 18 yrs are not excluded from the protocol. CT scans, MIBG scans and fluorodeoxyglucose PET scans will be offered to children as part of the protocol and as clinically indicated. However, children are excluded from the clonidine test under the protocol.
- (v) Patients at risk from injury from the MRI magnet due to implantable metal or who suffer from anxiety in enclosed spaces are excluded from parts of the study involving MRI.

Flow chart for patients with PPGLs illustrating the four phases of the study,
 (the summarized procedures for each phase and the numbers of patients expected to participate through each phase)



PHASE 1

1. Last Name: _____ 2. First Name: _____

3. Gender: _____ 4. DOB: _____

4. Address: _____

6. City: _____ 7. Post Code: _____

8. Tel (home): _____ 9. Mobile: _____

10. Email: _____

11. NOK:

A: Last Name: _____ B: First Name: _____

C: Address: _____

D: City: _____ E: Post Code: _____

F: Tel (home): _____ G: Mobile: _____

12. Referring or Personal Physician: _____

13. Study Center: _____

14. Subject type: _____

15. Entry/protocol: _____ If no, reason: _____

Unique patient
identifier and Date
Consent signed

16. Main inclusion criterion:

- Suspicion based primarily on signs and symptoms
- Therapy resistant hypertension
- Incidental finding on imaging for unrelated condition
- Routine screening due to known mutation or hereditary syndrome
- Routine screening due to previous history of pheochromocytoma
- Other: _____

17. Date: H&P Performed: _____ 18. EKG performed: _____

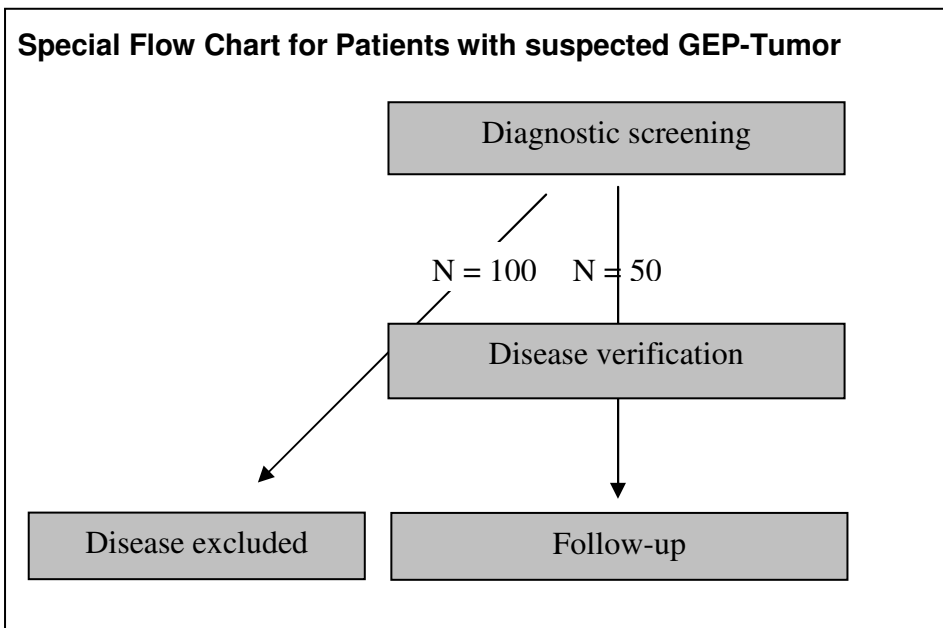
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PHASE 1 (additional sampling for patients with suspected GEP-tumor)

- 1. measurement of plasma Chromogranin A (EDTA): _____
- 2. measurement of plasma Serotonin (CTAD): _____
- 3. measurement of serum Serotonin: _____
- 4. urine 5HIAA (24 h; acidified): _____



5. Telephone follow-up: _____

6. persisting signs/symptoms: YES NO

History and Physical examination

History:

Medications:

Antihypertensive Medications: _____

Other prescribed and over the counter medications or dietary:

Specific questions:

A)

History of hypertension

Patient has history of hypertension If yes, since when Year

If yes, hypertension sustained or episodic

B)

Medical History

Patient has history of previous PPGL If YES, number of tumors

	Date diagnosed		Tumor Resected	Tumor location		Dimensions (cm)		
	Year	Mth		A or E	Details	x	y	z
1	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
2	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
3	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
4	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
5	<input type="text"/>	<input type="text"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>

Patient has residual disease Residual disease is metastatic

If YES, locations and no. of lesions

Bones	Lymph nodes	Lungs	Liver
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>

History of cardiovascular or metabolic disease History of other neoplasms

If YES, detail what disease

Diabetes mellitus	<input type="checkbox"/>
Cardiomyopathy	<input type="checkbox"/>
Heart failure	<input type="checkbox"/>
Coronary artery disease	<input type="checkbox"/>
Myocardial infarction	<input type="checkbox"/>
Cerebrovascular disease	<input type="checkbox"/>
Renal vascular disease	<input type="checkbox"/>
Renal insufficiency	<input type="checkbox"/>
Shock	<input type="checkbox"/>
Multiple organ failure	<input type="checkbox"/>
Other	<input type="text"/>

If YES, detail what neoplasms

Skin	<input type="checkbox"/>
Central nervous system	<input type="checkbox"/>
Gastrointestinal	<input type="checkbox"/>
Pancreas	<input type="checkbox"/>
Urogenital	<input type="checkbox"/>
Lung	<input type="checkbox"/>
Bone/Con. Tissue	<input type="checkbox"/>
Breast cancer	<input type="checkbox"/>
Prostate cancer	<input type="checkbox"/>
Leukemia/Lymphoma	<input type="checkbox"/>
Thyroid	<input type="checkbox"/>
Other	<input type="text"/>

Specific questions:

C)

Signs & symptoms

Symptom (s) Present	Presence in past 30 days	Symptom associated with others	Frequency of symptom occurrence	Duration of symptom occurrence
Headaches	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Sweatiness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Palpitations	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Tremor	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Pallor	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Flushing	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Panic/Anxiety	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Nausea/Vomitting	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Weakness/Fatigue	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Pain in abdomen	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Pain in chest	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Constipation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

D)

Hereditary PPGL syndromes

Patient has evidence of hereditary syndrome y/n

Evidence includes family history of PPGL`s y/n

Indicate number of 1e degree relatives with PPG

Indicate number of 2e degree relatives with PPGL`s

Evidence includes clinical stigmata y/n

Indicate syndrome

Specific details

Evidence includes clinical stigmata y/n

Specific affected gene(s)

VHL	MEN2	NF1
Ren cyst/carc	MTC	Cafe au lait
CNS HBLAST	PTH	Neurofibroma
Ret. Angiom	Muc.Neur.	Freckling skin
Pancr cyst/ad	Marfanoid	Opt. glioma
Endolymph.TU		Lisch noduli
Epid.cysts		Oss. Lesions

Other Considerations:

Physical Examination:

Blood Pressure L: _____ Pulse L: _____ Waist: _____

Blood Pressure R: _____ Pulse R: _____ Height: _____

2. Blood Pressure: _____ 2. Pulse: _____ Weight: _____

3. Blood Pressure: _____ 3. Pulse: _____ Allergy: _____

Physical Examination (continued):

Skin: • necrolytic migratory erythema: Yes No

Head:

Eyes:

Mouth/Pharynx:

Thyroid:

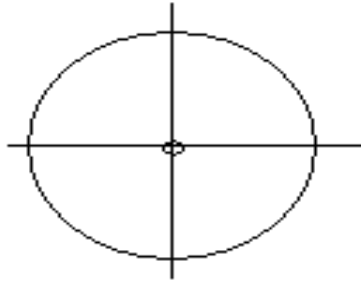
Thorax:

Heart:



Abdomen:

Extremities:



CNS:

PHASE 2 - (ENTRY-DATE: _____)

Has patient changed medications since previous phases: NO

Changed Medications:

Antihypertensive Medications: _____

Other prescribed and over the counter medications or dietary:

PHASE 2 for pregnant woman/teens and children/teens (5-18 years)

1. Pregnancy test positive: 2. Date Pregnancy test performed: _____

Other Considerations:

PHASE 2 (Pregnancy test negative, no child)

DATE: _____

Clonidine suppression test see also additional DATA COLLECTION SHEET

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HEP CLON 180
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with date of sample

Urine collection and Chromogranin A blood sample

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URIN ON MET
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URIN DY CAT
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PHASE 3 - (ENTRY-DATE: _____)

Has patient changed medications since previous phases: NO

Changed Medications:

Antihypertensive Medications: _____

Other prescribed and over the counter medications or dietary:

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PHASE 2 for pregnant woman/teens and children/teens (5-18 years)

1. Pregnancy test positive: 2. Date Pregnancy test performed: _____

No CT- or Nuclear tracer-scan in pregnant women

No CT-scan in children/teens (5-18 years)

Blood pressure measurements Phase 3:

Supine Blood Pressure 1: _____ / _____ ; **Heart Rate 1:** _____

Supine Blood Pressure 2: _____ / _____ ; **Heart Rate 2:** _____

2 minute standing BP: _____ / _____ ; **HR 2 min:** _____

3 minute standing BP: _____ / _____ ; **HR 3 min:** _____

PHASE 3 (Pregnancy test negative, no child)

	Ordered (Date)	Performed (Date)
A. ABPM:	_____	_____
B. Echocardiography:	_____	_____
C. MRI-Scan:	_____	_____
D. CT-Scan:	_____	_____
E. MIBG-Scan:	_____	_____
F. Ga-DOTATOC:	_____	_____

PHASE 3 – METABOLIC STUDIES (All patients):

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PHASE 4 – EXCLUSION (ENTRY-DATE: _____)

1. Telephone follow-up with patient or his physician: _____

2. PPGL ultimately excluded: YES NO

YES: a. all signs and symptoms of PPGL now resolved
b. alternative diagnosis established type: _____
c. incidentaloma resected – not PPGL type: _____
d. other

NO: Date of Outpatient visit: _____

Has patient changed medications since previous phases: NO

Changed Medications (also for respectable and unresectable tumors):

Antihypertensive Medications: _____

Other prescribed and over the counter medications or dietary:

<u>Questions:</u>	A) Blood pressure/HRT normal	YES	NO
	B) Signs/Symptoms present	YES	NO
	C) Biochemistry normal	YES	NO

<u>Final PPGL Confirmation:</u>	A) Tumor confirmed	YES	NO
	B) Tumor excluded	YES	NO
	C) Inconclusive	YES	NO

PHASE 4 – OPERATION (ENTRY-DATE: _____)

PHASE 4 – post OP (2-4 weeks after surgery)

1. Operation: YES, DATE OF SURGERY: _____

NO, go to PHASE 4- INOPERABLE PATIENTS

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Reason why patient was not operated:

2. Surgical pathology: _____

3. PPGL diagnosed by pathological examination: YES NO

4. Evidence of metastases from examination of resected lymph nodes: YES NO

5. Blood Pressure measurements post-OP:

Blood Pressure L: _____ Pulse L: _____

Blood Pressure R: _____ Pulse R: _____

2. Blood Pressure: _____ 2. Pulse: _____

3. Blood Pressure: _____ 3. Pulse: _____

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PHASE 4 – One Year

1. EKG: _____

2. Blood pressure measurements Phase 3:

Supine Blood Pressure 1: _____ / _____ ; Heart Rate 1: _____

Supine Blood Pressure 2: _____ / _____ ; Heart Rate 2: _____

2 minute standing BP: _____ / _____ ; HR 2 min: _____

3 minute standing BP: _____ / _____ ; HR 3 min: _____

Ordered (Date)

Performed (Date)

3. Echocardiography: _____

4. ABPM: _____

PHASE 4 – OPERATION continued

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PHASE 4 – METABOLIC STUDIES (All patients):

Affix
SER INS Record
Label with date of
sample

Affix
FLU HBA GLUC
Record Label with
date of sample

PHASE 4 – YEAR 2 FOLLOW UP

PHASE 4 – YEAR 3 FOLLOW UP

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PHASE 4 – YEAR 4 FOLLOW UP

PHASE 4 – YEAR 5 FOLLOW UP

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PHASE 4 – SPECIAL PROCEDURES

1. FDG-PET (Pregnancy excluded, no child) in inoperable patients, patients with SDHB mutation or metastatic disease confirmed on MRI/CT or MIBG:

Ordered (Date)

Performed (Date)

2. Positive Genetics (SDHB or SDHD mutations):

Ordered (Date)

Performed (Date)

MRI-scan: _____
(Neck, Thorax, Abdomen)

CT-scan: _____
(Neck, Thorax, Abdomen)
