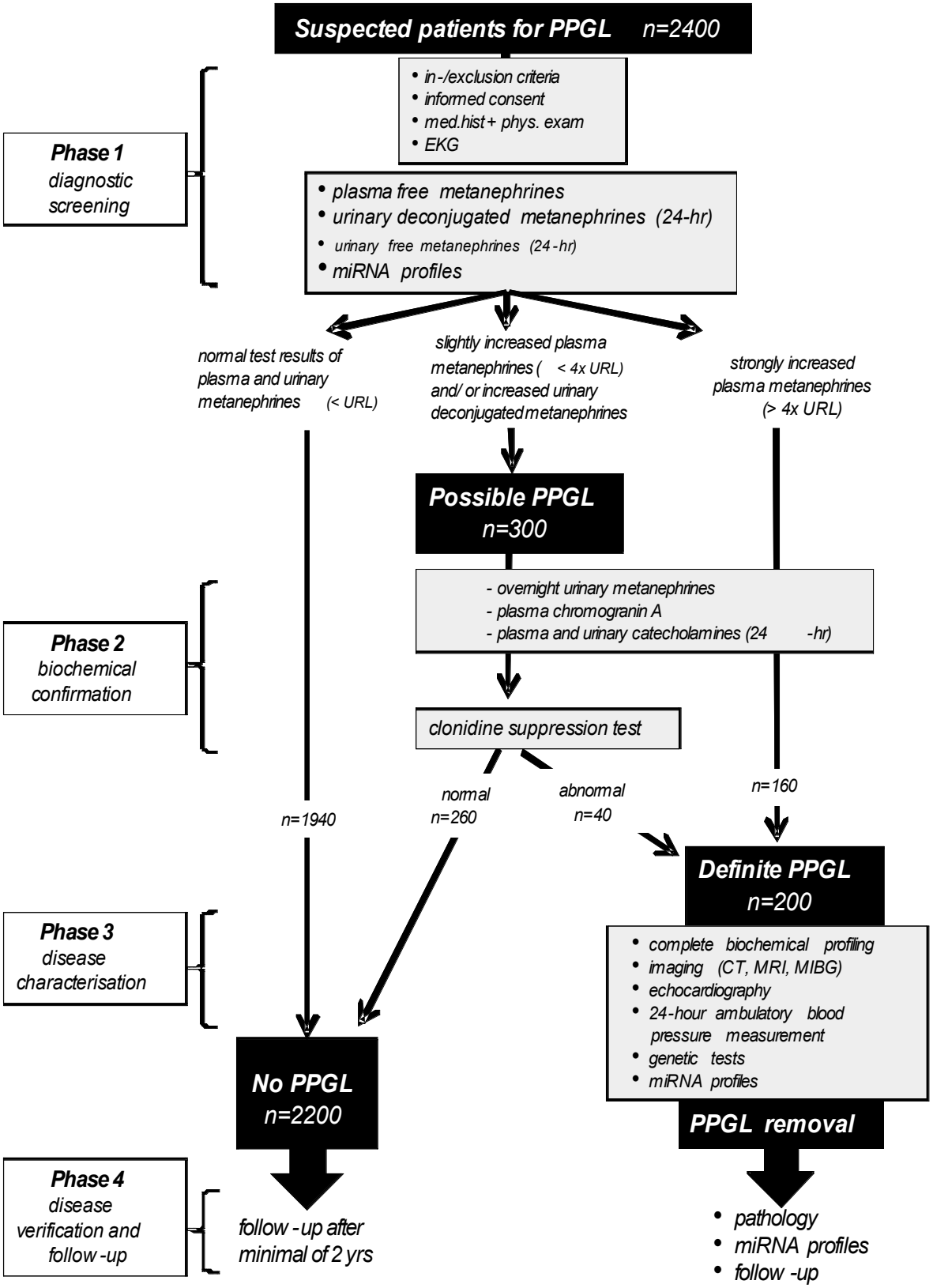
PMT (Prospective Monoamine-producing Tumour) Study

This is an international multicentre prospective study (conceived by Professors Graeme Eisenhofer, Dresden and Jacques Lenders, Nijmegen) directed at elucidating the catecholamine metabolomic profiles of monoamine-producing tumors — primarily phaeochromocytomas and paragangliomas (PPGLs) — and the utility of catecholamine-related biomarkers for diagnosis and as determinants of clinical presentation. The study combines liquid chromatographic electrochemical and mass spectrometric measurements of catecholamines and metabolites with comprehensive clinical examinations of patients subsequently diagnosed with PPGLs. The study is coordinated from the University Hospital of Dresden, where diagnostic specimens are received from participating centres.

The study follows from retrospective work indicating that measurements of the O-methylated metabolites of catecholamines (methoxytyramine normetanephrine, metanephrine) are not only useful for initial diagnosis of PPGLs, but also provide potentially useful predictive information about underlying disease-causing mutations and the presence of metastases. The **long-range goal** is to develop new and improved approaches for diagnosis, management and treatment of patients with PPGLs. As a step towards reaching this goal, the **primary objective** is to identify new and improved disease biomarkers and establish the biochemical and molecular basis for variations in the clinical presentation of the tumours. A **central hypothesis** is that the varied course of clinical manifestations and complications of PPGLs reflect underlying differences in biochemical phenotypes, which in turn depend on the specific tumour cell types and the underlying mutations responsible for PPGLs. The **rationale** underlying the project is that elucidation of the relationships between biochemical phenotypes, genotypes and the natural history of the disease will lead to improved understanding of tumour biology and development of new and improved approaches for diagnosis, management and treatment of PPGLs.

The study involves several ENS@T centres, with participation requiring approval of a central protocol by the ethics committee at each participating centre. Participating centres not only contribute to addressing the multiple specific aims of the central protocol, but are also encouraged to identify specific aims and subprojects of their own that can be addressed through the study and to which other participants may contribute. The study involves variable flow of subjects through 4 study phases over 5 years with a projected recruitment over the first three years of 2,400 patients, including at least 200 with subsequently confirmed tumors (see flow diagram). After the first three-years of recruitment (during which patients are streamed among three diagnostic work-up or disease verification phases), there is a fourth 2-year follow-up phase to satisfy requirements for exclusion of disease and post-surgical follow-up in patients in whom PPGLs have been confirmed and resected. Patient data, collected under established standard operating procedures, are entered into electronic case report forms at the ENS@T virtual research environment into which all biochemical test results are entered from the central reference laboratory at Dresden. The protocol also allows for banking of patient specimens (urine, plasma, germlineDNA, microRNA, tumor tissue) at the central Dresden laboratory or at each the participating ENS@T study centres.

Data collected from the study can be automatically entered into other ENS@T registries (e.g., the phaeochromocytoma and paraganglioma registry) or studies (e.g., EURINE-ACT) at the discretion of individual participating coinvestigators, and as dependent on the appropriate local permissions and patient consents. Conversely, patient data may be reciprocally entered from those registries or study databases into the PMT database. If you would like to participate in the PMT study, please contact Graeme Eisenhofer or Jacques Lenders, but also note the above stated requirements of participation and the finite duration of the study.


Suspected patients for PPGL n=2400
• in-/exclusion criteria
• informed consent
• med.hist + phys. exam
• EKG
Phase 1
diagnostic screening
• plasma free metanephrines
• urinary deconjugated metanephrines (24-hr)
• urinary free metanephrines (24-hr)
• miRNA profiles
normal test results of plasma and urinary metanephrines (< URL)
slightly increased plasma metanephrines (< 4x URL) and/ or increased urinary deconjugated metanephrines
strongly increased plasma metanephrines (> 4x URL)
Possible PPGL n=300
Phase 2
biochemical confirmation
- overnight urinary metanephrines
- plasma chromogranin A
- plasma and urinary catecholamines (24 -hr)
clonidine suppression test
n=1940
normal n=260
abnormal n=40
n=160
Definite PPGL n=200
Phase 3
disease characterisation
• complete biochemical profiling
• imaging (CT, MRI, MIBG)
• echocardiography
• 24-hour ambulatory blood pressure measurement
• genetic tests
• miRNA profiles
No PPGL n=2200
PPGL removal
Phase 4
disease verification and follow-up
follow-up after minimal of 2 yrs
• pathology
• miRNA profiles
• follow-up